P108

Lessons learned from analysis of bioisosteric substitution in ligands of a serotonin receptor family

Dawid Warszycki, Jakub Staroń, Rafał Kafel, Andrzej J. Bojarski

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

A bioisosteric replacement transforms an active compound into another one by exchanging a group of atoms with broadly similar (in physicochemical properties) groups. Implementations of this technique are aimed on increase of affinity, improvement of pharmacokinetic properties or exploration of new, unknown scaffolds.

For compounds with determined affinity for any serotonin receptor stored in the ChEMBL [1] database (version 16 May 2013) all possible bioisosteres were generated in Pipeline Pilot [2]. Analysis of this collection, consisting of more than 1 million structures, showed that in average 31% of known ligands of a particular target are mutual bioisosteres.

Data exploration revealed the most frequent and the most efficient replacements in modulating ligands activity for different subtypes of serotonin receptors. Statistical analysis shows the most appropriate fragments for increasing the ligands affinity for particular targets, providing a collection of tips for synthetic chemists how to modify existing ligands to obtain more potent compounds. Moreover, principles of modifying ligands of one target to create compounds acting on another one are also given.

[1] Gaulton, A., Bellis, L. J., Bento, A. et al. *Nucleic Acids Research*. 40 (2011), D1100-D1107.
[2] Pipeline Pilot, version 6.0, Accelrys, Inc., San Diego, CA, USA.

Acknowledgements

The study was partially supported by the Polish-Norwegian Research Programme operated by the National Centre for Research and Development under the Norwegian Financial Mechanism 2009-2014 in the frame of Project PLATFORMex (Pol-Nor/198887/73/2013).