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Novel (4-Piperazin-1-ylquinolin-6-yl) Arylsulfonamides with High Affinity and Selectivity for the 5-HT_6 Receptor

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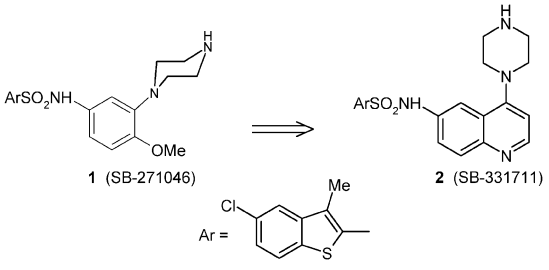
Abstract—The discovery of (4-piperazin-1-ylquinolin-6-yl) arylsulfonamides and their binding affinites for a selection of 5-HT and dopamine subreceptors is described. Many compounds show high affinity ($pK_i > 8$) for the 5-HT_6 receptor and >100-fold selectivity against a range of other receptors. Structure–activity relationships of these compounds are discussed.

The possible role of the 5-HT_6 receptor in learning and memory disorders has encouraged significant recent interest.[1] We have recently reported the discovery of a 5-HT_6 receptor antagonist, **1** (SB-271046).[2] This compound demonstrates high and selective affinity for the 5-HT_6 receptor (pK_i 8.9), is moderately brain penetrant and has excellent oral bioavailability. In separate behavioural[3] and neurochemical[4] studies, compound **1** produced indications of improvement in cognitive function.



The aim of this investigation was to further explore the scope of activity of related sulfonamide structures. Molecular modelling and single X-ray diffraction studies on **1** indicated that the preferred conformation of the piperazine ring is as indicated above with the unsubstituted nitrogen atom in a 'northerly' direction, away from the methoxy group. We reasoned that the corresponding basic piperazine nitrogen in a 4-piperazinylquinoline system, as in **2** (SB-331711), would place it in the same region of space and might thereby represent a biologically active replacement for the methoxyphenyl piperazine unit. Interestingly, naphthyl analogues of piperazinylquinolines of similar structure to **2** have been reported with high binding affinity for the 5-HT_1 subreceptor.[5] This Letter reports our key findings regarding the synthesis of piperazine derived quinoline arylsulfonamides, such as **2**, and their corresponding 5-HT_6 affinities and selectivities against a range of relevant 5-HT and dopamine receptors.

Chemistry

Novel 4-piperazinyl quinoline arylsulfonamides (**2**, **6a**–**s**) (Table 1) were prepared as shown in Scheme 1. Thus, displacement reactions on 4-chloro-6-nitroquinoline[6] **3** with excess functionalised or non-functionalised piperazines in refluxing toluene gave good yields of the 4-piperazine derivatives **4**. The intermediate *NH*-piperazines **4** were protected as *N*-Boc derivatives then catalytically reduced to the amines **5**. Subsequently, these amines were coupled with aromatic sulfonyl chlorides to give sulfonamides, which were deprotected by treatment with acidified THF at reflux to afford the target compounds **2, 6a**–**s**. The 2,6-dimethylpiperazine analogue **6t**

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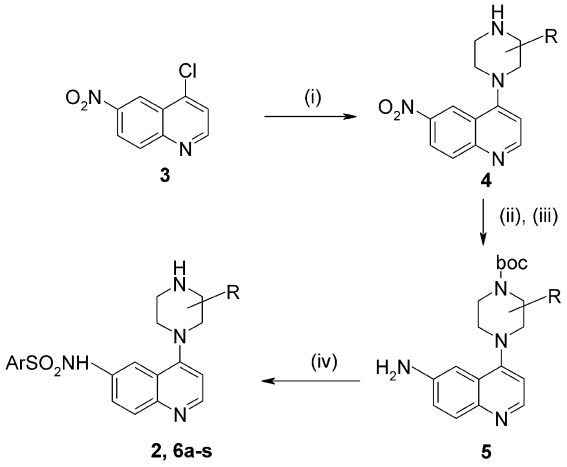


Scheme 1. Reagents and conditions: (i) Piperazine (4 equiv), toluene, reflux, 24 h (73–98%); (ii) $(BOC)_2O$, K_2CO_3, THF–H_2O (1:1), rt, 3 days (92–96%); (iii) H_2, 5% Pd/C, EtOH, rt, 24 h (11–99%); (iv) (a) $ArSO_2Cl$, CH_2Cl_2, pyridine (2 equiv), rt, 24 h; (b) c.HCl–THF (1:4.6 v/v), reflux, 1.5 h (9–85% over two steps).

(Table 2) was prepared by an analogous procedure except that Boc protection was not required for the coupling step due to steric hindrance. *N*-Substituted derivatives **6u** and **6v** were prepared similarly to **6t**. The 2- and 3-methyl quinolines **9a** and **9b** (Table 3) were prepared similarly, starting from 4-chloro-2-methyl-6-nitroquinoline,[7] and 4-chloro-3-methyl-6-nitroquinoline,[8] respectively.

The 3-piperazinyl analogue **8** was prepared starting from 3-bromo-6-nitroquinoline[9] (Scheme 2). A Buchwald[10] type palladium(0) catalysed cross-coupling reaction afforded the 3-piperazinyl nitroquinoline which was reduced to give the amino quinoline **7** in an overall yield of 56%. The coupling reaction to afford **8** was achieved in 32% yield.

Results and Discussion

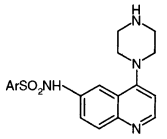
Variation of left-hand side aryl

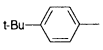
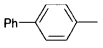
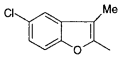
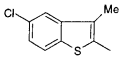
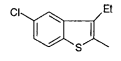
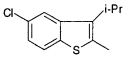
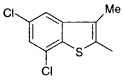
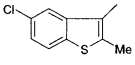
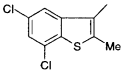
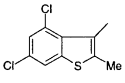
Parallel synthesis rapidly afforded a large number of compounds with a generally favourable range of 5-HT_6 affinities and selectivities, and a selection is shown in Table 1. Several compounds (e.g., **6c**, **6d** and **6f**) have nanomolar affinity for the 5-HT_6 receptor and >100-fold selectivity over a range of nine relevant receptor subtypes. Detailed selectivity profiles of selected compounds against 10 5-HT and dopamine subreceptors are shown in Table 4. Large 4-substituents (e.g., **6b**–**d**) were favoured over 3,5-dichlorosubstitution (**6a**). Consistent with this finding was that bicyclic aromatics also afforded generally excellent affinity and selectivity.

Chloronaphthyl derivatives **6f** and **6g** showed excellent affinities but variable selectivities, the 2-linked isomer **6f** being superior.

The benzothiophene derivative **2** showed a better binding profile than the corresponding benzofuran analogue

Table 1. Receptor binding affinites of 4-piperazinyl quinolines



Compd	Ar	pK_i 5-HT_6	Sel. versus 9 receptor subtypes[a]
6a		7.6	ND[b]
6b		8.8	100
6c		9.2	1260
6d		9.3	320
6e		8.9	500
6f		9.0	160
6g		8.5	80
6h		8.4	200
2		8.7	320
6i		8.9	1000
6j		8.8	160
6k		8.2	25
6l		9.0	250
6m		8.7	130
6n		8.7	200
6o		8.1	40

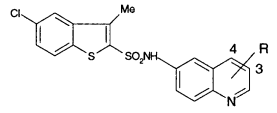
[a]Selectivity was determined against the nine receptor subtypes detailed in Table 4. Selectivity ratio is defined as the antilogarithm of the smallest difference between the pK_i value at the 5-HT_6 receptor and the range of comparator receptors.

[b]ND, not determined; generally if the binding affinity at the 5-HT_6 receptor has a value of pK_i <8.0, the selectivities at other receptors has not been determined.

6h. Generally, substituted benzothiophenes gave encouraging results and were investigated in some detail. The 5-HT_6 receptor affinity was relatively insensitive to the size of the 3-alkyl substitutent (**2**, **6i**, **6j**) whereas the substituent size had a significant effect on selectivity, the ethyl derivative **6i** being optimal. 5,7-Dichloro substitution (**6k**) led to poor selectivity.

The benzothiophene-3-sulfonamides, **6l** and **6n**, displayed excellent binding profiles. 5-, 7- and 5,7-dichloro-substitution (**6l**–**n**) was clearly favoured over 4,6-disubstitution as seen by the modest affinity and poor selectivity of **6o.**

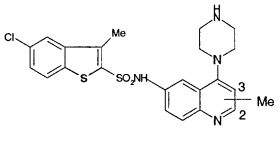
Table 2. Receptor binding affinites of substituted piperazine analogues



Compd	R[a]	pK_i 5-HT_6	Sel. versus 9 receptor subtypes[b]
6p		8.9	320
6q		8.7	320
6r		7.7	ND[c]
6s		7.5	ND
6t		8.3	160
6u		9.0	250
6v		8.7	130
8		7.1	ND

[a]Compounds **6p**–**6v** are 4-substituted, **8** is 3-substituted.
[b,c]As defined in Table 1.

Table 3. Binding affinities of methyl derivatives **9a** and **9b**



Compd	Postn Subtst.	pK_i 5-HT_6	Sel. versus 9 receptor subtypes[a]
9a	2—	8.9	250
9b	3—	8.6	100

[a]As defined in Table 1.

Variation of piperazine and quinoline substitution

Based on the encouraging activity of the benzothiophene derivatives, a limited study was undertaken to explore modifications to the piperazine and quinoline rings in combination with the favoured 3-methyl-5-chlorobenzothiophene left hand side. Substitution in the piperazine ring has a marked effect on 5-HT_6 receptor affinity (Table 2). A methyl substituent at the 3-position was tolerated with both enantiomers, **6p** and **6q,** showing almost identical profiles to compound **2**. However, increasing further the size of this substituent to ^{i}Pr (**6r**) led to a 10-fold drop in 5-HT_6 affinity. The 2,5-dimethyl (**6s**) and 3,5-dimethyl (**6t**) derivatives also had reduced affinity. *N*-Alkylation, however, was tolerated as exemplified by **6u** and **6v**, which had similar profiles to compound **2.**

The poor binding affinity of the 3-piperazine derivative **8** (Table 2), which was 80-fold lower than the corresponding 4-piperazine analogue **6u,** highlights the importance of the position of attachment of the piperazine ring in the quinoline nucleus.

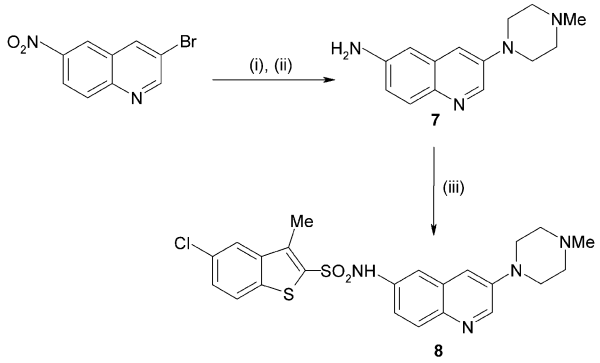
The 2- and 3-methylquinoline derivatives, **9a** and **9b**, showed no overall advantage compared to the des-methyl analogue **2** (Table 3).

Functional activity

When evaluated in a model of human cloned 5-HT_6 receptor function,[11] compounds **2**, **6g**, **6l**, **6p**–**r**, **6u**–**v** and **9a**–**b** were all found to reverse the 5-HT-stimulated adenylyl cyclase activity, which is consistent with antagonist profiles. However, when tested in the absence of 5-HT, the compounds produced some stimulation of basal adenylyl cyclase activity, consistent with partial agonism in this system. The functional profile of action of these compounds is under further investigation and will be the subject of a future publication.

Summary

A number of compounds have been identified (e.g., **2, 6c–e, 6i, 6p, 6q**) which show excellent 5-HT_6 binding



Scheme 2. Reagents and conditions; (i) Pd(0) bis(dibenzylideneacetone) (7 mol%), BINAP (16 mol%), Cs_2CO_3, *N*-methylpiperazine, reflux, 18 h (56%); (ii) Fe, NH_4Cl, EtOH–H_2O, reflux, 6 h (96%); (iii) $ArSO_2Cl$, CH_2Cl_2, pyridine (2 equiv), rt, 24h (32%).

Table 4. Receptor binding profiles of selected compounds

Receptor[a]	Affinity (pK_i)								
	2	**6c**	**6d**	**6f**	**6i**	**6l**	**6p**	**6u**	**9a**
5-HT$_{1A}$	6.0	6.1	6.2	6.8	<5.4	6.6	6.0	6.1	6.1
5-HT$_{1B}$	5.7	5.8	6.5	6.2	5.5	6.3	5.6	6.3	5.9
5-HT$_{1D}$	6.2	5.9	6.8	6.7	5.6	6.4	6.4	6.6	6.5
5-HT$_{2A}$	<5.6	<5.5	6.3	6	<5.9	<5.7	<5.6	6.0	<5.7
5-HT$_{2B}$	<5.3	<5.3	<5.1	<5.3	<5.4	5.9	<5.2	<5	<5.1
5-HT$_{2C}$	<5.6	<5.7	ND[b]	<5.6	5.9	5.9	<5.4	<5.3	5.6
5-HT$_6$	8.7±0.07 (n=3)	9.2±0.08 (n=3)	9.3±0.03 (n=3)	9.0±0.09 (n=9)	8.9±0.03 (n=3)	9.0±0.03 (n=3)	8.9±0.04 (n=3)	9.0±0.03 (n=3)	8.9±0.02 (n=6)
5-HT$_7$	<5.1	<5	<5	5.6	<5.3	5.8	<5.3	5.7	<5.3
Dopaminergic D$_2$	<5	<5	<5.3	<5.3	<6	<5.4	<5.5	<5.1	<5.2
Dopaminergic D$_3$	<5.8	<5.3	<5.5	5.6	<5	<5.8	<5.7	<5.4	<6

[a]Receptors and radioligands used in the binding assays: 5-HT$_{1A}$ (human cloned receptors [HCR] in HEK 293 cells, [^{3}H]-8-OH-DPAT); 5-HT$_{1B}$ (HCR in CHO cells, [^{3}H]-5-HT); 5-HT$_{1D}$ (HCR in CHO cells, [^{3}H]-5-HT); 5-HT$_{2A}$ (HCR in HEK 293 cells, [^{3}H]ketanserin); 5-HT$_{2B}$ (HCR in HEK 293 cells, [^{3}H]-5-HT); 5-HT$_{2C}$ (HCR in HEK 293 cells, [^{3}H]mesulergine); 5-HT$_6$ (HCR in HeLa cells, [^{3}H]LSD); 5-HT$_7$ (HCR in HEK 293 cells, [^{3}H]-5-CT); D$_2$ (HCR in CHO cells, [^{125}I]iodosulpride); D$_3$ (HCR in CHO cells, [^{125}I]iodosulpride).
[b]ND, not determined.

affinities and selectivities over a range of other receptors. Selectivities of 2-substituted benzothiophene derivatives are dependent on the size of the 3-substituent. The preferred point of attachment of the piperazine ring to the quinoline is at the 4-position. Those compounds tested in a functional model were shown to reverse 5-HT-stimulated adenyl cyclase activity. These compounds are under further investigation for potential utility in the treatment of CNS disorders.

References and Notes

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