Bioorganic & Medicinal Chemistry Letters 21 (2011) 698–703

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

1-(Arylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-one derivatives as 5-HT$_6$ serotonin receptor ligands

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ARTICLE INFO

Article history:
Received 14 October 2010
Revised 25 November 2010
Accepted 1 December 2010
Available online 8 December 2010

Keywords:
5-HT$_6$ receptor
Antagonist
Memory dysfunction
Brain penetrant

ABSTRACT

Piperazinyl derivatives of 1-(arylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-ones have been identified with high binding affinities for 5-HT$_6$ receptor. In particular, 2-methyl-5-(*N*-methyl-piperazin-1-yl)-1-(naphthalene-2-sulfonyl)-2,3-dihydro-1*H*-quinolin-4-one (**8g**) exhibits high binding affinity toward 5-HT$_6$ (IC$_{50}$ = 8 nM) receptor with good selectivity over other serotonin and dopamine receptors.

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.[1] It is almost exclusively expressed within the brain and located in areas important for memory formation and habituation.[2] Binding studies have disclosed that certain tricyclic antipsychotic drugs and antidepressants have significant affinities for 5-HT$_6$ receptor.[3] 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.[4,5] 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.

As the result of recent researches, several selective 5-HT$_6$ receptor antagonists have been reported including RO-04-6790 (**1a**, pK_i = 7.3), RO-63-0563 (**1b**, pK_i = 7.8),[6] SB-271046 (**2a**, pK_i = 8.9), **2b** (pK_i = 9.2),[7] MS-245 (**3**, pK_i = 8.6),[8] and RO-65-7674 (**4**, pK_i = 8.6)[9] as shown in Figure 1. According to the published pharmacophore models,[10,11] four common features were identified: two hydrophobic aromatic scaffolds, double electron acceptor functional group (commonly a sulfonamide), and basic side chain (protonated at physiological pH). Compounds **1a**–**2b** possess a sulfonamide moiety, and compound **3** has a tryptamine derivative. Compounds **1a** (Ro 04-6790) and **1b** (Ro 63-0563) have only moderate potency at the rat 5-HT$_6$ receptor and were found to be poorly brain penetrant. Compound **2a** (SB-271046), a potent and selective 5-HT$_6$ receptor antagonist which later entered into clinical trials, has excellent bioavailability, but its brain penetration is a little low (B/P = 0.1). As a trial to improve brain penetration, Roche researchers afforded **4**,[9,12] lacking the sulfonamide NH hydrogen bond donors of **1a**–**2b**. We also postulated that an insertion of an additional ring system to piperazinyl aromatic ring of **2a** would increase rigidity and lipophilicity to enhance its brain penetration, and found that quinolin-4-one moiety showed the improvement of the brain penetration (Fig. 2). This paper describes the synthesis and structure–activity relationship of piperazinyl derivatives of 1-(arylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-one derivatives for 5-HT$_6$ receptor antagonists.

Scheme 1 outlines synthetic routes toward 2,3-dihydro-1*H*-quinolin-4-one derivatives substituted at 5- or 7-position with piperazine analogues. 3-Phenylamino-propionic acid analogues **5** were required using three different methods. First, coupling with methyl acrylate, followed by hydrolysis of the resulting ester, produced the intermediate **5** (Method A). Second, direct coupling with acrylic acid under reflux condition was used (Method B). Third, reductive amination with methyl acetoacetates using NaBH$_3$CN in MeOH, followed by hydrolysis, afforded propionic acid analogues **5** (Method C). Treatment of **5** with polyphosphoric acid provided quinolin-4-one **6**, which was substituted with piperazine derivatives to afford (piperazin-1-yl)-quinolin-4-one **7**. Sulfonamide substituted quino-

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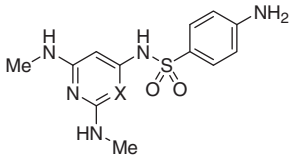
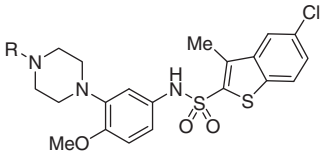
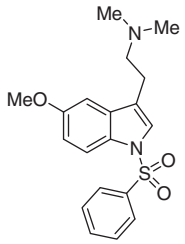
doi:10.1016/j.bmcl.2010.12.007



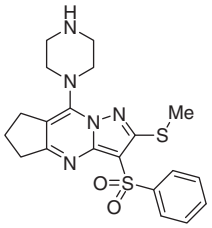
1a, **X = N**, RO-04-6790 (pKi = 7.3)
1b, **X = CH**, RO-63-0563 (pKi = 7.8)



2a, **R = H**, SB-271046 (pKi = 8.9; B/P = 0.10)
2b, **R = Me**, (pKi = 9.2; B/P = 0.18)



3, MS-245
(pKi = 8.6)



4, RO-65-7674
(pKi = 8.6; B/P = 0.10)

Figure 1. Structures of 5-HT$_6$ receptor antagonists.

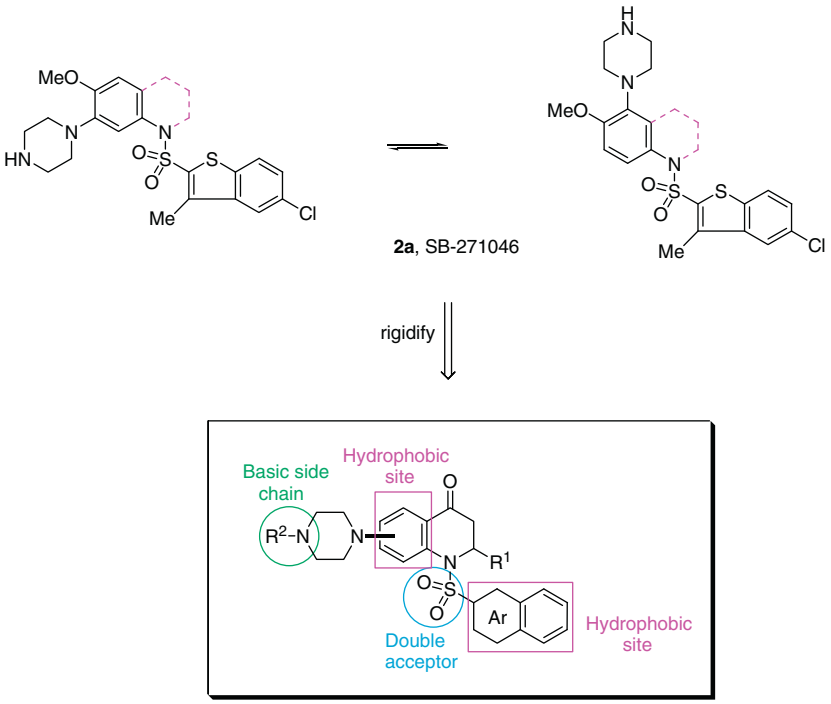


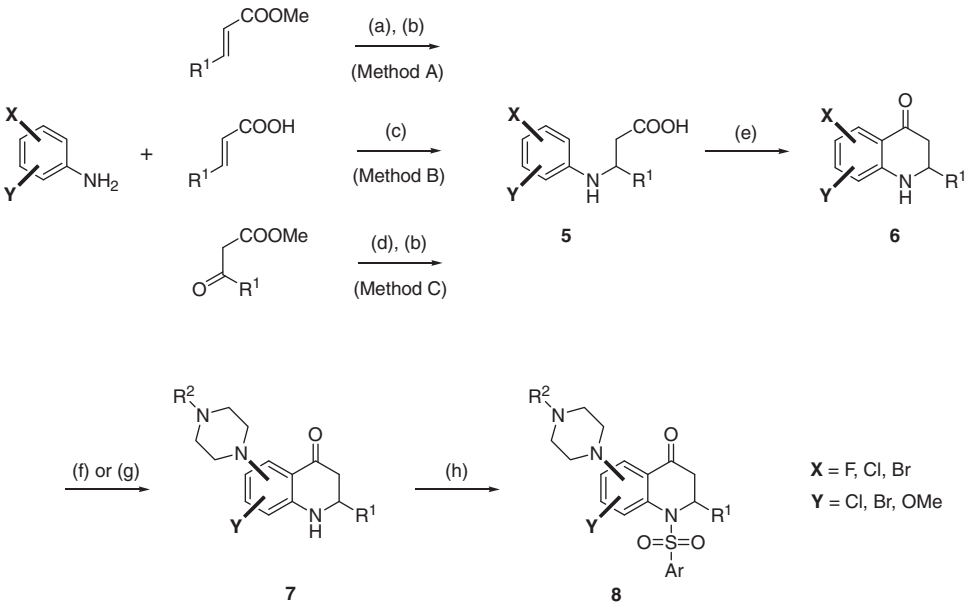
Figure 2. Design of 2,3-dihydro-1*H*-quinolin-4-one derivatives as a 5-HT$_6$ ligand.

lin-4-one **8** was provided by sulfonylation of **7** with arylsulfonyl chloride in pyridine.

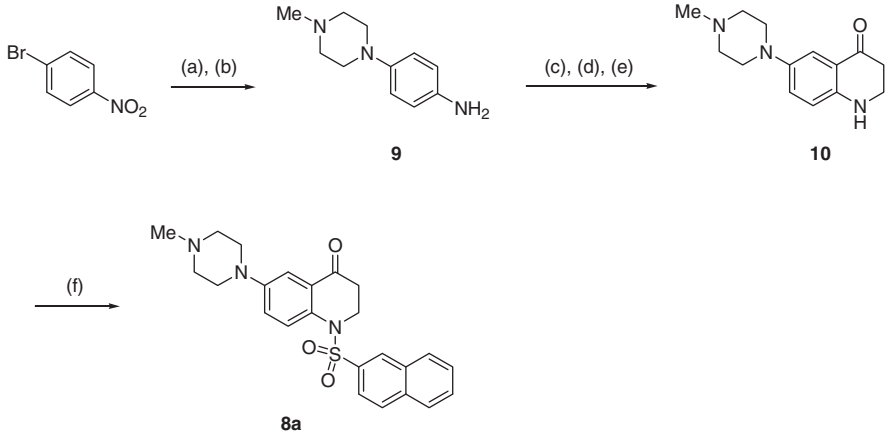
The synthetic approach to 2,3-dihydro-1*H*-quinolin-4-one derivatives substituted at 6-position with *N*-methylpiperazine is described in Scheme 2. 4-(*N*-Methyl-piperazin-1-yl)-phenylamine **9** was synthesized from 1-bromo-4-nitrobenzene by reacting with excess *N*-methylpiperazine at 80 °C, followed by reduction of the nitro functionality with catalytic hydrogenation. Phenylamine **9** was coupled with ethyl acrylate in the presence of acetic acid, hydrolyzed with NaOH in MeOH, and then cyclized to afford quinolin-4-one **10** by treatment with polyphosphoric acid at 120 °C. Functionalization of **10** could then be done with 2-naphthalenesulfonyl chloride to afford sulfonamide substituted quinolin-4-one **8a**.

The affinities of the compounds for the 5-HT$_6$ receptor were measured by means of radioligand binding studies conducted with a human recombinant 5-HT$_6$ receptor, expressed by HEK293 cell line using [^{3}H]-lysergic acid diethylamide (LSD) as radioligand.[13]

The binding affinities of the synthesized compounds are shown in Table 1. Initially, the effects of *N*-methylpiperazin-1-yl groups substituted at position 5, 6, or 7 of 1-(2-naphthalenesulfonyl)-2, 3-dihydro-1*H*-quinoline-4-one (**8a**–**c**) were investigated. Gratifyingly, quinolone nucleus **8b** and **8c** substituted at 5-or 7-position

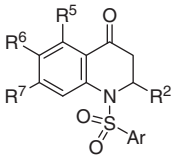


Scheme 1. Reagents and conditions: (a) $R^1CH{=}CHCOOMe$, AcOH, 80 °C; (b) NaOH, MeOH, rt; (c) $R^1CH{=}CHCOOH$, 110 °C; (d) $R^1C(=O)CH_2COOMe$, $NaBH_3CN$, MeOH, rt; (e) polyphosphoric acid, 120 °C; (f) *N*-methylpiperazine, 80 °C; (g) piperazine or *N*-methylpiperazine, CH_3CN, 80 °C; (h) $ArSO_2Cl$, pyridine, rt.



Scheme 2. Reagents and conditions: (a) *N*-methylpiperazine, 80 °C; (b) H_2, Pd/C, EtOH, rt; (c) ethyl acrylate, AcOH, reflux; (d) NaOH, MeOH, rt; (e) polyphosphoric acid, 120 °C; (f) 2-naphthalenesulfonyl chloride, pyridine, rt.

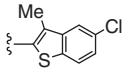
Table 1
5-HT_6 receptor binding properties of 2,3-dihydro-l/f-quinolin-4-one derivatives[a]



8a–n

Compound	Ar	R^2	R^5	R^6	R^7	IC_{50}[b] (nM)
8a	2-Naphthyl	H	H	$MeN(CH_2CH_2)_2N$–	H	311
8b	2-Naphthyl	H	H	H	$MeN(CH_2CH_2)_2N$–	26
8c	2-Naphthyl	H	$MeN(CH_2CH_2)_2N$–	H	H	61
8d	2-Naphthyl	Me	H	H	$MeN(CH_2CH_2)_2N$–	28

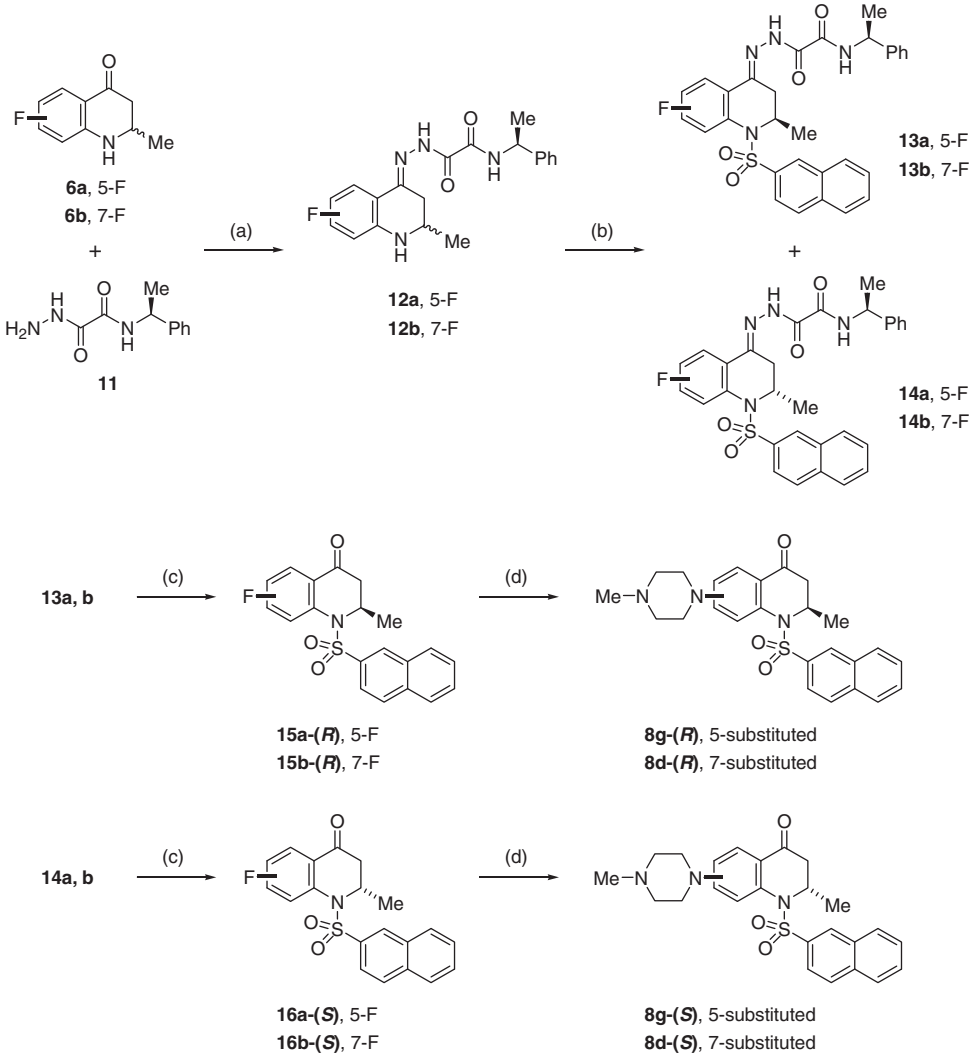
Table 1 (*continued*)

Compound	Ar	R^2	R^5	R^6	R^7	IC_{50}[b] (nM)
8e	2-Naphthyl	H	H	OMe	$MeN(CH_2CH_2)_2N$–	165
8f		H	H	H	$MeN(CH_2CH_2)_2N$–	419
8g	2-Naphthyl	Me	$MeN(CH_2CH_2)_2N$–	H	H	8
8h	2-Naphthy	Et	$MeN(CH_2CH_2)_2N$–	H	H	9
8i	2-Naphthy	Me	$MeN(CH_2CH_2)_2N$–	C	H	15
8j	2-Naphthy	Me	$MeN(CH_2CH_2)_2N$–	H	C	11
8k	4-Me-Ph	H	$MeN(CH_2CH_2)_2N$–	H	H	129
8l	2-Naphthy	H	$MeN(CH_2CH_2)_2N$–	H	C	47
8m	2-Naphthy	H	$MeN(CH_2CH_2)_2N$–	H	Br	58
8n	2-Naphthy	Me	$HN(CH_2CH_2)_2N$–	H	H	42

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors expressed in HEK293 cell line.
[b] All values are means of three separate competition experiments.

gave moderate binding affinities (IC_{50} = 26 nM and 61 nM, respectively) for 5-HT_6 receptor, which provided consistent results to support our rational design of potent 5-HT_6 receptor ligands. Further optimizations of **8b** were carried out by substitution at various positions. Compound **8d** (IC_{50} = 28 nM) containing methyl group at C2 position of 7-(*N*-methylpiperazin-1-yl)-substituted quinolone **8b** showed similar binding affinity to **8b**. Introduction of OMe substitute on C6 position in compound **8e** (IC_{50} = 165 nM) or substitution of 3-methyl-2-benzothiophenesulfonyl group in compound **8f** (IC_{50} = 419 nM) reduced binding affinities.

Next, the effects of substituents of 5-(*N*-methylpiperazin-1-yl)-substituted quinolone series **8c** were also observed. Replacement



Scheme 3. Reagents and conditions: (a) *p*-TsOH, cyclohexane, Dean–Stark, reflux; (b) 2-naphthalenesulfonyl chloride, pyridine, 80 °C; chromatographic separation; (c) 25% H_2SO_4, EtOH, rt; (d) *N*-methylpipeazine, CH_3CN, reflux.

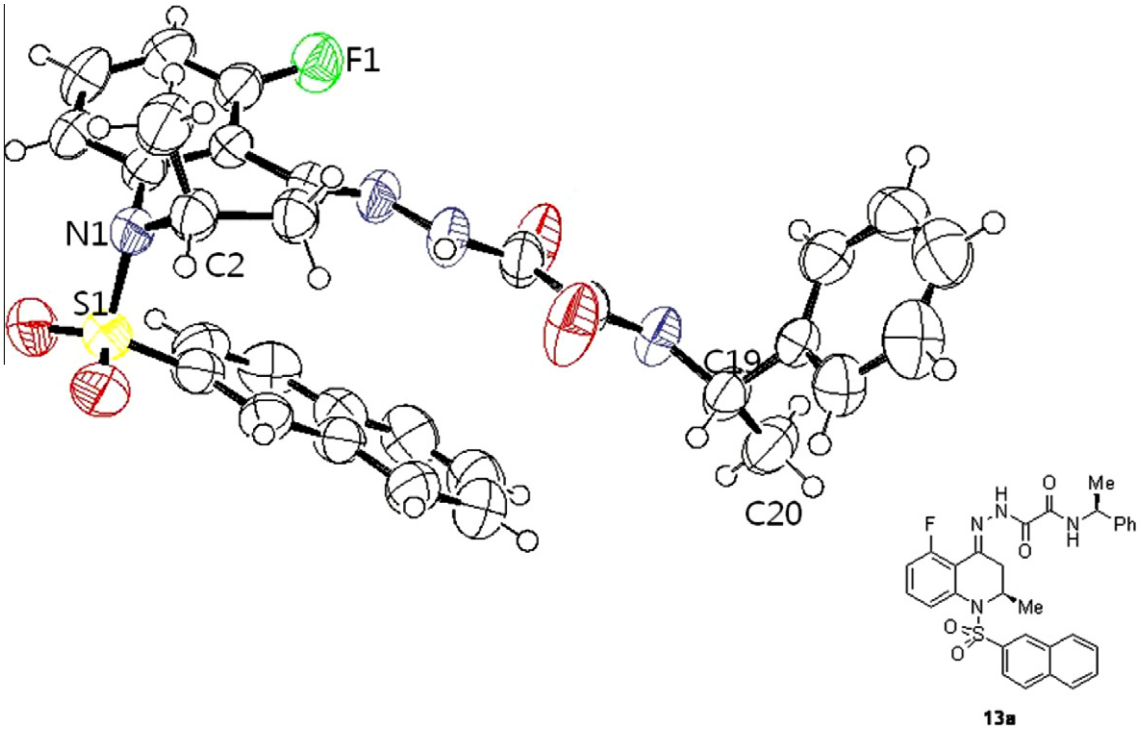


Figure 3. ORTEP representation of **13a**.

Table 2
5-HT_6 receptor binding properties of stereoisomers of **8d** and **8g**[a]

Compound	IC_{50}[b] (nM)
8d	28
8d-(*R*)	43
8d-(*S*)	17
8g	8
8g-(*R*)	353
8g-(*S*)	7

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors expressed in HEK293 cell line.
[b] All values are means of three separate competition experiments.

of 2-naphthalenesulfonyl group with *p*-toluenesulfonyl group (**8k**) gave lower binding affinity (IC_{50} = 129 nM). Substitution of aromatic ring of quinolone core by chlorine or bromine in 7-position (**8l** and **8m**) had little effect (IC_{50} = 47 and 58 nM). Alkyl substitution at 2- positions (i.e., **8g–j**; IC_{50} = 8–15 nM) gave higher binding affinity than **8c**. Replacement of *N*-methylpiperazin-1-yl group of **8g** with piperazin-1-yl group decreased affinity (i.e., **8n**; IC_{50} = 42 nM).

To elucidate the optimal configuration in binding for 5-HT_6 receptor, chiral separation method using (*S*)-(−)-5-(α-phenylethyl)-semioxamazide **11** was employed as shown in Scheme 3.[14–16] Fluoro-2-methyl-quinolin-4-ones (**6a** and **6b**) were condensed under Dean–Stark condition with (*S*)-(−)-5-(α-phenylethyl)-semioxamazide **11** to afford semioxamazones **12a** and **12b**, which were sulfonylated with 2-naphthylsulfonyl chloride in pyridine to give sulfonamide-substituted quinolin-4-ones (**13a** and **14a**) and (**13b** and **14b**). Diastereomeric mixture (**13a** and **14a**) was separated by column chromatography to provide **13a** and **14a**, which were hydrolyzed to afford optically pure enantiomer **15a**-(*R*) and **16a**-(*S*), respectively. The absolute configuration of **13a** was determined by X-ray analysis as shown in Figure 3. In the same way, chiral resolution of mixture (**13b** and **14b**) was also carried out. (*S*)-Isomer **8d**-(*S*) (IC_{50} = 17 nM) showed higher binding affinity than (*R*)-isomer **8d**-(*R*) (IC_{50} = 43 nM) and its racemate **8d** (IC_{50} = 28 nM). (*S*)-Isomer of **8g** also showed higher binding affinity, which implies that (*S*)-configuration on C2 in the quinolin-4-one nucleus is preferable in binding for 5-HT_6 receptor as shown in Table 2.

Table 3
Binding affinity at serotonin (5-HT_{1A}–5-HT_7) and dopamine (D_2–D_4) receptor subtypes[a]

Compound	IC_{50}[b] (nM)							
	5-HT_6	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_7	D_2	D_3	D_4
8b	26	672	366	5187	143	>10,000	1300	3613
8c	61	333	760	438	620	>10,000	2922	1789
8d	28	1598	1462	558	>10,000	136	1520	>10,000
8g	8	1210	48	30	2007	>10,000	482	5522
8h	9	999	455	4	>10,000	>1000	623	>10,000
8j	11	1226	704	19	>10,000	1784	180	>10,000

[a] 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).
[b] All values are means of two or three separate competition experiments.

The functional efficacy of compound **8b** was evaluated by measuring 5-HT-stimulated cAMP accumulation using HeLa cell line expressing the cloned human 5-HT_6 receptor.[17] Compound **8b** significantly inhibited 5-HT-stimulated cAMP accumulation (IC_{50} = 188 nM), indicating that compound **8b** is a potent 5-HT_6 receptor antagonist.

Pharmacokinetic studies demonstrated that **8d** and **8g** were more brain penetrant (B/P = 0.41 and 0.50, respectively) than **2b** (B/P = 0.18). This improvement may be due to the reduction of the number of H-donors of **8d** and **8g,** and also due to the higher lipophilicity of **8d** (log *D* = 3.2; polar surface area (PSA) = 69.3) and **8g** (log *D* = 3.6; PSA = 69.3) than **2b** (log *D* = 2.99; PSA = 100.6).[18]

Compounds **8b**–**d**, **8g**, **8h**, and **8j** were examined further for binding affinity toward several serotonergic and dopaminergic receptors (Table 3). All compounds displayed higher affinity for the serotonin 5-HT_6 receptor than for the serotonin 5-HT_{1A} or dopamine (D_2–D_4) receptors. Compound **8g** produced moderate binding affinity for the 5-HT_{2A} and 5-HT_{2C} receptors showing 48 and 30 nM of IC_{50} values, respectively. Meanwhile, compounds **8h** and **8j** expressed potent binding affinities for the 5-HT_{2C} receptor, with a severe decrease of the affinity for the 5-HT_{2A} receptor.

In conclusion, we report the synthesis and biological profiles of a series of piperazinyl derivatives of 1-(arylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-ones. Compounds **8d** and **8g** showed improved brain penetration, which indicated quinolone core is a suitable scaffold for the further development for serotonin 5-HT_6 receptor ligands. Compounds **8h** and **8j** showed high binding affinity toward both 5-HT_6 and 5-HT_{2C} receptors and good selectivity over other related serotonergic and dopaminergic receptor subtypes. Additional SAR and pharmacological investigation of 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.2010.12.007.

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15. Data for **13a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.9 Hz, 3H, NHCHC*H*$_3$), 1.58 (d, *J* = 6.9 Hz, 3H, PhCHC*H*$_3$), 2.21–2.43 (m, 2H, CH_2), 4.81 (m, 1H, NCH), 4.99 (m, 1H, PhCH), 7.07 (m, 1H, ArH), 7.26–7.62 (m, 11H, ArH), 7.83–7.92 (m, 3H, ArH + NH), 8.27 (d, *J* = 2.0 Hz, 1H, ArH), 9.45 (br s, 1H, NNH); mp 183–186 °C; MS (EI) *m*/*e* 410 (M^+−148), 191, 127, 105; Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with Cambridge Crystallographic Data Center (CCDC) as supplementary publication numbers CCDC 796561.
16. Data for **8g**-(*R*): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.9 Hz, 3H, CH_3), 2.17 (dd, *J* = 17.7 Hz, 1.6 Hz, 1H, COC*H*H), 2.31 (s, 3H, NCH_3), 2.40–2.57 (m, 5H, COCH*H* and 2NCH_2), 2.93 (m, 4H, 2NCH_2), 4.87 (m, 1H, CH), 6.94 (dd, *J* = 7.7 Hz, 1.8 Hz, 1H, ArH), 7.38–7.66 (m, 5H, ArH), 7.81–7.85 (m, 3H, ArH), 8.18 (d, *J* = 1.6 Hz, 1H, ArH); mp 65–70 °C; MS (EI) *m*/*e* 449 (M^+), 434, 405; HRMS *m*/*e* calcd for $C_{25}H_{27}N_3O_3S$ 449.1773; found 449.1771.
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