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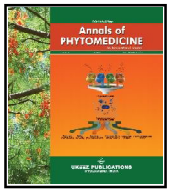

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In silico analysis of *Osciallatoria* sp. for SARS-CoV-2 protease inhibiting bioactive compounds

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Abstract

SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) was first reported in Hubei Province of the People's Republic of China, during a pneumonia outbreak in late 2019. COVID-19 became a viral pandemic causing higher mortalities across the globe. Increasing mutations in the spike proteins led to increased severity and speedy transmission. Since its appearece, the scientific world has been trying to develop an effective drug to treatment COVID-19. Main protease responsible for viral replication is found to be potent target irrespective of SARS-CoV-2 mutations. So, this investigation focuses on evaluating the protease inhibiting capabilities of *Oscillatoria* sp. derived bioactive compounds through *in silico* processes. The bioactive compounds with potential activities were identified, analysed and retrieved from database of KNApSAck. Binding sites of the target protein was examined using Cast P online server. Total of 29 bioactive compounds from *Osciallatoria* sp. were subjected to molecular docking against protease of SARS-CoV-2. From the analysis, 5 compounds showed binding energy (>-7 kcal/mol) and significant interactions on binding aminoacid residues. PASS prediction showed all the compounds have probable antiviral activity. Therefore, it was concluded that, the compounds Anabaenopeptin F, Oscillamide Y, Raocyclamide A, Anabaenopeptin B and Largamide A can be utilised for development of effective drugs in the treatment of COVID-19 infection.

1. Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) was first spotted and identified in Wuhan, Hubei Province of the People's Republic of China, during a pneumonia outbreak in late 2019, which later developed into the pandemic of recent history (Pavan *et al.*, 2022). World Health Organization (WHO) says that, as on November 02, 2022, the pandemic has been infected 628,035,553 people, in which 6,572,800 deaths patients were died (WHO, 2022).

Apart from SARS-CoV-2, other viruses like SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) are also known to cause serious pneumonia and are having higher mortalities of 9.6% and 36%, respectively. The other four major coronaviruses that affect human body are 229E, NL63, OC43 and HKU1, and their infections are self-limiting with mild symptoms (WuF *et al.*, 2020).

Patients with SARS-CoV-2 infection can have moderate to severe symptoms, while a considerable percentage of the population is asymptomatic carriers. Fever (83%), cough (82%), and shortness of breath are the most often reported symptoms (31%) (Albanghali, *et al.*, 2022; Jeong *et al.*, 2020; Wiersinga *et al.*, 2019). Chest X-rays in pneumonia patients typically reveal numerous mottling and ground-glass opacity. In 2-10% of COVID-19 patients, gastrointestinal disturbances like abdominal pain, diarrhoea, vomiting, *etc.* have also been found, and in ten out of hundred patients, of patients, nausea and diarrhoea have noticed to be seen before their spiratory symptoms and fever (WHO, 2019). Even though, morbidities and mortalities from COVID-19 was predicted to be increasing (Madabhavi *et al.*, 2020; Wan *et al.*, 2020), since the delivery of first COVID-19 vaccine outside a clinical trial on Dec 8, 2020 (The first COVID-19 vaccine was delivered outside of a clinical trial setting on Dec 8, 2020 (NHS, 2021), the rates have been declining across the globe (Oliver, 2022).

A mutation is described as a change in a genome's DNA or RNA sequences that gives a virus or illness a new phenotypic and/or genotypic advantage, potentially enhancing its virulence and survival. The original SARS-CoV-2 virus is currently known to have four major variants: the English variant (B.1.1.7), the South African variant (B.1.351), the Brazilian variants (VOC202101/02 (P.1) and VUI202101/01), and a variant similar to the South African variant found in North America (B.1.526). Each of these variants has varying degrees of resistance and infectivity (Tan *et al.*,2020). The alterations E484K and N501Y are the two most implicated mutations in the SARS-CoV-2 variations, which clearly represent a worldwide health danger. The most alarming is E484K, which assists in immune evasion and dramatically reduces the efficiency of existing vaccinations. The South African or B.1.351 variation, which has the foregoing mutations, is the most concerning (WHO, 2020).

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Viruses have sophisticated strategies for maximising the coding potential of genomes and evaluating them due to their short genome size. Meanwhile, genetics and bioinformatics have made significant contributions to understanding infectious disease pathophysiology, processes, and the transmission of antibiotic resistance, as well as host immune responses (Bah *et al*., 2018).

SARS-CoV-2, which has triggered a global epidemic by harming not only public health but also humanity's socioeconomic position. The genome of the new severe acute respiratory syndrome 2 (SARS-CoV-2) virus is between 29.8 and 29.9 kb in size, and its sequencing varies significantly from those of previously reported human coronaviruses such as SARS and Middle East respiratory disease (MERS) (Khailany *et al*., 2020). However, a thorough research of SARS-epidemiological, CoV-2's virological, and pathogenic properties is required before new therapeutic techniques and preventative strategies can be developed. Bioinformatics technologies and approaches have been used to accomplish the goals outlined above (Chaw *et al*., 2020).

Recent decades have seen a significant increase in the usage of molecular docking as a rapid and affordable tool in both academic and industrial contexts. Even though, this field has had enough time to develop, many aspects are still challenging. For example, there is still no quick or accurate way to quickly identify real ligands among a collection of molecules or to precisely identify the right ligand conformation inside the binding pocket of a specific target molecule (Messina *et al*., 2020).

Pharmaceutical research has successfully included a number of molecular modelling techniques into a variety of drug development activities to examine complex biological and chemical systems. Combining computational and experimental approaches has proven to be very helpful in the discovery and development of novel, promising compounds. Molecular docking techniques are frequently used in modern drug design to examine ligand conformations within the binding sites of macromolecular targets. This approach also calculates the ligand-receptor binding free energy by scrutinizing significant intermolecular recognition process events (Mohabeer *et al*., 2020).

Given the wide range of docking algorithms available today, knowing the benefits and drawbacks of each technique is critical to the formulation of successful strategies and the generation of meaningful outcomes. The most promising strategy for drug design and discovery is through computational molecular docking and scoring. Over traditional technologies, computational drug design and discovery is more cost-efficient, time-saving, and effective (Gautam *et al*., 2019).Therefore, the present study focuses on evaluating the protease inhibiting potential of *Oscillatoria* bioactive compounds through *in silico* analysis. Compounds were identified and retrieved from KNApSAck database. Binding sites of the target protein was examined using Cast P online server.

2. Materials and Methods

2.1 Preparation of target proteins

The SARS-Cov-2 protease (PDB ID: 6LU7) was utilised as target proteins in this study and from the Protein Data Bank, the 3D structures were recovered (http://www.rcsb.org/).The protein was screened and then the ligands, protein bound water molecules and co-crystal ligands were avoided by utilising PyMol tool (Figure1). Additionally, in Auto Dock Tools (an open-source software by familiarizing energy deprecation and charges in Swiss PDB viewer and then transformed into pdbqt format), protein was prepared,

2.2 Selection and preparation of ligands

The compounds in *Oscillatoria* sp. which were biologically active were identified and using KNApSAck (http://www.knapsack family.com/KNApSAcK/) database, they were retrieved. A total of 29 biologically active potential compounds were analysed in the study (Table 1). By noticing the, torsion root, optimizing utilising UFF (universal force field) modifying the torsion angle , the preparation of ligand is performed and then lastly to produce atomic coordinates (3D) of the molecules, it was changed into pdbqt format (Rédei, 2008).

Table 1: Compounds used in the study

S. No.	Compound name
1	beta-Echinenone
2	Anatoxin alpha
3	Mutatochrome
4	Aphanizophyll
5	3'-Hydroxyechinenone
6	Aeruginosin 205A
7	Aeruginosin 205B
8	Anabaenopeptin F
9	Anabaenopeptin G
10	Anabaenopeptin H
11	Lipopurealin A
12	Oscillamide H
13	Oscillamide Y
14	Prenylagaramide A
15	Prenylagaramide B
16	Raocyclamide A
17	Anabaenopeptin B
18	Microviridin I
19	Oscillacyclin
20	Largamide A
21	Largamide B
22	Largamide C
23	Largamide D
24	Largamide E
25	Largamide F
26	Largamide G
27	Largamide H
28	Viridamide A
29	Homoanatoxin-a

2.3 Active site prediction

Precise evaluation of the active site is essential in potential docking examination. Utilising the Cast P (Computed Atlas for Surface Topography) the amino acids in the active pocket site development for protease and RBD were recognized (Sanjay and Shanthi, 2020; Tian *et al*., 2018). To study the active site pockets and topology of the protein**.** Active site determination is vital to set the grid box at earlier docking.

2.4 Molecular docking and analysis of protein-ligand interaction

The molecular docking of all the compound libraries was showed Using the PyRx tool *via* autodock wizard as the docking engine. The ligands were expected to be elastic and the protein was predictable to be stiff, during the docking process. The grid parameter configuration file is produced utilising the grid box for 6LU7 (x = -9.73, y = 20.03, z = 68.89) in PyRx correspondingly (Dallakyan and Olson, 2015). Subsequent docking, the maximum binding energy (most negative) was recognized as the ligand with extreme binding affinity. Utilising Biovia Drug discovery studio 2019, the ligands showing higher binding energy (<-7 kcal/mol) were identified and the ligand-protein communication on the sites of binding were analysed.

2.5 Prediction of activity spectra for substances (PASS) for antiviral a activity

Using the prediction of activity spectra for substances (PASS) method, the antiviral activity of the bioactive compounds was predicted (Shamna *et al*., 2021; Hasan *et al.*, 2019). PASS programme is utilised to predict a several biological activities for a large number of compounds. The substance's activity is predicted and described as probable activity (Pa) and probable inactivity (Pi). The compounds that have a Pa greater than Pi are those that are potential for the particular biological activity.

Table 2: Amino acid residues in the active sites

S. No.	Target protein	Amino acid residues in binding sites
1.	Protease (PDB Id: 6LU7)	A: 24-THR, 25-THR, 26-THR, 27-LEU, 41-HIS, 44-CYS, 45-THR, 46-SER, 49-MET, 52-PRO, 54-TYR, 140-PHE, 141-LEU, 142-ASN, 143-GLY, 144-SER, 145-CYS, 163-HIS, 164-HIS, 165-MET, 166-GLU, 167-LEU, 168-PRO, 172-HIS, 187-ASP, 188-ARG, 189-GLN, 190-THR, 192-GLN

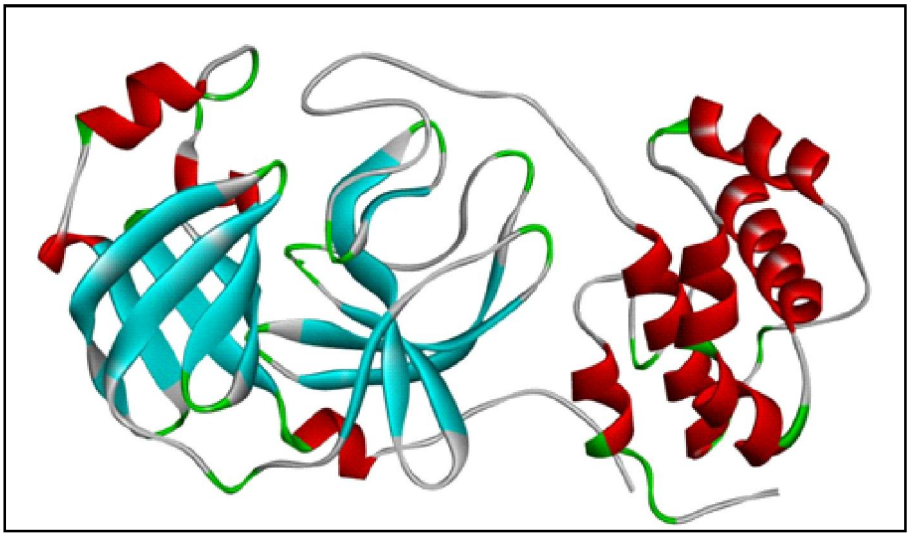

Figure 1: 3D structures of the target protein (PDB ID: 6LU7).

3. Results

3.1 Binding site analysis

The amino acid residues present in the binding sites are identified by Cast P program. The largest pocket in size is termed as the functional sites of the target protein. Table 2 shows the amino acid residues present in the SARS-CoV-2 protease. Grid box was set covering the binding sites (Figure 2) and docking was performed.

3.2 Molecular docking

Compounds identified from *Oscillatoria* sp. were subjected to docking against SARS-CoV-2 protease. The binding energies of the compounds were presented in Table 3. Compounds showing binding energy lesser than -7 kcal/mol were examined for protein-ligand interactions.

3.3 Protein-ligand interactions

Ligand interaction on binding sites of the target protein is as essential as the binding energies. Thus, binding amino acid residues and the bonds involved were identified using discovery studio visualizer. The total number of H-bonds formed and H-bonds formed in the binding sites are quantified and shown in Table 4. All the bioactive compounds showed H-bonds in binding sites of the target protein. Figures 3 to 7 shows the interactions of selected *Oscillatoria* compounds on the binding sites of the SARS-CoV-2 protease.

Table 3: Molecular docking analysis

S. No.	Compound	Binding energy (kcal/mol)
1	beta-Echinenone	-6.3
2	Anatoxin alpha	-5.1
3	Mutatochrome	-6.3
4	Aphanizophyll	-6.6
5	3'-Hydroxyechinenone	-6.4
6	Aeruginosin 205A	-5.8
7	Aeruginosin 205B	-6.4
8	Anabaenopeptin F*	-7.4
9	Anabaenopeptin G	-6.9
10	Anabaenopeptin H	-6.3
11	Lipopurealin A	-6.2
12	Oscillamide H	-6.6
13	Oscillamide Y*	-7.5
14	Prenylagaramide A	-6.5
15	Prenylagaramide B	-6.7
16	Raocyclamide A*	-7
17	Anabaenopeptin B*	-7.3
18	Microviridin I	-5.8
19	Oscillacyclin	-6.2
20	Largamide A*	-7.2
21	Largamide B	-6.3
22	Largamide C	-6.4
23	Largamide D	-6.9
24	Largamide E	-6.6
25	Largamide F	-6
26	Largamide G	-6.9
27	Largamide H	-5.5
28	Viridamide A	-4.8
29	Homoanatoxin-a	-4.8

Table 4: Protein-ligand interactions on binding site analysis

S. No.	Compound	Protein-ligand interactions		
		Total number of H-bond	No. of H-bond in binding site	Aminoacid residue
1	Anabaenopeptin F	5	1	A: THR-26
2	Oscillamide Y	3	1	A: HIS-41
3	Raocyclamide A	2	2	A: GLY-143; GLN-189
4	Anabaenopeptin B	5	3	A: THR-24; THR-25; CYS-44
5	Largamide A	4	4	A: HIS-41; HIS-164;GLN-189

Table 5: PASS prediction analysis of antiviral activity of the selected compounds

Plant compounds	Antiviral properties	
	Pa	Pi
Anabaenopeptin F	0.171	0.133
Oscillamide Y	0.218	0.082
Raocyclamide A	0.358	0.162
Anabaenopeptin B	0.170	0.134
Largamide A	0.274	0.047

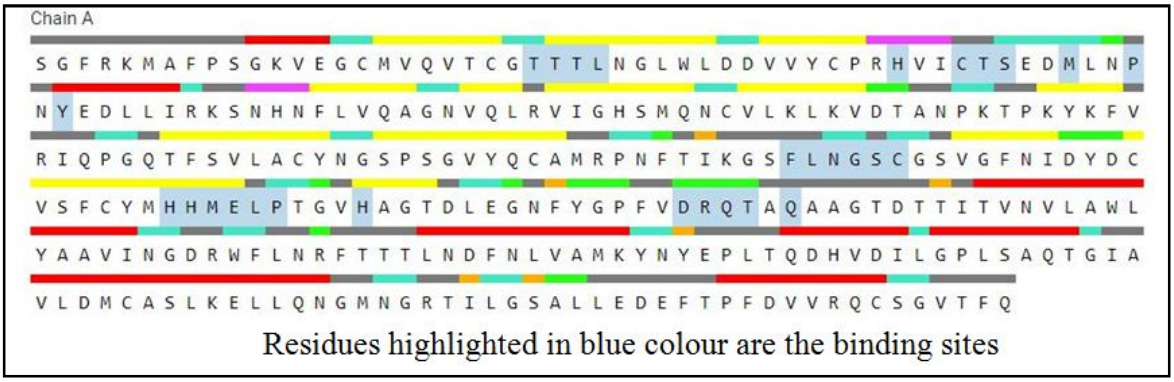

Figure 2: Binding sites of SARS-CoV-2 protease analysed using Cast P.

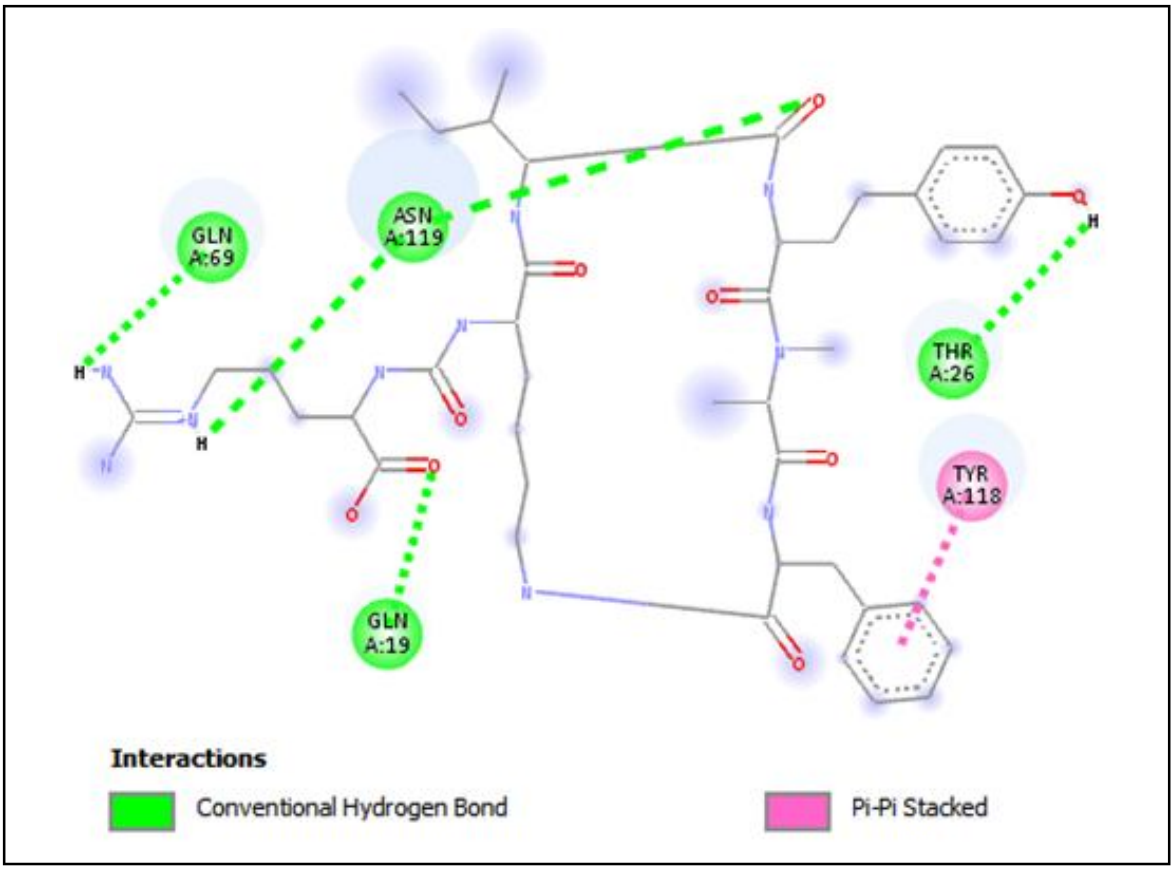

Figure 3: Interaction of Anabaenopeptin F on SARS-CoV-2 protease.

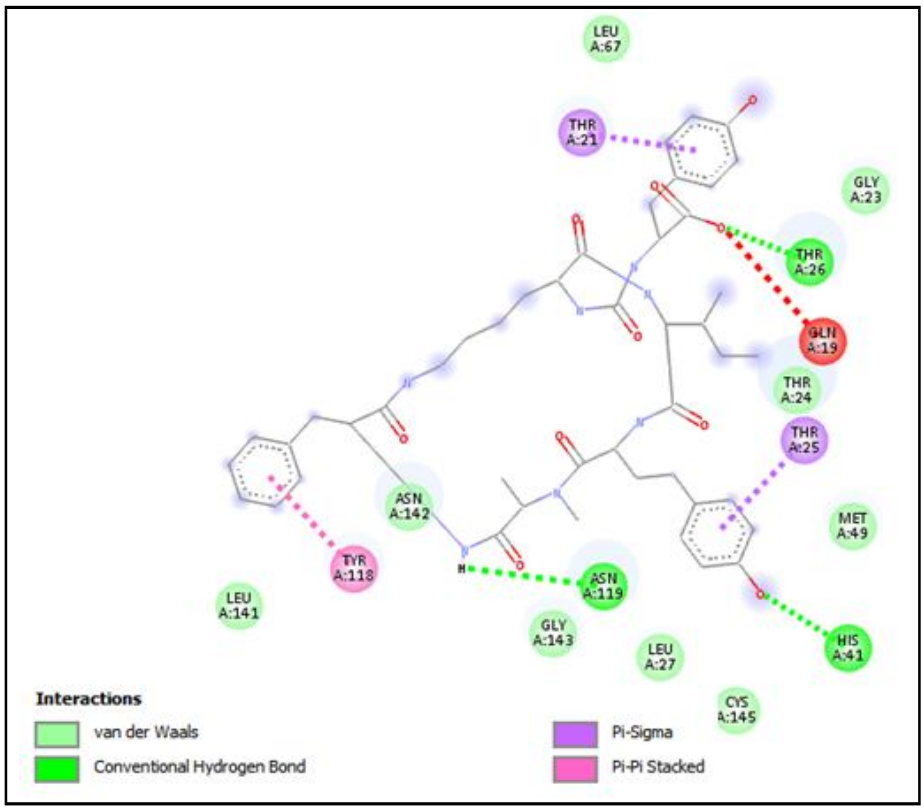

Figure 4: Interaction of Oscillamide Y on SARS-CoV-2 protease.

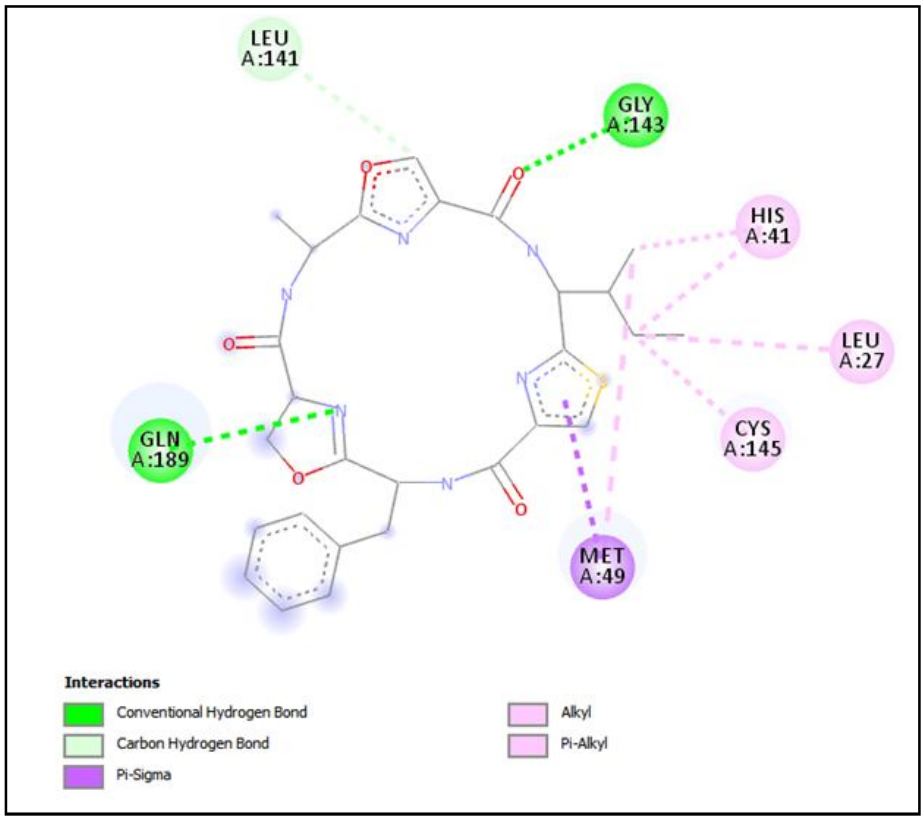

Figure 5: Interaction of Raocyclamide A on SARS-CoV-2 protease.

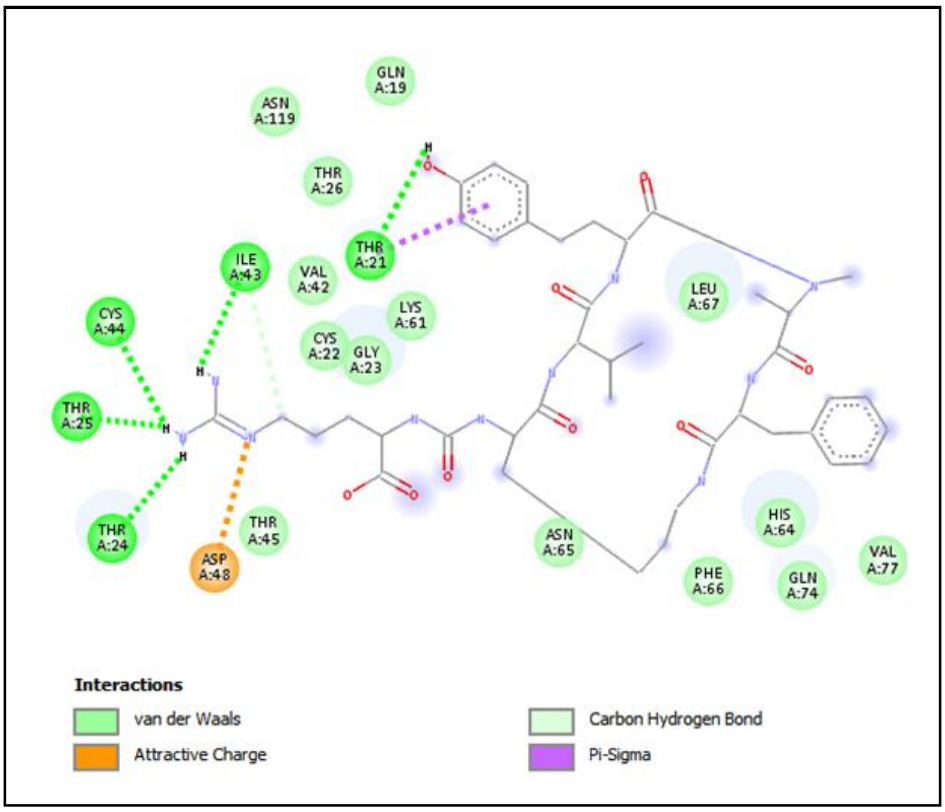

Figure 6: Interaction of Anabaenopeptin B on SARS-CoV-2 protease.

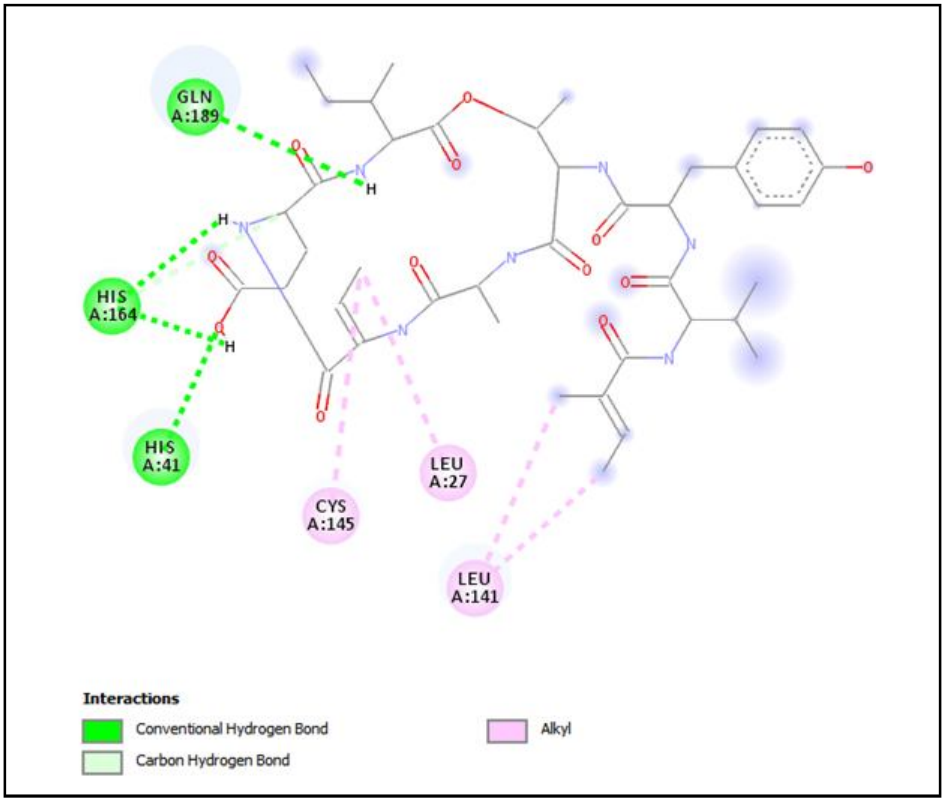

Figure 7: Interaction of Largamide A on SARS-CoV-2 protease.

3.4 PASS prediction analysis

PASS prediction for antiviral activity was carried out for the selected bioactive compounds. The probable activity (Pa) and probable inactivity (Pi) of the compounds were determined and shown in the Table 5. From the analysis, all the compounds showed possible antiviral activity (Pa>Pi).

4. Discussion

Proteases have long been thought to have a role in SARS-CoV-related viral transmissibility and replication. The binding of the surface subunit, S1, of the S glycoprotein to the cell surface has previously been shown to enhance viral entry into the host cell. Moreover, numerous researches have established the role of host proteases in priming the S glycoprotein at the S1/S2 and S2' sites. In order to possibly provide protease inhibitors to prevent viral entrance, Örd *et al*. (2020) revealed the function of kallikrein-related peptidase 13 (KLK13) in the particular cleaving of the S1/S2 region in human coronavirus HKU1. described the function of KLK13, a peptidase related to kallikrein, in the selective cleavage of the S1/S2.

Following the similarities in the method of entrance of SARS-CoV and SARS-CoV-2 through the ACE2 receptor, Hoffmann *et al*. (2020) found that providing the clinically established serine protease inhibitor camostat mesylate partially blocked S-protein driven entry of SARS-CoV-2. When the camostat mesylate was combined with the Cathepsin B/L inhibitor E-64d, complete inhibition was obtained, demonstrating alternative protein priming by endosomal cysteine proteases Cathepsin B/L. These findings matched those of another investigation in which a protease inhibitor encoded by the SPINT2 gene targeted TMPRSS2 and inhibited cleavage-activation and viral proliferation in a variety of influenza viruses (Straus *et al*., 2020). Therefore, SARS-CoV-2 protease is used as target protein in the present study.

The findings showed that *Oscillatoria* sp. is a powerful virucidal agent for HSV-1, as per to Mabroka *et al*. (2020). At lectin doses of 20, 200, 2000, and 20,000 ng/ml, *Oscillatoria* sp. was able to block HSV-1 infectivity and decrease plaque count in a dose-dependent manner, with viral neutralisation activity equalling 37.5 0.55%, 65 0.67%, 77.5 0.94%, and 100 0.12%, respectively. These findings were in line with the results of the current investigation. The experimental analysis of antibacterial effects by Azza *et al*. (2014) indicated that all examined bacterial strains were more sensitive to the acetone extract of *Oscillatoria* sp. *agardhii*, with *Salmonella senftenberg* having the greatest antibacterial activity (24 mm inhibition zone). The methanol extract, on the other hand, exhibited moderate efficacy against all bacterial species, with the greatest value in the cases of *Enterococcus facium* (9 mm inhibition zone) and *Salmonella typhimurium* (9 mm inhibition zone). These findings indicate that the *Oscillatoria* has antibacterial properties.

Md Foud *et al*. (2016) studied that,based on its capacity to decrease the ferric (Fe^{3+})/(Fe^{2+}) ferrous pair, the FRAP assay gives a direct assessment of the antioxidants or reductants present in a sample.The antioxidant potential of a sample can also be determined using the FRAP assay. All four strains of cyanobacteria from this investigation showed significant FRAP values, which are also higher than those previously reported (Tanvir *et al*., 2015). *Oscillatoria* sp. shows antioxidant activity.

Kim (2006) investigated that, antifungal activity was shown in *Nostoc commune* FK-103 and *Oscillatoria tenuis* FK-109 against *Phytophthora capsid*. At the late exponential growth phase, its antifungal activity is linked to growth temperature rather than growth factors such cell biomass and chlorophyll concentration. Antibiotic inhibition values for *O. tenuis* FK-109 and *N. commune* FK-103 were and 31.8 mm 22.5, respectively. These studies are relevant to the current research.

5. Conclusion

In the present study, 29 bioactive compounds from *Oscillatoria* sp. were subjected to molecular docking against SARS-CoV-2 protease. Compounds were retrieved from KNApSAck database. Binding sites of the target protein was examined using CastP online server. From the analysis, 5 compounds showed binding energy (>-7 kcal/mol) and significant interactions on binding aminoacid residues. Therefore, the compounds Anabaenopeptin F, Oscillamide Y, Raocyclamide A, Anabaenopeptin B and Largamide A can be utilised for development of antiviral drugs for treatment of COVID-19 infections.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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