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REVIEW ARTICLE

Medicinal Chemistry Approaches for Combatting SARS-CoV-2 and COVID-19 Therapeutics

Neelottama KUSHWAHA[*°], Swatantra K.S. KUSHWAHA[**], Anmol KUMAR[***]

Medicinal Chemistry Approaches for Combating SARS-CoV-2 and COVID-19 Therapeutics

SUMMARY

The COVID-19 pandemic has underscored the need for innovative and adaptable solutions in medicinal chemistry to address the growing global health challenges. New strategies, including structure-based drug design, AI-driven drug discovery, and drug repurposing, have shown promising advancements in accelerating the creation of treatments. Significant strides have been made in focusing on crucial viral proteins, particularly the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp), which have created new opportunities for small-molecule inhibitors. Additionally, advancements in peptide-based therapies, monoclonal antibodies, and nanotechnology-enhanced drug delivery systems have expanded the tools available against SARS-CoV-2. However, significant challenges persist, such as addressing viral mutations, improving access to medications, and ensuring rapid scalability of treatments. Ongoing investment in interdisciplinary collaborations, enhanced screening technologies, and real-time genetic monitoring will be essential for refining these strategies. By adopting a proactive approach, medicinal chemistry can respond to the current pandemic and lay the groundwork for effectively tackling future viral threats with greater precision and efficiency.

Keywords: *SARS-CoV-2, antiviral agents, viral protein, drug repurposing, ligand-based drug design, structure-based drug design.*

SARS-CoV-2 ve COVID-19 Tedavilerinde Tıbbi Kimya Yaklaşımları

ÖZ

COVID-19 pandemisi, artan küresel sağlık sorunlarıyla mücadele etmek için tıbbi kimyada yenilikçi ve uyarlanabilir çözümlere olan acil ilgiyi artırdı. Yapıya dayalı ilaç tasarımı, yapay zekâ destekli ilaç keşfi ve ilaçların yeniden kullanımı gibi yeni stratejiler, tedavilerin geliştirilmesini hızlandırma potansiyelini ortaya koydu. Proteaz (Mpro) ve RNA bağımlı RNA polimeraz (RdRp) gibi temel viral proteinleri hedeflemedeki ilerleme, küçük moleküllü inhibitörler için yeni fırsatlar yarattı. Ayrıca, peptit bazlı tedaviler, monoklonal antikorlar ve nanoteknoloji destekli ilaç salım sistemlerindeki gelişmeler, SARS-CoV-2'ye karşı mevcut araçları genişletti. Bununla birlikte, viral mutasyonların ele alınması, ilaçlara erişimin iyileştirilmesi ve tedavilerin hızlı ölçeklenebilirliğinin sağlanması gibi önemli zorluklar devam etmektedir. Disiplinlerarası iş birliklerine, gelişmiş tarama teknolojilerine ve gerçek zamanlı genetik izlemeye devam eden yatırımlar, bu stratejilerin geliştirilmesi için hayati önem taşıyacaktır. Tıbbi kimya, proaktif bir yaklaşım benimseyerek mevcut pandemiye yanıt verebilir ve gelecekteki viral tehditlerle daha fazla hassasiyet ve verimlilikle etkili bir şekilde mücadele etmek için zemin hazırlayabilir.

Anahtar Kelimeler: *SARS-CoV-2, antiviral ajanlar, viral protein, ilaçların yeniden kullanımı, ligand tabanlı ilaç tasarımı, yapı temelli ilaç tasarımı.*

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INTRODUCTION

The coronavirus is a type of virus characterised by a single RNA strand that ranges from 27 to 32 kilobases in length (Batool et al., 2025; Nagu et al., 2024). It is part of the Coronaviridae family, which includes various types such as alpha, beta, delta, and gamma coronaviruses. When viewed under an electron microscope, the spherical-shaped virus is adorned with viral surface spike proteins, giving it a unique crown-like appearance (Rut et al., 2020; Zhang et al., 2025). This virus can infect many animals, including humans, mammals, and birds, leading to various symptoms that can impact the respiratory, digestive, and genital systems. The most prevalent coronaviruses that affect humans include 229E, NL63, OC43, and HKU1. These viruses are responsible for a range of respiratory conditions, varying from mild cold-like symptoms to more serious illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (Han et al., 2024).

Structure of SARS-CoV-2

The virus has three main components: a genome composed of single-stranded RNA, accompanied by a lipid bilayer of viral membrane, and surface proteins (Mondal et al., 2023). The RNA genome consists of approximately 30,000 nucleotides and is responsible for encoding four key structural proteins: nucleocapsid (N), membrane (M), envelope (E), and spike (S). In addition to these structural components, the genome also produces various non-structural proteins (nsps), contributing to its overall functionality (Figure 1.).

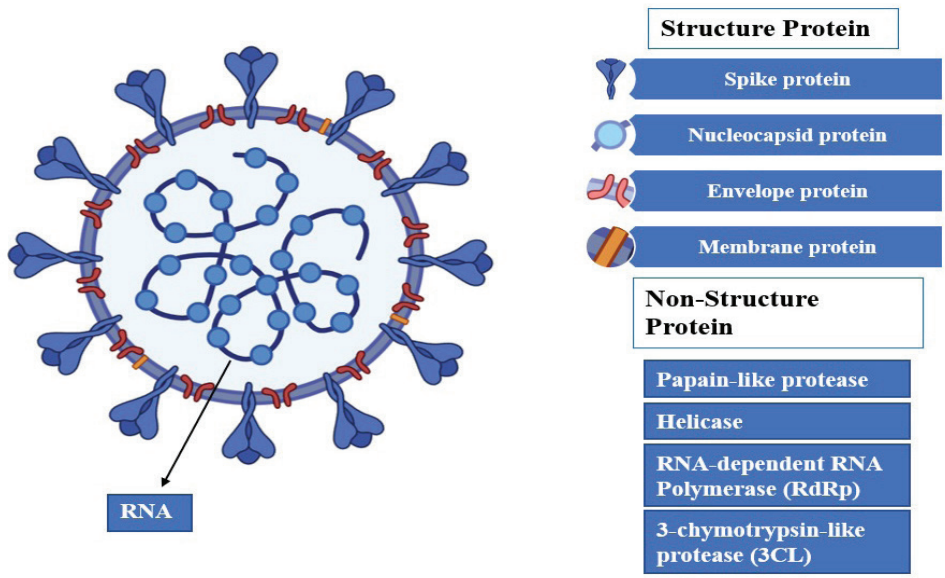

Figure 1. The virus SARS-CoV-2 and its molecular target proteins

The protein called Nucleocapsid (N) is essential for the construction of the nucleocapsid, which serves as a protective shield for the virus's genome. The genome of specific viral RNA is enclosed within a ribonucleoprotein complex, creating the nucleocapsid. The most abundant **M-protein** is a surface protein of the virus that facilitates viral assembly by inducing membrane curvature. The E-protein, the smallest of the membrane proteins, consists of 76 to 109 amino acid residues. It plays a vital role in several processes, including virus assembly, envelope formation, the permeability of host cell membranes, and overall pathogenicity. In contrast, the S protein, which ranges from 1,200 to 1,400 amino acid residues, serves as an essential structural transmembrane protein on the virus's outer envelope. This protein is critical for the virus to invade host cells, as it interacts with specific receptors located on the surface of human cells (Jain et al., 2022; Woo et al., 2023).

VIRAL TARGETS FOR ANTI-VIRAL AGENTS

Anti-coronavirus agents are categorised into various groups based on their site of action (Enjuanes et al., 2022; Niknamian, 2021).

1. **Targets of the drug on the Spike Protein or the entry of the virus:** Amiodarone
2. **ACE Inhibitors and ATR Blockers:** Losartan (Tikhomirova et al., 2024)
3. **TMPRSS2 Inhibitors:** Namafostat, Camostat, Upamostat
4. **Protease Inhibitors of the Virus:** Lopinavir, Ritonavir, Nirmatrelvir
5. **The Virus RNA Polymerase inhibitors:** Remdesivir (Eltayeb et al., 2024; GBD 2019 Meningitis Antimicrobial Resistance Collaborators, 2023).

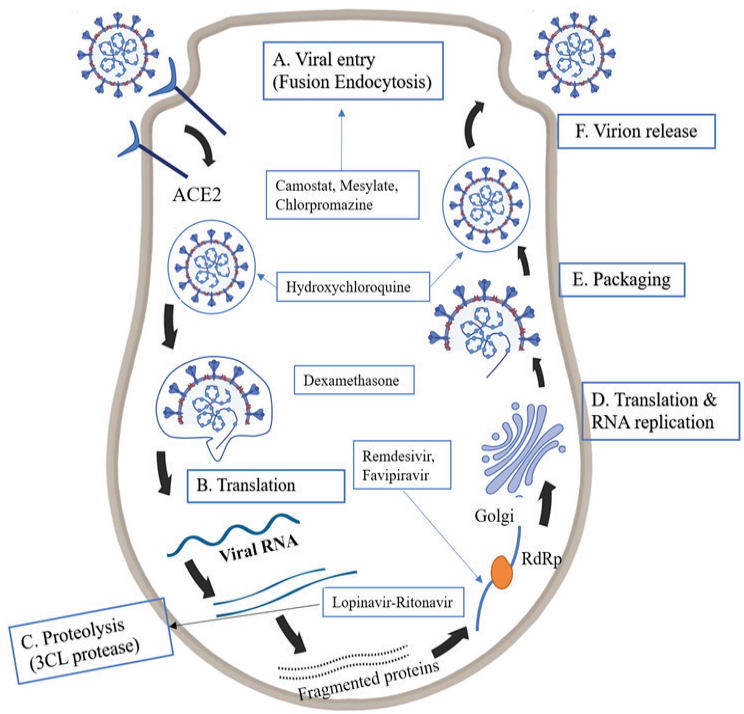

Figure 2. Various Drugs targeted at different viral target sites

DRUGS TARGETING THE SPIKE PROTEIN OR THE PROCESS OF VIRAL ENTRY

Infectious viruses bind to a crucial receptor on the surface of host cells called angiotensin-converting enzyme. After the first interaction, a serine protease called TMPRSS2 (transmembrane serine protease 2) helps fuse the membranes of the virus and the host cell (Cervantes et al., 2023). This allows the virus to enter the cell through a mechanism called endocytosis. Once inside, the virus begins its replication process. Several proteins play critical roles in this viral life cycle, including the spike protein of SARS-CoV-2, the ACE-2 receptor, and the TMPRSS2 protease. These components represent viable targets for developing antiviral treatments (Yaro et al., 2024)

THE RECEPTOR ACE INHIBITORS AND ATR BLOCKERS

Since ACE acts as the type of cell receptor for the specific spike protein of the virus, it has been specifically explored as a potential target for the specific treatment of COVID-19. Research has indicated that certain antihypertensive medications can enhance the production of the ACE-2 enzyme, which acts as the doorway for SARS-CoV-2 to enter cells. Consequently, at the onset of the COVID-19 pandemic, there was optimism that this category of drugs, including losartan, might assist in managing the infection. This optimism

was based on early mechanistic insights into the role of the renin–angiotensin–aldosterone system (RAAS) in SARS-CoV-2 pathogenesis. The virus was found to utilise angiotensin-converting enzyme 2 (ACE-2) as its cellular entry receptor, and ARBs were known to modulate the angiotensin-converting enzyme 2 (ACE2) expression and activity (Zipeto et al., 2020).

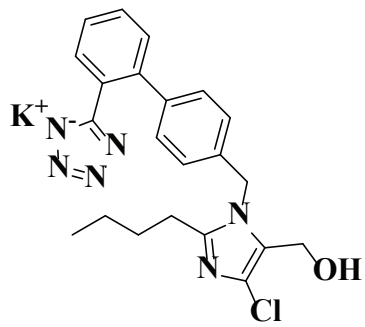

Figure 3. Losartan potassium (LOS-K)

Losartan potassium (LOS-K) is a synthetic antihypertensive agent known as an angiotensin II receptor antagonist. Its chemical structure is defined as a specific compound 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-((2-(1*H*-tetrazol-5-yl) (biphenyl-4-4-yl) methyl) imidazole (Magrone et al., 2020; Mostafa-Hedeab, 2020).

TMPRSS2 BLOCKERS

TMPRSS-2, a specific serine protease, is a possible and specific target for the COVID-19 treatment. In the beginning stage of the pandemic, nafamostat, a serine protease inhibitor that acts on TMPRSS-2, was investigated for its efficacy in treating COVID-19 pneumonia among elder patients who need oxygen therapy. Other similar compounds include Nafamostat, Camostat, and Upamostat (Gunathilaka, 2023; Zhang et al., 2024).

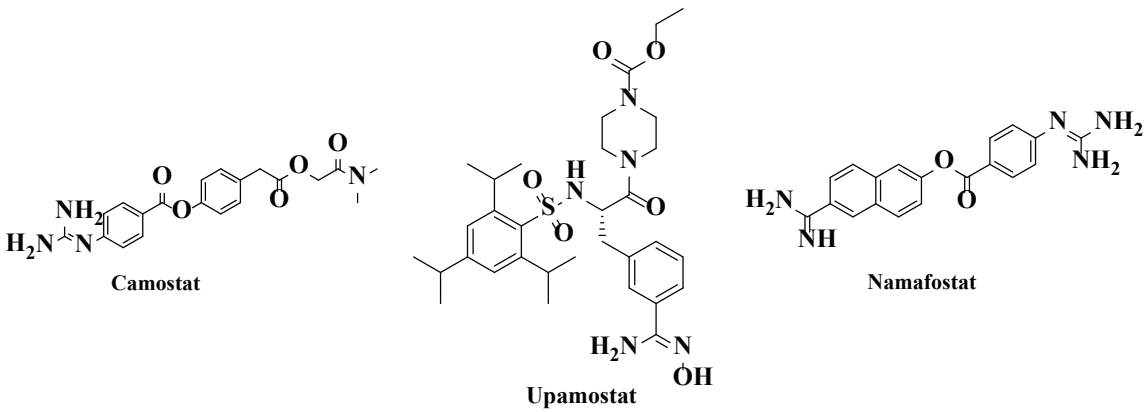

Figure 4. Structures of TMPRSS2 Inhibitors

THE VIRAL PROTEASE INHIBITORS

After the virus releases its genetic material into the host cell, the host's ribosomes translate it into a long polyprotein chain. However, this polyprotein must be broken down into smaller, functional viral proteins—including the essential RNA-dependent RNA polymerase (RdRp). To facilitate this cleavage, the virus relies on two key proteases: 3CLpro (also known as the main protease) and PLpro (papain-like protease). These enzymes systematically process the polyprotein, enabling the production of mature viral proteins necessary for replication and infection. Lopinavir was originally formulated as a therapeutic agent for HIV, specifically targeting the 3C-like protease (Figure 5.) (Sarkar et al., 2024). This enzyme is classified within the cysteine protease family and the medication functions by imitating the transition state of the hydrolysis reaction. Because of its low metabolic stability, lopinavir is often used in combination with ritonavir (Figure 6.). The combination of lopinavir and ritonavir was commonly used during the early phase of the COVID-19 pandemic. Consequent clinical trials demonstrated that incorporating it into standard care does not provide any benefits for patients (Keller et al., 2022; Singh et al., 2020).

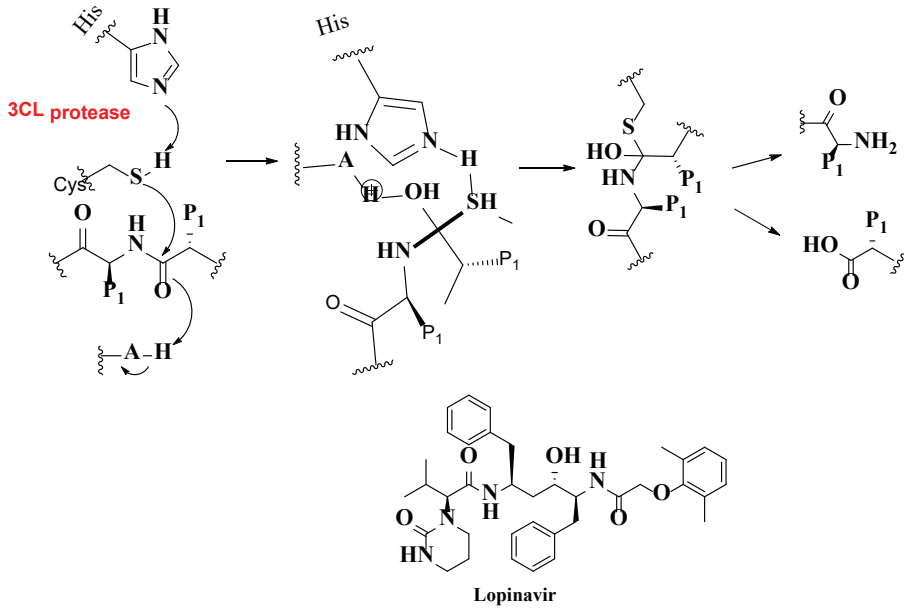

Figure 5. The Chemical representation of the mechanism of action of Lopinavir

The combination of nirmatrelvir and ritonavir shows great promise, as it is about 88% effective in preventing hospital admission or mortality in adult outpatients when administered within a specific 5 days following the appearance of the virus COVID-19 symptoms (Figure 7.). However, the cytochrome inhibitor ritonavir has the specific potential to cause significant interactions with other specific medications, which need to be carefully evaluated.

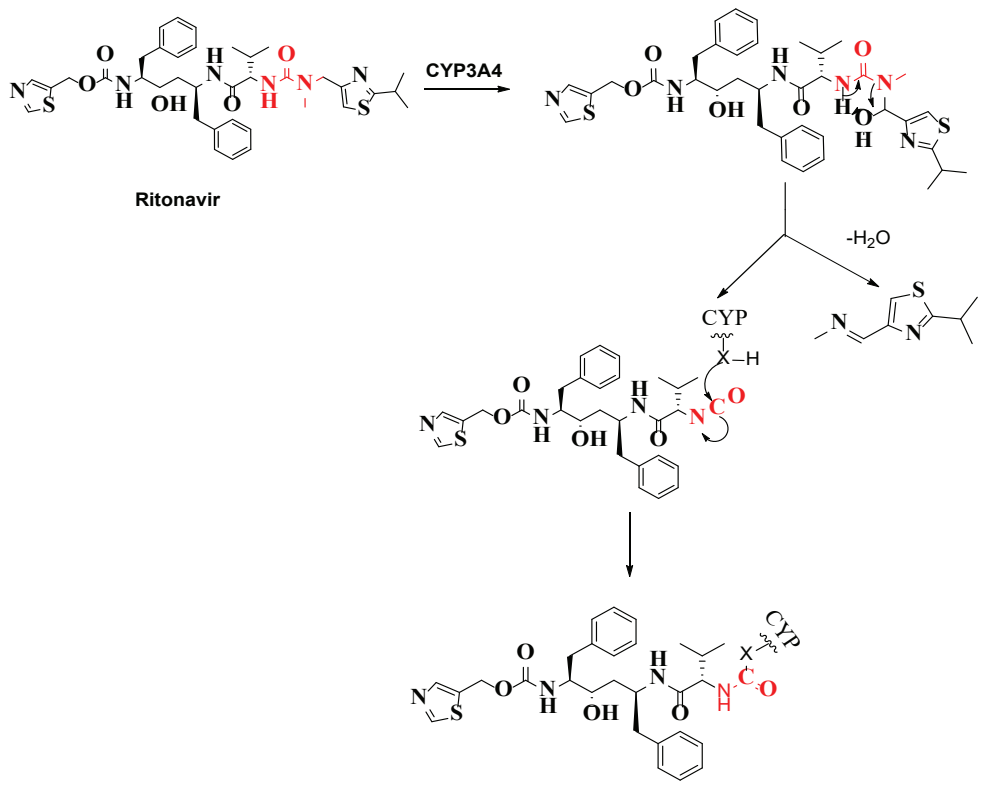

Figure 6. Ritonavir serves as a pharmacokinetic enhancer for Lopinavir

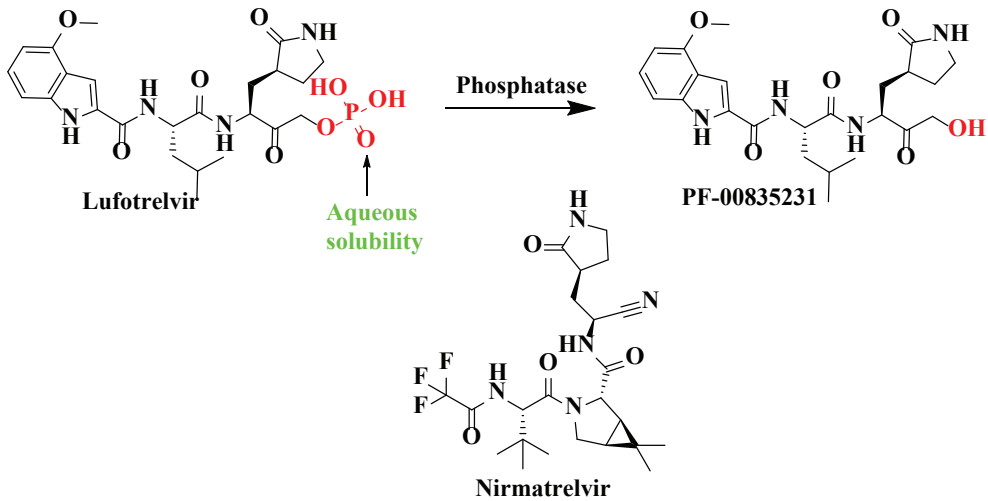

Figure 7. The molecular structures of Lufotrelvir, PF-00835231, and Nirmatrelvir

RNA POLYMERASE INHIBITORS

In the search for antiviral drugs, one common method is to inhibit RNA polymerase. Inhibitors of this enzyme are often addressed using modified nucleosides with altered ribose configurations (Kalkanli et al., 2021). Following tri-phosphorylation by kinases, these changed nucleosides can be recognised by RNA polymerase and used as substrates, resulting in their incorporation into the elongation of the RNA chain. However, these structural changes prevent the addition of further nucleotides, effectively terminating the elongation of the RNA chain (Figure 8.) (Patel et al., 2021a).

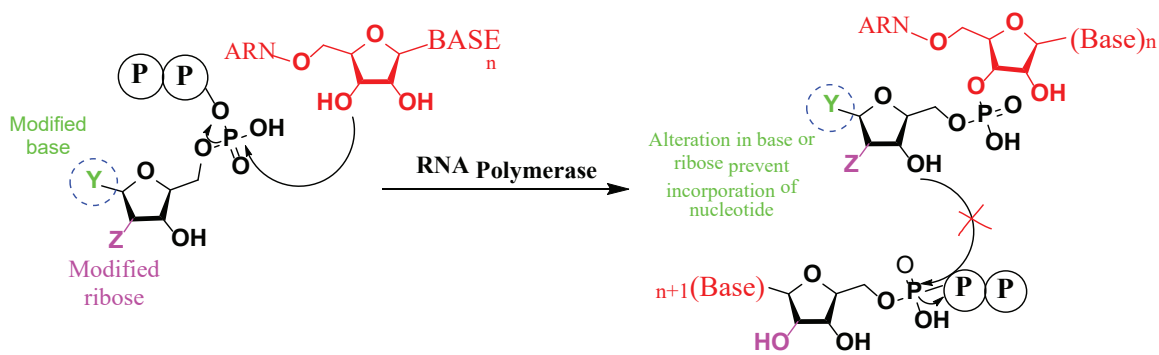

Figure 8. The fundamental mechanism by which nucleoside-type RNA polymerase inhibitors operate

Remdesivir, developed by Gilead Sciences, was the inaugural drug for COVID-19 to receive approval from the FDA. Following phosphorylation, this molecule can be regarded as an ATP analogue, which serves as a specific medium, like a substrate for RNA-dependent RNA polymerase. Remdesivir exhibits certain structural anomalies (Figure 9.). Its adenine component undergoes modification and C-C bond linkage to ribose, making it a C-nucleoside. The occurrence of the chemical cyano group at the anomeric carbon is rare, leading to decreased activity on mammalian RNA polymerases. As a prodrug, the phosphorus atom in Remdesivir is integral to the phosphoramidate group that must undergo hydrolysis to produce the corresponding phosphate.

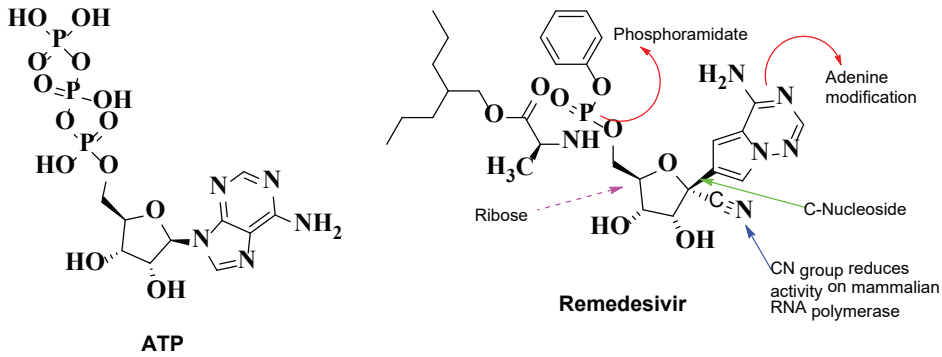

Figure 9. Structural comparison of Remedesivir with ATP

Another ProTide pro-drug, initially developed for hepatitis C treatment, is bemnifosbuvir (AT-527), which is orally available (Good et al., 2025) Atea Pharmaceuticals developed the product, which was subsequently licensed to Roche for markets outside the USA, identified by the research code RO7496998. The drug was subjected to bioactivation via the previously mentioned process, resulting in an adenosine fluoro analog (Figure 10.). After triphosphorylation, this medication inhibits and block the RNA polymerase enzyme of the virus SARS-CoV-2.

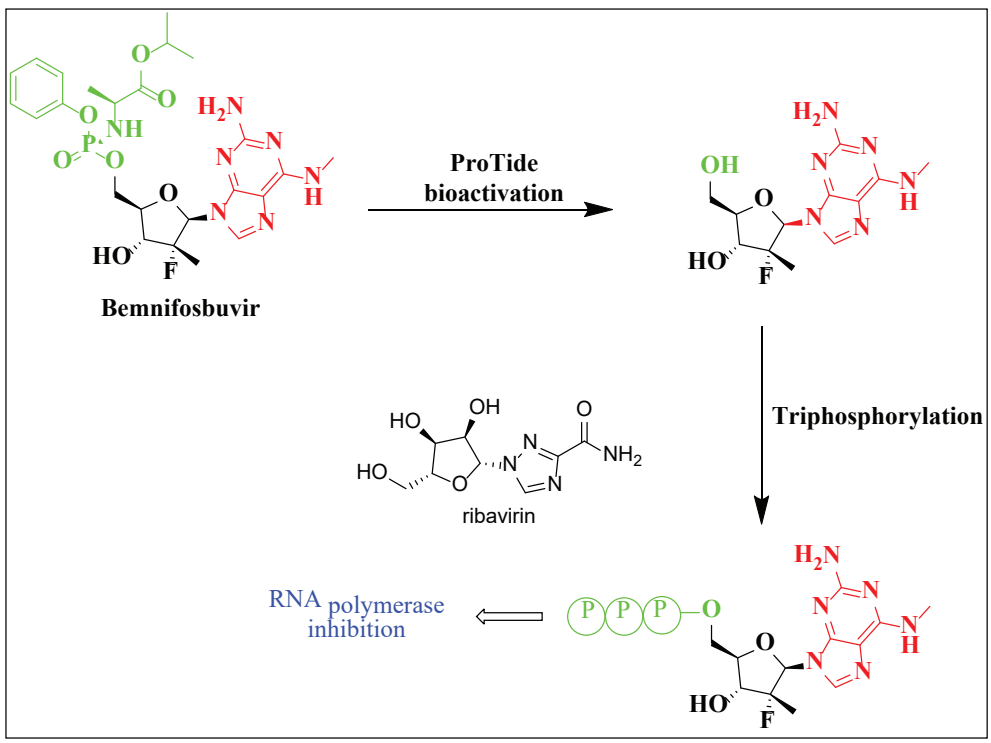

Figure 10. Bioactivation and mechanism of action of Bemnifosbuvir

STRATEGIES IN MEDICINAL CHEMISTRY SEEKING SPECIFIC, EFFECTIVE INHIBITORS OF THE SARS-COV-2 VIRUS

Identifying the specific lead compounds is an important step in researching and developing new medications. Insights gained from discovering and developing inhibitors for SARS-CoV can inform some standard medicinal chemistry methods to help find candidate drugs for SARS-CoV-2 in these urgent circumstances. A variety of strategies are employed in

the pursuit of new therapeutics. These methods encompass drug repurposing, comprehensive screening techniques that can involve either computational (*in silico*) or laboratory-based (*in vitro*) approaches, and the use of target-oriented rational drug design. Additionally, the integration of natural products, including elements from traditional Chinese medicine, plays a significant role in this research landscape (Cao et al., 2020; Sigfrid et al., 2019).

Repurposing of the drug / drug reposition

Drug repurposing is an interesting technique to identify new applications for existing drugs or substances. This strategy enables the rapid identification of new therapeutic alternatives that are either presently available for clinical use or may be expedited for approval to address a variety of diseases and disorders. Since the SARS-CoV-1 pandemic, there has been a concerted effort to repurpose approved drugs (Figure 11.). Additionally, we provide several examples of potential SARS-CoV-2 treatments identified through this strategy, as represented in the figure (Gordon et al., 2020; Zhang et al., 2023).

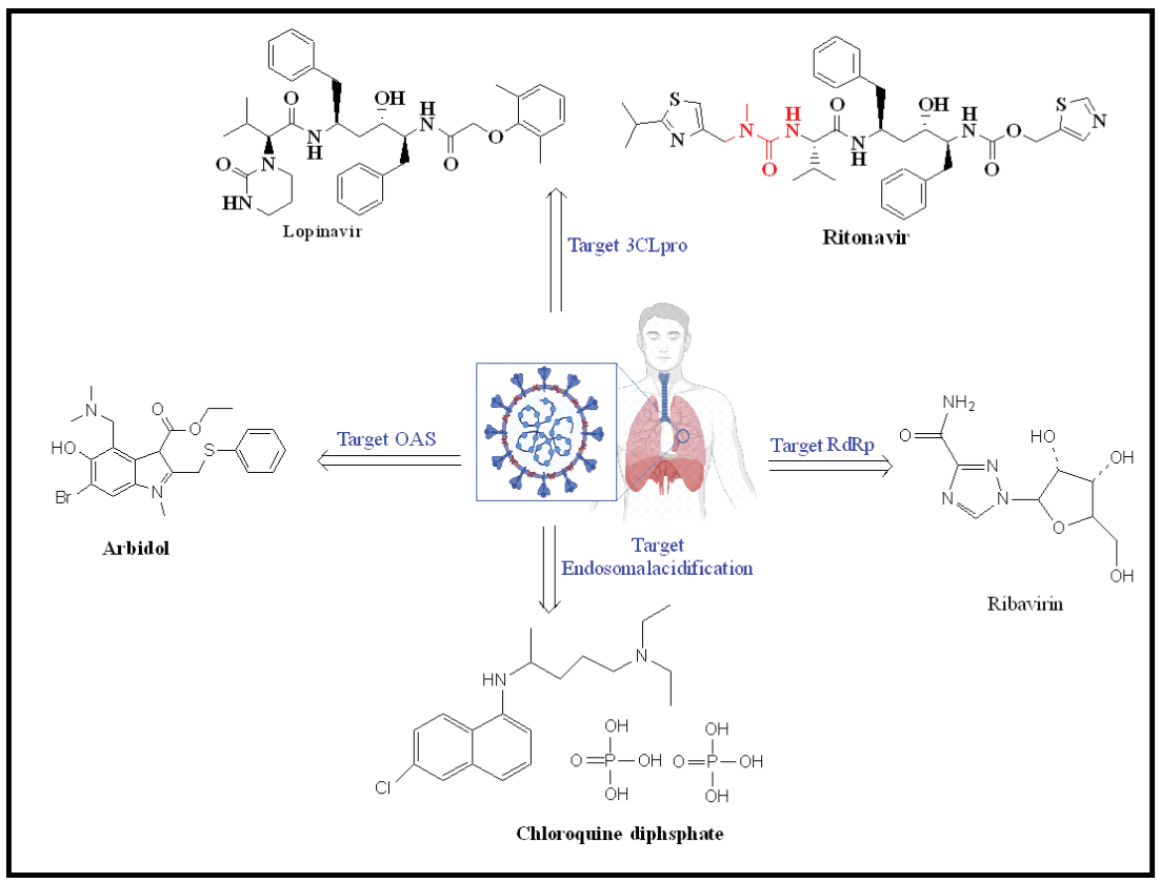

Figure 11. Schematic presentation of Repurposing of existing Anti-viral agents as possible inhibitors of SARS-CoV-2 (RdRp RNA RNA-dependent RNA polymerase, 3CLpro= 3 Chymotrypsin-like protease, OAS=Oligoadenylate synthetase)

Reposition of current extended-spectrum antiviral drugs

A promising way to identify and specify the potent treatments against the COVID-19 virus, SARS-CoV-2, is by repurposing existing broad-spectrum antiviral drugs. Several traditional methods can be considered to develop or evaluate new and specific broad-spectrum coronavirus inhibitors (Figure 12.).

One approach involves repurposing nucleoside analogues to inhibit and block the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), an enzyme that is conserved among various coronavirus families and is significant for the life cycle of the virus (Duflos et al., 2023). RdRp serves as an excellent target for broad-spectrum antiviral treatments. Inside the cell, kinases convert these nucleoside analogues into their active triphosphate forms, which are then involved and change into the expanding RNA chain, subsequent in the cessation of the replication process and contributing to their antiviral effects. However, some nucleoside analogues, like ribavirin, are ineffective against coronaviruses to probe the function of the 3'-5' exoribonuclease (ExoN). Remdesivir is an inhibitor of RdRp that has a wide range of activity against coronaviruses (Fearns & Deval, 2016; Wu et al., 2020).

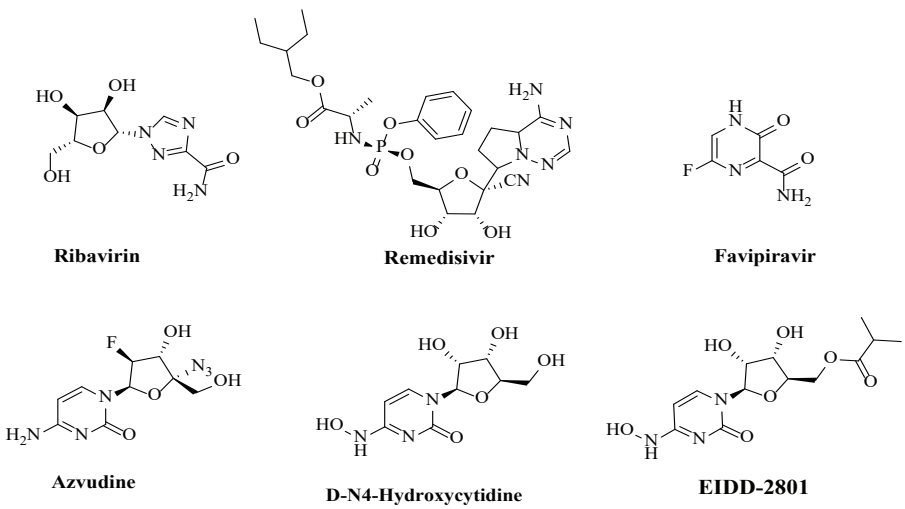

Figure 12. The chemical structure of Ribavirin, Remdesivir, Favipiravir, FNC, NHC, and EIDD-2801

Nitazoxanide is an antiparasitic agent with an extended spectrum activity that can suppress SARS-CoV-2 and exhibit an EC50 of 2.12 μM in Vero E6 cells. This drug, which induces interferon, is currently under investigation for its specific potential to treat a v variety of medical conditions. Niclosamide, ciclesonide, and nelfinavir exemplify antiparasitic or host-targeted agents with extended-spectrum activity, capable of suppressing SARS-CoV-2 through multifactorial mechanisms—including inhibition of viral entry, replication, protease activity, and host inflammatory pathways. Their study during the pandemic highlighted the strategic importance of drug repurposing, particularly for rapidly addressing emerging viral infections when specific antivirals are limited (Figure 13.).

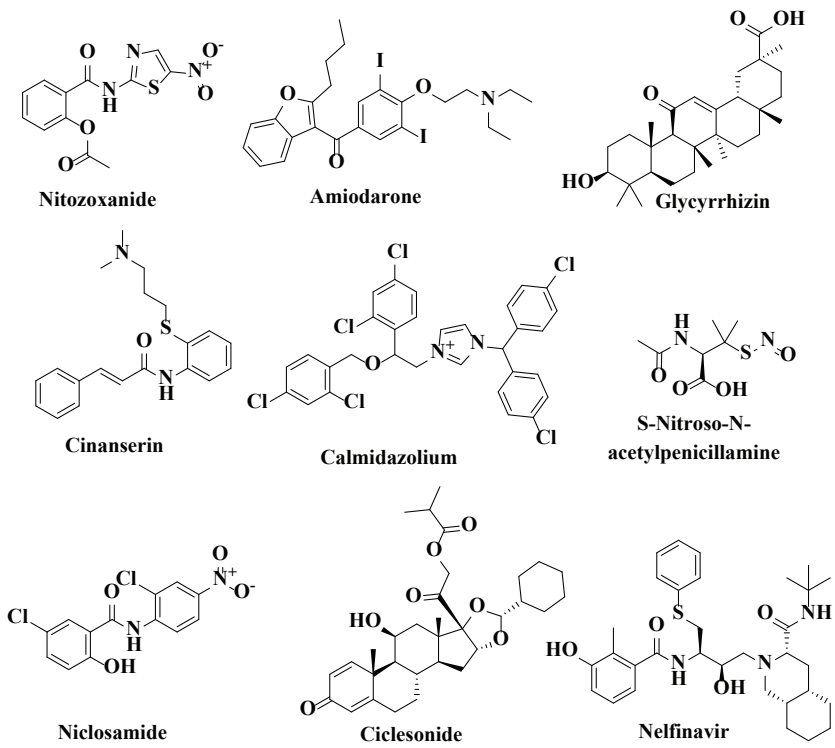

Figure 13. Selected drug structures suitable for repositioning in the treatment and prevention of SARS-CoV-1 & SARS-CoV-2, the viruses responsible for the more severe acute respiratory syndrome coronavirus

The antiarrhythmic medication amiodarone diminished the step of replication of SARS-CoV-1 in infected Vero cells (Hamilton et al., 2020). It seems to interfere with the endocytotic pathway, blocking the entry of the virus into endosomes (Stadler et al., 2008) **Glycyrrhizin** demonstrated the ability to inhibit viral replication in Vero cells, showing an EC50 of 300 mg/L, and may also help prevent the entry of the virus (Zhou et al., 2020). S-nitroso-N-acetylpenicillamine has emerged as a noteworthy nitric oxide donor with potential antiviral properties (Goudie et al., 2016) Research indicates that it can significantly reduce the replication of SARS-CoV-1 in a dose-dependent manner. In a thorough investigation of a library consisting of 8,000 approved drugs, cinanserin—acting as a serotonin antagonist—was identified as a promising inhibitor of SARS-CoV-1 (Rukthong et al., 2020). Its mechanism targets the virus's main protease (Mpro), showcasing an IC50 value of 4.0 μM. Additionally, the calmodulin antagonist calmidazolium has been demonstrated to inhibit SARS-CoV-1 Mpro with a Ki value of 61 μM, following virtual screening and molecular docking studies. virus (Han et al., 2023). Furthermore, compounds like cycloheximide and anisomycin, which are known to obstruct protein processing, have shown remarkable efficacy against both coronaviruses (Bustos-Hamdan et al., 2024). Lopinavir, an HIV protease inhibitor, demonstrated greater and specific efficacy against SARS-CoV-1 and the Middle East respiratory syndrome coronavirus. Loperamide, an antidiarrheal medication, demonstrated moderate inhibitory effects against both coronaviruses. Emetine, an alkaloid known for its anti-protozoal and emetic properties, has shown considerable antiviral effectiveness in combating MERS-CoV. The antiparasitic medications such as chloroquine, hydroxychloroquine, and mefloquine exhibited moderate efficacy against both coronaviruses (Figure 14.). Additionally, E-64-D, a cathepsin inhibitor, was effective in suppressing bothcoronaviruses (Luong et al., 2025).

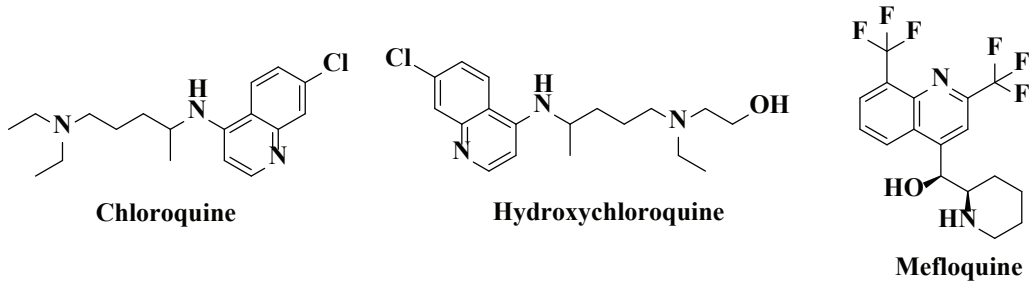

Figure 14. Structures of anti-protozoal agents effective against MERS-CoV

Azvudine, which was originally designed for HIV, a nucleoside-based inhibitor, is safe and highly effective for SARS-CoV-2 RdRp, demonstrating the potential use in the treatment of COVID-19. **β-D-N4-Hydroxycytidine** is an N-hydrolysed analogue of cytidine. Originally used to induce genetic mutations in bacteria, it has shown a wide range of effectiveness against specific and various RNA viruses, including SARS-CoV and HCoV-NL63 (Leger et al., 2022; Pinzi et al., 2021).

The second method of approach focuses on creating drugs for SARS-CoV-2 that disrupt key metabolic processes in the host's cell. The virus relies on the chemicals, enzymes, and organelles these cells supply to facilitate its replication. A prominent illustration of this strategy is the suppression of dihydroorotate dehydrogenase (DHODH), an enzyme involved in the de novo production of pyrimidine nucleotides. These nucleotides are vital for the formation of viral genomic RNA or DNA. Consequently, DHODH presents a promising target for developing inhibitors to halt coronavirus replication. Teriflunomide is the active metabolite derived from leflunomide (Figure 15.), is one such DHODH inhibitor that is used in clinical practice to treat immune diseases (Zhu et al., 2022).

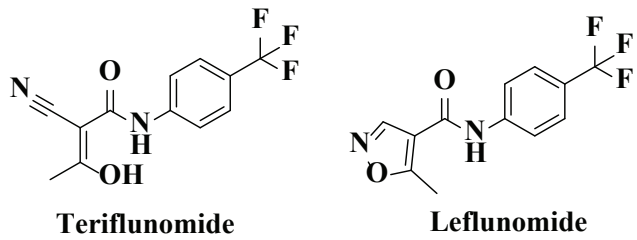

Figure 15. Structures of dihydroorotate dehydrogenase inhibitors

Ivermectin (Figure 16.) is a commercially available anti-parasitic medication that has been recognised for its specific broad-spectrum antiviral activity, showing a significant suppressive impact on SARS-CoV-2 in laboratory conditions. When Vero-hSLAM cells were disease-ridden with SARS-CoV-2 and treated with ivermectin, a reduction of the RNA of the virus by approximately 5000 times was observed after 48 hours (Parihar et al., 2022; Petty & Malani, 2022). Ranitidine has drawn scientific attention for its unexpected anti-parasitic and antiviral potential, including a significant suppressive impact on SARS-CoV-2, beyond its conventional role as an H_2-receptor antagonist. This interest emerged from drug-repurposing and *in silico* screening studies, which suggested that ranitidine may interfere with key molecular processes involved in viral survival and replication. Mechanistically, ranitidine is thought to modulate host cell pathways rather than directly targeting the virus, including alteration of endosomal pH, lysosomal function, and cellular protease activity, which are crucial for viral entry, uncoating, and replication.

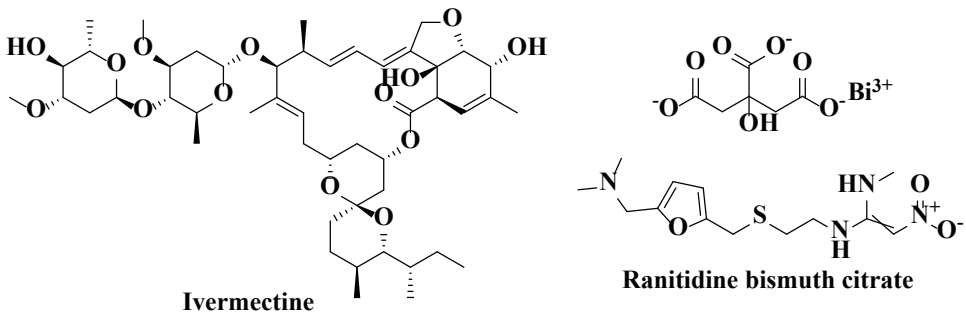

Figure 16. Structures of anti-parasitic agents having SARS-CoV-2 inhibitory activity

EXTENSIVE SCREENING CONDUCTED THROUGH *SPECIFIC IN SILICO* OR *IN VITRO* APPROACHES

Advancements in the bioscience and the utilisation of computer-assisted drug design (CADD), virtual screening has emerged as an important addition to the specific high-throughput screening in the quest for new anti-coronavirus treatments: A. Ligand-oriented virtual screening. B. Target-oriented virtual screening.

A. LIGAND-ORIENTED VIRTUAL SCREENING

A widely used method in CADD is ligand-oriented drug design, instrumental in the specific absence of the 3D structure of the target receptor. By analysing a collection of active agents that interact with a specific receptor target, researchers can uncover the physicochemical and structural characteristics that contribute to the observed biological activity, as similar structures often lead to similar biological effects. Various methods utilised in virtual screening ligand-based drug design include pharmacophore modelling, quantitative structure-activity relationships, and artificial intelligence.

Pharmacophore modeling

A pharmacophoric model illustrates how the chemical features of the ligands are spatially arranged, which is crucial for their binding with the target receptor. Pharmacophore modelling relies on several crucial chemical features that play a vital role in understanding molecular interactions. These features include hydrogen bond donors and acceptors, the presence of aromatic rings, regions that are hydrophobic, as well as entities that are positively or negatively charged and can be ionised. By analysing these characteristics, researchers can better predict how different compounds will interact within biological systems (Chen et al., 2023). By utilising pharmacophore-oriented virtual screening, one can discover ligands that possess distinct scaffolds while maintaining comparable spatial configurations of critical interacting functional groups. Some of the most widely used applications for automatically generating pharmacophore models incorporate Catalyst, PHASE, LigandScout, GALAHAD, and PharmMapper (Table 1.) (Williams et al., 2021; Yu & Chang, 2020).

Table 1. Tools for automatically generating pharmacophore models

S. N.	Tool	Description
1.	**Catalyst**	The Catalyst program employs an algorithm designed to recognise the 3D- structures of chemical properties that are prevalent among a group of ligands. Each configuration is assessed for its estimated rarity and its degree of similarity to the provided input set (Zaidi & Dehgani-Mobaraki, 2021).
2.	**LigandScout**	LigandScout functions as an automated tool designed to create pharmacophoric models that identify and classify interactions between proteins and ligands, such as hydrogen bonds, charge transfers, and lipophilic portions. These models serve as the basis for efficient virtual high-throughput screening (Gurung et al., 2021).
3.	**DISCO**	An automated pharmacophore approach is DISCO, which evaluates data to identify all appropriate pharmacophore hypotheses, serving as a complementary tool for 3D QSAR (Chang et al., 2022).
4.	**PharmaGist**	PharmaGist is a free online tool that creates ligand-based pharmacophore models using a collection of drug-like compounds (up to 32 specific molecules) that exhibit a binding affinity for the target protein (Hosseini, et al., 2021).
5.	**PharmMapper**	PharmMapper is a complementary online service frequently employed to determine possible receptor targets for a specific small molecule through the pharmacophore mapping method (Chang, et al., 2022).
6.	**Pharmer**	Pharmer is an innovative program designed for pharmacophore modelling that adeptly organises molecular data using the unique Pharmer KDB-tree and bloom fingerprints. This approach enables the swift assessment of millions of compounds in a timely and efficient manner, streamlining the evaluation process for researchers and scientists. With its advanced capabilities, Pharmer significantly enhances the speed and accuracy of pharmacophore analysis (Seidel et al., 2020).
7.	**PHASE**	PHASE is a tool for advanced pharmacophore-based methods that utilises an innovative, unique tree-based partitioning approach to delineate the shared spatial functional group configuration in a collection of bioactive ligands (Giordano et al., 2022).
8	**ZINCPharmer**	ZINCPharmer is an accessible web server that allows users to screen small compounds from the database of ZINC utilized by the search tool, i.e. Pharmer pharmacophore. You can create an initial pharmacophore hypothesis by using PDB structures or by importing pharmacophore models created with various third-party software (Qing et al., 2014).
9.	**e-Pharmacophore**	The e-pharmacophore method offers an innovative approach to pharmacophore modelling by focusing on energetically optimised, structure-based techniques. This advanced methodology efficiently screens a large array of chemical compounds while assessing the interactions between proteins and ligands. Utilising the Glide XP scoring function, it proves to be highly effective for database screening, providing a robust framework for identifying potential drug candidates (Riziotis et al., 2023).
10.	**GASP**	The GASP program utilises a genetic algorithm (GA) to overlay a collection of flexible ligands. It begins by selecting the ligand with the least complex chemical characteristics as a template, which is then used to effectively position the other molecules in the series. This method allows for a more optimised fit of the ligands, enhancing the overall molecular alignment (Jiang et al., 2020; Vuorinen et al., 2014).
11.	**GALAHAD**	GALAHAD functions as a pharmacophore program designed to flexibly align with specific small molecules that engage with a specific target protein, focusing on those that exhibit similar patterns and shapes in their interactions (Wang et al., 2017).

The quantitative structure-activity relationships (QSARs) studies of bioactive substances

QSAR research is based on the idea that differences in the bioactivity of drugs might be linked to changes in their molecular structures. These methods are frequently used in drug development, especially during hit-to-lead identification and optimisation (Liu et al., 2010). These correlation studies create a statistical model that can assess the biological efficacy of novel compounds (Table 2.). To generate a reliable QSAR model, several key requirements must be met: (a) an adequate quantity of data featuring biological activities derived from standardized experimental procedures, (b) careful screening of compounds for both training and test, and (c) ensuring there is no specific autocorrelation amongst the physicochemical specific properties of the ligands, as such a condition may result in data overfitting, and (d) The final model's applicability and predictability must be validated both internally and externally. Based on chemometric methodologies, QSAR techniques are classed as linear or nonlinear (Alzain et al., 2024; Koes & Camacho,

2011). The linear methodology involves a range of analytical techniques, including partial least squares (PLS), linear regression (LR), multiple linear regression (MLR), principal component analysis (PCA), and principal component regression (PCR). These methods are typically utilised for their straightforward approach to modelling relationships between variables.

On the other hand, nonlinear QSAR methodologies embrace more complex techniques such as k-nearest neighbours (kNN) and artificial neural networks (ANN), including Bayesian neural networks. These methods are designed to capture intricate patterns and relationships in data that linear models might overlook (Gaurav & Gautam, 2014; Song et al., 2009).

Table 2. Various software tools are available to compute molecular descriptors essential for developing QSAR models.

S. N.	Tool	Description
1.	**ADMET Predictor**	It predicts more than 140 attributes, including solubility, logP, pKa, Ames mutagenicity, and CYP metabolism sites (Salam et al., 2009).
2.	**ChemAxon**	The tool offers a comprehensive range of chemical calculations, including important metrics such as molecular weight, elemental composition, logP, pKa, logD, logS, and counts of hydrogen bond donors and acceptors (HBDA). Additionally, it provides both 2D topological and 3D geometric descriptors, enabling a thorough analysis of chemical properties (Creevey et al., 2023; Schneidman-Duhovny et al., 2008).
3.	**PaDEL-Descriptor**	PaDEL-Descriptor is an independent software tool designed to calculate molecular descriptors and fingerprints. It features a total of 797 descriptors, which include the specific 663 1D and 2D descriptors, along with 134 3D descriptors, as well as ten specific different types of fingerprints (Neves et al., 2018).
4.	**E-DRAGON**	E-DRAGON serves as the digital counterpart to the previously discussed software, DRAGON. This application is capable of calculating more than 1,600 molecular descriptors, which play a crucial role in examining the relationships between molecular structure and its corresponding activities or properties (Vilar & Costanzi, 2012).
5.	**CODESSA PRO**	CODESSA PRO is a powerful software tool designed for analysing quantitative structure-activity and structure-property relationships (QSAR/QSPR). It enables users to calculate a wide range of molecular descriptors derived from both two-dimensional and three-dimensional molecular geometries, as well as from quantum-chemical wave functions of small molecules. This program is particularly valuable for researchers looking to explore the relationships between molecular structure and biological activity or other properties in a detailed and computationally efficient manner (Serafim, et al., 2023; Megantara et al., 2022).
6.	**Pre-ADMET**	PreADMET is a web-based tool designed to evaluate a range of drug-like physicochemical characteristics. It analyses important factors such as molecular weight, lipophilicity (logP), water solubility, and polar surface area. This tool is essential for researchers and developers in the pharmaceutical industry, as it aids in assessing the potential of compounds during the early stages of drug discovery. By providing valuable insights into these properties, PreADMET helps streamline the process of identifying viable drug candidates (Patel et al., 2021b).

The impression of artificial intelligence on the discovery of novel anti-coronavirus therapeutics

The new technology, Artificial Intelligence (AI), refers to the capability of machines to learn from data. The application of various computational modelling techniques has been utilised to anticipate the biological outcomes and toxic effects of pharmaceutical compounds (Ashraf et al., 2023). AI significantly contributes to the process of drug discovery, with applications like predicting protein folding, analysing protein-protein interactions, conducting virtual screenings, performing QSAR assessments, evaluating ADMET properties, and creating new drugs from scratch. Two key technologies frequently utilised in the field of rational drug design are machine learning (ML) and deep learning. These advanced methods

have transformed the way researchers approach drug development, enabling them to analyse vast datasets and predict how different compounds will interact with biological targets. By leveraging these techniques, scientists can streamline the drug discovery process, making it more efficient and targeted (Tallei et al., 2021).

B. RATIONAL DRUG DESIGN WITH TARGET-ORIENTED METHOD

Recent advancements in high-resolution cocrystal structures have confirmed the mechanisms of action and provided valuable insights into the structural elements that influence binding interactions. In the field of drug development, target-based rational drug design focuses on identifying promising drug candidates with therapeutic relevance by analysing the interactions between ligands and their specific targets. This approach highlights the importance of understanding these relationships to enhance the efficacy of novel treatments (Ruusmann et al., 2014). Molecular docking serves as a robust method for exploring essential biological questions at the specific atomic level. The main pharmaceutical targets within the replication cycle of the virus SARS-CoV-2 include Mpro, PLpro, RdRp, Spike protein, and ACE2 (Murugavel et al., 2022).

Mpro as the target

The virus SARS-CoV-2 Mpro represents a compelling aim for COVID-19 treatment because of its unique structure. This enzyme protease is crucial for the replication cycle of all coronaviruses. It functions as a homodimer composed of two promoters, A and B, which, after dimerization and activation, achieve the correct shape for catalytic activity. The active site of the enzyme comprises four pockets (S1', S1, S2, and S3), with the S10 pocket containing a catalytic dyad. This dyad, made up of the Cys145 and His41 residues, is situated between domains I and II. Small-molecule inhibitors are capable of efficiently displacing two specific water molecules at the binding site, leading to a significant boost in efficacy. Mpro cleaves viral polyproteins at the unique Leu-Gln (Ser, Ala, Gly) sequence found in all coronaviruses (Figure 17.). The human host cell proteases are unable to perform this cleavage (Lionta et al., 2014; Zhang et al., 2025). Consequently, peptidomimetics and small-molecule Mpro inhibitors are anticipated to be highly selective. The catalytic dyad consists of Cys145 and His41, with the thiol (-SH) group of cysteine playing a crucial role in the hydrolysis reaction (Citarella et al., 2021). His41 creates the necessary pH conditions to activate the -SH group, leading to a nucleophilic attack on the substrate. Figure 4 illustrates the complete process of Mpro, which can be divided into four stages: (1) His41 deprotonates the -SH group of Cys145, creating the activated thiolated ion; (2) this ion then carries out a nucleophilic attack on the carbonyl carbon of the substrate, results in the creation of a tetrahedral adduct; (3) the component peptide hydrolysis product is released, resulting in a free N-terminus, while His41 is restored; and (4) thioester hydrolysis takes place, releasing the specific residual peptide fragment possessing a free C-terminus (Jin et al., 2020; Joshi et al., 2021).

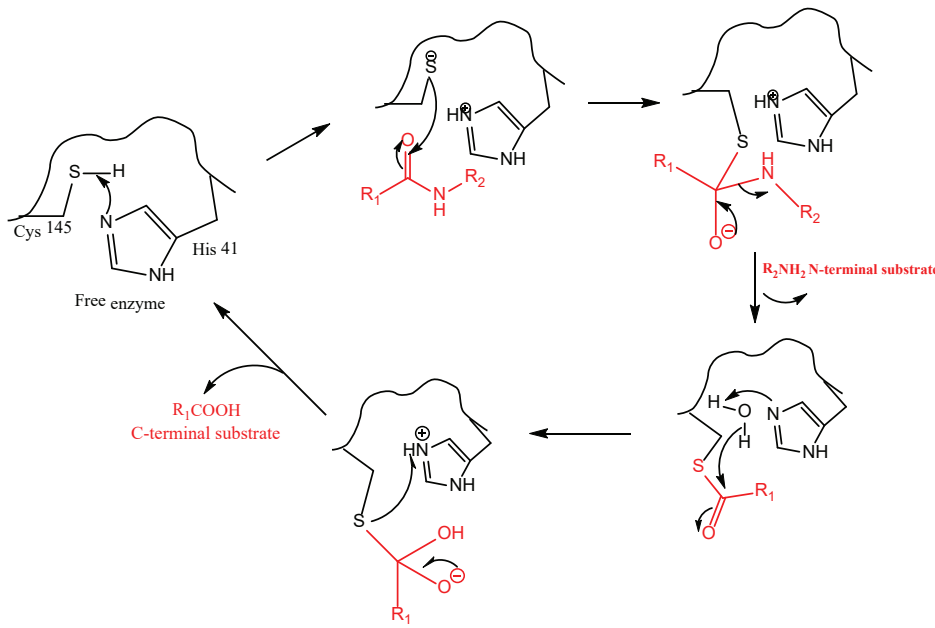

Figure 17. Understanding the Hydrolysis Mechanism of SARS-CoV-2 Mpro The hydrolysis mechanism of SARS-CoV-2 Mpro features the amino acids of the catalytic dyad highlighted in blue, while the substrate is represented in red.

SARS-CoV PLpro is an important target and is categorised as part of the CA Clan within the peptidase family. The enzyme features a precisely arranged catalytic triad made up of three key amino acids: Cys112, His273, and Asp287. These residues situate themselves at the junction of the thumb and palm subdomains, playing a critical role in the enzyme's function.

The proposed mechanism through which SARS-CoV PLpro operates is comparable to a hypothesised catalytic cycle typical of cysteine proteases. In this context, Cys112 serves as the nucleophile, while His273 functions as a versatile acid-base catalyst. Additionally, Asp287 collaborates closely with histidine to ensure proper alignment and facilitate the deprotonation of Cys112, thereby enhancing the catalytic efficiency of the enzyme (Figure 18.) (Shin et al., 2020; Zhang et al., 2020). In its unliganded form, ''E", the catalytic residues of SARS-CoV PLpro are situated in proximity sufficient to establish hydrogen bonds. This suggests that the protonation state of Cys112 may be in equilibrium with that of His273. This state of equilibrium shifts toward the reactive thiolate upon substrate binding (Figure 18, step a). Cys112 may undergo deprotonation upon binding with the substrate, leading to the formation of an enzyme-substrate (ES) complex. This complex then transitions through an addition-elimination mechanism, where the thiolate group of Cysteine112 attacks the carbonyl carbon of the peptide bond. This process results in a tetrahedral intermediate that is initially negatively charged and referred to as "TI-1" or "FP" (Figure 18, step b). The negative charge on the oxyanion within this tetrahedral intermediate is stabilised by an oxyanion hole situated near the active site of the PLpro enzyme. Notably, this oxyanion hole includes a vital tryptophan residue (Trp107), which plays a significant role in the enzymatic activity of PLpro, as demonstrated through site-directed mutagenesis studies (Gao et al., 2020; Osipiuk et al., 2021).

In its unliganded state, referred to as "E," the catalytic residues of SARS-CoV PLpro are positioned closely enough to facilitate hydrogen bonding between them. This proximity suggests that the protonation state of Cysteine112 may exist in a state of equilibrium

with that of His273. When a substrate binds, it appears to shift this equilibrium towards a more reactive thiolate form (Figure 18, step a). Another possibility is that the binding of the substrate induces the deprotonation of Cys112, resulting in the establishment of the "ES" complex. In its unliganded state, referred to as "E," the catalytic residues of SARS-CoV PLpro are positioned closely enough to facilitate hydrogen bonding between them. This proximity suggests that the protonation state of Cysteine112 may exist in a state of equilibrium with that of His273. When a substrate binds, it appears to shift this equilibrium towards a more reactive thiolate form (Figure 18, step a). Another possibility is that the binding of the substrate induces the deprotonation of Cys112, resulting in the establishment of the "ES" complex (Rut et al., 2020). An addition-elimination sequence follows, where Cys112 thiolate attacks the carbon of the carbonyl group within the peptide bond, resulting in the initial negatively charged tetrahedral intermediate, referred to as ''TI-1" or ''FP" (Figure 18, step b). The oxyanion formed during the tetrahedral intermediate is stabilised by an oxyanion hole situated near the active site of the PLpro enzyme. This crucial region includes a tryptophan residue (Trp107), which is vital for the enzymatic function of PLpro, as noted by (Baez-Santos et al. 2014). Additionally, an asparagine residue (Asn110) is highly conserved across coronaviral PLP2s and likely contributes significantly to the stability of the oxyanion hole, as it is positioned above the catalytic cysteine. When the amine group located at the C-terminal end of the substrate is removed, this results in the cleavage of the peptide bond, thereby leading to the production of the thioester precursor identified as "F (Figure 18, step c). Following this step, a sequence of addition and elimination occurs where water functions as a nucleophile, adding to the carbonyl carbon of the thioester. This reaction produces a second tetrahedral intermediate, designated as "TI-2" or "FQ" (Figure 18, step d). The negative charge on the oxyanion of this intermediate is stabilised by the oxyanion hole located within the PLpro active site (Liu et al., 2014). As the tetrahedral intermediate undergoes deconstruction, the cysteine is released, resulting in the formation of an N-terminal carboxylic acid known as "EQ." This acid may briefly be stabilized within the PLpro active site through a hydrogen bond that forms between its carbonyl carbon and the nitrogen of the indole ring in Trp107 (Figure 18, step e). The final step of this catalytic cycle involves the separation of the cleaved N-terminus from the peptide substrate, leading to the release of the end product "Q" from the active site and restoring the enzyme to its free form, referred to as "E" (Figure 18, step f) (Henderson et al., 2020).

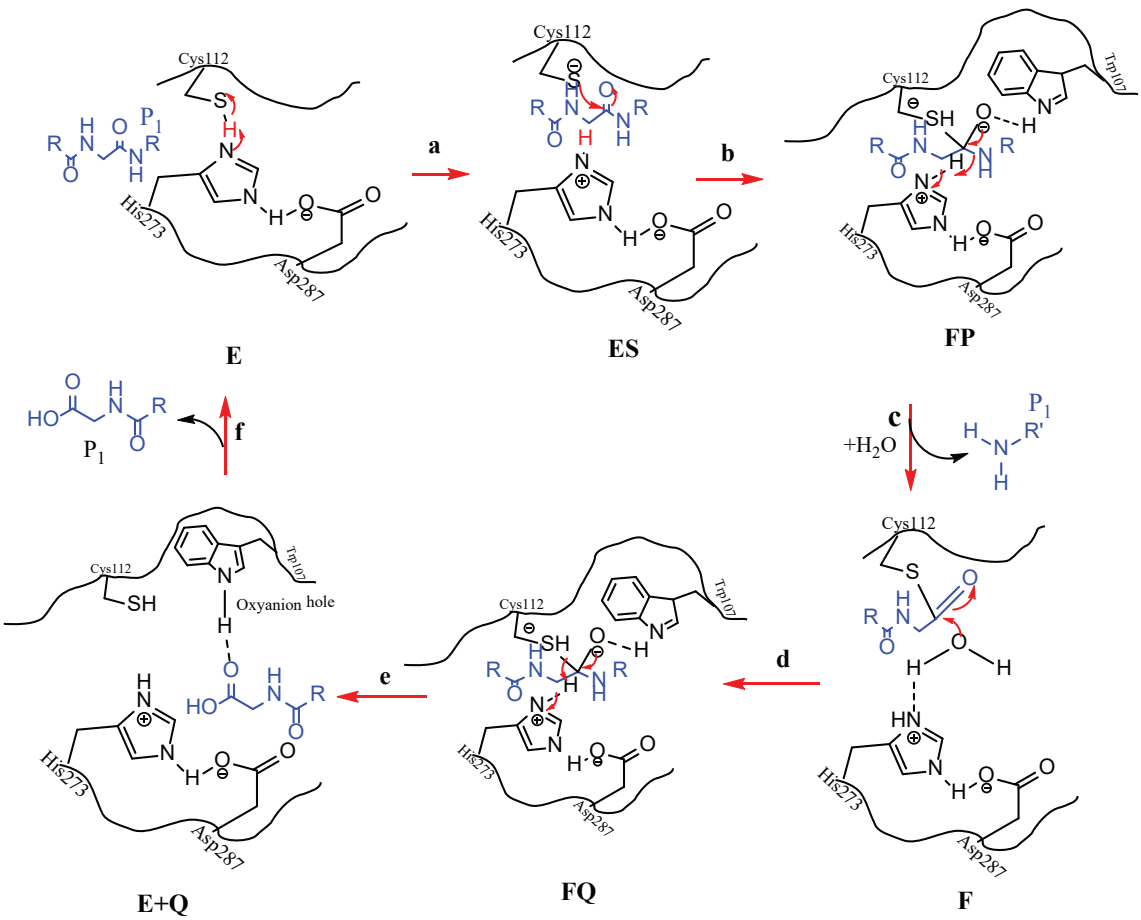

Figure 18. The catalytic mechanism of the SARS-CoV PLpro reaction is depicted in detail. Central to this process is the catalytic triad composed of cysteine (Cys112), histidine (His273), and aspartate (Asp287). The residue Trp107, which plays a critical role in forming the oxyanion hole, is also highlighted. In this illustration, the peptide substrate is shown in blue, while a water molecule involved in the catalysis is represented in black. This visual representation provides a clearer understanding of the enzyme's function and the molecular interactions at play.

The engagement of SARS-CoV PLpro inhibitors with Cys112 involves cysteine proteases that can interact with various electrophilic or "warhead" groups found in covalent inhibitors. Typically, these inhibitors begin by forming a noncovalent interaction complex within the active site of the cysteine protease, which helps position the warhead group near the reactive cysteine nucleophile (Narayanan et al., 2022). The process starts when the thiolate performs a nucleophilic attack on the electrophilic carbon of the warhead, leading to the formation of a covalently modified enzyme-inhibitor complex. This modification ultimately results in the inactivation of the enzyme.

A variety of reactive warhead groups have been recognised for their ability to inhibit cysteine proteases. These include aldehydes, epoxy-ketones, alkynes, Michael acceptors, alkyl halides, vinyl sulfones, activated esters, activated ketones, acrylamides, and nitriles (Lu et al., 2024; Machitani et al., 2020).

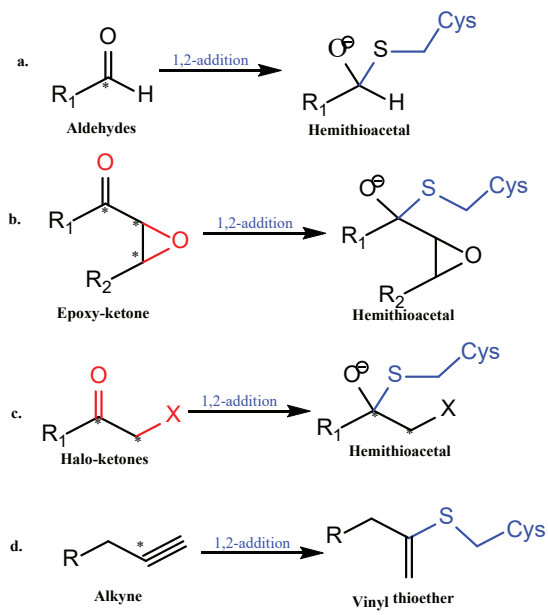

Figure 19. Several examples of cysteine protease inhibitors containing covalent "warheads" are shown here. The reactive electrophilic groups are highlighted in red, with the key electrophilic carbon—marked by an asterisk—serving as the critical site of interaction. The resulting covalent bonds between the inhibitor and the cysteine residue are depicted with arrows, while the cysteine components of the adducts are coloured in blue for clarity.

The virus SARS-CoV-2 PLpro enzyme was co-crystallised with a semisynthetic form of ubiquitin, which had its C-terminus altered to include an aldehyde functional group (Ubal).

RdRp as the target

RNA-dependent RNA polymerase (RdRp) is a viral enzyme present in nearly all RNA virus families, excluding Retroviridae, and belongs to the transferase class. Its primary function is to synthesise a complementary RNA strand by sequentially adding ribonucleotides to the growing 3′-hydroxyl end, ensuring elongation in the 5′→3′ direction. For this process, RdRp requires an RNA template, ribonucleotide triphosphates (ATP, GTP, UTP, and CTP) as substrates, and two Mg^{2+} ions within its active site to catalyse phosphodiester bond formation. Beyond its catalytic core, the enzyme also binds Zn^{2+} through tetrahedral coordination at a secondary site, where these ions help stabilise its three-dimensional structure (Vijay et al., 2024; Yi et al., 2024). Structurally, RdRp contains two distinct channels that converge at the active site: one accommodates the template RNA strand, while the other facilitates the entry of incoming nucleotide triphosphates (NTPs) (Figure 20.).

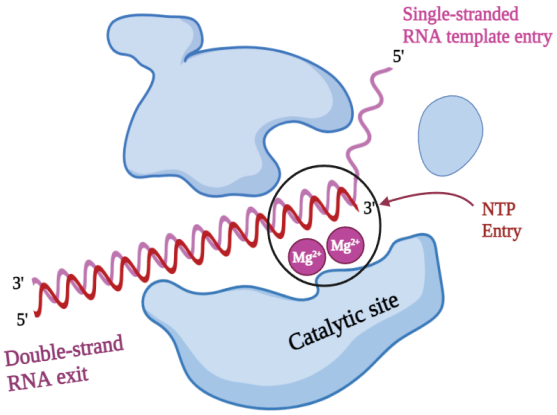

Figure 20. The Graphical depiction of the RdRp illustrates the RNA template as a blue line while the newly synthesised RNA is depicted as a red line. Mg^{2+} ions are shown in purple spheres.

The incoming nucleotide triphosphates (NTPs) are incorporated into the newly synthesised RNA strand following Watson-Crick base pairing rules: uracil (U) pairs with adenine (A) from the template strand, while guanine (G) pairs with cytosine (C). During catalysis, the 3'-hydroxyl group at the growing end of the RNA strand acts as a nucleophile, attacking the α-phosphate of the incoming NTP. This reaction results in the formation of a phosphodiester bond and the release of pyrophosphate (PPi) as a by-product (Figure 21.)

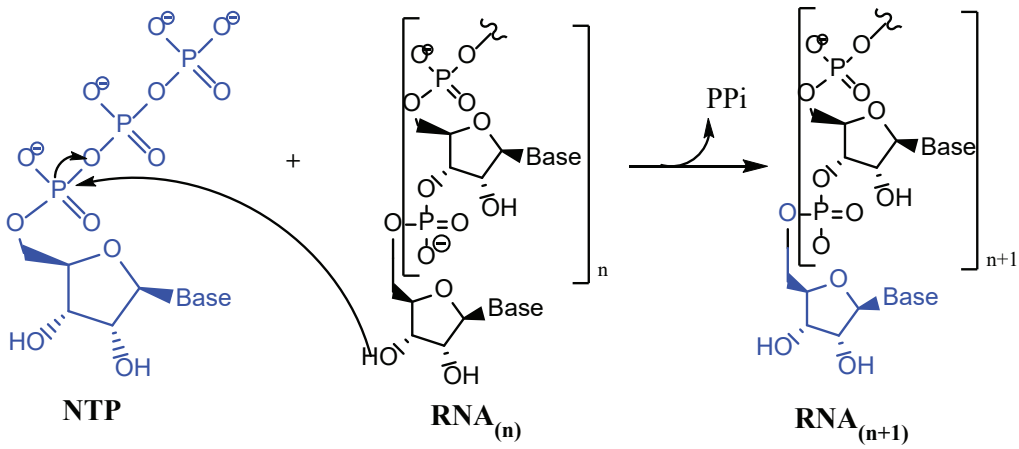

Figure 21. RdRp catalyses the RNA synthesis reaction

The facilitation of this procedure is achieved through the coordination of Mg^{2+} ions, which are arranged in an octahedral configuration via the phosphate of incoming NTP, along with three aspartate residues that exhibit a high degree of conservation across various viral RNA-dependent RNA polymerases (Figure 22.). One Mg^{2+} ion engages the specific nucleophilic attack of the 3'-hydroxyl group of the elongating RNA on the α-phosphate of the incoming nucleotide triphosphate (NTP). In contrast, another Mg^{2+} ion assists in the release of the PPi molecule. This catalytic mechanism, referred to as and is known as "two metal ions catalysis", is universally observed in all RdRps (Schimunek et al., 2024). Strategies for developing small-molecule RdRp inhibitors targeting RNA viruses have resulted in the creation of different categories of inhibitors, each acting through unique mechanisms of action: (i) nucleotide analogues (NIs), (ii) non-nucleotide analogues (NNIs), (iii) inhibitors of protein-protein interactions, and (iv) targeted covalent inhibitors (TCIs) (Godwin et al., 2024).

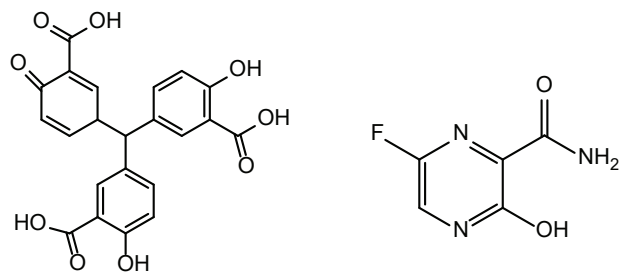

Figure 22. Small-molecule inhibitors targeting coronavirus RNA-dependent RNA polymerase (RdRp)

Nucleotide analogues (NIs) are synthetic compounds that mimic natural nucleotides and competitively bind to the RdRp active site, where their incorporation is mediated by metal ions and catalytic residues. These inhibitors compete with natural nucleotide triphosphates (NTPs) for incorporation into the elongating RNA strand, leading to either delayed or immediate chain termination depending on their specific chemical properties. A major pharmacological challenge with NIs is their intracellular delivery in the active triphosphate form. Under normal physiological conditions, the negatively charged phosphate groups significantly reduce cell membrane permeability. To overcome this limitation, researchers commonly employ prodrug strategies to improve drug absorption and bioavailability. A prominent example

is sofosbuvir (Figure 23.), an effective RdRp inhibitor pro-drug. After metabolic activation, its bioactive form (2'-deoxy-2'-fluoro-β-C-methyluridine-5'-triphosphate) functions as a potent chain terminator, effectively halting viral RNA replication (Huang et al., 2024; Molaei et al., 2024).

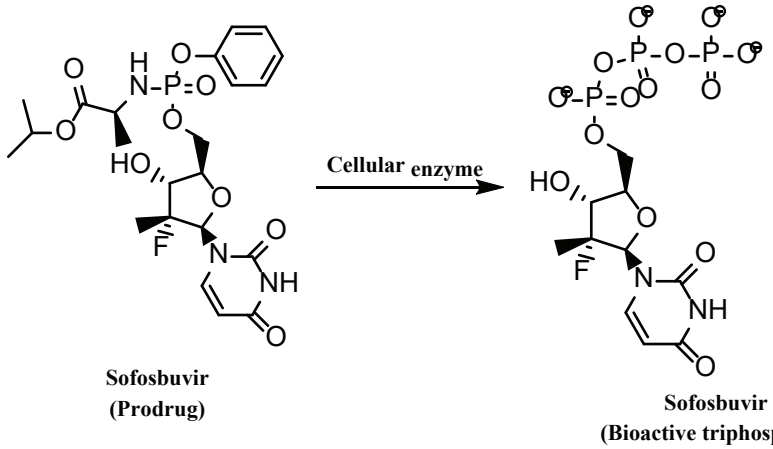

Figure 23. Schematic illustration of the enzyme-catalysed conversion of sofosbuvir prodrug into its biologically active form

Remdesivir was initially created as a therapeutic for hepatitis C but was later assessed from a collection of around 1,000 compounds for its potential against Ebola and Marburg viruses during the 2014 emergence of an epidemic in West Africa. It showed broad-spectrum antiviral properties, leading to its testing against MERS-CoV in laboratory cell-based studies. Remdesivir is a specific prodrug of an adenine derivative that belongs to the class of phosphoramidate, known for its wide-ranging antiviral effects and its role as a delayed chain terminator (Figure 24.) (Yang et al., 2024).

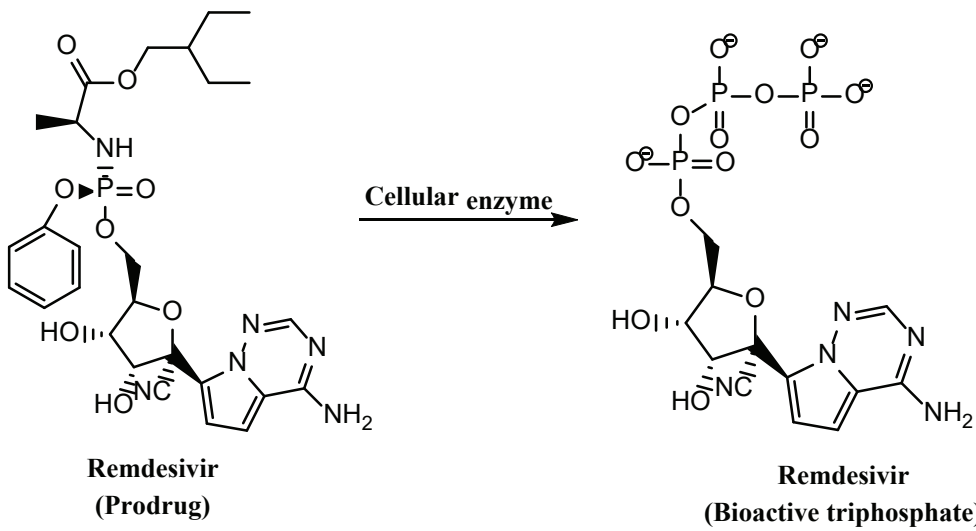

Figure 24. Schematic illustration of the specific enzymatic conversion of Remdesivir prodrug into its active biological form

Favipiravir is a prodrug that is metabolically converted into a specific favipiravir triphosphate, which is its bioactive form (Figure 25.).

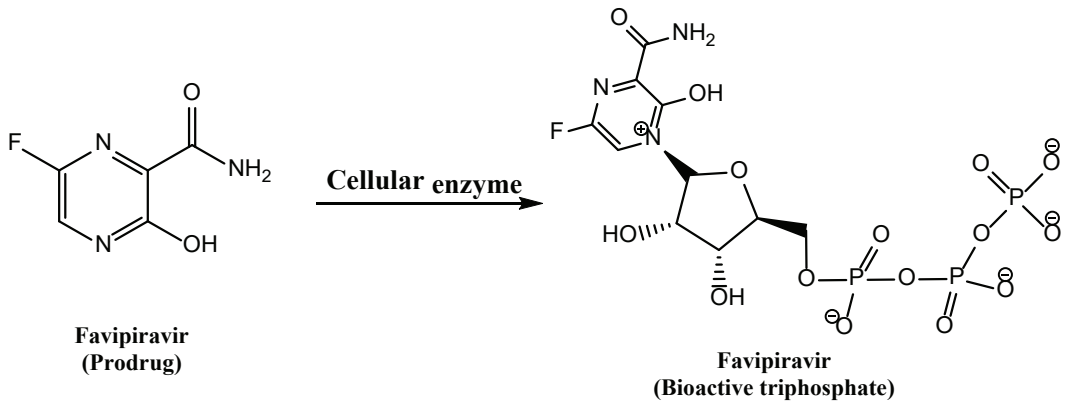

Figure 25. Metabolic activation of favipiravir from prodrug to bioactive form

Non-nucleoside inhibitors (NNIs) exert their antiviral effects through allosteric inhibition, binding to distinct pockets surrounding the polymerase active site. These include thumb domains I and II (T1/T2), palm regions I, II, and β (P1/P2/Pβ). By occupying these regulatory sites, NNIs prevent the conformational changes required for proper polymerase function. The inhibitory mechanism varies depending on the specific binding location and the polymerase's conformational state. For instance, NNIs targeting the T1 and T2 pockets primarily interfere with the initiation phase of RNA synthesis. They disrupt the critical interaction between the palm and thumb subdomains, preventing formation of a functional RdRp-RNA complex and reducing the enzyme's affinity for its RNA template (Lu et al., 2020).

Emerging as a promising new class of antiviral agents, protein-protein interaction (PPI) inhibitors target the critical interfaces between RNA-dependent RNA polymerase (RdRp) and its associated non-structural proteins. By disrupting these essential interactions, PPI inhibitors prevent proper assembly of the viral replication complex multi-protein machinery required for genome replication. One particularly compelling example involves the targeted disruption of the NS5 (RdRp)-NS3 (protease) interaction in dengue virus (DENV), which has been shown to effectively block viral replication (Goyal et al., 2020).

Targeted covalent inhibitors: reversible vs. irreversible mechanisms

Targeted covalent inhibitors (TCIs) represent another innovative strategy, incorporating specialised functional groups designed to form specific bonds with key amino acid residues on the target protein. These inhibitors fall into two distinct categories:

Reversible TCIs: These compounds establish transient interactions with their target, maintaining a dynamic equilibrium between bound and unbound states. The protein's activity can be restored upon inhibitor dissociation.

Irreversible TCIs: Characterised by their ability to form permanent covalent bonds, these inhibitors lead to sustained inactivation of the target protein (Luo et al., 2024).

Targeting host ACE2 in antiviral therapy

The initial step of coronavirus infection involves the virus attaching to specific receptors on the surface of host cells. Among these, ACE2 has been identified as a key receptor facilitating SARS-CoV-2 entry. As a result, therapeutic strategies have emerged that aim to modulate or inhibit ACE2 to block viral access. ACE2 is a zinc-dependent metalloprotease consisting of 805 amino acids, structurally divided into two primary domains: the amino-terminal catalytic domain and the carboxy-terminal domain (Lazou et al., 2024). Functionally, ACE2 plays a vital role in downregulat-

ing the renin-angiotensin system (RAS) by converting angiotensin II (Ang II) into the vasodilatory peptide angiotensin 1–7 (Ang 1–7). This enzyme is predominantly expressed in epithelial cells lining the lungs, liver, and testes. Notably, unlike the classical ACE enzyme, ACE2 is positioned on the apical surface of respiratory epithelial cells, which may enhance the likelihood of viral attachment and entry. Inhibiting the interaction between the viral spike protein and ACE2—through small molecules that disrupt critical protein-protein interactions—has been proposed as a possible intervention. Given the association of ACE2 with cardiac injury in COVID-19, therapeutic agents such as ACE inhibitors or angiotensin receptor blockers (ARBs) have been explored for their potential to mitigate heart-related complications. Among them, telmisartan has shown promise as a candidate for managing SARS-CoV-2 infection. Additionally, administering soluble recombinant ACE2 has garnered attention as a therapeutic approach. This form of ACE2 can act as a decoy receptor, binding to the viral spike protein and thereby preventing the virus from attaching to membrane-bound ACE2 on host cells. By doing so, it may help preserve endogenous ACE2 levels, which the virus tends to downregulate during infection.

CONCLUSION

The COVID-19 pandemic has triggered an extraordinary global response, placing pharmaceutical chemistry at the centre of efforts to combat the effects of SARS-CoV-2. Researchers have rapidly developed innovative methods for detecting, creating, and refining treatments for this growing threat through creative approaches and interdisciplinary collaboration. Structure-based drug design has effectively pinpointed small molecules that target essential viral components, including the main specific protease (Mpro), spike protein, and RNA-dependent RNA polymerase (RdRp). These targets have formed the basis for developing inhibitors that are both highly specific and effective, while computational modelling and molecular docking studies have significantly reduced the time needed for initial drug discovery. AI and ML have become transformative tools in drug discovery, helping to identify potential therapeutic options and repurpose existing medications. The integration of AI with medicinal chemistry has enabled the screening of extensive chemical libraries, the optimisation of pharmacokinetic properties, and the forecasting of drug resistance patterns. A significant strategy in this field is drug repurposing, which offers a cost-effective and efficient approach to finding FDA-approved drugs with antiviral effects. For instance, remdesivir and molnupiravir, originally developed for other RNA viruses, have shown effectiveness against SARS-CoV-2, leading to the creation of new formulations. In addition to small molecules, recent advancements in peptide-based therapies, monoclonal antibodies, and nanotechnology have significantly expanded the range of treatment options available. Monoclonal antibodies targeting the spike protein have been essential in preventing severe illness among high-risk groups, while nanoparticle delivery systems have enhanced the absorption and targeting of antiviral medications. Moreover, the creation of multifunctional materials that can simultaneously deliver drugs and immune modulators has opened up new avenues for combination therapies. Nevertheless, there are still significant challenges to overcome. The rise of viral variants that are more transmissible and can evade immune responses highlights the need for flexible and adaptable approaches in developing therapies. Tackling global disparities in the distribution of medical treatments and ensuring that new therapies remain affordable are also critical priorities. Finding a balance between quick medication development and thorough safety and efficacy evaluations continues to be a challenge. Moving forward, the insights gained from the COVID-19 pandemic highlight the importance of ongoing investment in medicinal chemistry

research, especially in areas like high-throughput screening, real-time genomic monitoring, and modular drug design platforms. Collaboration among academic institutions, industry, and regulatory agencies will be essential to accelerate the journey from discovery to clinical use.

The use of current technologies, teamwork, and a focus on translational research has tremendously aided our efforts to combat COVID-19. These measures not only provide hope for conquering the present pandemic, but also lay the framework for addressing future infectious disease epidemics with greater resilience and effectiveness.

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AUTHOR CONTRIBUTION STATEMENT

Study conception and design: NK; data collection: NK, SKSK; draft manuscript: NK, AK. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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