2019/06/19
Mandeep Mann

Virtual Screening with Molecular Forecaster

Objective: To identify commercially available compounds for USP5 zinc-finger ubiquitin binding domain (ZnF-UBD) with Molecular Forecasters (MFI) FITTED docking platform. Preliminary assessment of docking for USP5 ZnF-UBD with FITTED can be found here.

Methods & Results:

A. Compound Library Selection

ZINC15 commercially available compounds within the following tranches, and vendors was used for the virtual screening library:

- logP: -1 to 4
- Molecular Weight (MW): 200-375
- Vendors:
    - Acros (# of compounds: 14819)
    - Aksci (# of compounds: 190805)
    - Alfa (# of compounds: 34210)
    - Chemiprex (# of compounds: 15457)
    - Combiblocks (# of compounds: 81134)
    - Enamine (# of compounds: 94051)
    - Sial (# of compounds: 81134)
    - Synquest (# of compounds: 87903)

Please see sdf file for each vendor library in respective folder. A total of 607580 compounds were in the virtual screening library from 8 vendors.

B. Molecular Forecaster: SMART, REDUCE, SELECT and CONVERT

- SMART was used to prepare ligand files for docking by assigning rotatable torsion assignment (charges: DGH). See paramaters-smart.txt for keyword file.

- REDUCE was used to filter the chemical library. See parameters-reduce.txt for keyword file. The following filters were applied for each vendor library:
    - Min charge: -1
    - Max charge: +1
    - Min MW: 3
    - Max MW: 500
    - Min logP: -10
    - Max logP: 4
    - Excluded functional groups:
        - Acyl chloride
        - Aldehyde
        - Alkyl bromide
        - Alkyl iodide

- Anhydride
- Azide
- Boronic acid
- Boronate
- Isocyanate
- Sulfonyl chloride
- Vinyl bromide
- Vinyl chloride
- Vinyl iodide
- Michael acceptor

Library of 607580 compounds was reduced to 505772.

- SELECT was used to create a subset of the library to remove similar molecules that have already been screened or experimentally tested. See paramaters-select.txt for keyword file.
    - A sdf file of experimentally tested ligands (USP5cpd.sdf) was used for selection of dissimilars with max tanimoto: 50

225665 compounds were selected for the final library.

C. Molecular Forecaster: MATCHUP, PREPARE, PROCESS, CONVERT and FITTED

- MATCHUP: superposes protein structures [PDB: 6DXH, 6DXT, 6NFT]. See parameters-match-up.txt for keyword file
- PREPARE: optimizes physiochemical properties. See parameters-prepare.txt for keyword file.
- PROCESS: generates modified protein files for use with FITTED for docking
- CONVERT: select_output.sdf files were converted from 2D molecules into 3D representations for docking with FITTED
- FITTED: docking of ligands to protein. See parameters-fitted.txt for keyword file. See output folder for docking results and docked poses of ligands for each respective vendor library.

D. Visual Inspection of Top Scoring Ligands

- The docked poses of top scoring ligands from each vendor library was selected for visual inspection. Please see MFIlibraryselection.xlsx and MFI_top_scoring_ligands.sdf for top scoring compound information and docking scores.

<u>Conclusions and Future Directions</u>:

The MFI's flexible protein docking with MATCHUP and FITTED was used to virtually screen a library of 225, 665 commercial compounds. From the virtual screen, top scoring ligands from each vendor library were selected for visual inspection (total: 347). The majority of the top scoring ligands are fragments. Next, I will select scaffolds with interesting interactions in the binding pocket for ordering and experimental testing.

2019/06/19
Mandeep Mann

References

Therrien E., Englebienne P., Arrowsmith A.G., Mendoza-Sanchez R., Corbeil C.R., Weill N., Campagna-Slater V., Moitessier N. Integrating medicinal chemistry, organic/combinatorial chemistry, and computational chemistry for the discovery of selective estrogen receptor modulatorswith FORECASTER, a novel platform for drug discovery. *Journal of Chemical Information and Modeling* (2012), 52, 210-224

Moitessier N., Pottel J., Therrien E., Englebienne P., Liu Z., Tomberg A., Corbeil C.R. Medicinal Chemistry Projects Requiring Imaginative Structure-Based Drug Design Methods. *Accounts of Chemical Research* (2016), 49 (9), 1646-1657.