A Comparative Evaluation of Molecular Docking Between Nostoclide II With the Spike Glycoprotein of SARS-Cov-2 and Omicron Variant SARS-Cov-2

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**Abstract:**Cyanobacterial secondary metabolites are a vast group of molecules showing bioactivities such as antibacterial, antifungal, and antiviral properties. One such compound named Nostoclide II derived from the cyanobacterium Nostoc sp. was reported in the year 1993, however, its bioactivity was not elucidated so far. Thus, the current work aims to determine Nostoclide II's antiviral efficacy against the spike glycoprotein of SARS-CoV-2 (3JCL) and its variation (7TGW). Based on the results, it was found that the compound has a greater number of bond interactions and the lowest binding affinity against the S-protein of the omicron variant (8 interactions with a binding energy of -8.4 kcal/mol) than that of the SARS-CoV-2 (5 interactions that have an energy of binding of -7.2 kcal/mol). Comparatively, Nostoclide II has three hydrogen bonds with the S-protein of the omicron variant, whereas the same was only one in the case of SARS-CoV-2. Further, in vitro and in vivo investigations are required to have clarity on the antiviral activity of Nostoclide II.

**Keywords:** Nostoclide II; Antiviral; Spike glycoprotein; SARS-CoV-2, Omicron variant.

# Introduction

Nostoc sp., a symbiotic blue-green alga, is found in the common lichen Peltigera canina. One symbiotic cyanobacterium, *Nostoc* *punctiforme*, has been shown to harbor two Nostoclide I & II are two metabolites that include chlorine which are members of a class of naturally occurring chemicals known as γ-alkylidenobutenolides [(Carneiro, S. S., Marinho, M. M., & Marinho, E. S., 2020; Krumbholz et al., 2022; Yang et al., 1993)](https://paperpile.com/c/sdBIzL/n6dC+drse+IuVS). The nostoclides have been identified since 1993, but not all of their biological characteristics have been thoroughly studied. The transmembrane spike glycoprotein S facilitates coronavirus entry into cells by forming a trimer with receptor-binding domain (RBD) and membrane fusion capabilities [(Du et al., 2009)](https://paperpile.com/c/sdBIzL/9XoW). The target of neutralizing antibodies is S, which also possesses the primary antigenic determinants [(Ramsundar et al., 2023; Rieshy et al., 2023; S. Singh et al., 2023)](https://paperpile.com/c/sdBIzL/jkWoY+cv9BF+2p3Q0). Atypical pneumonia and mild respiratory infections account for 30% of the global human caseload of enveloped coronaviruses [(Coleman & Frieman, 2014)](https://paperpile.com/c/sdBIzL/vs1R). The 2002 and 2012 emergences of the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV) respectively showed that zoonotic viruses from different animal species can infect humans and indicated the likelihood of further emergence events. About 10–37% of MERS–CoV and SARS–CoV infections result in death [(Coleman & Frieman, 2014; Du et al., 2009)](https://paperpile.com/c/sdBIzL/9XoW+vs1R). S is a trimer-folding class I viral fusion protein. It is synthesised as a single chain precursor with roughly 1,300 amino acids [(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/sdBIzL/JuQp6+hdZh8+0z1Wy). It is made up of the carboxy-terminal S2 subunit, which drives membrane fusion, and the receptor-binding domain is found in the amino-terminal S1 subunit [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/sdBIzL/LEkhV+K3vJY+DAAUJ). The S2 cleavage site, which is the point where furin-like host proteases cleave certain coronaviruses during biogenesis, is where the mouse hepatitis virus (MHV), the most well-studied and archetypal coronavirus, occurs [(Bosch et al., 2003)](https://paperpile.com/c/sdBIzL/mN9E). The S1 and S2 subunits remain non-covalently bound in the metastable pre-fusion S trimer. Following the uptake of the virion by the target cells, endo-lysosomal proteases initiate a second cleavage (S2′ cleavage site) that facilitates the fusion activation of coronavirus S proteins [(Burkard et al., 2014)](https://paperpile.com/c/sdBIzL/LoKK). In the original strain of SARS-CoV-2, the spike protein's receptor-binding domain (RBD) takes on a combination of open ("standing up") and closed ("lying down") conformations, but the spike molecules found in omicrons are primarily with one upright RBD in the open configuration that is prepared for receptor binding. New mutations in the omicron strain result in improved inter-domain and inter-subunit packing, which stabilizes the omicron spike's open shape [(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/sdBIzL/gEL2C+sQN3R+r2FmJ). Additionally, the omicron variation has managed to avoid immunological monitoring aimed at the initial virus strain because of significant alterations in RBD regionsof the omicron spike that are known to be targeted by neutralizing antibodies [(Ye et al., 2022)](https://paperpile.com/c/sdBIzL/nnSp). Therefore, in drug development, it is imperative to have a single pharmacological target that encompasses all variants. Microalgae, rich in bioactive compounds like carotenoids and polyphenols, provide a host of health advantages, such as anti-inflammatory and antioxidant qualities. Their use has surged in food, pharmaceutical, and cosmetic industries. This review highlights microalgae's potential in combating neurodegenerative disorders like Huntington's, Alzheimer's, amyotrophic lateral sclerosis, and Parkinson's [(Parameswari & Lakshmi, 2022)](https://paperpile.com/c/sdBIzL/A7zX). Therefore, in order to determine Nostoclide II's antiviral effectiveness against both the S protein of SARS-CoV-2 (3JCL) and its omicron version (7TGW), an *in-silico* molecular docking method was taken into consideration in the current investigation.

# Materials and Methods

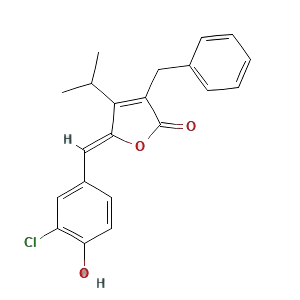
Nostoclide II (C21H19ClO3) is a chlorine containing monochlorophenol, reported as an extracellular metabolite derived from a cyanobacterium *Nostoc* sp., isolated from a lichen *Peltigera canina* with a molecular weight of 354.8 g/mol. The ligand structure of Nostoclide II (PubChem CID: (5468143) was retrieved from PubChem (National Library of Medicine, NCBI, NIH). The two important viral biomarker proteins such as Coronavirus Spike Glycoprotein of SARS-CoV-2 (PDB: 3JCL) [(Walls et al., 2016)](https://paperpile.com/c/sdBIzL/HK3L) and omicron variant of SARS-CoV-2 (7TGW) [(Ye et al., 2022)](https://paperpile.com/c/sdBIzL/nnSp) were chosen for the study and their molecular structure were taken from the RCSB PDB protein data bank. Using the BIOVIA Discovery Studio Studio Visualizer 2024, the protein structures were seen, undesirable ligands, chains, and water molecules were eliminated, and polar charges were inserted. (v24.1.0.23298) developed by Dassault Systems Biovia Corp. The spike glycoprotein facilitates the viral particle's attachment, entrance, and infection of the host cell. Compared to earlier variations, the Omicron spike (S) protein collected an unheard-of number of sequence alterations. The SARS-CoV-2 Omicron S protein's distinct structural and conformational characteristics control its capacity to attach to cell surface receptors and cause infection; change its shape in response to receptor interactions and cellular proteases; and elude immune attack by concealing antibody-binding epitopes. Molecular docking was performed between the ligand and spike glycoproteins of both SARS-CoV-2 and omicron variant using a Virtual screening software PyRx-Python Prescription 0.8 using Autodoc Vina (Molecular docking engine) [(Akshatha et al., 2021; Dallakyan & Olson, 2015)](https://paperpile.com/c/sdBIzL/bSdB+KxwH). The adjusted grid centre and dimensions coordinates were recorded and tabulated in Table 1. The low binding affinity was used to determine the best-fit model. The BIOVIA Discovery Studio Visualizer 2024 was used to record, analyze, and evaluate the bond interactions between the ligand and the protein.

**Table 1.** The grid centre and dimension parameters set for Spike glycoproteins of both SARS-CoV-2 and omicron variant of SARS-CoV-2.

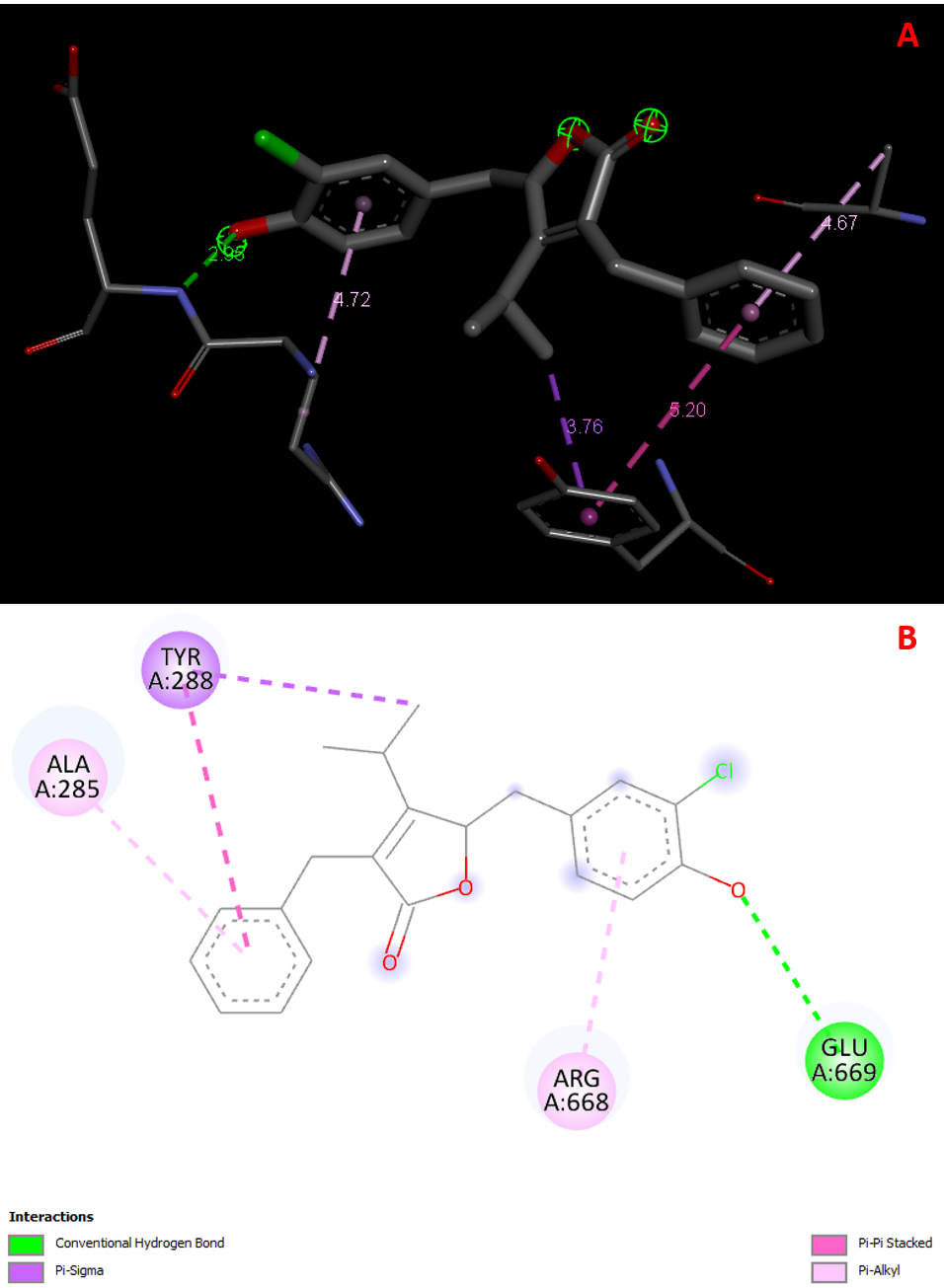
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Grid Centre** | | | **Dimensions (Å)** | | |
| **Protein** | **PDB** | **X** | **Y** | **Z** | **X** | **Y** | **Z** |
| **Spike glycoprotein (SARS-CoV-2)** | 3JCL | 229.71 | 221.76 | 205.8 | 102.06 | 128.8 | 154.58 |
| **Spike glycoprotein (SARS-CoV-2 Omicron variant)** | 7TGW | 183.26 | 191.03 | 172.61 | 119.4 | 90.57 | 204.05 |

# Results and Discussion

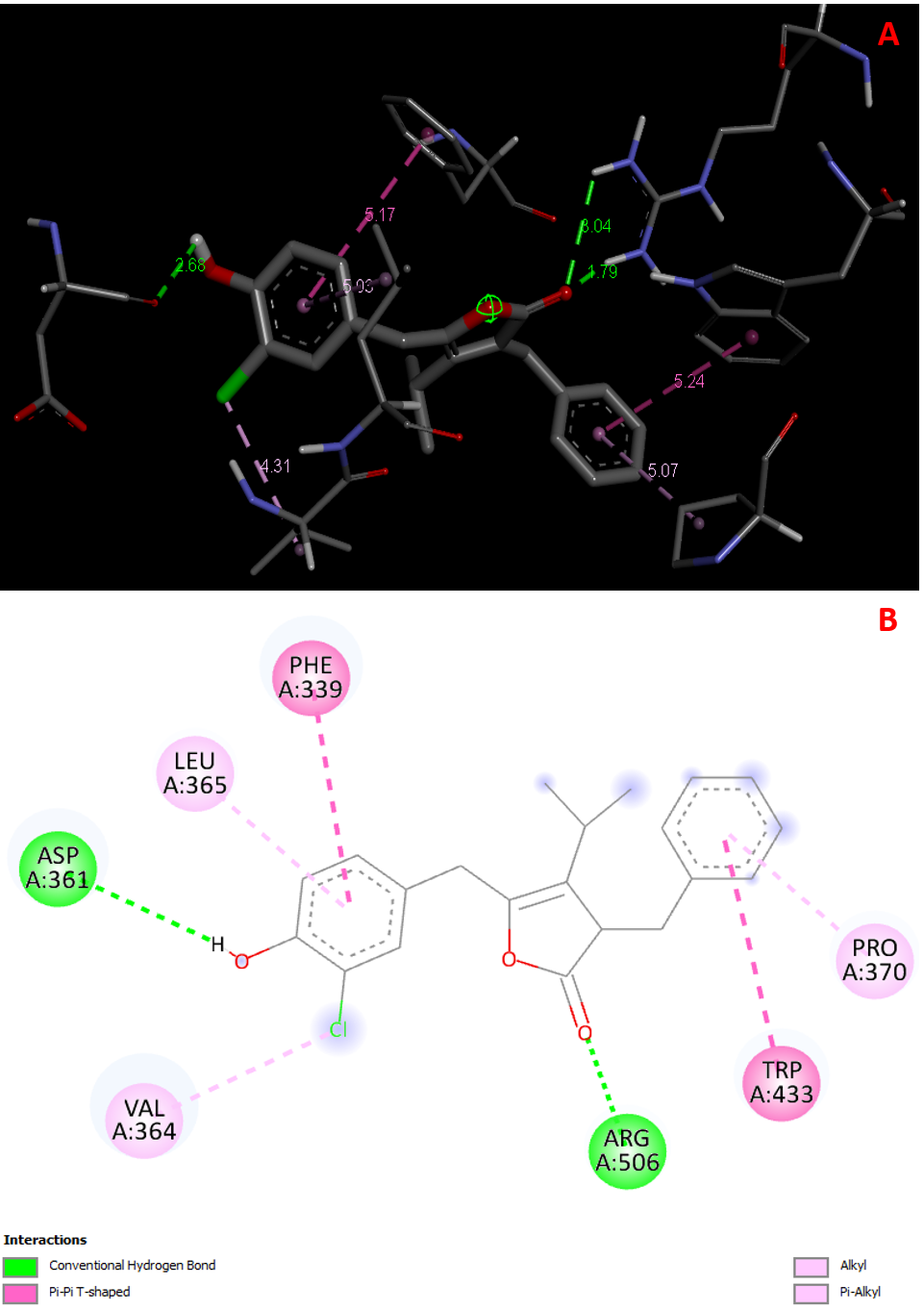
Active substances called cyanometabolites are produced by cyanobacteria and include fatty acids, alkaloids, lectins, oligosaccharides, phenols, and tiny low molecular weight peptides. With their antiviral qualities against harmful viruses including the Influenza A virus (IAV), Herpes simplex virus (HSV), Ebola virus (EBOV), and human immunodeficiency virus (HIV), they are well known to offer a number of health benefits. *Oscillatoria agardhii* agglutinin (OAAH), Scytovirin (SVN), *Microcystis viridis* lectin (MVL), cyanovirin-N (CV-N), and microvirin (MVN) are examples of cyanometabolites that are categorized as lectins and have the ability to recognize distinct viral epitopes. They also have strong antiviral activity against viral diseases. Research has demonstrated that microginin FR1, a tiny linear peptide derived from a Microcystis species water bloom, inhibits the angiotensin-converting enzyme (ACE), suggesting potential applications in the management of coronavirus illness 2019 (COVID-19) [(U. Singh et al., 2023)](https://paperpile.com/c/sdBIzL/lfAR). The herbal formulation showed strong antimicrobial effects and 91.5% anti-inflammatory inhibition, suggesting its potential for large-scale production of natural mouthwashes and mouth paints for wound healing [(Monica et al., 2022)](https://paperpile.com/c/sdBIzL/dMIR).More than 800 secondary metabolic chemicals have been identified from cyanobacteria throughout the past 20 years [(Pearson et al., 2010)](https://paperpile.com/c/sdBIzL/55to). But there is still a lack of adequate clarification regarding its bioactivity tests (Almatrafi et al., 2024). Therefore, an attempt was undertaken in the current investigation to investigate the antiviral activity of one of the cyanometabolites, named Nostoclide II, by docking with the S-glycoprotein of SARS-CoV-2 and its omicron version. The ligand Nostoclide II (**Fig. 1**) was docked with two spike glycoproteins of SARS-CoV-2 (3JCL) and omicron variant of SARS-CoV-2 (7TGW) and found out that the binding affinity was -7.2 kcal/mol and -8.4 kcal/mol respectively (**Table 2 & 3**). The ligand Nostoclide II forms a single conventional hydrogen bond with the spike glycoprotein SARS-CoV-2 (3JCL) and the amino acid residue involves in it was GLU669(Saadh et al., 2024). Similarly, π-sigma, π-π stacked, and π-alkyl bonds were also found between Nostoclide II and spike glycoprotein (3JCL) (**Fig. 2 & Table 4**). In the case of the spike glycoprotein of omicron variant (7TGW), the Nostoclide II forms three hydrogen bonds with ARG506 and ASP361. One alkyl bond, two π- π T-shaped, two π-alkyl bonds were other interactions (**Fig. 3 & Table 5**). Murrayanol showed the strongest inhibition, with a binding energy of -7.21 and two hydrogen bonds [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/sdBIzL/1XpdS+SGlW2+F8pT5). Molecular docking suggests that M. koenigii bioactive compounds, particularly murrayanol, may effectively target and inhibit EBNA-1 [(Mathivadani et al., 2020)](https://paperpile.com/c/sdBIzL/xEDR).According to the number of hydrogen bonds and other bond interactions, the binding affinity also varied with two spike glycoproteins of SARS-CoV-2 (3JCL) and omicron variant of SARS-CoV-2 (7TGW) [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/sdBIzL/ntai+yFCx+WtLb). The greater number of molecular interactions (total number of bonds = 8) between Nostoclide II and 7TGW showed a greater binding affinity of -8.4 kcal/mol (**Table 3 & 5**) [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/sdBIzL/wGbuG+9aq0m). However, lower number of molecular interactions (total number of bonds = 5) between Nostoclide II and 3JCL had a binding affinity of -7.2 kcal/mol (**Table 2 & 4**) [(Merchant et al., 2025; Shenoy et al., 2023; P. Singh et al., 2024)](https://paperpile.com/c/sdBIzL/MQNtu+8njTL+hdZh8). Two distinct metabolites of cyanobacteria After being docked to the SARS-CoV-2, ACE-2 receptor protein, mycosporine-glycine-valine and shinorine have binding energies of -7.2 and -7.0 kcal/mol, respectively [(Sahu et al., 2023)](https://paperpile.com/c/sdBIzL/4SRz). To verify the investigated drugs' antiviral capabilities, in vivo and in vitro validation is necessary for this experiment.



**Figure 1**. Molecular structure of Nostoclide II with a single chlorine



**Figure 2.** Molecular interactions between the ligand Nostoclide II and a spike glycoprotein chain A of SARS-CoV-2 showing one hydrogen bond and no interactions with the chlorine, A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand Nostoclide II and a spike glycoprotein chain A of SARS-CoV-2, Omicron variant showing three hydrogen bond and forms an alkyl bond with the chlorine. A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between Nostoclide II and spike glycoprotein of SARS-CoV-2 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 3jcl\_5468143 | -7.2 | 0 | 0 |
| 3jcl\_5468143 | -6.9 | 29.533 | 27.846 |
| 3jcl\_5468143 | -6.9 | 3.888 | 2.975 |
| 3jcl\_5468143 | -6.8 | 31.893 | 29.415 |
| 3jcl\_5468143 | -6.7 | 4.853 | 3.23 |
| 3jcl\_5468143 | -6.7 | 55.681 | 53.638 |
| 3jcl\_5468143 | -6.6 | 31.726 | 28.827 |
| 3jcl\_5468143 | -6.6 | 50.251 | 48.365 |
| 3jcl\_5468143 | -6.4 | 32.849 | 29.848 |

**Table 3.** The table retrieved after molecular docking between Nostoclide II and spike glycoprotein of omicron variant of SARS-CoV-2 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 7tgw\_5468143 | **-8.4** | 0 | 0 |
| 7tgw\_5468143 | -8 | 8.248 | 3.373 |
| 7tgw\_5468143 | -8 | 61.416 | 59.559 |
| 7tgw\_5468143 | -7.8 | 7.878 | 3.243 |
| 7tgw\_5468143 | -7.6 | 61.502 | 59.68 |
| 7tgw\_5468143 | -7.5 | 61.344 | 59.492 |
| 7tgw\_5468143 | -7.4 | 21.085 | 19.753 |
| 7tgw\_5468143 | -7.3 | 60.981 | 59.135 |
| 7tgw\_5468143 | -7.2 | 62.724 | 60.984 |

Table 4. The table showing bond interactions and its length between Nostoclide II and spike glycoprotein of SARS-CoV-2 showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Conventional Hydrogen bond | 1 | 2.17 | GLU669 |
| Pi-Sigma | 1 | 3.76 | TYR288 |
| Pi-Pi Stacked | 1 | 5.2 | TYR288 |
| Pi-Alkyl | 2 | 4.72 | ARG668 |
| 4.67 | ALA285 |
| Total number of bonds | 5 |  | |

**Table 5.** The table showing bond interactions and its length between Nostoclide II and spike glycoprotein of omicron variant of SARS-CoV-2 showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Conventional Hydrogen bond | 3 | 1.79 | ARG506 |
| 3.04 | ARG506 |
| 2.68 | ASP361 |
| Alkyl | 1 | 4.31 | VAL364 |
| Pi-Pi T-shaped | 2 | 5.24 | TRP433 |
| 5.17 | PHE339 |
| Pi-Alkyl | 2 | 5.07 | PRO370 |
| 5.03 | LEU365 |
| Total number of bonds | 8 |  | |

# Conclusion

A polyketide called Nostoclide II is produced as a secondary metabolite by some cyanobacteria. Numerous cyanobacterial metabolites have been shown to have antiviral properties; they prevent the entry of virus particles and reduce infection. In the current investigation, Nostoclide II's antiviral efficacy was evaluated against both SARS-CoV-2 and its omicron variant. The results indicated that Nostoclide II had a binding affinity of -7.2 kcal/mol and -8.4 kcal/mol, respectively, and that there were more bond interactions with the omicron variant than the former.

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