

Current Trends and Future Approaches in Small-Molecule Therapeutics for COVID-19

Running Title: Trends in Small-Molecule Therapeutics for COVID-19

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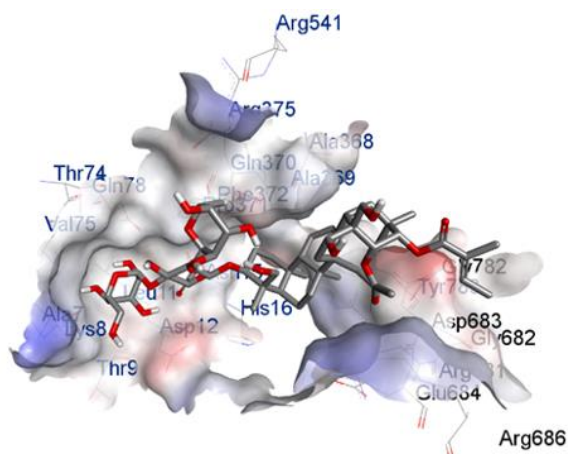
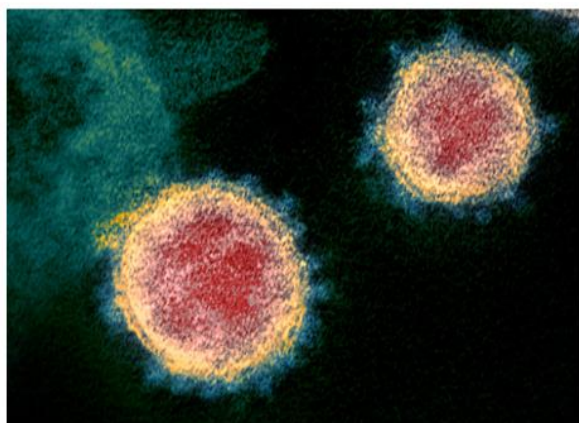
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Abstract

The novel coronavirus (SARS-CoV-2) pandemic has created a global public health emergency. The pandemic is causing substantial morbidity, mortality and significant economic loss. Currently, no approved treatments for COVID-19 are available, and it is likely to take at least 12-18 months to develop a new vaccine. Therefore, there is an urgent need to find new therapeutics that can be progressed to clinical development as soon as possible. Repurposing regulatory agency-approved drugs and experimental drugs with known safety profiles can provide important repositories of compounds that can be fast-tracked to clinical development. Globally, over 500 clinical trials involving repurposed drugs have been registered, and over 150 have been initiated, including some backed by the World Health Organisation (WHO). This review is intended as a guide to research into small-molecule therapies to treat COVID-19; it discusses the SARS-CoV-2 infection cycle and identifies promising viral therapeutic targets, reports on a number of promising pre-approved small-molecule drugs with reference to over 150 clinical trials worldwide, and offers a perspective on the future of the field.

Graphical Abstract



1. INTRODUCTION

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus that was first identified in Wuhan, China in December 2019. The rapid evolution of the COVID-19 crisis from regional outbreak to global pandemic has caught governments and healthcare systems off guard [1]. With over 10 million confirmed cases as of the 28th of June [2], treatments for SARS-CoV-2 infection and COVID-19 are urgently needed. Symptoms of the disease typically include fever, dry cough and dyspnoea; less common are malaise, myalgia, anosmia, nausea and pain in the head, throat and/or abdomen. Patients suffering from severe cases of COVID-19 may also present with symptoms such as respiratory distress, tachypnoea and hypoxia. The latter cases can progress from viral pneumonia to acute respiratory distress syndrome (ARDS), multiple organ failure and death [1].

SARS-CoV-2 belongs to a family of viruses known as the coronaviruses, members of the order *Nidovirales* that are spread broadly among humans, different domestic/wild animals and birds and can cause respiratory, hepatic and neurological diseases [3]. Among the seven coronavirus species which are capable of infecting humans, four viruses (229E, OC43, NL63 and HKU1) are common respiratory viruses that produce common cold symptoms but can also cause pneumonia. Three zoonotic viruses – SARS-CoV (severe acute respiratory syndrome coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus) and, the most recent to emerge, SARS-CoV-2 – can cause fatal respiratory illness in humans [4, 5]. Recent studies suggest that SARS-CoV-2 is more contagious than SARS-CoV [6].

The scientific community have responded to the threat posed by SARS-CoV-2 with rapid identification and subsequent publication of crystal and cryo-EM structures of important SARS-CoV-2 drug targets, including the spike protein [7], main protease [7] and Nsp15 ribonuclease [8]. However, targeted approaches to designing new drugs for clinical use will take considerable time. Rapid repurposing of clinically-approved small-molecule drugs in randomised trial-led efforts to identify effective COVID-19 medications may buy time with which to develop investigational treatments.

1.1. The SARS-CoV-2 Virus Infection Cycle

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus. Its RNA genome encodes three major surface proteins termed the spike (S), membrane (M), and envelope (E) proteins [9]. A fourth gene

encodes the nucleocapsid (N) [10]. The spike protein forms homotrimers on the viral surface [11] and is comprised of two domains, an N-terminal S1 domain that mediates receptor binding [12] and a C-terminal, transmembrane S2 domain for membrane fusion [9, 11]. The SARS-CoV-2 infection cycle (Figure 1) begins with the recognition of angiotensin-converting enzyme 2 (ACE2) on the host cell surface by the spike protein [13]. Interaction of the spike protein with ACE2 is thought to trigger a conformational change in the former, revealing a site between the S1 and S2 domains that can be cleaved by host cell membrane proteases. Now activated for membrane fusion, the cleaved S2 subunit inserts into the host cell membrane *via* its N-terminal fusion peptide so that it is connected to both the viral and cell membranes. The N- and C-terminal heptad repeats of the S2 subunit then fold to form a six-helix bundle, contracting the S2 subunit and bringing the two membranes into close proximity, whereupon they fuse [9].

Following a successful recognition event, virus internalisation can occur either by direct fusion with the plasma membrane or by endocytosis [13]. In the case of direct fusion, the host protease responsible for cleavage of the S1 and S2 domains is thought to be transmembrane protease serine 2 (TMPRSS2), whereas in endocytosis the cysteine protease cathepsin L is thought to be responsible [9]. In addition, it has recently become apparent that SARS-CoV-2 contains sites that can be processed by furin-like proteases; since furin is widely expressed in different cell types, this could increase the cell tropism of the virus beyond the respiratory and digestive systems [11, 14]. Fusion of the viral and cellular membranes triggers the release of viral genomic RNA into the host cell cytoplasm [13] and uncoating of the viral nucleocapsid [15]. If not targeted for degradation in the cytoplasm, the viral RNA then attaches to the host ribosome, whereupon the viral genes ORF1a and ORF1ab are translated into polyproteins [12] pp1a and pp1ab [1], respectively. These polyproteins are processed by the coronavirus main protease (M^{pro}) and a papain-like protease (PL^{pro}), both cysteine proteases [12, 16]. M^{pro} is also known as 3C-like protease ($3CL^{pro}$) because of its similar cleavage site specificity to the 3C protease ($3C^{pro}$) found in picornaviruses [17]. Proteolysis gives rise to a number of non-structural proteins which form the replicase-transcriptase, the only protein translated directly from the viral genome [15]. Alongside an ATP-dependent RNA helicase and various cofactors [15], this RNA-dependent RNA polymerase copies the viral RNA in membrane-associated replication-transcription complexes [1, 18] *via* negative-strand intermediates [13]. Copies of the full-length genomic RNA and a set of sub-genomic mRNAs are produced [13], the latter determined by transcriptional regulatory sequences located between open reading frames (ORFs) [1].

Once the replicase-transcriptase has replicated the viral genome and transcribed mRNAs, the sub-genomic mRNA templates are used for translation of structural and accessory viral proteins [13, 15], a process which occurs on the endoplasmic reticulum [15]. The full-length viral RNA is encapsidated and assembles with spike, envelope and membrane proteins in the endoplasmic reticulum-Golgi intermediate compartment [15]. At this stage, post-translational modifications will have occurred, such as S protein trimerization and glycosylation [9] and vesicles move to the plasma membrane for release of infectious virus particles from the host cell via exocytosis [15]. Upon viral release from the host cell, viral particles can be eliminated by a specific adapted immune response so that the disease does not progress in severity; if this does not happen, however, continued viral propagation downregulates ACE2, dysregulating the renin-angiotensin system and causing a cytokine storm which can lead to a host inflammatory response and ARDS (NCT04344041) [19].

1.2. Targeting the SARS-CoV-2 Virus with Small-Molecule Therapies

The severity of the current COVID-19 global pandemic necessitates immediate and decisive action to counter the threat posed by the SARS-CoV-2 virus. To this end, various different approaches for disrupting the SARS-CoV-2 infection cycle have been proposed using previously-approved drugs. Each of the structural and non-structural proteins encoded by its RNA genome are potential targets for existing antiviral agents [20] since many SARS-CoV-2 proteins have a high degree of sequence similarity to their SARS-CoV and MERS-CoV homologues [12].

Viral entry inhibitors are molecules able to interfere with either receptor recognition or spike protein proteolysis. This could involve drugs that target the spike protein, ACE2 inhibitors or inhibitors of host cell proteases like TMPRSS2, cathepsin L or furin, though combinations of protease inhibitors may be necessary to overcome the seemingly independent viral entry mechanisms. A high resolution crystal structure of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein with ACE2 has been published and has provided an important target to screen FDA- and EMA-approved drugs against to identify clinical candidates (Figure 2) [21]. Candidates that have been developed in the past for SARS-CoV or MERS-CoV may require more development beyond straightforward drug repurposing since the S1 subunit receptor binding domain in SARS-CoV-2 has only 73.5% sequence identity with its SARS-CoV counterpart [12]. Viral entry inhibitors are desirable because the opportunity for the virus to acquire resistance to these agents is minimal [22].

Viral replication inhibitors are another viable strategy, since the crystal structure of SARS-CoV-2 M^{pro} has been published [7] (Figure 2) and it shares 96% sequence identity with the corresponding enzyme in SARS-CoV. The SARS-CoV-2 RNA-dependent RNA polymerase is another promising target for drug repurposing since it also shares 96% sequence identity with the SARS-CoV homologue [12]. While PL^{pro} only has 83% sequence identity with its SARS-CoV homologue, active site conservation means it too is a promising target for drug repurposing [12]. Other possible targets include the viral helicase enzyme [23], 3'-to-5' exonuclease, endoRNase, 2'-O-ribose methyltransferase [24] and Nsp15 [8]. The structures of SARS-CoV-2 non-structural proteins have also been published [25] and it is expected that the crystal or cryo-EM structures of other targets will be published soon.

Viral release inhibitors are compounds capable of preventing the release of viral particles from host cells. While few agents have currently been identified that inhibit this step of the SARS-CoV-2 infection cycle, this approach has proven successful before in the case of the neuraminidase inhibitors, such as oseltamivir, which bind the membrane-anchored neuraminidase enzyme found in influenza viruses to prevent release of progeny viruses from infected cells [26]. With respect to SARS-CoV-2, the envelope protein may represent a promising target due to its role in viral release as a viroporin [27].

Immune response modulators are also necessary to combat the virus-induced lung inflammation that causes life-threatening respiratory disorders in severe cases of SARS-CoV-2 infection. ARDS is the major cause of death in clinical cases of COVID-19 [28, 29], caused by the uncontrollable activation of the antiviral immune response. Since this abnormal inflammatory response is mediated by macrophages and granulocytes, immune suppression *via* cytokine inhibitors can help in managing it. Various cytokines including IL-6 and TNF- α have been implicated in this immune response [19], with IL-6 thought to be responsible for cytokine release syndrome (CRS) which can lead to multiple organ failure [1, 30, 31]. High doses of corticosteroids have been traditionally considered effective in retarding multiple organ failure and decreasing ARDS-induced mortality, though their use to treat COVID-19 patients remains a matter of debate [32, 33]. Alternative approaches to the issue of SARS-CoV-2-induced ARDS must therefore be considered.

2. VIRAL ENTRY INHIBITORS

2.1. Spike Protein-Targeting Drugs

Umifenovir (Arbidol®; Figure 3), an antiviral medication used to treat influenza virus infections and approved for use in Russia and China [34], has been demonstrated to effectively inhibit SARS-CoV *in vitro* [35] and MERS-CoV [36] through disrupting virus-cell membrane fusion to block viral entry [37]. Although it appears to have a relatively low selectivity index (SI; CC_{50}/EC_{50}) against SARS-CoV-2 *in vitro* (SI >3.7 in Vero E6 cells; $EC_{50} = 10.7 \mu M$, $CC_{50} = >40 \mu M$, multiplicity of infection (MOI) 0.002) [38], variation in CC_{50} s between different cell lines (8 $\mu g/mL$ to 115 $\mu g/mL$) [39-41] has previously been noted. Work by Wu *et al.* would appear to confirm a similar mode of action against SARS-CoV-2; docking of umifenovir against possible drug target within SARS-CoV-2 indicated it would interact most favourably with the spike protein with an mfScore of -145.125 [36]. Touret *et al.* report an EC_{50} for umifenovir against SARS-CoV-2 of 10.7 μM [38]. Umifenovir is currently set to be investigated in a number of phase 4 clinical trials in China and Iran both as a monotherapy (NCT04260594, NCT04255017 and NCT04286503) and in combination with other therapies (NCT04254874 and NCT04350684) for treatment of patients with COVID-19. However, a retrospective study of 81 COVID-19 patients suggests that umifenovir is not an effective SARS-CoV-2 antiviral treatment [42].

Nitric oxide (GeNOsyl®, INOmax®, Noxivent™; Figure 3), a colourless gas known to have important roles in a number of different biological processes, has previously been shown to inhibit the replication of SARS-CoV. It achieves this through two distinct mechanisms; by reducing the palmitoylation of nascently expressed spike protein and thus interfering with receptor binding, and by reducing viral RNA production [43]. During the 2002-2004 SARS-CoV outbreak, low dose nitric oxide (<30 ppm) was found to reverse pulmonary hypertension, improve severe hypoxia and shorten the duration of ventilatory support needed in SARS-CoV-infected patients relative to a control group (NCT04305457). LC_{50} s are reported to be 315 ppm in rabbits, 320 ppm in mice and 854 ppm in rats, from which the National Institute for Occupational Safety and Health (NIOSH) has set an IDLH (Immediately Dangerous to Life or Health) value of 100 ppm for humans [44]. Nitric oxide is the subject of multiple planned phase 1-3 clinical trials in the US (NCT04398290, NCT04421508, NCT04397692, NCT04388683, NCT04305457, NCT04306393, NCT04312243 and NCT04338828) and Canada (NCT03331445 and NCT04383002) for the treatment of COVID-19 at concentrations ranging from 20 ppm to 300 ppm; doses of the drug in excess of the aforementioned IDLH value will be restricted to short periods of time (15-30 minutes, up to twice daily).

2.2. Angiotensin-Converting Enzyme 2-Targeting Drugs

The use of both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) for the treatment of SARS-CoV-2 infections remains controversial; while their use may block viral entry into cells through interfering with the prerequisite virus-ACE2 interaction, some experimental models have found these drugs to prompt increased ACE2 expression in several organs which could exacerbate the viral infection. Trials in the US (NCT04338009) and Ireland (NCT04330300) have been planned to investigate this area further; the latter, a 2,414-person phase 4 clinical trial at University Hospital Galway (NCT04330300), will evaluate the ACEIs **captopril** (Capoten®), **lisinopril** (Prinivil®), **enalapril** (Vasotec®), **perindopril** (Coversyl®), **ramipril** (Altace®), **trandolapril** (Mavik®), **fosinopril** (Monopril®), **quinapril** (Accupril®) and **benazepril** (Lotensin®) (Figure 4) and ARBs **irbesartan** (Avapro®), **candesartan** (Atacand®), **eprosartan** (Teveten®), **losartan** (Cozaar®), **olmesartan** (Benicar®), **telmisartan** (Micardis®) and **valsartan** (Diovan®) (Figure 5). Further phase 1-4 trials of some of these drugs are planned and/or recruiting participants in the Netherlands (NCT04335786), Pakistan (NCT04343001), Egypt (NCT04345406) and the US (NCT04328012, NCT04335123, NCT04312009, NCT04311177 and NCT04340557). While a Chinese retrospective study of 1,128 adults suffering from hypertension and COVID-19 has concluded that use of both ACEIs and ARBs was associated with a lower risk of all-cause mortality compared to COVID-19 patients not using these medications [45], other reviews of the available clinical evidence do not agree [46].

The Chinese herbal medicine **glycyrrhizin** (Figure 6), a glycosylated saponin comprised of one molecule of glycyrrhetic acid and two molecules of glucuronic acid [47] found in the roots of Chinese liquorice *Glycyrrhiza uralensis* [48], has been predicted to bind ACE2 in a number of separate *in silico* studies. Chen and Du predicted glycyrrhizin to bind ACE2 with a binding energy of -9 kcal/mol and interact with residues R559, Q388, R393 and D30 [48], while separate work by Cinatl *et al.* found glycyrrhizin to have a high SI against SARS-CoV strains FFM-1 and FFM-2 *in vitro* during and after virus adsorption (SI >67 in Vero cells; EC₅₀ = 300 µg/mL, CC₅₀ = >20,000 µg/mL) [50]. The double ammonium salt of the compound, diammonium glycyrrhizinate, is currently being studied in two small-scale clinical trials against COVID-19 in China (ChiCTR2000029768 and ChiCTR2000030490).

2.3. Endosome-Targeting Drugs

Chloroquine (Aralen®; Figure 7), an antimalarial drug, has been identified as a promising small-molecule therapy for SARS-CoV-2 in a number of recent *in vitro* studies [51-53]; Wang and colleagues report that it has a high SI against SARS-CoV-2 *in vitro* (SI >88.50 in Vero E6 cells; EC₅₀ = 1.13 µM, CC₅₀ = >100 µM, MOI 0.05) [53], although it is known to induce life-threatening cardiac toxicity on rare occasions [54]. Chloroquine and its analogues possess tertiary amine functional groups and are thus weakly basic; the neutral, freebase forms can diffuse across membranes into acidic cytoplasmic organelles such as endosomes, whereupon they become protonated and unable to diffuse out [55, 56]. Concentration of chloroquine within endosomes in this manner increases the pH within the endosome [55, 56], blocking the pH-dependent fusion of the viral and endosome membranes that leads to release of viral genetic material within the host cell [57]. This mode of action is well-documented in a wide variety of different viruses [56-59], though additional modes of action have also been reported/predicted in SARS-CoV-2 [57, 60]. To further evaluate chloroquine as a treatment for COVID-19, a number of phase 2, 3 and 4 clinical trials in countries including China (NCT04319900, ChiCTR2000029741, ChiCTR2000029609, ChiCTR2000029542, ChiCTR2000031204, ChiCTR2000029975, ChiCTR2000029988, ChiCTR2000029939, ChiCTR2000030054, ChiCTR2000029899 and ChiCTR2000029898), Israel (NCT04333628), Poland (NCT04331600), Greece (NCT04344951), Vietnam (NCT04328493), France (NCT04333914), the US, Australia, Ireland, South Africa (NCT04333732), the UK (NCT04303507), Brazil (NCT04323527 and NCT04342650) and Canada (NCT04324463) are either planned, recruiting or currently active; of note is a French 273-person phase 2 trial for COVID-19 patients also suffering from advanced or metastatic cancer (NCT04333914).

Hydroxychloroquine (Plaquenil®; Figure 7), an analogue of chloroquine with similar promise against SARS-CoV-2 *in vitro* (SI = 61.45 in Vero E6 cells; EC₅₀ = 4.06 µM, CC₅₀ = 249.50 µM, MOI 0.02) [52], as well as associated drawbacks [54], is also the subject of a number of planned or active phase 1-4 clinical trials worldwide. These include studies in Canada (NCT04329611, NCT04308668 and NCT04321993), the US (NCT04329832, NCT04334512, NCT04329923, NCT04334382, NCT04333225, NCT04335084, NCT04336332, NCT04318444, NCT04328961, NCT04334148, NCT04335552, NCT04334967, NCT04332991, NCT04333654, NCT04328467, NCT04308668, NCT04328012, NCT04345692, NCT04341441, NCT04345653, NCT04343677 and NCT04342169), Singapore (NCT04342156), France (NCT04328285, NCT04325893 and NCT04344379), Germany (NCT04342221 and NCT04340544), Spain

(NCT04331834 and NCT04330495), Israel (NCT04323631), Brazil (NCT04329572, NCT04321278 and NCT04322123), Mexico (NCT04315896, NCT04318015 and NCT04340349), Pakistan (NCT04328272), South Korea (NCT04330144 and NCT04307693), China (NCT04261517, ChiCTR2000030054, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029803 and ChiCTR2000029559), Norway (NCT04321616 and NCT04316377), Denmark (NCT04322396), Austria (NCT04336748), Turkey (NCT04326725) and Iran (NCT04343768). Of note are two large scale, multinational trials assessing the utility of both chloroquine and hydroxychloroquine as prophylactic therapies for frontline healthcare workers (NCT04333732 and NCT04303507); other, smaller studies investigating both pre-exposure (NCT04328467, NCT04333225, NCT04328285, NCT04331834, NCT04318015, NCT04336748 and NCT04343677) and post-exposure (NCT04318444, NCT04330144, NCT04308668, NCT04322396, NCT04330495, NCT04326725, NCT04342156 and NCT04343677) prophylaxis on both healthcare workers and the general population are also being conducted in multiple countries. Combination with the macrolide antibiotic **azithromycin** (Zithromax®), another drug observed to have a high SI against SARS-CoV-2 *in vitro* (SI >19 in Vero E6 cells; EC₅₀ = 2.12 µM, CC₅₀ = >40 µM, MOI 0.002) [38], is also being assessed. Trials evaluating azithromycin either as a monotherapy (NCT04332107 and NCT04344379) or in combination with chloroquine or hydroxychloroquine (NCT04324463, NCT04329832, NCT04334512, NCT04334382, NCT04329572, NCT04336332, NCT04328272, NCT04335552, NCT04322396, NCT04321278, NCT04322123, NCT04339816, NCT04341727, NCT04341207, NCT04344444, NCT04338698 and NCT04344457) as well as other drugs (NCT04339426 and NCT04338698) are being initiated worldwide. Preliminary results appear mixed; while there are reports that suggest hydroxychloroquine monotherapy is associated with an increase in COVID-19 patient survival when started in the early stages of the disease [61], a meta-analysis of 11 clinical studies with a total of 2,354 patients receiving hydroxychloroquine does not support this conclusion [62].

2.4. Host Protease Inhibitors

Camostat mesylate (Foipan®; Figure 8), a serine protease inhibitor, is another possible treatment option. Approved for clinical use in Japan since the 1990s for treating chronic pancreatitis and postoperative reflux esophagitis [63], it has a high SI *in vitro* (SI >62 in MDCK cells; EC₅₀ = 3.2 µg/mL, CC₅₀ = >200 µg/mL) [64] and is active against both SARS-CoV [9, 65] – Zhou *et al.* found it conferred a 60% survival rate on mice injected with the virus [66] – and SARS-CoV-2 [67]. In the case of the latter, camostat mesylate blocks cellular entry *via* inhibition of the TMPRSS2 protease; Hoffmann *et al.* found that pre-treatment of Caco-2 cells with the

drug reduced SARS-CoV-2 virus entry by ~90% relative to untreated control cells *in vitro* [67]. Combination of camostat mesylate with **aloxistatin** (E-64d; Figure 8), a non-specific cysteine protease inhibitor first isolated by scientists at Taisho Pharmaceutical [68] and a known inhibitor of cathepsin B and cathepsin L [67], may be advantageous [65]; Hoffmann *et al.* report that this combination caused full inhibition of SARS-CoV-2 entry into Caco-2 cells, improving on camostat mesylate alone [67]. Clinical trials evaluating camostat mesylate alone or in combination with other drugs for treatment of COVID-19 patients are currently being organised in the US (NCT04353284, NCT04435015 and NCT04374019), Denmark (NCT04321096), Germany (NCT04338906) and Israel (NCT04355052).

3. VIRAL REPLICATION INHIBITORS

3.1. RNA-Dependent RNA Polymerase Inhibitors

Favipiravir (Avigan®; Figure 9) is a nucleoside analogue and pyrazinecarboxamide derivative developed by Toyama Chemical [69]. The active form of the drug, favipiravir ribofuranosyl-5'-triphosphate, is generated *via* intracellular phosphoribosylation [70]. Favipiravir has been clinically approved in Japan for the treatment of influenza virus infections that are resistant to other classes of antivirals. Despite a low SI against SARS-CoV-2 *in vitro* (SI >6.46 in Vero E6 cells; EC₅₀ = 61.88 µM, CC₅₀ = >400 µM, MOI 0.05) [53], favipiravir is currently being evaluated in a number of clinical trials in COVID-19 patients. In China, favipiravir has recently been trialled in 80 confirmed COVID-19 patients, 35 of whom received favipiravir for 14 days while the rest received a placebo. An initial report concluded that patients receiving favipiravir showed a substantially shorter viral clearance time and improved infection progression [71], though at the time of writing this article has been temporarily withdrawn [72]. Further trials in the UK (NCT04373733), Italy (NCT04336904), Thailand (NCT04303299), the US (NCT04358549 and NCT04346628), Canada (NCT04448119), Iran (NCT04359615 and NCT04376814), Bangladesh (NCT04402203), Russia (NCT04434248), Egypt (NCT04349241 and NCT04351295), Turkey (NCT04411433), Bahrain (NCT04387760), Saudi Arabia (NCT04392973), Germany, Romania (NCT04425460) and China (NCT04333589, NCT04310228, NCT04319900, ChiCTR2000029600, ChiCTR2000030113, ChiCTR2000029548, ChiCTR2000029544 and ChiCTR2000030254) assessing the utility of favipiravir either as a monotherapy or in combination with other biologic or small-molecule therapies appear to be in various stages of progression.

Ribavirin (Copegus®; Figure 9) was first synthesised in 1972 and is a guanosine analogue broad-spectrum antiviral agent indicated to treat hepatitis C and E, Lassa, Hanta and respiratory syncytial viruses [73]. The active triphosphate form of the drug is generated intracellularly [74] and inhibits viral RNA-dependant RNA polymerase as well as mRNA capping, thus blocking RNA synthesis and consequently viral replication [73]. The inhibitory effects of ribavirin on SARS-CoV *in vitro* appear to vary between different cell lines; although it showed potent inhibitory activity in MA104 (African green monkey kidney cell line; EC₅₀ 9.4 ± 4.1 µg/mL), PK-15 (pig kidney cell line; EC₅₀ 2.2 ± 0.8 µg/mL), Caco-2 (human colon carcinoma cell line; EC₅₀ 7.3 ± 3.5 µg/mL), CL14 (human colon carcinoma cell line; EC₅₀ 8.2 ± 4.2 µg/mL) and HPEK (human primary epithelial kidney cell line; EC₅₀ 5.2 ± 2.9 µg/mL) cells, no observable inhibition was found in Vero cells (African green monkey kidney cell line; EC₅₀ >1,000 µg/mL) [75] and this may explain the low SI observed for SARS-CoV-2 by Wang and colleagues (SI >3.65 in Vero E6 cells; EC₅₀ = 109.5 µM, CC₅₀ = >400 µM, MOI 0.05) [53]. Recruitment is currently underway in China for a number of clinical studies involving co-administration of ribavirin, lopinavir/ritonavir and/or various interferons to treat COVID-19 (NCT04276688, ChiCTR2000029387 and ChiCTR2000030922) while other trials in Egypt (NCT04392427) and Bangladesh (NCT04402203) are planned or recruiting patients. Of note is a Canadian 50-person phase 1 trial evaluating different doses of an inhaled solution of ribavirin (Virazole®) in COVID-19 patients (NCT04356677).

Remdesivir (GS-5734™; Figure 9) is a broad-spectrum nucleoside analogue originally developed by Gilead Sciences to treat the Ebola virus [76]. It is the monophosphoramidate precursor of the adenosine-based nucleoside analogue GS-441524 [77] and is converted to its active triphosphate form intracellularly [74] where it inhibits viral RNA-dependent RNA polymerase [78]. Wang *et al.* report a high SI for remdesivir against SARS-CoV-2 (SI >129.87 in Vero E6 cells; EC₅₀ = 0.77 µM, CC₅₀ = >100 µM, MOI 0.05) [53]. In response to its potential, both Gilead Sciences and the US Army Medical Research and Development Command have offered expanded access to remdesivir for COVID-19 patients (NCT04323761 and NCT04302766). Six different phase 3 clinical trials evaluating remdesivir in up to 3,100 COVID-19 patients were initiated as of early April 2020 (NCT04292899, NCT04292730, NCT04252664, NCT04315948, NCT04280705 and NCT04257656), of which two are recruiting participants and two are active at the time of writing. Preliminary data from one of the aforementioned studies shows statistically improved time to recovery *versus* placebo [79], though similar data from another trial does not support this conclusion [80]. As of the 1st of May 2020, the FDA

has granted remdesivir emergency use authorisation for the treatment of COVID-19 in hospitalised patients with severe disease [81].

3.2. Main Protease (M^{pro}) Inhibitors

Lopinavir/ritonavir (Kaletra®; Figure 10) is an antiretroviral combination medication developed by Abbott Laboratories for the treatment and prevention of HIV and AIDS. The combination has previously received interest for treatment of coronavirus infections (NCT00578825 and NCT02845843). Lopinavir (SI = 12.99 in Vero E6 cells; EC_{50} = 5.73 μ M, CC_{50} = 74.44 μ M, MOI 0.01) has been reported to have a higher SI than ritonavir (SI = 8.59 in Vero E6 cells; EC_{50} = 8.63 μ M, CC_{50} = 74.11 μ M, MOI 0.01) [82]. As of early March 2020, current license holders AbbVie Inc. have offered expanded access to lopinavir/ritonavir for the treatment of COVID-19 patients [83]. A number of phase 2-4 clinical trials of the combination therapy in both prophylactic and interventional capacities have been organised in the US (NCT04328012), France (NCT04328285), Canada (NCT04321993, NCT04330690 and NCT04321174), Iran (NCT04331470 and NCT04343768) and China (NCT04295551, NCT04276688, NCT04252885, NCT04261907, ChiCTR2000029741, ChiCTR2000029548, ChiCTR2000029541, ChiCTR2000029468, ChiCTR2000029387, ChiCTR2000029308, ChiCTR2000030187 and ChiCTR2000029539). However, preliminary results from a 160-person Chinese study indicate that there are no benefits to lopinavir/ritonavir treatment of COVID-19 patients beyond those of standard hospital care (NCT04261907) [84].

In silico modelling conducted by Huang and colleagues has predicted that a number of Chinese herbal medicine ingredients might be capable of inhibiting the SARS-CoV-2 M^{pro} enzyme, including **quercetin** (a bitter-tasting flavonol found in a variety of fruit and vegetables [85]; -5.6 kcal/mol [86]) and **baicalin** (a flavone glucuronide found in the roots of Chinese skullcap *Scutellaria baicalensis* [87]; -6.4 kcal/mol [86]) (Figure 11). Both compounds have previously been investigated for use in treating infections of SARS-CoV; IC_{50} values reported for quercetin against SARS-CoV M^{pro} range from $23.8 \pm 1.9 \mu$ M [88] to $73 \pm 4 \mu$ M [89], while Chen *et al.* observed a low SI for baicalin against ten strains of SARS-CoV *in vitro* after 48 hours (SI >4 in FRhK-4 cells; EC_{50} = 12.5-25 μ M, CC_{50} = >100 μ M) [90]. A 50-person trial evaluating quercetin as both a COVID-19 treatment and prophylactic is currently recruiting in Turkey (NCT04377789).

4. IMMUNE RESPONSE MODULATORS

While inhibition of the SARS-CoV-2 infection cycle is undoubtedly a promising means of controlling the current pandemic, no review of small-molecule therapies here would be complete without also considering therapies for managing the associated disease COVID-19. Indeed, the major cause of death in clinical cases of SARS-CoV-2 infection is ARDS [28, 29], triggered by virus-mediated ACE2 downregulation disrupting the renin-angiotensin system, inducing a cytokine storm and leading to a host inflammatory response (NCT04344041) [19]. A number of different anti-inflammatory, immune modulatory and other drugs are currently being trialled with a view to preventing ARDS in severe cases of COVID-19 and thus reducing the associated mortality rate.

4.1. Corticosteroids

A recent publication by Russell and colleagues has recommended that **corticosteroids**, widely used to treat patients during the SARS-CoV and MERS-CoV outbreaks, should not be used in the case of COVID-19-related pneumonia, lung injury or septic shock except in clinical trial settings [32]. However, this advice is disputed in a subsequent publication by Zhao *et al.* which instead advises cautious use [33]. Despite the controversy surrounding their use, a number of different corticosteroids including **dexamethasone** (Dextenza®; NCT04381936, NCT04325061, NCT04347980, NCT04395105, NCT04360876, NCT04327401, NCT04445506, NCT04344730 and ChiCTR2000029656), **ciclesonide** (Alvesco®; NCT04330586, NCT04377711, NCT04435795 and NCT04381364), **budesonide** (Pulmicort®; NCT04331470, NCT04361474, NCT04416399, NCT04355637, NCT04193878 and NCT04331054), **prednisone** (Deltasone®; NCT04344288 and NCT04359511) and **methylprednisolone** (Medrol®; NCT03852537, NCT04329650, NCT04377503, NCT04345445, NCT04438980, NCT04355247, NCT04374071, NCT04273321, NCT04263402, NCT04244591, NCT04323592, NCT04343729 and NCT04341038) (Figure 12) are currently being trialled in COVID-19 patients across the world. Initial results from a 12,000-person UK randomised study evaluating dexamethasone in COVID-19 patients, with 2,104 patients receiving 6 mg of dexamethasone once daily for ten days *versus* 4,321 patients receiving standard-of-care, indicate that it is effective in reducing mortality rates in COVID-19 patients requiring ventilation (28-day mortality rate reduced by one third) or supplemental oxygen treatment (28-day mortality rate reduced by one fifth) [91].

4.2. Cytokine Production Inhibitors

A number of cytokines have been reported to be involved in the human immune response to COVID-19, including IL-1, IL-2, IL4, IL-6, IL-10, IL-12, IL-13, IL-17, GCSF, MCSF, IP-10, MCP-1, MIP-1 α , HGF, IFN- γ and TNF- α (NCT04334044), and thus inhibitors of their production may prevent ARDS [92]. **Colchicine** (Colcrys®; Figure 13), an anti-inflammatory approved for the management of acute gout that targets the NLRP3 inflammasome to reduce the release of cytokines IL-1 β and IL-6 [93], is currently the subject of various phase 2 and 3 clinical trials for COVID-19-associated ARDS in Italy (NCT04322565), Canada (NCT04322682 and NCT04328480), Greece (NCT04326790) and Argentina (NCT04328480). **Baricitinib** (Olumiant™), **ruxolitinib** (Jakafi®) and **tofacitinib** (Xeljanz®) (Figure 13), inhibitors of the Janus kinase family of enzymes that mediate an inhibition of cytokine signalling [94], are due to be trialled in different studies in Italy (NCT04320277 and NCT04332042), Germany (NCT04338958), Canada (NCT04331665), Mexico (NCT04334044), China (ChiCTR2000029580) and the US (NCT04340232), though their use is still the subject of debate [95-97]. **Deferoxamine** (Desferal®; Figure 13), an iron and aluminium chelator, has previously been observed to block IL-6 production in a porcine sepsis inflammatory response syndrome model [98] and intravenous deferoxamine therapy is currently the subject of a 50-person phase 1 trial for treatment of COVID-19 in Iran (NCT04333550). **Escin** (Reparil®), a mixture of saponins found in the horse chestnut *Aesculus hippocastanum* thought to suppress the release of pro-inflammatory cytokines via a reduction of high mobility group box 1 (HMGB1) secretion [99], is being evaluated in separate COVID-19 clinical trials in Italy (NCT04322344) and China (ChiCTR2000029742).

4.3. Cardioprotective Medications

While most infections of SARS-CoV-2 have resulted in COVID-19 as a mild respiratory illness, a subgroup of patients experience a severe illness and require invasive cardio-respiratory support in an ICU setting. There is evidence that severe COVID-19 requiring ICU treatment is correlated with incidence of acute cardiac injury; however, the details surrounding the latter are as yet poorly understood. A study by Imperial College London is seeking to investigate this further in a 3,170-person clinical trial assessing the utility of cardioprotective medicines **aspirin**, **clopidogrel** (Plavix®), **rivaroxaban** (Xarelto®), **atorvastatin** (Lipitor®) and **omeprazole** (Prilosec®) (Figure 14) in preventing cardiac complications in COVID-19 patients. The trial is currently at the recruitment stage (NCT04333407).

4.4. Other Drugs

Other drugs being investigated for their anti-inflammatory properties (Figure 15) include the nonsteroidal anti-inflammatory drugs **ibuprofen** (Advil®), **naproxen** (Aleve®), **aspirin** and **indometacin** (Indocid™) in clinical studies in the UK (NCT04334629), France (NCT04325633), Pakistan (NCT04343001) and the US (NCT04344457), respectively; the vasodilator **sildenafil** (Viagra®; NCT04304313); **thalidomide** (Thalomid®; NCT04273581 and NCT04273529); the sphingosine-1-phosphate receptor modulator **fingolimod** (Gilenya®; NCT04280588); and antifibrotic drug **pirfenidone** (Esbriet®; NCT04282902, ChiCTR2000031138 and ChiCTR2000030892).

Vitamin C (ascorbic acid; Figure 15) has previously been observed to exert effects on the immune system supporting adaptive and innate immunity [100]. Individuals suffering from acute respiratory infections such as pneumonia have reduced vitamin C plasma concentrations when compared to control subjects [101]; a trial by Mochalkin and co-workers using vitamin C at doses of 0.25-0.8 g/day in pneumonia patients reduced average duration of hospitalisation by 19% relative to a control group, while a higher dose of 0.5-1.6 g/day reduced average duration of hospitalisation by 36% [102]. A number of other studies have indicated a role for vitamin C in providing resistance to coronavirus infections [103, 104]. It is currently being studied as part of multiple COVID-19 clinical trials in the US (NCT04328961, NCT04344184 and NCT04342728), Turkey (NCT04337281), Italy (NCT04323514), Canada (NCT03680274) and China (ChiCTR2000029768). **Vitamin D** is also due to be studied as an immune modulatory agent for the treatment of COVID-19 patients in separate trials in France (NCT04344041) and Spain (NCT04334005).

5. CONCLUSION AND FUTURE PERSPECTIVE

The COVID-19 pandemic is currently predicted to cost the global economy up to and in excess of 1 trillion USD [105]. In recent years, a number of different commentators have opined that the world is ill-prepared to deal with the next pandemic [106-108] and it would appear their collective fears were well-founded. The current pandemic thus highlights the importance of strong anti-infective research and therapeutics development programmes. While research into therapies to tackle SARS-CoV-2 is a short term priority, governments worldwide must also take a longer term view. Specifically, countries need to come together to develop an investment and reimbursement model to encourage anti-infectives research and development so that humanity is better prepared to tackle future infectious disease pandemics.

442

443 Fortunately, global research into small-molecule therapies for SARS-CoV-2 and COVID-19 is progressing at an
 444 unprecedented rate. The fact that there are over 200 clinical trials currently being conducted worldwide into
 445 different small-molecule therapies is an incredible feat of organisation given the short amount of time the
 446 SARS-CoV-2 virus has been known to science and the medical personnel and scientists responsible are rightly
 447 deserving of high praise. However, it is essential that these clinical studies remain scientifically rigorous; the
 448 overwhelming demand for any form of treatment must not be allowed to detract from the quality of data
 449 gathered nor the validity of conclusions reported. Recent instances of trial design and protocol controversy [109-
 450 111], trial suspension with minimal explanation (NCT04252664 and NCT04257656) and improper
 451 dissemination of preliminary trial findings [112] cannot be allowed to become commonplace. Only when the
 452 randomised trials currently in progress begin to report properly vetted findings can conclusions be drawn.

453

454 Once effective small-molecule treatments for COVID-19 are identified, it is important that COVID-19 patients
 455 be started on courses of the drug(s) as soon as possible. This will depend on the widespread use of rapid
 456 diagnostic tests to determine whether a patient is infected with SARS-CoV-2. To this end, worldwide
 457 development of a variety of diagnostic approaches is proceeding in parallel with the aforementioned efforts to
 458 identify small-molecule treatments [113-121]. Widespread and expeditious testing is thought to have been key
 459 to South Korea's low COVID-19-related mortality rate [122] – approximately 2.2% as of the 28th of June 2020
 460 [2] – and increasing levels of testing worldwide in recent months are therefore encouraging [123].

461

462 If a previously experimental drug such as Gilead's remdesivir proves to be useful in treating COVID-19
 463 patients, the next hurdle to overcome will be the lack of an established unit price. Gilead has sought to downplay
 464 remdesivir's commercial potential throughout the current pandemic, even providing its existing stock of 1.5
 465 million doses free of charge [124], but this scenario cannot continue indefinitely. In deciding on a reasonable
 466 price, the promise of a faster return to normalcy must be weighed against the current plight of global economies
 467 and the limited funds available for population-wide distribution. Yet the production costs associated with
 468 remdesivir could prohibit its widespread use; the Institute for Clinical and Economic Review (ICER) estimates
 469 that a 10-day course of remdesivir costs 10 USD to produce [125], placing it far above many drugs on the WHO
 470 Essential Medicines List [126] as well as a number of other drugs being trialled against SARS-CoV-2 [127].
 471 With the market price of remdesivir all but guaranteed to exceed the production figure – the ICER estimate a

price of up to 4,500 USD as cost-effective [125] – it remains to be seen if use of remdesivir will be feasible on a global scale.

A decisive factor in determining how long a small-molecule therapy for SARS-CoV-2 will take to reach the clinic may well be the degree to which scientists of different nationalities, disciplines and industry sectors are able to cooperate. The field is where it currently is largely thanks to the effective organisation and execution of a number of large collaborative projects [7, 128-130]; with countries around the world imposing lockdown measures in a bid to ease the pressure on struggling healthcare systems, innovative schemes facilitating such large-scale collaborations are now more important than ever. PostEra, a US/UK startup specialising in machine learning-powered medicinal chemistry, is leading a crowdsourced initiative to harness the data generated by the XChem fragment screening experiment at the Diamond Light Source to create novel M^{pro} inhibitors by asking scientists around the world to analyse the data and suggest combinations of hit fragments for synthesis and *in vitro* testing [131]. The *Coronavirus Tech Handbook*, a crowdsourced resource library based around COVID-19, has been established by faculty members of Newspeak House in the UK to bring together expert contributors in a range of different disciplines to help tackle the pandemic [132]. Time will tell if these innovative approaches to drug design and research prove fruitful.

488 **Abbreviations**

489	3C ^{Pro}	3C Protease
490	ACE2	Angiotensin-Converting Enzyme 2
491	ACEI	Angiotensin Converting Enzyme Inhibitors
492	ARB	Angiotensin II Receptor Blockers
493	ARDS	Acute Respiratory Distress Syndrome
494	CC ₅₀	Half Maximal Cytotoxic Concentration
495	ChiCTR	Chinese Clinical Trial Registry
496	COVID-19	Coronavirus Disease 2019
497	CRS	Cytokine Release Syndrome
498	E	Envelope
499	EC ₅₀	Half Maximal Effective Concentration
500	HMGB1	High Mobility Group Box 1
501	HPEK	Human Primary Epithelial Kidney cell line
502	ICER	Institute for Clinical and Economic Review
503	IDLH	Immediately Dangerous To Life or Health
504	M	Membrane
505	MERS-CoV	Middle East Respiratory Syndrome Coronavirus
506	MOI	Multiplicity Of Infection
507	M ^{Pro} /3CL ^{Pro}	Coronavirus Main Protease
508	N	Nucleocapsid
509	NCTC	National Clinical Trials Consortium
510	NIOSH	National Institute for Occupational Safety and Health
511	ORF	Open Reading Frame
512	PDB	Protein Data Bank
513	PL ^{Pro}	Papain-Like Protease
514	RBD	Receptor Binding Domain
515	S	Spike
516	SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
517	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

518	SI	Selectivity Index
519	TMPRSS2	Transmembrane Protease Serine 2
520	US	United States of America
521	WHO	World Health Organisation

522

523 ***Contributions***

524 All authors researched data for the article, made substantial contributions to discussions of the content, wrote the
525 article and reviewed and edited the manuscript before submission.

526

527 ***Conflict of Interest Declarations***

528 None to declare.

529

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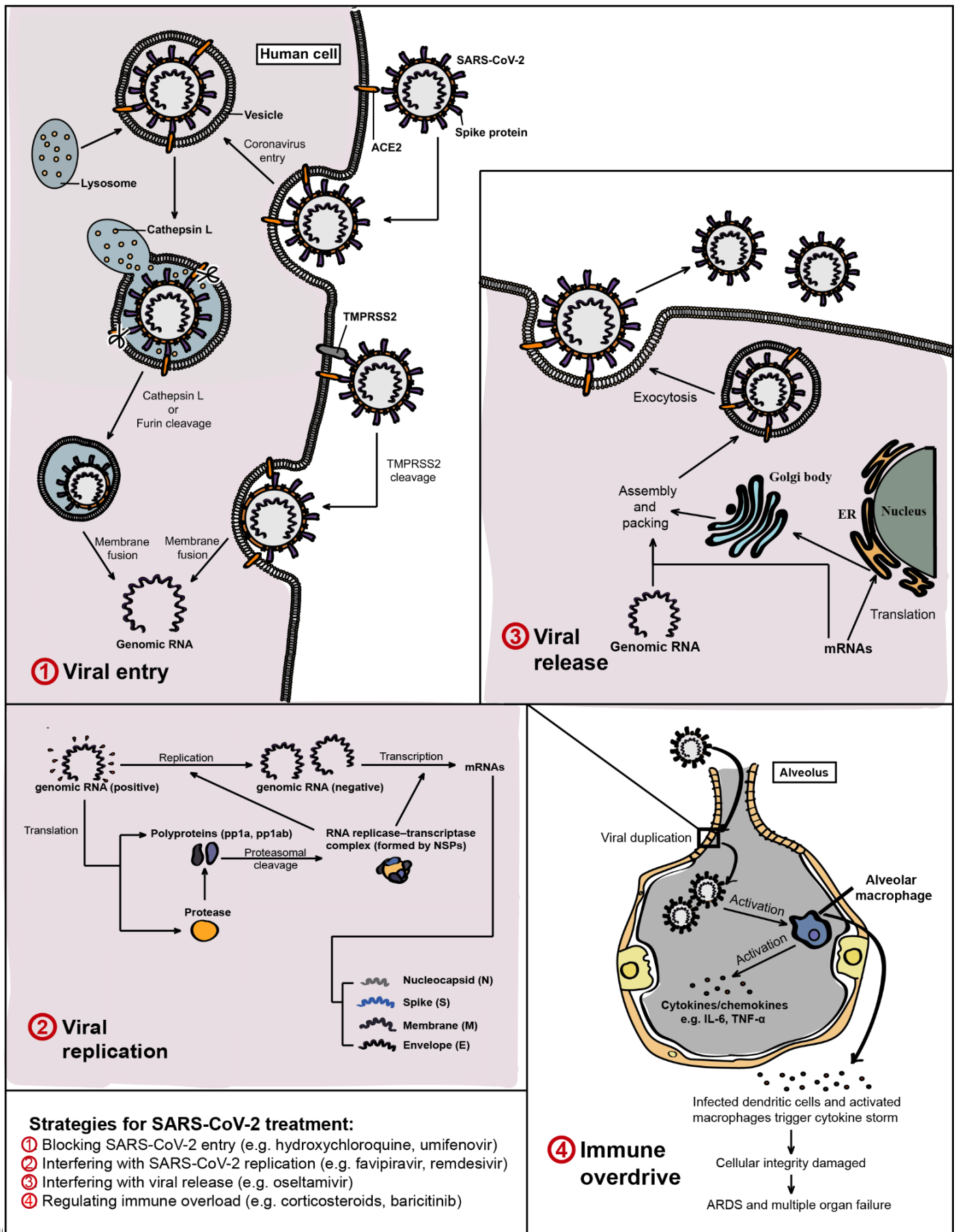
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962 **Figure 1.** The SARS-CoV-2 virus infection cycle.

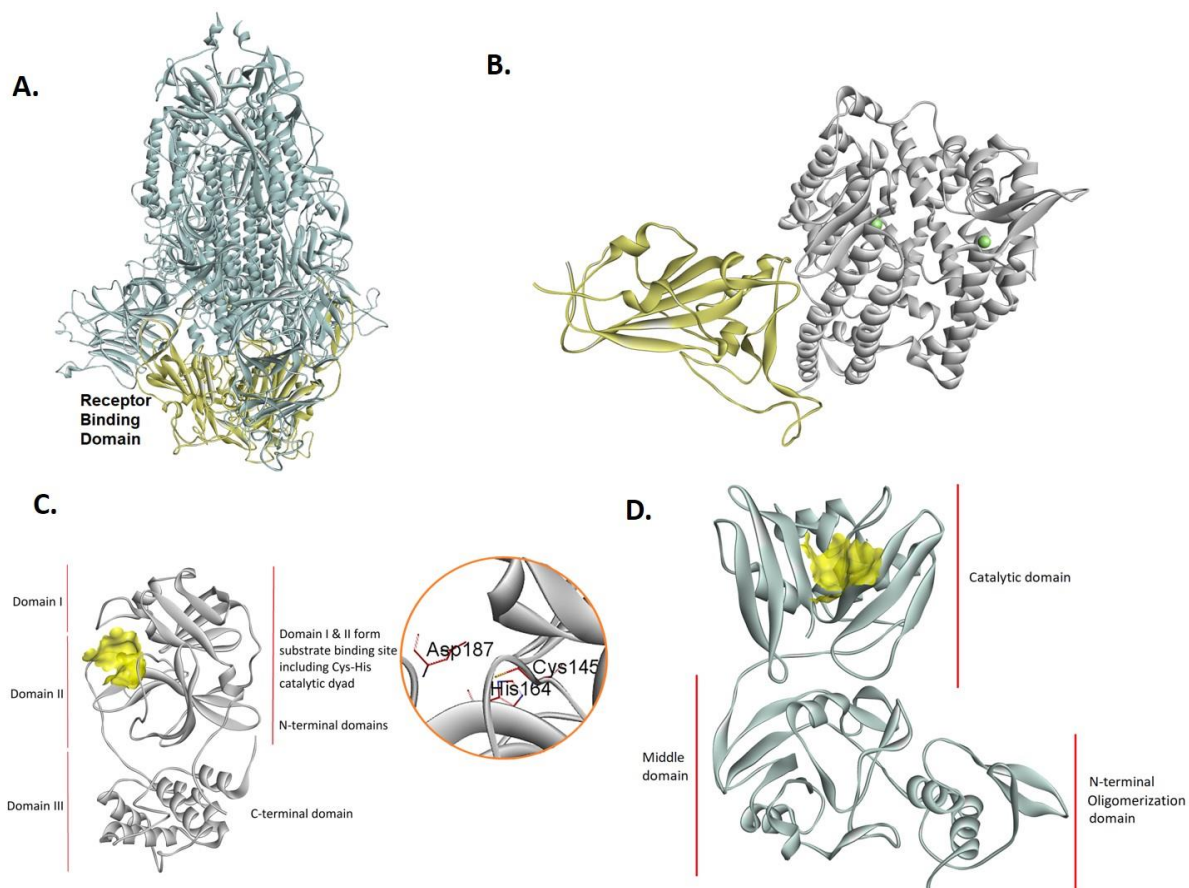
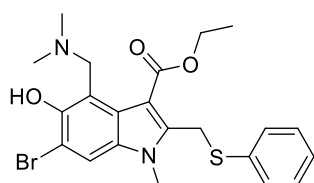


Figure 2. Different drug targets of SARS-CoV-2 that are currently being explored. A) Spike protein, B) spike protein-ACE2 docking interface (PDB ID 6LZG), C) main protease (PDB ID 6Y2E) and D) Nsp15 ribonuclease (PDB ID 6VWW).

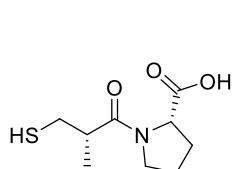


Umifenovir

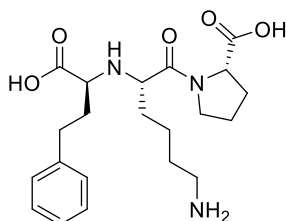


Nitric oxide

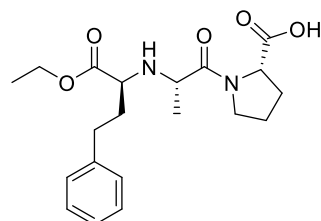
Figure 3. Spike protein targeting drugs umifenovir and nitric oxide.



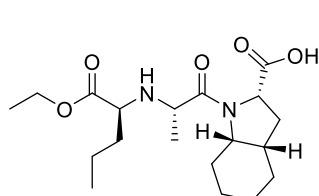
Captopril



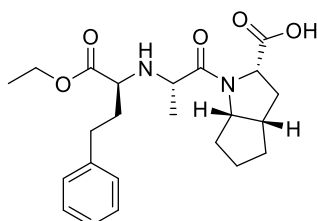
Lisinopril



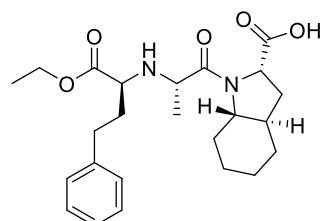
Enalapril



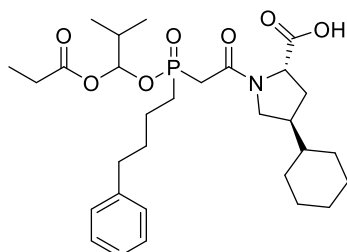
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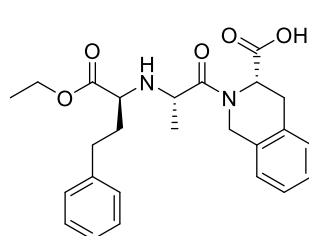
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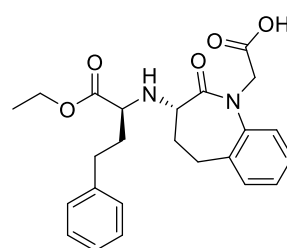
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Fosinopril

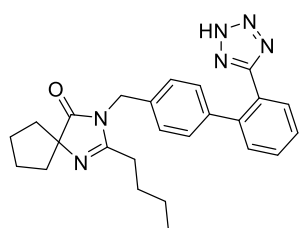


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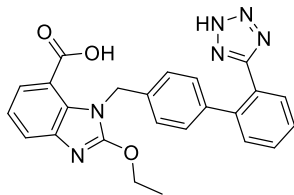


Benazepril

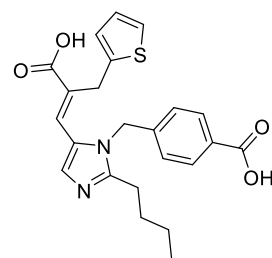
Figure 4. Structures of representative ACEIs.



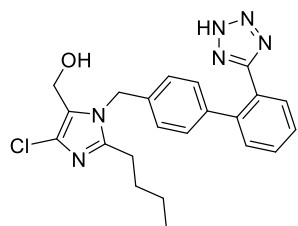
Irbesartan



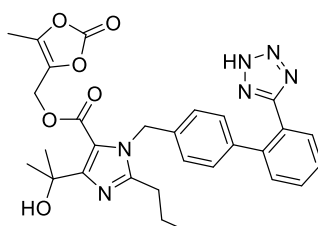
Candesartan



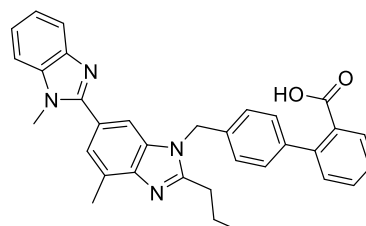
Eprosartan



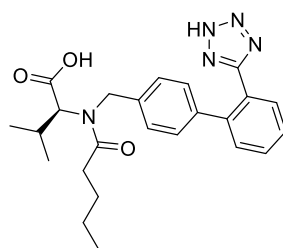
Losartan



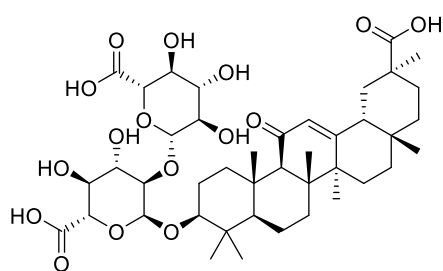
Olmesartan



Telmisartan

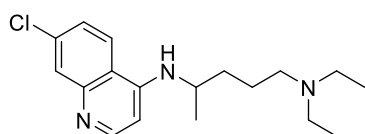


Valsartan

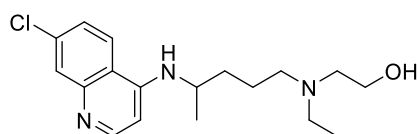


Glycyrrhizin

Figure 6. Structure of Chinese herbal medicine glycyrrhizin.



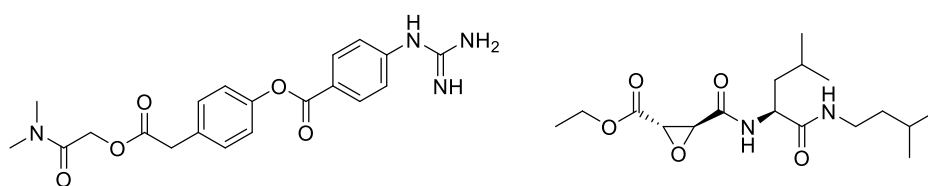
Chloroquine



Hydroxychloroquine

Figure 7. Endosome-targeting drugs chloroquine and hydroxychloroquine.

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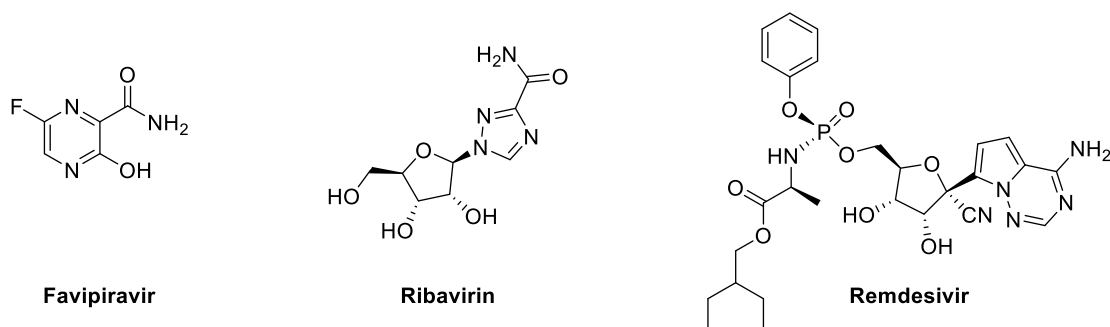
983

Camostat

Aloxistatin

984 **Figure 8.** Small-molecule therapies that target host proteases.

985



Favipiravir

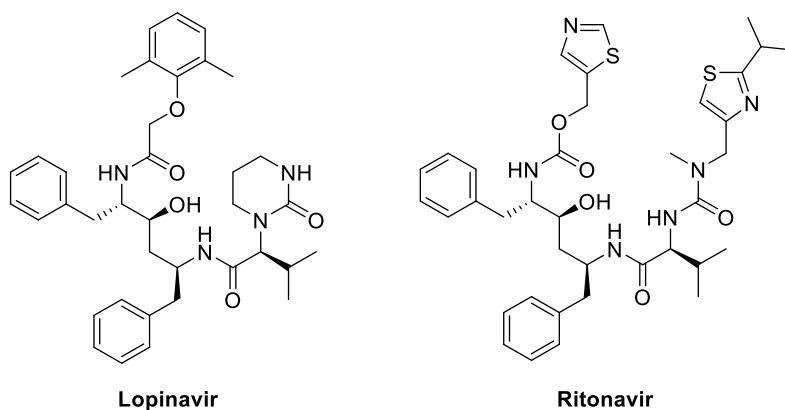
Ribavirin

Remdesivir

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987 **Figure 9.** Small-molecule therapies that target SARS-CoV-2 RNA-dependent RNA polymerase.

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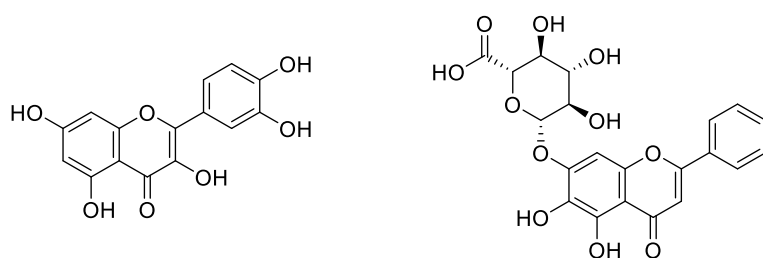
Lopinavir

Ritonavir

989

990 **Figure 10.** Small-molecule therapies that target SARS-CoV-2 M^{pro}.

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Quercetin

Baicalin

992

Figure 11. Structures of quercetin and baicalin.

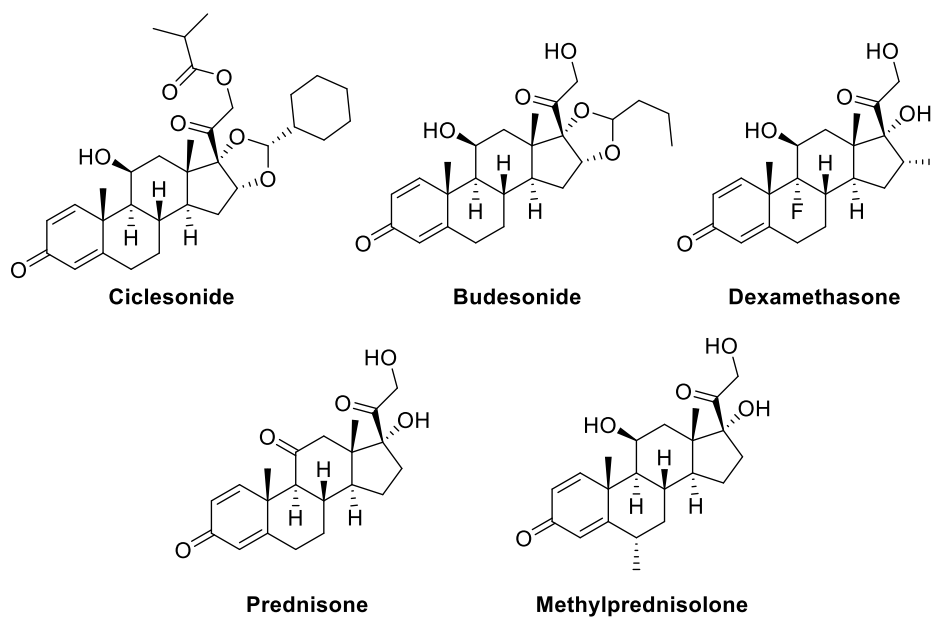


Figure 12. Corticosteroids being assessed for treatment of COVID-19-associated pneumonia.

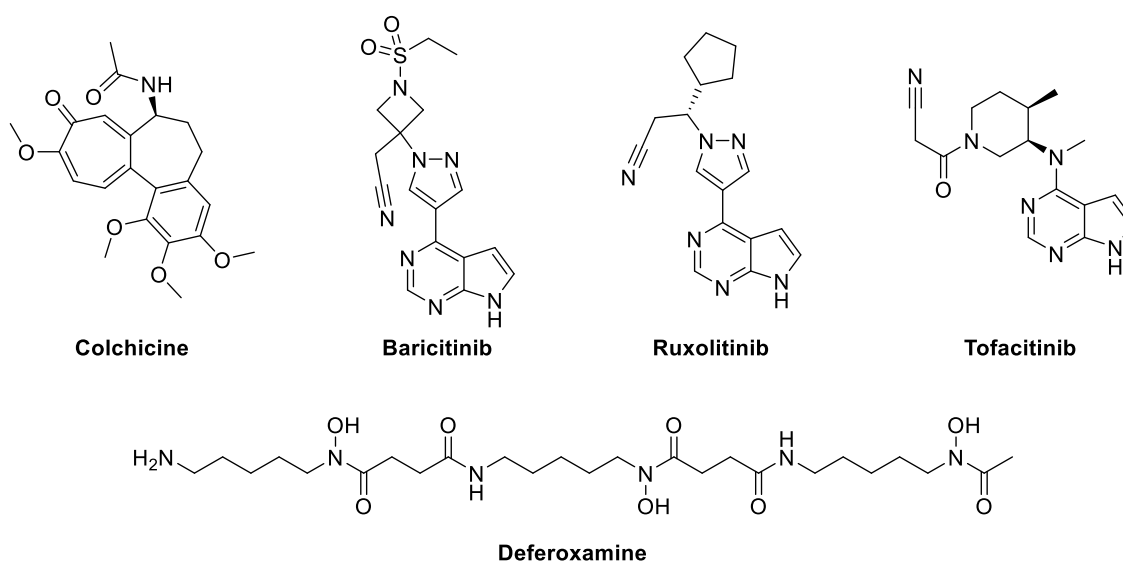
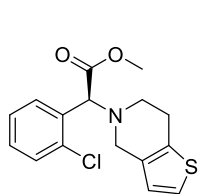
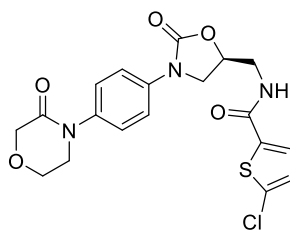


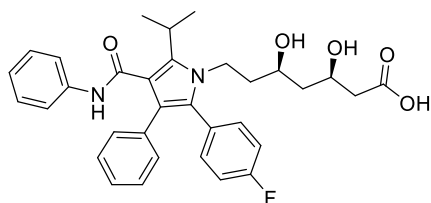
Figure 13. Cytokine production inhibitors being assessed for treatment of COVID-19-associated ARDS.



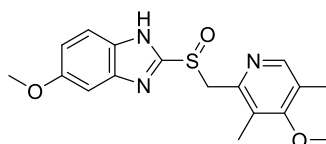
Clopidogrel



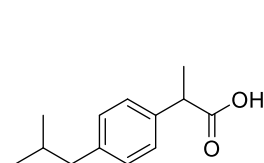
Rivaroxaban



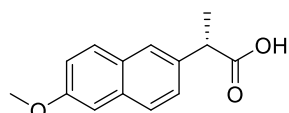
Atorvastatin



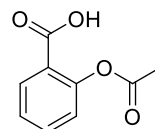
Omeprazole



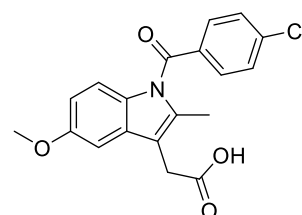
Ibuprofen



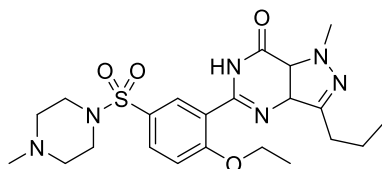
Naproxen



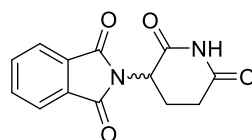
Aspirin



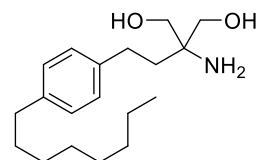
Indometacin



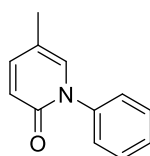
Sildenafil



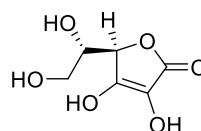
Thalidomide



Fingolimod



Pirfenidone



Vitamin C

Figure 14. Cardioprotective medicines being trialled in COVID-19 patients.

Figure 15. Other drugs being assessed for treatment of COVID-19-associated ARDS.