BIOISOSTERISM, THE USE IN DESIGNING 5-HT6 RECEPTOR LIGANDS

Jakub Staroń, Dawid Warszycki, Grzegorz Satała, Ryszard Bugno, Andrzej J. Bojarski

Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, 31-343 Cracow, Poland

The 5-HT6 receptor which is localized practically only in the brain [1] is a target for different psychotropic drugs. 5-HT6 receptors are supposed to be responsible mainly for motor control, memory and learning [2]. Because of that, substances acting on 5-HT6 receptors can be used to improve cognitive functions and memory. Up to date several thousands of ligands have been synthesized, they are very diverse in structure which is one of the reasons of uncertainty of binding mode.
Bioisosterism is one of the main strategy for designing new drugs. It is based on pursuing structural modification on the lead compound. These modifications may increase pharmacological activity, improve selectivity, reduce side effects or optimize pharmacokinetics [3,4]. Additionally, evaluating biological activity of bioisosteres helps to understand the structure of receptor-ligand complex.
With the use of specialized software (PipelinePilot - Accelrys, vBrood - OpenEye) thousands of molecular modifications were generated. Output compounds were selected based on synthetic accessibility and virtual screening cascade protocol which screens output compounds by similarity to 2D and 3D-pharmacophore, physicochemical properties, ADME/Tox properties and docking to receptor model [5].
During initial research a series of compounds was designed and synthesized. Methodology of computational studies, synthesis of selected compounds and pharmacological results are presented.

Acknowledgments

The study was partly supported by a grant PNRF-103-A1l-017 from Norway through the Norwegian Financial Mechanism.

References

1) Sleight, A. J.; Boess, F. G.; Bos, M.; Bourson, A. Annals of the New York Academy of Sciences 1998, 861, 91-96.
2) Hamon, M.; Doucet, E.; Lefèvre, K.; Miquel, M.-C.; Lanfumey, L.; Insausti, R.; Frechilla, D.; Del Rio, J.; Vergé, D. Neuropsychopharmacology 1999, 21, S68-S76.
3) Lima, L. M.; Barreiro, E. J. Current medicinal chemistry 2005, 12, 23-49.
4) Kier, L. B.; Hall, L. H. Chemistry & biodiversity 2004, 1, 138-51.
5) Kurczab, R.; Nowak, M.; Chilmonczyk, Z.; Sylte, I.; Bojarski, A . J. Bioorganic & medicinal chemistry letters 2010, 20, 2465-8.