ARYLSULFONAMIDES OF (ARYLOXY)ETHYL DERIVATIVES OF ALICYCLIC AMINES AS POTENT 5-HT\textsubscript{7} RECEPTOR ANTAGONISTS AND THEIR PSYCHOTROPIC PROPERTIES

Vittorio CANALE,\textsuperscript{1} Rafael KURCZAB,\textsuperscript{2} Anna PARTYKA,\textsuperscript{3} Grzegorz SATALA,\textsuperscript{2} Magdalena JASTRZĘBSKA-WIĘSEK,\textsuperscript{1} Anna WESOŁOWSKA,\textsuperscript{1} Andrzej J BOJARSKI,\textsuperscript{2} Paweł ZAJDEL\textsuperscript{1}

\textsuperscript{1}Department of Medicinal Chemistry, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland
\textsuperscript{2}Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland

Background
A growing body of preclinical and clinical data support the hypothesis that 5-HT\textsubscript{7} receptor (5-HT\textsubscript{7}R) may be regarded as potential target for the treatment of anxiety, stress, depression as well as for treatment of memory dysfunctions and cognitive disorders.\textsuperscript{1,2}

As a part of our efforts in developing 5-HT\textsubscript{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.\textsuperscript{3,4}

Aims
Continuing our studies in identifying potent 5-HT\textsubscript{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\textsubscript{7}Rs and their selectivity over 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A}, 5-HT\textsubscript{6}, D\textsubscript{1} and D\textsubscript{2}Rs, in \textit{in vitro} functional assay as well as in \textit{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\textsubscript{7}, 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A}, 5-HT\textsubscript{6}, D\textsubscript{2}Rs while \textalpha{1}-adrenoceptor binding assays were carried out on the rat cerebral cortex. The functional \textit{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\textsubscript{7}Rs. The \textit{in vivo} behavioral experiments were performed on male Albino Swiss.

Results
All library members displayed high-to-moderate affinity for 5-HT\textsubscript{7}Rs and selectivity over the 5-HT\textsubscript{1A}Rs. Structure–activity relationship studies within evaluated compounds confirmed that encumbered substituents in position-2 of the arylxy fragment were preferential for interaction with 5-HT\textsubscript{7}Rs. In particular, compounds with isopropyl, cyclopropyl, and phenyl substituents displayed high affinity for 5-HT\textsubscript{7}Rs (\textit{K}\textsubscript{i} < 50 nM), while the presence of a tert-butyl fragment decreased the affinity for 5-HT\textsubscript{7}Rs, yet maintaining high selectivity over 5-HT\textsubscript{1A} sites. Moreover, the replacement of the piperidino moiety (present in PZ-766 and PZ-1404) with the four-membered azetidine or the sterically hindered azabicyclo[3.2.1]-octane scaffolds resulted in compounds with high affinity for 5-HT\textsubscript{7}Rs (\textit{K}\textsubscript{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\textsubscript{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\textsubscript{7}Rs.