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Novel 5-HT$_7$R antagonists, arylsulfonamide derivatives of (aryloxy)propyl piperidines: add-on effect to the antidepressant activity of SSRI and DRI, and pro-cognitive profile

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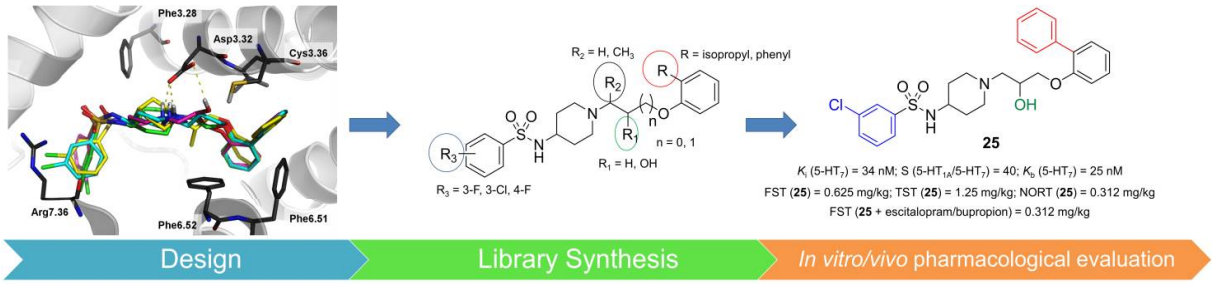
Targeting the 5-HT$_7$R has been proposed as an alternative strategy for the treatment of mood disorders including depression and may have beneficial effects in enhancing the therapeutic effects of clinically used antidepressant drugs.[1] We have recently reported on a series of arylsulfonamide derivatives of (aryloxy)alkyl alicyclic amines as potent and selective 5-HT$_7$R antagonists, with significant *in vivo* behavioral activities in rodent models of depression, anxiety and cognitive impairment.[2,3] In an attempt to extend the SAR studies toward this group of derivatives, we designed, employing machine learning-based algorithm and molecular docking studies, and synthesized a limited series of arylsulfonamide derivatives of (aryloxy)propyl piperidines. Chemical modifications included replacement of an ethyl spacer with a branched or linear propylene linker. Next, in an attempt to increase the stabilization of the ligand-receptor complex *via* the formation of a net of hydrogen bonds, a secondary hydroxyl group was introduced into the propylene spacer.



Among evaluated derivatives, the study allowed the identification of compound **25** (3-chloro-*N*-{1-[3-(1,1-biphenyl-2-yloxy)-2-hydroxypropyl]piperidin-4-yl}benzene sulfonamide, as potent 5-HT$_7$R antagonist (K_i = 34 nM, K_b=25 nM), displaying high selectivity over other serotonin and dopamine receptors, as well as over serotonin, noradrenaline and dopamine transporters. Compound **25** demonstrated significant antidepressant-like activity in the forced swim test (0.625–2.5 mg/kg, *i.p.*) and in the tail suspension test (1.25 mg/kg, *i.p.*), augmented the antidepressant effect of inactive doses of escitalopram (selective serotonin reuptake inhibitor) and bupropion (dopamine reuptake inhibitor) in the forced swim test in mice. Similarly to the reference 5-HT$_7$R antagonist SB-269970, exerted pro-cognitive properties in the novel object recognition task in cognitively unimpaired conditions in rats (0.3 mg/kg, *i.p.*). Such an extended pharmacological profile of the identified 5-HT$_7$R antagonist seems promising regarding the complexity of affective disorders and potentially improved outcomes, including mnemonic performance.

[1] Nikiforuk, A. *CNS Drugs* 29 (2015) 265-275
[2] Zajdel, P. *et al. Med. Chem. Comm.* 6 (2015) 1272-1277
[3] Canale, V. *et al. Eur. J. Med. Chem*. 108 (2016) 334-346

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