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

JLiang_Week8_2012

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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.

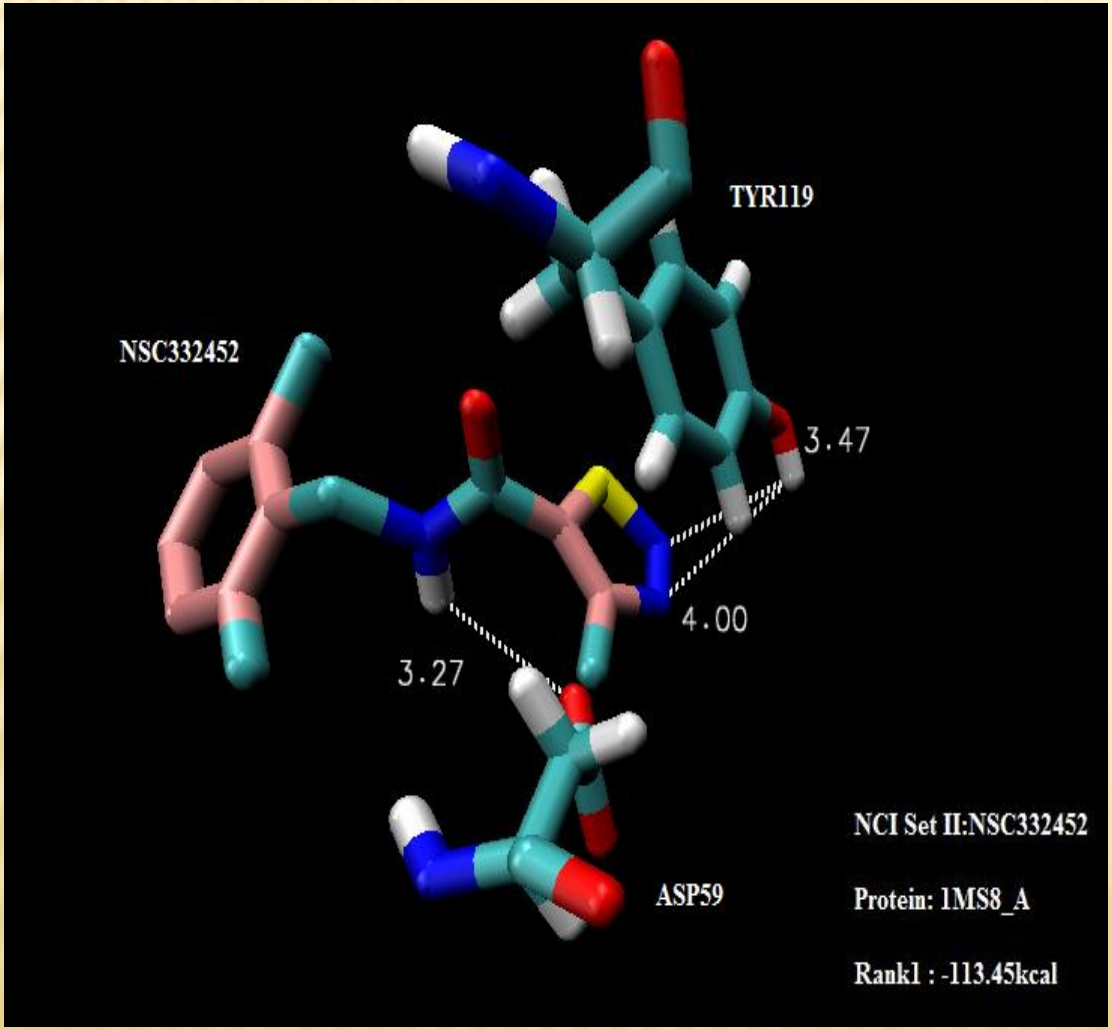
PROGRESS

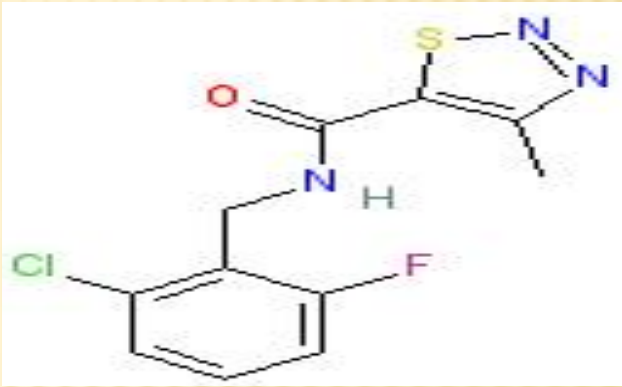
- Finished all virtual screenings and completed the last dockings for the top hits of each screening.
- Organized all data for analysis
- Ran SMAP for 1MS8 and waiting for results for 1LML
- Contacted developers of Modbase for homology models of the T. Cruzi proteome
- Looked at medicinal uses of top compounds from the screening to see if any relation to our targets
- Updated and improved all protein-ligand visualizations for presentation
- Finished draft of Final Report

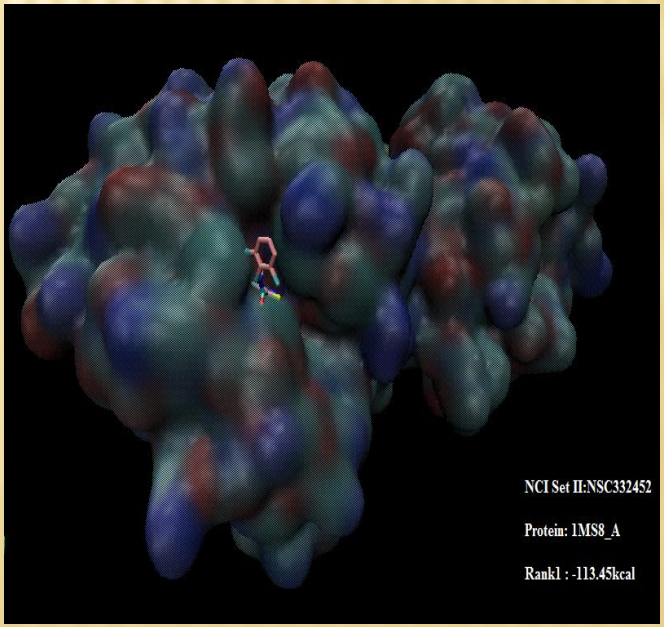
RESULTS

1MS8
NCI Diversity Set II

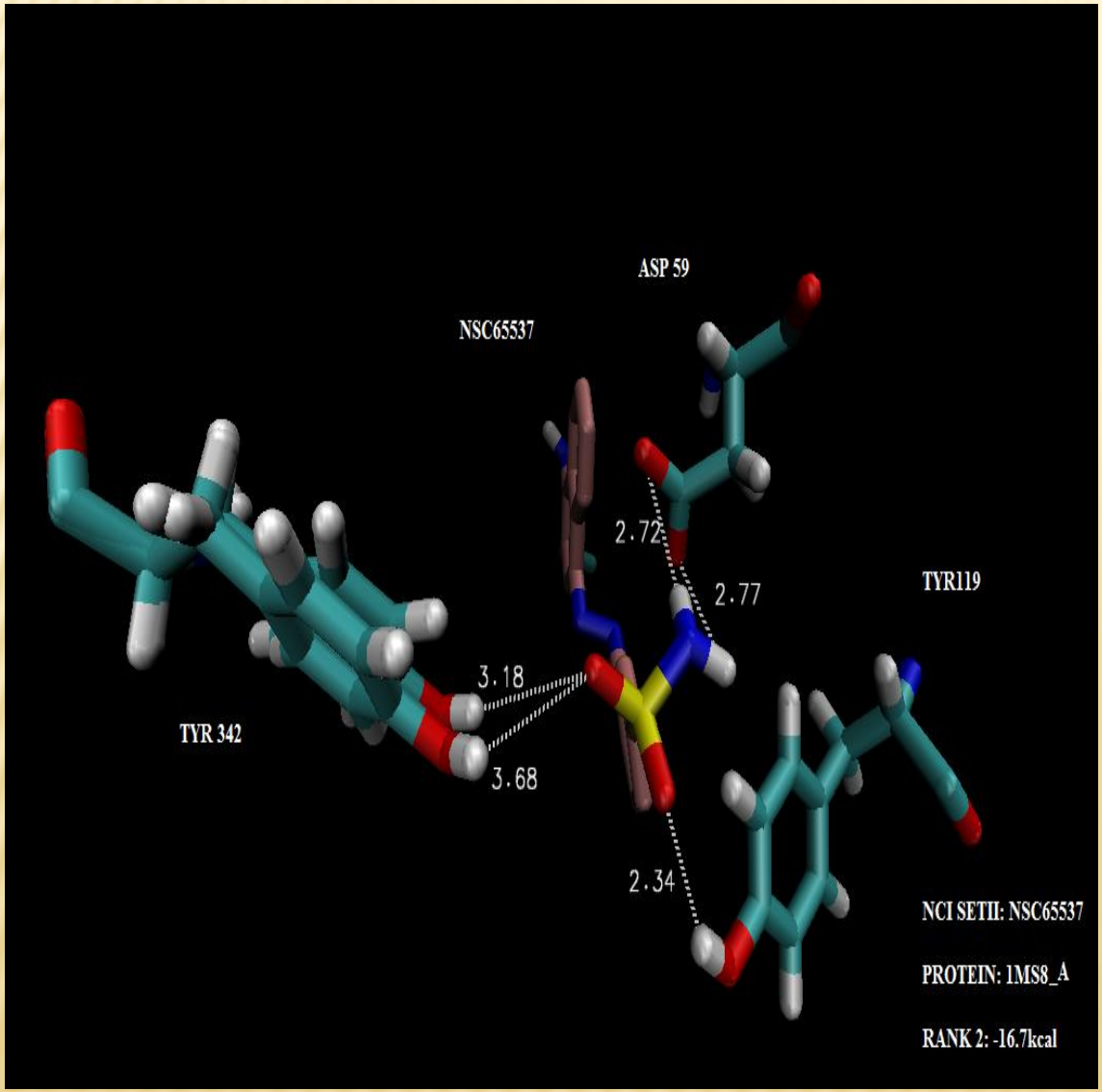
Rank 1: NSC332452 (N-(2-chloro-6-fluorobenzyl)methyl-1, 2, 3-thiadiazole-5-carboxamide)
Free Binding Energy: -113.45kcal

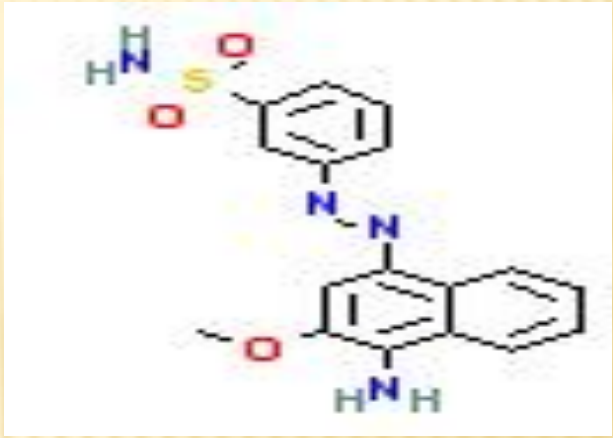


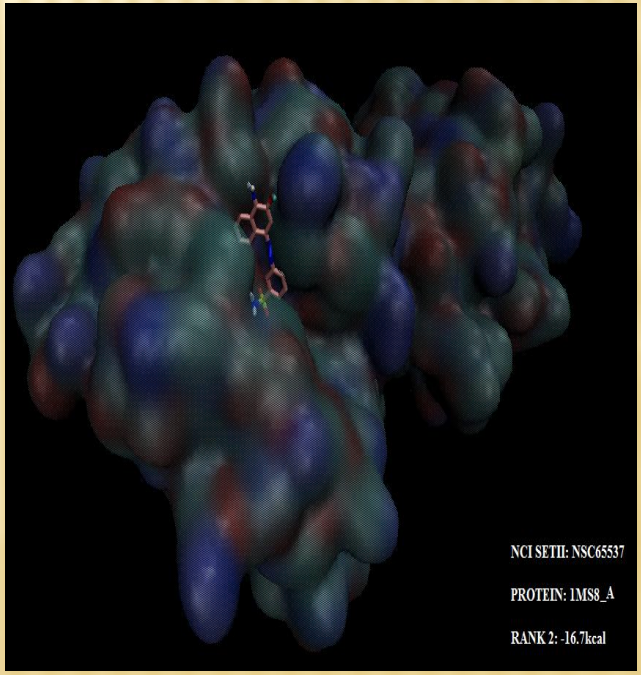




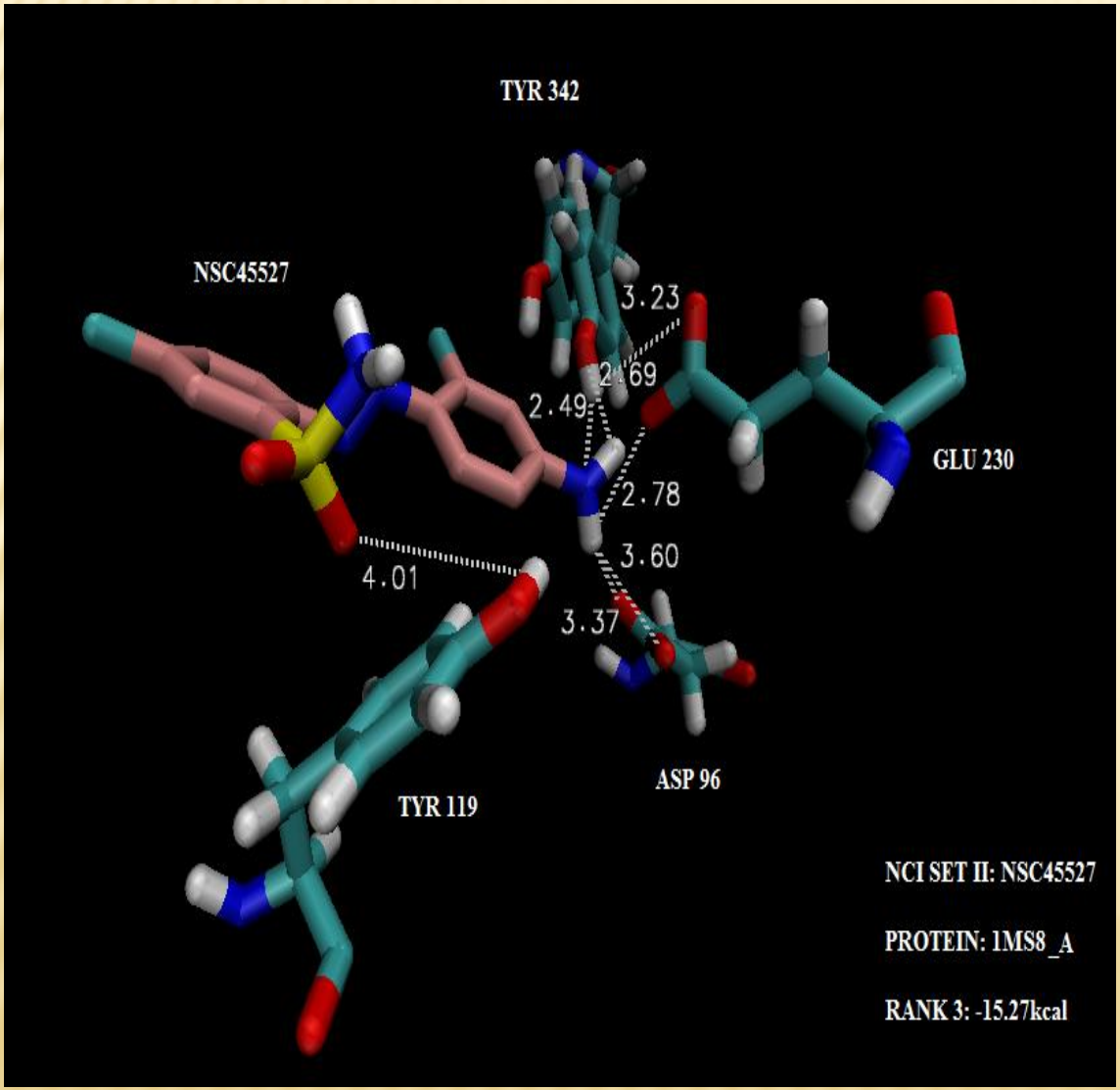
Rank 2: NSC65537 (3-((4-amino-3-methoxy-1-naphthyl)diazenyl)benzenesulfonamide)
Free Binding Energy: -16.70 kcal

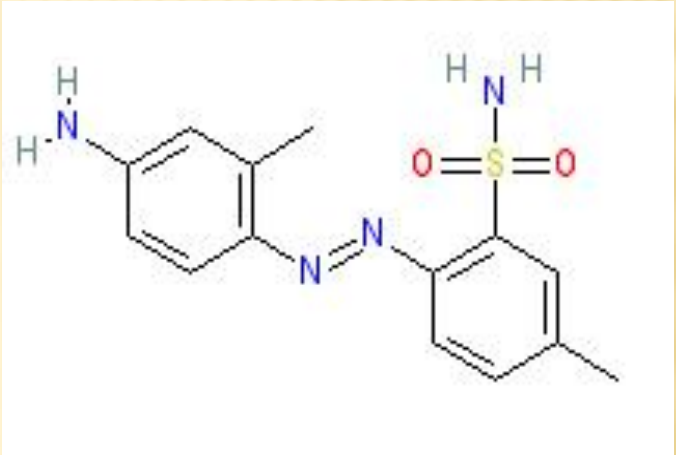


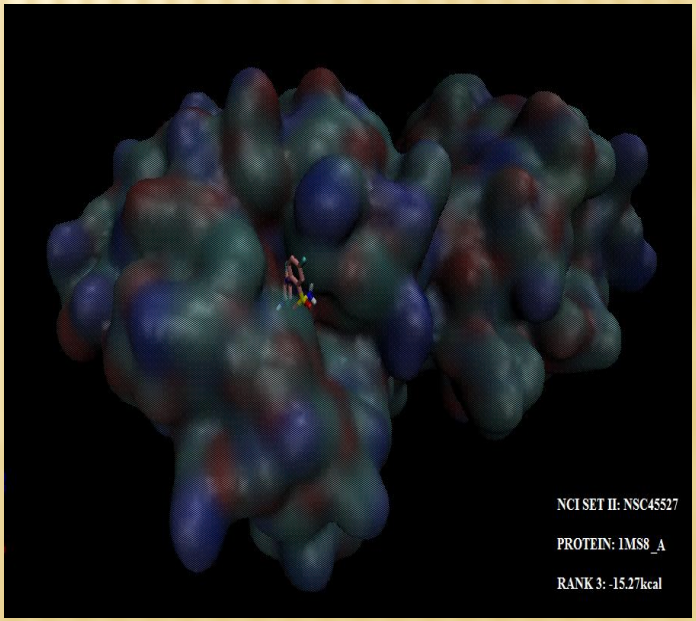




Rank 3: NSC45527 2-((4-amino-2-methylphenyl) diazenyl)-5-methylbenzenesulfonamide
Free Binding Energy: -15.27kcal



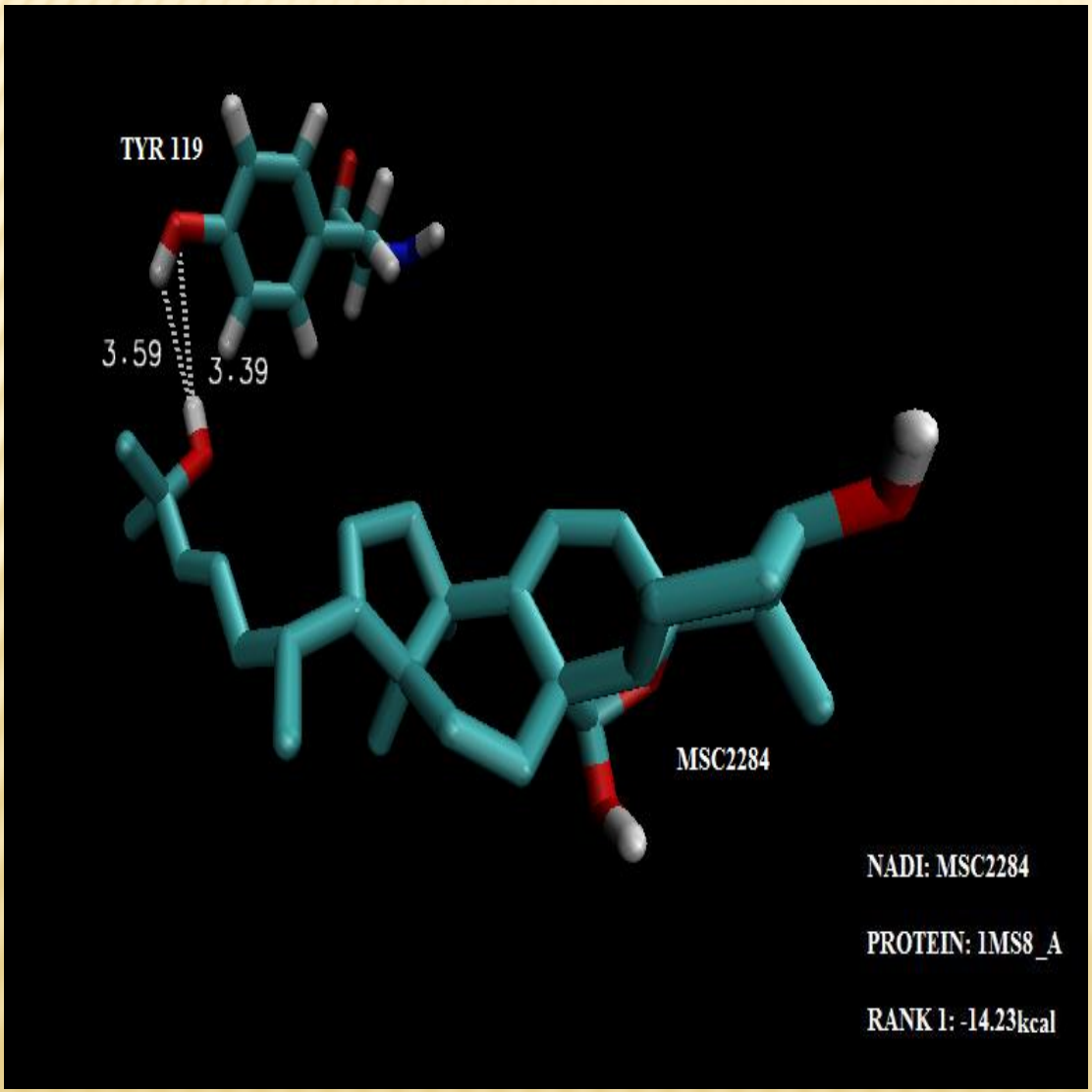


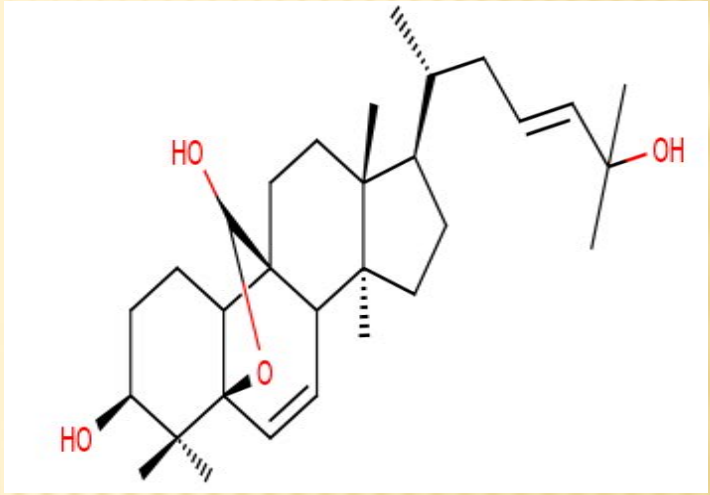


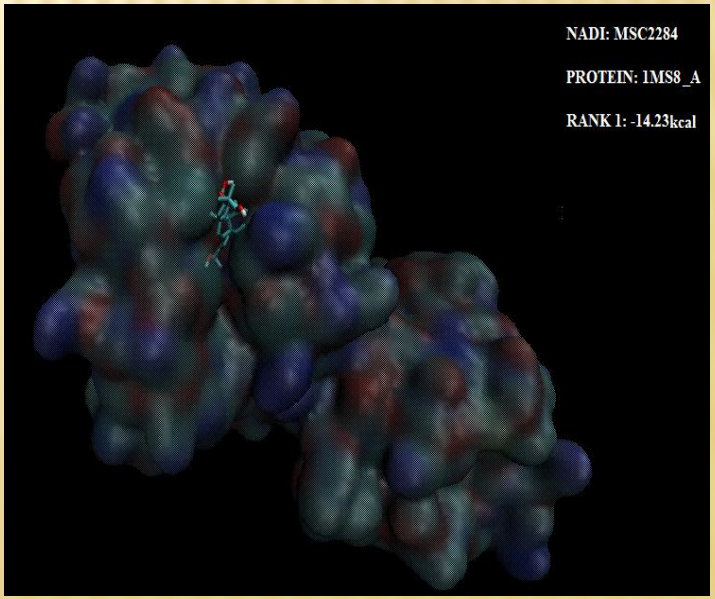
RESULTS

1MS8
NADI

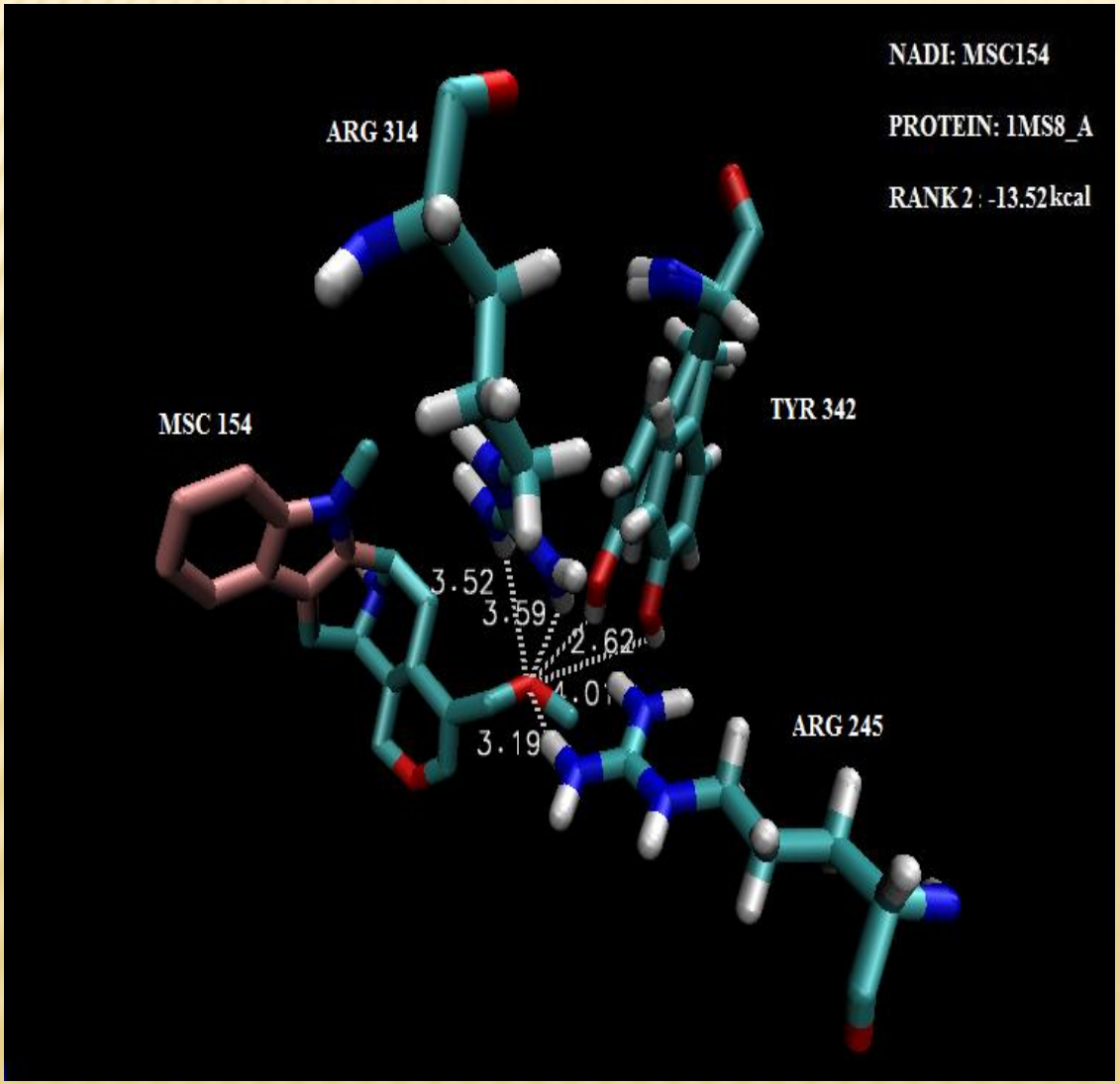
Rank 1:MSC2284, 5-beta-19-Epoxy-cucurbita-6-23(E)-diene-3-beta-19, 25-triol
Gourd of Momordica charantica
Free Binding Energy: -14.23kcal

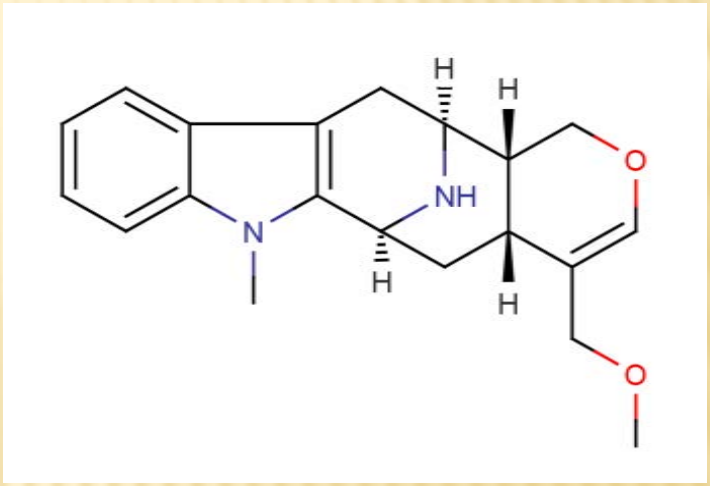


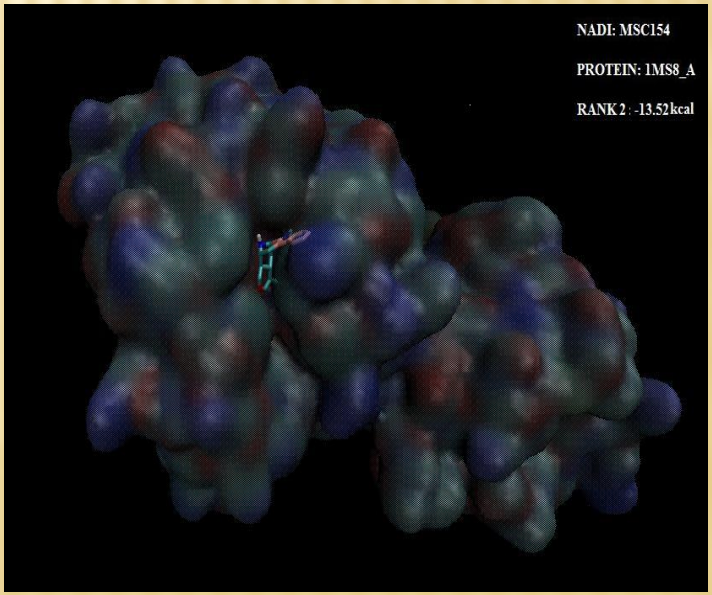




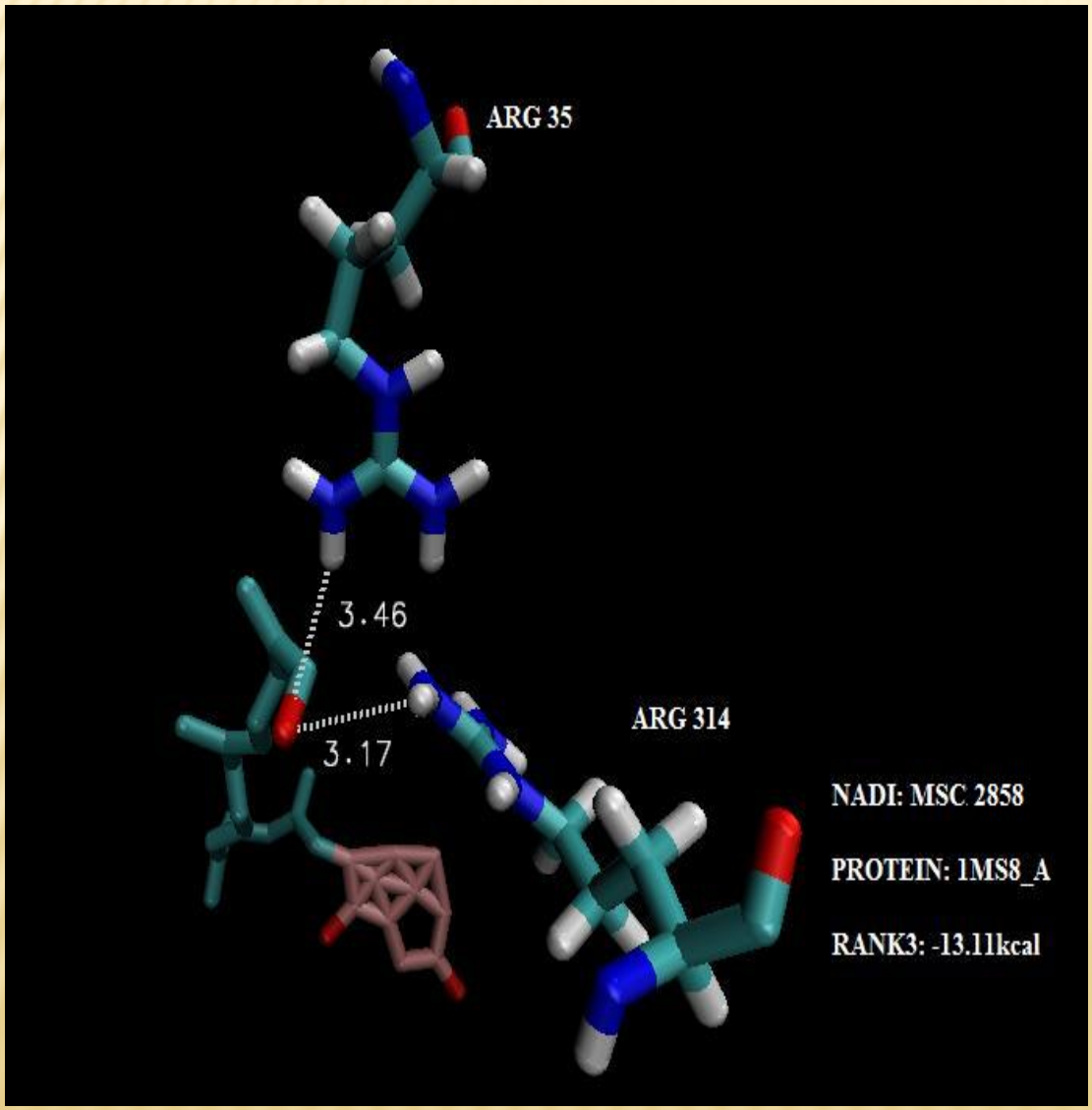
Rank 2: MSC154, N (4)-demethylalstonerine
Alstonia angustifolia leaf
Free Binding Energy:-13.52kcal

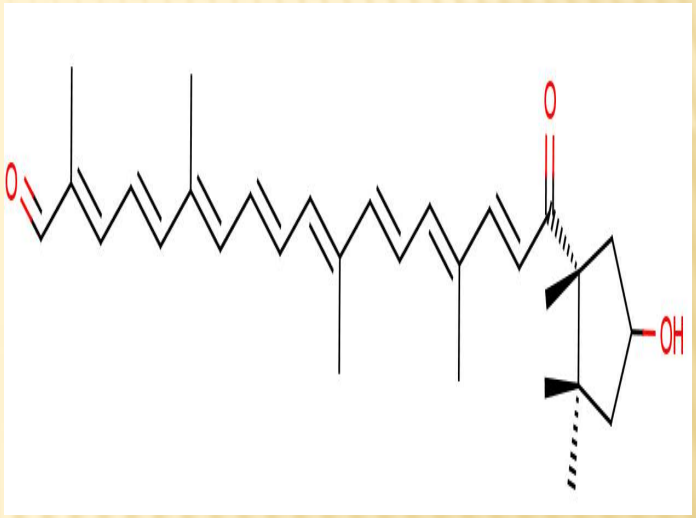


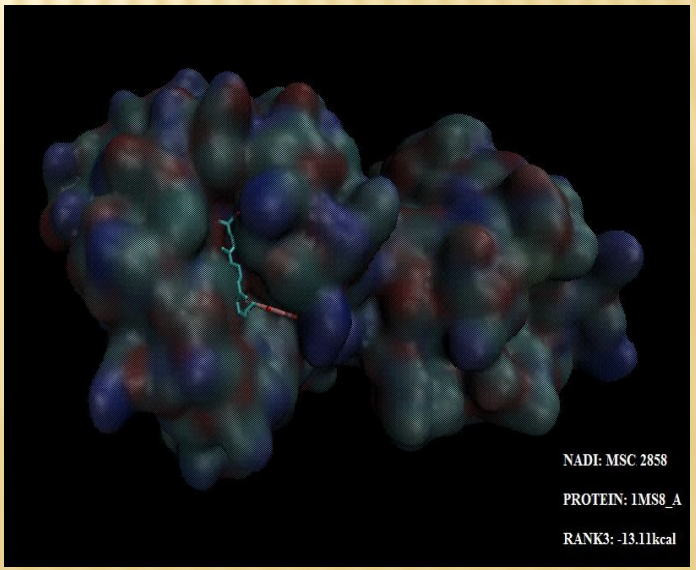




Rank 3: MSC2858, Capsorubinal
Fruit of Capsicum annum
Free Binding Energy:-13.11kcal



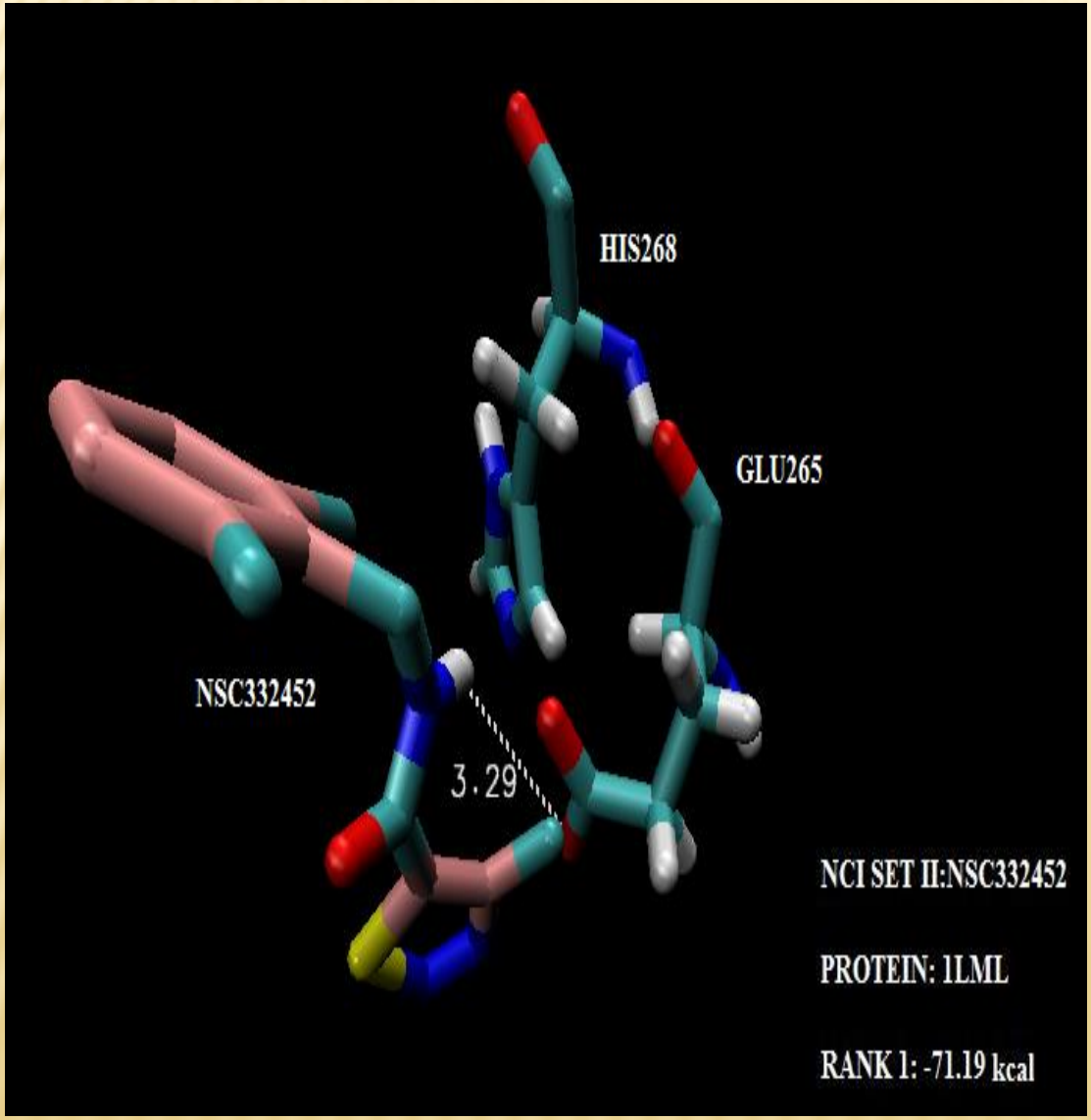


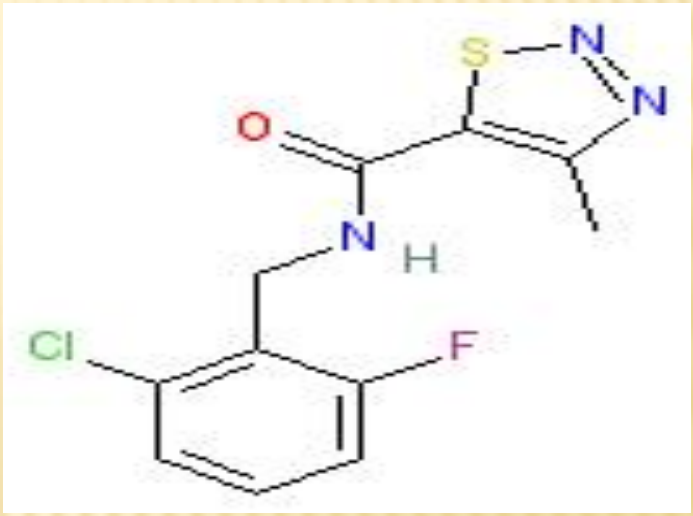


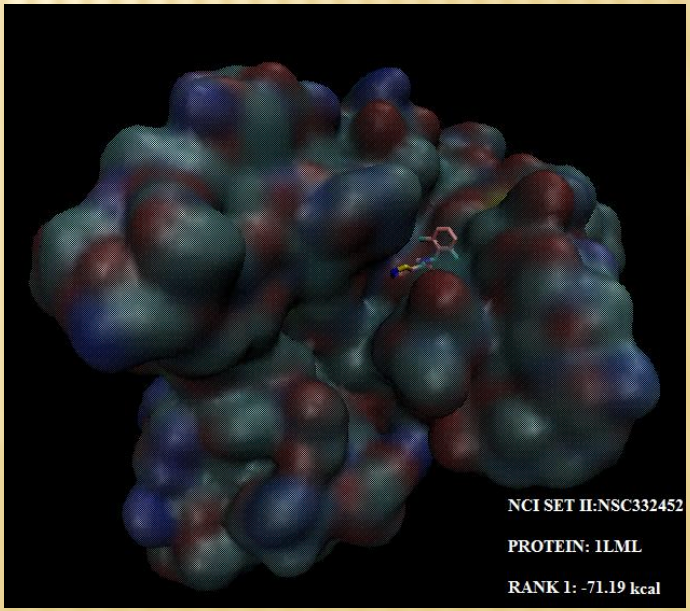
RESULTS

1LML
NCI DIVERSITY SET II

Rank 1: NSC332452, N-(2-chloro-6-fluorobenzyl)-4-methyl-1, 2, 3-thiadiazole-5-carboxamide
Free Binding Energy: -71.19kcal

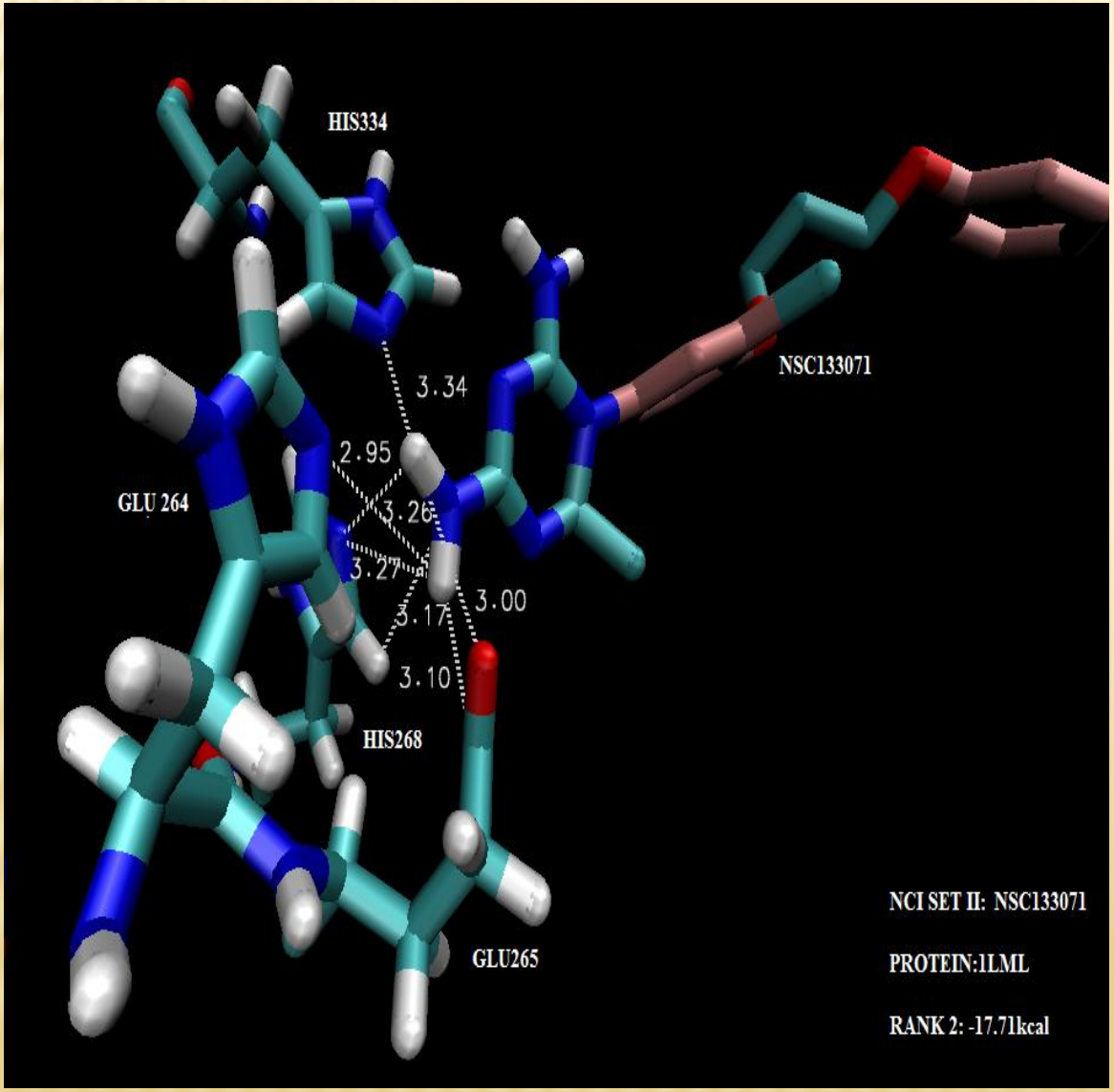


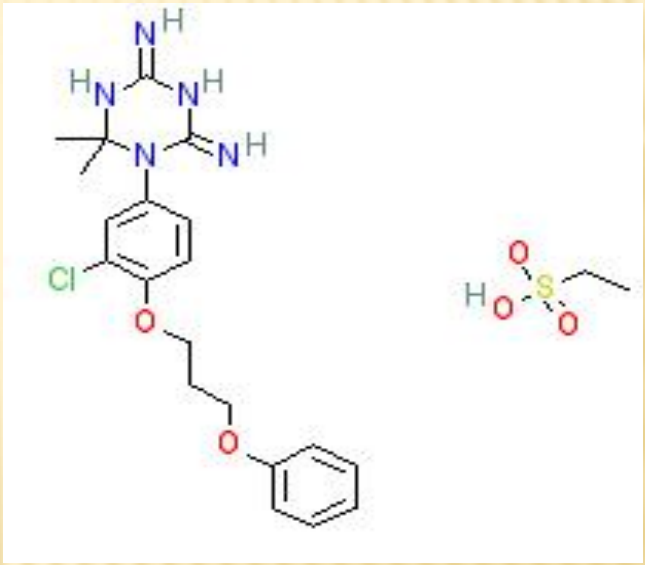


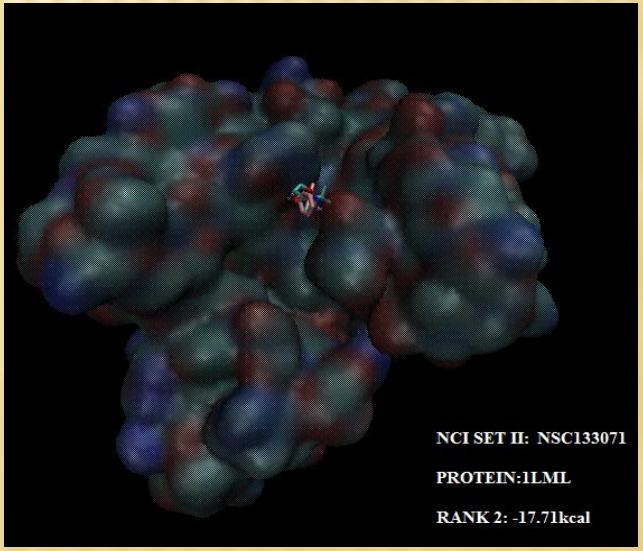


Rank 2: NSC133071, ethanesulfonic acid compound with 1-(3-chloro-4-(3-phenoxypropoxy) phenyl)-6, 6-dimethyl-1, 3, 5-triazinane-2, 4-diimine (1:1)

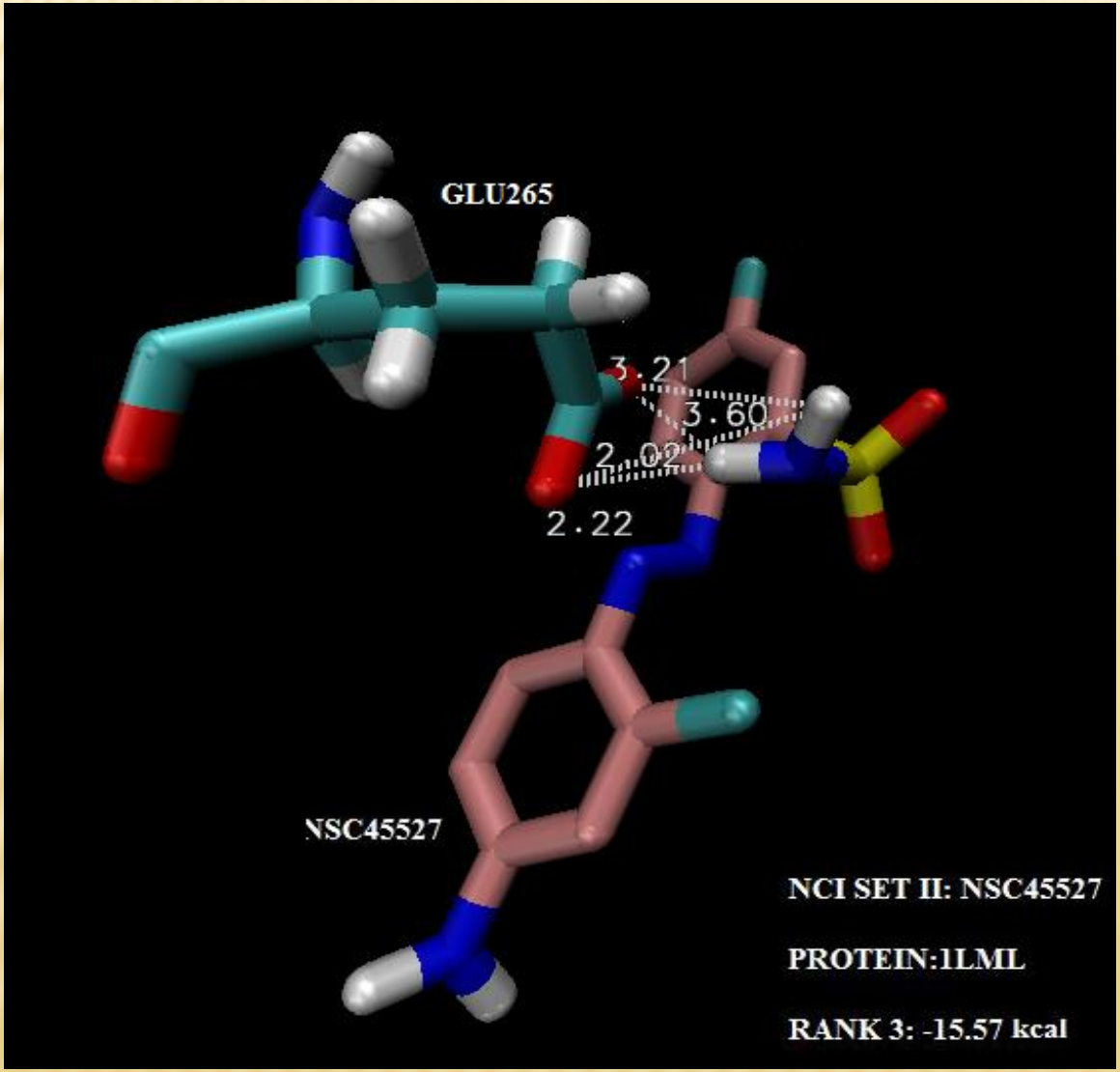
Free Binding Energy:-17.71kcal

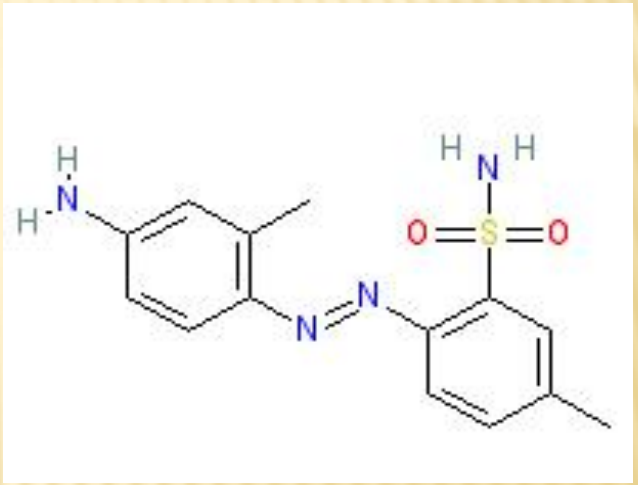


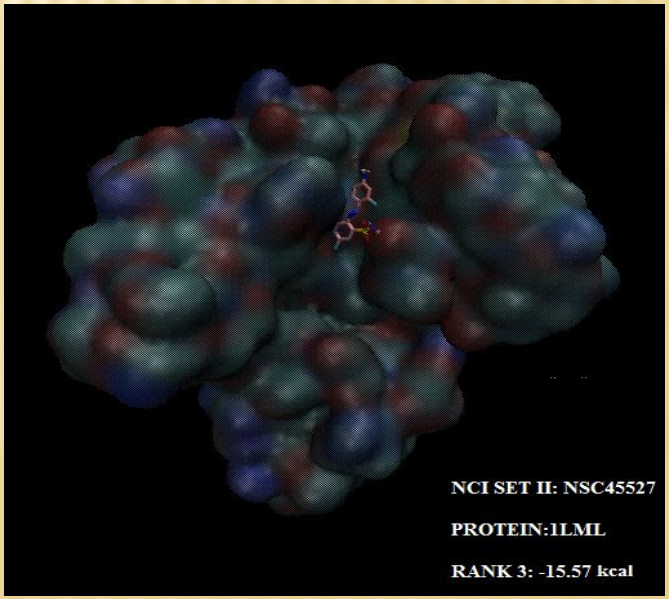




Rank 3: NSC45527, 2-((4-amino-2-methylphenyl)diazenyl)-5-methylbenzenesulfonamide
Free Binding Energy: -15.57kcal



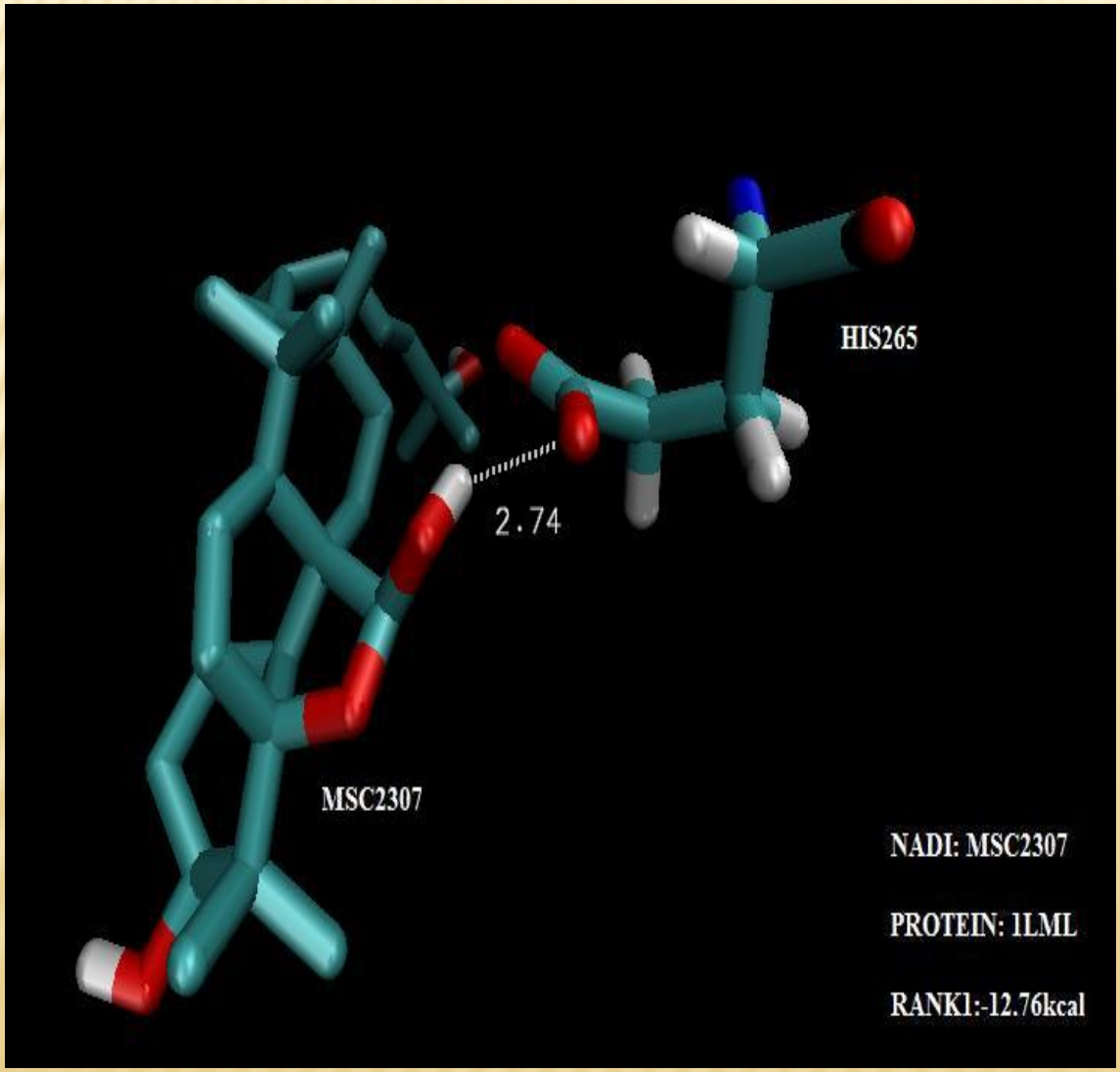


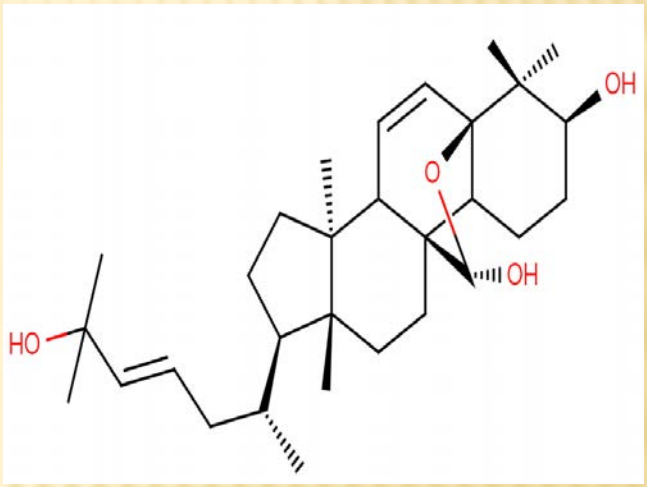


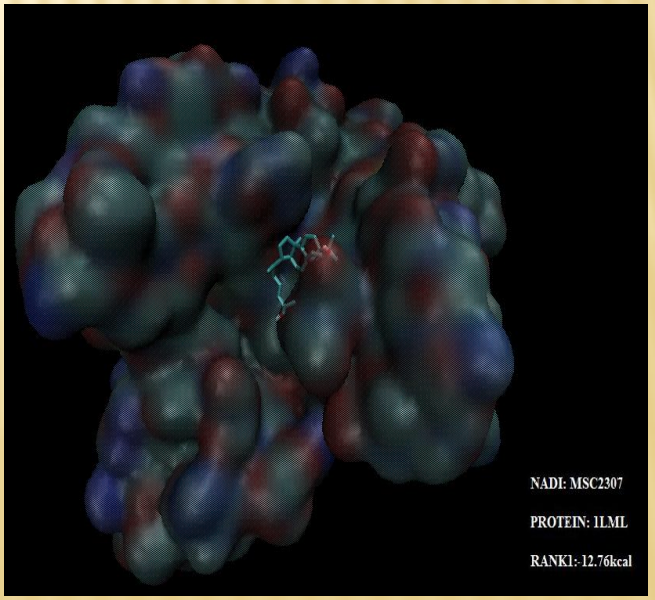
RESULTS

1LML
NADI

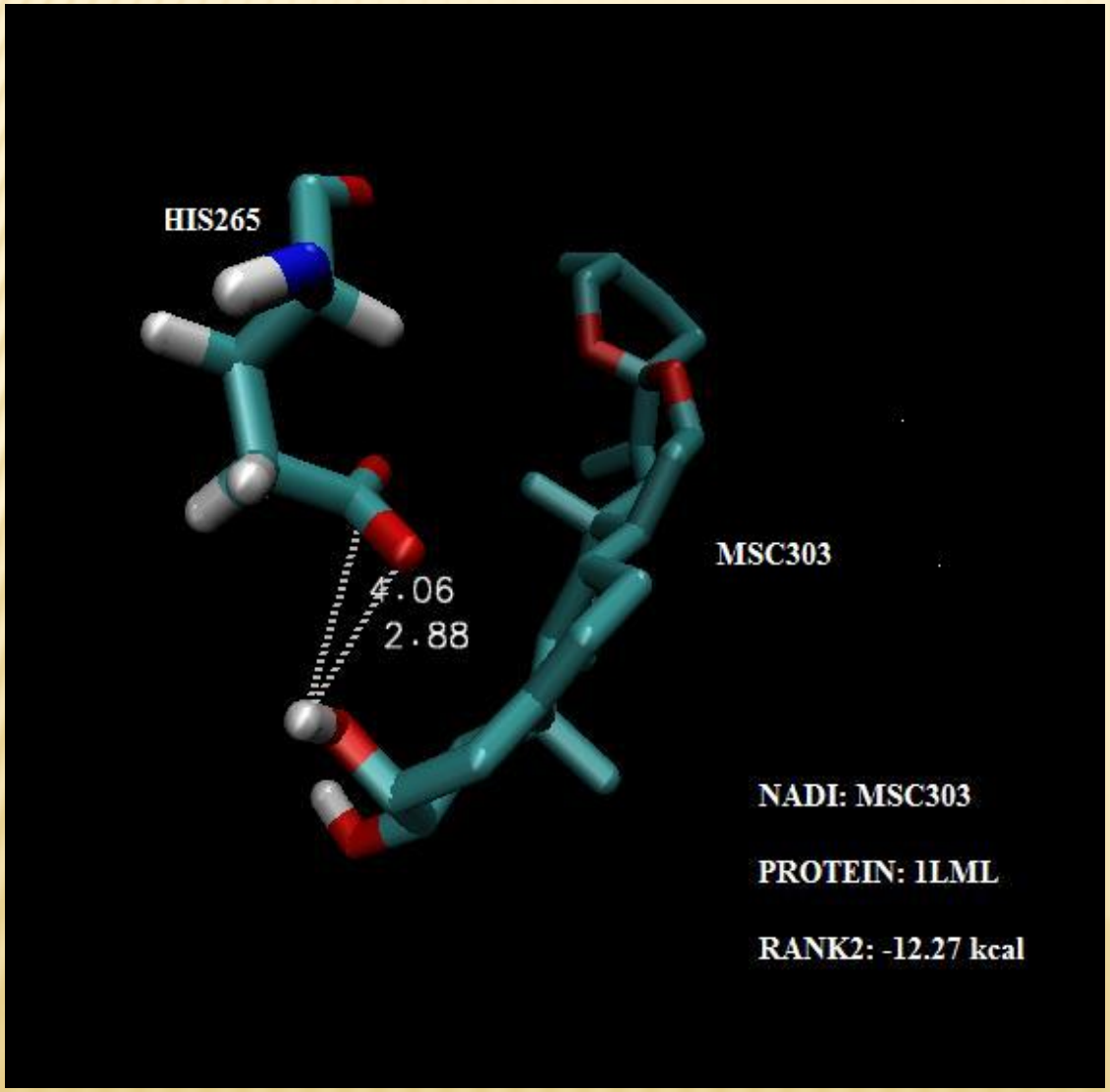
Rank 1: MSC2307, Kuguacin R
Leaf/Vine of Momordica charantica
Free Binding Energy: -12.76kcal

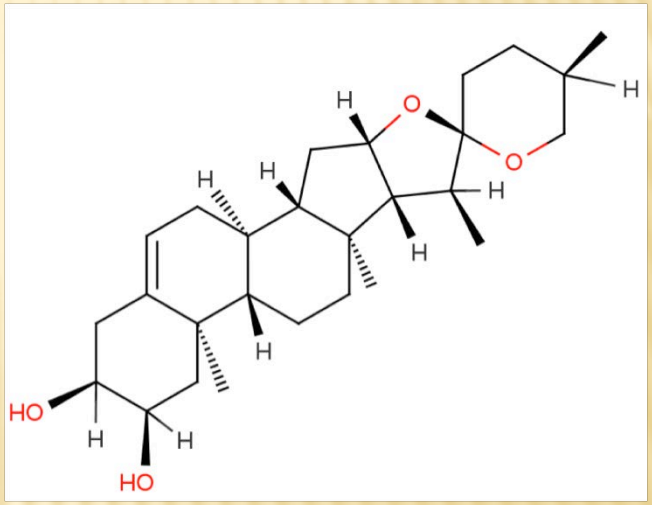


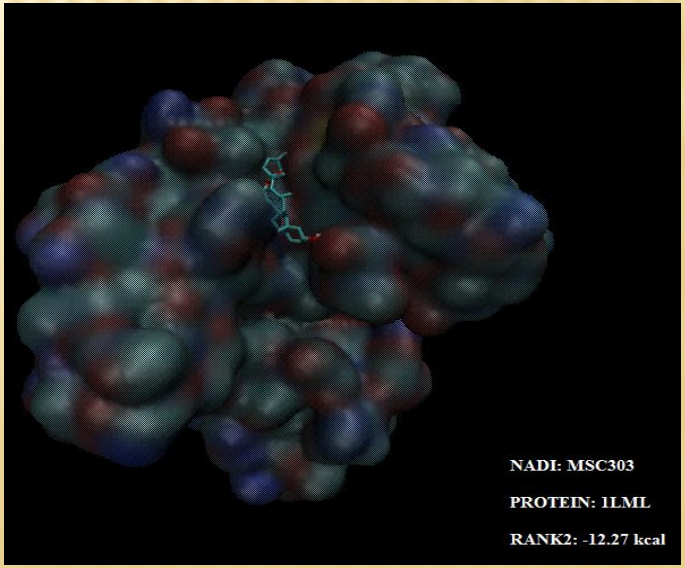




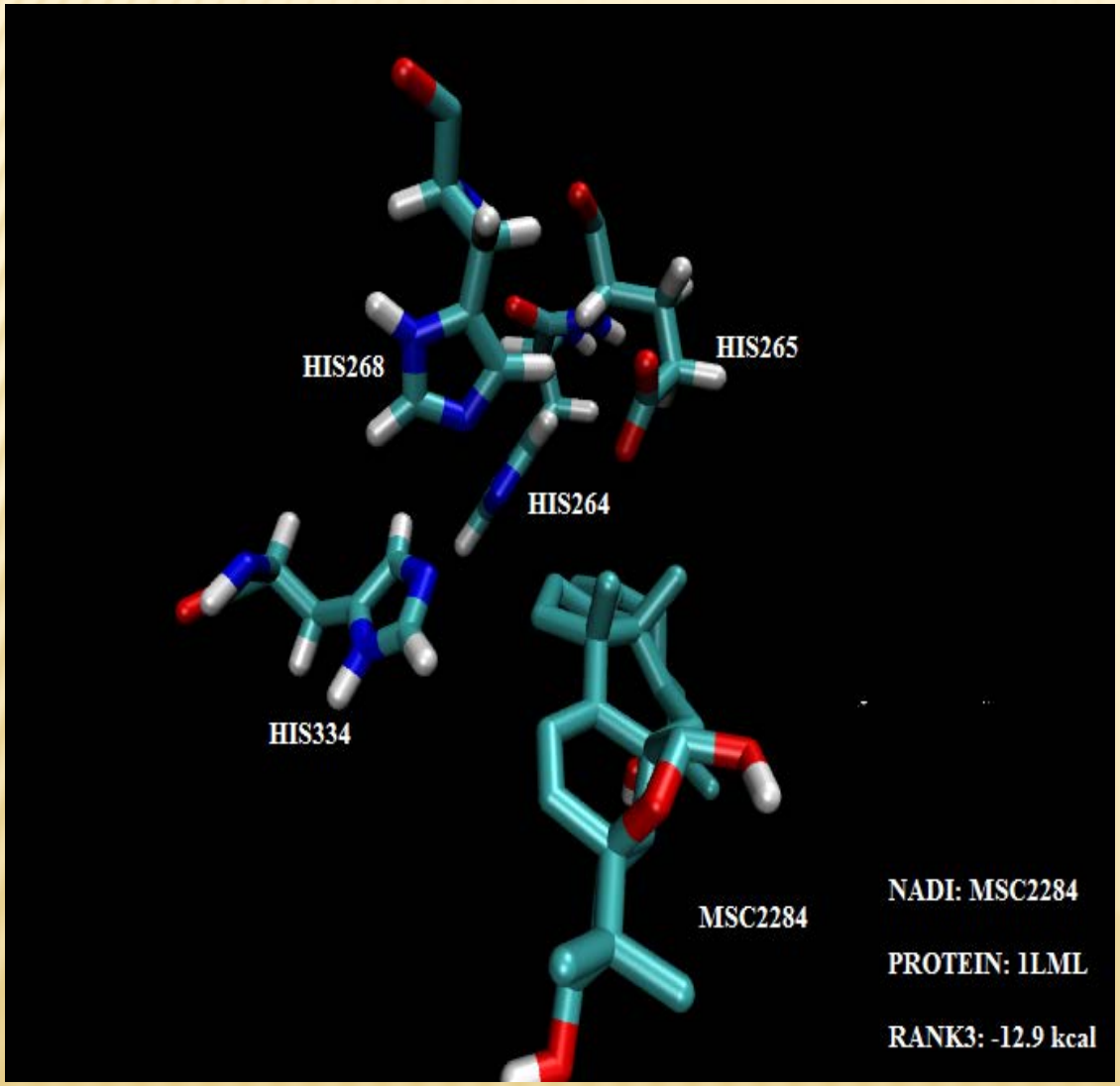
Rank 2: MSC303, Yuccagenin
Seed of Psophocarpus tetragonolobus
Free Binding Energy: -12.27kcal

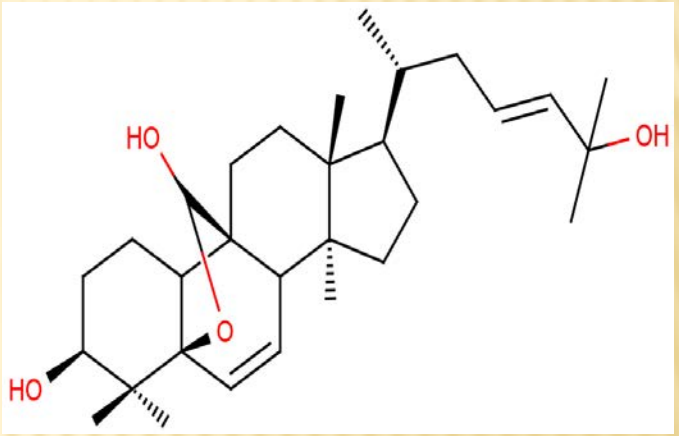






Rank 3:MSC2284, 5-beta-19-Epoxy-cucurbita-6-23(E)-diene-3-beta-19, 25-triol
Gourd of Momordica charantica
Free Binding Energy:-12.9kcal





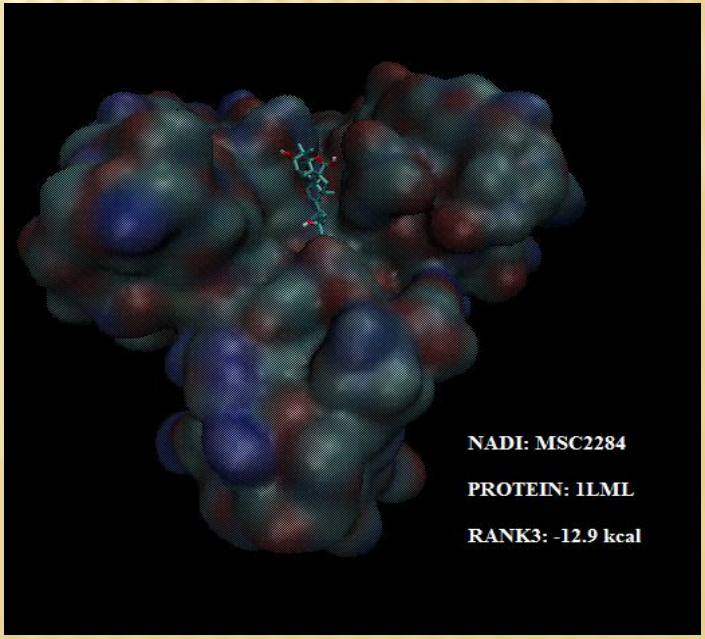


Table 1a. Output results ranked by only free binding energy (100RUNS)

	NCI	NADI
1MS8	1.NSC332452 -113.45 kcal 2.NSC65537 -16.70 kcal 3.NSC45527 -15.27 kcal 4.NSC114449 -14.88 kcal 5.NSC120290 -14.50 kcal 6.NSC3753 -13.88 kcal 7.NSC121861 -13.78 kcal 8.NSC49852 -13.71 kcal 9.NSC30663 -13.67 kcal 10.NSC133071 -13.66 kcal	1.MSC2284 -14.23 kcal 2.MSC154 -13.52 kcal 3.MSC155 -13.38 kcal 4.MSC2858 -13.11 kcal 5.MSC853 -13.03 kcal 6.MSC598 -13.02 kcal 7.MSC1645 -12.95 kcal 8.MSC385 -12.92 kcal 9.MSC2252 -12.89 kcal 10.MSC650 -12.87 kcal
1LML	1.NSC332452 -71.19 kcal 2.NSC133071 -17.71 kcal 3.NSC45527 -15.57 kcal 4.NSC114449 -15.35 kcal 5.NSC65537 -15.05 kcal 6.NSC120290 -14.85 kcal 7.NSC70959 -14.82 kcal 8.NSC71033 -14.41 kcal 9.NSC310365 -13.52 kcal 10.NSC96021 -13.48 kcal	1.MSC2284 -12.90 kcal 2.MSC2307 -12.76 kcal 3.MSC303 -12.27 kcal 4.MSC377 -11.97 kcal 5.MSC302 -11.81 kcal 6.MSC299 -11.52 kcal 7.MSC2246 -11.41 kcal 8.MSC2235 -11.31 kcal 9.MSC2283 -11.25 kcal 10.MSC91 -11.22 kcal

Table 1b. Final promising hits ranked by free binding energy and hydrogen bonding between protein and compounds (100 RUNS)

	NCI	NADI
1MS8	1.NSC332452 -113.45 kcal 2.NSC65537 -16.70 kcal 3.NSC45527 -15.27 kcal	1.MSC2284 -14.23 kcal 2.MSC154 -13.52 kcal 3.MSC2858 -13.11 kcal
1LML	1.NSC332452 -71.19 kcal 2.NSC133071 -17.71 kcal 3.NSC45527 -15.57 kcal	1.MSC2307 -12.76 kcal 2.MSC303 -12.27 kcal 3.MSC2284 -12.90 kcal

Table 1c. Results of 1000 runs with top three ligands of each database with 1MS8 and 1LML

	NCI	NADI
1MS8	1.NSC332452 -115.31 kcal 2.NSC65537 -17.49 kcal 3.NSC45527 -16.01 kcal	1.MSC2284 -15.25 kcal 2.MSC154 -13.87 kcal 3.MSC2858 -13.27 kcal
1LML	1.NSC332452 -74.04 kcal 2.NSC133071 -19.65 kcal 3.NSC45527 -16.19 kcal	1.MSC2307 -13.32 kcal 2.MSC303 -12.41 kcal 3.MSC2284 -13.70 kcal

SMAP RESULTS

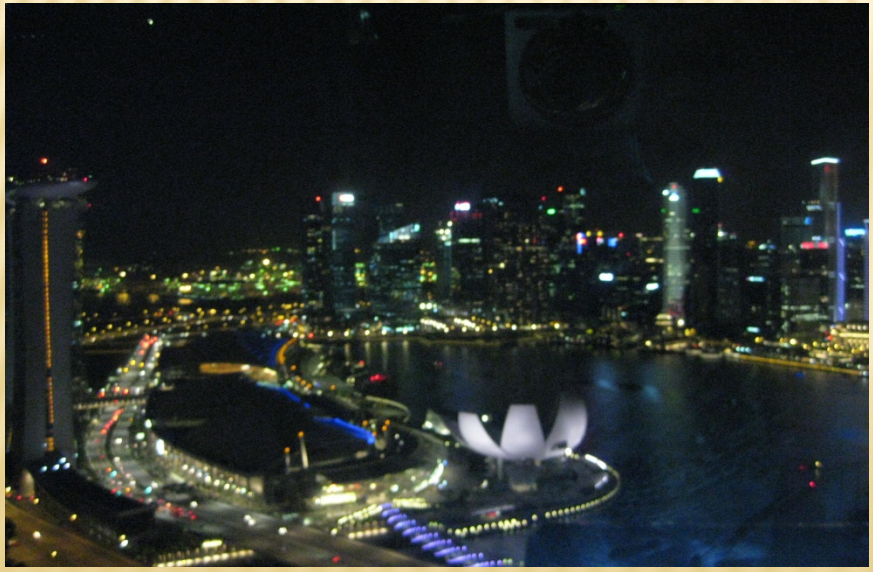
Only results that were below the cutoff were other T-Cruzi Trans-sialidase crystal structures.

A better representation of the T.Cruzi proteome is needed. Developers of Modbase were contacted for access to homology models of the T. Cruzi proteome

TENTATIVE PLANS

- Finish Final Report
- Follow up on the homology structures request
- Once a better representation of the proteome is obtained, continue with docking promising hits of the virtual screening to significantly similar protein matches.

CULTURAL ASPECT



ACKNOWLEDGEMENTS

UCSD PRIME

- Dr. Gabriele Wienhausen, Dr. Peter Arzberger, Teri Simas, Tricia Taylor

University of California, San Diego

- Dr. Philip Bourne, Dr. Li Xie and Chirag Krishna

Universiti Sains Malaysia

- Dr. Habibah Wahab and Dr. Sy Bing Choi

National Science Foundation, IOSE-0710726

Tosh Nomura Eureka! Scholarship