NUCLEOPHILIC SUBSTITUTION AND LIPOPHILICITY – STRUCTURE RELATIONS IN METHYLAZOLOPYRIDAZINES

Anna KATRUSIAK[a1,*], Małgorzata RATAJCZAK-SITARZ[b], Urszula SKIERSKA[a2] and Wiktoria ZINCZENKO[a3]

[a] *Department of Pharmacy, Poznań University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań, Poland; e-mail: [1] akatrus@amp.edu.pl, [2] uskiersk@amp.edu.pl, [3] wzinczen@amp.edu.pl*

[b] *Department of Crystal Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland; e-mail: sitarz@amu.edu.pl*

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Syntheses of methyl[1,2,4]triazolo- or methyltetrazolopyridazine isomers, their separation and nucleophilic substitution with morpholine, dimethylamine and hydrazine have been described. The lipophilicity of the azolopyridazines has been measured and related to the number and sites of the methyl substituents. The structures of new methylated azolopyridazines have been characterized by ^{1}H NMR, MS spectra, and X-ray diffraction.

Keywords: Nitrogen heterocycles; Triazolopyridazines; Tetrazolopyridazines; Azolopyridazines; Lipophilicity; X-ray diffraction.

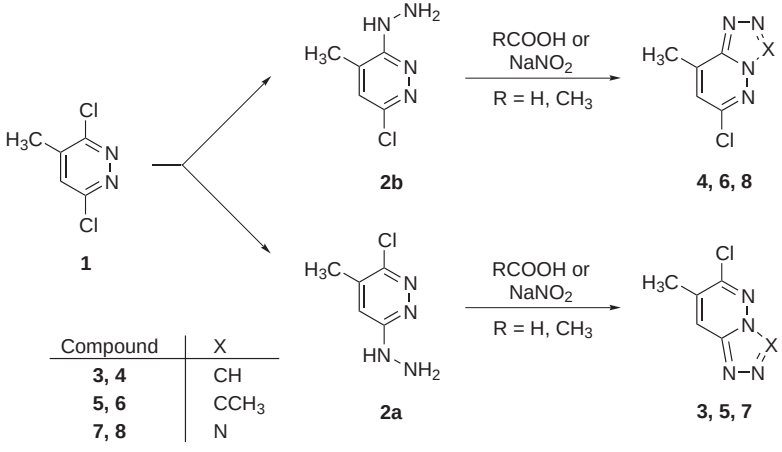
Azolopyridazines possess a versatile biological activity. They are applied as medicines, for example in therapy of bronchial diseases[1]. The pyridazine ring is in molecules of many biologically active compounds of broad activities, such as in anticonvulsants or sedatives[2]. Our preliminary tests on rats showed a positive effect of a series of azolopyridazines for lowering blood pressure without affecting the heart rate[3]. Methyl substituents can change pharmaceutical activity (cf. morphine and codeine). It is also known that the antihypertensive activity of 5-methylpyridazinone derivatives is considerably stronger than their lower homologues without 5-methyl, which are used as vasodilator/β-adrenoceptor antagonists[4]. In fact the decreased size of one alkyl group and increased size of another are likely to enhance the required property. Such modifications of molecular structure are termed methylene shuffle and have been used to modify the hydrophobicity of compounds. Increased lipophilicity facilitates penetration of drugs into the central nervous system, e.g. hexobarbitone with hypnotic and antiepileptic activity[5]. Methyl substituents in pyridazine or azole ring in azolopyrid-

azines increase their stability. In our search for new active pharmaceutical drugs based on azolopyridazines, their methyl derivatives were synthesized. In X-ray diffraction study of five methylpyridazine derivatives their crystal structures have been determined to establish the site of the methyl substituent in the pyridazine ring, their interactions and association.

RESULTS AND DISCUSSION

Syntheses and Molecular Structures of Methyl Derivatives of Azolopyridazine

6-Chloro-7-methyl- (**3**), 6-chloro-8-methyl- (**4**), 6-chloro-3,7-dimethyl- (**5**) and 6-chloro-3,8-dimethyl[1,2,4]triazolo[4,3-*b*]pyridazine (**6**) as well as 6-chloro-7-methyl- (**7**) and 6-chloro-8-methyltetrazolo[1,5-*b*]pyridazine (**8**) have been obtained by multistep syntheses starting from citraconic anhydride which, condensed with hydrazine hydrate and chlorinated with $POCl_3$, gave 3,6-dichloro-4-methylpyridazine (**1**). The presence of the methyl group at C-4 differentiates the chlorine atoms at C-3 and C-6. The reaction of compound **1** with a 50% aqueous solution of hydrazine hydrate, giving the 6-chloro-3-hydrazino-4-methylpyridazine (**2b**) as the main product, has already been described[6]. We have noticed that the treatment of **1** with ethanolic solution of 99% hydrazine hydrate in molar ratio 1:1 yields 3-chloro-6-hydrazino-4-methylpyridazine (**2a**) as a precipitate. The filtrate was used in the reaction with an excess of hydrazine hydrate and a mixture of compounds **2a** and **2b** was obtained. The routine separation of these



SCHEME 1

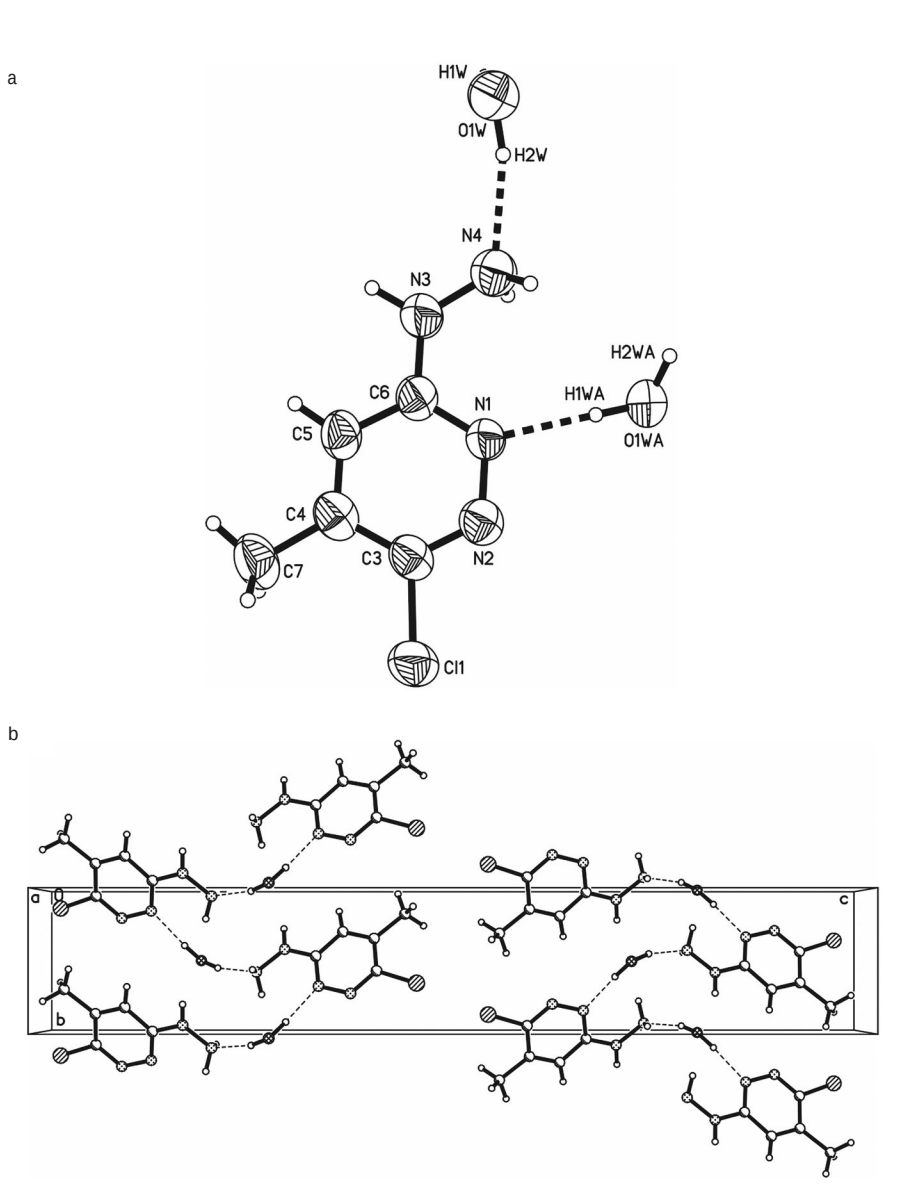


FIG. 1

a A fragment of the O–H···N hydrogen-bonded chain of molecules **2a** and water; b arrangement of molecules **2a** in the crystal lattice projected along the crystal [100] direction. The hydrogen bonds are shown as dashed lines. The thermal ellipsoids have been drawn at 50% probability level

compounds by column chromatography proved unsuccessful. By applying the best mobile solution phase (acetone–hexane) 3-chloro-6-(isopropylidenehydrazino)-5-methylpyridazine (**2c**) was isolated. So a mixture of compounds **2a** and **2b** was used for cyclization reactions by treatment with formic acid, acetic acid or sodium nitrite. Only 6-chloro-7-methyltetrazolo-[1,5-*b*]pyridazine (**7**), which precipitated directly from the reaction mixture, could be isolated, while the mixture of 7-methyl (**7**) and 8-methyl (**8**) derivatives remained in solution. The mixtures of the corresponding methylazolopyridazines (**3** and **4**, **5** and **6**, **7** and **8**) were separated by column chromatography (Scheme 1).

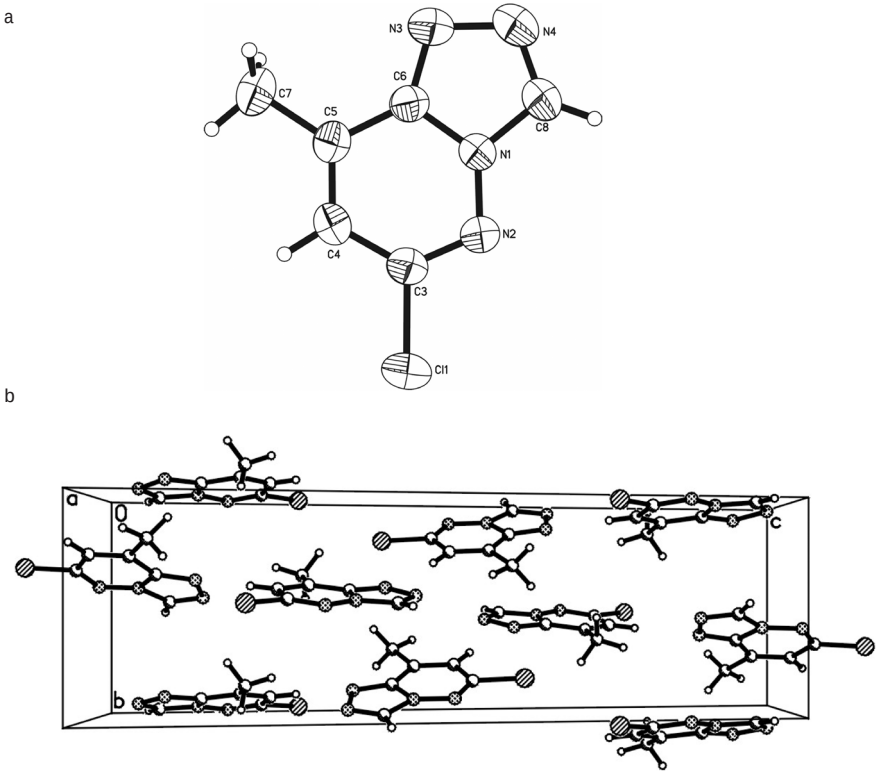


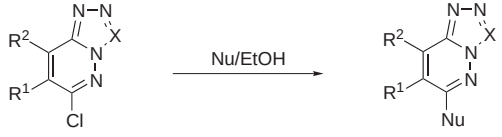
FIG. 2

a One of two symmetry-independent molecules **4**; b the arrangement of molecules **4** in the crystal lattice, projected along the crystal [100] direction. The thermal ellipsoids are plotted at 50% probability level

Compound **2a** crystallizes as a monohydrate, where two water-mediated hydrogen bonds (N(4)···O(1W) 2.892(8) Å and N(1)···O(1W^{i}) 2.898(2) Å; superscript "i" denotes the symmetry code for obtaining the interacting atom from the original atomic list: $2 - x$, $y - 1/2$, $3/2 - z$) form chains along crystal axis (y), shown in Fig. 1. As expected, the pyridazine ring and attached atoms form a planar system. The pyridazine ring and the azolopyridazine fragment are planar within experimental errors (root mean square deviations of the fitted atoms are 0.0023–0.0079 and 0.0057–0.0103 Å, respectively).

The molecular structure of compound **4** has been determined by X-ray diffraction. The fused pyridazine–triazole system is planar within measurement error (Fig. 2), and the molecular strains due to the fusion affect the bond length and valency angles (see Table I).

Isolated compounds **3**–**8** (identified by NMR, mass spectroscopy, and X-ray diffraction) were subjected to nucleophilic substitutions. The treatment of compounds **3**–**8** with morpholine, dimethylamine or hydrazine hydrate in ethanol gave products (**9**–**26**) as precipitates (Scheme 2). The structure of compounds **9**–**26** was confirmed by ^{1}H NMR and MS spectra. It



3–8 **9–26**

Comp.	R^1	R^2	X	Nu	Comp.	R^1	R^2	X	Nu
9	CH_3	H	CH	C_4H_8NO	18	H	CH_3	CCH_3	C_2H_6N
10	H	CH_3	CH	C_4H_8NO	19	CH_3	H	N	C_2H_6N
11	CH_3	H	CCH_3	C_4H_8NO	20	H	CH_3	N	C_2H_6N
12	H	CH_3	CCH_3	C_4H_8NO	21	CH_3	H	CH	N_2H_3
13	CH_3	H	N	C_4H_8NO	22	H	CH_3	CH	N_2H_3
14	H	CH_3	N	C_4H_8NO	23	CH_3	H	CCH_3	N_2H_3
15	CH_3	H	CH	C_2H_6N	24	H	CH_3	CCH_3	N_2H_3
16	H	CH_3	CH	C_2H_6N	25	CH_3	H	N	N_2H_3
17	CH_3	H	CCH_3	C_2H_6N	26	H	CH_3	N	N_2H_3

SCHEME 2

TABLE I

Bond lengths (in Å) and angles (in °). The atom labelling is shown in Figs 1a, 2a, 3a, and 4a. Bold values indicate narrower endocyclic valency angles at methyl substituted atoms

	2a	**4**	**4′**	**5**	**7**
C11–C3	1.734(7)	1.722(2)	1.730(2)	1.723(3)	1.713(2)
C3–C4	1.423(11)	1.414(3)	1.417(3)	1.433(4)	1.433(4)
C4–C5	1.335(8)	1.355(3)	1.359(3)	1.367(4)	1.348(4)
C5–C6	1.400(8)	1.424(3)	1.424(3)	1.406(4)	1.396(3)
C6–N1	1.336(9)	1.375(3)	1.369(3)	1.389(4)	1.343(3)
N1–N2	1.366(7)	1.357(3)	1.371(3)	1.366(3)	1.345(3)
N2–C3	1.305(8)	1.305(3)	1.294(3)	1.303(4)	1.294(3)
C4(C5)–C7	1.512(9)	1.494(3)	1.486(4)	1.501(4)	1.494(3)
C6–N3	1.355(9)	1.317(3)	1.320(3)	1.311(4)	1.324(3)
N3–N4		1.377(3)	1.390(3)	1.397(4)	1.342(3)
N4–C8(N5)		1.296(4)	1.302(3)	1.304(4)	1.295(3)
C8(N5)–N1		1.362(3)	1.351(3)	1.361(4)	1.344(3)
C11–C3–N2	115.2(6)	114.0(2)	114.2(2)	113.1(2)	113.8(2)
C11–C3–C4	120.0(6)	119.1(2)	118.9(2)	119.1(3)	118.9(2)
N1–N2–C3	119.5(7)	111.9(2)	111.8(2)	113.1(3)	112.2(2)
N2–C3–C4	124.8(7)	126.9(2)	126.9(2)	127.8(3)	127.3(2)
C3–C4–C5	**115.1(7)**	119.9(2)	120.3(2)	**116.1(3)**	**116.0(3)**
C4–C5–C6	119.7(7)	**115.8(2)**	**115.3(2)**	119.6(3)	119.5(2)
C5–C6–N1	123.1(6)	118.2(2)	118.5(2)	117.4(3)	117.1(2)
C6–N1–N2	117.8(6)	127.3(2)	127.2(2)	126.0(3)	128.0(2)
C3–C4–C7	121.6(7)			121.9(3)	121.2(3)
C5–C4–C7	123.3(7)			122.0(3)	122.8(3)
C4–C5–C7		123.9(2)	125.3(2)		
C6–C5–C7		120.3(2)	119.4(2)		
C5–C6–N3	119.4(6)	132.0(2)	131.9(2)	133.3(3)	135.7(3)
N1–C6–N3	117.5(6)	109.8(2)	109.5(2)	109.3(3)	107.2(2)
C6–N3–N4	124.0(7)	106.4(2)	106.8(2)	106.6(3)	106.0(2)
N3–N4–C8(N5)		108.6(2)	108.1(2)	109.0(3)	112.3(2)
N4–C8(N5)–N1		109.9(2)	110.2(2)	109.0(3)	104.7(2)
C8(N5)–N1–C6		105.3(2)	105.4(2)	106.1(3)	109.8(2)
C8(N5)–N1–N2		127.4(2)	127.4(2)	128.0(3)	122.2(2)
N1–C8–C9				123.5(3)	
N4–C8–C9				127.5(3)	

has been observed that in the ^{1}H NMR spectrum of 7-methylazolopyridazines the signal of proton at C-8 appears at ca. 8.00 ppm, whereas in the ^{1}H NMR spectrum of 8-methylazolopyridazines that at C-7 gave a signal at ca. 7.00 ppm. This shift facilitates the identification of the respective isomers. In each ^{1}H NMR spectrum a long-range coupling between the C-methyl group and hydrogen atom at neighbouring C-7(C-8) has been observed (see Experimental). The magnitude of this coupling is of about 0.8–1.4 Hz. Compounds **3**–**12** and **21**–**26** were described, and their characteristics has been compared with the literature data in the Experimental. The hypotensive activity of the 6-morpholino derivatives of 7- and 8-methylazolopyridazines (**9**–**14**) are being investigated, whereas the 6-hydrazino derivatives (**21**–**26**) have been used for further syntheses, aimed at fusion of a second azole ring, and for studying the azide-tetrazole tautomerism conversions[7].

The crystal structures of compounds **5** and **7** are shown in Figs 3 and 4, respectively. Again, the triazolopyridazine and tetrazolopyridazine ring systems are planar; bond angles mainly accommodate the strains due to the fusion of pyridazine with a five-membered ring (Table I). It can be observed that smaller, but equally systematic changes of the bond angles are induced by the methyl substituent. The methyl substitution decreases the endocyclic bond angle at the substituted atom by about 4° (Table I).

Lipophilicity Measurement[8]

The lipophilicity of methylazolopyridazines **3**–**8** has been measured and compared with those of the azolopyridazines without methyl substituent at C-7 or C-8: 6-chloro[1,2,4]triazolo[4,3-*b*]pyridazine (**A**), 6-chloro-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine (**B**) and 6-chlorotetrazolo[1,5-*b*]pyridazine (**C**). The results are listed in Table II. The R_M values have been calculated from the experimental R_f values according to the formula $R_M = \log [(1/R_f) - 1]$.

TABLE II
Lipophilicities of azolopyridazines (**A**, **C**) and their methyl derivatives (**B**, **3**–**8**)

Compound	**A**	**B**	**3**	**4**	**5**	**6**	**C**	**7**	**8**
R_f	0.71	0.70	0.68	0.63	0.59	0.61	0.72	0.62	0.59
R_M	–0.39	–0.35	–0.33	–0.23	–0.16	–0.19	–0.41	–0.21	–0.16

A, 6-chloro[1,2,4]triazolo[4,3-*b*]pyridazine; **B**, 6-chloro-3-methyl[1,2,4]triazolo[4,3-*b*]pyridazine; **C**, 6-chlorotetrazolo[1,5-*b*]pyridazine

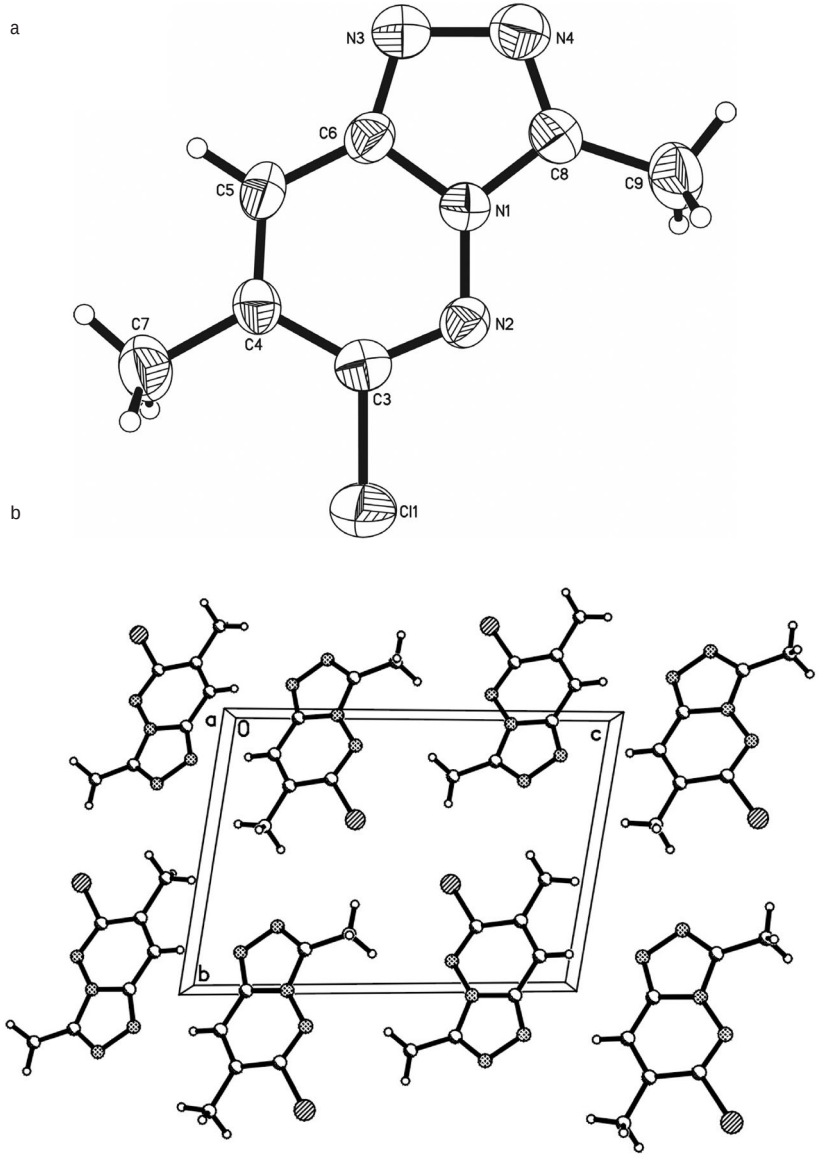


FIG. 3

a A perspective ORTEP drawing of molecule **5** viewed perpendicularly to the azolopyridazine fragment; b the arrangement of molecules **5** in the crystal lattice, projected along the crystal [100] direction. The thermal ellipsoids have been drawn at 50% probability level

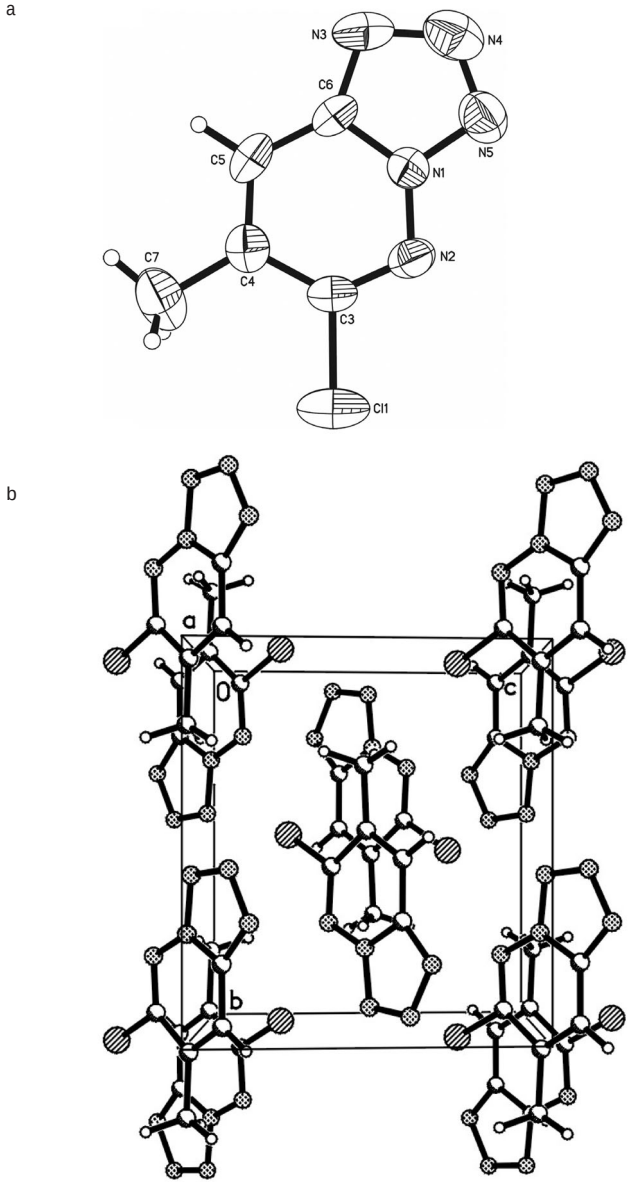


FIG. 4

a A perspective ORTEP drawing of molecule **7** viewed perpendicularly to the least-squares plane; **b** the arrangement of molecules **7** in the crystal structure, projected along the crystal [100] direction. The thermal ellipsoids are shown at 50% probability level; the hydrogen atoms are represented as small circles

Higher and/or positive R_M values indicate compounds more lipophilic than those compounds characterized by the lower and/or negative R_M values. A correlation between the lipophilicity and the number of methyl substituents in the azolopyridazine is apparent. The unmethylated compounds **A** and **C** have the lowest R_M magnitudes, and the highest R_M magnitudes are those of dimethylated **5** and **6** and monomethylated **7** and **8**.

EXPERIMENTAL

X-ray Diffraction

The diffraction data have been collected on a Kuma KM4-CCD diffractometer, λ = 0.71073 Å (**5**, **7**, **2c**) and on a Kuma KM4 diffractometer, λ = 1.54178 Å (**2a**, **4**), at room temperature. The structures of four compounds (**2a**, **4**, **5**, **7**) have been solved by direct methods[9] and refined on F^2 by program SHELXL97 [10]. The H atoms at N(3) and N(4) in **2a**, and all H atoms in **4** were located using difference Fourier maps and refined with isotropic temperature factors, all the other H atoms were calculated from the molecular geometry and their U_{iso} have been related to thermal vibrations of their carriers. The crystals of compound **2c** had the form of very small thin needles and were of low quality. Nevertheless, we managed to collect diffraction data and to solve the structure[10]. The skeletons of two symmetry-independent molecules have been obtained, but the measured intensities were not accurate enough to refine the structure. The crystal data and details of the X-ray analysis are given in Table III. CCDC 262568 (for **2a**), 262569 (for **4**), 262570 (for **5**), and 262571 (for **7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Chemical Syntheses

Melting points were determined on a Boetius apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian MH-300 spectrometer in $CDCl_3$ or trifluoroacetic acid (TFA), with TMS as a internal standard. The lipophilicity measurement was done according to the literature[8]. Separation was carried out on precoated RP-TLC plates of RP-18 F 254s (Merck, Darmstadt, Germany). The polar mobile phase was a mixture methanol–water (8:2). Each compound was dissolved in methanol (1 mg/ml) and the solution (5 µl) was applied onto the plate with aid of a HAMILTON syringe. After development the plates were dried and the spots were localized in UV 254 nm. Citraconic hydrazide was obtained from citraconic anhydride and hydrazine hydrate[11]. 3,6-Dichloro-4-methylpyridazine was obtained from citraconic hydrazide using $POCl_3$ [11]. 3-Chloro-6-hydrazino-4(5)-methylpyridazines (**2b** and **2a**) were synthesized from 3,6-dichloro-4-methylpyridazine (**1**) and hydrazine hydrate[6].

3-Chloro-6-(isopropylidenehydrazino)-5-methylpyridazine (**2c**). M.p. 142–143 °C (acetone). For $C_8H_{11}ClN_4$ (198.7) calculated: 48.37% C, 5.58% H, 28.20% N; found: 48.25% C, 5.62% H, 28.05% N. ^{1}H NMR ($CDCl_3$): 2.11 (s, 3 H, CH_3-C=N); 2.16 (s, 3 H, CH_3-C=N); 2.39 (d, 3 H, J = 0.9, CH_3-C=C); 8.06 (q, 1 H, J = 0.9, H-4). MS, *m/z*: 198.4.

TABLE III
Crystal data and structure refinement

	2a	**4**	**5**	**7**	**2c**
Empirical formula	$C_5H_7ClN_4 \cdot H_2O$	$C_6H_5ClN_4$	$C_7H_7ClN_4$	$C_5H_4ClN_5$	$C_8H_{11}ClN_4$
Formula weight	176.61	168.59	182.62	169.58	198.66
Crystal sysytem	orthorhombic	monoclinic	triclinic	monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
Unit cell: a, Å	4.030(1)	8.539(2)	4.006(2)	9.937(2)	12.165(2)
b, Å	5.790(1)	7.310(1)	8.598(3)	8.887(2)	23.208(5)
c, Å	33.556(7)	24.110(5)	12.005(4)	7.984(1)	7.588(2)
α, °			98.78(3)		
β, °		102.67(3)	96.96(3)	95.78(1)	108.02(3)
γ, °			93.10(3)		
Volume, Å^3	783.0(3)	1468.3(5)	404.5(3)	701.5(2)	2037.2(7)
Z	4	8	2	4	8
D_{cal}, g cm^{-3}	1.498	1.525	1.499	1.606	1.295
μ, mm^{-1}	3.929	4.073	0.416	0.477	0.336
F(000)	368	688	188	344	832
Limiting indices h	0/4	–10/0	–5/3	–13/13	–16/16
k	0/7	–8/0	–11/11	–12/12	–31/32
l	–40/40	–27/28	–15/15	–6/10	–5/10
Reflections: collected	1759	2495	2580	6691	19106
unique	1493	2403	1844	1839	5321
R_{int}	0.0708	0.0495	0.0627	0.0745	0.1491
GOF for F^2	1.195	1.068	1.052	0.978	
R_1 factors: all data	0.1555	0.0531	0.1295	0.1774	
for I>2σ(I)	0.0689	0.0466	0.0618	0.0515	
wR_2 factors: all data	0.1621	0.1306	0.1557	0.1125	
for I>2σ(I)	0.1305	0.1251	0.1259	0.0814	
ΔF max/min, e Å^{-3}	0.399/–0.326	0.423/–0.451	0.293/–0.281	0.154/–233	

3-Chloro-6-hydrazino-4-methylpyridazine (**2a**). Compound **1** (1.63 g, 0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol; 99%) were stirred at room temperature for 24 h. The precipitate was recrystallized from ethanol, m.p. 158–160 °C (lit.[6] gives 158 °C), yield 63%.

Triazolopyridazines **3**–**6**. General Procedure

A solution of 15.86 g (0.1 mol) of a mixture **2a** and **2b** was refluxed in 100 ml of formic or acetic acid for 1 h. The reaction mixture was cooled, poured into water and extracted with chloroform. The extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated. The azolopyridazines **3**–**6** were separated by column chromatography using the 3:2 acetone–hexane mixture as a mobile phase. The column (ID 2 cm, length 50 cm) was filled with silica gel (0.040–0.063 mm, 230–400 mesh ASTM, Merck).

6-Chloro-7-methyl[1,2,4]triazolo[4,3-b]pyridazine (**3**). In formic acid. White crystals, yield 87%, m.p. 158–160 °C (ethanol) (lit.[6] gives 157.5–158 °C). For $C_6H_5ClN_4$ (168.6) calculated: 42.75% C, 2.99% H, 33.23% N; found: 42.69% C, 3.01% H, 33.18% N. ^{1}H NMR ($CDCl_3$): 2.52 (d, 3 H, J = 1.374, CH_3-C=C); 7.98 (q, 1 H, J = 1.4, H-8); 9.03 (s, 1 H, H-3). MS, *m/z*: 168.5.

6-Chloro-8-methyl[1,2,4]triazolo[4,3-b]pyridazine (**4**). In formic acid. Light beige crystals, yield 62%, m.p. 135–136 °C (ethanol) (lit.[6] gives 134–134.5 °C). For $C_6H_5ClN_4$ (168.6) calculated: 42.75% C, 2.99% H, 33.23% N; found: 42.71% C, 3.06% H, 33.25% N. ^{1}H NMR ($CDCl_3$): 2.77 (d, 3 H, J = 1.4, CH_3-C=C); 6.98 (q, 1 H, J = 1.4, H-7); 9.03 (s, 1 H, H-3). MS, *m/z*: 168.5.

6-Chloro-3,7-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**5**). In acetic acid. Light brown crystals, yield 90%, m.p. 188–189 °C (ethanol) (lit.[12] gives 183–184 °C). For $C_7H_7ClN_4$ (182.6) calculated: 46.04% C, 3.86% H, 30.68% N; found: 46.10% C, 3.92% H, 30.70% N. ^{1}H NMR ($CDCl_3$): 2.48 (d, 3 H, J = 1.1, CH_3-C=C); 2.79 (s, 3 H, CH_3-C=N); 7.89 (q, 1 H, J = 1.1, H-8). MS, *m/z*: 182.0.

6-Chloro-3,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**6**). In acetic acid. Light brown crystals, yield 68%, m.p. 166–168 °C (ethanol) (lit.[12] gives 170–171 °C). For $C_7H_7ClN_4$ (182.6) calculated: 46.04% C, 3.86% H, 30.68% N; found: 46.00% C, 3.82% H, 30.71% N. ^{1}H NMR ($CDCl_3$): 2.09 (d, 3 H, J = 1.1, CH_3-C=C); 2.72 (s, 3 H, CH_3-C=N); 6.92 (q, 1 H, J = 1.1, H-7). MS, *m/z*: 182.0.

6-Chloro-7-methyltetrazolo[1,5-*b*]pyridazine (**7**) and
6-Chloro-8-methyltetrazolo[1,5-*b*]pyridazine (**8**)

To a solution of 15.86 g (0.1 mol) of a mixture of **2a** and **2b** in 100 ml of water and 150 ml of acetic acid, a solution of 4.5 g of sodium nitrite in 70 ml of water was added dropwise at 0 °C. Compound **7** precipitated during the addition. Beige crystals, yield 93%, m.p. 139 °C (ethanol) (lit.[6] gives 140.5 °C). For $C_5H_4ClN_5$ (169.6) calculated: 35.41% C, 2.38% H, 41.30% N; found: 35.40% C, 2.33% H, 41.28% N. ^{1}H NMR ($CDCl_3$): 2.64 (d, 3 H, J = 1.4, CH_3-C=C); 8.23 (q, 1 H, J = 1.4, H-8). MS, *m/z*: 169.0.

The residue (mixture of compounds **7** and **8**) was poured into water and extracted with chloroform. The extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated. The tetrazolopyridazines **7** and **8** were separated by column chromatography using the 3:2 acetone–hexane mixture as a mobile phase. The column (ID 2 cm, length 50 cm) was filled with silica gel (0.040–0.063 mm, 230–400 mesh ASTM, Merck). Compound **8**: beige crystals,

yield 61%, m.p. 100–101 °C (ethanol) (lit.[6] gives 107 °C). For $C_5H_4ClN_5$ (169.6) calculated: 35.41% C, 2.38% H, 41.30% N; found: 35.38% C, 2.35% H, 41.32% N. ^{1}H NMR ($CDCl_3$): 2.45 (d, 3 H, *J* = 0.8, CH_3-C=C); 7.43 (q, 1 H, *J* = 0.8, H-7). MS, *m/z*: 169.0.

6-Substituted Azolopyridazines **9**–**26**. General Procedure

Azolopyridazine (0.01 mol) with a threefold excess of morpholine (**9**–**14**), dimethylamine (**15**–**20**) or 99% hydrazine hydrate (**21**–**26**) in 30 ml of anhydrous ethanol was refluxed for 8 h. After cooling, the precipitate was filtered off and recrystallized from ethanol.

7-Methyl-6-morpholino[1,2,4]triazolo[4,3-b]pyridazine (**9**). Beige crystals, yield 79%, m.p. 157–158 °C (lit.[13] gives 172 °C). For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.76% C, 6.01% H, 31.92% N. ^{1}H NMR ($CDCl_3$): 2.51 (d, 3 H, *J* = 1.1, CH_3-C=C); 3.28–4.05 (m, 8 H, morpholine); 7.83 (q, 1 H, *J* = 1.1, H-8); 8.88 (s, 1 H, H-3). MS, *m/z*: 219.0.

8-Methyl-6-morpholino[1,2,4]triazolo[4,3-b]pyridazine (**10**). Beige crystals, yield 65%, m.p. 172–174 °C (lit.[14] gives 177–180 °C). For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.74% C, 5.96% H, 31.91% N. ^{1}H NMR ($CDCl_3$): 2.65 (d, 3 H, *J* = 1.1, CH_3-C=C); 3.22–3.88 (m, 8 H, morpholine); 6.74 (q, 1 H, *J* = 1.1, H-7); 8.88 (s, 1 H, H-C3). MS, *m/z*: 219.0.

3,7-Dimethyl-6-morpholino[1,2,4]triazolo[4,3-b]pyridazine (**11**). Beige crystals, yield 82%, m.p. 197–199 °C (lit.[13] gives 160–174 °C). For $C_{11}H_{15}N_5O$ (233.3) calculated: 56.64% C, 6.48% H, 30.02% N; found: 56.60% C, 6.51% H, 30.11% N. ^{1}H NMR ($CDCl_3$): 2.40 (d, 3 H, *J* = 1.1, CH_3-C=C); 2.72 (s, 3 H, CH_3-C=N); 3.23–3.87 (m, 8 H, morpholine); 7.71 (q, 1 H, *J* = 1.1, H-8). MS, *m/z*: 233.0.

3,8-Dimethyl-6-morpholino[1,2,4]triazolo[4,3-b]pyridazine (**12**). Beige crystals, yield 88%, m.p. 215–216 °C (lit.[14] gives 212–213 °C). For $C_{11}H_{15}N_5O$ (233.3) calculated: 56.64% C, 6.48% H, 30.02% N; found: 56.66% C, 6.53% H, 30.09% N. ^{1}H NMR ($CDCl_3$): 2.60 (d, 3 H, *J* = 1.1, CH_3-C=C); 2.67 (s, 3 H, CH_3-C=N); 3.02–3.56 (m, 8 H, morpholine); 6.71 (q, 1 H, *J* = 1.1, H-7). MS, *m/z*: 233.0.

7-Methyl-6-morpholinotetrazolo[1,5-b]pyridazine (**13**). White crystals, yield 64%, m.p. 163–165 °C. For $C_9H_{12}N_6O$ (220.2) calculated: 49.08% C, 5.49% H, 38.16% N; found: 49.10% C, 5.53% H, 38.19% N. ^{1}H NMR ($CDCl_3$): 2.54 (d, 3 H, *J* = 1.4, CH_3-C=C); 3.39–3.93 (m, 8 H, morpholine); 7.99 (q, 1 H, *J* = 1.4, H-8). MS, *m/z*: 220.0.

8-Methyl-6-morpholinotetrazolo[1,5-b]pyridazine (**14**). White crystals, yield 61%, m.p. 142–145 °C. For $C_9H_{12}N_6O$ (220.2) calculated: 49.08% C, 5.49% H, 38.16% N; found: 49.12% C, 5.43% H, 38.14% N. ^{1}H NMR ($CDCl_3$): 2.32 (d, 3 H, *J* = 1.4, CH_3-C=C); 3.39–3.93 (m, 8 H, morpholine); 6.99 (q, 1 H, *J* = 1.4, H-7). MS, *m/z*: 220.0.

6-Dimethylamino-7-methyl[1,2,4]triazolo[4,3-b]pyridazine (**15**). White crystals, yield 79%, m.p. 83–85 °C. For $C_8H_{11}N_5$ (177.2) calculated: 54.22% C, 6.26% H, 39.52% N; found: 54.20% C, 6.25% H, 39.58% N. ^{1}H NMR ($CDCl_3$): 2.43 (d, 3 H, *J* = 1.4, CH_3-C=C); 2.93 (s, 6 H, $(CH_3)_2$-N); 7.71 (q, 1 H, *J* = 1.4, H-8); 8.82 (s, 1 H, H-3). MS, *m/z*: 177.1.

6-Dimethylamino-8-methyl[1,2,4]triazolo[4,3-b]pyridazine (**16**). White crystals, yield 79%, m.p. 208–210 °C. For $C_8H_{11}N_5$ (177.2) calculated: 54.22% C, 6.26% H, 39.52% N; found: 54.26% C, 6.21% H, 39.50% N. ^{1}H NMR ($CDCl_3$): 2.64 (d, 3 H, *J* = 1.4, CH_3-C=C); 3.16 (s, 6 H, $(CH_3)_2$-N); 6.66 (q, 1 H, *J* = 1.4, H-7); 8.77 (s, 1 H, H-3). MS, *m/z*: 177.1.

6-Dimethylamino-3,7-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**17**). White crystals, yield 84%, m.p. 139–141 °C. For $C_9H_{13}N_5$ (191.2) calculated: 56.53% C, 6.85% H, 36.62% N; found:

56.59% C, 6.80% H, 36.58% N. ^{1}H NMR ($CDCl_3$): 2.41 (d, 3 H, *J* = 1.1, CH_3-C=C); 2.70 (s, 3 H, CH_3-C=N); 2.93 (s, 6 H, $(CH_3)_2$-N); 7.66 (q, 1 H, *J* = 1.1, H-8). MS, *m/z*: 191.2.

6-Dimethylamino-3,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**18**). White crystals, yield 80%, m.p. 69 °C. For $C_9H_{13}N_5$ (191.2) calculated: 56.53% C, 6.85% H, 36.62% N; found: 56.57% C, 6.81% H, 36.65% N. ^{1}H NMR ($CDCl_3$): 2.62 (d, 3 H, *J* = 1.4, CH_3-C=C); 2.68 (s, 3 H, CH_3-C=N); 3.13 (s, 6 H, $(CH_3)_2$-N); 6.62 (q, 1 H, *J* = 1.4, H-C7). MS, *m/z*: 191.2.

6-Dimethylamino-7-methyltetrazolo[1,5-b]pyridazine (**19**). White crystals, yield 60%, m.p. 143–145 °C. For $C_7H_{10}N_6$ (178.2) calculated: 47.18% C, 5.66% H, 47.16% N; found: 47.21% C, 5.68% H, 47.23% N. ^{1}H NMR ($CDCl_3$): 2.54 (d, 3 H, *J* = 1.4, CH_3-C=C); 3.08 (s, 6 H, $(CH_3)_2$-N); 7.90 (q, 1 H, *J* = 1.4, H-8). MS, *m/z*: 178.0.

6-Dimethylamino-8-methyltetrazolo[1,5-b]pyridazine (**20**). White crystals, yield 61%, m.p. 142–144 °C. For $C_7H_{10}N_6$ (178.2) calculated: 47.18% C, 5.66% H, 47.16% N; found: 47.23% C, 5.60% H, 47.19% N. ^{1}H NMR ($CDCl_3$): 2.31 (d, 3 H, *J* = 1.1, CH_3-C=C); 3.14 (s, 6 H, $(CH_3)_2$-N); 6.61 (q, 1 H, *J* = 1.1, H-7). MS, *m/z*: 178.0.

6-Hydrazino-7-methyl[1,2,4]triazolo[4,3-b]pyridazine (**21**). White crystals, yield 90%, m.p. 278–280 °C (lit.[6] gives 265 °C). For $C_6H_8N_6$ (164.2) calculated: 43.90% C, 4.91% H, 51.19% N; found: 43.95% C, 4.98% H, 51.21% N. ^{1}H NMR (CF_3COOH-d_6): 2.46 (d, 3 H, *J* = 1.4, CH_3-C=C); 4.23 (2 H, NH_2); 6.58 (q, 1 H, *J* = 1.4, H-7); 8.28 (1 H, NH); 9.12 (s, 1 H, H-3). MS, *m/z*: 164.0.

6-Hydrazino-8-methyl[1,2,4]triazolo[4,3-b]pyridazine (**22**). White crystals, yield 68%, m.p. 245–248 °C (lit.[15] gives 242 °C). For $C_6H_8N_6$ (164.2) calculated: 43.90% C, 4.91% H, 51.19% N; found: 43.94% C, 4.95% H, 51.14% N. ^{1}H NMR ($CDCl_3$): 2.43 (d, 3 H, *J* = 1.1, CH_3-C=C); 3.83 (2 H, NH_2); 7.72 (q, 1 H, *J* = 1.1, H-8); 8.28 (1 H, NH); 8.92 (s, 1 H, H-3). MS, *m/z*: 164.0.

6-Hydrazino-3,7-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**23**). Light brown crystals, yield 88%, m.p. 313–314 °C (lit.[15] gives 256 °C). For $C_7H_{10}N_6$ (178.2) calculated: 47.18% C, 5.66% H, 47.16% N; found: 47.21% C, 5.69% H, 47.19% N. ^{1}H NMR ($CDCl_3$): 2.17 (d, 3 H, *J* = 1.4, CH_3-C=C); 2.56 (s, 3 H, CH_3-C=N); 3.36 (2 H, NH_2); 7.72 (q, 1 H, *J* = 1.4, H-8); 8.08 (1 H, NH). MS, *m/z*: 178.0.

6-Hydrazino-3,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazine (**24**). Light brown crystals, yield 72%, m.p. 238–239 °C (lit.[15] gives 243 °C). For $C_7H_{10}N_6$ (178.2) calculated: 47.18% C, 5.66% H, 47.16% N; found: 47.23% C, 5.68% H, 47.13% N. ^{1}H NMR ($CDCl_3$): 2.41 (d, 3 H, *J* = 1.1, CH_3-C=C); 2.66 (s, 3 H, CH_3-C=N); 3.87 (2 H, NH_2); 6.52 (q, 1 H, *J* = 1.4, H-7); 8.38 (1 H, NH). MS, *m/z*: 178.0.

6-Hydrazino-7-methyltetrazolo[1,5-b]pyridazine (**25**). Light pink crystals, yield 83%, m.p. 274–277 °C (lit.[16] gives 285–287 °C). For $C_5H_7N_7$ (165.2) calculated: 36.36% C, 4.27% H, 59.37% N; found: 36.30% C, 4.31% H, 59.39% N. ^{1}H NMR (CF_3COOH-d_6): 2.67 (d, 3 H, *J* = 1.4, CH_3-C=C); 4.11 (2 H, NH_2); 8.42 (q, 1 H, *J* = 1.4, H-8). MS, *m/z*: 165.0.

6-Hydrazino-8-methyltetrazolo[1,5-b]pyridazine (**26**). Light pink crystals, yield 58%, m.p. 247–248 °C (lit.[16] gives 247–248 °C). For $C_5H_7N_7$ (165.2) calculated: 36.36% C, 4.27% H, 59.37% N; found: 36.32% C, 4.33% H, 59.31% N. ^{1}H NMR ($CDCl_3$): 2.48 (d, 3 H, *J* = 0.9, CH_3-C=C); 4.01 (2 H, NH_2); 7.43 (q, 1 H, *J* = 0.9, H-7); 8.23 (1 H, NH). MS, *m/z*: 165.0.

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