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Phenyl Benzenesulfonamides are Novel and Selective 5-HT$_6$ Antagonists: Identification of *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (SB-357134)

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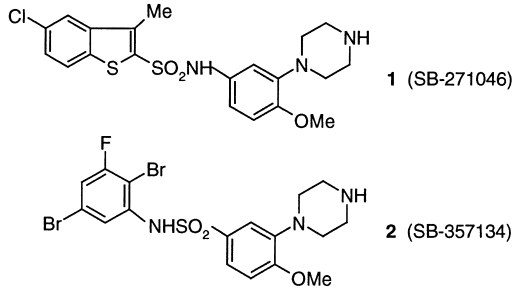
Abstract—Substituted *N*-phenyl-4-methoxy-3-piperazin-1-ylbenzenesulfonamides and conformationally restricted analogues have been identified as high affinity and selective 5-HT$_6$ antagonists. Compounds from this series had a range of pharmacokinetic profiles in rat and in general there was a correlation between clearance and CNS penetration. Based on its overall biological profile **2** (SB-357134) was selected for further pre-clinical evaluation.

The 5-HT$_6$ receptor is the latest serotonin receptor to be identified by molecular cloning. The intriguing distribution in the brain, together with its high affinity for a wide range of drugs used in psychiatry, has stimulated significant recent interest.[1] In particular a possible role for 5-HT$_6$ antagonists in the treatment of learning and memory disorders has been suggested.[1–3] We have recently disclosed[2,4] the sulfonamide **1** (SB-271046) as a potent and selective 5-HT$_6$ antagonist which is currently in phase 1 clinical trials for the treatment of cognitive disorders. This compound has been demonstrated to selectively enhance excitatory transmission within the frontal cortex[5] and to enhance the retention of memory in rats.[3]

We now report the discovery and structure–activity relationships (SAR) of a structurally distinct series of *N*-phenyl-4-methoxy-3-piperazin-1-ylbenzenesulfonamides such as **2** (SB-357134) which are also high affinity and selective 5-HT$_6$ receptor antagonists with good oral bioavailability in rats.



Chemistry

The final compounds were prepared according to Scheme 1.[6] 1-(2-Methoxyphenyl)-4-trichloroacetylpiperazine, prepared from commercially available 1-(2-methoxyphenyl)piperazine, was treated with chlorosulfonic acid to give the key intermediate sulfonyl chloride **3** in 79% overall yield. Coupling of **3** with the appropriate anilines afforded the trichloroacetylsulfonamides **4** in reaction times and yields that were dependent on the reactivity of the anilines. Removal of the protecting

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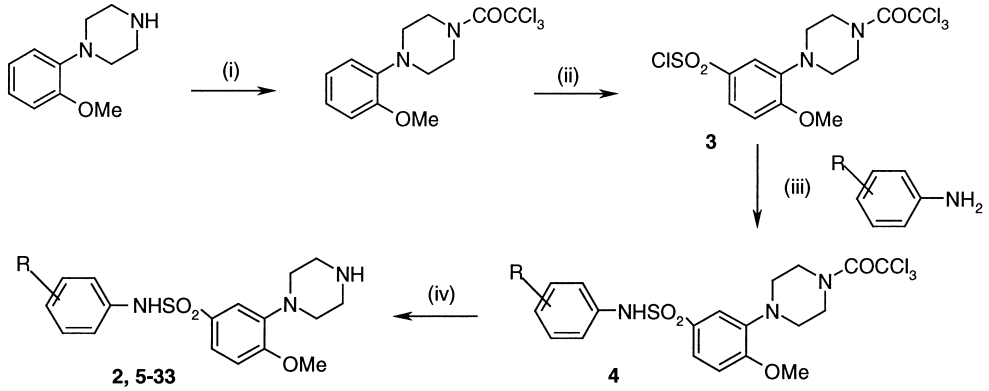


Scheme 1. Reagents and conditions: (i) $CCl_3COCl/{}^{i}Pr_2NEt$, CH_2Cl_2, rt, 18 h (84%); (ii) $ClSO_3H$, 0 °C, 1 h (94%); (iii) pyridine, CH_2ClCH_2Cl, reflux, 1–48 h (25–95%); (iv) 1 M aq KOH, THF, rt, 18 h (90%).

group under basic conditions afforded the final compounds (**2**, **5**–**33**) in efficient yields. Compounds **34**–**43** were prepared similarly by reacting **3** with the appropriately substituted indolines, tetrahydroquinolines and tetrahydroisoquinolines.[6] All the amines and anilines were commercially available or prepared by methods known in the literature.

Results and Discussion

As part of our SAR studies around bisaryl sulfonamides such as **1**, we investigated a number of modifications to the sulfonamide linker group including simply reversing the linker. Molecular modelling indicated that such compounds could adopt a low energy conformation very similar to that obtained with **1** (Fig. 1) although significant differences in electrostatic properties were anticipated.

A wide range of variously substituted *N*-aryl-4-methoxy-3-piperazin-1-ylbenzenesulfonamides were prepared by parallel synthesis and many of these compounds were found to demonstrate excellent binding profiles. In this series substituted phenyl left-hand sides (LHS) were optimal and a selection of these is illustrated in Table 1. A range of lipophilic aromatic LHS groups were tolerated giving compounds with high 5-HT_6 affinity and >100-fold selectivity over other serotinergic and dopaminergic receptors (totalling 13 subtypes: see Table 4). Halogen substitution at the 2- or 3-positions (e.g., **5**, **7**–**9**) was favourable compared to 4-substitution (**10**) and 3,5- and 2,5-disubstitution gave particularly impressive binding profiles (**11**–**15**). In contrast, 2,4- and 3,4-disubstitution was less favoured (**18**–**20**) as was incorporation of polar substituents (**17**). A number of these compounds were demonstrated to be antagonists in a functional model of 5-HT_6 receptor activation.[4]

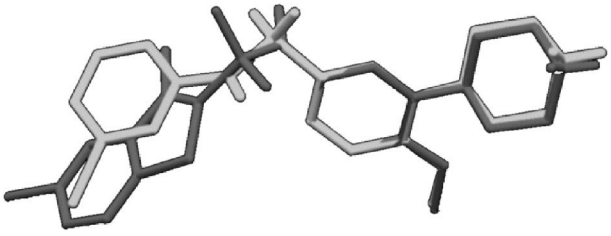
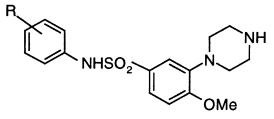


Figure 1. Overlap of low energy conformations of **1** (dark) and **8** (light).

Table 1. 5-HT_6 receptor binding affinity and selectivity[a] of substituted phenyl benzenesulfonamides **2**, **5**–**33**



Compound	R 2	3	4	5	6	p*Ki* 5-HT_6	Selectivity versus 13 receptor subtypes
5	Br					8.8	400
6	^{i}Pr					9.0	500
7		Cl				8.9	630
8		Br				8.9	630
9		I				9.3	400
10			I			8.7	160
11		Cl		Cl		9.2	1250
12		Br		Br		9.3	1600
13	Br			Br		9.0	2000
14	OMe			Cl		8.9	400
15	Me			I		9.1	1000
16	OMe			CF_3		8.4	60
17	Me			NO_2		7.7	—
18	CF_3		Cl			7.6	—
19	Br		Me			8.1	< 50
20		Cl	Cl			8.6	200
21	F		Br		F	6.8	—
22	OMe		Cl	Me		8.7	400
23	Cl		Cl	Cl		8.3	500
24	Cl	Cl		Cl		8.7	500
25	Br	Br		Br		8.6	400
26	Br	Cl		Cl		8.5	320
27	Cl	Br		Cl		8.7	800
28	Cl	Cl		Br		8.4	320
29	Cl	Br		Br		8.6	400
30	Br	Cl		Br		8.4	250
31	F	Br		Br		8.6	320
2	Br	F		Br		8.5	1300
32	Cl	F		Br		8.5	1600
33	Cl	F		F		7.5	—

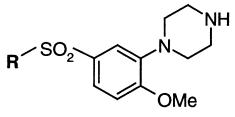
[a]Selectivity was determined against the 13 receptor subtypes detailed in Table 4.

Table 2. The pharmacokinetic profiles of bisaryl sulfonamides in rat

Compound	CLb iv[a] (mL/min/Kg)	AUC/dose po (μM min/μmol)	Fpo (%)	Brain: blood
1	8	300 ± 80[b]	82±16[b]	0.10
2	14	130±11[c]	65±11[c]	0.19
5	60			0.24
6	52			NQ[f]
9	58			0.13
11	4	450±60[d]	51±9[d]	0.02
13	43	17±4[e]	20 est.[e]	0.38
24	2	2450±200[e]	>80 est.[e]	0.02
36	73			0.41
41	83			NQ
42	76			0.10

[a]Measured at steady-state following iv infusion at 0.6 mg/kg/h ($n=1$); blood drug levels were determined by LC/MS/MS.
[b–e]Following oral (suspension) dose ($n=3$); blood drug levels were determined by LC/MS/MS.
[b]10 mg/kg in 10% (w/v) Encapsin™ and 2% DMSO (v/v) aq.
[c]2 mg/kg in 1% methylcellulose (v/v) aq.
[d]10 mg/kg in 1% methylcellulose (v/v) aq.
[e]3 mg/kg in 1% methylcellulose (v/v) aq.
[f]NQ, non quantifiable.

Table 3. 5-HT_6 receptor binding affinity and selectivity[a] of conformationally restricted bisaryl sulfonamides **34**–**43**



Compound	Ar	pK_i 5-HT_6	Selectivity versus 13 receptor subtypes
34		9.5	630
35		8.4	60
36		8.4	160
37		9.1	1000
38		9.5	400
39		8.5	200
40		9.1	250
41		8.9	200
42		9.3	800
43		8.8	100

[a]Selectivity was determined against the 13 receptor subtypes detailed in Table 4.

The pharmacokinetic profile of several of these compounds was assessed in rats (Table 2). Monosubstituted analogues such as **5, 6** and **9** were very rapidly cleared in vivo. In contrast, the 3,5-dichloro-analogue **11** demonstrated very low clearance and excellent oral bioavailability. However, the brain to blood ratio at steady state ($n=3$, following 8 h iv infusion) was very low (2%). In contrast, the 2,5-dibromo-analogue **13**, which had a similar in vitro binding profile to **11**, was found to have much improved CNS penetration (38%) but significantly higher clearance.

In an effort to combine the metabolic stability of the 3,5-disubstituted analogues with the apparently enhanced CNS penetration of the *ortho*-substituted analogues, a series of 2,3,5-trisubstituted analogues was prepared (Table 1). Most of these compounds had good 5-HT_6 affinity and exceptional selectivity, and several were further profiled in vivo (Table 2). The 2,3,5-trichloro sulfonamide **24** demonstrated a similar pharmacokinetic profile to **11** with extremely low clearance (2 mL/min/kg) but correspondingly low brain to blood ratio (2%). In contrast, the 2,5-dibromo-3-fluoro-analogue **2** showed markedly improved CNS penetration (19%) combined with increased but still low clearance (14 mL/min/kg) and excellent oral bioavailability. The 2,4,5-analogues **22**–**23** and the 2,4,6-analogue **21** had reduced 5-HT_6 affinity and selectivity.

In an attempt to further increase the brain penetration of these compounds, conformationally restricted indoline, tetrahydroquinoline and tetrahydroisoquinoline analogues

Table 4. Receptor binding profile of compounds **2, 13, 24** and **34**[a]

	Affinity (pK_i)			
Receptor	**2**	**13**	**24**	**34**
5-HT_{1A}	< 5.2	< 5.5	5.4	6.3
5-HT_{1B}	< 5.4	< 5.3	< 5.0	5.9
5-HT_{1D}	< 5.4	< 5.8	< 5.5	6.7
5-HT_{1E}	< 5.0	< 5.0	< 5.0	< 5.0
5-HT_{1F}	< 5.0	< 5.0	< 5.0	< 5.1
5-HT_{2A}	< 5.1	< 5.0	< 5.0	< 5.4
5-HT_{2B}	< 5.4	< 5.5	5.7	6.2
5-HT_{2C}	< 5.3	< 5.3	6.0	6.2
5-HT_4	< 5.3	5.5	< 5.0	5.4
5-HT_6	**8.54±0.03 (*n*=9)**	**8.99±0.08 (*n*=6)**	**8.7±0.03 (*n*=3)**	**9.5±0.1 (*n*=3)**
5-HT_7	< 5.0	< 5.4	< 5.0	7.0
Adrenergic α_{1B}	< 5.1	< 5.7	< 5.4	6.0
Dopaminergic D_2	< 5.3	< 5.0	< 5.0	5.6
Dopaminergic D_3	< 5.3	< 5.3	< 5.4	6.0

[a]All values represent the mean of at least two determinations, with each determination lying within 0.2 log unit of the mean. Receptors and radioligands used in binding assay: 5-HT_{1A} (human cloned receptors in HEK 293 cells; [^{3}H]-8-OH-DPAT); 5-HT_{1B} (human cloned receptors in CHO cells; [^{3}H]-5-HT); 5-HT_{1D} (human cloned receptors in CHO cells; [^{3}H]-5-HT); 5-HT_{1E} (human cloned receptors in CHO cells; [^{3}H]-5-HT); 5-HT_{1F} (human cloned receptors in CHO cells; [^{3}H]-5-HT); 5-HT_{2A} (human cloned receptors in HEK 293 cells; [^{3}H]-ketanserin); 5-HT_{2B} (human cloned receptors in HEK 293 cells; [^{3}H]-5-HT); 5-HT_{2C} (human cloned receptors in HEK 293 cells; [^{3}H]-mesulergine); 5-HT_6 (human cloned receptors in HeLa cells; [^{3}H]-LSD); 5-HT_7 (human cloned receptors in HEK 293 cells; [^{3}H]-5CT); D_2 (human cloned receptors in CHO cells; [^{125}I]-iodosulpride); D_3 (human cloned receptors in CHO cells; [^{125}I]-iodosulpride).

were prepared in the expectation that replacing the polar sulfonamide NH would increase CNS penetration. A number of these analogues maintained excellent binding affinity and selectivity (Table 3) and the 6-iodoindoline **34** and the 7-bromotetrahydro-quinoline **38** demonstrated the highest 5-HT_6 affinities yet achieved. Unfortunately, compounds from this series such as **36**, **41** and **42** had in vivo clearances in rat equal or greater than liver blood-flow (Table 2). In general in this series, attempts to increase CNS penetration by increasing lipophilicity have also led to increases in the in vivo clearance.

Summary

A number of substituted *N*-phenyl-4-methoxy-3-piperazin-1-ylbenzenesulfonamides and conformationally restricted analogues have been identified with excellent 5-HT_6 affinity and selectivity over a range of serotonergic and dopaminergic receptors (Table 4). In a human 5-HT_6 functional assay they were found to be full antagonists with no evidence of intrinsic activity. Compounds from this series had a range of pharmacokinetic profiles in rat and in general there was a positive correlation between clearance and CNS penetration. Based on its overall biological profile **2** (SB-357134) was selected for further pre-clinical evaluation.

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