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Short communication

Synthesis and α_1-antagonist activity of derivatives of 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone

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Abstract – The synthesis and evaluation of the biological activity of new 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone derivatives are reported. The blocking activity of these compounds was determined on the pre- and postsynaptic α-adrenoceptors of isolated rat vas deferens. © 2000 Éditions scientifiques et médicles Elsevier SAS

α_1-adrenoceptor antagonist / pyridazinone / structure–activity relationship / rat vas deferens

1. Introduction

In recent years the search for new α_1-adrenoceptor antagonists has increased with the development of postsynaptically selective α-adrenoceptor antagonists due to their importance in the treatment of hypertension [1], and of benign prostatic hypertrophy (BPH) [2]. It is well known that antihypertensive activity depends on a peripheral vasodilatation mediated by a postjunctional α_1-adrenoceptor block. In spite of their high α_1 selectivity, compounds like prazosin have side effects such as tachycardia, which is connected with a presynaptic α_2-adrenolytic action [3, 4].

In the course of studies on 3(2H)-pyridazinone derivatives as potential antagonists of α_1-adrenoceptor, we have in a previous work [5] synthesized a series of compounds such as alkane-bridged [4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinones and tested them on the epididymal or prostatic portion of the vas deferens to assess their α_1- and α_2-adrenoceptor blocking properties. Compounds bearing a linker of four or five carbon atoms (**1** and **1a**) showed a good activity and selectivity towards the α_1-adrenoceptor (*figure 1*).

As an extension of this work, in order to better define the structural requirements for optimum selectivity towards α_1-adrenoceptor and also to find out whether the selectivity observed for molecules **1** and **1a** depends on their symmetrical structure, we considered it of interest to synthesize compounds in which the 4-chloro-5-[4-(2-methoxyphenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinone portion was substituted with different groups, and a compound in which the flexibility of the chain was reduced by the introduction of the amide group (*figures 2* and *3*).

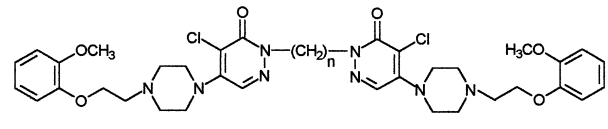

Figure 1. Compounds bearing a linker of four or five combinations.

2. Chemistry

Compounds **3** and **4** were prepared by alkylation of compound **2** with 4-chloro-5-(4-methyl-piperazin-1-yl)-2-(4-chlorobutyl)-pyridazin-3(2H)-one (**11**) or 4-chloro-5-(4-methyl-piperazin-1-yl)-2-(5-chloropentyl)-pyridazin-

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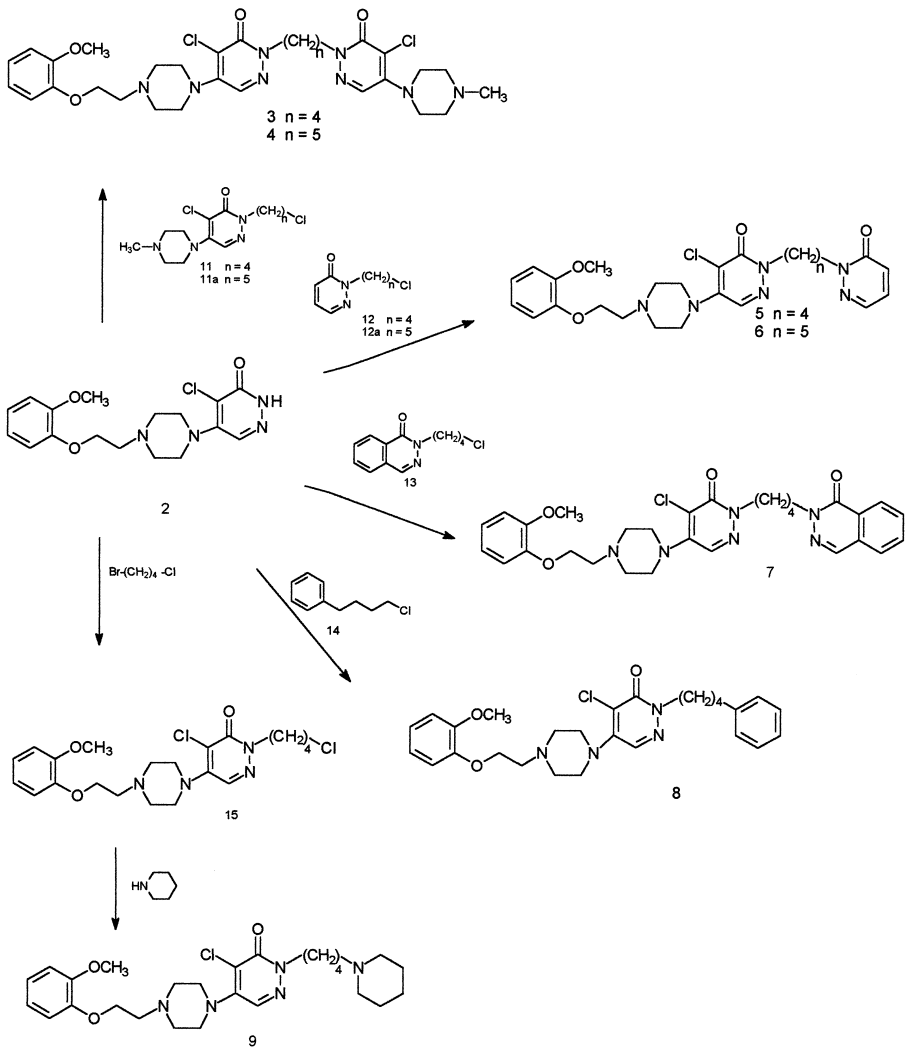

Reagents and conditions: **(a)** ethanol and sodium hydroxide pellets; **(b)** acetone and dry potassium carbonate

Figure 2. Synthesis of **3–9**.

3(2H)-one (**11a**), respectively, using two methods: ethanol and sodium hydroxide pellets (method A) or acetone and dry potassium carbonate (method B). No significantly different yields were obtained from the two pathways. The same procedures were used to prepare compounds **5**, **6**, **7** and **8**, using as fragments 2-(4-chlorobutyl)-pyridazin-3(2H)-one (**12**), 2-(5-chloropentyl)-pyridazin-3(2H)-one (**12a**), 2-(4-chlorobutyl)-phthalazin-1(2H)-one (**13**) and 1-(4-chlorobutyl)-benzene (**14**), respectively. Compound **9** was prepared by alkylation of compound **15** with piperidine in isoamyl alcohol and dry sodium carbonate. Finally the condensation between 2-[4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one-2-yl]-acetic acid (**16**) and 2-[phthalazin-1(2H)-one-2-yl)]-ethylamine (**17**) in chloroform, ethyl chlorocarbonate and triethylamine gave compound **10** (*figure 3*).

3. Pharmacology

The pharmacological profile of compounds **3–10** was evaluated at α_1- and α_2-adrenoceptors on isolated rat vas deferens tissues. Alpha$_1$-adrenoceptor blocking activity was assessed by antagonism of (–)-noradrenaline-induced contractions of the epididymal portion: α_2-adrenoceptor blocking activity was determined by antagonism of the

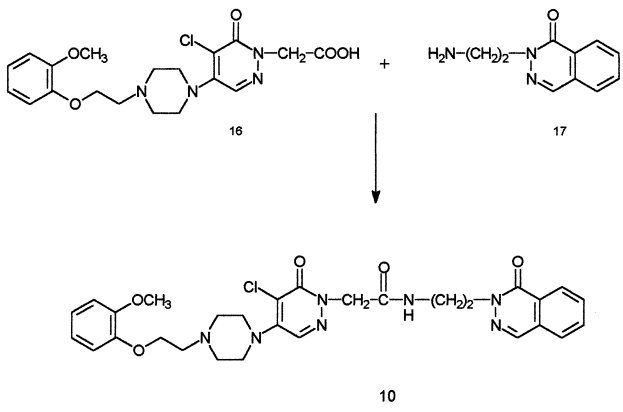

Figure 3. Synthesis of **10**.

clonidine-induced depression of the twitch responses of the field prostatic portion of rat vas deferens. The biological results were expressed as pK_b values, calculated according to Drew [6].

4. Results and discussion

The biological results of compounds **3**–**10** are reported in *table I*.

Relative to the observed pK_b values for α_1-AR α_2-AR, compounds **3** and **4** in which the 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one fragment was substituted with 4-chloro-5-(4-methyl-piperazin-1-yl)-pyridazin-3(2H)-one a decrease of selectivity was observed, although activity towards α_1-adrenoceptor is similar to that of compounds **1** and **1a**. Compound **5**, in which the 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one was substituted with a pyridazin-3(2H)-one ring, the activity and selectivity were preserved when the chain joining the two major constituents of the molecule was four carbon atoms, whereas selectivity decreases with the lengthening of the chain by one carbon unit (compound **6**). In compound **8**, in which an aromatic ring is present, the activity was preserved but not the selectivity, while the activity disappeared with the presence of a piperidine ring (compound **9**). It is interesting to observe that there was an increase of the activity and selectivity when the 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one portion was substituted with the phthalazin-1(2H)-one ring (compound **7**). While the activity and selectivity towards α_1-adrenoceptor showed by compound **7** decrease with the introduction of an amide group (compound **10**).

Table I. Blocking activity on the pre- and postsynaptic adrenoceptors of isolated rat vas deferens.

Compound	α_1	α_2	Selectivity ratio α_1/α_2 [a]
	pK_b	pK_b	
1 [b]	6.83 ± 0.22	<4.52	>100
1a [b]	6.83 ± 0.09	4.76 ± 0.20	>100
3	6.78 ± 0.23	5.28 ± 0.16	32
4	6.58 ± 0.13	5.20 ± 0.08	25
5	6.94 ± 0.14	<5	>87
6	6.57 ± 0.20	5.22 ± 0.10	>22
7	7.86 ± 0.09	5.04 ± 0.05	>660
8	6.50 ± 0.26	5.44 ± 0.17	13
9	inactive	inactive	–
10	6.42 ± 0.15	5.18 ± 0.07	17

[a] The selectivity ratio is the antilog of the difference between the pK_b values at post- and presynaptic α-adrenoceptors. [b] These values have been published in reference [5].

In conclusion, from these results we advanced the hypothesis that for a good selectivity towards α_1-adrenoceptor shown by compounds (**1** and **1a**) it is necessary to have either a symmetrical structure, or groups with a degree of steric hindrance capable of coupling through further bonds with an accessory site situated at an opportune distance from the active site. Moreover, it is necessary that the linker joining the two major constituents of the molecule shows a certain flexibility.

5. Experimental protocols

5.1. Biological methods

5.1.1. Blocking activity on the pre- and postsynaptic α-adrenoceptors 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 approximately 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. Propanolol 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:

$$Kb = [Ant]/DR - 1$$

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 five 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. [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 five times. Dose ratio (DR) values were then determined from the concentration causing 50% inhibition of the twitch response in the absence and presence of the antagonist.

5.2. Chemical synthesis

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The NMR spectra were recorded with a Bruker AC 200 MHz instrument in the solvent indicated below. The chemical shift values (ppm) are relative to tetramethylsilane as internal standard. Elemental analyses are within ± 0.4 % of theoretical values. Precoated Kiesegel 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.

5.2.1. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-{4-[4-chloro-5-(4-methyl-piperazin-1-yl)-butyl}-pyridazin-3(2H)-one-2-yl]-pyridazin-3(2H)-one **3**

5.2.1.1. General method

A: to 30 mL of dry ethanol was added 0.1 g (2.5×10^{-3} mol) of sodium hydroxide pellets and 0.73 g (2.0×10^{-3} mol) of 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one (**2**) [5], this mixture was refluxed for 30 min. Then 0.64 g (2.0×10^{-3} mol) of the 4-chloro-5-(4-methyl-piperazin-1-yl)-2-(4-chlorobutyl)-pyridazin-3(2H)-one (**11**) dissolved in dry ethanol was added, and this mixture was refluxed under stirring for 24 h.

After evaporation under reduced pressure, the residue was purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–12%) in CH_2Cl_2. A dense oil was obtained. Yield (0.65 g): 50%.

B: a mixture of 0.73 g (2.0×10^{-3} mol) of 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one (**2**), 0.30 g (2.2×10^{-3} mol) of dry potassium carbonate, 0.64 g (2.0×10^{-3} mol) of 4-chloro-5-(4-methyl-piperazin-1-yl)-2-(4-chlorobutyl)-pyridazin-3(2H)-one (**11**) in 30 mL of acetone was refluxed under stirring overnight. After cooling, the inorganic salts were filtered off, the solvent evaporated under vacuum and the residue was purified by flash-chromatography silica gel, as described above. Yield (0.77 g): 60%. ^{1}H-NMR ($CDCl_3$) δ: 1.70–1.85 (m, 4H, $2CH_2$), 2.35 (s, 3H, CH_3), 2.50–2.60 (m, 4H, H-pip), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, J = 6 Hz, 2H, CH_2), 3.30–3.50 (m, 8H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.30 (m, 6H, $3CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 2H, H-pyrid.). The corresponding hydrochloride had m.p.: 268–272 °C.

5.2.2. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-{5-[4-chloro-5-(4-methyl-piperazin-1-yl)-pentyl}-pyridazin-3(2H)-one-2-yl]-pyridazin-3(2H)-one **4**

This compound was prepared by alkylation of **2** with 4-chloro-5-(4-methyl-piperazin-1-yl)-2-(5-chloropentyl)-pyridazin-3(2H)-one (**11a**) using the two methods described above. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–12%) in CH_2Cl_2. A dense oil was obtained. Yield: 50%. ^{1}H-NMR ($CDCl_3$) δ: 1.30–1.50 (m, 2H, CH_2), 1.70–1.90 (m, 4H, $2CH_2$), 2.40 (s, 3H, CH_3), 2.50–2.60 (m, 4H, H-pip), 2.70–2.80 (m, 4H, H-pip.), 2.95 (t, J = 6 Hz, 2H, CH_2), 3.30–3.50 (m, 8H, H-pip.), 3.90 (s, 3H, OCH_3),

4.10–4.30 (m, 6H, $3CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 2H, H-pyrid.). The corresponding hydrochloride had m.p.: 30–33 °C.

5.2.3. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-{4-[pyridazin-3(2H)-one-2-yl]-butyl}-pyridazin-3(2H)-one **5**

This compound was prepared by alkylation of **2** with 2-(4-chlorobutyl)-pyridazin-3(2H)-one (**12**) using method B. Purified by chromatography silica gel using as eluent a stepwise gradient of ethanol (0–8%) in CH_2Cl_2. A dense oil was obtained. Yield: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.70–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 2.95 (t, J = 6 Hz, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.10–4.20 (m, 6H, $3CH_2$), 6.80–7.00 (m, 5H, 4H-arom., 1H-pyrid.), 7.15 (dd, J = 9 Hz e 5 Hz, 1H, H-pyrid.), 7.6 (s, 1H, H-pirid.), 7.75 (dd, J = 5 Hz e 2 Hz, 1H, H-pyrid.). The corresponding hydrochloride had m.p.: 35–38 °C.

5.2.4. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-{5-[pyridazin-3(2H)-one-2-yl]-pentyl}-pyridazin-3(2H)-one **6**

This compound was prepared by alkylation of **2** with 2-(5-chloropentyl)-pyridazin-3(2H)-one (**12a**) using method B. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–6%) in CH_2Cl_2. A dense oil was obtained. Yield: 50%. ^{1}H-NMR ($CDCl_3$) δ: 1.20–1.50 (m, 2H, CH_2), 1.70–2.00 (m, 4H, $2CH_2$), 2.70–2.85 (m, 4H, H-pip.), 2.95 (t, J = 6 Hz, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.10–4.20 (m, 6H, $3CH_2$), 6.80–7.00 (m, 5H, 4H-arom., 1H-pyrid.), 7.10 (dd, J = 9 Hz e 5 Hz, 1H, H-pirid.), 7.60 (s, 1H, H-pyrid.), 7.75 (dd, J = 5 Hz e 2 Hz, 1H, H-pyrid.). The corresponding hydrochloride had m.p.: 232–235°C.

5.2.5. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-[4-[phthalazin-1(2H)-one-2-yl]-butyl}-pyridazin-3(2H)-one **7**

This compound was prepared by alkylation of **2** with 2-(4-chlorobutyl)-phthalazin-1(2H)-one (**13**) using method B. Purified by chromatography silica gel using as eluent a stepwise gradient of ethanol (0–5%) in CH_2Cl_2. A dense oil was obtained. Yield: 60%. ^{1}H-NMR ($CDCl_3$) δ: 1.80–2.00 (m, 4H, $2CH_2$), 2.70–2.85 (m, 4H, H-pip.), 2.95 (m, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.30 (m, 6H, $3CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 1H, H-pyrid.), 7.70–7.85 (m, 3H, H-phthalaz.), 8.1 (s, 1H, H-phthalaz.), 8.35–8.45 (m, 1H, H-phthalaz). The corresponding hydrochloride had m.p.: 72–75 °C

5.2.6. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-(4-phenylbutyl)-pyridazin-3(2H)-one **8**

This compound was prepared by alkylation of **2** with 1-(4-chlorobutyl)-benzene (**14**) using method A. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–5%) in CH_2Cl_2. A dense oil was obtained. Yield: 30%. ^{1}H-NMR ($CDCl_3$) δ: 1.60–1.90 (m, 4H, $2CH_2$), 2.60 (t, J = 6 Hz, 2H, CH_2), 2.65–2.75 (m, 4H, H-pip.), 2.90 (t, J = 6 Hz, 2H, CH_2), 3.30–3.45 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.10–7.30 (m, 5H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had m.p.: 27–30 °C.

5.2.7. 4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-[4-(piperidin-1-yl)-butyl]-pyridazin-3(2H)-one **9**

This compound was prepared by alkylation of 0.45 g (1.0×10^{-3} mol) 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-2-(4-chlorobutyl)-pyridazin-3(2H)-one **15** [8] with 0.10 g (1.2×10^{-3} mol) of piperidine 0.20 g (1.2×10^{-3} mol) dry sodium carbonate in 15 mL of isoamyl alcohol. This mixture was refluxed under stirring for 24 h. After evaporation under reduced pressure, the residue was purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–50%) in CH_2Cl_2. A dense oil was obtained. Yield (0.176 g): 35%. ^{1}H-NMR ($CDCl_3$) δ: 1.40–1.60 (m, 2H, CH_2-piperid.), 1.70–1.90 (m, 10H, $2CH_2$-piperid., $3CH_2$), 2.55–2.80 (m, 10H, 4H-pip., $2CH_2$-piperid.), 2.90 (t, J = 6 Hz, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.25 (m, 4H, $2CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had m.p.: 235–238 °C.

5.2.8. N1-{2-[1(2H)-phthalazin-1-yl}ethyl]-2-(4-cloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3-one-2-yl)-acetamide **10**

Ethyl chlorocarbonate 1.10 g (5.1×10^{-3} mol) was added dropwise to a stirred and cooled (0 °C) solution of 2.10 g (5.0×10^{-3} mol) acid **16** and 0.51 g (5.0×10^{-3} mol) of triethylamine in 60 mL of chloroform, followed after 30 min by the addition of a solution of 0.95 g (5.0×10^{-3} mol) of amine **17** [9] in 15 mL of chloroform. The resulting reaction mixture was stirred for 7 h at room temperature and then was evaporated under reduced pressure. The residue was purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. A solid was obtained. m.p.: 100–105 °C. Yield (1.12 g): 40%. ^{1}H-NMR ($CDCl_3$) δ: 2.70–2.80 (m, 4H, H-pip.), 2.95 (t, J = 6 Hz, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip.), 3.70 (t, J =

6 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.20 (t, J = 6 Hz, 2H, CH_2), 4.40 (t, J = 6 Hz, 2H, CH_2), 4.80 (s, 2H, CH_2), 6.80–7.00 (m, 4H, H-arom.), 7.10 (s, 1H, NHCO), 7.60–7.90 (m, 4H, 3H-phthalaz., 1H-pyrid.), 8.15 (s, 1H, H-phthalaz.), 8.4 (m, 1H, H-phthalaz.). The corresponding hydrochloride had m.p.: 105–108°C.

5.2.9. 4-Chloro-5-(4-methyl-piperazin-1-yl)-2-(4-chlorobutyl)-pyridazin-3(2H)-one **11**

A mixture of 1.0 g (1.0×10^{-2} mol) of 1-methyl-piperazine, 1.6 g (1.0×10^{-2} mol) of 4,5-dichloropyridozin 3(2H)-one and 1.0 g (1.0×10^{-2} mol) of $KHCO_3$ in 25 mL of ethanol, was refluxed under stirring overnight. The inorganic salts were filtered off, the solvent evaporated under vacuum and the residue was purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2 (yield: 35%) obtaining 4-chloro-5-(4-methyl-piperazin-1-yl)-pyridazin-3(2H)-one, which was alkylated with 1-bromo-4-chlorobutane using method A. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–4%) in CH_2Cl_2. A dense oil was obtained. Yield (1.59 g): 50%. ^{1}H-NMR ($CDCl_3$) δ: 1.70–2.00 (m, 4H, $2CH_2$), 2.35 (s, 3H, CH_3), 2.50–2.60 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.65 (t, J = 6 Hz, 2H, CH_2), 4.20 (t, J = 6 Hz, 2H, CH_2), 7.60 (s, 1H, H-pyrid.).

5.2.10. 4-Chloro-5-(4-methyl-piperazin-1-yl)-2-(5-chloropentyl)-pyridazin-3(2H)-one **11a**

This compound was prepared by alkylation of 4-chloro-5-(4-methyl-piperazin-1-yl)-pyridazin-3(2H)-one with 1-bromo-5-chloropentane using method A. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–4%) in CH_2Cl_2. A dense oil was obtained. Yield: 55%. ^{1}H-NMR ($CDCl_3$) δ: 1.40–1.60 (m, 2H, CH_2), 1.70–2.00 (m, 4H, $2CH_2$), 2.40 (s, 3H, CH_3), 2.50–2.70 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.60 (t, J = 6 Hz, 2H, CH_2), 4.15 (t, J = 6 Hz, 2H, CH_2), 7.60 (s, 1H, H-pyrid.).

5.2.11. 2-(4-Chlorobutyl)-pyridazin-3(2H)-one **12**

This compound was prepared by alkylation of pyridazin-3(2H)-one with 1-bromo-4-chlorobutane using both methods A or B. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–2%) in CH_2Cl_2. A dense oil was obtained. Yield: 60% with method A, yield: 70% with method B. ^{1}H-NMR ($CDCl_3$) δ: 1.75–2.05 (m, 4H, $2CH_2$), 3.60 (t, J = 6 Hz, 2H, CH_2), 4.20 (t, J = 6 Hz, 2H, CH_2), 6.90 (dd, J = 9 Hz e 2 Hz, 1H, H-pyrid.), 7.20 (dd, J = 9 Hz e 5 Hz, 1H, H-pyrid.), 7.75 (dd, J = 5 Hz e 2 Hz, 1H, H-pyrid.).

5.2.12. 2-(5-Chloropentyl)-pyridazin-3(2H)-one **12a**

This compound was prepared by alkylation of pyridazin-3(2H)-one with 1-bromo-5-chloropentane using method A. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–2%) in CH_2Cl_2. A dense oil was obtained. Yield: 65%. ^{1}H-NMR ($CDCl_3$) δ: 1.40–1.60 (m, 2H, CH_2), 1.75–2.05 (m, 4H, $2CH_2$), 3.50 (t, J = 6 Hz, 2H, CH_2), 4.15 (t, J = 6 Hz, 2H, CH_2), 6.90 (dd, J = 9 Hz e 2 Hz, 1H, H-pyrid.), 7.15 (dd, J = 9 Hz e 5 Hz, 1H, H-pyrid.), 7.75 (dd, J = 5 Hz e 2 Hz, 1H, H-pyrid.).

5.2.13. 2-(4-Chlorobutyl)-phthalazin-1(2H)-one **13**

This compound was prepared by alkylation of phthalazin-1(2H)-one with 1-bromo-4-chlorobutane using method B. Purified by flash-chromatography silica gel using as eluent a stepwise gradient of ethanol (0–2%) in CH_2Cl_2. A dense oil was obtained. Yield: 65%. ^{1}H-NMR ($CDCl_3$) δ: 1.70–2.10 (m, 4H, $2CH_2$), 3.60 (t, J = 6 Hz, 2H, CH_2), 4.30 (t, J = 6 Hz, 2H, CH_2), 7.60–7.80 (m, 3H, H-phthalaz.), 8.10 (s, 1H, H-phthalaz.), 8.35–8.45 (m, 1H, H-phthalaz.).

5.2.14. 2-[4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one-2-yl]-acetic acid **16**

To a solution of 0.18 g (8.0×10^{-3} mol) sodium in 80 mL of dry ethanol there was added 2.91 g (8.0×10^{-3} mol) of 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one (**2**), this mixture was stirred and heated under reflux for 30 min. After cooling this mixture, was added dropwise 1.33 g (8.0×10^{-3} mol) of ethyl bromoacetate. After the addition was complete, the reaction mixture was heated under reflux for 24 h and filtered to remove sodium bromide. The filtrate was evaporated under vacuum and the residue was purified by chromatography silica gel using as eluent a stepwise gradient of ethanol (0–10%) in CH_2Cl_2. A dense oil was obtained corresponding to ethyl 2-[4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-piperazin-1-yl}-pyridazin-3(2H)-one-2-yl]-acetate . Yield (2.02 g): 60%. ^{1}H-NMR ($CDCl_3$) δ: 1.20–1.35 (t, 3H, CH_3), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, J = 6 Hz, 2H, CH_2), 3.40–3.50 (m, 4H, H-pip), 3.90 (s, 3H, OCH_3), 4.10–4.30 (m, 4H, $2CH_2$), 4.80 (s, 2H, CH_2), 6.80–7.00 (m, 4H, H-arom.), 7.65 (s, 1H, H-pirid.). This compound was treated with NaOH 2 N in EtOH and was refluxed under stirring for 4–5 h followed by acidification with acetic acid gave the corresponding acid. M.p.: 135–138 °C.

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