



Original article

Novel 4-aryl-pyrido[1,2-c]pyrimidines with dual SSRI and 5-HT_{1A} activity. part 3

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ABSTRACT

A number of 4-aryl-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine with 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole or 2-methyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole residues were synthesized for further investigation of SAR in a group of pyrido[1,2-c]pyrimidine derivatives with dual 5-HT_{1A}/SERT activity. Compounds **8a–8p** were found to be potent ligands for both 5-HT_{1A} and SERT with K_i ranging from 28,3 to 642 nM and 42,4 nM–1,8 μM, respectively. Moreover compounds **8a**, **8b**, **8c**, **8d**, **8e** and **8g** were found to be selective agonists, while **8i** as an antagonist of 5-HT_{1A} presynaptic receptors in the inducible hypothermia test in mice.

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1. Introduction

5-HT_{1A} receptors have a major role in the pathogenesis and treatment of mood disorders [1,2]. Clinical studies have provided evidence that a reduction in the 5-HT_{1A} receptor function is associated with depression [3–7]. Introduction of SSRIs has been a breakthrough in the treatment of depression compared to TCAs or MAO-Is. However, this group of drugs possesses some serious drawbacks that reflect on their efficacy (i.e., long latency period, moderate patient response, AEs).

It was found that the effects of the treatment with SSRIs can be augmented by the concomitant use of 5-HT_{1A} ligands (pindolol, WAY 100635) [8–15]. These observations led to the development of dual-action drugs as next-generation antidepressants [16–19].

In previous studies we described the synthesis and biological evaluation of a number of presynaptic 5-HT_{1A} agonists and SERT

inhibitor properties (Fig. 1) [20,21]. Such an activity may lead to a faster desensitization of the 5-HT_{1A} autoreceptors, which in turn could shorten the latency period, which is one of the major drawbacks of the current therapy, in depression [22–27]. Possessing an inhibitory action toward 5-HT transporters, these compounds can be considered a good entry point for novel antidepressant candidates [16–18,28].

In the course of our extensive synthetic studies we established a facile synthetic route for obtaining unsaturated and saturated derivatives of pyrido[1,2-c]pyrimidine containing 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole moiety with good yields [19,20,29].

This method was applied in a synthesis of new 4-aryl-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine with 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or 2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole residue, described herein.

2. Results and discussion

Several new derivatives of 4-aryl-tetrahydropyrido[1,2-c]pyrimidine containing 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole or its 2-methyl derivative in the pharmacophore portion of the molecule were obtained (Fig. 2). In the 4-aryl-tetrahydropyrido[1,2-c]pyrimidine system, an aryl substitute in compound **8a** consisted of a non-substituted phenyl ring, whereas, other derivatives possessed

Abbreviations: SERT, serotonin transporter; SAR, structure-activity relationship; 5-HT, serotonin; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetraline; K_i, inhibitor constant; TMS, tetramethylsilane; SSRIs, selective serotonin inhibitors; TCAs, tricyclic antidepressants; MAO-Is, monoamine oxidase inhibitors; AE, adverse event.

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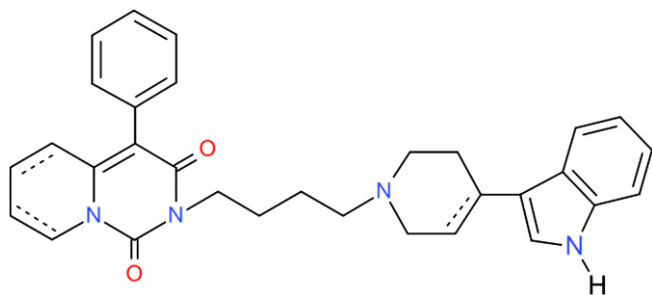


Fig. 1. Structure of pyrido[1,2-c]pyrimidines with dual 5-HT_{1A}/SERT activity.

additional –F (**8e**, **8j**), –Cl (**8f**, **8o**), –OCH₃ (**8g**, **8k**) or –CH₃ (**8h**, **8l**) groups at the *ortho* position of the phenyl ring, as well as –F (**8i**, **8p**), –Cl (**8b**), –OCH₃ (**8d**, **8n**) or –CH₃ (**8c**, **8m**) groups at the *para* position.

All new compounds (**8a–8p**) were characterized by physical constants, HRMS, ¹H, and ¹³C NMR spectroscopy.

3. In vitro studies

The *in vitro* affinity of target compounds **8a–8p** for 5-HT_{1A} receptors and SERT in rat brain was assessed using radioligand

binding assays ([³H]8-OH-DPAT and [³H]citalopram, respectively). The data was analyzed using iterative curve-fitting routines to obtain IC₅₀ values (GraphPAD/Prism, Version 3.0 – San Diego, CA, USA), which in turn were used to calculate the inhibition constant K_i according to the Cheng-Prusoff formula (Table 1) [30].

4. SAR analysis

The binding values for compounds **8a–8p** for the 5-HT_{1A} receptor and SERT were used for structure-activity relationship analysis. The influence of the substituents bound to the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole moiety (–CH₃ or –H at 2 position), the influence of various substituents at the *ortho/para* position of the aryl ring, and the impact of the degree of saturation of the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole system (compared to ref. 1,2) were analyzed.

In binding tests for compounds **8a–8p** a very high affinity of derivatives **8g** (K_i = 19.9 nM), **8a** (K_i = 28.3 nM), and **8d** (K_i = 32.4 nM) for 5-HT_{1A} receptors was confirmed. The remaining compounds possessed a high-to-weak binding activity with K_i ranging from 41.3 nM to 642 nM (Table 1).

When the effect of the substituent at the indole moiety on K_i values was analyzed, it was found that compounds with a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole group possessed a markedly higher affinity to the 5-HT_{1A} receptor than the analogous 2-methyl

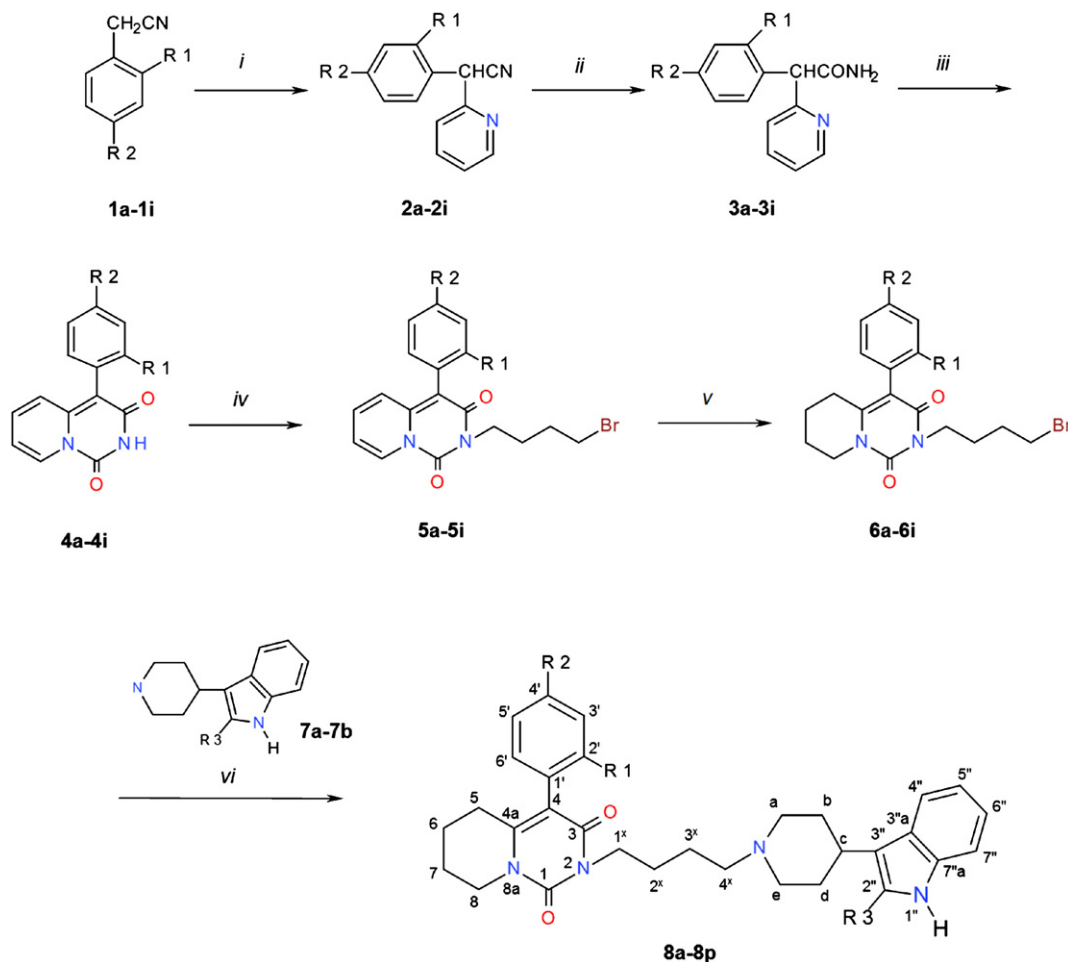


Fig. 2. Route of synthesis of derivatives **8a–8p**. Reagents and conditions: (i) 2-bromopyridine, KOH, DMSO, Δ; (ii) H₂SO₄, CH₃COOH, Δ; (iii) diethyl carbonate, EtONa, EtOH abs., Δ; (iv) 1,4-dibromobutane, K₂CO₃, acetone, Δ; (v) H₂, 10% Pt/C, CH₃COOH, 40 °C, 60 atm; (vi) **7a–7b**, acetonitrile, K₂CO₃, KI, Δ.

Table 1
K_i [nM] values for compounds **8a** – **8p**.

Compound	R ₁	R ₂	R ₃	K _i 5-HT _{1A}	K _i SERT
8a	H	H	H	28,3 ± 0,5	81,7 ± 6,2
8b	H	Cl	H	48,6 ± 5,0	44,1 ± 2,5
8c	H	CH ₃	H	46,2 ± 3,7	42,4 ± 5,2
8d	H	OCH ₃	H	32,4 ± 0,9	50,4 ± 2,6
8e	F	H	H	41,3 ± 0,3	68,4 ± 6,3
8f	Cl	H	H	62,3 ± 5,4	147,0 ± 5,9
8g	OCH ₃	H	H	19,9 ± 0,5	134,3 ± 3,9
8h	CH ₃	H	H	112,2 ± 1,1	69,1 ± 6,2
8i	H	F	H	62,3 ± 4,8	47,0 ± 0,4
8j	F	H	CH ₃	303,0 ± 25	1,3 ± 0,4 [μM]
8k	OCH ₃	H	CH ₃	319,0 ± 17	1,3 ± 0,3 [μM]
8l	CH ₃	H	CH ₃	642,0 ± 1,4	882,0 ± 22
8m	H	CH ₃	CH ₃	278,7 ± 16	1,8 ± 0,4 [μM]
8n	H	OCH ₃	CH ₃	152,9 ± 7,9	184,1 ± 9,5
8o	Cl	H	CH ₃	393,4 ± 1,7	1,3 ± 0,4 [μM]
8p	H	F	CH ₃	113,8 ± 5,2	147,4 ± 14

derivatives. Analyzing the effect of the substitution of the aryl ring in 4-aryl-tetrahydropyrido[1,2-c]pyrimidine, it could be noted that substitution with –OCH₃ both in *para* (**8d**) and *ortho* (**8g**) as well as –CH₃ at *para* position (**8c**) and fluorine in *ortho* position (**8e**) or lack of substitution (**8a**), resulted in higher binding values than in the remaining ligands.

Results of the studies on binding to SERT revealed that the high-to-weak affinity of the tested compounds to the K_i values ranged from 42.4 nM to 1.8 μM (Table 1).

Most of the methyl-substituted indole-derivatives possessed a lower affinity than the non-substituted compounds (compound **8c** vs. **8m**, **8d** vs. **8n**, **8e** vs. **8j**, **8f** vs. **8o**, **8i** vs. **8p**). Analyzing the influence of substitution in the aryl ring of the 4-aryl-tetrahydropyrido[1,2-c]pyrimidine moiety on the K_i value it was found that the highest affinity to SERT was characteristic of compounds with a fluorine atom at *para* (**8i**, **8p**) position as well as derivatives of the methoxy group in the *para* position (**8n**, **8d**).

Saturation of the tetrahydropyrido[1,2-c]pyrimidine system decreased SERT inhibition compared to the unsaturated pyrido[1,2-c]pyrimidine derivatives previously described in Part 1 [20]. However, the unsaturated 1,2,3,6-tetrahydropyridin-4-yl moiety had an influence on lowering K_iSERT values for 2-methyl-substituted indole-derivatives compared to the saturated derivatives described in Part 2 [21].

5. In vivo studies

Compounds with the most promising affinity for both the 5-HT_{1A} receptor and SERT (**8a–8e**, **8g**, and **8i**) were further evaluated in mice for their agonist/antagonist properties toward pre- and postsynaptic 5-HT_{1A} receptors, using the inducible hypothermia and forced swimming tests, respectively [31–34]. These pharmacological models are commonly used for evaluating 5-HT_{1A} receptor function.

Compounds **8a–8e**, **8g**, similar to 8-OH-DPAT, induced hypothermia in mice (Table 2), whereas, **8i** (data not shown), just as WAY 100635, did not change body temperature in mice (Table 2). The hypothermia induced by compounds **8a** (10 mg/kg), **8b** (5 mg/kg), **8c** (20 mg/kg), **8d** (20 mg/kg), **8e** (5 mg/kg), and **8g** (20 mg/kg) was attenuated by WAY 100635 (0.1 mg/kg) (Table 3). At the same time, the decrease in body temperature induced by 8-OH-DPAT (5 mg/kg) was completely blocked by WAY 100635 (0.1 mg/kg) (Table 3, 4). Therefore, the decrease in mouse body temperature, produced by **8a–8e** and **8g** could

Table 2
The effect of tested compounds on the body temperature in mice.

Treatment	Dose (mg/kg)	Δt ± SEM (°C)			
		30 min	60 min	90 min	120 min
Vehicle	–	–0.0 ± 0.0	–0.1 ± 0.1	–0.0 ± 0.1	–0.0 ± 0.0
8a	5	–0.7 ± 0.0 ^b	–0.3 ± 0.1	–0.2 ± 0.1	–0.1 ± 0.1
	10	–1.1 ± 0.2 ^c	–0.3 ± 0.1	–0.2 ± 0.1	–0.1 ± 0.0
	Vehicle	–	–0.0 ± 0.1	–0.0 ± 0.1	–0.1 ± 0.1
8b	2.5	–0.3 ± 0.1	–0.4 ± 0.2	–0.1 ± 0.0	–0.1 ± 0.0
	5	–1.0 ± 0.3 ^c	–0.5 ± 0.2 ^a	–0.4 ± 0.2	–0.3 ± 0.1
	Vehicle	–	–0.1 ± 0.1	–0.0 ± 0.1	–0.1 ± 0.1
8c	5	–0.5 ± 0.1 ^a	–0.4 ± 0.1	–0.3 ± 0.1	–0.2 ± 0.1
	10	–0.6 ± 0.1 ^a	–0.3 ± 0.1	–0.2 ± 0.1	–0.1 ± 0.0
	20	–1.3 ± 0.2 ^c	–0.9 ± 0.2 ^c	–0.4 ± 0.1	–0.3 ± 0.1
	Vehicle	–	–0.1 ± 0.1	–0.1 ± 0.1	–0.0 ± 0.1
8d	5	–0.6 ± 0.2 ^a	–0.2 ± 0.1	–0.2 ± 0.1	–0.2 ± 0.1
	10	–0.8 ± 0.2 ^c	–0.5 ± 0.2 ^a	–0.3 ± 0.1	–0.2 ± 0.1
	20	–1.6 ± 0.2 ^c	–0.9 ± 0.2 ^c	–0.5 ± 0.1 ^a	–0.3 ± 0.1
	Vehicle	–	–0.0 ± 0.1	–0.1 ± 0.0	–0.1 ± 0.1
8e	2.5	–0.5 ± 0.0	–0.2 ± 0.1	–0.1 ± 0.0	–0.1 ± 0.0
	5	–1.3 ± 0.2 ^c	–0.8 ± 0.3 ^c	–0.5 ± 0.2 ^a	–0.3 ± 0.1
	Vehicle	–	–0.0 ± 0.0	–0.1 ± 0.1	–0.1 ± 0.1
8f	5	–0.5 ± 0.1 ^a	–0.2 ± 0.1	–0.2 ± 0.1	–0.1 ± 0.1
	10	–0.7 ± 0.1 ^b	–0.2 ± 0.1	–0.1 ± 0.0	–0.0 ± 0.0
	20	–1.0 ± 0.2 ^c	–0.6 ± 0.1 ^a	–0.2 ± 0.1	–0.1 ± 0.0
	Vehicle	–	–0.0 ± 0.1	–0.5 ± 0.1 ^a	–0.3 ± 0.1
8g	5	–0.8 ± 0.2 ^c	–0.5 ± 0.1 ^a	–0.3 ± 0.1	–0.2 ± 0.0
	10	–0.9 ± 0.2 ^c	–0.5 ± 0.2 ^a	–0.3 ± 0.1	–0.2 ± 0.1
	20	–0.7 ± 0.2 ^b	–0.5 ± 0.2 ^a	–0.2 ± 0.1	–0.0 ± 0.1
	Vehicle	–	–0.0 ± 0.0	–0.1 ± 0.0	–0.1 ± 0.1
12-OH-DPAT	5	–1.4 ± 0.1 ^c	–1.2 ± 0.1 ^c	–0.7 ± 0.1 ^b	–0.2 ± 0.1
WAY 100635	0.1	–0.2 ± 0.1	–0.1 ± 0.1	–0.1 ± 0.0	–0.1 ± 0.1

The tested compounds were administered (*ip*) 30 min before the test. The absolute mean body temperatures were within a range of 36 ± 0.5 °C; n = 7–8 mice per group, ^ap < 0.05, ^bp < 0.01, ^cp < 0.001 vs. respective vehicle.

Table 3
The effect of WAY 100635 on the hypothermia induced by the tested compounds in mice.

Compound and dose (mg/kg)	Δt ± SEM (°C)	
	30 min	60 min
Vehicle + vehicle	–0.0 ± 0.0	–0.1 ± 0.1
Vehicle + 8a (10)	–1.1 ± 0.1 ^b	–0.2 ± 0.1
WAY 100635 (0.1) + 8a (10)	–0.5 ± 0.2 ^d	–0.2 ± 0.1
Vehicle + vehicle	–0.0 ± 0.0	–0.0 ± 0.0
Vehicle + 8b (5)	–1.1 ± 0.1 ^b	–0.6 ± 0.1 ^a
WAY 100635 (0.1) + 8b (5)	–0.2 ± 0.1 ^d	–0.1 ± 0.1 ^d
Vehicle + vehicle	–0.1 ± 0.0	–0.0 ± 0.0
Vehicle + 8c (20)	–1.1 ± 0.1 ^b	–0.4 ± 0.1
WAY 100635 (0.1) + 8c (20)	–0.4 ± 0.1 ^d	–0.2 ± 0.0
Vehicle + vehicle	–0.1 ± 0.0	–0.0 ± 0.1
Vehicle + 8d (20)	–1.2 ± 0.2 ^b	–0.7 ± 0.1 ^a
WAY 100635 (0.1) + 8d (20)	–0.3 ± 0.1 ^d	–0.2 ± 0.1
Vehicle + vehicle	–0.0 ± 0.0	–0.0 ± 0.1
Vehicle + 8e (5)	–1.3 ± 0.2 ^b	–0.8 ± 0.2 ^b
WAY 100635 (0.1) + 8e (5)	–0.2 ± 0.1 ^d	–0.1 ± 0.1 ^c
Vehicle + vehicle	–0.0 ± 0.1	0.0 ± 0.1
Vehicle + 8g (20)	–1.0 ± 0.2 ^b	–0.6 ± 0.1 ^a
WAY 100635 (0.1) + 8g (20)	–0.3 ± 0.1 ^d	–0.1 ± 0.1 ^c
Vehicle + vehicle	–0.1 ± 0.1	–0.1 ± 0.1
Vehicle + 8-OH-DPAT (5)	–1.4 ± 0.1 ^b	–1.2 ± 0.1 ^b
WAY 100635 (0.1)+8-OH-DPAT(5)	–0.2 ± 0.1 ^d	–0.1 ± 0.0 ^d

WAY 100635 was administered (*sc*) 15 min before the investigated compounds, n = 7–8 mice per group. The test was performed 30 min after injection of the tested compounds (*ip*). The absolute mean body temperatures were within a range 36.0 ± 0.5 °C, ^ap < 0.01, ^bp < 0.001 vs. respective vehicle + vehicle group, ^cp < 0.01, ^dp < 0.001 vs. respective vehicle + compound group.

Table 4

The effect of **8i** and WAY 100635 on the 8-OH-DPAT (5 mg/kg)-induced hypothermia in mice.

Treatment and dose (mg/kg)	$\Delta t \pm \text{SEM}$ ($^{\circ}\text{C}$)			
	15 min	30 min	45 min	60 min
Vehicle + vehicle	-0.1 ± 0.1	-0.0 ± 0.0	-0.1 ± 0.0	-0.1 ± 0.1
Vehicle + 8-OH-DPAT	-1.1 ± 0.1^b	-1.4 ± 0.1^b	-0.8 ± 0.1^a	-0.4 ± 0.1
8i (20) + 8-OH-DPAT	-0.7 ± 0.2^a	-1.6 ± 0.2^{bd}	-1.1 ± 0.2^{bd}	-0.6 ± 0.1^{ac}
Vehicle + vehicle	-0.0 ± 0.0	-0.1 ± 0.1	-0.1 ± 0.1	-0.0 ± 0.1
Vehicle + 8-OH-DPAT (5)	-1.3 ± 0.1^b	-1.4 ± 0.1^b	-0.7 ± 0.1^a	-0.2 ± 0.1
WAY100635(0.1)+8-OH-DPAT	-0.1 ± 0.1^d	-0.1 ± 0.1^d	-0.1 ± 0.1^d	-0.1 ± 0.1^d

8i was administered (*ip*) 45 min, while WAY 100635 (*sc*) 15 min prior to 8-OH-DPAT, $n = 7$ – 8 mice per group. The absolute mean initial body temperatures were within the range of 36.0 ± 0.5 $^{\circ}\text{C}$, $^a p < 0.01$, $^b p < 0.001$ vs. respective vehicle + vehicle group, $^c p < 0.01$, $^d p < 0.001$ vs. respective vehicle + 8-OH-DPAT.

be regarded as a measure of its presynaptic 5-HT_{1A} receptor agonistic activity. Compound **8i** (20 mg/kg) attenuated the effect of 8-OH-DPAT (5 mg/kg) in mice (in the first 15 min), therefore, **8i** could be regarded as an antagonist of presynaptic 5-HT_{1A} receptor (Table 4).

Compounds **8b** (2.5 and 5 mg/kg), **8c** (10 and 20 mg/kg), **8d** (10 and 20 mg/kg), **8e** (2.5 and 5 mg/kg), and **8i** (10 and 20 mg/kg) were ineffective in the forced swimming test (data not shown). 8-OH-DPAT at doses of 1 mg/kg and 2 mg/kg reduced by 45 and 57%, respectively, the immobility time of mice ($F(2,26) = 53.92$, $p < 0.0001$, data not shown).

6. Conclusion

Several new 4-aryl-5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidine derivatives possessing a 3-(1,2,3,6-tetrahydropyrid-4-yl)-1*H*-indole group or its 2-methyl derivatives were synthesized. These

compounds were considered to have a dual 5-HT_{1A} and SERT activity. *In vitro* receptor binding studies of newly synthesized ligands revealed a very high to low binding affinity for 5-HT_{1A} receptors, as well as a high-to-weak binding affinity for SERT. The K_i values for both the 5-HT_{1A} receptor and SERT showed that compounds **8a**–**8e**, **8g** and **8i** were characterized by the highest affinity among the new derivatives.

The rest of the described ligands bound both to the 5-HT_{1A} receptor and SERT with moderate or slight strength and were characterized by K_i values ranging from intermediate to very high.

It was confirmed that the presence of the non-substituted indole residue, as well as the fluorine atom at the *ortho* position or -OCH₃ at *ortho/para* or the -CH₃ group at the *para* position of the phenyl group in the aryl ring of the 4-aryl-5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidine system, had an impact on the affinity toward 5-HT_{1A} receptors and SERT.

It was also found that the degree of saturation pyridine moiety bound to the indole had an influence on K_{iSERT} values for 2-methyl-substituted indole-derivatives.

Results of behavioral studies confirmed that synthesized ligands possess anticipated agonistic activity toward presynaptic 5-HT_{1A} receptors, while displaying no postsynaptic action.

Compounds **8a**, **8d**, and **8g** have been successfully docked to the 5-HT_{1A} model receptor without any steric strains (Fig. 3) [35]. **8a** forms a pretty strong hydrogen bond with Asp30; similarly, **8d** interacts with Asp30 and Asn386, and **8g** with Asn386. The affinity of **8a**, **8d**, and **8g** ligands to the serotonin transporter SERT was also investigated. All three ligands were efficiently docked to the binding site of SERT, not encountering any steric hindrances (Fig. 4) [35]. The poses of the ligands, except **8g**, inside the binding SERT pocket seemed to be strongly stabilized by hydrogen bonds formed between **8d** and Asp400, Lys490, Glu493, and similarly between **8a** and Lys490 and Glu493. Compound **8g** does not bind with SERT via hydrogen bonds, which may prove its lower affinity to SERT than the **8a** and **8d** ligands.

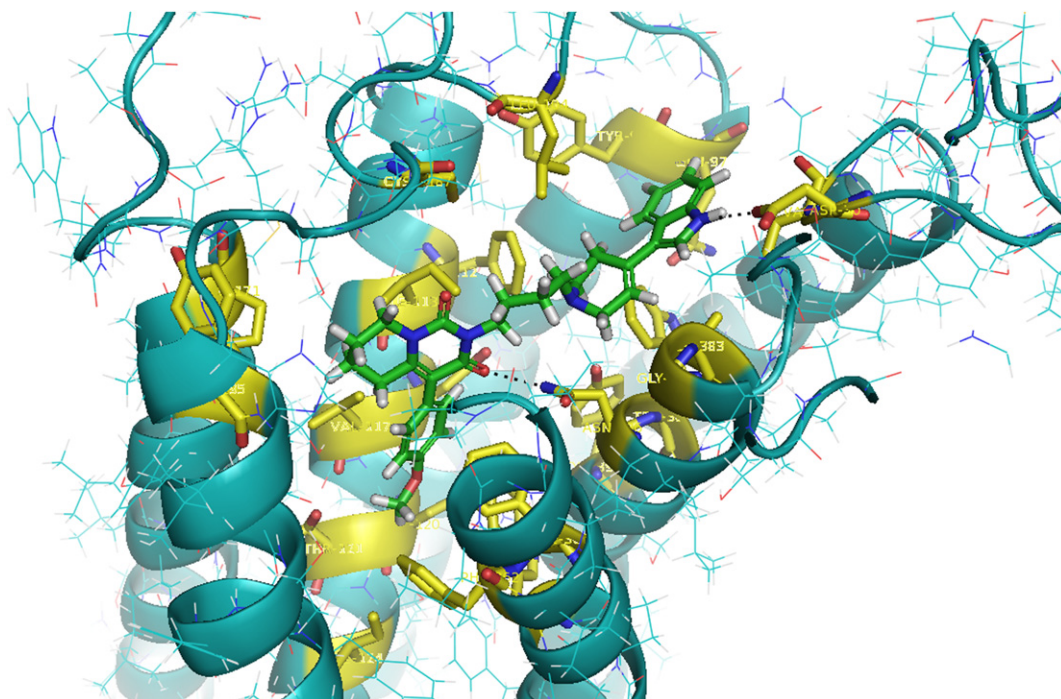


Fig. 3. Compound **8d** inside the binding 5HT_{1A} pocket. Black dash line denotes hydrogen bond.

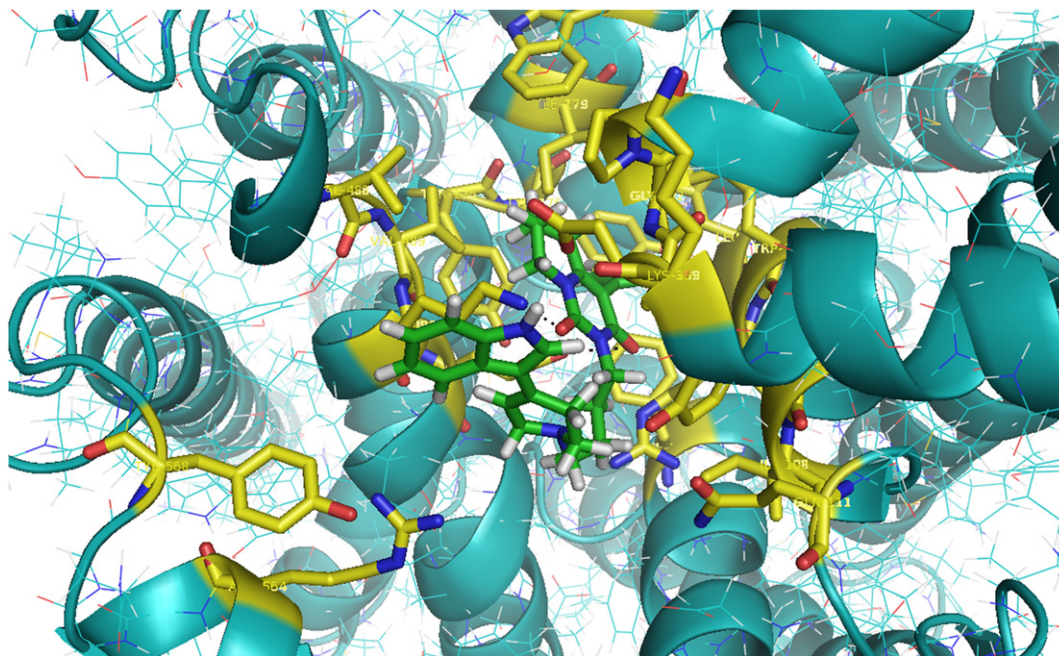


Fig. 4. Compound 8a inside the binding SERT pocket. Black dash line denotes hydrogen bond.

7. Experimental protocols

7.1. Chemistry

7.1.1. General remarks

The melting points were determined on an Electrothermal 9100 apparatus with open capillary tubes, and were uncorrected. The infrared spectra were recorded on a Shimadzu FTIR-8300 spectrometer. ^1H and ^{13}C -NMR spectra were obtained on a Bruker AVANCE DMX 400WB instrument in CDCl_3 (chemical shifts were reported in δ units). Coupling constants (J) were in hertz (Hz) and the internal reference was TMS. For the two-dimensional experiments, the pulse sequences, acquisition, and processing parameters were taken from the standard Bruker software library. ESI-HRMS spectra were obtained on Mariner (PE Biosystems) instrument.

Flash column chromatography was carried out on Merck Silica gel 60 (230–400 mesh ASTM) using the solvent methylene chloride/methanol (99:1, 97:3, 95:5, v/v). Thin layer chromatography was run on Merck Silica gel 60 F₂₅₄ plates, mobile phase of dioxane, toluene, ethanol, and 25% NH_4OH (6.0:3.2:0.5:0.2, v/v). Compounds were visualized by UV light (254 nm).

7.1.1.1. Preparation of 2-(4-bromobutyl)-4-aryl-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-diones (6a–i). The starting compounds **2a–i**, **3a–i**, **4a–i**, **5a–i**, and **6a–i** were obtained according to procedures described in [20,21,29,36,37].

7.1.1.2. Preparation of 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole (7a). The starting compounds **7a** were obtained according to procedures described in [38].

7.1.1.3. Preparation of 2-methyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole (7b). The starting compound **7b** was obtained according to procedures described in [39].

7.1.1.4. General procedure for synthesis of 2-{4-[4-(1H-indol-3-yl)-(3,6-dihydro-2H-pyridin-1-yl)-butyl]-4-aryl-5,6,7,8-tetrahydro-pyrido[1,2-c]pyrimidine-1,3-diones (8a–p). Appropriate substrates, that

is, bromobutylpyrido[1,2-c]pyrimidine-derivatives **6a–i** (0.0026 mol) and 1,2,3,6-tetrahydro-pyridin-4-yl-indoles **7a–b** (0.0026 mol), as well as K_2CO_3 (0.005 mol), 70 ml of acetonitrile, and a catalytic amount of KI were stirred and refluxed for four to 5 h. The reaction time was monitored using TLC. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. The crude residue was purified by crystallization from acetonitrile or by flash chromatography, using a mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97:3 v/v). Proper fractions were identified by TLC and evaporated to dryness, giving analytically pure compounds **8a–p**.

8. NMR data

8.1. 2-{4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-phenyl-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (8a)

The title compound was isolated as a white powder, yield: 45%; m.p. 175–176 °C. ^1H NMR (500 MHz) δ : 1.70 (q, $^3J = 6.5$, C-6H₂), 1.82 (m, C-2^xH₂, C-3^xH₂), 1.93 (q, $^3J = 6.5$, C-7H₂), 2.53 (t, $^3J = 6.5$, C-5H₂), 2.66 (ps, CdH₂), 2.88 (t, C-4^xH₂), 3.00 (ps, CeH₂), 3.48 (ps, CaH₂), 3.95 (t, $^3J = 6.5$, C-8H₂), 4.07 (t, $^3J = 6.5$, C-1^xH₂), 6.02 (ps, CbH), 7.04 (d, $^3J = 2.0$, C-2^{''}H), 7.12 (td, $^3J = 8.0$, $^4J = 1.0$, C-5^{''}H), 7.18 (td, C-6^{''}H), 7.21 (dt, $^3J = 7.0$, $^4J = 1.5$, C-2[']H, C-6[']H), 7.33 (tt, $^3J = 7.5$, $^4J = 1.5$, C-4[']H), 7.40 (m, C-3[']H, C-5[']H, C-7[']H), 7.77 (d, $^3J = 7.5$, C-4^{''}H), 8.92 (bs, NH). HRMS (ESI) calculated for $\text{C}_{31}\text{H}_{35}\text{N}_4\text{O}_2$:494.6273 (M + H)⁺ found 494.6294.

8.2. 4-(4-chlorophenyl)-2-{4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (8b)

The title compound was isolated as a white powder, yield: 55%; m.p. 139–140 °C. ^1H NMR (500 MHz) δ : 1.68 (m, C-6H₂, C-3^xH₂), 1.76 (q, C-2^xH₂), 1.91 (q, $^3J = 6.5$, C-7H₂), 2.50 (m, C5-H₂, CdH₂), 2.55 (ps, C-4^xH₂), 2.70 (t, $^3J = 6.0$, CeH₂), 3.20 (pd, CaH₂), 3.92 (t, $^3J = 6.5$, C-8H₂), 4.06 (t, $^3J = 7.0$, C-1^xH₂), 6.17 (ps, CbH), 7.10 (d, $^3J = 2.5$, C-2^{''}H), 7.13 (m, C-3[']H, C-5[']H, C-5^{''}H), 7.17 (td, $^3J = 7.0$, $^4J = 1.0$, C-6[']H), 7.36 (dt, $^3J = 8.5$, $^4J = 2.0$, C-2[']H, C-6[']H), 7.87 (d, $^3J = 7.5$, C-4^{''}H), 8.41 (bs,

NH). HRMS (ESI) calculated for $C_{31}H_{34}N_4O_2Cl$: 529.2365 (M + H)⁺ found 529.2345.

8.3. 2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-4-(4-tolyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8c**)

The title compound was isolated as a white powder, yield: 62%; m.p. 177–178 °C. ¹H NMR (500 MHz) δ: 1.70 (q, ³J = 6.5, C-6H₂), 1.79 (m, C-2^xH₂, C-3^xH₂), 1.92 (q, ³J = 6.5, C-7H₂), 2.36 (s, CH₃), 2.54 (t, ³J = 6.5, C-5H₂), 2.66 (ps, CdH₂), 2.81 (ps, C-4^xH₂), 2.96 (ps, CeH₂), 3.44 (ps, CaH₂), 3.94 (t, ³J = 6.5, C-8H₂), 4.06 (t, ³J = 6.5, C-1^xH₂), 6.05 (ps, CbH), 7.09 (m, C-3'H, C-5'H, C-2''H), 7.12 (m, ³J = 7.0, ⁴J = 1.5, C-5''H), 7.18 (td, ³J = 8.5, ⁴J = 1.5, C-6''H), 7.20 (m, C-2'H, C-6'H), 6.05 (ps, CbH), 7.80 (d, ³J = 8.0, C-4''H), 8.78 (bs, NH). HRMS (ESI) calculated for $C_{32}H_{37}N_4O_2$: 508.6538 (M + H)⁺ found 508.6527.

8.4. 2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-4-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8d**)

The title compound was isolated as a white powder, yield: 59%; m.p. 175–177 °C. ¹H NMR (400 MHz) δ: 1.67 (m, C-6H₂, C-3^xH₂), 1.76 (m, C-2^xH₂), 1.89 (q, ³J = 6.3, C-7H₂), 2.51 (m, C-5H₂, C-4^xH₂, CbH₂), 2.67 (pt, CaH₂), 3.19 (m, CeH₂), 3.79 (s, OCH₃), 3.91 (t, ³J = 6.4, C-8H₂), 4.07 (t, ³J = 7.2, C-1^xH₂), 6.15 (m, CdH₂), 6.91 (d, C-3'H, C-5'H), 7.04 (d, ³J = 2.4, C-2''H), 7.10 (d, ³J = 8.8, C-2'H, C-6'H), 7.10 (m, C-5''H), 7.15 (td, ³J = 8.1, ⁴J = 1.2, C-6''H), 7.31 (d, ³J = 8.0, C-7''H), 7.86 (d, ³J = 7.9, C-4''H), 8.64 (bs, NH). ¹³C NMR (400 MHz) δ: 18.6 (C-6), 21.7 (C-7), 24.6 (C-2^x), 25.7 (C-3^x), 26.7 (C-5), 29.0 (Cb), 41.6 (C-1^x), 42.6 (C-8), 50.3 (Ca), 55.2 (OCH₃), 58.2 (C-4^x), 111.3 (C-7''), 112.0 (C-4), 114.0 (C-3', C-5'), 117.7 (Cd), 118.9 (C-3''), 119.7 (C-2''), 120.6 (C-4''), 121.5 (C-5''), 121.8 (C-6''), 125.2 (C-3''a), 125.5 (C-1'), 129.8 (Cc), 131.8 (C-2', C-6'), 136.8 (C-7''a), 149.6 (C-4a), 151.7 (C-1), 159.0 (C-4'), 162.2 (C-3). HRMS (ESI) calculated for $C_{33}H_{39}N_4O_3$: 538.6798 (M + H)⁺ found 538.6805.

8.5. 4-(2-fluorophenyl)-2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8e**)

The title compound was isolated as a white powder, yield: 65%; m.p. 181–182 °C. ¹H NMR (500 MHz) δ: 1.63 (m, C-6H₂, C-3^xH₂), 1.76 (q, C-2^xH₂), 1.91 (q, ³J = 6.5, C-7H₂), 2.51 (m, C-5H₂, CdH₂), 2.52 (ps, C-4^xH₂), 2.71 (t, ³J = 6.0, CeH₂), 3.20 (d, ³J = 2.5, CaH₂), 4.01 (t, ³J = 7.0, C-1^xH₂), 6.19 (ps, CbH), 7.09–7.25 (m, 7H, C-2''H, C-5''H, C-6''H), 7.34 (d, ³J = 8.0, C-7''H), 8.01 (d, ³J = 8.0, C-4''H), 8.42 (bs, NH). HRMS (ESI) calculated for $C_{31}H_{34}N_4O_2F$: 513.2660 (M + H)⁺ found 513.2655.

8.6. 4-(2-chlorophenyl)-2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8f**)

The title compound was isolated as a white powder, yield: 57%; m.p. 172–173 °C. ¹H NMR (400 MHz) δ: 1.65 (m, C-5H₂), 1.79 (m, C-2^xH₂), 1.91 (m, C-7H₂), 2.38 (m, C-5H₂), 2.56 (m, C-4^xH₂, CbH₂), 2.75 (pt, CaH₂), 3.21 (Pd, CeH₂), 3.85 (m, C-8H), 4.08 (t, C-1^xH₂), 5.68 (bps, CdH), 7.02 (td, ³J = 6.9, ⁴J = 1.0, C-6''H), 7.05 (td, ³J = 7.4, ⁴J = 1.1, C-5''H), 7.22 (m, C-6'H, C-7''H), 7.29 (m, C-4'H, C-5'H), 7.44 (dd, ³J = 6.6, ⁴J = 2.7, C-3'H), 7.54 (d, ³J = 7.7, C-4''H), 8.16 (bs, NH). HRMS (ESI) calculated for $C_{31}H_{34}N_4O_2Cl$: 529.2365 (M + H)⁺ found 529.2339.

8.7. 2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-4-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8g**)

The title compound was isolated as a white powder, yield: 63%; m.p. 158–159 °C. ¹H NMR (500 MHz) δ: 1.70 (m, C-6H₂, C-3^xH₂), 1.76 (q, C-2^xH₂), 1.90 (q, ³J = 6.5, C-7H₂), 2.42 (t, ³J = 6.0, C-5H₂), 2.56 (pd, C-4^xH₂), 2.70 (t, ³J = 6.0, CeH₂), 3.20 (d, ³J = 2.0, CaH₂), 3.76 (s, OCH₃), 3.92 (m, C-8H₂), 4.06 (m, C-1^xH₂), 6.17 (pt, CbH), 6.93 (d, ³J = 8.0, C-3'H), 6.99 (td, ³J = 7.5, ⁴J = 1.0, C-5''H), 7.10 (m, C-4'H, C-2''H), 7.12 (td, ³J = 8.0, ⁴J = 1.0, C-5''H), 7.17 (td, ³J = 7.0, ⁴J = 1.0, C-6''H), 7.33 (m, C-6'H, C-7''H), 7.88 (d, ³J = 8.0, C-4''H), 8.35 (bs, NH). HRMS (ESI) calculated for $C_{32}H_{37}N_4O_3$: 525.2860 (M + H)⁺ found 525.2858.

8.8. 2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-4-(2-tolyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8h**)

The title compound was isolated as a white powder, yield: 59%; m.p. 174–175 °C. ¹H NMR (500 MHz) δ: 1.70 (q, ³J = 6.5, C-6H₂), 1.79 (m, C-2^xH₂, C-3^xH₂), 1.92 (q, ³J = 6.5, C-7H₂), 2.39 (s, CH₃), 2.54 (t, ³J = 6.5, C-5H₂), 2.66 (ps, CdH₂), 2.81 (ps, C-4^xH₂), 2.92 (ps, CeH₂), 3.48 (ps, CaH₂), 3.94 (t, ³J = 6.5, C-8H₂), 4.09 (t, C-1^xH₂), 6.05 (ps, CbH), 7.08 (m, C-3'H, C-5'H, C-2''H), 7.10 (m, ³J = 7.0, ⁴J = 1.5, C-5''H), 7.17 (td, ³J = 8.5, ⁴J = 1.5, C-6''H), 7.20 (d, C-6'H), 6.05 (ps, CbH), 7.80 (d, ³J = 8.0, C-4''H), 8.78 (bs, NH). HRMS (ESI) calculated for $C_{32}H_{37}N_4O_2$: 508.6538 (M + H)⁺ found 508.6537.

8.9. 4-(4-fluorophenyl)-2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8i**)

The title compound was isolated as a white powder, yield: 58%; m.p. 150–151 °C. ¹H NMR (500 MHz) δ: 1.68 (m, C-6H₂, C-3^xH₂), 1.74 (q, C-2^xH₂), 1.91 (q, ³J = 6.5, C-7H₂), 2.50 (m, C-5H₂, CdH₂), 2.56 (ps, C-4^xH₂), 2.70 (t, ³J = 6.0, CeH₂), 3.20 (d, ³J = 2.5, CaH₂), 4.06 (t, ³J = 7.0, C-1^xH₂), 6.17 (ps, CbH), 7.05–7.20 (m, 7H, C-2''H, C-5''H, C-6''H), 7.34 (d, ³J = 8.0, C-7''H), 7.88 (d, ³J = 8.0, C-4''H), 8.34 (bs, NH). HRMS (ESI) calculated for $C_{31}H_{34}N_4O_2F$: 513.2660 (M + H)⁺ found 513.2684.

8.10. 4-(2-fluorophenyl)-2-[4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8j**)

The title compound was isolated as a white powder, yield: 42%; m.p. 164–165 °C. ¹H NMR (500 MHz) δ: 1.64 (q, ³J = 7.0, C-6H₂), 1.72 (m, C-2^xH₂, C-3^xH₂), 1.91 (q, ³J = 7.0, C-7H₂), 2.42 (s, CH₃), 2.50 (t, ³J = 7.0, C-5H₂), 2.68 (m, C-4^xH₂, CdH₂), 2.86 (t, CeH₂), 3.27 (ps, CaH₂), 3.91 (t, ³J = 6.5, C-8H₂), 4.10 (t, ³J = 7.5, C-1^xH₂), 5.62 (m, CbH), 7.03 (m, ³J₁ = 8.0, ³J₂ = 7.0, ⁴J = 1.0, C-5''H), 7.00 (m, C-2'H, C-5'H, C-6''H), 7.12 (m, C-3'H, C-6'H), 7.25 (dt, ³J = 8.0, ⁴J = 5.0, C-7''H), 7.53 (d, ³J = 8.0, C-4''H), 8.25 (bs, NH). HRMS (ESI) calculated for $C_{32}H_{36}N_4O_2F$: 526.6443 (M + H)⁺ found 526.6438.

8.11. 2-[4-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl]-4-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8k**)

The title compound was isolated as a white powder, yield: 51%; m.p. 182–183 °C. ¹H NMR (500 MHz) δ: 1.71 (m, C-6H₂), 1.76 (m, C-2^xH₂, C-3^xH₂), 1.93 (q, C-7H₂), 2.40 (s, CH₃), 2.43 (t, ³J = 6.5, C-5H₂), 2.67 (ps, C-4^xH₂, CdH₂), 2.86 (ps, CeH₂), 3.32 (ps, CaH₂), 3.77 (s, OCH₃), 3.93 (m, C-8H₂), 4.06 (t, ³J = 7.0, C-1^xH₂), 5.63 (ps, CbH₂),

6.93 (dd, $^3J = 8.5$, $^4J = 1.0$, C-3'H), 6.99 (td, $^3J = 7.5$, $^4J = 1.0$, C-5'H), 7.04 (td, $^3J = 8.0$, $^4J = 1.0$, C-5''H), 7.10 (m, C-6'H, C-6''H), 7.26 (d, $^3J = 7.0$, C-7''H), 7.33 (4d, $^3J_1 = 8.5$, $^3J_2 = 6.0$, $^4J = 1.5$, C-4'H), 7.53 (d, $^3J = 7.5$, C-4''H), 8.06 (bs, NH). HRMS (ESI) calculated for $C_{33}H_{39}N_4O_3$: 539.3017 (M + H)⁺ found 539.3038.

8.12. 2-{4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-tolyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8l**)

The title compound was isolated as a white powder, yield: 74%; m.p. 162–163 °C. ¹H NMR (500 MHz) δ: 1.69 (m, C-6H₂, C-3^xH₂), 1.76 (q, C-2^xH₂), 1.91 (m, C-7H₂), 2.14 (s, CH₃-C₂''), 2.37 (s, CH₃-C₂'), 2.44 (m, C-5H₂), 2.57 (t, $^3J = 7.5$, C-4^xH₂), 2.60 (pd, CdH₂), 2.75 (t, $^3J = 5.5$, CeH₂), 3.21 (d, $^3J = 3.0$, CaH₂), 3.93 (m, C-8H₂), 4.07 (t, $^3J = 7.0$, C-1^xH₂), 5.65 (ps, CbH), 7.00–7.10 (m, C-3'H, C-5''H, C-6''H), 7.17–7.27 (m, C-6'H, C-7''H), 7.54 (d, $^3J = 7.5$, C-4''H), 8.16 (bs, NH). HRMS (ESI) calculated for $C_{33}H_{39}N_4O_2$: 523.3068 (M + H)⁺ found 523.3063.

8.13. 2-{4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-tolyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8m**)

The title compound was isolated as a white powder, yield: 52%; T.t. 168–170 °C. ¹H NMR (400 MHz) δ: 1.68 (m, C-6H₂, C-3^xH₂), 1.76 (m, C-2^xH₂), 1.90 (q, $^3J = 6.6$, C-7H₂), 2.35 (s, C-10H₃), 2.38 (s, C-9H₃), 2.52 (m, C-5H₂, CdH₂), 2.58 (m, CeH₂), 2.71 (t, $^3J = 5.7$, C-4^xH₂), 3.18 (m, CaH₂), 3.92 (t, $^3J = 6.3$, C-8H₂), 4.06 (t, $^3J = 7.3$, C-1^xH₂), 5.68 (m, CbH), 7.04 (m, C-5''H, C-6''H), 7.08 (dt, $^3J = 8.1$, $^4J = 1.7$, C-3'H, C-5'H), 7.20 (m, C-2'H, C-6'H, C-7''H), 7.56 (d, $^3J = 7.8$, C-4''H), 8.03 (bs, NH). ¹³C NMR (400 MHz) δ: 12.8 (C-10), 18.6 (C-6), 21.2 (C-9), 21.8 (C-7), 24.6 (C-2^x), 25.8 (C-3^x), 26.7 (C-5), 30.6 (Cb), 41.6 (C-1^x), 42.6 (C-8), 50.6 (Ca), 53.3 (Ce), 58.5 (C-4^x), 110.2 (C-7''), 112.4 (C-4), 115.0 (C-3''), 119.3 (C-4''), 119.3 (C-5''), 120.9 (C-6''), 123.3 (Cd), 127.7 (C-3'a), 129.2 (C-2', C-6'), 130.3 (C-7''), 130.3 (Cc), 130.6 (C-3', C-5'), 130.9 (C-1'), 135.1 (C-2''), 137.4 (C-4'), 149.5 (C-4a), 151.8 (C-1), 162.1 (C-3). HRMS (ESI) calculated for $C_{33}H_{39}N_4O_2$: 522.6804 (M + H)⁺ found 522.6809.

8.14. 2-{4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8n**)

The title compound was isolated as a white powder, yield: 42%; m.p. 142–143 °C. ¹H NMR (400 MHz) δ: 1.67 (m, C-6H₂, C-3^xH₂), 1.76 (bq, C-2^xH₂), 1.89 (q, $^3J = 6.5$, C-7H₂), 2.36 (s, CH₃), 2.52 (m, C-5H₂, C-4^xH₂), 2.57 (bps, CbH₂), 2.71 (pt, CaH₂), 3.17 (pd, CeH₂), 3.79 (s, OCH₃), 3.92 (t, $^3J = 6.3$, C-8H₂), 4.07 (t, $^3J = 7.2$, C-1^xH₂), 5.67 (bps, CdH₂), 6.91 (pd, C-3'H, C-5'H), 7.02 (td, $^3J = 6.9$, $^4J = 1.0$, C-5''H), 7.06 ($^3J = 6.4$, $^4J = 1.1$, C-6''H), 7.11 (pd, $^3J = 8.7$, C-2'H, C-6'H), 7.19 (d, $^3J = 7.8$, C-7''H), 7.54 (d, $^3J = 7.7$, C-4''H), 8.20 (bs, NH). ¹³C NMR (400 MHz) δ: 12.7 (CH₃), 18.5 (C-6), 21.7 (C-7), 24.5 (C-2^x), 26.6 (C-5), 26.6 (C-3^x), 30.5 (Cb), 41.5 (C-1^x), 42.5 (C-8), 50.5 (Ca), 55.2 (OCH₃), 58.3 (C-4^x), 110.1 (C-7''), 111.9 (C-4), 113.9 (C-3', C-5'), 114.8 (C-3''), 119.1 (C-5''), 119.1 (C-4''), 120.7 (C-6''), 123.1 (Cd), 125.4 (C-1'), 127.6 (C-3'a), 130.3 (Cc), 130.9 (C-7'a), 131.8 (C-2', C-6'), 135.0 (C-2''), 149.4 (C-4a), 151.7 (C-1), 158.9 (C-4'), 162.1 (C-3). HRMS (ESI) calculated for $C_{31}H_{35}N_4O_2$: 494.6273 (M + H)⁺ found 494.6294.

8.15. 4-(2-chlorophenyl)-2-{4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8o**)

The title compound was isolated as a white powder, yield: 42%; m.p. 154–155 °C. ¹H NMR (400 MHz) δ: 1.69 (m, C-5H₂), 1.77 (m, C-

2^xH₂), 1.91 (m, C-7H₂), 2.37 (s, CH₃), 2.38 (m, C-5H₂), 2.58 (m, C-4^xH₂, CbH₂), 2.75 (pt, CaH₂), 3.21 (Pd, CeH₂), 3.89 (m, C-8H(2)), 3.96 (m, $^2J = 13.8$, $^3J = 6.4$, C-8H(1)), 4.07 (t, $^3J = 7.1$, C-1^xH₂), 5.66 (bps, CdH), 7.02 (td, $^3J = 7.4$, $^4J = 1.1$, C-5''H), 7.06 (td, $^3J = 6.9$, $^4J = 1.0$, C-6''H), 7.20 (m, C-6'H, C-7''H), 7.28 (m, C-4'H, C-5'H), 7.44 (dd, $^3J = 6.6$, $^4J = 2.7$, C-3'H), 7.54 (d, $^3J = 7.7$, C-4''H), 8.16 (bs, NH). ¹³C NMR (400 MHz) δ: 12.8 (CH₃), 18.4 (C-6), 21.8 (C-7), 24.1 (C-2^x), 25.6 (C-3^x), 26.3 (C-5), 30.1 (Cb), 41.3 (C-1^x), 42.9 (C-8), 50.4 (Ca), 58.1 (C-4^x), 110.0 (C-4), 110.2 (C-7''), 114.7 (C-3''), 119.1 (C-5''), 119.2 (C-4''), 120.8 (C-6''), 122.6 (Cd), 127.1 (C-5'), 127.6 (C-3'a), 129.4 (C-4'), 129.6 (C-3'), 130.4 (Cc), 131.0 (C-7'a), 132.4 (C-1'), 132.5 (C-6'), 135.0 (C-2', C-2''), 150.4 (C-4a), 151.7 (C-1), 161.2 (C-3). HRMS (ESI) calculated for $C_{31}H_{34}N_4O_2Cl$: 529.0723 (M + H)⁺ found 529.0730.

8.16. 4-(4-fluorophenyl)-2-{4-[4-(2-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-5,6,7,8-tetrahydropyrido[1,2-c]pyrimidine-1,3-dione (**8p**)

The title compound was isolated as a white powder, yield: 63%; m.p. 164–165 °C. ¹H NMR (500 MHz) δ: 1.71 (q, $^3J = 7.0$, C-6H₂), 1.76 (m, C-2^xH₂, C-3^xH₂), 1.92 (q, $^3J = 7.0$, C-7H₂), 2.39 (s, CH₃), 2.51 (t, $^3J = 7.0$, C-5H₂), 2.66 (m, C-4^xH₂, CdH₂), 2.85 (t, CeH₂), 3.30 (ps, CaH₂), 3.94 (t, $^3J = 6.5$, C-8H₂), 4.06 (t, $^3J = 7.5$, C-1^xH₂), 5.62 (m, CbH), 7.03 (m, $^3J_1 = 8.0$, $^3J_2 = 7.0$, $^4J = 1.0$, C-5''H), 7.08 (m, C-3'H, C-5'H, C-6''H), 7.18 (m, C-2'H, C-6''H), 7.25 (dt, $^3J = 8.0$, $^4J = 5J = 1.0$, C-7''H), 7.53 (d, $^3J = 8.0$, C-4''H), 8.20 (bs, NH). HRMS (ESI) calculated for $C_{32}H_{36}N_4O_2F$: 526.6443 (M + H)⁺ found 526.6450.

9. Pharmacology

9.1. In vitro experiments

All compounds were tested for their affinity towards 5-HT1A and SERT receptors according to procedures described previously [20,21].

9.2. In vivo experiments

All the experimental procedures were approved by the Local Bioethics Commission at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

Compounds **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, and **8i** were tested in induced hypothermia test in mice as well as compounds **8b**, **8c**, **8d**, **8e**, and **8i** were tested in forced swimming test in mice according to procedures described previously [20,21].

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