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# NEW 5-HT6 RECEPTOR LIGANDS – VIRTUAL SCREENING, SYNTHESIS AND IN VITRO STUDIES

Andrzej J. Bojarski
*bojarski@if-pan.krakow.pl*

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

5-hydroxytryptamine 6 receptor (5-HT6R) is one of the most important members of the serotonin receptor family. 5-HT6R is a G-protein coupled receptor and it increases adenylate cyclase activity upon agonist binding. Numerous studies have shown that the 5-HT6R plays a role in cognitive function in Alzheimer's disease, anxiety, obesity, and depression. Interestingly, 5-HT6R was found almost exclusively in the brain which suggests that its selective ligands shouldn't cause peripheral side effects.
The majority of 5-HT6R ligands synthesized so far, can be classified into three clusters: bisaryl sulfonamides, indoles and indole-like derivatives, and they can be described by a 4-elements pharmacophore: a hydrophobic/aromatic group (e.g. phenyl), a double hydrogen bond acceptor (e.g. sulphonyl group), a hydrophobic core (e.g. indole, naphthalene) and a basic nitrogen atom.
In an attempt to identify new ligands for the 5-HT6 receptor, a hierarchical multi-step strategy of virtual screening (VS) based on fingerprint similarity, physicochemical scalar descriptors, an ADME/Tox filter, three-dimensional (3D) pharmacophore searches and a docking protocol was constructed. Using full chemical space of the 5-HT6R ligands as a query several VS campaigns of commercial compound libraries were performed [1,2]. Starting from VS hits and in vitro screening of an in-house compound collection different groups of selective 5-HT6R ligands were further developed as potential cognition enhancers.

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