Giuliana Biagi, Fabio Ciambrone, Irene Giorgi, Oreste Livi*, Valerio Scartoni,

Dipartimento di Scienze Farmaceutiche, Università di Pisa, via Bonanno 6, 56126 Pisa, Italy

Pier Luigi Barili

Dipartimento di Bioorganica e Biofarmacia, Università di Pisa, via Bonanno 6, 56126 Pisa, Italy
Received December 27, 2001

New tricyclic 1,2,3-triazolo-1,2,4-triazolo-pyridazine derivatives, bearing a methyl substituent on the 1,2,3-triazole ring, were prepared as potential biological agents. *N*-Methylation of dimethyl 1,2,3-triazole-4,5-dicarboxylate allowed synthesis of the isomeric 1-methyl-4,7-dihydroxy and 2-methyl-4,7-dihydroxy triazolo-pyridazines **4a** and **4b** which, by a chlorination reaction, gave the corresponding 1-methyl-4-chloro- (**6a**), 1-methyl-7-chloro- (**6b**) and 2-methyl-4-chloro- (**9**) substituted 1,2,3-triazolo-pyridazines. The nucleophilic substitution with hydrazine hydrate and the suitable cyclization to form the 1,2,4-triazole ring, provided the expected tricyclic isomeric derivatives **8a**, **8b** and **11** respectively. The *p*-methoxybenzyl substituent, introduced as a leaving group to obtain either v-triazolo-pyridazine or v-triazolo-s-triazolo-pyridazine derivatives unsubstituted on the 1,2,3-triazole ring, appeared inadequate. Some compounds underwent binding assays toward the adenosine A_1 and A_{2A} receptors.

J. Heterocyclic Chem., **39**, 889(2002).

Introduction.

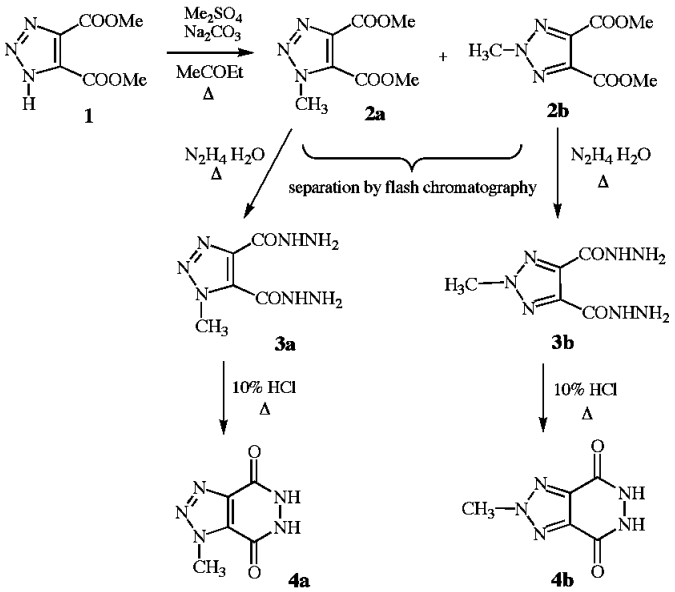
Previously we have prepared some 1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[3,4-*b*]pyridazine derivatives bearing lipophilic substituents (benzyl, *p*-methylbenzyl and *p*-methyphenyl) in the 3 position [1].

These compounds were tested, by binding assays, toward the adenosine and benzodiazepine receptors with disappointed results, but the planar nitrogen tricyclic pattern is appeared interesting to us and being worth further studies and experimentations.

Thus, according to the synthetic approach starting from the 1-substituted-1*H*-1,2,3-triazole, *via* triazolo[4,5-*d*]-pyridazine and further formation of the 1,2,4-triazole ring, we prepared new tricyclic derivatives bearing a methyl substituent in the place of the sterically hindered substituents or lacking of substituents on the 1,2,3-triazole ring.

The methyl 1,2,3-triazole 4,5-dicarboxylate **1** [2] underwent a methylation reaction with dimethyl sulphate in methyl ethyl ketone in the presence of anhydrous sodium carbonate (Scheme 1).

Scheme 1



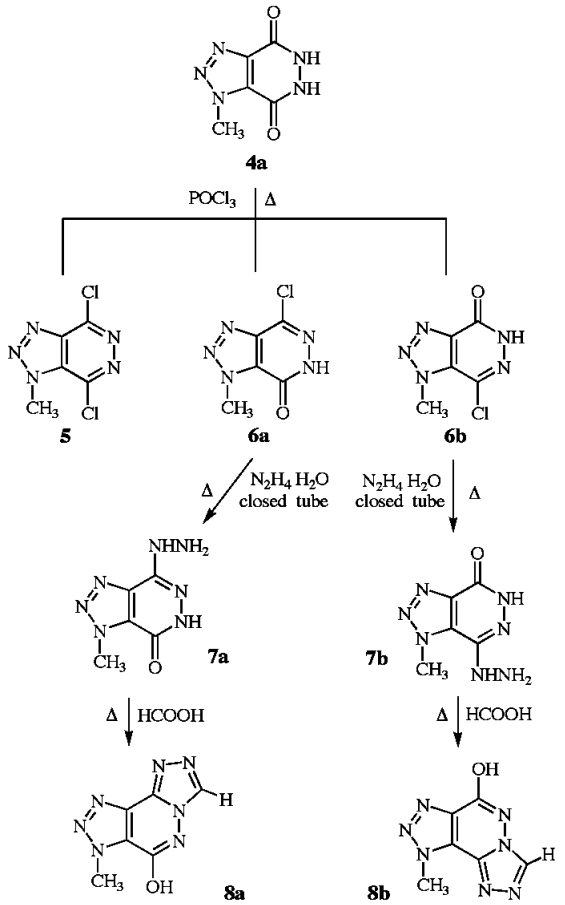
After 24 hours under reflux, the mixture of the *N*-methyl-substituted isomers **2a** and **2b** was isolated in quantitative yield and the gas-chromatographic analysis gave an isomer ratio 51.5:48.5 respectively. The mixture was separated by flash-chromatography through a silica-gel column and elution with ethyl acetate-petroleum ether 1:3 gave the 2-methyl isomer **2b** (45 %) followed by the 1-methyl isomer **2a** (47 %). The two compounds were characterized by analytical and spectroscopic methods and their structure was assigned according to the literature [3] where is reported the **2a** synthesis starting from the methylazide.

The isomeric triazole diesters **2a** and **2b** were converted to the corresponding dicarboxyhydrazides **3a** and **3b** by reaction with 98% hydrazine hydrate and these, in their turn, cyclized by heating with 10% hydrochloric acid, to give the expected 4,7-dihydroxy-pyridazines 1-methyl- (**4a**) and 2-methyl- (**4b**) substituted respectively, in high yield. Compounds **4a** and **4b** underwent chlorination reaction under experimental conditions optimized to minimize the formation of the respective 4,7-dichloro derivatives. As reported in Scheme 2, **4a** after 5 hours of reflux in phosphorus oxychloride provided a solid mixture consisting of the dichloroderivative **5** and of the two isomeric monochloroderivatives, 4-chloro- (**6a**) and 7-chloro- (**6b**) substituted, easily separable by TLC (Rf : 0.78, 0.57 and 0.45 respectively, acetonitrile-chloroform 2:5). Upon this basis the fractionation of the mixture was carried out by flash-chromatography through a silica–gel column; elution

with ethyl acetate-petroleum ether 2:1 gave **5**, **6a** and **6b** in 1.5 %, 26 % and 19 % yield respectively. The compounds have been characterized with analytical and spectroscopic methods and the structure of the two isomeric monochloroderivatives has been assigned on the basis of the Rf values and the relative amounts depending from the steric hindrance in the 7 position (even if in this case the methyl hindrance has a small influence).

These considerations fully agreed with those of analogous chlorinations of 1-substituted-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazines [4,5].

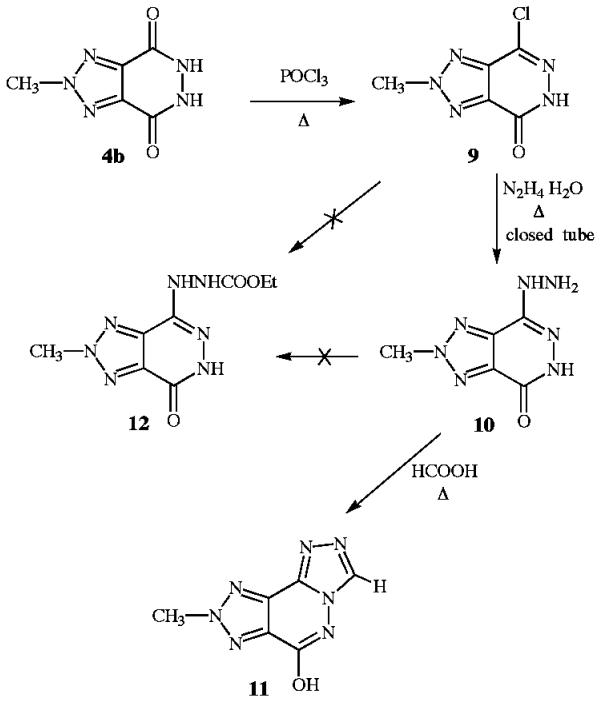
Scheme 2



Each monochloroderivative was then converted to the corresponding hydrazino compound **7a** and **7b** respectively, by nucleophilic replacement with an excess of 98% hydrazine hydrate, heating at 120° for 24 hours in a closed tube. Finally by treatment with refluxing formic acid, **7a** and **7b** cyclized to give the corresponding v-triazolo-s-triazolo-pyridazines, 3-methyl- (**8a**) and 1-methyl- (**8b**) substituted, in 77 % and 80 % yield respectively. Their structures agreed with the analytical and spectroscopic data reported in the experimental part.

The chlorination reaction of the symmetric 2-methyl-4,7-dihydroxy-triazolopyridazine **4b** (Scheme 3) can provide only the monochloroderivative **9** together with the eventual 4,7-dichloroderivative.

Scheme 3

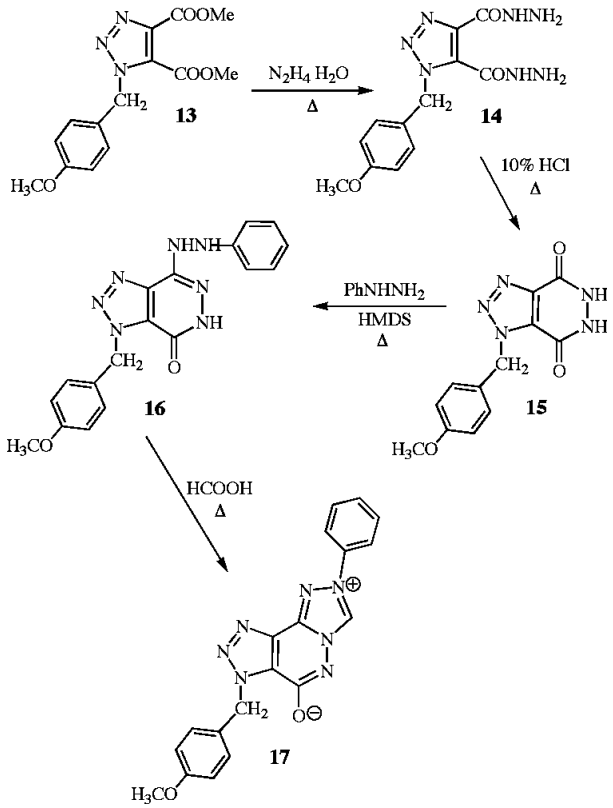


Thus heating under reflux **4b** in phosphorus oxychloride for 4 hours did not provide the dichloroderivative, but allowed the isolation of the monochloroderivative **9** in 40% yield, with a 30% recovery of the starting material **4b**. The separation was easily achieved by the different acidity, in fact **4b** was soluble in 5% sodium hydrogen carbonate whilst **9** was soluble in 10% sodium hydroxide solution. As reported above for **7a** and **7b**, by heating **9** with 98% hydrazine hydrate in a closed tube, the 4-hydrazino derivative **10** was obtained in 50% yield and the next reaction with formic acid led to the formation of the 1,2,4-triazole ring, to give the tricyclic compound **11** in 77% yield.

It has been reported in the literature [6] that the *p*-methoxybenzyl substituent is a good leaving group which can easily be removed from a nitrogen atom of the 1,2,3-triazole ring, by treatment with trifluoroacetic acid at 65-70°. Upon this hypothesis we undertook the synthesis of new triazolo-pyridazine derivatives starting from the *p*-methoxybenzylazide [6].

The thermal 1,3-dipolar cycloaddition reaction of the azide to methyl acetylendicarboxylate (Scheme 4) provided the triazole diester **13** which was converted to the corresponding dicarboxyhydrazide **14** by 98% hydrazine hydrate. Treatment of **14** with 10% hydrochloric acid under reflux, caused cyclization to give the 1-*p*-

Scheme 4



methoxybenzyl-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]-pyridazine (**15**).

Compound **15** reacted with phenylhydrazine in hexamethyldisilazane in the presence of a catalytic amount of ammonium sulphate at 140° for 24 hours to obtain the 4-phenylhydrazino-triazolopyridazine **16** in 60% yield. This silylation amination reaction of aromatic hydroxy-N-heterocycles [7] had been extensively applied to analogous 1-substituted triazolopyridazines [4,5,8,9]. Heating **16** with formic acid, the zwitterionic tricyclic derivative **17** was obtained in 87% yield; its structure agreed with the physical and spectroscopic properties and with our previous evidences [1]. Unfortunately attempts of removing the *p*-methoxybenzyl group from **17** as well as from **16** by solvolysis with trifluoroacetic acid failed.

The hydrazino derivatives **7a**, **7b** and **10**, the corresponding tricyclic derivatives **8a**, **8b** and **11** together with the compounds **16** and **17** underwent a biological evaluation by binding assays toward the benzodiazepine and adenosine A_1 and A_{2A} receptors. All results showed that these compounds lack activity.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. IR spectra in nujol mulls were recorded on a Mattson Genesis series FTIR spectrometer. UV spectra were obtained on a Perkin-Elmer Lambda 15 UV/VIS spectrophotometer in $CHCl_3$. ^{1}H-NMR spectra were recorded with a Varian Gemini 200 spectrometer in DMSO-d_6 or $CDCl_3$ in δ units, using TMS as internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988 A and a Perkin-Elmer SCIEX mod. API III. Elemental analyses (C,H,N) were within ± 0.4% of theoretical values and were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus. TLC data were obtained with Merck silica gel 60 $F_{254,}$ aluminum sheets. Gas Chromatographic analyses were performed on a GC Erba mod. 4200 apparatus. Short distillations were performed in a Buchi GKR 50 tubular oven. Petroleum ether corresponds to fraction boiling at 40-60 °. Hydrazine hydrate 98% is a very toxic and dangerous reagent that requires an appropriate personal protection.

Methyl 1-Methyl-1,2,3-triazolo-4,5-dicarboxylate (**2a**) and Methyl 2-Methyl-1,2,3-triazolo-4,5-dicarboxylate (**2b**).

To a solution of 14.47 g (78.2 mmol) of methyl 1,2,3-triazole-4,5-dicarboxylate (**1**) in 250 mL of methyl ethyl ketone, 9.0 mL (98.1 mmol) of dimethyl sulphate and 43 g of anhydrous sodium carbonate were added and the mixture was heated under reflux for 24 hours. After cooling the residue was filtered off, washed with methyl ethyl ketone and the combined filtrates were evaporated *in vacuo*. The solid residue consisted of a mixture of the two isomers **2a** and **2b**: TLC analysis (ethyl acetate-petroleum ether 1:3) Rf values 0.32 and 0.46 respectively; gas-chromatographic analysis, retention times 8.01 min (51.56%) and 5.15 min (48.44) respectively. The mixture, adsorbed on 150 g of silica-gel, was fractionated by flash-chromatography through a silica-gel column (30×8 cm), eluting with the TLC solvent mixture. The 2-methylsubstituted compound **2b** was first eluted followed by the 1-methylsubstituted compound **2a**.

Compound **2a** was obtained in 47% yield, 7.31 g; mp 65-68 °C (methanol); ir (cm^{-1}) : 1732 (COOMe); ^{1}H-NMR ($CDCl_3$): δ 4.28 (s, 3H), 4.02 (s, 6H); uv: λ_{max} 242.8 nm, log ε 3.506.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.39; H, 4.58; N, 20.95.

Compound **2b** was obtained in 45% yield, 7.00 g; mp 80-82 °C (methanol); ir (cm^{-1}): 1730 (COOMe); ^{1}H-NMR ($CDCl_3$): δ 4.32 (s, 3H), 3.99 (s, 6H); ms: 199 (M^+), 168 (base); uv: λ_{max} 241.4 nm, log ε 3.350.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.12; H, 4.50; N, 21.25.

1-Methyl-1,2,3-triazole-4,5-dicarboxyhydrazide (**3a**) and 2-Methyl-1,2,3-triazole-4,5-dicarboxyhydrazide (**3b**).

Using suitable safety measures, to a solution of 3.63 g (18.25 mmol) of **2a** or **2b** in 45 mL of methanol, 9.0 mL of 98% hydrazine monohydrate were added and the solution was heated under reflux for 4 hours. After cooling the precipitated solid was collected by filtration and crystallized from water.

Compound **3a** was obtained in 90% yield, 3.28 g; mp 230-233 °C; ir (cm^{-1}): 3295 (NH), 1626 (CO); ms: 200 (MH^+).

Anal. Calcd. for $C_5H_9N_7O_2$: C, 30.15; H, 4.55; N, 49.23. Found: C, 29.91; H, 4.57; N, 49.57.

Compound **3b** was obtained in 91% yield, 3.32 g; mp 218-220 °C; ir (cm^{-1}): 3298, 3186 (NH), 1678 (CO); ms: 200 (MH^+).

Anal. Calcd. for $C_5H_9N_7O_2$: C, 30.15; H, 4.55; N, 49.23. Found: C, 29.78; H, 4.53; N, 48.99.

1-Methyl-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**4a**) and 2-Methyl-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**4b**).

A solution of 5.50 g (27.6 mmol) of **3a** or **3b** in 12 mL of 10% hydrochloric acid was heated under reflux for 6 hours. After cooling the precipitated solid was collected by filtration.

Compound **4a** was obtained in 92% yield, 4.25 g; mp 303-305 °C (methanol); ir (cm^{-1}): 3190 (NH), 1665 (CO). ^{1}H-NMR (DMSO-d_6): δ 12.03 (s, 2H), 4.36 (s, 3H); ms: 168 (MH^+).

Anal. Calcd. for $C_5H_5N_5O_2$: C, 35.93; H, 3.02; N, 41.90. Found: C, 36.08; H, 3.22; N, 42.25.

Compound **4b** was obtained in 91% yield, 4.30 g; mp ≈320 °C (dec.) (ethanol); ir (cm^{-1}): 3172 (NH), 1637 (CO). ^{1}H-NMR (DMSO-d_6): δ 11.80 (s, 2H), 4.46 (s, 3H); ms: 167 (M^+), 167 (base).

Anal. Calcd. for $C_5H_5N_5O_2$: C, 35.93; H, 3.02; N, 41.90. Found: C, 36.12; H, 3.17; N, 41.75.

1-Methyl-4,7-dichloro-1,2,3-triazolo[4,5-*d*]pyridazine (**5**), 1-Methyl-4-chloro-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**6a**) and 1-Methyl-4-hydroxy-7-chloro-1,2,3-triazolo[4,5-*d*]pyridazine (**6b**).

A solution of 3.00 g (18.0 mmol) of **4a** in 34 mL of phosphorus oxychloride was heated under reflux for 5 hours. After cooling the reaction mixture was poured into crushed-ice and the aqueous solution continuously extracted with chloroform. The organic layer, dried and evaporated *in vacuo*, gave a solid residue consisting of **5**, **6a** and **6b**; TLC analysis (acetonitrile-chloroform 2:5) Rf values 0.78, 0.57 and 0.45 respectively. The mixture (1.70 g) was adsorbed on 17 g of silica-gel then fractionated by flash-chromatography through a silica-gel column (15×3 cm) eluting with ethyl acetate-petroleum ether 2:1, in the following order: **5** , **6a** and **6b**.

Compound **5** was obtained in 1.5% yield, 0.056 g; mp 110-113 °C (benzene). ^{1}H-NMR (DMSO-d_6): δ 4.41 (s, 3H); ms : 204 (MH^+).

Anal. Calcd. for $C_5H_3N_5Cl_2$: C, 29.44; H, 1.48; N, 34.33. Found: C, 29.80; H, 1.58; N, 34.14.

Compound **6a** was obtained in 26% yield, 0.870 g; mp 192-194 °C (benzene); ir (cm^{-1}): 3430 (NH), 1680 (CO). ^{1}H-NMR (DMSO-d_6): δ 4.42 (s, 3H), 13.3 (brs, 1H); ms: 186 (MH^+).

Anal. Calcd. for $C_5H_4N_5OCl$: C, 32.36; H, 2.17; N, 37.74. Found: C, 32.26; H, 2.26; N, 37.44.

Compound **6b** was obtained in 19% yield, 0.630 g; mp 240-243 °C (benzene); ir (cm^{-1}): 3181 (NH), 1698 (CO). ^{1}H-NMR (DMSO-d_6): δ 4.28 (s, 3H), 13.2 (brs, 1H); ms: 186 (MH^+).

Anal. Calcd. for $C_5H_4N_5OCl$: C, 32.36; H, 2.17; N, 37.74. Found: C, 32.37; H, 2.06; N, 37.95.

1-Methyl-4-hydrazino-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**7a**) and 1-Methyl-4-hydroxy-7-hydrazino-1,2,3-triazolo[4,5-*d*]pyridazine (**7b**).

Using suitable safety measures, a solution of 0.720 g (3.88 mmol) of **6a** or **6b** in 1.5 mL of 98% hydrazine monohydrate was heated at 120° for 24 hours in a closed tube. After cooling the reaction mixture was treated with slightly acidified water (pH ≈ 5) and the precipitated solid was collected by filtration, washed and crystallized.

Compound **7a** was obtained in 88% yield, 0.620 g; mp 310-313 °C (DMF); ir (cm^{-1}): 3314, 3247, 3186 (NH), 1670 (CO). ^{1}H-NMR (DMSO-d_6): δ 12.0 (s, 1H), 8.12 (s, 1H) 4.39 (s, 3H), 4.06 (s, 1H); ms: 182 (MH^+).

Anal. Calcd. for $C_5H_7N_7O$: C, 33.15; H, 3.89; N, 54.12. Found: C, 33.04; H, 3.80; N, 54.46.

Compound **7b** was obtained in 76% yield, 0.534 g; mp 320-323 °C (DMF); ir (cm^{-1}): 3183, 3113 (NH), 1679 (CO). ^{1}H-NMR (DMSO-d_6): δ 12.0 (s, 1H), 7.51 (s, 1H) 4.39 (s, 3H), 4.18 (s, 1H); ms: 181 (M^+), 42 (base).

Anal. Calcd. for $C_5H_7N_7O$: C, 33.15; H, 3.89; N, 54.12. Found: C, 33.47; H, 4.21; N, 53.89.

3-Methyl-4-hydroxy-1,2,3-triazolo[4,5-*d*]1,2,4-triazolo[3,4-*b*]-pyridazine (**8a**) and 1-Methyl-4-hydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[3,4-*b*]pyridazine (**8b**).

A solution of 0.630 g (3.48 mmol) of **7a** or **7b** in 3 mL of formic acid was heated under reflux for10 hours. After evaporation under reduced pressure, the residue was crystallized.

Compound **8a** was obtained in 78% yield, 0.518 g; mp 310-313 °C (water); ir (cm^{-1}): 3090 (OH). ^{1}H-NMR (DMSO-d_6): δ 9.3 (s, 1H), 4.43 (s, 3H); ms: 191 (M^+), 80 (base).

Anal. Calcd. for $C_6H_5N_7O$: C, 37.70; H, 2.64; N, 51.29. Found: C, 37.98; H, 2.61; N, 50.98.

Compound **8b** was obtained in 81% yield, 0.538 g; mp 313-317 °C (water); ir (cm^{-1}): 3119 (OH). ^{1}H-NMR (DMSO-d_6): δ 9.39 (s, 1H) 4.42 (s, 3H); ms: 191 (M^+), 136 (base).

Anal. Calcd. for $C_6H_5N_7O$: C, 37.70; H, 2.64; N, 51.29. Found: C, 37.47; H, 2.56; N, 51.58.

2-Methyl-4-chloro-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**9**).

A solution of 3.180 g (19.04 mmol) of **4b** in 36 mL of phosphorus oxychloride was heated under reflux for 4 hours. After cooling the reaction mixture was poured into crushed-ice and continuous extracted with chloroform. The organic layer was extracted with 5% sodium hydrogen carbonate, then with 10% sodium hydroxide. By acidification of the first alkaline layer the unreacted starting material **4b** precipitated and was collected by filtration (0.952 g, yield 30%). Acidification of the other alkaline extract precipitated the title compound which was collected and crystallized from benzene: 1.410 g, yield 40%; mp 210-213°C; ir (cm^{-1}): 3142 (NH), 1690 (CO). ^{1}H-NMR (DMSO-d_6): δ 4.47 (s, 3H). 13.3 (brs, 1H); ms: 186 (MH^+).

Anal. Calcd. for $C_5H_4N_5OCl$: C, 32.36; H, 2.17; N, 37.74. Found: C, 32.70; H, 2.33; N, 38.10.

2-Methyl-4-hydrazino-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**10**).

Using suitable safety measures, a mixture of 1.18 g (6.36 mmol) of **9** and 2.5 mL of 98% hydrazine hydrate was heated at 120° for 21 hours in a closed tube. After cooling the formed precipitate was collected by filtration, washed with acidified water (pH ≈5) and crystallized from water to give **10**: 0.633 g, yield 55%; mp 275-280 °C; ir (cm^{-1}); 3308, 3183 (NH), 1672 (CO); ^{1}H-NMR (DMSO-d_6): δ 11.7 (s, 1H), 7.97 (s, 1H), 4.45 (s, 3H), 4.05 (s, 2H); ms: 182 (MH^+).

Anal. Calcd. for $C_5H_7N_7O$: C, 33.15; H, 3.89; N, 54.12. Found: C, 33.50; H, 4.10; N, 54.46.

2-Methyl-4-hydroxy-1,2,3-triazolo[4,5-*d*]1,2,4-triazolo[3,4-*b*]-pyridazine (**11**).

A solution of 0.150 g (0.83 mmol) of **10** in 3 mL of formic acid was heated under reflux for 10 hours. After evaporation under reduced pressure, the residue consisting of **11** was

crystallized from water: 0.120 g, yield 77%; mp 325-329 °C; ir (cm^{-1}): 3074 (OH). ^{1}H-NMR (DMSO-d_6): δ 9.29 (s, 1H), 4.53 (s, 3H); ms: 192 (MH^+).

Anal. Calcd. for $C_6H_5N_7O$: C, 37.70; H, 2.64; N, 51.29. Found: C, 37.42; H, 2.82; N, 51.59.

Methyl 1-*p*-Methoxybenzyl-1,2,3-triazolo-4,5-dicarboxylate (**13**).

To a solution of 5.00 g (31.06 mmol) of *p*-methoxybenzylazide [6] in 60 mL of anhydrous benzene, 4.0 mL (32.6 mmol) of methyl acetylendicarboxylate were added dropwise and the solution was refluxed for 21 hours. The solvent was evaporated *in vacuo* and the viscous liquid residue was purified by short distillation at 220°/1 mmHg to give **13**: 7.80 g, yield 82%; ir (cm^{-1}): 1720 (COOMe); ^{1}H-NMR (DMSO-d_6): δ 7.22-6.87 (AA'BB', 4H), 5.69 (s, 2H), 3.82 (s, 6H), 3.67 (s, 3H); ms: 305 (M^+), 121 (base).

Anal. Calcd. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.95; H, 4.62; N, 14.10.

1-*p*-Methoxybenzyl-1,2,3-triazolo-4,5-dicarboxyhydrazide (**14**).

Using suitable safety measures, to a solution of triazole diester **13** (2.50 g, 8.19 mmol) in 30 mL of methanol, 6.0 mL of 98% hydrazine monohydrate were added and the mixture was refluxed for 4 hours. After cooling the precipitated solid was collected by filtration and crystallized from ethanol: 1.69 g, yield 68%; mp 167-170°C; ir (cm^{-1}): 3348, 3310, 3155, 3032 (NH), 1670 (CO); ^{1}H-NMR (DMSO-d_6): δ 11.8 (s, 1H), 10.5 (s, 1H), 7.25-6.86 (AA'BB', 4 H), 5.96 (s, 2 H), 4.81 (s, 4 H), 3.71 (s, 3 H) ; ms : 305 (M^+), 121 (base).

Anal. Calcd. for $C_{12}H_{15}N_7O_3$: C, 47.21; H, 4.95; N, 32.12. Found: C, 46.87; H, 4.96; N, 32.49.

1-*p*-Methoxybenzyl-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**15**).

A solution of **14** (0.830 g, 2.74 mmol) in 7 mL of 10% hydrochloric acid was heated under reflux for 6 hours. After cooling the precipitated solid was collected by filtration and crystallized from acetonitrile: 0.688 g, yield 92%; mp 232-235 °C; ir (cm^{-1}): 3179 (NH), 1662 (CO); ^{1}H-NMR (DMSO-d_6): δ 12.0 (s, 2H), 7.35-6.87 (AA'BB', 4 H), 5.89 (s, 2 H), 3.70 (s, 3 H); ms: 273 (M^+), 121 (base).

Anal. Calcd. for $C_{12}H_{11}N_5O_3$: C, 52.75; H, 4.06; N, 25.63. Found: C, 52.51; H, 3.95; N, 26.00.

1-*p*-Methoxybenzyl-4-phenylhydrazino-7-hydroxy-1,2,3-triazolo[4,5-d]pyridazine (**16**).

A mixture of **15** (0.390 g, 1.43 mmol), ammonium sulphate (0.040 g, 0.29 mmol), hexamethyldisilazane (2.5 mL, ≈ 12 mmol) and phenylhydrazine (0.770 g, 7.15 mmol) was heated at 140 °C for 24 hours, under stirring. The reaction mixture was evaporated *in vacuo* and the residue was heated in benzene for 30 minutes under reflux. After cooling, the solvent was removed by filtration and the residue was stirred with acidulated water (pH ≈5) for 30 minutes, then collected by filtration: 0.315 g, yield 60%; mp 216-220 °C (DMF-H_2O); ir (cm^{-1}): 3315, 3174 (NH), 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 12.0 (s, 1H), 9.1 (s, 1H), 7.67 (s, 1H), 7.41-6.59 (m, 9 H), 5.89 (s, 2 H), 3.74 (s, 3 H); ms: 363 (M^+), 121 (base).

Anal. Calcd. for $C_{18}H_{17}N_7O_2$: C, 59.50; H, 4.72; N, 26.98. Found: C, 59.17; H, 4.41; N, 27.33.

1-*p*-Methoxybenzyl-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]1,2,4-triazolo[3,4-*b*]pyridazine Zwitterione (**17**).

A solution of 0.080 g (0.22 mmol) of **16** in 2.5 mL of formic acid was heated under reflux for 24 hours. The reaction mixture was evaporated *in vacuo*, the residue treated with water and the insoluble material was collected by filtration: 0.072 g, yield 87%; mp >300 °C dec. (DMF-H_2O); ir (cm^{-1}): 1684 (CO);

^{1}H-NMR (DMSO-d_6): δ 11.2 (s, 1H), 8.09-7.67 (AA'BB', 4 H), 6.78 (s, 5H), 5.89 (s, 2 H), 3.66 (s, 3 H); ms: 375 (M^+), 121 (base).

Anal. Calcd. for $C_{19}H_{15}N_7O_2$: C, 61.12; H, 4.05; N, 26.26. Found: C, 60.76; H, 4.01; N, 26.52.

Acknowledgment.

We thank Dr. Laura Betti and Dr. Maria Letizia Trincavelli of the Psychiatry, Neurobiology, Pharmacology and Biotechnology Department, Pisa University, for the biological test evaluation.

REFERENCES AND NOTES

[1] G. Biagi, I. Giorgi, O. Livi, C. Manera and V. Scartoni, *J. Heterocyclic Chem.* **34**, 65 (1997).

[2] Y. Tanaka, S. R. Velen and S. I. Miller, *Tetrahedron*, **29**, 3271 (1973).

[3] G. Le Hetet, R. Danion-Bougot and R. Carrie, *Bull. Soc. Chim. Belg.* **105**, 259 (1996).

[4] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, A. Lucacchini, G. Senatore and P. L. Barili, *Farmaco*, **49**, 357 (1994).

[5] G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, A. Lucacchini and G. Senatore, *Farmaco*, **51**, 601 (1996).

[6] D. R. Buckle and C. J. M. Rockell, *J. Chem. Soc. Perkin Trans I*, 627 (1982).

[7] H. Vorbruggen and K. Krolikiewicz, *Chem. Ber.* **117**, 1523 (1984).

[8] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, S. Velo, C. Martini, G. Senatore and P. L. Barili, *Farmaco*, **50**, 99 (1995).

[9] G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, L. Betti, G. Giannaccini and A. Lucacchini, *Farmaco*, **54**, 615 (1999).