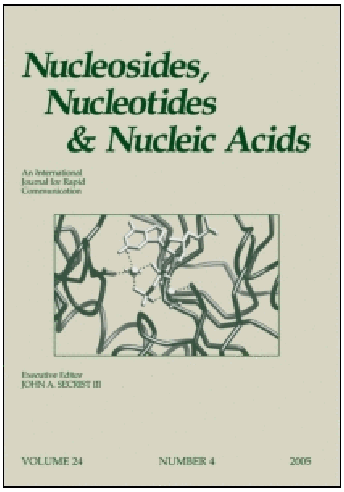

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Synthesis and Antiviral Study of Cyclopentano [*d*] Pyrimidine-2,4-diones and Octahydroquinazoline-2,4-diones Acyclic Nucleosides as Potential Anti-HIV Agents

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SYNTHESIS AND ANTIVIRAL STUDY OF CYCLOPENTANO [*d*] PYRIMIDINE-2,4-DIONES AND OCTAHYDROQUINAZOLINE-2,4-DIONES ACYCLIC NUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS.

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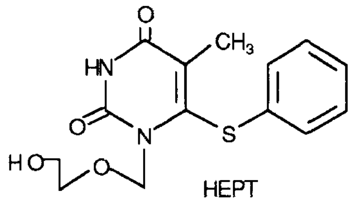
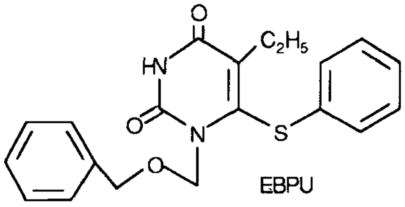
ABSTRACT :

The Vorbruggen and Niedballa's method(1) afforded new cyclopentano [*d*] pyrimidine-2,4-dione and octahydroquinazoline-2,4-dione nucleosides. Various modifications of these new derivatives enabled us to obtain HEPT related compounds which were tested against Human Immunodeficiency Virus-1 (HIV-1). Unfortunately, none of these compounds showed significant antiviral activity.

INTRODUCTION :

Among the various steps in the replicative cycle of HIV, the Reverse Transcriptase has been identified as a prime target for the treatment of Acquired Immunodeficiency Syndrome (AIDS)(2). A few nucleosides like 3'-azido-3'-deoxythimidine (AZT)(3) or 2',3'-dideoxyinosine (DDI)(4) present a clinical efficiency but their toxicity (5,6) prompted researchers to find new anti HIV agents. Acyclic nucleoside derivatives like the 1-[(2-hydroxyethoxy)-methyl)]-6-(phenylthio)-thymine (HEPT) or 5-ethyl-1-[(benzyloxy)-methyl]-6-(phenylthio)-uracil (EBPU) have been synthesized(7,8).


HEPT


EBPU

The HEPT presents a potent and selective activity against HIV-1 Reverse Transcriptase whereas its triphosphate derivative does not interact with this enzyme(9) and the presence of an acyclic chain with an intact free hydroxy function is not necessary for antiviral activity. These compounds and their numerous analogues show the presence of lipophilic groups on the C5 and C6 positions of the uracil which work cooperatively in terms of anti HIV-1 activity.

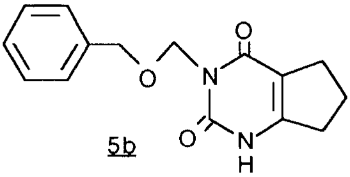
In this communication, we report the synthesis and antiviral evaluation of HEPT related compounds. These acyclic nucleosides present a lipophilic region constituted by a cyclopentane or a cyclohexane fused on the *d* side of the uracil ring. In order to increase the lipophilicity, 4-thioxo derivatives and 4-S-methyl derivatives were also synthesized.

The N1 position was alkylated by acyclic ethers that are found in HEPT and EBPU. The replacement of the hydroxy group by a benzyloxy group not only increases the lipophilicity but also prevents the phosporylation. Azido group instead of hydroxy group in the acyclic portion of the compounds 10 and 12 gave access to 13 and 14 which can not be phosphorylated.

CHEMISTRY :

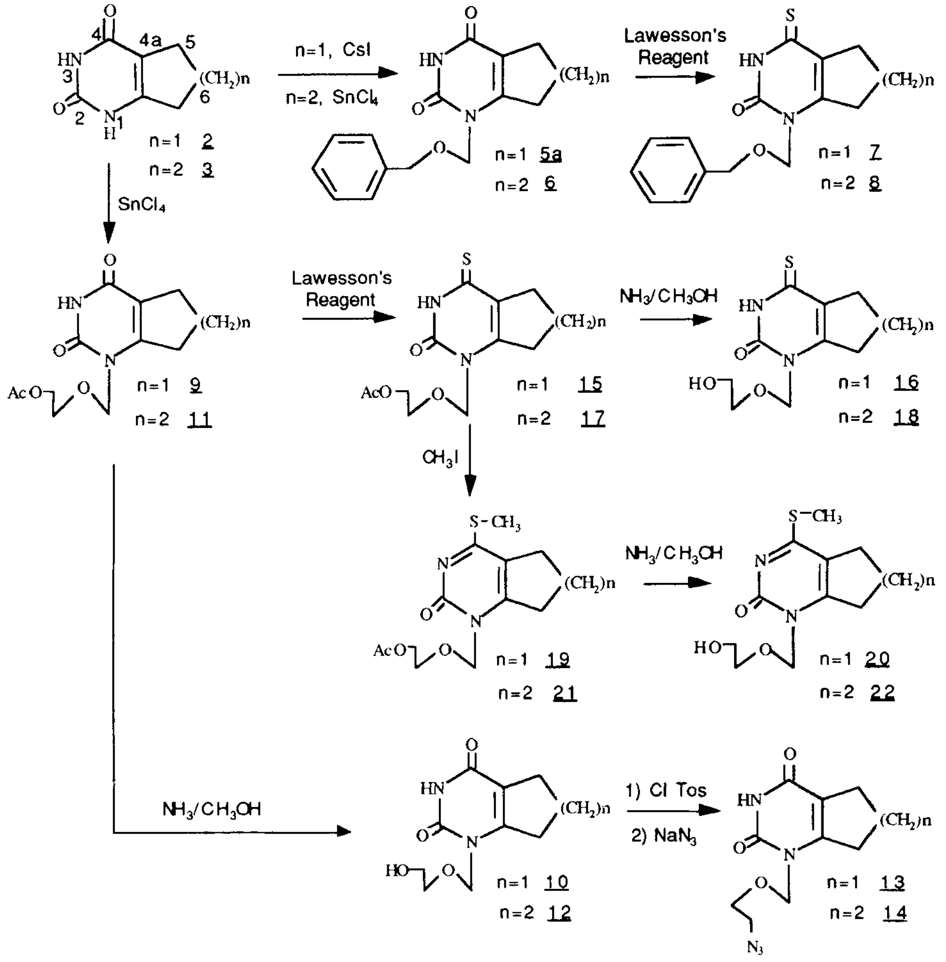
The heterocycles 2 and 3 were prepared by the reaction of ethyl-2-oxocyclopentane carboxylate or ethyl-2-oxocyclohexane carboxylate with S-ethylthiourea(10) to furnish 2-ethylthiocyclopentano [*d*] pyrimidin-4-one and 2-ethylthio-3,4,5,6,7,8-hexahydroquinazolin-4-one. Their final acidic hydrolysis yielded the compounds 2 and 3. The compound 2 was hydrolysed in acidic medium by refluxing during 50 hours. This procedure was replaced for 3 by the use of microwave energy (2 hr) with a better yield.

Their bis(trimethylsilyl) derivatives, resulting from the reaction with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulphate, were respectively subjected to reaction with 2-acetoxyethyl acetoxymethyl ether(11) and benzyloxymethyl acetate 4. These reactions, carried out in dry 1,2-dichloroethane with Tin (IV) chloride as a catalyst, furnished N1 protected nucleosides with an acceptable yield (40 to 70%) except for the reaction of the heterocycle 2 with the acetate 4: in this case, we only obtained the N3 substituted acyclic nucleoside 5b (revealed by the study of its UV spectra).



5b

In order to obtain the N1 alkylated compound, we attempted an other method(12): the silylated heterocycle was heated under reflux in dry acetonitrile in presence of the benzyloxymethyl



SCHEME I

acetate 4 and a catalytic amount of cesium iodide. In spite of a low yield (11%), this procedure enabled us to obtain N1 acyclic nucleoside 5a.

The deblocking of 9 and 11 was carried out with methanolic ammonia to yield free nucleosides 10 and 12. The preparation of 4-thioxo derivatives 15 and 17 required the use of acetylated derivatives 9 and 11 as starting material . The latter compounds on one hand, and the compounds 5a and 6 on the other hand, were subjected to reaction with Lawesson's reagent to give the corresponding thioxo derivatives 7, 8, 15 and 17 in a good yield (80%)(13). The removal of the ester group of 15 and 17 in methanolic ammonia at room temperature led to 16 and 18. Due to the thiocarbonyl group and its anisotropic effect, ^{13}C-NMR showed a clear deshielding of both C4 (CS) and C4a carbons:

δ (ppm)	10	16	12	18
C4	160,88	186,05	162,87	189,90
C4a	111,59	122,22	108,62	117,14

The thioxo derivatives 15 and 17 provided access to the 4-S-methyl protected acyclic nucleosides 19 and 21 after reaction with methyl iodide in dry tetrahydrofuran. The ester groups of 19 and 21 were removed with methanolic ammonia in smooth conditions to furnish the free acyclic nucleosides 20 and 22.

The azido nucleosides 13 and 14 resulted from the reaction of 10 and 12 with *p*-toluene sulfonyl chloride giving the corresponding tosyl derivatives. These tosyl compounds were then subjected to reaction with sodium azide(14) to yield the corresponding products 13 and 14 whose IR spectra showed strong N_3 bands at 2100 cm^{-1}. The azido groups induced a large C5' shielding in ^{13}C-NMR (10,04 ppm for 13 and 10,10 ppm for 14).

All final compounds were fully characterized using the following analytical techniques : ^{1}H-NMR, ^{13}C-NMR and IR spectra. UV spectra of the compounds 5a, 6, 10 and 12 in neutral and alkaline solutions allowed us to establish their isomeric structures. Following Fox and Shugar's method(15), the lack of bathochromic effect of an N-alkylated uracil derivative in alkaline medium indicates a N1-alkylation. This was obtained for these above-named compounds (see experimental section) whereas the compound 5b showed a bathochromic effect at pH 11:

λmax = 274nm at pH7 and 298nm at pH11
(λmax = 270nm at pH7 and 270nm at pH11 for 5a).

ANTIVIRAL EVALUATION :

All compounds except the protected forms 9, 11, 15, 17, 19 and 21 were tested and compared to AZT both for their toxicity and their ability to inhibit the cytopathic effect(16) 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 the virus suspension (LAV-Bru strain of HIV-1) and cultured for at least 7 days. Mock-infected cultures were carried out at the same time to determine the cytotoxicity of the compounds. Cells viability was then evaluated by the MTT method(17). Unfortunately, none of our compounds showed any significant activity under the conditions of this antiviral test.

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 (Merck). The compounds were analysed for C, H, N and S. The results were within 0,4% of the calculated theoretical values.

2-Ethylthiocyclopentano [*d*] pyrimidin-4-one 1.

To a suspension of S-ethylthiourea hydrobromide$^{(10)}$ (185g; 1mol) and sodium carbonate (106g; 1mol) in water (500ml) was added dropwise ethyl-2-oxocyclopentane carboxylate (156g; 1mol). This suspension was stirred at room temperature for 18hr. The resulting precipitate was collected and washed with water. 64g (65%) mp=220°C.

IR (KBr) cm^{-1}: 1620 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,27 (t, 3H, CH_3, *J* =7,3Hz) 1,94 (m, 2H, H6, *J* =7,4HZ) 2,56-2,68 (t, 2x2H, H5-7, *J* =7,4Hz) 3,09 (q, 2H, S-CH_2-, *J* =7,3Hz).

Cyclopentano [*d*] pyrimidine-2,4-dione 2.

The suspension of 2-ethylthiocyclopentano [*d*] pyrimidin-4-one (64g; 0,32mol) 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. 22g (45%) mp>260°C.

IR (KBr) cm^{-1}: 1650 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,94 (m, 2H, H6, *J* =7,3Hz) 2,47-2,62 (t, 2x2H, H5-7, *J* =7,3Hz) 10,73 (m, 2H, NH).^{13}C-NMR (DMSO-$_{d6}$) δ 20,84 (C6) 26,27-30,89 (C5-7) 109,49 (C4a) 152,18 (C7a) 155,86 (C2) 161,88 (C4).

1,2,3,4,5,6,7,8-Octahydroquinazoline-2,4-dione 3.

2-Ethylthio-3,4,5,6,7,8-hexahydroquinazolin-4-one was prepared from ethyl-2-oxocyclohexane carboxylate (170g; 1mol) by the same procedure as 2-ethylthiocyclopentano [*d*] pyrimidin-4-one to yield 90g (85%). The acidic hydrolysis was led in the same medium as for 2.

The mixture was refluxed in microwave oven for 2hr and the reaction was monitored by TLC. 50g (71%) mp>260°C. IR (KBr) cm^{-1}: 1650 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,60 (m, 4H, H6-7) 2,13-2,29 (m, 2x2H, H5-8) 10,60 (m, 2H, NH).^{13}C-NMR (DMSO-d6) δ 20,38-20,96-21,25-25,57 (C5-6-7-8) 105,58 (C4a) 148,63 (C8a) 150,72 (C2) 164,21 (C4).

Benzyloxymethyl acetate 4.

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 then hydrolysed with ice-water. The organic layer was washed with aqueous sodium hydrogenocarbonate 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 then concentrated. The residual oil was distilled under reduced pressure (90-100°C/4mmHg) to yield 15g (35%).

IR (KBr) cm^{-1}: 1720 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 2,02 (s, 3H, CH_3) 4,66-5,31 (s, 2x2H, CH_2) 7,31 (m, 5H, Ph).

1-(Benzyloxymethyl)-cyclopentano [*d*] pyrimidine-2,4-dione 5a.

A mixture of 2 (1,52g; 0,01mol) and ammonium sulphate (10mg) in HMDS (40ml) was stirred and heated under reflux for 4hr. HMDS in excess was evaporated under reduced pressure. A solution of benzyloxymethyl acetate 4 (1,8g; 0,01mol) in dry acetonitrile (75ml) and cesium iodide (2,60g; 0,01mol) were added to the silylated heterocycle. The suspension was heated under reflux for 2hr, then concentrated to dryness. The residue was diluted with dichloromethane (50ml) and the organic layer washed with water (2x50ml), dried over $MgSO_4$, filtered and concentrated to dryness.

A silicagel chromatography of the residue (CH_2Cl_2:CH_3OH 98/2) gave 5a. 0,3g (11%) mp=172°C.

IR (KBr) cm^{-1}: 1700-1650 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,98 (m, 2H, H6, *J* =7,3Hz) 2,50 (m, 2H) 2,87 (m, 2H, *J* =7,3Hz) 4,56 (s, 2H, H4') 5,21 (s, 2H, H1') 7,32 (s, 5H, Ph) 11,10 (s, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 20,67 (C6) 26,74-30,95 (C5-7) 70,13 (C4') 73,23 (C1') 111,77 (C4a) 127,42-128,12-137,52 (Ph) 152,24 (C7a) 156,30 (C2) 160,88 (C4). UV λmax (nm) 211-270 (pH7) 211-269 (pH1) 215-270 (pH11).

1-(Benzyloxymethyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,4-dione 6

The silylated heterocycle of 3 (1,66g; 0,01mol) was prepared by the same procedure as for 5a. HMDS in excess was evaporated under reduced pressure. A solution of benzyloxymethyl acetate 4 in dry 1,2-dichloroethane (50ml) and Tin IV chloride (1ml) were added to the residue of the silylated heterocycle. Then the solution was stirred at room temperature for 18hr. After an addition of pyridine (2ml), the mixture was stirred for 1hr. The inorganic materials were eliminated by filtration and the organic layer was diluted with chloroform (50ml). The organic layer was washed with a saturated solution of sodium hydrogenocarbonate then with brine, dried over $MgSO_4$, filtered and concentrated to drynes to yield 1,25g (43%) mp=170°C.

IR (KBr) cm^{-1}: 3150 (NH) 1650 (CO).

^{1}H-NMR ($CDCl_3$) δ 1,76 (m, 4H, H6-7) 2,38-2,67 (m, 2x2H, H5-8) 4,65 (s, 2H, H4') 5,41 (s, 2H, H1') 7,32 (m, 5H, Ph) 8,90 (s, 1H, NH).^{13}C-NMR (DMSO-$_{d6}$) δ 20,55-21,19-21,49-24,46 (C5-6-7-8) 70,13-71,36 (C4'-1') 108,79 (C4a) 127,42-128,12-137,64 (Ph) 149,26 (C8a) 151,31 (C2) 162,81 (C4).

UV λmax (nm) 213,6-270,6 (pH7) 213,4-270,8 (pH1) 215,5-271,2 (pH11).

1-(Benzyloxymethyl)-4-thioxocyclopentano [*d*] pyrimidine-2-one 7.

A mixture of 5a (0,30g; 0,0011mol) and Lawesson's reagent (0,22g; 0,00055mol) in toluene (15ml) was heated under reflux for 4hr. The solution was concentrated under reduced pressure. After cooling, the precipitate was collected then washed with toluene (10ml) and petroleum spirit (2x20ml) to yield 0,22g (70%) mp=164°C.

IR (KBr) cm^{-1}: 3200 (NH) 1680 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,96 (m, 2H, H6, *J* =6,8Hz) 2,61 (t, 2H, *J* =7Hz) 2,96 (t, 2H, *J* =7,5Hz) 4,58 (s, 2H, H1') 7,33 (m, 5H, Ph) 12,45 (s, 1H, NH). ^{13}C-NMR (DMSO-$_{d6}$) δ 20,14 (C6) 29,95-31,53 (C5-7) 70,48 (C4') 73,81 (C1') 113,58 (C4a) 127,54-128,12-132,15 (Ph) 149,67 (C7a) 152,94 (C2) 186,17 (C4).

1-(Benzyloxymethyl)-4-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 8

was prepared from 6 (1,4g; 0,005mol) and Lawesson's reagent (1g; 0,0025mol) by the same procedure as 7 to yield 1,1g (75%) mp=168°C. IR (KBr) cm^{-1}: 3200 (NH) 1680 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,62 (m, 4H, H6-7) 2,43-2,70 (m, 2x2H, H5-8) 4,58 (s, 2H, H4') 5,39 (s, 2H, H1') 7,32 (m, 5H, Ph) 12,64 (s,1H, NH).

^{13}C-NMR (DMSO-$_{d6}$) δ 21,08-25,05-26,04 (C5-6-7-8) 70,42-71,94 (C1'-4') 117,26 (C4a) 127,48-128,12-137,46 (Ph) 148,33-148,56 (C8a-2) 189,56 (C4).

1-[(2-Acetoxy ethoxy)methyl]-cyclopentano [*d*] pyrimidine-2,4-dione 9

was prepared from 2 (1,52g; 0,01mol) and 2-acetoxyethyl acetoxymethylether (1,76g; 0,01mol) by the same procedure as 6. A silicagel chromatography (CH_2Cl_2:CH_3OH 98/2) gave 9.
1,1g (40%) mp=140°C.

IR (KBr) cm^{-1}: 1730-1690-1650 (CO).^{1}H-NMR ($CDCl_3$) δ 2,05-2,06 (m, 5H, H6, CH_3) 2,72-2,93 (m, 2x2H, H5-7) 3,80 (m, 2H, H5') 4,19 (m, 2H, H4') 5,24 (m, 2H, H1') 9,13 (m, 1H, NH).

1-[(2-Hydroxy ethoxy)methyl]-cyclopentano [*d*] pyrimidine-2,4-dione 10.

The previous compound 9 (0,55g; 0,002mol) was dissolved in methanol and the resulting solution was saturated with ammonia. After 18hr, the solvent was evaporated under reduced pressure to yield 10. 0,43g (95%) mp=195°C.

IR (KBr) cm^{-1}: 3420 (OH) 3150 (NH) 1680 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,98 (m, 2H, H6) 2,51-2,91 (m, 2x2H, H5-7) 3,48 (m, 4H, H4'-5') 4,64 (m, 1H, OH) 5,13 (m, 2H, H1') 10,94 (m, 1H, NH).^{13}C-NMR (DMSO-$_{d6}$) δ 20,67 (C6) 26,74-30,89 (C5-7) 59,91 (C5') 70,31 (C4') 73,58 (C1') 111,59 (C4a) 154,24 (C7a) 156,62 (C2) 160,88 (C4).

Uv λmax (nm) 214,7-272,5 (pH7) 214,7-272,6 (pH1) 214,5-273,0 (pH11).

1-[(2-Acetoxy ethoxy)methyl]-1,2,3,4,5,6,7,8-octahydroquinazoline-2,4-dione 11

was prepared from 3 (1,66g; 0,01mol) and 2-acetoxymethyl acetoxyethyl ether (1,76g; 0,01mol) by the same procedure as 6 to yield 2,1g (74%) mp=112°C.

IR (KBr) cm^{-1}: 3200 (NH) 1740-1680 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,64 (m, 4H, H6-7) 2,00 (s, 3H, CH_3) 2,12-2,29 (m, 2x2H, H5-8) 3,71-4,08 (m, 2x2H, H4'-5') 5,23 (m, 2H, H1') 10,94 (m, 1H, NH).

1-[(2-Hydroxy ethoxy)methyl]-1,2,3,4,5,6,7,8-octahydroquinazoline-2,4-dione 12 was obtained from 11 (1g; 0,0035mol) by the same procedure as 10 to yield, after a silicagel chromatography (CH_2Cl_2:CH_3OH 95/5) 0,61g (73%) mp=145°C.

IR (KBr) cm^{-1}: 3450 (OH) 1680 (CO).^{1}H-NMR (DMSO-$_{d6}$) δ 1,60 (m, 4H, H6-7) 2,21-2,65 (m, 2x2H, H5-8) 3,48 (m, 4H, H4'-5') 4,52 (m, 1H, OH) 5,25 (m, 2H, H1') 10,30 (m, 1H, NH).

^{13}C-NMR (DMSO-$_{d6}$) δ 20,55-21,19-21,49-24,35 (C5-6-7-8) 59,97 (C5') 70,19-71,59 (C1'-4') 108,62 (C4a) 149,49 (C8a) 151,25 (C2) 162,87 (C4).

UV λmax (nm) 215,9-270,9 (pH7) 215,9-270,9 (pH1) 212,7-272,1 (pH11).

1-[(2-Azido ethoxy)methyl]-cyclopentano [*d*] pyrimidine-2,4-dione 13.

The compound 10 (0,84; 0,0037mol) was dissolved in dry pyridine (30ml) and *p*-toluene sulfonyl chloride (1,4g; 0,0074mol) was added. The solution was stirred at room temperature for 18hr. Then the pyridine was evaporated under reduced pressure and the residue was poured in water. The resulting precipitate (tosylate) was collected and dried (0,5g; 0,0013mol). This intermediate was dissolved in DMF (30ml) and sodium azide (0,35g; 0,0054mol) was added. The suspension was stirred at 100°C for 4hr. The DMF was evaporated under reduced pressure and the residue was dissolved in dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness to give 12, 0,22g (23%) mp=138°C. IR (KBr) cm^{-1}: 2100 (N_3) 1680 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 2,03 (t, 3H, H6, *J* =7,3Hz) 2,52-2,73 (m, 2x2H, H5-7) 3,40-3,68 (t, 2x2H, *J* =4,4Hz, H4'-5') 5,17 (m, 2H, H1') 11,15 (m, 1H, NH).^{13}C-NMR (DMSO-$_{d6}$) δ 20,73 (C6) 26,86-30,89 (C5-7) 49,87 (C5') 67,45 (C4') 73,40 (C1') 111,89 (C4a) 152,36 (C7a) 156,44 (C2) 160,94 (C4).

1-[(2-Azido ethoxy)methyl]-1,2,3,4,5,6,7,8-octahydroquinazoline-2,4-dione 14

was prepared from 12 (0,72g; 0,003mol) by the same procedure as 13 to yield 0,25g (31%) mp=128°C. IR (KBr) cm^{-1}: 2100 (N_3) 1700-1660 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,57-1,67 (m, 2x2H, H6-7) 2,20-2,64 (m, 2x2H, H5-8) 3,39-3,67 (t, 2x2H, H4'-5', *J* =4,6Hz) 5,29 (s, 2H, H1') 11,30 (s, 1H, NH).^{13}C-NMR (DMSO-$_{d6}$) δ 20,49-

21,19-21,49-24,35 (C5-6-7-8) 49,87 (C5') 67,27 (C4') 71,42 (C1') 108,79 (C4a) 149,26 (C8a) 151,31 (C2) 162,87 (C4).

1-[(2-Acetoxy ethoxy)methyl]-4-thioxocyclopentano [*d*] pyrimidin-2-one 15

was prepared from 9 (0,75g; 0,0028mol) and Lawesson's Reagent (0,56g; 0,0014mol) in toluene (30ml) by the same procedure as 7 to yield 0,66g (83%) mp=148°C. IR (KBr) cm^{-1}: 3200 (NH) 1740-1670 (CO). ^{1}H-NMR (CDCl$_3$) δ 2,06 (s, 3H, CH3) 2,12 (m, 2H, H6) 2,83-2,98 (t, 2x2H, H5-7, J =7,8Hz) 3,83-4,21 (t, 2x2H, H4'-5', J =4,6Hz) 5,27 (s, 2H, H1') 9,97 (s, 1H, NH).

1-[(2-Hydroxy ethoxy)methyl]-4-thioxocyclopentano [*d*] pyrimidin-2-one 16.

The compound 15 (0,5g; 0,0017mol) was dissolved in methanolic ammonia and stirred at room temperature for 18hr. The solution was concentrated and the residue was stirred in diethyl oxide to yield 0,37g (90%) mp=180°C. IR (KBr) cm^{-1}: 3450 (OH) 3200 (NH) 1670 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,97 (m, 2H, H6, J =7,3Hz) 2,62-2,98 (t, 2x2H, H5-7, J =7,3Hz) 3,49 (m, 4H, H4'-5') 3,80 (s, 1H, OH) 5,18 (s, 2H, H1'). ^{13}C-NMR (DMSO-$_{d6}$) δ 20,14 (C6) 29,95-31,47 (C5-7) 59,91 (C5') 70,66 (C4') 74,24 (C1') 122,22 (C4a) 149,67 (C7a) 153,29 (C2) 186,05 (C4).

1-[(2-Acetoxy ethoxy)methyl]-4-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 17

was prepared from 11 (1,3g; 0,0046mol) and Lawesson's reagent (0,93g; 0,0023mol) in toluene (30ml) by the same procedure as 7 to yield 15, 1,2g (87%) mp=165°C.

IR (KBr) cm^{-1}: 3200 (NH) 1730-1670 (CO). ^{1}H-NMR (CDCl$_3$) δ 1,37 (m, 4H, H6-7) 2,06 (s, 3H, CH$_3$) 2,65 (m, 4H, H5-8) 3,84-4,21 (t, 2x2H, H4'-5', J =4,6Hz) 5,41 (s, 2H, H1') 10,03 (s, 1H, NH).

1-[(2-Hydroxy ethoxy)methyl]-4-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one 18

was obtained from 17 (0,4g; 0,0013mol) by the same procedure as 16 to yield 0,26g (78%) mp=188°C. IR (KBr) cm^{-1}: 3490 (OH) 3180 (NH) 1670 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,62 (m, 4H, H6-7) 2,45-2,72 (m, 2x2H, H5-8) 3,49 (m, 4H, H4'-5') 3,74 (s, 1H, OH) 5,32 (s, 2H, H1'). ^{13}C-NMR (DMSO-$_{d6}$) δ 21,14-24,99-26,04 (C5-6-7-8) 59,91 (C5') 70,54-72,29 (C4'-1') 117,14 (C4a) 148,62 (C2-8a) 189,90 (C4).

1-[(2-Acetoxy ethoxy)methyl]-4-S-methylcyclopentano [*d*] pyrimidin-2-one 19.

To a solution of 15 (0,5g; 0,0017mol) in THF (30ml) were added successively methyl iodide (0,5g 0,0035mol) and sodium carbonate (1g). The resulting mixture was stirred at room temperature for 14hr. The mineral salts were collected by filtration and washed with THF (2x10ml). The combinated organic layers were evaporated to dryness under reduced pressure. A silicagel chromatography afforded 19 0,27g (53%) mp=132°C. IR (KBr) cm^{-1}: 1700-1660 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 2,05 (s, 3H, CH_3) 2,18 (m, 2H, H6, J=7,3HZ) 2,57 (s, 3H, S-CH_3) 2,69-2,98 (t, 2x2H, H5-7, J=7,3Hz) 3,85-4,15 (m, 2x2H, H4'-5') 5,41 (s, 2H, H1').

1-[(2-Hydroxy ethoxy)methyl]-4-S-methylcyclopentano [*d*] pyrimidin-2-one 20.

The compound 19 (0,27g; 0,0009mol) was dissolved in methanolic ammonia and stirred at room temperature for 18hr. The solvent was evaporated and the residue was stirred in diethyl oxide to yield 0,2g (87%) mp=136°C. IR (KBr) cm^{-1}:3350 (OH) 1640 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 2,06 (m, 2H, H6, J =7,3Hz) 2,46 (s, 3H, S-CH_3) 2,57-2,99 (t, 2x2H, H5-7, J =7,3Hz) 3,48 (m, 4H, H4'-5') 4,55 (s, 1H, OH) 5,29 (s, 2H, H1').^{13}C-NMR (DMSO-$_{d6}$) δ 11,50 (S-CH_3) 21,49 (C6) 27,09-30,77 (C5-7) 59,91 (C5') 70,72 (C4') 74,86 (C1') 114,69 (C4a) 154,81 (C7a) 159,83 (C2) 172,07 (C4).

1-[(2-Acetoxy ethoxy)methyl]-4-S-methyl-1,2,5,6,7,8-hexahydroquinazolin-2-one 21 was prepared from 17 (0,5g; 0,0016mol) and methyl iodide (0,47g, 0,0035mol) in THF (30ml) by the same procedure as 19. A silicagel chromatography (CH_2Cl_2:CH_3OH 98/2) afforded 19; 0,16g (33%) mp=78°C. IR (KBr) cm^{-1}: 1720-1650 (CO).

^{1}H-NMR ($CDCl_3$) δ 1,79 (m, 4H, H6-7) 2,04 (s, 3H, CH_3) 2,44-2,77 (m, 2x2H, H5-8) 2,54 (s, 3H, S-CH_3) 3,87-4,18 (t, 2x2H, H4'-5', J =4,9Hz) 5,54 (s, 2H, H1').

1-[(1-Hydroxy ethoxy)methyl]-4-S-methyl-1,2,5,6,7,8-hexahydroquinazolin-2-one 22 was obtained from 21 (0,16g; 0,00053mol) by the same procedure as 20 to yield 0,11g (75%) mp=124°C. IR (KBr) cm^{-1}: 3400 (OH) 1640 (CO).

^{1}H-NMR (DMSO-$_{d6}$) δ 1,69 (m, 4H, H6-7) 2,33-2,79 (m, 2x2H, H5-8) 2,43 (s, 3H, S-CH_3) 3,49 (m, 2x2H, H4'-5') 4,55 (s, 1H, OH) 5,41 (s 2H, H1'). ^{13}C-NMR (DMSO-$_{d6}$) δ 12,11 (S-CH_3) 20,64-20,81-22,39-24,84 (C5-6-7-8) 59,94 (C5') 70,57 (C4') 73,14 (C1') 110,34 (C4a) 152,06 (C8a) 153,82 (C2) 176,80 (C4).

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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. a) A.S. Fauci, Science, 239, 617 (1988).
   b) H. Mitsuya, R. Yarchoan and S. Broder, Science, 249, 1533 (1990).
3. 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).
4. H. Mitsuya, S. Broder, Proc. Natl. Acad. Sci. (USA), 83, 1911 (1986).
5. 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).
6. R. Yarchoan, H. Mitsuya, R.V. Thomas, J. Pluda, N.R. Hartman, C.F. Perno, K.S. Marczyk, J.P. Allain, D.G. Johns, S. Broder, Science, 245, 412 (1989).
7. T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R.T. Walker, J. Balzarini, E. De Clercq, J. Med. Chem., 32, 2507, (1989).
8. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigetta, R.T. Walker, E. De Clercq, T. Miyasaka, J. Med. Chem., 35, 4713 (1992).
9. 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, 1992 (4713).
10. Organic Syntheses, Collective volume 3, 440 (1955).
11. A. Rosowsky, S. Hyrik Kim and M. Wick, J. Med. Chem., 24, 1177 (1981).
12. Y.H. Kim, J.Y. Kim, C.H. Lee, Chem. Lett. 1045 (1988).
13. K. Kaneko, H. Katayama, T. Wakabayashi, T. Kumonaka, Synthesis, 152 (1988).
14. T.R. Webb, C. Eigenbrot, J. Org. Chem., 56, 3009 (1991).
15. 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).
16. M. Lemaitre and A. Zerial, Revue Française des Laboratoires, n° 216, 43 (1990).
17. T. Mosmann, J. Immunol. Methods, 65, 55 (1983).

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