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Short communication

New pyridazinones: synthesis and correlation between structure and α-blocking activity

S Corsano[1], R Scapicchi[1], G Strappaghetti[1]*, G Marucci[2], F Paparelli[2]

[1]*Institute of Pharmaceutical Chemistry, University of Perugia, Perugia;*
[2]*Department of Chemical Sciences, University of Camerino, 62032, Camerino, Italy*

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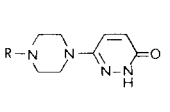
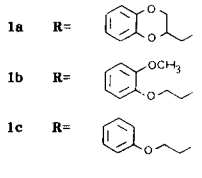
Summary — The synthesis of a series of 5-(4-piperazinyl)-3(2*H*)-pyridazinone has been reported. The blocking activity of these compounds was determined on the pre- and postsynaptic α-adrenoreceptors of isolated rat vas deferens.

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

Introduction

A great amount of attention has been paid to the compounds containing a 3(2*H*)-pyridazinone moiety due to its biological activity [1–3]. Recently, we have described the synthesis and α-adrenolytic effect of a series 6-piperazinyl-3(2*H*)-pyridazinone [4]. The results showed that the benzodioxane (**1a**), the 2-methoxyphenoxyethyl (**1b**) and phenoxyethyl group (**1c**), are indispensable for α-blocking activity. As an extension of this work, in order to better define the structural requirements for optimum activity, we carried out the synthesis of compounds in which the pyridazinone ring is attached in the 5-position to the benzodioxanyl, the 2-methoxyphenoxyethyl or the phenoxyethyl group through the piperazinic ring; furthermore, we synthesized compounds in which the acid hydrogen of the pyridazinone ring was differently substituted.





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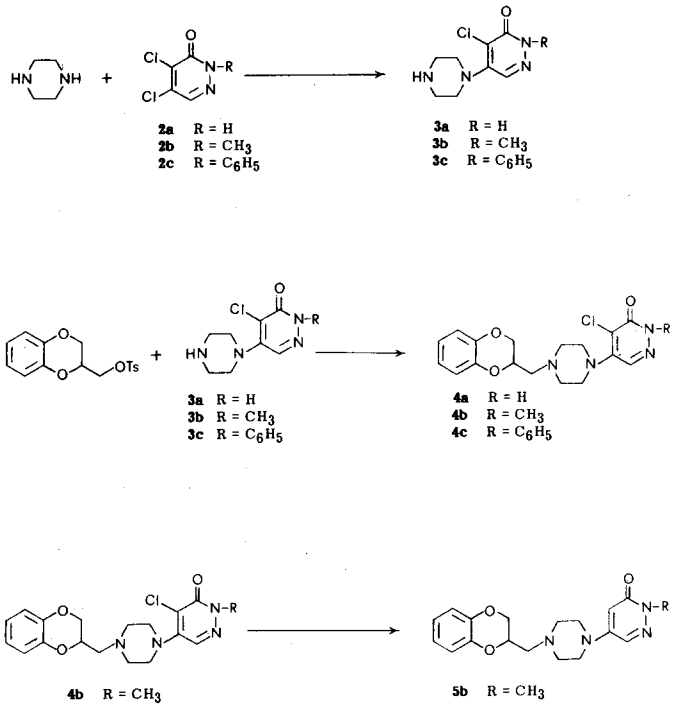
Chemistry

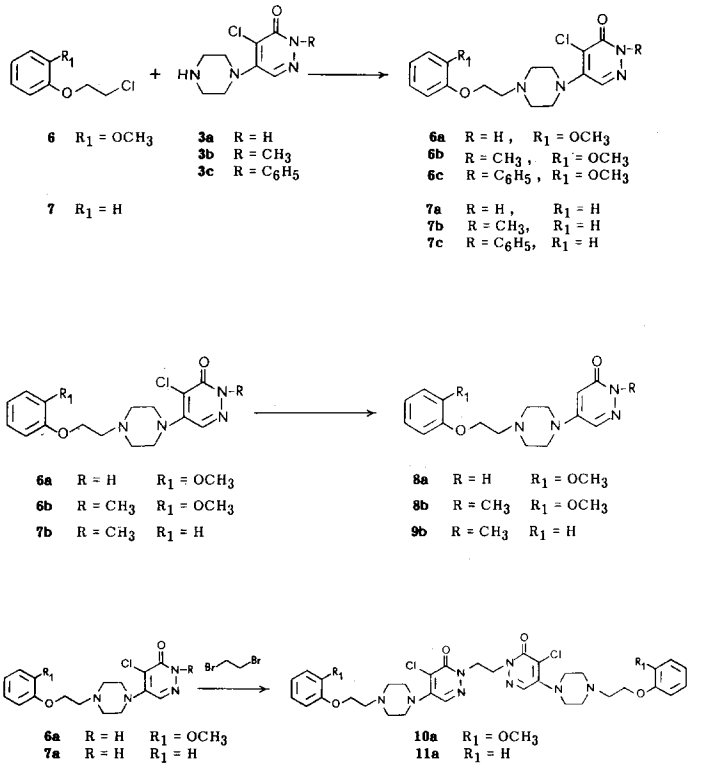
The 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone **3a** 2-methyl-4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone **3b** and 2-phenyl-4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone **3c** required as starting material were prepared by alkylation of piperazine with 4,5-dichloro-3(2*H*)-pyridazinone, 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone, 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinone. Alkylation of the appropriate 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinones with 2-tosyloxymethyl-1,4-benzodioxane, 2-(2-methoxy-phenoxy)-ethylchloride and 2-phenoxyethylchloride gave compounds **4a–c**; **6a–c**; and **7a–c**. Compounds **4b**, **6a**, **6b**, **7b**, were hydrogenated catalytically using 10% palladium on carbon at atmospheric pressure and gave **5b**, **8a**, **8b**, **9b**; alkylation of 2 mol **6a** and **7a** with 1 mol of 1,2-dibromoethane and NaOH in dry EtOH yielded compounds **10a** and **11a** (schemes 1, 2).

Results and discussion

The biological profile of investigated compounds at α_1-and α_2-adrenoreceptors was assessed on epididymal and prostatic portions of isolated rat vas deferens. The biological results (table I) were expressed in pK_b. It is evident that these compounds displayed a preferential blockade of the postsynaptic α-adrenoreceptor. Compounds **4a**, **6a** and **7a** showed increased activity



Scheme 1.



Scheme 2.

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

Compound	α_1	α_2	**Selectivity ratio* α_1/α_2
	pK_b	pK_b	
4a	6.57 ± 0.10	6.39 ± 0.047	1.5
4b	6.41 ± 0.092	6.63 ± 0.14	1.5
4c	6.55 ± 0.039	5.99 ± 0.025	4
5b	6.10 ± 0.091	6.68 ± 0.062	0.26
6a	7.29 ± 0.041	5.97 ± 0.024	21
6b	6.89 ± 0.067	5.50 ± 0.077	25
6c	6.96 ± 0.076	5.40 ± 0.034	36
7a	7.10 ± 0.10	6.18 ± 0.096	8.3
7b	6.31 ± 0.086	5.80 ± 0.092	3
7c	6.61 ± 0.11	5.41 ± 0.051	16
8a	6.24 ± 0.019	5.26 ± 0.15	9.5
8b	5.50 ± 0.1	4.76 ± 0.054	5.5
9b	5.60 ± 0.12	4.31 ± 0.15	19
10a	7.00 ± 0.084	5.14 ± 0.029	72
11a	6.68 ± 0.097	4.86 ± 0.07	66

*The selectivity ratio is the antilog of the difference between the pK_b values at post- and presynaptic α-adrenoreceptors.

in the comparison with compounds **1a–c** [4], in which the same groups were linked in the 6-position of the pyridazinone ring. These results also confirm that the benzodioxane ring is not necessary for the activity; in fact, the phenoxy group (**7a**) is sufficient and the activity increases *via* the presence of the methoxy group in the *ortho* position (**6a**). The substitution of the acid hydrogen of the pyridazinone ring with a methyl or a phenyl group (compounds **4b**, **4c**, **6b**, **6c** , **7b** and **7c**), leads to a reduction of the activity; this diminution is more pronounced when the substituent is the methyl group. The chlorine in the 4-position of the pyridazinone ring is necessary for the activity; in fact, the corresponding dehalogenated compounds (compounds **5b**, **8a**, **8b** and **9b**) show a reduction of activity; we are of the opinion that the chlorine interacts with the receptor through an electrostatic bond. Finally the dimers **10a** and **11a** show very interesting activity; although their activity on the α_1-adrenoreceptor is less that of **6a** and **7a**, they show good selectivity (ratio α_1/α_2, 72:66 respectively). We shall continue this study by lengthening the ethylenic chain in order to obtain more information on the interaction with the pharmacophores.

Experimental protocols

Material and methods

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 on the head and both vasa deferentia were isolated free from adhering connective tissue. A section of ≈ 2 cm of the epididymal or prostatic portion of the vas deferens was excised to study postsynaptic or presynaptic α-blocking activity, respectively. The isolated organs were mounted individually in baths of 20 ml working vol containing Krebs solution of the following composition: 118.4 mM NaCl, 4.7 mM KCl, 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 activity respectively, and the contractions were recorded by means of force transducers connected to a 2-channel Gemini 7070 polygraph. Field stimulation of the tissues was carried out by means of 2 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 in pK_b.

Postsynaptic α-blocking activity was determined on the epididymal portion of the vas deferens. The tissue 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 dose ratio, DR-1, was calculated at a concentration of 10^{-6} M and the compounds tested at least 5 times at this concentration.

Presynaptic α-blocking activity was assessed by 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 5 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 internal standard. Mass spectra were measured with Varian Mat 311. Elemental analyses are within ± 0.4% of theoretical values. Precoated Kieselgel 60 F 254 plates (Merck) were used for TLC. The corresponding hydrochlorides were prepared by bubbling of dry HCl into dry solution of the compound.

*General method for the preparation of compounds **3a, 3b, 3c***

*4-Chloro-5-(1-pinerazinyl)-3(2H)-pyridazinone **3a***

A mixture of 4.5 g ($2.7 \cdot 10^{-2}$ mol) of 4,5-dichloro-3(2*H*)-pyridazinone [7], 3.05 g ($3.5 \cdot 10^{-2}$ mol) of piperazine and 2.7 g ($2.7 \cdot 10^{-2}$ mol) of $(C_2H_5)_3N$ in 90 ml anhydrous EtOH was refluxed for 4 h. The mixture was filtered, the solid purified by flash-chromatography using EtOAc/MeOH (2/8) as eluent, crystallized from MeOH. Yield: 40%, mp: 265–268°C; ^{1}H-NMR (DMSO-d_6) δ: 2.9–3.1 (5H, m, piperazinic H, NH), 3.3–3.5 (4H, m, piperazinic H), 7.7 (1H, s, H6-pyridazinonic).

*2-Methyl-4-chloro-5-(1-piperazinyl)-3(2H)-pyridazinone **3b***

This was prepared by alkylation of 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone [8] with piperazine, purified by flash-chromatography using CH_2Cl_2/EtOH (1/1) as eluent; a dense oil was obtained. Yield: 50%, ^{1}H-NMR ($CDCl_3$) δ: 2.9–3.1 (5H, m, piperazinic H, NH), 3.3–3.4 (4H, m, piperazinic H), 3.8 (3H, s, N-CH_3), 7.6 (1H, s, H6-pyridazinonic).

*2-Phenyl-4-chloro-5-(1-piperazinyl)-3(2H)-pyridazinone **3c***

This was prepared by alkylation of 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinone [9] with piperazine in dry EtOH, and crystallized from ethyl acetate. Yield: 50%; mp: 142–143°C; ^{1}H-NMR ($CDCl_3$) δ: 2.5–2.8 (5H, m, piperazinic H, NH), 3.2–3.3 (4H, m, piperazinic H), 7.2–7.4 (5H, m, aromatic H), 7.6 (1H, s, H6-pyridazinonic).

*General method for the preparation of compounds **4a–c***

*4-Chloro-5-[4-(methyl-1,4-benzodioxane)-1-piperazinyl]-3(2H)-pyridazinone **4a***

A mixture of 2.14 g ($1.0 \cdot 10^{-2}$mol) 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone **3a**, 3.2 g ($1.0 \cdot 10^{-2}$ mol) 2-tosyloxymethyl-1,4-benzodioxane [10] and 1.8 g anhydrous Na_2CO_3 in 210 ml isoamylic alcohol was stirred and refluxed for 15 h. The mixture was filtered and evaporated under reduced pressure. The residue was purified by flash-chromatography using as eluent a stepwise gradient of EtOH (0–0.7%) in CH_2Cl_2. Yield: 25%, mp: 202–205°C; ^{1}H-NMR ($CDCl_3$)δ: 2.6–2.8 (6H, m, CH_2, piperazinic 4H), 3.3–3.5 (4H, m, piperazinic H), 4.0–4.3 (3H, m, OCH_2CHO), 6.7 (4H, s, aromatic proton of benzodioxane ring), 7.5 (1H, s, H6-pyridazinonic), 12 (1H, s, NHCO). The corresponding hydrochloride had an mp: 177–180°C.

*2-Methyl-4-chloro-5-[4-(methyl-1,4-benzodioxane)-1-piperazinyl]-3(2H)-pyridazinone **4b***

This compound was prepared using the same procedure as for compound **4a**, purified by flash-chromatography using CH_2Cl_2 as eluent; this gave a dense oil. Yield: 40%; ^{1}H-NMR ($CDC1_3$) δ: 2.6–2.85 (6H, m, CH_2, piperazinic 4H), 3.3–3.45 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 3.9–4.4 (3H, m, O-CH_2CHO), 6.65 (4H, s, aromatic proton of benzodioxane ring), 7.5 (1H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp:130–135°C.

*2-Phenyl-4-chloro-5-[4-(methyl-1,4-benzodioxane)-1-piperazinyl]-3(2H)-pyridazinone **4c***

This was prepared by the same procedure described above, purified by flash-chromatography using as eluent a stepwise gradient of CH_2Cl_2 (0–70%) in Et_2O. Yield: 55%, mp: 106–112°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.9 (6H, m, CH_2, piperazinic 4H), 3.4–3.6 (4H, m, piperazinic H), 4.0–4.4 (3H, m, O-CH_2-CH-O), 6.8 (4H, s, aromatic proton of benzodioxane

ring), 7.3–7.5 (6H, m, aromatic H), 7.6 (1H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 240–245°C.

2-Methyl-5-[4-(methyl-1,4-benzodioxane)-1-piperazinyl]-3(2H)-pyridazinone **5b**
A solution of **4b** 1.88 g ($5 \cdot 10^{-3}$ mol), KOH 0.34 g ($6 \cdot 10^{-3}$ mol) in 100 ml MeOH was hydrogenated catalytically using 10% palladium on carbon (200 mg) at atmospheric pressure and room temperature. After uptake of an equimolar amount of hydrogen, the catalyst was filtered off and the solvent removed *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The crude product obtained upon removal of $CHCl_3$ was recrystallized from ethyl acetate. Yield: 60%, mp:175–179°C; ^{1}H-NMR ($CDCl_3$) δ: 2.8–2.95 (6H, m, CH_2, piperazinic 4H), 3.2–3.35 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 4.0–4.35 (3H, m, O-CH_2-CH-O), 5.85 (1H, d, H4-pyridazinonic), 6.75 (4H, s, aromatic proton of benzodioxane ring), 7.55 (1H, d, H6-pyridazinonic). The corresponding hydrochloride had an mp: 244–247°C.

General method for the preparation of compounds ***6a, 6b, 6c–7a, 7b, 7c***

4-Chloro-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3-(2H)-pyridazinone ***6a***
A mixture of 2.04 g ($1.1 \cdot 10^{-2}$ mol) 2-(2-methoxyphenoxy)-ethylchloride **6** [4], 2.35 g ($1.1 \cdot 10^{-2}$ mol) 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone and 1.8 g anhydrous Na_2CO_3 in 200 ml isoamylic alcohol, was stirred and refluxed overnight. The mixture was filtered and the filtrate was evaporated under reduced pressure, the residue was purified by flash-chromatography using as eluent a stepwise gradient of EtOH (0–10%) in CH_2Cl_2. Yield: 50%, mp: 152–154°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–3.0 (6H, m, CH_2, piperazinic 4H), 3.35–3.55 (4H, m, piperazinic H), 3.85 (3H, s, OCH_3), 4.15 (2H, t, J = 6 Hz, CH_2), 6.8 (4H, s, aromatic H), 7.5 (1H, s, H6-pyridazinonic), 12.5 (1H, s, NH-CO). The corresponding hydrochloride had an mp: 232–237 °C.

2-Methyl-4-chloro-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***6b***
This was prepared by alkylation of 2-(2-methoxyphenoxy)-ethylchloride with 2-methyl-4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone, with purification by flash-chromatography using as eluent a stepwise gradient of EtOH (0–3%) in CH_2Cl_2. Yield: 40%, mp: 90–92°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.9 (6H, m, CH_2, piperazinic 4H), 3.2–3.5 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 3.8 (3H, s, OCH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 6.7 (4H, s, aromatic H), 7.4 (1 H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 225–230°C.

2-Phenyl-4-chloro-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***6c***
This was prepared in the similar manner to that described above. Yield: 40%, mp: 68–72°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–3.0 (6H, m, CH_2, piperazinic 4H), 3.3–3.6 (4H, m, piperazinic H), 3.8 (3H, s. OCH_3), 4.15 (2H, t, J = 6 Hz, CH_2), 6.8 (4H, m, aromatic H), 7.1–7.5 (5H, m, C_6H_5), 7.6 (1 H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 193–197°C.

4-Chloro-5-[4-(2-phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***7a***
This was prepared by alkylation of 2-phenoxyethylchloride with 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone, and purified by flash-chromatography using CH_2Cl_2/EtOH (9/1) as eluent. Yield: 30%; mp: 135–137°C; ^{1}H-NMR ($CDCl_3$)δ: 2.7–2.9 (6H, m, CH_2, piperazinic 4H), 3.4–3.6 (4H, m, piperazinic H), 4.1 (2H, t, J = 6 Hz, CH_2), 6.7–6.9 (3H, m, aromatic H), 7.0–7.2 (2H, m, aromatic H), 7.5 (1 H, s, H6-pyridazinonic), 12.3 (1H, s, NH-CO). The corresponding hydrochloride had an mp: 268–274°C.

2-Methyl-4-chloro-5-[4-(2-phenoxyethyl)-1-piperazinyl]-3-(2H)-pyridazinone ***7b***
Yield: 30%, mp:100–101°C; ^{1}H-NMR ($CDCl_3$)δ: 2.6–2.9 (6H, m, CH_2, piperazinic 4H), 3.25–3.5 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 6.7–6.95 (3H, m, aromatic H), 7.1–7.3 (2H, m, aromatic H), 7.5 (1H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 197–199°C.

2-Phenyl-4-chloro-5-[4-(2-phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***7c***
Yield: 20%, mp: 122–124°C; ^{1}H-NMR ($CDCl_3$) δ: 2.65–3.0 (6H, m, CH_2, piperazinic 4H), 3.35–3.6 (4H, m, piperazinic H), 4.1 (2H, t, J = 6 Hz, CH_2), 6.75–6.9 (3H, m, aromatic H), 7.1–7.5 (7H, m, aromatic-2H, C_6H_5), 7.6 (1H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 194–198°C.

5-[4-(2-Methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***8a***
A solution of **6a** (1.89 g, $5 \cdot 10^{-3}$ mol) and KOH (0.34 g, $6 \cdot 10^{-3}$ mol) in MeOH (100 ml) was hydrogenated catalytically using 10% palladium on carbon (200 mg) at atmospheric pressure and room temperature. After the uptake of an equimolecular amount of hydrogen, the catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The crude product obtained upon removal of $CHCl_3$, was crystallized from ethyl acetate to give **8a**. Yield: 40%; mp: 163–165°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.9 (6H, m, CH_2, piperazinic 4H), 3.2–3.4 (4H, m, piperazinic H), 3.8 (3H, s, OCH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 5.8 (1H, d, H4-pyridazinonic), 6.8 (4H, s, aromatic H), 7.5 (1H, d, H6-pyridazinonic), 11.5 (1H, s, NHCO). The corresponding hydrochloride had an mp: 265–269°C.

2-Methyl-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***8b***
This compound was prepared in the similar manner to that used for compound **8a**. Yield: 45%, mp: 84–86°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–3.0 (6H, m, CH_2, piperazinic H), 3.2–3.4 (4H, m, piperazinic H), 3.7 (3H, s, N–CH_3), 4.15 (2H, t, J = 6 Hz, CH_2), 5.85 (1H, d, H4-pyridazinonic), 6.8 (4H, s, aromatic H), 7.5 (1H, d, H6-pyridazinonic). The corresponding hydrochloride had an mp: 225–230°C.

2-Methyl-5-[4-(2-phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone ***9b***
Compound **7b** was hydrogenated catalytically with 10% palladium on carbon, KOH in MeOH by the same method as described for **8a**, crystallized from ethyl acetate. Yield: 50%, mp: 117–121°C; ^{1}H-NMR ($CDCl_3$)δ: 2.6–3.0 (6H, m, CH_2, piperazinic 4H), 3.2–3.4 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 5.7 (1H, d, H4-pyridazinonic), 6.7–6.9 (3H, m, aromatic H), 7.0–7.35 (2H, m, aromatic H), 7.5 (1 H, d, H6-pyridazinonic). The corresponding hydrochloride had an mp: 236–240°C.

1,2-Bis-{2-(4-chloro)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}-ethane ***10a***
To a mixture of 0.165 g ($4.1 \cdot 10^{-3}$ mol) of NaOH pellet, 1.5 g ($4.1 \cdot 10^{-3}$ mol) of **8b** in dry EtOH (25 ml), were added 0.38 g

($2.05 \cdot 10^{-3}$ mol) 1,2-dibromoethane. The mixture was refluxed for 6 h. The solution was evaporated and the residue digested with hot EtOAc. The solvent was evaporated and the residue was purified by chromatography on silica gel, using as eluent a stepwise gradient of ethanol (0–4%) in CH_2Cl_2 to give a solid with mp:159–163°C. Yield: 20%; ^{1}H-NMR ($CDCl_3$) δ: 2.5–3.0 (12H, m, $2CH_2$, piperazinic 8H), 3.2–3.5 (8H, m, piperazinic H), 3.8 (6H, s, $2OCH_3$), 4.1 (4H, t, J = 6 Hz, $2CH_2$), 4.5 (4H, s, $2CH_2$), 6.8 (8H, s, aromatic H), 7.4 (2H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 274–276°C.

1,2-Bis-{2-(4-chloro)-5-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}-ethane ***11a***

Compound **11a** was prepared by same method as described for **10a**. Yield: 30%, mp: 163–164°C; ^{1}H-NMR ($CDCl_3$) δ: 2.7–3.0 (12H, m, $2CH_2$, piperazinic 8H), 3.4–3.6 (8H, m, piperazinic H), 4.2 (4H, t, J = 6 Hz, $2CH_2$), 4.55 (4H, s, $2CH_2$), 6.8–7.0 (6H, m, aromatic H), 7.15–7.4 (4H, m, aromatic H), 7.5 (2H, s, H6-pyridazinonic). The corresponding hydrochloride had an mp: 278–281°C.

Acknowledgments

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