Docking Studies in the Inhibition of Human Serine Hydroxymethyltransferase

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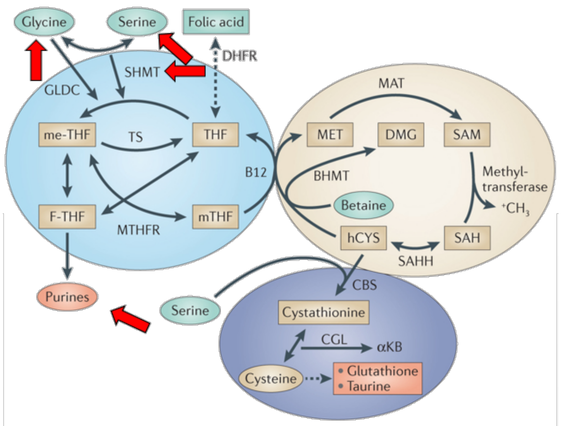
Abstract

Lung cancer is the most prevalent and deadly tumor, accounting for 25% of cancer-related deaths. Non-small cell lung cancer (NSCLC) comprises close to 90% of all lung cancers. The reprogramming of cellular metabolism is considered a hallmark of cancers. In NSCLC, cells redirect carbon to synthesize serine, a process catalyzed by serine hydroxymethylstrans-ferase (SHMT). This change fuels the uncontrolled cell division that characterizes cancer through the production of purines, pyrimidines, and antioxidants.

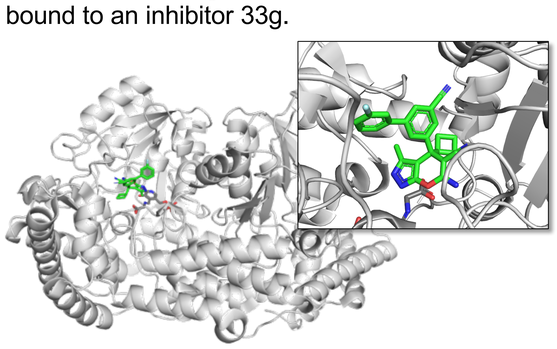
The goal of this project is to model existing inhibitors of *Plasmodium vivax* SHMT to aid in the computational identification of human SHMT inhibitors. Smina, a molecular docking program, calculates the best binding energies and outputs the positions of the ligands when bound to SHMT. Ideally, ligands have a high affinity (binding energy) and a docked pose that is similar to the crystal structure. We rationally modify the chemical structure of a known ligand to identify the key functional groups for binding and apply this knowledge to develop a pharmacophore model for virtual screening.

Background

Serine hydroxymethyltransferase acts as an integral enzyme in the folate-methionine cycle, specifically in serine-glycine one-carbon metabolism (SGOC). This complex pathway leads to the methylation and regulation of DNA, as demonstrated by uracil accumulation when SHMT is downregulated.



Many types (isoforms) of SHMT exist, including enzymes from different *Plamsodia*, mice, and humans. Each has its own unique structure and properties that affect ligand binding. A variety of SHMT structures are available in the Protein Databank including 4TN4, a *Plasmodium* SHMT bound to an inhibitor 33g.

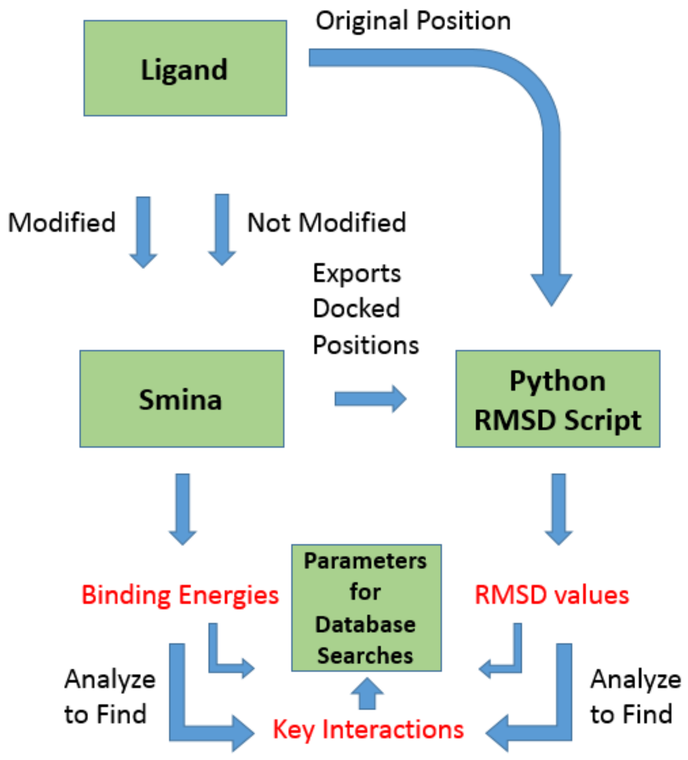


Methods

Smina calculates the binding energy between a ligand and a receptor, in this case a SHMT isoform. It exports the positions where the binding takes place to an output file. The position of the docked pose can then be compared to the original, aligned position with a Python script, which calculates RMSD. Root mean square deviation (RMSD) is operationally defined as the average distance between atoms of the same, superimposed molecule.

The key interactions of a ligand can be identified by modifying the chemical structure of a known ligand and evaluating the change in predicted binding energy and RMSD. Modifications that reduce the binding energy or result in incorrect binding poses are important, while modifications that don't change or increase the binding energy are considered unimportant.

The key interactions can then be used to develop a pharmacophore model for virtual screening.



Conclusions

An analysis of docking experiments with chemically modified ligands revealed several key interactions that are necessary to achieve high binding affinities and the correct binding pose. These key interactions define a pharmacophore hypothesis that can be used for virtual screening. Future work will evaluate this hypothesis by testing compounds identified through virtual screening.

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References

https://www.researchgate.net/publication/288786728_A_pyrazolopyran_derivative_preferentially_inhibits_the_activity_of_human_cytosolic_hydroxymethyltransferase_and_induces_cell_death_in_lung_cancer_cells
http://www.cell.com/cms/attachment/2012399047/2034501678/gr2.jpg
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3806315
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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3806315/
http://www.cell.com/cms/attachment/2012399047/2034501678/gr2.jpg
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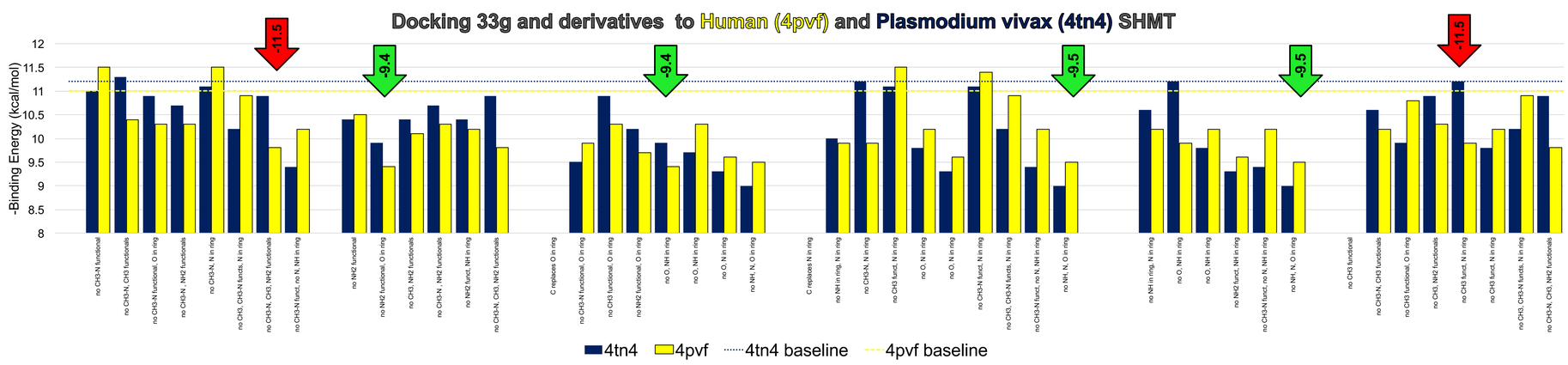
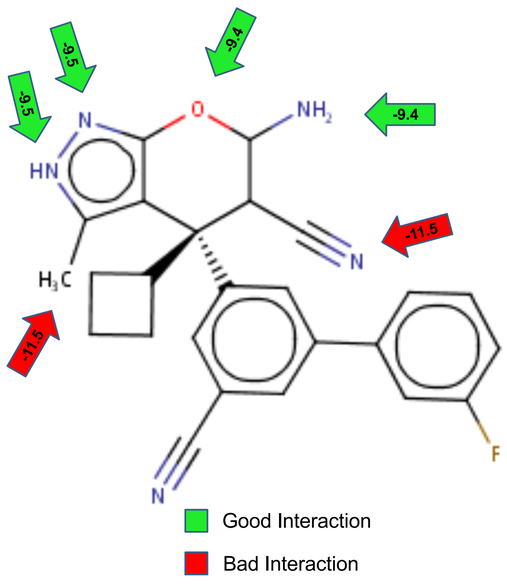
Results





Results show that very few modified ligands have a higher binding energy than 33g itself, including those that have some combination of the C≡N functional group removed and/or ring N replaced by carbon. This shows that they were not important for a high binding energy, while the other interactions were. The RMSD values were not able to be calculated for this specific data set, but it was checked that ligands were in fact binding to the active site. This information led to a search with the Pharmit interactive virtual screening website. A top result was Molport compound 020-230-054. It had a binding energy of -10.02.