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In silico analysis of cystic fibrosis and Molecular docking and modeling

M.Vinoth^{*1}, R. Priya², Mahendran Radha³

Department of Bioinformatics, Vels institute of Science and Technology & Advanced Studies,

Chennai.

*Corresponding e-mail: vinoth.sls@velsuniv.ac.in

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 placebocontrolled study¹.

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

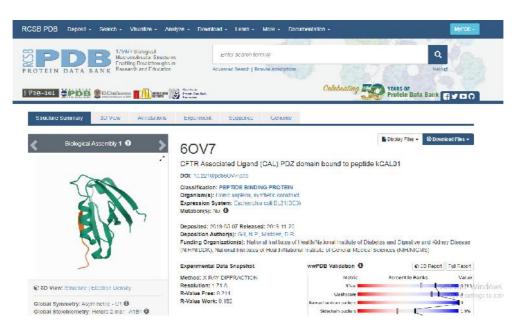
5. Molecular Docking: we use to find compound structure in pymol tool and we have binding compound to protein in ArgusLab

Results and Discussion

ul Raport +		Send to +
atr cystic fibrosis	transmembrane conductance regulator [Mus musculus (house mouse)]	土 Download Datasets
ene ID. 12638. updated on	22-Mer-2021	24
Summary		18. J.T
Official Symbol	Cftr playdee by MGI	
Official Luli Name	cystic fibroals transmembrane conductance regulator provided by MSB	
Primory source	MCLMCL26388	
See related	Ensembl FNSMUS300000011001	
Gene type	protein coding	
RefSeq status		
	Mus musculus	
Lineage	Eukaryota, Metazoa; Chordata; Graniata, Vertebrata; Euteleostomi, Mammalla; Eutheria; Euarchontogilres; Cilres; Rodenila; Murinoe; Mirs, Mirs, Mirs	Myomorpha; Muroldea; Muridae;
Also known us	Abec, Abec/, AW455483	
Summary	The nombrane-associated protein encoded by this gane is a membra of the upperfamily of ATF-Rindley cassets (ARO) team molecules across sets and into calcular molecules. ABC genes are civided into seven disinct coloninities (ABC) team (in protein is a membra of the M) of subtantly which is involved in multi-fung resistance. This gave encodes the syste three chlorids channel that controls the regulation of other transport patways. Multitanci is this group back between the second with a cyster (transis and congenital bilaterial spirals of the vas determs. Atemative splicing of exons 4, b, and 11 have been obser been fully described involved by ReSea. Jul 2000 [AP, MRP, ALD, OABP, GON20, White) sis transmemorane regulator and a utresonial reservice disorders such as
Expression Orthologe	Biased expression in large intestine adult ((CPKM 4.3), testis adult (RPKM 3.5) and 9 other issues See more	
NEW	Try the new Gene table	
Contract of Contra	try the new transcript table	

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

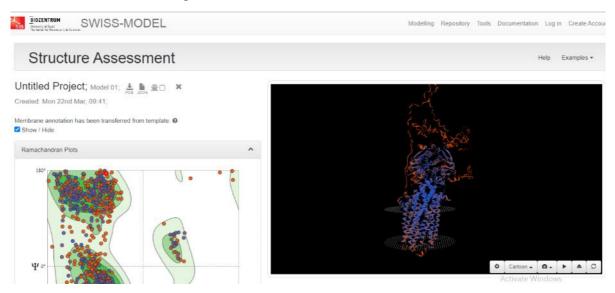


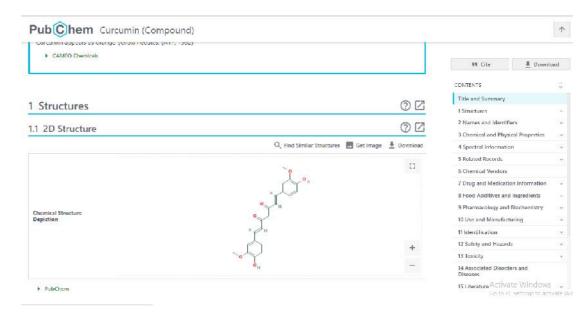
FIGURE 2:

The structure assessment and Ramachandran plot view for cftr

MulProhity Results		,	* · · · · · · · · · · · · · · · · · · ·	
Moll frebity Score	1.55		5 the	
📋 Clash Score	2 90	(A1445 PHE A1446 PHE), (A416 ASN A432 HIS) (A1166 GLU A1279 ARG)	and the second s	
Rameschandran Favoured	S2 46%			
- Ramardiandran Outliers	1 20%	A692 GUY, A680 LYS, A276 CYS, A331 ASR, A670 SER, A637 ARG, A1221 PRO, A738 DPRO, A638 PRO, A1054 A4 G, A531 LYB, Arth DHRO, Ar48 A394, A400 THU A417 CIV, A471 HIR, Ar153 CIN, A480 HHR, A1190 A5P A1106 WH, A701 A5H, A1951 LU, A166 PRO, A503 A5R, A222 GUJ, A1175 LLC		
Rolamer Outliers	0.48%	A1178 LEUL A691 VAL, A406 VAL, A671 VAL, A051 THR. A614 ASP	2	
C-Bela Deviations	18	6689 HTR, A412 GEN, A525 GEN, A1255 ARG, 6680 HYG, A1216 ASP, A395 THR, A727 GER, A136 ARG, A835 ASP, A672 ASP, A1331 LEU, A796 ARG, A1357 OLU, A508 PHE, A412 VAL, A215 CYS, A514 ASP		
- Bad Bonds	6711828	A835 ILE, A675 SER-A576 ALA, A1398 HIS, A830 ILE- A895 IPRO, <u>A742 ALA-A745 ALA</u> , A1220 ABN		
_ Bad Angles	1117 15001	A1220 ABN, A731 VAL A1301 / C.N. Davisier AL s 1 VAL, JARSE TELAGOS (2 Y), JATOM TARKATINA FRC), (A704 ST A A71 YAL, VARSH 1 JATOM FRC), (A744 LEU A745 PRC), A00 FILE, (A244 ALA A205 FRC), A21 THR A22 PRC), (A700 FILE A1251 FRC), A872 A811 ARX A22 PRC), (A700 FILE A1251 FRC), A872 A811 ARX A22 PRC), (A700 FILE A1251 FRC), A872 A811 ARX A711 FILEA/721 FRC)		Q Caroon
- Cis Non-	1/1407	(A1165 CEN-A116S THR)		Activate W

FIGURE3:

Moiprobity results and Ramachandran favoured is 92.40%



4. Ligand selection

The ligand selection for curcumin compound

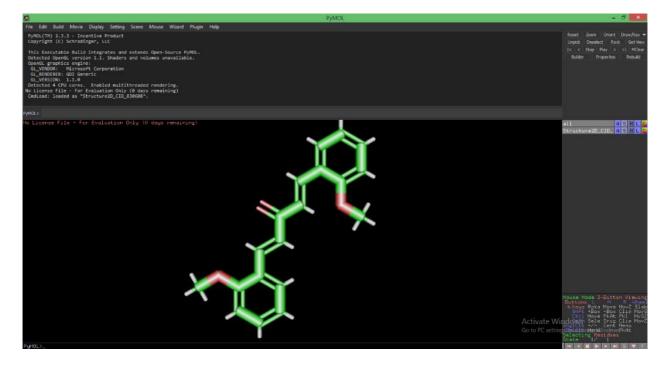
Table1:

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

4.	ZINGIBER OFFICINALE	Zingiber officinale	6850760	to the second se
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	in the second se

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

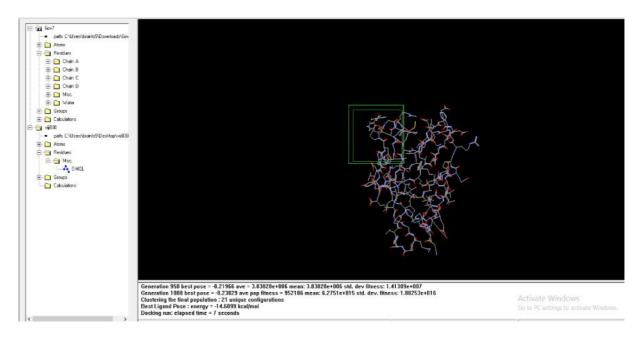


1. Curcumin

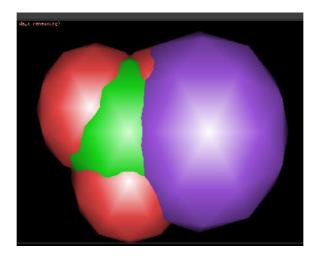
Pymol view in curcumin structure

		Tien et al., Nucleic Acids Res. 2018. PMD: 25060391 0	N 10.1012/ssr/gby472.
PostS & Area (SA) Volume (SA)	Pecto @ Area (54) Values (34) 1 10233.558 0171.857		Post er jakito
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CASTp(60v7) and there structure and amino acids

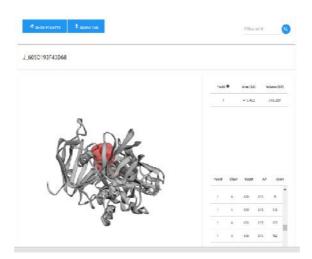


The curcumin best ligand pose is -14.68 in cystic fibrosis disease

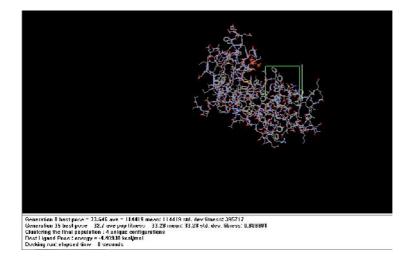


2. Althaea officinalis

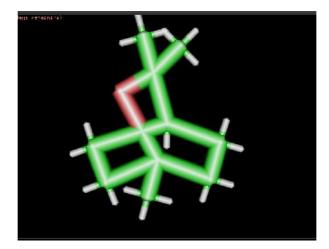
Sodium chlorate structure view in pymol



Castp(6gjs) strucuture view and their amino acids



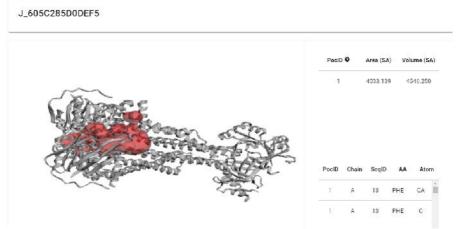
The sodium chlorate ligand pose in -4.40



3. Eucalyptus globulus labile

•

Eucalyptus globulus labile structure view inpymol

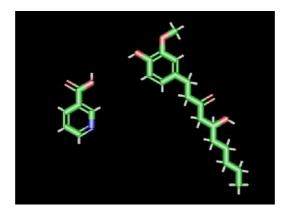


CASTp(5lij)structure and amino acids viewd



Refining structures of final candidates Clustering the linal population : / unique cantigurations Best Ligand Pose : energy = 7.5005 keal/mol Darking may islanced ling. 27 securates

The eucalyptol ligand pose in -7.60

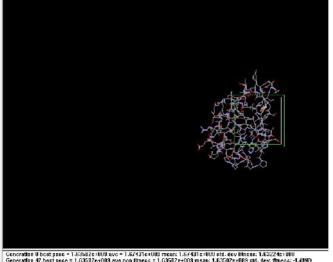


4. Zingiber officinale

Zingiber officinale structure view in pymol

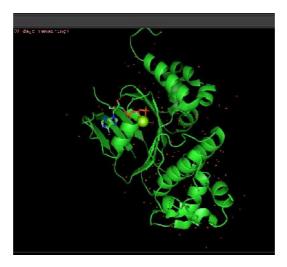
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	1 A 322 AIN C	08 06

CASTp(4nmo)structure and their amino acids

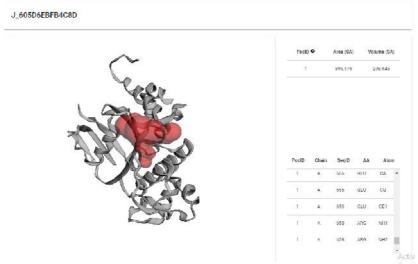


Cenoration V best pase = 1.83502 ar 009 evo = 1.574316+000 mean: 1.574316+000 std. dev Ninces: 1.632246+008 Generation 42 best pase = 1.03512e+008 ave pop Ninces = 1.03612e+008 mean: 1.63602e+008 std. dev. @neas: -1.21ND Clustering the final population : 5 unique configurations Hevel Ligural 1 wer: currys = 1.01535 keu/hou Decking run: cleased time = 1 seconds

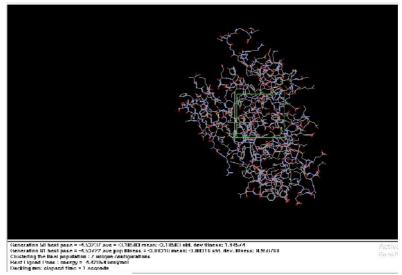
The Zingiberofficinale ligand pose in -10.15



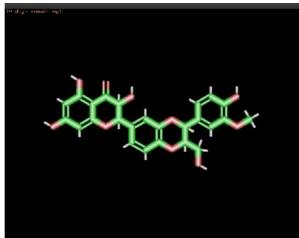
5. Glycyrrhiza glabra Glycyrrhiza glabra structure view in pymol



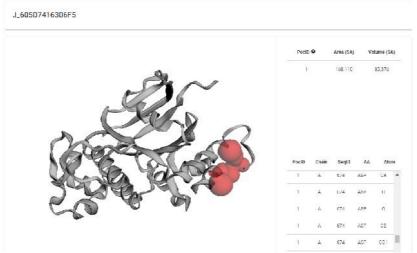
CASTp(1xmj)structure and their amino acids



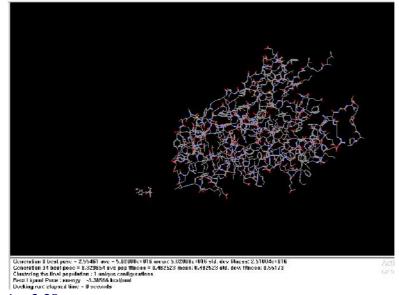
Iodinated glycerol best ligand pose in -4.42



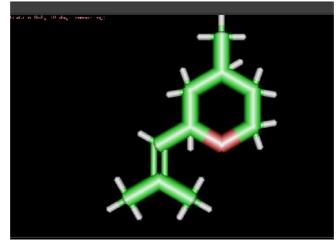
6.Silybum marianum Silybum marianum structure view in pymol



CASTp(2bb0)structure and their amino acids



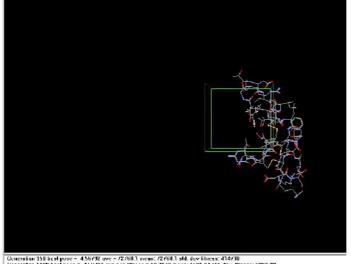
Milk thistle ligand pose in -3.38



7. Rosa canina l Rosa canina l structure view in pymol

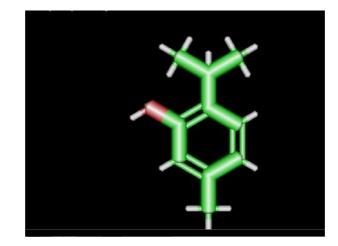
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CASTp(6cdx)structure and their amino acids



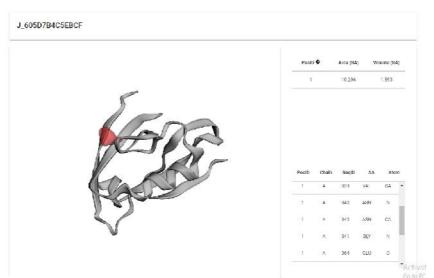
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Roxe oxide ligand pose in-8.61

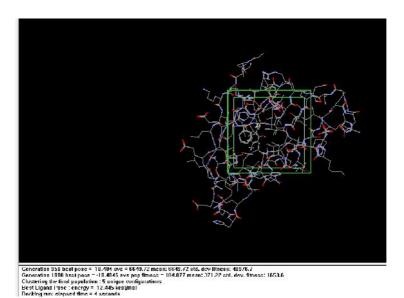


8. Thymus vulgaris

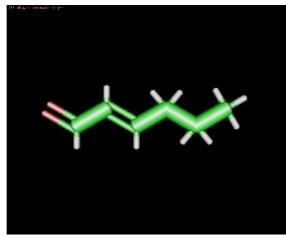
Thymus vulgaris structure view in pymol



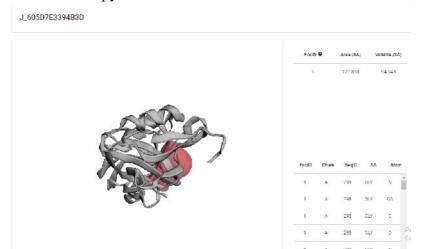
CASTp(4kj5) structure and their amino acids



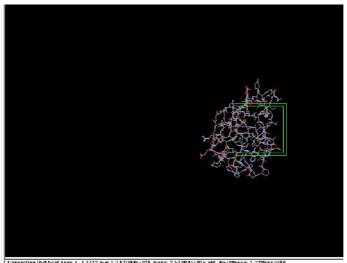
Thymol best ligand pose in -12.44



9. VerbascumThapsus Verbascum thapsus structure view in pymol



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



Generation USU Dost pass = 7,2/12 evc = 2,51004c1015 mean: 2,5100401015 std. dov titness: 1,22055c1015 Generation 1000 host pass = -7,2721 ave pap titness = 3,47,399 mean: 3,76506e+015 std. dev. fitness: 1,43025c+016 Clustering the final population : 5 unique configurations Best Liguel Vest: concept - 2,8025k kodinol Dischort run elopeod time = 3 seconds

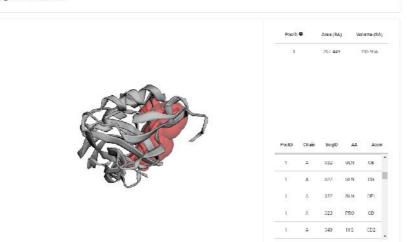
2-hexenal best ligand pose in -7.00



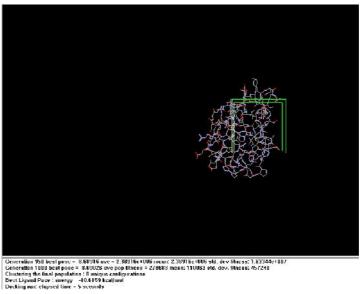
10. Ulmus rubra

Ulmus rubra structure view in pymol

J_605D9C0226A5C



(4k6y) structure and their amino acids



Fulvoplumierin best ligand pose in -10.61

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