Cyclic Guanidines: Synthesis of 4,6,7,8-Tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*d*]pyrimidin-7-ones and 1,4,6,7,8,9-Hexahydropyrazolo[3',4':4,5]pyrimido[2,1-*c*][1,2,4]triazin-7-ones

R. Ferroni, D. Simoni, P. Orlandini, and M. Guarneri

Dipartimento di Scienze Farmaceutiche dell'Università, via Scandiana 21, 44100 Ferrara, Italy

V. Bertolasi and V. Ferretti

Dipartimento di Chimica e Centro di Strutturistica Diffrattometrica della Universita', via L. Borsari 46, 44100 Ferrara, Italy

Received July 17, 1989

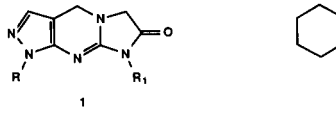
The synthesis of potential platelet aggregation inhibitors 4,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazolo[3,4-*d*]-pyrimidin-7-ones and 1,4,6,7,8,9-hexahydropyrazolo[3',4':4,5]pyrimido[2,1-*c*][1,2,4]triazin-7-ones derivatives is described starting from 4,6-dichloropyrazolo[3,4-*d*]pyrimidines.

J. Heterocyclic Chem., **27**, 823 (1990).

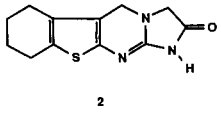
During our work aiming to obtain new compounds with antiplatelet activity, we synthesized some simple guanidinophenyl derivatives of pyrazole, which showed interesting platelet aggregation inhibitory activity [1].

Thus, in continuation of this program we turned our attention to the tricyclic guanidines **1** bearing both the pyrazole and guanidine moiety. Our interest in these heterocyclic compounds is due to their analogy with others cyclic guanidines, e.g., 1,2,3,5,6,7,8,9-octahydro[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidin-2-one **2** and 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one derivatives **3a,b** which are potent inhibitors of platelet aggregation [2,4] (Chart 1).

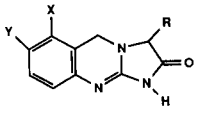
Chart 1



1



2



3a-b

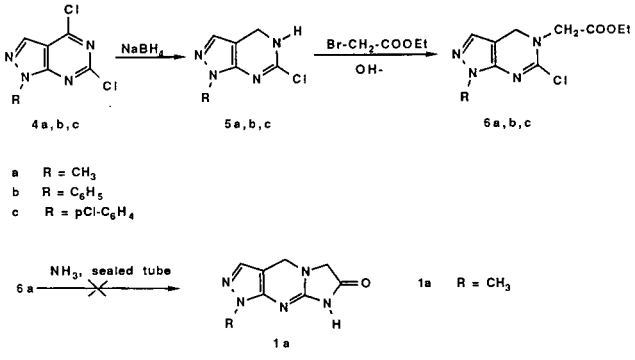
a R = H X = Y = Cl
b R = X = CH_3 Y = Br

To our knowledge, the preparation of 4,6,7,8-tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*d*]pyrimidin-7-ones **1** have not been reported. The synthetic pathway used in obtaining the title cyclic guanidines is summarized in Scheme 1.

The key intermediates 4,6-dichloropyrazolopyrimidines **4a-c** were prepared by use of the method described by Cheng and Robins [5].

Treatment of **4a-c** with sodium borohydride in a chloroform-ethanol solution produced the 4,5-dihydro-1*H*-6-chloropyrazolopyrimidine **5a-c** as white crystalline products. This reaction is in accord to the known reduction of

Scheme 1



2,4-dichloropyrimidine derivatives with sodium borohydride to give the corresponding 3,4-dihydropyrimidine derivatives [2], as well as reduction of imidoyl chlorides to amines [6].

The structures of the compounds **5a-c** were supported by analytical and spectral data. In particular ^{1}H-nmr spectra showed singlet signal of methylene protons at 4.00-4.70 ppm and ^{13}C-nmr spectra exhibited signal of C4 as triplets at 40.90 ppm.

Alkylation of **5a-c** with ethyl bromoacetate in the presence of sodium hydroxide and trace of tetrabuthylammonium iodide afforded the *N*-alkyl derivatives **6a-c** in good yield.

The ring closure of compounds **6** to the compounds **1** was carried out in the presence of ammonia, buthylammine and benzylamine.

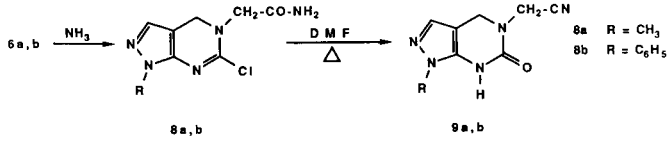
The reaction of **6b** and **6c** with the ethanolic ammonia in a sealed tube afforded compounds **1b** and **1c** respectively, as described by Ishikawa [2] for similar compounds.

Under the same conditions **6a** did not react; most of the material seems to decompose and no trace of the expected **1a** was detected (Scheme 1).

The cyclization of **6a,b** into **1d,e** was achieved in good yield by refluxing them in *N,N*-dimethylformamide in the presence of buthylamine, while **1f,g** were obtained directly from **6a,b** by simple reaction with benzylamine in ethanol at room temperature.

Attempts to obtain **1a,b** by carring out the ring closure of **6a,b** with ethanolic ammonia at room temperature or at reflux did not succeed; the only products isolated were the amides **8a,b**. Heating of this compounds in *N,N*-dimethylformamide at reflux for 3-5 hours produced the nitriles **9a,b** instead of cyclic guanidine **1a** and **1b** (Scheme 2).

Scheme 2



This reaction is due, possibly, by dehydration of the amide function and attack of water at the labile 6-position of the pyrazolo[3,4-*d*]pyrimidine.

The structures of **1** and **9** were assigned on the basis of Ir, ^{1}H-nmr, ^{13}C-nmr data and X-ray analysis.

Compounds **1** showed a carbonyl absorption at 1750 cm^{-1}; in the ^{1}H-nmr spectra, the methylene protons at 4 and 6 positions appeared as singlet at 3.8-4.1 ppm and 4.4-4.7 ppm; moreover ^{13}C-nmr spectra shoved C5 and C6 as triplets at 43-44 ppm and 50-55 ppm respectively.

Table 1. Crystal data

	Compound **9b**	Compound **1f**
Formula	$C_{13}H_{11}N_5O$	$C_{20}H_{17}N_5O$
Formula weight	253.27	343.39
Crystal size (mm)	0.2x0.2x0.5	0.3x0.2x0.4
Crystal system	monoclinic	monoclinic
Space group	P 2_1/c	P 2_1/c
a (Å)	6.713(1)	16.364(2)
b (Å)	16.121(2)	12.048(1)
c (Å)	10.990(1)	8.510(1)
β (°)	92.17(1)	93.89(1)
V (Å^3)	1188.5(3)	1673.9(3)
Z	4	4
D_c (g cm^{-3})	1.41	1.36
F (000)	528	720
μ (MoKα) (cm^{-1})	0.90	0.83
θ_{min} - θ_{max} (°)	2 - 27	2 - 27
Independent reflections	2541	3661
Reflections with I≥3σ(I)	1646	1770
R, Rw	0.037, 0.036	0.039, 0.051
S=error in a observation of unit weight	1.90	1.54
Largest peak (e Å^{-3}) in final difference map	0.21	0.15

Compounds **9** showed a carbonyl absorption at 1670 cm^{-1}; no differences in the ^{1}H- and ^{13}C-nmr spectra were found in respect to compounds **1**.

All the spectral data agree with the proposed structures **1** and **9** but not unequivocally: so we confirmed the assignment of these structures through the X-ray analysis of compounds **1f** and **9b** (Figures 1 and 2).

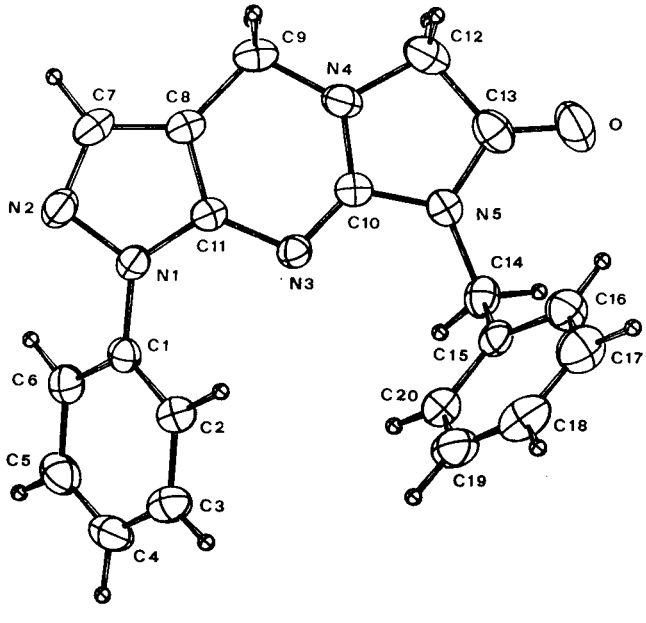


Figure 1. An ORTEP view of **1f** with thermal ellipsoids at the 40% probability level.

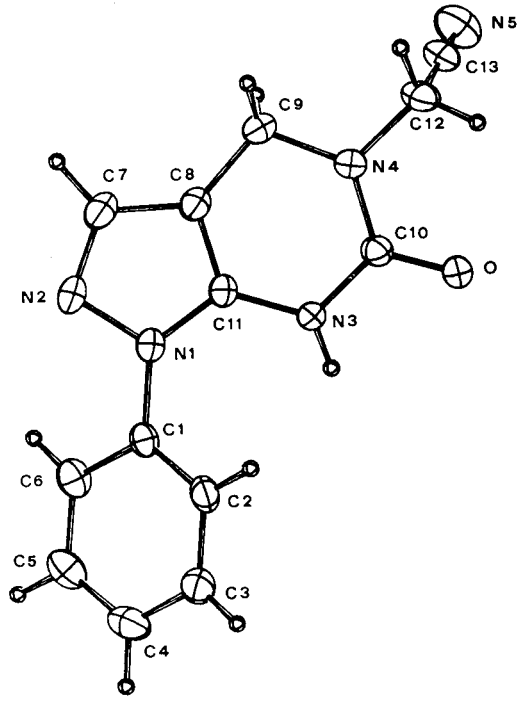
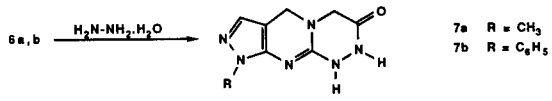


Figure 2. An ORTEP view of **9b** with thermal ellipsoids at the 40% probability level.

This synthetic pathway was also applied to the synthesis of other cyclic guanidines: 1-substituted-1,4,6,7,8,9-hexahydropyrazolo[3',4':4,5]pyrimido[2,1-*c*] [1,2,4]triazin-7-ones **7a,b** were obtained by reaction of **6a,b** with hydrazine in ethanol solution at room temperature (Scheme 3).

Scheme 3



7a,b

Analytical data of derivatives **1b-g** and **7a,b** are illustrated in the Table 6.

All these new cyclic guanidines will be investigated to determine their potential biological activity as blood platelet aggregation inhibitors.

Table 2. Positional Parameters and their estimated Standard Deviations for **9b**

Atom	x/a	y	z	B_{eq} or B ($Å^2$)
O	0.1057(2)	0.06101(9)	0.8983(1)	3.56(3)
N1	-0.4805(3)	0.1523(1)	1.0783(2)	3.12(3)
N2	-0.6048(3)	0.2194(1)	1.0582(2)	3.88(4)
N3	-0.1801(3)	0.0958(1)	0.9881(2)	3.26(3)
N4	-0.0519(3)	0.1780(1)	0.8339(2)	3.33(4)
N5	-0.0003(4)	0.1399(2)	0.5311(2)	5.89(6)
C1	-0.5223(3)	0.0951(1)	1.1721(2)	2.90(4)
C2	-0.3692(3)	0.0582(2)	1.2395(2)	3.51(4)
C3	-0.4130(4)	0.0017(2)	1.3292(2)	4.29(5)
C4	-0.6089(4)	-0.0161(2)	1.3537(2)	4.63(6)
C5	-0.7614(4)	0.0236(2)	1.2889(2)	4.31(5)
C6	-0.7204(3)	0.0785(2)	1.1969(2)	3.67(5)
C7	-0.5295(4)	0.2587(1)	0.9646(2)	4.03(5)
C8	-0.3611(3)	0.2185(1)	0.9215(2)	3.40(4)
C9	-0.2229(4)	0.2348(2)	0.8215(2)	4.15(5)
C10	-0.0350(3)	0.1093(1)	0.9050(2)	2.96(4)
C11	-0.3351(3)	0.1518(1)	0.9957(2)	2.95(4)
C12	0.1042(4)	0.1923(2)	0.7483(2)	3.86(5)
C13	0.0454(4)	0.1632(2)	0.6246(2)	4.00(5)
H3N	-0.174(3)	0.048(1)	1.021(2)	3.4(5)*
H2	-0.231(3)	0.072(1)	1.226(2)	3.7(5)*
H3	-0.309(3)	-0.022(1)	1.378(2)	4.5(6)*
H4	-0.635(3)	-0.056(2)	1.416(2)	5.1(6)*
H5	-0.900(4)	0.013(2)	1.308(2)	5.5(6)*
H6	-0.926(3)	0.104(1)	1.145(2)	4.7(6)*
H7	-0.590(4)	0.310(2)	0.934(2)	5.2(6)*
H91	-0.166(4)	0.295(2)	0.825(2)	5.6(6)*
H92	-0.297(3)	0.227(1)	0.737(2)	5.2(6)*
H121	0.231(3)	0.164(1)	0.777(2)	5.2(6)*
H122	0.136(4)	0.253(2)	0.746(2)	5.8(6)*

Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of isotropic equivalent thermal parameters defined as: $B_{eq} = 4/3 \Sigma_i\Sigma_j\beta_{ij}a_ia_j$.

Table 3. Positional Parameters and their estimated Standard Deviations for **1f**

Atom	x	y	z	B_{eq} or B ($Å^2$)
O	0.8178(1)	0.5277(2)	0.4962(3)	6.71(5)
N1	0.6269(1)	0.0393(2)	0.6904(2)	3.78(4)
N2	0.5595(1)	0.0297(2)	0.7774(3)	4.74(5)
N3	0.7136(1)	0.1817(2)	0.5908(2)	3.40(4)
N4	0.6737(1)	0.3618(2)	0.6703(3)	4.32(5)
N5	0.7797(1)	0.3454(2)	0.5233(2)	3.87(4)
C1	0.6570(1)	-0.0543(2)	0.6104(3)	3.49(5)
C2	0.7402(2)	-0.0700(2)	0.6060(3)	4.09(6)
C3	0.7683(2)	-0.1588(2)	0.5235(3)	4.99(6)
C4	0.7145(2)	-0.2315(2)	0.4471(3)	5.26(7)
C5	0.6320(2)	-0.2158(2)	0.4534(4)	5.29(7)
C6	0.6026(2)	-0.1268(2)	0.5342(3)	4.48(6)
C7	0.5422(2)	0.1340(2)	0.8141(3)	4.75(6)
C8	0.5948(1)	0.2106(2)	0.7529(3)	3.76(5)
C9	0.6005(1)	0.3344(2)	0.7511(3)	4.29(6)
C10	0.7194(1)	0.2884(2)	0.5957(3)	3.49(5)
C11	0.6484(1)	0.1470(2)	0.6748(3)	3.34(5)
C12	0.6996(2)	0.4739(2)	0.6417(4)	5.34(7)
C13	0.7728(2)	0.4576(2)	0.5453(3)	4.92(6)
C14	0.8417(2)	0.2917(2)	0.4336(3)	4.29(6)
C15	0.9159(1)	0.2551(2)	0.5333(3)	3.67(5)
C16	0.9726(2)	0.3321(2)	0.5942(3)	4.93(6)
C17	1.0408(2)	0.2995(3)	0.6843(4)	6.14(8)
C18	1.0543(2)	0.1899(3)	0.7163(4)	6.23(8)
C19	0.9999(2)	0.1121(3)	0.6559(4)	6.22(8)
C20	0.9305(2)	0.1450(2)	0.5641(3)	5.00(6)
H2	0.778(1)	-0.015(2)	0.659(3)	5.1(6)*
H3	0.823(1)	-0.166(2)	0.520(3)	4.9(6)*
H4	0.735(1)	-0.296(2)	0.399(3)	6.1(6)*
H5	0.593(2)	-0.267(2)	0.402(3)	6.4(7)*
H6	0.543(1)	-0.113(2)	0.542(3)	4.7(5)*
H7	0.496(1)	0.148(2)	0.874(3)	5.5(6)*
H91	0.551(1)	0.371(2)	0.694(3)	4.6(5)*
H92	0.610(1)	0.367(2)	0.861(3)	6.0(6)*
H121	0.715(2)	0.513(2)	0.739(3)	7.2(7)*
H122	0.655(2)	0.515(2)	0.581(3)	7.0(7)*
H141	0.814(1)	0.227(2)	0.378(3)	4.7(5)*
H142	0.858(1)	0.346(2)	0.358(3)	4.4(5)*
H16	0.960(1)	0.409(2)	0.575(3)	5.6(6)*
H17	1.081(2)	0.356(2)	0.726(3)	7.5(7)*
H18	1.107(2)	0.168(3)	0.784(4)	9.0(9)*
H19	1.006(2)	0.034(2)	0.673(3)	7.6(7)*
H20	0.891(1)	0.093(2)	0.521(3)	4.8(6)*

Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of isotropic equivalent thermal parameters defined as: $B_{eq} = 4/3\Sigma_i\Sigma_j\beta_{ij}a_ia_j$.

EXPERIMENTAL

Melting points were determined on Reichert Thermovar apparatus and are uncorrected. The ir spectra were obtained with Perkin-Elmer 299B infrared spectrophotometer; ^{1}H- and ^{13}C-nmr spectra were determined with a Bruker AC-200 spectrometer.

Crystallography.

Intensity data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-Kα radiation and $\omega/2\theta$ sean technique. Cell parameters were obtained from least squares refinement of the setting angles of 25 centered reflections in the range $9 < \theta < 13°$. Crystal data of compound **1f** and **9b** are reported in Table 1. Intensities were corrected

Table 4. Selected bond distances (Å) with e.s.d.'s in parentheses.

	Compound **9b**	Compound **1f**
O - C10	1.228(2)	
O - C13		1.213(4)
N1 - N2	1.379(2)	1.374(3)
N1 - C1	1.419(3)	1.422(3)
N1 - C11	1.358(3)	1.353(3)
N2 - C7	1.325(3)	1.330(3)
N3 - C10	1.378(3)	1.290(3)
N3 - C11	1.382(3)	1.388(3)
N4 - C9	1.471(3)	1.459(3)
N4 - C10	1.358(3)	1.345(3)
N4 - C12	1.453(3)	1.441(3)
N5 - C10		1.381(3)
N5 - C13	1.126(3)	1.370(3)
N5 - C14		1.461(3)
C7 - C8	1.401(3)	1.387(4)
C8 - C9	1.489(3)	1.495(3)
C8 - C11	1.357(3)	1.370(3)
C12 - C13	1.478(3)	1.510(5)

Table 5. Selected bond angles (°) with e.s.d.'s in parentheses.

	Compound **9b**	Compound **1f**
N2 - N1 - C1	119.4(2)	120.5(2)
N2 - N1 - C11	110.1(2)	110.9(2)
C1 - N1 - C11	130.4(2)	127.8(2)
C7 - N2 - N1	104.7(2)	103.8(2)
C11 - N3 - C10	119.3(2)	109.9(2)
C9 - N4 - C10	127.5(2)	125.0(2)
C9 - N4 - C12	114.9(2)	123.5(2)
C10 - N4 - C12	117.1(2)	110.9(2)
C10 - N5 - C13		111.2(2)
N2 - C7 - C8	112.2(2)	113.1(2)
C7 - C8 - C11	104.5(2)	104.1(2)
C9 - C8 - C11	120.9(2)	120.7(2)
N4 - C9 - C8	109.1(2)	106.5(2)
N3 - C10 - N4	117.7(2)	129.0(2)
N3 - C10 - O	120.3(2)	
N4 - C10 - O	122.0(2)	
N3 - C10 - N5		122.3(2)
N4 - C10 - N5		108.7(2)
N1 - C11 - N3	127.3(2)	123.6(2)
N1 - C11 - N8	108.5(2)	108.0(2)
N3 - C11 - C8	124.1(2)	128.4(2)
N4 - C12 - C13	111.8(2)	102.4(2)
N5 - C13 - C12	178.9(3)	106.2(2)
N5 - C13 - O		125.6(3)
O - C13 - C12		128.2(2)

from Lorenz and polarization. Scattering factors were taken from [7]. The intensities of three standard reflections measured after every 2 hours showed no significant variation during data collection.

The structures were solved by direct methods (MULTAN 81 [8]) and refined by full-matrix least-squares analysis with anisotropic temperature factors for all non-H atoms and isotropic ones for hydrogens. Weights were applied according to the scheme $w = 4Fo^2/[\sigma^2(Fo^2) + (0.04\ Fo^2)^2]$ and final statistical parameters: $R = \Sigma I\Delta FoI/\Sigma IFoI$ and $Rw = (\Sigma wI\Delta FoI^2/\Sigma wI FoI^2)^{1/2}$ were 0.037, 0.036 and 0.039, 0.051 for compounds **9b** and **1f** respectively. Final positional and equivalent isotropic vibrational parameters are reported in Tables 2 and 3. Selected bond distances and angles are given in Tables 4 and 5.

All calculations were done using the CAD4-SDP system of program [9] and PARST [10]. ORTEP [11] views of the molecules with the atom-labelling scheme are shown in Figures 1 and 2.

The crystal of compound **9b** is built up by dimers in which the two molecules are linked, through a centre of symmetry, by a double hydrogen bond N3-HN3---O (-x,-y,-z+2) with the following parameters N3-H3N = 0.85(2), N3---O = 2.855(2), H3N---O = 2.01(2)Å and N3-H3N---O1 = 170(2)°.

The packing of the dimers of compound **9b** and of the molecules of compound **1f** is controlled by Van der Waal interactions.

Chemistry.

6-Chloro-1-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5a**).

To a cooled and well stirred solution of **4a** (5 g, 25 mmoles) in chloroform (30 ml) and ethanol (30 ml), sodium borohydride (4.53 g, 120 mmoles) was added portionwise. The mixture was stirred at room temperature for 1 hour. After evaporation of the solvent, water was added and the solid residue was filtered and purified by column chromatography on silica gel eluting with ethyl acetate. Crystallization from ethyl acetate give **5a** (2.43 g, 58%, mp 197-199°); ir (potassium bromide): 3200, 1600, 1580, 1520 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 3.66 (s, 3H), 4.68 (s, 2H), 7.03 (s, 1H), 8.08 (br, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 32.95 (q), 40.94 (t), 94.62, 132.72 (d), 142.87, 148.10.

Anal. Calcd. for $C_6H_7ClN_4$: C, 42.24; H, 4.14; Cl, 20.78; N, 32.84. Found: C, 42.09; H, 4.20; Cl, 20.72; N, 32.76.

6-Chloro-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5b**).

Following a procedure similar to preparation of **5a**, **5b** was obtained (60%, mp 198-200° from ethyl acetate); ir (potassium bromide 3180, 1600, 1590, 1510 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 4.67 (s, 2H), 7.40 (s, 1H), 7.20-8.00 (m, 5H), 8.52 (br, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 40.82 (t), 97.03, 121.11 (d), 125.80 (d), 128.82 (d), 135.40 (d), 138.54, 143.40, 149.19.

Anal. Calcd. for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; Cl, 15.24; N, 24.08. Found: C, 56.53; H, 4.03; Cl, 15.12; N, 23.94.

6-Chloro-1-*p*-chlorophenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5c**).

Compound **5c** was obtained following a procedure similar to preparation of **5a** (65%, mp 204-206°, from ethyl acetate); ir (potassium bromide): 3200, 1600, 1585, 1570, 1500 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ [ppm] 4.71 (s, 2H), 7.30 (s, 1H), 7.40-8.00 (A_2B_2, 4H, J = 8.0 Hz), 8.51 (br, 1H). ^{13}C-nmr (DMSO-d_6): δ [ppm] 41.03 (t), 97.00, 122.11 (d), 128.35 (d), 130.35, 135.33 (d), 137.54, 143.75, 149.39.

Anal. Calcd. for $C_{11}H_7Cl_2N_4$: C, 49.65; H, 2.65; Cl, 26.65; N, 21.05. Found: C, 49.45; H, 2.51; Cl, 26.51; N, 20.93.

Ethyl 6-Chloro-1-methyl-4,5-dihydropyrazolo[3,4-*d*]pyrimidine-5-acetate (**6a**).

To a well stirred suspension of **5a** (2.6 g, 15 mmoles) in methylene dichloride (30 ml), ethyl bromoacetate (1.7 ml, 16 mmoles), sodium hydroxide solution (7.4 ml, 10 N) and tetrabuthylammonium iodide (0.1 g) were added. After stirring for 3 hours at room temperature the organic layer was separated, washed with water, dried and evaporated. The solid residue was

Table 6

Analytical Data of New Copmounds

Compound	IR (Potassium bromide) cm^{-1}	^{1}H-NMR (DMSO-d_6) ppm	^{13}C-NMR (DMSO-d_6) ppm	Molecular Formula	Analysis % Calcd./Found C	H	N
1b	3350, 3200, 1750, 1640, 1580, 1540	3.94 (s, 2H), 4.52(s, 2H), 7.40 (s, 1H), 7.20-8.00 (m, 5H), 8.80 (br, 1H)	41.95 (t), 52.41 (t), 97.11, 121.84 (d), 126.30 (d), 128.32 (d), 135.20 (d), 138.51, 145.42, 155.86, 171.80	$C_{13}H_{11}N_5O$	61.65 61.51	4.38 4.20	27.65 27.60
1c	3340, 3180, 1750, 1640, 1585, 1570	3.94 (s, 2H), 4.50 (s, 2H), 7.41 (s, 1H), 7.40-8.10 (A_2B_2, 4H, J = 8.8 Hz), 11.48 (br, 1H)	42.04 (t), 52.35 (t), 97.00, 122.35 (d), 128.78 (d), 129.69, 136.19, (d), 138.37, 145.38, 155.47, 171.85	$C_{13}H_{10}ClN_5O$ [a]	54.26 54.22	3.50 3.42	24.34 24.41
1d	1745, 1610, 1560, 1500	0.96 (t, 3H, J = 7.2 Hz), 1.37 (m, 2H), 1.68 (m, 2H), 3.67 (t, 2H, J = 7.2 Hz) 3.71 (s, 3H), 3.83 (s, 2H), 4.57 (s, 2H), 7.20 (s, 1H)	13.60 (q), 19.95 (t), 29.83 (t) 33.66 (q), 39.07 (t), 43.61 (t), 51.73, (t), 94.92, 133.50 (d), 144.25, 153.81, 169.87	$C_{12}H_{17}N_5O$	58.28 58.48	6.93 7.11	28.32 28.49
1e	1765, 1640, 1610, 1570	0.96 (t, 3H, J = 7.0 Hz), 1.38 (m, 2H), 1.68 (m, 2H), 3.66 (t, 2H, J = 7.0 Hz) 3.81 (s, 2H), 4.60 (s, 2H), 7.37 (s, 1H), 7.10-8.20 (m, 5H)	13.60 (q), 19.94 (t), 29.75 (t), 39.15 (t), 43.27 (t), 51.74 (t), 96.70, 121.40 (d), 125.82 (d), 128.70 (d), 135.32 (d), 139.54, 144.36, 154.06, 169.77	$C_{17}H_{19}N_5O$	66.00 66.05	6.19 6.22	22.64 22.83
1f	1750, 1625, 1560, 1530, 1500	3.61 (s, 3H), 4.02 (s, 2H), 4.48(s, 2H), 4.72 (s, 2H), 7.13 (s, 1H), 7.15-7.60 (m, 5H)	32.80 (q), 41..25 (t), 42.21 (t), 50.88 (t), 94.61, 127.00 (d), 127.96 (d), 132.80 (d), 135.90, 142.20, 153.43, 169.93	$C_{15}H_{15}N_5O$	64.04 63.89	5.37 5.18	24.89 24.75
1g	1755, 1620, 1600, 1530, 1500	3.83 (s, 2H), 4.57 (s, 2H), 4.79 (s, 2H), 7.41 (s, 1H), 7.10-8.10 (m, 10H)	42.95 (t), 43.30 (t), 51.76 (t), 96.75, 121.74 (d), 125.98 (d), 128.10 (d), 128.56 (d), 128.67 (d), 129.10 (d), 135.30 (d), 135.84, 139.40, 144.17, 153.70, 169.44	$C_{20}H_{17}N_5O$	69.96 70.11	4.99 4.93	20.39 20.22
7a	3300, 3200, 1750, 1640, 1620, 1560, 1530	3.58 (s, 3H), 3.91 (s, 2H), 4.45 (s, 2H), 4.92 (br, 2H), 7.13 (s, 1H)	33.45 (q), 42.80 (t), 50.16 (t), 95.53, 133.40 (d), 144.10, 154.80, 169.42	$C_8H_{10}N_6O$	46.59 46.70	4.89 5.03	40.76 40.66
7b	3340, 3280, 1760, 1640, 1620, 1580, 1570, 1500	4.00 (s, 2H), 4.57 (s, 2H), 5.02 (br, 2H), 7.45 (s, 1H), 7.20-8.20 (m, 5H)	42.18 (t), 49.82 (t), 96.85, 120.38 (d), 125.02 (d), 128.34 (d), 135.26 (d), 139.09, 144.27, 154.76, 168.53	$C_{13}H_{12}N_6O$	58.20 58.42	4.51 4.41	31.33 31.30

[a] Cl Calcd: 12.32. Found: 12.17.

crystallized from ethanol to give **6a** (1.9 g, 50%, mp 266-268°), ir (potassium bromide): 1740, 1590, 1580 cm^{-1}; 1H-nmr (DMSO-d_6): δ [ppm] 1.31 (t, 3H, J = 7.0 Hz), 3.74 (s, 3H), 4.14 (s, 2H), 4.26 (q, 2H, J = 7.0 Hz), 4.79 (s, 2H), 7.08 (s, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 13.05 (q), 32.79 (q), 49.10 (t), 52.92 (t), 60.60 (t), 95.35, 131.65 (d), 141.26, 148.29, 166.78.

Anal. Calcd. for $C_{10}H_{13}ClN_4O_2$: C, 46.79; H, 5.16; Cl, 13.81; N, 21.83. Found: C, 46.64; H, 5.08; Cl, 13.75; N, 21.62.

Ethyl 6-Chloro-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine (**6b**).

Following the same procedure used for preparation of **6a**, **6b** was obtained (64%, mp 86-88° from ethanol); ir (potassium bromide): 1730, 1600, 1590, 1570 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 1.30 (t, 3H, J = 7.0 Hz), 4.11 (s, 2H), 4.26 (q, 2H, J = 7.0 Hz), 4.79 (s, 2H), 7.38 (s, 1H), 7.20-8.00 (m, 5H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 14.17 (q), 49.94 (t), 54.28 (t), 61.98 (t), 98.24, 121.92 (d), 126.37 (d), 128.90 (d), 134.50 (d), 138.93, 142.42, 149.73, 167.67.

Anal. Calcd. for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; Cl, 11.12; N, 17.58. Found: C, 56.48; H, 4.81; Cl, 11.18; N, 17.43.

Ethyl 6-Chloro-1-*p*-chlorophenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]-pyrimidine-5-acetate (**6c**).

Compound **6c** was obtained as described for **6a** (80%, mp 93-95° from ethanol); ir (potassium bromide): 1740, 1600, 1580, 1565 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 1.30 (t, 3H, J = 7.2 Hz), 4.12 (s, 2H), 4.26 (q, 2H, J = 7.2 Hz), 4.78 (s, 2H), 7.26 (s, 1H), 7.40-8.00 (A_2B_2, 4H, J = 8.8 Hz); ^{13}C-nmr (DMSO-d_6): δ [ppm] 14.13 (q), 42.86 (t), 54.21 (t), 61.99 (t), 98.36, 122.79 (d), 128.89 (d), 131.61, 134.74 (d), 137.55, 142.53, 149.91, 167.54.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_4O_2$: C, 51.01; H, 3.99; Cl, 20.07; N, 15.86. Found: C, 49.83; H, 4.01; Cl, 20.15; N, 15.67.

1-Phenyl-4,6,7,8-tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*d*]-pyrimidin-7-one Hydrochloride (**1b**).

Compound **6b** (2.55 g, 8 mmoles) with 10% ammonia-ethanolic solution (10 ml) was heated for 3 hours at 120° in a sealed tube. After cooling, a precipitate was collected, washed with ethanol and dried. The free base was converted to hydrochloride by treatment with 5% hydrogen chloride-ethanol and crystallized from ethanol to give **1b** (1.6 g, 79%, mp 265-267°).

1-*p*-Chlorophenyl-4,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazolo[3,4-*d*]-pyrimidin-7-one Hydrochloride (**1c**).

Compound **1c** was obtained as described for **1b** (44%, mp 262-265° from ethanol).

8-Butyl-1-methyl-4,6,7,8-tetratrihydro-1*H*-imidazo[1,2-*a*]pyrazolo-[3,4-*d*]pyrimidin-7-one Hydrochloride (**1d**).

A solution of **6a** (1.28 g, 5 mmoles) in *N*,*N*-dimethylformamide (5 ml) containing butylamine (1.48 ml, 15 mmoles) was refluxed for 5 hours. The solvent was evaporated, and the residue was crystallized from ethanol to give **1d** (0.54 g, 45%, mp 141-143°).

8-Butyl-1-phenyl-4,6,7,8-tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo-[3,4-*d*]pyrimidin-7-one (**1e**).

Following a procedure similar to preparation of **1d**, **1e** was obtained (53%, mp 138-139° from ethanol).

8-Benzyl-1-methyl-4,6,7,8-tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo-[3,4-*d*]pyrimidin-7-one (**1f**).

A solution of **6a** (1.28 g, 15 mmoles) in ethanol (20 ml) containing benzylamine (1.6 ml, 15 mmoles) was stirred at room temperature for 5 days. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with chloroform/methanol. Crystallization from ethanol produced **1f** (0.28 g, 20%, mp 150-152°).

1-Phenyl-8-benzyl-4,6,7,8-tetrahydro-1*H*-imidazo[1,2-*a*]pyrazolo-[3,4-*d*]pyrimidin-7-one (**1g**).

Following a procedure similar to preparation of **1f**, **1g** was obtained (60%, mp 200-202° from ethanol).

1-Methyl-1,4,6,7,8,9-hexahydropyrazolo[3',4':4,5]pyrimido[2,1-*c*]-[1,2,4]triazin-7-one (**7a**).

A solution of **6a** (1.28 g, 5 mmoles) in ethanol (30 ml) containing hydrazine hydrate (0.73 ml, 15 mmoles) was stirred for 3 days at room temperature. The solvent was evaporated and the residual solid was mixed with water and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated *in vacuo*. Purification of the solid residue by column chromatography on silica gel eluting with chloroform/methanol 9.5/0.5 give **7a** (0.5 g, 48%, mp 240-242°).

1-Phenyl-1,4,6,7,8,9-hexahydropyrazolo[3',4':4,5]pyrimido[2,1-*c*]-[1,2-*a*]triazin-7-one (**7b**).

Following a procedure similar to preparation of **7a**, **7b** was obtained (90%, mp 258-260° from ethanol).

6-Chloro-1-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-5-acetamide (**8a**).

A solution of **6a** (1.5 g, 6 mmoles) in saturated ammonia solution (40 ml) was stirred at room temperature for 4 days. The precipitate was filtered off, washed with ethanol and the residue was crystallized from ethanol to give **8a** (0.6 g, 50%, mp 150-152°); ir (potassium bromide): 3350, 3140, 1700, 1680, 1630, 1610, 1590, 1560 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 3.58 (s, 3H), 4.00 (s, 2H), 4.67 (s, 2H), 7.06 (s, 1H), 7.29 (br, 1H), 7.68 (br, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 33.08 (q), 49.39 (t), 54.04 (t), 95.91, 132.18 (d), 141.85, 149.37, 168.05.

Anal. Calcd. for $C_8H_{10}ClN_5O$: C, 42.21: H, 4.43; Cl, 15.57; N, 30.76. Found: C, 42.08; H, 4.35; Cl, 15.48; N, 30.63.

6-Chloro-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-5-acetamide (**8b**).

Following the procedure similar to preparation of **8a**, **8b** was obtained (88%, mp 175-177° from ethanol); ir (potassium bromide): 3361, 3180, 1780, 1630, 1600, 1580, 1560, 1490 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 4.07 (s, 2H), 4.78 (s, 2H), 7.41 (s, 1H), 7.00-7.50 (v br, 2H), 7.10-7.80 (m, 5H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 47.62 (t), 52.90 (t), 96.62, 119.27 (d), 124.04 (d), 126.91 (d), 133.00 (d), 137.09, 140.73, 148.65, 166.48.

Anal. Calcd. for $C_{13}H_{12}ClN_5O$: C, 53.89; H, 4.17; Cl, 12.24; N, 24.17. Found: C, 53.72; H, 3.99; Cl, 12.17; N, 24.23.

1-Methyl-5-cyanomethyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]-pyrimidin-6-one (**9a**).

A solution of **8a** (1.13 g, 5 mmoles) in *N*,*N*-dimethylformamide (10 ml) was refluxed for 90 minutes. After evaporation of the solvent, the solid residue was poured into water and extracted with ethyl acetate. The organic layer was separated, dried and evaporated. The solid residue was crystallized from ethanol to give **9a** (0.8 g, 84%, mp 248-251°); ir (potassium bromide): 3160, 1670, 1630, 1595 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 3.61 (s, 3H),

4.42 (s, 4H), 7.14 (s, 1H), 10.30 (br, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 34.21 (q), 35.21 (t), 44.15 (t), 92.50, 116.41, 133.14 (d), 136.57, 151.40.

Anal. Calcd. for $C_8H_9N_5O$: C, 50.26; H, 4.74; N, 36.63. Found: C, 50.44; H, 4.62; N, 36.42.

1-Phenyl-5-cyanomethyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]-pyrimidin-6-one (**9b**).

Following the procedure similar to preparation of **9a**, **9b** was obtained (63%, mp 214-216° from ethanol); ir (potassium bromide): 3160, 1670, 1630, 1590 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ [ppm] 4.47 (s, 2H), 4.51 (s, 2H), 7.48 (s, 1H), 7.40-7.60 (m, 5H), 10.10 (br, 1H); ^{13}C-nmr (DMSO-d_6): δ [ppm] 35.72 (t), 44.11 (t), 95.18, 116.74, 123.08 (d), 127.22 (d), 129.20 (d), 136.00 (d), 136.52, 137.54, 151.88.

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.41; H, 4.32; N, 27.45.

REFERENCES AND NOTES

[1] R. Ferroni, E. Menegatti, S. Scalia, P. Orlandini, M. Guarneri and U. Taddeo, *Farmaco, Ed. Sci*, **41**, 747 (1986).

[2] F. Ischikawa, A. Kosasayama, H. Yamaguchi, Y. Watanabe, J. Saegusa, S. Shibamura, K. Sakuma, S. Ashida and Y. Abiko, *J. Med. Chem.*, **24**, 376 (1981); F. Ischikawa, J. Saegusa, K. Inamura, K. Sakuma and S. Ashida, *J. Med. Chem.*, **28**, 1387 (1985).

[3] M. S. Chodnekar and A. Kaiser, German Offen, 2,832,138 (1979); *Chem. Abstr.*, **90**, 186967 (1979).

[4] J. S. Fleming, J. P. Buyniski, *Thromb. Res.*, **15**, 373 (1979).

[5] C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **24**, 852 (1958).

[6] Atta-ur-Rahaman, A. Basha and N. Waheed, *Tetrahedron Letters*, 219 (1976).

[7] D. T. Cromer and J. T. Waber, "International Tables for X-Ray Crystallography", Vol **IV**, Table 2.2a, Birmingham Kynoch Press, 1974.

[8] P. Main, S. E. Hull, L. Lessinger, G. Germain, J-P. Declercq and M. M. Woolfson, MULTAN 81. A system of Computer Program for the Automatic solution of Crystal Structures from X-Ray Diffraction Data. University of York, England and Louvain, Belgium, 1981.

[9] B. A. Frenz, "Computing in Crystallography", H. Schenk, R. Olthof-Hazekamp, H. Van Koningsveld and G. C. Bassi, eds, Delft University Press, Delft, 1978, pp 41.

[10] C. K. Johnson, "Ortep" Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

[11] M. Nardelli, *Comput. Chem.*, **7**, 95, 1983.