Viper Ligand Design *…applying innovation*

Viper is DesertSci's powerful new ligand design software suite based on Scorpion technology.

Viper is a completely new approach for designing binding tight ligands. It identifies areas for improving protein-ligand interaction networks and cooperativity using pharmacophore searching and fragment scanning.

With Viper you can identify new ligand substituents that substantially improve binding affinities without having to add large groups.

Inclusions:

The Viper software suite includes Scorpion, our binding affinity prediction tool based on a network approach, and ViewContacts, a powerful tool for finding, classifying, and visualising SMARTs based protein-ligand non-covalent interactions

You can run Viper from either the command line or using our intuitive web interface, ViperWeb.

Viper can be integrated into DesertSci's Protein Structure Database and Visualisation System, Proasis3, providing you with a powerful and intuitive suite of tools for your research needs.

Viper Features

- highlight of pharmacophores for strong protein-ligand interaction networks and cooperativity
- grid sampling of a binding site based on combinations of ViewContacts interaction types
- multiple atom scanning around ligand based on the Scorpion scoring function
- able to scan fragment library at any ligand position, and rank with Scorpion
- able to scan fragment library guided by network hotspots
- interactions from each pharmacophore site to neighbouring protein atoms are easily explored in PyMOL
- chemistry knowledge built into fragment linking
- identification of favourable water binding sites

DesertSci

What is Scorpion Technology?

Scorpion technology underpins our modeling software by providing a new computational description of molecular recognition. Specifically, Scorpion technology uses a small world network approach to rationalize binding in protein-ligand complexes. It is based on the concept of cooperativity and offers you new insights into molecular recognition phenomena and rational drug design.

Using Viper with its incorporated Scorpion technology provides you with:

- a new computational description of molecular recognition
- new tools for exploring binding in protein-ligand complexes
- a completely new approach for designing tight binding ligands

Viper … *In Action*

A typical fragment scan computation is done in three stages:

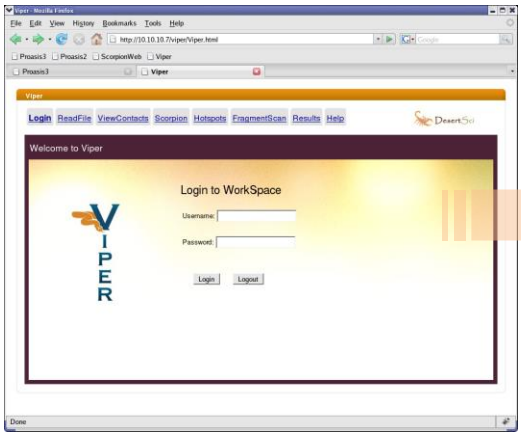
- pharmacophore search
- fragment scan
- full Scorpion scoring

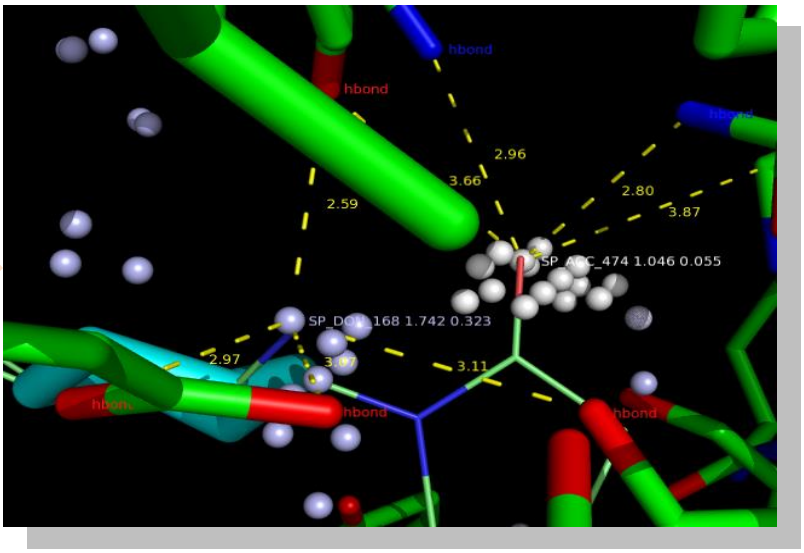
Multiple fragment scan computations can be done using the results from a single pharmacophore search. The search for explicit ligand substituents can be directed to maximize total binding affinity, or be fine-tuned in a wide variety of ways; for example, to optimize local hydrogen bonding cooperativity.

Hotspot searching

Hotspot searching suggests pharmacophores for strong protein-ligand network interactions. The software performs grid-like sampling of multiple atom types in a binding site and determines network interaction scores at each site point based on the Scorpion scoring function.

The following image shows the excellent agreement between theory (Viper identified acceptor point 474 and donor point 168) and experiment (ligand carbonyl oxygen and ligand amine nitrogen respectively).

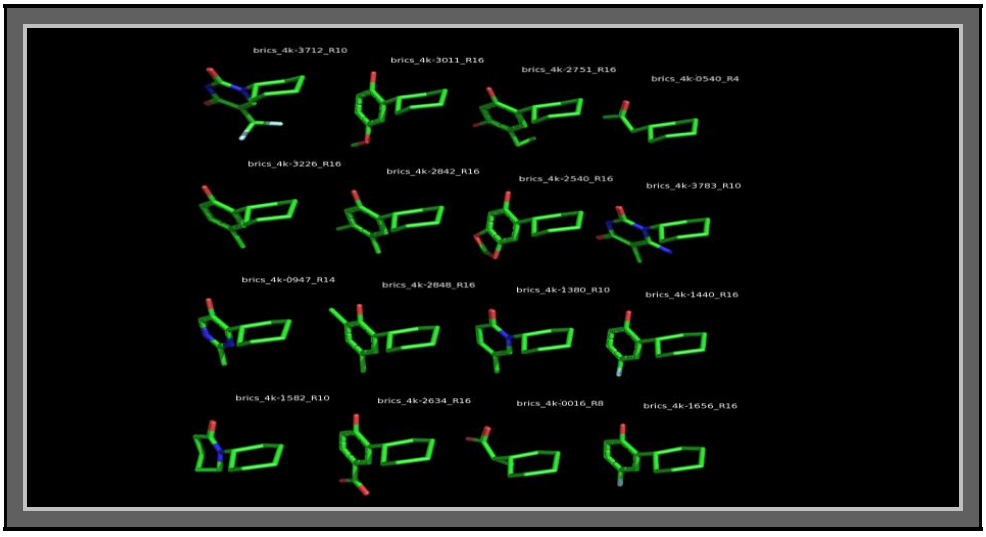




Fragment Scanning

Fragment scanning, guided by network hotspots enables the optimization of ligand binding affinity. Explicit ligand substituents from a fragment library are linked to the template, taking account of the allowed chemistry and ligand strain. Substituents that provide improved interactions, including those with high network scores, are saved.

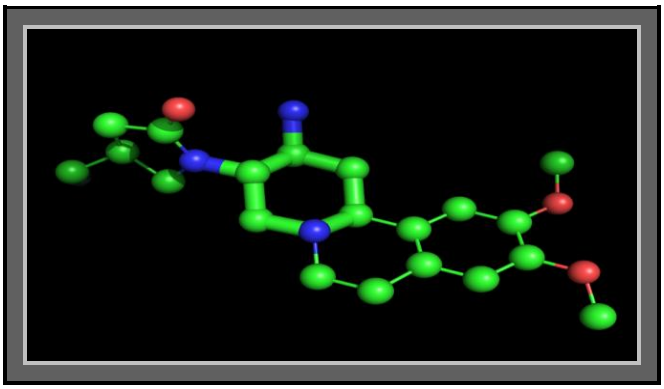
An example of 16 high scoring fragments from the BRICS library (http://www.zbh.uni-hamburg.de/BRICS), calculated for DPP4 (pdb id 3kwf), is given below to indicate a subset of the output calculated by Viper



Atom Scanning

Atom scanning identifies explicit single atom substituent patterns that lead to high network scores in binding sites. Viper computes ligand results and orders them from lowest to highest affinity. Halide scans are particularly powerful for optimizing molecules during lead development.

The Viper results reproduce experimental results closely, as seen below. Both nitrogens off the six membered ring in the ligand from the pdb entry 3kwf (spheres), are observed in the calculated results (sticks). The predicted highest scoring nitrogen is in the same position as in the pdb entry 3kwf



Installation

Viper server software runs under Linux and end users access the system using command line scripts or ViperWeb, and view structures using PyMOL.

Software requirements:

Viper software requires the following components to be installed

On the server machine:

- Python - version 2.7 is recommended (version 2.4 is minimum requirement)
- Python add on modules - networkx (version networkx-1.0.1.tar.gz recommended) and egenix-mx-base (version egenix-mx-base-3.1.3.tar.gz recommended)

For end users viewing protein ligand complexes, non-covalent interactions, atoms highlighted by Scorpion scores, network hotspots, and results from fragment scans:

- PyMOL (Incentive version recommended)
- MOE

Acknowledgements

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