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1-Sulfonyl-6-Piperazinyl-7-Azaindoles as potent and pseudo-selective 5-HT$_6$ receptor antagonists

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ABSTRACT

A series of 1-Sulfonyl-6-Piperazinyl-7-Azaindoles, showing strong antagonistic activity to 5-HT$_6$ receptor (5-HT$_6$R) was synthesized and characterized. The series was optimized to reduce activity on D$_2$ receptor. Based on the selectivity against this off-target and the analysis of the ADME-tox profile, compound **1c** was selected for in vivo efficacy assessment, which demonstrated procognitive effects as shown in reversal of scopolamine induced amnesia in an elevated plus maze test in mice. Compound **3**, the demethylated version of compound **1c**, was profiled against a panel of 106 receptors, channels and transporters, indicating only D$_3$ receptor as a major off-target. Compound **3** has been selected for this study over compound **1c** because of the higher 5-HT$_6$R/D$_2$R binding ratio. These results have defined a new direction for the design of our pseudo-selective 5-HT$_6$R antagonists.

Novel therapies against dementias and in particular Alzheimer's disease (AD) constitute one of the biggest medical needs in developed countries. With the morbidity reaching over 35 million cases worldwide[1] and the annual worldwide cost of above US$315 billion[2] this group of diseases remains in the center of interest of pharmaceutical industry and drug research around the world. Disease modifying treatments do not yet exist, and disadvantages of current standard symptomatic medications, namely inhibitors of acetyl cholinesterase (e.g., donepezil, rivastigmine, galantamine) and NMDA receptors (e.g., memantine) have poor tolerability, low efficacy and present challenges with patient compliance because of suboptimal dosing regimens and side effects (mainly gastrointestinal). These shortcomings result in symptomatic therapies which benefit the patient for only about one year on average,[3] whereas the potential need for therapy for AD patients can last for even 8.5 years (considering the duration from the onset of the disease to the severe stage).[4] Due to the above mentioned reasons an innovative approach to enhance cognition in AD patients is desirable.

One of the approaches to cognitive improvement is blocking the serotonin 5-HT$_6$ receptor with an antagonist. 5-HT$_6$R is expressed almost exclusively in the central nervous system in humans, mainly in hippocampus, striatum and nucleus accumbens. 5-HTRs couple to Gs-protein and stimulate adenylyl cyclase activity. Antagonism of 5-HT$_6$R was shown to improve cognitive performance in rodents in numerous memory related tasks.[5–9] Importantly, these effects seem to be translated to humans—Lundbeck has recently announced positive results from a Phase II clinical trial of its selective 5-HT$_6$R antagonist (idalopirdine; Lu AE58054) in improving cognitive performance in mild to moderate AD patients[10] and initiated Phase III.[11] Additionally, antagonizing 5-HT$_6$R provides a potential therapeutic strategy for cognitive symptoms of schizophrenia[12] and obesity.[13] The mode of action of 5-HT$_6$R antagonists has been elucidated in vivo by means of electrophysiology[14] and microdialysis[15] where it was shown that antagonizing 5-HT$_6$R enhances glutamatergic, cholinergic and monoaminergic neurotransmission.

Comprehensive reviews of 5-HT$_6$R related medicinal chemistry were published in recent years by Holenz,[16] Liu,[17] Ivachtchenko[18] and Lopez-Rodriguez.[19] According to Lopez-Rodriguez most of the known 5-HT$_6$R ligands can be clustered into four structural families taking into account the groups that occupy the main

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pharmacophoric features: bisarylsulfonamides, indoles, indole-like derivatives and non-sulfonyl compounds. Those key structural elements for 5-HT6 antagonism can be modeled into a simplified pharmacophore:[19,20] a positive ionizable atom, an aromatic ring-hydrophobic site, a hydrogen bond acceptor and a hydrophobic site. Some diversified atypical compounds have also been reported, although they share common structural part of those 4 main families. According to the recent review of Ivachtchenko, which is focused mainly on the selectivity profile of 5-HT_6 ligands, these can be further classified into three categories: multimodal/multi target, pseudo-selective and selective.

Here we report the discovery and pharmacological characterization of a series of 6-piperazinyl-7-azaindoles bearing an alkyl or hetero alkyl sulfone in position 1 and an aryl or hetero aryl in position 4 (compounds **1a**–**p**, **2a**–**f** and **3** represented in Scheme 1). Those compounds could be assigned to the indole-like family: azaindole is used here as a bioisostere of the typical indole core. We also synthesized the bisarylsulfonamides derivatives on this azaindole core[21] but those compounds were not selected for further studies due to the superior results obtained for the aliphatic analogs (results not reported) and tolerance of this new chemical series for non-lipophilic moieties. Furthermore, the removal of the sulfonyl group is not tolerated and results in losing the potency for 5-HT_6 receptor.

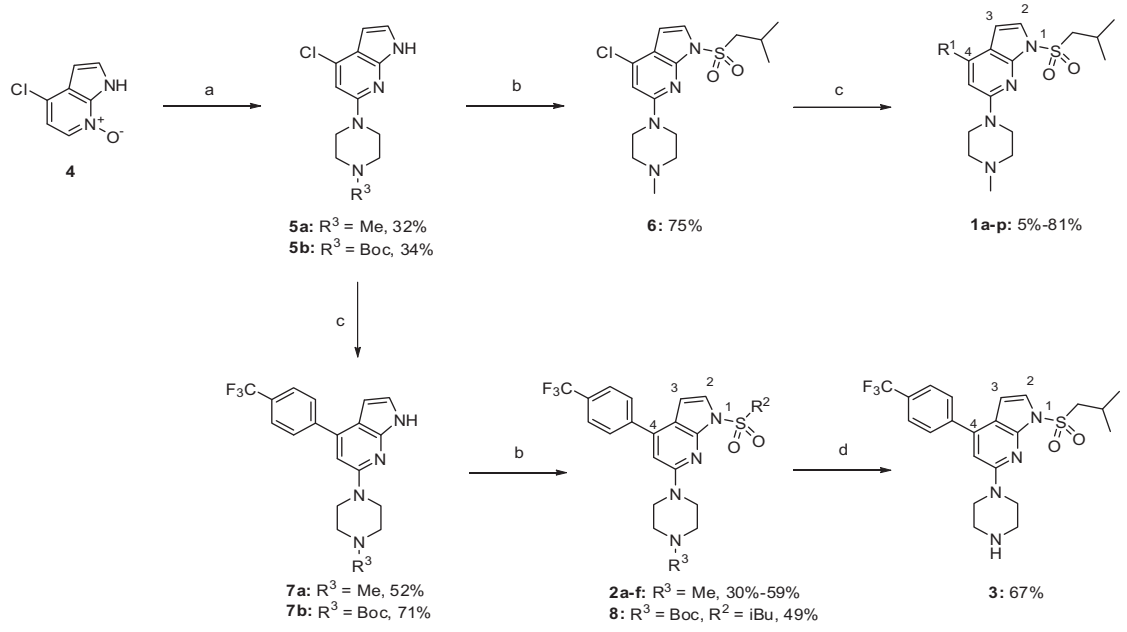
Most compounds from these series are potent and pseudo-selective according to the classification of Ivachtchenko. In our project we have defined D_2 receptor as an antitarget. This receptor is connected to extrapyramidal symptoms most commonly caused by typical antipsychotics. Additionally, the selectivity against a broad panel of diverse targets was checked for the selected representative example **3**. Full SAR for the series is available for 5-HT_6 and D_2 receptors.

As shown in Scheme 1, the lead structure template was divided into two structural regions for analog optimization, the aryl group R^1 and the pendant alkyl R^2. The synthesis of the proposed compounds was achieved as described in Scheme 1. 4-Chloro-7-azaindole **4** was transformed into *N*-oxide with *m*-CPBA.[22] *N*-Oxide **4** was alkylated with dimethyl sulfate and the obtained intermediate was treated with commercially available *N*-substituted piperazines in the presence of *N*,*N*-Diisopropylethylamine to afford 4-chloro-6-(*N*-substituted-piperazynyl)-1*H*-7-azaindoles **5** using the procedure of Reissert-Henze reaction.[22] In order to study the influence of the aryl group R^1, compound **5** was reacted with isobutyl sulfonyl chloride in the presence of sodium hydride, followed by a Suzuki coupling with the corresponding boronic acid to give compounds **1a**–**p**. Similarly to understand the role of R^2 on the sulfone, compounds **2a**–**f** were synthesized by exchanging the two previous steps. First, the Suzuki coupling was performed with 4-trifluoromethylphenyl boronic acid and then sulfonylation reaction was performed with the appropriate sulfonyl chloride. Demethylated compound **3** was obtained by following the same synthetic pathway using *N*-Boc-piperazine. An additional deprotection step with trifluoroacetic acid was needed to obtain the final compound.

All compounds were screened in search of high affinity ($K_i \leqslant 20$ nM) on the 5-HT_6R and low to negligible affinity to the dopamine D_2 receptor ($K_i \geqslant 200$ nM) in a radioligand binding assay. The affinities (K_i) of the studied compounds for the 5-HT_6R and D_2R were determined indirectly by displacement of [^{3}H]-LSD and [^{3}H]-NMSP, respectively. Results are displayed in Tables 1 and 2.

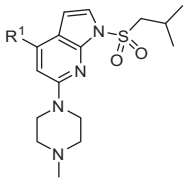
Our first compound **1a** (R^1 = Ph and R^2 = isobutyl) was found to have potent in vitro binding affinity toward 5-HT_6R (K_i = 16 nM) and an acceptable 5-HT_6R/D_2R binding ratio of 35. Initially, we were interested to know if R^1 = Ph was the optimal group in this chemical series. So we investigated the influence of the group R^1 (compounds **1a**–**p**, Table 1). A scan through various substitutions on the phenyl was initially tested (compounds **1a–j**, Table 1). Compound **1b** with an ethyl substituent in position 4 was shown to have similar potency and 5-HT_6R/D_2R binding ratio to **1a**. When ethyl was replaced with –CF_3, compound **1c** was 3 times more potent. Although the compound had higher affinity for D_2R, the 5-HT_6R/D_2R binding ratio was the best one among the three aforementioned compounds.

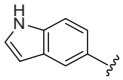
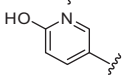
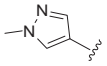
Next, we have tested effect of polar substituents on 5-HT_6R and D_2R affinities of the compounds. Interestingly, compound **1f** with –OMe was the most potent 5-HT_6R binder (K_i = 2nM). However, the 5-HT_6R/D_2R binding ratio was 10 fold lower than our prototype compound **1c**. Replacement of –OMe by –OBn (compound **1g**) reversed the binding ratio toward D_2R by a factor of 30. Compound



Scheme 1. Reagents and conditions: (a) Me_2SO_4, MeCN, piperazine derivatives; 60 °C, 6 days; (b) R_2SO_2Cl, NaH, dry DMF; 0 °C, 90 min; (c) boronic acid or boronic ester, Pd $(OAc)_2$, S-Phos, K_3PO_4, toluene; 130 °C, 24 h; (d) CF_3CO_2H, DCM; RT, 1 h. For the definition of R1 and R2, see Tables 1 and 2.

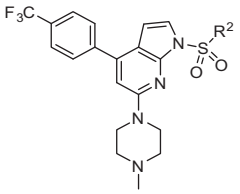
Table 1
SAR and 5-HT_6R/D_2R binding ratio profile: analysis of R^1

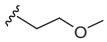


Compound	R^1	5-HT_6R K_i[a] (nM)	D_2R K_i[a] (nM)	Ratio 5-HT_6R/D_2R
1a	Ph	16	547	35
1b	C_6H_4(4-Et)	11	614	56
1c	C_6H_4(4-CF_3)	4	367	80
1d	C_6H_4(3-CF_3)	48	630	13
1e	C_6H_4(2-CF_3)	24	113	5
1f	C_6H_4(4-OMe)	2	22	9
1g	C_6H_4(4-OBn)	290	86	0.3
1h	C_6H_4(4-OH)	22	108	5
1i	C_6H_4(4-CN)	7	205	29
1j	C_6H_4(4-$CONMe_2$)	>2000	>2000	-
1k		5	382	76
1l		36	>2000	>55
1m		231	>2000	>8
1n		87	>2000	>23
1o		12	640	53
1p		129	>2000	>15

[a] Compounds at eight concentrations ranging from 5×10^{-6} to 5×10^{-13} M were tested in triplicates. Data analysis was performed in GraphPad Prism software and presented in the form of graphs on semi-log scale. Curve fitting was done using nonlinear regression using one site competition model.

Table 2
SAR and 5-HT_6R/D_2R binding ratio profile: analysis of R^2



Compound	R^2	5-HT_6R K_i[a] (nM)	D_2R K_i[a] (nM)	Ratio 5-HT_6R/D_2R
1c	Isobutyl	4	367	80
2a	Me	54	1231	22
2b	*i*Pr	6	25	4
2c	Cyclohexyl	15	>2000	>133
2d		7	>2000	>285
2e		8	52	6

[a] See footnote a of Table 1.

1i with –CN showed comparable potency as compound **1c**. However, this compound was 3 times less selective. The same was observed for a bicyclic version (compound **1k** bearing an indole substituted in position 5). Finally, the conversion of this –CN group to –Amide led to completely inactive compound (compound **1j**).

We then investigated the direct replacement of the phenyl group by a heteroaryl such as the pyridine **1l** or pyridone **1m**. Either of the compounds did not show any improvement. We also tried 5-membered ring analogs like pyrazole **1n**, thiophene **1o**, isoxazole **1p**. The most promising derivative in this set was the thiophene analog with respect to affinity and 5-HT_6R/D_2R binding ratio.

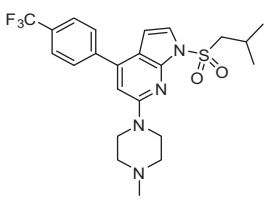
We also investigated variations on R^2 to determine if isobutyl was the optimum alkyl or heteroalkyl on the sulfone. This SAR analysis is described in Table 2. When R^2 = Me was tested, loss of potency and selectivity was observed compared to compound **1c**. The removal of one $-CH_2$ unit to the isobutyl group of compound **1c** gave us compound **2b**. This was sufficient to get similar activity, unfortunately in detriment of the selectivity over D_2R (K_i = 25 nM). The activity was 4 fold lower when a more rigid group R^2 = cyclohexyl was tried. Addition of polar substituents into the alkyl groups lead to compounds **2d** and **2e**, which did not provide improvements towards the desired overall profile.

The demethylated version of compound **1c** was also synthesized. The activity towards 5-HT_6R was similar for both compounds as it is shown in Figure 1. Interestingly, compound **3** gave better 5-HT_6R/D_2R binding ratio (567x). In order to confirm the antagonism on the 5-HT_6 receptor, the functional activity through measurement of cAMP levels in a cell-based assay was determined in Cerep. Kb value for compound **1c** is given in Figure 1.

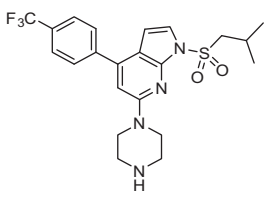
The selectivity of compound **3** was tested at a concentration of 1 μM against a Cerep panel consisting of 106 neurotransmitter receptors, transporters and ion channels (Fig. S1). Compound **3** has been selected for this study over compound **1c** because of the higher 5-HT_6R/D_2R binding ratio.

According to the new classification proposed recently by Ivachtchenko, compound **3** might be classified as pseudo-selective (the compound shows a ratio of its affinity to the 5-HT_6R compared to other biological targets affinities of less than 250).[18] It is worth noting though, that most of the off–targets detected for compound **3** show radioligand displacement only slightly above the threshold (50%) also used in Ivachtchenko classification to define weak interactions. 60% radioligand displacement at 1 μM for the D_2 receptor in the Cerep panel corresponds to K_i = 1.7 μM D_2R measured in our in-house assay. Only a single off-target (D_3 receptor) can be treated as equipotent to 5-HT_6R (94% vs 100% for 5-HT6). Strong radioligand displacement (72%) has also been observed for 5-HT1B receptor. Full results of Cerep panel have been included in Supporting information (Fig. S1).

To complement medicinal chemistry approach and gain some insight of the molecular interactions that could influence affinity and selectivity towards 5-HT_6R, we have performed in silico



1c
Ki 5-HT_6R = 4 nM
Ki D_2R = 367 nM
Kb 5-HT_6R = 250 nM



3
Ki 5-HT_6R = 3 nM
Ki D_2R = 1702 nM

Figure 1. Comparison of compounds **1c** and **3** (demethylated piperazine).

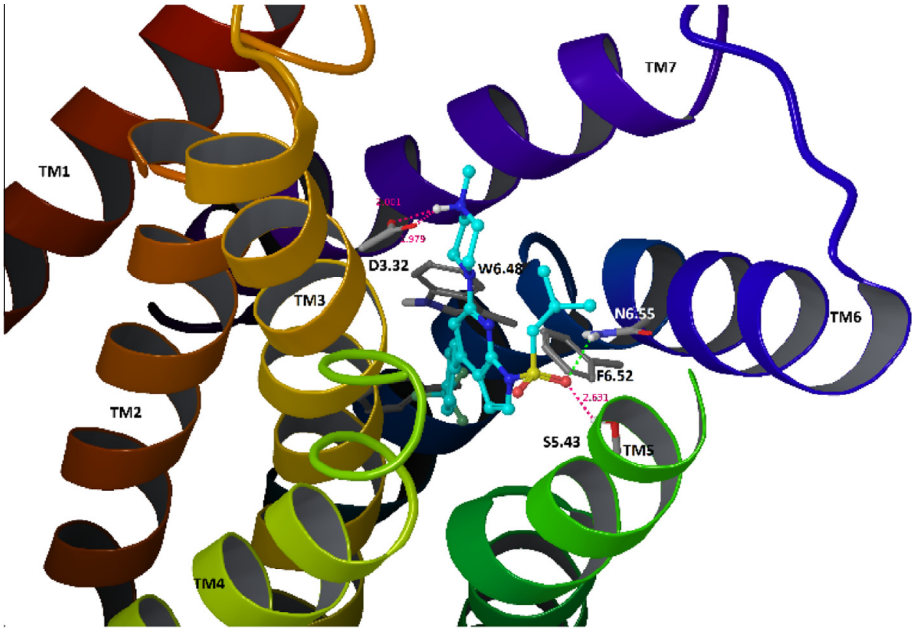


Figure 2. Compound **1c** docked to the 5-HT_6R. Key interaction residues of the receptor are shown in the stick representation. The view of the receptor from the extracellular side; extracellular loop 2 (ECL2) and a part of the transmembrane helix 5 (TM5) are removed for clarity.

flexible docking of studied compounds in homology models of 5-HT_6 and D_2 receptors.

All studied compounds were docked to the selected receptor models and binding poses were carefully analyzed. The predominantly observed binding mode is similar in both 5-HT_6R and D_2R. The compounds bind with the piperazine—core plane perpendicular to the long axis of a receptor and R^1–R^2 plane parallel to the long axis of the receptor (Fig. 2).

In this binding mode R^1 substituent binds deep between helices TM3, TM5 and TM6, while R^2 binds in the vestibule formed by the cytoplasmic ends of TM helices. Compounds are stabilized in the binding site of 5-HT_6R by a salt bridge between the charged nitrogen atom of the piperazine moiety and Asp 3.32, π–π stacking of the azaindole core with Phe 6.52, π–π stacking of the R^1 aromatic moiety with Trp 6.48 and hydrogen bonds between sulfone group and Ser 5.43 and predominantly Asn 6.55 (Fig. 2). Ligand–receptor interactions are in agreement with the available literature data[23,24] and with the results of other docking studies for 5-HT_6R.[25]

In the next step, docking studies were used to explain 5-HT_6R versus D_2R selectivity for the studied compounds. Generally, target-based investigations of selectivity are difficult for similar targets as affinity differences depend not only on the different shape of the binding site but also on the different hydration pattern of the binding site, different stabilities and free energies of water molecules in the active site, changes in general flexibility of the binding site and many more effects. Here, we analyzed differences in the sequence and shape of the binding sites of both studied receptors which may impact proposed binding mode. However, it should be noted that other factors, mentioned above, may contribute to a large extent to the observed selectivity of the studied compounds. Comparison of sequence and shape pointed to position 6.55, which is occupied by Asn in 5HT_6R and His in D_2R. Side chains of the residues in this position project to the upper vestibule and His 6.55 in D_2R is shifted upwards compared to Asn 6.55 in 5-HT_6R. As a consequence His 6.55 occupies considerably more space, effectively closing the upper vestibule for bulky R^2 substituents (Fig. 3). This structural observation is confirmed by SAR, where compounds **2a** and **2b** with small R^2 substituent have low selectivity ratio in the range of 4 to 22, which rises to several hundred (compounds are effectively inactive for D_2R) when R^2 is bulky.

Limited volume of the upper vestibule may also influence selectivity of the aromatic R^1 substituent. Aromatic binding pocket of R^1 moiety is closed at the bottom by a rigid lid formed by Phe 6.44 residue. This residue is conserved in GPCRs and forms ligand interactions in rhodopsin. As the bottom of the R^1 pocket is rigid compounds with longer R^1 fragments are shifted upwards toward the vestibule. However, they can easier accommodate in the larger vestibule of 5-HT_6R rather than D_2R. This explains the trend observed by SAR analysis, where compounds with longer R^1 are more selective. For example, among the compounds **1c**–**1e**, selectivity decreases going from the longest *p*-CF_3-Ph to the shortest *o*-CF_3-Ph. Other compounds also follow this trend.

Compounds **1c** and **3** were further profiled in ADME-toxicity assays to investigate potential liabilities linked to this particular type of scaffold. Both compounds had excellent permeability through the PAMPA membrane. The IC50 values for CYP 3A4 and CYP 2D6 were found to be better for compound **1c** than **3**, indicating less likely drug–drug interactions in humans through the major metabolic enzymes tested. Compound **1c** had acceptable in vitro metabolic stability in the three species human/mouse/rat as shown by the calculated intrinsic clearance. hERG liability was also evaluated using an automated patch clamp assay. The activities towards hERG were similar for both compounds as it is shown in Table 3.

Kinetic solubility was also determined for the free base of compound **1c** and showed to be a poorly soluble compound (8 μg/mL). A study of different salt form has been performed. As shown in Table 4, solubility was slightly improved when compound **1c** was converted to the hydrobromide salt.

Compound **1c** was selected for in vivo cognitive testing in mouse based on its biology and ADME-tox profile.

We used the Elevated Plus Maze (EPM) with scopolamine as an in vivo screening test to assess the effects of 5-HT_6R antagonism in mice. Briefly, mice were administered with the test compound, and 10 min later with scopolamine. In the acquisition phase (T1) the time spent in the open arm (OAT%; [open arm time/open + enclosed time] * 100) and the latency of entering the open arm

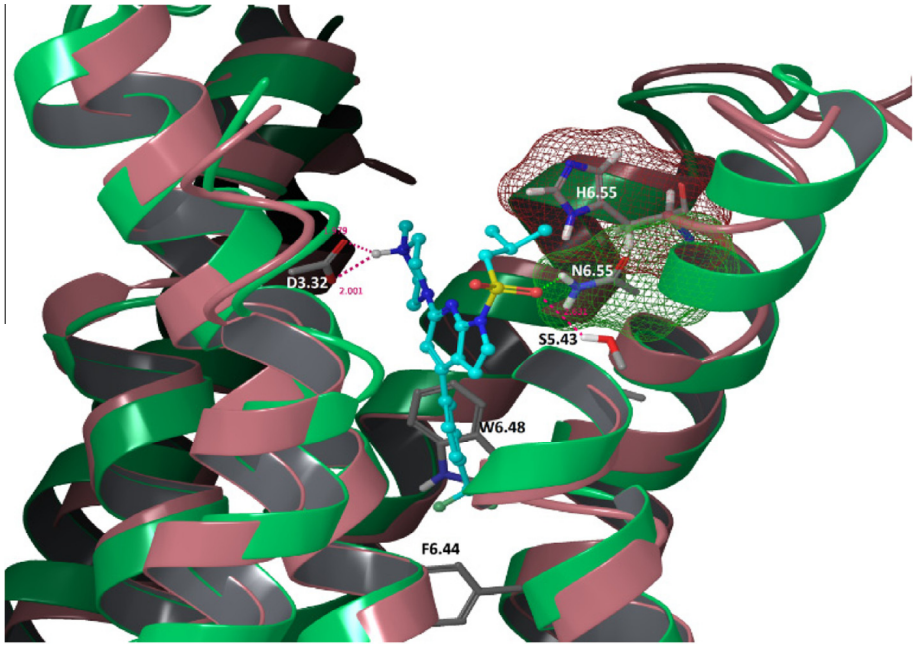


Figure 3. Superimposition of 5-HT_6R (green) and D_2R (pink) receptors. For residues in position 6.55 (stick representation) molecular surface is shown. Compound **1c** and key residues of the binding pocket responsible for ligand binding are shown as in Figure 2. The view of the receptor from the side. Extracellular loop 2 (ECL2) and part of the transmembrane helix 5 (TM5) removed for clarity.

Table 3
ADME-tox properties for selected compounds

Assays	Compound **1c**	Compound **3**
PAMPA (nm/s)	537	920
CYP (μM)	3A4: 1.1 <IC50 <3.3 2D6: 3.3 <IC50 <10	3A4: IC50 <1.1 2D6: IC50 >10
Clint (μL/min/mg protein)	h/m/r 20/63/55	—
hERG, IC50 (μM)	2.1	1.4

Table 4
Solubility study of compound **1c**

Salt	Free base	HCl	HBr	H_2SO_4	Fumaric/tartaric/ citric acid
Kinetic solubility (μg/mL)	8	14	65	10	20/11/14

(TL) were recorded. Mice prefer the less aversive closed compartments, and learn quickly to go there, if the spatial learning and memory are not disturbed with amnestic compound, like muscarinic receptor antagonist scopolamine. In the retention phase (T2) 24 h after the T1 phase decrease in OAT% and TL is believed to indicate learning and memory. The scopolamine treatment increased the OAT% and TL compared to vehicle treatment in both T1 and T2 phases which can be considered as disturbance of memory. The memory impairment could be prevented with the treatment of optimal low dose of compound **1c** as measured with OAT% (Fig. 4). Even if there was no clear dose response either in the acquisition or the retention phase, it can be concluded that compound **1c** showed in vivo efficacy with a narrow dose range in our in vivo screening model. These U-shaped dose response curves are common for nootropic compounds.

Thus we report a new series of potent and pseudo-selective $5HT_6$ receptor antagonists with procognitive efficacy in a mouse model of spatial learning and memory. Many of the tested

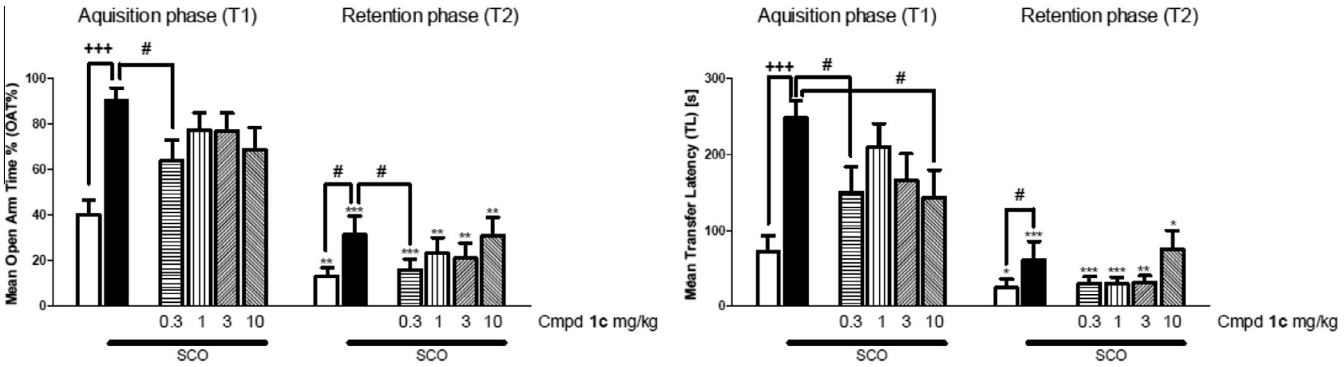


Figure 4. Total percentage of the time spent in the open arms (OAT%) and the transfer latency (TL) to the enclosed arm in the elevated plus maze after subcutaneous administration of compound **1c** at different doses. Data are presented as mean ± SEM and median (n = 13–15). White bar is the control group, black bar is the scopolamine (SCO) treated control group, and shaded bars are scopolamine treated test groups with different concentrations of compound **1c**. + significantly different from the vehicle group, # significantly different from the scopolamine group, ∗ T2 value significantly different from the respective T1 value of the group. All values measured after 24 h (phase T2) of acutely measured phase T1 values were lower reflecting spatial learning and memory. One symbol p <0.05, three symbols p <0.001.

compounds showed high activities in the nanomolar range with $5HT_6R/D_2R$ binding ratio over 100 for some compounds. Computational analysis helped us to rationalize observed SAR in terms of potency and selectivity and facilitated further development of compounds and optimization of ligand–receptor interactions in both R^1 and R^2 regions.

Optimization of compounds was driven not only by the improvement of on-target activity and $5HT_6R/D_2R$ binding ratio but also by in vitro ADME and safety parameters. Due to the most favorable balance between potency, selectivity, safety properties (hERG and CYP inhibition) and ADME properties (solubility, PAMPA and metabolic stability) compound **1c** was selected for further in vivo PK and efficacy studies. In the mouse model of spatial learning (EPM) experiment, compound **1c** prevented the amnestic effect of scopolamine in the memory acquisition (learning) and 24 h later in the retention phase (memory).

Supplementary data

Supplementary data (experimental protocols for all compounds, 5-HT_6R binding, D_2R binding, Cerep 5-HT_6 functional, Cerep diversity panel, automated patch clamp I_{hERG}, PAMPA, CYP 3A4/2D6 inhibition, metabolic stability, kinetic solubility assays, PK study, elevated plus maze test and homology modeling of $5HT_6$ and D_2 receptors) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.04.024.

References and notes

1. Querfurth, H. W.; LaFerla, F. M. *N. Engl. J. Med.* **2010**, *362*, 329.
2. http://www.alz.co.uk/research/files/WorldAlzheimerReport-ExecutiveSummary.pdf, accessed on 2015-08-24.
3. Sun, Y.; Lai, M. S.; Lu, C. J.; Chen, R. C. *Eur. J. Neurol.* **2008**, *15*, 278.
4. Francis, P. T.; Palmer, A. M.; Snape, M.; Wilcock, G. K. *J. Neurol. Neurosurg. Psychiatry* **1999**, *66*, 137.
5. King, M. V.; Sleight, A. J.; Woolley, M. L.; Topham, I. A.; Marsden, C. A.; Fone, K. C. *Neuropharmacology* **2004**, *47*, 195.
6. Foley, A. G.; Murphy, K. J.; Hirst, W. D.; Gallagher, H. C.; Hagan, J. J.; Upton, N.; Walsh, F. S.; Regan, C. M. *Neuropsychopharmacology* **2004**, *29*, 93.
7. Loiseau, F.; Dekeyne, A.; Millan, M. J. *Psychopharmacology (Berl)* **2008**, *196*, 93.
8. Perez-García, G.; Meneses, A. *Pharmacol. Biochem. Behav.* **2005**, *81*, 673.
9. Hatcher, P. D.; Brown, V. J.; Tait, D. S.; Bate, S.; Overend, P.; Hagan, J. J.; Jones, D. N. *Psychopharmacology (Berl)* **2005**, *181*, 253.
10. Wilkinson, D.; Windfeld, K.; Colding-Jørgensen, E. *Lancet* **2014**, *13*, 1092.
11. http://investor.lundbeck.com/releasedetail.cfm?ReleaseID=750931, accessed on 2015-08-24.
12. Arnt, J.; Bang-Andersen, B.; Grayson, B.; Bymaster, F. P.; Cohen, M. P.; DeLapp, N. W.; Giethlen, B.; Kreilgaard, M.; McKinzie, D. L.; Neill, J. C.; Nelson, D. L.; Nielsen, S. M.; Poulsen, M. N.; Schaus, J. M.; Witten, L. M. *Int. J. Neuropsychopharmacol.* **2010**, *13*, 1021.
13. Heal, D.; Gosden, J.; Smith, S. *Int. Rev. Neurobiol.* **2011**, *96*, 73.
14. Tassone, A.; Madeo, G.; Schirinzi, T.; Vita, D.; Puglisi, F.; Ponterio, G.; Borsini, F.; Pisani, A.; Bonsi, P. *Neuropharmacology* **2011**, *61*, 632.
15. Hirano, K.; Piers, T. M.; Searle, K. L.; Miller, N. D.; Rutter, A. R.; Chapman, P. F. *Life Sci.* **2009**, *84*, 558.
16. Holenz, J.; Pauwels, P. J.; Díaz, J. L.; Mercè, R.; Codony, X.; Buschmann, H. *Drug Discovery Today* **2006**, *11*, 283.
17. Liu, K. G.; Robichaud, A. J. *Drug Dev. Res.* **2009**, *70*, 145.
18. Ivachtchenko, A. V.; Ivanenkov, Y. A. *Curr. Bioact. Compd.* **2013**, *9*, 64.
19. Benhamú, B.; Martín-Fontecha, M.; Vázquez-Villa, H.; Pardo, L.; López-Rodríguez, M. L. *J. Med. Chem.* **2014**, *57*, 7160.
20. Holenz, J.; Mercè, R.; Díaz, J. L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B.; Hernández, S.; Monroy, X.; Sánchez, E.; Hernández, E.; Pérez, R.; Cubí, R.; Sanfeliu, O.; Buschmann, H. *J. Med. Chem.* **2005**, *48*, 1781.
21. Dunn, R.; Nguyen, T. M.; Xie, W.; Tehim, A.; W.O. Patent 101247, 2008.
22. Storz, T.; Bartberger, M. D.; Sukits, S.; Wilde, C.; Soukup, T. *Synthesis* **2008**, *2*, 201.
23. Hirst, W. D.; Abrahamsen, B.; Blaney, F. E.; Calver, A. R.; Aloj, L.; Price, G. W.; Medhurst, A. D. *Mol. Pharmacol.* **2003**, *64*, 1295.
24. Harris, R. N., 3rd; Stabler, R. S.; Repke, D. B.; Kress, J. M.; Walker, K. A.; Martin, R. S.; Brothers, J. M.; Ilnicka, M.; Lee, S. W.; Mirzadegan, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3436.
25. Pullagurla, M. R.; Westkaemper, R. B.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4569.