rank the binding affinities of a set of ligands for a given protein. Here we develop a novel, computationally efficient method, called Watermap, to assess the contribution of the solvent to the binding free energy of a small molecule and its associated receptor that captures the effects of the ligand displacing the solvent from the protein active site with atomic detail. We will present successful applications of this method to a number of different protein ligand systems such as GPCR, FXa, PDZ domain etc in understanding the ligand binding SAR. Additionally we will also show that detailed analysis of thermodynamics and locations of binding site waters in highly conserved kinase families can yield insight into previously inexplicable selectivity and structure-activity relationship.

P-67 : Insecticide and fungicide likeness: use of two-class Bayesian categorization models for the selection of molecules as screening inputs.

D. A. Demeter, C. Klittich
Discovery Research, Dow AgroSciences, Indianapolis, IN 46268, USA

Pharmaceutical and agricultural chemical companies are constantly in search of new chemicals worthy of testing in biological screening assays. Currently, there are over 11 million unique 3rd party vendor compounds[1] to choose from. Budget constraints and the logistics of handling millions of compounds means that for many companies, only a tiny fraction of the available compounds can be purchased annually, and methods to enrich the potential of compounds to generate hits are critical. At Dow AgroSciences, we have developed two-class Bayesian categorization models based on our own 2nd tier fungicide and insecticide assay results. Over 70,000 compounds (tested identically) were used to derive the individual statistical models. These have been applied as filters along with ag-like criteria in the purchase of compounds from commercial vendors. Hit rates for in vivo activity has been improved by 2-4X for insecticides and 6-15X for fungicides over previous methods.

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P-69 : The multi-conformations-receptor-based pharmacophore model generation schema and its potential applications in virtual screening

R. Kurczab, A. J. Bojarski
Department of Medicinal Chemistry, Institute of Pharmacology PAS, Krakow, Poland

The pharmacophore modelling technique is well-know and one of the major tools used in drug discovery for a long time. Up to date, various different approaches to pharmacophore model generation and its application in virtual screening, *de novo* design, lead optimization and multitarget drug design have been reported [1]. Depending on existing information about given biological target, the pharmacophore modelling approaches could be divided into two main types: ligand-based and structure-based pharmacophore modelling. In recent years, it also appeared a hybrid approaches [1,2] mixing those information in according to get pharmacophore model recognizing broader range of ligands and try to describing the dynamic of ligand-receptor complex.

We present here a methodology of generation of non static pharmacophore model based on docking of a collection of diverse know 5-HT7 antagonists to the set of different conformations of 5-HT7 receptor. For the different receptor geometries with the best enrichment factors, we obtained the static pharmacophore models using to build general dynamic one. The obtained averaged pharmacophore model was then validated by an external set build with known actives/decoys ligands [3] in order to assess it performance in virtual screening.

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P-71 : ChemTattoo3D: an open source drug design and analysis tool

N. MacCuish, J. MacCuish, M. Chapman
Mesa Analytics & Computing, Inc., Santa Fe, NM, USA

ChemTattoo3D is an analysis tool, which analyzes structures with similar shape overlays to find chemical features relevant to drug design. An interactive tool allows the user to visualize compounds which share both shape and pharmacophore features, defined by SMARTS patterns, within a certain distance in 3d space from a defined or perceived target, that the algorithm determines based on a frequency of occurrence modal. This program has been released under the GNU General Public License. This presentation will describe the development of ChemTattoo3D from its 2D predecessors, Stigmata and ChemaTattoo2D. It will also demonstrate applications in the area of lead hopping, shape cluster analysis, and hypothesis generation for structure based drug design.

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P-73 : Targeting of the tenase complex by rational design of factor viii-membrane interaction inhibitors

M. Kulharia [1], O. Sperandio [2], J. Voorberg [2], S. Wielders [1], B. O. Villoutreix [2], G. A.F. Nicolaes [1]
[1] *Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands*
[2] *University of Paris V, Paris, France*
[3] *Department of Blood coagulation, CLB, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands*

Coagulation Factor VIII (FVIII) is an essential cofactor molecule of the tenase complex. FVIII binds to the serine protease factor IXa and its substrate factor X, on a membrane surface in the presence of calcium. Formation of the tenase complex can be prevented by preventing the VIIIa-membrane association. The membrane interaction interface of the C2 domain in FVIII consists of solvent exposed, hydrophobic residues resident on two β-turns and an ω-loop. At the base of these hydrophobic protrusions a small pocket is encircled by a group of positively charged residues. For identification of possible inhibitors for the membrane binding activity of FVIII via its C2 domain we adopted a bipronged strategy. One approach involved the use of Omega software to create a conformer database for commercially available, drug-like molecules followed by their rigid docking using FRED. The top scoring molecules were clustered on the basis of various scores to short-list a diversified representative set of interacting molecules which were screened by flexible ligand docking using Surflex to further narrow down the list. In the second approach, structure based pharmacophores were created from a set of known inhibitors. Using these pharmacophores the database of small drug-like molecules was filtered and docking analysis was carried out for the selected molecules. In total 1000 potential lead compounds were purchased from a commercial vendor were tested in a direct interaction assay using the Biacore T100 biosensor instrument, wherein molecules were screened