ML-III

Virtual screening and supporting tools in search for new CNS agents

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The primary objective of virtual screening (VS) is to identify novel bioactive compounds using knowledge about the structure of a given protein target (structure-based, SBVS) or its ligands (LBVS). These approaches can be used separately (e.g. massive docking to the crystal structure or the model of a receptor, in the first case; and pharmacophore filtering, in the latter) or can be integrated in a VS cascade protocol. The most common sources of input compounds are in-house compound collections, commercially available compound libraries or virtual combinatorial libraries.

In 2010 we have developed and tested, a hierarchical multi-step VS (mVS) protocol (based on 2D pharmacophore similarity, physicochemical scalar descriptors, an ADME/Tox filter, 3D pharmacophore searches and a docking protocol), to search for new serotonergic 5-HT_7 receptor ligands in Enamine screening database. Since then, each new mVS application resulted in both finding new lead structures for an investigated target and substantial improvements of the protocol itself.

Several examples of our successful mVS application (5-HT_6R, SERT, 5-HT_7R) along with supporting tools, developed first independently, and next incorporated into the protocol (Structural Interaction Fingerprints, four-dimensional docking, optimal ensemble of pharmacophore models), is presented.

Literature:

[1] R. Kurczab, M. Nowak, Z. Chilmonczyk, I. Sylte, A. J. Bojarski, *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 2465

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