

Biologically Active 1-Arylpiperazines. Synthesis of New N-(4-Aryl-1-piperaziny)alkyl Derivatives of Quinazolidin-4(3H)-one, 2,3-Dihydrophthalazine-1,4-dione and 1,2-Dihydropyridazine-3,6-dione as Potential Serotonin Receptor Ligands

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Abstract: The synthesis of a series of new *n*-propyl and *n*-butyl chain containing 1-aryl-piperazine derivatives of quinazolidin-4(3H)-one (**7**) 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8**) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9**) as potential serotonin receptor ligands is described.

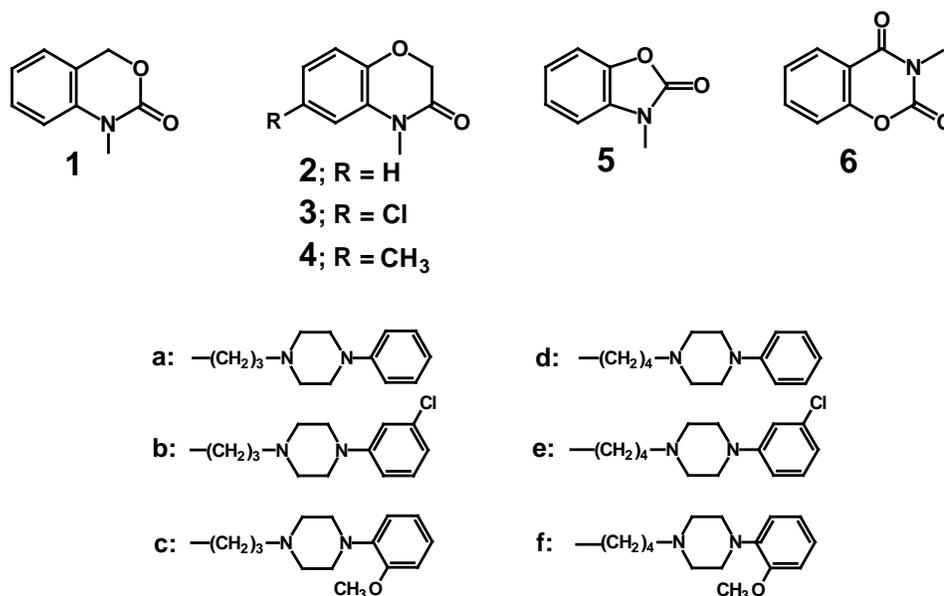
Keywords: Arylpiperazines, lactams, serotonin receptor ligands.

Introduction

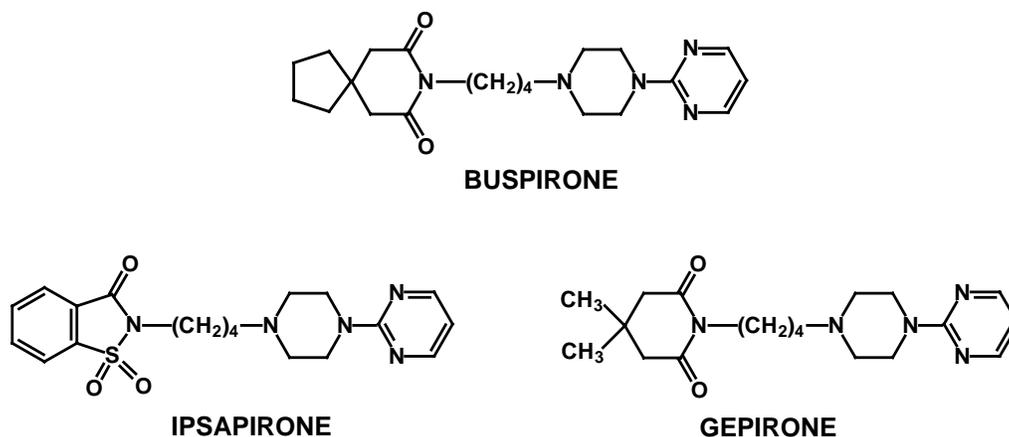
Early studies by Hibert et al. have shown that there are two basic pharmacophore groups common to all five classes of 5-HT_{1A} receptor ligands: a basic nitrogen atom and an aromatic ring with its centre positioned at a distance of 5.2-5.7 Å [1]. Since then several attempts have been made to extend that model, but the large diversity of ligand structures made definition of general interaction modes

impossible. In consequence, a search for other pharmacophore groups was limited to single classes or subgroups of ligands [2-5]. In the case of 1-arylpiperazine derivatives – the biggest and thoroughly investigated class of 5-HT_{1A} receptor ligands [6] – an amide moiety [7] or an amide oxygen atom [8] was suggested as a third interaction point; however, the authors developed those models on the basis of a relatively small group of compounds. Extensive CoMFA investigation of a large set of 1-arylpiperazine derivatives has revealed that in this third interaction region different forces, e.g. steric, electrostatic or lipophilic, may influence the ligand-receptor complex formation [9]. Since the role of the amide fragment in ligand-receptor interactions is still unclear systematic structure affinity relationship studies are necessary.

Recently we described the synthesis and pharmacological results concerning new arylpiperazine derivatives with systematic modifications in the amide part, *i.e.* 1-arylpiperazine derivatives of benzoxazinone **1-4**, benzoxazolinone **5** and benzoxazolindione **6** [10].

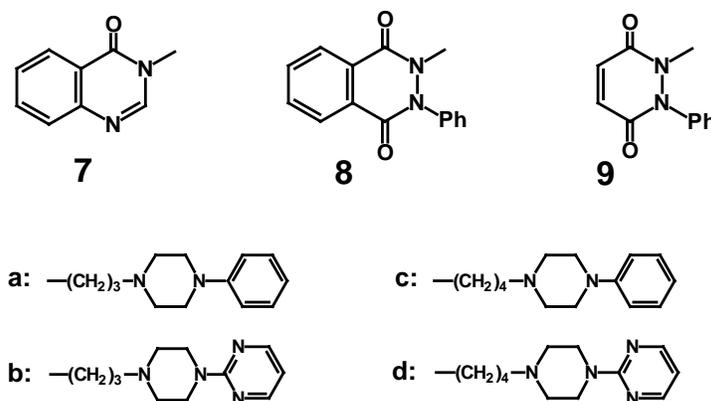


The majority of these compounds have a distinct affinity for 5-HT_{1A} and/or 5-HT_{2A} receptor binding sites. Radioligand binding studies have shown that compounds **1b**, **2a-b**, **2d-e**, **4b** and **6e-f** have a good ($K_i = 1.25 - 40$ nM) and compounds **1a**, **3a-b** and **5a-b** a moderate ($K_i = 72-110$ nM) affinity for 5-HT_{1A} receptors. The 5-HT_{2A} affinity of the obtained compounds was within a range of $K_i = 18 - 495$ nM. On the other hand Buspirone – {4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-8-azaspiro[4.5]decane-7,9-dione – approved as the anxiolytic drug, and its two analogues Ipsapirone and Gepirone bind with high affinity and selectivity to 5-HT_{1A} serotonin receptor sites. Therefore, in order to throw more light on ligand – 5-HT_{1A} receptor interactions we designed new model 1-phenylpiperazine and 1-(2-pyrimidinyl)piperazine derivatives with systematic structural changes within the terminal amide part.



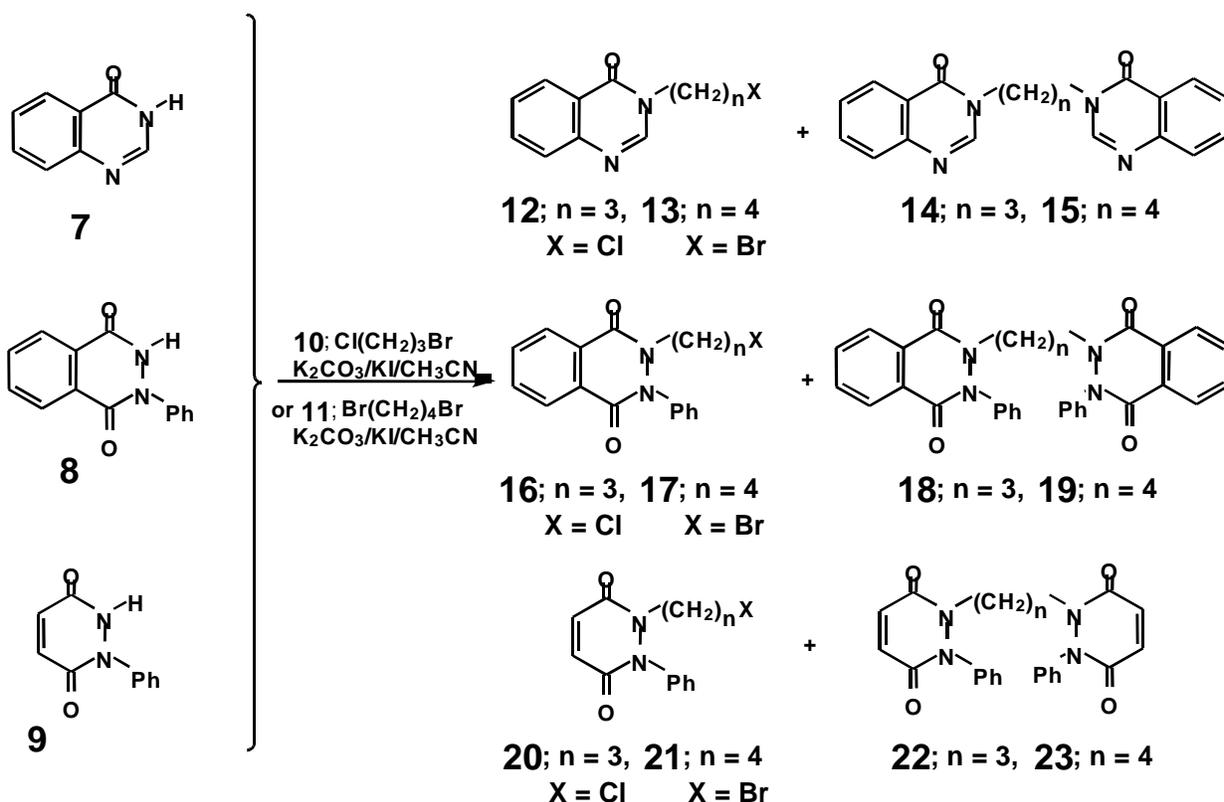
Results and Discussion

We present in this paper the synthesis of new N-[3-(4-aryl-1-piperazinyl)propyl] or N-[4-(4-aryl-1-piperazinyl)butyl] derivatives of quinazolidin-4(3*H*)-one (**7a-d**), 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8a-d**) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9a-d**) (Scheme 1) in which the length of a spacer, arylpiperazine and terminal amide fragment were systematically modified. Preliminary investigation results on affinities of obtained compounds for 5HT_{1A} and 5HT_{2A} receptor sites are also presented.



Scheme 1.

Starting materials quinazolidin-4(3*H*)-one (**7**), 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8**) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9**) were obtained according to procedures described in the literature. Quinazolidin-4(3*H*)-one (**7**) was obtained from antranilic acid [11], 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8**) from ftalic anhydride [12], while 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9**) from maleic anhydride [13].



Scheme 2.

Compounds **7a-d**, **8a-d**, **9a-d** were prepared by a two-step procedure. Alkylation of **7-9** with 1-bromo-3-chloropropane (**10**) or 1,4-dibromobutane (**11**) in the presence of K_2CO_3 in acetonitrile led to the formation of halogen intermediates **12**, **13**, **16**, **17**, **20** and **21** (Scheme 2). In the reaction, symmetrically disubstituted derivatives **14**, **15**, **18**, **19**, **22** and **23**, were also formed as byproducts. When in a place of 1-bromo-3-chloropropane (**10**) 1,3-dibromopropane was used, increased yields of the disubstituted derivatives (**14**, **18** and **22**) have been observed. The yields, melting points, and 1H -NMR signals observed in the regions characteristic of CH_2X and $CH_2NC=O$ protons as well as absorption of the carbonyl group in IR spectra of obtained compounds **12-23** are collected in Table 1.

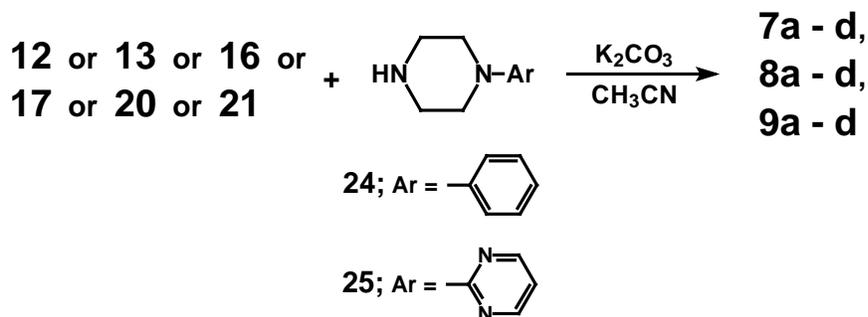
The presence of the carbonyl group in the compounds **12-15** is confirmed by the absorptions found in the usual carbonyl region at $1658-1680\text{ cm}^{-1}$. The 1H -NMR spectra of compounds **12-13** display typical signals arising from the methylene hydrogens in the $-CH_2X$ and $-CH_2NC=O$ fragments, while disubstituted derivatives **14** and **15** gave 1H -NMR spectra in which two equivalent methylene hydrogens have been detected in the $-CH_2NC=O$ fragment. The above analysis of the 1H -NMR and IR spectra indicated that under the applied reaction conditions quinazolidin-4(3H)-one (**7**) undergoes N-substitution. Application of the same reaction conditions to alkylation of 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8**) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9**) results in

formation of the N-substituted derivatives **16-19** and **20-23** respectively, in agreement with both our own and literature reports on the structural determination of substituted lactams [14-21].

Table 1. Reaction yields, physical properties and spectral data of halogen- (**12, 13, 16, 17, 20** and **21**) and disubstituted derivatives (**14, 15, 18, 19, 22** and **23**) of quinazolidin-4(3*H*)-one (**7**), 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**8**) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (**9**).

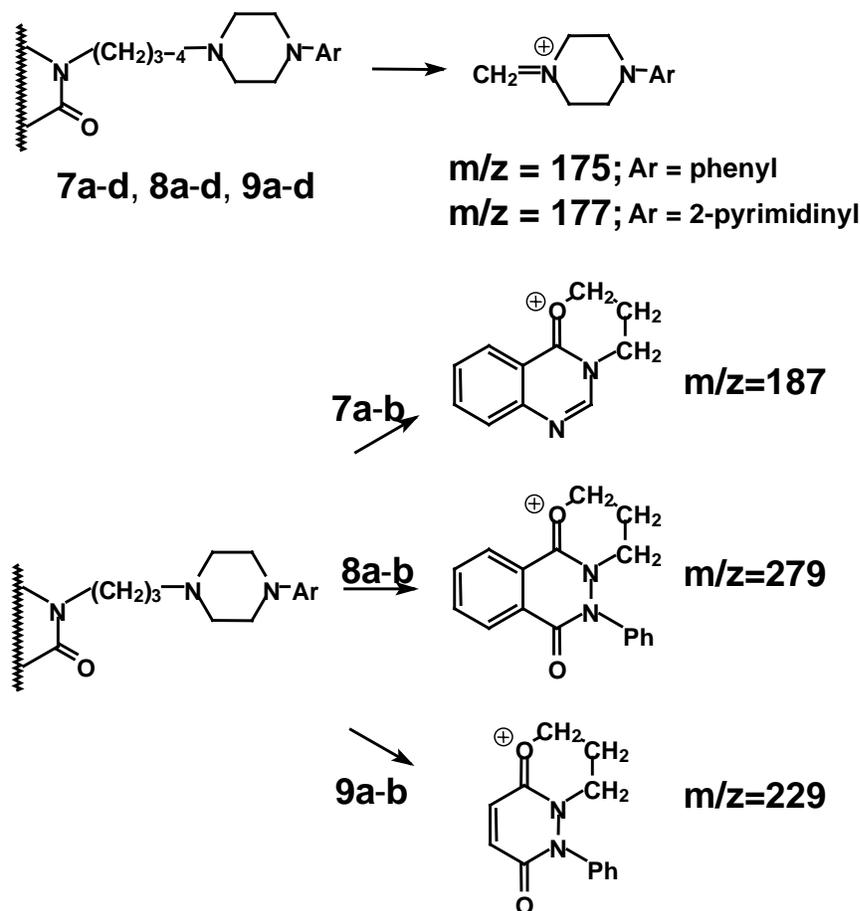
Comp. No.	Yield %	M.p. [°C]	Crystallization solvent	¹ H-NMR, δ (ppm)		IR, (cm ⁻¹) C=O
				CH ₂ X	CH ₂ NC=O	
12	51	105-107	methanol	3.61, t, 2H	4.20, t, 2H	1665
13	69	86-88	methanol	3.45, t, 2H	4.05, t, 2H	1658
14	5.3	194-196	methanol	-	4.23, t, 4H	1672
15	11	223-225	ethanol	-	4.10, t, 4H	1680
16	67	80-82	methanol	3.78, t, 2H	4.52, t, 2H	1656
17	49	65-67	methanol	3.52, t, 2H	4.39, t, 2H	1657
18	6.3	145-147	ethanol	-	4.61, t, 4H	1669
19	28	241-243	DMF	-	4.49, t, 4H	1657
20	65	70-72	acetone	3.70, t, 2H	4.33, t, 2H	1671
21	53	62-65	methanol	3.46, t, 2H	4.20, t, 2H	1670
22	7.1	202-204	methanol	-	4.33, t, 4H	1659
23	13	165-167	ethanol	-	4.23, t, 4H	1677

Target compounds **7a-d**, **8a-d**, **9a-d** were obtained upon condensation of intermediates **12, 13, 16, 17, 20** or **21** with 1-phenylpiperazine (**24**) or 1-(2-pyrimidinyl)piperazine (**25**), respectively (Scheme 3).



Scheme 3.

Reactions were carried out in acetonitrile in the presence of anhydrous K_2CO_3 . Reaction yields and the properties of the obtained compounds are presented in the Experimental section of the paper. The mass spectra of the compounds **7a-d**, **8a-d**, **9a-d** (Scheme 4) generally show the presence of molecular ions of weak intensity.



Scheme 4.

The base peaks of the investigated compounds mainly correspond to $[\text{CH}_2=\text{NR}_2]^+$ ion formation: $m/z=175$; $m/z=177$. This is in agreement with the general patterns observed for alkylamine fragmentation [22-23]. In case of derivatives **7a-b**, **8a-b**, **9a-b**, with a three member spacer chain, we find that fragmentation leads to fragments with $m/z=187$, $m/z=279$ and $m/z=229$ respectively, which are consistent with the behaviour of alkyl substituted lactams in mass spectroscopy [23]

Biological activity

Preliminary investigations of the affinity of the obtained compounds **7a-d**, **8a-d**, **9a-d** towards 5-HT_{1A} and 5-HT_{2A} receptors were performed using compound **8c** and **9c**. Affinities were assessed *in vitro* on the basis of their ability to displace [³H]-8-OH-DPAT [8-hydroxy-2-(*n*-propylamino)tetraline] and [³H]-ketanserin, respectively. Radioligand binding experiments were conducted in the rat hippocampus for 5-HT_{1A} receptors and in the cortex for 5-HT_{2A} receptors according to published procedures [24]. The results showed that compound **9c** has good affinity for 5-HT_{1A} receptors ($K_i = 19 \pm 1$ nM), better than that of compound **8c** ($K_i = 119 \pm 8$ nM), while both compounds have moderate affinity for 5-HT_{2A} receptors ($K_i = 309 \pm 1$ nM for **8c** and $K_i = 409 \pm 17$ nM for **9c**). Full experimental results on the affinities of all the obtained compounds **7a-d**, **8a-d**, **9a-d** for serotonin 5-HT_{1A}/5-HT_{2A} receptor sites will be presented soon in an appropriate pharmaceutical journals.

Experimental

General

Elemental analyses were performed on a Perkin-Elmer 2400 analyser. EI mass spectra were carried out with a Varian MAT 112 spectrometer at 70 eV. The ¹H-NMR spectra were recorded in deuteriochloroform with a Tesla 487C (80 MHz) spectrometer and using tetramethylsilane (TMS) as an internal standard; the chemical shifts are reported in ppm (δ); coupling constants were taken from the expanded spectrum. IR spectra were recorded on a Bio-Rad FTS-175C spectrophotometer in KBr pellets. Melting points were determined in a Boetius apparatus and are uncorrected. For biological experiments, free bases **7a-d**, **8a-d**, **9a-d** were converted into their hydrochloride salts and their molecular formulas and molecular weights were established on the basis of an elemental analysis.

General procedure for preparation of derivatives **12**, **13**, **16**, **17**, **20** and **21**

A mixture of the lactam **7** or **8** or **9** (0.1 mole), the appropriate 1-bromo-3-chloropropane (**10**) (0.12 mole) or 1,4-dibromobutane (**11**) (0.12 mole), powdered K₂CO₃ (20.7 g, 0.15 mole) and a catalytic amount of KI in acetonitrile (200 mL) was stirred and refluxed 24 h (Scheme 2). The cold reaction mixture was filtered and the filter cake washed with cold acetonitrile (20 mL). The combined filtrates were evaporated to dryness and the residue was purified by recrystallisation. Reaction yields and physical properties of the obtained compounds **12**, **13**, **16**, **17**, **20** and **21** are given in Table 1. From the dry filter cake, after suspending in water, byproducts **14**, **15**, **18**, **19**, **22** and **23** were isolated with moderate yields. Reaction yields and physical properties of compounds **14**, **15**, **18**, **19**, **22** and **23** are collected in Table 1.

General procedure for the preparation of compounds **7a-d**, **8a-d** and **9a-d**

A mixture of the corresponding chloro derivative (**12**, **16**, **20**) (0.01 mole), arylpiperazine (**24**, **25**) (0.01 mole), powdered K_2CO_3 (4.14 g, 0.03 mole) and catalytic amount of KI in acetonitrile (30 mL) was stirred for 48 h at 50–60° (Scheme 3). When in place of the chloro derivatives (**12**, **16**, **20**) a bromo derivative (**13**, **17**, **21**) (0.01 mole) was used, the reaction mixture was stirred at 50–60° for 24 h. The inorganic precipitate was filtered off, the filtrate was evaporated, and the residue was recrystallised from the appropriate solvent.

General procedure for the preparation of hydrochlorides

Free bases **7a-d**, **8a-d** and **9a-d** were converted into their hydrochlorides by dissolving the corresponding base in acetone (10mL/g) and treating with ethanol saturated with HCl. The precipitate was filtered off and washed with acetone. Some of the hydrochlorides were additionally purified by recrystallisation.

3-[3-(4-phenyl-1-piperazinyl)propyl]-quinazolidin-4(3H)-one (**7a**)

Base **7a** was obtained in 64% yield, m.p. 119–121°C (methanol); 1H -NMR: δ 1.92–2.17 (m, 2H, $CH_2CH_2CH_2$), δ 2.35–2.66 (m, 6H, $CH_2N(CH_2)_2$ and $CH_2N(CH_2)_2$), δ 3.10–3.24 (m, 4H, $(CH_2)_2NAr$), δ 4.12 (t, 2H, $CH_2NC=O$, $J=6.6$ Hz), δ 8.14 (s, 1H, $CH=N$), δ 6.87–8.38 (m, 9H_{Ar}); MS: m/z (I%); M 348 (92), 187 (100) 175 (56); Hydrochloride m.p. 210–213°C (acetone-methanol 10:1); Anal. Calcd. for $C_{21}H_{24}N_4O \cdot 2HCl \cdot 1.5H_2O$ (448.40): C, 56.25; H, 6.52; N, 12.50; Found: C, 55.96; H, 6.37; N, 12.58.

3-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-quinazolidin-4(3H)-one (**7b**)

Base **7b** was obtained in 71% yield, m.p. 102–103°C (acetone); 1H -NMR: δ 1.94–2.16 (m, 2H, $CH_2CH_2CH_2$), δ 2.34–2.59 (m, 6H, $CH_2N(CH_2)_2$ and $CH_2N(CH_2)_2$), δ 3.72–3.91 (m, 4H, $(CH_2)_2NAr$), δ 4.14 (t, 2H, $CH_2NC=O$, $J=6.6$ Hz), δ 6.48 (t, 1H, 5H_{Pyrim}, $J=4.7$ Hz), δ 8.16 (s, 1H, $CH=N$), δ 8.31 (d, 2H, 4H_{Pyrim} and 6H_{Pyrim}, $J=4.7$ Hz), δ 7.44–8.38 (m, 4H_{Ar}); MS: m/z (I%); M 350 (5), 187 (100), 177 (30); Hydrochloride m.p. 224–227°C (acetone-ethanol 10:1); Anal. Calcd. for $C_{19}H_{22}N_6O \cdot 2HCl$ (423.35): C, 53.91; H, 5.71; N, 19.85; Found: C, 53.99; H, 5.77; N, 19.76.

3-[4-(4-phenyl-1-piperazinyl)butyl]-quinazolidin-4(3H)-one (**7c**)

Base **7c** was obtained in 61% yield, m.p. 139–141°C (methanol); 1H -NMR: δ 1.56–2.03 (m, 4H, $CH_2CH_2CH_2CH_2$), δ 2.34–2.66 (m, 6H, $CH_2N(CH_2)_2$ and $CH_2N(CH_2)_2$), δ 3.12–3.25 (m, 4H, $(CH_2)_2NAr$), δ 4.05 (t, 2H, $CH_2NC=O$, $J=6.6$ Hz), δ 8.03 (s, 1H, $CH=N$), δ 6.81–8.37 (m, 9H_{Ar}); MS: m/z (I%); M 362 (69), 175 (100); Hydrochloride m.p. 216–219°C (acetone-ethanol 10:1); Anal. Calcd. for $C_{22}H_{26}N_4O \cdot 2HCl$ (435.40): C, 60.69; H, 6.48; N, 12.87; Found: C, 60.42; H, 6.58; N, 12.60.

3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-quinazolidin-4(3H)-one (7d)

Base **7d** was obtained in 70% yield, m.p. 95-97°C (acetone); ¹H-NMR: δ 1.62-2.01 (m, 4H, CH₂CH₂CH₂CH₂), δ 2.34-2.54 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.74-3.96 (m, 4H, (CH₂)₂NAr), δ 4.05 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.47 (t, 1H, 5H_{Pyrim}, J=4.7 Hz), δ 8.04 (s, 1H, CH=N), δ 8.30 (d, 2H, 4H_{Pyrim} and 6H_{Pyrim}, J=4.7 Hz), δ 7.50-8.37 (m, 4H_{Ar}); MS: m/z (I%); M 364 (21), 177 (100); Hydrochloride: m.p. 192-195°C (2-propanol-acetone 1:1); *Anal.* Calcd. for C₂₀H₂₄N₆O•HCl•0.5H₂O (409.92): C, 58.60; H, 6.39; N, 20.50; Found: C, 58.89; H, 6.64; N, 20.25.

3-[3-(4-phenyl-1-piperazinyl)propyl]-2-phenyl-2,3-dihydrophthalazine-1,4-dione (8a)

Base **8a** was obtained in 69% yield, m.p. 54-56°C (methanol); ¹H-NMR: δ 1.99-2.26 (m, 2H, CH₂CH₂CH₂), δ 2.56-2.75 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.11-3.28 (m, 4H, (CH₂)₂NAr), δ 4.45 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.91-8.55 (m, 14H_{Ar}); MS: m/z (I%); M 440 (10), 279 (6), 175 (100); Hydrochloride m.p. 215-218 °C (ethanol); *Anal.* Calcd. for C₂₇H₂₈N₄O₂•HCl•0.5H₂O (486.02): C, 66.73; H, 6.22; N, 11.53; Found: C, 66.62; H, 6.19; N, 11.50.

3-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-2-phenyl-2,3-dihydrophthalazine-1,4-dione (8b)

Base **8b** was obtained in 63% yield, m.p. 128-130°C (acetone); ¹H-NMR: δ 1.97-2.27 (m, 2H, CH₂CH₂CH₂), δ 2.45-2.72 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.78-3.93 (m, 4H, (CH₂)₂NAr), δ 4.44 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.48 (t, 1H, 5H_{Pyrim}, J=4.7 Hz), δ 8.30 (d, 2H, 4H_{Pyrim} and 6H_{Pyrim}, J=4.7 Hz), δ 7.34-8.55 (m, 9H_{Ar}); MS: m/z (I%); M 442 (16), 279 (56), 177 (100); Hydrochloride m.p. 226-229°C (acetone-ethanol 1:3); *Anal.* Calcd. for C₂₅H₂₆N₆O₂•2HCl•0.5H₂O (524.45): C, 57.26; H, 5.57; N, 16.02; Found: C, 57.34; H, 5.62; N, 15.92.

3-[4-(4-phenyl-1-piperazinyl)butyl]-2-phenyl-2,3-dihydrophthalazine-1,4-dione (8c)

Base **8c** was obtained in 73% yield, m.p. 111-113 °C (ethanol); ¹H-NMR: δ 1.72-2.03 (m, 4H, CH₂CH₂CH₂CH₂), δ 2.41-2.70 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.14-3.29 (m, 4H, (CH₂)₂NAr), δ 4.39 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.86-8.47 (m, 14H_{Ar}); MS: m/z (I%); M 454 (7), 175 (100); Hydrochloride m.p. 179-183°C (acetone-ethanol 10:1); *Anal.* Calcd. for C₂₈H₃₀N₄O₂•HCl•H₂O (491.03): C, 66.07; H, 6.13; N, 11.00; Found: C, 66.29; H, 6.50; N, 10.83.

3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2-phenyl-2,3-dihydrophthalazine-1,4-dione (8d)

Base **8d** was obtained in 58% yield, m.p. 154-156°C (methanol); ¹H-NMR: δ 1.72-1.99 (m, 4H, CH₂CH₂CH₂CH₂), δ 2.41-2.65 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.77-3.91 (m, 4H, (CH₂)₂NAr), δ 4.39 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.48 (t, 1H, 5H_{Pyrim}, J=4.7 Hz), δ 8.32 (d, 2H,

4H_{Pyrim} and 6H_{Pyrim}, J=4.7 Hz), δ 7.34-8.55 (m, 9H_{Ar}); MS: m/z (I%); M 456 (5), 177 (100); Hydrochloride m.p. 207-209°C (acetone-ethanol 10:1); *Anal.* Calcd. for C₂₆H₂₈N₆O₂•2HCl•H₂O (547.48): C, 57.04; H, 5.89; N, 15.35; Found: C, 57.31; H, 5.98; N, 15.26.

2-[3-(4-phenyl-1-piperazinyl)propyl]-1-phenyl-1,2-dihydropyridazine-3,6-dione (9a)

Base **9a** was obtained in 74% yield, m.p. 97-99°C (acetone); ¹H-NMR: δ 1.88-2.09 (m, 2H, CH₂CH₂CH₂), δ 2.44-2.69 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.12-3.26 (m, 4H, (CH₂)₂NAr), δ 4.25 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.85-7.74 (m, 12H_{Ar}); MS: m/z (I%); M 390 (22), 229 (14), 175 (100); Hydrochloride m.p. 219-221°C (acetone-ethanol 10:1); *Anal.* Calcd. for C₂₃H₂₆N₄O₂•HCl•H₂O (444.96): C, 62.08; H, 6.57; N, 12.59; Found: C, 62.13; H, 6.63; N, 12.33.

2-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-1-phenyl-1,2-dihydropyridazine-3,6-dione (9b)

Base **9b** was obtained in 72% yield, m.p. 152-154°C (methanol); ¹H-NMR: δ 1.84-2.06 (m, 2H, CH₂CH₂CH₂), δ 2.43-2.62 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.75-3.93 (m, 4H, (CH₂)₂NAr), δ 4.25 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.48 (t, 1H, 5H_{Pyrim}, J=4.7 Hz), δ 6.99-7.74 (m, 7H_{Ar}), 8.30 (d, 2H, 4H_{Pyrim} and 6H_{Pyrim}, J=4.7 Hz); MS: m/z (I%); M 392 (100), 229 (64), 177 (85); Hydrochloride m.p. 219-221°C (acetone-ethanol 10:1); *Anal.* Calcd. for C₂₁H₂₄N₆O₂•2HCl (465.38): C, 54.20; H, 5.63; N, 18.06; Found: C, 54.27; H, 5.74; N, 17.80.

2-[4-(4-phenyl-1-piperazinyl)butyl]-1-phenyl-1,2-dihydropyridazine-3,6-dione (9c)

Base **9c** was obtained in 71% yield, m.p. 91-93°C (methanol-H₂O 4:1); ¹H-NMR: δ 1.62-1.94 (m, 4H, CH₂CH₂CH₂CH₂), δ 2.37-2.66 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.13-3.27 (m, 4H, (CH₂)₂NAr), δ 4.20 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.86-7.72 (m, 12H_{Ar}); MS: m/z (I%); M 404 (9), 175 (100); Hydrochloride m.p. 199-202°C (methanol); *Anal.* Calcd. for C₂₄H₂₈N₄O₂•HCl (440.97): C, 65.37; H, 6.63; N, 12.71; Found: C, 65.12; H, 6.35; N, 12.53.

2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1-phenyl-1,2-dihydropyridazine-3,6-dione (9d)

Base **9d** was obtained in 66% yield, m.p. 104-106 °C (acetone); ¹H-NMR: δ 1.56-1.81 (m, 4H, CH₂CH₂CH₂CH₂), δ 2.44-2.58 (m, 6H, CH₂N(CH₂)₂ and CH₂N(CH₂)₂), δ 3.75-3.91 (m, 4H, (CH₂)₂NAr), δ 4.20 (t, 2H, CH₂NC=O, J=6.6 Hz), δ 6.48 (t, 1H, 5H_{Pyrim}, J=4.7 Hz), δ 6.97-7.74 (m, 7H_{Ar}), δ 8.30 (d, 2H, 4H_{Pyrim} and 6H_{Pyrim}, J=4.7 Hz); MS: m/z (I%); M 406 (33), 177 (100); Hydrochloride m.p. 203-205 °C (methanol); *Anal.* Calcd. for C₂₂H₂₆N₆O₂•HCl•H₂O (460.96): C, 57.32; H, 6.34; N, 18.23; Found: C, 57.49; H, 6.19; N, 18.19.

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