LCAP Biomimetic – 5-HT7 receptor antagonists with antidepressant and pro-cognitive properties

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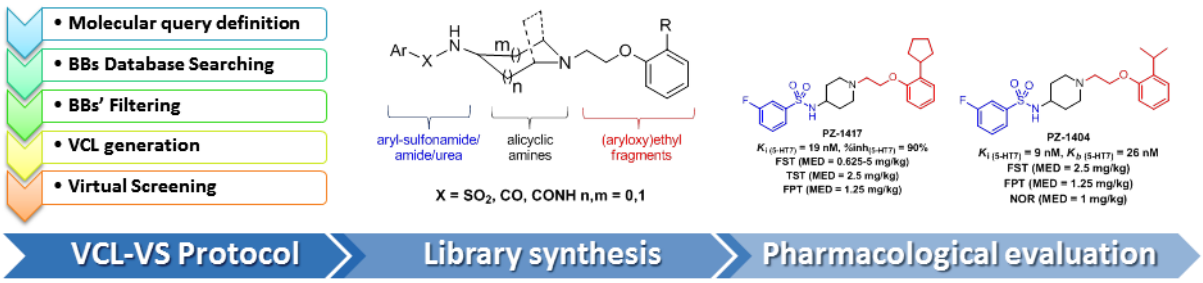
According to the World Health Organization (WHO), it has been estimated that by the year 2020, depression will be the second leading cause of severe disabilities, psychological and physical distress as well as of premature death. Despite progress in pharmacotherapy, efficacy of the clinically-used antidepressants is, however, quite limited. In only about 30–40% their use allow to achieve a remission, often with a risk of relapse, delayed onset of action, tolerance as well as with the sexual dysfunction, weight gain or cognitive impairment.



A growing body of preclinical and clinical data support the hypothesis that 5-HT$_7$R antagonists may be regarded as valid alternative of current drugs for the treatment of depression. Aiming to develop 5-HT$_7$R antagonists, we have recently confirmed the possibility to replace the long-chain arylpiperazine (LCAP) scaffolds, well-known 5-HT$_7$R ligands, with their biomimetic, namely arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines.[1,2] Virtual Combinatorial Library-Virtual Screening (VCL-VS) protocol integrated with solid-phase methodology has been applied for the selection and the synthesis of the library members. The study identified several 5-HT$_7$R antagonists which displayed distinct antidepressant-like properties in forced swim test (FST) and tail suspension test (TST) in mice and pro-cognitive activity in novel object recognition task (NOR) in rats.

Reference

1. Zajdel, P.; Kurczab, R.; Grychowska, K.; Satała, G.; Pawłowski, M.; Bojarski, A.J. *Eur J Med Chem*. **2012**, *56*, 348–360.
2. Zajdel, P.; Canale, V.; Partyka, A.; Marciniec, K.; Satała, G.; Kurczab, R.; Siwek, A.; Jastrzębska-Więsek, M.; Wesołowska, A.; Kos, T.; Popik, P.; Bojarski, A.J. *Med. Chem. Comm*. **2015**, (*accepted*).

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