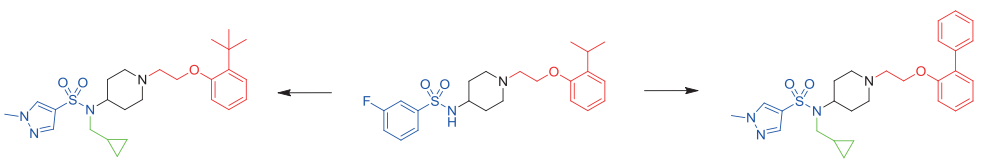
P27

N-alkylated arylsulfonamides of (aryloxy)ethyl piperidines: 5-HT$_7$ receptor selectivity *vs* multireceptor profile

Vittorio Canale[1], Rafał Kurczab[2], Grzegorz Satała[2], Anna Partyka[3], Magdalena Jastrzębska-Więsek[3], Karolina Słoczyńska[4], Tomasz Kos[5], Elżbieta Pękala[4], Piotr Popik[5], Andrzej J Bojarski[2], Anna Wesołowska[3], Paweł Zajdel[1]

[1]Department of Medicinal Chemistry,[3]Department of Clinical Pharmacy,[4]Department of Pharmaceutical Biochemistry Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland; [2]Department of Medicinal Chemistry,[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$_7$ receptors (5-HT$_7$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$_7$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$_7$ receptor affinity and selectivity over related monoaminergic receptors (i.e., 5-HT$_{1A}$, 5-HT$_{2A}$, D$_2$).



31
K_i (5-HT$_7$) = 49 nM K_i (5-HT$_{1A}$) = 17770nM
K_i (5-HT$_{2A}$) = 1479 nM K_i (D$_2$) = 230 nM
FST (MED) = 1.25 mg/kg
NOR (MED) = 1 mg/kg

PZ-1404
K_i (5-HT$_7$) = 9 nM K_i (5-HT$_{1A}$) = 356 nM
K_i (5-HT$_{2A}$) = 178 nM K_i (D$_2$) = 102 nM
FST (MED) = 2.5 mg/kg
NOR (MED) = 1 mg/kg

33
K_i (5-HT$_7$) = 10 nM K_i (5-HT$_{1A}$) = 159 nM
K_i (5-HT$_{2A}$) = 30 nM K_i (D$_2$) = 16 nM
FST (MED) = 1.25 mg/kg
NOR (MED) = 1 mg/kg

Synthetized compounds were identified as potent and selective 5-HT$_7$ receptor antagonists (i.e. **17** and **31**) or multimodal 5-HT/dopamine ligands with significant 5-HT$_7$/5-HT$_{2A}$/D$_2$ receptor antagonist properties (i.e. **20** and **33**). The most metabolically stable compounds **31** and **33** were further *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, *i.p*, respectively). Further studies in the area of selective 5-HT$_7$ receptor antagonist or mixed 5-HT/dopamine ligands might be beneficial to confirm their potential application in the treatment of CNS disorders.

[1] Matthys A. et al. *Mol. Neurobiol. 230* (2011) 555.

[2] Nikiforuk A. *CNS Drugs. 29* (2015) 265.

[3] Zajdel P. et al. *Eur. J. Med. Chem. 56* (2012) 348.

[4] Zajdel P. et al. *Med. Chem. Comm. 6* (2015) 1272.

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