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MOLECULAR DOCKING STUDY OF LEAVES COMPONENTS OF SYZYGIUM SAMARANGENSE ON BRUTON'S TYROSINE KINASE

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ABSTRACT

Syzygium species shows rich medicinal applications. The bioactive compounds from ethanolic extract of *Syzygium samarangense* using gas chromatography–mass spectrometry and their inhibition potential against the enzyme 3T9T were studied. The investigation focuses on the molecular simulation of bioactive compounds against the enzymes that acts as a potential drug target and supports the drug discovery process. Eighteen active compounds and their interactions with 3T9T were studied in this research work. In this study we analysed the binding affinity of 18 compounds with indicated target enzymes, through which Stigmastan-3,5-diene and Lupeol acetate is best inhibitors. Stigmastan-3,5-diene and Lupeol acetate shows highest binding energy when compared to scores obtained with the docking of remaining ligands to the respective enzymes 3T9T. And the compound Gallic acid (-5.5) shows lowest binding energies as compared to other compounds.

Keywords: *Syzygium Samarangense*, 3T9T, Autodock Vina, Lupeol Acetate.

INTRODUCTION

Arthritis' is a combinative word originated by mixing Latin and Greek .In Greek "Arthron" signifies joint and in Latin "Itis", indicates inflammation. Thus arthritis is a disease caused as a result of inflammation on joints. Congenitally, it is not a single disease but a collection of medical problems collectively termed as "Arthritis". Almost 47 million adults and 3lakhs children suffer in the US alone [1]. The disease cans delibiliate permanently, if proper treatments are not provided in time. Also globally, will impose a huge financial burden through wage loss along with the medication cost [2-3].

Molecular docking is one of the in silico technique which is more efficient compared to in vitro and in vivo method for its capability of finding the active compound in medicinal plants. A three dimensional structure become incredibly important in the molecular docking methods that depicts the compound [3-4].

All Syzygium species shows rich medicinal applications. Syzygium species are known to be useful in Pain, diabetes, cough, headaches, and fever. Its potential as an effective antidiabetic agent cannot be ruled out it accredited due to the presence of the various pharmacological active phytochemicals such as alkaloids, fatty acids, steroids and tannins. The present paper deals with the utility of compound isolated from Syzygium samarangense ethanolic leaf extract by molecular docking to assess its antiarthritic property [5].

MATERIALS AND METHODS

Bioactive compounds obtained from gas chromatography– mass spectrometry (GC-MS) analysis of *Syzygium samarangense*

The information regarding the bioactive compounds, such as IUPAC name, structures, and chemical formula, were retrieved from PubChem database. The bioactive compounds listed in Table 1 were used for molecular docking against the enzyme. The two-dimensional (2D) chemical structures of the bioactive compound were sketched using ChemDraw Ultra 2008, and the energy minimizations of the prepared ligands were carried out with Chem3D Ultra and were saved in pdb format.

Target Preparation and Validation of Docking Method

The three dimensional structure of protein was obtained from Brook haven protein databank (PDB ID: 3T9T). The docking study was available ahead with the definition of a binding site, in general a restricted region of the protein. The size and position of this binding site was visualized in PyMOL. The protein target was further

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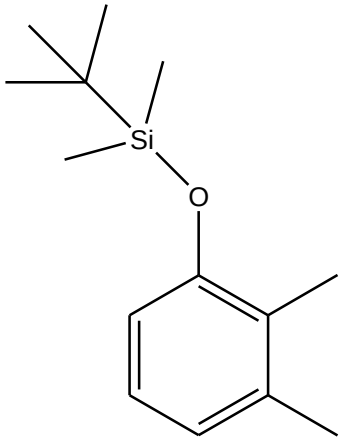
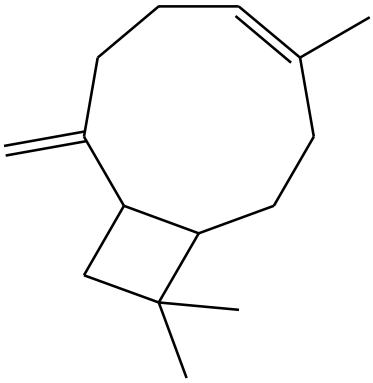
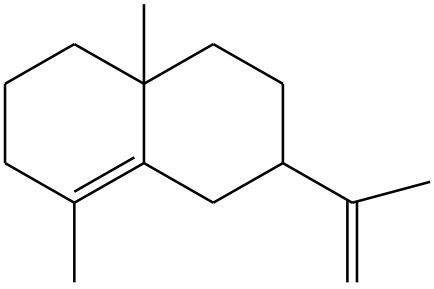
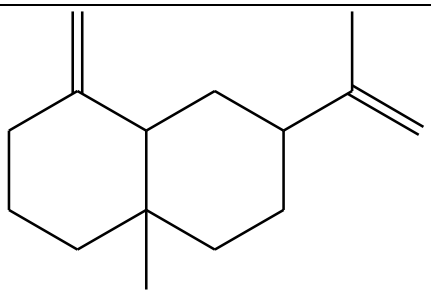
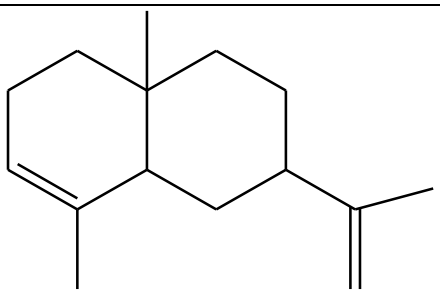
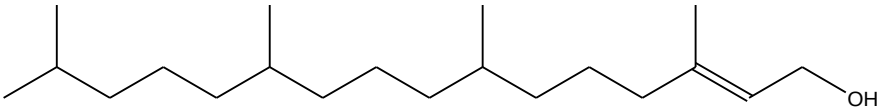
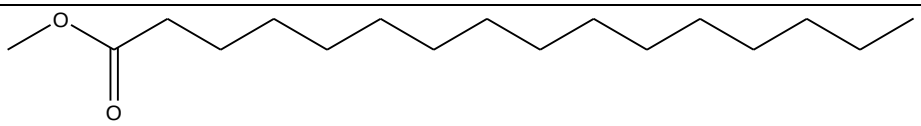
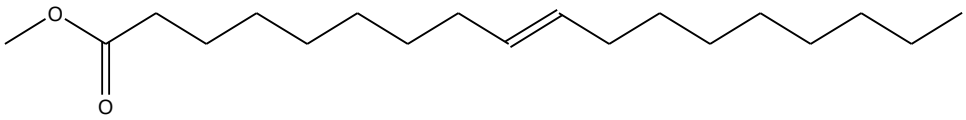
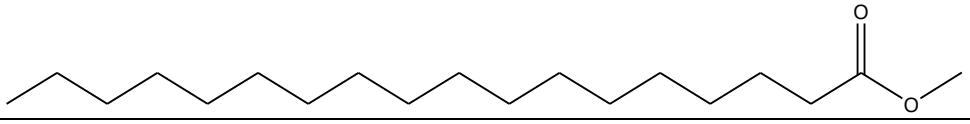
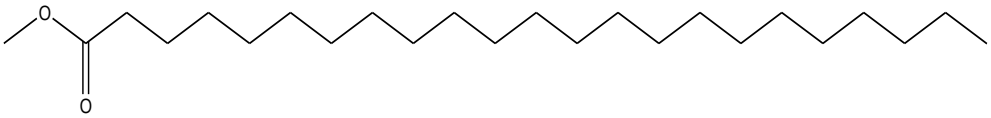
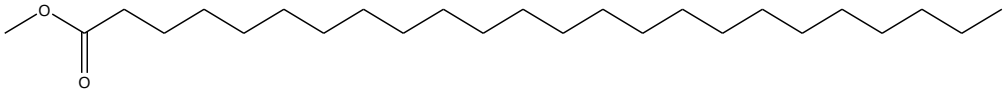
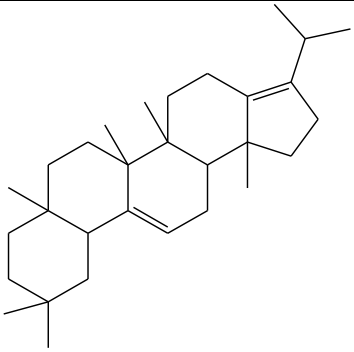
validated with AutoDock Vina in PyRx 0.8 by RMSD value determination 8.

Molecular Docking Analysis Binding mode and interaction of Protein (3T9T) with individual chemical constituent of *Syzygium samarangense*, was performed using AutoDock Vina software. Docking was performed to gain a population of possible conformations and orientations for the ligand at the binding site. The protein was loaded in PyRx software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues. All bonds of ligands are set to be rotatable. All calculations for protein-fixed ligand-flexible docking be done using the Lamarckian Genetic Algorithm (LGA) method. The docking site on protein target was defined by set up a grid box with the dimensions of X: 38.0729 Y: 33.3208 Z: 25.0000 Å, with a grid spacing of 0.375 Å, centered on X: 20.2892 Y: 10.3219 Z: 32.3218 Å. The best conformation was selected with the lowest docked energy, after the docking search was completed. Ten runs with AutoDock Vina were carrying out in all cases per each ligand structure, and for each run the best pose was saved. The average affinity for finest poses was taken as the final affinity value. The interactions of complex protein-ligand conformations, including hydrogen bonds and the bond lengths were analyzed using PyMol [6-9].

Table 1: Molecular Structure of Identified Compounds from the Ethanolic Leaf Extract of *Syzygium Samarangense*

S. No	**Name of the compound**	**Molecular structure**
01	2,3-Dimethylphenol, tert-butyldimethylsilyl ether	
02	Caryophyllene	
03	2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene	

04	β-Eudesmene	
05	α-Selinene	
06	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	
07	Hexadecanoic acid, methyl ester	
08	9-Octadecenoic acid, methyl ester	
09	Octadecanoic acid, methyl ester	
10	Methyl docosanoate	
11	Methyl tricosanoate	
12	Methyl tetracosanoate	
13	A-Neooleana-3(5),12-diene	

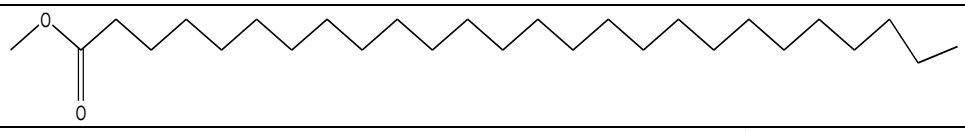
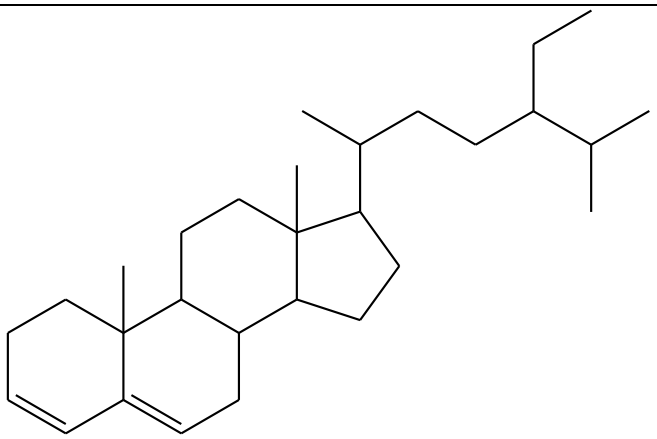
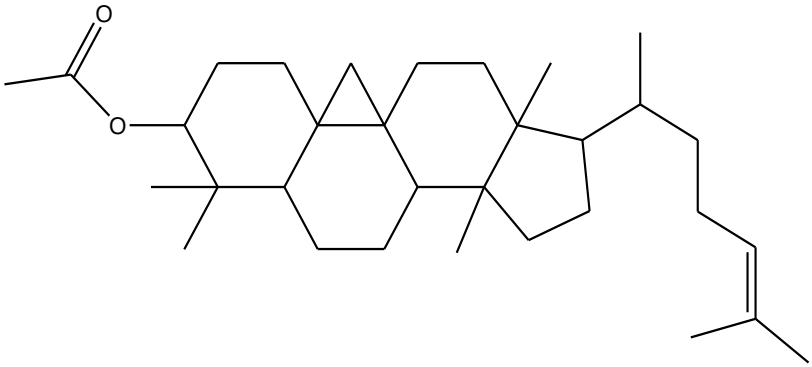
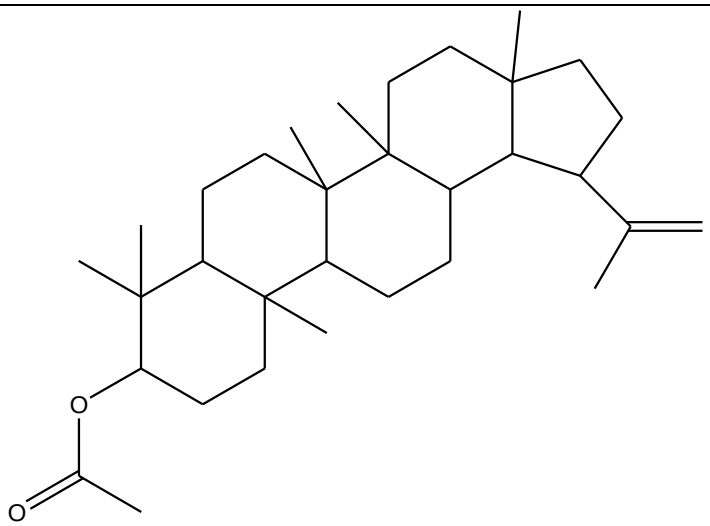
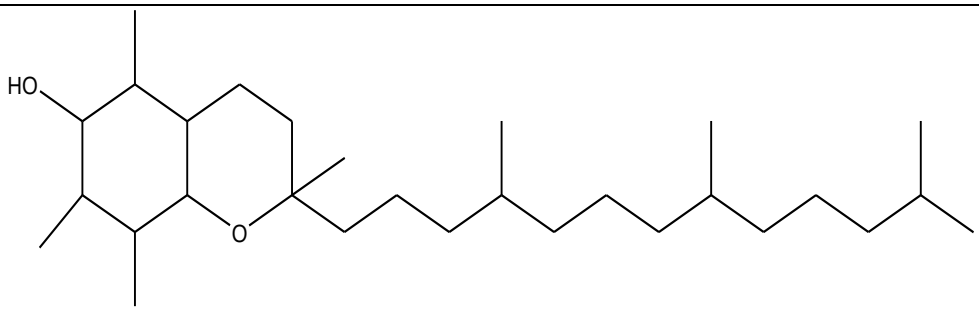
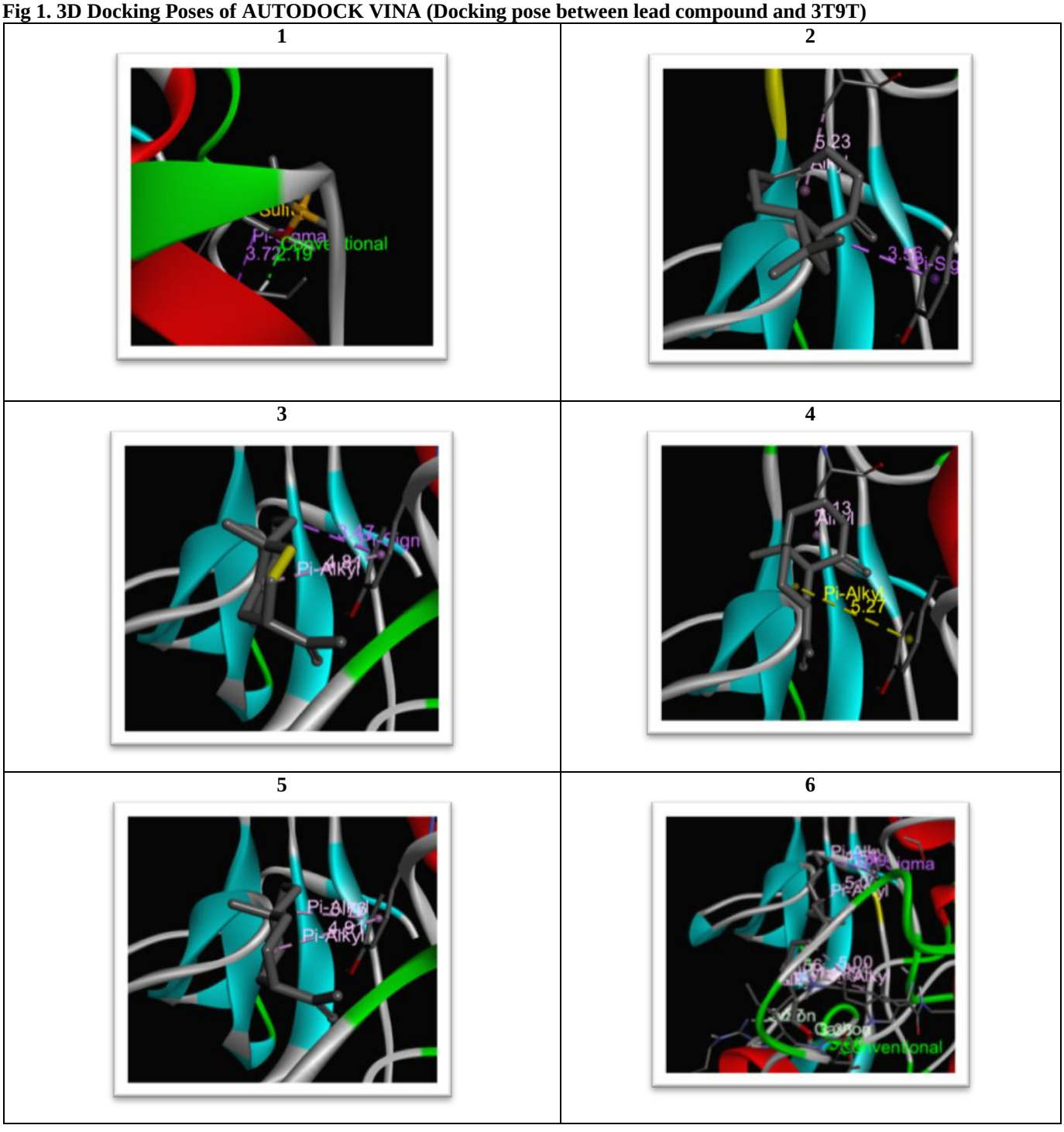
14	Methyl hexacosanoate	
15	Stigmastan-3,5-diene	
16	Cycloartenol acetate	
17	Lupeol acetate	
18	α-Tocopherol	

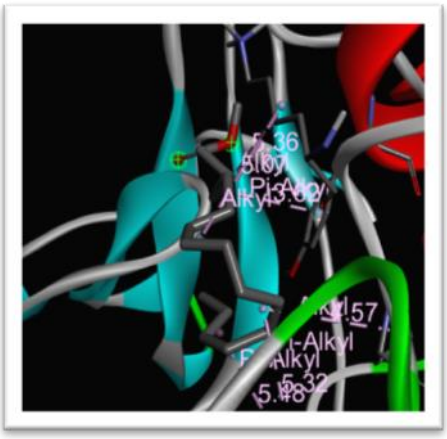
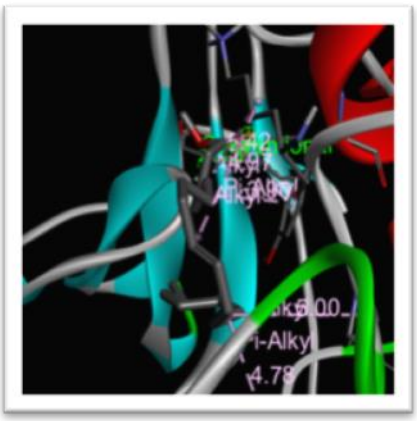
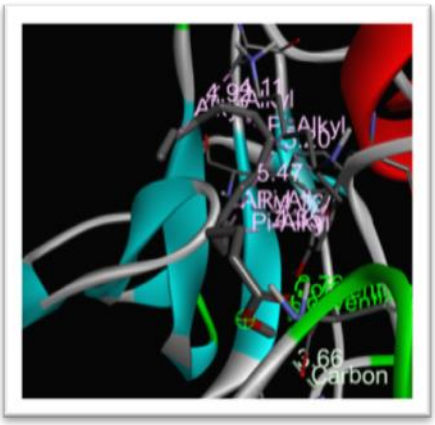
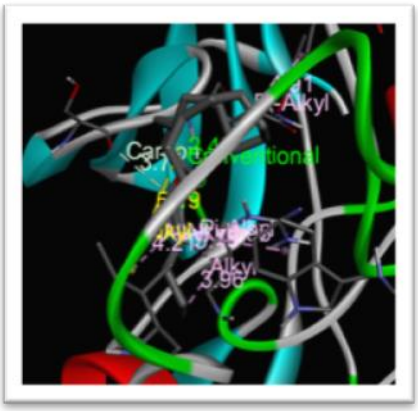
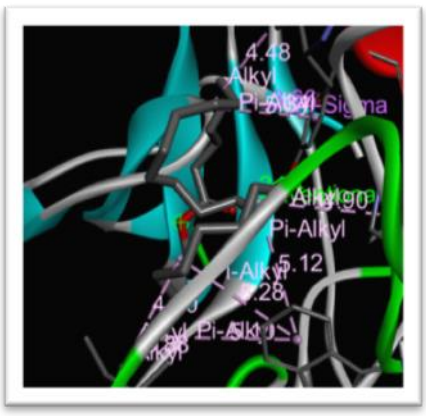
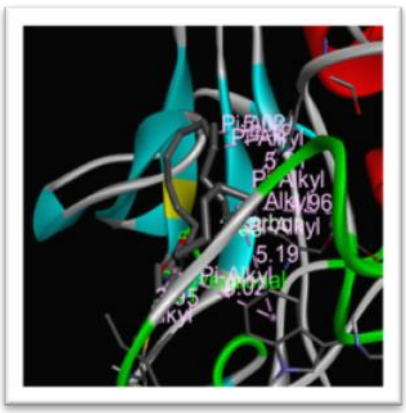
Table 2. The interaction energies (kcal mol-1) of 3T9T and ligands obtained from the molecular docking with AutoDock vina with PyRx

Comp code	Auto dock vina	H-Bonds	Vander waal forces	Pi-sigma	Alkyl	RMSD
	PyRx	Residues	Residues	Residues	Residues	Residues
1	-5.2	ILE A:479	VAL A:409, GLY A:502, ARG A:505, ARG A:481, CYS A:477	VAL A:478		0.0
2	-5.7		LYS A:519, GLY A:372, GLY A:375, ARG A:394, PHE A:374, GLN A:373, ASP A:509	TYR A:512	ALA A:397	0.0
3	-5.5		GLN A:373, ASP A:509, LYS A:519, ASN A:564, TRP A:524, PRO A:521, ARG A:486	TYR A:512	TYR A:512	0.0
4	-5.7		ASP A:509, ARG A:394, LYS A:519, GLN A:373, PHE A:374, VAL A:507		ALA A:397, TYR A:512,	0.0
5	-5.7		VAL A:507, ASP A:509, ARG A:394, LYS A:519, GLN A:373, PHE A:374		ALA A:397, TYR A:512	0.0
6	-4.9		GLN A:373, ASP A:509, LYS A:519, PHE A:520, ASN A:564, PRO A:521, ARG A:486, TRP A:524		TYR A:512	0.0
7	-4.3		ARG A:486, ASN A:564, PHE A:520, GLY A:372, GLN A:373, PHE A:374, ALA A:397		TRP A:524, PRO A:521, LYS A:519,	0.0
8	-4.4	PHE A:374, ARG A:486	ALA A:397, ARG A:394, LYS A:519, ASN A:564, TYR A:524, SER A:371, GLY A:372, GLN A:373		TRP A:524, PRO A:521, LYS A:519, TYR A: 512	0.0
9	-4.3	PHE A:374	ASN A:364, ARG A:486, GLN A:373, ASP A:509, VAL A:507, ARG A:394, ALA A:397			0.0
10	-4.5	ASN A:564 ARG A:486	TRP A:524, PRO A:521, PHE A:520, GLN A:373, ASP A:509, ARG A:394		TYR A:512, LYS A:519, ALA A:397, PHE A:374	0.0
11	-4.2	TYR A:512	ASN A:564, ARG A:448, ARG A:486, GLN A:373		PRO A:521, TRP A:524, ILE A:557, LYS A:519	0.0
12	-4.6	CYS A:442 ASP A:500	ARG A:448, ASN A:564, LYS A:523, LYS A:519, ARG A:486, PHE A:374, GLN A:373, GLY A:372, LYS A:391		ILE A:557, TRP A:524, PRO A:521, TYR A:512	0.0
13	-7.6		GLYA:461, ASP A:465, LYS A:417, GLU A:468, GLU A:617, ALA A:613, ARG A:610		LEU A:464, LEU A:609	0.0
14	-4.7	ARG A:448	ARG A:394, GLN A:373, GLY A:372, PHE A:374, ASP A:509, LYS A:519, ASN A:564, ILE A:557, ARG A:486, PRO A:558		ALA A:397, TYR A:512, PRO A:521, TRP A:524	0.0
15	-7.7		LYS A:523, ARG A:448, PRO A:558, PRO A:521, ASN A:564, GLN A:373, PHE A:374, ASP A:509		ARG A:486, TRP A:524, ILE A:557, LYS A:519, TYR A:512	0.0
16	-7.0	ARG	GLY A:372, ARG A:394, PHE	TYR A:512	ALA A:397	0.0

		A:486	A:374, ASP A:509, GLN A:373, GLY A:396, LYS A:519, ASN A:564, TRP A:524, ILE A:557			
17	-7.7		ASN A:564, LYS A:523, ILE A:557, ARG A:486, GLN A:373, PHE A:374, ASP A:509, ALA A:397, LYS A: 519, PRO A:521	TYR A:512	TRP A:524	0.0
18	-5.6		ASN A:493, ALA A:616, GLY A:461, THR A:458, VAL A:495, ASP A:465, GLN A:494, LYS A:417, GLU A:468, MET A:462, ARG A:610, ALA A:613,		LEU A:464, LEU A:609	0.0

Fig 1. 3D Docking Poses of AUTODOCK VINA (Docking pose between lead compound and 3T9T)



7	**8**
	
9	**10**
	
11	**13**
	
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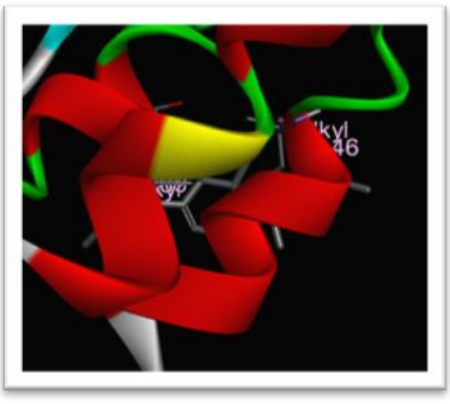	

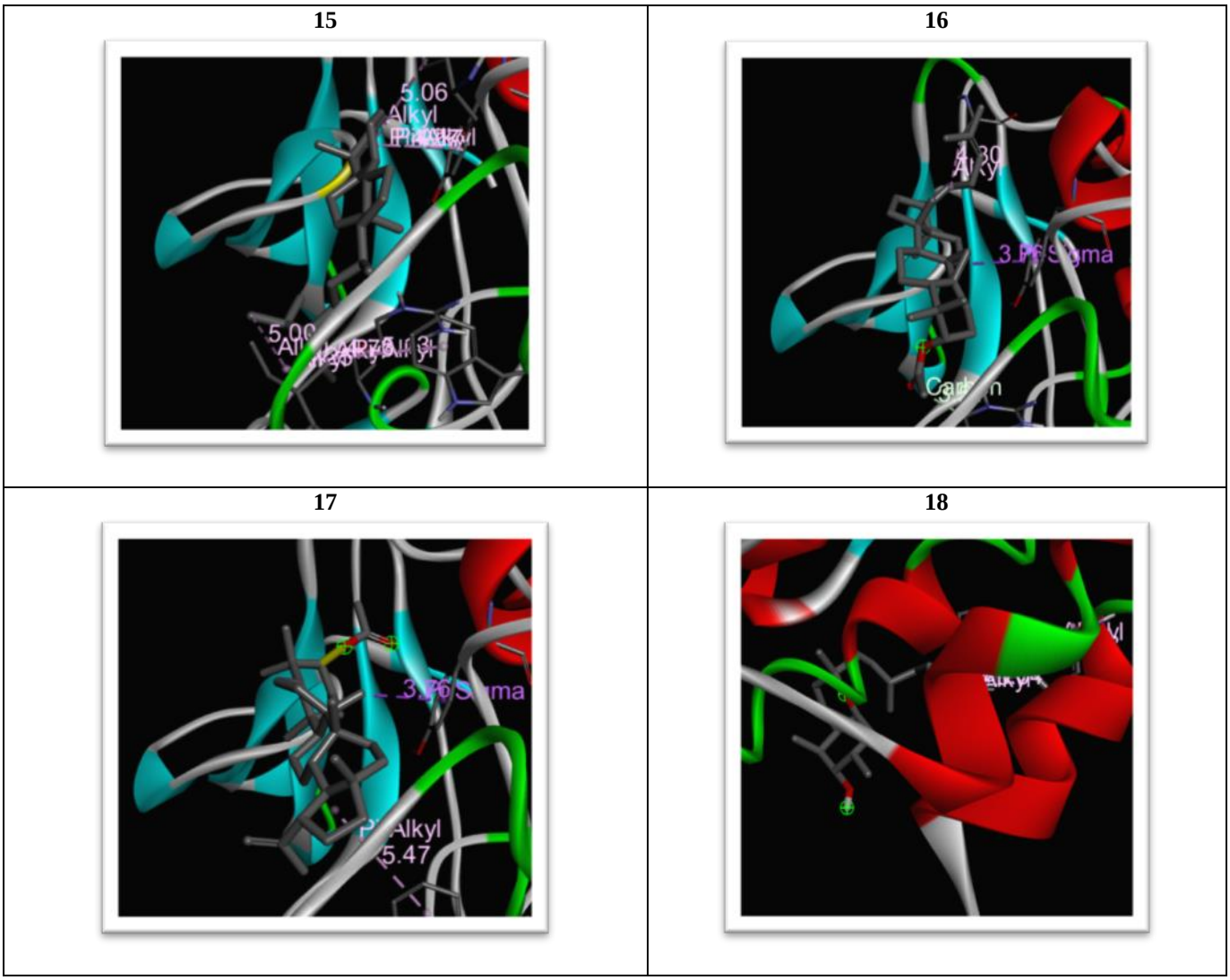

RESULTS AND DISCUSSION

Docking of small molecule ligands into the binding site of a receptor and approximate the binding affinity of the complex is an important part of the structure based drug design process. AutoDock Vina is a open-source program for drug discovery technology, molecular docking and virtual screening, offering multicore capability, high performance and enhanced accuracy and ease to of use.

Docking of 3T9T protein with 18 isolated plant compounds were done by AUTODOCK VINA software and dock scores of these molecules were represented in (Table 2, Fig 1), with their binding affinity and types of bonds with which different amino acids bonded to the ligand's different functional groups. Binding affinity of the protein-ligand interactions are important to describe how fit the drug binds to the target macromolecules. In the present study, the results generated by AutoDock Vina revealed that binding energies of the protein-ligand (drug) interactions are important to describe how fit the drug binds to the target macromolecule. The Ligands 1) 2,3-Dimethylphenol, tert-butyldimethylsilyl ether; 2) Caryophyllene; 3) 2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene; 4) β-Eudesmene; 5) α-Selinene; 6) 3,7,11,15-Tetramethyl-2-hexadecen-1-ol; 7) Hexadecanoic acid, methyl ester; 8) 9-Octadecenoic acid, methyl ester; 9) Octadecanoic acid, methyl ester; 10) Methyl docosanoate; 11) Methyl tricosanoate; 12) Methyl tetracosanoate; 13) A-Neooleana-3(5),12-diene; 14) Methyl hexacosanoate; 15) Stigmastan-3,5-diene; 16) Cycloartenol acetate; 17) Lupeol acetate; 18) α-Tocopherol.docks into good the binding pockets of 3T9T protein

In this study we analysed the binding affinity of 18 compounds with indicated target enzymes, through which Stigmastan-3,5-diene and Lupeol acetate is best inhibitors. Stigmastan-3,5-diene and Lupeol acetate shows highest binding energy when compared to scores obtained with the docking of remaining ligands to the respective enzymes 3T9T. And the compound Gallic acid (-5.5) shows lowest binding energies as compared to other compounds.

CONCLUSION

The molecular docking studies were carried out for the selected six bioactive compounds of Syzygium samarangense against BTK mutant protein. The approach utilized in this study resulted in identifying compound

Lupeol acetate with high binding affinity towards 3T9T. The docked pose of compound Lupeol acetate revealed more number of H-bond interactions than the cocrystallized ligand. Therefore, this study states the importance of small molecules from various plant sources as docking agents. This approach to screen compounds from plants depends on various parameters such as size and shape of the compound and pharmacophoric groups attached on the compounds, among others. Further, work can be extended to study the receptor-ligand interactions experimentally and evaluation of their biological activity would help in specific isolation and effective treatment of diseases.

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