Synthesis of Thieno[3,2-*d*]pyrimidine-2,4-diones Cyclic and Acyclic Nucleosides as Potential Anti HIV Agents

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Synthesis of cyclic and acyclic nucleosides was achieved by alkylation of 7-methyl or arylthieno[3,2-*d*]-pyrimidine-2,4-diones following the Vorbrüggen and Niedballa's method [1]. After a possible deprotection, potential anti HIV agents were obtained.

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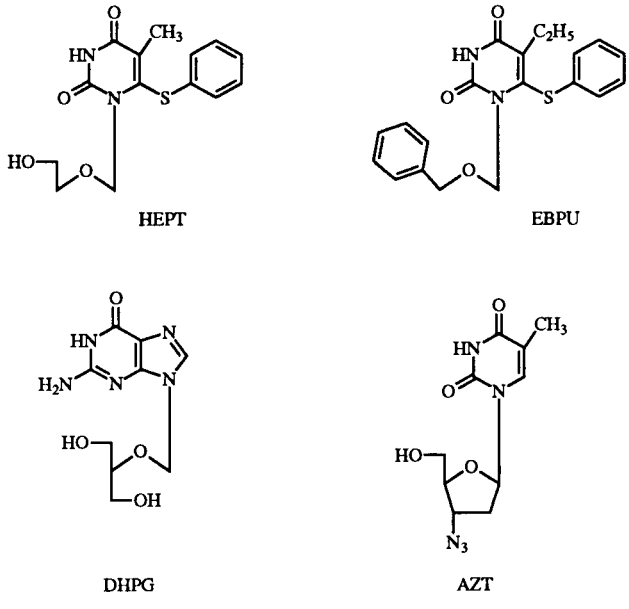
In spite of their toxic side effects [2,3], 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxyinosine (DDI) are nowadays the only anti HIV agents used to improve the quality of life for many AIDS patients. Furthermore, prolonged AZT treatment often leads to the emergence of resistant HIV-1 strains [4]. Those facts, added to the alarming expectations concerning the development of this desease show the need for better drugs.

A new class of anti HIV-1 agents has been identified by Miyasaka and co-workers [5]. These compounds, like 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT) and 1-(benzyloxymethyl)-5-ethyl-6-(phenylthio)uracil (EBPU) (Scheme 1), show a high selectivity for the HIV-1 reverse transcriptase. 1-(1,3-Dihydroxy-2-propoxymethyl)-guanine (DHPG) is also used for the treatment against cytomegalovirus (CMV) an opportunist virus of AIDS.

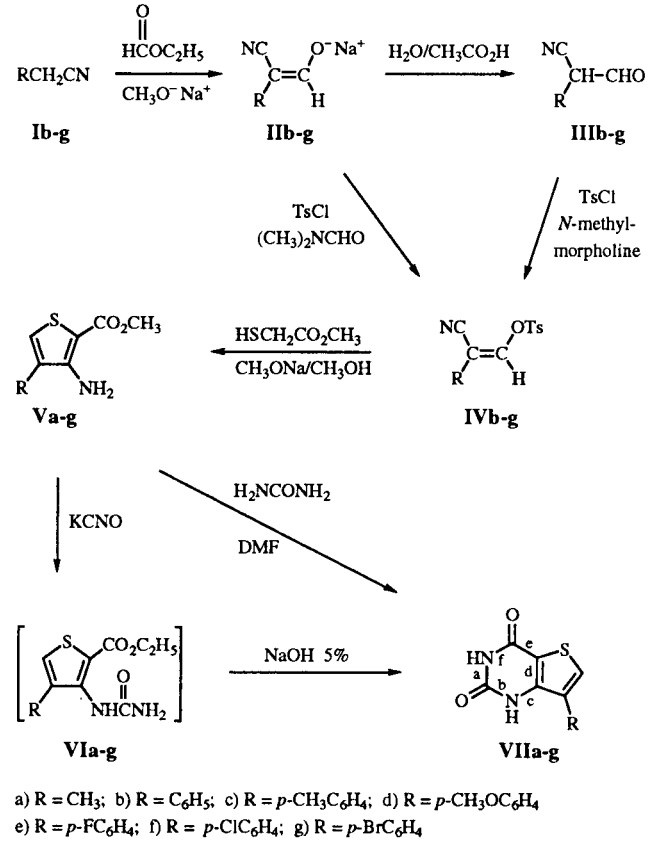
We describe in this article the synthesis of HEPT, EBPU and DHPG related acyclic nucleosides and ribofuranosyl nucleosides. The latter compounds will be precursors of modified nucleosides.

Scheme 1



The structure of HEPT and EBPU shows the presence of hydrophobic regions (the alkyl and phenylthio group) at the 5 and 6 positions of the pyrimidine. These previous observations suggest that for anti HIV-1 activity a certain size of hydrophobic surrounding is necessary between C5-C6 and an acyclic portion. In order to keep a similarity with this structure and to increase the lipophilicity, we have choosen a thieno[3,2-*d*]pyrimidine-2,4-dione structure substituted at the 7 position with an alkyl or aryl group. This aglycon is constituted from a uracil ring fused with its "d side" to a β-substituted thiophene nucleus.

Scheme 2



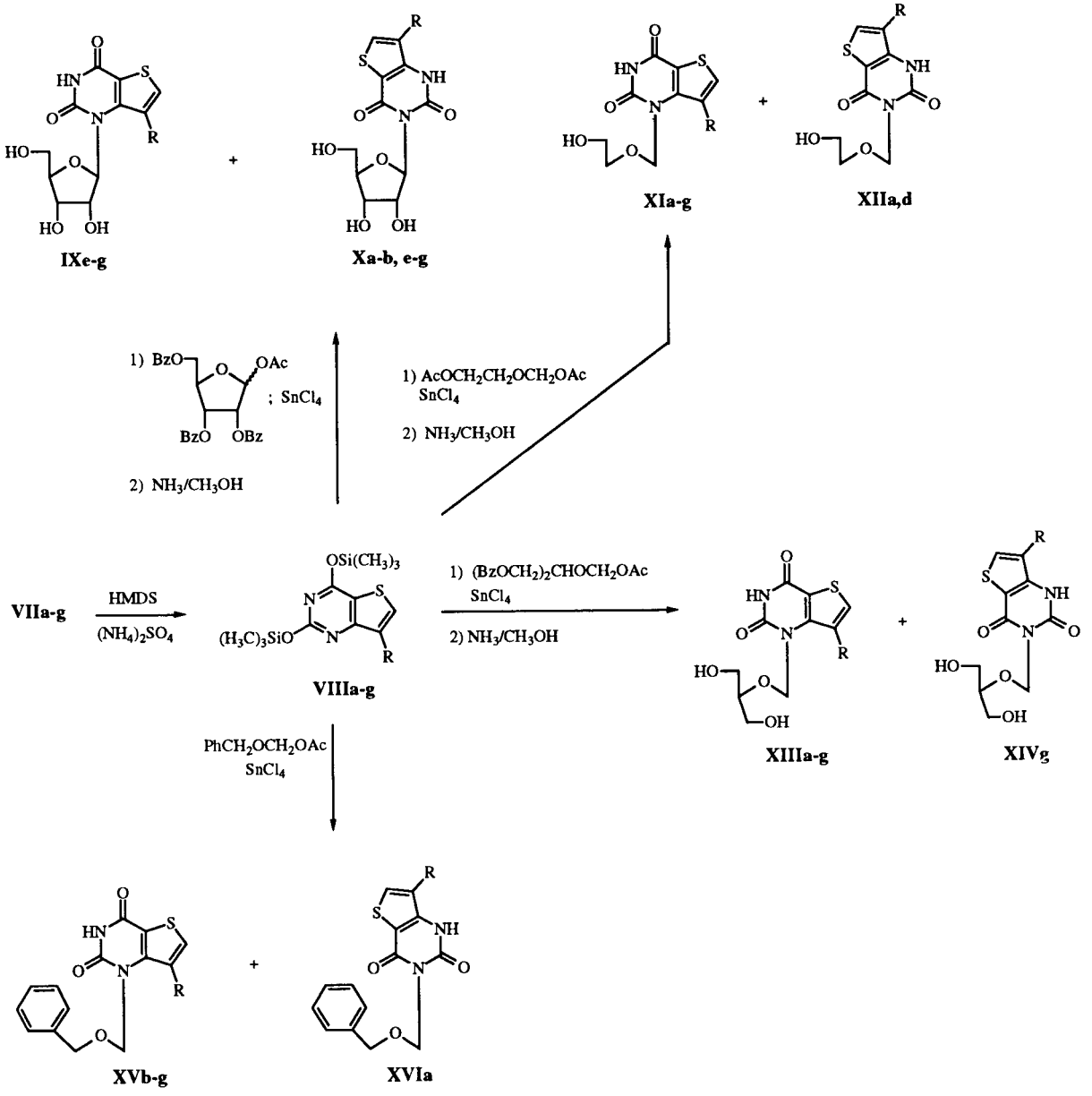
a) R = CH_3; b) R = C_6H_5; c) R = *p*-$CH_3C_6H_4$; d) R = *p*-$CH_3OC_6H_4$
e) R = *p*-FC_6H_4; f) R = *p*-ClC_6H_4; g) R = *p*-BrC_6H_4

Chemistry.

Our strategy for the synthesis of nucleosides was based on the alkylation of silylated heterocycles following Vorbrüggen and Niedballa's procedure [1].

We have first synthesised the heterocycles **VIIb-g** (Scheme 2) starting from arylacetonitriles **Ib-g** which reacted with ethyl formate in the presence of sodium methoxide to give the corresponding sodium enolates **IIb-g** [6]. Compound **II** could directly furnish 2-aryl-3-(*p*-toluenesulfonato)acrylonitriles **IVb-g** using *p*-toluenesulfonyl chloride in *N,N*-dimethylformamide. Acidic hydrolysis of **IIb-g** led to 2-formyl-2-arylacetonitriles **IIIb-g**. The latter compounds, treated with *p*-toluenesulfonyl chloride in the presence of an excess of 4-methylmorpholine in dichloromethane gave **IVb-g**. The thiophenes substituted by an alkyl or aryl group on the 4 position of **Vb-g** were obtained by treatment of **IVb-g** with methyl thioglycolate in the presence of sodium methoxide under reflux. Two different methods led to the 7-methyl or 7-arylthieno[3,2-*d*]-pyrimidine-2,4-diones **VIIa-g** starting from thiophenes **Va-g** [7]. In the first method, compounds **Va-g** were heated with urea in *N,N*-dimethylformamide and the resulting products precipitate at room temperature yielding **VIIa-g**. The second method gave ureas **VIa-g** as intermediates by treatment of **Va-g** with potassium cyanate in acetic acid medium. These ureas **VIa-g**, in alkaline medium, gave the different thieno[3,2-*d*]pyrimidine-2,4-diones **VIIa-g**.

Scheme 3



The bis(trimethylsilyl) derivatives **VIIIa-g** (Scheme 3), resulting from the silylation with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulphate, were subjected to reaction with 2-acetoxyethyl acetoxymethyl ether [9], 2-(acetoxymethoxy)propanediyl-1,3-dibenzoate [10] and benzyloxymethyl acetate **XV**. These reactions were carried out in dry 1,2-dichloroethane with tin(IV) chloride as a catalyst.

The same procedure was used with 1-acetate-2,3,5-tri-*O*-benzoate-β-D-ribofuranose giving the protected ribofuranosyl nucleoside.

The mechanism of glycosidation, described by Vorbrüggen and Niedballa [1] explain the reason why we only obtained β-D-ribonucleosides. This configuration has been confirmed following Imbach and co-worker's rule [11].

The alkylation of bis(trimethylsilyl) derivatives could provide the expected N1 alkylated compounds but also its N3 alkylated isomer. We preferentially obtained N1 alkylated compounds when operating at a low temperature (−30°). This was confirmed using an uv spectra analytical method [12]. Following this method no bathochromic effect of N1 alkylated uracil derivatives in alkaline medium indicates a N1 alkylation. In contrast the N3 alkylated uracil showed a 30 to 40 nanometers bathochromic effect. Compounds **IX** to **XIV** were obtained by removing esters blocking group with methanolic ammonia and often by the way of a silica gel column chromatography.

All the nucleosides were fully characterized using usual analytical methods as ^{1}H-nmr, ^{13}C-nmr, ir and uv spectra.

Compounds **IX** to **XIV**, **XVI** and **XVII** were tested by comparison with AZT both for their toxicity and their ability to inhibit the cytopathic effects [13] induced by HIV1 infection. None of them showed any significant activity. The structure of the aglycons might explain this absence of activity. Indeed, these ones are totally planar and therefore different from that of HEPT or EBPU which have been determined by a conformational analysis on SYBYL software. This study showed that the phenylthio group is perpendicular to the pyrimidine group.

EXPERIMENTAL

General Methods.

Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. UV spectra were recorded on a SECONAM.S 1000 C spectrometer and only the noteworthy absorption (nanometers) was listed. ^{1}H- and ^{13}C-Nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shift are reported in ppm downfield (δ) from TMS.

We describe here the general method for synthesis of each compound.

2-Formyl-2-arylacetonitrile Sodium Enolates **II**.

Aryl acetonitrile (**I**) (0.32 mole) was added dropwise to a solution of sodium methoxide (18.9 g, 0.35 mole) in methanol (250 ml). The mixture was stirred for 5 hours at room temperature. The resulting precipitate was collected and washed with diethyl oxide (100 ml).

2-Formyl-2-phenyl acetonitrile sodium enolate **IIb** had mp >260°, (44.3 g, 81%); ir (potassium bromide): 2170 (CN).

2-Formyl-2-(4-methylphenyl)acetonitrile sodium enolate **IIc** had mp >260°, (37.6 g, 65%); ir (potassium bromide): 2180 (CN).

2-Formyl-2-(4-methoxyphenyl)acetonitrile sodium enolate **IId** had mp >260°, (32.8 g, 52%); ir (potassium bromide) 2170 (CN).

2-Formyl-2-arylacetonitriles **III**.

The sodium enolates **II** previously prepared were dissolved in water (2 *l*). The solution was acidified with acetic acid and the precipitate was collected, washed with water and dried to give white solid. The yields were calculated relative to the arylacetonitrile **I**.

2-Formyl-2-phenyl acetonitrile **IIIb** had mp 160° (34.8 g, 75%); ir (potassium bromide): 2220 (CN) 1630 (CO).

2-Formyl-2-(4-methylphenyl)acetonitrile **IIIc** had mp 162° (32.6 g, 64%); ir (potassium bromide): 2205 (CN) 1635 (CO).

2-Formyl-2-(4-methoxyphenyl)acetonitrile **IIId** had mp 108° (28.1 g, 50%); ir (potassium bromide): 2230 (CN) 1640 (CO).

2-Formyl-2-(4-fluorophenyl)acetonitrile **IIIe** had mp 148° (39.4 g, 77%); ir (potassium bromide): 2220 (CN) 1640 (CO).

2-Formyl-2-(4-chlorophenyl)acetonitrile **IIIf** had mp 166° (35.6 g, 63%); ir (potassium bromide): 2250 (CN) 1655 (CO).

2-Formyl-2-(4-bromophenyl)acetonitrile **IIIg** had mp 174° (50.9 g, 71%), ir (potassium bromide): 2215 (CN) 1635 (CO).

2-Aryl-3-(*p*-toluenesulfonato)acrylonitrile **IV**.

First Method.

A solution of *p*-toluenesulfonyl chloride (20 g, 0.105 mole) in DMF (30 ml) was added at 10° to a stirred solution of **II** (0.1 mole) in DMF (90 ml). The reaction mixture was stirred at room temperature for 2 hours and then poured into water (500 ml). The resulting precipitate was collected and washed with water then diethyl ether (50 ml).

Second Method.

2-Formyl-2-arylacetonitrile (0.2 mole) was dissolved in a solution of *N*-methylmorpholine (30.8 ml, 028 mole) in dichloromethane (300 ml). A solution of *p*-toluenesulfonyl chloride (40 g, 0.21 mole) in dichloromethane (50 ml) was added dropwise at 10°. The reaction mixture was stirred at room temperature for 2 hours. The organic layer was washed with water (2 x 250 ml), dried (magnesium sulphate) and the solvent was removed under reduced pressure to give **IV** as white solids.

The yields below reported are those of the second method.

2-Phenyl-3-(*p*-toluenesulfonato)acrylonitrile **IVb** had mp 78° (45.7 g, 80%); ir (potassium bromide): 2220 (CN), 1200 (SO_2).

2-(4-Methylphenyl)-3-(*p*-toluenesulfonato)acrylonitrile **IVc** had mp 78°; (48.5 g, 81%); ir (potassium bromide): 2220 (CN), 1190 (SO_2).

2-(4-Methoxyphenyl)-3-(*p*-toluenesulfonato)acrylonitrile **IVd** had mp 76°; (53 g, 84%); ir (potassium bromide): 2225 (CN), 1200-1185 (SO_2).

2-(4-Fluorophenyl)-3-(*p*-toluenesulfonato)acrylonitrile **IVe** had mp 65°; (49.9 g, 82%); ir (potassium bromide): 2225 (CN), 1195-1180 (SO_2).

2-(4-Chlorophenyl)-3-(*p*-toluenesulfonato)acrylonitrile **IVf** had mp 98°; (54.4 g, 85%); ir (potassium bromide): 2220 (CN) 1195-1180 (SO_2).

2-(4-Bromophenyl)-3-(*p*-toluenesulfonato)acrylonitrile **IVg** had mp 88°; (64.4 g, 88%); ir (potassium bromide): 2220 (CN) 1190-1180 (SO_2).

Methyl 3-Amino-4-aryl-2-thiophenecarboxylate **V**.

Methyl thioglycolate (8.1 ml, 0.105 mole) was added dropwise, at 10°, to a 0.1*N* methanolic sodium methoxide solution (210 ml). The mixture was stirred for 30 minutes then **IV** (0.1 mole) was added dropwise still at 10°. The reaction mixture was next refluxed for 6 hours then concentrated under reduced pressure. The residue crystallized in water and was collected, washed with water and dried.

Methyl 3-amino-4-phenyl-2-thiophenecarboxylate **Vb** had mp 70° (12.6 g, 54%); ir (potassium bromide): 3440 and 3340 (NH_2), 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.66 (s, 1H, H5), 7.46 (broad, 5H, phenyl protons), 6.28 (s, 2H, NH_2), 3.76 (s, 3H, CH_3).

Methyl 3-amino-4-(4-toluyl)-2-thiophenecarboxylate **Vc** had mp 78° (12.3 g, 50%); ir (potassium bromide): 3460 and 3350 (NH_2), 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.59 (s, 1H, H5), 7.31 (m, 4H, phenyl proton), 6.23 (s, 2H, NH_2), 3.75 (s, 3H, CH_3O), 2.33 (s, 3H, CH_3).

Methyl 3-amino-4-(4-methoxyphenyl)-2-thiophenecarboxylate **Vd** hads mp 108° (14.8 g, 58%); ir (potassium bromide): 3460 and 3350 (NH_2), 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.55 (s, 1H, H5), 7.38 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 2H, phenyl protons), 7.03 (d, $J_{H\text{-}H}$ = 8.5 Hz, 2H, phenyl protons), 6.22 (s, 2H, NH_2), 3.79 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O).

Methyl 3-amino-4-(4-fluorophenyl)-2-thiophenecarboxylate **Ve** had mp 108° (16 g, 64%); ir (potassium bromide): 3480 and 3370 (NH_2), 1680 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.64 (s, 1H, H5), 7.51 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.29 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 6.32 (s, 2H, NH_2), 3.77 (s, 3H, CH_3).

Methyl 3-amino-4-(4-chlorophenyl)-2-thiophenecarboxylate **Vf** had mp 106° (17.4 g, 66%); ir (potassium bromide): 3460 and 3360 (NH_2), 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.69 (s, 1H, H5), 7.50 (s, 4H, phenyl protons), 6.32 (s, 2H, NH_2), 3.76 (s, 3H, CH_3).

Methyl 3-amino-4-(4-bromophenyl)thiophenecarboxylate **Vg** had mp 120° (20.1 g, 50%); ir (potassium bromide): 3460 and 3330 (NH_2), 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.70 (s, 1H, H5), 7.65 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2H, phenyl protons), 7.42 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2H, phenyl protons), 6.32 (s, 2H, NH_2), 3.76 (s, 3H, CH_3).

7-Methylthieno[3,2-*d*]pyrimidine-2,4-dione **VIIa** and 7-Arylthieno[3,2-*d*]pyrimidine-2,4-diones **VIIb-g**.

First Method.

Thiophene derivative **V** (0.1 mole) was dissolved in a solution of acetic acid (500 ml) and water (50 ml). Potassium cyanate (24.5 g, 0.3 mole) in water (80 ml) was added dropwise at room temperature and the mixture stirred for 12 hours. The precipitate of **VI** was collected, washed with water, diethyl ether then poured into a hot 5% sodium hydroxide solution. The resulting suspension was stirred for 2 hours. The precipitate was collected and washed with acetic acid (100 ml) then water to give **VIIb-g** as white solids.

Second Method.

Thiophene derivative **V** (0.1 mole) and urea (24 g, 0.4 mole) in DMF (50 ml) were heated at 200° for 90 minutes. The residue was poured into water and the resulting precipitate was washed with acetic acid, water and diethyl ether respectively to give **VII**.

7-Methylthieno[3,2-*d*]pyrimidine-2,4-dione **VIIa** had mp >260° (8.2 g, 45%, Method 1), (14 g, 77%, Method 2); ir (potassium bromide): 3200-3100 (NH), 1740-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.31 (s, 2H, NH), 7.69 (s, 1H, H6), 2.20 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 159.0 (C4), 152.0 (C2), 145.6 (C7a), 130.7 (C6), 126.7 (C7), 111.2 (C4a), 12.7 (CH_3).

7-Phenylthieno[3,2-*d*]pyrimidine-2,4-dione **VIIb** had mp >260° (9.8 g, 40%, Method 1), (20 g, 80%, Method 2); ir (potassium bromide): 3250-3100 (NH), 1760-1640 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.31 (s, 1H, NH), 11.14 (s, 1H, NH), 8.05 (s, 1H, H6), 7.46 (broad, 5H, phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 159.0 (C4), 151.8 (C2), 143.8 (C7a), 132.4 (C6), 132.3 (Ph), 131.8 (C7), 128.7, 128.4 and 128.1 (Ph), 112.5 (C4a).

7-(4-Methylphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **VIIc** had mp >260° (7.5 g, 29%, Method 1), (16 g, 62%, Method 2); ir (potassium bromide): 3280-3100 (NH), 1730-1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.32 (s, 1H, NH), 11.00 (s, 1H, NH), 7.96 (s, 1H, H6), 7.34 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2H, phenyl protons), 7.25 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 2H, phenyl protons), 2.35 (s, 2H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 158.9 (C4), 151.7 (C2), 143.5 (C7a), 137.8 (Ph), 131.8 (C6), 131.7 (C7), 129.3, 129.2 and 128.1 (Ph), 112.4 (C4a), 20.7 (CH_3).

7-(4-Methoxyphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **VIId** had mp >260° (10.9 g, 40%, Method 1), (17.8 g, 65%, Method 2); ir (potassium bromide): 3250-3100 (NH), 1710-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.30 (s, 1H, NH), 11.07 (s, 1H, NH), 7.95 (s, 1H, H6), 7.40 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.01 (d, $^3J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 3.80 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 159.3 (Ph), 158.9 (C4), 151.9 (C2), 144.2 (C7a), 131.9 (C6), 130.6 (C7), 129.4, 125.1 and 114.2 (Ph), 111.6 (C4a), 55.0 (OCH_3).

7-(4-Fluorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **VIIe** had mp >260° (16.7 g, 64%, Method 2): ir (potassium bromide): 3250-3100 (NH), 1730-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.33 (s, 1H, NH), 11.15 (s, 1H, NH), 8.03 (s, 1H, H6), 7.48 (m, 2H, phenyl protons), 7.26 (m, 2H, phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 162.0 (d, $^1J_{C\text{-}F}$ = 244.7 Hz, Ph), 159.0 (C4), 151.8 (C2), 143.7 (C7a), 132.5 (C6), 130.8 (C7), 130.7 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, Ph), 128.7 (Ph), 115.5 (d, $^2J_{C\text{-}F}$ = 20.5 Hz), 112.4 (C4a).

7-(4-Chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **VIIf** had mp >260° (11.4 g, 41%, Method 1), (19.2 g, 69%, Method 2); ir (potassium bromide): 3180-3100 (NH), 1710-1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.34 (s, 1H, NH), 11.16 (s, 1H, NH), 8.06 (s, 1H, H6), 7.49 (s, 4H, phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 159.0 (C4), 151.9 (C2), 143.8 (C7a), 132.8 (C6), 132.7 (C7), 131.1, 130.5, 130.3 and 128.6 (Ph), 112.4 (C4a).

7-(4-Bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **VIIg** had mp >260° (25 g, 80%, Method 1); ir (potassium bromide): 3200-3100 (NH), 1730-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.32 (s, 1H, NH), 11.18 (s, 1H, NH), 8.07 (s, 1H, H6), 7.64 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.42 (d, $^3J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 159.0 (C4), 151.8 (C2), 143.6 (C7a), 132.7 (C6), 131.5, 130.6 and 121.4 (Ph), 130.0 (C7), 112.5 (C4a).

1- and 3-(β-D-Ribofuranosyl)-7-arylthieno[3,2-*d*]pyrimidine-2,4-diones **IX**, **X** and 3-(β-D-Ribofuranosyl)-7-methylthieno[3,2-*d*]-pyrimidine-2,4-dione **Xa**.

A suspension of pyrimidine-2,4-dione **VII** (0.01 mole) and ammonium sulphate (15 mg, $1.1 \cdot 10^{-4}$ mole) in HMDS (40 ml) was

stirred and refluxed for 4 hours. HMDS in excess was evaporated under reduced pressure to give bis(trimethylsilyl) compound **VIII**. A solution of 1-acetate-2,3,5-tri-*O*-benzyloxyribofuranose (5.06 g, 0.01 mole) in 60 ml of dry 1,2-dichloroethane and tin(IV) chloride (2 ml) was added to the residue of **VIII** and stirred at −30° for 18 hours. After addition of pyridine (4 ml) the mixture was filtered to remove inorganic materials. The filtrate was diluted with chloroform (100 ml). The organic layer was washed with a saturated solution of sodium hydrogenocarbonate (150 ml), followed by a 1*N* solution of hydrochloric acid (150 ml), then brine (100 ml) and water successively, dried over magnesium and concentrated to dryness under reduced pressure. The protected forms of **IX** and **X** were separated by silica gel column chromatography (graduated mixtures of dichloromethane and methanol). Each protected nucleoside was dissolved in methanol saturated with ammonia and stirred for two days at room temperature. Then the solution was concentrated to dryness and the residue recrystallized in methanol to give deprotected nucleosides as white solids.

3-(β-D-ribofuranosyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-dione **Xa** had mp 193° (1.3 g, 41%); ir (potassium bromide): 3560-3400 (OH), 1700 and 1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.77 (s, 1H, NH), 7.75 (s, 1H, H6), 6.19 (d, J_{H-H} = 2.9 Hz, 1H, H1'), 5.07 (m, 1H, OH), 4.89 (m, 1H, H4'), 4.56 (m, 2H, OH), 4.14 (m, 1H, H2'), 3.68 (m, 2H, H5'), 3.58 (m, 1H, H3'), 2.20 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d$_6$): δ 158.2 (C4), 151.3 (C2), 144.2 (C7a), 131.8 (C6), 126.6 (C7), 111.1 (C4a), 88.0 (C1'), 84.4 (C4'), 71.2 (C2'), 70.9 (C3'), 62.3 (C5'), 12.6 (CH_3); uv (*p*H 7): λ max 300 nm; (*p*H 1): λ max 301 nm; (*p*H 14): λ max 333 nm.

Anal. Calcd. for $C_{12}H_{14}N_2O_6S$ (314.31): C, 45.86; H, 4.49; N, 10.2. Found: C, 45.88; H, 4.36; N, 10.02.

3-(β-D-Ribofuranosyl)-7-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **Xb** had mp 202° (1.35 g, 36%); ir (potassium bromide): 3600-3200 (OH), 1700 and 1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.71 (s, 1H, NH), 8.10 (s, 1H, H6), 7.50 (s, 5H, phenyl protons), 6.21 (m, 1H, H1'), 5.12 (m, 1H, OH), 4.94 (m, 1H, H4'), 4.59 (m, 2H, OH), 4.12 (m, 1H, H2'), 3.69 (m, 2H, H5'), 3.58 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 158.4 (C4), 151.4 (C2), 142.0 (C7a), 134.1 (Ph), 133.3 (C6), 131.8 (C7), 128.6, 128.3 and 128.0 (Ph), 112.1 (C4a), 88.0 (C1'), 84.4 (C4'), 70.9 (C2'), 70.1 (C3'), 62.3 (C5'); uv (*p*H 7): λ max 305 nm; (*p*H 1): λ max 305 nm; (*p*H 14): λ max 340 nm.

Anal. Calcd. for $C_{17}H_{16}N_2O_6S$ (376.38): C, 54.25; H, 4.28; N, 7.44. Found: C, 54.04; H, 4.25; N, 7.41.

3-(β-D-Ribofuranosyl)-7-(4-fluorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **Xe** had mp 155° (1.4 g, 34%); ir (potassium bromide): 3500-3200 (OH), 1700 and 1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.50 (s, 1H, NH), 7.89 (s, 1H, H6), 7.49 (m, 2H, phenyl protons), 7.27 (m, 2H, phenyl protons), 6.21 (m, 1H, H1'), 5.09 (s, 1H, OH), 4.93 (m, 1H, H4'), 4.59 (m, 2H, OH), 4.17 (m, 1H, H2'), 3.72 (m, 2H, H5'), 3.62 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 162.1 (d, $^1J_{C-F}$ = 244.7 Hz, Ph), 158.3 (C4), 151.1 (C2), 142.4 (C7a), 133.5 (C6), 131.1 (C7), 130.7 (d, $^3J_{C-F}$ = 7.3 Hz, Ph), 129.0 (Ph), 112.2 (C4a), 88.1 (C1'), 84.5 (C4'), 71.0 (C2'), 70.2 (C3'), 62.3 (C5'); uv (*p*H 7): λ max 305 nm; (*p*H 1): λ max 304 nm; (*p*H 14): λ max 340.1 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SF$ (394.37): C, 51.78; H, 3.83; N, 7.10. Found: C, 51.65; H, 3.81; N, 7.14.

3-(β-D-Ribofuranosyl)-7-(4-chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **Xf** had mp 142° (1 g, 23%); ir (potassium bromide): 3520-3120 (OH), 1700 and 1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.52 (s, 1H, NH), 7.95 (s, 1H, H6), 7.51 (s, 4H, phenyl protons), 6.18 (m, 1H, H1'), 5.09 (s, 1H, OH), 4.90 (m, 1H, H4'), 4.58 (m, 2H, OH), 4.14 (m, 1H, H2'), 3.70 (m, 2H, H5'), 3.60 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 158.2 (C4), 151.1 (C2), 142.4 (C7a), 133.8 (C6), 133.0 (C7), 131.1, 130.8, 130.5 and 128.6 (Ph), 112.2 (C4a), 88.1 (C1'), 84.4 (C4'), 70.9 (C2'), 70.1 (C3'), 62.3 (C5'); uv (*p*H 7): λ max 306 nm; (*p*H 1): λ max 306 nm; (*p*H 14): λ max 342 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SCl$ (410.83): C, 49.7; H, 3.68; N, 6.82. Found: C, 49.89; H, 3.74; N, 6.70.

3-(β-D-Ribofuranosyl)-7-(4-bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **Xg** had mp 167° (1.10 g, 24%); ir (potassium bromide): 3500-3200 (OH), 1710 and 1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.46 (s, 1H, NH), 8.13 (s, 1H, H6), 7.65 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, phenyl protons), 7.42 (d, J_{H-H} = 7.8 Hz, 2H, phenyl protons), 6.19 (d, J_{H-H} = 3.4 Hz, 1H, H1'), 5.09 (s, 1H, OH), 4.90 (m, 1H, H4'), 4.60 (m, 2H, OH), 4.13 (m, 1H, H2'), 3.69 (m, 2H, H5'), 3.44 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 158.2 (C4), 151.0 (C2), 142.3 (C7a), 133.7 (C6), 131.2 (C7), 131.5, 130.6, 130.4 and 121.5 (Ph), 112.2 (C4a), 88.0 (C1'), 84.4 (C4'), 70.9 (C2'), 70.1 (C3'), 62.2 (C5'); uv (*p*H 7): λ max 304 nm; (*p*H 1): λ max 304 nm; (*p*H 14): λ max 339 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SBr$ (455.28): C, 44.85; H, 3.32; N, 6.15. Found: C, 44.73; H, 3.18; N, 6.32.

1-(β-D-Ribofuranosyl)-7-(4-fluorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **IXe** had mp 162° (0.9 g, 24%); ir (potassium bromide): 3480-3200 (OH), 1690 and 1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.67 (s, 1H, NH), 7.98 (s, 1H, H6), 7.47 (m, 2H, phenyl protons), 7.26 (m, 2H, phenyl protons), 5.18 (m, 1H, H1'), 4.84 (s, 1H, OH), 4.54 (m, 2H, OH), 4.46 (m, 1H, H4'), 3.93 (m, 1H, H2'), 3.58 (m, 2H, H3'), 3.19 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 162.0 (d, $^1J_{C-F}$ = 244.7 Hz, Ph), 158.0 (C4), 150.9 (C2), 143.6 (C7a), 135.0 (C6), 131.9 (C7), 130.9 (d, $^3J_{C-F}$ = 8.8 Hz, Ph), 130.6 (Ph), 115.4 (C4a), 115.2 (d, $^2J_{C-F}$ = 22 Hz, Ph), 92.2 (C1'), 83.7 (C4'), 70.3 (C2'), 69.6 (C3'), 61.9 (C5'); uv (*p*H 7): λ max 296.4 nm; (*p*H 1): λ max 297 nm; (*p*H 14): λ max 296 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SF$ (394.37): C, 51.78; H, 3.83; N, 7.1. Found: C, 51.81; H, 3.75; N, 6.97.

1-(β-D-Ribofuranosyl)-7-(4-chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **IXf** had mp 146° (0.75 g, 18%); ir (potassium bromide): 3580-3400 (OH), 11700 and 1660 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.71 (s, 1H, NH), 8.00 (s, 1H, H6), 7.47 (s, 4H, phenyl protons), 5.17 (m, 1H, H1'), 4.89 (s, 1H, OH), 4.58 (m, 2H, OH), 4.46 (m, 1H, H4'), 3.92 (m, 1H, H2'), 3.53 (m, 2H, H5'), 3.22 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 158.0 (C4), 150.9 (C2), 143.5 (C7a), 135.2 (C6), 133.1 (Ph), 131.7 (C7), 130.6, 128.5 and 128.3 (Ph), 115.4 (C4a), 92.4 (C1'), 83.7 (C4'), 70.5 (C2'), 69.6 (C3'), 61.9 (C5'); uv (*p*H 7): λ max 300 nm; (*p*H 1): λ max 300 nm; (*p*H 14): λ max 301 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SCl$ (410.83): C, 49.7; H, 3.68; N, 6.82. Found: C, 49.82; H, 3.54; N, 6.88.

1-(β-D-Ribofuranosyl)-7-(4-bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **IXg** had mp 171° (0.9 g, 20%); ir (potassium bromide): 3480-3350 (OH), 1690 and 1660 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.71 (s, 1H, NH), 8.01 (s, 1H, H6), 7.62 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, phenyl protons), 7.39 (d, J_{H-H} = 8.3 Hz, 2H, phenyl protons), 5.17 (d, $J_{H1'-H2'}$ = 2.4 Hz, 1H, H1'), 4.93 (s, 1H, OH), 4.61 (m, 2H, OH), 4.43 (m, 1H, H4'), 3.90 (m, 1H, H2'), 3.42 (m, 2H, H5'), 3.19 (m, 1H, H3'); ^{13}C-nmr (DMSO-d$_6$): δ 158.0 (C4), 150.8 (C2), 143.4 (C7a), 135.2 (C6), 133.4 (Ph), 131.6 (C7), 131.2, 130.8 and 121.6 (Ph), 115.4 (C4a), 92.4 (C1'), 83.6 (C4'), 70.4 (C2'), 69.5 (C3'), 61.9 (C5'); uv (*p*H 7): λ max 294 nm; (*p*H 1): λ max 297 nm; (*p*H 14): λ

max 299 nm.

Anal. Calcd. for $C_{17}H_{15}N_2O_6SBr$ (455.28): C, 44.85; H, 3.32; N, 6.15. Found: C, 44.88; H, 3.31; N, 6.12.

1- and 3-(2-Hydroxyethoxymethyl)-7-arylthieno[3,2-*d*]pyrimidine-2,4-diones **XI** and **XII** and 1- and 3-(2-Hydroxyethoxymethyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-diones **XIa** and **XIIa**.

These compounds were prepared from 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mole) and **VII** (0.01 mole) by the same procedure as **IX** and **X**.

3-(2-Hydroxyethoxymethyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-dione **XIIa** had mp 226° (0.6 g, 23%); ir (potassium bromide): 3500-3420 (OH), 1720 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.72 (s, 1H, NH), 7.73 (s, 1H, H6), 5.33 (s, 2H, OCH_2N), 4.58 (s, 1H, OH), 3.53 (m, 2H, CH_2OH), 3.45 (m, 2H, OCH_2), 2.20 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 158.3 (C4), 151.7 (C2), 144.3 (C7a), 131.7 (C6), 126.8 (C7), 110.8 (C4a), 71.4 (OCH_2N), 70.1 (OCH_2), 60.2 (CH_2OH); uv (*p*H 7): λ max 298 nm; (*p*H 1) λ max 297 nm; (*p*H 14): λ max 331 nm.

Anal. Calcd. for $C_{10}H_{12}N_2O_4S$ (256.27): C, 46.87; H, 4.72; S, 12.51. Found: C, 46.71; H, 4.62; S, 12.36.

3-(2-Hydroxyethoxymethyl)-7-(4-methoxyphenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XIId** had mp 199° (1.8 g, 54%); ir (potassium bromide): 3500-3460 (OH), 1730 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.76 (s, 1H, NH), 7.99 (s, 1H, H6), 7.41 (m, 2H, phenyl protons), 7.04 (m, 2H, phenyl protons), 5.36 (s, 2H, OCH_2N), 4.53 (s, 1H, OH), 3.81 (s, 3H, CH_3), 3.59 (m, 2H, CH_2OH), 3.49 (m, 2H, OCH_2); ^{13}C-nmr (DMSO-d_6): δ 159.3 (Ph), 158.4 (C4), 151.4 (C2), 142.4 (C7a), 132.3 (C6), 131.6 (C7), 129.7, 124.4 and 114.1 (Ph), 111.8 (C4a), 71.4 (OCH_2N), 70.1 (OCH_2), 60.1 (CH_2OH), 55.2 (CH_3); uv (*p*H 7): λ max 313 nm; (*p*H 1): λ max 313 nm; (*p*H 14): λ max 339 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.37): C, 55.16; H, 4.63; N, 8.04. Found: C, 55.46; H, 4.50; N, 8.03.

1-(2-Hydroxyethoxymethyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-dione **XIa** had mp 177° (1.6 g, 62%); ir (potassium bromide): 3500-3480 (OH), 1690 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.64 (s, 1H, NH), 7.76 (s, 1H, H6), 5.01 (s, 2H, OCH_2N), 4.68 (s, 1H, OH), 3.56 (m, 2H, CH_2OH), 3.41 (m, 2H, OCH_2), 2.51 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 158.0 (C4), 152.2 (C2), 144.4 (C7a), 132.7 (C6) 128.3 (C7), 114.9 (C4a), 72.1 (OCH_2N), 70.2 (OCH_2), 60.0 (CH_2OH), 15.6 (CH_3); uv (*p*H 7): λ max 294 nm; (*p*H 1): λ max 294 nm; (*p*H 14): λ max 294 nm.

Anal. Calcd. for $C_{10}H_{12}N_2O_4S$ (256.27): C, 46.87; H, 4.72; N, 10.93. Found: C, 46.62; H, 4.64; N, 10.78.

1-(1-Hydroxyethoxymethyl)-7-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **XIb** had mp 201° (1.1 g, 35%); ir (potassium bromide): 3500-3450 (OH), 1690 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.71 (s, 1H, NH), 7.91 (s, 1H, H6), 7.44 (s, 5H, phenyl protons), 4.92 (s, 2H, OCH_2N), 4.52 (s, 1H, OH), 3.30 (m, 4H, $HOCH_2CH_2O$); ^{13}C-nmr (DMSO-d_6): δ 158.0 (C4), 152.0 (C2), 142.9 (C7a), 134.7 (C6), 133.3 (C7), 129.8, 128.5, 128.2 and 127.8 (Ph), 114.7 (C4a), 71.2 (OCH_2N), 69.0 (OCH_2), 59.7 (CH_2OH); uv (*p*H 7): λ max 297 nm; (*p*H 1): λ max 297 nm; (*p*H 14): λ max 299 nm.

Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.35): C, 56.59; H, 4.43; S, 10.07. Found: C, 56.42; H, 4.47; S, 9.95.

1-(2-Hydroxyethoxymethyl)-7-(4-methyphenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XIc** had mp 214° (0.9 g, 27%); ir (potassium bromide): 3500-3400 (OH), 1680 and 1640 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.75 (s, 1H, NH), 7.85 (s, 1H, H6), 7.28 (s, 4H, phenyl protons), 4.95 (s, 2H, OCH_2N), 4.56 (s, 1H, OH), 3.55 (m, 2H, CH_2OH), 3.31 (m, 2H, OCH_2), 2.36 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 158.0 (C4), 152.0 (C2), 142.9 (C7a), 137.5 (Ph), 134.5 (C6), 133.2 (C7), 131.7, 129.5 and 128.4 (Ph), 114.7 (C4a), 71.1 (OCH_2N), 69.1 (OCH_2), 59.7 (CH_2OH), 20.7 (CH_3); uv (*p*H 7): λ max 297 nm; (*p*H 1): λ max 296 nm; (*p*H 14): λ max 296 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_4S$ (332.37): C, 57.82; H, 4.85; N, 8.43. Found: C, 57.52; H, 4.88; N, 8.39.

1-(2-Hydroxyethoxymethyl)-7-(4-methoxyphenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XId** had mp 188° (1.6 g, 48%); ir (potassium bromide): 3460-3380 (OH), 1700-1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.77 (s, 1H, NH), 7.85 (s, 1H, H6), 7.33 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, phenyl protons), 6.98 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, phenyl protons), 4.95 (s, 2H, OCH_2N), 4.54 (s, 1H, OH), 3.80 (s, 3H, CH_3), 3.43 (m, 2H, CH_2OH), 3.25 (m, 2H, OCH_2); ^{13}C-nmr (DMSO-d_6): δ 159.1 (Ph), 158.0 (C4), 152.0 (C2), 143.1 (C7a), 134.7 (C6), 133.0 (C7), 130.9, 126.7 and 113.3 (Ph), 114.1 (C4a), 71.1 (OCH_2N), 69.1 (OCH_2), 59.7 (CH_2OH), 55.1 (OCH_3); uv (*p*H 7): λ max 300 nm; (*p*H 1): λ max 300 nm; (*p*H 14): λ max 301 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.37): C, 55.16; H, 4.63; N, 8.04. Found: C, 55.24; H, 4.73; N, 8.05.

1-(2-Hydroxyethoxymethyl)-7-(4-fluorophenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XIe** had mp 233° (0.8 g, 24%); ir (potassium bromide): 3460 (OH), 1690 and 1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.75 (s, 1H, NH), 7.92 (s, 1H, H6), 7.47 (m, 2H, phenyl protons), 7.25 (m, 2H, phenyl protons), 4.92 (s, 2H, OCH_2N), 4.56 (s, 1H, OH), 3.38 (t, $J_{H\text{-}H}$ = 5.4 Hz, 2H, CH_2OH), 3.10 (t, $J_{H\text{-}H}$ = 5.4 Hz, 2H, OCH_2); ^{13}C-nmr (DMSO-d_6): δ 161.9 (d, $^1J_{C\text{-}F}$ = 246 Hz, Ph), 157.9 (C4), 151.9 (C2), 142.9 (C7a), 134.9 (C6), 132.0 (C7), 131.9 (d, $^3J_{C\text{-}F}$ = 7.3 Hz, Ph), 114.8 (C4a), 114.6 (d, $^2J_{C\text{-}F}$ = 20.5 Hz, Ph), 71.2 (OCH_2N), 69.1 (OCH_2), 59.7 (CH_2OH); uv (*p*H 7): λ max 300 nm; (*p*H 1): λ max 300 nm; (*p*H 14): λ max 300 nm.

Anal. Calcd. for $C_{15}H_{13}N_2O_4SF$ (336.34): C, 53.57; H, 3.90; N, 8.33. Found: C, 53.48; H, 3.97; N, 8.19.

1-(2-Hydroxyethoxymethyl)-7-(4-chlorophenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XIf** had mp 241° (1.1 g, 31%); ir (potassium bromide): 3500-3460 (OH), 1690-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.58 (s, 1H, NH), 7.93 (s, 1H, H6), 7.47 (s, 4H, phenyl protons), 4.94 (s, 2H, OCH_2N), 4.51 (s, 1H, OH), 3.47 (m, 2H, CH_2OH), 3.14 (m, 2H, OCH_2); ^{13}C-nmr (DMSO-d_6): δ 157.9 (C4), 151.9 (C2), 142.8 (C7a), 135.1 (C6), 133.5 (C7), 133.0, 131.9, 131.7 and 127.8 (Ph), 114.8 (C4a), 71.2 (OCH_2N), 69.2 (OCH_2), 59.7 (CH_2OH); uv (*p*H 7): λ max 296 nm; (*p*H 1): λ max 297 nm; (*p*H 14): λ max 298 nm.

Anal. Calcd. for $C_{15}H_{13}N_2O_4SCl$ (352.79): C, 51.07; H, 3.71; N, 7.94. Found: C, 51.06; H, 3.77; N, 7.76.

1-(2-Hydroxyethoxymethyl)-7-(4-bromophenyl)thieno[3,2-*d*]-pyrimidine-2,4-dione **XIg** had mp 238° (1.05 g, 27%); ir (potassium bromide): 3460 (OH), 1680-1660 (CO); ^{1}H-nmr (DMSO-d_6: δ 11.56 (s, 1H, NH), 7.94 (s, 1H, H6), 7.62 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.38 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 4.93 (s, 2H, OCH_2N), 4.55 (s, 1H, OH), 3.32 (t, $J_{H\text{-}H}$ = 4.9 Hz, 2H, CH_2OH), 3.23 (t, $J_{H\text{-}H}$ = 4.9 Hz, 2H, OCH_2); ^{13}C-nmr (DMSO-d_6): δ 157.9 (C4), 151.9 (C2), 142.8 (C7a), 135.0 (C6), 133.9 (C7), 132.0, 130.6 and 121.6 (Ph), 114.8 (C4a), 71.2 (OCH_2N), 69.1 (OCH_2), 59.7 (CH_2OH); uv (*p*H 7): λ max 294 nm; (*p*H 1): λ max 293 nm; (*p*H 14): λ max 298 nm.

Anal. Calcd. for $C_{15}H_{13}N_2O_4SBr$ (397.24): C, 45.35; H, 3.30; N, 7.05. Found: C, 45.11; H, 3.36; N, 7.08.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-methylthieno-[3,2-*d*]pyrimidine-2,4-dione **XIIIa** and 1- and 3-[2-Hydroxy-1-(hy-

droxymethyl)ethoxymethyl]-7-arylthieno[3,2-*d*]pyrimidine-2,4-dione **XIII** and **XIV**.

These compounds were prepared from 2-(acetoxymethoxy-1,3-propanediyl dibenzoate (3.72 g, 0.01 mole) and **VII** (0.01 mole) by the same procedure as for **IX** an **X**.

3-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIVg**; (0.6 g, 15%) had 228° mp (0.6 g, 15%); ir (potassium bromide): 3450-3300 (OH), 1700 and 1645 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.47 (s, 1H, NH), 8.12 (s, 1H, H6), 7.66 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, phenyl protons), 7.41 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, phenyl protons), 5.44 (s, 2H, OCH_2N), 4.56 (m, 2H, OH), 3.70 (m, 4H, CH_2), 3.39 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 158.2 (C4), 151.5 (C2), 142.2 (C7a), 133.4 (C6), 131.5, 131.2 and 130.6 (Ph), 130.5 (C7), 121.5 (Ph), 112.1 (C4a), 81.2 (OCH_2N), 69.6 (CH), 61.0 (CH_2); uv (*p*H 7): λ max 303 nm; (*p*H 1): λ max 304 nm; (*p*H 14): λ max 341 nm.

Anal. Calcd. for $C_{16}H_{15}N_2O_5SBr$ (427.27): C, 45.07; H, 3.54; N, 6.56. Found: C, 44.86; H, 3.62; N, 6.45.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-methylthieno-[3,2-*d*]pyrimidine-2,4-dione **XIIIa** had mp 168° (1.8 g, 63%); ir (potassium bromide): 3520-3400 (OH), 1710 and 1645 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.85 (s, 1H, NH), 7.74 (s, 1H, H6), 5.54 (s, 2H, OCH_2N), 4.59 (m, 2H, OH), 3.62 (m, 4H, CH_2), 3.41 (m, 1H, CH), 2.51 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d$_6$): δ 158.1 (C4), 152.2 (C2), 144.5 (C7a), 132.5 (C6), 128.4 (C7), 114.7 (C4a), 80.1 (OCH_2N), 71.5 (CH), 60.8 (CH_2), 15.8 (CH_3); uv (*p*H 7): λ max 297.8 nm; (*p*H 1): λ max 299 nm; (*p*H 14): λ max 300 nm.

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$ (286.30): C, 46.15; H, 4.93; S, 11.2. Found: C, 46.01; H, 4.68; S, 10.94.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-phenylthieno-[3,2-*d*]pyrimidine-2,4-dione **XIIIb** had mp 227° (1.5 g, 43%); ir (potassium bromide): 3520-3330 (OH), 1680-1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.80 (s, 1H, NH), 7.88 (s, 1H, H6), 7.42 (s, 5H, phenyl protons), 5.09 (s, 2H, OCH_2N), 4.41 (m, 2H, OH), 3.24 (m, 4H, CH_2), 3.14 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 158.0 (C4), 152.2 (C2), 143.0 (C7a), 134.8 (C6), 134.5 (Ph), 133.2 (C7), 129.7, 128.1 and 127.8 (Ph), 114.8 (C4a), 79.4 (OCH_2N), 70.8 (CH), 60.6 (CH_2); uv (*p*H 7): λ max 301 nm; (*p*H 1): λ max 303 nm; (*p*H 14): λ max 300 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.37): C, 55.16; H, 4.63; S, 9.2. Found: C, 55.03; H, 4.51; S, 9.03.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-methylphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIIIc** had mp 217° (0.76 g, 32%); ir (potassium bromide): 3530-3400 (OH), 1680-1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.71 (s, 1H, NH), 7.83 (s, 1H, H6), 7.29 (m, 4H, phenyl protons), 5.12 (s, 2H, OCH_2N), 4.41 (m, 2H, OH), 3.31 (m, 4H, CH_2), 3.15 (m, 1H, CH), 2.36 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d$_6$): δ 158.1 (C4), 152.3 (C2), 143.1 (C7a), 137.4 (Ph), 134.4 (C6), 133.4 (C7), 131.1, 129.6 and 128.5 (Ph), 114.8 (C4a), 79.3 (OCH_2N), 70.7 (CH), 60.6 (CH_2), 20.8 (CH_3); uv (*p*H 7): λ max 295 nm; (*p*H 1): λ max 295 nm; (*p*H 14): λ max 298 nm.

Anal. Calcd. for $C_{17}H_{18}N_2O_5S$ (362.40): C, 56.34; H, 5.01; N, 7.73. Found: C, 56.22; H, 4.98; N, 7.84.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-methoxyphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIIId** had mp 188° (2.4 g, 64%); ir (potassium bromide): 3480-3380 (OH), 1700 and 1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.63 (s, 1H, NH), 7.81 (s, 1H, H6), 7.33 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, phenyl protons), 6.95 (d, J_{H-H} = 8.3 Hz, 2H, phenyl protons), 5.11 (s, 2H, OCH_2N), 4.40 (m, 2H, OH), 3.80 (s, 3H, CH_3), 3.25 (m, 4H, CH_2), 3.13 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 159.1 (Ph), 158.1 (C4), 152.3 (C2), 143.2 (C7a), 134.5 (C6), 133.2 (C7), 131.0, 126.9 and 113.4 (Ph), 114.8 (C4a), 79.5 (OCH_2N), 70.7 (CH), 60.7 (CH_2), 55.3 (OCH_3); uv (*p*H 7): λ max 291 nm; λ max (*p*H 1): 291 nm; (*p*H 14): λ max 294 nm.

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$ (378.40): C, 53.96; H, 4.79; S, 8.47. Found: C, 53.88; H, 4.63; S, 8.24.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-fluorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIIIe** had mp 234° (1.25 g, 31%); ir (potassium bromide): 3500-3400 (OH), 1690 and 1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.69 (s, 1H, NH), 7.89 (s, 1H, H6), 7.46 (m, 2H, phenyl protons), 7.23 (m, 2H, phenyl protons), 5.09 (s, 2H, OCH_2N), 4.44 (m, 2H, OH), 3.26 (m, 4H, CH_2), 3.14 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 160.4 (d, $^1J_{C-F}$ = 244.7 Hz, Ph), 158.1 (C4), 152.16 (C2), 143.1 (C7a), 134.9 (C6), 132.2 (C7), 132.0 (d, $^3J_{C-F}$ = 7.3 Hz, Ph), 131.0 (Ph), 114.8 (C4a), 114.6 (d, $^2J_{C-F}$ = 20.5 Hz, Ph), 79.5 (OCH_2N), 70.7 (CH), 60.6 (CH_2); uv (*p*H 7): λ max 298 nm; (*p*H 1): λ max 298 nm; (*p*H 14): λ max 301 nm.

Anal. Calcd. for $C_{16}H_{15}N_2O_5SF$ (366.36): C, 52.46; H, 4.13; N, 7.65. Found: C, 52.43; H, 4.00; N, 7.43.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIIIf** had mp 227° (0.9 g, 24%); ir (potassium bromide): 3500-3350 (OH), 1705-1650 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.74 (s, 1H, NH), 7.92 (s, 1H, H6), 7.48 (s, 4H, phenyl protons), 5.11 (s, 2H, OCH_2N), 4.45 (m, 2H, OH), 3.31 (m, 4H, CH_2), 3.16 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 158.0 (C4), 152.2 (C2), 143.0 (C7a), 134.8 (C6), 133.6 (C7), 133.0, 132.1, 131.8 and 127.7 (Ph), 114.9 (C4a), 79.5 (OCH_2N), 70.8 (CH), 60.7 (CH_2); uv (*p*H 7): λ max 297 nm; (*p*H 1): λ max 297 nm; (*p*H 14): λ max 299 nm.

Anal. Calcd. for $C_{16}H_{15}N_2O_5SCl$ (382.82): C, 50.2; H, 3.95; N, 7.32. Found: C, 50.4; H, 3.80; N, 7.28.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-7-(4-bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XIIIg** had mp 229° (1.5 g, 35%); ir (potassium bromide): 3450-3350 (OH), 1700-1640 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 11.75 (s, 1H, NH), 7.93 (s, 1H, H6), 7.61 (d, J_{H-H} = 8.3 Hz, 2H, phenyl protons), 7.41 (d, J_{H-H} = 8.3 Hz, 2H, phenyl protons), 5.11 (s, 2H, OCH_2N), 4.47 (m, 2H, OH), 3.30 (m, 4H, CH_2), 3.15 (m, 1H, CH); ^{13}C-nmr (DMSO-d$_6$): δ 158.1 (C4), 152.2 (C2), 143.0 (C7a), 135.0 (C6), 134.1 (C7), 132.1, 130.7 and 121.7 (Ph), 114.9 (C4a), 79.4 (OCH_2N), 70.7 (CH), 60.5 (CH_2); uv (*p*H 7): λ max 295 nm; λ max (*p*H 1): 296 nm; (*p*H 14): λ max 297 nm.

Anal. Calcd. for $C_{16}H_{15}N_2O_5SBr$ (427.27): C, 44.98; H, 3.54; N, 6.56. Found: C, 44.9; H, 3.44; N, 6.53.

Benzyloxymethyl Acetate.

Benzyl alcohol (27 g, 0.25 mole), dimethoxymethane (28.5 g, 0.375 mole) and phosphorus pentoxide (50 g, 0.35 mole) were stirred vigorously for 24 hours at room temperature in dry chloroform and then hydrolysed with ice-water. The organic phase was washed with aqueous sodium hydrogenocarbonate solution, dried over magnesium sulphate and concentrated under reduced pressure. Then boron trifluoride in diethyl ether (10.6 g, 0.075 mole) was added dropwise to the cooled solution (−20°) of the residue in diethyl ether (50 ml) and acetic anhydride (35 ml, 0.35 mole). The solution was stirred at 4° for 6 hours and concentrated. The distillation under reduced pressure (90-100°/4 mm Hg) furnished 15 g (35%) of colorless oil; ir (potassium bromide): 1720 (CO); ^{1}H-nmr (DMSO-d$_6$): δ 7.31 (m, 5H, phenyl protons), 5.31 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 2.02 (s, 3H, CH_3).

3-(Benzyloxymethyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-dione

XVIa and 1-(Benzyloxymethyl)-7-arylthieno[3,2-*d*]pyrimidine-2,4-diones **XVb-g**.

These compounds were prepared from benzyloxymethyl acetate (1.80 g, 0.01 mole) and **VII** (0.01 mole) by the same procedure as **IX** and **X**.

3-(Benzyloxymethyl)-7-methylthieno[3,2-*d*]pyrimidine-2,4-dione **XVIa** had mp 182° (1 g, 33%); ir (potassium bromide): 1710 and 1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.78 (s, 1H, NH), 7.73 (s, 1H, H6), 7.30 (s, 5H, phenyl protons), 5.41 (s, 2H, OCH_2N), 4.62 (s, 2H, CH_2), 2.21 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 158.3 (C4), 151.7 (C2), 144.3 (C7a), 138.1 (Ph), 131.6 (C6), 128.0 and 127.3 (Ph), 126.7 (C7), 110.1 (C4a), 70.9 (OCH_2N), 69.7 (CH_2), 12.6 (CH_3); uv (*p*H 7): λ max 300 nm; (*p*H 1): λ max 298 nm; (*p*H 14): λ max 328 nm.

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$ (302.35): C, 59.59; H, 4.67; S, 10.60. Found: C, 59.36; H, 4.54; S, 10.35.

1-(Benzyloxymethyl)-7-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **XVb** had mp 184° (1.5 g, 42%); ir (potassium bromide): 1710 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.69 (s, 1H, NH), 7.87 (s, 1H, H6), 7.41 (s, 5H, phenyl protons), 7.21 (s, 5H, phenyl protons), 5.03 (s, 2H, OCH_2N), 4.05 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ 157.9 (C4), 152.0 (C2), 142.8 (C7a), 137.4 (Ph), 134.7 (C6), 133.2 (C7), 134.8, 129.8, 128.0, 127.7, 127.3 and 126.8 (Ph), 115.0 (C4a), 71.4 (OCH_2N), 69.5 (CH_2); uv (*p*H 7): λ max 297 nm; (*p*H 1): λ max 298 nm; (*p*H 14): λ max 300 nm.

Anal. Calcd. for $C_{20}H_{16}N_2O_3S$ (364.42): C, 65.92; H, 4.43; S, 8.8. Found: C, 65.68; H, 4.49; S, 8.88.

1-(Benzyloxymethyl)-7-(4-methylphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XVc** had mp 194° (1.2 g, 32%); ir (potassium bromide): 1705 and 1665 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.66 (s, 1H, NH), 7.86 (s, 1H, H6), 7.28 (s, 4H, phenyl protons), 7.24 (s, 5H, phenyl protons), 5.08 (s, 2H, OCH_2N), 4.12 (s, 2H, CH_2), 2.37 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 157.9 (C4), 152.0 (C2), 142.8 (C7a), 137.6 and 137.5 (Ph), 134.5 (C6), 133.2 (C7), 131.8, 129.6, 128.5, 128.0, 127.3 and 126.8 (Ph), 115.1 (C4a), 71.4 (OCH_2N), 69.6 (CH_2), 20.8 (CH_3); uv (*p*H 7): λ max 294 nm; (*p*H 1): λ max 294 nm; (*p*H 14): λ max 296 nm.

Anal. Calcd. for $C_{21}H_{18}N_2O_3S$ (378.44): C, 66.65; H, 4.79; N, 7.4. Found: C, 66.69; H, 4.83; N, 7.32.

1-(Benzyloxymethyl)-7-(4-methoxyphenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XVd** was obtained in 32% yield (1.25 g); ir (potassium bromide): 1710 and 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.67 (s, 1H, NH), 7.85 (s, 1H, H6), 7.32 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.15 (m, 5H, phenyl protons), 6.95 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 5.07 (s, 2H, OCH_2N), 4.12 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3); ^{13}C-nmr (DMSO-d_6): δ 159.1 (Ph), 157.9 (C4), 152.0 (C2), 143.0 (C7a), 137.5 (Ph), 134.7 (C6), 132.9 (C7), 130.9, 128.0, 127.3, 126.8 and 113.4 (Ph), 114.3 (C4a), 71.3 (OCH_2N), 69.6 (CH_2), 55.1 (OCH_3); uv (*p*H 7): λ max 291 nm; (*p*H 1): λ max 291 nm; (*p*H 14): λ max 289 nm.

Anal. Calcd. for $C_{21}H_{18}N_2O_4S$ (394.44): C, 63.95; H, 4.61; S, 8.13. Found: C, 63.84; H, 4.61; S, 7.98.

1-(Benzyloxymethyl)-7-(4-fluorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XVe** was obtained in 37% yield (1.4 g); ir (potassium bromide): 1710-1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.70 (s, 1H, NH), 7.93 (s, 1H, H6), 7.47 (m, 2H, phenyl protons), 7.25 (m, 5H, phenyl protons), 7.12 (m, 2H, phenyl protons), 5.06 (s, 2H, OCH_2N), 4.17 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ 161.8 (d, $J_{C\text{-}F}$ = 244.7 Hz, Ph), 157.9 (C4), 152.0 (C2), 142.8 (C7a), 137.4 (Ph), 135.0 (C6), 132.1 (C7), 132.0 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, Ph), 131.0 (Ph), 128.0, 127.3 and 126.8 (Ph), 114.9 (C4a), 71.4 (OCH_2N), 69.7 (CH_2); uv (*p*H 7): λ max 296 nm; (*p*H 1): λ max 295 nm; (*p*H 14): λ max 299 nm.

Anal. Calcd. for $C_{20}H_{15}N_2O_3SF$ (382.41): C, 62.82; H, 3.95; N, 7.33. Found: C, 63.07; H, 4.0; N, 7.31.

1-(Benzyloxymethyl)-7-(4-chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XVf** was obtained in 34% yield (1.35 g), mp 222°; ir (potassium bromide): 1695 and 1670 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.72 (s, 1H, NH), 7.94 (s, 1H, H6), 7.46 (s, 4H, phenyl protons), 7.25 (m, 5H, phenyl protons), 5.08 (s, 2H, OCH_2N), 4.19 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ 157.9 (C4), 152.0 (C2), 142.7 (C7a), 137.4 (Ph), 135.0 (C6), 133.6 (Ph), 133.1 (C7), 131.9, 131.7, 128.0, 127.8, 127.3 and 126.8 (Ph), 115.0 (C4a), 71.6 (OCH_2N), 69.8 (CH_2); (*p*H 7): λ max 298 nm; (*p*H 1): λ max 298 nm; (*p*H 14): λ max 301 nm.

Anal. Calcd. for $C_{20}H_{15}N_2O_3SCl$ (398.86): C, 60.23; H, 3.79; S, 8.04. Found: C, 60.14; H, 3.71; S, 8.02.

1-(Benzyloxymethyl)-7-(4-bromophenyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XVg** was obtained in 24% yield (1.1 g); mp 228°; ir (potassium bromide): 1690-1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 11.72 (s, 1H, NH), 7.94 (s, 1H, H6), 7.60 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.38 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H, phenyl protons), 7.25 (m, 5H, phenyl protons), 5.08 (s, 2H, OCH_2N), 4.18 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ 157.8 (C4), 151.9 (C2), 142.6 (C7a), 137.3 (Ph), 134.9 (C6), 133.9 (C7), 131.9, 131.8, 130.7, 128.0, 127.3, 126.8 and 121.6 (Ph), 115.0 (C4a), 71.5 (OCH_2N), 69.7 (CH_2); uv (*p*H 7): λ max 296 nm; (*p*H 1): λ max 296 nm, (*p*H 14): λ max 297 nm.

Anal. Calcd. for $C_{20}H_{15}N_2O_3SBr$ (443.31): C, 54.19; H, 3.41; N, 6.32. Found: C, 53.89; H, 3.55; N, 6.25.

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