Bytes to Beside: Harnessing Computational Power in the Quest for COVID-19 Therapeutics

Calvin R. Wei[1], Saleha Tahir[2,*] and Muhammad Osama[3,4]

[1]Department of Research and Development, Shing Huei Group, Taipei, Taiwan
[2]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[3]Department of Pharmacology, University of Karachi, Karachi, Pakistan
[4]Department of Pharmacy Practice, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan
*Corresponding author: salehatahir999@gmail.com

Abstract

According to World Health Organization (WHO) statistics, COVID-19 is one of the greatest threats to mankind in the twenty-first century, with 636 million cases and up to 6.6 million deaths worldwide. With the high rate of COVID-19 infections worldwide, the emergence of SARS-CoV-2 variants was inevitable. Even though the US FDA has approved a variety of treatment plans under Emergency Use Authorization (EUA) and several vaccines have been developed to lessen the severity of the coronavirus. SARS-CoV-2 viral mutations continue to thwart scientists' efforts as the new variants avoid the suggested treatments. However, there are a variety of computational models available that provide a chance to get over the obstacles associated with creating novel medications. The application of several virtual screening methods, including pharmacophore modeling, homology modeling, QSAR, molecular docking, and molecular dynamics simulations, in repurposing SARS-CoV-2 medications. The outcomes of computer-aided drug design (CADD) investigations have been encouraging in terms of identifying possible drugs for the treatment of COVID-19 and aiding in the control effort.

Keywords: SARS-CoV-2, Drug Discovery, COVID-19, Molecular dynamic, Molecular docking, Drug repurposing, Virtual screening, Drug design

Cite this Article as: Wei CR, Tahir S and Osama M, 2025. Bytes to beside: Harnessing computational power in the quest for COVID-19 therapeutics. In: Abbas RZ, Akhtar T and Arshad J (eds), One Health in a Changing World: Climate, Disease, Policy, and Innovation. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 1-13. https://doi.org/10.47278/book.HH/2025.004

A Publication of Unique Scientific Publishers

Chapter No: 25-001

Received: 01-Feb-2025
Revised: 25-Feb-2025
Accepted: 21-Apr-2025

Introduction

Since its onset in late 2019, the COVID-19 pandemic continues to pose the greatest threat to global public health. According the World Health Organization (WHO) coronavirus illness dashboard reports that the illness has cuased more than 6.6 million deaths and 636 million infections (Kalita et al., 2023). The coronavirus, an RNA virus, is highly modified, which causes SARS-CoV-2 to evolve quickly and adds to the serious threat the disease poses to humanity. The virus's mutations have posed a huge challenge to scientists since they require constant modification of treatment protocols in order to demonstrate the most effective treatments (Cascella et al., 2023). Since outbreaks of this extremely infectious virus continue to rise in many places due to the virus's progressively developing mutant versions, significant advancements in experimental research towards a deeper understanding of SARS-CoV-2 are still being derailed. As a result, as the globe continues to struggle to contain the pandemic, substantial worldwide research is currently being conducted as researchers against time to discover suitable treatment medicines to treat COVID-19 (Cascella et al., 2023).

Antiviral, anti-inflammatory, and respiratory medicines are now the main treatments for COVID-19 ; supplementary antibody therapy are a vital and active component of treating SARS-CoV-2 infection (Niknam et al., 2022). For the treatment of COVID-19, remdesivir was the first drug authorized by the US Food and Drug Administration (FDA) and was approved on April 25, 2022, for the treatment of both children and adults (Chera et al., 2022). Because of its capacity to suppress SARS-CoV-2 in vitro, this drug was recognized as a possible candidate for use as a treatment agent for COVID-19 (Beigel et al., 2020). Early remdesivir administration dramatically decreased the viral load and pulmonary damage in SARS-CoV-2-infected monkey studies, while SIMPLE and National Institute for Allergy and Infectious Diseases (NIAID) studies supported the FDA's decision to grant emergency use authorization (EUA) on May 1st, 2022 for severe hospitalized Patients with COVID-19 (Rezagholizadeh et al., 2021; Abd-Elsalam et al., 2022; Gupte et al., 2022). The FDA has also authorized the oral antiviral medication Tocilizumab (Actemra), Paxlovid (nirmatrelvir and ritonavir), and Baricitinib (Olumiant) for people hospitalized with COVID-19 (Figure 1) (Muratov et al., 2021; Toussi et al., 2023). The use of computational software in the discovery of more efficacious therapeutic methods may prove to be useful in discovering novel drugs and drug combinations (Saloni et al., 2022) .

Drug rediscovery and repurposing offer a crucial system in a medical emergency like a coronavirus, as the process of creating new medications is time-consuming, costly, and constrained by other considerations including the present animal models' inability to anticipate outcomes. Computational tools and the use of in silico methods through computer-aided drug design (CADD) has proven useful in predicting a drug's quantum chemical properties efficiently. Through prioritizing potentially effective small molecules using techniques like molecular

docking simulations and network-based repurposing (Ghosh et al., 2022; Napolitano et al., 2022). In fact, docking has been used to suggest the effectiveness of statins. Molecular docking helped find remdesivir and suggest that it may be a useful medication since it targets the RNA-dependent RNA polymerase (RdRp) (Singh et al., 2020; Chang et al., 2022). Hence, exploring the use of computational software in finding COVID-19 therapeutics is a worthy cause as these tools provide insights about related molecular mechanisms as well as classifying drugs and predicting target specificity.

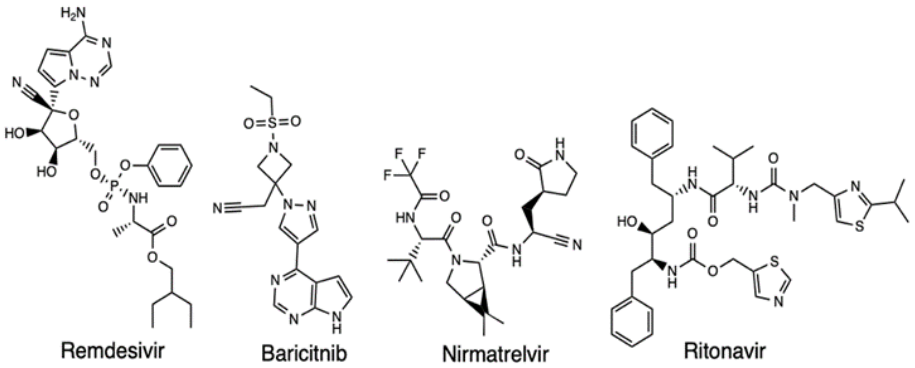

Fig. 1: Structure of Remdesivi, Baricitnib, Nimatrelvir, and Ritonavir

2. Computational Discovery of COVID-19 Therapeutics

Although several vaccines have been produced and authorized to control the spread of SARS-CoV-2, the highly mutated nature of the coronavirus as well as evidence of breakthrough infections by the different variants of the virus have necessitated the use of the advanced computational methods that are becoming increasingly powerful in pharmaceutical drug discovery and biomedical research (Wu et al., 2020). Three-dimensional (3D) structures of the main SARS-CoV-2 proteins have been determined and added to the Protein Data Bank (PDB) after researchers conducted thorough and in-depth studies on the coronavirus proteins. On the basis of structure-based calculations, these structures offer a helpful basis for drug discovery and design (structure-based drug design [SBDD]) (Dong et al., 2023). There are also ligand-based drug design (LBDD) methods that target the main protease (M^{pro}), such as quantitative structure-activity relationships (QSARs), modeling of pharmacophore, and homology modeling, all of which have been useful in screening potential candidates for treating COVID-19 (Alméciga-Díaz et al., 2020' Sharma et al., 2021). In this chapter, the focus is on how various CADD methods have been used and the drugs that have been developed and repurposed through virtual screening (VS) for use as SARS-CoV-2 therapeutics.

2.1 Molecular Docking

Following the sequencing of SARS-CoV-2 genome, it became possible to identify and characterize the proteins of the virus. Mpro is necessary for the processing of other viral proteins, and it has been identified as a possible therapeutic target. Further chances to characterize other compounds that inhibit these proteins were made possible by the description of the crystal structures of Mpro and its inhibitors, with a molecular docking-based virtual screening conducted against a library of experimental and approved drugs (Charoute et al., 2022). In this screening, the top 10 hits listed included pictilisib, Ergoloid mesylates, Cefuroxime, Nimorazole, Lumacaftor, Nilotinib, and Cepharanhine (Fig. 2).

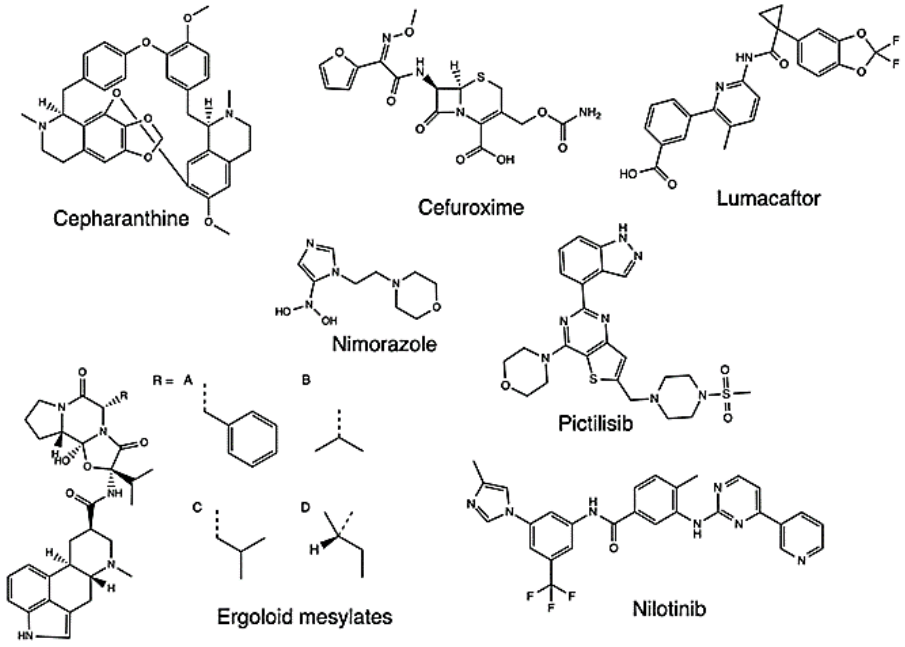

Fig. 2: Structure of pictilisib, Ergoloid mesylates, Cefuroxime, Nimorazole, Lumacaftor, Nilotinib, and Cepharanhine

The procedure entailed in the docking analysis for the Mpro structures PDB 6Y2E and 6LU7, after which molecular docking was performed and the 20 best conformations for each of the ligands inside the Mpro active cavity were analyzed with the ligand-protein interactions. The findings determined a higher binding affinity than the identified compounds for Mpro and could significantly control SARS-CoV-2 replication. Cephraranthine and Nimorazole (Fig. 3) were supported by literature for further in vitro and in vivo evaluations as potential drugs, with pictilisib predicted to have the highest affinity for Mpro, followed by Nimorazole and Ergoloid mesylates (Charoute et al., 2022).

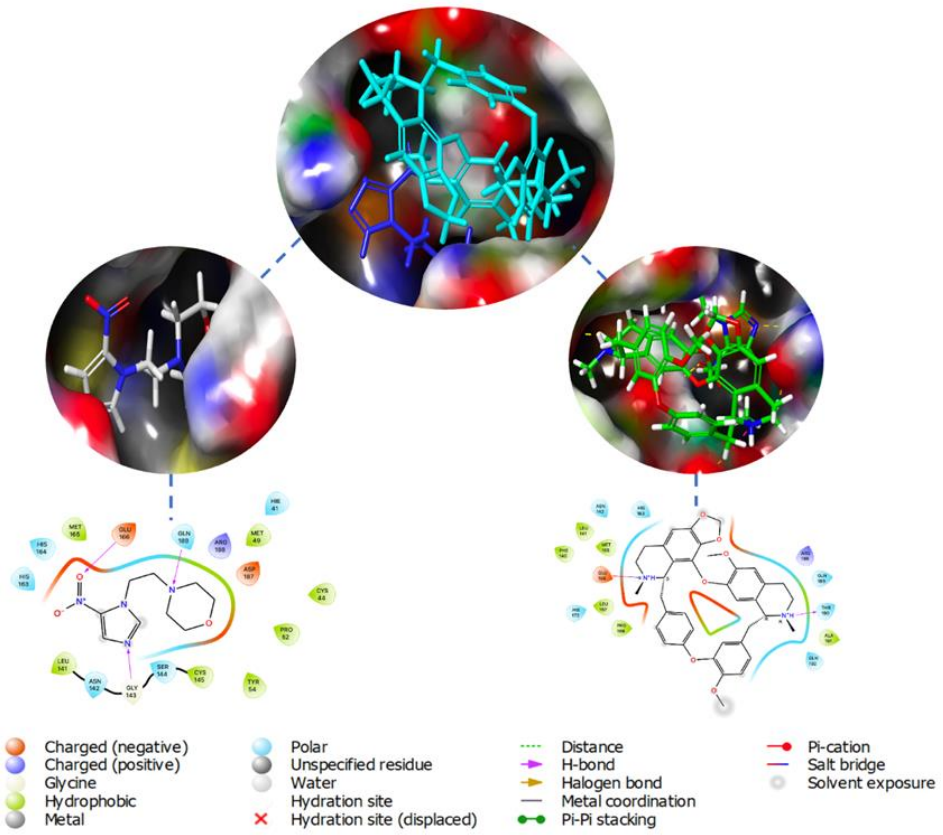

Fig. 3: Center Top: Overlay of docked Nimorazole (Blue) and Cephraranthine (Cyan) inside binding pocket of Mpro (PDB 6LU7); Left: Nimorazole inside binding pocket and ligand-protein interaction diagram; Right: Cephraranthine inside binding pocket and ligand-protein interaction diagram (Generated using Schrödinger Suites)

The transmembrane receptor Neuropilin-1 (NRP-1) has also been the focus of molecular docking because of its function as a host cell entry factor for SARS-CoV-2, which causes the COVID-19 sickness. One such study recognized that molecular compounds capable of interfering with SARS-CoV-2 binding to NRP-1 are potential antiviral drug candidates, based on a library of 1167 compounds which had been analyzed previously in Covid-related studies (Marinho et al., 2020) (Fig. 4). The virtual screening analysis procedure was carried out on AutoDock Vina targeting a library of compounds to find potent NRP-1 receptor inhibitors. Consequently, the Nafamostat drug was found to have the highest binding affinity to the NRP-1 protein as its binding energy was -8.6 kcal/mol. It also showed that the drug is stabilized by four hydrogen bonds, and is the second-ranking compound with a binding energy of -8.4 kcal/mol were Y96 and Selixenor. The other ligands found to have favorable binding energies were Ebastine and UGS, with all the top five chemicals depicting better binding affinities than the reference compounds EG00229 and EG01377 (Marinho et al., 2020) (Fig. 5). Hence, the screened compounds showed potential as good candidates for inhibiting the communication between the spike's protein and NRP-1 receptor.

In silico molecular docking studies have also been performed to evaluate the molecular interactions of drugs with therapeutic indications for COVID-19 treatment, such as Azithromycin, Hydroxychloroquine, and Baricitinib, and similarly structured drug compounds like chloroquine, Quinacrine, and Ruxolitinib based on docking from the Mpro protein (Eweas et al., 2021) (Figure 6). The most advantageous inhibitors were indicated by the lowest free-bond energy and the molecule's preference for the same bond location after they were docked with the major protease of SARS-CoV-2. The molecular simulations' research showed that all inhibitors are connected to the same enzyme site, with the N3 protease inhibitor's binding site being farther away and Mpro's domain III being more isolated (Eweas et al., 2021). Azithromycin had six interactions with COVID-19, including an alkyl bond with Leu287 amino acids and a typical hydrogen bond with Leu272. In the meanwhile, the baricitinib-formed receptor-ligand complex showed three types of conventional hydrogen bonds, ten interactions with the enzymes' amino acid remainder, and one each with Lys137, Asp197, and Leu287. The chloroquine inhibitor also interacted with Mpro, while hydroxychloroquine and chloroquine didn't show suffient binding energy with the enzyme (Al-Karmalawy, 2025). The docking routines further indicated that quinacrine formed three communications with the target protein, and ruxolitinib also interacted with the enzyme. Overall, the molecular docking simulations identified the creation of nine hydrogen bonds with analyzed inhibitors, which were categorized as hydrogen bonds covalent with chloroquine, baricitinib, and quinacrine while being balanced and mostly electrostatic with azithromycin, hydroxychloroquine, and ruxolitinib. Thus, baricitinib, quinacrine, and azithromycin were proposed as capable of being used alone or as combined therapeutics for COVID-19 (Abdollahpour et al., 2024).

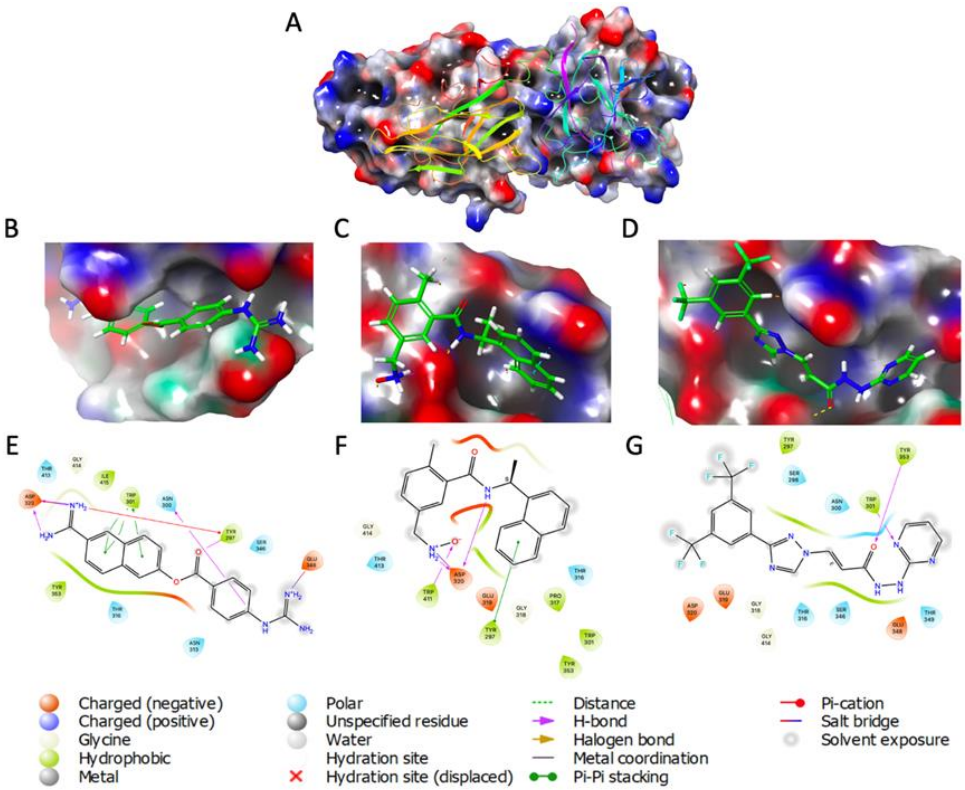

Fig. 4: PDB 2QQI of NRP-1 receptor visualized (A); Natamostat (B), Y96 (C), and Selinexor (D) visualized inside binding pocket; Natamostat (E), Y96 (F), and Selinexor (G) ligand protein interaction (Generated using Schrödinger Suites)

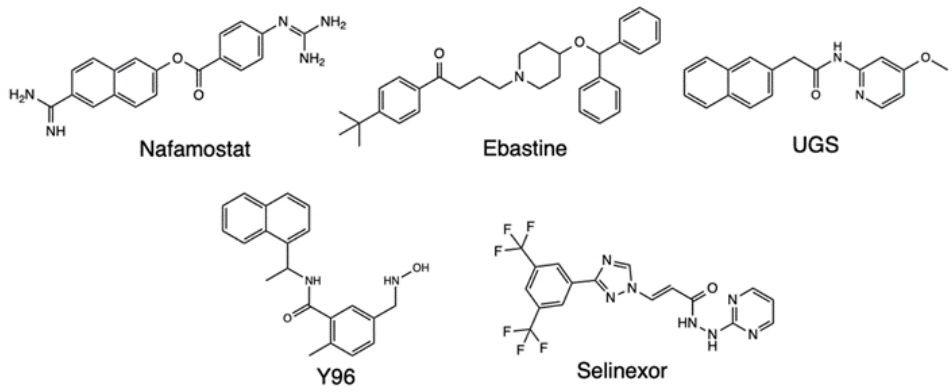

Fig. 5: Structure of Nafamostat, Ebastine, UGS, Y26, and Selinexor

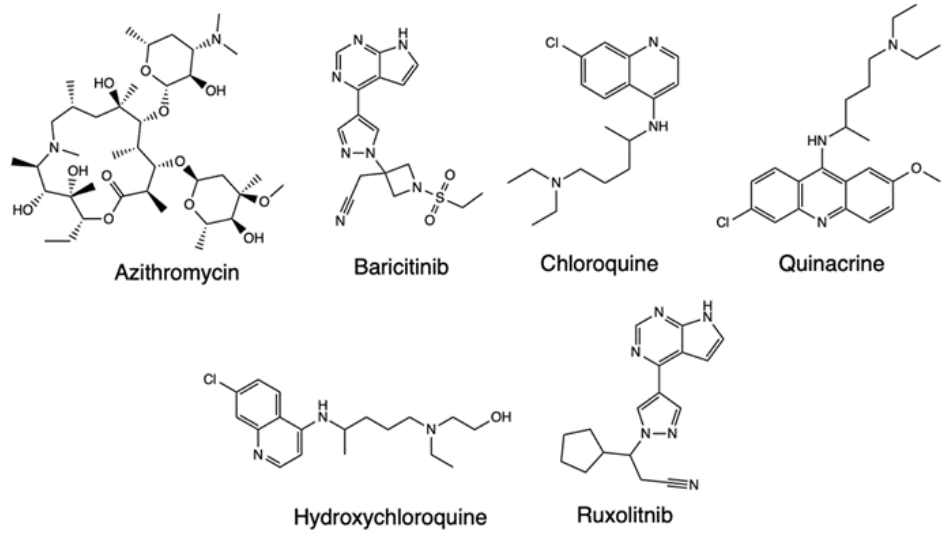

Fig. 6: Structures of Azithromycin, Baricitinib, Chloroquine, Quinacrine, Hydroxychloroquine, and Ruxolitnib

An earlier molecular docking study was done for repurposed therapeutics such as chloroquine, ivermectin, remdesivir, hydroxychloroquine, and favipiravir. They were screened with different SARS-CoV-2 target proteins including RdRp, membrane protein (M), spike (S protein) proteins, viral proteases, nucleocapsid protein (N protein), nucleoproteins, and nsp14 (exoribonuclease) (Figure 7) (Gholivand et al., 2022). After retrieving the proteins, molecular docking was performed on the MVD 6.0 platform and the potential binding sites (cavities) identified with the detection algorithm. The results indicated ivermectin had the maximum binding affinity to the predicted active site of the S glycoprotein and the protein-ligand interactions, while favipiravir had the lowest binding affinity and protein-ligand interactions, while remdesivir showed considerable outcomes. As for the binding interactions with RdRp, remdesivir had the highest binding affinity and protein-ligand interactions, and ivermectin showed considerable results (Gholivand et al., 2022).

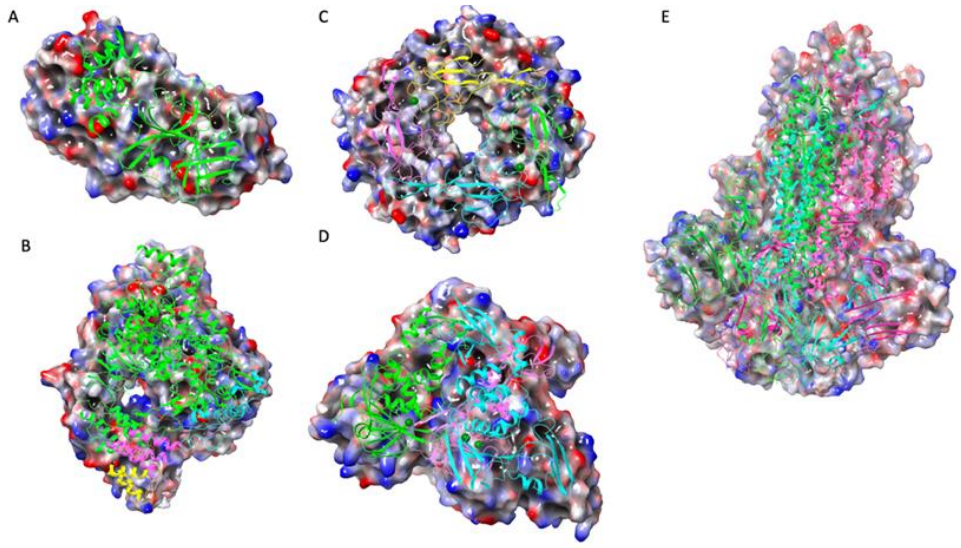

Fig. 7: (A) PDB 6Y2E (B) PDB 6M71 (C) PDB 6VY0 (D) PDB 6W9C (E) PDB 6VXX (Generated using Schrödinger Suites)

Furthermore, the docking scores with nsp14 indicated that ivermectin had the highest binding affinity and protein-ligand interactions. Remdesivir had relatively high results, while favipiravir showed the lowest values. Meanwhile, binding interactions with Mpro using lopinavir as a reference drug showed it had the highest binding scores, with remdesivir ranking with the uppermost values, followed by ivermectin, just as hydroxychloroquine and chloroquine while favipiravir did not depict considerable Mpro-binding. In sum, both ivermectin and remdesivir had high binding affinities to different viral proteins, making them the most effective medication choices to combat SARS-CoV-2 (Gholivand et al., 2022). In a molecular docking study, screening of rutin, a natural compound, ritonavir, emetine, hesperidin, lopinavir, and indinavir showed all the molecules could bind close to the essential catalytic regions of Mpro, making them worthy of further analysis as SARS-CoV-2 therapeutic candidates (Aldahham et al., 2022). Molecular docking studies have further revealed drugs like boceprevir, telaprevir, and narlaprevir, which are clinically approved for hepatitis C virus, also bind on the active site of SARS-CoV-2 Mpro (Figure 8) (Mengist et al., 2021).

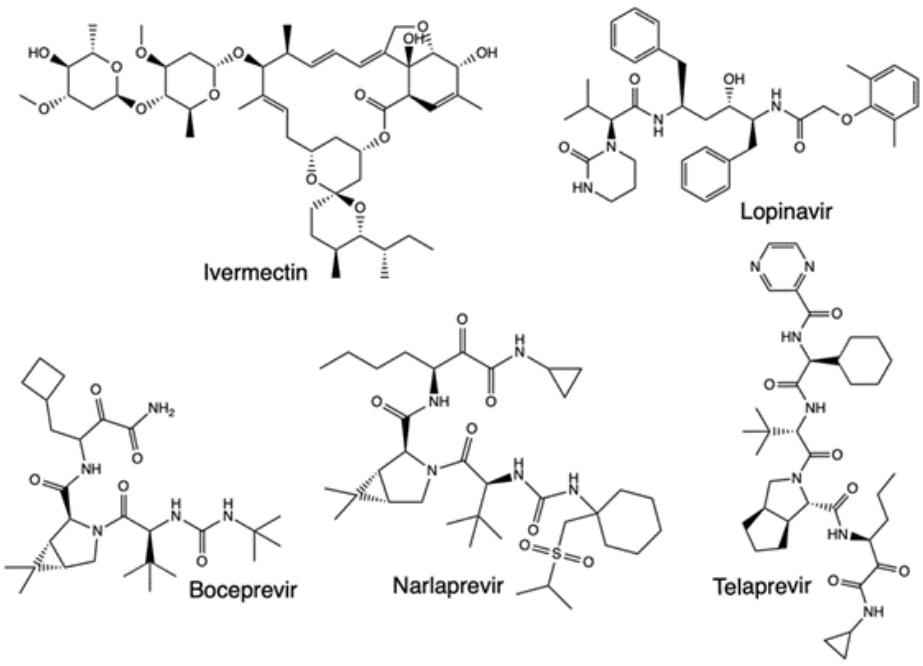

Fig. 8: Strcutres of Ivermectin, Lopinavir, Boceprevir, Narlaprevir, and Telaprevir

2.2 Quantitative Structure-activity Relationship (QSAR) Techniques

Quantitative structure-activity relationship (QSAR) techniques have been used in research to create phosphorus-based medications with strong Mpro inhibiting action, which are based on synthesizing and characterizing remdesivir derivatives as part of introducing a group of inhibitors to the coronavirus (Costa et al., 2022). QSAR techniques were used to investigate the biological activities of the selected compounds, involving N-morphplinemethylenephosphonicacid, N-piperidinemethylenephosphonicacid, N-piperidinecarboxylicacidmethylenephosphonicacid, 4-(2-methylenephosphonicacidpiperazine) ethanol, and 4-ethylpiperazinemethylenephosphonicacid, among other ligands. After docking with Auto Dock Tools (ADT), the QSAR calculations were carried out to study the activity of phosphonates in inhibiting COVID-19, using a range of mono, bis, and tetra phosphonates chosen to examine their binding affinities for the Mpro active site (S4). To build QSAR models, numerical characteristics of a set of inhibitors were built, with the descriptors representing quantitative properties dependent on the molecule's structure. According to the findings, structural descriptors such as non-H bonds (nBo), the Narumi simple topological index (SNar), and the number of hydrogen bond acceptors (nHAcc) are significant than electronic descriptors in the QSAR model. The non-hydrogen bonds and molecular typology are crucial in the inhibitory mechanism against SARS-CoV-2, as indicated by the fact that the nBo and SNar descriptors were two of the model's effective components (Ngo et al., 2020).

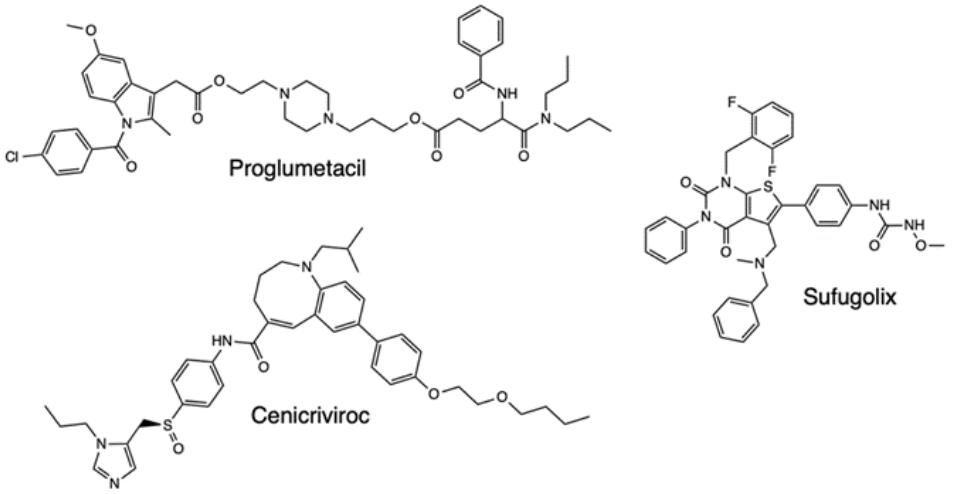

Fig. 9: Structures of Proglumetacil, Cenicriviroc, and Sufugolix

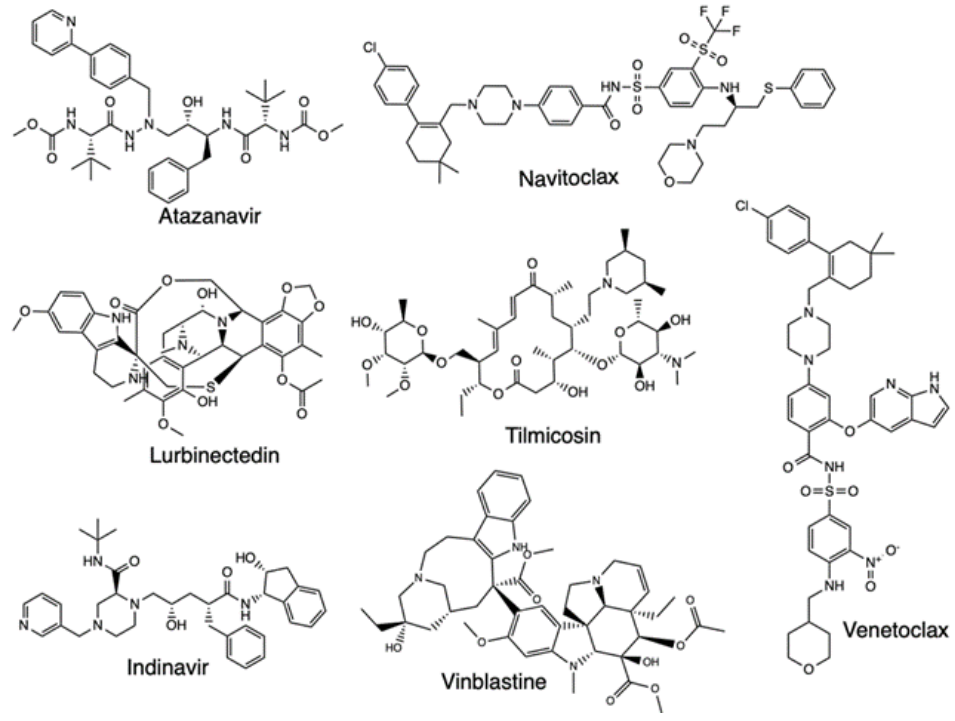

Fig. 10: Structures of Atazanavir, Navitoclax, Lurbinectedin, Tilmicosin, Indinavir, Vinblastine, and Venetoclax

The discovery of COVID-19 treatments has also used a QSAR study founded on the simplified molecular-input line-entry system (SMILES) strings of 32 bicycloproline derivatives. Calculating 0D, 1D, and 2D molecular descriptors is done using the strings (Qiao et al., 2021). Additionally, novel compounds have been identified using similar SMILES notation that may have the ability to inhibit 3C-like protease (3CLpro) to rediscover and repurpose medications for SARS-CoV-2 (Arun et al., 2021; Sharma et al., 2022; Oubahmane et al., 2023). In the reported

study, novel molecular Frameworks were searched using the 2D chemical structure of the congener series selected for the study. The dataset preparation relied on 32 bicycloproline derivatives synthesized and tested for Mpro suppression using a transgenic mouse model, deriving from the telaprevir and boceprevir molecules that can inhibit Mpro (Butt et al., 2012). Telaprevir and Boceprevir are protease inhibitors approved for the treatment of hepatitis C virus, and following in vivo studies showed that six compounds had protective effects on cells against viral infection with higher potency, while two showed strong antiviral activity in a mouse model (Fischer et al., 2023; La Monica et al., 2022). With QSAR combined with other computational models like molecular docking, MD simulations, and free binding energy MM/PBSA, the MI-09 and MI-30 compounds facilitated a computational protocol built to design new derivatives with higher inhibitory activities on Mpro in SARS-CoV-2 (Alves et al., 2021). Through virtual screening, it was revealed that a bicyclic moiety with a three-membered ring was important in the therapeutic potential at one binding pocket.

With Mpro proposed as a major drug target for COVID-19, studies have further developed QSAR models of the Mpro inhibitors whose inhibitory activity has been tested against the protease, with virtual screening then carried out for all drugs in the DrugBank database. One such study focused on 42 compounds as consensus computational hits, with three tested, which are cenicriviroc, proglumetacin, and sufugolix, working in a docking validation run (Figure 9) (Ničkčović et al., 2022). Based on the outcome of the study, the three compounds were found to be active, with cenicriviroc and sufugolix having AC50 of 8.9 μM and 12.6 μM respectively, and proglumetacin tested twice had two AC50 of 8.9 μM and12.6 μM. The other tested molecules, vinblastine, atazanavir, lurbinectedin, indinavir, barasertib, tilmicosin, navitoclax, and venetoclax were found to be inactive, with the overall results proving QSAR importance in finding COVID-19 treatment based on the ligands' activity against Mpro (Figure 10) (Ničkčović et al., 2022).

2.3 Molecular Dynamics (MD) Simulations

Repurposing of drugs against SARS-CoV-2 targeting Mpro has been studied using molecular dynamics (MD) simulations in conjunction with other computational techniques. One research used MD simulations to examine the stability of the connection between the chosen medications and the target (Kumar et al., 2025)). The Desmond tool of Schrodinger helped determine the stability binding of the specified therapies with Mpro in an explicit solvent system, with the docked poses of protein-ligand complexes acting as input structures. The MM-GBSA technique was then used to estimate the binding energy of each complex and MD simulations were conducted on the top four hits based on the binding free energy data, which were Macimorelin Acetate, Bamifylline, Binifibrate, and Rilmazafon in combination with Mpro (Figure 11). The conformational variations of the ligand and protein from the original structure were then expressed using the Root Mean Square Deviation (RMSD). The results indicated that the 4 complexes subjected to MD simulations recorded protein RMSD deviations below 3Å as compared with the initial frame. In studying globular protein conformations, RMSD of the C alpha atomic coordinates are used to measure the similarity in the 3D structure, and a large value indicates dissimilarity while zero means identical conformation (Cao et al., 2022).

A value of 3 Å is suitable for globular proteins, but significant deviations mean extensive conformational variations of the protein throughout the simulation, consequently, an unstable protein-ligand combination. As for the 4 complexes in the experiment, the protein RMSD deviations were below 3 Å compared to the initial frame

In particular, binifibrate and bamifylline did not show significant departures from the starting position, indicating stable binding; nevertheless, the RMSDs of macimorelin acetate and rilmazafone were greater, indicating less stable binding. The major hydrogen bonds ensuring the stability of Binifibrate and Bamifylline persisted throughout the MD simulations and this meant the two drugs had better binding affinity towards the Mpro active site (Charoute et al., 2022).

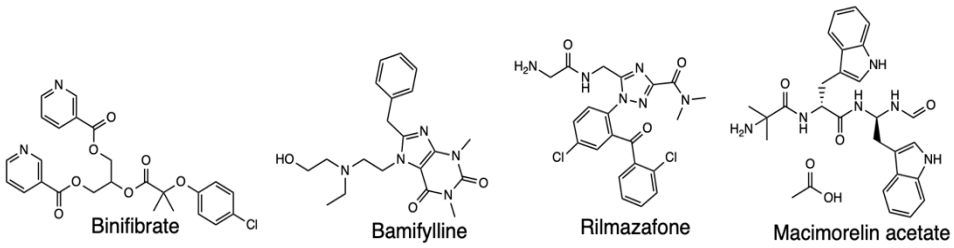

Fig. 11: Structures of Binifibrate, Bamifylline, Rilmazafone, and Macimorelin acetate

MD simulations have further been used to screen Licorice for its action against SARS-CoV-2, with the study obtaining the short molecule-protein compounds by molecular docking for the initial structures for all-atom MD simulations and MMGBSA used to calculate the binding free energy (Kumar et al., 2020). The MD simulations results showed RMSD variations of Glycyrol and Glyasperin F were within 4 Å, implying the system was less dynamic. The MMGBSA calculations also indicated that Glyasperin F had the highest binding energy value, and the binding energies of the complexes mostly contributed by electrostatic and energy van der Waals energy. Further analysis revealed the drug's tiny particles and protein compounds could retain a persistent binding state and exert therapeutic effects in treating SARS-CoV-2. Another study using MD simulations also screened Hydroxyethylamine (HEA) analogs to assess their action against 3CLpro protein targets of SARS-CoV-2, and the MD simulations was conducted for the complicated structure of 3CLpro receptor with the selected licensed drug, indinavir, and designed new HEA compound utilizing Desmond software (Rudrapal et al., 2022). The aim was to evaluate the stability of binding for the ligand-protein complex. The RMSD values of the protein-ligand complex were found to be below 2 Å, and the presence of water molecules within the protein's binding site suggested stability of the complex, which meant suitability of the compound as a potent candidate for further in vitro and in vivo studies for SARS-CoV-2 therapeutics (Rudrapal et al., 2022).

There are several other MD simulation studies for potential SARS-CoV-2 drugs, with one such exploring bioactive molecules from *Triphala*, an Ayurvedic herbal formulation that could inhibit Mpro (Nutho et al., 2020). The focus of this study was on the top four compounds with the

best binding energies, terflavin A, corilagin, chebulagic acid, and chebulinic acid, which were further assessed for flexibility and stability at Mpro's binding site and MM-PBSA calculations done to determine the binding free energies of the protein-ligand complexes (Figure 12). The Mpro-Corilagin and Mpro-Chebulagic acid complexes showed RMSD stability from the beginning until 100nm, meaning they are stable, Mpro-Terflavin A fluctuated at the beginning and at100 ns, and Mpro-Chebulinic acid fluctuated from the beginning but stabilized after 70nm until 100nm. Therefore, the overall RMSD results confirmed corilagin, chebulagic acid, and chebulinic acid had stable binding of the ligands in the Mpro active site, meaning *Triphala* formulation is a promising Mpro inhibitor in SARS-CoV-2. Another research screened Lopinavir and Ritonavir using all-atom MD simulations to assess connection with the molecules at the active site of SARS-CoV2 3CLpro, with four residues found for lopinavir and nine residues for ritonavir that were important for binding to 3CLpro (Padhi et al., 2021). Atomistic MD simulations have also screened Arbidol binding and inhibition of SARS-CoV-2, with attention on the receptor-binding domain (RBD)/angiotensin-converting enzyme 2 (ACE2) interface. The RBD/ACE2-arbidol complex stability during simulations was evaluated and the results showed stabilization of Arbidol at RBD-ACE2 complex, which also formed favorable interactions with both RBD and ACE2. Arbidol also exhibited a higher binding affinity for RBD than ACE2, and the findings further suggested Arbidol interferes with viral binding to host cells, making the compound derivatives potential candidates as treatment for SARS-CoV-2. Studies on Arbidol have also been carried out for its binding to S protein, and the results indicated Arbidol action by effectively blocking or impeding trimerization of SARS-CoV-2 spike glycoprotein (Vankadari, 2020). The S2 protein binding screening and assessment of the ACE2-RBD complex stability have further been carried out for Cefsulodin, Nilotinib, gonadorelin, fondaparinux, atorvastatin, and fexofenadine, with promising results for COVID-19 therapeutics (Deganutti et al., 2021; Kumar et al., 2021; Razizadeh et al., 2021; Pirolli et al., 2023) (Figure 13). Lisinopril and Alacepril have also been evaluated with MD simulations and shown to interact with human angiotensin-converting enzyme 2 (hACE2) due to the best binding affinity and favorable RMSD values (Al-Karmalawy et al., 2021). Likewise, Nsp16/nsp10 inhibition has been explored through a pharmacoinformatics study seeking to identify naphthyridine and quinoline derivatives as potential inhibitors of these proteins, with MD simulations revealing stable protein-ligand complexes (Aldahham et al., 2022).

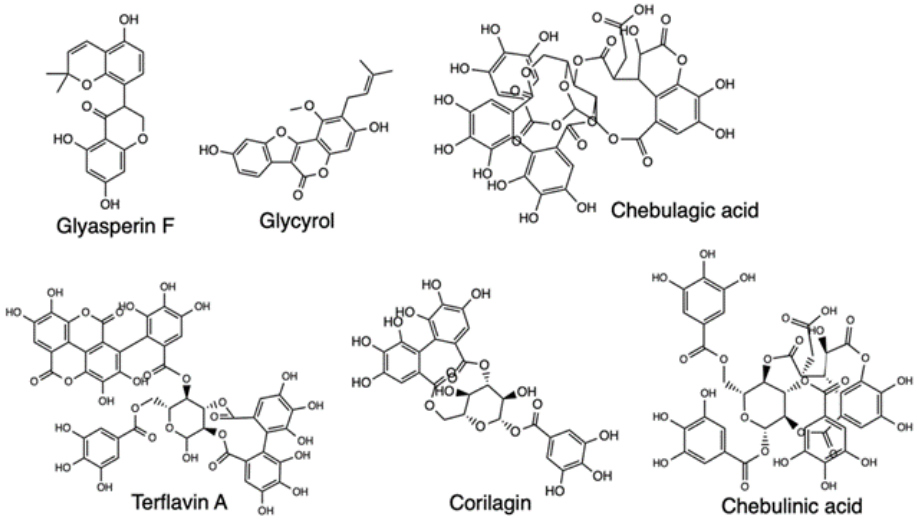

Fig. 12: Structures of Glyasperin F, Glycyrol, Chebulagic acid, Terflavin A, Corilagin, and Chebulinic acid

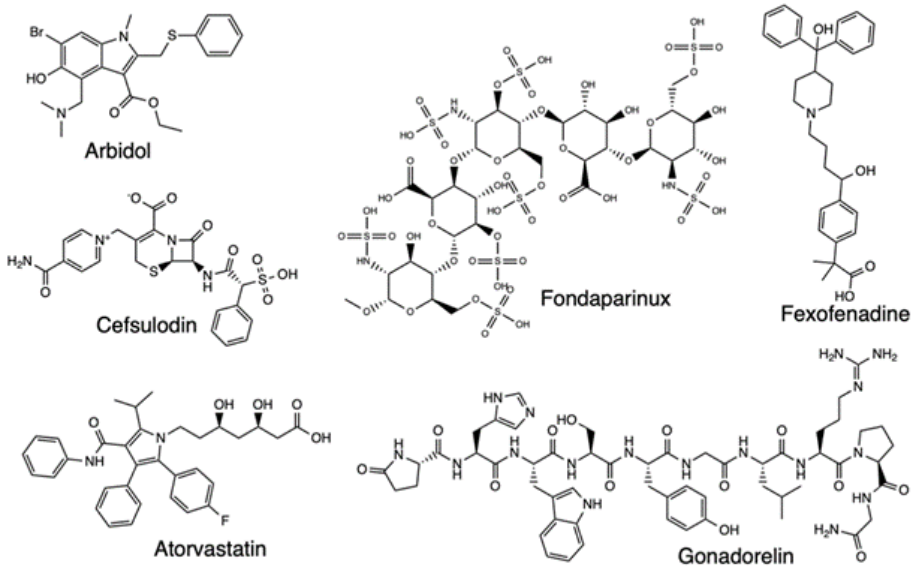

Fig. 13: Structures of Arbidol, Cefsulodin, Atorvastatin, Fondaparinux, Gonadorelin, and Fexofenadine

2.4 Pharmacophore Modeling

Pharmacophore modeling has been useful in researching Covid-19 therapeutics, i.e., application with Mpro to identify FDA-approved drugs and hits from natural products as potential treatment of SARS-CoV-2. One such study utilized Mpro to develop a pharmacophore model consisting of a hydrogen bond donor, acceptor, and hydrophobic features, which was combined with virtual screening undertaken using the ZINC database (Saeed et al., 2021). Ligand pharmacophore mapping was used to extract and filter 208,000 hits by applying the lead-like properties, resulting in minimization of impact to the top 200, and simultaneous docking carried out for 200 hits and 28 hits from the experiments selected owing to the promising predicted pharmacodynamic and pharmacokinetic characteristics. Based on the findings, Daidzin depicted hydrogen bond interactions with amino acids in the binding site, also with hydrophobic interactions. The other drugs screened were phloretin, rosmarinic acid, and psoralidin, all of which showed hydrophobic contacts with the amino acids, with all the drugs anticipated to be effective natural inhibitors of Mpro (Saeed et al., 2021) (Figure 14).

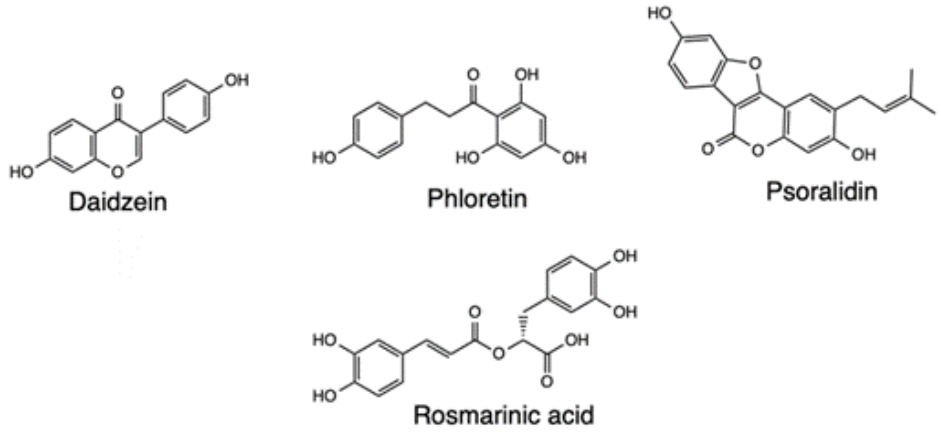

Fig. 14: Structures of Daidzein, Phloretin, Psoralidin, and Rosmarinic acid

Another pharmacophore modeling study was applied on the DrugBank compounds targeting the nonstructural proteins 16/10 (nsp16/nsp10) complex, following a structure-based pharmacophore model generated and used to screen the database that resulted in three compounds (Rampogu and Lee, 2021). The co-crystallized compound S-adenosylmethionine (SAM) was used as the reference compound, and hydroxychloroquine and remdesivir employed for comparative docking. Framycetin, kanamycin, and tobramycin were the three compounds retrieved as potential candidate drugs due to their higher dock score than the reference compound, and the molecules also formed hydrogen bonds with residues on the binding sites. The three compounds demonstrated the pharmacophore features of SAM and depicted key residue interactions and stable MDS results, which imply they are potential candidates as SARS-CoV-2 therapeutics (Rampogu and Lee, 2021).

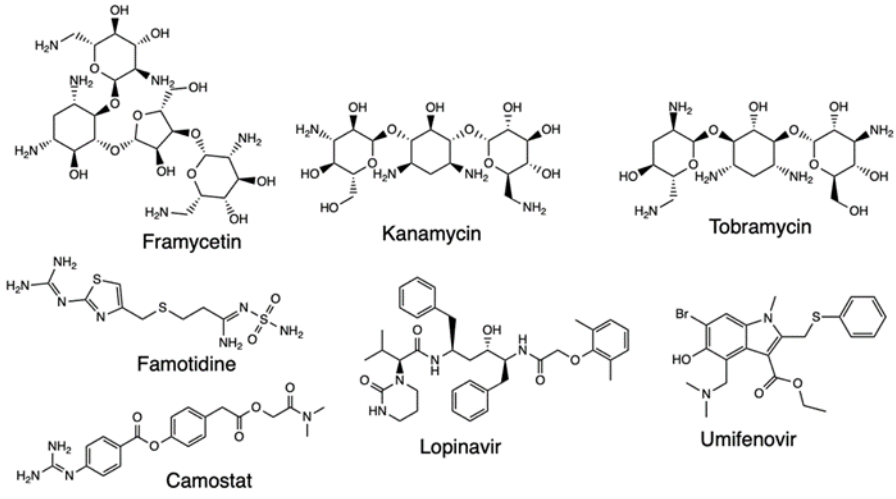

Fig. 15: Structures of Framycetin, Kanamycin, Tobramycin, Camostat, Lopinavir, and Umifenovir

Research has been conducted focusing on the CD146 receptor (human basigin) due to its presence on the host cell leading to SARS-CoV-2 infection and how drugs altering the formation of CD147 and S protein complex could inhibit the coronavirus replication (Pandit et al., 2023). This was based on an e-pharmacophore model developed using the receptor-ligand cavity of CD147 protein and further mapped against FDA-approved drugs. Eleven drugs were used for screening, and the results of the e-pharmacophore model revealed 19 non-bonded interactions found between the ligand and the receptor and 10 pharmacophores generated. The drugs that fitted to the pharmacophore pockets were famotidine, lopinavir, hydroxychloroquine, ritonavir, fluvoxamine, camostat, and umifenovir (Figure 15). From the subsequent docking results, ritonavir had the higher CDOCKER energy than the other compounds. Telaprevir has also been explored with the co-crystal structure of Mpro where the receptor-ligand pharmacophore models were developed and validated with pharmit (Halimi and Bararpour, 2022). Screening was

done on the ZINC database and decoy compounds used for comparison, and the results of the pharmacophore modeling study showed that telaprevir formed hydrogen bonds with residues of the catalytic dyad and could be a candidate for SARS-CoV-2 therapeutics (Halimi and Bararpour, 2022).

2.5 Homology Modeling

Homology modeling studies have been important in discovering treatment options for SARS-CoV-2, such as the research reported in a preprint focused on identifying repurposing candidates for the transmembrane serine protease family member II (TMPRSS2) (Rensi et al., 2020). The ensemble of structures represented by the seven homology models that were employed has an average RMSD of 1.27 Å and a maximum RMSD of 1.675 Å. Based on the findings, Camostat showed median binding energy, Nafamostat ranked third, and the accompanying docking studies indicated key electrostatic interactions between the docked chemical structure of Otamixaban, the best scoring ligand, and residues in the binding pocket of a TMPRSS2 homology model. Argatroban, Otamixaban, Letaxaban, Edoxaban, Betrixaban, Darexaban, and Nafamostat all ranked highly across a majority of model structures and clustered with known active ligands. The known inhibitors validated the results of providing a positive control, and the uniformly low docking scores meant the protocol generated homology models and docking results consistent with other completed studies (Bournez et al., 2024).

Homology modeling, combined with other computational methods, have screened Neflinavir as a potential Mpro inhibitor in SARS-CoV-2, a study based on SARS Mpro structures aiding to build the homology models then docking 1903 small molecule drugs to the models (Xu et al., 2020). Nelfinavir, perampanel, zopiclone, pitavastatin, eszeopiclone, and praziquantel were shown to exhibit good docking scores and binding modes, but MM/GBSA and SIE calculations proposed nelfinavir as a candidate that might be active against SARS-CoV-2 and the rest had moderate activities (Yang et al., 2021) (Figure 16). Tests of nelfinavir against SARS-CoV-2 infected cells demonstrated high antiviral activity and is a capable Mpro inhibitor (Sargolzaei et al., 2021).

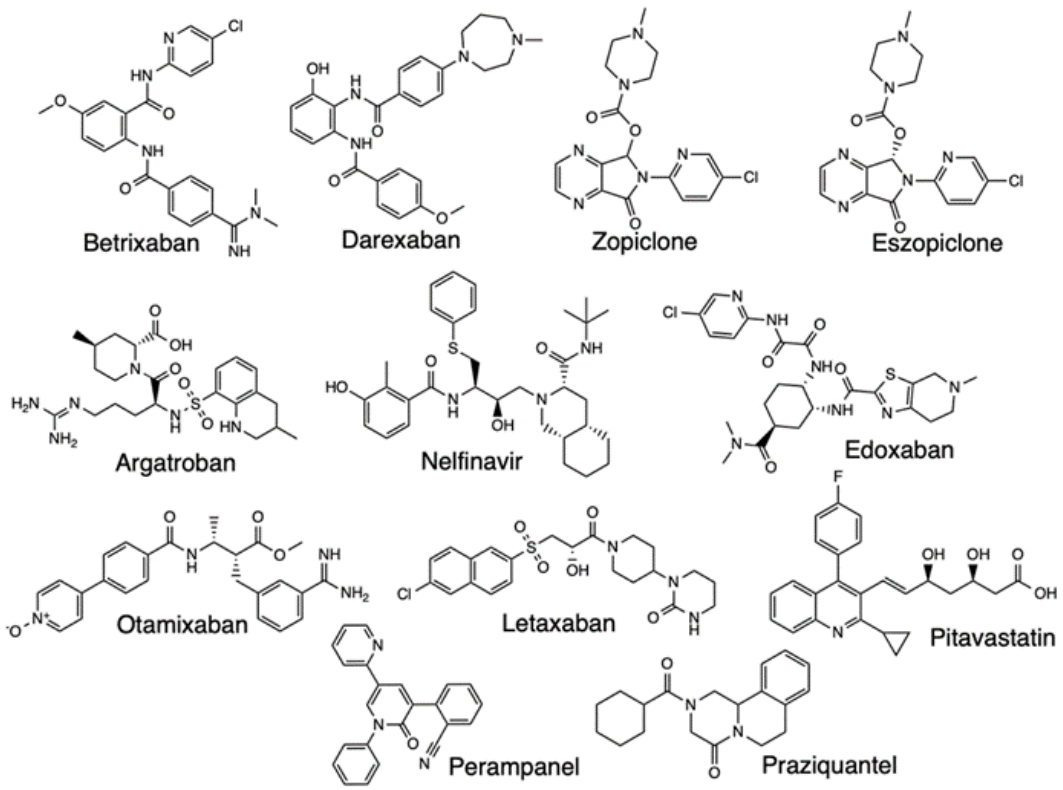

Fig. 16: Structures of Betrixaban, Darexaban, Zopiclone, Eszopiclone, Argatroban, Nelfinavir, Edoxaban, Otamixaban, Letaxaban, Pitavastatin, Perampanel, and Praziquantel

Conclusion

COVID-19 remains humanity's greatest threat in the 21st century, and though various vaccines have been developed to manage the spread of infections, the challenge still persists to get the pandemic under control. The existing computational drug repurposing and redesign models offer an opportunity for developing new drug candidates for treating SARS-CoV-2. Compounds that act on the Mpro active sites as well as inhibition of NRP-1 receptors and S protein have been screened using molecular dynamics simulations, molecular docking, QSAR, pharmacophore, and homology modeling research, and there is proof that there are strong contenders for more in vitro and in vivo examination.

References

Abd-Elsalam, S., Salama, M., Soliman, S., Naguib, A.M., Ibrahim, I.S., Torky, M., Abd El Ghafar, M.S., Abdul-Baki, E.A.R.M. and Elhendawy, M., (2022). Remdesivir efficacy in COVID-19 treatment: A randomized controlled trial. *The American Journal of Tropical Medicine and Hygiene*,

106(3), 886.

Abdollahpour, S., Rahbar, A., Mohammadhassan, R., Talebi, Y., & Hesari, Y. B. (2024). An in silico Drug Repurposing Study to Inhibit the Spike Protein of SARS-CoV2. *Momona Ethiopian Journal of Science*, *16*(2), 347-369.

Aldahham, B.J., Al-Khafaji, K., Saleh, M.Y., Abdelhakem, A.M., Alanazi, A.M. and Islam, M.A., (2022). Identification of naphthyridine and quinoline derivatives as potential Nsp16-Nsp10 inhibitors: a pharmacoinformatics study. *Journal of Biomolecular Structure and Dynamics*, *40*(9), 3899-3906.

Al-Karmalawy, A.A., Dahab, M.A., Metwaly, A.M., Elhady, S.S., Elkaeed, E.B., Eissa, I.H. and Darwish, K.M., (2021). Molecular docking and dynamics simulation revealed the potential inhibitory activity of ACEIs against SARS-CoV-2 targeting the h ACE2 receptor. *Frontiers in Chemistry*, *9*, 661230.

Alméciga-Díaz, C.J., Pimentel-Vera, L.N., Caro, A., Mosquera, A., Castellanos Moreno, C.A., Manosalva Rojas, J.P. and Díaz-Tribaldos, D.C., (2020). Virtual screening of potential inhibitors for SARS-CoV-2 main protease. *Preprints.org*, https://doi.org/10.20944/preprints202004.0146.v1.

Alves, V.M., Bobrowski, T., Melo-Filho, C.C., Korn, D., Auerbach, S., Schmitt, C., Muratov, E.N. and Tropsha, A., (2021). QSAR modeling of SARS-CoV Mpro inhibitors identifies sufugolix, cenicriviroc, proglumetacin, and other drugs as candidates for repurposing against SARS-CoV-2. *Molecular Informatics*, *40*(1), 2000113.

Al-Karmalawy, A. A. (2025). Nirmatrelvir, SIM0417, and RAY1216: potent and selective SARS-CoV-2 main protease inhibitors for the potential treatment of COVID-19. In *Drug Discovery Stories* (pp. 351-356). Elsevier.

Arun, K.G., Sharanya, C.S., Abhithaj, J., Francis, D. and Sadasivan, C., (2021). Drug repurposing against SARS-CoV-2 using E-pharmacophore based virtual screening, molecular docking and molecular dynamics with main protease as the target. *Journal of Biomolecular Structure and Dynamics*, *39*(13), 4647-4658.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S. and Lopez de Castilla, D., (2020). Remdesivir for the treatment of COVID-19 —Final Report. *New England Journal of Medicine*, *383*(19), 1813-1826.

Butt, A.A. and Kanwal, F., 2012. Boceprevir and telaprevir in the management of hepatitis C virus–infected patients. *Clinical Infectious Diseases*, *54*(1), 96-104.

Bournez, C., Gally, J. M., Aci-Sèche, S., Bernard, P., & Bonnet, P. (2024). Virtual screening of natural products to enhance melanogenosis. *Molecular Informatics*, *43*(9), e202300335.

Cao, J.F., Gong, Y., Wu, M., Yang, X., Xiong, L., Chen, S., Xiao, Z., Li, Y., Zhang, L., Zan, W. and Zhang, X., (2022). Exploring the mechanism of action of licorice in the treatment of COVID-19 through bioinformatics analysis and molecular dynamics simulation. *Frontiers in Pharmacology*, *13*, 1003310.

Cascella, M., Rajnik, M., Aleem, A., Dulebohn, S. and Di Napoli, R., (2023). Features, evaluation, and treatment of coronavirus (COVID-19). *StatPearls*.

Chang, C.C., Hsu, H.J., Wu, T.Y. and Liou, J.W., (2022). Computer-aided discovery, design, and investigation of COVID-19 therapeutics. *Tzu-Chi Medical Journal*, *34*(3), 276.

Charoute, H., Elkarhat, Z., Elkhattabi, L., El Fahime, E., Oukkache, N., Rouba, H. and Barakat, A., (2022). Computational screening of potential drugs against COVID-19 disease: The Neuropilin-1 receptor as molecular target. *VirusDisease*, *33*(1), 23-31.

Chera, A. and Tanca, A., (2022). Remdesivir: the first FDA-approved anti-COVID-19 Treatment for Young Children. *Discoveries*, *10*(2).

Costa, A.S., Martins, J.P.A. and de Melo, E.B., (2022). SMILES-based 2D-QSAR and similarity search for identification of potential new scaffolds for development of SARS-CoV-2 MPRO inhibitors. *Structural Chemistry*, *33*(5), 1691-1706.

Deganutti, G., Prischi, F. and Reynolds, C.A., (2021). Supervised molecular dynamics for exploring the druggability of the SARS-CoV-2 spike protein. *Journal of Computer-Aided Molecular Design*, *35*, 195-207.

Dong, J., Varbanov, M., Philippot, S., Vreken, F., Zeng, W.B. and Blay, V., (2023). Ligand-based discovery of coronavirus main protease inhibitors using MACAW molecular embeddings. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *38*(1), 24-35.

Eweas, A.F., Alhossary, A.A. and Abdel-Moneim, A.S., (2021). Molecular docking reveals ivermectin and remdesivir as potential repurposed drugs against SARS-CoV-2. *Frontiers in Microbiology*, *11*, 3602.

Fischer, C. and Feys, J.R., (2023). SARS-CoV-2 Mpro inhibitors: Achieved diversity, developing resistance and future strategies. *Future Pharmacology*, *3*(1), 80-107.

Gholivand, K., Barzegari, A., Mohammadpanah, F., Yaghoubi, R., Roohzadeh, R. and Valmoozi, A.A.E., (2022). Synthesis, characterized, QSAR studies and molecular docking of some phosphonates as COVID-19 inhibitors. *Polyhedron*, *221*, 115824.

Ghosh, D., Ghosh Dastidar, D., Roy, K., Ghosh, A., Mukhopadhyay, D., Sikdar, N., Biswas, N.K., Chakrabarti, G. and Das, A., (2022). Computational prediction of the molecular mechanism of statin group of drugs against SARS-CoV-2 pathogenesis. *Scientific Reports*, *12*(1), 6241.

Gupte, V., Hegde, R., Sawant, S., Kalathingal, K., Jadhav, S., Malabade, R. and Gogtay, J., (2022). Safety and clinical outcomes of remdesivir in hospitalised COVID-19 patients: a retrospective analysis of active surveillance database. *BMC Infectious Diseases*, *22*(1), 1.

Halimi, M. and Bararpour, P., (2022). Natural inhibitors of SARS-CoV-2 main protease: structure based pharmacophore modeling, molecular docking and molecular dynamic simulation studies. *Journal of Molecular Modeling*, *28*(9), 279.

Kalita, P., Tripathi, T. and Padhi, A.K., (2023). Computational Protein Design for COVID-19 Research and Emerging Therapeutics. *ACS Central Science*, *9*(4), 602-613.

Kumar, S., Sharma, P.P., Shankar, U., Kumar, D., Joshi, S.K., Pena, L., Durvasula, R., Kumar, A., Kempaiah, P., Poonam and Rathi, B., (2020). Discovery of new hydroxyethylamine analogs against 3CLpro protein target of SARS-CoV-2: Molecular docking, molecular dynamics simulation, and structure–activity relationship studies. *Journal of Chemical Information and Modeling*, *60*(12), 5754-5770.

Kumar, V., Liu, H. and Wu, C., (2021). Drug repurposing against SARS-CoV-2 receptor binding domain using ensemble-based virtual screening and molecular dynamics simulations. *Computers in Biology and Medicine*, *135*, 104634.

Kumar, N., Gond, C., Singh, J. D., & Datta, A. (2025). Molecular docking, pharmacological profiling, and MD simulations of glycolytic inhibitors targeting novel SARS CoV-2 main protease and spike protein. *In Silico Pharmacology*, *13*(1), 44.

La Monica, G., Bono, A., Lauria, A. and Martorana, A., (2022). Targeting SARS-CoV-2 main protease for treatment of COVID-19: Covalent inhibitors structure–activity relationship insights and evolution perspectives. *Journal of Medicinal Chemistry*, *65*(19), 12500-12534.

Marinho, E.M., de Andrade Neto, J.B., Silva, J., da Silva, C.R., Cavalcanti, B.C., Marinho, E.S. and Júnior, H.V.N., (2020). Virtual screening based on molecular docking of possible inhibitors of COVID-19 main protease. *Microbial Pathogenesis*, *148*, 104365.

Mengist, H.M., Dilnessa, T. and Jin, T., (2021). Structural basis of potential inhibitors targeting SARS-CoV-2 main protease. *Frontiers in Chemistry*, *9*, 622898.

Muratov, E.N., Amaro, R., Andrade, C.H., Brown, N., Ekins, S., Fourches, D., Isayev, O., Kozakov, D., Medina-Franco, J.L., Merz, K.M. and Oprea, T.I., (2021). A critical overview of computational approaches employed for COVID-19 drug discovery. *Chemical Society Reviews*, *50*(16), 9121-9151.

Napolitano, F., Xu, X. and Gao, X., (2022). Impact of computational approaches in the fight against COVID-19: An AI guided review of 17 000 studies. *Briefings in Bioinformatics*, *23*(1), 456.

Ngo, S. T., Quynh Anh Pham, N., Thi Le, L., Pham, D. H., & Vu, V. V. (2020). Computational determination of potential inhibitors of SARS-CoV-2 main protease. *Journal of Chemical Information and Modeling*, *60*(12), 5771-5780.

Ničkčović, V.P., Nikolić, G.R., Nedeljković, B.M., Mitić, N., Danić, S.F., Mitić, J., Marčetić, Z., Sokolović, D. and Veselinović, A.M., (2022). In silico approach for the development of novel antiviral compounds based on SARS-COV-2 protease inhibition. *Chemical Papers*, *76*(7), 4393-4404.

Niknam, Z., Jafari, A., Golchin, A., Danesh Pouya, F., Nemati, M., Rezaei-Tavirani, M. and Rasmi, Y., (2022). Potential therapeutic options for COVID-19: an update on current evidence. *European Journal of Medical Research*, *27*, 1-15.

Nutho, B., Mahalapbutr, P., Hengphasatporn, K., Pattaranggoon, N.C., Simanon, N., Shigeta, Y., Hannongbua, S. and Rungrotmongkol, T., (2020). Why are lopinavir and ritonavir effective against the newly emerged coronavirus 2019? Atomistic insights into the inhibitory mechanisms. *Biochemistry*, *59*(18), 1769-1779.

Oubahmane, M., Hdoufane, I., Delaite, C., Sayede, A., Cherqaoui, D. and El Allali, A., (2023). Design of Potent Inhibitors Targeting the Main Protease of SARS-CoV-2 Using QSAR Modeling, Molecular Docking, and Molecular Dynamics Simulations. *Pharmaceuticals*, *16*(4), 608.

Padhi, A.K., Seal, A., Khan, J.M., Ahamed, M. and Tripathi, T., (2021). Unraveling the mechanism of arbidol binding and inhibition of SARS-CoV-2: Insights from atomistic simulations. *European Journal of Pharmacology*, *894*, 173836.

Pandit, N.K., Mann, S.S., Mohanty, A. and Meena, S.S., (2023). e-Pharmacophore modeling and in silico study of CD147 receptor against SARS-CoV-2 drugs. *Genomics & Informatics*, *21*(2).

Pirolli, D., Righino, B., Camponeschi, C., Ria, F., Di Sante, G. and De Rosa, M.C., (2023). Virtual screening and molecular dynamics simulations provide insight into repurposing drugs against SARS-CoV-2 variants Spike protein/ACE2 interface. *Scientific Reports*, *13*(1), 1494.

Qiao, J., Li, Y.S., Zeng, R., Liu, F.L., Luo, R.H., Huang, C., Wang, Y.F., Zhang, J., Quan, B., Shen, C. and Mao, X., (2021). SARS-CoV-2 Mpro inhibitors with antiviral activity in a transgenic mouse model. *Science*, *371*(6536), 1374-1378.

Rampogu, S. and Lee, K.W., (2021). Pharmacophore modelling-based drug repurposing approaches for SARS-CoV-2 therapeutics. *Frontiers in Chemistry*, *9*, 636-362.

Razizadeh, M., Nikfar, M. and Liu, Y., (2021). Small molecule therapeutics to destabilize the ACE2-RBD complex: A molecular dynamics study. *Biophysical Journal*, *120*(14), 2793-2804.

Rensi, S., Keys, A., Lo, Y.C., Derry, A., McInnes, G., Liu, T. and Altman, R., (2020). Homology modeling of TMPRSS2 yields candidate drugs that may inhibit entry of SARS-CoV-2 into human cells. *ChemRxiv*.

Rezagholizadeh, A., Khiali, S., Sarbakhsh, P. and Entezari-Maleki, T., (2021). Remdesivir for treatment of COVID-19; An updated systematic review and meta-analysis. *European Journal of Pharmacology*, *897*, 173926.

Rudrapal, M., Celik, I., Khan, J., Ansari, M.A., Alomary, M.N., Alatawi, F.A., Yadav, R., Sharma, T., Tallei, T.E., Pasala, P.K. and Sahoo, R.K., (2022). Identification of bioactive molecules from Triphala (Ayurvedic herbal formulation) as potential inhibitors of SARS-CoV-2 main protease (Mpro) through computational investigations. *Journal of King Saud University-Science*, *34*(3), 101826.

Saeed, M., Saeed, A., Alam, M.J. and Alreshidi, M., (2021). Receptor-based pharmacophore modeling in the search for natural products for COVID-19 Mpro. *Molecules*, *26*(6), 1549.

Saloni, Kumari, D., Ranjan, P. and Chakraborty, T., (2022). A computational study of potential therapeutics for COVID-19 invoking conceptual density functional theory. *Structural Chemistry*, *33*(6), 2195-2204.

Sargolzaei, M., (2021). Effect of nelfinavir stereoisomers on coronavirus main protease: Molecular docking, molecular dynamics simulation and MM/GBSA study. *Journal of Molecular Graphics and Modelling*, *103*, 107803.

Sharma S., Khan Y., Saini K., Bhatia V., (2022). Role of QSAR in filling in the gaps of COVID-19 Therapeutics. *Chem Informatics, 8*(5).

Sharma, V., Wakode, S. and Kumar, H., (2021. Structure-and ligand-based drug design: Concepts, approaches, and challenges. *Chemoinformatics and Bioinformatics in the Pharmaceutical Sciences*, 27-53.

Singh, P.K., Pathania, S. and Rawal, R.K., (2020). Exploring RdRp–remdesivir interactions to screen RdRp inhibitors for the management of novel coronavirus 2019-nCoV. *SAR and QSAR in Environmental Research*, *31*(11), 857-867.

Toussi, S.S., Hammond, J.L., Gerstenberger, B.S. and Anderson, A.S., (2023). Therapeutics for COVID-19. *Nature Microbiology*, *8*(5), 771-786.

US Food and Drug Administration (FDA), 2023, June 28. Know your treatment options for COVID-19. https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-COVID-19

Vankadari, N., (2020). Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. *International Journal of Antimicrobial Agents*, *56*(2), 105998.

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X. and Zheng, M., (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, *10*(5), 766-788.

Xu, Z., Peng, C., Shi, Y., Zhu, Z., Mu, K., Wang, X. and Zhu, W., (2020). Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. *BioRxiv*, 2020-01.

Yang, H. and Yang, J., (2021). A review of the latest research on M pro targeting SARS-COV inhibitors. *RSC Medicinal Chemistry*, *12*(7), 1026-1036.