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Proteome Fishing: A Reverse Docking Study

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Introduction

Frankincense is an oleo-gum resin produced from the sap of the Boswellia genus of trees. Though it has traditionally been used for a variety of medicinal purposes, including anti-bacterial and anti-inflammatory applications, it is recognized as an essential oil rather than a pharmacological substance. This project sought to better characterize the potential pharmacological uses of frankincense through an *in silico* reverse-docking study. One major class of compounds found in frankincense, known as cembranoids[1], was chosen as the focus for reverse-docking against a database of "druggable" protein targets (sc-PDB[2]).

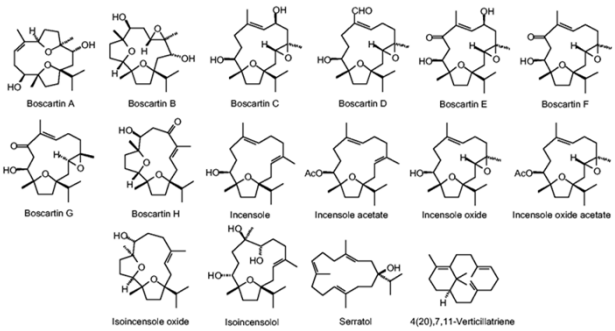

Figure 1: Compound structures of Cembranoids found in *Boswellia* species[1].

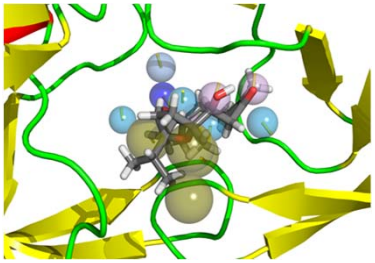

Figure 2: Ribbon structure of HIV1-Protease docked with Boscartin G (pose 2) showing pharmacophores.

Methods

In this study, 9277 proteins with co-crystallized ligand structures from the scPDB database of "druggable" protein targets[2] were prepared for reverse docking with SMINA using AutoDockTools. In addition, pharmacophore points were calculated for each ligand using Align-it, which was also used to evaluate the similarity to the cembranoid pharmacophores. Each of the 15 cembranoid structures were then docked to each of the scPDB receptor sites, keeping a maximum of 6 low-energy poses for each docking. These poses were then scored by pharmacophore similarity to each reference ligand. The score used for ranking hits (rank score) is a function of the Vinadro docking score, the number of pharmacophore points in the cembranoid ligand, and the Tanimoto index of similarity to the co-crystallized ligand.

Key Findings/Results

Out of 832,737 hits, poses with a rank score value of <= -30.0 were analyzed. Of the top 30,800 hits, the most common type of protein receptor found were proteases, appearing 1,063 times, with 712 protease hits belonging to HIV Type 1 Group M Subtype B. The top binding pose of these was Boscartin G docked in place of reference co-crystallized ligand Saquinavir (PDB ID: 3NDU), with a rank score of -118. Boscartin G has a mass of 336 a.u., 1 H-bond donor, 4 H-bond acceptors, a calculated logP of 3.56 and a calculated molar refractivity of 92.8. This meets all five of Lipinski rules, suggesting a capacity for oral druggability.

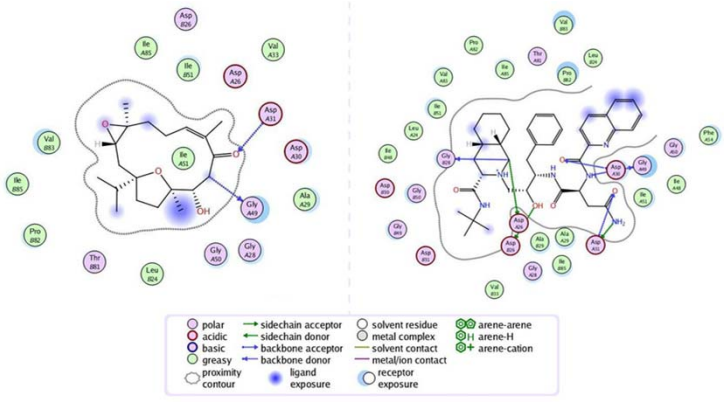

Figure 3: Ligand interactions with HIV1-Protease for Boscartin G (left) and Saquinivir (right). Both have interactions with residues Asp31 and Gly49.

Conclusions/Future Directions

By automating the fine tuning of the scoring function using pharmacophore alignments, the resolution of reverse docking is greatly enhanced, and the reliability of the top hits in this virtual screen should be much improved over molecular docking alone. We have identified several promising targets for cembranoid compounds such as Boscartin G, which showed several hits to HIV-1 protease. Enzyme assays of HIV-1 protease can confirm if Boscartin G has adequate binding affinity *in vitro* to match the calculated rank score. An *in vivo* study could then be done to discern if bioavailability of frankincense-based drugs would be sufficient to display an inhibitory effect. It is expected that Boscartin G would show pharmacological benefit as it binds similarly to Saquinavir, which is currently used as an HIV-1 protease inhibitor.

References

1. Setzer, W. (2018). Conformational analysis of macrocyclic frankincense (Boswellia) diterpenoids. *Journal of Molecular Modeling*, 24(3). https://doi.org/10.1007/s00894-018-3625-8
2. Kellenberger, E.; Muller, P.; Schalon, C.; Bret, G.; Foata, N.; Rognan, D. (2006). sc-PDB: an Annotated Database of Druggable Binding Sites from the Protein Data Bank. *Journal of Chemical Information and Modeling*, 46(2), 717-727. DOI: 10.1021/ci050372x

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