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Identification of a Novel Series of Selective 5-HT$_7$ Receptor Antagonists

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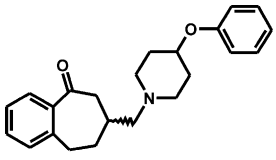
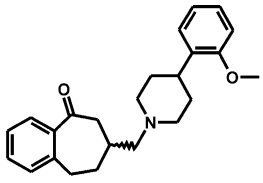
Abstract—Novel 5-HT$_7$ receptor antagonists containing the benzocycloheptanone core were identified from high throughput screening. Molecular modelling and SAR studies have converted these intractable hits into a more potent, selective and tractable series, exemplified by compound (**25**), SB-691673.

The 5-HT$_7$ receptor is the most recent addition to the serotonin sub-family of G-protein coupled receptors.[1] Receptor localisation studies in various species indicate the presence of 5-HT$_7$ receptors both centrally and peripherally, with the highest receptor densities being located in the thalamus, hypothalamus, limbic and cortical regions of the brain.[2] Although the biological function(s) of this receptor is poorly understood, recent reports suggest that 5-HT$_7$ receptors are involved in the control of circadian rhythms,[3] or in the aetiology of depression.[4] Further clarification of these hypotheses awaits the discovery and evaluation of selective tool compounds.

We have previously reported aryl sulfonamides as a rich source of selective 5-HT$_7$ receptor antagonists.[5] In parallel with this work, we were also interested in identifying a potential back-up series of 5-HT$_7$ receptor antagonists having a diverse chemical structure. Cross-screening of compounds from the former SmithKline Beecham collection identified structures **1** and **2**, both of which possessed good 5-HT$_7$ receptor activity and showed typically 10-fold selectivity over other 5-HT receptors. Thus it was considered that these structures provided an ideal opportunity for conversion into potential drug candidates having structures entirely distinct from our earlier sulfonamide series.



(1) pK$_i$ 5-HT$_7$ 7.73 ± 0.06



(2) pK$_i$ 5-HT$_7$ 7.95 ± 0.08

Unfortunately, the synthetic routes[6] to **1** and **2** were not straightforward, being both lengthy and low-yielding, and so we considered the possibility of re-locating the side chain from the 3-position on the benzocycloheptanone scaffold to the synthetically more accessible 2-position, whilst maintaining the same C_3 connectivity between the carbonyl group and the basic amine. In support of this proposition, we undertook some simple modelling work which demonstrated that the 2-isomer **7** could overlay effectively with the 3-isomer **2** in a low energy conformation (Figure 1).

Thus the initial targets **6** and **7** were synthesised as racemates, using the route shown in Scheme 1. Suberone **3** was alkylated at the 2-position with allyl bromide, via the pyrrolidine enamine intermediate and subsequent hydrolysis. Ozonolysis provided the aldehyde **5** which was then reductively alkylated with the appropriately substituted piperidine to give the target compounds **6** and **7**.

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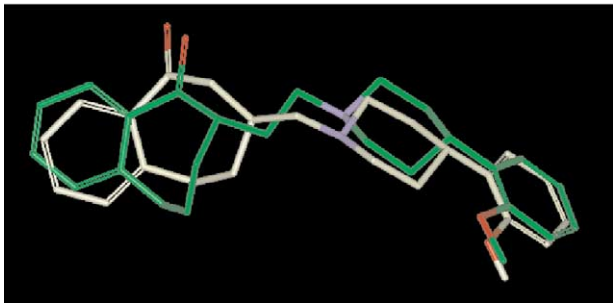
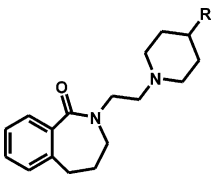


Figure 1. Molecular overlay of structures **2** (buff) and **7** (green).

Encouragingly, both **6** and **7** showed good 5-HT_7 receptor affinity with pK_i's of 7.60 and 7.95, respectively, thus validating our modelling hypothesis which related the structures **2** and **7**. Before embarking on a full SAR study, however, we addressed a potential issue with the chiral centre in these molecules. Although not precluding the progression of structures of this type, it was felt that the rapid racemisation of the single enantiomers in this series[7] could lead to protracted development issues. Accordingly, we investigated the replacement of the chiral carbon atom in **6** with a non-chiral nitrogen atom. Thus the lactam **8** was synthesised using similar methodology (Scheme 2) and gratifyingly **8** showed similar 5-HT_7 receptor affinity to the corresponding ketone analogue **6**. This key result demonstrated the equivalence of lactam and cyclic ketone with respect to 5-HT_7 receptor affinity.

Overall, through two rational modifications we have converted the original racemic lead **1** into a nonchiral, synthetically more accessible lead **8** with no loss of 5-HT_7 receptor affinity (Scheme 3). Because of selectivity issues with the 2-methoxyphenylpiperidine series, no further work was undertaken using the right-hand side template exemplified in structure **2**.

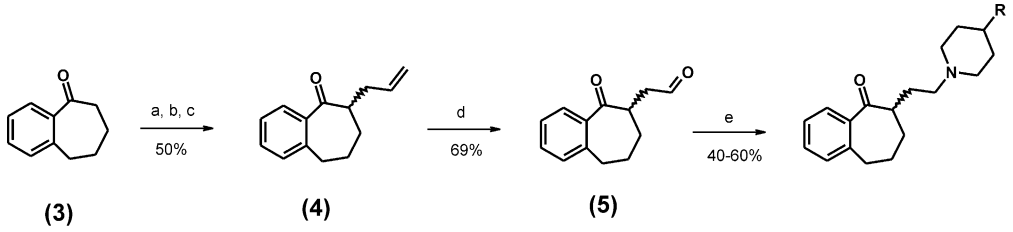
Table 1. Phenoxy substituted piperidines



No.	R	pK_i[8] 5-HT_7	pK_i[8] 5-HT_{2A}
8	PhO	7.69±0.04	6.81±0.05
12	4-FPhO	8.35±0.05	7.50±0.06
13	4-ClPhO	7.93±0.06	7.13±0.01
14	4-MePhO	8.04±0.04	7.26±0.05
15	4-FPh(C=O)	8.78±0.05	7.77±0.06
16	4-ClPh(C=O)	8.60±0.05	7.11±0.11

In view of the facile synthesis of the intermediate **11**, we undertook an array-based SAR study in this area focusing initially on varying the right-hand side aromatic moiety. Thus, a range of substituted phenoxy, benzoyl and heterocyclic substituted piperidine analogues was prepared, and the testing results shown in Tables 1 and 2. The 5-HT_7 data were compared with the corresponding 5-HT_{2A} affinity which proved to be the most potent unwanted receptor affinity in this series. In the phenoxy series (Table 1), introduction of a 4-substituent had a beneficial effect on 5-HT_7 receptor affinity, most marked with a 4-fluoro substituent, for example **12**, but this modification also brought about a parallel increase in 5-HT_{2A} affinity. Similar effects were observed with the related benzoyl substituted analogues **15** and **16**.

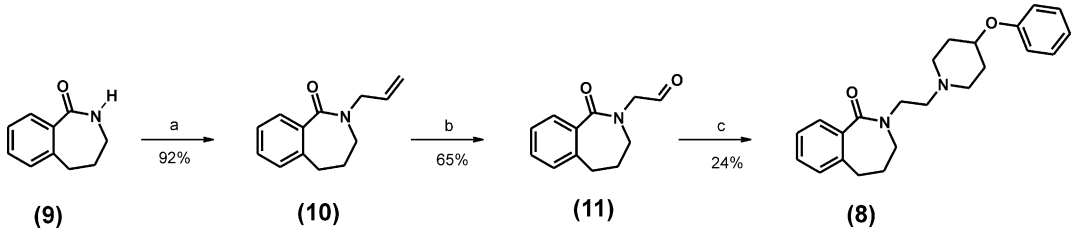
The most dramatic effects, however, were observed with a bicyclic heterocyclic group at the 4-position of the piperidine ring (Table 2). In this series, the 3-indolyl analogue **17** was the most potent compound with a pK_i



(6) R = OPh **pK$_i$ 5-HT$_7$ 7.60 ± 0.11**

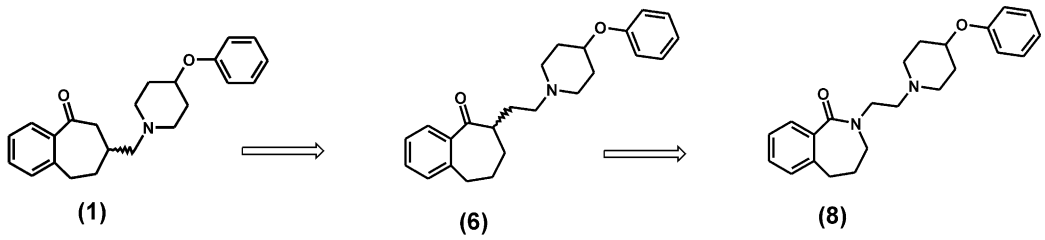
(7) R = 2-MeOPh **pK$_i$ 5-HT$_7$ 7.95 ± 0.08**

Scheme 1. Reagents and conditions: (a) pyrrolidine, toluene, *para*-toluenesulfonic acid, reflux, 18 h; (b) allyl bromide, acetonitrile, reflux, 3 h; (c) sodium hydroxide, room temperature; (d) O_3, dichloromethane, −78 °C; (e) amine, $NaBH(OAc)_3$, dichloroethane, room temperature, 18 h.



pK$_i$ 5-HT$_7$ 7.69 ± 0.04

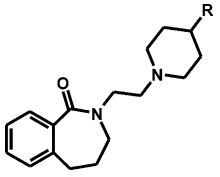
Scheme 2. Reagents and conditions: (a) NaH, dimethylformamide, allyl bromide, room temperature; (b) O_3, dichloromethane, −78 °C; (c) 4-phenoxypiperidine, $NaBH(OAc)_3$, dichloroethane, room temperature, 5 h.

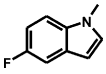
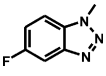
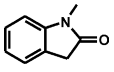
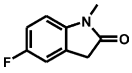
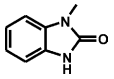
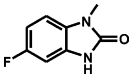
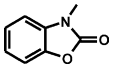
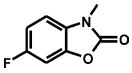


pK$_i$ 5-HT$_7$ 7.73 ± 0.06 **pK$_i$ 5-HT$_7$ 7.60 ± 0.11** **pK$_i$ 5-HT$_7$ 7.69 ± 0.04**

Scheme 3. Overall transformation from initial lead to modified template.

Table 2. Heterocyclic 4-substituted piperidines



No.	R	pK_i[8] 5-HT$_7$	pK_i[8] 5-HT$_{2A}$	No.	R	pK_i[8] 5-HT$_7$	pK_i[8] 5-HT$_{2A}$
17		9.39±0.06	8.77±0.13	—	—	—	—
18		8.56±0.02	7.71±0.02	**19**		9.25±0.01	8.16±0.08
20		7.85±0.02	6.57±0.01	**21**		8.69±0.04	7.31±0.03
22		7.43±0.09	6.65±0.03	**23**		8.16±0.06	7.37±0.03
24		7.99±0.14	<5.8	**25**		8.65±0.06	6.52±0.07
26		7.56±0.05	6.01±0.05	**27**		8.03±0.04	6.73±0.02

at the 5-HT$_7$ receptor of 9.39, but also of interest were the 1-indolyl isomer **18**, the benzotriazole **20** and benzimidazolone **24** with pK_i's of 8.56, 7.85 and 7.99, respectively. As in the phenoxy series, a significant enhancement of activity was also observed with the introduction of a fluoro substituent, typically giving a 5-fold potentiation of 5-HT$_7$ affinity (e.g., compare **20** with **21**, and **24** with **25**). Again, with most of these fluoro analogues we observed a parallel increase in 5-HT$_{2A}$ receptor affinity, with the notable exception of the benzimidazolones **24** and **25**, where the 5-HT$_{2A}$ levels of activity remained low, suggesting that polarity is not tolerated at the 5-HT$_{2A}$ receptor. Thus with both these compounds a 100-fold selectivity ratio was obtained for 5-HT$_7$ receptor affinity over the undesired 5-HT$_{2A}$ receptor affinity, indicating the unique nature of the benzimidazolone ring system being tolerated at the 5-HT$_7$ receptor but disfavoured at the 5-HT$_{2A}$ receptor.

Compound **25**, SB-691673 (free base) was identified as the most promising analogue in this series, and has undergone further investigation. SB-691673 was evaluated in a previously described functional model of 5-HT$_7$ receptor activation,[9] blocking 5-carboxamidotryptamine (5-CT) stimulated adenylyl cyclase activity with a calculated pK_B of 7.9 ($n=2$), confirming its antagonist profile.[10]

Cross screening of **25**, SB-691673 against a panel of serotonergic and dopaminergic receptors indicated ≥100-fold selectivity over a range of closely related receptors (Table 3).

Table 3. Receptor binding selectivity profile of **25** SB-691673

Receptor	Affinity (pK_i)[8]	Receptor	Affinity (pK_i)[8]
5-HT$_{1A}$	6.32±0.05	5-HT$_{2C}$	5.48±0.08
5-HT$_{1B}$	<5.4	5-HT$_{5A}$	5.83±0.06
5-HT$_{1D}$	5.62±0.19	5-HT$_6$	<5.3
5-HT$_{1E}$	<5.0	**5-HT$_7$**	**8.65±0.06**
5-HT$_{1F}$	<5.0	D2	6.63±0.07
5-HT$_{2A}$	6.52±0.05	D3	5.77±0.11
5-HT$_{2B}$	6.00±0.12	D4	5.91±0.16

Gratifyingly, this series was devoid of cytochrome P450 issues, with IC_{50}'s ≥ 10 μM for SB-691673 against the major human P450 isoforms.[11]

Human P450 isoform	IC_{50} (μM)
1A2	62
2C19	>100
2C9	35
2D6	10
3A4	>100

In summary, with **25** SB-691673 we have identified a novel and potent 5-HT_7 receptor antagonist, which has an excellent selectivity profile across serotonergic and dopaminergic receptors, and no major P450 liabilities. In the course of this work we have used small molecule modelling studies to identify a synthetically more accessible lead series, and removed the chiral centre in the early lead compounds by replacement with an amide functional group. Further studies in this area will be the subject of a future publication.

References and Notes

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6. Unpublished work in GSK.
7. Chiral HPLC separation of the individual enantiomers from two members of this series indicated rapid racemisation of the chiral centre, following isolation of the samples from each peak.
8. pK_i values represent the mean of at least three determinations using cell lines stably expressing the cloned human receptor. For details of the radioligand binding assays, see refs 5 and 9.
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10. The profile of SB-691673 is consistent with an inverse agonist as the basal response of adenyly cyclase was reduced in the absence of agonist (5-CT).
11. Cytochrome P450 enzyme activities were determined by quantifying the production of fluorescent metabolite following incubation of substrate with heterologously expressed cytochrome P450 enzymes obtained from the Gentest Corporation. A generic description of this approach can be found in: Anal. Biochem. **1997**, *248*, 188, or at www.gentest.com.