Bioisosteric replacement in search for novel 5-HT$_6$R ligands

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

Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Krakow, Poland

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

For the whole in-house database containing *circa* 4300 compounds acting on 5-HT$_6$ receptor, all synthetically accessible bioisosteres were generated in Pipeline Pilot[1]. Pre-analysis of this collection containing about 140 thousands of structures shows that 31% of known ligands are bioisosteres of another active compounds. The complete bioisosteres library was used as an input for multistep virtual screening procedure[2] (mVS), consisting of, among others, pharmacophore search, docking protocols and structural interactions fingerprints (SIFts) profiling[3]. The best performing compounds or their close analogues, present in commercial databases (Enamine, VitasM, UORSY, ChemDiv, ChemBridge), were found, ordered and biologically evaluated. In vitro tests results led to discover a group of compounds with novel scaffold acting on 5-HT$_6$ receptor with K_i about 100 nM.

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