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Benzimidazolone-based serotonin 5-HT$_{1A}$ or 5-HT$_7$R ligands: Synthesis and biological evaluation

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ABSTRACT

A new group of serotoninergic 5-HT$_{1A}$ or 5-HT$_7$ receptor ligands was identified. These compounds were designed and synthesized on a benzimidazolone scaffold and they enrich the well-known arylpiperazine class of 5-HT ligands. Diverse pharmacomodulations induced a shift in the affinity and selectivity profile with final identification of new potent hits.

Among the seven subtypes of receptors that mediate the serotonin (5-HT) functions,[1] the 5-HT$_7$Rs are the latest discovered (1993).[2–4] Their distribution both in the central nervous system and in the peripheral tissues[5,6] is highly associated with their implications in psychiatric disorders,[7,8] depression, anxiety and mood,[9–12] learning and memory,[13–15] epilepsy,[16] inflammatory processes,[17–19] ileum peristalsis,[20,21] just to cite a few recent studies on 5-HT$_7$R complex system.

Many ligands have been reported to bind with high affinity to 5-HT$_7$ receptors and their number is continuously increasing.[22–24] The advantage of a wide variety of completely different chemical patterns published to date may rapidly turn into a drawback making the understanding of a common binding pattern more difficult, especially when not enough SAR data associated with every class of ligand is available. Simple pyridines **1**[25] and more complex structures as triazine **2**[26] or pyrazole **3**[27] may serve as examples (see Fig. 1).

A number of studies defining 5-HT$_7$ pharmacophoric models have also been published,[28–34] and a recent review summarized them in the context of all the 5-HTRs.[35] Also, some 5-HT$_7$R homology models using Rho crystal structures as templates were proposed.[29,30,32,36] It is highly probable that recently solved structures of first GPCRs from the aminergic family[37–39] will enhance the research in 5-HT$_7$R area by supplying better templates for homology studies (for a review see Nichols et al.[40]).

Arylpiperazines, initially discovered as 5-HT$_{1A}$R ligands, show also good affinities for 5-HT$_7$Rs, most probably due to the strong similarities between the binding sites of these receptors.[28,32,41] In the present Letter, we enrich the class of arylpiperazine 5-HT$_{1A}$/5-HT$_7$R ligands, with the discovery of a new heterocyclic scaffold able to accommodate in the receptor-binding site, namely the benzimidazolone skeleton. The applied structural modifications influenced the 5-HT$_{1A}$ and 5-HT$_7$Rs affinities as well as selectivity profile of the investigated compounds.

Our starting point was the 5-HT$_7$/5-HT$_{1A}$ ligand **4** previously published by Rault and co-workers.[42] (K_i = 4.3 nM and K_i = 9.9 nM, respectively). The replacement of the central pyrrole with benzimidazolone was investigated in a first approach in order to evaluate the influence of this new heteroaromatic scaffold on the 5-HT$_7$R/5-HT$_{1A}$Rs affinity. The initial series, with a two-carbon linker, was

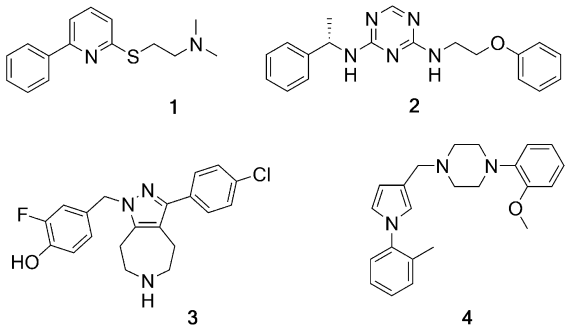

Figure 1. 5-HT$_7$ diversity ligands.

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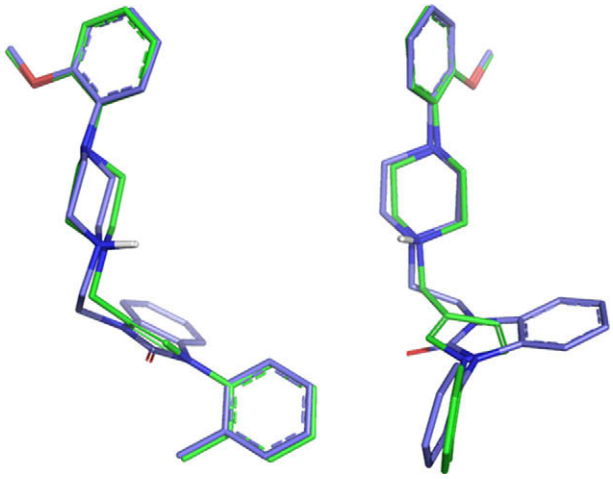
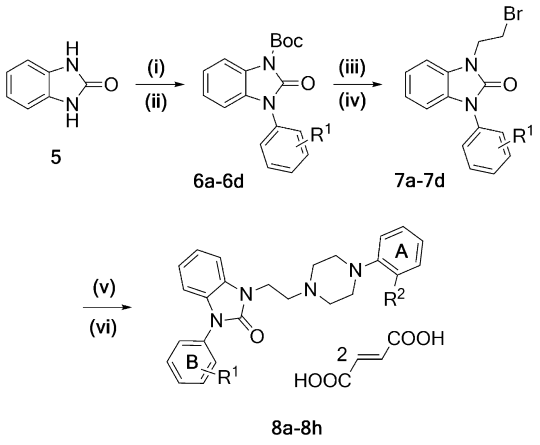


Figure 2. Orthogonal views of GASP (SYBYL) superposition between compound **4** (green) and the designed benzimidazolone analog (blue).[43]



Scheme 1. Reagents and conditions: (i) NaH, Boc_2O/DMF/10 h, rt, 89%; (ii) R^1–$PhB(OH)_2$, $Cu(OAc)_2$, TEMPO or PNO, TEA, Air/DCM, m.s. 4 Å/2–4 d, rt, 62–70%; (iii) TFA/DCM/2 h, rt, 99%; (iv) 1,2-dibromoethane, K_2CO_3, Bu_4NBr or Bu_4NI/H_2O/10 h, reflux, 70–90%; (v) arylpiperazine, K_2CO_3/THF/15–30 min, 160 °C, mw, 54–93%; (vi) fumaric acid (2 equiv)/MeOH, Et_2O/10 min, 35 °C, 99%.

supported by a good superposition between these two structures (see Fig. 2).

The developed synthetic route is detailed in Scheme 1.

After protection of one benzimidazolone's nitrogen with a Boc group, the second was coupled with various substituted aryls. The coupling procedure described by Lam et al.[44] was applied with commercially available boronic acids. Acidic deprotection of Boc group was followed by nitrogen alkylation with 1,2-dibromoethane in water, using potassium carbonate as base and tetrabutylammonium bromide (or iodide) as phase transfer catalyst. The subsequent substitution of bromine with diverse arylpiperazines was initially performed under classical heating conditions. Since long reaction times were required for the total conversion of the starting material (usually 1–2 days), the reaction was optimized under microwave irradiation. In general, 15–30 min at 160 °C in THF were sufficient for the completion of the reaction. An additional step involved the conversion of final oily compounds into their corresponding solid salts. Fumaric acid was found appropriate, and 2 equiv were required for quaternisation of two nitrogens (as proven by ^{1}H NMR spectra).[45]

All the final compounds were tested in competition binding experiments for native serotonin 5-HT_{1A} (rat hippocampus), and cloned human 5-HT_7 (stably expressed in HEK-293 cells) receptors, according to the previously published procedures.[46]

Table 1
Binding affinities for compounds **8a–h**

Compound	R^1	R^2	5-HT_{1A} K_i[a] (nM)	5-HT_7 K_i[a] (nM)
8a	H	H	467	1230
8b	2-Me	H	636	902
8c	3-OMe	H	646	864
8d	4-OMe	H	340	566
8e	H	Me	168	1867
8f	2-Me	Me	375	17,960
8g	3-OMe	Me	182	2500
8h	4-OMe	OMe	22	296

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

As shown in Table 1, for unsubstituted phenyl **A** (R^2 = H) the 5-HT_7R affinity increases as the substituents on the phenyl **B** are more remote from the benzimidazolone central skeleton (entries **8a–d**). The introduction of a methyl substituent on the aromatic ring **A** (R^2 = Me) has a major negative impact on the 5-HT_7 affinity, while rather improving affinities for 5-HT_{1A}Rs (see entries **8e–g**). It is well known that ortho-methoxy substituent on the phenylpiperazine moiety enhances the 5-HT_{1A} affinity. Following this assumption, we synthesized the compound **8h** to check if this trend is also confirmed in the case of our benzimidazolone-based ligands. The best K_i values are observed indeed in the case of R^2 = OMe; the compound **8h** shows an affinity of 22 nM on 5-HT_{1A}Rs.

Because the overall affinities of these compounds were higher for 5-HT_{1A}R, in order to improve the biological activities on the 5-HT_7Rs, two structural changes were applied: (a) an increase of the linker length and (b) removal of the aryl moiety **B**. The above modifications were based on structures of some published long chain arylpiperazine (LCAP) ligands such as **9**,[47] **10**,[33] and more recently **11**[48] and **12**[49] (see Fig. 3) which incorporated 4–5 carbon atoms in the linker in order to obtain a higher 5HT_7 affinity. The impact of the spacer's length on the 5-HT_{1A}/5-HT_7Rs selectivity was also the subject of a previously published paper, which concluded that, in the case of arylpiperazine 5-HT_7R ligands, a more flexible compound could adopt more easily the active conformation within the binding receptor.[50]

The synthetic strategy was more convergent, that is, the cross-coupling step followed the introduction of the phenylpiperazine moiety (Scheme 2).

The synthesis started with the Boc protection of one benzimidazolone nitrogen as previously described. In the next step, the remaining nitrogen was alkylated with different dibromoalkanes (3–6 carbon atoms linker). The subsequent substitution of bromine

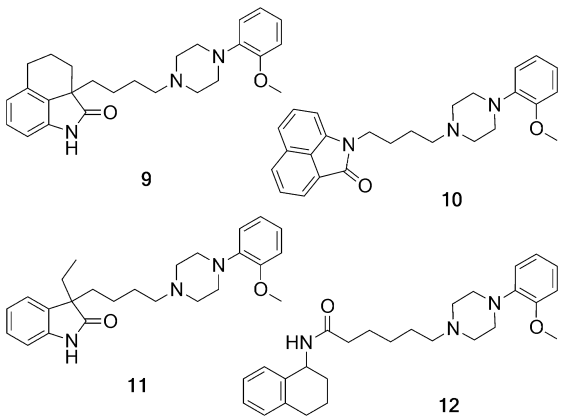
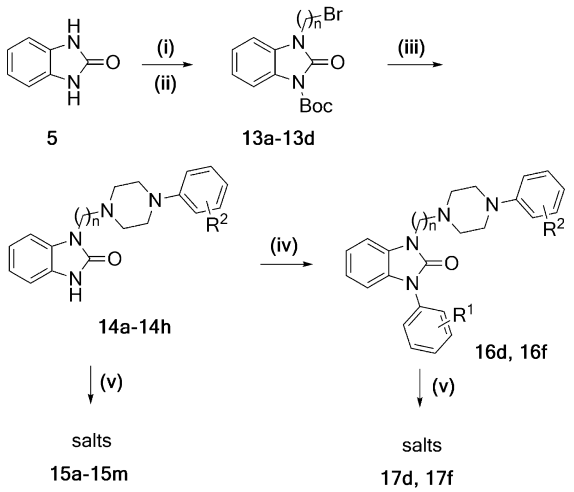


Figure 3. Examples of LCAP 5-HT_7 ligands.



Scheme 2. Reagents and conditions: (i) NaH, Boc_2O/DMF/10 h, rt, 89%; (ii) 1,2-dibromoalcane, K_2CO_3, Bu_4NI/H_2O/10 h, reflux, 73–90%; (iii) arylpiperazine, K_2CO_3/THF/15–30 min, 160 °C, mw, 74–93%; (iv) R^1–$PhB(OH)_2$, $Cu(OAc)_2$, TEMPO or PNO, TEA, Air/DCM, m.s. 4 Å/3 d, rt, 32–40%; (v) fumaric acid (2 equiv)/MeOH, Et_2O/10 min, 35 °C, 99%.

Table 2
Binding affinities for compounds **17d** and **17f**

Compds	*n*	R^1	R^2	5-HT_{1A} K_i[a] (nM)	5-HT_7 K_i[a] (nM)
8h	2	4-OMe	2-OMe	22	296
17d	3	4-OMe	2-OMe	26	168
17f	4	4-OMe	2-OMe	36	267

[a] See Table 1 for details.

with aryl-piperazines was conducted as before. The Boc group was also removed during this step, which was in accordance with a previous study on the mild deprotection of amines.[51]

To evaluate the influence of the linker's length on N-arylated benzimidazolone compounds, both **14d** and **14f** were N-arylated using *p*-methoxyphenylboronic acid as a coupling partner producing **17d** and **17f**, respectively (Table 2).

The increased linker length does not have an important effect on 5-HT_{1A}/5-HT_7 affinity, since both **17d** and **17f** showed comparable affinities as compound **8h**. Because of the overall lower 5-HT_7R affinities of N-arylated compounds than unsubstituted derivatives (vide infra) further studies on these structures were abandoned.

As a next step, the influence of the linker's length of the NH free benzimidazolones on the 5-HT_{1A}/5-HT_7Rs affinity was evaluated. This structure simplification is beneficial both to 5-HT_{1A} and 5-HT_7 receptor affinity (Table 3). In the case of 5-HT_{1A} receptors, the previously reported tendency of enhanced affinity of the *o*-methoxy derivatives compared to the non-substituted analogs was also confirmed for our compounds (see couples **15b**/**15a**, **15d**/**15c**, **15f**/**15e** and **15h**/**15g**). For these receptors, the optimum 3 carbons linker induced an affinity of 3.4 nM in the case of ligand **15d**.

As regards the 5-HT_7 receptors, the observed affinity systematically increased with the length of the linker, to an optimum of 5 carbon atoms. The best K_i value of 6 nM was observed for compound **15g**. The trend seems to be reversed for longer aliphatic chain (6 carbons linker). For the same compound **15g**, a 45-fold selectivity is gained over 5-HT_{1A}Rs.

Two further pharmacomodulations were subsequently conducted, following the article of Volk et al.[48] who reported that replacing the methoxy with chlorine substituents on the phenylpiperazine moiety could lead to a better 5-HT_7/5-HT_{1A}Rs selectivity

Table 3
Binding affinities for compounds **15a**–**j**

Compds	*n*	R^2	5-HT_{1A} K_i[a] (nM)	5-HT_7 K_i[a] (nM)
15a	2	H	392	1029
15b	2	2-OMe	25	1838
15c	3	H	26	243
15d	3	2-OMe	3.4	40
15e	4	H	84	48
15f	4	2-OMe	6	26
15g	5	H	269	6
15h	5	2-OMe	33	38
15i	6	H	48	20
15j	6	2-OMe	12	78

[a] See Table 1 for details.

Table 4
Binding affinities for compounds **15k** and **15m**

Compds	*n*	R^2	5-HT_{1A} K_i[a] (nM)	5-HT_7 K_i[a] (nM)
15k	5	3-Cl	66	11
15m	5	4-Cl	454	7

[a] See Table 1 for details.

profile. These compounds were synthesized in the same way as indicated in Scheme 2, using appropriate phenylpiperazines for the step (iii). The corresponding affinities are given in Table 4.

The 4-Cl substitution on phenylpiperazine moiety enhanced 65-fold the selectivity profile of compound **15m** in the favor of 5-HT_7Rs. On the other hand, in the case of ligand **15k**, the 3-Cl substitution does not improve its binding qualities compared to the non-substituted compound **15g**.

In conclusion, we identified new benzimidazolone derivatives able to selectively bind to 5-HT_7 receptors over the 5-HT_{1A}Rs. We also demonstrated the influence of the phenyl-piperazine moiety on the 5-HT_7R selectivity and the impact of the aliphatic linker on the 5-HT_{1A}/5-HT_7Rs affinity. Further pharmacological studies are currently conducted in order to improve the biological properties of our best hits **15g** and **15m**, the benzimidazolone skeleton being easily modulated on the aromatic ring.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.02.008.

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