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ARYLSULFONAMIDE DERIVATIVES OF (ARYLOXY)ETHYL ALICYCLIC AMINES AS POTENT 5-HT$_7$ RECEPTOR ANTAGONISTS AND THEIR PSYCHOTROPIC PROPERTIES

V. Canale[1], R. Kurczab[2], A. Partyka[3], G. Satała[2], M. Jastrzębska-Więsek[3], A. Wesołowska [3], A.J. Bojarski[2], P. Zajdel[1]
vittoriobcanale@gmail.com

[1] Department of Medicinal Chemistry,[3]Department of Clinical Pharmacy,
Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland
[2] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences,
12 Smętna Street, 31-343 Kraków, Poland

The 5-HT$_7$ receptors (5-HT$_7$Rs) are typical metabotropic receptors (GPCRs) positively coupled with adenylyl cyclase through the stimulatory Gαs and Gα12 proteins [1]. A growing body of preclinical and clinical data support the hypothesis that 5-HT$_7$Rs may be regarded as potential target for the treatment of anxiety, stress, depression as well as for the treatment of memory dysfunctions and cognitive disorders [2,3]. Aiming to develop selective 5-HT$_7$R antagonists, our research group has recently identified compounds PZ-766 and PZ-1404 which displayed distinct antidepressant-like properties in forced swim test (FST) in mice and pro-cognitive activity in novel object recognition task (NOR) in rats [4,5]. In the present study we designed and synthesized a focused library of arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines. Virtual Combinatorial Library-Virtual Screening (VCL-VS) protocol was applied for the selection of library members which were synthesized according to a solid-phase methodology.

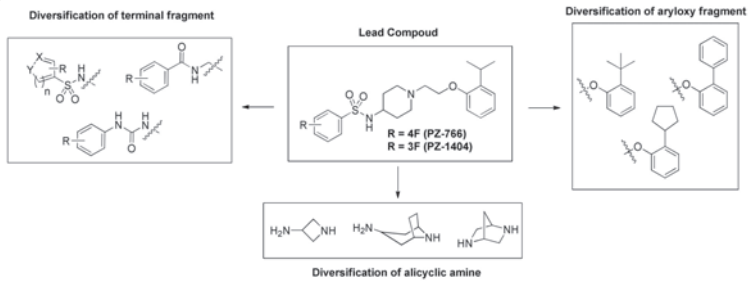

Fig. 1: Structural modifications based around the lead compounds PZ-766 and PZ-1404.

Structural modifications comprised the replacement of the piperidine fragment, present in PZ-766 and PZ-1404, with four-membered azetidine or sterically hindered azabicyclo[3.2.1]octane (tropane) and diazabicyclo[2.2.1]heptane, the introduction of encumbered substituents (*i.e.*, t-butyl, cyclopentyl, phenyl) in the *ortho* position of the aryloxy fragment as well as replacement of the sulfonamide group with amide and urea bonds. All library members displayed high affinity for 5-HT$_7$R and high-to-moderate selectivity over 5-HT$_1$A, 5-HT$_2$A, 5-HT$_6$, D$_2$ and α$_1$Rs in radioligand binding studies. Selected compounds, classified as potent 5-HT$_7$R antagonist, reduced the immobility time of mice in the force swim test (FST, animal model of depression) at doses 4–16 times lower (MED = 0.625 – 2.5 mg/kg) than the active dose of the SB-269970 (MED = 10 mg/kg), used as active comparator. Moreover, selected compounds showed anxiolytic-like activity in the four plate test (FPT) in mice at doses 0.625 – 1.25 mg/kg with the similar effect as diazepam used as a reference drug . The results provide valuable insight into the development of potential therapeutic agents for the treatment of CNS disorders.

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