Identification of Novel 5-HT$_7$R Ligands via Multistep Virtual Screening of Commercially Available Compounds Databases

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Introduction:

The 5-HT$_7$ receptor (5-hydroxytryptamine7) is a seven-transmembrane–domain G protein-coupled receptor located in the central nervous system (thalamus, hypothalamus, hippocampus, cortex) and in peripheral tissues (pancreas, spleen, coronary artery, ileum). It plays an important role in thermoregulation, circadian rhythm, learning and memory, hippocampal signaling and sleep. It is suggested that the 5-HT$_7$ receptor is also involved in psychiatric and neurological disorders, such as schizophrenia, epilepsy and migraine. Current research strongly indicate that the development and investigation of 5-HT$_7$ antagonists determine new direction in the field of novel antidepressant agents.

The virtual screening (VS) is a set of many techniques that allows discovery of novel ligand from large libraries of diverse and commercially available compounds by using information about the structure of protein binding site and/or known ligands. The VS was effectively employed to identify new ligands for different GPCRs. Recently, we have shown the usefulness of our hierarchical approach to the virtual screening of commercially available database as a source of novel ligands for a 5-HT$_7$R.[1]

Using a similar apprach we now explored a chemical screening space offered by the ChemBridge [3] and ChemDiv [4] companies (800 000 and 700 000 organic compounds, respectively). Starting from the same set of 31 diversified 5-HT7 receptor antagonists and our rhodopsin-based homology models [2], we applied our Virtual Screening Cascade Protocol which consists of two-dimensional (2D) pharmacophore similarity searching, physicochemical scalar descriptors, ADME/Tox filter and three-dimensional (3D) pharmacophore searches and docking protocol. Additionally, in order to increase chemotype's diversity of virtual hits, the chemical and pharmacophore topology fingerprints were applied at the stage of similarity search.

Results and discussion:

The computational approach used in the present study combines miscellaneous well-known methodologies and different software within an integrated framework. A flowchart illustrating phases of the Virtual Screening Cascade Protocol implemented is shown in Figure 1. At the initial stage the Screening Databases were reduced to the library of drug-like subsets by application of Lipinsky's Rule of five and the Veber's rule.[5] The set of 31 well-know 5-HT$_7$R antagonists, divided into six structural classes as shown in Figure 2, were used as query structures.

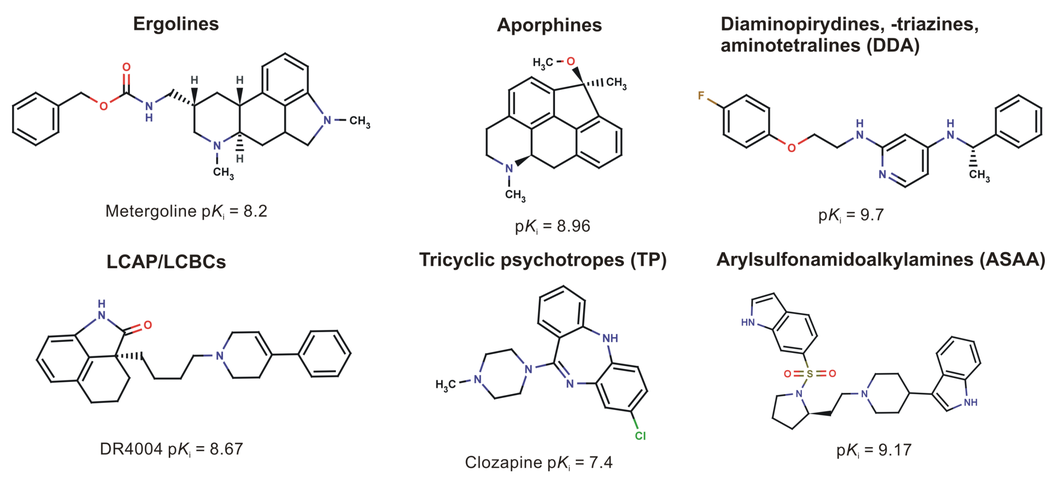

Figure 2. Representatives of 5-HT7R antagonists used in the study.

The 2D Fingerprint-based similarity searches were performed using two-dimensional chemical and pharmacophore topology fingerprints. All the fingerprints were generated from 2D molecular structures in the two complementary ways to provide more detailed coverage of chemical screening space (as shown in Figure 3), and were then handled numerically.

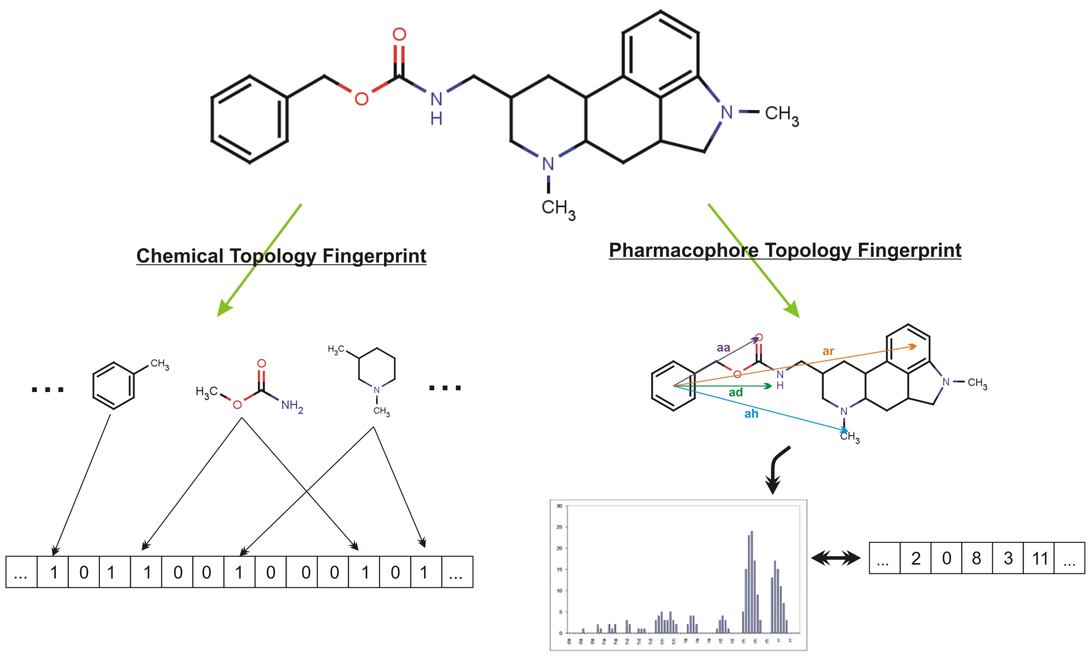

Figure 3. The schematic representation of how Chemical Topology and Pharmacophore Topology Fingerprints were generated and handled numerically.

Since the presence of a basic amine group is required to create the crucial ionic interaction with Asp3.32 of the receptor, only the strongest basic pKa, as a physicochemical property filter criterion, was applied.

Next, there ADME/Tox descriptors were used to further limit the number of compounds: Human Intestinal Absorption after oral administration (HIA Level < 2), the compound's solubility in water at 25 °C (2 < Aqueous Solubility Level < 5), and the blood brain barrier penetration (BBB Level < 3).

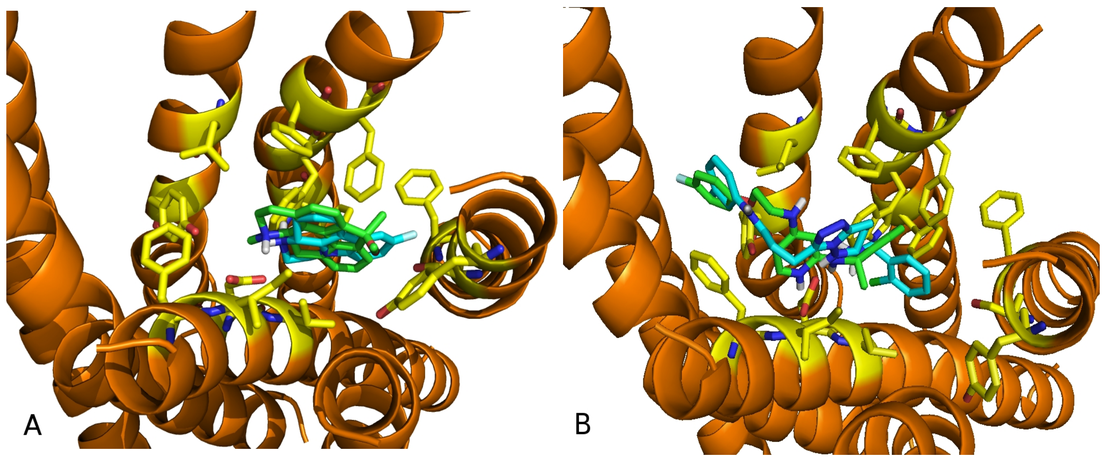

Figure 4. The binding mode of selected virtual hits (cyan sticks) in comparison to those of known antagonists (A) aporphine, (B) DDA (green sticks).

Figure 1. A scheme of the multi-step virtual screening protocol used for identification of 5-HT$_7$R antagonists. Numbers indicate the quantity of compounds at the output of each step.

The automated docking with interaction constraint (ionic interaction between the protonated amine group of the ligand and Asp3.32 side chain) was performed using Virtual Screening Workflow within Glide software, consecutively at three accuracy levels: HTVS, SP, and XP. The binding mode of only two selected virtual hits are shown in comparison to those of known antagonists (see Figure 4).

Finally, the sets of 74 and 31 compounds, selected on the basis of structural diversity and visual inspection of their binding modes, were acquired from ChemBridge and ChemDiv, respectively, in order to determine their affinity for 5-HT$_7$ receptor.

Acknowledgments

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