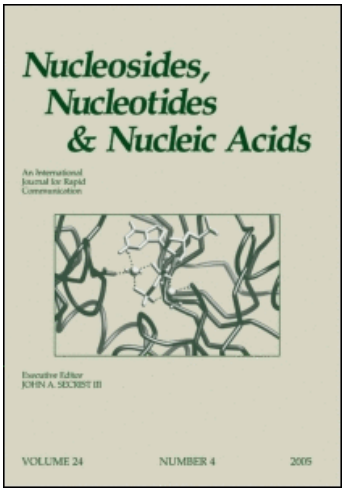

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Synthesis of Acyclic Thieno[3,2-*d*]Pyrimidine Nucleosides and Azido Derivatives as Potential Anti-HIV Agents

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SYNTHESIS OF ACYCLIC THIENO[3,2-*d*]PYRIMIDINE NUCLEOSIDES AND AZIDO DERIVATIVES AS POTENTIAL ANTI-HIV AGENTS.

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ABSTRACT

A series of thieno[3,2-*d*]pyrimidine-2,4-diones alkylated with acyclic chains have been synthesized related to the antiherpetic agents (acyclovir and ganciclovir) and to EBPU which was reported to display *in vitro* antiviral activity against human immunodeficiency virus type 1 (HIV-1). Conversion of the hydroxy-acyclic nucleosides into their azido derivatives was then examined using triphenylphosphine - carbon tetraiodide - sodium azide. All the compounds, however, did not exhibit any significant inhibitory activity against HIV-1 in CEM cl 13 cells.

INTRODUCTION

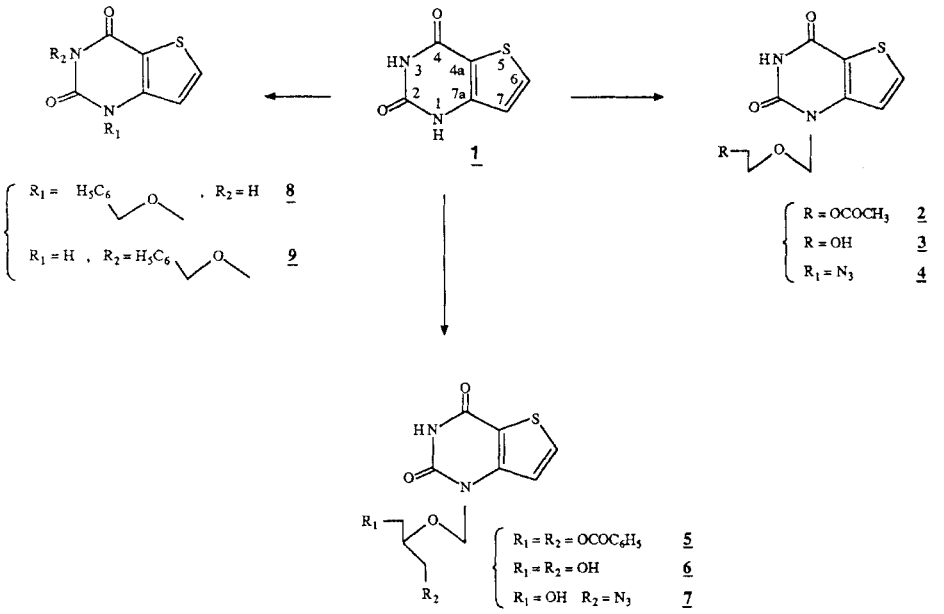
The successful development of 9-[(2-hydroxyethoxy)methyl]-guanine (Acyclovir-ACV) [1] and 9-(1,3-dihydroxy-2-propoxymethyl)-guanine (DHPG-Ganciclovir) [2] has stimulated an extensive search for acyclic nucleosides. Continuous efforts are being made to find effective chemotherapeutic agents against HIV-1, the causative agent of AIDS. Recently it was reported that 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)-thymine (HEPT) is potent and selective inhibitor of HIV-1 but not of human immunodeficiency virus type 2 (HIV-2) [3]. This compound does not require phosphorylation in order to inhibit HIV-1 reverse transcriptase, consequently the presence of an hydroxy group in HEPT may not be necessary for its anti-HIV-1 activity. This was confirmed by the fact that 1-benzyloxymethyl-5-ethyl-6-phenylthio-uracil (EBPU) displays higher anti-HIV-1 properties than HEPT [4]. Moreover EBPU shows an important improvement in the activity by replacing the 5-substituent with an ethyl group. Further studies on the structure-activity relationships show that the increase in the size of the C-5 substituent causes a conformational change of the 6-phenylthio group. Steric hindrance between C-5 and C-6 substituents involves that the phenyl ring of the 6-phenylthio group appears perpendicular to the uracil ring. Thus the conformation of the 6-substituent seems to contribute to the anti-HIV activity of HEPT analogues.

These previous observations suggest that for anti-HIV-1 activity a certain size of hydrophobic surrounding is needed between C(5) - C(4) and an acyclic portion. In order to increase the lipophilicity of the HEPT, we have investigated the syntheses of heterocyclic series of thieno [3,2-*d*]pyrimidine-2,4-diones possessing both open acyclic chain functions and thiophen ring on the "*d* side" of uracil. Since 3'-azido-3'-deoxythymidine (AZT) is commonly used as inhibitor of the HIV in the treatment of AIDS [5], a second part of our synthetic program was to prepare acyclic azido-nucleosides. Several acyclo AZT lacking the C(3') - C(4') bond were already prepared by Scheiner and co- workers [6]. A more recent synthesis of acyclo AZT has been reported using triphenylphosphine - carbon tetraiodide - sodium azide for conversion of dihydroxy acyclic nucleoside to mono-azido mono-hydroxy acyclic nucleoside [7].

CHEMISTRY

The general procedure for the preparation of acyclic nucleosides is based on a direct alkylation of silylated heterocycle with an acyclic acetoxymethyl ether.

The thieno[3,2-*d*]pyrimidine-2,4-dione 1 prepared according to a known procedure [8] was refluxed with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulfate under anhydrous conditions to give the bis(trimethylsilyl) derivative as an oil after evaporation of the excess of HMDS [9]. According to the procedure developed by NIEDBALLA & VORBRÜGGEN [10], the 2-acetoxyethyl acetoxymethyl ether [11] and the 2-(acetoxymethoxy)-1,3-propanediyl dibenzoate [12] were then condensed with the above aglycon 1 under stannic chloride catalysis in 1,2-dichloroethane to produce respectively the corresponding acyclic nucleosides 2 and 5 in highly regioselective manner.



Subsequent removal of the ester blocking groups allowing the employment of mild deprotecting agents such as methanolic sodium methoxide for 2 and sodium carbonate for 5 provided respectively the expected crystallized acyclic nucleosides: 1-[(2-hydroxyethoxy)methyl]-thieno[3,2-*d*]pyrimidine-2,4-dione 3 and 1-[(2-hydroxy-1-(hydroxymethyl)ethoxymethyl]-thieno[3,2-*d*]pyrimidine-2,4-dione 6. The possibility in which the chain portion could be attached to the 3-nitrogen (N-3) seemed highly unlikely because of the presence of an absorption maxima at 292 ± 2 nm for 3 and 296 ± 2 nm for 6 (both pH 1 and 11) in the ultraviolet spectra [13]. These facts indicated an heterocyclic substitution at N-1 position on the uracil ring for both compounds 3 and 6.

We have then developed transformation of the chain of parent acyclic nucleosides 3 and 6 into target structures as their azido derivatives 4 and 7. Treatment of 3 with triphenylphosphine, sodium azide and carbon tetraiodide in *N,N*-dimethylformamide at room temperature yielded the expected 1-[(2-azidoethoxy)methyl]-thieno[3,2-*d*]pyrimidine-2,4-dione 4 (27%) which showed an azide stretching at 2060 cm^{-1} in its infrared spectrum [14]. The structure of 4 was apparent from its NMR spectra. Its ^1H NMR spectrum showed the methylene substituted with an azide group at 3.70 ppm while the (CH_2) of 3 appeared at 3.52 ppm. Moreover the ^{13}C NMR spectrum of 4 exhibited a strong upfield shift for the methylene ($\Delta\delta$ = 10.2 ppm) when compared to 3, indicating that the azide group was effectively introduced on the terminal chain position. The same procedure applied to compound 6 afforded directly the acyclic analogue 7 purified by silica gel chromatography (16%) which showed an azide stretching at 2060 cm^{-1} in its infrared spectrum [14].

In order to increase the lipophilicity of these compounds, the remplacement of [(2-hydroxyethoxy)methyl] or [(2-hydroxy-1-(hydroxymethyl)ethoxymethyl] by benzyloxymethyl group in acyclic chain portion was investigated. For that the bis(trimethylsilyl) derivative of 1 was condensed with acetoxymethyl benzyl ether yielding a mixture of two nucleosides which we assigned the structures 8 and 9. These compounds were found to have different *Rf* values [0.80 and 0.70, respectively, in CH_2Cl_2-CH_3OH (98:2)], which suggested that we had in hand a pair of isomers. The nucleoside mixture was separated by column chromatography to furnish 1-(benzyloxymethyl)-thieno[3,2-*d*]pyrimidine-2,4-dione 8 (16%) and the N-3 isomer 9 (3.5%). Structure elucidation of these products was based on spectroscopic methods such as their mass spectral data both showing a molecular ion peak at m/z 288. The presence of an absorption maxima at 295 ± 1 nm (both pH 1 and 11) in the ultraviolet spectra of the first-eluted product indicated that the chain portion was attached to N-1 position on the uracil ring. The second-eluted compound showed an absorption maxima at 299 nm (pH 1 and 7) and at 330 nm (pH 11) in the UV spectra. This difference of 31 nm allowed us to assign the site of alkylation to be the N-3 position on the uracil ring [13].

ANTIVIRAL ASSAYS on CEM cl 13 CELLS

Acyclic pyrimidine nucleosides 3, 4, 6, 7, 8 and 9 were evaluated by comparison to AZT for their protective activity against the cytopathic effect (CPE) induced by the human HIV-1 (LAV strain) in cell cultures in the concentration range of 0-30 µg/ml. The CEM cl 13 cells (a subclone enriched in CD4 receptors, 5.10^4 cells/ml) were added with each compound dilution or PBS alone. After 1 hr incubation at 37°C, cells were infected with HIV-1 suspension (100-200 $CCID_{50}$). After culturing for 7 days, cell viability was determined by colorimetric staining as described previously [16]. The cellular toxicity of the compounds was also assessed by treating uninfected cells

with various concentrations of the products. The in vitro antiviral potencies and cellular toxicities of both compounds at the above concentrations (<30mg/ml) and AZT did not appear comparable in this assay system.

EXPERIMENTAL SECTION

Melting points (mp) were determined with a KOFLER apparatus and are uncorrected. Infrared (IR) spectra were obtained on a PHILIPS SP-3 Pye Unicam spectrophotometer with samples in KBr disk. Ultraviolet (UV) spectra were recorded on a SECONAM S-1000G spectrometer. Mass spectra (MS) were recorded with a JEOL D-300 instrument using the ionisation by electronic impact technique. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX 200 spectrometer, and chemical shifts were expressed in δ ppm relative to tetramethylsilane (TMS) as an internal standard. Thin layer chromatography (TLC) was performed on silica gel 60F-254 plates purchased from E. MERCK and Co.with UV light for visualization and column chromatography was performed on a silica gel 60 (230-400 mesh, ASTM, Merck).

Thieno[3,2-*d*]pyrimidine-2,4-dione (1) [8] (white crystalline solid- 80%) mp > 260°C; IR (KBr) cm^{-1} : 3480-3380 (NH), 1670 (CO), 1570, 1540, 1450, 780; ^{1}H NMR (DMSO-d_6) : δ 6.90 (d, 1H, H-7, J =5.4 Hz), 8.05 (d, 1H, H-6), 11.20 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 111.0 (C-4a), 117.0 (C-7), 135.8 (C-6), 146.3 (C-7a), 151.4 (C-2), 158.9 (C-4).

General procedure for the silylation of thieno[3,2-*d*]pyrimidine-2,4-dione A mixture of 1 (1.68 g, 10 mmol), hexamethyldisilazane (HMDS, 40 ml) in the presence of a catalytic amount of ammonium sulfate was heated at reflux with exclusion of moisture for 5 hr. The excess HMDS was removed by vacum distillation to give the bis(trimethylsilyl) intermediate.

1-[(2-acetoxyethoxy)methyl]-thieno[3,2-*d*]pyrimidine-2,4-dione (2) 2-acetoxyethyl acetoxymethyl ether (1.90 g, 10 mmol) was added to a solution of the above silylated base in 1,2-dichloroethane (60 ml). The reaction mixture was then added with stannic chloride (2 ml) and stirred at room temperature for 24 hr. In order to avoid the heavy emulsion which is generally formed during the extraction of the reaction mixture with sodium hydrogencarbonate, pyridine (2 ml) was added to complex the excess of catalyst. The mixture was stirred for an additionnal 90 min and the precipitate of inorganic materials which had formed was collected by filtration. The precipitate was washed with $CHCl_3$ (2X30 ml) and the combined filtrates were washed successively with HCl (1N, 3X150 ml), aqueous saturated $NaHCO_3$ (2X100 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, the drying agent was removed by filtration, and the organic layer evaporated *in vacuo* to give 2 (white crystalline solid- 1.78 g- 63%) mp : 130°C; IR (KBr) cm^{-1} : 3380 (NH), 1660-1630 (CO), 1400, 1150, 1120, 640; ^{1}H NMR (DMSO-d_6) : δ 1.91 (s, 3H, CH_3), 3.71 (t, 2H, OCH_2CH_2O), 4.08 (t, 2H, OCH_2CH_2O), 5.43 (s, 1H, NCH_2), 7.25 (d, 1H, H-7, J =5.4 Hz), 8.12 (d, 1H, H-6); Anal. Cald. For $C_{11}H_{12}N_2O_5S$ (284.3) : C, 46.47 ; H, 4.25 ; N, 9.85 ; S, 11.28. Found : C, 46.39 ; H, 4.16 ; N, 9.69 ; S, 11.01.

1-[(2-hydroxyethoxy)methyl]-thieno[3,2-*d*]pyrimidine-2,4-dione (3) Compound 2 (1.70 g, 5.98 mmol) was dissolved in 1N methanolic sodium methoxide (30 ml) and the reaction mixture was stirred for 2 hr at room temperature. The solution was then cooled at 0°C and acidified to pH 1 with hydrochloric acid (1N). The precipitate which had formed was collected by filtration and washed with boiling methanol. The combined methanolic filtrates were evaporated to dryness*in vacuo*. The resulting oil was crystallized from a mixture of diethyl oxide/petroleum ether (50/50) to afford 3 (white crystalline solid- 0.8 g- 55%) mp : 168°C; IR (KBr) cm^{-1} : 3470 (NH), 1690 (CO), 1490, 1110, 1070, 790; ^{1}H NMR (DMSO-d_6) : δ 3.52 (t, 2H, OCH_2CH_2O), 4.57 (1H, OH), 5.42 (2H, NCH_2), 7.27 (d, 1H, H-7, J =5.4 Hz), 8.14 (d, 1H, H-6), 8.39

(1H, NH); ^{13}C NMR (DMSO-d_6) : δ 59.9 (CH_2OH), 70.2 (OCH_2CH_2O), 73.8 (NCH_2), 112.8 (C-4a), 118.0 (dd, C-7, ^1J =175.7Hz, ^2J =4.3Hz), 135.7 (dd, C-6, ^1J =184.3Hz, ^2J =4.3Hz), 146.6 (m, C-7a), 151.4 (s, C-2), 158.0 (s, C-4); UV λ_{max}: 292 (pH 1, HCl), 294 (pH 7, H_2O), 294 (pH 14, NaOH); Anal. Cald. For $C_9H_{10}N_2O_4S$ (242.2) : C, 44.62 ; H, 4.16 ; N, 11.56 ; S, 13.23. Found : C, 44.37 ; H, 4.46 ; N, 11.31 ; S, 13.26.

1-[(2-azidoethoxy)methyl]-thieno[3,2-*d*]pyrimidine-2,4-dione (4) Triphenylphosphine (2.2 g, 8.26 mmol), sodium azide (2.7 g, 8.26 mmol) and carbon tetraiodide (4.3 g, 8.26 mmol) were added successively to a solution of 3 (1 g, 4.13 mmol) in DMF (85 ml). The reaction mixture was stirred at room temperature for 14 hr and evaporated *in vacuo* to afford an oil which crystallized from diethyl oxide. (white crystalline solid- 300 mg, 27%, TLC CH_2Cl_2:CH_3OH 95:5 Rf=0.51) mp : 176°C; IR (KBr) cm^{-1} : 2060 (N_3), 1630 (CO), 1150, 1100, 700, 670; ^1H NMR (DMSO-d_6) : δ 3.39 (t, 2H, OCH_2,J = 4.9Hz), 3.70 (t, 2H, CH_2N_3, J = 4.9 Hz), 5.46 (2H, NCH_2), 7.27 (d, 1H, H-7, J =5.4 Hz), 8.14 (d, 1H, H-6), 11.60 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 49.7 (CH_2N_3), 67.1 (OCH_2), 73.6 (NCH_2), 112.8 (C-4a), 117.7 (C-7), 135.5 (C-6), 146.3 (C-7a), 151.4 (C-2), 157.9 (C-4); Anal. Cald. For $C_9H_9N_5O_3S$ (267.3) : C, 40.45 ; H, 3.39 ; N, 26.20 ; S, 12.00. Found : C, 40.32 ; H, 3.12 ; N, 26.34 ; S, 11.86.

1-[(2-benzoyloxy-1-benzoyloxymethyl)ethoxymethyl]-thieno[3,2-*d*]pyrimidine-2,4-dione (5) Compound 5 was prepared by a method similar to that described for 2 except for the glycosylation which was carried out with 2-acetoxymethoxy-1,3-propanediyl dibenzoate (3.72 g, 10 mmol) to yield 1.9 g (40%) of 5 as a white crystalline solid. mp : 170°C; IR (KBr) cm^{-1} : 3160 (NH), 1690-1630 (CO), 1250, 1090, 1040, 690; ^1H NMR (DMSO-d_6) : δ 3.17 (d, 1H, CH, J =4.89Hz), 4.39 (d, 2H, CH_2O), 4.54 (d, 2H, CH_2O), 5.51 (2H, NCH_2), 6.85 (d, 1H, H-7, J =5.4 Hz), 7.43-7.91 (m, 15H, benzoyl H), 8.06 (d, 1H, H-6), ^{13}C NMR (DMSO-d_6) : δ 63.9 (CH_2O), 69.6 (CH), 74.9 (NCH_2), 110.7 (C-4a), 117.7 (C-7), 128.5-128.9-136.8 (benzoyl C), 133.3 (C-6), 145.0 (C-7a), 151.2 (C-2), 158.2 (C-4), 165.3 (CO); Anal. Cald. For $C_{25}H_{20}N_2O_7S$ (480.5) : C, 59.99 ; H, 4.20 ; N, 5.83 ; S, 6.67. Found : C, 60.19 ; H, 4.25 ; N, 5.61 ; S, 6.44.

1-[(2-hydroxy-1-(hydroxymethyl)ethoxymethyl]- thieno[3,2-*d*]pyrimidine-2,4-dione (6) A mixture of 6 (500 mg, 1.04 mmol) in methanol (70 ml) and sodium carbonate (50 mg) was stirred at room temperature for 12 hr. The mineral salts were collected by filtration and washed with boiling methanol. The combined filtrates were acidified to pH 4 by rapid addition of Dowex 50W-X8 (H^+) resin and filtered. The filtrate was evaporated to dryness *in vacuo* to afford an oil which crystallized from methanol (white crystalline solid- 120 mg, 42%) mp : 192°C; IR (KBr) cm^{-1} : 3300 (NH), 1685-1610 (CO), 1525, 1420, 1050, 1030; ^1H NMR (DMSO-d_6) : δ 3.40 (m, 3H, CH and CH_2OH), 5.41 (2H, NCH_2), 6.93 (d, 1H, H-7, J =5.4 Hz), 8.09 (d, 1H, H-6), 11.55 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.7 (CH_2OH), 73.3 (CH), 79.9 (NCH_2), 112.5 (C-4a), 118.1 (C-7), 135.4 (C-6), 146.7 (C-7a), 151.2 (C-2), 158.0 (C-4); UV λ_{max} (log ε) : 295 (3.79) (pH 1, HCl), 295 (3.92) (pH 7, H_2O), 297 (3.41) (pH 14, NaOH); Anal. Cald. For $C_{10}H_{12}N_2O_5S$ (272.3) : C, 44.11 ; H, 4.44 ; N, 10.29 ; S, 11.77. Found : C, 44.07 ; H, 4.43 ; N, 10.46 ; S, 11.66.

1-[(2-azido-1-(hydroxymethyl)ethoxymethyl]-thieno[3,2-*d*]pyrimidine-2,4-dione (7) Compound 7 was prepared as the same procedure as 4. After purification by column chromatography using a gradient of 0 to 80 % methanol in dichloromethane as eluent, the pure 7 was separated in 16% yield (140 mg as a white crystalline solid, TLC CH_2Cl_2:CH_3OH 85:15 Rf = 0.58) mp : 154°C; IR (KBr) cm^{-1} : 3440 (NH), 2060 (N_3), 1670 (CO), 1470, 1290, 1070, 1040; ^1H NMR (DMSO-d_6) : δ 3.43–3.78 (m, 3H, CH and CH_2), 4.87 (1H, OH), 5.52 (2H, NCH_2), 7.26 (d, 1H, H-7, J =5.4 Hz), 8.13 (d, 1H, H-6), 11.58 (1H, NH);

^{13}C NMR (DMSO-d_6) : δ 51.0 (CH_2N_3), 60.7 (CH_2OH), 73.3 (CH), 77.8 (NCH_2), 112.7 (C-4a), 117.8 (C-7), 135.4 (C-6), 146.5 (C-7a), 151.3 (C-2), 157.9 (C-4); Anal. Cald. For $C_{10}H_{11}N_5O_4S$ (297.3) : C, 40.40 ; H, 3.73 ; N, 23.56 ; S, 10.78. Found : C, 40.45 ; H, 3.67 ; N, 23.24 ; S, 10.43.

benzyloxymethyl ether Benzyl alcohol (27 g, 250 mmol), dimethoxymethane (28.5 g, 375 mmol) and phosphorus pentoxide (50 g) were stirred vigorously for 24 hr at room temperature in dry $CHCl_3$ then hydrolysed with ice-water. The organic layer was washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The boron trifluoride in diethyl oxide (75 mmol) was added dropwise to the cooled solution (-20°C) of the residue in diethyl oxide (50 ml) and acetic anhydride (35 ml, 350 mmol). The solution was stirred at 4°C for 6 hr then concentrated. The resulting oil was distilled under reduced pressure (90 - 100 °C / 4 mmHg) to yield 15 g of benzyloxymethyl ether (35%) ; IR (KBr) cm^{-1} : 1720 (CO); ^1H NMR (DMSO-d_6) : δ 2.02 (s, 3H, CH_3), 4.66 - 5.31 (s, 2X2H, CH_2), 7.31 (m, 5H, Ph).

1-(benzyloxymethyl)-thieno[3,2-*d*]pyrimidine-2,4-dione (8) Reaction conditions were similar to those utilized for the preparation of 2 except for the glycosylation which was carried out with acetoxymethyl benzylether (1.8 g, 10 mmol). After purification by column chromatography using a gradient of 0 to 90 % methanol in dichloromethane as eluent, the pure 8 was separated in 16% yield (450 mg as a white crystalline solid, TLC CH_2Cl_2:CH_3OH 98:2 Rf = 0.80) mp : 150°C; IR (KBr) cm^{-1} : 1690-1640 (CO), 1470, 1410, 1070, 740; ^1H NMR (DMSO-d_6) : δ 4.59 (s, 2H, OCH_2benzyl), 5.51 (s, 2H, NCH_2), 7.29 (5H, benzyl H), 8.14 (d, 1H, H-6, J =5.4 Hz), 11.55 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 70.0 (OCH_2benzyl), 73.5 (NCH_2), 112.8 (C-4a), 117.8 (C-7), 127.4-128.0-137.4 (benzyl C), 135.5 (C-6), 146.4 (C-7a), 151.4 (C-2), 158.0 (C-4); UV λ_{max} (log ε) : 295 (3.92) (pH 1, HCl), 295 (3.97) (pH 7, H_2O), 296 (3.81) (pH 14, NaOH), MS m/z=288; Anal. Cald. For $C_{14}H_{12}N_2O_3S$ (288.3) : C, 58.32 ; H, 4.19 ; S, 11.12 Found : C, 58.10 ; H, 4.27 ; S, 10.92.

3-(benzyloxymethyl)-thieno[3,2-*d*]pyrimidine-2,4-dione (9) (white crystalline solid-3.5%-TLC CH_2Cl_2:CH_3OH 98:2 Rf = 0.70) mp : 224°C; IR (KBr) cm^{-1} : 1660-1610 (CO), 1400, 1060, 760, 670; ^1H NMR (DMSO-d_6) : δ 4.62 (s, 2H, OCH_2benzyl), 5.40 (s, 2H, NCH_2), 6.92 (d, 1H, H-7, J=4.9 Hz), 7.31 (5H, benzyl H), 8.10 (d, 1H, H-6), 11.90 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 69.6 (OCH_2benzyl), 70.7 (NCH_2), 111.1 (C-4a), 117.0 (C-7), 127.2-127.9-137.2 (benzyl C), 136.6 (C-6), 145.1 (C-7a), 151.1 (C-2), 169.5 (C-4); UV λ_{max} (log ε) : 299 (3.79) (pH 1, HCl), 299 (3.80) (pH 7, H_2O), 330 (3.75) (pH 14, NaOH), MS m/z=288; Anal. Cald. For $C_{14}H_{12}N_2O_3S$ (288.3) : C, 58.32 ; H, 4.19 ; S, 11.12 Found : C, 58.24 ; H, 4.12 ; S, 11.16.

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