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BIOISOSTERIC APPROACH TO INVESTIGATION OF LIGAND BINFING MODE AT 5-HT6R

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The 5-HT_6 receptor,[1] localized practically only in the brain,[2] is a promising target for different new psychotropic drugs. These receptor is thought to be responsible mainly for motor control, memory and learning and its ligands can be used to improve cognition[3] and also as an antiobesity drugs.[4] So far, one compound – Idalopirdine, made it to the Phase 3 clinical trials as a therapeutic agent in augmentation therapy for Alzheimer disease. The large number (several thousand) of ligands, and their structural diversity makes consensus binding mode very difficult to be defined.

Among many techniques used in drug discovery isosterism is one of the most important. An isosteric replacement can change compound activity, bioavailability, pharmacokinetics and metabolism. A bioisosteric replacement appears when structural change of a compound doesn't substantially alter its biological properties. Additionally, bioisosterism can be used, through carefully planned isosteric replacements, to study interactions between ligand and receptor. This concept utilizes ligands as specific probes to scan certain regions of receptor binding pocket.

In presented study the use of specialized software (PipelinePilot, vBrood) allowed for generation of of high number of isosters. All of them were screened with virtual screening (VS) protocol and compounds to be synthesized were chosen individually from those that met all the requirements of VS protocol.

As a result, a group of pairs of substances, consisting of known ligand and its isosteres were synthesized. The combination of of structure-activity relationships with crystal structures and molecular modelling, allowed to expand the hypothesis of ligand–5-HT_6R interactions.

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