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Short communication

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 4

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Abstract

New 4-aryl-2H-pyrido[1,2-*c*]pyrimidine-1,3-dione derivatives of arylpiperazine (**6**–**18**) were prepared and evaluated in vitro for their affinity for 5-HT_{1A}, 5-HT_{2A}, and α_1 receptors. The influence of *ortho* substitution in the phenyl ring, substitution at position 4 of the pyrido[1,2-*c*] pyrimidine system, and its unsaturation degree were explored. The tested compounds showed high affinity for the 5-HT_{1A} receptor (K_i = 1.3–79.2 nM) and moderate to low affinity for the 5-HT_{2A} (K_i = 51.7–1405 nM) and α_1 receptors (K_i = 19.7–382.3 nM). Compounds **8** and **10** showed the highest 5-HT_{1A} receptor affinity (K_i = 1.3 and 2.2 nM, respectively) and were 37- and 35.9-fold, respectively, more selective in relation to α_1 adrenoreceptors.

Keywords: Disubstituted piperazines; Pyrido[1,2-*c*]pyrimidine; 5-HT_{1A} receptor ligand; 5-HT_{2A} receptor ligand

1. Introduction

Serotonin (5-HT) is an important neurotransmitter that mediates a wide variety of physiological responses in both the peripheral and central nervous systems [1–3]. Serotonin 5-HT_{1A} receptors have been intensively studied because of their implication in several physiological processes and psychiatric disorders such as anxiety and depression [2–5]. In addition to these therapeutic uses, serotoninergic 5-HT_{1A} agonists have been proposed recently as neuroprotective agents, and the effect of these drugs may be therapeutically relevant [6,7]. For these reasons, the discovery of new 5-HT_{1A} receptor ligands with high affinity and selectivity is an area of focus in medical chemistry.

Several potent 5-HT_{1A} receptor ligands are already known and, from a chemical point of view, they can be subdivided into different classes [8–10]. Long-chain arylpiperazines (LCAPs) represent one of the most important classes of 5-HT_{1A} receptor ligands [e.g. buspirone, tandospirone, NAN-190, flesinoxan, WAY 100135, and WAY 100635 (see Fig. 1)] [10–31]. Among LCAPs are compounds that show different 5-HT_{1A} receptor functional activities, i.e. agonistic, partial agonistic, or antagonistic. The most frequently investigated member of the LCAPs is buspirone, used in the treatment of anxiety [2,10,15,23,27,32–34]. Arylpiperazine 5-HT_{1A} receptor ligands such as tandospirone, ipsapirone, gepirone, flesinoxan, and many others in various phases of clinical studies are regarded as potential therapeutics for anxiety, depression, and memory and learning dysfunction [2,10,15,32,34]. 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 degree of similarity (45%) in their amino acid sequence [35]. Structural modification within LCAPs occurs mainly at the two opposite ends of the molecule and has been described in many papers [12,16,19,24–31] and reviews [2,3,36,37].

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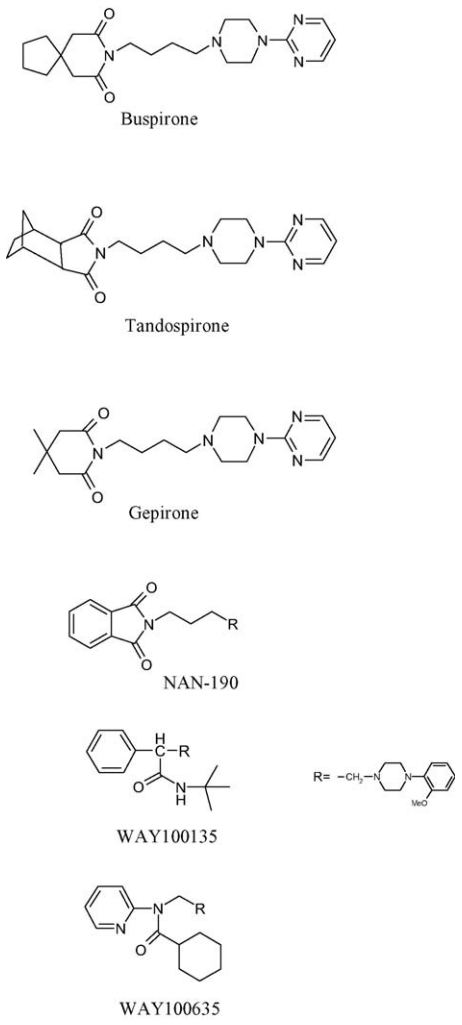

Fig. 1. LCAPs with an imide or amide moiety.

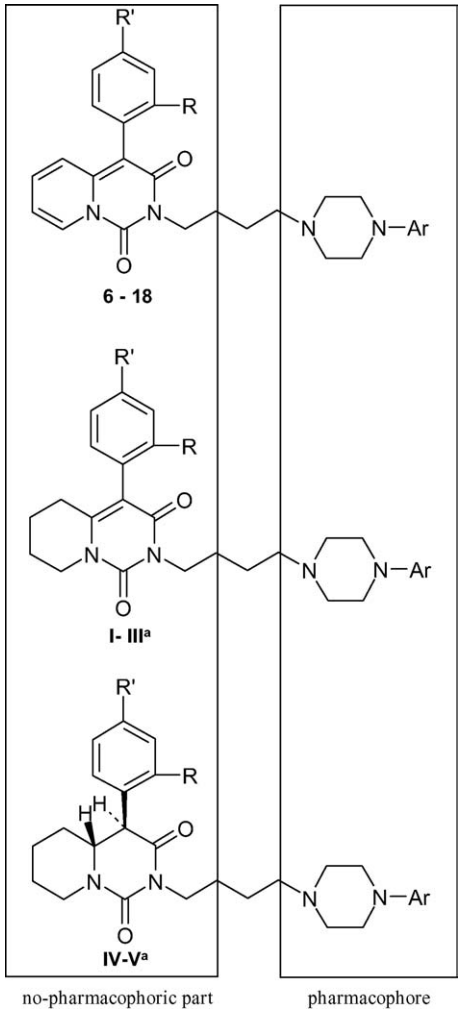

Fig. 2. Structure modification.

The aim of this work was the design, synthesis, and biological evaluation of new compounds with higher affinity and selectivity for 5-HT_{1A} receptors. We synthesized 16 new compounds with a novel 4-aryl-2H-pyrido[1,2-*c*]pyrimidine fragment as a terminal part of the LCAPs (Fig. 2). Other modifications were made in the pharmacophoric part by introduction of different substituents at the N-4 piperazine ring nitrogen (Fig. 3). New compounds **6**–**18** were tested for their affinity for 5-HT_{1A}, 5-$HT_{2A,}$ and α_1 adrenergic receptors, using a radioligand binding assay.

2. Chemistry

The compounds **6**–**18** described in this work were synthesized according to Fig. 3. The respective nitriles **2a**–**f**, used as substrates, were synthesized by a new method previously described in [40,41]. The reaction of C-arylation of the stabilized anion (Ar–CH–CN) was carried out in the presence of 2-bromopyridine in aprotic polar solvent (with the addition of potassium hydroxide). As the next step in the synthesis, the nitriles **2a**–**f** were hydrolyzed using a mixture of sulfuric and acetic acids, to obtain the amides **3a**–**f** in good yields. The compounds **4a**–**f** were formed in the intermolecular cyclization reaction (in the presence of sodium ethoxide and diethyl carbonate) of **3a**–**f**.

Then the imide group of compounds **4a**–**f** was N-alkylated by the 1,4-dibromobutane, yielding the new monobutyl derivatives **5a**–**f**.

The final new targets were obtained by the condensation of the appropriate 1-aryl piperazines with the above-described bromobutyl derivatives **5a**–**f**. The purified compounds **6**–**18** were converted into their hydrochloride salts to be better dissolved in water.

All new compounds **5a**–**f** and **6**–**18** were characterized by physical constants, elemental analysis, IR, ^{1}H, and ^{13}C-NMR spectroscopy (see Section 6). The structures of these compounds were elucidated from their analytical and spectroscopic data.

3. Pharmacology

Target compounds **6**–**18** were assessed for in vitro affinity for serotoninergic 5-HT_{1A} and 5-HT_{2A} receptors by radioligand binding assays, using [^{3}H]-8-OH-DPAT and [^{3}H]ketanserin, respectively, in rat cerebral cortex membranes. The ligands

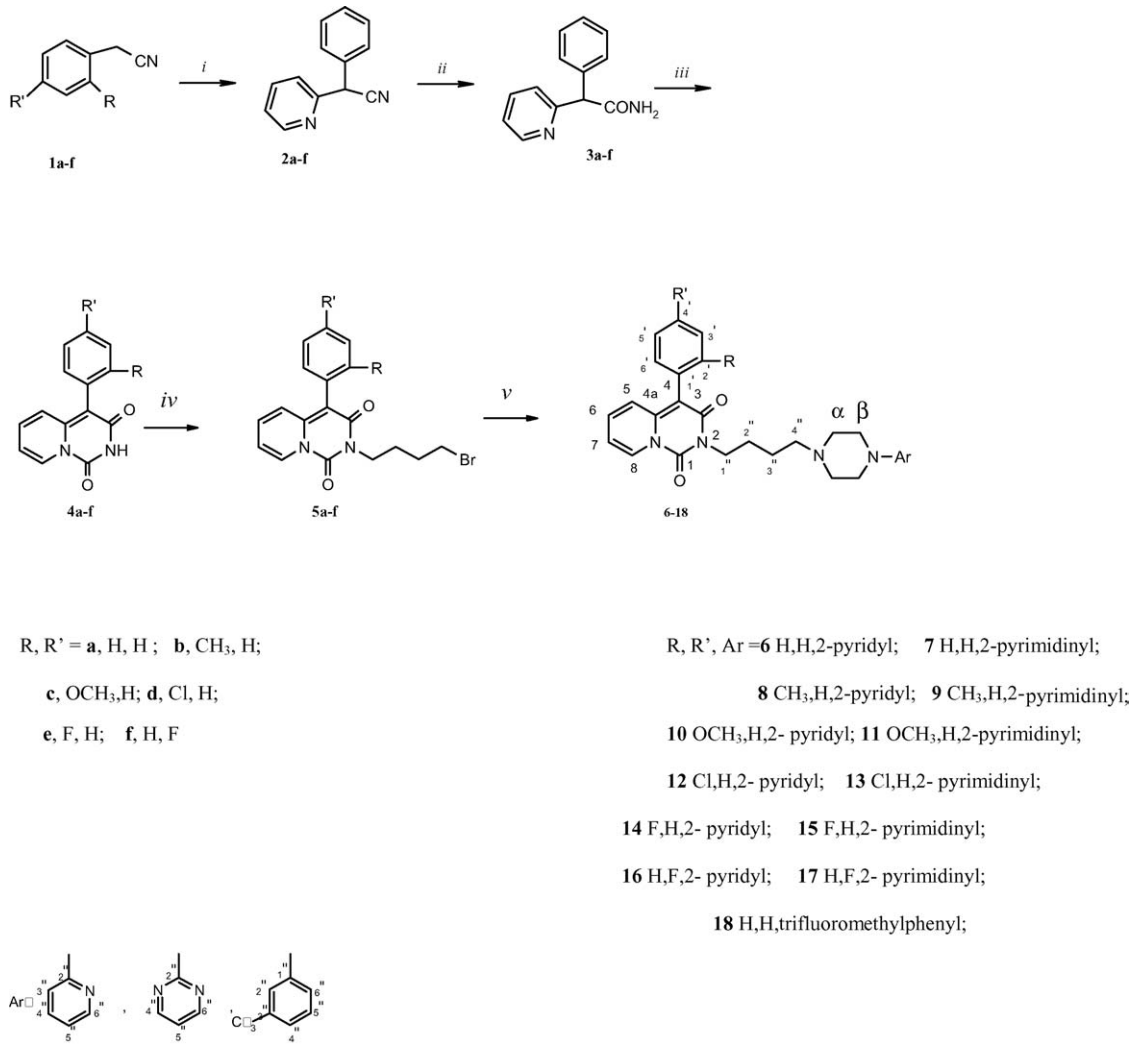

Fig. 3. Reagents: (*i*) 2-bromopyridine, KOH, dimethylsulfoxide, Δ; (*ii*) sulfuric and acetic acid, Δ; (*iii*) diethyl carbonate, sodium ethoxide, abs. ethanol, Δ; (*iv*) 1,4-dibromobutane, K_2CO_3, acetone Δ; (*v*) heteroarylpiperazine, acetonitrile, K_2CO_3, KJ, Δ.

were also evaluated for in vitro affinity for α_1 adrenergic receptors ([^{3}H] prazosin) in rat cerebral cortical tissue. 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 constant K_i according to the Cheng–Prusoff formula [42]. The affinity constants and selectivity obtained for the tested compounds are listed in Table 1.

4. Results and discussion

A number of new derivatives of pyrido[1,2-*c*]pyrimidine belonging to the so-called long-chain piperazines was synthesized in study. In these derivatives, the piperazine moiety was bound to three different aryl substituents (in the pharmacophore), either the 2-pyridyl, 2-pyrimidinyl, or m-trifluormethylphenyl residue. In turn, the no-pharmacophore part of the molecule consisted of a 4-aryl-2H-pyrido[1,2-*c*]pyrimidine-1,3-dione system in which the imide group is important. The aryl at the 4-position of this system was *ortho*-substituted with the following groups: –H, $–CH_3$, $–OCH_3$, –F, and –Cl (compounds **6**–**15**). In two derivatives (compounds **16** and **17**), the aryl group was *para*-substituted with a fluorine atom. Results of the receptor study concerning three subtypes of receptors (5-HT_{1A}, 5-HT_{2A}, and α_1) were analyzed with regard to the effect that a 2-pyridyl or 2-pyrimidinyl substituent bound to an N-4 piperazine ring nitrogen might have on affinity of ligands for the 5-HT_{1A} receptor (Table 1).

The first group of ligands were from derivatives with a 2-pyridyl substituent bound to the N-4 piperazine ring nitrogen (ligands **6**, **8**, **10**, **12**, **14**, and **16**). In this group, three derivatives exhibited very high affinity for the 5-HT_{1A} receptor: ligand **8** (K_i = 1.3 nM), ligand **10** (K_i = 2.2 nM), and ligand **6** (K_i = 7.0 nM). Remaining derivatives were characterized by a high affinity for the 5-HT_{1A} receptor, and K_i values ranged from 23.8 to 36.8 nM (ligands **16**, **14**, and **12**, in ascending K_i order). Two of these ligands (**16** and **12**) also showed higher affinity for the α_1 receptor (compound **16** exhibited a very high value of K_i = 6.5 nM, and for compound **12,** K_i = 19.7 nM).

Next, ligands belonging to the second group (with 2-pyrimidinyl substituent bound to N-4 piperazine ring nitrogen) were investigated. These revealed, in general, lower affinity for the

Table 1
Binding affinities and selectivities of compounds **6**–**18**

Compound	R	R′	Ar	K_i nM (± S.E.M.) 5-HT_{1A} [^{3}H]8-OH-DPAT	5-HT_{2A} [^{3}H]ketanserin	α_1 [^{3}H]prazosin	Selectivity versus 5-HT_{1A}receptor K_i ratio 5-HT_{2A}	α_1
6	H	H	2-pyridyl	7.0 ± 0.7	470.8 ± 21.2	23.5 ± 4.3	67.2	3.0
7	H	H	2-pyrimidinyl	10.7 ± 0.3	83.9 ± 3.8	152.4 ± 8.2	7.8	14.2
8	CH_3	H	2-pyridyl	1.3 ± 0.1	5.7 ± 0.3	46.7 ± 18.1	4.4	35.9
9	CH_3	H	2-pyrimidinyl	51.0 ± 2.4	136.4 ± 9.7	367. 6± 56.6	2.7	7.2
10	OCH_3	H	2-pyridyl	2.2 ± 0.2	56.8 ± 1.8	81.4 ± 8.7	25.8	37.0
11	OCH_3	H	2-pyrimidinyl	254.4 ± 22.5	1405 ± 280	321.8 ± 44.9	5.5	1.3
12	Cl	H	2-pyridyl	36.8 ± 12.0	145.2 ± 3.2	19.7 ± 3.7	3.9	0.5
13	Cl	H	2-pyrimidinyl	74.0 ± 2.9	99.4 ± 22.2	204.4 ± 14.6	1.3	2.8
14	F	H	2-pyridyl	25.7 ± 13.2	93.1 ± 9.9	34.1 ± 1.4	3.6	1.3
15	F	H	2-pyrimidinyl	75.6 ± 2.4	51.7 ± 2.8	103.8 ± 36.8	0.7	1.4
16	H	F	2-pyridyl	23.8 ± 2.6	261.2 ± 38.1	6.5 ± 0.2	11.0	0.3
17	H	F	2-pyrimidinyl	30.6 ± 7.8	100.3 ± 15.3	250.1 ± 46.3	3.3	8.2
18	H	H	3-CF_3-Ph	472.8 ± 7.1	179.5 ± 2.1	382.3 ± 7.3	0.4	0.8
I[a]	H	H	2-pyrimidynyl	45.6 ± 7.9	336.0 ± 169.0	1202.0 ± 457.0	7.4	26.4
II[a]	H	H	2-pyridyl	79.2 ± 20.0	102.0 ± 1.7	94.1 ± 15.4	1.3	1.2
III[a]	OCH_3	H	2-pyrimidynyl	56.4 ± 7.1	871.0 ± 306.0	1597.0 ± 58.6	15.4	28.3
IV[a]	H	H	2-pyridyl	27.3 ± 14.5	69.7 ± 23.1	68.5 ± 8.1	2.6	2.5
V[a]	H	H	2-pyrimidynyl	99.8 ± 27.4	220.0 ± 4.1	559.0 ± 26.0	2.2	5.6

[a] Data from Ref. [38].

5-HT_{1A} receptor (compounds **7**, **9**, **11**, **13**, **15**, and **17**). Values of affinity for this subtype of receptor were high only for two ligands (numbers **7** and **17**, K_i = 10.7 and 30.6 nM, respectively). Remaining values of affinity may be regarded as intermediate (K_i = 51.0–254.4 nM for compounds **9**, **13**, **15**, and **11**, in ascending K_i order).

It was also of interest to determine whether or not the type of substituent bound to the aryl group of pyrido[1,2-*c*]pyrimidine system would affect the affinity of ligands for the 5-HT_{1A} receptor. Results of an in vitro study confirmed that presence of the substituent at the *ortho*-position of the phenyl group is of great importance, depending on the substituent type. Such substituents can have the highest impact on affinity for receptor 5-HT_{1A}. Rank for ligands of the first group (i.e. with 2-pyridyl bound to piperazine) was R = –CH_3 (compound number **8**, K_i = 1.3 nM) > R = –OCH_3 (**10**, K_i = 2.2 nM) > R = –H (**6**, K_i = 7.0 nM) > R = –F (**14**, K_i = 25.7 nM) > R = –Cl (**12**, K_i = 36.8 nM). In the second group of ligands, the impact of substituents on affinity was different and can be presented as follows: R = –H (**7**, K_i = 10.7 nM) > R = –F (**17**, K_i = 30.6 nM) > R = –CH_3 (**9**, K_i = 51.0 nM) > R = –Cl (**15**, K_i = 75.6 nM) > R = –OCH_3 (**11**, K_i = 254.4 nM). For a fluorine substituent at the *ortho*-position of the phenyl group, the following values of affinity for the 5-HT_{1A} receptor were established: K_i = 25.5 nM (ligand **14**) and K_i = 75.6 nM (ligand **15**). Both of these ligands revealed low selectivity and bound also with the 5-HT_{2A} and α_1 receptors.

When analyzing values of affinity for the 5-HT_{2A} receptors obtained from in vitro studies, we found that in general, it was lower than affinity observed for the 5-HT_{1A} receptor, and K_i values ranged from 51.7 to 1405 nM. Only ligand **8**, which had very high affinity values for the 5-HT_{1A} receptor (K_i = 1.3 nM) also had very high affinity values for the 5-HT_{2A} receptor (K_i = 5.7 nM). Some of the investigated derivatives also had high affinity for the α_1 receptor (ligands **16**, **12**, **6**, and **14**).

Analyzing investigated compounds with regard to selectivity, we found that a few derivatives showed high selectivity (measured as a 5-HT_{1A}/5-HT_{2A} ratio), especially ligand **6** (67.2) and ligand **10** (25.8). Selectivity of compounds expressed as a 5-HT_{1A}/α_1 ratio was as follows: ligand **10** (37.0), ligand **8** (35.9), and ligand **7** (14.2).

Of all compounds investigated, ligand **10** showed the highest selectivity for 5-HT_{1A} receptor relative to 5-HT_{2A} and α_1 receptors. Values for the 5-HT_{1A}/5-HT_{2A} ratio and 5-HT_{1A}/α_1 ratio amounted to 25.8 and 37.0, respectively.

The 4-aryl-2H-pyrido[1,2-*c*]pyrimidine derivatives **6–18** possessing three double bounds in the heterocyclic system (Fig. 2), obtained in the work compounds, were analyzed at an angle of influence for the no-pharmacophoric part unsaturation degree on the affinity to 5-HT_{1A} receptor.

In previous studies we described 4-aryl-hexahydro-(with one double bound) and 4-aryl-octahydro-pyrido[1,2-*c*]pyrimidine (full saturated) derivatives [38]. The derivatives of 4-aryl-octahydro-pyrido[1,2-*c*]pyrimidine series were (*R*,*R*);(*S*,*S*) diastromers (Fig. 2).

When comparing the influence of these parts in the no-pharmacophoric part of ligands **6–18** and **I–III** and **IV–V** (Fig. 2 and Table 1), but possessing the same substituents in the pharmacophoric part (2-pyridyl or 2-pyrimidynylpiperazines), on the affinity to 5-HT_{1A}, 5-HT_{2A} and α_1 receptors and selectivity, it was found that the unsaturation degree of the no-pharmacophoric part has significant influence on this receptor.

The 4-aryl-2H-pyrido[1,2-*c*]pyrimidine derivatives **6–18** in our study when compared with the previously described 4-aryl-hexahydro- **I–III** and 4-aryl-octahydropyrido[1,2-*c*] pyrimidine **III**, **IV** analogs, showed a much higher affinity to the 5-

HT_{1A} receptor and also a higher selectivity was observed in the 5-HT_{1A}/5-HT_{2A} and 5-HT_{1A}/α_1 ratio (Table 1).

5. Conclusion

A series of new arylpiperazines, ligands of the 5-HT_{1A} receptor that contain a 4-aryl-2H-pyrido[1,2-*c*]pyrimidine moiety in the molecule, was synthesized.

New derivatives revealed high affinity for the 5-HT_{1A} receptor in vitro studies, while a few of these derivatives may be regarded as ligands with a mixed (type 5-HT_{1A}/5-HT_{2A}) profile of receptor affinity.

Compounds **8** (K_i = 1.3 nM), **10** (K_i = 2.2 nM), and **6** (K_i = 7.0 nM) exhibited the highest values of affinity for 5-HT_{1A} receptor. High selectivity of these ligands for the 5-HT_{2A} and α_1 receptors was also established. 5-HT_{1A}/5-HT_{2A} and 5-HT_{1A}/α_1 ratio values for ligand **10** were 25.8 and 37.0, respectively.

It was also established that the presence of a 2-pyridyl group bound to the piperazine N-4-moiety in the pharmacophore, as well as the existence of substituents at the *ortho*-position of the aryl bound to the 2H-pyrido[1,2-*c*]pyrimidine had a considerable impact on high affinity values for the 5-HT_{1A} receptor.

When evaluating impact of degree of unsaturation of the 4-aryl-pyrido[1,2-*c*]pyrimidine residue (no-pharmacophore part, Fig. 2), we established in turn that the 4-aryl-2H-pyrido[1,2-*c*]pyrimidine system inserted into ligands had the most favorable influence on the affinity of derivatives for the 5-HT_{1A} receptor in comparison with 4-aryl-hexahydro- and 4-aryl-octahydro-pyrido[1,2-*c*]pyrimidine residues inserted into compounds, as had been described before (Table 1) [38,39].

6. Experimental protocols

6.1. Chemistry

6.1.1. General remarks

Melting points were measured on a Mel-Temp® 3.0 (Brensted/Thermolyne, USA) apparatus without corrections. Elemental analyses were performed on a Perkin–Elmer 2400 analyzer (located in the Department of Chemistry, Technical University of Warsaw) and were within ± 0.4% of the theoretical values. Infrared spectra were recorded with a Shimadzu FTIR-8300. The ^{1}H and ^{13}C-NMR spectra were performed on a Bruker Avance DMX WB 400 MHz in $CDCI_3$ or D_2O using tetramethyl silane as an internal standard (chemical shifts are reported in δ units). Two-dimensional NMR ^{1}H–^{1}H COSY and ^{1}H–^{13}H HETCOR experiments were run on a Brüker Avance DMX WB 400 MHz spectrometer. For the two-dimensional experiments, the pulse sequences, acquisition, and processing parameters were taken from the standard Bruker software library.

Flash column chromatography was carried out on a Merck Kieselgel 60 (230–400 mesh) using the solvent methylene chloride/methanol (99:1; 97:3; 95:5, v/v). TLC was performed using Merck's DC-Platten Kiesel gel 60 F_{254} plates and a mobile phase of dioxane, toluene, ethanol, and 25% NH_4OH (6.0:3.2:0.5:0.2, v/v), and visualized using a UV lamp.

6.1.2. Preparation of 4-aryl-2H-pyrido[1.2-c]pyrimidine-1,3-diones

The starting compounds **2a–f**, **3a–f** and **4a–f** were obtained according to the described procedures in [40,41].

6.1.3. General procedure for the synthesis of 2-(4-bromobutyl)-4-aryl-2H-pyrido[1,2-c]pyrimidine derivatives (*5a–f*)

We added 0.06 mol of K_2CO_3 and 0.2 mol of 1,4-dibromobutane to a mixture of imide **4a–f** (0.04 mol) and 70 ml acetone, while stirring. The obtained mixture was stirred and refluxed for 2 h. Reaction time was monitored by TLC. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. The crude residue was purified by flash chromatography, using the mixture CH_2Cl_2/MeOH (97:3 v/v) and then using the mixture CH_2Cl_2/MeOH (99:1 v/v) as eluents. After thickening of proper eluates was qualified by TLC, the analytically pure compounds **5a–f** were obtained.

*6.1.3.1. 2-(4-Bromobutyl)-4-phenyl-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5a**)*. Yield 71%; yellow crystals, m.p. 93–94 °C ^{1}H-NMR (400 MHz) δ: 1.93 (m, 4H, C-2^xH_2, C-3^xH_2), 3.45 (t, ^3J = 6.4 Hz, 2H, C-4^xH_2), 4.18 (t, ^3J = 6.6 Hz, 2H, C-1^xH_2), 6.38 (m, 1H, C-7H), 6.90 (m, 2H, C-5H, C-6H), 7.20–7.60 (m, 5H, C-2′H, C-3′H, C-4′H, C-5′H, C-6′H), 8.32 (dd, ^3J = 7.6 Hz, ^4J = 1.0 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 26.2 (C-3^x), 30.1 (C-2^x), 33.1 (C-4^x), 41.5 (C-1^x), 104.7 (C-4), 110.7 (C-7), 121.4 (C-5), 127.7 (C-4′), 127.8 (C-8), 128.7 (C-2′, C-6′), 131.1 (C-3′, C-5′), 132.4 (C-6), 132.6 (C-1′), 143.5 (C-4a), 148.9 (C-1), 160.0 (C-3); IR *v*: 1680 (C=O), 1690 (C=O). Anal. ($C_{18}H_{17}N_2O_2Br$) C, H, N.

*6.1.3.2. 2-(4-Bromobutyl)-4-(2-tolyl)-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5b**)*. Yield 79%; yellow crystals, m.p. 81.0–82.5 °C; ^{1}H-NMR (400 MHz) δ: 1.94 (m, 4H, C-2^xH_2, C-3^xH_2), 2.15 (s, 3H, CH_3), 3.46 (t, ^3J = 6.0 Hz, 2H, C-4^xH_2), 4.20 (t, ^3J = 6.8 Hz, 2H, C-1^xH_2), 6.39 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.56 (d, ^3J = 9.2 Hz, 1H, C-5H), 6.89 (t, ^3J = 7.6 Hz, 1H, C-6H), 7.14 (d, ^3J = 7.2 Hz, 1H, C-6′H), 7.31 (m, 3H, C-3′H, C-4′H, C-5′H), 8.33 (d, ^3J = 7.6 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 19.8 (CH_3), 26.5 (C-3^x), 30.3 (C-2^x), 33.3 (C-4^x), 41.6 (C-1^x), 104.3 (C-4), 110.8 (C-7), 121.6 (C-5), 126.6 (C-5′), 128.2 (C-8), 128.6 (C-4′) 130.7 (C-3′), 131.8 (C-6′), 132.2 (C-2′), 132.7 (C-6), 138.7 (C-1′), 143.7 (C-4a), 149.3 (C-1), 159.8 (C-3); IR *v*: 1699 (C=O), 1710 (C=O). Anal. ($C_{19}H_{19}N_2O_2Br$) C, H, N.

*6.1.3.3. 2-(4-Bromobutyl)-4-(2-methoxyphenyl)-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5c**)*. Yield 89%; yellow crystals, m.p. 98.5–99.0 °C; ^{1}H-NMR (400 MHz) δ: 1.94 (m, 4H, C-2^{x}H, C-3^{x}H), 3.46 (t, ^3J = 6.4 Hz, 2H, C-4^xH_2), 3.76 (s, 3H, OCH_3), 4.19 (t, ^3J = 7.2 Hz, 2H, C-1^{x}H), 6.37 (t, ^3J = 7.2 Hz, 1H, C-7H), 6.64 (d, ^3J = 9.2 Hz, 1H, C-5H), 6.88 (m, ^3J = 7.6 Hz, 1H, C-6H), 6.99 (d, ^3J = 8.4 Hz, 1H, C-3′H), 7.03 (t, ^3J

= 7.6 Hz, 1H, C-5′H), 7.20 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, C-6′H), 7.37 (m, ^3J = 8.4 Hz, 1H, C-4′H), 8.31(d, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 26.5 (C-3^x), 30.3 (C-2^x), 33.4 (C-4^x), 41.6 (C-1^x), 55.8 (OCH_3), 101.4 (C-4), 110.7 (C-7), 111.6 (C-3′), 121.1 (C-5′), 121.5 (C-1′), 122.1 (C-5), 128.0 (C-8), 129.9 (C-4′), 132.2 (C-6), 133.1 (C-6′), 143.8 (C-4a), 149.3 (C-1), 158.1 (C-2′), 160.0 (C-3); IR *v*: 1696 (C=O), 1641 (C=O). Anal. ($C_{19}H_{19}N_2O_3Br$) C, H, N.

*6.1.3.4. 2-(4-Bromobutyl)-4-(2-chlorophenyl)-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5d**)*. Yield 95%; yellow crystals, m.p. 77–80 °C; ^{1}H-NMR (400 MHz) δ: 1.67 (s, 2H, C-3^{x}H$_2$), 1.86 (s, 2H, C-2^{x}H$_2$), 3.38 (d, ^3J = 6.0 Hz, 2H, C-4^{x}H$_2$), 4.13 (d, ^3J = 6.0 Hz, 2H, C-1^{x}H$_2$), 6.36 (t, 1H, C-7H), 6.48 (d, ^3J = 9.2 Hz, 1H, C-5H), 6.89 (t, 1H, C-4′H), 7.20 (s, 1H, C-6H), 7.23 (d, ^3J = 9.2 Hz, 1H, C-5′H), 7.26 (d, 1H, C-3′H), 7.43 (d, 1H, C-6′H), 8.29 (d, ^3J = 7.6 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 26.4 (C-2^x), 30.2 (C-3^x), 33.3 (C-4^x), 41.6 (C-1^x), 102.3 (C-4), 111.0 (C-7), 121.3 (C-5), 127.5 (C-5′), 128.3 (C-6), 129.8 (C-4′), 130.2 (C-3′), 131.8 (C-1′), 133.4 (C-8), 133.6 (C-6′), 135.9 (C-2′), 144.1 (C-4a), 149.1 (C-1), 159.6 (C-3); IR *v*: 1646 (C=O), 1707 (C=O). Anal. ($C_{18}H_{16}N_2O_2BrCl$) C, H, N.

*6.1.3.5. 2-(4-Bromobutyl)-4-(2-fluorophenyl)-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5e**)*. Yield 70%; yellow crystals, m.p. 95.5–97 °C; ^{1}H-NMR (400 MHz) δ: 1.93 (t, 2H, C-3^{x}H$_2$), 1.94 (t, 2H, C-2^{x}H$_2$), 3.46 (t, ^3J = 6.0 Hz, 2H, C-4^{x}H$_2$), 4.19 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$), 6.43 (t, 1H, C-7H), 6.74(d, ^3J = 9.6 Hz, 1H, C-5H), 6.98 (q, 1H, C-3′H), 7.22 (q, 1H, C-4′H), 7.33 (t, 1H, C-6′H), 7.37 (q, 1H, C-6H), 7.69 (t, ^3J = 9.2 Hz, 1H, C-5′H), 8.37 (d, ^3J = 7.6 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 26.2 (C-2^x), 30.1 (C-3^x), 33.1 (C-4^x), 41.6 (C-1^x), 98.3 (C-4), 110.9 (C-7), 115.8 ($^2J_{3'\text{-F}}$ = 22.2 Hz, C-3′), 120.2 ($^2J_{1'\text{-F}}$ = 16.0 Hz, C-1′), 121.3 (C-5), 124.4 ($^4J_{5'\text{-F}}$ = 3.4 Hz, C-5′), 128.1 (C-6), 130.1 ($^3J_{4'\text{-F}}$ = 8.2 Hz, C-4′), 133.2 (C-8), 133.4 ($^3J_{6'\text{-F}}$ = 2.9 Hz, C-6′), 144.1 (C-4a), 148.9 (C-1), 159.6 (C-3), 159.6 ($^1J_{2'\text{-F}}$ = 247.0 Hz, C-2′); IR *v*: 1638 (C=O), 1703 (C=O). Anal. ($C_{18}H_{16}N_2O_2BrF$) C, H, N.

*6.1.3.6. 2-(4-Bromobutyl)-4-(4-fluorophenyl)-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**5f**)*. Yield 57%; yellow crystals, m.p. 112–113 °C; ^{1}H-NMR (400 MHz) δ: 1.94 (m, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 3.46 (t, ^3J = 6.4 Hz, 2H, C-4^{x}H$_2$), 4.18 (t, ^3J = 7.2 Hz, 2H, C-1^{x}H$_2$), 6.41 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.87 (d, ^3J = 9.6 Hz, 1H, C-5H), 6.95 (t, ^3J = 6.8 Hz, 1H, C-5H), 7.01 (m, 2H, C-3′H, C-5′H) 7.30 (m, 2H, C-2′H, C-6′H), 8.34 (d, ^3J = 7.2 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 26.4 (C-3^x), 30.3 (C-2^x), 33.3 (C-4^x), 41.8 (C-1^x), 103.9 (C-4), 111.0 (C-7), 116.0 (^2J = 21.5 Hz, C-3′, C-5′), 121.4 (C-5), 128.3 (C-8), 128.7 (^4J = 3.0 Hz, C-1′), 133.0 (C-6), 133.2 (^3J = 8.2 Hz, C-2′, C-6′), 143.9 (C-4a), 149.1 (C-1), 160.3 (C-3), 162.5 (^1J = 247.2 Hz, C-4′); IR *v*: 1658 (C=O), 1701 (C=O). Anal. ($C_{18}H_{16}N_2O_2BrF$) C, H, N.

*6.1.4. General procedure for the synthesis of 2-[4-[4-aryl-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-diones (**6**–**18**)*

The following were added to acetonitrile (160 ml) under stirring: the appropriate bromobutyl derivatives **5a–f** (10 mmol), the respective arylpiperazine (10 mmol), K_2CO_3 (40 mmol), and KJ (1 mmol). The reaction mixture was refluxed while stirring for 10–15 h, and the completion time was assigned chromatographically (TLC). The mixture was filtered to remove inorganic salts, and the filtrate was evaporated to dryness under vacuum. The oily residue was purified by column flash chromatography with the eluent consisting of CH_2Cl_2/MeOH (97:3 and 99:1, v/v.) After thickening of proper eluates was qualified by TLC, the pure bases were obtained as oils. All final compounds were converted into hydrochloride.

*6.1.4.1. 4-Phenyl-2-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**6**)*. Yield 79%; yellow crystals, m.p. 286–287 °C; ^{1}H-NMR (400 MHz) δ: 1.90 (m, 2H, C-2^{x}H$_2$), 2.03 (m, 2H, C-3^{x}H$_2$), 3.46 (m, 2H, C-4^{x}H$_2$), 3.46 (m, 2H, CαH$_{ax}$), 3.85 (bpt, 2H, CβH$_{ax}$), 3.95 (bpd, 2H, CαH$_{eq}$), 4.23 (pt, 2H, C-1^{x}H$_2$), 4.52 (bpd, 2H, CβH$_{eq}$), 6.77 (t, ^3J = 6.8, 1H, C-7H), 6.92 (d, ^3J = 9.6, 1H, C-5H), 7.20 (t, ^3J = 7.6 Hz, 1H, C-5″H), 7.31 (m, 1H, C-6H), 7.31 (m, 2H, C-2′H, C-6′H), 7.57 (m, 2H, C-3′H, C-5′H), 7.57 (m, 1H, C-4′H), 7.57 (m, 1H, C-3″H), 8.19 (d, ^3J = 6.0 Hz, 1H, C-8H), 8.31 (t, ^3J = 8.4 Hz, 1H, C-4″H), 8.38 (d, ^3J = 7.2 Hz, 1H, C-6″H), N^+H.

^{13}C-NMR (100 MHz) δ: 23.4 (C-2^x), 26.4 (C-3^x), 44. (C-1^x) 45.7 (Cβ), 53.0 (Cα), 58.9 (C-4^x), 106.3 (C-3″), 115.4 (C-4), 115.7 (C-5″), 117.3 (C-7), 123.3 (C-5), 130.0 (C-8), 130.7 (C-4′), 131.5 (C-3′,C-5′), 133.7 (C-6″), 134.7 (C-2′, C-6′), 137.2 (C-1′), 139.0 (C-6), 147.1 (C-4″), 148.0 (C-4a), 151.6 (C-1), 154.4 (C-2″), 163.6 (C-3). IR *v*: 1645 (C=O), 1707 (C=O). Anal. ($C_{27}H_{29}N_5O_2 \times 2$ HCl $\times$ 0.5 H_2O) C, H, N.

*6.1.4.2. 4-Phenyl-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**7**)*. Yield 83%; yellow crystals, m.p. 258–259 °C; ^{1}H-NMR (400 MHz) δ: 1.86 (m, 2H, C-2^{x}H$_2$), 1.96 (m, 2H, C-3^{x}H$_2$), 3.39 (m, 2H, C-4^{x}H$_2$), 3.39 (m, 2H, CαH$_{ax}$), 3.74 (pt, 2H, CβH$_{ax}$), 3.87 (d, 2H, CαH$_{eq}$), 4.19 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$), 4.81 (d, 2H, CβH$_{eq}$), 6.75 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.93 (d, ^3J = 9.2 Hz, 1H, C-5H), 7.21 (m, 1H, C-6H), 7.21 (m, 1H, C-4″H), 7.31 (d, ^3J = 7.2 Hz, 2H, C-2′H, C-6′H), 7.53 (t, 1H, C-4′H), 7.56 (t, 2H, C-3′H, C-5′H), 8.37 (d, ^3J = 7.6 Hz, 1H, C-8H), 8.73 (d, ^3J = 4.8 Hz, 1H, C-3″H), 8.73 (d, ^3J = 4.8 Hz, 1H, C-5″H).

^{13}C-NMR (100 MHz) δ: 23.5 (C-3^x), 26.4 (C-2^x), 44.3 (Cβ), 44.4 (C-1^x), 53.3 (Cα), 59.0 (C-4^x), 106.5 (C-4), 113.9 (C-4″), 115.6 (C-7), 123.5 (C-5), 130.1 (C-8), 130.8 (C-4′), 131.6 (C-3′, C-5′), 133.8 (C-2′, C-6′), 134.9 (C-1′), 137.3 (C-6), 147.4 (C-4a), 151.8 (C-1), 156.9 (C-1″), 159.9 (C-3″), 159.9 (C-5″), 163.9 (C-3). IR *v*: 1641 (C=O), 1708 (C=O). Anal. ($C_{26}H_{28}N_6O_2 \times 2$ HCl $\times$ H_2O) C, H, N.

*6.1.4.3. 4-(2-Tolyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**8**)*. Yield 76%; yellow

crystals, m.p. 285–288 °C; ^{1}H-NMR (400 MHz) δ: 1.88 (m, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 2.11 (s, 3H, CH$_3$), 3.37 (m, 4H, C-4^{x}H$_2$, CαH$_{ax}$), 3.68 (bs, 2H, CβH$_{ax}$), 3.81 (bs, 2H, CαH$_{eq}$), 4.21 (t, ^3J = 6.4 Hz, C-1^{x}H$_2$), 4.36 (bs, 2H, CβH$_{eq}$), 6.72 (d, ^3J = 9.2 Hz, 1H, C-5H), 6.76 (t, ^3J = 7.6 Hz, 1H, C-7H), 7.16 (t, ^3J = 6.8 Hz, 1H, C-5″H), 7.20 (d, ^3J = 7.6 Hz, 1H, C-6′H), 7.24 (t, ^3J = 7.2 Hz, 1H, C-6H), 7.36 (t, ^3J = 7.2 Hz, 1H, C-5′H), 7.39 (d, ^3J = 9.2 Hz, 1H, C-3″H), 7.44 (m, 2H, C-3′H, C-4′H), 8.03 (d, ^3J = 6.0 Hz, 1H, C-6″H), 8.15 (t, ^3J = 7.6 Hz, 1H, C-4″H), 8.45 (d, ^3J = 7.2 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 19.7 (CH$_3$), 22.1 (C-3^x), 25.1 (C-2^x), 42.9 (C-1^x), 44.4 (2C, Cβ), 51.8 (2C, Cα), 57.7 (C-4^x), 104.3 (C-4), 114.2 (C-3″), 114.3 (C-5″), 116.1 (C-7), 122.3 (C-5), 127.8 (C-5′), 129.1 (C-8), 130.1 (C-4′), 131.7 (C-3′), 133.0 (C-6′), 133.2 (C-2′), 136.3 (C-6), 138.0 (C-4″), 140.3 (C-1′), 146.6 (C-4a), 146.6 (C-6″), 151.2 (C-1), 151.2 (C-2″), 162.8 (C-3). IR *v*: 1641 (C=O), 1703 (C=O). Anal. (C$_{27}$H$_{30}$N$_6$O$_3$ × 2 HCl × H$_2$O) C, H, N.

*6.1.4.4. 4-(2-Tolyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**9**)*. Yield 51%; yellow crystals, m.p. 267–270 °C; ^{1}H-NMR (400 MHz) δ: 1.90 (m, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 2.11 (s, 3H, CH$_3$), 3.30 (pt, 2H, CαH$_{ax}$), 3.38 (t, ^3J = 7.6 Hz, 2H, C-4^{x}H$_2$), 3.66 (pt, 2H, CβH$_{ax}$), 3.83 (pd, 2H, CαH$_{eq}$), 4.22 (t, ^3J = 6.4 Hz, 2H, C-1^{x}H$_2$), 4.76 (pd, 2H, CβH$_{eq}$), 6.70 (d, ^3J = 9.6 Hz, 1H, C-5H), 6.77 (t, ^3J = 7.2 Hz, 1H, C-7H), 7.13 (t, ^3J = 5.2 Hz, 1H, C-5″H), 7.18 (d, ^3J = 7.2 Hz, 1H, C-6′H), 7.24 (t, ^3J = 7.6 Hz, 1H, C-6H), 7.37 (t, ^3J = 6.8 Hz, 1H, C-5′H), 7.45 (m, 2H, C-3′H, C-4′H), 8.44 (d, ^3J = 7.6 Hz, 1H, C-8H), 8.66 (d, ^3J = 5.6 Hz, 2H, C-4″H, C-6″H).

^{13}C-NMR (100 MHz) δ: 21.2 (CH$_3$), 23.5 (C-3^x), 26.5 (C-2^x), 44.3 (2C, Cβ), 44.3(C-1^x), 53.4 (2C, Cα), 59.1 (C-4^x), 105.7 (C-4), 114.0 (C-5″), 115.6 (C-7), 123.7 (C-5), 129.2 (C-5′), 130.5 (C-8), 131.5 (C-4′), 133.2 (C-3′), 134.4 (C-6′), 134.5 (C-2′), 137.7 (C-6), 141.7 (C-1′), 147.9 (C-4a), 152.5 (C-1), 157.6 (C-2″), 160.1 (C-4″, C-6″), 164.1 (C-3). IR *v*: 1641 (C=O), 1701 (C=O). Anal. (C$_{27}$H$_{30}$N$_6$O$_3$ × 2 HCl × 1.5 H$_2$O) C, H, N.

*6.1.4.5. 4-(2-Methoxyphenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**10**)*. Yield 45%; yellow crystals, m.p. 250–251 °C; ^{1}H-NMR (400 MHz) δ: 1.83 (q, 2H, C-2^{x}H$_2$), 1.87 (q, 2H, C-3^{x}H$_2$), 3.34 (t, ^3J = 8.4 Hz, 2H, C-4^{x}H$_2$), 3.66 (bs, 2H, Cα_{ax}), 3.74 (s, 3H, OCH$_3$), 3.79 (bs, 4H, CαH$_{eq}$, CβH$_{ax}$), 4.15 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$], 4.33 (bs, 2H, CβH$_{eq}$), 6.71 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.74 (d, ^3J = 10.0 Hz, 1H, C-5H), 7.11 (t, ^3J = 7.6 Hz, 1H, C-6H), 7.14 (d, ^3J = 6.4 Hz, 1H, C-3′H), 7.19 (m, 3H, C-5′H, C-6′H, C-5″H), 7.37 (d, ^3J = 9.6 Hz, 1H, C-3″H), 7.49 (t, ^3J = 7.6 Hz, 1H, C-4′H), 8.00 (d, ^3J = 6.0 Hz, 1H, C-6″H), 8.12 (t, ^3J = 7.6 Hz, 1H, C-4″H), 8.38 (d, ^3J = 7.6 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 21.0 (C-3^x), 23.9 (C-2^x), 41.8 (C-1^x), 43.3 (Cβ), 50.6 (Cα), 55.8 (OCH$_3$), 56.6 (C-4^x), 100.0 (C-4), 112.3 (C-7), 113.1 (C-3′), 113.3 (C-3″), 115.0 (C-5″), 120.9 (C-1′), 121.3 (C-5′), 121.7 (C-5), 127.9 (C-8), 130.6 (C-4′), 133.1 (C-6), 135.0 (C-6′), 136.7 (C-4″), 145.6 (C-4a), 145.6 (C-6″), 149.9 (C-1), 152.2 (C-2″), 157.6 (C-2′), 165.9 (C-3). IR *v*: 1641 (C=O), 1700 (C=O). Anal. (C$_{28}$H$_{31}$N$_5$O$_3$ × 2 HCl × H$_2$O) C, H, N.

*6.1.4.6. 4-(2-Methoxyphenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**11**)*. Yield 46%; yellow crystals, m.p. 235–236 °C; ^{1}H-NMR (400 MHz) δ: 1.83 (m, 4H, C-2^{x}H, C-3^{x}H), 3.20 (pt, 2H, CαH$_{ax}$), 3.31 (t, ^3J = 6.8 Hz, 2H, C-4^{x}H$_2$), 3.52 (pt, 2H, CβH$_{ax}$), 3.72 (bs, 2H, CαH$_{eq}$), 3.75 (s, 3H, OCH$_3$), 4.16 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$), 4.68 (pd, 2H, CβH$_{eq}$), 6.72 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.76 (d, ^3J = 9.6 Hz, 1H, C-5H), 7.00 (t, 1H, C-5″H), 7.13 (t, ^3J = 7.2 Hz, 1H, C-6H), 7.17-7.26 (m, 3H, C-3′H, C-5′H, C-6′H), 7.50 (t, ^3J = 6.8 Hz, 1H, C-4′H), 8.40 (d, ^3J = 7.6 Hz, 1H, C-8H), 8.54 (d, ^3J = 5.2 Hz, 2H, C-4″H, C-6″H).

^{13}C-NMR (100 MHz) δ: 20.9 (C-3^x), 23.9 (C-2^x), 41.6 (Cβ), 41.8 (C-1^x), 51.0 (Cα), 55.8 (OCH$_3$), 56.5 (C-4^x), 100.0 (C-4), 111.6 (C-5″), 112.3 (C-7), 113.1 (C-3′), 120.9 (C-1′), 121.3 (C-5′), 121.8 (C-5), 127.9 (C-8), 130.6 (C-4′), 133.1 (C-6), 135.1 (C-6′), 145.7 (C-4a), 149.9 (C-1), 156.5 (C-2″), 157.6 (C-2′), 157.8 (C-4″, C-6″), 161.7 (C-3). IR *v*: 1631(C=O), 1701 (C=O). Anal. (C$_{27}$H$_{30}$N$_6$O$_3$ × 2 HCl × H$_2$O) C, H, N.

*6.1.4.7. 4-(2-Chlorophenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**12**)*. Yield 84%; yellow crystals, m.p. 273–275 °C (decomposition); ^{1}H-NMR (400 MHz) δ: 1.89 (s, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 3.37 (d, 4H, C-4^{x}H$_2$, CαH$_{ax}$), 3.69 (t, 2H, CβH$_{ax}$), 3.82 (bs, 2H, CαH$_{eq}$), 4.22 (m, ^3J = 5.6 Hz, 2H, C-1^{x}H$_2$), 4.38 (bs, 2H, CβH$_{eq}$), 6.79 (q, 2H, C-5H, C-7H), 7.18 (t, 1H, C-5″H), 7.29 (q, ^3J = 7.2 Hz, 1H, C-6H), 7.37 (t, 1H, C-3″H), 7.40 (t, 1H, C-6′H), 7.51 (k, 2H, C-4′H, C-5′H), 7.66 (d, 1H, C-3′H), 8.05 (d, 1H, C-6″H), 8.17 (t, 1H, C-4″H), 8.48 (d, ^3J = 7.2 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) δ: 23.5 (C-3^x), 26.5 (C-2^x), 44.3 (C-1^x), 45.8 (Cβ), 53.2 (Cα), 59.1 (C-4^x), 104.1 (C-4), 115.8 (C-7), 115.8 (C-3″), 117.6 (C-5″), 123.5 (C-5), 130.6 (C-5′), 130.7 (C-6′), 132.6 (C-4′), 133.1 (C-3′), 133.9 (C-1′), 136.2 (C-6), 138.0 (C-2′), 138.3 (C-8), 139.4 (C-4″), 148.1 (C-6″), 148.3 (C-4a), 152.4 (C-1), 154.8 (C-2″), 164.0 (C-3). IR *v*: 1649 (C=O), 1701 (C=O). Anal. (C$_{27}$H$_{28}$ClN$_5$O$_2$ × 2 HCl) C, H, N.

*6.1.4.8. 4-(2-Chlorophenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2- c]pyrimidine-1,3-dione (**13**)*. Yield 70%; yellow crystals, m.p. 268–270 °C (decomposition); ^{1}H-NMR (400 MHz) δ: 1.76 (s, 2H, C-3^{x}H$_2$), 1.88 (s, 2H, C-2^{x}H$_2$), 3.27 (t, 2H, CαH$_{ax}$), 3.36 (d, ^3J = 6.8 Hz, 2H, C-4^{x}H$_2$), 3.62 (t, 2H, CβH$_{ax}$), 3.80 (d, 2H, CαH$_{eq}$), 4.21 (d, ^3J = 5.2 Hz, 2H, C-1^{x}H$_2$), 4.74 (d, 2H, CβH$_{eq}$), 6.78 (q, 2H, C-5H, C-7H), 7.10 (d, 1H, C-5″H), 7.28 (t, ^3J = 7.2 Hz, 1H, C-6H), 7.36 (t, 1H, C-6′H), 7.50 (k, 2H, C-4′H, C-5′H), 7.64 (d, 1H, C-3′H), 8.47 (d, ^3J = 7.2 Hz, 1H, C-8H), 8.62 (d, 2H, C-4″H, C-6″H).

^{13}C-NMR (100 MHz) δ: 23.5 (C-3^x), 26.5 (C-2^x), 44.3 (C-1^x, Cβ), 53.4 (Cα), 59.1 (C-4^x), 104.1 (C-4), 114.1 (C-5″), 115.8 (C-7), 123.5 (C-5), 130.6 (C-5′), 130.7 (C-6′), 132.6 (C-4′), 133.1 (C-3′), 133.8 (C-1′), 136.2 (C-6), 138.0 (C-2′),

138.2 (C-8), 148.3 (C-4a), 152.4 (C-1), 158.0 (C-2″), 160.1 (C-4″, C-6″), 163.9 (C-3). IR *v*: 1650 (C=O), 1704 (C=O). Anal. ($C_{26}H_{27}ClN_6O_2 \times 2$ HCl × 1.25 H_2O) C, H, N.

*6.1.4.9. 4-(2-Fluorophenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl] butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**14**)*. Yield 88%; yellow crystals, m.p. 282–284 °C (decomposition); ^{1}H-NMR (400 MHz) *δ*: 1.89 (q, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 3.39 (t, 4H, C-4^{x}H$_2$, C*α*H$_{ax}$), 3.69 (q, 2H, C*β*H$_{ax}$), 3.84 (bs, 2H, C*α*H$_{eq}$), 4.21 (t, ^3J = 5.6 Hz, 2H, C-1^{x}H$_2$), 4.39 (bs, 2H, C*β*H$_{eq}$), 6.79 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.92 (d, ^3J = 9.2 Hz, 1H, C-5H), 7.19 (d, ^3J = 6.8 Hz, 1H, C-5′H), 7.30 (q, 2H, C-3′H, C-3″H), 7.36 (s, 1H, C-5″H), 7.37 (s, 1H, C-6H), 7.42 (d, 1H, C-6′H), 7.56 (m, 1H, C-4′H), 8.06 (d, 1H, C-6″H), 8.19 (t, 1H, C-4″H), 8.45 (d, 1H, C-8H).

^{13}C-NMR (100 MHz) *δ*: 20.9 (C-3^x), 23.9 (C-2^x), 41.8 (C-1^x), 43.3 (C*β*), 50.6 (C*α*), 56.5 (C-4^x), 97.6 (C-4), 113.3 (C-7), 115.0 (C-3″, C-5″), 116.1 (d, ^2J = 22.1 Hz, C-3′), 119.8 (d, ^2J = 16.2 Hz, C-1′), 121.0 (C-5), 125.1 (d, ^4J = 3.3 Hz, C-5′), 128.0 (C-4′), 131.0 (d, ^3J = 8.3 Hz, C-6′), 133.5 (C-6), 135.6 (C-8), 136.7 (C-4″), 145.5 (C-6″), 145.8 (C-2″), 149.7 (C-4a), 152.2 (C-1), 161.4 (C-3), 162.1 (s, ^1J = 244.3 Hz, C-2′). IR *v*: 1648 (C=O), 1703 (C=O). Anal. ($C_{27}H_{28}FN_5O_2 \times 2$ HCl × 0.25 H_2O) C, H, N.

*6.1.4.10. 4-(2-Fluorophenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2- c]pyrimidine-1,3-dione (**15**)*. Yield 98%; yellow crystals, m.p. 265–267 °C (decomposition); ^{1}H-NMR (400 MHz) *δ*: 1.65 (d, ^3J = 6.4 Hz, 2H, C-3^{x}H$_2$), 1.80 (k, 2H, C-2^{x}H$_2$), 2.44 (s, 2H, C-4^{x}H$_2$), 2.50 (bs, 4H, C*α*H$_2$), 3.82 (bs, 4H, C*β*H$_2$), 4.19 (t, ^3J = 7.2 Hz, 2H, C-1^{x}H$_2$), 6.43 (t, 1H, C-5″H), 6.47 (t, 1H, C-7H), 6.74 (d, ^3J = 9.6 Hz, 1H, C-5H), 6.98 (q, 1H, C-3′H), 7.17 (t, ^3J = 9.2 Hz, 1H, C-5′H), 7.24 (q, 1H, C-4′H), 7.33 (t, 1H, C-6′H), 7.38 (d, 1H, C-6H), 8.30 (d, 2H, C-4″H, C-6′'H), 8.37 (d, ^3J = 7.6 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) *δ*: 24.4 (C-3^x), 25.6 (C-2^x), 42.6 (C-1^x), 43.8 (C*β*), 53.3 (C*α*), 58.5 (C-4^x), 98.6 (C-4), 110.0 (C-5′'), 111.0 (C-7), 116.3 (d, ^2J = 22.2 Hz, C-3'), 120.5 (d, ^2J = 15.8 Hz, C-1'), 121.4 (C-5), 124.6 (d, ^4J = 3.3 Hz, C-5'), 128.4 (C-6), 130.3 (d, ^3J = 8.2 Hz, C-4′), 133.3 (C-8), 133.6 (d, ^3J = 2.7 Hz, C-6′), 144.2 (C-4a), 149.1 (C-1), 157.9 (C-4″, C-6″), 159.8 (C-3), 161.8 (C-2″), 162.3 (s, ^1J = 247.1 Hz, C-2′). IR *v*: 1624 (C=O), 1707 (C=O). Anal. ($C_{26}H_{27}FN_6O_2 \times 2$ HCl × 0.5 H_2O) C, H, N.

*6.1.4.11. 4-(4-Fluorophenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl] butyl]-2H-pyrido[1,2-c]pyrimidine-1,3-dione (**16**)*. Yield 40%; yellow crystals, m.p. 269–272 °C; ^{1}H-NMR (400 MHz) *δ* : 1.86 (m, 4H, C-2^{x}H$_2$, C-3^{x}H$_2$), 3.37 (pt, 4H, C-4^{x}H$_2$, C*α*H$_{ax}$), 3.70 (bs, 2H, C*β*H$_{ax}$), 3.83 (bs, 2H, C*α*H$_{eq}$), 4.19 (t, ^3J = 6.8 Hz, 2H, C1^{x}H$_2$), 4.37 (bs, 2H, C*β*H$_{eq}$), 6.76 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.97 (d, ^3J = 9.2 Hz, 1H, C-5H), 7.16 (d, ^3J = 6.8 Hz, 1H, C-5″H), 7.25 (t, ^3J = 7.2 Hz, 1H, C-6H), 7.29-7.37 (m, 4H, C-2′H,C-3′H, C-5′H, C-6′H), 7.40 (d, ^3J = 9.2 Hz, 1H, C-3″H), 8.04 (d, ^3J = 6.0 Hz, 1H, C-6″H), 8.16 (d, ^3J = 7.6 Hz, 1H, C-4″H), 8.42 (d, ^3J = 7.2 Hz, 1H, C-8H).

^{13}C-NMR (100 MHz) *δ*: 23.6 (C-3^x), 26.5 (C-2^x), 44.5 (C-1^x), 45.8 (C*β*), 53.2 (C*α*), 59.1 (C-4^x), 105.8 (C-4), 115.7 (C-3′′), 115.8 (C-5″), 117.6 (C-7), 118.7 (d, ^2J = 20.0 Hz, C-3′, C-5′), 123.8 (C-5), 130.4 (C-8), 131.2 (d, ^4J = 3.0 Hz, C-1′), 136.0 (d, ^3J = 8.4 Hz, C-2′, C-6′), 137.6 (C-4″), 139.4 (C-6), 148.1 (C-4a), 148.2 (C-1), 152.4 (C-6″), 154.9 (C-2″), 164.6 (C-3), 165.0 (d, ^1J = 244.8 Hz, C-4′). IR *v*: 1659 (C=O), 1703 (C=O). Anal. ($C_{27}H_{28}FN_5O_2 \times 2$ HCl) C, H, N.

*6.1.4.12. 4-(4-Fluorophenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2H-pyrido[1,2- c]pyrimidine-1,3-dione (**17**)*. Yield 74%; yellow crystals, m.p. 248-251 °C; ^{1}H-NMR (400 MHz) *δ*: 1.83 (m, 4H, C-2^{x}H$_2$, C3^{x}H$_2$), 3.23 (pt, 2H, C*α*H$_{ax}$), 3.33 (t, ^3J = 6.8 Hz, 2H, C-4^{x}H$_2$), 3.77 (pd, 2H, C*β*H$_{ax}$), 4.18 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$), 4.72 (m, 4H, C*α*H$_{eq}$, C*β*H$_{eq}$), 6.75 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.97 (d, ^3J = 9.2 Hz, 1H, C-5H), 7.03 (t, 1H, C-5″H), 7.24 (t, 1H, C-6H), 7.25–7.37 (m, 4H, C-2′H, C-3′H, C-5′H, C-6′H), 8.42 (d, ^3J = 7.6 Hz, 1H, C-8H), 8.57 (d, ^3J = 5.2 Hz, 2H, C-4″H, C-6″H).

^{13}C-NMR (100 MHz) *δ*: 23.5 (C-3^x), 26.5 (C-2^x), 44.2 (C*β*), 44.2 (C*β*), 44.4 (C-1^x), 53.6 (C*α*), 59.1 (C-4^x), 105.9 (C-4), 114.2 (C-5″), 115.7 (C-7), 118.7 (d, ^2J = 21.5 Hz, C-3′, C-5′), 123.8 (C-5), 130.4 (C-8), 131.3 (C-1′), 136.0 (d, ^3J = 8.3 Hz, C-2′, C-6′), 137.6 (C-6), 148.3 (C-4a), 152.5 (C-1), 159.0 (C-2″), 160.4 (C-4″, C-6″), 164.7 (C-3), 165.0 (d, ^1J = 245.2 Hz, C-4′). IR *v*: 1657 (C=O), 1703 (C=O). Anal. ($C_{26}H_{27}FN_6O_2 \times 2$ HCl × H_2O) C, H, N.

*6.1.4.13. 4-Phenyl-2-[4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl]-2H-pyrido[1,2- c]pyrimidine-1,3-dione (**18**)*. Yield 76%; yellow crystals, m.p. 227–229 °C; ^{1}H-NMR (400 MHz) *δ*: 1.88 (m, 2H, C-2^{x}H$_2$), 2.02 (m, 2H, C-3^{x}H$_2$), 2.97 (bm, 2H, C-4^{x}H$_2$), 3.17 (bps, 2H, C*α*H$_{ax}$), 3.70 (pt, 2H, C*α*H$_{eq}$), 4.20 (t, ^3J = 6.8 Hz, 2H, C-1^{x}H$_2$), 5.59 (pt, 2H, C*β*H$_{eq}$), 5.59 (pt, 2H, C*β*H$_{ax}$), 6.43 (t, ^3J = 6.8 Hz, 1H, C-7H), 6.89 (m, 1H, C-5H), 6.94 (m, 1H, C-6H), 7.04 (d, 1H, C-4″), 7.09 (s, 1H, C-2″H), 7.17 (d, 1H, C-6″H), 7.31 (d, ^3J = 7.6 Hz, 2H, C-2′H, C-6′H), 7.38 (t, 1H, C-4′H), 7.38 (t, 1H, C-5′'H), 7.45 (t, 2H, C-3'H, C-5'H), 8.33 (d, ^3J = 7.6 Hz, C-8H), 12.74 (bs, 1H, N$^+$H).

^{13}C-NMR (100 MHz) *δ*: 20.5 (C-3^x), 24.5 (C-2^x), 40.8 (C-1^x), 46.2 (C*β*), 51.5 (C*α*), 56.7 (C-4^x), 104.6 (C-4), 111.1 (C-7), 113.6 (k, ^3J = 3.8 Hz, C-2′'), 117.8 (k, ^3J = 3.7 Hz, C-4′'), 119.9 (C-6′'), 121.4 (C-5), 126.7 (k, ^1J = 272.5 Hz, CF_3), 128.0 (C-8), 128.0 (C-4′), 128.9 (C-3′, C-5′), 130.0 (C-5″), 131.2 (C-2′, C-6′), 131.7 (k, ^2J = 32.0 Hz, C-3″), 132.7 (C-1′), 132.9 (C-6), 144.0 (C-1″), 148.9 (C-4a), 149.8 (C-1), 160.3 (C-3). IR *v*: 1645 (C=O), 1707 (C=O). Anal. ($C_{29}H_{29}F_3N_4O_2 \times$ HCl) C, H, N.

6.2. Pharmacology

6.2.1. 5-HT$_{1A}$ 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. The assay (plates MAFCNOB 10,

Multiscreen®-FC, Millipore) contained a membrane suspension (~0.15 mg of protein), 1.0 nM [^{3}H] 8-OH-DPAT (219 Ci/mmol Amersham), buffer, and/or 10 μM serotonin (to ascertain non-specific binding), or nine concentrations of testing compound in a final volume of 0.3 ml. The assay also 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 a 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 performed in duplicate [38].

6.2.2. 5-HT_{2A} 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. The assay (plates MAFCNOB 10, Multiscreen®-FC, Millipore) contained a membrane suspension (~0.15 mg of protein), 0.6 nM [^{3}H] ketanserin (60 Ci/mmol, NEN), buffer, and/or 1 μM mianserin (to ascertain non-specific binding), 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 a 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 performed in duplicate [38].

6.2.3. α_1 Adrenergic 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. The assay (plates MAFCNOB 10, Multiscreen®-FC, Millipore) contained a membrane suspension (~0.15 mg of protein), 0.2 nM [^{3}H] prazosin (26 Ci/mmol, NEN), buffer, and/or 1 μM phentolamine (to ascertain non-specific binding), 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 a 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 [38].

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