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A NEW CRYSTAL STRUCTURE FRAGMENT-BASED PHARMACOPHORE METHOD FOR GPCRS

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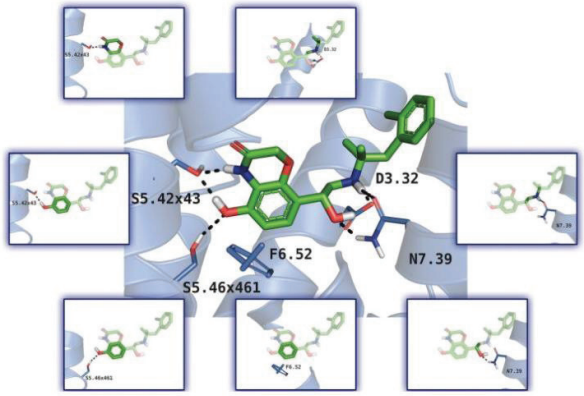

A pharmacophore model is a generalized description of a compound defined as a spatial orientation of different features of a molecule(s) [1]. Such a model can describe a vast number of chemical compounds with only a handful of common features, and thus is broadly used in virtual screening to identify novel ligands.

We present a new method for building pharmacophore models for GPCRs that combines the ligand- and target-based methods by extracting interacting ligand moiety – receptor residue pairs from crystal structures complexes [2]. Our library covers 250 such fragments and 29 residue positions (Ballesteros-Weinstein numbering [3]) within the binding pockets of class A GPCRs. The library fragments are recombined and inferred to construct pharmacophore models for novel targets, for which no (homologous) crystal structures or ligands are known. The method has a significant screening potential – supported by a case study on histamine H1 and H3 receptors yielded a hit rate of 14% and best potency of 660 nanomolar. 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 current fragment library makes it possible to target ~47% of the class A GPCRs with at least four-element pharmacophores. The fragment library, along with an online tool aligning them with a receptor structure is available on the GPCRDB tools website (tools.gpcr.org).

References:

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