Carbazoles Treatment for COVID-19 Infection

Subjects: Chemistry, Medicinal

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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. Carbazoles represent an interesting class of heterocycles known by their anticancer activity: antibacterial, anti-inflammatory, antifungal, antioxidant, antimicrobial, antiepileptic, antihistamine, antiviral. In addition, numerous carbazole derivatives have also been found to be useful for Alzheimer's disease.

COVID-19 carbazoles alkaloids Coronaviruses SARS-CoV-2

1. SARS-CoV-2 M-Pro Inhibitors

Protease M-pro, also known as chymotrypsin-like protease, (3CL-pro) is an enzyme that only exists in the virus and not in humans [1][2]. For this reason, Mpro is an interesting target for the discovery of new antivirals [3]. Gimeno et al. in 2020 [4] 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 [4].

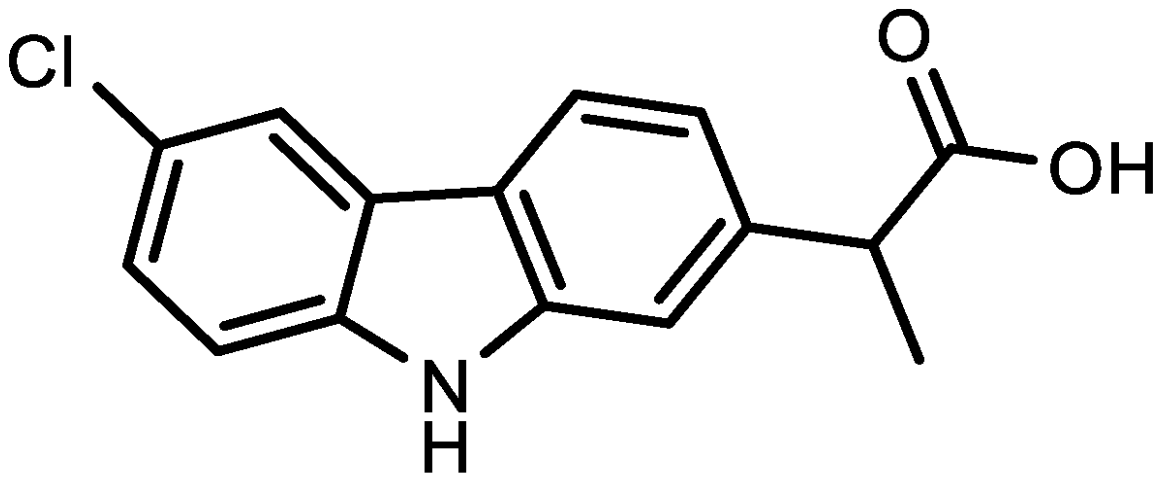

Figure 1. Structure of carprofen (**1**).

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.

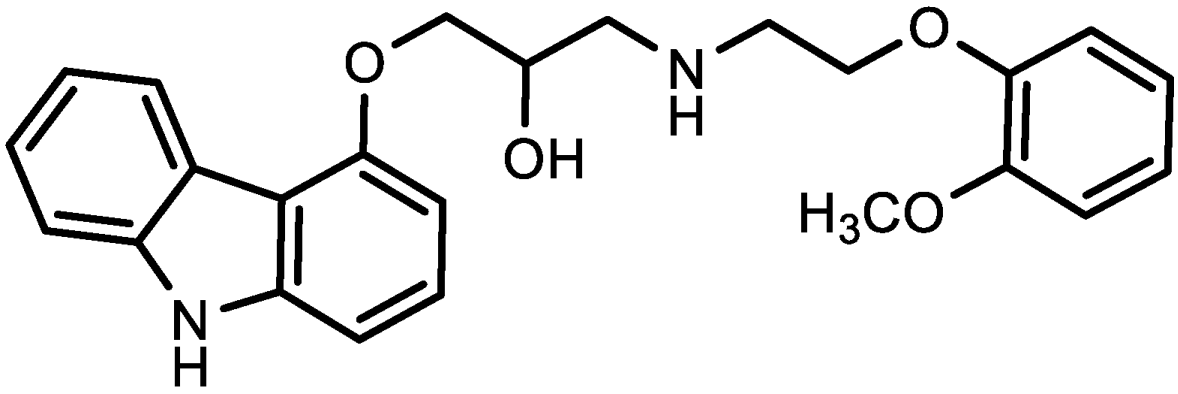

Figure 2. Structure of carvedilol (**2**).

In silico studies allowed researchers 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 research supports the computational work carried out in 2020 by Zhou et al., showing the important role of carvedilol in the treatment of COVID-19 [6][7] and

that of Wu et al. [8] 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. [9] 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 [10]. Also, according to the report of Onohuean et al. [11] 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 [12]. 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 [13]. Also, **2** effectively manages Coronavirus disease 2019 complications such as esophageal varices [14] and post-COVID-19 sinus tachycardia [15]. 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 [16].

Several studies show the antiviral property of plant-derived molecules against RNA viruses [17]. 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 [18][19]. For such evidence, Wadanambi et al. in 2022 [20] 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.

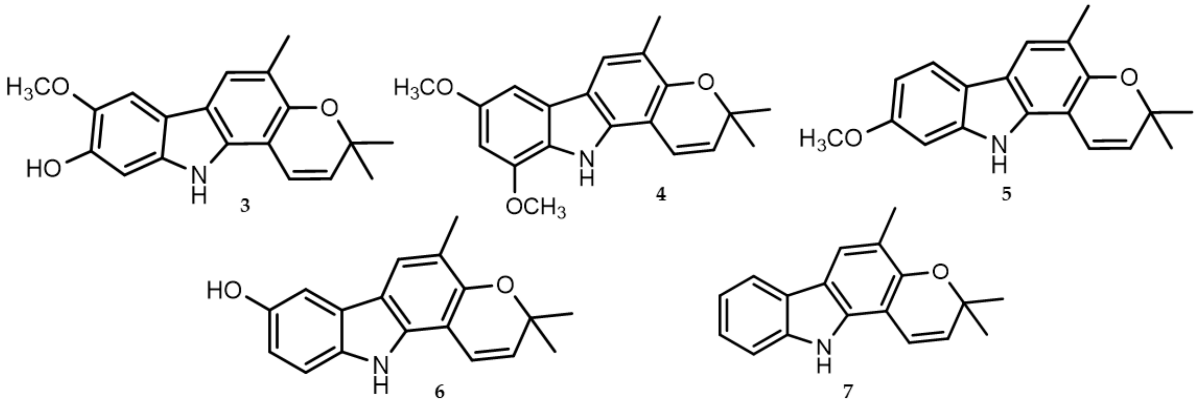

Figure 3. Structures of: koenigicine (**3**), mukonicine (**4**), O-methylmurrayamine A (**5**), koenine (**6**) and girinimbine (**7**).

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 [21]. 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 [22], 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 [20].

2. Viral-Entry Inhibitors Targeting Human Angiotensin 2 Converting Enzyme Receptor

Terali et al. in 2020 [23] 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 angiotensin 2 converting enzyme receptor (ACE2) by molecular docking.

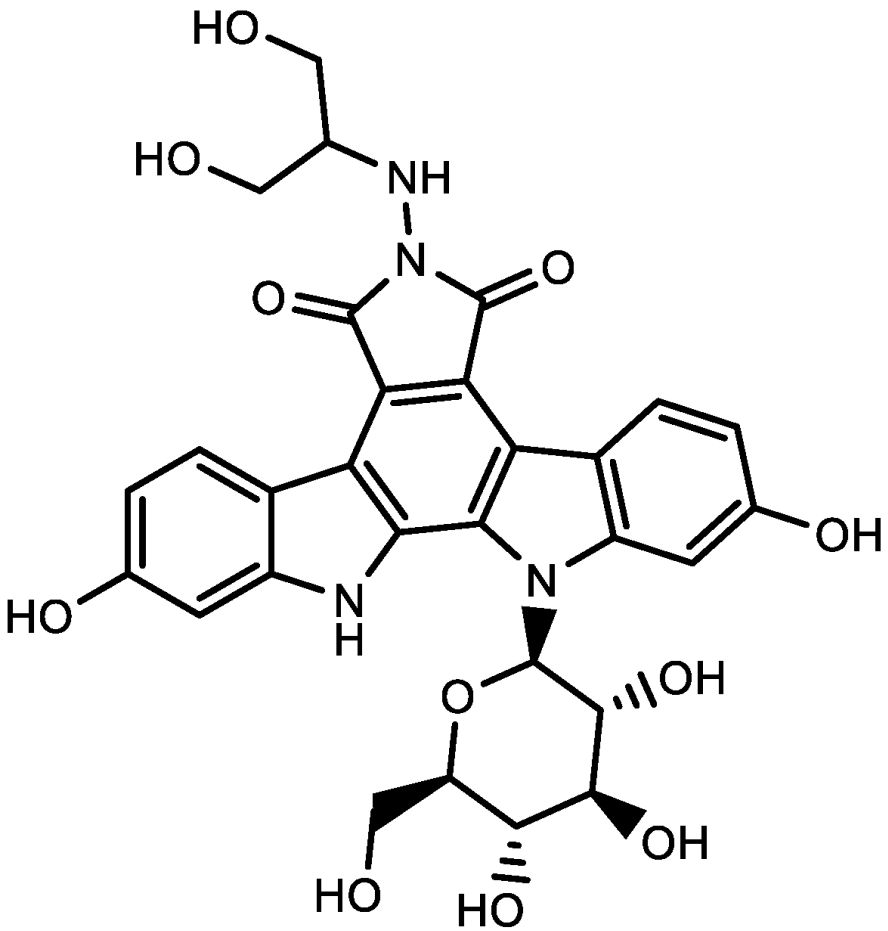

Figure 4. Structure of edotecarin (**8**).

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 [14]. As already discussed, modulators of expression levels of proteins such as ACE2 may control the SARS-CoV-2 infection [24].

In 2022, Serra et al. [25] 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.

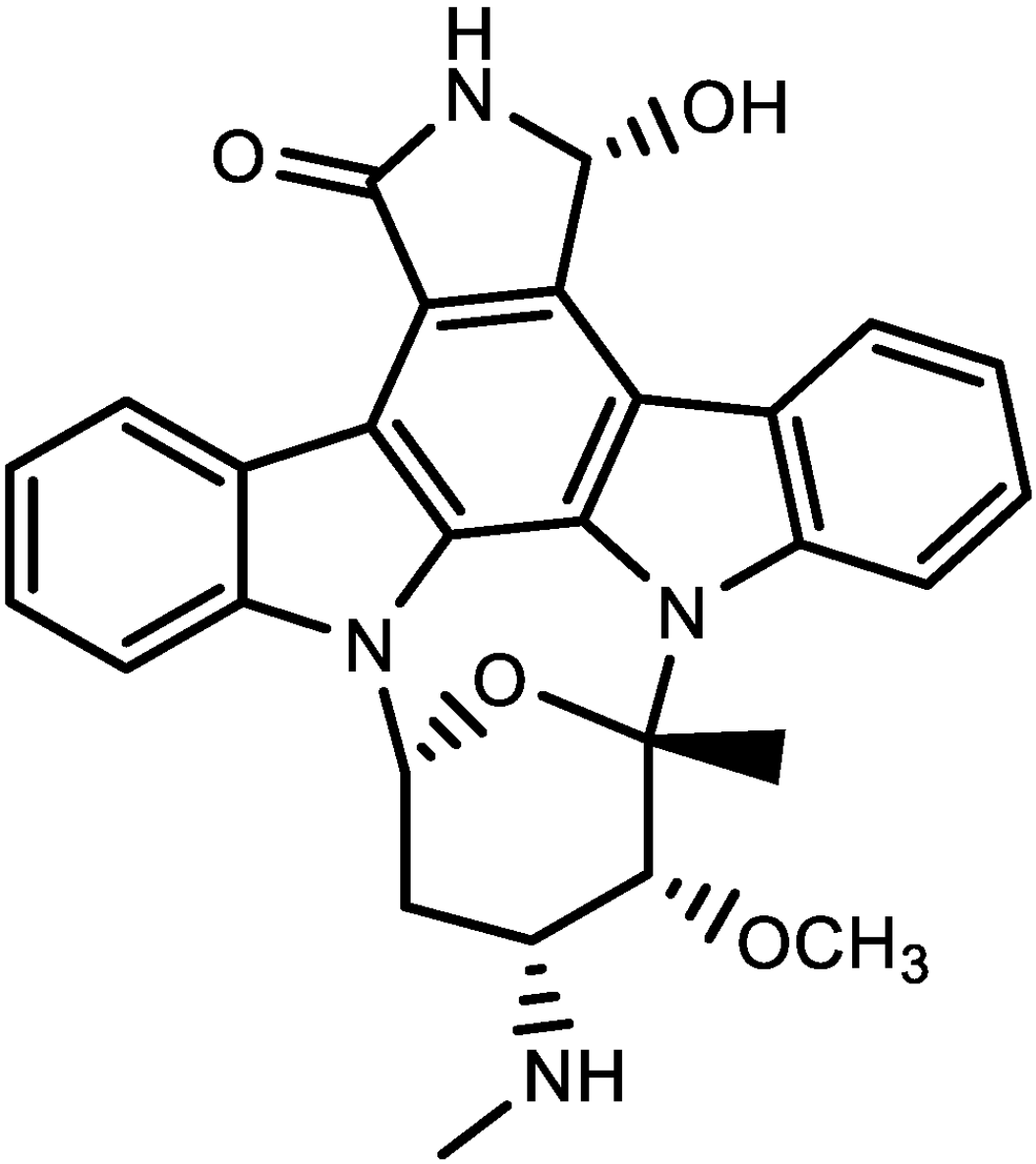

Figure 5. Structure of 7-hydroxystaurosporine (**9**).

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 [25][26][27]. 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) [28].

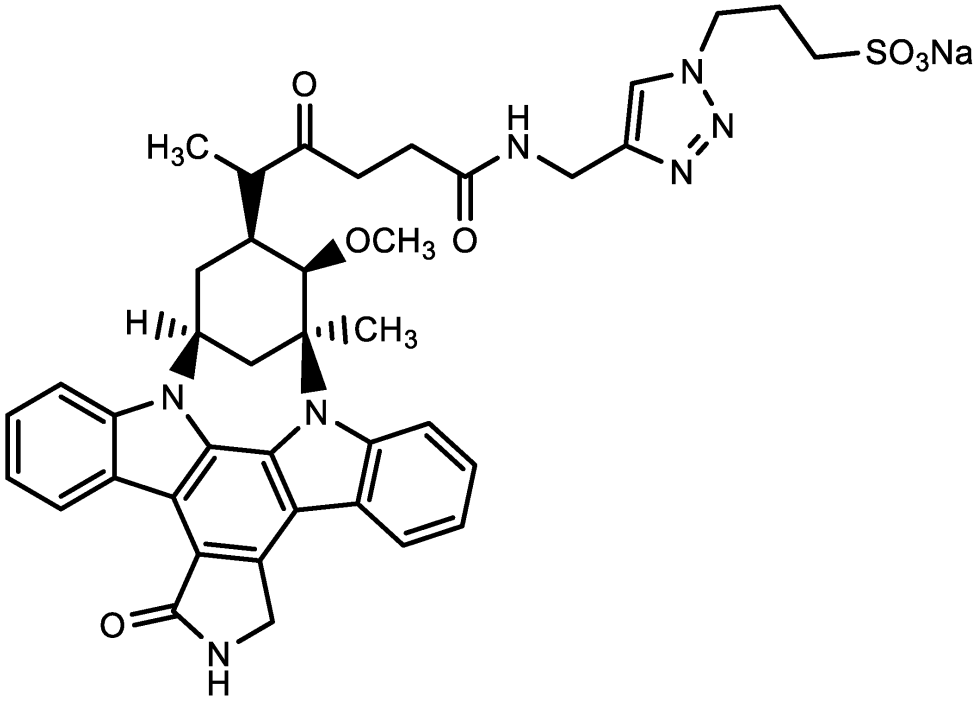

Figure 6. Structure of CIMSSNa (**10**).

Intead, Tanimoto et al. in 2021 [29] 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 [30]; 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 [29].

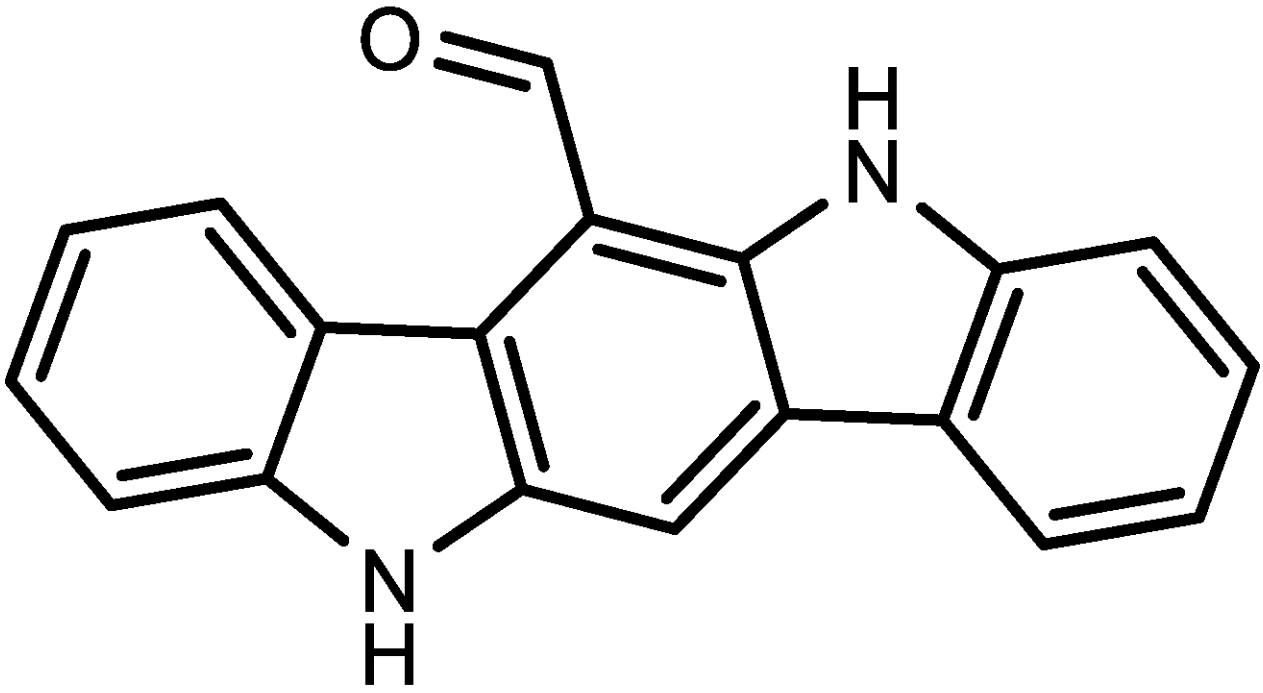

Figure 7. Structure of 6-formylindolo(3,2-*b*)carbazole (**11**).

3. Niemann-Pick Type C1 Inhibitor

García-Dorival et al. in 2021 [31] reported a link between the SARS-CoV-2 nucleoprotein (N) and NPC1. They have pointed out that several molecules interact with Niemann-Pick type C1 (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 [31].

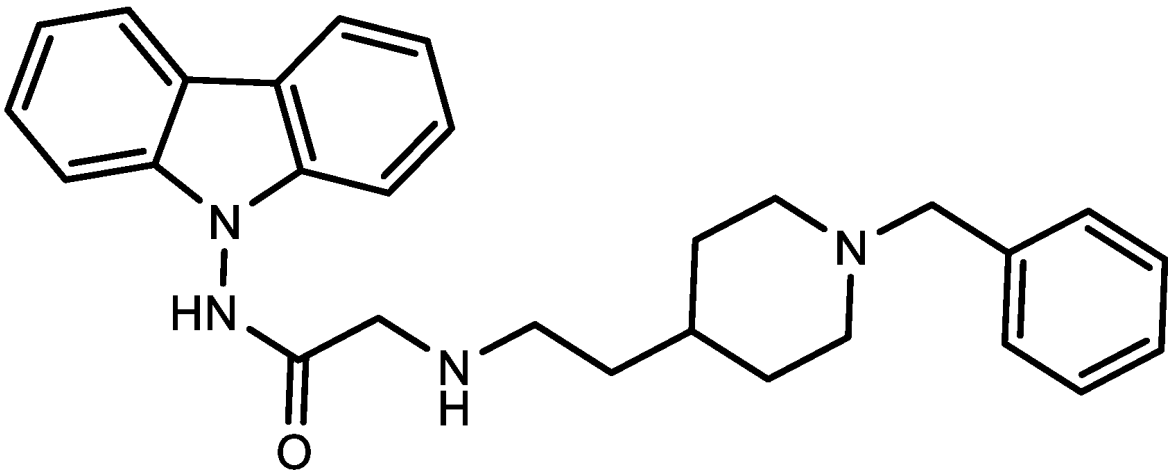

Figure 8. Structure of 2-((2-(1-benzylpiperidin-4-yl)ethyl)amino)-*N*-(9*H*-carbazol-9-yl)acetamide (**12**).

4. Antiviral against Papain-Like Protease

Elkaeed et al. in 2022 [32] 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 papain-like protease (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 [32].

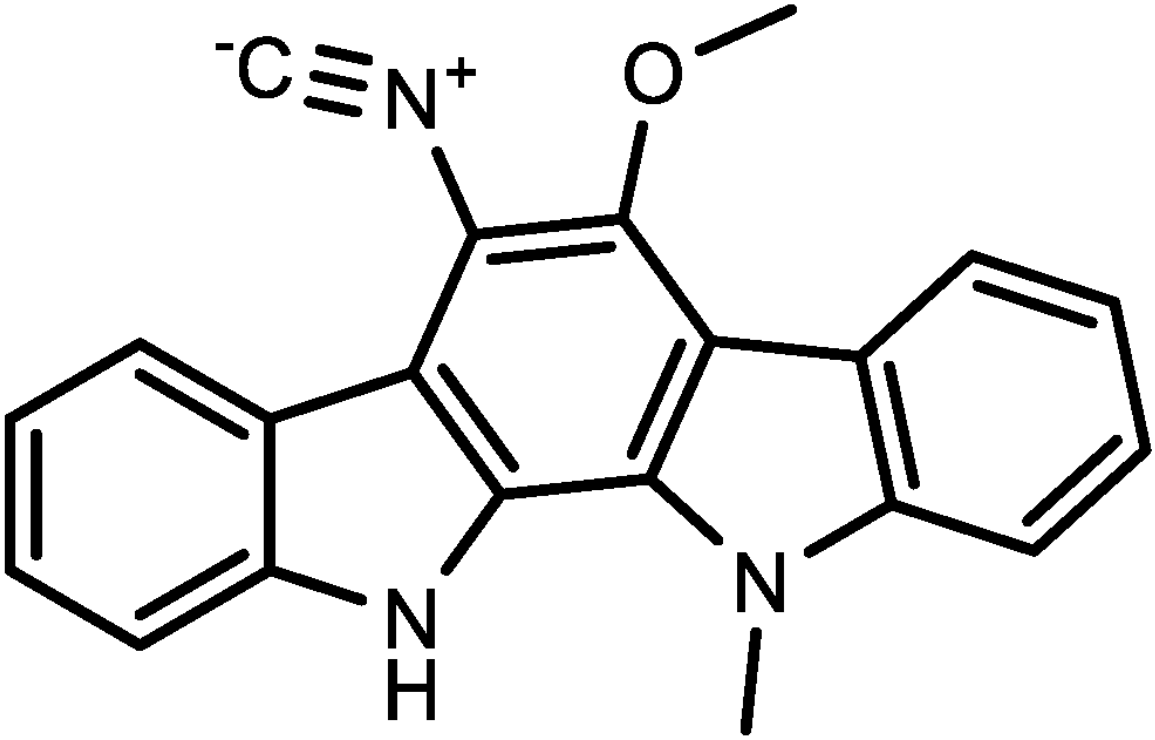

Figure 9. Structure of 6-cyano-5-methoxy-12-methylindolo [2,3A] carbazole (**13**).

5. Immunotherapy Treatment

As suggested by Gupta and Chiang in 2020 [33], 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.

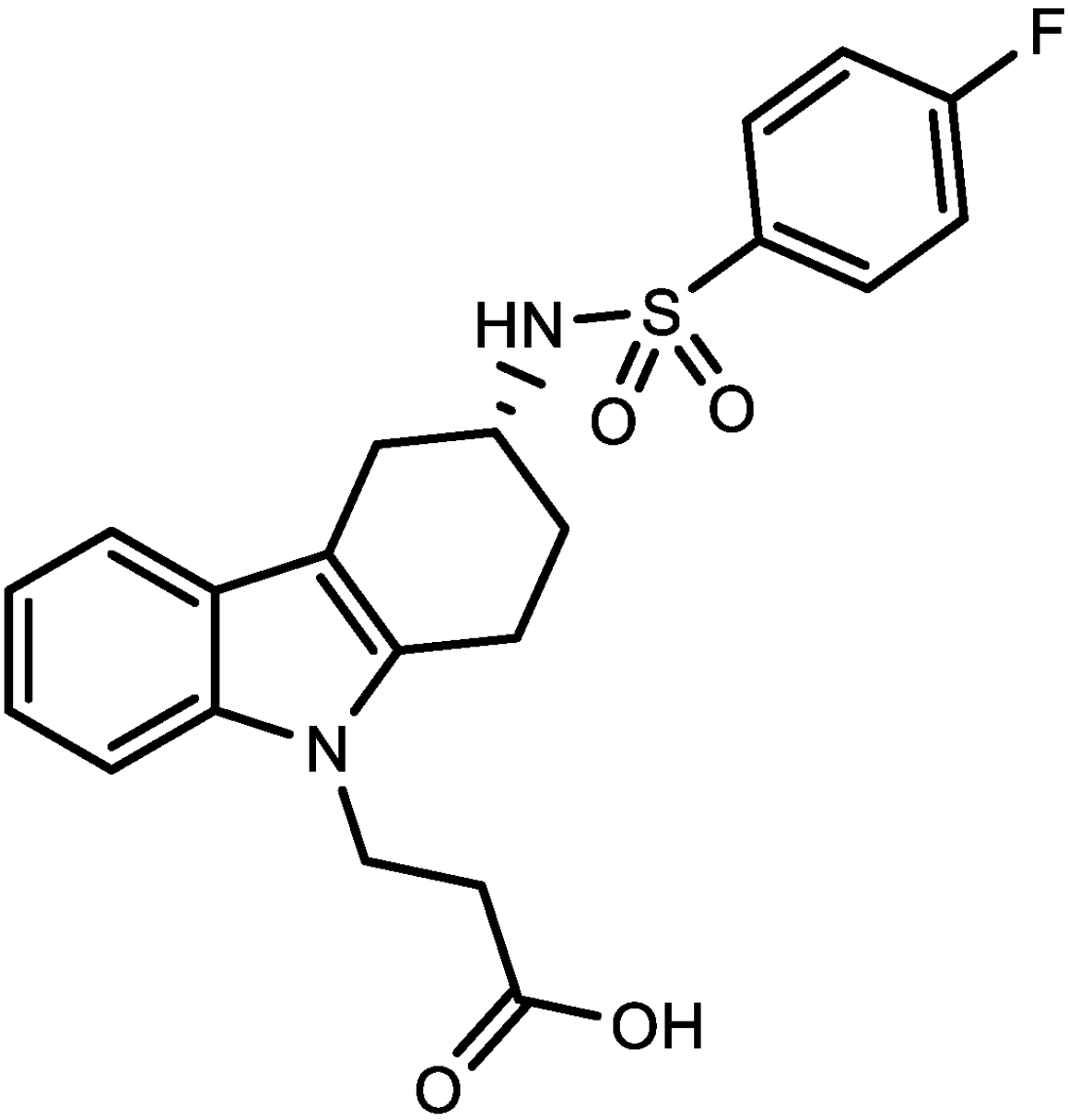

Figure 10. Structure of ramatroban (**14**).

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. [34] 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. [35] in 2022, it was possible to avoid hospitalization.

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