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Letter

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N1-azinylsulfonyl-1H-indoles: 5-HT6 receptor antagonists with pro-cognitive and antidepressant-like properties

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KEYWORDS: isoquinoline/quinoline sulfonamides, 5-HT$_6$ receptor antagonist, Alzheimer's disease, cognitive decline, novel object recognition task, forced swim test, Vogel test

ABSTRACT: A series of *N*1-azinylsulfonyl-3-(1,2,3,6,tetrahyrdopyridin-4-yl)-1*H*-indole derivatives was designed to obtain highly potent 5-HT$_6$ receptor ligands. The study allowed for the identification of **25** (4-{[5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-1-yl]sulfonyl}isoquinoline), a potent and selective 5-HT$_6$ receptor antagonist. The selected compound, with good brain penetrability, was evaluated *in vivo* in a novel object recognition (NOR) and forced swim (FST) tests in rats, demonstrating distinct pro-cognitive and antidepressant-like properties (MED = 1 mg/kg and 0.1 mg/kg, *i.p.*, respectively). Compound SB-742457, used as comparator, reversed memory deficits in NOR task in similar doses, while in FST was active in 10–30 folds higher dose (3 mg/kg). In contrast to SB-742457, which was active in Vogel test (MED = 3 mg/kg), compound **25** displayed no anxiolytic activity.

The most devastating neurodegenerative form of dementia is Alzheimer's disease (AD). The number of AD patients was estimated at 35.6 mln in 2012 and is expected to double every twenty years to 65.7 mln in 2030 and 115.4 in 2050. Current AD treatments provide only brief symptomatic relief and are based on the use of acetylcholinesterase inhibitors and NMDA receptor antagonist. One approach that has recently garnered significant interest is selective 5-HT$_6$ receptor (5-HT$_6$R) antagonism.[1]

The 5-HT$_6$R belongs to the G-protein coupled receptor (GPCR) superfamily, and it stimulates adenylyl cyclase via Gs, as well as extracellular-regulated kinase (ERK) signaling via the Src-family tyrosine kinase Fyn. Furthermore, 5-HT$_6$R activates mTOR Complex 1 (mTORC1) in the prefrontal cortex which is related to cognitive deficits,[2] and the receptor constitutively activates Cdk5 to control cortical neurons migration and promote neurite growth.[3]

Blockade of 5-HT$_6$R enhances cognitive performance in a broad range of tasks in rodents[4,5] and phase II clinical studies have demonstrated efficacy of 5-HT$_6$R antagonists (Iladopirdine = LuAE58054, SB742457, and AVN-211, Figure 1) in conjunction with donepezil in mild-to-moderate AD patients. Currently, Iladopirdine is being evaluated in phase III clinical trials.[6] The pro-cognitive effects of 5-HT$_6$R antagonists are typically attributed to their ability to promote cortico-limbic release of acetylcholine, glutamate and monoamines.[7–8]

Further, 5-HT$_6$R antagonists might be effective in the treatment of anxiety and depressive symptoms that often accompany AD. The results of *in vivo* tests have indicated that 5-HT$_6$R antagonists produce antidepressant-like and anxiolytic-like responses in animal models.[9]

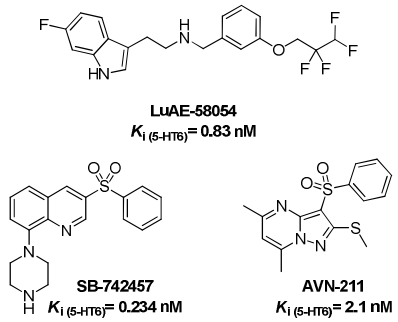


Figure 1. 5-HT$_6$R antagonists under clinical trials.

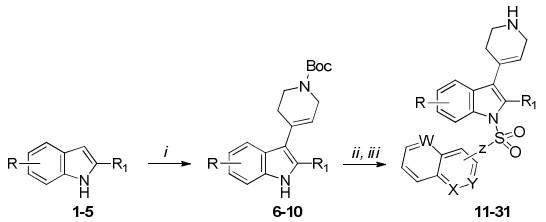
Almost exclusive localization of 5-HT$_6$R in the cerebral cortex, nucleus accumbens and hippocampus suggests that compounds, which selectively affect this receptor might have relatively few peripheral side effects.

A vast group of 5-HT$_6$R ligands is based on an indole scaffold.[10,11] Structure-activity relationship studies within this class revealed that incorporating the tryptamine aminoethyl group into the constrained basic side chain of the tetrahydropyridynyl moiety and the sulfonylation at the *N*1 position on the indole scaffold is a good strategy for developing selective 5-HT$_6$R antagonists. Many studies have investigated the effects of a kind of central aromatic core (indole, azaindole, indazole, benzoxazine, tetrahydroquinoline), localization and the nature of amino centers (tetrahydropyridine, piperazine, pyrrolidine).[12–14] However, the type of arylsulfonyl moiety has not been extensively explored considering azinyl (quinolinyl, isoquinolinyl) fragments.[15]

Herein we report on the synthesis of *N*1-azinylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles, *in vitro* biological evaluations, preliminary pharmacokinetic studies, and behavioral profiling in animal model of memory cognitive decline, i.e., novel

object recognition (NOR) test. Since biochemical data suggest that neurotransmitters deficits in AD contribute to aggressive behavior, sleep disturbance and depression, the compounds were also evaluated in the forced swim (FST) and Vogel tests to verify their potential antidepressant and anxiolytic properties.

Scheme 1.



R = H, 5-Cl, 5- MeO, 6-Cl; R_1 = H, Me; X = CH, N; Y = CH, N; W = CH, N; z = 3, 4, 5, 6, 7

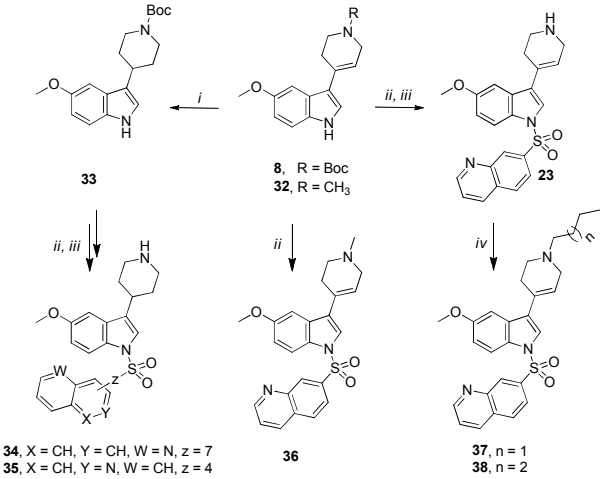
Reagents and conditions: *i*) KOH, MeOH, 60°C, 12 h, 65–70%; *ii*) $ArSO_2Cl$, BTPP, CH_2Cl_2, 0°C, 2 h, 70–75%; *iii*) 1N HCl in MeOH, r.t.

The final compounds **11**–**31** and **34**–**38** were synthesized as shown in Scheme 1 and 2.Condensation of differently substituted indole derivatives **1**–**5** with *N*-Boc-piperidinone in presence of potassium carbonate under refluxing methanol, yielded intermediates **6**–**10**. Next, strong, non-ionic, basic conditions involving phosphazene base P_1-*t*-Bu-tris(tetramethylene (BTPP) in CH_2Cl_2 were employed for the *N*1-indole sulfonylation with the respective quinoline-/isoquinolinesulfonyl chlorides.[16] Removal of the Boc-protecting group under stirring with a 1N HCl solution in methanol gave the final compounds **11**–**31**.

Alternatively, three-step procedure involving hydrogenation of intermediate **8** over palladium on carbon, followed by the treatment of intermediate **33** with azinylsulfonyl chloride, and removal of Boc group in acidic conditions, yielded piperidine analogs **34** and **35** (Scheme 2). On the other hand, condensation of 5-MeO-indole with *N*-methyl-piperidone resulted in intermediate **32**, which was subsequently sulfonylated to obtain compound **36**. Finally, the *N*-alkyl tetrahydropyridinyl analogs **37** and **38** were obtained by alkylation of compound **23** with the appropriate alkyl bromide under biphasic conditions.

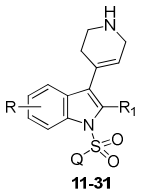
N-azinylsulfonyl derivatives **11**–**31** displayed high affinity for 5-HT_6R (Table 1). Most importantly, replacement of naphthyl moiety present in compounds **I** and **II**[13] with azinyl fragment, apart from improvement of physicochemical properties (logD, logP, pKa), has increased affinity for 5-HT_6R.Thus, the contribution of the azinesulfonyl moiety to the compound affinity for 5-HT_6R was subsequently investigated.

Scheme 2.



Reagents and conditions: *i*) H_2, Pd/C, MeOH, r.t., 2 h, 75%; *ii*) $ArSO_2Cl$, BTPP, CH_2Cl_2, 0°C, 2 h, 73%; *iii*) 1N HCl in MeOH, r.t.; *iv*) Alkyl bromide, K_2CO_3, KI, Acetone, 60°C, 48 h, 63–67%.

Table 1. The binding data of the synthesized compounds 11–31 for 5-HT_6R



Compd	Q	R	R_1	5-HT_6 K_i [nM][a]
I[b]	2-Napthtyl	H	H	27 ± 6
11	3-Quinolinyl	H	H	13 ± 3
12	6-Quinolinyl	H	H	20 ± 4
13	7-Quinolinyl	H	H	7 ± 2
14	3-Isoquinolinyl	H	H	12 ± 1
15	4-Isoquinolinyl	H	H	5 ± 1
16	3-Quinolinyl	5-Cl	H	11 ± 2
17	5-Quinolinyl	5-Cl	H	11 ± 3
18	7-Quinolinyl	5-Cl	H	9 ± 2
19	4-Isoquinolinyl	5-Cl	H	18 ± 3
II[b]	2-Napthtyl	5-MeO	H	19 ± 2
20	3-Quinolinyl	5-MeO	H	8 ± 1
21	5-Quinolinyl	5-MeO	H	4 ± 1
22	6-Quinolinyl	5-MeO	H	14 ± 3
23	7-Quinolinyl	5-MeO	H	2 ± 0.4
24	3-Isoquinolinyl	5-MeO	H	6 ± 1
25	4-Isoquinolinyl	5-MeO	H	3 ± 0.2
26	3-Quinolinyl	6-Cl	H	37 ± 5
27	6-Quinolinyl	6-Cl	H	112 ± 9
28	7-Quinolinyl	6-Cl	H	22 ± 2
29	3-Isoquinolinyl	6-Cl	H	102 ± 12
30	7-Quinolinyl	H	Me	18 ± 3
31	3-Isoquinolinyl	H	Me	20 ± 2

[a] Mean K_i values ± SEM based on three independent binding experiments, [b] data from (13)

The type of azinesulfonamide moiety (position of the sulfonamide group in the α- or β-position of the azine moiety, and the localization of the sulfonamide group in pyridine or benzene rings) affected the receptor affinity, but the quantitative influence of quinolinyl/isoquinolinyl moieties toward 5-HT_6R was difficult to establish. However, the 7-quinolinyl fragment was the most preferential among the quinoline set, and 4-isoquinolinyl was more preferable than its 3-counterpart.

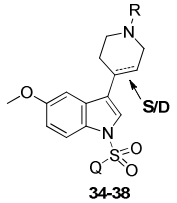
The effect of indole substitution on affinity for 5-HT_6Rs was observed using 3-quinolinyl, and 4-quinolinyl derivatives, which gave the following rank order: 5-MeO > 5-H > 5-chloro > 6-chloro. This is in contrast to data reported by Cole *et al.*[13] where chloro substituent in position-6 of indole core was well tolerated. Further, introduction of methyl substituent in position-2 of the indole, slightly decreased affinity for 5-HT_6 sites (**11** *vs* **30**, and **13** *vs* **31**).

Yet another modification involving reduction of double bond in 1,2,3,6-tetrahydropyridin-4-yl giving *N*1-azinylsulfonyl-3-piperidin-4-yl derivatives, decreased affinity for 5-HT_6Rs (**23** *vs* **34**, and **25** *vs* **35**; Table 1, Table 2), which is in line with data reported by others.[13]

Finally, as shown by the binding data outlined in Table 2, alkyl substituents at the tetrahydropyridine nitrogen atom were unfavorable. Introducing a small methyl substituent decreased

affinity for 5-HT$_6$R up to 11-fold, while compounds with unbranched alkyl substituents (*n*-propyl, *n*-butyl) displayed even 100-fold lower affinity. It thus seem, that alkyl substituents in this position are not able to accommodate the restriction of the binding site.

Table 2. The binding data of the synthesized compounds 34–38 for 5-HT$_6$R



34-38

Compd	Q	R	S/D	5-HT$_6$ K_i [nM][a]
34	7-Quinolinyl	H	S	30 ± 4
35	4-Isoquinolinyl	H	S	24 ± 4
36	7-Quinolinyl	Me	D	82 ± 10
37	7-Quinolinyl	*n*-propyl	D	247 ± 19
38	7-Quinolinyl	*n*-butyl	D	219 ± 24

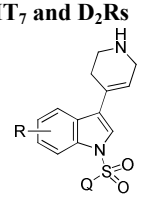
[a] Mean K_i values ± SEM based on three independent binding experiments

Certain selected 5-HT$_6$R ligands were subsequently examined in a panel of serotonin (5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_7$) and dopamine D$_2$ receptors demonstrating at least 70-fold selectivity (Table 3).[17]

In the next step, compounds **23** and **25** with the highest affinity for 5-HT$_6$R were investigated *in vitro* for their functional activity in cAMP assays, behaving as potent antagonists at h5-HT$_6$Rs (Table 4).[18] The same compounds were evaluated for their affinity for ''off-target'' receptor panel at CEREP and displayed weak affinity for adrenergic α_1 and α_{2C}, histamine H$_1$, muscarinic M$_1$ and M$_5$, serotonin 5-HT$_{2C}$ receptors, and the serotonin transporter (SerT). Finally, neither **23** nor **25** displayed agonist properties at 5-HT$_{2B}$ receptors (<13% @ 1 μM) and did not bind at hERG (@ 10 and 50 μM). These results suggested a low risk that the tested compounds would evoke undesirable cardiovascular or CNS side effects. Interestingly, compounds **23** and **25** displayed high to moderate affinity for dopamine D$_3$ receptors with K_i = 32 and 150 nM, respectively, but did not exhibit antagonist properties in an *in vitro* functional test.[19]

Assay Type		23	25
Cytochrome P450 inhibition, IC50 (μM)	1A2	100	100
	2C9	>100	>100
	2C19	>100	>100
	2D6	>100	>100
	3A4	20	26
Solubility mg/mL	pH 7.4	>5	>5
	pH 2.0	>5	>5
Microsomal stability CL_{int} [μl/min/mg]	Rat	18	10

Table 3. The binding data of the selected compounds for 5-HT$_6$, 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_7$ and D$_2$Rs



[a] Mean K_i values (SEM ± 27%) based on two independent binding experiments

Compd	K_i [nM]	K_b [nM][a]	%inh[a]						
	5-HT$_6$		α_1	α_{2C}	H$_1$	M$_1$	M$_5$	5-HT$_{2C}$	SerT
23	2 ± 0.4	4.4	41	18	9	11	NT	18	4
25	3 ± 0.2	5.6	40	21	15	0	3	15	6

Subsequently, the effects of the selected 5-HT$_6$R antagonists **23** and **25** were determined on cytochrome P450 (CYP) enzyme catalytic activity in human liver microsomes and metabolic stability in rat *in vitro* assays (Table 5). Compounds **23** and **25** had no effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and moderately inhibited CYP3A4 activity. Compounds **23** and **25** were slowly metabolized in rat liver microsomes. Additionally, compounds **23** and **25** were not mutagenic in an Ames test (Table 1-SI).

Table 4. The antagonist activity of selected compounds 23 and 25 for 5-HT$_6$R

[a] K_b values and percentage of inhibition were determined at Eurofins Cerep.

Next, compounds **23** and **25** were submitted to the preliminary pharmacokinetic profiling after a single 3 mg/kg *i.p.* dose in male Wistar rats. Experiments carried out 15, 30, and 90 min after drug administration, showed the highest concentrations at 30 min (21.9 and 18.6 ng/g of brain tissue for **23** and **25**, respectively). The data indicated moderate blood-brain barrier penetration with a brain to plasma concentration ratio within 0.1–0.6 in the investigated time intervals, being higher for compound **25**.

Many pieces of evidence suggest that 5-HT$_6$R antagonists modulate cognitive processes and their pro-cognitive properties may be beneficial for the treatment of Alzheimer's disease. Thus, compounds **23** and **25** were tested in a NOR test and dose-dependently (MED 1 mg/kg, *i.p.*) ameliorated PCP-induced memory deficits in rats.[20,21] Compound SB-742457 was used as a model selective 5-HT$_6$ receptor antagonist and reversed memory deficits and the effect reached statistical significance at doses ranging from 0.3–1 mg/kg (*i.p.*) (Figure 2)

Table 5. Interaction of selected compounds 23 and 25 with cytochrome P450 and their metabolic stability.

In the next step of behavioral evaluation, the potential antidepressant and anxiolytic activity of compounds **23** and **25** was evaluated in rats using a modified FST test[22,23] and Vogel conflict drinking test,[24] respectively.

Compd	Q	R	K_i [nM][a]				
			5-HT$_6$	5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_7$	D$_2$
12	6-Quinolinyl	H	20	1872	1412	6660	1410
18	7-Quinolinyl	5-Cl	9	2467	2589	7322	1168
21	5-Quinolinyl	5-MeO	4	2944	1552	2352	302
23	7-Quinolinyl	5-MeO	2	5036	1003	6248	240
25	4-Isoquinolinyl	5-MeO	3	5009	3355	7832	3319

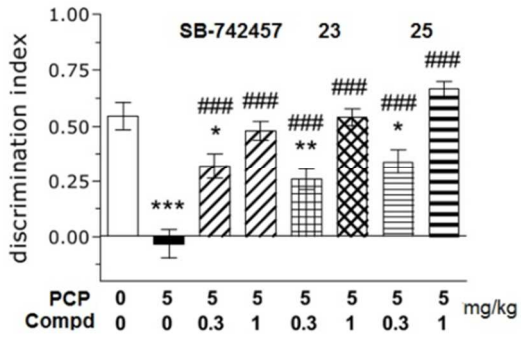


Figure 2. Effects of compounds **23**, **25** and SB-742457 in the novel-object recognition test in rats. Data are presented as the mean ± standard error of the mean of N = 7–12 animals per group. *p <0.05 *vs* vehicle, **p <0.01 *vs* vehicle,***p <0.001 *vs* vehicle, ###p <0.001 *vs* PCP.

For comparison, the selective 5-HT$_6$ receptor antagonist, SB-742457, was tested under the same conditions. Both **23** and **25** and SB-742457, significantly decreased the immobility time and increased the climbing time of rats in the forced swim test (Figure 3). The literature data indicated that 5-HT$_6$R antagonists enhance the extracellular levels of dopamine (DA) and noradrenaline (NA) without altering serotonin (5-HT) neurotransmission in microdialysis *in vivo* study in rats.[25] Moreover, the results of behavioral studies in rats demonstrate that the antidepressant-like effect of 5-HT$_6$R antagonists in the FST is not related to 5-HT signaling but rather to activation of DA and NA systems.

Given the above, the antidepressant-like effect of the tested compounds remains in agreement with the previously published data,[23] which showed that noradrenergic system-affecting drugs modify climbing behavior, without any significant changes in the swimming. Notably, the tested compounds, **23** and **25** displayed antidepressant-like activity in relatively low doses (0.3 mg/kg for **23** and 0.1 and 0.3 mg/kg for **25**) in the test, while SB-742457 was active in 10–30-fold higher dose (3 mg/kg). The antidepressant-like activity of both compounds and SB-742457 seems specific, because they did not affect the rats locomotor activity in the open field paradigm (data not shown). Further, neither **23** nor **25** showed anti-anxiety properties in the Vogel conflict drinking test. On the other hand, SB-742457, which was used as a reference, produced an anti-conflict effect at dose of 3 mg/kg (Table 3-SI).

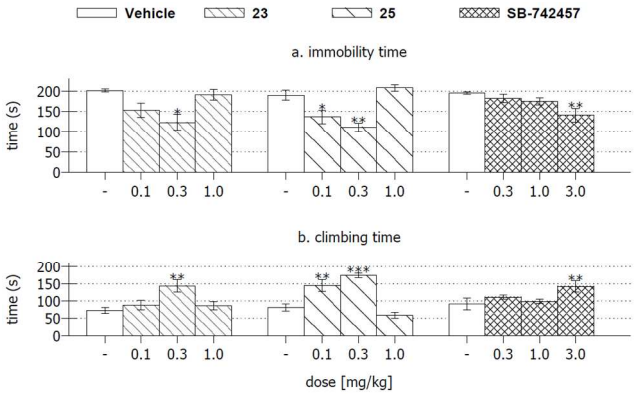


Figure 3. Effects of the active compounds 23, 25 and SB-742457 on the immobility time and climbing of rats in the forced swim test. Data are presented as the mean ± standard error of the mean of N = 7–8 animals per group. *p <0.05, **p <0.01, ***p <0.001 vs vehicle-treated group

In conclusion, SAR studies around *N*1-azinylsulfonyl-tetrahydropiridynyl indoles, led to the finding that replacing the naphthyl fragment with quinolinyl or isoquinolinyl moieties increased affinity for 5-HT$_6$ receptors. The most potent compounds **23** and **25** behaved as 5-HT$_6$R antagonists in the cAMP assay and showed good selectivity over a panel of other receptors tested. The lead compound **25** displayed good brain penetration and was active in a NOR test in similar doses to SB-742457 (1 mg/kg), while in FST was active in 10–30 folds lower dose. In contrast to SB-742457, which was active in the Vogel test (MED = 3 mg/kg), compound **25** displayed no anxiolytic activity. These data further support the potential utility of 5-HT$_6$ receptor antagonists for the treatment of cognitive dysfunction and accompanying affective disorders.

ASSOCIATED CONTENT

Supporting Information Available: characterization data for final compounds, and full experimental procedures. This material is available free of charge on the ACS Publications website at DOI:

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Notes: The authors declare no competing financial interest.

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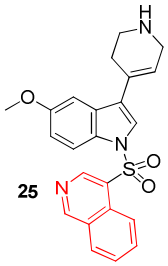

	25	**SB-742457**
	K_i (5-HT$_6$) = 3 nM	K_i (5-HT$_6$) = 0.23 nM
	K_b (5-HT$_6$) = 5.6 nM	K_b (5-HT$_6$) = 0.21 nM
	NOR (MED) = 0.3 mg/kg	NOR (MED) = 0.3 mg/kg
	FST (MED) = 0.1 mg/kg	FST (MED) = 3 mg/kg