ADVANCEMENT OF CHAGAS DISEASE TREATMENT THROUGH THE IDENTIFICATION OF POTENTIAL NATURAL PRODUCT TARGETS IN THE *TRYPANOSOMA CRUZI* PROTEOME

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RATIONALE

Chagas disease, (American Trypanosomiasis), is a tropical disease linked to *Trypanosoma cruzi,* a protozoan parasite infection which can be spread via triatomine insects and contact with bodily fluids. Approximately 8-10 million people in Latin American countries have Chagas which is most prevalent in rural areas. Current drugs, Nifurtimox and Benznidazole, are effective treatments for the disease in acute phases, but are limited in the chronic stages and display detrimental side effects. Further research and annotation of the *T. cruzi* proteome is critical in polypharmaceutical advancement or repositioning of existing drugs .

PROPOSED RESEARCH

- Identification of natural products that might be effective against Chagas through the screening of the natural based drug library against the surface proteins Transialidase and GP63 of the *T. Cruzi* proteome.

- Search for similar binding sites across the *T. Cruzi* proteome and determine if identified natural products display similar affinity

PROGRESS

Criteria for choosing promising hits was based on free binding energy of the ligand to receptors 1MS8 and 1LML and possible hydrogen bonding interactions with important residues of the active site

Residues include:

1MS8: TYR342,TYR119,ARG35,ARG245,ARG314,ASP59,ASP96,GLU230

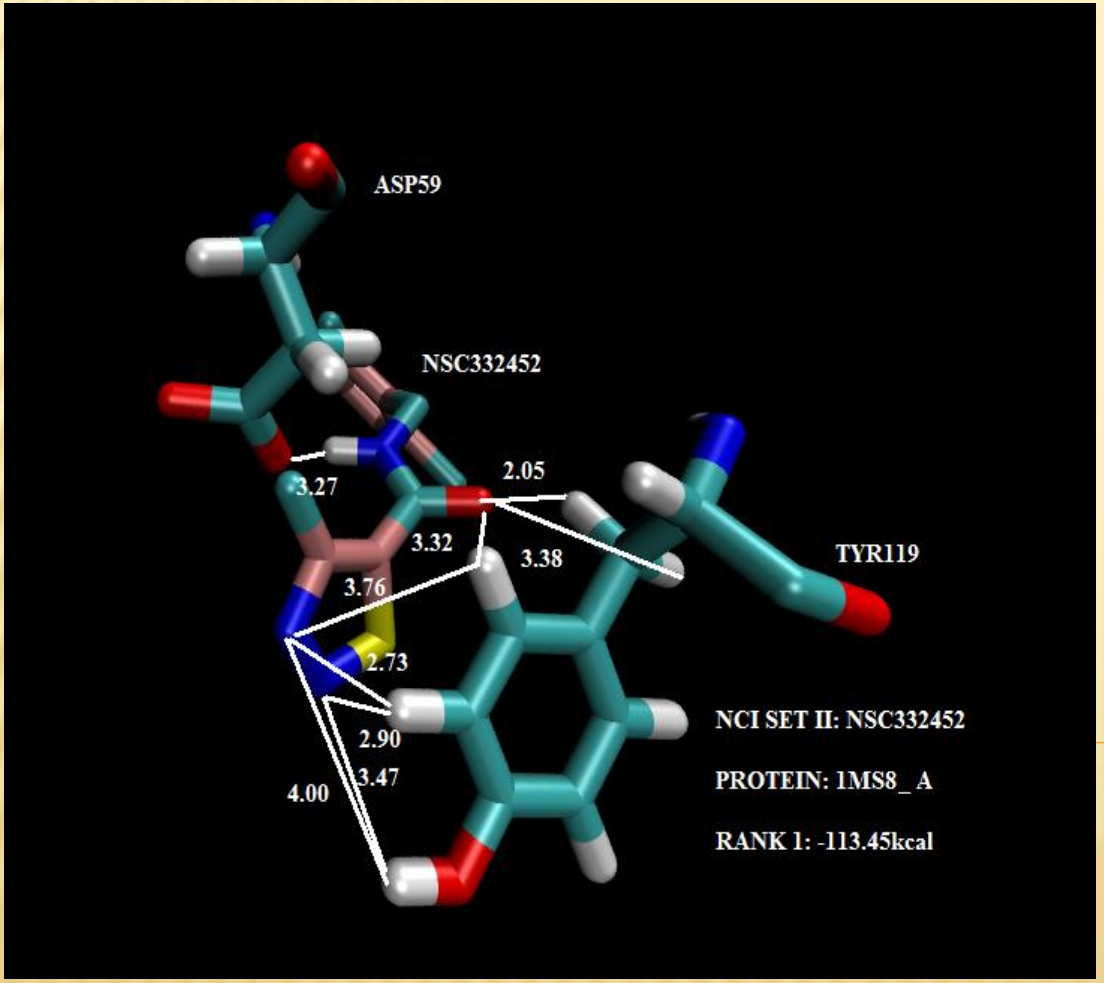
1LML:HIS264,GLU265,HIS268,HIS334

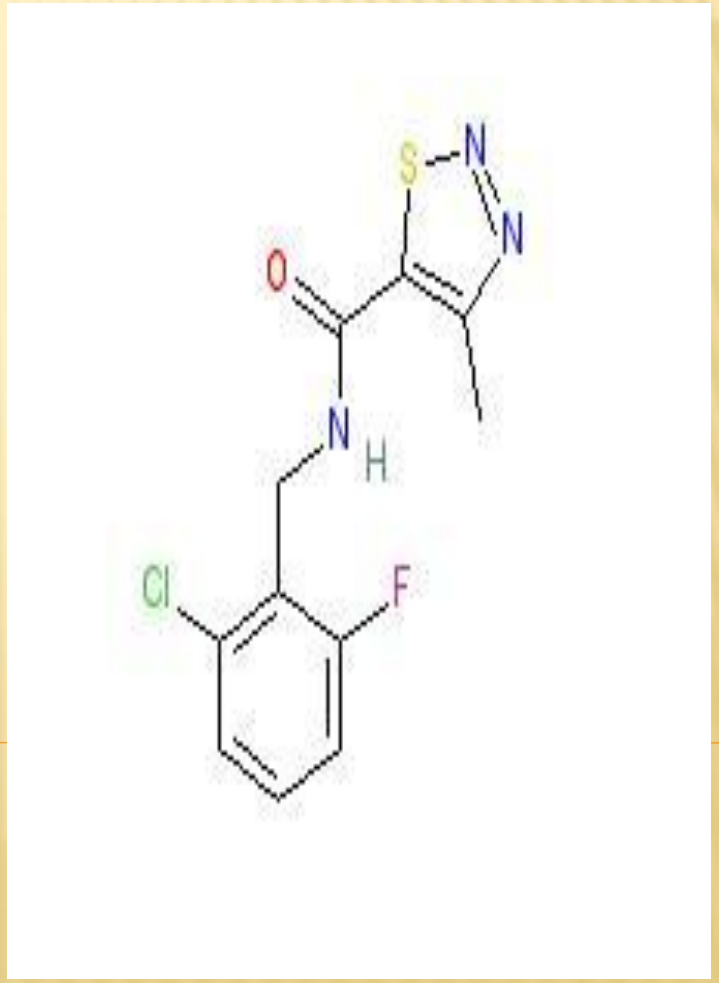
However MSC155 for 1MS8 and MSC2284 for 1LML don't have any hydrogen bonding interactions with the studied residues despite having a lower binding energy. Further analysis of the other compounds that exhibit H bonding, but have a higher binding energy is needed to determine the top 3 promising results of the screening.

Visualizations using VMD are shown in the following slides. Interaction cutoffs for distance are 2-4 angstroms. Only significant H bonding interactions are shown along with the 2D of the compound from the NADI or NCI databases

PROGRESS

Results:1MS8 Virtual Screening with NCI database
Rank 1: NSC332452 -113.45kcal

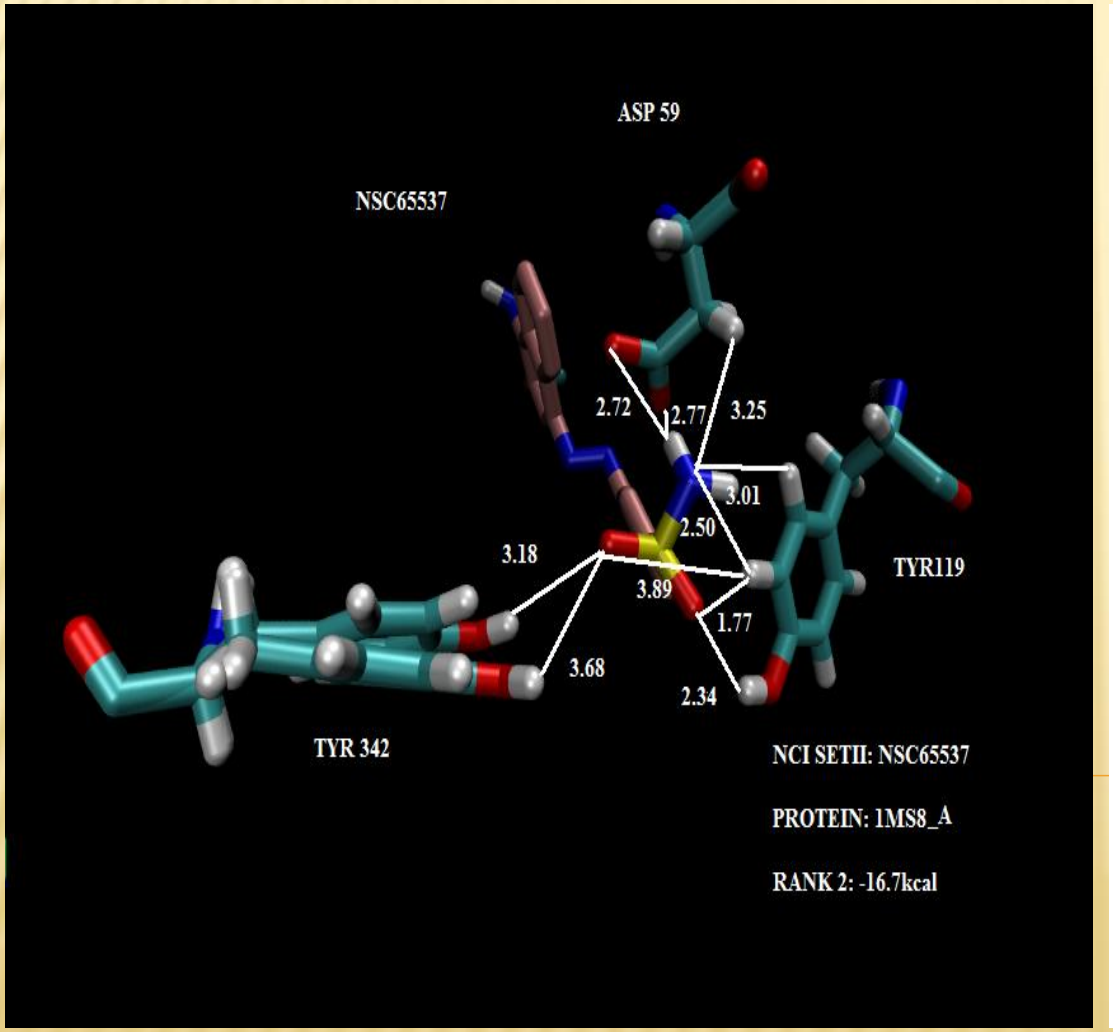


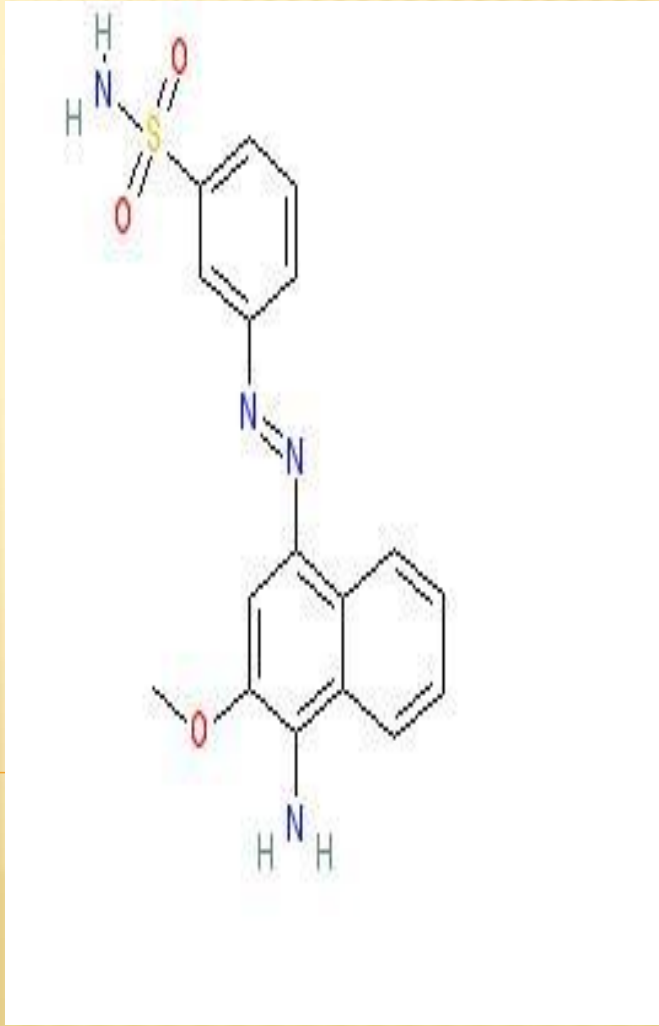


PROGRESS

Results:1MS8 Virtual Screening with NCI database

Rank 2: NSC65537 -16.7kcal

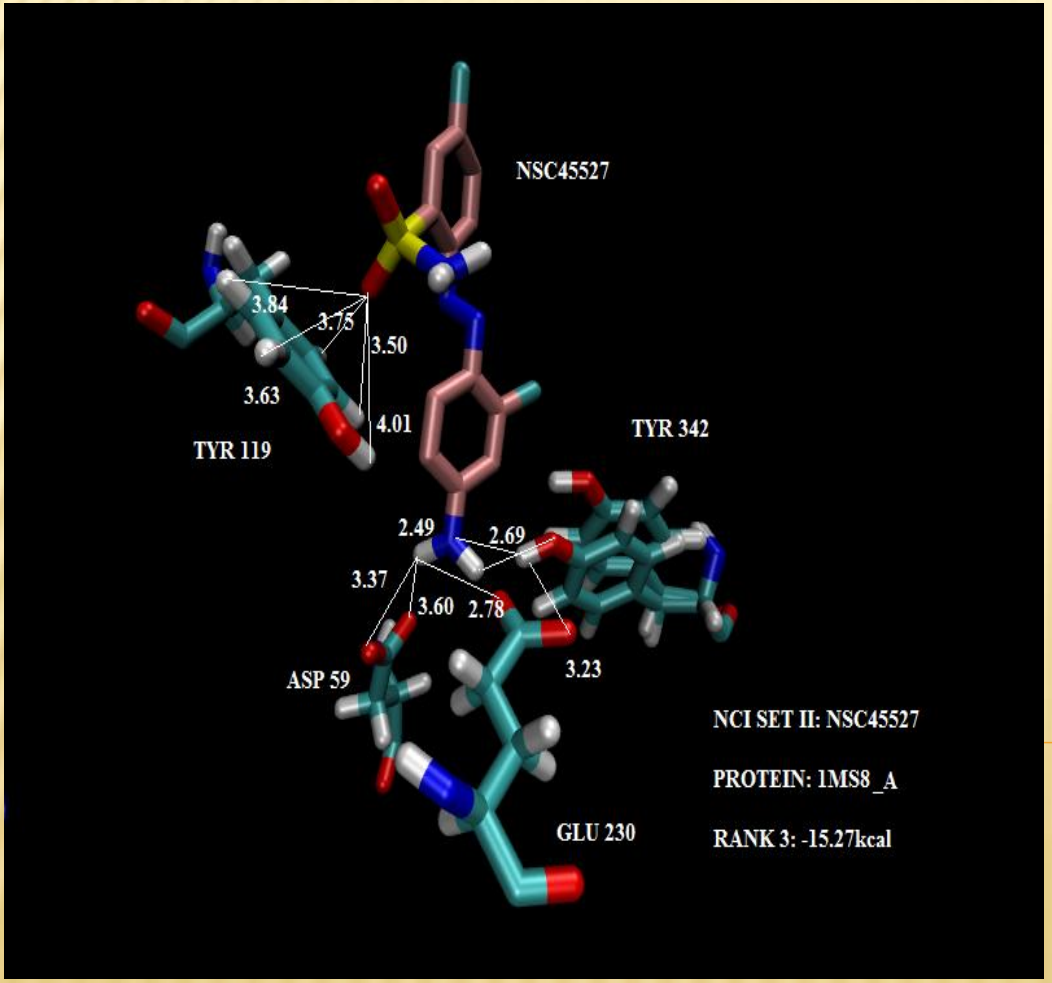


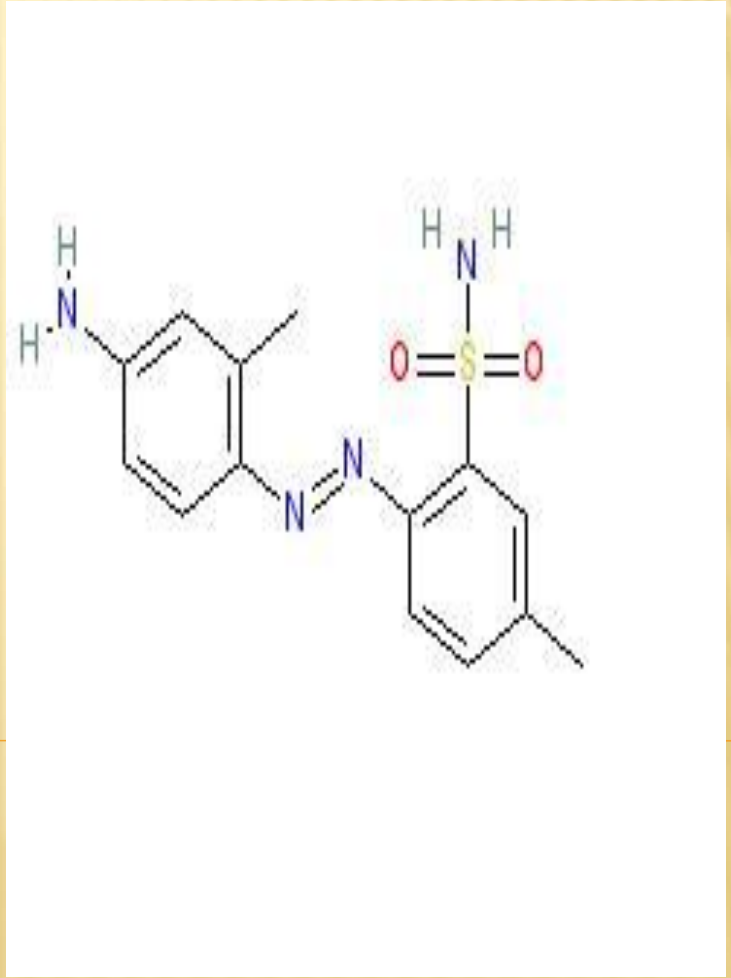


PROGRESS

Results:1MS8 Virtual Screening with NCI database

Rank 3: NSC45527 -15.27kcal

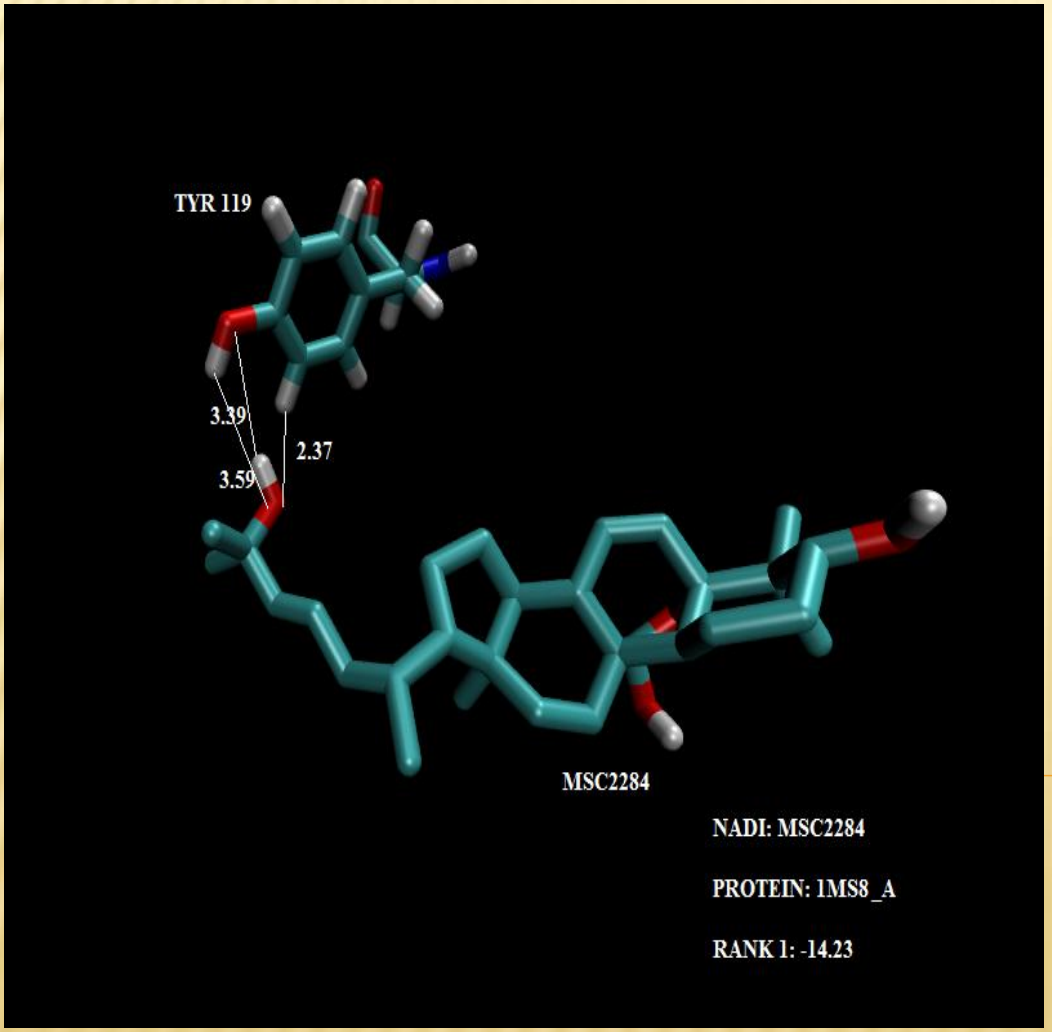


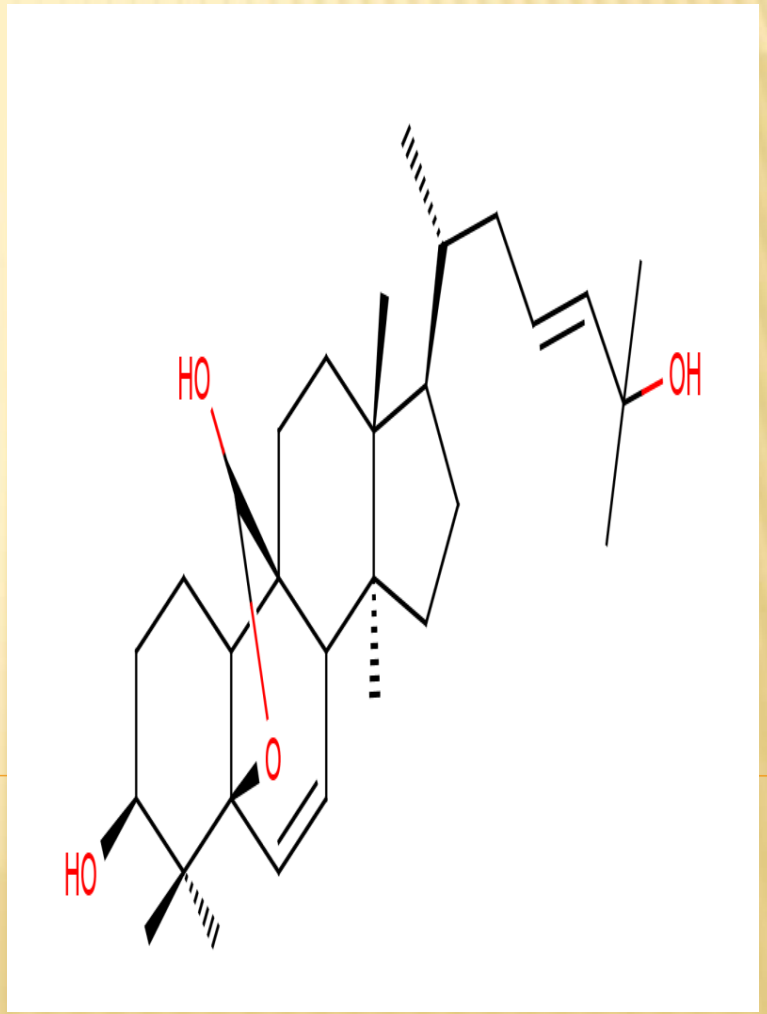


PROGRESS

Results:1MS8 Virtual Screening with NADI database

Rank 1: MSC2284 -14.23kcal

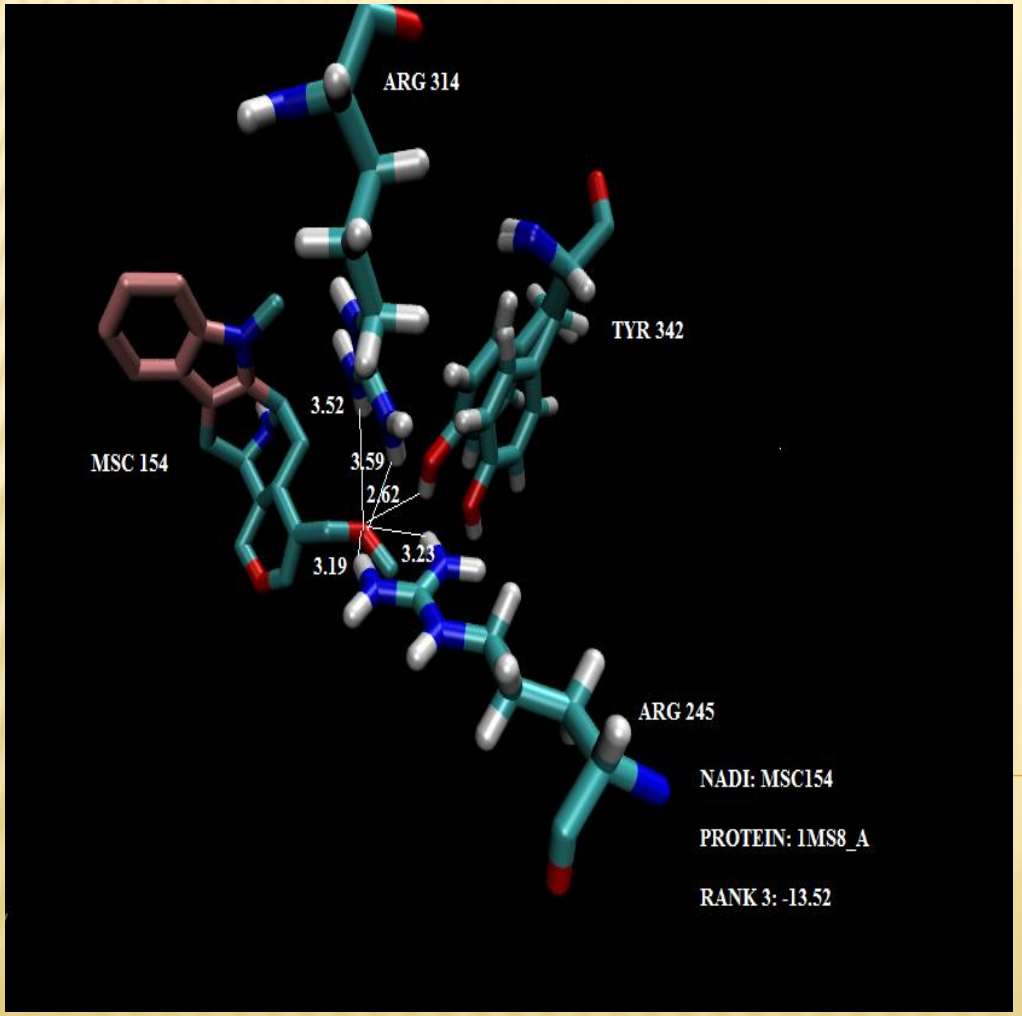


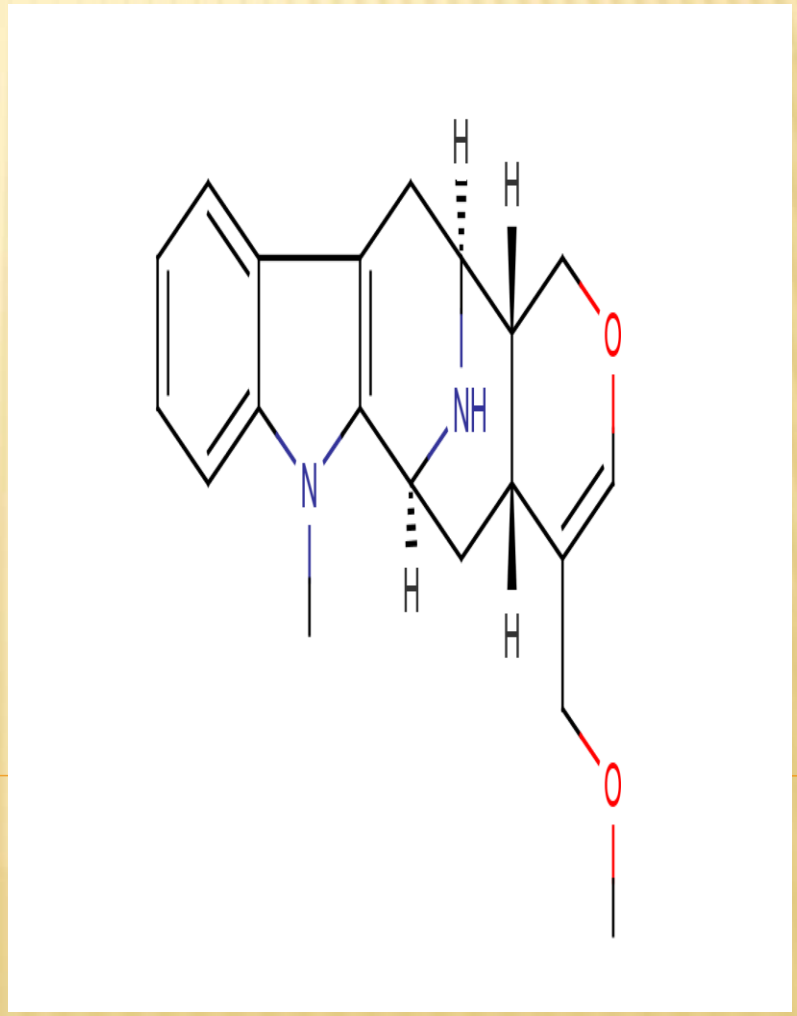


PROGRESS

Results:1MS8 Virtual Screening with NADI database

Rank 2: MSC154 -13.52kcal

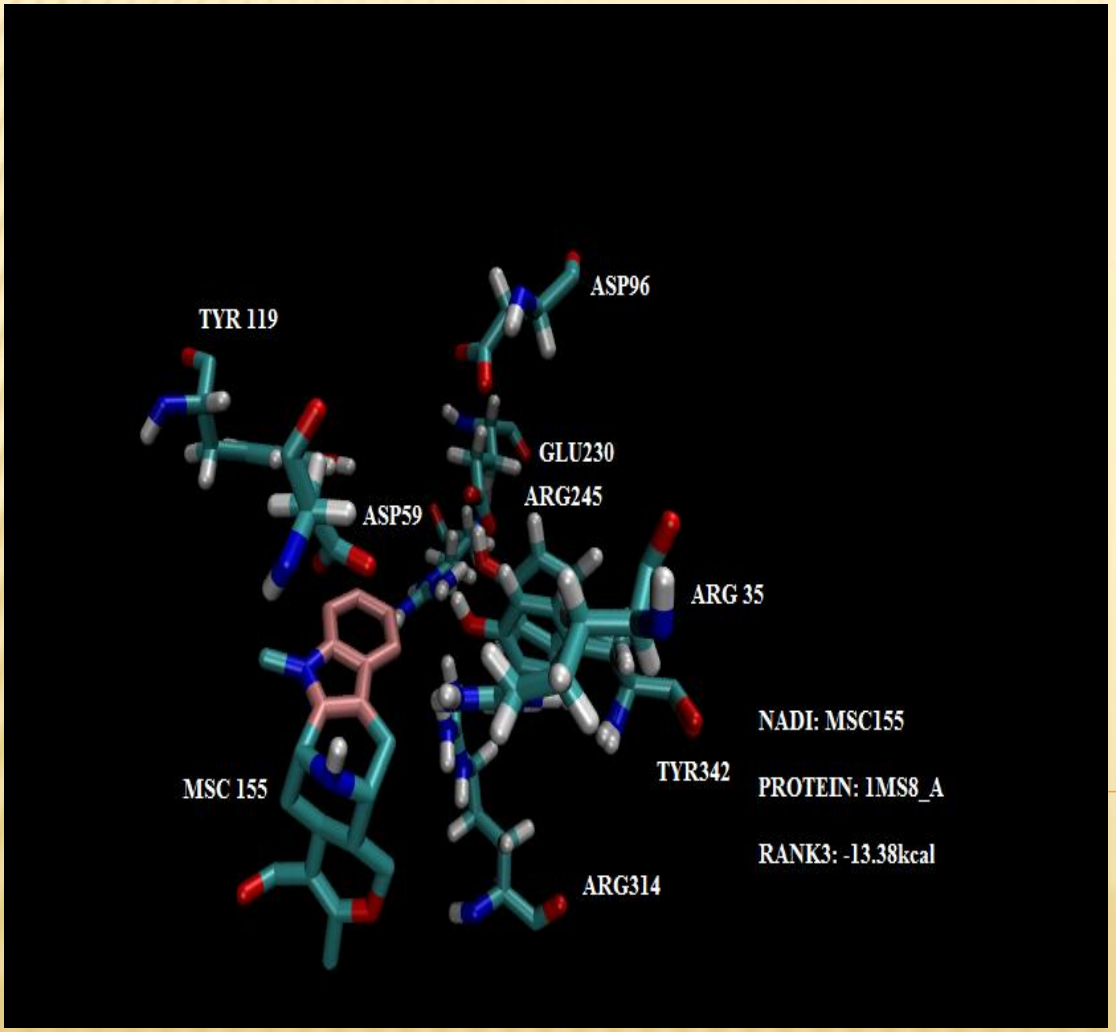


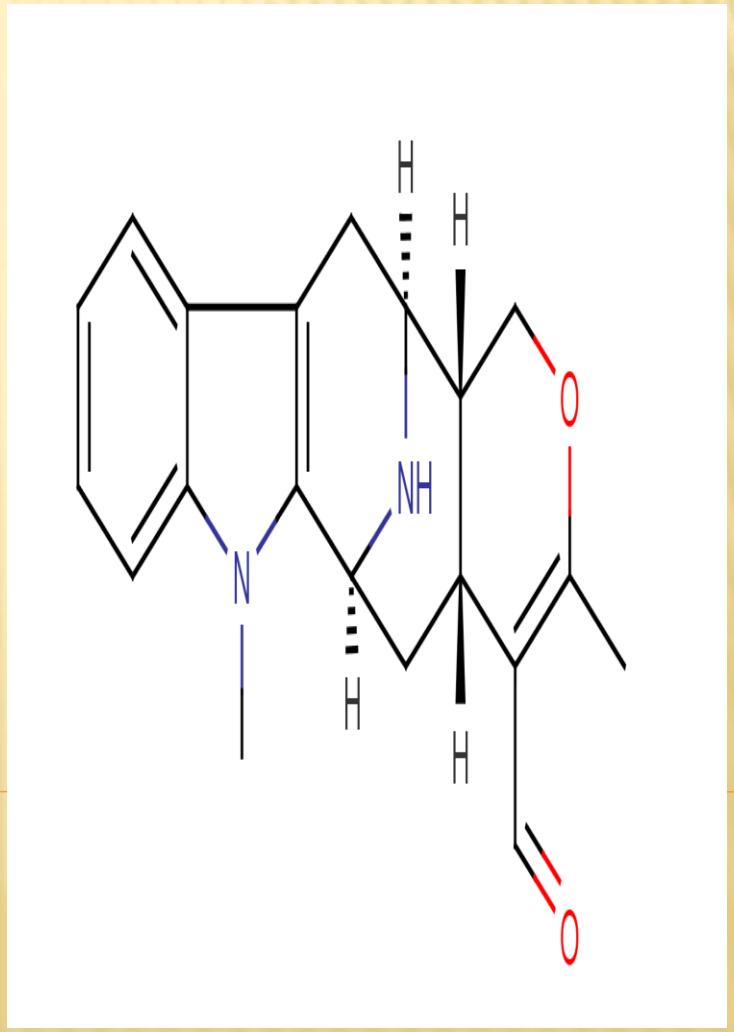


PROGRESS

Results:1MS8 Virtual Screening with NADI database

Rank 3: MSC155 -13.32kcal

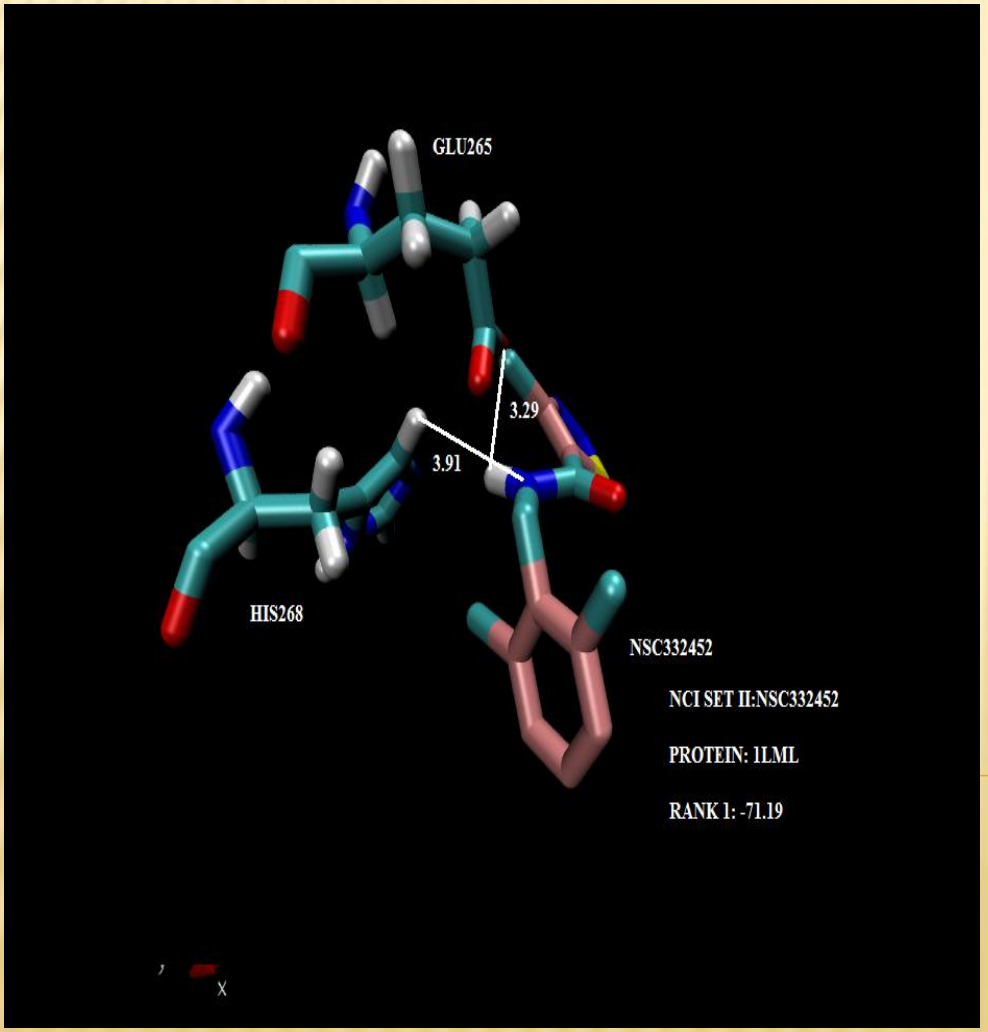


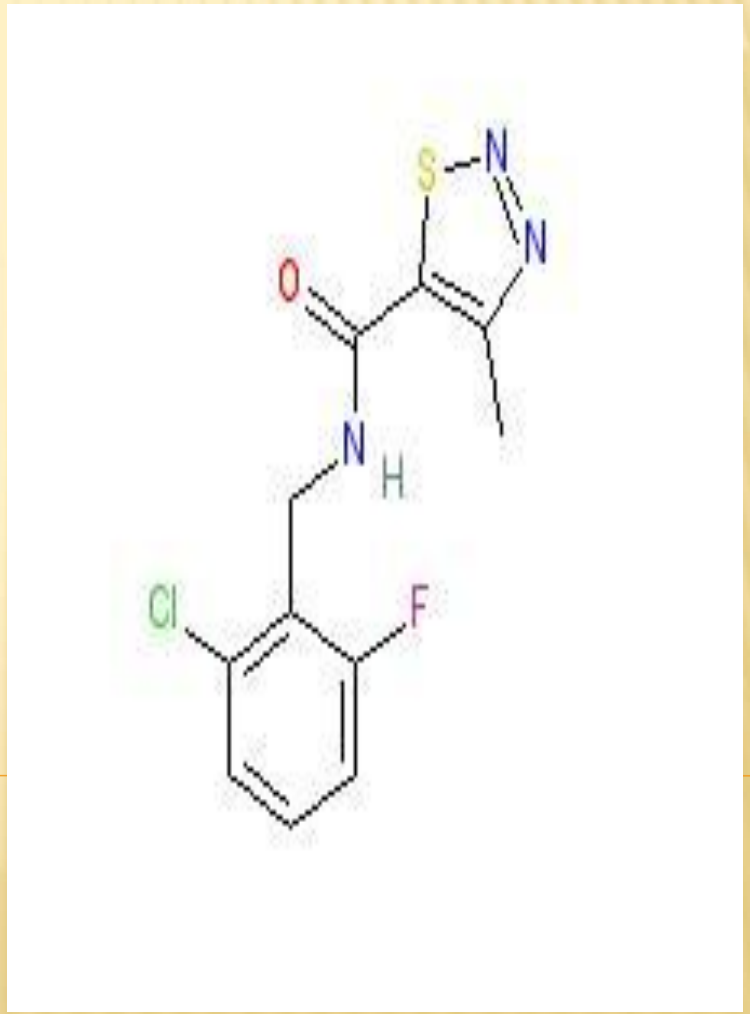


PROGRESS

Results:1LML Virtual Screening with NCI database

Rank 1: NSC332452 -71.19 kcal

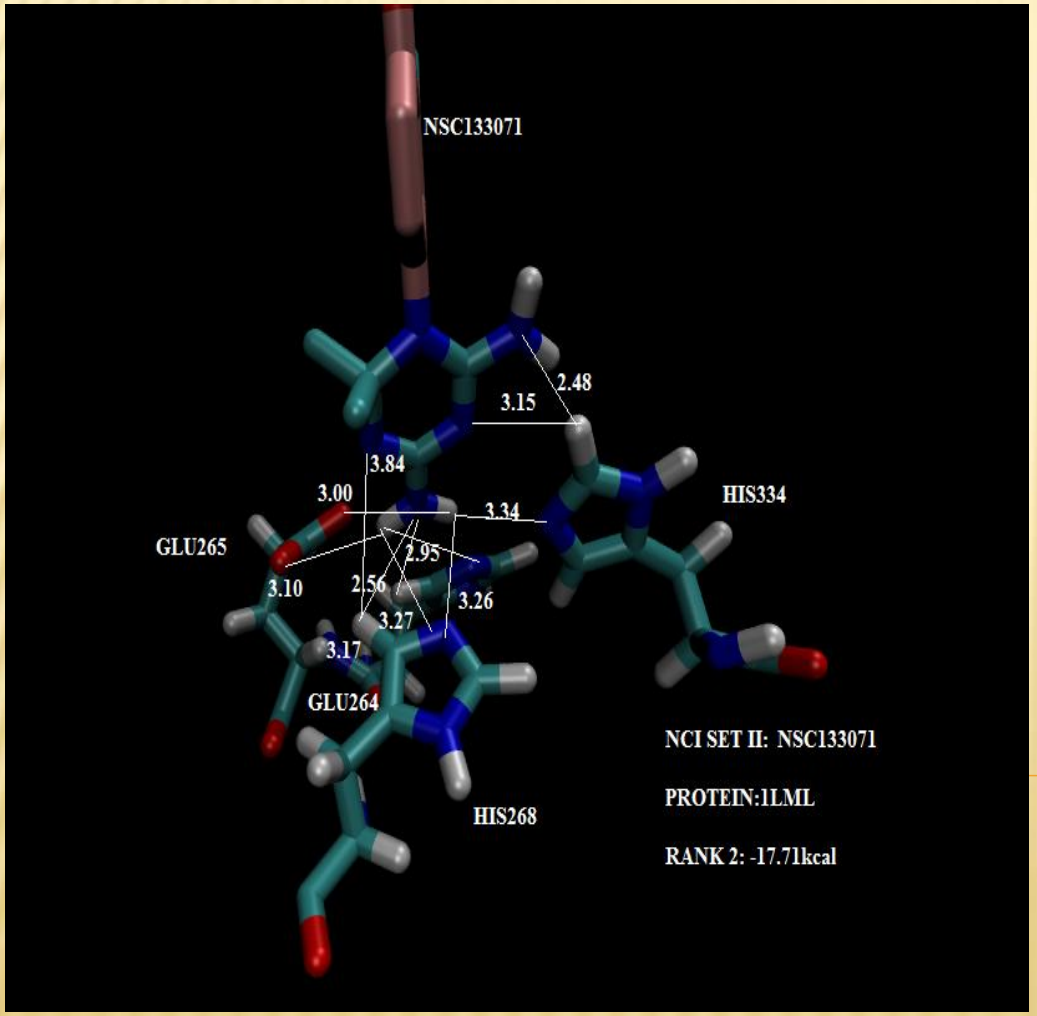


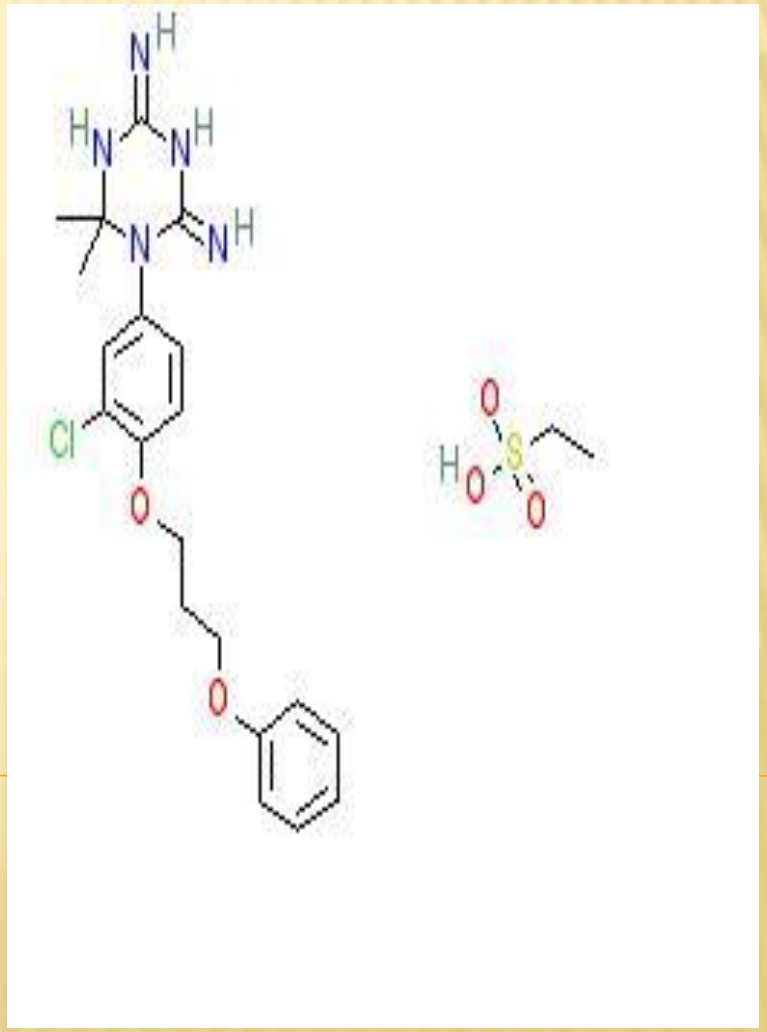


PROGRESS

Results:1LML Virtual Screening with NCI database

Rank 2: NSC133071 -17.71kcal

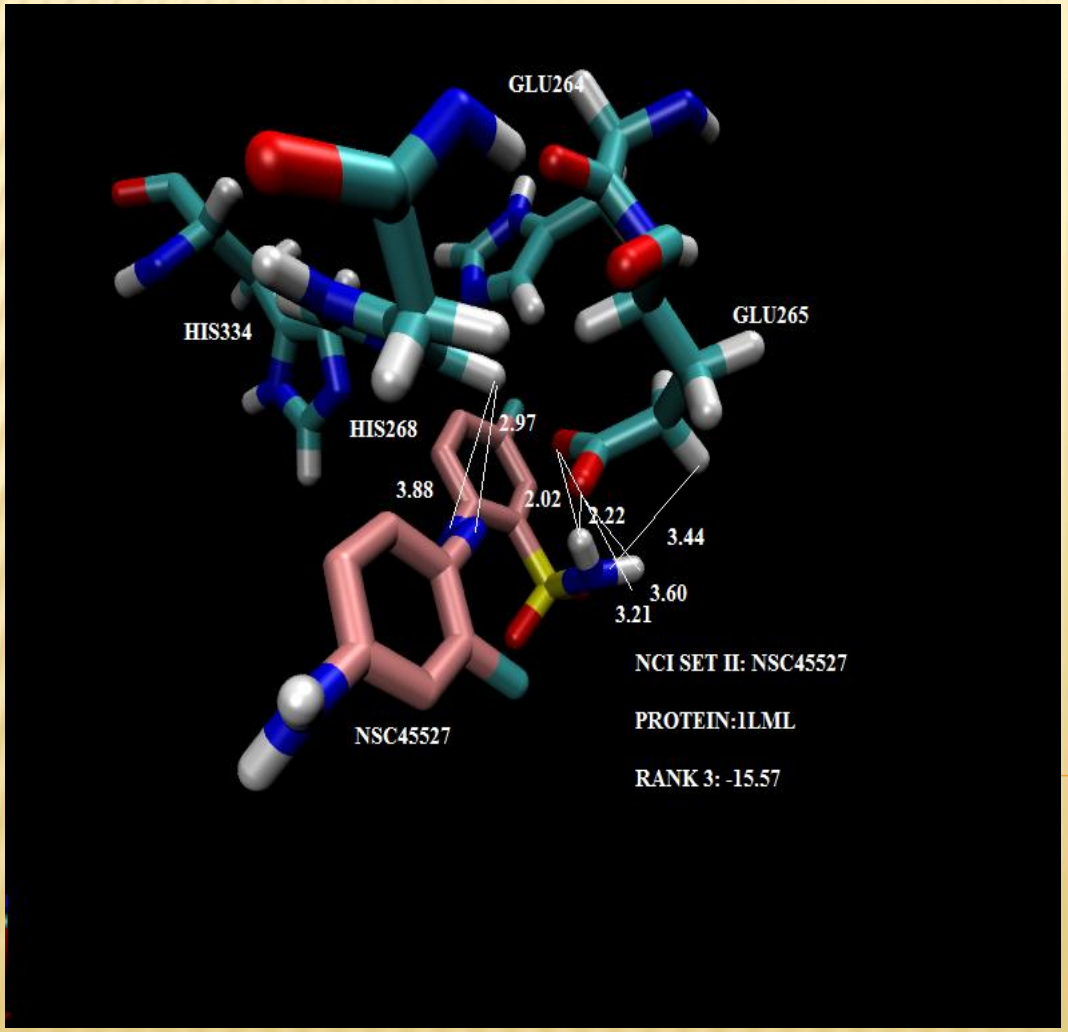


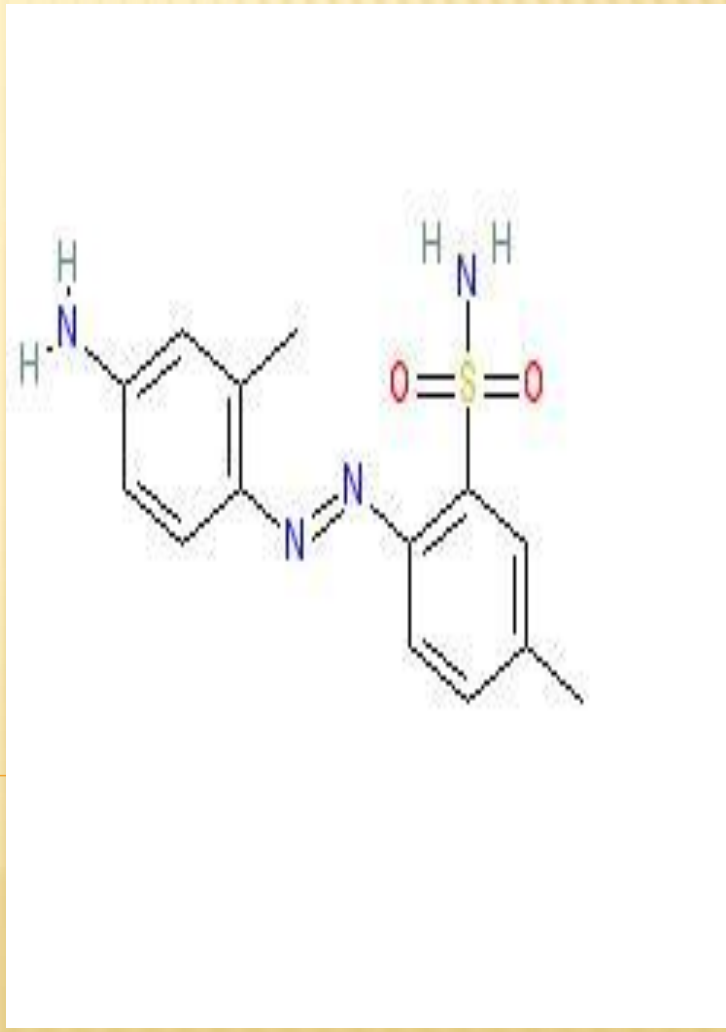


PROGRESS

Results:1LML Virtual Screening with NCI database

Rank 3: NSC45527 -15.57kcal

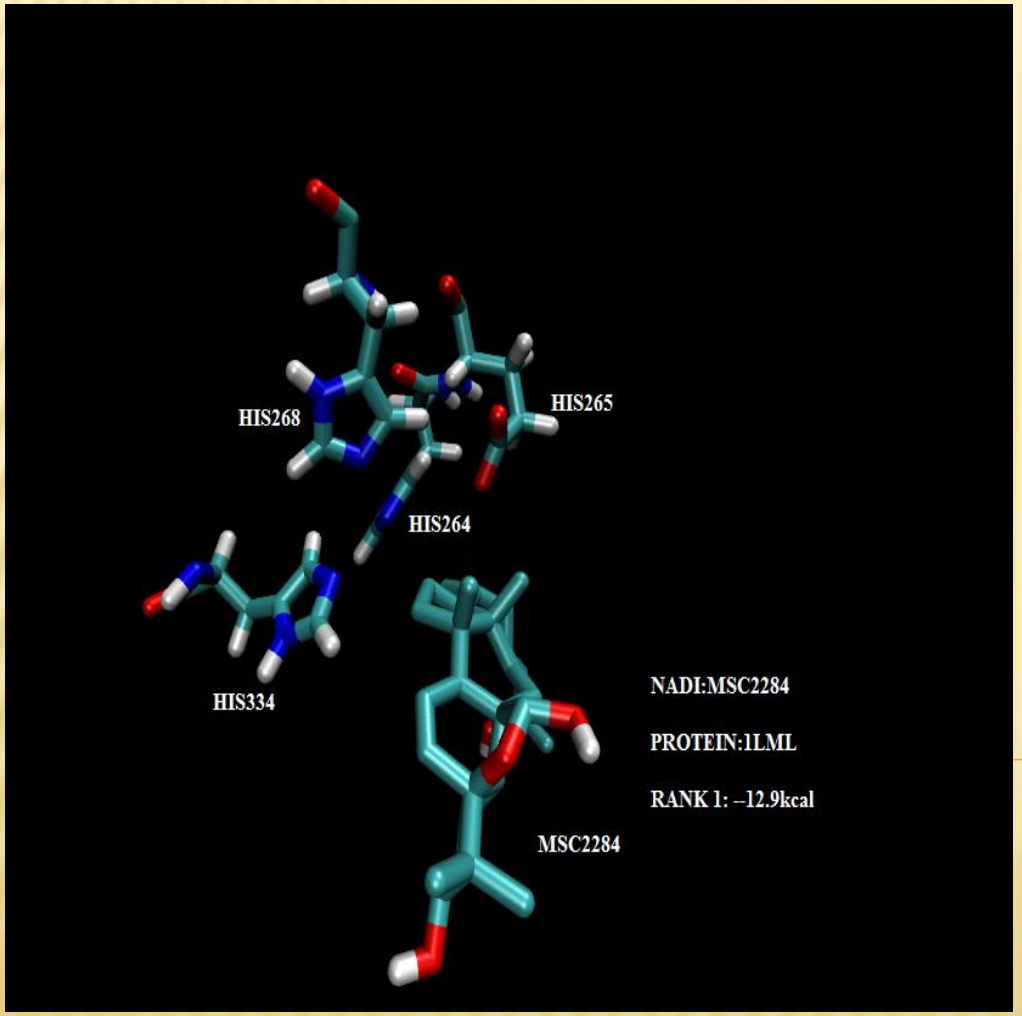


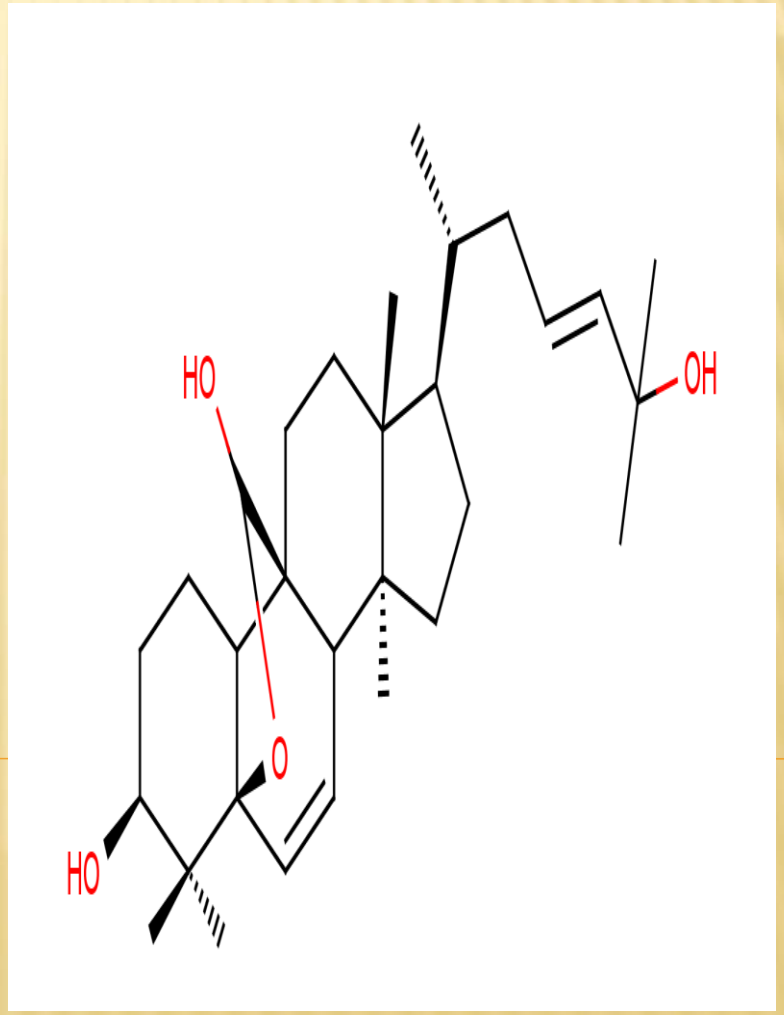


PROGRESS

Results:1LML Virtual Screening with NADI database

Rank 1: MSC2284 -12.9kcal

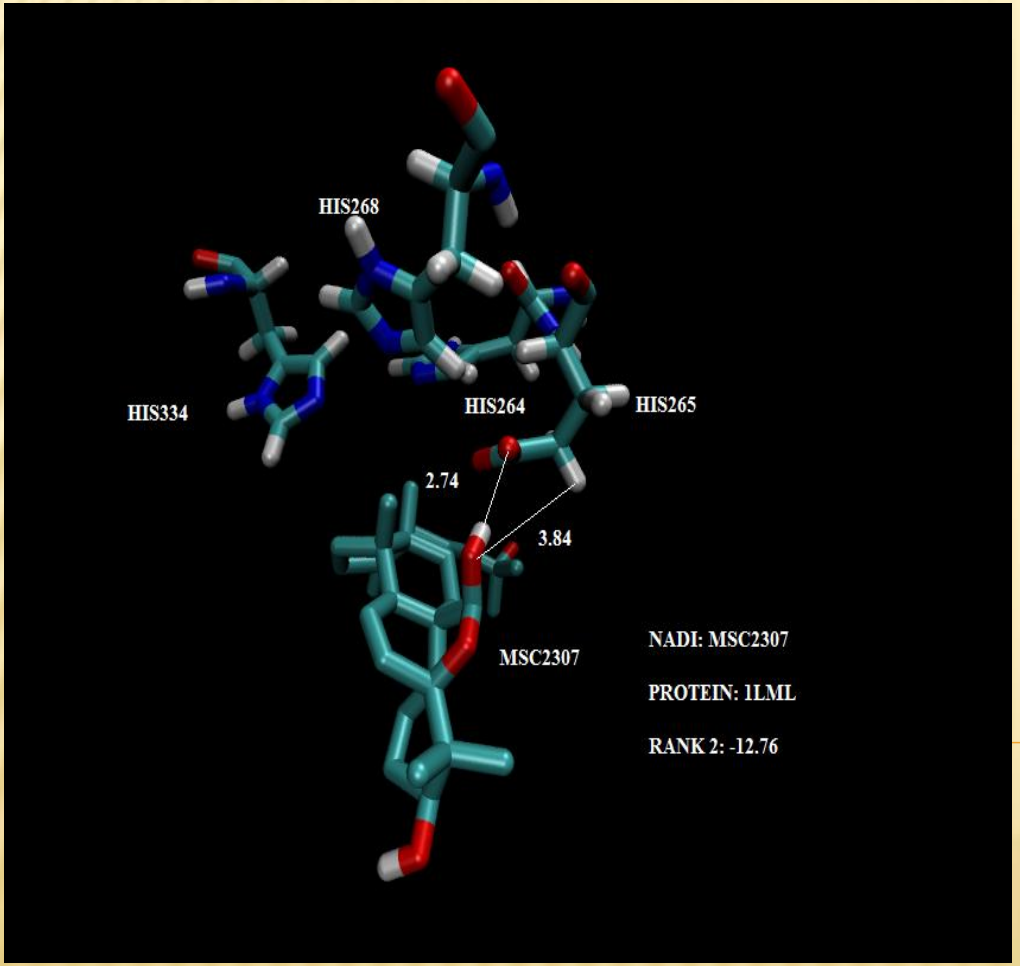


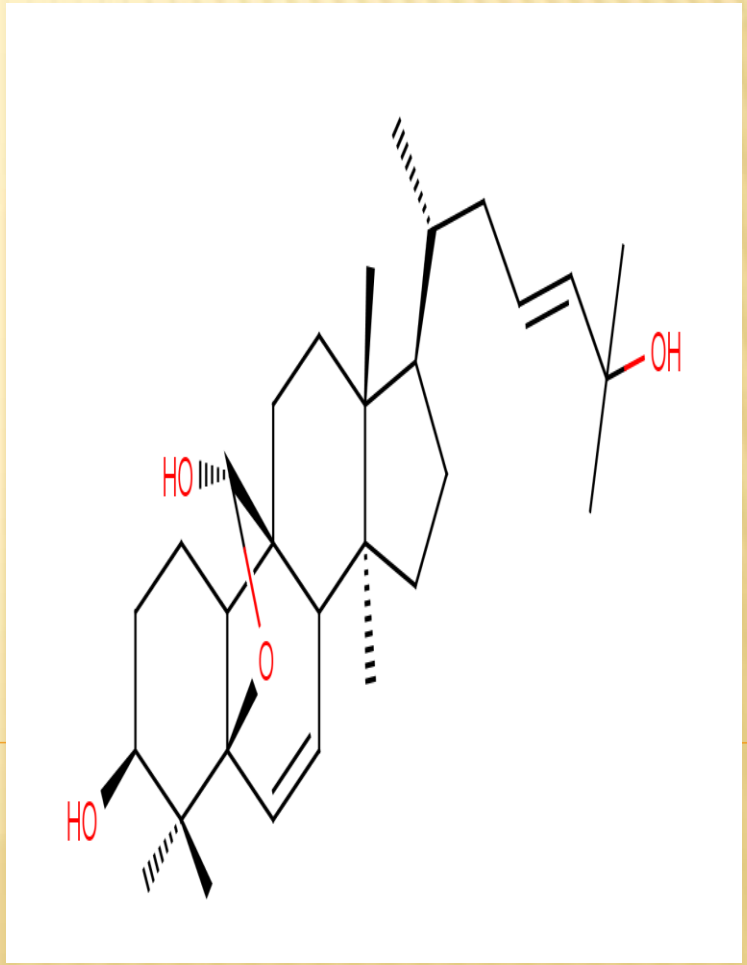


PROGRESS

Results:1LML Virtual Screening with NADI database

Rank 2: MSC2307 -12.76kcal

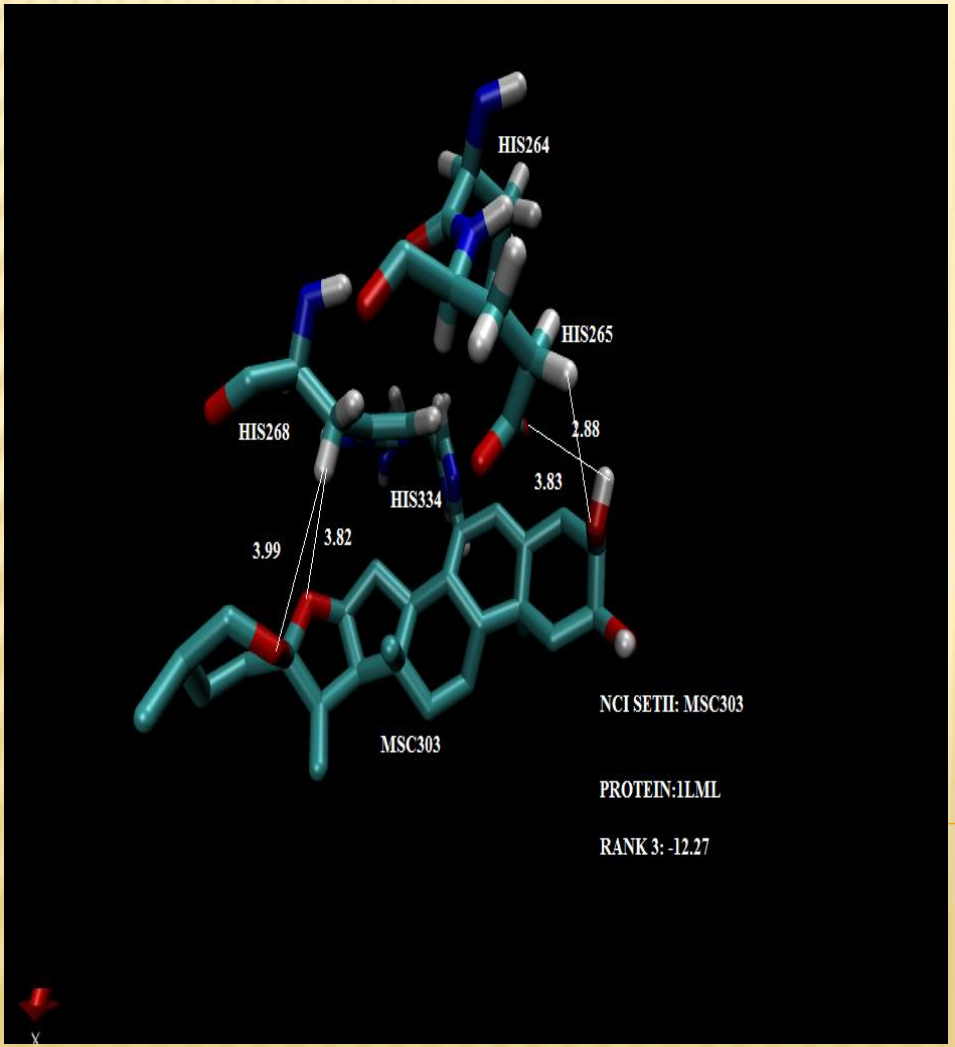


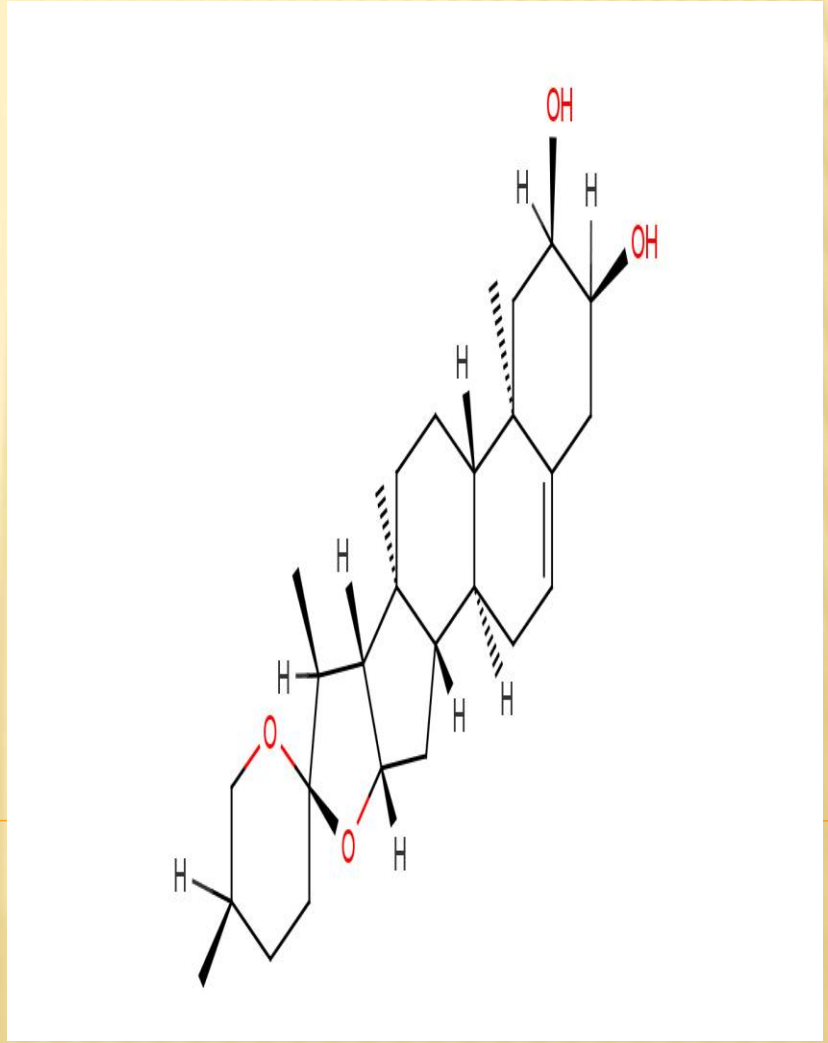


PROGRESS

Results:1LML Virtual Screening with NADI database

Rank 3: MSC155 -12.27kcal





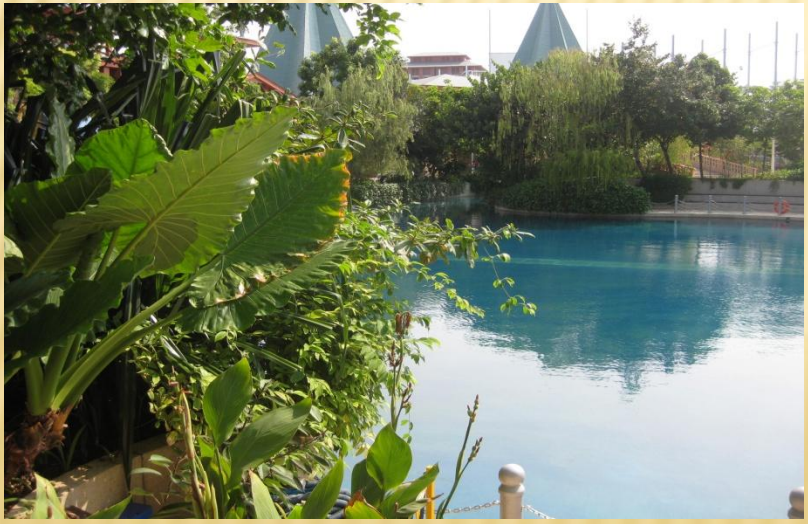
TENTATIVE PLANS

- Finalize the top 3 NADI and NCI promising compounds for each receptor
- Finish SMAP analysis
- Begin docking top compounds to receptor results from SMAP and visualize
- Write report to show mentors results of the screening and justifications for selected structures

SUCCESSES AND SETBACKS

- Problem with running SMAP, but was later fixed by Dr. Xie.

CULTURAL ASPECT



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