N-alkylated arylsulfonamides of (aryloxy)ethyl piperidines: 5-HT\textsubscript{7} receptor selectivity vs multireceptor profile

Vittorio Canale\textsuperscript{1}, Rafał Kurczab\textsuperscript{2}, Grzegorz Satała\textsuperscript{2}, Anna Partyka\textsuperscript{3}, Magdalena Jastrzębska-Więsek\textsuperscript{3}, Karolina Stoczyńska\textsuperscript{4}, Tomasz Kos\textsuperscript{5}, Elżbieta Pękala\textsuperscript{4}, Piotr Popik\textsuperscript{5}, Andrzej J Bojarski\textsuperscript{2}, Anna Wesołowska\textsuperscript{3}, Paweł Zajdel\textsuperscript{1}

\textsuperscript{1}Department of Medicinal Chemistry, \textsuperscript{2}Department of Medicinal Chemistry, \textsuperscript{3}Department of Clinical Pharmacy, \textsuperscript{4}Department of Pharmaceutical Biochemistry Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland; \textsuperscript{5}Department of Medicinal Chemistry, \textsuperscript{5}Department of Drug Development, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland

According to recent preclinical data, antagonism at 5-HT\textsubscript{7} receptors (5-HT\textsubscript{7}Rs) may represent a clinically relevant target for the treatment of depression, negative symptoms of psychosis as well as for the treatment of memory dysfunction in cognitive disorders [1,2]. Continuing our efforts in development of potent 5-HT\textsubscript{7}R antagonists (i.e. PZ-1404) [3,4], we designed a series of N-alkylated arylsulfonamide derivatives of (aryloxy)ethyl piperidines. Structural modifications, which comprised the introduction of an N-methyl and N-cyclopropylmethyl moiety at the sulfonamide as well as the diversification of an ortho substituent at the (aryloxy)ethyl fragment, were aimed to establish the influence of these modifications on 5-HT\textsubscript{7} receptor affinity and selectivity over related monoaminergic receptors (i.e., 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A}, D\textsubscript{2}).

Synthesized compounds were identified as potent and selective 5-HT\textsubscript{7} receptor antagonists (i.e. 17 and 31) or multimodal 5-HT/dopamine ligands with significant 5-HT\textsubscript{7}/5-HT\textsubscript{2A}/D\textsubscript{2} receptor antagonist properties (i.e. 20 and 33). The most metabolically stable compounds 31 and 33 were further \textit{in vivo} evaluated in forced swim test (FST) in mice and novel object recognition (NOR) task in rats, demonstrating distinct antidepressant-like and pro-cognitive properties (MED = 1.25 mg/kg and 1 mg/kg, \textit{i.p.}, respectively). Further studies in the area of selective 5-HT\textsubscript{7} receptor antagonist or mixed 5-HT/dopamine ligands might be beneficial to confirm their potential application in the treatment of CNS disorders.


Acknowledgements
Supported by the National Science Center Grant No DEC-2012/05/B/NZ7/03076.