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Letters

Discovery of N_1-(6-Chloroimidazo[2,1-*b*][1,3]-thiazole-5-sulfonyl)tryptamine as a Potent, Selective, and Orally Active 5-HT_6 Receptor Agonist

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Abstract: N_1-Arylsulfonyltryptamines have been identified as 5-HT_6 receptor ligands. In particular, N_1-(6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl)tryptamine (**11q**) is a high affinity, potent full agonist (5-HT_6 K_i = 2 nM, EC_{50} = 6.5 nM, E_{max} = 95.5%). Compound **11q** is selective in a panel of over 40 receptors and ion channels, has good pharmacokinetic profile, has been shown to increase GABA levels in the rat frontal cortex, and is active in the schedule-induced polydipsia model for obsessive compulsive disorders.

The 5-hydroxytryptamine-6 (5-HT_6) receptor was identified in the 1990s[1−3] and was shown to belong to a group of 5-HT receptors, including 5-HT_4 and 5-HT_7 that stimulate adenylate cyclase activity.[4] The 5-HT_6 receptor has no known functional splice variants, is expressed almost exclusively in the central nervous system (CNS), and is localized in the striatal, limbic, and cortical regions of the rat brain.[5] Their CNS localization and high affinity for many antipsychotic and antidepressants drugs[1,3] have promoted much interest in 5-HT_6 receptors as attractive targets for antipsychotic therapeutic agents, with the possibility of relatively few noncentrally mediated peripheral side effects.[6]

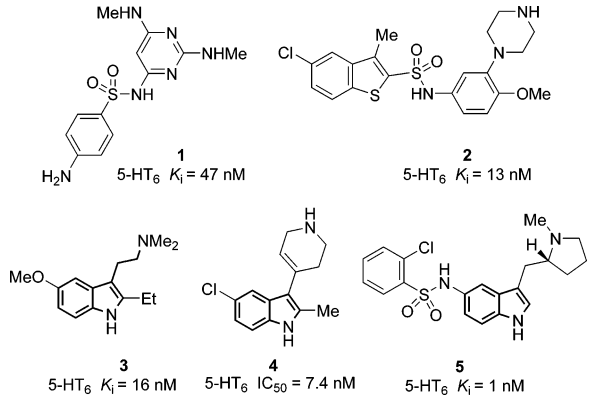

Figure 1. Structures of 5-HT_6 receptor antagonists (**1**, **2**) and agonists (**3**−**5**).

Much research has focused on the identification of selective 5-HT_6 receptor antagonists, which have been reported to play a significant role in memory formation under normal and dysfunctional conditions. Meneses et al. have shown that the 5-HT_6 receptor antagonist Ro-04-6790[7] (**1**, Figure 1) improved learning consolidation in an autoshaping task and that SB-271046[8] (**2**) improved memory retention in the water maze and produced a significant performance improvement in aged rats, and a series of analogues based on **1** reversed scopolamine-induced retention deficit in a passive avoidance learning test.[9] 5-HT_6 antisense oligonucleotides facilitate a reduction in food intake and body weight in rats, an effect also seen with the antagonists **1** and **2**.[10]

In contrast to 5-HT_6 antagonists, the identification of selective 5-HT_6 agonists has proven much more difficult. Tsai et al. reported the 5-HT_6 receptor full agonist 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMDT, **3**), which binds with high affinity at 5-HT_6 receptors (K_i = 16 nM).[11] However, **3** is only 10- to 30-fold selective over 5-HT_{1A}, 5-HT_{1D}, and 5-HT_7 receptors. Mattsson et al. reported that 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**4**) is a high affinity (5-HT_6 IC_{50} = 7.4 nM) full agonist (EC_{50} = 1.0 nM).[12] But **4** also

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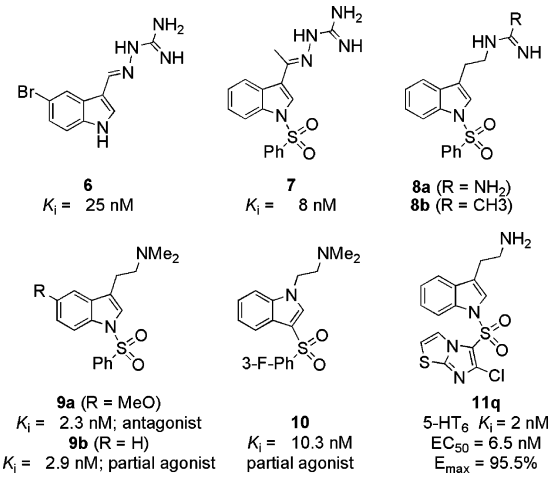


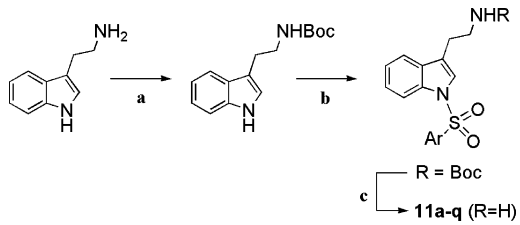
Figure 2. N_1-Arylsulfonyltryptamine type 5-HT$_6$ ligands.

possesses significant affinity for other 5-HT receptors, in particular 5-HT$_3$ (IC_{50} = 34 nM). We have described 5-arylsulfonamidoindoles in which the (*R*)-isomers generally act as full agonists, for example, **5** (5-HT$_6$ K_i = 1 nM, EC_{50} = 1.1 nM).[13] Unfortunately, **5** also suffers from modest selectivity (15- and 16-fold vs 5-HT$_{1B}$ and 5-HT$_{1D}$, respectively). Thus, the usefulness of these compounds as tools to probe the pharmacology of the 5-HT$_6$ receptors is somewhat limited by their modest selectivity.

Herein, we report the discovery of N_1-(6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl)tryptamine (**11q**, WAY-181187, SAX-187), a novel 5-HT$_6$ agonist with >50-fold selectivity against serotonin and other receptors. The synthesis, structure−activity relationships, and physiochemical, pharmacokinetic, and in vivo profiles are the subjects of this communication.

Our 5-HT$_6$ receptor discovery efforts began with a focused screen of the biogenic amine-type compounds in Wyeth's compound collection. Compounds were tested for displacement of [^{3}H]LSD from 5-HT$_6$ receptors stably expressed in cultured HeLa cells and led to the identification of 5-bromoindole aminoguanidine (**6**: 5-HT$_6$ K_i = 25 nM, Figure 2). Synthesis of analogues around this hit demonstrated that N_1-arylsulfonyl substitution on the indole gave compounds (e.g., **7**) with enhanced 5-HT$_6$ receptor binding affinity and selectivity over 5-HT$_7$. However, the aminoguanidine imine bond is acid-labile, so we sought other basic moieties such as the guanidines (**8a**) and amidines (**8b**) as replacements. The N_1-arylsulfonyltryptamine intermediates (**11**) were assayed and found to have high affinity for 5-HT$_6$ receptors and in some cases potent agonist activity. N_1-Aryltryptamine derivatives have previously been reported as high-affininty 5-HT$_6$ receptor ligands, for example, the antagonist **9a**,[11] partial agonist **9b**,[14] and the "flipped" tryptamine derivative **10**.[15]

Scheme 1[a]



[a] (a) $(Boc)_2O$, K_2CO_3, acetone, water (96%); (b) $ArSO_2Cl$, Aliquat 336, 50% aqueous NaOH, DCM (60%); (c) 4 N HCl/dioxane, THF (95%).

The N_1-arylsulfonyl tryptamine array was readily prepared by Boc protection of the tryptamine primary amine, base-mediated sulfonylation of the indole nitrogen, and removal of the protecting group (Scheme 1). N_1-Phenylsulfonyltryptamine (**11a**) and substituted phenylsulfonyltryptamines (**11b**−**k**) are high-affinity 5-HT$_6$ receptor ligands (5-HT$_6$ K_i = 1−30 nM) and many behave as partial or full agonists with modest potency (EC_{50} = 73−191 nM) (Table 1). The 4-aminophenyl analogue **11j** has the highest affinity (5-HT$_6$ K_i = 1 nM), consistent with other series in which the *p*-amino substitution gave the highest 5-HT$_6$ receptor affinity.[13] Interestingly, the 3,4-dimethoxyphenylsulfonyl (**11l**, K_i = 7 nM, IC_{50} = 17.5 nM) and 2-amino-3-methyl-5-thiazolylsulfonyl analogues (**11p**, K_i = 10 nM, IC_{50} = 9.6 nM) failed to show any agonist activity but instead behaved as antagonists. The mono- and bishalothiophenesulfonyl derivatives (**11m**−**o**, K_i = 6−31 nM, EC_{50} = 54−181 nM) had high affinity with modest agonist activity. Most intriguing was 6-chloroimidazo[2,1-*b*][1,3]thiazolesulfonyl analogue **11q**, which was a very high affinity, potent full agonist (5-HT$_6$ K_i = 2 nM, EC_{50} = 6.5 nM).

When **11q** was examined for selectivity against a panel of serotonergic receptors, significant affinity was only seen for the 5-HT$_{2C}$ (agonist) receptor binding site, but **11q** still showed greater than 50-fold selectivity (Table 2). In a panel of 31 other receptors and ion channels, **11q** showed less than 50% displacement at 100 nM at the α-adrenergic (1A, 1B, 2A−C), *β*-ad-

Table 1. 5-HT$_6$ Receptor Binding and Functional Activity

compd	Ar	K_i (nM)[a,d]	EC_{50} (nM)[b,d]	E_{max} (%)[b,d]	IC_{50} (nM)[c,d]	I_{max} (%)[c,d]
11a	Ph	10 ± 1	73 ± 39	92 ± 8		
11b	2-Br-Ph	11 ± 1	148 ± 28	97.5 ± 2.5		
11c	2-I-Ph	16 ± 1				
11d	3-Cl-Ph	6 ± 1	108.5 ± 2.5	100 ± 0		
11e	4-F-Ph	21 ± 2				
11f	4-Cl-Ph	10 ± 1	174 ± 8	93.5 ± 0.3		
11g	4-I-Ph	14 ± 1				
11h	4-Me-Ph	8 ± 1	191 ± 8	87.5 ± 1.1		
11i	4-MeO-Ph	47 ± 5				
11j	4-NH_2-Ph	1 ± 0	91 ± 15	73 ± 8		
11k	3,4-di-Cl-Ph	30 ± 3				
11l	3,4-di-MeO-Ph	7 ± 1			17.5 ± 4.6	80.5 ± 0.4
11m	5-Cl-2-thienyl	6 ± 1	181 ± 23	100 ± 0		
11n	5-Br-thienyl	7 ± 1	54 ± 12	72 ± 4		
11o	4,5-di-Cl-2-thienyl	31 ± 2				
11p	2-NH_2-3-Me-5-thiazolyl	10 ± 1			9.6 ± 1.0	83 ± 0
11q	6-Cl-imidazothiazole	2 ± 0	6.5 ± 0.5	95.5 ± 4.5		

[a] Displacement of [^{3}H]LSD binding to cloned h5-HT$_6$ receptors stably expressed in HeLa cells. [b] Agonism of cAMP production in HeLa cells stably transfected with human 5-HT$_6$ receptors. [c] Antagonism of 5-HT stimulated cAMP production in HeLa cells stably transfected with human 5-HT$_6$ receptors. [d] All values are the mean ± SD (n = 3).

Table 2. Binding Affinity of **11q** at Other 5-HT Receptors[a]

receptor	K_i (nM)	inhibition at 100 nM (%)	inhibition at 1 μM (%)
5-HT_{1B}			36
5-HT_{1D}			21
5-HT_{1F}			40
5-HT_{2A} (antagonist)			25
5-HT_{2A} (agonist)			49
5-HT_{2B}	458		
5-HT_{2C} (antagonist)			51
5-HT_{2C} (agonist)	124		
5-HT_3		<50	
5-HT_4		<50	
5-HT_5		<50	
5-HT_7	679		

[a] Receptors were all human clones stably expressed in CHO cells. Radioligands were as follows. 5-HT_{1A}: 8-hydroxy[^{3}H]DPAT. 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2C}: [^{3}H]-5-HT. 5-HT_{2A}: [^{125}I]DOI. 5-HT_6, 5-HT_7: [^{3}H]LSD. K_i values were determined in triplicate.

Table 3. Physiochemical and Metabolic Profile for **11q**

assay type	
aqueous solubility (mg/mL)[a]	
at pH 3−6	>10
at pH 8	0.24
permeability (cm/s)[b]	
PAMPA[18]	13.6×10^{-6}
BBB[17]	1.2×10^{-6}
cytochrome P450 inhibition, IC_{50} (μM)[a]	
1A2	149
2A6	41
2C19	112
2C8	>500
2C9	>500
2D6	196
3A4	33
microsomal stability, $t_{1/2}$ (min)[a]	
mouse	>60
rat	8
dog	26
monkey	6.4
human	>60

[a] Determined in duplicate with standard error of <20%. [b] Determined in triplicate with standard error of <20%.

renergic (1, 2), adenosine (1, 2), dopamine (D1−4), histamine (1−3), muscarinic (1−5), GABA A (agonist and benzodiazepine binding), glutamate (AMPA, kainate, NMDA, glycine), purinergic P2Y, and σ (1, 2) receptors. Greater than 50% displacement was only observed at the highest concentration of 10 μM in six receptors (D1, α2A, α2B, β1, β2, and σ2).

Selective 5-HT_6 receptor agonist **11q** was further evaluated for its physiochemical profile and metabolic stability in a series of in vitro assays (Table 3). With a pK_a of 10.2, **11q** had solubility of >10 mg/mL at pH 3−6, decreasing above pH 7.4. Compound **11q** is predicted to be membrane and blood−brain barrier (BBB) permeable based on in vitro assays.[16−18] The effect of **11q** on cytochrome P450 (CYP) enzyme catalytic activity was determined in human liver microsomes in which it had no effect on CYP2C8 and CYP2C9 activity at the highest concentration tested (100 μM), weakly inhibited CYP1A2, CYP2C19, and CYP2D6 activity (IC_{50} > 100 μM), and moderately inhibited CYP2A6 and CYP3A4 activity ($IC_{50} \approx$ 30−40 μM). Compound **11q** was rapidly metabolized in monkey and rat, moderately metabolized in dog, and minimally metabolized in mouse and human liver microsomes. It was nonmutagenic in Ames and genotoxicity assays.

The rat pharmacokinetic profile of **11q** (Table 4) was characterized by high apparent volume of distribution (V_{ss}) with high systemic clearance (7.4 L h^{-1} kg^{-1}) approximately twice

Table 4. Pharmacokinetic Profile of **11q** in Rats and Dogs

	1 mg/kg iv[a,e] (rat)	10 mg/kg oral[b,e] (rat)	1 mg/kg iv[c,e] (dog)	5 mg/kg oral[d,e] (dog)
AUC (μg h mL^{-1})	0.14 ± 0.03	0.19 ± 0.05	0.52 ± 0.15	1.43 ± 0.37
C_{max} (μg mL^{-1})		0.049 ± 0.007		0.13 ± 0.05
t_{max} (h)		1.7 ± 0.6		2.3 ± 1.5
$t_{1/2}$ (h)	5.4 ± 1.0	3.1 ± 0.0	2.9 ± 0.3	6.6 ± 0.7
Cl (L h^{-1} kg^{-1})	7.4 ± 1.4		1.8 ± 0.5	
V_{ss} (L kg^{-1})	24.0 ± 4.0		7.9 ± 1.5	
F (%)		23		55

[a] In 2% Tween-80 at 1 mL/kg. [b] In 2% Tween/0.5% methyl cellulose at 10 mL/kg. [c] In saline at 1 mL/kg. [d] In 2% Tween/0.5% MC at 1 mL/kg. [e] Results are the mean ± SD of $n = 3$.

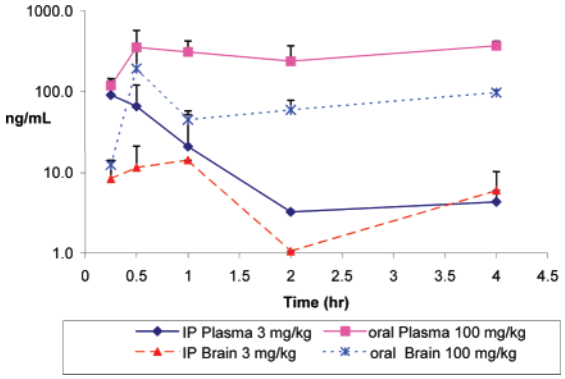


Figure 3. Mean plasma and brain concentration of **11q** after a single ip (3 mg/kg) or oral (100 mg/kg) dose in rats.

the hepatic blood flow (~3.3 L h^{-1} kg^{-1}), suggesting other clearance pathways in addition to hepatic metabolic clearance. A 10 mg/kg oral dose was rapidly absorbed, had an elimination half-life ($t_{1/2}$) of 3.1 h, and an oral bioavailabilty (F) of 23%. The low oral bioavailability of **11q** in rats is consistent with its high metabolic instability in rat liver microsomal incubations. The oral bioavailablility in rats decreased with increasing dose above 100 mg/kg (data not shown), suggesting that oral absorption might have become limiting. In dogs the plasma clearance was high and approximately equal to hepatic blood flow (1.8 L h^{-1} kg^{-1}). The volume of distribution (V_{ss}) was large (7.9 L/kg) and with a half-life ($t_{1/2}$) of 6.6 h and an oral bioavailability (F) of 55%. The higher oral bioavailability of **11q** in dogs also is consistent with its higher microsomal stability in this species. In contrast to rats, the oral bioavailability in dogs increased with increasing dose above 5 mg/kg (data not shown), suggesting saturation of hepatic first-pass or metabolic clearance. The brain and plasma ratio (0.1−0.7) of **11q** after a single 3 mg/kg ip or 100 mg/kg oral dose in rats indicates moderate blood−brain barrier penetration (Figure 3).

The in vivo activity of **11q** was demonstrated in the schedule-induced polydipsia (SIP) model in rats, a model, which may be predictive of efficacy in obsessive compulsive disorder (OCD).[19] Selective serotonin reuptake inhibitors (SSRIs) have been shown to decrease adjunctive drinking under SIP conditions but have a delayed onset of action cosistent with clinical findings using SSRIs to treat OCD.[19] In comparison, **11q** decreased adjunctive drinking in a dose-related fashion following acute ip and oral administration. The high oral dose required for efficacy may be due the instability in rat liver microsomal incubations. Importantly, control studies demonstrated that **11q** did not

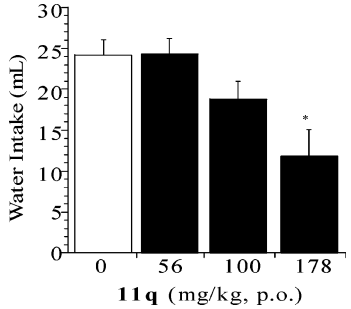


Figure 4. Scheduled-induced polydipsia in rats after oral dosing with **11q**: (∗) $P < 0.05$ compared to vehicle treatment.

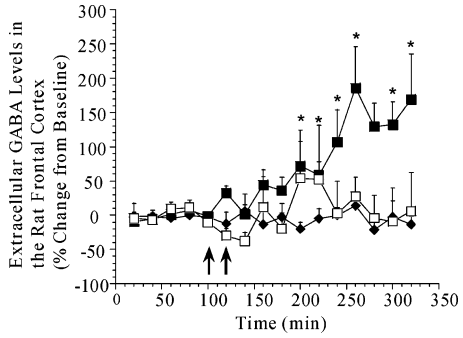


Figure 5. Microdialysis studies demonstrate that acute **11q** administration elevates GABA levels in the rat frontal cortex. First and second arrows represent time of 5-HT_6 antagonist and **11q** administration, respectively: (∗) $P < 0.05$ compared to vehicle treatment; (◆) vehicle; (■) **11q** (10 mg/kg sc); (□) **2** (10 mg/kg, sc) then **11q** (10 mg/kg, sc).

modify food or water intake when administered under non-SIP conditions, suggesting that the effects are specific for compulsive behaviors.

In vivo microdialysis experiments were used to explore the neurochemical effects of acute treatment with **11q** in the rodent brain (Figures 4 and 5). In the frontal cortex, **11q** (10 mg/kg, sc) significantly increased extracellular GABA concentrations without altering levels of glutamate or norepinephrine (data not shown). Subsequent studies showed that the GABAergic effects of **11q** were blocked by pretreatment with the 5-HT_6 antagonist **2** (10 mg/kg, sc), further implicating 5-HT_6 receptor mechanisms in mediating this response.

In conclusion, a novel 5-HT_6 receptor agonist with >50-fold selectivity against serotonergic and other receptors has been identified. On the basis of its acceptable physiochemical properties and pharmacokinetic profile, **11q** has been studied in vivo and initial findings suggest a role for 5-HT_6 agonists in treating OCD, considered a type of anxiety disorder.

Supporting Information Available: Experimental procedures for the synthesis and characterization of **11q** and analogues; binding, functional, physiochemical, and PK results; and details of in vivo experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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