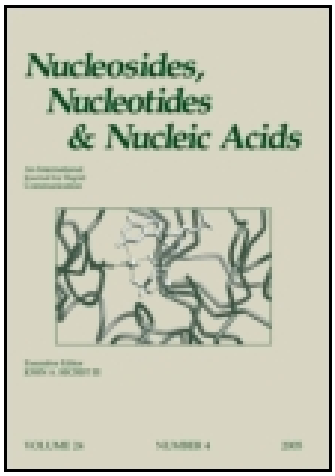

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Synthesis of Novel Acyclonucleosides Analogs of Pyridothienopyrimidine as Antiviral Agents

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SYNTHESIS OF NOVEL ACYCLONUCLEOSIDES ANALOGS OF PYRIDOTHIENOPYRIMIDINE AS ANTIVIRAL AGENTS

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▫ *Nucleoside analogs of pyridothienopyramidines were prepared by condensing the sodium salt* ***2a,b*** *with an acyclic side chain in the form of acetylated haloalkoxyalcohol, and subsequent removal of the protecting acetyl group in ammonia/methanol afforded* ***4a,b****. The O-tosyl derivative of* ***4a*** *could then be modified to azido- and amino derivatives. Reaction of the sodium salt of* ***2b*** *with halo-ether, benzyl halo-ether and/or halo-thioether gave N- and S-alkylated products,* ***8*** *and* ***9****, respectively. Coupling of* ***10*** *with the sodium salt of* ***2a,b*** *gave the corresponding dioxolane derivatives* ***11****,* ***13****, and* ***14****, which were treated with 80% acetic acid at room temperature to give diols* ***12****,* ***15****, and* ***16****. Treatment of* ***16*** *with tosyl chloride afforded the ditosylate* ***17*** *and this could then be modified to diazido and diamino derivatives. Some of the products were screened for their biological activity.*

Keywords Acyclonucleosides, Pyridothienopyrimidines, Alkylation

INTRODUCTION

Acyclonucleosides are a group of nucleosides which differ from the ribonucleoside only in the sugar portion. The general feature of the important members of this class of nucleosides is the absence of one or more of the bonds of the pentose moiety to have an open chain residue, they possess portions of the pentose residue. Those nucleosides missing one bond of the furanosyl residue are called *seco*-nucleosides. The term di*seco*-, tri*seco*-, tetra*seco*- and penta*seco*-nucleosides are given by El Ashry et al.[1–3] Since the discovery of Acyclovir 1 [9-(2-hydroxyethoxy)methyl]guanine as a selective antiherpes agent,[4] attention has focused to the synthesis and antiviral evaluation of an increasing number of acyclonucleoside analogues.[5–7] Furthermore, De Clercq et al.[8,9] reported the

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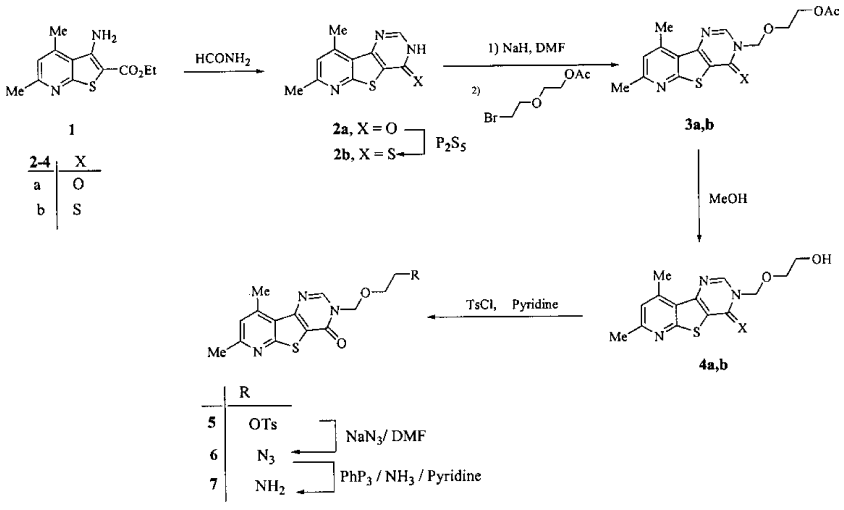
antiviral properties of (*S*)-9-(2,3-dihydroxypropyl)adenine (*S*-DHPA). Several viruses including vaccinia, HSV-1 and HSV-2, measles, and vascular stoimatitis were inhibited by (*S*)-DHPA. Several acyclonucleosides analogues of DHPA were investigated.[10] This observation leads us to report our work on the synthesis of a new series of acyclic nucleoside analogs of pyridothienopyrimidines as a continuation of our interest in this area.[11,12] The tricyclic pyridothienopyrimidines are chosen as nucleobases in this series because of their known interesting biological activities.[13–18] Moreover, in the previous report,[19] we reported that pyridothienopyrimidine is a heterocyclic ring system that is able to co-stack with a DNA or RNA duplex.

RESULTS AND DISCUSSION

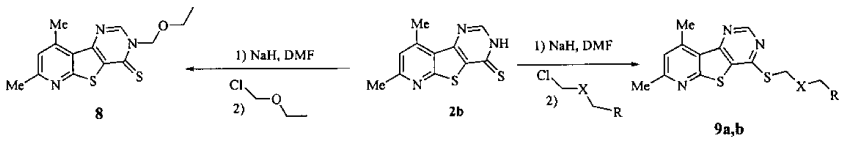
The starting pyridothienopyrimidine derivative **2a** was prepared from thienopyridine derivative **1** and formamide by the method of Shvedov and co-workers.[20] Reaction of **2a** with phosphorus pentasulfide in dry pyridine at reflux temperature afforded the corresponding thioxo derivative **2b** in good yield. Compunds **2a,b** were alkylated with (2-acetoxyethoxy)methyl bromide by the method of Sasaki et al.[21] to afford the corresponding *N*-alkylated products **3a,b** in 59 and 55% yields, respectively. Treatment of **3a,b** with 1:1 mixture of methanol and conc. ammonia at room temperature for 24 h resulted in complete deprotection of the hydroxyl group and the corresponding 3-[(2-hydroxyethoxy)methyl]pyrido-thienopyrimidones **4a,b** were obtained in good yields. The hydroxy compounds **4a** was tosylated by reaction with tosyl chloride in anhydrous pyridine to give tosylate **5**, which could then be converted to the azide **6** upon treatment with sodium azide in dry DMF, the IR, NMR and elemental analysis established the



SCHEME 1

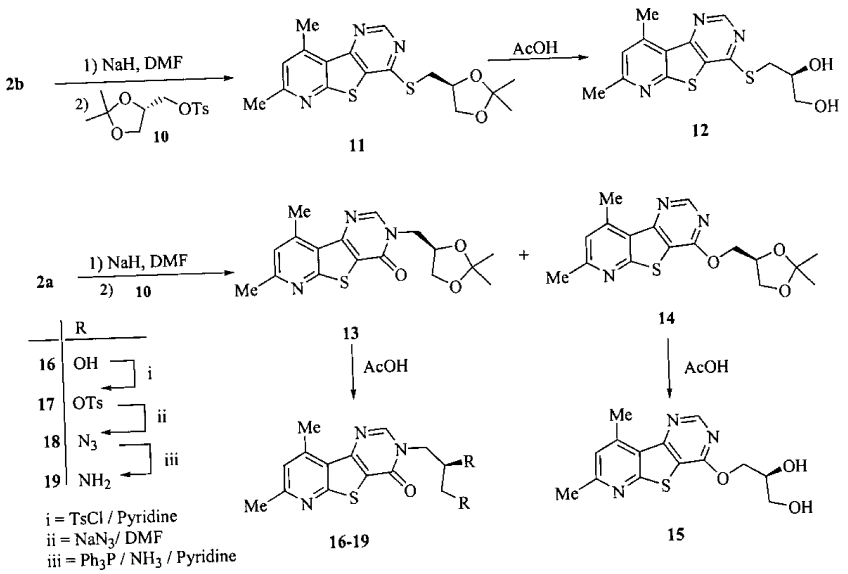
structure of compound **6**. The IR spectrum showed an absorption band for an azodi group at 2103 cm^{-1}. The azide **6** was reduced by reaction with triphenylphosphine in pyridine to give the corresponding amine **7**, whose structure was confirmed using NMR, HRMS and the presence of the characteristic IR band for an NH_2 group at 3430–3410 cm^{-1} (Scheme 1). The reaction of compound **2b** (X = S), after treatment with NaH in dry DMF, with chloromethyl ethyl ether gave the *N*-3 alkylated product **8**, whereas its reaction with either benzyl chloromethyl ether or chloromethyl methyl sulfide under the same reaction conditions, afforded the *S*-alkylated products **9a** and **9b**. The sites of alkylation were confirmed by the ^{13}C-NMR spectra of these compounds, which showed a chemical shift of δ 177.87 for C = S in compound **8**. The absence of this peak in the spectra of compounds **9a** and **9b** indicates that the alkylation occurred at the S atom to afford the *S*-alkylated products (Scheme 2).

As we are interested in the synthesis of chiral acyclonucleosides,[11,12] we devised the reaction of the starting compounds **2a,b**, after treatment with 60% sodium hydride in dry DMF, with (*S*)-(2,2-dimethyl-1,3-dioxalane-4-yl)methyl-*p*-toluenesulfonate **10**.[22] As reported in Scheme 3, *S*-alkylated product **11** was obtained as the sole product, in fairly good yield, on treatment of thione **2b** with **10**. The structure of compound **11** was confirmed using elemental analysis, MS, ^{1}H-NMR, and ^{13}C-NMR. ^{13}C-NMR spectrum of **11** lacked the characteristic peak of C = S that appear at δ 175.43 in the spectrum of **2b**. Two alkylated products **13** and **14** were obtained (TLC) on treatment of **2a** with **10**, which could be separated by column chromatography using ethyl acetate in chloroform (0–5%) to give 45% and 32% yields, respectively. The ^{1}H-NMR spectrum showed that the 1,3-dioxalanyl moiety of the *O*-alkylated product is shifted downfield compared with that of the *N*-alkylated product. The methylene signals appeared at δ 3.99–4.21 ppm for *O*-alkylated product **14**, compared to δ 3.79–3.99 ppm for *N*-alkylated product **13**. Also, the ^{13}C-NMR spectra showed a chemical shift of δ 66.46 for O-CH_2- in compound **14**, but a chemical shift of δ 48.70 for N-CH_2- in compound **13**, which indicates that alkylation of **2a** occurred on the nitrogen atom to give **13** and on the oxygen atom to give **14**. That **13** is an *N*-alkylated product of **2a** was confirmed by the presence of characteristic peak for an amide carbonyl at



9	X	R
a	O	C_6H_5
b	S	H

SCHEME 2



SCHEME 3

1666 cm^{-1} in its IR spectrum. Subsequent treatment of compounds **11**, **13**, and **14** with 80% aqueous acetic acid at room temperature gave the corresponding diols **12**, **16** and **15**, respectively. Tosylation of **16** was easily performed in anhydrous pyridine with *p*-toluenesulfonyl chloride and the product **17** was identified using NMR, MS, elemental analysis and by a characteristic peak for ether linkage at 1175 cm^{-1} in its IR spectrum. The intermediate ditosylate **17** could then be converted to the diazido derivative **18** with sodium azide. IR, NMR, MS and elemental analysis established the structure of **18**. The IR spectrum showed characteristic peaks at 2110 and 2103 cm^{-1} corresponding to the azido groups. Diazide compound **18** was converted to diamine compound **19** via its treatment with triphenylphosphine/ammonia in anhydrous pyridine (Scheme 3).

Antiviral activity against HBV was tested at the Liver Institute, Monoufiya University, Egypt. Preliminary screening indicated that compounds **4b**, **8**, **9a**, and **19** showed moderate viral replication inhibition and low cytotoxicity, while compounds **5**, **6**, and **12** showed high inhibition with moderate cytotoxicity.

EXPERIMENTAL

Melting points (uncorrected) were determined using an electrothermal melting MEL-TEMP II apparatus. IR spectra were recorded on a Perkin-Elmer 1430 spectophotometer using KBr disc technique. NMR spectra were recorded on a varian Germini 2000 NMR spectrometer at 300 MHZ for ^{1}H and 75 MHZ for ^{13}C or on a Bruker AC-250 FT spectrometer at 250 MHZ for ^{1}H and at 62.9 MHZ for ^{13}C with TMS as an internal standard. EI mass spectra were recorded on a finnigan

MAT SSQ 710. MALADI mass spectra were recorded on a Kratos MS50RF spectrometer. Elemental analyses were performed at Chemistry Institute, Copenhagen University. The progresses of reactions were monitored by TLC (analytical silica gel plates 60 F_{254}). Merck silica gel (0.040–0.063 mm) was used for CC.

7,9-Dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-(1H)-thione (2b). Compound **2a** (4.6 g, 20 mmol) and P_2S_5 (8.9 g, 40 mmol) were suspended in dry pyridine (30 mL) and then the mixture was heated under reflux for 11 h. After cooling, the mixture was poured into cold water, and the product was collected by filtration. The product was recrystallized from DMF to obtain pale yellow crystals in 86% yield; mp > 320°C (DMF) (lit.[20] mp > 320°C); IR (KBr) 3122 (NH), 1220 (C = S) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.61 (s 3H, C*H*$_3$), 2.87 (s, 3H, C*H*$_3$), 3.59 (br s, 1H, N*H*), 7.29 (s, 1H, arom), 8.55 (s, 1H, arom). ^{13}C-NMR (DMSO-d_6) δ 18.23, 23.62 (2*C*H$_3$), 122.19, 123.40, 134.59, 145.83, 147.07, 147.20, 159.59, 161.94 (*C*-arom), 175.43 (C = S); MS-EI *m/z* (%): 247 (M^+, 100).

General Procedure for the Preparation of Compounds 3a,b

To a stirred suspension of **2a,b** (5 mmol) in dry DMF (10 mL), 0.2 g (5 mmol) of sodium hydride (60% dispersion in mineral oil) was added. When liberation of hydrogen had ceased (2 h), the (2-acetoxyethoxy)methyl bromide (1.0 g, 5.1 mmol) was added, and the reaction mixture was stirred at room temperature 24 h. The solvent was evaporated under reduced pressure, co-evaporated with dry toluene (3 × 10 mL) and purified with silica gel chromatography using 5% ethyl acetate in chloroform to give compounds **3a,b** as pure products.

3-[(2-Acetoxyethoxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-one (3a). Yield (0.99 g); mp 149–152°C (diethyl ether). IR (KBr) 1741 (C = O, ester), 1673 (C = O), cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.04 (s, 3H, COC*H*$_3$), 2.68 (s, 3H, C*H*$_3$), 2.92 (s, 3H, C*H*$_3$), 3.91 (t, *J* = 4 Hz, 2H, OC*H*$_2$CH$_2$OAc), 4.24 (t, *J* = 4 Hz, 2H, OCH$_2$C*H*$_2$OAc), 5.59 (s, 2H, NCH$_2$O), 7.10 (s, 1H, arom), 8.28 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.33, 20.74, 24.55 (3 *C*H$_3$), 62.99, 68.24 (O*C*H$_2$*C*H$_2$OAc), 75.08 (N*C*H$_2$O), 122.07, 122.76, 124.38, 146.88, 147.07, 152.00, 157.70, 160.19, 163.02 (*C*-arom, *C* = O), 170.73 (*C*OCH$_3$). MS-EI *m/z* (%): 347 (20) [M^+], 43 (100). $C_{16}H_{17}N_3O_4S$ (347.39): C, 55.32; H, 4.93; N, 12.10. Found: C, 55.12; H, 4.90; N, 11.99.

3-[(2-Acetoxyethoxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-thione (3b). Yield (55%); mp 134–136°C (diethyl ether). IR (KBr) 1740 (C = O, ester), 1573 (C = C), 1218 (C = S) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.07 (s, 3H, COC*H*$_3$), 2.66 (s, 3H, C*H*$_3$), 2.87 (s, 3H, C*H*$_3$), 3.99 (t, *J* = 4.5 Hz, 2H, OC*H*$_2$CH$_2$OAc), 4.27 (t, *J* = 4.5 Hz, 2H, OCH$_2$C*H*$_2$OAc), 6.07

(s, 2H, OCH_2N), 7.05 (s, 1H, arom), 8.55 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.32, 20.76, 24.66 (3CH$_3$), 62.90, 68.72 (OCH$_2$$CH_2$OAc), 79.96 (N$CH_2$O), 122.95, 124.51, 137.43, 145.45, 146.02, 147.97, 160.58, 164.40 (*C*-arom), 170.67 (*C*OCH$_3$), 177.94 (C = S); MS-EI *m/z* (%): 363 (M^+, 10), 43 (100). $C_{16}H_{17}N_3O_3S_2$ (363.44): C, 52.88; H, 4.71; N, 11.56. Found: C, 52.77; H, 4.77; N, 11.51.

General Procedure for the Deprotection of Compounds 3a,b

Compound **3a** or **3b** (1 mmol) in a mixture of methanol (10 mL) and concentrated ammonia (10 mL) was stirred at RT for 24 h (TLC). The solvent was evaporated to dryness under reduced pressure. The residue was triturated with small volume of ethanol to give **4a** or **4b** as a colorless product.

7,9-Dimethyl-3-[(2-hydroxyethoxy)methyl]pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-one (4a). Yield (77%); mp 202–205°C (MeOH); ^{1}H-NMR (DMSO-d$_6$) δ 2.62 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.54 (t, J = 5.0 Hz, 2H, OCH_2CH$_2$OH), 3.66 (t, J = 5.0 Hz, OCH$_2$CH_2OH), 4.89 (br s, 1H, OH), 5.55 (s, 2H, OCH_2N), 7.31 (s, 1H, arom); 8.71 (s, 1H, arom); ^{13}C-NMR (DMSO-d$_6$) δ 18.78, 23.97 (2CH$_3$), 59.93, 71.14 (OCH$_2$$CH_2$N), 75.34 (N$CH_2$O), 120.67, 122.76, 123.83, 146.51, 149.47, 151.69, 156.79, 159.87, 161.58 (*C*-arom and C = O); MS-EI *m/z* (%): 305 (M^+, 20) 231 (100). $C_{14}H_{15}N_3O_3S$ (305.35): C, 55.07; H, 4.95; N, 13.76. Found: C, 55.03; H, 4.76; N, 13.59.

7,9-Dimethyl-3-[(2-hydroxyethoxy)methyl]pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-thione (4b). Yield (67%); mp 188–191°C (MeOH); ^{1}H-NMR (DMSO-d$_6$) δ 2.60 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.55 (t, J = 4.5 Hz, 2H, OCH_2CH$_2$OH), 3.72 (t, J = 4.5 Hz, 2H, OCH$_2$CH_2OAc), 5.97 (s, 2H, OCH_2N), 7.29 (s, 1H, arom), 8.99 (s, 1H, arom); ^{13}C-NMR (DMSO-d$_6$) δ 18.81, 24.09 (2CH$_3$), 59.95, 71.72 (OCH$_2$$CH_2$), 80.38 (N$CH_2$O), 123.03, 124.07, 136.09, 145.61, 147.58, 148.58, 160.43, 163.13 (*C*-arom), 176.93 (C = S). HRMS *m/z* Calcd for $C_{14}H_{15}N_3NaO_2S_2$ (M^++ Na) 344.0498, found 344.0494.

7,9-Dimethyl-3-[[2-(p-tolylsulfonyloxy)ethoxy]methyl]pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-one (5). *p*-Toluenesulfonyl chloride (0.19 g, 1 mmol) was added to an ice-cooled of **4a** (0.3 g, 1 mmol) in dry pyridine (5 mL) and left to stand overnight at 4°C, then 4 h at RT. The pyridine was removed under reduced pressure at 25°C and the resulting gum was treated with ice water. The product solidified as a white precipitate, was collected by filtration, washed with water, a small amount of cold ethanol and ether to get the white product. Yield (64%); mp 144–146°C (ethanole); IR (KBr) 1678 (C = O), 1573 (C = C), 1170 (C-O-SO$_2$) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3H, p-CH_3), 2.67 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 3.90 (t, J = 5 Hz, 2H, OCH_2CH$_2$OTs), 4.18 (t, J = 5 Hz, 2H, OCH$_2$CH_2OTs), 5.49 (s, 2H, OCH_2N), 7.10 (s, 1H, arom), 7.30 (d, 2H,

J = 8 Hz, Tolyl-*H*), 7.75 (d, 2H, J = 8 Hz, Tolyl-*H*), 8.19 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.36, 2157, 24.56 (3*C*H_3), 67.90, 68.56 (2*C*H_2), 75.12 (N*C*H_2O), 121.99, 122.81, 124.42, 127.84, 129.80, 132.70, 144.95, 146.90, 147.16, 152.11, 157.70, 160.23, 163.03 (*C*-arom and C = O). MS-EI *m/z* (%): 459 (M^+, 5), 91 (100); $C_{21}H_{21}N_3O_5S_2$ (459.54): C, 54.89; H 4.61; N, 9.14. Found: C, 55.14; H, 4.49; N, 8.84.

3-[(2-Azidoethoxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-one (6). A mixture of compound **5** (0.15 g, 0.3 mmol) and NaN_3 (0.02 g, 0.3 mmol) in dry DMF (5 mL) was heated for 2 h at 80°C (TLC). The solvent was removed under reduced pressure and the remaining syrup was triturated with ice-water. A white solid was collected by filtration, washed with ether and recrystallized from MeOH. Yield (75%); mp 132–134°C; IR (KBr) 2103 (N_3), 1680 (C = O), 1573 (C = C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.67 (s, 3H, C*H*$_3$), 2.92 (s, 3H, C*H*$_3$), 3.44 (t, J = 5 Hz, 2H, OC*H*$_2$CH$_2$N), 3.89 (t, J = 5 Hz, 2H, OCH$_2$C*H*$_2$N), 5.60 (s, 2H, OC*H*$_2$N), 7.09 (s, 1H, arom), 8.28 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.47, 24.67 (2*C*H_2), 50.62, 69.23 (2*C*H_2), 75.15 (N*C*H_2O), 122.15, 122.34, 124.52, 146.98, 147.26, 152.18, 157.85, 160.33, 163.14 (*C*-arom and C = O). MS-EI *m/z* (%): 330 (M^+, 3), 245 (100); $C_{14}H_{14}N_6O_2S$ (330.37): C, 50.90; H, 4.27; N, 25.44. Found: C, 50.85; H, 4.22; N, 25.18.

3-[(2-Aminoethoxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4-one (7). Azide **6** (0.17 g, 0.5 mmol) and Ph_3P (0.21 g, 0.82 mmol) were dissolved in dry pyridine (15 mL) and the mixture was stirred at RT for 1 h. Concentrated ammonia was added (5 mL) and the solution was stirred for 2 h. The solvent was removed under reduced pressure. Water was added (5 mL), and then Ph_3P and Ph_3PO were removed by filtration. The filtrate was extracted with benzene and to remove residual Ph_3P and then concentrated until dryness to give **7**. Yield (67%); mp 147–150°C (acetic acid); IR (KBr) 3430–3510 (NH_2), 1678 (C = O) cm^{-1}; ^{1}H-NMR (D_2O) δ 2.68 (s, 3H, C*H*$_3$), 2.93 (s, 3H, C*H*$_3$), 3.61 (br s, 2H, OC*H*$_2$CH$_2$NH$_2$), 4.47 (br s, 2H, OCH$_2$C*H*$_2$NH$_2$), 5.53 (br s, 2H, N*H*$_2$), 6.09 (s, 2H, OC*H*$_2$N), 7.20 (s, 1H, arom), 8.83 (s, 1H, arom); ^{13}C-NMR (D_2O) δ 18.58, 22.74 (2*C*H_3), 39.98, 71.33, 76.19 (3*C*H_2), 120.12, 122.00, 122.58, 146.8, 147.96, 150.40; 157.28; 159.52, 160.01 (*C*-arom and C = O). HRMS *m/z* calcd for $C_{14}H_{16}N_4NaO_2S$ (M^++ Na) 327.0886, Found: 327.0884.

General Procedure for the Preparation of Compounds 8, 9a, and 9b

Compound **2a** or **2b** (5 mmol) was suspended in dry DMF (20 mL), 0.2 g (5 mmol) of sodium hydride (60% dispersion in mineral oil) was added and the mixture was stirred at RT for 2 h, until hydrogen evolution had ceased. Then the appropriate chloroether (5.1 mmol) was added, and the reaction mixture was stirred for additional 24 h. The mixture was then evaporated to dryness under

reduced pressure and co-evaporated with dry toluene (3 × 10 mL). The residue was purified with silica gel chromatography using 5% ethyl acetate in chloroform to give the alkylated products **8** and **9a,b**.

7,9-Dimethyl-3-ethoxymethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-thione (8). Yield (40%); mp 128–130°C (pet. ether); ^{1}H-NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7 Hz, OCH_2CH_3), 2.65 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.66 (q, 2H, J = 7 Hz, CH_2), 6.03 (s, 2H, CH_2), 7.04 (s, 1H, arom), 8.52 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 15.04, 19.43, 24.76 ($3CH_3$), 64.55 (CH_2), 77.78 (NCH_2O), 123.02, 124.69, 137.27, 145.53, 146.72, 148.08, 160.59, 164.48 (*C*-arom), 177.83 (C = S). MS-EI *m/z* (%): 305 (M^+, 2), 59 (100); $C_{14}H_{15}N_3OS_2$ (305.41): C, 55.06; H, 4.95; N, 13.76. Found: C, 55.14; H, 4.99; N, 13.52.

4-(Benzyloxymethylthio)-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine (9a). Yield (66%); mp 149–150°C (diethyl ether); ^{1}H-NMR ($CDCl_3$) δ 2.69 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.72 (s, 2H, SCH_2OCH_2Ph), 5.71 (2s, 2H, SCH_2OCH_2Ph), 7.12 (s, 1H, arom), 7.30–7.36 (m, 5H, $PhCH_2$), 9.09 (s, 1H, arom). ^{13}C-NMR ($CDCl_3$) δ, 19.71, 24.64 ($2CH_3$); 69.85, 71.22 ($2CH_2$); 122.87, 123.43, 128.01, 128.22, 128.42, 128.50, 136.73, 147.99, 153.63, 155.32, 161.11, 161.35, 162.56 (*C*-arom). MS-EI *m/z* (%): 3.67 (M^+, 20), 91 (100). Anal. Calcd for $C_{19}H_{17}N_3OS_2$ (367.5): C, 62.10; H, 4.66; N, 11.43. Found: C, 62.25; H, 4.67; N, 11.23.

7,9-Dimethyl-4-(1,3-dithiabutyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (9b). Yield (42%); mp 114–116°C (diethyl ether); ^{1}H-NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.00 (s, 3H, SCH_3), 4.63 (s, 2H, SCH_2S), 7.12 (s, 1H, arom), 9.06 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ, 15.73, 19.66 ($2CH_3$), 24.6 (SCH_3), 35.31 (SCH_2S), 122.81, 123.28, 127.79, 147.88, 153.45, 154.60, 161.01, 161.86, 162.34 (*C*-arom). MS-EI *m/z* (%): 307 (M^+, 2), 260 (100); $C_{13}H_{13}N_3S_3$ (307.46): C, 50.78; H, 4.26; N, 13.67. Found: C, 50.79; H, 4.25; N, 13.43.

General Procedure for the Preparation of Compounds 11, 13, and 14

To a stirred suspension of compound **2a** and **2b** (5 mmol) in dry DMF (15 mL), 0.2 g (5 mmol) of sodium hydride (60% dispersion in mineral oil) was added. After hydrogen had ceased (2 h), (*S*)-(2,2-dimethyl-1,3-dioxalane-4-ylmethyl) *p*-toluenesulfonate **10** (0.78 g, 5.1 mmol) was added, and the reaction mixture was stirred for 24 h at 80°C. The reaction mixture was worked up as described in preparation of compounds **3a,b** give compounds **11**, **13**, and **14**.

4-[[(S)-2,2-Dimethyl-1,3-dioxalan-4-yl]methylthio]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (11). Yield (71%); mp

113–115°C (diethyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.68 (s, 3H, C*H*$_3$), 2.99 (s, 3H, C*H*$_3$), 3.66 (dd, 2H, *J* = 6 Hz, *J* = 13, Hz, C*H*$_2$), 3.86 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz, *H* of CH_2), 4.17 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz, *H* of CH_2), 4.51 (t, 1H, *J* = 6 Hz, CH), 7.11 (s, 1H, arom), 9.10 (s, H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.95, 24.60 (2*C*H$_3$), 25.46, 26.96 (2*C*H$_3$), 32.36, 68.53 (2*C*H$_2$), 74.54 (*C*H), 109.85 [*C*(CH$_3$)$_2$], 122.82, 123.31, 127.63, 147.87, 153.47, 154.78, 160.99, 162.06, 162.39 (*C*-arom). MS-EI *m/z* (%): 361 (M^+, 100); $C_{17}H_{19}N_3O_2S_2$ (361.48): C, 56.48; H, 5.30; N, 11.62. Found: C, 56.75; H, 5.37; N, 11.53.

3-[[(S)-2,2-Dimethyl-1,3-dioxalan-4-yl]methyl]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-one (13). Yield (45%); mp 140–143°C (diethyl ether); IR (KBr) 1666 (C = O), 1573 (C = C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.33 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 2.66 (s, 3H, C*H*$_3$), 2.91 (s, H, C*H*$_3$), 3.79 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz, *H* of CH_2), 3.99 (dd, 1H, *J* = 7 Hz, *J* = 14 Hz, *H* of CH_2), 4.19 (dd, 1H, *J* = 7 Hz, *J* = 9 Hz, *H* of CH_2), 4.44–4.54 (m, 2H, C*H* and *H* of CH_2), 7.07 (s, 1H, arom), 8.25 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.50, 24.50 (2*C*H$_3$); 24.97, 26.71 (2*C*H$_3$), 48.70 (N-*C*H$_2$-C), 66.52 (*C*H$_2$), 73.36 (*C*H), 109.92 [*C*(CH$_3$)$_2$], 121.88, 122.59, 124.43, 146.94, 148.08, 152.14, 157.62, 162.87, 159.92 (*C*-arom and C = O); MS-EI *m/z* (%): 345 (M^+, 5), 231 (100); $C_{17}H_{19}N_3O_3S$ (345.42): C, 59.11; H, 5.54; N, 12.17. Found: C, 59.29; H, 5.53; N, 12.01.

4-[[(S)-2,2-Dimethyl-1,3-dioxalan-4-yl]methoxy]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (14). Yield (30%); mp 105–107°C (diethyl ether). IR (KBr) 1574 (C = C), 1519 (C = N) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 3H, C*H*$_3$), 1.50 (s, H, C*H*$_3$), 2.68 (s, 3H, C*H*$_3$), 3.00 (s, 3H, C*H*$_3$), 3.99 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz, C*H*), 4.21 (dd, 1H, *J* = 6 Hz, *J* = 9 Hz, C*H*), 4.57–4.68 (m, 3H, C*H*, C*H*$_2$), 7.11 (s, 1H, arom), 8.83 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.58, 24.54, (2*C*H$_3$), 25.41, 26.67 (2*C*H$_3$), 66.46 (O-*C*H$_2$-C), 66.85 (*C*H$_2$), 73.64 (*C*H), 109.90 [*C*(CH$_3$)$_2$], 116.25, 122.56, 123.71, 147.32, 153.81, 157.88, 160.50, 162.92, 163.59 (*C*-arom and C = O). MS-EI *m/z* (%): 345 (M^+, 2), 43 (100); $C_{17}H_{19}N_3O_3S$ (345.42): C, 59.11; H, 5.54; N, 12.17. Found: C, 59.12; H, 5.65; N, 11.99.

General Procedure for the Deprotection of Compounds 11, 13, and 14

Compound **11**, **13**, or **14** (1 mmol) was stirred in 80% aqueous AcOH (10 mL) for 24 h at RT. The solvent was removed under reduced pressure and the residue was co-evaporated with water (4 × 5 mL), and finally with ethanol (3 × 5 mL). The residue was purified by silica gel chromatography using 5% MeOH in $CHCl_3$ to give pure **12**, **15**, and **16**.

4-(2,3-Dihydroxypropylthio)-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine (12). Yield (66%); mp 165–168°C (EtOH);

^{1}H-NMR (DMSO, d_6) δ 2.60 (s, 3H, CH_3), 288 (s, 3H, CH_3), 3.38–3.49 (m, 2H, CH_2), 3.71–3.82 (m, 3H, C*H*, CH_2), 4.82 (br s, 1H, O*H*), 5.22 (br s, 1H, O*H*); 7.29 (s, 1H, arom), 9.04 (s, H, arom); ^{13}C-NMR (DMSO, d_6) δ 19.00, 24.02 (2*C*H$_3$); 33.35, 64.63 (2*C*H$_2$), 69.93 (*C*H), 122.42, 122.88, 126.05, 147.24, 153.69, 153.78, 160.94, 162.68 (*C*-arom). MS-EI *m/z* (%): 321 (M^+, 2), 247 (100); $C_{14}H_{15}N_3O_2S_2$ (321.40): C, 52.31; H, 5.30; N, 13.07. Found: C, 52.22; H, 5.15; N, 12.99.

4-(2,3-Dihydroxypropoxy)-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine (15). Yield (75%); mp 190–193°C (EtOH); ^{1}H-NMR (DMSO, d_6) δ 2.63 (s, 3H, CH_3), 283 (s, 3H, CH_3), 3.52 (d, 2H, *J* = 6 Hz, CH_2), 3.77–3.99 (m, 1H, C*H*), 4.49–4.67 (m, 2H, CH_2), 4.75 (br s, 1H, O*H*), 5.35 (br s, H, O*H*), 7.25 (s, 1H, arom), 8.89 (s, 1H, arom); ^{13}C-NMR (DMSO, d_6) δ 18.95, 23.96 (2*C*H$_3$), 62.54, 68.76 (2*C*H$_2$), 69.25 (*C*H), 114.90, 122.62, 146.46, 154.22, 154.27, 156.97, 160.46, 161.59, 163.51 (*C*-arom); MS-EI *m/z* (%): 305 (M^+, 5), 231 (100); $C_{14}H_{15}N_3O_3S$ (305.35): C, 55.07; H, 4.95; N, 13.76. Found: C, 55.01; H, 4.78; N, 13.58.

3-(2,3-Dihydroxypropyl)-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4 one (16). Yield (75%); mp 209–212°C (EtOH); ^{1}H-NMR (DMSO, d_6) δ 2.61 (s, 3H, CH_3), 288 (s, 3H, CH_3), 3.46 (dd, 2H, *J* = 5 Hz, *J* = 11 Hz, CH_2), 3.77–3.83 (m, 2H, CH_2), 4.42 (d, 1H, *J* = 11 Hz, C*H*), 4.55 (br s, 1H, O*H*), 5.19 (br s, 1H, O*H*), 7.29 (s, 1H, arom), 8.47 (s, H, arom); ^{13}C-NMR (DMSO, d_6) δ 18.73, 23.94 (2*C*H$_3$), 49.66, 63.77 (2*C*H$_2$), 68.38 (*C*H), 120.27, 122.64, 123.87, 146.37, 150.33, 151.64, 156.87, 161.42, 159.61 (*C*-arom and C = O); MS-EI *m/z* (%): 305 (M^+, 20), 231 (100); $C_{14}H_{15}N_3O_3S$ (305.35): C, 55.07; H, 4.95; N, 13.76. Found: C, 54.99; H, 4.78; N, 13.58.

3-[(2,3-Di-*p*-toluenesulfonyloxy)propyl]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-one (17). *p*-Toluenesulfonyl chloride (0.76 g, 4 mmol) was added to an ice-cooled solution of **16** (0.61 g, 2 mmol) in anhydrous pyridine (15 mL) and left to stand overnight at 4°C and then 4 h at RT. The reaction mixture was worked up as described in preparation of compound ***5*** to afford the ditosylate **17**. Yield (75%); mp 203–205°C (diethyl ether); IR (KBr) 1674 (C = O), 1175 (ether linkage) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.68 (s, 3H, p-CH_3), 249 (s, 3H, p-CH_3), 2.70 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.92 (dd, 1H, *J* = 10 Hz, *J* = 14 Hz, *H* of CH_2), 4.42–4.52 (m, 3H, C*H*, CH_2), 4.95 (dd, 1H, *J* = 10 Hz, *J* = 14 Hz, *H* of CH_2), 6.80 (d, 2H, *J* = 8 Hz, tolyl-*H*), 7.15 (s, 1H, arom), 7.43 (q, 4H, *J* = 6 Hz, tolyl-*H*), 7.87 (d, 2H, *J* = 8 Hz, tolyl-*H*), 7.94 (s, 1H, arom); ^{13}C-NMR ($CDCl_3$) δ 19.37, 20.88 (2*C*H$_3$), 21.70, 42.58 (tolyl-*C*H$_3$), 47.42, 68.72 (2*C*H$_2$), 74.62 (*C*H), 120.66, 122.79, 124.22, 127.25, 128.11, 129.35, 130.17, 131.30, 131.76, 145.16, 145.60, 147.04, 147.15, 152.04, 156.84, 160.36, 162.82, 160.36 (*C*-arom and C = O). MS-EI *m/z* (%): 613 (M^+, 5), 286 (100); $C_{28}H_{27}N_3O_7S_3$ (613.73): C, 54.80; H, 4.43; N, 6.85. Found: C, 54.66; H, 4.16; N, 6.79.

3-(2,3-Diazidopropyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-one (18). A mixture of compound **17** (0.6 g, 1 mmol) and NaN_3 (0.13 g, 2 mmol) in dry DMF (10 mL) was heated for 2 h at 80°C, the reaction mixture was worked up as described in the preparation of compound **6** to give the product **18**. Yield (95%); mp 173–176°C (diethyl ether); IR (KBr) 2110, 2103 ($2N_3$), 1673 (C = O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.86 (s, 3H, CH_3), 2.92 (s, 3H, C*H*$_3$), 3.53 (dd, 1H, *J* = 6 Hz, *J* = 13 Hz, *H* of CH_2), 3.73–3.88 (m, 2H, C*H*$_2$), 4.18–4.21 (m, 1H, C*H*), 4.41 (dd, 1H, *J* = 6 Hz, *J* = 13 Hz, *H* of CH_2), 7.09 (s, 1H, arom), 8.16 (s, H, arom); ^{13}C-NMR ($CDCl_3$) δ, 19.31, 42.55 (2*C*H_3), 48.08, 52.56 (2*C*H_2); 59.34 (*C*H); 121.15, 122.76, 124.34, 147.12, 147.45, 152.31, 157.55, 162.94, 160.23 (*C*-arom and C = O); MS-EI *m/z* (%): 355 (M^+, 2), 245 (100); $C_{14}H_{13}N_9OS$ (355.37): C, 47.32; H, 3.69; N, 35.47. Found: C, 47.28; H, 3.58; N, 34.41.

3-(2,3-Diaminopropyl)-7,9-dimethylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-4-one (19). The diazide **18** (0.17 g, 0.5 mmol) and Ph_3P (0.43 g, 1.63 mmol) were dissolved in anhyd. pyridine (10 mL) and the mixture was stirred for 1 h at RT Conc ammonia (10 mL) was then added and then the solution was stirred for additional 2 h at RT. The reaction mixture was worked up as described for compound **7**. Yield (71%); mp 220–223°C (MeOH); ^{13}C-NMR (D_2O) δ 18.64, 22.77 (2*C*H_3), 43.70 (*C*H_2), 50.77 (*C*H_2); 50.96 (*C*H) 120.04, 122.21, 122.60, 146.71, 148.57, 150.34, 157.62, 159.95, 159.38 (*C*-arom and C = O); HRMS *m/z* calcd for $C_{14}H_{17}N_5ONaS$ (M^++ Na) 326.1046, found 326.1047; calcd for $C_{14}H_{18}N_5OS$ (M^++ H) 304.1227, found 304.1234.

Biological Activity Studies

Maintenance media were added to the cell culture (Hep G2 2.2.15) together with the tested compounds (final concentration = 10 μM). The supernatant liquid was collected after one, two, and/or three weeks. The DNA replication was estimated by the polymerase chain reaction technique. The percentage inhibition could be calculated by the relation between the blank experiment (containing maintenance media without the tested compounds) and the results obtained after the mentioned periods. The percentage cytotoxicity could be estimated by the relation between the number of the living and dead cells after three weeks counted by the Haemocytometer.

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