

SYNTHESIS OF ISOMERIC N-(3-FLUORO-2-HYDROXYPROPYL) AND N-(2-FLUORO-3-HYDROXYPROPYL) DERIVATIVES OF PURINE AND PYRIMIDINE BASES

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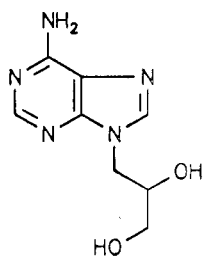
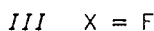
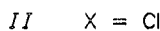
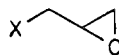
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Reaction of fluoromethyloxirane (*III*) with heterocyclic bases in the presence of potassium carbonate afforded N-(3-fluoro-2-hydroxypropyl) derivatives of adenine (*VI*), 3-deazaadenine (*VII*), 2-amino-6-chloropurine (*XII*), 6-nitro-1-deazapurine (*IX*), 4-methoxy-2-pyrimidone (*XVIII*) and its 5-methyl derivative (*XIX*). Acid hydrolysis of compounds *XII*, *XVIII*, and *XIX* gave 9-(3-fluoro-2-hydroxypropyl)guanine (*XIII*), 1-(3-fluoro-2-hydroxypropyl)uracil (*XX*) and -thymine (*XXI*). The intermediates *XVIII* and *XIX* were ammonolyzed to give 1-(3-fluoro-2-hydroxypropyl)cytosine (*XXII*) and -5-methylcytosine (*XXIII*). Reaction of chloro derivative *XII* with sodium azide followed by hydrogenation of the formed 2-amino-6-azidopurine (*XIV*) led to 9-(3-fluoro-2-hydroxypropyl)-2,6-diaminopurine (*XV*). 9-(3-Fluoro-2-hydroxypropyl)-1-deazaadenine (*X*) was obtained by hydrogenation of compound *IX*. Benzyloxymethyloxirane (*XXIV*) was reacted with pyridine-hydrogen fluoride adduct to give 3-benzyloxy-2-fluoropropanol (*XXV*) whose tosylate *XXVI* on reaction with sodium salt of adenine and subsequent hydrogenolysis of the intermediate *XXVII* afforded 9-(2-fluoro-3-hydroxypropyl)adenine (*XXVIII*). The same compound was obtained by reaction of 3-benzyloxy-1-bromo-2-fluoropropanol (*XXX*) with sodium salt of adenine followed by methanolysis. Condensation of sodium salt of *XI*, *XVI*, and *XVII* with synthon *XXX* and subsequent acid deblocking gave 9-(2-fluoro-3-hydroxypropyl)guanine (*XXXIII*), 1-(2-fluoro-3-hydroxypropyl)uracil (*XXXVI*), and 1-(2-fluoro-3-hydroxypropyl)thymine (*XXXVII*). 1-(2-Fluoro-3-hydroxypropyl) derivatives of cytosine (*XXXVIII*) and 5-methylcytosine (*XXXIX*) were obtained by ammonolysis of the corresponding 4-methoxy-pyrimidine intermediates *XXXIV* and *XXXV*.

The acyclic analogue of adenosine, 9-(*S*)-(2,3-dihydroxypropyl)adenine¹ (*I*), inhibits *S*-adenosyl-L-homocysteine hydrolase (SAH hydrolase), an enzyme involved in the regulation in methylation reactions which utilize *S*-adenosyl-L-methionine (SAM) as a methyl donor. Since such reactions are particularly important in proliferating systems, this compound exhibits a whole spectrum of interesting biological effects¹. One of them is the important nonspecific antiviral effect which is directed primarily against rhabdoviruses, rota- and rheoviruses, but also against the vaccinia virus². The analogue *I* is also used in the clinical practice as antiherpeticum. In our previous communication of this series we studied systematically the structure-activity relationships in the series of acyclic adenosine analogues and proved the connection between inhibition of SAH

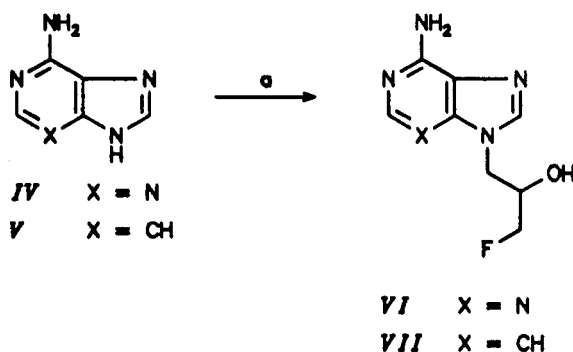
hydrolase and the antiviral effect³; these results were later confirmed by others⁴. The presence of hydroxyl functionality in positions 2 and 3 of the side chain of compound *I* (as well as the absolute configuration *2S*) represents a necessary condition for the interaction with SAH hydrolase. The design of analogues of hydroxylated bioorganic molecules has often and successfully used the principle of replacing the hydroxyl by fluorine atom. In this compound, the hydroxyl groups have not the usual function of bearing the phosphomonoester bonds because neither compound *I* nor its analogues are phosphorylated *in vivo*^{2,5}. For this reason, we intended to synthesize analogues of compound *I* in which one of the hydroxyl groups is replaced by an atom of fluorine. The present study concerns the method of preparation of isomeric racemic compounds in the series of purine and pyrimidine derivatives.

*I*

The simplest synthesis of N-(3-fluoro-2-hydroxypropyl) derivatives consists in alkylation of heterocyclic bases with fluoromethyloxirane (*III*) which can be prepared by exchange reaction of epichlorohydrin (*II*) with potassium fluoride⁶ in the presence of a crown ether. An analogous method was used e.g. in the preparation of N-(3-alkoxy-2-hydroxypropyl) derivatives of these bases^{3,7}. This alkylation is catalyzed by traces of hydroxides or carbonates of alkali metals and proceeds regiospecifically, leading exclusively to 3-fluoro-2-hydroxypropyl derivatives. The bases were alkylated with oxirane *III* in dimethylformamide in the presence of potassium carbonate.

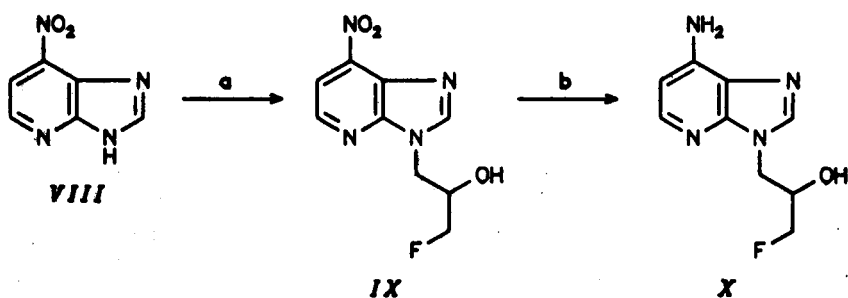
In the purine series, adenine (*IV*) and 3-deazaadenine (*V*) are alkylated with oxirane *III* almost completely in the position 1⁹. The arising N-(3-fluoro-2-hydroxypropyl) derivatives *VI* and *VII* can easily be purified by chromatography (Scheme 1). The alkylation of 1-deazaadenine is not so regioselective. 9-(3-Fluoro-2-hydroxypropyl)-1-deazaadenine (*X*) can be prepared better and in a higher yield by alkylation of 6-nitro-1-deazapurine (*VIII*) with oxirane *III* and subsequent hydrogenation of the intermediate *IX* on palladium (Scheme 2).

Analogously to other alkylated guanines, the guanine-9-yl derivative *XIII* was prepared by an indirect method: 2-amino-6-chloropurine (*XI*) was reacted with oxirane *III* to give intermediate *XII* which was easily converted into the guanine derivative *XIII* by acid hydrolysis. It is worth notice that the alkylation of chloro derivative *XI* with oxirane *III* affords only insignificant amounts of the 7-isomer which in alkylations with other reagents represents a minor but not negligible component of the reaction mixture⁸. Reaction of the same intermediate *XII* with sodium azide afforded 2-amino-6-



a *III*, K_2CO_3 , DMF

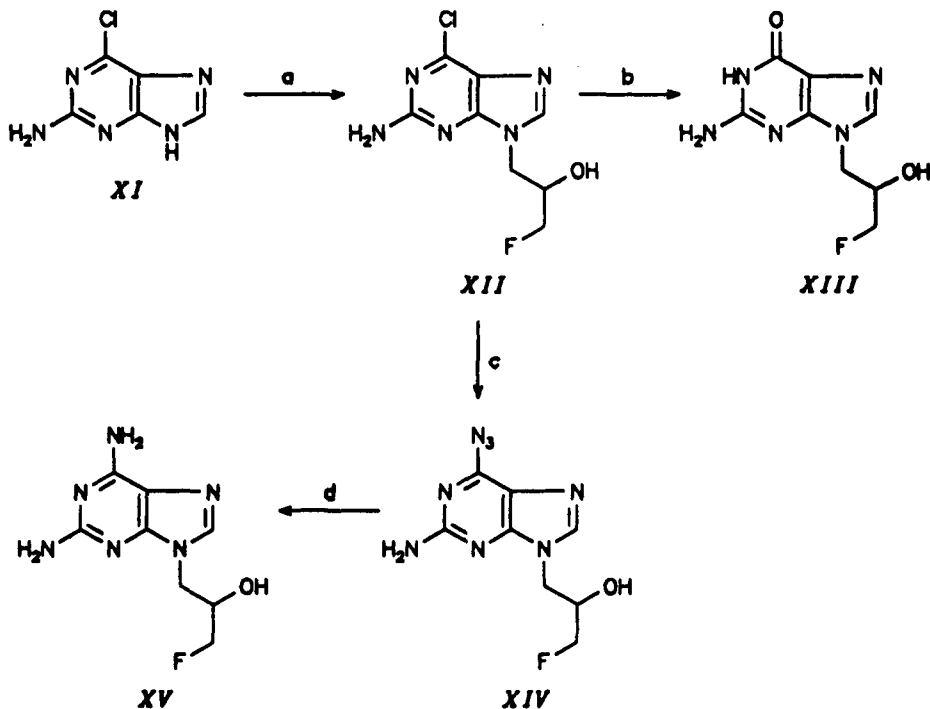
SCHEME 1



a *III*, K_2CO_3 , DMF; b H_2 , Pd/C, MeOH

SCHEME 2

azidopurine derivative *XIV* which was converted to 9-(3-fluoro-2-hydroxypropyl)-2,6-diaminopurine (*XV*) by hydrogenation on palladium (Scheme 3).

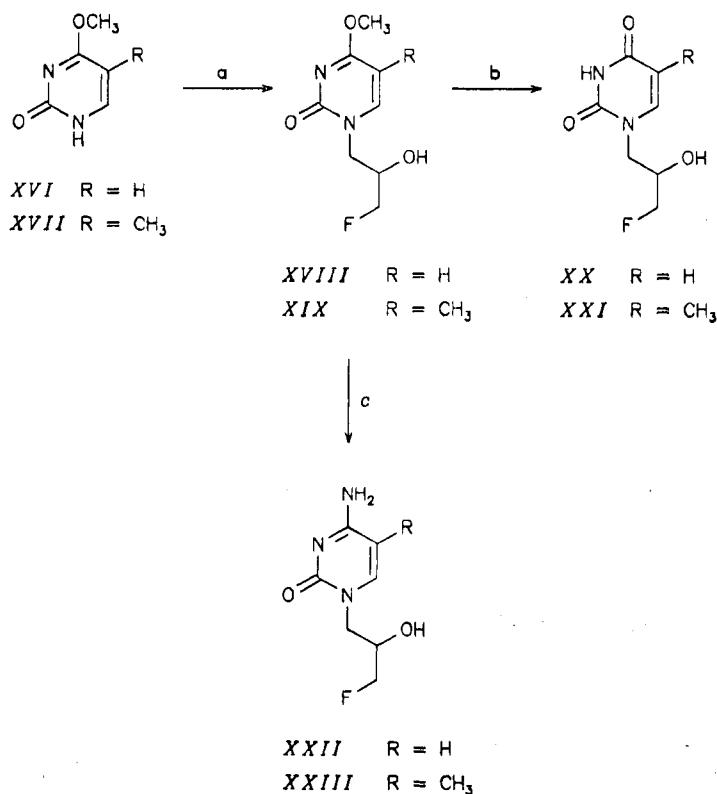


a *XII*, K_2CO_3 , DMF; b HCl, H_2O ; c NaN_3 , DMF; d H_2 , Pd/C, MeOH

SCHEME 3

Selective alkylation of pyrimidine derivatives in the position N^1 is most easily effected using O^4 -alkyl derivatives⁹. Acid hydrolysis of the obtained N^1 -substituted derivatives can lead to uracil or thymine derivatives, whereas ammonolysis with alcoholic ammonia at elevated temperatures affords cytosine or 5-methylcytosine derivatives. This method (Scheme 4) was employed in the preparation of 1-(3-fluoro-2-hydroxypropyl) derivatives of uracil (*XX*) and cytosine (*XXII*) from 4-methoxy-2-pyrimidone (*XVI*), whereas the corresponding 5-methyl derivative *XVII* gave 1-(3-fluoro-2-hydroxypropyl)thymine (*XXI*) and 5-methylcytosine (*XXIII*). It is important that the ammonolysis is not accompanied by cleavage of the C-F bond in the side chain of the 3-fluoro-2-hydroxypropyl derivatives *XXI* and *XXIII*.

The isomer of compound VI, racemic 9-(2-fluoro-3-hydroxypropyl)adenine (XXVIII), was prepared using the procedure in Scheme 5: epichlorohydrin (II) was first converted into benzyloxymethyloxirane¹⁰ (XXIV). This compound was treated with hydrogen fluoride-pyridine adduct to give 3-benzyloxy-2-fluoropropanol¹¹ (XXV) which was then converted into the tosyl derivative XXVI. This synthon was used for alkylation of adenine sodium salt, generated in situ from the base with sodium hydride. The obtained 9-(3-benzyloxy-2-fluoropropyl)adenine (XXVII) was isomerically homogeneous as shown by the ¹H NMR spectrum. Its hydrogenolysis over a palladium catalyst afforded compound XXVIII.

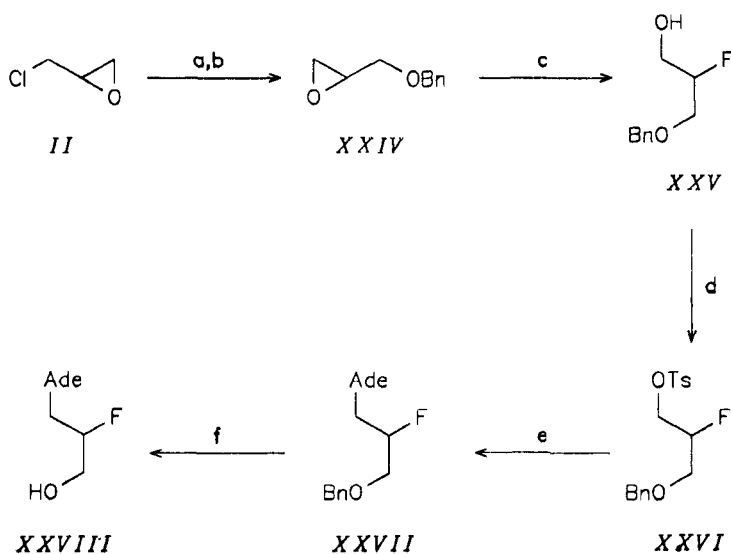


a III , K_2CO_3 , DMF; b HOAc, H_2O ; c NH_3 , MeOH

SCHEME 4

However, this method cannot be applied to a general preparation of N-(2-fluoro-3-hydroxypropyl) derivatives because some heterocyclic bases (e.g. cytosine, thymine

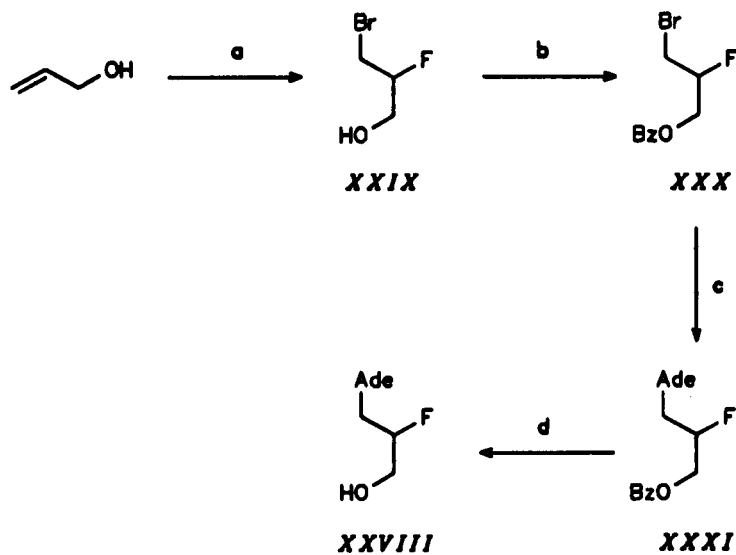
etc.) undergo reduction under conditions of the hydrogenolytic removal of the benzyl group. For this reason we prepared a synthon in which the benzyl ether protecting group is replaced by the alkali-labile benzoyl group: 3-bromo-2-fluoropropanol (*XXIX*) was prepared by described procedure¹² from allyl alcohol by reaction with N-bromo-succinimide and hydrogen fluoride-pyridine adduct. Benzoylation of compound *XXIX* with benzoyl cyanide afforded benzoyl derivative *XXX*. This compound was condensed with adenine sodium salt to give the intermediate *XXXI* whose acid hydrolysis gave racemic 9-(2-fluoro-3-hydroxypropyl)adenine (*XXVIII*) (Scheme 6), identical with the product obtained according to Scheme 5.



a BnOH, BF₃·Et₂O; **b** NaOH, H₂O; **c** (HF)_xpy; **d** TsCl, py;
e IV, NaH, DMF; **f** H₂, Pd/C, MeOH

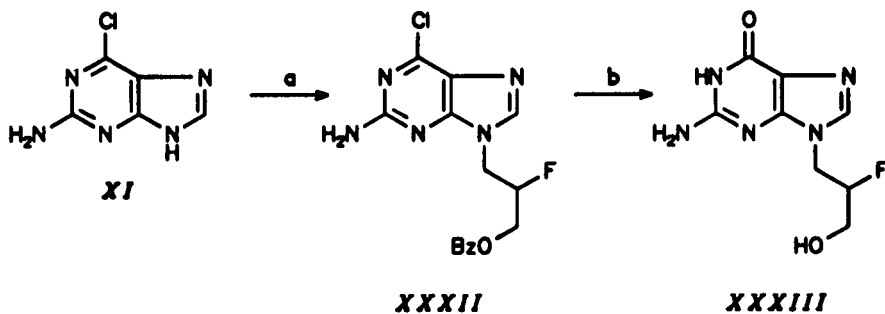
SCHEME 5

The synthon *XXX* was similarly used in the reaction with sodium salt of 2-amino-6-chloropurine (*XI*). The predominant product, 9-isomer *XXXII*, was acid-hydrolyzed to 9-(2-fluoro-3-hydroxypropyl)guanine (*XXXIII*) (Scheme 7). Also pyrimidine derivatives were obtained by reaction of the synthon *XXX*: reaction with sodium salts of 4-methoxy-2-pyrimidone (*XVI*) or its 5-methyl derivative *XVII* gave the protected derivatives *XXXIV* and *XXXV* which on acid cleavage lost simultaneously the methoxyl and



a NBS, (HF)₂py, Et₂O; b BzCN, Et₃N, CH₂Cl₂; c IV, NaH, DMF;
d NaOMe, MeOH

SCHEME 6

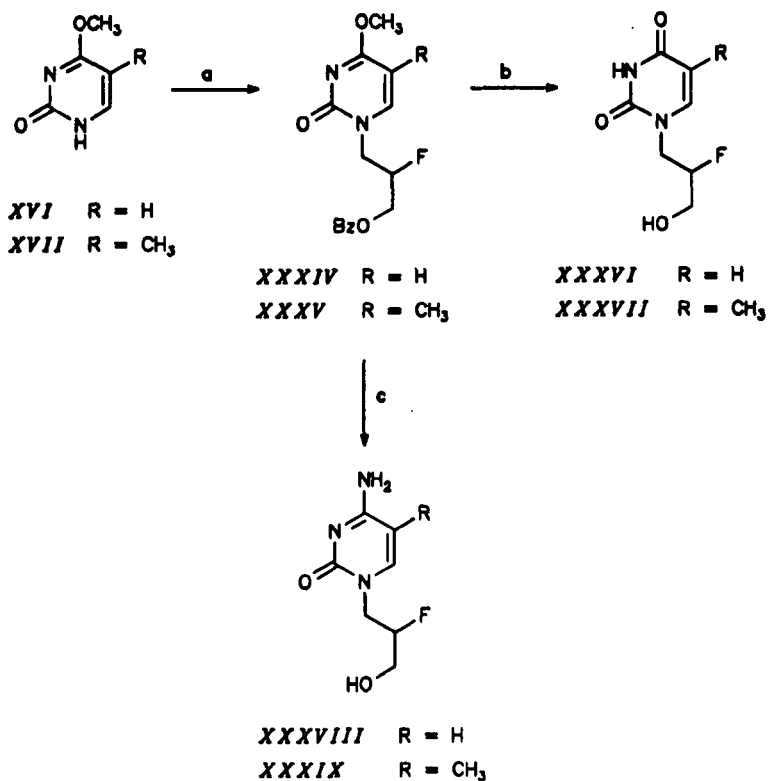


a XXX, NaH, DMF; b HCl, H₂O

SCHEME 7

benzoyl functionalities and afforded 1-(2-fluoro-3-hydroxypropyl) derivatives of uracil (*XXXVI*) and thymine (*XXXVII*). Compounds *XXXIV* and *XXXV* were then ammonolyzed to give the respective derivatives of cytosine (*XXXVIII*) and 5-methylcytosine (*XXXIX*) (Scheme 8).

All the compounds prepared in this study have been characterized by their ^1H NMR



a XXX , NaH, DMF; b HCl, H_2O ; c NH_3 , MeOH

SCHEME 8

spectra and molecular peaks and fragmentation in their mass spectra. Their UV spectra corresponded to N-alkyl derivatives of the corresponding heterocyclic bases.

Biological properties. The isomeric fluorohydroxypropyl derivatives were tested on antiviral activity against selected group of RNA viruses (VSV, Reovirus type 1,

parainfluenza type 3, Sindbis virus, poliovirus type 1, coxsackie B4) and DNA viruses (HSV-1, HSV-2, vaccinia, VZV and CMV) on tissue cultures under standard conditions¹³. Neither of the studied compounds had any extraordinary antiviral effect up to 200 µg/ml of the medium.

EXPERIMENTAL

Methods. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 25 °C. NMR spectra were taken on a Varian 200 XL instrument in FT mode at 200 MHz (¹H spectra) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Thin-layer chromatography was carried out on Silufol UV₂₅₄, column chromatography on silica gel Silpearl (both Kavalier, Votice, Czechoslovakia). Solvent systems for TLC: S1 chloroform-methanol (3 : 1), S2 chloroform-methanol (4 : 1), S3 chloroform-methanol (5 : 1), S4 chloroform-methanol (6 : 1), S5 chloroform-methanol (10 : 1), S6 chloroform-methanol (20 : 1), S7 toluene-ethyl acetate (3 : 1), S8 toluene-ethyl acetate (15 : 1), S9 ethyl acetate-acetone-ethanol-water (10 : 2 : 2 : 1). HPLC was carried out on columns (250 × 4 mm and 250 × 17 mm) packed with Separon SGXC18 (5 µm and 10 µm, respectively; Laboratorní přístroje, Prague, Czechoslovakia). UV absorption spectra were measured on a Pye Unicam 8800 UV/VIS spectrophotometer, wavelengths of extrema are given in nm. The solutions were evaporated on a rotary vacuum evaporator at 40 °C. Analytical samples were dried at 25 °C and 6.5 Pa for 8 h.

Materials and reagents. Adenine, epichlorohydrin, and palladium on carbon were purchased from Janssen (Belgium), 2-amino-6-chloropurine was a Merck (Germany) product. All the other chemicals were obtained from Lachema (Czechoslovakia). 4-Methoxy-2-pyrimidone and 4-methoxy-5-methyl-2-pyrimidone were prepared as described in ref.¹⁴, 3-deazaadenine according to ref.¹⁵, and 6-nitro-1-deazapurine according to ref.¹⁶. Dimethylformamide was dried by distillation from phosphorus pentoxide and stored over molecular sieves (5Å).

Epifluorohydrin⁶ (III)

A mixture of finely ground potassium fluoride (77.0 g, 1.33 mol) and 18-crown-6 (5.0 g, 18.5 mmol) was heated (together with the stirring bar) to 100 °C at 10 Pa in a flask equipped with reflux condenser for 4 h. Freshly distilled epichlorohydrin (II; 100 ml, 1.28 mol) was added and the reaction mixture was stirred under exclusion of moisture at 190 °C for 18 h. The product was distilled from the mixture and fraction boiling at 84 – 86 °C was collected. Yield 41 g (42%) of compound III. For C₃H₅FO (76.1) calculated: 47.37% C, 6.62% H, 24.97% F; found: 47.47% C, 6.68% H, 24.85% F.

9-(3-Fluoro-2-hydroxypropyl)adenine (VI)

A stirred mixture of adenine (IV; 1.35 g, 10 mmol), anhydrous potassium carbonate (70 mg, 0.5 mmol), epifluorohydrin (III; 0.9 ml, 12.6 mmol), and dimethylformamide (30 ml) was heated to 70 – 75 °C for 6 h. The dimethylformamide was evaporated and the residue was boiled with ethanol (200 ml), filtered while hot and the filtrate was concentrated to about 100 ml. After standing at –20 °C, the product was collected, yielding 1.33 g (63%) of compound VI, m.p. 202 – 208 °C (ethanol), *R_F* 0.30 (S2). For C₈H₁₀FN₅O (211.2) calculated: 45.49% C, 4.77% H, 8.99% F, 33.16% N; found: 45.51% C, 4.69% H, 9.07% F, 31.91% N. ¹H NMR spectrum: 4.18 m, 3 H (H-1' and H-2'); 4.38 ddd, 2 H (FC₂H₂, *J*(3',F) = 50); 5.55 d, 1 H (OH, *J*(OH,2') = 5); 7.20 s, 1 H (NH₂); 8.08 s, 1 H (H-8); 8.14 s, 1 H (H-2). MS (*m/e*): 211 (M⁺, 18); 194 (M – NH₃, 15); 178 (M – CH₂F, 20); 148 (M – CHO₂CH₂F, 41); 135 (Ade, 20); 108(17). UV spectrum (λ_{max} (ε)): pH 1: 257 (12 400); pH 7: 254 (6 700); pH 13: 259 (12 640).

9-(*RS*)-(3-Fluoro-2-hydroxypropyl)-3-deazaadenine (*VII*)

A mixture of 3-deazaadenine (*V*; 1.34 g, 10 mmol), potassium carbonate (73 mg, 0.5 mmol), dimethylformamide (30 ml), and fluoromethyloxirane (0.9 ml) was heated to 100 °C for 5 h (the starting base not detectable by HPLC (5% acetonitrile in 0.05M-TEAB)). The reaction mixture was separated by preparative HPLC using water-methanol gradient (0.5% methanol/min, 60 min). The product-containing fraction was evaporated and the residue was codistilled with ethanol and crystallized from ethanol (ether added to turbidity). Yield 0.33 g (16%), m.p. 178 – 180 °C, $k = 8.1$ (from 2% to 10% acetonitrile in 0.05M-TEAB, 0.3 %/min). For $C_9H_{11}FN_4O \cdot 2 H_2O$ (246.2) calculated: 7.72% F, 22.74% N; found: 7.54% F, 22.17% N. 1H NMR spectrum: 8.00 s, 1 H (H-8 arom.); 7.67 d, 1 H (H-2, $J(2,3) = 5.7$); 6.82 d, 1 H (H-3, $J(2,3) = 5.7$); 6.11 brs, 2 H (NH₂); 5.54 br, 1 H (OH); 4.60 d, 2 H (H-1', $J(1',2') = 4.0$); 3.80 – 4.40 m, 3 H (H-2' and H-3'). UV spectrum (λ_{max} (ε)): pH 2: 262 (10 700); pH 13: 266 (11 600).

9-(*RS*)-(3-Fluoro-2-hydroxypropyl)-6-nitro-1-deazapurine (*IX*)

A mixture of 6-nitro-1-deazapurine (*VIII*; 1.82 g, 10 mmol), potassium carbonate (73 mg, 0.5 mmol), dimethylformamide (30 ml), and fluoromethyloxirane (*III*, 0.9 ml) was heated under argon for 6 h (until the starting base was not detectable by HPLC (9% acetonitrile in 0.05M-TEAB)). The reaction mixture was adsorbed on silica gel (20 g) and chromatographed on silica gel (100 g). The product was eluted with chloroform-ethanol (95 : 5) and crystallized from ethanol (ether added to incipient turbidity), affording 0.90 g (43%) of nitro derivative *IX*, m.p. 144 – 145 °C, $k = 3.8$ (9% acetonitrile in 0.05M-TEAB) For $C_9H_9FN_4O_3$ (240.2) calculated: 7.91% F, 23.32% N; found: 7.74% F, 23.12% N. 1H NMR spectrum: 8.75 s, 1 H (H-8 arom.); 8.65 d, 1 H (H-2, $J(2,1) = 5.4$); 7.98 d, 1 H (H-1, $J(1,2) = 5.4$); 5.59 d, 1 H (OH, $J = 4.9$); 4.15 – 4.70 unresolved m (other protons). UV spectrum (λ_{max} (ε)): pH 2: 318 (5 600); pH 13: 295 (6 100).

9-(*RS*)-(3-Fluoro-2-hydroxypropyl)-1-deazaadenine (*X*)

A solution of compound *IX* (0.5 g, 2.1 mmol) in methanol (10 ml) was hydrogenated over 10% Pd/C (0.3 g) for 2 h. After filtration of the reaction mixture through a layer of Celite and evaporation of the solvent, the residue was crystallized from ethanol; yield 0.32 g (73%), m.p. 120 – 122 °C, R_F 0.3 (S5). For $C_9H_{11}FN_4O$ (210.2) calculated: 9.04% F, 26.64% N; found: 9.32% F, 26.81% N. 1H NMR spectrum: 8.32 s, 1 H (H-8 arom.); 8.01 d, 1 H (H-2, $J(2,1) = 6.8$); 6.67 d, 1 H (H-1, $J(1,2) = 6.8$); 8.26 brs, 2 H (NH₂); 5.30 br, 1 H (OH); 4.00 – 4.70 unresolved m (other protons). UV spectrum (λ_{max} (ε)): pH 2: 281 (17 000), 260 (15 800); pH 13: 275 (10 300), 263 (12 800).

9-(3-Fluoro-2-hydroxypropyl)-2-amino-6-chloropurine (*XII*)

A stirred mixture of 2-amino-6-chloropurine (*XI*; 7.1 g, 41.9 mmol), anhydrous potassium carbonate (280 mg, 2 mmol), epifluorohydrin (*III*; 6 ml, 84.2 mmol), and dimethylformamide (150 ml) was heated to 80 °C for 6 h. The solvent was evaporated in vacuo (oil pump) at 40 °C, the reaction mixture was dissolved in methanol and evaporated with silica gel (50 g). This material was applied on a column of silica gel (800 ml) and chromatographed in S5, affording 6.2 g (60%) of compound *XII*, m.p. 180 – 182 °C, R_F 0.56 (S2). For $C_8H_9ClFN_5O$ (245.6) calculated: 39.11% C, 3.69% H, 14.43% Cl, 7.73% F, 28.51% N; found: 35.45% C, 3.28% H, 14.45% Cl, 6.32% F, 27.89% N. 1H NMR spectrum: 4.15 m, 3 H (H-2' + H-1'); 4.38 ddd, 2 H (FCH₂, $J(3',F) = 50$); 5.55 d, 1 H (OH, $J(OH,2') = 5$); 6.91 s, 2 H (NH₂); 8.05 s, 1 H (H-8). MS (*m/e*): 245 (M, 100); 228 (M – NH₃, 20); 212 (M – CH₂F, 48); 183 (M – ClOHICH₂F, 90); 169 (C₅H₃ClN₅, 44); 146(70); 134 (C₅H₃N₅, 62); 119(20); 104(20); 92(23); 83(19); 69(22); 57(31); 40(62). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 308 (8 850); pH 7: 308 (8 900); pH 12: 308 (8 900).

9-(3-Fluoro-2-hydroxypropyl)guanine (XIII)

A solution of compound XII (9.0 g, 36.7 mmol) in 80% acetic acid (100 ml) was refluxed for 3 h. The reaction mixture was taken down, the dry residue codistilled with ethanol, dissolved in water and applied onto a column of Dowex 50X4 (H⁺-form; 90 ml). The column was washed with water to negative reaction to chloride ions and the product was eluted with 2.5% aqueous ammonia. The obtained solution was evaporated to dryness and the residue was crystallized from methanol; yield 5.6 g (67%) of XIII, m.p. 260 – 265 °C, R_F 0.10 (S1). For C₈H₁₀FN₅O₂ (227.2) calculated: 42.28% C, 4.43% H, 8.36% F, 30.82% N; found: 42.31% C, 4.89% H, 7.95% F, 31.20% N. ¹H NMR spectrum: 3.99 m, 3 H (NCH₂ + OCH); 4.34 dd, 2 H (FCH₂, $J(3',F) = 50$); 5.52 d, 1 H (OH, $J(OH,2') = 5$); 6.44 bs, 2 H (NH₂); 7.63 s, 1 H (H-8); 10.59 bs, 1 H (NH). UV spectrum (λ_{max} (ε)): pH 7: 248.5 (12 800); pH 1: 252.5 (14 500); pH 13: 266 (12 600).

2-Amino-6-azido-9-(3-fluoro-2-hydroxypropyl)purine (XIV)

A stirred mixture of compound XII (4.00 g, 16.3 mmol), sodium azide (6 g, 92 mmol), and dimethylformamide (80 ml) was heated to 100 °C for 6 h. The solvent was evaporated and the residue extracted with water (2 × 15 ml). The solid residue was crystallized from methanol; yield 2.80 g (68%) of compound XIV, m.p. 208 °C (decomp.), R_F 0.61 (S1). For C₈H₉FN₆O (252.2) calculated: 38.10% C, 3.60% H, 7.53% F, 44.43% N; found: 37.16% C, 3.52% H, 8.26% F, 43.87% N. ¹H NMR spectrum: 4.20 m + 4.65 bs, 4 H + 1 H (FCH₂ + NCH₂ + OCH, $J(3',F) = 40$); 5.53 d, 1 H (OH, $J(OH,2') = 4$); 8.11 s, 1 H (H-8); 8.38 s, 2 H (NH₂). MS (m/e): 252 (M, 50); 224 (M - N₂, 100); 209 (M - N₃H, 7); 193(11); 163(25); 148(80); 119(25); 108(13); 94(18); 81(18); 68(40); 57(9); 43(21); 28(37).

2,6-Diamino-9-(3-fluoro-2-hydroxypropyl)purine (XV)

Compound XIV (255 mg, 1.0 mmol) was hydrogenated over 10% Pd/C (150 mg) in methanol (30 ml) (the reaction was monitored by TLC in S3). The mixture was filtered through Celite and the material on the filter was washed with methanolic ammonia. Evaporation of the filtrate gave compound XV (201 mg, 88%), m.p. 219 °C (decomp.), R_F 0.30 (S1). For C₈H₁₁FN₆O (226.2) calculated: 42.48% C, 4.90% H, 8.40% F, 37.15% N; found: 41.22% C, 5.21% H, 8.06% F, 38.99% N. ¹H NMR spectrum: 4.03 m + 4.56 dd, 4 H + 1 H (CF₂ + NCH₂ + OCH, $J(3',F) = 50$); 5.56 d, 1 H (OH, $J(OH,2') = 4$); 5.78 s, 2 H (NH₂); 6.65 s, 2 H (NH₂); 7.63 s, 1 H (H-8). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 290.5 (11 750); pH 7: 279 (12 000); pH 12: 279.5 (11 850).

1-(3-Fluoro-2-hydroxypropyl)-4-methoxypyrimidone (XVIII)

A stirred mixture of 4-methoxy-2-pyrimidone (XVI; 6.0 g, 47.6 mmol), anhydrous potassium carbonate (320 mg, 2.3 mmol), epifluorohydrin (III; 5.2 ml, 72.9 mmol), and dimethylformamide (100 ml) was heated to 85 °C for 5 h. The solvent was evaporated under diminished pressure, the residue was codistilled with toluene and separated on a column of silica gel (800 ml) in chloroform-methanol (25 : 1) to give 9.0 g (93%) of compound XVIII as a sirup, R_F 0.20 (S6). For C₈H₁₁FN₂O₃ (202.2) calculated: 47.52% C, 5.48% H, 9.39% F, 13.88% N; found: 45.96% C, 5.82% H, 4.35% F, 13.36% N. ¹H NMR spectrum: 3.42 – 4.10 m, 3 H (H-1' + H-2'); 3.81 s, 3 H (OCH₃); 4.36 ddd, 2 H (H-3', $J(3',F) = 48$); 5.43 d, 1 H (OH, $J(OH,2') = 6$); 5.97 d, 1 H (H-5, $J(5,6) = 7$); 7.84 d, 1 H (H-6, $J(6,5) = 7$). MS (m/e): 202 (M, 5); 185 (M - OH, 5); 169 (M - CH₂F, 25); 139 (M - CHOCH₂F, 91); 127(100); 109(26); 82(30); 70(14); 55(15); 42(15). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 273.5 (8 000); pH 7: 273.5 (8 050); pH 12: 273 (7 950).

1-(3-Fluoro-2-hydroxypropyl)uracil (XX)

A solution of compound XVIII (300 mg) in 80% acetic acid (10 ml) was refluxed for 0.5 h. The solution was evaporated to dryness and the residue was codistilled with toluene, yielding 190 mg (68%) of compound XX, m.p. 110 – 115 °C, R_F 0.70 (S1). For $C_7H_9FN_2O_3$ (188.2) calculated: 44.68% C, 4.82% H, 10.09% F, 14.88% N; found: 44.88% C, 4.84% H, 10.18% F, 14.54% N. 1H NMR spectrum: 3.50 – 4.16 m, 3 H (H-1', H-2'); 4.36 dd, 2 H (H-3', $J(3',F) = 50$); 5.52 dd, 1 H (H-5, $J(5,6) = 8$, $J(5,NH) = 2$); 7.52 d, 1 H (H-6, $J(6,5) = 8$); 11.2 bs, 1 H (NH). MS (m/e): 188 (M, 27); 168 (M – HF, 19); 155 (M – CH_2F , 16); 149(10); 126 (M – $CHFCHOH$, 50); 82(100), 69(15); 57(16); 43(11); 28(68). UV spectrum (λ_{max} (ϵ)): pH 7: 265 (6 600); pH 1: 263 (6 300); pH 13: 263 (4 900).

1-(3-Fluoro-2-hydroxypropyl)cytosine (XXII)

A solution of compound XVIII (9.0 g, 44.5 mmol) in 3.3M methanolic ammonia (100 ml) was heated to 100 °C for 24 h in a sealed ampoule. The reaction mixture was concentrated to a minimum volume and the residue was crystallized from methanol; yield 6.1 g (73%) of XXII, m.p. 200 °C (methanol), R_F 0.16 (S1). For $C_7H_{10}N_3O_2$ (187.2) calculated: 44.91% C, 5.38% H, 22.45% N, 10.15% F; found: 44.45% C, 5.59% H, 24.68% N, 10.19% F. 1H NMR spectrum: 3.46 m, 1 H (H-2'); 4.32 ddd, 2 H (FCH_2 , $J(3',F) = 48$); 5.40 d, 1 H (OH, $J(OH,2') = 6$); 5.63 d, 1 H (H-5, $J(5,6) = 8$); 6.96 bs, 2 H (NH_2); 7.42 d, 1 H (H-6, $J(6,5) = 8$). MS (m/e): 187 (M, 9); 167 (M – HF, 11); 124 (M – CH_2FCHOH , 58); 112 ($C_4H_6N_3O$, 100); 96(10); 81(91); 69(28); 57(22); 43(19). UV spectrum (λ_{max} (ϵ)): pH 7: 272 (8 350); pH 1: 280.5 (12 750); pH 13: 272 (8 700).

1-(3-Fluoro-2-hydroxypropyl)-4-methoxy-5-methyl-2-pyrimidone (XIX)

A mixture of 4-methoxy-5-methylpyrimidone (XVII; 513 mg, 3.6 mmol), epifluorohydrin (III; 394 μ l, 5.5 mmol), and potassium carbonate (26 mg, 0.2 mmol) in dimethylformamide (15 ml) was heated to 70 °C for 19 h. The reaction mixture was filtered and concentrated to a minimum volume. The residue was chromatographed on silica gel (70 g) in chloroform–methanol (30 : 1); yield 622 mg (78%) of XIX, m.p. 95 – 105 °C. For $C_9H_{13}FN_2O_3$ (216.2) calculated: 49.99% C, 6.06% H, 8.78% F, 12.95% N; found: 50.43% C, 6.19% H, 8.75% F, 13.13% N. MS (m/e): 216 (M, 17); 196 (M – HF, 11); 183 (M – CH_2F , 32); 165(8); 153(82); 141(100); 123(40); 112(12); 96(32); 82(13); 70(12); 55(20); 42(25). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 281 (6 100); pH 7: 281.5 (6 150); pH 12: 281 (6 200).

1-(3-Fluoro-2-hydroxypropyl)-5-methyluracil (XXI)

A solution of compound XIX (200 mg, 0.9 mmol) in 80% acetic acid (5 ml) was refluxed for 2 h. The reaction mixture was evaporated to dryness and chromatographed on a column of silica gel (20 g) in chloroform–methanol (30 : 1); yield 112 mg (60%) of product XXI, m.p. 119 – 121 °C, R_F 0.27 (S5). For $C_8H_{11}FN_2O_3$ (202.2) calculated: 47.52% C, 5.48% H, 9.39% F, 13.85% N; found: 46.26% C, 5.65% H, 8.35% F, 14.20% N. 1H NMR spectrum: 1.75 s, 3 H (CCH_3); 3.41 – 4.10 m, 3 H ($NCH_2 + H-2'$); 4.35 dd, 2 H (FCH_2 , $J(3',F) = 48$); 5.45 d, 1 H (OH); 7.41 s, 1 H (H-6); 11.21 s, 1 H (NH). MS (m/e): 202 (M, 22); 182 (M – HF, 13); 169 (M – CH_2F , 9); 139 (M – CH_2FCHOH , 31); 126 (MeUra, 14); 96(100); 83(7); 69(12); 55(17); 41(29). UV spectrum (λ_{max} (ϵ)): pH 7: 265 (10 450); pH 1: 270 (13 500); pH 13: 268 (10 400).

1-(3-Fluoro-2-hydroxypropyl)-5-methylcytosine (XXIII)

A mixture of compound XIX (113 mg, 0.5 mmol) and 3.3M methanolic ammonia (2 ml) was heated to 100 °C for 21 h in a sealed ampoule. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol–ether; yield 41 mg (39%) of compound XXIII, m.p. 201 – 203 °C, R_F 0.25 (S9). For

$C_8H_{12}FN_3O_2$ (201.2) calculated: 47.75% C, 6.01% H, 9.44% F, 20.88% N; found: 9.59% F, 22.11% N. UV spectrum (50% methanol) (λ_{max}): pII 2: 290; pII 7: 281; pII 12: 278.

Benzyl Glycidyl Ether (XXIV)

Epichlorohydrin (30 ml, 383 mmol) was added dropwise during 4 h at 55 °C to a stirred mixture of benzyl alcohol (41 g, 380 mmol) and 1.5% solution of boron trifluoride etherate in ether (7.6 ml). After cooling to 25 °C, a solution of sodium hydroxide (19 g, 475 mmol) in water (19 ml) was added under stirring during 1 h. The reaction mixture was washed with water and fractionated on a column, fraction 54 – 56 °C/12 Pa being collected; yield 24 g (38%). Reported¹⁰ b.p. is 257 °C. For $C_{10}H_{12}O_2$ (164.2) calculated: 73.14% C, 7.36% H; found: 72.59% C, 7.21% H. ¹H NMR spectrum: 2.58 dd, 1 H; 2.78 dd, 1 H; 3.18 m, 1 H (H-2); 3.43 dd, 1 H; 3.76 dd, 1 H; 4.57 s, 2 H ($C_6H_5CH_2$); 7.33 s, 5 H (C_6H_5). MS (*m/e*): 164 (M, 11); 107 (BnO, 50); 91 (Bn, 100); 79(40); 65(30); 57 (M – BnO, 10); 51(15); 39(15), 29(10).

3-Benzoyloxy-2-fluoro-1-propanol (XXV)

Benzoyloxymethyloxirane (XXIV; 8 g) was added at –5 °C to 70% adduct of hydrogen fluoride and pyridine (10 ml). The mixture was stirred for 15 min and poured into a solution of sodium hydrogen carbonate (35 g) in water (500 ml). The aqueous layer was extracted with chloroform (3 × 100 ml), the combined chloroform extracts were dried over sodium sulfate and the solvent was evaporated in vacuo. The residue was chromatographed on a column of silica gel (200 g) in toluene–ethyl acetate (10 : 1, 5 : 1); yield 1.57 g (17%) of compound XXV, R_F 0.14 (S7). For $C_{10}H_{13}FO_2$ (184.2) calculated: 65.19% C, 7.11% H, 10.31% F; found: 66.49% C, 7.54% H, 9.41% F. ¹H NMR spectrum: 3.30 – 3.81 m, 4 H (H-1, H-3); 4.41 m + 4.91 m, 1 H (H-2, $J(2,F) = 50$); 4.51 s, 2 H ($C_6H_5CH_2$); 7.34 s, 5 H (C_6H_5). MS (*m/e*): 184 (M, 15); 165 (M – F, 3); 107 (BnO, 53); 91 (Bn, 100); 79(13); 65(11).

1-Benzoyloxy-2-fluoro-3-*p*-toluenesulfonyloxypropane (XXVI)

A mixture of compound XXV (851 mg, 4.6 mmol), *p*-toluenesulfonyl chloride (1.0 g, 5.25 mmol), and pyridine (3 ml) was allowed to stand at room temperature for 18 h and then partitioned between an ice-water mixture (90 ml) and toluene (50 ml). The organic layer was separated, washed with water (2 × 50 ml) and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel (50 g) in toluene–ethyl acetate (25 : 1); yield 630 mg (40%), R_F 0.54 (S8). For $C_{17}H_{19}FO_4S$ (338.4) calculated: 60.33% C, 5.65% H, 5.61% F, 9.47% S; found: 60.33% C, 5.66% H, 6.05% F, 9.21% S. ¹H NMR spectrum: 3.32 s, 3 H ($C_6H_4CH_3$); 3.60 dd, 1 H (H-1, $J(1,F) = 23$); 4.24 dd, 2 H (H-3, $J(3,F) = 23$); 4.46 s, 2 H ($C_6H_5CH_2$); 4.62 m + 5.12 m, 1 H (H-2, $J(2,F) = 49$); 7.30 m, 5 H (C_6H_5); 7.48 m + 7.80 m, 2 H + 2 H (C_6H_4). MS (*m/e*): 338 (M, 3); 202(5); 183 (M – Ts, 3); 165 (M – TsOH, 21); 153 (M – TsOCH₂, 7); 107 (Bn, 16); 91 (Bn, 100); 65(15).

9-(3-Benzoyloxy-2-fluoropropyl)adenine (XXVII)

A mixture of adenine (IV; 111 mg, 0.8 mmol) and sodium hydride (19.8 mg, 0.85 mmol) in dimethylformamide (10 ml) was heated to 80 °C for 15 min. Tosylate XXVI (306 mg, 0.9 mmol) was added and the mixture was heated to 100° for 3 h. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (10 g) in chloroform–methanol (20 : 1), affording 120 mg (48%) of compound XXVII, m.p. 135 – 144 °C, R_F 0.69 (S1). For $C_{15}H_{16}FN_5O$ (301.3) calculated: 59.78% C, 5.35% H, 6.30% F, 23.24% N; found: 59.80% C, 5.36% H, 6.96% F, 24.04% N. MS (*m/e*): 301 (M, 7); 284 (M – NH₃, 4); 256(7); 224 (M – Ph, 11); 210 (M – Bn, 30); 195(100); 175(15); 149(56); 135(Ade, 42); 108 (BnOH, 12);

91 (Bn, 89); 81(22); 69(40); 55(22); 41(26); 28(40). UV spectrum (50% methanol) (λ_{\max} (ϵ)): pH 2: 257 (13 500); pH 7: 260 (14 200); pH 12: 257 (13 472).

3-Bromo-2-fluoro-1-propanol (XXIX)

Adduct of hydrogen fluoride and pyridine (70%, 120 g), followed by allyl alcohol (40 g, 690 mmol) was added under stirring and ice-cooling to N-bromosuccinimide (120 g, 674 mmol) in ether (240 ml). The mixture was stirred at 0 °C for 2 h and then at room temperature for 2 h, diluted with ether (500 ml), neutralized with anhydrous sodium carbonate (450 g) and filtered. The solvent was evaporated and the residue was fractionated on a column in vacuo; yield 5.3 g (5%) of compound XXIX, b.p. 85 °C/2 kPa. For C_3H_6BrFO (157.0) calculated: 22.95% C, 3.85% H, 50.90% Br, 12.10% F; found: 22.46% C, 4.08% H, 50.24% Br, 11.72% F. 1H NMR spectrum: 3.47 – 3.84 m, 4 H ($BrCH_2 + OCH_2$); 4.09 bs, 1 H (OH); 4.41 m + 4.89 m, 1 H (FCH, $J(2',F) = 48$). MS (m/e): 136 (M – HF, 10); 77 (M – Br, 72); 57(17); 46(26); 31(100).

3-Benzoyloxy-1-bromo-2-fluoropropane (XXX)

Triethylamine (0.5 ml) was added at room temperature to a stirred mixture of compound XXIX (4.4 g, 28.3 mmol), benzoyl cyanide (4.7 g, 35.8 mmol), and dichloromethane (4 ml). After stirring for 15 min, the reaction mixture was chromatographed on silica gel (200 g) in chloroform; yield 5.73 g (78%) of compound XXX. For $C_{10}H_{10}BrFO_2$ (261.1) calculated: 46.00% C, 3.86% H, 30.60% Br, 7.28% F; found: 44.54% C, 4.67% H, 31.57% Br, 9.00% F. 1H NMR spectrum: 4.14 ddd + 4.85 ddd, 2 H + 2 H ($OCH_2 + BrCH_2$); 4.90 m + 5.38 m, 1 H (FCH, $J(2',F) = 52$); 7.62 m + 7.97 m, 3 H + 2 H (Bz). MS (m/e): 260 (M, 2); 181 (M – Br, 12); 122(13); 105 (Bz, 100); 77(48); 51(25).

9-(3-Benzoyloxy-2-fluoropropyl)adenine (XXXI)

A mixture of adenine (IV; 335 mg, 2.5 mmol), sodium hydride (72 mg, 3.0 mmol), and dimethylformamide (5 ml) was heated to 100 °C for 15 min. Compound XXX (974 mg, 3.7 mmol) was then added and the mixture was further heated to 100 °C for 3 h. The solvent was evaporated and the residue chromatographed on a column of silica gel (150 g) in chloroform–methanol (25 : 1); yield 250 mg (32%), m.p. 205 – 207 °C, R_F 0.53 (S4). For $C_{15}H_{14}FN_5O_2$ (315.3) calculated: 57.13% C, 4.47% H, 6.02% F, 22.21% N; found: 58.07% C, 5.18% H, 6.23% F, 22.30% N. 1H NMR spectrum: 4.26 – 4.92 m, 4 H ($NCH_2 + OCH_2$); 5.13 m + 5.60 m, 1 H (FCH, $J(2',F) = 49.1$); 7.25 s, 2 H (NH_2); 7.45 – 8.04 m, 5 H (Bz); 8.15 s + 8.18 s, 2 H (H-2 + H-8). MS (m/e): 315 (M, 31); 210 (M – Bz, 72); 194 (M – BzO, 44); 191 (M – Bz – F, 43); 174 (M – BzO – HF, 78); 148 (AdeCH₂, 22); 135 (Ade, 21); 105 (Bz, 100); 77 (Ph, 36); 51(6); 28(12). UV spectrum (50% methanol) (λ_{\max} (ϵ)): pH 2: 257 (14 200); pH 7: 259 (14 850); pH 12: 258 (15 000).

9-(2-Fluoro-3-hydroxypropyl)adenine (XXVIII)

A) From compound XXVII. Compound XXVII (120 mg, 0.4 mmol) in methanol (6 ml) was hydrogenated over 5% Pd on charcoal (50 mg) in the presence of conc. hydrochloric acid (0.2 ml) at room temperature for 20 h. The reaction mixture was neutralized with triethylamine, concentrated to a minimum volume and the product was crystallized from methanol; yield 40 mg (48%) of compound XXVIII, m.p. 240 °C, R_F 0.47 (S1). For $C_8H_{10}FN_5O$ (211.2) calculated: 45.45% C, 4.77% H, 8.99% F, 33.16% N; found: 45.85% C, 5.21% H, 9.46% F, 33.70% N. MS (m/e): 211 (M, 20); 191 (M – H₂, 33); 194 (M – NH₃, 7); 181 (M – CH₂O, 10); 174(10); 162(6); 148(25); 135 (Ade, 100); 108(41). UV spectrum (50% methanol) (λ_{\max} (ϵ)): pH 2: 257 (15 500); pH 7: 259 (16 000); pH 12: 259 (15 700).

B) From compound *XXXI*. To a solution of compound *XXXI* (111 g, 0.35 mmol) in methanol (20 ml) was added 0.1M methanolic sodium methoxide (2 ml) at room temperature. After 15 min the solution was neutralized with a cation-exchanging resin (Dowex 50; H⁺-form), filtered, the resin was washed with methanol and the filtrate was evaporated to a minimum volume. The residue was washed with acetone to give a product (59 mg, 80%) identical with compound *XXVIII* prepared under *A*).

2-Amino-9-(3-benzoyloxy-2-fluoropropyl)-6-chloropurine (*XXXII*)

A stirred mixture of 2-amino-6-chloropurine (*XI*; 546 mg, 3.2 mmol), compound *XXX* (1.266 g, 4.8 mmol), sodium hydride (116 mg, 4.8 mmol), and dimethylformamide (14 ml) was heated to 100 °C for 6 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel (130 g) in chloroform-methanol (30 : 1). Crystallization from toluene afforded 714 mg (63%) of compound *XXXII*, m.p. 167 – 168 °C (toluene), *R_F* 0.64 (S4). For C₁₅H₁₃ClFN₅O₂ (349.8) calculated: 51.51% C, 3.75% H, 10.14% Cl, 5.43% F, 20.02% N; found: 52.79% C, 4.19% H, 10.44% Cl, 5.78% F, 20.22% N. ¹H NMR spectrum: 4.17 – 4.90 m, 4 H (NCH₂ + OCH₂); 5.09 m + 5.57 m, 1 H (FCH, *J*(2',F) = 48); 6.89 s, 2 H (NH₂); 7.44 – 8.06 m, 5 H (Bz); 8.16 s, 1 H (H-8). MS (*m/e*): 349 (M, 41); 244 (M – Bz, 10); 208 (M – Bz – Cl, 7); 105 (Bz, 100); 77 (Ph, 29). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 308 (6 900); pH 7: 308 (7 000); 307 (7 200).

9-(2-Fluoro-3-hydroxypropyl)guanine (*XXXIII*)

A solution of compound *XXXII* (200 mg, 0.6 mmol) in 2M-HCl (5 ml) was refluxed for 6 h. The reaction mixture was extracted with chloroform (3 × 2 ml) and the aqueous phase was applied onto a column of Dowex 50 (H⁺-form, 5 ml). The column was washed with water to negative reaction to chloride ions, then with methanol. The product was eluted with 2.5% ammonia. Evaporation of the ammonia eluate to dryness and crystallization of the residue from methanol afforded the desired product *XXXIII* (102 mg, 78%), m.p. 220 °C, *R_F* 0.25 (S1). For C₈H₁₀FN₅O₂ (227.2) calculated: 42.29% C, 4.44% H, 8.36% F, 30.82% N; found: 43.30% C, 4.80% H, 7.07% F, 31.42% N. ¹H NMR spectrum: 3.37 – 4.37 m, 4 H (NCH₂ + OCH₂); 4.57 m + 5.11 m, 1 H (FCH, *J*(2',F) = 54); 5.17 t, 1 H (OH, *J*(OH,3') = 6); 6.47 s, 2 H (NH₂); 7.69 s, 1 H (H-8); 10.57 bs, 1 H (NH). MS (*m/e*): 227 (M, 71); 210 (M – OH, 3); 197 (M – CH₂O, 10); 179(4); 164(29); 151(100); 134(13); 109(47); 96(3); 54(9); 43(28); 28(68). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 253 (14 900); pH 7: 251 (15 850); pH 12: 266 (12 700).

1-(3-Benzoyloxy-2-fluoropropyl)-4-methoxy-2-pyrimidone (*XXXIV*)

A mixture of 4-methoxy-2-pyrimidone (*XVI*; 1.0 g, 7.9 mmol), compound *XXX* (2.5 g, 9.5 mmol), sodium hydride (190 mg, 7.9 mmol), and dimethylformamide was heated to 80 °C for 6 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel (150 g) in chloroform; yield 1.39 g (57%), m.p. 104 – 109 °C, *R_F* 0.72 (S5). For C₁₅H₁₅FN₂O₄ (306.3) calculated: 58.82% C, 4.94% H, 6.20% F, 9.15% N; found: 58.07% C, 5.07% H, 7.55% F, 9.25% N. ¹H NMR spectrum: 3.81 s, 3 H (OCH₃); 4.00 – 4.75 m, 4 H (NCH₂ + OCH₂); 4.88 m + 5.38 m, 1 H (FCH, *J*(2',F) = 50); 6.03 d, 1 H (H-5, *J*(5,6) = 7); 7.60 m + 7.96 m, 3 H + 3 H (Bz + H-6). MS (*m/e*): 306 (M, 4); 286 (M – HF, 8); 256(12); 201 (M – Bz, 21); 185 (M – BzO, 32); 139 (M – BzO – C₂H₃F, 35); 105 (Bz, 100); 77(45); 57(50); 41(48). UV spectrum (50% methanol) (λ_{max} (ε)): pH 2: 273 (7 100); pH 7: 273 (7 200); pH 12: 273 (7 200).

1-(2-Fluoro-3-hydroxypropyl)uracil (*XXXV*)

A solution of compound *XXXIV* (244 mg, 0.8 mmol) in 2M-HCl (5 ml) was refluxed for 8 h. The reaction mixture was neutralized with sodium hydrogen carbonate, extracted with chloroform (2 ml), the aqueous layer was evaporated and the residue was chromatographed on silica gel (10 g), first in chloroform, then in

chloroform-methanol (10 : 1); yield 115 mg (77%) of compound *XXXVI*, m.p. 170 – 175 °C, R_F 0.35 (S4). For $C_7H_9FN_2O_3$ (188.2) calculated: 44.68% C, 4.82% H, 10.10% F, 14.89% N; found: 45.28% C, 5.41% H, 9.65% F, 14.69% N. 1H NMR spectrum: 3.40 – 4.20 m, 4 H (NCH₂ + OCH₂); 4.44 m + 4.96 m, 1 H (FCH₂, $J(2',F) = 52$); 5.06 bs, 1 H (OH); 5.57 d, 1 H (H-5, $J(5,6) = 7$); 7.55 d, 1 H (H-6, $J(6,5) = 7$). MS (m/e): 188 (M, 18); 158 (M – CH₂O, 6); 149(12); 125 (UraCH₂, 15); 112 (Ura, 61); 82(100); 73(22); 55(26); 43(31); 32(23). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 262 (11 500); pH 7: 262.5 (11 550); pH 12: 261 (7 900).

1-(2-Fluoro-3-hydroxypropyl)cytosine (*XXXVIII*)

To a solution of compound *XXXIV* (250 mg, 0.8 mmol) in methanol (4 ml) was added 3.3M methanolic ammonia solution (6 ml) and the mixture was heated to 100 °C for 5 h. After evaporation, the residue was chromatographed on a column of silica gel (20 g) in chloroform-methanol (10 : 1 and then 4 : 1); yield 98 mg (64%) of compound *XXXVIII*, R_F 0.23 (S1). For $C_7H_{10}FN_3O_2$ (187.2) calculated: 44.92% C, 5.38% H, 10.15% F, 22.45% N; found: 47.87% C, 5.77% H, 10.28% F, 21.66% N. 1H NMR spectrum: 3.56 – 4.25 m, 4 H (NCH₂ + OCH₂); 4.42 m + 4.96 m, 1 H (FCH, $J(2',F) = 50$); 5.04 bs, 1 H (OH); 5.67 d, 1 H (H-5, $J(5,6) = 7$); 7.08 bs, 2 H (NH₂); 7.50 d, 1 H (H-6, $J(6,5) = 7$). MS (m/e): 187 (M, 7); 167 (M – HF, 73); 156 (M – CH₂O, 15); 124 (M – C₂H₄FO, 32); 111 (Cyt, 98); 96(11); 81(100); 69(19); 55(20); 41(26). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 281 (12 600); pH 7: 272.5 (8 250); pH 12: 272 (8 100).

1-(3-Benzoyloxy-2-fluoropropyl)-4-methoxy-5-methyl-2-pyrimidone (*XXXV*)

A mixture of 4-methoxy-5-methyl-2-pyrimidone (*XVII*; 500 mg, 3.5 mmol), compound *XXX* (1.12 g, 3.4 mmol), sodium hydride (85 mg, 3.5 mmol), and dimethylformamide (10 ml) was heated to 80 °C for 6 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel (70 g) in chloroform, affording 405 mg (35%) of compound *XXXV*, m.p. 122 – 124 °C, R_F 0.60 (S5). For $C_{16}H_{17}FN_2O_4$ (320.3) calculated: 60.00% C, 5.35% H, 5.93% F, 8.75% N; found: 59.80% C, 5.51% H, 5.99% F, 8.63% N. 1H NMR spectrum: 1.87 s, 3 H (C-CH₃); 3.85 s, 3 H (OCH₃); 3.97 – 4.72 m, 4 H (NCH₂ + OCH₂); 4.91 m + 5.41 m, 1 H (FCH, $J(2',F) = 50$); 7.62 m + 8.00 m, 5 H (Bz); 7.83 s, 1 H (H-6). MS (m/e): 320 (M, 11); 300 (M – HF, 4); 215 (M – Bz, 44); 199 (M – BzO, 49); 195 (M – BzO – HF, 33); 185 (M – BzOCH₂, 23); 165(28); 140(21); 123(11); 105 (Bz, 100); 77 (Ph, 40); 57(27); 41(18). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 279 (6 800); pH 7: 279 (6 850); pH 12: 279 (6 800).

1-(2-Fluoro-3-hydroxypropyl)-5-methyluracil (*XXXVII*)

A solution of compound *XXXV* (406 mg, 1.3 mmol) in 2M-HCl (10 ml) was refluxed for 2 h. The reaction mixture was washed with chloroform (10 ml), and the aqueous phase was neutralized with sodium hydrogen carbonate. After evaporation to dryness, the residue was chromatographed on a column of silica gel (20 g) in chloroform-methanol (10 : 1); yield 195 mg (76%) of compound *XXXVII*, m.p. 150 – 154 °C, R_F 0.20 (S5). For $C_8H_{11}FN_2O_3$ (202.2) calculated: 47.52% C, 5.48% H, 9.40% F, 13.86% N; found: 48.12% C, 5.70% H, 8.76% F, 14.00% N. 1H NMR spectrum: 1.76 s, 3 H (CH₃); 3.35 – 4.23 m, 4 H (NCH₂ + OCH₂); 4.45 m + 4.96 m, 1 H (FCH, $J(2',F) = 51$); 5.07 t, 1 H (OH, $J(3',OH) = 6$); 7.45 s, 1 H (H-6); 11.27 s, 1 H (NH). MS (m/e): 202 (M, 30); 172 (M – CH₂O, 18); 139 (M – C₂H₄FO, 18); 126 (MeUra, 85); 110(3); 96(82); 83(7); 68(5); 55(17); 41(18); 28(100). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 269 (9 950); pH 7: 268.5 (9 600); pH 12: 266.5 (6 900).

1-(2-Fluoro-3-hydroxypropyl)-5-methylcytosine (XXXIX)

Compound XXXV (390 mg, 1.2 mmol) in a mixture of 3.3M methanolic ammonia (5 ml) and methanol (5 ml) was heated in a sealed ampoule to 100 °C for 24 h. The solvent was evaporated and the residue was crystallized from methanol (4 ml) to give 140 mg (57%) of compound XXXIX, m.p. 210 - 213 °C, R_F 0.35 (S1). For $C_8H_{12}FN_3O_2$ (201.2) calculated: 47.75% C, 6.01% H, 9.44% F; 20.88% N; found: 47.50% C, 5.30% H, 9.63% F, 20.77% N. 1H NMR spectrum: 1.82 s, 3 H (CH_3); 3.57 - 4.25 m, 4 H ($NCH_2 + OCH_2$); 4.42 m + 4.96 m, 1 H (FCH, $J(2',F) = 54$); 5.06 t, 1 H (OH, $J(OH,3') = 6$); 6.93 bs, 2 H (NH_2); 7.36 s, 1 H (H-6). MS (m/e): 201 (M, 20); 181 (M - HF, 45); 170 (M - CH_2OH , 12); 149(10); 138 (M - C_2H_4FO , 15); 125 (MeCyt, 100); 110 (Cyt, 10); 95 (Cyt - NH, 70), 81(18); 70(19); 54(21); 41(19). UV spectrum (50% methanol) (λ_{max} (ϵ)): pH 2: 289 (13 371); pH 7: 278 (8 800); pH 12: 278 (8 700).

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