Molecular modeling of the ligand/receptor complex for drug discovery

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The application of several technologies is required at each stage of the drug discovery process (Fig.1).   Structure-based drug design (SBDD) is an integral technology that employs the 3D structural information of biological macromolecules such as receptors and enzymes for the discovery and optimization of lead compounds.   One of the principal components of SBDD is referred to as computational docking. The technique attempts to predict the bound model of a set of compounds from a ligand library onto the binding site of a target receptor.   The difficulty with ligand-receptor docking is, in part, due to (1) the translational and rotational freedom of the ligand onto the protein structure with its conformational flexibility, (2) the lack of a suitable score function for estimating the binding energy, and, (3) the dependence on the structural resolution of target proteins.   To deal with these problems, we developed a molecular modeling technique for the prediction of ligand-receptor binding using comparative ligand-binding analysis (**CoLBA**) that not only considers interaction energy, but also similarity of interaction profiles among ligands.   Here, the interaction profile is comprised of two physicochemical factors, hydrogen bonding and hydrophobic contact between a ligand and the binding interface of a receptor, where the similarity of the interaction profiles is inferred from the Tanimoto coefficient.   Normalized interaction energies and profile similarity scores in all-against-all comparisons of the docking poses between two (or more) different activate ligands are mapped on a dispersion diagram to give reliable docking-pose pairs that can be screened and measured using their statistical Z-scores.   The advantage of CoLBA is that it can facilitate intuitive and flexible screening based on docking results when protein structures with low resolution (or theoretical models) are targeted.

We applied CoLBA to ligand binding prediction in several G protein-coupled receptors (GPCRs).   GPCRs play an important role in living organisms and are of major interest to the pharmaceutical industry.   However, structural data of ligand binding forms for GPCRs from experiments to elucidate structural templates for docking simulations are lacking due to the difficulties associated with crystallization and crystallography.   Therefore, structural prediction of GPCRs in the ligand-bound state using a computational methods has been introduced, but the prediction of ligand conformation onto target GPCRs is still constructed manually by human experts.   We have already succeed in fully automating the prediction of ligand bind models for human histamine H1 (Fig.2) and dopamine 2 receptors using CoLBA.   The predicted ligand binding models were evaluated by site-directed mutagenesis experiments in collaborative research and the enrichment rate of activated ligands was compared with the random compounds in virtual screening simulations.   We propose that CoLBA can be applied to large scale modeling of ligand-receptor complexes for GPCRs.
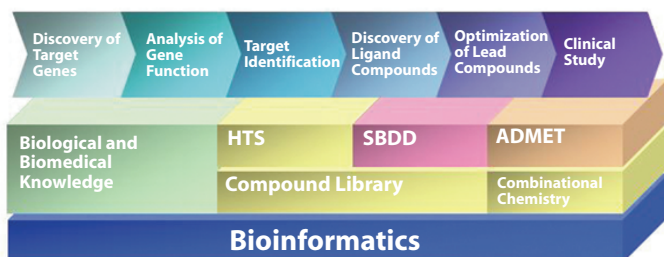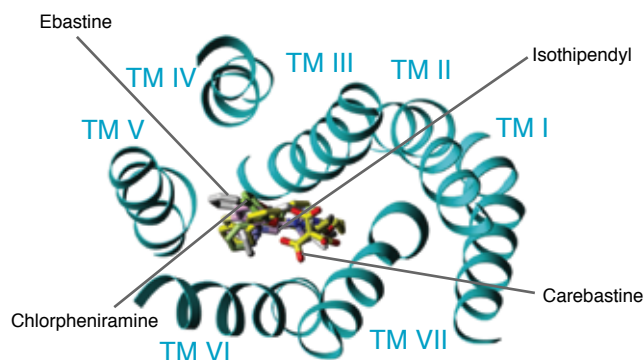

Fig.1

Drug discovery process and bioinformatics

Fig.2

Structure alignment of four antagonists (chlorpheniramine, carebastine, ebastine and isothipendyl) for human histamine H1 receptor by comparative ligand binding analysis