Compound Library Preparation in Galaxy: Application to HT Docking

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Introduction

A variety of software tools exists for compound analysis and drug discovery research. This includes tools for ligand- and structure-based *in silico* screenings. In high-throughput (HT) screening large amounts of compounds are tested with the aim to distinguish between active and inactive molecules. The selection of the compounds to be included in the screening step is crucial. As HT docking methods are common in rational drug design, the preparation of custom compound libraries requires fully traceable workflows which ensure the repeatability of the results.

Thus, several tools for library preparation were integrated into a well-established workflow management system. Subsequently, these tools were applied in an HT docking experiment aiming to evaluate the performance of our HT docking protocol for the detection of known inhibitors of BET bromodomain-containing proteins out of a set of compounds.

Methods

Several tools for library preparation and compound selection were implemented in the Galaxy workflow management system[1] as part of a cheminformatics package to enhance and facilitate:

- similarity searches based on 2D descriptors and Spectrophores™[,2] –chemical features 2D descriptors,
- substructure searches,
- pharmacophore-based searches,
- filtering of compounds by physico-chemical properties (e.g. drug-like constraints [1]), and
- searches in multiple databases.

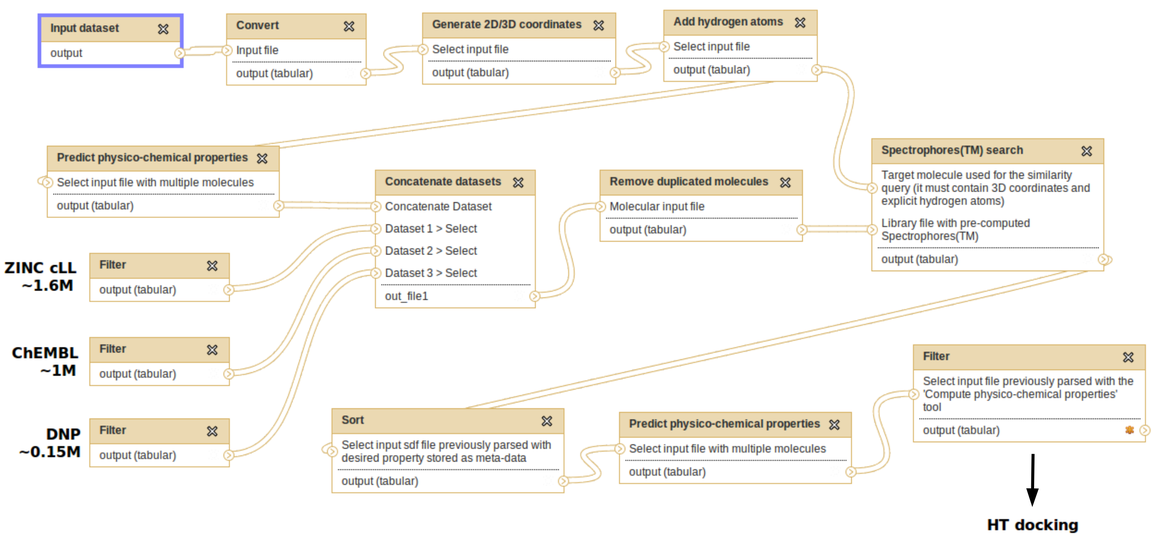

Fig. 1: Implemented Spectrophores™ similarity search workflow querying multiple libraries of small compounds and filtering by drug-like rules.

Case study: BET Bromodomain

Bromodomain-containing proteins are of substantial biological interest as components of transcription factor complexes and determinants of epigenetic memory. The BET bromodomain family member BRD4 has been proposed as a promising pharmacologic target in cancer [2,3]. Recently, crystallographic structures of BRD2, BRD3, and BRD4 in complex with active compounds have been published [2,4] and thus can be used for the rational drug design of novel inhibitors.

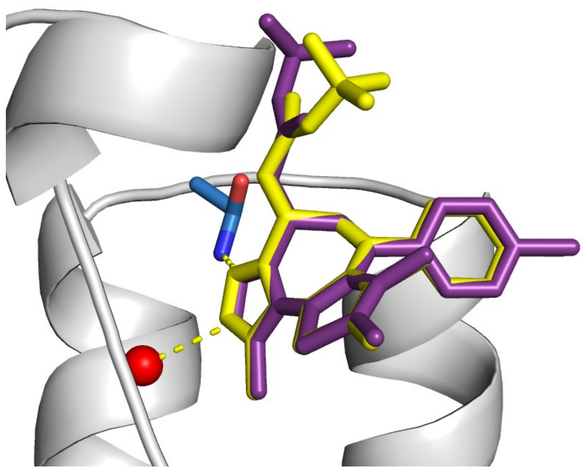

Fig. 2: Crystallographic and experimental binding poses for inhibitor JQ1, in yellow and purple. Hydrogen-bond interactions of the ligand with highly conserved Asn429 (blue) and crystallographic water molecule (red sphere) are depicted as yellow lines. Image generated using PyMOL[6].

We have used our cheminformatics suite to select drug-like compounds substructurally and chemically related to the known inhibitors from the ZINC[3], ChEMBL[4] and DNP (Dictionary of Natural Products)[5] libraries of small compounds. The selected non-redundant sets of compounds have been docked to a crystal structure of BRD4 (PDB entry 3ONI) using Glide docking software (Schrödinger Inc.). The experiment has been carried out using the fast docking (HTVS) and eXtra Precision (XP) methods.

Virtual screening results

HTVS' (HTVS + accurate re-scoring) and XP docking methods were used to dock 243 unique compounds substructurally related to the known inhibitors. 118 unique compounds interacting by hydrogen-bond (HB) with Asn429 were found.

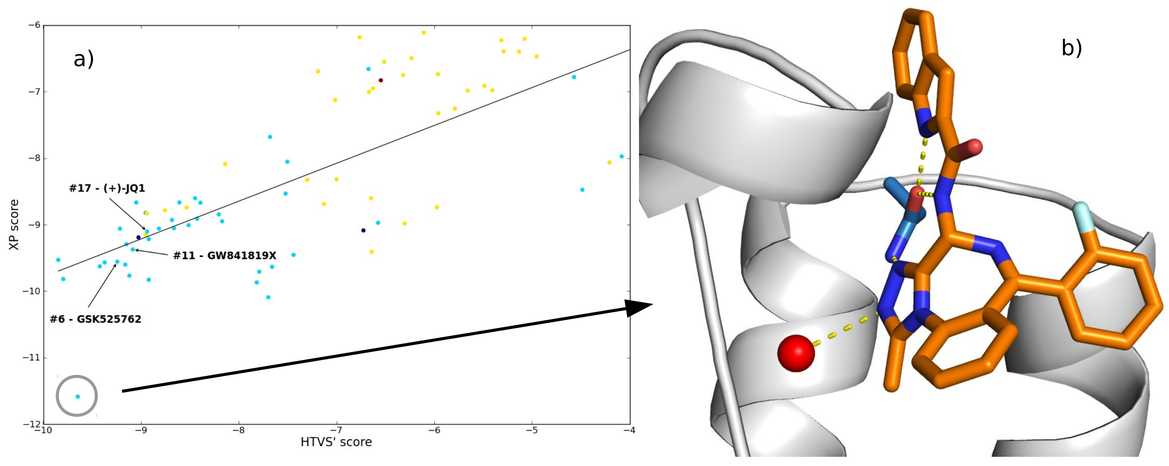

Fig. 3: a) XP vs HTVS' scores plot (r^2 = 0.57). Known active inhibitors were ranked on top (p<0.005)*. Ligand scores are coloured by net charge (0: cyan, +1: yellow). Charge distribution indicates that HTVS' and XP scores correlate better for neutral compounds, and they exhibit higher affinity values for the receptor. Low affinity compounds have been omitted for clarity reasons.
b) Binding mode of a compound predicted to have high affinity for the target. Possible HB interactions of the ligand with Asn429 and water molecule are shown.

In order to identify novel chemical scaffolds affine for the target, 5000 compounds were selected by our Spectrophores™ similarity search workflow and docked using the HTVS' protocol. 2489 unique compounds interacting by HB with Asn429 were found.

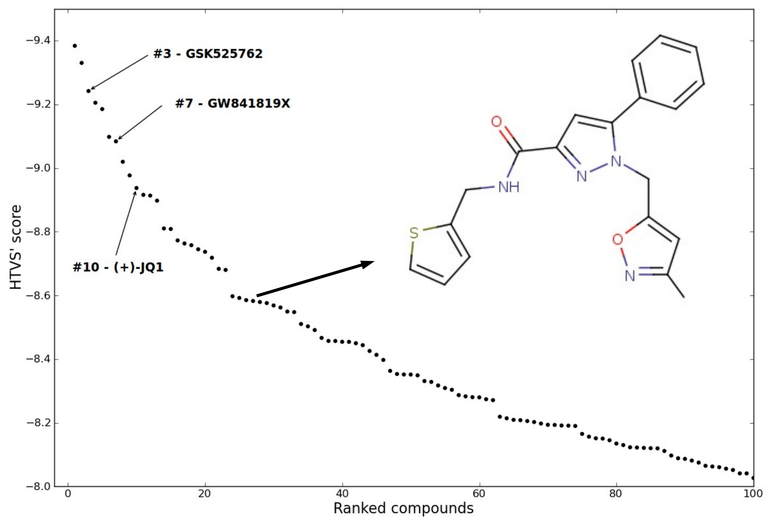

Fig. 4: HTVS' score plot for the top 100 docking results. Known inhibitors were ranked in the top 10 positions (p<0.005)*. Several compounds with novel chemical cores were identified and will be tested experimentally to assess their activity *in vitro*. 2D structure of compound ranked #27 is shown.

Our HT docking protocol will be used for the identification of novel inhibitors of pharmaceutically relevant protein targets and protein-protein complexes.

References

[1] Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Methods. 2000. 44(1):235-49

[2] Filippakopoulos P, Qi J, Picaud S *et al.* Selective inhibition of BET bromodomains. Nature. 2010. 468:1067-73

[3] Zuber J, Shi J *et al.* RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. Nature. 2011. DOI: 10.1038/nature10334

[4] Chung C *et al*. Discovery and characterization of small molecule inhibitors of the BET family bromodomains. J. Med. Chem. 2011. 54:3827-38

Links

[1] http://galaxy.psu.edu
[2] http://www.silicos.be
[3] http://zinc.docking.org
[4] https://www.ebi.ac.uk/chembldb
[5] http://dnp.chemnetbase.com
[6] http://www.pymol.org

* Probability values computed using the hypergeometric distribution for the obtained ranking.

Black Forest Grid

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