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Bicyclic Piperazinylbenzenesulphonamides are Potent and Selective 5-HT$_6$ Receptor Antagonists

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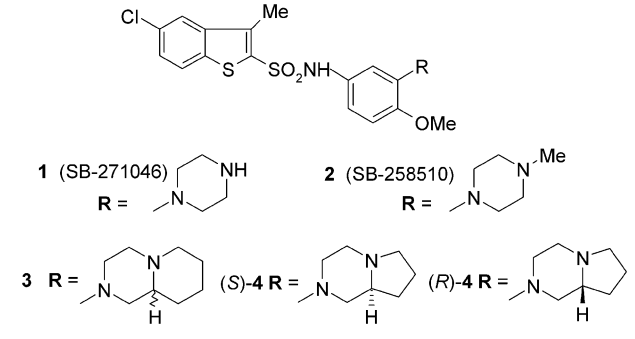
Abstract—The synthesis of novel 3-(octahydropyrido[1,2-*a*]pyrazin-2-yl)- and 3-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl-2-benzo[*b*]thiophene sulphonamide derivatives **3**, (*S*)-**4** and (*R*)-**4** is described. The compounds show high affinity for the 5-HT$_6$ receptor, excellent selectivity against a range of other receptors and good brain penetration.

The 5-HT$_6$ receptor is one of the most recently identified serotonin receptors. It was first isolated from rat striatal mRNA[1,2] in 1993 and subsequently the human 5-HT$_6$ gene was cloned and characterised.[3] The 5-HT$_6$ receptor is positively coupled to the adenylate cyclase second-messenger system and is primarily found in the central nervous system.[4] The exact functional role of the receptor has yet to be ascertained, however its unique distribution in the brain and high affinity for therapeutic atypical antipsychotics and antidepressants suggest a possible role for 5-HT$_6$ receptor antagonists in the therapy of schizophrenia and depression.[5,6]



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A number of studies[7–9] have also indicated that 5-HT$_6$ antagonists could be of value in the treatment of memory dysfunction.[10] Recently, we reported that the selective 5-HT$_6$ antagonist **1** (SB-271046)[11] improved cognitive performance in animal models[12] providing further support for this hypothesis. Moreover, this compound has been demonstrated to selectively enhance excitatory transmission within the frontal cortex in rats.[13]

We now report the preparation and biological profile of some bicyclic piperazine derivatives of **1** with improved CNS penetration.

Chemistry

The synthesis of the 3-(octahydropyrido[1,2-*a*]pyrazin-2-yl)phenyl analogue **3** was carried out according to Scheme 1.[14] Thus, alkylation of 2-methoxy-5-nitroaniline with 2-bromomethylpiperidine afforded **5** which in turn was alkylated with ethyl bromoacetate in refluxing ethanol to give the piperidinyl-1-acetic acid ethyl ester **6** in 64% yield. Cyclisation of **6** using sodium in dioxane[15] gave the required lactam **7**. Sequential reduction of the nitro and carbonyl groups in **7** provided the bicyclopiperazinylaniline **8** in 82% yield for the two steps. Finally, **8** was coupled with 5-chloro-3-methyl[*b*]ben-

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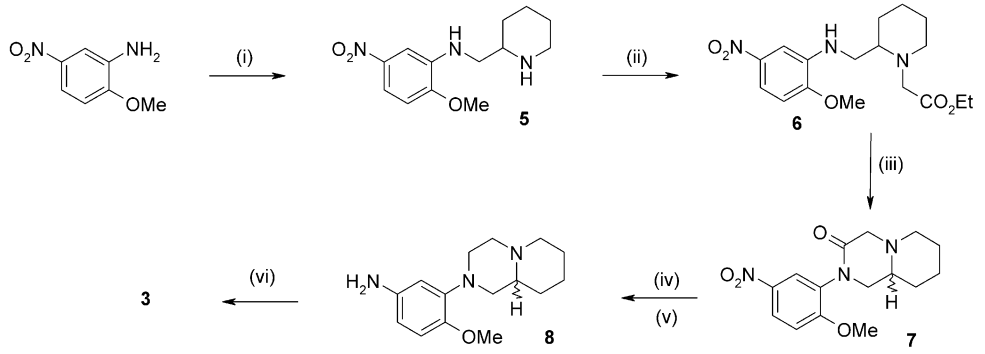


Scheme 1. Reagents and conditions: (i) 2-(bromomethyl)piperidine, DMF or chlorobenzene, reflux (47%); (ii) ethyl bromoacetate/Et_3N, ethanol, reflux (64%); (iii) Na, dioxane, reflux (31%); (iv) H_2/Pd/C, ethanol, rt (91%); (v) BH_3, THF, reflux (90%); (vi) 5-chloro-3-methylbenzo[*b*]thiophene-2-sulphonyl chloride/$^i Pr_2EtN$, CH_2Cl_2, rt (32%).

zothiophene-2-sulphonyl chloride to afford the target sulphonamide **3**.[16]

Initial attempts at the preparation of the corresponding 3-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl analogue (*S*)-**4** using a similar synthetic approach were unsuccessful. Rather unexpectedly, alkylation of 2-methoxy-5-nitroaniline with 2-bromo-1-((*S*)-2-bromomethylpyrrolidin-1-yl) ethanone **9** led to the formation of the hydroxymethyl derivative **10** as a major product: presumably via amide carbonyl assisted hydrolysis during aqueous work up (Scheme 2). An alternative strategy based on the use of enantiomerically pure diketopiperazine **13** was therefore adopted (Scheme 3). Thus, acylation of 2-methoxy-5-nitroaniline with the mixed anhydride of Boc-L-proline provided the amide **11** in 75% yield. After removal of the Boc group, the pyrrolidinyl nitrogen was selectively acylated with bromoacetyl bromide to give the diamide **12**. Cyclisation of **12** using NaH in DMF afforded the desired diketopiperazine **13** which was 98% pure by chiral HPLC. Sequential reduction of the nitro and keto groups in **13** yielded the amino intermediate **14** which was converted into the sulphonamide (*S*)-**4**,[16] in a similar way to that described for **3**. The corresponding *R*-enantiomer (*R*)-**4** was prepared from Boc-D-proline by the same synthetic sequence that was employed for (*S*)-**4**.

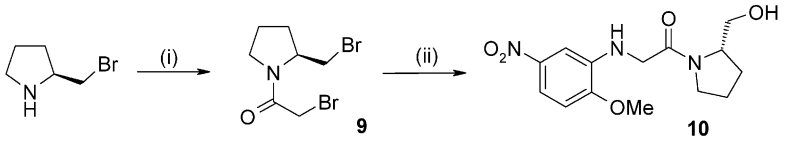
Results and Discussion

5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl-phenyl]-2-benzo[*b*]thiophene sulphonamide **2**, developed in our laboratory,[11] showed subnanomolar binding affinity (pK_i 9.2) for the 5-HT_6 receptor and moderate brain penetration (18%) combined with low clearance (12.5 mL/min/kg) in rats. However, this compound was found to be metabolised by N-dealkylation to yield the NH-piperazine **1**. Although the latter analogue had similar affinity (pK_i 8.9) to that of its N-methylated counterpart, it was somewhat less brain penetrant.[11] Therefore, analogues with constrained bicyclic systems such as **3** and **4** were targeted in the hope of enhancing metabolic stability and CNS penetration by precluding dealkylation to the active NH metabolite.

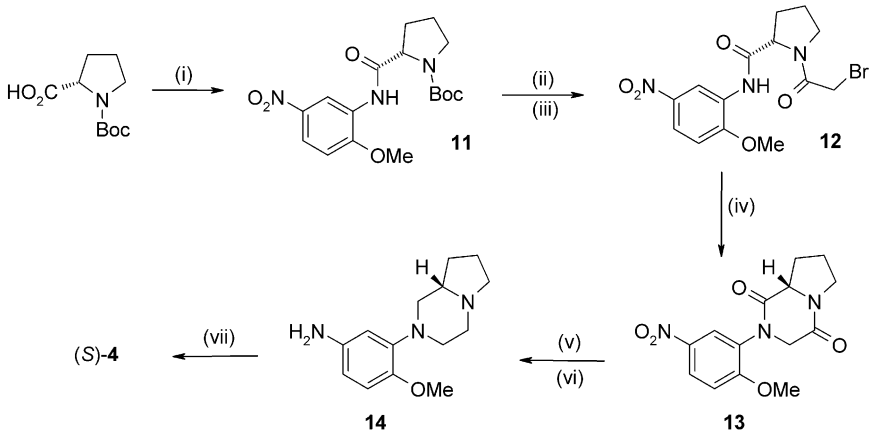
The binding profile of **3**, (*S*)-**4** and (*R*)-**4** across a range of receptor subtypes was determined and is shown in Table 1 along with that of **1** and **2** for comparison.[11] The 3-(octahydropyrido[1,2-*a*]pyrazin-2-yl)phenyl analogue **3** had good 5-HT_6 affinity (pK_i 8.3) and selectivity profile (>80-fold). The more compact (*S*)-3-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl derivative (*S*)-**4** was found to have almost 10-fold increased affinity for the 5-HT_6 receptor (pK_i 9.1) and greater than 200-fold selectivity against a range of other receptors (totaling 13 subtypes). The enhanced target affinity of (*S*)-**4** relative to **3** points towards a size constraint for the bicyclopiperazines in the 5-HT_6 receptor binding pocket. Interestingly, the *R*-enantiomer (*R*)-**4** had identical 5-HT_6 affinity and a very similar selectivity profile to that of (*S*)-**4** suggesting that both the enantiomers had almost identical binding modes.

Similar binding pattern was also observed by us for (*R*) and (*S*) enantiomers of the 3-methylpiperazinyl arylsulphonamide in the structure–activity study of conformationally restricted analogues of **1** reported recently.[17]

Compound (*S*)-**4** was evaluated in a functional model of 5-HT_6 receptor activation.[11] In the presence of (*S*)-**4**, the 5-HT concentration-response curve had the same maximal response but was shifted rightward in a parallel manner with an apparent pK_b of 7.7 ± 0.1 ($n = 3$). The reason for the difference between the affinity value (pK_i) for (*S*)-**4**, derived from radioligand binding assays and antagonist potency (pK_b), derived from functional



Scheme 2. Reagents and conditions: (i) bromoacetyl bromide/$^i Pr_2EtN$, CH_2Cl_2, 10 °C (95%); (ii) 2-methoxy-5-nitroaniline/K_2CO_3, NMP, rt (22%).



Scheme 3. Reagents and conditions: (i) EtOCOCl/2-methoxy-5-nitroaniline/4-methylmorpholine, THF, −10 °C to rt (75%); (ii) CF_3COOH, CH_2Cl_2, rt (91%); (iii) bromoacetyl bromide/$^{i}Pr_2EtN$, CH_2Cl_2, −10 °C; (iv) NaH, DMF, rt (34% for two steps); (v) H_2/Pd/C, ethanol/ethyl acetate, rt (89%); (vi) BH_3/THF, reflux (51%); (vii) 5-chloro-3-methylbenzo[*b*]thiophene-2-sulphonyl chloride/pyridine, CH_2Cl_2, rt (75%).

Table 1. 5-HT_6 Receptor binding affinity and selectivity[a] of compounds **1**, **2**, **3**, (*S*)-**4** and (*R*)-**4**

	Affinity (pK_i)				
Receptor	**1**	**2**	**3**	(*S*)-**4**	(*R*)-**4**
5-HT_{1A}	6.4	6.3	6.2	6.9	6.7
5-HT_{1B}	6.1	6.1	5.4	6.2	6.2
5-HT_{1D}	6.6	6.7	6.5	7.0	6.9
5-HT_{1E}	< 5.0	5.6	< 6.0	5.8	6.0
5-HT_{1F}	< 6.0	6.6	< 6.0	6.5	6.7
5-HT_{2A}	< 5.6	6.0	6.2	6.6	5.9
5-HT_{2B}	< 5.4	6.0	5.7	5.9	5.9
5-HT_{2C}	5.7	6.3	< 5.5	6.4	6.2
5-HT_4	5.4	5.5	< 5.1	5.3	5.8
5-HT_6	**8.9** (n = 3)	**9.2** (n = 3)	**8.3** (n = 3)	**9.1** (n = 9)	**9.1** (n = 3)
5-HT_7	5.4	5.5	< 5.1	6.0	6.2
Adrenergic α_{1B}	5.7	5.7	5.7	5.8	6.0
Dopaminergic D_2	5.6	6.1	6.4	5.8	5.7
Dopaminergic D_3	6.3	6.7	6.0	6.5	6.2

[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 293cells, [^{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]-5-CT); D_2 (human cloned receptors in CHO cells, [^{125}I]iodosulpride); D_3 (human cloned receptors in CHO cells, [^{125}I]iodosulpride).

assays is unclear, but may be due to methodological differences between the binding and functional assays. Pharmacokinetic studies at steady state in rats (n = 3) following a 16 h infusion demonstrated that (*S*)-**4** was slightly more brain penetrant (24%) than **1**, but was subject to increased blood clearance (38 mL/min/kg). We have previously observed a positive correlation between in vivo clearance and CNS penetration in rats with a related series of compounds.[18]

Summary

The 6,6- and 5,6-bicyclic piperazines **3**, (*S*)-**4** and (*R*)-**4** have been identified as high affinity 5-HT_6 antagonists with excellent selectivity over a range of serotonergic and dopaminergic receptors. The more compact 6,5-system **4** displayed higher affinity compared to the 6,6-system **3** presumably for the steric reasons. Consistently with our recent findings,[17] the enantiomers (*S*)-**4** and (*R*)-**4** had very similar 5-HT_6 affinities and selectivity profiles. The 5,6-bicyclic piperazine (*S*)-**4** showed marginally improved CNS penetration but increased in vivo clearance in rat relative to **1**. In conclusion, this study together with our previous work[11,17,18] adds significantly to the knowledge of selective, brain penentrant 5-HT_6 antagonists and their rational design.

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16. Compounds **3**, (*S*)-**4** and (*R*)-**4** were purified by column chromatography on silica gel and were isolated as amorphous solids. **3**: δ_H (250 MHz, $CDCl_3$-d_6), 1.28 (3H, m), 1.73 (3H, m), 2.08 (3H, m), 2.19 (3H, s), 2.43 (1H, m), 2.68 (1H, m), 2.84 (2H, m), 3.00 (1H, m), 3.21 (1H, m), 3.82 (3H, s), 6.46 (1H, d, J = 2.34 Hz), 6.73 (2H, m), 7.42 (1H, m), 7.65 (1H, d, J = 1.91 Hz), 7.72 (1H, d, J = 8.62 Hz). MS: m/z (MH+) = 506.
(*S*)-**4**: δ_H (250 MHz, $CDCl_3$-d_6), 1.31 (1H, m), 1.82 (3H, m), 2.10 (3H, m), 2.22 (3H, s), 2.41 (1H, m), 2.60 (1H, m), 3.02 (1H, m), 3.17 (3H, m), 3.81 (3H, s), 6.51 (1H, d, J = 2.08 Hz), 6.70 (2H, m), 7.43 (1H, m), 7.66 (1H, d, J = 1.90 Hz), 7.74 (1H, d, J = 8.60 Hz). MS: m/z (MH+) = 492.
(*R*)-**4**: δ_H (250 MHz, $CDCl_3$-d_6), 1.30 (1H, m), 1.81 (3H, m), 2.11 (3H, m), 2.22 (3H, s), 2.38 (1H, m), 2.60 (1H, m), 3.01 (1H, m), 3.18 (3H, m), 3.80 (3H, s), 6.50 (1H, d, J = 2.16 Hz), 6.70 (2H, m), 7.44 (1H, m), 7.66 (1H, d, J = 1.90 Hz), 7.74 (1H, d, J = 8.60 Hz). MS: m/z (MH+) = 492.
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