Notes

Structure-Based Design of Inhibitors of Purine Nucleoside Phosphorylase. 5. 9-Deazahypoxanthines

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The synthesis and evaluation as inhibitors of purine nucleoside phosphorylase of six 9-deazahypoxanthines (**2a–f**) are reported. In contrast to reports in the literature of other hypoxanthine–guanine analog pairs, these inhibitors (**2a–f**) are equipotent with the corresponding 9-deazaguanines.

Introduction

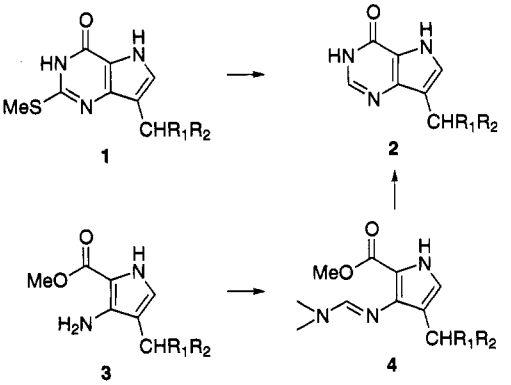
The K_i of guanine for the inhibition of mammalian purine nucleoside phosphorylase (PNP) is 5 μM whereas the K_i of hypoxanthine is 17 μM, less than one-third as potent.[1] 8-Aminoguanine, the first significant inhibitor of the enzyme, is 10–50-fold as potent as 8-aminohypoxanthine,[1,2] and there are many other comparisons in the literature that indicate that the 2-amino group of guanine adds a significant increment of binding to inhibitors of PNP.[3–8] In an extreme case, the K_i of 8-amino-9-benzylhypoxanthine is 750 times that of 8-amino-9-benzylguanine.[3]

Using the 3D structure of PNP, we have designed a variety of 9-substituted 9-deazaguanines[9] that are the most potent membrane-permeable inhibitors of this enzyme yet described.[10,11] These studies revealed that substitution of an amino group at the 8-position (purine numbering) of these compounds, in contrast to other PNP inhibitors,[4] not only failed to improve activity but was actually detrimental.[10]

We have now prepared a series of 9-substituted-9-deazahypoxanthines and compared their activity with that of the corresponding 9-deazaguanines.

Chemistry

The 9-deazahypoxanthines were prepared in two ways. In the first method, the 2-(methylthio)-9-deazahypoxanthines, obtained as byproducts in the preparation of the 9-deazaguanines,[10–12] were reduced with hydrazine hydrate and 30% Pd/C[13] in ethanol. This reduction worked well with the 30% Pd/C catalyst, which is no longer available, but the use of a commercially available 20% Pd/C[14] catalyst was not so satisfactory, giving incomplete reduction of the methylthio group. Compounds **2a,b,d–f** were obtained using the latter catalyst in yields that ranged from 11 to 39% along with 1:1 mixtures of **1** and **2** that were difficult to separate (method A). Raney nickel alone in refluxing ethanol gave a satisfactory result in reducing the benzyl compound **1d** to **2d** but was found to remove the chloro group from the 3-chlorobenzyl analog[10] of **1d** (method B).



a: R_1 = H, R_2 = cyclopentyl
b: R_1 = H, R_2 = 3-pyridyl
c: R_1 = CH_2CN, R_2 = 3-chlorophenyl
d: R_1 = H, R_2 = phenyl
e: R_1 = H, R_2 = 3-benzyloxyphenyl
f: R_1 = H, R_2 = 3-thienyl
g: R_1 = H, R_2 = 4-pyridyl

Since we did not find a single, universally-applicable reduction procedure and since we were able to essentially eliminate the methylthio compounds as byproducts in cyclization to the 9-deazaguanines, we developed a second procedure for the preparation of the 9-deazahypoxanthines. In this procedure, the methyl esters of the 3-amino-4-substituted-pyrrole-2-carboxylic acids (**3**)[10–12] was converted to the corresponding [[(dimethylamino)methylene]amino]pyrrole **4** by treatment with *N,N*-dimethylformamide dimethyl acetal.[15] Treatment of these compounds (**4**) with methanolic ammonia (saturated at 0 °C) at 95–100 °C for 24 h in a stainless steel bomb gave the desired 9-deazahypoxanthine in good overall yield (method C). It is not necessary to isolate the intermediate **4**.

Inhibition of PNP. A comparison of the K_i's for the inhibition of PNP of a variety of guanines with the corresponding hypoxanthines shows that the ratio of K_i values (H/G) varies between >3 and 750, but in all cases, the guanine is more potent (Table 1). In the case of the 8-amino-9-benzylpurines, the ratio is greatest at 750. In most reported studies the hypoxanthine derivatives were not even prepared for evaluation as PNP inhibitors, presumably because of the expected superiority of the guanine derivatives. In fact, Sircar *et al.*[6] have stated that "the N_1-nitrogen and the C_2-NH_2 are

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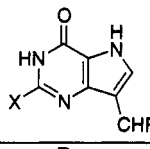
Table 1. Inhibition of PNP (Literature)

substitution	K_i (μM) guanine	K_i (μM) hypoxanthine	ratio[a]	ref
none	5	17	3.4	1, 2
8-amino	0.1–1.2	10	8–50	1, 2
8-amino-9-benzyl	0.2	150 ± 20	750	3
9-(5-phosphonopentyl)	0.17	1	6	5
9-(3,3-dimethyl-5-phosphonopentyl)	0.045[b]	0.21	5	5
9-(4-hydroxybutyl)	77	>200	>3	7
9-(2-amino-3,4-dihydroxybutyl)	~13.8	>100	7	7
9-(2-azido-3,4-dihydroxybutyl)	~5.1	~35	7	7

[a] K_i hypoxanthine/K_i guanine. [b] Bennett, L. L., Jr.; Elliott, R. D. Unpublished data.

Table 2. Inhibition of PNP[a] by 9-Deazapurines



2	R_1	R_2	IC_{50} (nM) X = NH_2	IC_{50} (nM) X = H	ratio (H/G)
c	3-chlorophenyl	CH_2CN	11 ± 2	10	0.9
d	phenyl	H	51 ± 12	35	0.7
b	3-pyridyl	H	25 ± 2.8	40	1.6
a	cyclopentyl	H	29	29	1
f	3-thienyl	H	25	28	1.1
e	3-(benzyloxy)phenyl	H	147 ± 70	190	1.3

[a] Calf spleen enzyme. Values without standard deviations are averages of results of two determinations that did not differ by more than 15%. Other values are the results of three or more determinations. The determinations were made in 1 mM phosphate.

necessary for activity and potency." Furthermore, our X-ray crystallographic studies have shown that the 2-amino group of guanine, or 9-deazaguanine, participates in the binding to Glu-201 of the active site of PNP.[10] With this background, it was somewhat surprising to find that in the 9-deazapurine series, the H/G ratios were about one or, in other words, the 2-amino group did not appear to contribute significant additional binding to the enzyme (Table 2). Although some differences have been observed between the binding of purines and 9-deazapurines,[10] these differences cannot account for this lack of contribution to binding of the 2-amino group. No detectable differences such as hydrogen bond lengths were observed in the binding of 9-benzyl-9-deazahypoxanthine (**2d**) and that of 9-benzyl-9-deazaguanine in the active site of PNP as determined by X-ray crystallographic analysis.

Experimental Section

Chemistry. All evaporations were carried out *in vacuo* with a rotary evaporator or by short-path distillation into a dry ice/acetone-cooled receiver under high vacuum. Analytical samples were normally dried *in vacuo* over P_2O_5 at room temperature for 16 h; high-melting compounds were dried at 110 °C. Analtech precoated (250 μm) silica gel G(F) plates (9 $CHCl_3$:1 MeOH or 17 MeCN:3 NH_4OH (1 N)) were used for TLC analyses; the spots were detected by irradiation with a Mineralight and absorption of iodine vapor. All analytical samples were homogeneous by TLC. Melting points were determined by the capillary method with a Mel-Temp apparatus and are uncorrected. The UV absorption spectra were determined in 0.1 N HCl (pH 1), pH 7 buffer, and 0.1 N NaOH (pH 13) with a Cary 17 spectrophotometer and a Perkin-Elmer UV–visible near-infrared spectrophotometer Model Lambda 9: the maxima are reported in nanometers ($\epsilon \times 10^{-3}$ M^{-1} cm^{-1}). The ^{1}H-NMR spectra of all compounds were determined with a Nicolet/GE NT 300NB(N) spectrometer or a Bruker WH-400-(B). Chemical shifts (δ, ppm) quoted in the case of multiplets are measured from the approximate center. The mass spectra were obtained with a Varian-MAT 311A mass spectrometer in the fast-atom-bombardment (FAB) mode or the electron-impact (EI) mode or with a Fisons VG Trio 2000 in the electrospray (ES) mode. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All solvates were confirmed by NMR. Infrared spectra were determined in pressed KBr disks with a Nicolet Model 10DX spectrophotometer; values are reported in reciprocal centimeters (cm^{-1}). Illustrative procedures are given below.

Method A. 3-(4-Oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-3-(3-chlorophenyl)propanenitrile (2c). To a solution of 3-[2-(methylthio)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl]-3-(3-chlorophenyl)propanenitrile[3] (**1c**, 1.0 g) in ethanol (100 mL) was suspended 30% Pd/C (1.00 g), and the suspension was refluxed for a few minutes. Hydrazine hydrate (300 μL) was added with stirring, and the reaction mixture was refluxed for 2 days. Additional portions of hydrazine hydrate (300 μL) and Pd/C (0.5 g) were added, and the reaction mixture was refluxed for an additional 4 days. The catalyst was removed by filtration, and the filtrate was reduced to 75 mL, filtered, and evaporated to give the desired product **2c** as a white solid: yield 0.82 g (94.7%); mp 230 °C; MS (FAB) 299 $(M + 1)^+$; IR (KBr) 3166, 3155, 3150, 3142, 3133, 3093, 2248, 1673, 1595, 1414; UV (0.1 N HCl) 237 (27.8); pH 7 262 (9.9), 233 (31.1); 0.1 N NaOH 268 (8.9). ^{1}H-NMR (DMSO-d_6) δ 3.3–3.52 (m, CH_2CN), 4.6 (t, $CHCH_2CN$), 7.24–7.56 (m, aromatic CH and H-6), 7.84 (s, H-2), 11.95 (s, NHCO), 12.11 (s, pyrrole NH). Anal. ($C_{15}H_{11}ClN_4O$) C, H, N.

Compounds **2a,b** and **2d–f** were prepared by the same procedure but using the 20% Pd/C catalyst.

7-(Cyclopentylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2a). 7-(Cyclopentylmethyl)-2-(methylthio)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1a**, 220 mg) gave **2a**, which was recrystallized from ethanol: yield 45 mg (25%); mp >340 °C; MS (FAB) 217 (M^+); ^{1}H-NMR (DMSO-d_6) δ 1.2 and 1.51 (m, cyclopentyl CH_2), 2.51 (m, CH_2), 7.15 (s, H-6), 7.75 (s, H-2), 11.75 (s, NH). Anal. ($C_{12}H_{15}N_3O$) C, H, N.

7-(3-Pyridylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2b). The methylthio compound **1b** (400 mg) gave **2b**, which was obtained pure by column chromatography (SiO_2, EtOAc/MeOH): yield 35 mg (11%); mp 318–20 °C; MS (FAB) 226 (M^+); ^{1}H-NMR (DMSO-d_6) δ 3.96 (s, CH_2), 7.25 (d, H-6), 7.27 and 7.65 (2m, pyridyl), 7.79 (s, H-2), 8.36 (dd, pyridyl), 8.52 (d, pyridyl), 11.85 and 11.95 (2s, NH). Anal. ($C_{12}H_{10}N_4O$) C, H, N.

7-Benzyl-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2d). Methylthio compound **1d** (140 mg) gave **2d**, which was recrystallized from ethanol: yield 45 mg (39%); mp 340 °C dec; MS (FAB) 225 (M^+); ^{1}H-NMR (DMSO-d_6) δ 3.95 (s, CH_2), 7.10–7.35 (m, phenyl), 7.23 (s, H-6), 7.80 (s, H-2), 11.85 and 11.90 (2s, NH). Anal. ($C_{13}H_{11}N_3O$) C, H, N.

7-[2-(Benzyloxy)benzyl]-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2e). Methylthio compound **1e** (500 mg) gave **2e**, which was recrystallized from ethanol: yield 52 mg (12%); mp 298–300 °C; MS (FAB) 331 (M^+); ^{1}H-NMR (DMSO-d_6) δ 3.92 (s, CH_2), 5.04 (s, OCH_2), 6.78 (dd, phenyl), 6.85 (d, phenyl), 6.92 and 7.15 (2m, phenyl), 7.18 (d, H-6), 7.28–7.43 (multiplets, phenyl), 7.9 (s, H-2), 11.83 and 11.87 (2s, NH). Anal. ($C_{20}H_{17}N_3O_2 \cdot 0.2H_2O$) C, H, N.

7-(3-Thienylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2f). Methylthio compound **1f** (243 mg) gave **2f**, which was recrystallized from ethanol: yield 55 mg (27%); mp 320 °C dec; MS (FAB) 231 (M^+), ^{1}H-NMR (DMSO-d_6) δ 3.95 (s, CH_2), 7.12 (dd, H-2'), 7.17 (s, H-6), 7.40 (q, H-5'), 7.79 (s, H-2), 7.94 (dd, H-4'), 11.85 and 11.90 (2s, NH). Anal. ($C_{11}H_9N_3OS$) C, H, N.

Method B. 7-Benzyl-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2d). A mixture of 7-benzyl-2-(methylthio)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**1d**, 200 mg, 0.738 mmol) and Raney nickel (500 mg) in ethanol (50 mL) was heated at reflux for 8 h. More Raney nickel (200 mg) was added and the mixture refluxed for 16 h. TLC indicated the presence of starting material; therefore, more Raney nickel (200 mg) was added and the mixture refluxed for 4 h. The mixture was filtered through Celite and the filtrate concentrated to 20 mL. On cooling, the white solid which separated out was collected by filtration: yield 90 mg (54%). This material was identical to that prepared by method A.

Method C. 7-(Cyclopentylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2a). Methyl 3-amino-4-(cyclopentylmethyl)-1*H*-pyrrole-2-carboxylate (**3a**, 6.8 g, 30.6 mmol) was heated under reflux with *N*,*N*-dimethylformamide dimethyl acetal (52 mL, 94%) for 16 h. The volatiles were evaporated in a rotoevaporator at 50–60 °C. The residue was placed in the glass liner of a 300-mL pressure reaction vessel followed by 100 mL of methanolic ammonia (saturated at 0–5 °C) and the reaction vessel sealed. This vessel was heated to 75–80 °C (140–150 psi) for 20 h and then cooled to 0 °C. The reaction vessel was opened, the white solid was collected by filtration and dissolved in about 800 mL of methanol by boiling for about 3 h, the mixture was cooled to room temperature, and the resulting crystals were collected by filtration and dried in air followed by drying in a pistol at 110 °C *in vacuo* to give a white powder: yield 4.8 g (72%). This material was identical to that prepared by method A.

7-(3-Pyridylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2b). 3-[[(Dimethylamino)methylene]amino]-2-(methoxycarbonyl)-4-[(3-pyridyl)methyl]-1*H*-pyrrole (**4b**, 8.9 g, 31 mmol) was placed in the glass liner of a 125-mL pressure reaction vessel followed by 70 mL of methanolic ammonia (prepared by passing ammonia gas into anhydrous methanol at 0–5 °C until saturation) and the reaction vessel sealed. This vessel was heated to 100–120 °C for 20 h and then cooled to 0 °C. The reaction vessel was opened and the cream-colored solid collected by filtration, washed with about 15 mL of methanol, dried in air followed by drying at 110 °C *in vacuo*, giving an off-white powder, 5.5 g (78.5%). This material was identical to that prepared by method A.

3-(4-Oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-3-(3-chlorophenyl)propanenitrile (2c). In the same manner, **4c** (3 g, 14.0 mmol) gave 2.2 g (88%) of **2c**. This material was identical with that prepared by method A.

7-(4-Pyridylmethyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine-4-one (2g). Methyl 3-amino-4-(pyridylmethyl)-1*H*-pyrrole-2-carboxylate (2.81 g, 12.15 mmol) was heated under reflux with *N*,*N*-dimethylformamide dimethyl acetal (14 mL, 94%) for 16 h. The volatiles were evaporated at 50–60 °C. The residue was placed in the glass liner of a 125-mL pressure reaction vessel followed by 50 mL of methanolic ammonia (prepared by passing ammonia gas into anhydrous methanol at 0–5 °C until saturation) and the reaction vessel sealed. This vessel was heated to 120 °C (140–150 psi) for 16 h and then allowed to cool to room temperature. The reaction vessel was opened, the residue was transferred into a 500-mL round-bottom flask, and volatiles were evaporated. The residue on crystallization from chloroform–ethanol furnished a solid which was dried in air followed by drying at 110 °C *in vacuo* to give 1.8 g (65%) of a cream-colored powder: mp 305–307 °C; MS (ES) 226 ($M + 1$)$^+$; ^{1}H-NMR (DMSO-d_6) δ 3.96 (s, CH_2), 5.97 and 7.25 (m, pyridyl), 7.28 (d, H-6), 7.79 (s, H-2), 8.41 (d, pyridyl), 11.86, 11.97 (2s, NH). Anal. ($C_{12}H_{10}N_4O\cdot0.1H_2O$) C, H, N.

3-[[(Dimethylamino)methylene]amino]-2-(methoxycarbonyl)-4-(3-pyridylmethyl)-1*H*-pyrrole (4b). Methyl 3-amino-4-(3-pyridylmethyl)-1*H*-pyrrole-2-carboxylate (**3b**, 10 g, 43.29 mmol) was placed in a 100-mL round-bottom flask and *N*,*N*-dimethylformamide dimethyl acetal (50 mL) added to it. The reaction mixture was heated to 80–90 °C using an oil bath for 16 h. The volatiles were evaporated on a rotevaporator at 45–50 °C. The light brown syrupy residue was dissolved in about 50 mL of chloroform and filtered through a funnel containing silica gel (22 g; diameter of the funnel, 4 cm; thickness of silica gel about 5 cm) to remove the baseline impurities. The silica gel cake was washed further with 200 mL of chloroform. The combined chloroform filtrates were evaporated to give a light yellow solid, which was crystallized from an ether–hexane mixture. The light yellow needles weighed 9.1 g (73.4%): mp 97–98 °C; MS (ES) 287 ($M + 1$); ^{1}H-NMR (DMSO-d_6) δ 2.98 (s, $N(CH_3)_2$), 3.75 (s, CH_2), 3.76 (s, OCH_3), 6.5 (d, H-5), 7.15 (m, H-5'), 7.55 (m, H-4'), 7.58 (s, N=C*H*N), 8.4 (d of d, H-6'), 8.5 (d, H-2'), 8.52 (s, NH). Anal. ($C_{15}H_{18}N_4O_2$) C, H, N.

Methyl 3-[[(Dimethylamino)methylene]amino]-4-[2-cyano-1-(3-chlorophenyl)ethyl]-1*H*-pyrrole-2-carboxylate (4c). Methyl 3-amino-4-[2-cyano-1-(3-chlorophenyl)ethyl]-1*H*-pyrrole-2-carboxylate (5 g) (**3c**) was treated with *N*,*N*-dimethylformamide dimethyl acetal (50 mL) under argon and the mixture heated 24 h at 60–70 °C. After the reaction mixture was evaporated to dryness, it was redissolved in 50 mL of CH_2Cl_2, filtered, and diluted with petroleum ether (PE) until cloudy. The mixture was scratched to induce crystallization and slowly diluted with an additional 400 mL of petroleum ether. The product was collected, washed with PE, and dried: yield 5.0 g (80%); mp 122–124 °C; MS (FAB) 359 ($M + H$)$^+$, 327 ($358 - OCH_3$)$^+$; ^{1}H-NMR (DMSO-d_6) δ 2.91 (s, $N(CH_3)_2$), 3.14–3.30 (m, CH_2CN), 3.64 (s, OCH_3), 4.20 (t, $CHCH_2CN$), 6.83 (d, pyrrole ring C*H*), 7.23–7.35 (m, aromatic CH), 7.42 (d, aromatic C*H*), 7.54 (s, N=C*H*NMe$_2$), 10.96 (bs, pyrrole NH). Anal. ($C_{18}H_{19}ClN_4O_2$) C, H, N.

Compound Evaluations. The X-ray crystallographic analysis, computer modeling studies, and enzyme inhibition studies were carried out as previously described.[10]

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