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RESEARCH ARTICLE

New insights into homopiperazine-based 5-HT$_{1A}$/5-HT$_7$R ligands: synthesis and biological evaluation

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Abstract

The synthesis of new *N*-homopiperazinyl-based ligands is reported. Various structural modifications along with the corresponding biological activities on 5-HT$_{1A}$/5-HT$_7$ receptors give further insights into this class of serotoninergic ligands. Among the tested central heterocyles, the 7-azaindole gave the best results on the above-mentioned receptors.

Keywords: *Homopiperazinyl; 7-azaindole; 5-HT$_7$; 5-HT$_{1A}$ receptor affinity*

Introduction

The most recently discovered type of serotoninergic receptor, 5-HT$_7$R[1-3], seems to play a complex role in both the peripheral and central nervous systems. Psychiatric disorders related to depression, anxiety, and mood, learning and memory, epilepsy, inflammatory processes, and ileum peristalsis are only a few examples among all known implications of the 5-HT$_7$ receptors[4-8].

Even though the number of ligands cited in the literature is considerable[6,9-11] and mostly of antagonist character (**1**[12] and **2**[13], Figure 1), the 5-HT$_7$R functions are still hindered because of the small number of highly selective ligands of agonist type, compound **3**[14] belonging to the few examples reported to date (Figure 1).

Designing new 5-HT$_7$ ligands remains a very difficult task, mainly because no crystal structure for this receptor has yet been reported. One of the alternatives in this case implies a screening approach to find new hits. Subsequently, these hits can be optimized in terms of both affinity and selectivity over other transmembrane receptors. Another more rational alternative is the pharmacophoric approach, but, unfortunately, this is generally applicable to a small class of ligands, no generalization yet being published[15].

The discovery of the binding pattern based only on ligands remains complex, especially when not enough structure–activity relationships associated with each class of ligand are reported in the literature.

It is also worth mentioning that some discoveries can be made by chance. A few years ago, during their studies on the 5-HT$_{1D}$ receptor, Isaac *et al.* serendipitously discovered a new series of indole-based 5-HT$_7$ ligands[16]. The most potent agent (**4**, K_i = 3 nM for 5-HT$_7$R; % inhibition at 1 μM = 99 for 5-HT$_7$R and % inhibition at 1 μM ≤35 for 5-HT$_{1A, 1B, 1D, 1F, 2A, 2C}$, M_1 and

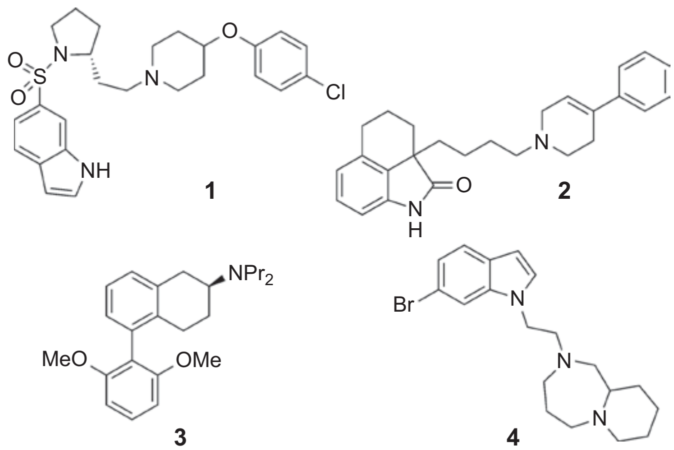

Figure 1. 5-HT$_7$ agonists and antagonists.

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M_2, D_1–D_5) shows an interesting selectivity profile over the other tested G-protein coupled receptors (GPCRs) (Figure 1). Diverse structural modifications were described, including variation of the amine moiety and of the substituent on the indole scaffold. However, no changes within the central skeleton were reported.

In the present article we describe the synthesis and biological evaluation of a few hetero-analogs of the 6-bromo-substituted indole **4**. These analogs were obtained by replacement of the central skeleton with some new heterocycles, namely 6-azaindole, 7-azaindole, and benzimidazolone.

Experimental

^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Bruker Avance DPX250 spectrometer (250.131 MHz), in $CDCl_3$ and using tetramethylsilane as internal standard; multiplicities were determined by the DEPT 135 sequence, and chemical shifts are reported in parts per million (ppm). Coupling constants are reported in units of hertz (Hz) if applicable. Infrared (IR) spectra were recorded on a PerkinElmer Paragon 1000 PC Fourier transform infrared (FTIR) spectrometer using NaCl films or KBr pellets. Mass spectra (MS) were recorded on a PerkinElmer SCIEX AOI 300 spectrometer. Flash chromatography was performed on Merck 40–70 nM (230–400 mesh) silica gel under nitrogen pressure. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} precoated plates. Visualization was made with ultraviolet light at 254 nm.

General procedure for synthesis of final compounds 5,6,8,10,11

Under a nitrogen atmosphere, a solution of the appropriate halide (1 mmol) in acetonitrile (10 mL) was treated with decahydropyrido[1,2-*a*][1,4]diazepine (1 mmol), potassium carbonate (3 mmol), and potassium iodide (0.1 mmol). The mixture was heated overnight at 60°C and then the solvent removed *in vacuo*. The residual oil was hydrolyzed with 20 mL of water and then extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated. The crude compound was purified by column chromatography (dichloromethane/methanol 9/1), to give the corresponding final derivatives.

2-(2-Pyrrolo[2,3-b]pyridin-1-ylethyl) decahydropyrido[1,2-a][1,4]diazepine (5)

$C_{18}H_{26}N_4$; Yield 44%; orange oil; IR (NaCl) cm^{-1}: 3408, 2934, 1594, 1510, 1426, 1348, 1316, 753; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.28 (dd, 1H, *J* = 1.5 Hz, *J* = 4.7 Hz), 7.87 (dd, 1H, *J* = 1.5, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 3.5 Hz), 7.01 (dd, 1H, *J* = 4.7 Hz, *J* = 7.8 Hz), 6.42 (d, 1H, *J* = 3.5 Hz), 4.34 (dd, 2H, *J* = 5.9 Hz, *J* = 6.9 Hz), 2.93 (t, 2H, *J* = 6.5 Hz), 1.16–2.76 (m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.5 (C), 142.5 (CH), 128.6 (CH), 128.5 (CH), 120.6 (C), 115.5 (CH), 99.2 (CH), 65.8 (CH), 60.5 (CH_2), 58.4 (CH_2), 57.2 (CH_2), 56.1 (CH_2), 54.0 (CH_2), 42.9 (CH_2), 30.9 (CH_2), 27.6 (CH_2), 25.7 (CH_2), 24.1 (CH_2); MS *m/z* = 299.5 $[M + H]^+$.

2-[2-(7-Chloropyrrolo[2,3-c]pyridin-1-yl)ethyl] decahydropyrido[1,2-a][1,4]diazepine (6)

$C_{18}H_{25}ClN_4$; Yield 79%; dark orange oil; IR (NaCl) cm^{-1}: 3415, 2934, 1597, 1545, 1497, 1323, 953, 825, 753; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J* = 5.4 Hz), 7.43 (d, 1H, *J* = 5.4 Hz), 7.29 (d, 1H, *J* = 3.1 Hz), 6.52 (d, 1H, *J* = 3.1 Hz), 4.58 (td, 2H, *J* = 3.0 Hz, *J* = 6.6 Hz), 2.95 (td, 2H, *J* = 3.0 Hz, *J* = 6.6 Hz), 1.20–2.82 (m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 137.4 (CH), 136.9 (C), 134.6 (CH), 133.5 (C), 128.5 (C), 115.3 (CH), 101.3 (CH), 65.7 (CH), 60.2 (CH_2), 57.3 (CH_2), 56.2 (CH_2), 54.3 (CH_2), 47.4 (CH_2), 31.1 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 24.2 (CH_2); MS *m/z* = 333.5 $[M + H]^+$.

1-[2-(Octahydropyrido[1,2-a][1,4]diazepin-2-yl)ethyl]-1,3-dihydrobenzo-imidazol-2-one (8)

$C_{18}H_{26}N_4O$; Yield 48%; dark red oil; IR (NaCl) cm^{-1}: 3198, 2936, 1694, 1488, 754; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.32 (bs, 1H), 6.97–7.13 (m, 4H), 3.96 (t, 2H, *J* = 6.8 Hz), 1.17–2.69 (m, 19H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.8 (C), 130.4 (C), 128.2 (C), 121.6 (CH), 121.4 (CH), 109.8 (CH), 108.0 (CH), 66.6 (CH), 59.4 (CH_2), 57.1 (CH_2), 56.1 (CH_2), 55.7 (CH_2), 53.5(CH_2), 39.5 (CH_2), 29.8 (CH_2), 26.3 (CH_2), 24.7 (CH_2), 23.7 (CH_2); MS *m/z* = 315.5 $[M + 1]^+$.

2-[2-(6-Bromopyrrolo[2,3-b]pyridin-1-yl)ethyl] decahydropyrido[1,2-a][1,4]diazepine (10)

$C_{18}H_{25}BrN_4$; Yield 47%; dark orange oil; IR (NaCl) cm^{-1}: 3405, 2934, 1591, 1506, 1418, 1094, 903, 753; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (d, 1H, *J* = 8.1 Hz), 7.28 (d, 1H, *J* = 3.5 Hz), 7.19 (d, 1H, *J* = 8.1 Hz), 6.44 (d, 1H, *J* = 3.5 Hz), 4.25–4.39 (m, 2H), 2.94 (t, 2H, *J* = 6.1 Hz), 1.33–2.77 (m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.3 (C), 134.4 (C), 130.8 (CH), 128.5 (CH), 119.2 (CH), 99.9 (CH), 66.4 (CH), 59.7 (CH_2), 58.5 (CH_2), 57.2 (CH_2), 55.8 (CH_2), 53.6 (CH_2), 43.0 (CH_2), 30.2 (CH_2), 26.9 (CH_2), 25.2 (CH_2), 23.8 (CH_2); MS *m/z* = 377.5 $[M + H]^+$ for ^{79}Br, 379.5 $[M + H]^+$ for ^{81}Br.

2-[2-(6-Chloropyrrolo[2,3-b]pyridin-1-yl)ethyl] decahydropyrido[1,2-a][1,4]diazepine (11)

$C_{18}H_{25}ClN_4$; Yield 49%; dark brown oil; IR (NaCl) cm^{-1}: 3385, 2934, 1595, 1507, 1422, 1120, 913, 752; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J* = 8.1 Hz), 7.29 (d, 1H, *J* = 3.5 Hz), 7.04 (d, 1H, *J* = 8.1 Hz), 6.43 (d, 1H, *J* = 3.5 Hz), 4.31 (td, 2H, *J* = 1.4 Hz, *J* = 6.1Hz), 2.92 (td, 2H, *J* = 1.4 Hz, *J* = 6.1Hz), 1.20–2.71 (m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 146.7 (C), 144.1 (C), 130.9 (CH), 128.7 (CH), 118.9(C), 115.5 (CH), 99.6 (CH), 66.0 (CH), 60.2 (CH_2), 58.4 (CH_2), 57.2 (CH_2), 55.9 (CH_2), 53.8 (CH_2), 42.9 (CH_2), 30.7 (CH_2), 27.4 (CH_2), 25.6 (CH_2), 24.0 (CH_2); MS *m/z* = 333.5 $[M + H]^+$.

2-[(2-Pyrrolo[2,3-c]pyridin-1-yl)ethyl] decahydropyrido[1,2-a][1,4]diazepine (7)

To a solution of compound **6** (0.12 g, 0.36 mmol) in methanol (14 mL) was added 10% Pd/C (0.014 g) and potassium carbonate (0.06 g, 0.47 mmol), and the reaction mixture was stirred overnight under hydrogen pressure (7 bar). The catalyst was filtered on Celite and the filtrate evaporated. Water (30 mL) and 50% NaOH aq. (3 mL) were added to the

obtained residue and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were dried on magnesium sulfate and evaporated under reduced pressure, and the crude product purified by flash chromatography to give the final dehalogenated derivative **7**. $C_{18}H_{26}N_4$; Yield 74%; orange oil; IR (NaCl) cm^{-1}: 3396, 2931, 1665, 1603, 1471, 1321, 816, 752; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.23 (d, 1H, *J* = 5.5 Hz), 7.50 (dd, 1H, *J* = 1.0 Hz, *J* = 5.5 Hz), 7.31 (d, 1H, *J* = 3.1 Hz), 6.49 (d, 1H, *J* = 3.1 Hz), 4.25 (td, 2H, *J* = 2.3 Hz, *J* = 6.3 Hz, *J* = 6.4 Hz), 2.94 (t, 2H, *J* = 6.6 Hz), 1.16–2.86 (m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.4 (CH), 133.2 (C), 132.8 (CH), 131.8 (CH), 115.2 (CH), 100.6 (CH), 65.8 (CH), 60.8 (CH_2), 58.6 (CH_2), 57.2 (CH_2), 56.0 (CH_2), 54.1 (CH_2), 45.5 (CH_2), 30.8 (CH_2), 27.3 (CH_2), 25.5 (CH_2), 24.0 (CH_2); MS *m/z* = 299.5 $[M + H]^+$.

Chemistry and pharmacological results

In a first stage, the non-substituted analogs were synthesized, in order to investigate their binding potential with 5-HT$_7$ and 5-HT$_{1A}$ receptors. The synthesis route for each compound is presented below.

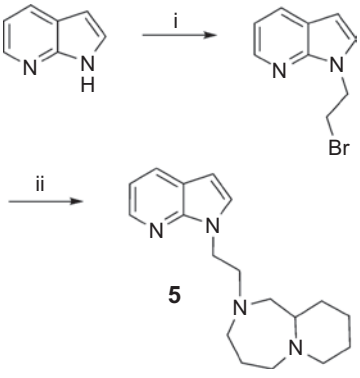
The 7-azaindole analog **5** was obtained in two steps: alkylation of the nitrogen with dibromoethane and subsequent substitution of the bromine by the amine moiety (Scheme 1)[17].

Synthesis of the 6-azaindole analog started with preparation of the key intermediate 7-chloro-6-azaindole. This derivative was obtained via Bartoli indole synthesis between 2-chloro-3-nitropyridine and an excess of vinyl magnesium bromide[18]. Additional alkylation of the nitrogen and introduction of the bulky amine gave the intermediate **6**, which was subsequently hydrogenated in order to obtain the non-halogenated compound **7** (Scheme 2)[19].

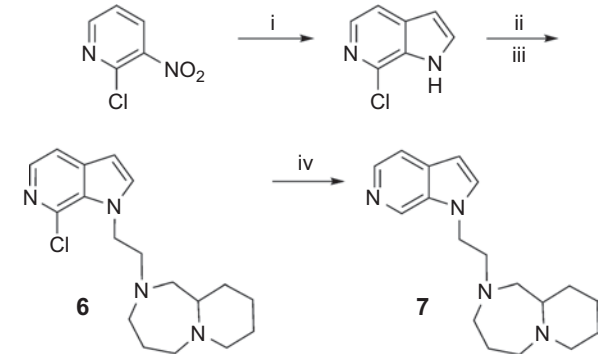
In the case of the benzimidazolone analog, synthesis followed the same pattern as described before. After protection of one nitrogen with a carbamate group (Boc), the other available nitrogen was alkylated with dibromoethane in water, using potassium carbonate as the base and tetrabutylammonium bromide as the transferring agent. Introduction of the amine moiety and final deprotection of the nitrogen gave the desired compound **8** in a good overall yield (Scheme 3).

The final compounds were tested in competition binding experiments for native serotonin 5-HT$_{1A}$ (rat hippocampus) and cloned human 5-HT$_{7b}$ (stably expressed in HEK-293 cells) receptors, according to previously published procedures[20]. Briefly, [^{3}H]-8-OH-*N*,*N*-dipropyl-2-aminotetralin (DPAT) (170 Ci/mmol, PerkinElmer) and [^{3}H]-5-carboxamidotryptamine (CT) (93.0 Ci/mmol, Hartmann Analytic GmbH) were used as radioligands in 5-HT$_{1A}$ and 5-HT$_7$ assays, respectively. In both experiments, serotonin was used for nonspecific binding. K_i values were calculated on the basis of at least three independent experiments with the use of 7–8 compound concentrations, run in triplicate. The biological results (Table 1) show that among the tested heterocyclic scaffolds, benzimidazolone was less tolerated than the azaindole skeleton (compound **7**).

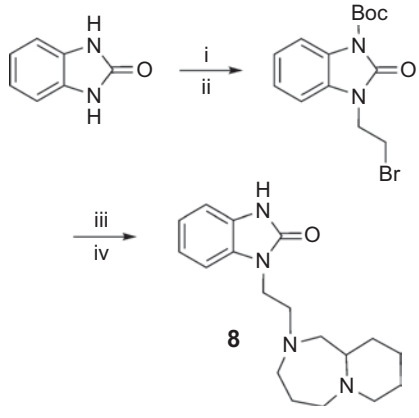
The overall lower affinities seem to suggest the importance of the additional hydrophobic area, represented by a halogen in the reference ligand **4**. In consequence, it seemed interesting



Scheme 1. Reagents and conditions: (i) 1,2-dibromoethane, K_2CO_3, Bu_4NBr, H_2O, 100°C, 12 h, 93%; (ii) decahydropyrido[1,2-*a*][1,4]diazepine, K_2CO_3, KI, MeCN, 60°C, 12 h, 44%.



Scheme 2. Reagents and conditions: (i) vinylmagnesium bromide, tetrahydrofuran (THF), –20°C, 8 h, 43%; (ii) 1,2-dibromoethane, Bu_4NBr, 50% NaOH, room temperature (r.t.), 12 h, 89%; (iii) decahydropyrido[1,2-*a*][1,4]diazepine, K_2CO_3, KI, MeCN, 60°C, 12 h, 79%; (iv) H_2, Pd/C, MeOH, r.t., 12 h, 74%.



Scheme 3. Reagents and conditions: (i) NaH, Boc_2O, dimethylformamide (DMF), r.t., 12 h, 90%; (ii) 1,2-dibromoethane, K_2CO_3, Bu_4NBr, H_2O, 100°C, 12 h, 88%; (iii) decahydropyrido[1,2-*a*][1,4]diazepine, K_2CO_3, KI, MeCN, 60°C, 12 h, 49%; (iv) trifluoroacetic acid (TFA), dichloromethane (DCM), r.t., 3 h, 98%.

Table 1. Radioligand binding results for compounds **5**, **6**, **7**, and **8**.

Compound	K_i (μM)[a]	
	5-HT_7	5-HT_{1A}
5	14	24.5
6	5.31	16
7	>10	>10
8	23.6	—

[a]Values are means of three experiments run in triplicate, SEM ≤12%.

to also evaluate the intermediate **6**, as this compound incorporates a chlorine atom. Indeed, as revealed by the biological tests, ligand **6** presented a higher affinity of 5.31 μM for the 5-HT_7R compared to its bioisoster **7**, being three-fold more active than the 5-HT_{1A}R (K_i = 16 μM). Although slightly higher, the affinity still remained low, most probably because substitution in this position of 6-azaindole has a direct impact on sterical hindrance within the 5-HT_7R binding pocket.

We further continued our investigation on the 7-azaindole scaffold; synthesis of the 6-halogen derivative allowed us to compare it directly with the reported compound **4**. The choice of the 7-azaindole heterocycle seemed also to be reinforced by the similarity with the ligands of Thomson *et al.*[21], and more particularly with the reported bromopyridine **9** (K_i = 4.1 nM for 5-HT_7R, Figure 2), which has the halogen in the ortho position on the pyridine ring.

The synthesis route detailed in Scheme 4 involved protocols described in the literature[22–24]. Briefly, halogenation of the 6-position was performed through a Reissert–Henze type reaction on 7-azaindole-*N*-oxide using benzoyl bromide or chloride as halogen source. After *N*-deprotection, 6-halogeno-7-azaindoles were engaged in the same synthesis sequence as described for **5** to obtain the target compounds **10** and **11** (Scheme 4).

The biological evaluation of these compounds (Table 2) showed that their affinity was enhanced more than 30-fold compared to the non-substituted analog **5**. Interestingly, in contrast to the Isaac results on the indole-based compounds, in the case of our 7-azaindole ligands, the bromide compound **10** had a lower affinity compared with its chloride analog **11**. Both halogenated compounds had a good selectivity over 5-HT_{1A}R. In the particular case of compound **11**, the selectivity ratio 5-HT_7/5-HT_{1A} was almost 100.

In conclusion, we analyzed the impact of the central heterocyclic scaffold on 5-HT_{1A}/5-HT_7 binding affinities. Among the tested heterocycles, 7-azaindole was best accommodated by the 5-HT_7 receptors. A positive influence of halogen substitution in the 6-position on this heterocycle was observed, and seems to indicate a promising selectivity profile versus 5-HT_{1A}R.

***Declaration of interest*:** All authors declare that the study has not been funded by external funds or grants and that there is no conflict of interests of any kind.

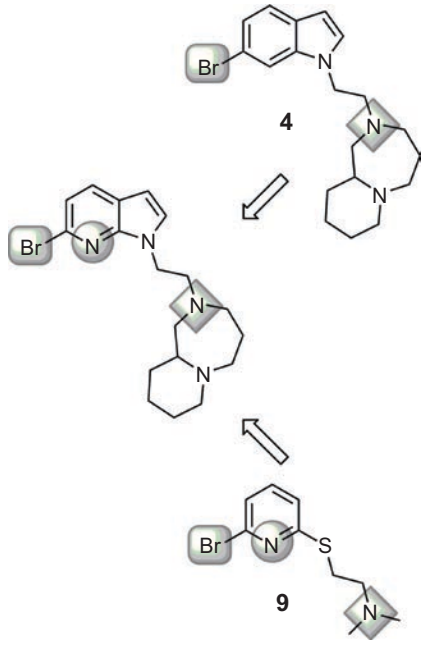
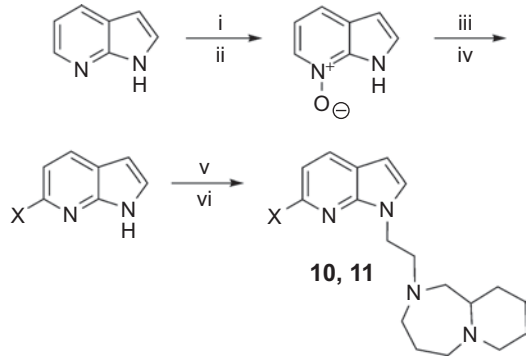


Figure 2. Analogy between published ligands **4** and **9** and proposed derivative.



Scheme 4. Reagents and conditions: (i) *m*-chloroperoxybenzoic acid (CPBA), acetone, r.t., 20 h, 81%; (ii) K_2CO_3, r.t., 15 min, 98%; (iii) hexamethyldisilazane (HMDS), PhCOBr or PhCOCl, THF, r.t., 2 h, 58–63%; (iv) 1M NaOH, MeOH, r.t., 14 h, 98%; (v) 1,2-dibromoethane, Bu_4NI, 50% NaOH, r.t., 18 h, 86–94%; (vi) decahydropyrido[1,2-*a*][1,4]diazepine, K_2CO_3, KI, MeCN, 60°C, 2 h, 47–49%.

Table 2. Radioligand binding results for compounds **5**, **10**, and **11**.

Compound	X	K_i (μM)[a]	
		5-HT_7	5-HT_{1A}
5	H	14	24.5
10	Br	0.492	14.9
11	Cl	0.16	15

[a]Values are means of three experiments run in triplicate, SEM ≤12%.

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