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Non-basic antagonists of the 5-HT6 receptor - a structure-activity relationship study

Justyna Kalinowska-Tłuścik,[a] *Jakub Staroń,*[b] *Andrzej J. Bojarski*[b]

[a]*Department of Crystal Chemistry and Crystal Physics, Faculty of Chemistry, Jagiellonian University, ul. Ingardena 3, 30-060 Kraków, Poland*
[b]*Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, ul. Smętna 12, 31-343 Kraków, Poland*

e-mail: kalinows@chemia.uj.edu.pl

Antagonists of the 5-HT_6R are a promising class of biologically active compounds due to their procognitive and/or antiamnesic effects [1]. Until recently it was believed that the molecule of the aminergic receptor's ligand must consist of the basic nitrogen atom. This ionization center is responsible for crucial interaction with the highly conserved aspartic acid residue in the third transmembrane helix of the aminergic receptor [2]. However, in the last few years new, non-basic ligands of the 5-HT_6R have been discovered. This suggests possibility of the distinct mode of action of the non-basic ligands [3], nevertheless the binding mechanism of this new class of ligands is still unclear.

The aim of our study was to apply the X-ray crystal structure analysis in order to search for the structural features and geometrical parameters which could explain more selective binding of chosen non-basic ligands to the 5-HT_6R. Therefore, the consistent series of 1-(phenylsulfonyl)-1H-indole derivatives were synthesized and crystallized. For all obtained crystals the X-ray diffraction experiment was performed, followed by crystal structure solution and model refinement. For all determined structures, molecular conformations as well as the intra- and intermolecular interactions were compared. Results were correlated with binding affinities assessed in radioligand binding experiments.

According to our findings, the mutual orientation of the two aromatic fragments of the 1-(phenylsulfonyl)-1H-indole derivatives seems to be essential for better ligand-receptor recognition. Both aromatic moieties are in "facing" position. The indole π-electron system is less delocalised by the arylsulfonyl substituent due to the weaker electron withdrawing effect of the sulfonyl linker. It has been proven by the increased pyramidalisation of the N1 atom, which additionally allows more bent conformation of the investigated 5-HT_6R ligands.

[1]Huerta-Rivas, A.; Pérez-García, G.; González-Espinosa, C.; Meneses, A. Neurobiol. Learn. Mem. 2010, 93 (1), 99.
[2] Kalani, M.Y.S.; Vaidehi, N.; Hall, S.E., Trabanino, R.J.; Freddolino, P.L.; Kalani, M.A.; Floriano, W.B.; Kam, V.W.T.; Goddard III, W.A. PNAS USA 2004, 101, 3815.
[3]Ivachtchenko, A. V.; Golovina, E. S.; Kadieva, M. G.; Kysil, V. M.; Mitkin, O. D.; Tkachenko, S. E.; Okun, I. M. J. Med. Chem. 2011, 54, 8161.

Acknowledgements:
The work was financially supported by the Polish National Science Centre grant OPUS 2014/13/B/NZ7/02210.