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Aminoalkyl phenyl sulfones—a novel series of 5-HT$_7$ receptor ligands

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Abstract—A novel series of 5-HT$_7$ receptor ligands has been identified and evaluated, providing compounds showing a broad spectrum of functional activities and good selectivity over selected receptors and ion channels.

The human 5-HT$_7$ receptor is the most recently discovered subtype of the serotonin receptor family.[1] The biological functions of this receptor are not well understood, but recent reports suggest that 5-HT$_7$ receptors may be implicated in a variety of physiological and pathophysiological processes such as cognition,[2] schizophrenia,[3] migraine,[4] regulation of circadian rhythm,[5] epilepsy[6] and in the aetiology of depression.[7]

The development of selective agonists and antagonists would greatly facilitate determination of the actual role of the 5-HT$_7$ receptor. Recently, a number of structurally diverse 5-HT$_7$ receptor ligands have been disclosed[8] (e.g., **SB-656104**, **DR4004**, **1** and **2**; Fig. 1).

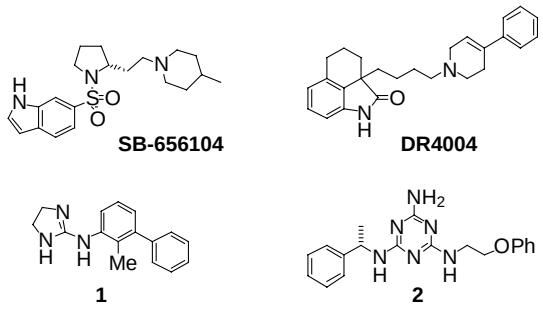

Figure 1.

As part of our 5-HT$_7$ receptor programme, we were interested in the identification of new, structurally diverse chemical classes of selective 5-HT$_7$ receptor ligands that could be used for in vivo studies of 5-HT$_7$ receptor function. Here, we report the aminoalkyl phenyl sulfones as a new class of 5-HT$_7$ receptor ligands.

Preliminary modelling studies suggested that a *gem*-disubstituted cyclobutyl sulfone derivative **3** could overlay with one of the low-energy conformations of **SB-269970** (Fig. 2). **SB-269970** was subjected to a torsion search and the resulting conformers were minimised with the MMFF94 forcefield implemented within SYBYL.

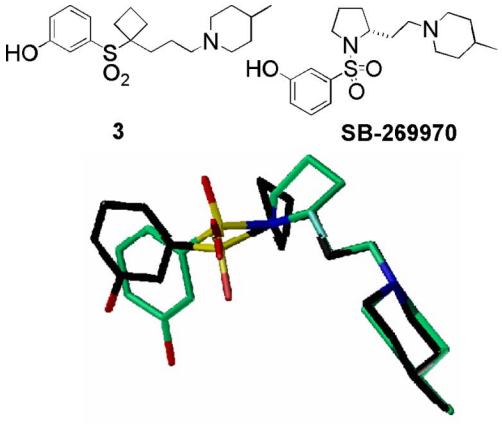

Figure 2. Molecular overlay of structures **3** (black) and **SB-269970** (green).

Keywords: 5-HT$_7$ receptor; Selective ligands; Antagonist; Agonist; Sulfones.
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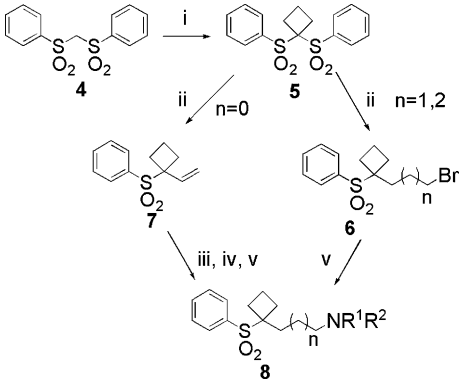
Conformers that were within 5 kcal of the minimum were examined, and the most favoured was used as the starting point for the modelling of the cyclobutyl derivative **3**. Once constructed the derivative **3** was also minimised using the MMFF94 forcefield and overlaid with the starting sulfonamide template as shown in Figure 2.

A series of cyclobutyl sulfones was prepared from **4** as outlined (Scheme 1). The cyclobutyl ring was installed via dialkylation of the bis-sulfone **4** with 1,3-dibromopropane under phase-transfer catalysis. Mono desulfonylation of **5** using 1 equiv of lithium naphthalenide followed by alkylation with the appropriate dibromoalkane provided the bromide **6**, a key intermediate for the synthesis of the desired amino sulfones (**8**). When 1,2-dibromoethane was used, spontaneous β-elimination of HBr occurred, giving the olefin **7**. Thus, an alternative protocol involving hydroboration–oxidation of the double bond in **7** was applied providing **8** ($n = 0$) in three steps.

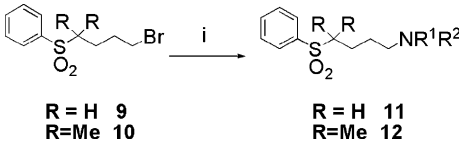
The 4-bromobutyl phenyl sulfone[9] **9** was used for preparation of **11** (Scheme 2). *gem*-Dimethyl sulfone **10** was prepared by alkylation of lithiated isopropyl phenyl sulfone with 1,3-dibromopropane and this product was coupled with appropriate amines to produce the series **12**.

The oxazole ring in **12f** was constructed by a three-step sequence beginning with conversion of **12a** to the Weinreb amide, followed by reduction to the corresponding aldehyde which underwent reaction with TOSMIC® (Scheme 3).

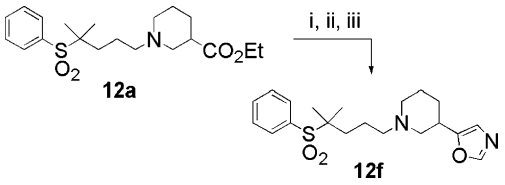
A structure–activity relationship (SAR) study on compounds of generic structure **8** initially focussed on varying the amine fragment and length of the alkyl chain (Table 1).



Scheme 1. Reagents: (i) NaOH, $Br(CH_2)_3Br$, *n*-Bu_4NBr, DCM, H_2O, 71%; (ii) lithium naphthalenide, then $Br(CH_2)_{n+2}Br$, THF, 28–65%; (iii) BH_3–THF complex, THF, then H_2O_2, NaOH, 23%; (iv) MsCl, Et_3N, DCM, 58%; (v) HNR^1R^2, K_2CO_3, MeCN, 70–95%.

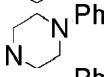
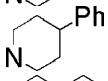
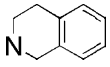
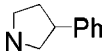
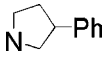
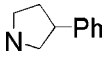


Scheme 2. Reagents: (i) HNR^1R^2, K_2CO_3, MeCN, 70–95%.



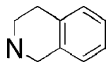
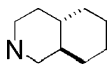
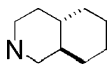
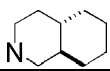
Scheme 3. Reagents: (i) NH(OMe)Me hydrochloride, *i*-PrMgCl, THF, 98%; (ii) DIBAL-H (1.6 equiv), DCM, 99%; (iii) TOSMIC®, K_2CO_3, MeOH.

Table 1. 5-HT_7 receptor binding affinity of cyclobutyl sulfones **8**

Compound	NR^1R^2	*n*	5-HT_7 (K_i/nM)[10]
8a		1	>7000
8b		1	2700
8c		1	>7000
8d		1	550
8e		1	5800
8f		1	22
8g		1	26
8h		1	8
8i[a]		1	9
8j[a]		0	53
8k[a]		2	13

Values represent the geometric mean of 2–5 determinations.
[a] Racemate.

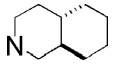
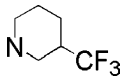
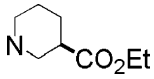
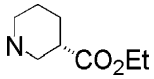
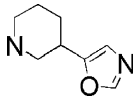
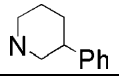
Table 2. Receptor binding selectivity and functional profile of sulfones

Compound	NR^1R^2	5-HT_7 (K_i/nM)[10]	5-HT_{1A} (K_i/nM)[12]	5-HT_{2A} (K_i/nM)[13]	5-CT (%)[11]
8h		8	35	65	5
8l[a]		6	210	570	39
11[a]		96	NT	NT	NT
12b[a]		8	1500	2000	83

Values represent the geometric mean of 2–5 determinations. NT = not tested.
[a] Racemate.

Thus, a range of amines, that included substituted piperazine, and piperidine analogues, were prepared and tested in a 5-HT_7 receptor binding assay. A dramatic

Table 3. Receptor binding selectivity and functional profile of sulfones **12**

Compound	NR^1R^2	5-HT_7 (K_i/nM)[10]	5-HT_{1A} (K_i/nM)[12]	5-HT_{1B} (K_i/nM)[14]	5-HT_{2A} (K_i/nM)[13]	D_2 (K_i/nM)[15]	α_1 (K_i/nM)[16]	hERG (K_i/nM)[17]	5-CT (%)[11]
12b[a]		8	1500	>7000	2000	900	3900	>4000	83
12c[a]		54	>7000	>7000	>2000	>1000	>4000	>5000	0
12d		24	2400	>7000	1870	710	>4000	>5000	0
12e		455	NT	NT	NT	NT	NT	NT	NT
12f[a]		15	>7000	>5000	>1000	1500	>4000	>8000	12
12g[a]		7	400	7700	1800	220	540	>5000	0

Values represent the geometric mean of 2–5 determinations. NT = not tested.
[a] Racemate.

improvement in binding affinity was observed with pendant aromatic groups at the 4-position of piperazine (**8f**) or piperidine (**8g**) rings as well as with 1,2,3,4-tetrahydroisoquinoline (**8h**). The three-carbon linker ($n = 1$) was chosen for further SAR evaluation.

1,2,3,4-Tetrahydroisoquinoline derivative **8h** was counterscreened against selected serotonergic (h5-HT_{1A} and h5-HT_{2A}) receptors (Table 2) and showed modest 4- to 8-fold selectivity.

This compound was also evaluated in a functional model of 5-HT_7 receptor activation[11] and found to behave as an antagonist, giving 5% of the response of the full agonist 5-carboxamidotryptamine (5-CT) at 10 μM concentration. A notable improvement in selectivity was observed when 1,2,3,4-tetrahydroisoquinoline was replaced with *trans*-perhydroisoquinoline providing **8l**. The sulfone **11** having no substituent at the position α to the sulfonyl group was 16-fold less potent than **8l** in inhibiting [^{3}H]-5-HT binding to the human 5-HT_7 receptor. Introduction of *gem*-dimethyl substitution at the α-position to afford **12b** resulted in a compound with an excellent selectivity profile (>100-fold) over those of receptors tested, as indicated in Table 3. However, **12b** was found to behave as a partial agonist, giving 83% of the response of 5-CT at h5-HT_7 receptors. Evaluation of amine SAR in the *gem*-dimethyl series demonstrated that functional activity can be attenuated by installing a pendant substituent at the 3-position, as exemplified by **12c**–**g** (Table 3). This was accomplished without diminution of the selectivity profile. A variety of substituents were tolerated in the 3-position. The *R* ester **12d** was found to be 19-fold more potent than the *S* enantiomer (**12e**) at inhibiting [^{3}H]-5-HT binding to the human 5-HT_7 receptor. Sulfones **12d** and **12f** exhibited high affinity at the human 5-HT_7 receptor with minimal or no functional activity and >30-fold selectivity over selected receptors and ion channels.

In conclusion, a novel series of 5-HT_7 receptor ligands was identified and evaluated, providing compounds showing a broad spectrum of functional activities and good selectivity over selected receptors and ion channels.

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References and notes

1. Eglen, R. M.; Jasper, J. R.; Chang, D. J.; Martin, G. R. *Trends Pharmacol. Sci.* **1997**, *18*, 104.
2. Meneses, A.; Terron, J. A. *Behav. Brain Res.* **2001**, *21*, 21.
3. Pouzet, B.; Didriksen, M.; Arnt, J. *Pharmacol. Biochem. Be.* **2002**, *71*, 655.
4. Terron, J. A. *Eur. J. Pharmacol.* **2002**, *439*, 1.
5. Lovenberg, T. W.; Baron, B. M.; de Lecea, L.; Miller, J. D.; Prosser, R. A.; Rea, M. A.; Foye, P. E.; Racke, M.; Slone, A. L.; Siegel, B. W.; Danielson, P. E.; Sutcliffe, J. G.; Erlander, M. G. *Neuron* **1993**, *11*, 449.
6. Graf, M .; Jakus, R.; Kantor, S.; Levay, G.; Bagdy, G. *Neurosci. Lett.* **2004**, *359*, 45.
7. Sleight, A. J.; Carolo, C.; Petit, N.; Zwingelstein, C.; Bourson, A. *Mol. Pharmacol.* **1995**, *47*, 99.
8. (a) Lopez-Rodriguez, M. L.; Benhamu, B.; Morcillo, M. J.; Porras, E.; Lavandera, J. L.; Pardo, L. *Curr. Med. Chem. Cent. Nerv. Syst. Agents* **2004**, *4*, 203; (b) Forbes, I. T.; Dabbs, S.; Duckworth, D. M.; Jennings, A. J.; King, F. D.; Lovell, P. J.; Brown, A. M.; Collin, L.; Hagan, J. J.; Middlemiss, D. N.; Riley, G. J.; Thomas, D. R.; Upton, N. *J. Med. Chem.* **1998**, *41*, 655; (c) Lovell, P. J.; Bromidge, S. M.; Dabbs, S.; Duckworth, D. M.; Forbes, I. T.; Jennings, A. J.; King, F. D.; Middlemiss, D. N.; Rahman, S. K.; Saunders, D. V.; Collin, L. L.; Hagan, J. J.; Riley, G. J.; Thomas, D. R. *J. Med. Chem.* **2000**, *43*,

342; (d) Forbes, I. T.; Douglas, S.; Gribble, A. D.; Ife, R. J.; Lightfoot, A. P.; Garner, A. E.; Riley, G. J.; Jeffrey, P.; Stevens, A. J.; Stean, T. O.; Thomas, D. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3341; (e) Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. *J. Med. Chem.* **1999**, *42*, 533; (f) Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A. M. *J. Med. Chem.* **2001**, *44*, 1337; (g) Linnanen, T.; Brisander, M.; Mohell, N.; Johansson, A. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 367; (h) Holmberg, P.; Sohn, D.; Leideborg, R.; Caldirola, P.; Zlatoidsky, P.; Hanson, S.; Mohell, N.; Rosqvist, S.; Nordvall, G.; Johansson, A. M.; Johansson, R. *J. Med. Chem.* **2004**, *47*, 3927; (i) Parikh, V.; Welch, W. M.; Schmidt, A. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 269; (j) Perrone, R.; Berardi, F.; Colabufo, N. A.; Lacivita, E.; Leopoldo, M.; Tortorella, V. *J. Med. Chem.* **2003**, *46*, 646; (k) Mattson, R. J.; Denhart, D. J.; Catt, J. D.; Dee, M. F.; Deskus, J. A.; Ditta, J. L.; Epperson, J.; King, H. D.; Gao, A.; Poss, M. A.; Purandare, A.; Tortolani, D.; Zhao, Y.; Yang, H.; Yeola, S.; Palmer, J.; Torrente, J.; Stark, A.; Johnson, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4245; (l) Denhart, D. J.; Purandare, A. V.; Catt, J. D.; King, H. D.; Gao, A.; Deskus, J. A.; Poss, M. A.; Stark, A. D.; Torrente, J. R.; Johnson, G.; Mattson, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4249; (m) Kikuchi, C.; Ando, T.; Watanabe, T.; Nagaso, H.; Okuno, M.; Hiranuma, T.; Koyama, Ma. *J. Med. Chem.* **2002**, *45*, 2197; (n) Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549; (o) Paillet-Loilier, M.; Fabis, F.; Lepailleur, A.; Bureau, R.; Butt-Gueulle, S.; Dauphin, F.; Delarue, C.; Vaudry, H.; Rault, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3753; (p) Forbes, I. T.; Cooper, D. G.; Dodds, E. K.; Douglas, S. E.; Gribble, A. D.; Ife, R. J.; Lightfoot, A. P.; Meeson, M.; Campbell, L. P.; Coleman, T.; Riley, G. J.; Thomas, D. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1055; (q) Leopoldo, M.; Berardi, F.; Colabufo, N. A.; Contino, M.; Lacivita, E.; Niso, M.; Perrone, R.; Tortorella, V. *J. Med. Chem.* **2004**, 47; (r) Vermeulen, E. S.; Van Smeden, M.; Schmidt, A. W.; Sprouse, J. S.; Wikstroem, H. V.; Grol, C. J. *J. Med. Chem.* **2004**, 47; (s) Bojarski, A. J.; Duszynska, B.; Kolaczkowski, M.; Kowalski, P.; Kowalska, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5863; (t) Thomson, C. G.; Beer, M. S.; Curtis, N. R.; Diggle, H. J.; Handford, E.; Kulagowski, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 677; (u) Lopez-Rodriguez, M. L.; Porras, E.; Morcillo, M. J.; Benhamu, B.; Soto, L. J.; Lavandera, J. L.; Ramos, J. A.; Olivella, M.; Campillo, M.; Pardo, L. *J. Med. Chem.* **2003**, *46*, 5638.

9. Decesare, J. M.; Corbel, B.; Durst, T.; Blount, J. F. *Can. J. Chem.* **1981**, *59*, 1415.
10. Displacement of [^{3}H]-5-HT from the cloned human receptor expressed in CHO cells; for details, see Ref. 8s.
11. Percentage of the response of the full agonist 5-CT in $h5HT_7$ receptors; for details, see Ref. 8t.
12. Displacement of [^{3}H]-5-HT from the cloned human receptor expressed in HeLa cells: Stanton, J. A.; Beer, M. S. *Eur. J. Pharmacol.* **1997**, *320*, 267.
13. Displacement of [^{3}H]-ketanserin from the cloned human receptor expressed in CHO cells: Fletcher, S. R.; Burkamp, F.; Blurton, P.; Cheng, S. K. F.; Clarkson, R.; O'Connor, D.; Spinks, D.; Tudge, M.; van Niel, M. B.; Patel, S.; Chapman, K.; Marwood, R.; Shepheard, S.; Bentley, G.; Cook, G. P.; Bristow, L. J.; Castro, J. L.; Hutson, P. H.; MacLeod, A. M. *J. Med. Chem.* **2002**, *45*, 492.
14. Displacement of [^{3}H]-5-HT from the cloned human receptor expressed in CHO cells: Veldman, S. A.; Bienkowski, M. *Mol. Pharmacol.* **1992**, *42*, 439.
15. Displacement of [^{3}H]-spiperone from the cloned human receptor expressed in CHO cells: Patel, S.; Freedman, S.; Chapman, K. L.; Emms, F.; Fletcher, A. E.; Knowles, M.; Marwood, R.; McAllister, G.; Myers, J.; Patel, S.; Curtis, N.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M.; Graham, M.; Matheson, S.; Rathbone, D.; Watt, A. P.; Bristow, L. J.; Rupniak, N. M. J.; Baskin, E.; Lynch, J. J.; Ragan, C. I. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 636.
16. Displacement of [^{3}H]-prozosin from α-1 adrenergic receptors in rat cortex: Lumma, W. C.; Randall, W. C.; Cresson, E. L.; Huff, J. R.; Hartman, R. D.; Lyon, T. F. *J. Med. Chem.* **1983**, *26*, 357.
17. Displacement of [^{35}S]-labelled MK-499 from the cloned receptor expressed in HEK cells; Cooper, L. C.; Carlson, E.; Castro, J.; Chicchi, G.; Dinnell, K.; Di Salvo, J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*.