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Arylsulfonamide analogs of PZ-766 as potent 5-HT$_7$ receptor antagonists

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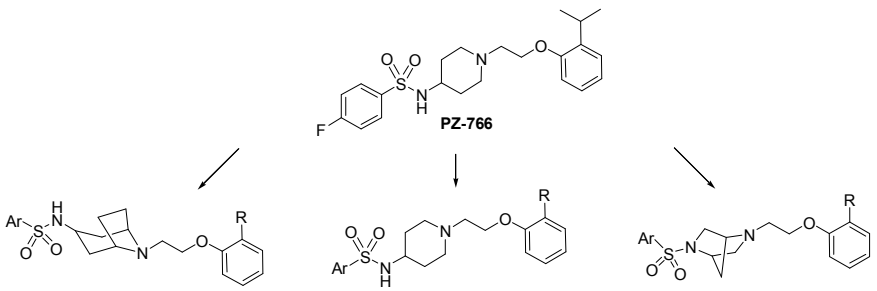
A growing body of preclinical and clinical data supports the hypothesis that 5-HT$_7$ receptor (5-HT$_7$R) antagonists may be regarded as an alternative for currently available drugs for the treatment of depression and/or anxiety as well as for the treatment of memory dysfunction in cognitive disorders (Alzheimer's disease, age-related decline) [1, 2]. Aiming at development of selective 5-HT$_7$R antagonists, our research group has recently designed and synthesized a library of arylsulfonamide derivatives of 3-amino-pyrrolidines, 4-amino-piperidines and 4-aminomethyl-piperidines. The study allowed us to identify compound PZ-766 as potent 5-HT$_7$R ligand ($K_i = 0.3$ nM) with strong antagonist properties ($K_b = 1$ nM) and a 1450-fold selectivity over 5-HT$_{1A}$ subtypes [3, 4].



In the present study we synthesized a focused library of new arylsulfonamide derivatives of alicyclic amines, as close analogs of PZ-766. Structural modifications comprised the replacement of the piperidine fragment with the steric hindered azabicyclo-[3.2.1]-octane and diazabicyclo-[2.2.1]-heptane as well as the introduction of phenyl substituents in *ortho* position at the aryloxy moiety. All library members displayed high affinity for 5-HT$_7$R and were classified as potent 5-HT$_7$R antagonists in *in vitro* functional assays. The most potent compounds were further investigated for *in vivo* studies towards potential antidepressant activity in force swim test (FST) in mice. Results showed that compounds PZ-1130 given in a dose of 5 and 10 mg/kg produced a distinct antidepressant-like effect similar to that exerted by PZ-766 (5 mg/kg). These preliminary results are promising to provide further detailed studies aimed at the developing of 5HT$_7$R agents for the treatment of depression.

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[4] Grychowska K, Marciniec K, Canale V. *et al.* 346 (2013) 180-188.