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Tricyclic azepine derivatives as selective brain penetrant 5-HT$_6$ receptor antagonists

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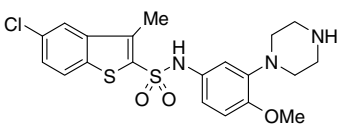
ABSTRACT

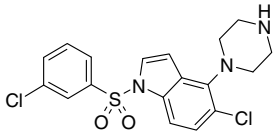
Starting from a benzazepine sulfonamide 5-HT$_6$ receptor antagonist lead with limited brain penetration, application of a strategy of conformational constraint and reduction of hydrogen bond donor count led to a novel series of tricyclic derivatives with high 5-HT$_6$ receptor affinity and excellent brain:blood ratios.

5-HT$_6$ receptor mRNA is almost exclusively expressed within the brain, and many CNS drugs have high affinity for the 5-HT$_6$ receptor. Hence, there has been interest in elucidating the role of the 5-HT$_6$ receptor in CNS disorders through the development of selective agents. Several classes of ligands have been disclosed in recent years,[1] including the highly potent and selective 5-HT$_6$ receptor antagonist SB-271046 **1**,[2] and a number of 5-HT$_6$ receptor antagonists are currently in clinical trials for treatment of cognitive disorders, for example, Alzheimer's disease. The discovery that 5-HT$_6$ receptor antagonists, such as **1**, have a beneficial effect on memory consolidation in animal models of cognitive enhancement, such as the Morris water maze and Object Recognition paradigms,[3,4] suggested a possible role for 5-HT$_6$ receptor antagonists in the treatment of learning and memory disorders.[5] The proposed involvement of 5-HT$_6$ receptor antagonism in memory consolidation is further supported by the effect of **1** on neuronal cell adhesion molecule (NCAM) polysialylation in rat brain.[6] NCAM polysialylation is a process which contributes to learning-associated neuronal remodelling in the adult central nervous system. Acute and chronic administration of **1** has been shown to increase the frequency of NCAM polysialylated neurons, activated in the entorhinal and perirhinal cortex, as well as the dentate gyrus in response to water maze spatial learning.[7] These data imply that 5-HT$_6$ receptor antagonists may have a beneficial effect on synaptic plasticity in brain regions that are critical to information processing, a property which may underpin their broad spectrum of activity in preclinical models of cognition enhancement.

Although **1** had activity in a range of centrally mediated cognition models, its brain:blood ratio in rat was low (0.05:1) and the compound was shown to be a substrate for the P-glycoprotein (P-gp) efflux pump with low passive permeability. A successful strategy for improving the brain penetration of **1** has been described,[8] in which conformational constraint and concomitant removal of an acidic NH group led to the highly brain penetrant and orally bioavailable indolylpiperazine 699929 **2**.



SB-271046, **1**



699929, **2**

A cross screen against the 5-HT$_6$ receptor led to the identification of benzazepine **3** as a potent and selective 5-HT$_6$ receptor antagonist lead (pK_i = 8.7).[9] Although compound **3** had brain:blood ratio 0.5:1, we reasoned that by applying the same strategy of conformational constraint to **3**, to give compounds such as **4**, we could further improve the brain:blood ratio.

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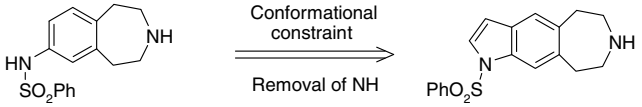


3 4

This *Letter* describes the successful application of the same strategy to a benzazepine sulfonamide starting point, leading to a novel series of selective tricyclic 5-HT_6 receptor antagonists with examples demonstrating excellent brain:blood ratio.

Novel compounds **4** and **14**–**24** (Table 1) were prepared as shown in Schemes 1–3. The benzazepine nitrate salt **5** was selectively nitrated at C-7 with nitric acid, then the product was protected as a Boc derivative **6**. Catalytic hydrogenation followed by reaction with *N*-iodosuccinimide led to the formation of compound **7** which underwent a Sonogashira coupling with trimethylsilylacetylene to afford **8** in excellent yield. Treatment of **8** with an arylsulfonyl chloride in the presence of pyridine, in some cases, led to the formation of the bis-sulfonylated material. This problem was overcome by treating **8** with bis-TMS-trifluoroacetamide, which enabled a transient TMS-protection of the nitrogen; the subsequent in situ addition of the phenylsulfonyl chloride, followed by aqueous work up, afforded the desired monosulfonylated product **9** in 98% yield.[10] Ring closure to form **10** was effected in 86% yield using copper (I) iodide, and removal of the phenylsulfone and the trimethylsilyl protecting group was achieved with sodium methoxide in methanol to form **11** in 99% yield (Scheme 1).

Sulfonylation of **11** with a range of arylsulfonyl chlorides and removal of the Boc group using HCl afforded final compounds **4** and **14**–**19** in good yields. Compounds **20** and **21** were obtained by chlorination of **11** with *N*-chlorosuccinimide followed by sulfonylation and Boc removal. Compound **22** was obtained by reductive alkylation of **15** with formaldehyde in the presence of sodium triacetoxyborohydride.

Variation of the point of attachment of the arylsulfonyl group was also investigated (Scheme 2). Anion formation on **11** was followed by reaction with diphenyldisulfide and oxidation with magnesium monoperoxyphthalate (MMPP) to form sulfone **12**. This was alkylated with methyl iodide, then the Boc group was removed using HCl to afford the desired product **23** in 38% overall yield.

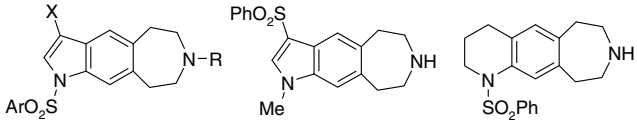
In order to investigate the effect of ring size and aromaticity, compound **24** (Scheme 3) was synthesised starting from intermediate **7**. A Sonogashira coupling with 3,3-bis(ethyloxy)-1-propyne followed by catalytic hydrogenation afforded **13** in 74% yield. Ring closure was performed in 66% yield by hydrogenation under aqueous acidic conditions, the resulting tricycle was sulfonylated with benzenesulfonyl chloride and the Boc group was removed using HCl to afford the desired product.

All final compounds were purified by flash chromatography and converted to hydrochloride salts and were evaluated for functional potency in a cAMP accumulation assay,[11] and data are shown in Table 1.

Tricyclic compound **4** encouragingly showed high potency as a functional antagonist at the 5-HT_6 receptor (fpK_i = 8.8). Unfortunately, it had low in vitro metabolic stability in rat microsomes (Table 1). We therefore investigated variations at the arylsulfone moiety and indole portion of the tricyclic core. 3-Substituted phenylsulfones (**15**, **17**) were favoured for optimal potency and improved metabolic stability within the series. However, more lipophilic substituents (**14**, **15**) gave rise to increased P450 inhibition against the 3A4 isoform with IC_{50} values < 10 μM (Table 1). Encouragingly, analysis of brain and blood samples following oral dosing of **15** in the rat showed that the brain:blood ratio was 5:1, demonstrating that the strategy for improving CNS penetration was successful. However, absolute concentrations in blood were low (38 nM at 1 mg/kg oral dose), suggesting that further improvement in metabolic stability was required. Replacement of the phenyl ring with a heterocycle led to either a decrease in potency (pyridine **18**) or a greater in vitro metabolic instability (thiophene **19**). Introduction of a chlorine substituent at the 3-position of the indolyl core (**20**, **21**) was targeted in order to block a potential metabolically labile centre. Both compounds **20** and **21** showed improved in vitro metabolic stability in rat microsomes relative to both **4** and **15**, and an IC_{50} against the 3A4 isoforms of >10 μM.

Methylation of the azepine nitrogen (**22**) gave excellent 5-HT_6 antagonist potency but led to high in vitro metabolic instability,

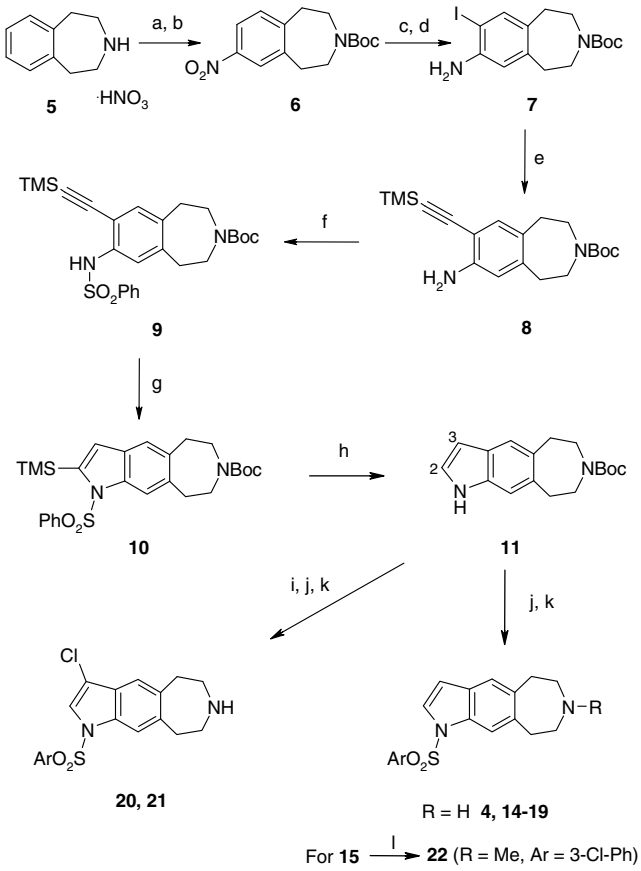
Table 1
5-HT_6 receptor functional activity (fpK_i),[a] rat microsomal clearance and cytochrome P450 inhibition at the 3A4 isoform



23 24

Compound[b]	Ar	X	R	fpK_i	Rat CLi[12] (mL/min/g liver)	P450 IC_{50}[13] (μM)	
						3A4 DEF	3A4 PPR
4	Ph	H	H	8.8	7.1	12	20
14	C_6H_4(2-Cl)	H	H	8.1	4.5	2.5	3.2
15	C_6H_4(3-Cl)	H	H	8.8	2.5	3	7
16	C_6H_4(4-Cl)	H	H	8.1	nd[c]	nd[c]	nd[c]
17	C_6H_4(3-OMe)	H	H	8.7	2.7	17	27
18	2-Pyridyl	H	H	7.0[d]	3.6	39	77
19	3-Thienyl	H	H	8.1	21	9.7	22
20	Ph	Cl	H	8.6	1.7	12	19
21	C_6H_4(3-Cl)	Cl	H	8.4	<0.5	12	20
22	C_6H_4(3-Cl)	H	Me	8.9	22	15	71
23	—	—	—	8.7	4.6	7.8	13
24	—	—	—	7.4[d]	nd[c]	nd[c]	nd[c]

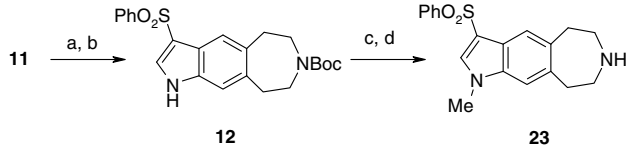
[a] Unless otherwise stated all fpK_i values represent the mean of at least three experiments, each within 0.3 of the mean.
[b] All new compounds gave satisfactory analytical and/or mass spectral data.[14]
[c] Not determined.
[d] N = 2.



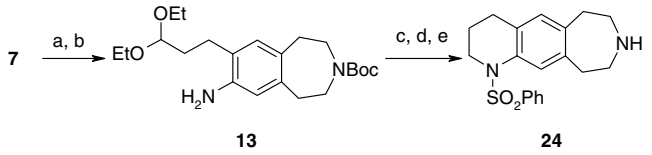
Scheme 1. Reagents and conditions: (a) conc. HNO_3, RT, 15 h, 66%; (b) Boc_2O, Et_3N, CH_2Cl_2, RT, 3 h, 83%; (c) H_2 (50 psi), Pd/C, EtOH/dioxane, RT, 2 h, quantitative; (d) *N*-iodosuccinimide, MeCN, 0 °C–RT, 20 h, 68%; (e) TMS-acetylene, CuI, $PdCl_2(PPh_3)_2$, Et_2NH, RT, 15 h, 98%; (f) bis-TMS-trifluoroacetamide, pyridine, $PhSO_2Cl$, CH_2Cl_2, 0 °C, 3 h, 98%; (g) CuI, DMF, Et_3N, 80 °C, 20 h, 86%; (h) NaOMe, MeOH, 45 °C, 3 h, 99%; (i) *N*-chlorosuccinimide, CH_2Cl_2, RT, 1 h, 69%; (j) $ArSO_2Cl$, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), CH_2Cl_2 or THF, RT, up to 20 h, 44–99%; (k) HCl (4 M in 1,4-dioxane) 50 °C, up to 3 h or MeOH, HCl (1 M in Et_2O), 40 °C, up to 15 h, 8–93%; (l) H_2CO, $NaBH(OAc)_3$, AcOH, NaOAc, MeOH, RT, 10 min, 55%.

possibly due to N-dealkylation. Sulfone **23** was prepared as a regioisomer of **4** with the view to blocking a potential metabolic site on the pyrrole ring. Whilst the change was tolerated potency-wise, compound **23** also had low in vitro metabolic stability. Expanding the conformational constraint from a five- to a six-membered ring (**24**) led to a loss of potency at the 5-HT_6 receptor.

In summary, the conformational constraint of benzazepine **3** and concomitant removal of an acidic NH proved to be a successful strategy for obtaining compounds with the potential for improved brain penetration, as exemplified by compound **15**, which proved to be approximately 10-fold more brain penetrant than the starting benzazepine **3.** Compound **20** combined high 5-HT_6 antagonist potency (fpK_i = 8.6), good selectivity against a number of receptors (for example, fpK_i at 5-HT_{2A} = 7.6, 5-HT_{2B} = 6.4, 5-HT_{2C} = 6.8), a good P450 and in vitro metabolic stability profile, and was therefore progressed to a rat ex vivo binding assay,[15] showing an ED_{50} = 4 mg/kg following oral dosing.



Scheme 2. Reagents and conditions: (a) NaH, PhSSPh, DMF, RT, 15 h, 64%; (b) MMPP, MeOH/H_2O, RT, 22 h, 77%; (c) K_2CO_3, MeOH, RT, 0.5 h, then MeI, DMF, RT, 20 h, 93%; (d) HCl, 1,4-dioxane, RT, 1 h, 83%.



Scheme 3. Reagents and conditions: (a) 3,3-bis(ethyloxy)-1-propyne, CuI, $PdCl_2(PPh_3)_2$, Et_2NH, 45 °C, 20 h, 80%; (b) H_2, Pd/C, EtOH, RT, 2 h, 92%; (c) H_2 (50 psi), Pd/C, THF/AcOH/H_2O, 50 °C, 3 days, 66%; (d) $PhSO_2Cl$, Et_3N, DCM, RT, 2 days, 15%; (e) HCl (1 M in Et_2O), MeOH, 40 °C, 15 h, 53%.

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10. Preparation of **9**. To a solution of 1,1-dimethylethyl 7-amino-8-[(trimethylsilyl)ethynyl]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (4.1 g, 11.45 mmol) and pyridine (3.7 ml, 45.8 mmol) in CH_2Cl_2 (45 ml) cooled to 0 °C in an ice bath was added N, *O*-bis(trimethylsilyl) trifluoroacetamide (6.1 ml, 23 mmol) dropwise under argon atmosphere. Then, phenylsulfonylchloride (1.53 ml, 12 mmol) was added dropwise over a period of 15 min at 0 °C. After 3 h, the reaction mixture was poured into water, and the aqueous solution extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude material was purified by flash chromatography with a gradient of acetone in toluene to afford the desired compound **9** (5.6 g, 98%); δ_H ($CDCl_3$) 0.24 (9H, s), 1.47 (9H, s), 2.76 (2H, br s), 2.86–2.88 (2H, m), 3.47–3.51 (4H, m), 7.06 (2H, d), 7.39–7.44 (3H, m), 7.52 (1H, t), 7.75 (2H, d).
11. Membranes of HeLa cells expressing the 5-HT_6 receptor were treated with the test compound as a solution in DMSO, the agonist 5-HT and ATP. The resulting mixture was incubated to allow the production of cAMP which was then measured using a DiscoveRx HitHunter chemiluminescence cAMP assay kit.
12. Rat microsomal intrinsic clearance (CLi) determination: A 2 mM stock solution of the 5-HT_6 receptor antagonist in dimethylsulfoxide (DMSO) was prepared and used to generate a 0.1 mM final working solution in DMSO. This was spiked into 50 mM phosphate buffer (pH 7.4) containing 0.5 mg/mL microsomal protein to give a final incubation concentration of 0.5 μM substrate after the addition of NADP co-factor solution. The solutions were mixed well and pre-incubated for 5 min at ca. 37 °C before the reaction was started with the addition of co-factor. Samples (50 μL) were then taken at 0, 3, 6, 9, 12, 15, 18, 24 and 30 min and at 30 min for the controls into 200 μL acetonitrile containing internal standard. This method was carried out in triplicate. Samples were analysed for parent compound using a specific HPLC/MS/MS method.
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14. ^1H NMR spectra were recorded at 250 or 400 MHz in $CDCl_3$ or DMSO-d_6 as solvent. Compound **20**, (HCl salt); δ_H (DMSO-d_6) 3.15–3.28 (8H, m), 7.42 (1H, s), 7.62 (2H, t), 7.73 (1H, t), 7.89 (1H, s), 8.06 (2H, d), 8.10 (1H, s), 9.11 (2H, br s). Mass Spectrum: $C_{18}H_{17}{}^{35}ClN_2O_2S$ requires 360; found 361 (MH^+).
15. Rats received vehicle or the selective 5-HT_6 receptor antagonist, dosed orally, 4 h pre-treatment. Animals were then sacrificed, and striatum was removed. Tissue was homogenised, and a binding assay performed with the selective 5-HT_6 receptor antagonist radioligand [^{125}I]-258585. An ED_{50} value was determined from the dose–response curve. Drug analysis of blood and brain samples using LC/MS/MS allowed direct measurement of brain:blood ratio.