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Marine natural compounds as potents inhibitors against the main protease of SARS-CoV-2—a molecular dynamic study

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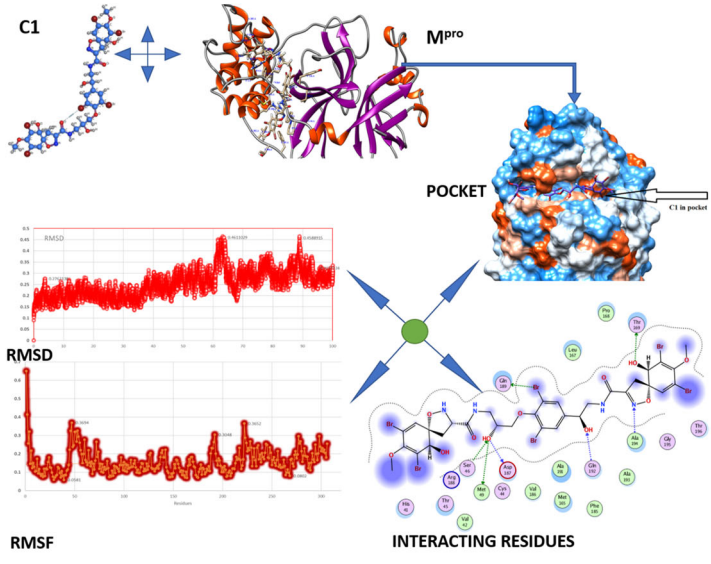
ABSTRACT

Sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA (ssRNA) virus, responsible for severe acute respiratory disease (COVID-19). A large number of natural compounds are under trial for screening compounds, possessing potential inhibitory effect against the viral infection. Keeping in view the importance of marine compounds in antiviral activity, we investigated the potency of some marine natural products to target SARS-CoV-2 main protease (M^{pro}) (PDB ID 6MO3). The crystallographic structure of M^{pro} in an apo form was retrieved from Protein Data Bank and marine compounds from PubChem. These structures were prepared for docking and the complex with good docking score was subjected to molecular dynamic (MD) simulations for a period of 100 ns. To measure the stability, flexibility, and average distance between the target and compounds, root mean square deviations (RMSD), root mean square fluctuation (RMSF), and the distance matrix were calculated. Among five marine compounds, C-1 (PubChem CID 11170714) exhibited good activity, interacting with the active site and surrounding residues, forming many hydrogen and hydrophobic interactions. The C-1 also attained a stable dynamic behavior, and the average distance between compound and target remains constant. In conclusion, marine natural compounds may be used as a potential inhibitor against SARS-CoV-2 for better management of COVID-19.



Abbreviations: ADME: adsorption, distribution, metabolism and excretion; HCV: Hepatitis C virus; MD: molecular dynamic simulations; M^{Pro}: Main protease; MOE: molecular operating environment; PDB: Protein Data Bank; RMSD: Root mean square deviation,; Rg: radius of gyration; RMSF: root mean square fluctuation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

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Table 1. Marine compounds docked against SARS-COV-2 main protease.

Compound no.	Formula	Molecular mass (kDa)	PubChem CID	Source
1	$C_{31}H_{30}Br_6N_4O_{11}$	1114.02[a]	11170714	Family Aplysinidae
2	$C_{19}H_{40}O_3$	316.53	21646261	Family Aplysinidae
3	$C_{16}H_{30}O_2$	254.41	445638	Soft coral *Pterogorgia citrina*
4	$C_{22}H_{32}O_4$	360.49	21591485	*Petrosia strongylophora sp.*
5	$C_{21}H_{26}O_3$	326.44	460087	*Petrosia strongylophora sp.*

[a]www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/; DeGoey et al. (2018).

1. Introduction

Coronavirus pandemic-19 (COVID- 19) is an ongoing disease caused by severe acute respiratory syndrome (SARS-CoV-2). According to the WHO latest report, 3,442,234 are confirmed SARS-CoV-2 infected people including 239,740 deaths. Among the six WHO regions, the largest number of cases has been reported from Europe (1,544,145) followed by Americas (1,433,756), Eastern Mediterranean (211,555), Western Pacific (152,774), South-East Asia (68,756), and Africa (30,536) (WHO COVID-19 Dashboard, n.d.). Since it was first identified in December 2019, COVID-19 has infected a large population of people around the world (Coronavirus Disease 2019 (COVID-19) Situation Report-35, n.d.).

The SARS-CoV-2, previously known as 2019-nCoV, is a single-stranded RNA (ssRNA) betacoronavirus, responsible for a severe pathological condition (Guarner, 2020). The COVID-19 is expanding rapidly as compared with previous coronaviruses (SARS-CoV and MERS-CoV) with the absence of therapeutic agents (Heymann et al., 2020; Zhang & Liu, 2020). On January 2020, the International Health Regulations Emergency Committee of the World Health Organization declared the outbreak as 'public health emergency' in responding to SARS-COVID-19.

Unfortunately, the timeline for characterizing a typical drug discovery process badly couples with the urgency of finding a therapy. It is important to accelerate the early stages of the drug discovery for all possible future emergencies (Mani et al., 2019). The early extraction of the COVID-19 genome to highlight sequence identity (~80% of conserved nucleotides) with respect to the original SARS-CoV (Gralinski & Menachery, 2020) has paved the way for rapid research.

Although commercially synthetic sources prepared many drugs but the major hurdles, drug side effects, resistance, cell toxicity, and long-term treatment, were some factors behind the failure. The potential marine products are playing a pivotal role in the identification of novel prototypes and also developing drugs using natural products of the marine environment (Vo & Kim, 2010; Wittine et al., 2019). Over two-thirds of the planet has been covered by marine species, making them a major source for novel drug-like compounds (Aneiros & Garateix, 2004; Mayer et al., 2019). Further, a possible vaccine target is viral structural proteins, the development of which is desirable and it is foreseen that the first candidates will be advanced to clinical phase I around mid-2020 (Boopathi et al., 2020; Keener, 2020; Khan, Jha et al., 2020; Letko & Munster, 2020; Sarma et al., 2020; Wrapp et al., 2020). In the meantime, however, a great effort involves the targeting of nonstructural viral proteins which are instead essential for the viral replication and the maturation processes, representing a specific target for anti-COVID-19 drug development (Ahmed et al., 2020; Anand et al., 2005; Gan et al., 2006; Gupta et al., 2020; Hasan et al., 2020; Khan, Zia et al., 2020; Sirois et al., 2007; Wei et al., 2006; Zhang & Liu, 2020). In the current scenario, the crystallographic structure of the SARS-CoV-2 main protease (M^{pro}) also called 3CL hydrolase or C30 endopeptidase, was made available to the scientific community, just a few weeks after the first COVID-19 outbreak (PDB ID: 6LU7 in complex, 6MO3 apo). The structural characterization of the main protease (M^{pro}) shares 96.1% of its sequence with those of previous SARS-CoV, contained a highly conserved architecture of the catalytic binding site. We took advantage of the recently solved crystallographic structure of SARS-COVID-19 to perform a cutting edge *in-silico* investigation.

Once the cell is infected with COVID-19, the existing molecular machinery of the host cell is taken over by the virus to translate its RNA into long chains of proteins, producing more copies. These long viral proteins are activated when cut into smaller pieces by proteases. Hence, viral proteases have a critical role in the propagation of the virus. Identification of specific inhibitors from natural products against the COVID-19 M^{pro} might be of great importance in terms of proposing the treatment regimen. Here in the current study, we searched some marine compounds and docked into the M^{pro}, shows a good binding interactions that might be useful against COVID-19.

2. Material and methods

2.1. Protein preparation

The recently submitted crystal structure of COVID-19 M^{pro} in an apo form (PDB ID: **6M03**; Berman et al., 2000) was extracted from Protein Data Bank. The structure was subjected to preparation by Protein Preparation Wizard in molecular operating environment (MOE; Vilar et al., 2008). The missing hydrogens were added, and partial charges were assigned.

2.2. Ligand preparation

The 2 D structures of marine compounds (Table 1) from PubChem converted to 3 D structure *via* the Ligprep module in MOE. The protonation and ionization states of the compounds were corrected, and proper bond orders were assigned. Afterward, the tautomeric and ionization states were created for each ligand.

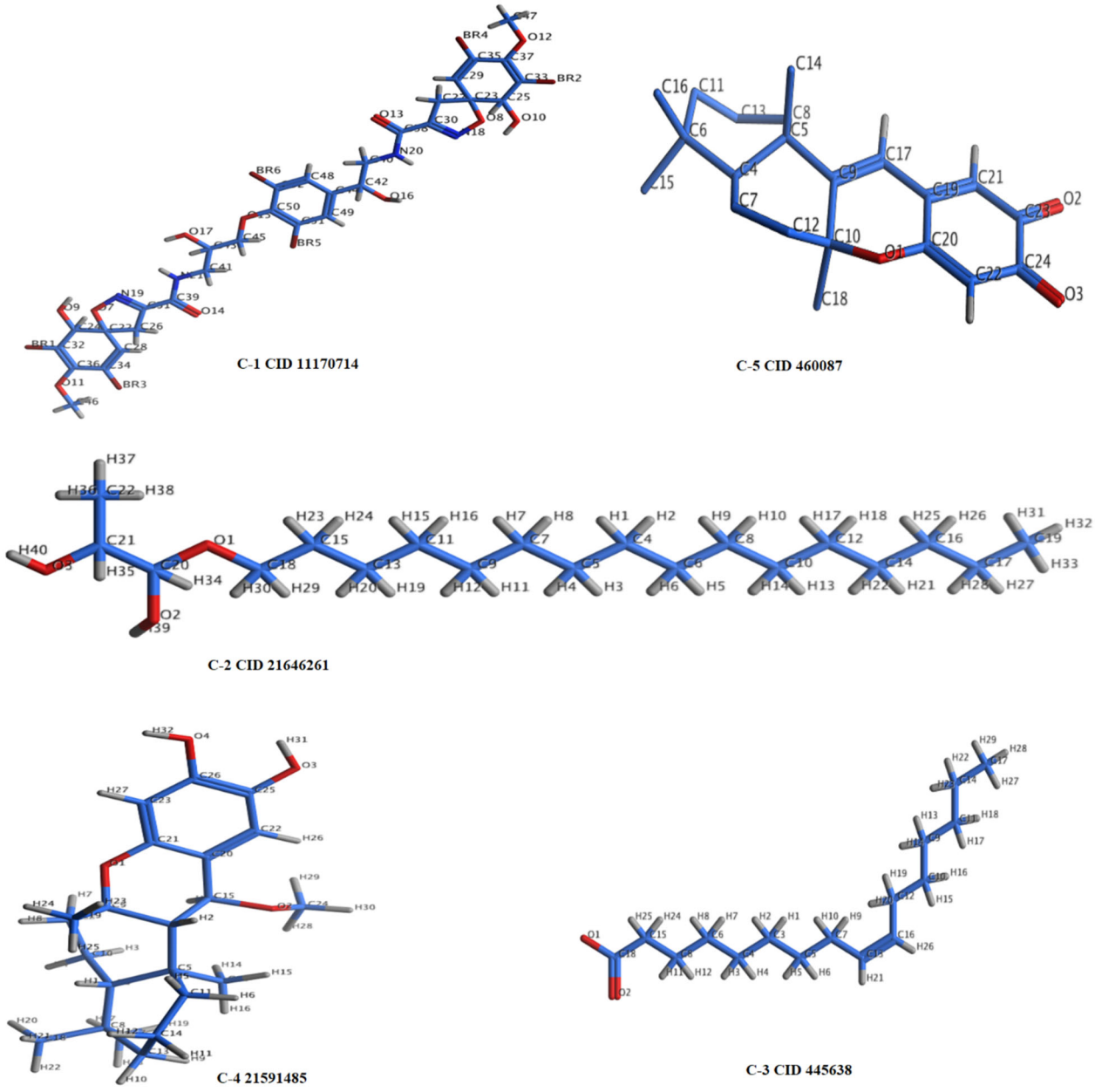

Figure 1. Structure of marine compounds. C-1 CID 11170714 containing halogen group (Br). These marine drugs have been identified in the previous study (Felix et al., 2017), active against latent *Mycobacterium tuberculosis* isolates. The drug has been observed as potent against M^{pro}, forming many hydrogen and hydrophobic interactions.

2.3. Molecular docking

Five marine compounds reported earlier in the study (Felix et al., 2017) were docked using rigid receptor docking protocol in MOE. During the process of docking, the protein was fixed, while ligands were kept flexible. Residue selenomethionines were converted into methionine and side-chain polar hydrogen were refined. Molecular docking grid was specified and centered using $20 \times 20 \times 20$ with 0.375 grid spacing. A total of 50 runs were performed to observe a wide range of conformational orientations.

2.4. Molecular dynamics (MD) simulation

MD simulation was carried out via Gromacs 5.1 [54] for a period of 100 ns. The system was stabilized by adding Na^+/Cl^- ions. Energy minimization (NVT and NPT) was performed in two-step for a duration of 50,000, continued till the maximum force reached below 1000 kJ/mol/nm. An overall pressure and temperature equal to 1 bar and 300 K were kept with a time gap of 2 fs to achieve a stable state. To maintains a constant temperature inside the box, the v-rescale, an optimized Berendsen thermostat temperature coupling technique, was used. Once the MD was completed, all the obtained trajectories were examined for conformational drifts. The root mean square deviation (RMSD) and root mean square fluctuation (RMSF) were calculated to measure the stability and flexibility of protein and compound. Cpptraj was used to calculate the average distance between marine natural compound and proteins during the simulation period (Bernardi et al., 2019; Gajula et al., 2016; Roe & Cheatham,

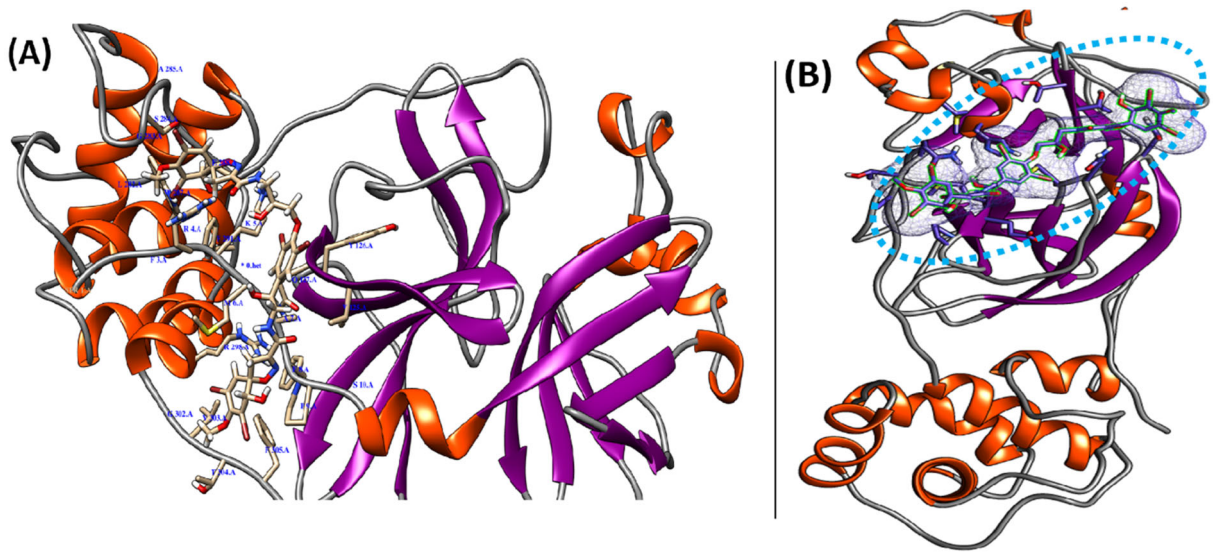

Figure 2. Interaction between C-1 CID 11170714 and M^{pro} apo. Drug has been shown, enclosed in black color blanket, signifying the binding pocket (Vilar et al., 2008).

2013). Radius of gyration (Rg) was calculated to infer the stable protein folding.

2.5. ADME prediction

To analyze the pharmacodynamics of the marine compounds, Adsorption, Distribution, Metabolism, and Excretion (ADME) is important which could be used as a drug. SWISS-ADME (https://www.swissadme.ch) allows the user to include SMILES data from PubChem and provides lipophilicity, water solubility, and drug likeness rules. SMILES files of all the marine compounds retrieved from the PubChem was entered into the search bar and the results were analyzed.

3. Result and discussion

3.1. Marine drug and m^{pro} interactions

In the current study, five marine compounds, designated as C-1, C-2, C-3, C-4, and C-5 (Table 1) have been docked in the crystal structure of viral M^{pro}. The compounds (Figure 1) exhibited a good interaction with viral M^{pro}, forming many hydrogen bonds (Figure 2). The ADME properties (supplementary data S1) shows that these compounds may be applied in the therapy of SARS-CoV-2. Although the molecular weight of C1 is very high but the new FDA approval seems beyond the Lipinski's rule of five (www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/). This may due be the increasing focus that offer potential for promising new therapeutic compounds for the treatment of diseases, particularly in the areas of virology and oncology. However, conducting drug discovery 'beyond rule of 5' chemical space offerings important drug design and challenges to medicinal scientist to achieve oral pharmacokinetics. In some cases, including HCV NS3/4A protease, and hepatitis C virus (HCV) NS5A inhibitors the Lipinski's rule of five has not been considered (DeGoey et al., 2018).

In the last 20 years, SARS and MERS have been found as new infectious agents, emerged to cause epidemics (de Wit et al., 2016; Guarner, 2020). Conventional drug development methods take years and costly, offering more time for transmission of pathogens. The appropriate and timely development of potent antiviral agents for clinical use is of central interest, using cost-effective and fast computational approaches. Moreover, the approved pharmaceutical drugs may be repurposed as alternative method to screen for rapid identification of potential leads (Chu et al., 2006; Enayatkhani et al., 2020; Muralidharan et al., 2020; Pillaiyar et al., 2016; Yang et al., 2005). In this regard, recently a large number of in-silico studies have been performed on medicinal plants, drug designing, and vaccine development (Aanouz et al., 2020; Elfiky, 2020a, 2020b; Elfiky & Azzam, 2020; Elmezayen et al., 2020; Enmozhi et al., 2020; Joshi et al., 2020; Pant et al., 2020).

Hundreds and thousands of humans have been died in many epidemics, broken out over the centuries. Some infections have been found, more deadly, especially viral pathogens. These pathogens have resisted in majority of cases to all kinds of medical treatment. Synthesizing drugs against rapidly replicated viruses resulting in acute syndromes is a laborious and time-consuming procedure, requires a lot of financial aid. However, the natural compounds are lying around on the earth on land and water (Abdelli et al., 2020; Das et al., 2020; Islam et al., 2020; Kumar et al., 2020; Sinha et al., 2020; Umesh et al., 2020; Wahedi et al., 2020) that could be screened for potential compounds against SARS-CoV-2 main targets.

Over a 1000 of novel marine compounds isolated from marine organisms are being pharmacologically tested, and over 40 are being existed in the medicine market. In modern pharmacological industry, marine products are paving the way for a new trend (Ahmadi et al., 2015; Che, 1991; Gogineni et al., 2015; Khan et al., 2019; Moghadamtousi et al., 2015; Raveh et al., 2013; Sagar et al., 2010; Uzair et al., 2011; Vijayakumar & Menakha, 2015).

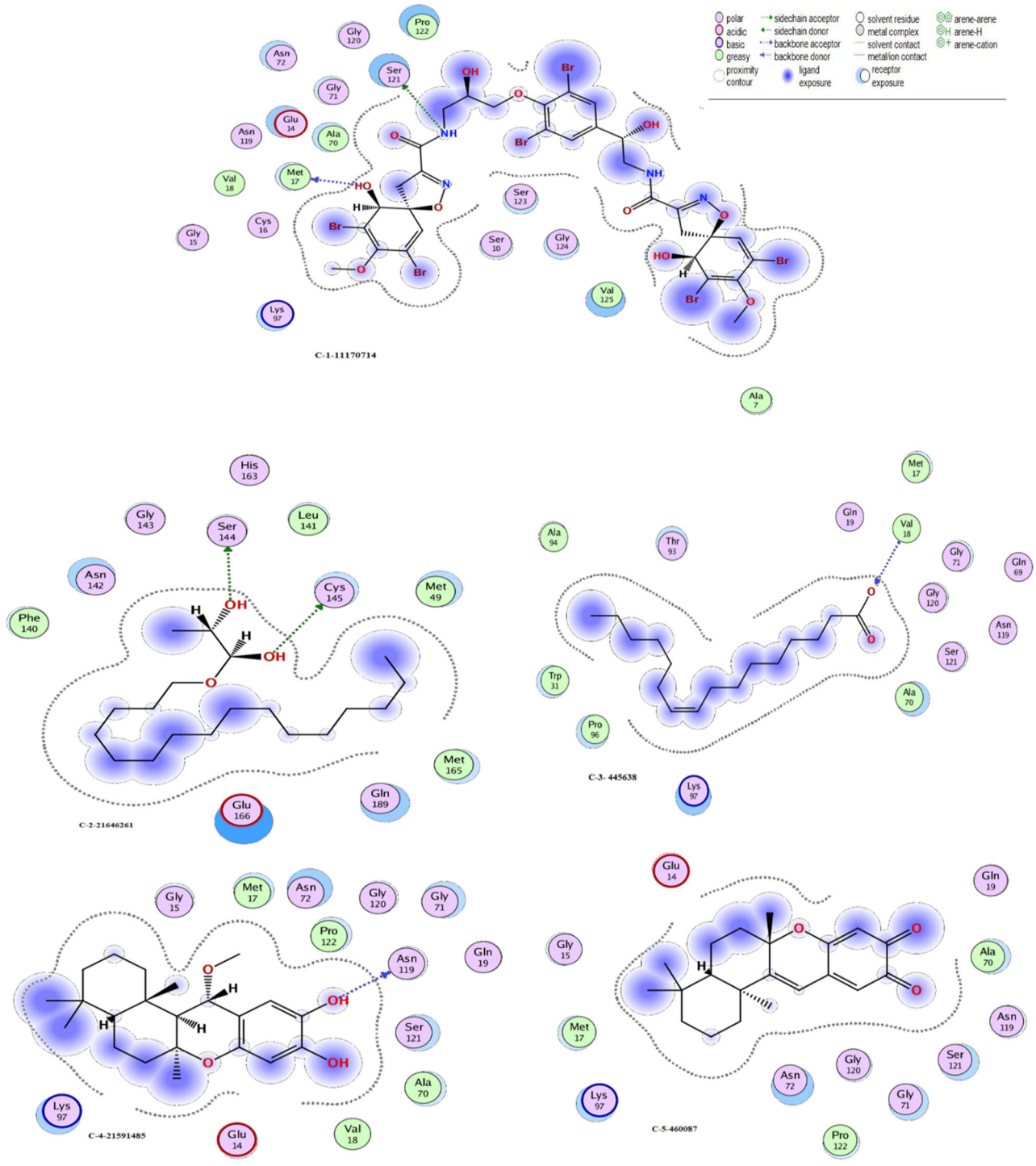

Figure 3. COVID-19 M^{pro} residues forming hydrogen and hydrophobic interactions with five marine compounds. Compound C1 CID 11170714 exhibited more hydrogen and hydrophobic interactions. C2 interaction with Cys145, the active site of SARS-CoV 3CLpro creating a catalytic dyad (Cys145 and His41).

Interactions of five marine natural products have been shown (Figures 2 and 3). Residues Thr24, Leu27, His41, Phe140, Cys145, His163, Met165, Pro168, and His172 are present in the active site and its surrounding (Wu et al., 2020). The drug C1 shows good binding affinity, forming many hydrogen and hydrophobic interactions. Compound C2 also exhibited interactions with active site of M^{pro}, creating a catalytic dyad, consist of Cys145 and His41, where the cysteine is a nucleophile in the proteolytic process (Figure 3). The best interacting pose was selected based on E_refine and E_score2. The more negative score shows a good ligand and protein complex (Table 2).

Natural products may provide lead compounds, especially as antimicrobial agents (Dias et al., 2012; Hu et al., 2015; Newman & Cragg, 2016). A large range of marine products displays chemical structures with good biological activities to discover drug like for various human diseases caused by virus, including COVID-19. An additional advantage of marine

products, as most of them has the property of drug-likeness with high degrees of bioavailability, and effective drugs against viral diseases shortly.

M^{pro} (3CLpro) monomer has three domains: domain I, domain II, and domain III containing residues 8–101, residues 102–184, and residues 201–303 respectively, and a long loop (residues 185–200) connects domains III and II (Wu et al., 2020). The active site (Cys145 and His41) is located in the gap between domains I and II, while hydrophobic amino acids, T24, L27, H41, F140, C145, H163, M165, P168, and H172 also form a hydrophobic surrounding in the pocket (Yang et al., 2003). The identification of compounds fitting in the pockets is one of the fundamental step in structure-based drug design. The recent progress and developments of the computational analysis of pockets have been found useful to screen potent inhibitors (Zheng et al., 2013). Analysis of M^{pro} complex with C1 shows many hydrogen and hydrophobic interaction (Figure 4). The compound exhibited affinity with SARS-CoV-2 M^{pro} from all sides, showing its best fitting in the pocket. Drug interactions and fitting in the pocket is essential for drug designing and lead optimization. it It is also important to identify the locations of binding sites to infer protein–ligand binding or protein–protein interaction.

Table 2. Docking score of marine drugs and COVID-19 M^{pro}.

S	E_place	E_score1	E_refine	E_score2
−7.58	−84.29	−7.82	−46.55	−7.58
−7.55	−85.64	−8.22	−44.93	−7.55
−7.54	−77.91	−8.73	−44.70	−7.54
−7.26	−62.71	−8.39	−43.95	−7.26
−7.22	−77.08	−8.60	−43.06	−7.22
−5.86	−55.39	−6.97	−28.48	−5.86
−5.73	−62.11	−7.06	−28.53	−5.73
−5.50	−70.48	−7.93	−25.24	−5.50
−5.22	−70.33	−8.13	−22.25	−5.22
−5.21	−71.26	−6.90	−26.29	−5.21
−5.16	−37.99	−6.90	−23.32	−5.16
−5.09	−41.22	−7.20	−23.20	−5.09
−5.09	−35.11	−6.61	−21.29	−5.09
−5.08	−29.77	−6.34	−24.76	−5.08
−5.06	−31.38	−7.00	−21.46	−5.06
−5.42	−32.23	−7.39	−28.69	−5.42
−5.39	−25.44	−7.81	−26.96	−5.39
−5.29	−24.91	−7.40	−23.56	−5.29
−5.22	−33.38	−7.69	−24.96	−5.22
−5.03	−35.70	−8.80	−27.37	−5.03
−5.27	−28.55	−7.35	−26.48	−5.27
−5.13	−42.11	−7.75	−25.53	−5.13
−5.07	−37.36	−6.29	−20.07	−5.07
−5.04	−34.24	−8.03	−24.74	−5.04
−4.96	−20.93	−7.26	−24.26	−4.96

In addition to hydrogen bonds, hydrophobic and electrostatic interactions are also important. The hydrogen bonds may play as an 'anchoring' role, defining the spatial location of the druggable compounds in the binding pocket, facilitating the electrostatic and hydrophobic interactions. In rational drug design, it is equally essential to recognize the hydrophobic groups of the compound and receptor, facing to each other upon binding. These interactions have been detected while analyzing the Connolly surface (Connolly, 1993) of the complex of SARS-CoV M^{pro} and marine compounds. It is the steric complementarity between the ligand and receptor site that performs the role of the principal driving force for mechanical interlocking (Chou et al., 2009; Sirois et al., 2007; Wei et al., 2006).

RMSD and RMSF are calculated in MD simulations to infer the stability and flexibility, a fundamental property of biomolecules. High deviation and fluctuation of proteins during a simulation may show weak stability and stability in thermodynamics (Chen & Shen, 2009). SARS-CoV-2 M^{pro} in complexed with C1 exhibited a stable RMSD between 0.2 and 0.45 nm (Figure 5) and the initial and final RMSDs during the whole simulation period were not found in the significance difference (0.2 and 0.3 nm). This shows a stable binding of

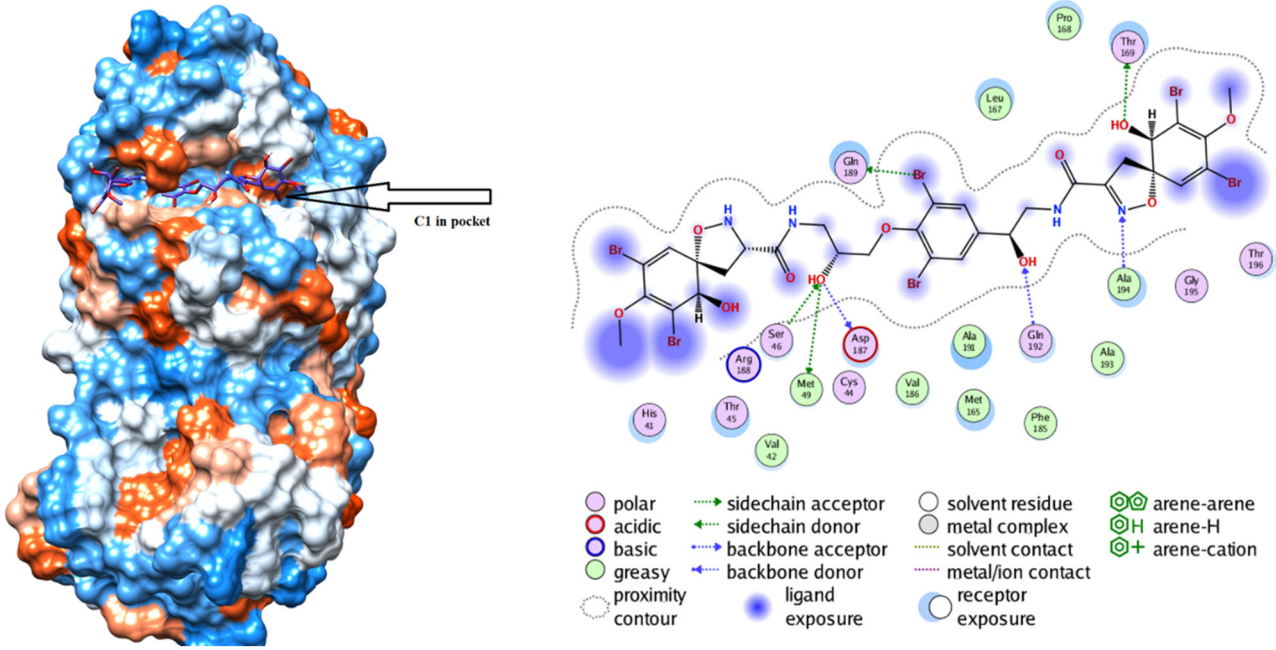

Figure 4. Interaction of C1 after MD simulation. Residues, Ser46, Met49, Asp187, Gln192, Ala194, Thr169, and Gln189, are involved in hydrogen bonding.

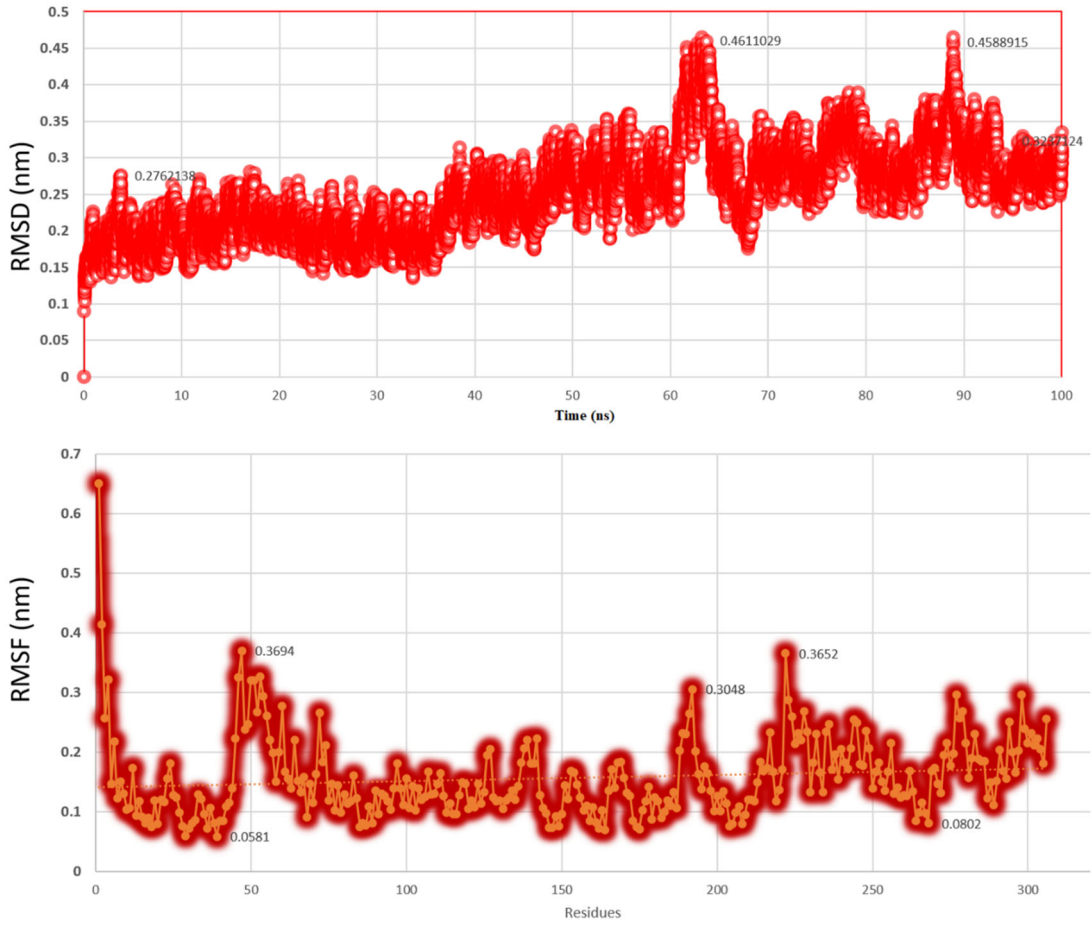

Figure 5. RSMD and RMSF of M^{pro} in complex with C1 compound. The complex exhibited a stable RMSD and RMSF during a 100 ns MD simulation period.

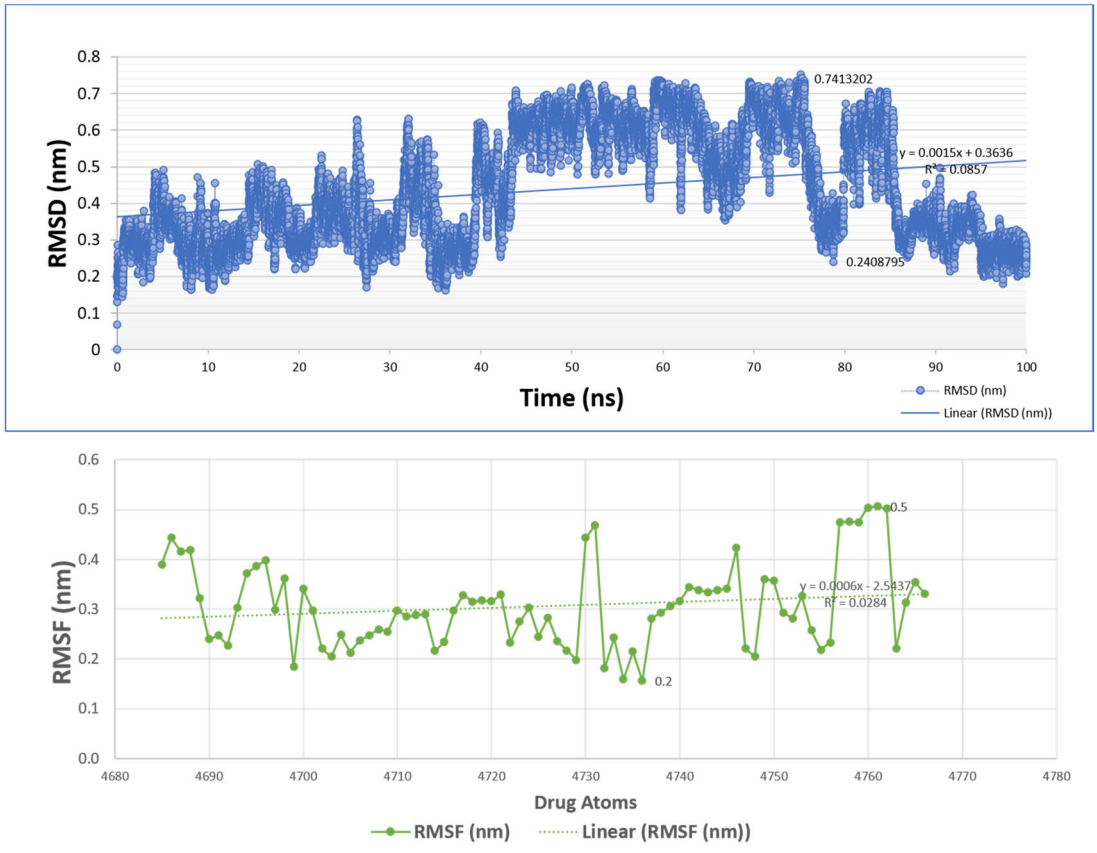

Figure 6. RMSD and RMSF of compound C1.

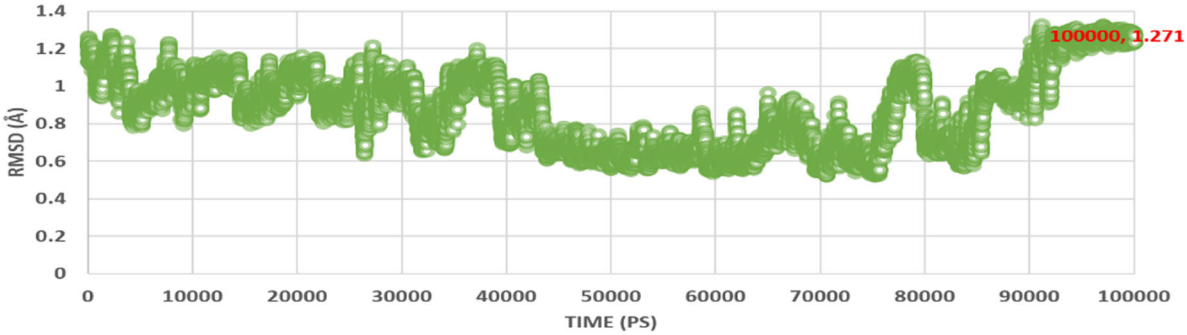

Figure 7. Distance matrix between C1 and M^{pro} during 100 ns (100,000 ps).

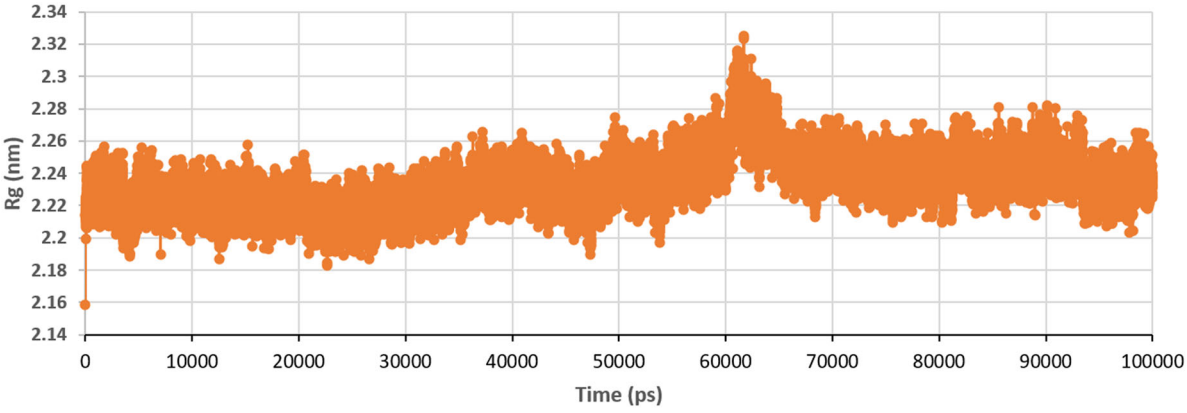

Figure 8. Radius of gyration. The degree of folding is constant during the whole simulation period.

C1 with M^{pro} that might be a useful as a good inhibitor. Moreover, residues fluctuations were also observed, not too flexible in motion (0.05–0.36 nm). Both, RMSD and RMSF stabilities are essential to infer good binding affinities (Doniach & Eastman, 1999; Dubey et al., 2013; Figure 6).

The initial and final RMSD of C1 atoms is almost similar. The residues atoms fluctuations have been detected in a range of 0.2–0.5 nm. However, the majority of C1 atoms exhibited RMSF below 0.3 nm.

The average distance of C1 and M^{pro} is approximately in range, with little fluctuation during the simulation period. However, the final and initial distance is almost similar (Figure 7). The distant matrix signifies the C1 and M^{pro} distance stability during the simulation period. This approach might be useful to infer the strong binding affinity during the simulation period (Ernst et al., 2015; Khan, Ashfaq-Ur-Rehman et al., 2020). The average distance is commonly affected when a variant occurs at the active site of target proteins during the course of therapy, causing drug resistance (Figure 8).

The degree of compactness and folding is plotted against time, which is commonly measured through the radius of gyration (Rg). A long range variations in proteins show their weak folding (Lobanov et al., 2008; Smilgies & Folta-Stogniew, 2015). A stable Rg value shows compactness and stable folding maintains a steady value of Rg, required for proper function, whereas in case of misfolding, the Rg will show a long range of variation over time.

In conclusion, marine natural product is the most diverse group, containing potential inhibitors against RNA viruses. Among marine natural products, C1 forming many interactions with Thr24, Leu27, His41, Phe140, Cys145, His163, Met165, Pro168, and His172, present in the active site and its surrounding. These compounds have been observed as best fitting in the binding pocket, that might be good inhibitor of SARS-CoV-2 M^{pro} for better management of COVID-19.

Disclosure statement

No potential conflict of interest was reported by the authors.

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