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Research paper UGC CARE Listed (Group -I) Journal Volume 11 , Iss 8, Dec 2022

MOLECULAR DOCKING STUDY OF THE PACHAI KARPOORA MATHIRAI COMPOUNDS TARGETING SARS COV-2 RNA DEPENDENT RNA POLYMERASE(nsp12)

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ABSTRACT:

Pachai karpoora mathirai traditionally used to treat all type of fever .The covid -19 has now been declared a global pandemic by WHO.No approved drug is currently available so need to developed anti viral theraphy for covid -19 .Pachai karpoora mathiar effective against covid symptoms of fever, cough,sore throat,shortness of breath,body ache, abdominal bloating ,loss of smell,loss of taste and constipation.The present study aims to identify molecules from Pachai karpoora mathirai sars –cov-2 RNA-dependent RNA polymerase(RdRp) inhibitors by molecular docking study. Binding of phytocomponents with the core amino acids (618 ASP, 760 ASP, 761 ASP) of the targets by forming hydrogen bond will hinder the function of the targets RNA dependent RNA polymerase (PDB)-6NUR possess versatile action in mediating nonstructural protein (nsp 12) essential for viral replication. Thereby phytocomponents in **Pachai karpoora mathirai** which inhibit the target RdRp may act as a potential therapeutic agent for management of COVID-19 and related symptoms.

INTRODUCTION:

The corona virus disease 2019 caused by severe acute respiratory syndrome –corona virus (SARS-cov-2) affect the human health.Across the globally more than 200 countries suffered by SARS-cov-2 belongs to the coronaviridae family.RNA genome of SARS-COV-2 surrounded by a lipid envelope which contains the spike proteins as well as membrane protein. The spike protein of SARS-COV-2 bind to the host cell receptors and the virus release the viral genome into the host cell where it is translated into 2 poly protein and structural protein .Replication of the viral genome is initiated. The 2/3 viral genome of SARS –coV_2 encode viral RNA-dependendent RNA polymerase (RdRp),the associated accessory protein and two large non structural protein.The remaining 1/3 of the genome codes for four structural proteins(spike,envelope,membrane and nucleocapsid)and other helper protein.RdRp is very important for replication and transcription of viral genome and highly conserved among different RNA viruses.The core protein of.RdRp consisting of single chain of approximately 900 amino acid residues,shows minimal activity.The enhanced activity is achieved by attachement of additional key subunits. RNA viruses including SARS-Cov-2 RdRp is the active site of RdRp it is the main drug target for SARS –Co-V-2 and other corona viruses.[5][6]

The virus generally spreads from infected person through close contact along with droplets spelled during talking, Sneezing and coughing.Vaccine for COVID -19 is the main concern of the ongoing pandemic. So Authers decided to research the drug molecule from the pachai karpoora mathirai for the covid 19 disease in siddha system of medicine. Total of 10 bioactive lead compounds retrieved from the Drug in accordance with the reported literature, the lead compound's such as Cinnamaldehyde, Grandisin, LicarinA, Elemicin, Aloin-A and Aloe-emodin possess 100% binding efficacy by interacting with all three core target amino acid (618 ASP, 760 ASP, 761 ASP) present on the target receptor RdRp.

KEY WORDS: RNA dependent RNA polymerase(RdRp),COVID -19,Amino acids, pachai karpoora mathirai, Ligand.

ISSN PRINT 2319 1775 Online 2320 7876

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Name of the formulation: ***Pacchai Karpoora Mathirai[7]***

List of Herbs in Pacchai Karpoora Mathirai

- **Cinnamomum Verum[9]**
- **Myristical fragrans[15] [8]**
- **Crotin tiglium[15] [8]**
- **Aloe vera[15] [8]**

List of Phytocomponents Selected for docking

S.N	Name of the Herb	Phyto components
	Cinnamomum Verum[8] [15]	Cinnamaldehyd Caryophyllene Cinnamic acid[11]
	Myristical fragrans[8] [15]	Grandisin LicarinA Elemicin[12]
	Crotin tiglium [8] [15]	Vaccenic acid Gibberellic acid[13]
	Aloe vera[8] [15]	Aloin Aloe-emodin[14]

Objective:[1][2][3][4]

Binding of phytocomponents with the core amino acids (618 ASP, 760 ASP, 761 ASP) of the targets by forming hydrogen bond will hinder the function of the targets RNA dependent RNA polymerase (PDB)-6NUR possess versatile action in mediating nonstructural protein (nsp 12) essential for viral replication. Thereby phytocomponents which inhibit the target RdRp may act as a potential therapeutic agent for management of COVID-19 and related symptoms.

PDB	Name of the Target
6NUR	RNA dependent RNA polymerase

3D- Structure of RNA dependent RNA polymerase (PDB)-6NUR

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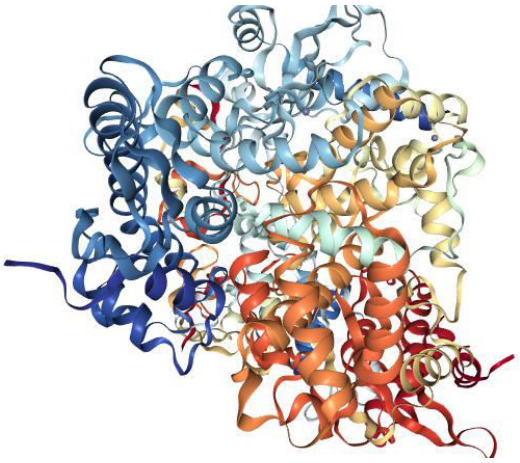

RECEPTOR STRUCTURE

Preparation of RdRp for molecular docking

Crystalline structure of the target protein RNA dependent RNA polymerase (PDB)-6NUR was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

Preparation of Ligand and Methodology

Docking calculations were carried out for retrieved phytocomponents against target protein RdRp. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (*Morris, Goodsell et al., 1998*). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

2D and 3D Structure of Selected Ligands

Cinnamaldehyde

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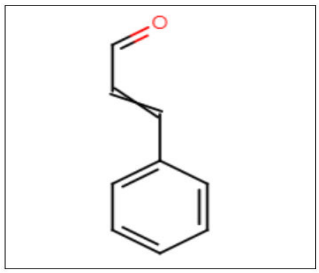
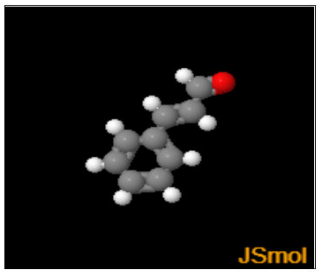
Ligand in 2D

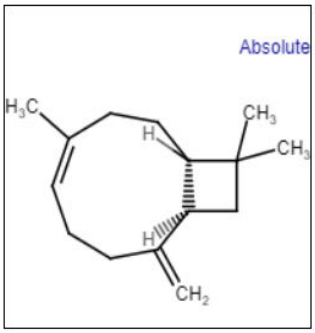


Ligand in 3D

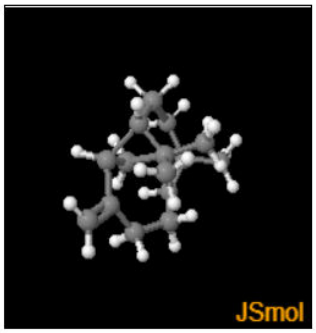


Caryophyllene

Ligand in 2D

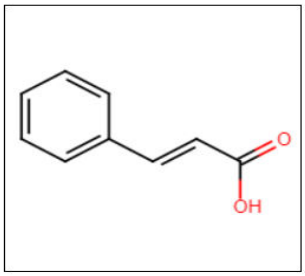


Ligand in 3D

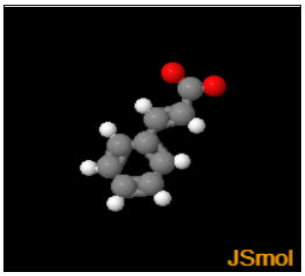


Cinnamic acid

Ligand in 2D



Ligand in 3D



Grandisin

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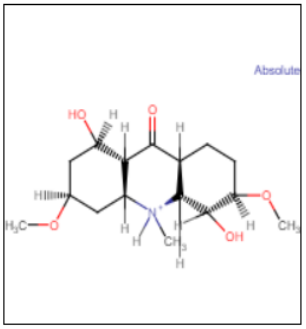
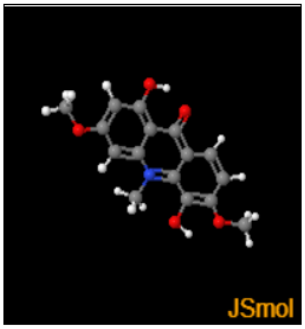
Ligand in 2D

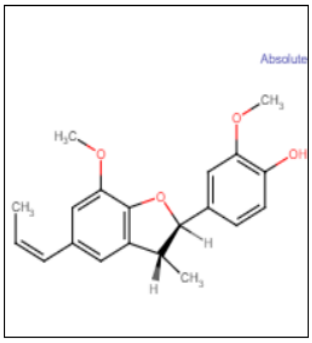


Ligand in 3D



licarinA

Ligand in 2D



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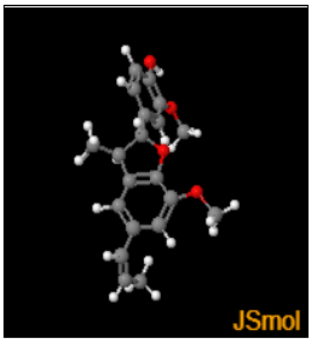
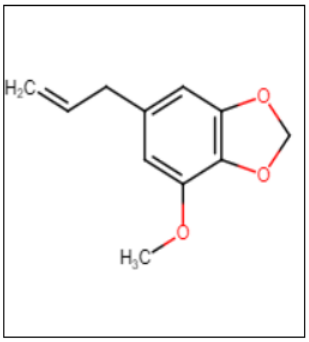
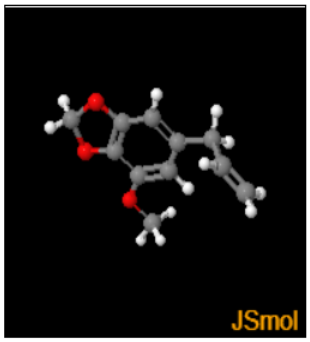


Elemicin

Ligand in 2D



Ligand in 3D



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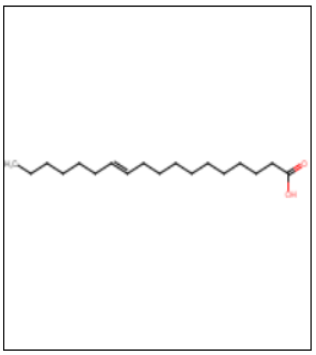
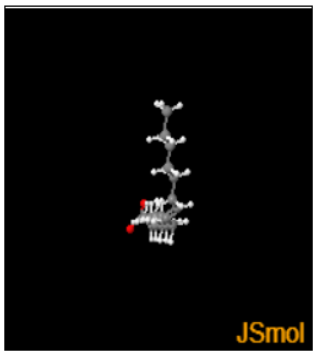
cis-Vaccenic acid

Ligand in 2D

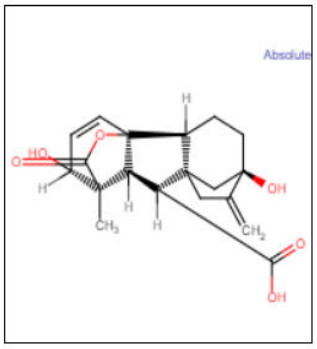


Ligand in 3D

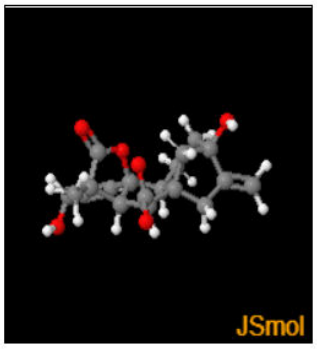


Gibberellic acid

Ligand in 2D

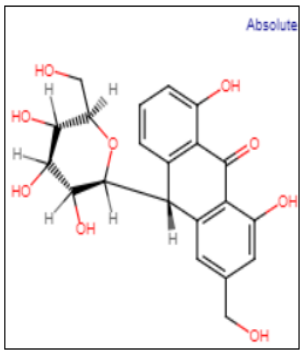


Ligand in 3D

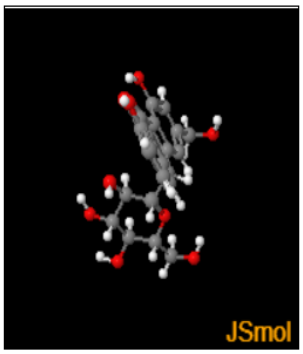


Aloin-A

Ligand in 2D



Ligand in 3D



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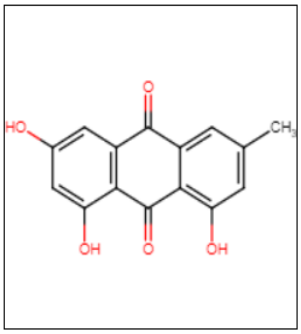
Aloe-emodin

Ligand in 2D



Ligand in 3D

Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Cinnamaldehyde	132.162 g/mol	C9H8O	0	1	2
Caryophyllene	204.35 g/mol	$C_{15}H_{24}$	0	0	0
Cinnamic acid	148.16 g/mol	$C_9H_8O_2$	1	2	2
Grandisin	276.37 g/mol	$C_{16}H_{24}N_2O_2$	1	4	0
licarinA	326.4 g/mol	$C_{20}H_{22}O_4$	1	4	4
Elemicin	208.25 g/mol	$C_{12}H_{16}O_3$	0	3	5
cis-Vaccenic acid	282.5 g/mol	$C_{18}H_{34}O_2$	1	2	15
Gibberellic acid	346.4 g/mol	$C_{19}H_{22}O_6$	3	6	1
Aloin-A	418.4 g/mol	$C_{21}H_{22}O_9$	7	9	3
Aloe-emodin	270.24 g/mol	$C_{15}H_{10}O_5$	3	5	1

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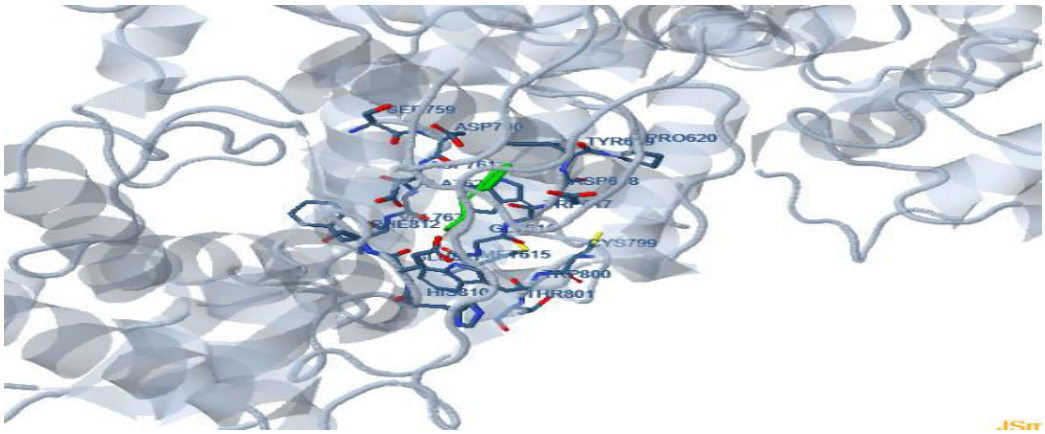
Summary of the molecular docking studies of compounds against RNA dependent RNA polymerase (PDB)-6NUR

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM (*mM)(**nM)	Electrostatic energy Kcal/mol	Intermolecular energy Kcal/mol	Total Interaction Surface
Cinnamaldehyde	-4.26	748.74	-0.08	-4.85	423.19
Caryophyllene	-6.11	33.24	-0.01	-6.11	530.46
Cinnamic acid	-4.73	341.76	-1.80	-5.33	407.42
Grandisin	-5.90	47.47	-0.25	-5.91	624.64
LicarinA	-6.77	10.94	-0.35	-7.45	763.09
Elemicin	-4.37	631.37	-0.15	-5.23	497.25
cis-Vaccenic acid	-12.34	904.37**	-0.49	-7.48	890.78
Gibberellic acid	-5.74	62.22	-1.90	-6.61	678.98
Aloin-A	-7.92	1.56	-0.58	-6.73	670.89
Aloe-emodin	-5.02	210.62	-0.42	-5.94	538.87

Docking Pose

Cinnamaldehyde with RNA dependent RNA polymerase (PDB)-

2D Interaction Plot Analysis



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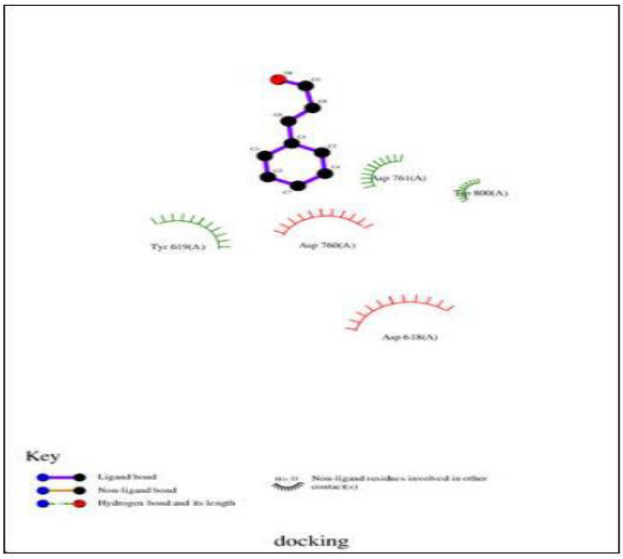
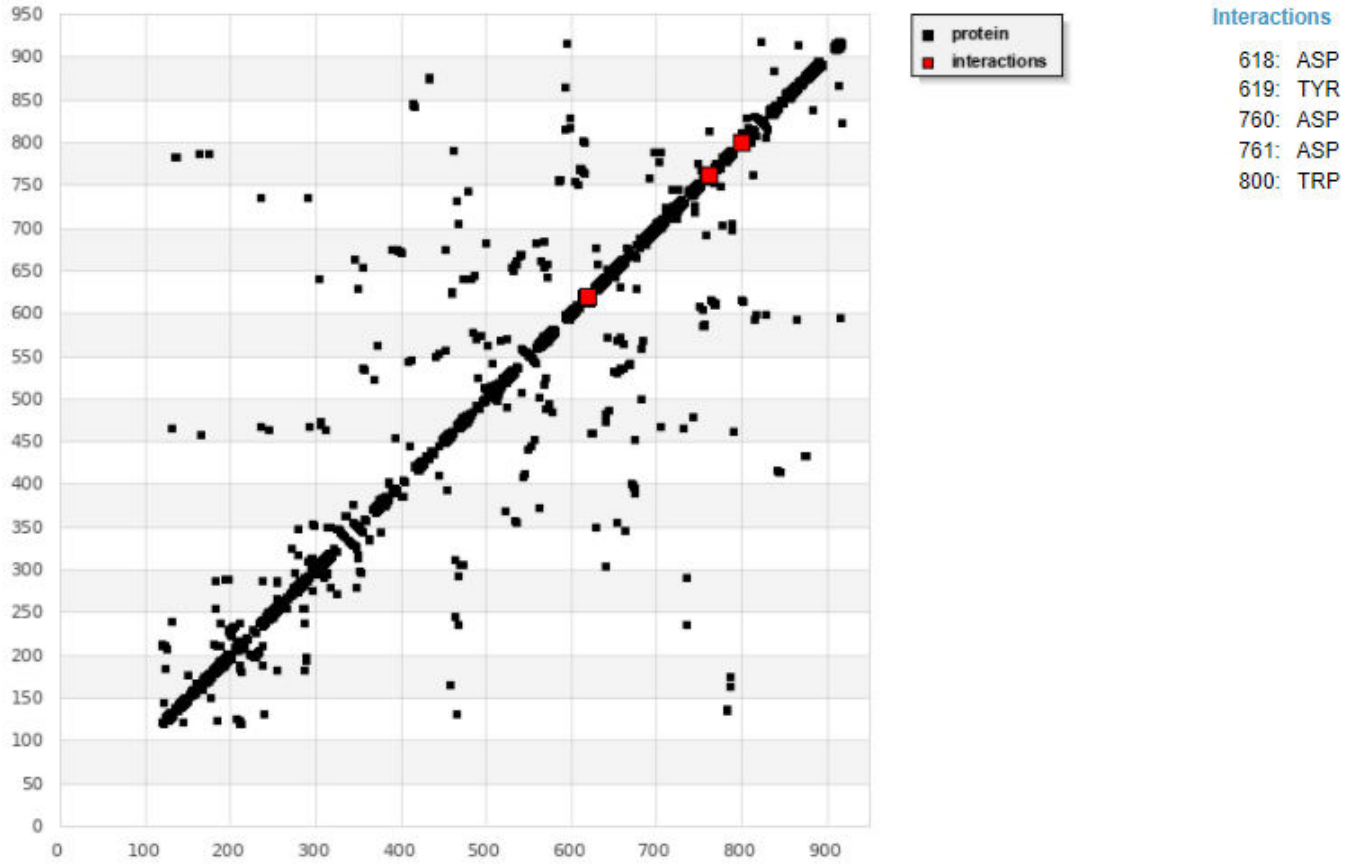


Hydrogen bond plotting with core amino acid Residues



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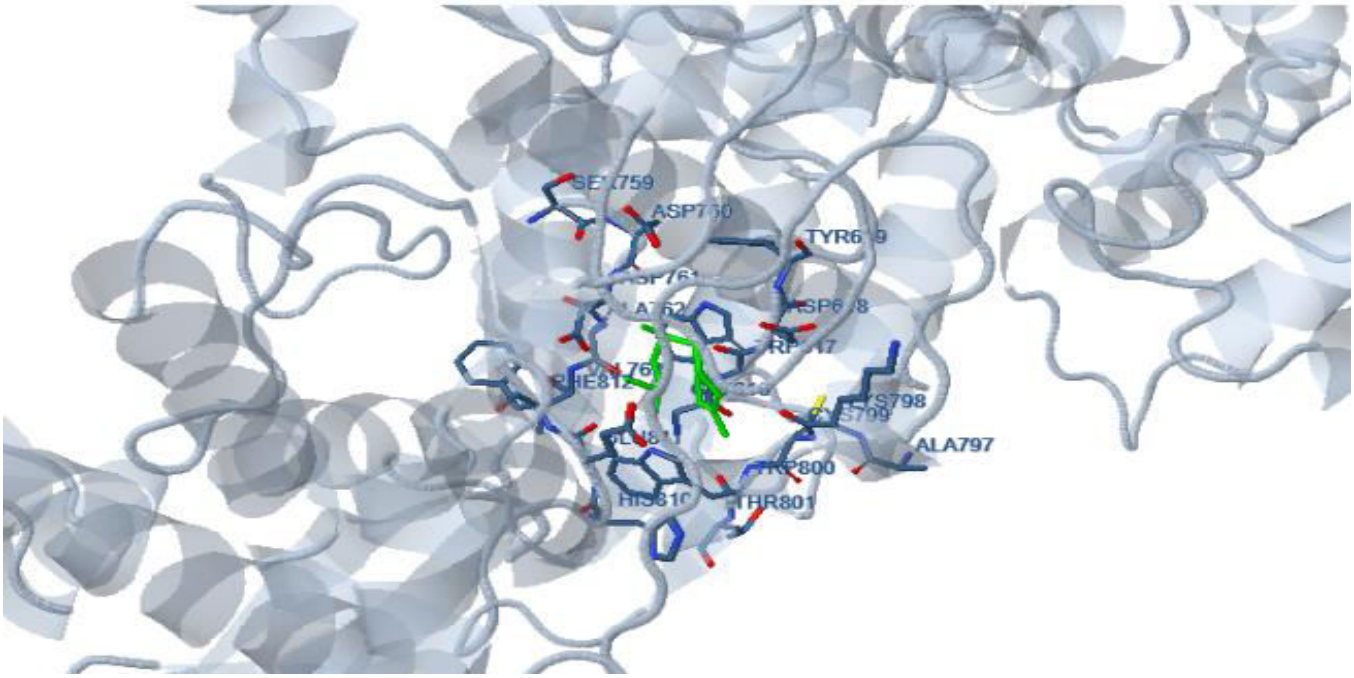
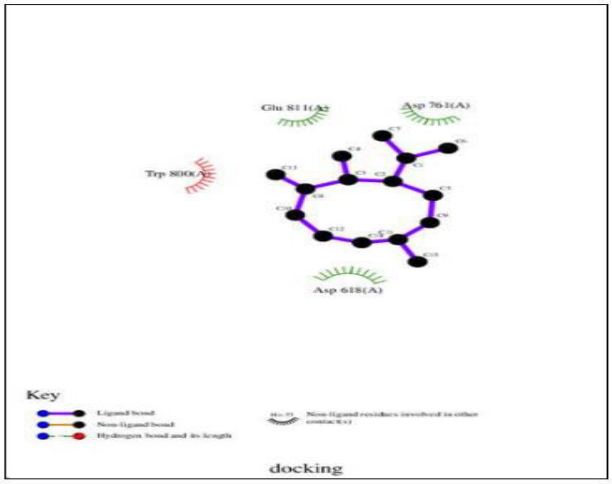
Caryophyllene with RNA dependent RNA polymerase (PDB)-6NUR



2D Interaction Plot Analysis



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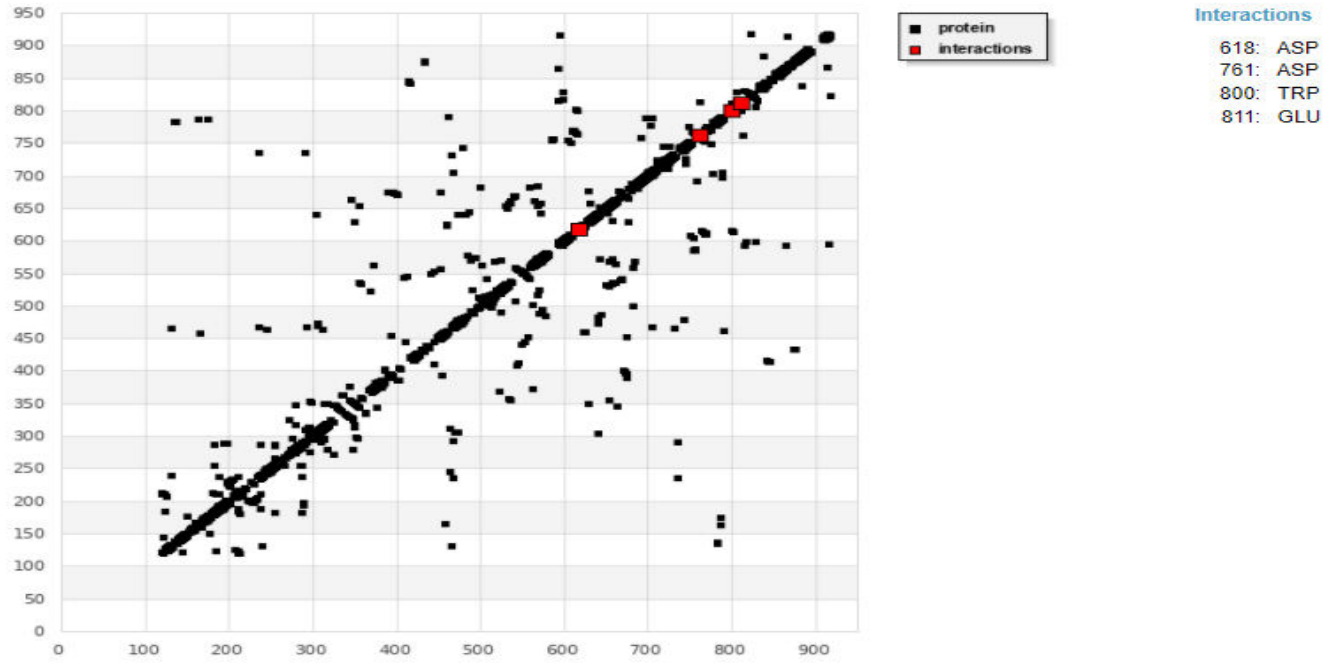
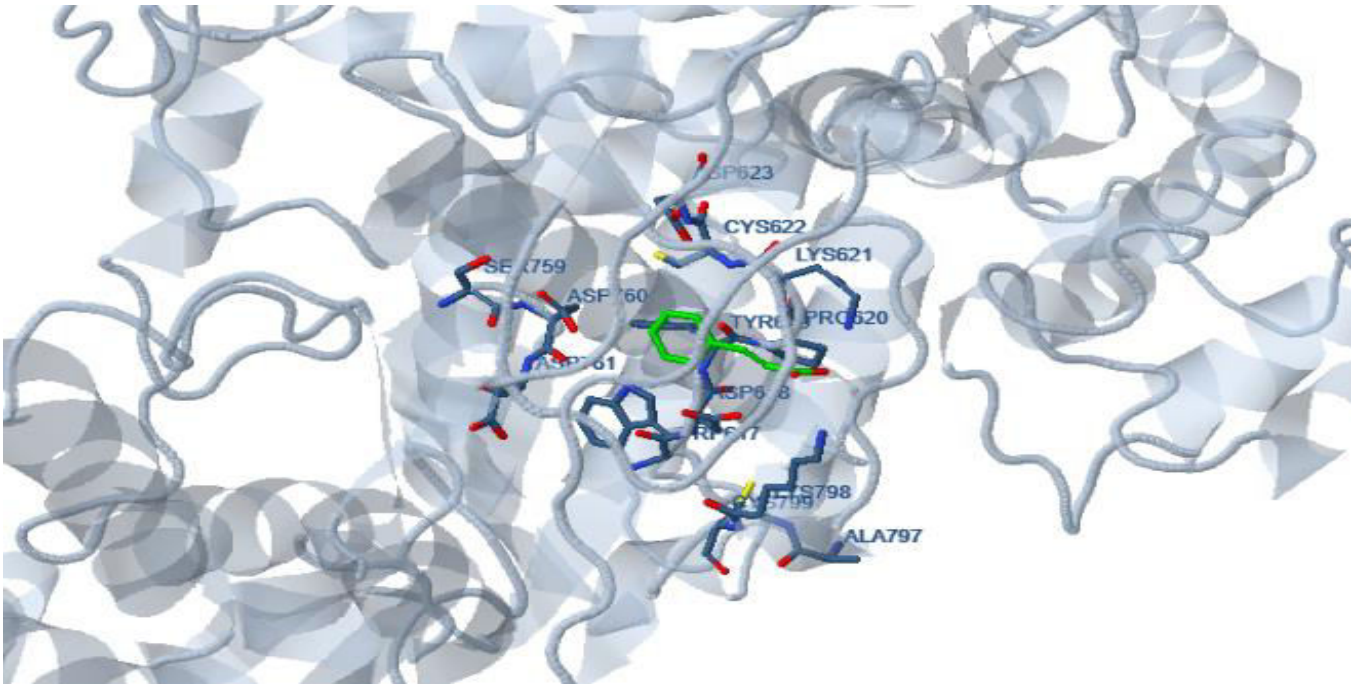
Hydrogen bond plotting with core amino acid Residues



Cinnamic acid with RNA dependent RNA polymerase (PDB)-6NUR



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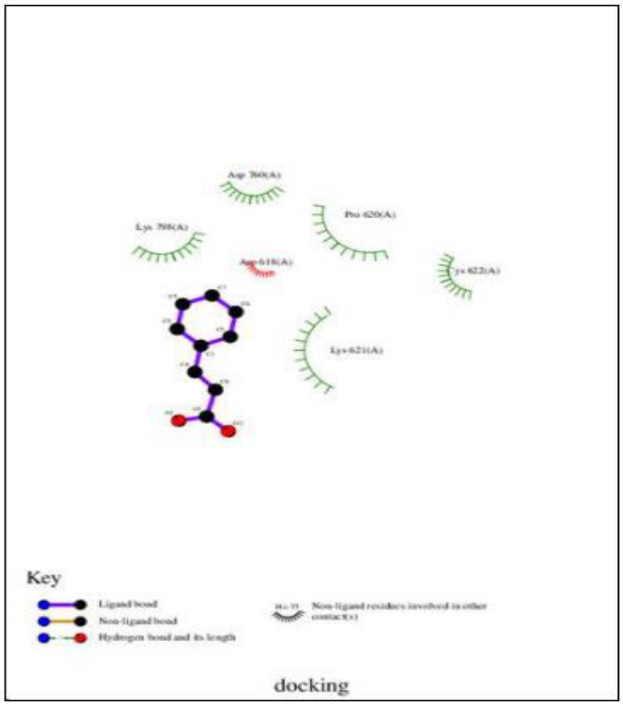
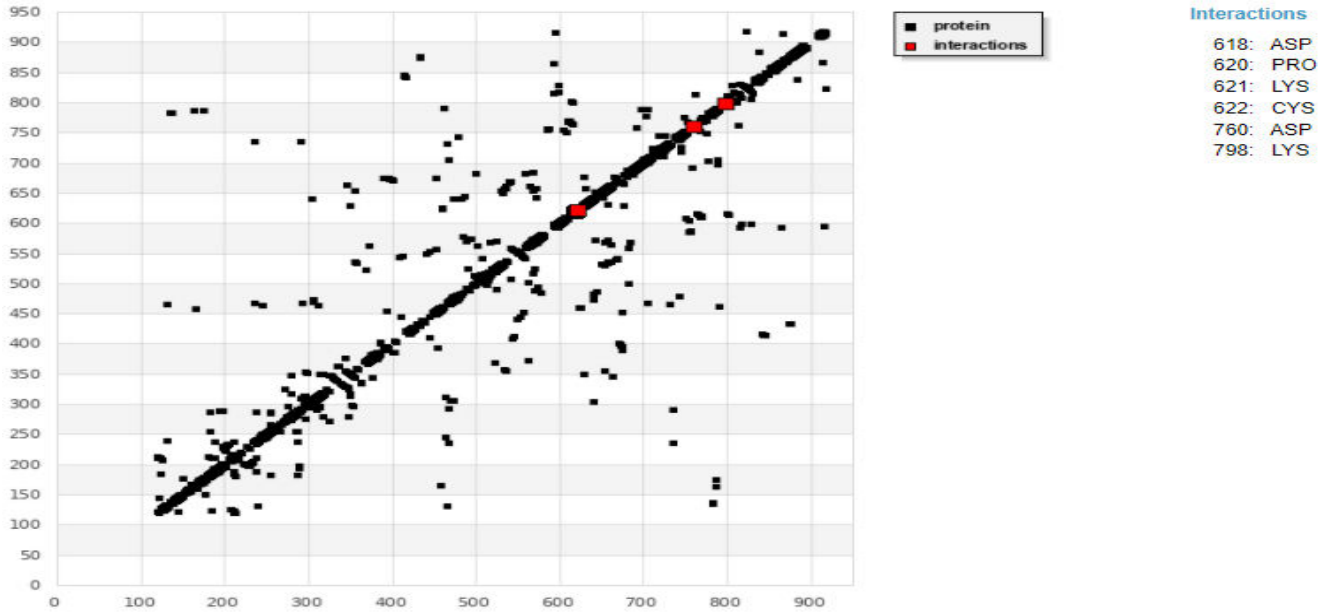
2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Residues



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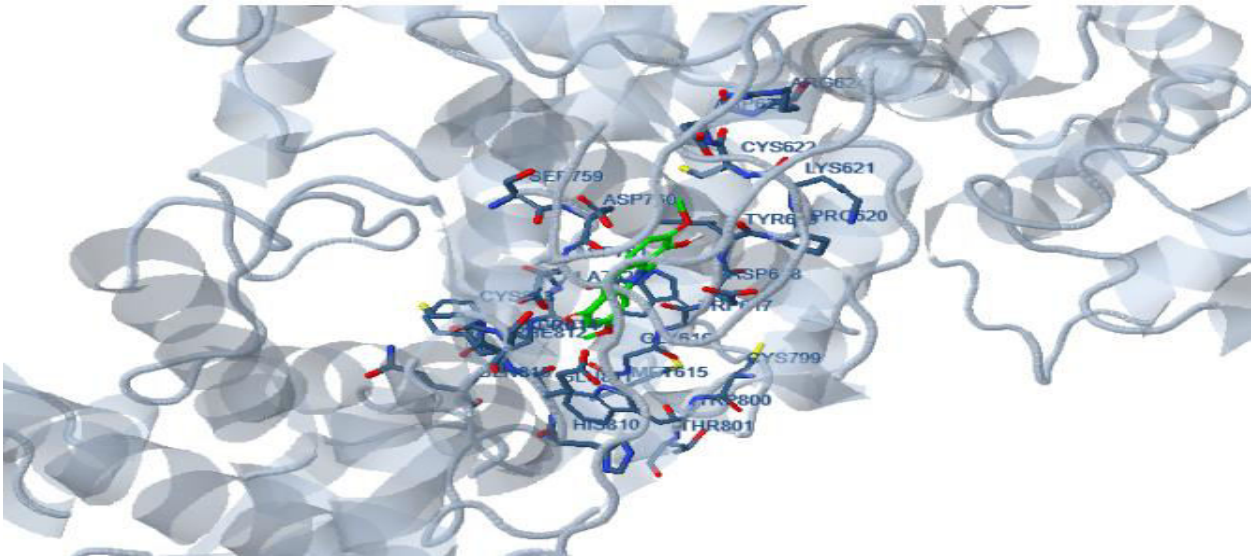
Grandisin with RNA dependent RNA polymerase (PDB)-6NUR



2D Interaction Plot Analysis

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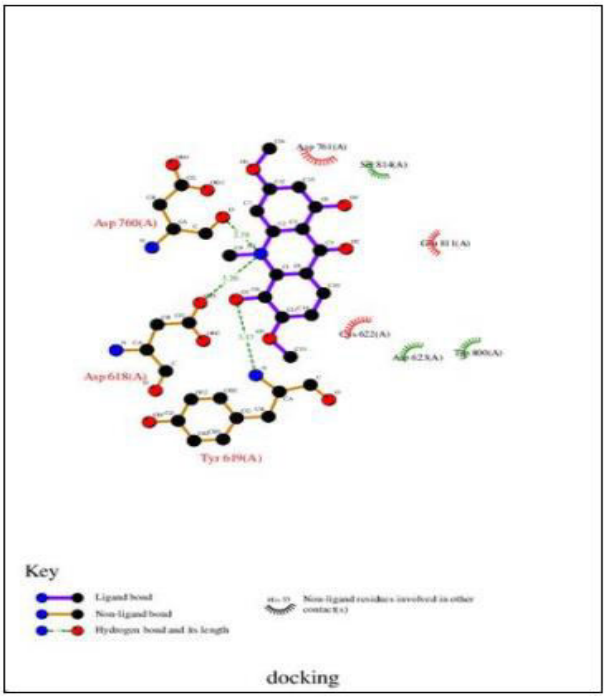
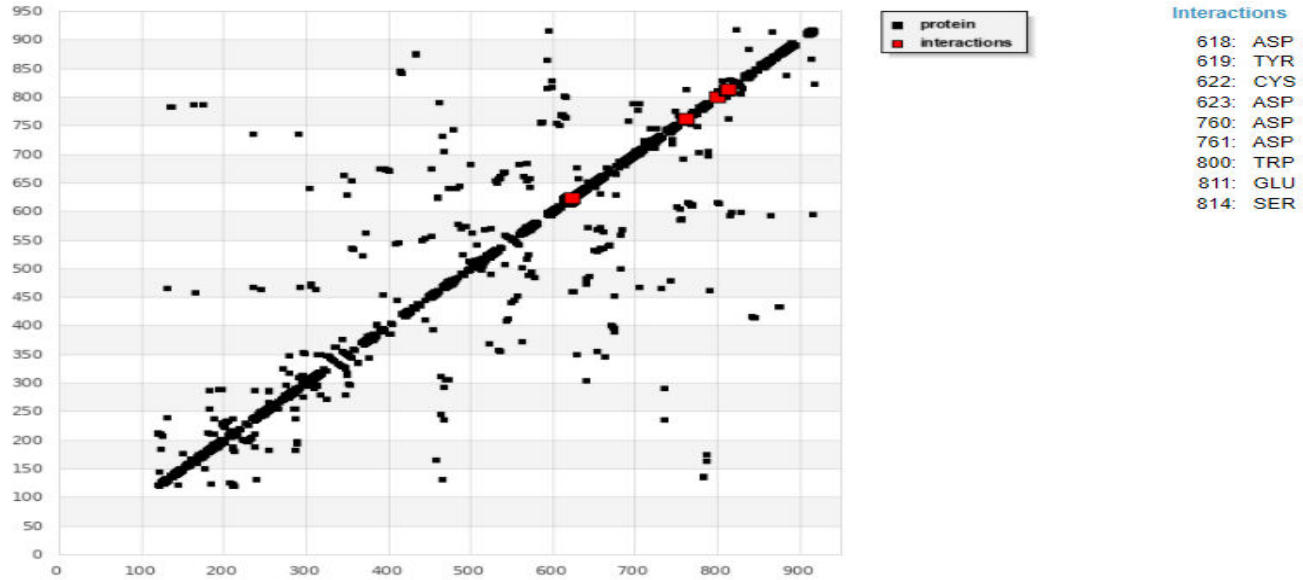


Hydrogen bond plotting with core amino acid Residues



LicarinA with RNA dependent RNA polymerase (PDB)-6NUR

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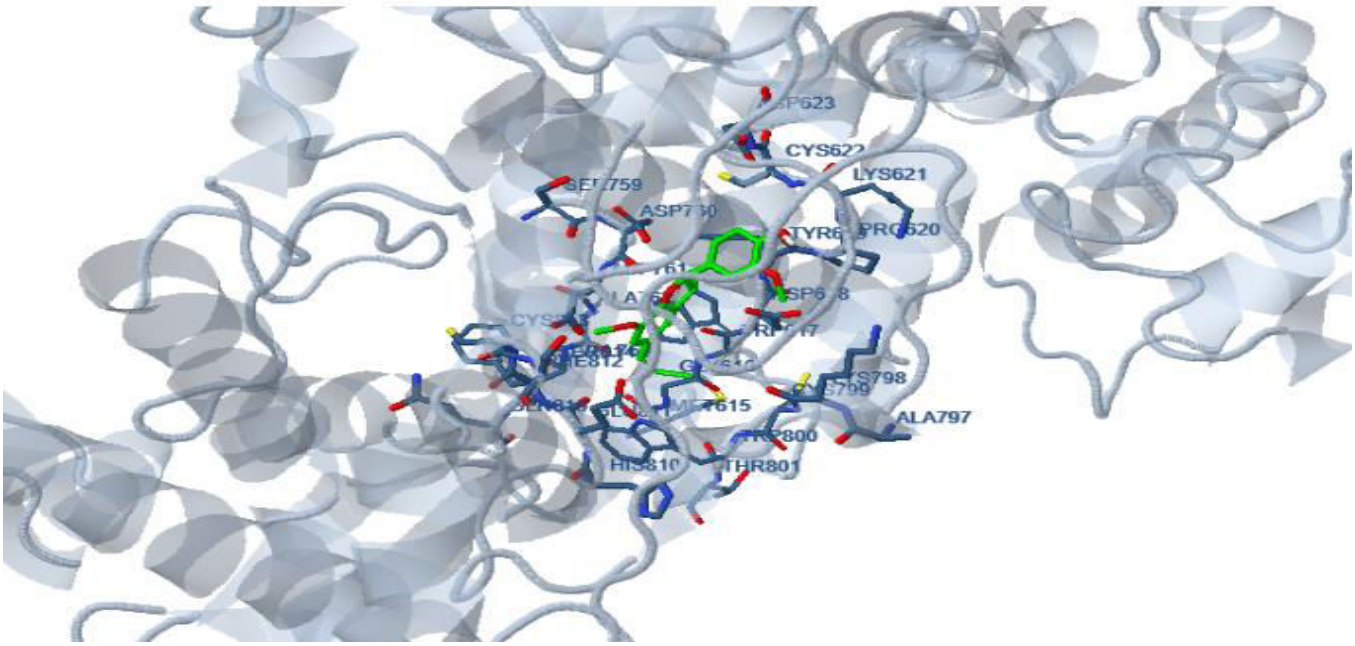
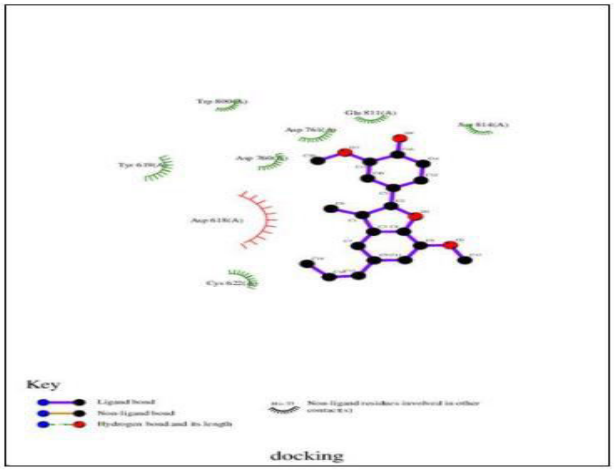


2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Residues

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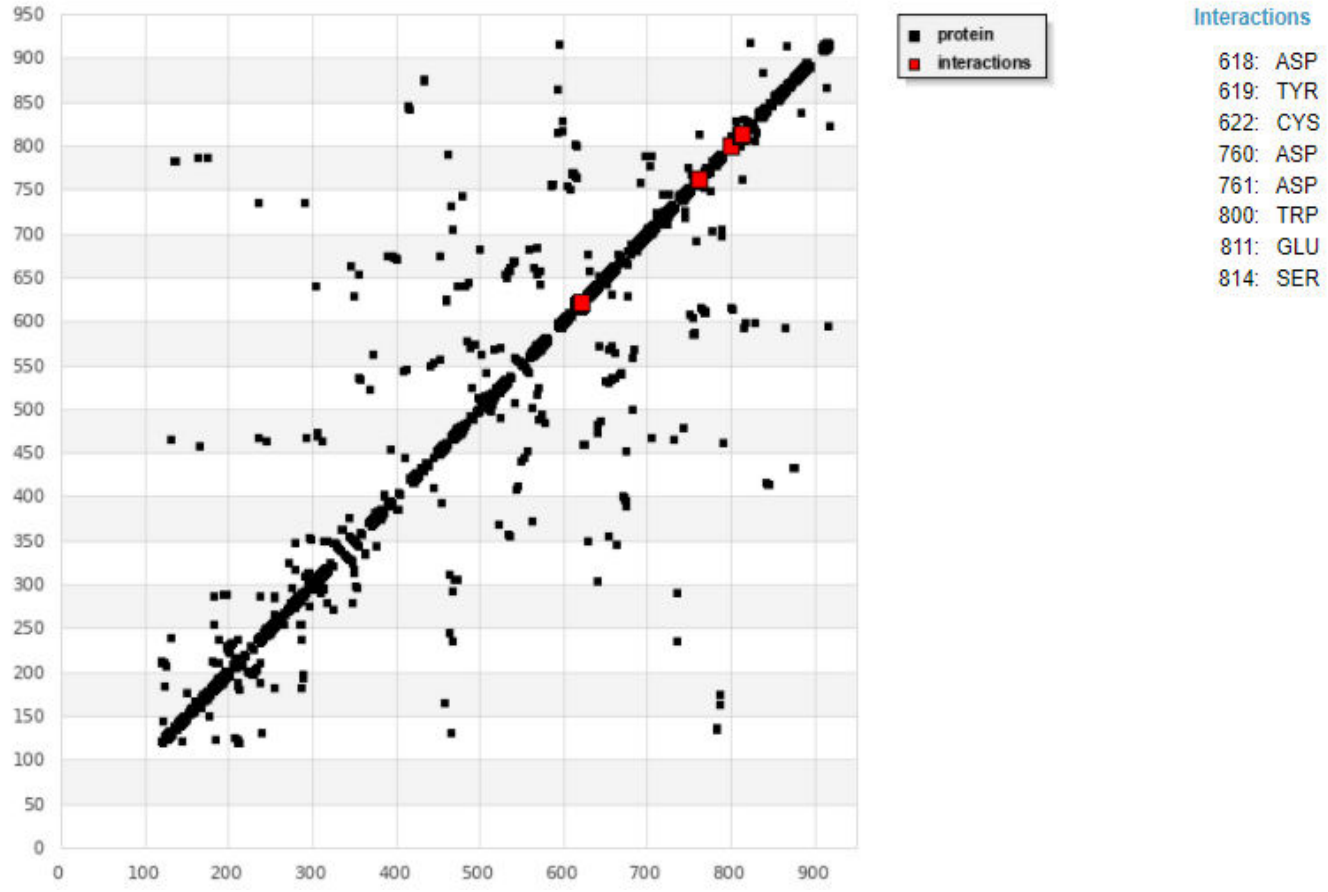

Elemicin with RNA dependent RNA polymerase (PDB)-6NUR

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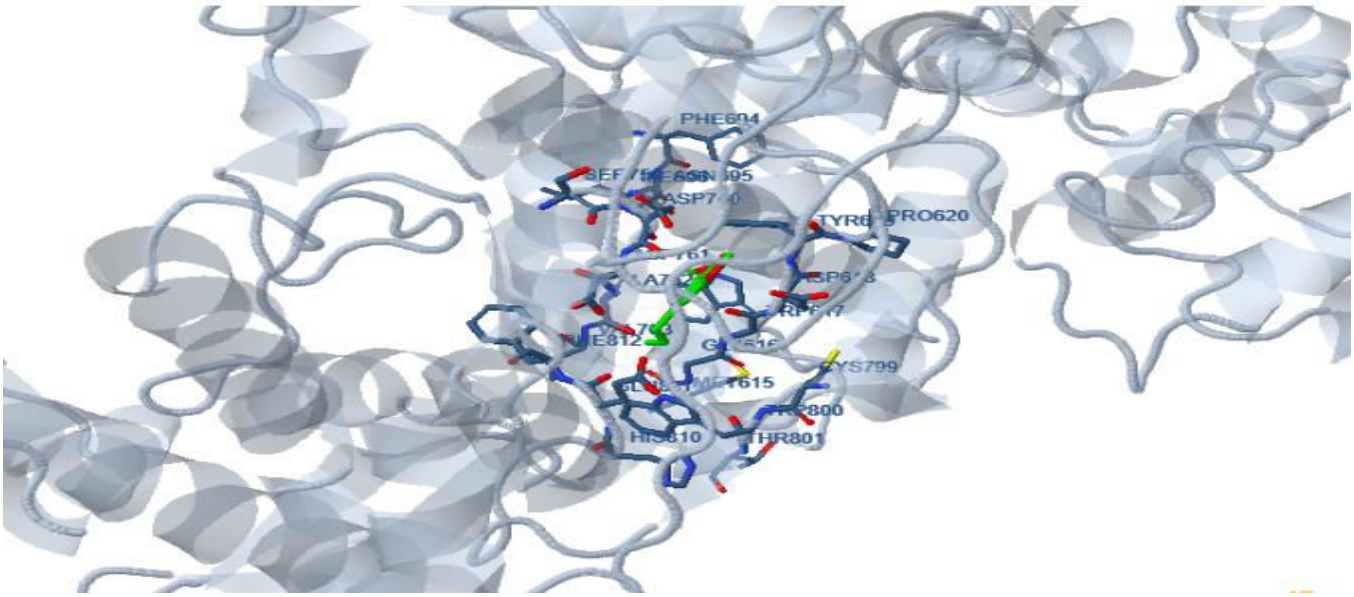

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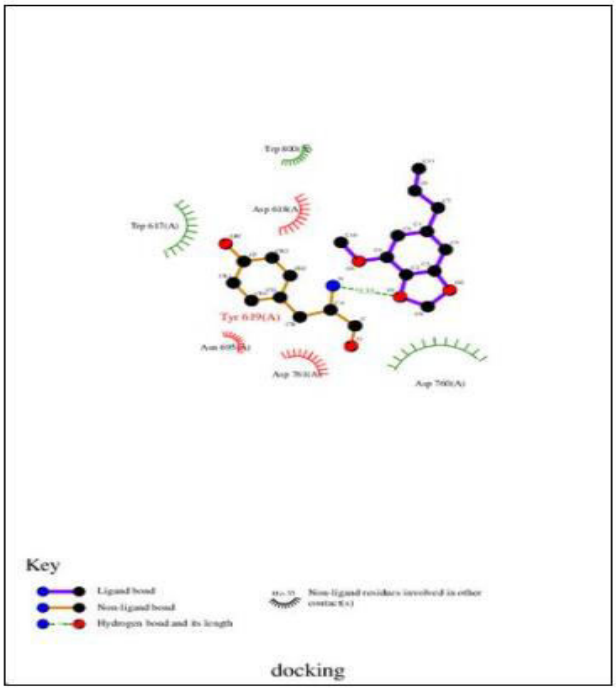

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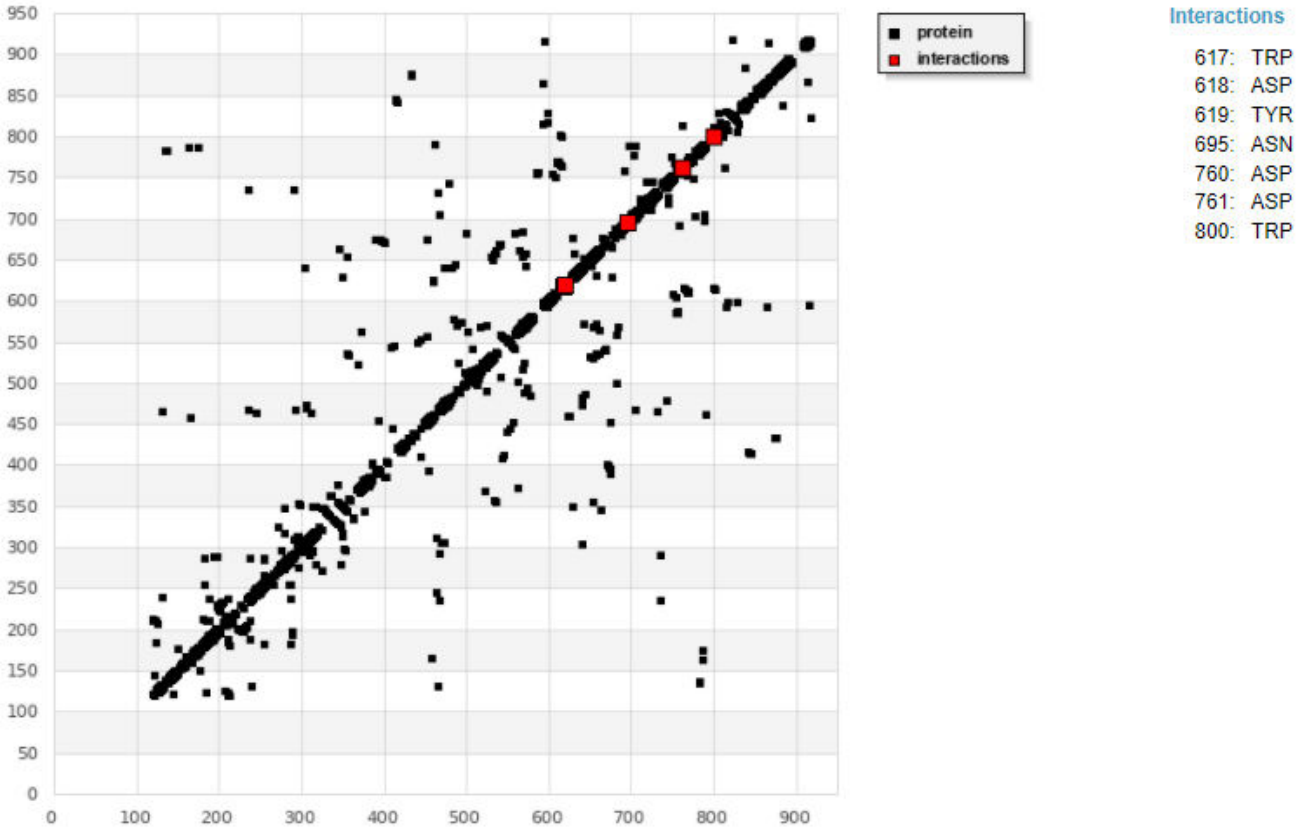
Hydrogen bond plotting with core amino acid Residues



cis-Vaccenic acid with RNA dependent RNA polymerase (PDB)-6NUR

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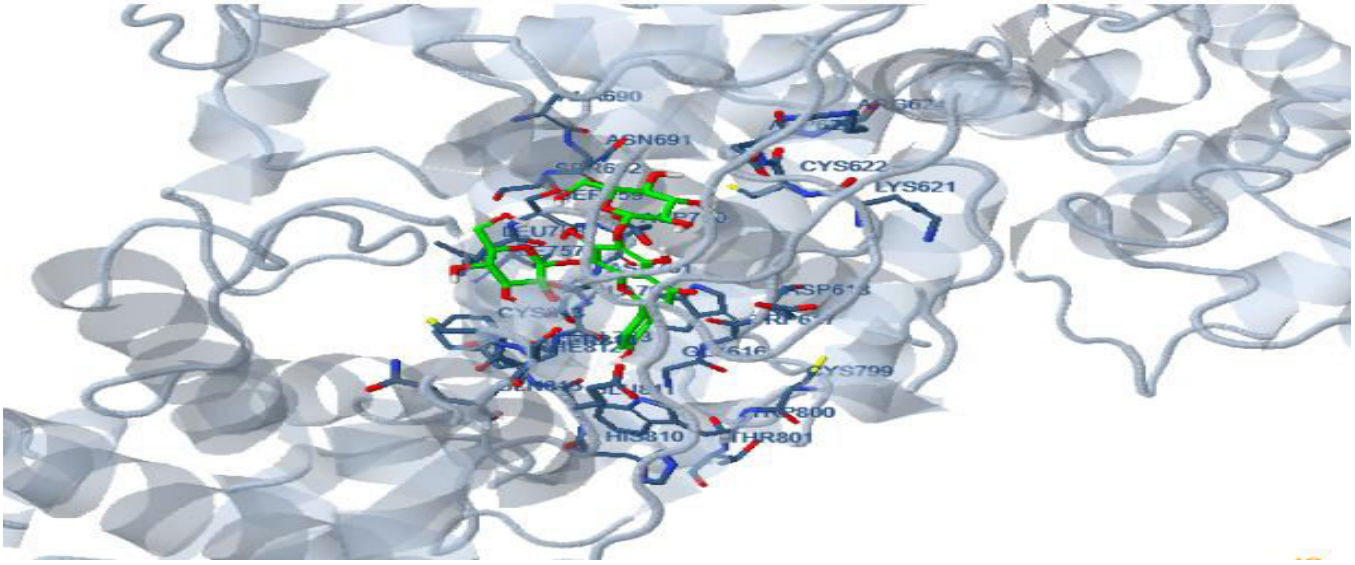

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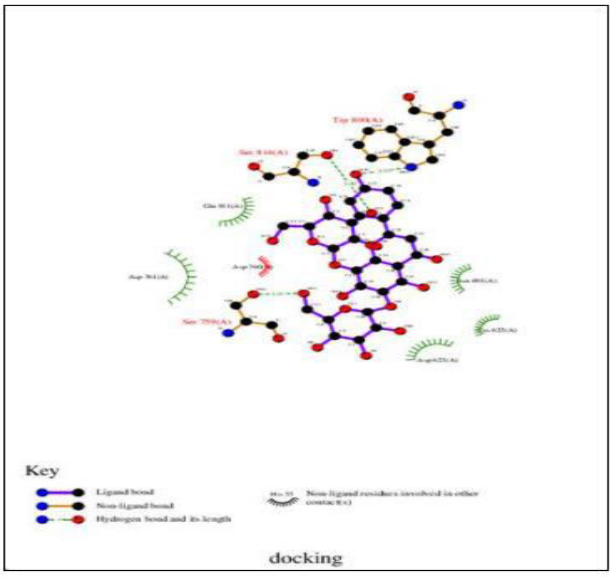

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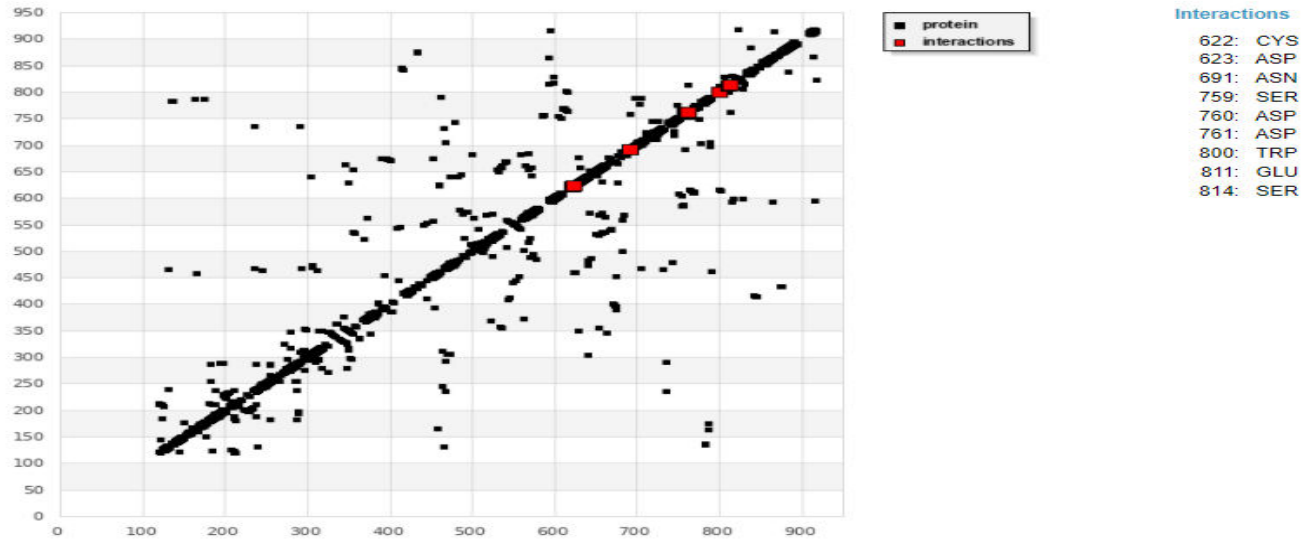
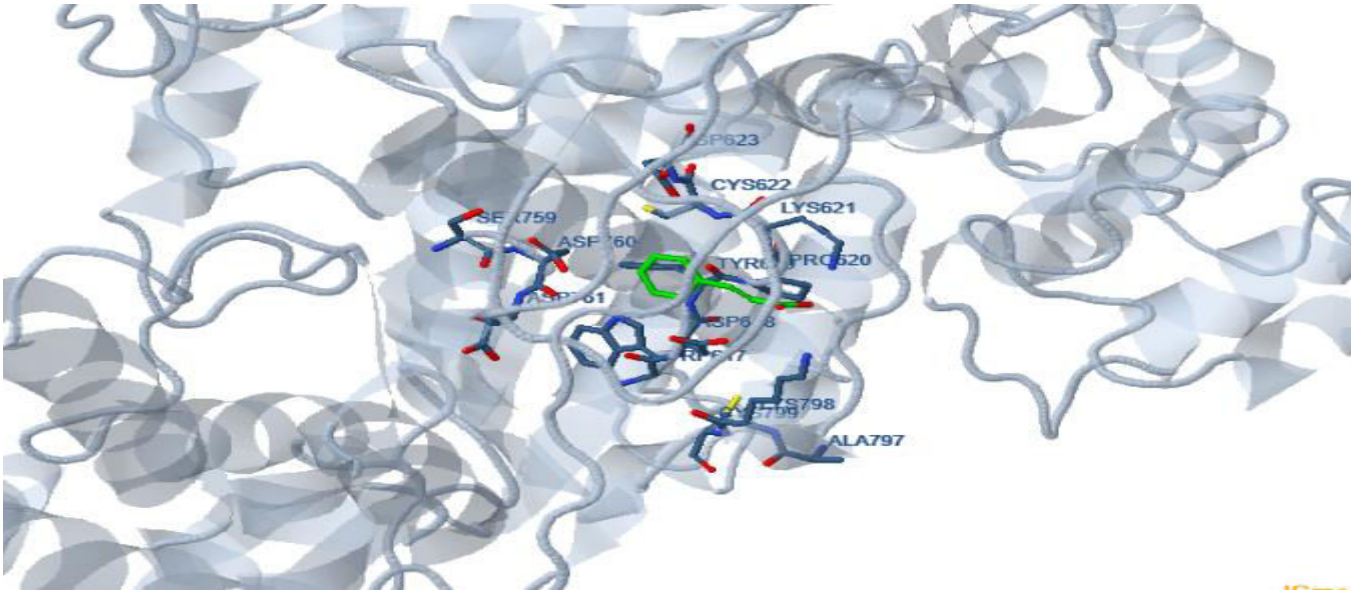


Gibberellic acid with RNA dependent RNA polymerase (PDB)-6NUR



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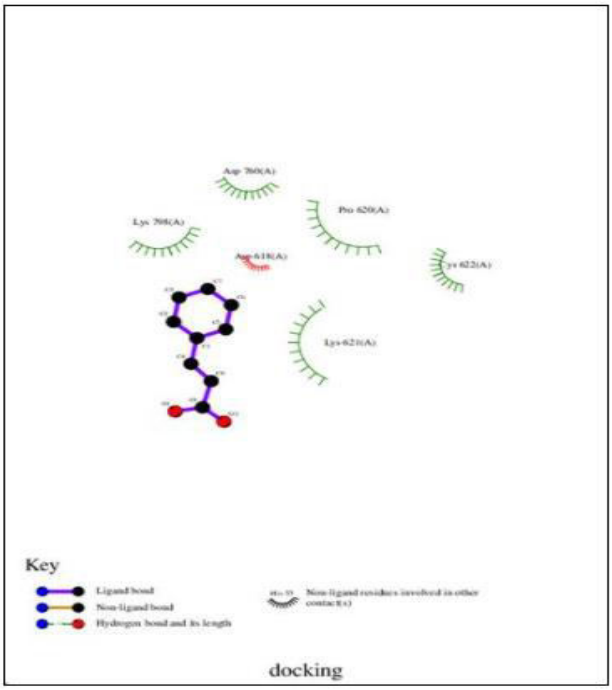

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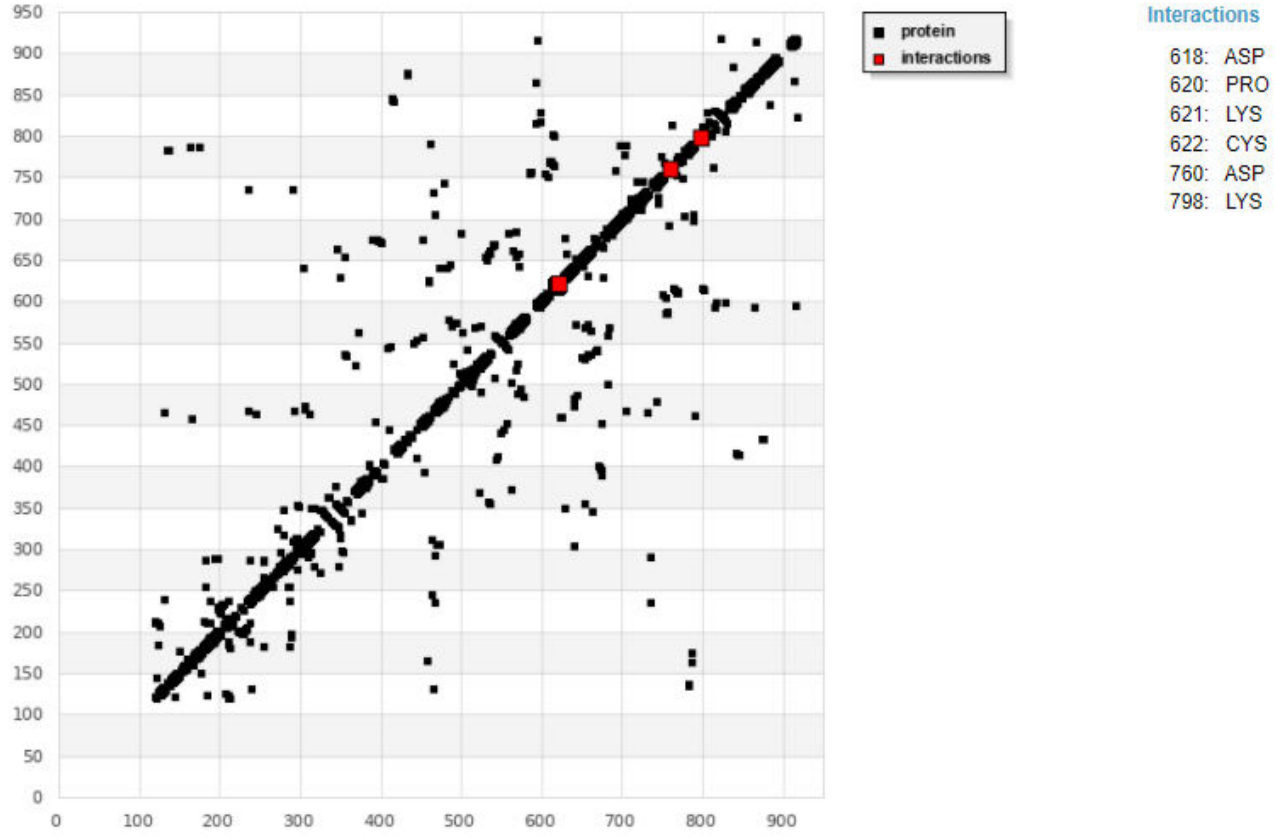
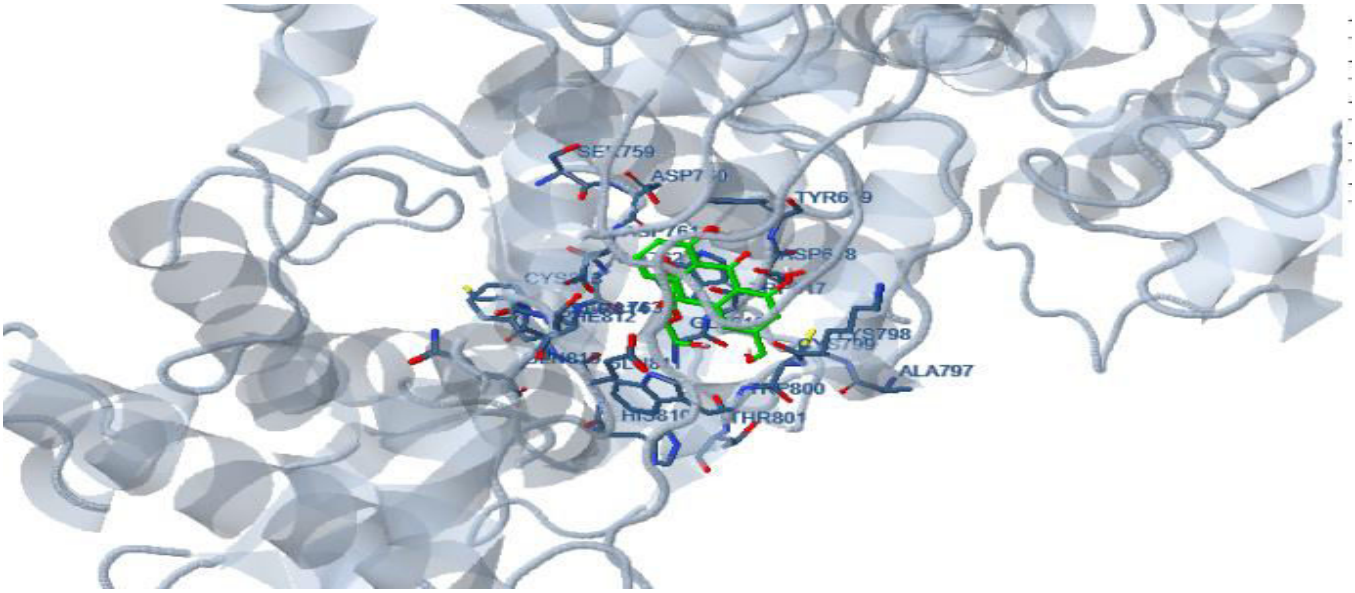


Aloin-A with RNA dependent RNA polymerase (PDB)-6NUR



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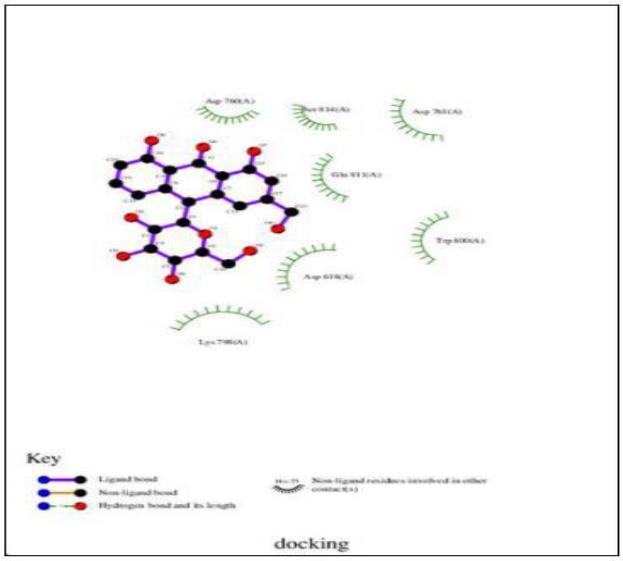

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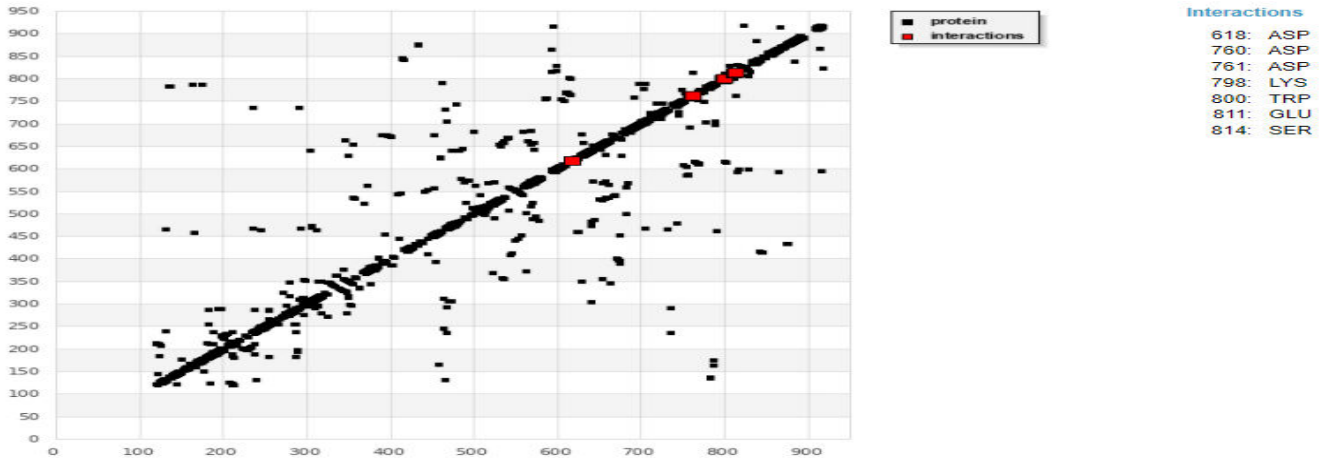

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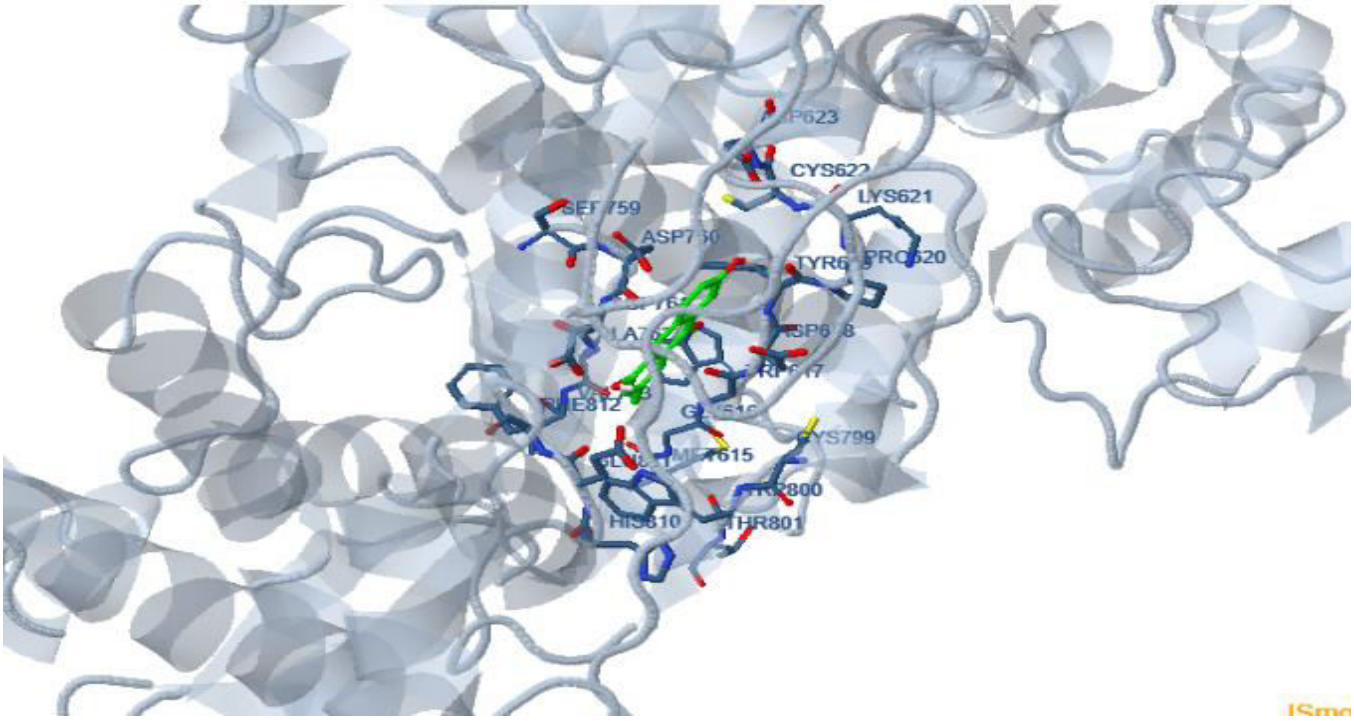
Aloe-emodin with RNA dependent RNA polymerase (PDB)-6NUR



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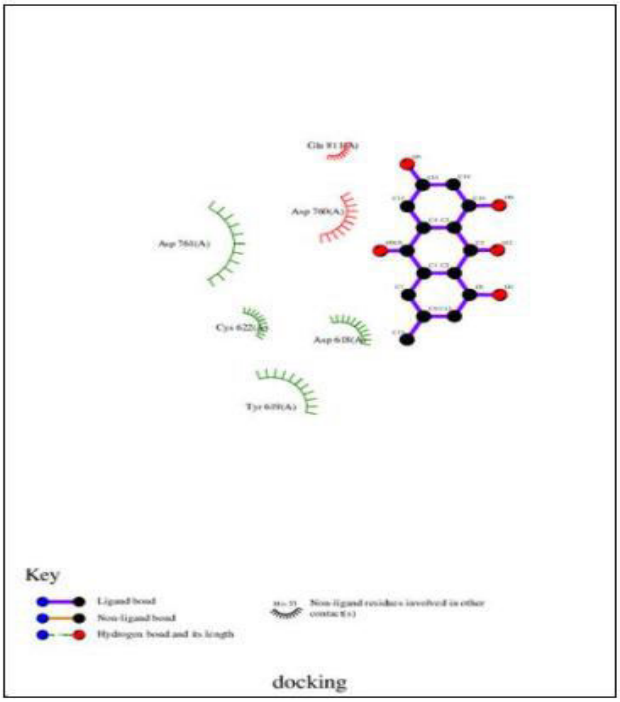
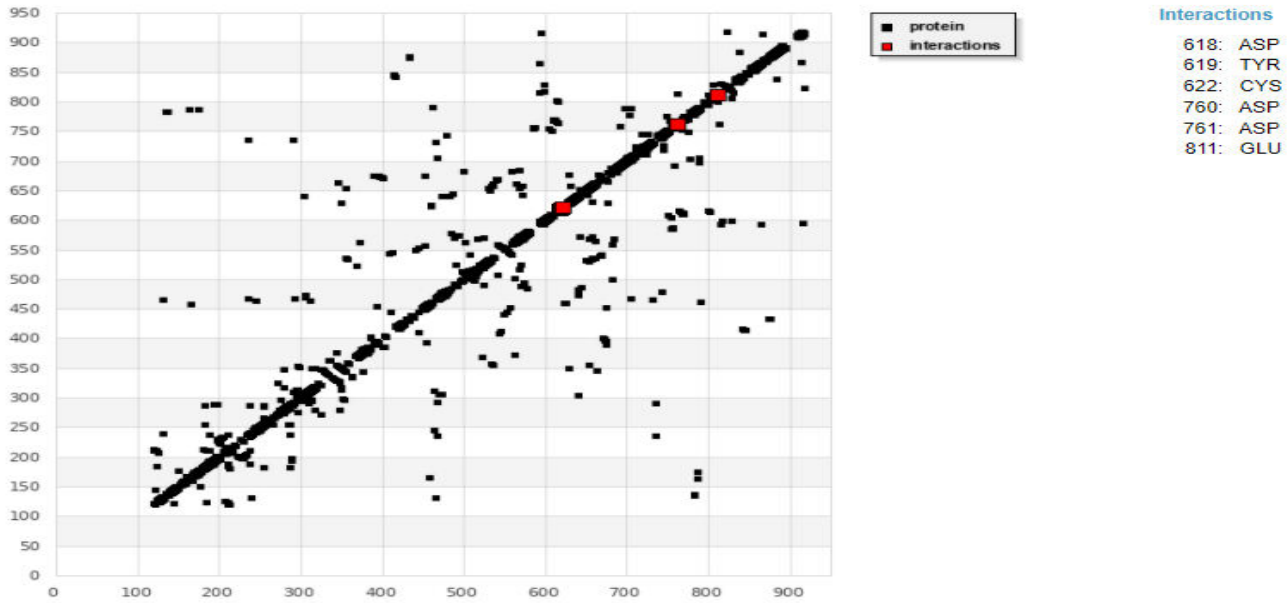


Hydrogen bond plotting with core amino acid Residues



Amino acid Residue Interaction of Lead against RNA dependent RNA polymerase (PDB)-6NUR

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Molecules	Interaction	Amino Acid - Residue Interactions								
Cinnamaldehyde	3	618 ASP	619 TYR	760 ASP	761 ASP	800 TRP				
Caryophyllene	2	618 ASP	761 ASP	800 TRP	811 GLU					
Cinnamic acid	2	618 ASP	620 PRO	621 LYS	622 CYS	760 ASP	798 LYS			
Grandisin	3	618 ASP	619 TYR	622 CYS	623 ASP	760 ASP	761 ASP	800 TRP	811 GLU	814 SER
LicarinA	3	618 ASP	619 TYR	622 CYS	760 ASP	761 ASP	800 TRP	811 GLU	814 SER	
Elemicin	3	617 TRP	618 ASP	619 TYR	695 ASN	760 ASP	761 ASP	800 TRP		
cis-Vaccenic acid	2	622 CYS	623 ASP	691 ASN	759 SER	760 ASP	761 ASP	800 TRP	811 GLU	814 SER
Gibberellic acid	1	553 ARG	618 ASP	621 LYS	623 ASP	798 LYS				
Aloin-A	3	618 ASP	760 ASP	761 ASP	798 LYS	800 TRP	811 GLU	814 SER		
Aloe-emodin	3	618 ASP	619 TYR	622 CYS	760 ASP	761 ASP	811 GLU			

Observation and Inference

Total of 10 bioactive lead compounds retrieved from the herbs in accordance with the reported literature, the lead compound's such as Cinnamaldehyde, Grandisin, LicarinA, Elemicin, Aloin-A and Aloe-emodin possess 100% binding efficacy by interacting with all three core target amino acid (618 ASP, 760 ASP, 761 ASP) present on the target receptor RdRp.

Conclusion

Based on the results of the computational analysis it was concluded that the compound's such as Cinnamaldehyde, Grandisin, LicarinA, Elemicin, Aloin-A and Aloe-emodin present in the herbal ingredients of the formulation Pacchai Karpoora Mathirai revels significant binding efficacy against the target protein thereby it was concluded that these compounds exerts promising RdRp enzyme inhibition potential and thereby halt the viral replication.

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