C-abl is a kinase that has important roles in the normal process of the cell cycle. It has a typical kinase structure [1] and a unique ability to auto-regulate itself by inserting a myristolated group at its N-terminus to a specific hydrophobic cleft near its C-terminus (the *myristoyl pocket*) thus resulting in structural changes that block the kinase activity [2].

The loss of self-regulation is a result of the genetic translocation known as the "Philadelphia chromosome" which is the direct cause of Chronic Mylogenic Leukemia (CML), a type of blood cancer, due to a fusion protein, Bcr-Abl that possesses C-abl kinase activity but lacks the myristolated N-terminus.

Clinically used inhibitors of Bcr-Abl that are aimed at the ATP - binding site. Unfortunately, in a later phase of the treatment, most CML patients develop resistance to the available drugs, as a result of point mutations in and around that site.

Two allosteric inhibitors of Bcr-Abl were developed recently - GNF2 and GNF5 [3], and were later expanded into a series of chemically related compounds [4].

Recent studies have shown to produce a major reduction in cell proliferation rate (including cell lines that express the resistant form of Bcr-Abl) due to a combination of treatment with both an ATP binding site inhibitor and an allosteric inhibitor [5].

In order to develop allosteric inhibitors to Bcr-Abl that significantly differ structurally from the GNF variants, we incorporated several approaches to design pharmacophore models based on information from different ligand- interactions with the protein [6]. We use a novel approach, in which the pharmacophore models are based on a search by our Iterative Stochastic Elimination algorithm [7]. Applying this kind of models to large databases leads to the discovery of novel candidate allosteric inhibitors of Bcr-Abl.

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P-76 : Comparison of various strategies in pharmacophore models generation – application to 5-HT1A receptor ligands

D. Warszycki [1], K. Kristiansen [2], R. Kurczab [1], I. Sylte [2], A. J. Bojarski [1]

[1] *Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Kraków, Poland*

[2] *Medical Pharmacology and Toxicology, Department of Medical Biology, Faculty of Health Sciences, University of Tromsø, N-9037 Tromsø, Norway*

In ChEMBL database [1] there are over 6 thousands 5-HT_{1A} receptor ligands (both, active compounds and decoys) extracted from about 520 papers. Among them 3616 are relatively strong binders, with Ki (or equivalent) below 100 nM. Those ligands were clustered by three different approaches: using 3D pharmacophore or MOLPRINT 2D fingerprints (as implemented in Canvas software [2]) or based on a classical method grouping compounds by a common core (aminotetralines, arylpiperazines, ergolines, etc.). For representative compounds selected from each cluster separate pharmacophore hypotheses were

developed and tested using Phase software [3]. Next, they were reduced by grouping similar models and the less effective ones were discarded. The remaining hypotheses and their linear combinations were tested on external test set consisting of 200 active compounds (unused in pharmacophore development), 200 decoys (extracted from ChEMBL database) and 200 assumed inactives (already used drugs with confirmed inactivity against 5-HT_{1A} receptor). The described study discusses efficiency of single hypotheses in comparison to their linear combinations and relation between quality of pharmacophore models and methodology of generating clusters for their development. Created pharmacophore models will be used in further studies in multistep virtual screening for searching new compounds acting on 5-HT_{1A} receptor.

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P-78 : Fighting molecular obesity with sub-pharmacophore screening

M. von Korff [1], J. Freyss [1], T. Sander [1], C. Boss [2], C-L. Ciana [2]
[1] *Department of Research Informatics*
[2] *Drug Discovery Chemistry*
Actelion Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

Pharmacophore based virtual screening is a commonly used methodology to investigate scaffold hopping. Often molecules developed in lead optimization programs are too large to be good seeds. These molecules are complex, exhibiting multiple pharmacophore points. But the probability of detecting biosimilars in commercially available compound collections decreases as the number of pharmacophore points grows. In this contribution, we demonstrate how automatically generated sub-pharmacophore models can be used to increase the number of virtual screening hits worth testing in biological assays. A 3D pharmacophore descriptor developed in-house was used to generate the sub-pharmacophore models [2]. The DUD dataset was used to compare the pharmacophores with docking and chemical fingerprints. The DUD is the first published dataset providing active molecules, decoys and references for crystal structures of ligand-target complexes [1]. It contains 2,950 active compounds against a total of 40 target proteins. Furthermore, the dataset contains 36 structurally dissimilar decoy compounds with similar physicochemical properties for every ligand.

The ligands were extracted from the target proteins to extend the applicability of the dataset to include ligand based virtual screening. Of the 40 target proteins, 37 contained ligands that were used as query molecules for virtual screening evaluation. With this dataset, a comparison between the pharmacophores, three different chemical fingerprints and docking was done. In terms of enrichment rates, the chemical fingerprint descriptors performed better than the pharmacophores and the docking tool. After removing molecules chemically similar to the query molecules, the pharmacophores outperformed the chemical descriptors.

Encouraged by these results, the sub-pharmacophores were applied to some in-house drug discovery projects. In one project, only one highly active but large (800 Daltons) molecule was available as seed. Neither the full pharmacophore model nor the chemical fingerprints were able to detect any similars in a database of seven million commercially available molecules. However, a sub-pharmacophore search resulted in the detection of hundreds of interesting molecules. These molecules were purchased and biologically tested. Biological assay results for this and other virtual screening experiments will be reported here. Resulting was new series of molecules with much higher ligand efficiency than the seed molecule.

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