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Towards metabolically stable arylsulfonamide derivatives of (aryloxy)ethyl piperidines as potent and selective 5-HT$_7$ receptor antagonists with antidepressant and anxiolytic properties

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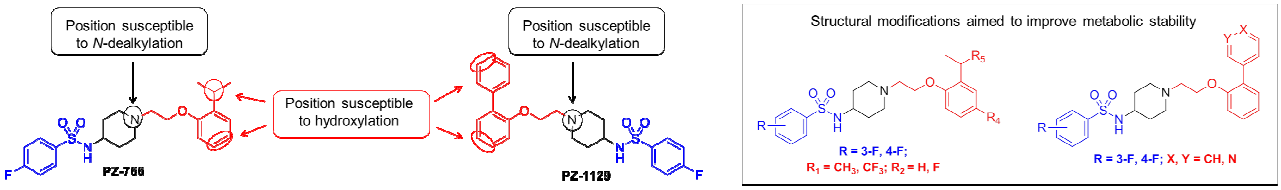
The type 7 Serotonin receptor (5-HT$_7$R) is the most recently identified member of serotonin family positively coupled with adenylyl cyclase through the stimulatory $G_{\alpha s}$ and $G_{\alpha 12}$ proteins.[1] Recent preclinical and clinical data support the hypothesis that 5-HT$_7$R antagonists may represent a valid alternative strategy for the treatment of affective disorders and neurodegenerative processes.[2]
We have recently developed a new class of potent and selective 5-HT$_7$R antagonists, namely arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines, identifying lead structures which displayed behavioral activities in animal model of depression, anxiety and cognitive impairment.[3,4]
In silico simulation and *in vitro* biotransformation studies on these derivatives revealed the potential sites susceptible to metabolic liability (i.e., enzymatic hydroxylation) which may lead to poor bioavailability. In an attempt to optimize the physicochemical properties with respect to the metabolic processes, we designed and synthesized metabolically stable arylsulfonamide derivatives of (aryloxy)ethyl piperidines as analogs of lead compounds PZ-766 and PZ-1129. To achieve this goal, structural modifications comprised the introduction of fluorine atom or trifluoromethyl moiety in the aryloxy fragment as well as the replacement of the *ortho* phenyl substituent with 3- or 4-pyridine moieties.



Synthetized compounds were evaluated in *in vitro* biotransformation studies displaying from moderate-to-low intrinsic clearance (Cl_{in} = 25–100 µg/mg/min) using rodent liver microsomes. Then, the most metabolically stable compounds were identified as highly potent 5-HT$_7$R antagonists (K_i < 50 nM, K_b = 1–40 nM) and selective over other monoaminergic 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$ and D$_2$Rs in *in vitro* cellular assays. Finally, tested compounds exerted antidepressant-like activity and anxiolytic properties (MED = 1.25 and 1 mg/kg, *i.p.*, respectively) in rodent models. Further studies would provide additional information regarding pharmacokinetic profile of these derivatives and their potential applications for the treatment of cognitive deficits.

[1] Kvachnina, E. et al. *J. Neurosci*. 25 (2005) 7821–7830; [2] Nikiforuk, A. *CNS Drugs* 29 (2015) 265–275; [3]. Zajdel et al. *Med. Chem. Comm.* 6 (2015) 1272–1277; [4] Canale, V. et al. *Eur. J. Med Chem.* 108 (2016), 334–346.

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