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Synthesis of New Pyridazinone Derivatives and their Affinity Towards α_1–α_2-Adrenoceptors

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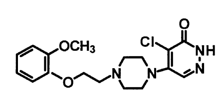
Abstract—A series of 3(2*H*)-pyridazinone derivatives was evaluated for their affinity in vitro towards α_1–α_2-adrenoceptors by radioligand receptor binding assays. All target compounds showed good affinities for the α_1-adrenoceptor (with K_i values in the subnanomolar range), and a gradual increase in affinity was observed by increasing the polymethylene chain length of this series up to a maximum of six and seven carbon atoms, when the fragment 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl is linked in 5 position of the 3(2*H*)-pyridazinone ring, while a slight decrease was found for the higher homologues. Increasing the chain length when the 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl group is linked in 6 position of the 3(2*H*)-pyridazinone ring, had a different effect: there is the highest affinity when the polymethylene chain is of four carbon atoms. The alkylic chain, a spacer between the two major constituents of the molecule, can influence the affinity and the selectivity.

Introduction

The α_1–α_2-adrenoceptors (α_1 AR and α_2 AR) are members of the superfamily of G protein coupled receptors. Molecular cloning studies[1,2] have shown that these receptors have many common features which could reflect their similar mechanisms of action.

In recent years, the search for new α_1-adrenoceptor antagonists has increased, in parallel with the development of postsynaptically selective α-adrenoceptor antagonists, due to their importance in the treatment of hypertension[3] and of benign prostatic hypertrophy[4] (BPH).

In the course of our studies on 3(2*H*)-pyridazinone derivatives as potential antagonists of the α-adrenoceptor, we have recently synthesized compounds **1**[5] and **1a**,[6] which showed good activity towards α_1-adrenoceptor. It is well known that the 1-arylpiperazines and their 4-alkyl derivatives, such as Urapidil and SL8905[7] (**2**), are postsynaptic α-blockers with activity on BPH.



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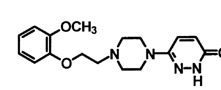
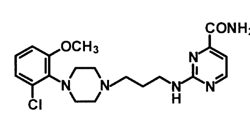


1a



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The objective of our work has been the synthesis of new compounds that are highly selective towards the α_1-receptor, as potential antihypertensive drugs, and as molecular probes for the study of binding sites. In this paper we report the synthesis and biological affinity of compounds in which the 3(2*H*)-pyridazinone ring has been linked in the 2-position with variations of 1-arylpiperazine, by a chain variable for 2 to 8 carbon atoms.

Chemistry

The synthesis of novel pyridazinone derivatives **3**–**28** are reported in Scheme 1.

Compounds **3**[8] and **10** were prepared by alkylation from **30a** with 1-(2-methoxyphenyl)-piperazine or 1-(2-chlorophenyl)-piperazine respectively in isoamylic alcohol and sodium carbonate. Compound **30a** was prepared by

Key words: Pyridazinone; affinity α_1,α_2-blocking; 1-arylpiperazine and RAS.
Abbreviations: TBAB = tetrabutyl ammonium bromide; DMF = *N*,*N*-Dimethylformamide.
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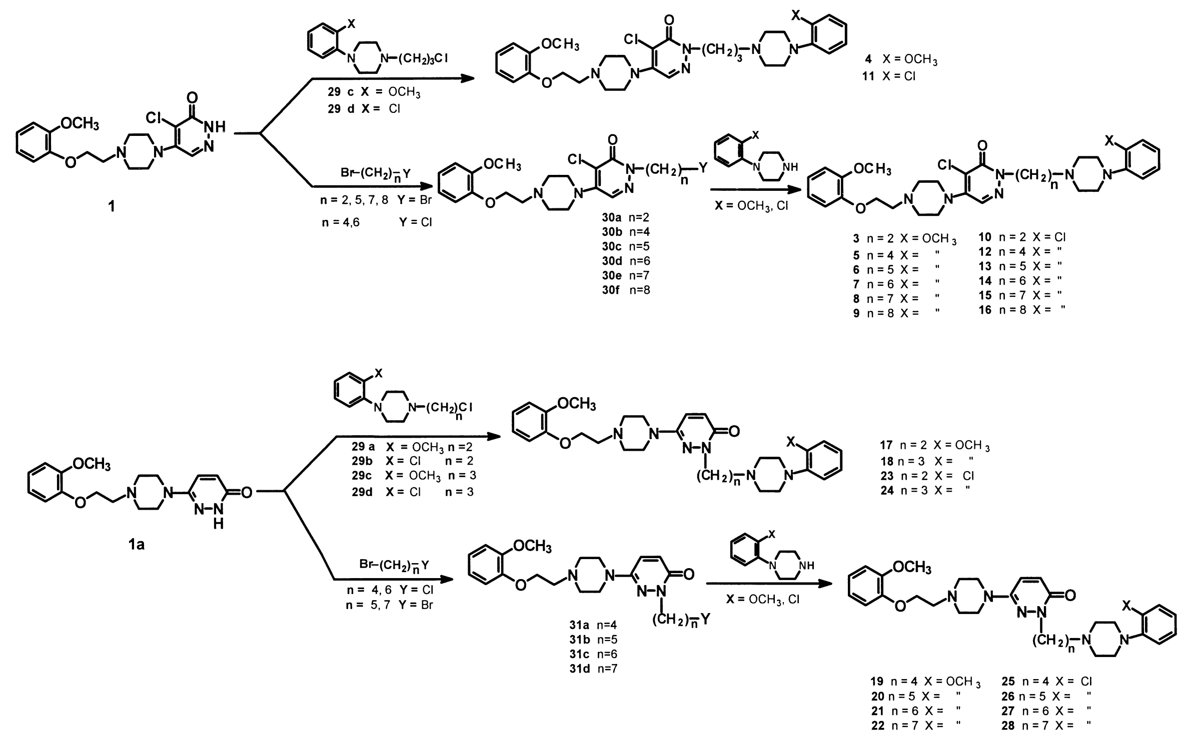


Scheme 1.

treatment of the 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone **1**[5] with 1,2-dibromoethane using benzene, TBAB and KOH according to the method of Yamada et al.[9]

Compounds **4**, **11**, **18** and **24** were prepared by alkylation of the 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**1**) or 6-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**1a**)[6] with 1-(2-methoxyphenyl)-4-(3-chloropropyl)-piperazine (**29c**) or 1-(2-chlorophenyl)-4-(3-chloropropyl)-piperazine (**29d**), in dry ethanol and sodium hydroxide pellets. Intermediates **29c** and **29d** were prepared using the method of J. Bourdais[10] in DMF in the presence of potassium carbonate.

Compounds **17** and **23** were prepared, using as starting compound **1a** by alkylation with 1-(2-methoxyphenyl)-4-(2-chloroethyl)-piperazine (**29a**) or 1-(2-chlorophenyl)-4-(2-chloroethyl)-piperazine (**29b**) (prepared by the method of J. Bourdais)[10] in dry ethanol and sodium hydroxyde pellets, respectively.

Alkylation of compound **1** with the dihalogenates with polymethylene chain length from four to eight carbon atoms, in acetone and potassium carbonate, gave the intermediates **30b–f**, which by reacting with 1-(2-methoxyphenyl)-piperazine or 1-(2-chlorophenyl)-piperazine gave the compounds **5–9**, **12–16**, respectively.

For the synthesis of compounds **19–22** and **25–28** the same procedure described above was used. Finally, the intermediates **31a–d** were prepared using the method described for compounds **30b–f**.

Pharmacology

The pharmacological profile of compounds **3–28** was evaluated for their affinities towards α_1- and α_2-adrenoceptors by determining for each compound the ability to displace [^{3}H]-prazosin or [^{3}H]-rauwolscine, respectively, from specific binding sites on rat cerebral cortex.

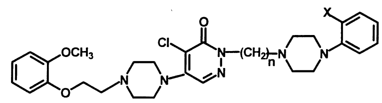
Results and Discussion

In Table 1a–b are reported competition binding experiments of compounds **3–28**.

Relative to the K_i values observed for the α_1-AR and α_2-AR, show that, all the synthesized compounds have higher affinities towards the α_1-adrenoceptor than towards the α_2-adrenoceptor. In the series a gradual increase in affinity was observed by promoting the polymethylene chain length up to a maximum of six or seven carbon atoms, when the fragment 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl is linked in 5 position of the 3(2*H*)-pyridazinone ring (compounds **7**, **8** and **14**, **15**), while a slight decrease was found for the higher homologues **9** and **16**. Increasing the chain length when the 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinil group was linked in 6 position of the 3(2*H*)-pyridazinone ring had a different effect: there is the highest affinity when the polymethylene chain has four carbon atoms (compounds **19** and **25**). Thus, the position of the fragment 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl influences the affinity and it is strictly dependent on the carbon-chain length. In the series of compounds **3–16** a peak potency was observed with a six or seven carbon chain, while in

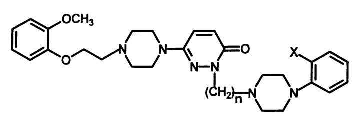
Table 1. Affinity towards α_1- and α_2-adenoceptors

(a)



Compound	n	X	K_i α_1 (nM)	K_i α_2 (nM)	Ratio α_2/α_1
3	2	-OCH_3	16.0 ± 1.7	409.0 ± 35.7	25.5
4	3	-OCH_3	14.5 ± 1.3	245.0 ± 25.3	17.0
5	4	-OCH_3	4.3 ± 0.3	230.0 ± 20.0	53.0
6	5	-OCH_3	3.9 ± 0.2	15.0 ± 1.9	3.8
7	6	-OCH_3	1.5 ± 0.1	3.5 ± 0.4	2.3
8	7	-OCH_3	1.4 ± 0.1	4.6 ± 0.5	3.2
9	8	-OCH_3	3.5 ± 0.4	22.7 ± 3.0	6.5
10	2	-Cl	58.8 ± 3.7	292.3 ± 30.2	5.0
11	3	-Cl	27.8 ± 3.0	219.0 ± 15.8	7.8
12	4	-Cl	10.0 ± 1.5	39.3 ± 5.3	4.0
13	5	-Cl	4.5 ± 0.2	29.0 ± 4.5	6.4
14	6	-Cl	4.2 ± 0.6	25.2 ± 3.8	6.0
15	7	-Cl	2.7 ± 0.3	7.4 ± 0.5	2.7
16	8	-Cl	5.6 ± 0.7	22.8 ± 2.5	4.0
Prazosin			0.24 ± 0.05		
Rauwolscine				4.0 ± 0.3	

(b)



Compound	n	X	K_i α_1 (nM)	K_i α_2 (nM)	Ratio α_2/α_1
17	2	-OCH_3	38.0 ± 5.0	1261.0 ± 210.0	33.2
18	3	-OCH_3	73. ± 0.6	254.0 ± 40.3	34.8
19	4	-OCH_3	0.6 ± 0.1	62.0 ± 8.0	103.3
20	5	-OCH_3	12.9 ± 1.5	69.8 ± 9.2	5.4
21	6	-OCH_3	7.0 ± 0.8	71.8 ± 6.3	10.2
22	7	-OCH_3	2.3 ± 0.2	45.8 ± 6.3	20.0
23	2	-Cl	18.0 ± 2.0	370.0 ± 50.2	20.5
24	3	-Cl	6.8 ± 0.6	316.0 ± 40.3	46.5
25	4	-Cl	0.8 ± 0.1	69.4 ± 6.0	86.7
26	5	-Cl	7.0 ± 0.9	138.0 ± 25.0	20.0
27	6	-Cl	8.4 ± 1.2	138.8 ± 20.3	16.5
28	7	-Cl	15.0 ± 2.5	139.0 ± 15.3	9.3
Prasosin			0.24 ± 0.05		
Rauwolscine				4.0 ± 0.3	

The K_i binding data were calculated as described in the Experimental section. The K_i values are mean ± SD of series separate assays, each performed in triplicate. Inhibition constants (K_i) were calculated according to the equation of Cheng and Prousoff[11] $K_i = IC_{50}/1 + (L/K_d)$ when [L] is the ligand concentration and K_d is dissociation constant. K_d of [^{3}H]-prazosin binding to rat cortex membranes was 0.24 nM (α_1) and K_d of [^{3}H]-rauwolscine binding to rat cortex membranes was 4 nM (α_2).

the series of **17**–**28** the highest affinity was observed when the chain had four carbon atoms. It is evident from these pharmacological results that the presence of a methoxy group in the *ortho* position of the arylpiperazine fragment increases the affinity more than a chlorine atom. Moreover comparing the ratios of the K_i values (α_2/α_1), one can readily see that the length of the alkyl spacer has an effect on selectivity for both the 5- and 6-substituent methoxy series (for example compound **19** shows the highest selectivity). Similar results have been obtained for the 6-substituent chlorine series and little effect was observed for 5-substituted chlorine series.

In conclusion, the length of the alkyl chain, a spacer between the two major constituents of the molecule, can influence the affinity and the selectivity.

Experimental Protocols

Biological methods

α_1-Receptor binding. Rat cerebral cortex was homogenized in 20 volumes ice-cold 50 mM Tris–HCl buffer at pH 7.7 containing 5 mM EDTA (buffer T_1) in an ultra-turrax homogenizer. The homogenate was centrifuged at 48000 *g* for 15 min at 4 °C. The pellet (P_1) was suspended in 20 volumes of ice-cold buffer T_1. It was then homogenized and centrifuged at 48000 *g* for 15 min at 4 °C. The resulting pellet (P_2) was frozen at −80 °C until the time of assay.

The pellet was suspended in 20 volumes of ice-cold 50 mM Tris–HCl buffer at pH 7.7 (T_2 buffer) and α_1 binding assay was performed in triplicate by incubating at 25 °C for 60 min in 1 mL T_2 buffer containing aliquots of the membrane fraction (0.2–0.3 mg protein) and 0.1 nM [^{3}H]-prazosin in the absence or presence of unlabeled 1 μM prazosin. The binding reaction was terminated by filtering through Whatman GF/C glass fiber filters under suction and washing twice with 5 mL ice-cold Tris buffer. The filters were placed in scintillation vials and 4 mL Ultima Gold MN Cocktail-Packard solvent scintillation fluid was added. The radioactivity was counted with an Packard 1600 TR scintillation counter. Specific binding was obtained by subtracting non-specific binding from total binding and was approximated to 85–90% of the total binding.

α_2-Receptor binding. Cerebral cortex was dissected from rat brain and the tissue was homogenized in 20 volumes of ice-cold 50 mM Tris–HCl buffer at pH 7.7 containing 5 mM EDTA, as reported above (buffer T_1). The homogenate was centrifuged at 48000 *g* for 15 min at 4 °C. The resulting pellet was diluted in 20 volumes of 50 mM Tris–HCl buffer at pH 7.7 and used in the binding assay.

Binding assay was performed in triplicate, by incubating aliquots of the membrane fraction (0.2–0.3 mg protein) in Tris–HCl buffer at pH 7.7 with approximately 2 nM [^{3}H]-rauwolscine in a final volume of 1 mL. Incubation was carried out at 25 °C for 60 min. Non-specific binding was defined in the presence of 10 μM rauwolscine. The binding reaction was concluded by filtration through Whatman GF/C glass fiber filters under reduced pressure. Filters were washed four times with 5 mL aliquots of ice-cold buffer and placed in scintillation vials. Specific binding was obtained by subtracting non specific binding from total binding and approximated to 85–90% of total binding. The receptor-bound radioactivity was measured as described above.

Compounds were dissolved in buffer or DMSO (buffer/concentration of 2%) and added to the assay mixture. A blank experiment was carried out to determine the effect of the solvent on binding.

Protein estimation was based on a reported method,[12] after solubilization with 0.75 N sodium hydroxide, using bovine serum albumin as standard.

The concentration of tested compound that produces 50% inhibition of specific [^{3}H]-prazosin or [^{3}H]-rauwolscine binding (IC_{50}) was determined by log-probit analysis with seven concentrations of the displacer, each performed in triplicate. Inhibition constants (K_i) were calculated according to the equation:[11] $K_i = IC_{50}/1 + ([L]/K_d)$ where [L] is the ligand concentration and K_d its dissociation constant. K_d of [^{3}H]-prazosin binding to cortex membranes was 0.24 nM (α_1) and K_d of [^{3}H]-rauwolscine binding to cortex membranes was 4 nM (α_2)

Experimental

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.

General method A

4-Chloro-2-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (3). A mixture of (1 g, 2.3 mmol) of 4-chloro-2-(2-chloroethyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30a**), (0.45 g, 2.3 mmol) of 1-(2-methoxyphenyl)-piperazine, (0.3 g, 2.9 mmol) of dry sodium carbonate in 40 mL of isoamylic alcohol, was refluxed under stirring for 24 h, after filtration, the solvent was removed under reduced pressure, and the residue was purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (4/96) to give a dense oil, (50%). ^{1}H NMR ($CDCl_3$) δ: 2.60–2.95 (m, 12H, 8H-pip., $2CH_2$), 3.05–3.15 (m, 4H, H-pip.), 3.40–3.55 (m, 4H, H-pip.), 3.85 (s, 6H, 2-OCH_3), 4.20 (t, *J* = 6 Hz, 2H, CH_2), 4.35 (t, *J* = 6 Hz, 2H, CH_2), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 128–129 °C. Anal. calcd for $C_{30}H_{39}ClN_6O_4$. 2HCl: C, 54.93; H, 6.25; N, 12.81, found: C, 54.65; H, 6.04; N, 12.54.

Compounds **5–10**, **12–16** were synthesized following general method A.

4-Chloro-2-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (5). By 4-chloro-2-(4-chlorobutyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30b**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (7/93), a dense oil was obtained (60%), ^{1}H NMR ($CDCl_3$) δ: 1.50–1.65 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.50 (t, *J* = 8 Hz, 2H, CH_2), 2.60–2.80 (m, 8H, H-pip.), 2.90 (t, *J* = 6 Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10–4.30 (m, 4H, $2CH_2$), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 126–128 °C. Anal. calcd for $C_{32}H_{43}ClN_6O_4$. 3HCl: C, 53.35; H, 6.39; N, 11.67, found: C, 53.31; H, 6.78; N, 11.36.

4-Chloro-2-{5-[4-(2-methoxyphenyl)-1-piperazinyl]pentyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (6). From 4-chloro-2-(5-bromopentyl)-5-{4-

[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30c**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (5/95), a dense oil was obtained (30%). ^1H NMR ($CDCl_3$) δ: 1.35–1.45 (m, 2H, CH_2), 1.55–1.70 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.55–2.65 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.15 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, 2-OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 95–98 °C. Anal. calcd for $C_{33}H_{45}ClN_6O_4$. 3HCl : C, 53.96; H, 6.54; N, 11.44, found: C, 54.20; H, 6.75; N, 11.65.

4-Chloro-2-{6-[4-(2-methoxyphenyl)-1-piperazinyl]hexyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (7). From 4-chloro-2-(6-chlorohexyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30d**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (69%). ^1H NMR ($CDCl_3$) δ: 1.30–1.40 (m, 4H, $2CH_2$), 1.50–1.65 (m, 2H, CH_2), 1.70–1.85 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.55–2.75 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 138–140 °C. Anal. calcd for $C_{34}H_{47}ClN_6O_4$. 3HCl: C, 54.56; H, 6.68; N, 11.20, found: C, 55.00; H, 6.91; N, 11.32.

4-Chloro-2-{7-[4-(2-methoxyphenyl)-1-piperazinyl]heptyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (8). From 4-chloro-2-(7-bromoheptyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30e**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (75%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 6H, $3CH_2$), 1.50–1.60 (m, 2H, CH_2), 1.70–1.85 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.70–2.80 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, 2-OCH_3), 4.10–4.25 (m, 4H, $2CH_2$), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 125–128 °C. Anal. calcd for $C_{35}H_{49}ClN_6O_4$. 3HCl: C, 55.35; H, 6.45; N, 11.07, found: C, 55.36; H, 7.00; N, 10.95.

4-Chloro-2-{8-[4-(2-methoxyphenyl)-1-piperazinyl]octyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (9). From 4-chloro-2-(8-chlorooctyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30f**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (7/93), a dense oil was obtained (40%). ^1H NMR ($CDCl_3$) δ: 1.30–1.40 (m, 8H, $4CH_2$), 1.50–1.60 (m, 2H, CH_2), 1.65–1.75 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.60–2.70 (m, 8H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10–4.30 (m, 4H, $2CH_2$), 6.70–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride is hygroscopic. Anal. calcd for $C_{36}H_{51}ClN_6O_4$.3HCl: C, 55.90; H, 6.98; N, 10.87, found: C, 55.78; H, 6.60; N, 10.73.

4-Chloro-2-{2-[4-(2-chlorophenyl)-1-piperazinyl]ethyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (10). From 4-chloro-2-(2-chloroethyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30a**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (75%). ^1H NMR ($CDCl_3$) δ: 2.70–2.80 (m, 8H, H-pip.), 2.85–2.95 (m, 4H, $2CH_2$), 3.05–3.15 (m, 4H, H-pip), 3.40–3.50 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.20 (t, $J=6$ Hz, 2H, CH_2), 4.35 (t, $J=6$ Hz, 2H, CH_2), 6.90–7.05 (m, 6H, H-arom.), 7.15–7.35 (m, 2H, H-arom.), 7.65 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 247–250 °C. Anal. calcd for $C_{29}H_{36}Cl_2N_6O_3$. 2HCl: C, 52.74; H, 5.76; N, 12.70, found: C, 52.63; H, 6.05; N, 12.46.

4-Chloro-2-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (12). From 4-chloro-2-(4-chlorobutyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30b**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (10/90), a dense oil was obtained (35%). ^1H NMR ($CDCl_3$) δ: 1.50–1.70 (m, 2H, CH_2), 1.85–2.00 (m, 2H, CH_2), 2.55 (t, $J=8$ Hz, 2H, CH_2), 2.65–2.75 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.95–7.10 (m, 6H, H-arom.), 7.15–7.35 (m, 2H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 127–130 °C. Anal. calcd for $C_{31}H_{40}Cl_2N_6O_3$. 3HCl: C, 54.10; H, 6.10; N, 12.20, found: C, 54.45; H, 6.41; N, 11.95.

4-Chloro-2-{5-[4-(2-chlorophenyl)-1-piperazinyl]pentyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (13). From 4-chloro-2-(5-bromopentyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30c**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (7/93), a dense oil was obtained (40%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 2H, CH_2), 1.50–1.70 (m, 2H, CH_2), 1.75–1.85 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.65–2.75 (m, 8H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.35–3.45 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–6.95 (m, 5H, H-arom.), 7.05 (d, 1H, H-arom.), 7.20 (t, 1H, H-arom.), 7.25–7.35 (m, 1H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 120–123 °C. Anal. calcd for $C_{32}H_{42}Cl_2N_6O_3$. 4HCl: C, 49.56; H, 65.42; N, 10.80, found: C, 49.62; H, 5.90; N, 10.95.

4-Chloro-2-{6-[4-(2-chlorophenyl)-1-piperazinyl]hexyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (14). From 4-chloro-2-(6-chlorohexyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30d**) with 1-(2-chlorophenyl)-piperazine.

Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (58%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 4H, $2CH_2$), 1.55–1.65 (m, 2H, CH_2), 1.75–1.85 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.65–2.75 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.00–3.10 (m, 4H, H-pip.), 3.35–3.45 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–6.95 (m, 5H, H-arom.), 7.05 (d, 1H, H-arom.), 7.20 (t, 1H, H-arom.), 7.25–7.35 (m, 1H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 219–222 °C. Anal. calcd for $C_{33}H_{44}Cl_2N_6O_3$. 2HCl: C, 55.00; H, 6.40; N, 11.70, found: C, 55.11; H, 6.54; N, 11.57.

4-Chloro-2-{7-[4-(2-chlorophenyl)-1-piperazinyl]heptyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (15). From 4-chloro-2-(7-bromoheptyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30e**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (75%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 6H, $3CH_2$), 1.55–1.65 (m, 2H, CH_2), 1.75–1.85 (m, 2H, CH_2), 2.40 (t, $J=8$ Hz, 2H, CH_2), 2.60–2.70 (m, 8H, H-pip.), 2.95 (t, 2H, CH_2), 3.00–3.10 (m, 4H, H-pip.), 3.35–3.45 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.20 (m, 4H, $2CH_2$), 6.80–6.95 (m, 5H, H-arom.), 7.05 (d, 1H, H-arom.), 7.20 (t, 1H, H-arom.), 7.25–7.35 (m, 1H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride is hygroscopic. Anal. calcd for $C_{34}H_{46}Cl_2N_6O_3$. 4HCl: C, 50.82; H, 5.70; N, 10.40, found: C, 50.86; H, 5.80; N, 10.26.

4-Chloro-2-{8-[4-(2-chlorophenyl)-1-piperazinyl]octyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (16). From 4-chloro-2-(8-chlorooctyl)-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**30f**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (6/94), a dense oil was obtained (40%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 8H, $4CH_2$), 1.50–1.60 (m, 2H, CH_2), 1.65–1.75 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.60–2.75 (m, 8H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.30 (m, 4H, $2CH_2$), 6.70–6.90 (m, 5H, H-arom.), 7.05 (d, 1H, H-arom.), 7.20 (t, 1H, H-arom.), 7.25–7.35 (m, 1H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride is hygroscopic. Anal. calcd for $C_{35}H_{48}Cl_2N_6O_3$. 3HCl: C, 53.82; H, 6.53; N, 10.76, found: C, 53.91; H, 6.75; N, 10.83.

Compounds **19**–**22** and **25**–**28** were prepared using the general method A, starting from 6-(4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**1a**).[6]

2-{4-[4-(2-Methoxyphenyl)-1-piperazinyl]butyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (19). From 2-(4-chlorobutyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31a**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (12/88), a dense oil was obtained (50%). ^1H NMR ($CDCl_3$) δ: 1.60–1.75 (m, 2H, CH_2), 1.80–1.90 (m, 2H, CH_2), 2.50 (t, $J=8$ Hz, 2H, CH_2), 2.70–2.80 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.30–3.40 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.80–7.00 (m, 9H, 8H-arom., 1H-pyrid.), 7.10 (d, 1H, H-pyrid.). The corresponding hydrochloride had mp: 125–128 °C. Anal. calcd for $C_{32}H_{44}N_6O_4$. 5HCl: C, 50.64; H, 6.46; N, 11.08, found: C, 50.58; H, 6.76; N, 10.95.

2-{5-[4-(2-Methoxyphenyl)-1-piperazinyl]pentyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (20). From 2-(5-bromopentyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31b**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (7/93), a dense oil was obtained (45%). ^1H NMR ($CDCl_3$) δ: 1.40–1.50 (m, 2H, CH_2), 1.60–1.70 (m, 2H, CH_2), 1.80–1.90 (m, 2H, CH_2), 2.50 (t, $J=8$ Hz, 2H, CH_2), 2.70–2.80 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.25–3.35 (m, 4H, H-pip.), 3.90 (s, 6H, $2OCH_3$), 4.10 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.80–7.00 (m, 9H, 8H-arom., 1H-pyrid.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.). The corresponding hydrochloride had mp: 131–134 °C. Anal. calcd for $C_{33}H_{46}N_6O_4$. 5HCl: C, 51.27; H, 6.60; N, 10.80, found: C, 51.47; H, 6.86; N, 10.55.

2-{6-[4-(2-Methoxyphenyl)-1-piperazinyl]hexyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (21). From 2-(6-chlorohexyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31c**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (10/90), a dense oil was obtained (47%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 4H, $2CH_2$), 1.60–1.70 (m, 2H, CH_2), 1.80–1.90 (m, 2H, CH_2), 2.45 (t, $J=8$ Hz, 2H, CH_2), 2.70–2.80 (m, 8H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.25–3.35 (m, 4H, H-pip.), 3.90 (s, 6H, $2OCH_3$), 4.10 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.80–7.00 (m, 9H, 8H-arom., 1H-pyrid.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.). The corresponding hydrochloride had mp: 132–135 °C. Anal. calcd for $C_{34}H_{48}N_6O_4$. 5HCl: C, 51.89; H, 6.70; N, 10.60, found: C, 51.75; H, 7.03; N, 10.34.

2-{7-[4-(2-Methoxyphenyl)-1-piperazinyl]heptyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (22). From 2-(7-bromoheptyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31d**) with 1-(2-methoxyphenyl)-piperazine. Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (10/90), a dense oil was obtained (70%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 6H, $3CH_2$), 1.60–1.85 (m, 4H, $2CH_2$), 2.70 (t, $J=8$ Hz, 2H, CH_2), 2.75–2.80 (m, 4H, H-pip.), 2.85–3.00 (m, 6H, 4H-pip., CH_2), 3.20–3.30 (m, 4H, H-pip.), 3.35–3.40 (m, 4H, H-pip.), 3.90 (s, 6H, $2OCH_3$), 4.10 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.85 (d, $J=9$ Hz, 1H, H-pyrid.), 6.80–7.00 (m, 8H, H-arom.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.). The corresponding hydrochloride had mp:

137–140 °C. Anal. calcd for $C_{35}H_{50}N_6O_4$. 5HCl: C, 52.48; H, 6.87; N, 10.49, found: C, 52.75; H, 6.95; N, 10.64.

2-{4-[4-(2-Chlorophenyl)-1-piperazinyl]butyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (25). From 2-(4-chlorobutyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31a**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (13/87), a dense oil was obtained (30%). ^1H NMR ($CDCl_3$) δ: 1.55–1.75 (m, 2H, CH_2), 1.80–1.95 (m, 2H, CH_2), 2.55 (t, $J = 8$ Hz, 2H, CH_2), 2.65–2.70 (m, 8H, H-pip.), 2.95 (t, $J = 6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.30–3.40 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.10 (t, $J = 8$ Hz, 2H, CH_2), 4.25 (t, $J = 6$ Hz, 2H, CH_2), 6.85 (d, $J = 9$ Hz, 1H, H-pyrid.), 6.90–7.10 (m, 7H, H-arom.), 7.15 (d, $J = 9$ Hz, 1H, H-pyrid.), 7.20–7.40 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 115–118 °C. Anal. calcd for $C_{31}H_{41}ClN_6O_3$. 3HCl: C, 53.90; H, 6.37; N, 12.70, found: C, 53.84; H, 6.20; N, 11.95.

2-{5-[4-(2-Chlorophenyl)-1-piperazinyl]pentyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (26). From 2-(5-bromopentyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31b**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (14/86), a dense oil was obtained (35%). ^1H NMR ($CDCl_3$) δ: 1.40–1.45 (m, 2H, CH_2), 1.50–1.70 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.40 (t, $J = 8$ Hz, 2H, CH_2), 2.65–2.70 (m, 8H, H-pip.), 2.90 (t, $J = 6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.30–3.40 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.05 (t, $J = 8$ Hz, 2H, CH_2), 4.15 (t, $J = 6$ Hz, 2H, CH_2), 6.85 (d, $J = 9$ Hz, 1H, H-pyrid.), 6.90–7.00 (m, 7H, H-arom.), 7.10 (d, $J = 9$ Hz, 1H, H-pyrid.), 7.15–7.35 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 136–138 °C. Anal. calcd for $C_{32}H_{43}ClN_6O_3$. 4HCl: C, 52.87; H, 6.35; N, 11.30, found: C, 52.76; H, 6.20; N, 10.95.

2-{6-[4-(2-Chlorophenyl)-1-piperazinyl]hexyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (27). From 2-(6-chlorohexyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31c**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (15/85), a dense oil was obtained (30%). ^1H NMR ($CDCl_3$) δ: 1.35–1.45 (m, 4H, $2CH_2$), 1.55–1.70 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.50 (t, $J = 8$ Hz, 2H, CH_2), 2.65–2.75 (m, 8H, H-pip.), 2.95 (t, $J = 6$ Hz, 2H, CH_2), 3.10–3.20 (m, 4H, H-pip.), 3.30–3.40 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.05 (t, $J = 8$ Hz, 2H, CH_2), 4.20 (t, $J = 6$ Hz, 2H, CH_2), 6.85 (d, $J = 9$ Hz, 1H, H-pyrid.), 6.90–7.15 (m, 7H, H-arom.), 7.20–7.25 (m, 1H, H-pyrid.), 7.30–7.40 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 127–130 °C. Anal. calcd for $C_{33}H_{45}ClN_6O_3$. 3HCl: C, 55.10; H, 6.50; N, 11.70, found: C, 55.35; H, 6.81; N, 11.42.

2-{7-[4-(2-Chlorophenyl)-1-piperazinyl]heptyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (28). From 2-(7-bromoheptyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**31d**) with 1-(2-chlorophenyl)-piperazine. Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (15/85), a dense oil was obtained (65%). ^1H NMR ($CDCl_3$) δ: 1.30–1.45 (m, 6H, $3CH_2$), 1.50–1.65 (m, 2H, CH_2), 1.70–1.85 (m, 2H, CH_2), 2.45 (t, $J = 8$ Hz, 2H, CH_2), 2.65–2.75 (m, 8H, H-pip.), 2.90 (t, $J = 6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.25–3.40 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.00 (t, $J = 8$ Hz, 2H, CH_2), 4.15 (t, $J = 6$ Hz, 2H, CH_2), 6.85 (d, $J = 9$ Hz, 1H, H-pyrid.), 6.90–7.05 (m, 7H, H-arom.), 7.10 (d, $J = 9$ Hz, 1H, H-pyrid.), 7.20–7.35 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 137–140 °C. Anal. calcd for $C_{34}H_{47}ClN_6O_3$. 4HCl: C, 54.64; H, 6.92; N, 10.27, found: C, 54.10; H, 6.65; N, 10.50.

General method B

4-Chloro-2-{3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (4). To 30 mL of dry ethanol was added (0.1g, 2.5 mmol) of sodium hydroxide pellets, after was added 4-chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (**1**) (0.9g, 2.5 mmol) and the suspension was refluxed under stirring for 30 min, then 1-(2-methoxyphenyl)-4-(3-chloropropyl)-piperazine (**29c**) (0.67 g, 2.5 mmol) dissolved in dry ethanol was added, after the reaction mixture was refluxed under stirring for 15 h. After cooling and evaporation under reduced pressure of the solvent, the residue was purified by chromatography on a silica gel, eluting with EtOH/CH_2Cl_2 (7/93). A dense oil was obtained (45%). ^1H NMR ($CDCl_3$) δ: 1.90–2.10 (m, 2H, CH_2), 2.50 (t, $J = 8$ Hz, 2H, CH_2), 2.60–2.80 (m, 8H, H-pip.), 2.90 (t, $J = 6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10–4.30 (m, 4H, $2CH_2$), 6.80–7.00 (m, 8H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride had mp: 113–115 °C. Anal. calcd for $C_{31}H_{41}ClN_6O_4$. 2HCl: C, 55.57; H, 6.42; N, 12.54, found: C, 55.83; H, 6.65; N, 12.70.

4-Chloro-2-{3-[4-(2-chlorophenyl)-1-piperazinyl]propyl}-5-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (11). From **1** with 1-(2-chlorophenyl)-4-(3-chloropropyl)-piperazine (**29d**). Purified by chromatography on a silica gel column eluting with EtOH/CH_2Cl_2 (8/92), a dense oil was obtained (30%). ^1H NMR ($CDCl_3$) δ: 2.00–2.15 (m, 2H, CH_2), 2.55 (t, $J = 8$ Hz, 2H, CH_2), 2.65–2.75 (m, 4H, H-pip.), 2.75–2.85 (m, 4H, H-pip.), 2.95 (t, $J = 6$ Hz, 2H, CH_2), 3.05–3.15 (m, 4H, H-pip.), 3.40–3.50 (m, 4H, H-pip.), 3.90 (s, 3H, OCH_3), 4.15–4.30 (m, 4H, $2CH_2$), 6.90–7.10 (m, 6H, H-arom.), 7.15–7.35 (m, 2H, H-arom.), 7.60 (s, 1H, H-pyrid.). The corresponding hydrochloride is hygroscopic. Anal. calcd for $C_{30}H_{38}Cl_2N_6O_3$. 3HCl: C, 50.68; H, 5.80; N, 11.60, found: C, 50.28; H, 6.00; N, 11.25.

Compounds **17**, **18**, **23** and **24** were prepared with the same procedure described for compound **4** starting from compound **1a**.

2-{2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone

(17). From **1a** with 1-(2-methoxyphenyl)-4-(2-chloroethyl)-piperazine (**29a**). Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (8/92), a dense oil was obtained (50%). ^1H NMR ($CDCl_3$) δ: 2.60–2.80 (m, 8H, H-pip.), 2.85–2.90 (m, 4H, $2CH_2$), 3.05–3.15 (m, 4H, H-pip.), 3.25–3.40 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.15–4.30 (m, 4H, $2CH_2$), 6.80–6.95 (m, 9H, 8H-arom., 1H-pyrid.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.). The corresponding hydrochloride had mp: 231–234 °C. Anal. calcd for $C_{30}H_{40}N_6O_4$. 2HCl: C, 57.98; H, 6.76; N, 13.52, found: C, 57.67; H, 6.82; N, 13.70.

2-{3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (18). From **1a** with 1-(2-methoxyphenyl)-4-(3-chloropropyl)-piperazine (**29c**). Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (10/90), a dense oil was obtained (35%). ^1H NMR ($CDCl_3$) δ: 2.10–2.20 (m, 2H, CH_2), 2.65–2.80 (m, 8H, H-pip.), 2.85–2.95 (m, 4H, $2CH_2$), 3.20–3.30 (m, 4H, H-pip.), 3.35–3.40 (m, 4H, H-pip.), 3.85 (s, 6H, $2OCH_3$), 4.10–4.30 (m, 4H, $2CH_2$), 6.80–7.00 (m, 9H, 8H-arom., 1H-pyrid.), 7.10 (d, 1H, H-pyrid.). The corresponding hydrochloride is hygroscopic. Anal. calcd for $C_{31}H_{42}N_6O_4$. 2HCl: C, 58.60; H, 6.93; N, 13.23, found: C, 58.27; H, 6.63; N, 12.95.

2-{2-[4-(2-chlorophenyl)-1-piperazinyl]ethyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (23). From **1a** with 1-(2-chlorophenyl)-4-(2-chloroethyl)-piperazine (**29b**). Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (12/88), a dense oil was obtained (45%). ^1H NMR ($CDCl_3$) δ: 2.60–2.70 (m, 8H, H-pip.), 2.75–2.80 (m, 4H, $2CH_2$), 2.95–3.05 (m, 4H, H-pip.), 3.20–3.30 (m, 4H, H-pip.), 3.80 (s, 6H, $2OCH_3$), 4.05–4.25 (m, 4H, $2CH_2$), 6.75 (d, $J=9$ Hz, 1H, H-pyrid.), 6.90–7.05 (m, 6H, H-arom.), 7.15 (d, $J=9$ Hz, 1H-pyrid.), 7.20–7.25 (m, 1H, H-arom.), 7.35–7.45 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 228–232 °C. Anal. calcd for $C_{29}H_{37}ClN_6O_3$. 2HCl: C, 55.64; H, 6.23; N, 13.43, found: C, 55.73; H, 6.40; N, 13.60.

2-{3-[4-(2-chlorophenyl)-1-piperazinyl]propyl}-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (24). From **1a** with 1-(2-chlorophenyl)-4-(3-chloropropyl)-piperazine (**29d**). Purified by chromatography on a silica gel column eluting with $EtOH/CH_2Cl_2$ (12/88), a dense oil was obtained (35%). ^1H NMR ($CDCl_3$) δ: 2.05–2.25 (m, 2H, CH_2), 2.65–2.75 (m, 6H, 4H-pip., CH_2), 2.80–2.95 (m, 6H, 4H-pip, CH_2), 3.15–3.25 (m, 4H, H-pip.), 3.30–3.40 (m, 4H, H-pip.), 3.85 (s, 3H, OCH_3), 4.10–4.25 (m, 4H, $2CH_2$), 6.85 (d, $J=9$ Hz, 1H, H-pyrid.), 6.90–7.10 (m, 7H, H-arom.), 7.15–7.25 (m, 1H, H-pyrid.), 7.30–7.40 (m, 1H, H-arom.). The corresponding hydrochloride had mp: 189–192 °C. Anal. calcd for $C_{30}H_{39}ClN_6O_3$. 2HCl: C, 56.30; H, 6.72; N, 13.13, found: C, 56.11; H, 6.40; N, 12.97.

4-Chloro-2-(2-chloroethyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30a). This compound was prepared from **1**, with 1,2-dibromoethane in benzene, potassium hydroxide and tetrabutyl ammonium bromide (TBAB) using the method of Yamada.[9] The residue was purified by chromatography on a silica gel using $EtOH/CH_2Cl_2$ (4/96) (35%). ^1H NMR ($CDCl_3$) δ: 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.), 3.70 (t. $J=6$ Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.20 (t, $J=6$ Hz, 2H, CH_2), 4.50 (t, $J=6$ Hz, 2H, CH_2), 6.85–6.95 (m, 4H, H-arom.), 7.65 (s, 1H, H-pyrid.).

General method C

4-Chloro-2-(4-chlorobutyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30b). A mixture of 1 g (20 mmol) of **1**, 1-bromo-4-chlorobutane (0.7 g, 30 mmol), dry potassium carbonate (0.56 g, 30 mmol) in 20 mL of the acetone, was refluxed under stirring for 15 h. After the filtered residue was evaporated under reduced pressure and was purified by chromatography on silica gel eluting with $EtOH/CH_2Cl_2$ (3/97) (70%). ^1H NMR ($CDCl_3$) δ: 1.75–2.05 (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.), 3.60 (t. $J=6$ Hz, 2H, CH_2), 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.)

Compounds **30c–f** were prepared using the method described for compound **30b**.

4-Chloro-2-(5-bromopentyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30c). From **1** with 1,5-dibromopentane, reaction time 6 h, (50%). ^1H NMR ($CDCl_3$) δ: 1.40–1.60 (m, 2H, CH_2), 1.70–2.00 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.35–3.55 (m, 6H, 4H-pip., CH_2), 3.90 (s, 3H, OCH_3), 4.10–4.30 (m, 4H, $2CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 1H, H-pyrid.).

4-Chloro-2-(6-chlorohexyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30d). From **1** with 1-bromo-6-chlorohexane, reaction time 8 h, (50%). ^1H NMR ($CDCl_3$) δ: 1.30–1.35 (m, 4H, $2CH_2$), 1.70–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.35–3.55 (m, 6H, 4H-pip., CH_2), 3.90 (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.).

4-Chloro-2-(7-bromoheptyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30e). From **1** with 1,7-dibromoheptane, reaction time 7 h, (75%). ^1H NMR ($CDCl_3$) δ: 1.30–1.50 (m, 6H, $3CH_2$), 1.70–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.40–3.50 (m, 6H, 4H-pip., CH_2), 3.85 (s, 3H, OCH_3), 4.05–4.20 (m, 4H, $2CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 1H, H-pyrid.).

4-Chloro-2-(8-bromooctyl)-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (30f). From **1** with 1,8-dibromooctane, reaction time 18 h, (50%). ^1H NMR ($CDCl_3$) δ: 1.20–1.45 (m, 8H, $4CH_2$), 1.60–1.90 (m, 4H, $2CH_2$), 2.75–2.85 (m, 4H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.25–3.50 (m, 6H, 4H-pip., CH_2), 3.90 (s, 3H, OCH_3), 4.00–4.20 (m, 4H, $2CH_2$), 6.80–7.00 (m, 4H, H-arom.), 7.60 (s, 1H, H-pyrid.).

Compounds **31a–d** were prepared using the general method C starting compound **1a**.

2-(4-Chlorobutyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (31a). Reaction time 20 h, (70%). ^{1}H NMR ($CDCl_3$) δ: 1.50–2.00 (m, 4H, $2CH_2$), 2.70–2.85 (m, 4H, H-pip.), 3.00 (t, $J=6$ Hz, 2H, CH_2), 3.30–3.40 (m, 4H, H-pip.), 3.60 (t, $J=8$ Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.10 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.80 (d, $J=9$ Hz, 1H, H-pyrid.), 6.90–7.00 (m, 4H, H-arom.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.).

2-(5-Bromopentyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (31b). Reaction time 20 h, (70%). ^{1}H NMR ($CDCl_3$) δ: 1.40–1.60 (m, 2H, CH_2), 1.75–2.00 (m, 4H, $2CH_2$), 2.70–2.85 (m, 4H, H-pip.), 2.95 (t, $J=6$ Hz, 2H, CH_2), 3.30–3.50 (m, 6H, 4H-pip., CH_2), 3.90 (s, 3H, OCH_3), 4.05 (t, $J=8$ Hz, 2H, CH_2), 4.25 (t,$J=6$ Hz, 2H, CH_2), 6.85 (d, 1H, H-pyrid.), 6.90–7.00 (m, 4H, H-arom.), 7.10 (d, 1H, H-pyrid.).

2-(6-Chlorohexyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (31c). Reaction time 18 h, (70%). ^{1}H NMR ($CDCl_3$) δ: 1.30–1.50 (m, 4H, $2CH_2$), 1.75–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 3.00 (t, $J=6$ Hz, 2H, CH_2), 3.30–3.40 (m, 4H, H-pip.), 3.55 (t, $J=8$ Hz, H, CH_2), 3.90 (s, 3H, OCH_3), 4.05 (t, $J=8$ Hz, 2H, CH_2), 4.25 (t, $J=6$ Hz, 2H, CH_2), 6.85 (d, $J=9$ Hz, 1H, H-pyrid.), 6.90–7.00 (m, 4H, H-arom.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.).

2-(7-Bromoheptyl)-6-{4-[2-(2-methoxyphenoxy)ethyl]-1-piperazinyl}-3(2*H*)-pyridazinone (31d). Reaction time 20 h, (50%). ^{1}H NMR ($CDCl_3$) δ: 1.30–1.50 (m, 6H, $3CH_2$), 1.70–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, H-pip.), 2.90 (t, $J=6$ Hz, 2H, CH_2), 3.30–3.50 (m, 6H, 4H-pip., CH_2), 3.95 (s, 3H, OCH_3), 4.05 (t, $J=8$ Hz, 2H, CH_2), 4.20 (t, $J=6$ Hz, 2H, CH_2), 6.80 (d, $J=9$ Hz, 1H, H-pyrid.), 6.90–7.00 (m, 4H, H-arom.), 7.10 (d, $J=9$ Hz, 1H, H-pyrid.).

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