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The Synthesis of Fluorine-containing Pterins

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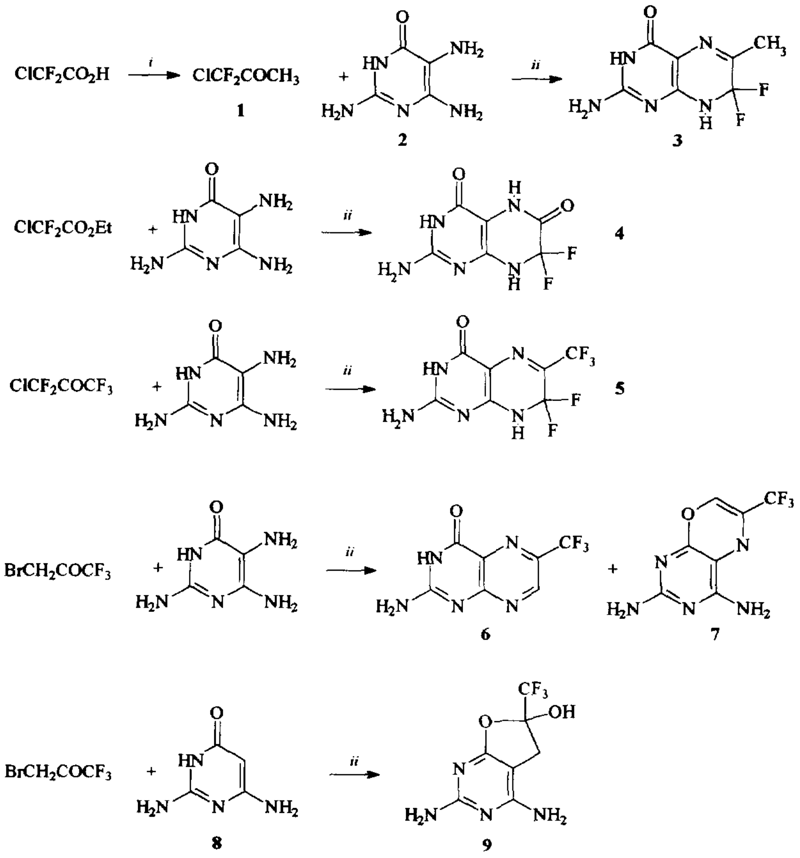
Abstract: The synthesis of some 7,7-difluoro-7,8-dihydropterins and pterins with fluoroalkyl subsitutents at the 6 or 7 positions from fluorine-containing aliphatic precursors and suitably substituted pyrimidines is described. The fluorine-containing pterins were found to be very insoluble and also stable to nucleophiles and bases in dilute aqueous solution Copyright © 1996 Elsevier Science Ltd

The substitution of fluorine into a molecule has been extensively used to modify the properties of that molecule to establish a specific biological function. Thus fluorine substitution confers stability towards oxidation in drugs,[1] provides a spectroscopic probe for mechanistic studies,[2] and in several cases, plays a direct role in the action of an enzyme inhibitor as for example, in thymidylate synthase,[3] the inhibition of pyridoxal phosphate dependent enzymes,[4] and the inhibition of peptidases.[5]

Cofactors composed of the pteridine ring system are involved in one carbon transfer and in redox reactions.[5,6] For the former, they depend upon the nucleophilicity of N-5 and N-10 and for the latter upon hydrogen transfer to the pyrazine ring of the pteridine. The importance of these reactions in biosynthesis is immense and in particular, the coupling of pterin-dependent processes to the synthesis of components of DNA and the production of essential amino acids is noteworthy.[7] Recently, there has been a revival of interest in the design of inhibitors of enzymes in the folate pathway to find new, selective herbicides and antibacterial drugs, especially in view of the increasing resistance of certain bacteria to current drugs. Although fluorine substitution has been effected in folic acid derivatives both in the benzene ring of the side chain for spectroscopic purposes[2] and in the glutamate side chain to influence polyglutamation reactions,[8] no reports have been made of the synthesis of pterins in which fluorine is substituted in positions that would affect the nucleophilicity of N-5 or N-10 or the redox properties of the pyrazine ring. In this paper, we report the synthesis of 7- and 9-difluoro substituted pterins using routes that will be extendable to the synthesis of the natural cofactors for one carbon transfer and hydroxylation.[9]

Synthesis of 7,7-difluoropterins 7,7-Difluoropterins belong to the class of blocked dihydropterins in which oxidation to the fully conjugated system is not possible. There is some synthetic interest in this class of compounds with respect to their stability because of the potential for the elimination of hydrogen fluoride to form a 7,8-double bond. Such compounds with methyl substituents have been greatly exploited as enzyme inhibitors.[10] In those cases, the most effective general synthetic route has been *via* 6-chloro-5-nitropyrimidines which requires the availability of nucleophilic amino precursors. The fluoro analogues of these compounds, although less hindered than their dimethyl analogues would be expected to be poorly nucleophilic and we therefore investigated the preparation of the required 7,7-difluoro compounds from 2,4,5-triaminopyrimidin-5(1H)-one 2 (Scheme 1).

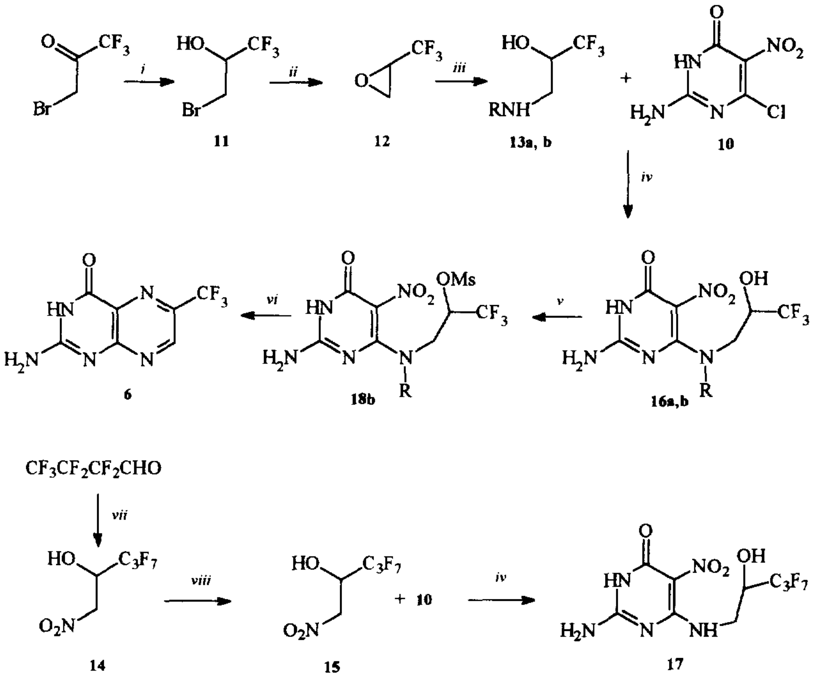


Scheme 1 *Reagents:* *i* MeMgI, *ii* Et_3N / EtOH

We found that chlorodifluorocarbonyl compounds were generally suitable for the synthesis of simple 7,7-difluoropterins. Thus the hydrate of 1-chloro-1,1-difluoroacetone 1, prepared by treatment of chlorodifluoroacetic acid with methylmagnesium iodide,[11] reacted with the triaminopyrimidine 2 in the presence of triethylamine to afford the required pteridine 3 in 79% yield. This reaction appeared to be fairly general in scope because ethyl chlorodifluoroacetate and 1-chloro-1,1,3,3,3-pentafluoroacetone reacted similarly to afford the corresponding pteridin-4(3H),6(5H)-dione 4 and pentafluoropteridine 5 in 76% and 71% yields respectively. Although chlorodifluoro carbonyl compounds appear to be satisfactory precursors for this synthesis, 1-bromo-3,3,3-

trifluoroacetone reacted differently affording a mixture of products including the 6-trifluoromethylpterin **6** and the pyrimidooxazine **7** both in low yield. Cyclisation involving the carbonyl group of the pyrimidine **2** has been reported previously[12] and we recently found that a related reaction occured with 2,4-diaminoprimidin-6(1H)-one **8** affording a dihydrofuropyrimidine **9**.[13]

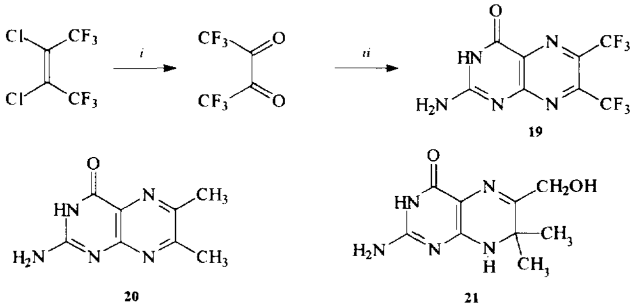
Synthesis of 9-substituted pterins Unlike the 7,7-disubstituted compounds described above, there was no readily available precursor for the synthesis of 9-fluoropterins since the reaction of bromotrifluoroacetone with the diaminopyrimidine **2** was unsatisfactory. With fluorine in the side chain, the restriction on the synthesis imposed by the reduction in nucleophilicity of the fluorosubstituted amines did not apply and we were able to use the unambiguous route through the chloronitropyrimidine **10** (Scheme 2).



Scheme 2 *Reagents:* *i* LiAlH$_4$; *ii* aq. NaOH, 100°C; *iii* RNH$_2$ R = **a** H, **b** PhCH$_2$; *iv* Et$_3$N; *v* MsCl / pyridine; *vi* H$_2$ / Pd, DDQ; *vii* CH$_3$NO$_2$; *viii* Raney Ni.

Many routes for the preparation of suitably substituted aminofluoroketones following established methods or the synthesis of alkylaminoketones were investigated (e.g. Dakin reaction,[14] hexamine alkylation,[15] and Gabriel synthesis[16]) but none was successful. We were, however, able to obtain suitable precursors using longer routes and in one case, to achieve the synthesis of 6-trifluoromethylpterin **6**. Reduction of bromotrifluoroacetone with lithium aluminium hydride afforded the corresponding alcohol **11** (86%)[17] which on treatment with sodium hydroxide gave the epoxide **12** (84%). Ring opening with ammonia occurred in low yield (26%) to give 2-amino-1,1,1-trifluoropropan-2-ol **13a** but in high yield with benzylamine (96%) affording **13b**. Alternatively, heptafluorobutanal was treated with nitromethane under basic conditions to afford the nitroalcohol **14** (84%) which was reduced with

Raney Nickel to give the aminoalcohol **15** (26%) isolated as its hydrochloride salt. Coupling of the aminoalcohols with the nitrochloropyrimidine **10** in the presence of triethylamine[10] was successful with all three aminoalcohols to give **16a** and **b** and **17** in yields ranging between 88% and 94%. The standard synthetic routes leading to pteridines from such compounds involve cyclisation via the carbonyl oxidation state of the side chain. Many experiments were undertaken in attempts to oxidise the pyrimidinyl aminoalcohols (**16a**, **b** and **17**) to the corresponding ketones (using chromium trioxide in acetic acid, sulphuric acid, or dimethyl formamide; pyridinium chlorochromate; potassium permanganate; dimethylsulphoxide/ trifluoroacetic anhydride; oxalyl chloride/dimethylsulphoxide; aluminium isopropoxide) but without success. Cyclisation was, however, possible at the alcohol oxidation level *via* the mesylate **18b** which was prepared in 93% yield. Reduction of the nitro group and concomitant cleavage of the benzyl protecting group afforded the saturated pyrazine ring which was oxidised to the conjugated 6-trifluoromethylpterin **6** with DDQ (28% overall). One example, 6-trifluoromethylpterin, was synthesised by this method but the routes have sufficient flexibility to permit the synthesis of more complex molecules. 6,7-Bis(trifluoromethyl)pterin **19** was also synthesised (55%) by the condensation of the triaminopyrimidine **2** with hexafluorobiacetyl obtained from the oxidation of 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene (Scheme 3).[19]



Scheme 3 *Reagents: i* CrO_3 / H_2SO_4; *ii* 2,4,5-triaminopyrimidin-6(1H)-one / DMF

Properties of the fluoropterins Pterins are notoriously insoluble and the fluoropterins prepared in this study had even poorer solubility properties than usual; consequently, full spectroscopic analysis (^{13}C and ε_{max} data) was difficult. Uv spectra, however, showed a bathochromic shift as has been reported previously for trifluoromethyl-substituted lumazines.[20] The pK_as were measured and are shown in table 1 in comparison with some nonfluorinated reference compounds measured under the same conditions. The fact that the pK_as were found to be essentially the same in the presence or absence of fluorine in the compounds examined suggests that the acid/base reactions are largely associated with the pyrazine ring which does not bear fluorine substituents. In view of the increased electron deficiency of the pyrazine rings substituted by fluorine in comparison with the unsubstituted compounds, it was of interest to investigate their interaction with nucleophilic and basic reagents. No evidence was obtained by uv/visible spectroscopy for the formation of covalent adducts with hydroxide, methoxide, thiophenolate, and ammonia. The spectra remained unchanged over many hours. In contrast, covalent adducts are well-known with lumazines including those bearing trifluoromethyl groups.[20] It might have been anticipated that the 7,7-difluoropterins in particular would be insufficiently stable for use as probes of biological reactions and the apparent stability of these compounds under the conditions investigated is also of interest in terms of the well-known lability of fluorine α- to nitrogen or oxygen in aliphatic system.[21] With the 7,7-difluoropterins because the adjacent nitrogen is part of an extensively delocalised system (a vinylogous amide) and therefore does not promote hydrolysis of the α-difluoromethylene group. The establishment of these synthetic methodologies therefore opens the way to the synthesis of close analogous of biologically important cofactors.

Table 1 Properties of Fluoropterins and Related Compounds

Compound	**pK_a (methanol)**	**λ_{max} (acid)**	**λ_{max}(neutral)**	**λ_{max} (base)**
3	2.7, 7.9	197, 265, 330	200, 270, 340	203, 223 311, 380
5	2.5, 7.5	195, 278, 380	203, 260, 406	206, 223 247, 417
19	2.4	200, 287, 356	199, 275, 361	203, 273, 366
20	2.2	206, 257, 318	195, 275, 345	194, 235, 340
21	2.3, 7.7	193, 275, 368	203, 230, 277 318, 406	215, 275, 320 416

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on Perkin-Elmer R32 (90 MHz), Bruker WH-250 (250 MHz) or 400-AMX (400 MHz) spectrometers using TMS as internal standard. Ultra-Violet (U.V.) spectra were recorded on a Philips PU8800 UV/VIS spectrophotometer. Infra-Red (I.R.) spectra were recorded on a Perkin-Elmer 397 spectrometer or on a Unicam Mattson 1000 series FTIR spectrometer. Fast Atom Bombardment Mass Spectrometry (FAB-MS) experiments were conducted on a Kratos MS-50 TC mass spectrometer. A static FAB probe was used. The sample was ionised by Ar atom bombardment (99.5% purity). Potentiometric titrations were carried out using a calomel electrode with a sintered glass diaphragm and a pH set standardised (pH 9).

1-Chloro-1,1-difluoroacetone monohydrate **1**[11] Magnesium turnings (2.8g, 0.115mol) were treated with methyl iodide dropwise (16.3g, 0.115mol) in anhydrous ether (40cm^3) to form methyl magnesium iodide. The reaction vessel was surrounded by a water bath at 10°C while the chlorodifluoroacetic acid (5g, 38mmol) in anhydrous ether (20cm^3) was added dropwise with continuous stirring. The reaction was stirred for further 30 min at 10°C, then it was cooled to 0°C and water (10cm^3) was added dropwise. Hydrochloric acid (25cm^3, 7 mol dm^{-3}) was also added slowly, then the aqueous layer separated and extracted three times with ether (20cm^3). The combined organic layers were dried over sodium sulphate and the solution concentrated under reduced pressure to give the ketone **1** as an unstable pale brown liquid, which was stored in ether under nitrogen at 0°C (18.7g, 34mmol, 90%. b.p. = 18°C) ν_{max}/cm^{-1} (film) 3500-3200, 1100 δ_H ($CDCl_3$) 1.1 (3H, s, CH_3), 3.4 (2H, q, OH x 2, J_{HH} = 5Hz). δ_c ($CDCl_3$) 22.9 (CH_3), 93.9, 94.4, 94.8 ($C(OH)_2$, t, J_2 = 31.5Hz), 125.6, 130.4, 135.1 (CF_2Cl, t, J_1 = 302.4Hz).

7,7-Difluoro-6-methylpterin **3** 2,4,5-Triaminopyrimidin-6(1H)-one **2**, (1g, 4.6mmol), was dissolved in dry ethanol (20cm^3), and dry triethylamine (1.416g, 14mmol) was added. The ketone monohydrate **1** (0.67g, 4.6mmol) was added dropwise to the reaction mixture under nitrogen over 30 min. After 48 h refluxing, the solvent was evaporated off under reduced pressure, and the resulting oil triturated with ether, which produced a pale orange solid. The solid was purified by dissolution in dilute ammonia solution, then re-precipitated at pH 7 to afford the required *pterin* **3** as a pale brown solid (784mg, 3.4mmol, 79%. m.p. >360°C (decomp)). (Found: C, 39.4; H, 2.9; N, 32.6 $C_7H_7N_5F_2O$ requires: C, 39.1; H, 3.3; N, 32.5%. FAB-MS Found: 216.07 Da. $C_7H_8N_5F_2O$ requires: 216.17 Da) ν_{max}/cm^{-1} (KBr) 3500, 3400, 2900, 1690, 1170. λ_{max}/nm (MeOH) 197, 273, 340. δ_H (DMSO) 2.55 (3H, s, CH_3), 6.49 (2H, s, NH_2), 6.8-6.x (2H, m, 2 NH). δ_c (DMSO) 17.8 (CH_3), 98.4 (C-4a), 111.9, 116.1, 120.3 (C-7, t, J_1 = 264.6Hz), 141.2, 141.7, 142.2 (C-6, t, J_2 = 31.5Hz), 154.9 (C-8a), 160.9 (C-2), 161.7 (C-4). Similarly prepared were

7,7-Difluoro-6-oxopteridin-4(3H)-one **4** from ethyl 2,2-difluoro-2-chloroacetate (76%. m.p. >360°C (decomp). (Found: C, 33.0; H, 2.1; N, 32.6; $C_6H_5N_5F_2O_2$ requires: C, 33.2; H, 2.3; N, 32.2%. FAB-MS Found 218 Da $C_6H_6N_5F_2O_2$ requires 218 Da) ν_{max}/cm^{-1} (KBr) 3400, 3300, 1710, 1690, 1170. λ_{max}/nm (MeOH) 198, 250, 283, 404.

7,7-Difluoro-6-trifluoromethylpterin **5** from 2-chloro-1,1,1,2,2-pentafluoroacetone (71%. m.p. >360°C (decomp)). (Found: C, 31.5; H, 1.5; N, 25.2 $C_7H_4N_5F_5O$ requires C, 31.2; H, 1.5; N, 26.0%. FAB-MS Found 268.123 Da $C_7H_5N_5F_5O$ requires 268.15 Da) ν_{max}/cm^{-1} (KBr) 3550, 3460, 1690, 1170. λ_{max}/nm (MeOH) 203, 268, 418.

2,6-Diaminopyrimido-4,5-(2'-trifluoromethyl)oxazine **7** and *6-Trifluoromethylpterin* **6** 2,5,6-Triaminopyrimidin-4(3H)-one dihydrochloride **2** (0.36g, 2.6mmol), dry dimethylformamide (40cm^3) and dry triethylamine (0.48cm^3, 7.8mmol), were stirred together then bromotrifluoroacetone (0.487g, 2.6mmol) was added dropwise. The mixture was heated under nitrogen at 80°C overnight, the solution turned pale purple. The reaction mixture was cooled, then filtered. The filtrate was diluted with chloroform, washed with dilute hydrochloric acid, water, then dried over calcium chloride. Evaporation of the solvent under reduced pressure yielded a purple solid. Trituration with dry ether yielded a pale orange solid which was purified by dissolution in dilute ammonia solution then reprecipitated at pH7 to afford the required *pterin* **6**. Evaporation of the ether filtrate yielded the pyrimidooxazine **7** as a purple solid. Yield of **6** = 0.06g, 0.26mmol, 10%. m.p. >360°C (decomp). (Found: C, 36.0; H, 1.7; N, 30.0. $C_7H_4N_5F_3O$ requires C, 36.4; H, 1.74; N, 30.3%. FAB-MS Found: 232.08 Da $C_7H_5N_5F_3O$ requires 232.145 Da) ν_{max}/cm^{-1} (KBr) = 3625, 3400, 1688, 1193, 1137. λ_{max}/nm (MeOH) 196, 284, 361. Yield of **7** = 0.12g, 0.5mmol, 20%. m.p. = 300°C (decomp). (Found: C, 35.5; H, 3.1; N, 30.3. $C_7H_6N_5F_3O$ requires C, 36.1; H, 2.6; N: 30.0%) ν_{max}/cm^{-1} (KBr) 3336, 1651, 1140. λ_{max}/nm (MeOH) 389. δ_c (DMSO) 55.7, 56.2, 56.7, 57.2 (CH, q, J_2 = 31.5Hz), 69 (CH_2), 115.7 (C-5), 156.4 (C-2), 160.3 (C-6), 162.1 (C-5), 165.3 (C-4), 151.6, 156.2, 160.8, 165.4 (CF_3, q J_1 = 289.8Hz).

3-Bromo-1,1,1-trifluoropropan-2-ol **11**[17] 3-Bromo-1,1,1-trifluoropropan-2-one (7g, 36.7mmol), in dry ether (15cm^3), was gradually added to a stirred solution of lithium aluminium hydride (0.436g, 11.5mmol), in ether (15cm^3), and a gentle reflux was produced. After stirring for 3h, water, then dilute hydrochloric acid was added dropwise to the reaction mixture. Extraction of the resulting solution with ether then vacuum distillation, yielded the required product as a colourless liquid. (6.09g, 32mmol, 86%. b.p. = 25°C/1mmHg (Lit[17] b.p. = 124°C/360mmHg)). (Found C, 18.9; H, 2.1; Br, 41.2. $C_3H_4F_3BrO$ requires C, 18.7; H, 2.1; Br, 41.4%) ν_{max}/cm^{-1} (film) 3500, 2700, 1100. δ_H (DMSO) 3.8 - 4.4 (1H, m, CH, $J_{HH} = 4.8Hz$, $J_{HF} = 25Hz$), 4.3 (2H, d, CH_2, $J_{HH} = 4.2Hz$). δ_c(DMSO) 38.2 (CH_2), 66.9, 67.2, 67.5, 67.8 (CHOH, q, $J_2 = 19Hz$), 119.5, 122.8, 126.1, 129.4 (CF_3, q, $J_2 = 208Hz$).

1,1,1-Trifluoroepoxypropane **12** The above bromoalcohol **11** (14.12g, 73.1mmol) was dehydrohalogenated in a stirred 57% by weight aqueous sodium hydroxide solution (50 cm^3) at 100°C. The low-boiling epoxide distilled out of the hot reaction mixture with water as the only contaminant, which was frozen out, yielding the epoxide **12** as a sweet smelling colourless liquid. (7.17g, 64mmol, 88%. b.p. = 39.5°C (760mm Hg)). (Found C, 32.0; H, 2.7 $C_3H_3F_3O$ requires C, 32.2; H, 2.7%) ν_{max}/cm^{-1} (film) 3489, 1269, 1191. δ_H (DMSO) 2.9-3.03 (2H, m, CH_2), 3.8-3.95 (1H, m, CH). δ_c (DMSO) 43.1 (CH_2), 46.5, 47.1, 47.8, 48.4 (CH, q, $J_2 = 38Hz$), 116.8, 121.2, 125.6, 130 (CF_3, q, $J_1 = 277Hz$).

3-Amino-1,1,1-trifluoropropan-2-ol **13a**[17] The epoxide **12** (1g, 9mmol) was added dropwise *via* a syringe to a cooled (-78°C) solution of liquid ammonia (20cm^3) in a two-necked flask fitted with a dry ice condenser. After the addition was complete, the solution was stirred for 30 min., then brought to room temperature, and excess ammonia evaporated off. A white solid formed which was recrystallised from ether affording the aminoalcohol **13a**. (0.3g, 2.7mmol, 26%. M.p. = 99°C). (Found: C, 27.6; H, 5.0; N, 10.8. $C_3H_5F_3NO$ requires C, 28.0; H, 4.7; N, 10.9%) ν_{max}/cm^{-1} (Nujol) 3376, 3311, 1164. δ_H (DMSO) 3.4-3.9 (2H, m, CH_2, $J_{HH} = 16Hz$, $J_{HF} = 54Hz$), 4.1 - 4.4 (1H, m, CH). δ_c (DMSO) 41.4 (CH_2), 69.9, 70.3, 70.8, 71.2 (CHOH, q, $J_2 = 27Hz$), 118.9, 123.4, 127.9, 132.4 (CF_3, q, $J_1 = 283.5Hz$).

3-Benzylamino-1,1,1-trifluoropropan-2-ol **13b**[17] The epoxide **12** (0.5g, 5mmol) was added dropwise to dry benzylamine (0.491g, 5mmol) in order to produce a slight reflux. After the addition was complete, the mixture was stirred for a further 30 min. at room temperature. A white solid precipitated out, which was recrystallised from ether to afford the *benzylaminoalcohol* **13b** (1g, 5mmol, 96%.m.p. = 78°C). (Found: C, 54.7; H, 5.6; N, 6.2 $C_{10}H_{12}NF_3O$ requires C, 54.8; H, 5.5; N, 6.4%) ν_{max}/cm^{-1} (KBr) 3438-3300, 1172. δ_H (DMSO) 2.1-2.6 (2H, m, CH_2, $J_{HH} = 14Hz$, $J_{HF} = 68Hz$), 3.7 (2H, s, CH_2Ph), 3.7 - 4.3 (1H, m, CH), 6.9 - 7.4 (5H, m, C_6H_5, $J_{HH} = 9.5Hz$). δ_c (DMSO) 47.9 (CH_2), 52.6 (CH_2Ph), 67.6, 68.1, 68.6, 69.1 (CHOH, q, $J_2 = 31.5Hz$), 123.3, 127.4, 131.5, 135.6 (CF_3, q, $J_1 = 258.3Hz$).

2-Amino-6-(1-amino-2-hydroxy-3,3,3-trifluoropropyl)-5-nitropyrimidin-4(3H)-one **16a**[10] The aminoalcohol **13a** (63.3mg, 0.49mmol), 2-amino-6-chloro-5-nitropyrimidin-4(3H)-one **10** (85mg, 0.49mmol), dry triethylamine (0.05g, 0.49mmol), and dry ethanol (15cm^3) were refluxed together under nitrogen overnight. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure yielding the required *pyrimidine* **16a** as a yellow solid which was purified by dissolution in hot dilute sodium hydroxide and re-precipitated with dilute acid. (124mg, 0.43mmol, 89%. m.p. >360°C (decomp)). (Found: C, 28.7; H, 4.0; N, 22.6 $C_7H_8N_5F_3O_4$ requires C, 28.9; H, 3.75; N, 22.8%) ν_{max}/cm^{-1} (KBr) 3512, 3498, 1680, 1164. δ_H (DMSO) 3.4-3.9 (2H, m, CH_2, J_{HH} =

15Hz, J_{HF} = 65Hz) 3.7 - 4.3 (1H, m, CH), 6.6 (1H, d, NH, J_{HH} = 7.5Hz). δ_c (DMSO) 46 (CH_2), 66.3, 66.9, 67.5, 68.1 (CHOH, q, J_2 = 37.8Hz), 110 (C-5), 117.5, 122.3, 127.1, 131.9 (CF_3, q, J_1 = 302.4Hz), 154 (C-6), 156 (C-2), 161 (C-4). λ_{max}/nm (MeOH) 262, 326.8.

2-Amino-6-(1-benzylamino-2-hydroxy-3,3,3-trifluoropropyl)-5-nitropyrimidin-4(3H)-one **16b**[10] The benzylaminoketone **13b** (0.3g, 1.3mmol), 2-amino-6-chloro-5-nitropyrimidin-4(3H)-one **10** (0.272g, 1.3mmol), dry triethylamine (0.14g, 1.3mmol) and dry ethanol (25cm^3) were refluxed together for 48 h under nitrogen. The solvent was evaporated under reduced pressure, and the residue triturated with ether. This afforded a yellow solid after filtration, which was purified by dissolution in hot sodium hydroxide solution (0.5 mol dm^{-3}), then reprecipitation with dilute hydrochloric acid to give the required *pyrimidine* **16b** as a yellow solid. (0.428g, 1.1mmol, 88%. m.p. >360°C (decomp)). (Found: C, 44.8; H, 4.0; N, 18.6 $C_{14}H_{14}N_5F_3O_4$ requires C, 45.2; H, 3.5; N, 18.8%) ν_{max}/cm^{-1} (KBr) 3515, 3336, 1661, 1185. δ_H (DMSO) 3.2-3.51 (2H, m, CH_2, J_{HH} = 15Hz, J_{HF} = 60Hz), 4.33 (1H, m, CH), 4.67 (2H, s, CH_2Ph), 6.6 (1H, d, NH, J_{HH} = 7.5Hz), 6.8 - 7.2 (5H, m, C_6H_5, J_{HH} = 9.5Hz). δ_c (DMSO) 48.6 (CH_2Ph), 52.9 (NCH_2), 65.8, 66.3, 66.8, (CHOH, q, J_2 = 31.5Hz), 113.5 (C-5), 118.9, 123.1, 127.3, 131.5 (CF_3, q, J_2 = 270.6Hz), 127.4, 128.5, 136.6, 150.2 (C_6H_5), 152.9 (C-6), 156.8 (C-2), 160.5 (C-4). λ_{max}/nm (MeOH) 265, 331.

Methanesulfonyl ester of 2-Amino-6-(1-benzylamino-2-oxo-3,3,3-trifluoropropyl)-5-nitropyrimidin-4(3H)-one **18b** The alcohol **16b** (0.2g, 0.5mmol) was added to dry dichloromethane (20cm^3) and dry triethylamine (0.074g, 0.6mmol), then dry methanesulfonyl chloride (0.08g, 0.6mmol) was added dropwise at room temperature. The mixture was stirred for 4h and the precipitate filtered off. Evaporation of the solvent afforded the required *mesylate* (0.21g, 0.5mmol, 94%. m.p. >360°C). (Found: C, 39.9; H, 3.7; N, 15.6; S, 7.0 $C_{15}H_{16}N_5F_3SO_6$ requires C, 39.9; H, 3.6; N, 15.1; S, 7.0%) ν_{max}/cm^{-1} (KBr) 3500, 3400, 1170. δ_H (DMSO) 2.08 (3H, s, CH_3), 3.1 - 3.8 (2H, m, CH_2, J_{HH} =15Hz, J_{HF} = 105Hz), 4.7 (2H, s, CH_2Ph), 5.3 -5.8 (1H, m, CHOMs), 7.0 - 7.5 (5H, m, C_6H_5, J_{HH} = 9.5Hz) δ_c (DMSO) 8.5 (CH_3), 30.7 (CH_2Ph), 45.6 (CH_2), 66.9, 67.4, 67.9, 68.4 (CHOMs, q, J_2 = 31.5Hz), 112 (C-5), 118.6, 122.8, 127, 131.2 (CF_3, q, J_1 = 270.6Hz), 127.4, 128.5, 128.6, 136.1 (C_6H_5), 153 (C-6), 156 (C-2), 159.7 (C-4)

6-Trifluoromethylpterin **6** The mesylate **18b** (0.1g, 0.2mmol), was added to a solution of dry, distilled ethanol (30cm^3) and activated palladium on charcoal (0.5g). This was hydrogenated at atmospheric pressure and at 50°C for 24 h, the reaction mixture changing colour from yellow to pale yellow. The solution was cooled, and filtered through kieselguhr then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (45mg, 0.2mmol) was added to the methanolic solution. This stood for 18h, the filtrate was evaporated, and the resulting brown oil triturated with water. The required *pterin* **6** was isolated as a yellow solid, which was purified by dissolution in dilute ammonia solution, then reprecipitation at pH7. (13mg, 0.06mmol, 28%. m.p. >360°C (decomp)). (Found C, 36.1; H, 1.6; N, 29.9 $C_7H_4N_5F_3O$ requires C, 36.4; H, 1.74; N, 30.3% FAB-MS Found: 232.05 Da $C_7H_5N_5F_3O$ requires 232.145 Da) ν_{max}/cm^{-1} (KBr) 3625, 3400, 1688, 1193, 1137. λ_{max}/nm (MeOH) 195, 284, 361.

3,3,4,4,5,5,5-Heptafluoro-1-nitropentan-2-ol **14**[18] 3,3,4,4,5,5,5-Heptafluorobutyraldehyde hydrate (5g, 23 mmol) was stirred with distilled nitromethane (1.55g, 26mmol) in the presence of potassium carbonate (0.01g, 0.7mmol). After heating the mixture at 50 - 60°C for 3 h, the potassium carbonate was washed out with water, the water layer was extracted with ether, and the ether-oil fractions combined and dried over sodium sulphate. Evaporation under reduced pressure yielded the nitroalcohol **14** as a clear liquid. (5.0g, 23mmol, 84%. b.p. = 90°C / 20 mmHg). (Found: C, 25.9; H, 1.6; N, 5.8 $C_5H_4NF_7O_3$ requires C, 26.4; H, 1.8; N, 6.2%) ν_{max} /cm^{-1} (film) 3500, 1600, 1170. δ_H (DMSO) 4.7 - 5.0 (2H, m, CH_2, J_{HH} = 12.5Hz, J_{HF} = 100Hz), 4.3 - 4.9 (1H, m, CH), 7.3 (1H, d, OH, J_{HH} = 7.5Hz). δ_c (DMSO) 65.9, 66.3, 66.7 (CHOH, t, J_2 = 25.2Hz), 75.1 (CH_2), 158 - 162 (C_3F_7, m).

1-Amino-3,3,4,4,5,5,5-heptafluoropentan-2-ol hydrochloride **15**[18] The foregoing nitroalcohol **14** (2g, 7.7mmol) was dissolved in dry, distilled ethanol (70cm^3), and reduced under hydrogen at 40 psi in the presence of Raney nickel (0.5g). After 3 h, the alcoholic solution was filtered through kieselguhr under nitrogen and conc. hydrochloric acid (10cm^3) was added to the filtrate, which was then evaporated under reduced pressure. White, greasy crystals of the required *aminoalcohol* **15** were obtained and were recrystallised from ethyl acetate/ethanol. (0.552g, 2mmol, 27%. m.p. = 133°C). (Found: C, 22.0; H, 2.8; N, 5.5; Cl, 14.2 $C_5H_7NClF_7O$ requires C, 22.6; H, 2.7; N, 5.3; Cl, 13.4%) ν_{max}/cm^{-1} (Nujol) 3500, 3400, 1170. δ_H (DMSO) 2.9 - 3.1 (2H, m, CH_2, J_{HH} = 12.5Hz, J_{HF} = 37.5Hz), 4.5 - 4.8 (1H, m, CH), 7.1 (1H, d, OH, J_{HH} = 7.5Hz), 8.4 (2H, s, NH_2). δ_c (DMSO) 65.1, 65.5, 65.9 (CHOH, t, J_2 = 25.2Hz), 119.7 (CH_2), 158 - 163 (C_3F_7, m).

2-Amino-6-(1-amino-3,3,4,4,5,5,5-heptafluoro-2-hydroxypentyl)-5-nitropyrimidin-4(3H)-one **18**[10] 2-Amino-6-chloro-5-nitropyrimidin-4(3H)-one **10** (0.105g, 0.5mmol), the aminoalcohol **15**, (0.14g, 0.5mmol), dry triethylamine (0.107g, 1mmol), and dry ethanol (20cm^3) were refluxed together under nitrogen overnight. The reaction mixture was filtered when cool, yielding the required *pyrimidine* as off-white crystals (0.18g, 0.5 mmol, 94%. m.p. > 360°C). (Found: C, 27.7; H, 1.8; N, 17.9 $C_9H_8N_5F_7O_4$ requires C, 28.2; H, 2.1; N,18.3%) ν_{max}/cm^{-1} (KBr) 3510, 3430, 1690, 1600, 1164. λ_{max}/nm (MeOH) 262, 343.

Methanesulfonyl ester of 2-Amino-6-(1-amino-3,3,4,4,5,5,5-heptafluoro-2-hydroxypentyl) -5-nitropyrimidin-4(3H)-one **18** The foregoing pyrimidine **17** (0.1g, 0.2mmol) was added to dry dichloromethane (20cm^3) and dry triethylamine (0.03g, 0.3mmol), then dry, distilled methanesulfonyl chloride (0.032g, 0.3mmol) was added dropwise at room temperature. The mixture was stirred for 48 h and the precipitate was filtered off. A pale yellow solid was isolated which was purified by dissolution in aqueous ammonia solution to afford the required *mesylate* **18** (85mg, 0.2mmol, 92%. m.p. >360°C). (Found: C, 25.9; H, 2.1; N, 16.1; S, 6.7 $C_{10}H_{10}N_5F_7SO_6$ requires C, 26.0; H, 2.2; N, 15.2; S, 6.9%) ν_{max}/cm^{-1} (KBr) 3500, 3400, 1170.

6,7-Bistrifluoromethylpterin **19** 2,4,5-Triaminopyrimidin-6(1H)-one **2** (0.3g, 1.4mmol) was dissolved in dimethylformamide (10cm^3), and a solution of hexafluorobiacetyl (0.262g, 1.4mmol) in dry dimethylformamide (5cm^3) was added at room temperature. The reaction mixture was stirred for 7 h then evaporated under reduced pressure. The resulting orange oil was triturated with ether and yielded a pale yellow solid after filtration. This solid was purified by dissolution in dilute ammonia solution then reprecipitation at pH7 to give the required *pterin* **19** (0.23g, 0.8mmol, 55%.m.p. >360°C(decomp)). (Found: C, 31.8; H, 0.2; N, 23.4 $C_8H_3N_5F_6O$ requires C, 32.1; H, 0.01; N, 23.4% FAB-MS Found: 300.03 Da $C_8H_3N_5F_6O$ requires: 300.147 Da) ν_{max}/cm^{-1} (KBr) 3620, 3465, 1690, 1190, 1140. δ_c (DMSO) 115.1, 118, 120.9, 123.8 (CF_3, q, J_1 = 182.7Hz), 116.9, 119.8, 122.7, 125.6 (CF_3, q, J_1 =182.7Hz), 130.5, 130.7, 130.9, 131.1 (C-7, q, J_2 = 12.6Hz), 131.3 (C-4a), 142.6, 142.9, 143.2, 143.5 (C-6, q, J_2 = 18.9Hz), 156.4 (C-8a), 157.7 (C-2), 159.1 (C-4). λ_{max}/nm (MeOH) 198, 280, 366.

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