Synthesis of 2',3'-Dideoxy-3'-fluorouridines with Potential Anti-HIV Activity According to Neural Network Calculations

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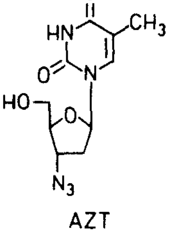
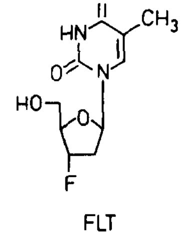
Received 23 June 1993; revised 3 November 1993

Methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside was condensed with trimethylsilylated 5-substituted uracils to give nucleosides using trimethylsilyl trifluoromethanesulfonate as catalyst. In the case of 5-nitrouracil an acyclic nucleoside believed to be an intermediate for the corresponding nucleoside was isolated. The 5-substituents were selected from neural network calculations on compounds with potential activity against HIV-1. All compounds from the condensation reactions were deacylated by treatment with sodium methoxide in methanol.

In the treatment of the acquired immunodeficiency syndrome (AIDS),[3] many nucleoside derivatives have been recognized as potent and selective inhibitors of replication of the human immunodeficiency virus (HIV), particularly 2',3'-dideoxynucleosides, such as 3'-azido-3'-deoxythymidine (AZT)[4] and 3'-fluoro-3'-deoxythymidine (FLT).[5,6] Although AZT slows down the progress of the AIDS disease, serious side effects, particularly bone marrow suppression, are severe and often require cessation of treatment.[7,8] FLT is in fact more potent as an inhibitor of HIV than AZT, however, its toxicity deserves further investigation.[9] In fact, reduced toxicity has been reported for 5-chlorinated derivatives.[10,11] Moreover, other 3'-fluoro analogs demonstrate a selectivity against HIV that is quite comparable to that of their 3'-azido counterparts.[12]



AZT

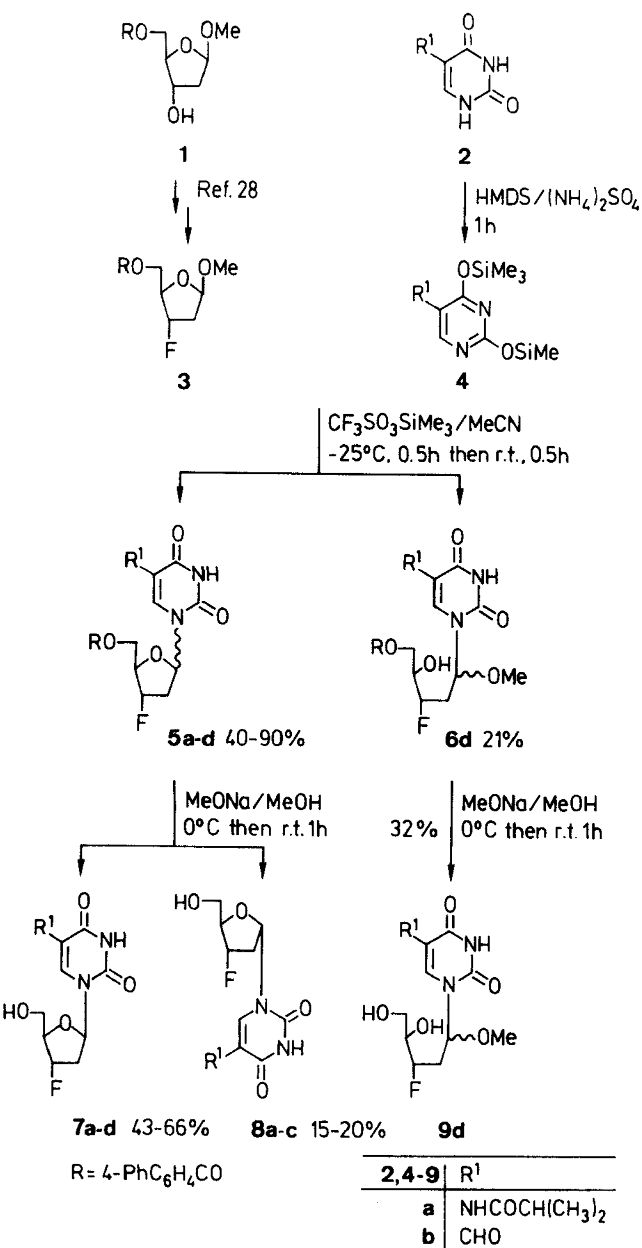


FLT

Although several reviews[13-15] discuss the relationship between the structure of dideoxynucleosides and their activity against HIV, no quantitative structure–activity relationships (QSAR)[16,17] have been found. The antiviral activity of nucleosides has also been associated with their conformational feature in solid-state.[18] Back propagation neural networks (NN) is a new technology which is useful for modeling non-linear functions of several variables. Andrea and Kalayeh[19] have found enhanced prediction accuracy when NN was used instead of regression models for relating dehydrofolate reductase inhibitory activities of 256 2,4-diamino-6,6-dimethyl-5-phenyldihydrotriazines with π, MR and $\Sigma\sigma$ values of the 2, 3, and 4, substituents of the phenyl ring. We found it tempting to use NN for suggesting new analogs of FLT with other substituents in the 5-position of the pyrimidine ring, i.e. replacement of 5-methyl. A large number of adjustable parameters has to be fixed during the training of a typical NN. If the number of experiments for the training is low, the training set is overfitted and predictions of new experiments will be poor. For the training set we selected data from the literature[5,9-12,19-26] describing the anti-HIV activity of 5-substituted 3'-azido and 3'-fluoro-3'-deoxythymidines. As input data we used π, MR, and R values[27] of the 5-substituent. These parameters were chosen because they are related to lipophilicity size and resonance effects of the substituent, respectively. Furthermore, an indicator variable was used to distinguish 3'-azido from 3'-fluoro compounds. In order to have a sufficient number of experiments for the training set we also used two output parameters describing the effective dose (ED$_{50}$) of inhibiting the replication of HIV: one for experiments using MT-4 cells and one for experiments using PBM cells in the *in vitro* tests. After training the NN, we predicted very few new 5-subtituents that obviously should be investigated in the 3'-azido series of nucleosides (AZT analogs) whereas a large number of 5-substituents were predicted to lead to active compounds in the 3'-fluoro series (FLT analogs). From these we selected formyl, ethoxycarbonylamino and nitro as promising 5-substituents in a new series of 2',3'-dideoxy-3'-fluorouridines. Isobutyrylamino was selected as a substituent in the nucleoside for a control experiment as an inactive compound according to NN.

Recently, our group has used[28] methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (**3**) as a synthetic intermediate for 2',3'-dideoxy-3'-fluoronucleosides. The synthon **3** was synthesized as previously described.[28] 2-Deoxy-D-ribose was glycosylated by treatment with methanolic hydrogen chloride and subsequently acylated with 4-phenylbenzoyl chloride to give **1** which in turn was epimerized at C-3 by oxidation with a chromium trioxide/pyridine/acetic anhydride complex followed by reduction with sodium borohydride. The so formed epimerized compound was reacted with diethylaminosulfur trifluoride (DAST) to give **3**. The nucleobases **2a–c** were prepared from 5-aminouracil by treatment with ethyl chloroformate or isobutyryl chloride in dry pyridine or from uracil as previously described.[29]

In the synthesis of the nucleosides **5**, we used the Friedel–Crafts catalyzed Silyl-Hilbert–Johnson reaction as modified by Vorbrüggen et al.[30,31] Trimethylsilyl trifluoromethanesulfonate (TMS triflate) was added to a mixture of **3** and the silylated base **4** in anhydrous acetonitrile to give an anomeric mixture of the nucleosides **5a–c** (73–90%) for which the β/α ratio typically was 3:1. After chromatographic purification, pure **5** was obtained in high yield. Treatment of **5** with a solution of sodium methoxide in methanol resulted in deprotection of the 5'-OH group to give the anomerically pure compounds



2,4-9	R^1
a	NHCOCH(CH$_3$)$_2$
b	CHO
c	NHCOOEt
d	NO$_2$

Scheme

7 and 8 which in turn were separated by silica gel column chromatography.

When 5-nitrouracil was used as the nucleobase, the nucleoside **5d** was isolated as the β-anomer in only 40% yield. Instead, two C-1′ epimeric acyclic nucleosides **6d** were obtained in 21% yield. An inseparable mixture of the deprotected epimers **9d** was obtained in 32% yield when the epimeric mixture **6d** was treated with sodium methoxide in methanol. In the ^{13}C NMR spectrum of the acyclic nucleosides the resonance of the methoxy group was found around $\delta = 56.8$. The resonances of the sugar carbons had changed into typical values of an acyclic nucleoside similar to those reported by Jørgensen et al.[32] who isolated acyclic nucleosides when nucleobases were condensed with methyl 2,3,5-*O*-tribenzoyl-D-arabinofuranoside. They proposed that such acyclic nucleosides or their silylated counterparts were the true intermediates in the synthesis of nucleosides from methyl glycosides. Isolation of **6d** now indicates that this type of acyclic nucleosides also seem to be the intermediates for formation of 2′,3′-dideoxy-3′-fluoro nucleosides when they are synthesized by condensation of nucleobases with an appropriate methyl glycoside under the Vorbrüggen conditions with TMS triflate in acetonitrile. This means that the initial step in the nucleoside condensation reaction most likely is attack on the ring oxygen of the sugar **3** by TMS triflate which results in an endocyclic cleavage of the C–O bond with formation of an acyclic carbonium ion which in turn can condense with the nucleobase to produce the acyclic nucleoside **6**. Consequently, the nucleoside **5** can be formed, not only through a direct route from **3** via a glycosyl cation, but also by ring closure of the acyclic nucleoside **6**. This is in agreement with the observation of Hager and Liotta[33] that an appropriate aminal, of similar type as **9d**, can be cyclized to AZT under acidic conditions. Although endocyclic cleavage of pyranosides is disputed[34,35] for their hydrolysis, the situation in the case of aldofuranosides is particularly instructive.[36] Both endocyclic and exocyclic fission is observed, the latter being favored by electronegative aglycons. Bennett et al.[37] found in an investigation of the ^{18}O kinetic isotope effect on the perchloric acid catalyzed hydrolysis of α-arabinofuranoside that a 4-nitrophenyl aglycon results in exocyclic C–O cleavage whereas propan-2-yl results in endocyclic C–O cleavage of the sugar.

The assignment of the anomeric configuration of **7** and **8** was based on ^{1}H NMR spectra: The resonance of 4′-H in the α-anomer appears downfield from that observed for the β-anomer, and the resonance of 5′-H of the α-anomer appears upfield from that observed for the β-anomer.[29,38,39] The 2α-H resonance of **8a–c** exhibited doublet of a doublet due to a large geminal coupling and a coupling to fluorine. The vicinal *trans* couplings between 2′-α-H and 1′-H and between 2′α-H and 3′-H were close to zero and resulted in a small line broadening, only. This confirmed the assignment of **8a–c** as α-configuration because small coupling constants are typical of vicinal hydrogens in a *trans* relationship.[40–42] In conformity with α-configuration of **8a** we also observed a small coupling constant (0.09 Hz) of C-6 which was ascribed to through-space coupling to fluorine. Through-space ^{13}C-^{19}F couplings are already known for adenine derivatives.[43] For compound **8a**, the through-space ^{13}C-^{19}F coupling also indicates *anti* conformation around the glycoside bond to the nucleobase.

Compounds **5a,b,d**, **6d**, **7a–d**, **8a–c** and **9d** were devoid of any activity against HIV-1 (strain HTLV-IIIB) in MT-4 cells at non-toxic concentrations. MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound containing culture medium (RPM 1640 containing 10% FCS) for 2 h. The MT-4 cells were maintained in culture medium likewise containing the test compound at 100 μM when non-toxic. Expression of HIV in culture medium was quantitated by HIV antigen detection ELISA. Only the compounds **5a,b** and **6d** showed cytotoxicity against MT-4 cells at 100 μM, but at 10 μM these compounds did not show any significant activity against HIV-1. In the light of the incorrect neural network calculation predicting that nucleosides **7b–d** should be active against HIV-1 in MT-4 cells, we conclude that still a large number of nucleosides has to be synthesized in order to establish a reliable quantitative structure–activity relationship. The nucleosides **7a–d** were added to the training set of the NN and after a new training the number of 3′-fluoro nucleosides predicted active against HIV-1 in MT-4 cells was now considerably lower. In fact, there was no longer predicted any highly active new 5-substituted 2′,3′-dideoxy-3′-fluorouridines. No outliers were found among the input of biological activities if an uncertainty of a factor 15 was accepted for ED_{50}. This uncertainty corresponds to what is found when data from different research groups are compared.

The compounds were also tested for activity at 100 μM against Herpes Simplex Virus, type 1 (HSV-1), strain McIntyre, in a continuous cell line from rabbit cornea (SIRC) which was maintained in Eagle's MEM containing 1 % fetal calf serum (FCS) and the test compound. Interestingly, the nitro compounds **5d** and **6d** showed 80 % and 90 % protection, respectively, against HSV-1 at 100 μM, whereas cell viability was reduced only by 30 % and 20 %, respectively, at the same concentration. The compounds **5a,b** were toxic at 100 μM, but no activity against HSV-1 was found at 10 μM. All other compounds were devoid of any activity against HSV-1.

For all new compounds satisfactory microanalyses obtained: C ± 0.44, H ± 0.47, N ± 0.048. Exception 5d, N − 0.55.

2′,3′-Dideoxy-3′-fluorouridines 5a–c:

A mixture of the uracil derivative **2** (4.8 mmol), $(NH_4)_2SO_4$ (50 mg) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 30 mL) was refluxed for 1 h (clear solution after 0.5 h). After evaporation under reduced pressure, the residue was dissolved in anhydr. MeCN (20 mL) and the fluoro sugar **3** (3 mmol) was added. The mixture was stirred and cooled to −40 °C. A solution of $CF_3SO_3SiMe_3$ (0.7 mL, 3.3 mmol) in anhydr. MeCN (5 mL) was added dropwise to the mixture. The mixture was stirred for 0.5 h at −25 °C and then at r.t. for 0.5 h. The mixture was diluted with CH_2Cl_2 (200 mL), washed with a cold sat. aq $NaHCO_3$ (3 × 150 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column using $CHCl_3$ as eluent to obtain the anomeric mixtures of **5a–c**; yield: **5a**, 1.08 g (73 %); **5b**, 1.18 g (90 %); **5c**, 1.24 g (83 %).

1-[2,3-Dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranosyl]-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (5d) and 2,3-Dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-1-*O*-methyl-1-(5-nitro-uracil-1-yl)-D-*erythro*-pentitol (6d):

$CF_3SO_3SiMe_3$ (0.7 mL, 3.3 mmol) was added with stirring to a solution of 3-fluoro sugar **3** (1.0 g, 3 mmol) and silylated 5-nitrouracil **4d** (4.8 mmol) in anhydr. MeCN (30 mL) at −40 °C. After 0.5 h at −25 °C the temperature was allowed to increase to r.t. After 0.5 h the mixture was diluted with CH_2Cl_2 (200 mL) and quenched with cold sat. aq $NaHCO_3$ (3 × 150 mL). The organic phase was dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue chromatographed on a silica gel column (eluent: $CHCl_3$) to give compounds **5d** and **6d**.

5d; yield: 550 mg (40 %); mp 166 °C.

^{1}H NMR (DMSO-d_6): δ = 2.5–2.9 (m, 2 H, 2′α-H and 2′β-H), 4.4–4.7 (m, 2 H, 5-H), 4.76 (d, 1 H, 4′-H, $J_{4',F}$ = 24.8 Hz), 5.56 (dd, 1 H, 3′-H, $J_{3',F}$ = 53.3 Hz, $J_{2',3'}$ = 4.1 Hz), 6.15 (t, 1 H, 1′-H, $J_{1',2'}$ = 6.2 Hz), 7.4–8.1 (m, 9 H_{arom}), 8.96 (s, 1 H, C-6), 12.15 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 38.62 (C-2′, $J_{2',F}$ = 20.1 Hz), 63.73 (C-5′), $J_{5',F}$ = 11.0 Hz), 83.30 (C-4′, $J_{4',F}$ = 25.9 Hz), 87.84 (C-1′), 93.97 (C-3′, $J_{3',F}$ = 176.4 Hz), 125.3 (C-5), 126.79, 126.88, 127.75, 128.32, 128.96, 129.75, 138.71, 144.88 (C_{arom}), 144.49 (C-6), 154.46 (C-2), 154.46 (C-4), 165.18 (C=O).

MS: *m*/*z* (%) = 455 (M^+, 4), 278 (29), 181 (82), 81 (100).

6d; yield: 310 mg (21 %); mp 201 °C.

^{1}H NMR (DMSO-d_6): δ = 2.2–2.6 (m, 2 H, 2′-H), 3.32, 3.38 (2 × s, 3 H, OCH_3), 3.99 (m, 1-H, 4′-H), 4.2–4.4 (m, 2 H, 5′-H), 4.4–4.9 (m, 1 H, 3′-H), 5.6–5.8 (m, 2 H, 1′-H, OH), 7.4–8.1 (m, 9 H_{arom}), 8.87, 8.88 (2 × s, 1 H, 6-H), 12.12 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6) of (predominant epimer): δ = 35.41 (C-2′, $J_{2',F}$ = 20.6 Hz), 56.65 (OCH_3), 69.06 (C-4′, $J_{4',F}$ = 23.0 Hz), 85.95 (C-1′), 89.69 (C-3′, $J_{3',F}$ = 171.7 Hz), 126.57, 126.69, 126.80, 126.90, 128.32, 128.98, 129.81, 138.79 (C-5, C_{arom}), 144.37 (C-6), 149.22 (C-2), 154.60 (C-4), 165.34 (C=O).

Formation of 7a–d, 8a–c and 9d by Deprotection:

NaOMe (from 50 mg Na) in MeOH (10 mL), was added to **5a–d** or **6d** (0.4–2 mmol) in MeOH (30 mL) at 0 °C. The mixture was stirred at r.t. for 1 h. After neutralization with NH_4Cl (120 mg, 2.3 mmol), the solvent was removed in vacuo and the residue was chromatographed on silica gel using 0–5 % MeOH in $CHCl_3$ as eluent to give **7a–d** and **8a–c** or **9d**.

1-(2,3-Dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-5-isobutyrylamino-2,4(1H,3H)-pyrimidinedione (**7a**); yield: 412 mg (66 %); mp 153 °C.

^{1}H NMR (DMSO-d_6): δ = 1.04 (d, 6 H, CH_3, *J* = 6.8 Hz), 2.1–2.6 (m, 2 H, 2′-H), 2.77 (heptet, 1 H, CH, *J* = 6.8 Hz), 3.50 (dd, 1 H, 5′-H, *J* = 5.9, 11.4 Hz), 3.62 (dd, 1 H, 5′-H, *J* = 3.7, 11.4 Hz), 4.15 (dt, 1 H, 4′-H, *J* = 27.0, 4.8 Hz), 5.30 (dd, 1 H, 3′-H, *J* = 53.8, 4.4 Hz), 6.23 (dd, 1 H, 1′-H, *J* = 9.1, 5.6 Hz), 8.45 (s, 1 H, 6-H), 9.00 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 19.41 (CH_3), 19.44 (CH_3), 33.80 (CH), 36.63 (C-2′, $J_{2',F}$ = 20.4 Hz), 60.82 (C-5′, $J_{5',F}$ = 10.9 Hz), 84.23 (C-1′), 84.81 (C-4′, $J_{4',F}$ = 22.7 Hz), 94.67 (C-3′, $J_{3',F}$ = 174.2 Hz), 114.33 (C-5), 127.79 (C-6), 148.81 (C-2), 159.65 (C-4), 175.73 (C=O).

MS: *m*/*z* (%) = 315 (M^+, 5), 285 (3), 197 (60), 127 (100).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-isobutyrylamino-2,4(1H,3H)-pyrimidinedione (**8a**); yield: 100 mg (15 %), semisolid.

^{1}H NMR (DMSO-d_6): δ = 1.03 (d, 6 H, CH_3, *J* = 6.8 Hz), 2.25 (dd, 1 H, 2′α-H, $J_{2'\alpha,F}$ = 25.5 Hz, $J_{2'\alpha,2'\beta}$ = 15.8 Hz), 2.26 (m, 1 H, 2′β-H), 2.80 (heptet, 1 H, CH, *J* = 6.8 Hz), 3.48 (m, 2 H, 5′-H), 4.51 (td, 1 H, 4′-H, *J* = 4.3, 24.1 Hz), 5.05 (t, 1 H, OH, *J* = 5.4 Hz), 5.29 (dd, 1 H, 3′-H, *J* = 54.3, 5.1 Hz), 6.23 (dd, 1 H, 1′-H, *J* = 7.5, 1.4 Hz), 8.51 (s, 1 H, 6-H), 9.00 (s, 1 H, NH), 11.70 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 19.42 (CH_3), 19.49 (CH_3), 33.75 (CH), 38.41 (C-2′, $J_{2',F}$ = 20.4 Hz), 60.91 (C-5′, $J_{5',F}$ = 11.2 Hz), 85.94 (C-1′), 87.16 (C-4′, $J_{4',F}$ = 21.7 Hz), 94.27 (C-3′, $J_{3',F}$ = 174.0 Hz), 114.12 (C-5), 127.14, (C-6), 148.55 (C-2), 159.68 (C-4), 175.54 (C=O).

MS: *m*/*z* (%) = 315 (M^+, 2), 197 (45), 127 (100).

1-(2,3-Dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-5-formyl-2,4(1H,3H)-pyrimidinedione (**7b**); yield: 320 mg (54 %); mp 154 °C.

^{1}H NMR (DMSO-d_6): δ = 2.2–2.4 (m, 2 H, 2′-H), 3.65 (m, 2 H, 5′-H), 4.30 (td, 1 H, 4′-H, *J* = 3.5, 26.4 Hz), 5.32 (dd, 1 H, 3′-H, *J* = 53.6, 4.5 Hz), 6.17 (dd, 1 H, 1′-H, *J* = 8.3, 5.8 Hz), 8.65 (s, 1 H, 6-H), 9.78 (s, 1 H, CHO).

^{13}C NMR (DMSO-d_6): δ = 38.46 (C-2′, $J_{2',F}$ = 20.4 Hz), 60.55 (C-5′, $J_{5',F}$ = 10.8 Hz), 85.75 (C-4′, $J_{4',F}$ = 22.8 Hz), 85.82 (C-1′), 94.68 (C-3′, $J_{3',F}$ = 174.5 Hz), 110.84 (C-5), 146.61 (C-6), 149.50 (C-2), 161.63 (C-4), 186.12 (CHO).

MS: *m*/*z* (%) = 258 (M^+, 11), 140 (19), 119 (100), 112 (91).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-formyl-2,4(1H,3H)-pyrimidinedione **(8b)**; yield: 0.12 g (20 %); mp 159 °C.

^{1}H NMR (DMSO-d_6): δ = 2.43 (dd, 1 H, 2′α-H, $J_{2'\alpha,F}$ = 23.3 Hz, $J_{2'\alpha,2'\beta}$ = 15.6 Hz), 2.6–2.9 (m, 1 H, 2′β-H), 3.51 (m, 2 H, 5′-H), 4.68 (td, 1 H, 4′-H, J = 4.4, 24.7 Hz), 5.33 (dd, 1 H, 3′-H, J = 53.7, 4.6 Hz), 6.17 (d, 1 H, 1′-H, J = 6.4 Hz), 8.20 (s, 1 H, 6-H), 9.80 (s, 1 H, CHO), 11.8 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 38.6 (C-2′, $J_{2',F}$ = 20.9 Hz), 60.7 (C-5′, $J_{5',F}$ = 11.3 Hz), 87.34 (C-1′), 87.99 (C-4′, $J_{4',F}$ = 21.3 Hz), 94.43 (C-3′, $J_{3',F}$ = 172.9 Hz), 110.27 (C-5), 145.55 (C-6, $J_{6,F}$ = 0.09 Hz), 149.43 (C-2), 161.65 (C-4), 186.23 (CHO).

MS: m/z (%) = 258 (M$^+$, 17), 140 (14), 119 (100), 112 (32).

1-(2,3-Dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-5-ethoxycarbonylamino-2,4(1H,3H)-pyrimidinedione **(7c)**; yield: 330 mg (43 %); mp 160 °C (Et$_2$O).

^{1}H NMR (DMSO-d_6): δ = 1.18 (t, 3 H, CH$_3$, J = 7.1 Hz), 2.1–2.6 (m, 2 H, 2′-H), 3.54 (dd, 1 H, 5′-H, J = 11.4, 4.6 Hz), 3.64 (dd, 1 H, 5′-H, J = 11.4, 3.1 Hz), 4.05 (q, 2 H, CH$_2$, J = 7.1 Hz), 4.16 (dt, 1 H, 4′-H, J = 27.4, 3.7 Hz), 5.30 (dd, 1 H, 3-H, J = 53.8, 4.3 Hz), 6.23 (dd, 1 H, 1′-H, J = 5.5, 9.1 Hz), 8.02 (s, 1 H, 6-H), 8.25 (s, 1 H, NH), 11.63 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.34 (CH$_3$), 37.00 (C-2′, $J_{2',F}$ = 20.4 Hz), 60.40 (CH$_2$), 60.79 (C-5′, $J_{5',F}$ = 11.1 Hz), 84.16 (C-1′), 84.88 (C-4′, $J_{4',F}$ = 22.8 Hz), 94.77 (C-3′, $J_{3',F}$ = 173.9 Hz), 113.54 (C-5), 131.93 (C-6), 149.23 (C-2), 154 (C-4), 160.07 (C=O).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)-5-ethoxycarbonylamino-2,4(1H,3H)-pyrimidinedione **(8c)**; yield: 120 mg (16 %); mp 153 °C (Et$_2$O).

^{1}H NMR (DMSO-d_6): δ = 1.21 (t, 3 H, CH$_3$, J = 7.1 Hz), 2.26 (dd, 1 H, 2′α-H, J = 23.0, 15.9 Hz), 2.6–2.9 (m, 1 H, 2′β-H), 3.35 (m, 2 H, 5′-H), 4.06 (q, 2 H, CH$_2$, J = 7.1 Hz), 4.54 (td, 1 H, 4′-H, J = 4.3, 24.1 Hz), 5.30 (dd, 1 H, 3′-H, J = 5.0, 54.3 Hz), 6.22 (dd, 1 H, 1′-H, J = 1.3, 7.5 Hz), 7.83 (s, 1 H, 6-H), 8.18 (s, 1 H, NH), 11.6 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.32 (CH$_3$), 38.41 (C-2′, $J_{2',F}$ = 20.3 Hz), 60.40 (CH$_2$), 60.85 (C-5′, $J_{5',F}$ = 11.3 Hz), 85.88 (C-1′), 87.13 (C-4′, $J_{4',F}$ = 21.3 Hz), 94.34 (C-3′, $J_{3\,F}$ = 173.78 Hz), 113.21 (C-5), 130.02 (C-6), 148.92 (C-2), 154.14 (C-4), 159.96 (C=O).

1-(2,3-Dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-5-nitro-2,4(1H,3H)-pyrimidinedione **(7d)**; yield: 56 mg (50 %); white foam.

^{1}H NMR (DMSO-d_6): δ = 2.2–2.7 (m, 2 H, 2′-H), 3.7 (m, 2 H, 5′-H), 4.35 (d, 1 H, 4′-H, J = 25.7 Hz), 5.33 (dd, 1 H, 3′-H, J = 4.5, 53.5 Hz), 6.15 (t, 1 H, 1′-H, J = 6.8 Hz), 9.35 (s, 1 H, C-6), 12.05 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 38.6 (C-2′, $J_{2',F}$ = 21.1 Hz), 60.39 (C-5′, $J_{5',F}$ = 10.8 Hz), 86.1 (C-4′, $J_{4',F}$ = 22.9 Hz), 86.51 (C-1′), 94.5 (C-3′, $J_{3',F}$ = 174.7 Hz), 125.6 (C-5), 145.1 (C-6), 148.6 (C-2), 154.51 (C-4).

MS: m/z (%) = 275 (0.07), 157 (3.6), 119 (100), 81 (71), 41 (78).

2,3-Dideoxy-3-fluoro-1-O-methyl-1-(5-nitrouracil-1-yl)-D-erythro-pentitol **(9d)**; yield: 39 mg (32 %); semi-solid material.

^{1}H NMR (DMSO-d_6): δ = 2.0–2.5 (m, 2 H, 2′-H), 3.1–3.7 (m, 6 H, OMe, 5′-H, 4′-H), 4.4–4.8 (m, 1 H, 3′-H), 5.71 (m, 1 H, 1′-H), 8.81, 8.82 (2 s, 1 H, 6-H), 11.72, 12.1 (2 s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 35.1 (C-2′, $J_{2',F}$ = 20.3 Hz), 38.61 (C-2′, $J_{2',F}$ = 21.1 Hz), 56.68 (OCH$_3$), 56.88 (OCH$_3$), 61.46 (C-5′, $J_{5',F}$ = 16.3 Hz), 61.71 (C-5′, $J_{5',F}$ = 6.4 Hz), 71.99 (C-4′, $J_{4',F}$ = 21.7 Hz), 72.08 (C-4′, $J_{4',F}$ = 21.1 Hz), 85.75 (C-1′), 89.77 (C-3′, $J_{3',F}$ = 170.0 Hz), 90.69 (C-3′, $J_{3',F}$ = 169.4), 126.6 (C-5), 144.35 (C-6), 149.23 (C-2), 154.63 (C-4).

Danish Ministry of Education and ENRECA, Danish Minsitry of Foreign Affairs are gratefully acknowledged for their support.

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