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In silico analysis of cystic fibrosis and Molecular docking and modeling

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Abstract

The aim of docking is to accurately predict the structure of a ligand within the constraints of a receptor binding site and to correctly estimate the strength of binding. We discuss, in detail, methodological developments that occurred in the docking field with a particular focus on the more difficult, and sometimes controversial, aspects of this promising computational discipline. The main developments in docking in this period, covered in this review, are receptor flexibility, solvation, fragment docking, post processing, docking into homology models, and docking comparisons. Several new, or at least newly invigorated, advances occurred in areas such as nonlinear scoring functions, using machine-learning approaches. This review is strongly focused on docking advances in the context of drug design, specifically in virtual screening and fragment-based drug design.

Molecular docking is a computational method for predicting the placement of ligands in the binding sites of their receptor(s). In this review, we discuss the methodological developments that occurred in the docking field with a particular focus on the more difficult aspects of this computational discipline. The main challenges and therefore focal points for developments in docking, covered in this review, are receptor flexibility, solvation, scoring, and virtual screening. We specifically deal with such aspects of molecular docking and its applications as selection criteria for constructing receptor ensembles, target dependence of scoring functions, integration of higher-level theory into scoring, implicit and explicit handling of solvation in the binding process, and comparison and evaluation of docking and scoring methods.

Fueled by advances in molecular structure determination, tools for structure-based drug design are proliferating rapidly. Lead discovery through searching of ligand databases with molecular docking techniques represents an attractive alternative to high-throughput random screening. The size of commercial databases imposes severe computational constraints on molecular docking, compromising the level of calculation detail permitted for each putative ligand. We describe alternative philosophies for docking which effectively address this challenge With respect to the dynamic aspects of molecular recognition, these strategies lie along a spectrum of models

Keywords: Receptor flexibility, solvation, fragment docking, postprocessing, docking into homology models and docking comparisons.

Introduction

Cystic Fibrosis CF is a chronic disease that you inherit. It mainly affects the lungs and digestion. CF affects people in varied ways. The basic problem in CF is an error in the salt and water exchange in some cells. This causes the body to make thick, sticky mucus. The mucus clogs the lungs and pancreas.

The most commonly affected organs included the
1. Lungs
2. Pancreas
3. Liver
4. Instines

CF is caused by a mutation in the gene that encodes for the CFTR protein; mutations can be separated into 5 different classes. Ivacaftor is a new CFTR potentiator that helps the CFTR channel open properly in patients with the CFTR mutation, G551D. Patients in one study had significant decreases in sweat chloride values and increases in pulmonary function tests. Ivacaftor was approved by the Food and Drug Administration (FDA) to be taken orally at a dose of 150 mg twice a day in G551D CF patients older than 6 years. Additional studies are investigating the use of ivacaftor in other gating mutations and in younger patients. VX-809 is a CFTR corrector that modulates the folding and trafficking of CFTR. VX-809 was originally studied alone in patients with F508del mutation but is now being used in combination with ivacaftor in Phase 2 studies. Ataluren allows the read through of premature stop codons, and studies in patients with CF with nonsense mutations show an increase in chloride transportation. Ataluren requires 3 times a day dosing and is currently in a Phase 3 placebo-controlled study[1].

Materials and Methods

Materials:

1. **NCBI** - {The **National Center for Biotechnology Information** advances science and health by providing access to biomedical and genomic information}.
2. **PDB**-{This resource is powered by the **Protein Data Bank** archive-information about the 3D shapes of proteins}
3. **PUBCHEM-{**PubChem is the world's largest collection of freely accessible chemical information. Search chemicals by name, molecular formula, structure, and other identifier}
4. **ARGUSLAB-{**ArgusLab is a molecular modeling, graphics, and drug design program for Windows operating systems}
5. **PYMOL**-{pymol is user-sponsored molecular visualization system on an open source foundation maintain and distributed by schrodinger}
6. **CASTp**-{**computed atlas of surface topography of protiens** is a web server that provides online services for locating, delineating and measuring these geometric and topological properties of protein structures}
7. **UNIPROT-{**The mission of *UniProt* is to provide the scientific community with a comprehensive, high-quality and freely accessible resource of protein sequence }
8. **SWISSMODEL-{***Swiss model* is a fully automated protein structure homology-modelling server. The purpose of this server is to make protein modelling accessible to all life}

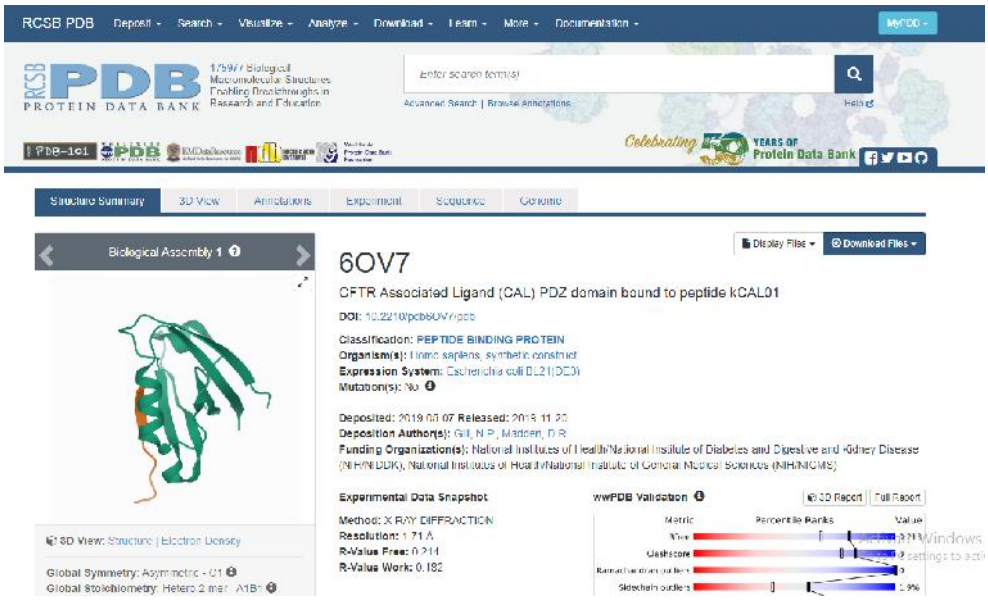
Methods:

1. **Gene identification**: the disease name is cystic fibrosis and cftr gene identification in ncbi database
2. **Target protein selection:(60v7)**cftr associated ligand(Cal) pdz domain bond to peptide kcal01 this classification is peptide bond protein
3. **Homology Modelling:**the structure viewd for cftr gene and their structure assessment Ramachandran plot view and favoured
4. **Ligand Selection:**the ligand selection for curcumin compound they are PubChem id, molecular formula, molecular weight and canonical smiles
5. **Molecular Docking:** we use to find compound structure in pymol tool and we have binding compound to protein in ArgusLab

Results and Discussion

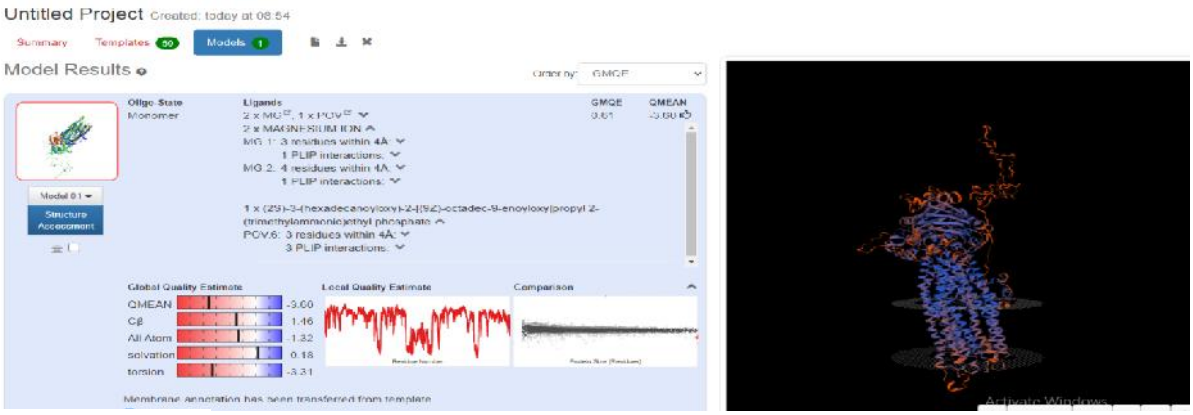
1. Gene identification: (cftr gene)

The cystic fibrosis disease gene identification official symbol, full name and gene type



2. Target protein selection

The protein selection in PDB (protein data bank) for cystic fibrosis disease



3. Homology modelling:

FIGURE1:

The protein structure view for cftr gene inSwiss model database

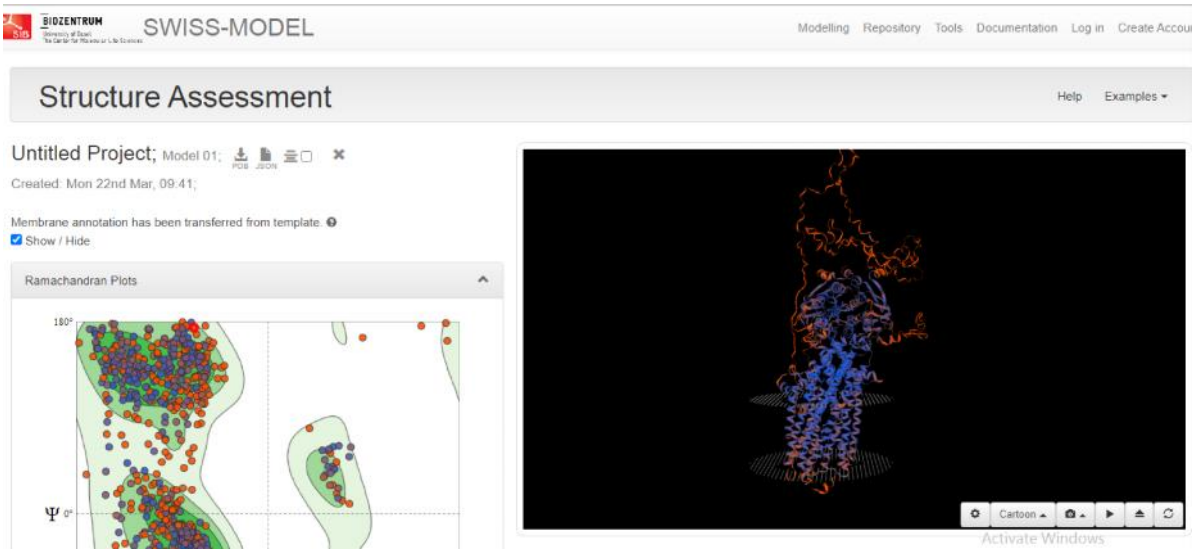
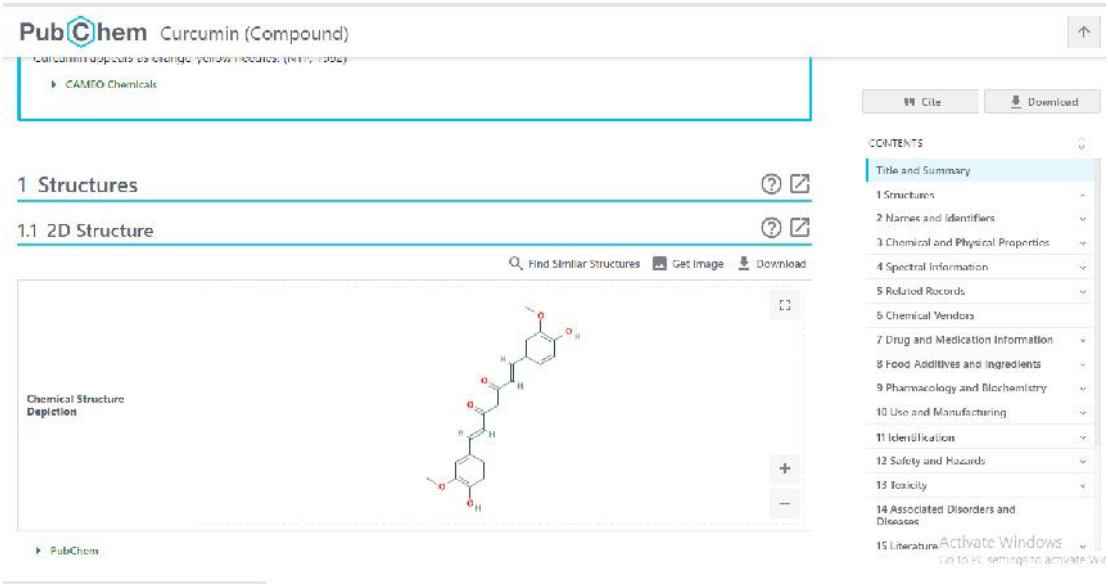


FIGURE 2:

The structure assessment and Ramachandran plot view for cftr

FIGURE3:

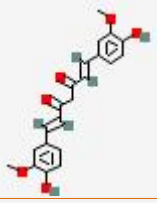
Moiprobity results and Ramachandran favoured is **92.40%**



4. Ligand selection

The ligand selection for curcumin compound

Table1:

s.no	SCIENTIFIC NAME	COMPOUND NAME	PubChem id	structure
1.	CURCUMIN	curcumin	969516	
2.	ALTHAEA OFFICINALIS	Sodium chlorate	516092	
3.	EUCALYPTUS GLOBULUS LABIL	Eucalyptol	2758	

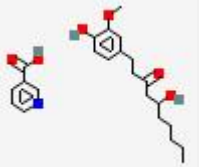
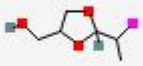
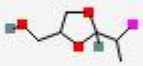
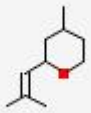
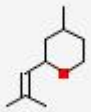
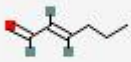
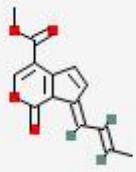
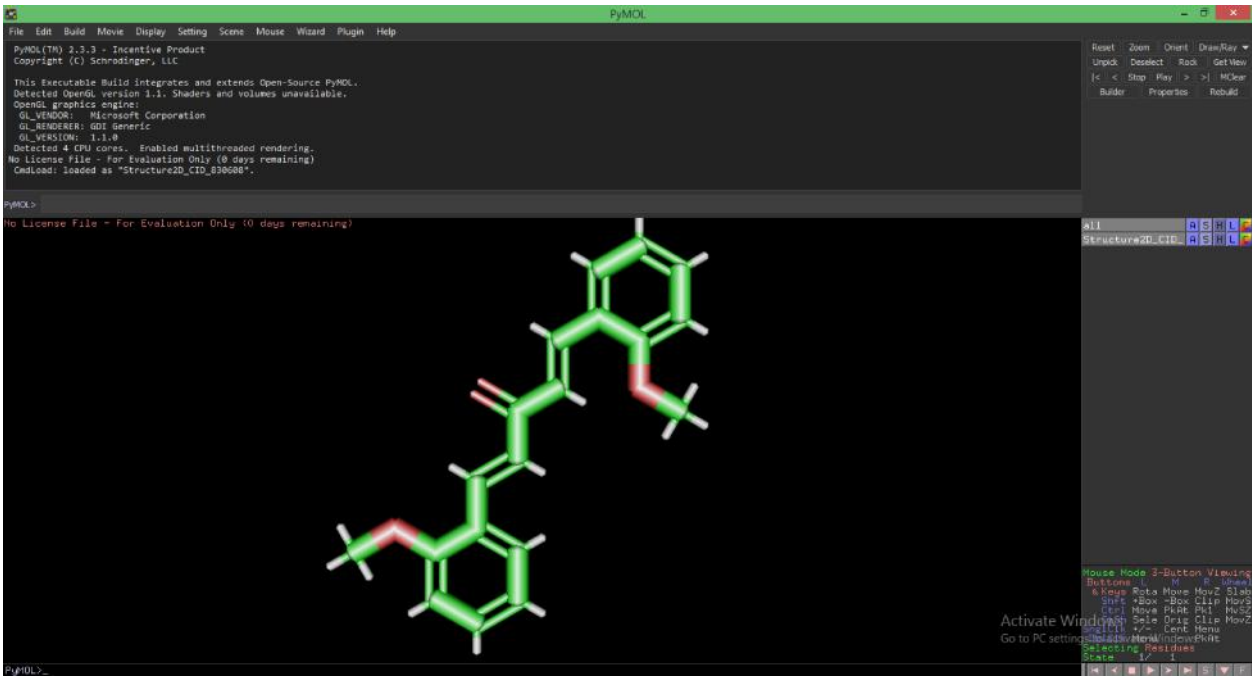
4.	ZINGIBER OFFICINALE	Zingiber officinale	6850760	
5.	GLYCYRRHIZA GLABRA	Iodinated glycerol	21852	
6.	SILYBUM MARIANUM	Milk thistle	1548994	
7.	ROSA CANINA L	Rose oxide	27866	
8.	THYMUS VULGARIS	Thymol	6989	
9.	VERBASCUM THAPSUS	2-Hexenal	5281168	
10.	ULMUS RUBRA	Fulvoplumierin	5281541	

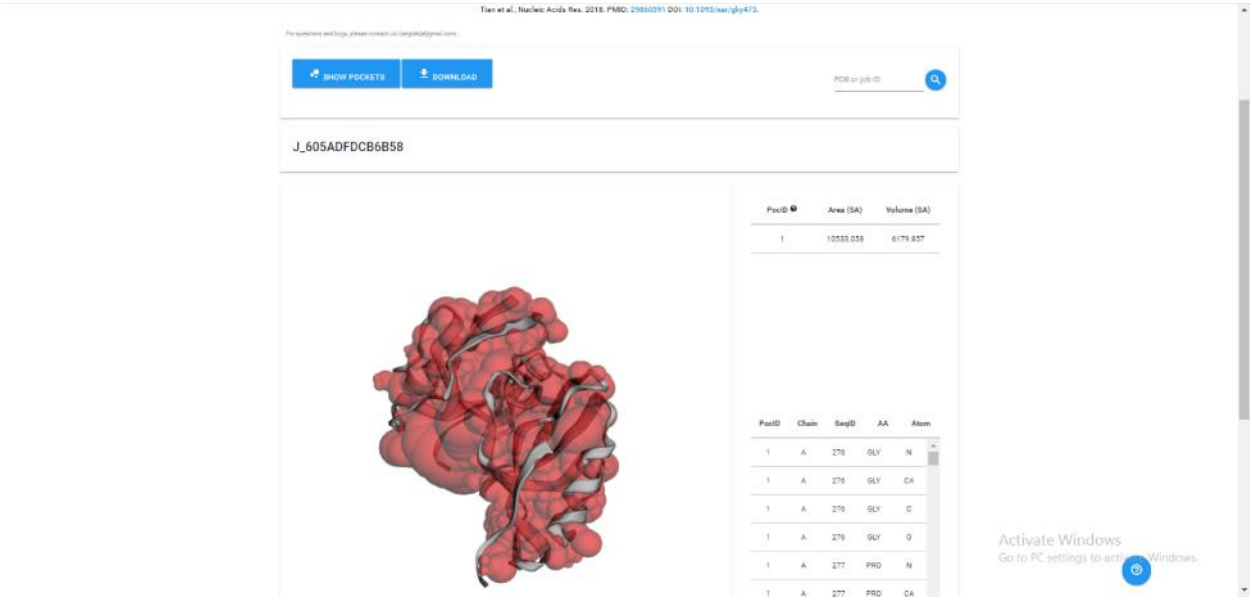
Table: 2

s.no	Scientific name	Compound name	Energy minimization value
1.	Curcumin	curcumin	-14.6
2.	Althaea officinalis	Sodium chlorate	-4.4
3.	Eucalyptus globulus labile	eucalyptol	-7.6
4.	Zingiber officinale	Zingiber officinale	-10.15
5.	Glycyrrhiza glabra	Iodinated glycerol	-4.42
6.	Silybum marianum	Milk thistle	-3.38
7.	Rosa canina l	Roxe oxide	-8.61
8.	Thymus vulgaris	Thymol	-12.44
9.	Verbascum Thapsus	2-hexenal	-7.00
10.	Ulmus rubra	fulvoplumierin	-10.61

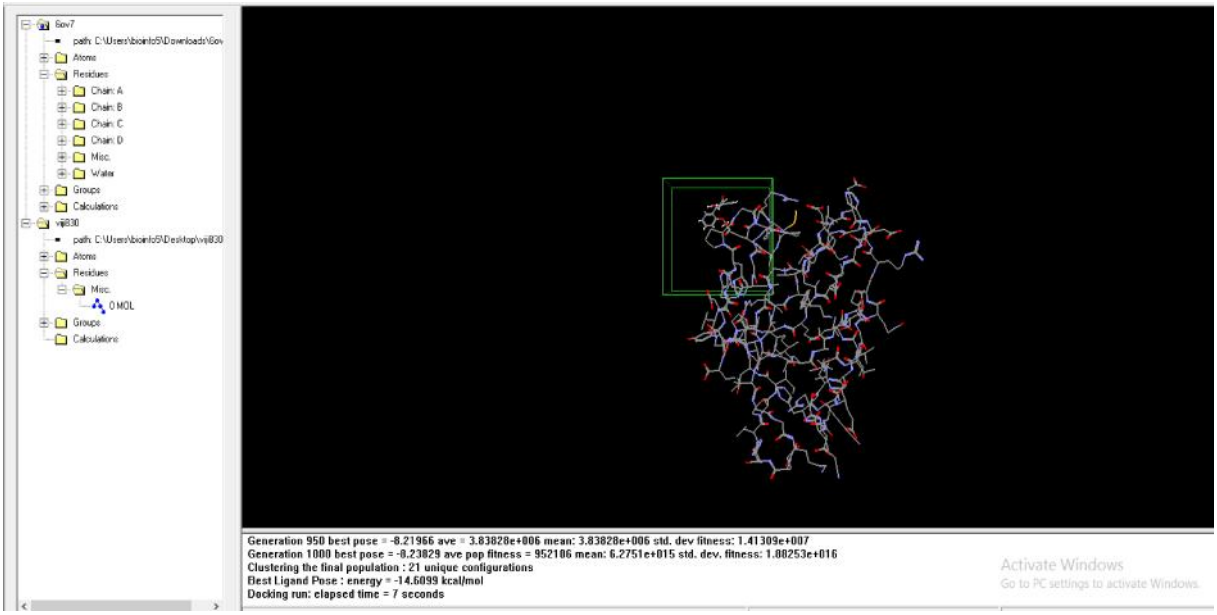


1. Curcumin

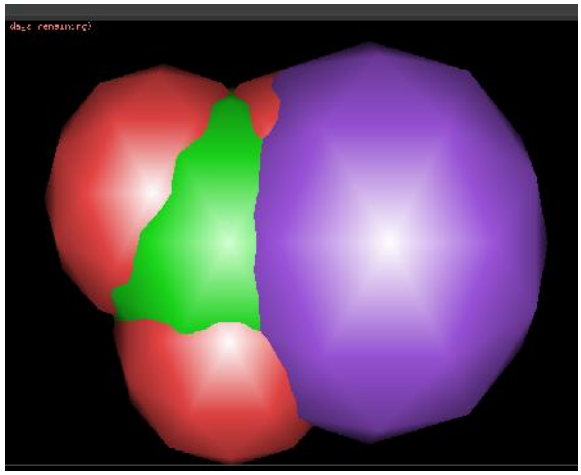
Pymol view in curcumin structure



CASTp**(60v7)** and there structure and amino acids

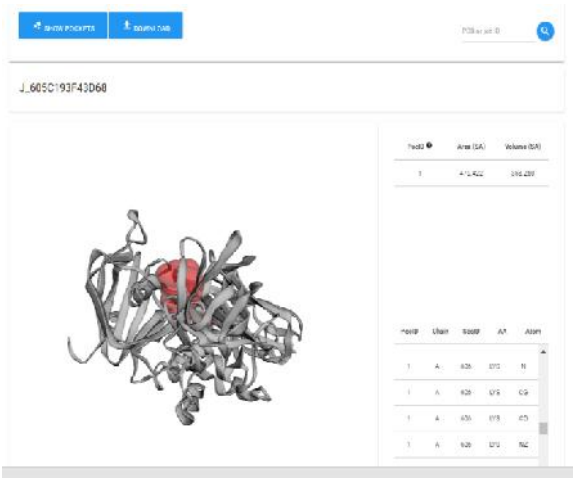


The curcumin best ligand pose is **-14.68** in cystic fibrosis disease

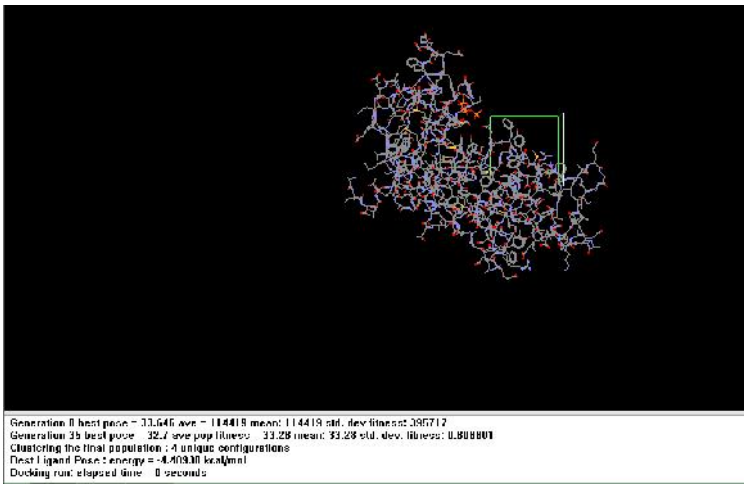


2. Althaea officinalis

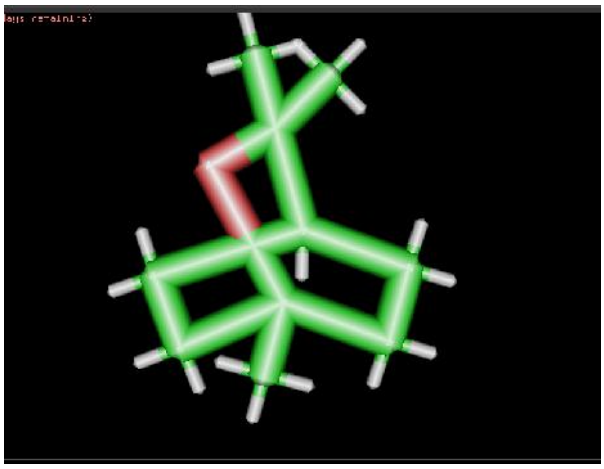
Sodium chlorate structure view in pymol



Castp**(6gjs)** strucuture view and their amino acids

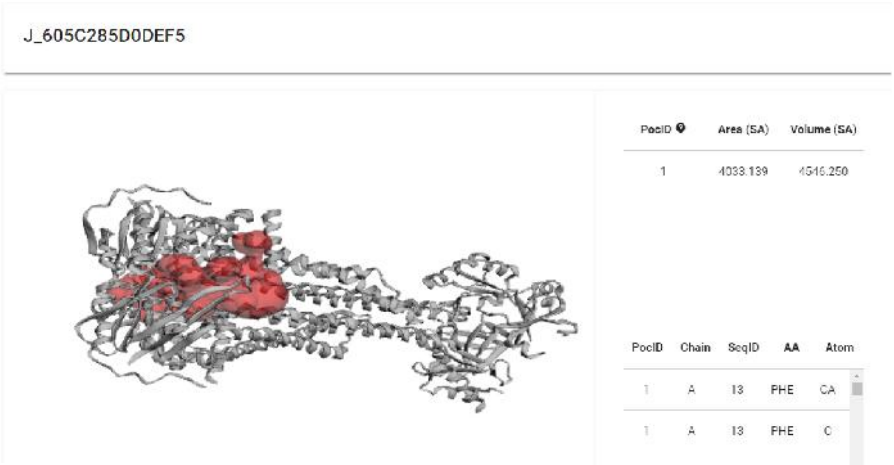


The sodium chlorate ligand pose in **-4.40**

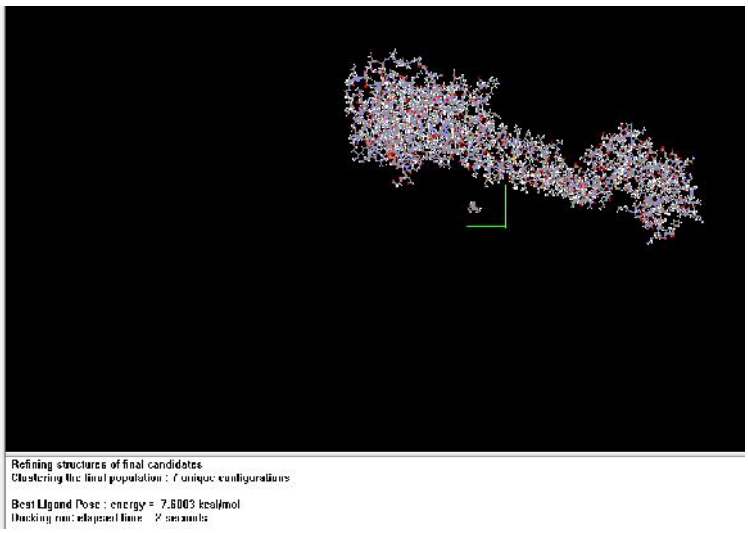


3. Eucalyptus globulus labile

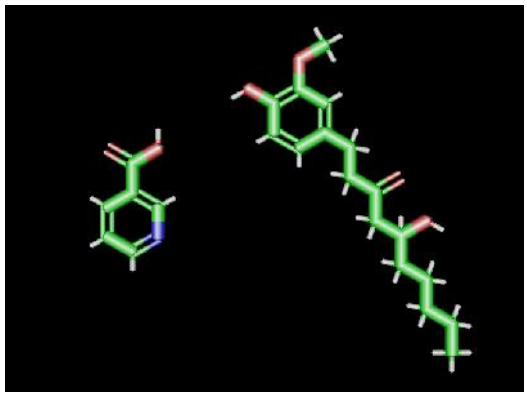
Eucalyptus globulus labile structure view inpymol



CASTp**(5lij)**structure and amino acids viewd

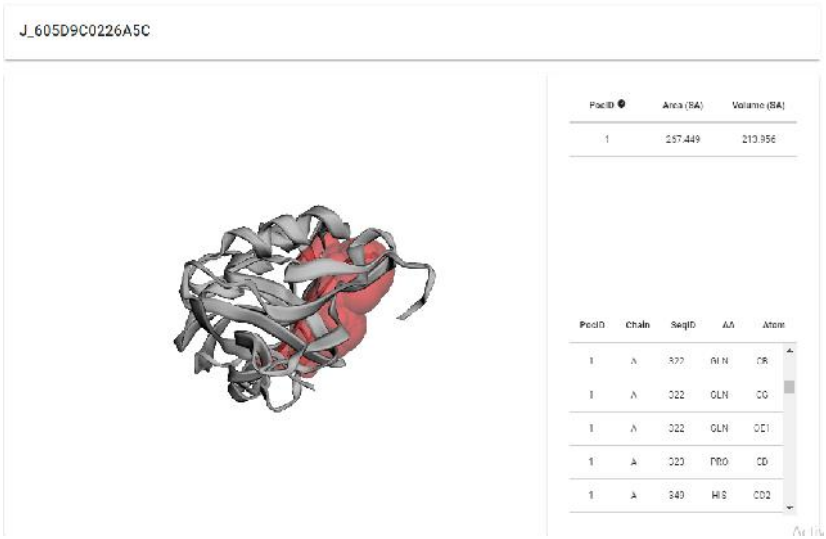


The eucalyptol ligand pose in **-7.60**

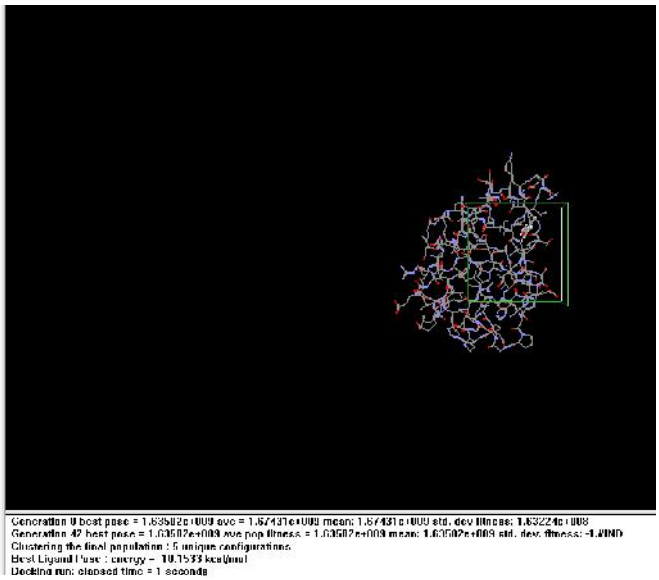


4. Zingiber officinale

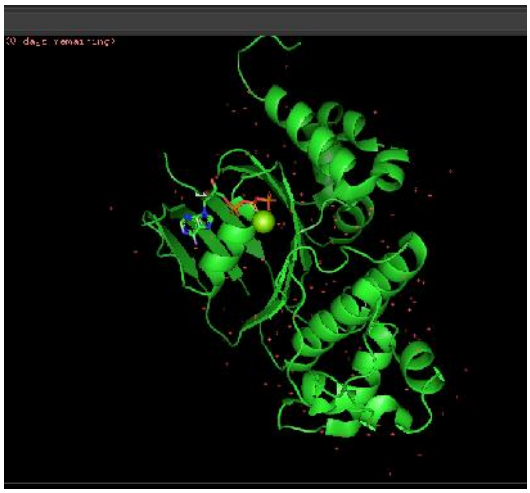
Zingiber officinale structure view in pymol



CASTp**(4nmo)**structure and their amino acids

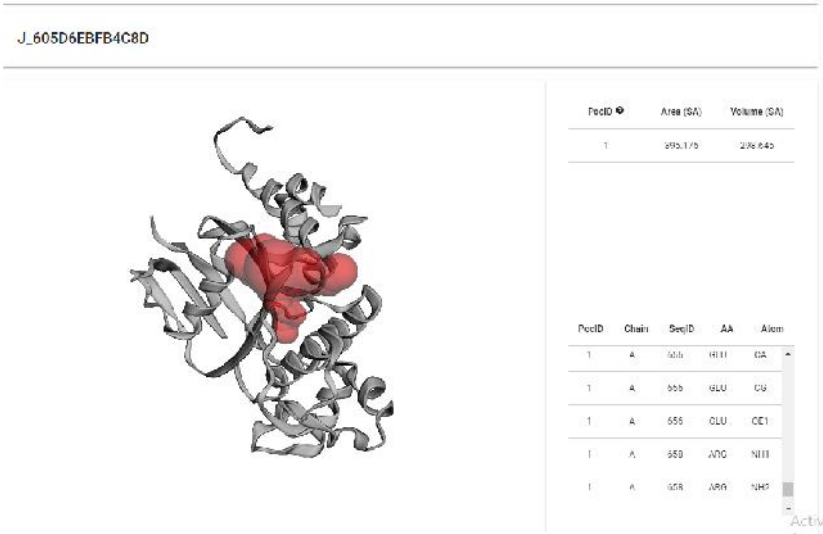


The Zingiberofficinale ligand pose in **-10.15**

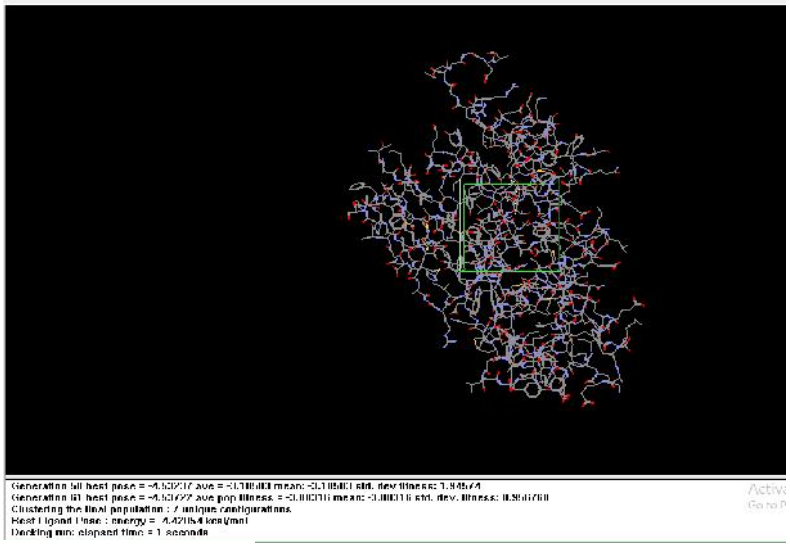


5. Glycyrrhiza glabra

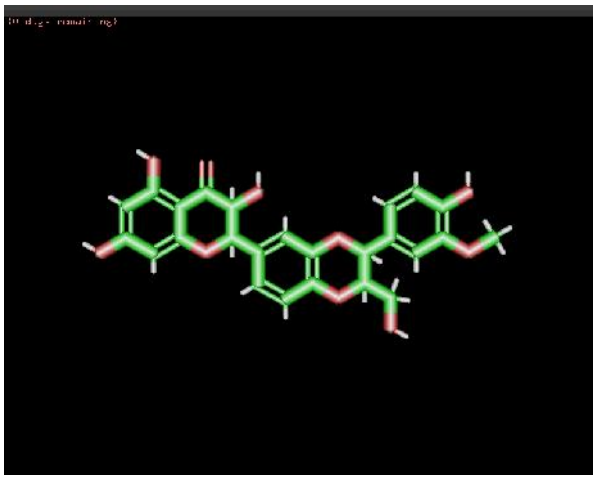
Glycyrrhiza glabra structure view in pymol



CASTp**(1xmj)**structure and their amino acids

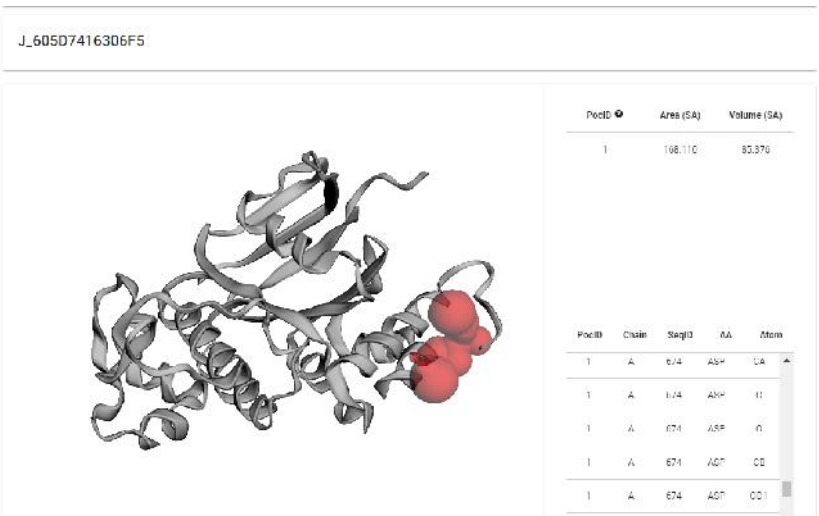


Iodinated glycerol best ligand pose in **-4.42**

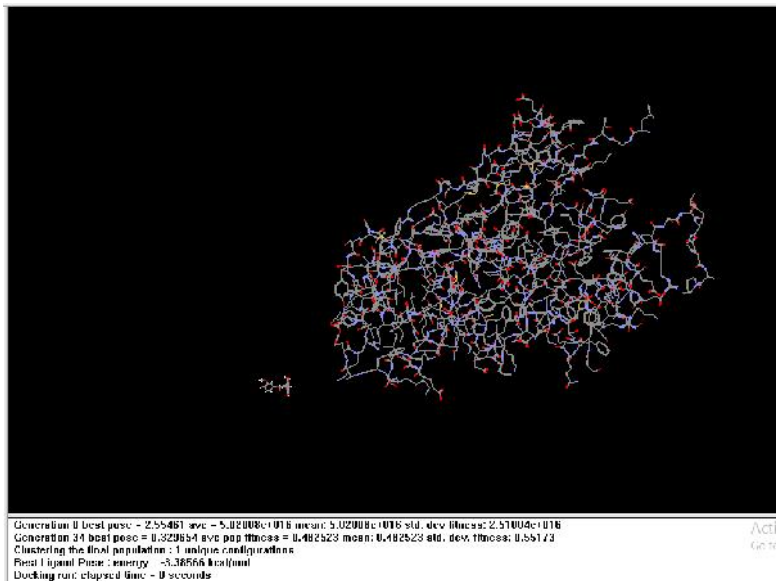


6.Silybum marianum

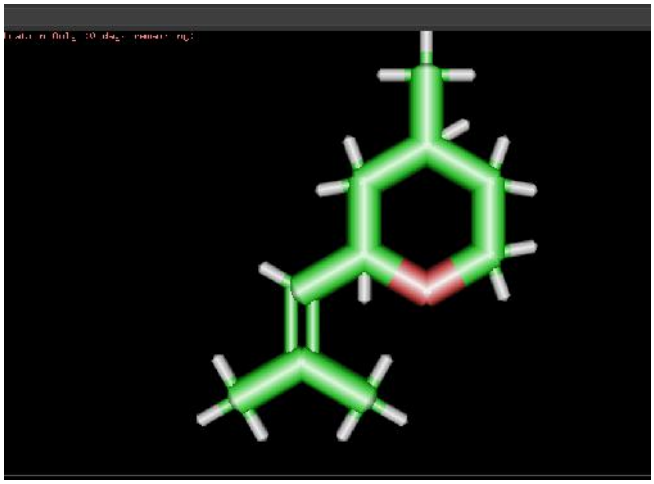
Silybum marianum structure view in pymol



CASTp**(2bb0)**structure and their amino acids

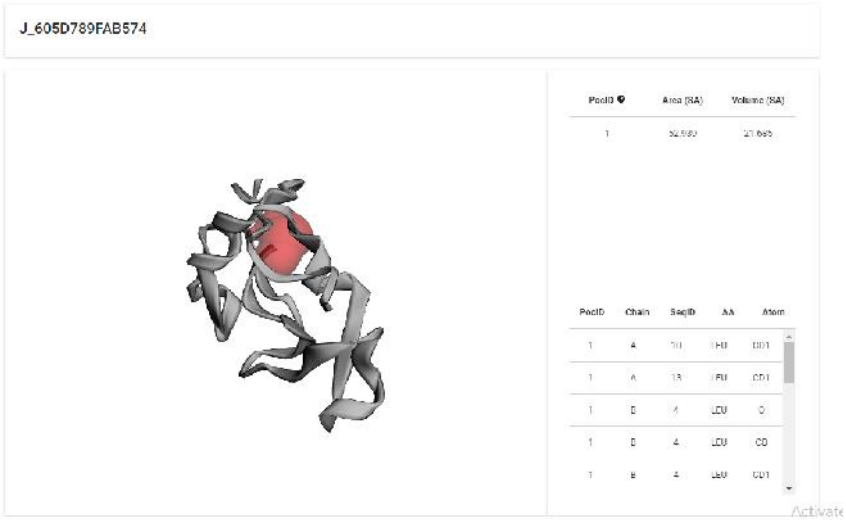


Milk thistle ligand pose in **-3.38**

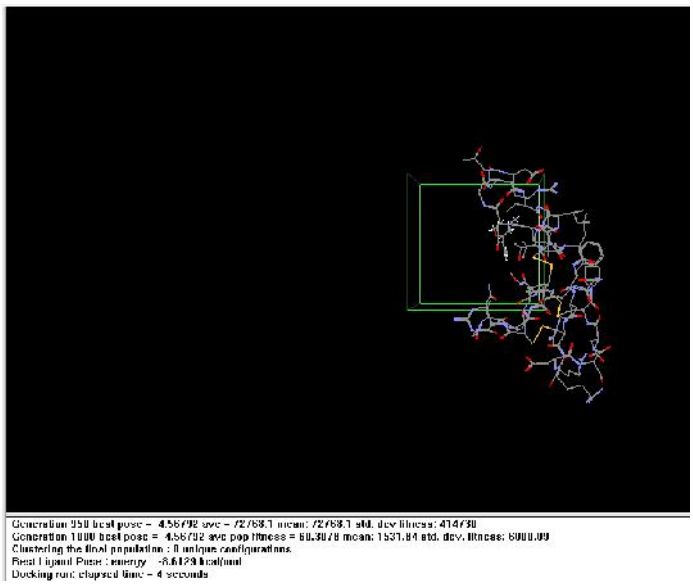


7. Rosa canina l

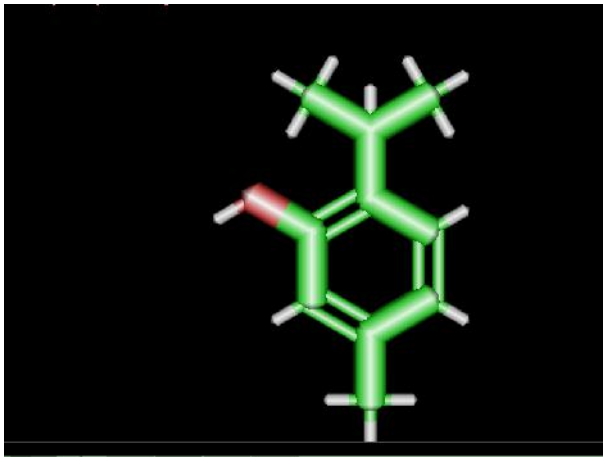
Rosa canina l structure view in pymol



CASTp**(6cdx)**structure and their amino acids

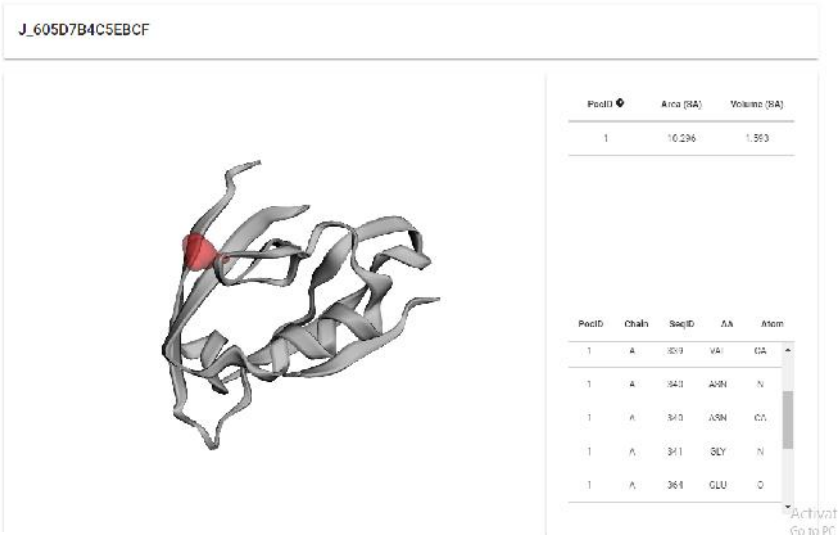


Roxe oxide ligand pose in**-8.61**

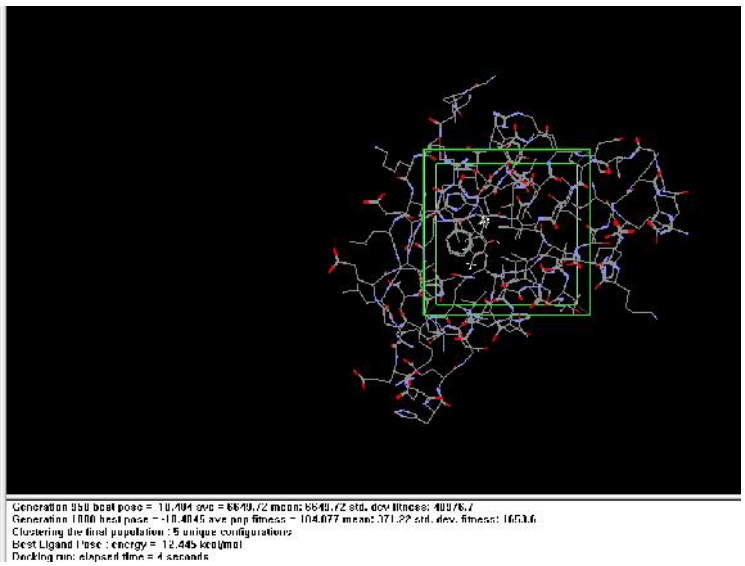


8. Thymus vulgaris

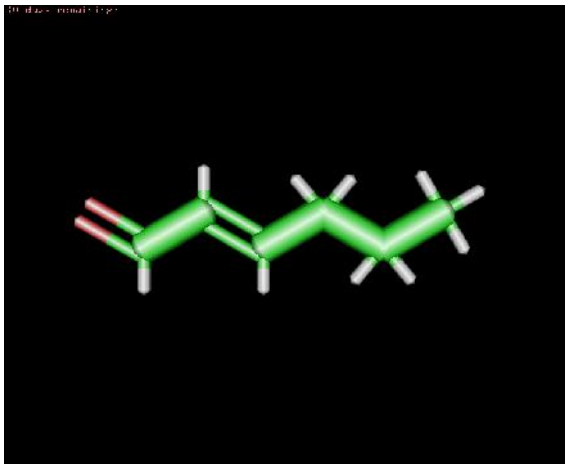
Thymus vulgaris structure view in pymol



CASTp**(4kj5)** structure and their amino acids

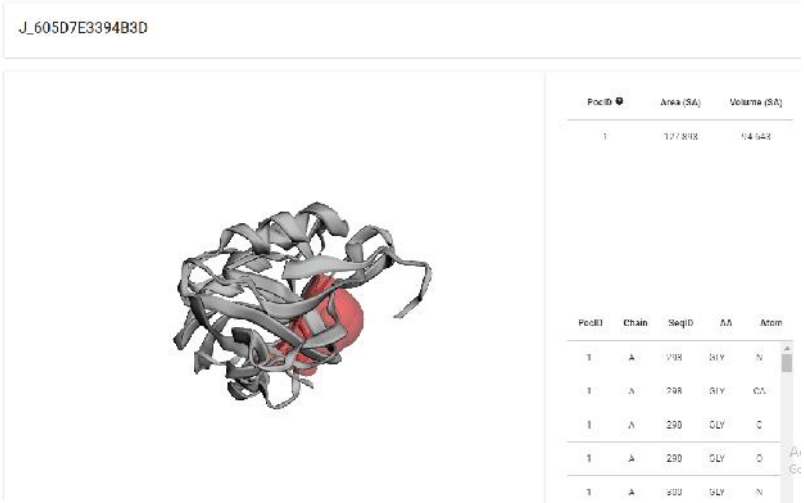


Thymol best ligand pose in **-12.44**

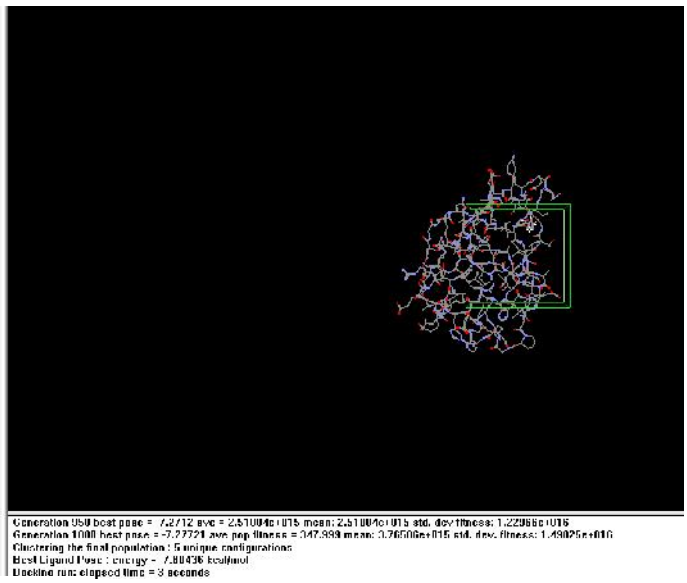


9. VerbascumThapsus

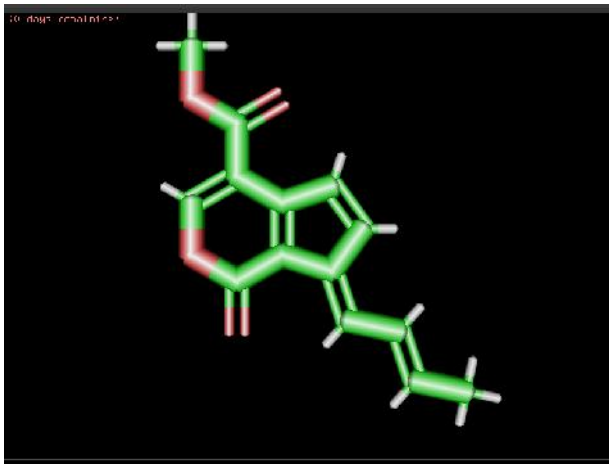
Verbascum thapsus structure view in pymol



CASTp**(4nmv)** structure and their amino acids

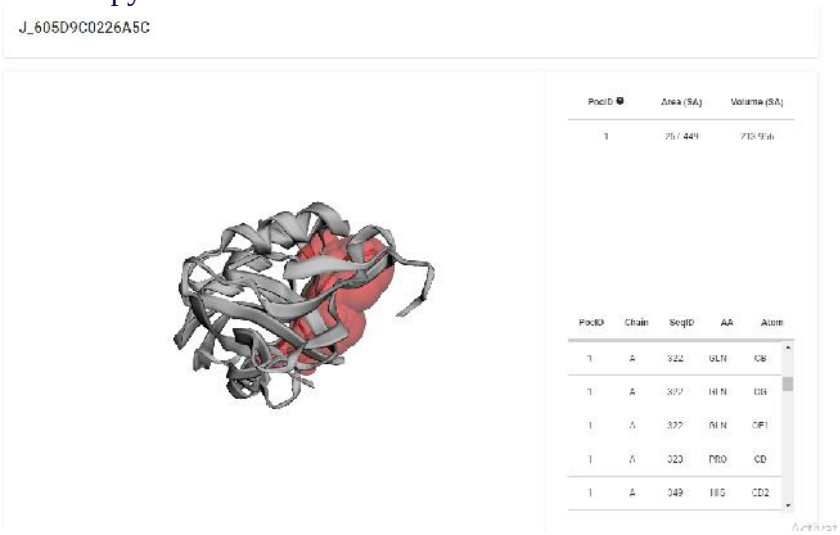


2-hexenal best ligand pose in **-7.00**

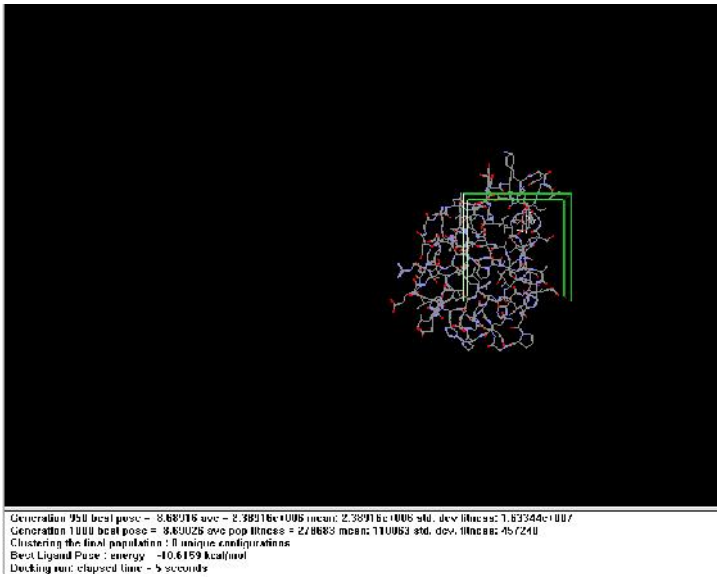


10. Ulmus rubra

Ulmus rubra structure view in pymol



(4k6y) structure and their amino acids



Fulvoplumierin best ligand pose in **-10.61**

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