ARYLSULFONAMIDES OF (ARYLOXY)ETHYL DERIVATIVES OF ALICYCLIC AMINES AS POTENT 5-HT$_7$ RECEPTOR ANTAGONISTS AND THEIR PSYCHOTROPIC PROPERTIES

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Background

A growing body of preclinical and clinical data support the hypothesis that 5-HT$_7$ receptor (5-HT$_7$R) may be regarded as potential target for the treatment of anxiety, stress, depression as well as for the treatment of memory dysfunctions and cognitive disorders.[1,2]
As a part of our efforts in developing 5-HT$_7$R antagonists, we have recently identified compounds PZ-766 and PZ-1404 which displayed distinct antidepressant-like properties in forced swim test in mice and pro-cognitive activity in novel object recognition task in rats.[3,4]

Aims

Continuing our studies in identifying potent 5-HT$_7$R antagonists, we designed and synthesized a focused library of arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines. Compounds were biologically evaluated for their affinity for 5-HT$_7$Rs and their selectivity over 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$, D$_2$ and □$_1$Rs, in *in vitro* functional assay as well as in *in vivo* behavioral tests in animal model of depression and anxiety (FST, forced swim test and FPT, four-plate test, respectively).

Methods

Virtual Combinatorial Library-Virtual Screening (VCL-VS) protocol was applied for the selection of library members which were synthesized according to a solid-phase methodologies using a BAL-linker functionalized polystyrene resin. Radioligand binding assays were performed on HEK293 cells which stably expressed human 5-HT$_7$, 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$, D$_2$Rs while α_1-adrenoceptor binding assays were carried out on the rat cerebral cortex. The functional *in vitro* activity of compounds were evaluated using their ability to inhibit cAMP production induced by 5-CT (10 nM), in a HEK293 cells overexpressing the human 5-HT$_7$Rs. The *in vivo* behavioral experiments were performed on male Albino Swiss.

Results

All library members displayed high-to-moderate affinity for 5-HT$_7$Rs and selectivity over the 5-HT$_{1A}$Rs. Structure–activity relationship studies within evaluated compounds confirmed that encumbered substituents in position-2 of the aryloxy fragment were preferential for interaction with 5-HT$_7$Rs. In particular, compounds with isopropyl, cyclopentyl, and phenyl substituents displayed high affinity for 5-HT$_7$Rs (K_i < 50 nM), while the presence of a *tert*-butyl fragment decreased the affinity for 5-HT$_7$Rs, yet maintaining high selectivity over 5-HT$_{1A}$ sites. Moreover, the replacement of the piperidine moiety (present in PZ-766 and PZ-1404) with the four-membered azetidine or the sterically hindered azabicylico[3.2.1]-octane scaffolds resulted in compounds with high affinity for 5-HT$_7$Rs (K_i = 1–50 nM). On the other hand, the introduction of the diazabicyclo[2.2.1]-heptane core significantly decreased the affinity for 5-HT$_7$Rs. Additionally, it was confirmed that bioisosteric replacement of the tetrahedral configuration of sulfonamide fragment with a planar one presented in amide and urea derivatives was unfavorable for interaction with 5-HT$_7$Rs.