The Synthesis of Substituted Pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines

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The synthesis of 1,2,4-triazolo[4,3-*b*]pyridazines and the unknown ring system, pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine, has been achieved. The preparation of the new tricyclic 1,2,4-triazole was accomplished first by ring closure of the triazole ring followed by formation of the pyrazine ring. Substitution of the pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine ring system was carried out in order to provide information of its reactivity and to provide a variety of interesting compounds for biological testing.

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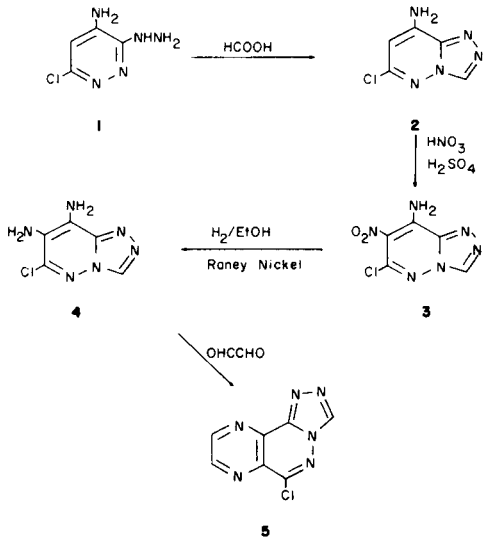
The synthesis of condensed 1,2,4-triazoles has been of interest because of the biological activity they possess, such as the 1,2,4-triazolo[4,3-*a*]quinoxalines which are active fungicides against *Piricularia oryzae* (3). Mild central nervous system activity has been reported in substituted 1,2,4,-triazolo[4,3-*b*]pyridazines (4). 8,9-Dimethoxy-1,2,4-triazolo[4,3-*c*]quinazolines and 7,8,9,10-tetrahydro-1,2,4-triazolo[4,3-*a*]phthalazines exhibited antiinflammatory activity (5,6). Ishii, *et al.*, (7) reported that 2*H*-1,2,4-triazolo[4,3-*a*]phthalazin-3-one, 3-methyl-1,2,4-triazolo[4,3-*a*]phthalazines and 3-ethyl-1,2,4-triazolo-[4,3-*a*]phthalazine, which are metabolites of the active drugs ecarazine and hydralazine, were potent inhibitors of cyclic adenosine monophosphate phosphodiesterase, equal to theophylline in potency and that they possess smooth muscle relaxant activity.

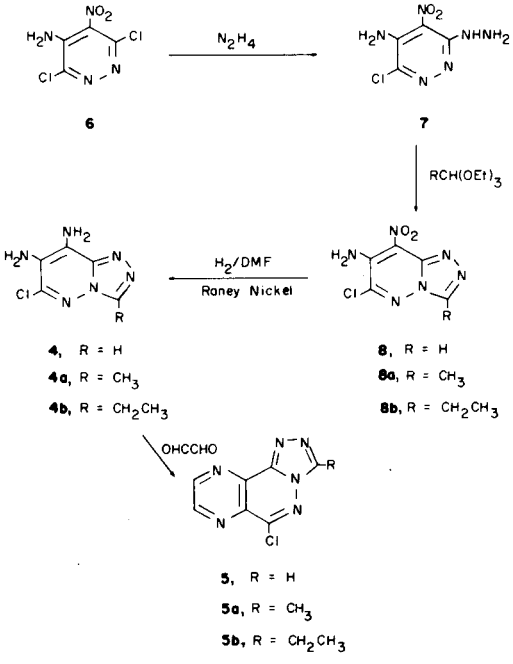
Because of the biological activity exhibited by the 1,2,4-triazolo[4,3-*a*]phthalazine ring system and its relationship to the active antihypertensive drugs ecarazine and hydralazine, it was of interest to study the chemistry of an unknown diaza analog of 1,2,4-triazolo[4,3-*a*]-phthalazine, in which the 7,8,9 and/or 10 carbon atoms have been replaced with two nitrogen atoms. Biological testing of a variety of substituted compounds also appeared to be of interest.

Kuraishi and Castle (8) reported the synthesis of 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-8-amine (**2**) in a 94% yield from 6-chloro-3-hydrazinopyridazin-4-amine (**1**) and formic acid (Scheme 1). It appeared that the well known nitramine rearrangement (9) on compound **2** should provide a key intermediate to the pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine ring system. Therefore reaction of the amino compound **2** with fuming nitric acid and sulfuric acid afforded 6-chloro-7-nitro-1,2,4-triazolo-[4,3-*b*]pyridazin-8-amine (**3**) in a yield of 30%. Reduction of the nitro group was achieved by hydrogenation at atmospheric pressure, using Raney nickel as a catalyst, to give the diamino compound **4** in a 50% yield (10). 6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazine-7,8-diamine (**4**) reacted with glyoxal in methanol to yield 89% of the desired 6-chloropyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]-

Scheme I



Scheme II



4, R = H
4a, R = CH_3
4b, R = CH_2CH_3

8, R = H
8a, R = CH_3
8b, R = CH_2CH_3

5, R = H
5a, R = CH_3
5b, R = CH_2CH_3

pyridazine (**5**).

Since nitration of the amino compound **2** resulted in a poor yield, we wished to obtain a better route. An investigation by Yanai, *et al.*, (10) revealed that the chlorine atom at position 6 of 3,6-dichloro-5-nitropyridazin-4-amine (**6**) (Scheme II) is quite reactive. Thus, reaction of the chloro compound **6** with hydrazine in absolute ethanol gave a 94% yield of 3-chloro-6-hydrazino-5-nitropyridazin-4-amine (**7**). When the hydrazino compound **7** was allowed to react with triethyl orthoformate, triethyl orthoacetate or triethyl orthopropionate the 1,2,4-triazolopyridazine **8**, methyl-1,2,4-triazolopyridazine **8a** and ethyl-1,2,4-triazolopyridazine **8b**, respectively, were produced in yields of 95%. Reduction of the nitro compounds **8**, **8a** and **8b** with hydrogen, using Raney nickel as a catalyst, in *N,N*-dimethylformamide gave the diamines **4**, **4a** and **4b** in yields of 80, 71 and 80%, respectively (mixed melting points of the diamine **4** from both routes showed no depression and the ir, nmr and mass spectra were identical). Ring closure to the substituted tricyclic compounds **5a** and **5b** was achieved in the same manner as described for 6-chloropyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**5**) in similar yields.

Scheme III

5, R = H

5a, R = CH_3

5b, R = CH_2CH_3

9-27

Reaction of 6-chloropyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazine (**5**) with ammonia and alkylamines afforded pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**9**) and *N*-substituted pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazin-6-amines (**10-18**) (Table 1) in yields of 40 to 77% (Scheme III). The chloromethyl compound **5a** and chloroethyl compound **5b** reacted similarly with ammonia, methyl amine and ethyl amine to give the expected amino compounds **19-24** (Scheme III) (Table 1). All three chloro compounds, **5**, **5a**, and **5b** reacted with sodium methoxide in dry methanol to give the 6-methoxy compounds **25**, **26**, and **27** (Scheme III) (Table 1).

Table 1
Substitution of Pyrazino[2,3-*d*]-1,2,4-triazolo-[4,3-*b*]pyridazine
Scheme III
dl

	R	R′
9	H	NH_2
10	H	$NHCH_3$
11	H	$NHCH_2CH_3$
12	H	$NHCH_2CH_2OH$
13	H	$NHCH_2CH_2NH_2$
14	H	$NHCH_2CH_2NH^+(CH_3)_2Cl^-$
15	H	$NHCH_2Ph$
16	H	(d)$NHCH(CH_3)Ph$
17	H	(*l*)$NHCH(CH_3)Ph$
18	H	1-piperidyl
19	CH_3	NH_2
20	CH_3	$NHCH_3$
21	CH_3	$NHCH_2CH_3$
22	CH_3CH_2	NH_2
23	CH_3CH_2	$NHCH_3$
24	CH_3CH_2	$NHCH_2CH_3$
25	H	OCH_3
26	CH_3	OCH_3
27	CH_3CH_2	OCH_3

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained on a Beckmann Acculab 2 spectrophotometer. The ir spectral data are recorded in reciprocal centimeters (cm^{-1}). ^1H nmr spectra were obtained on a Varian EM 390 spectrometer or JEOL FX 90Q spectrometer in the solvents as indicated. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Mass spectra were obtained on a Hewlett-Packard model 5980A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

6-Chloro-7-nitro-1,2,4-triazolo[4,3-*b*]pyridazin-8-amine (**3**).

Compound **2** (2 g, 12 mmoles) was dissolved in 16 ml of concentrated sulfuric acid at room temperature and then cooled to 0° in an ice-salt bath. Fuming nitric acid (1.8 ml, 90%, d = 1.52) was added dropwise, keeping the temperature between 5 and 10°. The solution was heated with stirring at 50 to 55° for two hours and 60 to 65° for an additional two hours. The cooled solution was poured on crushed ice to give a yellow precipitate. Filtration, followed by washing with cold water, gave 0.76 g (30%) of yellow solid, mp 207-209°. An analytical sample was obtained by recrystallization from absolute ethanol to give yellow prisms, mp 208-209°; ir (potassium bromide): 1285 and 1565 (NO_2), 1465 and 1640 (C=N), 3420 (NH_2); nmr (DMSO-d_6): 8.8-10.1 (broad s, 2H, NH_2), 9.57 (s, 1H, H-3); ms: 216 (M^+, ^{37}Cl, 33), 214 (M^+, 100), 199 (M-OH, ^{37}Cl, 30), 187 (M-OH, 84.5).

Anal. Calcd. for $C_5H_3ClN_6O_2$ (214.57): C, 27.99; H, 1.41; Cl, 16.52; N, 39.17. Found: C, 28.05; H, 1.56; Cl, 16.25; N, 39.29.

6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazine-7,8-diamine (**4**).

Method A.

The crude compound **3** (6 g, 28 mmoles), about 4 g of Raney nickel T-1 (11) and 350 ml of absolute ethanol was hydrogenated at room temperature and atmospheric pressure until 2 liters of hydrogen were taken up. Ethanol (500 ml) was added and the solution boiled and filtered while hot to remove the catalyst. Removal of the ethanol *in vacuo* followed by recrystallization from water/ethanol gave 2.6 g (50%) of light brown needles, mp 295-296°; ir (potassium bromide): 1660 (C=N), 3150 and 3320 (NH_2); nmr (DMSO-d_6): 5.03 (broad s, 2H, NH_2-8), 6.89 (broad s, 2H, NH_2-7); 9.25 (s, 1H, H-3); ms: 186 (M^+, ^{37}Cl, 22), 184 (M^+, 100), 149 (M-Cl, 72).

*Anal.*Calcd. for $C_5H_5ClN_6$ (184.59): C, 32.53; H, 2.73; Cl, 19.21; N, 45.53. Found: C, 32.38; H, 2.88; Cl, 19.40; N, 45.62.

Method B.

Compound **4** was prepared from compound **8** in the same manner as described in Method A except *N,N*-dimethylformamide was used in place of absolute ethanol as solvent. The product was isolated by recrystallization from water/*N,N*-dimethylformamide in 81% yield. Mixed melting

point showed no depression. The ir, nmr and mass spectra were identical.

6-Chloro-3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine-7,8-diamine (**4a**).

Compound **4a** was prepared in the same manner as described for compound **4** (Method B), thus, 13 g (57 mmoles) of crude **8a**, 4 g of Raney nickel T-1 and 350 ml of *N,N*-dimethylformamide gave 8 g (71%) of long brown needles from water/*N,N*-dimethylformamide, mp 301-303°; ir (potassium bromide): 1380 (CH_3), 1470 and 1670 (C=N), 3130 and 3350 (NH_2); nmr (DMSO-d_6): 2.57 (s, 3H, CH_3), 4.93 (broad s, 2H, NH_2-8), 6.73 (broad s, 2H, NH_2-7); ms: 200 (M^+, ^{37}Cl, 35), 198 (M^+, 98), 163 (M-Cl, 66), 109 (M-89, 100).

Anal. Calcd. for $C_6H_7ClN_6$ (198.62): C, 36.28; H, 3.55; Cl, 17.85; N, 42.31. Found: C, 36.21; H, 3.72; Cl, 17.65; N, 42.09.

6-Chloro-3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine-7,8-diamine (**4b**).

Compound **4b** was prepared in the same manner as described for compound **4** (Method B), thus, 12 g (59 mmoles) of crude **8b**, 4 g of Raney nickel T-1 and 350 ml of *N,N*-dimethylformamide gave 8.4 g of long brown needles from water/*N,N*-dimethylformamide, mp 226-228°; ir (potassium bromide): 1560 and 1640 (C=N), 3150 and 3300 (NH_2); nmr (DMSO-d_6): 1.34 (t, 3H, CH_2CH_3), 3.00 (q, 2H, CH_2CH_3), 4.35 (broad s, 2H, NH_2-8); 6.85 (broad s, 2H, NH_2-7); ms: 214 (M^+, ^{37}Cl, 30), 212 (M^+, 95), 177 (M-Cl, 56), 123 (M-89, 100).

Anal. Calcd. for $C_7H_9ClN_6$ (212.64): C, 39.54; H, 4.27; Cl, 16.67; N, 39.52. Found: C, 39.62; H, 4.49; Cl, 16.51; N, 39.42.

6-Chloropyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**5**).

A mixture of **4** (1.5 g, 8.1 mmoles), 1.5 ml of 40% glyoxal and 100 ml of methanol was refluxed for 24 hours. The methanol (60 ml) was evaporated and the solution cooled for crystallization (charcoal was added if necessary). The light yellow prisms were filtered to give 1 g of product. Further concentration of the mother liquor gave an additional 0.5 g, to give a total yield of 1.5 g (89%), mp 214-216°; ir (potassium bromide): 1470, 1510 and 1550 (C=N), 3060 (aromatic); nmr (DMSO-d_6): 9.29 (d, 1H, H-8 or H-9, $J_{8,9}$ = 2.1 Hz), 9.37 (d, 1H, H-9 or H-8, $J_{8,9}$ = 2.1 Hz), 9.76 (s, 1H, H-3); ms: 208 (M^+, ^{37}Cl, 33), 206 (M^+, 100).

Anal. Calcd. for $C_7H_3ClN_6$ (206.60): C, 40.70; H, 1.46; Cl, 17.16; N, 40.68. Found: C, 40.78; H, 1.61; Cl, 16.95; N, 40.72.

6-Chloro-3-methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**5a**).

Compound **5a** was prepared in the same manner as described for compound **5** except a mixture of methanol/benzene was used as the solvent. Thus 5 g (25 mmoles) of **4a**, 4.5 ml of 40% glyoxal, 300 ml of methanol and 200 ml of benzene gave 4.8 g (86%) from benzene, mp 277-279° dec; ir (potassium bromide): 1600 and 1610 (C=N), nmr (DMSO-d_6): 2.79 (s, 3H, CH_3), 9.26 (d, 1H, H-8 or H-9, $J_{8,9}$ = 2.0 Hz), 9.33 (d, 1H, H-9 or H-8, $J_{8,9}$ = 2.0 Hz); ms: 222 (M^+, ^{37}Cl, 32), 220 (M^+, 100).

Anal. Calcd. for $C_8H_5ClN_6$ (220.62): C, 43.55: H, 2.28; Cl, 16.07; N, 38.09.Found: C, 43.56; H, 2.34; Cl, 15.96; N, 38.14.

6-Chloro-3-ethylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**5b**).

Compound **5b** was prepared in the same manner as described for compound **5a**, thus, 5 g (24 mmoles) of **4b**, 4 ml of 40% glyoxal, 300 ml of methanol and 200 ml of benzene 4.8 g (87%) of yellow prisms from methanol, mp 208-209°; ir (potassium bromide): 1455, 1505, 1545 and 1590 (C=N), 2990 (aromatic); nmr (DMSO-d_6): 1.44 (t, 3H, CH_2CH_3), 3.14 (q, 2H, CH_2CH_3), 9.25 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.9 Hz), 9.32 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.9 Hz); ms: 236 (M^+, ^{37}Cl, 30), 235 (M-H, ^{37}Cl, 39), 234 (M^+, 100), 233 (M-H, 99), 199 (M-Cl, 93).

Anal. Calcd. for $C_9H_7ClN_6$ (234.65): C, 46.07; H, 3.01; Cl, 15.11; N, 35.82. Found: C, 46.22; H, 3.10; Cl, 14.99; N, 35.58.

3-Chloro-6-hydrazino-5-nitropyridazin-4-amine (**7**).

Compound **6** (20.9 g, 0.1 mole) was dissolved in 400 ml of absolute ethanol and cooled in an ice bath, after which 15 ml of anhydrous hydrazine (97%) diluted with 50 ml of absolute ethanol was added in one portion. The solution immediately turned red followed by an orange-brown precipitate. The mixture was stirred for 15 minutes, filtered and the precipitate added to 400 ml of water (the solid turned from orange-brown to brown) and stirred for 5 minutes. Filtration of the precipitate, followed by washings with water, ethanol and then ether gave 19 g (93%) of crude product. An analytical sample was otained by recrystallization from ethanol/water to give dark brown prisms, mp 188° dec; ir (potassium bromide): 1270 and 1550 (NO_2), 3300 and 3380 (NH_2 and $NHNH_2$); nmr (DMSO-d_6): 4.75-5.25 (broad s, 2H, NH_2), 8.10-9.40 (broad s, 3H, NH and NH_2); ms: 206 (M^+, ^{37}Cl, 15), 204 (M^+, 50), 129 (M-75, 100).

Anal. Calcd. for $C_4H_5ClN_6O_2$ (204.58): C, 23.48, H, 2.46; Cl, 17.33; N, 41.08. Found: C, 23.67; H, 2.52; Cl, 17.39; N, 40.82.

6-Chloro-8-nitro-1,2,4-triazolo[4,3-*b*]pyridazin-7-amine (**8**), 6-Chloro-3-methyl-8-nitro-1,2,4-triazolo[4,3-*b*]pyridazin-7-amine (**8a**) and 3-Ethyl-8-nitro-1,2,4-triazolo[4,3-*b*]pyridazin-7-amine (**8b**).

A mixture of crude **7** (0.6 mole), 24 ml of the appropriate triethyl orthoester and 180 ml of toluene was refluxed for 10 minutes (the solid turned from brown to yellow). The flask was converted to downward distillation and distilled until a temperature of 100° was reached (about 30 to 45 minutes). The mixture was cooled, filtered, washed with toluene and dried to give the crude triazoles **8**, **8a** and **8b** as yellow powders. Thus compound **8** was prepared in a 95% yield from compound **7** and triethyl orthoformate. An analytical sample was obtained by recrystallization from DMSO/water to give dark yellow needles, mp > 300° (darkens at 255°); ir (potassium bromide): 1290 and 1525 (NO_2), 1610 (C=N), 3300 (NH_2); nmr (DMSO-d_6): 9.09 (broad s, 2H, NH_2), 9.40 (s, 1H, H-3); ms: 216 (M^+, ^{37}Cl, 31), 214 (M^+, 93), 199 (M-OH, ^{37}Cl, 33), 197 (M-OH, 100).

Anal. Calcd. for $C_5H_3ClN_6O_2$ (214.57): C, 27.99; H, 1.41; Cl, 16.52; N, 39.17. Found: C, 27.80; H, 1.57; Cl, 16.33; N, 39.38.

Compound **8a** was prepared in a 95% yield from compound **7** and triethyl orthoacetate. An analytical sample was obtained by recrystalization from *N,N*-dimethylformamide/water to give yellow needles, mp > 300° (darkens at 245°); ir (potassium bromide): 1270 and 1525 (NO_2). 1630 (C=N), 3340 (NH_2); nmr (DMSO-d_6): 2.57 (s, 3H, CH_3), 9.03 (broad s, 2H, NH_2); ms: 230 (M^+, ^{37}Cl, 32), 228 (M^+, 96), 213 (M-OH, ^{37}Cl, 30), 211 (M-OH, 100).

Anal. Calcd. for $C_6H_5ClN_6O_2$ (228.60): C, 31.53; H, 2.21; Cl, 15.51; N, 36.73. Found: C, 31.78; H, 2.41; Cl, 15.36; N, 36.80.

Compound **8b** was prepared in a 95% yield from compound **7** and triethyl orthopropionate. An analytical sample was obtained by recrystallization from *N,N*-dimethylformamide/water to give yellow needles, mp > 300° (darkens at 240-243°); ir (potassium bromide): 1265 and 1520 (NO_2), 1620 (C=N), 3380 (NH_2); nmr (DMSO-d_6): 1.35 (t, 3H, CH_2CH_3), 3.00 (q, 2H, CH_2CH_3); 8.87 (broad s, 2H, NH_2); ms: 244 (M^+, ^{37}Cl, 34), 242 (M^+, 100), 227 (M-CH_3, 64), 225 (M-OH, 36).

Anal. Calcd. for $C_7H_7ClN_6O_2$ (242.63): C, 34.65; H, 2.91; Cl, 14.61; N, 34.64. Found: C, 34.53; H, 3.11; Cl, 14.64; N, 34.59.

Pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**9**).

Compound **5** (1 g, 4.84 mmoles) and 30 ml of absolute ethanol saturated with ammonia in a dry ice-isopropyl alcohol bath were heated for 5 hours at 120-130° in a stainless steel bomb. Upon cooling, the precipitate was filtered and recrystallized from water/ethanol to give 0.7 g (77%) of light brown needles, mp > 300°; ir (potassium bromide): 1630 (C=N), 3120 (aromatic), 3400 and 3480 (NH_2); nmr (DMSO-d_6): 7.13 (s, 2H, NH_2), 9.03 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.7 Hz), 9.07 (s, 1H, H-3), 9.16 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.7 Hz), ms: 187 (M^+, 100).

Anal. Calcd. for $C_7H_{15}N_7$ (187.16): C, 44.92; H, 2.69; N, 52.39. Found: C, 44.92; H, 2.82; N, 52.57.

N-Methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**10**) and *N*-Ethylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**11**).

Compound **5** (1 g, 4.84 mmoles), 10 ml of 40% methyl amine or pure ethylamine and 40 ml of absolute ethanol were heated for 5 hours at 100

to 110° in a stainless steel bomb. Upon cooling, the ethanol was removed *in vacuo* to give a light yellow solid. Recrystallization from water/ethanol gave the amine **10** or **11**. Thus, compound **5** gave 0.6 g (62%) of **10** as light yellow needles, mp 289-290°; ir (potassium bromide): 1150 (C-N), 1570 and 1605 (C=N), 3505 (NH); nmr (DMSO-d_6): 3.02 (d, 3H, N-CH_3), 8.05 (broad s, 1H, NH), 9.10 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.24 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz), 9.29 (s, 1H, H-3); ms: 201 (M^+, 100), 173 (M-CH_2N, 25).

Anal. Calcd. for $C_8H_7N_7$ (201.19): C, 47.76; H, 3.51; N, 48.73. Found: C, 47.75; H, 3.69; N, 48.78.

Compound **5** gave 0.75 g (72%) of the amine **11** as yellow needles, mp 239-240°; ir (potassium bromide): 1145 (C-N), 1535, 1545, 1570 and 1610 (C=N), 3230 (NH); nmr (DMSO-d_6): 1.27 (t, 3H, CH_2CH_3), 3.49 (m, 2H, CH_2CH_3), 7.78 (broad s, 1H, NH), 9.08 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.23 (s, 2H, H-3 and H-8 or H-9); ms: 215 (M^+, 74); 200 (M-CH_3, 100).

Anal. Calcd. for $C_9H_9N_7$ (215.22): C, 50.23; H, 4.22; N, 45.56. Found: C, 50.06; H, 4.23; N, 45.53.

General Procedure for the Preparation of the Amino Compounds **12-18**.

A mixture of **5** (1 g, 4.84 mmoles), the appropriate amine (10.6 mmoles) and 70 ml of absolute ethanol was refluxed for 2-3 hours. The ethanol was removed *in vacuo*, water added and filtered to give the crude amine. Recrystallization from ethanol/water gave the pure amine.

N-(2-Hydroxyethyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**12**).

Compound **12** was prepared in a 76% yield as light yellow needles, mp 276-277°; ir (potassium bromide): 1140 (C-N), 1530, 1545, 1570 and 1610 (C=N), 3250 (NH_2); nmr (DMSO-d_6): 3.59 (t, 2H, N-CH_2),3.74 (t, 2H, CH_2-O), 4.88 (t, 1H, OH), 7.64 (broad s, 1H, NH), 9.12 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.7 Hz), 9.21 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.7 Hz); 9.23 (s, 1H, H-3); ms: 231 (M^+, 100); 213 (M-H_2O, 32), 201 (M-CH_2O, 52).

*Anal.*Calcd. for $C_9H_9N_7O$ (231.22): C, 46.75; H, 3.92; N, 42.40. Found: C, 47.00; H, 4.09; N, 42.23.

N-(2-Aminoethyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**13**).

Compound **13** was prepared in a 63% yield as yellow plates, mp 225-227°; ir (potassium bromide): 1140 (C-N), 1530, 1545, 1570 and 1605 (C=N), 3200 and 3400 (NH and NH_2); nmr (DMSO-d_6): 2.88 (broad s, 2H, NH_2), 3.48 (m, 4H, CH_2CH_2), 7.82 (broad s, 1H, NH), 9.10 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.20 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz); 9.22 (s, 1H, H-3); ms: 230 (M^+, 6); 201 (M-CH_3N, 50), 173 (M-$C_2H_5N_2$, 100).

Anal. Calcd. for $C_9H_{10}N_8$ (230.23): C, 46.95; H, 4.38; N, 48.67. Found: C, 47.17; H, 4.55; N, 48.47.

N-(2-Dimethylaminoethyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine Hydrochloride (**14**).

Compound **14** was prepared in the same manner as described in the general procedure except for the amount of the amine used (4.8 mmoles). Recrystallization from ethanol/ethyl acetate gave a 50% yield as yellow needles, mp 293-294°; ir (potassium bromide): 1150 (C-N), 1390 (CH_3), 1535, 1545, 1575 and 1610 (C=N), 2710 (NH^+), 3400 (NH_2); nmr (DMSO-d_6): 2.92 (s, 6H, CH_3), 3.27-3.55 (broad s, 3H, NH^+ and H_2O), 3.86 (m, 4H, CH_2CH_2), 8.20 (t, 1H, NH), 9.14 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.9 Hz), 9.23 (s, 3H, H-3 and H-8 or H-9); ms: 258 (M-HCl, 4); 58 (M-234, 100).

*Anal.*Calcd. for $C_{11}H_{15}ClN_8 \cdot H_2O$ (312.77): C, 42.24; H, 5.48; Cl, 11.34; N, 35.83. Found: C, 42.50; H, 5.48; Cl, 11.51; N, 36.03.

N-Benzylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**15**).

Compound **15** was prepared in a 75% yield as light yellow needles, mp 230-231°; ir (potassium bromide): 1135 (C-N), 1520, 1540, 1560 and 1610 (C=N), 3400 (NH_2); nmr (DMSO-d_6): 4.62 (d, 2H, CH_2), 7.28-7.55 (m, 5H, phenyl), 8.51 (broad s, 1H, NH), 9.13 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.24 (s, 2H, H-3 and H-8 or H-9), ms: 277 (M^+, 43); 173 (M-C_7H_6N, 68), 91 (M-186, 100).

Anal. Calcd. for $C_{14}H_{11}N_7$ (277.29): C, 60.64; H, 4.00; N, 35.36. Found: C, 60.59; H, 4.02; N, 35.26.

d-*N*-(1-Phenyl-1-ethyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**16**).

Compound **16** was prepared in a 57% yield as light yellow needles, mp 83-84°; ir (potassium bromide): 1140 (C-N), 1525 and 1610 (C=N), 3400 (NH); nmr (DMSO-d_6): 1.62 (d, 3H, CH_3), 5.20 (t, 1H, CH-CH_3), 7.22-7.62 (m, 5H, phenyl), 8.07 (d, 1H, NH), 9.13 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.22 (s, 1H, H-3), 9.24 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz), ms: 291 (M^+, 31); 276 (M-CH_3, 35), 187 (M-C_8H_8, 51), 105 (M-186, 100).

Anal. Calcd. for $C_{15}H_{13}N_7$ (291.32): C, 61.85; H, 4.50; N, 33.66. Found: C, 61.77; H, 4.46; N, 33.67.

l-*N*-(1-Phenyl-1-ethyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**17**).

Compound **17** was prepared in a 70% yield as light yellow needles, mp 82-83°; ir (potassium bromide): 1140 (C-N), 1530 and 1610 (C=N), 3400 (NH); nmr (DMSO-d_6): 1.66 (d, 3H, CH_3), 5.20 (t, 1H, CH-CH_3), 7.21-7.58 (m, 5H, phenyl), 8.11 (d, 1H, NH), 9.12 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.7 Hz), 9.20 (s, 1H, H-3), 9.24 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.7 Hz); ms: 291 (M^+, 27); 276 (M-CH_3, 30), 187 (M-C_8H_8, 42), 105 (M-186, 100).

Anal. Calcd. for $C_{15}H_{13}N_7$ (291.32): C, 61.85; H, 4.50; N, 33.66. Found: C, 61.69; H, 4.44; N, 33.48.

6-(1-Piperidyl)pyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**18**).

Compound **18** was prepared in a 49% yield as yellow needles, mp 175-176°; ir (potassium bromide): 1140 (C-N), 1500 and 1590 (C=N); nmr (DMSO-d_6): 1.69 (broad s, 6H, $CH_2CH_2CH_2$), 3.70 (broad s, 4H, CH_2-N-CH_2), 9.12 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.20 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.5 Hz), 9.39 (s, 1H, H-3); ms: 255 (M^+, 100).

Anal. Calcd. for $C_{12}H_{13}N_7$ (255.28): C, 56.46; H, 5.13; N, 38.41. Found: C, 56.22; H, 5.22; N, 38.56.

3-Methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**19**).

Compound **19** was prepared in the same manner as described for compound **9**, thus, 1 g (4.5 mmoles) of **5a** and 30 ml of absolute ethanol gave 0.5 g (55%) of light yellow needles from water/*N*,*N*-dimethylformamide, mp >300°; ir (potassium bromide): 1520 and 1630 (C=N), 3350 (NH_2); nmr (DMSO-d_6): 2.57 (s, 3H, CH_3), 7.37 (broad s, 2H, NH_2), 9.01 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz), 9.13 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz); ms: 201 (M^+, 100).

Anal. Calcd. for $C_8H_7N_7$ (201.19): C, 47.76; H, 3.51; N, 48.73. Found: C, 47.63; H, 3.62; N, 48.97.

N,3-Dimethylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**20**).

Compound **20** was prepared in the same manner as described for compound **10**, thus, 1 g (4.5 mmoles) of **5a**, 10 ml of 40% methyl amine and 30 ml of absolute ethanol gave 0.7 g (72%) of long dark yellow needles from water/ethanol, mp 295-297°; ir (potassium bromide): 1240 (C-N), 1390 (CH_3), 1510, 1530, 1545, 1570 and 1610 (C=N), 3350 (NH); nmr (DMSO-d_6): 2.65 (s, 3H, CH_3), 3.01 (d, 3H, N-CH_3), 7.88 (broad s, 1H, NH), 9.02 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.7 Hz), 9.19 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.5 Hz); ms: 215 (M^+, 100), 187 (M-CH_2N, 12), 131 (M-84, 63).

Anal. Calcd. for $C_9H_9N_7$ (215.22): C, 50.23; H, 4.22; N, 45.56. Found: C, 49.99; H, 4.31; N, 45.30.

N-Ethyl-3-methylpyrazino[2,3,-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**21**).

Compound **21** was prepared in the same manner as described for compound **11**, thus, 1 g (4.5 mmoles) of **5a**, 10 ml of ethyl amine and 40 ml of absolute ethanol gave 0.6 g (58%) of yellow needles from water/ethanol, mp 239.5-240°; ir (potassium bromide): 1240 (C-N), 1615 (C=N), 3410 (NH_2); nmr (DMSO-d_6): 1.30 (t, 3H, $NHCH_2CH_3$), 2.62 (s, 3H, CH_3), 3.50 (m, 2H, $NHCH_2CH_3$), 7.82 (broad s, 1H, NH), 9.06 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.19 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.5 Hz); ms: 229 (M^+, 100), 214

(M-CH_3, 97), 187 (M-C_2H_4N, 30).

*Anal.*Calcd. for $C_{10}H_{11}N_7$ (229.25): C, 52.39; H, 4.84; N, 42.77. Found: C, 52.49; H, 4.95; N, 42.64.

3-Ethylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**22**).

Compound **22** was prepared in the same manner as described for compound **9**, thus, 1 g (4.26 mmoles) of **5b** and 40 ml of absolute ethanol gave 0.6 g (65%) of yellow needles from water/*N,N*-dimethylformamide, mp >300°; ir (potassium bromide): 1635 (C=N), 3400 (NH_2); nmr (DMSO-d_6): 1.35 (t, 3H, CH_2CH_3), 2.99 (d, 2H, CH_2CH_3), 7.38 (broad s, 2H, NH_2), 9.02 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.14 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz); ms: 215 (M^+, 87), 214 (M-H, 100), 200 (M-CH_3, 26), 186 (M-C_2H_5, 23), 105 (M-110, 41).

Anal. Cacld. for $C_9H_9N_7$ (215.22): C, 50.23; H, 4.22; N, 45.56. Found: C, 50.40; H, 4.47; N. 45.60.

3-Ethyl-*N*-methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**23**).

Compound **23** was prepared in the same manner as described for compound **10**, thus, 1 g (4.26 mmoles) of **5b** and 10 ml of 40% methylamine and 30 ml of absolute ethanol gave 0.7 g (72%) of yellow plates from water/ethanol, mp 257-258°; ir (potassium bromide): 1230 (C-N), 1505, 1545, 1570 and 1610 (C=N), 3320 (NH); nmr (DMSO-d_6): 1.43 (t, 3H, CH_2CH_3), 3.02 (q, 2H, CH_2CH_3), 3.53 (d, 3H, N-CH_3), 7.92 (broad s, 1H, NH), 9.02 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.18 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz); ms: 229 (M^+, 97), 228 (M-H, 100).

Anal. Calcd. for $C_{10}H_{11}N_7$ (229.25): C, 52.39; H, 4.84; N, 42.77. Found: C, 52.30; H, 4.87; N, 42.82.

N,3-Diethylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**24**).

Compound **24** was prepared in the same manner as described for compound **10**, thus, 1 g (4.26 mmoles) of **5b**, 10 ml of ethylamine and 40 ml of absolute ethanol gave 0.6 g (60%) of yellow needles from water/ethanol, mp 181-183°; ir (potassium bromide): 1520, 1575 and 1610 (C=N), 3280 (NH); nmr (DMSO-d_6): 1.30 (t, 3H, $NHCH_2CH_3$), 1.42 (t, 3H, CH_2CH_3), 3.01 (q, 2H, CH_2CH_3), 3.54 (m, 2H, $NHCH_2CH_3$), 7.82 (broad s, 1H, NH), 9.04 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.8 Hz), 9.18 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.8 Hz); ms: 243 (M^+, 100), 242 (M-H, 66), 228 (M-CH_3, 65).

Anal. Calcd. for $C_{11}H_{13}N_7$ (243.27): C, 54.31; H, 5.39; N, 40.30. Found: C, 54.39; H, 5.34; N, 40.34.

6-Methoxypyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**25**).

A mixture **5** (1 g, 4.84 mmoles), sodium (0.11 g, 0.0048 g-atom) and 50 ml of dry methanol was refluxed for four hours. Methanol (25 ml) was evaporated and the mixture cooled. The light brown precipitate was filtered, washed with water and recrystallized from methanol/ benzene to give 0.73 g (75%) of light brown needles, mp 244-246°; ir (potassium bromide): 1040, 1090 and 1140 (C-O-C), 1380 (CH_3), 1460, 1530, 1565 and 1610 (C=N), 3040 (aromatic); nmr (DMSO-d_6): 4.20 (s, 3H, OCH_3); 9.20 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.27 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.5 Hz), 9.51 (s, 1H. H-3); ms: 202 (M^+, 90), 173 (M-CHO, 100), 104 (M-98, 40).

*Anal.*Calcd. for $C_8H_6N_6$ (202.18): C, 47.53; H, 2.99; N, 41.57. Found: C, 47.32; H, 3.01; N, 41.42.

6-Methoxy-3-methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-6-amine (**26**).

Compound **26** was prepared in the same manner as described for compound **25**, except for the work up. After the methanol (25 ml) was evaporated, the solution was set aside for crystallization. Thus, 1 g (4.5 mmoles) of **5a**, sodium (0.1 g, 0.0045 g-atom) and 50 ml of dry ethanol gave 0.64 g (65%) of light brown prisms from methanol mp 236-238°; ir (potassium bromide): 1040, 1095 and 1160 (C-O-C), 1380 and 1390 (CH_3), 1450, 1520 and 1595 (C=N) 2980, 3010 and 3040 (aromatic); nmr (deuteriochloroform): 2.82 (s, 3H, CH_3), 4.32 (s, 3H, OCH_3), 9.08 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.5 Hz), 9.21 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.5 Hz); ms: 216 (M^+, 100), 187 (M-CHO, 64), 104 (M-112, 77).

Anal. Calcd. for $C_9H_8N_6O$ (216.20): C, 50.00; H, 3.73; N, 38.87. Found: C, 50.23; H, 3.74; N, 38.63.

3-Ethyl-6-methylpyrazino[2,3-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**27**).

Compound **27** was prepared in the same manner as described for compound **25**, except for the work up. Thus, 1 g (4.26 mmoles) of **5b**, sodium (0.1 g, 0.0043 g-atom) and 50 ml of methanol was allowed to react. After the reaction was complete, the methanol was removed *in vacuo* to give a brown solid. Chromatography of the brown solid on a column of silica gel using chloroform/methanol (9:1) as eluent gave 0.9 g of a light brown solid. Recrystallization from chloroform/cyclohexane gave 0.85 g (82%) of white prisms, mp 177-178°; ir (potassium bromide): 1060, 1110 and 1170 (C-O-C), 1460, 1510, 1535, and 1610 (C=N) 2980 and 3000 (aromatic); nmr (deuteriochloroform): 1.53 (t, 3H, CH_2CH_3), 3.22 (q, 2H, CH_2CH_3), 4.30 (s, 3H, OCH_3), 9.06 (d, 1H, H-9 or H-8, $J_{8,9}$ = 1.6 Hz), 9.17 (d, 1H, H-8 or H-9, $J_{8,9}$ = 1.6 Hz); ms: 230 (M-CH_2, 74); 229 (M-CH_3, 100), 215 (M-CHO, 27).

Anal. Calcd. for $C_{10}H_{10}N_6O$ (230.23): C, 52.17; H, 4.38; N, 36.50. Found: C, 52.12; H, 4.32; N, 36.18.

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