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Review article

Druggable targets of SARS-CoV-2 and treatment opportunities for COVID-19

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ABSTRACT

COVID-19 caused by the novel SARS-CoV-2 has been declared a pandemic by the WHO is causing havoc across the entire world. As of May end, about 6 million people have been affected, and 367 166 have died from COVID-19. Recent studies suggest that the SARS-CoV-2 genome shares about 80% similarity with the SARS-CoV-1 while their protein RNA dependent RNA polymerase (RdRp) shares 96% sequence similarity. Remdesivir, an RdRp inhibitor, exhibited potent activity against SARS-CoV-2 *in vitro*. 3-Chymotrypsin like protease (also known as M^{pro}) and papain-like protease, have emerged as the potential therapeutic targets for drug discovery against coronaviruses owing to their crucial role in viral entry and host-cell invasion. Crystal structures of therapeutically important SARS-CoV-2 target proteins, namely, RdRp, M^{pro}, endoribonuclease Nsp15/NendoU and receptor binding domain of CoV-2 spike protein has been resolved, which have facilitated the structure-based design and discovery of new inhibitors. Furthermore, studies have indicated that the spike proteins of SARS-CoV-2 use the Angiotensin Converting Enzyme-2 (ACE-2) receptor for its attachment similar to SARS-CoV-1, which is followed by priming of spike protein by Transmembrane protease serine 2 (TMPRSS2) which can be targeted by a proven inhibitor of TMPRSS2, camostat. The current treatment strategy includes repurposing of existing drugs that were found to be effective against other RNA viruses like SARS, MERS, and Ebola. This review presents a critical analysis of druggable targets of SARS CoV-2, new drug discovery, development, and treatment opportunities for COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic faced by the global community nearly a century after the Spanish flu [1]. The current pandemic is due to a novel beta coronavirus, SARS-CoV-2, taxonomically belonging to the coronaviridae family, other members of which are known to cause respiratory infections in humans [2]. The rapid torrent of COVID-19 infections around the globe at an alarming rate is due to the estimated basic reproductive number R0 value between 1 and 3, predicted to be higher than the SARS-CoV-1, with the main transmission route being respiratory droplets and contact. Based on phylogenetic analysis, the natural host of the virus was found in bats, but to date, there has not been any confirmation regarding the intermediate host [3,4]. The virus was found to have been first identified in the city of Wuhan, Hubei province China in December 2019, and was declared as a pandemic by the WHO on March 11 and, as of May end, about for 6 million have been affected, and 367 166 have died from COVID-19. [5,6].

Broadly pyrexia, cough, hemoptysis, diarrhea, dyspnoea, muscle soreness, lymphopenia, dysosmia, and dysgeusia are the symptoms associated with COVID-19, but certain symptoms atypical from other coronavirus infections are to be acknowledged. They include the presence of Gastro-Intestinal distress in some of the cases, and clinical manifestations of lower respiratory tract infection, which are to be

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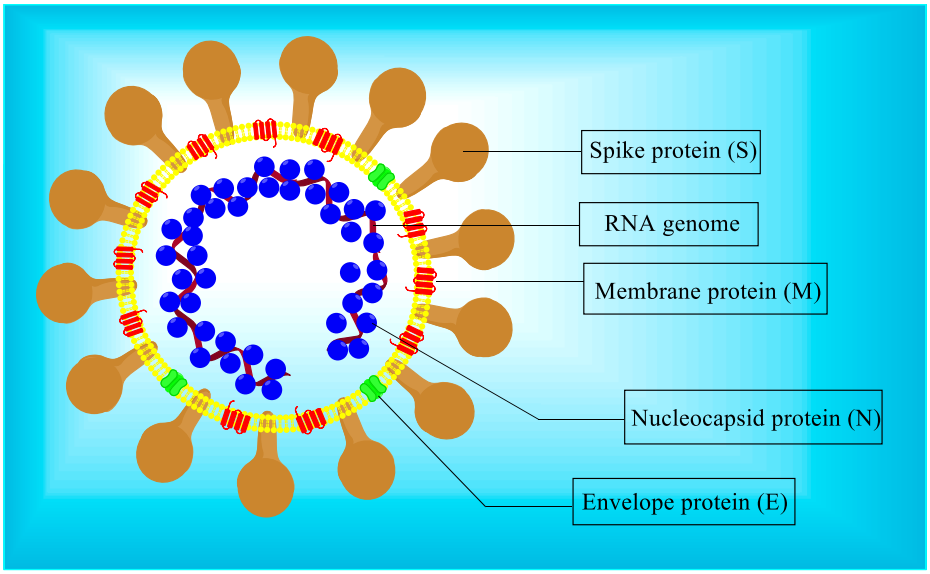


Fig. 1. Structure of SARS-CoV-2.

addressed [7,8]. Current diagnostic approaches range from nucleic acid assays- Reverse transcriptase- quantitative Polymerase Chain Reaction (RT-qPCR), Computed Tomography (CT) scans to immunological detection kits [9].

SARS-CoV-2 is an enveloped, single-stranded positive-sense RNA virus. The viral RNA genome contains 29,903 nucleotide bases and has ten open reading frames (ORF). The ORF1ab encodes for the large replicase polyprotein PP1ab, which is cleaved by Papain Like protease (PLpro) and 3-Chymotrypsin like Protease (3CLpro) to non-structural proteins (nsps) 1–16. The structural proteins S, N, E, M, and auxiliary proteins are encoded by ORF2-10 [10,11] (Figs. 1 and 2).

Entry of the virus into the host's cells is aided by the attachment of the Spike protein (S) onto the host's Angiotensin Converting Enzyme-2 (ACE-2) receptor resulting in conformational changes that lead to the fusion of viral and cell membranes. Inside the endocytic vesicle, pH-dependent activation of cathepsin L leads to priming of the spike proteins that result in the release of the viral RNA genome into the cytoplasm (endocytic pathway). Alternatively, Transmembrane Protease Serine type 2 (TMPRSS2) is also involved in priming of the spike proteins at the cell surface, enabling entry of the viral genome (non-endocytic pathway). Once inside the cytoplasm, the ORF1ab fragment of the viral RNA genome is translated into the replicase polyprotein PP1ab, which is acted upon by viral enzymes like PLpro and 3CLpro (M^{pro}) to produce nsps 1–16 including RdRp and helicase that play a crucial role in the replication of the virus. The nsps assemble to form the replication-transcription complex. The positive strand of RNA genome is transcribed to produce a negative-strand template for the synthesis of the new viral RNA genome. The transcribed mRNAs are translated to produce structural proteins S, M, E, and N. The viral RNA genome along with the N protein interacts with other structural proteins, and the assembled virions are delivered outside of the cell via exocytosis (Fig. 3).

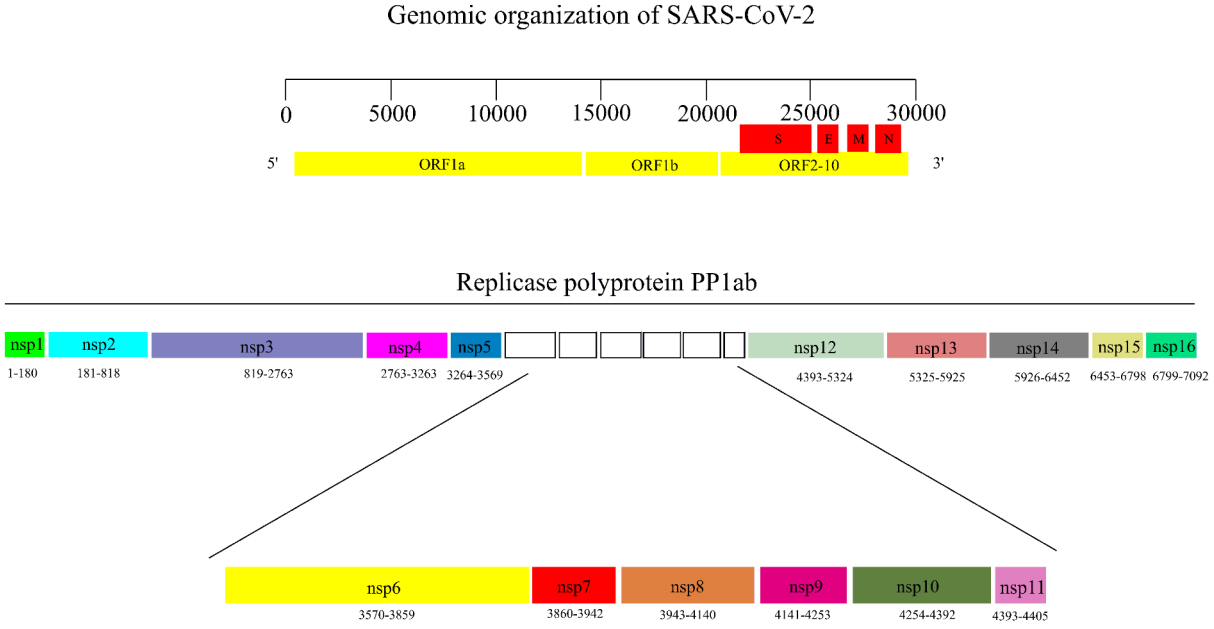


Fig. 2. (A) Genomic organization of SARS-CoV-2. (B) non-structural proteins 1–16. (the numbers below each of the nsps represent the amino acid residues). **ORF:** Open reading frame, **S:** spike protein, **E:** Envelope protein, **N:** Nucleocapsid protein, **M:** Membrane protein, **nsp:** non-structural protein.

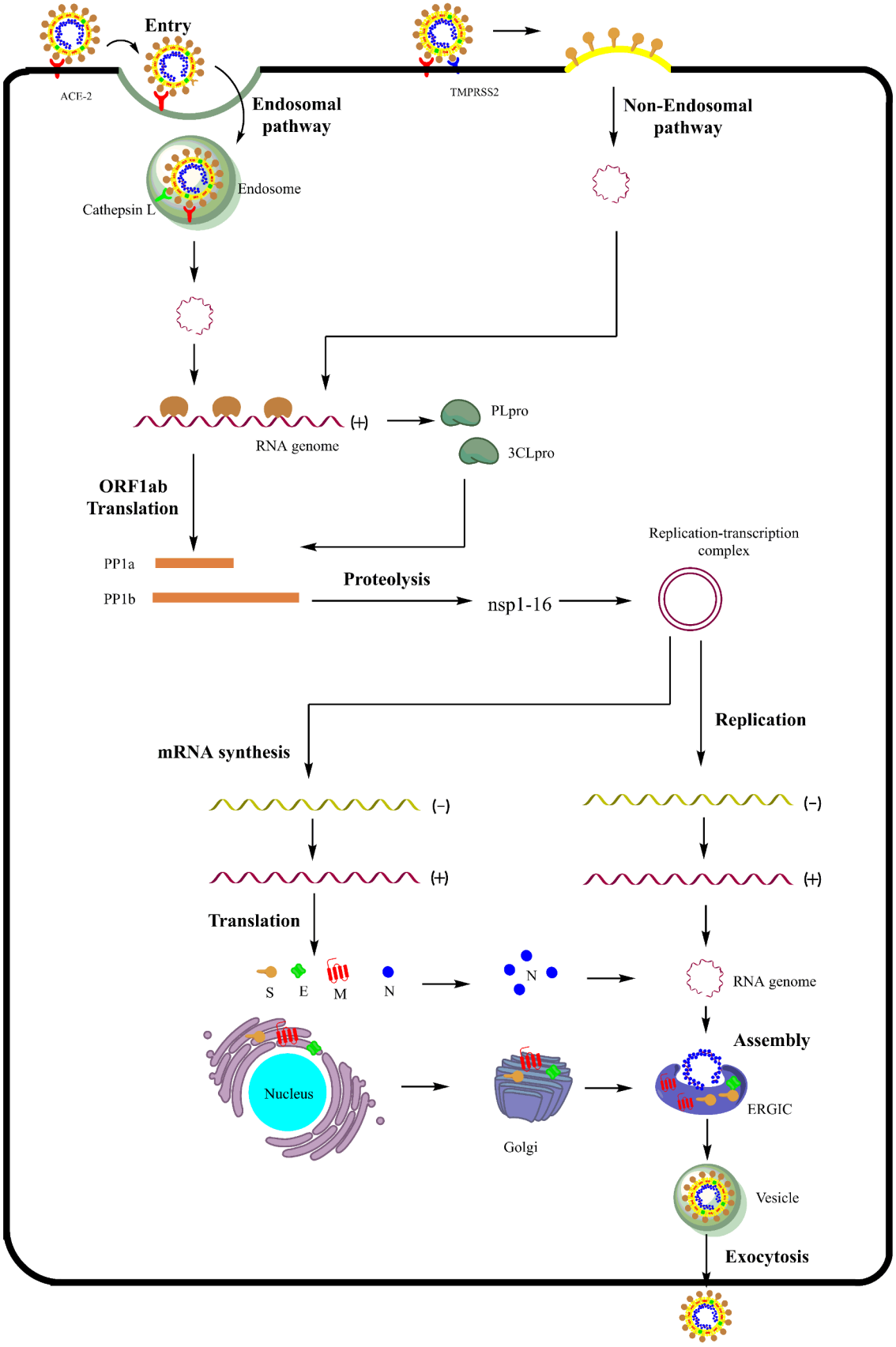


Fig. 3. The life cycle of SARS-CoV-2. **ACE-2:** Angiotensin converting enzyme-2, **TMPRSS2**: Transmembrane protease serine 2, **PLpro:** Papain-like protease, **3-CLpro:** 3-Chymotrypsin-like protease, **ORF1ab:** Open reading frame 1ab, **PP1ab:** Polyprotein 1ab, **nsp:** non-structural protein, **S:** spike protein, **E:** Envelope protein, **N:** Nucleocapsid protein, **M:** Membrane protein, **ERGIC:** Endoplasmic reticulum-Golgi intermediate compartment.

2019-nCoV-HR1P ANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQ

2019-nCoV-HR2P DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQEL

EK1 SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL

EK1P SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL — PEG4-C-Palm

EK1C SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL — PEG4-C-Chol

Fig. 4. Peptide viral entry inhibitors.

1.1. Approaches to anti-coronavirus drug discovery

In general, three approaches were followed for the discovery and treatment options for the pathogenic coronaviruses- SARS and MERS [12]. Similar approaches were also being followed for the current pathogenic SARS-CoV-2. The first approach is the testing of broad-spectrum antiviral agents (mostly drugs) that have been used or previously tested for other viral infections by using standardized assays that measures the effects of these compounds on virus yields, infection rates, virus entry, and plaque formation. Some of the drugs identified via this approach during the previous two epidemics- SARS and MERS include ribavirin, Interferon-α, β, and γ [13–15]. A similar approach for the current pandemic has also identified antiviral agents like remdesivir, lopinavir/ritonavir, favipiravir, etc. A significant advantage of this approach is that the pharmacodynamic, pharmacokinetic, toxicity, dosing, etc. of the drugs will be readily available, thus reducing significant time in the drug discovery process. The second approach to the anti-coronavirus drug discovery involves the *in-silico* screening of chemical libraries that contains a large number of compounds. Rapid, high-throughput virtual screening (HTVS) of a large number of compounds is possible via this approach, which can be further validated by suitable antiviral assays. Drugs or investigational molecules belonging to different categories have been identified for the past epidemics- SARS and MERS as well for the current pandemic [15–19]. The major con associated with this approach is that, although the identified compounds exhibit antiviral activity, they are associated with several side effects. The third approach is the *de-novo* design and development of novel inhibitors based on the biophysical and genomic understanding of the individual coronaviruses. Examples include the development of antiviral peptides targeting the spike proteins, development of novel inhibitors targeting different viral enzymes, development of inhibitors targeting host cellular proteases., development of monoclonal antibody (MAbs). Theoretically, this approach will lead to potent compounds, but the development of these compounds usually takes years, as they undergo the entire drug discovery process.

2. Druggable molecular targets of SARS-CoV-2

2.1. Spike proteins of novel SARS-CoV-2

The entry of SARS-CoV-2 depends upon the binding of its spike protein to the cell surface receptor. The spike proteins of SARS-CoV-2 are 1273 amino acids long and structurally consists of two domains- the *N*-terminal S1 domain for binding to the cellular receptor and C-terminal S2 domain for fusion with the cell membrane [20]. The S1 subunit (aa 14-685) encompasses an *N*-terminal domain (aa 14-305) and a receptor-binding domain (RBD) (aa 319-541) [21,22]. The RBD consists of core and external sub-domains responsible for forming trimer particle and for interaction with the receptor, respectively [23,24]. The S2 sub-domain encompasses Heptad repeat 1 (HR1), Heptad repeat 2 (HR2), Fusion peptide (FP), and transmembrane domain. After binding of the S1 domain of spike protein to the host receptor, conformational changes take place in the S2 domain. The heptad repeat domains, HR1 and HR2, interact with themselves to form a six-helix bundle fusion core bringing about the close association of cellular and viral membranes for fusion [22]. Xia et al. designed novel peptides based on the HR1 and HR2 domains as fusion inhibitors [22] similar to the approach that was undertaken against SARS-CoV and MERS-CoV [25–27]. The two peptides designed were designated as 2019-nCoV-HR1P and 2019-nCoV-HR2P. 2019-nCoV-HR2P was shown to potently inhibit fusion in 2019-nCoV spike mediated cell-cell fusion assay with a half-maximal inhibitory concentration (IC_{50}) value of 0.18 μM. EK1, reported previously as a pan CoV fusion inhibitor targeting the HR1 domain [27], also showed potent fusion inhibition (IC_{50} = 0.19 μM). Furthermore, 2019-nCoV-HR2P and EK1 were also found to effectively inhibit 2019-nCoV pseudovirus infection in 293 T cells with IC_{50} values of 0.98 μM and 2.38 μM, respectively (Fig. 4).

Following the initial findings, Xia et al. and others designed a series of derivatives based on EK-1 [28]. EK-1 was covalently linked with cholesterol (designated as EK1C) and palmitic (designated as EK1P) at their C-terminus end with a polyethylene glycol (PEG) spacer (Fig. 4). Both the peptides exhibited potent fusion inhibition in SARS-CoV-2 mediated cell-cell fusion (IC_{50} = 48.1 and 69.2 nM for EK1C and EK1P, respectively). Based on the inhibitory potential of EK1C, further derivatives were designed with glycine / serine-based linkers (GSG) and PEG-based spacers. The peptides were designated as EK1C1-EK1C7 (Table 1). The presence of the linker/spacer and length of the spacer influenced the activity, especially increased the activity of these lipopeptides. The most potent lipopeptide, EK1C4, contained the optimal five residues linker/spacer GSGSG-PGE4. EK1C4 also exhibited potent activity against SARS-CoV-2 pseudovirus infection and live SARS-CoV-2 infection *in vitro* with IC_{50} values of 15.8 nM and 36.5 nM, respectively.

Table 1
Derivatives of EK1C.

DESIGNATION	PEPTIDE	LINKER	LIPID	INHIBITION OF SARS-CoV-2 MEDIATED CELL-CELL FUSION (IC_{50} in nM)	INHIBITION OF SARS-CoV-2 PSEUDOVIRUS INFECTION (IC_{50} in nM)
EK1C1	EK1		CHOLESTEROL	56.8	480.3
EK1C2	EK1	GSG	CHOLESTEROL	48.2	418.6
EK1C3	EK1	GSG-PGE4	CHOLESTEROL	10.6	86.8
EK1C4	EK1	GSGSG-PGE4	CHOLESTEROL	1.3	15.8
EK1C5	EK1	GSGSG-PGE8	CHOLESTEROL	3.1	31.3
EK1C6	EK1	GSGSG-PGE12	CHOLESTEROL	3.9	77.4
EK1C7	EK1	GSGSG-PEG24	CHOLESTEROL	3.9	84.4

SBP-1 IEEQAKTFLDKFNHEAEDLFYQS

SBP-2 TFLDKFNHEAED

Fig. 5. Peptide viral entry inhibitors.

Furthermore, *in vivo* studies were conducted to evaluate the prophylactic and post-infection potential of EK1C4 on the HCoV-OC43 infection mouse model. The studies revealed that EK1C4 was effective prophylactically up to 12 h before challenging with the infection at a dose of 0.5 mg/kg intranasally, suggesting good stability and half-life of the peptide. EK1C4 also afforded protection to mice when administered at 0.5 h post-infection [28]. Considering these results together, EK1C4 has all the potential to be a drug candidate for treating COVID-19.

Similarly, Zhang et al. designed and synthesized two peptides streptavidin-binding peptide-1 (SBP-1) and streptavidin-binding peptide-2 (SBP-2) based on the sequence of ACE-2 alpha-1 helix peptidase domain targeting RBD of the SARS-CoV-2 Spike protein in an attempt to disrupt the interaction between SARS-CoV-2- RBD and ACE-2 receptors (Fig. 5) [29]. Although SBP-2 did not show any affinity towards SARS-CoV-2 RBD, SBP-1 was found to potently bind to the SARS-CoV-2 RBD with a K_D value of 47 nM, which was comparable to the binding of ACE-2 to SARS-CoV-2 RBD (K_D = 14.7 nM).

2.2. Extracellular proteases

Entry and invasion of SARS-CoVs into the host cells are facilitated through the concerted action of membrane proteases. These proteases have been confirmed as valuable therapeutic targets, and the inhibitors have been identified as promising drug leads against SARS-CoV-2.

2.2.1. Angiotensin converting enzyme-2 (ACE-2)

Coronaviruses make use of the host receptors as a doorway for entry into the host cell. Spike proteins of MERS-CoV use human dipeptidyl peptidase-4 (DPP-4) enzymes as its receptor for attachment [30] while SARS-CoV uses human angiotensin converting enzyme-2 (ACE-2) as a gateway for entry into the host cell [31]. Recent studies have shown that spike proteins of SARS-CoV-2 bind to the human ACE-2 for entry into the host cell, thus making ACE-2 a druggable target for COVID-19 [32,33]. However, the simplicity ends there. ACE-2, apart from being used as a receptor for cellular entry by SARS coronaviruses, has several protective functions. Angiotensin I is synthesized from angiotensinogen, a process catalyzed by renin. Angiotensin I then serve as a substrate for the two enzymes Angiotensin converting enzyme-1 (ACE-1) and Angiotensin converting enzyme-1 (ACE-2). Angiotensin I is converted to an octapeptide angiotensin II by ACE-1 and a heptapeptide Angiotensin 1-7 by ACE-2. Angiotensin II and Angiotensin 1-7 have opposing effects on the vascular dynamics, the former being vasoconstrictive in nature and latter being vasodilative in nature, mediated by binding to their receptor Angiotensin-1 (AT-1) and Mas, respectively. Thus ACE-2/Ang 1-7/Mas receptor complex serves as the suppressive axis of the classical renin-angiotensin system (RAS) [34]. Chronic administration of Angiotensin Receptor Blockers (ARBs) leads to the upregulation of ACE-2 [35,36]. Both SARS-CoV and SARS-CoV-2 use ACE-2 as the receptor for binding, and hence it might sound absurd to suggest ARBs for SARS patients. Studies have shown downregulation in ACE-2 levels following viral attachment and fusion. This leads to the elevation of Angiotensin I levels due to the enhanced action of ACE-1 and repressed action of ACE-2, resulting in catastrophic changes in lung physiology mediated via AT-1 receptors [37]. Therefore, treating COVID-19 patients with ARBs, although paradoxical, may do more good than harm to the lungs. However, it is too early to recommend such therapy for COVID-19 due to its complexity. Currently, no molecule in the clinical or preclinical trial is known to inhibit ACE-2. The drug discovery directed against it for treating COVID-19 may not be a fruitful approach considering its protective effects on the lungs. However, a rational approach would be to use a recombinant form of soluble ACE-2 that can act as a decoy receptor and bind to the spike proteins of SARS-CoV-2 to slow its entry into the host cell as well as to afford protection to the lungs [38]. Ou et al. demonstrated that the entry of SARS-CoV-2 into 293/hACE2 cells was significantly suppressed by the pre-incubation of the pseudoviruses with a soluble form of hACE2 at 10 and 50 μg/ml [39].

2.2.2. Transmembrane protease serine 2 (TMPRSS2)

As previously described, spike proteins of SARS-CoV-2 bind to the ACE-2 receptor in order to enter into the host cell. However, other players are also associated with the entry of the virus into the host cell. Transmembrane protease serine 2 (TMPRSS2) is a host cellular protease encoded by the TMPRSS2 gene. TMPRSS2 is predominantly localized in the cell membrane of the lung's epithelial cells and aids in priming the spike proteins, a process that results in the fusion of viral and cellular membranes. Previous results have shown that the priming of spike proteins of SARS-CoV by TMPRSS2 is crucial for the entry of the virus into the host cells [40,41]. Recently, it was shown that entry of the novel SARS-CoV-2 also depends upon the priming of its spike proteins by TMPRSS2 and was blocked by a clinically known inhibitor of TMRSS2, camostat [33]. Hence, TMPRSS2 based therapeutics could prove to be useful armory in the war against COVID-19. Recently, Rensi et al. developed seven protein models of TMPRSS2 based on homology modeling and screened them against the clinically known serine protease inhibitors [42]. The top six molecules (anticoagulants with significant and potentially dangerous clinical effects and side effects), along with their average docking scores (kcal/mol), are given in Fig. 6. An advantage of screening clinical molecules is that the safety and adverse effects of these molecules would have been already established, and priority thus would be to prove their efficacy. Further, *in vitro* studies of these molecules are currently underway to validate the predictions.

2.2.3. Furin

Furin belonging to the family of proprotein convertases, an enzyme that is responsible for activating precursor proteins like hormones, growth factors, cell surface receptors [48]. Furin selectively cleaves the proteins at multi-basic motifs of the sequence R-X-K/R-R↓ [49]. Furin is also known to activate fusion proteins of viruses like Human immunodeficiency virus (HIV), Ebola, highly pathogenic avian influenza A virus (HPAIV) as well as human coronaviruses like MERS and HCoV-OC43 [49–52]. However, no such activation is reported for SARS-CoV. Recently, the genetic sequence analysis of SARS-CoV-2 S protein identified a polybasic cleavage site that may be accessible for proteases like furin, making it distinct from SARS-CoV [53–55]. Four amino acid sequence (RRAR) was found to be present in the S1/S2 site of SARS-CoV-2 S protein, thus corresponding to a canonical furin cleavage site. Hence, furin can also prime SARS-CoV-2 S proteins and aid in the entry of the virus. Bestle et al. and others demonstrated that furin activates SARS-CoV-2 S protein [56]. Furin was shown to cleave the S1/S2 site in the S protein of SARS-CoV-2 in HEK293 cells, which was decreased in the presence of furin inhibitor MI-1851 (Fig. 7). They also demonstrated that TMPRSS2 cleaves the S2′ site of SARS-CoV-2 S protein. Inhibition of either of these enzymes was shown to inhibit the replication of the virus in Calu-3 cells while inhibition of cathepsin L did not have any effect on the replication indicating that furin and TMPRRS2 are required for S protein activation while cathepsin L may or may not have a role in the activation of S protein in Calu-3 cells [56]. Thus, furin is essential for the multiplication of SARS-CoV-2 in airway epithelial cells and hence provides a favorable target of further exploration.

2.3. Intracellular proteases

After the virus enters into the host cells, some of the critical

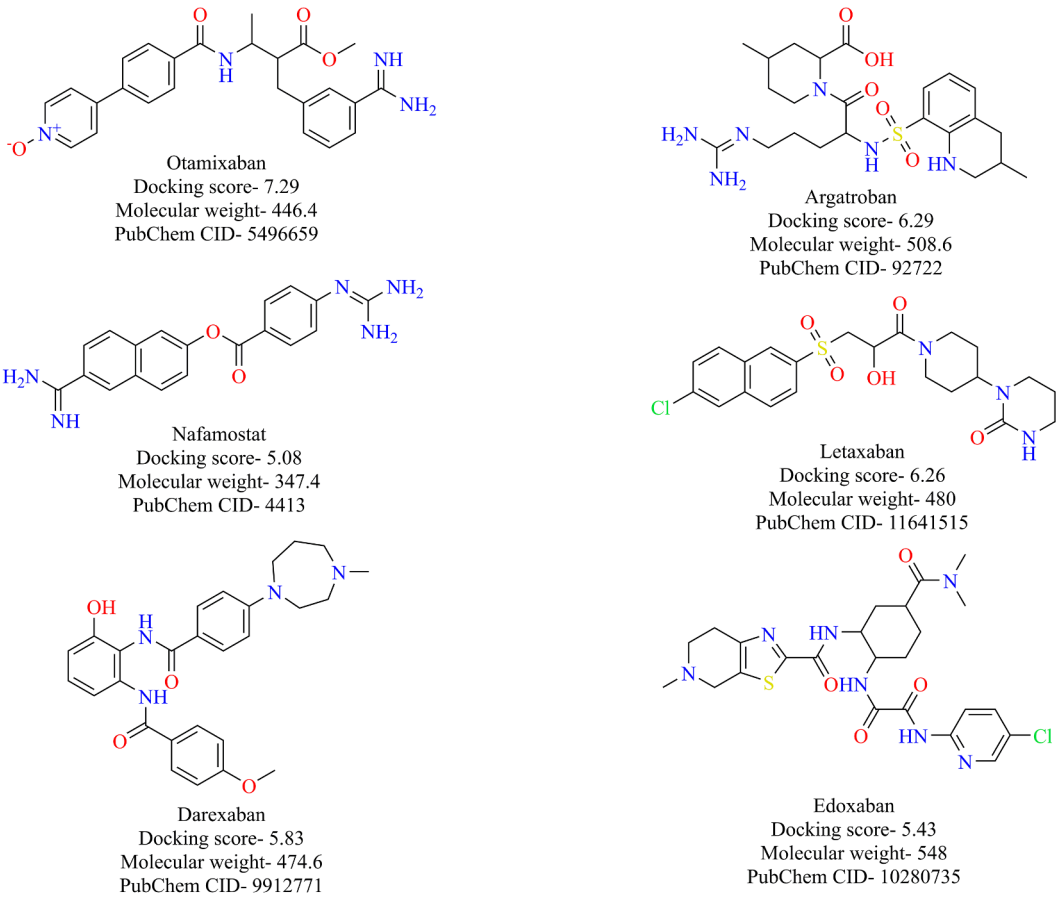


Fig. 6. Structure of reported TMPRSS2 inhibitors.

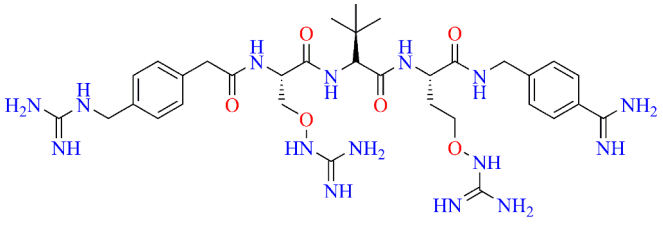


Fig. 7. Structure of furin inhibitor- MI-1851.

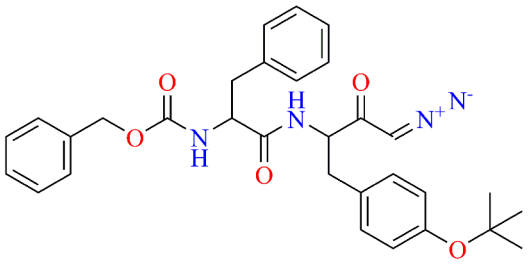
processes regarding endosomal proliferation and assembly of viral proteins require the processing of these proteins through intracellular proteases. These processes are essential for the proliferation of the virus. Disruption of these process through target protease inhibitors breaks the cyclic of virus proliferation and have been suggested as the antiviral drug targets.

2.3.1. Cathepsin L

Cathepsins are cysteine proteases that play a crucial role in protein catabolism in the endosomes and lysosomes. The ubiquitously expressed cathepsin L plays a fundamental part in the entry of the SARS-CoV into the host cells [43,44]. Once the virus enters the endosomes after binding onto the ACE-2 receptor, the spike proteins of SARS-CoV are activated by the pH-dependent cathepsin L, which results in the fusion of virus and endosomal membranes releasing the genetic material of virus into the cytoplasm [45]. SID 26681509, Z-Phe-Tyr(*t*-Bu)-diazomethylketone, and E-64-d are some of the well-known cathepsin L inhibitors (Fig. 8). Teicoplanin, a glycopeptide antibiotic, was also shown to inhibit the entry of SARS-CoV and MERS-CoV by blocking cathepsin L [46]. It was also shown to inhibit the entry of SARS-CoV-2 pseudoviruses [47]. Ou et al. demonstrated that cathepsin L is specifically required for the entry of SARS-CoV-2 S pseudovirus into 293/hACE2 cells. Broad-spectrum cathepsin inhibitor, E-64-d, reduced the SARS-CoV-2 S pseudovirus entry by 92.5% and cathepsin L inhibitor, SID 26681509, reduced the entry by about 76% while cathepsin B inhibitor, (CA-074), had no significant effect on the virus entry [39]. Taken together, the priming of spike proteins of SARS-CoV-2 is dependent on cathepsin L in the endosomes, making it an attractive therapeutic target for further exploration.

2.4. RNA dependent RNA Polymerase (RdRp)

RNA dependent RNA Polymerase (RdRp) is an enzyme that is responsible for the replication of RNA from an RNA template. RdRp is one of the nsp (nsp-12) that play an essential role in the life cycle of RNA viruses like hepatitis C virus, Zika virus, and coronaviruses [57,58]. In SARS-Cov-1 RdRp (nsp-12) functions as a tripartite polymerase complex with nsp-7 and nsp-8. The nsp7 and nsp8 activate and confer processivity to the RNA-synthesizing activity of nsp12. This tripartite polymerase complex further associates with nsp-14, which confers proofreading exonuclease function [59]. Remarkably, RdRp of SARS-CoV and SARS-CoV-2 share 96% sequence similarity [60]. Therefore, it is very likely that the agents that target RdRp of SARS-CoV might also target the RdRp of SARS-CoV-2. Some of the compounds that target RdRp of SARS-CoV include favipiravir, ribavirin, penciclovir, galidesivir, remdesivir, among others (Fig. 9) [61]. Recently, ribavirin, favipiravir, penciclovir, and remdesivir were shown to inhibit SARS-CoV-2 *in vitro*, probably due to their inhibitory activity towards RdRp [62].



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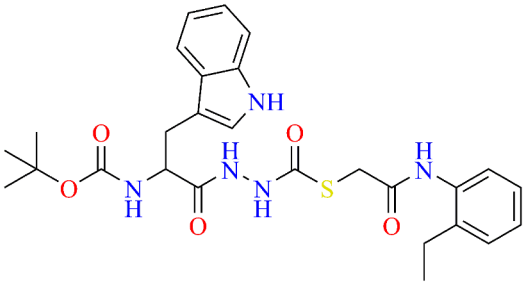

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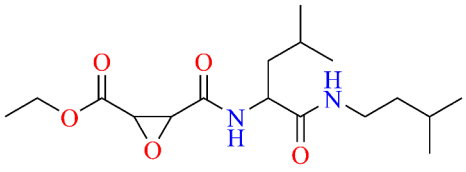

E-64-d
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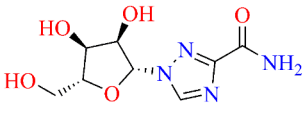
Fig. 8. Structure of reported cathepsin L inhibitors.



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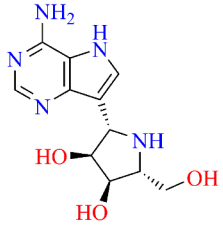

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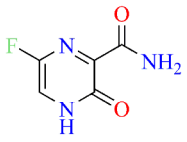

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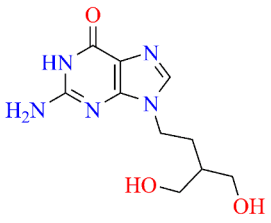
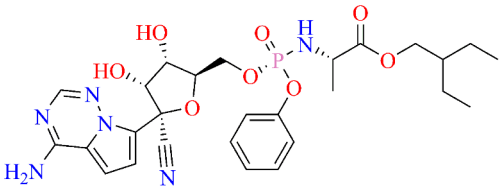
PubChem CID- 492405



Penciclovir
Molcular weight- 253.2
PubChem CID- 135398748



Remdesivir
Molecular weight- 602.6
PubChem CID- 121304016

Fig. 9. Antiviral drugs targeting RdRp functions.

Several computer-aided molecular modeling studies have been done to find potential candidates that target RdRp of SARS-CoV-2. Elfiky et al. evaluated the effectiveness of antiviral agents to bind to SARS-CoV-2 RdRp through a combination of homology modeling and molecular modeling studies [63]. The structures of the antiviral agents, along with their docking scores in kcal/mol, are given in Fig. 10. Datta et al. constructed a model of SARS-CoV-2 RdRp using sequence alignment and homology modeling and screened the model against antiviral drugs. Beclabuvir, an HCV RdRp inhibitor, was shown to bind effectively to SARS-CoV-2 with a docking score of −9.95 kcal/mol and inhibition constant of 51.03 nM [64]. Recently, the structure of RdRp of SARS-CoV-2 was resolved in complex with nsp-7 and nsp-8 by the cryo-EM [65]. The overall architecture of the SARS CoV-2 nsp12/nsp7/nsp8 complex was observed to be similar to the RdRp complex of SARS-CoV-1. Binding of remdesivir diphosphate, the RdRp inhibitor under clinical trials for the treatment of COVID-19, to SARS CoV-2 nsp12, was investigated based on modeling with sofosbuvir bound to hepatitis C virus (HCV) ns5b. The nsp12 of the SARS CoV-2 virus showed the highest similarity with the Apostate of ns5b. Sofosbuvir, a nucleoside prodrug, targets HCV ns5b polymerase and selectively binding catalytic site of

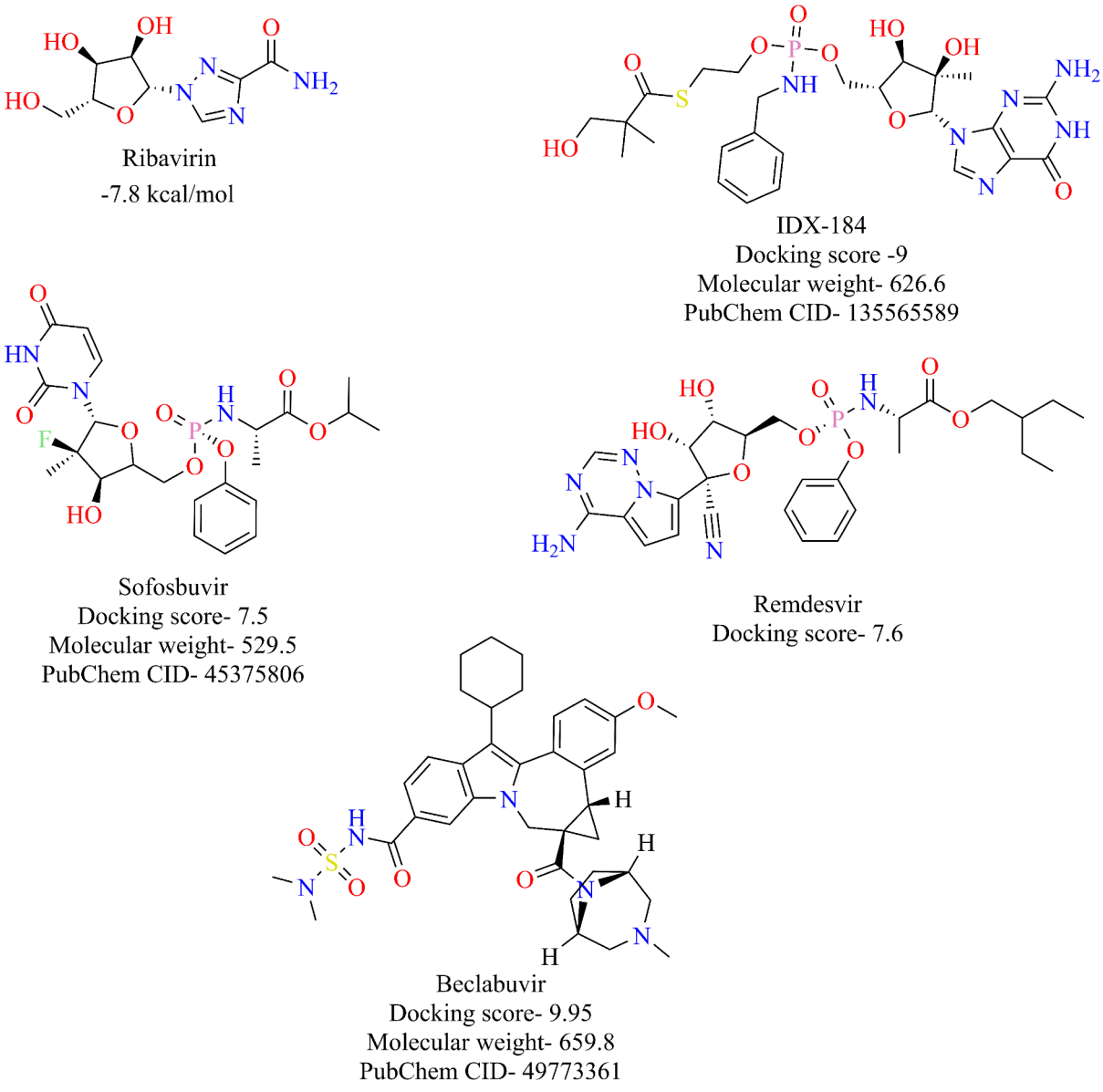


Fig. 10. Structure of reported RdRp inhibitors along with their docking scores.

the HCV polymerase. Sofosbuvir has been approved for the treatment of chronic HCV infection [66]. The catalytic site of SARS CoV-2 nsp13 shows remarkable structural similarity to HCV ns5b polymerase. The antiviral RdRp inhibitors (Fig. 9) are likely to target SARS CoV-2 RdRp and are excellent drug candidates for the treatment of COVID-19.

2.5. 3-Chymotrypsin like protease or main protease (3CLpro or M^{pro})

3-Chymotrypsin like Protease or Main protease (M^{pro}) is one of the two crucial proteolytic enzymes that help in cleaving the replicase polyprotein 1ab in SARS-CoV-2. The M^{pro}, which is also known as non-structural protein 5 (nsp5), is 306 amino acid long and is translated from the Orf1ab of viral RNA genome[67]. M^{pro} is known to cleave the replicase polyprotein at 11 specific sites, the recognition sites being Leu-Gln$_{\downarrow}$(Ser, Ala, Gly), to release 12 nsps (nsp4, nsp6-16) that are essential for viral replication as well as viral assembly [10,67]. Structurally, M^{pro} is a dimer, and each monomer has three domains- domain I, which includes residues 8-101, domain II which includes residues 102-184 and domain III, which includes residues 201-303. The domains II and III are connected through the loop region that includes 185-200 residues. The substrate-binding site containing the catalytic dyad (Cys145-His41) is located between domain I and domain II [19]. The functional importance of the enzyme in the life cycle of SARS-CoV-2 and the fact that no human proteases possess similar cleavage recognition site makes M^{pro} appealing target for drug discovery. Zhang et al. reported the optimization of α-ketamides for activity against the M^{pro} of SARS-CoV-2 [68] (Fig. 11). The lead compound **1** was found to be active against the SARS-CoV M^{pro} in picomolar concentration [69]. However, short half-life in plasma and unfavorable pharmacokinetic profile of compound **1** prevented further development and study. In order to improve its pharmacokinetic profile, the amide linkage between *P*2-*P*3 was replaced with a pyridine ring for improved metabolic stability, and the cinnamoyl moiety was replaced with a butyloxycarbonyl (BOC) group for increased solubility and reduced plasma protein binding. However, the better pharmacokinetic profile met with a decreased activity against the M^{pro} of SARS-CoV-2 of compound **2** (IC_{50} = 2.39 μM) when compared with compound **1** (IC_{50} = 0.18 μM). In the next modification, *P*2 cyclohexyl moiety was replaced with a smaller cyclopropyl moiety in order to improve the antiviral activity. The resulting compound **3** inhibits M^{pro} of SARS-CoV-2 with an IC_{50} of

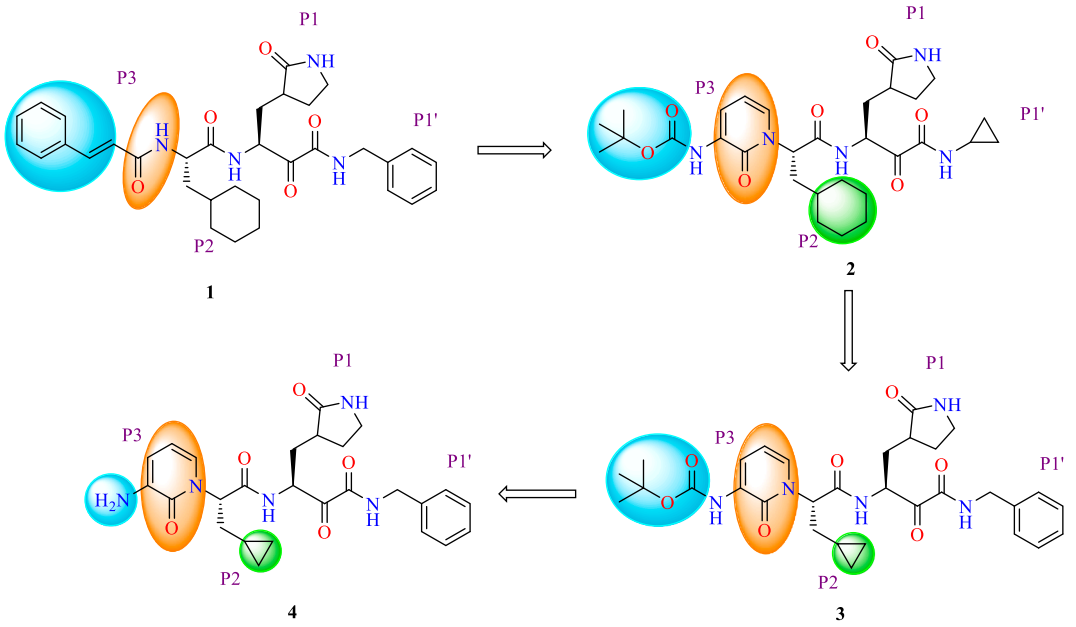


Fig. 11. Lead optimization of α-ketamides as M^{pro} inhibitor (Color representation indicates groups that are modified during the lead optimization of compound **1**).

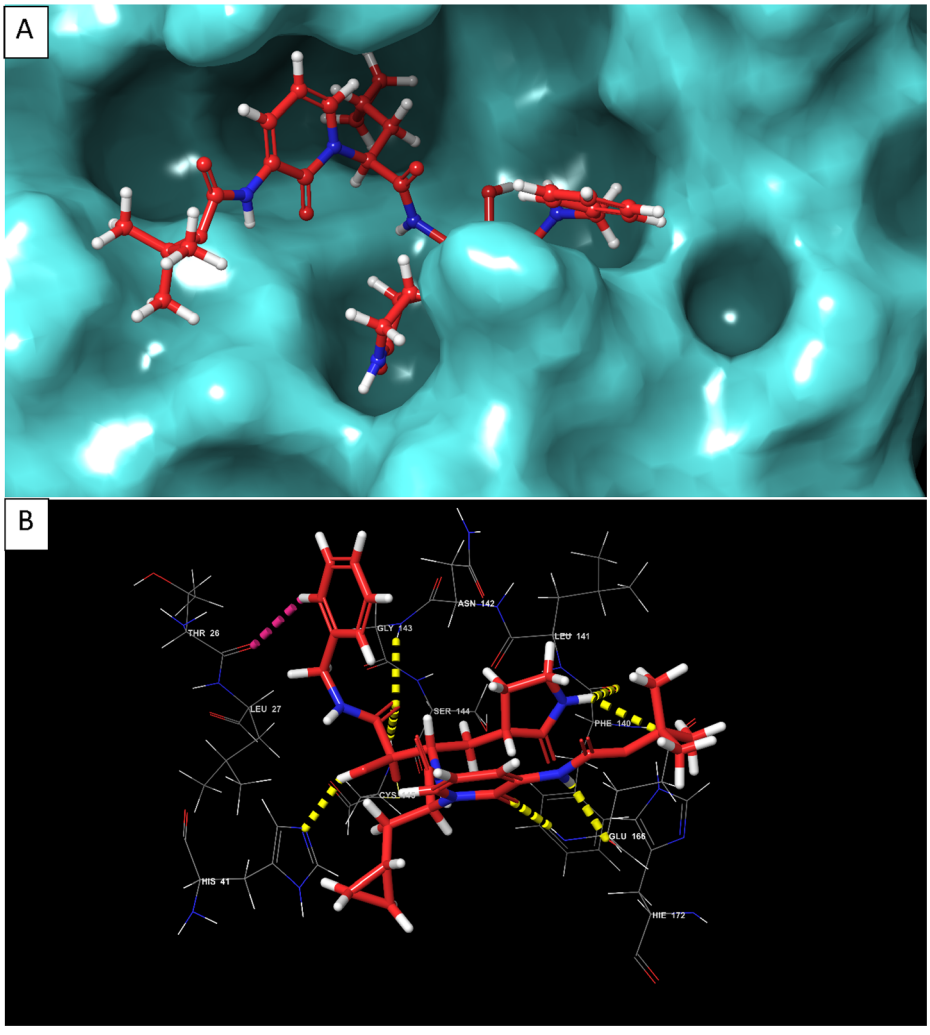


Fig. 12. (A) 3D view of compound **3** inside the binding pocket of SARS-CoV-2 M^{pro} (B) 3D interaction diagram of compound **3** with active site residues of the target protein (C) 2D interaction diagram of compound **3** with active site residues of the target protein (PDB ID- 6Y2F) (Visualized using Maestro visualizer) [70].

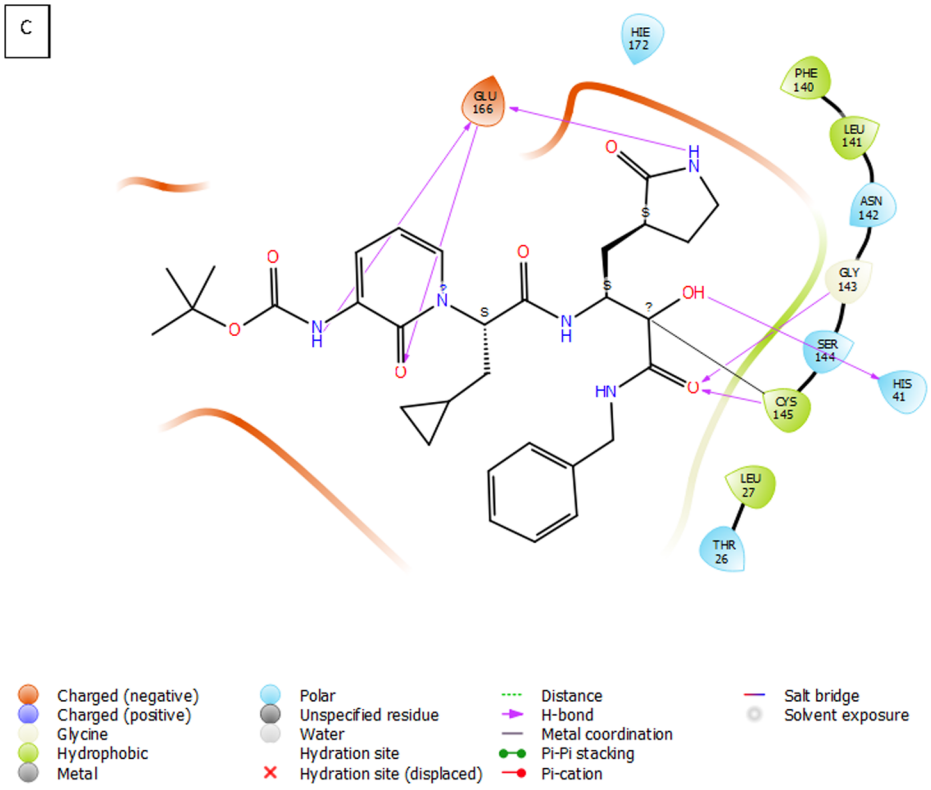


Fig. 12. (*continued*)

0.67 μM. Further, compound **3** effectively inhibited the replication of SARS-CoV-2 in Calu3 cells, while compound **4** formed by the removal of the BOC group was almost inactive, emphasizing that the BOC group is indispensable. The X-ray crystal structure of compound **3** with SARS-CoV-2 M^{pro} is depicted in Fig. 12. Compound **3** also had a favorable pharmacokinetic profile *in vivo*, suggesting it as an ideal lead for further development.

Jin et al. developed a strategy encompassing structure-based drug design, virtual screening, and high throughput screening to repurpose existing drugs or agents to target M^{pro} of SARS-CoV-2 [19]. N3 (Fig. 13) was designed based on computer-aided drug design to target the M^{pro} of SARS-CoV and MERS-CoV [71,72]. Since M^{pro} is highly conserved among coronaviruses, compound N3 was also tested against M^{pro} of SARS-CoV-2, and it was found to be a potent inhibitor of M^{pro}. Enzyme kinetics studies revealed compound N3 as an irreversible inhibitor. The X-ray crystal structure of compound N3 in the binding pocket of SARS-CoV-2 ^{Mpro} is shown in Fig. 13. Based on the crystal structure of SARS-CoV-2 M^{pro} with N3, a virtual screening study identified cinanserin, a serotonin antagonist, as a promising antiviral candidate. Cinanserin exhibited activity against SARS-CoV-2 M^{pro} *in vitro* (IC_{50} = 125 μM). A high-throughput screening study consisting of approved drugs, natural products, and clinical drug candidates was performed to identify hit compounds against SARS-CoV-2 M^{pro}. The top six compounds, along with their IC_{50} values, are depicted in Fig. 14. These compounds were evaluated for the potential to inhibit the replication of SARS-CoV-2 in Vero E6 cells. Ebselen (also called PZ 51, DR3305, and SPI-1005, is a synthetic organoselenium drug molecule with anti-inflammatory, antioxidant and cytoprotective activity) and N3 with half-maximal Effective Concentration (EC_{50}) values of 4.67 and 16.77 μM, respectively were found to be the most potent compounds. Ebselen has low cytotoxicity, and its safety has been evaluated in a previous clinical trial [73,74], making it an ideal candidate for further development.

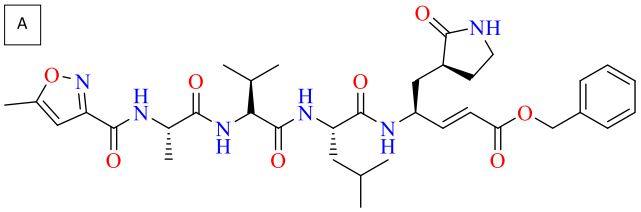
Dai et al. reported the synthesis and evaluation of two peptidomimetic aldehydes targeting the M^{pro} of SARS-CoV-2 [75]. The two peptidomimetic aldehydes **5** and **6** potently inhibited SARS-CoV-2 M^{pro} with IC_{50} values of 0.053 μM and 0.040 μM, respectively (Fig. 15). The crystal structures of SARS-CoV-2 Mpro with both the inhibitors were resolved and were found to bind with the substrate-binding site of the protein and showed vital interactions with the active site residues. Compounds **5** and **6** were also shown to possess potent antiviral activity against SARS-CoV-2 in Vero E6 cells with EC_{50} values of 0.42 and 0.33 μM, respectively. Furthermore, *in vivo* pharmacokinetic and toxicity studies were conducted to substantiate these compounds as promising candidates for COVID-19. Both the compounds exhibited good pharmacokinetic properties, and compound **5** exhibited low toxicity *in vivo*.

Fintelman-Rodrigues and co-workers shed light on the promising potential of atazanavir and atazanavir/ritonavir combination for the treatment of COVID-19 [76]. Through a combination of molecular docking and molecular dynamics, atazanavir was shown to bind to the active site of SARS-CoV-2 M^{pro}. It was also shown to inhibit the enzyme through zymographic studies. Atazanavir and atazanavir/ritonavir combination were evaluated for their inhibitory potential against SARS-CoV-2 in Vero E6 cells and human epithelial pulmonary cell lines (A549). The solo treatment, as well as the combination treatments, was found to inhibit SARS-CoV-2 in both the cell lines potently. The EC_{50} values of atazanavir and atazanavir/ritonavir combination against SARS-CoV-2 in Vero E6 cells and A549 cells are shown in Fig. 16. Furthermore, atazanavir and atazanavir/ritonavir also prevented pro-inflammatory cytokine production in monocytes infected with SARS-CoV-2, as confirmed by the low levels of lactate dehydrogenase (LDH) and Interleukin-6 (IL-6).

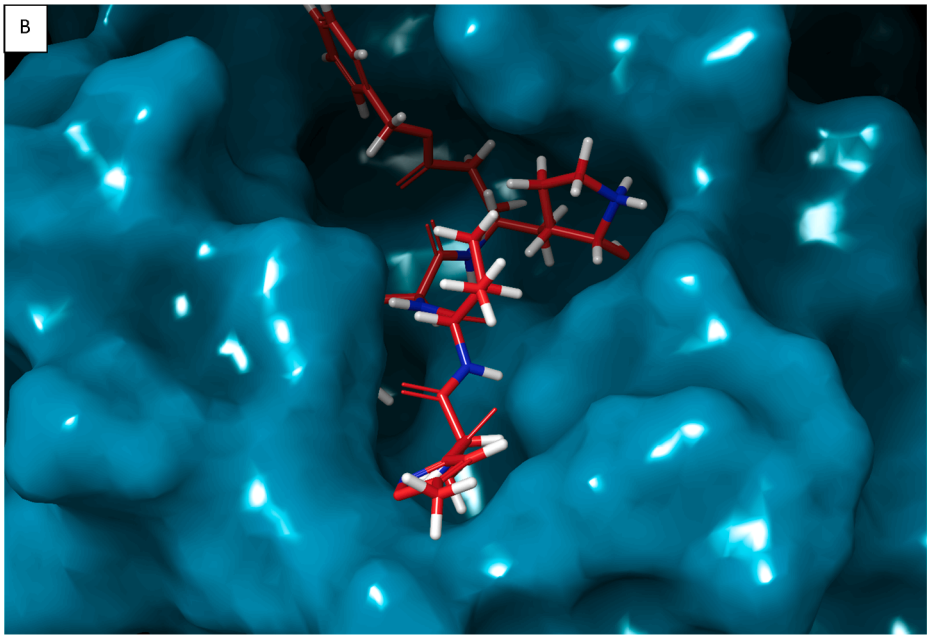
2.6. Papain like protease (PLpro)

Papain like protease is the other proteolytic enzyme that helps in processing of the replicase polyprotein. PLpro is known to cleave the replicase polyprotein at three sites releasing the nsp-1, nsp-2, and nsp-3, which are essential for viral replication [10]. Apart from its proteolytic function, PLpro is also reported to possess de-ubiquitinating property

[77]. It also plays a central role in countering the strength of host immune response to viral infection by shutting down crucial pathways [78–80]. Currently, no *in vitro* studies have been performed against PLpro of SARS-CoV-2. However, computational studies have been performed which could provide a direction for further exploitation of PLpro. Wu et al. constructed a homology modeling of SARS-CoV-2 PLpro and screened it virtually against the ZINC drug database and an in-house database of Chinese medicine and natural products. The virtual screening study identified ribavirin, valganciclovir, β-thymidine, and natural products Platycodin D, Chrysin, and Neohesperidin as potential leads with high binding affinity with SARS Cov-2 PLpro [10]. Arya et al. also constructed a homology model of SARS-CoV-2 PLpro



N3
Molecular weight- 680.8
PubChem ID- 6323191



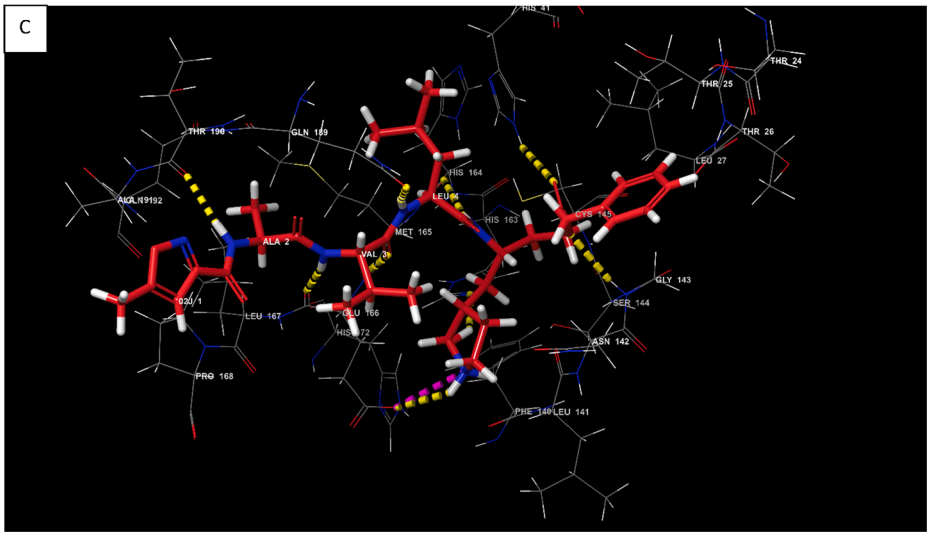


Fig. 13. (A) Structure of compound N3 (B) 3D view of compound N3 inside the binding pocket of SARS-CoV-2 M^{pro} (C) 3D interaction diagram of compound N3 with active site residues of the target protein (D) 2D interaction diagram compound N3 with active site residues of the target protein (PDB ID- 6LU7) (Visualized using Maestro visualizer) [70].

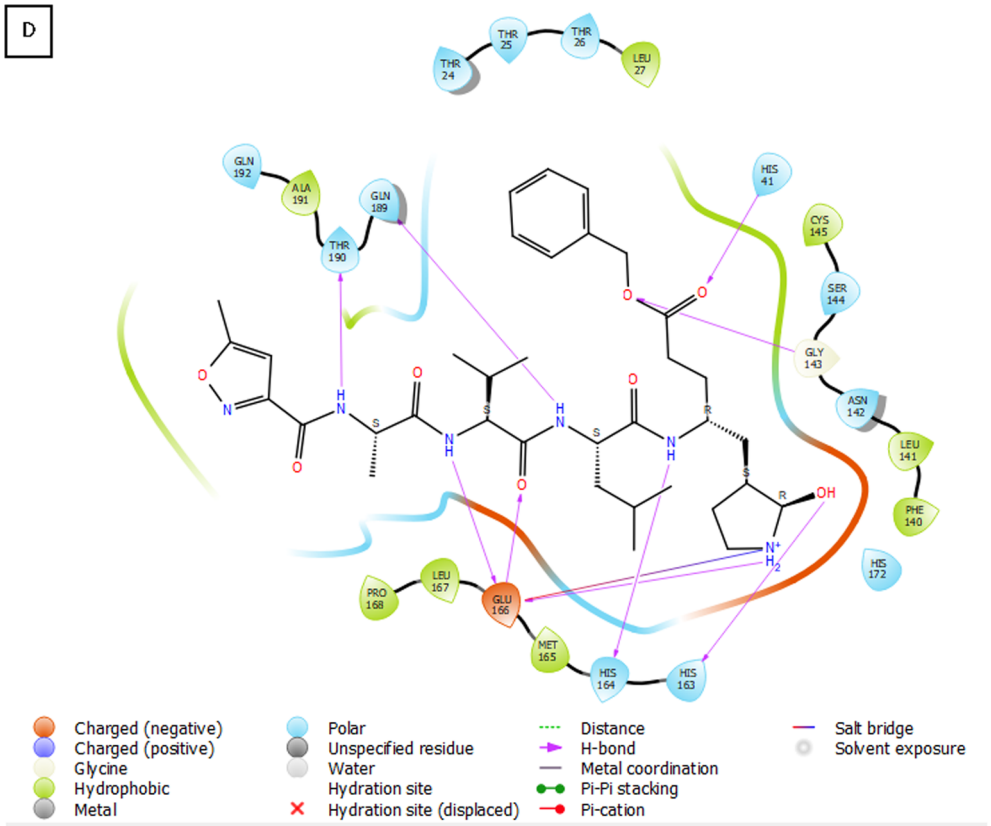
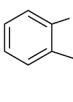
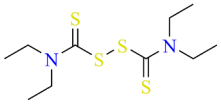


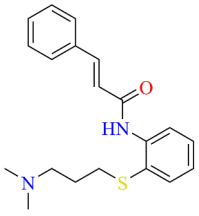
Fig. 13. (*continued*)



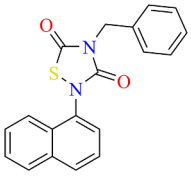
Ebselen
IC_{50}= 0.67 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 274.2
PubChem CID- 3194



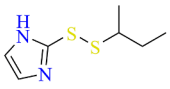
Disulfiram
IC_{50}= 9.35 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 296.5
PubChem CID- 3117



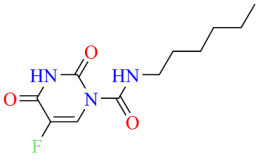
Cinanserin
IC_{50}= 125 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 340.5
PubChem CID- 5475158



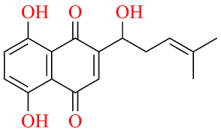
Tideglusib
IC_{50}= 1.55 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 334.4
PubChem CID- 11313622



PX-12
IC_{50}= 21.39 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 188.3
PubChem CID- 219104

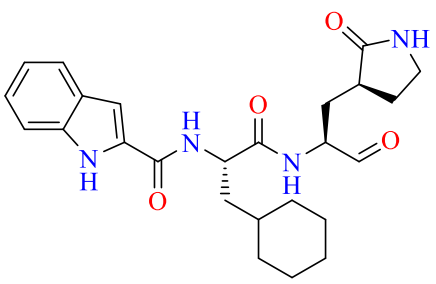


Carmofur
IC_{50}= 1.82 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 257.2
PubChem CID- 2577



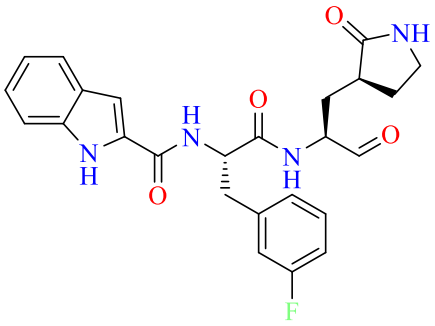
Shikonin
IC_{50}= 15.75 μM against SARS-CoV-2 M^{Pro}
Molecular weight- 288.2
PubChem CID- 479503

Fig. 14. Structure of reported M^{pro} inhibitors.



5

IC_{50}= 0.053 μM against SARS-CoV-2 M^{pro}



6

IC_{50}= 0.040 μM against SARS-CoV-2 M^{pro}

Fig. 15. Peptidomimetic aldehydes **5** and **6** targeting SARS-CoV-2 M^{pro}.

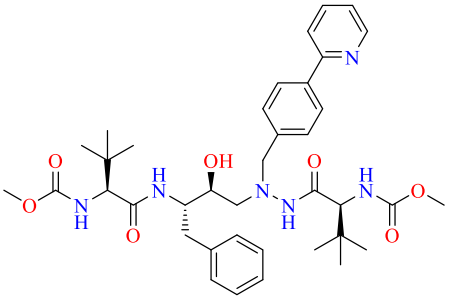
and screened it against a library of 2525 FDA approved drugs. Praziquantel (anti-parasitic), cinacalcet (anti-hyperparathyroidism), procainamide (anti-arrhythmic), terbinafine (antifungal) and pethidine (opioid analgesic) were identified with potent binding affinity with SARS-CoV-2 PLpro [81] (Fig. 17). No major adverse effects have been reported for praziquantel and cinacalcet. However, procainamide, terbinafine, and pethidine have major adverse effects like cardiac abnormalities, hepatic failure, and respiratory depression, respectively [82–84].

3. Treatment opportunities for COVID-19

3.1. Antivirals

3.1.1. Remdesivir

Remdesivir, a prodrug of adenosine analog GS-441524 (Fig. 18), is an investigational antiviral molecule that was developed by Gilead Sciences for the treatment of the Ebola virus [85]. Remdesivir is in the frontline in ongoing clinical trials for COVID-19. Remdesivir is a direct-acting antiviral drug, which stops replication of SARS-CoV-2 in host-



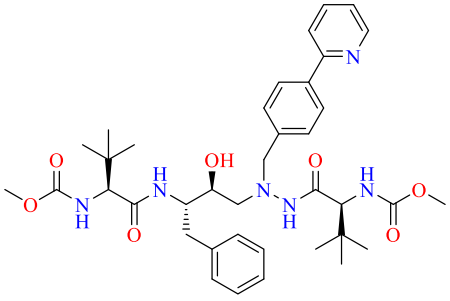
Atazanavir

EC_{50}= 2 μM against SARS-CoV-2 in Vero E6 cells

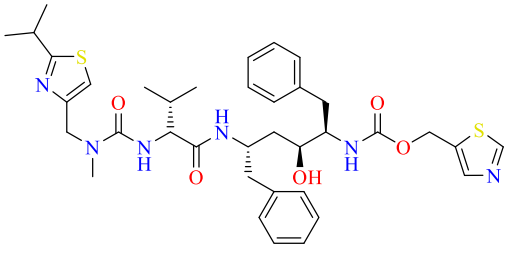
0.22 μM against SARS-CoV-2 in A549 cells

Molecular weight- 704.9

PubChem CID- 148192



Atazanavir



Ritonavir

Molecular weight- 720.9

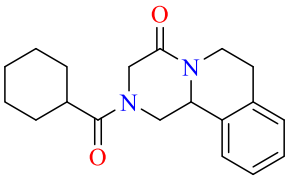
PubChem CID- 392622

Atazanavir/Ritonavir combination

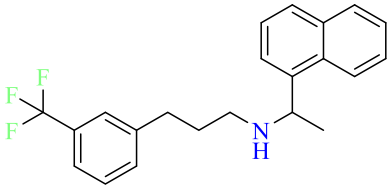
EC_{50}= 0.5 μM against SARS-CoV-2 in Vero E6 cells

0.60 μM against SARS-CoV-2 in A549 cells

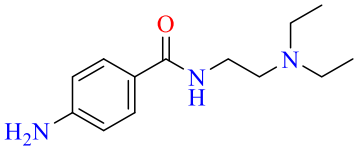
Fig. 16. Structure of atazanavir and ritonavir.



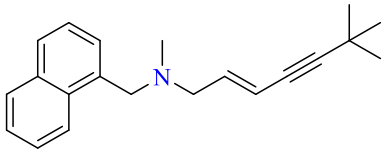
Praziquantel
Binding affinity= 8 nM- 8 μM
Molecular weight- 312.4
PubChem CID- 4891



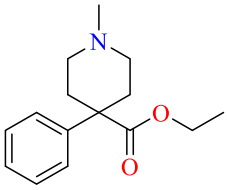
Cinacalcet
Binding affinity= 26 nM- 3 μM
Molecular weight- 357.4
PubChem CID- 156419



Procainamide
Binding affinity= 30 nM- 3 μM
Molecular weight- 235.3
PubChem CID- 4913



Terbinafine
Binding affinity= 33 nM- 3 μM
Molecular weight- 291.4
PubChem CID- 1549008



Pethidine
Binding affinity= 53 nM- 5 μM
Molecular weight- 247.3
PubChem CID- 4058

Fig. 17. Structure of top 5 compounds reported as PLpro inhibitor.

cells [86]. Remdesivir was also found to exhibit antiviral activity against other flavo viruses like Marburg virus, Pneumo viruses like respiratory syncytial virus, and paramyxoviruses like mumps, measles, Nipah virus, and Hendra virus [87]. A recent study reported prophylactic as well as the therapeutic potential of remdesivir in the rhesus macaque model of MERS-CoV infection [88]. Remdesivir potently inhibited the replication of SARS-CoV and MERS-CoV in human airway epithelial cell cultures with IC_{50} values of 0.069 and 0.074 μM, respectively [89]. In addition, it was also effective against zoonotic coronaviruses [89,90]. Recently, remdesivir was shown to exhibit potent activity against the novel coronavirus SARS-CoV-2 *in vitro*. Remdesivir was effective in blocking the viral infection in Vero E6 cells infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019 (EC_{50} = 0.77 μM) [62]. Remdesivir was also shown to afford clinical benefits in rhesus macaques infected with SARS-CoV-2 [91]. The preliminary results of a double-blinded, randomized, placebo-controlled study evaluating the effectiveness of intravenous remdesivir for the treatment of COVID-19 was recently published. The study findings revealed that remdesivir was superior to placebo in reducing the time to recovery in adults hospitalized with COVID-19 with a median recovery time of 11 days as compared to 15 days for the placebo-treated group [92]. Recently, Gilead Sciences announced that a 5-day treatment course of remdesivir was associated with significantly greater clinical improvement in hospitalized patients with moderate COVID-19 when compared with standard care in a Phase-3 clinical study, further demonstrating the importance of remdesivir in the battle against COVID-19 [93]. The adverse effects that have been reported due to remdesivir administration include hypersensitivity- infusion-related and anaphylaxis and elevation in liver transaminases [94]. In the USA, the Food and Drug Administration (FDA) has granted remdesivir an Emergency Use Authorization (EUA) for the management of hospitalized patients with severe COVID-19.

3.1.1.1. Mechanism of action. Remdesivir being a nucleoside analog inhibits the viral genome replication process by targeting the RdRp enzyme. After host-dependent conversion to its active form- nucleoside triphosphate (NTP) (Fig. 18), it incorporates into the RNA strand after fending off Adenosine triphosphate (ATP), the natural nucleotide incorporated in this process resulting in premature termination of RNA synthesis [85,86,95]

3.1.2. Lopinavir/ritonavir combination

Lopinavir and ritonavir are two structurally related protease inhibitors that were developed for the treatment of (HIV). Lopinavir exhibited higher selectivity, about 10-fold against both the wild and mutant strains of HIV-1 protease enzyme *in vitro* than ritonavir. However, it lacked the same potency *in vivo* due to metabolic inactivation by cytochrome *P*-450 (CYP) enzymes [96]. Ritonavir inhibits cytochrome *P*-450-3A4 (CYP3A4) at sub-therapeutic levels and hence is always co-administered with lopinavir to prevent its metabolic degradation [97]. Lopinavir was found to inhibit both SARS-CoV and MERS-CoV replication *in vitro* (EC_{50} = 17.1 and 8 μM against SARS-

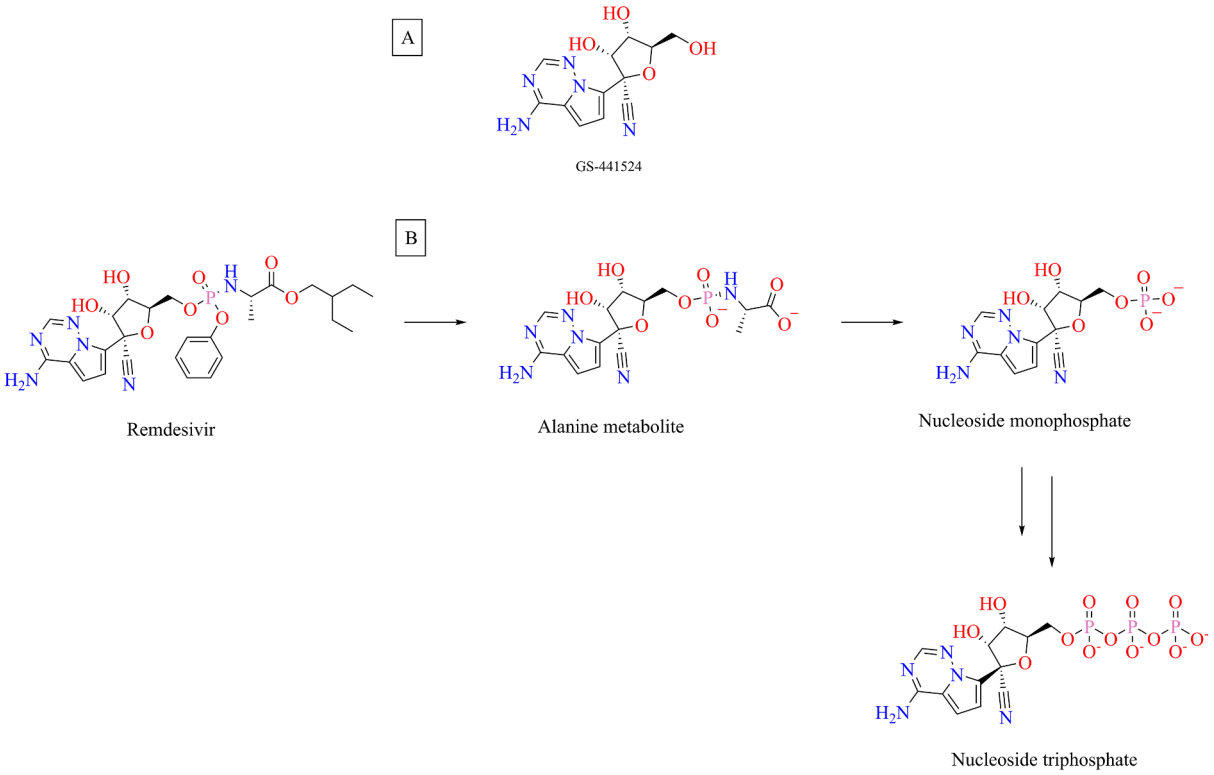


Fig. 18. (A) Structure of GS-441524 (B) Metabolic activation of remdesivir.

CoV and MERS-CoV, respectively). The combination of lopinavir/ritonavir was found to be effective in the animal model as well [98,99]. It was proposed that the 3CLpro inhibition capacity of lopinavir/ritonavir partly contributes to their anti-CoV activity [100]. It was postulated that the combination could be effective against SARS-CoV-2. A study on analysis of molecular complexation between lopinavir and ritonavir with SARS-CoV-2 3CLpro suggested interaction of these drugs with residues at the active site of the enzyme [101]. There are 39 ongoing studies registered in ClinicalTrial.gov on clinical evaluation of lopinavir/ritonavir for the treatment of COVID-19. The results posted on a recently conducted clinical trial, Lopinavir Trial for Suppression of SARS-Cov-2 in China (LOTUS China), revealed that the combination of lopinavir/ritonavir offered no benefits over the standard care in hospitalized adult COVID-19 patients [102]. Considering the dynamic situation and differential pathologies of COVID-19 in different areas, it is important to wait for reports and outcomes of other ongoing clinical trials before drawing any conclusion on the therapeutic utility of this combination for COVID-19.

3.1.3. Favipiravir

Favipiravir is an antiviral drug approved for the treatment of the influenza virus. Favipiravir is a prodrug that is metabolically activated by the human hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to its active metabolite-favipiravir-ribofuranosyl-5′-triphosphate (favipiravir-RTP) [103]. Favipiravir is an RdRp inhibitor that has shown promise as a therapeutic intervention for the Ebola virus [104–107]. Favipiravir was shown to inhibit the replication of SARS-CoV-2 *in vitro* (EC_{50} = 61.88 μM) [62]. An open-label non-randomized control study was undertaken to compare the clinical effectiveness of favipiravir and lopinavir/ritonavir as a treatment strategy for COVID-19. The study findings revealed that favipiravir had better treatment outcomes on COVID-19 in terms of viral clearance and disease progression [108]. A clear understanding of clinical pharmacokinetics and pharmacodynamics profiles of favipiravir based on its previous clinical trials for influenza treatment [109] may be useful for determining the appropriate doses and course of treatment for COVID-19.

3.1.4. Ribavirin

Ribavirin, a guanosine analog, has been used for the treatment of RNA viruses like hepatitis and respiratory syncytial virus. It interferes with the viral RNA synthesis and viral mRNA capping after undergoing metabolic activation to its active metabolite [110]. Past studies have highlighted the combination of ribavirin and interferon therapy as an effective treatment strategy for SARS-CoV and MERS-CoV [111–113]. Recently, Wang et al. highlighted the potential of ribavirin to inhibit SARS-CoV-2 *in vitro* in Vero E6 cells (EC_{50} = 109.50 μM). Clinical trials are underway to evaluate the efficacy of ribavirin in the treatment of COVID-19 [62].

3.1.5. Other antiviral drugs

Other antivirals that are currently being tested include umifenovir, oseltamivir, darunavir/cobicistat combination (Fig. 19). Umifenovir is used for the treatment of influenza in Russia and China. Umifenovir exhibits its action by preventing the fusion of the virus with the cell membrane blocking its entry into the host cell [114]. Oseltamivir, also used for the treatment of influenza viruses, acts as a neuraminidase inhibitor, preventing the release of new virus particles [115]. Darunavir is a protease inhibitor approved for the treatment of HIV, and cobicistat prevents the catabolism of darunavir [116]. Clinical trials are underway to evaluate the efficacy of these drugs for treating COVID-19.

3.2. Antibiotics

3.2.1. Teicoplanin

Teicoplanin belonging to the class of glycopeptide antibiotic is used for the treatment of gram-positive bacterial infections. The previous report suggested that teicoplanin and its derivatives were capable of blocking the viral entry of the Ebola virus, SARS-CoV, and MERS-CoV

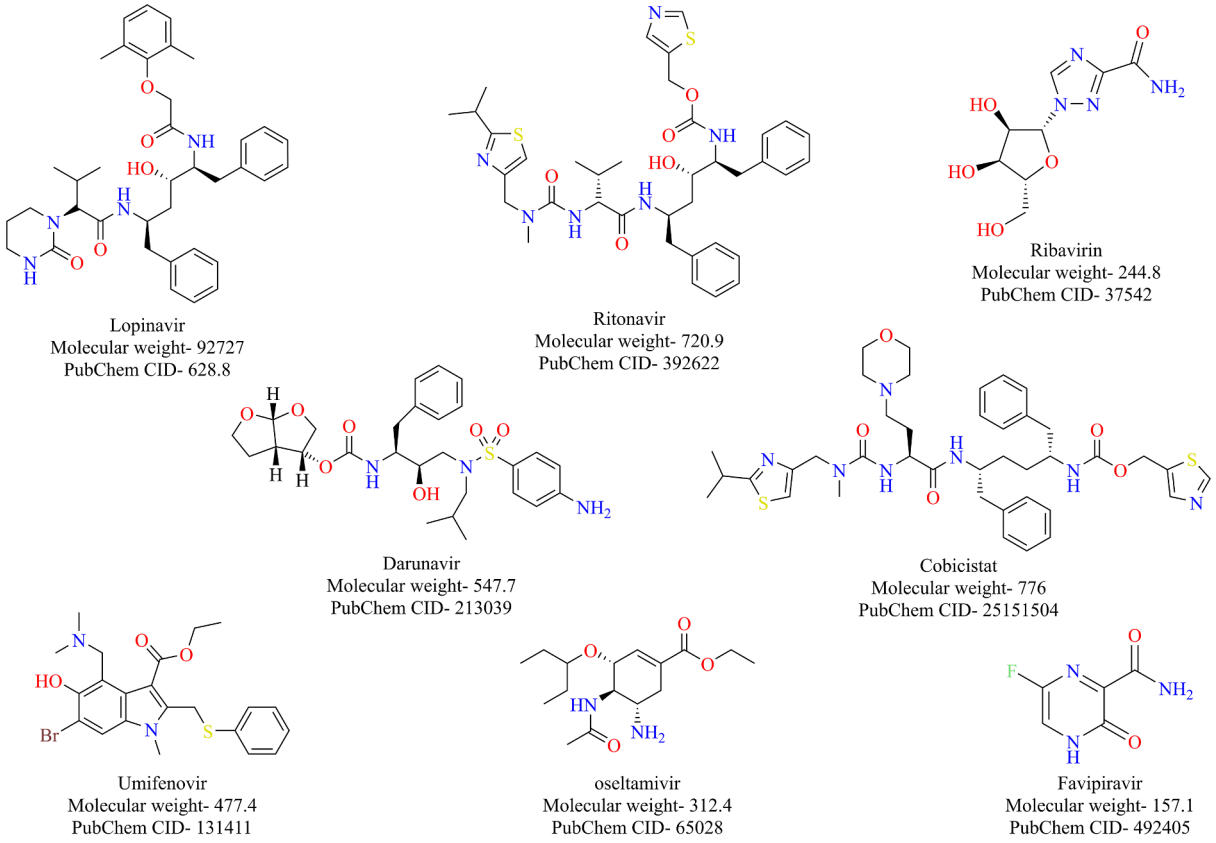


Fig. 19. Antiviral drugs currently being repurposed for treating COVID-19.

into the cell by blocking cathepsin L [46]. A recent report by the same research group suggests that teicoplanin potently inhibits the entry of SARS-CoV-2-S-pseudoviruses by blocking cathepsin L. (IC_{50} = 1.66 μM) [47]. Given its antibacterial prowess, teicoplanin could be considered as a dual inhibitor of the SARS-CoV-2 and its associated bacterial co-infections. However, further evidence is required to support such a claim.

3.2.2. Azithromycin

Azithromycin is a broad-spectrum antibiotic that is used for the management of several bacterial infections (Fig. 20). A recently conducted clinical trial highlighted the importance of azithromycin for the management of SARS-CoV-2 infection [117]. A total of 36 patients were enrolled for the study, out of which 20 patients received chloroquine, and 16 patients served as control. Among the chloroquine treated patients, six patients received azithromycin as a precautionary measure against bacterial superinfection. At the end of day 6, 100% of the patients treated with chloroquine and azithromycin were cured off the virus while only 57.1% of the patients were cured who received chloroquine alone (negative PCR results). These outcomes should be further dwelled on to consider azithromycin as viable adjuvant therapy for SARS-CoV-2 infection. Fascinatingly, azithromycin has been reported to be active against other RNA viruses like Ebola and Zika virus *in vitro* [118,119]. Further studies might shed light on its potential against SARS-CoV-2.

3.2.3. Carrimycin

Carrimycin, a macrolide antibiotic, is under clinical investigation (NCT04286503) to evaluate its efficacy in treating patients with COVID-19. Carrimycin has been patented for the treatment of mycobacterial infections (European patent EP 3384915 A1). However, after a thorough search, no information could be obtained regarding the structure or mechanism of action of this drug.

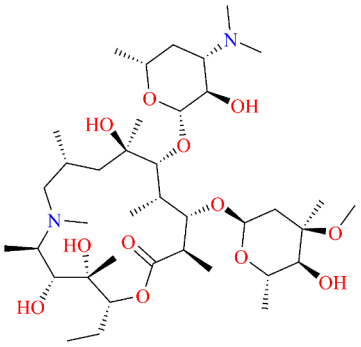
3.3. Antiprotozoal drugs

3.3.1. Chloroquine and hydroxychloroquine

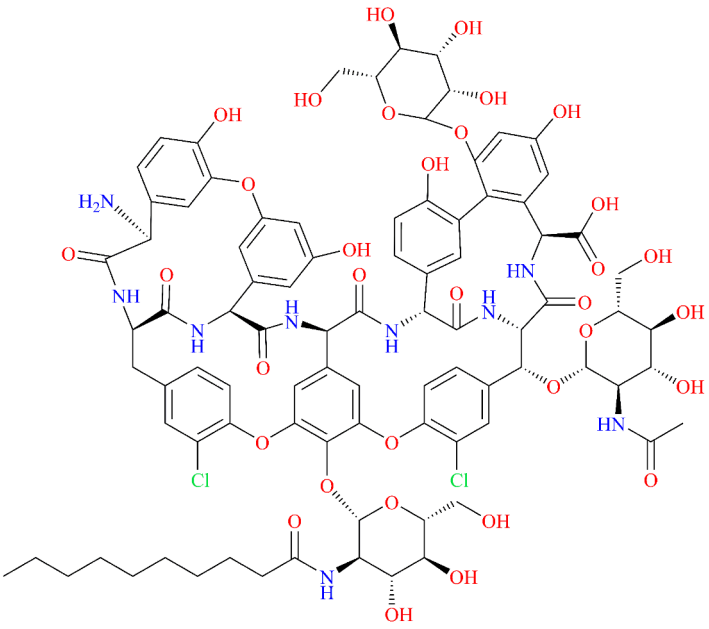
Chloroquine and hydroxychloroquine belonging to the class of 4-aminoquinolines are primarily used as antimalarials. Structurally, hydroxychloroquine differs from chloroquine by the presence of one extra hydroxyl group. Besides its antimalarial prowess, chloroquine has established itself as a broad-spectrum antiviral agent exhibiting potent activity against both DNA and RNA viruses [120–123]. Concerning coronaviruses, chloroquine has been reported to be potent against the SARS-CoV-1 [124]. A recent report by Wang et al. shed light on the antiviral prowess of chloroquine against the SARS-CoV-2. Chloroquine effectively blocked the viral infection with a high selectivity index (EC_{50} = 1.13 μM) [62]. Gao et al., in a recent publication, disclosed that chloroquine treatment offered superior efficacy than control treatment in a trial that involved a hundred infected patients [125].

Now answering the elephant in the room- Can hydroxychloroquine also be used for the treatment of Covid-19? A recent report demonstrated that hydroxychloroquine is also effective against the SARS-CoV-2, and a study also highlighted that hydroxychloroquine is more potent against SARS-CoV-2 than chloroquine [126,127]. More arguments favor the use of hydroxychloroquine over chloroquine. Firstly, the presence of an extra hydroxyl group makes it more hydrophilic and hence faster clearance lessening the risk of retinal toxicity than chloroquine. Secondly, hydroxychloroquine is a safer option than chloroquine with respect to therapeutic window and safety margins. Thirdly, owing to its proven immunomodulatory properties, hydroxychloroquine can act as an ideal treatment intervention in severely ill cases where cytokine storm is a significant issue to deal with COVID-19 [128].

Recently, a controversial observational study on the effectiveness of chloroquine or hydroxychloroquine with or without a macrolide for the treatment of COVID-19 was published. The study comprising data from over 600 hospitals in six continents concluded that chloroquine or



Azithromycin
Molecular weight- 749
PubChem CID- 447043



Teicoplanin
Molecular weight- 1879.7
PubChem CID- 133065662

Fig. 20. Antibiotics that are being explored for the treatment of COVID-19.

hydroxychloroquine treatment afforded no protection to COVID-19 patients and was associated with an increased incidence of ventricular arrhythmias. However, serious questions were raised on the validity of the data published in the study. The study was later retracted from the journal as independent auditing of the data was not possible [129]. Reports from clinical trials like solidarity trials, RECOVERY trials have demonstrated that hydroxychloroquine offers no benefit to COVID-19 patients [130,131]. USFDA has also withdrawn its EUA status given to chloroquine and hydroxychloroquine in view of the recent developments [132].

3.3.1.1. Mechanism of action of chloroquine. Chloroquine is claimed to act via two mechanisms. Chloroquine, in its unprotonated state, spontaneously moves across the cell membranes and gets accumulated in highly acidic vesicles like lysosomes and endosomes and organelles like Golgi, where it gets ionized and raises their pH thereby inactivating several proteolytic enzymes. Evidence suggests that viral entry, replication, and infection requires an acidic environment in the endosome-lysosomes and the catalyzing efficiency of endosomal-lysosomal enzymes. By raising the pH of the vesicles, chloroquine can effectively inhibit the entry and replication process [133].

Chloroquine indirectly interferes with the interaction between the SARS-CoV-1 spike proteins and ACE-2 receptors. Interactions between the glycosylated form of ACE-2 receptor and SARS-CoV-1 S protein is necessary for the viral entry into the cell. Chloroquine impairs the Golgi mediated *N*-terminal glycosylation of ACE-2, which results in decreased affinity to SARS-CoV-1 S proteins. Hence weak interaction ensues, and the viral entry is prevented [124].

3.3.2. Nitazoxanide

Nitazoxanide, a thiazolide class of drugs, is an antiprotozoal agent used for the treatment of various protozoal and helminthic infections [134]. Apart from its antiprotozoal potential, nitazoxanide has established itself as a broad-spectrum antiviral agent showing potency against both the DNA and RNA viruses [135]. Recently, nitazoxanide was shown to effectively inhibit the SARS-CoV-2 in Vero E6 cells (EC_{50} = 2.12 μM) [62]. Considering its antiviral property along with its anti-inflammatory potential [136], nitazoxanide could act as a possible therapeutic intervention for COVID-19. However, further studies must be conducted to warrant such a claim.

3.3.3. Ivermectin

Ivermectin (Fig. 21) is a broad-spectrum anti-parasitic agent [137]. It has also been reported to possess antiviral activity against viruses such as HIV and dengue [138]. Ivermectin was shown to inhibit the replication of SARS-CoV-2 *in vitro* [139]. A single treatment of ivermectin at the dose of 5 μM resulted in an about 5000-fold reduction in viral titers following 48 h of ivermectin treatment. The safety profile of ivermectin is well established, and hence ivermectin can be potentially repurposed against COVID-19.

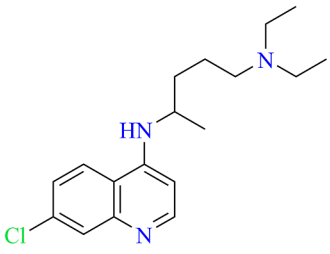
3.4. Fusion inhibitors

3.4.1. Camostat

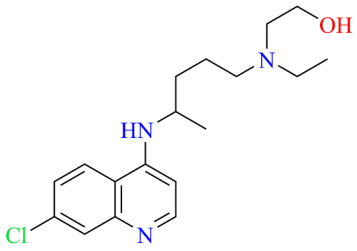
As previously mentioned, SARS-CoV-2 also uses the ACE-2 receptor for its attachment and TMPRSS2 for S-protein priming [33]. Camostat, a serine protease inhibitor that has been approved in Japan for the treatment of pancreatitis, was shown to block the cellular entry of SARS-CoV-2 by inhibiting TMPRSS2 [33]. Having already established its safety profile, camostat might prove to be a valuable drug in the arsenal, which can be repurposed to combat COVID-19. Camostat is currently under clinical trials (NCT04338906, NCT04321096) to prove its efficacy for the treatment of COVID-19.

3.4.2. Nafamostat

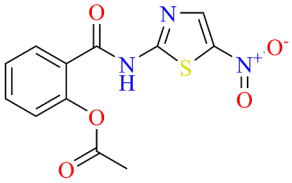
Following the footsteps of camostat is nafamostat (Fig. 22), a serine protease inhibitor used as an anticoagulant [140]. Nafamostat has been shown to inhibit the entry of MERS-CoV by inhibiting cellular TMPRSS2 [141]. Recently, nafamostat was also shown to inhibit the novel SARS-CoV-2 *in vitro* (EC_{50} = 22.50 μM) [62]. Scientists from Research Center for Asian Infectious Diseases of the Institute of Medical Science, the University of Tokyo, have disclosed that nafamostat prevents the entry of novel SARS-CoV-2 by potently binding to the transmembrane



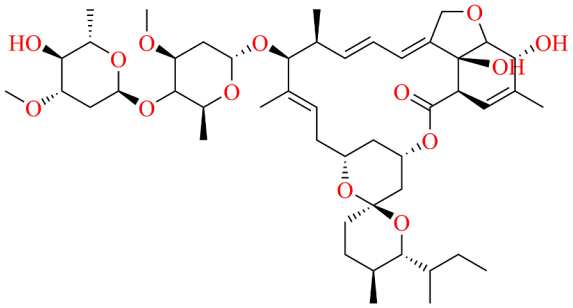
Chloroquine
Molecular weight- 319.9
PubChem CID- 2719



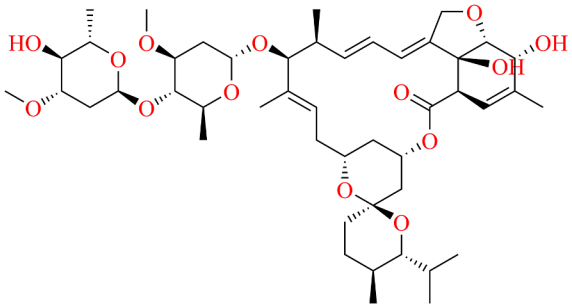
Hydroxychloroquine
Molecular weight- 335.9
PubChem CID- 3652



Nitazoxanide
Molecular weight- 307.28
PubChem CID- 41684



Ivermectin B_{1a}
Molecular weight- 875.1
PubChem CID- 6321424



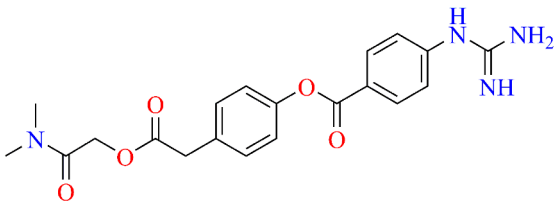
Ivermectin B_{1b}
Molecular weight- 861.1
PubChem CID- 6321425

Fig. 21. Antiprotozoal drugs that are being repurposed for treatment of COVID-19.

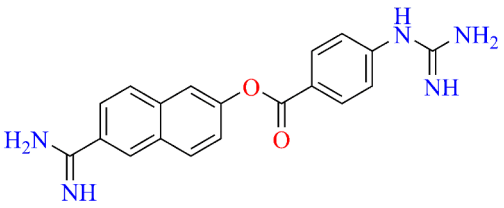
protease TMPRSS2. Nafamostat was able to achieve the fusion inhibition at less than one-tenth of the concentration required by camostat [142]. Nafamostat can also be repurposed for therapeutic utility against COVID-19.

3.5. Immunomodulators and anti-inflammatory drugs

A coordinated effort by the host's immune system is essential for battle against SARS-CoV-2. However, a dysregulated immune response has been reported in patients with COVID-19. Patients who were admitted to ICU on account of severe COVID-19 were reported to possess higher levels of IL-7, IL-2, IL-10, Granulocyte colony-stimulating factor (GCSF), Monocyte chemoattractant protein-1 (MCP-1), Tumor necrosis factor- α (TNF-α) compared with non-ICU patients suggesting a possible cytokine storm that ultimately culminates in Acute Respiratory Distress Syndrome (ARDS) [143]. Therefore, corticosteroids can be considered as an adjunct treatment option. However, currently, corticosteroid therapy is a topic of debate. Recently, Russel et al. suggested that there is no clinical evidence to support the use of corticosteroids in COVID-19 patients [144]. Notably, in a retrospective study, it was demonstrated that early, low-dose treatment intervention with corticosteroids was associated with quicker improvement of clinical symptoms [145]. Therefore, the use of corticosteroids for patients with COVID-19 is still under debate, and additional evidence is needed to be considered as a treatment intervention. Currently, a clinical trial is underway to evaluate the efficacy of dexamethasone in patients with ARDS secondary to SARS-CoV-2 infection (NCT04325061). Zhou et al. demonstrated that inflammatory and pro-inflammatory mediators like Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 are highly expressed following viral infection [146]. Therefore, blocking GM-CSF and IL-6 receptors can reduce the inflammatory response. In accordance with this, Mavrilimumab, a monoclonal antibody targeting the GM-CSF receptor, is currently under clinical trials (NCT04337216) to evaluate its efficacy. Clinical trials are also underway to evaluate the safety and efficacy of IL-6 receptor blockers like Sarilumab (NCT04315298), Tocilizumab (NCT04320615, NCT04315480) and Siltuximab (NCT04329650) for treating COVID-19. Baricitinib has been proposed as a potential drug for the treatment of COVID-19 [147]. AP-2



Camostat
Molecular weight- 398.4
PubChem CID- 2536



Nafamostat
Molecular weight- 347.4
PubChem CID- 4413

Fig. 22. Fusion inhibitors- camostat and nafamostat.

associated protein kinase 1 (AAK1) is a promoter of endocytosis. Baricitinib is known to bind and inhibit AAK1 potently even at therapeutic doses (2 mg or 4 mg) and hence has the potential to prevent the virus entry. Moreover, it is also a known inhibitor of Janus kinases (JAK1 and JAK2), essential enzymes that are involved in signal transduction initiated by cytokines [147]. Therefore, inhibiting JAK enzymes contributes to its anti-inflammatory properties. However, inhibition of JAK1 and JAK2 by baricitinib appears to be a double-edged sword with respect to the treatment of COVID-19 [148]. Interferons are essential soldiers deployed by host's immune system in response to virus entry. Interferons mediate their antiviral effects via the JAK-STAT pathway. Hence, inhibiting JAK enzymes by baricitinib can inhibit interferon mediated antiviral response and might aid in the replication of SARS-CoV-2 [148]. Currently, baricitinib is under clinical investigation (NCT04321993) as a potential drug for treating SARS-CoV-2 infection.

3.6. Traditional Chinese Medicine (TCM) and natural products

Traditional Chinese Medicine (TCM) has played a substantial role in the treatment and prevention of past epidemics. Past clinical studies have underlined the importance of TCM in the treatment and prevention of SARS and H1N1 influenza [149,150]. Since there is a high correlation between SARS-CoV and SARS-CoV-2, it was proposed that TCM can also be beneficial for the management of COVID-19 [151]. National Health Commission (NHC) of the People's Republic of China has recommended the use of TCM for Covid-19 since the fourth version of Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [152]. The TCM recommended in the current version (seventh trial version) of Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia are highlighted in Table 2 [153].

Ni et al. reported the treatment of 3 COVID-19 patients in Wuhan with Shuanghuanglian oral liquid (SHL). SHL is a patented TCM that is used for the treatment of cough, cold, and fever. The symptoms of all three patients improved after the consumption of SHL, and the patients finally recovered without any side effects [154]. Currently, it is under clinical investigation (ChiCTR2000029605). Lianhuaqingwen (LH), a TCM formula consisting of 13 herbs, was found to exhibit antiviral activity against the SARS-CoV-2 *in vitro* [155]. LH inhibited the replication of SARS-CoV-2 with an IC_{50} value of 411.2 μg/ml. Electron microscopic studies revealed that LH caused viral deformities. Furthermore, LH was also shown to suppress the levels of inflammatory cytokines like TNF-α and IL-6 [155]. Though TCM seems to be a treatment strategy for COVID-19, the safety aspects of TCM needs further warranting. Recently, Gray et al. addressed the potentially harmful effects of TCMs [156]. Although TCMs were found to exhibit potential beneficial effects in clinical trials conducted for SARS-CoV, most of these studies were poorly designed [152,157]. Hence, double-blinded, randomized, placebo-controlled clinical trials should be conducted to prove safety as well as efficacy aspects of TCMs.

Chen et al. identified five natural compounds- baicalin, hesperetin, scutellarin, nicotianamine, and glycyrrhizin that could potently bind to ACE-2 by molecular docking studies [158]. Incidentally, glycyrrhizin (Fig. 23), a triterpene saponin found in liqourice roots, has been previously reported to inhibit the replication of SARS-CoV [159,160]. A derivative of glycyrrhizin with 2-acetamido-β-d-glucopyranosyl amine into the glycoside chain showed 10-fold increased activity *in vitro* against SARS-CoV. An amine derivative of glycyrrhizin and the conjugates of glycyrrhizin with two amino acid residues and a free 30-COOH function showed 70-fold increased activity against SARS-CoV. However, these modifications also increased cytotoxicity [161]. Since the safety and toxicity profiles of glycyrrhizin are well established, further studies are needed to establish the efficacy of glycyrrhizin against SARS-CoV-2.

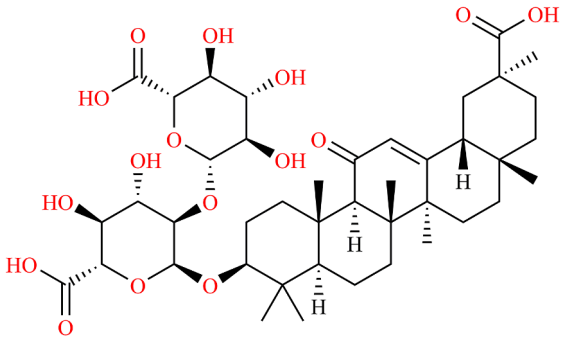


Fig. 23. Structure of Glycyrrhizin.

4. Conclusion and future perspectives

Extensive efforts are being made across the whole globe to find potential vaccines and therapeutic agents against COVID-19. However, until now, no vaccine or therapeutic agent has shown the results required for the approval for the treatment of COVID-19 or protection against SARS-CoV-2 infections. This review summarizes the potential druggable targets of SARS-CoV-2 for the discovery and development of novel therapeutics against COVID-19 based on the current understanding of molecular structures and functions of the targets as well as an understanding of the pathogenesis of the disease. The treatment approaches that are currently being explored have also been highlighted. The drugs that are currently being explored for the treatment of COVID-19 is summarized in Table 3.

Infectious diseases resulting from novel pathogens will continue to be a global health concern, further epitomized by COVID-19. The world is still unprepared for such epidemics/pandemics despite former coronaviruses infections SARS-CoV and MERS-CoV. Although vaccines are the only way to prevent/eradicate SARS-CoV-2, at least a year is needed to develop vaccines with desired protection and address their safety issues before they can be deployed for large scale vaccination campaigns. Given the lengthy process associated with drug development, repurposing of approved drugs appears to be an appropriate solution to answer the short-term goals for the management of COVID-19. Only the

Table 2
Chinese patent medicines recommended under the diagnosis and treatment protocol for novel Coronavirus Pneumonia (Trial version seven) [153].

Disease stage	Clinical manifestation	Recommended Chinese patent medicine
Medical observation	Fatigue and Gastrointestinal discomfort	HuoxiangZhengqi capsules
	Fatigue and fever	Jinhua Qinggan granules, LianhuaQingwen capsules (granules), ShufengJiedu capsules (granules), FangfengTongsheng pills (granules)
Clinical treatment (confirmed cases)	Severe cases	Xiyanping injection, Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection
	Critical cases	Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection, Shenfu injection, Shengmai injection, Shenmai injection

Table 3
Summary of the Drugs/investigational agents that are currently being explored for the treatment of COVID-19.

Compound name	Category	Potency against SARS-CoV-2 (*in vitro* EC_{50} or IC_{50} values in μM)	Mechanism of action	Major Adverse effects	Status	Reference
Remdesivir	Antiviral	0.77	RdRp inhibitor	hypersensitivity- infusion-related and anaphylaxis, elevation in liver transaminases	Phase 3 clinical trial (NCT04292899), EAU in the USA	[62,94]
Lopinavir	Antiviral	26.63	M^{pro} inhibitor	Serious cardiotoxicity, lactic acidosis, acute renal failure reported in preterm neonates	Phase 2 clinical trial (NCT04330690)	[162,163]
Favipiravir	Antiviral	61.8	RdRp inhibitor	Teratogenic	Phase 3 clinical trials (NCT04336904)	[62,164]
Ribavirin	Antiviral	106.5	RdRp inhibitor	Teratogenic, hemolytic anemia	Phase 3 clinical trials (NCT04392427)	[62,165]
Umifenovir	Antiviral	4.11	Fusion inhibitor	No major adverse effects have been reported.	Phase 4 clinical trials (NCT04252885)	[166]
Oseltamivir	Antiviral	–	–	Steven-Johnson syndrome, anaphylactic reactions, cardiac arrhythmia, seizures have been reported	Phase 3 clinical trials (NCT04338698)	[167]
Darunavir	Antiviral	–	M^{pro} inhibitor	Liver injury, severe skin reactions like erythema multiforme and Steven-Johnson syndrome	Phase 3 clinical trial (NCT04252274)	[168]
Teicoplanin	Antibiotic	1.66	Cathepsin L inhibitor	Not much information is available on the adverse effects associated with teicoplanin	–	[47]
Azithromycin	Antibiotic	–	–	QT interval prolongation, severe hypersensitivity reactions have been reported	Phase 3 clinical trial (NCT04332107)	[169]
Carrimycin	Antibiotic	–	–	Not much clinical data is available on Carrimycin	Phase 4 clinical trial (NCT04286503)	
Chloroquine	Antiprotozoal	1.13	Raises the pH in the endocytic vesicles, interferes with terminal glycosylation of ACE-2	Prolongation of QT interval, hypoglycemia, neuropsychiatric effects	Phase 3 clinical trial (NCT04303507)	[62,170]
Hydroxychloroquine	Antiprotozoal	0.72	Raises the pH in the endocytic vesicles, interferes with terminal glycosylation of ACE-2	Prolongation of QT interval, hypoglycemia, neuropsychiatric effects	Phase 3 clinical trial (NCT04340544)	[127,170]
Nitazoxanide	Antiprotozoal	2.12	–	No major adverse effects have been reported	Phase 2 clinical trial (NCT04423861)	[62]
Ivermectin	Antiprotozoal	~2	–	No major adverse effects reported	Phase 2 clinical trial (NCT04438850)	[139]
Camostat	Antifibrinolytic	–	TMPRSS2 inhibitor	Not much information is available on the adverse events	Phase 2 clinical trial (NCT04374019)	
Nafamostat	Anticoagulant	22.5	TMPRSS2 inhibitor	Hyperkalemia, agranulocytosis, anaphylaxis	Phase 2 clinical trial (NCT04418128)	[62,171]

efficacy of these drugs needs to be established against COVID-19 since their safety profiles are already well established. Many clinical studies are currently underway to repurpose existing drugs for COVID-19 management.

The long-term goals for management of COVID-19 should be directed against the development of novel inhibitors aimed at any of the druggable targets discussed in this review. The starting point of such a journey would be to modify the agents that have been shown to be promising against other coronaviruses like SARS-CoV, as demonstrated by Xia et al. and Zhang et al. in their respective studies [28,68]. The main protease of SARS-CoV-2 appears to be an attractive target for the discovery and development of novel drug candidates because of its importance in virus replication and the fact that its active site is highly conserved among coronaviruses. Peptidomimetics targeting the entry of the virus and small peptide molecules targeting M^{pro} have shown the potential to combat SARS-CoV-2. However, questions regarding their stability inside the body, selectivity against the target protease, and their delivery to the target site should be addressed. Structures and functions of RdRp have been extensively investigated for RNA viruses. Considerable efforts have also been made, and several lead compounds have been identified targeting specific RdRp functions through extensive structure-activity-relationship studies. A few of them have been advanced to the clinical use and are clinical evaluation. Current repertoire of lead RdRp inhibitors offer unparalleled starting point for optimization of their efficacy against SARS CoV-2. The inhibitors of RdRp may have low propensity to development of resistance, due to requirement of high fidelity for CoV RdRp functions.

Well-coordinated efforts between various disciplines are required to contain this global pandemic. Clinically proven therapeutics and vaccines are the needs of the hour to curb the growth of this pandemic and ensure global safety.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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