Specific inhibitors in vitamin biosynthesis. Part 10. Synthesis of 7- and 8-substituted 7-deazaguanines

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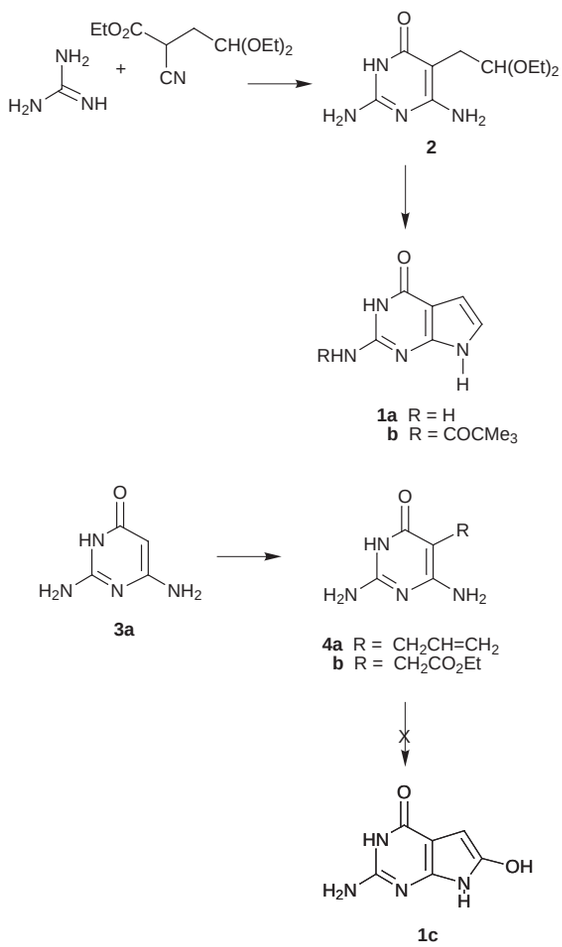
Versatile syntheses of 7- and 8-substituted 7-deazaguanines including *N*-alkyl derivatives have been developed by identifying selective annulation reactions with 2,6-diaminopyrimidin-4(3*H*)-one as substrate and β-halocarbonyl compounds as electrophiles. A new synthesis of 8-substituted 7-deazaguanines using nitrosoalkenes as electrophiles is described. With some combinations of reactants, furo[2,3-*d*]pyrimidines are significant products in place of or in addition to the required 7-deazaguanines [pyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-ones]. When 2,4-diamino-6-chloropyrimidine was used as a substrate, imidazo-pyrimidines were produced.

Modified nucleosides are well-known as drugs with structural variations in the heterocyclic ring[1] or in the ribose substrate.[1,2] A principal focus for interest in such compounds in the past decade has been in the field of antiviral compounds.[3,4] With the increasing emergence of resistance of bacteria to existing drugs, interest has been rekindled in the discovery of novel anti-bacterial compounds, in particular in compounds that act upon new targets.[5] Many successful antibacterial drugs interfere with folate metabolism either through blocking biosynthesis[6] or by inhibiting dihydrofolate reductase.[7] In another field of therapy, thymidylate synthase inhibitors with modified heterocyclic systems have become well-known and some examples have included deazaguanines.[8,9] We have been interested in GTP-cyclohydrolase I (GTPCH-I[10]) and in dihydropteroate synthase[11] as targets for new inhibitors, in both cases using mechanistic concepts in the design of the inhibitors. This work has required the development of new methodologies for the synthesis of deazaguanines and highly functionalised pyrimidines; the former are described here and the latter in an accompanying paper. The biological activity of the compounds prepared will be reported elsewhere in due course.

Linear syntheses of 8-alkyl-7-deazaguanines have been known for some time[12] and have recently been exploited in the case of the 8-methyl derivative for the preparation of modified oligonucleotides of DNA.[13] With GTPCH-I as a target, however, it is necessary to include polar substituents either to take advantage of hydrogen bonding at the active site or to stabilise a tetrahedral intermediate analogue corresponding to the ring-opening step in the enzyme-catalysed reaction.[10] Moreover, it would be valuable if the synthetic routes were adaptable to solid phase synthesis so that libraries of relevant compounds could be readily prepared. For these reasons, we required flexible synthetic routes that would accommodate a wide range of substituents attached to the five-membered ring.



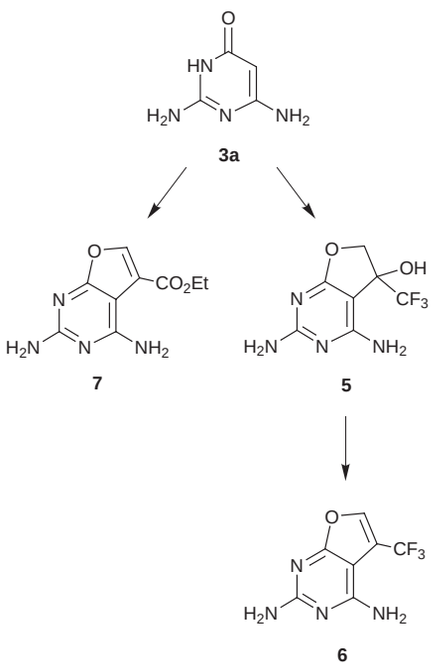
Scheme 1

The reactivity of some 6-substituted 2,4-diaminopyrimidines with ambident electrophiles

The parent compound, 7-deazaguanine **1a**, has been prepared by condensation of ethyl (2,2-diethoxyethyl)cyanoacetate and guanidine[12] to afford **2** followed by quantitative cyclisation in boiling water (Scheme 1).[14] It is notable that a tetrahedral intermediate is not isolable in this reaction. A similar cyclisation in the presence of pivalic anhydride led directly to the pivalamide of **1**. The cyclisation step, which goes in such good yield, encouraged the investigation of the substituent of 2,6-diaminopyrimidin-4(3*H*)-one **3a** at C-5 with 2-halocarbonyl equivalents. The simplest compound, bromoacetaldehyde diethyl acetal, failed to react under a variety of conditions, as did ethyl chlorodifluoroacetate and ethyl 2-bromo-3,3-diethoxypropanoate. Surprisingly, diethyl 2-bromomalonate converted **3a** into its 5-bromo derivative in DMF in the presence of base. Presumably this unexpected reaction is driven by the stability of the malonate anion as a leaving group in a

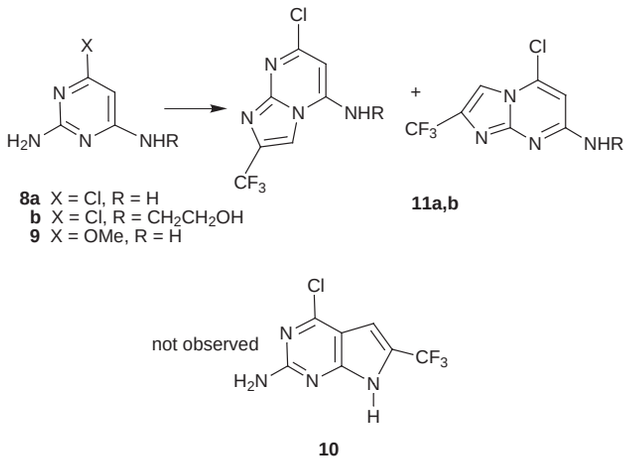
nucleophilic substitution by position 5 of the pyrimidine on bromine. Other reagents that led to mono-substitution at C-5 were allyl bromide and ethyl bromoacetate, leading to **4a** and **b**. Bearing in mind the ease of cyclisation of **2**, it might have been expected that **4b** would cyclise similarly easily to afford an 8-hydroxy-7-deazaguanine **1c**. Many attempts at this reaction proved unsuccessful as did cyclisations in the presence either of triethyl orthoformate with acid catalysis or of ethyl formate and sodium hydride. Complex mixtures and decomposition of starting material were the outcome. Subtle but so far unpredictable balances in reactivity seem to control the success of these reactions.

Although 8-alkyl substituents were not attractive from the point of view of the synthesis of inhibitors of GTPCH-I, the simplicity of their synthesis from α-chloro ketones[15] encouraged us to examine this type of reaction further. With the possibility of a tetrahedral intermediate in the enzyme-catalysed reaction in mind, we treated **3a** with bromotrifluoroacetone (Scheme 2). Unlike chloroacetone, which affords a 4 : 1 mixture



Scheme 2

of the pyrrolo[2,3-*d*]pyrimidine and furo[2,3-*d*]pyrimidine as cyclisation products, bromotrifluoroacetone gave the 5-hydroxy-5-trifluoromethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine **5** as the only product. Although the cyclisation had taken place in the unwanted direction, it is interesting that the anticipated tetrahedral structure had been obtained. The conditions required to dehydrate **5** to the furopyrimidine **6** were surprisingly vigorous (conc. sulfuric acid). A further reactant bearing a suitable electron withdrawing substituent is ethyl bromopyruvate; this compound cyclised directly to afford the corresponding ethoxycarbonyl furopyrimidine **7** without detection or isolation of the intermediate alcohol. Similar examples of cyclisation at oxygen have been described in the synthesis of pteridines.[16] One possible approach to avoiding the nucleophilic reactivity of the oxo group of **3a** is to carry out substitution reactions on the corresponding 6-chloropyrimidine **8a** or 6-methoxypyrimidine **9** (Scheme 3). Neither of these compounds reacted with ethyl bromoacetate under conditions that led to 5-substitution of **3a**. However both **8a** and its *N*-hydroxyethyl analogue **8b** reacted with bromotrifluoroacetone to afford heterocyclic products that were not the expected pyrrolopyrimidines **10** but imidazo[1,2-*a*]pyrimidines **11**. Evidence for

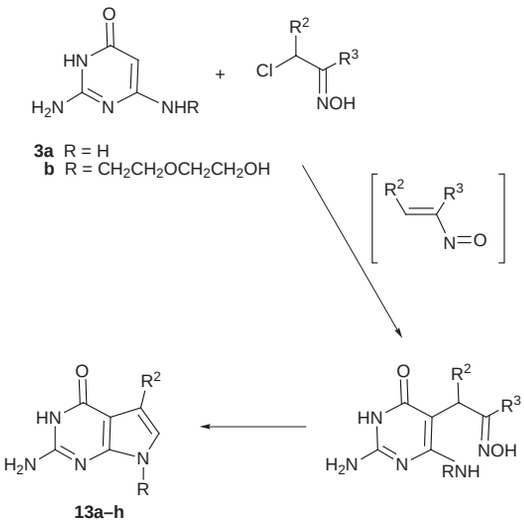


Scheme 3

this structural assignment comes from the ^{1}H NMR spectra: if the pyrrolopyrimidine structure **10** were correct, exchange with D_2O would remove resonances associated with the amino group and N-9 proton. However when the product of cyclisation of **8a** was examined in this way, two broad singlets associated with the amino group of each isomer disappeared but two sets of singlets associated with the carbon bound protons remained. Similarly for the hydroxyethyl analogue **8b**, exchange with D_2O led to the retention of two resonances at δ 6.40 and 8.59 but to the disappearance of a triplet at δ 8.40 corresponding to the -N*H*-CH_2- moiety. These data exclude the pyrrolopyrimidines but do not distinguish between the possible isomeric imidazopyrimidines with the trifluoromethyl substituent at either the 6-position (as illustrated in Scheme 3) or the adjacent 5-position. These two series of products arise through the possibility of a Dimroth rearrangement either of an intermediate during the cyclisation or of a product. The assignment of the structures **11** is based upon substantial literature precedent that shows that substituents on the five-membered ring preferentially occupy a site β to the six-membered ring.[17] Such a thermodynamic preference would avoid *peri* interactions between substituents on the fused rings.

Synthesis of 8-substituted 7-deazaguanines

The failure of 6-substituted 2,6-diaminopyrimidines to yield 7-deazaguanines in the many reactions described above forced an evaluation of alternative approaches. We required to reduce the reactivity of the α-halocarbonyl compound significantly at one end, paralleling the reactivity of ethyl bromoacetate, but to include the high reactivity of the aldehyde group in the cyclisation of **2**. Two precedents led us to employ oximes in a new synthesis of 8-substituted 7-deazaguanines. Firstly, oximes derived from chloronitroso compounds have proved versatile intermediates in the synthesis of 7,7-disubstituted 7,8-dihydropteridines.[18] Secondly, nitrosoalkenes, generated *in situ*, from α-halo oximes are powerful electrophiles that have been shown to react with carbon nucleophiles at the β-carbon.[19] We anticipated that the reaction of the diaminopyrimidine **3a** with nitrosoalkenes would provide a short synthesis of deazaguanines. Accordingly, the oxime of bromotrifluoroacetone was reacted with **3a** (excess) in DMF to afford the C-5 alkylated pyrimidinone **12a** in 80% yield (Scheme 4). Similarly the oximes derived from ethyl bromopyruvate, 2-chlorocyclohexanone, and bromoacetophenone were reacted with **3a** in the presence of a weak base (sodium acetate, triethylamine, or sodium carbonate) at temperatures between 50 and 120 °C (see Experimental) to afford the C-5 alkylated pyrimidinones **12a**–**f** in yields ranging from 38 to 80%. No products of substitution at any other position were isolated. Cyclisation of the C-5 alkylated derivative **12a** occurred thermally at 120 °C giving the required 8-



3a R = H
b R = $CH_2CH_2OCH_2CH_2OH$

13a–h

12 **a** R = H, R^2 = H, R^3 = CF_3
b R = H, R^2 = H, R^3 = CO_2Et
c R = H, R^2 = H, R^3 = Ph
d R = $(CH_2)_2O(CH_2)_2OH$, R^2 = H, R^3 = CF_3
e R = $(CH_2)_2O(CH_2)_2OH$, R^2 = H, R^3 = CO_2Et
f R = H, R^2–R^3 = $[CH_2CH_2]_2$

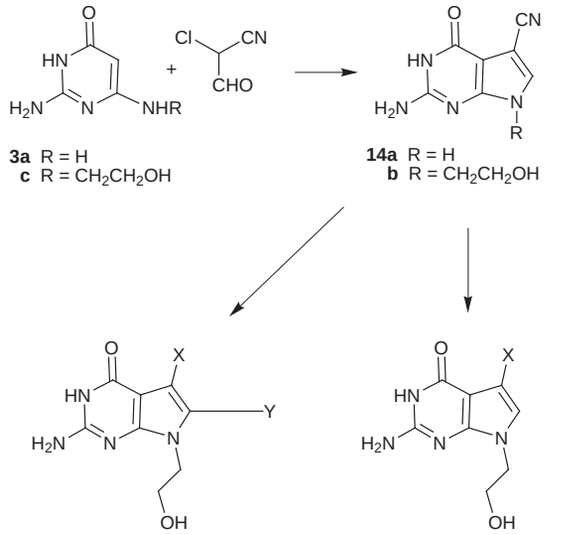
13 **a** R = H, R^2 = H, R^3 = CF_3
b R = H, R^2 = H, R^3 = CO_2Et
c R = H, R^2 = H, R^3 = Ph
d R = $(CH_2)_2O(CH_2)_2OH$, R^2 = H, R^3 = CF_3
e R = $(CH_2)_2O(CH_2)_2OH$, R^2 = H, R^3 = CO_2Et
f R = H, R^2–R^3 = $[CH_2CH_2]_2$
g R = H, R^2 = H, R^3 = CO_2H
h R = $(CH_2)_2O(CH_2)_2OH$, R^2 = H, R^3 = CO_2H

Scheme 4

trifluoromethyldeazaguanine **13a**. However other compounds **12b**–**e** required acid-catalysed transoximation with benzaldehyde or acetaldehyde to afford the corresponding 8-substituted deazaguanines **13b**–**e** (7,8-disubstituted in the case of **13f**). The esters **13c** and **13d** were easily hydrolysed to the corresponding acids with lithium hydroxide. These reactions substantiate a new synthesis of 8-substituted deazaguanines with both hydrogen and alkyl substitutents at N-9.

Synthesis of 7-substituted 7-deazaguanines

Pyrrolopyrimidines have become important as thymidylate synthase inhibitors and hence as potential anticancer drugs.[8,9] Taylor has utilised the condensation of substituted bromo aldehydes with suitably substituted pyrimidines to access the basic heterocyclic system for his compounds.[9] Whereas methyl 2-chloro-3-oxopropanoate affords the usual mixture of pyrrolopyrimidine (deazaguanine) and furopyrimidine (Scheme 5), several groups have shown that 2-chloro-2-cyanoethanal[20] reacts with **3a** to afford exclusively the 7-cyano-7-deazaguanine **14a**.[21] We have found in previous work that alkylation of N-9 in deazaguanines and similar situations in pteridines is capricious. With the ease of preparation of alkylaminopyrimidines such as **3b** and **c** in mind, the extension of Gangjee's method[21a] to *N*-alkylpyrimidines seemed the way ahead. A wide range of 7-substituted and 7,8-disubstituted deazaguanines has been prepared starting with this cyclisation (Scheme 5). The primary cyclisation product **14b** was converted directly into the corresponding carboxylic acid **14c**, amide **14d**, methoxyethyl ester **14e** and, *via* the acid **14c**, into the ethyl ester **14f**. A simple *N*-alkyl amide was not prepared but it is known that esters similar to **14e** can be converted into the corresponding *N*-alkyl amide by heating with a primary amine at 100 °C.[22]



3a R = H
c R = CH_2CH_2OH

14a R = H
b R = CH_2CH_2OH

15a X = CN, Y = Br
b X = CN, Y = SMe
c X = $CONH_2$, Y = SO_2Me

14c X = CO_2H
d X = $CONH_2$
e X = $CO_2CH_2CH_2OMe$
f X = CO_2Et

Scheme 5

Synthesis of 7,8-disubstituted 8-deazaguanines

The preparation of a cycloalkyl 7,8-disubstituted deazaguanine **13f** has been described above. Access to compounds with different substituents at C-7 and C-8 was obtained by brominating the primary deazaguanine **14b** with *N*-bromosuccinimide in DMF to afford the 7-cyano-8-bromo derivative **15a**. Displacement of bromide, which is formally activated by the cyano group, proved to be difficult in that substitution by ethanolamine at 120 °C and by hydroxide or water above 100 °C did not occur. Following Taylor[23] it was possible to displace bromide with methylthiolate at 120 °C to afford **15b** and subsequently to create a polar substituent by oxidation with alkaline peroxide at room temperature. As expected, the latter also converted the cyano group into the corresponding amide **15c**. Taken all together, these transformations establish methods for the synthesis of a wide range of 7-substituted, 8-substituted, and 7,8-disubstituted deazaguanines required for the investigation of the inhibition of enzymes such as GTPCH-I.

Experimental

Where multiplicities are reported without coupling constants in the ^{13}C NMR spectra, they refer to the multiplicity observed in the off-resonance decoupled spectrum. *J* Values are given in Hz.

2-Pivaloylamino-7-deazaguanine (1b)

2,6-Diamino-5-(2,2-diethoxyethyl)pyrimidin-4(3*H*)-one (373 mg, 1.54 mmol) was suspended in pivalic anhydride (4 mL) and the mixture stirred under nitrogen at 170 °C for 17 h and at 190 °C for 24 h. Methanol (5 mL) was added to the cooled mixture and the resulting solution heated under reflux for 30 min. Volatile components were evaporated under reduced pressure and the residue triturated with methanol (1 mL) and light petroleum (5–6 mL). The required *deazaguanine* precipitated on refrigeration (289 mg, 80%), mp 298–300 °C (Found: C, 56.1; H, 6.3; N, 23.8. $C_{11}H_{14}N_4O_2$ requires C, 56.40; H, 6.02; N, 23.92%); δ_H [250 MHz, $(CD_3)_2SO$] 11.85, 11.60, 10.85 (3 × 1H, 3 × br s, N*H*), 6.95 (1H, d, *J* 3.4, *H*-7), 6.40 (1H, d, *J* 3.4, *H*-8), 1.23 (9H, s, CH_3); δ_C [63 MHz, $(CD_3)_2SO$] 180.9 (s, *C*ON), 157.0, 147.8, 146.5 (3s, *C*-4, *C*-2, *C*-6), 119.7 (d, *C*-8), 103.9 (s, *C*-5), 102.2 (d, *C*-7), 39.9 (s, *C*CH_3), 26.4 (q, *C*H_3).

2,6-Diamino-5-ethoxycarbonylmethylpyrimidin-4(3*H*)-one (4b)
To a suspension of 2,6-diaminopyrimidin-4(3*H*)-one (3.78 g, 30 mmol) and sodium hydrogen carbonate (5.87 g, 33 mmol) in DMF (40 mL) was added ethyl bromoacetate (5.87 g, 33 mmol). The mixture was stirred at room temperature for 3 d, then evaporated to dryness under reduced pressure. The residue was suspended in water (100 mL) and the pH was brought to 7, which caused the required *pyrimidine* to crystallise (4.04 g, 64%), mp >280 °C (decomp.) (Found: C, 45.1; H, 5.80; N, 26.4. $C_8H_{12}N_4O_3$ requires C, 45.28; H, 5.70; N, 26.40%); ν_{max}/cm^{-1} 1711 (CO_2Et); δ_H [$(CD_3)_2SO$] 1.18 (3H, t, *J* 7.0, CH_3), 3.38 (2H, s, CH_2CO), 4.01 (2H, q, *J* 7.0, O*C*H_2CH$_3$), 5.85 (2H, br s, 2-NH_2), 6.07 (2H, br s, 4-NH_2); δ_C [$(CD_3)_2SO$] 171.0 (*C*O_2Et), 162.5, 162.4, 153.5 (*C*-6, *C*-4, *C*-2), 81.6 (*C*-5), 59.6 (*C*H_2O), 28.6 (*C*H_2CO), 14.2 (*C*H_3).

2-Amino-6-(2-hydroxyethylamino)pyrimidin-4(3*H*)-one (3c)
To a suspension of 2-amino-6-chloropyrimidin-4(3*H*)-one (10.0 g, 68.7 mmol containing *ca*. 1.2 mol equiv. H_2O) in methoxyethanol (80 mL) was added ethanolamine (10.1 g, 165 mmol). The mixture was refluxed for 6 h, then the solvent was removed under reduced pressure. The residue, crystallised from water (*ca*. 80 mL), was filtered off, washed with water, ethanol, and then diethyl ether, affording the product (7.74 g, 66%). The filtrate was concentrated to 30 mL, and cooled to give a second crop (1.10 g, 9%), mp 233–234 °C (lit.,[24] 238 °C).

2-Amino-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidin-4(3*H*)-one (3b)
2-Amino-6-chloropyrimidin-4(3*H*)-one hydrate (7.0 g, 42.8 mmol), 2-(2-aminoethoxy)ethanol (14.6 g, 139 mmol) and triethylamine (10 mL) were dissolved in ethanol (170 mL) and the solution heated under reflux for 3 d. The solution was concentrated under reduced pressure to 10–15 mL and chloroform (50 mL) was added. The resulting precipitate was filtered by suction and dried under reduced pressure to afford the required *pyrimidine* as colourless crystals [3.12 g, mp 184–186 °C (decomp.)]. A further crop (1.09 g) was obtained by the addition of ethyl acetate and diethyl ether to the mother liquor (total yield 46%) (Found: C, 44.8; H, 6.8; N, 26.3. $C_8H_{11}N_4O_3$ requires C, 44.85; H, 6.59; N, 26.15%); δ_H [250 MHz, $(CD_3)_2SO$] 9.90 (1H, br s, N*H*), 6.43 (1H, br s, N*H*), 6.28 (2H, br s, NH_2), 4.71 (1H, br s, O*H*), 4.51 (1H, s, *H*-5), 3.55–3.30 (8H, m, OCH_2H_2O), 3.23 (2H, br s, NH_2); δ_C [63 MHz, $(CD_3)_2SO$] 164.4, 163.3, 155.1 (3 × s, *C*-6, *C*-3, *C*-4), 75.5 (d, *C*-5), 72.3, 69.1, 60.3 (3 × t, O*C*H_2), 40.7 (t, N*C*H_2).

Reactions of 2,6-diaminopyrimidin-4(3*H*)-one with α-halo ketones: general method
2,6-Diaminopyrimidin-4(3*H*)-one **3a** (375 mg, 3 mmol), the appropriate α-halo ketone and triethylamine (670 mg, 3.5 mmol) were dissolved in DMF (6 mL) and stirred under nitrogen at 60 °C for the time required to complete reaction as shown by TLC. The solvent was evaporated under reduced pressure by successive co-evaporation with toluene and ethanol. The residue was recrystallised from the solvent stated.

2,4-Diamino-5-hydroxy-5-trifluoromethyl-5,6-dihydrofuro-[2,3-*d*]pyrimidine (5). Prepared from **3a** and 1-bromo-3,3,3-trifluoroacetone with a reaction time of 17 h. The product (847 mg) was crystallised by dissolution of the residue in dichloromethane–ethyl acetate and precipitation with light petroleum. Recrystallisation from ethanol afforded the *dihydrofuropyrimidine* (**5**) as the hydrobromide [591 mg, 67%, mp 320 °C (decomp.)] (Found: C, 26.5; H, 2.49; N, 17.7. $C_7H_7F_3N_4O_2$·HBr requires C, 26.52; H, 2.54; N, 17.67%); δ_H [250 MHz, $(CD_3)_2SO$] 8.5, 8.0, 7.5 (6H, 3 × br s, NH_2, NH_3^+, O*H*), 4.91, 4.49 (2H, AB pattern, *J* 11, *H*-7); δ_C [63 MHz, $(CD_3)_2SO$] 175.7, 156.9, 152.9 (3 × s, *C*-6, *C*-2, *C*-4), 125.0 (q, J^1_{C-F} 285, *C*F_3), 82.7 (s, *C*-5), 78.2 (q, J^2_{C-F} 32, *C*-CF_3), 77.3 (t, O*C*H_2).

2,4-Diamino-5-ethoxycarbonylfuro[2,3-*d*]pyrimidine (7). Prepared from **3a** and ethyl bromopyruvate with a reaction time of 1 h. The *furopyrimidine* **7** was obtained in 93% yield as the hydrobromide salt and was recrystallised from ethanol (mp 241–242 °C (decomp.)] (Found: C, 35.8; H, 3.8; N, 18.5. $C_9H_{10}N_4O_3$·HBr requires C, 35.66; H, 3.66; N, 18.48%); δ_H [250 MHz, $(CD_3)_2SO$] 8.76 (1H, br s, N*H*), 8.41 (1H, s, *H*-7), 8.35 (1H, br s, N*H*), 5.55 (3H, br s, NH_3^+), 4.32 (2H, q, *J* 7.2, O*C*H_2), 1.29 (3H, t, *J* 7.2, CH_3); δ_C [63 MHz, $(CD_3)_2SO$] 168.3 (s, *C*O_2Et), 163.3 (s, *C*-6), 154.2, 152.7 (2 × s, *C*-2, *C*-4), 147.1 (d, *C*-7), 114.1 (s, *C*-8), 89.2 (s, *C*-5), 62.1 (t, O*C*H_2), 14.0 (q, N*C*H_2).

2,4-Diamino-5-trifluoromethylfuro[2,3-*d*]pyrimidine (6)
The crude dihydrofuropyrimidine **5** (3 g) was suspended in a mixture of dichloromethane and light petroleum, and concentrated sulfuric acid (6 mL) was added. The mixture was stirred for 30 min at room temperature and then cooled to 0 °C before neutralisation with concentrated aqueous ammonia. The solid was filtered and washed with water and diethyl ether under suction to afford the crude product (1.64 g, 86%). Recrystallisation from ethanol–water gave the *furopyrimidine* **6** [1.36 g, 71%, mp 230–232 °C (decomp.)] (Found: C, 38.4; H, 1.9; N, 25.4. $C_7H_5F_3N_4O$ requires C, 38.5; H, 2.31; N, 25.68%); δ_H [250 MHz, $(CD_3)_2SO$] 8.14 (1H, q, J^3_{H-F} 2.0, *H*-7), 6.46 (4H, br s, NH_2); δ_C [63 MHz, $(CD_3)_2SO$] 170.0, 162.0, 157.7 (3 × s, *C*-6, *C*-2, *C*-4), 138.6 (dq, J^3_{C-F} 7, *C*-7), 122.5 (q, J^1_{C-F} 266, *C*F_3), 110.3 (q, J^2_{C-F} 37, *C*-CF_3), 86.8 (s, *C*-5).

2,6-Diamino-5-(1-bromo-2-hydroxy-1,1,3,3,3-pentafluoropropan-2-yl)pyrimidin-4(3*H*)-one dimethylformamide solvate
This was prepared essentially quantitatively from **3a** and bromopentafluoroacetone in 1.5 h as an amorphous solid, mp >180 °C (decomp.). On attempted recrystallisation or storage the product decomposes to afford the starting materials. The DMF of solvation could not be removed by co-evaporation even under substantially reduced pressure (Found: C, 28.4; H, 3.0; N, 16.3. $C_7H_6BrF_5N_4O_3$·CHONMe$_3$ requires C, 28.18; H, 3.07; N, 16.43%); δ_H [250 MHz, $(CD_3)_2SO$] 12.92 (1H, s, N*H*), 10.88 (1H, br s, O*H*), 7.96 (1H, s, C*H*ONMe$_2$), 6.69, 6.18 (2H, 2 × br s, NH_2), 2.89, 2.74 (2 × 3H, 2 × s, CH_3); δ_C [63 MHz, $(CD_3)_2SO$] 167.7, 162.6, 153.3 (3 × s, *C*-6, *C*-4, *C*-2), 162.0 (d, *C*HONMe$_2$), 126.7 (t, J^1_{C-F} 320, *C*F_2Br), 123.8 (q, J^1_{C-F} 290, *C*F_3), 83.3 (m, J^2_{C-F} 20, *C*-7), 78.8 (s, *C*-5), 35.9, 30.8 (2 × q, CHON*Me*$_3$).

2-Amino-4-chloro-6-(2-hydroxyethylamino)pyrimidine (8b)
To a suspension of 2-amino-4,6-dichloropyrimidine (1.31 g, 8.0 mmol) in ethanol (40 mL) was added ethanolamine (0.98 g, 1.6 mmol). The mixture was refluxed for 2 h, then evaporated to dryness under reduced pressure. The residue, crystallised from water, afforded the product (1.26 g, 84%), mp 142–144 °C (lit.,[25] 146–148 °C).

5-Amino-7-chloro-2-trifluoromethylimidazo[1,2-*a*]pyrimidine and 7-amino-5-chloro-2-trifluoromethylimidazo[1,2-*a*]pyrimidine (11a)
To a suspension of 2,4-diamino-6-chloropyrimidine (**8a**) (0.231 g, 1.6 mmol) in DMF (15 mL) was added 1-bromo-3,3,3-trifluoroacetone (0.548 g, 2.4 mmol). The mixture was stirred at 60 °C for 3 d. A second portion of the ketone (0.180 g, 0.942 mmol) was added. The mixture was further stirred at room temperature for 1 d, and evaporated to dryness under reduced pressure. The residue was digested with isopropyl alcohol and filtered off. The filtrate was evaporated to a syrup which was crystallised twice from 50% aqueous methanol to give the products **11a** (0.077 g, 20%), mp 241–243 °C; δ_H [$(CD_3)_2SO$] 6.19, 6.97 (2 × 1H, 2 × s, *H*-3), 8.26, 8.30 (2H, 2 × br s, NH_2), 8.43, 8.50 (2 × 1H, 2 × s, *H*-5).

7-Chloro-5-(2-hydroxyethylamino)-2-trifluoromethylimidazo-[1,2-*a*]pyrimidine or 5-chloro-7-(2-hydroxyethylamino)-2-trifluoromethylimidazo[1,2-*a*]pyrimidine (11b)

To a suspension of 2-amino-4-chloro-6-(2-hydroxyethylamino)pyrimidine (**8b**) (0.302 g, 1.6 mmol) in DMF (15 mL) was added 1-bromo-3,3,3-trifluoroacetone (**3**) (0.548 g, 2.4 mmol). The mixture was stirred for 1 d at 60 °C, then evaporated under reduced pressure. The syrup obtained was solidified by addition of water and a drop of methanol. The solid was filtered off to give the first crop (0.146 g, 33%). The filtrate was neutralised with potassium carbonate, and the resulting precipitate was also filtered off to give the second crop (0.052 g, 12%). The first and second crop were combined and crystallised from methanol gave the product (**11b**) (0.051 g, 11%), mp 239–240 °C; δ_H [$(CD_3)_2SO$] 3.49 (2H, q, *J* 5.4, NC*H*$_2$), 3.65 (2H, t, *J* 5.4, C*H*$_2$O), 6.40 (1H, s, *H*-3), 8.40 (1H, t, *J* 5.4, N*H*), 8.60 (1H, s, *H*-5).

Reactions of 2,6-diaminopyrimidin-4(3*H*)-one with α-halo oximes: general method

The pyrimidinone (**3a** or **3b**) (5.0 mmol) was dissolved in dry DMF (10–25 mL) and a base added (pyrimidinone in excess, triethylamine, or sodium hydrogen carbonate, 5 mmol) under nitrogen. The appropriate oxime (5.0 mmol) dissolved in an equal volume of dry DMF was added slowly dropwise at 0–5 °C at a rate such that the concentration of the reactive nitrosoalkene intermediate was minimised to avoid oligomerisation. The reaction was monitored by TLC and on completion, the solvent was removed under reduced pressure by successive co-evaporation with toluene–ethanol. The products were crystallised and recrystallised from the stated solvents and dried in a drying pistol at low pressure.

2,6-Diamino-5-(2-hydroxyimino-3,3,3-trifluoropropyl)-pyrimidin-4(3*H*)-one (12a). Prepared from bromotrifluoroacetone oxime and **3a** using excess **3a** as base in 80% yield, mp >280 °C (from methanol–water) (Found: C, 33.4; H, 3.3; N, 27.8. $C_7H_8F_3N_5O_2$ requires C, 33.47; H, 3.21; N, 27.88%. *m*/*z* found 251.0635; $C_7H_8F_3N_5O_2$ requires 251.0630); δ_H [250 MHz, $(CD_3)_2SO$] 12.70 (1H, s, N*H*), 9.91 (1H, s, NO*H*), 6.08, 5.74 (2H, 2 × s, N*H*$_2$), 3.48 (2H, s C*H*$_2$); δ_C [63 MHz, $(CD_3)_2SO$] 162.1, 161.7, 153.6 (3 × s, *C*-6, *C*-2, *C*-4), 147.4 (q, J^2_{C-F} 29, *C*-CF$_3$), 121.1 (q, J^1_{C-F} 276, *C*F$_3$), 80.0 (s, *C*-5), 16.9 (t, *C*H$_2$).

2,6-Diamino-5-(2-ethoxycarbonyl-2-hydroxyiminoethyl)-pyrimidin-4(3*H*)-one (12b). Prepared from ethyl bromopyruvate oxime (**12b**) using excess **12b** as base in 79% yield as the hemihydrate, mp >250 °C (from ethanol–water) (Found: C, 41.2; H, 5.5; N, 26.6; $C_9H_{12}N_5O_4{\cdot}0.5H_2O$ requires C, 40.91; H, 5.34; N, 26.5%); δ_H [250 MHz, $(CD_3)_2SO$] 12.19, 10.15 (2 × 1H, 2 × br s, N*H*, NO*H*), 6.15, 5.77 (2 × 2H, 2 × br s, N*H*$_2$), 4.10 (2H, q, *J* 7.1, OC*H*$_2$), 3.39 (2H, s, C*H*$_2$), 1.17 (3H, t, *J* 7.1, C*H*$_3$); δ_C [63 MHz, $(CD_3)_2SO$] 164.0 (s, *C*O$_2$Et), 162.3, 161.9, 153.5 (3 × s, *C*-6, *C*-2, *C*-4), 151.3 (s, *C*NOH), 82.1 (s, *C*-5), 60.6 (t, OC*H*$_2$), 19.0 (t, *C*H$_2$), 14.0 (q, *C*H$_3$).

2,6-Diamino-5-(2-hydroxyimino-2-phenylethyl)pyrimidin-4(3*H*)-one (12c). Prepared from phenacyl bromide oxime using triethylamine as base in 47% yield as a hydrate, mp >200 °C (decomp.) [*m*/*z* found 260.1128 ($M^+ + 1$); $C_{12}H_{13}N_5O_2$ requires 260.1148]; δ_H [250 MHz, $(CD_3)_2SO$] 11.78 (1H, br s, N*H*), 9.88 (1H, br s, NO*H*), 7.88–7.84 and 7.31–7.26 (2H and 3H, 2 × m, *C*$_6$*H*$_5$), 6.03, 5.89 (2H, 2 × s, N*H*$_2$), 3.74 (2H, s, C*H*$_2$), 3.36 (2H, br s, *H*$_2$O); δ_C [63 MHz, $(CD_3)_2SO$] 162.1, 161.9, 155.8 (3 × s, *C*-6, *C*-2, *C*-4), 153.4 (s, *C*NOH), 135.1, (s, *ipso*-*C*, C$_6$H$_5$), 128.7, 127.9, 126.2 (3d, C$_6$H$_5$), 82.1 (s, *C*-5), 17.2 (t, *C*H$_2$).

2-Amino-6-[2-(2-hydroxyethoxy)ethylamino]-5-(2-hydroxyimino-3,3,3-trifluoropropyl)pyrimidin-4(3*H*)-one (12d). Prepared from the 5-unsubstituted pyrimidinone (**3b**) using triethylamine as base in 55% yield as the hydrate, mp 202–205 °C (decomp.) from ethanol–water (Found: C, 37.5; H, 4.9; N, 19.7. $C_{11}H_{15}F_3N_5O_4$ requires C, 37.08; H, 4.81, N, 19.66%); δ_H [250 MHz, $(CD_3)_2SO$] 12.08 (1H, s, N*H*), 9.99 (1H, br s, NO*H*), 6.26 (2H, s, N*H*$_2$), 5.88 (1H, s, N*H*), 4.98 (1H, s, O*H*), 3.50, 3.42 (overlapping m, C*H*$_2$, OC*H*$_2$, N*H*$_2$, *H*$_2$O); δ_C [63 MHz, $(CD_3)_2SO$] 161.8, 160.7, 153.7 (3 × s, *C*-6, *C*-2, *C*-4), 147.4 (q, J^2_{C-F} 30, *C*-CF$_3$), 121.0 (q, J^1_{C-F} 275, *C*F$_3$), 80.0 (s, *C*-5), 72.1, 69.5, 60.3 (3 × t, OC*H*$_2$), 40.7 (t, NC*H*$_2$), 16.5 (t, *C*H$_2$).

2-Amino-6-[2-(2-hydroxyethoxy)ethylamino]-5-(2-ethoxycarbonyl-2-hydroxyiminoethyl)pyrimidin-4(3*H*)-one (12e). Prepared from the 5-unsubstituted pyrimidinone (**3b**) using triethylamine as base in 61% yield as the hydrate, mp 176–178 °C (decomp.) from water (Found: C, 43.5; H, 6.1; N, 19.5. $C_{13}H_{21}N_5O_6$ requires C, 43.21; H, 6.42; N, 19.38%); δ_H [250 MHz, $(CD_3)_2SO$] 12.25 (1H, br s, N*H*), 10.05 (1H, br s ,NO*H*), 6.22 (2H, br s, N*H*$_2$), 5.92 (1H, br s, N*H*), 4.86 (1H, br s, O*H*), 4.09 (2H, q, *J* 7.1, OC*H*$_2$), 3.55–3.35 (10H, overlapping m, OC*H*$_2$, N*H*$_2$, C*H*$_2$), 1.17 (3H, t, *J* 7.1, C*H*$_3$); δ_C [63 MHz, $(CD_3)_2SO$] 164.0 (s, *C*O$_2$Et), 161.8, 160.8, 153.3 (s, *C*NOH), 81.9, (s, *C*-5), 72.1, 69.6, 60.6, 60.3 (4 × t, OC*H*$_2$), 40.7 (q, NC*H*$_2$), 18.6 (t, *C*H$_2$), 13.9 (q, *C*H$_3$).

8-Trifluoromethyl-7-deazaguanine (13a) (by direct thermal cyclisation)

The diaminopyrimidine **3a** (504 mg, 5.0 mmol) was suspended in dry DMF (3 mL) and the mixture heated to 80 °C. A solution of bromotrifluoroacetone oxime (412 mg, 2.0 mmol) in dry DMF (2 mL) was added dropwise over 15 min. The reaction mixture was stirred for 4 d at 80 °C, 1 d at 100 °C, and 1 d at 120 °C. The solvent was then removed by co-evaporation with toluene under reduced pressure and the residue extracted with a mixture of methanol and water (2:1 v/v, 2 × 10–15 mL). Evaporation of the extract afforded a crystalline product that was shown by NMR analysis to be a mixture of the required deazaguanine **13a** and the starting oxime. The cyclisation was completed by dissolving the mixture in dimethyl sulfoxide (2 mL) and water (0.5 mL) and heating the solution at 140–150 °C for 16 h. On cooling and dilution with water (10 mL) the required *trifluoromethyldeazaguanine* was obtained as a hydrate (203 mg, 43%), mp >350 °C. This compound was also prepared by the general method given below using benzaldehyde in 81% yield (Found: C, 35.9; H, 3.2; N, 23.6. $C_7H_5F_3N_4O$ requires C, 35.6; H, 2.99; N, 23.73%); δ_H [250 MHz, $(CD_3)_2SO$] 12.15, 10.53 (2 × 1H, 2 × br s, N*H*), 6.74 (1H, s, *H*-7), 6.40 (2H, s, N*H*$_2$), 3.38 (2H, s, *H*$_2$O); δ_C [63 MHz, $(CD_3)_2SO$] 158.8, 153.9, 152.9 (3 × s, *C*-6, *C*-2, *C*-4) 121.4 (q, J^1_{C-F} 266, *C*F$_3$), 116.7 (q, J^2_{C-F} 39, *C*-8), 104.3 (q, J^3_{C-F} 3.5, *C*-7), 99.9 (s, *C*-5).

2-Amino-4,5,6,7,8,9-hexahydropyrimido[4,5-*b*]indol-4(3*H*)-one (13f). Prepared directly from 2-chlorocyclohexanone oxime and the pyrimidinone **3a** without isolating the intermediate oxime (**12f**) in 44% yield after 3 d reaction at room temperature and 4 d at 60 °C using sodium carbonate as base (Found: C, 54.2; H, 6.1; N, 25.1. $C_{10}H_{12}N_4O$ requires C, 54.05; H, 6.35; N, 25.21%); δ_H [250 MHz, $(CD_3)_2SO$] 10.51, 10.06 (2 × 1H, 2 × br s, N*H*), 2.91 (2H, br s, N*H*$_2$), 3.36 (*H*$_2$O), 2.55, 2.44 (2 × 2H, 2 × m, C*H*$_2$), 1.68 (m, C*H*$_2$); δ_C [250 MHz, $(CD_3)_2SO$] 158.8, 151.6, 150.6 (3 × s, *C*-6, *C*-2, *C*-4), 124.7 (s, *C*-8), 110.4 (s, *C*-7), 98.2 (s, *C*-5), 22.9, 33.6, 22.0, 21.9 (4 × t, *C*H$_2$).

8-Substituted 7-deazaguanines: general preparation from the corresponding oximinopyrimidine

The oxime (*ca*. 2 mmol) was suspended in a mixture of ethanol (50 mL) and water (15 mL) and conc. hydrochloric acid (6 drops). The transoximinating aldehyde [benzaldehyde or acetaldehyde (4 mL)] was added and the reaction mixture heated under reflux under nitrogen until reaction was complete as shown by TLC. The solvent was removed under reduced pressure using co-evaporation with toluene to remove residual water. The deazaguanines were recrystallised from ethanol–water.

[2-(2-Hydroxyethoxy)ethyl]-8-trifluoromethyl-7-deazaguanine (13d). Prepared from **12d** with a reaction time of 3 d in 71% yield as the hemihydrate, mp 188–191 °C (Found: C, 42.1; H,

4.4; N, 17.8. $C_{11}H_{13}F_3N_4O_3 \cdot 0.5H_2O$ requires C, 41.91; H, 4.48; N, 17.77%); δ_H [250 MHz, $(CD_3)_2SO$] 10.62 (1H, s, N*H*), 6.86 (1H, s, *H*-7), 6.61 (2H, s, NH_2), 4.60 (1H, t, *J* 5.0, O*H*), 4.14, 3.65 (2 × 2H, 2 × t, *J* 6.7, OCH_2), 3.46–3.35 (overlapping m, OCH_2, NCH_2, H_2O); δ_C [63 MHz, $(CD_3)_2SO$] 158.6, 154.2, 153.0 (3 × s, *C*-6, *C*-2, *C*-4), 121.4 (q, J^1_{C-F} 267, *C*F_3), 117.7 (q, J^2_{C-F} 38, *C*-8), 105.9 (q, J^3_{C-F} 4, *C*-7), 99.1 (s, *C*-5), 72.4, 68.1, 60.2 (3 × t, OCH_2), 42.5 (t, NCH_2).

8-Ethoxycarbonyl-7-deazaguanine (13b). Prepared from **12b** in 60% yield after 26 h reaction, mp >280 °C (decomp.) (Found: C, 48.4; H, 4.5; N, 24.87. $C_9H_{10}N_4O_3$ requires C, 48.65; H, 4.54; N, 25.22%); δ_H [250 MHz, $(CD_3)_2SO$] 11.9, 10.5 (2 × 1H, 2 × s, N*H*), 6.93 (1H, d, *J* 2.2, *H*-7), 6.45 (2H, s, NH_2), 4.22 (2H, q, *J* 7.1, OCH_2), 1.27 (3H, t, *J* 7.1, CH_3); δ_C [63 MHz, $(CD_3)_2SO$] 160.5 (s, *C*O_2Et), 158.9, 154.0, 153.0 (3 × s, *C*-6, *C*-2, *C*-4), 120.1 (s, *C*-8), 109.8 (d, *C*-7), 101.6 (s, *C*-5), 59.8 (t, OCH_2), 14.3 (q, OCH_3).

8-Ethoxycarbonyl-9-[2-(2-hydroxyethoxy)ethyl]-7-deazaguanine (13e). Prepared from **12e** after 2.5 d reaction time in 71% yield, mp 238–241 °C (decomp.) (Found: C, 50.3; H, 5.7; N, 18.1. $C_{13}H_{18}N_4O_5$ requires C, 50.32; H, 5.85; N, 18.06%); δ_H [250 MHz, $(CD_3)_2SO$] 10.58 (1H, s, N*H*), 7.04 (1H, d, *J* 2.2, *H*-7), 6.61 (2H, br s, NH_2), 4.55 (1H, br s, O*H*), 4.45 (2H, t, *J* 6.1, OCH_2), 3.42–3.30 (5H, overlapping m, OCH_2, NCH_2, H_2O), 1.26 (3H, t, *J* 7.1, CH_3); δ_C [63 MHz, $(CD_3)_2SO$] 160.4 (s, *C*O_2Et), 158.7, 154.2, 153.4, (3 × s, *C*-6, *C*-2, *C*-4), 120.1 (s, *C*-8), 111.7 (d, *C*-7), 100.2 (s, *C*-5), 72.2, 68.9, 60.2, 59.8 (4 × t, OCH_2), 42.0 (t, NCH_2), 14.2 (q, CH_3).

8-Carboxy-7-deazaguanine (13g)

The ethyl ester **13b** (70 mg, 0.315 mmol) was suspended in a mixture of water (4 mL) and ethanol (1 mL) containing lithium hydroxide monohydrate (42 mg, 1.0 mmol). The mixture was stirred for 24 h at room temperature and the resulting solution acidified (dil. HCl). On cooling, the required *deazaguanine carboxylate* (55 mg, 85%) separated as hydrated crystals, mp 280–282 °C (decomp.) (Found: C, 40.8; H, 3.4; N, 27.2. $C_7H_6N_4O_3 \cdot 0.75H_2O$ requires C, 40.48; H, 3.64; N, 26.98%); δ_H [250 MHz, $(CD_3)_2SO$–C_5D_5N] 12.32, 10.78 (2 × 1H, 2 × br s CO_2H, N*H*), 7.17 (1H, d, *J* 1.6, *H*-7), 6.70 (2H, br s, NH_2); δ_C [63 MHz, $(CD_3)_2SO$–C_5D_5N] 162.3 (*C*O_2H), 159.2, 154.1, 153.0 (3 × s, *C*-6, *C*-2, *C*-4), 121.4 (s, *C*-8), 109.5 (s, *C*-7), 101.8 (s, *C*-5).

8-Carboxy-[2-(2-hydroxyethoxy)ethyl]-7-deazaguanine (13h)

The ethyl ester **13e** (360 mg, 1.13 mmol) was suspended in a mixture of water (13 mL) and THF (3 mL) containing lithium hydroxide monohydrate (142 mg, 3.38 mmol). The mixture was stirred for 2 d at room temperature and the resulting solution acidified (dil. HCl). On cooling, the required *deazaguanine carboxylate* (268 mg, 83%) separated as hydrated crystals, mp 216–218 °C (decomp.) (Found: C, 46.3; H, 5.15; N, 19.3. $C_{11}H_{14}N_4O_5 \cdot 0.25H_2O$ requires C, 46.07; H, 5.10; N, 19.54%); δ_H [250 MHz, $(CD_3)_2SO$] 12.38 (1H, br s, CO_2H), 10.54 (1H, br s, N*H*), 7.01 (1H, s, *H*-7), 6.56 (2H, br s, NH_2), 4.55–4.43 (3H, overlapping m, OCH_2, *H*O), 3.60 (2H, t, *J* 6.5, OCH_2), 3.41 (6H, overlapping m, OCH_2, NCH_2, H_2O); δ_C [63 MHz, $(CD_3)_2SO$] 162.0 (s, *C*O_2H), 158.7, 154.0, 153.3 (3H, *C*-6, *C*-2, *C*-4), 120.9 (s, *C*-8), 111.6 (d, *C*-7), 100.1 (s, *C*-5), 72.2, 69.0, 60.2 (3 × t, OCH_2), 41.9 (t, NCH_2).

7-Cyano-9-(2-hydroxyethyl)-7-deazaguanine (14b)

To a suspension of 2-amino-6-(2-hydroxyethylamino)pyrimidin-4(3*H*)-one (5.10 g, 30 mmol) and sodium acetate (4.92 g, 60 mmol) in water (80 mL) was added chloro(formyl)-acetonitrile, freshly prepared from chloroacetonitrile (3.02 g, 40 mmol). The mixture was stirred at 50 °C for 20 h. The precipitate was collected by filtration, then washed with water, ethanol, and diethyl ether to afford the product (5.42 g, 83%). Crystallisation from methanol gave analytically pure compound, mp >320 °C (Found: C, 49.2; H, 3.8; N, 31.7. $C_9H_9N_5O_2$ requires C, 49.31; H, 4.14; N, 31.95%); ν_{max}/cm^{-1} 2222 (C≡N); δ_H [$(CD_3)_2SO$] 3.67 (2H, m, β-CH_2), 4.01 (2H, t, *J* 5.7, α-CH_2), 4.97 (1H, t, *J* 5.1, O*H*), 6.52 (2H, br s, NH_2), 7.66 (1H, s, *H*-5), 10.76 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$] 157.5, 153.7, 150.8 (*C*-6, *C*-4, *C*-2), 131.1 (*C*-8), 115.7 (*C*-7), 98.9 (*C*-5), 84.9 (*C*N), 59.4 (*C*H_2O), 47.2 (*C*H_2N).

9-(2-Hydroxyethyl)-7-deazaguanine-7-carboxamide (14d)

The nitrile **14b** (164 mg, 0.75 mmol) was dissolved in 1 M KOH (5 mL). To the solution was added 6% aqueous H_2O_2 (3 mL). The mixture was stirred at room temperature overnight, then neutralised by 1 M aqueous HCl. The resulting precipitate was filtered off, washed with water, ethanol, then diethyl ether afforded the product (162 mg, 91%). An analytically pure sample was obtained by crystallisation from water, mp >340 °C (decomp.) (Found: C, 45.7; H, 4.6; N, 29.4. $C_9H_{11}N_5O_3$ requires C, 45.57; H, 4.67; N, 29.52%); ν_{max}/cm^{-1} ($CONH_2$); δ_H [$(CD_3)_2SO$ 3.67 (2H, m, β-CH_2), 4.02 (2H, t, *J* 5.7, α-CH_2), 4.89 (1H, br s, O*H*), 6.41 (2H, br s, NH_2), 6.97 (1H, br s, NH of CONH_2), 7.36 (1H, s, *H*-5), 9.51 (1H, br s, NH of CONH_2), 10.83 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$] 164.2 (*C*ONH$_2$), 160.1, 152.5, 151.4 (*C*-6, *C*-4, *C*-2, 127.1 (*C*-8), 113.3 (*C*-7), 96.1 (*C*-5), 59.6 (*C*H_2O), 46.7 (*C*H_2N).

9-(2-Hydroxyethyl)-7-deazaguanine-7-carboxylic acid (14c)

The nitrile **14b** (0.880 g, 4.02 mmol) was dissolved in 5 M aqueous KOH (5 mL). The solution was refluxed for 5 h. After cooling, the mixture was neutralised with glacial acetic acid and cooled. The precipitate was filtered off, washed with water, ethanol, and diethyl ether, to give the required carboxylic acid (0.925 g, 97%). An analytically pure sample was obtained by crystallisation from water, mp >310 °C (decomp.) (Found: C, 45.3; H, 4.10; N, 23.5. $C_9H_{10}N_4O_4$ requires C, 45.38; H, 4.23; N, 23.52%); δ_H [$(CD_3)_2SO$] 3.70 (2H, m, β-CH_2), 4.05 (2H, t, *J* 5.7, α-CH_2), 4.91 (1H, br s, O*H*), 6.66 (2H, br s, NH_2), 7.56 (1H, s, *H*-5), 11.45 (1H, br s, *H*-3), 14.02 (1H, br s, CO_2H), δ_C [$(CD_3)_2SO$] 162.8 (*C*O_2H), 161.3, 152.9, 151.3 (*C*-6, *C*-4, *C*-2), 129.5 (*C*-8), 109.2 (*C*-5), 96.3 (*C*-5), 59.4 (*C*H_2O), 46.9 (*C*H_2N).

2-Methoxyethyl 9-(2-hydroxyethyl)-7-deazaguanine-7-carboxylate (14e)

To a suspension of the nitrile **14b** (55.0 mg, 0.25 mmol) in methoxyethanol (5 mL) was added toluene-*p*-sulfonic acid monohydrate (64 mg, 0.34 mmol). The mixture was refluxed for 3 d, then evaporated to dryness under reduced pressure. The residue was suspended in water (3 mL) and the mixture neutralised with conc. aqueous NH_3. The resulting precipitate was filtered off, washed with water, ethanol, and diethyl ether, to give the required ester (38.3 mg, 51.5%). An analytically pure sample was obtained by crystallisation from water, mp 242–243 °C (Found: C, 48.5; H, 5.4; N, 18.7. $C_9H_{10}N_4O_4$ requires C, 48.65; H, 5.44; N, 18.91%); ν_{max}/cm^{-1} 1724 (CO_2R); δ_H [$(CD_3)_2SO$] 3.38 (3H, s, OCH_3), 3.69 (2H, m, β-CH_2), 3.76 (2H, t, *J* 4.9, COCH$_2$CH$_2$O), 4.11 (2H, t, *J* 5.4, α-CH_2), 4.33 (2H, t, *J* 4.9, CO*C*H$_2$CH$_2$O), 5.03 (1H, br s, O*H*), 6.43 (2H, br s, NH_2), 7.55 (1H, s, *H*-5), 10.47 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$] 162.3 (*C*O_2R) 157.1, 153.0, 151.8 (*C*-6, *C*-4, *C*-2), 128.6 (*C*-8), 108.4 (*C*-7), 97.6 (*C*-5), 70.0 (CO_2CH_2), 62.2 (OCH_3), 59.5, 58.0 (*C*H_2O), 46.8 (*C*H_2N).

Ethyl 9-(2-hydroxyethyl)-7-deazaguanine-7-carboxylate (14f)

To a suspension of the carboxylic acid **14c** (58.0 mg, 0.244 mmol) in dry ethanol (5 mL) was added $BF_3 \cdot OEt_2$ (0.5 mL). The mixture was refluxed for 24 h, then evaporated to dryness. The residue was suspended in water (50 mL), and the mixture was neutralised with aq. 1 M KOH. The precipitate was collected by filtration and recrystallised from water to afford the required ester (33.8 mg, 52%), mp 281–282 °C (Found: C, 49.7;

H, 5.10; N, 31.1. $C_{11}H_{14}N_4O_4$ requires C, 49.62; H, 5.30; N, 21.04%); ν_{max}/cm^{-1} 1713 (CO_2Et); δ_H [$(CD_3)_2SO$] 1.33 (3H, t, *J* 7.3, CH_2CH_3), 3.76 (2H, m, β-CH_2), 4.10 (2H, t, *J* 5.4, α-CH_2), 4.25 (2H, q, *J* 7.3, OCH_2CH_3), 4.98 (1H, t, *J* 5.4, O*H*), 6.39 (2H, br s, NH_2), 7.53 (1H, s, 5-H), 10.41 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$], 162.6 (CO_2Et), 157.1, 153.0, 151.7 (*C*-6, *C*-4, *C*-2), 128.4 (*C*-8), 108.8 (*C*-7), 97.5 (*C*-5), 59.4, 58.9 (CH_2O), 46.7 (CH_2N), 14.3 (CH_3).

8-Bromo-7-cyano-9-(2-hydroxyethyl)-7-deazaguanine (15a)

To a suspension of the nitrile **14b** (0.876 g, 4.0 mmol) in DMF (10 mL) was added *N*-bromosuccinimide (0.783 g, 4.4 mmol). The mixture was stirred at room temperature for 6 h. The mixture was evaporated to dryness under reduced pressure. The residue was triturated with water (10 mL), the resulting solid filtered off, washed with water, ethanol, and then diethyl ether to afford the product (1.05 g, 88%). Further purification for microanalysis was accomplished by crystallisation from water, mp 295–296 °C (Found: C, 36.26; H, 2.70; N, 23.49; Br, 26.80. $C_9H_8N_5O_2Br$ requires C, 36.38; H, 2.71; N, 23.22; Br, 26.80%); ν_{max}/cm^{-1} 2230 (C≡N); δ_H [$(CD_3)_2SO$] 3.65 (2H, m, β-CH_2), 4.07 (2H, t, *J* 5.9, α-CH_2), 4.94 (1H, t, *J* 5.7, O*H*), 6.58 (2H, br s, NH_2), 10.82 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$] 156.3, 153.8, 151.1 (*C*-6, *C*-4, *C*-2), 114.9 (*C*-8), 114.5 (*C*-7), 99.4 (*C*-5), 88.2 (*C*N), 58.7 (CH_2O), 46.5 (CH_2N).

7-Cyano-9-(2-hydroxyethyl)-8-methylthio-7-deazaguanine (15b)

To a suspension of bromodeazaguanine **15a** (100 mg, 0.34 mmol) in *N*,*N*-dimethylacetamide (5 mL) was added sodium methylthiolate (50 mg, 0.71 mmol). The mixture was heated at 120 °C for 20 h. The solvent was removed under reduced pressure. The residue was triturated with water (5 mL), and the solid filtered off and washed with water, ethanol, and diethyl ether to afford the product (63.4 mg, 71%), mp 309–311 °C [*m*/*z* found 266.0731; $C_{10}H_{12}N_5O_2S$ (M+1) requires 266.0712]; ν_{max}/cm^{-1} 2215 (C≡N); δ_H [$(CD_3)_2SO$] 2.45 (3H, s, SCH_3), 3.68 (2H, m, β-CH_2), 4.15 (2H, t, *J* 5.9, α-CH_2), 4.92 (1H, t, *J* 5.7, O*H*), 6.57 (2H, br s, NH_2), 10.77 (1H, br s, *H*-3); δ_C [$(CD_3)_2SO$] 156.6, 153.9, 151.5 (*C*-6, *C*-4, *C*-2), 134.3 (*C*-8), 114.8 (*C*-7), 99.7 (*C*-5), 92.5 (*C*N), 59.0 (CH_2O), 45.3 (CH_2N), 19.9 (CH_3S).

7-Cyano-9-(2-hydroxyethyl)-8-methylsulfonyl-7-deazaguanine (15c)

To a solution the thioether **15b** (52.7 mg, 0.20 mmol) in aq. KOH (2 mL, 1 M) was added 6% aqueous hydrogen peroxide (2 mL). The mixture was stirred at room temperature for 20 h. After neutralisation with 1 M HCl, the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in methanol. The insoluble material was filtered off. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethanol, then diethyl ether was added. The precipitate was filtered off to afford the sulfone **15b** [*m*/*z* found 316.0732; $C_{10}H_{14}N_5O_5S$ (M+1) requires 316.0716]; δ_H [$(CD_3)_2SO$] 3.11 (3H, s, SO_2CH_3), 3.71 (2H, m, β-CH_2), 4.38 (2H, t, *J* 5.9, α-CH_2), 4.88 (1H, t, *J* 5.7, O*H*), 6.91 (2H, br s, NH_2), 7.35 (1H, br s NH_2), 9.77 (1H, br s, NH_2), 11.31 (1H, br s, *H*-3).

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