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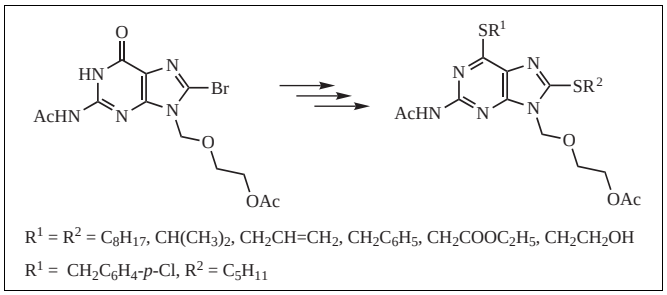
Received September 22, 2005




The synthesis of novel 2-amino-9-alkoxyalkylpurine derivatives with both identical and different sulfur containing substituents at positions 6 and 8 of the purine cycle has been accomplished. The thionation and alkylation of the key intermediate – 2-[2-(acetylamino)-6,8-dichloro-9*H*-purin-9-yl]methoxyethyl acetate or its reactions with thiolates were used. The structures of compounds obtained were confirmed by spectroscopic data and X-ray diffraction analysis.

*J. Heterocyclic Chem.*, **43**, 943 (2006).

## Introduction.

The synthesis of thioxopurine derivatives has attracted the attention of chemists because of their various biological activities. Sulfur containing purines have been demonstrated to possess cytostatic [1] and antibacterial properties [2]. Besides, they may serve as novel potential PET cancer imaging agents for hepatitis B virus and herpes simplex virus thymidine kinase *in vivo* [3]. Among these compounds, investigation of 2-amino-6,8-dithioxopurine derivatives has been less active. Hence, there is sufficient scope for the search and development of new thioxopurines with potential pharmaceutical importance.

Only a few 2-amino purines bearing sulphur-containing substituents at positions 6 and 8 of the purine cycle have been prepared so far. 2-Amino-6,8-dithioxopurine and its 9-*n*-hexylderivative were synthesized from the corresponding 2-amino-6-oxo-8-thioxo (or 8-methylsulfanyl) purine or 2-amino-8-bromo-6-oxopurine in the reaction with phosphorus pentasulfide in boiling pyridine [4-6]. The S-alkylation of 2-amino-6,8-dithioxopurine has been carried out only with methyl iodide in aqueous potassium hydroxide solution [5]. To our knowledge, the direct nucleophilic displacement of halogens by thiols in 2-amino-6,8-dichloropurines has not been reported. However, the method has found application in the synthesis of some 6-alkylsulfanyl-, 6,8-dialkylsulfanyl- and 2-amino-6-alkylsulfanylpurine derivatives using sodium thiolates in water or dioxane as well as thiols in $K_2CO_3$/1,2-dimethoxyethane system [7-9]. 2-Amino-6-phenylsulfanyl- or 2-amino-6-oxo-8-phenylsulfanyl-9-substituted purines can be synthesized by treating appropriate 6-chloropurine or 8-bromopurine with phenylthiol in methanol or DMF in the presence of triethylamine, pyridine or sodium acetate [3,10,11].

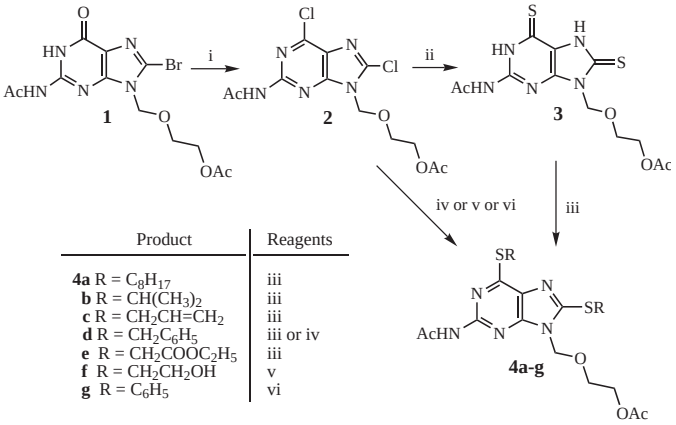
In continuation of our investigation of thioxopurines [12] and in view of the limited work previously done in this field we decided to synthesize and characterize a series of novel 2-amino-6,8-dithioxo-9-alkoxyalkylated purine derivatives in order to make them available for biological studies.

## Results and Discussion.

The first pathway for the preparation of target compounds is outlined in Scheme 1. The derivative chosen as a starting material was 8-bromo-6-oxo-9-substituted purine **1** [13]. Chlorination of derivative **1** to give 2-[2-(acetylamino)-6,8-dichloro-9*H*-purin-9-yl]methoxyethyl acetate (**2**) was successfully accomplished with phosphorus oxychloride and *N*,*N*-diethylaniline as described in the literature for similar systems [**11**]. The treatment of compound **2** with sodium thiosulfate in water in the presence of $AlCl_3$ [14] converted it into 6,8-dithioxopurine **3**. Further alkylation with two equivalents of alkyl, allyl and benzyl halides or ethylbromoacetate under standard conditions ($K_2CO_3$/DMF) at ambient temperature gave the corresponding 6,8-bis(octylsulfanyl)-, 6,8-bis(isopropylsulfanyl)-, 6,8-bis(allylsulfanyl)-, 6,8-bis(benzylsulfanyl)- and 6,8-bis[(2-ethoxy-2-oxoethyl)sulfanyl)]purine derivatives (**4a-e**) in high yields. The lower yield of product **4b** was connected with its purification problems which were solved by hydrolysis of the protecting N- and O-acetyl groups followed by recrystallization from ethanol of the resulting 2-{[2-

amino-6,8-bis(isopropylsulfanyl)-9*H*-purin-9-yl]methoxy}-1-ethanol.

Scheme I




Reagents: (i) $POCl_3$, N,N-diethylaniline, $CH_3CN$; (ii) $Na_2S_2O_3$, $AlCl_3$, $H_2O$; (iii) RBr, $K_2CO_3$, DMF, (iv) BnSH, $Et_3N$, MeOH, (v) $HOCH_2CH_2SH$, NaH, DMF, (vi) PhSH, NaOAc, MeOH

The structural assignment of new compounds **4a-e** was based on the analytical and spectral data (Table 1), but attention had to be paid to the interpretation of the $^1$H nmr spectra because a competitive alkylation of the purine cycle nitrogen atoms in compound **3** could take place due to tautomerism. However, the chemical shifts of the introduced substituent $CH_2$- or CH-group protons in products **4a-e** (~3.3-4.5 ppm) corresponded more to those of S-alkylated than N-alkylated derivatives [15]. Besides, the upfield shift of the exocyclic acetylamino group NH-proton in comparison with starting material **3** up to 10.4-10.6 ppm excluded N1-alkylation [16], but the absence of the slight downfield shift of the $NCH_2$-group protons singlet at position 9 of the heterocycle typical to 7,9-disubstituted-8-thioxopurines [15] contradicted the N7-alkylation.

An additional structural proof was presented by X-ray diffraction analysis of the crystals of compound **4c** that unambiguously established its S-alkylation (Figure 1) [17]. The formation of regioisomeric N-alkylated or mono-S-alkylated products was not observed. Even using one equivalent of the alkylating agent the only by-product of the alkylation was unchanged starting material. Besides, 6,8-dithioxopurine **3** had a higher reactivity in alkylation reactions compared with the analogous 2-(acetylamino)-6-oxo-8-thioxo-9-substituted purine derivative described in our recent publication [15].

Our further interest was to find out whether the target 2-amino-6,8-dithioxosubstituted-9-alkoxyalkylpurines could be prepared from the corresponding halogen derivatives in a one-step reaction with thiols. The treatment of 6,8-dichloropurine **2** with benzyl thiol in boiling methanol in the

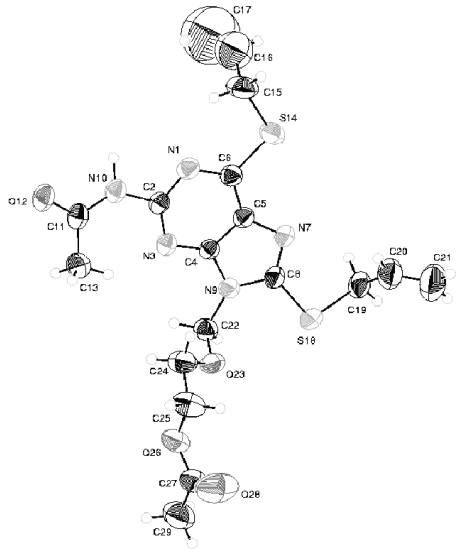
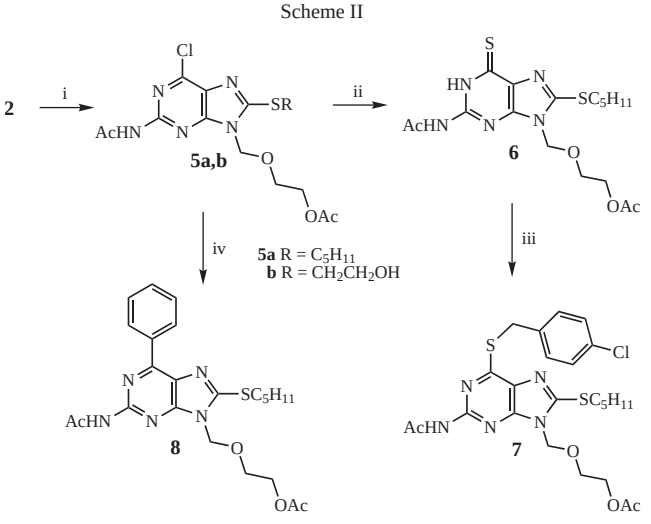



Figure 1. The ORTEP picture of the X-ray determined structure of compound **4c**.

presence of triethylamine resulted in 6,8-bis(benzylsulfanyl)purine **4d** identical to the product obtained in the alkylation of 6,8-dithioxopurine **3** with benzyl bromide (Scheme 1). By using less nucleophilic thiols (1-pentanethiol or (2-hydroxyethane)thiol) only one of the halogen atoms in the purine ring was substituted by an alkylthio group even using two-fold excess of the thiol (Scheme 2). As a result, 2-(acetylamino)-6-chloro-8-(pentylsulfanyl)- and 2-(acetylamino)-6-chloro-8-[(2-hydroxyethyl)sulfanyl]-purine derivatives **5a**, **b** were obtained in good yields.

Scheme II




Reagents: (i) RSH, $Et_3N$, MeOH; (ii) thiourea, DMF; (iii) 4-Cl-$C_6H_4$-$CH_2Cl$, NaOH, $H_2O$; (iv) $PhB(OH)_2$, $Pd(OAc)_2$, tri-O-tolylphosphine, $K_3PO_4$, $PhCH_3$

We succeeded to synthesize the target 2-(acetylamino)-6,8-bis[(2-hydroxyethyl)sulfanyl]purine **4f** carrying out the reaction with thiol in the presence of sodium hydride in DMF at ambient temperature. The attempt to perform the reaction with thiols in sodium ethylate/ethanol medium [7] led to the partial splitting of the acetyl protecting groups. Treatment of 6,8-dichloropurine **2** with two equivalents of thiophenol in the presence of sodium acetate in methanol [11] resulted in 2-[2-(acetylamino)-6,8-bis(phenylsulfanyl)-9*H*-purin-9-yl]methoxyethyl acetate (**4g**), but this method did not work with alkanethiols.

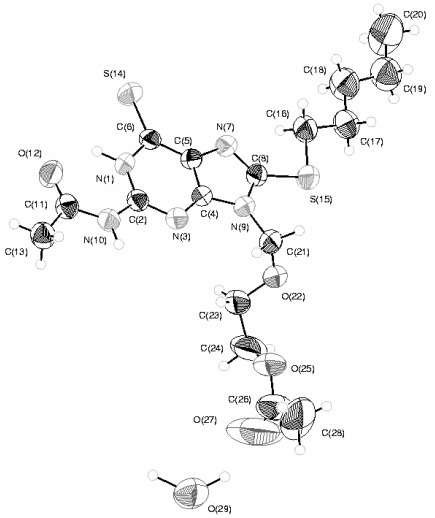



Figure 2. The ORTEP picture of the X-ray determined structure of compound **6**.

The analytical and spectral data confirming the structures of products **5a,b** and **6a**,**b** are given in Table 1. The presence of only one alkylthio substituent in compounds **5a**,**b** was corroborated by $^1$H nmr spectra. In order to ascertain the position of this substituent, the

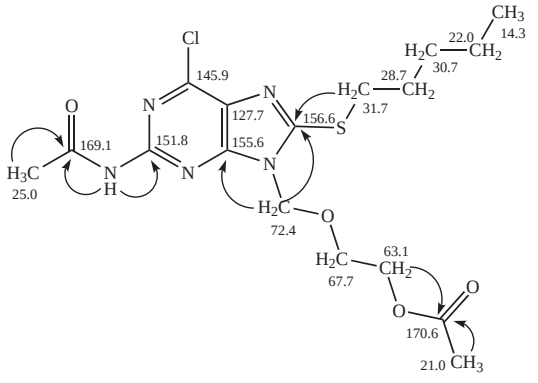



Figure 3. $^{13}$C-Chemical shifts (δ, ppm) and main correlations detected in the HMBC spectrum of compound **5a**

derivative **5a** was treated with thiourea in ethanol to obtain 2-[2-(acetylamino)-8-(pentylsulfanyl)-6-thioxo-1,6-dihydro-9*H*-purin-9-yl]methoxyethyl acetate (**6**), whose crystals were subjected to X-ray diffraction analysis. It obviously indicated the presence of the alkylsulfanyl substituent at position 8 of the purine cycle (Figure 2). However, to exclude the possible migration of the pentylsulfanyl group during the thionation reaction, the correct position of this group in compound **5a** was also supported by two-dimensional HMBC $^{13}$C nmr experiment. In this experiment the interactions of $SCH_2$- and $NCH_2$-group protons with carbon 8 were observed (Figure 3). Therefore, in contrast to the previous data about a higher reactivity of 6-chloro atom in the reactions of 6,8-dichloropurine with usual nucleophiles [7], in our case position 8 was preferable for the nucleophilic substitution.

Synthesized 6-chloro-8-thiosubstituted purine derivatives **5a**,**b** are good starting materials for further modification. For example, the mentioned above thionation of compound **5a** and following alkylation with 4-chlorobenzyl chloride in aqueous sodium hydroxide solution gave 2-[2-(acetylamino)-6-[(4-chlorobenzyl)sulfanyl]-8-(pentyl-sulfanyl)-9*H*-purin-9-yl]methoxyethyl acetate (**7**) thereby showing possibility to synthesize 2-amino-6,8-dithioxosubstituted purines with different substituents at thio groups. 6-Chloro-8-thiosubstituted purine **5a** is also suitable for metal catalyzed C-C coupling reactions. The Suzuki-Miyaura protocol was successfully adopted and 2-[2-(acetylamino)-8-(pentylsulfanyl)-6-phenyl-9*H*-purin-9-yl]methoxyethyl acetate (**8**) was prepared from 6-chloro-8-(pentylsulfanyl)purine **5a** under standard conditions [18].

In conclusion, we have demonstrated that the thionation of the corresponding chloro purines with sodium thiosulphate or thiourea offers an alternative method for the synthesis of 6,8-dithioxo- and 6-thioxo-8-(alkylsulfanyl)purine derivatives. This procedure is more convenient and less hazardous than the most widely used thionation of oxopurines with phosphorus pentasulfide. The nucleophilic displacement of one of the halogens in 2-(acetylamino)-9-alkoxyalkyl-6,8-dichloro-9-alkoxyalkyl-purine may offer a possibility for the synthesis of the corresponding 6-chloro-8-(alkylsulfanyl) purine derivatives suitable for various transformations. Further experiments are required to establish the scope of this process. The biological activity measurements of the new compounds are under investigation.

## EXPERIMENTAL

Melting points were determined using a Boetius apparatus and are uncorrected. $^1$H nmr spectra were recorded on Varian Gemini 200 MHz spectrometer, in DMSO-$d_6$ solution with hexamethyl disiloxane as internal standard. $^1$H-$^{13}$C nmr HMBC spectrum was recorded on Varian UNITY INOVA 600 MHz

Table 1
Physical and Spectral Data of Compounds **2-8**

| Nr | Yield, % [a] | Mp (°C) | $^1$H nmr (δ, ppm) | Molecular formula | Analysis % Calcd./Found | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | S |
| **2** | 60 | 147 | 1.93 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 3.75-3.80 (m, 2H, $CH_2$), 4.05-4.09 (m, 2H, $CH_2$), 5,57 (s, 2H, $NCH_2$), 10.59 (s, 1H, NH). | $C_{12}H_{13}Cl_2N_5O_4$ | 39.80<br>40.02 | 3.62<br>3.80 | 19.34<br>19.55 | - |
| **3** | 70 | 249-251 | 1.95 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 3.78-3.85 (m, 2H, $CH_2$), 4.03-4.08 (m, 2H, $CH_2$), 5,51 (s, 2H, $NCH_2$), 10.59 (s, 1H, NH), 13.33 (s, 1H, NH), 13.55 (s, 1H, NH). | $C_{12}H_{15}N_5O_4S_2$ | 40.33<br>40.50 | 4.23<br>4.06 | 19.60<br>19.31 | 17.94<br>17.56 |
| **4a** | 87 | 56-57 | 0.80 (t, 6H, J=6.3 Hz, $CH_3$), 1.18-1.49 (m, 20H, $CH_2$), 1.61-1.80 (m, 4H, $CH_2$), 1.92 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 3.34 (m, 4H, $SCH_2$) 3.66-3.73 (m, 2H, $CH_2$), 4.01-4.08 (m, 2H, $CH_2$), 5,43 (s, 2H, $NCH_2$), 10.43 (s, 1H, NH). | $C_{28}H_{47}N_5O_4S_2$ | 57.80<br>58.16 | 8.14<br>8.17 | 12.04<br>12.11 | 11.02<br>10.79 |
| **4b** [b] | 55 | 86-87 | 1.35 (d, 6H, J=6.8 Hz, $CH_3$), 1.39 (d, 6H, J=6.8 Hz, $CH_3$), 3.44 (s, 4H, $CH_2CH_2$), 3.88 (sep, 1H, J=6.8 Hz, SCH), 4.24 (sep, 1H, J=6.8 Hz, SCH), 4.63 (t, 1H, J=5.4 Hz, OH), 5,31(s, 2H, $NCH_2$), 6.49 (s, 2H, $NH_2$). | $C_{14}H_{23}N_5O_2S_2$ | 47.04<br>47.32 | 6.48<br>6.50 | 19.59<br>19.40 | 17.94<br>17.80 |
| **4c** | 95 | 114-115 | 1.93 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 3.67-3.74 (m, 2H, $CH_2$), 4.01-4.05 (m, 2H, $CH_2$), 4.00 (d, 2H, J=5.8 Hz, $SCH_2$), 4.06 (d, 2H, J= 5.8 Hz, $SCH_2$), 5.07-5.20 (m, 2H, $CH_2$), 5.30-5.44 (m, 2H, $CH_2$), 5,45 (s, 2H, $NCH_2$), 5.90-6.14 (m, 2H, CH), 10.51 (s, 1H, NH). | $C_{18}H_{23}N_5O_4S_2$ | 49.41<br>49.62 | 5.06<br>5.22 | 13.03<br>13.25 | 11.93<br>12.22 |
| **4d** | 90 | 128-130 | 1.87 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$), 3.61-3.68 (m, 2H, $CH_2$), 3.99-4.04 (m, 2H, $CH_2$), 4.57 (s, 2H, $SCH_2$), 4.68 (s, 2H, $SCH_2$), 5.41 (s, 2H, $NCH_2$), 7.19-7.53 (m, 10H, Ar-H), 10.60 (s, 1H, NH). | $C_{26}H_{27}N_5O_4S_2$ | 58.08<br>58.29 | 5.11<br>4.90 | 15.44<br>15.43 | 14.14<br>14.11 |
| **4e** | 93 | 128-129 | 1.19 (t, 3H, J=7.8 Hz, $CH_3$), 1.22 (t, 3H, J=7.8 Hz, $CH_3$), 1.94 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 3.69-3.75 (m, 2H, $CH_2$), 4.05-4.09 (m, 2H, $CH_2$), 4.13 (q, 2H, J=7.8 Hz, $CH_2$), 4.18 (q, 2H, J=7.8 Hz, $CH_2$), 4.24 (s, 2H, $SCH_2$), 4.32 (s, 2H, $SCH_2$), 5.49 (s, 2H, $NCH_2$), 10.47 (s, 1H, NH). | $C_{20}H_{27}N_5O_8S_2$ | 45.36<br>45.04 | 5.14<br>5.06 | 13.22<br>13.41 | 12.11<br>12.08 |
| **4f** | 60 | 102-103 | 1.93 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 3.37-3.45 (m, 4H, $SCH_2$), 3.63-3.76 (m, 6H, $CH_2$), 4.04-4.08 (m, 2H, $CH_2$), 4.94 (t, 1H, J=4.9 Hz, OH), 5.11 (1, 1H, J=4.9 Hz, OH), 5.44 (s, 2H, $NCH_2$), 10.47 (s, 1H, NH). | $C_{16}H_{23}N_5O_6S_2$ | 43.14<br>43.00 | 5.20<br>4.90 | 15.72<br>15.49 | 14.39<br>13.93 |
| **4g** | 68 | 95-97 | 1.87 (s, 3H, $CH_3$), 1.93 (s, 3H, $CH_3$), 3.72-3.78 (m, 2H, $CH_2$), 4.01-4.09 (m, 2H, $CH_2$), 5.56 (s, 2H, $NCH_2$), 7.44-7.66 (m, 10H, Ar-H), 10.47 (s, 1H, NH). | $C_{24}H_{23}N_5O_4S_2$ | 56.57<br>56.70 | 4.55<br>4.30 | 13.74<br>13.52 | 12.58<br>13.06 |
| **5a** | 76 | 133-134 | 0.87 (t, 3H, J=7.1 Hz, $CH_3$), 1.27-1.44 (m, 4H, $2CH_2$), 1.76 (qui, 2H, J=7.1 Hz, $CH_2$), 1.93 (s, 3H, $CH_3$), 2.18 (s, 3H, $CH_3$), 3.37 (t, 2H, J=7.1 Hz, $SCH_2$), 3.70-3.74 (m, 2H, $CH_2$), 4.04-4.09 (m, 2H, $CH_2$), 5.47 (s, 2H, $NCH_2$), 10.79 (s, 1H, NH). | $C_{17}H_{24}ClN_5O_4S$ | 47.49<br>47.18 | 5.63<br>5.42 | 16.29<br>16.49 | 7.46<br>7.34 |
| **5b** | 65 | 140-142 | 1.93 (s, 3H, $CH_3$), 2.18 (s, 3H, $CH_3$), 3.47 (t, 2H, J=6.1 Hz, $SCH_2$), 3.71-3.79 (m, 4H, $2CH_2$), 4.05-4.09 (m, 2H, $CH_2$), 5.11 (t, 1H, J=5.9 Hz, OH), 5.48 (s, 2H, $NCH_2$), 10.82 (s, 1H, NH). | $C_{14}H_{18}ClN_5O_5S$ x ½ $H_2O$ | 40.73<br>40.52 | 4.64<br>4.25 | 16.96<br>17.00 | 7.77<br>7.90 |
| **6** | 71 | 151-152 | 0.87 (t, 3H, J=6.4 Hz, $CH_3$), 1.23-1.49 (m, 4H, $CH_2$), 1.72 (qui, 2H, J=6.4 Hz, $CH_2$), 1.94 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 3.32 (q, 2H, J=6.4 Hz, $CH_2$), 3.65-3.70 (m, 2H, $CH_2$), 4.04-4.08 (m, 2H, $CH_2$), 5.36 (s, 2H, $NCH_2$), 12.02 (s, 1H, NH), 13.32 (s, 1H, NH). | $C_{17}H_{25}N_5O_6S_2$ | 47.76<br>47.73 | 5.89<br>5.76 | 16.38<br>16.00 | 15.00<br>15.32 |
| **7** | 82 | 108-110 | 0.85 (t, 3H, J=6.8 Hz, $CH_3$), 1.20-1.42 (m, 4H, $2CH_2$), 1.70 (qui, 2H, J=6.8 Hz, $CH_2$), 1.89 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 3.30 (q, 2H, J=6.8 Hz, $CH_2$), 3.67-3.71 (m, 2H, $CH_2$), 4.02-4.07 (m, 2H, $CH_2$), 4.65 (s, 2H, $SCH_2$), 5.43 (s, 2H, $NCH_2$), 7.33 (d, 2H, J=8.3 Hz, Ar-H), 7.53 (d, 2H, J=8.3 Hz, Ar-H), 10.60 (s, 1H, NH). | $C_{24}H_{30}ClN_5O_4S_2$ | 52.21<br>52.25 | 5.48<br>5.23 | 12.68<br>12.70 | 11.61<br>11.60 |
| **8** | 56 | 97-99 | 0.88 (t, 3H, J=6.9 Hz, $CH_3$), 1.31-1.50 (m, 4H, $2CH_2$), 1.83 (qui, 2H, J=6.7 Hz, $CH_2$), 1.91 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_3$), 3.41 (q, 2H, J=6.7 Hz, $CH_2$), 3.72-3.77 (m, 2H, $CH_2$), 4.05-4.09 (m, 2H, $CH_2$), 5.51 (s, 2H, $NCH_2$), 7.54-7.57 | $C_{23}H_{29}N_5O_4S$ | 58.58<br>58.43 | 6.20<br>6.07 | 14.85<br>14.93 | 6.80<br>6.81 |

[a] Isolated yield. [b] N,O-Deacetylated derivative.

spectrometer equipped with a cryoprobe and pulse-field gradient system in DMSO-$d_6$ solution at 25 °C using the system the coupling evolution delay for the generation of multiple-bond correlations set to 62.5 ms. 2D spectrum consisted of 4096*1024 points data matrix, giving t2max=250ms for $^{1}H$ nucleus in acquisition dimension and tlmax =50ms for $^{13}C$ for indirect dimension. Prior to Fourier transform the data matrix was zero filled twice and multiplication by shifted sine-bell window function applied. After the FT the magnitude spectrum was calculated. Magnesium sulfate was used as drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc was carried out on Merck 0.2 mm pre-coated silica gel aluminum sheets (60 F-254) in the solvent system chloroform/ethanol (10/0.5). Flash chromatography was carried out on silica gel 60 (Merck, 230-400 mesh, 60 Å) using the indicated solvents. The X-ray structure determination was performed on Bruker-Noniuss Kappa CCD automated diffractometer. Crystals of compounds **4c** and **6** were obtained by crystallization from ethanol. 2-[2-(Acetylamino)-8-bromo-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxyethyl acetate (**1**) was synthesized according to a literature procedure [13]. All solvents and reagents were obtained from ACROS and were used without further purification.

2-[2-(Acetylamino)-6,8-dichloro-9*H*-purin-9-yl]methoxyethyl acetate (**2**).

To a suspension of **1** (1.76 g, 4.0 mmol) in acetonitrile (20 ml) *N*,*N*-diethylaniline (0.70 ml, 4.4 mmol) and $POCl_3$ (1.90 ml, 20 mmol) were added. The mixture was refluxed for 20 min in a 100 °C oil bath. The resulting solution was evaporated to red oil, and then ice was added and mechanically stirred. The mixture was extracted with methylene chloride (3 x 25 ml). The combined extracts were washed with 5% $NaHCO_3$ solution (2 x 10 ml), water (3 x 10 ml), brine (10 ml) and dried. After filtration the solution was evaporated and the residue was crystallized from ethanol to give pure **2** (60% yield).

2-[2-(Acetylamino)-6,8-dithioxo-1,6,7,8-tetrahydro-9*H*-purin-9-yl]methoxyethyl acetate (**3**).

To a suspension of **2** (0.46 g, 1.27 mmol) in water (400 ml) $Na_2S_2O_3$ x $5H_2O$ (2.15 g, 8.67 mmol) and $AlCl_3$ x $6H_2O$ (0.15 g, 0.64 mmol) were added. The mixture was refluxed for 4 hours, any solid substance was filtered off and the filtrate was cooled in refrigerator. The resulting precipitate was collected by filtration, washed with cold water and crystallized from ethanol to give product **3** (70% yield).

2-[2-(Acetylamino)-6,8-bis(octylsulfanyl)-9*H*-purin-9-yl]-, 2-[2-(Acetylamino)-6,8-bis(isopropylsulfanyl)-9*H*-purin-9-yl]-, 2-[2-(Acetylamino)-6,8-bis(allylsulfanyl)-9*H*-purin-9-yl]-, 2-[2-(Acetylamino)-6,8-bis(benzylsulfanyl)-9*H*-purin-9-yl]methoxyethyl acetate (**4a-d**), Ethyl 2-(2-(acetylamino)-9-[2-(acetyloxy)-ethoxy]methyl-6-[(2-ethoxy-2-oxoethyl)sulfanyl]-9*H*-purin-8-ylsulfanyl)acetate (**4e**).

To a solution of **3** (0.050 g, 0.14 mmol) in *N*,*N*-dimethylformamide (1.0 ml) $K_2CO_3$ was added (0.038 g, 0.28 mmol). A solution of appropriate alkyl or benzyl halide or ethylbromoacetate (0.28 mmol) in *N*,*N*-dimethylformamide (0.5 ml) was added dropwise during ten minutes and the reaction mixture was stirred at room temperature for 3-6 hours. The mixture was diluted with water (5 ml) and extracted with EtOAc (3 x 10 ml). The combined extracts were washed with water (2 x 5 ml), brine (5 ml) and dried. After filtration the solution was evaporated and the residue was crystallized from ethanol to give products **4a-e** (87-95% yields).

Compound **4b** was treated with methylamine 40 wt % water solution (2 ml) at room temperature for 3 hours. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol to give 2-{[2-amino-6,8-bis(isopropyl-sulfanyl)-9*H*-purin-9-yl]methoxy}-1-ethanol (55 % yield).

2-[2-(Acetylamino)-6,8-bis[(2-hydroxyethyl)sulfanyl]-9H-purin-9-ylmethoxy]ethyl acetate (**4f**).

To a solution of (2-hydroxyethane)thiol (0.027 ml, 0.28 mmol) in *N*,*N*-dimethylformamide (1.0 ml) 60 % dispersion of NaH in oil (11.03 mg, 0.28 mmol) was added. After stirring at room temperature for 30 min compound **2** (0.10 g, 0.28 mmol) solution in *N*,*N*-dimethylformamide (1.0 ml) was added, and the stirring was continued at room temperature for 3 hours. The reaction mixture was filtered, the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using methylene chloride/ethanol (100/5) as eluent to give homogeneous residue, which was crystallized from ethanol to yield **4f** (60% yield).

2-[2-(Acetylamino)-6,8-bis(phenylsulfanyl)-9*H*-purin-9-yl]-methoxyethyl acetate (**4g**).

To a suspension of **2** (0.20 g, 0.51 mmol) in methanol (10 ml) and water (0.5 ml) sodium acetate (0.097 g, 1.20 mmol) and thiophenol (0.058 ml, 0.051 mmol) were added. The reaction mixture was refluxed for 14 hours, cooled to room temperature, filtered, evaporated to dryness and the residue was purified by column chromatography on silica gel using methylene chloride/ ethanol (100/1) as eluent to give homogeneous residue, which was crystallized from ethanol to yield 4g (68% yield).

2-[2-(Acetylamino)-6,8-bis(benzylsulfanyl)-9*H*-purin-9-yl]-, 2-[2-(Acetylamino)-6-chloro-8-(pentylsulfanyl)-9*H*-purin-9-yl]-, 2-[2-(Acetylamino)-6-chloro-8-[(2-hydroxyethyl)sulfanyl]-9*H*-purin-9-yl]methoxyethyl acetate (**4d**, **5a**, **b**).

The mixture of **2** (0.15 g, 0.41 mmol), thiol (1.0 mmol for **4d** or 0.50 mmol for **5a**, **b**) and triethylamine (1.40 ml, 1.0 mmol for **4d** or 0.70 ml, 0.50 mmol for **5a**, **b**) in methanol was refluxed for 8 hours. The clear mixture was cooled to room temperature, the resulting precipitate was collected by filtration, washed with cold ethanol and crystallized from ethanol to give products **4a** (51% yield) and **5a**,**b** (76% and 65% yield).

2-[2-(Acetylamino)-8-(pentylsulfanyl)-6-thioxo-1,6-dihydro-9*H*-purin-9-yl]methoxyethyl acetate (**6**).

To a suspension of **5a** (0.15 g, 0.35 mmol) in methanol thiourea (0.13 g, 1.75 mmol) was added. The reaction mixture was refluxed for 8 hours, cooled to room temperature, evaporated to dryness and the residue was purified by column chromatography on silica gel using methylene chloride/ethanol (100/2) as eluent to give homogeneous substance, which was crystallized from ethanol to yield **6** (71% yield).

2-[2-(Acetylamino)-6-[(4-chlorobenzyl)sulfanyl]-8-(pentylsulfanyl)-9*H*-purin-9-yl]methoxyethyl acetate (**7**).

To a suspension of **6** (0.10 g, 0.23 mmol) in water (2 ml) 0.4 *N* solution of NaOH (0.6 ml) and 4-chlorobenzyl chloride (0.037

g, 0.23 mmol) were added. The mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration, washed with cold water and crystallized from ethanol to give product **7** (82% yield).

2-[2-(Acetylamino)-8-(pentylsulfanyl)-6-phenyl-9*H*-9-yl]methoxy-ethyl acetate (**8**).

To a suspension of **5a** (0.10 g, 0.23 mmol) in toluene (5 ml) $Pd(OAc)_2$ (5.22 mg, 0.02 mmol), tri-O-tolylphosphine (14.16 mg, 0.05 mmol) and $K_3PO_4$ (0.10 g, 0.46 mmol) were added. The reaction mixture was stirred at room temperature for 10 min and then phenylboronic acid (0.056 g, 0.46 mmol) was added. After heating at 80 °C for 6 hours, the reaction mixture was filtered, evaporated to dryness and the residue purified by column chromatography on silica gel using methylene chloride/ethanol (100/1) as eluent to give homogeneous substance, which was crystallized from ethanol to yield **8** (56 %).

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[17] X-Ray crystallographic files (CIF) have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 275794 and 275795 for compound **4c** and **6**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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