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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

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Abstract

Synthesis applied to prepare compounds **5**–**15** and **17**–**22** discussed in this paper has been presented in Scheme 1. Multi-stage preparation techniques were used to obtain 4-aryl-hexahydro **1**–**4** and (*R*,*R*) and (*S*,*S*) 4-aryl-octahydropyrido[1,2-*c*]pyrimidine-1,3-dione (**16**) derivatives, being the starting compounds for further modification. N-Alkylation of the imide group in compounds **1**–**4** and **16** followed, using 1,4-dibromobutane to yield monobromobutyl derivatives **5**–**8** and **17**. Subsequent condensation of those compounds with appropriate 1-aryl or 1-heteroarylpiperazine led to the final hexahydro- **9**–**15** and octahydro- **18**–**22** pyrido[1,2-*c*]pyrimidine-1,3-dione derivatives. The final products were subjected to screening test to elucidate the affinity to 5-HT_{1A} and 5-HT_{2A} receptors.

Keywords: Hexahydro- and octahydropyrido[1,2-*c*]pyrimidine derivatives with an arylpiperazine moiety; Ligands for 5-HT_{1A} and 5-HT_{2A} receptors

1. Introduction

Serotonin (5-HT, 5-hydroxytryptamine) is one of the most important and universal neurotrasmitters in vertebrates. It is implicated in numerous physiological and psychological functions that vary from cardiovascular and respiratory activity and platelet aggregation to various mood states and neuroendocrine processes. Furthermore, serotoninergic dysfunction is reported to be involved in several pathophysiological processes. Numerous studies have shown that aberrant central 5-HT neurotransmission is associated with several psychiatric disorders, such as depression, anxiety, behavioral disturbances [1–8]. Taking into account highly complex pharmacology of the 5-HT system, one must consider the widespread distribution of the 5-HT innervation and various subpopulations of 5-HT.

Serotonin exerts its pharmacological effects through activation of membrane receptors located in different structures of the brain. The 5-HT receptors have been divided into seven main classes (5-HT_1–5-HT_7) on the basis of the receptor binding profiles, common second messenger coupling, amino acid sequences and the functional activity of ligands. Each of these classes has been subdivided further into several subtypes. The 5-HT_1 receptor class consists of five different subtypes, termed: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} [9–14].

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 [15–19].

Several groups of ligands for the 5-HT_{1A} receptor have been reported in the literature. Arylpiperazines (e.g. buspirone, ipsapirone, gepirone) are one of such ligand groups that has been shown to have agonist

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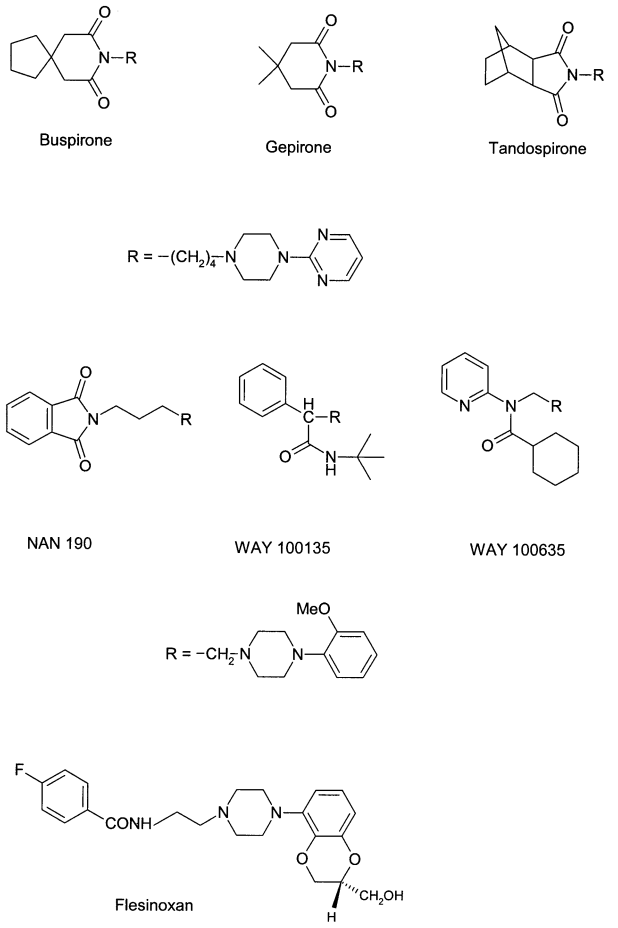


Fig. 1.

properties at 5-HT_{1A} receptors (Fig. 1). These compounds are partial agonists with high affinity for the 5-HT_{1A} binding sites. All arylpiperazine molecules contain the arylpiperazinyl group attached to the imide or amide moiety [20–23].

Analysis of 5-HT_{1A} receptor ligand structures suggests that affinity for the mentioned receptor depends on the presence of two characteristic structural elements, namely: arylpiperazinylalkyl and the imide or amide [24–32]. However, opinions of authors on this subject matter differ.

The role of arylpiperazinyl substituent is probably connected with the ligand activity, but the precise role of the imide group is still not fully established. According to the latest literature, high affinity of the ligand for the 5-HT_{1A} receptor is connected with a high lipophilicity of the imide group and a lesser lipophilicity to the α adrenergic receptor [25]. Other authors suggest an important role of the steric factor [31–33]. Moreover, numerous publications describe relationship between the moiety containing the imide group and stability of the 5-HT_{1A} receptor–ligand complex, through a π–π dipole interaction [34–38].

The arylpiperazines are a relatively new class of psychotherapeutic drugs which posses high affinity for the 5-HT_{1A} receptor site, however with low selectivity [22,23].

Buspirone along with other structurally related pyrimidinylpiperazine compounds, such as ipsapirone and gepirone, binds with particular affinity to the 5-HT_{1A} receptors, and also displays pronounced affinity to other receptor types. Buspirone as the first drug of this class has reached wide acceptance, and is used in the treatment of psychotic disorders accompanied by anxiety. Nevertheless, a need for agents with even greater selectivity still exist [19].

The aim of the present study was to synthesize the new analogues of buspirone with hypothetically higher affinity and selectivity to 5-HT_{1A} receptors. In this study buspirone was the key structure to which certain modifications were made, namely by introducing the pyrido[1,2-*c*]pyrimidine-1,3-dione residue with different substituents into the imide part. Other modifications were made by introducing different substituents at the piperazine ring nitrogen. Thus, we designed and synthesized a number of new arylpiperazinylalkyl derivatives **9**–**15** and **18**–**22**. These derivatives contain a fragment of hexahydro- and octahydro-pyrido[1,2-*c*]pyrimidine-1,3-dione ring system in which the imide group is incorporated (Fig. 2). The obtained compounds were tested for their affinity towards 5-HT_{1A}, 5-HT_{2A} and α_1 adrenergic receptors, using radioligand binding assay.

2. Chemistry

The compounds described in this paper (**5**–**15** and **17**–**22**) were obtained as shown in Scheme 1.The substrate for the synthesis were 4-aryl-hexahydro- **1**–**4** and (*R*,*R*) and (*S*,*S*) 4-aryl-octahydropyrido[1,2-*c*]pyrimidine-1,3-dione (**16**) derivatives, obtained as final products of the several stages synthesis [39,40].

Then the imide group of the above-described compounds **1**–**4** and **16** was N-alkylated by the 1,4-

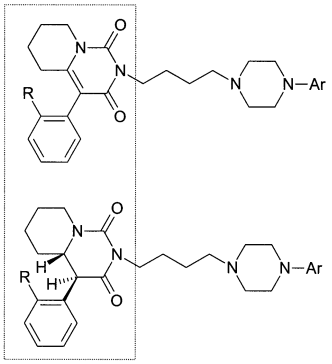
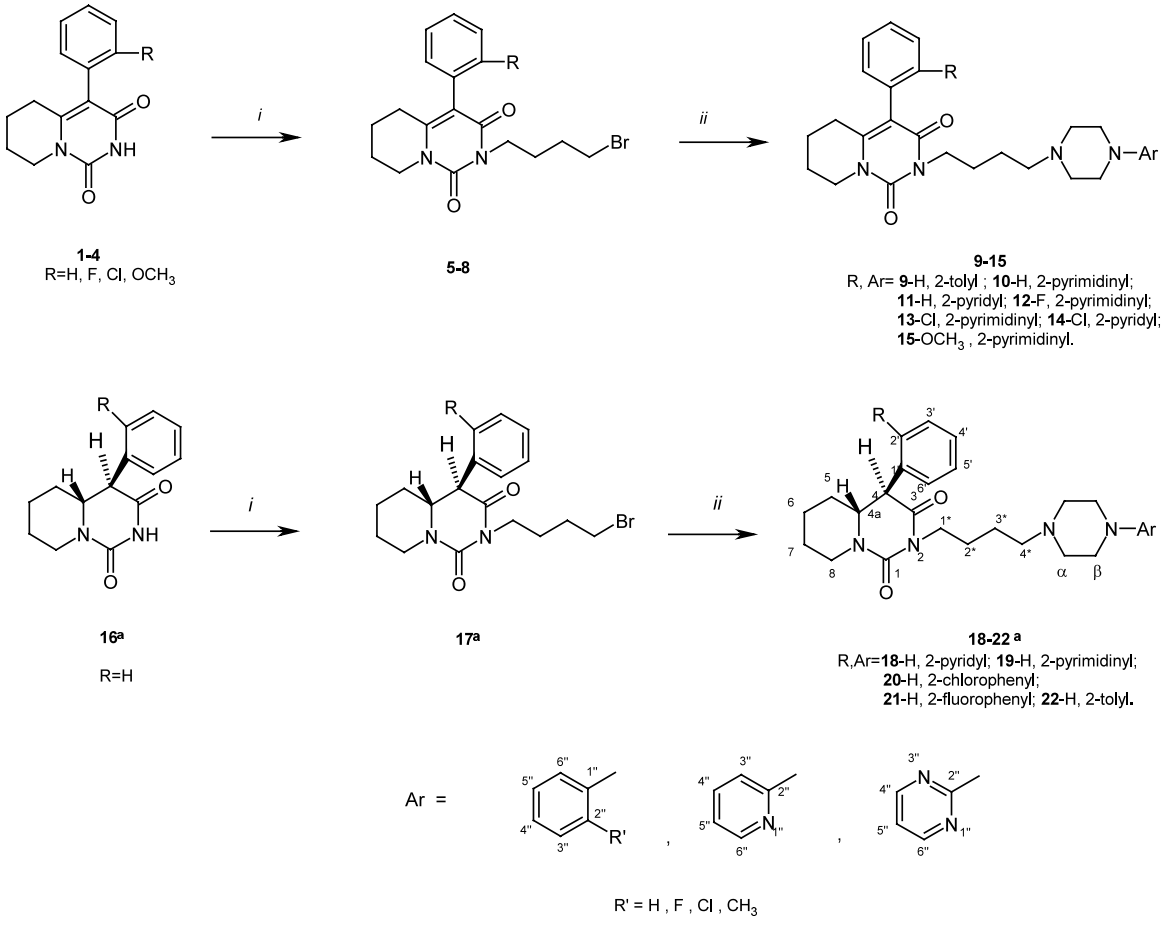


Fig. 2.



[a] only (*R*,*R*) form is presented, as on illustration, however the compounds **16**, **17**, **18-22** to constitute the (*R*,*R*) and (*S*,*S*) enantiomeric pair.

Scheme 1. Reagents: (i) $Br(CH_2)_4Br$, K_2CO_3, acetone, Δ; (ii) 1-aryl or heteroarylpiperazine, K_2CO_3, acetonitrile, Δ.

dibromobutane, yielding the monobromobutyl derivatives **5**–**8** and **17**.

The final products in the series of hexahydro- **9**–**15** and octahydro- **18**–**22** derivatives were obtained by the condensation of the appropriate 1-aryl or 1-heteroarylpiperazine with the above-described bromobutyl derivatives **5**–**8** and **17**.

The obtained bases, after purification, were transformed into the hydrochloride and were submitted to primary screening tests for the affinity to 5-HT_{1A}, 5-HT_{2A} and α_1 receptors.

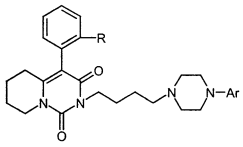
All new compounds **5**–**15** and **17**–**22** were identified and proven by the IR and elemental analysis (Table 1), ^1H (Table 2) and ^{13}C NMR (Table 3).

Moreover, COSY, HETCOR, HMBC and GHMQC experiments of the starting bromoderivatives **5**–**8**, **17** and the final targets **9**–**15** and **18**–**22** were carried out in order to assign all the protons and carbons of these new structures as well as to define the configuration at C4, C4a chiral centers to constitute (*R*,*R*) and (*S*,*S*) pair for **17**–**22** [40]. XRD experiments were carried out for compound **9**. The ORTEP view of the molecule is shown in Fig. 3. The phenyl ring is planar and the piperazine ring adopts a chair conformation with the nitrogens N19 and N16 above and below the plane formed by piperazine ring carbons. The piperidine ring adopts a boat conformation; this ring is fused with the almost planar uracil moiety.

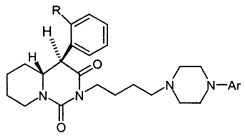
3. Pharmacology

The selected compounds **10**–**15** and **18**–**21** 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 (GraphPAD/Prism, v. 3.0-San Diego, CA, USA) to obtain IC_{50} values (i.e. the concentration of the compound required to occupy 50% of receptors). These values were used to calculate inhibition constants (K_i) according to the Cheng–Prus-

Table 1
Physical, analytical and IR spectroscopic data of compounds **5**–**15** and **17**–**22**



9-15



18-22

No.	R	Ar	Yield (%)	Base/hydrochloride m.p. (°C)	Formula	Analysis Calc./Found			IR (C=O)
						C	H	N	
5	H	–	79.8	106–107	$C_{18}H_{21}BrN_2O_2$	57.29 57.32	5.61 5.57	7.42 7.34	1679, 1628
6	F	–	72.3	100.0–100.5	$C_{18}H_{20}BrFN_2O_2$	54.68 54.72	5.10 5.02	7.08 7.12	1692, 1645
7	Cl	–	55.9	85.5–86.5	$C_{18}H_{20}BrClN_2O_2$	52.50 52.45	4.90 4.80	6.80 6.87	1694, 1643
8	OCH_3	–	43.4	115–118	$C_{19}H_{23}BrN_2O_3$	56.01 56.19	5.69 5.69	6.87 6.89	1689, 1659
9	H	2-toyl	91.0	126.5–127 243.5–243.8	$C_{29}H_{36}N_4O_2$	73.70 73.62	7.68 7.68	11.85 11.73	1670, 1610
10	H	2-pyrimidinyl	60.0	120-121 241.2-242	$C_{26}H_{32}N_6O_2 \cdot 2HCl$	58.54 58.61	6.42 6.34	15.75 15.70	1690. 1640
11	H	2-pyridyl	93.0	118-119 219-219.5	$C_{27}H_{33}N_5O_2 \cdot 2HCl \cdot H_2O$	58.91 59.01	6.77 6.74	12.72 12.81	1680, 1620
12	F	2-pyrimidinyl	74.2	140-141 246.5-247	$C_{26}H_{31}FN_6O_2 \cdot 2HCl$	56.63 56.60	6.03 6.10	15.23 15.14	1685, 1630
13	Cl	2-pyrimidinyl	87.5	161.7-162.0 234.4-235.9	$C_{26}H_{31}ClN_6O_2 \cdot 2HCl$	54.99 55.07	5.86 5.98	14.79 14.80	1693, 1637
14	Cl	2-pyridyl	58.3	139.3-140.0 253.6-255.3	$C_{27}H_{32}ClN_5O_2 \cdot 2HCl \cdot 0.5H_2O$	56.21 56.28	6.12 5.91	12.13 12.26	1690, 1637
15	OCH_3	2-pyrimidinyl	50.6	106-110 248.4-249	$C_{27}H_{34}N_6O_3 \cdot 2HCl \cdot 1.25H_2O$	55.39 55.60	6.54 6.45	14.35 14.40	1691, 1636
17	H	–	66.6	83.9-85.5	$C_{18}H_{23}BrN_2O_2$	56.98 56.89	6.11 6.03	7.38 7.41	1710, 1662
18	H	2-pyridyl	53.5	128.4-130.4 226.4-228.8	$C_{27}H_{35}N_5O_2 \cdot 2HCl \cdot 0.25H_2O$	60.22 60.12	6.93 6.62	12.99 12.99	1697, 1667
19	H	2-pyrimidinyl	56.2	147.8-149.2 172.1-175.9	$C_{26}H_{34}N_6O_2 \cdot 2HCl \cdot 0.5H_2O$	57.35 57.42	6.85 6.78	15.43 15.43	1698, 1668
20	H	2-chlorophenyl	50.2	131.0-131.7 158.0-162.5	$C_{28}H_{35}ClN_4O_2 \cdot HCl \cdot H_2O$	61.20 61.52	6.97 6.88	10.19 10.22	1700, 1660
21	H	2-fluorophenyl	92.0	115.0-118.4 105.7-108.5	$C_{28}H_{35}FN_4O_2 \cdot 2HCl \cdot 3H_2O$	55.54 55.42	7.16 7.20	9.25 9.19	1700, 1661
22	H	2-tolyl	60.0	123.1-124.1 128.5-131.2	$C_{29}H_{38}N_4O_2 \cdot 2HCl \cdot 2.25H_2O$	59.18 59.25	7.71 7.29	9.51 9.47	1700, 1662

off formula [41]. The obtained K_i values are presented in Table 4.

4. Results and discussion

The search for new substances based on buspirone as the model drug seems fully justified in light of its interesting pharmacological properties. Buspirone is one of the 'new' anxiolythic drugs, unaffecting the GABA–benzodiazepine receptors, whose action is related with 5-HT subgroup 5-HT_{1A} receptors. As generally known, those receptors play a significant role in regulating behavioral processes. Being an agonist of the 5-HT_{1A} receptors, buspirone inhibits central activity related with the 5-HT area of the brain. Its anxiolythic action (without anticonvulsive and muscle relaxant activity) extremely valuable and moreover, does not lead to distinct drug dependence, does not impair memory and, may also be used in treatment of alcohol dependence due to its ability to inhibit the 'augmentation' system. In turn, undesired effects are quite infrequent and have minor intensities. Thus, all these features of the drug compared with classic anxiolythics

Table 2
^{1}H NMR chemical shifts (δ, ppm, deuteriochloroform) and coupling constants (Hz) of hexahydropyrido[1,2-*c*]pyrimidine derivatives: **5**–**15** (A) and octahydropyrido[1,2-*c*]pyrimidine derivatives **17**–**22** (B) [a]

Comp.	C-5H_2	C-6H_2	C-7H_2	C-8H_2	C-1^xH_2	C-2^xH_2	C-3^xH_2	C-4^xH_2	Cα H_2	Cβ H_2	Aromatic rings
5	2.53 (t, 2H), $^3J = 6.5$	1.69 (q, 2H), $^3J = 6.5$	1.91 (m, 4H) + C-2^xH_2	3.93 (t, 2H), $^3J = 6.5$	4.03 (t, 2H), $^3J = 7.0$		1.84 (m, 2H)	3.44 (t, 2H), $^3J = 7.0$			7.39 (m, 2H, C-2′H, C-6′H), 7.32 (m, 1H, C-4′H), 7.19 (m, C-3′H, C-5′H), $^3J_o = 6.5$, $J_m = 1.0$
6	2.50 (m, 2H), $^2J = 17.5$, $^3J = 6.0$	1.72 (m, 2H), $^2J = 13.0$, $^3J = 6.5$	1.93 (m, 4H) + C-2^xH_2	3.94 (m, 2H), $^2J = 14.0$, $^3J = 6.0$	4.04 (t, 2H), $^3J = 6.5$		1.84 (m, 2H)	3.44 (t, 2H), $^3J = 6.5$			7.31–7.37 (m, 1H, C-6′H), 7.16–7.25 (m, 2H, C-4′H, C-5′H), 7.12 (m, 1H, C-3′H)
7	2.40 (m, 2H), $^2J = 17.0$, $^3J = 6.5$	1.71 (m, 2H), $^2J = 13.5$, $^3J = 6.5$	1.92 (m, 4H) + C-2^xH_2	3.93 (m, 2H), $^2J = 14.0$, $^3J = 6.0$	4.04 (m, 2H), $^3J = 7.5$		1.85 (m, 2H)	3.44 (m, 2H), $^3J = 6.5$			7.46 (m, 1H, C-6′H), 7.30 (m, 2H, C-4′H, C-5′H), 7.20 (m, 1H, C-3′H)
8	2.43 (t, 2H), $^3J = 7.0$	1.69 (m, 2H), $^2J = 13.5$, $^3J = 7.0$	1.92 (m, 4H) + C-2^xH_2	3.92 (m, 2H), $^2J = 14.0$, $^3J = 7.0$	4.03 (t, 2H), $^3J = 7.0$		1.84 (m, 2H)	3.44 (m, 2H), $^3J = 6.5$			7.33 (m, 1H, C-4′H), 7.11 (m, 1H, C-6′H), 6.99 (m, 1H, C-5′H), 6.95 (d, 1H, C-3′H, $J_o = 8.5$), 3.78 (s, 3H, OCH_3)
9	2.53 (t, 2H), $^3J = 6.5$	1.69 (q, 2H)	1.92 (q, 2H), $^3J = 7.0$	3.94 (t, 2H)	4.04 (t, 2H), $^3J = 7.5$	1.74 (m, 2H)	1.61 (m, 2H)	2.46 (t, 2H), $^3J = 7.5$	2.61 (bs, 4H)	2.94 (pt, 4H), $^3J = 4.5$	7.39 (m, 2H, C-2′H, C-6′H), 7.32 (m, 1H, C-4′H), 7.19 (m, 2H, C-3′H, C-5′H), 7.15 (m, 2H, C-3″H, C-5″H), 7.02 (pd, 1H, C-4″H), 6.96 (m, 1H, C-6″H), 2.29 (s, 3H, CH_3)
10	2.41 (t, 2H), $^3J = 7.5$	1.70 (q, 2H), $^3J = 7.0$	1.92 (q, 2H), $^3J = 6.5$	3.94 (t, 2H), $^3J = 6.5$	4.04 (t, 2H), $^3J = 7.0$	1.73 (q, 2H), $^3J = 7.0$	1.60 (q, 2H), $^3J = 7.0$	2.53 (t, 2H), $^3J = 5.0$	2.49 (t, 4H), $^3J = 5.0$	3.82 (t, 4H), $^3J = 5.0$	8.30 (d, 2H, C-4″H, C-6″H, $^3J_o = 5.0$), 7.40 (t, 2H, C-3′H, C-5′H, $^3J_o = 7.5$), 7.33 (tt, 1H, C-4′H, $^3J_o = 7.5$, $^4J_m = 1.0$), 7.19 (m, 2H, C-2′H, C-6′H, $^3J_o = 7.0$), 6.47 (t, 1H, C-5″H, $^3J_o = 4.5$)
11	2.54 (m, 6H) + Cα H_2	1.69 (q, 2H)	1.92 (q, 2H), $^3J = 6.5$	3.94 (t, 2H), $^3J = 6.5$	4.04 (t, 2H), $^3J = 7.5$	1.73 (m, 2H)	1.61 (m, 2H)	2.42 (pt, 2H)	2.54 (m, 6H) + C-5H_2	3.53 (pt, 4H)	8.18 (m, 1H, C-6″H), 7.46 (m, 1H, C-4″H), 7.39 (m, 2H, C-3′H, C-5′H), 7.32 (m, 1H, C-4′H), 7.19 (m, 2H, C-2′H, C-6′H), 6.61 (m, 2H, C-3″H, C-5″H)

Table 2 (*Continued*)

Comp.	C-5H_2	C-6H_2	C-7H_2	C-8H_2	C-1^xH_2	C-2^xH_2	C-3^xH_2	C-4^xH_2	Cα H_2	Cβ H_2	Aromatic rings
12	2.38–2.60 (m, 8H)+C-4^xH_2+Cα H_2	1.67–1.82 (m, 4H)+C-2^xH_2	1.94 (q, 2H), $^3J = 6.5$	3.94 (m, 2H), $^2J = 14.0$, $^3J = 6.5$	4.04 (t, 2H), $^3J = 7.5$	1.67–1.82 (m, 4H)+C-6H_2	1.62 (m, 2H)	2.38–2.60 (m, 8H)+C-5H_2+Cα H_2	2.38–2.60 (m, 8H)+C-5H_2+C-4^xH_2	3.84 (bs, 4H)	8.29 (d, 2H, C-4″H, C-6″H, $^3J_o = 4.5$), 7.34 (m, 1H, C-5″H), 7.20 (m, 2H, C-4′H, C-6′H), 7.11 (pt, 1H, C-3′H), 6.47 (pt, 1H, C-5′H)
13	2.34–2.47 (m, 4H)+C-4^xH_2	1.66–1.79 (m, 4H)+C-2^xH_2	1.93 (q, 2H), $^3J = 6.0$	3.93 (m, 2H), $^2J = 14.0$, $^3J = 6.0$	4.04 (t, 2H), $^3J = 7.5$	1.66–1.79 (m, 4H)+C-6H_2	1.61 (q, 2H), $^3J = 7.0$	2.34–2.47 (m, 4H)+C-5H_2	2.50 (pt, 4H)	3.83 (pt, 4H)	8.29 (d, 2H, C-4″H, C-6″H, $^3J_o = 4.5$), 7.46 (m, 1H, C-3′H), 7.30 (m, 2H, C-4′H, C-5′H), 7.20 (m, 1H, C-6′H), 6.46 (t, 1H, C-5″H, $^3J_o = 5.0$)
14	2.34–2.46 (m, 4H)+C-4^xH_2	1.64–1.79 (m, 4H)+C-2^xH_2	1.93 (m, 2H)	3.93 (m, 2H), $^2J = 14.5$, $^3J = 6.0$	4.04 (t, 2H), $^3J = 7.5$	1.64–1.79 (m, 4H)+C-6H_2	1.60 (m, 2H)	2.34–2.46 (m, 4H)+C-5H_2	2.54 (t, 4H), $^3J = 5.0$	3.53 (t, 4H), $^3J = 5.0$	8.18 (m, 1H, C-6″H), 7.46 (m, 2H, C-4″H, C-3′H), 7.30 (m, 2H, C-4′H, C-5′H), 7.20 (m, 1H, C-6′H), 6.61 (m, 2H, C-3″H, C-5″H)
15	2.42 (m, 4H)+C-4^xH_2	1.63–1.78 (m, 4H)+C-2^xH_2	1.91 (q, 2H), $^3J = 6.5$	3.92 (m, 2H), $^2J = 13.5$, $^3J = 6.7$, $^3J = 6.5$	4.03 (t, 2H), $^3J = 7.5$	1.63–1.78 (m, 4H)+C-6H_2	1.60 (m, 2H)	2.42 (m, 4H)+C-5H_2	2.49 (t, 4H), $^3J = 5.0$	3.82 (t, 4H)	8.29 (m, 2H, C-4″H, C-6″H), 7.32 (m, 1H, C-4′H), 7.10 (d, 1H, C-6′H), 6.99 (t, 1H, C-5′H), 6.64 (dd, 1H, C-3′H, $^3J_o = 8.5$), 6.46 (t, 1H, C-5″H, $^3J_o = 4.5$), 3.77 (s, 3H, OCH_3)
	C-4H	C-4aH	C-5H_a, C-6H_a	C-5H_e, C-2^xH_2	C-6H_e/C-7H_e	C-7H_a, C-3^xH_2	C-8H_a	C-8H_e	C-1^xH_2/C-4^xH_2	Cα H_2/Cβ H_2	Aromatic rings
17	3.57 (d, 1H), $^3J_{4-4a} = 7.5$	3.45 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 7.5$, $^3J_{4a-5e} = 3.0$	1.35 (m, 2H)	1.64 (m, 21H)	1.84 (m, 3H)+C-3^xH_2/1.73 (m, 3H)+C-2^xH_2	1.52 (m, 1H), $^2J_{7a-7e} = 13.0$, $^3J_{7a-8a} = 13.0$, $^3J_{7a-6a} = 13.0$, $^3J_{7a-8e} = 4.0$, $^3J_{7a-6e} = 4.0$	2.75 (m, 1H) [c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 3.0$	4.44 (m, 1H) [d], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.5$, $^3J_{8e-7e} = 2.5$, $^3J_{8e-6a} = 2.5$	3.87 (m, 2H) [e]/3.39 (t, 2H), $^3J = 6.5$		7.28–7.38 (m, 3H, C-3′H, C-4′H, C-5′H), 7.20 (m, 2H, C-2′H, C-6′H, $^3J_o = 7.0$, $^4J_m = 1.5$)
18	3.57 (d, 1H), $^3J = 8.0$	3.45 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 8.0$, $^3J_{4a-5e} = 3.0$	1.40 (m, 2H)	1.62 (m, 3H)	1.84 (m, 1H)/1.75 (m, 1H)	1.54 (m, 3H)	2.75 (m, 1H) [c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 3.0$	4.45 (m, 1H) [d], $^2J_{8e-8a} = 13.5$, $^3J_{8e-7a} = 4.0$, $^3J_{8e-7e} = 2.5$, $^4J_{8e-6a} = 2.5$	3.88 (m, 2H) [e], $^2J = 11.5$, $^3J = 3.0/2.42$ (bs, 2H)	2.54 (bs, 4H)/3.55 (bs, 4H)	8.18 (m, 1H, C-6″H), 7.46 (m, 1H, C-4″H), 7.28–7.39 (m, 3H, C-3′H, C-4′H, C-5′H), 7.21 (m, 2H, C-2′H, C-6′H), 6.62 (m, 2H, C-3″H, C-5″H)

Table 2 (*Continued*)

	C-4H	C-4aH	C-5H$_a$, C-6H$_a$	C-5H$_e$, C-2^{x}H$_2$	C-6H$_e$/C-7H$_e$	C-7H$_a$, C-3^{x}H$_2$	C-8H$_a$	C-8H$_e$	C-1^{x}H$_2$/C-4^{x}H$_2$	Cα H$_2$/Cβ H$_2$	Aromatic rings
19	3.57 (d, 1H), $^3J = 8.0$	3.44 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 8.0$, $^3J_{4a-5e} = 3.0$	1.35 (m, 2H)	1.62 (m, 3H)	1.84 (m, 1H)/1.75 (m, 1H)	1.52 (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], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.0$, $^3J_{8e-7e} = 2.0$, $^4J_{8e-6a} = 2.0$	3.88 (m, 2H) [e], $^2J = 12.0$, $^3J = 2.5/2.38$ (t, 2H), $^3J = 7.5$	2.46 (t, 4H), $^3J = 5.0/3.81$ (t, 4H), $^3J = 5.0$	8.29 (d, 2H, C-4″H, C-6″H, $^3J = 4.5$), 7.35 (t, 2H, C-3′H, C-5′H), 7.31 (t, 1H, C-4′H), 7.20 (m, 2H, C-2′H, C-6′H), 6.46 (t, 1H, C-5″H, $^3J = 4.5$)
20	3.58 (d, 1H), $^3J = 8.0$	3.45 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 8.0$, $^3J_{4a-5e} = 3.0$	1.35 (m, 2H)	1.63 (m, 3H)	1.84 (m, 1H)/1.75 (m, 1H)	1.54 (m, 3H)	2.75 (m, 1H) [c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 2.5$	4.45 (m, 1H) [d], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.0$, $^3J_{8e-7e} = 2.0$, $^4J_{8e-6a} = 2.0$	3.88 (m, 2H) [e], $^2J = 11.5$, $^3J = 3.0/2.46$ (t, 2H), $^3J = 7.0$	2.64 (bs, 4H)/3.09 (bs, 4H)	7.28–7.38 (m, 4H, C-3′H, C-4′H, C-5′H, C-2′H), 7.21 (m, 3H, C-3″H, C-5″, C-6′H), 7.04 (dd, 1H, C-6″H), 6.96 (td, 1H, C-4″H, $^3J_o = 7.8$, $^4J_m = 2.0$)
21	3.57 (d, 1H), $^3J = 8.0$	3.45 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 8.0$, $^3J_{4a-5e} = 3.0$	1.35 (m, 2H)	1.62 (m, 3H)	1.84 (m, 1H)/1.75 (m, 1H)	1.53 (m, 3H)	2.75 (m, 1H) [c], $^2J_{8a-8e} = 13.0$, $^3J_{8a-7a} = 13.0$, $^3J_{8a-7e} = 2.5$	4.45 (m, 1H) [d], $^2J_{8e-8a} = 13.0$, $^3J_{8e-7a} = 4.5$, $^3J_{8e-7e} = 2.0$, $^4J_{8e-6a} = 2.0$	3.88 (m, 2H) [e], $^2J = 11.5$, $^3J = 3.0/2.43$ (t, 2H), $^3J = 6.5$	2.62 (bs, 4H)/3.11 (bs, 4H)	7.33 (m, 3H, C-3′H, C-4′H, C-5′H), 7.21 (m, 2H, C-2′H, C-6′H), 6.98–7.07 (m, 2H, C-3″H, C-5″H), 6.89–6.97 (m, 2H, C-4″H, C-6″H)
22	3.57 (d, 1H), $^3J = 7.5$	3.44 (m, 1H) [b], $^3J_{4a-5a} = 11.0$, $^3J_{4a-4} = 7.5$, $^3J_{4a-5e} = 3.0$	1.35 (m, 2H)	1.62 (m, 3H)	1.84 (m, 1H)/1.75 (m, 1H)	1.53 (m, 3H)	2.74 (m, 1H) [c], $^2J_{8a\text{-}8e} = 12.5$, $^3J_{8a-7e} = 13.0$, $^3J_{8a-7e} = 2.5$	4.45 (m, 1H) [d], $^2J_{8e-8a} = 12.5$, $^3J_{8e-7a} = 4.0$, $^3J_{8e-7e} = 2.0$, $^4J_{8e-6a} = 2.0$	3.88 (m, 2H) [e], $^2J = 12.0$, $^3J = 3.0/2.42$ (t, 2H), $^3J = 8.0$	2.57 (bs, 4H)/2.92 (t, 4H), $^3J = 4.5$	7.28–7.38 (m, 3H, C-3′H, C-4′H, C-5′H), 7.21 (m, 2H, C-2′H, C-6′H), 7.15 (t, 2H, C-3″H, C-5″H), 7.02 (d, 1H, C-6″H), 6.96 (td, 1H, C-4″H, $^3J_o = 8.0$), 2.29 (s, 3H, CH_3)

[a] d, doublet; pd, pseudodoublet; bs, broad singlet; *o*, ortho; *m*, meta; m, multiplet; t, triplet; *a*, axial; *e*, equatorial.
[b] Multiplet seven lines.
[c] Multiplet six lines.
[d] Multiplet 10 lines.
[e] Multiplet six lines.

Table 3
^{13}C NMR spectral data of compounds **9**–**15** and **18**–**22** (A) and bromobutyl derivatives **5**–**8**, **17** (B) [a]

	9	**10**	**11**	**12**	**13**	**14**	**15**	**18**	**19**	**20**	**21**	**22**
C-1	151.7	151.7	151.7	151.7	151.8	151.8	152.0	153.5	153.5	153.6	153.6	153.6
C-3	162.0	162.0	162.0	161.7	161.7	161.2	161.7	169.5	169.5	169.5	169.5	169.5
C-4	**112.5**	**112.5**	**112.5**	**106.1**	**110.1**	**110.2**	**108.6**	53.9	53.8	53.8	53.8	53.9
C-4a	**151.5**	**149.7**	**149.6**	**150.9**	**150.4**	**150.4**	**150.0**	57.1	57.1	57.1	57.1	57.1
C-5	26.7	26.7	26.7	26.5 [b]	26.4	26.4	26.3	32.0	32.0	32.0	32.0	32.0
C-6	18.6	18.6	18.6	18.4	18.5	18.5	18.5	23.8	23.8	23.8	23.8	23.8
C-7	21.8	21.8	21.8	21.8	21.8	21.9	21.9	24.5	24.5	24.5	24.5	24.5
C-8	42.6	42.6	42.6	43.5	43.6	43.0	42.8	45.5	45.6	45.6	45.6	45.6
C-1′	**133.4**	**133.3**	**133.4**	**120.9** [b]	**132.5**	**132.5**	**122.2**	**136.4**	**136.4**	**136.4**	**136.4**	**136.4**
C-2′	128.5	128.5	128.5	**160.5** [b]	**135.1**	**135.1**	**157.4**	128.9	128.9	128.9	128.9	128.9
C-3′	130.8	130.7	130.8	115.8 [b]	132.6	129.5	111.1	128.5	128.5	128.5	128.5	128.6
C-4′	127.7	127.7	127.7	130.0 [b]	129.7	129.7	129.5	127.9	128.0	127.9	127.9	127.9
C-5′	130.8	130.7	130.8	124.2 [b]	127.1	127.1	120.8	128.5	128.5	128.5	128.5	128.6
C-6′	128.4	128.5	128.5	133.0 [b]	129.5	132.6	132.4	128.9	128.9	128.9	128.9	128.9
C-1[x]	41.6	41.6	41.6	41.5	41.4	41.5	41.5	41.1	41.2	41.2	41.2	41.3
C-2[x]	25.7	25.7	25.7	25.6	25.7	25.7	25.7	26.4	26.5	26.5	26.4	26.5
C-3[x]	24.3	24.3	24.4	21.8	24.2	24.3	24.3	24.0	24.1	24.0	24.0	24.2
C-4[x]	58.4	58.5	58.4	58.4	58.4	58.4	58.5	58.3	58.4	58.2	58.2	58.4
C-α	53.7	53.1	53.1	53.1	53.1	53.1	53.1	52.9	53.1	53.3	53.2	53.7
C-β	51.6	43.7	45.2	42.9	43.0	45.2	43.7	45.5	43.6	51.0	50.4	51.7
C-1″	**149.6**									**149.3**	**140.1** [b]	**151.6**
C-2″	**132.6**	**161.6**	**159.6**	**161.4**	**161.2**	**159.6**	**161.7**	**159.5**	**161.7**	**128.8**	**155.7** [b]	**132.6**
C-3″	126.5		107.0			107.0		107.0		130.6	116.1 [b]	126.5
C-4″	123.0	157.7	137.4	157.7	157.7	137.4	157.7	137.4	157.7	123.6	122.4 [b]	123.0
C-5″	131.0	109.7	113.2	109.8	109.8	113.2	109.7	113.3	109.7	127.6	118.9 [b]	131.0
C-6″	119.0	157.7	148.0	157.7	157.7	148.0	157.7	148.0	157.7	120.4	124.4 [b]	119.0
R	17.9						55.6 [b]					17.9

	5	**6**	**7**	**8**	**17**
C-1	151.6	151.7	151.7	151.9	153.4
C-3	161.9	161.4	161.1	161.7	169.5
C-4	**112.3**	**106.1**	**110.0**	**108.7**	53.7
C-4a	**149.9**	**151.0**	**150.6**	**150.1**	57.1
C-5	26.7	26.5 [b]	26.4	26.5	32.0
C-6	18.5	18.4	18.4	18.5	23.7
C-7	21.7	21.7	21.8	21.9	24.5
C-8	42.6	42.9	43.0	43.0	45.7
C-1′	**133.3**	**120.7** [b]	**132.4**	**122.1**	**136.3**
C-2′	128.4	**160.4** [b]	**135.1**	**157.4**	128.9
C-3′	130.7	115.8 [b]	132.6	111.2	128.5
C-4′	127.7	130.0 [b]	129.7	129.5	127.9
C-5′	130.7	124.2 [b]	127.1	120.8	128.5
C-6′	128.4	132.9 [b]	129.5	132.3	128.9
C-1[x]	40.7	40.8	40.5	40.6	40.3
C-2[x]	26.4	26.4	26.4	26.4	33.2
C-3[x]	30.2	30.2	30.1	30.3	30.1
C-4[x]	33.3	33.2	33.3	33.3	27.1
R				55.6	

Coupling constants $^{n}J(^{13}C-^{19}F)$ (Hz) for compounds **6** $^{1}J_{2'\text{-F}} = 246.0$, $^{2}J_{3'\text{-F}} = 21.9$, $^{2}J_{1'\text{-F}} = 16.5$, $^{3}J_{4'\text{-F}} = 8.3$, $^{3}J_{6'\text{-F}} = 8.3$, $^{4}J_{5'\text{-F}} = 3.7$, $^{5}J_{5\text{-F}} = 1.8$; **12** $^{1}J_{2'\text{-F}} = 241.8$, $^{2}J_{3'\text{-F}} = 22.5$, $^{2}J_{1'\text{-F}} = 16.5$, $^{3}J_{4'\text{-F}} = 8.3$, $^{3}J_{6'\text{-F}} = 2.8$, $^{5}J_{5'\text{-F}} = 1.9$; **21** $^{1}J_{2''\text{-F}} = 245.8$, $^{2}J_{3''\text{-F}} = 20.6$, $^{2}J_{1''\text{-F}} = 8.2$, $^{3}J_{4''\text{-F}} = 4.2$, $^{3}J_{6''\text{-F}} = 3.6$, $^{4}J_{5''\text{-F}} = 3.3$; **15** $^{1}J = 1.4$ Hz ($^{13}C-^{17}O$).

[a] ^{13}C chemical shifts of the *ipso* carbon atoms of the pyridopyrimidine and phenyl rings are given in bold numbers (δ, ppm), in deuteriochloroform, TMS as the internal standard.

[b] Appear as doublet.

justify the search for new derivatives within the primary chemical structure. Also, generation of derivatives with distinctly pronounced agonistic properties in respect to serotonic 5-HT_{1A} receptors or inhibition of effects resulting from their effect on the α_1 adrenergic receptor could further increase their value.

The newly generated compounds discussed in this paper have been investigated for their ability of binding

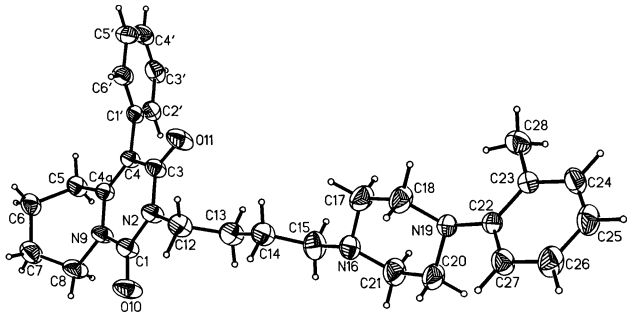


Fig. 3. ORTEP view of compound **9** with 50% probability of thermal ellipsoids.

Table 5
Crystal data, data collection and structure refinement of **9**

Molecular formula	$C_{29}H_{36}N_4O_2$
Molecular weight	472.62
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	triclinic
Space group	*P*-1
Unit cell dimensions	
a (Å)	7.679(2)
b (Å)	10.332(2)
c (Å)	16.808(3)
α (°)	84.72(3)
β (°)	79.53(3)
γ (°)	82.95(3)
V (Å^3)	1298.1(5)
Z	2
D_{calc} (Mg/m^3)	1.209
Absorption coefficient (/mm)	0.606
F(000)	508
θ Range for data collection (°)	4.32–60.0
Index ranges	$-8 \le h \le 8$, $-11 \le k \le 11$, $0 \le l \le 18$
Reflections collected	3829
Independent reflections	3752 [$R_{int} = 0.0155$]
Data/restraints/parameters	3752/0/317
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0599$, $wR_2 = 0.1651$
R indices (all data)	$R_1 = 0.1325$, $wR_2 = 0.1878$
Goodness-of-fit on F^2	1.002
Largest difference peak and hole (e/Å^3)	0.310 and −0.231

with the serotonergic type 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors, as well as the α_1 adrenergic receptor. Special attention should be given to derivatives containing a 2-pyrimidinylpiperazinylbutyl substituent at position 2 of the hexahydropyrido[1,2-*c*]pyrimidine ring system **10**, **12**, **13**, **15**. Such compounds have manifested moderate affinities to the 5-HT$_{1A}$ receptor, and weak affinities to the 5-HT$_{2A}$ and α_1 adrenergic receptors (see Table 4). Binding affinity to the 5-HT$_{1A}$ receptor depends in this case on substituents present in position 2 of the benzene ring associated with the hexahydropyrido[1,2-*c*]pyrimidine ring. Binding affinity towards 5-HT$_{1A}$ receptor decreases in the following sequence: **10**–H; **15**–CH_3O; **12**–F; **13**–Cl. The highest affinity was reported for compound **18** (Table 4). Compound **15** has manifested lower affinity to the 5-HT$_{1A}$ receptor, but at the same time this compound shows lower affinity in relation to the 5-HT$_{2A}$ receptor and decisively lower affinity in relation to the α_1 adrenergic receptor.

Similar investigations for receptor affinities were performed for octahydropyrido[1,2-*c*]pyrimidine derivative **19** containing an unsubstituted phenyl. Results show that the highest binding affinity to the receptor is manifested by the analog hexahydropyrido[1,2-*c*]pyrimidine derivative **10**. It is worth mentioning that derivative **10** manifested higher 5-HT$_{1A}$ binding affinity than compound **19**. Further tests were made on hexahydropyrido[1,2-*c*]pyrimidine derivatives marked **11** and **14**, as well as on octahydropyrido[1,2-*c*]pyrimidine derivative **18**, with 2-pyridylpiperazinylbutyl substituent in position 2. The highest binding affinity to the 5-HT$_{1A}$ receptor was obtained for the compound **18** (analog to compound **11**). All three compounds, i.e. **11**, **14** and **18** had relatively low selectivity towards 5-HT$_{2A}$ and α_1 adrenergic receptors.

In summary, it may be concluded that of the 10 newly synthesized and tested compounds **10**–**15** and **18**–**21**, special attention should be given to compound marked as **15**. Its parameters are: 5-HT$_{1A}$/5-HT$_{2A}$ = 15.4, 5-

Table 4
Binding affinities data for 5-HT$_{1A}$, 5-HT$_{2A}$ and α_1 receptors in compounds **10**–**15** and **18**–**21**

Comp.	K_i (nM) ± SEM			Selectivity versus 5-HT$_{1A}$ receptor K_i ratio	
	5-HT$_{1A}$ [^{3}H]8–OH–DPAT	5-HT$_{2A}$ [^{3}H]Ketanserin	α_1 [^{3}H]Prazosin	5-HT$_{2A}$	α_1
10	45.6 ± 7.9	336 ± 169	1202 ± 457	7.4	26.4
11	79.2 ± 20.0	102 ± 1.7	94.1 ± 15.4	1.3	1.2
12	69.2 ± 19.4	374 ± 40.3	742 ± 17	5.4	10.7
13	78.7 ± 10.0	607 ± 121	642 ± 133	7.7	8.2
14	33.4 ± 15.3	31.3 ± 11.4	114 ± 40.7	0.9	3.4
15	56.4 ± 7.1	871 ± 306	1597 ± 586	15.4	28.3
18	27.3 ± 14.5	69.7 ± 23.1	68.5 ± 8.1	2.6	2.5
19	99.8 ± 27.4	220 ± 4.1	559 ± 26	2.2	5.6
20	38.9 ± 26.4	35.9 ± 3.5	17.7 ± 5.3	0.9	0.5
21	37.9 ± 14.3	117 ± 59.2	20.6 ± 5.3	3.1	0.5

Table 6
Selected bond lengths (Å) and angles (°) for compound **9**

Bond lengths	
C(1)–O(10)	1.215(4)
C(1)–N(2)	1.372(4)
C(1)–N(9)	1.375(4)
N(2)–C(3)	1.389(4)
N(2)–C(12)	1.466(3)
C(3)–O(11)	1.224(3)
C(3)–C(4)	1.439(4)
C(4)–C(4a)	1.350(4)
C(4)–C(1′)	1.489(4)
C(4a)–N(9)	1.374(4)
C(4a)–C(5)	1.500(4)
C(5)–C(6)	1.507(5)
C(6)–C(7)	1.501(5)
C(7)–C(8)	1.486(5)
C(8)–N(9)	1.472(4)
C(12)–C(13)	1.482(5)
C(13)–C(14)	1.532(4)
C(14)–C(15)	1.473(5)
C(15)–N(16)	1.471(4)
N(16)–C(17)	1.433(4)
N(16)–C(21)	1.435(4)
C(17)–C(18)	1.524(4)
C(18)–N(19)	1.433(4)
N(19)–C(22)	1.432(4)
N(19)–C(20)	1.451(4)
Bond angles	
O(10)–C(1)–N(2)	122.7(3)
O(10)–C(1)–N(9)	121.5(3)
N(2)–C(1)–N(9)	115.8(3)
C(1)–N(2)–C(3)	124.7(2)
C(1)–N(2)–C(12)	118.0(2)
C(3)–N(2)–C(12)	117.2(3)
O(11)–C(3)–N(2)	119.4(3)
O(11)–C(3)–C(4)	124.5(3)
N(2)–C(3)–C(4)	116.1(3)
C(4a)–C(4)–C(3)	119.7(3)
C(4a)–C(4)–C(1′)	123.2(2)
C(3)–C(4)–C(1′)	117.1(2)
C(4)–C(4a)–N(9)	120.7(2)
C(4)–C(4a)–C(5)	125.6(3)
N(9)–C(4a)–C(5)	113.6(3)
C(4a)–C(5)–C(6)	110.8(3)
C(4a)–C(5)–H(5A)	109.5
C(6)–C(5)–H(5A)	109.5
C(4a)–C(5)–H(5B)	109.5
C(6)–C(5)–H(5B)	109.5
H(5A)–C(5)–H(5B)	108.1
C(7)–C(6)–C(5)	111.8(3)
C(8)–C(7)–C(6)	114.9(3)
C(7)–C(8)–N(9)	112.8(3)
C(4a)–N(9)–C(1)	122.7(3)
C(4a)–N(9)–C(8)	119.1(2)
C(1)–N(9)–C(8)	118.0(2)
N(2)–C(12)–C(13)	113.4(3)
C(12)–C(13)–C(14)	110.5(3)
C(15)–C(14)–C(13)	111.8(3)
N(16)–C(15)–C(14)	114.9(3)
C(17)–N(16)–C(21)	109.2(3)
C(17)–N(16)–C(15)	112.4(3)
C(21)–N(16)–C(15)	110.7(3)
N(16)–C(17)–C(18)	111.7(3)
N(19)–C(18)–C(17)	110.4(3)
C(22)–N(19)–C(18)	114.2(3)
C(22)–N(19)–C(20)	115.7(2)
C(18)–N(19)–C(20)	109.6(3)
N(19)–C(20)–C(21)	110.2(3)
N(16)–C(21)–C(20)	111.5(3)
C(27)–C(22)–C(23)	119.0(3)
C(27)–C(22)–N(19)	121.8(3)
C(23)–C(22)–N(19)	199.2(3)

$HT_{1A}/\alpha_1 = 28.3$; $K_i = 56.4$ nM relative to 5-HT_{1A} receptor.

The newly synthesized compound **15** showed highest selectivity and high affinity towards the serotonergic type 5-HT_{1A} receptor.

5. Experimental

5.1. Chemistry

The IR spectra (potassium bromide pellets) were recorded on either a Bio-Rad FTS-135 or a Perkin–Elmer FT-IR spectrometer Spectrum 1000, PE Auto IMAGE System. The NMR spectra were recorded on a UNITY plus 500 MHz spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, respectively). Two-dimensional NMR ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR and GHMQC experiments were performed on a Varian UNITY plus 500 MHz spectrometer. For the 2D experiments, the pulse sequences, acquisition and processing parameters were taken from standard Varian software library. The crystals suitable for X-ray analysis were grown from C_7H_{16} solution by slow evaporation. Data were collected on a kappa-geometry KM4 KUMA diffractometer [42], with graphite monochromated Cu Kα radiation. The accurate unit cell dimensions were obtained by the least-squares fit of setting angles of 29 reflections ($11 < 2\theta < 48^\circ$). The θ–2θ scan method and a variable scan speed, depending on reflection intensity, were used. Two control reflections were measured after every 100 reflections and showed no systematic changes during data collection. Intensity data were corrected for Lp effects [42]. The structure was solved by direct methods with the SHELXL-97 [43] program and refined by the full-matrix least-squares method with the SHELXL-97 [44] program. Refinement was carried out for reflections with positive values of F^2 and one of them was excluded from reflection files due to their large ($|F_o|^2 - |F_c|^2$) differences. Scattering factors incorporated in SHELXL-97 were used. The function $\Sigma\, w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.1254P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.

All non-hydrogen atoms were refined with anisotropic thermal parameters. The coordinates of the hydrogen atoms were calculated from the geometry and refinement as a riding model with their thermal parameters calculated as 1.2 (1.5 for methyl group) times U_{eq} of the bonded atom. An empirical extinction correction was also applied according to the formula $F'_c = kF_c[1 + (0.001\chi F_c^2\lambda^3/\sin 2\theta)^{-1/4}]$, and the extinction coefficient χ was equal to 0.0029(8) [44].

Crystal data together with the data collection and structure refinement details are listed in Table 5. Selected bond lengths and angles are listed in Table 6. The displacement ellipsoid representations of the molecule, together with the atomic numbering scheme is shown in Fig. 3 [45]. All geometric and thermal parameters are given in Section 6.

The flash column chromatography 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 dioxan, $C_6H_5CH_3$, EtOH and 25% NaOH and visualized using a UV long or dyed with C_6H_6 solution of *p*-chloranil.

M.p.s were determined on a Laboratory Devices MEL-TEMP® 3.0 (Branstead/Thermolyne; USA) instrument without corrections.

Microanalytical data were obtained on a Perkin–Elmer Analyzer CHN 2400 in the Department of Chemistry, Technical University of Warsaw.

The starting materials, 4-aryl-hexahydro- and (*R*,*R*) and (*S*,*S*) 4-aryl-octahydropyrido[1,2-*c*]pyrimidine-1,3-diones **1**–**4** and **16** were prepared by the reported procedure **1**–**4** [39] and **16** [40].

5.1.1. General procedure for the synthesis of 2-(4-bromobutyl)-4-aryl-1H,3H-hexahydro- and (R,R) and (S,S) octahydropyrido[1,2-c]pyrimidine-1,3-diones (5–8, 17)

To the mixture of 0.04 mol of appropriate imide **1**–**4**, **16** and 70 ml of C_3H_6O was added, while stirring 0.06 mol of K_2CO_3 and 0.12 mol of 1,4-dibromobutane. The obtained mixture was stirred under reflux. The time of the reaction was monitored by the TLC (~ 25 h). After cooling the mixture was filtered and the filtrate was evaporated to dryness. The obtained residue was purified by flash chromatography (with CH_2Cl_2–MeOH, 97:2 v/v) to provide compounds **5**–**8** and **17** as colorless solids. The compounds were crystallized: **5** from EtOH, **6** and **8** from C_6H_{14}, **7** from C_7H_{16} and **17** from ligroine. The reaction yields, m.p.s, analytical and IR data are given in Table 1. The results of ^{1}H NMR analysis are collected in Table 2 and of ^{13}C NMR in Table 3.

5.1.2. General procedure for the synthesis of 2-[4-[4-aryl or heteroaryl-1-piperazinyl]butyl]-4-aryl-hexahydro-1H,3H- and (R,R) and (S,S) octahydropyrido[1,2-c]pyrimidine-1,3-diones (9–15 and 18–22)

The 5 mmol of the appropriate bromobutyl derivatives **5**–**8**, **17** was added under stirring to a mixture composed of 80 ml MeCN and 5 mmol at the piperazine derivatives, 20 mmol of K_2CO_3 and 0.5 mmol of potassium iodate. The mixture was refluxed under stirring for about 25 h. The time of the reaction was controlled by TLC. The reaction mixture was cooled, filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (with CH_2Cl_2–MeOH, 98:3 v/v) to afford the product as white solid. The purified compounds were crystallized from: **9**–**11** from EtOH; **12**, **13**, **14**, **20**, **21**, **22** from C_7H_{16}; **15**, **18** from C_6H_{14} and **19** from MeCN.

The reaction yields, m.p.s, the result of elemental analysis and IR data are given in Table 1. The results obtained by NMR are collected in Table 2 (^{1}H NMR) and Table 3 (^{13}C NMR).

5.2. Pharmacology

5.2.1. 5-HT$_{1A}$ binding assay

Frozen Wistar rat cortices stored at −80 °C were used for 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 MAFCNOB 10, MultiScreen®-FC, Millipore) contained membrane suspension (~ 0.15 mg of protein), 1.0 nM [^{3}H]8–OH–DPAT (219 Ci/mmol, Amersham) and buffer and/or 10 μM serotonin (non-specific binding defining drug) or nine concentrations of testing compound in a final volume of 0.3 ml. Assay contained 10 μM pargyline, 5.7 mM $CaCl_2$ and 0.1% ascorbic acid. The mixture was incubated for 30 min at 37 °C. 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 [46].

5.2.2. 5-HT$_{2A}$ binding assay

Frozen Wistar rat cortices stored at −80 °C were used for 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 MAFCNOB 10, MultiScreen®-FC, Millipore) contained membrane suspension (~ 0.15 mg of protein), 0.6 nM [^{3}H]Ketanserin (60 Ci/mmol, NEN) and buffer and/or 1 μM mianserin (non-specific binding

defining drug) or nine concentrations of testing compound in a final volume of 0.3 ml. The mixture was incubated for 30 min at 25 °C. 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 [46].

5.2.3. α_1-Adrenergic binding assay

Frozen Wistar rat cortices stored at −80 °C were used for 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 MAFCNOB 10, MultiScreen®-FC, Millipore) contained membrane suspension (~0.15 mg of protein), 0.2 nM [^{3}H]Prazosin (26 Ci/mmol, NEN) and buffer and/or 1 μM phentolamine (non-specific binding defining drug) or nine concentrations of testing compound in a final volume of 0.3 ml. The mixture was incubated for 30 min at 25 °C. 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 [46].

6. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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