Eur J Med Chem (1995) 30, 71–75

Short communication

Novel and highly selective postsynaptic α-adrenoreceptor antagonists: synthesis and structure–activity relationships of alkane-bridged [4-(phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinones

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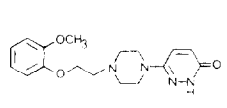
(Received 6 June 1994; accepted 29 September 1994)

Summary — The synthesis of selected 4-[4-(phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinones and alkane-bridged dimers of 4-, 5- and 6-[4-(phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinones is reported. The blocking activity of these compounds was determined on the pre- and postsynaptic α-adrenoreceptors of isolated rat vas deferens.

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

Introduction

In the recent years, the search for new α_1-adrenoreceptor antagonists has increased in parallel with the development of postsynaptically selective α–adrenoreceptor antagonists due to their importance in the treatment of hypertension [1] and for prostatic hypertrophy [2]. In the course of our studies on 3(2*H*)-pyridazinone derivatives as potential antagonists of the α-adrenoreceptor, we have recently synthesized compounds **1** [3] and **2** [4] which show a good activity. In agreement with the model for α_1-adrenoreceptor antagonists advanced by De Marinis *et al* [5], the 3(2*H*)-pyridazinone derivatives that we have synthesized show a planar aromatic region, a chain with basic nitrogen atoms, and a planar polar region corresponding to the 3(2*H*)-pyridazinone ring.



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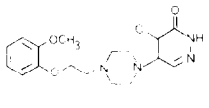

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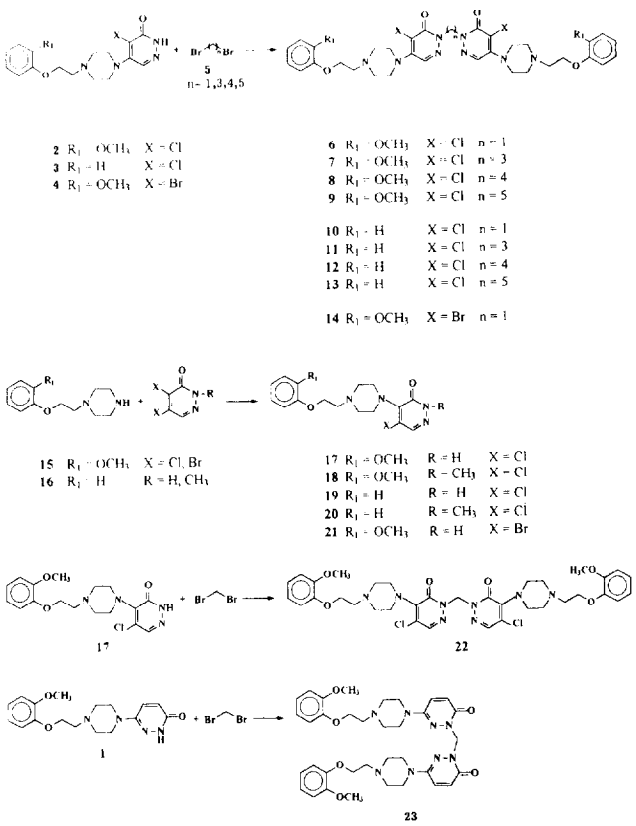
In order to obtain more information on the activity as α_1-antagonists we have synthesized the new pyridazinone derivatives reported in the scheme 1.



Scheme 1.

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Chemistry

Compounds **6–9** were prepared by alkylation of 2 mol of compound **2** [4] with 1 mol of dibromo derivative **5** where n = 1 and 3–5 and NaOH in dry EtOH. The same procedure was used for compounds **10–14**. The starting materials were compound **3** [4] or compound **4**, which was prepared by alkylation of the 4-[2-(2-methoxyphenoxy)ethyl]piperazine **15** with 4,5-dibromo-3(2*H*)-pyridazinone as described later.

The 4-substituted isomers **17–21** were prepared by alkylation of 4-[2-(2-methoxyphenoxy)ethyl]piperazine **15** or 4-(2-phenoxyethyl)piperazine **16** with the appropriate 4,5-dihalo-3(2*H*)-pyridazinones in 1,4-dioxane and anhydrous $KHCO_3$. The product was separated and purified from the 5-substituted isomer obtained in small percentages. Alkylation of 2 mol of **17** with 1 mol of dibromomethane and NaOH in dry EtOH yielded compound **22**, while compound **23** was prepared using the same procedure starting from compound **1** [3].

Results and discussion

The biological profile of the compounds listed in table I was investigated at the α_1- and α_2-adrenoreceptors. This was assessed on epidymal and prostatic portions of isolated rat vas deferens. The biological results were expressed as pK_b. The results show that all the compounds studied have a significant activity toward α-adrenoreceptors and it is evident that these compounds displayed a preferential blockade of the postsynaptic α-adrenoreceptor. The 4-substituted isomers **17–20** showed an activity and selectivity toward α-adrenoreceptors similar to that of 5-substituted isomers (compounds **2** and **3**). Similar results were also obtained for 4- and 5-substituted compounds **21** and **4** in which the chloro substituent is replaced by a bromo substituent. The dimers **6**, **8** and **9** are particularly interesting: although their activity is slightly lower than that of starting monomer (compound **2**), they show a high selectivity (ratio α_1/α_2 > 100 respectively). Similar results were ob-

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

Compound	α_1 pK_b	α_2 pK_b	*Selectivity ratio* α_1/α_2[a]
1	6.09 ± 0.04	4.86 ± 0.03	17
2[b]	7.29 ± 0.04	5.97 ± 0.03	21
3[b]	7.10 ± 0.10	6.18 ± 0.10	8.3
4	7.28 ± 0.20	6.21 ± 0.09	11
6	6.96 ± 0.02	< 4.52	> 100
7	6.45 ± 0.04	< 4.52	86
8	6.83 ± 0.22	< 4.52	> 100
9	6.83 ± 0.09	4.76 ± 0.20	> 100
10	6.77 ± 0.07	< 4.52	> 100
11	6.69 ± 0.14	4.75 ± 0.04	87
12	6.84 ± 0.11	< 4.52	> 100
13	6.92 ± 0.07	4.66 ± 0.12	> 100
14	7.42 ± 0.04	< 4.52	> 100
17	7.15 ± 0.08	5.63 ± 0.17	33
18	7.19 ± 0.09	6.02 ± 0.02	15
19	6.73 ± 0.09	6.12 ± 0.15	4
20	7.04 ± 0.18	6.45 ± 0.06	4
21	6.88 ± 0.06	5.58 ± 0.08	10
22	7.29 ± 0.10	5.54 ± 0.19	56
23	6.90 ± 0.05	4.75 ± 0.18	> 100
24[b]	7.00 ± 0.08	5.14 ± 0.03	72
25[b]	6.68 ± 0.10	4.86 ± 0.07	66

[a]The selectivity ratio is the antilog of the difference between the pK_b values at post- and presynaptic α-adrenoreceptors. [b]These values have been published in reference [4].

tained for compounds **10**, **12** and **13**, in which the methoxy group was eliminated, and compound **14**, in which the chlorine atom was substituted by a bromine atom. For the 6-substituted dimer (compound **23**), in which there is a chain with one carbon atom, a high selectivity was maintained, which decreases when the substitution is in the 4-position (compound **22**). In conclusion, the synthesis of alkane-bridged 5- and 6-[4-(phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinones leads to a high selectivity for the α_1-adrenoreceptor and this selectivity is high when one carbon atom is present in the chain (compounds **6**, **10**, **14** and **23**) and decreases when there are 2 carbon atoms (compounds **24** and **25**) [4] and when there are 3 carbon atoms (compounds **7** and **11**). The selectivity increases again with 4 and 5 carbon atoms (compounds **8**, **9**, **12** and **13**). One explanation of this behaviour could be that conformation modification changes their interaction with α_1- and α_2-adrenoreceptors.

On the basis of the high selectivity found, we will test these new compounds as antihypertensive agents.

Experimental protocols

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 volume 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 two-channel Gemini 7070 polygraph. 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 pK_b values according to the following equation:

$$K_b = \frac{[Ant]}{DR - 1}$$

where K_b is the dissociation constant of the antagonist; and DR is the ratio of (–)noradrenaline (NA) ED_{50} in the presence and in the absence of the antagonist.

Postsynaptic α-blocking activity was determined on the epididymal portion of the vas deferens. The tissue was 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 was 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 [6, 7]. The procedure reported by Drew [6] 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 presence of the antagonist.

Chemistry

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. 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 dry HCl into the dry solution of the compound.

The corresponding oxalate was prepared by adding an equimolar solution of oxalic acid into the dry solution of the compound.

1,1-Bis{-2-(4-chloro)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}methane ***6***

To a mixture of 0.23 g (5.75×10^{-3} mol) of NaOH pellets, 2.1 g (5.75×10^{-3} mol) of 4-chloro-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinone **2** [4] in dry EtOH (15 ml), was added 0.5 g (2.87×10^{-3} mol) of dibromomethane. The mixture was refluxed for 5 h. The solution was evaporated and the residue digested with hot EtOAc. Removal of solvent after drying gave a residue which was purified by chromatography on alumina Brockmann II using a stepwise gradient of EtOH (0–0.8%) in CH_2Cl_2 as an eluent. Yield: 20%; mp: 42–48°C; ^{1}H-NMR ($CDCl_3$) δ: 2.55–2.9 (12H, m, $2CH_2$, piperazinic 8H), 3.3–3.5 (8H, m, piperazinic H), 3.8 (6H, s, $2OCH_3$), 4.1 (4H, t, J = 6 Hz, $2CH_2$), 6.2 (2H, s, CH_2), 6.8 (8H, s, aromatic H), 7.5 (2H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 58–60°C.

1,3-Bis{-2-(4-chloro)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}propane ***7***

Compound **7** was prepared by the same procedure as described for compound **6**. Yield: 25%; mp: 35–38°C; ^{1}H-NMR ($CDCl_3$) δ: 2.3 (2H, q, CH_2), 2.65–2.8 (8H, m, piperazinic H), 2.9 (4H, t, $2CH_2$), 3.35–3.45 (8H, m, piperazinic H), 3.85 (6H, s, $2OCH_3$), 4.1–4.35 (8H, m, $4CH_2$), 6.9 (8H, s, aromatic H), 7.55 (2H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 46–48°C.

1,4-Bis-{2-(4-chloro)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}butane ***8***
This compound was prepared in a similar manner to compound **6**. Yield: 30%; mp: 110–112°C; ^{1}H-NMR ($CDCl_3$) δ: 1.75–1.9 (4H, m, $2CH_2$), 2.65–2.9 (12H, m, $2CH_2$, piperazinic 8H), 3.35– 3.5 (8H, m, piperazinic H), 3.8 (6H, s, $2OCH_3$), 4.1 (8H, t, J = 6 Hz, $4CH_2$), 6.8 (8H, s, aromatic H), 7.45 (2H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 77–78°C.

1,5-Bis-{2-(4-chloro)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}pentane ***9***
This compound was prepared by the same procedure described above and a dense oil was obtained with yield 25%; ^{1}H-NMR ($CDCl_3$) δ: 1.7–2.0 (6H, m, $3CH_2$), 2.7–3.0 (12H, m, $2CH_2$, piperazinic 8H), 3.4–3.55 (8H, m, piperazinic H), 3.85 (6H, s, $2OCH_3$), 4.0–4.2 (8H, m, $4CH_2$), 6.85 (8H, s, aromatic H), 7.5 (2H, s, H6-pyridazinonic).

The corresponding oxalate had mp: 68–72°C.

1,1-Bis-{2-(4-bromo)-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}methane ***14***
This compound was prepared by alkylation of 4-bromo-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinone **4** with dibromomethane, and was purified by chromatography on alumina Brockmann II using a stepwise gradient of EtOH (0–2%) in CH_2Cl_2 as an eluent. A dense oil was obtained with yield 35%. ^{1}H-NMR ($CDCl_3$) δ: 2.7–3.0 (12H, m, $2CH_2$, piperazinic 8H), 3.4–3.6 (8H, m, piperazinic H), 3.9 (6H, s, $2OCH_3$), 4.2 (4H, t, J = 6 Hz, $2CH_2$), 6.35 (2H, s, CH_2), 6.9 (8H, s, aromatic H), 7.6 (2H, s, H6-pyridazinonic).

The corresponding oxalate had mp: 116–121°C.

General method for the preparation of compounds ***10–13****. 1,1-Bis-{2-(4-chloro)-5-[4-phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}methane* ***10***
To a mixture of 0.23 g (5.75 x 10^{-3} mol) NaOH pellets and 1.92 g (5.75 x 10^{-3} mol) 4-chloro-5-[4-(2-phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinone **3** [4] in dry EtOH (15 ml) was added 0.5 g (2.87 x 10^{-3} mol) of dibromomethane. The mixture was refluxed for 10 h. The solution was evaporated and the residue digested with hot EtOAc. The dry solution was evaporated under reduced pressure and the residue was purified by chromatography on alumina Brockmann II using a stepwise gradient of EtOH (0–1%) in CH_2Cl_2 as an eluent. Yield: 25%; mp: 58–62°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.9 (12H, m, $2CH_2$, piperazinic 8H), 3.35–3.5 (8H, m, piperazinic H), 4.1 (4H, t, J = 6 Hz, $2CH_2$), 6.2 (2H, s, CH_2), 6.7–6.9 (6H, m, aromatic H), 7.05–7.25 (4H, m, aromatic H), 7.5 (2H, s, H6 -pyridazinonic).

The corresponding hydrochloride had mp: 158–162°C.

1,3-Bis-{2-(4-chloro)-5-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}propane ***11***
Yield: 20%, mp: 34–36°C; ^{1}H-NMR ($CDCl_3$) δ: 2.3 (2H, q, CH_2), 2.80–2.95 (12H, m, $2CH_2$, piperazinic 8H), 3.35–3.5 (8H, m, piperazinic H), 4.05–4.3 (8H, m, $4CH_2$), 6.8–7.0 (6H, m, aromatic H), 7.1–7.35 (4H, m, aromatic H), 7.55 (2H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 134–138°C.

1,4-Bis-{2-(4-chloro)-5-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}butane ***12***
Yield: 25%, mp: 117–120°C; ^{1}H-NMR ($CDCl_3$) δ: 2.3 (4H, q, $2CH_2$), 2.65–2.95 (12H, m, $2CH_2$, piperazinic 8H), 3.3–3.5 (8H, m, piperazinic H), 4.0–4.25 (8H, m, $4CH_2$), 6.5–6.9 (6H, m, aromatic H), 7.05–7.25 (4H, m, aromatic H), 7.5 (2H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 256–259°C.

1,5-Bis-{2-(4-chloro)-5-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}pentane ***13***
A dense oil was obtained in yield 30%; ^{1}H-NMR ($CDCl_3$) δ: 1.65–1.95 (6H, m, $3CH_2$), 2.65–2.9 (12H, m, $2CH_2$, piperazinic 8H), 3.3–3.5 (8H, m, piperazinic H), 4.1 (8H, t, J = 6 Hz, $4CH_2$), 6.75–6.95 (6H, m, aromatic H), 7.1–7.3 (4H, m, aromatic H), 7.5 (2H, s, H6-pyridazinonic).

The corresponding oxalate had mp: 97–101°C.

4-[4-(2-Methoxyphenoxyethyl)-1-piperazinyl]-5-chloro-3(2H)-pyridazinone ***17***
A mixture of 1 g (4.23 x 10^{-3} mol) of 4-[2-(2-methoxyphenoxy)ethyl]piperazine **15** [8], 0.58 g (4.23 x 10^{-3} mol) of 4,5-dichloro-3(2*H*)-pyridazinone [9] and 0.42 g (4.23 x 10^{-3} mol) of anhydrous $KHCO_3$ in 50 ml 1,4-dioxane was refluxed for 15 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash-chromatography using CH_2Cl_2/EtOH as an eluent.

The 4-substituted isomer **17** was eluted with CH_2Cl_2/EtOH (9.8:0.2). Yield: 35%, mp: 129–134°C. ^{1}H-NMR ($CDCl_3$) δ: 2.7–3.0 (6H, m, CH_2, piperazinic 4H), 3.4–3.5 (4H, m, piperazinic H), 3.85 (3H, s, OCH_3), 4.2 (2H, t, J = 6 Hz, CH_2), 6.85 (4H, s, aromatic H), 7.6 (1H, s, H6-pyridazinonic), 11.6 (1H, s, NH-CO).

The corresponding oxalate had mp: 139–143°C.

The 5-substituted isomer was eluted with CH_2Cl_2/EtOH (9.2:0.8). Yield: 20%, mp: 152–154°C. The spectral data are consistent with those reported in the literature [4].

2-Methyl-4-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-5-chloro-3(2H)-pyridazinone ***18***
This compound was prepared in a similar manner to that described for compound **17** using 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone [10] and 4-[2-(2-methoxyphenoxy)ethyl]-piperazine **15** [8] for alkylation and was purified by flash-chromatography using CH_2Cl_2/EtOH as an eluent.

The 4-substituted isomer **18** was eluted with CH_2Cl_2/EtOH (9.8:0.2); yield: 35%, mp: 71–73°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.9 (6H, m, CH_2, piperazinic 4H), 3.45–3.6 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 3.85 (3H, s, OCH_3), 4.2 (2H, t, J = 6 Hz, CH_2), 6.85 (4H, s, aromatic H), 7.5 (1H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 160–161°C.

The 5-substituted isomer was eluted with CH_2Cl_2/EtOH (9.6:0.4); yield: 10%, mp: 90–92°C. The spectral data are consistent with those reported in the literature [4].

4-[4-(2-Phenoxyethyl)-1-piperazinyl]-5-chloro-3(2H)-pyridazinone ***19***
This compound was prepared by alkylation of 4-(2-phenoxyethyl)piperazine **16** [8] with 4,5-dichoro-3(2*H*)-pyridazinone and was purified by flash-chromatography using CH_2Cl_2/EtOH as an eluent.

The 4-substituted isomer **19** was eluted with CH_2Cl_2/EtOH (9.8:0.2). Yield: 35%, mp: 128–129°C; ^{1}H-NMR ($CDCl_3$) δ: 2.7–2.95 (6H, m, CH_2, piperazinic 4H), 3.5–3.7 (4H, m, piperazinic H), 4.15 (2H, t, J = 6 Hz, CH_2), 6.75–6.95 (3H, m, aromatic H), 7.1–7.35 (2H, m, aromatic H), 7.6 (1H, s, H6-pyridazinonic), 11.0 (1H, s, NH-CO).

The corresponding oxalate had mp: 100–101°C.

The 5-substituted isomer was eluted with CH_2Cl_2/EtOH (7:3). Yield: 15%; mp 135–137°C. The spectral data are in agreement with those reported in the literature [4].

2-Methyl-4-[4-(2-phenoxyethyl)-1-piperazinyl]-5-chloro-3(2H)-pyridazinone ***20***

This compound was prepared in a similar manner to that used for compound **19** using 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone [10] and 4-[2-(phenoxyethyl)]piperazine **16** for alkylation. The product was purified by flash chromatography using CH_2Cl_2/EtOH as an eluent.

The 4-substituted isomer **20** was eluted with CH_2Cl_2/EtOH (8.5:1.5) and a dense oil was obtained, yield: 30%; ^{1}H-NMR ($CDCl_3$) δ: 2.65–2.95 (6H, m, CH_2, piperazinic 4H), 3.4–3.6 (4H, m, piperazinic H), 3.7 (3H, s, N-CH_3), 4.1 (2H, t, J = 6 Hz, CH_2), 6.75–6.9 (3H, m, aromatic H), 7.1–7.25 (2H, m, aromatic H), 7.55 (1H, s, H6-pyridazinonic).

The corresponding hydrochloride had mp: 163–165°C.

The 5-substituted isomer was eluted with CH_2Cl_2/EtOH (7:3); yield: 10%, mp: 100–101°C. The spectral data are in agreement with those reported in the literature [4].

4-[4-(2-Methoxyphenoxyethyl)-1-piperazinyl]-5-bromo-3(2H)-pyridazinone ***21*** *and 4-bromo-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2 H)-pyridazinone* ***4***

These compounds were prepared by alkylation of 4-[2-(2-methoxyphenoxy)ethyl]piperazine **15** [8] with 4,5-dibromo-3(2*H*)-pyridazinone [11] and $KHCO_3$ in 1,4-dioxane. The mixture was then filtered under reduced pressure. The dry organic phase was evaporated under reduced pressure, the residue was purified by flash-chromatography using CH_2Cl_2/EtOH as an eluent.

The 4-substituted isomer **21** was eluted with CH_2Cl_2/EtOH (9.8:0.2), yield: 25%; mp: 108–113°C; ^{1}H-NMR ($CDCl_3$) δ: 2.6–3.0 (6H, m, CH_2, piperazinic 4H), 3.45–3.7 (4H, m, piperazinic H), 3.95 (3H, s, OCH_3), 4.25 (2H, t, J = 6 Hz, CH_2), 7.0 (4H, s, aromatic H), 7.8 (1H, s, H6-pyridazinonic), 11.75 (1H, s, NH-CO).

The corresponding oxalate had mp: 87–93°C.

The 5-substituted isomer **4** was eluted with CH_2Cl_2/EtOH (9.2:0.8), yield: 10%; mp: 137–139°C; ^{1}H-NMR ($CDCl_3$) δ: 2.8–3.1 (6H, m, CH_2, piperazinic 4H), 3.45–3.65 (4H, m, piperazinic H), 4.0 (3H, s, OCH_3), 4.25 (2H, t, J = 6 Hz, CH_2), 7.0 (4H, s, aromatic H), 7.65 (1H, s, H6-pyridazinonic), 12.0 (1H, s, NH-CO).

The corresponding oxalate had mp: 122–127°C.

1,1-Bis-{2-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-5-chloro-3(2H)-pyridazinonyl}methane ***22***

This compound was prepared by alkylation of compound **17** with dibromomethane in solution of NaOH and dry EtOH in condition of reflux for 7.5 h. The solution was evaporated and the residue digested with hot EtOAc. The dry solvent was evaporated under reduced pressure and purified by chromatography on alumina Brockmann II using CH_2Cl_2/EtOH (9.8:0.2) as an eluent. A dense oil was obtained with yield 20%; ^{1}H-NMR ($CDCl_3$) δ: 2.5–2.9 (12H, m, $2CH_2$, piperazinic 8H), 3.3–3.5 (8H, s, piperazinic H), 3.85 (6H, s, $2OCH_3$), 4.15 (4H, t, J = 6 Hz, CH_2), 6.2 (2H, s, CH_2), 6.8 (8H, s, aromatic H), 7.6 (2H, s, H6-pyridazinonic). The corresponding oxalate had mp: 97–102°C.

1,1-Bis-{2-{6-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinonyl}}methane ***23***

This compound was prepared from 6-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinone **1** [3] and dibromomethane in a similar manner to that described for compound **22**, purified by chromatography on alumina Brockmann II using CH_2Cl_2/EtOH (9.8:0.2) as an eluent and obtaining a dense oil with yield 20%; ^{1}H-NMR ($CDCl_3$) δ: 2.6–2.7 (8H, m, piperazinic H), 2.95 (4H, t, J = 6 Hz, $2CH_2$), 3.15–3.25 (8H, m, piperazinic H), 3.85 (6H, s, OCH_3), 4.15 (4H, t, J = 6 Hz, $2CH_2$), 6.15 (2H, s, CH_2), 6.8–6.95 (10H, m, pyridazinonic 2H, aromatic 8H), 7.10 (2H, d, J = 10 Hz, pyridazinonic H).

The corresponding oxalate had mp: 63–68°C.

Acknowledgment

This work was supported by the MURST (Ministry of University and Scientific Research).

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