P-79

PHENOXYMETHYL DERIVATIVES OF 1,3,5-TRIAZINE AS NOVEL CLASS OF 5-HT$_6$ RECEPTOR LIGANDS

Dorota Łażewska,[a],* Małgorzata Więcek,[a] Michał Stelmasiński,[a] Grzegorz Satała,[b] Rafał Kurczab,[b] Andrzej J. Bojarski,[b] Katarzyna Kieć-Kononowicz[a] and Jadwiga Handzlik[a]

[a] Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, 9 Medyczna Street, *30-688 Kraków, Poland*
[b] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland
* dlazewska@cm-uj.krakow

The serotonin 5-HT$_6$ receptor (5-HT$_6$R) is the most recently identified member of the 5-HT receptor superfamily. The 5-HT$_6$R, distributed in the central nervous system, is especially involved in the regulation of cognitive and mood processes as well as eating behaviors. Intensive medicinal chemistry efforts led to obtain many potent 5-HT$_6$R ligands and some of them have reached to clinical studies, even to phase III as e.g. LUAE58054 (idalopirdine; Alzheimer's disease).[1]
For proper understanding of the complicity of 5-HT$_6$R pharmacology more potent and selective ligands are necessary. Recently, we have developed a new class of 5-HT$_6$ receptor ligands – benzyl derivatives of 1,3,5-triazine.[2] The most active compounds displayed 5-HT$_6$R affinities in the nanomolar range (K_i = 20-30 nM).
As a continuation of that work, a series of phenoxymethyl derivatives of 1,3,5-triazine was synthesized and tested for 5-HT$_6$ receptor affinity. Among obtained structures a potent compound - 4-((2-isopropyl-5-methylphenoxy)methyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine (**MST4**) - was identified. **MST4**, while having high nanomolar binding affinity (K_i = 11 nM) for 5-HT$_6$R demonstrated also good selectivity towards other 5-HT receptors (5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_7$) and starts a new class of potent 5-HT$_6$R ligands.

Acknowledgments: *Supported by the Polish National Science Centre (NCN) grants: UMO-2015/17/B/NZ7/02973 and DEC-2011/02/A/NZ4/00031.*

[1] D. Karila, T. Freret, V. Bouet, M. Boulouard, P. Dallemagne, C. Rochais, *J. Med. Chem.*, **2015**, *58*, 7901.
[2] D. Łażewska, R. Kurczab, M. Więcek, K. Kamińska, G. Satała, A.J. Bojarski, K. Kieć-Kononowicz, J. Handzlik, *Eur. J. Med. Chem.* – manuscript submitted.