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COVID-19 therapy: What weapons do we bring into battle?

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ABSTRACT

Urgent treatments, in any modality, to fight SARS-CoV-2 infections are desired by society in general, by health professionals, by Estate-leaders and, mainly, by the scientific community, because one thing is certain amidst the numerous uncertainties regarding COVID-19: knowledge is the means to discover or to produce an effective treatment against this global disease. Scientists from several areas in the world are still committed to this mission, as shown by the accelerated scientific production in the first half of 2020 with over 25,000 published articles related to the new coronavirus. Three great lines of publications related to COVID-19 were identified for building this article: The first refers to knowledge production concerning the virus and pathophysiology of COVID-19; the second regards efforts to produce vaccines against SARS-CoV-2 at a speed without precedent in the history of science; the third comprehends the attempts to find a marketed drug that can be used to treat COVID-19 by drug repurposing. In this review, the drugs that have been repurposed so far are grouped according to their chemical class. Their structures will be presented to provide better understanding of their structural similarities and possible correlations with mechanisms of actions. This can help identifying anti-SARS-CoV-2 promising therapeutic agents.

1. Introduction

The world is facing a huge challenge in the coronavirus disease (COVID-19) pandemic: How to fight an enemy without weapons in terms of therapy? Unfortunately, even before the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) worldwide spread, there were no clinical treatments nor prevention strategies available for any human coronavirus.[1] It is understandable that both society and researchers urge the discovery of new compounds or even of a drug that is commercially available that can be employed by physicians mainly for patients with the extreme presentation of COVID-19. There is also urgency in the discovery of medicine with prophylactic action to prevent the entry of the virus in host cells after exposure. Vaccine research experts already indicate that rescue from SARS-CoV-2 will come from a long but effective journey to produce a vaccine.[2] While this is not a reality, the scientific community, including medicinal chemists and doctors who accompany patients, are trying to identify therapeutic alternatives. This is a meritorious attitude: The commitment with the protection of humanity. Nevertheless, the rigorous feature of science in the discovery of a new drug cannot be disregarded, even during a pandemic and in the face of the urgent demand for a treatment, to avoid eventual mistakes and spurious hope.

The increase in studies related to SARS-CoV-2 during the first semester in 2020 has allowed the rather speedy identification of promising therapeutic targets for both developing immunotherapies and producing/identifying antiviral drugs. It is noteworthy the increase in outbreaks of SARS-CoV (2002) and MERS-CoV (2013), with accelerated production of knowledge on these HCoVs, which has been very useful for ongoing investigations on SARS-CoV-2. One example is the availability of technological devices that allowed the fast sequencing of SARS-CoV-2 genome and the elucidation of a promising antigen target, the S glycoprotein. Nonetheless, the development of a human vaccine can take years, especially because employing emergent technologies requires extensive safety tests and expansion to large scale production in order to assist the world population, as demanded in the case of the COVID-19 pandemic.[3]

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The development of new medicine also demands many years of research that involve stages of reasonable planning, synthesis, structural characterization, formulation of prototypes, preclinical and clinical trials. Therefore, the literature highlights, as alternative treatments for COVID-19, the repurposing of drugs, which is fast and useful in emergencies such as the one experienced today. The repurposing of drugs means the use of broad-spectrum medicine for a new disease, once its metabolic characteristics, doses, potential efficacy and adverse effects are pre-established due to drug studies conducted for their approval.[4,5]

Repurposing of antiviral drugs can be motivated by either (1) Same target - new virus; (2) same target – new indication and; (3) new target – new indication. In the first case, a new virus shows the same therapeutic target than the virus for which the drug was approved. The drug can act through endocyclic vias or DNA polymerase. In the second case, the targeted virus displays an essential protein for the pathogenic process that can be modulated by a marketed drug, which becomes a potential antiviral therapeutic agent. Finally, the third is the case in which an approved drug, with established bioactivity for a path or mechanism, is given a new molecular target essential in the replication of the virus under investigation for new therapies.[6]

Identifying drugs that can be repurposed has its starting point in the techniques of virtual triage and molecular modelling to verify possible interactions between the selected viral targets and the drug structures present in their molecular libraries.[7–9] Such approaches have enabled the identification of molecules with promising results against SARS-CoV-2. In addition to advanced clinical assays for more conclusive information, a number of *in-vitro* investigations have also provided data on drugs to be repurposed against COVID-19. It is important to highlight that, if one compound is active against a viral disease such as COVID-19, there can be a mechanism of action that explains its efficacy and supports its use. Hence, the present article highlights the already known or proposed mechanisms of action of molecules or drugs pointed out as promising, or even tested, in patients with COVID-19. In our opinion, the key for a chemical molecule with antiviral activity might be found on its biological basis or in one of the stages of infection. Thus, before discussing the therapeutic alternatives and its pharmacological characteristics, that include probable antiviral mechanisms, this article presents general information on the SARS-CoV-2 biology, the pathophysiology and symptoms of COVID-19 as well as the features that are indispensable to understand this challenging disease.

2. What do we know about SARS-CoV-2?

Coronaviruses (CoVs) are members of *Coronaviridae* family, *Coronaviridae* subfamily, order *Nidovirales* and they are separated into four genera based on their phylogenetic relationships and genomic structures: *Alphacoronavirus* (αCoV), *Betacoronavirus* (βCoV), *Gammacoronavirus* (γCoV) and *Deltacoronavirus* (δCoV).[1] The last two can infect animals such as birds, pigs and bats,[10,11] whereas αCoV and βCoV are considered human pathogens (HCoVs) usually related to respiratory illness and gastroenteritis. In the past few years, HCoVs have developed rapidly due to their adaptive mutation capacity, high levels of nucleotide substitutions, their efficiency in causing infection in new hosts and interspecies transmission.[12] HCoVs, such as HCoV-229E, HCoV-OC43, HCoV-NL63 and HKU, also commonly identified in different animal hosts, did not draw attention until November 2002, when the coronavirus of severe acute respiratory syndrome (SARS-CoV) emerged in Guangdong province, China.[13] Since then, the now called SARS-CoV has infected over 8000 human beings and caused 774 deaths in 37 countries. In September 2012, the second highly pathogenic human coronavirus arose in Saudi Arabia and spread across Middle Eastern countries.[14] The virus was named the Middle East respiratory syndrome coronavirus (MERS-CoV) and infected 2494 individuals and caused 858 deaths, with a mortality rate of 34%.[10]

SARS-CoV and MERS-CoV are zoonotic βCoV that began to be transmitted through wild animals including bats and dromedary camels, animals that served as their natural hosts. Later, they started infecting humans due to their high pathogenic potential[15] with a distinct lethality for human beings.[16] In December 2019, a new coronavirus emerged in Wuhan, Hubei province of China. It was isolated and sequenced by January 2020 and named SARS-CoV-2.[17] SARS-CoV-2 is associated with an ongoing outbreak of atypical pneumonia (COVID-2019). It has already affected over 8,506,107 people and killed more than 455,231 of those affected in 216 countries as of June 20, 2020.[18]

Biologically, CoVs are positive-sense and single-stranded RNA (ssRNA) viruses, enveloped and with genome ranging from 26 to 32 kilobases (kb).[4] The genome is enclosed by a helical capsid and an envelope with glycoproteins spike (S) forming saliences like a crown, which is responsible for the virus "*corona*" appearance.[1,19] For all CoVs, about two-thirds of the genome are open reading frames (ORFs). In a typical CoV, there are at least six ORFs responsible for the codification of structural and non-structural virus proteins.[20] Among these ORFs of SARS-CoV-2, two of them identified as ORF1a and ORF1b encode the polyproteins pp1a and pp1ab, respectively. Afterwards, these polyproteins are cleaved by two viral proteases, the papain-like protease (PL^{pro}) and the 3 chymotrypsin-like protease ($3CL^{pro}$), yielding 16 non-structural proteins (Nsps) encompassed in genome transcription and replication.[11,21,22] Other ORFs of the virus genome encode structural proteins, including those related to physical structure of viral particles (capsid, envelope), such as the glycoproteins spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins. The N protein has the RNA genome and the S, E and M proteins constitute the viral envelope.[23]

Since the announcement of the pandemic by the World Health Organization (WHO), due to the worldwide spread of SARS-CoV-2, scientists have begun fast and detailed investigations on this coronavirus. The results achieved thus far show that SARS-CoV-2 displays a typical HCoVs structure, once its overall genome sequence, from samples of five patients, presented homology of about 79.5% to sequence of SARS-CoV[24,25] and 50% to MERS-CoV genome.[10] Besides, it was verified 96% of likeness between SARS-CoV-2 genome and a CoV sampled from a *Rhinolophus affinis* bat (BatCoV RaTG13), which suggests bats act as intermediate hosts for SARS-CoV-2.[17]

It is important to keep in mind that many viruses in their natural reservoirs can spill over to humans and other animals due to human activities, including eating habits and urbanization.[1] The absence of caution or barriers between natural reservoirs and human society can lead to the rise of many CoVs and cause severe losses, such as the ones by the current SARS-CoV-2. Therefore, it is important to study this class of virus not only in the event of a pandemic, but because exploring its biological properties allow ourselves to be prepared, through better understanding, to face diseases caused by CoVs infections.

The SARS-CoV-2 broke out rapidly due to the virus adaptation and human-to-human transmission through contact via respiratory droplets generated when an infected person speaks, coughs or sneezes, and a different person inhales the aerosols, which depend on the viral shedding for dissemination.[26] The droplet reaching power varies according to their sizes as visually demonstrated in the experiment performed by Anfinrud et al.[27] These authors also showed that masks can prevent the diffusion of droplets and recommend its use as preventive measure to avoid SARS-CoV-2 person-to-person transmission. Other well-established preventive strategies to mitigate the SARS-CoV-2 spread are washing hands as many times as possible, social distancing and covering the face when coughing or sneezing.[28] These prophylactic procedures are efficient but reinforce the necessity of more studies on the virus biology in order to broaden knowledge and identify opportunities for best combating COVID-19 and improving prevention. It is important to highlight that this is a unique moment for humanity, and it is not easy to adopt and to maintain preventive behaviours against the virus dissemination.[29]

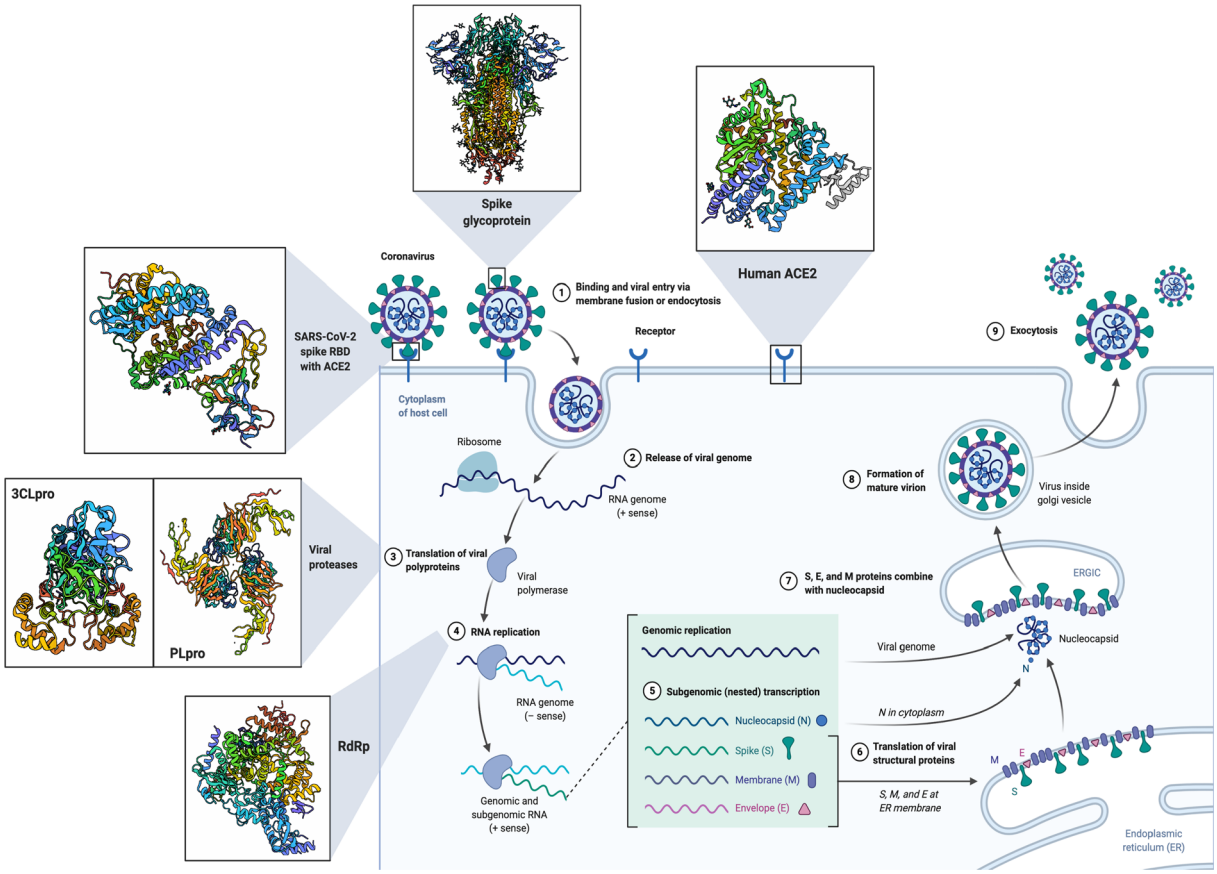

Fig. 1. SARS-CoV-2 life cycle and putative therapeutic targets. SARS-CoV-2 life cycle starts with the activation of protein S and link to the angiotensin-converting enzyme 2 (ACE2) receptor. After host cell entrance by via endosomal, SARS-CoV-2 releases the RNA into the cytoplasm to be translated into viral replicase polyproteins including proteases (3CLpro and PLpro), which cleavage products (nonstructural proteins- Nsps) form the transcription and replication complex. The positive RNA strand is translated into a template of negative strand that allows the synthesis of new genomics and sub genomics mRNAs. These mRNAs are translated and transcribed producing structural and accessory proteins. Next, the virions are prepared at endoplasmic reticulum and Golgi complex, transported through vesicles and finally released by exocytosis. The structures of some promising therapeutic targets available on Protein Data Bank are: (a) SARS-CoV-2 Spike glycoprotein (PDB ID 6VXX); (b) SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID 6M0J); (c) Native Human ACE2 (PDB ID 1R42); (d) papain-like protease (PL^{pro}) of SARS CoV-2 (PDB ID 6W9C); (e) structure of COVID-19 main protease (M^{pro}) in complex with an inhibitor N3 (PDB ID 6LU7); (f) SARS-Cov-2 RdRp in complex with cofactors (PDB ID 6 M71). Figure created with biorender.com.

The diagnosis of COVID-19 was rapidly implemented through the identification of the virus in human samples due to prior understanding of its molecular biology as well as available advances and technology. SARS-CoV-2 infection is generally detected by reverse transcriptase–polymerase chain reaction (RT-PCR) technique or by enzyme-linked immunosorbent assay (ELISA) that enable identification of IgM and IgG immunoglobulins, nucleocapsid (NC) antigens and receptor-binding domain of S (RBD-S).[30–32] Serological tests have 95% of specificity and have become an important research tool on the community extension of COVID-19 to identify potential immune individuals.[31] There is no evidence that the antibodies produced will protect from a new SARS-CoV-2 infection, and people infected respond differently from asymptomatic infection, moving from mild to severe infections. We suppose that explanations for the various presentations of COVID-19 rely on the virus inherent pathogenicity and on the host susceptibility, both of which are described on the next topic.

3. COVID-19 pathophysiology and symptoms

A virus is a small parasite that cannot reproduce by itself (Fig. 1). Once it infects a susceptible cell, however, a virus can direct the cell machinery to produce more viruses.[33] A viral infection is successful when the virus crosses the host cell membrane through binding and fusions with the cellular membrane, a process mediated by specialized viral proteins.[34] In relation to SARS-CoV-2, its life cycle starts with the activation of protein S by the cellular serine protease (TMPRSS2) and trypsin-like protease from airways (TMPRSS11D), to link to the angiotensin-converting enzyme 2 (ACE2) receptor.[4,35] The ACE2 is a counterbalance enzyme responsible for controlling the extracellular liquid volume and arterial pressure of the human body. It is largely expressed in fifteen human tissues, including ciliated bronchial epithelial cells and type II pneumocytes form pulmonary alveoli, the main location of lesions caused by SARS-CoV-2.[36,37]

After ACE2 receptor-binding, a conformational alteration occurs in protein S allowing the fusion between the viral envelope and the host cell membrane via endosomal. Then, SARS-CoV-2 releases the RNA into the cytoplasm to be translated into viral replicase polyproteins pp1a and pp1ab, which are processed by $3CL^{pro}$ and PL^{pro} proteases, respectively. The cleavage products are 16 Nsps that form the transcription and replication complex.[38] Next, the positive RNA strand is translated into a template of negative strand that allows the synthesis of new genomics and sub genomics mRNAs. These mRNAs are translated and transcribed producing structural and accessory proteins. Viral proteins and RNA genomic are put together in virions at endoplasmic reticulum and Golgi complex, finally transported through vesicles and released from the cell host for infecting new cells.[38,39]

The COVID-19 symptomatology starts after the virus is installed in host cells. In general, the symptoms include lasting and high fever, dry

cough, shortness of breath, muscles aches or tiredness, sputum production, headaches, and a small percentage of individuals presented gastrointestinal symptoms such as diarrhoea and vomit.[40] The incubation period of SARS-CoV-2, from exposure to first symptoms, lasts 2 to 14 days. The pre-symptomatic stage lasts from 1 to 3 days (possibly more) before the beginning of symptoms. The post-symptomatic stage lasts at least 7 days after the beginning of symptoms and 3 days after lowering of fever and improvement of respiratory symptoms.[41] There are many unanswered questions such as the duration of potential immunity of both symptomatic and asymptomatic individuals when infected with SARS-CoV-2.[31]

It is noteworthy that efficient strategies to fight the disease should not depend on the symptoms of patients, once asymptomatic or pre-symptomatic subjects can play an important role in the direct and indirect transmission to others, as demonstrated by Arons et al.[42] This investigation reports that half the residents in a nursing facility, who tested positive, were asymptomatic when tested and probably contributed to the transmission to other residents. Thus, control strategies focused on symptomatic residents were not sufficient to prevent transmission once SARS-CoV-2 had been introduced in the facility.

Laboratory exams of infected patients showed alterations in haematology and biochemistry. It was verified the increase of leukocytes and the reduction of lymphocytes; increased D-dimer and erythrocyte sedimentation rate (ESR), prolongation in prothrombin times (PT), followed by increase in bilirubin levels, aspartate transaminase (AST), alanine transaminase (ALT), creatinine, lactate dehydrogenase (LDH), protein C reactive (PCR), hypoalbuminemia (low albumin), microcytosis and thrombocytopenia.[43]

In addition, inflammatory factors that indicate the immune condition of patients, such as interleukins (IL) IL-2, IL-6, IL-7, and IL-10 and the tumoral necrosis factor-α (TNF-α) become elevated. Plasma levels of Granulocyte-colony stimulating factor (GCSF), protein induced by interferon gamma, Monocyte Chemoattractant Protein-1 (MCP-1), macrophages inflammatory protein 1α and TNF-α also display significant increase.[44]

Potential risk factors or comorbidities that can lead to complications of COVID-19 include elderly individuals (specially above 65 years of age), cardiovascular issues, cerebrovascular, chronic pulmonary diseases, immunocompromising, renal problems, hepatic disease, hypertension, diabetes and obesity.[44–49]

There is a notorious concern regard the medicine administered to fight these comorbidities because some of them can lead to greater expression of ACE2, such as treatments for diabetes[48] or hypertension.[50] This may favour or even aggravate COVID-19 infection. These facts justify the urgency of research that contemplate alternative therapeutic targets such as calcium channels blockers for hypertensive individuals as suggested by Fang et al.[48] However, there is little clinical evidence on the risk of treating COVID-19 patients with therapies that induce greater expression of ACE2. Further investigation is necessary to explore whether these medicines inhibit or trigger the viral entry into the cells of an infected host.[51]

A frequent report in epidemiological data regarding the mortality of COVID-19 concerns the sex of individuals, as men are the predominant fatal victims of the disease. Therefore, being of the male sex is considered a bad prognostic factor for infection.[52,53] A possible explanation lies in the relation between gonadal hormones and the expression of ACE2 enzymes or even an alleged Vitamin D deficiency, according to Vignera et al.[54] The latter suggest monitoring of serum levels of testosterone and Vitamin D in infected patients for a better understanding of the different fatality rates between sexes, including the hypothesis that women's hygiene justify a lesser rate of infection.

Understanding the pathogenic effects of SARS-CoV-2 for the different organs affected by the disease has also been object of investigation, such as gut-lung crosstalk.[55] Data from research conducted thus far indicate that the infection caused by SARS-CoV-2 is not only capable of causing pneumonia, but it can also damage other organs such as the heart, the liver, the kidneys and organic systems such as the blood and the immune system.[44,56,57] Patients with the extreme form of the disease frequently manifest lymphopenia,[30,57] hepatic insufficiency[58] and viral sepsis diagnostic,[51] whose complications can be related to the severity of the cases and the mortality of patients.[56,57] There are reports that the eventual death of such patients is due to multiple organ insufficiency, acute respiratory distress syndrome (ARDS), cardiac insufficiency, arrhythmia and renal insufficiency.[56,59] Therefore, great attention is necessary to the disease's potential damage to multiple organs and to therapeutic alternatives to fight COVID-19,[49] given that some of these alternatives can have side effects on organs initially unrelated to the respiratory system, but that may be susceptible to a systemic compromise prompted by the virus once the treatment has begun.

Hence, it is possible to observe the existence of different forms of aggravating the disease.[41] In this regard, Wang et al.[49] recommend the creation of a system to categorize patients with the severe form of COVID-19. Several investigations report that all HCoVs, SARS-CoV, MERS-CoV and SARS-CoV-2 induce exaggerated immune responses in the host, which are associated to the severity of pulmonary pathology and might lead to the development of acute respiratory distress syndrome (ARDS) or death.[57] The incidence of the extreme form of the infection is associated with cytokine storm syndrome, characterized by high plasma concentration of several interleukin, inflammatory cytokine, inflammatory chemokines, among other factors that cause infiltrated inflammatory in the organs.[44,60,61] Survivors of this excessive response by the immune system can develop long-term fibrosis and pulmonary damages that might culminate in functional injuries to these organs, thus reducing the patient's quality of life.[62]

4. SARS-CoV-2 therapeutic targets

During the development of drugs to fight microorganisms, the adoption of strategies that allow the design of molecules to act against specific biological targets of bacteria, parasites or viruses is preferred. Therapies for CoVs can be divided into several categories, based on specific paths: (1) CoVs proteins or functional enzymes that are essential for viral replication; (2) structural proteins of the virus that prevent its binding to the respective receptors in human cells or its assembly process; (3) some viral factor that restores the host's inherent immunity and; (4) host-specific enzymes or receptors, that prevent the entry of the virus in the host cells.[5,63]

So far, structural proteins and enzymes that participate actively in the process of viral replication are the most investigated targets for the development of molecules for anti-CoVs therapies (Fig. 1). Investigations by Wu et al.[5] through bioinformatics, analysed possible SARS-CoV-2 therapeutic targets. The proteins coded by this virus were verified and compared to proteins coded by other CoVs. The results enabled the detection of structural similarities to SARS-CoV, from which it was possible to conduct homology modelling to build 19 proteins for SARS-CoV-2. Among the targets were spike (S) glycoprotein, Nsp (RNA-dependent RNA polymerase - RdRp), enzyme helicase, $3CL^{pro}$ and PL^{pro}, TMPRSS, ORF7a factor and ACE2 presents in the host cells.[5] These targets have pivotal roles in the development of the virus and have great influence on its pathogenicity, hence, some details are provided next.

Molecular modelling showed that spike (S) glycoprotein is a transmembrane protein of approximately 180–200 kDa type I whose *N*-terminal turns to the exterior of the virus and its C-terminal segment turns to the interior of the virus. The typical structure of CoVs is given by the assemble of a bulbous projection of a corolla as trimers of protein S and it is cleaved into two important subunits from the pathogenic perspective: S1 and S2. SARS-CoV and SARS-CoV-2 (S) glycoprotein share about 76% of amino acid identity and enable the entry of the virus in the host cells. Therefore, S glycoprotein present in CoVs has been considered a promising biological target for antiviral mechanisms.[35,64]

The moment when the virus approximates the target cell prompts the recognition by the receptor-binding domain (RBD) in the S glycoprotein of its receptor, which leads to the binding to subunit S1. Next, the subunit S2 allows fusion of viral and cellular membranes, which enables entry in the cell and the release of viral RNA genome.[35,65,66] Some investigations suggest that the strong binding affinity between S protein and ACE2 is essential for viral entry, hence, ACE2 is also relevant for the development of drugs.[5,67] Molecules that bind to the surface of the virus can destabilize the formation of S glycoproteins and interfere both with the trimerization of the protein and with the continuity of the life cycle of CoVs.[68]

Several studies have been conducted on S protein to clarify its SARS-CoV-2 structure and its binding process as well as to evaluate its relevance as target for *in-silico* and *in-vitro* assays on molecules for anti-SARS-CoV-2 therapies. One study conducted by Hoffman et al.[35] investigated how the SARS-CoV-2 S protein facilitates viral entry in the target cells and how this process could be blocked. Results showed that ACE2 is used as receptor for the entry of SARS-CoV-2 in host cells and that the spread of this CoV in the infected host depends on the activity of TMPRSS2 (a cellular serine protease responsible for initiating the binding process between S protein and ACE2). This process can be blocked with clinically approved TMPRSS2 inhibitor. Prior to this, the relevance of TMPRSS2 was highlighted in the dissemination of several types of viruses such as Influenza A and other CoVs, which also makes it a relevant target for COVID-19 therapeutic intervention.[69–75]

Binding between S proteins and ACE2 receptors was corroborated through X-ray crystallography conducted by Lan et al.[66] to elucidate the interaction between the SARS-CoV-2 RBD and ACE2 at a higher resolution. In spite of different interactions with ACE2, the SARS-CoV-2 RBD /ACE2 and SARS-CoV RBD /ACE2 interfaces share a substantial similarity regarding the surface area, the number of interacting residues and the networks of hydrophilic interactions. Such similarity strongly points to a convergent evolution of both SARS-CoV-2 and SARS-CoV RBD structure which improves the binding affinity for the same receptor, the ACE2. The non-conserved RBD regions in S protein, such as subunit S2, could be potential targets for cross-reactive antibodies. Considering RBD as a critical region for receptor binding, antibodies that target the conserved epitopes in the RBD are also good candidates for the development of highly potent cross-reactive therapeutic agents against several species of CoVs, including SARS-CoV-2.[66]

Investigations on ligands obtained from DrugBank 5.1 used molecular Docking to identify target regions in the pockets of the quaternary structure of SARS-CoV-2 S glycoprotein (from Protein Data Bank-PDB). Six pockets present in S glycoprotein deserve further investigation in medicinal chemistry due to suitable features for small molecule binding. Among the six pockets, the eight best ligand candidates from DrugBank were all binding pocket #1, which contained residues of amino acids Proline, Leucine, Lysine, Asparagine, Phenylalanine, Glycine, Threonine, Glutamine, Alanine, Methionine and Tyrosine. One of the best ligands was the drug Saquinavir, an antiviral from the class of protease inhibitors, used in anti-HIV therapy.[68]

Nsps are involved in the RNA transcription, translation, protein synthesis, processing and modification, viral replication and infection of the host. Significant functional proteins, $3CL^{pro}$, PL^{pro}, helicases and RdRp are important targets for the development of small-molecule inhibitors, due to their biological function and vital enzyme active site.[76] Factors Nsp1, Nsp3c and ORF7a are related to assistance to the immune evasion of SARS-CoV-2. Interaction between Nsp 1 and the host ribosomal subunit induce the degradation of mRNA, allowing the virus to develop resistance to the host innate immunity. Binding between ORF7a and Bone marrow matrix antigen 2 (BST-2) inhibits activity and blocks BST-2 glycosylation. These results suggest that all three structures are potential targets for antiviral medicine.[5]

Proteases PL^{pro} and $3CL^{pro}$ mediate the proteolytic cleavage of polypeptides produced by β-coronavirus SARS after genome transcription, thus generating other proteins. The $3CL^{pro}$, known as Nsp5, cleavages several non-structural proteins of importance for viral replication and the maturation of Nsps, which is essential in the life cycle of the virus. Therefore, it is an attractive biological target for that has been inhibited *in-silico* by several antiviral, anti-inflammatory and anti-hypertensive drugs from the database ZINC (FDA).[5] In addition, docking and molecular dynamic studies conducted by Qamar et al.[77] showed that non-toxic natural products formed strong bonds with SARS-CoV-2 catalytic dyad Cis145-His41 of $3CL^{pro}$.

Moreover, the proteinase PL^{pro} is responsible for cleavages of *N*-terminus in the replicase polyprotein to release Nsp1, Nsp2 and Nsp3, which are essential for correcting virus replication significant to antagonize the host's innate immunity. Analysis of the docking model showed that ribavirin formed Hydrogen bonds with residues Gly164, Gln270, Tyr274, Asp303 as well as hydrophobic interactions between Tyr265 and the PL^{pro} residue. These results indicate ribavirin as a powerful PL^{pro} enzyme inhibitor, which means it has promising features for anti-COVID-19 therapy given the inhibition of a likely PL^{pro} therapeutic target.[5]

Helicase (Nsp13) has been identified as a promising target for antiviral drug discovery, particularly against SARS-CoV-2. It is a multifunctional protein necessary for a wide range of biological processes, such as genome replication, recombination and dislocation of proteins related to chromatin and nucleic acid remodelling. For CoVs, helicase is indispensable for viral replication. In studies on molecular modelling, several antibacterial, antifungal and antiviral drugs were analysed and presented elevated affinity to helicase, suggesting it as a good target for SARS-CoV-2 therapy.[5]

RNA-dependent RNA polymerase (RdRp – also nominated Nsp12) catalyses the viral RNA, which performs a key role in the replication/transcription complex of SARS-CoV-2, possibly aided by Nsp7 and Nsp8 complex as cofactor.[5,78] Nsp12 has been studied as potential target for several SARS-CoV and MERS-CoV inhibitors, due to its importance for viral control. Satisfactory results of RdRp inhibition by several ligands were presented in the modelling studies by Gao et al.[78] and by Yin et al.[79] Those ligands included antiviral analogous to nucleotides, such as Remdesivir, which already shows great potential in the treatment of COVID-19 infections. In addition, some non-structural proteins, including Nsp3b, Nsp3e, Nsp7, Nsp8, Nsp9, Nsp10, Nsp14, Nsp15 and Nsp16, also stood out as useful targets due to their significant role in the synthesis and replication of viral RNA.[5]

$3CL^{pro}$ is key enzyme for CoVs, also called Main protease (M^{pro}), that plays a pivotal role in mediating viral replication and transcription, making it an attractive target for anti-SARS-CoV-2 drugs. Such claim is reinforced by studies by Jin et al.[80] after the virtual screening of N3 inhibitor. Results show that N3 **(1)** is a time-dependent irreversible inhibitor of this enzyme and that a stable covalent bond is formed between N3 and $3CL^{pro}$. High-throughput screening (HTS) was applied to 10,000 drugs and drug candidates, demonstrating that Ebselen **(2)**, PX-12 **(3)** and Carmofur **(4)** are all able to covalently bind to $3CL^{pro}$ do SARS-CoV-2, with IC_{50} that varied from 0.67 to 21.4 μM (Fig. 2). It is likely that a part of the hits identified by HTS are bonded to the catalytic cysteine of $3CL^{pro}$ through their sulfhydryl groups. *In-vitro* studies on antiviral activity were performed to corroborate the results. Real Time Quantitative PCR (qRT-PCR) demonstrated that Ebselen and N3 had the strongest antiviral effects at a concentration of 10 μM treatment in SARS-CoV-2 infected Vero cells. After plaque-reduction assay, the dose-response curves suggested that both could penetrate cellular membrane to access their targets. This result strongly supports the hypothesis that developing a single antiviral agent targeting $3CL^{pro}$ or in combination with other therapies could provide an effective first line of defence against all CoVs related diseases.

In relation to SARS-CoV-2 therapy, some of the aforementioned targets have been explored for both new drug proposition as well as for SARS-CoV-2 drug repurposing. Our focus is on this last type, and for each medicine, the putative mechanism of action and viral target will

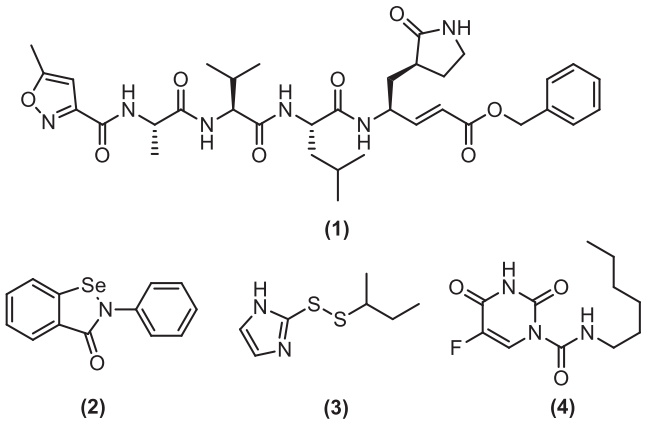

Fig. 2. Chemical structure of proteinase $3CL^{pro}$ inhibitors: N3 **(1)**; Ebselen **(2)**; PX-12 **(3)** and Carmofur **(4)**.

be described trying to find an understandable rational therapy even for an immediate illness situation like COVID-19 pandemic.

5. Drug repurposing for COVID-19

As previously mentioned, SARS-CoV-2 is an enveloped virus, whose nucleocapsid consists of a positive RNA genome surrounded by multiple copies of nucleocapsid protein. This virus, after entry in the host cell, replicates fast the viral genome with new virion production. The RNA replication into the cell host depends on enzymes and substrates for RNA synthesis, such as ribonucleotides (adenine, guanine, cytosine or uracil) that have nitrogenous bases in the purine or pyrimidine classes. Compounds can mimic these chemical structures and interfere with the formation or use of one of these essential normal organism metabolites. The interference is generally prompted by enzyme inhibition in the biosynthetic pathway of the metabolite or by incorporation, as a false building block, into vital macromolecules such as proteins and polynucleotides. So, this class of therapeutic agents is called antimetabolites.[81,82] Diverse antimetabolites have been indicated as promising anti-SARS-CoV-2. They are described next.

5.1. Pyrimidine derivatives

Pyrimidine derivatives are aromatic organic compounds necessary for all life forms. Examples of pyrimidine derivatives are nitrogenous bases cytosine **(5)**, uracil **(6)** and thymine **(7)** (Fig. 3). They are found in DNA and RNA and participate in the metabolic process that involves carbohydrate and lipids.[83,84] These heterocyclic rings share two nitrogen atoms at 1 and 3 positions, but display variations between themselves, such as an amine group at 4-position in the cytosine and a methyl at 5-position in the thymine. From the pharmacologic perspective, nitrogenous bases are investigated as pharmacophores and are found in the structure of many drugs and experimental substances with various activities,[85] such as antitumoral,[86] antibacterial,[87] antiparasitic,[88] and antiviral.[89,90]

Regarding antiviral activity, there are several approved drugs that are classified as pyrimidine nucleotide biosynthesis inhibitors (PNBI) because, after phosphorylation, they are incorporated either into the DNA or into the RNA and inhibit hosts or pathogenic enzymes, such as polymerases.[84] Therefore, the likely mechanism of action of some pyrimidine derivative drugs has been considered for repurposing. Some pyrimidine derivatives with antiviral activity are often formulated as prodrugs. This format solves issues of high polarity in its final structure prompted by the phosphonic acid, which interferes with pharmacological properties and causes low cellular permeability and low oral bioavailability.[90]

5.1.1. 5-Fluorouracil (5-FU)

One compound appointed as potential anti-SARS-CoV-2 is the 5-Fluorouracil **(8)** (5-FU) (Fig. 3), a heterocyclic aromatic amine similar to uracil (U) that presents a fluorine-carbon bond at 5-position. This compound is used in the treatment of oesophageal cancer,[82] stomach cancer,[91] breast and colon cancer.[92] The similarity between 5-FU and uracil allows the direct action on nuclei acid as it is incorporated into the genetic material and inhibits replication.[82] Tests with 5-FU as monotherapy confirmed its failure against any coronaviruses. The reason proposed to such failure relied on the fact that coronaviruses RNA proofreading activities involve a 3′ → 5′ exoribonuclease in the Nsp14, which removes 5-FU during replication and metabolism. Hence, the combination between 5-FU and deoxyribonucleoside and deoxyribose was suggested so that, after its insertion in the RNA, it escapes RNA proofreading and prompt lethality and/or lethal mutagenesis in the virus. Despite the proposition of using a widely marketed drug to treat several types of cancer, which means it has well-established efficiency and safety, no other type of test has been made to confirm its efficacy against SARS-CoV-2. Therefore, further experiments are necessary to explore 5-FU potentialities.[93]

5.1.2. Gemcitabine (GCT)

Another antitumoral drug considered for its anti-SARS-CoV-2 potential is gemcitabine (GCT) **(9)** (Fig. 3), an analogue of deoxycytidine whose pharmacological action is triggered after the intracellular transformation into triphosphate gemcitabine. The latter competes with endogenous nucleoside triphosphates by incorporation into the genetic material, thus inhibiting DNA synthesis.[94] Initially, GCT was developed for antiviral activity, however, initial results caused it to be redirected for anticancer therapy. It became, then, widely used against non-small cell lung cancer, pancreas, bladder and breast cancers as well.[95–97] *In-vitro* analyses of gemcitabine hydrochloride inhibited MERS-CoV and SARS-CoV, with a CE_{50} of 1.2 μM and 4.9 μM, respectively, in addition to low cell toxicity for VERO E6 cells.[98,99] These data are indicative of a possible activity against SARS-CoV-2, but complementary preclinical investigations are necessary before clinical trials. Albeit considered a safe drug under predetermined doses, GCT adverse effects are noteworthy and include myelosuppression and disruption of liver functions.

5.1.3. Baricitinib

In February 2017, the European Union (EU) approved Baricitinib **(10)** as second-line oral treatment for mild to severe active rheumatoid arthritis in adults (Fig. 3).[9] A differential feature of Baricitinib structure is the azetidine ring bearing an ethylsulfonyl, beyond an acetonitrile group at 3-position. The same ring binds to the N atom at 1-position in the pyrazole, which, in its turn, binds to the pyrimidine conjugated to a pyrrole ring.[100] This medicine can modulate human innate and adaptive immune system. Based on this property, presumably, one of the important mechanisms of action of baricitinib in the treatment of rheumatoid arthritis is the inhibition of the IL-6 / JAK1 / JAK2 pathway.[101]

The promising nature of Baricitinib and other small molecule inhibitors against SARS-CoV-2 was pointed by Richardson et al.[9] through *in-silico* tests using Benevolent AI. The authors evaluated 378 compounds to show that sunitinib **(11)** and erlotinib **(12)** inhibit AP2-associated protein kinase 1 (AAK1) interrupting the virus entry to the cells and the intracellular assembly of new viral particles (Fig. 3). Regarding these two antitumor drugs, it is known that sunitinib is an oral oxindole multitargeted kinase inhibitor that inhibits certain tyrosine kinases including vascular endothelial growth factor receptors (VEGFR types 1 and 2), platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT3), glial cell-line derived neurotrophic factor receptor (RET) and the receptor of macrophage-colony stimulating factor (CSF1R).[102] Concerning erlotinib, it was developed as reversible and highly specific small-molecule tyrosine kinase inhibitor that competitively blocks the

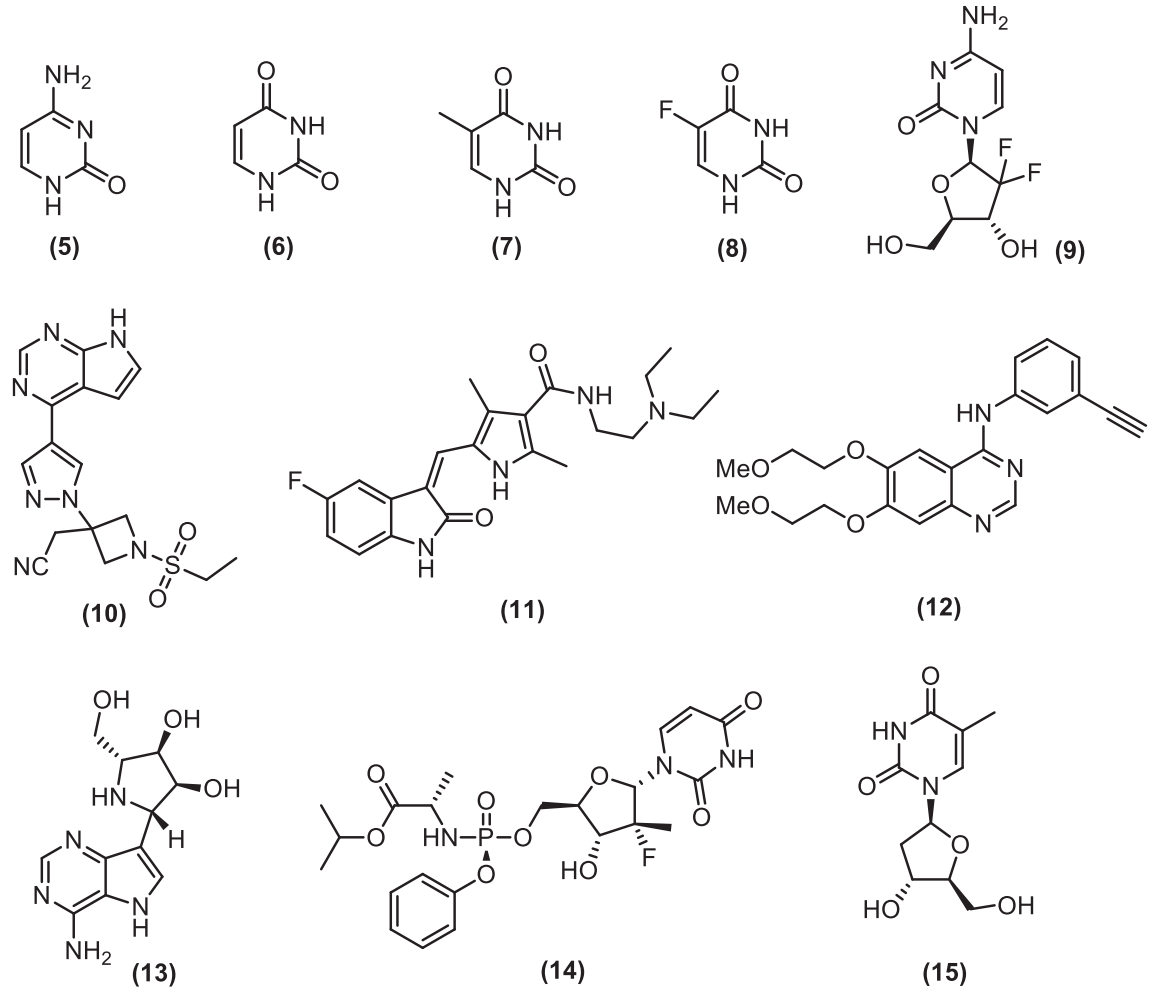

Fig. 3. Chemical structures of pyrimidine nitrogenous bases cytosine **(5),** uracil **(6)** and thymine **(7)** and pyrimidine derivatives drugs: 5-Fluorouracil **(8)**; Gemcitabine **(9)**; Baricitinib **(10)**; Sunitinib (**11**); Erlotinib **(12);** Galidesivir (**13**); Sofosbuvir (**14**); Telbivudine (**15**).

binding of adenosine triphosphate to its binding site in the tyrosine kinase domain of epidermal growth factor receptor (EGFR), thereby inhibiting autophosphorylation and blocking downstream signalling.[103] However, these oncological drugs have serious adverse effects such as diarrhoea, loss of appetite and skin rashes. In addition, high doses of these medications can aggravate those effects.

In relation to baricitinib, its anti-SARS-CoV-2 potential was explained in three ways: AAK1 inhibition like sunitinib and erlotinib; the kinase associated to cyclin G, which is another endocytosis regulator; and the Janus kinase, that inhibits the action of cytosines that triggers the inflammatory process. Because Baricitinib can inhibit AAK1 at the therapeutic dose (2 or 4 mg/day), the drug is indicated for clinical trials. It is highlighted that Baricitinib is not indicated for patients with neutropenia or lymphopenia, once it lowers rates of neutrocytes and lymphocytes, which can lead the disease to progress and increase anaemia. Furthermore, treatment with Baricitinib can reactivate varicella-zoster, herpes simplex and Epstein-Barr viruses. This implicates in a conflict between the potential effect and the adverse effects of Baricitinib against COVID-19 to prevent aggravating the disease and the mortality of patients.[104]

5.1.4. Galidesivir (GSV)

An analogue of adenosine, Galidesivir (GSV) **(13)** is a broad-spectrum antiviral drug that blocks viral RNA polymerase by replacing a natural nucleotide with galidesivir triphosphate. This alteration prompts changes in electrostatic interactions and prevents the formation of the RNA elongated strand.[105,106] Adenosine and GSV differ in that galidesivir has one Carbon at 7-position in the pyrimidine ring and Nitrogen in the ribose ring, whereas adenosine has one Nitrogen in the former and Oxygen in the latter (FIG. 3).[105] It is noteworthy that GSV has not been approved for clinical trial and is an experimental drug in advanced stages of development.[107] GSV was first developed against hepatitis C (HCV) but first clinical trials were conducted to ensure its safety (in healthy individuals) and efficacy against yellow fever. Furthermore, GSV displayed *in-vitro* and *in-vivo* antiviral activity against *Filoviridae, Alphavirus*, bunyavirus, arenavirus, paramyxovirus, flavivirus, orthomyxovirus, picornavirus and SARS and MERS coronaviruses.[11,105,108]

Recent *in-silico* studies have shown the existence of a strong bond between GSV and SARS-CoV-RdRp to demonstrate the capacity of alterations in RNA polymerase, which can eradicate the virus. Although, preclinical and clinical trials are necessary to either confirm or deny this hypothesis.[7] It is noteworthy that investigations have pointed the inactivity of GSV against SARS-CoV-2 at concentrations lower than 100 mM.[109] The existence of antiviral activity against other coronaviruses indicates that more investigations on GSV against SARS-CoV-2 are required to elucidate its potential activity in advanced testing.

5.1.5. Sofosbuvir (SBV)

Next, sofosbuvir (SBV) **(14)** is an example of successful nucleotide prodrug, approved by the Food Drug Administration (FDA) since 2013, against chronic hepatitis C infections. SBV is also combined with other antiviral drugs, such as ledipasvir, velpatasvir and voxilaprevir.[110,111] The structural similarity between SBV (Fig. 3) and uridine allows that drug to act on HCV RdRp, incorporate itself into the viral RNA and

terminate the synthesis of the nucleotide sequence.[81] Structural analysis of SBV revealed that its elevated potential is partly due to the presence of the 5′-phosphate, which terminates the primary enzyme transformation monophosphate inhibitor.[112] The antiviral activity has been explored against other viruses through *in-vitro* and *in-silico* studies and shown potential for inhibiting the dengue virus,[113] yellow fever,[114] zika virus,[115] and chikungunya virus.[116]

Regarding SARS-CoV-2 results, *in-silico* evaluation of SBV indicated the existence of a strong bond to SARS-CoV-RdRp, which confirms the mechanism of this molecule against other viruses and reinforces its potential against COVID-19.[7] This was confirmed by another *in-silico* investigation that suggested repurposing of sofosbuvir/velpatasvir (Epclusa) or sofosbuvir/ledipasvir (Harvoni). Such indication is grounded on the fact that these drugs induce two coronaviruses enzymes and reduce risks of resistance.

Further advantages of the drugs are the minimal adverse effects (headache, tiredness and nausea) and oral administration. The outcomes encourage clinical trials to verify the combined activity of SBV and antiviral drugs to treat COVID-19.[117] Reports of ongoing clinical trials in the Iranian Registry of Clinical Trials (IRCT) regard the efficacy and safety of SBV (46784) monotherapy or plus Velpatasvir (46790), Daclatasvir (46463), Ledipasvir (46567) in patients diagnosed with SARS-CoV-2 showing mild, moderate and extreme symptoms.[118] The data can indicate and, possibly, redirect the repurposing of drugs against COVID-19.

5.1.6. Telbivudine (TBV)

Telbivudine (TBV) **(15)** (Fig. 3) is a thymidine nucleoside analogue used with specific activity against the hepatitis B virus (HBV). It starts acting after phosphorylation by cellular kinases, which results in the active metabolite, Telbivudine 5′–triphosphate, enabling DNA polymerase and inhibiting viral replication. The hydroxyl at 3-position in the sugar β-L-2′-desoxirribose provides specificity to HBV polymerase.[119] Suggesting repurposing TBV to fight COVID-19 was prompted by virtual screening to find drugs that act on viral M^{pro}. Among other results were Ribavirin, TBV and two vitamins, cyanocobalamin (B12) and nicotinamide (B3). Researchers suggest that these four drugs can be combined and used against COVID-19, once they are safe, marketed and approved by the authorities.[8] Notwithstanding, the suggestion of repurposing these drugs requires more information, including on drug interaction parameters. In spite of well-tolerated and safe for monotherapy, associating TBV and ribavirin, another antiviral drug, can increase hepatotoxic activities of TBV.[120,121] It is also important to consider the elevated risk of resistance to TBV, which was verified in preclinical trials against HIV, herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (HSV-4) and adenovirus, in order to be considered for tests with SARS-CoV-2 patients.[120,122]

5.2. Purine derivatives

Purine is a 5 and 6-membered bicyclic ring. Similar to pyrimidines, purine derivatives are essential to life. They are basic constituents of nitrogenous bases adenine (A) **(16)** and guanine (G) **(17)** (Fig. 4).[83,123] Chemically, they differ in the presence of the amino group at 6-position in A **(16)** and at 2-position in the ring in G **(17)**, and by a carboline at 6-position in G **(17)**. Exploring the biological activities of purine derivatives has led to the development of promising candidates to treat cancer,[123] asthma,[124] inflammations and autoimmune diseases,[125] rheumatoid arthritis and various diseases.[126] The antiviral potential of purine derivatives has been pointed out, as for example, against HIV[127] and some of these nucleoside analogues achieved good results against SARS-CoV-2 and MERS-CoV.[128]

5.2.1. Remdesivir (RDV)

Purine derivatives are largely investigated for antiviral activity in general, including SARS-CoV-2. Since the beginning of COVID-19 pandemic, Remdesivir (RDV) **(18)** (FIG. 4) was considered a repurposed drug with promising therapeutic results. RDV is an antiviral agent developed by Gilead Sciences in 2017 under the name of GS-5734. It is an adenosine analogue prodrug first developed to treat Ebola (EBOV), but it presents a broad antiviral spectrum including diverse RNA viruses such as human respiratory syncytial virus (HSRV), MERS-CoV, SARS-CoV and Nipah virus.[129,130] RDV inhibits RdRp after intracellular metabolization, that is, the conversion of GS-441524 monophosphate into the pharmacologically active GS-443902 nucleoside triphosphate. The latter works as adenosine triphosphate (ATP) analogue, which means it competes with the natural ATP substrate and inhibits RdRp causing premature termination of RNA chains during replication.[129]

RDV therapy promising results are described for several viral infections. Regarding EBOV, primary evaluation includes evidence of its efficacy both *in-vitro* (primary macrophage and human endothelial cells) and *in-vivo* (rhesus monkey) by suppressing viral replication and completely protecting animals as clinical symptoms of the disease and pathophysiology markers improved.[131] The safety of RDV for humans infected with EBOV was evaluated in the Democratic Republic of Congo. Results confirmed its safety but did not point RDV as the best therapeutic option, once its mortality rate reached 53% of treated group.[132]

It has been proved that GS-5734 inhibits epidemic and zoonotic HCoV.[133] Inhibition tests for MERS-CoV in human nasal and bronchial airway cells (Calu3 2B4) showed that GS-5734 prevented MERS-CoV replication with maximal inhibitory concentration (IC_{50}) of 0.025 μM and cytotoxicity (CC_{50}) estimated as superior to 10 μM. The assay was conducted on a secondary cell line (HAE) and confirmed the low concentrations necessary for viral inhibition with average values of 0.069 μM (SARS-CoV) and 0.074 μM (MERS-CoV).[133] More recently, *in-vitro* and *in-silico* assays on MERS-CoV demonstrated that administration of RDV plus Interferon beta (IFNb) was more effective than lopinavir/ritonavir-IFNb. Findings from *in-vivo* tests with prophylactic and therapeutic RDV indicate improvement of lung functions, decrease of the severe pulmonary form of the disease and reduction of viral loads and weight loss in murine.[134] Therefore, RDV is a potential drug to treat MERS-CoV infections.

Regarding COVID-19, RDV was used to treat the first US case. The patient was 35 years old, had slight cough, low fever and no evidence of pneumonia at day 4 of the disease. When the clinical symptoms became worse, the patient was given vancomycin and cefepime. As the symptoms worsened, intravenous treatment with RDV was administered at day 7, and vancomycin and cefepime were no longer administered. At day 8, the patient displayed clinical improvement, unfortunately details on the doses and duration of treatment were not provided.[135] After this first case, a clinical trial with a larger number of COVID-19 patients was conducted.[136] This study of efficacy involved 53 patients infected with SARS-CoV-2 who displayed saturation equal or inferior to 94% while they were breathing ambient air or receiving oxygen support. The treatment lasted 10 days, patients were given 200 mg intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. Follow up of patients treated for 18 days indicated that, after the first dose of RDV, 68% improved oxygen support whereas 15% of patients got sicker, 47% were discharged and mortality rate was 13%. The most common adverse events (60% of patients) were increased hepatic enzymes, diarrhoea, rash, renal impairment, and hypotension. Some limitations were noted in the study, such as the small size of the cohort, the short duration of follow-up and the lack of information on the patients. Hence, the efficacy of RDV requires validation by the ongoing randomized, placebo-controlled trials.

One advantage of repurposing RDV is the availability of data on safety and pharmacokinetics, which were obtained previously at phase 1 clinical trial. Intravenous infusions of 3–225 mg were well-tolerated without any evidence of liver or kidney toxicity. RDV demonstrated linear pharmacokinetics within the dose range and intracellular half-life longer than 35 h. Investigations on the ideal dose point to a single

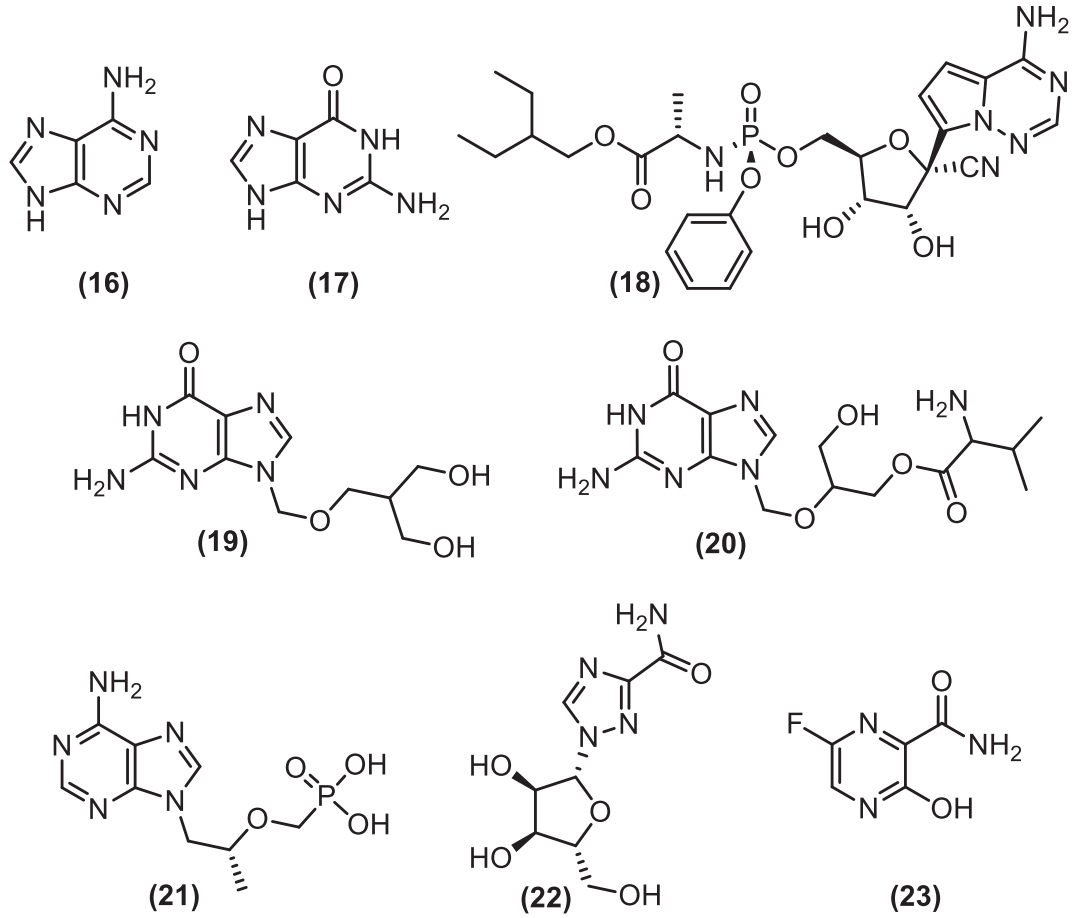

Fig. 4. Chemical structures of purine nitrogenous bases adenine **(16)** and guanine **(17)** and others nitrogen-based analogue drugs: Remdesivir **(18);** Ganciclovir **(19);** Valganciclovir **(20);** Tenofovir **(21);** Ribavirin **(22);** Favipiravir **(23)**.

200 mg loading dose, followed by 100 mg daily. Until the present date, there is no recommendation of hepatic or kidney adjustments, but the drug is not recommended in patients with an estimated glomerular filtration rate inferior to 30 mL/min.[137] Ongoing investigations focus on the safety and validation of RDV for COVID-19. Clinical trial outcomes will confirm its general use to treat COVID-19, once it is already approved by the FDA for extreme cases in children and adults.[129]

5.2.2. Ganciclovir (GCV) and Valganciclovir

In addition to the promising results shown by RDV, other purine analogues have been investigated for SARS-CoV-2. Ganciclovir (GCV) **(19)** also named, according to its chemical structure, 9-(1,3-dihydroxy-2-propoxymethyl) guanine (Fig. 4), is a guanine analogue, similar to acyclovir, except for the bond between the methyl group and one hydroxyl. GCV inhibits the Human Herpesvirus and is also indicated in the treatment of cytomegalovirus infections related to Acquired Immunodeficiency Syndrome (AIDS).[138] GCV is converted into ganciclovir triphosphate by cellular kinase, which inhibits dGTP and disrupts viral DNA synthesis due to substitution of various adenosine bases in the DNA chain.[139] Recently, GCV was used to treat COVID-19 patients in China.[140] The drug was administered with other antivirals, such as oseltamivir and Kaletra. As a descriptive study, the relation between GCV as key factor in clinical outcome of the 99 patients (31% of which were discharges) was not possible.[140] Therefore, GCV efficacy as monotherapy or part of combined therapy is yet necessary for more robust investigations.

Valganciclovir **(20)** (Fig. 4) is the antiviral prodrug of GCV taken by mouth. It is indicated for the same treatments as GCV (cytomegalovirus in people who have AIDS, gastrointestinal disorders related to AIDS). The drug has great bioavailability and is converted by hydrolysis into ganciclovir. Using valganciclovir in its oral form enables clinical treatment and makes patients more comfortable.[141–143] The mechanism of action is the same of GCV.[144] Valganciclovir was computationally evaluated for COVID-19.[5] The assay with the main proteins coded for SARS-CoV-2 allowed the determination of 21 possible binding targets, of which 19 were proteins and 2 host targets. Valganciclovir, one of the drugs used in the study, was presented as a possible anti-SARS-CoV-2 therapeutic drug due to its high binding affinity to two well-established viral targets. The first target was PL^{pro}, indispensable enzyme in viral replication; the second, RdRp, conserved Nsp12 in coronavirus, which is vital for its replication/transcription. Therefore, valganciclovir could be a significant antiviral drug to treat SARS-CoV-2. But there are no clinical reports on valganciclovir used to treat COVID-19 in addition to what has been reported about GCV.[140] Hence, its efficacy is yet to be confirmed as anti-SARS-CoV-2 therapeutic.

5.2.3. Tenofovir (TFV)

Tenofovir (TFV) **(21)** is another adenine analogue pointed as promising COVID-19 therapeutic (Fig. 4), it is also called Tenofovir disoproxil fumarate or alafenamide Tenofovir (TAF). Approved by the FDA in 2001, TFV is a prodrug used to treat HIV and cases of nucleoside resistance.[145] TFV is an analogue reverse-transcriptase inhibitor (NtRTI). Inside cells, TFV is phosphorylated and competes with deoxyadenosine 5′-monophosphate (d-AMP), thus preventing the formation of DNA. Once incorporated into a growing DNA strand, it causes premature termination of DNA transcription and prevents viral replication.[145,146] Modelling and docking studies evaluated the antiviral effects of TFV and verified a strong bond to SARS-CoV-RdRp, which can

disrupt this polymerase and terminate the viral infection.[7] However, *in-vitro* tests showed that TFV lacks apparent antiviral effect at concentrations inferior to 100 μM for SARS-CoV-2.[109]

In spite of lukewarm *in-vitro* and *in-silico* outcomes, an ongoing clinical study on TFV (ChiCTR2000029468), expected to end in June 2020, aims at assessing the effect of the combination Tenofovir + emtricitabine (cytidine analogue) related to LPV/r in COVID-19 patients.[130] In addition to the efficacy of treatment, clinical trials can validate the prevalence of adverse effects related to the toxicity of TFV in patients. TFV is also a powerful nephrotoxic drug causing damage to proximal tubular cells. In spite of that, interrupting the treatment is sufficient to improve adverse effects, which makes monitoring of patients essential.[144]

5.3. Others nitrogenous bases analogues

Heterocyclic compounds with different heteroatoms such as Nitrogen, Sulphur and Oxygen can present different pharmacological properties. One such property is to serve as analogue of nitrogenous bases of nucleic acids, such as triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms. This aromatic ring can assume two isometric forms, 1,2,3-triazole and 1,2,4-triazole. The former is stable under acid and basic conditions and becomes more reactive when binding to electronegative elements.[147,148] Triazoles are important and stand out for their various biological activities, such as anticancer,[149] antituberculosis,[150] anti-inflammatory,[151] antimicrobial,[152] and antiviral.[153] Specifically for the latter action, triazole-based derivatives have shown promising *in-vitro* activity against coronavirus, probably by $3CL^{Pro}$ inhibition.[154]

5.3.1. Ribavirin

Ribavirin **(22)** (Fig. 4) is a powerful triazole-based antiviral analogue to guanosine. It presents a wide range of pharmacological activities related to several viruses, for instance: herpes simplex virus, human immunodeficiency (HVI-1), influenza, respiratory syncytial (RSV) and hepatitis C.[148,155] The drug was initially used in 1980 to treat syncytial virus in children, generally combined with Interferon (INF). However, ribavirin treatment presents undesirable adverse effects, like lowering of haemoglobin, which limit clinical use.[156] Its action mechanism relies on the inhibition of enzyme inosine monophosphate dehydrogenase, necessary in the synthesis of guanosine triphosphate, which prevents viral DNA and, mainly, RNA replication. The necessary concentration for *in-vitro* inhibition of RSV and influenza ranges from 3 to 10 μg/mL.[157] Because of the range of antiviral actions, ribavirin has been thoroughly investigated as an alternative for SARS-CoV, MERS-CoV and, most recently, SARS-CoV-2 treatment.

Falzarano et al.[158] investigated the effects of Interferon-α2b and ribavirin in the replication of nCoV isolate hCoV-EMC/2012 replication in Vero and LLC-MK2 cells. IFN-α2b displayed complete cytopathogenic effect (CPE) at 1000 U/ml and above, whereas ribavirin presented complete CPE at 200 μg/ml and above. The IC_{50} of IFN-α2b and ribavirin was subsequently determined to be 58.08 U/ml and 41.45 μg/ml, respectively. Tests against LLC-MK2 cells were also conducted. IFN-α2b, at the maximum concentration tested (2000 U/ml), reduced infectious titers by 3.97-log. On the other hand, ribavirin treatment, at 200 μg/ml or higher, reduced infectious virus below the detection threshold of 13.7 $TCID_{50}$/ml. Next, these drugs were tested in combination to determine whether one compound would augment the activity of the other. *In-vitro* cell combined treatment lowered the threshold at which a decrease in CPE was noted. For Vero cells, the absence of CPE was verified at and above 125 U/ml IFN-α2b and 25 μg/ml ribavirin. This represents an 8-fold decrease of IFN-α2b and 16-fold decrease of ribavirin. These data suggest that combining IFN-α2b and ribavirin is a likely an alternative treatment.

Tests of ribavirin against SARS-Cov-2 were conducted either *in-silico* or *in-vitro*. Wang et al.[159] conducted an *in-vitro* evaluation on the efficacy of seven antiviral drugs, including ribavirin, against a SARS-CoV-2 clinical isolate. Vero E6 cells were infected with nCoV-2019BetaCoV/Wuhan / WIV04 / 2019 at a Multiplicity of Infection (MOI) of 0,05 for different concentrations of the drugs. Results showed that high concentrations of ribavirin were necessary to reduce viral infection, with EC_{50} = 109,50 μM and CC_{50} > 400 μM. A docking study by Elfiky[160] evaluated the interaction of anti-HCV drugs and RdRp SARS-CoV-2. In addition, Wu et al.[5] also conducted *in-silico* evaluation of ribavirin against PL^{pro}. It was verified that ribavirin bonds to the enzyme active site similar to other SARS-PL^{pro} inhibitors. The formation of hydrogen bonds and π–π stacking were also predicted. These findings suggest ribavirin as a powerful PL^{pro} inhibitor. Nonetheless, investigation on triazole derivatives for anti-SARS-CoV-2 therapy are still preliminary.

5.3.2. Favipiravir (FPV)

On the other hand, Favipiravir (FPV) **(23)** (Fig. 4) is a prodrug, approved in 2014 in Japan, to treat cases of influenza A and B that displayed resistance to first line drugs. It has provided results that indicate a promising character and is currently undergoing clinical trials against COVID-19. Its antiviral efficacy has also been investigated in different countries to fight Ebola and Lassa, for example. The molecular structure of the drug consists of a pyrazine heterocyclic ring with fluorine at 5-position, carboxamide at 3-position and a double bond between oxygen and Carbon 2, which renders its analogue to guanine **(17)**.[161,162] The metabolization of the prodrug into its active form, favipiravir-ribofuranosyl-5′-triphosphate, requires intracellular ribosylation and phosphorylation.[162] FPV therapeutic targets are RdRp enzymes, necessary in viral transcription and replication, and its inhibition blocks synthesis of viral RNA for a spectrum of viruses, including human coronavirus. Thus, it is a promising drug against SARS-CoV-2.[107]

A prospective randomized, controlled, open-label multicentre trial involving 236 adult patients with COVID-19 was conducted to compare FPV (therapy dose of 1600 mg*2/first day followed by 600 mg*2/day) and Arbidol (200 mg*3/day) for 10 days. There was no significant improvement in the clinical recovery rate at day 7. It is important to highlight that FPV improved latency to relief for pyrexia and cough. Adverse effects were the elevation of uric acid.[163] This investigation allowed the National Medical Products Administration in China to approve, in March 2020, FPV as the first anti-COVID-19 drug in the country.[164]

A different investigation compared patients treated with FPV plus interferon inhalation to LPV/RTV. Patients under FPV therapy responded better to the progression of the disease with accentuated viral depuration. Also, the incidence of nausea and vomit was higher for LPV/RTV.[165] In addition to these clinical trials, the antiviral activity of FPV against SARS-CoV-2 was also evaluated but no clear antiviral effect was noted for doses lower than 100 μM.[109] Albeit its relative safety and efficacy, information obtained thus far are inconclusive regarding FPV for anti-SARS-CoV2 activity. Signs of clinical improvement of patients reinforce the need for monitoring outcomes of current clinical trials as they can elucidate the role of FPV in the fight against COVID-19.[166]

5.4. Peptide derivatives and analogues drugs

5.4.1. Lopinavir/Ritonavir (LPV/RTV)

Numerous drugs derived from carboxylic acid under investigation are considered promising to fight COVID-19. The combination lopinavir **(24)**/ritonavir **(25)** (Kaletra) is the most outstanding (Fig. 5). These are antiretroviral drugs often used in combination to treat HIV patients because ritonavir increases concentrations of lopinavir in the body. Also, the combination of both drugs is valuable given their availability in the market and the possibility of immediate prescription.[167] The mechanism of action implicates protease inhibition which consequently interferes with HIV synthesis and replication.[168]

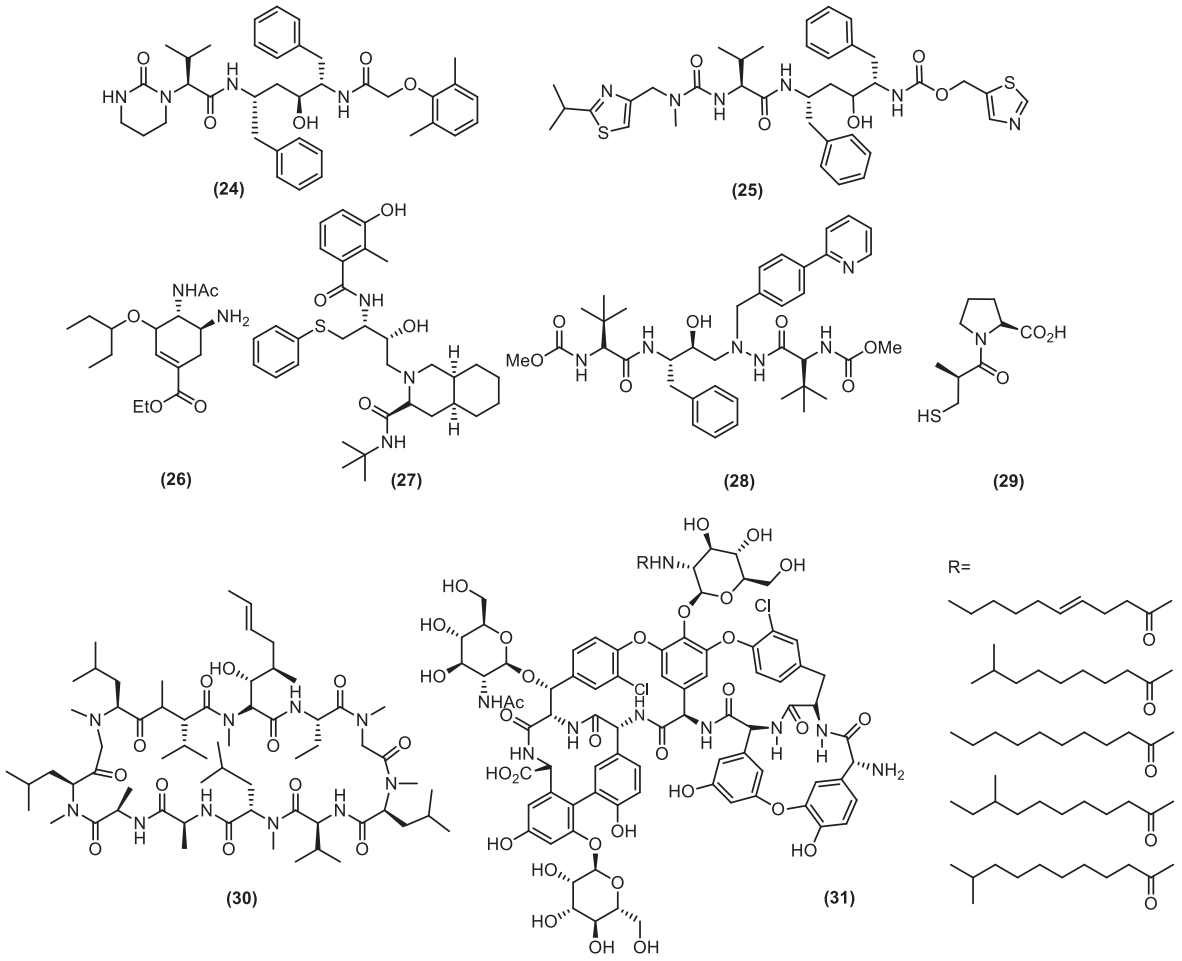

Fig. 5. Chemical structures of peptide derivatives, amino acids and analogues drugs: Lopinavir (**24**); Ritonavir (**25**); Oseltamivir (**26**); Nelfinavir (**27**); Atazanavir (**28**); Captopril (**29**); Ciclosporin A (**30**), Teicoplanin (**31**).

There are several studies on the use of ritonavir/lopinavir to treat SARS-CoV-2 infection, once these drugs have had positive results against SARS-CoV and MERS-CoV. After an outbreak of SARS-CoV, Chu et al.[169] conducted a study with positive outcomes to lopinavir/ritonavir treatment, like lesser incidence of death and acute respiratory syndrome, decreasing viral load and increased peripheral lymphocyte numbers. A different study conducted by Chan et al.[170] consisted of an *in-vivo* analysis of the effects of lopinavir/ritonavir on MERS-CoV in common marmoset. Four groups were established: control, lopinavir/ritonavir treatment, Interferon-Beta-1b and; mycophenolate mofetil. The lopinavir/ritonavir group achieved better clinical results than the control group, such as limited weight loss, stabilization of temperature, little pulmonary infiltration and smaller viral load. The outcomes are corroborated by a Korean case study with an individual of 64 years of age, positive for MERS-CoV and treated with LPV/ritonavir by mouth (lopinavir 400 mg/ritonavir 10 mg 2*day), ribavirin and IFN-2a.[171] The patient displayed absence of fever and MERS-CoV at day 9 of treatment, in a respiratory sample, achieving full recovery.

A recent randomized clinical assay was conducted in the city of Wuhan, China, with 199 adult patients infected with SARS-CoV-2, saturation inferior to 94% and ratio of partial pressure arterial oxygen and fraction of inspired oxygen inferior to 300 mmHg. Patients were divided into two groups: the first was treated with lopinavir/ritonavir (400 mg and 100 mg, respectively) and the second received the standard treatment. Both the mortality rate (19.2% LPV/RTV and 25% standard treatment) and the percentages of detectable viral RNA and time of the treatment were similar in both groups. The total time of treatment was one day shorter for LPV/RTV. Also, gastrointestinal adverse effects were noted in LPV/RTV alone, which discourages use. Notwithstanding, it is noteworthy that treatments began at a late stage of the disease and a relatively high concentration of lopinavir was used to inhibit viral replication.[167,172]

Different researches also focused on the administration of LPV/RTV with other drugs to improve their efficacy in COVID-19 patients. A randomized clinical assay in six hospitals in Hong Kong conducted by Hung et al.[173] investigated whether the administration of LPV/RTV plus interferon beta-1b and ribavirin could present better outcomes than the treatment with LPV/RTV alone. The 127 adult patients were randomly divided into two groups: the combination group was given LPV/RTV (400 mg/100 mg respectively) every 12 h, ribavirin (400 mg) each 12 h and subcutaneous injections of 1–3 doses of interferon beta-1b (1 mL) in alternate days. Control group was given lopinavir/ritonavir (400 mg/100 mg respectively) every 12 h. Both groups were medicated for 14 days. The treatment that combined the three drugs suppressed viral loads in all clinical samples (nasopharyngeal, saliva from the throat, back of the oropharyngeal and faeces) after 8 days of treatment whereas the control group suppressed viral load after 12 days of treatment in average. The triple combination also achieved relief of symptoms at day 4, as well as reduction of IL-6 levels and shorter hospital stays. Adverse effects in both groups involved diarrhoea and vomiting. Therefore, the therapeutic efficacy of the triple combination was confirmed, and demands clinical trials. The mechanism of actions responsible for the good results of LPV/RTV against SARS-CoV-2 are not fully elucidated. The *in-vitro* assays that analysed the effects of LPV/RTV and two coronavirus

proteases, endopeptidase C30 (a homo-dimer with no ligand, built by taking PDB:4MDS $3CL^{pro}$ as template) and papain like viral protease (PLVP), suggest that effects of Kaletra are related to protease C30 inhibition with consequent antiviral effects through inhibition of SARS-CoV-2 protein synthesis.[174]

5.4.2. Oseltamivir

Oseltamivir (Tamiflu) **(26)** is an antiviral used to treat influenza virus A and B (FIG. 5). It is indicated for adults, children and infants with clinical symptoms for two days at least. The drug is available as oseltamivir phosphate prodrug. It is converted in the liver into the active metabolite oseltamivir carboxylate. Its mechanism of action inhibits neuraminidase, which are glycoproteins that help new virions to exit the cell and prevents intercellular viral transmission. The virions remain on the surface of infected cells, trapped in the respiratory secretion. Then, oseltamivir disrupts viral dissemination in the respiratory system and reduces the time of infection.[144,175] Because of that mechanism of action, oseltamivir has been widely investigated and assessed in COVID-19 clinical trials. It is one of the most evaluated drugs for both monotherapy and combine therapy[130,176] because the outbreak of COVID-19 in China happened at the same time the flu reached its apex. Hence, the proportion of patients treated with oseltamivir before the discovery of SARS-CoV-2.[137] One research involving 1.099 patients infected with SARS-CoV-2 from different hospitals in China identified that 35,8% of patients were treated with oseltamivir. However, the study presented several limitations, including the absence of complete data on patients, which hinders the publication of concrete information on the efficacy of oseltamivir.[46]

According to Yan et al.[141], a 71-year-old woman in China presented positive results for combined treatment with oseltamivir and LPV/RTV, testing negative for viral infection after 48 h. A different study by Chen et al.[140] in the city of Wuhan, China, monitored 99 patients, who were mostly 55-year-old-men, with pneumonia symptoms confirmed as COVID-19. About 75% of these patients were treated with a combination of oseltamivir (75 mg each 12 h oral), ganciclovir (0.25 g each 12 h, intravenously) and Kaletra (500 mg*2/day, oral) for 3–14 days. Most patients were also treated with antibiotics for 3–16 days and 13 patients were on mechanical ventilation. Finally, 31 patients were discharged, 11 deceased, and the others remained hospitalized. Results do not express clearly the efficacy of oseltamivir. Therefore, more studies are to be conducted to confirm its efficacy against COVID-19.

An *in-vitro* study using molecular docking focused on the binding properties of SARS-CoV-2 protein structures to 61 antiviral agents, including oseltamivir. The study showed that 37 molecules form bonds to SARS-CoV-2 crystal proteins. However, data did not show oseltamivir as the best structure because Lopinavir, Asunaprevir and Remdesivir interacted with more than two protein structures in the virus. Hence, they are likely more promising than oseltamivir.[177] Notwithstanding, we suggest further look into oseltamivir against other enzyme targets since different studies achieved positive results regarding its use as anti-SARS-CoV-2.

5.4.3. Nelfinavir

Nelfinavir **(27)** (Fig. 5) is a safe anti-retroviral drug largely used for HIV-1 protease inhibition with strong *in-vivo* activity.[178] Generally, Nelfinavir is combined with other anti-retroviral medication as part of a highly active antiretroviral therapy (HAART) that reduces significantly the viral load by increasing cell number to 200 mm^{-3} CD4(+) lymphocytes. The drug is prescribed for children, young individuals, adults and pregnant women.[179,180] Nelfinavir and its active metabolite M8 strongly bind to serum proteins, displaying optimal tissue distribution. A frequent adverse effect is light to moderate diarrhoea, reported for 15–20% of patients.[179] The SARS-CoV outbreak in several countries triggered the search for antiviral drugs active against the disease. Among the 24 drugs likely to inhibit SARS-CoV, nelfinavir stands out in all assays.[180] The mechanism of action suggested for nelfinavir involves preventing SARS-CoV replication after its entry in the host cell and disrupting virion production. Based on results from previous studies as well, nelfinavir was considered a likely therapy for COVID-19 after its indication for clinical trials as a promising anti-SARS drug.

Recently, 1903 drugs were evaluated for their binding affinity to SARS-CoV-2 M^{pro}.[181] Among the compounds, 15 drugs were selected based on the docking score and three-dimensional (3D) similarity to the available M^{pro} inhibitors. Consequently, 10 additional models of SARS-CoV-2 M^{pro} were generated and docked against those 15 drugs. This revealed 6 drugs with good binding modes: nelfinavir, praziquantel, pitavastatin, perampanel, eszopiclone, and zopiclone. Nelfinavir was identified as the best drug with predicted binding free energies of -24.69 ± 0.52 kcal/mol by MM/GBSA and -9.42 ± 0.04 kcal/mol by SIE, respectively. In addition, the binding model of nelfinavir in its docking complex turned out to be very similar with that of the original ligand (TG-0205221), which inhibits M^{pro}, and is able to form 3 hydrogen bonds similar to its original inhibitor (GLU-166 and GLN-189). The result suggests that electrostatic interaction performs an important role in the bond between nelfinavir and the potential target M^{pro}.

5.4.4. Atazanavir

Atazanavir **(28)** (Fig. 5) is an antiretroviral drug protease inhibitor used to treat HIV infections with *in-vitro* inhibitory concentration of 2,6–5,3 nmol. Compared to other protease inhibitors, atazanavir has the advantage of allowing a daily posology regimen with a favourable metabolic profile and low frequency of adverse effects.[182,183] Several HIV-1 resistant to protease inhibitors are still sensitive to *in-vitro* atazanavir, which is considered safe and well tolerated.[184] The atazanavir acts to inhibit HIV-1 protease, which is indispensable in the processing of polyproteins precursors of viral structures and prevents the formation of infectious and mature viral particles.[182]

The good activities reported for this drug as well as the search for safe and fast therapy for COVID-19 have prompted investigations on atazanavir. Marketed drugs that could act on the viral components of SARS-CoV-2 were analysed by Beck et al.[185] through a model of drug-target interaction called Molecule Transformer-Drug Target Interaction (MT-DTI). The binding affinity of 3.410 FDA-approved-drugs against $3CL^{pro}$ proteinase, RdRp, helicase, exonuclease 3′–5′, endoRNAse and SARS-CoV-2 2′-O-ribose methyltransferase. Results suggested atazanavir as the best drug because of its strong binding affinity to proteinase $3CL^{pro}$ (K_d 94.94 nM), RdRp (K_d 25,92 nM), helicase (K_d 25,92 nM), 3′-*para*-5 'exonuclease (K_d 82,36 nM), 2′-o-ribose methyltransferase (K_d de 390,67 nM), and endoRNAse (K_d 50,32 nM). Therefore, it is likely that atazanavir can inhibit all subunits in the SARS-CoV-2 replication complex at the same time.

The potential of atazanavir was supported by computational assays for SARS-CoV-2 M^{pro}. Interactions between the aromatic ring and M^{pro} amino acid residues (Cys44, Met49, Leu50, Tyr54 e Cys145) and between the amide and amino acid Cys145[186] were established through hydrogen bonds. Borgio et al.[187] triaged 23 clinically approved antiviral SARS-CoV-2 helicase inhibitor drugs through molecular docking based on binding affinity and binding free energy. Results suggest that atazanavir is a potent helicase inhibitor with affinity of −11,28; score S: −9,32 kcal/mol. Furthermore, the formation of hydrogen bonds between protein residue GLN331 and the drug was observed. Another relevant characteristic of atazanavir is meeting the Lipinski rule of five as the partition coefficients, and hydrogen bond acceptors and donors. Given the results reported in the literature, *in-vitro*, *in-vivo* studies and clinical trials are recommended to confirm efficacy and safety against COVID-19.

5.4.5. Captopril

Captopril **(29)** (Fig. 5) is an angiotensin-converting enzyme inhibitor (ACEi). It is a zinc metallopeptidases inhibitor that converts angiotensin-I into angiotensin-II, an essential function that regulates arterial pressure. It is predominantly indicated as vasodilator in patients

with cardiac insufficiency. This drug was suggested as potential antibiotic capable of inhibiting zinc succinyls/dipeptidase by blocking its zinc catalytic center.[188,189] Tolerance to captopril has been largely investigated; its single dose by mouth is well-established and confirms the pharmacological activity in the short term (10–30 min) at the cellular level. This capacity is related to captopril transport mainly through plasma proteins such as albumins with absorption rate between 70 and 75%. Reported adverse effects are neutropenia, proteinuria, dysgeusia and cough, but less frequent for low doses.[188,189] Some investigations have suggested captopril as possible COVID-19 treatment. Serafin et al.[99] indicated captopril as potential for inhibiting the bond between human SARS-CoV-2 and ACE2 and reduce severe pneumonia symptoms.

In-silico studies using molecular docking were conducted with FDA-approved drugs capable of binding to the main active site in proteinase $3CL^{pro}$.[188] Two drugs were identified as ligands for the enzyme active site: captopril and disulfiram. The former binds to the active site at the same position of N3 inhibitor (a standard inhibitor that reacts irreversibly in the same site with $3CL^{pro}$ Cys145). It is, thus, suggested that captopril binds to the same site of N3, obstructing the function of Cys145–His41 catalytic dyad. Captopril probably inhibits the enzyme in two stages. Initially, it establishes non-covalent bonds to sites in the enzyme targets, then, a reaction takes place between the critic groups, which results in a more stable inhibitor complex. The hypothesis is that captopril can bind covalently to $3CL^{pro}$ Cys145. Although the potential of captopril on the enzyme has been demonstrated, therapeutic use against COVID-19 is controversial, once the drug induces overexpression of ACE2 – the main receptor used by SARS-CoV-2 to entry the cells. Therefore, combination with other drugs, such as angiotensin-II receptor blockers, needs analysis to clarify the effects of captopril in COVID-19 treatment.

5.4.6. Ciclosporin A (CsA)

The cyclosporin A (CsA) **(30)** (Fig. 5) is isolated from the fungus *Beauveria nivea* and was approved for use by the FDA in 1983. This drug has been used for decades to prevent organ rejection and to treat T cell-associated autoimmune diseases such as Behcet's disease, psoriatic arthritis, lupus nephritis, rheumatoid arthritis, systemic lupus erythematosus or interstitial lung disease. Such drug exerts its immunosuppressive function and anti-inflammatory effects by inhibiting the transcription of genes required for T cell proliferation, notably interleukin-2.[190–192] Due to the severity of COVID-19, CsA can be potential to prevent hyperinflammation-induced lung injury.[193]

In this regard, it is known SARS-CoV Nps1 induces the expression of interleukin-2 via nuclear factor of activated T cell (NF-AT) activation,[194] which can trigger the cytokine storm seen in patients with severe COVID-19 status.[137] Another advantage presented by CsA in relation to other anti-inflammatory drugs is its already known anti-CoV action against all genus, including SARS-CoV,[194–196] at low and non-cytotoxic micromolar concentrations verified in cell culture assays. This antiviral property is thought to be mediated by the inhibition of cyclophilin-A-dependent viral assembly as well as inhibition of the NF-AT pathway or even by genetic or pharmacological specific inhibition of cyclophilin-D, hindering the viral replication.[194,197]

As already reported, SARS-CoV and SARS-CoV-2 are very similar (79.5% sequence identity).[17] In this regard, drugs that show antiviral activity against SARS-CoV presumably have the same pharmacological anti-SARS-CoV-2 properties. Based on this premise, Jeon et al.[198] conducted an *in-vitro* study with 48 FDA-approved drugs utilizing Vero cells. Each drug was added to the cells prior to the virus infection. At 24 h after the infection, the infected cells were scored by immunofluorescence analysis with an antibody specific for the viral N protein of SARS-CoV-2. Among the 48 drugs evaluated, the authors indicated that 24 of them, including CsA, had potential activity against SARS-CoV-2, given IC_{50} values between 0.1 and 10 μM. Another study by Sayad & Sayad[199] performed a gene-compound interaction, using the RGD database to search for any drugs that mimic the SARS-CoV-DeltaE top 10 genes upregulation and downregulation patterns. They found CsA to be a perfect match because it upregulates all nine upregulated genes and downregulates the only downregulated gene. Hence, the authors declared that CsA showed the same upregulation/downregulation effect on the top 10 genes as SARS-CoV without the envelope (E) gene. The authors conclude that CsA is a strong candidate for a clinical trial to test his ability to prevent the spread of COVID-19 or to flatten his epidemic curve.

On the other hand, there are concerns regarding the capacity of CsA to increase ACE2 shedding and, consequently, to augment SARS-CoV-2 infection by increment the ACE2 upregulation.[200] Furthermore, the CsA has serious side effects, which can cause hyperlipidaemia, gingival hyperplasia, nausea, vomiting, abdominal pain, headache, susceptibility to infections, triggering of cancer development, blood pressure increase, nephrotoxicity, and immune suppression. Its nephrotoxic effect is dose and duration dependent.[201] Therefore, it is not clear whether CsA may mitigate or aggravate the SARS-CoV-2 infection, since there is no CsA clinical studies published up to now, even has been suggested that low-dose CsA can be useful for patients presenting SARS-CoV-2-induced cytokine storm.[200]

5.4.7. Teicoplanin

Teicoplanin **(31)** (Fig. 5) is an antibiotic used against gram-positive bacteria with 5 major compounds at different side chains. It prevents polymerization of peptidoglycans and inhibits the development of the cell-wall, thus prompting cell death.[202] It is a big molecule that has displayed antiviral activity on an early stage of the viral life cycle by inhibiting the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes thereby preventing release of viral RNA and replication. This compound has already shown inhibitory activity against Ebola virus, MERS-CoV and SARS-CoV.[202]

Recent investigations have suggested teicoplanin as alternative treatment for COVID-19 after an *in-vitro* assay achieved IC_{50} value of 1.66 μM, thus proving its efficacy against SARS-CoV-2. These results need to be confirmed through randomized clinical trials, which are still to be conducted.[99,203,204] Using antibiotics to fight viruses, albeit completely ignored, can become useful to treat COVID-19.[205,206]

Some studies report the possibility of repurposing drugs like terconazole, which displayed good *in-vitro* results against MERS-CoV and SARS-CoV,[99,186] and nicotinamide, after virtual triage tests with M^{pro} target.[8]

5.5. Aryl- or benzene-sulfonamide

5.5.1. Dasabuvir

Dasabuvir **(32)** (Fig. 6) is a drug from the naphthalene class and phenyl-naphthalene subclass due to the bond between its naphthalene ring and a phenyl group. Dasabuvir is a first line drug used as combined therapy for chronic hepatitis C.[207] Dasabuvir is a non-nucleoside inhibitor that binds to Nps5B (non-structural protein 5B – RdRp) and induces conformational change that makes RdRp incapable of elongating the viral RNA.[208] Repurposing of this drug can be useful as SARS-CoV-2 therapy due to its antiviral activity.[209]

Dasabuvir was subjected to docking studies against SARS-CoV-2 by Shah, Modi & Sagar[209] in order to identify possible *in-silico* interactions with different viral proteins. According to the parameters in the study, Dasabuvir did not display sufficient interactions in docking on SARS-CoV-2 targets compared to other antiviral drugs. On the other hand, Ekins et al.[186] claim that Dasabuvir is viable for *in-vitro* studies based on the drug *in-silico* outcome against the S-ACE2 protein complex. Briefly, Dasabuvir forms π-cation interactions with Lys31a (present in the ACE2), π- π interactions with Phe170b (S Protein residue) and hydrogen bonds to ACE2 residues Glu35a and Asp38a and Gly176b and Ser174b (S Protein residue). The authors highlight the importance of repurposing drugs as new therapeutic alternatives not only for the new coronavirus but for the next viral outbreaks.

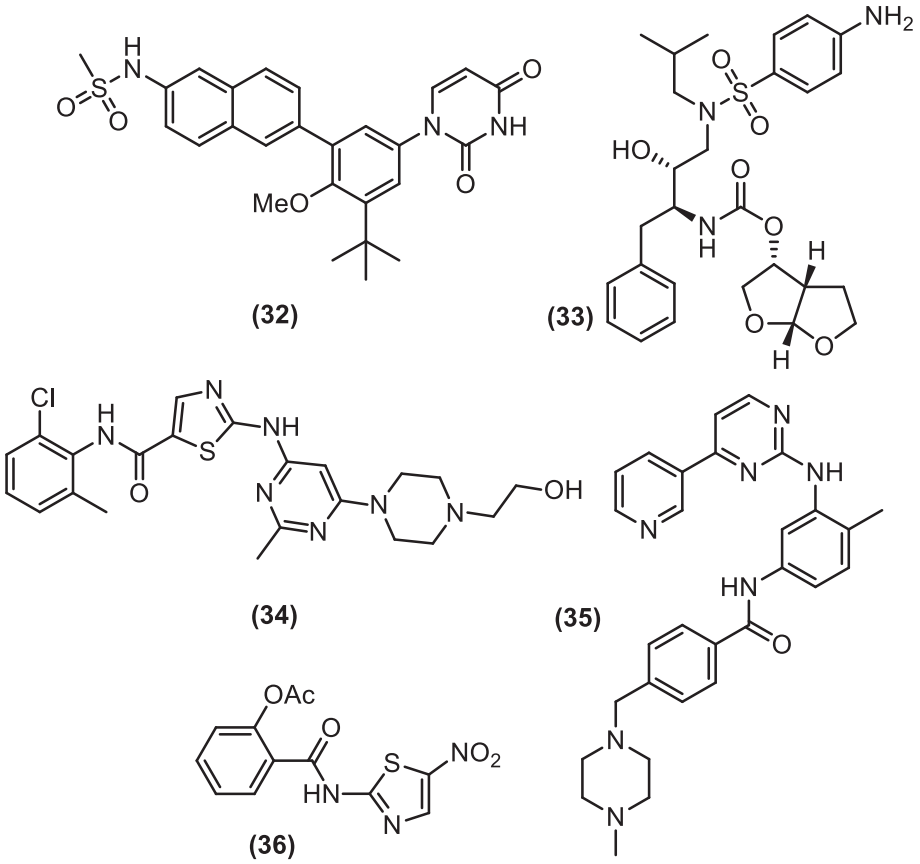

Fig. 6. Chemical structures of Dasabuvir (**32**), Darunavir (**33**), Dasatinib (**34**), Imatinib (**35**) and Nitazoxanide (**36**) drugs.

5.5.2. Darunavir

Darunavir **(33)** (Fig. 6) is a benzene derivative that has been evaluated for repurposing against COVID-19. This drug is an antiviral used in the treatment of HIV-1 infections. It provides a great genetic barrier to resistance and is highly active against resistant strains of HIV-1 that are not susceptible to other protease inhibitors.[210] Darunavir is administered orally as pills or suspension and is often used with low doses of ritonavir as part of a combined ART protocol.[211] Its mechanism of actions works by protease inhibition. Darunavir establishes high affinity bonds to HIV-1 protease forming a stable complex, thereby selectively inhibiting polyprotein gag-pol coded by the virus. This prevents the formation of mature viral particles.[210] A report by Chinese researchers on February 4th, 2020 announced darunavir inhibited replication of SARS-CoV-2 at the concentration of 300 μM.[212] Nonetheless, the combination of darunavir and ritonavir displayed low *in-vitro* effectiveness against SARS-CoV-2.[213]

A number of *in-silico* studies have demonstrated that darunavir is a possible anti-SARS-CoV-2 drug. Beck at al.[185] used a model of drug-target interaction MT-DTI to identify commercially available drugs to act on SARS-CoV-2 viral proteins. They evaluated the binding affinities of 3.410 FDA-approved drugs against $3CL^{pro}$, RdRp, helicase, exonuclease 3′ a 5′, endoRNAse e 2′-O-ribose methyltransferase. Among the best drugs in the assay, darunavir was a surprise because, despite inhibiting viral proteinase, the study showed that it binds to the replication complex components of SARS-CoV-2 with inhibitory potency $K_d < 1000$ nM. One example is RdRp, whose K_d value was 148.74 nM and exonuclease 3′ to 5′ with K_d value of 195.73 nM.

A docking study was conducted by Sang et al.[214] as *in-silico* evaluation of anti-HIV drugs in their interaction capacity to proteinase $3CL^{pro}$. Results suggest that all drugs have higher binding affinity to SARS-CoV-2 $3CL^{pro}$ than to the homolog SARS-CoV proteinase. Among the evaluated drugs, indinavir and darunavir displayed the highest docking scores, therefore, they were subjected to molecular dynamic (MD) simulations, free binding energy calculations and Molecular Mechanics Poisson–Boltzmann Surface Area (MM-PBSA) to detail molecular interactions between inhibitors and proteinase. The data suggest darunavir had better binding affinity to SARS-CoV-2 $3CL^{pro}$ with value of −10,24 kJ/mol. In addition, darunavir bind to SARS-CoV-2 $3CL^{pro}$ via 19 contact residues and to SARS-CoV $3CL^{pro}$ via 17 residues. This difference explains the lower binding energy values between darunavir and SARS-CoV $3CL^{pro}$. It was also noted 5 hydrogen bonds between darunavir and SARS-CoV-2 $3CL^{pro}$ but none for indinavir and this proteinase. Because hydrogen bonds are important in the stability of the inhibitor-enzyme complex, darunavir is probably more promising against COVID-19. Finally, a different *in-silico* assay was conducted by Pant at al.[215] to assess a large variety of compounds (300) from several data banks and 66 potential compounds from FDA-approved drugs. The compounds were tested against SARS-CoV-2 $3CL^{pro}$. Darunavir was among the 20 best FDA-approved drugs, with a score of −7.208. All data collected from *in-silico* studies still require experimental studies to validate the anti-SARS-CoV-2 activity of darunavir.

5.6. Anilides

5.6.1. Dasatinib

A research conducted by Dyall et al.[98] performed a robust *in-vitro* assay and showed that the drug Dasatinib **(34)** (Fig. 6), a kinase signalling inhibitor developed to treat human cancers, inhibited MERS-CoV and SARS-CoV, exhibiting EC_{50} values 5.4 and 2.1, respectively. This study also revealed that kinase signalling may also be important for replication of this HCoVs. Nevertheless, the authors reported that dasatinib may be valuable against coronaviruses infections if a dosing regimen that minimizes immunotoxicity while still blocking viral replication can be defined. Results indicated this drug as a likely

therapeutic alternative against SARS-CoV-2 infection. An *in-silico* study carried out by Qiao et al.[216] showed that dasatinib, among others, is one of the most promising drugs for the inhibition of SARS-CoV-2 $3CL^{pro}$. More preclinical and clinical studies are required to prove whether dasatinib is really promising for COVID-19 patient treatment.

5.6.2. Imatinib

Imatinib **(35)** (Fig. 6) is an oral anticancer agent that inhibits the activity of some tyrosine kinases, most prominently the BCR-ABL fusion oncoprotein (whose overactivation can lead to chronic myeloid leukaemia, CML), c-kit (involved in gastrointestinal stromal tumours development), platelet-derived growth factor receptor (PDGFR), and the native ABL kinase, which has a ubiquitous expression and plays important roles in several biological processes.[217] In addition to this well-known antitumor effect, imatinib has also shown *in-vitro* antiviral properties against several virus, such as infectious bronchitis virus (a viral model for studying the role of tyrosine kinase activity during CoV infection), by interfering with virus–cell fusion,[218] and other RNA viruses including coxsackie virus,[219] hepatitis C virus,[220] Ebola,[221] among others, mainly by blocking viral entry or egress from the host cell. Besides, this drug showed activity against SARS-CoV and MERS-CoV,[222] both phylogenetically related to SARS-CoV-2.[24] In this regard, it is reported that imatinib has anti-CoV activity in two points of the virus life cycle. In the early phases of infection, it inhibits virion fusion with the endosome and subsequent release into the cytoplasm, thus preventing viral entry and viral replication via ABL-mediated cytoskeletal rearrangement. In a later phase of the infection, ABL2 protein expression, which is inhibited by this drug, enables SARS-CoV and MERS-CoV replication, which suggests that ABL2 is a new host cell protein required for viral growth.[222]

Furthermore, evidences suggest that imatinib can modulate the immune response by sundry mechanisms,[223–225] for several diseases, such as rheumatoid arthritis,[226] asthma,[227] and Crohn's disease.[228] This information insinuates that such drug might perform its potentially beneficial immunomodulatory role as a treatment alternative for COVID-19 pneumonia. In addition, the use of imatinib as treatment appears to be reasonable from an economic point of view and its high availability in hospitals,[229] since this drug is well tolerated and the risk of severe adverse effects is relatively low, especially in short-term administration.[230] It is also recognized that adverse effects, mostly mild to moderate in intensity, will be easily controlled by dose reduction or discontinuation.[231]

In light of this information, Tatar and Turhan[232] used the docking methodology to better understand the mechanism of inhibition of the SARS-CoV-2 N protein with 34 antiviral compounds. Based on this study results, imatinib was one of the highly binding affinities performed against the aforementioned target, with the lowest micromolar Ki values among the compounds evaluated. In line with this study, an *in-vitro* research carried out by Weston et al.[233] found 17 FDA approved drugs that inhibited SARS-CoV-2 at non-cytotoxic concentrations. The authors indicate imatinib as one of the hits, since it exhibited IC_{50} value of 3.24 μM. They subsequently determined the mechanism of action, demonstrating this drug inhibits fusion of CoVs with cellular membranes, precluding their entry. This result indicates imatinib use against SARS-CoV-2. However, its efficacy and safety need to be better confirmed in further preclinical and clinical trials in order to elect him as candidate drug in the treatment of COVID-19.

5.6.3. Nitazoxanide (NTZ)

Synthesized for the first time by Jean Francois Rossignol in the beginning of the 1970s, the 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamide, sold under the name nitazoxanide (NTZ) **(36)** (Fig. 6), is the result of a structural modification in the antiparasitic niclosamide when a benzene ring is replaced with a nitrothiazole.[234,235] Developed and sold as antiparasitic, NTZ is also a first line broad spectrum antiviral with good results against parainfluenza, coronavirus, rotavirus, hepatitis and other respiratory infections.[235–238]

Following oral administration, NTZ is absorbed in the intestine, where it is rapidly hydrolysed by plasma esterase into the active metabolite tizoxanide.[235] The mechanism of action of NTZ varies according to the pathogen. In relation to antiviral activity, NTZ blocks the maturation of the viral hemagglutinin at the post-translation stage in treatments against influenza. In treatments against HCV (hepatitis C), it activates protein kinase R (PKR), which leads to phosphorylation of the eukaryotic initiation factor-2α thereby preventing translation.[239]

Cao et al.[240] conducted an *in-vitro* evaluation of NTZ against recombinant murine coronavirus expressing the firefly luciferase (MHV-2aFLS). The strand was pivotal to triage the 727 drugs with likely anti-CoV activity. The first assay resulted in 84 molecules among which was NTZ. The antiviral effect of NTZ was verified for mouse astrocytoma (DBT) and fibroblasts (17Cl-1).[240] The DBT cells infected with MHV-2aFLS were treated with NTZ at 5 μM for 12 h, after which the viral titer ($TCID_{50}$) was determined and viral N protein was subjected to Western blot. Results show the strong inhibitory effect of NTZ on the viral titer.[240] *In-vitro* studies on NTZ or its metabolite tizoxanide were also conducted to verify efficacy against different coronaviruses. The replication of Canine coronavirus (strain K378) in A72 cells, for instance, was blocked by the tizoxanide with IC_{50} of 1 μg/mL. On the other hand, NTZ inhibited the viral N protein in bovine coronavirus L9 (βCoV-L9) and human enteric coronavirus 4408 (HECoV-4408) with approximate values of 0.3 μg/mL.[238,240]

NTZ is also responsible for inhibiting pro-inflammatory cytokines, such as TNF-α, IL-2, IL-4, I-5, IL-6, IL-8 and IL-10 in peripheral blood mononuclear cells (PBMCs). Suppressing the overproduction of cytokines favours control of ARDS, the main cause of death by COVID-19 triggered by the development of cytokine storms. *In-vitro*, NTZ inhibits lipopolysaccharides (LPS) induced IL-6 in both RAW 264.7 cells and peritoneal macrophages with IC_{50} values of 1.54 mM and 0.17 mg/kg (2 mM), respectively.[241] Despite the fact that *in-vitro* suppression of cytokines was only assessed in animal models, the positive outcomes indicate that cytokine inhibition can improve results for patients infected with β-CoVs.

5.7. Quinolines

5.7.1. Chloroquine (CQ) and Hydroxychloroquine (HCQ)

More recently, molecules with a quinoline group have been widely investigated as treatment for the new coronavirus (SARS-CoV-2), such as Chloroquine (CQ) **(37)** and Hydroxychloroquine (HCQ) **(38)** (Fig. 7) that belong to the quinoline class and aminoquinoline subclass. Both are quick-absorption synthetic drugs approved to treat malaria (*Plasmodium falciparum*) by several regulating agencies in the world. CQ and HCQ are water soluble; the latter is more soluble due to presence of hydroxyl group. They are currently used to treat autoimmune diseases such as lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis as they have immunomodulatory and antithrombosis properties.[242–244] Therefore, these drugs could be useful against COVID-19 due to the elevated levels of cytokine caused by CoV infections in humans.[245]

The mechanism of action of CQ for anti-malarial treatment is not entirely clear, but the interference with the digestion of haemoglobin by the parasite has been suggested.[244] HCQ has a similar mechanism, however, in regard to SARS-CoV-2, clinical trials showed it to be safer.[245–247] Therefore, HCQ, rather than CQ, is used against SARS-CoV-2. Recent studies report antiviral activity of CQ and HCQ as they impair viral entry and release in different *in-vitro* and *in-vivo* models.[243,248] A factor that can also justify antiviral mechanisms is the aminoquinoline bioaccumulation in the tissues, as defended by Patil, Singhal & Masand.[242]

A factor that facilitates viral replication is the acidic pH of endosomes, lysosomes and Golgi complex of the host. Thus, CQ is promising because it increases the pH of intracellular vacuoles, binds to the cellular receptors, changes the glycosylation and because of its selective

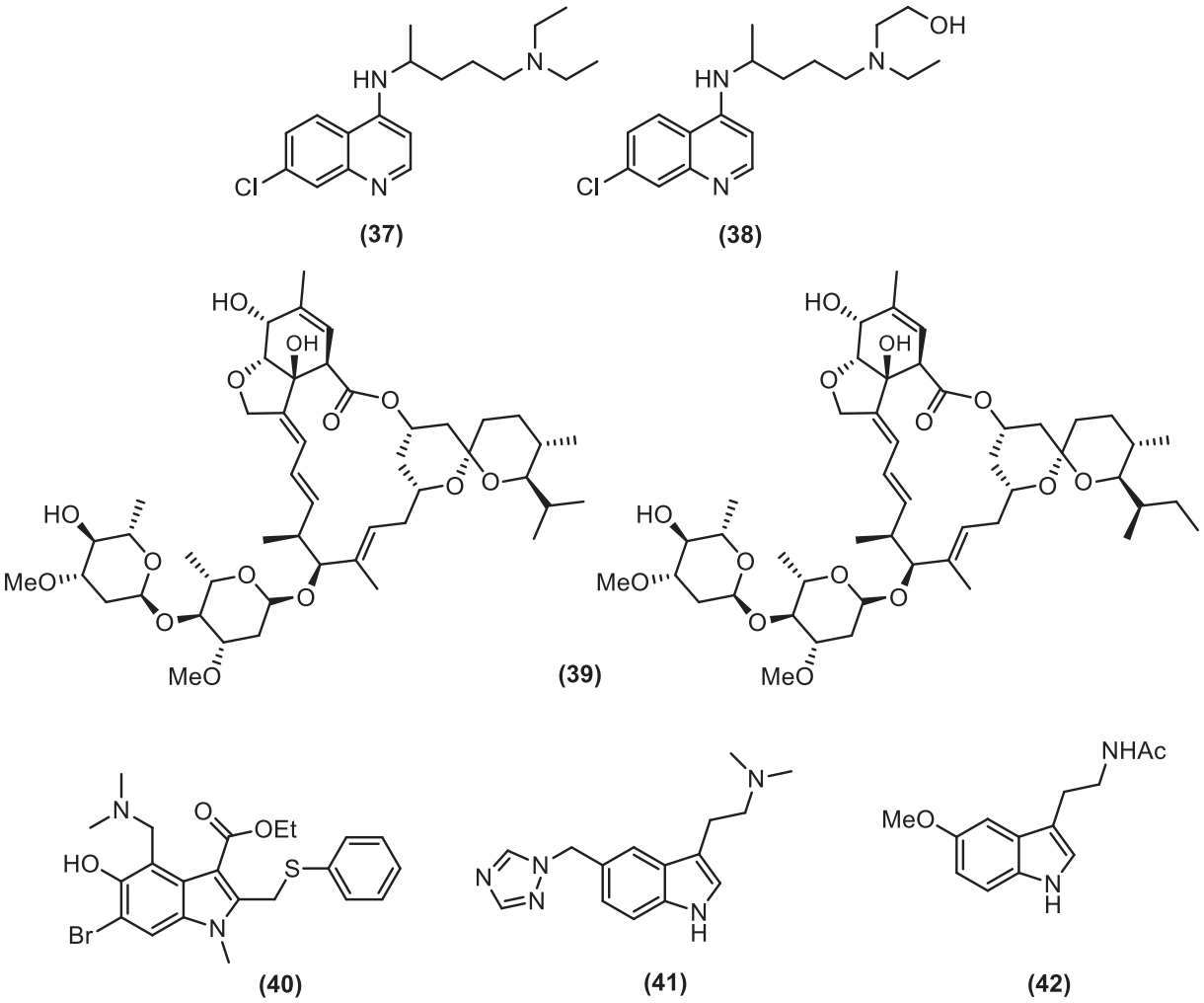

Fig. 7. Chemical structures of quinolines, macrolides and indole derivatives drugs: Chloroquine (**37**); Hydroxychloroquine (**38**); Ivermectin (**39**); Arbidol (**40**); Rizatriptan (**41**); Melatonin (**42**).

and reversible immunomodulator effect on human CD4 + T cells. HCQ exerts similar mechanism of action: a) increases the pH; b) modulation of activated immune cells; c) reduces the number of pro-inflammatory cytokine and other mediators to control inflammation.[242] It has also been suggested by Roldan et al.[243] a likely involvement of HCQ in iron homeostasis during SARS-CoV-2 infection, which is a similar mechanism to other viral infections in humans.[249–251]

The little difference between the therapeutic and the toxic dose of CQ is also known, and poisoning is related to cardiovascular complications that can be fatal. Using either CQ or HCQ, then, requires strict prescription and self-medication is not advised.[248,252] Since the 1960 s, there are *in-vitro* signs of antiviral activity of CQ as well as reports of viral inhibition for both CQ and HCQ, including SARS virus.[248,253–256] In the past months, an extensive debate has focused on the indication of CQ and HCQ against SARS-CoV-2 infections given the lack of necessary information on their mechanisms of action.[248]

The potential use of CQ against viral infections, specially SARS-CoV-2, relies on non-clinical evidences, as argued by Cortegiani et al.[257] Based on a systematic review, the authors defend the *in-vitro* efficacy of CQ as it reduces viral replication of SARS-CoV-2 and CQ is already known for blocking viral infections by increasing endosome pH and for interfering with glycosylation of viral cell receptors. They also claim that the immunomodulatory potential of this drug can favour *in-vitro* antiviral effects and highlight the low costs of CQ, particularly for countries with financial restrictions for medical assistance. Singh et al.[258] defend that, in spite of the limited evidences of CQ and HCQ against the new coronavirus, and considering its potentially favourable risk-benefit relation in the absence of a valid treatment, both are useful in the present COVID-19 pandemic. The low costs also facilitate their use against COVID-19 (specially for diabetic individuals or patients with other comorbidities of elevated mortality rate). Using quinoline derivatives, specially HCQ, as initial therapy for patients infected with SARS-CoV-2 is also defended by Fantini et al.[259], based on *in-silico* studies, and by Gautret et al.[260], given the outcomes of a small sized clinical assay.

Notwithstanding, the dangers of using both drugs as anti-coronavirus therapy have been shown by Taccone et al.[261] who criticized the strategy employed by Gautret et al.[260]. In fact, Taccone et al.[261] claim that HCQ clinical data obtained by Gautret et al.[260] are far from convincing due to the small size of the sample (only 20 patients) given HCQ (six of which also received azithromycin) and to the short observation time (6 days) for all 16 control patients included in the final analysis. In addition, the absence of a randomized investigation and no report on adverse effects during clinical evolution raised concerns about the outcomes. Taccone et al.[261] also criticized clinical outcomes that were misinterpreted and invalid in order to highlight the need for prospective, randomized, placebo-controlled and adequate clinical trials. The authors sustain the inadequacy of considering drugs with promising *in-vitro* and/or *in-silico* results as more beneficial than harmful.

Rosenberg et al.[262] in mid-March 2020, verified the efficacy of HCQ with and without azithromycin in a Retrospective multicentre cohort

study with COVID-19 patients in New York. The study monitored the application of these drugs until April 24th, considering pre-existing conditions, clinical conditions on admission, results and adverse effects reported on medical records. It was verified that from the 1.438 admissions, only patients who received HQ exclusively, or Azithromycin exclusively, or both drugs had greater chances of developing diabetes than control group. Mortality rate did not show significant difference when the drugs were used either in isolation or combined or when no medication was administered.

An observational study conducted by Geleris et al.[263] focused on the association of HCQ and intubation or death of 1.376 patients also in New York for 22 days. There was no relevant association to either an elevated or reduced risk of intubation or death, which demands more robust evidences from randomized and controlled clinical trials with COVID-19 patients.

HCQ clinical trials started with RECOVERY (Randomised Evaluation of COVID-19 Therapy), established as randomized controlled clinical trial to test several potential drugs against COVID-19. RECOVERY began in March 2020.[264] It is sponsored by Oxford University in the UK and the National Institute for Health Research (NIHR) and funded by the Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding. The main researchers in RECOVERY have released a statement on June 5th 2020 to interrupt ongoing investigations on HCQ since there was no clinical benefit in using the drug to treat patients admitted with COVID-19 and no relevant change in mortality at 28 days of the study and no improvements on the time of admission. The data was obtained from comparing 1.542 random HCQ patients to 3.132 random patients under the usual care. Based on the RECOVERY data, it was concluded that HCQ is not effective in patients admitted with COVID-19. This highlights the importance of randomized clinical trials and the collection of clear data on the efficacy and safety of medications.

5.8. Macrolides

5.8.1. Ivermectin

Ivermectin **(39)** (Fig. 7) is an FDA-approved broad-spectrum antiparasitic agent used in the treatment of tropical diseases, such as onchocerciasis, lymphatic filariasis, strongyloidiasis and lice. There is also evidence of its effectiveness in the management of myiasis, trichinosis, malaria, leishmaniasis, trypanosomiasis, Chagas disease and schistosomiasis as well as bed bugs, inflammatory skin lesions, epilepsy, neurological diseases, tuberculosis and some cancers.[265] It is known that ivermectin is capable of inhibiting the bond between a virus and the nuclear transport mediated by the superfamily of importin proteins (IMP α/β1)[266] or even by targeting the viral helicase,[267,268] which inhibits viral RNA replication. There are several studies showing the antiviral activity of ivermectin against HIV-1 and dengue virus,[266] influenza,[269] DENV 1–4,[270] yellow fever virus[268] and west Nile virus.[271]

Based on the fact that SARS-CoV-2 is a RNA virus deeply related to SARS-CoV, studies on SARS-CoV proteins have revealed a potential role for IMP α/β1 during infection in signal-dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein.[272] Furthermore, the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMP α/β1 on the rough ER/Golgi membrane.[273] Considering the ivermectin nuclear transport inhibitory activity, such drug is widely believed as a promising therapeutic approach against SARS-CoV-2.

Recently, Caly et al.[274] analysed the SARS-CoV-2 inhibitory activity of ivermectin, reporting the mechanism of action of the IMP α/β1 proteins upon bonding to the protein of this coronavirus. IMP α bonds to the nuclear localization signal of the protein to be imported to the nucleus of the host cell. IMP β1 assists in anchoring the importin protein to the nuclear pore complex (NPC), translocating the ternary complex (viral protein and IMP α/β1) to the nucleus of the host cell. Thus, the dissociation of the ternary complex occurs in the nucleus of the host cell and the viral DNA unites with the human DNA, undergoing successive mitoses, releasing viral proteins and infecting other healthy cells. At this point, ivermectin bonds to and destabilizes IMP α/β1, impeding the viral protein of the CoV from bonding to importins and consequently impeding the passage of the virus through the NPC to the nucleus of the host cell, thereby inhibiting viral replication. In order to provide further scientific support to the use of ivermectin against SARS-CoV-2, Caly et al.[274] conducted *in-vitro* experiments on Vero-hSLAM cells. Two hours after infection with SARS-CoV-2, a single 5 μM dose of ivermectin was administered, which reduced in 5,000 times the viral RNA in the samples for the first 48 h. Data showed IC_{50} value of 2 μM.

A different mechanism of action that consolidates the use of ivermectin against COVID-19 is its immunomodulatory property. The inflammatory response (proinflammatory cytokine) is exaggerated in patients with the extreme case of the disease, which is likely explained by the hypoxia-inducible factor (HIF-1α) that is activated by the virus when no inhibitory medication is administered. This understanding can be explained by the study conducted by Kosyna et al.[275], whose lab tests with and without ivermectin aimed to examine whether the properties of the bond between HIF-1α and IMP α/β1 and between HIF-1 and nuclear localization signals were affected by the hypoxia mechanism on the cellular level. The authors concluded that ivermectin inhibited both IMP α/β1 and HIF-1α.

Regarding the proper time of administration, Yavuz & Unal[276] claim that ivermectin is beneficial if taken in the early stages of the disease, when symptoms can change. They concluded that ivermectin is a viable molecule for urgent antiviral therapies against several infections. A different investigation conducted by Patrì & Fabbrocini[277] suggested combining ivermectin and HCQ against COVID-19 on the hypothesis that both drugs work in synergy: the HCQ would act as a primary shield against the viral penetration through cellular membrane while ivermectin reduced viral replication. However, there are no randomized clinical trials described in the literature to support either the isolated or the combined effect of ivermectin as prophylactic or therapeutic drug against COVID-19. This hinders its indication and clinical decisions. Thus far, data indicate ivermectin is useful at the early stages of the disease, even the epidemiologic profile of COVID-19 shows significant differences regarding the age of patients for the affected countries and patients with comorbidity.[278] Therefore, large scale randomized clinical trials are necessary to standardize clinical, laboratory and image evaluations, as well as combined drug therapy with vitamins and zinc, for example.[279] Financially, ivermectin is inexpensive and its doses and protocols are well established for different purposes. In addition, this drug has little side effects.[280]

5.9. Indole derivatives

Indole, also named benzo [b] pyrrole, is a planar bicyclic heteroaromatic, whose ten π electrons move across its structure making this chemical group behave as a weak base.[281,] The indole ring is the most abundant heterocyclic in nature and is commonly found in biologically active natural products, such as vegetables and seafood. It is also present in the structure of the essential amino acid tryptophan, which interferes with protein synthesis and with the regulation of physiological mechanisms such as precursors for serotonin and vitamin B3.[282,283] Its outstanding versatility makes it an important building block in synthetic molecules for various pharmacological purposes, among which antiviral.[283–286] For example, indol-2-carboxylate derivatives demonstrated antiviral activity against RNA viruses (Influenza A and Cox B3),[287] and adding the indole ring to spirothiazolidinones conducted to better influenza A/H3N2 inhibition.[288] Now, the antiviral activity of indole and its derivatives for COVID-19 therapy is supposed.

5.9.1. Arbidol

Arbidol **(40)** is also a promising drug to fight COVID-19 (Fig. 7). This drug is classified as antiviral and has been used for 25 years in Russia and for 14 years in China as prophylaxis and treatment of influenzas A and B. Arbidol has become the object of recent investigations to compare effects of monotherapy or combined therapy with drugs used for HIV infections.[289,290] Umifenovir, as it is called commercially, has an indole ring with one bromine atom at 6-position, one hydroxyl at 5-position, one trimethyl at 4-position, one ethyl ester at 3-position and one methylsulfanyl benzene at 2-position.

Arbidol displayed effective inhibition of SARS-CoV-2 after *in-vitro* assay on Vero E6 (ATCC-1586) with EC_{50} = 4.11 μM. The outcome was superior than drugs like baloxavir, which partially inhibited the virus at elevated concentrations (50 μM), or drugs like laninamivir, oseltamivir, peramivir and zanamivir were ineffective for anti-SARS-CoV-2 activity. Data also show that Arbidol not only mitigates viral infection but also interferes with the release of intracellular vesicles that contain the virus.[291] In addition to the promising *in-vitro* results, one of the first clinical trials concluded that Arbidol plus LPV/RTV delayed the progression of pulmonary injuries, compared to LPV/RTV in isolation; decreased the possibility of respiratory and faecal transmission by reaching elevated faecal concentrations that interrupts viral replication in the gastrointestinal system – where there is high expression of ACE2, identified as human receptor for virus entry.[289] Notwithstanding, a different clinic trial concluded that Arbidol monotherapy is best for the patient than LPV/RTV.[290] Despite the results, both investigations recognize their own limitations due to small cohort size and lack of placebo-control group. According to the authors, these limitations are inherent to pandemic times when placebo-control groups are difficult to conduct due to life-threatening conditions.

Most studies with Arbidol use 200 mg/3*day[163,289,290] following the Chinese guidelines. Previous investigations on the pharmacokinetics of Arbidol in healthy Chinese patients showed that a single 800 mg oral dose is sufficient for Cmax de ~4,1 μM.[292] This value was obtained through *in-vitro* assays that pointed the drug as effective and promising against SARS-CoV-2. Hence, clinical trials are still necessary to confirm the efficacy of Arbidol at elevated doses to treat COVID-19.[292]

5.9.2. Rizatriptan (RZT)

Rizatriptan (RZT) **(41)** (Fig. 7) is used to treat migraine and is a selective receptor of serotonin (5-HT) type 1B and 1D, structurally and pharmacologically related to other selective antagonists at these receptors.[293] Its structure is based on an indole ring replaced with methyltriazole at 5-position and unsubstituted ethanamine replaced with methyl at 3-position, the substitution sites are the same of melatonin (MLT). After virtual triage through molecular dock at spike-ACE2 interface, ligations π-cation, interactions π-π and hydrogen bonds were identified between RZT and the SARS-CoV-2 protein complex. As one of the outstanding compounds in the analysis, *in-vitro* tests are still necessary.[186] It is noteworthy that overdosing of the drug can trigger dizziness, fainting, cardiac issues, hypertension, bradycardia and vomiting. Despite the safety of the drug in regular doses, there are no reports on either *in-vitro* or *in-vivo* tests to support the theoretical data and the antiviral action thus far.

5.9.3. Melatonin (MLT)

One last indole derivative that could be repurposed to treat COVID-19 is melatonin (MLT) **(42)** (Fig. 7). MLT is classified as a hormone and nutraceutical, as it is naturally produced by the pineal gland and released into the bloodstream. It regulates the sleep-wake cycle as well as our mood, learning and memory, fertility, reproduction and the immune system. From a chemical perspective, it is an indole derivative with a methoxy group at 5-position and one ethylacetamide at 3-position.[294] Regarding its antiviral potential, MLT acts indirectly through anti-inflammatory, antioxidant and immune modulating activities.[295] An investigation with murine infected with Semliki Forest Virus (SFV) and West Nile Virus (WNV) showed the efficiency of MLT in reducing mortality rates for these viruses as well as in reducing the levels of pro-inflammatory cytokines.[296]

The anti-inflammatory and antioxidant properties of MLT point to its antiviral effects in humans.[297] Based on computational data, Zhou et al.[298] suggested using combined medication to fight SARS-CoV-2. One such combination involves MLT plus mercaptopurine in synergic action against the following targets: PL^{pro}, ACE2, c-Jun signal and anti-inflammatory vias. Therefore, experimental studies on modifications of ACE2 pathways caused by MLT are useful to understand this drug.[298] On the other hand, it has been suggested that using this neuro-hormone can mitigate the extreme form of the disease, the acute respiratory syndrome that has caused most deaths by SARS-CoV-2 cases. Despite its safety for humans, the lack of data on the relevance of its use for COVID-19 patients implicate monitoring of MLT effects on patients who are either healthy or infected with SARS-CoV-2.[298,299]

5.10. Alkaloids and derivatives

Emetine **(43)** is an approved anti-protozoal drug used against amebae with reported inhibitory activity for enterovirus infections,[300] Zika virus and Ebola by interfering with the process of viral replication and entry in host cells.[301] Emetine is an isoquinoline alkaloid that presents 4 methoxy groups in its structure (Fig. 8). Studies also confirm emetine has *in-vitro* activity against coronaviruses, including SARS-CoV and MERS-CoV.[98,302] Regarding SARS-CoV-2, *in-vitro* assays with emetine showed effective viral inhibition at concentrations of 0.5 μM,[109] which is much superior to the concentration of 0.075 μg/mL used for therapeutic purposes. In order to reduce the effective concentrations of emetine and fit it into acceptable therapeutic parameters, Choy et al.[109] tested combinations of RDV and emetine and achieved inhibition of 64.9% at concentrations of 6.25 μM for RDV and 0.195 μM for emetine. Nonetheless, researchers highlight the need for further *in-vitro* assays to clarify the activity of these drugs and the mechanism involved in the antiviral action of emetine both in isolation and combined to other drugs.

Another alkaloid candidate to repurpose against COVID-19 is homoharringtonine (HHT) **(44)** (Fig. 8). HHT is an FDA-approved drug in semi-synthetic form known as omacetaxine. This drug displays antitumoral activity in the treatment of myeloid chronic leukaemia. The mechanism of action implicates the ribosomal bond to prevent protein translation. In addition to antitumor activity, there are data in the literature that describe antiviral activity of HHT against several types of viruses including CoVs.[303,304] A recent *in-vitro* evaluation of anti-SARS-CoV-2 activity displayed EC_{50} of 2.10 μM. However, the mechanism of action is not yet clear, which demands further investigation on ideal doses of HHT to achieve the clinical results expected of a COVID-19 therapeutic drug.[109]

5.11. Thioamide

5.11.1. Disulfiram

The first reports on tetraethylthiuram disulfide, disulfiram (DSF) **(45)** (Fig. 8), date back to 1881. However, only in the 1940s that DSF would become popular when it was discovered that it could form copper chelates which favoured the death of micro-organisms and enabled treatment of intestinal parasites.[305–307] In 1945, DSF alcohol sensitivity was discovered accidentally and it was soon used in the clinical treatment of alcohol dependence.[308,309] DSF is used to treat alcohol dependence because it irreversibly inhibits the acetaldehyde dehydrogenase enzyme and modifies cysteine residues in its active site. This change prompts the formation of a disulphide bond between two cysteine residues in the active site.[310] DSF effectiveness is based on its similarly to several proteins yielding a range of biological activities,

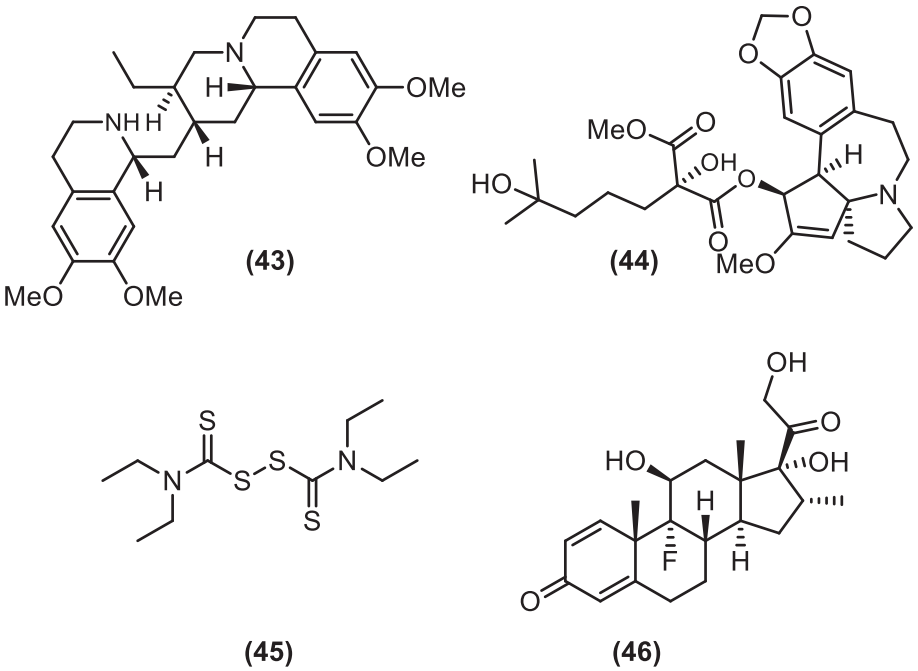

Fig. 8. Chemical structures of alkaloids and derivatives, glycopeptides, amides, peptidomimetics and steroid derivatives drugs: Emetine **(43);** Homoharringtonine **(44);** Disulfiram **(45);** Dexamethasone **(46).**

such as antitumoral,[311,312] antimicrobial,[309] and anti-SARS and MERS-CoV.[313] Adding to the list of drugs to be repurposed against SARS-CoV-2, recent studies indicate that DSF is able to inhibit other enzymes, such as methyltransferase, urease and kinase, all by reacting with important cysteine residues that suppress the natural cycle of the enzymes, suggesting broad-spectrum characteristics.[311,313]

CoVs have two viral enzymes, M^{pro} and PL^{pro}, that are cysteine protease involved in the formation of structural and non-structural proteins that constitute the viruses and favour control of host cells.[314] DSF, as mentioned, can covalently modify cysteine residues interfering with viral replication[313,315] investigated whether DSF can inhibit MERS-CoV and SARS-CoV PL^{pro} by measuring the deubiquitinating (DUB) activity of PL^{pro} in the presence of different concentrations of DSF. DSF showed a dose-dependent inhibitory effect with IC_{50} values of 14.6 μM for MERS-CoV, and 24.1 μM for SARS-CoV. Different assays, such as proteolytic and binding synergy assays, were also conducted and described.[313] Although outcomes indicate DSF for anti-MERS-CoV and anti-SARS-CoV therapy, to the present date (15th June 2020), no other article was published claiming the availability of the compound as promising anti-SARS-CoV-2.

5.12. Corticosteroid

Recently, an announcement was published on the Oxford University website on the results of one Randomized Evaluation of COVID-19 therapy.[316] More specifically, the study focused on dexamethasone (**46**), a corticosteroid with fluorine at 9-position (Fig. 8). The drug is mostly used as anti-inflammatory, which works by inhibiting vasodilation, reducing leukocyte migration to the inflammation site and increasing vascular permeability.[317] The promising results showed reduction in mortality for cases with severe respiratory complications and no significant results for cases that dispensed oxygen support. Dexamethasone reduced death for ventilated patients by one-third and for patients receiving oxygen only deaths were reduced by one fifth. The announcement highlights that high quality and robust clinical trials, such as RECOVERY, that elucidated the utility and efficacy of dexamethasone, must be conducted to collect data that subsidize the repurposing of drugs for COVID-19 therapy.[316]

6. Beyond drug repurposing: Immunotherapeutic approaches

Immunotherapy is an effective intervention in viral infections. Most attempts at immunotherapy were successful in fighting viruses similar to SARS-CoV-2. The principal methods include vaccine, neutralizing antibodies (nAbs) candidates and convalescent plasma.[35,60,66,67,155,318,319] In addition, according to the evidences from viral infections (Ebola, Influenza, SARS and MERS), immunotherapeutic interventions can reduce viral load and mortality rate of patients.[320,321]

Development of either monoclonal (mAbs) or polyclonal (pAbs) neutralizing antibodies is a commonly adopted immunotherapeutic alternative due to its specificity, purity, low contamination by blood-transmitted pathogens and relative safety. However, there are limitations to the use of nAbs once its development and large-scale production for clinical use are a complex, expensive and slow process.[320] Promising scientific investigations have suggested using mAbs or pAbs as prophylactic and therapeutic measures against influenza[322] and HCoVs, such as MERS-CoV[323] and SARS-CoV.[324] Targets reported as promising for HCoVs immunotherapy were cytokine,[325] S1- receptor-binding domain (S1-RBD), S1 *N*-terminal domain (S1-NTD) and some other region of subunit S2 in order to block the RBDs bonds to their respective receptors and to interfere either with S2-mediated membrane fusion or with the entry in the host cells, thus inhibiting infection.[326] These researchers have encouraged the development of nAbs with cross reactivity potential and/or cross neutralization effect on SARS-CoV-2 infections, as shown by Tian et al.[327] Data suggest that mAb CR3022 can be developed as therapeutic candidate, either isolated or combined with neutralizing antibodies to prevent and treat COVID-19, given that it could potently form bonds with SARS-CoV-2 RBD (K_D of 6.3 nM). A different study by Wang et al.[328] reported the discovery of a human mAb (47D11) that promoted cross neutralization of SARS-CoV and SARS-CoV-2 in a culture of cells through an independent receptor-binding inhibition mechanism that targets a conserved epitope on the spike HCoVs RBD mentioned above.

It is also reported the on-going investigation of convalescent plasma or immunoglobulin as last resource to improve the survival rate of patients with several viral infections such as H_5N_1 avian influenza,[329]

pandemic 2009 influenza A H_1N_1,[330] severe Ebola virus infection,[331] HCoVs SARS-CoV[332] and MERS-CoV.[333] A possible explanation for the efficacy of convalescent plasma is that immunoglobulin antibodies in the plasma of recovered patients can suppress viremia.[155] Shen et al.[334] reported that five patients with extreme symptoms of COVID-19 received blood transfusion containing convalescent plasma with specific SARS-CoV-2 antibodies. After a series of blood transfusions, the improvement in clinical status of patients was observed. Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and nAbs titers increased following the transfusion. In spite of the limited sample, the authors concluded that convalescent plasma transfusion benefited patients infected with SARS-CoV-2. Therefore, testing safety and efficacy of transfusing convalescent plasma in patients infected with SARS-CoV-2 can be of value.[318,335]

Among the modalities of immunotherapy, vaccines are expected to be more promising, hence the global engagement in their production. Over the last decade, the scientific community and the vaccine industry had to answer urgently to the epidemics of H1N1, Ebola, Zika and, more recently, SARS-CoV-2. Vaccine development is an expensive and slow process with high risks of failure, which often motivate developers to follow a linear sequence of steps with several breaks for data analysis and fabrication processes. Therefore, it is fundamental that vaccines be developed through faithful methods even if it takes longer to move them onto clinical trials or to make a large number of doses available, a challenge during a pandemic.[336]

Developing efficient vaccines for SARS-CoV-2 will be essential to reduce the severity of the disease, viral shedding and transmission to control future outbreaks. Prior to the COVID-19 pandemic, multiple strategies were used to generate vaccines for the first HCoVs (SARS-CoV and MERS-CoV).[337] Several studies related to SARS-CoV vaccine production targeting the protein S, due to its function in the receptor binding and fusion to the host membrane, were successful in animal tests against that coronavirus.[338–340] These vaccines employed live-attenuated virus vaccines, killed virus, DNA vaccines and viral vector vaccines. Theoretically, these techniques could be applied to develop SARS-CoV-2 vaccines given their similarities from both the genomic perspective and the mechanisms employed in the invasion and infection of host cells.[325] Gao et al.[341] promoted the pilot-scale production of a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc), which induced SARS-CoV-2-specific nAbs in mice, rats and non-human primates. In addition, three immunizations using two different doses (3 μg or 6 μg per dose) in macaques provided partial or complete protection against the SARS-CoV-2 challenge, respectively, without observable antibody-dependent enhancement of infection. These data reinforce the use of PiCoVacc in the next steps of clinical trials targeting SARS-CoV-2 still for the present year.

Given the magnitude of the COVID-19 pandemic, it has become indispensable to work as fast as possible to develop vaccines for global distribution. However, protocols are necessary to safekeep the population's health. Hence, before allowing human testing of COVID-19 vaccines, regulatory organizations must evaluate their safety against a series of virus strains and more than one animal model. They also must demand preclinical evidences that experimental vaccines prevent infection – even if it means waiting weeks or months for models to become available. This is time well-spent, once testing vaccines without investing the due amount of time to completely understand the risks can lead to setbacks for current and future pandemics.[342]

7. Concluding remarks

Considering the time necessary to develop a new medication, in a pandemic, such as the current one, repurposing drugs is useful, and a good part of the literature on the treatment of COVID-19 so far presents possible alternatives. Hence, this comprehensive review of the literature produced in the last six months on the repurposing of drugs for anti-SARS-CoV-2 therapy. Based on the evidences published through theoretical, *in-vitro* and *in-vivo* investigations, several drugs from different classes were identified and considered promising candidates for repurposing against COVID-19. Among purine and pyrimidine derivatives, RDV is the most promising adenosine analogue for clinical trials, probably due to the importance of enzyme SARS-CoV-2 RdRp that is inhibited by its action, whereas SBV, structured as uridine analogue, is undergoing clinical trials at different stages of COVID-19. Analyses of carboxylic acids pointed Kaletra®, a combination of LPV/RTV, as the most effective drug after various studies, in isolation or combined therapy, with good results but without a clear mechanism of action against COVID-19. Data on the naphthalene derivative Dasabuvir are still inconclusive as *in-silico* studies came to divergent data.[177,186] Its repurposing potential relies on the mechanism for other viruses, such as Hepatitis C, by inducing conformational changes that compromise RdRp activity. It was also possible to identify benzene derivatives used to treat cancer (Dasatinib and Imatinib) and one antiviral (Darunavir), but predominant *in-silico* and some *in-vitro* outcomes demand more conclusive studies. Representative of benzoic derivatives, NTZ displayed significant inhibitory activity against pro-inflammatory cytokines, which can benefit control of ARDS, in spite of an unclear mechanism against SARS-CoV-2.

Quinoline derivatives, HCQ and CQ, were some of the first drugs investigated. After several *in-silico*, *in-vitro* and *in-vivo* assays, based on results presented by RECOVERY to the present date, unfortunately, these drugs were proven ineffective in hospitalized COVID-19 patients. Ivermectin represents macrolide derivatives and is suggested as promising due to both immunomodulatory activity and inhibitory activity on nuclear transport when administered at the early stages of the disease. Among indole derivatives, Arbidol was pointed out as useful for reducing viral binding and releasing of intracellular vacuoles that contain the virus. Nonetheless, clinical trials are still necessary after dose adjustment for better outcomes. Both indole derivatives (emetine and HHT), in spite of promising results, were only submitted to *in-silico* and *in-vitro* tests, thus demanding further investigation on their toxicity and mechanism of control.

Hence, the currently available data on the classes of drugs investigated here revealed that drugs were considered promising mainly after *in-silico* tests only. In fact, the inefficacy of some of these drugs became evident after *in-vitro* or *in-vivo* tests, as CQ and HCQ, whose clinical trials failed to confirm the so-expected anti-SARS-CoV-2 activity. It is necessary to highlight the importance of clinical trials with drugs considered promising in theoretical studies, with due calm and openness to question and refute hypotheses, in the absence of scientific evidence to support their use to treat COVID-19. Similarly, the careful analysis of practices involving patients with the extreme form of the disease is also important to identify new alternatives, such as the results recently published by RECOVERY on dexamethasone. It is also expected that detailed clinical trials are conducted with some of the drugs described in this article as potential anti-SARS-CoV-2, for instance Sofosbuvir, Remdesivir, Lopinavir/Ritonavir plus interferon beta-1b and ribavirin, Ivermectin and Arbidol. These studies could establish new therapeutic alternatives that are safer and capable of effectively fighting COVID-19, which already infected millions of people in the world. Moreover, it is fundamentally relevant to develop a broader spectrum of effective and safe antivirals, beyond other pharmacological classes that might be useful for combating HCoVs diseases. Otherwise, likely the feeling of déjà vu, due to the lack of antivirals to treat disease as previous and the current pandemic,[186] will be repeated several times in future new viral outbreaks.

In relation to immunotherapy development, several technological platforms are being manipulated to develop a COVID-19 vaccine. Still, the obtainment of vaccines to prevent the spreading of SARS-CoV-2 requires a careful evaluation of possible immunological complications before releasing the vaccine to the world. Therefore, while the vaccine for SARS-CoV-2 is in development, it is necessary to continue investigating therapeutic options via repurposing in order to identify

promising chemical structures and plan new antiviral prototypes specific for SARS-CoV-2 or, even, to find immediate use alternatives to save the lives of patients with the extreme form of COVID-19.

Declaration of Competing Interest

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Author contributions

All authors researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and edited the manuscript before submission.

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