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Original Article

Lipopeptides against COVID-19 RNA-dependent RNA polymerase using molecular docking

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is caused by a novel virus that is responsible for the largest pandemic in recent times. Although numerous studies have explored methods to cope with COVID-19 and targeted drugs and vaccines have been developed, the spread of disease remains rapid due to the high infectivity and mutation capability of SARS-CoV-2, the causative virus of COVID-19. Therefore, there is an urgent necessity to seek more efficient treatments and approaches to combat the disease.

Methods: In this study, molecular docking was used to predict the binding of different lipopeptides, which exhibit significant biological functions, to the RNA-dependent RNA polymerase (also known as nsp12) of SARS-CoV-2, the central component of coronaviral replication and transcription machinery.

Results: The results showed that seven lipopeptides bound to nsp12 at the same location as the FDA-approved drug remdesivir, with higher affinities. Notably, iron-chelating ferrocin A (ferrocin A–iron complex [FAC]) bound to nsp12 most tightly, releasing up to 9.1 kcal mol^{-1} of free energy. Protein-ligand interaction analysis revealed that FAC formed four hydrogen bonds, two hydrophobic interactions, and three salt bridges with nsp12. These active amino acids are mainly distributed in the fingers and thumb subdomains of nsp12 and are highly conserved.

Conclusions: Our findings suggest that the abovementioned lipopeptides can tightly bind to nsp12, and thus represent promising drug candidates for anti-coronaviral treatments with the potential to fight SARS-CoV-2.

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At a glance of commentary

Scientific background on the subject

The spread of Coronavirus disease remains rapid due to the high infectivity and mutation capability of SARS-CoV-2, the causative virus of COVID-19. Researchers are investigating effective antiviral drugs to address the global threat of COVID-19. Many innovative approaches to drug discovery are being used to identify novel therapeutic drug candidates

What this study adds to the field

In this study, we performed molecular docking to test lipopeptides, a kind of secondary metabolites of microorganisms that exist widely in nature, against nsp12, a viral RNA-dependent RNA polymerase of SARS-CoV-2. This work shows that it is feasible to find and produce highly effective anti-COVID-19 drugs from lipopeptides.

Coronavirus disease 2019 (COVID-19) was declared a pandemic in 2020, and is the largest global health threat in recent times. More than 230 million people worldwide have been reported to be infected with COVID-19, with 4.79 million deaths at the time of writing, and this number is still growing rapidly. The major symptoms of COVID-19 infection include cough, fever, and breathing difficulties, and no drugs have been discovered to cure this life-threatening coronavirus so far. Although vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2: the causative virus of COVID-19) have been developed, uncertainty on long-term protection and breakthrough infections in fully vaccinated people has led to concerns of their safety and effectiveness. Additionally, newly occurring mutants of SARS-CoV-2 have also caused widespread panic to the public. Moreover, COVID-19 has ignited fears of impending economic recession in many countries. Thus, there is a long way to go until the COVID-19 crisis is overcome.

SARS-CoV-2 is a member of the *Betacoronavirus* genus in the Coronaviridae family [1]. It consists of two groups of proteins: structural proteins, which include the S (spike) glycoprotein, E (envelope) protein, M (membrane) protein, and N (nucleocapsid) phosphoprotein, as well as non-structural proteins [2]. The S glycoprotein is a transmembrane protein that forms homotrimers on the viral surface and facilitates binding to host cells. The E protein plays a role in viral production and maturation, while the M protein is important in determining viral envelope shape. The N protein structurally binds to viral nucleic acids and is involved in processes related to viral genome and replication cycle. Coronaviruses use non-structural proteins, including the accessory units nsp7 and nsp8 [3,4] and the catalytic unit nsp12 [5], to replicate and transcribe their RNA genome. Nsp12 is a viral RNA-dependent RNA polymerase (RdRp) and possesses high polymerase activity [6]. Thus, it is considered an attractive drug target for antiviral therapy.

At present, researchers are investigating effective antiviral drugs to address the global threat of COVID-19. Several existing drugs, such as remdesivir and sofosbuvir, have demonstrated promising effectiveness against SARS-CoV-2 [7], and their pharmacology and mechanism of action are well-investigated [8]. Besides, due to the high cost of laboratory and clinical trials, innovative approaches to drug discovery are being used to identify novel therapeutic drug candidates. Among the most important bioinformatics methods in drug design, molecular docking, which involves investigating the interactions of small molecule ligands inside the pocket of a target protein, is a promising tool for drug development. Indeed, molecular docking has been used to predict potential inhibitors of SARS-CoV-2, including plant-derived compounds [9] and drugs with well-known antiviral activities [10]. Despite the lack of experimental studies, these *in-silico* findings offer considerable opportunities to identify promising SARS-CoV-2 inhibitors.

Lipopeptides, which are usually composed of a peptide ring linked to a fatty acid chain, are natural products that are predominantly synthesized by species of *Pseudomonas* and *Bacillus* [11]. Lipopeptides may also contain non-canonical amino acids, such as non-proteinogenic amino or D-amino acids, which confer unique properties. Lipopeptides play important roles in the survival of microorganisms, including by antagonizing other microorganisms [12] and regulating the environment [13]. Some lipopeptides, such as surfactin and fengycin, have also been reported to exhibit antiviral activities [14,15].

However, few studies have explored the use of lipopeptides as potential therapeutic drugs to combat SARS-CoV-2. Therefore, in this study, we performed molecular docking to test several lipopeptides against nsp12 from SARS-CoV-2, which is the central component of the coronaviral replication and transcription machinery [16]. We used the bio-activated triphosphate forms of two FDA-approved medications, remdesivir and sofosbuvir, as positive control compounds. Our findings revealed that the binding mode of several lipopeptides to nsp12 was similar to that of remdesivir and sofosbuvir triphosphates, with certain candidates exhibiting higher binding affinities.

Materials and methods

Protein structure acquisition

The publicly available three-dimensional structure of nsp12 was retrieved from the Protein Data Bank (PDB, www.rcsb.org, PDB ID: 6M71, 2.9 Å) [16]. The structure was refined and optimized to prepare for the docking study, including removing cofactors nsp7, nsp8-1, and nsp8-2, adding missed hydrogen atoms, and fixing the bonds and orientations.

Acquisition of lipopeptide structures

The structures of fengycin, polymyxin B_1, daptomycin, iturin A, surfactin A, surfactin C, remdesivir, and sofosbuvir were obtained from ChEBI (Chemical Entities of Biological Interest,

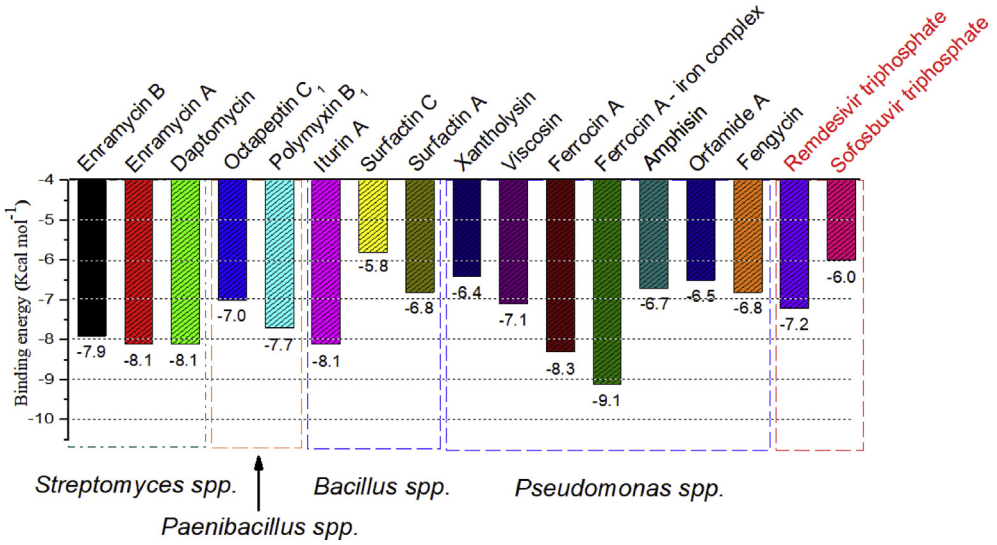


Fig. 1 Histogram representing the binding energies (in kcal mol^{-1}) of different lipopeptides to nsp12 calculated by AutoDock Vina software, including enramycin B, enramycin A, daptomycin, octapeptin C_1, polymyxin B_1, iturin A, surfactin C, surfactin A, xantholysin, viscosin, ferrocin A, ferrocin A–iron complex (FAC), amphisin, orfamide A, and fengycin. Remdesivir triphosphate (RTP) and sofosbuvir triphosphate (STP) (highlighted in red) were used as positive controls. The dashed and colored rectangles mark the four species which are used to synthesize the indicated lipopeptides, including *Streptomyces*, *Paenibacillus*, *Bacillus*, and *Pseudomonas*.

www.ebi.ac.uk/chebi/init.do). Amphisin, orfamide A, octapeptin C_1, enramycin A, enramycin B, viscosin, ferrocin A, xantholysin, poaeamide A, putisolvin I, viscosinamide A, massetolide A, pseudomycin A, remdesivir triphosphate (RTP), and sofosbuvir triphosphate (STP) were constructed using ChemDraw professional 17.0.0.206 (CambridgeSoft, Cambridge, UK) according to literature reports [17]. The structure of each lipopeptide was energy-minimized (classical mechanical, MM3 force field) with assistance from the computational chemistry workspace SCIGRESS Explorer 7.7.0.47 (Fujitsu, Fukuoka, Japan).

Molecular docking

The molecular docking procedure was performed using AutoDock Vina [18], with the nsp12 model as the docking target. A total of 22 compounds were tested against nsp12, including RTP and STP as controls. The binding energy of the lipopeptide whose binding site with nsp12 was consistent with that of the control molecules [16] was recorded, while other lipopeptides with mismatched binding sites were removed. The interactions between nsp12 and lipopeptides were identified using the Protein–Ligand Interaction Profiler (PLIP) web server [19].

Conserved sequence analysis

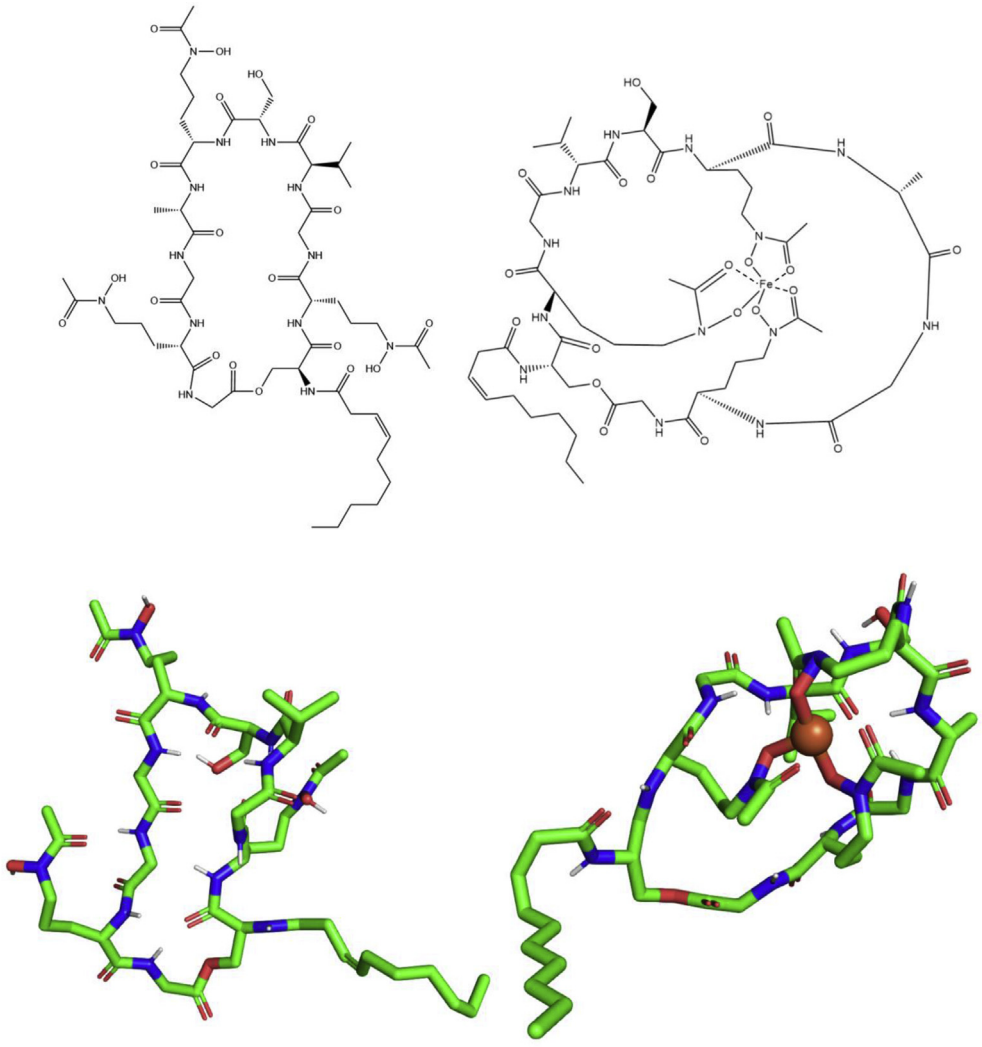
Homologs of nsp12 were searched using the Basic Local Alignment Search Tool (BLAST) at NCBI. Nine proteins from different sources were selected for multiple sequence alignment (MSA) with SARS-CoV-2 nsp12, including Betacoronavirus Erinaceus, *Pipistrellus abramus* bat coronavirus, Hypsugo bat coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), human betacoronavirus 2c Jordan, Rousettus bat coronavirus, SARS-like coronavirus WIV16, pangolin coronavirus, and bat coronavirus RaTG13. Dash-bio was used to assess the conservation of protein sequences [20].

Results

Lipopeptides binding to SARS-CoV-2 nsp12

We docked 20 short cycle lipopeptides (CLPs) with SARS-CoV-2 nsp12. These lipopeptides represent almost all known short CLPs [17] and have been previously reported to have significant biological functions, such as antibiotic, antiviral, or antitumor activities (Table S1). We also docked RTP and STP, which are the active forms of remdesivir and sofosbuvir in cells [7,21], with SARS-CoV-2 nsp12. Before testing, the structure of each chemical was adjusted using the classical MM3 force field [22] and ensured to be in the optimized active form. Molecules were treated as flexible in all docking experiments.

Considering that drug candidates targeting nsp12 should have similar binding modes and inhibition mechanisms, we removed lipopeptides whose binding poses with nsp12 were inconsistent with those of RTP and STP [16]. As a result, only 15 lipopeptides were bound to nsp12 at the expected position with low binding energies (Fig. 1). These lipopeptides (Fig. S1) were synthesized by four different species, including *Streptomyces*, *Bacillus*, *Paenibacillus*, and *Pseudomonas*. Seven lipopeptides out of these screened candidates (enramycin B, enramycin A, daptomycin, Polymyxin B1, Iturin A, ferrocin A, ferrocin A–iron complex) showed better docking scores than RTP (−7.2 kcal mol^{-1}), with lower binding energies of −7.9, −8.1, −8.1, −7.7, −8.1, −8.3, and −9.1 kcal mol^{-1}, respectively (Fig. 1). This finding indicates that these lipopeptides may bind to SARS-CoV-2 nsp12 more efficiently than the two FDA-approved drugs.



AA1	AA2	AA3	AA4	AA5	AA6	AA7	AA8	AA9	AA10
L-Ser	N^5-Ac-N^5-OH-Orn	Gly	D-Val	L-Ser	N^5-Ac-N^5-OH-Orn	L-Ala	Gly	N^5-Ac-N^5-OH-Orn	Gly

Fig. 2 The energy-minimized structures of ferrocin A and ferrocin A–iron complex (FAC). Amino acids (AAs) are written in three-letter codes, and AA1 represents the N-terminus of the peptide. Abbreviation: N^5-Ac-N^5-OH-Orn: N^5-acetyl-N^5-hydroxy-ornithine.

Notably, the binding of ferrocin A to nsp12 released a free energy of 8.3 kcal mol^{-1}, which was among the highest of the tested compounds. Furthermore, iron-chelating Ferrocin A (ferrocin A–iron complex, FAC) seemed to bind to nsp12 more tightly, releasing up to 9.1 kcal mol^{-1} of free energy (Fig. 1). Ferrocin A is produced by *Pseudomonas*, and its peptide ring contains 10 amino acids, including one D-valine and three ornithines (Fig. 2). As iron-chelating peptides, ferrocins can reduce the concentration of freely available iron in the environment via complexation, thereby inhibiting the growth of bacteria by repressing the acquisition of essential metal cations [23]. Additionally, ferrocins usually exist in the form of FAC in oxygenated environments [24].

Interactions of ferrocin A and FAC with nsp12

The RNA-dependent RNA polymerase nsp12 is a nonstructural protein of SARS-CoV-2, which is responsible for catalyzing the synthesis of viral RNA [4]. It is considered a therapeutic target against COVID-19 infection as it plays a crucial role in viral replication and the transcriptional cycle [25]. Nsp12 is composed of the following five subdomains: a nidovirus RdRp-associated nucleotidyltransferase (NiRAN) subdomain, an interface subdomain, a fingers subdomain, a palm subdomain, and a thumb subdomain (Fig. 3). The primer-template entry, NTP entry, and nascent strand are all gathered in the central cavity formed by the fingers, palm, and thumb

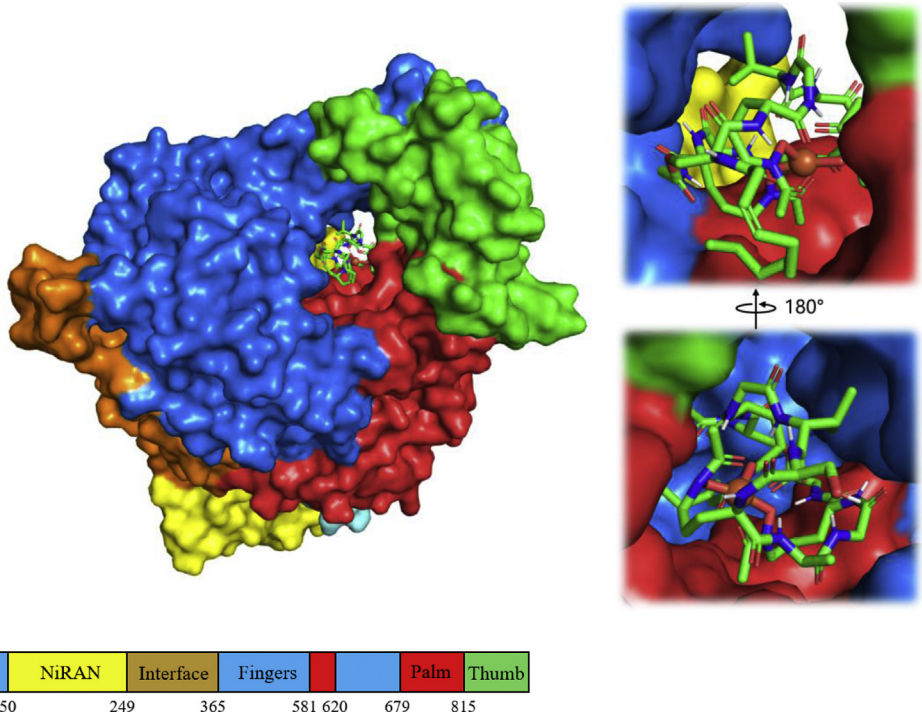


Fig. 3 Incorporation model of ferrocin A–iron complex (FAC) in SARS-CoV-2 nsp12 and nsp12 domain organization. Different subdomains of nsp12 are colored as follows: NiRAN subdomain, yellow; interface subdomain, brown; fingers subdomain, blue; palm subdomain, red; thumb subdomain, green. The interdomain borders are indicated by residue numbers.

subdomains, where nsp12 motifs mediate RNA synthesis. Remdesivir and sofosbuvir are predicted to bind to nsp12 at this central cavity (Fig. S2), shutting off the synthesis of RNA, and subsequently inhibiting the expression of SARS-CoV-2 [16]. Ferrocin A and FAC also bind to nsp12 at the same site as the active form of remdesivir, RTP (Fig. S3 and Fig. 3).

To investigate the interaction patterns of ferrocin A and FAC with nsp12, we employed PLIP to examine the protein-ligand binding modes. FAC was found to form four hydrogen bonds with nsp12 residues R553, R555, S814, and R836, two hydrophobic interactions with L758 and E811, and three salt bridges with R555, D760, and E811 (Fig. 4). Ferrocin A showed six hydrophobic interactions with nsp12 residues D623, K593, W598, D761, E811, and Q815, as well as ten hydrogen bonds with R553, R555, K621, D623, R624, S759, D761, K798, S814, and R836 (Fig. 5). RTP formed eight hydrogen bonds with S549, A550, K551, R553, K621, C622 and R624, one hydrophobic interaction with K621, and one π-cation interaction with R553 of nsp12 (Fig. 6).

According to the above observations, the interaction patterns were similar among FAC, ferrocin A, and RTP. Both FAC and ferrocin A hydrogen-bonded with nsp12 R553, R555, S814, and R836, and formed hydrophobic interactions with E811. Ferrocin A and RTP shared common interactions with amino acids in the 621–624 AA (amino acid) region of nsp12 (Figs. 5 and 6). In addition, the AA region 549–555 in the fingers subdomain of nsp12 is especially important because all the three chemicals established stable bonds with amino acids in this region, such as the hydrophilic residue R553 (Fig. 4–6). Interestingly, the 549–555 AA region was reported to form the NTP entry channel [16]. The vast number of interactions gives the nsp12-Ferrocin A complex its stability with the -8.3 kcal mol^{-1} binding energy. RTP showed a reduced number of interactions with nsp12, which was reflected in the binding energy values (-7.2 kcal mol^{-1}). However, as for FAC, the three salt bridges formed by FAC with nsp12 may result in firmer binding (-9.1 kcal mol^{-1}) compared with ferrocin A, even with a smaller number of interactions.

Although from the point of view of the docking studies, FAC and ferrocin A bind to nsp12 with the same patterns as RTP, the underlying inhibition mechanisms may not be the same. When delivered into cells, remdesivir is metabolized to yield an active NTP analog [26], RTP. Nsp12 can use RTP as a substrate and integrate remdesivir monophosphate (RMP) into the growing RNA product. After incorporation of RMP, nsp12 extends RNA by three more nucleotides and stalls [8,27,28]. Apparently, FAC and ferrocin A are not NTP analogs, and therefore cannot be incorporated into RNA products. They may simply bind to the active sites of central cavity, interfere with conformational stability, and prevent the RNA synthesis mediated by nsp12 motifs. So far, to our knowledge, there have been no crystallographic studies defining the interactions of virus–lipopeptide complex. Thus, further experiments are necessary to validate the molecular docking results, and our data encourage future *in vitro* and *in vivo* investigations.

Conservation analysis of active amino acids in nsp12

To investigate the conservation of the active amino acids in nsp12 interacting with FAC, NCBI BLAST was used to search for nsp12 homologs. Nine proteins, with 65%–90% sequence identity values to SARS-CoV-2 nsp12 from different sources

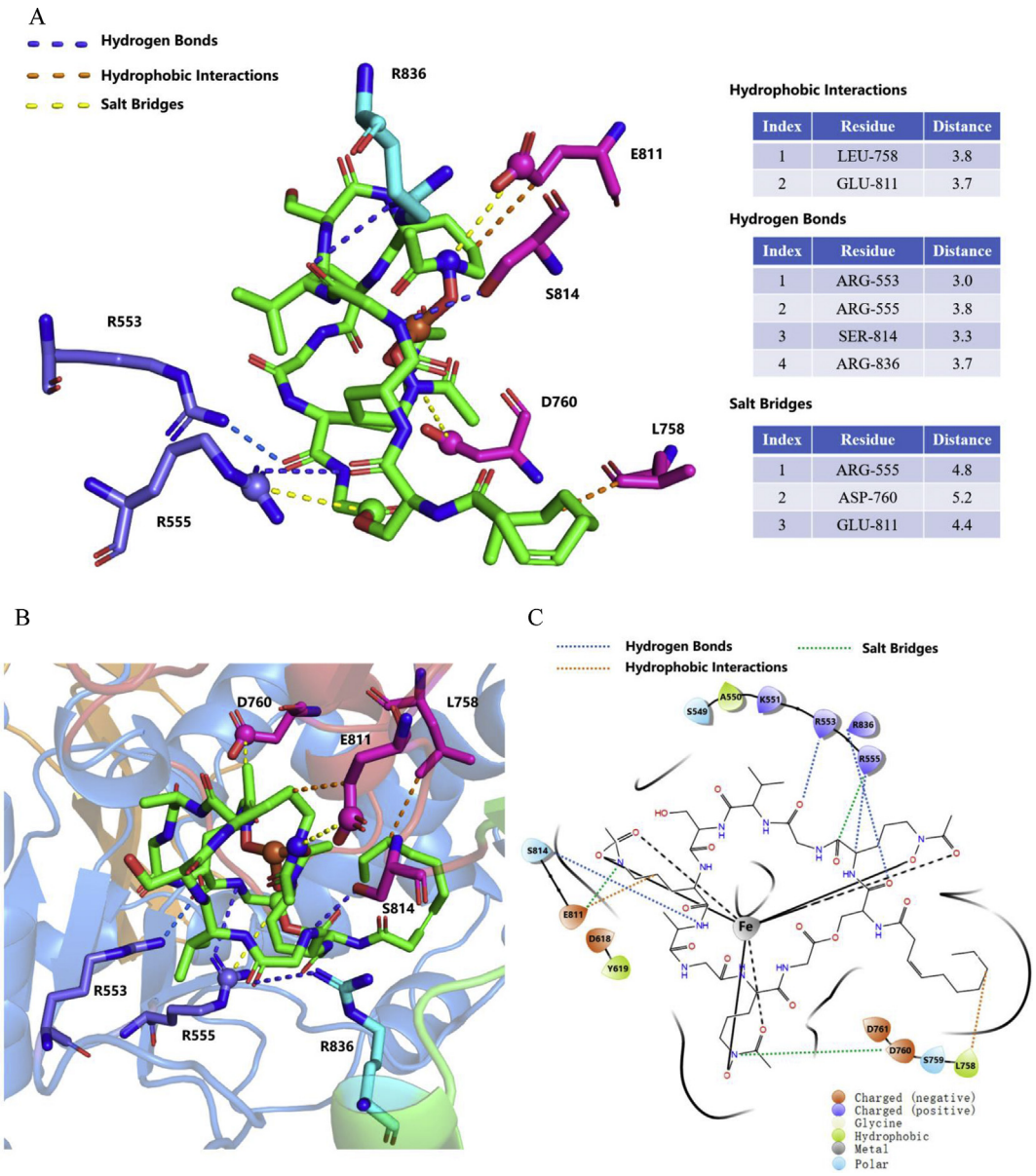
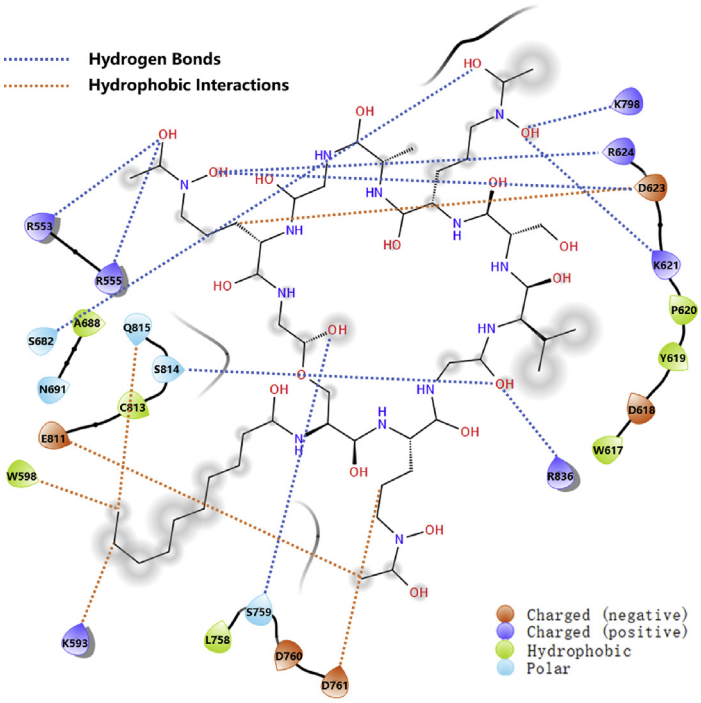


Fig. 4 Interactions established after docking ferrocin A—iron complex (FAC) against SARS-CoV-2 nsp12, showing (A) amino acid residues involved in the interactions, (B) best binding mode in the protein pocket, and (C) specific binding interactions of FAC with amino acids. The ligand is shown as sticks and nsp12 residues are labeled. Hydrogen bonds, hydrophobic interactions, and salt bridges are represented by blue dashed lines, orange dashed lines, and yellow (A) or green (C) dashed lines, respectively.

were obtained, including Betacoronavirus Erinaceus, *P. abramus* bat coronavirus, Hypsugo bat coronavirus, Middle East respiratory syndrome coronavirus, human betacoronavirus 2c Jordan, Rousettus bat coronavirus, SARS-like coronavirus WIV16, pangolin coronavirus, and bat coronavirus RaTG13. Multiple sequence alignment (MSA) analysis showed that the fingers and thumb subdomains of nsp12 were relatively conserved, with total counts of amino acid mutations less than 35%. In contrast, the mutation counts of the remaining subdomains of nsp12 were higher than 45%, among which, those of the palm subdomain exceeded 50% (Fig. 7, Figs. S4–S8). As shown in Fig. 7, the active amino acid residues in nsp12 that interacted with FAC, which were mainly located in the fingers and thumb subdomains, were highly conserved. Only the D760 in the palm subdomain mutated from ASP to GLU in the Hypsugo bat coronavirus, while remaining conserved among other homologous proteins. These results suggest that FAC also possesses high affinity for these nsp12 homologs.

Recently, several novel variants of SARS-CoV-2 have appeared and spread, including B.1.1.7, B.1.167, and B.1.351. Viral variants usually demonstrate enhanced infectivity or virulence, or even cause existing vaccines to fail. However, no mutations have been found in nsp12 thus far; taking the B.1.1.7 variant as an example, the sequences of nps12 in B.1.1.7 and SARS-CoV-2 strains were identical (data not shown). Thus, nsp12 is highly conserved and represents a promising and appropriate drug target for treating COVID-19.



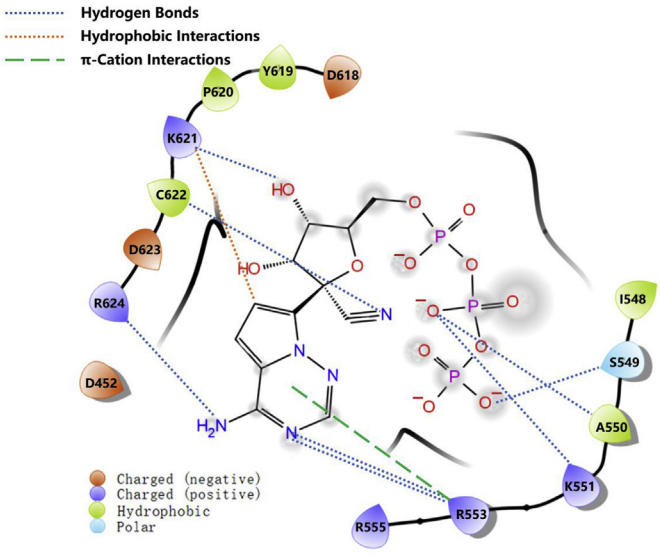
Hydrophobic Interactions

Index	Residue	Distance
1	ASP-623	3.7
2	LYS-593	3.7
3	TRP-598	3.7
4	ASP-761	4.0
5	GLU-811	3.7
6	GLN-815	4.0

Hydrogen Bonds

Index	Residue	Distance
1	ARG-553	2.9
2	ARG-555	3.7
3	LYS-621	2.8
4	ASP-623	2.9
5	ARG-624	3.8
6	SER-759	3.5
7	ASP-761	3.6
8	LYS-798	3.2
9	SER-814	2.9
10	ARG-836	3.9

Fig. 5 Interactions established after docking ferrocin A against SARS-CoV-2 nsp12. Hydrogen bonds and hydrophobic interactions are represented by blue dashed lines and orange dashed lines, respectively.



Hydrophobic Interactions

Index	Residue	Distance
1	LYS-621	3.77

Hydrogen Bonds

Index	Residue	Distance
1	SER-549	2.94
2	ALA-550	3.58
3	LYS-551	3.83
4	ARG-553	3.44
5	ARG-553	3.46
6	LYS-621	3.13
7	CYS-622	2.91
8	ARG-624	3.77

π-Cation Interactions

Index	Residue	Distance
1	ARG-553	3.73

Fig. 6 Interactions established after docking remdesivir triphosphate against SARS-CoV-2 nsp12. Hydrogen bonds, hydrophobic interactions, and π-cation stacking are represented by blue dashed lines, orange dashed lines, and green dashed lines, respectively.

Discussion

It has been more than a year and a half since COVID-19 pneumonia first emerged in Wuhan, China in December 2019. During this period, scientists worldwide have been racing to understand the pathophysiology of this disease and develop various vaccines and drugs in an attempt to prevent further outbreaks and establish effective treatments. However, so far, the number of newly infected people is more than 390,000 each day, with more than 6000 confirmed deaths, indicating that the battle between humans and SARS-CoV-2 remains difficult. Therefore, it is imperative to find more effective therapeutic options for this novel coronavirus.

In this study, we applied computer-aided approaches to assist with the effort in developing antiviral agents to fight COVID-19. Molecular docking is one of the most important

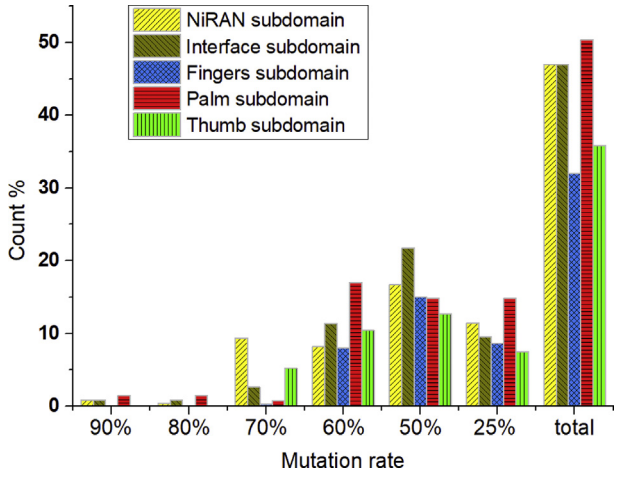


Fig. 7 Conserved sequence analysis of nsp12. Nine homologous proteins of nsp12 from different sources were selected for multiple sequence alignment, including Betacoronavirus Erinaceus, *Pipistrellus abramus* bat coronavirus, Hypsugo bat coronavirus, Middle East respiratory syndrome coronavirus, human betacoronavirus 2c Jordan, Rousettus bat coronavirus, SARS-like coronavirus WIV16, pangolin coronavirus, and bat coronavirus RaTG13. The X-axis represents the mutation rate of the amino acids in the same order in proteins. The Y-axis represents the ratio of the number of amino acids with the same mutation rate in one subdomain to the total number of amino acids in this subdomain.

bioinformatics tools used for drug screening and design. In addition to the synthesis of chemicals, the search for inhibitors among natural compounds is a novel strategy to derive antiviral drugs with minimal side effects. Among these, lipopeptides are of particular interest given their known medicinal properties, including antibacterial, antitumor, and antiviral activation (Table S1).

Nsp12 is a crucial enzyme in the RNA virus life cycle and has been the target of numerous viral infection treatments, such as for the Zika virus [29] and hepatitis C virus (HCV) [30]. The active site of nsp12 is highly conserved, with two surface-accessible ASPs in a beta-turn structure (Fig. 3). Additionally, nsp12 appears to be a primary target of the FDA-approved drug remdesivir. In this study, we performed molecular docking to test several short CLPs against this nsp12 enzyme and evaluated their binding properties alongside the two positive control compounds remdesivir and sofosbuvir (Fig. 1). Based on the binding energies, the best lipopeptides were discovered to be FAC (−9.1 kcal mol^{-1}) and ferrocin A (−8.3 kcal mol^{-1}), both of which can bind tightly to nsp12. To further explore the possible reasons for the differences in docking scores, we inspected the formed complexes using PLIP (Figs. 4–6). We found that Ferrocin A and FAC form numerous interactions with this crucial component of coronaviral replication, which is responsible for the high binding affinity, suggesting their potential to contradict the function of SARS-CoV-2. Furthermore, as they bound to nsp12 more efficiently than the FDA-approved drug, they may have a greater capability to inhibit and compromise the RNA polymerase function. However, future studies are needed to validate the molecular docking results and evaluate the therapeutic potential.

Human coronaviruses are long positive-sense viruses with single-stranded RNAs. Based on its nucleotide sequences, SARS-CoV-2 belongs to the genus *Betacoronaviruses*, which also include SARS and MERS human coronaviruses. We performed

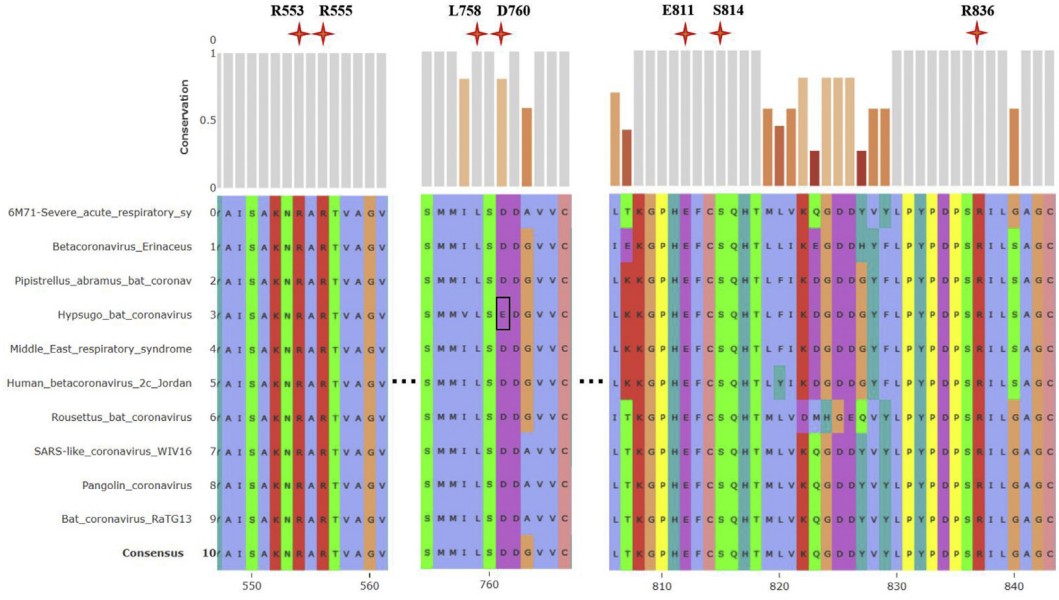


Fig. 8 Conservation analysis of the active amino acids in nsp12 interacting with ferrocin A–iron complex (FAC). Multiple sequence alignment (MSA) was performed for the nsp12 sequences from ten homologs as indicated. The active amino acids in nsp12 interacting with FAC are marked with stars in the MSA. The mutated D760 in the Hypsugo bat coronavirus is marked with a black box.

conservation analysis for ten nsp12 homologs (Figs. 4–8), and found that active amino acid residues in nsp12 that interacted with FAC were highly conserved and located mainly in the fingers and thumb subdomains (Figs. 7 and 8). These findings suggest that nsp12 is a promising drug target for this newly emerged coronavirus, and that FAC may also be capable of binding firmly to nsp12 homologs.

Lipopeptides are secondary metabolites of microorganisms that exist widely in nature, and are therefore relatively easy to obtain. Additionally, some lipopeptides have been reported to contribute to viral eradication, such as surfactin against enveloped viruses [31] or Semliki Forest virus [32], and fengcin against Pseudorabies virus [14], suggesting that lipopeptides serve as a reservoir of inhibitors to fight viruses. Another advantage of lipopeptides is their safety; indeed, they are frequently used in cosmetics [33], vaccines [34], and antifungal and antibacterial agents in food [35–37]. Furthermore, the mechanism of lipopeptide synthesis has been elucidated [17], and biocombinatorial synthesis of novel lipopeptides is possible [38]. Thus, the structure and composition of lipopeptides can be modified to produce novel candidates with better viral inhibition effects. Taken together, it is feasible to find and produce highly effective anti-COVID-19 drugs from lipopeptides. This article provides clues for the applications of such substances in SARS-CoV-2 viral eradication.

Conclusion

The global spread of COVID-19 has emphasized the urgency to develop effective vaccines and therapeutics. This study tested lipopeptides as possible inhibitors of SARS-CoV-2 using molecular docking. The results revealed that several lipopeptides could be accommodated in the cavity formed by the fingers, palm, and thumb subdomains of nsp12, similar to remdesivir. Among them, ferrocin A and its iron complex FAC exhibited excellent binding scores with high affinity. Sequence conservation analysis showed that the active amino acids of nsp12 interacting with FAC were highly conserved, indicating that FAC may also interact with nsp12 homologous proteins from similar viruses. Although the inhibitory effects of lipopeptides on SARS-CoV-2 need to be verified by further experiments, this study provides a novel basis for developing anticoronavirus treatments, and further optimizations of these compounds may result in therapeutic drugs that are capable of preventing newly emerging infections.

Data availability

The docking structures are available upon request from the corresponding author.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2021.11.010.

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