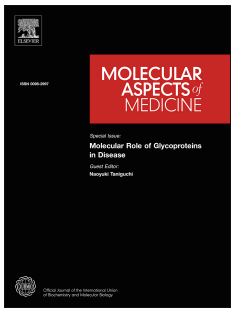
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Protein structure-based *in-silico* approaches to drug discovery: Guide to COVID-19 therapeutics

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Abstract:

With more than 5 million fatalities and close to 300 million reported cases, COVID-19 is the first documented pandemic due to a coronavirus that continues to be a major health challenge. Despite being rapid, uncontrollable, and highly infectious in its spread, it also created incentives for technology development and redefined public health needs and research agendas to fast-track innovations to be translated. Breakthroughs in computational biology peaked during the pandemic with renewed attention to making all cutting-edge technology deliver agents to combat the disease. The demand to develop effective treatments yielded surprising collaborations from previously segregated fields of science and technology. The long-standing pharmaceutical industry's aversion to repurposing existing drugs due to a lack of exponential financial gain was overrun by the health crisis and pressures created by front-line researchers and providers. Effective vaccine development even at an unprecedented pace took more than a year to develop and commence trials. Now the emergence of variants and waning protections during the booster shots is resulting in breakthrough infections that continue to strain health care systems. As of now, every protein of SARS-CoV-2 has been structurally characterized and related host pathways have been extensively mapped out. The research community has addressed the druggability of a multitude of possible targets. This has been made possible due to existing technology for virtual computer-assisted drug development as well as new tools and technologies such as artificial intelligence to deliver new leads. Here in this article, we are discussing advances in the drug discovery field related to target-based drug discovery and exploring the implications of known target-specific agents on COVID-19 therapeutic management. The current scenario calls for more personalized medicine efforts and stratifying patient populations early on for their need for different combinations of prognosis-specific therapeutics. We intend to highlight target hotspots and their potential agents, with the ultimate goal of using rational design of new therapeutics to not only end this pandemic but also uncover a generalizable platform for use in future pandemics.

Key words: *SARS-CoV-2*, COVID-19, Drug targeting, Rational improvement, Artificial Intelligence, Target-based drug discovery, Mathematical modeling

Introduction

Since the beginning of the COVID-19 pandemic, which is caused by SARS-CoV-2, there has been an impending question 'what can be the standard course of therapy, and which agents need to be trialed. The first year of the pandemic followed Murphy's Law (Bloch, 2003) with the ensuing chaos causing severe mortality rates due to a lack of population immunity and the use of ineffective interventions. The rapid global spread of the disease overwhelmed medical care systems due to exponential regional surges. As of July 4^{th,} 2022, the pandemic has claimed 6.35 million lives worldwide and caused over 0.5 billion cases of infection ("WHO Coronavirus Disease (COVID-19) Dashboard," n.d.). The USA has been the worst hit with more than a million deaths out of 87.5 million cases (Dong et al., 2020; Ruhm, 2022). The surge in cases is often at an intensity that its severity is made worse by a shortage of medical resources. This has stymied trials conducted for several agents (Robinson et al., 2022). Many promising initial reports of therapeutic approaches became proven failures, and yet they often were needlessly *trialed* repeatedly by different groups. Hampering effective therapeutic development, the rush to trials often fell short in the number of patients recruited. This under empowerment and the varying degree of symptom sets leads to prognosis and therapeutic response variability which makes it difficult to stratify patient populations. This was further exacerbated by the changing pathophysiology caused by newer variants, which combined with the evolving self-medication landscape, resulted in inconsistent trial data for some agents and ultimately unreliable outcome results (Watson, 2022). Prohibitive costs of newer drugs, as well as antibody therapies, have generated worldwide interest in trying a variety of agents to reduce the severity of COVID-19 infection. For instance, preliminary evidence suggested that hydroxychloroquine (HQ) therapy can reduce viral load (Gautret et al., 2020). However, a recent meta-analysis of multiple trial data has now concluded

that although HQ therapy is safe at the trial doses used, it remains ineffective in reducing mortality and severity of disease (T. Gupta et al., 2022). Conversely, other trials have shown more promising results, such as the use of Oseltamivir (Theraflu), which statistically demonstrated to reduce mortality in COVID-19 patients (Zendehdel et al., 2022). Additionally, various comorbidities like old age, diabetes, obesity, hypertension, and the immunocompromised state contribute to COVID-19 mortality, their associations are still not enough to stratify patients and take universal prophylactic measures (Gentile and Schiano Moriello, 2022) and as a result, new therapeutic interventions remain in high demand.

Computational structural biology is a interdisciplinary field performed on computer or via computer simulation that encompasses the theory and application of approaches to model, predict, and explain biological function at the molecular level, well-known as *in silico* experiment. Proteins are flexible molecules that undergo conformational changes (such as folding and unfolding or domain motions) as part of their interactions with other biopolymers as partners or drug molecules. Conformational changes of the proteins might reflect a closed, open, or intermediate states and this dynamical aspect plays a critical role in drug discovery. Nowadays, molecular dynamics makes it possible to simulate these conformational changes with a timescale ranging from nanoseconds to microseconds of time. Molecular dynamics simulations is a computer (*in silico*) technique that makes it possible to predict how a system will evolve over time and, consequently, to predict the movement of the molecules in the system. *In silico* methods (molecular modeling, molecular docking or screening, molecular dynamics, etc) could be used to efficiently identify and design drug candidates, to study their interactions with their targets. The Nobel Prize in Chemistry 2013 has been awarded to Martin Karplus, Michael Levitt and Arieh Warshel for development of

multiscale models of complex chemical systems as computational techniques for structural biology (https://www.nobelprize.org).

In silico drug discovery has proved to be instrumental in suggesting numerous agents and many of the predicted agents have been used to manage COVID-19. It has been a long-standing principle that the fixed 3D structure of protein dictated by amino acid composition is the basis for assigning function. There have been exceptions to this principle in multiple instances when proteins have multiple structures owing to disordered regions (Anjum et al., 2022; Prateek Kumar et al., 2022a; J. Zhang et al., 2022). This is more evident in RNA viral proteomes due to a higher rate of mutations and a protein often has more than one function. For instance, PLpro is a protease and a deubiquitinase and ion channel 3a, all of which are important for viral envelope formation, and their functional activities are associated with inflammasome formation in infected cells (Lewis et al., 2022; J. Zhang et al., 2022). Such redundancy, size limitations, and genetic instabilities call for highly flexible proteins which are generally seen in the experimentally solved crystal structure, their variabilities in viral proteins in the form of multiple 'states' and confirmations (Fornasier et al., 2022; Siragusa et al., 2022). As starting crystal structure is the bottleneck of any virtual screening effort, this variability led to numerous 'false' hits that had no agreement between binding prediction and biological activity (Martin et al., 2020). Like all the other fields, the field of computational biology methods also had multiple breakthroughs which now have more applications than just COVID-19 drug discovery research. Additionally, we now have AI predictions for the shape of nearly every known protein, which can be structurally complementary to drug discovery (Callaway, 2022). Many laboratories have been pioneering novel technologies in the machine learning, AI, and conformational dynamics space (Caulfield and Medina-Franco,

2011; Coban et al., 2021b, 2021a, 2020; Hines et al., 2019b, 2019a; Kayode et al., 2016; Puschmann et al., 2017; Savytskyi et al., 2013).

Recently, the anti-cancer drug Pralatrexate was discovered to have in vitro EC50 values of 0.008μM. While being a strong immunosuppressant it's usability in COVID-19 is highly debatable the pipeline that delivered this compound comprised of deep learning models and force field dynamics simulations (Zhang et al., 2020). With newer and faster methods made available there are multiple methods producing a similar pipeline (Rapicavoli, Alaimo, Ferro, & Pulvirenti, 2022; Zhang et al., 2022). Free energy perturbation calculations enabled Zhang et.al in 2022 to improve main protease Triarylpyridinone inhibitors to have EC50 values as low as 0.080 μM (Ramos, Zeze, Velut, & Jan, 1987).

In this review, we try to boil down protein-inhibitor relationships that have been exploited as anti-COVID-19 therapeutics or have a high validated potential for the same. Such information should be used to steer the computational learning approaches through AI to understand why these work and others don't despite having positive classic predicted interactions. Additionally, we provide a comprehensive analysis of existing, approved, and experimental therapeutics with their mechanism of action against either the viral or host protein targets.

Drugging COVID-19: what constitutes a "good" drug?

There have been some controversial agents that have undergone trials against SARS-CoV-2 due to some *in vitro* reports or proposed mechanisms of action (Ivanova et al., 2022). Many of these agents did not have a consistent effect and had surprising side effects such as QT prolongations (abnormal heart rhythms and sudden cardiac arrest) e.g Chloroquine and Hydroxychloroquine (Deng et al., 2022). While others were not fully effective at tolerable doses

e.g. Ivermectin (Hariyanto et al., 2022), some were mildly effective even though they had no interaction with SARS-CoV-2 targets, e.g. oseltamivir (Zendehdel et al., 2022). Some were highly dangerous, especially with the misinformation inspired panicked patient self-medications e.g. Chlorine Dioxide (Chejfec-Ciociano et al., 2022). Since the beginning of the pandemic, Ibuprofen was contraindicated as it is known to increase ACE2 receptor expression in the cells exacerbating viral infectiousness. However, there was widespread use of nebulized ibuprofen (NaIHS) as a wonder cure and reported to be highly effective, had negative correlations and so-called positive effects were probably due to concomitant aggressive corticosteroid therapy (Calonico et al., 2022). As a result, there is a need to understand both classical drug targets and other modalities that may be therapeutic.

Techniques for elucidation of drug-target interaction and efficacy

One of the foundations of drug design is to utilize a molecular model of druggable targets. Today's drug discovery labs can draw from a multitude of techniques for determining experimental structures, yet the different techniques have their strengths and weaknesses. For example, membrane proteins are notoriously difficult to crystallize, so the gold standard x-ray crystallography is generally not successful. Typically, cryo-EM is utilized for large proteins/complexes, such as membrane proteins. The caveat here is that cryo-EM is in general a lower resolution technique and may bias conformations because of the air-water interface. A relatively new structural technique is x-ray free-electron laser (XFEL), coupled with lipid-cubic phase crystallization (Ono et al., 2022). Essentially, this consists of growing small crystals in a lipidic environment that is more amenable for membrane proteins, which are then injected at

random orientations and illuminated with extremely brilliant x-ray photons to generate diffraction patterns. This has been successfully applied to a variety of membrane proteins recently, though not as yet any COVID-19-related target; however, this technique has potential application in the field as shown with other viruses (Townsend et al., 2021). Proteases and kinase inhibitors have traditionally held roles as drugs of choice for inhibiting virion production (Bain et al., 2003; Mahdi et al., 2020; Pearlman, 2012; "Protein Kinase Inhibitors," 2012; Zhou et al., 2015), however, in recent times the shift to virus centric proteins has made progress (Chakraborty et al., 2021; Dai et al., 2020; Narayanan et al., 2022; Prajapat et al., 2020; Y.-X. Zheng et al., 2021). Added to these new targets has been the implementation of new computational tools to more quickly address the urgency of the need (Callaway, 2022; Coban et al., 2021b).

Enter the era of the machine: learning to use algorithm-guided drug design

The complex multivariate approaches to drug modeling on a molecular structure are well suited to the application of machine learning (ML) techniques. Generative chemistry is at the forefront of new medicinal chemistry design workflows, where the implementation of layered data with context to various data sources allows us to integrate complex datasets into the framework of a deep learning or machine-based intelligence that can find associations otherwise not possible. Both ML and artificial intelligence (AI) are being applied to many areas of biological research. With respect to COVID-19, ML has been used to help screen drug targets, druggable sites on the targets, drugs, and drug-target interactions (El-Behery et al., 2021). This has led to the repurposing of drugs that are already FDA-approved for COVID-19 therapy, the discovery of novel molecules as potential drugs, and the identification of cryptic binding pockets introduced by virus/host protein-protein interaction (Dang and Song, 2022). In addition, ML has been used to mine bioinformatics data and

analyze biological pathways to identify novel pathways that can lead to a greater understanding of the disease mechanism, as well as detect additional points of intervention (Auwul et al., 2021). AI has assisted in the analysis of samples to help make rapid diagnoses with a less expensive assay that is highly sensitive, selective, and accurate (Jaroenram et al., 2022; Lai et al., 2022). The method works by employing two pH-dependent dyes and a reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay; the colorimetric readout data was used to train an algorithm for classification i.e. diagnosis of positive or negative infection status. Other uses of ML related to COVID-19 are the large-scale screening for anti-COVID-19 biomolecules in foods (Laponogov et al., 2021). The study used a similar approach to standard drug screening but started with a database of food-based bioactive molecules; they identified 52 molecules predicted to disrupt the COVID-19-host interactome. Engaging in multiple treatment paradigms is beneficial in that it increases the likelihood of therapeutic benefit to the patient, decreases the chance of the virus developing resistance, and can reduce dosing to limit adverse side effects. Interruption of COVID-19 progression with multi-drug therapy looking for synergetic effect with computational biology for high-throughput screening has been successful (Coban et al., 2021b), which has the capability of using mixed algorithms to examine the impact of structural changes. As a result, the application of ML and AI techniques is expected to yield rapid progress in the discovery of new candidates for antiviral use.

In silico deduced target-specific leads that reached clinical trials

Favipiravir is a purine analog that is a potent RNA-dependent RNA polymerase (RdRp) inhibitor initially selected on basis of similarities with known target EBOLA RdRp (da Silva et al., 2022; Mashayekhi-Sardoo and Hosseinjani, 2022). Favipiravir showed a 62.8% viral clearance in 4 days compared to untreated (Ivashchenko et al., 2021). While favipiravir has little effect on

nonhospitalized patients, its use among hospitalized patients has led to faster viral clearance and better radiological imaging endpoints in multiple trials (Hung et al., 2022). With upcoming reports of long-term lung damage in both hospitalized and nonhospitalized patients (C. Wang et al., 2022; J. Yu et al., 2022), there is a need for a retrospective follow-up trial needed to assess favipiravir's long-term benefits. Icatibant is a known bradykinin type 2 receptor antagonist that was computationally predicted to target the SARS-CoV-2 main protease (Liu and Wang, 2020). However, the clinical trial (NCT04978051) results were inconclusive (Malchair et al., 2022) and there is no target-specific inhibition data available. Lopinavir & Ritonavir are other predicted inhibitors of 3CLpro (Reina and Iglesias, 2022), however, numerous clinical trials have failed to establish their clinical usefulness as anti-COVID-19 medications (Cao et al., 2020; Sheahan et al., 2020). PF-07321332 (nirmatrelvir) a rationally improved second-generation frontrunning drug from Pfizer is in the Phase3 clinical trial, It targets 3CLpro and thereby inhibits viral replication (Vandyck and Deval, 2021). Ciclosporin/Cyclosporine immunomodulatory drug is a calcineurin inhibitor that was discovered through computational host interactome modeling for the SARS virus (SARS-CoV) (Pfefferle et al., 2011) and was predicted to have a positive effect on COVID-19 through immunosuppression (Ellinger et al., 2021). Further, it was found to have antiviral activity *in vitro* (Dittmar et al., 2021). Later HR (hazard ratio) improvement value of 2.15 was observed in a combination trial with a low dose of steroid (Galvez-Romero et al., 2021) and was an efficacious treatment option in the COQUIMA cohort (Schuurmans and Hage, 2021) and multiple variants (Fenizia et al., 2022). Another 3CLpro inhibitor, found through *in silico* screenings was Cepharanthine (CEP), a small phyto-alkaloid obtained from the *Stephania cepharantha*. CEP had IC_{50} of 1.90 μm (Hijikata et al., 2022) against the Wuhan strain (wild type) and consistent activity against three other VOCs (Prabhakaran Kumar et al., 2022). It's a promising anti-COVID-19

candidate in animal testing offering significant protection from lung fibrosis in bleomycin (BLM)-challenged rats (Li et al., 2022).

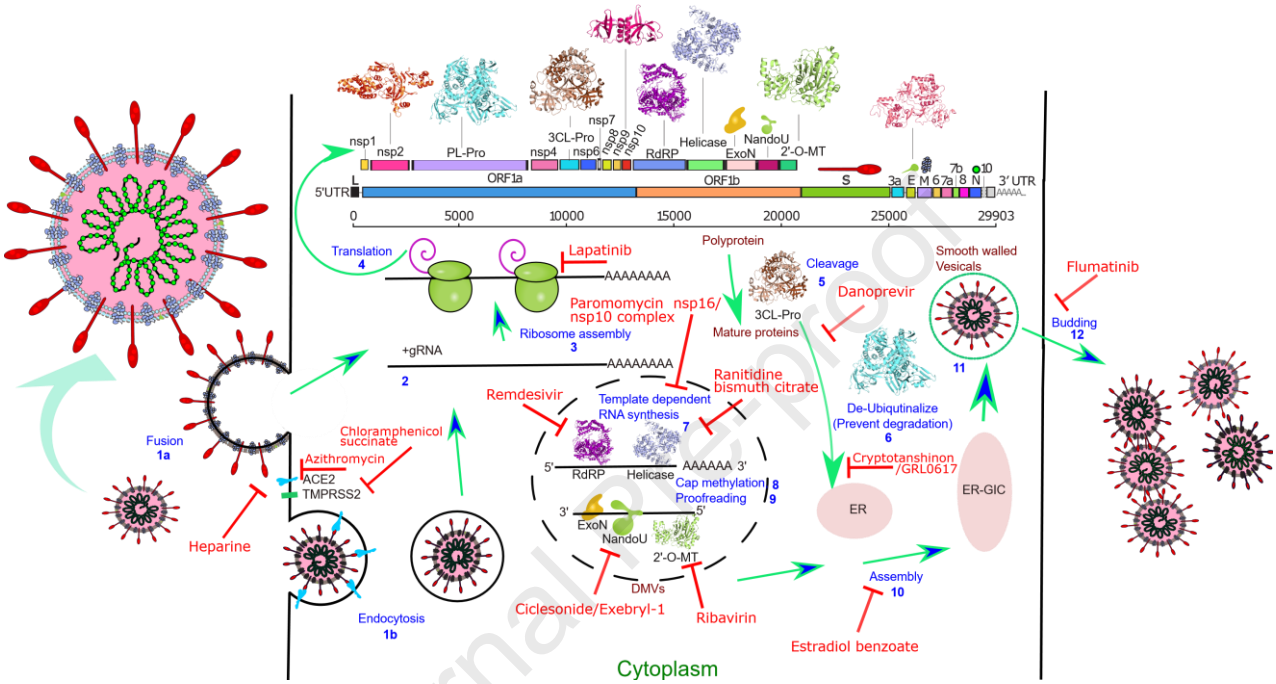
Cytotherapy

Cellular therapies have been proven to protect immunosuppressed patients (>20% mortality rate) by providing anti-viral cellular immunity and immune modulation for vulnerable patient populations (Farhangnia et al., 2022; Verma et al., 2022). Different trials with SARS-CoV-2 specific T-cell trials (allogeneic CSTs familial or HLA matched), Natural killer (NK) cell (e.g. FT516 cells), Tregs (T regulatory cell), and Mesenchymal Stem Cell Infusion or Stem Cell Products have shown therapeutic potential comparable to available antiviral therapies (Conway et al., 2022). With a longer lifespan of T-cells, there is longer-lasting protection than humoral immunity.

Biological activities of SARS-CoV-2 components as potential therapeutic targets

A wide variety of targets are addressable for attenuating the infection progression of SARS-CoV-2 as depicted in Figure 1. As previously mentioned, therapeutics active on some of these targets are now in clinical trials. Yet many more Non-Structural Protein (NSP) targets have been identified and are in various stages of development (Table 1). In this review, we will address both classical drug targets (enzymatic vs non-enzymatic) and new modalities for possible use as COVID therapies.

Figure 1. Schematic depiction of different SARS-CoV-2 proteome (ORF map) coded targets(3D ribbons or cartoons) involved in different steps of viral replication (labeled blue) and various example inhibitors (labeled red). *The infection cycle starts when the SARS-CoV-2 Spike protein binds to a Human receptor followed by either viral-host cell fusion (1a) or endocytosis*



(1b). Fusion directly allows the viral RNA to enter the host cell (2), The large viral script is known to encode 29 viral proteins (3), A viral-specific translation yields two replicase polyproteins, pp1a and pp1ab, and many small ORFs(4). The two major polyproteins are processed by two proteases, PLpro and 3CLpro(5), generating 16 NSPs. ExoN possesses a viral exoribonuclease activity (9). Viral Helicase plays a critical role in viral replication by unwinding dsRNA formed during replication as well as tertiary structures of genomic RNA. (7). The enzyme 2'-O-MT methylates the viral 2' end which is important for selective translation and protection from host RNA degradation (8). RdRP along with different NSPs is involved in viral-host cell replication through catalyzing template synthesis of polynucleotides in the 5' to 3' direction (7). NendoU is an Mn^{2+} dependent hexamer (dimer of trimer) enzyme responsible for protein interference with the innate immune system. For viral assembly of structural proteins (S, E, and M) in the endoplasmic reticulum, along with the N protein is combined with the (+) gRNA to become a compact helical nucleoprotein complex(10). They assemble to form a virus particle in the endoplasmic reticulum-Golgi apparatus compartment

and are then excreted from the cell through budding mediated by the fusion of smooth-walled vesicles to the plasma membrane (11–12).

Table 1. *In vitro* validated anti-SARS-CoV-2 agents reported with a known target

Agent name & SARS-CoV-2 target	**Kind of agent**	**Assay/ validation with *SARS-CoV-2***	**IC50 (µM) If available**	**Previously known target?**	**Mechanism of action of approved use**	**Reference**
Darunavir ***NSP enzymatic* - Main peptidase**	Protease inhibitors (synthetic compound)	It was done using the High-performance liquid chromatography (HPLC) method.	5.55	Target decreasing the risk of HIV transmission to other people.	Works by decreasing HIV amount in the blood.	(Costanzo et al., 2020)
Teicoplanin ***NSP enzymatic* - Main peptidase**	Glycopeptide antibiotic	It was done using the ultra-high performance liquid chromatography–high-resolution mass spectrometry method.	8.78	Target various infections caused by gram-positive bacteria.	It inhibits peptidoglycan polymerization, leading to the inhibition of bacterial cell wall synthesis and cell death.	(F. Yu et al., 2022)

Nelfinavir ***NSP enzymatic* - Main peptidase**	A viral protease inhibitor	Done using *in vitro* and *in vivo* genetic toxicology assays.	37	Targets HIV in adults and children.	Works by preventing HIV virion from fully maturing and becoming infective.	(Foo et al., 2021; Ohashi et al., 2021)
Bortezomib ***NSP enzymatic* - Main peptidase**	A proteasome inhibitor	Done using HPLC-UV Method	1.39	Targets multiple myeloma, or mantle cell lymphoma in patients.	Works by preventing uncontrolled degradation of IκB, an inhibitory protein of NF-κB.	(Shen et al., 2022)
α-ketoamide inhibitor compound 13b ***NSP enzymatic* - Main peptidase**	Protease inhibitor	It was done using MD simulation.	0.67 ± 0.18	Targets M^{pro} of α-and β-coronaviruses in addition to 3C proteases of enterovirus.	Works by inhibiting the replication of SARS-CoV-2 in human Calu3 lung cells.	(Zhang et al., 2020)

Telaprevir ***NSP enzymatic* - Main peptidase**	An NS3/4A viral protease inhibitor	It was done using *in-vitro* analysis.	11.54	Targets chronic Hepatitis C Virus infections.	Works by inhibiting viral HCV genotype 1 replication.	(Mahmoud et al., 2021).
Boceprevir ***NSP enzymatic* - Main peptidase**	Protease inhibitor.	It was done through molecular docking and subsequent experimental validation.	1.95± 1.62 (EC50)	Targets chronic Hepatitis C, an infectious liver disease caused by infection with Hepatitis C Virus (HCV).	Works by binding the serine (S139) residue in the active site via an (α)-ketoamide functional group, inhibiting the proteolytic activity of the HCV 1a and 1b encoded enzyme.	(Ma et al., 2020b)
Ebselen ***NSP enzymatic* - Main peptidase**	Antioxidant drug	It was done using in vitro and in vivo studies.	4.67	Targets Meniere's Disease, Type 2 Diabetes Mellitus, and Type 1 Diabetes Mellitus.	Works by modulating metalloproteins, enzymatic	(Jin et al., 2020)

					cofactors, gene expression, epigenetics, antioxidant defenses, and immune systems.	
Dactolisib ***NSP enzymatic* - Main peptidase**	An imidazoquinoline derivative.	It was done using *in vitro* and *in vivo* studies.	0.225	Targets Cancer, Solid Tumor, Renal Cancer, Breast Cancer, and Cowden Syndrome, among others.	Works by inhibiting PI3K kinase and mTOR kinase in the PI3K/AKT/ mTOR kinase signaling pathway, which may result in tumor cell apoptosis and growth inhibition in PI3K/mTOR - overexpressing tumor cells.	(Garcia et al., 2021)

Alvocidib ***NSP enzymatic* - Main peptidase**	A synthetic flavonoid	It was done using bioanalytical methods.		Targets cancer.	Works by inhibiting cyclin-dependent kinases, arresting cell division, and causing apoptosis in non-small lung cancer cells.	(Fong, 2020)
Methotrexate ***NSP enzymatic* - Main peptidase**	Antimetabolites	It was done using the HPLC-SRM-MS plasma analysis.		It targets severe psoriasis, certain types of cancer including uterine, breast, and lung cancer, certain types of lymphoma, certain cancers of the head and neck, and leukemia.	Works by slowing the growth of cancer cells. Equally, it decreases the activity of the immune systems to treat rheumatoid arthritis.	(Stegmann et al., 2021)
Carmofur ***NSP enzymatic* -**	Antineoplastic drug or chemotherapeutic agent.	It was done using In Vitro and in Vivo biological evaluations.	28.2 ± 9.5	Targets colorectal and breast cancer.	Works by controlling cancer cell proliferation, suppressing	(Ma et al., 2020a)

Main peptidase					N-acylethanolamine acid amidase (NAAA) activity.	
Conivaptan ***NSP enzymatic - Main peptidase***	An antidiuretic hormone inhibitor.	Done using bio-analytical HPLC-MS/MS method	12.2 ± 4.20	Target euvolemic or hypervolemic hyponatremia in hospitalized patients.	Works by raising serum levels.	(Yang et al., 2020)
Atovaquone ***NSP enzymatic - Main peptidase***	An antiprotozoal agent.	It was done using a spectrophotometric method.	6.78 ± 0.73	Targets Pneumocystis pneumonia in adults and teenagers.	Works by stopping specific protozoa from causing pneumonia.	(Yang et al., 2020)
Vilazodone ***NSP enzymatic -***	An antidepressant	It was done using the Spectrofluorimetric Detection method.	below 15	Targets depression in adults.	Works by raising the serotonin activity in the brain.	(Ghasemiyeh et al., 2021)

Main peptidase						
Michael acceptor inhibitor N3 ***NSP enzymatic*** - **Main peptidase**	Protease inhibitor.	It was done using QM/MM simulations.	16.77 (EC50)	Targets SARS-CoV-2.	Works by inhibiting SARS-CoV-2 3CLpro.	(Jin et al., 2020)
Raloxifene ***NSP enzymatic*** - **Main peptidase**	A selective estrogen receptor modulator.	It was done using competitive binding assays.	4.50 - 7.99	Targets osteoporosis and breast cancer in high-risk postmenopausal women.	Works by promoting estrogen-like effects on lipid metabolism.	(Imamura et al., 2021)
Ouabain ***NSP enzymatic*** - **Main peptidase**	A cardioactive glycoside.	It was done through cell biological studies.	0.030 μM - 0.075	It targets atrial fibrillation and flutter, and heart failure.	Works by inhibiting the Na-K-ATPase membrane pump.	(Farag et al., 2020)
GC373 ***NSP enzymatic*** - **Main peptidase**	Feline drug	It was done using downstream biochemical assays.	0.40 ± 0.05	Targets SARS-CoV-2.	Works by inhibiting SARS-CoV-2 M^{pro}.	(Vuong et al., 2020)

GC376 ***NSP enzymatic* - Main peptidase**	Prodrug	It was done using a fluorescence resonance energy transfer (FRET)–based cleavage assay.	0.19 ± 0.04	Targets SARS-CoV-2.	Works by inhibiting SARS-CoV-2 M^{pro}.	(Vuong et al., 2020)
Imatinib ***NSP enzymatic* - Main peptidase**	A tyrosine kinase inhibitor	It was done using UPLC-MS/MS assay and ultrafiltration method.	0.17	Targets gastrointestinal stromal tumors, leukemias, systemic mastocytosis, myelodysplastic/myeloproliferative disease, dermatofibrosarcoma protuberans, and hypereosinophilic syndrome.	Works by inhibiting the Bcr-Abl tyrosine kinase and proliferation of cells and induces apoptosis in fresh leukemia cells and Bcr-Abl positive cell lines.	(Han et al., 2021)
Triclabendazole ***NSP enzymatic* - Main peptidase**	An anthelmintic drug.	It was done using in Vitro and animal studies.	70	Targets fascioliasis in livestock and humans.	Works by reducing resting membraned and inhibiting tubulin function and	(Gao et al., 2020)

					enzyme and protein necessary for Fasciola species survival.	
Emedastine ***NSP enzymatic* - Main peptidase**	A selective H1-receptor antagonist.	It was done using an in Vitro study.	82 ± 7	Targets allergic conjunctivitis.	Works by managing symptoms of allergic conjunctivitis.	(Gao et al., 2020)
Bendamustine ***NSP enzymatic***	An antineoplastic agent	It was done using an *in-vitro* study.	26 ± 1	Targets chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma.	Working by causing intra- and inter-strand crosslinks between DNA bases resulting in cell death.	(Gao et al., 2020)
Mebendazole ***NSP enzymatic* -**	An anthelmintic or anti-worm medication.	It was done using a spectrophotometric method in the UV region.	0.25-1.2	Targets infections caused by hookworm, pinworm, whipworm, and roundworm infections.	Works by preventing newly hatched insect larvae (worms)	(Ahmed et al., 2021)

Main peptidase					from growing or multiplying in your body.	
Carprofen ***NSP enzymatic* - Main peptidase**	A nonsteroidal anti-inflammatory drug	It was done using an *in vitro* Study.	3.97 ± 0.60%	Targets arthritic symptoms in geriatric dogs.	Works by inhibiting cyclooxygenase activity.	(Gimeno et al., 2020)
Lapatinib ***NSP enzymatic* - Main peptidase**	An anti-cancer drug	It was done using in Vitro and animal studies.	31.1	Targets solid tumors such as breast and lung cancer.	Works by binding to the intracellular phosphorylation domain to prevent receptor autophosphorylation upon ligand binding.	(Lau et al., 2021)
Celecoxib ***NSP enzymatic* - Main peptidase**	A nonsteroidal anti-inflammatory drug.	It was done using a validated HPLC analytical method.	13.02	Targets mild to moderate pain and symptoms of arthritis.	Works by suppressing hormones causing inflammation and pain.	(Mostafa et al., 2020)

Retapamulin ***NSP enzymatic - Main peptidase***	A topical antibiotic agent.	It was done through In Vitro studies.		Targets impetigo.	Works by inhibiting the initiation of protein synthesis by binding to a specific site on the 50S subunit of the bacterial ribosome.	
Bafetinib ***NSP enzymatic - Main peptidase***	Antineoplastic drug	It was done through a quantitative readout performed by mass spectrometry.	0.79	Targets Adult Gliosarcoma, Adult Mixed Glioma, Adult Glioblastoma, Chronic Myeloid Leukemia, and Acute Lymphocytic Leukemia, among others.	Works by inhibiting the Bcr/Abl fusion protein tyrosine kinase.	(Meyer et al., 2021)
Masitinib ***NSP enzymatic - Main peptidase***	Antineoplastic and immunomodulating agents.	It was done using randomized, placebo-controlled phase trial studies.	3.8	Targets cell tumors in dogs.	Works by inhibiting tyrosine-kinase.	(Drayman et al., 2021)

Simeprevir ***NSP enzymatic* - Main peptidase**	A direct-acting antiviral agent	It was done using HPLC with Fluorescence Detection.	9.6 ± 2.3	Targets chronic hepatitis C viral infection in adults with HCV genotype 1 or 4.	Works by inhibiting HCV NS3/4A protease.	(Lo et al., 2021)
Grazoprevir ***NSP enzymatic* - Main peptidase**	An antiviral and NS3/4A protease inhibitor	It was done using the RP-HPLC method.		Targets hepatitis C infections.	Works by inhibiting viral HCV replication.	(Abidi et al., 2021)
Ciluprevir ***NSP enzymatic* - Main peptidase**	An orally active inhibitor of the HCV NS3 protease.	It was done using a randomized, multiple-dose, double-blind, placebo-controlled pilot study.	20.77	Targets hepatitis treatment.	Works by blocking NS3 protease-dependent polyprotein processing in HCV replicon-containing cells.	(Baker et al., 2021)
Narlaprevir ***NSP enzymatic* -**	An antiviral drug and protease and proteinase inhibitor.	It was done using In Vivo and In Vitro studies.	1.10	Targets chronic hepatitis.	Works by inhibiting hepatitis C protease, SARS	(Bai et al., 2021; Baker et al., 2021)

Main peptidase					coronavirus main proteinase, and coronavirus.	
Silibinin ***NSP enzymatic*** - **Main peptidase**	An antioxidant and antineoplastic agent.	It was done using in Vitro and anima research studies.		Targets toxic liver damage and cancer.	Works by altering cell proliferation, metastasis, invasion, apoptosis, and angiogenesis.	(Hamdy et al., 2022)
Suramin & Quinacrine ***NSP enzymatic*** - **Main peptidase**	Protease inhibitor	It was done using in Vitro studies.	6.3 ± 1.4	Targets SARS-CoV-2.	Works by inhibiting ARS-CoV-2 main protease ($3CL^{pro}$).	(Eberle et al., 2021)
Bisindolmaleimide-IX ***NSP enzymatic*** - **Main peptidase**	An enzyme inhibitor.	It was done using a virtual screening pipeline and in-vitro validation assays.	113.7 ± 5.2	Targets chronic lymphocytic leukemia.	Works by inhibiting protein kinase C and inducing apoptosis.	(Gupta et al., 2021b)

NSP Enzymatic targets

Main Peptidase

The 3CLpro/Mpro gene is the Main Peptidase of SARS coronavirus and is responsible for ~11 cleavage sites in viral propeptide. As a result, it is an essential target for both viral replicase as well as structural assembly for completing the viral cycle (Gupta et al., 2021b). This 306 amino acid long protease has a catalytic core with C145 and H41 and is highly conserved among variants to preserve essential function (Gupta et al., 2021a) but also has multiple conformation states making drug targeting difficult (Savytskyi and Kornelyuk, 2022). The most recent PF-07321332 (**nirmatrelvir**) is a Pfizer anti-SARS-CoV-2 compound targeting 3CLpro (Reina and Iglesias, 2022). In combination with ritonavir, a xenobiotic degradation reducing agent for PF-07321332 (Lamb, 2022), the drug combination has shown a strong efficacy across multiple SARS-CoV-2 variants (Ullrich et al., 2022). Additional research on combinations with other antiviral agents targeting different components (e.g. Monupiravir/remdesivir for RdRp) is ongoing (Table 1). Earlier, *in silico* predictions discovered a 3CLpro inhibitor, Atazanavir, that was later shown to block viral replication (Fintelman-Rodrigues et al., 2020) and showed positive outcomes in various trials (Kalantari et al., 2021). However, due to many side effects such as hepatotoxicity, Atazanavir failed to be a drug of choice in the long run (Mazaherpour et al., 2021). Daclatasvir is a well-accepted HCV therapeutic and its combination with sofosbuvir is well tolerated and efficacious (Merat, 2020). While both Daclatasvir and sofosbuvir had anti-SARS-CoV-2 activity, the combination showed inconsistent results in different trials but had an overall positive effect (Chan

et al., 2021, p. 2). Another anti-HCV protease inhibitor Danoprevir showed some efficacy in initial trials (H. Chen et al., 2020) but was abandoned in Phase 4 trials (NCT04345276).

Papain-like proteinases

Papain-like viral protease (Plpro) is named NSP 3 and is a versatile enzyme that processes the viral polypeptide into functional proteins similar to 3CLpro but has Catalytic triad C111, H272, and D286 which is also highly conserved (Fu et al., 2021). While activating it also protects viral peptides being attacked by host proteasome machinery and de-ubiqutinylase Lys-linked polyUb chains (Lewis et al., 2022). Although a potential therapeutic target, drugs blocking Plpro have yet to be identified.

RNA-dependent RNA polymerase

Viral RNA-dependent RNA polymerase (RdRp) is identified in the SARS-CoV-2 genome as the NSP 12, It's part of a large replicase complex carrying out RNA replication. This protein class has been a highly exploited target in several RNA viruses and the resulting inhibitors have served as a rich pool for many repurposable antivirals (Abolhassani et al., 2021). While all the natural variants in SARS-CoV-2 are highly susceptible to remdesivir (Pitts et al., 2022), studies have shown the possibility of mutational resistance which is contraindicated for monotherapy (Stevens et al., 2022). Azvudine is a 4′-Modified Nucleoside and a potent anti-HIV drug candidate (Chang, 2022). Early trials showed Azvudine as a promising anti-COVID-19 agent with evident shortening of nucleic acid negative conversion (Ren et al., 2020), but it has only been regionally approved as an anti-HIV therapeutic in China and has not been trialed elsewhere. AT527 (RO-7496998) *a.k.a.* bemnifosbuvir is an oral purine nucleotide prodrug that has potent *in vitro* antiviral activity SARS-CoV-2 (Shannon et al., 2022) and has also shown a shortening of disease tenure in early trials (Good et al., 2021). Clevudine a pyrimidine analog is an anti-HBV drug that underwent a trial in

the Korean republic but was grossly ineffective (Song et al., 2021). Sofosbuvir (PSI-7977), an approved anti-HCV phosphoramidite prodrug (Messina et al., 2022), is a treatment that has been shown to reduce mortality and improve associated clinical outcomes in patients with COVID-19 (Hsu et al., 2022). Molnupiravir is a prodrug and it is hydrolyzed by esterases to form intermediate ribonucleoside N-hydroxycytidine (NHC) which is further phosphorylated intracellularly yielding active agent NHC triphosphate (NHC-TP) (Cox et al., 2021; Wahl et al., 2021). It is a well-tolerated and highly effective anti-COVID-19 treatment owing to its high bioavailability (Table.2) (Caraco et al., 2022; Jayk Bernal et al., 2022; Whitley, 2022).

Helicase

NSP 13 is an ATP-dependent Helicase with a 5'to 3' polarity acting on either double-stranded RNA/DNA (Shu et al., 2020). Among all SARS-CoV-2 NSPs, Helicase is the most conserved among different beta coronavirus species (Jang et al., 2020). There are reports of helicase forming a complex with RdRp/replicase complex suggesting a role in proofreading during RNA replication (J. Chen et al., 2020). Also, there are isolated reports of helicase affecting infected cell interferon (IFN) signaling to neighboring healthy cells by altering JAK1 phosphorylation of SAT1 (Fung et al., 2022). While there were multiple helicase inhibitors discovered against SARS and MERS there were not many interesting leads for SARS-CoV-2 despite high sequence similarity (Cimolai, 2020) except amantadine or memantine that have been shown in isolated reports to be effective in COVID-19 with neurological symptoms (Rejdak and Grieb, 2020). Ranitidine bismuth citrate also targets helicases and was initially shown to be highly effective in protecting Syrian hamster COVID-19 animal models (Yuan et al., 2020). While SARS-CoV-2 helicase is highly susceptible to bismuth salts, which are accepted to be the primary mechanism (Shu et al., 2020), zinc chelation (Zamai, 2021, p. 20) and allosteric main protease inhibition (Tao et al., 2021) additional

mechanisms in play. A pilot study showed that 50% of patients receiving Bismuth Subsalicylate (BSS) became RT-PCR negative, however, authors state issues with dosage and bioavailability.

NendoU

NSP 15 is a uridylate-specific endoribonuclease (NendoU) that exists as a homo hexamer (Tran et al., 2022). While NendoU is highly conserved among most of the nidoviruses, especially vertebrates infecting coronaviruses, its knockouts are known to replicate at par with wild types (Grellet et al., 2022). The role of NendoU is to protect viral RNA from host intracellular defenses (Boodhoo et al., 2022). A few of the known corticosteroids can inhibit SARS/MERS *in vitro* and were also reported to have potent activity against SARS-CoV-2 with IC_{50}s niclosamide (0.28 μM), ciclesonide (4.33 μM), and tilorone (4 μM) (Ko et al., 2021). Ciclesonide has been shown to lose antiviral activity on MERS-Nendou mutants (Matsuyama et al., 2020). While Ciclesonide has been part of many therapeutic combinations, there have been a few focused monotherapy randomized trials with inhaled formulations that have resulted in lower hospitalizations and reduced respiratory symptoms in treated patients (Clemency et al., 2022; Ezer et al., 2021). Ciclesonide is of particular interest for long-haul patient management for preventing severe lung damage (Ruggiero et al., 2022). Exebryl-1 a known ß-amyloid anti-aggregation molecule (Alzheimer's therapy) was shown to have consistent antiviral activity between 10 to 66 μM, in various cell lines and was discovered through high throughput screens (Choi et al., 2021). Exebryl-1 has been shown to disturb hexamerization of NendoU critical for its activity (Tran et al., 2022). So far there are no trials with Exebryl-1 against COVID-19, but negative drug interactions with COVID-19 medications with Alzheimer's disease does suggest a utility for this repurposable agent (Balli et al., 2020).

Other targets

ADP ribose phosphatase (NSP3) is another interesting target playing a role in cellular immune evasion by SARS-CoV-2 by resisting ADP-ribosylation of host proteins induced by IFN (Russo et al., 2021). Exoribonuclease (ExoN, NSP14) is a 5‘-to-3‘ exonuclease and has been the focus of many computational drug screening pipelines (Castillo-Garit et al., 2021; Gupta et al., 2021b). ExoN is inhibited by S-adenosylhomocysteine (Riccio et al., 2022) which is a marker for severe COVID-19 (Ponti et al., 2021) and its abundance may have been protecting liver cholangiocytes expressing ACE-2. NSP16 is another critical target which is an Mn^{2+} dependant putative 2'-O-methyl transferase that forms a heterodimer with NSP10 (Minasov et al., 2021).

Non-enzymatic targets

3a Ion channel

ORF3a encodes an accessory protein that forms K+ channels that trigger NLRP3 activation resulting in the maturation of IL-1β and cleavage/activation of Gasdermin via NFκB (Kern et al., n.d.; J. Zhang et al., 2022). ORF3a is susceptible to amantadine (Toft-Bertelsen et al., 2021) which has been shown to improve patient conditions suffering from COVID-19-Related Diffuse Leukoencephalopathy (Lam et al., 2022). In a larger trial with co-morbidities in Parkinson's and multiple sclerosis patients already receiving amantadine, there was significant prevention of COVID-19 infection (Kamel et al., 2021). A larger trial is in progress and its results are awaited (Rejdak and Grieb, 2020). Tomar et.al. 2021 reported many more FDA-approved drugs with significant *in vitro* activity against heterologously expressed 3a Ion channel; Plerixafor, Kasugamycin, Capreomycin, Pentamidine, Spectinomycin, Flumatinib, Darapladib, Floxuridine, and Fludarabine (Tomar et al., 2021, 2021).

Non-structural protein 1

NSP-1 is the host shutoff factor that halts the translational machinery of SARS-CoV-2 infected cells by binding with the mRNA channel within the ribosome (Simeoni et al., 2021). The main c-terminal domain playing a role in the ribosome binding can be blocked by Mitoxantrone hydrochloride (Novantrone) (Prateek Kumar et al., 2022b). Notably, Mitoxantrone HCL also blocks viral entry through perturbing spike-heparan sulfate interactions (Q. Zhang et al., 2022).

Other SARS-CoV-2 targets

NTD-N-protein or N terminal domain of Nucleocapsid protein is responsible for binding and thereby assembling the RNA genome of SARS-CoV-2 (Ye et al., 2020). Recently multiple *in vitro* anti-*SARS-CoV-2* molecules were discovered as interacting with the NTD-N-protein through isothermal titration calorimetry with EC_{50}s: Telmisartan (1.02 μM), Bictegravir (8.11 μM), Bisdemethoxycurcumin (1.64 μM), and MCC-555 (4.26 μM) (Dhaka et al., 2022). Additional targets have been proposed and investigated as drug targets *in silico*. NSP2 is involved in host signaling interferences, NSP3 mediates a bipartite shift of host translational machinery to translate viral RNA only, NSP4 plays a role in the replicase complex assembly, and NSP18 is critical for replication (Yan et al., 2022).

Structural protein targets

Envelope protein

The E protein is a transmembrane cation-selective viroporin with Ca^{2+} and/or K^{+} selectivity (Hong et al., 2020; Mandala et al., 2020). Similar to previous reports with SARS/MERS, SARS-CoV-2, the E protein also forms an inflammasome by TLR2 or NRLP5 activation through NF-kB due to K^{+} influx (Yalcinkaya et al., 2021; M. Zheng et al., 2021). β-boswellic acid and glycyrrhizic

acid natural product combinations have been shown to shorten the recovery time (Gomaa et al., 2022), and in a suggestion of a possible mechanism, they have shown positive binding with the E protein *in vitro* (Fatima et al., 2022). There are a few phytochemicals i.e. proanthocyanidins (PAC), wortmannin, and veliparib reported to block E protein *in vitro* (Y. Wang et al., 2022).

Spike glycoprotein

Spike protein, (S1, S2, S3) is the largest protein coded by the SARS-CoV-2 genome. It has various domains including transmembrane, S1 & S2 domains. S1 binds to different receptors (ACE2, CD147, B0AT1, and NRP1) and interacts with heparan sulfate and the S2 domain is a viral fusion domain. S1 domain has open and closed states to maintain the receptor-binding domain (RBD) specificity (Gupta et al., 2021c; Jackson et al., 2022). The fusion inhibitors are discussed in detail in later RBD-ACE-2 interaction inhibition. S2 activation requires cleavage of spike protein mediated by furin and TMPRSS2 (Y. Gupta et al., 2022). Itraconazole and Estradiol Benzoate were found to be interacting with the S2 domain of spike protein and had *in vitro* activities of IC50 0.45 (μM) and 1.02 (μM) respectively (Yang et al., 2021). Itraconazole synergistically improved the remdesivir efficacy *in vitro* (Schloer et al., 2021). Pan-CoV fusion inhibitor EK1 (fusion domain S2) is efficacious against all variants suggesting high target conservancy despite the high degree of amino acid mutations in SARS-CoV-2 variants (Lan et al., 2021). Further, a designer peptide mimicking the HR2 sub-domain of the S2 fusion domain (VVNIQKEIDRLNEVAKNLNESLID) was designed *in silico* and validated both by MD simulations and *in vitro* testing (Kandeel et al., 2021; Manna et al., 2020).

Table 2. Descriptions of anti-viral agents from clinical trials

	Name of the agent	The total no of patients and trials	No of days of treatment	Outcome (Negative SARS-CoV-2 test conversions (NSTC))	Contraindications	Reference(s)
1	**Remdesivir**	13 studies >100000 patients	Dosing was usually 200 mg on day 1 followed by 100 mg for 5 days or up to 10 days	Found significant greater improvement in mortality, hospitalization, symptoms, and ICU dependency incidence of mechanical ventilation, in patients with no oxygen or low oxygen (efficacy 74% - 87%) however, did		(Angamo et al., 2022; Barratt-Due et al., 2021; Beckerman et al., 2022; Beigel et al., 2020; Costanzo et al., 2020)

				not lower any kind of risk in patients receiving high-flow oxygen		
2	**Lopinavir/Ritonavir**	38 studies 12352 patients	Dosing was usually Lopinavir/ritonavir 400mg/100mg BID for 5-10days. Along with standard-of-care	Found no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC (MD: 1.09)		(Bahman Amani et al., 2021; Costanzo et al., 2020; Kalantari et al., 2021; Mazaherpour et al., 2021)
3	**Oseltamivir**	5 studies >100000 patients	Dosing was usually 30mg,45mg,75mg, and BID for 5 days. Along with standard-of-care	Found no reductions in mortality, hospitalization, symptoms and ICU dependency	increased severity of disease and risk of mortality OR= 4.20,	(Zendehdel et al., 2022)

				incidence of mechanical ventilation, and NSTC (SMD of 1.65 days)		
4	**Umifenovir(arbidol)**	16 studies and 1 phase 3 trails	Dosing was usually Umifenovir 800 mg BID, maximum 14 days, along with standard-of-care	Found no reductions in mortality, hospitalization, symptoms, and ICU dependency incidence of mechanical ventilation, and NSTC RR=1.1	associated with higher adverse events RR: 2.24	(Behnam Amani et al., 2021; Y. Lin et al., 2021; Ramachandran et al., 2022)
5	**Sofosbuvir-based** (Daclatasvir, ledipasvir, velpatasvir, ravidasvir)	8 articles and 11 trials and 4 studies 3079 patients	Dosing was usually 400 mg Sofosbuvir and 60 mg Daclatasvir	Found lower mortality OR= 0.49 to 0.59 RR=0.31, ICU dependency		(Chan et al., 2021; Hsu et al., 2022; Kow et al., 2022; Merat, 2020; Messina et al., 2022; A.

				incidence of mechanical ventilation (RR=1.20, P=0.011), and some certainty of the evidence for clinical recovery with combination with Sofosbuvir/ Daclatasvir.		F. M. Z. Zein et al., 2022)
6	**Molnupiravir**	1 Phase 3 trial 1433 patients	Dosing was usually 800 mg orally BID daily for 5 days only	initiated within 5 days after the onset of symptoms found reductions in mortality, hospitalizatio n, symptoms and ICU dependency incidence of	there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations	(Caraco et al., 2022; Jayk Bernal et al., 2022; Wong et al., 2022)

				mechanical ventilation, and NSTC		
7	**Nirmatrelvir** based	1 Phase 2-3 trial 2246 patients	Dosing was usually 300 mg of nirmatrelvir plus 100 mg of ritonavir BID for 5 days	Found reductions in progression to severe RR reduction 88.9%, along with reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and viral load was lower at day 5 of treatment		(Hammond et al., 2022; Lamb, 2022; Reina and Iglesias, 2022; Wong et al., 2022)

8	**GIAPREZA** **(Angiotensin II receptor blocker)**	1 study 132 patients	Dosing was usually One-time inclusion	Found faster decrease in Fio2 and positive effect on BP in the first 12H of infusion and later no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		(Serpa Neto et al., 2022)
9	**Losartan** **(Angiotensin II receptor blocker)**	2 studies 1683 patients	Dosing was usually Max 50 mg orally twice daily for 10 days	Found losartan has a protective role against COVID-19 mortality in hypertensive patients only. No reductions in mortality, hospitalization, symptoms and		(Puskarich et al., 2022)

				ICU dependency incidence of mechanical ventilation, and NSTC in non-hypertensive patients		
0	**Famotidine** **(Selective histamine H2-receptor (H2R) antagonist)**	9 studies 39745 patients	Dosing was usually 20 or 40 mg oral or IV median of 5 to 6 days	Found no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		(Freedberg et al., 2020)
1	**Plitidepsin**	1 phase 1 trial 46 patients	Dosing was usually 1.5 mg (n = 15), 2.0 mg (n = 16), or 2.5 mg (n = 15) OD for 3 days.	Found reductions in viral load concerning their baseline value, and improvement of biomarkers		(Varona et al., 2022)

				associated with inflammatory processes. There were reports of prompt clearance of pneumonia infiltrates in some participants with available chest imaging performed for medical reasons		
2	**Heparin (Standard heparin, and low molecular weight heparin)**	3 Trials, 33 studies 25768 patients	No fixed does was used	Found significant reduction in mortality, invasive mechanical ventilation, and any thrombotic event in moderately ill patients and found no reductions in mortality,		(Giossi et al., 2021; Thachil, 2020)

				hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		

Homo sapiens (Host) COVID-19 therapeutic targets

In addition to targeting SARS-CoV-2 proteins, another therapeutic approach is to target host proteins that enable viral infection, replication, and spread (Figure 2). The interventions range from interfering with the host receptors for SARS-CoV-2 (e.g. ACE2), to blocking the proteolytic processing needed for viral particle internalization (e.g. Cathepsin L),

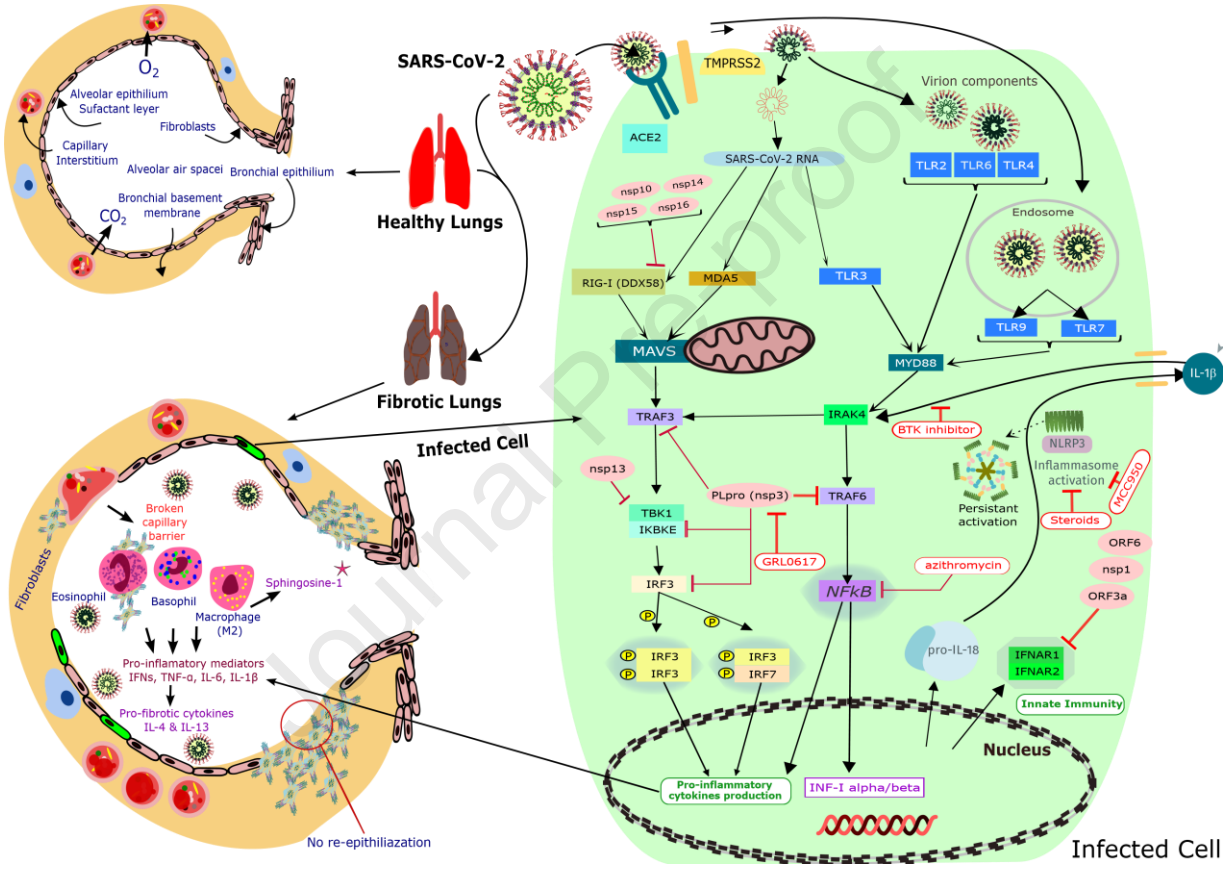


Figure 2. Host proteome targets involved in COVID-19 hyperimmune and their inhibitors. *Cartoon representation of molecular components involved in hyperimmune reaction leading to the severe clinical presentation (ARDS) among COVID-19 patients. The lung fibrosis observed in COVID-19 patients and resulting hypoxia is the main reason for mortality in severe cases along with immunosuppressed conditions and concomitant infections. Classic pathways are hijacked in COVID-19-associated lung fibrosis by various proteins coded by SARS-CoV-2.In COVID-19 patients due to inflammation mediators such as IL-6 and cytokine storm or increased release from damaged/dying cells, there is a loss of lung surface area to fibrosis. There is an aggravation of the infection cycle due to hypoxia-induced ACE2, TMPRSS2 overexpression, and furin cell surface localization. Multiple immune*

suppressants and modulators have been effective in reducing the severity and mortality as seen in large trials. However, the mechanism for which is still not well established. There are many other agents known to modulate many members of this cascade, especially the NLRP3 pathway responsible for characteristic COVID-19 storm but not yet exploited due to a rather recent elucidation.

Viral receptors targets of human host

Table 3. Drugs targeting different viral/host proteins with *in vitro* validations

Name & discovered target	**Type**		**Indication**	**Mechanism of Action (General)**	**IC_{50}**	**Refs**
Haloperidol ***Peptides***	Conventional antipsychotic agent: Haloperidol works by inhibiting the SARS-CoV-2.	Psychotic patients	It is administered in the treatment of mental disorders such as schizophrenia.	It works by inducing a high potency suppression of undesired mental reactions in schizophrenia patients.	6.5µM	(Daniel et al., 2015; Pandey et al., 2020)
PD-144418 ***Peptides***	Sigma 1 agent works by exerting antiviral effects on SARS-CoV-2 protein.	Psychotic activities of patients	It is the highest selective sigma receptor ligand.	It works through selecting the stimuli that are insignificant	0.08 Mm	(Vela, 2020)

				to ion channels or enzyme actions in patients.		
Clemastine ***Peptides***	Antihistamine agent Works by blocking interactions between SARS-CoV-2 nonstructural protein NSP6 and host sigma-1 receptor.	Rhinitis, allergic skin, or pruritus patients.	It is a significant histamine H1 remedy for treating rhinitis, skin allergy, and pruritus.	It works by inducing sedative and anticholinergic reactions in patients.	8.32μM	(Reznikov et al., 2021)
Cloperastine ***Peptides***	Antitussive agent Works by blocking interactions between SARS-CoV-2 nonstructural protein NSP6 and host sigma-1 receptor	Bronchus infections	It cures coughs associated with bronchus infection.	It acts through an antihistaminic activity that causes mild broncho relaxant. effect on patients	0.08μM	(Reznikov et al., 2021; Vela, 2020)
Progesterone	Steroid hormone Works by inhibiting the SARS-CoV-2	Ovaries and adrenal cortices.	It is produced by the corpus	It works by regulating	173-196μM.	(Shah, 2021;

Peptides	priming protease TMPRSS2.		luteum in the second half of the menstrual cycle.	the inner lining of the uterus.		Vela, 2020)
Aprotinin ***Spike processing enzymatic - Serine protease 10***	It is a fibrinolytic agent that Works by controlling SARS-CoV-2 replication	It occurs in the bovine lung	It is a naturally occurring inhibitor which is a polypeptide of 58 amino acids.	It functions by inhibiting the action of certain serine proteases such as trypsin, plasmin, and chymotrypsin.	20µM	(Bojkova et al., 2020; da Silva et al., 2022)
MI-1900 ***Spike processing enzymatic - Serine protease 10***	It is an antithrombin agent that works by reducing 25-fold virus titer in SARS-CoV-2 Calu-3 infected cells.	Myocardial patients	It is applied to restore coronary patency in myocardial patients	This drug acts by reducing the size of the infarct on patients' heart structure.	10µM	(Lin et al., 2022; Russo et al., 2021)
MI-432	It is an antiviral agent	Used by patients	It reduces the rate of	It is applied as a	1.30 ± 0.14 µM	(Lin et al.,

Spike processing enzymatic - Serine protease 10	Works by inhibiting the protease TMPRSS2.	suffering from herpes simplex virus	virus growth and development and therefore suppresses any potential survival of the virus.	cream on herpes simplex patients to relieve pain and irritations that cause sores.		2022)
Nafamostat ***Spike processing enzymatic - Serine protease 10***	Synthetic serine protease Works by blocking SARS-CoV-2 infection of Calu-3 cells.	Patients with inflammatory reactions.	It acts alongside anticoagulant and anti-inflammatory effects.	It performs by inhibiting the activities of proteases such as plasmin, kallikrein, and trypsin.	0.010 μM	(Yamamoto et al., 2020)
E-64d ***Spike processing enzymatic - Serine protease 10***	Prodrug ethyl ester Works by inhibiting coronaviral entry in certain cell types.	Patients with inflammatory reactions.	It is only active in its acidic form (E64c).	It hydrolyzed from E64d to E64c in the gut to inhibit cysteine proteases.		(Mellott et al., 2021)

PCI-27483 ***Spike processing enzymatic - Serine protease 10***	Selective inhibitor Works by inhibiting TMPRSS2 in biochemical and cell infection assays.	It is administered on TF-expressive cancer patients	It inhibits tumor invasiveness in cancer patients	It performs by inhibiting cell migration and angiogenesis reactions that cause tumor invasiveness.	1.41 ± 0.04μM	(Sun et al., 2021, p. 2)
Otamixaban ***Spike processing enzymatic - Serine protease 10***	FXa agent Works by suppressing TMPRSS2 activity and SARS-CoV-2 infection.	Patients with acute coronary diseases	This is an activated factor X (FXa) inhibitor involved applied in acute coronary syndrome patients	It acts through a high selection of FXa compounds to inhibit the generation of thrombin.		(Hempel et al., 2021)
MI-1851	Novel furin inhibitor agent Works by	SARS-Cov-2 patients	It prevents proteolytic processing of	It acts by inhibiting the conversion	10μM	(Devi et al., 2022)

Spike processing enzymatic - Furin	inhibiting furin to prevent the spread of SARS-CoV-2		S-protein	of furin in HEK293 cells to S protein.		
Terifumide ***Spike processing enzymatic - Cathepsin***	Malononitilamide agent Works by inhibiting SARS-CoV-2 replication.	Beta-1a patients	It inhibits the proliferation of both T and B cells.	It acts by blocking the mitochondrial enzyme hydro-orotate dehydrogenase	67μM	(Rabie, 2021)
Leflunomide ***Spike processing enzymatic - Cathepsin***	Immunomodulatory agent Works by inhibiting SARS-CoV-2 replication.	Rheumatoid arthritis.	It decreases inflammation and slows the rate of arthritis inflammation.	It performs by inhibiting the action of pyrimidines in synthesis.	200μM	(Rabie, 2021)
Favipiravir ***Spike processing enzymatic - Cathepsin***	Therapeutic agent Works by inhibiting SARS-CoV-2 infections.	Influenza patients	It is used to cure influenza.	It works as a chain terminator during the incorporation of viral	200μM	(Costanzo et al., 2020)

				RNA and hence reducing the viral load.		
Amantadine ***Spike processing enzymatic - Cathepsin***	Antiviral agent Works by inhibiting SARS-CoV-2 replication.	Influenza patients	It is used to treat patients with advanced influenza symptoms.	It works by reducing dopamine release and blocking dopamine reuptake.	83-119μM.	(Fink et al., 2021; Rejdak and Grieb, 2020)
Sulfated polysaccharides Homo Sapien Targets	Sulfate agent Works by binding to the viral spike glycoprotein, preventing virus entry into the host cell	adipocytes	Induces the extraction of algae type called sargassum Hymenophyllum	It acts by reducing inflammatory reactions.	512~289μM	(Yim et al., 2021)
Teicoplanin Structural protein targets	Bacteriostatic agent Works by preventing entry of SARS-CoV-2 into the cellular cytoplasm.	Bacterial infection	It inhibits the synthesis of bacterial peptidoglycan	It acts by binding to the d-alanyl-d-alanine moiety.	2.038 μM	(F. Yu et al., 2022)

Nelfinavir Structural protein targets	Anticancer agent Works by inhibiting SARS-CoV-2 replication	Cancer patients	It induces stress in the endoplasmic.	It acts through HIV protease inhibition.	3.3µM	(Foo et al., 2021)
Cepharanthine Structural protein targets	Antiviral agent Works by inhibiting SARS-CoV-2 entry into the host cell.	Covid-19 patients	It is used to derail the entry of the COVID-19 virus into a host	It acts by blocking target cells of viral binding.	2.8µM	(Hijikata et al., 2022)
Trimipramine Structural protein targets	Antiviral agent Works to inhibit SARS-CoV-2 by targeting viral proteins.	Influenza patients	It is used to treat patients with advanced influenza symptoms.	It works by reducing dopamine release and blocking dopamine reuptake.	1.5µM	(Xiang et al., 2022)
Osimertinib Structural protein targets	Selective inhibitor Works by preventing SARS-CoV-2 entry into host cells.	It is administered to patients	It inhibits tumor invasiveness in cancer patients	It performs by inhibiting cell migration and angiogenesi	3.98µM	(Xiang et al., 2022)

				s reactions that cause tumor invasiveness .		
Abemaciclib\ Structural protein targets	Sensitizing agent Works by preventing SARS-CoV-2 entry into host cells.	Cancer patients	It inhibits the conversions of 2-anilino-2, 4-pyrimidine from palbociclib	The drug blocks the spread of cancer infections by inhibiting the replication of associated cells.	3.16µM	(Xiang et al., 2022)
Ingenol Structural protein targets	Mebutate agent Works by preventing SARS-CoV-2 entry into host cells.	Keratosis patients	It cures skin conditions.	It is applied to the skin to kill cells causing scaly skin patches.	0.06µM	(Xiang et al., 2022)
Imatinib Structural protein targets	Fusion agent Works by preventing SARS-	Leukemia patient	It is an inhibitor of the fusion process	It functions by inhibiting protein	5.32µM	(Xiang et al., 2022)

	CoV-2 entry into host cells.			fusion of Bcr-Abl		
Itraconazole Structural protein targets	Antiviral agent Works by preventing SARS-CoV-2 S protein-mediated intercellular fusion	Covid-19 patients	It is used to derail the entry of the COVID-19 virus into a host	It acts by blocking target cells of viral binding.	0.45 µM	(Yang et al., 2021)
Estradiol benzoate Structural protein targets	Ester agent Works by preventing SARS-CoV-2 protein-mediated intercellular fusion.	Adult human	It is a steroid sex hormone	It acts by maintaining fertility and secondary behaviors.	1.02 µM	(Yang et al., 2021)
Fluoxetine Structural protein targets	Serotonin agent Works by inhibiting cytokine release to prevent SARS-CoV-2 in human lung tissue.	Mentally disorder patients	It is used to treat depression	It acts by preventing serotonin reuptake.	0.8 µM	(Zimniak et al., 2021)
Citalopram	Serotonin agent	Mentally disorder	It helps to maintain	Its acts by	27.51 µM	(Fred et al.,

Structural protein targets	Work by reducing viral infection by SARS-CoV-2.	patients	mental balance.	increasing the amount of serotonin.		2022)
Reboxetine Structural protein targets	Antidepressant agent Work by reducing viral infection by SARS-CoV-2.	Mentally disorder patients	It reduces panic disorder and attention deficit hyperactivity.	It acts by reducing norepinephrine reuptake inhibitor	17.69 µM	(Fred et al., 2022)
Chlorpromazine Structural protein targets	Antitussive agent Work by reducing viral infection by SARS-CoV-2.	Bronchus infections	It cures coughs associated with a bronchial infection.	It works by reducing dopamine release and blocking dopamine reuptake.	0.972 µM	(Fred et al., 2022)
Flupenthixol Structural protein targets	Antiviral agent Work by reducing viral infection by SARS-CoV-2.	Covid-19 patients	It is used to treat patients with advanced influenza symptoms.	It works by reducing dopamine release and blocking dopamine reuptake.	1.072 µM	(Fred et al., 2022)
Pimozide	Oral	Butyroph	It induces	It acts	4.539	(Fred

Structural protein targets	diphenylbutylpiperidine antipsychotic agent Work by reducing viral infection by SARS-CoV-2.	enones patients	stress in the endoplasmic.	through HIV protease inhibition	µM	et al., 2022)
Mitoxantrone hydrochloride ***non-enzymatic targets***	Bacteriostatic agent Works by inhibiting ROS1 fusion protein and its downstream signaling minimizing cell apoptosis.	Bacterial infection	It inhibits the synthesis of bacterial peptidoglycan	It acts by binding to the d-alanyl-d-alanine moiety.	2.99 ± .608µM	
Capreomycin ***non-enzymatic targets***	Selective inhibitor Works by inhibiting SARS-CoV2 protease.	It is administered to patients	It inhibits tumor invasiveness in cancer patients	It performs through inhibiting cell migration and angiogenesis reactions that cause	1 µM	(Kumar et al., 2021)

				tumor invasiveness		
Pentamidine ***non-enzymatic targets***	Anti-infective agent Works by blocking the SARS-CoV-2 3a-channel.	Pneumonia patients	It treats pneumonia caused by organisms.	It acts by blocking the spread of cold in the host body.	7.5 µM.	(Andreana et al., 2022)
Spectinomycin ***non-enzymatic targets***	Ester agent Works by blocking the SARS-CoV-2 3a-channel.	Adult human	It is a steroid sex hormone	It acts by maintaining fertility and secondary behaviors.	50 µM.	(Tomar et al., 2021, 2021)
Kasugamycin ***non-enzymatic targets***	Serotonin agent Works by blocking the SARS-CoV-2 3a-channel.	Mentally disorder patients	It is used to treat depression	It acts by preventing serotonin reuptake.	50 µM.	(Tomar et al., 2021, 2021)
Plerixafor ***non-enzymatic targets***	Mebutate agent Works by blocking the SARS-CoV-2 3a-channel.	Keratosis patients	It cures skin conditions.	It is applied to the skin to kill cells causing scaly skin	50 µM.	(Tomar et al., 2021, 2021)

				patches.		
Flumatinib ***non-enzymatic targets***	Antiviral agent Works by blocking the SARS-CoV-2 3a-channel.	Covid-19 patients	It is used to derail the entry of the COVID-19 virus into a host	It acts by blocking target cells of viral binding	50 µM.	(Tomar et al., 2021, 2021)
Darapladib ***non-enzymatic targets***	Fusion agent Works by blocking the SARS-CoV-2 3a-channel.	Leukemia patient	It is an inhibitor of the fusion process	It functions by inhibiting protein fusion of Bcr-Abl	50 µM.	(Tomar et al., 2021, 2021)
Floxuridine ***non-enzymatic targets***	Therapeutic agent Works by blocking the SARS-CoV-2 3a-channel.	Influenza patients	It is used to cure influenza.	It works as a chain terminator during the incorporation of viral RNA and hence reducing the viral load.	50 µM.	(Tomar et al., 2021, 2021)
Fludarabine	Antidepressant agent	Mentally disorder	It reduces panic disorder	It acts by reducing	50 µM.	(Tomar et al.,

non-enzymatic targets	Works by blocking the SARS-CoV-2 3a-channel.	patients	and attention deficit hyperactivity	norepinephrine reuptake inhibitor		2021, 2021)
Ciclesonide **RNA-dependent RNA polymerase**	Antitussive agent Works by suppressing the replication of SARS-CoV-2 in cultured cells.	Bronchus infections	It cures coughs associated with a bronchial infection.	It performs through inhibiting cell migration and angiogenesis reactions that cause tumor invasiveness	5.1 µM.	(Matsuyama et al., 2020)
Exebryl-1 **RNA-dependent RNA polymerase**	Mebutate agent Work by promoting SARS-CoV-2 antiviral activity in Vero 76, Caco-2, and Calu-3 cells.	Keratosis patients	It cures skin conditions	It is applied to the skin to kill cells causing scaly skin patches.	10 to 66µM.	(Choi et al., 2021)
Sofosbuvir	Selective inhibitor	It is administered	It inhibits tumor	It performs	6.2 - 9.5 µM	(Shabani et

RNA-dependent RNA polymerase	Works by inhibiting SARS-CoV-2 replication in brain and lung cells.	to patients	invasiveness in cancer patients	through inhibiting cell migration and angiogenesis reactions that cause tumor invasiveness	(EC_{50})	al., 2021)
Alovudine **RNA-dependent RNA polymerase**	Anticancer agent Works by terminating RNA synthesis of SARS-CoV-2 virus.	Cancer patients	It inhibits the conversions of 2-anilino-2, 4-pyrimidine from palbociclib	It performs by inhibiting the activities of proteases such as plasmin, kallikrein, and trypsin.	100 µM	(Kumar et al., 2021)
Tenofovir alafenamide **RNA-dependent RNA polymerase**	FXa agent Works by blocking the SARS-CoV-2 polymerase extension.	Patients with acute coronary diseases	This is an activated factor X (FXa) inhibitor involved applied in acute	It acts through a high selection of FXa compounds to inhibit the		(Kocabaş and Uslu, 2021; Zanella et al.,

			coronary syndrome patients	generation of thrombin.		2021)
Zidovudine **RNA-dependent RNA polymerase**	Prodrug ethyl ester Can work by inhibiting SARS-CoV-2 replication and transcription.	Patients with inflammatory reactions.	It is only active in its acidic form (E64c).	It hydrolyzed from E64d to E64c in the gut to inhibit cysteine proteases		(Matsuyama et al., 2020)
Suramin **RNA-dependent RNA polymerase**	Malononitilamide agent Works by inhibiting SARS-CoV-2 replication.	Rheumatoid arthritis.	It decreases inflammation and slows the rate of arthritis inflammation.	It acts by blocking target cells of viral binding.	20μM (EC_{50})	(Mostafa, 2020)
Atorvastatin **RNA-dependent RNA polymerase**	Anti-infective agent Works by inhibiting SARS-CoV-2 replication.	Pneumonia patients	It treats pneumonia caused by organisms.	It performs through inhibiting cell migration and angiogenesis reactions	3.9-15.7 μM	(Zapata-Cardona et al., 2021)

				that cause tumor invasiveness		
Flupenthixol **RNA-dependent RNA polymerase**	Novel furin inhibitor agent Works by preventing SARS-CoV-2 spike protein pseudovirus cell entry in the host cell.	It is administered to patients	It inhibits the synthesis of bacterial peptidoglycan	It acts by inhibiting the conversion of furin.	0.56µM	(Devi et al., 2022)
Raloxifene **RNA-dependent RNA polymerase**	Mebutate agent Works by modulating SARS-CoV-2 replication.	Keratosis patients	It cures skin conditions	It is applied to the skin to kill cells causing scaly skin patches.	40 µM to 0.31 µM	(Nicastri et al., 2022)
Disulfiram **Papain-like proteinases**	Selective inhibitor Works by inhibiting SARS-CoV-2 papain-like proteases	It is administered to patients	It inhibits tumor invasiveness in cancer patients	It works by reducing dopamine release and blocking dopamine reuptake.	9.35 µM	(Fillmore et al., 2021)

GRL0617 **Papain-like proteinases**	Serotonin agent Works by inhibiting SARS-CoV-2 PL^{pro}.	Mentally disorder patients	It is used to treat depression	It acts by preventing serotonin reuptake.	2.1 µM	(Fu et al., 2021, p. 202)
Maprotiline **Papain-like proteinases**	Antitussive agent Works by preventing SARS-CoV-2 infection on Vero cells.	Bronchus infections	It cures coughs associated with a bronchial infection.	It acts by reducing norepinephrine reuptake inhibitor	5µM to 35µM	(Carpinteiro et al., 2020)
Reserpine **Papain-like proteinases**	Anti-infective agent Works by inhibiting SARS-CoV-2 activities.	Pneumonia patients	It is used to cure influenza.	It works as a chain terminator during the incorporation of viral RNA and hence reducing the viral load.	3.4 to 6.0µM.	(Xian et al., 2020)
Levothyroxine	Therapeutic agent Works by	Influenza patients	It is used to cure influenza.	It works by reducing dopamine release and	5.0±1.9 to 11±3µM	(Brewitz et al., 2022)

Papain-like proteinases	inhibiting SARS-CoV-2 PL^{pro}			blocking dopamine reuptake.		
Proanthocyanidin **Papain-like proteinases**	Antiviral agent Works by inhibiting SARS-CoV-2.	Covid-19 patients	It is used to derail the entry of COVID-19 virus into a host.	It acts by blocking target cells of viral binding.		(Sugamoto et al., 2022)
Sepantronium bromide **Papain-like proteinases**	Novel furin inhibitor agent	It is administered to patients	It inhibits the synthesis of bacterial peptidoglycan	It acts by inhibiting the conversion of furin.		(Devi et al., 2022)
Cryptotanshinone **Papain-like proteinases**	Bacteriostatic agent Works by inhibiting SARS-CoV-2 protease	Bacterial infection	It inhibits the synthesis of bacterial peptidoglycan	It acts by blocking target cells of viral binding.	13.6µM	(Zhao et al., 2021)
Tanshinone I	Anti-infective agent	Bronchus infections	It cures coughs associated	It is applied to the skin to	0.7µM	(Elebeedy et

Papain-like proteinases	Works by inhibiting viral protease, SARS-CoV-2 3CLpro, and PLpro		with a bronchial infection.	kill cells causing scaly skin patches.		al., 2021)
Ranitidine Bismuth citrate **Helicase**	Oral diphenylbutylpiperidine antipsychotic agent Works by suppressing SARS-CoV-2 replication.	Butyrophenones patients	It induces stress in the endoplasmic	It acts through HIV protease inhibition	0.69μM	(Shu et al., 2020)

Host receptors

ACE2 is the most abundant and highest affinity receptor of SARS-CoV-2 spike protein and is the first step in viral entry into the host cell. There are multiple reports that ACE2 polymorphisms and Spike protein modulate viral infectivity (Suryamohan et al., 2021). Various known ACE2 inhibitors, as well as expression modulators, have been proposed to be viable anti-COVID-19 therapeutics. There is another novel approach of molecular mimicry where B38-CAP an ACE2 homolog carboxypeptidase of bacterial origin protected patients from lung injury without apparent viral neutralization, but through a mechanism of RAS inactivation and decreased Acute Respiratory Distress Syndrome (ARDS) (Yamaguchi et al., 2021). This is coherent with the previous reports of lung damage protection with recombinant soluble ACE2 in animal models

(Imai et al., 2005, p. 20). Also, soluble recombinant human ACE2 has a high SARS-CoV-2 neutralizing potential as shown *in vitro* (Monteil et al., 2020). Giapreza, the angiotensin II substrate of ACE2, had variable outcomes from different studies. The conclusive multicentric trial concluded a decrease in blood pressure and improved fraction of inspired oxygen (FiO2) levels but there was no apparent benefit in terms of mortality among severe ARDS patients. ACE2 agonists have also shown a decrease in Spike-ACE2 interaction as their binding site is closer to the interface compare to antagonists e.g. Losartan/Valsartan that bind in the catalytic core and have no positive effect as reported in multiple trials (Geriak et al., 2021; Puskarich et al., 2022, 2021). A small randomized trial with 51 patients receiving C21 and an ACE2 agonist showed a significant reduction in the requirement of mechanical ventilation (Tornling et al., 2021). Methylene Blue is a nonspecific ACE2-Spike interaction inhibitor and has been used to inactivate residual viruses in convalescent plasma (Alemany et al., 2022). Ceftazidime is an injectable broad-spectrum beta-lactam antibiotic that is a third-generation cephalosporin. Ceftazidime was found to effectively block ACE-2 spike interactions *in vitro* (C. Lin et al., 2021). It was trialed on 136 patients in a study and showed a significant reduction in recovery (PCR negativity) (Eid et al., 2021). On the contrary, Ramipril is highly contraindicated in COVID-19 patients as it is known to highly up-regulate ACE2 and increase SARS-CoV-2 virion loads (Theodorakopoulou et al., 2022).

Neuropilin-1 (NRP1) is another host surface receptor mediating SARS-CoV-2 entry (Cantuti-Castelvetri et al., 2020; Kyrou et al., 2021) and has been associated with neurological morbidities seen in COVID-19 (Davies et al., 2020). Apart from protein receptor binding spike protein also interacts with cell surface heparan sulfate and is the basis for antiviral activity of heparin (Gupta et al., 2021c) and sulfated polysaccharides (Kwon et al., 2020) abundant in many natural products. There is a high interest in using sulfated polysaccharides as anti-COVID-19 also due to the

reduction in coagulopathy seen in COVID-19 patients (B. Tu et al., 2022). There is still a possibility of SARS-CoV-2 variants evolving or already evolved to use different receptors like other coronaviruses (Nassar et al., 2021).

Spike processing enzymatic targets

Cathepsin L

Cathepsin L (CTSL) is a transmembrane peptidase/serine subfamily member 2/4 and plays an important role in spike activation in endosomes. The widespread now-dominant mutation in the SARS-CoV-2 Spike glycoprotein D614G is predicted to confer a site loss for CTSL (Gobeil et al., 2020; Y. Gupta et al., 2022). Amantadine acts as a lysosomotropic agent by disturbing Cathepsin L's functional environment(Smieszek et al., 2020). A few reports are showing decreased leukopathy (Lam et al., 2022) and the slowdown of neurodegeneration presentations of COVID-19 by amantadine (Rejdak and Grieb, 2020).

Furin

Furin is a Ca^{2+}-dependent endopeptidase that processes many secretory proteins as well as protein digestion (Than et al., 2005). During hypoxia, furin can translocate to the cell surface and is thought to be responsible for the rapid worsening of hypoxia patients in COVID-19 by increased spike processing at the cell surface resulting in direct fusion (Arsenault et al., 2012; Y. Gupta et al., 2022). Both Furin is essential for SARS-CoV-2 invasion (Bestle et al., 2020) and known furin inhibitors MI-1851 and E-64d have both shown *in vitro* efficacy against SARS-CoV-2 (Table 3)

TMPRSS2

Transmembrane serine protease 2 (TMPRSS2) is a cell surface activator of spike protein essential to exposing and activating the viral fusion domain (Bestle et al., 2020; Hoffmann et al.,

2020). Nafamostat (CKD-314/Nafabelltan) a TMPRSS2 inhibitor was found to instigate a significantly higher recovery rate among treated patients and was well tolerated (Zhuravel et al., 2021). Another TMPRSS2 inhibitor Camostat mesylate (FOY-305) in contrast didn't show any positive effect in a phase III trial (Kinoshita et al., 2022). One speculation for inconclusive outcome with Camostat is the drug might need a better dosage formulation for effective treatment (Kosinsky et al., 2022). There are additional inhibitors of TMPRSS2 with promising results *in vitro* e.g. Aprotinin, MI-1900, MI-432, E-64d, PCI-27483, and Otamixaban.

Targets associated with host immune response

The TLR 2/6/9 agonist PUL-042 is a phase III investigational compound that can induce epithelial resistance to SARS-CoV-2 in animal models (Evans et al., 2020). Famotidine is a selective histamine H2-receptor (H2R) antagonist (Malone et al., 2021) that also inhibits 3CLpro of SARS-CoV-2 (Loffredo et al., 2021). Famotidine had a positive effect with a reduced risk of clinical deterioration leading to intubation or death when tested in a small retrospective cohort (Freedberg et al., 2020). Currently, famotidine is part of multiple combinations in various trials. There are hypothetical reports of targeting different immune components such as Basigin CD_antigen: CD147, 5F7, Collagenase stimulatory factor, Leukocyte activation antigen M6, Extracellular matrix metalloproteinase inducer, Tumor cell-derived collagenase stimulatory factor, GCSF-Receptor Signaling Complex CSF3, IL-1β, leukocytic pyrogen, leukocytic endogenous mediator, and mononuclear cell factor, yet discussing all of these is beyond the scope of the current review. Major confounding comorbidity arising in a portion of the SARS-CoV-2 infected populations is the activation of a cytokine storm leading to the development of ARDS. To block the cytokine storm from activating in COVID-19 patients, various antibody cocktails blocking these factors have been used in ongoing trials (Elahi et al., 2022; Harrison, 2020; Harrison

et al., 2021). Many recombinant proteins e.g. Recombinant TNF (INB03) and Recombinant human interferon α1β (Novaferon) have also been tried (Drożdżal et al., 2021). Other targets include Peginterferon Lambda-1a, and Chemokine Receptor Type 2 (CCR2) (Hu et al., 2021). The Interleukin-1 receptor-associated Kinase 4 (IRAK4) Inhibitor PF-06650833 is predicted to restore immunological balance (Gupta and Chun, 2021) and is under trial (Franchin, 2021). Sigma-1 receptor (sigma non-opioid intracellular receptor 1) is an important factor associated with the mortality of COVID-19 patients (Lehrer and Rheinstein, 2021) several inhibitors have been predicted to be anti-COVID-19 e.g. Haloperidol, PD-144418, clemastine, Cloperastine, and progesterone. Naringenin, targeting the endo-lysosomal Two-Pore Channels (TPCs) has been shown as having anti-SARS-CoV-2 activity (Clementi et al., 2021)

Mechanistic targets

Dihydroorotate dehydrogenase

Dihydroorotate dehydrogenase (mitochondrial DHODH), is a Dihydroorotate oxidase involved in pyrimidine synthesis within cells. DHODH inhibition has been shown to decrease viral replication/turnover rates (Kaur et al., 2021) as well as increase the incorporation of nucleoside analog antivirals such as N4-hydroxycytidine (NHC) which is an activated metabolite of Molnupiravir (Stegmann et al., 2021). Brequinar (DUP 785, NSC 368390) in combination with nucleoside analog Dipyridamole has shown high *in vitro* efficacy (Demarest et al., 2022; Xiong et al., 2020) and is in Phase II trials. There are many more DHODH inhibitors showing high anti-SARS-CoV-2 activities e.g. PTC299 (Luban et al., 2021), Teriflunomide (Maghzi et al., 2020), and Leflunomide (Hu et al., 2020). Leflunomide also showed faster PCR negativity in COVID-19 patients in a small trial (Hu et al., 2020).

Cathepsin B

Cathepsin B (APP secretase/Cathepsin B1) is an important enzyme overexpressed in hyperimmune inflammatory disorders and hence can be a target for ARDS mitigation (Ding et al., 2022).

Caspase

COVID-19 inflammasome causes cell death through caspase pathways, specifically caspase 8 (Li et al., 2020). Belnacasan and Emricasan are Caspase inhibitors that showed inhibition of inflammasome *in vitro* (Jeong et al., 2022).

Calpain

Calpain inhibitor BLD-2660 is an anti-fibrotic and part of many ongoing trials shown to mitigate lung fibrosis in combinations with antivirals (Djordje et al., 2021).

Ferroportin

Multiple reports point to SARS-CoV-2 mediated lung injury being mediated by ferroptosis with a portion of spike protein mimicking hepcidin hormone (Y. Gupta et al., 2022). Vitamin D is known to induce ferroportin overexpression which effluxes out the excess iron thereby preventing ferroptosis to reduce lung injury (Moran-Lev et al., 2018). Low levels of vitamin D were associated with higher COVID-19 mortality and it has been part of various combinations as an inexpensive therapeutic supplement for COVID-19 patients (Z. Wang et al., 2022).

Eukaryotic Elongation Factor 1A2 (eEF1A2)

Nitazoxanide is a thiazolide chemical compound that induces eIF2α (eukaryotic translation initiation factor-2) overexpression and PKR (double-stranded-RNA-activated protein kinase) phosphorylation, which has been used clinically to control Japanese encephalitis virus replication

(Elazor et al., 2008; Shi et al., 2014). Nitazoxanide has been part of various combinations for SARS-CoV-2 infections and has shown depression in disease trajectory if started early on (Mendieta Zerón et al., 2021; Miorin et al., n.d.; Rocco et al., 2021). Paradoxically, Plitidepsin (dehydrodidemnin B/ Aplidin) is a marine-derived cyclic depsipeptide inhibiting eEF1A2 that is authorized in a few countries for treating refractory multiple myeloma. Preclinical and randomized phase-I trials showed Plitidepsin to be well tolerated and block the SARS-CoV-2 virus at the nanomolar range (Varona et al., 2022). Both eEF1A2 inhibition and overexpression seem to be detrimental to SARS-CoV-2 pathogenesis.

Inosine-5'-monophosphate dehydrogenase (IMPDH)

Merimepodib (MMPD) is a IMPDH inhibitor that showed 2.5-log decrease in viral titers (p-value = 0.0004) with 4hr pretreatment (Bukreyeva et al., 2020). When used in combination with Remdesivir, there was a rapid undetected level of achievement of viral load *in vitro*; a trial with the same combination is ongoing (Wimmer and Keestra, 2022).

Target independent drugs

NSAIDs

Indomethacin is an NSAID that inhibits prostaglandin E synthase 2 (PGES-2) (Lucas, 2016). Its mechanism of action is still an enigma, while its primary target is IL6 suppression through PGES-2 inhibition, it is also proposed to block multiple factors for severe COVID-19 e.g. suppressing ACE2, TMPRSS2, cytokines, and inflammation in general (Alkotaji and Al-Zidan, 2021). Indomethacin has shown 100% protection from the development of hypoxia/desaturation with $SpO2 \leq 93$ compared to 16-22% in the untreated pool of patients (Ravichandran et al., 2022).

Table 4. Descriptions of anti-COVID-19 agents (non-virus-specific) with data from clinical trials

	Name of the Agent	Total no of patients and trials	No of days of treatment	Outcome (Negative SARS-CoV-2 test conversions (NSTC))	Contraindications	Refs
1	**Chloroquine and Hydroxychloroquine**	50 trials 619 91 patients	dosing was usually 400 mg orally BID on day 1 and 200 mg BID on days 2–5.	Found no reductions in mortality, hospitalization, symptoms, and ICU dependency incidence of mechanical ventilation, and NSTC OR= 0.97.	Significant increased odds of QT prolongations (rates 0.39 vs 0.29 treated vs. 0.13 vs 0.09 control)	(Barratt-Due et al., 2021; Deng et al., 2022; Kalantari et al., 2021; Taccone et al., 2020)
2	**Ivermectin**	19 studies 432 8 Patients	Dosing was usually 400 μg per kilogram for 3 days or placebo	Found no reductions in mortality, hospitalization, symptoms and ICU dependency, incidence of mechanical		(Hariyanto et al., 2022; Reis et al., 2022; Shafiee et al., 2022)

				ventilation, and NSTC OR= 0.25		
3	**Steroids (Methylprednisolone and Glucocorticoid)**	62 studies, 5 trials,7 works of literature 235 97 patients	Dosing was usually (1–2 mg/kg/day for ≤ 7 days).	Found great reductions in mortality up to 20% (RR=73 TO 77), hospitalization, symptoms and ICU dependency, the incidence of mechanical ventilation (RR 0.77, increased 28-day ventilator-free days (MD= 0.5 TO 2.81) low-dose (≤2mg/kg/day) methylprednisolone treatment for ≤ 7 days was associated with relatively better clinical outcomes, without increasing	could slightly prolong the duration of viral shedding (MD 1.03)	(Ebrahimi Chaharom et al., 2022; Hong et al., 2022; Salvarani et al., 2022; J. Tu et al., 2022; J. G. Zein et al., 2022)

				the duration of viral shedding		
4	**Clevudine**	1 study 61 patients	Dosing was usually 120 mg orally per day for 14 days	Found no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		(Song et al., 2021)
5	**Methylene Blue**	1 study 63 patients	Dosing was usually Methylene blue 0.5 mg via nebulization TID	Found no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		(Alemany et al., 2022; Patidar et al., 2022)
6	**Nitazoxanide**	4 studies	Dosing was usually	Found improvement in the inflammatory		(Blum et al., 2021; Mendieta

		1926 patients	500 to 600 mg TID for 5 - 7 days	outcome but no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		Zerón et al., 2021; Miorin et al., n.d.; Rocco et al., 2021; Rossignol et al., 2022)
7	**C21**	1 phase 2 trial 106 patients	Dosing was usually 100 mg C21 BID 7 days in addition to standard of care	Found marked reduction of requirement for O2 on day 14. along with no reductions in mortality, hospitalization, symptoms, and ICU dependency incidence of mechanical ventilation, and NSTC		(Tornling et al., 2021)
8	**Niclosamide**	1 phase 2 trial	Dosing was usually 2	Found no reductions in mortality,		(Cairns et al., 2022)

		73 patients	g orally daily for 7 days	hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC		
9	**Nafamostat (Nafabelltan)**	1 Pase 2 trial 104 patients	Dosing was usually 4.8 mg/kg/day plus standard-of-care	Found a shorter median time to clinical improvement in a small group of high-risk patients requiring O2 treatment and no reductions in mortality, hospitalization, symptoms and ICU dependency incidence of mechanical ventilation, and NSTC in other patient groups		(Zhuravel et al., 2021)
0	**Indomethacin**	1 study 210 patients	Dosing was usually 75 mg (OD for BMI < 30	Found significant symptomatic relief and improved		(Ravichandran et al., 2022)

		(N= 103)	and BID for BMI > 30) For 5 days	oxygen saturation level, none in the indomethacin group was desaturated. The median days for the resolution of fever is less than 7 days, and cough and myalgia are significantly reduced		

Newer approaches to drugging targets

A variety of novel targets are being investigated with non-standard drug targeting. Ensovibep (MP0420) is a DARPins derivative that is an emerging class of novel therapeutics. This molecule's three distinct DARPin domains are designed to simultaneously target the receptor binding ridge on each RBD of the spike trimer (Chonira et al., 2022). MP0420 had an IC50 of an average of 2.3ng/ml except for the mutation F486V, it was twice as effective as neutralizing antibodies; REGN10933 and REGN10987, and had a better efficacy against variants of concern (Reichen et al., n.d.).

A novel therapeutic paradigm is a proteolysis-targeting chimera (PROTAC), an application of targeted protein degradation, which has successfully been applied toward COVID-19 targets (Shaheer et al., 2021). Essentially, PROTACs have a region that binds the viral target and the same region that binds a ubiquitin ligase, thereby positioning it to traffic the target for degradation. Since the virus must enter the cell, it is thereafter susceptible to PROTACs. Viral proteins are also

exogenous, making them good targets from a standpoint of specificity. Furthermore, fragments generated from degradation can result in novel antigens that stimulate the host immune response. MPRO in particular has been selected as a viable candidate for PROTACs (Shaheer et al., 2021). Other potential targets include viral envelope proteins, PLpro, and RNA-dependent RNA polymerase (RdRp). PROTACs use a ligand as the basis for targeted protein degradation, novel therapeutics can be based on existing drugs or those in development, for the appropriate intracellular targets. For example, indomethacin has gained attention after drug repurposing studies identified its antiviral capabilities (Shekhar et al., 2022; Zeng et al., 2020). A recent study investigated the effectiveness of indomethacin-based PROTACs in pan anti-coronavirus therapy (Desantis et al., 2021). Their findings indicated the indomethacin-PROTAC was more potent at inhibiting coronavirus, as well as was able to be effective against multiple strains of coronavirus.

A major limitation of PROTACs is that they are only usable for intracellular targets, or at least ones with an intracellular component; this limitation precludes a vast range of potential targets of high importance. A very recent technique called molecular degraders of extracellular proteins through the asialoglycoprotein receptor (MoDE-As) addresses the glaring weakness of targeted protein degradation. MoDE-As can target extracellular proteins for degradation (Caianiello et al., 2021). This is accomplished via the formation of a ternary complex between a target protein, the ligand, and hepatocyte ASGPRs; this complex is then endocytosed, trafficked to the lysosome and the target protein is degraded by the host machinery. While MoDE-As has not yet been applied to COVID-19 therapy, it is a viable technique to intervene with viral protein targets before they enter the cells. Furthermore, there is evidence that the SARS-CoV-2 spike protein interacts with the ASGPR in hepatocytes through a lesser-known mechanism of entry (Collins and Steer, 2021; Gu et al., 2022).

Conclusion

COVID-19 disease can be safely called a virus-induced hyper-immune disorder. There are thus numerous factors still being discovered from the host point of view which can be mitigated by various therapeutics to reduce the severe clinical presentations (W. Zhang et al., 2022). Also with new roles assigned to various viral components essential in pathogenesis and severe disease progression, numerous virus-coded proteins have been proposed as drug targets albeit only a few have bioactive inhibitors (Martin et al., 2020). Although there are numerous agents with known *in vitro* activity, there is an urgent need to form suitable combinations based on the synergy of the agents, a stratified patient population taking into consideration important pathways leading to either ARDS or Long-haul disorders. Also, various *trialed* agents with borderline protection or a population-specific activity can be used to fortify newly discovered strong antivirals like Nirmatrelvir or Molnopiravir. As there is no single pathway in this COVID-19 sequela, there is an urgent need for utilizing personalized medicine combinations composed of the most tolerated and active agent combinations.

Intriguingly, when viewing from a drug discovery perspective, there is a learning phase we must endeavor to better understand the druggability of identified viral targets with known and potential inhibitors to continue developing new antivirals to be better prepared for the emergence of drug resistance to current candidates and therapeutics (Gandhi et al., 2022), especially when it's now known as immunocompromised patients are the source of new resistant variant emergence (Chen et al., 2021; Gandhi et al., 2022; Leung et al., 2022).

Within this realm of rapidly advancing, technology is a convergent race between computational and experimental methods, which furthers the acceleration of drug discovery(Dara et al., 2022; Hinton, 2007; Jiménez-Luna et al., 2021; Lima et al., 2016; Patel et al., 2020; Sherrington and

Kirkpatrick, 1975; Talevi et al., 2020). We are using ML increasingly in multiple areas of science and even in other areas (e.g. social science), whilst we are making stronger strides in computational design techniques. ML is now commonplace in digital pathology, search engines, recognition (voice, facial, pattern), market and financial predictions, astronomy, cryptography, agriculture, and more. The use of AL, ML, and deep learning techniques is to better find and rapidly identify data from multiple sources, extract valuable insights, visualize the data meaningfully, and give context. Within drug discovery, there is an ongoing explosion of the use of ML with molecular modeling for protein structure prediction and drug-protein interaction analyses. For example, the pioneering of Boltzmann machines using decision trees and then adaptive rules for protein structures was a crucial development that allowed the generation of predetermined global variables on molecular structures to dictate conformational searches in directions under the reinforced learning pattern dictated (Caulfield and Devkota, 2012; Caulfield, 2011; Caulfield et al., 2011; Coban et al., 2021b; Kayode et al., 2016; von Roemeling et al., 2018). The particularly useful application of this allowed such things as cryo-EM fitting and rapid space searches (Caulfield and Devkota, 2012; Caulfield et al., 2011) using entropy as the controller.

Particularly of note is the emergence of AI and ML to the forefront of protein structural modeling, conformational dynamics exploratory mission of many labs to find key druggable states, and the determination of the human genomic variance as a contributing factor to the way viruses capitalize on variation. Virus exploitation of human genetic variance is also being tackled by computationalists to better understand how genetics plays a role in virus proliferation, which will allow better tools to predict potential virus offshoots in the future. One can imagine a day when there will be a virtual medicine cabinet pre-stocked with the needed antivirals specific to the patient's genetic predispositions and particular cell pathways. In such a scenario, we will have AI-

based medicine that has the genetic profile, molecular structures for the targets needed, rapidly available custom chemistry, and rapid safety-profiling needed for the new chemical entities to be used in humans on-demand with acceptable safety tolerances. While this particular view of AI and ML is not anytime soon, the palatability of this particular star trek viewpoint is very realizable and within our horizon.

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