IN THE SEARCH OF METABOLICALLY STABLE ARYLSULFONAMIDES OF (ARYLOXY)ETHYL PIPERIDINES: AN INFLUENCE OF *ORTHO* SUBSTITUENTS ON 5-HT$_7$ RECEPTOR AFFINITY AND SELECTIVITY

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Recent advances in neuropharmacology have demonstrated that pharmacological blockade of 5-HT$_7$ receptor (5-HT$_7$R) may be represent a valid alternative strategy for the treatment of depression and might offer advantages over currently available drugs.[1] As part of our efforts in discovering of 5-HT$_7$R ligands, we have recently a new class of potent 5-HT$_7$R antagonists, namely arylsulfonamide derivatives of (aryloxy)ethyl alkyl amines, identifying several lead structures which displayed distinct antidepressant-like and pro-cognitive activity in rodent models.[2,3]

In silico simulations and preliminary *in vitro* biotransformation experiments revealed the structural features susceptible to metabolic oxidation. In an attempt to improve the metabolic stability of compounds PZ-766 and PZ-1129, an introduction of halogen and/or electron withdrawing substituents in an *ortho* position at the aryloxy fragment as well as a replacement of the phenyl substituent with different five- or six-membered heterocyclic moieties has been employed.

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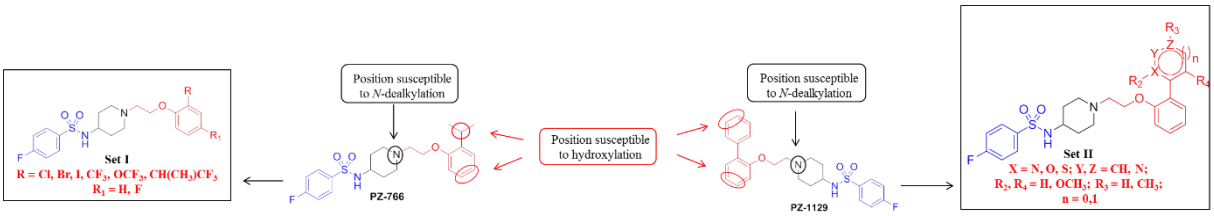

All of the synthesized compounds were tested *in vitro* binding assays to evaluate their affinity for 5-HT$_7$R and selectivity over 5-HT$_{1A}$R subtype. Having identified highly potent 5-HT$_7$R antagonists, the metabolic stability of the most selective compounds were determined in *in vitro* biotransformation studies using rodent liver microsomes. Further studies would provide additional information regarding pharmacokinetic profile of these derivatives and their potential applications for the treatment of cognitive deficits.

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