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SAR studies on new bis-aryls 5-HT$_7$ ligands: Synthesis and molecular modeling

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ABSTRACT

Structure–activity relationships of a series of bis-arylic compounds, investigated as 5-HT$_7$R ligands, are reported. The main structural modifications involved a central aryl moiety (phenyl, pyridine, diazine, triazine) and the nature and position of an amine-containing aliphatic chain. The affinity of the synthesized compounds (26 nM–10 μM) was systematically correlated with other previously reported series of bis-arylic ligands and rationalized by a ligand-based pharmacophore approach.

1. Introduction

Due to serotonin's multiple implications in many physiological processes in both the CNS and at periphery,[1] the discovery of potent and selective serotoninergic ligands keeps motivating the scientific community. Since the crystal structure of its receptors is still unresolved, many of the newly discovered serotoninergic hits were identified via a high-throughput screening (HTS) approach. Subsequently, these hits were improved in terms of their biological properties by various structural modifications. Identification of the essential chemical features of ligands, indispensable to their biological activity seems of crucial importance, as it allows a rational design of future derivatives. One of the most straightforward methods consists in conducting different simplifications on more complex, biologically active, chemical structures. In the case of 5-HT$_7$ receptors, such simplifications led Rault and co-workers to discover the bis-aryl compound **3** (Fig. 1).[2] Using the same approach, we are presenting the design, synthesis and SAR studies of new bis-aryl 5-HT$_7$ receptor ligands.

One of the several methods for rationalizing SAR data, which has proven its efficacy in the case of transmembrane receptors, is the pharmacophore-based approach. This method helps to better understand ligand-protein interactions through the discovery of a common binding pattern (a pharmacophore model) of particular classes of ligands. In the case of 5-HT$_7$Rs, several pharmacophore models have been published,[3–8] and they are characterized by the presence of at least four pharmacophore features: a positive ion (PI, a basic nitrogen proven to interact with an Asp residue in the binding site), a hydrogen-bond acceptor (HBA, usually an oxygen or an aromatic nitrogen) and two hydrophobic regions (HYD, aromatic or aliphatic, specific to each reported model). Beside the PI feature (mandatory for all the monoamine-type neurotransmitters or ligands), it has to be stressed that all the previously 5-HT$_7$ validated models also included an HBA feature. However, a significant number of potent ligands do not have hydrogen-bond acceptor groups. Thus,

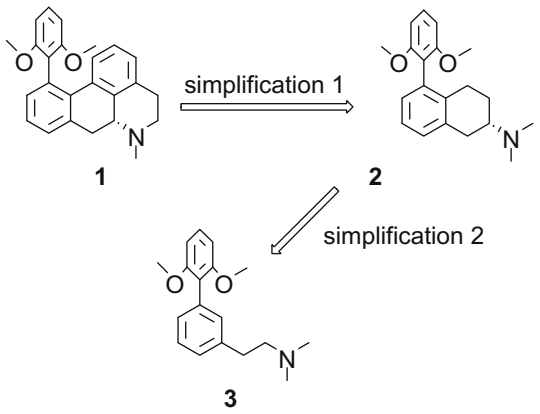

Figure 1. Rational simplifications of aporphine-based ligand **1** leading to discovery of bis-arylic ligand **3**.

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on the basis of a representative group of those ligands, we generated a pharmacophore model devoid of the HBA feature and used it for rationalizing the activity of newly synthesized bis-aryl derivatives. This model, complementary to the classical one, could give a more general insight into the binding within 5-HT_7Rs.

2. Results and discussion

2.1. Chemistry

The first series of compounds were designed on a pyridine scaffold. Starting from the commercially available 2,6-dibromopyridine, a first substitution step of one bromine with the corresponding aminoalkyl chain led to intermediates **4a** and **4b**. The resulting derivatives were subsequently engaged in a Suzuki-coupling reaction with various boronic acids to give the desired final compounds **4c**–**f** (Scheme 1).

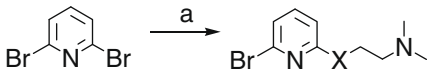
Other derivatives built on a triazine and diazine scaffold were subsequently synthesized. Using the triazine chemistry, we chose an S_NAr approach with a methylsulfonyl function as a leaving group and the desired aminoalkyl chain as a nucleophile.[9] Thus, 3-methylsulfanyl-1,2,4-triazine and 2-methylsulfanyl-1,3-diazine were arylated at positions C_5 and C_4, respectively, following protocols previously described in the literature.[10,11] The oxidation of thiomethyl moieties to the corresponding sulfones with *m*-CPBA in dichloromethane, and the subsequent substitution of methylsulfones with the aminoalkyl chains led to the desired final derivatives **5a**–**g** (Scheme 2).

Subsequent modulations involved different aryl substituents in the *ortho* position to the aliphatic chain. Following the previously described synthetic route, the desired compounds **8d**–**i** were obtained in two steps: alkylation of the corresponding bromothiophenol or bromophenol with 1-dimethylamino-2-chloroethane, and subsequent arylation of the halogenated substrate via a palladium-catalyzed cross coupling step (Scheme 3).

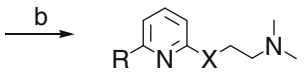
A last series of compounds were obtained starting with the previously synthesized methylsulfonyl diazine/triazine intermediates (described in Scheme 2). Those sulfones reacted with vinylmagnesium bromide under anhydrous conditions. The 1,4-addition of secondary amines to the resulting vinylhetaryl derivatives **9** proceeded smoothly at room temperature, and led to the desired derivatives **10a**–**d** in good yields (Scheme 4).

2.2. Biological evaluation and molecular modeling

Our studies into designing new compounds with 5-HT_7Rs properties started from a series of 8-azachromanes **11**, previously syn-

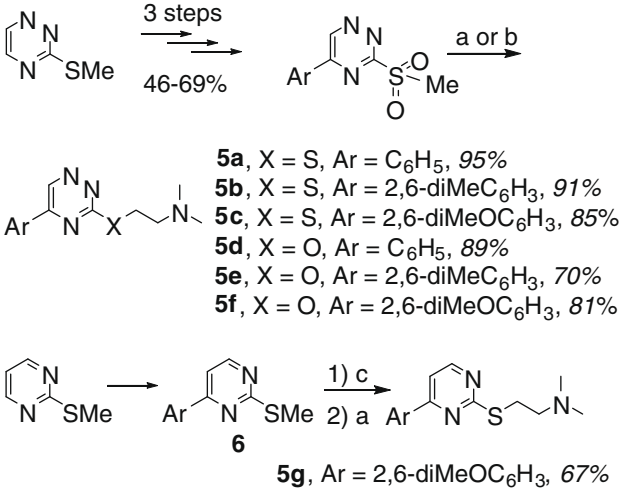


4a, X = S, *73%*
4b, X = O, *80%*



4c, X = S, R = 2,6-diMeC$_6$H$_3$, *75%*
4d, X = O, R = 2,6-diMeC$_6$H$_3$, *67%*
4e, X = S, R = 3-Furyl, *49%*
4f, X = S, R = C$_6$H$_5$, *89%*

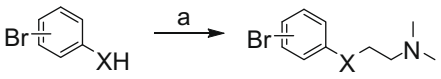
Scheme 1. Reagents and conditions: (a) dimethylaminoethanol/ethanethiol, NaH, THF, 12 h, 0–25 °C; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, satd $NaHCO_3$, toluene/EtOH, 12 h, 110 °C.



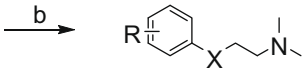
5a, X = S, Ar = C$_6$H$_5$, *95%*
5b, X = S, Ar = 2,6-diMeC$_6$H$_3$, *91%*
5c, X = S, Ar = 2,6-diMeOC$_6$H$_3$, *85%*
5d, X = O, Ar = C$_6$H$_5$, *89%*
5e, X = O, Ar = 2,6-diMeC$_6$H$_3$, *70%*
5f, X = O, Ar = 2,6-diMeOC$_6$H$_3$, *81%*

5g, Ar = 2,6-diMeOC$_6$H$_3$, *67%*

Scheme 2. Reagents and conditions: (a) dimethylaminoethanethiol, triethylamine, DCM, 12 h, 0 to 25 °C; (b) dimethylaminoethanol, NaH, THF, 1 h, 0–25 °C. (c) *m*-CPBA, DCM, 3 h, 0 to 25 °C, 85% (**7**).

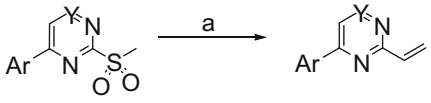


8a, 2-Br, X = S, *74%*
8b, 2-Br, X = O, *60%*
8c, 3-Br, X = S, *74%*

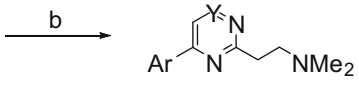


8d, X = S, R = 2-C$_6$H$_5$, *75%*
8e, X = O, R = 2-C$_6$H$_5$, *62%*
8f, X = O, R = 2-(2-MeOC$_6$H$_4$), *63%*
8g, X = S, R = 2-(2,6-diMeC$_6$H$_3$), *62%*
8h, X = S, R = 3-C$_6$H$_5$, *91%*
8i, X = S, R = 3-(2,6-diMeC$_6$H$_3$), *69%*

Scheme 3. Reagents and conditions: (a) 1-dimethylamino-2-chloroethane, NaOH, EtOH, H_2O, 3 h, 80 °C; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, satd $NaHCO_3$, toluene/EtOH, 12 h, 110 °C.



9a, Y = N, Ar = Ph *91%*
9b, Y = N, Ar = 2,6-diMeC$_6$H$_3$ *96%*
9c, Y = N, Ar = 2,6-diMeOC$_6$H$_3$ *96%*
9d, Y = CH, Ar = 2,6-diMeOC$_6$H$_3$ *96%*



10a, Y = N, Ar = Ph *67%*
10b, Y = N, Ar = 2,6-diMeC$_6$H$_3$ *79%*
10c, Y = N, Ar = 2,6-diMeOC$_6$H$_3$ *68%*
10d, Y = CH, Ar = 2,6-diMeOC$_6$H$_3$ *89%*

Scheme 4. Reagents and conditions: (a) vinylmagnesium bromide, THF, 30 min, −78 °C; (b) dimethylamine, MeOH, 1 h, 35 °C.

thesized in our laboratory.[12] Those molecules were developed as analogs of the potent 5-HT$_7$ receptor ligands **A** and **B** (Fig. 2), initially reported by Johansson,[13,14] yet with an aryl substituent in an unexplored position on the central scaffold. Unfortunately, 8-azachroman bioisosters **11** were found inactive at 5-HT$_7$ receptors (K_i >10,000 nM).

Apart from the similarity to the chromane-based 5-HT$_7$ ligands **A** and **B**,[13,14] the 8-azachromanes are also related to the potent 5-HT$_7$ agent **4f** described by Thomson et al. (Fig. 3).[15] For instance, in the particular case of compound **11a**, the difference in the 5-HT$_7$R affinity between these two compounds (**11a** and **4f**) could be explained by either (i) a more flexible structure allowing different positioning of the amine inside the protein binding site, or (ii) the heteroatom change in the *ortho* position to the aromatic nitrogen (O instead of S), or (iii) the di-*ortho*-methyl substituent on the aryl. To verify the two latter hypotheses, we synthesized the easily accessible derivatives **4c** and **4d**, as intuitively shown in the Figure 3.

The various compounds, synthesized according to Scheme 1, were tested in competition binding experiments, following the previously published procedures[16] (Table 1).

A direct comparison between compounds **4a**/**4b** or **4c**/**4d** shows a 70-fold and a 100-fold decrease in affinity, respectively, caused by the replacement of sulfur with oxygen. Therefore, the hydrophobic zone proves mandatory in this region of the molecule. The negative impact on binding caused by the presence of an oxygen atom may partly explain the decrease in the activity of our initial 8-azachroman derivatives **11**.

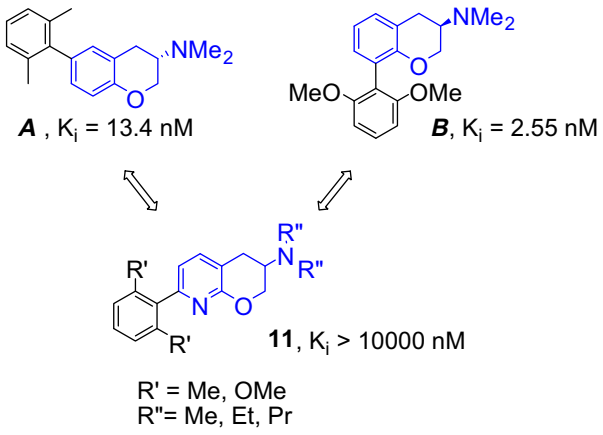


Figure 2. Similarity between our derivatives **11** and the previously reported 5-HT$_7$ ligands **A** and **B**.

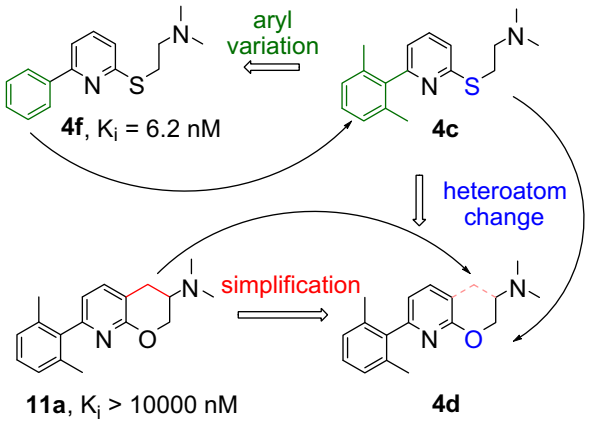
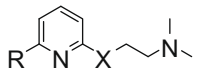


Figure 3. An intuitive design of the simplified oxygenated analog **4d**.

Table 1
Binding affinities for pyridinic analogs **4**



Compound	X	R	5-HT$_7$ K_i[a,b] (nM)	5-HT$_{1A}$ K_i[a,c] (nM)
4a	S	Br	37 (4.1[d])	133
4b	O	Br	2240	902
4c	S	2,6-diMeC$_6$H$_3$	128	927
4d	O	2,6-diMeC$_6$H$_3$	1614	7220
4e	S	3-Furyl	26	28
4f	S	C$_6$H$_5$	6.2 (0.6[d])	43

[a] Values are means of three experiments run in triplicate, SEM ⩽ 16%.
[b] Competition binding experiments for cloned human 5-HT$_7$ receptors (stably expressed in HEK-293 cells).
[c] Competition binding experiments for native serotonin 5-HT$_{1A}$ receptors (rat hippocampus).
[d] Values reported in the literature.[15]

In the sulfur series, the hypothesis about the enhanced selectivity profile over the 5-HT$_{1A}$Rs, induced by an increased torsion angle between the planes of the two aryl rings (a consequence of the disubstitution on the aryl substituent)—as stated earlier in the literature,[13] was verified. The selectivity ratio remains constant to a value of seven when passing from compound **4f** to compound **4c**, which suggests that these ligands bind differently compared to aporphine derivatives and their simplified chroman analogs. Finally, furyl proved to be a good substituent that could be accommodated in the 5-HT$_7$Rs binding site, most probably through a hydrophobic/aromatic interaction, like in the case of the phenyl substituent.

As initially remarked by Thomson,[15] the affinity for the 5-HT$_7$ receptors is extremely sensitive to the variation of the central scaffold. Since the nitrogen between *meta* substituents seemed essential for good affinity, we introduced supplementary nitrogen atoms in previously unexplored positions, and synthesized 1,3-diazine and 1,2,4-triazine analogs (see Scheme 2).

Unfortunately compounds **5a**–**g** were devoid of affinity for 5-HT$_7$Rs (K_i >10,000 nM), proving that additional nitrogens have a negative impact on the 5-HT$_7$ binding.

Then, starting with simplification of the rigid skeleton of Johansson's chroman **12** (Fig. 4), the importance of the heteroatom (S or O) in the *ortho* position to the aryl substituent on 5-HT$_7$R affinity was analyzed (Scheme 3, Table 2).

Following the same approach, the parent compound **12** was simplified to bis-aryls **10** (Fig. 5). Since Rault and co-workers had shown active derivatives in the carbocyclic series,[2] taking advantage of the availability of some previously synthesized intermediates, we explored the affinity profile of their heterocyclic analogs (Scheme 4, Table 3).

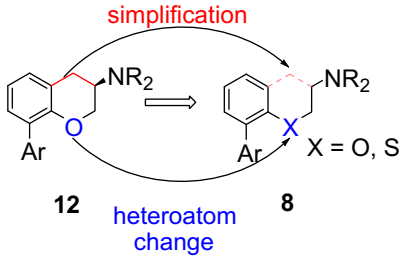
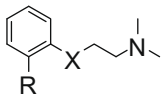


Figure 4. Design of the simplified bis-aryl structures **8** in correlation with the ligands of Johansson **12**.

Table 2
Binding affinities for compounds **8**



Compound	X	R	5-HT$_7$ K_i[a] (nM)
8a	S	Br	4110
8b	O	Br	2663
8d	S	C_6H_5	553
8e	O	C_6H_5	156
8f	O	2-MeOC_6H_4	669
8g	S	2,6-diMeC_6H_3	1429

[a] See Table 1 for details.

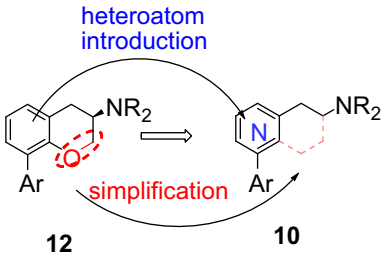
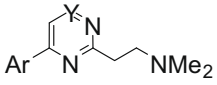


Figure 5. Design of the simplified heteroaromatic bis-aryls in correlation with the ligands of Johansson[13] and Rault.[2]

Table 3
Binding affinities for compounds **10**



Compound	Y	R	5-HT$_7$ K_i[a] (nM)
10a	N	C_6H_5	>10,000
10b	N	2,6-diMeC_6H_3	>10,000
10c	N	2,6-diMeOC_6H_3	>10,000
10d	CH	2,6-diMOeC_6H_3	1485

[a] See Table 1 for details.

The above-mentioned compounds were synthesized following the steps described in Schemes 3 and 4 and were tested for their affinity for the 5-HT$_7$ receptors (Tables 2 and 3).

Interestingly, unlike S over O preference in the case of *meta*-substituted compounds (see Table 1), for the *ortho* derivatives the affinity of the oxygenated compounds was higher than that of their sulfur analogs (see couples **8a**/**8b** or **8d**/**8e**, Table 2). Unexpectedly, the affinity of the simplified structures **8e** and **8f** decreased dramatically (approx. 100-fold) compared to the data published for the reference ligands.[13] Furthermore, the poly-nitrogenated compounds **10a**–**d** showed a strong decrease in their activity.

Taking account of all the affinity results and the data reported in the literature, at this stage of our study we decided to develop a pharmacophore model to rationalize the structure–activity relationships.

One of the most important steps in designing a ligand-based pharmacophore model is the choice of compounds for the 'training set'. The vast majority of derivatives with 5-HT$_7$ activity described in the literature[17,18] include oxygen or aromatic nitrogen atoms that could act as potential HBA features. However, as already mentioned in the Section 1, there are also potent ligands devoid of this pharmacophore feature. Consequently, we selected a representative training set from among three classes of 5-HT$_7$ agents (Fig. 6).

3D conformations for the input ligands, generated via a stochastic research coupled to a polling method as implemented in Discovery Studio[19] (the '*Best*' generation routine), were used in the 'Common Feature Pharmacophore Generation' protocol in order to construct different pharmacophore hypotheses. At least one of the following features was imposed during the pharmacophore search: Hydrophobic (HYD), Hydrophobic aromatic (HYD_Ar), Hydrophobic alifatic (HYD_alif) and Positive ionisable (PI). The top 10 ranked pharmacophores (energy threshold = 20 Kcal, inter-site distance = 2.0 Å) were subjected to a careful analysis in order to comply with the SAR data described in the literature. For example, particular attention was devoted to the fitting of one aromatic *methyl* substituent of compound **16** to the HYD feature; the hypothesis that led to the fitting of the *aromatic ring* substituent to the HYD area was rejected, since the phenyl analog of **16** was reported by Johansson to be inactive.[14] On the basis of internal fitting scores (see Table 4 for details), we selected the hypothesis (Hyp1) shown in Figure 7A.

A similar hypothesis (Hyp2) was generated with compound **19** excluded from the training set. Because of differences in the 3D arrangement of the selected features, both hypotheses were further used during our study. Matrix distances between the chemical features are represented in Table 5.

Since the new compounds are related to those from the training set, they often fit well into the model, showing good scoring values. That phenomenon was observed, for example, for 8-azachroman derivatives, (Fig. 8A), and for disubstituted phenyl triazine or diazine derivatives (**5b**, **5c**, **5e**, **5f**, **5g**). However, the latter derivatives

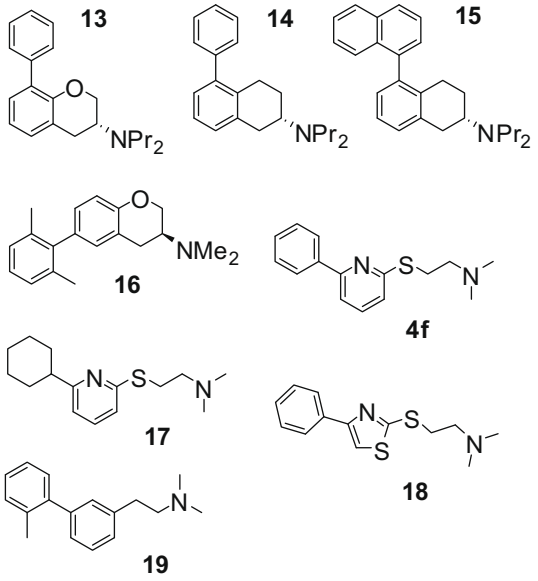


Figure 6. Compounds selected for the training set.

Table 4
Affinities and fitting scores for the training set

Compound	K_i (5-HT$_7$)	FitValue (Hyp1)	FitValue (Hyp2)
13	3.38	3.94	3.13
14	2.91	3.99	3.13
15	0.3	3.89	2.84
16	13.4	3.80	3.38
4f	0.6	3.55	3.91
17	0.7	3.51	3.31
18	12.0	3.41	3.99
19	7.6	2.28	–

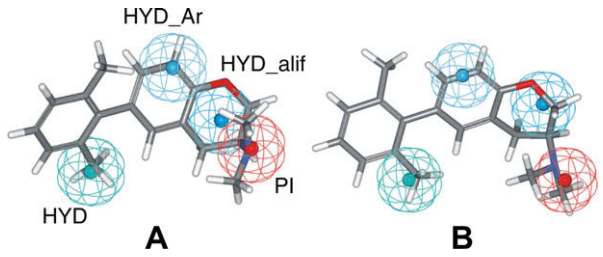


Figure 7. Compound **16** fitted to the selected hypotheses Hyp1 (**A**) and Hyp2 (**B**).

Table 5
Matrix distances for the selected hypothesis: Hyp1 and Hyp2

Distances	PI	HYD	HYD_Ar	HYD_Alif
PI	–	6.65[a]	4.58[a]	2.57[a]
HYD	6.67[b]	–	5.39[a]	5.71[a]
HYD_Ar	6.25[b]	4.99[b]	–	3.23[a]
HYD_Alif	3.46[b]	6.74[b]	3.89[b]	–

[a] values obtained for Hyp1
[b] Values obtained for Hyp2

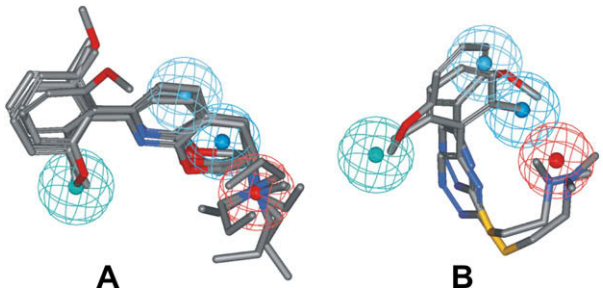


Figure 8. The mapping of the inactive 8-azachromans (**A**) and triazines **5b** and **5c** (**B**) using hypothesis Hyp1.

were mapped differently (Fig. 8B), because the central polynitrogen ring cannot be accommodated to an HYD_Ar feature.

Since both 8-azachromans and triazine analogs were found to be experimentally inactive, further tuning of the models was necessary.

The previously obtained pharmacophores were therefore submitted to a 'Steric Refinement with Excluded Volumes' step, using as inactive compounds our pyrano-pyridine derivatives and triazines (**5b** and **5c**), as well as ligands **20** and **21** previously reported by Thomson (Fig. 9). Default parameters, as implemented under DS v2.1,[19] were used. Of the two optimized models, Hyp2 with 16 excluded volumes was able to correctly discriminate between active and inactive derivatives. In consequence, Hyp2 was the only model used for the rest of our study.

New derivatives were designed in order to validate the newly defined pharmacophore. As appears from the model analysis, the central pyridine could be replaced with a phenyl moiety (Fig. 10), thus compounds **8c**, **8h** and **8i** were subsequently synthesized (see Scheme 3, vide supra) and biologically evaluated (Table 6). The 5-HT$_7$ affinity of the new derivatives was well correlated with the obtained fit values (2.46, 3.32 and 3.13 for **8c**, **8h** and **8i**,

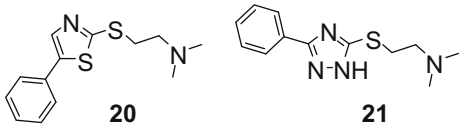


Figure 9. Thomson's derivatives included in the inactive set.[15]

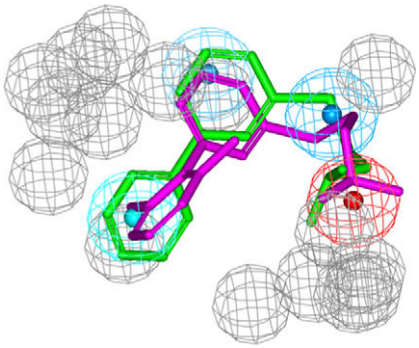
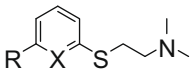


Figure 10. The mapping of compounds **8h** (green) and **8i** (magenta) with the pharmacophore. Hydrogen atoms were omitted for clarity

Table 6
Binding affinities for compounds **11a–c**



Compound	X	R	5-HT$_7$ K_i[a] (nM)	5-HT$_{1A}$ K_i[a] (nM)
4a	N	Br	37	133
4f	N	C_6H_5	6.2	43
8c	CH	Br	511	676
8h	CH	C_6H_5	116	516
8i	CH	2,6-diMeC_6H_3	284	2350

[a] See Table 1 for details.

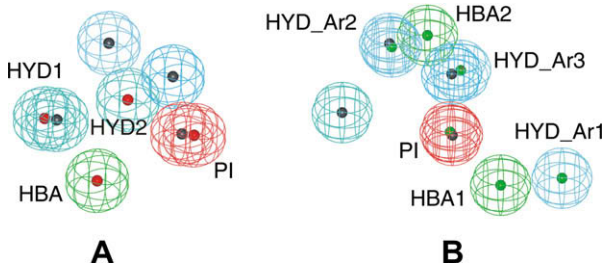


Figure 11. The superposition of the new pharmacophore model (gray centers) over Rault's[7] (**A**, red centers) and Kolaczkowski's[8] (**B**, green centers) models.

respectively). As can be seen in Figure 10, steric restrictions are located in the vicinity of PI and outside HYD and HYD_Ar features.

Finally, the new pharmacophore model was compared with two others, previously reported by Rault and Kolaczkowski (which were regenerated following the same protocols as originally described). In the first case (Fig. 11A), HYD1 and PI features are overlapping, while the other two hydrophobic regions of the new hypothesis are well differentiated from Rault's HYD2 feature. Interestingly, these two hydrophobic regions and the PI feature are very well superposed on similar features from the receptor-based pharmacophore model proposed by Kolaczkowski (Fig. 11B). However, our third HYD feature has a different spatial arrangement.

3. Conclusions

The present study describes interesting SAR data of new 5-HT$_7$ ligands built on a bis-arylic structure. Their biological properties were systematically correlated with the activity of other classes of ligands already described in the literature. A new pharmacophore model was generated in order to identify a common binding pattern for the synthesized compounds. This model devoid of the

HBA feature was designed complementarily to the previously reported 5-HT_7 pharmacophores and should give a more general insight into the interaction between the 5-HT_7Rs and its ligands.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (250.131 MHz) and a Bruker Avance II (400 MHz), in $CDCl_3$ and using tetramethylsilane as internal standard, multiplicities were determined by the DEPT 135 sequence, chemical shifts (δ) were reported in parts per million (ppm). Coupling constants were reported in units of hertz (Hz) if applicable. Infrared (IR) spectra were recorded on Perkin–Elmer Paragon 1000 PC FTIR using NaCl films or KBr pellets, and on a ATR Nicolet iS10 equipped with a diamond crystal (ATR-D). Low-resolution mass spectra (MS) were recorded on a Perkin–Elmer SCIEX AOI 300 spectrometer. High-resolution mass spectra were recorded on a Q-Tof micro Waters spectrometer. Melting points were determined in open capillary tubes and are uncorrected. 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 and, if necessary, an ethanolic solution of potassium permanganate. Reactions requiring anhydrous conditions were performed under nitrogen. Toluene and tetrahydrofuran were freshly distilled from sodium/benzophenone under argon prior to use. Dichloromethane was distilled from calcium hydride under argon prior to use.

4.2. General procedure employed for the synthesis of compounds 4a–b

Under nitrogen atmosphere, sodium hydride (10.13 mmol) was added at 0 °C to a solution of dimethylaminoetanol or dimethylaminoetanthiol (9.29 mmol) in anhydrous tetrahydrofuran (25 mL). After 30 min of steering at 0 °C, 2,6-dibromopyridine (8.44 mmol) dissolved in anhydrous tetrahydrofurane (5 mL) was added, and the mixture was allowed to return to room temperature and continued stirring until the complete consumption of the starting material. Then, the reaction was quenched by slowly adding water (35 mL). Subsequently, the aqueous layer was separated and extracted with ethyl acetate (3 × 30 mL), the combined organic layers ware dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired compounds.

4.2.1. 2-(6-Bromopyridin-2-ylthio)-*N*,*N*-dimethylethanamine (4a)

$C_9H_{13}N_2SBr$; Yield 69%; colorless oil; IR (ATR-D) cm^{-1} 2940, 2770, 1567, 1537, 1408, 1156, 1114, 769. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.28 (s, 6H), 2.58 (t, 2H, *J* = 7.2 Hz), 3.25 (t, 2H, *J* = 7.2 Hz), 7.08 (ta, 2H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.6 Hz). ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 28.0 (CH_2), 45.4 (CH_3), 58.5 (CH_2), 120.9 (CH), 123.0 (CH), 137.9 (CH), 141.6 (C), 160.3 (C). MS *m*/*z* = 216.0 [M-NMe_2] for ^{79}Br, 218.0 [M−NMe_2] for ^{81}Br, 261.0 $[M+H]^+$ for ^{79}Br, 263.0 $[M+H]^+$ for ^{81}Br.

4.2.2. 2-(6-Bromopyridin-2-yloxy)-*N*,*N*-dimethylethan-amine (4b)

$C_9H_{13}N_2OBr$; Yield 80%; colorless oil; IR (ATR-D) cm^{-1} 2945, 1585, 1553, 1433, 1402, 1295, 1156, 784. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.27 (s, 6H), 2.63 (t, 2H, *J* = 5.5 Hz), 4.34 (t, 2H, *J* = 5.5 Hz), 6.68 (d, 1H, *J* = 7.8 Hz), 6.98 (d, 1H, *J* = 7.8 Hz), 7.35 (t, 1H, *J* = 7.8 Hz). ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 45.8 (CH_3), 58.2 (CH_2), 64.3 (CH_2), 109.9 (2CH), 120.3 (2CH), 138.4 (C), 140.4 (CH), 163.4 (C). MS *m*/*z* = 245 $[M+H]^+$ for ^{79}Br, 247 $[M+H]^+$ for ^{81}Br.

4.3. General procedure employed for the Suzuki palladium coupling reaction

To a solution of the corresponding bromide (0.77 mmol) in toluene (12 mL) were added the appropriate boronic acid (0.92 mmol), ethanol (6 mL) and satd $NaHCO_3$ (4 mL). The mixture was degassed and flushed with nitrogen several times before adding palladium tetrakis(triphenylphosphine) (0.08 mmol) in one portion. The mixture was degassed one more time and then refluxed under nitrogen atmosphere for 20 h. The organic solvent was removed, the residue hydrolyzed with water (15 mL) and the aqueous phase extracted with DCM (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, the solvent evaporated and the crude product purified by flash chromatography (petroleum ether/ethyl acetate 7/3) to give the desired coupling derivatives **4c–f**.

4.3.1. 2-(6-(2,6-Dimethylphenyl)pyridin-2-ylthio)-*N*,*N*-dimethylethanamine (4c)

$C_{17}H_{22}N_2S$; yield 75%; light-yellow oil; IR (ATR-D) cm^{-1} 2914, 2770, 1571, 1556, 1439, 1416, 1154, 1139, 1046, 798; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.08 (s, 6H), 2.23 (s, 6H), 2.59 (t, 2H, *J* = 7.2 Hz), 3.28 (t, 2H, *J* = 7.2 Hz), 6.89 (d, 1H, *J* = 7.4 Hz), 7.09 (d, 2H, *J* = 7.5 Hz), 7.14 (d, 1H, *J* = 7.4 Hz), 7.18 (dd, 1H, *J* = 7.5 Hz, *J* = 8.2 Hz), 7.52 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 20.4 (CH), 27.7 (CH_2), 45.4 (CH), 58.9 (CH_2), 120.2 (CH), 120.3 (CH), 127.5 (2CH), 127.8 (CH), 135.9 (C), 136.1 (CH), 140.6 (C), 158.4 (C), 159.6 (C); MS *m*/*z* = 287.5 $[M+H]^+$; HRMS calculated for $C_{17}H_{22}N_2S$ 287.1582, found 287.1575.

4.3.2. 2-(6-(2,6-Dimethylphenyl)pyridin-2-yloxy)-*N*,*N*-dimethylethanamine (4d)

$C_{17}H_{22}N_2O$; yield 67%; light-yellow oil; IR (ATR-D): cm^{-1} 2946, 2767, 1588, 1571, 1446, 1309, 1239, 1026, 805, 769; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.09 (s, 6H), 2.32 (s, 6H), 2.69 (t, 2H, *J* = 5.6 Hz), 4.40 (t, 2H, *J* = 5.6 Hz), 6.76 (t, 2H, *J* = 7.3 Hz), 7.10 (m, 2H) , 7.18 (dd, 1H, *J* = 6.0 Hz, *J* = 8.8 Hz), 7.61 (dd, 1H, *J* = 7.3 Hz, *J* = 8.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.4 (CH), 45.9 (CH), 58.5 (CH_2), 63.7 (CH_2), 109.2 (CH), 117.4 (CH), 127.6 (2CH), 127.7 (CH), 136.0 (C), 138.6 (CH), 140.6 (C), 157.1 (C), 163.6 (C); MS *m*/*z* = 271.0 $[M+H]^+$; HRMS calculated for $C_{17}H_{22}N_2O$ 271.1810, found 271.1795.

4.3.3. 2-(6-(Furan-3-yl)pyridin-2-yloxy)-*N*,*N*-dimethyl-ethanamine (4e)

$C_{13}H_{16}N_2OS$; yield 49%; yellow oil; IR (ATR-D): cm^{-1} 2970, 2769, 1556, 1433, 1158, 1139, 1061, 1009, 781; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.23 (s, 6H), 2.68 (t, 2H), 3.37 (t, 2H), 6.87–6.88 (m, 1H), 7.03 (d, 1H, *J* = 7.8 Hz), 7.12 (d, 1H, *J* = 7.8 Hz), 7.45 (t, 1H, *J* = 7.8 Hz), 7.47–7.48 (m, 1H), 8.02 (s, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 27.6 (CH_2), 45.5 (CH), 59.1 (CH_2), 108.7 (CH), 115.4 (CH), 120.4 (CH), 127.2 (C), 136.5 (CH), 141.5 (CH), 143.9 (CH), 151.5 (C), 158.5 (C); MS *m*/*z* = 249.0 $[M+H]^+$; HRMS calculated for $C_{13}H_{16}N_2OS$ 249.1062, found 249.1056.

4.3.4. 2-(6-Phenylpyridin-2-ylthio)-*N*,*N*-dimethylethan-amine (4f)

$C_{15}H_{18}N_2S$; Yield 89%; colorless oil; IR (ATR-D): cm^{-1} 2939, 2767, 1557, 1427, 1140, 755, 691. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.33 (s, 6H), 2.71 (t, 2H, *J* = 7.3 Hz), 3.44 (t, 2H, *J* = 7.3 Hz), 7.12 (dd, 1H, *J* = 0.9 Hz, *J* = 7.7 Hz), 7.40–7.56 (m, 5H), 8.03–8.07 (m, 2H). ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 27.7 (CH_2), 45.6 (CH_3), 59.1 (CH_2), 115.8 (CH), 120.8 (CH), 126.8 (2CH), 128.8 (2CH), 129.2 (CH), 136.7 (CH), 139.1 (C), 156.7 (C), 158.5 (CH). MS *m*/*z* = 214.0 $[M-NMe_2]^+$, 259.0 $[M+H]^+$.

4.4. General protocol used for the synthesis of compounds 5a–c and 5g

To a solution of the corresponding arylsulfone (0.85 mmol) in dichloromethane (4 mL) were successively added dimethylaminoethanthiol (0.144 g, 1.02 mmol) and triethylamine (0.48 mL, 3.40 mmol). After stirring the mixture for 1 h at room temperature, the reaction was quenched by addition of a solution of sodium bicarbonate (10%, 15 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent evaporated and the crude product purified by flash chromatography (dichloromethane/methanol 95/5) to give the derivatives **5a–c** or **5g**.

4.4.1. *N,N*-Dimethyl-2-(5-phenyl-1,2,4-triazin-3-ylthio)-ethanamine (5a)

$C_{13}H_{16}N_4S$; yield 95%; dark-yellow oil; IR (NaCl): cm^{-1} 2946, 2774, 1536, 1502, 1134; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.25 (s, 6H), 2.66 (t, 2H, J = 7.2 Hz), 3.35 (t, 2H, J = 7.2 Hz), 7.39–7.52 (m, 3H), 8.02–8.06 (m, 2H), 9.27 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 28.4 (CH_2), 45.2 (CH), 58.0 (CH_2), 127.4 (2CH), 129.2 (2CH), 132.5 (CH), 132.9 (C), 141.8 (CH), 154.3 (C), 173.2 (C); MS m/z = 260.5 $[M+H]^+$.

4.4.2. 2-(5-(2,6-Dimethylphenyl)-1,2,4-triazin-3-ylthio)-*N,N*-dimethylethanamine (5b)

$C_{15}H_{20}N_4S$; yield 91%; light-yellow oil; IR (NaCl): cm^{-1} 2950, 2820, 1531, 1486, 1237, 1127; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.13 (s, 6H), 2.32 (s, 6H), 2.74 (t, 2H, J = 7.1 Hz), 3.43 (t, 2H, J = 7.1 Hz), 7.14 (d, 2H, J = 7.6 Hz), 7.28 (dd, 1H, J = 6.8 Hz, J = 8.3 Hz), 8.87 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.2 (CH), 28.6 (CH_2), 45.3 (CH), 58.0 (CH_2), 128.2 (2CH), 129.7 (CH), 133.9 (C), 135.7 (C), 146.4 (CH), 159.2 (C), 173.8 (C); MS m/z = 289.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{20}N_4S$ 289.1487, found 289.1487.

4.4.3. 2-(5-(2,6-Dimethoxyphenyl)-1,2,4-triazin-3-ylthio) *N,N*-dimethylethanamine (5c)

$C_{15}H_{20}N_4O_2S$; yield 85%; yellow solid; mp 73–75 °C; IR (KBr): cm^{-1} 2946, 2778, 1599, 1537, 1242, 1113, 754; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.28 (s, 6H), 2.71 (t, 2H, J = 7.2 Hz), 3.36 (t, 2H, J = 7.2 Hz), 3.73 (s, 6H), 6.61 (d, 2H, J = 8.4 Hz), 7.36 (t, 1H, J = 8.4 Hz), 8.86 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 28.5 (CH_2), 45.3 (CH), 56.0 (CH), 58.2 (CH_2), 104.2 (2CH), 112.7 (C), 132.3 (CH), 147.9 (CH), 155.1 (C), 158.3 (C), 173.0 (C); MS m/z = 321.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{20}N_4O_2S$ 321.1385, found 321.1379.

4.4.4. 2-(4-(2,6-Dimethoxyphenyl)pyrimidin-2-ylthio)-*N,N*-dimethylethanamine (5g)

$C_{16}H_{21}N_3O_2S$; yield 67%; colorless oil; IR (ATR-D): cm^{-1} 2939, 2772, 1592, 1559, 1533, 1471, 1332, 1250, 1200, 1108, 725; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.28 (s, 6H), 2.68 (t, 2H, J = 7.4 Hz), 3.25 (t, 2H, J = 7.4 Hz), 3.71 (s, 6H), 6.60 (d, 2H), 6.95 (d, 1H, J = 5.0 Hz), 7.31 (t, 1H, J = 8.4 Hz), 8.48 (d, 1H, J = 5.0 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 28.5 (CH_2), 45.3 (2CH), 56.0 (2CH), 58.7 (CH_2), 104.2 (2CH), 116.8 (C), 119.1 (CH), 130.7 (CH), 156.5 (CH), 157.9 (C), 163.1 (C), 171.4 (C); MS m/z = 320.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{21}N_3O_2S$ 320.1433, found 320.1427.

4.5. General procedure employed for the synthesis of compounds 5d–f

Under nitrogen atmosphere, sodium hydride (1.02 mmol) was added at 0 °C to a solution of dimethylaminoetanol (0.09 mL, 0.094 mmol) in anhydrous tetrahydrofuran (3 mL). After 30 min of steering at 0 °C, the corresponding triazine (0.85 mmol) dissolved in anhydrous tetrahydrofurane (3 mL) was added, and the mixture was allowed to return to room temperature and continued stirring until the complete consumption of the starting material. Then, the reaction was quenched by slowly adding sodium hydrogenocarbonate (10% aqueous solution, 15 mL). Subsequently, the aqueous layer was separated and extracted with dichloromethane (3 × 20 mL), the combined organic layers ware dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired compounds **5d–f**.

4.5.1. *N,N*-Dimethyl-2-(5-phenyl-1,2,4-triazin-3-yloxy)-ethanamine (5d)

$C_{13}H_{16}N_4O$; yield 89%; red oil; IR (NaCl): cm^{-1} 2972 et 2824, 1540, 1520, 1288, 768, 754; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.30 (s, 6H), 2.79 (t, 2H, J = 5.9 Hz), 4.65 (t, 2H, J = 5.9 Hz), 7.42–7.52 (m, 3H), 8.08–8.12 (m, 2H), 9.34 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 46.8 (CH), 57.7 (CH_2), 66.3 (CH_2), 127.8 (2CH), 129.2 (2CH), 132.6 (CH), 133.0 (C), 141.4 (CH), 157.8 (C), 165.3 (C); MS m/z = 244.5 $[M+H]^+$; HRMS calculated for $C_{13}H_{16}N_4O$ 245.1402, found 245.1402.

4.5.2. 2-(5-(2,6-Dimethylphenyl)-1,2,4-triazin-3-yloxy)-*N,N*-dimethylethanamine (5e)

$C_{15}H_{20}N_4O$; yield 70%; beige oil; IR (NaCl): cm^{-1} 2968, 2770, 1544, 1506, 1293, 775; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.12 (s, 6H), 2.37 (s, 6H), 2.85 (t, 2H, J = 5.8 Hz), 4.69 (t, 2H, J = 5.8 Hz), 7.14 (d, 2H, J = 7.6 Hz), 7.28 (dd, 1H, J = 6.8 Hz, J = 8.3 Hz), 8.91 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.2 (CH), 46.0 (CH), 57.8 (CH_2), 66.8 (CH_2), 128.1 (2CH), 129.7 (CH), 133.9 (C), 135.7 (C), 145.9 (CH), 162.4 (C), 165.4 (C); MS m/z = 273.0 $[M+H]^+$; HRMS calcd for $C_{15}H_{20}N_4O$ 273.1715, found 273.1709.

4.5.3. 2-(5-(2,6-Dimethoxyphenyl)-1,2,4-triazin-3-yloxy)-*N,N*-dimethylethanamine (5f)

$C_{15}H_{20}N_4O_3$; yield 81%; orange solid; mp 111–113 °C; IR (KBr): cm^{-1} 2950, 2774, 1599, 1514, 1255, 784, 746; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.32 (s, 6H), 2.81 (t, 2H, J = 5.9 Hz), 3.72 (s, 6H), 4.64 (t, 2H, J = 5.9 Hz), 6.60 (d, 2H, J = 8.4 Hz), 7.35 (t, 1H, J = 8.4 Hz), 8.89 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 46.0 (CH), 56.0 (2CH), 57.8 (CH_2), 66.5 (CH_2), 104.1 (2CH), 112.6 (C), 132.2 (CH), 147.4 (CH), 158.2 (C), 158.3 (C), 165.3 (C); MS m/z = 305.0 $[M+H]^+$; HRMS calcd for $C_{15}H_{20}N_4O_3$ 305.1614, found 305.1611.

4.6. 4-(2,6-Dimethoxyphenyl)-2-(methylthio)-pyrimidine (6)

$C_{13}H_{14}N_2O_2S$; yield 73%; yellow solid; mp 84–86 °C; IR (ATR-D): cm^{-1} 2929, 1590, 1560, 1530, 1420, 1320, 1250, 1208, 1106, 826; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.56 (s, 3H), 3.72 (s, 6H), 6.61 (d, 2H, J = 8.4 Hz), 6.97 (d, 1H, J = 5.1 Hz), 7.31 (t, 1H, J = 8.4 Hz), 8.51 (d, 1H, J = 5.1 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 14.3 (CH), 56.0 (2CH), 104.3 (2CH), 116.8 (C), 119.0 (CH), 130.7 (CH), 156.4 (CH), 157.9 (C), 163.1 (C), 172.1 (C); MS m/z = 263.0 $[M+H]^+$.

4.7. 4-(2,6-Dimethoxyphenyl)-2-(methylsulfonyl)-pyrimidine (7)

Under nitrogen atmosphere, *meta*-chloroperbenzoic acid (tech. 70–75%, 0.41 g, 1.68 mmol) was added at 0 °C to a solution of pyrimidine **6** (0.20 g, 0.76 mmol) in anhydrous dichloromethane (10 mL). After 1 h of reaction at room temperature, the suspension was filtered on a glass sintered funnel and the filtrate washed with satd $NaHCO_3$ and $Na_2S_2O_3$. The organic phase was then concen-

trated under *vacuum* and the obtained crude product purified by flash chromatography (petroleum ether/ethyl acetate 5/5) to conduct to the desired sulfone **7**. $C_{13}H_{14}N_2O_4S$; yield 85%; yellow solid; mp 159–161 °C; IR (ATR-D): cm^{-1} 2936, 1603, 1572, 1474, 1300, 1132, 1112, 780, 755; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 3.32 (s, 3H), 3.71 (s, 6H), 6.62 (d, 2H, J = 8.4 Hz), 7.36 (t, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 5.1 Hz), 8.85 (d, 1H, J = 5.1 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 39.3 (CH), 56.0 (2CH), 104.3 (2CH), 115.0 (C), 126.6 (CH), 131.9 (CH), 157.5 (CH), 157.9 (C), 164.8 (C), 165.5 (C); MS m/z = 295.0 $[M+H]^+$.

4.8. 2-(2-Bromophenylthio)-*N*,*N*-dimethylethanamine (8a)

To a solution of 2-bromothiophenol (3.00 g, 15.87 mmol) in ethanol (30 mL) were added sodium hydroxide (1.46 g, 36.50 mmol) and a solution of 2-chrolorethylamine chlorhydrate (2.29 g, 15.87 mmol) in ethanol (10 mL). The mixture was refluxed for 2 h, allowed to return to room temperature and then extracted with diethyl ether (3 × 30 mL). The organic phase was subsequently extracted with 2 N HCl (2 × 40 mL), the pH of the combined aqueous phases was adjusted at 9 with 4 N NaOH, and then the extracted with diethyl ether (2 × 100 mL). The recovered organic phases were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the derivative **8a**, which was used further without any supplementary purification. $C_{10}H_{14}BrNS$; yield 74%; colorless liquid; IR (ATR-D): cm^{-1} 2791, 2767, 1447, 1298, 1247, 1018, 741; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.29 (s, 6H), 2.61 (dd, 2H, J = 6.3 Hz, J = 8.4 Hz), 3.05 (dd, 2H, J = 6.3 Hz, J = 8.4 Hz), 7.01 (dt, 1H, J = 4.5 Hz, J = 4.5 Hz, J = 8.0 Hz), 7.26 (d, 2H, J = 4.5 Hz), 7.53 (d, 1H, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 31.0 (CH_2), 45.4 (2CH), 58.0 (CH_2), 123.5 (C), 126.5 (CH), 127.8 (2CH), 133.1 (CH), 138.2 (C); MS m/z = 260.0 $[M+H]^+$ for ^{79}Br, 262.0 $[M+H]^+$ for ^{81}Br; HRMS calcd for $C_{10}H_{14}BrNS$ 260.0109, found 260.0104.

4.9. 2-(2-Bromophenoxy)-*N*,*N*-dimethylethanamine (8b)

The compound **8b** was obtained following the same experimental procedure employed for the synthesis of compound **8a**. $C_{10}H_{14}BrNO$; yield 60%; colorless liquid; IR (ATR-D): cm^{-1} 2941, 2770, 1586, 1477, 1277, 1246, 1029, 745, 663; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.38 (s, 6H), 2.81 (t, 2H, J = 5.9 Hz), 4.13 (t, 2H, J = 5.9 Hz), 6.82 (td, 1H, J = 1.4 Hz, J = 7.8 Hz), 6.90 (dd, 1H, J = 1.2 Hz, J = 8.2 Hz), 7.21–7.28 (m, 1H), 7.53 (dd, 1H, J = 1.6 Hz, J = 7.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 46.4 (2CH), 58.1 (CH_2), 68.0 (CH_2), 112.4 (C), 113.4 (CH), 122.1 (CH), 128.5 (CH), 133.5 (CH), 155.4.2 (C); MS m/z = 244.0 $[M+H]^+$ for ^{79}Br, 246.0 $[M+H]^+$ for ^{81}Br.

4.10. 2-(3-Bromophenylthio)-*N*,*N*-dimethylethanamine (8c)

The compound **8c** was obtained following the same experimental procedure employed for the synthesis of compound **8a** $C_{10}H_{14}BrNS$; yield 74%; colorless oil; IR (ATR-D): cm^{-1} 2970, 2767, 1574, 1555, 1458, 1053, 753, 676; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.27 (s, 6H), 2.56 (t, 2H, J = 7.2 Hz), 3.03 (t, 2H, J = 7.2 Hz), 7.12 (t, 1H, J = 8.3 Hz), 7.26 (dd, 2H, J = 8.3 Hz, J = 10.1 Hz), 7.45 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 31.4 (CH_2), 45.4 (2CH), 58.4 (CH_2), 122.9 (C), 127.1 (CH), 128.8 (CH), 130.0 (CH), 131.0 (CH), 139.3 (C); MS m/z = 260.0 $[M+H]^+$ for ^{79}Br, 262.0 $[M+H]^+$ for ^{81}Br; HRMS calcd for $C_{10}H_{14}BrNS$ 260.0109, found 260.0102.

4.11. 2-(Biphenyl-2-ylthio)-*N*,*N*-dimethylethanamine (8d)

The compound **8d** was obtained following the Suzuki palladium coupling protocol used for the synthesis of derivative **4c**. $C_{16}H_{19}NS$; yield 75%; slightly green oil; IR (ATR-D): cm^{-1} 2963, 2768, 1460, 1258, 1039, 1008, 791, 746; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.21 (s, 6H), 2.45–2.49 (m, 2H), 2.85–2.89 (m, 2H), 7.24–7.44 (m, 9H); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 31.3 (CH_2), 45.4 (2CH), 58.5 (CH_2), 125.7 (CH), 127.5 (CH), 128.0 (CH), 128.2 (2CH), 129.5 (2CH), 130.5 (2CH), 135.3 (C), 140.8 (C), 142.5 (C); MS m/z = 213.0 $[M\text{-}NMe_2]^+$, 258.5 $[M+H]^+$; HRMS calcd for $C_{16}H_{19}NS$ 258.1316, found 258.1310.

4.12. 2-(Biphenyl-2-yloxy)-*N*,*N*-dimethylethanamine (8e)

The compound **8e** was obtained following the Suzuki palladium coupling protocol used for the synthesis of derivative **4c**. $C_{16}H_{19}NO$; yield 62%; beige oil; IR (ATR-D): cm^{-1} 2941, 2769, 1596, 1480, 1433, 1261, 1229, 1122, 1030, 751, 731, 697; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.27 (s, 6H), 2.69 (t, 2H, J = 6.0), 4.08 (t, 2H, J = 6.0 Hz), 7.0 (d, 1H, J = 7.0 Hz), 7.05 (td, 1H, J = 1.0 Hz, J = 7.5 Hz), 7.29–7.35 (m, 3H), 7.38–7.42 (m, 2H), 7.55–7.57 (m, 2H); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 46.1 (2CH), 58.2 (CH_2), 67.3 (CH_2), 113.0 (CH), 121.2 (CH), 126.9 (CH), 127.9 (2CH), 128.7 (CH), 129.7 (2CH), 131.0 (CH), 131.3 (C), 138.6 (C), 155.9 (C); MS m/z = 242.0 $[M+H]^+$; HRMS calcd for $C_{16}H_{19}NO$ 242.1545, found 242.1537.

4.13. 2-(2'-Methoxybiphenyl-2-yloxy)-*N*,*N*-dimethyl-ethan amine (8f)

The compound **8f** was obtained following the Suzuki palladium coupling protocol used for the synthesis of derivative **4c**. $C_{17}H_{21}NO_2$; yield 63%; greenish oil; IR (ATR-D): cm^{-1} 2939, 2769, 1593, 1503, 1445, 1259, 1233, 1110, 1028, 748; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 2.19 (s, 6H), 2.59 (t, 2H, J = 6.0 Hz), 3.75 (s, 3H), 4.05 (t, 2H, J = 6.0 Hz), 6.93–7.02 (m, 4H), 7.22–7.25 (m, 2H), 7.28–7.32 (m, 2H); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 46.0 (2CH), 55.6 (CH), 58.2 (CH_2), 67.3 (CH_2), 110.7 (CH), 112.7 (CH), 120.3 (CH), 120.8 (CH), 128.0 (C), 128.5 (C), 128.6 (CH), 128.7 (CH), 131.6 (CH), 131.7 (CH), 156.4 (C), 157.1 (C); MS m/z = 272.5 $[M+H]^+$; HRMS calcd for $C_{16}H_{19}NO_2$ 272.1651, found 272.1635.

4.14. 2-(Biphenyl-3-ylthio)-*N*,*N*-dimethylethanamine (8h)

The compound **8h** was obtained following the Suzuki palladium coupling protocol described above for the derivative **4c**. $C_{16}H_{19}NS$; yield 91%; colorless oil; IR (ATR-D): cm^{-1} 2939, 2768, 1587, 1461, 752, 695; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.30 (s, 6H), 2.61 (t, 2H, J = 7.4 Hz), 3.10 (t, 2H, J = 7.4 Hz), 7.33–7.48 (m, 6H), 7.56–7.59 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 31.6 (CH_2), 45.5 (2CH), 58.7 (CH_2), 125.0 (CH), 127.3 (2CH), 127.7 (2CH), 127.8 (CH), 128.9 (2CH), 129.4 (CH), 137.1 (C), 140.7 (C), 142.1 (C); MS m/z = 258.5 $[M+H]^+$; HRMS calcd for $C_{16}H_{19}NS$ 258.1316, found 258.1304.

4.15. 2-(2,6-Dimethylbiphenyl-3-ylthio)-*N*,*N*-dimethyl-ethanamine (8i)

The compound **8i** was obtained following the Suzuki palladium coupling protocol described above for the derivative **4c**. $C_{18}H_{23}NS$; yield 69%; colorless oil; IR (ATR-D): cm^{-1} 2939, 2768, 1587, 1461, 752, 695; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.05 (s, 6H), 2.27 (s, 6H), 2.58 (t, 2H, J = 7.4 Hz), 3.04 (t, 2H, J = 7.4 Hz), 6.95–6.99 (m, 1H), 7.09–7.21 (m, 4H), 7.30–7.38 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.9 (2CH), 31.4 (CH_2), 45.5 (2CH), 58.7 (CH_2), 126.7 (CH), 127.2 (CH), 127.3 (CH), 127.4 (2CH), 129.1 (CH), 129.2 (CH), 136.0 (2C), 136.7 (C), 141.3 (C), 141.9 (C); MS m/z = 286.5 $[M+H]^+$; HRMS calcd for $C_{18}H_{23}NS$ 286.1629, found 286.1621.

4.16. General procedure employed for the synthesis of vinylic derivatives 9a–d

Under nitrogen atmosphere, the corresponding sulfone was dissolved in anhydrous tetrahydrofuran (30 mL) and the mixture was cooled to −78 °C. Then, vinyl magnesium bromide was added (1 M solution in hexane, 10.2 mL, 10.2 mmol) and the mixture was stirred at low temperature 1 h, before quenching it with sat. NaCl (30 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 50 mL) and the combined organic layers dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The final compounds **9a–d** were isolated by flash chromatography (petroleum ether/ethyl acetate 9/1).

4.16.1. 5-Phenyl-3-vinyl-1,2,4-triazine (9a)

$C_{11}H_9N_3$; yield 91%; orange solid; mp 85–87 °C; IR (KBr): cm^{-1} 3060, 1548, 1506, 987, 942, 772; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 5.92 (dd, 1H, J = 1.7 Hz, J = 10.5 Hz), 6.88 (dd, 1H, J = 1.7 Hz, J = 17.4 Hz), 7.14 (dd, 1H, J = 10.5 Hz, J = 17.4 Hz), 7.51–7.60 (m, 3H), 8.18–8.22 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$, 25 °C) δ = 126.0 (CH_2), 127.7 (CH), 129.5 (CH), 132.6 (CH), 133.7 (C), 134.0 (CH), 144.5 (CH), 155.1 (C), 163.2 (C); MS m/z = 184.0 $[M+H]^+$, 206.0 $[M+Na]^+$.

4.16.2. 5-(2,6-Dimethylphenyl)-3-vinyl-1,2,4-triazine (9b)

$C_{13}H_{13}N_3$; yield 96%; yellow solid; mp 38–40 °C; IR (KBr): cm^{-1} 3038, 1598, 1544, 1498, 1322, 1066, 774; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.13 (s, 6H), 5.92 (dd, 1H, J = 1.5 Hz, J = 10.6 Hz), 6.82 (dd, 1H, J = 1.5 Hz, J = 17.4 Hz), 7.09–7.21 (m, 3H), 7.30 (dd, 1H, J = 6.7 Hz, J = 8.4 Hz), 9.04 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.3 (2CH), 126.4 (CH_2), 128.4 (2CH), 129.9 (CH), 133.9 (CH), 134.4 (C), 135.9 (C), 148.8 (CH), 159.8 (C), 163.6 (C); MS m/z = 212.0 $[M+H]^+$, 206.0 $[M+Na]^+$.

4.16.3. 5-(2,6-Dimethoxyphenyl)-3-vinyl-1,2,4-triazine (9c)

$C_{13}H_{13}N_3O_2$; yield 96%; yellow solid; mp 162–164 °C; IR (KBr): cm^{-1} 2972, 1599, 1250, 1108, 782; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 3.74 (s, 6H), 5.84 (dd, 1H, J = 1.7 Hz, J = 10.6 Hz), 6.65 (d, 2H, J = 8.4 Hz), 6.77 (dd, 1H, J = 1.7 Hz, J = 17.4 Hz), 7.09 (dd, 1H, J = 10.5 Hz, J = 17.4 Hz), 7.39 (t, 1H, J = 8.4 Hz), 9.03 (s, H_6); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 56.1 (2CH), 104.4 (2CH), 113.3 (C), 125.5 (CH_2), 132.2 (CH), 134.2 (CH), 150.1 (CH), 155.6 (C), 158.4 (C), 163.4 (C); MS m/z = 244.0 $[M+H]^+$.

4.16.4. 4-(2,6-Dimethoxyphenyl)-2-vinylpyrimidine (9d)

$C_{14}H_{14}N_2O_2$; yield 96%; white solid; mp 141–143 °C; IR (ATR-D): cm^{-1} 2930, 1597, 1560, 1534, 1468, 1428, 1243, 1108, 844, 780; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 3.71 (s, 6H), 5.67–5.70 (m, 1H), 6.59–6.64 (m, 3H), 6.95 (dd, 1H, J = 10.6, J = 17.3 Hz), 7.13 (dd, 1H, J = 0.9 Hz, J = 5.0 Hz), 7.32 (dt, 1H, J = 1.4 Hz, J = 8.4 Hz), 8.69 (dd, 1H, J = 0.9 Hz, J = 5.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 56.0 (2CH), 104.4 (2CH), 117.1 (C), 121.7 (CH), 123.3 (CH_2), 130.7 (CH), 137.2 (CH), 156.3 (CH), 157.9 (C), 163.0 (C), 164.3 (C); MS m/z = 243.0 $[M+H]^+$.

4.17. General procedure employed for the synthesis of compounds 10a–d

Dimethylamine (solution 40% in water, 0.18 mL, 2.46 mmol) was added to a solution of the corresponding compound **9a–d** (0.82 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature until the total consumption of the starting material (approx. 1 h). Then, the solvents were evaporated in vacuo and the residue purified by flash chromatography (dichloromethane/methanol 95/5) to give the desired corresponding compounds **10a–d**.

4.17.1. *N,N*-Dimethyl-2-(5-phenyl-1,2,4-triazin-3-yl)-ethanamine (10a)

$C_{13}H_{16}N_4$; yield 67%; orange oil; IR (NaCl): cm^{-1} 3446, 2942, 2770, 1548, 764; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.32 (s, 6H), 2.94 (t, 2H, J = 7.4 Hz), 3.33 (t, 2H, J = 7.4 Hz), 7.50–7.57 (m, 3H), 8.13–8.17 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 35.5 (CH_2), 45.4 (2CH), 57.7 (CH_2), 127.7 (C), 129.4 (C), 132.4 (C), 133.7 (C), 144.3 (CH), 155.2 (C), 168.6 (C); MS m/z = 229.0 $[M+H]^+$; HRMS calcd for $C_{13}H_{16}N_4$ 229.1453, found 229.1447.

4.17.2. 2-(5-(2,6-Dimethylphenyl)-1,2,4-triazin-3-yl)-*N,N*-dimethylethanamine (10b)

$C_{15}H_{20}N_4$; yield 79%; beige oil; IR (NaCl): cm^{-1} 3450, 2976, 2766, 1597 et 1544, 1505, 1462, 1296, 1051, 780; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.09 (s, 6H), 2.29 (s, 6H), 2.90 (t, 2H, J = 7.4 Hz), 3.36 (t, 2H, J = 7.4 Hz), 7.15 (d, 2H, J = 7.6 Hz), 7.28 (dd, 1H, J = 6.7 Hz, J = 8.4 Hz), 9.06 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 20.3 (2CH), 35.6 (CH_2), 45.4 (2CH), 57.9 (CH_2), 128.3 (2CH), 129.8 (CH), 134.4 (C), 135.9 (C), 148.6 (CH), 159.8 (C), 169.1 (C); MS m/z = 257.0 $[M+H]^+$; HRMS calcd for $C_{15}H_{20}N_4$ 257.1766, found 257.1766.

4.17.3. 2-(5-(2,6-Dimethoxyphenyl)-1,2,4-triazin-3-yl)-*N,N*-dimethylethanamine (10c)

$C_{15}H_{20}N_4O_2$; yield 68%; dark-yellow oil; IR (NaCl): cm^{-1} 3442, 2942, 2778, 1599, 1472, 1253, 1109, 784; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.32 (s, 6H), 2.94 (t, 2H, J = 7.6 Hz), 3.33 (t, 2H, J = 7.6 Hz), 3.74 (s, 6H), 6.65 (d, 2H, J = 8.4 Hz), 7.39 (t, 1H, J = 8.4 Hz), 9.06 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 35.6 (CH_2), 45.4 (2CH), 56.1 (2CH), 57.9 (CH_2), 104.4 (2CH), 113.1 (C), 132.2 (CH), 150.0 (CH), 155.5 (C), 158.3 (C), 168.4 (C); MS m/z = 289.0 $[M+H]^+$; HRMS calcd for $C_{15}H_{20}N_4O_2$ 289.1665, found 289.1658.

4.17.4. 2-(4-(2,6-Dimethoxyphenyl)pyrimidin-2-yl)-*N,N*-dimethylethanamine (10d)

$C_{16}H_{21}N_3O_2$; yield 89%; yellow oil; IR (ATR-D): cm^{-1} 2939, 1597, 1570, 1545, 1471, 1433, 1248, 1108, 727; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ = 2.36 (s, 6H, H_{16}), 2.96 (t, 2H, H_{14}, J = 7.7 Hz), 3.24 (t, 2H, H_{13}, J = 7.7 Hz), 3.73 (s, 6H, H_{12}), 6.64 (d, 2H, H_9, J = 8.4 Hz), 7.14 (d, 1H, H_5, J = 5.1 Hz), 7.33 (t, 1H, H_{10}, J = 8.4 Hz), 8.66 (d, 1H, H_4, J = 5.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C) δ = 37.3 (C_{13}), 45.2 (C_{16}), 55.9 (C_{12}), 58.1 (C_{14}), 104.3 (C_9), 116.9 (C_q), 121.1 (C_5), 130.6 (C_{10}), 156.3 (C_4), 157.8 (C_8), 162.9 (C_q), 169.1 (C_q); MS m/z = 288.0 $[M+H]^+$; HRMS calcd for $C_{16}H_{21}N_3O_2$ 288.1712, found 288.1712.

4.18. Binding experiments

Membrane preparation and general assay procedures for 5-HT_7 and 5-HT_{1A} receptors were performed exactly as previously described.[16]

For 5-HT_7 binding assay, membranes from HEK-293 cells, stably expressing human 5-HT_{7b} receptor and [^{3}H]-5-CT (93.0 Ci/mmol, Hartmann) as radioligand were used.

The 5-HT_{1A} receptor affinity was determined for selected compounds, with the use of native rat hippocampal membranes and [^{3}H]-8-OH-DPAT (170 Ci/mmol, PerkinElmer). For both 5-HT_7 and 5-HT_{1A} binding experiments 7–9 sample concentrations, each run in triplicate, were used to determine inhibition constant (K_i), whereas nonspecific binding was defined in the presence of 10 μM 5-HT.

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