Quinones as Promising Compounds against Respiratory Viruses

Subjects: Others

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Respiratory viruses represent a world public health problem, giving rise to annual seasonal epidemics and several pandemics caused by some of these viruses, including the COVID-19 pandemic. Some antiviral drugs have been licensed for the treatment of influenza and respiratory syncytial virus, but they cause side effects, lead to resistant viral strains, or possess various limitations. On the other hand, no specific drugs are licensed to treat other viral respiratory diseases. In this sense, natural products have appeared as promising alternatives in searching for new compounds with antiviral activity. Quinones have demonstrated activity against respiratory viruses, so the activity of the different types of natural and synthetic quinones against these pathogens and their molecular targets are summarized.

Keywords: influenza ; SARS-CoV-2 ; naphthoquinone ; anthraquinone

1. Introduction

Respiratory viruses are a group of pathogens that elicit upper or lower respiratory tract infections [1]. Upper respiratory tract infections affect the nasal cavity through the larynx and have common symptoms, such as cough, sore throat, nasal congestion, sneezing, rhinorrhea, sinus pain, myalgia, headache, fever, chills, and loss of appetite. Lower respiratory tract infections occur below the larynx and can also cause bronchitis, bronchiolitis, and pneumonia [2]. Human respiratory viruses cause these symptoms after infecting and replicating in cells of the respiratory tract. Subsequently, these pathogens are transmitted mainly through the respiratory secretions of infected people by direct (physical) or indirect contact (contaminated objects or surfaces), as well as by droplets or aerosols [3][4].

Viral respiratory diseases represent an important problem for global public health with an enormous economic burden. These respiratory infections are among the most frequent illness in humans, mainly in children, older adults, and immunosuppressed people, making them the most vulnerable populations. In children and older adults, viruses cause 95% and 40% of all respiratory infections, respectively. In addition, respiratory tract infections are associated with significant mortality worldwide. According to the World Health Organization (WHO), in 2019, lower respiratory infections ranked fourth among the leading causes of death in the world, with 2.6 million deaths. WHO also ranked respiratory infections as the second leading cause of death worldwide in children <5 years of age, estimating 1.9 million deaths annually for complications related to acute respiratory infections [5][6][7]. Respiratory viruses include the parainfluenza viruses (PIVs), human metapneumoviruses (HMPVs), respiratory syncytial viruses (RSVs), adenoviruses (AdVs), rhinoviruses (RVs), bocaviruses (BoVs), influenza viruses, and coronaviruses (CoVs) [8].

2. Respiratory Viruses

2.1. Parainfluenza Virus (PIV), Human Metapneumovirus (HMPV), and Respiratory Syncytial Virus (RSV)

PIV, HMPV, and RSV are respiratory viruses belonging to the *Paramyxoviridae* family. These pathogens are enveloped viruses containing a non-segmented negative-sense single-stranded RNA (ssRNA) genome. Globally, these viral agents are characterized by causing significant morbidity and mortality, mainly among children in developing countries [9][10]. RSV is among the most important pathogens causing lower respiratory tract infections in childhood. However, immunosuppressed people and older adults are also at high risk of developing complications from RSV infections. There is a single RSV serotype with two antigenic subtypes (A and B), which circulate together, but only one subtype predominates. Although RSV mortality is more common in developing countries, the social and economic burden associated with this virus is high worldwide [11][12].

Human PIVs (HPIVs) include four serotypes (HPIV1-4) and represent one of the main causes of acute respiratory infections. These viruses affect people of all ages but cause lower respiratory tract infections that can lead to serious illness in infants and young children. HPIVs infection rates are highest in children <5 years of age, followed by patients >60 years of age. In healthy young adults, this disease is usually mild and restricted to the upper respiratory tract [13][14].

2.2. Adenovirus (AdV)

AdVs are non-enveloped icosahedral pathogens that possess a double-stranded DNA (dsDNA) genome and belong to the *Adenoviridae* family [15]. These viruses are divided into seven species (A to G) with 103 recognized types. Respiratory infections associated with human AdVs (HAdVs) are mainly caused by genera B (types 3, 7, 14, 21, and 55), C (types 1, 2, and 5), and E (types 4 and 41). Although most respiratory infections caused by these viruses are mild to moderate in severity, HAdV-B types 3, 7, 14, and 55 can cause severe infections and life-threatening outbreaks.

2.3. Rhinovirus (RV)

Human RVs (HRVs) belong to the *Picornaviridae* family and are non-enveloped viruses with positive-sense ssRNA. HRVs are classified into A, B, and C species, which have approximately 80, 32, and 57 types, respectively. RVs are among the most frequent respiratory viruses in humans, causing significant morbidity and high annual economic losses. These pathogens are responsible for the common cold and cause more than 50% of upper respiratory tract infections. HRVs are involved in lower respiratory illnesses such as pneumonia, bronchitis, and bronchiolitis, as well as exacerbations of chronic obstructive pulmonary disease (COPD) and asthma.

2.4. Bocavirus (BoV)

Recently, human BoVs (HBoVs) have appeared as new respiratory pathogens. These non-enveloped viruses are found in the *Parvoviridae* family and contain a linear negative- or positive-sense ssDNA genome. There are four types of HBoVs (HBoV1-4), and infections caused by these viral agents are more common during winter and spring, although they are present all year.

2.5. Influenza Virus

Influenza viruses are another group of enveloped respiratory viruses that belong to the *Orthomyxoviridae* family and contain a genome consisting of negative-sense ssRNA segments. The *Orthomyxoviridae* family includes four types of influenza viruses (A to D). Influenza A and B viruses mainly affect humans, being responsible for annual seasonal epidemics. Influenza B infections are highly contagious and sometimes lead to severe illness. In contrast, influenza A infections are the most common and cause mild to severe respiratory illness. Influenza C viruses are the least common and produce milder infections compared to influenza A and B, while there are no reports of influenza D viruses infecting humans [16][17].

2.6. Coronavirus (CoV)

CoVs are enveloped viruses with a non-segmented positive-sense ssRNA. These viruses belong to the *Coronaviridae* family and are divided into four genera (alpha, beta, gamma, and delta CoVs). Gamma and delta CoVs cause avian CoV infections (birds are the natural reservoirs of these viruses), whereas mammalian CoV diseases are mainly associated with alpha and beta CoVs (bats and rodents are the natural reservoirs). There are seven human CoVs (HCoVs) that cause infections, four of which (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) cause mild seasonal respiratory tract diseases around the world. In contrast, three highly pathogenic HCoVs have been identified this century: severe acute respiratory syndrome CoV (SARS-CoV), Middle East respiratory syndrome CoV (MERS-CoV), and severe acute respiratory syndrome CoV 2 (SARS-CoV-2) [18][19][20].

3. Pharmacological Treatments for Respiratory Virus Infections

Viral respiratory infections represent one of the main causes of medical consultations in the world, so the prevention and treatment of these diseases remain an important objective. Antiviral therapy drugs prevent the activity of viral proteins involved in the multiple stages of the replication cycle of respiratory viruses, such as structural proteins or replication enzymes [21][22][23]. Antiviral drugs also play an important role in the prophylaxis and treatment of influenza infections. Ion channel protein (M2) blockers, NA inhibitors, and viral polymerase inhibitors are the three classes of antivirals approved for clinical use. The first drugs licensed for influenza treatment were adamantanes (amantadine and rimantadine), which act by blocking M2 ion channels. Nevertheless, adamantanes are only effective against influenza A viruses, and even

resistant strains to these therapeutic agents have emerged, which are still in circulation. Therefore, adamantanes are no longer recommended in therapy against this disease [24][25].

Currently, the only class of antivirals appropriate for influenza therapy is NA inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir). Although these drugs can inhibit all NA types and subtypes of influenza viruses by binding to the catalytic site of the enzyme, influenza A and B viruses resistant to NA inhibitors have also recently emerged [26][27].

On the other hand, aerosolized ribavirin is the only antiviral drug licensed for the treatment of RSV infections, although its use is limited due to issues with efficacy, toxicity, and cost. Therefore, this drug has only been employed for the treatment of life-threatening infections in immunosuppressed patients. The use of ribavirin has not caused a significant decrease in mortality or duration of hospitalization in patients with RSV disease, so other alternatives for the treatment of RSV infections are being explored. Still, it will be several years until they are approved [28].

Unlike the previous viruses, there are currently no specific drugs approved for the prophylaxis and therapy of infections by HPIVs, HMPVs, HAdVs, HRVs, and HBoVs. In many cases, management of infections by these pathogens consists of supportive care to control symptoms or the off-label use of broad-spectrum antiviral agents, such as ganciclovir, cidofovir, or ribavirin for the treatment of HAdVs infections [29][30][31][32][33].

4. Quinones and Respiratory Viruses

Various studies have reported the anti-influenza activity of naphthoquinone-type molecules isolated from different natural sources. The chemical structures of these natural quinones (compounds **1**–**19**) are shown in **Figure 1**.

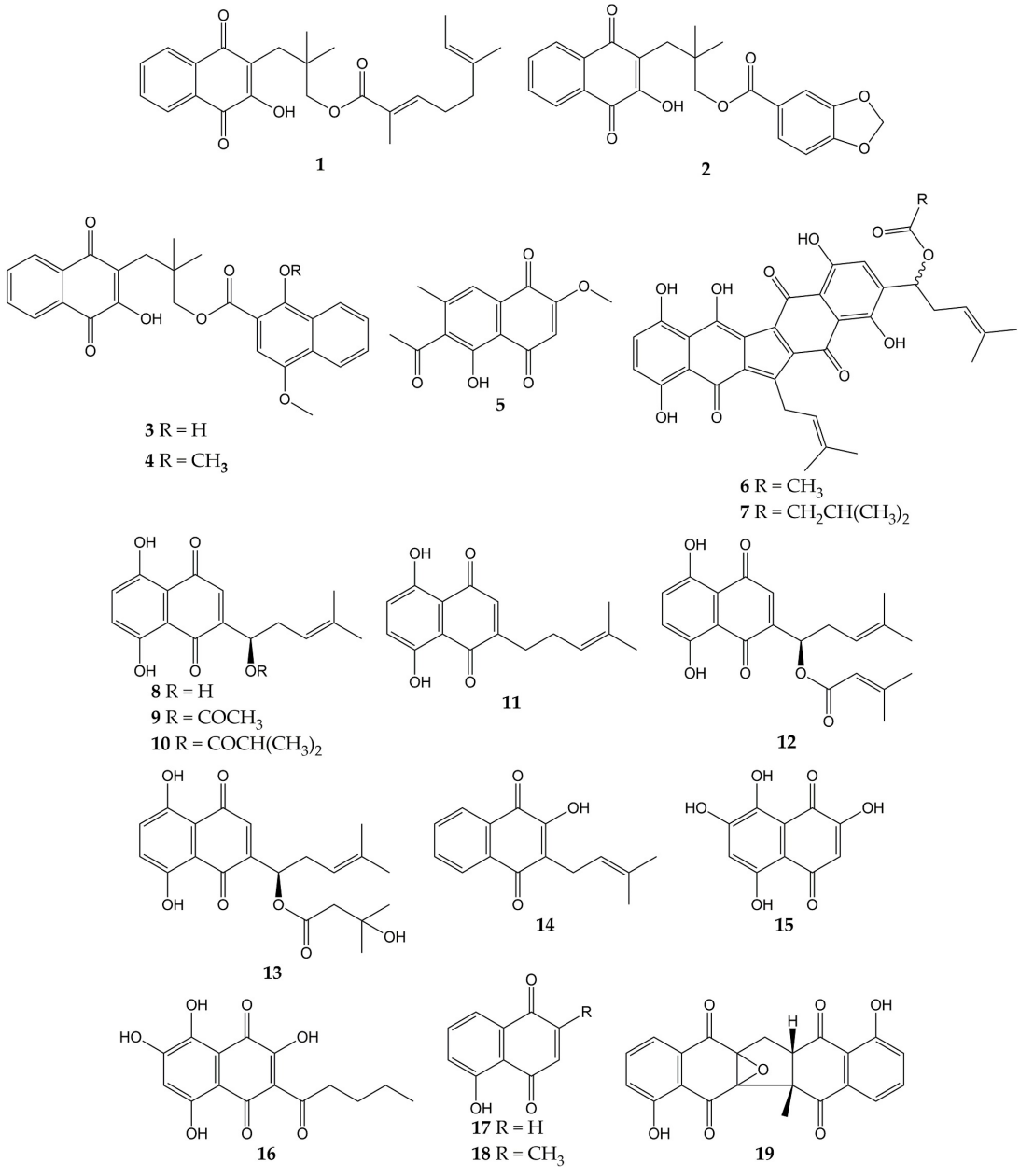

Figure 1. Chemical structures of natural naphthoquinones **1**–**19**.

The antiviral activity of rhinacanthins C (**1**), D (**2**), N (**3**), and Q (**4**) from the roots of *Rhinacanthus nasutus* (a medicinal plant belonging to the Acanthaceae family and employed for the treatment of herpes virus infections) was assessed in infected cells. All compounds inhibited the activity of the influenza virus A/PR/8/34 (H1N1), with mean inhibitory concentration (IC_{50}) values of 0.30, 0.95, 1.95, and 23.7 µM for **1**, **2**, **3**, and **4**, respectively. Previously, the molecules did not show significant cytotoxicity in Vero cells, with mean cytotoxic concentration (CC_{50}) values of 25.89 (**1**) and >50 µM (**2**, **3**, and **4**) [34].

The monomeric naphthoquinone 2-methoxy-6-acetyl-7-methyljuglone (**5**) obtained from the roots of *Polygonum cuspidatum* (a Chinese medicinal herb from the Polygonaceae family with various uses) evidenced an inhibitory activity on NA from *C. perfringens*, with IC_{50} of 8.9 µM [35]. In another research, the anti-NA activity of shikometabolins E (**6**) and F (**7**) was evaluated. The results showed that these dimeric naphthoquinones isolated from the roots of *Lithospermum erythrorhizon* (a perennial herb from the Boraginaceae family with red pigments that are used as dyestuffs in different products) inhibited the functions of the NA from *C. perfringens*, with IC_{50} values of 1.91 µg/mL for **6** and 2.79 µg/mL for **7** [36]. *L. erythrorhizon* roots also contain 1,4-naphthoquinones such as shikonin (**8**) and its derivatives acetylshikonin (**9**), isobutylshikonin (**10**), deoxyshikonin (**11**), β,β-dimethylacrylshikonin (**12**), and β-hydroxyisovalerylshikonin (**13**). These molecules were tested in two NA inhibition assays with sialidases from glycosyl hydrolase (GH) family 33 (*C. perfringens*) and GH34 (influenza virus A/Bervig_Mission/1/18 H1N1). All the natural products exhibited inhibitory activity over the bacterial NA, with IC_{50} of 53.8 (**8**), 2.5 (**9**), 2.9 (**10**), 27.5 (**11**), 1.9 (**12**), and 3.4 µM (**13**). Likewise, these naphthoquinones inhibited the activity of recombinant viral sialidase, with IC_{50} of 34.1 (**8**), 41.4 (**9**), 40.5 (**10**), 63.4 (**11**), 47.3 (**12**), and 40.5 µM (**13**) [37].

In addition to NA glycoprotein, several investigations have explored the potential effect of naphthoquinones on other viral targets, either in computational tests or in vitro experiments. One of these targets is the PA (polymerase acidic) subunit of viral RNA polymerase, which contains an endonuclease active pocket in its N-terminal domain that participates in viral transcription and replication [38]. Recent work revealed the inhibitory activity of some molecules over the N-terminal domain of the influenza A virus PA subunit (the protein was obtained from coding RNA DNA of viral strain A/California/07/09 H1N1) in a novel assay based on AlphaScreen technology (amplified luminescent proximity assay system). Among the evaluated compounds, an endonuclease inhibition was reported by lapachol (**14**), as well as mompain (**15**) and quambalarine B (**16**) obtained from the fungus *Quambalaria cyanescens* (IC_{50} values of 19, 0.43, and 0.29 µM, respectively). In the same study, an X-ray crystallography test evidenced that **16** binds to the N-terminal domain of the PA protein through its 7,8-dihydroxynaphthoquinone moiety and ketone moiety [39].

On the other hand, flexible docking and molecular dynamic simulations have demonstrated that juglone (**17**) was able to interact with active sites of the NA and HA (the most abundant glycoprotein on the viral surface; HA initiates infection by recognizing host cell-surface glycoconjugates with sialic acid as receptors and then by HA-mediated fusion of viral and host cellular membranes). The 2-cyclohexene-1,4-dione moiety of **17** bound to HA from the influenza A(H5N1) virus through hydrophobic interactions with residues Ile155, His183, and Tyr195. The 2-cyclohexene-1,4-dione ring was also bound to NA key binding site residues (Arg156 and Arg292) via electrostatic interactions. Strong H-bond interaction between the -OH group of **17** and the carboxylate group of Glu276 was observed [40][41][42]. According to in silico studies, plumbagin (**18**) can also bind specifically to the active sites of HA and NA proteins of influenza virus A/2009 (H1N1), as well as the M2 ion channel protein, which is involved in the virion entry and assembly of new infectious particles [43][44].

Several studies have focused on the synthesis of naphthoquinones and the evaluation of their activity against influenza viruses. The structures of the anti-influenza synthetic naphthoquinones **20**–**27** are represented in **Figure 2**.

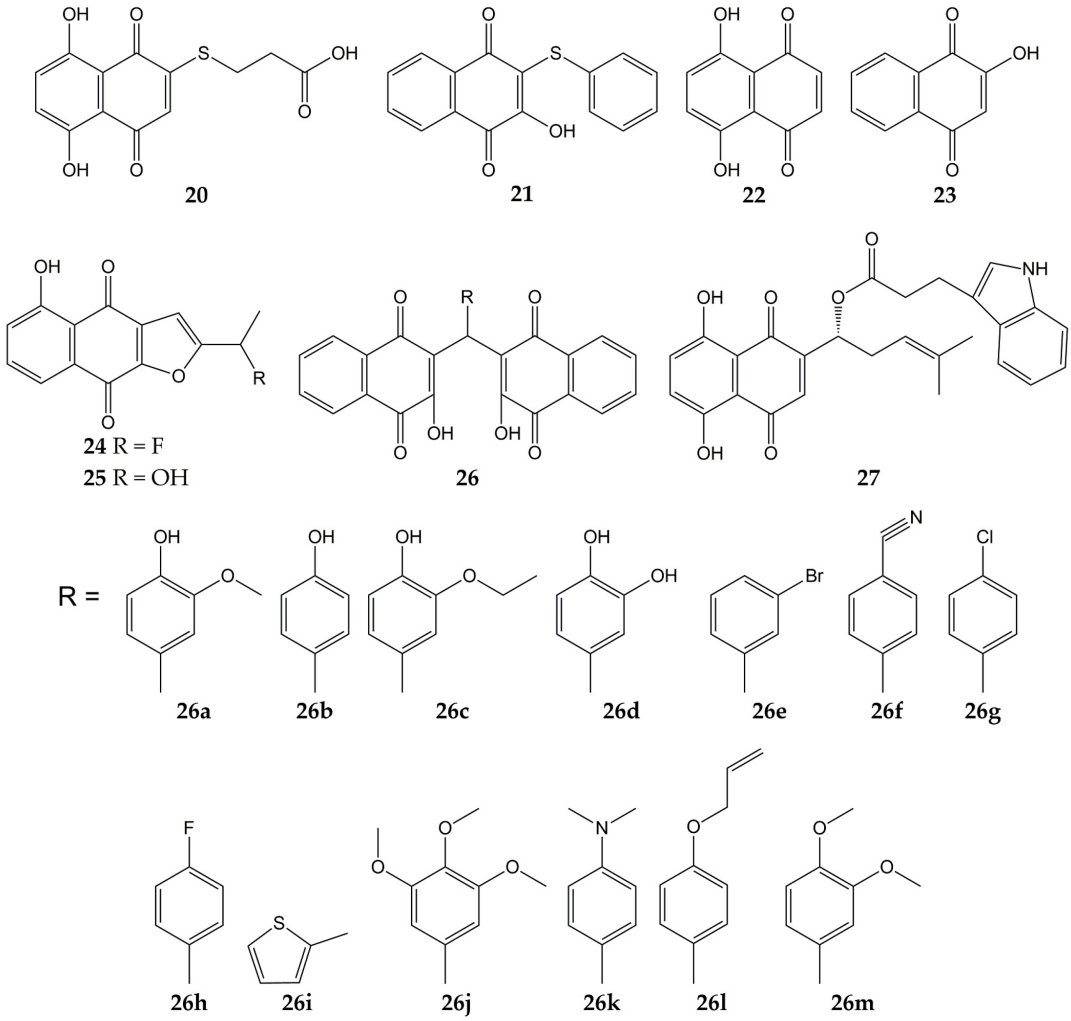

Figure 2. Chemical structures of synthetic naphthoquinones **20**–**27**.

Synthetic naphthoquinone derivatives **20** and **21** (2-substituted- and 2,3-disubstituted-1,4-naphthoquinones) were obtained from naphthazarin (**22**; a natural product present in plants of the families *Boraginaceae*, *Droseraceae*, and *Nepenthaceae*) and lawsone (**23**; a secondary metabolite found in leaves and flowers of *Lawsonia inermis*), respectively. Both synthetic compounds showed in vitro antiviral activity against a strain of influenza A virus (52% for **20** and 50% for **21**) [45][46].

In another research, 3,3′-(arylmethylene)bis(2-hydroxy-1,4-naphthoquinone) analogs (**26a–m**) were synthesized from **23** and substituted aromatic aldehydes. These dimeric derivatives were evaluated with in vitro assays against two NA (*C. perfringens* and influenza A H5N1 virus). All molecules inhibited bacterial NA (percentages of inhibition ranging from 70.9 to 96.6%). Then, the ten analogs with percentages of inhibition >80% were assessed in viral NA inhibition assay; molecules **26a** and **26b** exhibited the lowest IC_{50} values (29 and 26.5 µM, respectively). Further, the docking simulation evidenced that compound **26b** interacts with amino acids of binding pocket from the NA of influenza A(H5N1) virus through H-bonds with Arg118, Arg371, Tyr406, Glu277, Asp151, and Arg152, as well as hydrophobic interactions with Tyr347 [47].

Likewise, the synthesis and antiviral activity of (R)-1-(5,8-dihydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-4-methylpent-3-en-1-yl-3-(1H-indol-3-yl) propanoate (**27**) has been reported. This esterified derivative of **8** promoted cell viability in A549 (human lung carcinoma) and MDCK cells infected with influenza virus A/PR/8/34 (H1N1), with CC_{50} values of 316 and 730 µg/mL, respectively. Compound **27** also reduced viral yield and inhibited influenza virus A/PR/8/34 (H1N1) replication in a dose-dependent manner. Then, the scholars evaluated the effect of the synthesized naphthoquinone on other viral targets and found that **27** inhibited the viral NA activity. Molecular docking analysis showed that **27** could bind specifically to the active site of NA through H-bond interactions with the -NH groups of Arg118, Arg152, and Arg371 and the -OH group of Glu227. Finally, **27** caused a decrement in expression levels of viral NP mRNA in infected cells [48][49].

The anti-influenza activity of several anthraquinones has also been investigated. The structures of these molecules (anthraquinones **28**–**47**) are shown in **Figure 3**.

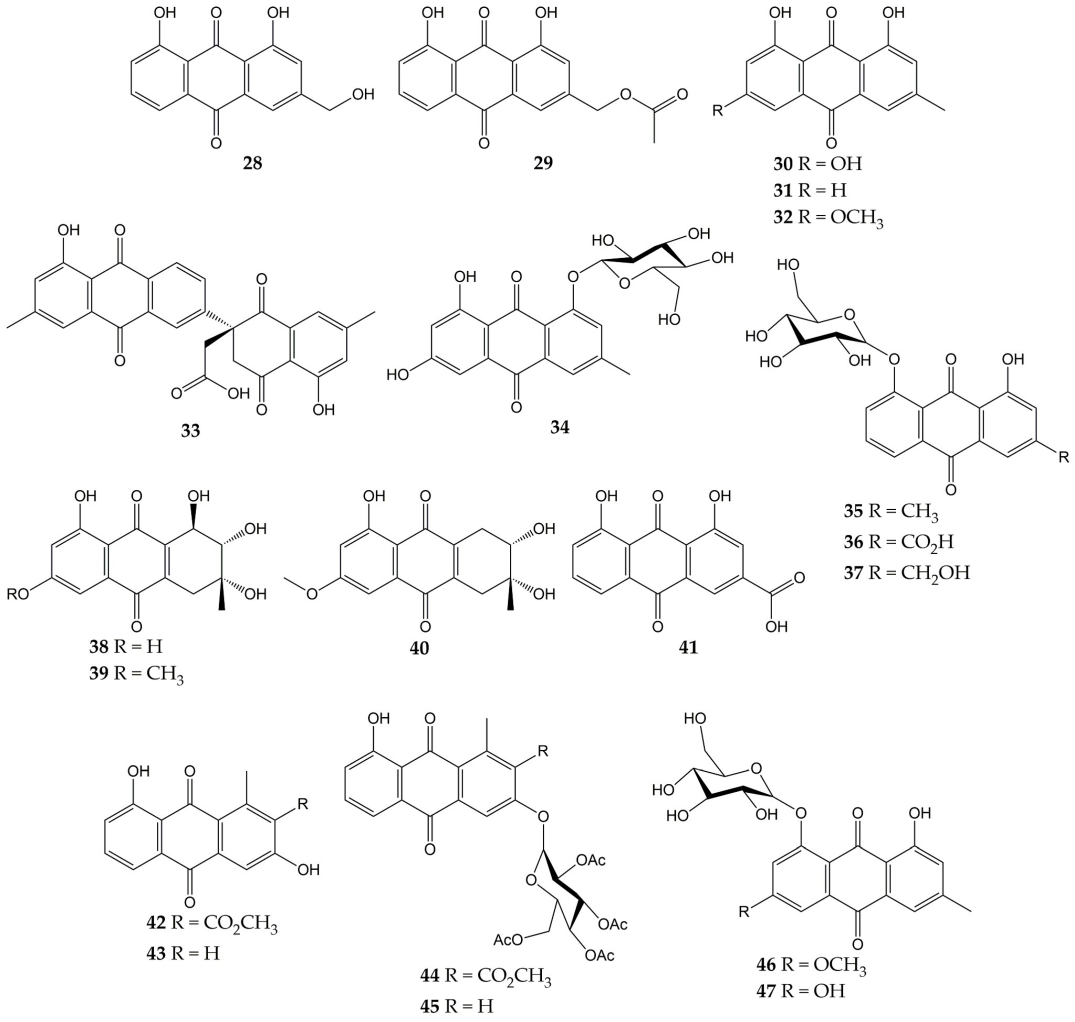

Figure 3. Chemical structures of natural and synthetic anthraquinones **28**–**47**.

In a previous study, the antiviral activity of aloe-emodin (**28**) and aloe-emodin acetate (**29**) was evaluated in infected MDCK cells. These anthraquinones were isolated from the leaves of *Cassia roxburghii* (a medicinal plant from the Fabaceae/Leguminosae family employed due to its laxative and purgative properties), and the results evidenced an inhibitory activity against influenza virus A/WSN/33 (H1N1), with IC_{50} values of 2.00 (**28**) and 10.23 µg/mL (**29**), as well as CC_{50} values of 0.47 (**28**) and 1.32 µg/mL (**29**). The scholars concluded that the antiviral effect of **28** and **29** could be attributed to the number of -OH groups in these structures [50].

Moreover, the antiviral activity of anthraquinone **28** and two derivatives was assessed against another influenza virus strain (A/Taiwan/CMUH01/07 H1N1). After evaluation on MDCK cells, compounds exhibited CC_{50} values of 76.6, 25.7, and 18.3 µg/mL for **28**, emodin (**30**), and chrysophanol (**31**), respectively. Although the three metabolites were demonstrated to reduce the cytopathic effect (CPE) in infected MDCK cells, compound **28** showed the strongest inhibition of virus yield, with an IC_{50} value of less than 0.05 µg/mL.

In another investigation, anthraquinone **30** was isolated from the roots of *Polygonatum odoratum* (a herbaceous plant belonging to the Liliaceae family and used to treat diabetes or rheumatic heart disease), along with physcion (**32**) and a new derivative called polygodoquinone A (**33**; a naphthoquinone analog linked to an anthraquinone via a C-C bond). The three anthraquinones showed inhibitory activity against influenza virus A/WSN/33 (H1N1), with IC_{50} values of 11.0, 11.4, and 2.3 µM for **30**, **33**, and **32**, respectively. The compounds exhibited CC_{50} values of 36.5 (**33**), 79.5 (**30**), and 94.0 µM (**32**) after cytotoxicity evaluation on 293 T-Gluc cells [51].

Furthermore, the cytotoxic and anti-influenza activities of **28**, **30**, **32**, emodin-1-O-β-D-glucopyranoside (**34**), chrysophanol 8-O-glucoside (**35**), rhein 8-glucoside (**36**), and aloe-emodin-8-O-β-D-glucopyranoside (**37**) have been determined. All compounds had no significant cytotoxicity in A549 and MDCK cells (<25 µg/mL). Likewise, these anthraquinones inhibited the activity of influenza virus A/PR/8/34 (H1N1) at concentrations ranging from 12.5 to 25 µg/mL. Natural product **30** also demonstrated to inhibit the activity of several human and avian influenza A virus strains at 6.25–25 µg/mL, which were A/PR/8/34 (H1N1), A/ShanTou/16/09 (H1N1), A/ShanTou/1233/06 (H1N1), A/ShanTou/602/06 (H3N2), A/ShanTou/364/05 (H3N2), A/Quail/HongKong/G1/97 (H9N2), A/Chicken/Guangdong/A1/03 (H9N2), and A/Chicken/Guangdong/1/05 (H5N1).

Finally, the scholars concluded that the pharmacological mechanism of **30** could be attributed to the regulation of various markers involved in the PPARα/γ-AMPK pathway and fatty acid metabolism after numerous biological tests [52].

Several investigations have also focused on evaluating the anti-influenza activity of other types of quinones, such as anthrones, hydroquinones, and benzoquinones. The structures of these quinone derivatives (compounds **48**–**55**) are shown in **Figure 4**.

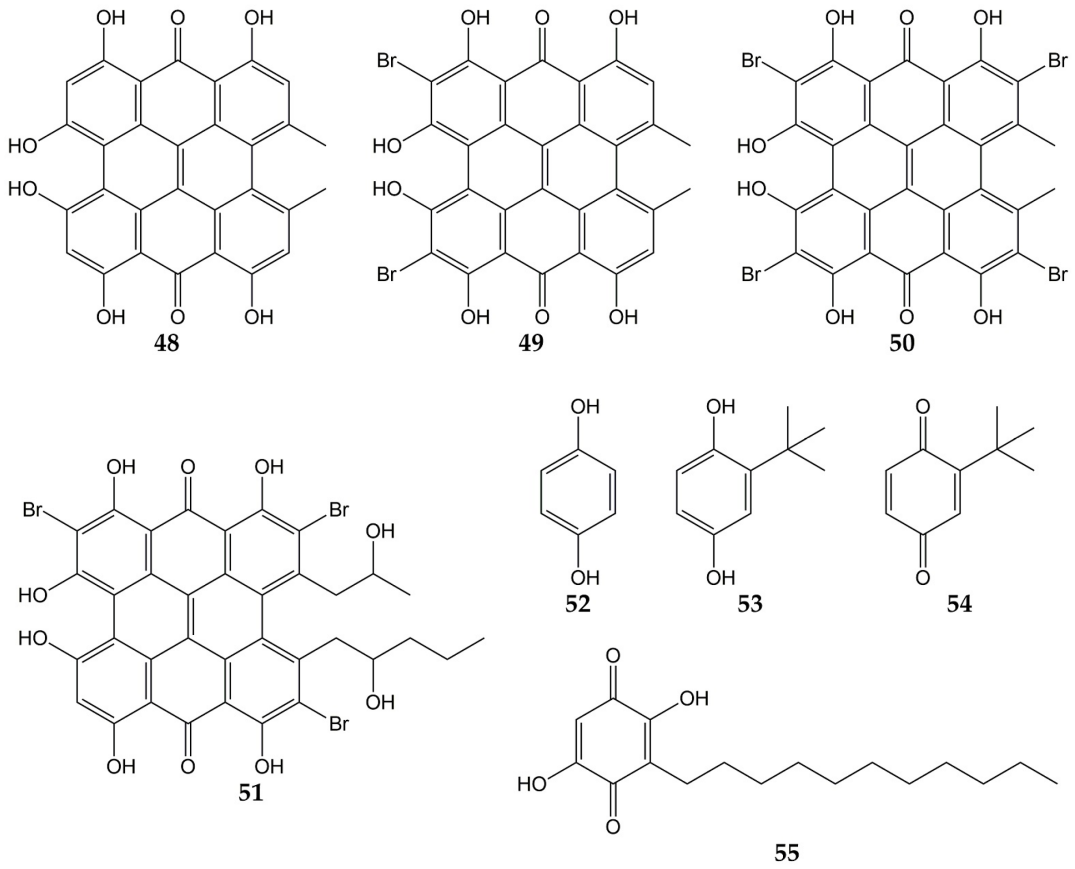

Figure 4. Chemical structures of quinones **48**–**55**.

In this sense, hypericin (**48**; an aromatic polycyclic anthrone present in *Hypericum triquetrifoliurn*) exhibited a virucidal effect against influenza virus A/Brazil at concentrations ranging from 3.12 to 50 µg/mL [53]. Compound **48** and its analogs dibromohypericin (**49**), tetrabromohypericin (**50**), and gymnochrome B (**51**) were evaluated against the influenza A virus. All molecules showed antiviral activity, with minimum 100% inhibitory concentrations (MIC_{100}) of 13 (**48**), <5 (**49**), 250 (**50**), and 78 nM (**51**) [54].

Other quinone derivatives with antiviral activity are hydroquinones, particularly 1,4-hydroquinone (**52**). This compound was isolated from the leaves of *Elaeocarpus tonkinensis* (a medicinal plant from Vietnam that belongs to the Elaeocarpaceae family) and inhibited the activity of influenza viruses A/PR/8/34 (H1N1), A/HongKong/8/68 (H3N2), and B/Lee/40, with EC_{50} values of 31.9, 19.7, and 54.3 µg/mL, respectively. Previously, **52** did not show significant cytotoxicity on MDCK cells (CC_{50} > 300 µg/mL) [55].

Unlike influenza viruses, studies with quinones and their activity against CoVs are limited. Some quinones have exhibited inhibitory properties against SARS-CoV and its protein targets. The chemical structures of these compounds (quinones **56**–**67**) are represented in **Figure 5**.

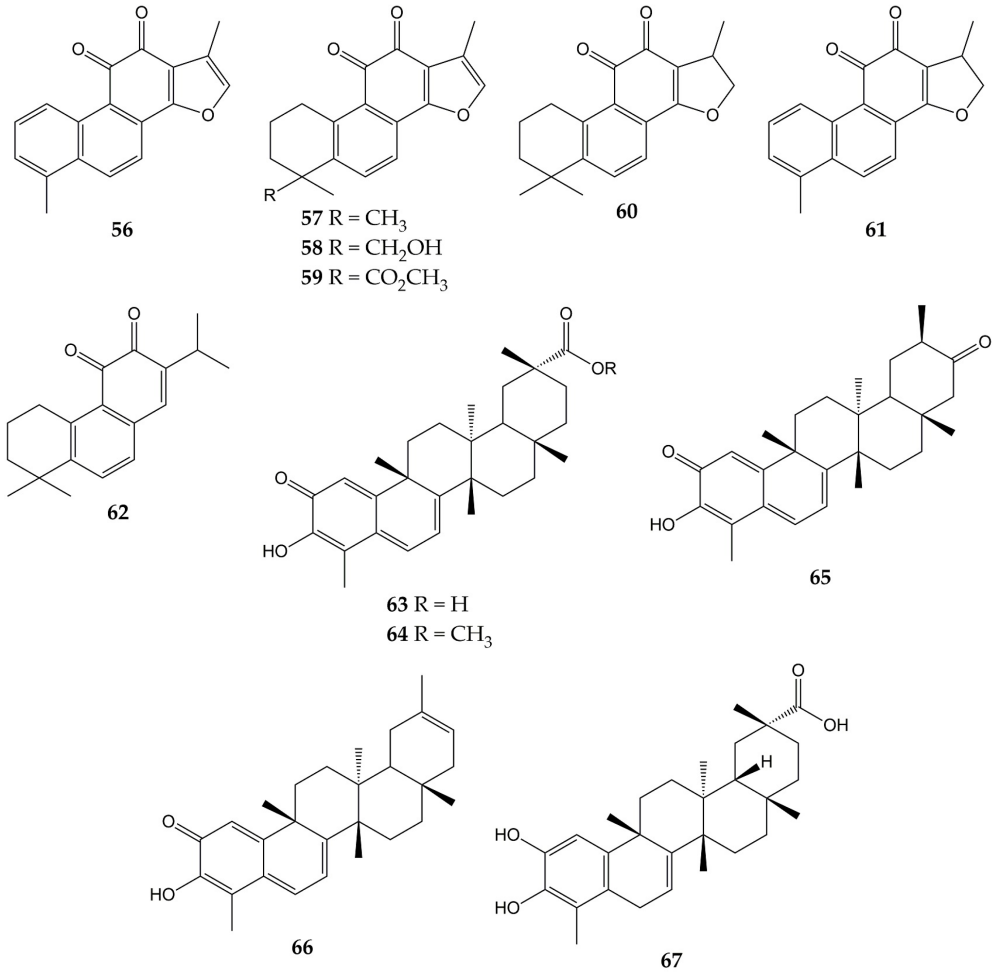

Figure 5. Chemical structures of quinones **56**–**67**.

One of the interesting molecular targets of SARS-CoV is $3CL^{pro}$, which has a conserved structure among CoVs (despite sequence variation). $3CL^{pro}$ and another protease (papain-like cysteine protease or PL^{pro}) cleave two polyproteins (pp1a and pp1ab) and produce various nonstructural proteins implicated in viral genome transcription and replication [56]. The activity of aloe-emodin (**28**) against $3CL^{pro}$ has been previously reported. Anthraquinone **28** exerted inhibitory effects on the $3CL^{pro}$ cleavage activity from SARS-CoV by cell-free and cell-based cleavage assays, with IC_{50} values of 132 and 366 µM, respectively. This compound did not show significant cytotoxicity in Vero cells, with CC_{50} of 11,592 µM [57].

Spike (S) protein has been another attractive viral target of CoVs since it is involved in host cell entry. This glycoprotein consists of two subunits (the S1 subunit, which binds to the host cell receptor angiotensin-converting enzyme 2 or ACE2, and the S2 subunit, which leads the fusion of the viral and host cell membranes) and requires to be cleaved by the transmembrane protease/serine subfamily member 2 (TMPRSS2) to trigger its functions [58]. Anthraquinones have also shown inhibitory effects on this protein. In this sense, emodin (**30**) inhibited the interaction of the S protein with ACE2 in a dose-dependent manner (IC_{50} of 200 µM), while rhein (**41**) slightly inhibited the interaction between the protein and the receptor. Then, the inhibitory effect of **30** on the interaction of SARS-CoV S protein with Vero E6 cell receptors was determined using an S protein-pseudotyped retrovirus. Compound **30** blocked the interaction between protein S and Vero E6 cells, as well as reduced infectivity of S protein-pseudotyped retrovirus in a dose-dependent manner [59].

Due to the global health emergency derived from the current pandemic, various studies have focused on the search for compounds with activity against the novel SARS-CoV-2 and its molecular targets. Among the molecules evaluated are quinones, and the chemical structures of these compounds (quinones **68**–**83**) are shown in **Figure 6**.

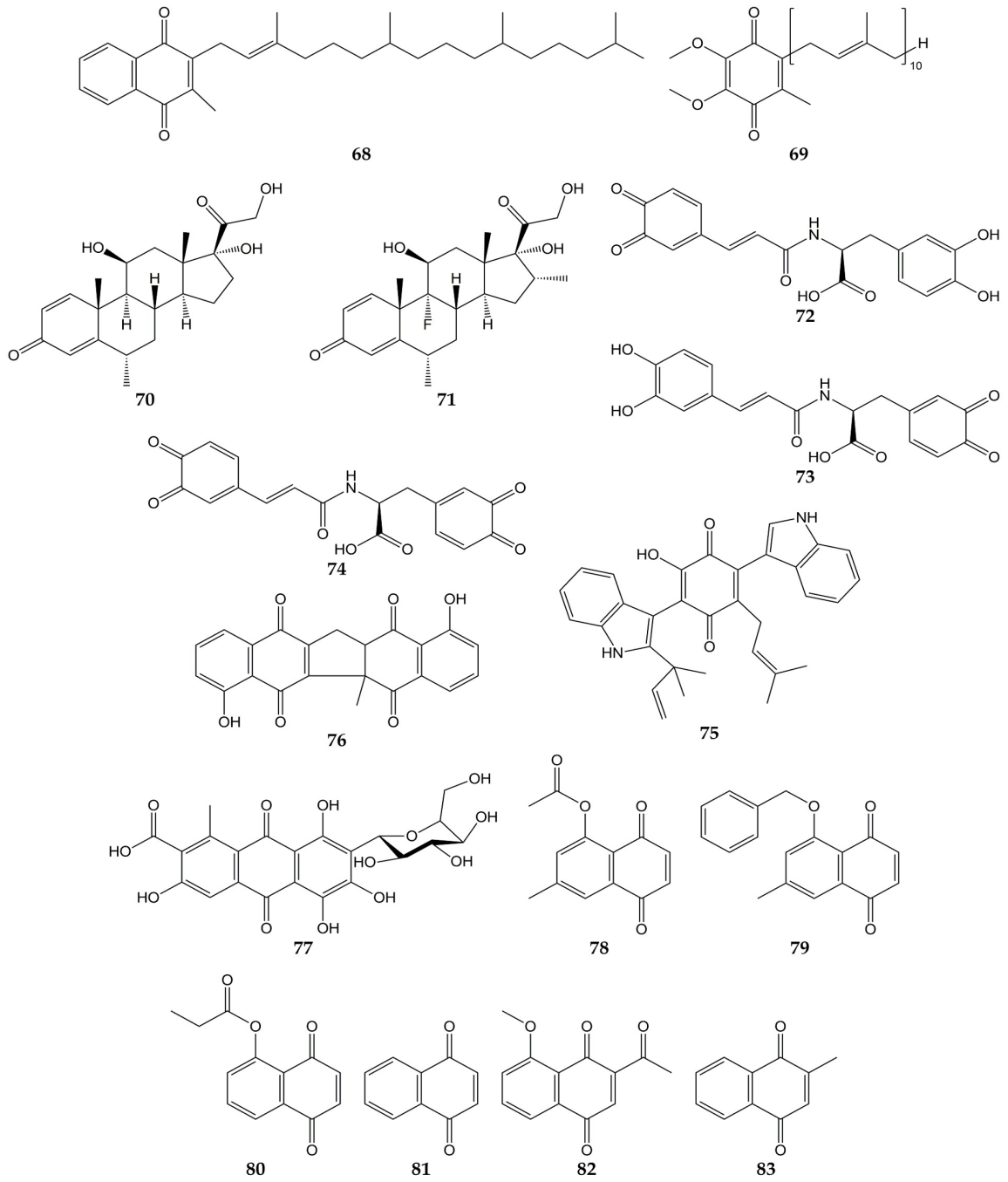

Figure 6. Chemical structures of quinones **68**–**83**.

Molecular docking analyses have demonstrated that different types of quinones are able to interact with $3CL^{pro}$ residues from SARS-CoV-2. The -OH and carbonyl groups of embelin (**55**) bound to Leu141, Gly143, Ser144, His163, and Glu166 through H-bonds, while π-sulfur, alkyl, and π-alkyl interactions between Cys145 and His41 residues with **55** were observed. On the other hand, anthraquinone **30** was bound to $3CL^{pro}$ through H-bond between its carbonyl group with Glu166, as well as Asn142 through its two hydrogen atoms. Vitamin K1 (**68**; phylloquinone form of vitamin K) and coenzyme Q10 (**69**) also interacted with Gly143 and Asn142 through H-bonds, while H-bond interactions were noted between the carbonyl group of the quinone methides methylprednisolone (**70**) and dexamethasone (**71**) and the -NH group of Gly143 [60].

In addition to influenza viruses and CoVs, there are some studies that reported the antiviral effect of quinones on other respiratory viruses. The structures of these molecules (quinones **84**–**88**) are represented in **Figure 7**.

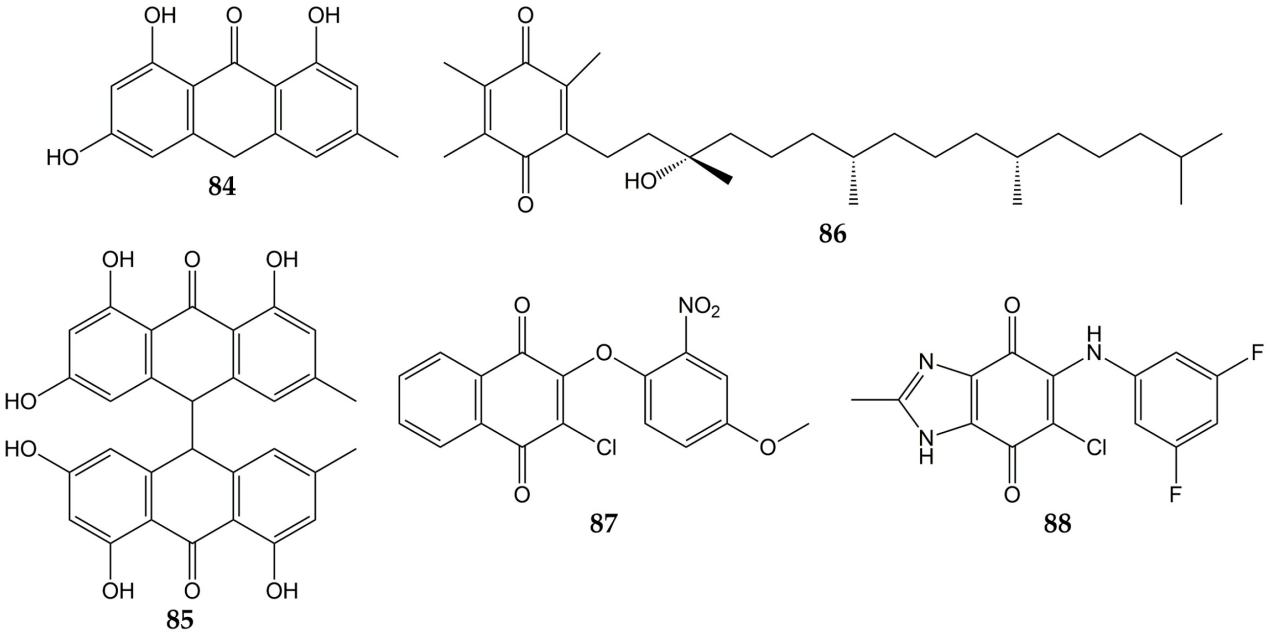

Figure 7. Chemical structures of quinones **84**–**88**.

Previously, the activity of emodin (**30**) and the anthraquinone derivatives hypericin (**48**), emodin anthrone (**84**), and emodin bianthrone (**85**) were evaluated against PIV type-3. The concentrations required to reduce the virus titer (1 $\log_{10}$) were 0.1 (**48**), >10 (**30** and **84**), and 4 µg/mL (**85**) [61]. Compound **30** has been demonstrated to inhibit RSV activity. This anthraquinone from *R. palmatum* had no significant cytotoxicity on human laryngeal carcinoma cells (HEp-2) at low concentrations (CC_{50} of 76.783 µmol/L). The natural product **30** reduced CPE in infected HEp-2 cells (>80% of inhibition in replication of RSV at 30 µmol/L). Furthermore, when **30** was added post-infection, this metabolite inhibited RSV activity according to the results of MTT and plaque reduction assays (EC_{50} values of 14.27 and 13.06 µmol/L, respectively). Time-of-addition experiments demonstrated that **30** inhibited the replication of RSV when added 0–4 h post-inoculation so that this compound could affect the early stages of the viral replication cycle. Quantitative PCR also showed that **30** increased mRNA levels of IFN-γ and decreased tumor necrosis factor α (TNF-α) mRNA expression in infected HEp-2 cells [62]. Vitamin E quinone (**86**) obtained from the stems of *Celastrus hindsii* also decreased the CPE in infected HEp-2 cells with RSV A2 strain (IC_{50} of 3.13 µM) [63].

Finally, the anti-HRV activity of several quinones has been reported. The aforementioned rhinacanthins C (**1**), D (**2**), N (**3**), and Q (**4**) from the roots of *R. nasutus* caused an inhibition on the HRV-1B activity, with IC_{50} values of 0.29, 0.24, 0.97, and 5.35 µM, respectively [34]. Later, the effect of quinones against $3C^{pro}$ from HRV was demonstrated since the quinone analogs **87** and **88** inhibited the activity of recombinant $3C^{pro}$ (IC_{50} of 0.85 for **87** and 8.4 µM for **88**), while SDS-PAGE analysis verified that **87** and **88** completely suppressed the catalytic activity of the protease (5 µM for **87** and 50 µM for **88**). Then, flexible docking simulations were carried out and showed that these derivatives interacted with the active site of $3C^{pro}$ from HRV-14 [64].

5. Conclusions

For many years, respiratory viruses have represented a global public health problem, resulting in annual economic losses and numerous pandemics, including the current pandemic caused by SARS-CoV-2. This situation has motivated researchers to search for new and promising antiviral molecules from natural sources or synthetics. Although a large number of quinones with potent antiviral activity have been reported, none of them are currently used as drugs to treat viral respiratory diseases. There is still research to be done in the field of quinones with activity against respiratory viruses. Therefore, it is important to continue the work at different levels (in silico, in vitro, and in vivo) until reaching the clinical trials, taking advantage of the versatile quinone scaffold for the development of future drugs against respiratory viruses.

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