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ALKALOIDS AND ALKALOID-LIKE COMPOUNDS ARE POTENTIAL SCAFFOLDS OF ANTIVIRAL AGENTS AGAINST SARS-COV-2 (COVID-19) VIRUS

Prasat Kittakoop,^{a,b,c*} Dhanushka Darshana,^a Rapeepat Sangsuwan,^b and Chulabhorn Mahidol^{a,b}

^a Chulabhorn Graduate Institute, Program in Chemical Sciences, Chulabhorn Royal Academy, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand.

^b Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand.

^c Center of Excellence on Environmental Health and Toxicology (EHT), OPS, Ministry of Higher Education, Science, Research and Innovation, Bangkok, Thailand.

*E-mail address: prasat@cri.or.th

Dedicated to the 80th anniversary of Prof. Dr. Somsak Ruchirawat

Abstract – COVID-19 pandemic has an enormous impact on humans, and it has disrupted daily life of people. Moreover, COVID-19 pandemic has significant negative effects on the world economics. To prevent the viral infection, vaccines are rapidly developed and available for certain strains of SARS-CoV-2 virus. However, the emerging of new variants has caused the problems for COVID-19 vaccines due to immune escape ability, challenging the vaccine development process which usually takes years. In this regard, there is a critical need of new antiviral compounds that can be used to combat SARS-CoV-2 virus safely and effectively. This review provides an overview on alkaloids and alkaloid-like compounds, which have antiviral activity against SARS-CoV-2 virus and related coronaviruses. Drug repurposing has played a crucial role for the drug discovery of COVID-19, and many effective antiviral agents against SARS-CoV-2 virus are from commonly used drugs or antiviral leads. Antiviral natural alkaloids and derivatives, which have the activity toward SARS-CoV-2 virus and related coronaviruses, are also discussed in this review.

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1. INTRODUCTION

SARS-CoV-2 virus (COVID-19) was first discovered in December 2019, Wuhan, Hubei province, China.¹ Since then, the world has experienced the outbreak of this virus with high infectivity rate, generating several discussions of what the origin of it could be. Comparative analysis of genomic data revealed that SARS-CoV-2 virus is not originated from a laboratory construct or a manipulated virus but likely originated in animals.^{1,2} SARS-CoV-2 is one of seven coronaviruses known to infect humans, and some can cause severe disease, but certain coronaviruses exhibit only mild symptoms in human.² Apart from the unresolved evidence of its origin, the COVID-19 pandemic has caused significant effects worldwide, the problems covering the disruptions to everyday life of people. COVID-19 has threatened not only human life but also the world economics. According to the WHO report, as of 23 December 2021, there were 276,436,619 cases of COVID-19 with the total 5,374,744 deaths.³ Although many COVID-19 vaccines are recently available, mutations of SARS-CoV-2 virus have produced new variants, which could have potential ability of immune escape. Some variants have specific virulence, for example, the Delta variant with potential severe lung inflammation, causing serious symptoms of the disease. The reduced sensitivity of the Delta variant to antibody neutralization of vaccines was also observed.⁴ Recently, the emerging of the Omicron variant has become the world health problem because the available vaccines could not provide protection against this new variant. Moreover, the Omicron variant has been spreading faster than any previous variants.

In the future, it is expected that the emerging of new variants of COVID-19 virus will be the major health problem worldwide. Vaccine could protect the infection of SARS-CoV-2 virus at certain levels because the new variants are more likely to have immune escape. Antiviral agents have emerged as a promising therapeutic option as they can target several components/biological events during virus life cycle. To date, only a handful of drugs are approved for the emergency use in adult to tackle COVID-19 (US FDA). However, some of them showed conflicting results in the clinical study. Thus, new antiviral agents with potential use as antiviral drugs for treatment of COVID-19 and the control of its spread are urgently needed. Among natural products, alkaloids are important scaffolds for drug development, and they have been reported to elicit several biological activities including antibacterial, anti-inflammatory, anticancer,

and antiviral activity.⁵ With regard to ongoing pandemic, several studies have shown that alkaloids are a source of bioactive compounds with great potential as novel anti-coronavirus agents. This review provides an overview on alkaloids and alkaloid-like compounds as antiviral compounds against COVID-19 virus and related coronaviruses, i.e., SARS-CoV, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E.

2. ANTIVIRAL ALKALOIDS AND ALKALOID-LIKE COMPOUNDS FROM COMMONLY USED DRUGS OR ANTIVIRAL LEADS

Drug repurposing or drug repositioning approach has gained attentions because it can accelerate the drug discovery process. Moreover, commonly used drugs have been well studied for their safety and pharmacokinetics, particularly the safety profile in human. For these reasons, drug repurposing can significantly reduce time and cost for the drug development processes. The outbreak of SARS-CoV-2 virus in December 2019 has stimulated research on drug repurposing, which has initially been conducted by *in silico* molecular docking study.^{6,7} Recently, many commonly used drugs have also been screened and tested for antiviral activity against SARS-CoV-2 virus. This section provides the information of antiviral alkaloids and alkaloid-like drugs or antiviral leads, which have potential use as antiviral drugs for the treatment of COVID-19.

Clofazimine (**1**), a commonly used drug for the treatment of leprosy and multidrug-resistant tuberculosis, was recently found to inhibit coronaviruses, i.e. MERS-CoV, HCoV-229E, HCoV-OC43, and SARS-CoV-2 (Figure 1).⁸ Clofazimin could inhibit the activity of helicase and inhibit cell fusion mediated by the viral spike glycoprotein of COVID-19 virus. In an animal model, clofazimine (**1**) could reduce viral loads in the lung of hamster, and it alleviated the inflammation caused by COVID-19 virus. Clofazimine (**1**) showed antiviral synergy with remdesivir, a drug for COVID-19 treatment; the activity was observed in both *in vitro* and *in vivo*.⁸ Antiviral synergy of clofazimine (**1**) and remdesivir provided the effective COVID-19 control, preventing body-weight loss and suppressing pulmonary virus titre and nasal virus shedding.⁸ Clofazimine (**1**) could therefore be a potential drug for the control of the pandemic of COVID-19. Clofazimine (**1**) has phenazine skeleton in its molecule. Phenazine natural products are produced by bacteria, i.e. *Pseudomonas* and *Streptomyces* species, and they have broad biological activities, for example, antibacterial and anticancer activities.⁹ In addition, phenazine scaffold has been found to have antiviral activity, for example, neutral red (**2**) that exhibited potent activity against hepatitis C virus by inhibiting internal ribosome entry site (IRES) (Figure 1).¹⁰ Neutral red (**2**) is normally used as a dye for staining in histology, for example lysosomes red. Lomofungin (**3**) is an antimicrobial phenazine natural product isolated from *Streptomyces lomondensis* (Figure 1).¹¹ Lomofungin (**3**) and redoxal were found to exhibit antiviral activity against human immunodeficiency virus type 1 (HIV-1) virus.¹²

Phenazine derivatives **4-6** displayed antiviral activity against bovine viral diarrhea virus (Figure 1).¹³ Moreover, phenazine scaffold is also used in other research fields, for example, its conjugation with erythromycin as a prodrug for antibacterial applications,¹⁴ and being used in biosensor and materials.^{15,16}

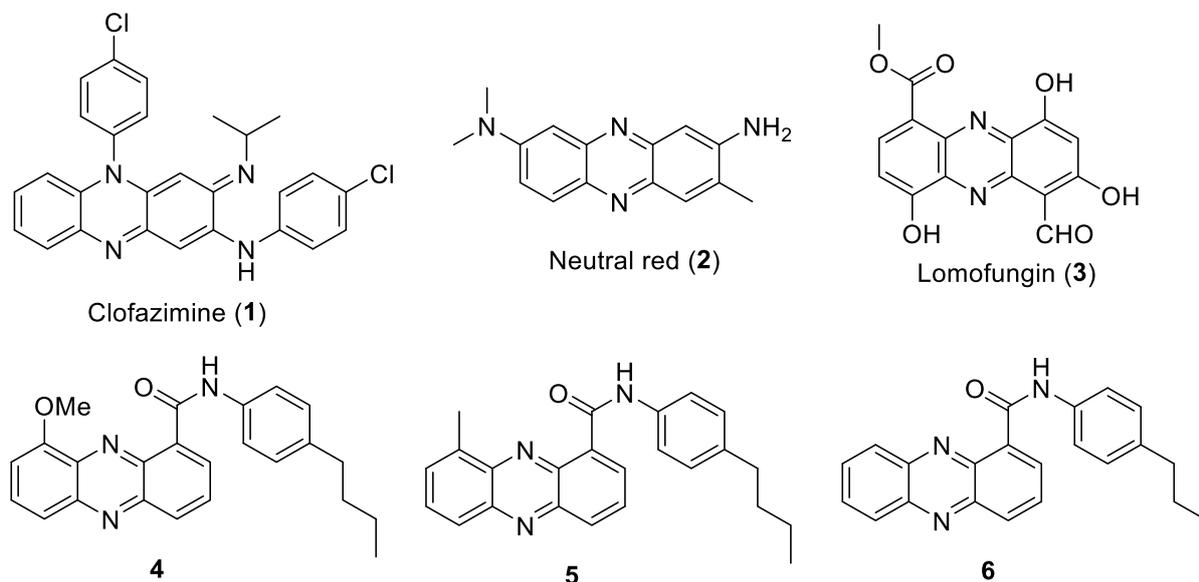


Figure 1. Antiviral phenazine derivatives **1-6**

Three core structures of heterocycles including phenothiazine (**7**), phenoxazine (**8**), and phenoxathiin (**9**) were tested against SARS-CoV virus (Figure 2), which was first found in Guangdong, China, in 2002.¹⁷ SARS-CoV virus causes influenza-like symptoms with high mortality rate. Phenoxazine (**8**) is a core structure of many antipsychotic drugs used for the treatment of schizophrenia and manifestations of psychotic disorders, and it could inhibit SARS-CoV replication with EC₅₀ value of 21.5 μ M. Phenoxazine

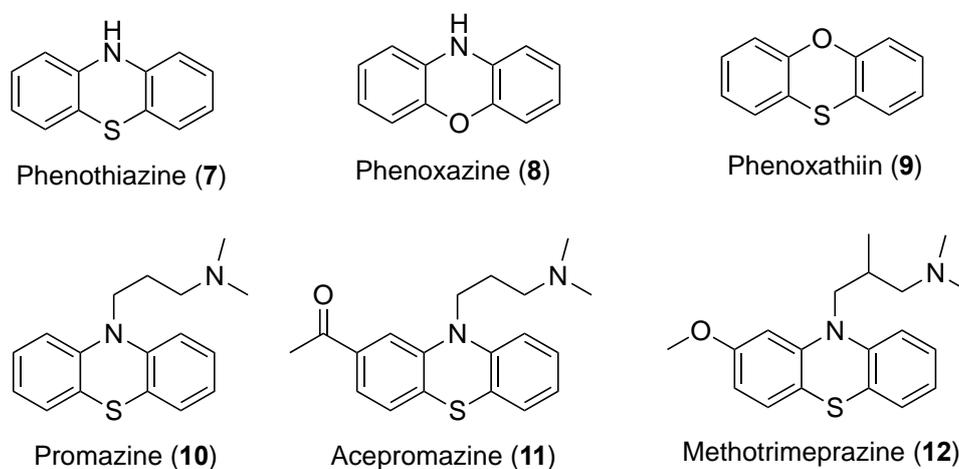


Figure 2. Core structures of phenothiazine (**7**), phenoxazine (**8**), and phenoxathiin (**9**); and antiviral antipsychotic drugs **10-12**

(**8**) and phenoxathiin (**9**) were found to inhibit SARS-CoV replication with EC_{50} values of 89.5 and 763 μM , respectively.¹⁷ Three antipsychotic drugs, promazine (**10**), acepromazine (**11**) and methotrimeprazine (**12**) or levomepromazine, showed antiviral activity against SARS-CoV virus with respective EC_{50} values of 10.8, 21.0 and 19.0 μM (Figure 2). The drug promazine (**10**) was tested in mice; however, it displayed toxicity and did not reduce virus in lung.¹⁷

Ceftazidime (**13**), an antibiotic drug, is used to treat bacterial infections, both Gram-negative and Gram-positive bacteria (Figure 3). Recently, ceftazidime (**13**) was found to inhibit SARS-CoV-2 infection by blocking the interaction of viral spike protein-angiotensin-converting enzyme 2 (ACE2) interaction.¹⁸ This study screened 3581 small molecule compounds including the FDA approved drug library; among these compounds, ceftazidime (**13**) showed the efficient inhibition on spike receptor-binding domain (S-RBD) binding to human pulmonary alveolar epithelial cells (HPAEPiC). Preliminary structure-activity relationship (SAR) analysis suggested that the functional groups, i.e. 2-aminothiazole, oxime protected with isobutyric acid, and pyridine with a positive charge, could mediate the inhibition of protein interaction between S-RBD and ACE2.¹⁸ 2-Aminothiazole is considered as a scaffold for the discovery of anticancer agents,¹⁹ while pyridine moiety is found in alkaloids, which have the activity in the central nervous system.²⁰

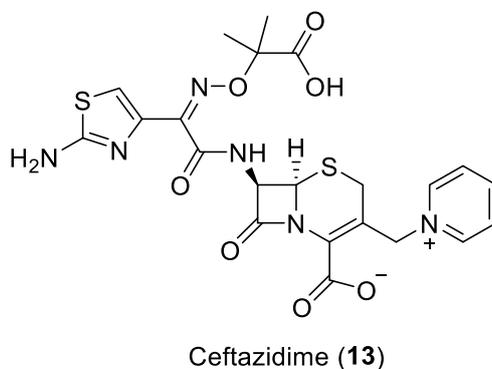


Figure 3. Structure of a drug ceftazidime (**13**), an inhibitor of viral spike protein-ACE2 interaction

GRL0617 (**14**) is an antiviral drug lead, and it was found to be a noncovalent class of papain-like protease (PLpro) inhibitor of SARS-CoV virus (Figure 4).²¹ Among the library of 50,080 compounds, GRL0617 (**14**) was found to be the most potent PLpro inhibitor, and it was co-recrystallized with the enzyme PLpro. The X-ray crystal structure of PLpro in complex with GRL0617 (**14**) was successfully established, providing the key binding sites of GRL0617 (**14**) with PLpro of SARS-CoV.²¹ Recently, GRL0617 (**14**) and its derivative **15** (Figure 4) were found to be PLpro inhibitor of SARS-CoV-2, showing respective IC_{50} values of 2.1 and 11.0 μM .²² Binding sites of GRL0617 (**14**) with PLpro of COVID-19 were revealed by NMR and X-ray analyses, indicating that GRL0617 (**14**) is a potent protein-protein interaction (PPI)

inhibitor against PLpro by blocking the binding of interferon stimulated gene 15 (ISG15) to PLpro.²² Currently, the target PLpro of COVID-19 has been gaining more attention as a potential drug target for antiviral drug design.^{23,24} A structure-based antiviral drug design led to the discovery of 2-phenylthiophene PLpro inhibitors **16-19** (Figure 4) with a tenfold binding affinity over GRL0617 (**14**).²⁵ Other than antiviral properties, natural products containing a thiophene moiety have broad biological activities, i.e. antiviral, antimicrobial, anticancer, insecticidal, and antileishmanial activities.²⁶

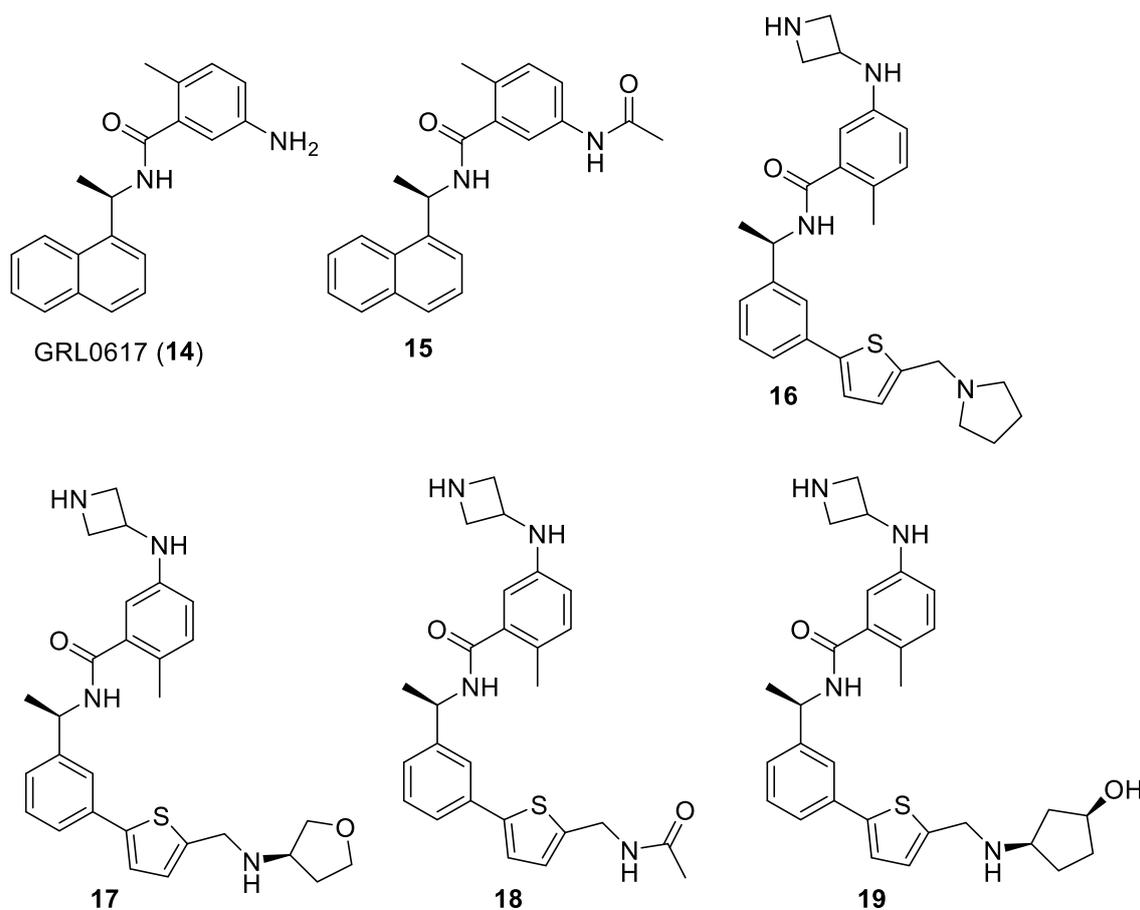


Figure 4. Structures of GRL0617 (**14**) and its derivatives **15-19** as PLpro inhibitors

3-Chymotrypsin like protease (3CLpro) of SARS-CoV-2 virus is one of the targets for antiviral drug design, especially for the treatment of COVID-19. Using computational molecular modeling of 3987 commonly used drugs for the inhibition of 3CLpro, 47 drugs as potential 3CLpro inhibitors were revealed.²⁷ Among them, two heterocycle alkaloid-like drugs, tipranavir (**20**) and boceprevir (**21**) (Figure 5), had IC_{50} values of 27.66 and 31.36 μ M, respectively.²⁶ Tipranavir (**20**) is an antiviral drug for the treatment of human immunodeficiency virus (HIV), while boceprevir (**21**) is used to treat hepatitis C virus that causes hepatitis.

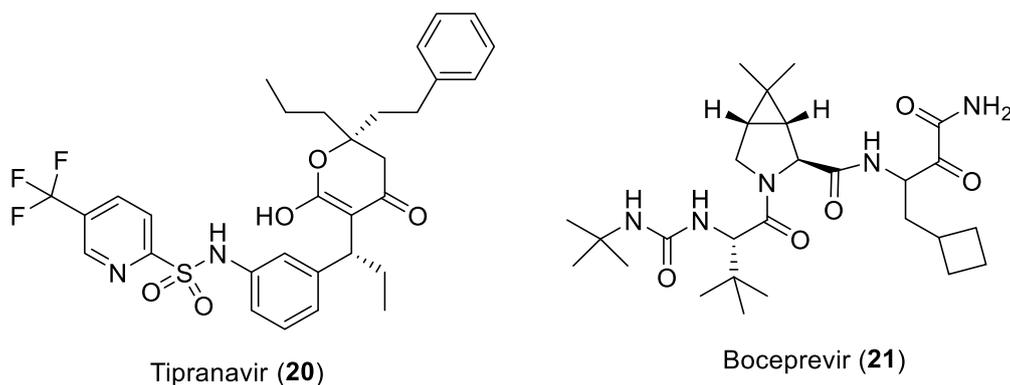


Figure 5. Structures of tipranavir (**20**) and boceprevir (**21**)

As mentioned earlier, 3CLpro is one of the promising targets for the design of anti-COVID-19 drug. The 3CLpro inhibitor, PF-00835231 (**22**) (Figure 6), has been used in clinical trials to treat COVID-19 by intravenous administration.²⁸ A phosphate derivative, PF-07304814 (**23**), was used as a prodrug that has better solubility in water than PF-00835231 (**22**) (Figure 6). Alkaline phosphatase was able to convert the prodrug PF-07304814 (**23**) to the active drug PF-00835231 (**22**), which exhibited antiviral activity both *in vitro* and *in vivo*, displaying substantial reduction of viral load in a SARS-CoV-2 animal model.²⁸ PF-00835231 (**22**) also has synergistic activity with remdesivir, a drug for the treatment of COVID-19. Moreover, when PF-07304814 (**23**) was administered to rats via intravenous infusion, no adverse effects were observed in rats. Overall, PF-07304814 (**23**) is a potential drug candidate that will enter clinical trials in human shortly.

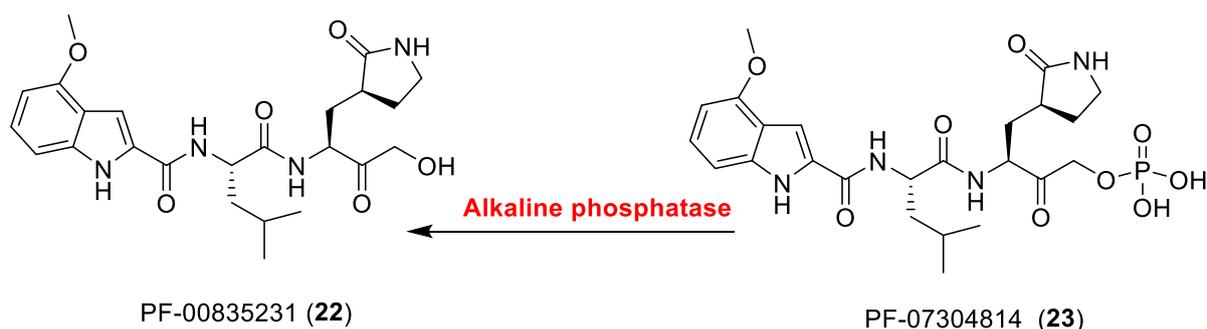


Figure 6. Structures of PF-00835231 (**22**) and PF-07304814 (**23**) and conversion of PF-07304814 (**23**) to PF-00835231 (**22**) by alkaline phosphatase

The core structure of PF-00835231 (**22**) is an indole alkaloid. Information from the complex of ligand-protease structure obtained from X-ray crystallographic analysis and molecular docking study was used for the design and synthesis of antiviral indole derivatives **24-28** (Figure 7). The compounds were tested for the inhibition of 3CLpro of SARS CoV-1 and it was found that indole derivatives **24** and **25**

exhibited 3CLpro inhibitory activity with respective IC_{50} values of 74 and 17 nM, while the derivatives **26** and **27** showed respective IC_{50} values of 7 and 44 nM, as revealed by fluorescence resonance energy transfer (FRET) assay.²⁹ From this drug design, the indole derivative **28** was obtained as an antiviral lead compound with potent antiviral activity (EC_{50} value of 2.4 μ M).²⁹

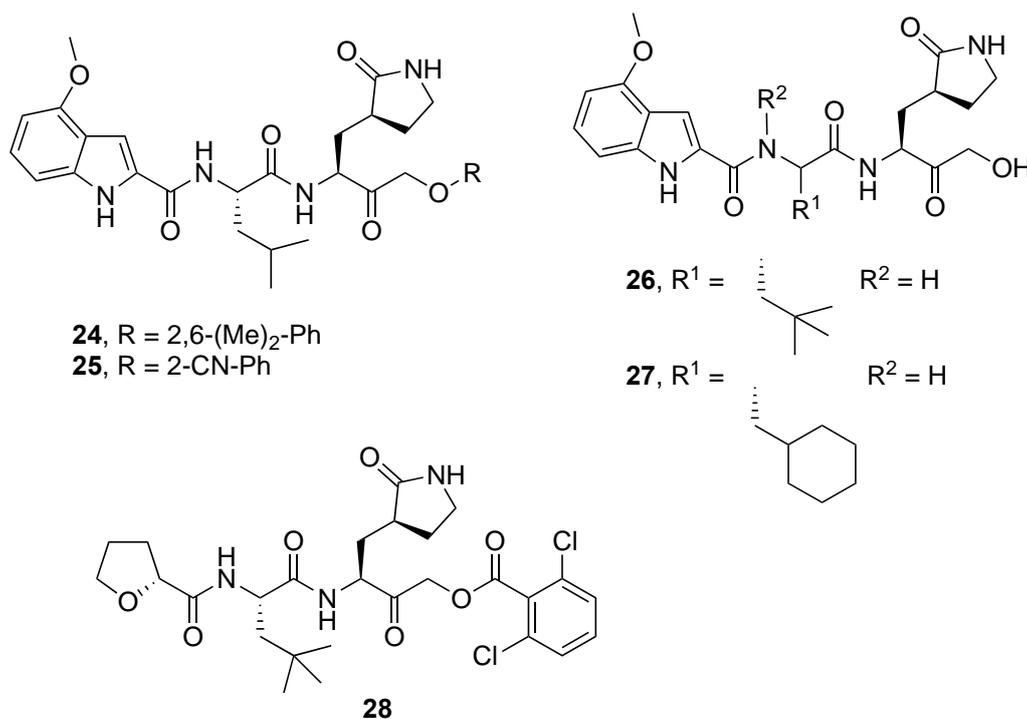


Figure 7. Structures of antiviral indole derivatives **24-28** as 3CLpro inhibitors

Indole alkaloid is found to be an important scaffold for antiviral drug design against COVID-19 virus. Indole chloropyridinyl ester, GRL-0920 (**29**), and its corresponding indoline derivative, GRL-1720 (**30**), could block SARS-CoV-2 infection (Figure 8).^{30,31} GRL-0920 (**29**) exhibited antiviral activity against SARS-CoV-2 virus with EC_{50} value of 2.8 μ M,³⁰ whereas the corresponding indoline derivative GRL-1720 (**30**) displayed antiviral activity with EC_{50} value of 15 μ M.³¹ Moreover, an antiviral indole derivative **31** was also discovered (Figure 8), and it could inhibit main protease (M^{pro}) enzyme of SARS-CoV-2 virus. The derivative **31** exhibited antiviral activity against SARS-CoV-2 virus with EC_{50} value of 4.2 μ M.³¹ In this study, the drug remdesivir showed antiviral activity against SARS-CoV-2 virus with EC_{50} value of 1.2 μ M, which was comparable to that of compound **31**. Therefore, the indole **31** is considered as an antiviral lead for the development of a drug for the treatment of COVID-19. Further study on indole chloropyridinyl ester GRL-0920 (**29**) and indoline derivative GRL-1720 (**30**) revealed that they could inhibit 3CLpro enzyme of COVID-19 virus. The X-ray structure of SARS-CoV-2 3CLpro enzyme co-crystallized with GRL-1720 (**30**) was investigated.³² The study also designed new indole

derivatives based on molecular docking toward 3CLpro of SARS-CoV-2, and indole derivatives **31** and **32** were found to be potent inhibitors of 3CLpro (Figure 8).³² The X-ray structure of SARS-CoV-2 3CLpro bound with the indole **31** was also obtained from this study.³² Among the indole derivatives, compound **32** was a potent 3CLpro inhibitor with IC₅₀ value of 0.073 μM, and it exhibited antiviral activity against SARS-CoV-2 virus with EC₅₀ value of 15 μM.³²

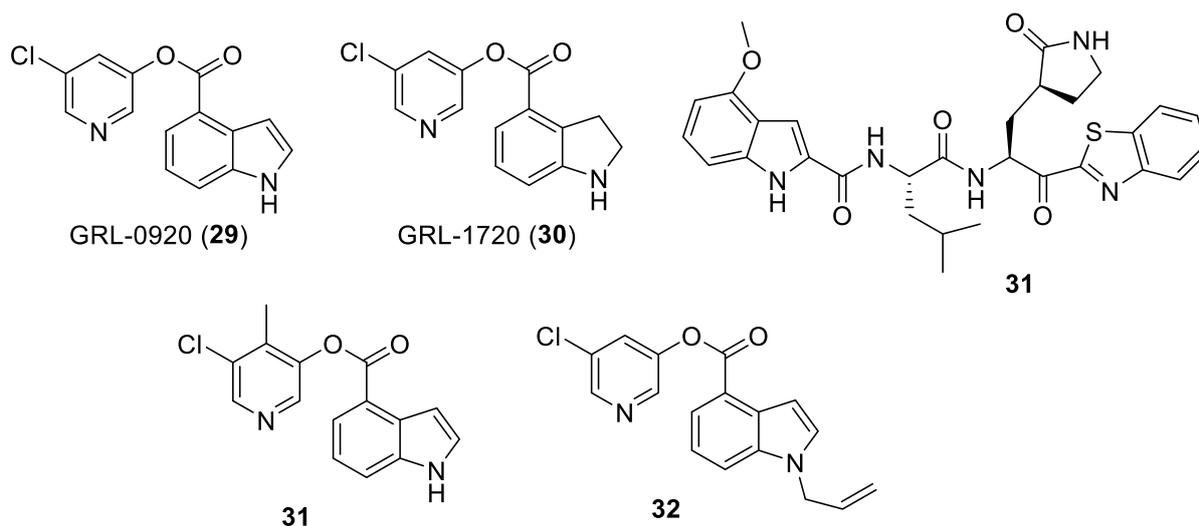


Figure 8. Structures of antiviral indole derivatives **29-32** as lead compounds for the development of anti-COVID-19 drugs

Bai et. al. designed the structures of indole derivatives **33-35** from an antiviral drug rupintrivir (**36**) (or AG-7088 or rupinavir), which was initially developed for the treatment of rhinoviruses (Figure 9).³³ Indole derivatives **33-35** were 3CLpro inhibitors, and displayed *in vitro* inhibition of SARS-CoV-2 replication. The derivatives **33-35** had selectivity for SARS-CoV-2 3CLpro over the protein targets, cathepsin B and cathepsin S.³³ Compound **35** exerted inhibitory effect against 3CLpro of SARS-CoV-2 with IC₅₀ value of 19 nM. The derivative **35** was co-crystallized with 3CLpro of COVID-19 virus, and X-ray crystallographic analysis revealed a formation of a covalent bond between compound **35** and the sulfur of Cys145 amino acid in 3CLpro.³³ In general, indole derivatives **33-35** exhibited potent antiviral activity against an alphacoronavirus and non-SARS betacoronavirus with comparable activity to the drug remdesivir.³³ Bai et. al. also designed the structures of indole derivatives with nitrile warheads, which were SARS-CoV-2 3CLpro inhibitors, and they exhibited *in vitro* antiviral activity against SARS-CoV-2 virus.³⁴ Therefore, these experiments underscore the importance of an indole core structure as an important scaffold for the drug design of SARS-CoV-2 3CLpro inhibitors.

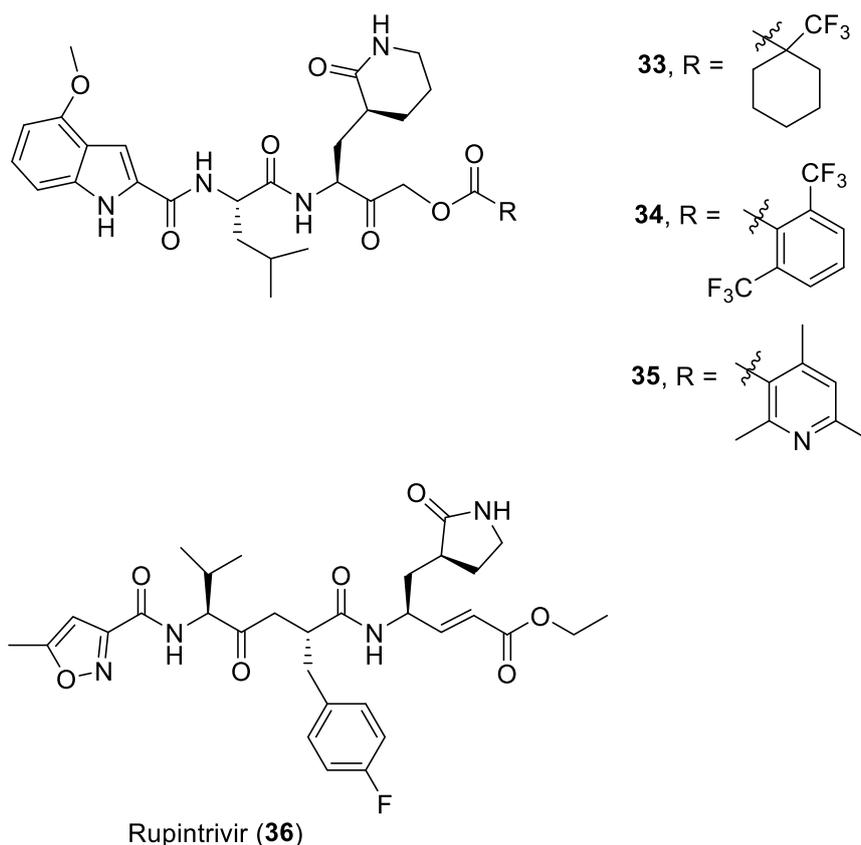


Figure 9. Structures of antiviral indole derivatives **33-35** and an antiviral drug rupintrivir (**36**)

Recently, the rational drug design strategies based on the inhibition of M^{pro} of SARS-CoV-2 virus led to the identification of 2-phenyl-1,2-benzoselenazol-3-one derivatives as antiviral leads, and the derivatives **37-41** were found to be potent M^{pro} inhibitors (Figure 10).³⁵ Ebselen (**42**), an organoselenium drug, was used as the lead molecule for this study. Ebselen (**42**) has broad spectrum of biological activities including cytoprotective, anti-inflammatory, and antioxidant activities (Figure 10). It is currently studied for the treatment of hearing loss and tinnitus,³⁶ stroke,^{37,38} and bipolar disorder.³⁹ Ebselen (**42**) showed the

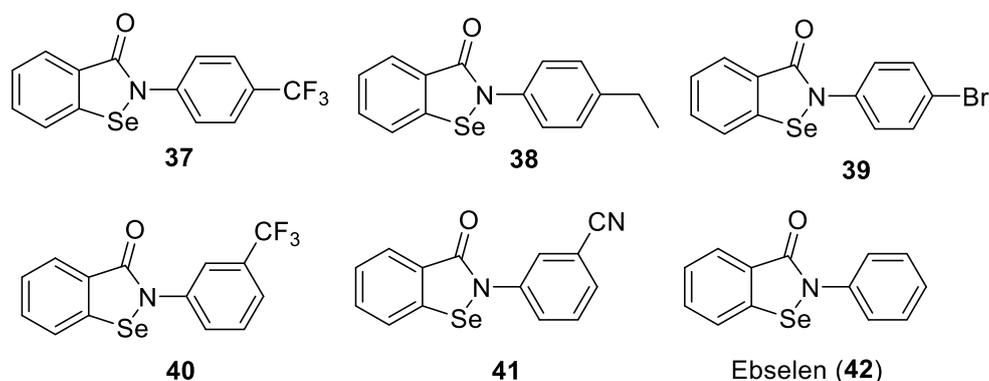


Figure 10. Structures of 2-phenyl-1,2-benzoselenazol-3-one derivatives **37-41** and ebselen (**42**) as M^{pro} inhibitors of COVID-19 virus

inhibition of SARS-CoV-2 M^{Pro} with IC₅₀ value of 0.33 μ M, but it did not exhibit antiviral activity at 20 μ M.³⁵ Organoselenium derivatives **37-41** displayed M^{Pro} inhibitory activity with respective IC₅₀ values of 0.90, 6.18, 2.77, 2.77, and 0.38 μ M, and exhibited antiviral activity against SARS-CoV-2 virus with EC₅₀ values of 11.2, 6.5, 5.2, 0.8, and 2.0 μ M, respectively.³⁵ In this study, the antiviral drug remdesivir showed the activity against SARS-CoV-2 virus with EC₅₀ value of 1.8 μ M, which was comparable to those of compounds **40** and **41**. Overall, the derivative **40** that has with EC₅₀ value of 0.8 μ M is therefore considered as a lead compound for antiviral drug development.³⁵

The scaffold of bispidine or 3,7-diazabicyclo[3.3.1]nonane (**43**) is known to be a “privileged structure” in medicinal chemistry research (Figure 11).⁴⁰ Bispidine was functionalized with different heterocycles, for example, pyrazole and triazole, giving derivatives **44-47** (Figure 11), and they were tested for the inhibition of 3CLpro of SARS-CoV-2 virus.⁴¹ Most bispidine derivatives could inhibit 3CLpro with IC₅₀ values of 1-10 μ M, and a few derivatives exhibited inhibitory activity with IC₅₀ values at sub-micromolar levels.⁴¹ Among the bispidine derivatives, compound **48** displayed inhibitory activity with IC₅₀ value of 0.75 μ M (Figure 11).⁴¹

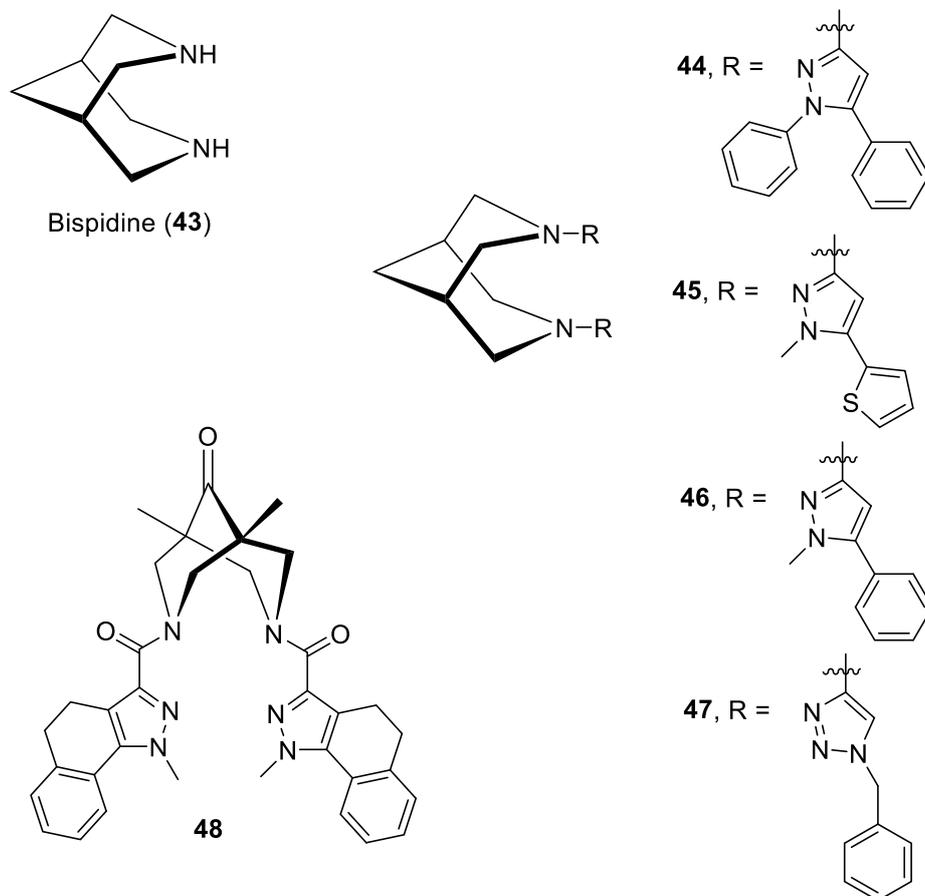


Figure 11. Structures of bispidine (**43**) and its derivatives **44-48**

ML300 (**49**) and ML188 (**50**) were previously found to be lead antiviral compounds because they were inhibitors of SARS-CoV 3CLpro (Figure 12).^{42,43} They are noncovalent 3CLpro inhibitors of SARS-CoV virus with IC₅₀ values at sub-micromolar or nanomolar levels. Guided by the noncovalent 3CLpro inhibitor ML300 (**49**), derivatives **51**, **52** and CCF981 (**53**) were synthesized and tested for 3CLpro inhibitory activity against 3CLpro of SARS-CoV-2 virus (Figure 12).⁴⁴ X-Ray co-crystal structures of derivatives **51** and **52** complexed with 3CLpro were obtained, providing the information of multiple hydrogen-bonding interactions between heterocyclic azole nitrogens and the enzyme.⁴⁴ Finally, the design of new antiviral compounds led to the identification of CCF981 (**53**) that could inhibit 3CLpro with IC₅₀ value of 68 nM, and it had comparable *in vitro* antiviral activity to the antiviral drug remdesivir.⁴⁴

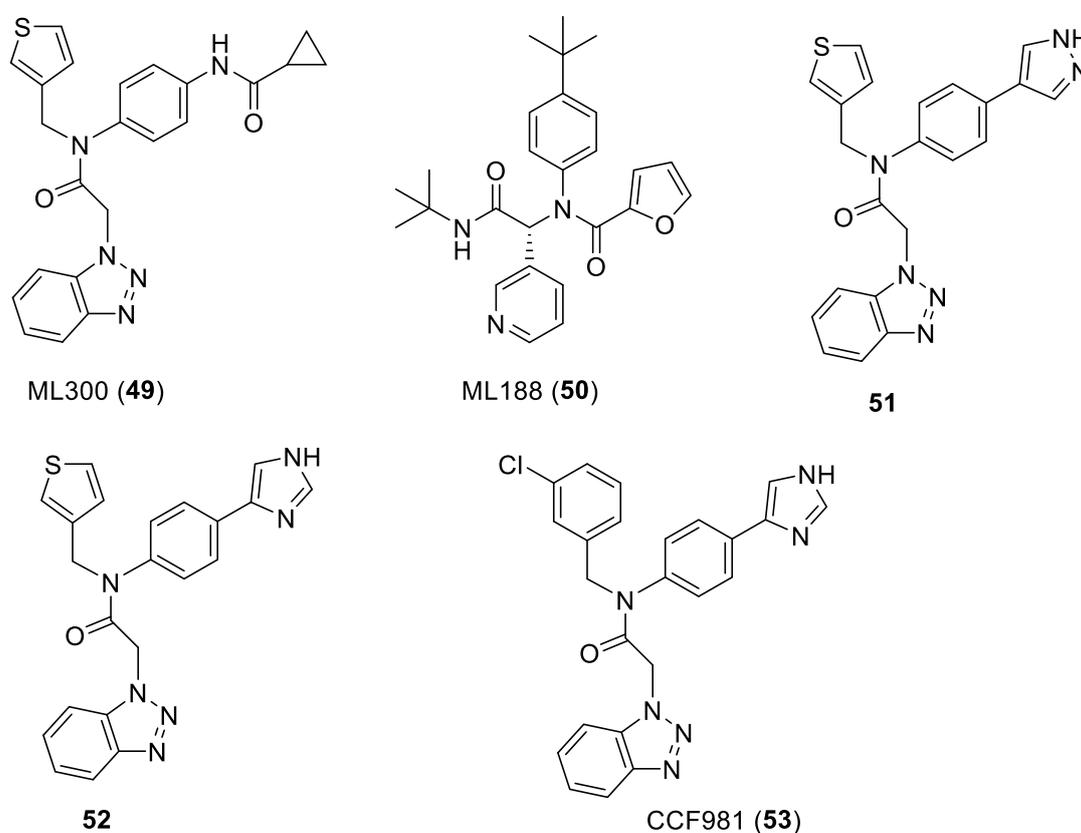


Figure 12. Structures of ML300 (**49**), ML188 (**50**), derivatives **51**, **52** and CCF981 (**53**)

Recently, Paxlovid (**54**) composing of two active drugs, nirmatrelvir or PF-07321332 (**54-a**) and ritonavir (**54-b**) (Figure 13), was found to be orally active M^{pro} inhibitor for the treatment of COVID-19 (Figure 13).⁴⁵ Paxlovid (**54**) exhibited antiviral activity in a mouse-adapted SARS-CoV-2 model, and it showed efficacy in a phase I clinical trial in healthy human participants.⁴⁵ In November 2021, the clinical trial phase 2/3 revealed that Paxlovid (**54**) showed 89% viral reduction within three days after symptom onset in COVID-19 patients, and thus cutting the risk of hospitalization and death of patients. Therefore, it is anticipated that Paxlovid (**54**) will be an effective antiviral drug for the treatment of COVID-19 in the

near future. PF-07321332 (**54-a**) was developed from the lead antiviral compound, PF-07304814 (**23**), whose structure is shown in Figure 6. While PF-07304814 (**23**) has to be administered intravenously, which is difficult to use for patients, PF-07321332 (**54-a**) is orally active, providing a convenient way of the treatment by oral administration. MK-4482 or EIDD-2801 (**55**) or Molnupiravir is a pro-drug of the nucleoside analogue known as *N*⁴-hydroxycytidine, which has broad-spectrum activity against RNA virus (Figure 13). Previously, it was found that MK-4482 or EIDD-2801 (**55**) displayed potent anti-influenza virus activity in animal models, i.e. ferrets and human airway epithelia,⁴⁶ and in ferret model.⁴⁷ This drug candidate exerts its antiviral action during viral RNA replication by introduction of copying errors. Recent experiments revealed that MK-4482 or EIDD-2801 (**55**) could reduce SARS-CoV-2 virus in the upper respiratory tract and was able to control the virus spread by oral administration twice a day.⁴⁸ Moreover, in phase II/III clinical trials, MK-4482 or EIDD-2801 (**55**) inhibited SARS-CoV-2 replication in human.⁴⁹ It could provide efficacies both therapeutic and pre-exposure prophylaxis strategies, and thus having dual potentials, i.e. prevention and treatment of COVID-19.⁴⁹ In November 2021, U.K. approves MK-4482 or EIDD-2801 (**55**) as an antiviral drug for the treatment of mild-to-moderate COVID-19 in adults. Paxlovid (**54**) and MK-4482 or EIDD-2801 (**55**) will play a crucial role for the treatment and control of COVID-19 worldwide, and these antiviral drugs may change COVID-19 pandemic course of the world.

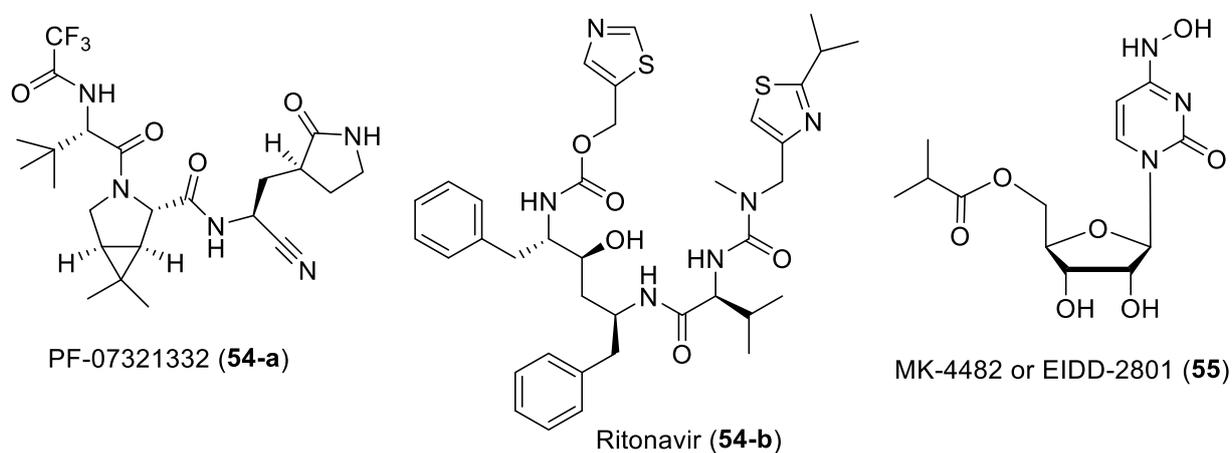


Figure 13. Structure of Paxlovid (**54**) composing of nirmatrelvir or PF-07321332 (**54-a**) and ritonavir (**54-b**), and structure of MK-4482 or EIDD-2801 (**55**)

3. ANTIVIRAL ALKALOIDS AND ALKALOID-LIKE COMPOUNDS AGAINST COVID-19 AND RELATED VIRUSES FROM NATURAL PRODUCTS AND THEIR DERIVATIVES

Natural products are good sources of drugs, and many drugs are derived or inspired from natural products.⁵⁰ Natural products also provide structures of pharmacophores for the new drug design.^{51,52}

Shikimic acid isolated from star anise (*Illicium verum*) is a good example of a natural product used for the preparation of an antiviral drug, Oseltamivir or Tamiflu, the drug for the treatment of influenza viruses A and B.⁵³ Recently, natural products were found to be potential ACE2 blockers, one of the antiviral drug targets, which are revealed by many methods and techniques.⁵⁴ Moreover, a review on natural products based on the information of SARS-CoV virus is proposed for the management of the new coronavirus or COVID-19 infection.⁵⁵ A review on Asian herbal medicines and their bioactive compounds covering many antiviral natural products from plants was recently reported.⁵⁶ A number of natural products, which have potential to treat RNA virus such as COVID-19 virus, were also reported in the recent review.⁵⁷ Antiviral alkaloids and alkaloid-like compounds isolated from natural resources, i.e. plants, microorganisms, and marine invertebrates, which have the activity toward COVID-19 virus, are presented in this section.

Recent work investigated natural products, which could block SARS-CoV-2 entry using HEK-293T cells overexpressing human angiotensin-converting enzyme 2 (293T-ACE2 cells) for screening.⁵⁸ Among 188 natural compounds screened in this study, the alkaloids cepharanthine (**56**), hernandezine (**57**), tetrandrine (**58**), neferine (**59**), and SC171 (**60**) were found to be anti-SARS-CoV-2 entry inhibitors (Figure 14).

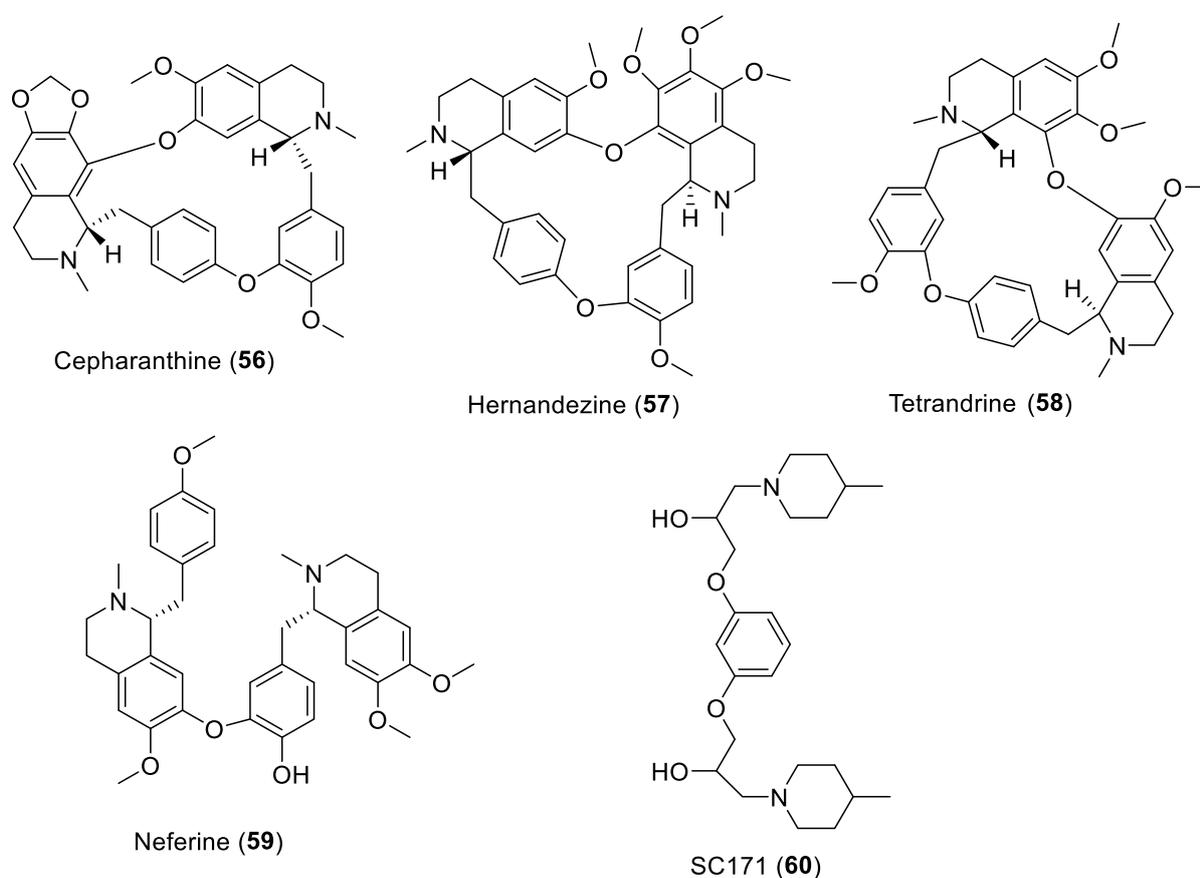


Figure 14. Structures of cepharanthine (**56**), hernandezine (**57**), tetrandrine (**58**), neferine (**59**), and SC171 (**60**)

Compounds **56-59** are bis-benzylisoquinoline alkaloids, which are metabolites of plants, and they have broad biological activities, particularly on anticancer property.⁵⁹⁻⁶² The alkaloids **56-59** displayed potent antiviral activity against the two emerging SARS-CoV-2 variants N501Y.V1 and N501Y.V2, which are found in the United Kingdom and South Africa. These alkaloids could protect certain cell lines, i.e. 293T-ACE2, Calu-3, and A549, from infection by coronaviruses including SARS-CoV-2, SARS-CoV, and MERS-CoV. This study also revealed that the alkaloids **56-59** were able to block host calcium channels that led to the inhibition of Ca^{2+} -mediated fusion, and thus blocking virus entry.⁵⁸ An independent study revealed that cepharanthine (**56**) had SARS-CoV-2 Nsp13 helicase ATPase inhibitory activity, and this finding was obtained from virtual screening of 970,000 chemical compounds, based on their ability to bind with the ATP-binding site of the enzyme.⁶³

Gallinamide A (**61**) or symprostatin 4 is a marine natural product, which was isolated from the marine cyanobacteria of the *Schizothrix* genus⁶⁴ and from the genus *Symploca* (Figure 15).⁶⁵ It is a modified depsipeptide with a heterocyclic moiety, methyl-1,5-dihydro-2*H*-pyrrol-2-one or pyrrolinone. Gallinamide A (**61**) was previously found to be a potent inhibitor of human cysteine protease cathepsin L and *Trypanosoma cruzi* cysteine protease,⁶⁶ and it also exhibited potent antimalarial activity by inhibiting the

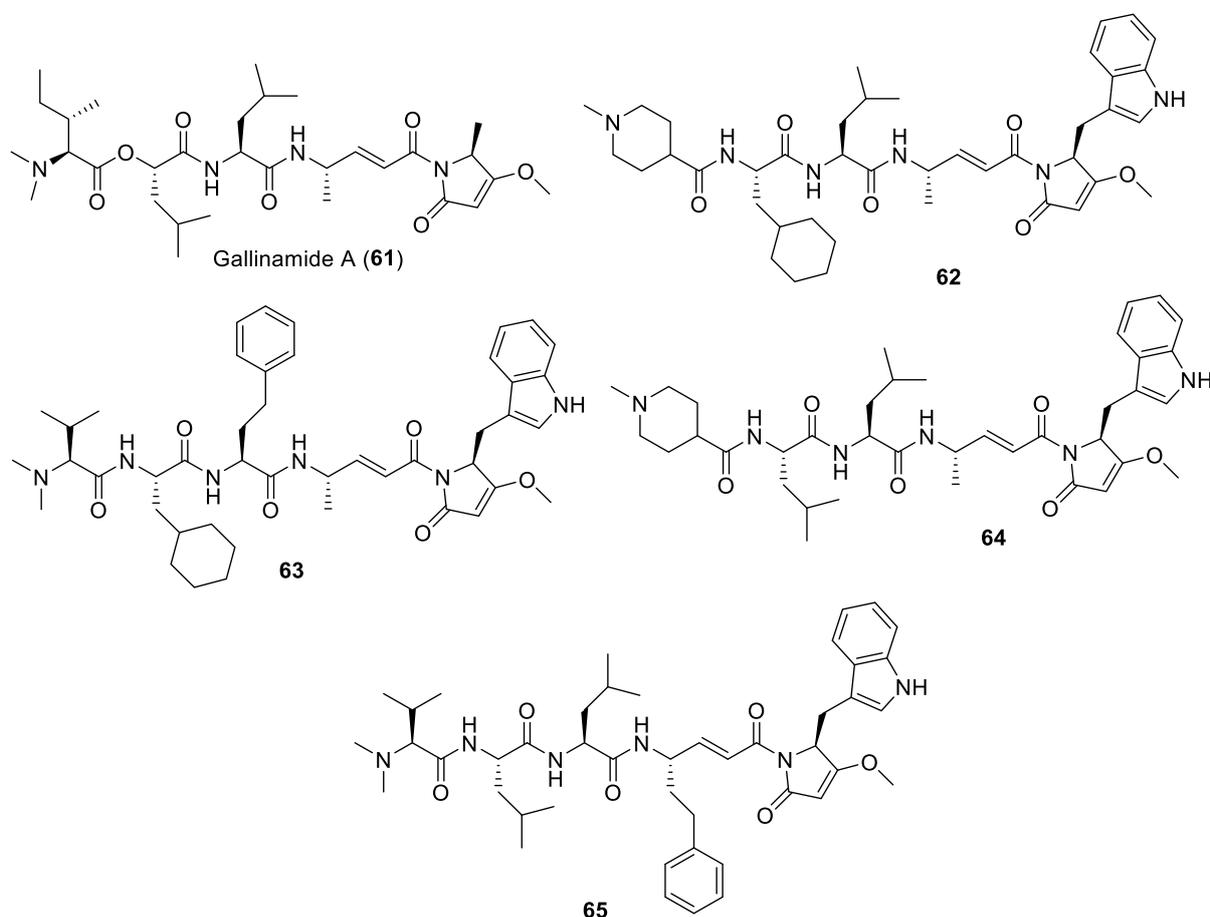


Figure 15. Structures of gallinamide A (**61**) and its derivatives **62-65**

food vacuole falcipains of the malarial parasite at nanomolar levels.⁶⁷ When tested against COVID-19 virus, gallinamide A (**61**) could decrease viral load with an IC_{90} of 88 nM in a SARS-CoV-2 viral infection assay using Vero 76 clone E6 cells as a host.⁶⁸ Further study revealed that gallinamide A (**61**) displayed antiviral activity against SARS-CoV-2 virus with an EC_{50} of 28 nM. Detailed mechanistic study revealed that gallinamide A (**61**) exerted antiviral activity by the inhibition of human cathepsin L, which is a key human cysteine protease by which coronaviruses used for cell entry.⁶⁸ Several derivatives of gallinamide A (**61**) were prepared and compounds **62-65** were found to be potent antiviral agents against COVID-19 virus (Figure 15).⁶⁸ It is worth mentioning that the derivatives **62-65** have an indole moiety in their molecules. Gallinamide A (**61**) inhibited cathepsin L with an IC_{50} of 17.6 pM, while the derivatives **62-65** inhibited cathepsin L with IC_{50} values ranging from 6 to 17 pM. The analogue **65** was 1.4-fold more potent than the parent compound, gallinamide A (**61**). The derivatives **63** and **65** exhibited more potent antiviral activity than gallinamide A (**61**); however, compounds **62** and **64** had relatively weak antiviral activity with EC_{50} values greater than 5 μ M.⁶⁸

Plitidepsin (**66**) or dehydrodidemnin B or aplidin is a marine natural product isolated from the marine ascidian *Aplidium albicans*,⁶⁹ and it is a derivative of didemnin B (**67**) isolated from a tunicate of the genus *Trididemnum* (Figure 16).⁷⁰ Didemnin B (**67**) was previously found to have antiviral and cytotoxic activities,⁷⁰ while plitidepsin (**66**) had potent antitumor activity.⁷¹ Plitidepsin (**66**) and didemnin B (**67**) have a heterocyclic pyrrolidine moiety of proline amino acid in their molecules. Plitidepsin (**66**) was recently found to exhibit antiviral activity against SARS-CoV-2 virus *in vitro* with 90% inhibitory concentration (IC_{90}) of 0.88 nM, which is more potent than the drug remdesivir by a factor of 27.5.⁷² Plitidepsin (**66**) inhibited SARS-CoV-2 replication at nanomolar level, with an IC_{90} value of 3.14 nM. It was found that plitidepsin (**66**) exerted antiviral activity against SARS-CoV-2 by inhibition of eukaryotic translation elongation factor 1A (eEF1A). In an animal model of SARS-CoV-2 infection, plitidepsin (**66**) could reduce SARS-CoV-2 virus by two orders of magnitude, and it could also reduce lung inflammation in mice.⁷² Previously, plitidepsin (**66**) had been in clinical trials for the treatment of cancer, i.e. multiple myeloma, and its safety profile and pharmacokinetics were well established.⁷³⁻⁷⁵ Upon these reasons, plitidepsin (**66**) is a potential drug candidate for the treatment of COVID-19. (-)-Ternatin (**68**) is a natural cyclic heptapeptide isolated from a mushroom *Coriolus versicolor* (Figure 16),⁷⁶ which is commonly used in traditional Chinese medicine. (-)-Ternatin (**68**) was found to inhibit hyperglycemia and hepatic fatty acid synthesis in diabetic mice,⁷⁶ and it inhibited adipogenesis and lipid metabolism in 3T3-L1 cells.⁷⁷ Further study revealed that the β -turn structure of (-)-ternatin (**68**) is essential for fat-accumulation inhibitory activity against 3T3-L1 murine adipocytes.⁷⁸ (-)-Ternatin (**68**) and its derivatives could kill cancer cells by the inhibition of eEF1A, which is the same target as plitidepsin (**66**).⁷⁹ Ternatin-4 (**69**) is a

derivative of (–)-ternatin (**68**), containing a piperidine moiety as a heterocycle in its molecule (Figure 16).⁷⁷ Ternatin-4 (**69**) was previously found to be the inhibitor of eEF1A.⁷⁹ Recent study found that ternatin-4 (**69**) had potential interactions with multiple coronavirus proteins,⁸⁰ and it displayed *in vitro* antiviral activity against SARS-CoV-2 virus with an IC₉₀ of 15 nM.⁷² However, ternatin-4 (**69**) was 9 times less active against SARS-CoV-2 virus than plitidepsin (**66**).⁷²

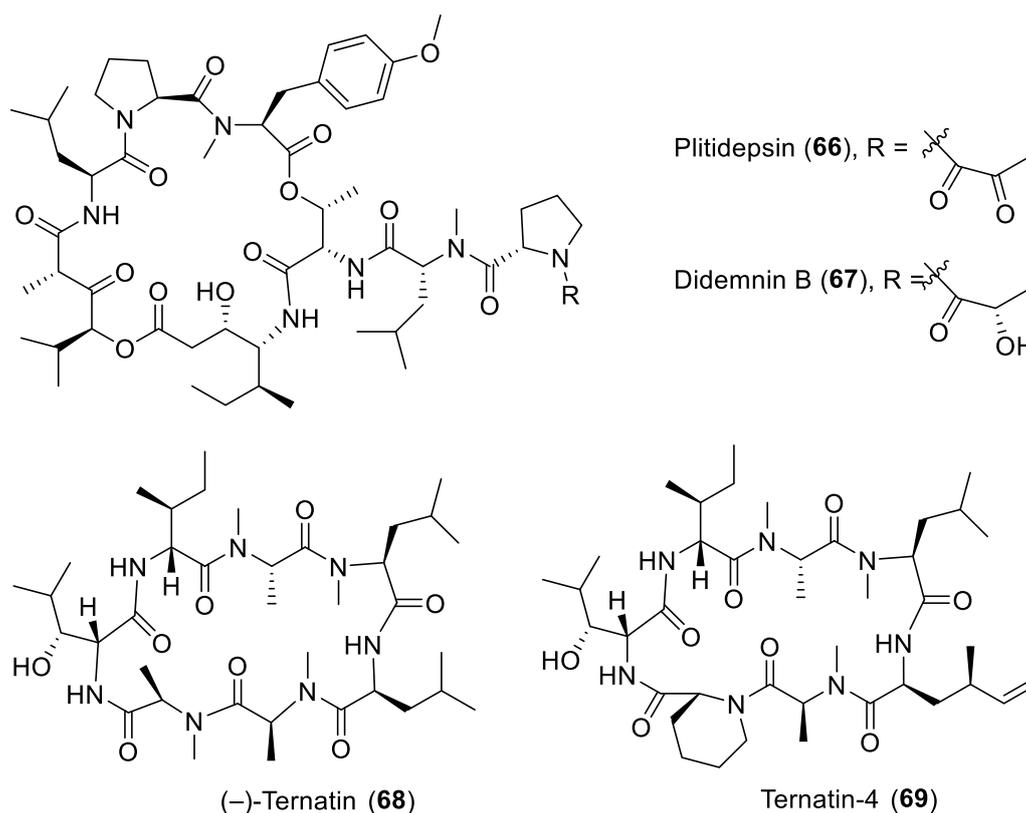


Figure 16. Structures of plitidepsin (**66**), didemnin B (**67**), (–)-ternatin (**68**), and ternatin-4 (**69**)

Colchicine (**70**) is a tricyclic alkaloid isolated from plants, such as *Colchicum autumnale* and *Gloriosa superba* (Figure 17), and it is normally used as a drug for treatment of gout and Behçet's disease. In Colombia, five cases of COVID-19 patients were treated with colchicine (**70**); these patients had a clinical history of biopolymers in the gluteal region, and thus having iatrogenic allogenosis.⁸¹ Colchicine (**70**) was found to provide beneficial effects as it might reduce cytokine levels and activation of macrophages, neutrophils, and inflammasome. Therefore, it is proposed that colchicine (**70**) may be used to prevent acute respiratory distress syndrome in COVID-19 patients.⁸¹ Colchicine (**70**) was also used with doxycycline (**71**) to treat patients with COVID-19 pneumonia (Figure 17).⁸² Doxycycline (**71**) is tetracycline-class antibiotic drug, exhibiting broad-spectrum of antibacterial activity. COVID-19 patients were first treated with doxycycline (**71**) in the first week, and they received doxycycline (**71**) plus

colchicine (**70**) in the second week; this treatment led to the reduction of symptoms and disease severity, showing good clinical and radiological outcomes in patients.⁸² Further randomized and controlled clinical studies are recommended for the use of colchicine (**70**) and doxycycline (**71**) for COVID-19 patients.

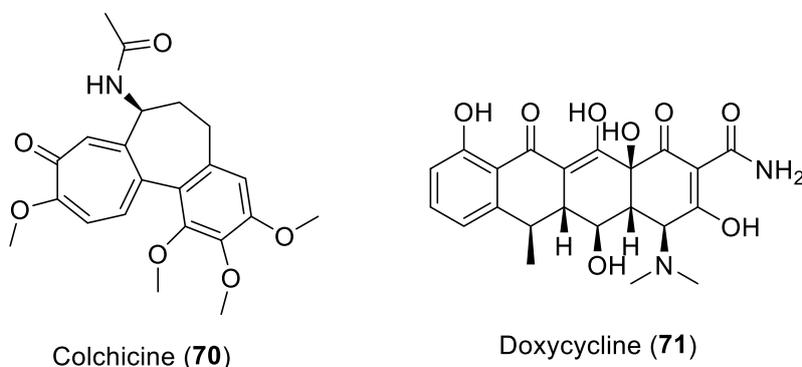


Figure 17. Structures of colchicine (**70**) and doxycycline (**71**)

Chromene (**72**) and coumarin (**73**) are core structures of many natural products (Figure 18).⁸³⁻⁸⁶ Recent study revealed that natural coumarins, inophyllum P (**74**), mesuol (**75**), and oxypeucedanin (**76**) are potential 3CLpro of SARS-CoV virus (Figure 18); this study employed *in silico* method, i.e. molecular docking, molecular dynamics simulation, ADMET prediction, and MM-PBSA binding energy calculation.⁸⁷ This investigation revealed that inophyllum P (**74**), mesuol (**75**), oxypeucedanin (**76**), and glycycomarin (**77**) showed the highest binding affinity with the best negative energy scores (Figure 18), and they interacted with one or both of His41 and Cys145 residues of 3CLpro through hydrophilic and hydrophobic bonding.⁸⁷ These coumarins also had good pharmacokinetics, as well as drug-likeness. An independent docking analysis also revealed that glycycomarin (**77**) and isodispar B (**78**) were promising coumarins against COVID-19 virus (Figure 18).⁸⁸ Moreover, a few additional coumarins were proposed to be potential protease inhibitors of COVID-19 virus as revealed by *in silico* molecular docking.⁸⁹ The prediction by these computational methods underscores the importance of chromene (**72**) and coumarin (**73**) core structures as antiviral drug candidates. Recent study revealed that the introduction of heterocyclic pyrazole and piperazine moieties into the core structure of chromene (**72**) led to the benzopyranylpyrazole structures, which had antiviral activity against SARS-CoV-2 virus.⁹⁰ Among benzopyranylpyrazole derivatives, C01 (**79**) exhibited potent antiviral activity by inhibiting the replication of SARS-CoV-2, as well as by inducing stress granule formation (Figure 18).⁹⁰ C01 (**79**) was tested against SARS-CoV-2 in Vero cells in combination with antiviral drug lopinavir. C01 (**79**) considerably enhanced antiviral activity (IC₅₀ from 7.64 to <0.78 μM), suggesting that the drug combination of stress granule enhancers, i.e. C01 (**79**), with other antiviral drugs could be a potential strategy for treating viral diseases.⁹⁰

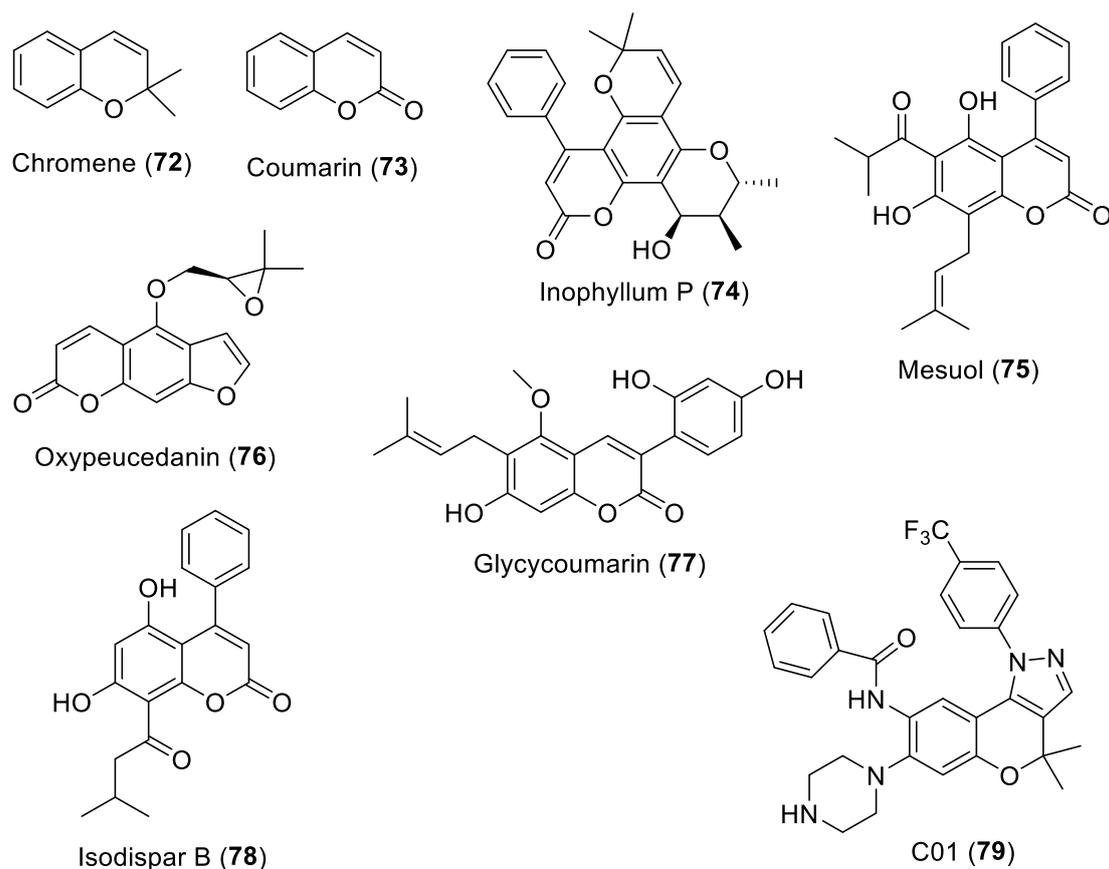


Figure 18. Structures of chromene (72), coumarin (73), inophyllum P (74), mesuol (75), oxypeucedanin (76), glycycoumarin (77), isodispar B (78), and C01 (79)

Lycorine (80) is a phenanthridine alkaloid of the plants, *Rhodolirum speciosum*, *Lycoris radiate*, and *Clivia miniata* (Figure 19).^{91,92} Lycorine (80) has broad biological activities including antiviral, antitumor, antileukemia, anti-inflammatory, anti-angiogenesis, antibacterial, and antimalarial activities,⁹³ and it is considered as a lead compound for a new generation of anticancer drug design.⁹⁴ Recently, lycorine (80) was found to have antiviral activity against coronaviruses, MERS-CoV, SARS-CoV, and SARS-CoV-2, with IC₅₀ values of 2.123, 1.021, and 0.878 μM , respectively, which was comparable to antiviral drug remdesivir.⁹⁵ Lycorine (80) was found to inhibit RNA dependent RNA polymerase of MERS-CoV virus with an IC₅₀ value of 1.406 μM , while remdesivir had IC₅₀ value of 6.335 μM toward this enzyme.⁹⁵ Molecular docking revealed that lycorine (80) could bind through hydrogen bonding with RNA polymerase of SARS-CoV-2 at the amino acids, Asp623, Asn691, and Ser759 residues. Another study also indicated that lycorine (80), together with two alkaloids, emetine (81) and cephaeline (82), displayed antiviral activity against SARS-CoV-2 at nanomolar levels with EC₅₀ values of 0.439 μM , 0.00771 μM , and 0.0123 μM , respectively (Figure 19).⁹⁶ It was suggested that lycorine (80), emetine (81), and cephaeline (82) may involve in the prevention of the virus maturation, and thus destroying viral core assembly because these alkaloids could bind with nucleocapsid protein (N protein).⁹⁶ Emetine (81) is an

alkaloid isolated from the plant *Hedera helix*,⁹⁷ while cephaeline (**82**) was isolated from the roots of *Cephaelis acuminata*.⁹⁸

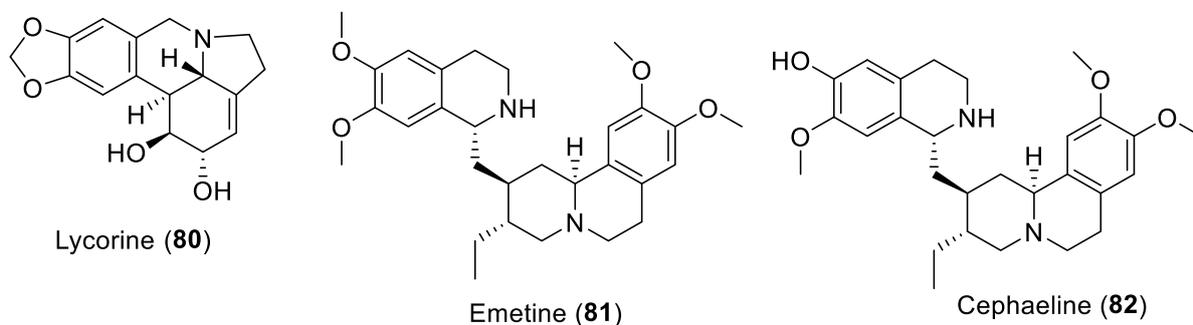


Figure 19. Structures of lycorine (**80**), emetine (**81**), and cephaeline (**82**)

Natural products and derivatives, walrycin B (**83**), faspaplysin (**84**), and beta-lapachone (**85**), were found to be 3CLpro inhibitors of COVID-19 virus (Figure 20), and they had IC₅₀ values of 0.26, 9.96, and 13.33 μ M, respectively.⁹⁹ However, only walrycin B (**83**) exhibited antiviral activity against SARS-CoV-2 virus with EC₅₀ value of 3.55 μ M, while faspaplysin (**84**) and beta-lapachone (**85**) were inactive against the virus at 20 μ M.⁹⁹ Walrycin B (**83**) was previously reported to be the inhibitor of the bacterial WalR, one of the targets for the design of antimicrobial compounds.¹⁰⁰ Walrycin B (**83**) is a derivative of a natural

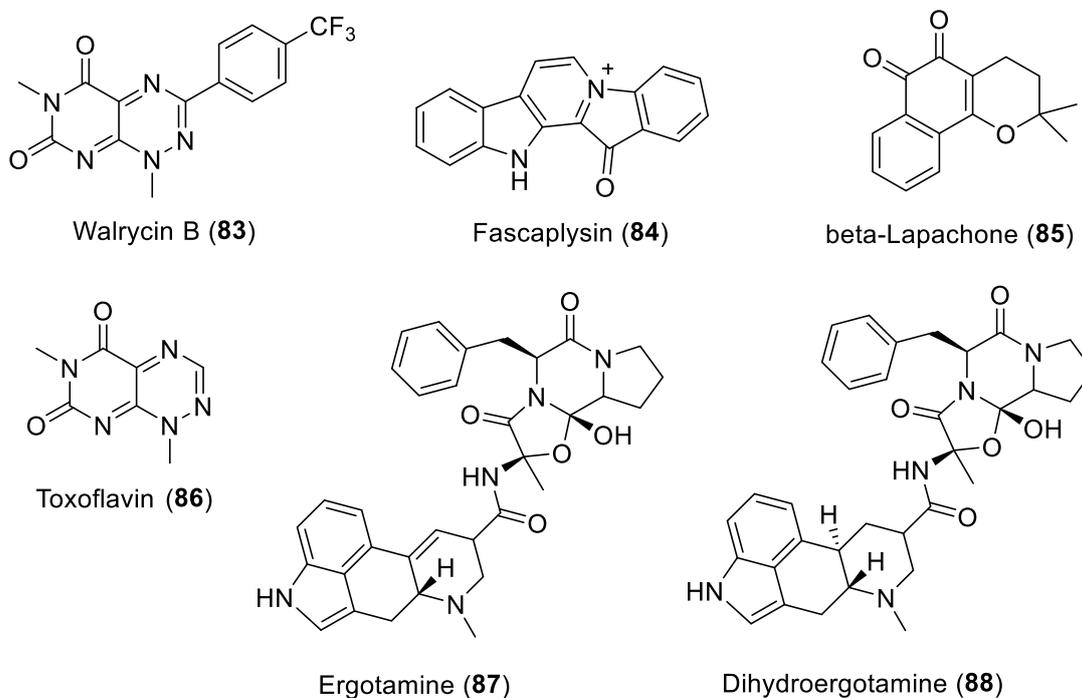


Figure 20. Structures of walrycin B (**83**), faspaplysin (**84**), beta-lapachone (**85**), toxoflavin (**86**), ergotamine (**87**), and dihydroergotamine (**88**)

product, toxoflavin (**86**) (Figure 20), isolated from Gram-negative bacteria, *Burkholderia gladioli* and *Burkholderia glumae*,^{101,102} and it was reported to have broad-spectrum of antifungal activity.¹⁰² Fascaplysin (**84**) is a marine natural product, which was isolated as an antimicrobial pigment from the marine sponge *Fascaplysinopsis* sp.¹⁰³ beta-Lapachone (**85**) is a quinone isolated from the plants *Tabebuia avellanedae* and *Handroanthus impetiginosus*, exhibiting potent anticancer activity by inducing apoptosis in HepG2 hepatoma cell line.¹⁰⁴ The derivative of beta-lapachone (**85**), namely ARQ 761, had reached phase I clinical trial for the treatment of cancer, and it exerted the activity through the expression of NAD(P)H:quinone oxidoreductase 1 in cancer cells.¹⁰⁵ The study on virtual screening of 970,000 chemical compounds against the ATP-binding site of Nsp13 helicase ATPase revealed that ergotamine (**87**) and dihydroergotamine (**88**) were potential inhibitors of Nsp13 helicase ATPase of SARS-CoV-2 virus (Figure 20).⁶³ Ergotamine (**87**) is an alkaloid produced by the fungus, *Claviceps purpurea*, while dihydroergotamine (**88**) a semi-synthetic derivative prepared from ergotamine (**87**). Both ergotamine (**87**) and dihydroergotamine (**88**) are commonly used drugs for the treatment of migraine.¹⁰⁶ The molecular dynamics (MD) simulation revealed that noscapine (**89**) was potential inhibitor for M^{pro} of SARS-CoV-2 (Figure 21).¹⁰⁷ Noscapine (**89**) is a benzyloquinoline alkaloid, isolated from the opium poppy *Papaver somniferum*, and it is a potential anticancer drug, whose biosynthesis pathway has received attentions from scientists.¹⁰⁸ Noscapine (**89**) is an antitussive drug, and it also has anticancer

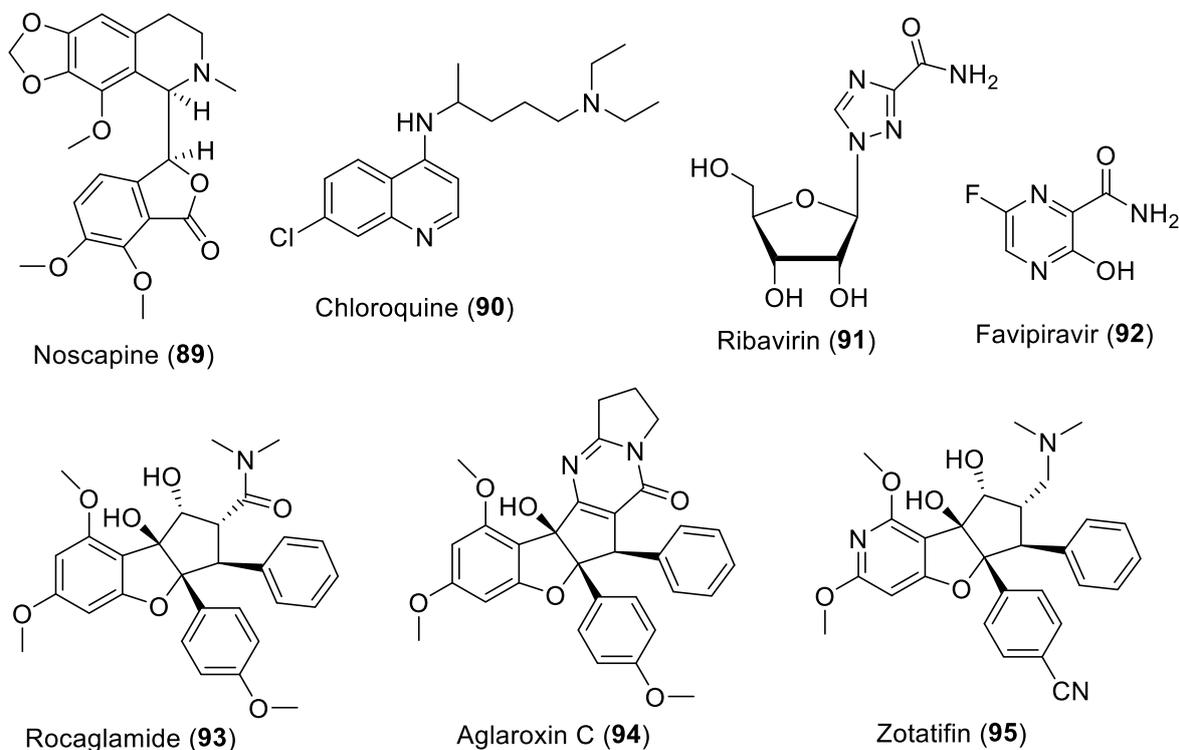


Figure 21. Structures of noscapine (**89**), chloroquine (**90**), ribavirin (**91**), favipiravir (**92**), rocaglamide (**93**), aglaroxin C (**94**), and zotatifin (**95**)

property by binding with tubulin at the colchicine site.¹⁰⁹ When analyzing the binding ability with M^{pro} of SARS-CoV-2 of two alkaloids noscapine (**89**) and chloroquine (**90**), compared with the two antiviral drugs, ribavirin (**91**) and favipiravir (**92**) (Figure 21), the alkaloid noscapine (**89**) was found to be potential inhibitor of M^{pro} of SARS-CoV-2.¹⁰⁷ Noscapine (**89**) could bind at 155-306 amino acid residues of the binding pocket-3 of M^{pro} of SARS-CoV-2. Flavaglines are natural products of the plants of the genus *Aglaiia*, and they have cyclopenta[*b*]benzofuran moiety. Flavaglines, i.e. rocaglamide (**93**) and aglaroxin C (**94**), have antiviral activity against many viruses, including coronaviruses (Figure 21).¹¹⁰ Since flavaglines or rocaglates have antiviral activity, a number of its derivatives have been generated by chemical synthesis, and they showed the inhibition of hepatitis C viral entry.¹¹¹ This compound class also displays anticancer activity, for example, zotatifin (**95**) or eFT226 A, which is in phase I/II clinical trials (Figure 21). Recently, zotatifin (**95**) was found to exhibit potent antiviral activity against COVID-19 virus with IC₉₀ value of 0.037 μ M.⁸⁰

Bafilomycins are antibiotics produced by many bacterial strains of the genus *Streptomyces*. Recently, a few bafilomycins, i.e. bafilomycin B1 (**96**), bafilomycin B2 (**97**), were isolated from *Streptomyces* sp., which was isolated from animal feces (Figure 22).¹¹² Among bafilomycins from *Streptomyces* sp., bafilomycin B1 (**96**) and bafilomycin B2 (**97**) exhibited potent antiviral activity against influenza A virus with IC₅₀ values at nanomolar levels. Detailed mechanistic study revealed that they inhibited the activity

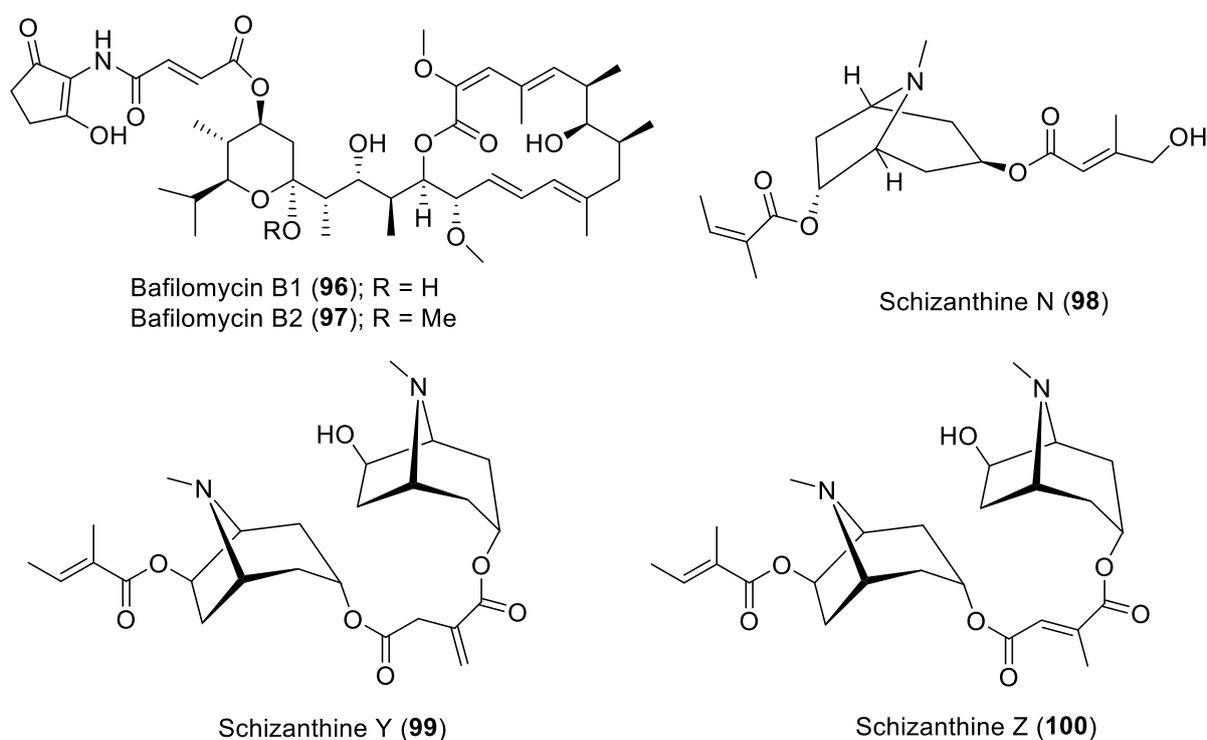


Figure 22. Structures of bafilomycin B1 (**96**), bafilomycin B2 (**97**), schizanthine N (**98**), schizanthine Y (**99**), and schizanthine Z (**100**)

of endosomal ATP-driven proton pumps. Bafilomycin B2 (**97**) was found to exhibit antiviral activity against COVID-19 virus with the IC₅₀ value less than 10 nM.¹¹² Plants of the genus *Schizanthus* produces tropane alkaloids, for example, schizanthine N (**98**) from *Schizanthus tricolor*,¹¹³ and schizanthine Y (**99**) and schizanthine Z (**100**) from *Schizanthus porrigens* (Figure 22).¹¹⁴ Molecular docking study revealed that schizanthine Z (**100**) could bind to papain-like protease of COVID-19 virus with high affinity and good ADME properties.¹¹⁵

4. CONCLUSION

COVID-19 has posed great threats to the health of people worldwide. However, effective drugs for the treatment of COVID-19 are not widely available for patients. Recently, two drugs, Paxlovid (**54**) and EIDD-2801 (**55**) or Molnupiravir, were approved for the treatment of COVID-19, and these antiviral drugs may change the course of COVID-19 pandemic. However, new variants of SARS-CoV-2 virus have potential abilities of immune escape from vaccines, and may eventually resist to antiviral drugs. Therefore, searching for new antiviral agents is critically important for the development of drugs for the treatment of COVID-19. Many alkaloids and alkaloid-like molecules presented in this review show antiviral activity against SARS-CoV-2 virus and related coronaviruses, and some of them are potential antiviral drug candidates.

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Dr. Prasat Kittakoop received B.Sc. in 1989 (1st Class Honors, Chemistry) from Chiang Mai University, Thailand, and received Ph.D. in Biochemistry from University of Wales, Swansea, U.K., in 1992. His research interests are natural products chemistry, green chemistry, and medicinal chemistry. Dr. Prasat Kittakoop is a regular reviewer for many peer-reviewed journals, <https://publons.com/researcher/1301118/prasat-kittakoop/>.



Dhanushka Darshana received Bachelor of Pharmacy in 2016 with Second Class Upper Division from Faculty of Medicine, University of Ruhuna, Sri Lanka. He pursued his Ph.D. in Chemical Biology, Chulabhorn Graduate Institute, Bangkok, Thailand, under the supervision of Assoc. Prof. Dr. Prasat Kittakoop. He obtained his Ph.D. in 2021. Currently, he works as a lecturer in Department of Pharmacy, Faculty of Allied Health Sciences, University of Ruhuna, Sri Lanka. His research interests are pharmacognosy, green synthesis, drug discovery, natural products and medicinal chemistry.



Rapeepat Sangsuwan received her Bachelor of Science in Chemistry from Silpakorn University, Thailand in 2011, and worked in the laboratory of Dr. Nantanit Wanichacheva. There, her interest lied in fluorescence-based sensors which could emit light by fluorescence and provide high sensitivity and selectivity for the detection of mercury ions in aqueous solutions. She subsequently earned her master's degree in Chemical Biology at Chulabhorn Graduate Institute where she joined Dr. Prasat Kittakoop's group in 2011. During that time, she used an organocatalyst from renewable materials to develop an environmentally benign preparation of coumarins and chromenes. In 2013, she finished her master's degree in Chemical Biology and moved to California, USA, where she received her Ph.D. under the supervision of Dr. Matthew B. Francis at University of California, Berkeley. Her research focused on using bioconjugations for protein detection and intracellular delivery. She then worked for Dr. Jamal Lewis as a postdoctoral scholar to expand her training skills and interest in biomaterials and biological applications in cancers, immunomodulation, and osteoarthritis. Currently, she serves as a researcher at Chulabhorn research institute. Her research focuses on drug development and delivery for the treatment of metabolic diseases and cancers.



Professor Dr. Her Royal Highness Princess Chulabhorn Mahidol, the President of the Chulabhorn Research Institute, has been a lecturer in Chemistry Department at Mahidol University since 1985, with special interests in chemistry and synthesis of natural products. She was awarded the UNESCO's Einstein Medal for her continuous efforts in promoting scientific collaborations in Asia and Pacific. She was also the first Asian who has been invited to join the Royal Society of Chemistry, England, as an Honorary Fellow. Currently, she is the chairperson of the Working Group on the Chemistry of Natural Products Collaborative Programme between the Japan Society for the Promotion of Science and the National Research Council of Thailand. H.R.H. Princess Chulabhorn Mahidol has received international recognition for her scientific accomplishments. She has also been appointed to various United Nations posts, namely, a special advisor to the United Nations Environment Programme, and a member of the Special High-Level Council for the International Decade for Natural Disaster Reduction of the United Nations.