Discovery of new anti-fungal agents

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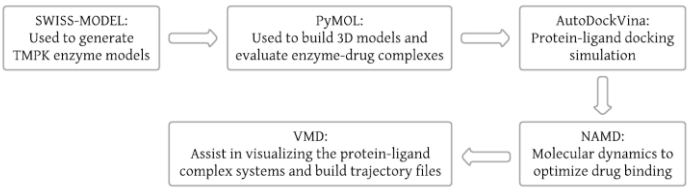
Introduction:

Nowadays more than 600 fungal pathogens are associated with humans, causing several lethal infectious diseases mostly in immunocompromised patients and jeopardizing successful treatment of already existing disease. Due to the fact that the basic cell structure and molecular biology of fungi are very similar to that of humans, there are only four classes of anti-fungal drugs available to treat these life-threatening diseases, only two of which are highly used in the clinic. Considering this challenge, the research project aims to investigate the possibility of selectively targeting fungal pathogens and to test potential of Thymidylate kinase (TMPK) inhibitors as anti-fungal drugs. To test the hypothesis, the models of two pathogens, *Candida auris* and *Cryptococcus gattii* will be examined for successful docking of TMPK inhibitors using AutoDock Vina and NAMD, protein-ligand docking simulation software.

Methods:



Results and Discussion:

1. *Candida auris* and *Cryptococcus gattii* models were built based on Candida albicans and human enzyme liganded to three different ligands, namely ADP, TMP and ATP, using SWISS-MODEL (Figure 1 & 2).

Figure 1: The alignment of four models of *Cryptococcus gattii's* TMPK

Figure 2: The alignment of four models of *Candida auris's* TMPK

2. Preparation of TMPK inhibitors, using MarvinSketch, and their visualization on PyMOL. Inhibitor structures were retrieved from the research paper, which analysed and assessed the potency of a-Thymidine analogues as novel antimalarials [3].

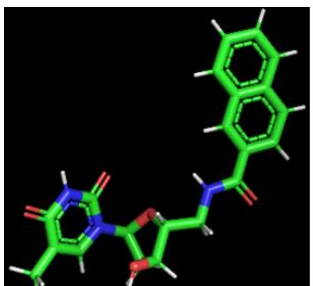


Figure 3: Inhibitor 11 visualized on PyMOL

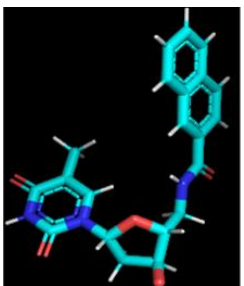


Figure 4: Inhibitor 36 visualized on PyMOL

3. Performing dockings with AutoDock Vina.

The most potent, moderate and least potent inhibitors were chosen to assess their inhibitory activity against TMPK models of *Cryptococcus gattii*, *Candida auris* and human.
The docking was considered successful if the binding energy was less than -9.0 kcal/mol.

4. AutoDock Vina output and selection of the most potent two inhibitors

High binding affinity was observed in models **11** and **36** (Figure 3 & 4). The results suggest that these inhibitors can be used as anti-fungal agents due to their low affinity to the human TMPK enzyme and higher affinity to fungal TMPK enzyme.

5. The molecular dynamics simulation using NAMD was performed with the two most potent inhibitors, namely **11** and **36**. According to trajectory file (Figure 5), the most stable frame 62 for each inhibitor was chosen for further analysis.

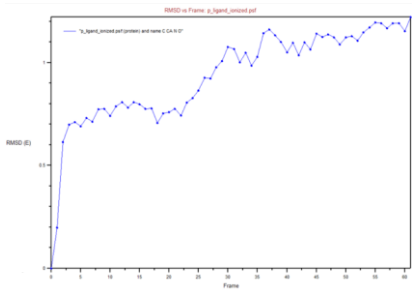


Figure 5: Trajectory graphs illustrate the change in RMSD value over 62 frames. The docking of the inhibitor 11 against TMPK of Cryptococcus gattii.

6. Analysis of NAMD results and comparison with AutoDock Vina output.

NAMD verified the results from the AutoDock Vina and performed better dockings, illustrating the presence of more favourable interactions (Hydrogen bonding) between inhibitors and TMPK enzymes (Figure 6).

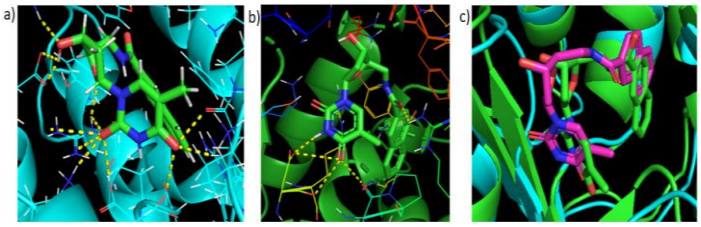


Figure 6: Comparison of results of docking the inhibitor 36 against Candida auris using AutoDock Vina and NAMD. a) NAMD 62nd frame. b) AutoDock Vina. c) Overlay of both to show the shift in the position. (yellow dashes represent H-bonding)

Conclusion & Future Work:

- ✓ The docking simulations verified selectivity of inhibitors against human TMPK enzymes, which may overcome the most important challenge in the drug design.
- ✓ Inhibitors successfully interacted with TMPK enzymes of fungal pathogens referring to the results obtained from NAMD.
- ✓ For this reason, TMPK inhibitors can be used as potential anti-fungal drug agents that stop the proliferation of cells, leading to the cycle of events lethal for fungal pathogens.

The next step of this research project will be working in the lab and verifying the hypothesis experimentally. The activity of TMPK enzyme of three organisms will be tested by introducing chosen inhibitors. The experiment will help validate the conclusions drawn from the results of docking.

Acknowledgement:

I'd like to acknowledge and thank Prof. Gordon Rule for guiding me through this project and introducing to the field of Computational Biology. I hope to continue working on this project and many more in the future.

References:

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