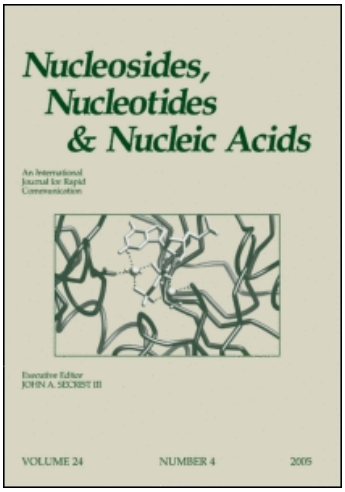


**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Sulfur Containing Acyclovir Derivatives: Synthesis, Cytotoxic Activity, and Cell Phenotype Studies

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**To cite this Article** Ikaunieks, Martins , Shestakova, Irina , Domracheva, Ilona , Belyakov, Sergey and Madre, Marina(2007) 'Sulfur Containing Acyclovir Derivatives: Synthesis, Cytotoxic Activity, and Cell Phenotype Studies', Nucleosides, Nucleotides and Nucleic Acids, 26: 10, 1269 — 1271
**To link to this Article: DOI:** 10.1080/15257770701528354
**URL:** http://dx.doi.org/10.1080/15257770701528354

*Nucleosides, Nucleotides, and Nucleic Acids*, 26:1269–1271, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701528354

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# SULFUR CONTAINING ACYCLOVIR DERIVATIVES: SYNTHESIS, CYTOTOXIC ACTIVITY, AND CELL PHENOTYPE STUDIES

**Martins Ikaunieks, Irina Shestakova, Ilona Domracheva, Sergey Belyakov, and Marina Madre** □ *Latvian Institute of Organic Synthesis, Riga, Latvia*

□ *New 2-amino-6-oxo-8-thioxo-9-substituted purine derivatives were prepared and assayed for the in vitro cytotoxic activity. Some products exhibited moderate activity on HT-1080 cells and rather high activity on MG-22A cells.*

**Keywords** Sulfur; acyclovir; antiherpetic drugs



## INTRODUCTION

Acyclovir is a well-known highly potent and selective antiherpetic drug. At the same time, it has been found to have the growth inhibitory activity against murine leukemia L 1210,[1a] but some of its 8-substituted or/and 1,N-2-bridged (tricyclic) analogues have demonstrated moderate activity and remarkable cytotoxic selectivity against KB and HeLa tumour cells.[1b] This article describes the synthesis and the in vitro cytotoxic activity of a series of new 2-amino-6-oxo-8-thioxo-9-(2-hydroxyethoxymethyl)purine derivatives as well as several 2-amino-6-oxo-8-thioxopurines bearing an alternative substituent at position 9 of the heterocycle.

## RESULTS AND DISCUSSION

The synthesized derivatives of 2-amino-6-oxo-8-thioxopurine are listed in Figure 1. Products **2a–c** were prepared and described previously.[2a] Compounds **1a–d** were obtained by N, O- or N-deacetylation of the corresponding 2-acetamido-9-(2-acetoxyethoxymethyl)-6-oxo-8-thioxopurines.[2a] The interaction of 8-(2-hydroxyethyl)thiopurine **1b** with adipic anhydride led to the formation of dicarboxylic acid **1f.** The N,N-dimethylaminomethylene protecting group removal in 8-(ethoxycarbonylmethyl)thiopurine

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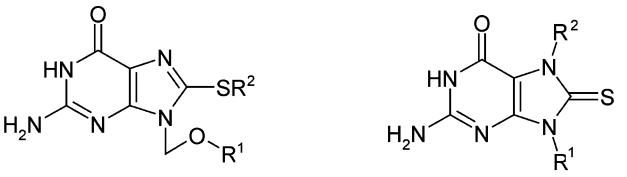


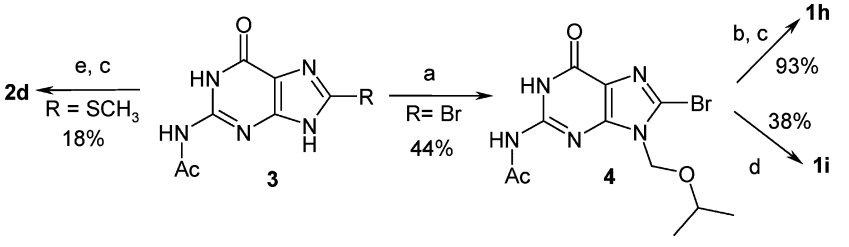
**1a-i** **2a-d**

**1a** $R^1$=$(CH_2)_2OH$, $R^2$= $CH_2CH{=}CH_2$; **1b** $R^1$=$R^2$=$(CH_2)_2OH$; **1c** $R^1$=$(CH_2)_2OH$, $R^2$=$CH_2C_6H_3$-3,4-di$CF_3$; **1d** $R^1$=$(CH_2)_2OAc$, $R^2$=$CH_2OC_{18}H_{37}$; **1e** $R^1$=$(CH_2)_2OAc$, $R^2$=$C_6H_5$; **1f** $R^1$=$R^2$=$(CH_2)_2OCO(CH_2)_2COOH$; **1g** $R^1$=$(CH_2)_2OH$, $R^2$= $CH_2CONHNH_2$; **1h** $R^1$=$CH(CH_3)_2$, $R^2$=H; **1i** $R^1$=$CH(CH_3)_2$, $R^2$=$C_6H_4$-3-$OCH_3$; **2a** $R^1$=$CH_2O(CH_2)_2OH$, $R^2$=$CH_2OC_8H_{17}$; **2b** $R^1$=$CH_2O(CH_2)_2OH$, $R^2$=$CH(CH_3)OC_4H_9$; **2c** $R^1$=$CH_2O(CH_2)_2OCH(CH_3)OC_4H_9$, $R^2$=$CH(CH_3)OC_4H_9$; **2d** $R^1$=$R^2$= $CH_2C_6H_5$

**FIGURE 1** Structural formulas of 2-amino-6-oxo-8-thioxopurine derivatives.



derivative[2b] with hydrazine hydrate brought about simultaneous amidation of the ester fragment yielding product **1g**. For the incorporation of a phenylthio substituent at position 8 of the purine cycle (**1e**) the reaction of 2-acetamido-9-(2-acetoxyethoxymethyl)-8-bromo-6-oxopurine with PhSH/NaOAc/EtOH system was used. Simultaneous splitting of the N-acetyl protecting group occurred during this reaction yielding **1e** in one step. Scheme 1 presents the synthesis of products **1i, h** via intermediate **4** prepared by alkylation of purine **3** (R = Br) with isopropoxymethyl chloride. The formation of the 9- and 7-alkoxyalkylated products in equal ratio and in good overall yield (88%) was observed in this reaction. The transformation of **4** into compound **1i** was carried out via routine thionation and deprotection.[2c] To obtain product **1h** intermediate **4** was treated with 3-methoxyphenyl thiol similar to the synthesis of **1e**. 7,9- Dibenzyl-8-thioxopurine **2d** was obtained by alkylation of **3** (R = $SCH_3$) with benzyl bromide and isolated alongside with the corresponding 7-benzyl- and 9-benzyl-8-methylthiopurine. The structures of compounds **1, 2** were supported by $^1H$ NMR spectra and elemental analysis data as well as by single crystal X-ray analysis for product **2d**.[3] The cytotoxic activity of



**SCHEME 1** Reagents: (a) $ClCH_2OCH(CH_3)_2$, $Et_3N$, THF; (b) $Na_2S_2O_3$, $AlCl_3$, $H_2O$; (c) $MeNH_2$, $H_2O$ (d) ArSH, NaOAc, MeOH, $H_2O$; (e) BnBr, $K_2CO_3$, DMF.

**TABLE 1** In vitro cytotoxicity of 8-thioxopurine derivatives **1**, **2** on monolayer tumor cell lines HT-1080, MG-22A, and on normal mouse fibroblasts cells (NIH 3T3)

| | HT-1080 | | MG-22A | | NIH 3T3 | |
|---|---|---|---|---|---|---|
| Cmpd. | $TD_{50}$[a] | NO, 100% | $TD_{50}$ | NO, 100% | $TD_{50}$ | $LD_{50}$ mg/kg |
| **1d** | 0.024 | 367 | 0.003 | 275 | 0.127 | 1000 |
| **1e** | 0.099 | 75 | NA[b] | 9 | 2.664 | 2403 |
| **1i** | 0.019 | 650 | NA | 20 | 0.278 | 872 |
| **2a** | 0.200 | 28 | NA | 17 | 2.503 | 2517 |
| **2d** | 0.048 | 233 | 0.018 | 300 | 0.036 | 360 |

[a]$TD_{50}$-Concentration (mole/l $\times$ $10^3$) providing 50% cell killing effect [(CV+ MTT)/2]; NO Concentration (%).
[b]NA-inactive.

products **1, 2** as well as their influence on cell morphology were tested in vitro on monolayer tumour cell lines HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and on normal mouse fibroblasts cells (NIH 3T3). The results obtained are summarized in Table 1. Compound **1a–c**, **f; 2b, c** were inactive in both test systems (data not shown). However, the inspection of the cell morphology demonstrated that one of these compounds, namely **1h** dramatically increased the speed of fibrosarcoma cell growth. Products **1d,e,i** and **2a,d** exhibited moderate cytotoxic effect on HT-1080 cell line but derivatives **1d, 2d** had rather high activity also on MG-22A cells. All cytotoxic products showed low acute toxicity except for **2d** that had similar values on the three cell lines.



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3. Selected data for the synthesized compounds. **1e**: m.p. 215–217°C. $^1$H-NMR (if not stated otherwise, 200 MHz, DMSO-$d_6$, $\delta$): 1.91 (s, 2H, $CH_3$); 6.64 (s, 2H, $NH_2$); 7.26–7.38 (m, 5H, ArH), **1h**: m.p. >250°C, $^1$H-NMR: 1.07 (d, 6H, 2 $\times$ $CH_3$, $J$ = 6.8 Hz); 3.99 (septet, 1H, CH, $J$ = 6.8 Hz); 5.36 (s, 2H, $CH_2$); 6.70 (s, 2H, $NH_2$); 10.93 (bs, 1H, NH); 12.85 (bs, 1H, NH), **1i**: m.p. 218–220°C. $^1$H-NMR: 3.71 (s, 3H, $CH_3$); 6.67 (s, 2H, $NH_2$); 6.80–6.90 (m, 3H, ArH); 7.22–7.29 (m, 1H, ArH), **2d**: m.p. 259–260°C, $^1$H-NMR: 5.28 (s, 2H, $CH_2$); 5.50 (s, 2H, $CH_2$), 6.76 (s, 2H, $NH_2$); 7.20–7.42 (m, 10H, Ar-H); 10.82 (bs, 1H, NH). X-ray crystal structure CCDC deposition number 289468.