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Inhibition of Prostaglandins by Selective Lignansand Anthraquinones Using Molecular Docking

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Abstract: *This study employs molecular docking techniques to explore the selective inhibition of prostaglandins by lignans and anthraquinones. By analyzing the binding affinities of these phytocompounds, we aim to uncover potential candidates for targeted prostaglandin inhibition. The docking of the target protein Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) (PDB ID: 1Z9H) with the phytochemical ligands was carried out flexible docking for six structurally diverse phytocompounds lignans (Niranthin, Phyllanthin, Hypophyllanthin) and anthraquinones (Rubiadin, Emodin, Purpurin) for their selective prostaglandin inhibitory activity. The results offer insights into novel therapeutic avenues for managing inflammation and associated disorders.*

Key Words: *Phytocompounds, Prostaglandin molecular docking.*

1. INTRODUCTION:

Prostaglandins, lipid compounds derived from arachidonic acid, are key mediators in inflammation, immune response, and various physiological processes. Dysregulation of prostaglandin synthesis is implicated in numerous diseases, including inflammatory disorders and cancer. This study focuses on the potential of phytocompounds, naturally occurring plant-derived molecules, as selective inhibitors of prostaglandin synthesis enzymes. Molecular docking, a powerful computational technique, was employed to predict the binding affinity and selectivity of these phytocompounds towards key prostaglandin-related enzymes, such as cyclooxygenase (COX) enzymes. Prostaglandins play a crucial role in various physiological processes and pathological conditions, making them attractive targets for therapeutic intervention. The aim is to identify candidates with the ability to selectively modulate prostaglandin production, minimizing off-target effects and offering a foundation for the development of targeted therapies. This study explores the potential of phytocompounds as selective inhibitors of prostaglandins through molecular docking analysis. In view of our previous biological and phytochemical studies employing bioassays relevant to the neuropharmacological screening of these two class of compounds [Lignans and Anthraquinones] has guided us to explore anti-inflammatory activity of the studied class of compounds **[6,7].** In order to assist in determining potential mechanisms of action of the selected variousphytochemical compounds (Niranthin, Phyllanthin, Hypophyllanthin, Rubiadin, Emodin, Purpurin) we have carried out flexible docking analysis for six structurally diverse phytocompounds for their selective inhibitory activity with Crystal Structure and Possible Catalytic Mechanism of Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) (PDB ID: 1Z9H).

2. MATERIALS AND METHOD:

Docking Methodology:

Retrieval of Sequences: The protein utilized for this study consists of more stable arachidonate metabolites (PGD2, PGE2, and PGF2) by the action of three groups of enzymes and the proteins searching for Prostaglandin E synthase catalyzes an isomerization reaction, PGH2 to PGE2. The name of the receptor as the Crystal Structure and Possible Catalytic Mechanism of Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) (PDB ID: 1Z9H). The receptors

collected from the Data Bank of Proteins (www.rcsb.com). The receptor derived by method of X-ray diffraction having a resolution of less than 3 A °. Such structures of Microsomal prostaglandin E synthase type-2 (mPGES-2) have been crystallized with an anti-inflammatory drug Indomethacin. The search functions for rotation and translation were determined with data between 12.0–4.0 A° resolution ranges.

Ligand Preparation: The marked compounds are named as Niranthin,Hypophyllanthin, Phyllanthin,Rubiadin, Emodin and Purpurinwere considered as ligands. The phytocompounds were downloaded in.sdf format from the PubChem, and the SDF files were translated to PDB file format using Chimera.

Lipinski screening: The toxicity of the phytocompounds was measured using SCFBio's Lipinski Filter and Lipinski Rule of Five methods for study Table No.1. To determine the drug similarity of the proposed ligand, this screening technique was introduced. Lipinski's rule of 5 is an important technique for screening rational design of drugs. The present study's ligand has been well trained in the Lipinski filter.

Docking Analysis:

Receptor screening using Discovery Studio 2016 Client: The receptor is virtually screened on the programming on BIOVIA Discovery Studio version 16.1.0.15350. All the missing residues are added provides the residues that participate in the macromolecule's active site including the area and volume of the active site. The active site residues are further mapped to the structure to check exactly where the residues occur in Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) receptor. The binding site residues are further mapped to the structure to check exactly where the residues occur.

Molecular docking studies: A technique used to examine the position of the protein and the ligand and their interaction with inhibition is molecular docking. Docking was performed using Auto Dock Vina with the Chimera software. As a preprocessing stage, receptors from PDB format and ligand molecules are in SDF format are converted to PDBQT format from Auto dock. The receptor was supplied to the Chimera software and Auto Dock Vina with a Gasteiger Partial charge, and additional hydrogen was introduced. The docking of the ligand molecules to the receptor PDB ID: 1Z9H focused on the binding site determined in receptor screening on BIOVIA Discovery Studio. The cumulative number of the ligands' rotatable bonds has been determined. The grid was established at the protein structure binding site with x/y/z coordinate configurations set to size x= 3.097898, size y= 30.233022, size z= 18.921447, and the Radius center was set to center 87.642685 in X, Y, Z dimensions, where the grid was covered to the macromolecule binding site. The Binding energies are measured in terms of Kcal / mol between the receptor and the ligands. After the docking finished the dock poses are determined on BIOVIA Discovery Studio. The final 2D and 3D dock poses ligand molecules are extracted from the receptor.

3. DISCUSSION:

The present study describes screening studies of the reported phytoconstituents Niranthin, Phyllanthin, Hypophyllanthin, Rubiadin, Emodin, Purpurin by applying molecular docking technique. This research highlights the significance of lignans and anthraquinones as potential selective inhibitors of prostaglandins. The study provides a comprehensive analysis of their binding affinities, offering a foundation for further experimental validation and drug development. Harnessing the therapeutic potential of these natural compounds may lead to the development of safer and more effective anti-inflammatory agents, addressing the growing need for alternatives to conventional pharmaceuticals.

This study highlights the potential of phytocompounds as selective inhibitors of prostaglandin synthesis through a comprehensive molecular docking analysis. By specifically targeting key enzymes involved in prostaglandin production, these phytocompounds offer a novel approach to anti-inflammatory therapy. The significance of this research lies in the identification of candidates that demonstrate high selectivity, which is crucial for minimizing unwanted side effects commonly associated with non-selective inhibition. The findings contribute to the growing field of computational drug discovery and provide a solid foundation for further experimental investigations. Ultimately, the development of selective prostaglandin inhibitors has the potential to revolutionize anti-inflammatory treatments, offering more precise and targeted therapeutic interventions.

Our molecular docking analysis has identified several phytocompounds with promising potential as selective inhibitors of prostaglandins. These candidates exhibit favorable binding affinities and specific interactions with key enzymes involved in prostaglandin synthesis.This study provides valuable insights into the molecular interactions governing the inhibition of prostaglandin-related enzymes by phytocompounds. Future experimental validations are essential to confirm the efficacy and safety of these candidates, paving the way for the development of novel therapeutic agents with selective anti-inflammatory properties. The selective inhibition of prostaglandins holds great promise for more targeted and efficacious treatment strategies, minimizing adverse effects associated with non-selective interventions. This research opens new avenues for developing targeted and sustainable therapies, aligning with the current trends in the quest for natural and selective anti-inflammatory agents.

4. RESULT:

The details of molecular structures and properties of the six compounds is summarized in Table 1 and 2. The structures of nine phytocompounds (ligands) were drawn in 2D and converted into 3D mol form. The ligands were first optimized for the docking analysis. The nine molecular structures of phytocompounds have affinity to the Prostaglandin which was optimized for the final docking analysis.

Protein ligand interaction Molecular Docking against Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) (PDB ID: 1Z9H).

As the study showed, a variety of proteins are encoded in the Prostaglandin E Synthase Type 2 (mPGES-2) receptor. We reproduce the gene, a major component of the encoded Prostaglandin E. Crystal Structure and Possible Catalytic Mechanism of Microsomal Prostaglandin E Synthase Type 2 (mPGES-2) is chosen for the present research arachidonate metabolites (PGD2, PGE2, and PGF2) by the action of three groups of enzymes as the docking target for the work. A. Prostaglandin E Synthase Type 2 (mPGES-2) receptor as docking target and Docking is performed with Chimera with autodockVina, outlined in Start Method mPGES-2. The files for the protein structure are given in Table 2. And the ligand such as Rubiadin, Niranthin have the most strong interaction with Prostaglandin E (PDB ID: 1Z9H) receptor crystal structure. The protein domains are shown in the solid ribbon configuration while the compounds are shown in yellow. The labeled amino acids were those that bind with compounds.

A molecular interaction of Rubiadin and Niranthin was discovered through virtual screening as a potent binder to the Prostaglandin E Synthase catalytic pockets. Predicted free binding energy, inhibitory constant, and Rubiadin predicted dock energy is -9.3 kcal / mol and Niranthin is -7.9kcal / mol, against Crystal structure of Prostaglandin E Synthase receptorreceptor. Table no. 2 Description of the unique interactions between the enzyme active site Rubiadin and Niranthin are the two highest binding energy compounds. The findings clearly showed that the Rubiadin molecule forms interactions of the hydrogen bond with mPGES-2 residues LEU102, ARG99L, TRY175, ARG13, HOH1, ARG146, IMN379, TYR107, and VAL148. During the meantime the inhibitor forms three residue hydrogen bonds in the vicinity of the catalytic binding pocket shown in Figure 1 and Table 2. Niranthin with the THR174 amino main A chain atoms form two hydrogen bonds with distances of 9.82 A˚ shown in Figure 3& 4 also data was expressed in table 2. while the Rubiadin ligand from VDW, Pi-Cation, Pi-Anion, alkyl PI-alkyl bonds with the amino acid like HOH1, ARG146, IMN379, TYR107, and VAL148 having side chain atoms as O and C = O forms a distances of 1.23, 0.73, 6.76, 1.41 and 4.61 A˚ respectively. This binding of the model points to ARG146, ARG 99L IMN 379 has a crucial residue which provides the main elements of interaction for binding Rubiadin with Prostaglandin E Synthase receptor (PDB ID:1Z9H). Logically then, ligands (Rubiadin, Niranthin) binds to residue with the main interaction a site of the hydrogen bond and thus substantially undermines the binding affinity. Binding to the LEU102, ARG99L, TRY175, ARG13, HOH1, ARG146, IMN379, TYR107, and VAL148 is seen from the crystal structure of Prostaglandin E Synthase in the long loop region (residues 102 to378), isolated from the active sites of mPGES-2 with their respective residues in Figure 2. Niranthin, Rubiadin showed good docking scores and maximum number of docking poses. The results suggest these compounds are potent selective Prostaglandin inhibitors. This study will be useful for the designing of novel Prostaglandin inhibitors based on the docking analysis.

5. CONCLUSION:

In conclusion, the molecular docking study presented in this article elucidates the inhibitory interactions between selective lignans, anthraquinones, and prostaglandins. The findings underscore the promise of natural compounds as potential candidates for anti-inflammatory drug development. The structural insights gained from the molecular docking simulations provide a foundation for further experimental validation and optimization of these compounds. The research contributes to the expanding knowledge of natural product-based therapeutics and highlights the significance of computational approaches in elucidating molecular interactions. As the pharmaceutical industry continues to seek safer and more effective anti-inflammatory agents, the identified lignans and anthraquinones may offer valuable leads for future drug discovery endeavors. Overall, this study advances our understanding of the molecular basis of prostaglandin inhibition by natural compounds, opening avenues for the development of novel pharmaceutical interventions.

6. SUMMARY:

The article explores the potential of selective lignans and anthraquinones as inhibitors of prostaglandins through a comprehensive molecular docking study. Prostaglandins, known for their pivotal roles in inflammation and various physiological processes, have become therapeutic targets for several medical conditions. The researchers employed molecular docking techniques to investigate the binding affinities and interactions between selected lignans, anthraquinones, and prostaglandin targets. The study involved a systematic examination of the structural features of

lignans and anthraquinones that contribute to their inhibitory effects on prostaglandin synthesis. Utilizing computational tools, the researchers predicted the binding modes and energetics of these compounds within the prostaglandin binding sites. The results shed light on the molecular mechanisms underlying the inhibitory potential of these natural compounds, providing valuable insights for drug development and design.

Furthermore, the article discuss the implications of these findings in the context of developing novel anti-inflammatory agents with enhanced selectivity and reduced side effects. The exploration of natural compounds as prostaglandin inhibitors adds a dimension to the ongoing efforts in drug discovery, emphasizing the importance of harnessing the therapeutic potential of plant-derived molecules.

FIGURES/ TABLES/CHARTS:

Table No.1. 1. Toxicity of the Phytocompounds evaluated through Lipinski's Filter

Ligand	Mass	Hydrogen Bond Donor	Hydrogen Bond Acceptors	LOGP	Molar Refractivity
Rubiadin	254	2	4	1.578800	64.743385
Niranthin	432	2	4	2.181620	67.815582
Emodin	269	3	5	1.043640	66.840378
Purpurin	256	0	7	3.751499	116.802963
Hypophyllanthin	430	0	7	3.421599	114.008965
Phyllanthin	418	0	6	4.031399	117.231956
High lipophilicity (expressed as LogP, acceptable range: <5). Molar refractivity should be in between 40-130					

Table No. 1.2. Summary of docking analysis of Prostaglandinwith selected Phytocompounds.

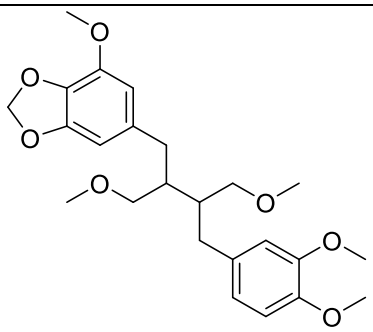
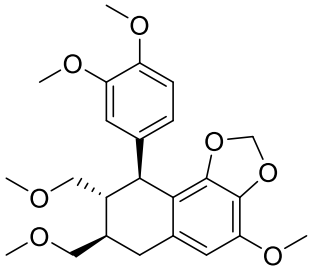
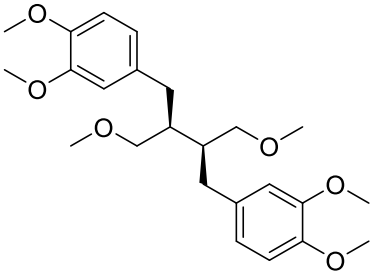
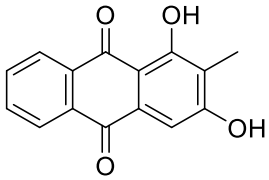
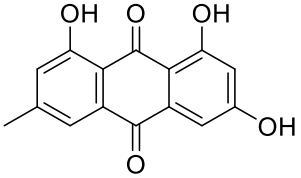
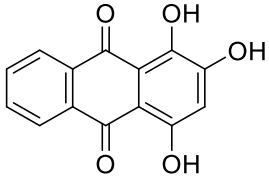
Name of Compound	Structure
Niranthin	
Hypophyllanthin	
Phyllanthin	
Name of Compound	**Structure**
Rubiadin	
Emodin	
Purpurin	

Table No. 2. List of Phytochemical classes and individual selected Phytoconstituents in the present study.

Class compounds	Phytoconstituents	Molecular formula	Molecular weight	Mass	Hydrogen Bond Donor	Hydrogen Bond Acceptors	LOGP a	Molar Refractivity b
Lignans	**Niranthin,**	$C_{24}H_{32}O_7$	432.21	432	2	4	2.181620	67.815582
	Phyllanthin	$C_{24}H_{34}O_6$	418.5	418	0	6	4.031399	117.231956
	Hypophyllanthin	$C_{24}H_{30}O_7$	430.5	430	0	7	3.421599	114.008965
Anthraquinones	**Rubiadin,**	$C_{15}H_{10}O_4$	254.24	254	2	4	1.578800	64.743385
	Emodin,	$C_{15}H_{10}O_5$	270.24	269	3	5	1.043640	66.840378
	Purpurin	$C_{14}H_8O_5$	256.21	256	0	7	3.751499	116.802963

Table No. 3. Molecular docking Ligand interaction with amino acid

LIGAND	DOCK ENERGY	Interaction of Amino Acid With Binding Distance									
		LEU D:102	HIS D:377	ARG D:99 L	TRY D:175	ARGA :137	HOH A:1	ARG A:146	IMN A:379	TYR A:107	VAL A:148
Rubiadin	-9.3	6.28	5.50	5.94	11.42	6.03	1.23	0.73	6.76	1.41	4.61
Niranthin	-7.9	3.44	6.65	8.90	9.82	3.35	5.07	6.03	7.62	1.13	4.97
Emodin	-7.4	3.17	5.53	3.5	9.64	4.29	4.61	3.35	2.93	0.15	4.36
Purpurin	-7.1	3.50	8.03	8.50	7.00	5.65	4.97	4.29	4.36	1.15	1.51
Hypophyllanthin	-6.9	7.29	4.55	7.53	6.75	6.42	4.36	5.65	2.77	6.46	0.78
Phyllanthin	-6.6	9.18	6.10	10.47	4.09	4.22	1.51	6.42	3.55	8.38	5.61

Figure No.1. 3D Dock Pose ofRubiadin against 1Z9H receptor

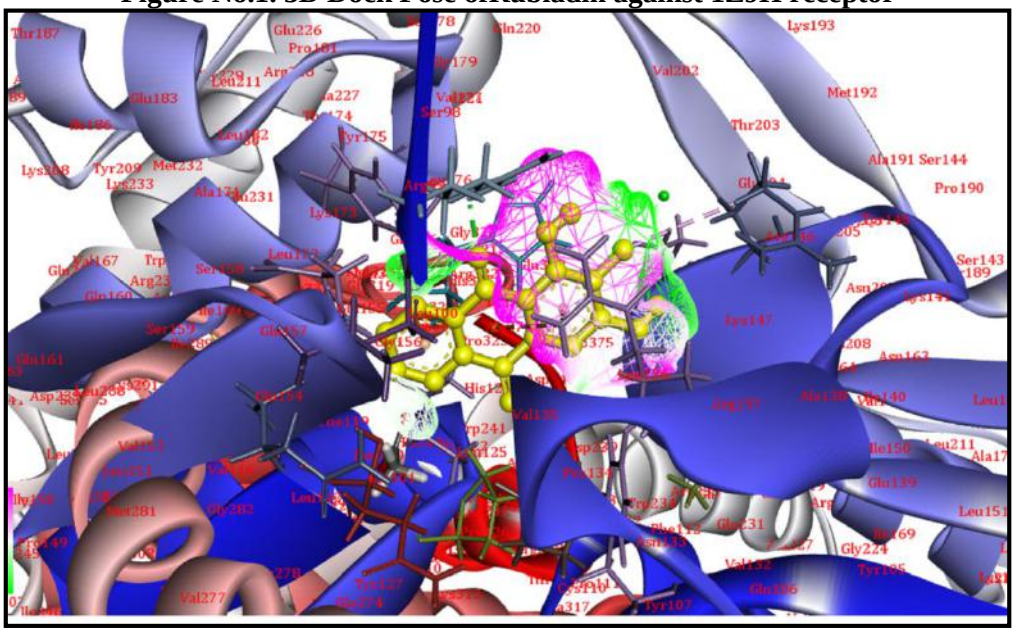


Figure No.2. 2D Dock Pose ofRubiadin against 1Z9H receptor

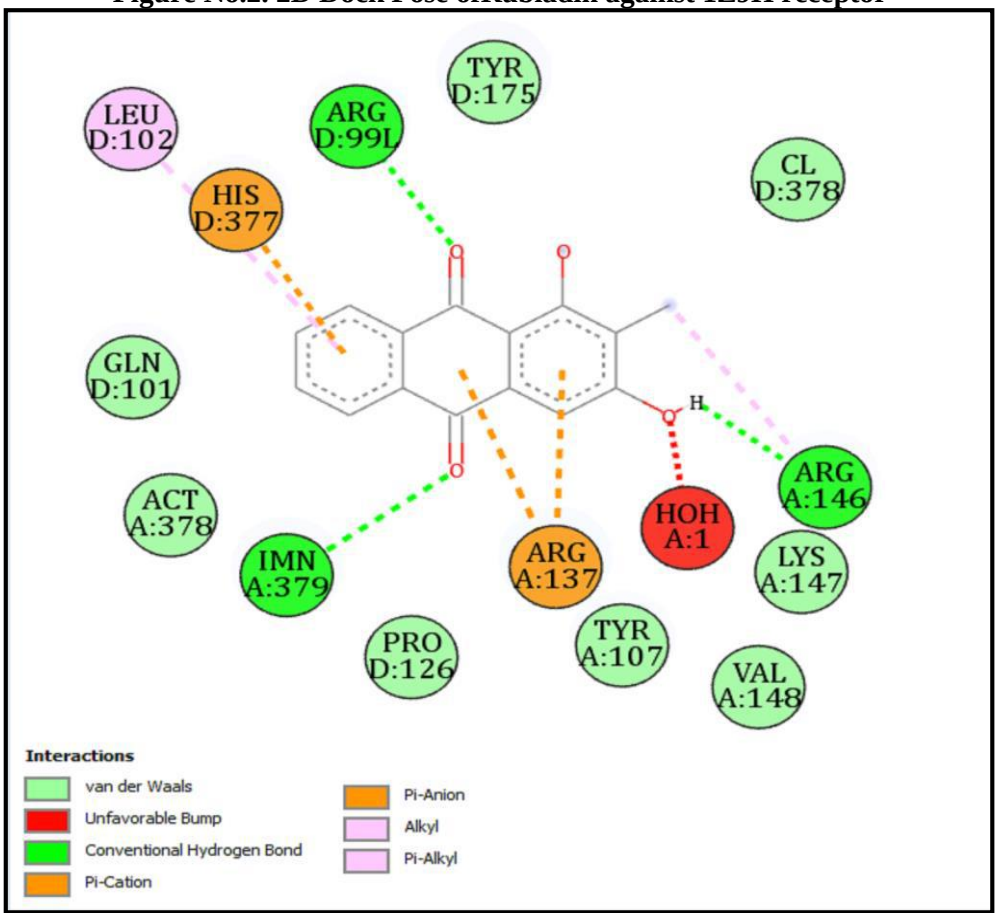


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Figure No 3. 3D Dock Pose ofNiranthin against 1Z9H receptor

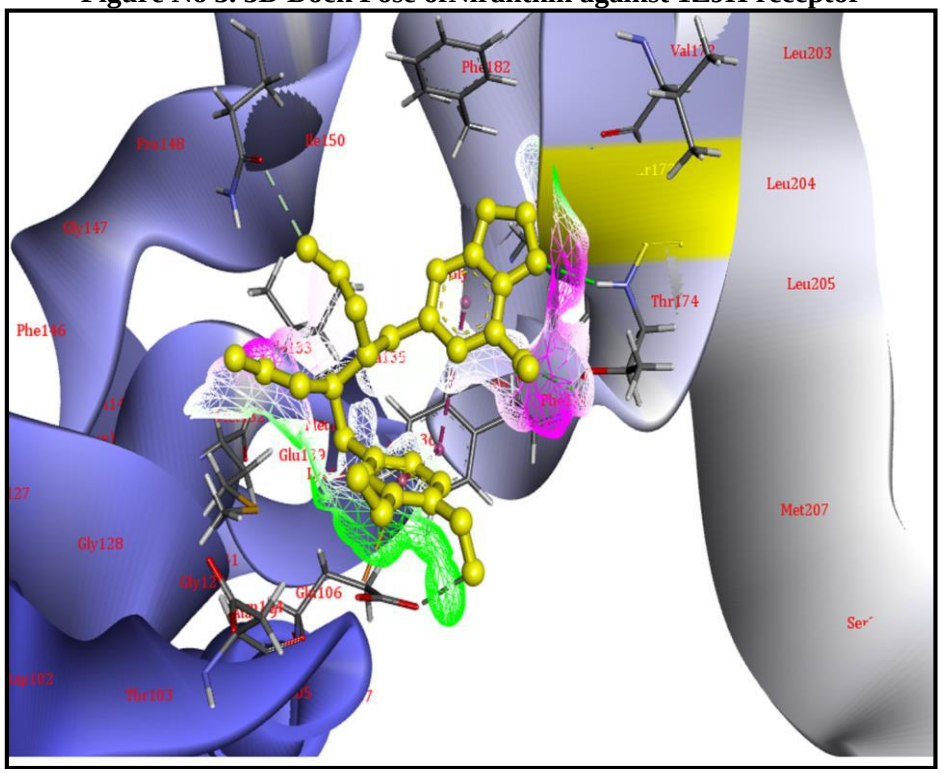
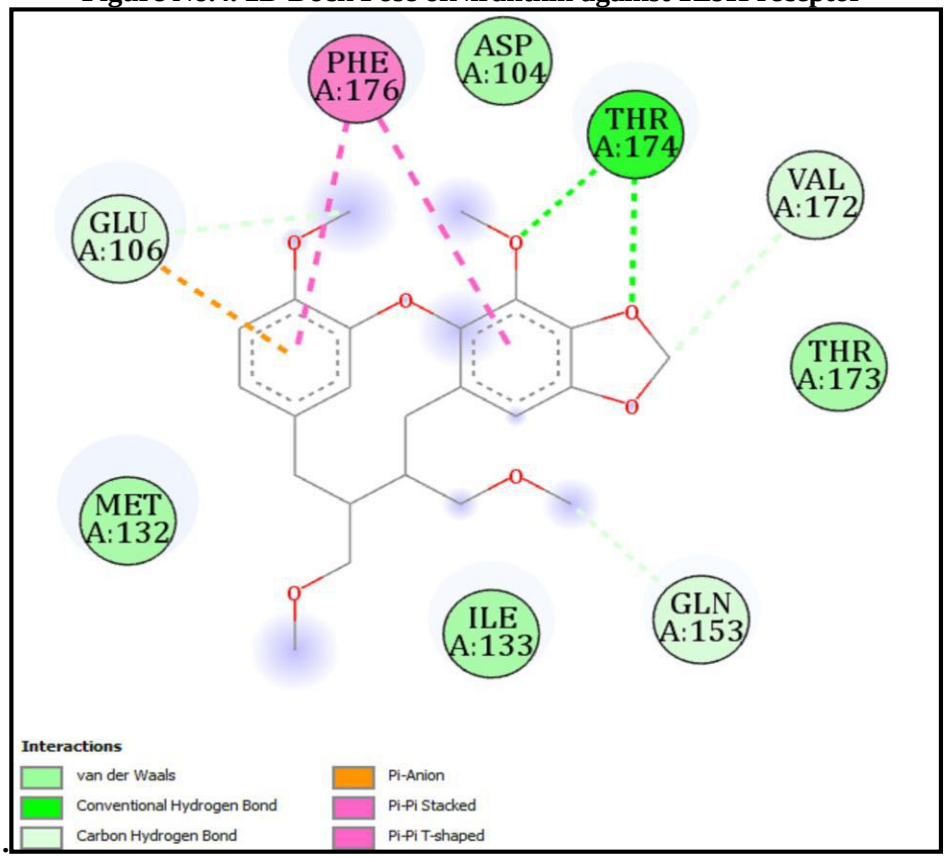


Figure No.4. 2D Dock Pose ofNiranthin against 1Z9H receptor



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