Full Paper

New Arylpiperazines with Flexible versus Partly Constrained Linker as Serotonin 5-HT_{1A}/5-HT_7 Receptor Ligands

Piotr Kowalski[1], Katarzyna Mitka[1], Jolanta Jaśkowska[1], Beata Duszyńska[2], and Andrzej J. Bojarski[2]

[1] Cracow University of Technology, Institute of Organic Chemistry and Technology, Kraków, Poland
[2] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

A series of new long-chain arylpiperazine (LCAP) derivatives with flexible and partly constrained alkyl linker were synthesized and investigated *in vitro* as potential serotonin 5-HT_{1A} and 5-HT_7 receptor ligands. The compounds were prepared by a two-step procedure using naphthalimide and 2*H*-1,3-benzoxazine-2,4(3*H*)-dione as imides, and 1-(2-methoxyphenyl)piperazine (*o*-OMe-PhP) and 1,2,3,4-tetrahydroisoquinoline (THIQ) as amine pharmacophores. Modifications of the spacer structure included introduction of flexible penta- and hexamethylene chains as well as partly constrained *m*- and *p*-xylyl moieties. In general, the new compounds were more active at the 5-HT_{1A} than at the 5-HT_7 receptor, and the *o*-OMe-PhP derivatives displayed higher affinities than their respective THIQ analogs. The spacer modifications had little effect on the observed *in vitro* activities. Within the *o*-OMe-PhP series, except for a small binding reduction for ligands containing the *m*-xylyl moiety, there was no substantial change in the compounds' potency at both receptors, while for the THIQ derivatives a clear structure–activity relationship was visible only for the interaction of the compounds with the 5-HT_7 receptor, which strongly favored flexible analogs.

Keywords: Arylpiperazines / NAN-190 / Serotonin 5-HT_{1A}/5-HT_7 receptor ligands / Structure–activity relationship (SAR)

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Introduction

Long-chain arylpiperazines (LCAP) are one of the commonly studied classes of bioactive compounds due to their large spectrum of potential therapeutic applications [1–10]. Among them, a prominent place is occupied by pharmacological effects caused by interactions with different subtypes of serotonin receptors, which are known to be involved in the etiology of various mental diseases [1, 10].

Arylpiperazines are also a group of compounds for which accumulated knowledge and published SAR studies provide comprehensive data to design active ligands with a relatively high degree of accuracy [2, 3, 11–20].

Indeed, a number of studies have been aimed at examining the impact of LCAP structure modifications on the affinity, selectivity and function at a given receptor protein [1, 5, 8, 10, 12]. Nevertheless, there is still the chemical space for further investigations, especially within the central part of LACP, i.e. a bridge connecting two terminal parts of a ligand molecule.

This issue was also a subject of our previous studies where various linkers (*n*-butyl, *cis*/*trans*-but-2-enyl, *o*-xylyl, 1,4-cyclohexyl) had been introduced to the LCAP structure and the obtained affinity data on the respective derivatives displayed different preferences at serotonin 5-HT_{1A} and 5-HT_7 receptor subtypes [21]. While derivatives containing a flexible alkyl chain and those with cyclohexyl moiety were the most active at the 5-HT_{1A} receptor, their analogs with *trans*-2-butenyl spacer always displayed the highest affinity for the 5-HT_7 receptor.

The present communication describes the results of our successive research on the impact of spacer structure on 5-HT_{1A} and 5-HT_7 receptor affinity. New compounds are structural analogs of the well-known serotonin 5-HT_{1A} antagonist NAN-190 (**1**) [22] and the previously reported 2*H*-1,3-benzoxazine-2,4(3*H*)-dione derivative (**2**) [23], to which four different

Correspondence: Dr. Piotr Kowalski, Cracow University of Technology, Institute of Organic Chemistry and Technology, 24 Warszawska Street, 31-155 Kraków, Poland
E-mail: kowapi@pk.edu.pl
Fax: +48-12-6282037

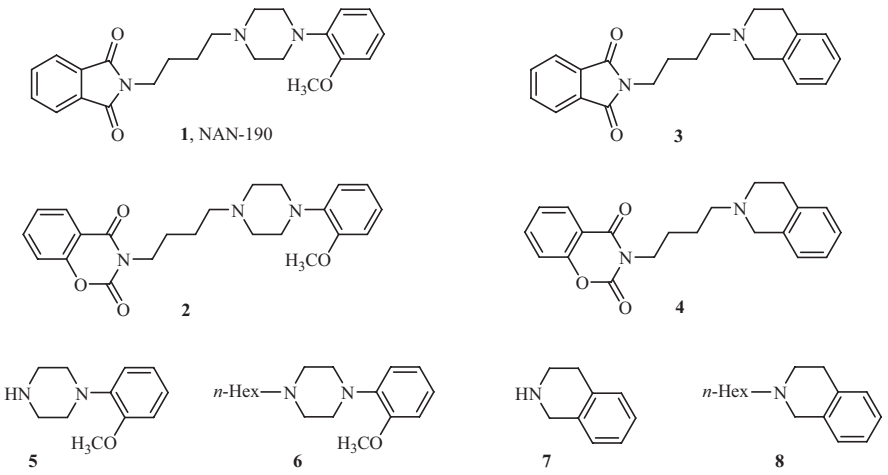


Figure 1. Structures of the model compounds.

spacers, i.e. penthamethylene (**a**), hexamethylene (**b**), *m*-xylyl (**c**) and *p*-xylyl (**d**), have been introduced. The first two sets of compounds are structural analogs of NAN-190 (**1**) (**9a–d**) and **2** (**10a–d**), which contain a 1-(2-methoxyphenyl)piperazine moiety (*o*-OMe-PhP) as an amine pharmacophore, whereas in the remaining two groups (compounds **11a–d** and **12a–d**) 1,2,3,4-tetrahydroisoquinoline (THIQ) isostere [18] was used. Additionally, *m*-xylyl (**13c–d**) and *p*-xylyl (**14c–d**) derivatives of simplified structure (without imide terminals) were synthesized to test the influence of imide function on serotonin receptors activity. The affinity of the new compounds is discussed in relation to the previously obtained results for parent molecules **1–8** (Fig. 1) [17, 21, 23–25].

Results and discussion

Chemistry

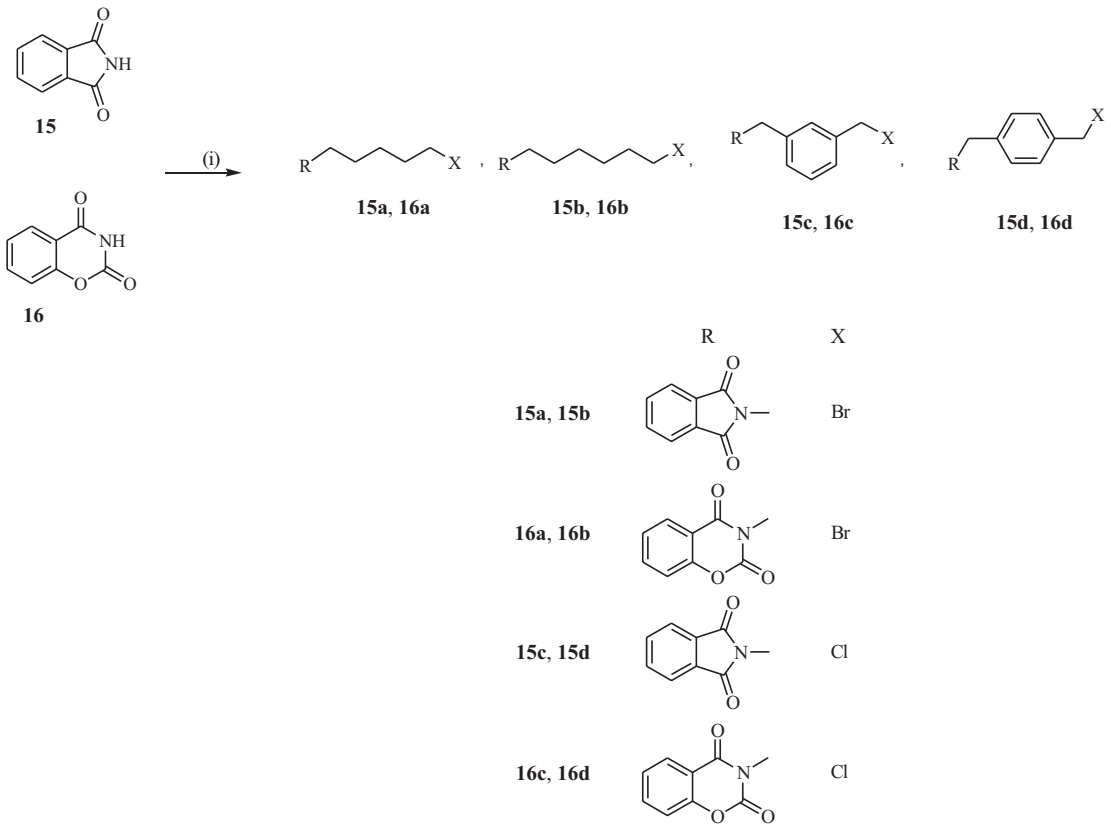
The synthesis of the compounds under study was carried out by a two-step procedure according to the paths presented in Schemes 1, 2, and 3. The structures of the obtained compounds are shown in Fig. 2.

In the first step, *N*-alkylation of imides **15** and **16** with 1,5-dibromopentane (**a**), 1,6-dibromohexane (**b**), α,α′-dichloro-*m*-xylene (**c**), and α,α′-dichloro-*p*-xylene (**d**) was conducted (Scheme 1). The reaction, carried out at an ambient temperature in the presence of K_2CO_3 and DMF as a solvent, gave an efficient yield of *N*-(ω-haloalkyl)imides (**15a–d** and **16a–d**). In order to reduce formation of disubstituted by-products, imides **15** and **16** were added stepwise to the reaction mixture of dihaloalkanes **a–d**. *N*-(ω-Haloalkyl)imides and disubstituted by-products were easily separated due to the difference in their solubility. *N*-(ω-Haloalkyl)imides (**15a–d** and **16a–d**) had good solubility in acetone, while the disubstituted by-products showed no solubility in several organic solvents and could thus be easily separated by filtration. In the case of 1,5-dibromopentane (**a**) and 1,6-dibromobutane (**b**), the reaction was carried out for 48 h, whereas using α,α′-dichloro-*m*-xylene (**c**) and α,α′-dichloro-*p*-xylene (**d**) it was completed after 24 h (Scheme 1). The reaction yields and physical properties of the obtained *N*-(ω-haloalkyl)imides **15a–d** and **16a–d** are shown in Table 1.

N-(ω-Bromoalkyl)imides **16a** and **16b** were also obtained by alkylation of imide **16** with 1,ω-dibromoalkanes (**a**, **b**) in the presence of K_2CO_3 and TBAB (tetrabutylammonium bromide) as a PTC catalyst, in solvent-free conditions, according to the method developed for solvent-free alkylation of imides [26, 27] (see the Experimental section). The advantage of this protocol is short reaction time (60 min), solvent-free conditions and formation of a small quantity of disubstituted by-products; on the other hand, the inconvenience is the use of a threefold excess of dibromoalkanes (**a**, **b**).

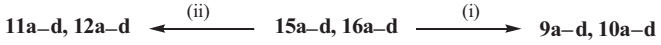
The second step, i.e. condensation of *N*-(ω-alkyl)imides **15a–d** and **16a–d** with 1-(2-methoxyphenyl)piperazine (**17**) or 1,2,3,4-tetrahydroisoquinoline (**18**), afforded compounds **9–12** (Scheme 2, Table 2). The condensation was carried out at an ambient temperature in the presence of K_2CO_3 using DMF as a solvent; under the same conditions, the reaction of α-chloro-*m*-xylene (**19**) and α-chloro-*p*-xylene (**20**) with **17** or **18** yielded compounds **13c–d** and **14c–d**, respectively (Scheme 3, Table 2).

For biological experiments, free bases **9–14** were converted into hydrochloride salts with ethanol saturated with HCl, and their molecular weights were established on the basis of an elemental analysis.



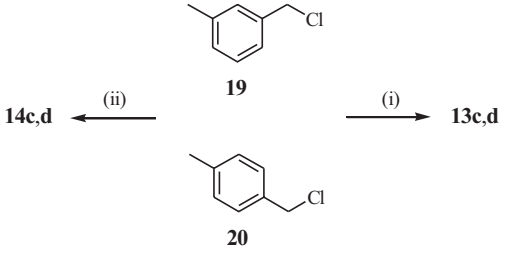
Conditions and Reagents:
(i) DMF, K_2CO_3, 24–48 h, room temp;
1,5-dibromopentane (**a**), 1,6-dibromohexane (**b**), α,α'-dichloro-*m*-xylene (**c**), or α,α'-dichloro-*p*-xylene (**d**).

Scheme 1. Synthesis of *N*-(**ω**-haloalkyl)imides **15a–d** and **16a–d**.



Conditions and Reagents:
(i) DMF, K_2CO_3, 24–48 h, room temp, 1-(2-methoxyphenyl)piperazine hydrochloride (**17**),
(ii) DMF, K_2CO_3, 24–48 h, room temp, 1,2,3,4-tetrahydroisoquinoline (**18**).

Scheme 2. Synthesis of the investigated compounds **9a–d, 10a–d, 11a–d,** and **12a–d**.



Conditions and Reagents:
(i) DMF, K_2CO_3, 24–48 h, room temp, 1-(2-methoxyphenyl)piperazine hydrochloride (**17**),
(ii) DMF, K_2CO_3, 24–48 h, room temp, 1,2,3,4-tetrahydroisoquinoline (**18**).

Scheme 3. Synthesis of the investigated compounds **13c–d** and **14c–d.**

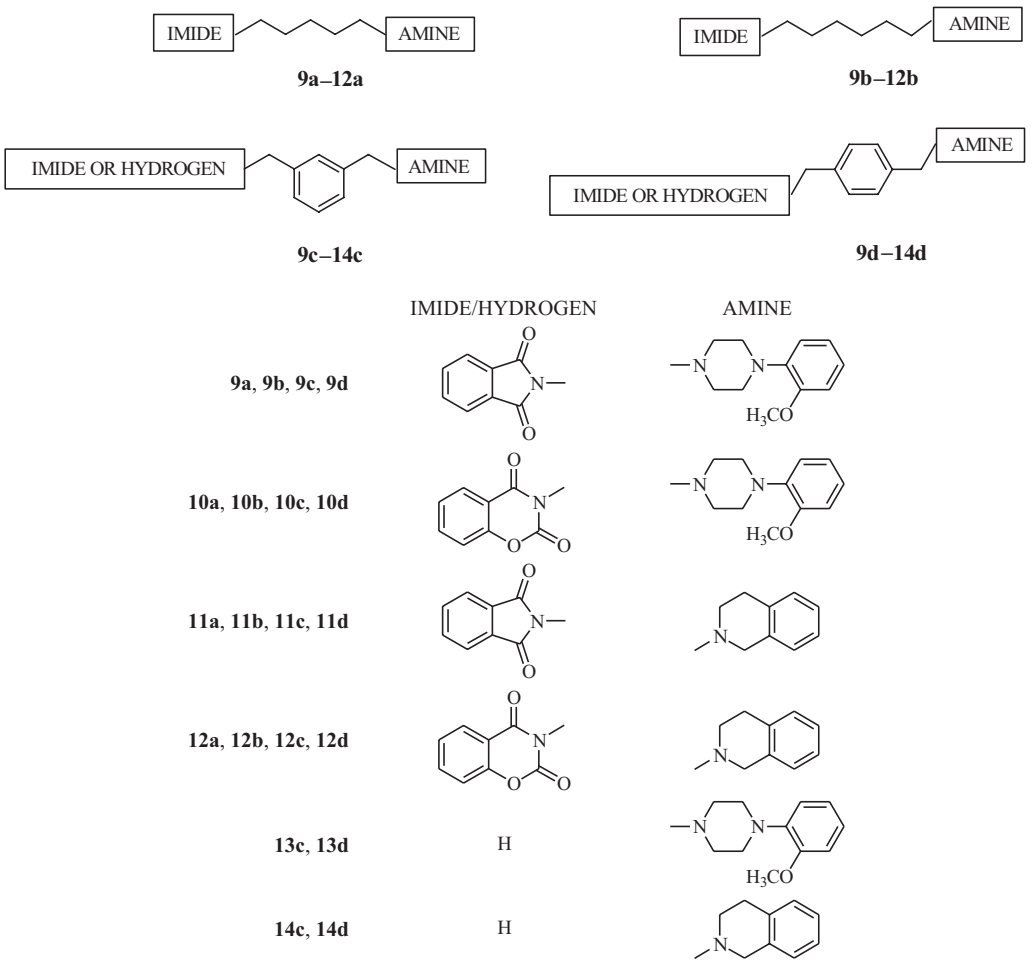


Figure 2. Structures of the compounds obtained.

Biological evaluation

The investigated compounds were tested in competition binding experiments for native 5-HT_{1A} receptors and for cloned human 5-HT_7 ones according to the previously published procedures [28, 29].

As regards 5-HT_{1A} receptors, experiments were carried out using membranes from rat hippocampus and [3H]-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin; spec. act. 170 Ci/mmol, NEN Chemical) as a radioligand. Following incubation, the receptor preparations were rapidly filtered under vacuum through GF/B glass fiber filters which were washed extensively with an ice-cold 50 mM Tris buffer (pH 7.4) using a Brandel harvester. Radioactivity was determined by liquid scintillation counting in the Beckman LS 6500 apparatus [28].

Binding assays on membranes from HEK 293 cells stably expressing human 5-HT_{7b} receptors [29] were performed with the use of [3H]-5-CT (5-carboxamidotryptamine; spec. act. 93 Ci/mmol, Amersham) as a radioligand. The experiment was carried out in a 96-well plate using the MultiPROBE II Liquid Handling System. After 1-h incubation at 37°C, the assay samples were rapidly filtered using a Unifilter harvester and plates were subsequently washed with an ice-cold 50 mM Tris buffer (pH 7.4). Radioactivity retained on the filters was quantified on a Microbeta plate reader.

In both experiments 10 μM of serotonin was used for nonspecific binding. Inhibition constants (K_i) were calculated from the Cheng–Prushoff equation [30]. Results are expressed as means of at least three separate experiments, each performed for 7–9 concentrations of a compound, run in triplicate.

At the same time, the two well-known reference serotonin drugs buspirone and methiothepin were examined, and the obtained results were consistent with our previous data as well as with those reported in the literature [24, 31] (Table 3).

Table 1. Physical properties of *N*-(ω-haloalkyl)imides **15a–d** and **16a–d** obtained in the reaction of imides **15** and **16** with dihaloalkanes (**a–d**) in the presence of K_2CO_3 and DMF as a solvent.

Compound	Yield (%)	mp (°C)	Recryst. solvent	^{1}H NMR ($CDCl_3$), δ ppm
15a	67	61–63[a]	Ligroine	1.42–2.09 (6H, cluster, 3xCH_2), 3.41 (2H, t, J = 6.9 Hz, CH_2-Br), 3.70 (2H, t, J = 7.0 Hz, CH_2-N_{imide}), 7.66–7.71 (2H, m, H-Ar), 7.88–7.95 (2H, m, H-Ar)
15b	49	55–57[b]	Methanol	1.40–1.89 (8H, cluster, 4xCH_2), 3.40 (2H, t, J = 7.0 Hz, CH_2-Br), 3.69 (2H, t, J = 7.1 Hz, CH_2-N_{imide}), 7.64–7.70 (2H, m, H-Ar), 7.85–7.92 (2H, m, H-Ar)
15c	57	129–130	Acetone–methanol	4.55 (2H, s, CH_2-Cl), 4.84 (2H, s, CH_2-N_{imide}), 7.26–7.36 (3H, m, H-Ar), 7.43 (1H, s, H-Ar), 7.63–7.70 (2H, m, H-Ar), 7.83–7.91 (2H, m, H-Ar)
15d	75	153–155.5[c]	Acetone	4.53 (2H, s, CH_2–Cl), 4.83 (2H, s, CH_2-imide), 7.26–7.49 (4H, m, H-Ar), 7.62–7.69 (2H, m, H-Ar), 7.82–7.90 (2H, m, H-Ar)
16a	71	81–83	Methanol	1.51–2.01 (6H, cluster, 3xCH_2), 3.42 (2H, t, J = 7.1 Hz, CH_2-Br), 4.05 (2H, t, J = 7.5 Hz, CH_2-N_{imide}), 7.22–7.46 (2H, m, H–Ar), 7.60–7.82 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.6, 1.9 Hz, H-Ar)
16b	56	58–60	Methanol	1.41–1.95 (8H, cluster, 4xCH_2), 3.40 (2H, t, J = 6.9 Hz, CH_2-Br), 4.04 (2H, t, J = 7.6 Hz, CH_2-N_{imide}), 7.21–7.43 (2H, m, H-Ar), 7.65–7.82 (1H, m, H-Ar), 8.07 (dd, 1H, J = 7.6, 2.0 Hz, H–Ar)
16c	75	137–137	Acetone–ligroine	4.56 (2H, s, CH_2–Cl), 5.20 (2H, s, CH_2-N_{imide}), 7.21–7.55 (6H, m, H-Ar), 7.60–7.79 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.5, 1.8 Hz, H-Ar)
16d	51	141–143	Acetone	4.54 (2H, s, CH_2-Cl), 5.19 (2H, s, CH_2-N_{imide}), 7.20–7.51 (6H, m, H-Ar), 7.59–7.78 (1H, m, H-Ar), 8.06 (1H, dd, J = 7.6, 1.9 Hz, H-Ar)

[a] For **15a** mp 59–61°C (light petroleum) [34] and 59.5–60°C (ethanol) [35] has been reported.
[b] For **15b** mp 58.5–59.5°C [35] and 50–52°C [36] has been reported.
[c] For **15d** mp 143–146°C [37] has been reported.

Table 2. Physical properties of the compounds obtained.

Compound	Base			Hydrochloride
	Yield (%)	mp (°C)	Recryst. solvent	mp (°C)
9a	70	135–137[a]	Ethanol	195–197
9b	75	66–68	Acetone–*n*-hexane	203–204
9c	74	128–130	Butan-1-ol	245–248
9d	57	124–126	Methanol	234–237[b]; >220°C sublim.
10a	53	134–135	Acetone	161–164
10b	52	84–86	Acetone	205–207
10c	47	65–70[c]	Acetone–methanol	>250[b]
10d	72	119–120	Acetone	>240[b]
11a	72	69–71	Acetone–water	194–197; >180°C sublim.
11b	71	Oil	–	229–231; >200°C sublim.
11c	79	143–145	Butan-1-ol	226–228
11d	64	129–130	Acetone–water	>250[b]; >210°C sublim.
12a	43	79–81	Acetone	214–216; >190°C sublim.
12b	60	67–70	Acetone–water	218–222
12c	47	122–124	Acetone–methanol	235–238; >210°C sublim.
12d	68	145–146	Acetone	>240[b]; >220°C sublim.
13c	86	64–65	Methanol–water	202–204; >170°C sublim.
13d	89	82–83	Methanol–water	234–236; >190°C sublim.
14c	61	Oil	–	175–177; >150°C sublim.
14d	76	Oil	–	232–233; >160°C sublim.

[a] For **9a** mp 133–134 °C (propan-2-ol) [36].
[b] mp with decomposition.
[c] Amorphous substance.

Table 3. The affinity data[a] on the serotonin 5-HT_{1A} and 5-HT_7 receptors of the investigated compounds.

o-OMe-PhP derivatives	K_i [nM] ± SEM		THIQ derivatives	K_i [nM] ± SEM	
	5-HT_{1A}	5-HT_7		5-HT_{1A}	5-HT_7
1, NAN-190	0.6 ± 0.1[b]	87 ± 2[c]	**3**	140 ± 10[d]	60 ± 7
9a	7.2 ± 0.6[e]	80 ± 5	**11a**	324 ± 29	245 ± 17
9b	22 ± 2	118 ± 7	**11b**	108 ± 22	324 ± 38
9c	68 ± 8	292 ± 19	**11c**	278 ± 42	768 ± 94
9d	16 ± 2	50 ± 3	**11d**	459 ± 63	781 ± 56
2	3.2 ± 0.25[f]	100 ± 8	**4**	293 ± 11[f]	237 ± 20
10a	20 ± 3	106 ± 13	**12a**	746 ± 87	342 ± 45
10b	18 ± 2.5	112 ± 16	**12b**	62 ± 5	290 ± 33
10c	69 ± 8	152 ± 9	**12c**	1141 ± 121	1060 ± 132
10d	34 ± 3	83 ± 11	**12d**	572 ± 49	1097 ± 88
5	168 ± 14[g]	832 ± 43	**7**	>50,000[d]	29,680
6	1.5 ± 0.3[g]	–	**8**	1240 ± 60[h]	–
13c	182 ± 14	573 ± 95	**14c**	3800 ± 538	5470 ± 654
13d	121 ± 17	535 ± 48	**14d**	2005 ± 176	5350 ± 870

[a] Buspirone and methiothepin were used as reference drugs for 5-HT_{1A} (K_i = 12 nM) and 5-HT_7 (K_i = 2.7 nM) receptors, respectively, and the obtained affinities were comparable with those reported elsewhere [24, 31].
[b] K_i = 0.55 nM according to Glennon et al. [22].
[c] Data from [21].
[d] Data from [24].
[e] K_i = 5.0 nM according to Glennon et al. [38].
[f] Data from [23].
[g] Data from [17].
[h] Data from [25].

Results and discussion

In general, all *o*-OMe-PhP derivatives (**9a–d** and **10a–d**) were active serotonin 5-HT_{1A} receptor ligands with K_i values below 100 nM. At the same time, these compounds had lower, but still significant, affinity for 5-HT_7 receptors whose value oscillated around 100 nM (Table 3). The 5-HT_{1A} receptor preferred ligands with a flexible *n*-alkyl spacer, whereas the 5-HT_7 binding pocket more easily accommodated compounds with a middle *p*-xylyl group; thus **9d** and **10d** showed the highest activity in both sets of *o*-OMe-PhP derivatives (K_i = 50 and 83 nM, respectively), which also exceeded the values presented by the parent compounds **1** and **2**.

The replacement of 1-(2-methoxyphenyl)piperazine moiety with 1,2,3,4-tetrahydroisoquinoline group (series **11a–d** and **12a–d**) decreased the affinity for both receptors. In these series, ligands with an *n*-hexyl chain were the most active for the 5-HT_{1A} receptor, while the 5-HT_7 receptor also preferred compounds with fully flexible *n*-alkyl linkers, but did not discriminate between them (i.e. similar K_i values were obtained for **11a** and **11b**, as well as for **12a** and **12b**). Unfortunately, comparison of the obtained results with those characterizing parent ligands **3** and **4** revealed unfavorable tendency of diminishing affinity to both investigated receptors (Table 3).

The decreased activity of THIQ derivatives versus *o*-OMe-PhP analogs at the 5-HT_{1A} receptor is a known phenomenon attributed to the properties of these amine fragments themselves [25]. As was shown in our previous papers, unsubstituted THIQ (**7**) is totally inactive (K_i > 50,000 nM), while *o*-OMe-PhP (**5**) itself is a fairly potent 5-HT_{1A} receptor ligand (K_i = 168 nM) [25]. Substitution of both those amines with *n*-hexyl chains resulted in the enhancement of the affinities of **6** and **8** due to hydrophobic interactions (K_i = 1.5 and 1240 nM, respectively) [17, 25], which indicates that weaker interactions of the amine moiety and the 5-HT_{1A} receptor binding site can be compensated by hydrophobic forces [17, 25, 32, 33]. Nevertheless, 5-HT_{1A} binding results obtained in the present study for *o*-OMe-PhP derivatives with no imide function (**13c** and **13d**) did not differ from the K_i values for the unsubstituted *o*-OMe-PhP (**5**) molecule, showing lack of engagement of the middle benzene group in the process of binding with the 5-HT_{1A} receptor (Table 3). Similar conclusions can be drawn on the basis of binding results obtained for 5-HT_7 receptor. Replacement of the polymethylene chain with a benzene group in *o*-OMe-PhP derivatives **13c–d** did not affect 5-HT_7 affinity, and in the case of THIQ analogs **14c–d** improved it. In each case, however, structure simplification of parent **9c–d** and **10c–d** ligands led to a decrease in affinity to both investigated serotonin receptors,

which points to an important role exerted by the imide function of LCAPs in the process of ligand recognition.

Summing up, the applied spacer modifications did not influence the preference of 5-HT_{1A} binding over 5-HT_7 one, as was observed in our previous investigation [21]. Within *o*-OMe-PhP series, except small binding reduction for ligands containing the *m*-xylyl moiety (**9c** and **10c**), there was no substantial change in compounds potency at either receptor, and several of the new compounds were characterized by dual 5-HT_{1A}/5HT_7 receptor activity. For the less active THIQ derivatives, clear SAR was visible only for compound interactions with the 5-HT_7 receptor, which favored flexible analogs.

Experimental

Melting points were determined on a Böetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 analyzer and the results are within ±0.4% of the calculated values. Infrared spectra were recorded as pressed KBr discs on a Bio-Rad FTS 175B spectrometer. ^{1}H NMR spectra were taken on a Varian 300 MHz Mercury-VX spectrometer in $CDCl_3$ using TMS as an internal standard; chemical shifts are given in ppm (δ). Mass spectra were recorded using an Esquire 3000 mass spectrometer (Bruker Daltonik, Bremen, Germany) equipped with an electrospray source. ESI-MS spectra were registered in a positive-ion mode. The reactions and purifications were monitored by TLC (UV detection) on aluminum sheets coated with silica gel 60 F254 (Merck) using a chloroform/methanol (90:10) mixture as eluent. All starting materials were purchased from commercial sources (Sigma–Aldrich and Merck) and were used without further purification.

General procedure for preparation of *N*-(ω-haloalkyl)-imides 15a–d and 16a–d in the presence of a solvent

To a stirred suspension of 0.045 mol dihaloalkane **a**–**d** and 0.030 mol (4.14 g) of K_2CO_3 in 60 mL of DMF the appropriate imide **15** or **16** (0.030 mol) was added in six portions at room temperature over a period of 6 h. In the case of reaction of 1,5-dibromopentane (**a**) or 1,6-dibromohexane (**b**), the reaction mixture was stirred at room temperature for an additional 40–42 h, and for 16–18 h while using α,α′-dichloro-*m*-xylene (**c**) or α,α′-dichloro-*p*-xylene (**d**). Then the inorganic precipitate was filtered off and the solvent and the excess of dihaloalkane was evaporated under vacuum. The residue was extracted with acetone, leaving insoluble disubstituted by-products. Crude products were obtained from the acetone solution, and were then purified by crystallization. Reaction yields and physical properties of the obtained compounds are shown in Table 1.

Preparation of *N*-(ω-haloalkyl)imides 16a and 16b in solvent-free conditions

A powdered mixture of 1.63 g (0.01 mol) of 2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**16**), 4.14 g (0.03 mol) of anhydrous potassium carbonate and 0.32 g (0.001 mol) of TBAB was placed in a reaction vessel. Then, three equivalents of 1,5-dibromopentane (**a**) or 1,6-dibromohexane (**b**) were added and the mixture was stirred with a spatula for *ca.* 1 min. The reaction mixture was left at ambient temperature. Within 15–20 min, the mixture was slightly warmed up to 30–35°C, and after another 30–40 min the temperature dropped down, which indicated that the reaction was completed. Next, the reaction mixture was poured into 100 mL of water, and the products were extracted with chloroform. After evaporation of the solvent and the excess of dibromoalkane, crude products were purified in the same manner as it was described above. The yields of *N*-(5-bromopentyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**16a**) and *N*-(6-bromohexyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**16b**) were 69 and 60%, respectively.

General procedure for the synthesis of 9a–d, 10a–d, 11a–d, 12a–d, 13c–d, and 14c–d

A mixture of 0.01 mol of the respective *N*-(ω-haloalkyl)imide (**15a–d** or **16a–d**), α-chloro-*m*-xylene (**19**) or α-chloro-*p*-xylene (**20**), 0.01 mol of the respective amine **17** or **18**, 0.02 mol of anhydrous potassium carbonate (when a hydrochoride salt of an amine was used, an equivalent of potassium carbonate was also added) and a few crystals (~0.01 g) of potassium iodide in 20 mL of dimethylformamide was stirred with a magnetic stirrer at room temperature. In the case of compound **15a**, **15b**, **16a,** or **16b**, the reaction time was 48 h, while for **15c**, **15d**, **16c**, **16d**, **19,** or **20** it was 24 h. Then the reaction mixture was poured into 100–150 mL of water, and the precipitate was either collected by filtration or extracted with chloroform. Solid products were purified by crystallization, and oils by column chromatography using a mixture of chloroform/methanol (90:10) as eluent. The yields and physical properties of **9a–d**, **10a–d**, **11a–d**, **12a–d**, **13c–d**, and **14c–d** are shown in Table 2.

Hydrochloride preparation

Free bases **9a–d**, **10a–d**, **11a–d**, **12a–d**, **13c–d**, or **14c–d** (100 mg) were dissolved in 10 mL of acetone, treated with ethanol saturated with HCl, and kept overnight in a refrigerator to give colorless, crystalline products.

*N-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}phthalimide **9a***

Base: colorless plates; ^{1}H NMR δ: 1.50–1.95 (6H, cluster, 3xCH_2), 2.41 (2H, t, J = 7.0 Hz, CH_2-N_{pip}), 2.58–2.69 (4H, m, 2xCH_2), 3.03–3.15 (4H, m, 2xCH_2), 3.70 (2H, t, J = 6.9 Hz, CH_2-N_{imide}), 3.86 (3H, s, OCH_3), 6.89–7.02 (4H, m, H-Ar), 7.63–7.80 (2H, m, H-Ar), 7.85–7.91 (2H, m, H-Ar); ESI-MS: *m/z* 408 $(MH)^+$; IR (KBr) cm^{-1}: 2931, 2815, 1766, 1711, 1394, 1239. Anal. calcd. for $C_{24}H_{29}N_3O_3$ HCl 0.5H_2O (452.98): C, 63.64; H, 6.90; N, 9.28. Found: C, 63.77; H, 6.67; N, 9.22.

*N-{6-[4-(2-Methoxyphenyl)piperazin-1-yl]hexyl}phthalimide **9b***

Base: colorless needles; ^{1}H NMR δ: 1.42–1.80 (8H, cluster, 4xCH_2), 2.39 (2H, t, J = 7.1 Hz, CH_2-N_{pip}), 2.57–2.69 (4H, m, 2xCH_2), 3.04–3.15 (4H, m, 2xCH_2), 3.69 (2H, t, J = 7.1 Hz, CH_2-N_{imide}), 3.86 (3H, s, OCH_3), 6.90–7.00 (4H, m, H-Ar), 7.64–7.80 (2H, m, H-Ar), 7.85–7.91 (2H, m, H-Ar); ESI-MS: *m/z* 422 $(MH)^+$; IR (KBr) cm^{-1}: 2939, 2813, 1768, 1713, 1397, 1237. Anal. calcd. for $C_{25}H_{31}N_3O_3$ 2HCl (494.45): C, 60.73; H, 6.73; N, 8.50. Found: C, 60.66; H, 6.91; N, 8.43.

N-{3-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}phthalimide ***9c***

Base: pale yellow needles; ^{1}H NMR δ: 2.63–2.72 (4H, m, 2xCH_2), 3.02–3.15 (4H, m, 2xCH_2), 3.56 (2H, s, CH_2-N_{pip}), 3.85 (3H, s, OCH_3), 4.85 (2H, s, CH_2-N_{imide}), 6.89–6.99 (4H, m, H-Ar), 7.22–7.30 (3H, m, H-Ar), 7.41 (1H, s, H-Ar), 7.63–7.81 (2H, m, H-Ar), 7.85–7.91 (2H, m, H-Ar); ESI-MS: *m/z* 442 $(MH)^+$; IR (KBr) cm^{-1}: 2933, 2815, 1766, 1714, 1394, 1240. Anal. calcd. for $C_{27}H_{27}N_3O_3$ HCl (477.98): C, 67.85; H, 5.90; N, 8.79. Found: C, 67.89; H, 5.76; N, 8.73.

N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}phthalimide ***9d***

Base: pale yellow plates; ^{1}H NMR δ: 2.55–2.67 (4H, m, 2xCH_2), 3.00–3.12 (4H, m, 2xCH_2), 3.54 (2H, s, CH_2-N_{pip}), 3.83 (3H, s, OCH_3), 4.83 (2H, s, CH_2-N_{imide}), 6.87–6.97 (4H, m, H-Ar), 7.33–7.47 (4H, m, H-Ar), 7.63–7.80 (2H, m, H-Ar), 7.85–7.91 (2H, m, H-Ar); ESI-MS: *m/z* 442 $(MH)^+$; IR (KBr) cm^{-1}: 2934, 2805, 1767, 1716, 1396, 1239. Anal. calcd. for $C_{27}H_{27}N_3O_3$ HCl (477.98): C, 67.85; H, 5.90; N, 8.79. Found: C, 67.66; H, 5.97; N, 8.59.

N-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}2H-1,3-benzoxazine-2,4(3H)-dione ***10a***

Base: colorless solid; ^{1}H NMR δ: 1.45–1.87 (6H, cluster, 3xCH_2), 2.43 (2H, t, J = 7.2 Hz, CH_2-N_{pip}), 2.59–2.71 (4H, m, 2xCH_2), 3.04–3.16 (4H, m, 2xCH_2), 3.86 (3H, s, OCH_3), 4.06 (2H, t, J = 7.6 Hz, CH_2-N_{imide}), 6.90–7.00 (4H, m, H-Ar), 7.21–7.47 (2H, m, H-Ar), 7.60–7.79 (1H, m, H-Ar), 8.08 (1H, dd, J = 7.6, 1.9 Hz, H-Ar); ESI-MS: *m/z* 424 $(MH)^+$; IR (KBr) cm^{-1}: 2943, 2815, 1762, 1700, 1471, 1351, 1238. Anal. calcd. for $C_{24}H_{29}N_3O_4$ HCl H_2O (477.99): C, 60.31; H, 6.75; N, 8.79. Found: C, 59.96; H, 6.42; N, 9.03.

N-{6-[4-(2-Methoxyphenyl)piperazin-1-yl]hexyl}2H-1,3-benzoxazine-2,4(3H)-dione ***10b***

Base: colorless solid; ^{1}H NMR δ: 1.40–1.86 (8H, cluster, 4xCH_2), 2.43 (2H, t, J = 7.2 Hz, CH_2-N_{pip}), 2.58–2.70 (4H, m, 2xCH_2), 3.04–3.15 (4H, m, 2xCH_2), 3.85 (3H, s, OCH_3), 4.03 (2H, t, J = 7.7 Hz, CH_2-N_{imide}), 6.88–6.95 (4H, m, H-Ar), 7.20–7.43 (2H, m, H-Ar), 7.59–7.80 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.6, 1.9 Hz, H-Ar); ESI-MS: *m/z* 438 $(MH)^+$; IR (KBr) cm^{-1}: 2942, 2817, 1764, 1693, 1472, 1391, 1241. Anal. calcd. for $C_{25}H_{31}N_3O_4$ HCl H_2O (492.01): C, 61.03; H, 6.97; N, 8.54. Found: C, 61.34; H, 6.74; N, 8.59.

N-{3-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}2H-1,3-benzoxazine-2,4(3H)-dione ***10c***

Base: colorless solid; ^{1}H NMR δ: 2.57–2.69 (4H, m, 2xCH_2), 3.02–3.13 (4H, m, 2xCH_2), 3.57 (2H, s, CH_2-N_{pip}), 3.84 (3H, s, OCH_3), 5.21 (2H, s, CH_2-N_{imide}), 6.89–6.98 (4H, m, H-Ar), 7.26–7.49 (6H, m, H-Ar), 7.59–7.81 (1H, m, H-Ar), 8.09 (1H, dd, J = 7.5, 1.9 Hz, H-Ar); ESI-MS: *m/z* 458 $(MH)^+$; IR (KBr) cm^{-1}: 2938, 2808, 1763, 1708, 1469, 1383, 1240. Anal. calcd. for $C_{27}H_{27}N_3O_4$ HCl H_2O (512.00): C, 63.34; H, 5.91; N, 8.21. Found: C, 63.14; H, 5.72; N, 8.00.

N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}2H-1,3-benzoxazine-2,4(3H)-dione ***10d***

Base: colorless solid; ^{1}H NMR δ: 2.56–2.68 (4H, m, 2xCH_2), 3.00–3.12 (4H, m, 2xCH_2), 3.56 (2H, s, CH_2-N_{pip}), 3.83 (3H, s, OCH_3), 5.19 (2H, s, CH_2-N_{imide}), 6.88–6.98 (4H, m, H-Ar), 7.22–7.43 (6H, m, H-Ar), 7.56–7.79 (1H, m, H-Ar), 8.09 (1H, dd, J = 7.6, 1.9 Hz, H-Ar, m, H-Ar); ESI-MS: *m/z* 458 $(MH)^+$; IR (KBr) cm^{-1}: 2936, 2820, 1759, 1699, 1472, 1346, 1240. Anal. calcd. for $C_{27}H_{27}N_3O_4$ 2HCl H_2O (548.46): C, 59.13; H, 5.70; N, 7.66. Found: C, 59.29; H, 5.77; N, 7.50.

N-[5-(1,2,3,4-Tetrahydroisoquinolin-2-yl)pentyl]phthalimide ***11a***

Base: pale yellow needles; ^{1}H NMR δ: 1.49–1.96 (6H, cluster, 3xCH_2), 2.54 (2H, t, J = 7.3 Hz, CH_2-N_{THIQ}), 2.72–2.91 (4H, m, 2xCH_2), 3.64 (2H, s, CH_2), 3.70 (2H, t, J = 6.9 Hz, CH_2-N_{imide}), 6.95–7.15 (4H, m, H-Ar), 7.63–7.80 (2H, m, H-Ar), 7.84–7.90 (2H, m, H-Ar); ESI-MS: *m/z* 349 $(MH)^+$; IR (KBr) cm^{-1}: 2929, 2815, 1768, 1714, 1394. Anal. calcd. for $C_{22}H_{24}N_2O_2$ HCl (384.90): C, 68.65; H, 6.55; N, 7.28. Found: C, 68.69; H, 6.68; N, 7.10.

N-[6-(1,2,3,4-Tetrahydroisoquinolin-2-yl)hexyl]phthalimide ***11b***

Base: pale yellow oil; ^{1}H NMR δ: 1.45–1.81 (8H, cluster, 4xCH_2), 2.49 (2H, t, J = 7.4 Hz, CH_2-N_{THIQ}), 2.70–2.90 (4H, m, 2xCH_2), 3.60 (2H, s, CH_2), 3.69 (2H, t, J = 6.9 Hz, CH_2-N_{imide}), 7.00–7.12 (4H, m, H-Ar), 7.63–7.79 (2H, m, H-Ar), 7.84–7.91 (2H, m, H-Ar); ESI-MS: *m/z* 363 $(MH)^+$; IR (KBr) cm^{-1}: 2933, 2812, 1766, 1715, 1384. Anal. calcd. for $C_{23}H_{26}N_2O_2$ HCl 0.5H_2O (407.94): C, 67.72; H, 6.92; N, 6.87. Found: C, 67.58; H, 6.99; N, 7.02.

N-{3-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]benzyl}phthalimide ***11c***

Base: pale yellow plates; ^{1}H NMR ($CDCl_3$) δ: 2.70–2.88 (4H, m, 2xCH_2), 3.62 (2H, s, CH_2), 3.66 (2H, s, CH_2-N_{THIQ}), 4.85 (2H, s, CH_2-N_{imide}), 7.05–7.12 (4H, m, H-Ar), 7.30–7.34 (3H, m, H-Ar), 7.44 (1H, s, H-Ar), 7.72–7.79 (2H, m, H-Ar), 7.87–7.92 (2H, m, H-Ar); ESI-MS: *m/z* 383 $(MH)^+$; IR (KBr) cm^{-1}: 2951, 2804, 1768, 1714, 1393. Anal. calcd. for $C_{25}H_{22}N_2O_2$ HCl (418.92): C, 71.68; H, 5.53; N, 6.69. Found: C, 71.53; H, 5.72; N, 6.76.

N-{4-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]benzyl}phthalimide ***11d***

Base: colorless needles; ^{1}H NMR ($CDCl_3$) δ: 2.71–2.93 (4H, m, 2xCH_2), 3.61 (2H, s, CH_2), 3.64 (2H, s, CH_2-N_{THIQ}), 4.84 (2H, s, CH_2-N_{imide}), 7.01–7.11 (4H, m, H-Ar), 7.36–7.39 (4H, m, H-Ar), 7.44 (1H, s, H-Ar), 7.68–7.78 (2H, m, H-Ar), 7.86–7.92 (2H, m, H-Ar); ESI-MS: *m/z* 383 $(MH)^+$; IR (KBr) cm^{-1}: 2897, 2805, 1773, 1710, 1395. Anal. calcd. for $C_{25}H_{22}N_2O_2$ HCl H_2O (436.93): C, 68.72; H, 5.77; N, 6.41. Found: C, 68.58; H, 5.55; N, 6.60.

N-[5-(1,2,3,4-Tetrahydroisoquinolin-2-yl)pentyl]2H-1,3-benzoxazine-2,4(3H)-dione ***12a***

Base: colorless solid; ^{1}H NMR ($CDCl_3$) δ: 1.47–1.79 (6H, cluster, 3xCH_2), 2.52 (2H, t, J = 7.3 Hz, CH_2-N_{THIQ}), 2.71–2.89 (4H, m, 2xCH_2), 3.61 (2H, s, CH_2), 4.06 (2H, t, J = 7.6 Hz, CH_2-N_{imide}), 7.02–7.10 (4H, m, H-Ar), 7.21–7.46 (2H, m, H-Ar), 7.60–7.81 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.6, 1.8 Hz, H-Ar); ESI-MS: *m/z* 365 $(MH)^+$; IR (KBr) cm^{-1}: 2941, 2860, 1756, 1690, 1470, 1360. Anal. calcd. for $C_{22}H_{24}N_2O_3$ HCl (400.90): C, 65.91; H, 6.29; N, 6.99. Found: C, 65.80; H, 6.12; N, 7.23.

N-[6-(1,2,3,4-Tetrahydroisoquinolin-2-yl)hexyl]2H-1,3-benzoxazine-2,4(3H)-dione **12b**

Base: colorless plates; ^{1}H NMR ($CDCl_3$) δ: 1.45–1.79 (8H, cluster, 4xCH_2), 2.51 (2H, t, J = 7.4 Hz, CH_2-N_{THIQ}), 2.71–2.89 (4H, m, 2xCH_2), 3.61 (2H, s, CH_2), 4.04 (2H, t, J = 7.6 Hz, CH_2-N_{imide}), 7.03–7.12 (4H, m, H-Ar), 7.21–7.46 (2H, m, H-Ar), 7.60–7.81 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.6, 1.8 Hz, H-Ar); ESI-MS: *m/z* 379 $(MH)^+$; IR (KBr) cm^{-1}: 2934, 2859, 1758, 1689, 1470, 1361. Anal. calcd. for $C_{23}H_{26}N_2O_3$ HCl (414.17): C, 66.58; H, 6.56; N, 6.75. Found: C, 66.77; H, 6.40; N, 6.61.

N-{3-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]benzyl}2H-1,3-benzoxazine-2,4(3H)-dione **12c**

Base: colorless solid; ^{1}H NMR ($CDCl_3$) δ: 2.73–2.88 (4H, m, 2xCH_2), 3.63 (2H, s, CH_2), 3.67 (2H, s, CH_2-N_{THIQ}), 5.21 (2H, s, CH_2-N_{imide}), 7.01–7.12 (4H, m, H-Ar), 7.26–7.53 (6H, m, H-Ar), 7.59–7.81 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.8, 1.9 Hz, H-Ar); ESI-MS: *m/z* 399 $(MH)^+$; IR (KBr) cm^{-1}: 2912, 2804, 1747, 1698, 1469, 1387, 1343. Anal. calcd. for $C_{25}H_{22}N_2O_3$ HCl (434.91): C, 69.04; H, 5.33; N, 6.44. Found: C, 68.98; H, 5.51; N, 6.34.

N-{4-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]benzyl}2H-1,3-benzoxazine-2,4(3H)-dione **12d**

Base: pale yellow solid; ^{1}H NMR ($CDCl_3$) δ: 2.71–2.92 (4H, m, 2xCH_2), 3.61 (2H, s, CH_2), 3.65 (2H, s, CH_2-N_{THIQ}), 5.20 (2H, s, CH_2-N_{imide}), 7.00–7.11 (4H, m, H-Ar), 7.21–7.48 (6H, m, H-Ar), 7.59–7.80 (1H, m, H-Ar), 8.07 (1H, dd, J = 7.6, 1.9 Hz, H-Ar); ESI-MS: *m/z* 399 $(MH)^+$; IR (KBr) cm^{-1}: 2900, 2804, 1756, 1698, 1467, 1390, 1348. Anal. calcd. for $C_{25}H_{22}N_2O_3$ HCl 0.5H_2O (443.92): C, 67.64; H, 5.45; N, 6.31. Found: C, 67.69; H, 5.60; N, 6.21.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}toluene **13c**

Base: colorless plates; ^{1}H NMR δ: 2.35 (3H, s, CH_3), 2.59–2.71 (4H, m, 2xCH_2), 3.04–3.16 (4H, m, 2xCH_2), 3.54 (2H, s, CH_2-N_{pip}), 3.84 (3H, s, OCH_3), 6.89–6.98 (4H, m, H-Ar), 7.11–7.24 (4H, m, H-Ar); ESI-MS: *m/z* 297 $(MH)^+$; IR (KBr) cm^{-1}: 2933, 2804, 1490, 1240. Anal. calcd. for $C_{19}H_{24}N_2O$ HCl (332.87): C, 68.56; H, 7.57; N, 8.42. Found: C, 68.60; H, 7.49; N, 8.52.

4-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}toluene **13d**

Base: colorless needles; ^{1}H NMR δ: 2.34 (3H, s, CH_3), 2.58–2.70 (4H, m, 2xCH_2), 3.03–3.15 (4H, m, 2xCH_2), 3.54 (2H, s, CH_2-N_{pip}), 3.85 (3H, s, OCH_3), 6.89–6.98 (4H, m, H-Ar), 7.07–7.31 (4H, m, H-Ar); ESI-MS: *m/z* 297 $(MH)^+$; IR (KBr) cm^{-1}: 2936, 2811, 1500, 1454, 1236. Anal. calcd. for $C_{19}H_{24}N_2O$ HCl 0.5H_2O (341.88): C, 66.75; H, 7.67; N, 8.19. Found: C, 66.81; H, 7.89; N, 8.01.

3-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]toluene **14c**

Base: pale yellow oil; ^{1}H NMR δ: 2.35 (3H, s, CH_3), 2.69–2.96 (4H, m, 2xCH_2), 3.64 (4H, s, CH_2 + CH_2-N_{THIQ}), 7.03–7.26 (8H, m, H-Ar); ESI-MS: *m/z* 238 $(MH)^+$; IR for hydrochloride (KBr) cm^{-1}: 3031, 2923, 2538, 2492, 2427, 1454. Anal. calcd. for $C_{17}H_{19}N$ HCl (273.80): C, 74.57; H, 7.36; N, 5.12. Found: C, 74.59; H, 7.30; N, 4.91.

4-[(1,2,3,4-Tetrahydroisoquinolin-2-yl)methyl]toluene **14d**

Base: pale yellow oil; ^{1}H NMR δ: 2.35 (3H, s, CH_3), 2.66–2.95 (4H, m, 2xCH_2), 3.64 (4H, s, CH_2 + CH_2-N_{THIQ}), 7.02–7.34 (8H, m, H-Ar); ESI-MS: *m/z* 238 $(MH)^+$; IR for hydrochloride (KBr) cm^{-1}: 3029, 2922, 2540, 2492, 2415, 1454. Anal. calcd. for $C_{17}H_{19}N$ HCl (273.80): C, 74.57; H, 7.36; N, 5.12. Found: C, 74.50; H, 7.42; N, 5.20.

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