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Synthesis and SAR of (piperazin-1-yl-phenyl)-arylsulfonamides: A novel series of atypical antipsychotic agents

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ABSTRACT

(Piperazin-1-yl-phenyl)-arylsulfonamides were synthesized and identified to show high affinities for both 5-HT_{2C} and 5-HT_6 receptors. Among them, naphthalene-2-sulfonic acid isopropyl-[3-(4-methyl-piperazin-1-yl)-phenyl]-amide (**6b**) exhibits the highest affinity towards both 5-HT_{2C} (IC_{50} = 4 nM) and 5-HT_6 receptors (IC_{50} = 3 nM) with good selectivity over other serotonin (5-HT_{1A}, 5-HT_{2A}, and 5-HT_7) and dopamine (D_2–D_4) receptor subtypes. In 5-HT_{2C} and 5-HT_6 receptor functional assays, this compound showed considerable antagonistic activity for both receptors.

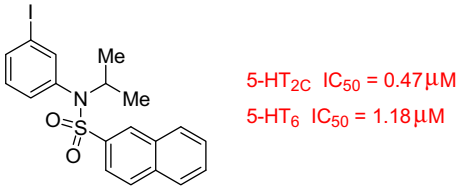
Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and plays an important role in the modulation of anger, aggression, body temperature, mood, sleep, human sexuality, appetite, and metabolism, as well as stimulating vomiting.[1,2] There are at least 15 different serotonin receptors that have been cloned and divided into seven subclasses (5-HT_{1-7}).[3,4]

The 5-HT_2 subfamily consists of three G-protein coupled receptors (GPCRs) which are coupled to Gq-protein and mediate excitatory neurotransmission, including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes.[5–7] The non-selective 5-HT agonist, *m*-chlorophenyl piperazine (*m*CPP), is known to induce symptoms of compulsive disorder, depression, and anxiety in several animal models.[8,9] As this *m*CPP-induced anxiety seems to be mediated via 5-HT_{2C} receptor, it has been hypothesized that 5-HT_{2C} receptor antagonists might be potential drugs for the treatment of anxiety and other psychiatric disorders.[10,11]

The 5-HT_6 receptor, one of the most recently identified serotonin receptors, consists of 440 amino acids with seven transmembrane domains and is positively coupled to the adenylate cyclase secondary messenger system.[12,13] Initial in vivo experiments showed that administration of antisense oligonucleotides (AOs), directed at 5-HT_6 receptor mRNA, elicited a behavioral syndrome in rats consisting of yawning, stretching, and chewing, which could be dose dependently blocked by the muscarinic antagonist atropine.[14–16] This study implies that 5-HT_6 receptors modulate cholinergic neurotransmission and hence 5-HT_6 receptor antagonists may be useful for the treatment of memory dysfunction.

Thus, 5-HT_{2C}/5-HT_6 receptor antagonism would be important for synergistically modulating schizophrenia, depression, and anxiety which are induced from Alzheimer's disease. Herein, we describe the identification of (piperazin-1-yl-phenyl)-arylsulfonamides antagonizing both 5-HT_{2C} and 5-HT_6 receptors.

In our research program to discover selective 5-HT_{2C}/5-HT_6 receptor antagonists, we began our investigation by high throughput screening with in-house compounds. We found that compound **1** exhibited moderate affinity for 5-HT_{2C} (IC_{50} = 0.47 μM) and 5-HT_6 receptor (IC_{50} = 1.18 μM) as shown in Figure 1. Because arylsulfonamides were already found as good inhibitors of 5-HT_6 receptor,[17,18] the major focus in our optimization was to enhance binding affinity towards 5-HT_{2C} receptor.



1

Figure 1. Hit compound acquired from HTS.

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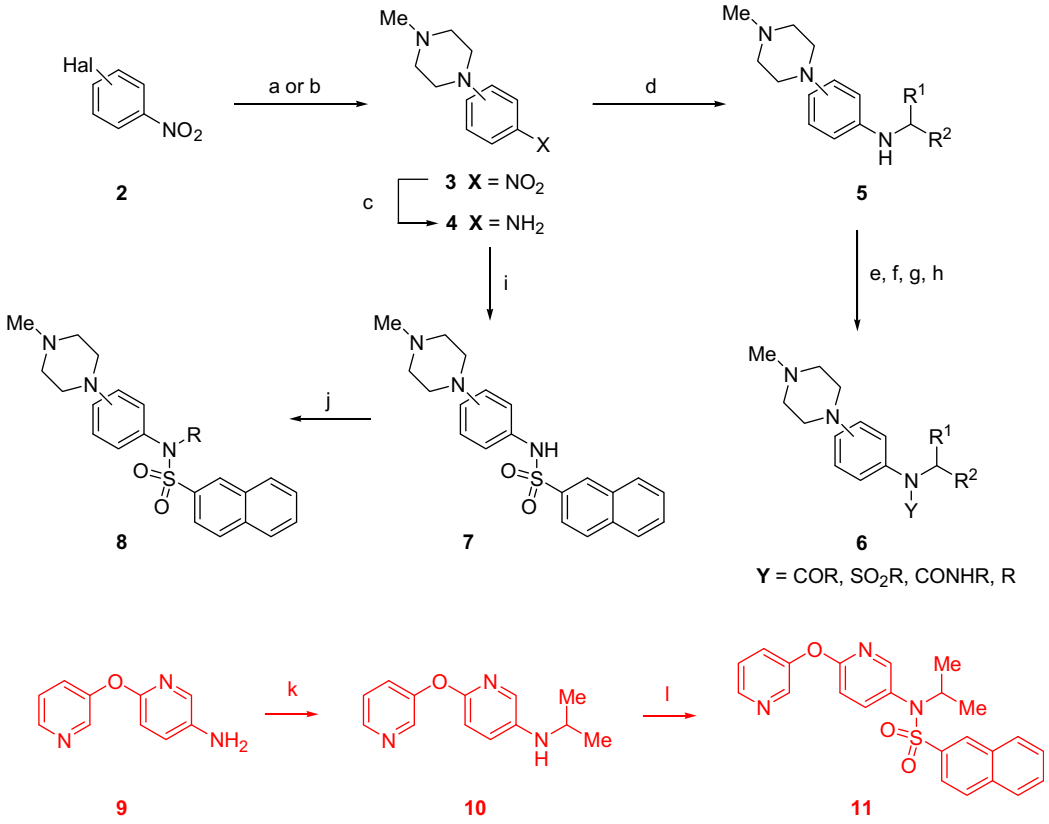


Scheme 1. Reagents and conditions: (a) *N*-methylpiperazine (neat), 80 °C; (b) *N*-methylpiperazine, Pd_2dba_3, 1,1′-bis(diphenylphosphino)ferrocene, NaO-*t*-Bu, 1,4-dioxane, 60 °C, 2 h; (c) Sn(II)Cl_2·H_2O, EtOH/concd HCl, 60 °C, 1 h; (d) R^1COR^2, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, rt, 8 h; (e) RCOCl, Et_3N, CH_2Cl_2, rt; (f) RSO_2Cl, Et_3N, CH_2Cl_2, rt; (g) RNCO, pyridine, CH_2Cl_2, rt; (h) R–X, NaH, tetrabutylammonium iodide, DMF, rt; (i) 2-naphthalenesulfonyl chloride, pyridine, rt; (j) R–X, K_2CO_3, DMF, rt; (k) acetone, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, AcOH, 50 °C, 8 h; (l) 2-naphthalenesulfonyl chloride, Et_3N, CH_2Cl_2, rt, 3 h.

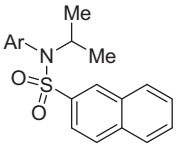
The general synthetic approaches to (piperazin-1-yl-phenyl)-arylsulfonamides are presented in Scheme 1. The (*N*-methy-piperazin-1-yl)-nitrobenzene **3** were synthesized from the halosubstituted nitrobenzene **2** by reacting with excess *N*-methylpiperazine (neat) at 80 °C or by Buchwald type palladium(0) catalyzed cross-coupling reaction.[19] Nitrobenzenes **3** were reduced with $SnCl_2$ in EtOH and concentrated HCl to afford aromatic amines **4**, which were reductive alkylated with ketones using acetic acid and $NaBH(OAc)_3$ in 1,2-dichloroethane at room temperature to furnish *N*-alkyl-amines **5**.[20] Basic nitrogen of aromatic amines **5** were functionalized using acid chlorides, sulfonyl chlorides, isocyanates, or alkyl halides to afford trisubstituted amines **6**. Coupling of 2-naphthalenesulfonyl chloride with aromatic amines **4** were conducted in pyridine at room temperature to give arylsulfonamides **7**, which were alkylated with R–X (X = Br or I) in DMF at room temperature in the presence of K_2CO_3 as a base to afford *N*-alkyl arylsulfonamides **8**. The known bipyridylamine **9**[21] was reductive alkylated with acetone using acetic acid and $NaBH(OAc)_3$ in 1,2-dichloroethane at 50 °C to afford *N*-isopropylamine **10**, which was coupled with 2-naphthalenesulfonyl chloride to furnish arylsulfonamide **11**.

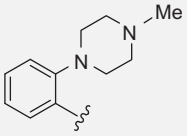
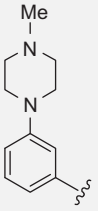
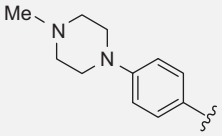
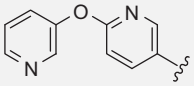
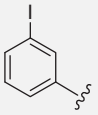
Earlier studies showed that the introduction of the pyridyl ether[21] or the terminal basic pharmacophore[22] is important for increasing binding affinities for 5-HT_{2C} receptor. The functionalization of phenyl moiety of the aniline unit of compound **1**, with the introduction of piperazine group or pyridyl ether motif, was screened (Table 1). In particular, compound **6b** containing an *N*-methyl-piperazin-1-yl group at *meta*-position of the phenyl moiety gave high binding affinity for 5-HT_{2C} receptor (IC_{50} = 4 nM). In contrast, the binding affinities of compounds **6a** and **6c** containing *N*-methyl-piperazin-1-yl groups at *ortho*- or *para*-position of the phenyl group were detrimental. Introduction of pyridin-3-yloxy group on the 6-position of 3-pyridyl group (**11**) was not effective, either. Gratifyingly, compounds **6a–c** and **11** showed higher binding affinities of 5-HT_6 receptor than 5-HT_{2C} receptor as we expected.

Having established that 3-substitution of the *N*-methyl-piperazin-1-yl group was optimal, a series of analogues were prepared investigating modifications of 2-naphthylsulfonyl moiety (Table 2). Although incorporation of a phenyl group (**6e**) instead of 2-naphthyl retained affinity for 5-HT_{2C} receptor, substitutions in the region of *para*-position of this phenyl group (**6k**, **6l**, and **6n**) reduced binding affinities and 1-naphthylsulfonyl derivative **6j** also showed reduction in affinity. 1-Naphthylcarbonyl substituted analogue **6h** showed the similar efficacy to its corresponding sulfonyl analogue **6j** and carbonyl analogues **6f**, **6m**, and **6o** were less efficacious than their corresponding sulfonyl analogues **6e**, **6b**, and **6l**. Substitution of the sulfonyl linker with methylene or amido (**6g** or **6i**) was detrimental. The effect of nitrogen substitution of arylsulfonamide **6b** was also carried out (Table 2). Substitution with 1-propyl and cyclopropylmethyl (**8b** and **8d**) had similar binding affinities for 5-HT_{2C} receptor, while replacement with methyl, ethyl, cyclopentylmethyl, benzyl, and 3-pyridylmethyl (**8a**, **8c**, **8e**, **8f**, and **8g**) gave weaker binding affinities. N-Unsubstituted derivative **5h** showed significantly lower binding affinity (IC_{50} = 5147 nM). Replacement of 2-propyl with 3-pentyl and 2-butyl (**6p** and **6q**) led to the reductions in binding affinities. Within this series, arylsulfonamides with 2-propyl substituents **6b** showed most potent compounds. As we expected, most of arylsulfonamides also showed good binding affinities for 5-HT_6 receptor.

Compounds **6b**, **6e**, **6j**, **8a–d**, **8f**, and **5h** were examined further for binding affinity toward several serotonergic and dopaminergic

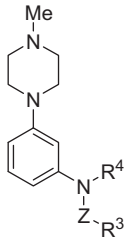
Table 1
Binding affinities for 5-HT_{2C} and 5-HT_6 receptors of phenyl moiety derivatives in aniline unit of hit compound (IC_{50} values, unit: nM)[a]



Compound	Ar	5-HT_{2C}[b]	5-HT_6[c]
6a		4638	2191
6b		4	3
6c		1715	27
11		>10000	422
1		467	1180

[a] All values are means of two or three separate competition experiments.
[b] Displacement of [^{3}H]-mesulergine binding to cloned human 5-HT_{2C} receptors expressed in CHO-K1 cell line.
[c] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors expressed in HEK293 cell line.

Table 2
Binding affinities for 5-HT_{2C} and 5-HT_6 receptors of *N*-[3-(4-methyl-piperazin-l-yl)-phenyl]-arylsulfonamides (IC_{50} values, unit: nM)[a]



Compound	Z	R^3	R^4	5-HT_{2C}[b]	5-HT_6[c]
6b	SO_2	2-Naphthyl	2-Propyl	4	3
6e	SO_2	Ph	2-Propyl	21	644
6f	CO	Ph	2-Propyl	4164	—
6g	CH_2	Ph	2-Propyl	>10000	—
6h	CO	1-Naphthyl	2-Propyl	97	—
6i	CO	NHPh	2-Propyl	>10000	—
6j	SO_2	1-Naphthyl	2-Propyl	100	16
6k	SO_2	4-Me-Ph	2-Propyl	106	—
6l	SO_2	4-Cl-Ph	2-Propyl	243	—
6m	CO	2-Naphthyl	2-Propyl	420	—
6n	SO_2	4-NO2-Ph	2-Propyl	462	—
6o	CO	4-Cl-Ph	2-Propyl	7702	—
6p	SO_2	2-Naphthyl	3-Pentyl	159	—
8a	SO_2	2-Naphthyl	Methyl	36	7
8b	SO_2	2-Naphthyl	1-Propyl	7	4
8c	SO_2	2-Naphthyl	Ethyl	16	3
8d	SO_2	2-Naphthyl	Cyclopropylmethyl	6	6
8e	SO_2	2-Naphthyl	Cyclopentylmethyl	11	—
6q	SO_2	2-Naphthyl	2-Butyl	168	—
8f	SO_2	2-Naphthyl	Benzyl	32	3
8g	SO_2	2-Naphthyl	3-Pyridylmethyl	34	—
5h	SO_2	2-Naphthyl	H	5147	13

[a] All values are means of two or three separate competition experiments.
[b] Displacement of [^{3}H]-mesulergine binding to cloned human 5-HT_{2C} receptors expressed in CHO-Kl cell line.
[c] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors expressed in HEK293 cell line.

receptors (Table 3). All compounds except **5h** and **6e** showed higher binding affinities for 5-HT_{2C} and 5-HT_6 receptor than other serotonergic and dopaminergic receptor. In particular, the 5-HT_{2C}/5-HT_6 receptor selectivity of compounds **6b** and **8b** was greater than 25-fold over 5-HT_{1A}, 5-HT_{2A}, 5-HT_7, and dopamine (D_2–D_4) receptors.

The functional efficacies of compound **6b** were evaluated by measuring 5-HT-stimulated binding of [^{35}S]GTPγS using CHO cells expressing the cloned human 5-HT_{2C} receptors[23,24] and 5-HT-stimulated cAMP accumulation using HeLa cell line expressing the cloned human 5-HT_6 receptor.[25] Compound **6b** was able to block 5-HT-stimulated binding of [^{35}S]GTPγS in a dose-dependent manner with IC_{50} value of 94 nM. It also blocked 5-HT-stimulated cAMP binding (IC_{50} = 21 nM). These results showed that compound **6b** has antagonistic activities at both 5-HT_{2C} and 5-HT_6 receptors.

In summary, we report the synthesis and biological profiles of a series of (piperazin-1-yl-phenyl)-arylsulfonamides. Most of compounds, particularly **6b** and **8b**, have been identified to possess the high binding affinity towards 5-HT_{2C} and 5-HT_6 receptors and

Table 3
Binding profiles over serotonin (5-HT_{1A}–5-HT_7) and dopamine (D_2–D_4) receptor subtypes (IC_{50} values, unit: nM)[a]

Compound	IC_{50}[b] (nM)							
	5-HT_{2C}	5-HT_6	5-HT_{1A}	5-HT_{2A}	5-HT_7	D_2	D_3	D_4
6b	4	3	>1000	118	NR	>10000	248	>1000
6e	21	644	3399	172	1006	>10000	2893	>10000
6j	100	16	298	122	2874	>10000	1195	>10000
8a	36	7	95	1423	4425	>10000	2416	>10000
8b	7	4	3756	389	3865	>10000	2508	>10000
8c	16	3	485	218	2059	>10000	1171	>10000
8d	6	6	672	88	3038	>10000	1426	>10000
8f	32	3	280	50	2044	>10000	943	>10000
5h	5147	13	57	1616	1582	>10000	2102	>10000

[a] All values are means of two or three separate competitive experiments.
[b] Receptors were all cloned human receptors expressed in CHO, HEK293 or SF9 cells, and [^{3}H] radioligands were as follows: 8-OH-DPAT (5-HT_{1A}), ketanserin (5-HT_{2A}), mesulergine (5-HT_{2C}), LSD (5-HT_6 and 5-HT_7), and spiperone (D_2–D_4).

good selectivity over the 5-HT_{2A} receptor and other related serotonergic and dopaminergic receptor subtypes. Additional studies with such compounds are now in progress.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.150.

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