SYNTHESIS OF 2- AND 6-(DIALKYLAMINOALKYLTHIO)- AND 2,6-BIS(DIALKYLAMINOALKYLTHIO)-7-METHYLPURINES

Alicja Kowalska* and Krystian Pluta

Department of Organic Chemistry, The Medical University of Silesia, Jagiellońska 4, 41-200 Sosnowiec, Poland. E-mail: kowalska@sum.edu.pl

Abstract – An efficient synthesis of 21 new thiopurines being 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines, 6-substituted 2-(dialkylaminoalkylthio)-7-methylpurines, and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines was reported. 2-Substituted 6-(dialkylaminoalkylthio) and 2,6-bis(dialkylaminoalkylthio) derivatives were obtained via direct S-dialkylaminoalkylation of the appropriate purinethiones. The different reactivities of the dialkylaminoalkylthio groups in positions 2 and 6 towards sodium alkoxides were the key processes in a few step synthesis of 2-(dialkylaminoalkylthio) derivatives from 2,6-bis(dialkylaminoalkylthio) derivatives.

INTRODUCTION

The purine ring system is a key structural element of substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins, and polymerases. Thiopurine antimetabolites such as 6-mercaptopurine, 6-thioguanine and azathioprine form an important group of cytotoxic drugs used in treating in several diseases including cancer. They have been used as immunosuppressants and anti-inflammatory agents in organ transplantation and chemotherapy, exhibited antineoplastic, antileukemic, antiviral, antibacterial and antifungal activities.

6-Substituted mercaptopurine derivatives possessing the pyrimidyl, imidazolyl, quinolyl or aminoalkyl groups at the sulfur atom were very effective against Mycobacterium paratuberculosis, Leishmania amazonensis and L. chagasi. Alkylaminoalkylthiopurines alone and with the phenyl or pyridyl substituents showed antibacterial and antithrombotic activities. There was also described the synthesis of the thiopurinyl piperazine derivatives usefull as cardiotonic and antiarrythmic agents and the quinoline, steroid, and triazole conjugates with 6-mercaptopurine possessing antimalarial and antileishmanial activity.
Recently it has been revealed a new mechanism of action the thiopurine drugs by which they regulate dendritic cells (DC) integrated functions, inducing a functionally less immunogenic phenotype.\textsuperscript{15} 6-Thioguanine (6-TG) incorporated into the DNA of macrophages sensitizes them to killing by endogenously produced reactive oxygen species. The findings suggests that the low oxidation potential of DNA 6-TG may influence the immunomodulatory effects of thiopurines and suggests a potential new therapeutic role for this long established class of drugs.\textsuperscript{16}

In our previous papers,\textsuperscript{17,18} we reported the effective synthesis of the azathioprine analogs containing one or two 1-methyl-4-nitroimidazol-5-yl groups at the sulfur atom in positions 2 or/and 6 of 7-methylpurines. In continuation of our studies on the thiopurine derivatives, we describe in this paper the synthesis of a series of new 7-methylpurines with pharmacophoric dialkylaminoalkyl substituents: diethylaminoethyl, dimethylaminopropyl, pyrrolidinylethyl, piperidinylethyl and morpholinylethyl groups at the sulfur atoms in positions 2 and 6.

RESULTS AND DISCUSSION

We started our synthesis from the reactions of 2-substituted 7-methyl-6-purinethiones 1a-c, possessing the chloro, methoxy and methylthio groups, with hydrochlorides of 2-diethylaminoethyl or 3-dimethylaminopropyl chlorides in boiling ethanol in the presence of sodium hydroxide to give 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines 2a-f in very good yields (77.5-95%, Scheme 1).

When the similar reactions were carried out using 7-methyl-2,6-dithioxanthine (3) and hydrochlorides of dialkylaminoalkyl chlorides in refluxing ethanol, to obtain the double dialkylaminoalkylation products, 7-methyl-2,6-bis(dialkylaminoalkythio)purines 4a-e, the yields were not quite satisfactory (48-56%). Only the reactions carried out in refluxing dioxane in the presence of sodium hydroxide led to the desired products 4 in high yields (80-95%) (Scheme 2). These conditions enabled to introduce the
dialkylaminoalkyl substituent possessing not only acyclic but also cyclic amino groups (pyrrolidine, piperidine and morpholine) at the sulfur atoms in both positions 2 and 6.

Scheme 2

Next step was synthesis of 2-(dialkylaminoalkylthio)-7-methylpurines, isomeric to compounds 2. The isomeric substrates, 6-substituted 7-methylpurine-2(3H)thiones, are not available in a simple way but in a few step synthesis from 2-chloro-7-methylpurin-6(1H)-one.¹⁹ As the substituents in position 6 are much more susceptible for nucleophilic reagents than in position 2,¹⁷-¹⁹ 2,6-disubstituted products 4 were used as the substrates. Our previous regioselective results with 2,6-dialkylthio]7-methylpurines with nucleophilic reagents¹⁷-¹⁹ prompted us to carried out the reaction with boiling phosphorus oxychloride to obtain the 6-chloro derivatives. Unfortunately, this reaction and the reactions with a mixture POCl₃-DMF or phenyl dichlorophosphate at 105-110 °C led to S-de(dialkylaminoalkylation) products, 2,6-dithio compound 3 (in 52–61% yield) and 2-(dialkylaminoalkylthio)-7-methylpurine-6(1H)thiones 5a and 5b in low yields (5-17%, the details in Experimental) (Scheme 3). Unlike the 1-methyl-4-nitroimidazol-5-ylthio group, the diethylaminoethylthio and dimethylaminopropylthio groups did not undergo the chlorination with phosphorus oxychloride and its derivatives.

Next we carried out the reactions with sodium alkoxides in boiling alcohols (methyl and ethyl). This time the reaction did not run as the dialkylaminoalkyl-sulfur bond cleavage process but as the monoalkoxylation to give 2-(dialkylaminoalkylthio)-6-alkoxy-7-methylpurines (7a-d) in very good yields (74-85.5%). The structural problem (which dialkylaminoalkylthio group was substituted by the alkoxy group) was solved comparing the physical (mp), chromatographical (Rᶠ) and spectroscopical (¹H NMR spectra) data of compounds 7a and 7c with compounds 2b and 2e, which turned out to be different.
Compounds 7b and 7d treated with phenyl dichlorophosphate at 105-110 °C gave 2-(dialkylaminoalkylthio)-6-chloro compounds 8a and 8b (in 72% and 76% yields), and 6-chloro-2-purinethione 9 (in 15% and 12% yield, respectively) as S-de(dialkylaminoalkylation) product. The chloro derivatives 8 in the reaction with thiourea gave the same thio compounds 5a and 5b (in 83% and 85.5% yields) directly from compound 4. S-Methylation of compounds 5a and 5b with methyl iodide led to methylthio compounds 6a and 6b in 82% and 83% yields (being isomeric to compounds 2c and 2f). The dialkylaminoalkyl groups in position 6 in thiopurines 4a and 4b turned out to be quite good leaving groups in the reactions with sodium alkoxides.

Scheme 3

All 2- and 6-(dialkylaminoalkylthio)-7-methylpurines (2, 5-8) and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines (4) exhibit promising potential antitumoral, antiaggregation, anti-inflammatory, cardiotonic, antiviral and nootropic activity, and could be useful as anticancer, and in particular as cardioprotective agents.20
CONCLUSION
Here, we report an efficient synthesis of 21 new thiopurines being 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines, 6-substituted 2-(dialkylaminoalkylthio)-7-methylpurines, and 2,6-bis(dialkylaminoalkylthio)-7-methylpurines. 2-Substituted 6-(dialkylaminoalkylthio) and 2,6-bis(dialkylaminoalkylthio) derivatives were obtained via the direct S-dialkylaminoalkylation of the appropriate purine-thiones. The different reactivities of the dialkylaminoalkylthio groups in positions 2 and 6 towards sodium alkoxides were the key processes in a few step synthesis of 2-(dialkylaminoalkylthio) derivatives from 2,6-bis(dialkylaminoalkylthio) derivatives.

EXPERIMENTAL
Melting points were determined in open capillary tubes on a Boetius melting point apparatus and were uncorrected. The $^1$H NMR spectra were recorded on a Varian Unity-Inova 300 spectrometer (300 MHz) in CDCl$_3$ and DMSO-$d_6$ with TMS as an internal standard. EI MS and FAB MS (in the m-nitrobenzyl alcohol and glycerol matrix) were run on a Finnigan MAT 95 spectrometer at 70eV.

General synthesis of 2-substituted 6-(dialkylaminoalkylthio)-7-methylpurines (2)
A mixture of 6-purinethione 1a-c ($1$ mmol), 2-diethylaminoethyl or 3-dimethylaminopropyl chloride hydrochloride ($1.5$ mmol), 10% aqueous NaOH solution ($0.25$ mL) and absolute EtOH ($20$ mL) was refluxed for 2 h. After cooling the small amount of resulting solid was filtered off, and the ethanolic filtrate was evaporated in vacuo. The residue was extracted with CHCl$_3$ ($3$ x $10$ mL), dried with anhydrous Na$_2$SO$_4$ and evaporated in vacuo. Crude products were purified by crystallization from EtOH and column chromatography (aluminium oxide, CHCl$_3$-EtOH, 9:1 v/v) to give the 6-(dialkylaminoalkylthio) derivatives 2a-f:

2-Chloro-6-(2-diethylaminoethylthio)-7-methylpurine ($2a$) ($0.284$ g, 95%); mp 158-159 °C (EtOH). $^1$H NMR (CDCl$_3$), $\delta$: 1.08 (t, $J = 7.1$ Hz, 6H, 2CCH$_3$), 2.67 (q, $J = 7.1$ Hz, 4H, 2NCH$_2$), 2.85 (t, $J = 7.2$ Hz, 2H, SCH$_2$), 3.14 (t, $J = 7.2$ Hz, 2H, NCH$_2$), 4.05 (s, 3H, NCH$_3$), 7.87 (s, 1H, H-8), FAB MS $m/z$: 300 (M+1, 55), 201 (M+1-C$_2$H$_3$N(C$_2$H$_5$)$_2$, 18), 100 (C$_2$H$_4$N(C$_2$H$_5$)$_2$, 100). Anal. Calcd for C$_{12}$H$_8$ClN$_5$S: C 48.07, H 6.05, N 23.36. Found C 48.33, H 5.98, N 23.58.

6-(2-Diethylaminoethylthio)-2-methoxy-7-methylpurine ($2b$) ($0.255$ g, 86.5%); mp 165-166 °C (EtOH). $^1$H NMR (CDCl$_3$), $\delta$: 1.04 (t, $J = 7.1$ Hz, 6H, 2CCH$_3$), 2.57 (q, $J = 7.1$ Hz, 4H, 2NCH$_2$), 2.75 (t, $J = 7.2$ Hz, 2H, SCH$_2$), 3.14 (t, $J = 7.1$ Hz, 2H, NCH$_2$), 4.05 (s, 3H, NCH$_3$), 4.12 (s, 3H, OCH$_3$), 7.87 (s, 1H, H-8), FAB MS $m/z$: 296 (M+1, 100), 197 (M+1-C$_2$H$_3$N(C$_2$H$_5$)$_2$, 16). Anal. Calcd for C$_{13}$H$_{21}$N$_5$OS: C 52.86, H 6.05, N 23.71. Found C 52.62, H 7.12, N 23.98.

6-(2-Diethylaminoethylthio)-7-methyl-2-methylthiopurine ($2c$) ($0.270$ g, 87%); mp 143-144 °C (EtOH). $^1$H NMR (CDCl$_3$), $\delta$: 1.08 (t, $J = 7.1$ Hz, 6H, 2CCH$_3$), 2.63 (s, 3H, SCH$_3$), 2.67 (q, $J = 7.1$ Hz, 4H, 2NCH$_2$), 2.83 (t, $J = 7.2$ Hz, 2H, SCH$_2$), 3.31 (t, $J = 7.1$ Hz, 2H, NCH$_2$), 4.07 (s, 3H, NCH$_3$), 7.88 (s, 1H,

2-Chloro-6-(3-dimethylaminopropylthio)-7-methylpurine (2d) (0.238 g, 83%); mp 186-187 °C (EtOH).
$^1$H NMR (CDCl3), δ: 2.11 (m, 2H, CH2), 2.71 (s, 6H, 2NCH3), 3.40 (t, J = 7.1 Hz, 2H, SCH2), 3.70 (t, J = 7.1 Hz, 2H, NCH2), 4.03 (s, 3H, NCH3), 8.11 (s, 1H, H-8), FAB MS m/z: 286 (M+1, 100), 201 (M+1-C3H5N(CH3)2, 9). Anal. Calcd for C11H16ClN5S: C 46.23, H 5.64, N 24.50. Found C 46.48, H 5.78, N 24.31.

6-(3-Dimethylaminopropylthio)-2-methoxy-7-methylpurine (2e) (0.223 g, 79%); mp 169-170 °C (EtOH).
$^1$H NMR (CDCl3), δ: 2.01 (m, 2H, CH2), 2.36 (s, 6H, 2NCH3), 2.55 (t, J = 7.1 Hz, 2H, SCH2), 3.29 (t, J = 7.1 Hz, 2H, NCH2), 3.92 (s, 3H, OCH3), 4.01 (s, 3H, NCH3), 7.86 (s, 1H, H-8), FAB MS m/z: 282 (M+1, 100), 197 (M+1-C3H5N(CH3)2, 8). Anal. Calcd for C12H19N5OS: C 51.22, H 6.81, N 24.89. Found C 51.53, H 6.73, N 25.12.

6-(3-Dimethylaminopropylthio)-7-methyl-2-methylthiopurine (2f) (0.230 g, 77.5%); mp 147-148 °C (EtOH). 1H NMR (CDCl3), δ: 2.10 (m, 2H, CH2), 2.61 (s, 3H, SCH3), 2.68 (s, 6H, 2NCH3), 2.93 (t, J = 7.1 Hz, 2H, NCH2), 2.91 (t, J = 7.1 Hz, 2H, NCH2), 3.55 (t, J = 7.1 Hz, 2H, SCH2), 3.34 (t, J = 7.1 Hz, 2H, SCH2), 3.45 (t, J = 7.1 Hz, 2H, NCH2), 4.05 (s, 3H, NCH3), 7.98 (s, 1H, H-8), FAB MS m/z: 298 (M+1, 100), 213 (M+1-C3H5N(CH3)2, 19). Anal. Calcd for C12H19N5S2: C 48.46, H 6.44, N 23.55. Found C 48.22, H 6.52, N 23.86.

General synthesis of 2,6-bis(dialkylaminoalkyl or 2-pyrrolidinylethyl, piperidinylethyl and morpholinylethylthio)-7-methylpurines (4)

To a mixture of 7-methylpurine-2(3H),6(1H)-dithione (3) (0.198 g, 1 mmol) and NaOH (0.4 g, 10 mmol) in stirred (10 mL) dry dioxane at rt for 1 h, 2.5 mmol of 2-diethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidinylethyl, 2-piperidinylethyl or 2-morpholinylethyl chloride hydrochloride was added and the mixture was refluxed for 2 h. After cooling the solid was filtered off and the solvent removed in vacuo. The residue was extracted with CHCl3 (3 x 10 mL), dried with anhydrous Na2SO4 and evaporated in vacuo.

The residue was extracted with CHCl3 (3 x 10 mL), dried with anhydrous Na2SO4 and evaporated in vacuo. Crude products were crystallized from EtOH and purified by column chromatography (aluminium oxide, CHCl3-EtOH, 9:1 v/v) to give the bis(dialkylaminoalkythio) derivatives 4a-e.

2,6-Bis(2-diethylaminoethylthio)-7-methylpurine (4a) (0.343 g, 86.5%); an oil. $^1$H NMR (CDCl3), δ: 1.07 (t, J = 7.2 Hz, 6H, 2CCH3), 1.12 (t, J = 7.2 Hz, 6H, 2CCH3), 2.63 (q, J = 7.2 Hz, 4H, 2NCH2), 2.70 (q, J = 7.2 Hz, 4H, 2NCH2), 2.82 (t, J = 7.2 Hz, 2H, SCH2), 2.91 (t, J = 7.2 Hz, 2H, SCH2), 3.34 (t, J = 7.2 Hz, 2H, NCH2), 3.45 (t, J = 7.2 Hz, 2H, NCH2), 4.05 (s, 3H, NCH3), 7.84 (s, 1H, H-8), FAB MS m/z: 397 (M+1, 100), 298 (M+1-C2H3N=C2H5, 19). Anal. Calcd for C18H32N6S2: C 54.51, H 8.13, N 21.19. Found C 54.81, H 8.04, N 20.96.

2,6-Bis(3-dimethylaminopropylthio)-7-methylpurine (4b) (0.296 g, 80.5%); mp 147-148 °C (EtOH). $^1$H NMR (CDCl3), δ: 2.10 (m, 2H, CH2), 2.61 (s, 3H, SCH3), 2.68 (s, 6H, 2NCH3), 2.93 (t, J = 7.1 Hz, 2H, CH2), 3.55 (t, J = 7.1 Hz, 2H, SCH2), 3.92 (s, 3H, OCH3), 4.06 (s, 3H, NCH3), 7.98 (s, 1H, H-8), FAB MS m/z: 282 (M+1, 100), 197 (M+1-C3H5N(CH3)2, 8). Anal. Calcd for C12H19N5S: C 51.22, H 6.81, N 24.89. Found C 51.53, H 6.73, N 25.12.
4.05 (s, 3H, NCH₃), 7.86 (s, 1H, H-8), FAB MS m/z: 369 (M+1, 100), 284 (M+1-C₂H₃N(CH₃)₂, 15). Anal. Calcd for C₁₆H₂₈N₆S₂: C 52.14, H 7.66, N 22.80. Found C 52.40, H 7.56, N 22.53.

2,6-Bis(2-pyrrolidinylethylthio)-7-methylpurine (4c) (0.364 g, 93%); mp 116-117 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.29 (m, 8H, 4CH₂), 2.67 (m, 8H, 4CH₂), 2.82 (t, J = 7.5 Hz, 2H, SCH₂), 2.87 (t, J = 7.5 Hz, 2H, SCH₂), 3.38 (t, J = 7.5 Hz, 2H, NCH₂), 3.50 (t, J = 7.5 Hz, 2H, NCH₂), 4.04 (s, 3H, NCH₃), 7.84 (s, 1H, H-8), FAB MS m/z: 393 (M+1, 100), 296 (M+1-C₂H₃NC₄H₈, 18). Anal. Calcd for C₁₈H₃₂N₆S₂: C 55.07, H 7.19, N 19.98. Found C 55.35, H 7.14, N 20.21.

2,6-Bis(2-piperidinylethylthio)-7-methylpurine (4d) (0.400 g, 95%); an oil. ¹H NMR (CDCl₃), δ: 1.45 (m, 4H, 2CH₂), 1.61 (m, 8H, 4 CH₂), 2.55 (m, 8H, 4CH₂), 2.69 (t, J = 7.5 Hz, 2H, SCH₂), 2.78 (t, J = 7.5 Hz, 2H, SCH₂), 3.39 (t, J = 7.5 Hz, 2H, NCH₂), 3.51 (t, J = 7.5 Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.84 (s, 1H, H-8), FAB MS m/z: 421 (M+1, 19), 308 (M+1-C₂H₅NC₅H₁₀, 7), 112 (C₂H₄NC₅H₁₀, 100). Anal. Calcd for C₂₀H₃₂N₆S₂: C 57.11, H 7.67, N 19.98. Found C 56.82, H 7.60, N 20.21.

2,6-Bis(2-morpholinylethylthio)-7-methylpurine (4e) (0.385 g, 90.5%); an oil. ¹H NMR (CDCl₃), δ: 2.58 (m, 8H, 4CH₂), 2.67 (m, 8H, 4CH₂), 2.73 (t, J = 7.5 Hz, 2H, SCH₂), 2.78 (t, J = 7.5 Hz, 2H, SCH₂), 3.39 (t, J = 7.5 Hz, 2H, NCH₂), 3.51 (t, J = 7.5 Hz, 2H, NCH₂), 4.06 (s, 3H, NCH₃), 7.86 (s, 1H, H-8), FAB MS m/z: 425 (M+1, 44), 312 (M+1-C₂H₃NO₄H₈, 14), 114 (C₂H₄NO₄H₈, 100). Anal. Calcd for C₁₈H₂₈N₆O₂S₂: C 50.92, H 6.65, N 19.79. Found C 51.19, H 6.71, N 19.51.

Synthesis of 7-methyl-6-purinethiones (5a, 5b)

A. From 8a,b

A solution of the 6-chloro derivative 8a or 8b (1 mmol) and thiourea (0.152 g, 2 mmol) in absolute EtOH (10 mL) was refluxed for 1 h. The solvent was removed in vacuo and the residue was dissolved in 5% aqueous NaOH solution. The reaction product was precipitated with 15% hydrochloric acid and the process was repeated twice to give pure 6-purinethiones 5a or 5b in 83% and 85.5% yields, respectively.

B. From 4a,b

A solution of anhydrous substrates 4a (or 4b) (1 mmol) in POCl₃ (5 mL) or in a mixture of POCl₃-DMF (1:2 v/v, 10 mL) or in phenyl dichlorophosphate (5 mL) was stirred on oil bath at 105-110 °C for 4 h. After cooling the reaction mixture was poured into crushed ice (10 g), neutralized with concentrated NH₄OH solution at 0-5 °C up to pH = 4-5 and the resulted solid was filtered off to give the mixture of products 3 and 5a (or 5b). The resulting mixture was separated by extraction with absolute EtOH (3 x 15 mL). The solvent was removed in vacuo and the residue was dissolved in 5% aqueous NaOH solution. The product 5a (or 5b) was precipitated with 15% aqueous HCl. The residue after extraction with EtOH was also dissolved in 5% aqueous NaOH solution and the product 3 was precipitated by acidification with 15% aqueous HCl to pH = 3.
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<td>3 (57), 5b (17)</td>
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2-(2-Diethylaminoethylthio)-7-methylpurine-6(1H)-thione (5a) (0.246 g, 83%); mp 177-178 °C (EtOH). 
¹H NMR (DMSO-d₆), δ: 1.38 (t, J = 7.2 Hz, 6H, 2CCH₃), 2.68 (t, J = 7.2 Hz, 2H, SCH₂), 2.98 (q, J = 7.2 Hz, 4H, 2NCH₂), 3.23 (t, J = 7.2 Hz, 2H, NCH₂), 4.07 (s, 3H, NCH₃), 8.05 (s, 1H, H-8), 9.44 (s, 1H, NH), FAB MS m/z: 298 (M+1, 100), 255 (M+1-(C₂H₅)₂NH, 6). Anal. Calcd for C₁₂H₁₉N₅S₂: C 48.46, H 6.44, N 23.55. Found C 48.73, H 6.35, N 23.38.

2-(3-Dimethylaminopropylthio)-7-methylpurine-6(1H)-thione (5b) (0.242 g, 85.5%); mp 193-194 °C (EtOH). ¹H NMR (DMSO-d₆), δ: 2.12 (m, 2H, CH₂), 2.83 (s, 6H, 2NCH₃), 3.47 (t, J = 7.2 Hz, 2H, SCH₂), 3.75 (t, J = 7.2 Hz, 2H, NCH₂), 4.08 (s, 3H, NCH₃), 8.10 (s, 1H, H-8), 10.81 (s, 1H, NH), FAB MS m/z: 284 (M+1, 100), 239 (M+1-(CH₃)₂NH, 9). Anal. Calcd for C₁₁H₁₇N₅S₂: C 46.62, H 6.05, N 24.71. Found C 46.89, H 6.08, N 24.52.

Synthesis of 2-(dialkylaminoalkylthio)-7-methyl-6-methylthiopurines (6a, b)

To a stirred solution of 6-purinethione 5a (or 5b) (1 mmol) in 4% aqueous KOH solution at rt, methyl iodide (0.28 g, 2 mmol) was added. After 20 min the resulting solid was filtered off and washed with water. The crude products were purified by column chromatography (aluminium oxide, CHCl₃, and CHCl₃-EtOH, 9:1, v/v) to give compound 6a (or 6b).

2-(2-Diethylaminoethylthio)-7-methyl-6-methylthiopurine (6a) (0.256 g, 82%); mp 134-135 °C (EtOH). ¹H NMR (CDCl₃), δ: 1.10 (t, J = 7.1 Hz, 6H, 2CCH₃), 2.68 (q, J = 7.1 Hz, 4H, 2NCH₂), 2.72 (s, 3H, SCH₃), 2.91 (t, J = 7.1 Hz, 2H, SCH₂), 3.41 (t, J = 7.1 Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.90 (s, 1H, H-8), FAB MS m/z: 312 (M+1, 100), 239 (M+1-(C₂H₅)₂NH, 16). Anal. Calcd for C₁₃H₂₁N₅S₂: C 50.13, H 6.80, N 22.48. Found C 49.89, H 6.73, N 22.48.

2-(3-Dimethylaminopropylthio)-7-methyl-6-methylthiopurine (6b) (0.246 g, 83%); mp 139-140 °C (EtOH). ¹H NMR (CDCl₃), δ: 2.08 (m, 2H, CH₂), 2.45 (s, 6H, 2NCH₃), 2.74 (s, 3H, SCH₃), 3.03 (t, J = 7.1 Hz, 2H, SCH₂), 3.81 (t, J = 7.1 Hz, 2H, NCH₂), 4.05 (s, 3H, NCH₃), 7.96 (s, 1H, H-8), FAB MS m/z: 298 (M+1, 100), 253 (M+1-(CH₃)₂NH, 12). Anal. Calcd for C₁₂H₁₉N₅S₂: C 48.46, H 6.44, N 23.55. Found C 48.74, H 6.36, N 23.24.

Reaction of 2,6-bis(dialkylaminoalkylthio)-7-methylpurines (4a,b) with alcohols
A solution of 4a or 4b (1 mmol) and sodium methoxide or ethoxide (1 mmol) in respective dry alcohol (methanol or ethanol, 10 mL) was refluxed for 2 h. After cooling small amount of resulting solid was filtered off and the alcoholic filtrate was evaporated to dryness in vacuo. The residue was crystallized from EtOH and purified by column chromatography (aluminium oxide, CHCl₃-EtOH, 9:1 v/v) to give compounds 7a-d.

2-(2-Diethylaminoethylthio)-6-methoxy-7-methylpurine (7a) (0.220 g, 74.5%); mp 155-156 °C (EtOH).

1H NMR (CDCl₃), δ: 1.11 (t, J = 7.2 Hz, 6H, 2CCH₃), 2.68 (q, J = 7.2 Hz, 4H, 2NCH₂), 2.90 (t, J = 7.1 Hz, 2H, SCH₂), 3.44 (t, J = 7.1 Hz, 2H, OCH₃), 3.67 (s, 3H, NCH₃), 7.85 (s, 1H, H-8), FAB MS m/z: 296 (M+1, 100), 223 (M+1-(C₂H₅)₂NH, 6). Anal. Calcd for C₁₃H₂₁N₅O₅S: C 52.86, H 7.17, N 23.71. Found C 52.59, H 7.23, N 23.89.

2-(2-Diethylaminoethylthio)-6-ethoxy-7-methylpurine (7b) (0.242 g, 78%); mp 124-125 °C (EtOH).

1H NMR (CDCl₃), δ: 1.13 (t, J = 7.1 Hz, 6H, 2CCH₃), 1.45 (t, J = 7.2 Hz, 3H, CCH₃), 2.69 (q, J = 7.1 Hz, 4H, 2NCH₂), 2.98 (t, J = 7.1 Hz, 2H, SCH₂), 3.51 (t, J = 7.1 Hz, 2H, OCH₂), 3.99 (s, 3H, NCH₃), 4.58 (q, J = 7.2 Hz, 2H, OCH₂), 7.84 (s, 1H, H-8), FAB MS m/z: 310 (M+1, 100), 237 (M+1-(C₂H₅)₂NH, 20). Anal. Calcd for C₁₄H₂₃N₅O₅S: C 54.34, H 7.49, N 22.63. Found C 54.61, H 7.54, N 22.32.

2-(3-Dimethylaminopropylthio)-6-methoxy-7-methylpurine (7c) (0.223 g, 79%); mp 159-160 °C (EtOH).

1H NMR (CDCl₃), δ: 1.97 (m, 2H, CH₂), 2.29 (s, 6H, 2NCH₃), 2.65 (t, J = 7.1 Hz, 2H, SCH₂), 3.42 (t, J = 7.1 Hz, 2H, NCH₃), 3.69 (s, 3H, OCH₃), 4.04 (s, 3H, NCH₃), 7.85 (s, 1H, H-8), FAB MS m/z: 282 (M+1, 100), 237 (M+1-(CH₃)₂NH, 10). Anal. Calcd for C₁₂H₁₉N₅O₅S: C 51.22, H 6.81, N 24.89. Found C 50.94, H 6.88, N 24.63.

2-(3-Dimethylaminopropylthio)-6-ethoxy-7-methylpurine (7d) (0.252 g, 85.5%); mp 130-131 °C (EtOH).

1H NMR (CDCl₃), δ: 1.45 (t, J = 7.1 Hz, 6H, 2CCH₃), 2.07 (m, 2H, CH₂), 2.40 (s, 6H, 2NCH₃), 2.67 (t, J = 7.1 Hz, 2H, SCH₂), 3.26 (t, J = 7.1 Hz, 2H, OCH₂), 3.97 (s, 3H, NCH₃), 4.57 (q, J = 7.2 Hz, 2H, OCH₂), 7.83 (s, 1H, H-8), FAB MS m/z: 296 (M+1, 100), 251 (M+1-(CH₃)₂NH, 19). Anal. Calcd for C₁₃H₂₁N₅O₅S: C 52.86, H 7.17, N 23.71. Found C 52.59, H 7.17, N 23.94.

**Synthesis of 2-(dialkylaminoalkylthio)-6-chloro-7-methylpurines (8a,b)**

A solution of 6-ethoxy derivatives 7b or 7d (1 mmol) in phenyl dichlorophosphate (5 mL) was stirred on oil bath at 105-110 °C for 2 h. After cooling the reaction mixture was poured into crushed ice (20 g), neutralized with concentrated NH₄OH solution at 0-5 °C up to pH = 7 and extracted with CHCl₃ (3 x 15 mL). The combined extracts were dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo and the residue was purified by column chromatography (aluminium oxide, CHCl₃-EtOH, 9:1 v/v) and preparative thin layer chromatographies to give compounds 8a (0.216 g, 72%) or 8b (0.217 g 76%).

6-Chloro-2-(2-diethylaminoethylthio)-7-methylpurine (8a) (0.216 g, 72%); mp 146-147 °C (EtOH).

1H NMR (CDCl₃), δ: 1.45 (t, J = 7.1 Hz, 6H, 2CCH₃), 3.12 (q, J = 7.1 Hz, 4H, 2NCH₂), 3.22 (t, J = 7.1 Hz,
2H, SCH₂), 3.85 (t, J = 7.1 Hz, 2H, NCH₂), 4.10 (s, 3H, NCH₃), 8.05 (s, 1H, H-8), FAB MS m/z: 300 (M+1, 100), 227 (M+1-(C₂H₅)₂NH, 9). Anal. Calcd for C₁₂H₁₈ClN₅S: C 48.07, H 6.05, N 23.36. Found C 48.35, H 5.97, N 23.17.

6-Chloro-2-(3-dimethylaminopropylthio)-7-methylpurine (8b) (0.217 g, 76%); mp 173-174 °C (EtOH).

¹H NMR (CDCl₃), δ: 2.14 (m, 2H, CH₂), 2.62 (s, 6H, 2NCH₃), 3.46 (t, J = 7.1 Hz, 2H, SCH₂), 3.85 (t, J = 7.1 Hz, 2H, NCH₂), 4.09 (s, 3H, NCH₃), 8.15 (s, 1H, H-8), FAB MS m/z: 286 (M+1, 100), 241 (M+1-(CH₃)₂NH, 7). Anal. Calcd for C₁₁H₁₆ClN₅S: C 46.23, H 5.64, N 24.50. Found C 46.44, H 5.70, N 24.26.

The aqueous solution (after extraction with CHCl₃) was acidified with 15% aqueous HCl up to pH = 4-5 and the resulting solid was filtered off and crystallized from EtOH to give 6-chloro-7-methylpurine-2(3H)-thione¹⁹ (9) (0.030 and 0.025 g, 15% and 12%); mp > 300 °C (EtOH). ¹H NMR (DMSO-d₆), δ: 4.15 (s, 3H, NCH₃), 8.28 (s, 1H, H-8), 12.18 (s, 1H, NH).

ACKNOWLEDGEMENTS

This work was supported by The Medical University of Silesia (grant KNW-1-073/P/1/0).

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