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Short communication

Synthesis and pharmacological activity of some new pyridazinones

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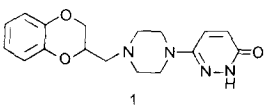
Summary — The synthesis of a series of piperazinyl-pyridazinones is reported. The blocking activity of these compounds was determined on the pre- and postsynaptic α-adrenoreceptors of isolated rat vas deferens. For compounds **7**, **17** and **18**, the hypotensive activity was also evaluated.

pyridazinone / α-adrenoreceptors / α-antagonist / structure–activity relationship / rat vas deferens / hypotensive activity

Introduction

Pyridazinone derivatives show many pharmacological activities: reduction of blood pressure [1], inhibition of platelet aggregation [2], positive inotropic activity [3]. Recently we have reported that the pyridazinone **1** [4] shows high and long lasting hypotensive effects, which must be attributed to α_1-receptor blocking activity. We have considered of interest to synthesize a series of 6-piperazinyl-3(2H)-pyridazinones variously N-4 substituted and to test their activity on the α-receptors.



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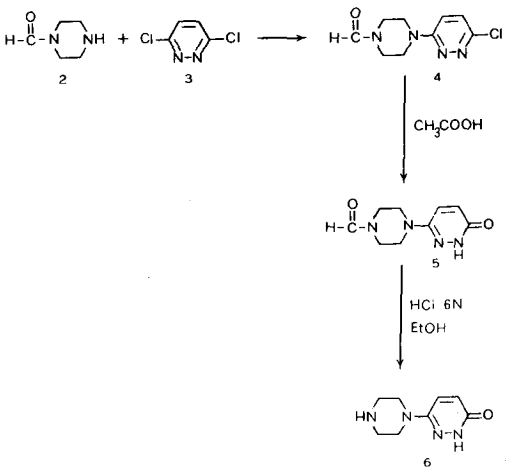
Chemistry

The 6-piperazinyl-3(2H)-pyridazinone (**6**) required as starting material was prepared by alkylation of 1-formylpiperazine with 3,6-dichloropyridazine, followed by hydrolysis with glacial acetic acid, then by heating with 6 N HCl in ethanol (scheme 1). The 6-piperazinyl-3(2H)-pyridazinone derivatives were synthesized by condensation of **6** with the appropriate halogenide, as reported in scheme 2.

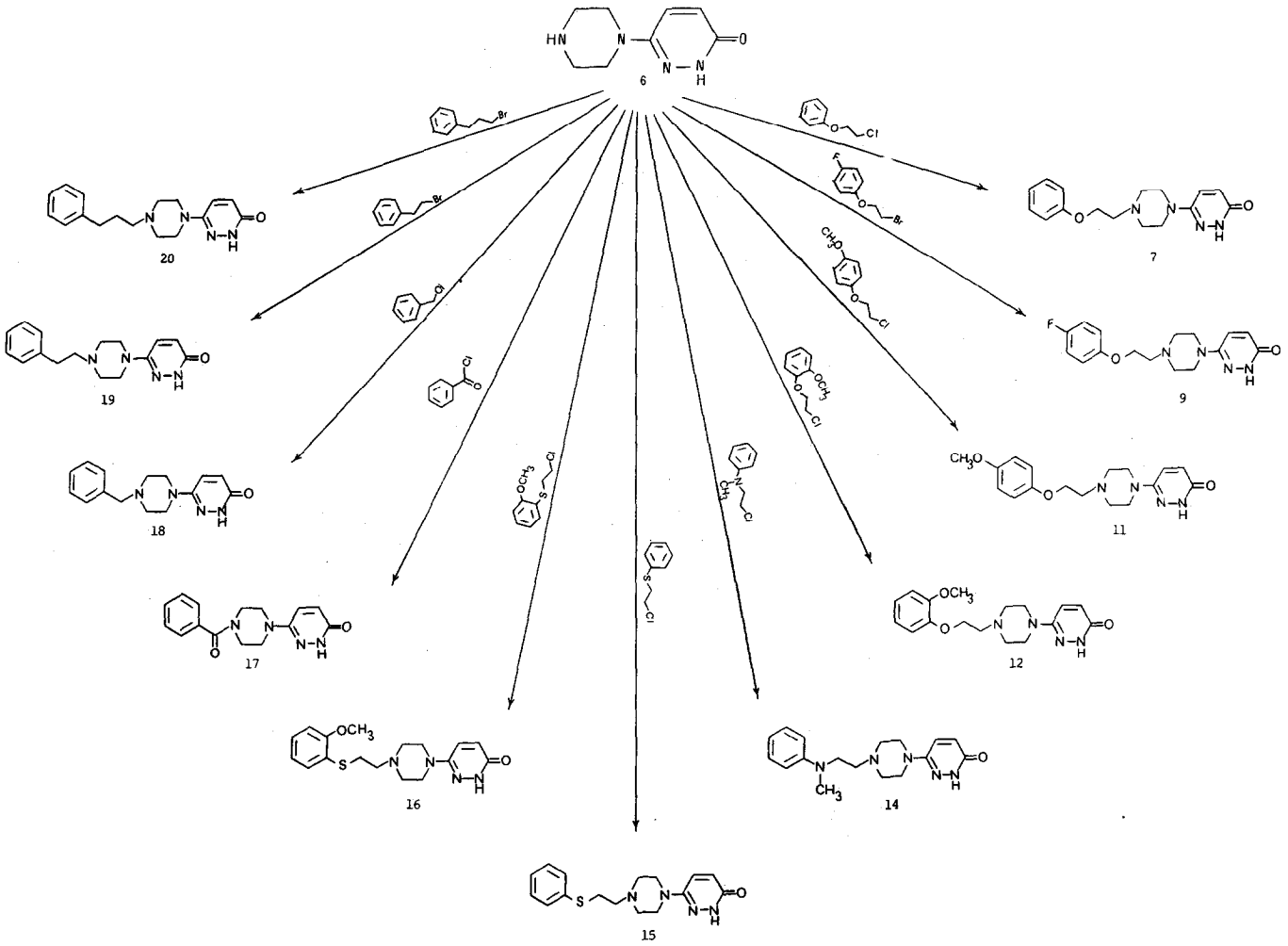


Scheme 1.

Results and discussion

The blocking activity on pre- and-post-synaptic α-adrenoreceptors was determined and the results are reported in table I; moreover for compounds **7**, **17** and **18** the hypotensive activity was determined on anesthetized cats (table II).

The replacement of the benzodioxane ring of **1** with a benzyl group or a benzoyl group gives inactive compounds (**18**, **17**). The replacement with phenyl-



Scheme 2.

ethyl group and phenylpropyl group gives slightly active compounds (**19**, **20**) whereas the phenoxyethyl bioisoster of **20** (compound **7**) exhibits an activity comparable to that of compound **1**. The introduction of an *o*-methoxy substituent on the phenyl group of **7** (**12**) increases activity, contrary to the *p*-methoxy (**11**) and the *p*-fluoro (**9**) substitution. The replacement of the oxygen atom of **7** or **12** with the less electronegative sulfur (**15**, **16**), as well as with a -N-CH_3 (**14**) markedly reduces activity.

These results show that the presence of an oxygen atom is necessary for the activity, probably because of the formation of a hydrogen bond with the receptor. Since the opened analogue **12** shows the same α_1-blocking activity as **1**, the benzodioxane nucleus seems not essential. Finally, comparison of the results presented in tables I and II shows a good relationship between α_1-blocking and hypotensive activities.

Experimental protocols

Materials and methods

Hypotensive activity

The compounds under investigation were administered intravenously to anesthetized cats at doses of 0.3, 1 and 3 mg/kg. The products were tested for their effect on arterial blood pressure and heart rate (table II).

Blocking activity on the pre- and postsynaptic α-adrenoreceptors of isolated rat vas deferens

Male albino rats (175–200 g) were killed by a sharp blow to the head and both vasa deferentia were isolated free from adhering connective tissue. A section of *ca* 2 cm of the epididymal or prostatic portion of the vas deferens was excised to study postsynaptic or presynaptic α-blocking activities, respectively. These isolated organs were mounted individually in baths of 20 ml working volume containing Krebs solution of the following composition: 118.4 mM NaCl, 4.7 mM KCl,

Table I. Blocking activity on the α_2- and α_1-adrenoceptors of isolated rat vas deferens.

Compound	*pKb* α_1	*pKb* α_2
1	6.05 ± 0.057	5.92 ± 0.052
7	5.74 ± 0.018	5.52 ± 0.039
9	4.89 ± 0.066	4.88 ± 0.018
11	< 4.52	< 4.52
12	6.09 ± 0.040	4.86 ± 0.031
14	4.83 ± 0.020	NA
15	4.77 ± 0.029	NA
16	NA	NA
17	NA	NA
18	NA	NA
19	5.24 ± 0.069	NA
20	5.38 ± 0.067	5.07 ± 0.041

Table II. Hypotensive activity: % variations of the response. MAP = mean arterial pressure, HR = heart rate.

Compound	*Dose mg/kg*	*Animal no*	*MAP Δ mmHg*	*HR Δb/min*
	0.3	1	− 35	− 10
1	1.0	1	− 48	− 3
	3.0	2	Continuous fall in pressure up to the animal's death	
	0.3	2	− 29	+ 1
7	1.0	2	− 35	+ 5
	3.0	5	− 47	+ 12
	0.3	1	0	0
17	1.0	1	− 9	0
	3.0	2	+ 2	+ 16
	0.3	1	0	− 5
18	1.0	1	− 7	0
	3.0	2	− 16	+ 14

2.52 mM $CaCl_2$, 1.2 mM $MgSO_4 \cdot 7H_2O$, 1.2 mM KH_2PO_4, 25.0 mM $NaHCO_3$, 11.1 mM glucose. The concentration of $MgSO_4 \cdot 7H_2O$ was reduced to 0.6 mM when the twitch response to field stimulation was studied. The medium was maintained at 37°C and gassed with 95% O_2–5% CO_2. The loading tension was 0.4 g or 0.5–0.8 g to assess post- or presynaptic α-blocking activities respectively, and the contractions were recorded by means of force transducers connected to a two-channel Gemini 7070 polygraph. The field stimulation of the tissues was carried out by means of two platinum electrodes, placed near the top and the bottom of the vas deferens at 0.1 Hz using square pulses of 3 ms duration at a voltage of 10–15 V. The stimulation voltage was fixed throughout the experiments. Propranolol hydrochloride (1 μM) and cocaine hydrochloride (10 μM) were present in the Krebs solution throughout the experiments outlined below to block the adrenergic β-receptor and neuronal and extraneuronal uptake mechanisms respectively. The biological results were expressed as pKb.

Postsynaptic α-blocking activity was determined on the epididymal portion of the vas deferens. The tissues were allowed to equilibrate for at least 30 min before the addition of any drug. Cumulative dose–response curves to (–)NA were obtained for each tissue at 30-min intervals, a second curve being used as control. It was verified that a third dose–response curve was always identical to the second. Each antagonist was incubated for 30 min before the initial challenge with NA. The DR-1 was calculated at the concentration of 10^{-5} M and at this concentration the compounds were tested at least five times.

Presynaptic α-blocking activity was assessed by the antagonism with the adrenergic α_2-receptor agonist clonidine. Clonidine inhibits twitch responses of the field-stimulated vas deferens by acting on the presynaptic adrenergic α_2-receptor [5, 6]. The procedure reported by Drew [5] was therefore used. In other tissues the dose–response curves were determined after 30 min incubation with the antagonist. Each antagonist was tested at 10^{-5} M concentration, and this concentration was investigated at least five times. Dose ratio (DR) values were then determined from the concentrations causing 50% inhibition of the twitch response in the absence and in the presence of the antagonist.

Chemical synthesis

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The NMR spectra were recorded with a Varian EM-390 (90 MHz) instrument in the solvents indicated. The chemical shift values (ppm) are relative to tetramethylsilane as the internal standard. Mass spectra were measured with Varian Mat 311. Elemental analyses are within ± 0.4% of the theoretical values. Precoated Kieselgel 60 F 254 plates (Merck) were used for TLC .

6-(4-Formyl-1-piperazinyl)-3-chloropyridazine ***4***

A mixture of 10 g ($6.7\ 10^{-2}$ mol) of 1-formylpiperazine, 7.65 g ($6.7\ 10^{-2}$ mol) of 3,6-dichloropyridazine in 200 ml of anhydrous EtOH, was refluxed for 16 h. The mixture after concentration under reduced pressure, was purified by flash-chromatography using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. Yield: 50%, mp 155–160°C; ^{1}H NMR ($CDCl_3$) δ: 3.3–3.8 (8H, m, piperazinic H), 6.8 (1H, d, J = 9 Hz, pyridazinic H), 7.2 (1H, d, J = 9 Hz, pyridazinic H), 8.0 (1H, s, HCO). Mass $C_9H_{11}ClN_4O$: M^+.

6-(4-Formyl-1-piperazinyl)-3(2H)-pyridazinone ***5***

A solution of 2 g ($8.8\ 10^{-3}$ mol) of **4** in 25 ml of glacial acetic acid, was refluxed for 8.5 h. After concentration under reduced pressure the residue was purified by flash-chromatography using CH_2Cl_2/EtOH 9/1 as eluent. Yield: 60%, mp 205–210°C; ^{1}H NMR ($CDCl_3$) δ: 3.1–3.3 (4H, m, piperazinic H), 3.4–3.6 (4H, m, piperazinic H), 6.8 (1H, d, J = 10 Hz, pyridazinonic H), 7.4 (1H, d = 10 Hz, pyridazinonic H), 8.0 (1H, s, HCO), 12 (1H, s, NHCO).

6-Piperazinyl-3(2H)-pyridazinone ***6***

A solution of 2 g ($3.6\ 10^{-3}$ mol) of **5** in 33 ml of 6 N HCl in 140 ml of EtOH was refluxed for 12 h. After cooling the solution was concentrated under reduced pressure and the residue crystallized from ethanol to give **6** as the hydrochloride, mp 298–305°C. The free base was obtained by treatment of the hydrochloride with a $NaHCO_3$ solution at pH 8. The mixture

was evaporated to dryness and extracted several times by heating with ethyl acetate. The solution was dried over Na_2SO_4 anhydrous and evaporated *in vacuo*, a dense oil was obtained. Yield: 40%; ^1H NMR ($CDCl_3$) δ: 2.0 (1H, s, NH), 2.7–3.0 (4H, m, piperazinic H), 3.1–3.3 (4H, m, piperazinic H), 6.7 (1H, d = 10 Hz, pyridazinonic H), 7.1 (1H, d, J = 10 Hz, pyridazinonic H), 12 (1H, s, NHCO). Anal $C_8H_{14}Cl_2N_4O$ = 252.8.

6-[4-(2-Phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone **7**
A solution of 2.3 g (1.2 10^{-3} mol) of **6**, 2 g (1.2 10^{-3} mol) of 2-phenoxyethylchloride [7] in 50 ml of anhydrous ethanol, was refluxed for 8 h. The solvent was removed under reduced pressure, the residue was purified by flash-chromathography using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. Yield: 40%, mp 135–140°C; ^1H NMR ($CDCl_3$) δ: 2.6–2.7 (4H, m, piperazinic H), 2.8 (2H, t, J = 6 Hz, CH_2), 3.2–3.4 (4H, m, piperazinic H), 4.2 (2H, t, J = 6 Hz, CH_2), 6.8–7.0 (4H, m, aromatic 3H, pyridazinonic 1H), 7.2–7.4 (3H, m, aromatic 2H, pyridazinonic 1H), 12.5 (1H, s, NHCO). Anal $C_{16}H_{20}N_4O_2$ = 300.0. The corresponding hydrochloride shows mp 185–189°C.

2-(4-Fluorophenoxy)-ethylbromide **8**
To a solution of 1.25 g of NaOH in 25 ml MeOH , was added 5 g (4.4 10^{-2} mol) of 4-fluorophenol and 8.2 g (4.4 10^{-2} mol) of 1,2-dibromoethane. The mixture was refluxed for 15 h. Subsequently it was concentrated under reduced pressure, and the residue dissoved in CH_2Cl_2, was washed with a solution of NaOH 5%. The solution dried over Na_2SO_4 anhydrous was concentrated under reduced pressure and the residue was purified by chromatography using hexane as eluent. Yield: 50%, mp 55–60°C; ^1H NMR ($CDCl_3$) δ: 2.8 (2H, t, J = 6 Hz, CH_2), 4.0 (2H, t, J = 6 Hz, CH_2) 6.7–7.0 (4H, m, aromatic H).

6-{4-[2-(4-Fluorophenoxy)ethyl]-1-piperazinyl}-3(2H)-pyridazinone **9**
It was prepared from 2-(4-fluorophenoxy)-ethylbromide (**8**) and **6**. Yield: 30%, mp 154–156°C; ^1H NMR ($CDCl_3$) δ: 2.5–2.8 (6H, m, CH_2, piperazinic 4H), 3.5–3.7 (4H, m, piperazinic H), 4.0 (2H, t, J = 6 Hz, CH_2), 6.6–7.0 (6H, m, pyridazinonic 2H, aromatic H), 12.0 (1H, s, NHCO). Anal $C_{16}H_{19}N_4FO_2$ = 318.0. The corresponding hydrochloride shows mp 234–237°C.

2-(4-Methoxyphenoxy)-ethylchloride **10**
1.2 g (9.6 10^{-3} mol) of 4-methoxyphenol and 1.5 g (1.0 10^{-2} mol) of 2-bromo-1-chloroethane were added to a solution of 0.3 g of sodium hydroxide in 6 ml of methanol, the mixture was refluxed for 22 h. After evaporation under reduced pressure, the residue was diluted with water and extracted with ethyl ether. The organic phase was washed with water, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography on silica gel using as eluent a stepwise gradient of ether (0–10%) in hexane. Yield: 30%, mp 47–48°C; ^1H NMR ($CDCl_3$) δ: 3.6–3.8 (5H, m, OCH_3, CH_2) 4.1 (2H, t, J = 6 Hz, CH_2), 6.8 (4H, s, aromatic H). Mass $C_9H_{11}ClO_2$: M^+.

General method for the preparation of compounds ***11***, ***12***, ***14–16***, ***18–20***. *Typical procedure*

6-[4-(4-Methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone **11**
A mixture of 0.58 g (3.0 10^{-3} mol) of 2-(4-methoxyphenoxy)-ethylchloride and 0.56 g (3.0 10^{-3} mol) of **6** in 45 ml of isoamyl alcohol, was refluxed for 2–3 h. After cooling the mixture was concentrated *in vacuo* and the residue was diluted with water, alkalinized with 1 N NaOH and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the residue was purified by flash-chromatography using as eluent a stepwise gradient of ethanol (0–20%) in CH_2Cl_2. Yield: 30%, mp 153–156°C; ^1H NMR ($CDCl_3$) δ: 2.5–2.8 (6H, m, CH_2, piperazinic 4H), 3.1–3.3 (4H, m, piperazinic H), 3.7 (3H, s, OCH_3), 4.0 (2H, d, J = 6 Hz, CH_2), 6.6–6.8 (5H, m, pyridazinonic H, aromatic 4H), 7.1 (1H, d, J = 10 Hz, pyridazinonic H), 12.5 (1H, s, NHCO). Anal $C_{17}H_{22}N_4O_3$ = 330.0. The corresponding hydrochloride shows mp 189–194°C.

6-[4-(2-Methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone **12**
Prepared from 2-(2-methoxyphenoxy)-ethylchloride [8] and **6**. Yield: 70%, mp 76–78°C; ^1H NMR ($CDCl_3$) δ: 2.6–2.7 (4H, m, piperazinic H), 2.8 (2H, t, J = 6 Hz, CH_2), 3.5–3.7 (4H, m, piperazinic H), 3.8 (3H, s, OCH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 6.6–6.8 (5H, m, pyridazinonic H, aromatic 4H), 7.0 (1H, d, J = 10 Hz, pyridazinonic H), 12.0 (1H, s, NHCO). Anal $C_{17}H_{22}N_4O_3$ = 330.0. The corresponding hydrochloride shows mp 205–208°C.

2-(N-Methyl-N-phenyl)-ethylaminochloride **13**
To a solution of 3.2 g (2.9 10^{-2} mol) of N-methylaniline in 50 ml of 2-butanone, was added 3 g of Na_2CO_3 anhydrous, and 4.7 g (3.2 10^{-2} mol) of 1-bromo-2-chloroethane, the mixture was refluxed for 30 h. After cooling the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash-chromatography using hexane as eluent. Yield: 30%; ^1H NMR ($CDCl_3$) δ: 3.0 (3H, s, CH_3), 3.3–3.7 (4H, m, $2CH_2$), 6.5–6.7 (3H, m, aromatic H), 7.0–7.3 (2H, m, aromatic H).

6-{4-[2-(N-Phenyl-N-methyl), ethylamino]-1-piperazinyl}-3(2H)-pyridazinone **14**
This was prepared from 2-(*N*-phenyl-*N*-methyl)-ethylaminochloride (**13**) and **6**, purified by flash-chromatography using as eluent a stepwise gradient of ethanol (0–50%) in ethyl acetate. Yield: 30%, mp 165–170°C; ^1H NMR ($CDCl_3$) δ: 2.3–2.6 (6H, m, piperazinic 4H, CH_2), 2.9 (3H, s, CH_3), 3.1–3.4 (6H, m, piperazinic H, CH_2), 6.5–7.1 (7H, m, pyridazinonic 2H, aromatic 5H), 12.0 (1H, s, NHCO). Anal $C_{17}H_{23}N_5O$ = 313.0.

6-[4-(2-Phenylthioethyl)-1-piperazinyl]-3(2H)-pyridazinone **15**
It was prepared from 2-phenylthioethylchloride [9] and **6**, purified by flash-chromatography using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. Yield: 25%; ^1H NMR ($CDCl_3$) δ: 2.4–2.7 (6H, m, CH_2, piperazinic 4H), 3.2–3.4 (6H, m, CH_2, piperazinic 4H), 6.7 (1H, d, J = 10 Hz, pyridazinonic H), 7.1–7.3 (6H, m, pyridazinonic H, aromatic 5H), 12.0 (1H, s, NHCO). The corresponding hydrochloride shows mp 170–175°C. Anal $C_{16}H_{22}Cl_2N_4OS$ = 388.8.

6-{4-[2-(2-Methoxy-phenylthio)ethyl]-1-piperazinyl}-3(2H)-pyridazinone **16**
It was prepared from 2-(2-methoxyphenylthio)ethylchloride [8] and **6**, purified by flash-chromathography using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. Yield: 40%, ^1H NMR ($CDCl_3$) δ: 2.4–2.7 (6H, m, CH_2, piperazinic 4H), 3.2–3.4 (6H, m, CH_2, piperazinic 4H), 3.9 (3H, s, OCH_3), 6.7–7.2 (6H, m, aromatic 4H, pyridazinonic H), 12.5 (1H, s, NHCO). The corresponding hydrochloride shows mp 225–230°C. Anal $C_{17}H_{24}Cl_2N_4O_2S$ = 418-8.

6-[4-Benzyl-1-piperazinyl]-3(2H)-pyridazinone ***18***
It was prepared from benzylchloride and **6**, purified by flash-chromatography using a stepwise gradient of ethanol in CH_2Cl_2. Yield: 30%, mp 155–163°C; ^1H NMR ($CDCl_3$) δ: 2.4–2.6 (4H, m, piperazinic H), 3.1–3.4 (4H, m, piperazinic H), 3.5 (2H, s, CH_2), 6.75 (1H, d, J = 10 Hz, pyridazinonic H), 7.1 (1H, d, J = 10 Hz, pyridazinonic H), 7.2 (5H, s, aromatic H), 12.0 (1H, s, NHCO). The corresponding hydrochloride shows mp 209–214°C. Anal $C_{15}H_{20}Cl_2N_4O$ = 342.8.

6-[4-(2-Phenylethyl)-1-piperazinyl]-3(2H)-pvridazinone ***19***
It was prepared from 2-phenylethylbromide and **6**, the residue was purified by flash-chromatography using as eluent a stepwise gradient of ethanol in CH_2Cl_2. Yield: 40%, mp 163–168°C; ($CDCl_3$) δ: 2.3–2.8 (m, 8H, piperazinic 4H, $2CH_2$), 3.2–3.4 (4H, m, piperazinic H), 6.8 (1H, d, J = 10 Hz, pyridazinonic H), 7.0–7.3 (6H, m, aromatic 5H, pyridazinonic H), 12.5 (1H, s, NHCO). Anal $C_{16}H_{20}N_4O$ = 284.0. The corresponding hydrochloride shows mp 193–198°C.

6-[4-(3-Phenylpropyl)-1-piperazinyl]-3(2H)-pyridazinone ***20***
It was prepared from 3-phenylpropylbromide and **6**. Yield: 60%, mp 154–158°C; ^1H NMR ($CDCl_3$) δ: 2.4–2.7 (10H, m, CH_2, piperazinic ring), 3.1–3.3 (4H, m, 2 CH_2), 7.0–7.3 (7H, m, pyridazinonic 2H, aromatic 5H), 12.5 (1H, s, NHCO). Anal $C_{17}H_{22}N_4O$ = 298.0. The corresponding hydrochloride shows mp 190–194°C.

6-[4-Benzoyl-1-piperazinyl)-3(2H)-pyridazinone ***17***
To 0.8 g (2.7 10^{-3} mol) of **6** dissolved in 20–25 ml of $CHCl_3$, was added 1.5 g of $NaHCO_3$ and 0.33 g (2.7 10^{-3} mol) of benzoyl chloride. The mixture was stirred at room temperature for 24 h. After removal of $NaHCO_3$ by filtration, the filtrate was concentrated and the residue was purified by flash-chromatography using CH_2Cl_2/MeOH as eluent. The residue was crystallized from ethyl acetate. Yield: 30%, mp 225–230°C; ^1H-NMR ($CDCl_3$) δ: 3.2–3.4 (4H, m, piperazinic H), 3.5–3.8 (4H, m, piperazinic H), 6.9 (1H, d, J = 10 Hz, pyridazinonic H), 7.2 (1H, d, J = 10 Hz, pyridazinonic H), 7.4 (5H, s, aromatic H), 12.5 (1H, s, NHCO). Anal $C_{15}H_{16}N_4O_2$ = 284.0. The corresponding hydrochloride shows mp 163–168°C.

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References

1 Curran WV, Ross A (1974) *J Med Chem* 17, 273–281
2 Thyes M, Lehmann MD, Gries J, Konig H, Kretzschmar R, Kunze J, Lebkucher R, Lenke D (1983) *J Med Chem* 26, 800–807
3 Sircar I, Duell BL, Bobowski G, Bristol JA, Evans DB (1985) *J Med Chem* 28, 1405–1413
4 Corsano S, Strappaghetti G, Codagnone A (1989) *Arch Pharm* 322, 833–836
5 Drew GM (1977) *Eur J Pharmacol* 42, 123–130
6 Doxey JC, Smith CF, Walker JM (1977) *Br J Pharmacol* 60, 91–96
7 Zikolova SV, Naumova M (1972) *Tr Nauchnoizsled Khim-Farm Inst* 8, 41–48
8 Strappaghetti G, Brasili L (1986) *Il Farmaco* 41, 794–800
9 Angeletti E, Montanari F, Negrini A (1957) *Gazz Chim Ital* 87, 1115–1124