Review

An Update of Carbazole Treatment Strategies for COVID-19 Infection

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Abstract: The Coronavirus disease 2019 (COVID-19) outbreak was declared by the World Health Organization (WHO) in March 2020 to be a pandemic and many drugs used at the beginning proved useless in fighting the infection. Lately, there has been approval of some new generation drugs for the clinical treatment of severe or critical COVID-19 infections. Nevertheless, more drugs are required to reduce the pandemic's impact. Several treatment approaches for COVID-19 were employed since the beginning of the pandemic, such as immunomodulatory, antiviral, anti-inflammatory, antimicrobial agents, and again corticosteroids, angiotensin II receptor blockers, and bradykinin B2 receptor antagonists, but many of them were proven ineffective in targeting the virus. So, the identification of drugs to be used effectively for treatment of COVID-19 is strongly needed. It is aimed in this review to collect the information so far known about the COVID-19 studies and treatments. Moreover, the observations reported in this review about carbazoles as a treatment can signify a potentially useful clinical application; various drugs that can be introduced into the therapeutic equipment to fight COVID-19 or their molecules can be used as the basis for designing new antivirals.

Keywords: COVID-19; coronaviruses; SARS-CoV-2; carbazoles; alkaloids

1. Introduction

Coronaviruses (CoV) are a wide respiratory class of viruses that can induce mild to moderate diseases, ranging from the common cold to respiratory syndromes, such as Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and recently Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1,2]. Coronaviruses are widespread in species of animals (such as camels and bats), but in different cases they can infect humans and then spread over among people. To date, seven types of human coronaviruses are known and are common around the world. The former ones were identified in the mid-1960s, others were only discovered in the new millennium. SARS-CoV-2 belongs to the family of Coronavirus discovered in humans and it's the cause of the worldwide human respiratory disease pandemic coronavirus 2019 (COVID-19), owing to its high ability to inter-transfer with humans [3]. The COVID-19 pandemic was discovered initially in Wuhan City, Central China, and it quickly spread over other countries and became a threat to the world health as it affected millions of people [4]; to date, COVID-19 represents a critical threat to global health and economy as more than 520 million people were infected and about 6 million died [5].

The pandemic outbreak has reached alarming proportions, blocking and putting pressure on national health systems and requiring a significant deployment of forces and

resources around the world. The WHO declared it a pandemic on 11 March 2020 because of its very rapid transmission and the considerable rate of mortality and morbidity [6,7]. The majority of the infected people (80%) are asymptomatic or have non-severe symptoms, nevertheless, 15–20% of other patients need hospitalization as a result of the development of acute lung injury (ALI) and/or distress syndrome respiratory (ARDS) [8,9].

Recently, COVID-19 has been considered a multi-organ disease characterized by a wide spectrum of manifestations. Early variants of COVID-19 [10] cause a rise in body temperature, cough, fatigue and myalgia, and bacterial superinfection in most patients infected with SARS-CoV-2. Symptoms became worse in more severe infections, leading to the development of COVID-19-associated acute respiratory distress syndrome (CARDS) with respiratory failure. In such a case, patients should be hospitalized in an intensive care unit (ICU). Currently, COVID-19 has become very flu-like in most cases, but we don't know what will happen next; so, even though the COVID-19 era is not over yet [7], we have entered now the era of post-COVID-19. Many people who recovered from COVID-19 present a condition called "post-COVID syndrome" [11], in which they develop new or persisting symptoms that continue for a long time; this syndrome has been termed a second pandemic and has gradually been accepted as a new clinical problem to be addressed in relation with SARS-CoV-2 infection [12]. The increasing number of patients suffering from post-SARS-CoV-2 infection have numerous symptoms, such as neurocognitive, autonomic, gastrointestinal, respiratory, musculoskeletal, psychological, and other symptoms and manifestations related to post-COVID [7,13].

2. Viral Features

SARS-CoV-2 is a single-stranded RNA+ virus that belongs to the *Coronaviridae* family. It is broadly spread among humans and other mammals. The Severe Acute Respiratory Syndrome Coronavirus-2 possesses a broad genome (around 29,700 nucleotides) encoding structural and non-structural proteins [14]. The replication and transcription processes of the SARS-CoV-2 virus occur at the level of the cytoplasmic membrane by the action of viral replicase; the replicase gene encodes two overlapping polyproteins, pp1a and pp1ab, which allow viral replication and transcription [15]. These polyproteins are digested by the 33.8 kDa Mpro protease activity in at least 11 conserved sites. Mpro is known as an interesting target for the design of antiviral drugs because of the functional importance that Mpro has in the virus life cycle and because of the absence of closely related homologs in humans [16]. Other proteins have also been identified for their implication in the pathogenesis of the virus, such as the spike glycoprotein, which allows virus entry by binding to the angiotensin 2 converting enzyme receptor (ACE2) widely expressed in human tissues [5]. Possible drug targets include RNA polymerase-dependent RNA and spike (S) proteins [17] that bind to ACE2 and allow the virus to enter cells. Consequently, the virus's RNA polymerase enzyme is primed for the rapid mutation required to resist current antiviral drugs [2].

3. Different COVID-19 Treatments

In March 2020, he WHO declared the outbreak of COVID-19 as a pandemic, and several drugs used at the beginning proved useless in fighting the infection [6,7]. Lately, there has been the approval of some new-generation drugs for the clinical treatment of severe and critical COVID-19 symptoms. Nevertheless, more medications are required to attenuate the pandemic impact [5]. Many of the employed therapeutic approaches since the start of the pandemic were shown to be ineffective against the virus. So, the identification of drugs to be used effectively for the treatment of COVID-19 is strongly needed [18–20]. COVID-19 is considered to be a multisystem disease, and its pathogenesis involves severe lung inflammation and immune deficiency linked to inadequate immune response and enhanced cytokine production. Therefore, therapeutic approaches currently being studied concern antiviral and anti-proinflammatory cytokines, anti-infective and life support treatments, monoclonal antibodies, and passive immunotherapy, mostly in people

with severe disease [21]. The antiviral treatments used so far for SARS-CoV-2 virus can be presented into two categories [22,23]:

(A)   Agents that target the virus proteins: S protein and viral proteases or virus RNA which are the main viral targets.

(B)   Agents that target host proteins that allow the virus to enter the cell, such as the enzyme ACE-2, TMPRSS2 (transmembrane protease serine 2), furin, and cathepsin-L, the proteins which can promote the attachment of viral cells such as HSPG (heparin sulfate proteoglycans), eukaryotic translation proteins such as S1R (endoplasmic reticulum chaperone protein), and transcriptional system proteins such as inosine monophosphate dehydrogenase and dihydroorotate dehydrogenase [22,23].

Several studies and laboratory works are still in demand to discover new and effective antiviral drugs against SARS-CoV-2. These studies could deal with the following areas [23]:

(1)   Inhibitors that block the virus from entering the human cell:

    a.   S Protein inhibitors: plasma from convalescing infected persons, miniproteins, monoclonal antibodies, nanocods, soluble human ACE-2 protein;

    b.   Fusion entry inhibitors;

    c.   inhibitors of TMPRSS2, such as nitazoxanid, camostat, nafamostat, gabexat, dutasteride, bromhexine, niclosamide, and proxalutamide;

    d.   Endosomal entry inhibitors: NIP1 inhibitors (EG00229), niclosamide, hydroxychloroquine, umifenovir, nitazoxanide; furin inhibitors (dec-RVKR-cmk); cathepsin L inhibitors (teicoplanin, SSAA09E1, K1777);

    e.   Inhibitors of HSPG (lactoferrin).

(2)   Viral proteases inhibitors: inhibitors of Mpro, the main protease of the virus (lopinavir/ritonavir, PF-07321332, PF-07304814, GC376, carprofen (**1**, Figure 1)); viral papain-like protease inhibitors (PLpro).

(3)   Viral RNA inhibitors, RNA-dependent RNA polymerase (RdRp) inhibitors (AT-527, remdesivir, molnupiravir, favipiravir), host protein inhibitors that support the synthesis of viral RNA (dihydroorarate dehydrogenase inhibitor (PTC299), inosine monophosphate dehydrogenase inhibitor (merimepodib).

(4)   Host protein inhibitors that support the synthesis of viral protein: S1R agonists (fluvoxamine); inhibitors eEF1A (plitidepsin).

(5)   Viral immunomodulation inhibitors: host α/β importin inhibitors (ivermectin).

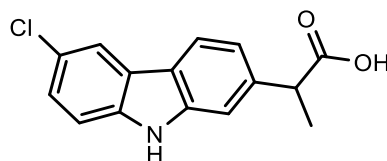(6)   Agents that support natural host immunity: interferons [23].

Figure 1. Structure of carprofen (**1**).

Previous studies to develop anti-virus SARS-CoV-2 therapies relied on the design of medicaments that obstruct the viral life cycle, so: (1) the inhibition of viral entry into the cell by blocking the spike protein and/or ACE2; (2) the inhibition of viral proteases; (3) the prevention of viral replication via the RNA dependent viral RNA polymerase (RdRp) inhibition [24]. Much of this research is based on the medicaments reuse strategy to find new therapies from already adopted drugs, speeding up like this the drug discovery process and providing the benefit of instant use of medicaments that have previously proven safety safe [25]. De novo drug identification is a long and costly process, so several scientists around the world have tested the action of already approved drugs on SARS-CoV-2. Lately, the FDA has agreed to a combination of lately developed antiviral drugs to treat severe or critical cases. However, the impact of this pandemic can be reduced by using other drugs [5]. It has been shown that emodin, omipalisib, and tipifarnib possess an

inhibitory effect on RdRp [26], while in other studies it was shown that raltitrexed, cytarabin, lamivudine, tenofovir, cidofovir, and fludarabine are capable to bind the viral spike protein [27,28]. In clinical trials, antivirals such as ritonavir and ribavirin, have been utilized to treat COVID-19 [29–31]. The efficacious treatment development for this disease has been hindered by the limited data available on this coronavirus during the pandemic's start. The repurposing of drugs allows exploration of the possible antiviral activity of approved drugs. Furthermore, pharmacological synergism has better efficacy and reduced toxicity in antiviral treatment [5]. In an interesting study by Abdel-Halim et al. [5] an *in-silico* method has been proposed to observe the effect of approved drugs on an essential target of SARS-CoV-2, the principal protease (Mpro), to search rapid antiviral treatments and/or drug combinations, because of the reduced time and urgency of treatment; the inhibiting activity of three pharmaceutical compounds and two drug combinations on this protease was established. It has been proven, by *in-silico* and in-vitro assays, that favipiravir, carvedilol (**2**, Figure 2), and cefixime are Mpro inhibitors. The various conformational changes of the enzyme that can be induced by the binding of ligands were investigated using molecular dynamics simulations that identified potential drug combinations that show a synergistic effect when tested on Mpro; two drug combinations (favipiravir/cefixime and favipiravir/carvedilol (**2**, Figure 2)) have been shown to be active against this enzyme [5]. The study of Ahmad et al. [2] developed a potential strategy for the use of plant extracts, and in particular active phytochemicals from *Daphne* species plants, to tackle the SARS-CoV-2 pandemic. The studied compounds showed good antioxidant activity, which could be interesting if evaluated as radical scavenging capacity. Phytochemicals analyzed were found to be able inhibitors of SARSCoV-2 as they prevent the development of viral proteins along with the spread of infection, inhibiting the viral protein, leading the virus to lose the 6LU7 protein, the main viral protease. The synergic interactions of twelve coumarins showed good inhibition of the 6LU7 viral protein [2].
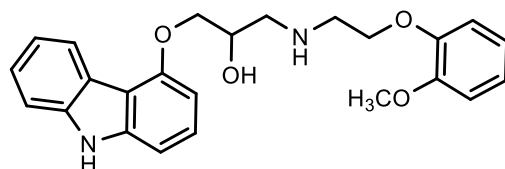

Figure 2. Structure of carvedilol (**2**).

Therefore, conventional treatments for COVID-19 include the use of anti-inflammatory, antiviral, and antimicrobial drugs, along with the use of immunomodulators, bradykinin B2 receptor antagonists, angiotensin II receptor blockers, and corticosteroids. Furthermore, an advantageous treatment to prevent or treat COVID-19 disease or post-COVID-19 syndrome is represented by the use of nutraceuticals [32–36]. For the COVID-19 treatment, the nutraceuticals' use was assessed by their interaction with the ACE2 enzyme. When the spike glycoprotein of the SARS-CoV-2 virus binds to the ACE2 receptor, there is the downregulation of ACE2 and the consequent improvement of the level of angiotensin-2 (Ang II) and the increase of the activation of the type 1 axis (AT1R) of the Ang II/Ang II receptor which is correlated with pro-inflammatory responses. Consequently, natural compounds play an important role in the treatment of COVID-19 because they decrease the activity of ACE2; the SARS-CoV-2 virus uses spike glycoprotein to enter host cells because the binding domain of the spike glycoprotein receptor (RBD) interacts with ACE2 on host cells; in the omicron variant of the virus, spike glycoprotein is characterized by 32 mutations, of which 15 are in RBD [37,38]. However, when there is a lack of effective curative and prophylactic drugs or when several mutants of the SARS-CoV-2 virus develop and spread rapidly among people, a key defense is a strong immune system [7], as the weakened immune system along with the older age, obesity and other diseases are risk factors that increase the severity of COVID-19 disease, and therefore supplements, nutraceuticals, and probiotics can reduce the risk of SARS-CoV-2 infection or alleviate COVID-19

symptoms [39,40]. Other studies highlighted the role that some bacterial substances and molecular compounds can play in the immune response to respiratory viruses and in the regulation of two main COVID-19 disease manifestations, which are systemic inflammation and endothelial damage. Additionally, the use of prebiotics, probiotics, and postbiotics has also been investigated in the battle against SARS-CoV-2 infection because the lack of these nutrients could result in a better susceptibility to infections and immune system dysfunctions. A clinical study demonstrated that the progression of COVID-19 can be regulated by the use of these supplements that modify the gut microbiota with a reduction of disease course and the severity of the symptoms [41,42]. The high dose administration of vitamin D, vitamin C, vitamin E, flavonoids, zinc, probiotics, prebiotics, omega-3 fatty acids, and melatonin are being used as principal dietary supplements in COVID-19 and presented a clinical benefit for the hospitalized; the viral load, the severity of the disease, and, therefore, the hospital stay are reduced by the immunomodulatory and antioxidant effects of these supplements [7,43].

It is of interest to note that the U.S. Food and Drug Administration (FDA) has approved the antiviral drug Remdesivir (Veklury) for the treatment of coronavirus disease 2019. This drug was prescribed as a treatment for hospitalized patients who are in need of supplemental oxygen or are at higher risk. This drug blocks the specific enzyme activity needed for the COVID-19 virus to replicate. Another approved medicament is Paxlovid. This medicament is used to treat patients with mild to moderate infections who are at higher risk of serious illness. Paxlovid is composed of two medicaments: nirmatrelvir and ritonavir. Nirmatrelvir blocks the activity of a specific enzyme needed for the virus to replicate, while the antiviral ritonavir helps to slow the breakdown of nirmatrelvir. Also, another drug named molnupiravir was approved for the treatment of mild to moderate infections in patients who are at higher risk of serious illness and are not able to take other medications. The anti-rheumatoid arthritis drug baricitinib (Olumiant) possesses also antiviral activity and it likely works against the virus by reducing the inflammation. The anti-inflammatory therapy, using anti-inflammatory drugs such as the corticosteroid dexamethasone, can treat or prevent organ dysfunction and lung injury from inflammation [44].

4. Carbazoles Treatment

Several studies [5,9,17,45–62] describing the important role of carbazole derivatives in the treatment of COVID-19 are included in this review, cf. Table 1.

Table 1. Carbazole derivatives-based drugs for the treatment of COVID-19.

Compound	Name	Reference
SARS-CoV-2 M-pro inhibitors		
1	Carprofen 2-(6-Chloro-9*H*-carbazol-2yl)propanoic acid	[45]
2	Carvedilol 1-(9*H*-Carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy) ethylamino]propan-2-ol	[5,9,17,46–52]
3	Koenigicine 8-Methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazol-9-ol	[53]
4	Mukonicine 9,11-Dimethoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole	[53]
5	O-methylmurrayamine A 9-Methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole	[53]
6	Koenine 3,3,5-Trimethyl-11*H*-pyrano[3,2-*a*]carbazol-8-ol	[53]
7	Girinimbine 3,11-Dihydro-3,3,5-trimethyl-pyrano[3,2-*a*]carbazole	[53]

Table 1. *Cont.*

Compound	Name	Reference
SARS-CoV-2 M-pro inhibitors		
Viral-entry inhibitors targeting human ACE2		
8	Edotecarin 6-((1,3-Dihydroxypropan-2-yl)amino)-2,10-dihydroxy-12-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione	[54,55]
9	7-Hydroxystaurosporine (5*S*,6*R*,7*R*,9*R*,16*R*)-16-hydroxy-6-methoxy-5-methyl-7-(methylamino)-6,7,8,9,15,16-hexahydro-17-oxa-4b,9a,15-triaza-5,9-methanodibenzo[b,h]cyclonona[jkl]cyclopenta[e]-as-indacen-14(5*H*)-one	[56]
10	CIMSSNa sodium 3-(4-(((S)-5-((5*S*,7*S*,8*R*,9*S*)-8-methoxy-9-methyl-16-oxo-6,7,8,9,15,16-hexahydro-5*H*,14*H*-4b,9a,15-triaza-5,9-methanodibenzo[b,h]cyclonona[jkl]cyclopenta[e]-as-indacen-7-yl)-4-oxohexanamido)methyl)-1*H*-1,2,3-triazol-1-yl)propane-1-sulfonate	[57]
11	6-Formylindolo(3,2-b)carbazole	[58]
NPC1 inhibitor		
12	2-((2-(1-Benzylpiperidin-4-yl)ethyl)amino)-*N*-(9*H*-carbazol-9-yl)acetamide	[59]
Antiviral against PLpro		
13	6-Cyano-5-methoxy-12-methylindolo [2, 3A] carbazole	[60]
Immunotherapy treatment		
14	Ramatroban 3-[(3*R*)-3-[(4-fluorophenyl)sulfonylamino]-1,2,3,4-tetrahydrocarbazol-9-yl]propanoic acid	[53,61,62]

Carbazole containing heterocycles can be of synthetic or natural origin, many are alkaloids extracted from the leaves of *Ochrosia Elliptica Labill* [63]. Carbazoles represent an interesting class of heterocycles known by their anticancer activity [64,65]: antibacterial, anti-inflammatory [66], antifungal, antioxidant, antimicrobial, antiepileptic, antihistamine, antiviral [67,68]. In addition, numerous carbazole derivatives have also been found to be useful for Alzheimer's disease [69]. Several carbazoles were assessed by research groups for a SARS-CoV-2 virus study [5,45,53,54,56–60,70]. Despite vaccination against COVID-19, there is an urgent priority to identify additional antiviral drugs due to immune loss due to new variants of SARS-CoV-2; computational approaches have made a big contribution to the identification of antivirals by lowering costs and time and by accelerating analyzes of target interactions with candidate drugs [45,71]. A therapeutic strategy for drug development is the targeting of the main protease (Mpro) for its important role in the viral replication cycle. The overlapping polyproteins (pp1a and pp1ab) are cleaved, in an autoproteolytic way, by SARS-CoV-2 Mpro (SC2-Mpro), and mature non-structural proteins (11 proteins) necessary for viral replication and transcription are produced [72]. The lack of a Mpro-like human protease, such as its unique selective ability of cleavage site, makes it a major therapeutic target for the detection of anti-SARS-CoV-2 drugs [53,70]. Moreover, ACE2 is used as a therapeutic target to control the COVID-19 outbreak, as an ACE2-mediated mechanism allows the virus to enter permissive cells. ACE2 has a defensive role in heart disease as it is a membrane-bound zinc metallopeptidase that produces the vasodilator peptide angiotensin 1e7 [54]. Additionally, in order to identify new anti-COVID-19 drugs, an interaction between the SARS-CoV-2 nucleoprotein (N) and the cholesterol transporter Niemann-Pick type C1 (NPC1) [59] was evaluated. The NPC1 receptor, an endosomal membrane protein, regulates intracellular cholesterol transport. Another important protein

in coronavirus is PLpro (papain-like protease), which performs an essential action in the processing mechanism of viral polyproteins [73] and has fundamental action against human immunity through post-translational modifications on human proteins [60,74]. Below, we report the drugs with a carbazole structure (**1**–**14**) that have been studied and selected to date, which can be inserted into the therapeutic equipment of the battle against COVID-19, or their scaffolds can be used as skeletons for the design of new antiviral compounds.

4.1. SARS-CoV-2 M-Pro Inhibitors

As already reported, protease M-pro, also known as chymotrypsin-like protease, (3CL-pro) is an enzyme that only exists in the virus and not in humans [75,76]. For this reason, Mpro is an interesting target for the discovery of new antivirals [77]. Gimeno et al. in 2020 [45] applied a virtual screening (VS) method for checking approved medicines to verify which of them could inhibit this protease. The drugs studied were docked against the structure of the protease involved using docking programs such as Glide, FRED, and AutoDock Vina. Thanks to these studies, drugs were selected, including one with a carbazole structure, carprofen (**1**, Figure 1), as possible M-pro inhibitors. Carprofen (2-(6-chloro-9*H*-carbazol-2yl) propanoic acid) (**1**) is a selective COX-2 (cyclooxygenase-2) inhibitor. Compound **1**, in the active site of M-pro, makes many interactions, such as hydrophobic interactions, with Gln189 and Met49, π-π interaction with His41 through its ring system, hydrogen interaction, for example with His164, Ser144, and Cys145, and halogen bond interaction with the thiol group of Cys44 through its chloro group. In-vitro studies show a limited inhibitory capacity on M-pro (3.97% at 50 μM) of drug **1** therefore this molecule could be considered a promising compound for the synthesis of more potent and effective inhibitors [45].

In 2022, Abdel-Halim et al. [5] identified carvedilol ((1-(9*H*-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol)) (**2**, Figure 2), a *β*-adrenergic receptor blocker, as Mpro inhibitor by *in-silico* and in-vitro assays.

In silico studies allowed us to study the conformational changes in the enzyme induced by the different ligands. From the evaluation of the data obtained, it was possible to identify combinations of molecules that gave a synergistic effect on protease Mpro. In fact, the drug combination favipiravir (6-fluoro-3,4-dihydro-3-oxo-2-pyrazinecarboxamide)/carvedilol (**2**) was found to be active against this enzyme. The inhibitory activity tests the evaluation of the synergistic effect and was evaluated by using the "3CL Protease (SARS-CoV-2) Assay Kit" from "BPS Bioscience." The best results have been obtained by mixing 2 μM compound **2** and 1 μM favipiravir showing an inhibition percentage of 98 and a contact-dependent growth inhibition (CDI) of 0.89. CF analysis (analysis of contact frequency) and MD simulation (molecular dynamics simulations) were able to identify the amino acid residues that affect the bond between compound **2** and Mpro (for example His41, Met49, and Thr25 showed more than 80% CF; Cys44, Ser46, and Glu166 more than 70%) [5]. This study supports the computational work carried out in 2020 by Zhou et al., showing the important role of carvedilol in the treatment of COVID-19 [46,78] and that of Wu et al. [17] reporting carvedilol as a potential protease inhibitor similar to 3-chymotrypsin SARS-CoV-2. Carvedilol (**2**) was also used in a clinical trial to evaluate the clinical outcomes of hypertensive patients infected with SARS-CoV-2, who commonly use inhibitors of the renin-angiotensin-aldosterone system. The study conducted by Najmeddin et al. [47] confirmed that there are no deleterious effects following the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in hypertensive patients with COVID-19 [48]. Also, according to the report of Onohuean et al. [9] in 2021, drugs such as carvedilol (**2**) may control the development of HF by reducing the infectivity of the 2019 novel coronavirus (SARS-CoV-2) and prevent the production of cytokine storms in severely affected COVID-19 people. Compound **2** downregulates cardiac ACE2 and inhibits SARS-CoV-2-induced acute cardiac injury [49]. Amirshahrokhi et al. demonstrated that **2** can moderate the development of paraquat-induced ALI through suppression of oxidative stress and NF-*κ*B signaling pathway [79]. Also, **2** effectively manages Coronavirus

disease 2019 complications such as esophageal varices [50] and post-COVID-19 sinus tachycardia [51]. Therefore, for its antiviral and anti-inflammatory activities, carvedilol may have dual protective effects in COVID-19 by mitigating the development of HF and ALI [52].

Several studies show the antiviral property of plant-derived molecules against RNA viruses [80]. Some of these, such as carbazole alkaloids from *Murraya koenigii* have been evaluated for SARS-CoV-2 infection. *Murraya koenigii,* known as the "Curry leaf tree" is a plant very widespread and of considerable pharmaceutical interest due to its numerous beneficial activities (antioxidant, antidiabetic, anticancer, anti-inflammatory, hepatoprotective, nephroprotective, cardioprotective, neuroprotective and antimicrobial, and antiviral activities). These activities are mainly due to the presence of compounds with a carbazole structure in its leaves, roots, and bark [81,82]. For such evidence, Wadanambi et al. in 2022 [53] evaluated the inhibitory potential of carbazole alkaloids from *Murraya koenigii* against Mpro by computational study. Using 3WL (5,6,7-trihydroxy-2-phenyl-4*H*-chromen-4-one) as a reference inhibitor, five carbazole alkaloids **3**–**7** (Figure 3) (koenigicine (8-methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazol-9-ol) (**3**), mukonicine (9,11-dimethoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole) (**4**), O-methylmurrayamine A (9-methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole) (**5**), koenine (3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazol-8-ol) (**6**), and girinimbine (3,11-dihydro-3,3,5-trimethyl-pyrano[3,2-*a*]carbazole) (**7**) displayed interactions in the active site of SARS-CoV-2 Mpro.
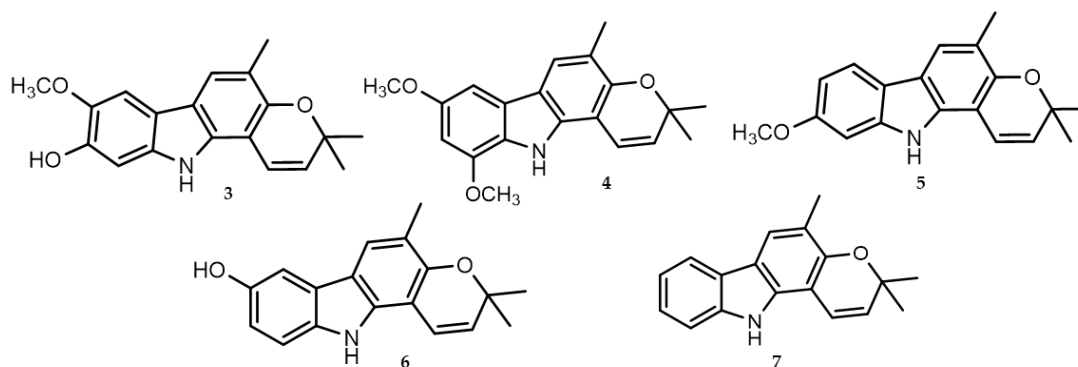

Figure 3. Structures of: koenigicine (**3**), mukonicine (**4**), O-methylmurrayamine A (**5**), koenine (**6**) and girinimbine (**7**).

Mainly, **4**–**7** may have the features to reduce SARS-CoV-2 replication by inactivating the Mpro catalytic activity. The carbazoles studied (**3**–**7**), compared with 3WL and showed higher binding affinity and lower binding energies towards the active site of the SC2-Mpro [83]. These compounds form hydrogen bonds with numerous aminoacid residues of the active site (for example with His41, Cys145, Asn142, etc.). In particular, the oxygen atom of the pyran ring forms a hydrogen interaction with Gly143 (for **3** and **4**), Asn142 (for **5** and **7**), and Glu166 (for **6**). Compounds **3**–**7** were also found to be effective against the Alpha, Beta, Gamma, and Omicron variants. Toxicity test data shows that **3**, **4,** and **5** may have carcinogenic and mutagenic effects [84], instead, **6** and **7** did not show any toxic effects to hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. Therefore, bioactive natural compounds **4**–**7**, with good oral bioavailability, represent a starting point for the synthesis of new potential SC-2 Mpro inhibitors [53].

4.2. Viral-Entry Inhibitors Targeting Human ACE2

Terali et al. in 2020 [54] have identified the carbazole edotecarin (**8**, Figure 4), (6-((1,3-dihydroxypropan-2-yl)amino)-2,10-dihydroxy-12-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy- 6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione) as viral-entry inhibitors targeting human ACE2 by molecular docking.
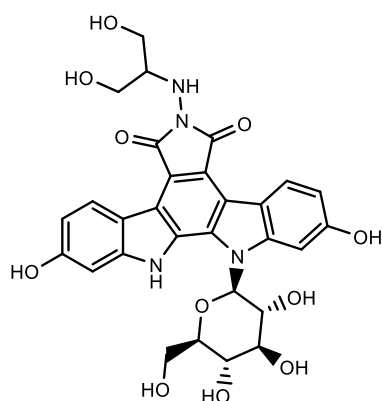
Figure 4. Structure of edotecarin (**8**).

Compound **8**, by means of electrostatic interactions, favors the closed (substrate/inhibitor-bound) conformation of angiotensin-converting enzyme 2 modifying the positions of the receptor's amino acids interested in recognition by SARS-CoV-2. Specifically, the diol group of topoisomerase I inhibitor (**8**) is crucial for the interaction; the catalytic residues of ACE2 mainly interested in interacting with **8** are Glu375, Tyr515, and Asn149. Furthermore, **8** with conjugative *p*-planes performs pep interactions (sandwich or T-shaped) with the amino acids Phe274, His345, and Tyr510 [50]. As already discussed, modulators of expression levels of proteins such as ACE2 may control the SARS-CoV-2 infection [55].

In 2022, Serra et al. [56] studied the synergistic effect of an analog of edotecarin (**9**, Figure 5) and bafetinib. In particular, with computational methods, they found that 7-hydroxystaurosporine (**9**), ((5*S*,6*R*,7*R*,9*R*,16*R*)-16-hydroxy-6-methoxy-5-methyl-7-(methylamino)-6,7,8,9,15,16-hexahydro-17-oxa-4*b*,9*a*,15-triaza-5,9-methanodibenzo[*b,h*] cyclonona[*jkl*]cyclopenta[*e*]-as-indacen-14(5*H*)one), and bafetinib (4-[[(3*S*)-3-(dimethyl amino)pyrrolidin-1-yl]methyl]-*N*-[4-methyl-3-[(4-pyrimidin-5-ylpyrimidin-2-yl)amino] phenyl]-3-(trifluoromethyl)benzamide), inhibit viral infection when combined together.
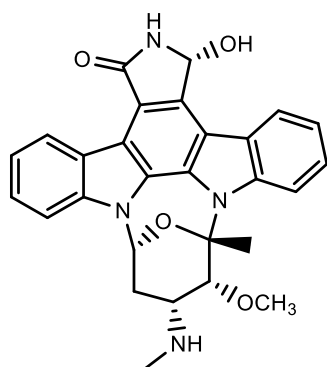

Figure 5. Structure of 7-hydroxystaurosporine (**9**).

In vitro studies confirmed that these compounds, used in combination, hinder a post-entry mechanism of the virus and efficacy against the Delta variant. HEK-293 T cells stably expressing human ACE2 and TMPRSS2 (HEK-293 TAT), infected with the SARS-CoV-2 strain isolated from Wuhan, were used for the experiments. The drugs were tested at concentrations of 0.09, 0.9, and 9 μM. Antineoplastic agent **9** and bafetinib (second-generation tyrosine kinase inhibitor) showed significant inhibition at 9 μM. The combination of bafetinib and 7-hydroxystaurosporine (**9**) on Caco2-ACE2 cells (Caco2 is an immortalized cell linehuman colorectal adenocarcinoma cells) has also been studied using 1 or 3 μM concentrations of drug **9** in combination with 3 μM bafetinib. At 3 μM, the treatment decreased infection by >70%. The synergistic effect was also observed for the Delta variant in a concentration-dependent manner [56,85,86]. Another staurosporine analog (**10**, Figure 6)

(sodium 3-(4-(((*S*)-5-((5*S*,7*S*,8*R*,9*S*)-8-methoxy-9-methyl-16-oxo-6,7,8,9,15,16-hexahydro-5*H*,14*H*-4*b*,9*a*,15-triaza-5,9-methanodibenzo[b,h]cyclonona[jkl]cyclopenta[e]-as-indacen-7-yl)-4-oxohexanamido)methyl)-1*H*-1,2,3-triazol-1-yl)propane-1-sulfonate), called CIMSSNa, was studied in 2022 by Cheshenko et al. as SARS-CoV-2 inhibitor. Experiments conducted on three cell lines (Vero, Huh7 and Calu-3 cells) confirmed that **10** inhibits SARS-CoV-2 and that SARS-CoV-2 enters the cells by direct fusion (at least partly) [57].
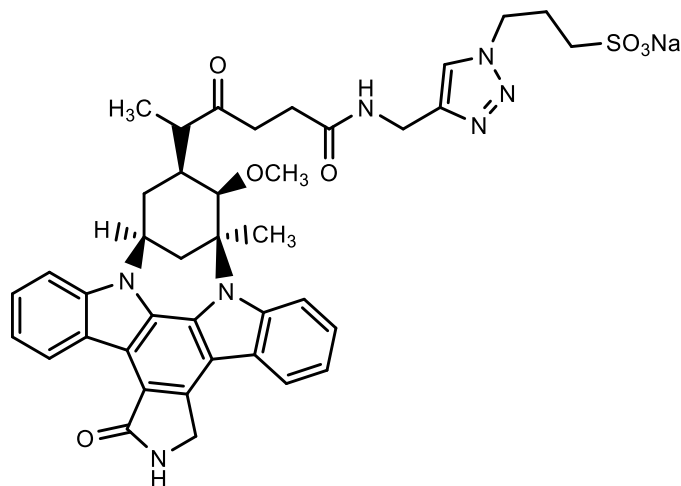

Figure 6. Structure of CIMSSNa (**10**).

Intead, Tanimoto et al. in 2021 [58] proved that treatment with AHR agonists (aryl hydrocarbon receptor agonists), as 6-formylindolo(3,2-*b*)carbazole (**11**, Figure 7), decreases expression of ACE2 via AHR activation, resulting in the suppression of SARS-CoV-2 disease in mammalian cells. The studies were conducted on HepG2 cells. RNA-seq analysis demonstrated that **11** increased CYP1A1 gene expression in a dose-dependent manner and inhibited the expression of the ACE2 gene. Also, the ACE2 expression in Vero E6 cells (Vero C1008 African green monkey kidney cell LIne, Clone E6) was valued [87]; again ACE2 expression is downregulated by treatment with **11**. Therefore, these results demonstrated that formylindolo carbazole **11**, the agonist of AHR, blocks the expression of ACE2 in mammalian cells, limits the entry of SARS-CoV-2, and stimulates the immune system [58].
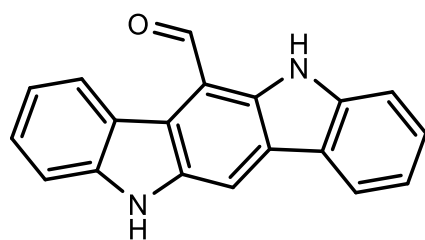

Figure 7. Structure of 6-formylindolo(3,2-*b*)carbazole (**11**).

4.3. NPC1 Inhibitor

García-Dorival et al. in 2021 [59] reported a link between the SARS-CoV-2 nucleoprotein (N) and NPC1. They have pointed out that several molecules interact with NPC1, as 2-((2-(1-benzylpiperidin-4-yl)ethyl)amino)-*N*-(9*H*-carbazol-9-yl)acetamide (**12**, Figure 8) were able to decrease SARS-CoV-2 infection with excellent selectivity in human cell infection models. In fact, **12** inhibited more than 95% of the infection of SARS-CoV-2 in Vero-E6 (Vero C1008 African green monkey kidney Cell Line, Clone E6) and A549 (epithelial cells) cells. These data suggest the importance of NPC1 for SARS-CoV-2 viral infection; NPC1, therefore, represents a potential therapeutic target to fight against SARS-CoV-2 infection [59].
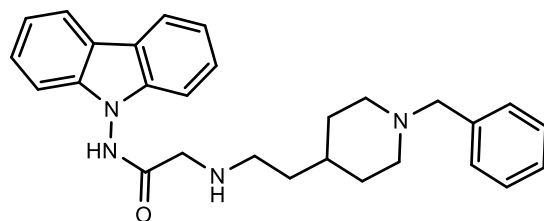
Figure 8. Structure of 2-((2-(1-benzylpiperidin-4-yl)ethyl)amino)-*N*-(9*H*-carbazol-9-yl)acetamide (**12**).

4.4. Antiviral against PLpro

Elkaeed et al. in 2022 [60] carried out computational methods such as similarity assessment, fingerprints check, docking, absorption, distribution, metabolism, excretion, toxicity (ADMET), and density-functional theory (DFT) on different metabolites of natural origin as carbazole **13** (Figure 9), (6-cyano-5-methoxy-12-methylindolo [2,3A] carbazole). This was reported as antiviral against PLpro. The binding ability against PLpro was screened through docking studies. In order to confirm the inhibitory effect of the compounds they examined against PLpro and SARS-CoV-2, other studies such as in-vitro and in-vivo studies are needed [60].
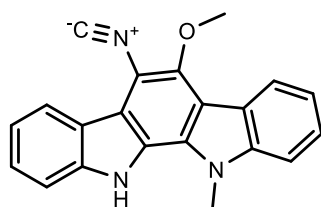

Figure 9. Structure of 6-cyano-5-methoxy-12-methylindolo [2,3A] carbazole (**13**).

4.5. Immunotherapy Treatment

As suggested by Gupta and Chiang in 2020 [70], in the development of the COVID-19 infection, an immunotherapy treatment, for example with ramatroban (**14**, Figure 10) ((3-[(3*R*)-3-[(4-fluorophenyl)sulfonylamino]-1,2,3,4-tetrahydrocarbazol-9-yl]propanoic acid)), could be necessary in case of lymphopenia, a predictor of disease severity and outcomes.
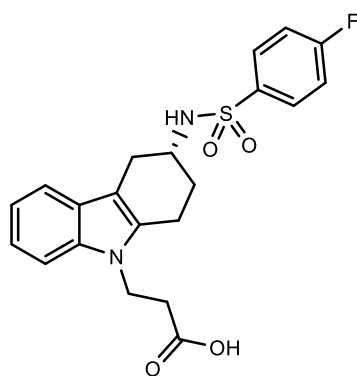

Figure 10. Structure of ramatroban (**14**).

Ramatroban (**14**), a selective PGD2 inhibitor and IL-13 secretion stimulator (IC_{50} = 118 nM) may be needed to restore immune dysfunction during the symptomatic phase of COVID-19. Also, in 2002, Chiang et al. [61] reported in a review that **14** produces beneficial effects at all stages of SARS-CoV-2 infection as it is an immunomodulator, antithrombotic, anti-inflammatory, and antifibrotic agent. For these reasons, drug **14** gave relief of dyspnea and hypoxemia in patients with COVID-19 and, as reported in the study by Ogletree et al. [62] in 2022, it was possible to avoid hospitalization.

5. Conclusions

COVID-19 is a multi-organ disease involving immune deficiency and severe lung inflammation related to an inappropriate immune response and increased cytokine production. Therefore, the therapeutic methods currently being studied include the treatment with a combination of dual agents such as anti-proinflammatory cytokines and antivirals, passive immunotherapy and monoclonal antibodies, or anti-infectious and life-support therapies.

Several treatment approaches for COVID-19 have been employed since the beginning of the pandemic, such as antiviral, antimicrobial, anti-inflammatory, immunomodulator agents, antagonists of bradykinin B2 receptor, blockers of angiotensin II receptor, and corticosteroids, but many of them were found to be ineffective. Thus, the identification of effective drugs to treat COVID-19 is badly needed. Studies and observations reported in this review about treatment with carbazoles (Table 1) may represent a potentially useful clinical application, however, further investigations are required to clarify the details.

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