

N1-Azinylsulfonyl-1H-indoles: 5-HT₆ Receptor Antagonists with Procognitive and Antidepressant-Like Properties

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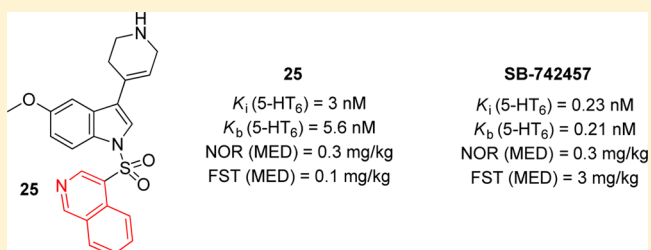
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S Supporting Information

ABSTRACT: A series of N1-azinylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives was designed to obtain highly potent 5-HT₆ receptor ligands. The study allowed for the identification of **25** (4-[[5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl]sulfonyl]isoquinoline), a potent and selective 5-HT₆ receptor antagonist. The selected compound, 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 it was active in 10–30-fold 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.

KEYWORDS: Isoquinoline/quinoline sulfonamides, 5-HT₆ receptor antagonist, Alzheimer's disease, cognitive decline, novel object recognition task, forced swim test, Vogel test



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 20 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-HT₆ receptor (5-HT₆R) antagonism.¹

The 5-HT₆R belongs to the G-protein coupled receptor (GPCR) superfamily, and it stimulates adenylyl cyclase via G_s as well as extracellular-regulated kinase (ERK) signaling via the Src-family tyrosine kinase Fyn. Furthermore, 5-HT₆R 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-HT₆R enhances cognitive performance in a broad range of tasks in rodents,^{4,5} and phase II clinical studies have demonstrated efficacy of 5-HT₆R antagonists (Iladopirdine = LuAE58054, SB742457, and AVN-211, Figure 1) in conjunction with donepezil in mild-to-moderate AD patients.

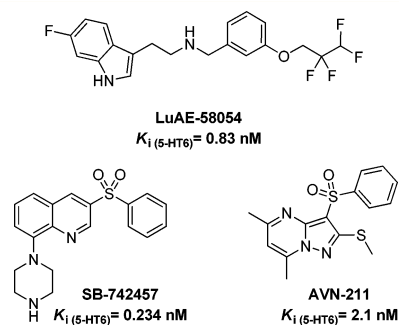


Figure 1. 5-HT₆R antagonists under clinical trials.

Currently, Iladopirdine is being evaluated in phase III clinical trials.⁶ The pro-cognitive effects of 5-HT₆R antagonists are

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typically attributed to their ability to promote cortico-limbic release of acetylcholine, glutamate, and monoamines.^{7,8}

Further, 5-HT₆R 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-HT₆R antagonists produce antidepressant-like and anxiolytic-like responses in animal models.⁹

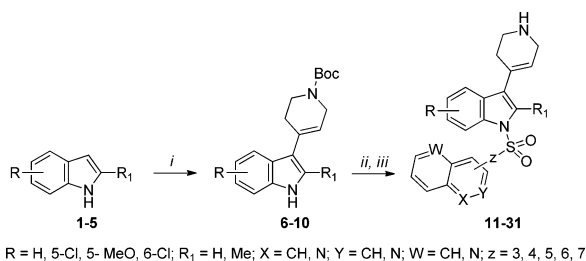
Almost exclusive localization of 5-HT₆R in the cerebral cortex, nucleus accumbens, and hippocampus suggests that compounds, which selectively affect this receptor, might have relatively few peripheral side effects.

A vast group of 5-HT₆R 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 tetrahydropyridinyl moiety and the sulfonylation at the N1 position on the indole scaffold is a good strategy for developing selective 5-HT₆R antagonists. Many studies have investigated the effects of a kind of central aromatic core (indole, azaindole, indazole, benzoxazine, and tetrahydroquinoline), localization, and the nature of amino centers (tetrahydropyridine, piperazine, and pyrrolidine).^{12–14} However, the type of arylsulfonyl moiety has not been extensively explored considering azinyl (quinolinyl and isoquinolinyl) fragments.¹⁵

Herein we report on the synthesis of N1-azinylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-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.

The final compounds 11–31 and 34–38 were synthesized as shown in Schemes 1 and 2. Condensation of differently

Scheme 1^a

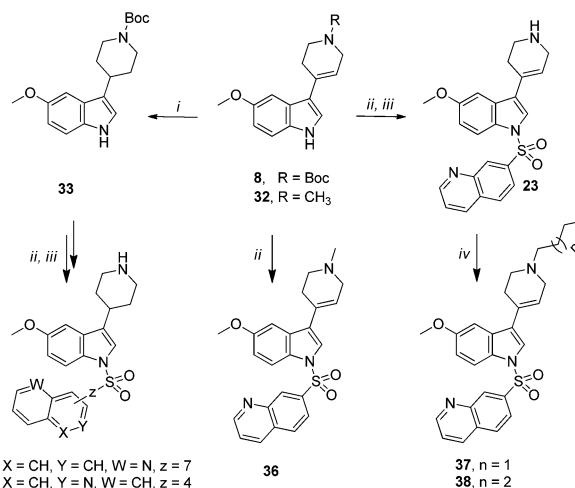


^aReagents and conditions: i) KOH, MeOH, 60 °C, 12 h, 65–70%; ii) ArSO₂Cl, BTTP, CH₂Cl₂, 0 °C, 2 h, 70–75%; iii) 1 N HCl in MeOH, r.t.

substituted indole derivatives 1–5 with *N*-Boc-piperidone in the presence of potassium carbonate under refluxing methanol yielded intermediates 6–10. Next, strong, nonionic, basic conditions involving phosphazene base P₁-*t*-Bu-tris-(tetramethylene) (BTTP) in CH₂Cl₂ were employed for the N1-indole sulfonylation with the respective quinoline-/isoquinolinesulfonyl chlorides.¹⁶ Removal of the Boc-protecting group under stirring with a 1 N 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

Scheme 2^a



^aReagents and conditions: i) H₂, Pd/C, MeOH, r.t., 2 h, 75%; ii) ArSO₂Cl, BTTP, CH₂Cl₂, 0 °C, 2 h, 73%; iii) 1 N HCl in MeOH, r.t.; iv) alkyl bromide, K₂CO₃, KI, acetone, 60 °C, 48 h, 63–67%.

removal of Boc group in acidic conditions yielded piperidine analogues 34 and 35 (Scheme 2). However, 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 analogues 37 and 38 were obtained by alkylation of compound 23 with the appropriate alkyl bromide under biphasic conditions.

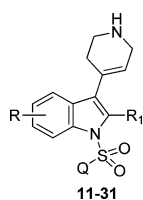
N-Azinylsulfonyl derivatives 11–31 displayed high affinity for 5-HT₆R (Table 1). Most importantly, replacement of naphthyl moiety present in compounds I and II¹⁵ with azinyl fragment, apart from improvement of physicochemical properties (logD, logP, and pK_a), has increased affinity for 5-HT₆R. Thus, the contribution of the azinesulfonyl moiety to the compound affinity for 5-HT₆R was subsequently investigated.

The type of azinesulfonyl 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-HT₆R 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-HT₆R 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-HT₆ sites (11 vs 30, and 13 vs 31).

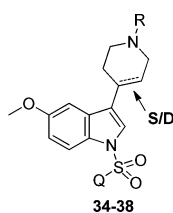
Yet another modification involving reduction of double bond in 1,2,3,6-tetrahydropyridin-4-yl giving N1-azinylsulfonyl-3-piperidin-4-yl derivatives, decreased affinity for 5-HT₆R (23 vs 34, and 25 vs 35; Table 1, Table 2), which is in line with data reported by others.¹³

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-HT₆R up to 11-fold, while compounds with unbranched alkyl substituents (*n*-propyl and *n*-butyl) displayed

Table 1. Binding Data of the Synthesized Compounds 11–31 for 5-HT₆R

compd	Q	R	R ₁	5-HT ₆ K _i [nM] ^a
I ^b	2-naphthyl	H	H	27 ± 6
11	3-quinolinylnyl	H	H	13 ± 3
12	6-quinolinylnyl	H	H	20 ± 4
13	7-quinolinylnyl	H	H	7 ± 2
14	3-isoquinolinylnyl	H	H	12 ± 1
15	4-isoquinolinylnyl	H	H	5 ± 1
16	3-quinolinylnyl	5-Cl	H	11 ± 2
17	5-quinolinylnyl	5-Cl	H	11 ± 3
18	7-quinolinylnyl	5-Cl	H	9 ± 2
19	4-isoquinolinylnyl	5-Cl	H	18 ± 3
II ^b	2-naphthyl	5-MeO	H	19 ± 2
20	3-quinolinylnyl	5-MeO	H	8 ± 1
21	5-quinolinylnyl	5-MeO	H	4 ± 1
22	6-quinolinylnyl	5-MeO	H	14 ± 3
23	7-quinolinylnyl	5-MeO	H	2 ± 0.4
24	3-isoquinolinylnyl	5-MeO	H	6 ± 1
25	4-isoquinolinylnyl	5-MeO	H	3 ± 0.2
26	3-quinolinylnyl	6-Cl	H	37 ± 5
27	6-quinolinylnyl	6-Cl	H	112 ± 9
28	7-quinolinylnyl	6-Cl	H	22 ± 2
29	3-isoquinolinylnyl	6-Cl	H	102 ± 12
30	7-quinolinylnyl	H	Me	18 ± 3
31	3-isoquinolinylnyl	H	Me	20 ± 2

^aMean K_i values ± SEM based on three independent binding experiments. ^bData from ref 13.

Table 2. Binding Data of the Synthesized Compounds 34–38 for 5-HT₆R

compd	Q	R	S/D	5-HT ₆ K _i [nM] ^a
34	7-quinolinylnyl	H	S	30 ± 4
35	4-isoquinolinylnyl	H	S	24 ± 4
36	7-quinolinylnyl	Me	D	82 ± 10
37	7-quinolinylnyl	<i>n</i> -propyl	D	247 ± 19
38	7-quinolinylnyl	<i>n</i> -butyl	D	219 ± 24

^aMean K_i values ± SEM based on three independent binding experiments.

even 100-fold lower affinity. It thus seems that alkyl substituents in this position are not able to accommodate the restriction of the binding site.

Certain selected 5-HT₆R ligands were subsequently examined in a panel of serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT₇) and dopamine D₂ receptors demonstrating at least 70-fold selectivity (Table 3).¹⁷

In the next step, compounds **23** and **25** with the highest affinity for 5-HT₆R were investigated *in vitro* for their functional activity in cAMP assays, behaving as potent antagonists at h5-HT₆Rs (Table 4).¹⁸ The same compounds were evaluated for their affinity for “off-target” receptor panel at CEREP and displayed weak affinity for adrenergic α₁ and α_{2C}, histamine H₁, muscarinic M₁ and M₅, 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 D₃ receptors with K_i = 32 and 150 nM, respectively, but did not exhibit antagonist properties in an *in vitro* functional test.¹⁹

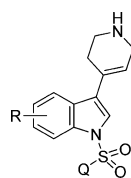
Subsequently, the effects of the selected 5-HT₆R antagonists **23** and **25** were determined on cytochrome P450 (CYP) enzyme catalytic activity in human liver microsomes and metabolic stability in rat *in vitro* assays (Table 5). Compounds **23** and **25** had no effect on CYP1A2, CYP2C9, CYP2C19, and 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).

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-HT₆R antagonists modulate cognitive processes and that 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-HT₆ 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).

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. For comparison, the selective 5-HT₆ 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-HT₆R 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-HT₆R 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

Table 3. Binding Data of the Selected Compounds for 5-HT₆, 5-HT_{1A}, 5-HT_{2A}, 5-HT₇, and D₂Rs

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

^aMean K_i values (SEM ± 27%) based on two independent binding experiments.

Table 4. Antagonist Activity of Selected Compounds 23 and 25 for 5-HT₆R

compd	5-HT ₆		%inh ^a						
	K _i [nM]	K _b [nM] ^a	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

^aK_b values and percentage of inhibition were determined at Eurofins Cerep.

Table 5. Interaction of Selected Compounds 23 and 25 with Cytochrome P450 and Their Metabolic Stability

assay type		23	25
cytochrome P450 inhibition, IC ₅₀ [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

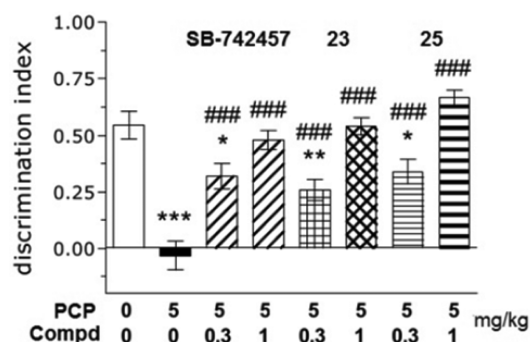


Figure 2. Effects of compounds 23 and 25 and SB-742457 in the novel-object recognition test in rats. Data are presented as the mean ± standard error of the mean of *N* = 7–12 animals per group. **p* < 0.05 vs vehicle, ***p* < 0.01 vs vehicle, ****p* < 0.001 vs vehicle, ###*p* < 0.001 vs PCP.

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 antianxiety properties in the Vogel conflict drinking test. However, SB-742457, which was used as a

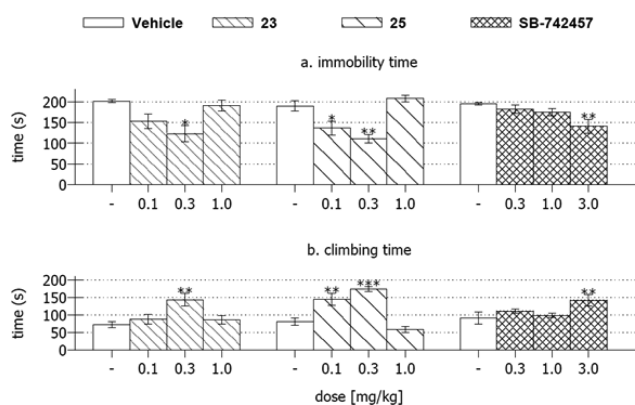


Figure 3. Effects of the active compounds 23 and 25 and SB-742457 on the immobility time and climbing of rats in the forced swim test. Data are presented as the mean ± standard error of the mean of *N* = 7–8 animals per group. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 vs vehicle-treated group.

reference, produced an anticonflict effect at dose of 3 mg/kg (Table 3-SI).

In conclusion, SAR studies around *N*1-azinylsulfonyl-tetrahydropyridinyl indoles, led to the finding that replacing the naphthyl fragment with quinolinyl or isoquinolinyl moieties increased affinity for 5-HT₆ receptors. The most potent compounds 23 and 25 behaved as 5-HT₆R 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 it was active in 10–30-fold 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-HT₆ receptor antagonists for the treatment of cognitive dysfunction and accompanying affective disorders.

■ ASSOCIATED CONTENT**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.6b00056.

Characterization data for final compounds and full experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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