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JAIPRAKASH
SEWA SANSTHAN

Identification of Potential Inhibitors Against SARS-CoV-2 PL^{pro}

A Project Report

Submitted in partial fulfilment for the

requirements for degree of

BACHELOR OF TECHNOLOGY

IN

BIOINFORMATICS

BY

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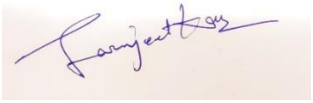
UNDER THE GUIDANCE OF

Dr. RAJ KUMAR

STUDENT DECLARATION

We hereby declare that the work represented in the given report entitled "**Identification of Potential Inhibitors Against SARS-CoV-2 PL^{pro}**" is solely done by both of us for the fulfilment for the requirements of degree in **Bachelor of Technology in Bioinformatics** under the supervision of our respected teacher **Dr. Raj Kumar**, Assistant Professor at Department of Biotechnology and Bioinformatics. This report is not being copy pasted from any of the resources and if the following report will be caught with copy pasted content, then we will be the one responsible for that. Also we've not submitted this work elsewhere for any other degree or diploma.



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CERTIFICATE

This is to certify that the project entitled "**Identification of Potential Inhibitors Against SARS-CoV-2 PL^{pro}**", submitted by Sarvjeet Kaur and Srishti Thakur is in its partial achievement for the award of degree of Bachelor of Technology in Bioinformatics to Jaypee University of Information Technology Waknaghat, Solan, (H.P), India is an authentic record of both of them is being assisted and carried out under my guidance.

This work has not been set forth partially or fully to any of the other universities or institute in order to attain any award or other degree.

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ABSTRACT

As we all are familiar that it is been almost about to be two years since the coronavirus has been emerged and is responsible for taking many of the lives and has caused a great setback to the economy around the globe. Despite the discovery of two drugs namely Covishield and Covaxin the conditions are not getting any better, so we tried to describe by doing the molecular docking of papain like protease**(PL^{pro})** that how it can prove to be an effective drug target also, we have also discussed about all the important aspects involved in the life cycle of the SARS-CoV PL^{pro} that is helpful in knowing that how it can prove itself as an important point for the drug to attach because they are also one of important component of the corona virus which helps it to multiply and make its count increase. Though the main function of the PL^{pro} is in the processing of the viral proteins in a very organized manner, in addition to this it also performs the function of removing all the covering of ubiquitin which is a compound that is found in living cells which plays an important role in degradation of defective and superficial proteins. PL^{pro} also removes the covering of Interferon-Stimulated gene 15(**ISG15**)which in turn helps the coronavirus to destroy the immunity of the host cell, thus by attacking or blocking the function of PL^{pro} we can stop the production of more viral particles. We have done the molecular docking of 12prep inhibitors with SARS-CoV-2 PL^{pro} protease molecule and tried to find out their binding energies with which they will interacts with the target molecule.

1. INTRODUCTION

1.1.Genetic makeup and Replication of SARS-CoV-2

The multiplication of corona virus consists of a very coordinated procedure which includes very complex replicating machinery so that the genome of the virus does not get destroyed [1].As there are many ongoing studies on the corona virus people have tried their best to find the best possible drug targets out of which many are known to encode in the 5' terminal of the two third portion of the entire corona virus genome, within the range of the two reading frames that code for the non-structural proteins that are also called replicase proteins this protein is produced by the translation of orf1a and orf1ab through -1 ribosomal frame shifting process[2]. This process is known to produce two viral poly-protein namely pp1a and pp1ab whose processing is done once again by papain like protease and a 3C-like protease (3CLpro).This processing is required for the release and maturation of the 16 non-structural proteins whose

function is the formation of membrane associated, cytoplasmic enzyme complex which is a replicase complex and helps in the multiplication of the corona virus particles[3].

The viral replication site starts when the replicase or we can say the non-structural proteins are being hired to the host membrane the non-structural proteins involved in it are mainly nsp3, nsp4, nsp6. With the help of electron tomography and 3D image rebuilding studies it is known that the replicase complex make use of reticulon-vesicular network of double membrane vesicles with outer membranes that are connected with each other and are seen coming out from the endoplasmic reticulum[4,5]. Due to which the replication mechanism of the corona virus is restricted to a local place and leads to increase in the count of macromolecules and forms a network of ribonucleic acid(RNA)synthesis. The important thing to note here is that this mechanism aids in providing a micro environment which preserves and fight from host nuclease to protect the viral RNA. Out of all the non-structural proteins nsp3 is a very significant one as it is involved in the process of getting two or more proteins together so that their arrangement becomes stable this process is known as central scaffolding of the replication complex ,as it has large contacts with the rest of the non-structural proteins.

1.2. Multi domain nsp3

The nsp3 is known as the multi domain protein as it provides the largest subunit for replication having around 1922 amino acids[5]. It is popular for its great contacts with the remaining non-structural proteins with great attention to two main proteins that are nsp4 and nsp 6 [6].Many domains are plotted in nsp3 and are conserved in entire corona virus. The largest size of the nsp3 is the reason why it is being used in most of the in vitro and cellular studies .

The region which remains same around the entire genome of the SARS-CoV-2 is the N terminal which has a ubiquitin globular fold succeeding an acidic which has a glutamic acid concentration of 38 percent**[7]** after the acidic domain next comes an ADP- ribose -1 phosphate domain which is highly catalytically active whose role is to produce sub genomic RNA of corona virus.After all these domains there comes a unique domain that is known as SARS unique domain which is till now not found in other corona virus only known to be identified in alpha and beta coronavirus. The role of the SARS unique domain is to bind oligonucleotides which forms G quadruplex. In the latter stages of SARS unique domain there comes another ubiquitin 1(**UB1**) domain and the PL^{pro} domain that is also catalytically active domain like Adenosine di-phosphate **(ADP)**domain the PL^{pro} domain breaks down the non-structural proteins namely nsp1 or nsp 2 and nsp 2 or nsp 3 into smaller poly peptide or amino acids at their respective cleavage sites. In the Direction of PL^{pro} a next domain whose name is nucleic

acid binding domain is found which has a gamma corona virus and also has a marker domain G2M which is very uncommon. Downstream G2M their comes two trans membrane proteins namelyTropomyosin1-2**(TM1-2)** and Tropomyosin3-4**(TM3-4).**

As the nsp3 has an ability of performing multiple functions at a time the probability of having a point-mutations is very high and as the involvement of nsp3 in the arrangement of the structure of the replicase complex is considerably high and also the vesicles that are double member may cause the production by single gene of two or more apparently unrelated effects which is called pleiotropic effects on how SARS-CoV-2 causes a disease. The different domains of SARS-CoV-2 PL^{pro} is shown in the Figure 1 below:

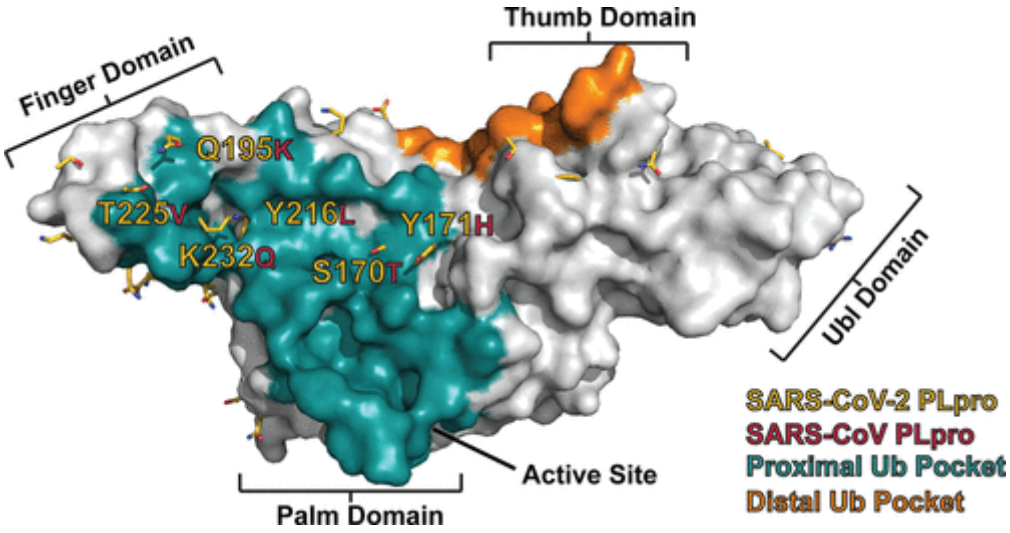


Figure1. Different domains of SARS-CoV-2 PL^{pro}

1.3. Nsp3 domain containing SARS-COV-2 PL^{pro} domain with in itself

As the nsp3 has an ability of performing multiple functions at a time the probability of having a point-mutations is very high and as the involvement of nsp3 in the arrangement of the structure of the replicase complex is considerably high and also the vesicles that are double member may cause the production by single gene of two or more apparently unrelated effects which is called pleiotropic effects on how SARS-CoV-2 causes a disease . The SARS-CoV-2 PL^{pro} catalytic domain is surrounded by many active enzymes, transmembrane domains, and unknown activity domains, and all nsp3 is converted into ER structures where most domains reside in cell cytosol[8]. In cytosol, the membrane associated with the PL^{pro} domain detects the P4-P1 sequence LXGG sequence, which is found in the parameters of nsp1/2, nsp2/3 and nsp3 / 4 where membrane interactions are required to resolve nsp3 / 4 [9]. Proteolytic cleavage of the peptide bond after P1-based glycine leads to the release of nsp1, nsp2 and nsp3 from the

polyprotein virus an important process in viral replication. Therefore, SARS-CoV-2 PL^{pro} is proposed to be the best member of the prescription drug development drug.

1.4. Part of SARS-CoV-2 PL^{pro} in a deubiquitinating (DUB) and deISGylating enzymatic activities

To remind you of the complete formation of deubiquitinating enzymes (DUBs) in the specific family of ubiquitin protease (USP), the PL^{pro} catalytic domain cell structure is composed of a canonical structure, right hand - N-fingers on the sides of the N - terminus with additional base of -ubiquitin-like (UBL) unknown function [9]. The in vitro description of PLpro enzymatic activities suggests that PLpro can also detect and hydrolyse the cellular proteins ubiquitin (Ub) and ISG15 both of which carry the cause of LXGG adoption at their C terminuses. protein regulation by forming an isopeptide bond between their C-terminus and the ε-amino group of the lysine side protein [10]. These isopeptide bonds can be dehydrated by the action of DUB isopeptidase and the deISGlating enzyme to remove Ub and ISG15 from regulated protein cells.

1.5. Part of SARS-CoV-2 PL^{pro} in innate immunity

The DUB and deISGylating activities of SARS-CoV-2 PLpro have a significant impact on the immune response during SARS-CoV-2 infection. Both Ub and ISG15 are important indicators of a natural anti-inflammatory response in the fight against infection, which can be effectively controlled by the DUB virus and the deizGylating enzyme [11]. SARS-CoV-2 PLpro has been shown to act as a potent antagonist of many Ub-dependent cellular responses to infection [12]. Although the process of PL^{pro}-Mediated antagonism of mobile methods is not well understood, the evidence strongly suggests that regenerative function is important in combat and, therefore, DUB and deISGylating functions have been suggested as a mechanism of action.

Because many of the mobile features of CoV-2 PLpro DUB / deISGylating activities have been reviewed elsewhere [12], a brief preview is provided here and the reader should visit other sources to get the full review of this topic. The antagonistic activity of SARS-CoV-2 PLpro has been shown to inhibit the production of vital cytokines involved in the activation of the body's immune response in the fight against viral infections, including Type I interferon β (IFNβ) and chemicals such as CXCL10 and CCL5. Based on in vitro and cultural data obtained from SARS-CoV-2 PLpro and other homologous coronaviral PLPs, a summary of the ways in which PLpro is likely to interfere with the expression of inflammatory cytokines, such as interferon β (IFN-β), and inhibits its formation of the antiviral state shown in Figure 2. Initially,

SARS-CoV-2 PLpro was shown to interfere with IRF3 production and NF-κB showed that the antagonist between SARS-CoV-2 PLpro-mediated interferon (IFN) in increasing IRF3 activity by inhibiting IRF3 phosphorylation, homodimerization, and as a result of nuclear transfer. On the other hand, Frieman et al. it has been shown that PLpro stabilizes the NF-κB inhibitor, VerBcy, and thus inhibits NF-κB signaling pathway. Recently, Mielech et al. demonstrates the ability of SARS-CoV-2 PLpro to lower endogenous levels of cytokines and chemokines in active cells

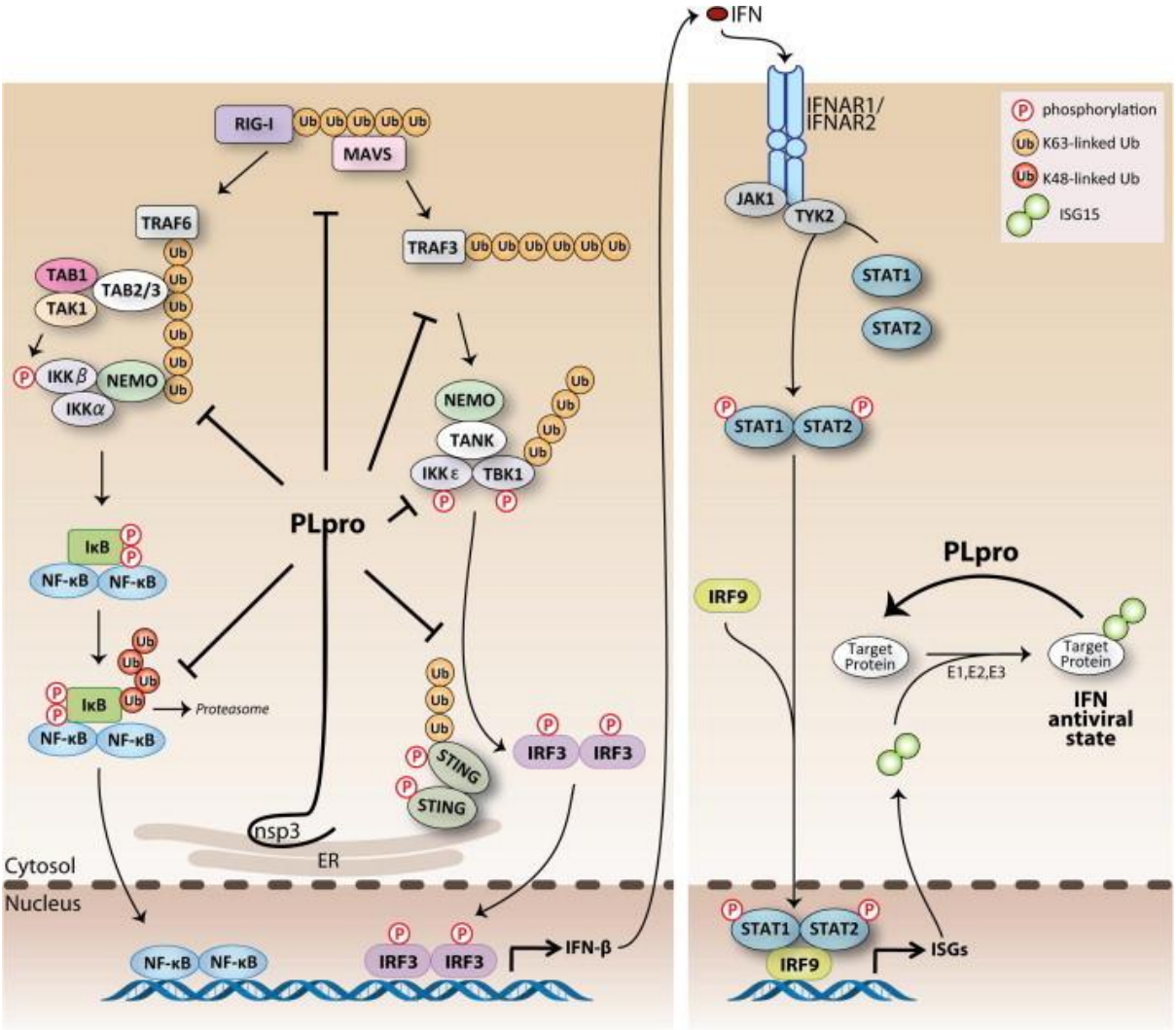


Figure2. Shows possible ways in which PL^{pro} can interfere with the expression of proinflammatory cytokines

2. Composition and purpose of SARS-CoV-2 PL^{pro}

2.1. Composition of SARS-CoV-2 PL^{pro} active site structure and its catalytic activities

2.1.1. Composition of active site

The family to which SARS-CoV-2PL^{pro} belong is termed as CA family . The substrate binding site of the PL^{pro} molecules contains a catalytic group of three genes namely Cys112-His273-Asp 287 (shown in Figure 3) that are properly placed in the thumb and palm sub domains.Cys112 contains sulphurchains. The structures of SARS-CoV-2PL^{pro} is very identical to the papain of Carica papaya and it also contains cysteine,histidine and asparagine in the catalytic centre .The studies have revealed that overall tertiary structure of the SARS-CoV-2 is very much similar to the ubiquitin specific protein degrading enzymes namely USP14, USP 7 however when the ligands are not attached to the PL^{pro} then it only forms a triad with USP 14 not USP 7.In order to keep the structure of SARS-CoV-2 PL^{pro} stable the finger region of SARS-CoV-2 PL^{pro} which contains zinc should be forming tetrahedral bond with the cysteine.

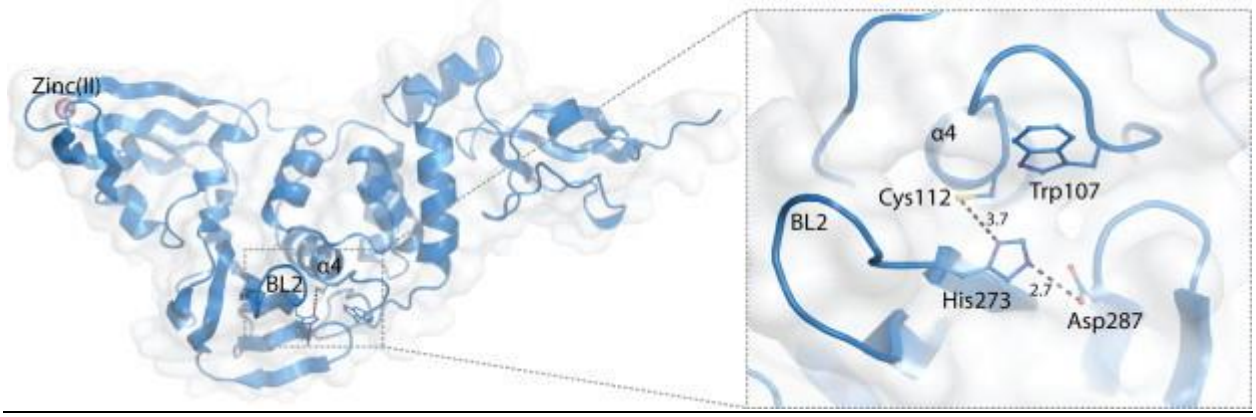


Figure3. The given figure represents the point where the catalytic activities active site is present

SARS-CoV protease inhibitors can destroy itself and can be a scope for SARS-CoV PL^{pro}-2 also. Protease inhibitors are known to be a very basic requirement for antiviral drug therapies the examples of such inhibitors can be taken as HIV and Hepatitis c. Inside the corona virus also the most important protease inhibitor is the one accountable for reversing the movement of deadly corona virus so that it can stop the spread of infection. As there is no such vaccine or treatment available for the recent SARS-CoV-2 it has become the need of the hour to identify important drug leads that can bind to the target molecule or we can say the active site of this. As the gene GRL0617 has a very minute micromolar effectiveness against it, so we can use it as an effective drug along with compound 6,the compound 6 is non covalent and is also known to have a low effectiveness it is also very low in terms of cellular toxicity in multiple text lines.

2.1.2. Catalytic mechanism

The cysteine degradation proteins enzyme is responsible for a catalytic loop where cysteine112 has the function to donate it's electron the other parts of the catalytic triad that are histidine 273 and aspartate 287 has the duty to act as general acid base and in the removal of a proton mainly a hydron or hydrogen cation it is responsible for removing +1 charge from a chemical compound.

3. Inhibitory categories of SARS-CoV PL^{pro}

3.1. Identification of inhibitors by the method of yeast based screening

In 2011, two new PLPRO inhibitors were accounted. These inhibitors have been recognized with yeast test questions intended to identify SARS-CoV PLpro inhibitors [13]. The preliminary includes the statement of SARS-CoV PLpro in the Saccharomyces cerevisiae prompting an aggregate of moderate development. The 2000 NIH Diversity Set library was concentrated by particles fit for switching the quickly developing aggregate of PLpro. The synthetics recognized as hits in these essential preliminary were then tried for viability against SARS-CoV duplication and hindrance of PLpro execution in cell culture models. This exploratory methodology prompted the ID of NSC158362, a compound that can explicitly forestall the repeat of SARS-CoV in cell culture without cytotoxic impacts. In any case, NSC158362 has been discovered to be not able to repress the exercises of PLPRO protease, deubiquitinase and against interferon - demonstrating another possible instrument for forestalling duplication of SARS-CoV. A subsequent compound, NSC158011 was found to can hinder PLpro protease action in cell-based tests; nonetheless, this hasn't prevailing with regards to forestalling the repeat of the SARS-CoV infection.

3.2. GRL0617 a potential inhibitor for SARS-CoV PL^{pro}

GRL0617 has proven to be an active inhibitor against SARS CoV PL^{pro} many kinetic studies were done on the process by which an enzyme inhibition complex is formed the studies have also revealed that the inhibitor that has proven effective against SARS CoV PL^{pro} has a ki value around 0.49 ,+0.08 ,-0.08μm it is also known that GRL0617 is a non-covalent inhibitor [13].When the experiment on SARS-CoV PL^{pro} and GRL0617 gene was performed it was revealed that the after incubating them both for a period of 60 minutes the complex so formed has an

ability to purify and hence resulting in the restoration of the enzymatic activities . After the formation of the complex the PL^{pro} was only active around 20-25%. GRL0617 is found in ubiquitin specific domain of SARS-CoV PL^{pro}. The difference between SARS-CoV $PL^{pro}$and SARS-CoV PL^{pro}-2 is that they have 54 residues that are not similar in them but they also

share some similarity that they have same residues lining they p3 and p4 regions of the active sites. As in Figure 4, SARS-CoV-2 PL^{pro} along with GRL-0617 as well as enzymatic and antiviral data for PL inhibitors against SARS-CoV-2 PL^{pro} and SARS-CoV-2 is represented. Also in Figure 5 the images explains how the gene GRL0617 stops the activities of SARS-CoV PL^{pro}.

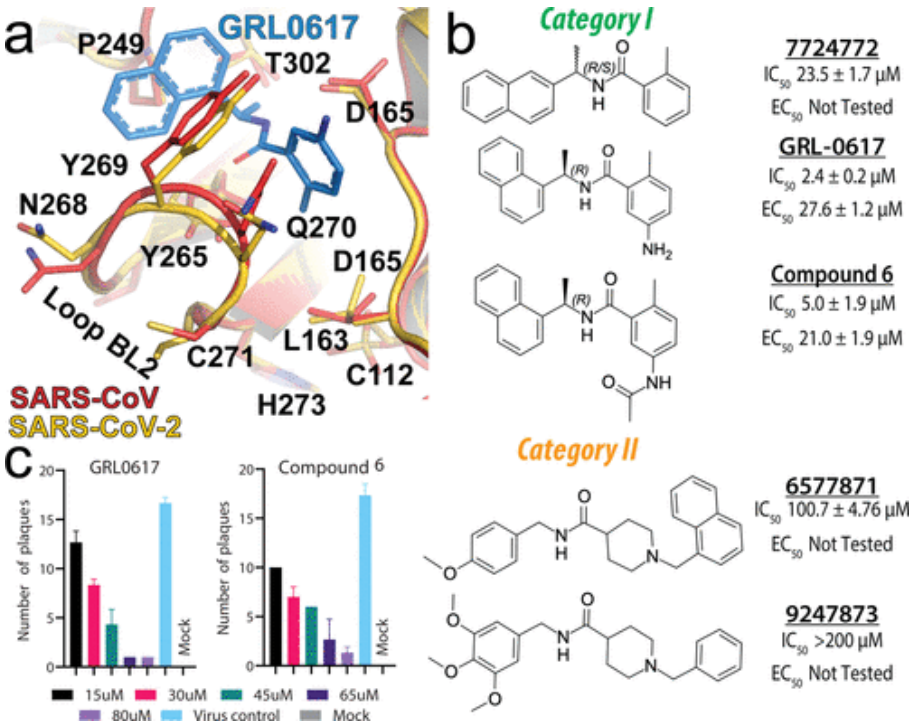


Figure4. Represents SARS-CoV-2 PL^{pro} along with GRL-0617 as well as enzymatic and antiviral data for PL^{pro} inhibitors against SARS-CoV-2 PL^{pro} and SARS-CoV-2.

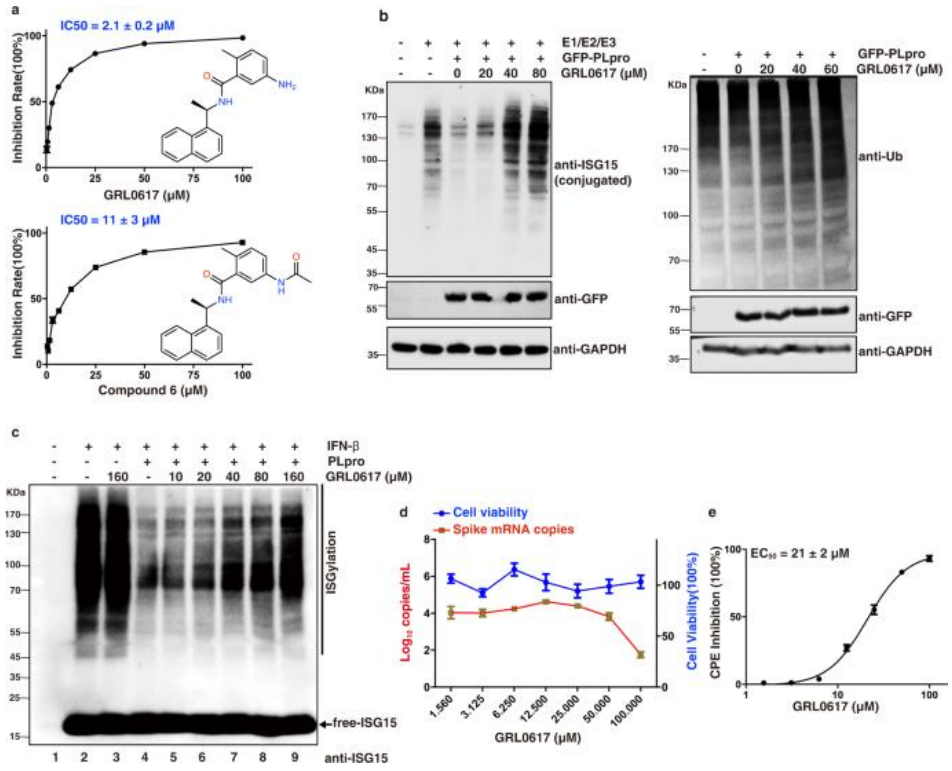


Figure5. The following image represents how the gene GRL0617 stops the activities of SARS-CoV PL^{pro}

4. MATERIALS AND METHOD

4.1. Optimization of the ligand's 3D data.

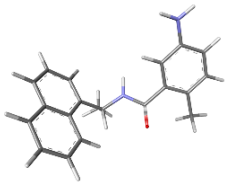
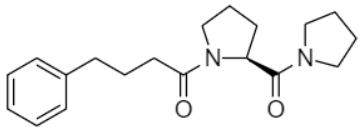
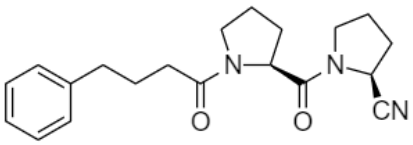
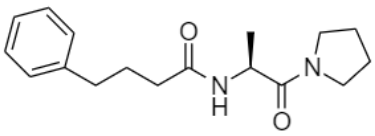
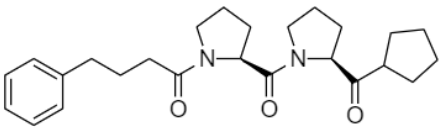
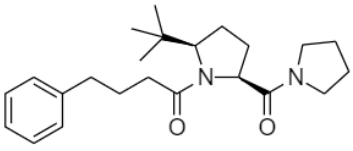
CHIMERA was used to acquire the 3D coordinates of the 12 drug ligands. The following steps were completed to get minimised structure of the ligand:

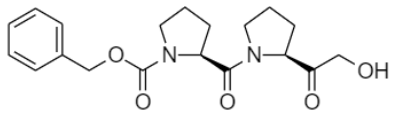
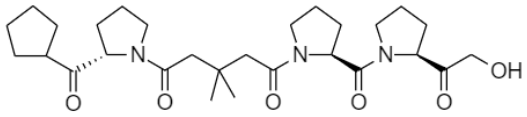
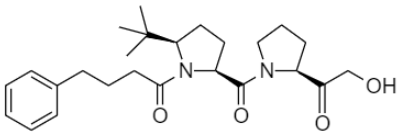
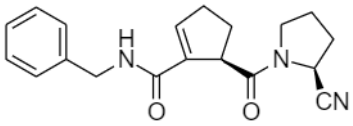
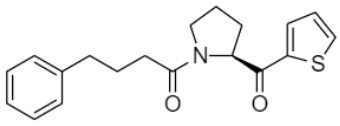
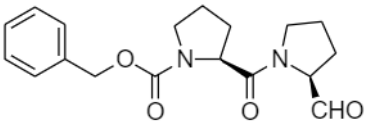
- 1.Firstly, clicked on data, followed by reading the molecule (opened ligand we had).
- minimised structure by clicking on structure editing in tools.
- .pdb file saved

We selected 12 known structurally diverse PREP inhibitors:

The given table 1 represents all the PREP inhibitors that we selected for docking along with their respective molecular weight and IC_{50} . We have also given a representation of their 2D structures.

Sr. No.	Compound	2D Structure	Molecular weight	IC_{50} value

1	Reference molecule (TTT401)		-----	--
2	SUAM-1221	 SAUM-1221	314.4290	2.0
3	KYP-2047	 KYP-2047	333.4412	0.2
4	KYP-2087	 KYP-2087	288.3910	1.47
5	KYP-2091	 KYP-2091	410.5580	1.010
6	KYP-2101	 KYP-2101	370.5730	1.2

7	KYP-2108	 KYP-2108	360.4100	0.28
8	KYP-2112	 KYP-2112	517.6600	0.32
9	KYP-2117	 KYP-2117	428.5730	0.26
10	KYP-2153	 KYP-2153	323.3960	0.38
11	KYP-2189	 KYP-2189	327.4420	3
12	ZPP	 ZPP	330.3840	0.4

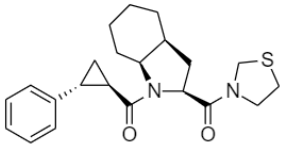
13	S17092	 S17092	384.5830	1.5

Table1. Show compounds we selected for docking, along with their 2D structure, molecular weight and IC50 value.

4.2. PLpro's structure preparation for molecular docking

For molecular docking, the SARS-CoV-2 papain-like protease (PDB:7CJM) was used as a template. The structure is solved through X-ray diffraction with 3.20 angstrom resolution. Using Discovery Studio, water molecules and ligands were removed from the PDB file it can be erased manually in a text editor or it can also be removed in discovery studio visualizer.

4.3. Molecular Docking done using AutodockTools-1.5.7

Step 1: Preparing coordinates

The first step is to prepare the ligand and receptor coordinate files to include the information needed by AutoGrid and AutoDock.

1. First step is to set preferences as:
    - File -> Preferences -> Set -> Start up Directory -> copy pasted the path of folder we'd worked on.
2. Steps for receptor molecules:
    - File -> Read Molecule -> 7CJM
    - Edit -> Hydrogen -> Add -> Polar Only
    - Edit -> Charges -> Add -> Kollman Charges
    - Edit -> Atoms -> Assign AD4
    - Edit -> Hydrogen -> Merge non-polar
    - Edit -> Charges -> Check totals on residues
    - File -> save -> 7CJM.pdbq
3. Steps followed for ligand preparation:
    - File -> Read molecule -> Ligand
    - Edit -> Hydrogen -> Add -> All Hydrogen

- Edit -> Charges -> Add -> Compute Gasteiger
- Edit -> Atoms -> Assign AD4
- Edit -> Charges -> Check totals on residues
- File -> save -> Ligand.pdbq

4. Saved .pdbqt file from raw files (.pdbq files prepared earlier)
    - Ligand -> Input -> Choose -> Ligand -> Select molecule for autodock
    - Ligand -> Output -> Molecule saved (Ligand.pdbqt)
    - Grid ->Macromolecules -> Choose ->Molecule selected (7CJM.pdbq) -> Select molecule -> Molecule saved (7CJM.pdbqt)
5. Grid -> Set map type -> Choose ligand -> Ligand.pdbqt
    - Grid -> Grid box -> Chosen dimensions are: x center (5.029), y center (26.263) and z centre (-1.835) ; number of points in x- dimensions(40), number of points in y- dimensions(44) and number of points in z-dimensions(32)
    - File -> Close current saving
    - Grid -> output -> File saved(**Grid.gpf**)
6. Docking -> Macromolecule -> Set rigid frame -> 7CJM.pdbqt
    - Docking -> Ligand -> Choose -> Ligand.pdbqt -> Accept
    - Docking -> Search parameters -> Genetic Algorithm -> Run changed from 10 to 100
    - Docking -> Output -> Lamarckian -> File saved (Dock.dpf)

Step 2: Running Auto Grid & Auto Dock

Auto Dock contains grid maps that have been pre-calculated, one for each atom form in the ligand to be docked. This aids in increasing the speed of docking calculations. Auto Grid is the programme that outputs and displays these maps. Grid point spacing will range from 0.2 to 1.0, with 0.375 being the norm (roughly a quarter of the length of a carbon-carbon single bond). The potential energy of a ‘probe' atom or functional group due to all the atoms in the macromolecule is stored at each point on the grid diagram. To define the files and parameters used in the calculation, Auto Grid includes a grid parameter file. The extension ".gpf" is commonly used for grid parameter files.

- The following command is used to run AutoGrid:

autogrid4 -p Grid.gpf -l Grid.glg

- Command used to run AutoDock:
  autodock4 -p Dock.dpf -l Dock.dlg

Step 3: Analysing result

Result analysed using BIOVIA Discovery Studio. We extract the docked conformations from the AutoDock file i.e. Dock.dlg by opening it in notepad. File contains docked conformations of the ligand. These are sorted in order of increasing energy, and in accordance with the conformational clustering. The file puts each docked conformation in between MODEL and ENDMDL records. Steps in this, we've followed are below:

1. Making .pdb file form Dock.dlg file
- Opened Dock.dlg file in notepad
- Analyse the file, as it contains docked conformations along with their binding energies. They are sorted in order of increasing energies.
- Copy pasted first 3 or 4 docked conformations (i.e. starting from Model; ends with ENDMDL) in new text file and saved it as ligand_top_conformations.pdb

2. Steps followed in BIOVIA Discovery Studio
    - File -> open -> 7CJM.pdb
    - Scripts -> Visualisation -> Publication Quality
    - Select -> protein(from the top left corner)
    - Display style -> protein -> color -> choosed light color so that we can easily observed the binding of the ligand.
    - Drag and drop ligand_top_conformations.pdb file
    - Structure -> Monitor -> H Bonds
    - Select -> ligand -> Define Ligand
    - Show 2D diagram
    - Select all molecules interacting with ligand by: shift+click
    - Left click on 3D structure -> display style -> stick -> apply
    - Left click on 3D structure -> label -> add -> object -> AminoAcid -> attribute -> 3-letter &ID#
    - Select ligand -> display style -> stick -> color -> light grey
    - Select ->labels -> chain -> custom text -> name of the ligand

- File -> save -> .png file

4. RESULT

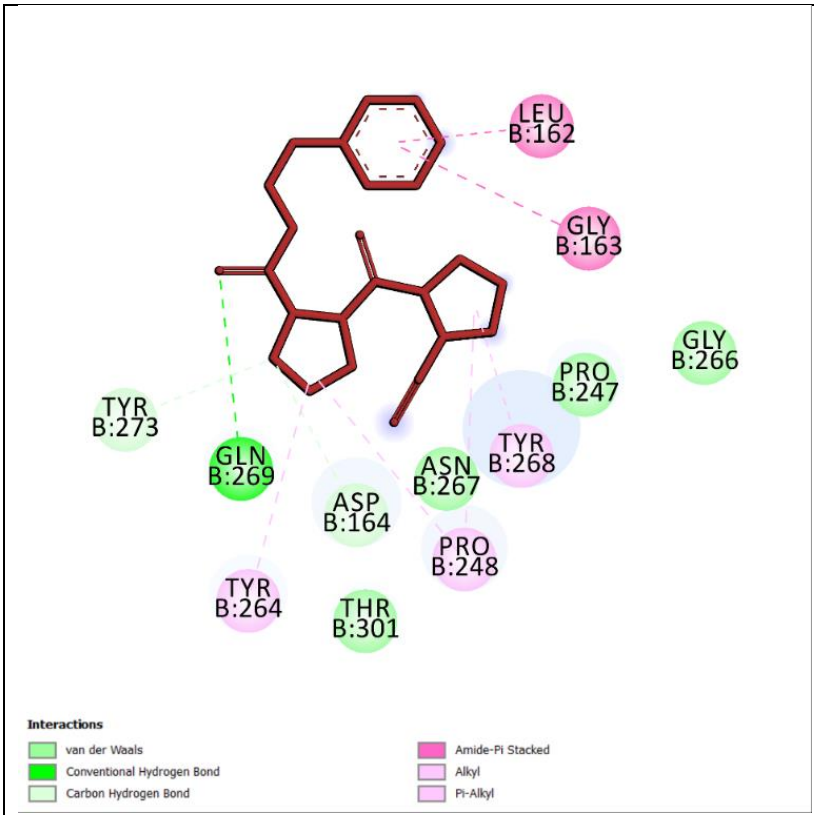
The PREP inhibitors were screened using the crystal structure of SARS-CoV-2 PL^{pro}. In Table 2 docked PREP inhibitors are arranged with respect to the lowest binding energy order along with their respective compound names.

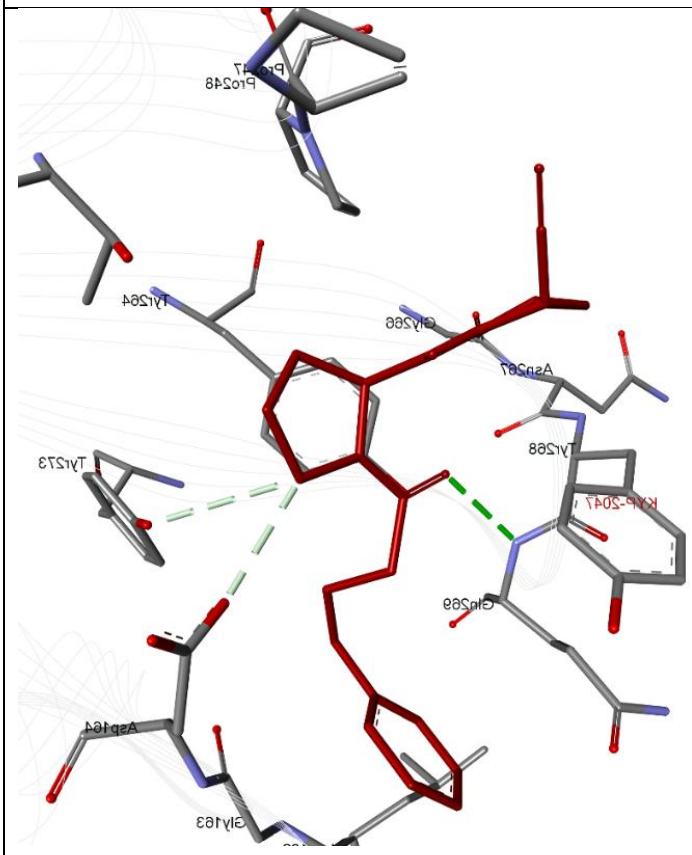
Sr. No.	Compound Name	Lowest Binding Energy
1	**KYP-2153**	**-9.75**
2	KYP-2101	-9.01
3	KYP-2091	-8.68
4	KYP-2087	-8.42
5	KYP-2189	-8.18
6	KYP-2108	-8.16
7	SUAM	-7.99
8	ZPP	-7.75
9	KYP-2117	-7.57
10	KYP-2112	-7.33
11	S17092	-7.14
12	KYP-2047	-6.17

Table 2. Showing PREP inhibitors with their binding energies starting with lowest binding energy.

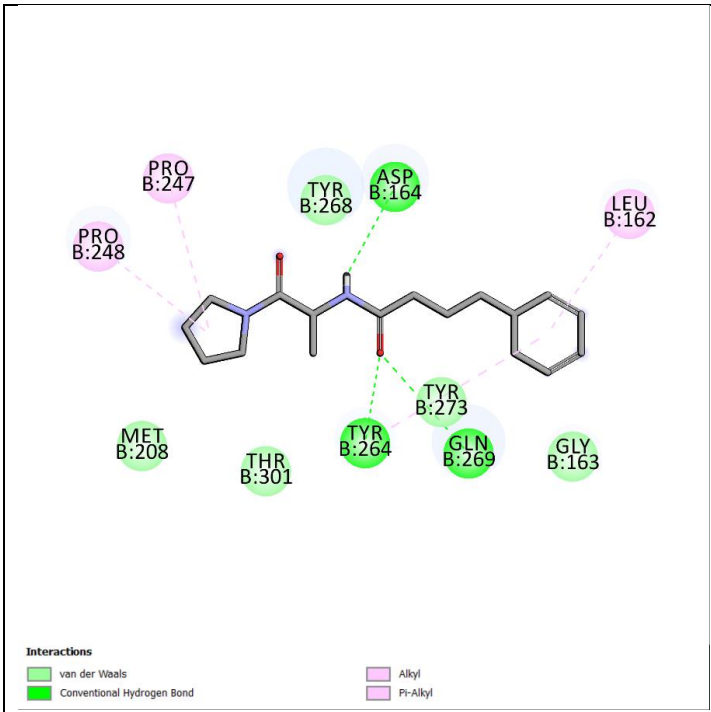
Table 3 shows the results of the docking analysis, which included 12 PREP inhibitors. The ligand interactions of 2D and 3D structures are also shown in this table, along with their binding energies (kcal/mol) and their names.

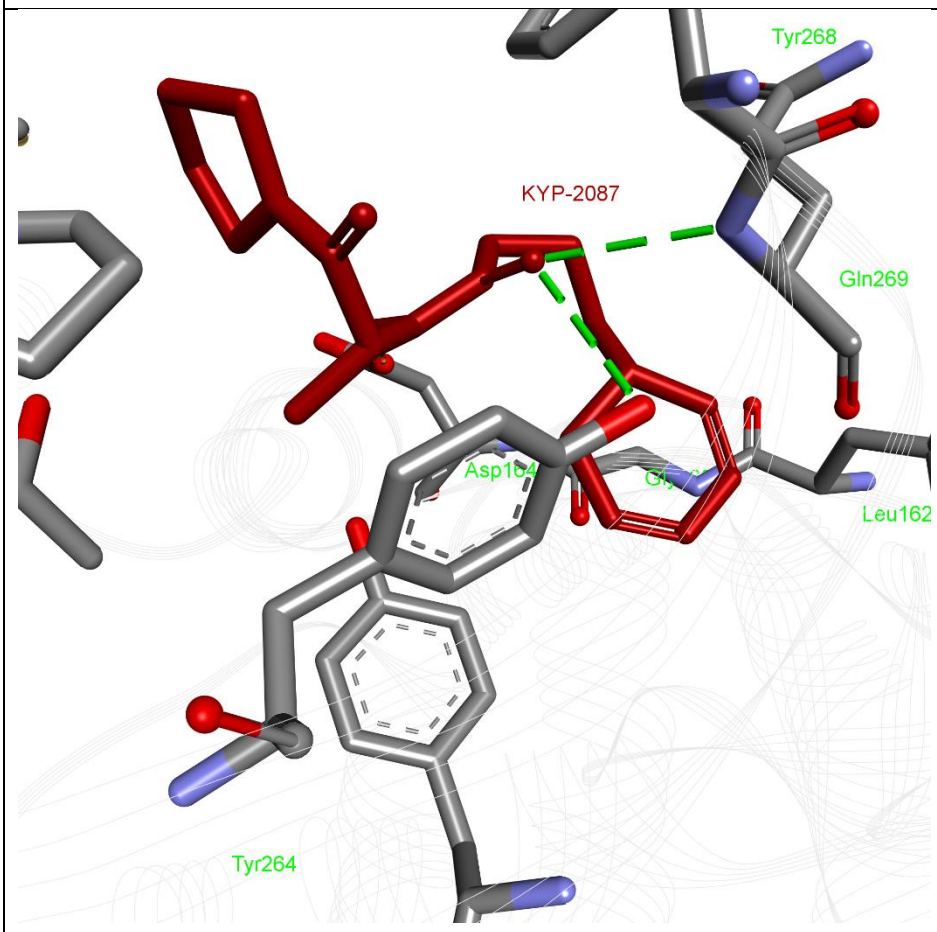
LIGAND NAME: KYP-2047
BINDING ENERGY: -6.17



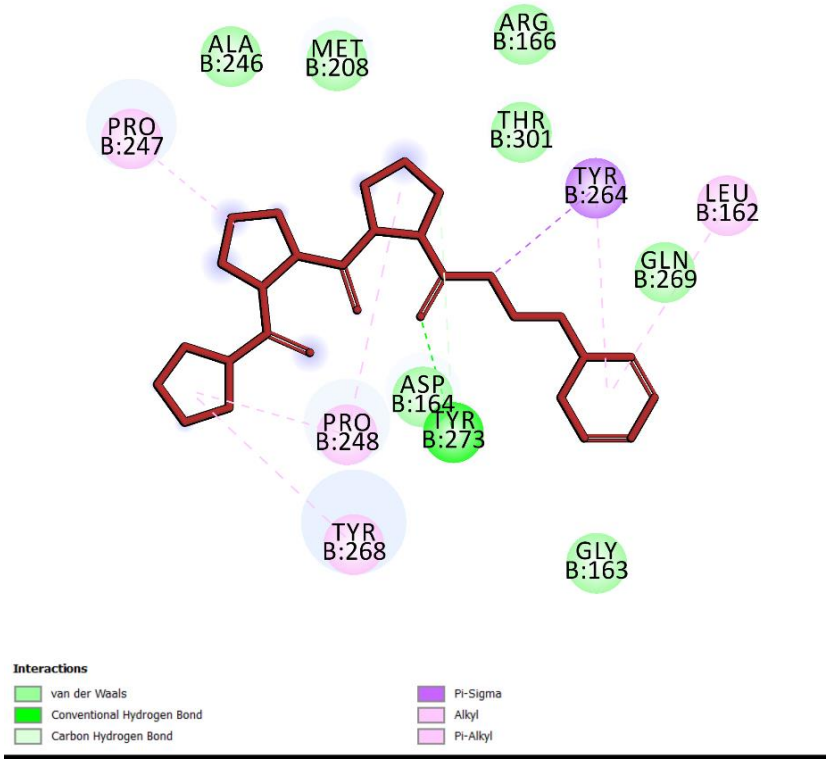


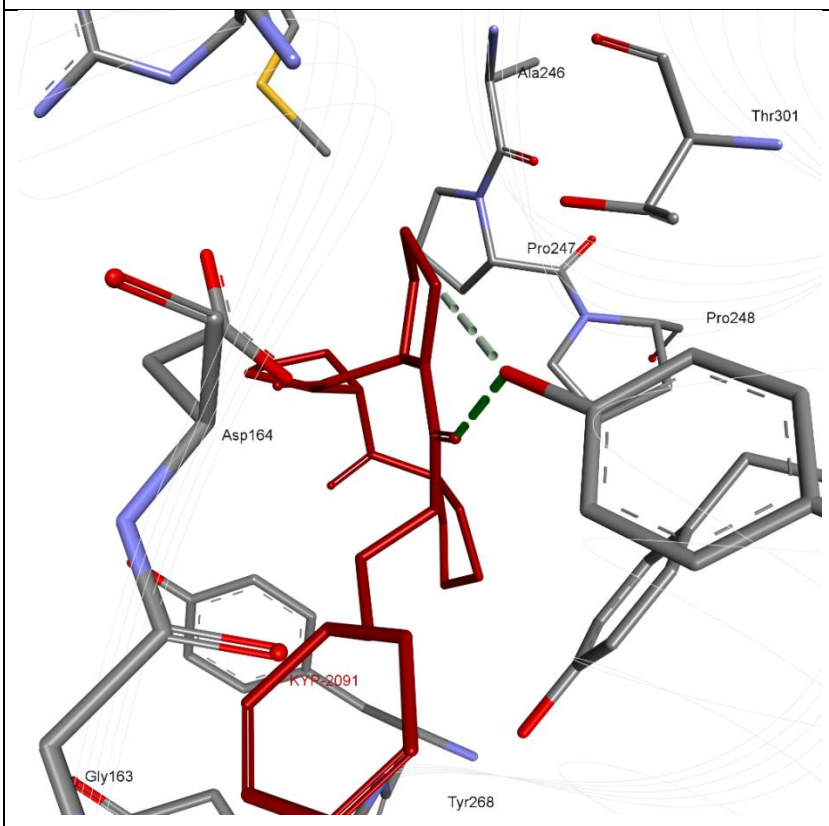
LIGAND NAME: KYP-2087
BINDING ENERGY: -8.42



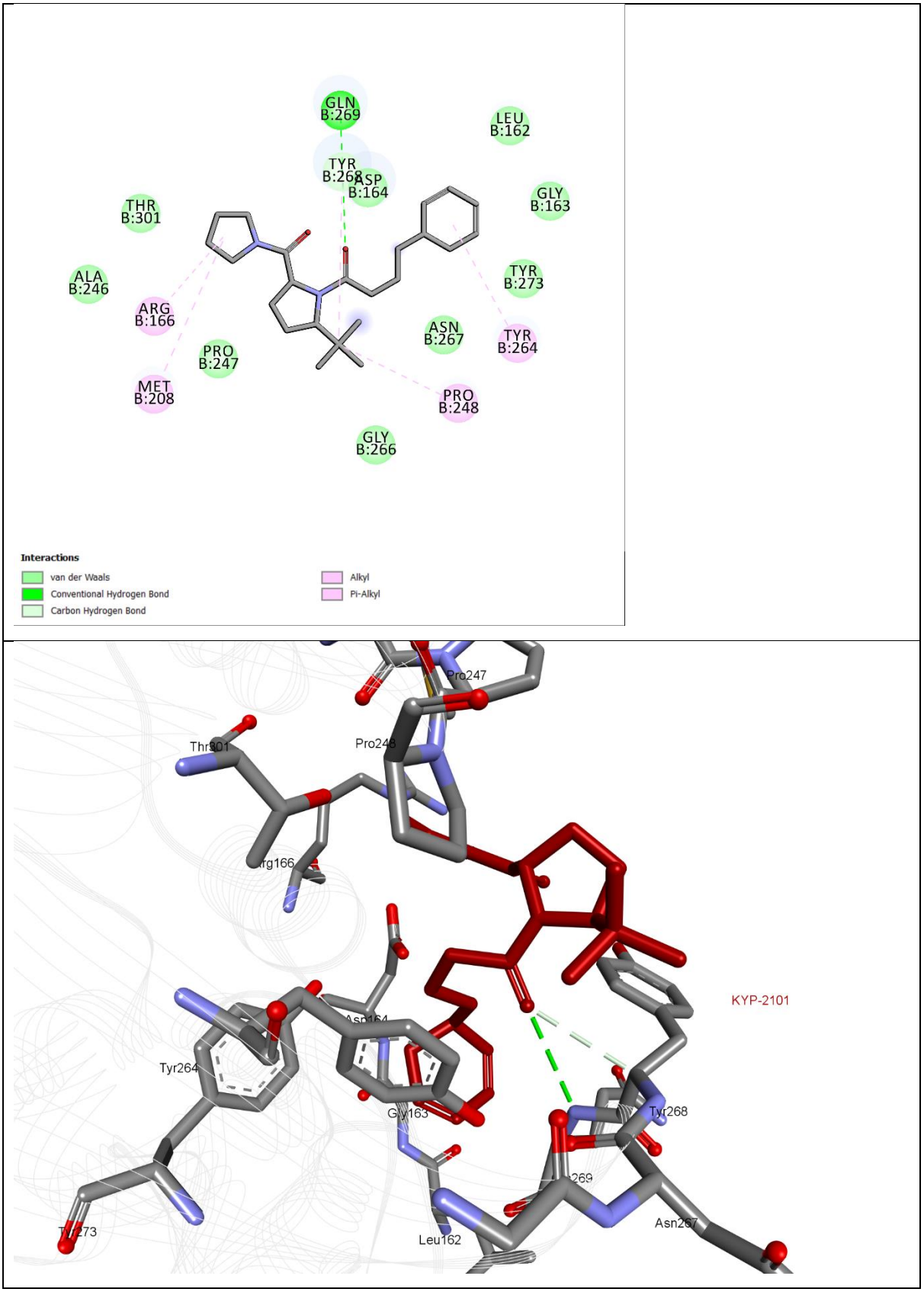


LIGAND NAME: KYP-2091
BINDING ENERGY: -8.68

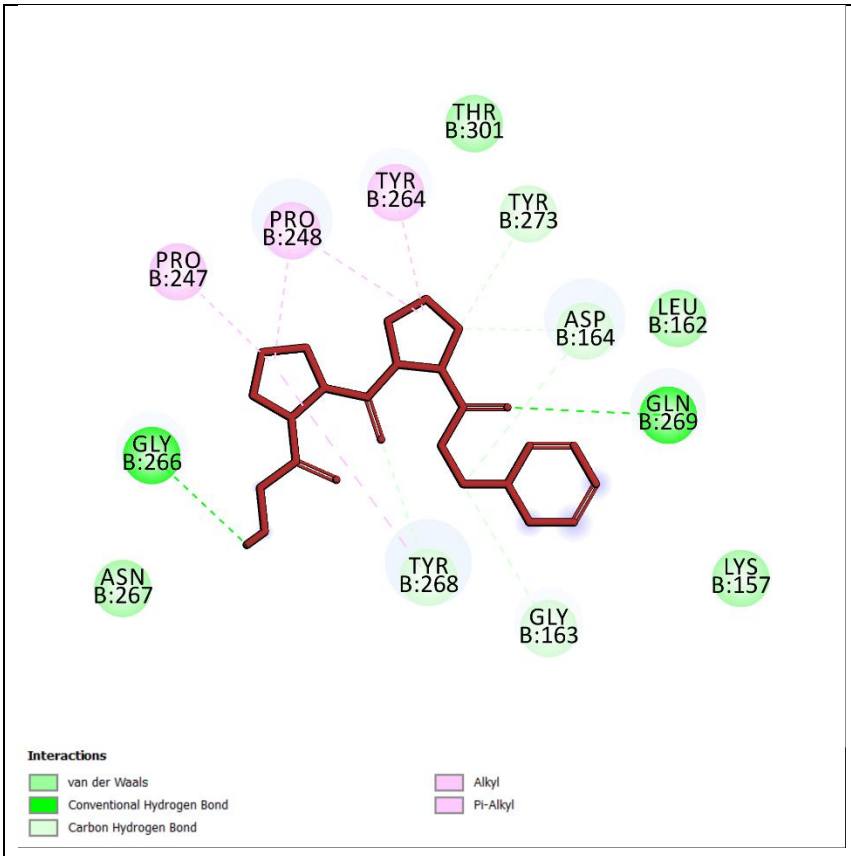


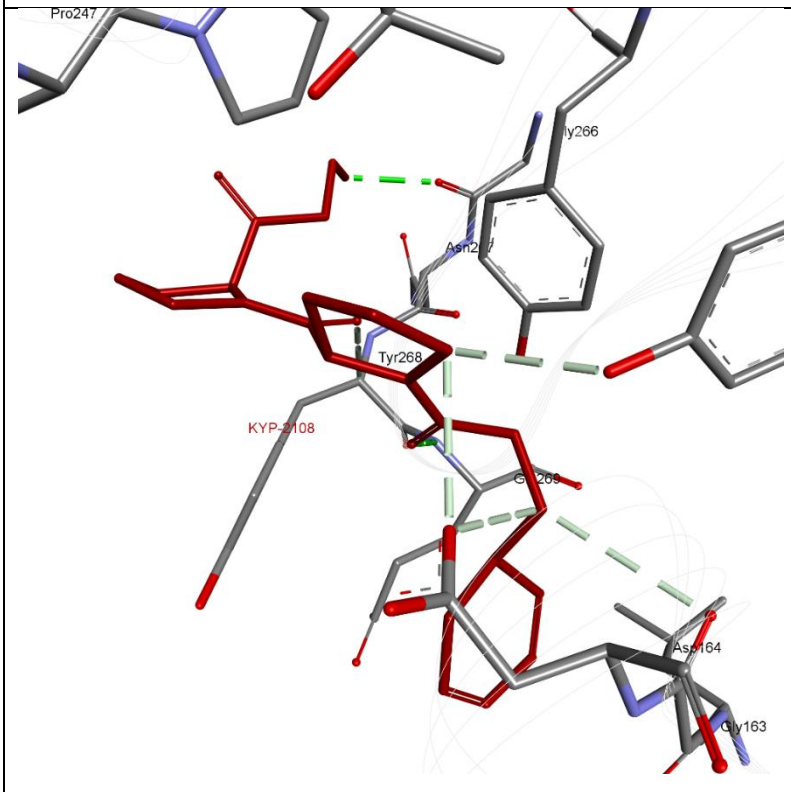


LIGAND NAME: KYP-2101
BINDING ENERGY: -9.01

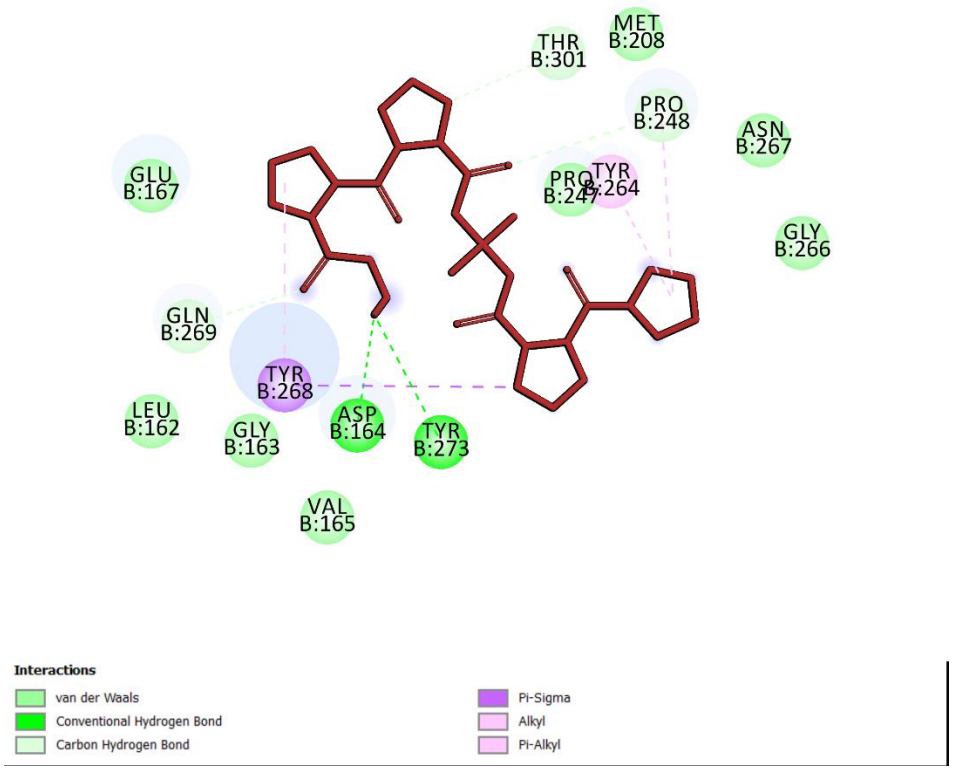


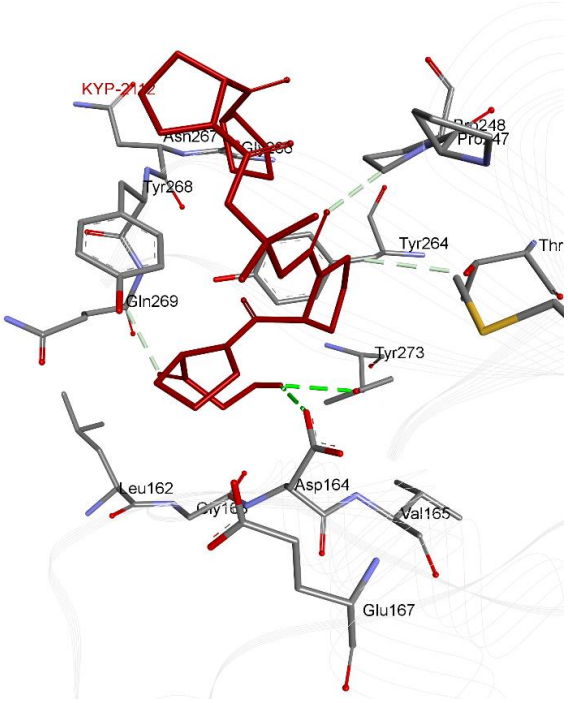
LIGAND NAME: KYP-2108
BINDING ENERGY: -8.16





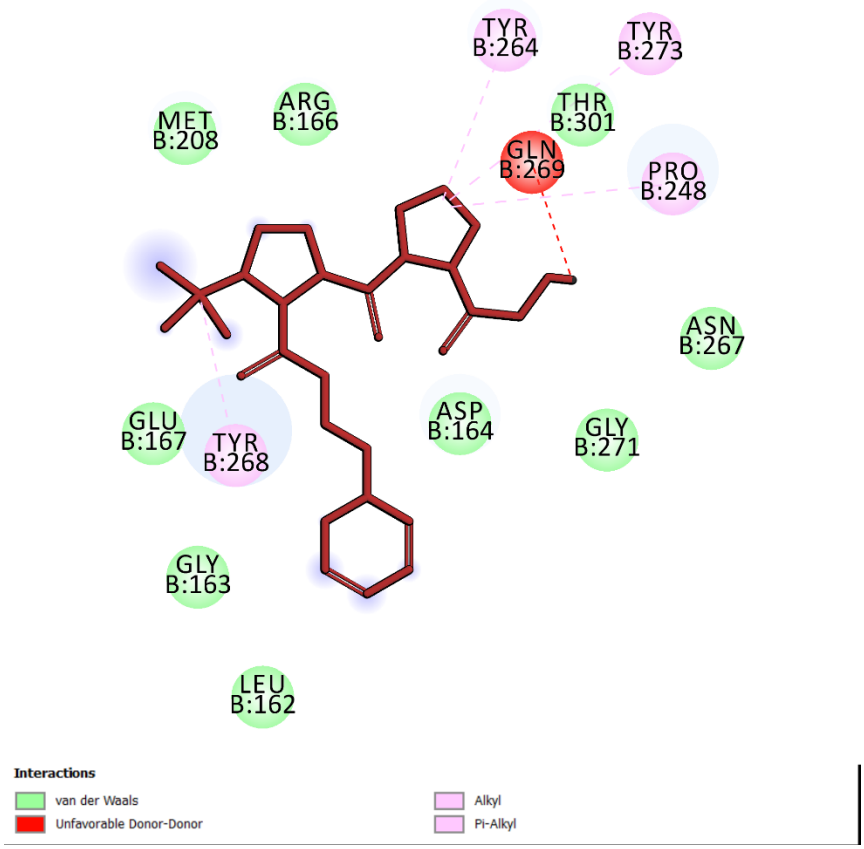
LIGAND NAME: KYP-2112
BINDING ENERGY: -7.33

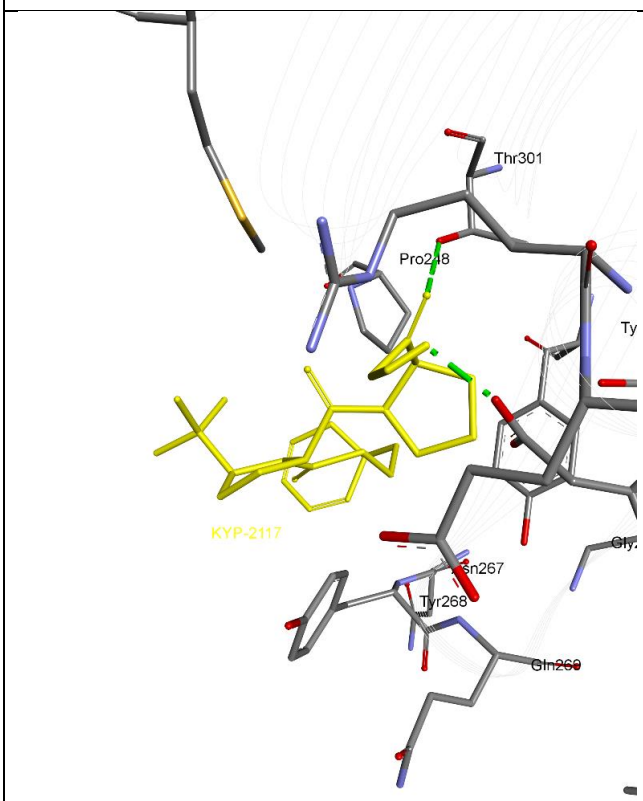




LIGAND NAME: KYP-2117

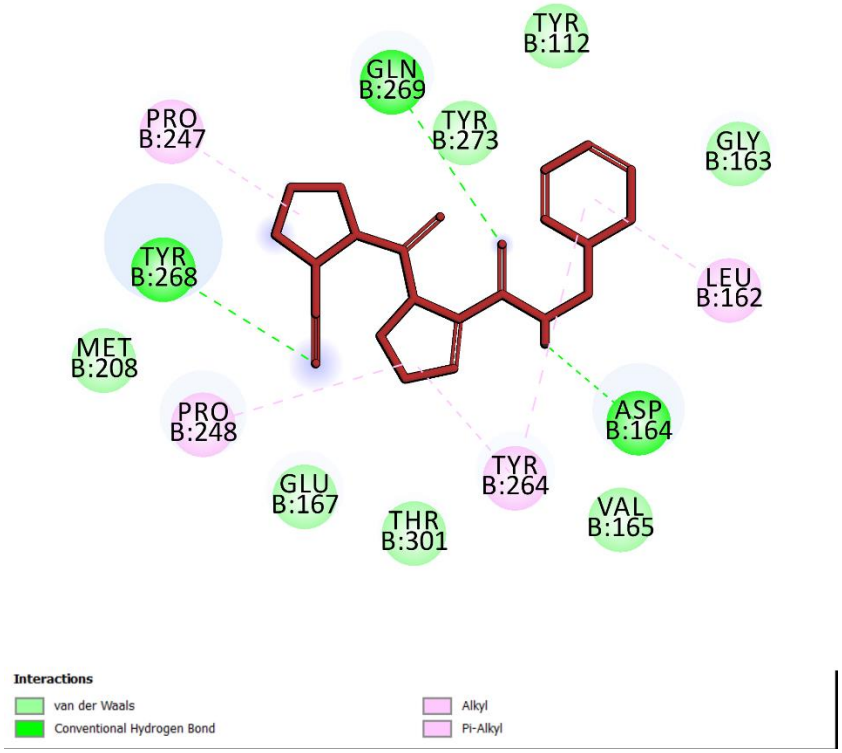
BINDING ENERGY: -7.57

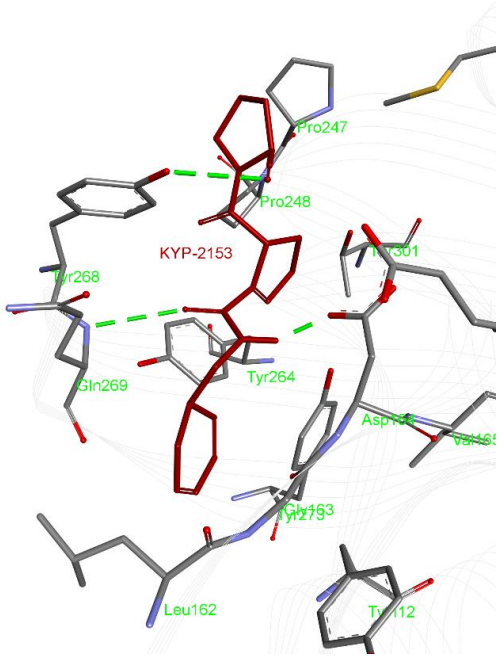




LIGAND NAME: KYP-2153

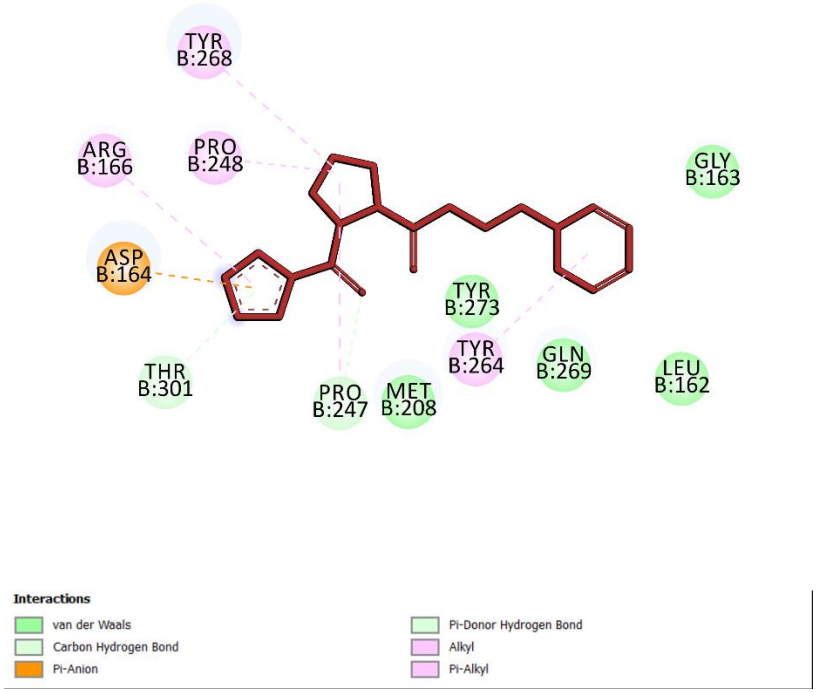
BINDING ENERGY: -9.75

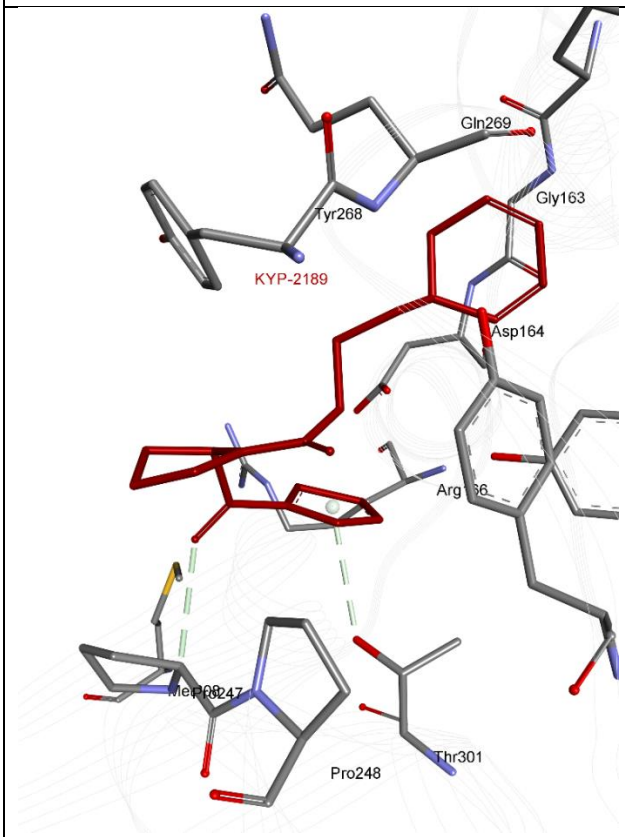




LIGAND NAME: KYP-2189

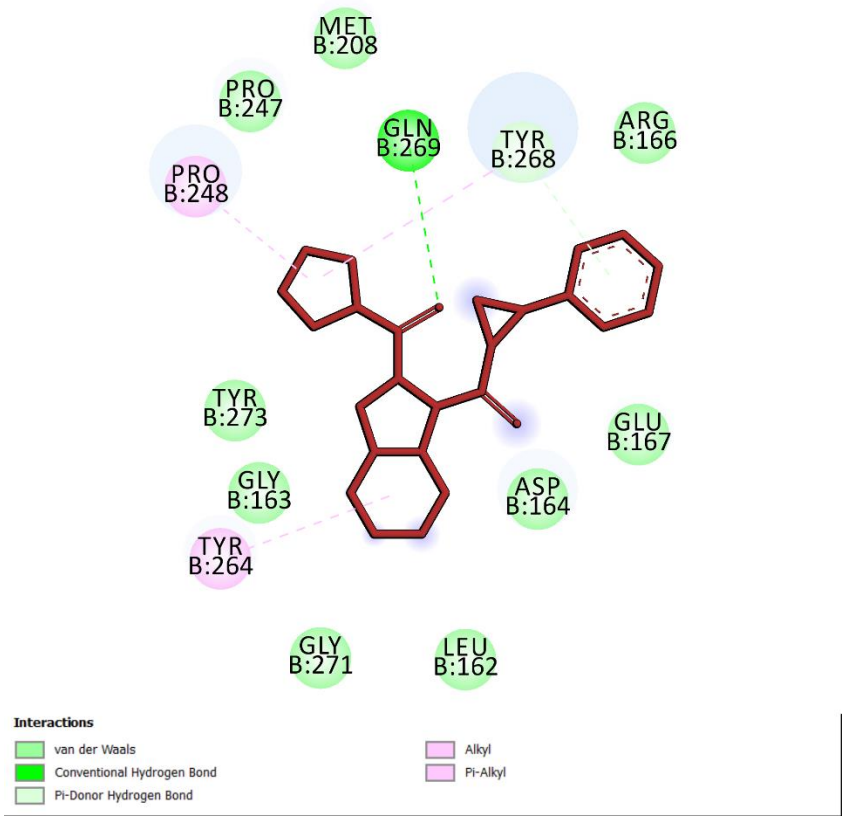
BINDING ENERGY: -8.18

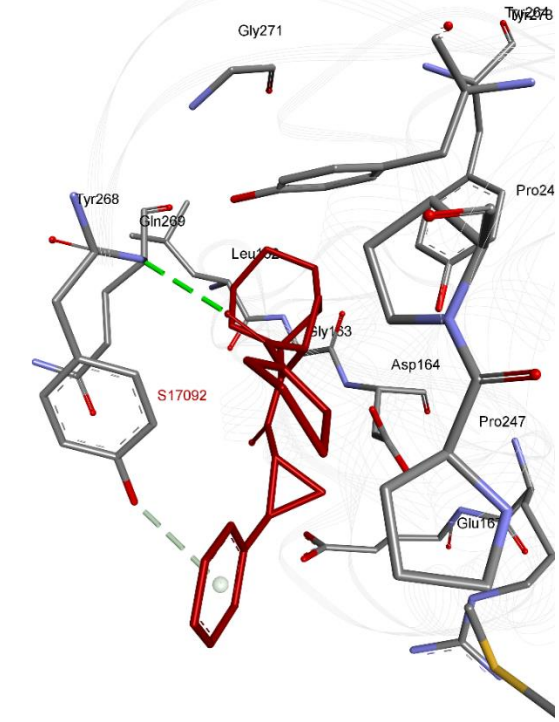




LIGAND NAME: S17092

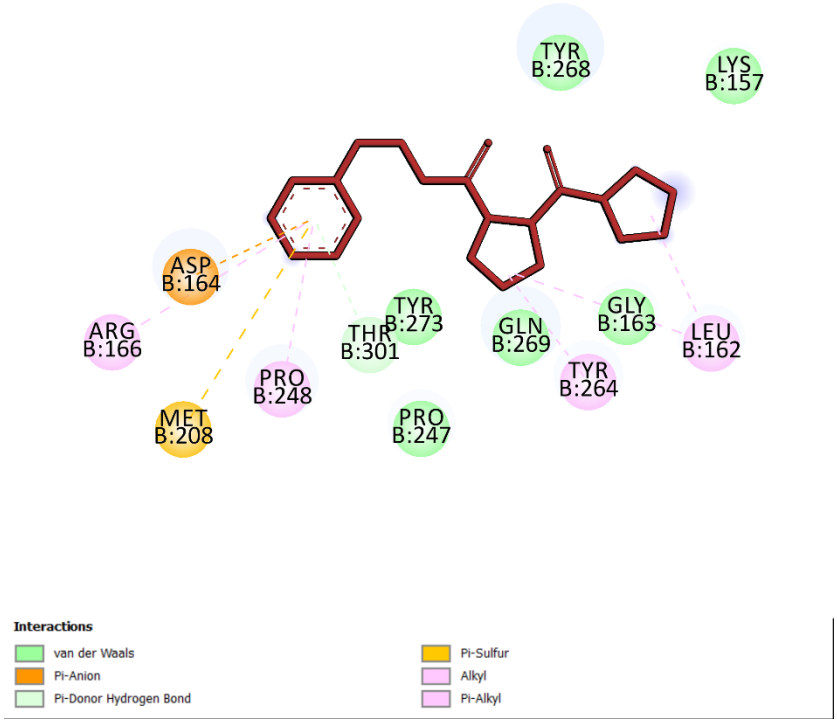
BINDING ENERGY: -7.14

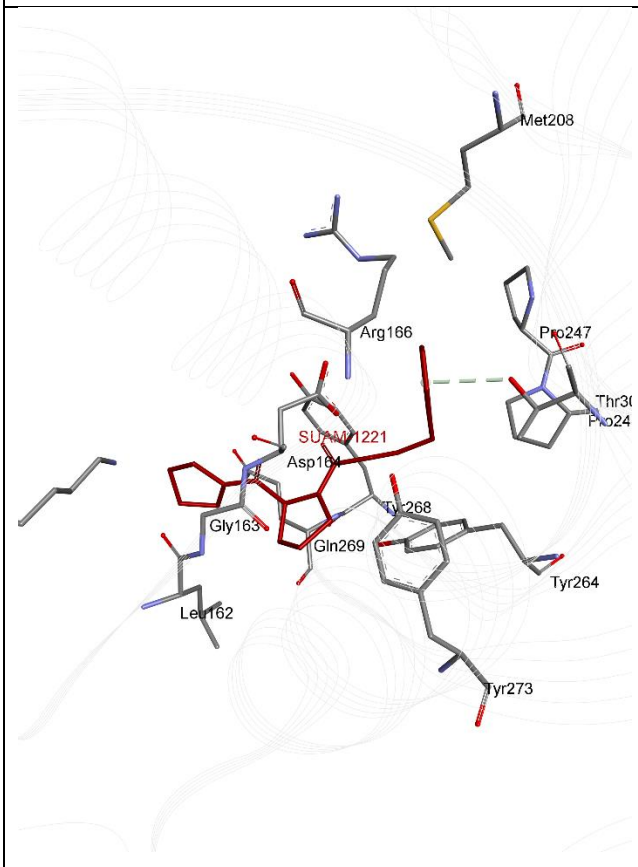




LIGAND NAME: SUAM-1221

BINDING ENERGY: -7.99





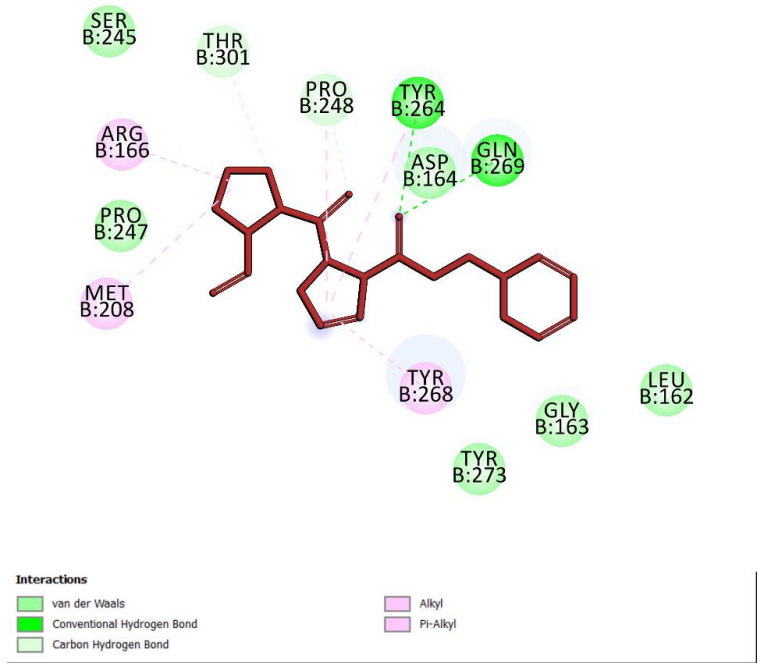
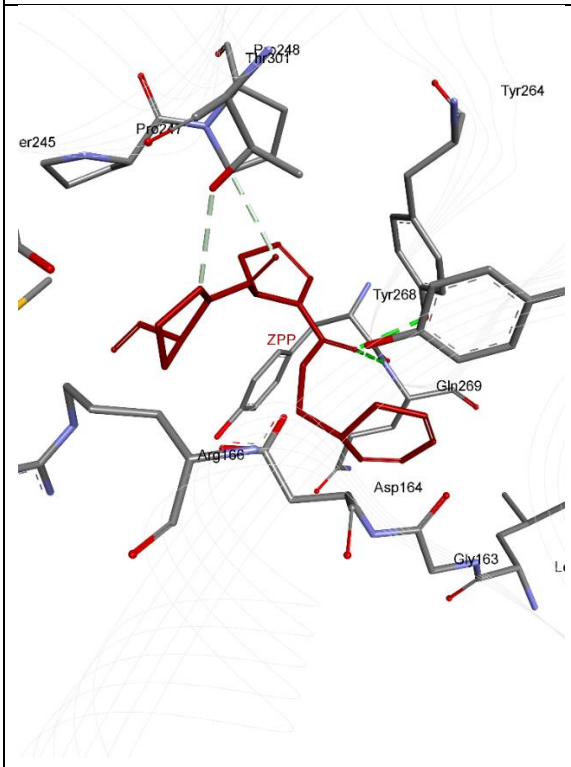
LIGAND NAME: ZPP
BINDING ENERGY: -7.75



Table 3. Showing the results by analysing the docked molecule in discovery studios, two consecutive pictures show 2D and 3D structure respectively.

DISCUSSIONS

After doing the molecular docking of 12 ligands be calculated their binding affinity that is the total sum of all the intermolecular interactions that took place between the ligand molecule and the target molecule it is same as lock and key mechanism where the proper or we can say correct key has to attach then only the lock will be unlocked and as it is well known that more negative the binding energy comes out to be the better the ligand is going to attach with the target molecule

Out of all ligands, docked the ligand named as KYP-2153 has the most negative binding energy with a magnitude of -9.75kcal/mol so it can be one of the best target molecules amongst all the molecules also the binding energy of the reference molecule kYP-2101 was also considerably low with a magnitude of -9.01kcal/mol.Along with finding the binding energy we also observed the hydrogen bonds due to which the ligand is attached to the drug molecule.

CONCLUSION

At last we conclude that we've docked the PREP inhibitors against SARS-CoV-2 PL^{pro} protease. Compound which shows better result with the docking score more than that of reference molecule is KYP-2153 with binding energy of -9.75kcal/mol. Better affinities and common molecular interactions as compared to reference inhibitor.

These results show that the given inhibitor KYP-2153 can be used as therapeutic agent against the SARS-CoV-2 PL^{pro}.

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