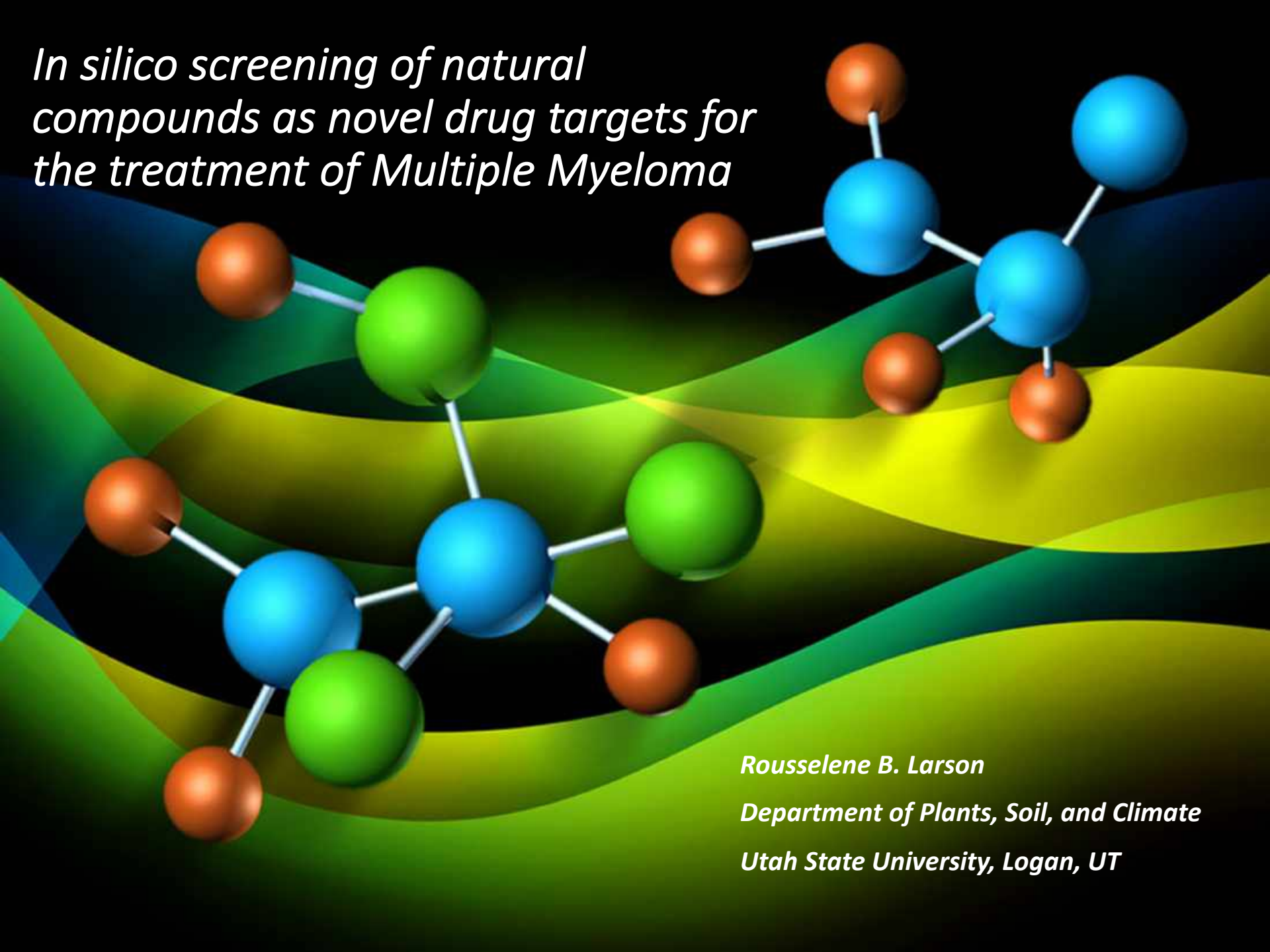
In silico screening of natural compounds as novel drug targets for the treatment of Multiple Myeloma



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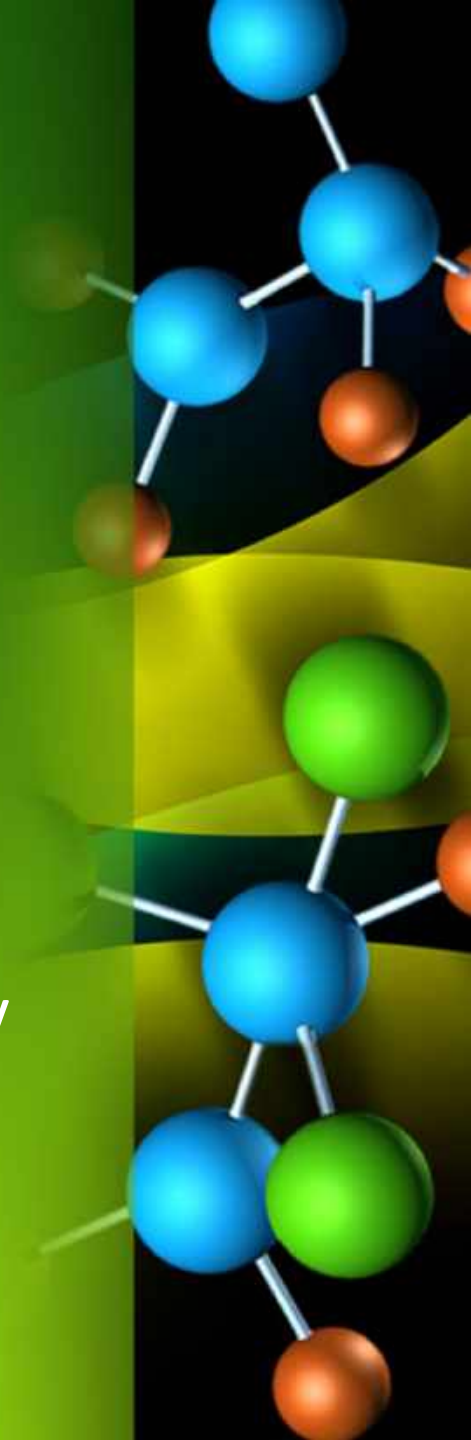
Objective

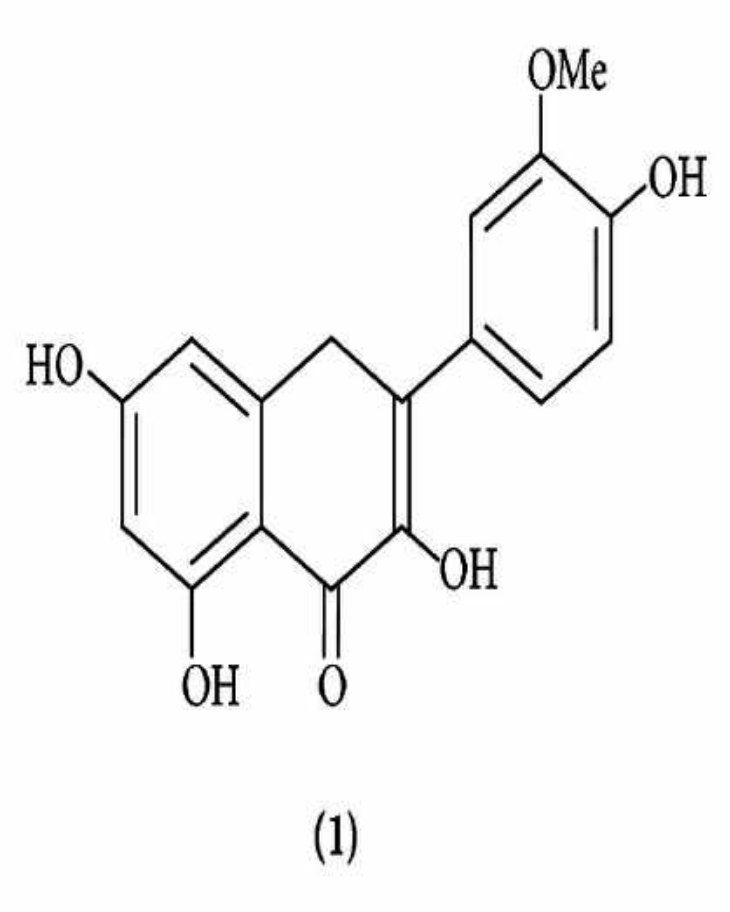
- Understanding the need for therapeutics.
- Benefits of natural products.
- Docking methods used for predictions models.
- Models used to predict and prioritize natural products for therapeutics.

Natural compounds

Plant natural products have been intensively investigated during the past decades with a considerable amount of generated data.

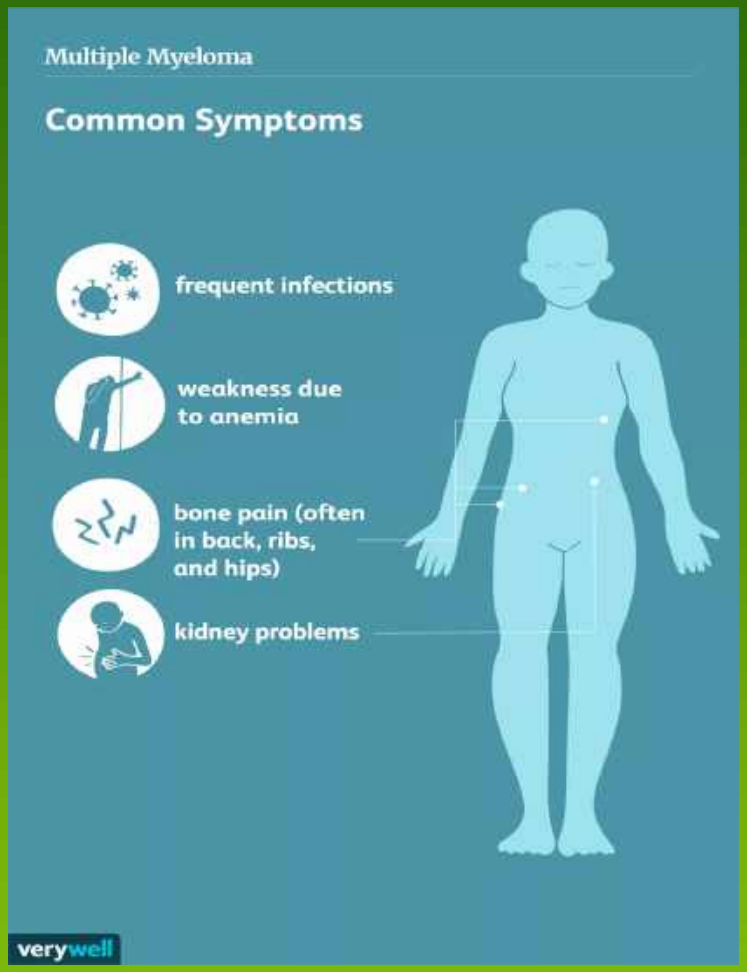


Natural Compound



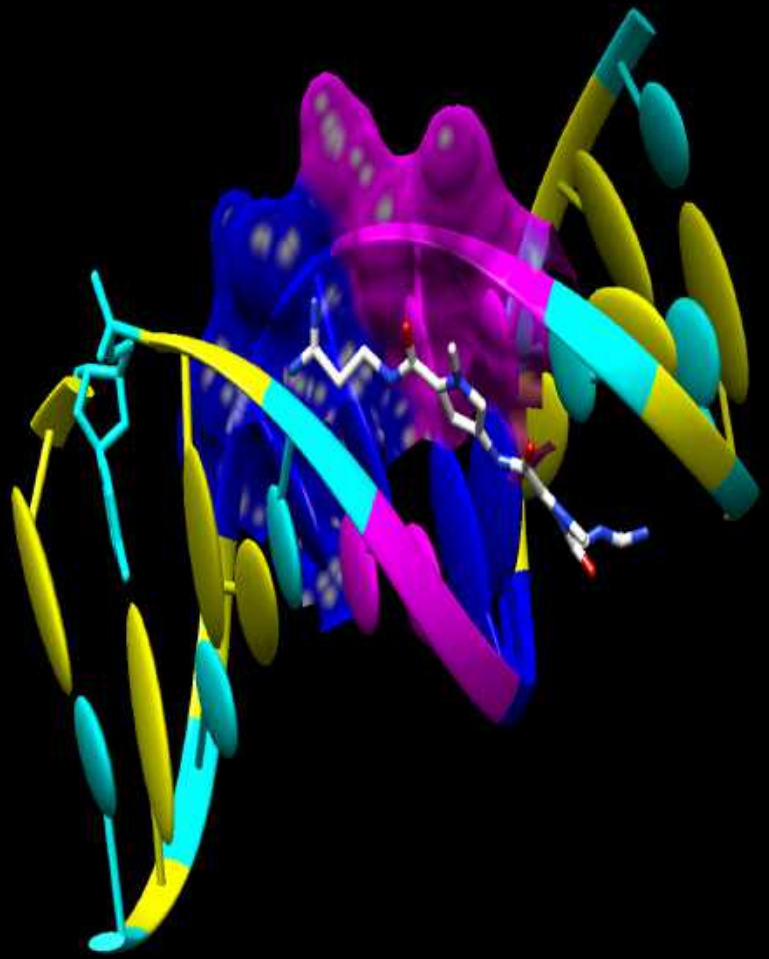
- Small molecules found in natural products(many are plants based).
- Biological activities
- Pharmacological activity.

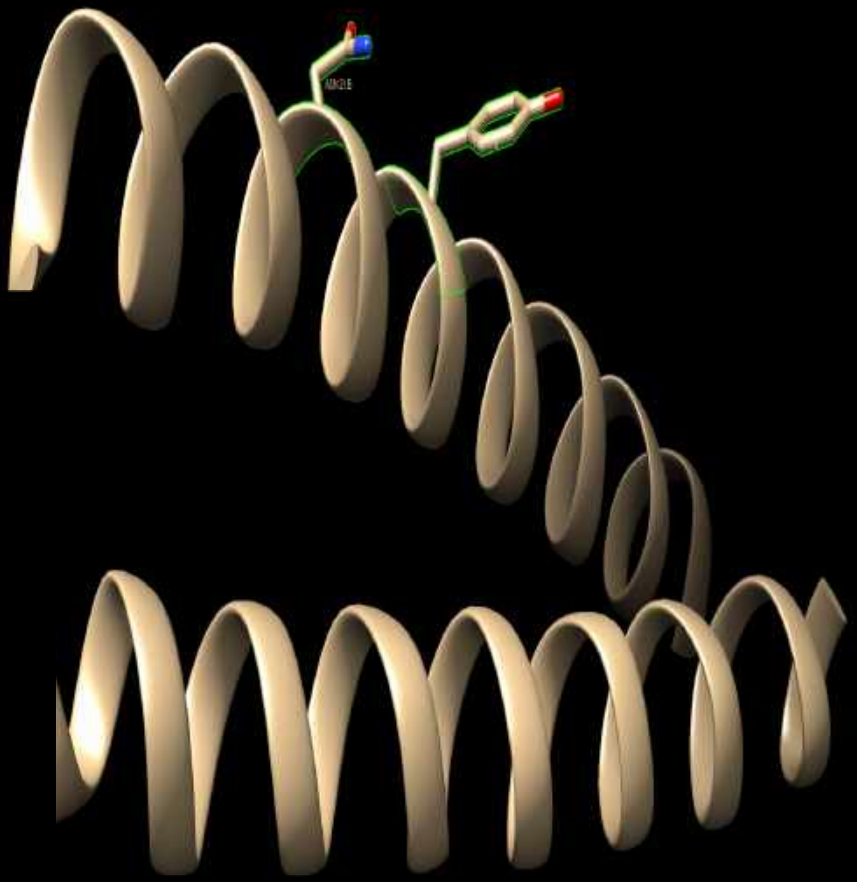
Multiple Myeloma



- Multiple Myeloma (MM) is an incurable hematological malignancy cancer characterized by excessive clonal plasma cell proliferation in the bone marrow.
- In the United States, MM is the second most prevalent type of cancer that affects about 4 in 100,000 Americans.

In this study, we are performing large scale *in silico* molecular protein-ligand docking





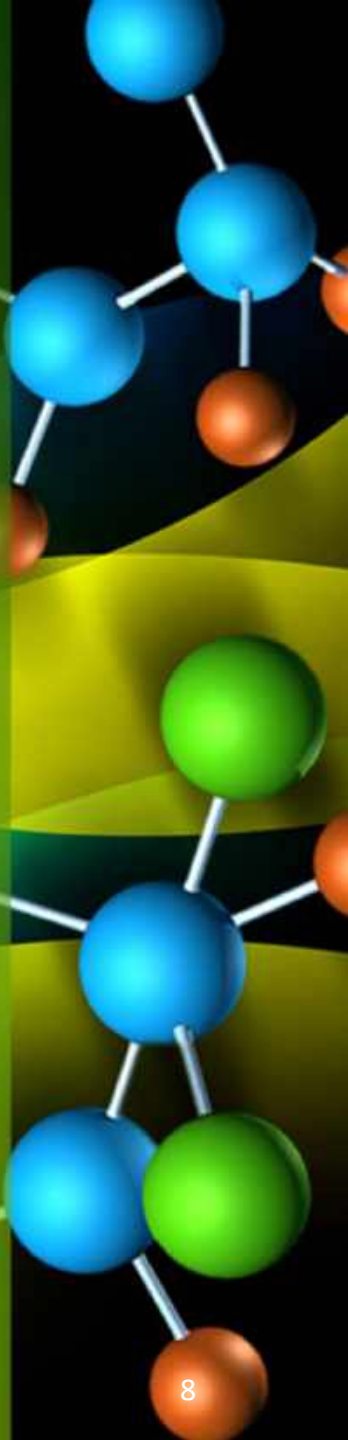
Method

As a preliminary step, we have prepared:

- ~200,000 natural compounds as ligands
- Several MM target proteins like CDH1, LCP1, ALDH1A1, MAFB, and HIF1A as receptor molecules.
- Over 500 target proteins are being tested.
- These proteins have been found to be present in MM patients that are actually tested for the disease.

Method

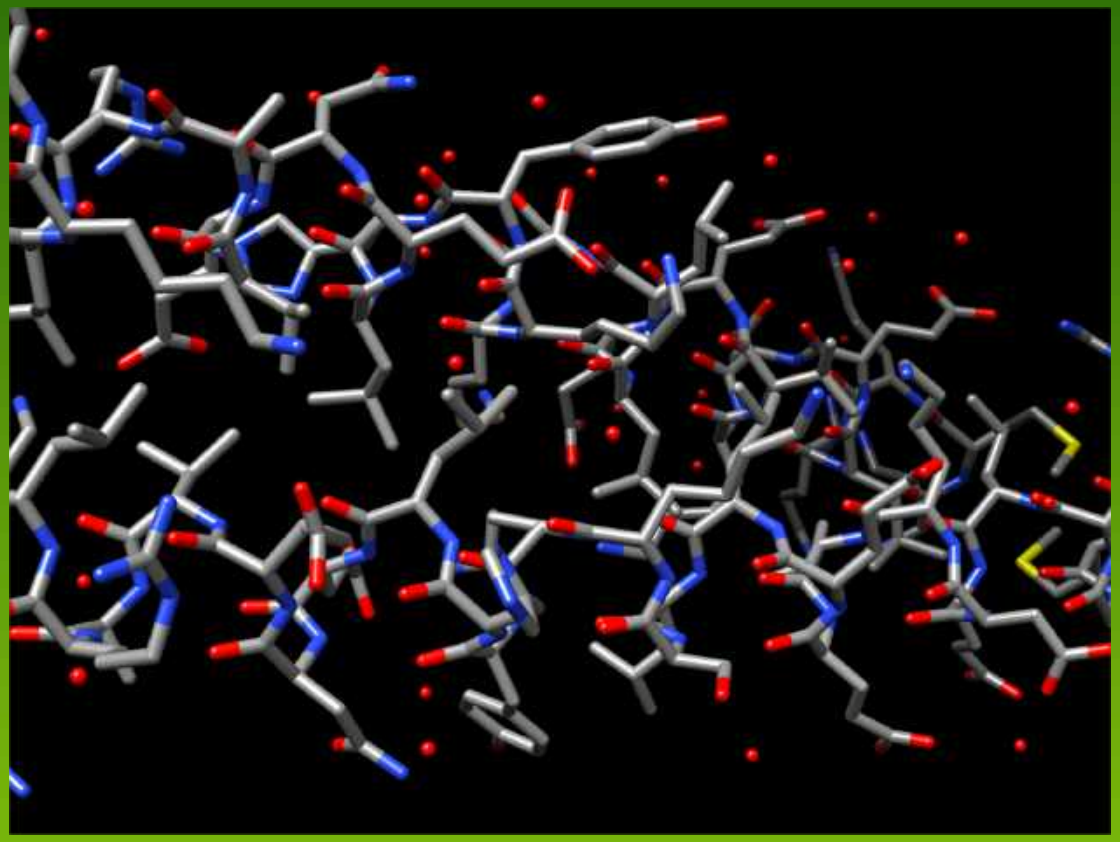
- The protein-ligand complexes obtained from molecular docking will be subjected for molecular dynamics simulation at ~10-100ns to explore the protein and complex conformational energy landscape.
- A webserver of these docking complexes will be implemented using PHP, HTML5, JQuery, JavaScript.
- The tool will allow users to select a human MM target protein and natural compound and check their binding affinity with a protein-ligand complex.
- Additionally, it will provide options to run molecular dynamics simulation on the complex using the High-Performance Computing cluster



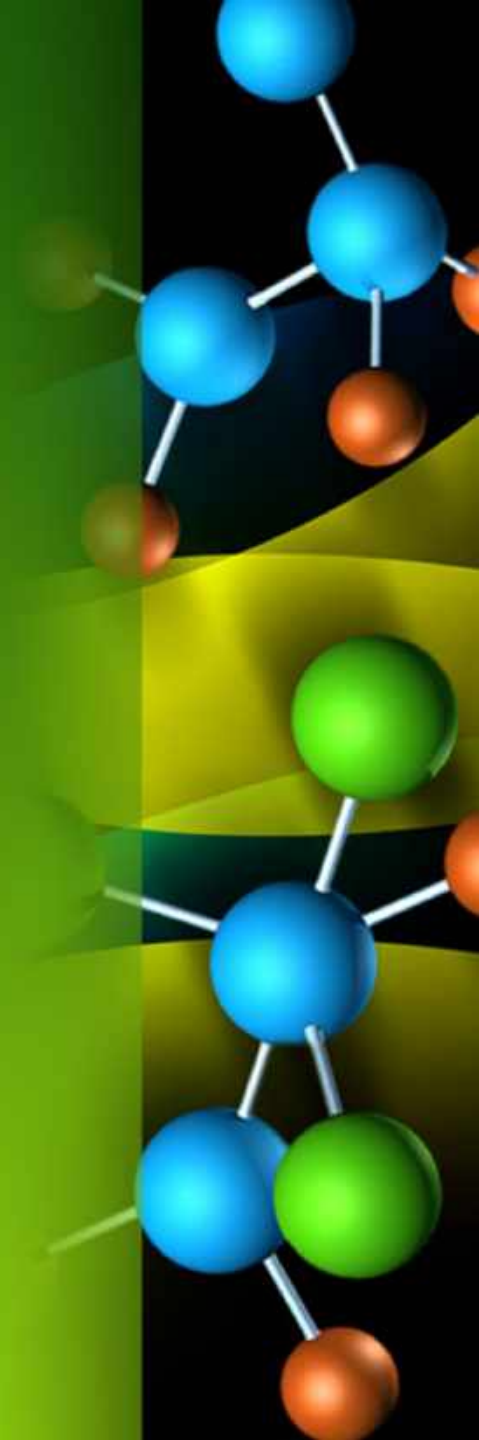
Drugs for Drug Designer

- A compound(ligand) that binds to biological target(protein) and either activate(agonist) or inactivate(antagonist) the protein function.
- The structure (3D) of drug is complementary to the active site (biding pocket) of biological target (protein).
- This biding is stabilized by many electrostatic hydrophobic and hydrogen bonds

Protein Docking



Given the 3D structures of two molecules, determine the best binding modes.



Protein Docking

- Molecular docking is the study of how two or more molecular structures (e.g., drug and enzyme or protein) fit together.

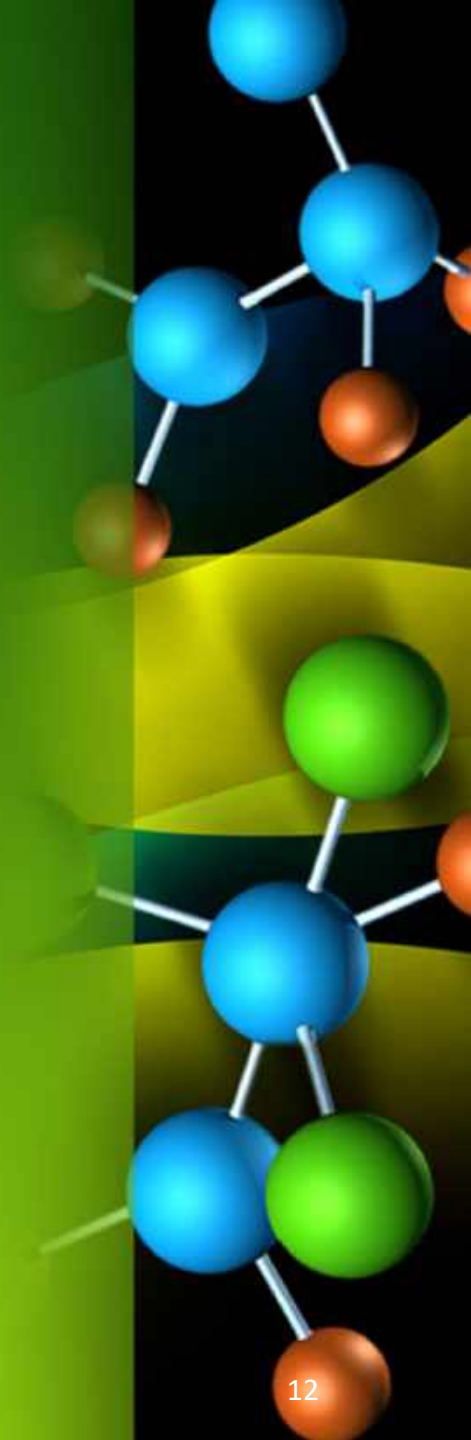
- In a simple definition, docking is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands).

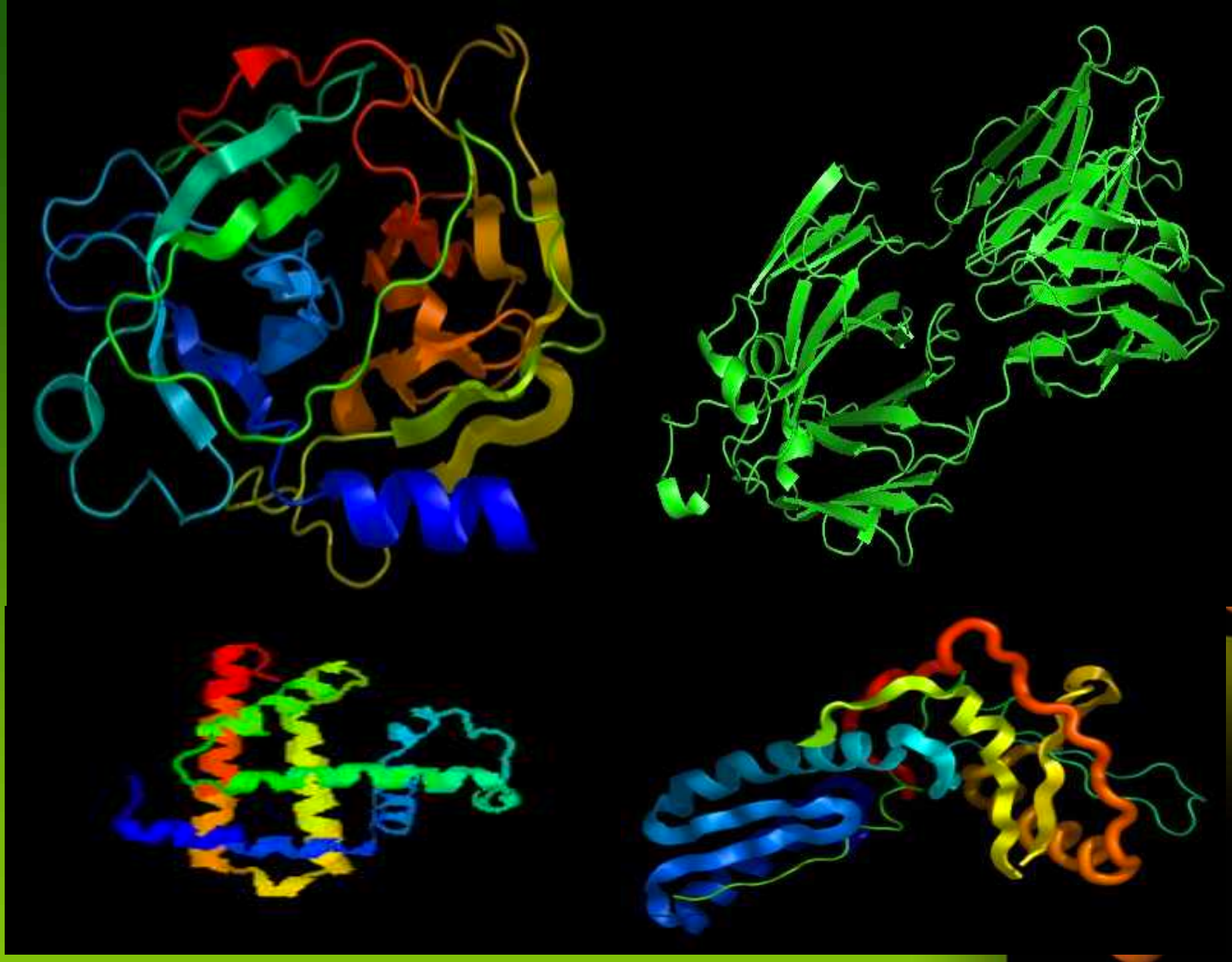
Target Selection & Structure

Protein has the following secondary structures:

- Helix
- Strands
- Loop

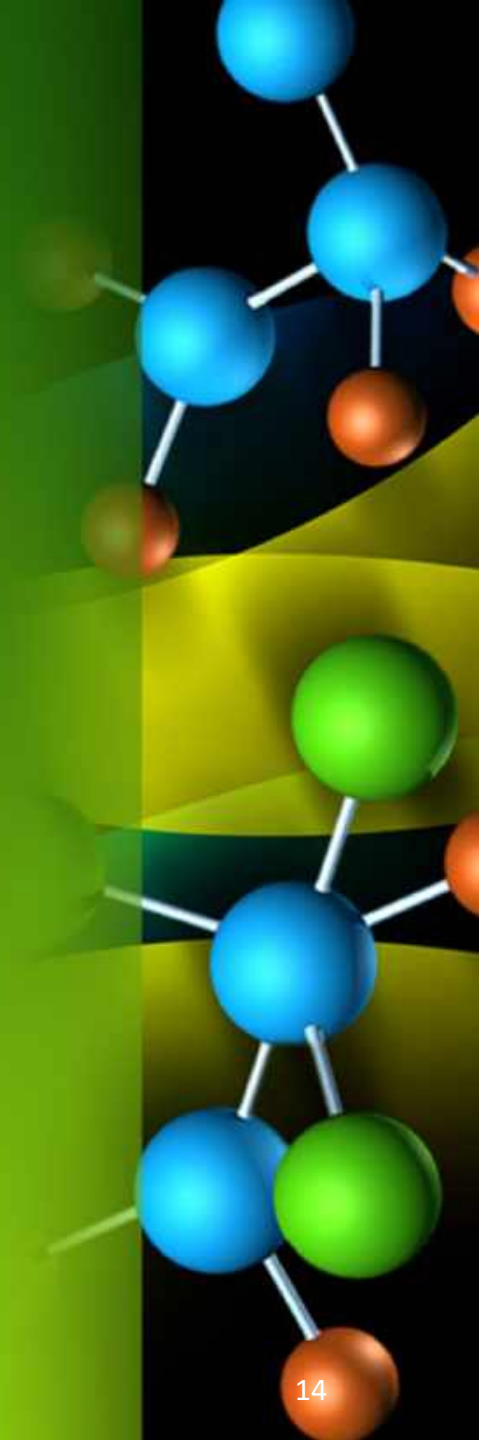
These secondary structures combine to form 3D structures.





Protein Docking

- Need protein 3D structure
- Need binding pocket in the protein
- Need candidate ligand that need to be docked
- Docking place the candidate ligand in binding pocket
- It results in multiple poses/conformation of candidate molecule inside the pocket



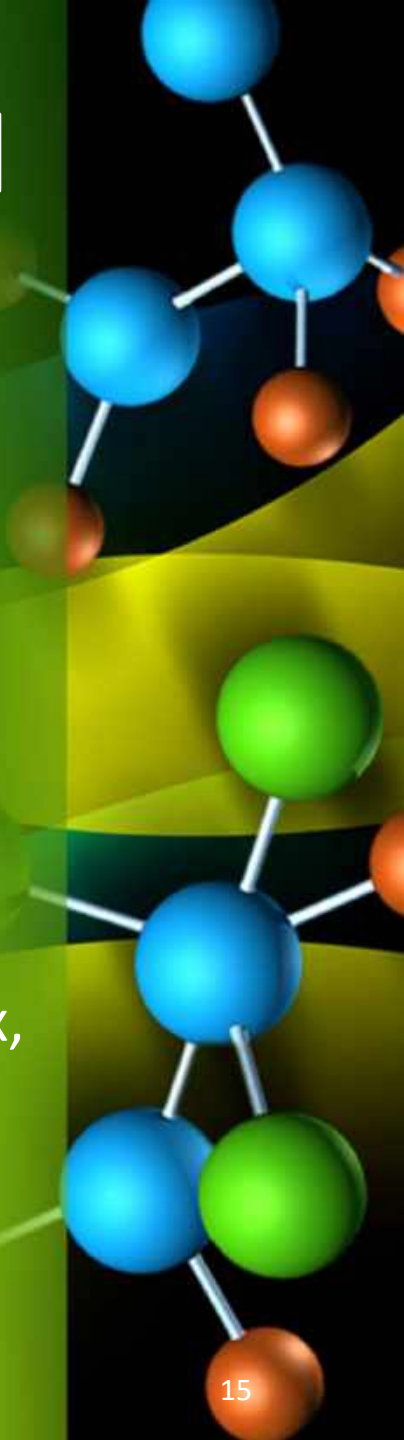
Binding Energy Protein-Ligand

- Binding energy between protein-ligand calculated for docked pose.

- Physical binding energy constitutes:
    1. Electrostatic
    2. Van der Waal
    3. Hydrophobic
    4. Solvation

- Lower binding energy shows a more stable complex, rank docked poses.

- Knowledge based binding energy calculation is also used.



RCSB PDB PROTEIN DATA BANK

176773 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

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RCSB PDB is funded by the National Science Foundation (DBI-1832184), the US Department of Energy (DE-SC0019749), and the National Cancer Institute, National Institute of Allergy and Infectious Diseases, and National Institute of General Medical Sciences of the National Institutes of Health under grant R01GM133198.

PubChem Data Counts

Data Collection	Live Count	Description
Compounds	109,890,299	Unique chemical structures extracted from contributed PubChem Substance records
Substances	270,897,840	Information about chemical entities provided by PubChem contributors
BioAssays	1,366,260	Biological experiments provided by PubChem contributors
Bioactivities	296,905,680	Biological activity data points reported in PubChem BioAssays
Genes	90,426	Gene targets tested in PubChem BioAssays and those involved in PubChem Pathways
Proteins	96,561	Protein targets tested in PubChem BioAssays and those involved in PubChem Pathways
Taxonomy	4,849	Organisms of targets tested in PubChem BioAssays and those involved in PubChem Pathways
Pathways	237,925	Interactions between chemicals, genes, and proteins
Literature	32,360,473	Scientific publications with links in PubChem
Patents	24,942,506	Patents with links in PubChem
Data Sources	781	Organizations contributing data to PubChem

ZINC15

Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 230 million purchasable compounds in ready-to-dock, 3D formats. ZINC also contains over 750 million purchasable compounds you can search for analogs in under a minute.

ZINC is provided by the Irwin and Shoichet Laboratories in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). We thank NIGMS for financial support (GM71896).

To cite ZINC, please reference: Sterling and Irwin, *J. Chem. Inf. Model, 2015* http://pubs.acs.org/doi/abs/10.1021/acs.jcim.5b00559. You may also wish to cite our previous papers: Irwin, Sterling, Mysinger, Bolstad and Coleman, *J. Chem. Inf. Model, 2012* DOI: 10.1021/ci3001277 or Irwin and Shoichet, *J. Chem. Inf. Model. 2005;45(1):177-82* PDF, DOI.

Getting Started

- Getting Started
- What's New
- About ZINC 15 Resources
- Current Status / In Progress
- Why are ZINC results "estimates"?

Explore Resources

Chemistry

Tranches, Substances, 3D Representations, Rings, Patterns

And More

Ask Questions

You can use ZINC for **general** questions such as

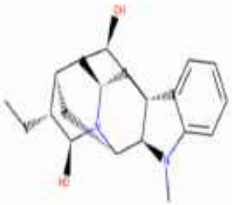
- How many substances in current clinical trials have PAINS patterns? (150)
- How many natural products have names in ZINC and are not for sale? (9296) get them as SMILES, names and calculated logP
- How many endogenous human metabolites are there? (47319) and how many of these can I buy? (8271) How many are FDA approved drugs? (94)
- How many compounds known to aggregate are in current clinical trials? (60)
- How many epigenetic targets have compounds known? (53) and Which of these substances can I buy? (278)

ZINC15 News

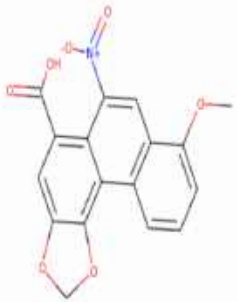
- 2018-02-14 - ZINC reaches 213,235,528 purchasable leadlike 3D!
- 2018-02-13 - ZINC reaches 736,001,654 purchasable molecules 2D!
- 2018-01-14 - Klara Anu is born! Welcome Klara Anu, sister to Lisa!
- 2018-01-01 - Chinzo Dandar joins our team. Welcome Chinzo! Follow us on twitter @chem4biology Known limitations What's new

Caveat Emptor: We do not guarantee the quality of any molecule for any purpose and take no responsibility for errors arising from the use of this

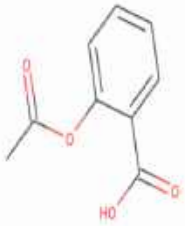
ZINC14



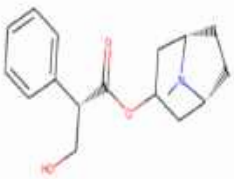
ZINC52
Aristolochic Acid



ZINC53
Aspirin



ZINC56
Endo-Atropine



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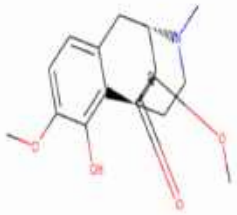

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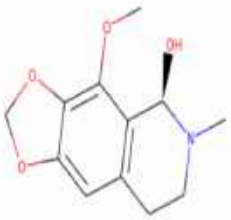

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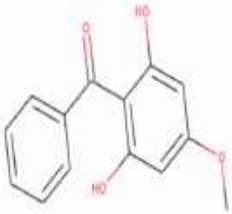
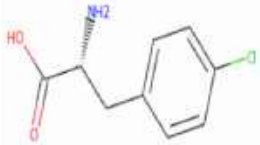
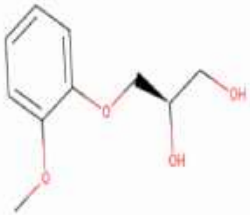


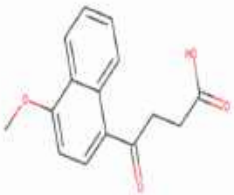
ZINC290
Fenclonine



ZINC353
Tussin

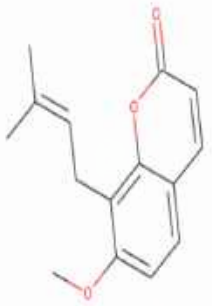


ZINC446
Menbutone



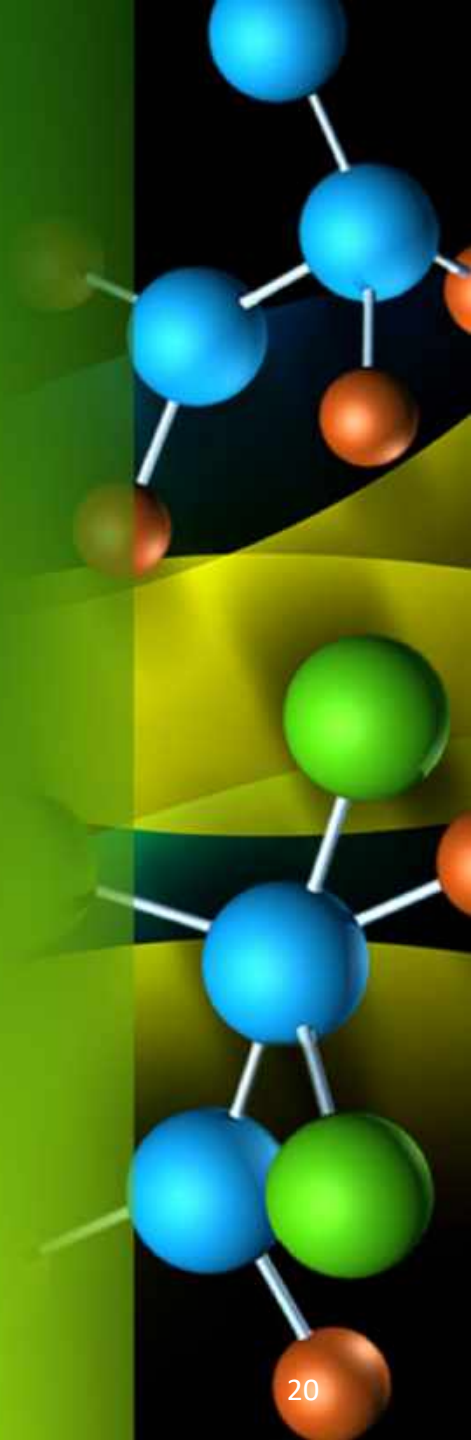
ZINC491
Methylephedrin

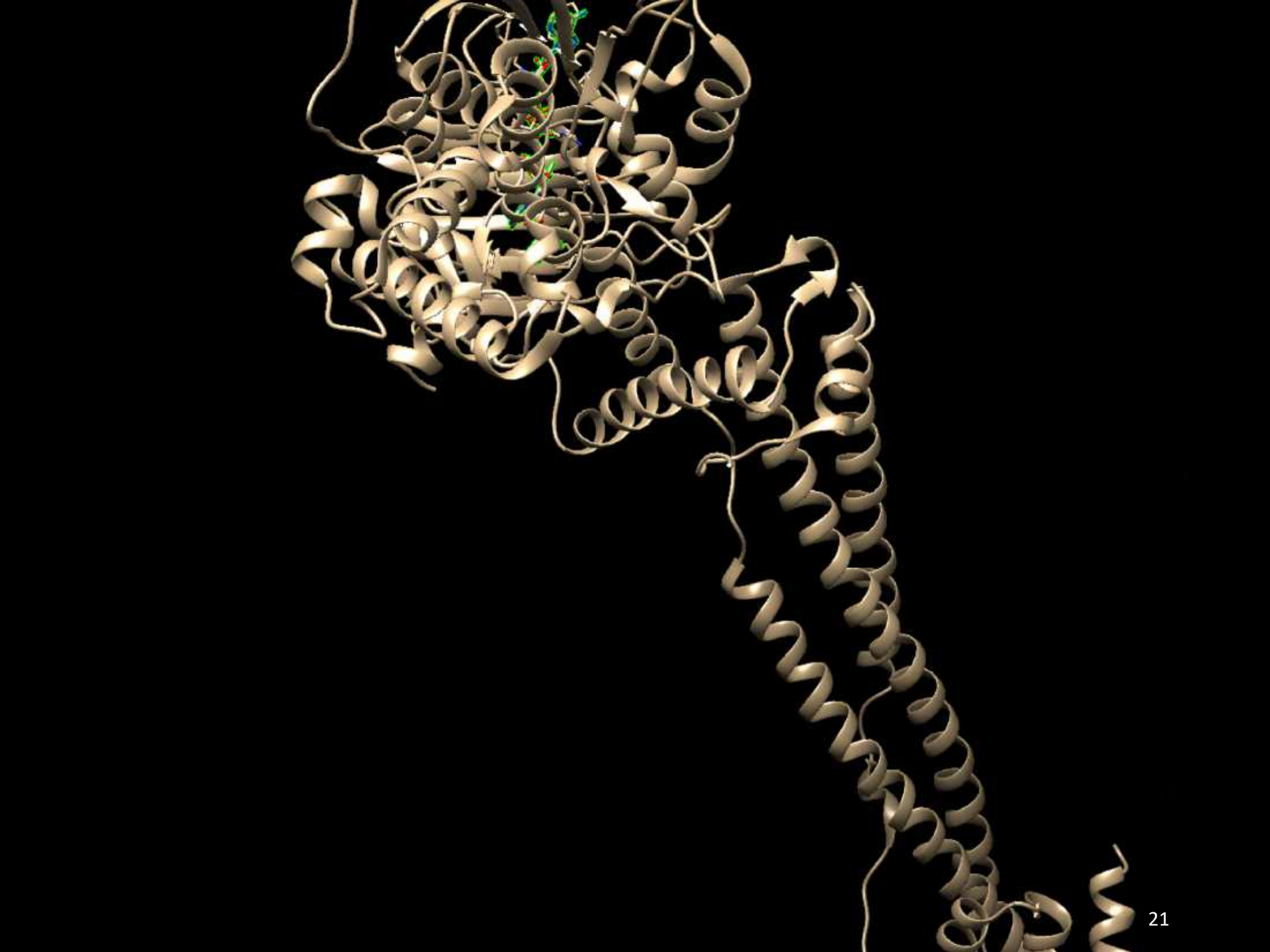
ZINC566
Osthole



4UVA

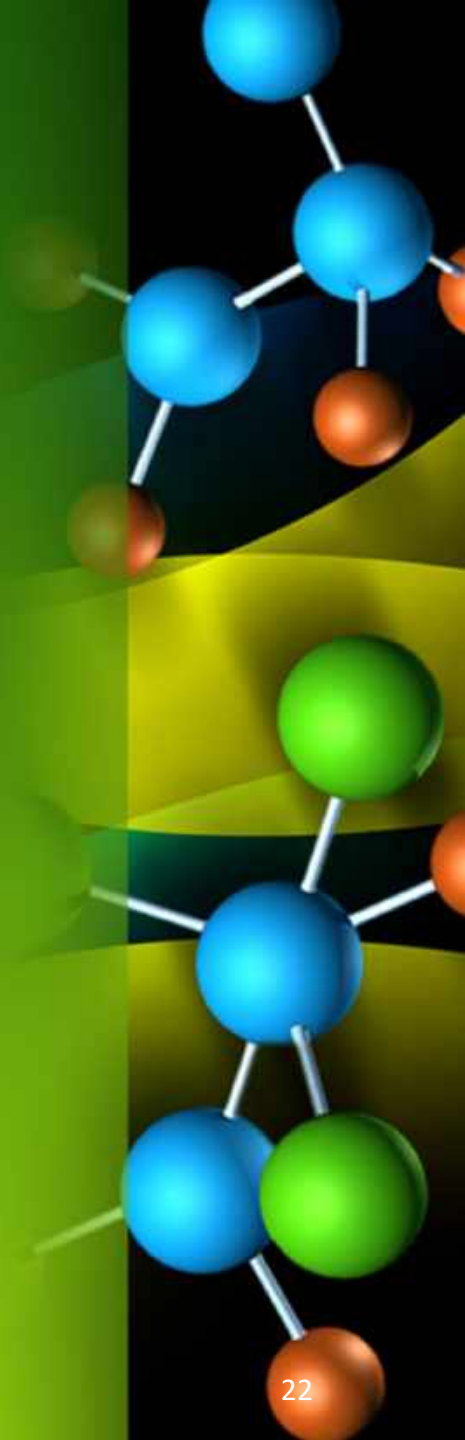
Histone demethylase KDM1A (also known as LSD1) has become an attractive therapeutic target for the treatment of cancer as well as other disorders such as viral infections.





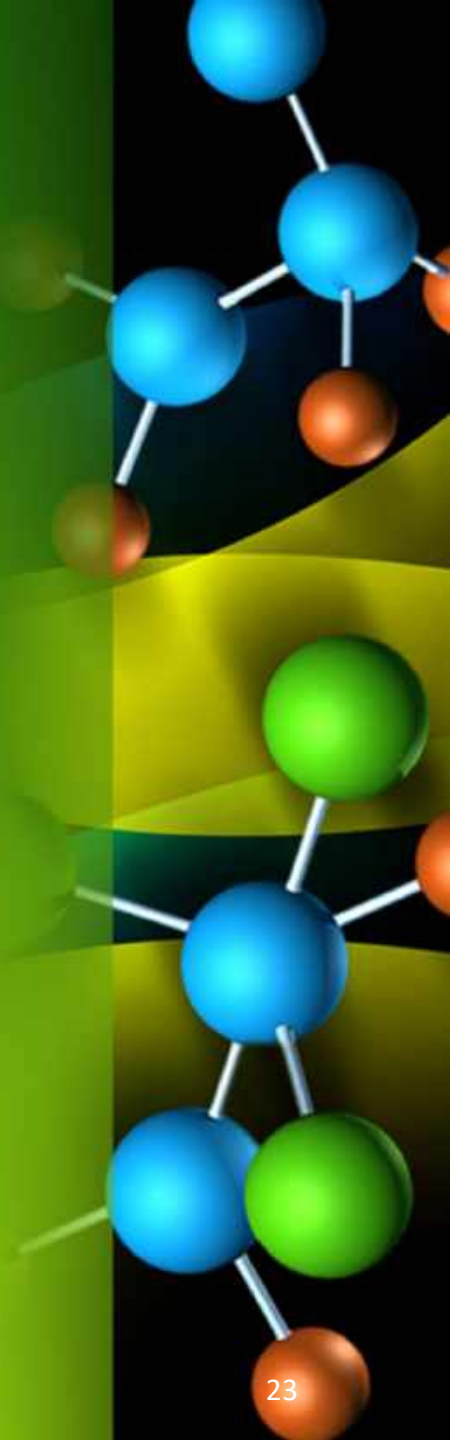
Model 1

- Estimated Free Energy of Binding = +6.11e+03 kcal/mol
- Final Intermolecular Energy = +6.10e+03 kcal/mol
- vdW + Hbond + desolv Energy = +6.10e+03 kcal/mol
- Electrostatic Energy = +0.48 kcal/mol
- Final Total Internal Energy = -2.36 kcal/mol
- Torsional Free Energy = +5.07 kcal/mol
- Unbound System's Energy = -2.36 kcal/mol

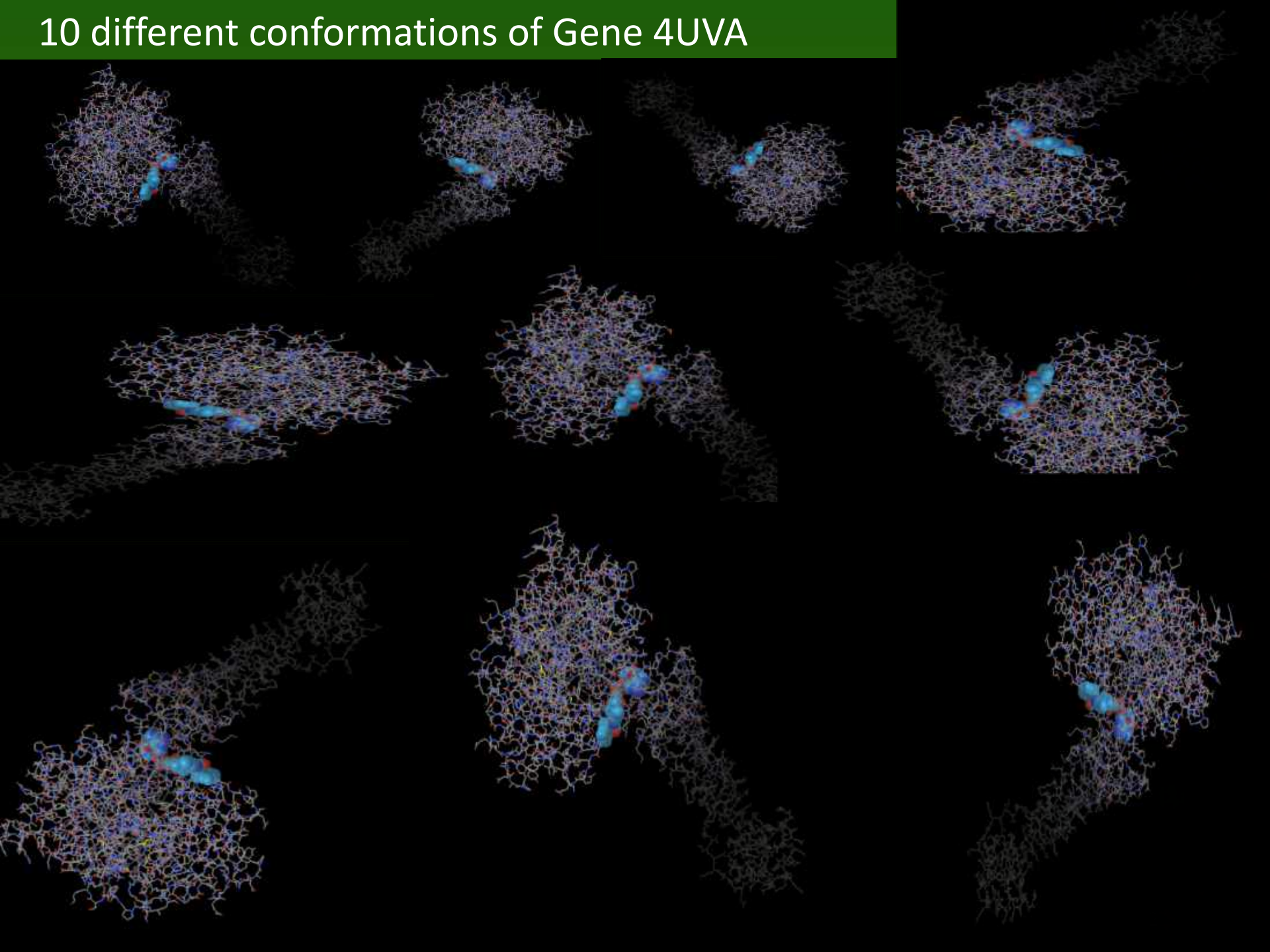


Model 2…

- Estimated Free Energy of Binding = +3.47e+03 kcal/mol
- Final Intermolecular Energy = +3.46e+03 kcal/mol
- vdW + Hbond + desolv Energy = +3.46e+03 kcal/mol
- Electrostatic Energy = +0.33 kcal/mol
- Final Total Internal Energy = -0.82 kcal/mol
- Torsional Free Energy = +5.07 kcal/mol
- Unbound System's Energy = -0.82 kcal/mol



10 different conformations of Gene 4UVA



Benefit

- Protein–protein docking can help us better understand how natural compounds play a role in treatments for patients with Multiple Myeloma.
- Can Provide structural and mechanistic insights for the proteins involved in MM.
- Can help us characterize the behavior of small molecules in the binding site of each protein (protein-ligand interaction).
- Design models that can be used to predict and prioritize natural products for therapeutics.