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MOLECULAR DOCKING STUDY ON DIPEPTIDYL PEPTIDASE-4 INHIBITORS

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ABSTRACT

Prevalence of diabetes is rising dramatically, world-wide in 2010 prevalence is 221 million and it is projected to be a 300 million in 2030. The majority of patients suffering from type II diabetes mellitus and associated with deficient insulin secretion and insulin resistance with islet-cell dysfunction. The majority of currently available therapeutic options for treatment of type II diabetic mellitus are associated with one or more adverse events like weight gain and hypoglycaemia, gastrointestinal toxicities, edema, congestive heart failure, bladder cancer and no one addressing the progressive loss of islet-cell and thus, there is a need to develop novel therapeutic agents. Recent developed DPP-IV inhibitor offers advantages, counting no or less weight gain and no risk of hypoglycemia. Still, some side effects are with them, including throat infection, GIT problems like diarrhea and URT infection. Apart from these side effects, reported compounds are of less potent. Hence, we have performed molecular docking studies on recently designed cyanopyrrolidine derivatives by using Vlife-MDS software to get detailed information regarding interaction of DPP-IV enzyme and ligands. **Materials and Methods:** All docking studies performed using Vlife MDS suit installed in Dell inspiron 15 Laptop running on a 1.50 GHz Intel core i3 processor with 2GB RAM and 500 GB hard disk with Windows 8 operating system. Protein Structure and Ligand Preparation were performed and ligands selection were done by applying Lipinski's Rule of Five.0 Batch Docking Module of Vlife MDS used for docking. **Results:** The top low energy structures of all 11 DPP IV inhibitors had docking energies ranging from 45.56 to 89.96 kcal/mol. The key interaction between receptor amino acid and ligands are Hydrogen bond interactions with ASP708, ASP709, HIS712 and PHE713 amino acids. Added to these Aromatic interactions are also found with TRP201, TYR238, TYR256 and HIS712 amino acids. Further VDW interactions with TYR241, TRP201, ILE236, TYR238, VAL254, TYR256, HIS704, GLY705, THR706, ALA707, ASP708, HIS712, PHE713, GLN714 amino acids and Hydrophobic interactions with SER239, PRO249, TRP201, ILE236, TYR238, VAL254, TYR256, THR706, ALA707, ASP709, HIS712, PHE713, GLN714 were found.

INTRODUCTION

Type II diabetes is a major public health issue all over the world, and world becoming a "diabetes epidemic" as stated by Zimmet [1].Type II diabetes occurs when 2 major abnormalities co-exist first a reduction of insulin effects on liver and skeletal muscle); and second a quantitative and qualitative reduction of insulin secretion [2-5]. TCF7L2, has been identified as major gene for diabetes 2 susceptibility [6].Non genetic factors, particularly insufficient supply of nutrients and amino-acids during the foetal life may result in a reduced β-cell mass, and a reduction in the ability to compensate when insulin resistance is present [7] Hales et al. have shown that subjects with birth weight in the lowest quintiles are more prone to IGT and type II diabetes in adulthood [8].

Current antidiabetic therapies are also accompanied by a range of adverse effects. These include hypoglycemia and weight gain with sulfonylureas, insulin, and glinides; and edema, weight gain, and increased risk of bone fracture with thiazolidinediones. Metformin appears to modestly reduce weight when given as monotherapy, but it can produce hypoglycemia and gastrointestinal adverse events and has been linked to lactic acidosis [9] Type II diabetes is associated with additional cardiovascular risk factors, including obesity, hypertension, and an atherogenic dyslipidemia profile typified by high levels of triglycerides, low levels of high-density lipoprotein cholesterol, and an increased fraction of atherogenic small, dense low-density lipoprotein cholesterol particles. [10-11] Glucagon-like peptide-1 is an insulinotropic hormone with antidiabetic potential due to its spectrum of effects, which include glucose-dependent stimulation of insulin and inhibition of glucagon secretion, tropic effects on the pancreatic β-cells, inhibition of gastric emptying and the reduction of appetite. Glucagon-like peptide-1 is, however, extremely rapidly inactivated by the serine peptidase, dipeptidyl peptidase IV, so that the native peptide is not useful clinically. A new approach to utilize the beneficial effects of glucagon-like peptide-1 in the treatment of type II diabetes has been the development of orally active dipeptidyl peptidase IV inhibitors which inhibit DPP-4 and prolong the duration of GLP-1 and GIP activity, resulting in lower blood glucose level [12] Early preclinical experiments and smaller human studies of GLP1 analogs (exenatide, liraglutide) and DPPIV inhibitors (saxagliptin, sitagliptin, vildagliptin) suggested that targeting the incretin axis might address the elusive goal of an antidiabetic agent that improves cardiovascular disease [13-14]

Clinical data reveals that the recent DPP-IV inhibitor offers many prospective advantages, counting no or less weight gain and no risk of hypoglycemia. Still, some side effects are with them, including throat infection, GIT problems like diarrhea and URT infection. Apart from these side effects, reported compounds are of less potent. Hence, great opportunities still present for computer-aided drug design in search of potent DPP-IV and accordingly to obtain insights into the active site of enzyme, docking will help to recognize the connection among the structural information of the known compounds.

To discover out the novel, selective and potent DPP-IV inhibitor for the treatment of diabetes, we executed molecular docking studies on recently designed cyanopyrrolidine derivatives by using Vlife-MDS software.

MATERIALS AND METHODS [15]

All computational studies were carried out using V-life MDS suit installed in Dell inspiron 15 Laptop running on a 1.50 GHz Intel core i3 processor with 2GB RAM and 500 GB hard disk with Windows 8 operating system.

Steps involved in Molecular Docking

1) **Protein Structure Preparation**

For the molecular docking study, protein structure was obtained from the RCSB Protein Data Bank (www.rcsb.org/); the DPPIV structure PDB ID was 3BJM (Enzyme structure is shown in fig no 1). The co crystallized Ligand (Sexagliptin i.e. BMS-477118) in the DPP-IV structure was removed. Addition to this some modification were performed are removal of the water molecules from the cavity, filling in the missing residues and addition of hydrogen atoms. After modification the receptor was found to biological active and stable.

2) **Ligand Preparation**

Ligand 2D structures were sketched using ChemDraw Ultra 8.0 (ChemOffice 2004). 2D structure converted into 3D by Chem3D Ultra 8.0 and the energy minimization was done by using semi empirical AM1 method. Minimize energy to minimum RMS gradient of 0.100 was set in each iteration. While selecting the ligands, the LIPINSKY'S RULE OF 5 which is important for drug development where a pharmacologically active lead structure is optimized stepwise for increased activity and selectivity, as well as drug-like properties was applied.

3) Selection of a ligands using Lipinski's Rule of Five:

H bond donors: Not More Than 5

Molecular Weight: Not More Than 500 Da.

Log P: Not More Than 5

H bond acceptors: Not More Than 10

Rotatable Bond Count: Not More Than 10

Application of Lipinski's rule of 5: Lipinski's rule of 5 were applied and molecular weight, H-Acceptor Count, H-Donor Count, Rotatable Bond Count and XlogP values were calculated by using V-Life Software to filter the compounds on the basis of Lipinski's rule of 5

4) Docking

This is the last step, where the ligands were docked onto the receptor and the interactions are checked. The scoring function generates scores depending on which the ligand with the best fit is selected. Procedure for molecular docking:

1: Grid Based Batch Docking Module was selected
2: DPP-IV Receptor and different newly designed cyanopyrrolidine ligands were selected and following parameters were chosen for docking
Size of Rotation Angle for ligands rotation step: 100
Fitness Function: Dock Score
No of bump allowed: 4
3: Cavity for docking was specified
4: Grid Based Batch Docking was started
5: Results of docking in the form of minimum score were obtained on the Task Manager and in the log1.log file.

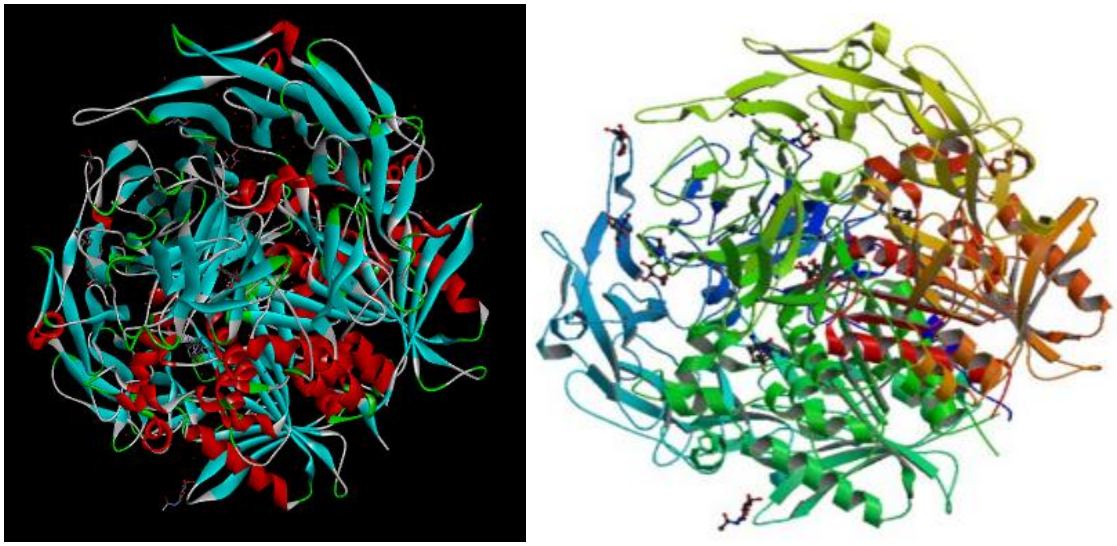

Fig. No. 1 Structure of Dipeptidyl Peptidase-IV enzyme 3BJM with Sexagliptin inhibitors

RESULT AND DISCUSSION

The best compounds were selected on the basis of result of Docking obtained in docking_3BJM file in docker's folder available with VLife MDS™. This file provides list of compound in descending order with best poses and their docking score. The best pose is a one which have lowest binding energy conformation in all cluster and reported docking score represent the sum of the torsional free, intermolecular and internal energy minus the energy of the unbound system. The docking score were generated by Batch Docking Module of VLife MDS along with best poses were shown in Table 1.

The docked structures of 11 DPP IV inhibitors with their respective scores are shown in Table 2. The top low energy structures of all 11 DPP IV inhibitors had docking energies ranging from 45.56 to 89.96 kcal/mol.

The key interaction between receptor amino acid and ligands are shown in Table 3. All the 11 DPP IV inhibitors in common shows 1) Hydrogen bond interactions with ASP708, ASP709, HIS712 and PHE713. 2) Aromatic interactions with TRP201, TYR238, TYR256 and HIS712. 3) VDW interactions with TYR241, TRP201, ILE236, TYR238, VAL254, TYR256, HIS704, GLY705, THR706, ALA707, ASP708, HIS712, PHE713, GLN714 4) Hydrophobic interactions with SER239, PRO249, TRP201, ILE236, TYR238, VAL254, TYR256, THR706, ALA707, ASP709, HIS712, PHE713, GLN714

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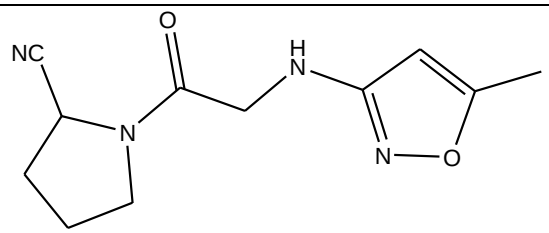
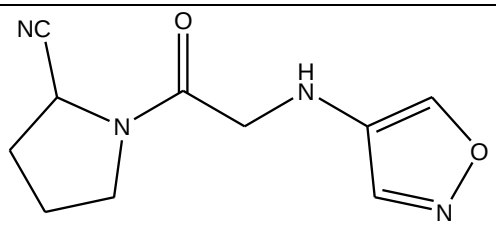
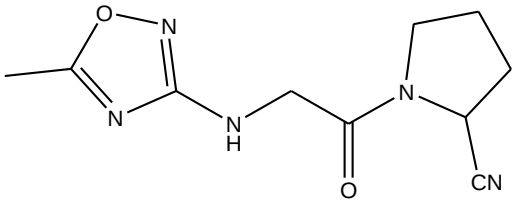
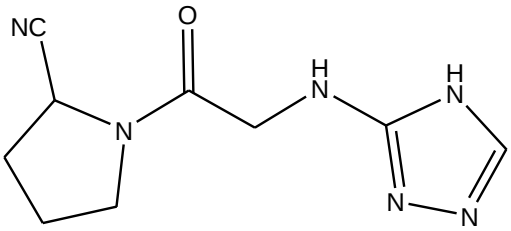
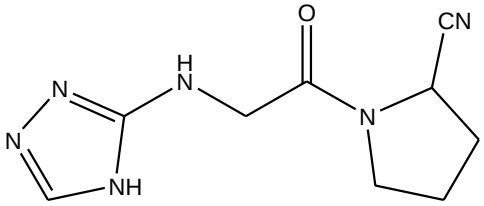
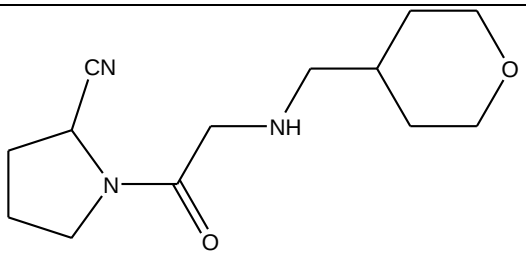
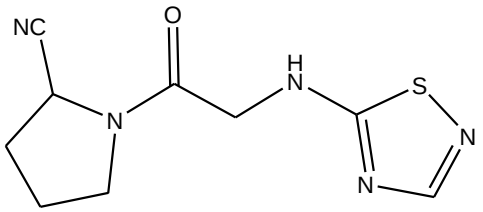
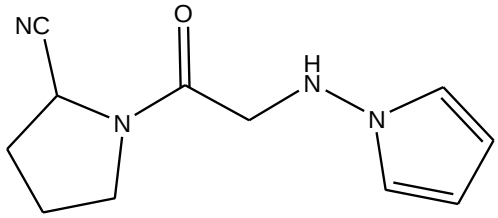
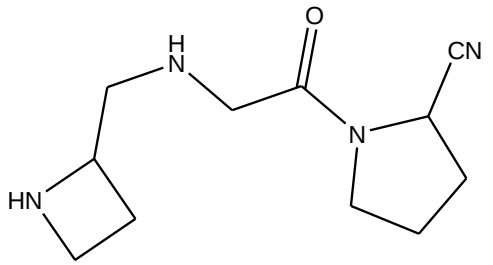
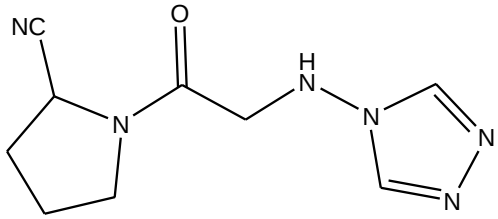
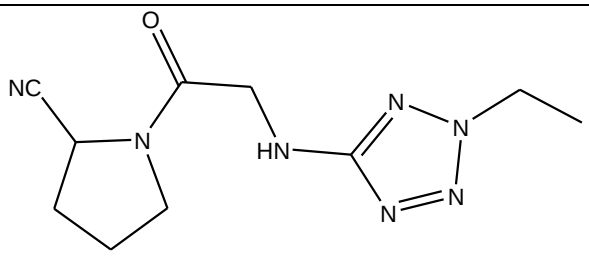
Table No. 1 Docking score of best docked compounds with structure

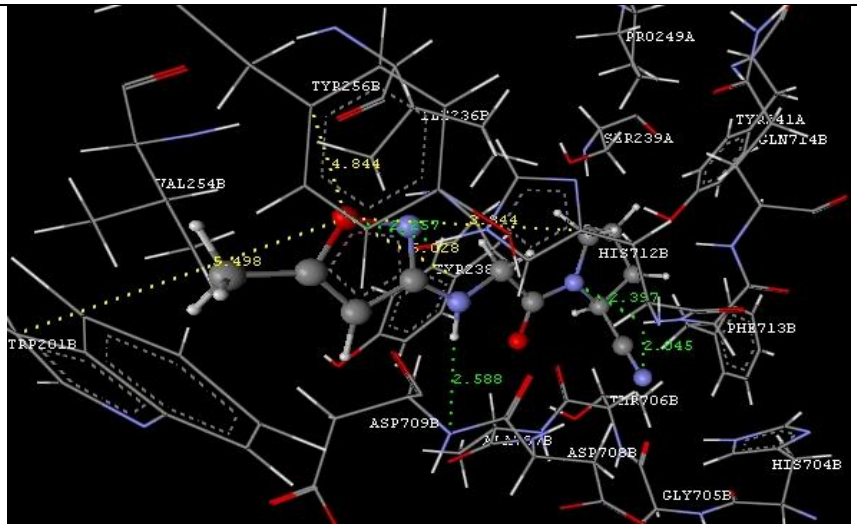
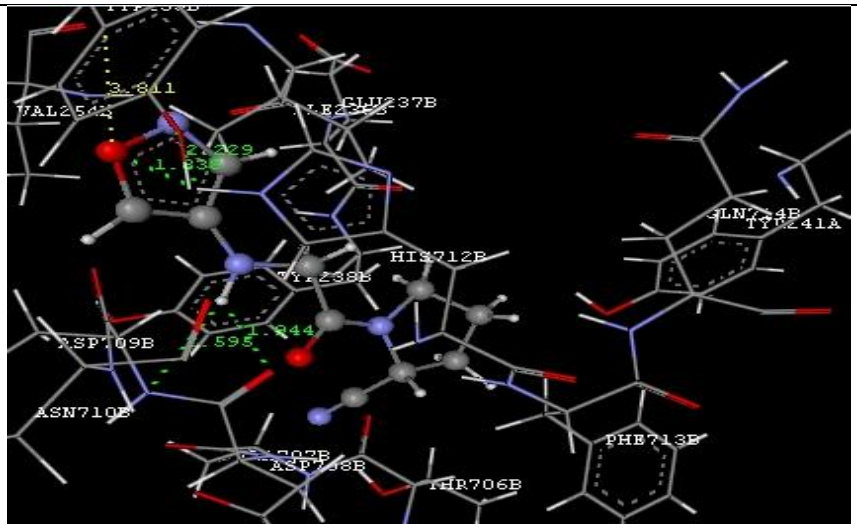
Sr. No.	Placement	Score	Structure
1	CYP89_332_3D_opt_P15	45.56	
2	CYP87_330_3D_opt_P5	70.07	
3	CYP94_338_3D_opt_P20	73.01	
4	CYP242_159_3D_opt_P11	73.08	
5	CYP37_274_3D_opt_P28	74.34	
6	CYP173_82_3D_opt_P18	84.43	

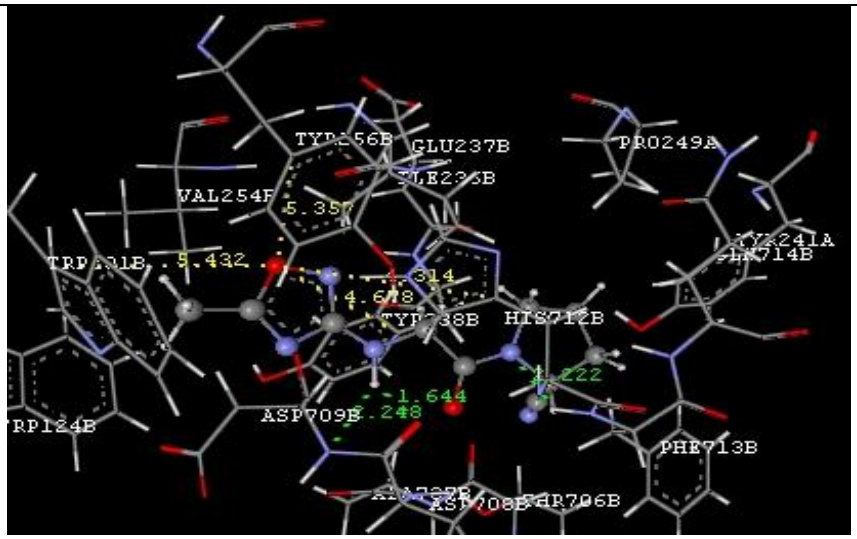
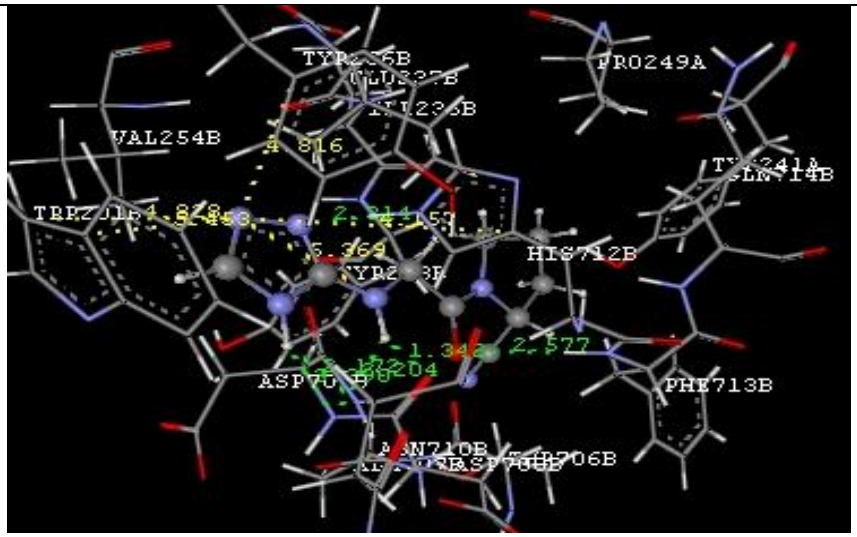
7	CYP296_218_3D_opt_P9	84.87	
8	CYP328_254_3D_opt_P14	85.17	
9	CYP41_279_3D_opt_P1	85.88	
10	CYP241_158_3D_opt_P26	89.96	
11	CYP305_229_3D_opt_P8	89.96	

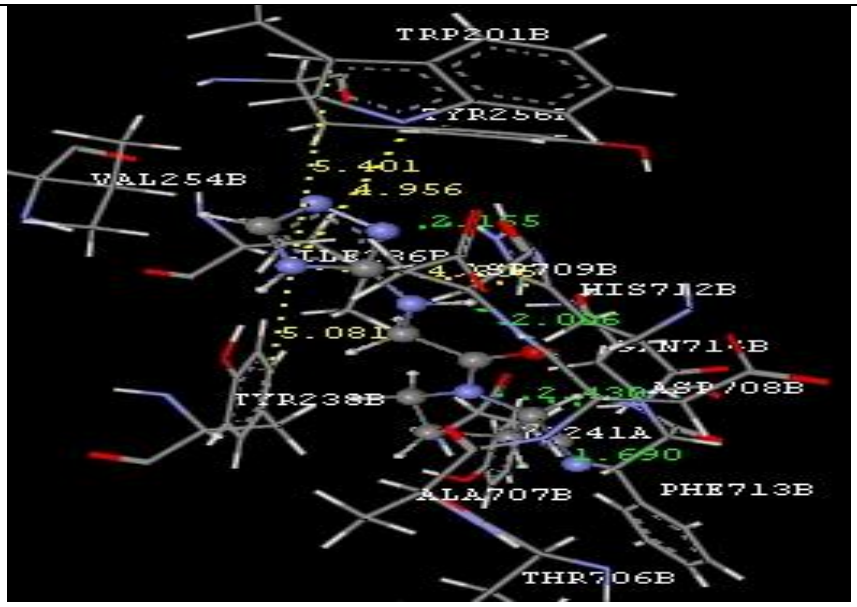
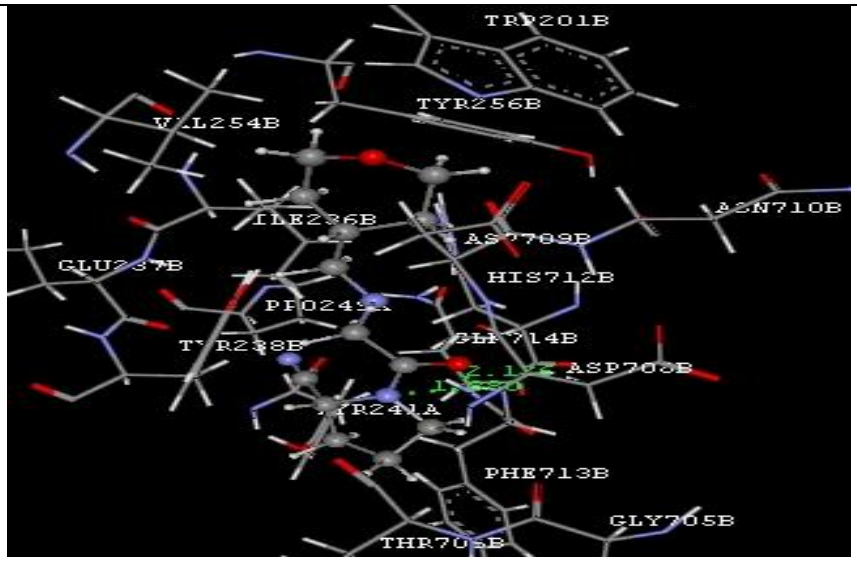
Minimum Score :Molecule Name = CYP89_332_3D_opt_P15 score = 45.562372

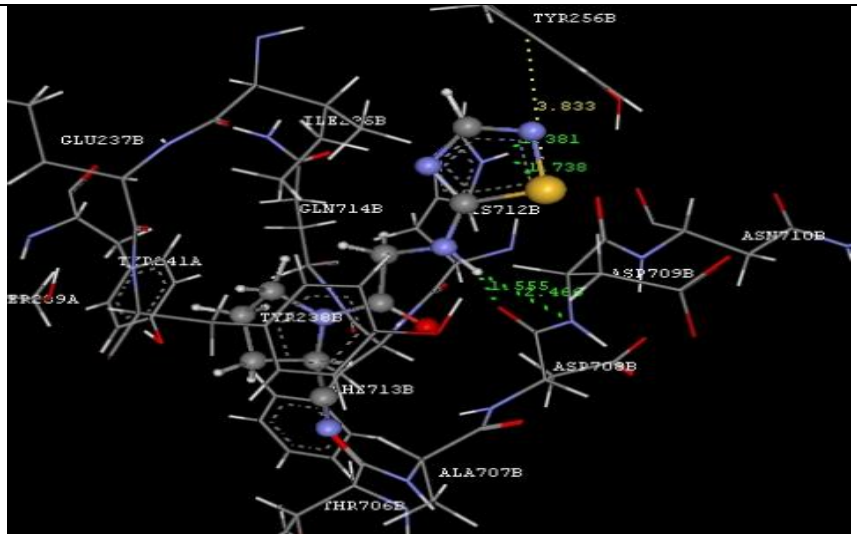
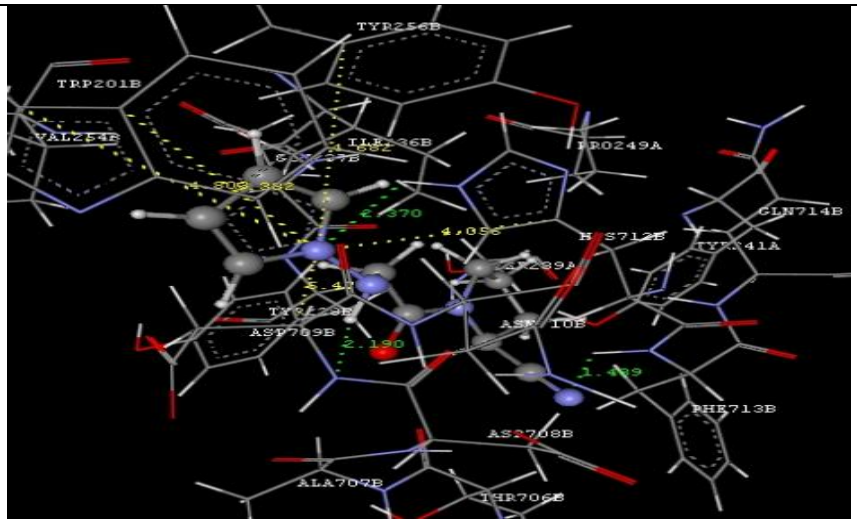
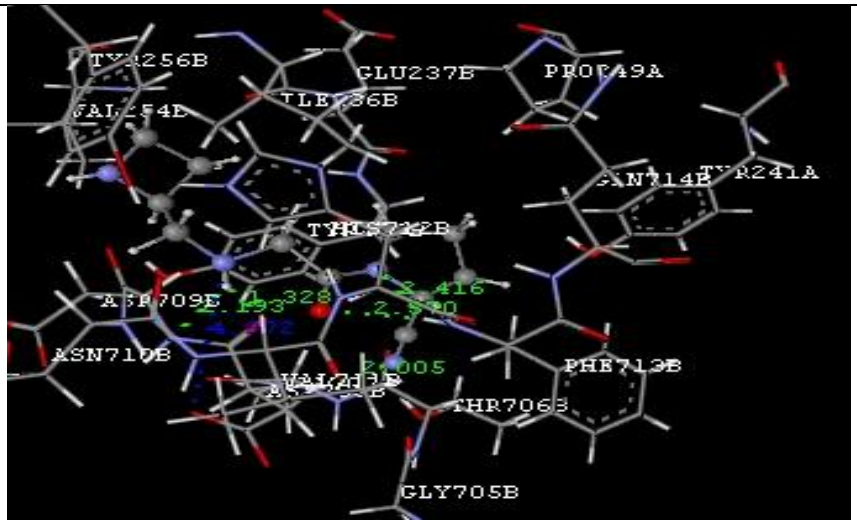
Original Ligand Score = 919.365035

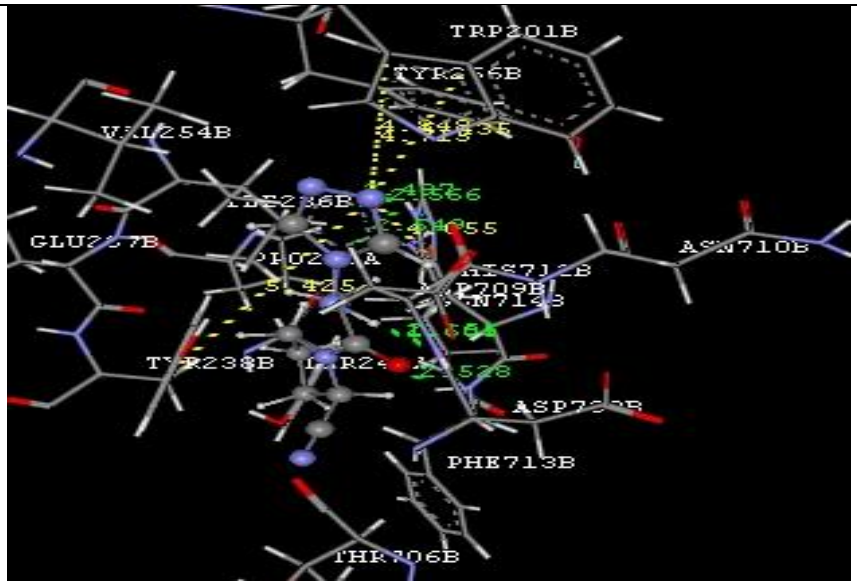
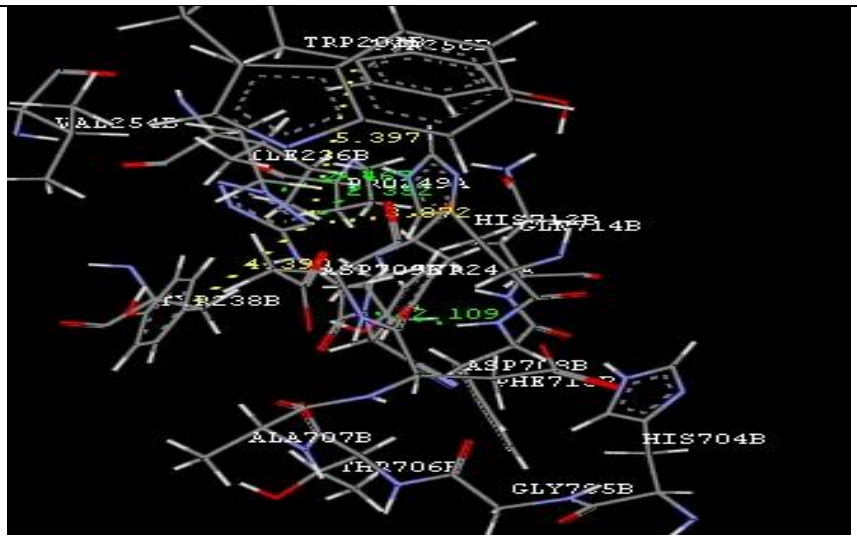
Table No. 2. Selected compounds after docking 3BJM based on score with best pose.

Placement	Score	Best Pose Image
CYP89 _P15	45.56	
CYP87 _P5	70.07	

CYP94 _P20	73.01	
CYP242 _P11	73.08	

CYP37 _P28	74.34	
CYP173 _P18	84.43	

CYP296 _P9	84.87	
CYP328 _P14	85.17	
CYP41 _P1	85.88	

CYP241 _P26	89.96	
CYP305 _P8	89.96	

Minimum Score: Molecule Name = CYP89_332_3D_opt_P15 score = 45.562372

Original Ligand Score = 919.365035

Table No. 3. The key interaction between receptor amino acid and ligands

SR.NO.	VDW	HYDROPHOBIC	AROMATIC	H-BOND
CYP89	TYR241,TRP201, ILE236, TYR238, VAL254, TYR256 HIS704, GLY705, THR706 ALA707, ASP708, HIS712 PHE713, GLN714	SER239, PRO249, TRP201 ILE236,TYR238, VAL254 TYR256, THR706, ALA707, ASP709, HIS712 PHE713, GLN714	TRP201 TYR238 TYR256 HIS712	ASP709, PHE713 PHE713 HIS712
CYP87	TYR241, ILE236,GLU237 TYR238, THR706,VAL254, TYR256, ALA707, ASP708, ASN710, HIS712, PHE713, GLN714	ILE236, TYR238,THR706, ALA707,ASP708, HIS712 GLN714	TYR256	ASP708 ASP709 HIS712 HIS712
CYP94	TYR241, PRO249, TRP124, ILE236, GLU237, TYR238, VAL254, TYR256, THR706, ALA707, ASP708, HIS712, PHE713, GLN714	PRO249, TRP201, ILE236, TYR238, VAL254, ASP708, HIS712, PHE713, GLN714	TRP201 TYR238 TYR256 HIS712	ASP708 ASP709 PHE713
CYP 242	TYR241, PRO249, TRP201, ILE236, GLU237, TYR238, VAL254, TYR256, THR706, ALA707, ASP708,ASP709, ASN710, HIS712 , PHE713, GLN714	PRO249, ILE236, TYR238, THR706, ASP709, HIS712, PHE713, GLN714	HIS712 TYR256 TYR238 TRP201	PHE713, HIS712 ASN710, ASP708
CYP 37	TYR241,ILE236, TYR238 VAL254, TYR256, THR706 ALA707, ASP708 ,HIS712 PHE713, GLN714	ILE236, TYR238, ASP708 HIS712, PHE713, GLN714	TRP201 TYR238 TYR256 HIS712	ASP708 HIS712 PHE713
CYP 243	ILE236, TYR238, VAL254 TYR256, GLY705, THR706 ASP708, ASP709, HIS712 ASN710, PHE713	TRP201, ILE236, TYR238, VAL254, TYR256, ASP708 ASN710, HIS712, PHE713	-	-
CYP 173	TYR241, PRO249, TRP201 ILE236 , GLU237, TYR238, VAL254 TYR256 GLY705, THR706, ASP708, ASN710, HIS712,PHE713, GLN714	TRP201, ILE236, TYR238 VAL254, TYR256, THR706, ASP708, ASN710, HIS712, PHE713		
CYP 296	TYR241, ILE236, GLU237, TYR238, TYR256, THR706 ALA707, ASP708, ASN710 HIS712, PHE713, GLN714	SER239, ILE236, TYR238, THR706, ALA707, ASP709, HIS712, PHE713	TYR256	ASP708 ASP709 HIS712
CYP 328	TYR241, TRP201, PRO249 ILE236, GLU237, TYR238 VAL254, TYR256, THR706 ALA707, ASP708, ASN710 HIS712, PHE713, GLN714	PRO249, SER239, ILE236 TYR238, THR706, ASP709 HIS712, PHE713, GLN714	TRP201 TRP201 TYR238 TYR256 HIS712	ASP709 HIS712 PHE713
CYP 41	TYR241, ILE236, GLU237 TYR238, VAL254,TYR256 GLY705, THR706, ALA707 ASP708,ASN710, HIS712 VAL711, PHE713, GLN714	ILE236, PRO249, TYR238 VAL254, TYR256, THR706, ASP708, HIS712 PHE713, GLN714	ASP708	ASP708 ASP708 ASP709 PHE713
CYP 241	TYR241, PRO249, TRP201 ILE236, GLU237, TYR238 VAL254, TYR256, THR706 ASP708, ASN710, HIS712 PHE713, GLN714	PRO249, ILE236, TYR238 THR706, ASP709, HIS712 PHE713, GLN714	TRP201 TRP201 TYR238 TYR256 HIS712	ASP708 ASP709 HIS712 HIS712 HIS712 PHE713
CYP 305	TYR241, PRO249, TRP201 ILE236, TYR238, VAL254 TYR256, HIS704, GLY705 THR706, ALA707, HIS712 PHE713, GLN714	PRO249, TRP201, ILE236 TYR238, VAL254, TYR256, ASP708, HIS712 PHE713, GLN714	HIS712 TYR256 TYR238	HIS712 HIS712 PHE713

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