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Original Research Article

PRCP- One Possible Novel Key Gene for the Entry of 2019-nCoV into Human Cells

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Abstract

The ACE2 (Angiotensin I Converting Enzyme 2) receptor has been considered to be the major receptor of 2019-nCOV, the causative pathogen of the world wide prevailing COVID-19. Since, ACE2 is widely expressed across a variety of organs and moderately expressed in lungs, itraises a confusion about what makes the lung tissue the most infected in the Corona Virus Disease. Thus we hypothesized that there could be certain other genes playing key roles in the entry of 2019-nCOV into the human cells. Here, we found that PRCP (prolyl-carboxypeptidase) which is highly expressed in lungs than ACE2, has interactions with Bradykinin and has been proved as a potential target for obesity, could be a possible gene playing important role in the Corona Virus entry. In this study we have tried to dock the PCRP protein with two ligands [Epigallocatechin and Theaflavin] which could possibly reduce the effect of this protein.

Keywords: Prolyl- Carboxypeptidase, Epigallocatechin. Theaflavin, Corona Virus, ACE2.

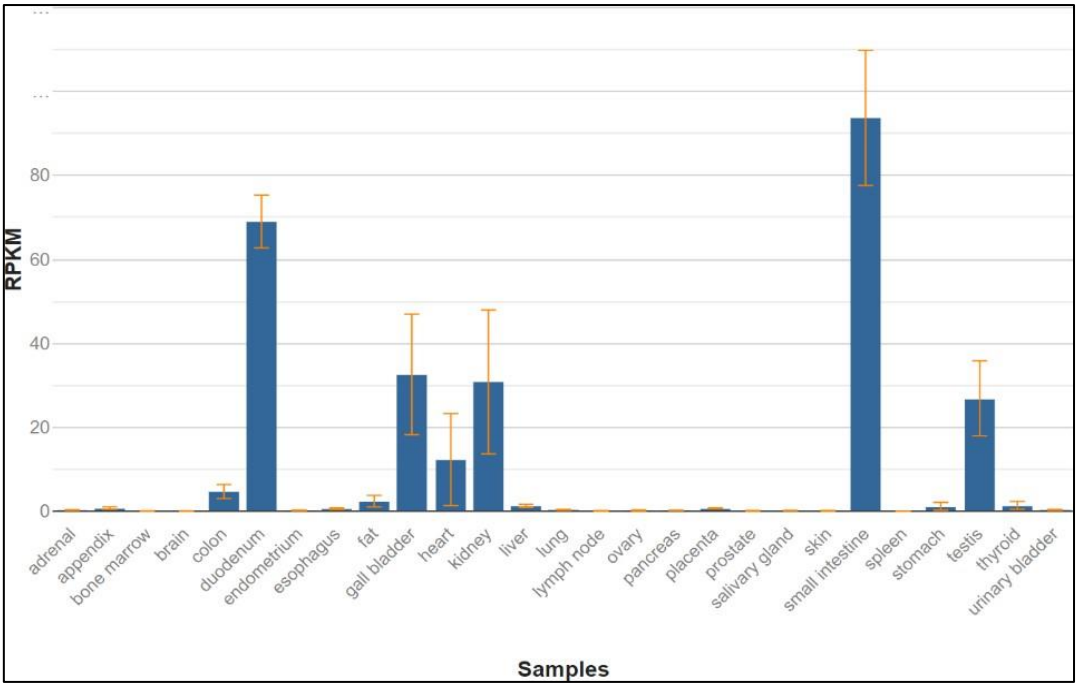
INTRODUCTION

Corona Virus Disease (COVID-19) is an infectious disease caused by a newly discovered Corona Virus, which includes symptoms like fever, dry cough, tiredness and mild to moderate respiratory illness. Sequence analysis revealed that this Corona Virus is highly similar with SARS Virus, confirming that the human angiotensin-converting enzyme 2 (ACE2) is also the receptor for the entry of 2019-novel Corona Virus into human cells which is also involved in the SARS infection [1]. Gene expression analysis of ACE2 shows that it doesn't have high or specific expression in lung, which, however, is the major infected tissue in Covid-19 patients. It is still not clear about why it is the lung but not other tissues which express high level of ACE is mainly infected. In this study, we found that PRCP can interact with ACE2. Moreover PRCP has higher expression level in lungs than that of ACE2. PRCP also interacts with Bradykinin and has been proven as a potential target for obesity treatment. Given, these observations, we suggest that PRCP gene could be involved in the entry of 2019-nCOV into human cells.

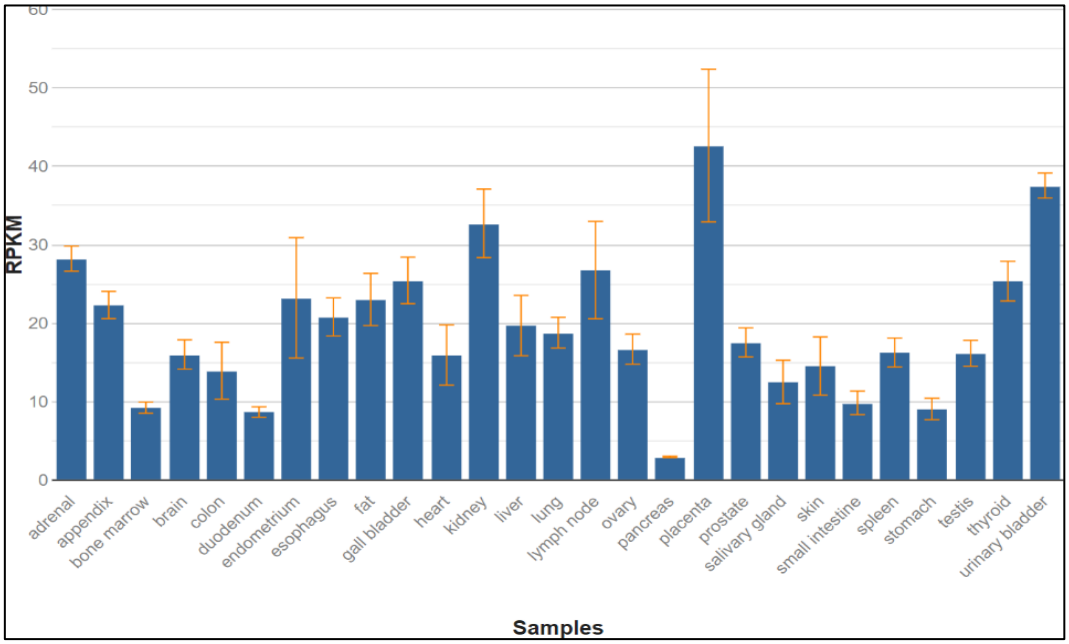
MATERIALS AND METHODS

Expression and protein functional association network data

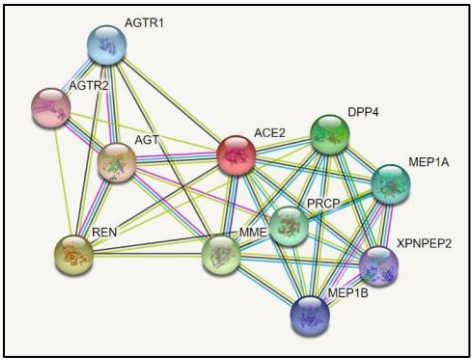
Gene expression profiles were obtained from the data set of HPA RNA-seq normal tissues at NCBI (https://www.ncbi.nlm.nih.gov) and also from Genotype-Tissue Expression (GTEx) database [2]. To identify human proteins interacting with ACE2, we searched ACE2 in STRING [3], a visualizing tool for analysis of protein-protein interactions, and selected homo sapiens. Then we constructed a PPI network centering on ACE2 with default parameters of website. We also constructed a network to view how PRCP is functionally connected with Bradykinin.



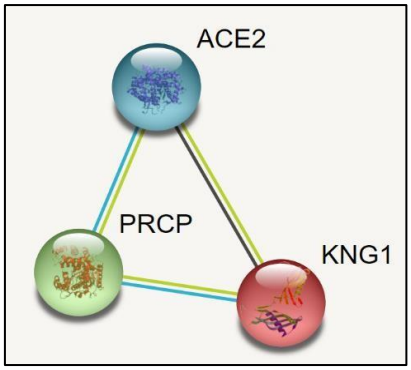
Expression profile of ACE2



Expression profile of PRCP



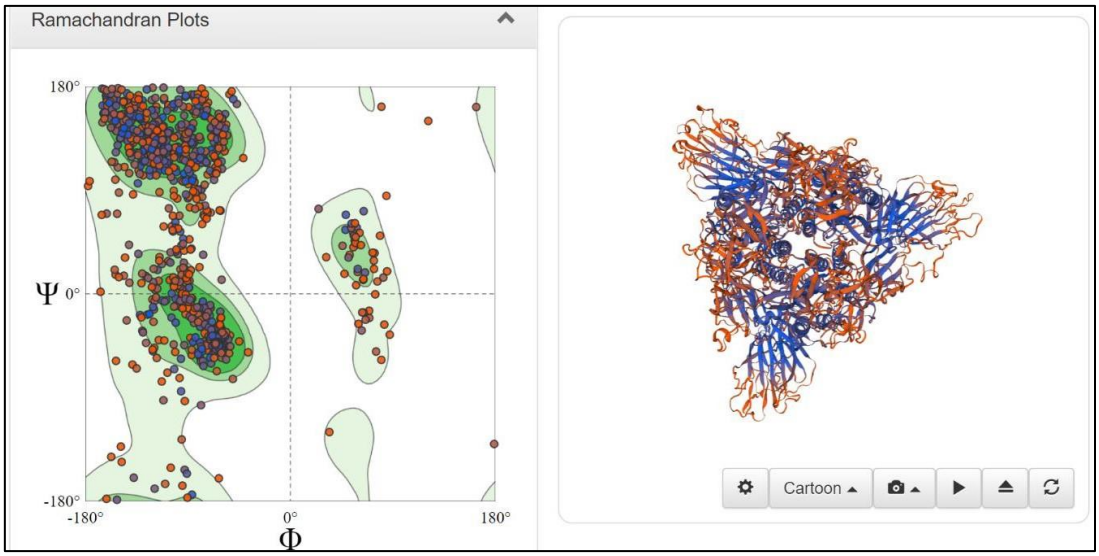
Potential functional association network of ACE2 built by STRING



Functional network of PRCP, ACE2 and Bradykinin

Simulating interaction between 2019-nCOV spike protein and PRCP

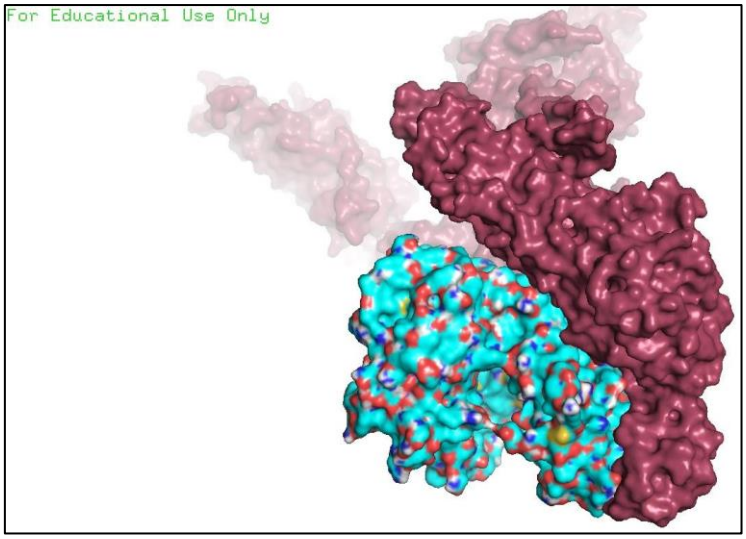
The protein structure of PRCP was downloaded from the PDB database (entry number 3N22). The experimental protein structure of ACE2 was downloaded from the PDB (https://www.rcsb.org) database (entry number IR42). The monomer structure of spike protein (Spro, NCBI seq ID: QHR63290) was predicted by SWISS-MODEL (https://swissmodel.expasy.org), using template PDB structure 6ACD, chain C (the subunit binds to ACE2 from SARS-COV Spro homo-trimer, covering residues 23=1146 of nCOV-2019 spike glycoprotein, with sequence identity =76.79% and 87.11% residues lying in most favored region of Ramachandran Plot). Protein-protein interaction was studied by submitting the structures of ACE2 and spike protein to the ClusPro server which is an online protein - protein docking tool (https://cluspro.bu.edu). Out of 30 models generated by ClusPro, the one with the best docking score was chosen for further docking with the ligands.



Spike protein structure predicted using Swiss Model along with Ramachandran Plot analysis

Docking scores of PRCP and Spike protein generated by ClusPro

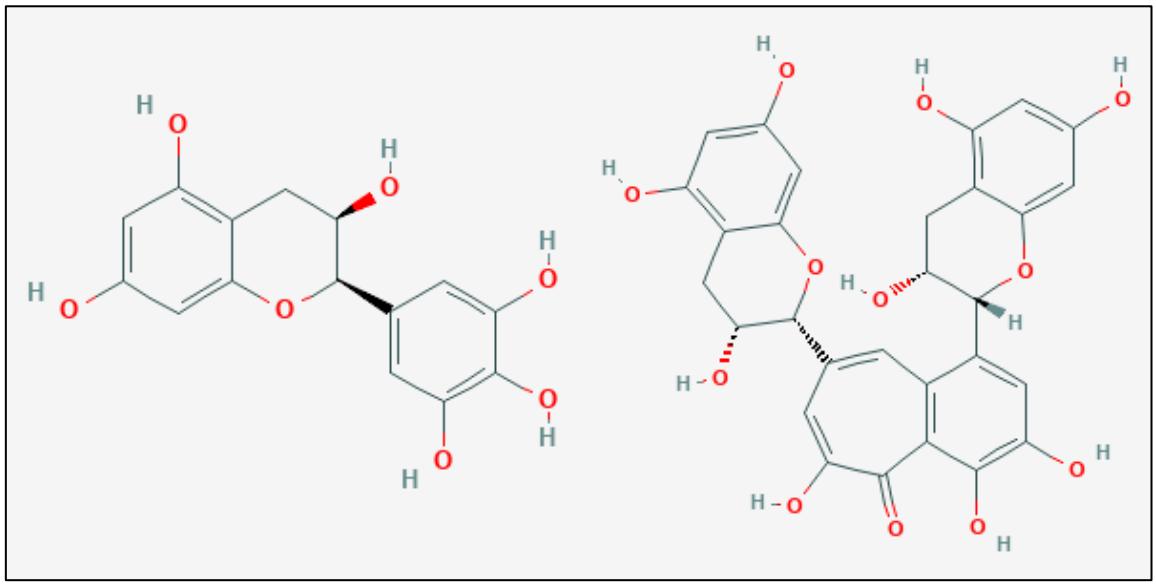
Cluster	Members	Representative	Weighted Score
0	43	Center	-946.9
		Lowest Energy	-1066.2
1	35	Center	-919.1
		Lowest Energy	-1098.3
2	26	Center	-912.3
		Lowest Energy	-947.0
3	24	Center	-881.0
		Lowest Energy	-924.0
4	22	Center	-978.5
		Lowest Energy	-978.5
5	22	Center	-971.6
		Lowest Energy	-971.6
6	21	Center	-923.2
		Lowest Energy	-983.6
7	20	Center	-848.9
		Lowest Energy	-1082.7
8	19	Center	-891.6
		Lowest Energy	-1073.0



Visualization of protein-protein interaction between PRCP and Spike protein using PyMol

Agents that could decrease the expression level of PRCP

Epigallocatechin and the theaflavin from green and black tea leaves have been reported to exhibit antiviral activities against various viruses. The 3D structures of Epigallocatechin [compound ID:72277] and Theaflavin [compound ID: 135403798] were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov). The reason for choosing these two compounds as ligands is that they exhibit antioxidant effects, anti-obesity effect and anti-inflammatory effect along with antiviral effect.



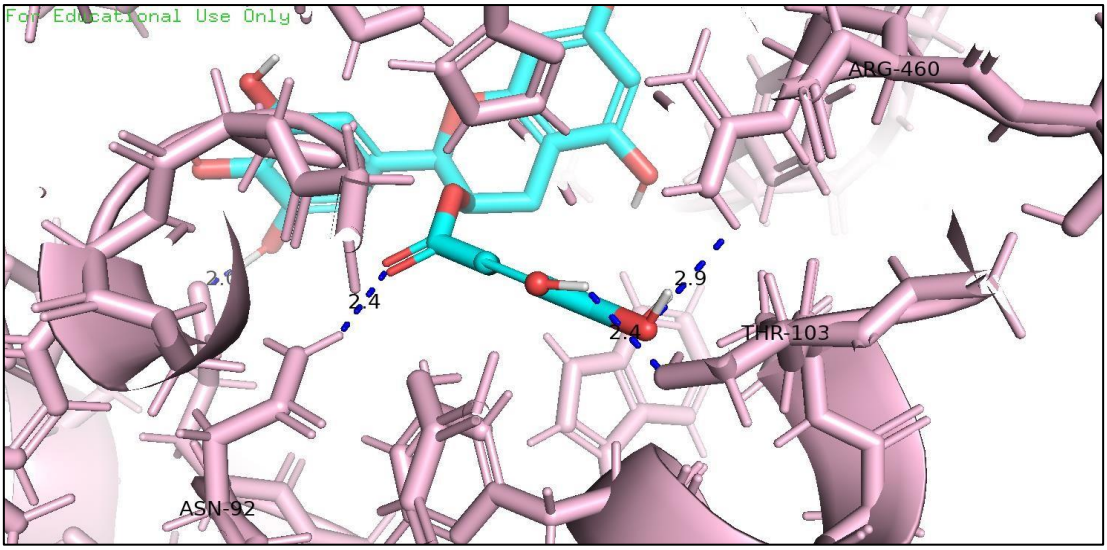
2D structure of Epigallocatechin and Theaflavin

Docking

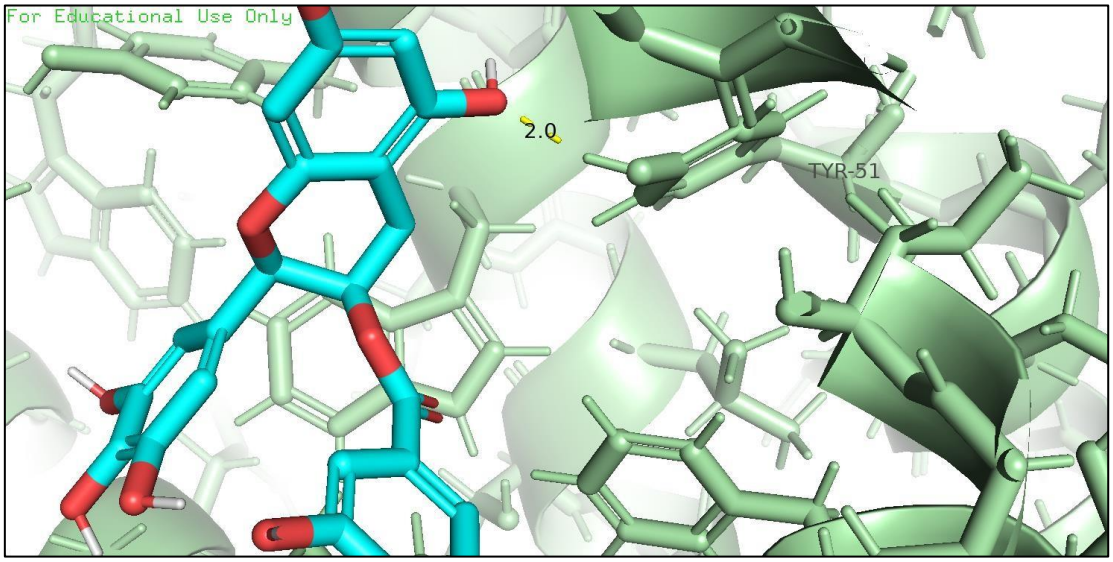
The two selected ligands were converted into Auto Dock ligands (pdbqt) and added to PyRx for docking with PRCP using Vina Wizard. Also the two selected ligands were docked with ACE2 to compare the docking scores with that of PRCP. The interactions were analyzed using PyMol.

RESULTS AND DISCUSSION

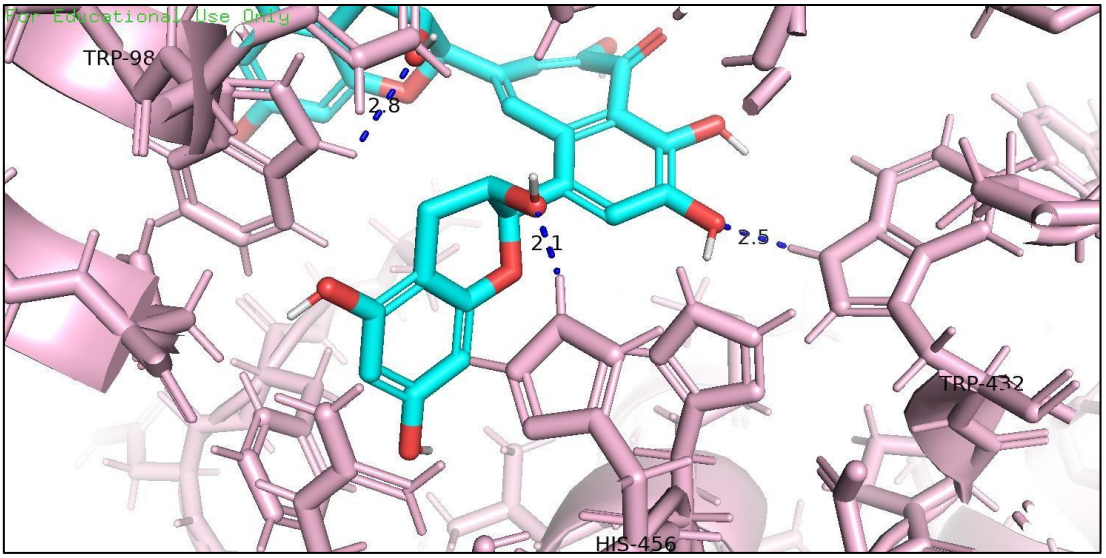
Both Epigallocatechin and Theaflavin showed better docking scores with PCRP when compared to the docking scores with ACE2. The relative low expression of ACE2 in lung suggest that there should be more genes that play key roles in the entry of 2019 n-COV into human cells. Here we have tried to show the different roles of PRCP gene in different metabolic pathways that increases the severity of COVID-19 and also two ligand interactions that could possibly reduce the effect in the human body.



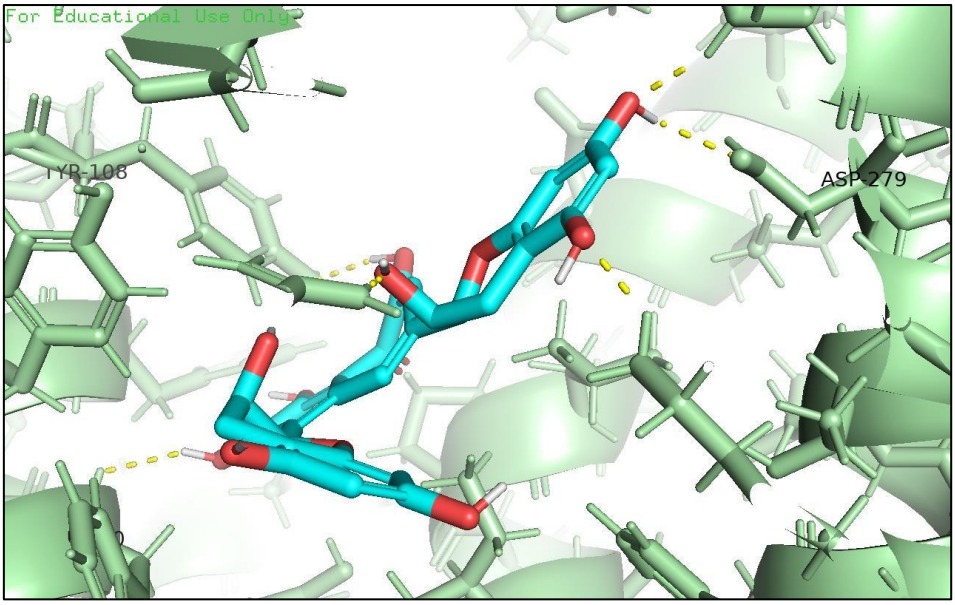
Epigallocatechin interaction with ASN-92, THR-103 and ARG-460 residues of PRCP. Docking Score: -9.9 kcal/mol



Epigallocatechin interaction with TYR-51 residue of ACE2. Docking Score: -9.2 kcal/mol



Theaflavin interaction with TRP-98, HIS-456 and TRP-432 residues of PRCP. Docking Score: -10.1 kcal/mol



Theaflavin interaction with ASP-279 and TYR-108 residues of ACE2. Docking Score: 9.9 kcal/mol

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