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Synthesis and SAR of tolylamine 5-HT$_6$ antagonists

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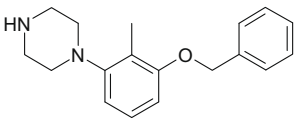
ABSTRACT

The synthesis and SAR of tolylamines with 5-HT$_6$ receptor antagonist activity is presented. The amine, core aromatic, peripheral aromatic, and ether linker moieties of HTS hit **1** were modulated and the effect on potency at 5-HT$_6$ examined. Tolylpiperidine ether **9h** was found to possess desirable pharmacokinetic (PK) properties, and was also shown to enhance cognition in the rat novel object recognition paradigm.

The serotonin-6 (5-HT$_6$) receptor is the most recently discovered in the family of serotonin receptors and has generated intense research activity from a number of groups.[1] It has been postulated that 5-HT$_6$ ligands may afford useful therapies for the treatment of obesity,[2] as well as cognitive enhancement in schizophrenia[3] and Alzheimer's disease[4] owing to preferential expression of the receptor in the central nervous system. Numerous clinical candidates have been advanced including SB-742457, PRX-07034, and SGS-518, all for which positive clinical study data have been reported.[5] Herein, we wish to disclose the discovery of a series of novel tolylamine 5-HT$_6$ antagonists and their evaluation as potential drug candidates.



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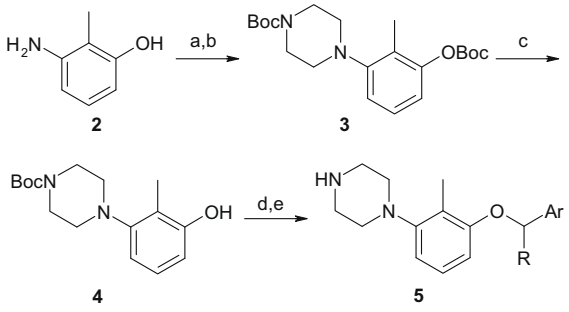
High throughput screening led to the identification of tolylpiperazine ether **1** as a potent 5-HT$_6$ receptor ligand. The toluene methyl group enhanced the potency for 5-HT$_6$ eightfold compared to the des-methyl version, and as such this moiety was included in all subsequent analogs. Initially we focused on the effect of modulating the aromatic periphery of **1** on potency for the 5-HT$_6$ receptor, owing to the potential for rapid analog generation (Scheme 1). Hence, 2-methyl-3-amino-2-methyl-phenol **2** was converted to the piperazine with the nitrogen mustard. Protection with Boc anhydride afforded the desired phenol **4** in addition to some bis-BOC intermediate **3**. The mixture was of no consequence as hydrolysis with carbonate liberated pure phenol **4** for further manipulation. The aromatic moiety could be introduced either via Mitsunobu displacement with various benzyl alcohols or alkylation in the presence of a potassium base, and subsequent removal of the carbamate with acid provided tolylpiperazines **5**.

Tolylpiperazines with close chemical similarity had in fact been reported[6] which led us to examine the corresponding piperidine analogs (Scheme 2). This modification also served to eliminate the aniline moiety, which has been shown in the case of nefazodone to form a reactive metabolite via *para*-hydroxylation and for-



Scheme 1. Preparation of tolylpiperazine analogs **5**. Reagents and conditions: (a) $(ClCH_2CH_2)_2NH$, NaI, iPr_2NEt, *n*-hexanol, PhCl; (b) Boc_2O, NaOH; (c) K_2CO_3, MeOH (27%, 3 steps); (d) ArCH(R)OH, DIAD, PPh_3, or $ArCH_2Br$, KHMDS, THF; (e) 4 M HCl in dioxane.

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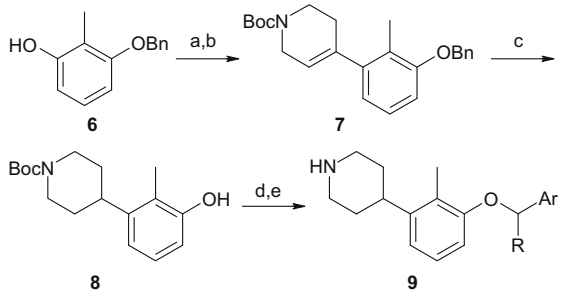
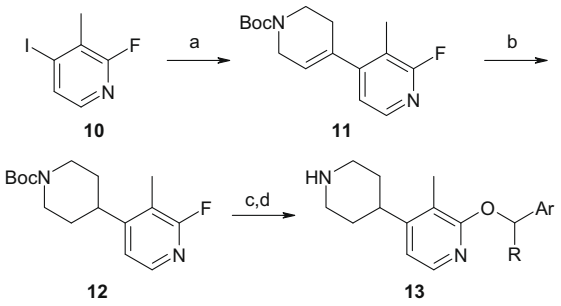


Scheme 2. Preparation of tolylpiperidine analogs **9**. Reagents and conditions: (a) Tf_2O, Et_3N (64%,); (b) 4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester,[10] 30% $Pd(dppf)Cl_2$, Cs_2CO_3, CsF, DMF (37%); (c) H_2, Pd/C (61%); (d) ArCH(R)OH, DIAD, PPh_3, or $ArCH_2Br$, KHMDS; (e) 4 M HCl in dioxane.



Scheme 3. Preparation of piperidinylpyridine analogs **13**. Reagents and conditions: (a) 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester, $Pd(PPh_3)_2Cl_2$, K_2CO_3, toluene/EtOH (27%,); (b) H_2, PtO_2, MeOH/THF (88%); (c) ArCH(R)OH, NaH, THF; (d) 4 M HCl in dioxane.

mation of the iminoquinone species.[7] Hence, starting with 2-methyl-3-benzyloxy-phenol **6**,[8] conversion to the triflate and coupling to a dehydropiperidine boronate afforded tetrahydropyridine **7**.[9] Saturation of the piperidine ring was accomplished by hydrogenation, with concomitant unmasking of the phenol to furnish intermediate **8**. As before, either Mitsunobu displacement or direct alkylation followed by removal of the carbamate provided tolylpiperidine ethers **9**.

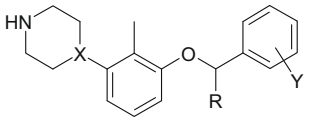
Compounds **5a**–**j** and **9a–p** were tested for their ability to displace [^{3}H]-LSD from human recombinant 5-HT_6 receptors (Table 1).[11] For the piperazines, aromatic halogens as well as a nitrile (**5c**) were tolerated. Mono-halogenation was preferred for the piperidines (**9a**,**b** vs **9c–f**). Pyridine was less potent in both series (**5g**, **9g**). The potency of benzylic substitution depended on stereochemistry, with the (*S*)-configuration being preferred as in **5h** and **9h**,**k**. Benzylic hydroxylation on the piperidine motif (**9p**) was not tolerated by 5-HT_6.

Next, we examined the effect of installing a heteroatom into the core aromatic ring as a pyridine in an effort to attenuate the clogP, as an increased likelihood of in vivo toxic events may be expected from drug candidates with high lipophilicity.[12] Suzuki coupling of 2-fluoro-4-iodo-3-methyl-pyridine **10**[13] with a similar dehydropiperidine boronate[9] to that used previously furnished fluoropyridine **11** (Scheme 3). Hydrogenation of the olefin, displacement of the fluoropyridine with a suite of benzyl alcohols, and finally carbamate deblocking afforded pyridyl ethers **13**.

Binding data for the pyridyl ethers **13** is shown in Table 2. As previously observed, *meta*-chlorination of the aromatic was preferred as in **13a**,**m**,**p**. The most potent compounds from the series resulted from substitution of CF_3 at the benzylic ether carbon [(±)-**13q**,**r**].

Finally, we sought to examine the effect of modifying the ether linker of piperidines **9** on potency. Transposition of the ether oxy-

Table 1
Affinity of tolylpiperazines **5** and tolylpiperidines **9** for h5-HT_6 receptors



Compound	X	R	Y	5-HT_6 binding K_i[a] (nM)
SB-271046	—	—	—	0.66[b]
1	N	H	H	1.3
5a	N	H	*m*-F	10.3
5b	N	H	*m*-Cl	0.60
5c	N	H	*m*-CN	15.3
5d	N	H	*o*-F	11.6
5e	N	H	3,4-Di-F	9.3
5f	N	H	3,4-Di-Cl	61.6
5g	N	H	3-Pyridine[c]	126
5h	N	Me (*S*)	H	45.6
5j	N	Me (*R*)	H	70.7
9a	CH	H	*m*-F	2.5
9b	CH	H	*m*-Cl	3.3
9c	CH	H	*m*-CN	174
9d	CH	H	*m*-Me	92.5
9e	CH	H	3,4-Di-F	42.0
9f	CH	H	3,4-Di-Cl	219
9g	CH	H	3-Pyridine[c]	>440
9h	CH	Me (*S*)	*m*-F	6.9
9j	CH	Me (*R*)	*m*-F	39.8
9k	CH	Me (*S*)	*m*-Cl	2.8
9m	CH	Me (*R*)	*m*-Cl	39.5
9n	CH	Et (*R*/*S*)	*m*-Cl	17.9
9p	C–OH[d]	H	*m*-Cl	>440

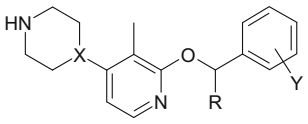
[a] $K_i = IC_{50}/\{1 + ([\text{free radioligand}]/K_d)\}$, where IC_{50} is the concentration (nM) producing half-maximal inhibition of the specific binding of [^{3}H]LSD to human recombinant 5-HT_6, and K_d is the dissociation constant determined by saturation binding (=3.5). Each K_i represents an average of three replicates run in three separate experiments ($n = 3$).

[b] Lit.[11b] $K_i = 0.7$ nM.

[c] Y = H.

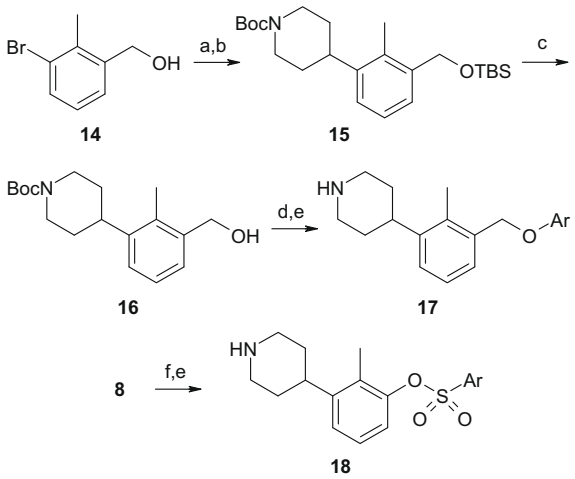
[d] Prepared by lithiation of TBS-protected 3-bromo-2-methyl-phenol, addition to 1-Boc-4-piperidone, desilylation, and alkylation as per Scheme 2.

Table 2
Affinity of pyridylpiperidines **13** for h5-HT_6 receptors



Compound	X	R	Y	5-HT_6 binding K_i (nM)
13a	CH	H	*m*-Cl	8.1
13b	CH	H	*m*-F	17.8
13c	CH	H	*m*-CF_3	19.1
13d	CH	H	*o*-Cl	>440
13e	CH	H	*p*-Cl	50.0
13f	CH	H	*o*-F	>440
13g	CH	H	*p*-F	>440
13h	CH	H	2,4-Di-F	239
13j	CH	Me (*S*)	H	48.5
13k	CH	Me (*R*)	H	>440
13m	CH	Me (*S*)	*m*-Cl	10.5
13n	CH	Me (*R*)	*m*-Cl	208
13p	CH	Et (*R*/*S*)	*m*-Cl	6.4
13q	CH	CF_3 (*R*/*S*)	*m*-Cl	2.4
13r	CH	CF_3 (*R*/*S*)	*m*-F	4.3
13s	C–OH[a]	H	*m*-F	>440

[a] Prepared by addition of *m*-fluorobenzyl alcohol to **10** followed by lithiation and addition to 1-Boc-4-piperidone, and subsequent deprotection.



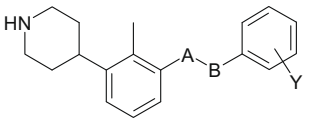
Scheme 4. Preparation of transposed ethers **17** and sulfonyl esters **18**. Reagents and conditions: (a) TBSCl, imidazole (64%,); (b) 4-piperidinylzinc iodide, 30% $Pd(dppf)Cl_2$, CuI, DMA (53%); (c) TBAF, THF (34%); (d) $ArCH_2OH$, DIAD, PPh_3; (e) 4 M HCl in dioxane; (f) $ArSO_2Cl$, K_2CO_3, 1:1 acetone:CH_3CN.

gen and carbon atoms was performed according to Scheme 4. 2-Bromo-6-hydroxymethyltoluene **14**[14] was first protected (TBS), then subjected to a Negishi coupling reaction with 4-piperidinylzinc iodide[15] to give **15**. Deprotection to benzyl alcohol **16** and ether formation under Mitsunobu conditions provided the desired reverse ethers **17**. A second linker modification was envisioned based on the literature agent diF-BAMPI containing a sulfonyl ester.[16] These analogs were prepared in high yield from phenol **8** via straightforward coupling with various sulfonyl chlorides, followed by deprotection to give **18**.

Binding data for the reverse ethers **17** and sulfonyl esters **18** is shown in Table 3. Potency of **17a** and **17b** was similar to that of the tolylamines **5a**,**b** and **9a**,**b** in Table 1. Interestingly, sulfonyl esters **18** seemed to slightly prefer *ortho*-substitution although in general were widely tolerant. Naphthylsulfonates **18m** and **18n** represented the most potent analogs from the series.

Tolylpiperidine **9h** was selected for further biological profiling owing to its favorable in vitro ADME and receptor selectivity

Table 3
Affinity of tolylpiperidines **17** and **18** for h5-HT_6 receptors



Compound	A	B	Y	5-HT_6 binding K_i (nM)
17a	CH_2	O	*m*-Cl	3.5
17b	CH_2	O	*m*-F	6.5
18a	O	SO_2	H	19.6
18b	O	SO_2	*m*-Cl	26.1
18c	O	SO_2	*m*-F	18.4
18d	O	SO_2	*o*-Cl	5.8
18e	O	SO_2	*p*-Cl	24.7
18f	O	SO_2	*o*-F	13.6
18g	O	SO_2	*o*-CH_3	10.1
18h	O	SO_2	*m*-CH_3	15.1
18j	O	SO_2	*p*-CH_3	28.9
18k	O	SO_2	*p*-Et	11.3
18m	O	SO_2	1-Naphthyl[a]	1.5
18n	O	SO_2	2-Naphthyl[a]	2.7

[a] Fused.

Table 4
Rat pharmacokinetic parameters for tolylpiperidine **9h**

Parameter	Tolylpiperidine **9h**
Bioavailability (%F)	90
Clearance (mL/min/kg)	66
Vdss[a] (L/kg)	12
Plasma half-life[b] ($t_{1/2}$, h)	5.9
Brain/plasma (total)	23

[a] Volume of distribution at steady state.
[b] From PO dosing.

profile. Although highly lipophilic, owing to the free amine some free drug was available (Fu ~ 0.05). PK data is shown in Table 4. High clearance in rat accompanied with large volume of distribution resulted in a moderate half life of 5.9 h. Importantly, **9h** was selectively partitioned into rat brain, which would be required for achieving in vivo activity against neuropsychiatric indications.

Functional efficacy of **9h** was determined by quantifying the accumulation of cAMP levels by ELISA in cells expressing recombinant human or rat 5-HT_6 receptors. While 5-HT markedly increased cAMP levels, **9h** did not stimulate levels of cAMP production in either rat or human cell line at 1, 3 and 10 μM, indicating no agonist activity for the 5-HT_6 receptor. Compound **9h** did behave as an antagonist by inhibiting 5-HT stimulated cAMP accumulation in both human and rat 5-HT_6 cells (K_b values of 159 and 153 nM for human and rat 5-HT_6 receptors, respectively). No appreciable binding of **9h** to the 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} receptor subtypes was observed (all IC_{50} > 1.0 μM).[17] In addition, there appeared to be no agonist activity and nominal antagonist activity in the FLIPR $5HT_{2A}$ and $5HT_{2B}$ functional assays.[18] Compound **9h** was tested in the novel object recognition paradigm[19] using a 24 hour delay procedure in which non-treated rats no longer show memory for a previously viewed object. Doses of 3 and 10 mg/kg **9h** resulted in significantly greater exploration of the novel versus the familiar object, thereby demonstrating efficacy for reversing natural forgetting (Fig. 1).

In summary, a number of tolylamine analogs were prepared and tested to assess their 5-HT_6 antagonist activity. The piperazine motif of HTS hit **1** could be replaced by piperidine as in **9**. The core toluene group could be replaced by methylpyridine as in **13**. The ether linker could be reversed or replaced by a sulfonate ester (**17** and **18**). Finally, tolylpiperidine **9h** was tested in rats and found to have an acceptable PK profile including excellent CNS exposure, and in addition improved cognition in the novel object recognition paradigm.

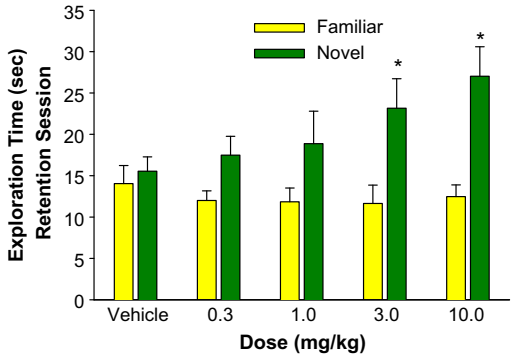


Figure 1. Rat novel object recognition assay data for tolylpiperidine **9h** at t = 1 h post IP dose (* = P < 0.05 for novel versus familiar object. N = 9–10 rats per dose group).

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