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A New Crystal Structure Fragment-Based Pharmacophore Method for G Protein-Coupled Receptors

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A pharmacophore model is a generalized description of a compound defined as a spatial orientation of different features of a molecule(s)[1]. Such model can describe a vast number of chemical compounds with only a handful of common features, and thus is broadly used in virtual screening experiments as a filter of molecules fitting given model. The method, although powerful, is strongly dependent on the input data.

This research presents a new method for building pharmacophore models specific to G Protein-Coupled Receptors (GPCRs), being a combination of the ligand- and target-based approaches, utilizing extracted ligand moiety – amino acid pairs acquired from crystal structures. The library of fragments consists of over 250 members and covers 29 generalized residue positions (Ballesteros-Weinstein numbering scheme[2]) within the binding pockets of GPCRs. The fragment library allows relatively easy construction of pharmacophore models for novel targets, and the resulting hypotheses bear a significant screening potential – a case study on histamine H1 and H3 receptors yielded hit rate of 14%. In addition, the side chains of residues extracted from the crystal structures constitute a library of position specific rotamers, that can be applied for refinement of homology models. The fragment library, along with an online tool allowing aligning them with a submitted receptor structure is available on the GPCRDBTools website[3].

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[1]Güner, O. F. History and evolution of the pharmacophore concept in computer-aided drug design. Curr. Top. Med. Chem. 2002, 2, 1321–32.

[2]Ballesteros, J.A., Weinstein, H. Integrated methods for the construction of three-dimensional models and computational probing of structure-function relations in G protein-coupled receptors, Methods Neurosci., 1995, 25, 366-428.

[3]http://tools.gpcr.org/