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Synthesis of new hexahydro- and octahydropyrido[1,2-c]pyrimidine derivatives with an arylpiperazine moiety as ligands for 5-HT_{1A} and 5-HT_{2A} receptors, part 2

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The synthesis of new of 4-aryl-hexahydro- (**11**–**16**) and (*R*,*R*)(*S*,*S*)4-aryl-octahydropyrido[1,2-c]pyrimidine (**23**–**27**) derivatives bearing a aryl- or heteroarylpiperazinyl moiety in position 2 is described. The derivatives of 4-aryl-hexahydro- (**1**–**5**) and (*R,R*)(*S,S*)4-aryl-octahydropyrido[1,2-*c*]pyrimidin-1,3-dion (**17**–**19**) served as starting compounds for further synteses. The N-alkylation of the imide moiety in compounds **1**–**5** and **17**–**19** by 1,4-dibromobutane gave the respective monbromobutyl derivatives **6**–**10** and **20**–**22**. The final derivatives **11**–**16** and **23**–**27** have been produced by condensation of the obtained bromoderivatives with selected 1-aryl and 1-heteroarylpiperazines. Compounds **11**–**16** and **23**–**27** were tested for their affinity towards 5-HT_{1A}, 5-HT_{2A} and α_1 receptors, using a radioligand binding assay.

1. Introduction

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is involved in various physiological and pathophysiological processes (Fletcher et al. 1993; Raymond et al. 1999; Zifa and Fillion 1992). Numerous studies have shown that aberrant central 5-HT neurotransmission is associated with psychiatric disorders, such as depression, anxiety, and behavioral disturbances (Barnes and Sharp 1999; Dekeyne et al. 2000; Fletcher et al. 1993; Hamon 1997; Millan et al. 1997).

5-HT_{1A} receptors have been of particular interest because they appear to be involved in the regulation of emotional and affective behavior. Both clinical and preclinical investigations into the 5-HT_{1A} receptor confirmed its role in a variety of psychiatric disorders including anxiety and depression (Barnes and Sharp 1999; Dekeyne et al. 2000; Fletcher et al. 1993; Hamon 1997; Millan et al. 1997). Long chain arylpiperazines with an amide or imide moiety represent one of the most important classes of 5-HT_{1A} receptor ligands (e.g. buspirone, tandospirone, NAN-190, flesinoxan, WAY 100135, WAY 100635, Abou-Gharbia et al. 1999; Bronowska et al. 2001; Caliendo et al. 2000; Hamon 1997; Kuipers et al. 1997; Lopez-Rodriguez et al. 1999; Lopez-Rodriguez et al. 2001; Orjales et al. 1995; Peglion et al. 2002; Perrone et al. 2000; Sabb et al. 2001; Sarva et al. 2002). Buspirone, an arylpiperazine derivative with high 5-HT_{1A} receptor affinity, was the first agent to be approved for clinical use (Abou-Gharbia et al. 1999; Hamon 1997; Orjales et al. 1995). Most of the ligands with high affinity for the 5-HT_{1A} receptor exhibit a high level of undesired affinity for the α_1-adrenergic receptor, because these receptors have a high degree of similarity (45%) in their amino acid sequence (Trumpp-Kallmeyer et al. 1992).

The aim of the present work was to synthesize new analogues of buspirone with hypothetically higher affinity and selectivity to 5-HT_{1A} receptors (Herold et al. 2002a). In this study buspirone was the key structure to which certain modifications were made in the nonpharmacophoric part, namely by introducing the 4-aryl-pyrido[1,2-c]pyrimidine-1,3-dione residue. Other modifications were made in the pharmacophoric part by introducing different substituents at the N-4 piperazine ring nitrogen (Fig.).

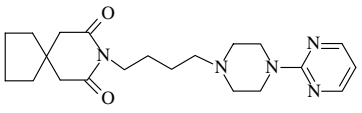
A series of new arylpiperazinylalkyl derivatives **11**–**16** and **23**–**27** have been obtained. These compounds contain a fragment of 4-aryl-hexahydro- and 4-aryl-octahydropyrido[1,2-*c*]pyrimidine-1,3-dione ring system in which the imide group is incorporated (Fig.).

Compounds **11**–**16** and **23**–**27** were tested for their affinity towards 5-HT_{1A}, 5-HT_{2A} and α_1 receptors, using a radioligand binding assay.

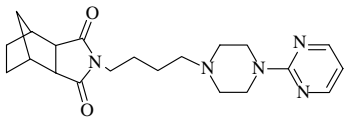
2. Investigations, results and discussion

2.1. Synthesis of the derivatives

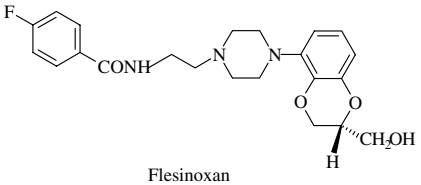
The compounds **10**–**16** and **22**–**27** described in this work were obtained according to Scheme 1. The starting compounds for the synthesis were derivatives of 4-aryl-hexahydro- (**1**–**5**) and (*R*,*R*)(*S*,*S*)4-aryl-octahydropyrido[1,2-c]pyrimidin-1,3-dion (**17**–**19**) derivatives, which have been synthesized according to literature data, (Herold et al. 1999 and 2002b).



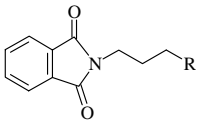
Buspirone



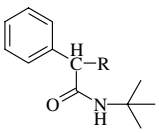
Tandospirone



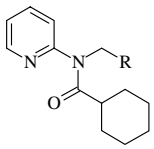
Flesinoxan



NAN 190



WAY 100135



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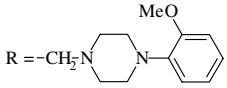


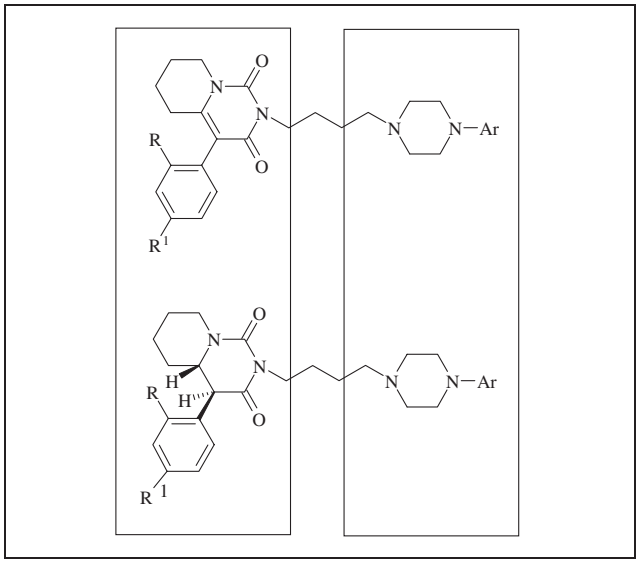


Fig: Structure modifications

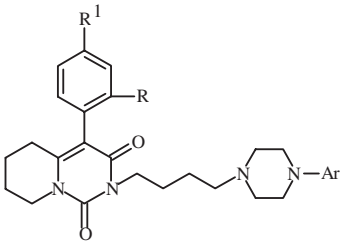
The monobromobutyl derivatives **6**–**10** and **20**–**22** were obtained according to a known procedure (Herold et al. 2002a) by N-alkylation of the imide group in compounds **1**–**5** and **17**–**19** using 1,4-dibromobutane. The obtained compounds **10** and **22** are unknown so far.

The final new products in the series of hexahydro- (**11**–**16**) and octahydropyrido[1,2-*c*]pyrimidine (**23**–**27**) were obtained by condensation of the appropriate 1-aryl or 1-heteroarylpiperazines with the above described bromobutyl derivatives **6**–**10** and **20**–**22**.

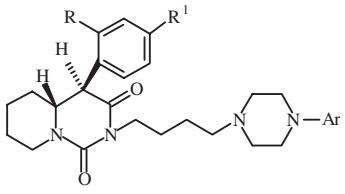
Purified bases **11**–**16** and **23**–**27** were transformed into their hydrochlorides and were submitted to screening tests for the affinity to 5-HT_{1A}, 5-HT_{2A} and α_1 receptors.

Compositions and structures of the new compounds **10**–**16** and **22**–**27** were confirmed by elemental analysis (C,

Table 1: Physical and analytical data of compounds 11–16 and 23–27



11 - 16

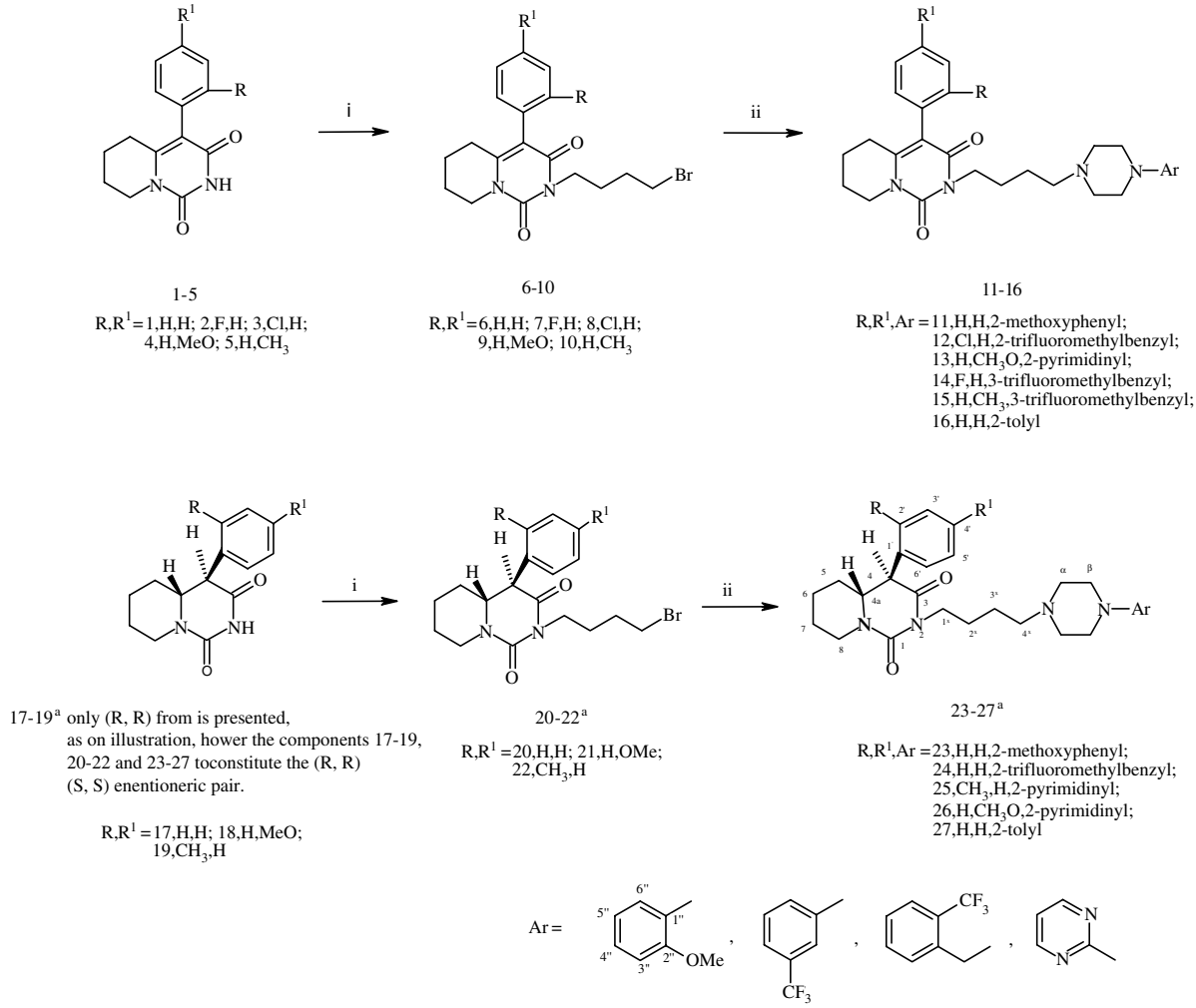


23 - 27

Compd.	R	R^1	Ar	Formula[a]	M.p. (°C)	Yield[b]	IR (cm^{-1}, KBr)
11	H	H	2-CH_3O-phenyl	$C_{29}H_{36}N_4O_3 \cdot 2\ HCl \cdot 0.5\ H_2O$	197.5–198.0	74.4	1690, 1640
12	Cl	H	2-CF_3-benzyl	$C_{30}H_{34}F_3Cl\ N_4O_2 \cdot 2\ HCl \cdot 3.5\ H_2O$	218.3–220.8	73.5	1693, 1642
13	H	CH_3O	2-Pyrimidinyl	$C_{27}H_{34}N_6O_3 \cdot 2\ HCl$	252.6–253.0	80.4	1700, 1660
14	F	H	3-CF_3-phenyl	$C_{29}\ H_{32}F_4N_4O_2 \cdot 2\ HCl \cdot H_2O$	152.5–155.0	87.4	1693, 1640
15	H	CH_3	3-CF_3-phenyl	$C_{30}H_{35}F_3N_4O_2 \cdot 2\ HCl \cdot 2.25\ H_2O$	148.0–149.5	86.0	1738, 1689
16[c]	H	H	2-Tolyl	–	–	–	–
23	H	H	2-CH_3O-phenyl	$C_{29}H_{38}N_4O_3 \cdot 2\ HCl \cdot H_2O$	176.2–179.2	70.4	1706, 1660
24	H	H	2-CF_3-benzyl	$C_{30}H_{37}F_3N_4O_2 \cdot 2\ HCl \cdot H_2O$	214.5–217.6	73.5	1709, 1658
25	CH_3	H	2-Pyrimidinyl	$C_{27}H_{36}N_6O_2 \cdot 2\ HCl \cdot 0.5\ H_2O$	193.6–196.2	76.5	1710, 1661
26	H	CH_3O	2-Pyrimidinyl	$C_{27}H_{36}N_6O_3 \cdot 2\ HCl \cdot 0.5\ H_2O$	211.0–211.6	76.2	1710, 1655
27[c]	H	H	2-Tolyl	–	–	–	–

[a] Satisfactory microanalyses obtained: C, H, N values are within ± 0.4% of the theoretical values
[b] Cryst. solvent: **13** from methyl alcohol; **11**, **12**, **14**, **15**, **16**, **23**–**27** from abs. ethyl alcohol
[c] See Herold et al. (2002a)

Scheme



Reagents: (i) 1,4-dibromobutane, K_2CO_3, acetone, reflux, 10–20 h (TLC); (ii) arylpiperazine, K_2CO_3 KJ, acetonitrile, reflux, 12–30 h (TLC)

H, N), IR spectroscopy (Table 1), ^{1}H NMR (Table 2) and ^{13}C NMR (Table 3). The 2D NMR (COSY, HETCOR) investigations of the final targets **11**–**16** and **23**–**27** were carried out in order to assign all the protons and carbons of the new structures as well as to define the configuration at C-4, C-4a chiral centers to constitute (*R,R*) and (*S,S*) pair for **22**–**27** (Herold et al. 2002b).

2.2. Binding studies

The compounds **11**–**16** and **23**–**27** were tested for their potency to inhibit binding of labelled ligands to serotonin 5-HT_{1A} and 5-HT_{2A} receptors and to α_1 adrenoceptors using *in vitro* radioligand binding assays in rat cerebral cortical tissue. The following labelled ligands were used: 5-HT_{1A} receptors – [^{3}H] 8-OH-DPAT; 5-HT_{2A} receptors – [^{3}H] ketanserin; α_1 receptors – [^{3}H] prazosin. Data were analyzed using iterative curve fitting routines (Graph PAD/Prism, v. 3.0 San Diego, CA, USA) to obtain IC_{50} values. These values were used to calculate inhibition constants K_i according to the Cheng-Prusoff formula (Cheng and Prusoff 1973).

Table 4 presents K_i [nM] values obtained for derivatives **11**–**16** and **23**–**27** relative to 5-HT_{1A}, 5-HT_{2A} and α_1 receptors.

Derivatives **11**, **12**, **15**, **16**, **23** and **27** exhibited high affinity to the α_1 adrenergic receptor, much higher than to the 5-HT_{1A} and 5-HT_{2A} serotoninergic receptors.

Derivatives **13**, **25** and **26** are characterized by the same common 2-pyrimidinyl substituent related with piperazine, situated in the pharmacophoric part of the ligand. The nonpharmacophoric part of those compounds contains the 4-aryl-hexahydro-pyrido[1,2-*c*]pyrimidine (compound **13**) or 4-aryl-octahydropyrido[1,2-*c*]pyrimidine (compounds **25** and **26**) system. The highest affinity to the 5-HT_{1A} receptor in this group was exhibited by ligand **25** ($K_i = 28.1$ [nM]), with the other values being $K_i = 57.2$ [nM] (**26**) and $K_i = 89.7$ [nM] (**13**).

Ligand **14** being a 4-aryl-hexahydropyrido[1,2-*c*]pyrimidine (nonpharmacophoric part) derivative and possessing the 3-trifluoromethylphenyl radical boned to piperazine in the pharmacophoric part exhibited average affinity values to the 5-HT_{1A} receptor ($K_i = 72.2$ [nM]).

Analysis of the effect of 4-aryl-hexahydro- or 4-aryl-octahydropyrido[1,2-*c*]pyrimidine radicals in the nonpharmacophoric part of the ligand on affinity and selectivity showed that the 4-aryl-octahydropyrido[1,2-*c*]pyrimidine radicals exhibit higher affinity to the 5-HT_{1A} receptor (compounds **25** and **26**) than the 4-aryl-hexahydropyri-

Table 2: ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (Hz) of hexahydropyrido[1,2-c]pyrimidine derivatives **11**–**15** and octahydropyrido[1,2-c]pyrimidine derivatives **23**–**26**[a]

Compd.	C-5H$_2$	C-6H$_2$	C-7H$_2$	C-8H$_2$	C-1^{x}H$_2$	C-2^{x}H$_2$	C-3^{x}H$_2$	C-4^{x}H$_2$	CαH$_2$	CβH$_2$	Aromatic rings
11	2.50 (t, 2H), $^3J = 6.5$	1.66 (q, 2H),	1.89 (q, 2H), $^3J = 6.5$	3.91 (t, 2H), $^3J = 6.5$	4.04 (t, 2H), $^3J = 7.0$	1.45–1.80 (m, 4H) + C-3^{x}H$_2$		2.45 (pt, 2H)	2.64 (bs, 4H)	3.08 (bs, 4H)	7.25–7.48 (m, 3H, C-2H, C-6′H, C-4′H), 7.19 (m, 2H, C-3′H, C-5′H), 6.75–7.04 (m, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 3.84 (s, 3H, OCH$_3$)
12	2.39 (m, 2H)[c]	1.72 (m, 4H) + C-2^{x}H$_2$	1.92 (m, 2H)[d], $^3J = 7.0$	3.92 (m, 2H)[d], $^2J = 14.0$, $^3J = 7.5$	4.03 (t, 2H), $^3J = 7.5$		1.58 (t, 2H), $^3J = 7.5$	2.43 (t, 2H)	2.53 (bs, 8H) + CβH$_2$		7.77 (d, 1H, C-3″H, $^3J = 8.0$), 7.61 (d, 1H, C-6″H, $^3J = 8.0$), 7.50 (t, 1H, C-5″H), 7.45 (m, 1H, C-3′H), 7.27–7.34 (m, 3H, C-4′H, C-5′H, C-4″H), 7.20 (m, 1H, C-6′H), 3.66 (s, 2H, CH$_2$)
13	2.42 (t, 2H), $^3J = 6.4$	1.54 (q, 2H), $^3J = 6.4$	1.79 (q, 2H)	3.79 (t, 2H), $^3J = 6.0$	3.91 (t, 2H), $^3J = 6.8$	1.64 (q, 2H)	1.74 (q, 2H)	3.20 (t, 2H), $^3J = 7.6$	3.12 (t, 2H) CαHa, 3.66 (d, 2H) CαHe	3.47 (t, 2H) CβHa, 4.61 (d, 2H) CβHe	8.48 (d, 2H, C-4″H, C-6″H, $^3J = 4.8$), 7.07 (d, 2H, C-2′H, C-6′H, $^3J = 8.0$), 6.95 (m, 3H, C-3′H, C-5′H, C-5″H), 3.77 (s, 3H, OCH$_3$)
14	2.49 (t, 2H), $^3J = 7.5$	1.74 (m, 4H) + C-2^{x}H$_2$	1.93 (q, 2H)	3.94 (m, 2H)	4.04 (t, 2H), $^3J = 7.6$		1.61 (m, 2H)	2.45 (t, 2H), $^3J = 7.2$	2.60 (pt, 4H)	3.24 (bs, 4H)	7.33 (m, 2H, C-4′H, C-6″H), 7.18 (m, 2H, C-5′H, C-6′H), 7.10 (m, 2H, C-3′H, C-2″H), 7.06 (m, 2H, C-4″H, C-5″H)
15	2.54 (t, 2H), $^3J = 7.9$	1.69 (q, 2H)	1.92 (q, 2H), $^3J = 6.7$	3.93 (t, 2H), $^3J = 6.4$	4.04 (t, 2H), $^3J = 7.2$	1.74 (q, 2H)	1.62 (q, 2H)	2.47 (bs, 2H)	2.62 (bs, 4H)	3.25 (bs, 4H)	7.33 (t, 1H, C-5″H, $^3J = 7.9$), 7.20 (d, 2H, C-2′H, C-6′H, $^3J = 7.9$), 7.08 (d, 2H, C-3′H, C-5′H), 7.03–7.11 (m, 3H, C-2″H, C-4″H, C-6″H), 2.36 (s, 3H, CH$_3$)

No.	C-4H	C-4aH	C-5Ha, C-6Ha	C-5He, C-2^{x}H$_2$	C-6He/ C-7He	C-7Ha, C-3^{x}H$_2$	C-8Ha	C-8He	C-1^{x}H$_2$/ C-4^{x}H$_2$	CαH$_2$/CβH$_2$	Aromatic rings
23		3.68 (pt, 1H)	1.35 (m, 2H)	1.60 (m, 1H), 1.70 (m, 2H)	1.77 (m, 4H) + C-3^{x}H$_2$	1.49 (m, 1H)	2.87 (pt, 1H)	4.29 (pd, 1H)	/3.36 (t, 2H), $^3J = 7.6$	3.88 (m, 9H) + C-4H + C-1^{x}H$_2$ + CαHa + CαHe + CβHe/3.55 (bs, 2H) CβHa	7.39–7.53 (m, 5H, C-3′H, C-4′H, C-5′H, C-4″H, C-6″H), 7.32 (d, 2H, C-2′H, C-6′H, $^3J = 7.2$), 7.26 (d, 1H, C-3″H, $^3J = 8.0$), 7.16 (t, 1H, C-5″H), 4.0 (s, 3H, OCH$_3$)
24	3.36 (d, 1H), $^3J_{4-4a} = 8.0$	3.43 (m, 1H)[b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-5e} = 2.8$	1.34 (m, 2H)	1.59 (m, 3H)	1.83 (m, 1H)/ 1.74 (m, 1H)	1.49 (m, 3H)	2.74 (m, 1H)[c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 3.0$	4.44 (m, 1H)[d], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.3$, $^3J_{8e-7e} = 2.1$, $^3J_{8e-6a} = 2.1$	3.86 (m, 2H), $^3J = 8.0$/ 2.34 (t, 2H), $^3J = 7.0$	2.49 (bs, 4H)/ 2.45 (bs, 4H)	7.78 (d, 1H, C-3″H, $^3J = 8.0$), 7.61 (d, 1H, C-4″H), 7.50 (t, 1H, C-6″H), 7.28–7.38 (m, 4H, C-3′H, C-4′H, C-5′H, C-5″H), 7.20 (dd, 2H, C-2′H, C-6′H, $^3J = 7.0$, $^4J = 1.0$), 3.65 (s, 2H, CH$_2$)
25	3.85 (d, 1H), $^3J_{4-4a} = 9.0$	3.42 (m, 1H)[b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-5e} = 3.0$	1.32 (m, 2H)	1.64 (m, 3H)	1.80 (m, 1H)/ 1.75 (m, 1H)	1.40–1.60 (m, 3H)	2.72 (m, 1H)[c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 3.0$	4.43 (m, 1H)[d], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.5$, $^3J_{8e-7e} = 2.0$ $^4J_{8e-6a} = 2.0$	3.89 (m, 2H)[b], $^3J = 7.5$/ 2.40 (t, 2H)	2.48 (pt, 4H)/ 3.82 (pt, 4H)	8.28 (d, 2H, C-4″H, C-6″H, $^3J = 5.0$), 7.15–7.22 (m, 3H, C-3′H, C-4′H, C-5′H), 7.07 (dd, 1H, C-6′H, $^3J = 6.0$, $^4J = 2.0$), 6.45 (t, 1H, C-5″H), 2.35 (s, 3H, CH$_3$)
26	3.76 (m, 4H) + C-4aH + C-1^{x}H$_2$		1.35 (m, 2H)	1.61 (m, 1H), 1.68 (m, 2H)	1.78 (m, 4H) + C-3^{x}H$_2$	1.49 (m, 1H)	2.87 (m, 1H)	4.29 (pd, 1H)	/3.29 (m, 2H)	3.22 (pt, 2H) CαHa/3.64 (m, 4H) CαHe + CβHa, 4.74 (pd, 2H) CβHe	8.66 (d, 2H, C-4″H, C-6″H, $^3J = 5.2$), 7.26 (d, 2H, C-2′H, C-6′H, $^3J = 8.4$), 7.14 (t, 1H, C-5″H), 7.03 (d, 2H, C-3′H, C-5′H), 3.88 (s, 3H, OCH$_3$)

[a] d, doublet; pd, pseudodoublet; bs, broad singlet; m, multiplet; t, triplet; a, axial; e, equatorial
[b] Multiplet 7 lines, [c] Multiplet 6 lines, [d] Multiplet 10 lines
Compounds **11**, **12**, **14**, **15**, **24**, **25** were performed as bases ($CDCl_3$); compounds **13**, **23**, **26** were performed as hydrochloride (D_2O)

Table 3: ^{13}C NMR spectral data of compounds 11–15 and 23–26

	11	12	13	14	15	23	24	25	26
C-1	152.1	151.8	152.9	151.7	151.7	155.3	153.6	153.7	154.6
C-3	161.7	168.2	164.6	161.4	162.1	173.6	169.5	169.4	173.1
C-4	*112.2*	*110.1*	*112.0*	*106.1*	*112.4*	53.6	53.9	50.2	50.9
C-4a	*151.5*	*150.5*	*154.0*	*150.9*	*149.5*	57.2	58.3	58.3	55.6
C-5	26.5	26.4	26.9	26.5	26.7	32.1	32.0	31.9	31.4
C-6	18.4	18.5	17.9	18.4	18.6	23.6	23.8	23.6	20.8
C-7	21.5	21.8	21.2	21.8	21.8	24.9	24.2	24.5	24.3
C-8	42.4	43.0	43.9	42.9	42.6	46.3	45.6	45.3	45.7
C-1′	*133.2*	*132.5*	*125.9*	*120.9*[a]	*130.3*	*136.9*	*136.4*	*135.1*	*128.8*
C-2′	128.2	*135.1*	132.3	*160.5*[a]	129.2	129.7	128.9	*136.6*	130.2
C-3′	130.6	132.6	157.8	115.8[a]	130.5	130.1	128.5	130.9	114.7
C-4′	127.4	129.7	*158.8*	130.0[a]	*137.4*	129.2	127.9	127.7	*158.8*
C-5′	130.6	127.1	157.8	124.2[a]	130.5	130.1	128.5	126.5	114.7
C-6′	128.2	129.5	132.3	133.0	129.2	129.7	128.9	127.9	130.2
C-1^x	41.4	41.4	41.1	41.6	41.4	41.2	41.3	41.1	40.5
C-2^x	25.5	25.6	24.2	25.6	25.6	25.6	26.5	26.4	25.0
C-3^x	24.2	24.0	21.0	24.2	24.2	21.6	24.5	24.0	23.0
C-4^x	58.2	58.1	55.6	58.2	58.2	57.1	57.1	56.9	50.8
C-α	53.3	53.2	51.0	53.0	52.9	50.7	53.3	53.0	56.6
C-β	50.4	52.9	41.7	48.6	48.5	50.1	53.2	43.5	41.8
C-1″	*141.2*	*137.8*	–	*151.4*	*151.5*	*131.7*	*138.0*[b]	–	–
C-2″	*149.5*	*128.6* [b]	*156.1*	112.1	112.2	*152.5*	*128.6*[b]	*161.4*	*155.1*
C-3″	111.0	125.7 [b]	–	*129.5*	*129.5*	113.9	125.6[b]	–	–
C-4″	120.8	126.7	157.8	115.7	115.8	130.9	126.6	157.6	157.6
C-5″	122.6	131.7	111.7	118.6	118.6	122.4	131.1	109.7	111.6
C-6″	118.0	130.3	157.8	129.5	129.5	121.2	130.3	157.6	157.6
OCH_3	55.2	–	56.6	–	–	56.8	–	–	52.1
C-5^x	–	65.8	–	–	–	–	58.2	–	–
CF_3	–	124.5	–	124.2	125.4	–	124.5	–	–
CH_3	–	–	–	–	21.2	–	–	20.1	–

[a] appear as doublet
[b] appear as quartet
^{13}C chemical shifts of the ipso carbon atoms of the pyridopyrimidine and phenyl rings are given in italics (δ, ppm); compounds **11**, **12**, **14**, **15**, **24**, **25** were performed as bases ($CDCl_3$); compounds **13**, **23**, **26** were performed as hydrochloride (D_2O), TMS as internal standard
Coupling constant ^nJ (^{13}C -^{19}F) (Hz) for compounds **12** $^1J = 273.8$, $^2J_{2''\text{-}F} = 30.2$, $^3J_{3''\text{-}F} = 5.9$; **14** $^1J = 241.1$, $^1J_{2'\text{-}F} = 245.5$, $^2J_{1'\text{-}F} = 20.9$, $^2J_{3'\text{-}F} = 22.1$, $^3J_{4'\text{-}F} = 8.4$, $^4J_{5'\text{-}F} = 3.3$; **15** $^1J = 277.7$; **24** $^1J = 274.3$; $^2J_{2''\text{-}F} = 30.2$, $^3J_{1''\text{-}F} = 1.4$, $^3J_{3''\text{-}F} = 5.9$.

do[1,2-*c*]pyrimidine derivatives. The same conclusion was earlier drawn by Herold et al. (2002a).

Comparison of selectivity results between the 5-HT_{1A}, 5-HT_{2A} and α_1 receptors obtained for the ligands showed that decisively higher selectivity values were obtained for the ligands containing 4-aryl-hexahydropyrido[1,2-*c*]pyrimidine, e.g. the selectivity of compound **14** was 3.0 and 31.8. Similarly high selectivity values of 15.4 and 28.3 were obtained from the previously described 4-(2-methoxyphenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-hexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-dion ligand (Herold et al. 2002a). 4-Aryl-octahydropyrido[1,2-*c*]pyrimidine derivatives showed lower 5-HT_{1A} receptor selectivities than the 5-HT_{2A} and α_1 receptors, i.e. **25** (11.4 and 19.9), **26** (7.8 and 6.3). Thus, compounds **13** and **26** possessing a methoxy group in *para*-phenyl position shows 5-HT_{1A} receptor selectivities as compared with the 5-HT_{2A} and α_1 receptors of 8.4 and 5.9; and 7.8 and 6.3, respectively. However, selectivities of an analogous compound, 4-(2-methoxyphenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl]-hexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-dion, with the methoxy group in *ortho* position were 15.4 and 28.3, respectively. This compound has been described earlier (Herold et al. 2002a). In turn, *para* position substitution which is shown, taking the OCH_3 ligands as example, in compounds **13** and **26,** decreases affinity and selectivity.

Table 4: Binding affinities data for 5-HT_{1A}, 5-HT_{2A} and α_1 receptors in compounds 11–16 and 23–27

Compd.	K_i (nM)		α_1 [^{3}H] Prazosin	Selectivity versus 5-HT_{1A} receptor K_i ratio	
	5-HT_{1A} [^{3}H] 8-OH-DPAT	5-HT_{2A} [^{3}H] Ketanserin		5-HT_{2A}	α_1
11	71.7 ± 34.1	130.3 ± 15	11.9 ± 1.4	1.8	6.0
12	303.8 ± 95.7	794.4 ± 134.3	168.9 ± 32.3	2.6	1.8
13	89.7 ± 5.9	749.7 ± 20.5	530 ± 80	8.4	5.9
14	72.2 ± 8.6	216.9 ± 46.8	2300 ± 40	3.0	31.8
15	469.3 ± 69.3	542.5 ± 20.7	121.4 ± 3.4	1.2	3.9
16	169.3 ± 50	236.5 ± 14.3	21.9 ±4.2	1.4	7.7
23	145.4 ± 26.8	145.4 ± 17.8	6.4 ± 0.8	0.0	22.7
24	365.2 ± 51.8	457.8 ± 37.9	1140 ± 270	1.3	3.1
25	28.1 ± 4.7	320 ± 40.9	560 ± 30	11.4	19.9
26	57.2 ± 12	445.5 ± 55.8	361 ± 8.5	7.8	6.3
27	160.3 ± 29.1	118 ± 5.6	8.6 ± 5.3	1.4	18.6

It could be concluded that ligands in this group of derivatives with higher affinity to the 5-HT_{1A} receptor along with higher selectivity to the 5-HT_{2A} and α_1 receptors require introduction into the nonpharmacophoric part of the substance of a 4-aryl-hexahydropyrido[1,2-*c*]pyrimidine radical with F (**14**) substituent in *ortho* position of the benzene ring.

It was also observed that the presence of 3-trifluoromethylphenyl (**14**) and 2-pyrimidinyl radicals (**25**, **26**, **13**) bound to piperazine in the pharmacophoric part has an influence on affinity and selectivity of the compounds investigated.

3. Experimental

IR spectra (KBr pellets) were carried out on a Perkin-Elmer spectrometer FT-IR Spectrum 1000, PE Auto Image System. The NMR spectra were recorded by a Varian Unity plus 500 MHz spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, respectively). The correlation study COSY ^{1}H-^{1}H and HETCOR ^{1}H-^{13}C has also been performed. For the 2D experiments, the pulse sequences, acquisition and processing parameters were taken from standard Varian software library.

Elemental analyses for C, H, N were performed on a Perkin-Elmer Analyser CHN 2400 in the Department of Chemistry, Warsaw Technical University and are within ± 0.4% of the theoretical values.

The m.p.'s were determined using a Mel-Temp®3.0 instrument (Barnstead/Thermolyne; USA) and are given without corrections.

Flash CC was carried out on Merck Kieselgel 60 (230–400 mesh). TLC was performed on the plates DC-Platten Kieselgel 60 F_{254} of Merck, using a mobile phase comprised of dioxan, toluene, EtOH and 25% NH_4OH (6.0 : 3.2 : 0.5 : 0.2 v/v). For detection the UV lamp was used or, alternatively, the plates were dyed by the benzene solution of *p*-chloranil.

The derivatives of phenylacetonitrile and 2-bromopyridine used as substrates were purchased from Aldrich. The derivatives of the following starting systems were obtained according to published procedures: 4-aryl-hexahydro- (**1**–**5**) (Herold et al. 1999); (*R,R*)(*S,S*)4-aryl-octahydropyrido[1,2-*c*]pyrimidin-1,3-dion (**17**–**19**) (Herold et al. 2002b); monobromobutyl- (**6**–**8**) and **20** (Herold et al. 2002a); compounds **9** and **21** in an analogous way and the physical and analytical data of the compounds will be published elsewhere.

3.1. Chemistry

3.1.1. General procedure for the synthesis of 2-(4-bromobutyl)-derivatives of 4-aryl-hexahydro- and 4-aryl-octahydropyrido[1,2-c]pyrimidine **10** *and* **22**

1,4-Dibromobutane (0.2 mol) was added while stirring to the suspension of the appropriate imide **5** or **19** (0.04 mol) and K_2CO_3 (0.06 mol) in 70 ml acetone and than then the mixture was heated to boiling for 15 h (**19**) or 19 h (**5**). The reaction time was evaluated by TLC. Subsequently the reaction mixture was filtered from the inorganic salts, and the filtrate was evaporated to dryness under vacuum. The crude residue was purified by CC (flash method), using the mixture CH_2Cl_2−MeOH 98 : 2 v/v as eluent. After thickening of proper eluates qualified by TLC the analytically pure compounds **10** and **22** were obtained.

3.1.1.1. 2-[4-bromobutyl)-4-(4-tolyl)-hexahydro-1H,3H-pyrido[1,2-*c*]pyrimidin-1,3-dion (**10**)

Yield: 62%; m.p. 99–100 °C (hexane-ethyl acetate 1 : 1 v/v); IR (cm^{-1}): 1670, 1628; ^{1}H NMR (ppm, 500 MHz): 1.70 (q, 2 H, C-6H$_2$, ^{3}J = 6.8 Hz); 1.83 (q, 2 H, C-2^{x}H$_2$); 1.92 (m, 4 H, C-7H$_2$, C-3^{x}H$_2$); 2.37 (s, 3 H, CH_3); 2.55 (t, 2 H, C-5H$_2$, ^{3}J = 6.8 Hz); 3.44 (t, 2 H, C-4^{x}H$_2$, ^{3}J = 6.4 Hz); 3.94 (t, 2 H, C-8H$_2$, ^{3}J = 6.0 Hz); 4.03 (t, 2 H, C-1^{x}H$_2$, ^{3}J = 6.4 Hz); 7.08 (d, 2 H, C-3′H, C-5′H); 7.21 (d, 2 H, C-2′H, C-6′H, ^{3}J = 7.6 Hz); ^{13}C NMR (ppm, 125 MHz): 18.8 (C-6), 21.5 (CH_3), 22.0 (C-7), 26.7 (C-5), 26.9 (C-4^x), 30.4 (C-3^x), 33.5 (C-2^x), 40.9 (C-1^x), 42.8 (C-8), 112.5 (C-4), 129.4 (C-2′, C-6′), 130.4 (C-1′), 130.7 (C-3′, C-5′), 137.7 (C-4′), 149.8 (C-4a), 151.9 (C-10), 162.3 (C-3).

$C_{19}H_{23}BrN_2O_2$

3.1.1.2. (*R,R*)(*S,S*) 2-[4-Bromobutyl)-4-(2-tolyl)-octahydropyrido[1,2-*c*]pyrimidin-1,3-dion (**22**)

Yield: 70%; oil; IR (cm^{-1}):1700, 1665; ^{1}H NMR (ppm, 500 MHz): 1.33 (m, 2 H, C-5Ha, C-6Ha); 1.52 (m, 1 H, C-7Ha, ^{2}J$_{7a-7e}$ = 13.0 Hz, ^{3}J$_{7a-8a}$ = 13.0 Hz, ^{3}J$_{7a-6a}$ = 13.0 Hz; ^{3}J$_{7a-8e}$ = 4.0 Hz, ^{3}J$_{7a-6e}$ = 4.0 Hz); 1.67 (m, 1 H, C-5He); 1.76 (m, 3 H, C-7He, C-2^{x}H$_2$); 1.82 (m, 1 H, C-6He); 1.87 (m, 2 H, C-3^{x}H$_2$); 2.35 (s, 3 H, CH_3); 2.72 (m, 1 H, C-8a, ^{2}J$_{8a-8e}$ = 13.0 Hz, ^{3}J$_{8a-7a}$ = 13.0 Hz, ^{3}J$_{8a-7e}$ = 3.0 Hz); 3.41 (t, 2 H, C-4^{x}H$_2$, ^{3}J = 7.0 Hz); 3.43 (m, 1 H, C-4aH); 3.85 (d, 1 H, C-4H, ^{3}J$_{4-4a}$ = 9.0 Hz); 3.89 (m, 2 H, C-1^{x}H$_2$, ^{3}J = 7.0 Hz); 4.43 (m, 1 H, C-8He, ^{2}J$_{8e-8a}$ = 13.0 Hz, ^{3}J$_{8e-7a}$ = 4.5 Hz, ^{3}J$_{8e-7e}$ = 2.0 Hz; ^{3}J$_{7a-8e}$ = 4.0 Hz, ^{4}J$_{8e-6a}$ = 2.0 Hz); 7.06 (dd, 1 H, C-6′H, ^{3}J = 6.0 Hz, ^{4}J = 2.0 Hz); 7.15–7.23 (m, 3 H, C-3′H, C-4′H, C-5′H); ^{13}C NMR (ppm, 125 MHz): 20.2 (CH_3); 23.7 (C-6), 24.5 (C-7), 27.2 (C-4^x), 30.2 (C-3^x), 31.9 (C-5), 33.2 (C-2^x), 40.3 (C-1^x), 45.4 (C-8), 50.2 (C-4), 56.9 (C-4a), 126.6 (C-5′), 127.8 (C-6′), 127.9 (C-4′), 131.0 (C-3′), 135.0 (C-2′), 136.6 (C-1′), 153.7 (C-1), 169.5 (C-3).

$C_{19}H_{25}BrN_2O_2$

3.1.2. General procedure for the synthesis of 2-[4-[4-aryl or heteroaryl-1-piperazinyl]butyl]-4-aryl-hexahydro-1 H,3H- (**11**–**16**) *and (R,R)(S,S) 4-aryl-octahydropyrido[1,2-c]pyrimidin-1,3-diones* **23**–**27**

To acetonitrile (160 ml) were added under stirring: bromobutyl derivative **6**–**10**, **20**–**22** (10 mmol), respective arylpiperazine (10 mmol), K_2CO_3 (40 mmol) and KJ (1 mmol). The reaction mixture was boiled while stirring for 25–30 h, the completion time was assigned chromatographically (TLC). The mixture was filtered in order to remove inorganic salts and the filtrate was evaporated to dryness under vacuum. The oily residue was purified by CC (flash) with an eluent consisting of CH_2Cl_2 – MeOH 97 : 3 and 99 : 1 v/v. After thickening of proper eluates qualified by TLC the pure bases of **11**–**13**, **25**, **26** were obtained as oils. The remaining bases were crystalline: **14** (m.p. 118.5–120.0 °C, from heptane); **15** (m.p. 101.0–102.0 °C, from heptane); **23** (m.p. 108.6–112.5 °C, from benzene-hexane 1 : 3 v/v); **24** (m.p. 120.5–121.4 °C, from heptane).

The obtained bases **11**–**16** and **23**–**27** were converted into their hydrochlorides, which were analyzed and investigated on the affinity to 5-HT_{1A} and 5-HT_{2A} receptors. The yields, m.p.'s, and positions of IR bands are collected in Table 1, the ^{1}H and ^{13}C NMR data are shown in Tables 2 and 3, respectively. The K_i [nM] values of the investigated compounds **11**–**16** and **23**–**27** are displayed in Table 4.

3.2. Biochemical tests

3.2.1. Radioligand receptor binding assay

Frozen Wistar rat cortices stored at −80 °C were used for the radioligand binding assay. Tissues were thawed in 50 volumes of ice-cold 50 mM TRIS-HCl buffer, pH 7.4, homogenized and centrifuged at 20,000 × g for 20 min (i.e. washed). Tissue pellets were washed once more. Assay (plates MAFC-NOB 10, MultiScreen®-FC, Millipore) contained membrane suspension (∼0.15 mg of protein), nine concentrations of testing compounds, [^{3}H] ligand and buffer and/or non-specific binding defining drug in a final volume of 0.3 ml. The following [^{3}H] ligands, non-specific binding defining drugs and incubation parameters were applied: 5-HT_{1A} receptors: 1.0 nM [^{3}H] 8-OH-DPAT (219 Ci/mmol, Amersham), 10 μM serotonin, 30 min at 37 °C; 5-HT_{2A} receptors: 0.6 nM [^{3}H] ketanserin (60 Ci/mmol, NEN), 1 μM mianserin, 30 min at 25 °C; α_1 receptors: 0.2 nM [^{3}H] prazosin (26 Ci/mmol, NEN), 1 μM phentolamine, 30 min at 25 °C. For 5-HT_{1A} receptors assays buffer contained 10 μM pargyline, 5.7 mM $CaCl_2$ and 0.1% ascorbic acid. Samples were incubated for appropriate time and temperature. The incubation was terminated by rapid filtration (over Glass Fiber Type C Filter) using a Vacuum Manifold (Millipore). The filters were then washed twice with 0.1 ml ice-cold buffer and placed in scintillation vials with liquid scintillation cocktail. Radioactivity was measured in a Beckman LS 6500 liquid scintillation counter. All assays were done in duplicates.

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