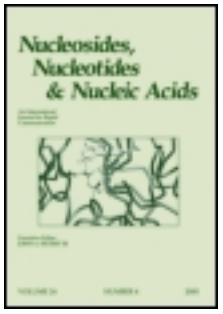

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Synthesis and Antiviral Study of Dihydrothieno and Thianopyrimidine Diones Acyclic Nucleosides As Potential Anti-HIV Agents

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SYNTHESIS AND ANTIVIRAL STUDY OF DIHYDROTHIENO AND THIANOPYRIMIDINE DIONES ACYCLIC NUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS.

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ABSTRACT :

Acyclic nucleosides were prepared by alkylation of dihydrothieno and thianopyrimidines diones following Vorbruggen and Niedballa's method.(1)

None of these HEPT analogues showed significant activity against Human Immunodeficiency Virus-1 (HIV-1).

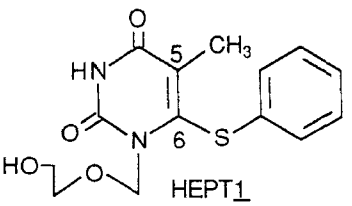
INTRODUCTION :

Despite the clinical efficacy of 3'-azido-3'-deoxythimidine (AZT) and 2',3'-dideoxyinosine (DDI) on Acquired Immuno Deficiency Syndrome (AIDS), long term administration of these compounds leads to toxic side effects (2,3). Furthermore, prolonged AZT treatment often ends in the emergence of resistant HIV-1 strains (4). Therefore there is a relevant need to find new anti HIV agents having low toxicity and preferably different site of action.

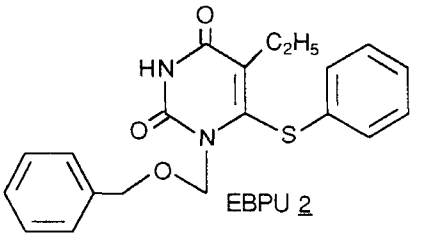
The 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio) thymine (HEPT 1), a lead compound with high selectivity for the HIV-1 reverse transcriptase has been synthesized (5). This compound, whose triphosphate derivative does not interact with reverse transcriptase, shows the presence of an hydrophilic region (a part of the pyrimidine) and an hydrophobic region (the phenylthio group at the 6 position of the pyrimidine), which seem to be important determinants for the anti HIV-1 activity(6).

As for C5 modifications, the replacement of the 5-methyl group in HEPT by an ethyl enhanced activity. Moreover, HEPT derivatives as EBPU 2 did not require an hydroxyl group since its replacement by a substituent without an hydroxyl group in acyclo moiety of HEPT has been shown to improve the activity[7].

In this article, we report the synthesis and biological evaluation of HEPT related compounds. In order to increase the lipophilicity of both the C5 and C6 positions of the uracil moiety, which works cooperatively in terms of anti HIV-1 activity, an hydrogenated ring as dihydrothiophene or thiane was fused on the *d* bond of uracil.



HEPT1



EBPU 2

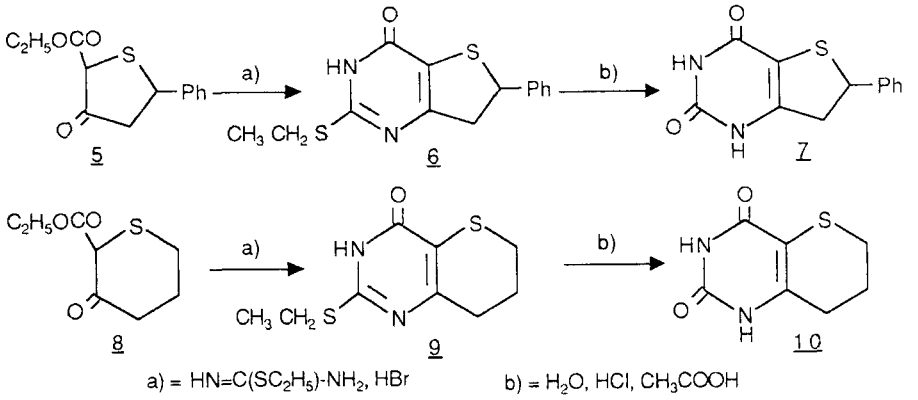
CHEMISTRY:

Our general strategy for the synthesis of the new HEPT analogues was based on a direct alkylation of silylated heterocycles following Vorbruggen and Niedballa's procedure [1].

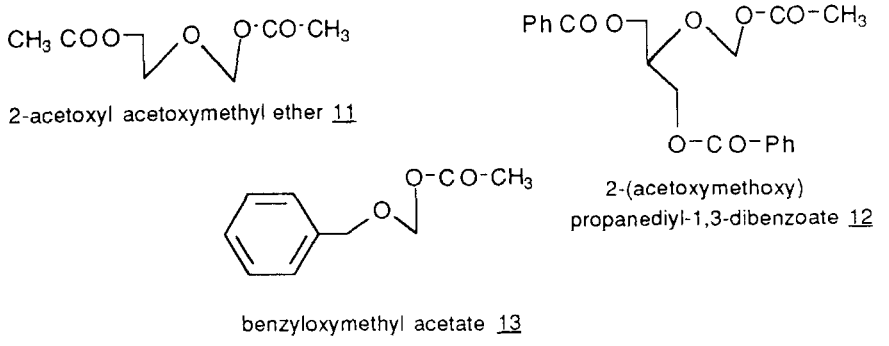
The heterocyclic derivatives 3 and 4 (Scheme III) were prepared by cyclization of 2-amino-4-phenyl-4,5-dihydrothiophene-3-carboxamide [8,9] or 2-amino-4,5-dihydrothiophene-3-carboxamide[8,9], using ethyl chloroformate then treatment in alkaline medium. The cyclisation between ethyl-3-oxo-5-phenyltetrahydrothiophene-2-carboxylate 5, on one hand, ethyl-3-oxothiane-2-carboxylate 8 [10,11] on the other hand with S-ethylthiourea hydrobromide[12] yielded the intermediate compounds 6 and 9, whose acidic hydrolysis led to 7 and 10 (Scheme I).

The silylated derivatives of the compounds 3 ,4, 7 and 10, resulting from the silylation with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulphate, were subjected to reaction with the various alkyl acetoxymethyl ethers : 2- acetoxyethyl acetoxymethyl ether 11 [13], 2-(acetoxymethoxy) propanediyl-1,3-dibenzoate 12 [14] and benzyloxymethyl acetate 13 (Scheme II).

These reactions were carried out in dry 1,2-dichloroethane with tin (IV) chloride as a catalyst. This general procedure gave acceptable yields for most of our protected derivatives except for 21. The protected form of this latter was obtained by a different procedure: the silylated heterocyclic derivative 10 dissolved in dry acetonitrile was added to a mixture of 2-acetoxyethyl acetoxymethyl ether 11 in the presence of sodium iodide, molecular sieves and chlorotrimethylsilane instead of tin (IV) chloride[15]. In spite of this, the reaction yield remained very low (5%).



SCHEME I



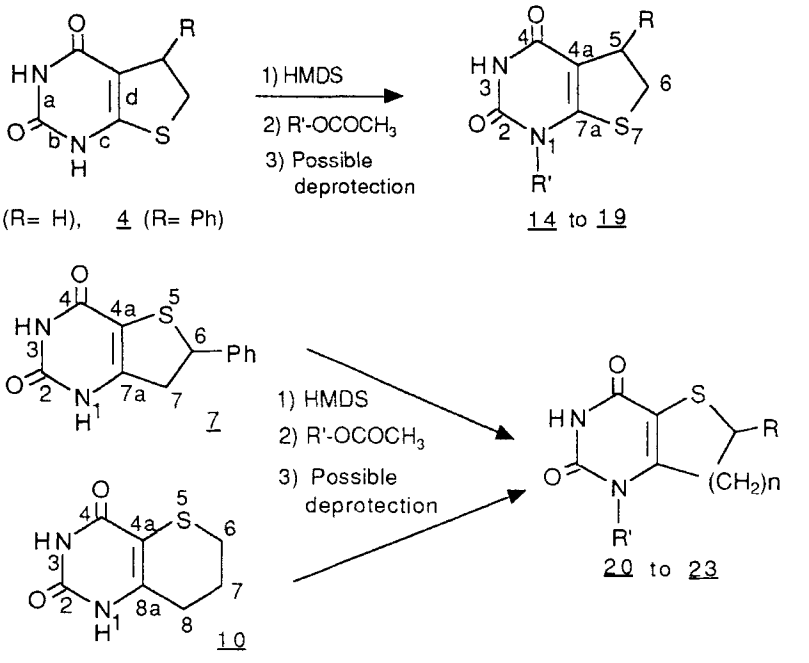
SCHEME II

The unprotected compounds 14, 17 and 21 were obtained after removal of the acetate group with methanolic ammonia followed by a column chromatography.

Alkylation of the pyrimidine heterocycles with (acetoxymethoxy) propanediyl-1,3-dibenzoate 12, followed by deprotection and purification by the same procedures, furnished the free acyclo nucleosides 15, 18 and 22.

The compounds 16, 19, 20 and 23, analogues of EBPU 2, were obtained by the same procedure of alkylation but did not require any deprotection.

All the synthesized compounds were fully characterized using usual analytical methods as ^{1}H-NMR, ^{13}C-NMR and IR spectra on one hand, and UV spectra for the alkylation site on the other hand.



	R	R'
14	H	$-CH_2O(CH_2)_2OH$
15	H	$-CH_2OCH(CH_2OH)_2$
16	H	$-CH_2OCH_2Ph$
17	Ph	$-CH_2O(CH_2)_2OH$
18	Ph	$-CH_2OCH(CH_2OH)_2$
19	Ph	$-CH_2OCH_2Ph$

	R	n	R'
20	Ph	1	$-CH_2OCH_2Ph$
21	H	2	$-CH_2O(CH_2)_2OH$
22	H	2	$-CH_2OCH(CH_2OH)_2$
23	H	2	$-CH_2OCH_2Ph$

SCHEME III

Fox and Shugar[16] compared UV spectra of 1- and 3-methyl uracil with those of 1-glycosil uracil and pointed out the close similarity of 1-methyl uracil and 1-glycosyl uracil UV spectra. They stated that 1- and 3-methyl uracil showed identical UV spectra in a neutral medium while their spectra were clearly different in an alkaline solution. Thus, unlike 1-methyl uracil, 3-methyl uracil was likely to take anionoid lactim form, in alkaline medium, resulting in a bathochromic effect due to an extension of the conjugated system.

UV spectra of our compounds at pH1, 7 and 11 showed no bathochromic effect, leading us to conclude that these were N1 alkylated for all heterocyclic compound.

ANTIVIRAL EVALUATION :

These compounds were tested in cells cultures in comparison with AZT both for their toxicity and their ability to inhibit the cytopathic effect[17] induced by HIV-1 infection. The CEM cl 13, a subclone enriched in CD_4 receptors, was treated with each compound dilution (0 to 30 µg/ml) or PBS alone and incubated for 1hr at 37°C. Cells were then infected with a virus suspension (LAV-Bru strain of HIV-1) and cultured for at least 7 days. Mock-infected cultures were carried out in parallel to determine the cytotoxicity of the compounds. Cells viability was then evaluated by MTT method[18].

Unfortunately, none of these showed any significant activity. The phenylthio group in HEPT is out of plane with the uracil ring. This conformation may be a contributory factor in an efficient hydrophobic interaction with reverse transcriptase whereas the conformation of our compounds, which possess an hydrogenated ring instead of two lipophilic groups on C5 and C6 positions, was too different and could not permit a good interaction with reverse transcriptase.

EXPERIMENTAL SECTION :

Melting points were determinated with a Kofler apparatus and are uncorrected. IR spectra were recorded on a SP3 Pye Unicam spectrometer (Philips). ^{13}C-NMR and ^{1}H-NMR at 200 MHz, were obtained on a Jeol FX 200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as an internal standard. UV spectra were recorded on a SECOMAM S 1000 G spectrometer. TLC was performed on precoated silicagel plates (60 F 254, Merck) and column chromatography was carried out on silicagel 60 (Merck). The compounds were analysed for C, H, N and S. The results were within 0,4% of the calculated theoretical values.

1*H*,3*H*-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 3.

To a stirred suspension of 2-amino-4,5-dihydrothiophene-3-carboxamide (13g; 0,09mol) and dry pyridine (0,1mol) in 1,4-dioxane (100ml), ethyl chloroformate (10,8g; 0,1mol) was added dropwise. The reactional mixture was heated under reflux with stirring for 1hr. The solvent was evaporated under reduced pressure and the residue poured into ice-water. The precipitate was dissolved in a hot 5% potassium hydroxide solution. After filtration of insoluble material, the solution was adjusted to pH1 with concentrated aqueous hydrochloride solution. The resulting precipitate was collected and washed with water then with diethyl oxide to yield 12g (70%) mp>260°C. IR (KBr) cm^{-1}: 3500 (NH) 1700 to 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,89 (t, 2H, H5, J = 8,2Hz) 3,42 (t, 2H, H6, J = 8,2Hz). ^{13}C-NMR (DMSO-$_{d6}$) δ 29,20 (C5) 31,77 (C6) 105,52 (C4a) 151,31 (C7a) 156,02 (C2) 159,48 (C4).

1*H*,3*H*-5-phenyl-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 4 was obtained from 2-amino-4-phenyl-4,5-dihydrothiophene-3-carboxamide (19,8g; 0,09mol) by the same procedure as 3 to yield

16g (73%) mp>260°C. IR (KBr) cm^{-1} : 3480 (NH) 1700 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,16 (dd, 1H, H6, *J* gem =11Hz, *J* trans =1Hz) 3,99 (dd, 1H, H6, *J* gem#*J* cis =11Hz) 4,48 (dd, 1H, H5, *J* cis=10Hz, *J* trans=1Hz) 7,25 (m, 5H, Ph). ^{13}C-NMR (DMSO-$_{d6}$) δ 46,71 (C6) 52,38 (C5) 108,38 (C4a) 126,66-128,30-142,37 (Ph) 151,42 (C7a) 157,15 (C2) 159,19 (C4).

3*H*-2-ethylthio-6-phenyl-6,7-dihydrothieno [3,2-*d*] pyrimidin-4-one 6 .

To a suspension of S-ethylthiourea hydrobromide (87g; 0,47mol) and sodium carbonate (50g; 0,47mol) in water (50ml) was added dropwise 3-oxo-5-phenyl tetrahydrothiophen-2-ethyl carboxylate 5 (59g; 0,23mol). This suspension was stirred at room temperature for 18hr. The resulting precipitate was collected and washed with water. 45g (65%) mp=210°C. IR (KBr) cm^{-1}: 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 1,28 (t, 3H, CH_3, *J* =7Hz) 3,10 (q, 2H, -S-CH_2-, *J* =7Hz) 3,39 (m, 1H, H7) 3,55 (m, 1H, H7) 5,11 (t, 1H, H6).

1*H*,3*H*-6-phenyl-6,7-dihydrothieno [3,2-*d*] pyrimidine-2,4-dione 7.

The suspension of the previous compound 6 (44,5g; 0,15mol) in a mixture of water (500ml), concentrated HCl (50ml) and acetic acid (100ml) was refluxed for 50hr. After cooling, the precipitate was collected and washed with water to yield 11g (30%) mp>260°C. IR (KBr) cm^{-1}: 1710 and 1630 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,27 (dd, 1H, H7) 3,42 (dd, 1H, H7) 5,13 (t, 1H, H6) 7,39 (m, 5H, Ph) 11,23 (s, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 41,69 (C7) 48,58 (C6) 106,75 (C4a) 126,95-127,60-128,53-140,91 (Ph) 147,51 (C7a) 151,31 (C2) 159,07 (C4).

3*H*-2-ethylthio thiano [3,2-*d*] pyrimidin-4-one 9 was obtained from 3-oxothian-2-ethyl carboxylate 8 (39g; 0,2mol) by the same procedure as 6 to yield 42,5g (90%) mp=225°C. IR (KBr) cm^{-1}: 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 1,25 (m, 3H, CH_3) 1,97-2,55-2,83-3,00 (m, 2H, CH_2).

1*H*,3*H*-Thiano [3,2-*d*] pyrimidine-2,4-dione 10.

Acidic hydrolysis was similar to the one used for the preparation of 7 and furnished 17,5g (50%) mp>260°C. IR (KBr) cm^{-1}: 1700 and 1650 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 1,96-2,42-2,83 (m,3x 2H, CH_2) 11,01 (m, 1H, NH).

^{13}C-NMR (DMSO-$_{d6}$) δ 21,89 (C7) 24,93-25,16 (C6-C8) 102,95 (C4a) 143,42 (C8a) 149,79 (C2) 161,76 (C4).

Benzyloxymethyl acetate 13. Benzyl alcohol (27g; 0,25mol), dimethoxymethane (28,5g; 0,375mol) and phosphorus pentoxide (50g) were stirred vigorously for 24hr at room temperature in dry chloroform and then hydrolysed with ice-water. The organic phase was washed with aqueous

sodium hydrogen carbonate solution, dried over $MgSO_4$ and concentrated under reduced pressure. Then boron trifluoride in ether (0,075mol) was added dropwise to the cooled solution (-20°C) of the residue in diethyl ether (50ml) and acetic anhydride (35ml; 0,35mol). The solution was stirred at 4°C for 6hr and concentrated. The distillation under reduced pressure (90-100°C/4mm Hg) furnished 15g (35%) IR (KBr) cm^{-1}: 1720 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,02 (s, 3H, CH_3) 4,66 (s, 2H, CH_2) 5,31 (s, 2H, CH_2) 7,31 (m, 5H, Ph).

1*H*,3*H*-1-[(2-hydroxyethoxy) methyl]-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 14.

A mixture of 3 (1,7g; 0,01mol) and ammonium sulphate (10mg) in HMDS (40ml) was stirred and heated under reflux for 3hr. HMDS in excess was evaporated under reduced pressure. A solution of 2-acetoxyethyl acetoxymethyl ether 11 (1,76g; 0,01mol) in dry 1,2-dichloroethane (50ml) and tin (IV) chloride were added to the residue of silylated heterocycle. Then, the solution was stirred at room temperature for 18hr. After addition of pyridine (1ml), the inorganic materials were filtered and the filtrate was diluted with chloroform (50ml). The resulting organic layer was washed with a saturated solution of sodium hydrogen carbonate then with brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue of protected nucleoside was dissolved in methanol, then the solution was saturated with ammonia. After evaporation under reduced pressure, a silicagel chromatography (CH_2Cl_2:CH_3OH 90/10) afforded the deprotected nucleoside 14.

0,8g (33%) mp=215°C. IR (KBr) cm^{-1}: 3500 to 3200 (OH, NH) 1720 to 1650 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,97 (t, 2H, H5, *J* =8,3Hz) 3,35 (m, 2H, H6) 3,49 (m, 4H, HO-$\underline{CH_2}$-$\underline{CH_2}$-) 4,60 (m, 1H, OH) 5,12 (s, 2H, -O-CH_2-N) 11,18 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 30,13 (C5) 32,23 (C6) 59,85 (HO-CH_2-) 70,72 (-CH_2-$\underline{C}H_2$-O-) 76,32 (-O-CH_2-N) 107,39 (C4a) 151,31 (C7a) 157,79-158,49 (C2-C4). UV λmax (nm) 224,1-301,8 (pH7) 224,1-301,8 (pH1) 218,1-297,0 (pH11).

1*H*,3*H*-1-[(1,3-dihydroxy-2-propoxy)methyl]-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 15 was prepared from 2-(acetoxymethoxy)-propanediyl-1,3-dibenzoate 12 (3,72g; 0,01mol) and 3 (1,70g; 0,01mol) by the same procedure as 14 to yield, after a silicagel chromatography (CH_2Cl_2:CH_3OH 90/10), 1,1g (35%) mp=155°C.

IR (KBr) cm^{-1}: 3400 (OH) 3150 (NH). 1650 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,96 (m, 2H, H5) 3,40 (m, 7H, H6 -$\underline{CH}(\underline{CH_2}OH)_2$) 4,60 (1H, OH) 5,20 (s, 2H,-O-CH_2-N).^{13}C-NMR (DMSO-$_{d6}$) δ 30,13 (C5) 32,23 (C6) 60,79 (-CH($\underline{C}H_2OH)_2$) 75,91 (-$\underline{C}H(CH_2OH)_2$) 80,88 (-O-CH_2-N) 107,21 (C4a) 151,25 (C7a) 157,96-158,55 (C2-C4). UV λmax (nm) 224,1-301,9 (pH7) 224,2-301,8 (pH1) 216,1-296,8 (pH11).

1*H*,3*H*-1-[(benzyloxy)methyl]-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 16 was prepared from 13 (1,8g; 0,01mol) and 3 (1,70g; 0,01mol) by the same procedure as 14 to yield 1,2g (41%)

mp=160°C. IR (KBr) cm^{-1}: 1700 and 1630 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,15 (t, 2H, H5, *J* =8Hz) 3,45 (t, 2H, H6, *J* =8Hz) 4,64 (s, 2H,-O-$\underline{CH_2}$-Ph) 5,32 (s, 2H, -O-CH_2-N) 7,34 (m, 5H, Ph) 9,30 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 30,48 (C5) 33,11 (C6) 71,71 (-O-$\underline{C}H_2$-Ph) 76,03 (-O-CH_2-N) 108,21 (C4a) 127,83-128,06-128,41-136,82 (Ph) 151,48 (C7a) 158,72-159,42 (C2-C4). UV λmax (nm) 216,1-302,6 (pH7) 216,1-302,2 (pH1) 214,7-300,2 (pH11).

1*H*,3*H*-1-[(2-hydroxyethoxy)methyl]-5-phenyl-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 17 was obtained from 4 (2,46g; 0,01mol) and 2-acetoxyethyl acetoxymethyl ether 11 (1,76g; 0,01mol) by the same procedure as 14 to yield after silicagel chromatography (CH_2Cl_2:CH_3OH 95/5) 0,47g (15%) mp=150°C. IR (KBr) cm^{-1}: 3600 to 3200 (OH, NH) 1700 to 1630 (CO). ^{1}H-NMR ($CDCl_3$) δ 3,15 (m, 1H, H6) 3,30 (m, 1H) 3,74 (m, 4H, HO-$\underline{CH_2}$-$\underline{CH_2}$-) 3,99 (t, 1H, H6, *J* =10,5Hz) 4,63 (m 1H, H5) 5,38 (m, 3H, -O-CH_2-N, OH) 7,30 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) δ 41,17-48,58-61,61- (CH_2) 71,07 (-O-CH_2-N) 11,30 (C4a) 126,84-127,19-128,88-141,14 (Ph) 151,84 (C7a) 157,96-159,48 (C2-C4). UV λmax (nm) 223,7-301,9 (pH7) 223,6-301,9 (pH1) 215,8-298,5 (pH11).

1*H*,3*H*-1-[(1,3-dihydroxy-2-propoxy)methyl]-5-phenyl-5,6-dihydrothieno [2,3-*d*] pyrimidine-2,4-dione 18 was obtained from 4 (2,46g; 0,01mol) and 2-(acetoxymethoxy) propanediyl-1,3-dibenzoate 12 (3,72g; 0,01mol) by the same procedure as 14 to yield, after a silicagel chromatography (CH_2Cl_2:CH_3OH 95/5) 0,48g (15%). mp=204°C.
IR (KBr) cm^{-1}: 3600 to 3200 (OH) 1680 and 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,22 (m, 1H, H6) 3,40 (m, 4H,-CH($\underline{CH_2}$OH)$_2$) 4,01 (t, 1H, H6, *J* =9,8Hz) 4,52 (m, 1H, H5) 4,64 (m, 2H, OH) 5,13 (d, 1H, -O-CH_2-N, *J* =10,7Hz) 5,43 (d, 1H, -O-CH_2-N, *J* =10,7Hz) 7,28 (m, 5H, Ph) 11,16 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 47,36 (C6) 60,79 (C5) 61,02 (-CH($\underline{C}H_2$OH)$_2$) 75,91 (-$\underline{C}$H(CH_2OH)$_2$) 81,05 -O-CH_2-N) 109,30 (C4a) 128,35-129,00-141,90 (Ph) 151,31 (C7a) 158,25-159,31 (C2-C4). UV λmax (nm): 223,8-301,3 (pH7) 223,8-301,2 (pH1) 214,1-296,3 (pH11).

1*H*,3*H*-1-[(benzyloxy)methyl]-5-phenyl-5,6-dihydrothieno [2,3-*d*] pyrimidine2,4-dione 19 was prepared from 13 (1,8g; 0,01mol) and 4 (2,46g; 0,01mol) by the same procedure as 14 to yield, after a silicagel chromatography (CH_2Cl_2:CH_3OH 95/5) 1,2g (33%). mp=185°C. IR (KBr) cm^{-1}: 1680 and 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,23 (m, 1H, H6) 4,01 (t, 1H, H6, *J* =10,2Hz) 4,59 (m, 1H, H5) 4,62 (s, 2H, -O-$\underline{CH_2}$-Ph) 5,17 (d, 1H, -O-CH_2-N, *J* =11,2Hz) 5,37 (d, 1H, -O-CH_2-N, *J* =11,2Hz) 7,26-7,34 (m, 10H, Ph) 11,21 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 47,36 (C6) 52,50 (C5) 70,54 (-O-$\underline{C}H_2$-Ph) 75,85 (-O-CH_2-N) 110,08 (C4a) 126,66-127,54-128,12-

128,35-128,71-137,35-141,79 (Ph) 151,31 (C4a) 158,14-158,90 (C2-C4). UV λmax (nm) 211,7-223,9-300,2 (pH7) 211,6-224,0-300,2 (pH1) 214,9-295,8 (pH11).

1*H*,3*H*-1-[(benzyloxy)methyl]-6-phenyl-6,7-dihydrothieno [3,2-*d*] pyrimidine-2,4-dione 20 was prepared from 7 (2,46g; 0.01mol) and 13 (1.8g; 0.01mol) by the same procedure as 14 to yield 0,75g (20%) mp=215°C. IR (KBr) cm^{-1}: 3120 (NH) 1690 and 1620 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 3,55 (dd, 1H, H7) 3,74 (dd, 1H, H7) 4,57 (s, 2H, -O-$\underline{CH_2}$-Ph) 5,12 (m, 1H, H6) 5,22 (d, 1H,-O-CH_2-N, *J* =11Hz) 5,35 (d, 1H,-O-CH_2-N, *J* =11Hz) 7,30 (m, 10H, Ph) 11,57 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 41,81 (C7) 47,82 (C6) 70,19 (-O-$\underline{C}H_2$-Ph) 73,75 (-O-CH_2-N) 109,61 (C4a) 126,89-127,60-128,12-128,83-137,35-141,38 (Ph) 147,16 (C7a) 151,60 (C2) 158,14 (C4). UV λmax (nm): 212,4-328,9 (pH7) 212,3-327,6 (pH1) 214,2-319,7 (pH11).

1*H*,3*H*-1-[(2-hydroxy ethoxy)methyl]-thiano [3,2-*d*] pyrimidine-2,4-dione 21.

A mixture of NaI (3,95g; 0,026mol) and chlorotrimethylsilane (2,82g; 0,026mol) was stirred with molecular sieves 4Å (0,40g) in dry acetonitrile (30ml) for 5 min. A solution of 2-acetoxyethyl acetoxymethyl ether 11 (1,76g; 0,01mol) in dry acetonitrile (30ml) was added. The mixture was stirred for 30 min. Then, a solution of the silylated heterocycle 10 (0,01mol), obtained by the same procedure as previously, in dry acetonitrile (30ml) was added. The mixture was stirred at room temperature for 3hr, then filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (100ml) and washed with saturated solutions of $NaHCO_3$, sodium thiosulphate and then with water. The solution was dried over $MgSO_4$, filtered and concentrated to dryness.The deprotection was carried out in methanol saturated with ammonia. The crude product was purified by a silicagel chromatography (CH_2Cl_2:CH_3OH 90/10) to afford 19. 0,28g (5%). mp=210°C. IR (KBr) cm^{-1}: 3420 (OH) 3150 (NH) 1680 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 2,03 (m, 2H, H7) 2,78 (m, 4H, H6-H8) 3,48 (m, 4H,-O-$\underline{CH_2}$-$\underline{CH_2}$-OH) 4,60 (s, 1H, OH) 5,29 (m, 2H, -O-$\underline{CH_2}$-N) 9,60 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 22,60 (C7) 23,82-24,17 (C6-C8) 59,91 (HO-$\underline{C}H_2$-CH_2-) 70,19 (HO-CH_2-$\underline{C}H_2$-) 71,83 (-O-$\underline{C}H_2$-N) 106,46 (C4a) 144,06 (C8a) 150,43 (C2) 160,53 (C4). UV λmax (nm): 229,9-316,1 (pH7) 230,0-315,8 (pH1) 212,3-306,7 (pH11).

1*H*,3*H*-1-[(1,3-dihydroxy-2-propoxy)methyl]-thiano [3,2-*d*] pyrimidine-2,4-dione 22 was obtained from 10 (1,84g; 0,01mol) and 2-(acetoxymethoxy)-propanediyl-1,3-dibenzoate 12 (3,72g; 0,01mol) by the same procedure as 14 to yield after a silicagel chromatography (CH_2Cl_2:CH_3OH 85/15) 0,52g (20%). mp=210°C. IR (KBr) cm^{-1}: 3450 (OH) 1690-1640 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,03 (m, 2H, H7) 2,81 (m, 4H, H6-H8) 3,33 (m, 5H, -$\underline{CH}(\underline{CH_2}OH)_2$) 4,59 (m, 2H, OH)

5,36 (m, 2H, O-CH_2-N) 11,53 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 21,89 (C7) 24,93-25,16 (C6-C8) 60,79 -CH($\underline{C}H_2OH)_2$) 71,30 (-$\underline{C}H(CH_2OH)_2$) 80,06 (-O-CH_2-N) 106,22 (C4a) 144,36 (C8a) 150,43 (C2) 160,59 (C4). UV λmax (nm): 230,2-315,8 (pH7) 230,2-315,8 (pH1) 214,2-306,6 (pH11).

1*H*,3*H*-1-[(benzyloxy)methyl]-thiano [3,2-*d*] pyrimidine-2,4-dione 23 was prepared from 10 (1,84g; 0,01mol) and 13 (1,8g; 0,01mol) by the same procedure as 14 to yield after a silicagel chromatography (CH_2Cl_2:CH_3OH 95/5) 1,4g (46%) mp=170°C. IR (KBr) cm^{-1}: 3150 (NH) 1700-1650 (CO). ^{1}H-NMR (DMSO-$_{d6}$) δ 2,03 (m, 2H, H7) 2,78 (m, 4H, H6-H8) 4,57 (s, 2H, -O-$\underline{CH_2}$-Ph) 5,38 (s, 2H, -O-CH_2-N) 7,32 (m, 5H, Ph) 11,60 (m, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 22,60 (C7) 23,94-24,17 (C6-C8) 70,19 (-O-$\underline{C}H_2$-Ph) 71,59 (-O-CH_2-N) 106,69 (C4a) 127,48-128,12-137,58 (Ph) 143,66 (C8a) 150,49 (C2) 160,47 (C4). UV λmax (nm): 230,2-315,8 (pH7) 230,15-315,8 (pH1) 214,2-306,7 (pH11).

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REFERENCES

1. a) U. Niedballa and H. Vorbruggen, Angew. Chem. Internat. Ed., 9, 461 (1970).
   b) U. Niedballa and H. Vorbruggen, J. Org. Chem., 39, 3654 (1974).
   c) U. Niedballa and H. Vorbruggen, J. Org. Chem., 41, 2084 (1976).
2. H. Mitsuya, K.J. Weingold, P.A. Furman, M.H. Saint Clair, S.N. Lehrman, R.C. Gallo, D.P. Bolognesi, D.W. Barry and S. Broder, Proc. Natl. Acad. Sci. (USA), 82, 7096 (1985).
3. D.D. Richman, M.A. Fischl, M.H. Grieco, M.S. Gottlieb, P.A. Volberding, O.L. Laskin, J.M. Leedom, J.E. Groopman, D. Mildvan, M.S. Hirsch, G.G. Jackson, D.T. Durack, N.S. Lehrman and the AZT Collaborative Working Group, N. Engl. J. Med., 317,192 (1987).
4. B.A. Larder, G.Darby, D.V. Richman, Science (Washington, D.C.), 243, 1731 (1989).
5. T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R.T. Walker, J. Balzarini and E. De Clercq, J. Med. Chem., 32, 2507 (1989).
6. E. De Clercq, Trends Pharmacol. Sci.(TIPS), 11, 198 (1990).
7. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. baba, S. Shigeta, R.T. Walker, E. De Clercq and T. Miyasaka, J. Med. Chem., 35, 4713, (1992).
8. T. Matsuda, K. Yamagata, Y. Tomioka, M. Yamazaki, Chem. Pharm. Bull., 33, 937 (1985)
9. H. Maruska, K. Yamagata, M. Yamazaki, Heterocycles, 31, 2011 (1990).

10. A.R. Surrey, H.F. Hammer and C.M. Suter, J. Am. Chem. Soc., 66, 1933 (1944).
11. F. Duus, Tetrahedron, 37, 2633 (1981).
12. Organic Syntheses, Collective Volume 3, 440.
13. A. Rosowsky, S. Hyrik Kim and M. Wick, J. Med. Chem., 24, 1177 (1981).
14. L. Beauchamp, B.L. Serling, J.E. Kelsey, K.K. Biron, P.Collins, J. Selway, J.C. Lin and H.J. Schaeffer, J. Med. Chem., 31, 144 (1988).
15. A. Matsuda, Y. Kurasawa and K.A. Watanabe, Synthesis, 748 (1981).
16. a) J.J. Fox and S. Shugar, Biochimica and Biophysica Acta, 9, 369 (1952).
b) J.J. Fox and S. Shugar, Biochimica and Biophysica Acta, 9, 199 (1952).
c) M. Sano, Chem. Pharm. Bull., 10, 320 (1962).
17. M. Lemaitre and A. Zerial, Revue Française des laboratoires, n°216 (1990).
18. T. Mosmann, J. Immunol. Methods, 65, 55 (1983).

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