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REVIEW

To the 70th anniversary of Academician of the Russian Academy of Sciences V.N. Charushin

Main Chemotypes of SARS-CoV-2 Reproduction Inhibitors

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Abstract—The COVID-19 pandemic has forced scientists all over the world to focus their effort on searching for targeted drugs for coronavirus chemotherapy. The present review is an attempt to systematize low-molecular-weight compounds, including well-known pharmaceuticals and natural substances that have exhibited high anti-coronavirus activity, not in terms of action on their targets, but in terms of their structural type.

Keywords: coronavirus, antiviral agents, COVID-19, SARS-CoV-2

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Active study of coronaviruses began as late as 2002 after the outbreak of severe acute respiratory syndrome (SARS) in China. Further impetus to this line of research was given in 2012 after the outbreak of Middle East respiratory syndrome (MERS) in Saudi Arabia. The emergence of a highly pathogenic strain of the SARS-CoV2 virus in China at the end of 2019 and its spreading, which lead to the current pandemic, posed an intellectual challenge for the global scientific community, necessitating multidisciplinary collaboration to overcome the emerging systemic crisis in both healthcare and society as a whole.

Despite the success in the development of vaccines, their use is not the key to completely stopping the pandemic. There are social groups of the population, among which vaccination is impossible. In many countries, persistent rejection of vaccination has arisen. The limited immune protection time suggests repeated vaccination in about a year, which will result to a sharp decrease in the proportion of vaccinated population. The duration of immunity after new mRNA vaccines is an open question at all. At the time of this writing, 60% of the population was vaccinated in Israel and almost 50% of the population in the UAE, but the incidence is still quite high.

The constant emergence of mutant strains of coronaviruses, including more pathogenic ones resistant to the existing vaccines should also be taken into account [1]. All these aspects provide unequivocal evidence for the need to create an effective chemotherapeutic response that would allow coronavirus infections to be fought with a line of virus-specific drugs. The problem stimulates innovations and drives, in part, the development of both medicinal chemistry and modern organic synthesis. The urgency of the problem has prompted chemical community to perform in silico analysis the affinity of compounds in the existing libraries for the known SARS-CoV2 targets [2–7] and urgently consider the possibility of repurposing existing drugs [3, 4, 8–17]. In view of the sharply increased global demand, there is an urgent need for the development and scaling of new methods of synthesis, as well as cost-effective technological solutions for the production of antiviral pharmaceutical substances [18–20]. However, the main effort of organic chemists should be focused on the creation of new molecules, primarily new structural types of molecules, which would form the basis for future antiviral therapy.

The genome of the coronavirus is large and, therefore, it contains a lot of sites for interfering in its reproductive cycle [21]. Most of the existing laboratory models for assessing antiviral activity still imply work with the native virus [22, 23], which does provide insight in the details of the specific mechanism of antiviral action. At the same time, the structural diversity of active molecules created by the combined intellectual effort of organic

chemists is an incentive and a tool for identifying new targets for suppressing viral reproduction.

The relevance of the problem has caused the appearance of quite a few reviews [12, 14, 24–29] that describe the existing SARS-CoV-2 target and organic molecules capable of interacting with the binding sites of viral proteins.

The present review attempts to analyze the avalanche of publications and classify low-molecular-weight compounds, whose activity against coronaviruses has been proved either in vitro or in vivo, not from the viewpoint of their interaction with a particular target, but from the viewpoint of the molecular structure (chemotype) of the inhibitor of viral reproduction.

The structural types are presented in order of descending frequency of mentioning in the literature without dividing into synthetic, semisynthetic, and natural compounds, and, therewith, the most active individual compounds of each chemotype are considered. Taking into account that at the time of writing the review, almost 2500 compounds had been assessed for their activity against coronaviruses, the selection of the most active compounds in the present review is quite representative.

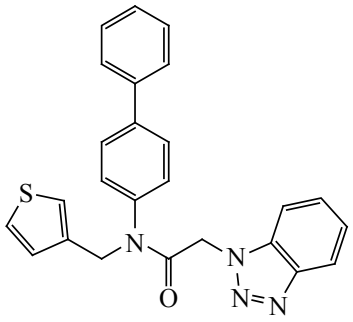
The first group of compounds with a significant antiviral effect is peptidomimetics **1–23** [30–48] (Figs. 1, 2). The only proven target of peptidomimetics is the viral chymotrypsin-like protease 3CLpro/Mpro. Among the representatives of this type of coronavirus reproduction inhibitors, there are both drugs already used in clinical practice, such as boceprevir **21** [36, 42] and lopinavir **23** [48], and new compounds. Compounds of this group can be conditionally divided into aryl(hetaryl)-aminoacetic acid derivatives **1** [30], **3** [32], **6** [33], and **10** [36] and benzotriazolylacetic acid derivatives **2** [31], **4** [32], and **5** [32], serine and isoserine derivatives **7–9** [34, 35] (Fig. 1), as well as compounds **11–23** [36–48] (Fig. 2), which contain several amino acid units, often leucine units **11** [36, 37, 38], **12** [39], **14** [41], **15** [36, 42], **19** [45], **20** [42], and **22** [47]. A common feature of peptidomimetics is that they contain lipophilic substituents (most frequently *tert*-alkyl, aromatic, or heteroaromatic), which suggests the importance of binding to hydrophobic sites of the target.

The antiviral activity of peptidomimetics (IC_{50}) varies over a wide range (0.051–74 μm), and the most active are benzotriazolylacetic acid derivatives **2** [31], **4** [32], and **5** [32] and polysubstituted threonylphenylalanine **17** [44]. Peptidomimetics have shown high potential against SARS-CoV-2, because the coronaviral 3CLpro/Mpro protease is required for replication of coronaviruses, and its active site is highly conservative. For example, the IC_{50} values of diphenyl derivative **6** [33] are nearly the same for both SARS-CoV and SARS-CoV-2 proteases. However, for successful use of peptidomimetics one should solve a number of problems associated with their bioavailability and metabolic stability, selectivity for the target protease, and methods of delivery to the target. Compounds of this class are characterized by a noticeable predominance in their structures of H-bond acceptors over H-bond donors.

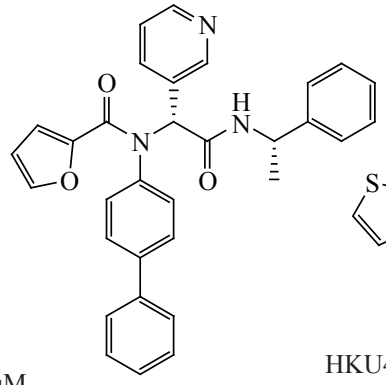
The second most mentioned group of compounds with proven anticoronavirus activity is the group of polyphenols, including flavonoids and chalconoids, as well as substituted chromones and polycyclic quinones. Most compounds of these structural types inhibit the viral proteases 3CLpro and Mpro, but also there are also inhibitors of the Plpro protease, NTP helicase, and viral E protein ion channel. The polyphenol group includes chromones **24** [49], **25** [53], flavone and isoflavone derivatives **26–37** [50–52, 54–57] (Fig. 3), catechin **38** [58], flavanone **39** [58], flavan **40** [52], coumarin **41** [59], naphthoquinones shikonin **42** [60] and plumbagin **43** [61], and anthraquinone **44** [62]. Transhinones **45** [63] and **46** [63] (Fig. 4) and chalconoids **47–49** [64–66], benzophenone derivatives **50** [61], **51** [62], and dibenzodioxane **52** [67], and **53** [67] (Fig. 5), too, proved to be quite active.

The IC_{50} values of polyphenols span the range 1–50 μM, but most values were obtained by biochemical tests against the 3CLpro/Mpro and PLpro proteases, as well as helicase and *N*-methyltransferase. The net virus-inhibiting effect was established only for compounds **36** [57] and **37** [57] and is at the micromolar level. In general, compounds containing no carbohydrate residue are more active, isoflavonoids are more active than flavone derivatives, and the highest IC_{50} values were found in quinones **42** [60] and **45** [63].

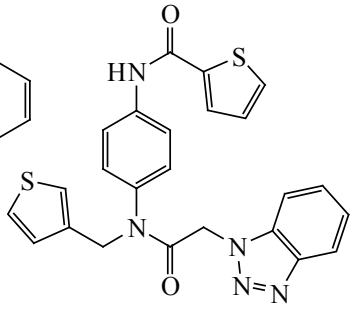
Modified nucleoside analogs quite active against coronaviruses are both pyrimidine derivatives **54–58** [60, 68–71] and purine derivatives **60** [73], **61** [74], **63** [74], and **64** [77] (Fig. 6), which was also confirmed by in vitro testing. The main target of inhibitors of this chemotype is the viral guanine-*N*7-methyltransferase nsp14. Carmofur **55** [60, 69] is the only to exhibit



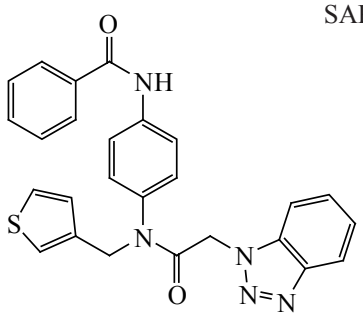
1 [30]
SARS-CoV 3CLpro IC_{50} = 0.051 uM



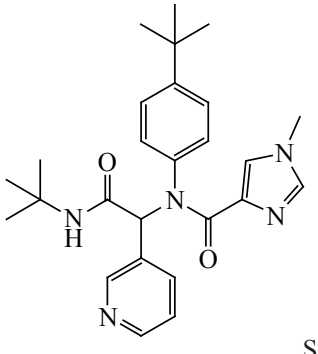
2 [31]
SARS-CoV-2 Mpro IC_{50} = 0.31 uM
SARS-CoV Mpro IC_{50} = 0.27 uM



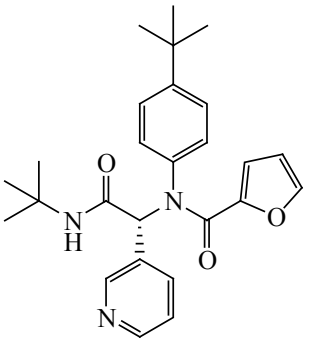
3 [32]
HKU4-CoV 3CLpro IC_{50} = 0.33 uM



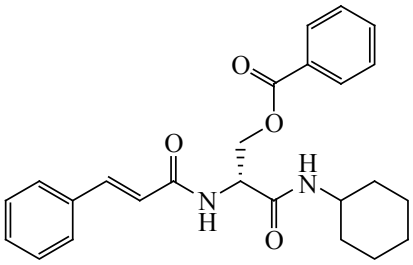
4 [32]
HKU4-CoV 3CLpro IC_{50} = 0.41 uM



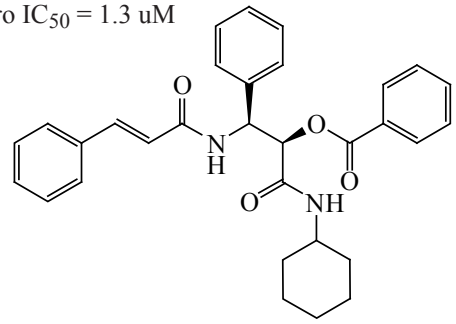
5 [32]
HKU4-CoV 3CLpro IC_{50} = 1.3 uM



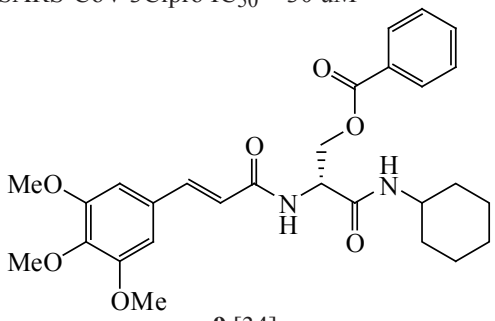
6 [33]
SARS-CoV 3CLpro IC_{50} = 1.5 uM



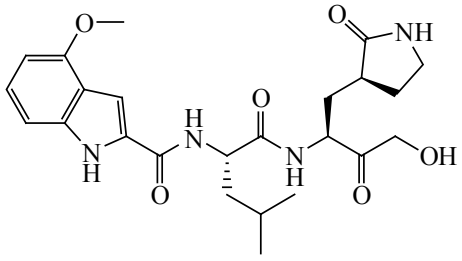
7 [34]
SARS-CoV 3Clpro IC_{50} = 30 uM



8 [35]
SARS-CoV 3CLpro IC_{50} = 43 uM

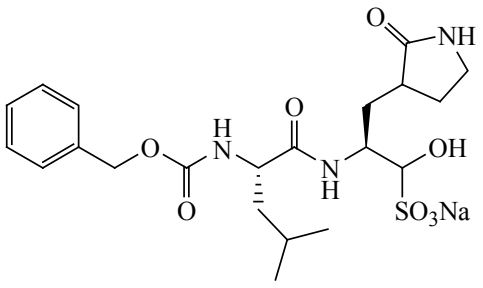


9 [34]
SARS-CoV 3CLpro IC_{50} = 65 uM

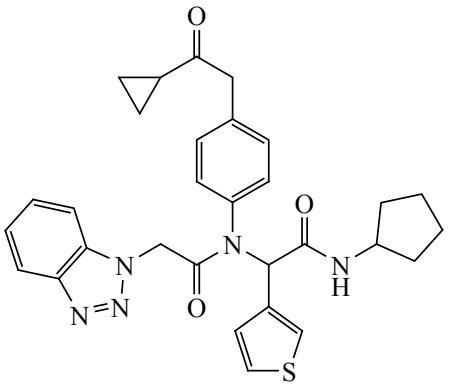


10 [36]
SARS-CoV-2 3CLpro IC_{50} = 0.0057 uM

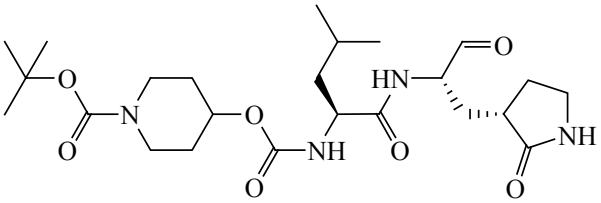
Fig. 1. Structures of peptidomimetics **1–10**.



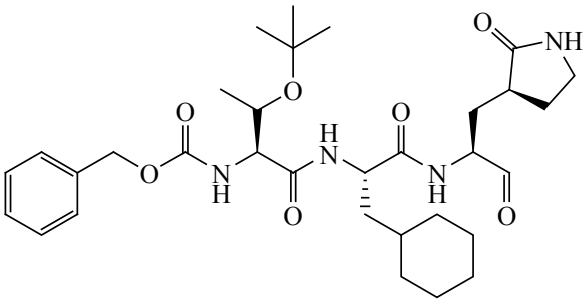
11 [36, 37, 38]
SARS-CoV-2 3CLpro IC_{50} = 0.15 uM



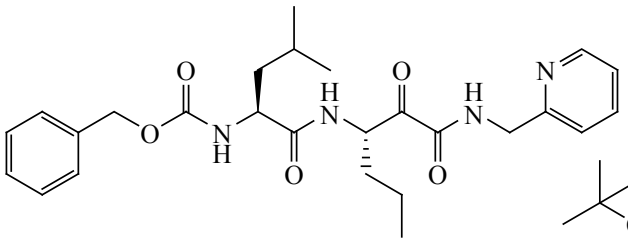
12 [39]
SARS-CoV 3CLpro IC_{50} = 0.5 uM



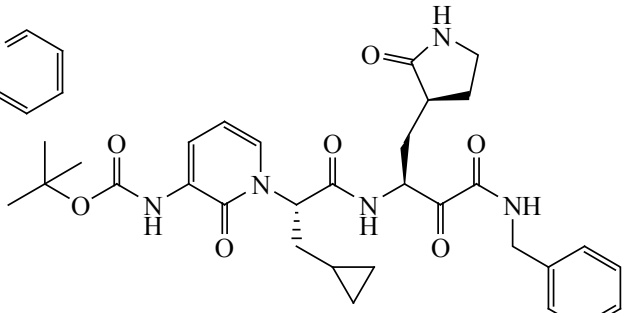
13 [40]
MERS-CoV-3Clpro IC_{50} = 2.1 uM



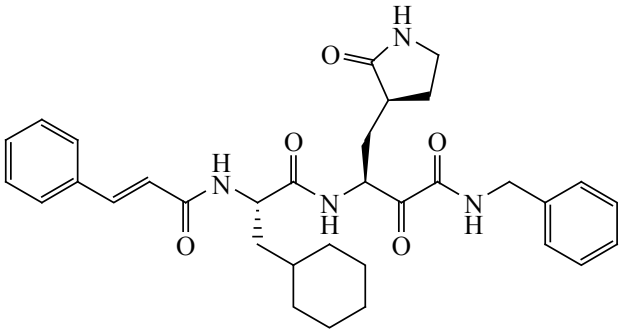
14 [41]
SARS-CoV 3CLpro K_i = 0.053 uM



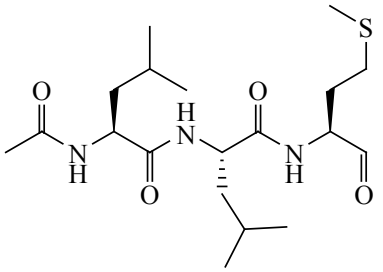
15 [36, 42]
SARS-CoV-2 Mpro IC_{50} = 0.453 uM



16 [43]
SARS-CoV-2 Mpro IC_{50} = 0.68 uM

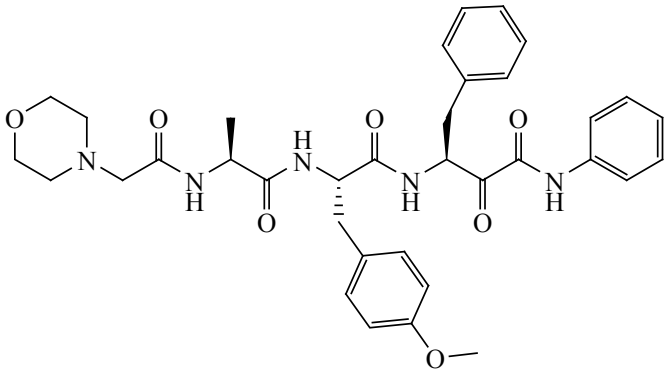


17 [44]
SARS-CoV Mpro IC_{50} = 0.71 uM
repl. EC_{50} = 2.1 uM

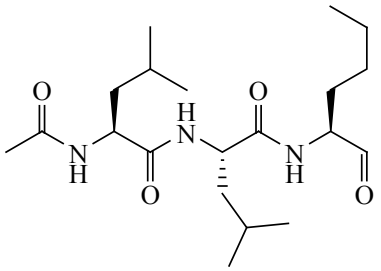


18 [36, 42]
SARS-CoV-2 Mpro IC_{50} = 0.97 uM

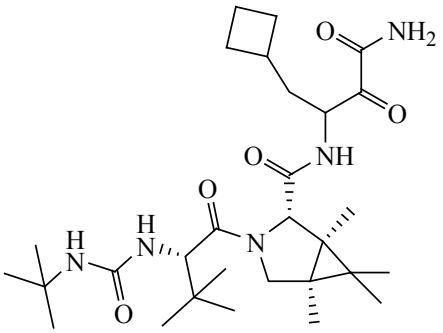
Fig. 2. Structures of peptidomimetics **11–23**.



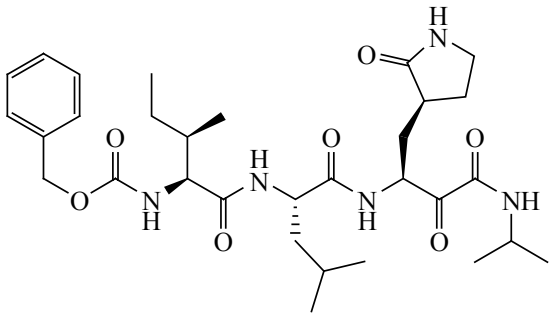
19 [45]
SARS-CoV-2 repl. EC_{50} = 1.28 uM



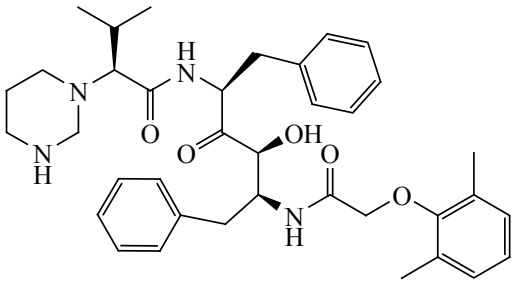
20 [42]
SARS-CoV-2 Mpro IC_{50}= 1.46 uM



21 Boceprevir [46]
SARS-CoV-2 Mpro IC_{50} = 5.40 uM



22 [47]
SARS-CoV 3CLpro IC_{50} = 6.8 uM

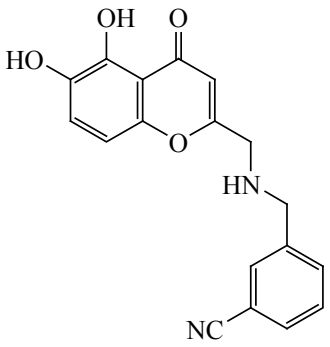


23 Lopinavir [48]
SARS-CoV-2 repl. EC_{50} = 26.63 uM

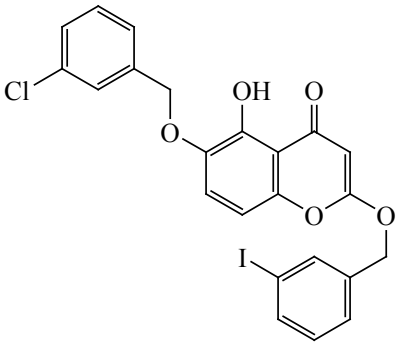
Fig 2. (Contd.)

pronounced activity (IC_{50} 0.2 μM) against the protease SARS-CoV-2 3CLpro/Mpro protease. In general, pyrimidine derivatives are more active than purine derivatives. In this group, a particular place belongs to pyrrolo[2,1-*f*][1,2,4]triazine derivative **62** [75, 76] (remdisivir), which is actually a prodrug. Evidence for the efficiency of remdisivir **62** was obtained in clinical trials, and it already actively used in medical practice. The same can be said about favipiravir **59** [72], a prodrug which is widely used in the treatment of COVID-19 and is an analog of both pyrimidine and purine nucleosides.

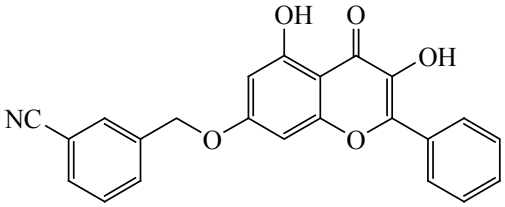
Unexpected is the presence of a sufficiently high antiviral activity in sulfides **65–67** [78–82] and disulfides **68–74** [83, 84], containing aromatic and nitrogenous heteroaromatic substituents, unexpectedly showed quite a high antiviral activity. In this group, disulfiram **68** [83] (Fig. 7) deserves special mention: it contains no cyclic fragments but has an appreciable activity against the MERS-CoV virus.



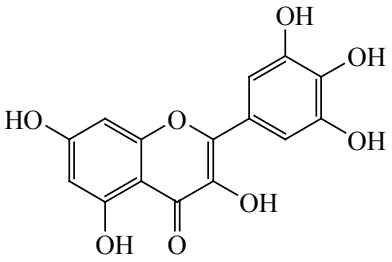
24 [49]
SARS-CoV NTPase/helicase EC_{50} = 2.7 uM



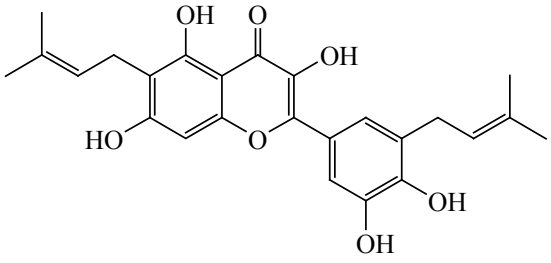
25 [53]
SARS-CoV NTPase IC_{50} = 4 uM
helicase IC_{50} = 11uM



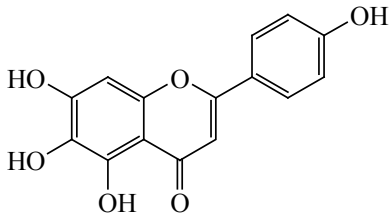
26 [50]
SARS-CoV helicase IC_{50} = 2.7 uM



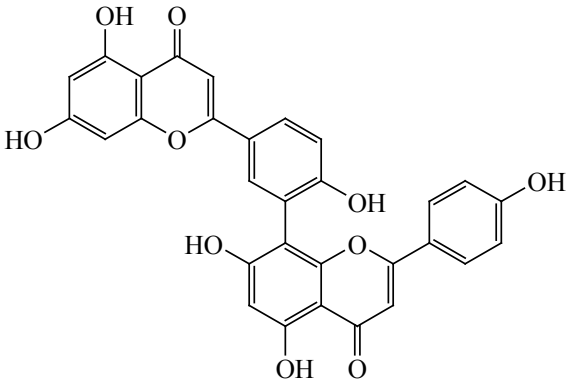
27 Myricetin [51]
SARS-CoV nsp13 IC_{50} = 2.71 uM



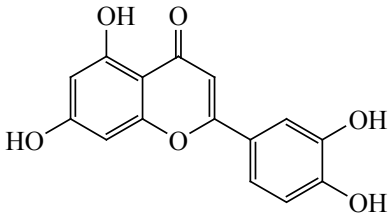
28 [52]
SARS-CoV PLpro IC_{50} = 3.7 uM



29 Scutellarein [51]
SARS-CoV nsp13 IC_{50} = 0.86 uM

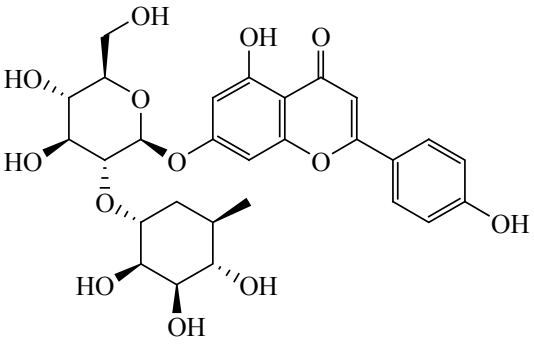


30 [54]
SARS-CoV 3CLpro IC_{50} = 8.3 uM

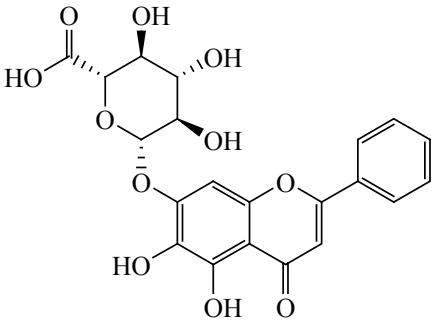


31 Luteolin [54]
SARS-CoV 3CLpro IC_{50} = 20.2 uM

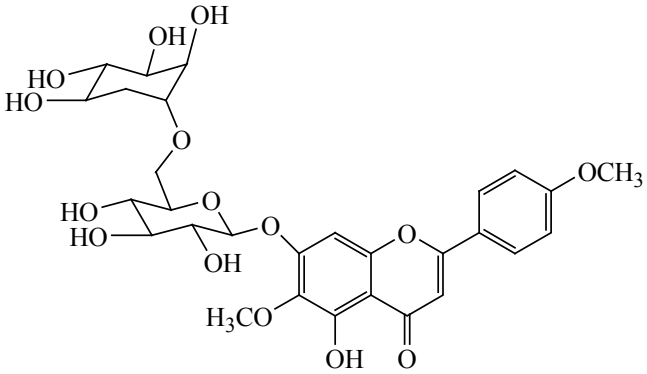
Fig. 3. Structures of polyphenols **24–37**.



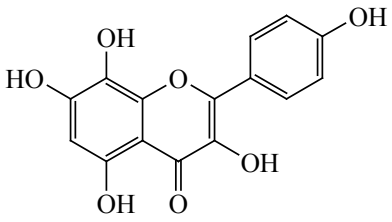
32 Roifolin [55]
SARS-CoV 3CLpro IC_{50} = 27.45 uM



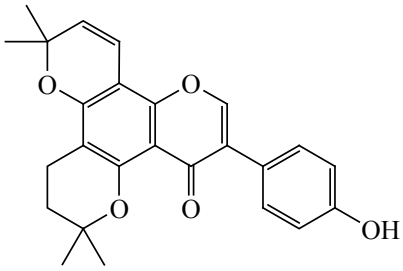
33 Baicalin [56]
SARS-CoV-2 3CLpro IC_{50} = 34.71 uM



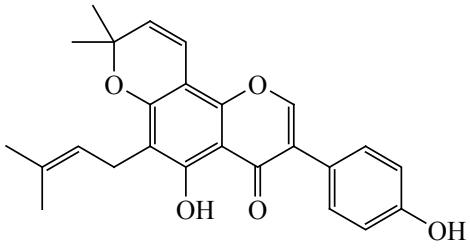
34 Pektolinarin [56]
SARS-CoV-2 3CLpro IC_{50} = 51.64 uM



35 Herbacetin [56]
SARS-CoV-2 3CLpro IC_{50} = 53.90 uM



36 [57]
SARS-CoV-2 repl. IC_{50} = 3.22 uM



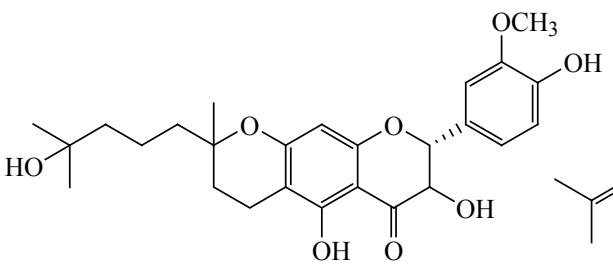
37 [57]
SARS-CoV-2 repl. IC_{50} = 3.87 uM

Fig 3. (Contd.)

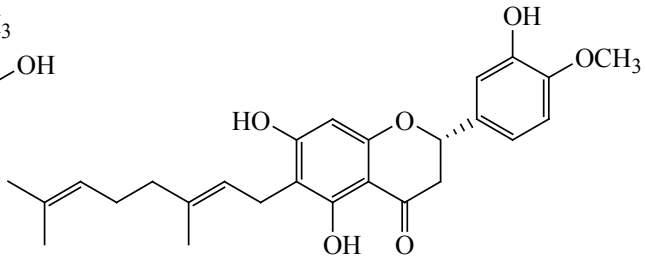
Six-membered nitrogenous heterocycles, including widely known protein kinase inhibitors (tinibs) **75–80** [57, 85, 86], occupy a large place among compounds active against coronaviruses. Among tinibs, we would like to mention nilotinib **75** [85] (IC_{50}<0.01 μM) (Fig. 8).

Quinoline derivatives **81–91** [57, 86–95] are often mentioned among heterocyclic compounds active against coronaviruses. This group of compounds includes well-known antimalarial agents, specifically hydroxychlorolroquine **82** [87–89], which has been used in clinical practice for some time to treat patients with COVID-19 (Fig. 9).

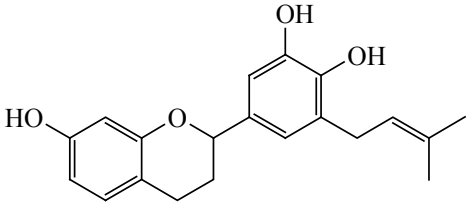
The antiviral activity of different levels was found in pyrans **92** [96] and **93** [62], pyridines **94–101** [21, 57, 85, 90, 91, 97, 98], isoquinoline **102** [99], thiazolopyridine **103** [100], oxazolopyridine **104** [101] (Fig. 10), pyrimidines **105–110** [90, 102–105], benzopyrimidines **111–113** [93, 106, 107], imidazolopyrimidines **114** [96] and **115** [109], pyrazolopyrimidine **116** [96],



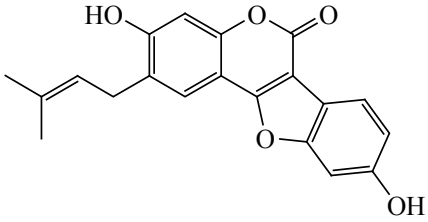
38 [58]
SARS-CoV PLpro IC_{50} = 5.0 uM



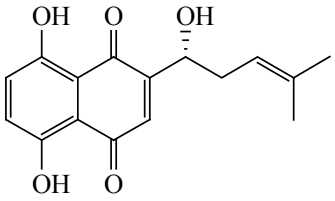
39 [58]
SARS-CoV PLpro IC_{50} = 9.2 uM



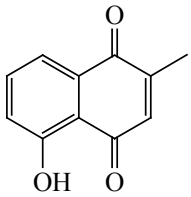
40 [52]
SARS-CoV 3CLpro IC_{50} = 30.2 uM
MERS-CoV 3CLpro 34.7 uM
SARS-CoV PLpro 35.8 uM
MERS-CoV PLpro 48.8 uM



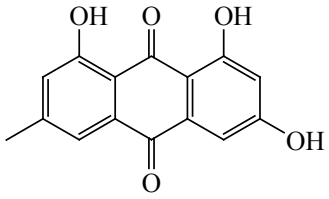
41 [59]
SARS-CoV PLpro IC_{50} = 4.2 uM



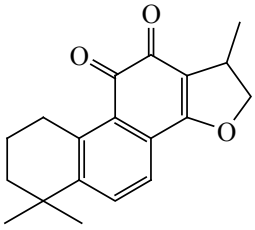
42 Shikonin [60]
SARS-CoV-2 Mpro IC_{50}= 1.5 uM



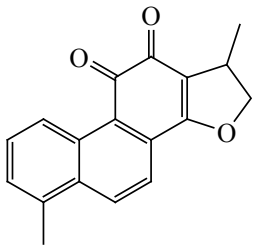
43 Plumbagin [61]
SARS-CoV-2 Mpro IC_{50} = 17.1 uM



44 [62]
SARS-CoV-2 E – 60% inh. at 10 mmol
Orf7b – 75% inh. at 10 mmol



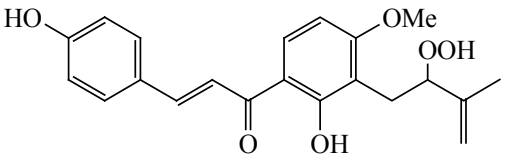
45 [63]
SARS-CoV PLpro IC_{50} = 0.8 uM



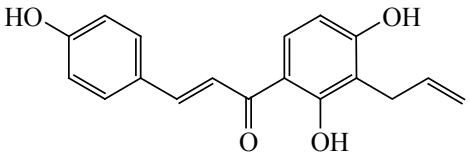
46 [63]
SARS-CoV 3CLpro IC_{50} = 14.4 uM
PLpro IC_{50} = 4.9 uM

Fig. 4. Structures of polyphenols **38**–**46**.

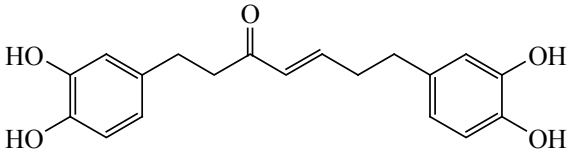
pyrazine **117** [110], benzopyrazines **118** [90] and **119** [85], benzothiazine **120** [111] (Fig. 11), and saturated heterocyclic compounds **121**–**127** [21, 57, 6, 85, 90, 99] (Fig. 12). Among them, such popular antihypertensive as amlodipine **99** [85] and papaverine **102** [99] deserve special mention. The activity of most compounds of this group was assessed in cell models, and, therefore, it is not quite clear what are their real targets in coronaviruses.



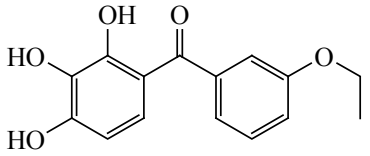
47 [64]
SARS-CoV IC_{50} = 11.4 uM (3CLpro)
1.2 uM (PLpro)



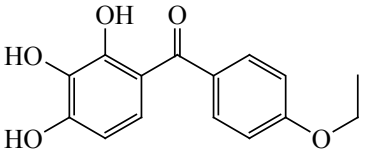
48 [65]
MERS-CoV 3CLpro IC_{50} = 38.85 uM



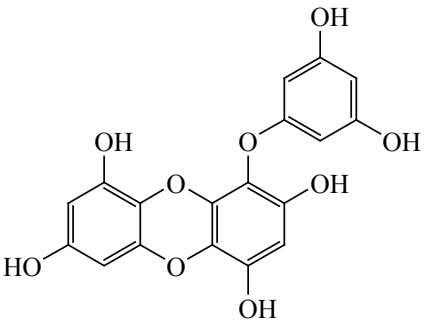
49 [66]
SARS-CoV 3CLpro IC_{50} = 36.2 uM



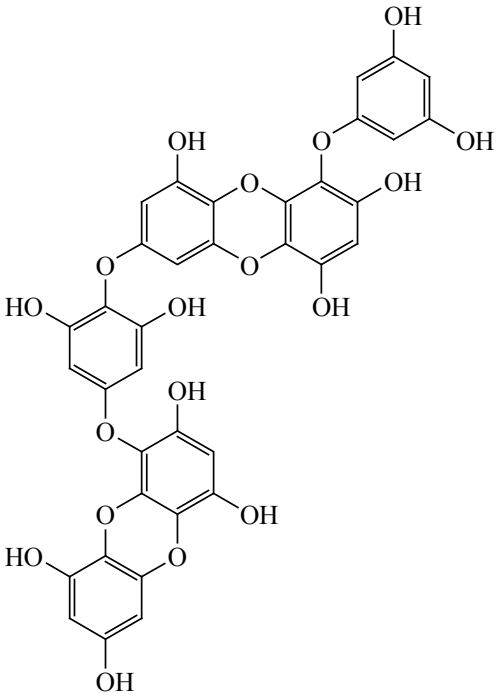
50 [61]
SARS-CoV-2 Mpro IC_{50} = 10.6 uM



51 [62]
SARS-CoV-2 Mpro IC_{50} = 10.6 uM



53 [67]
SARS-CoV 3CLpro IC_{50} = 8.8 uM

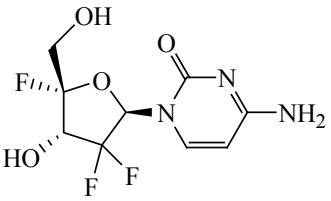


52 [67]
SARS-CoV 3CLpro IC_{50} = 2.7 uM

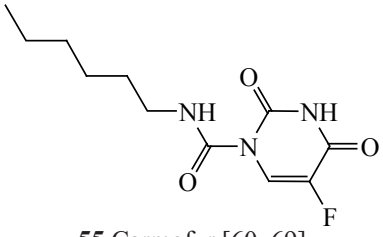
Fig. 5. Structures of polyphenols **47–53**.

At the same time, compounds **93** [62], **95–98** [91, 97, 98], **103** [100], **104** [101], **106** [103], **107** [104], **109** [105], **111** [93], **112** [106], **114** [96], and **127** [61] were found to inhibit the viral main protease 3CLpro/Mpro.

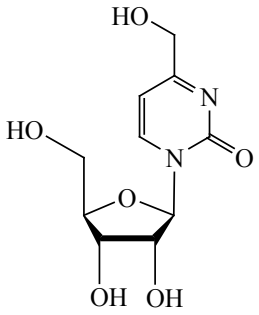
Among tetra- **128–131** [48, 57, 99] and decahydroisoquinoline **132–134** [112–115] and octahydrobenzopyran derivatives **135** [113, 114], there are many compounds that inhibit the replication of coronaviruses (Fig. 13). Noteworthy is a noticeable activity against SARS-CoV-2 of isoquinoline alkaloids **128–131** [48, 57, 99] and HIV protease inhibitor nelfinavir **132** [112]. Basically, the activity of these compounds was assessed



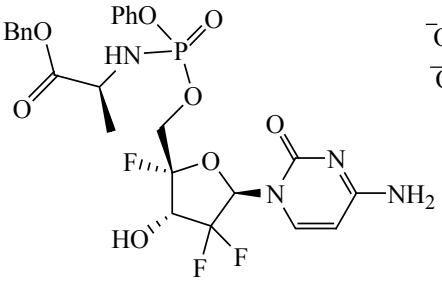
54 [68]
SARS-CoV-2 repl. EC_{50} = 0.096 uM



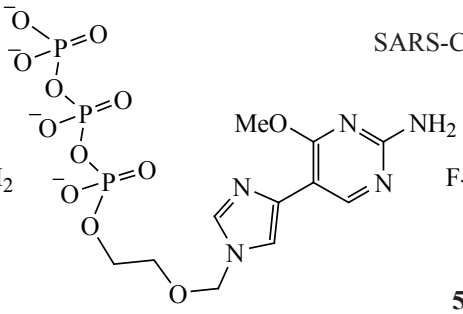
55 Carmofur [60, 69]
SARS-CoV-2 Mpro IC_{50} = 0.2 uM



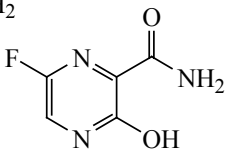
56 [70]
SARS-CoV-2 repl. EC_{50} = 0.3 uM



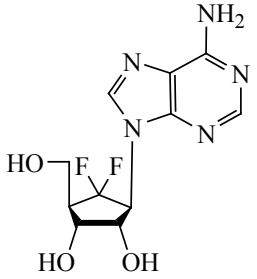
57 [68]
SARS-CoV-2 repl. EC_{50} = 0.73 uM



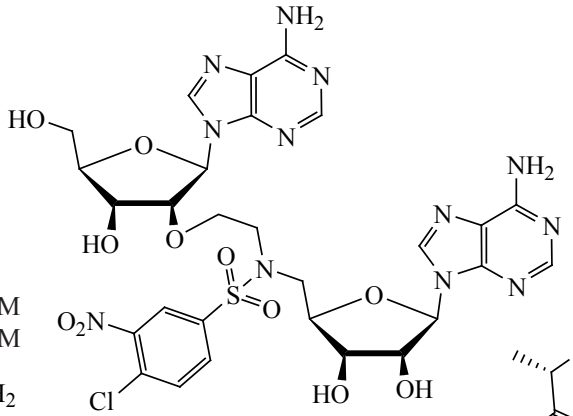
58 [71]



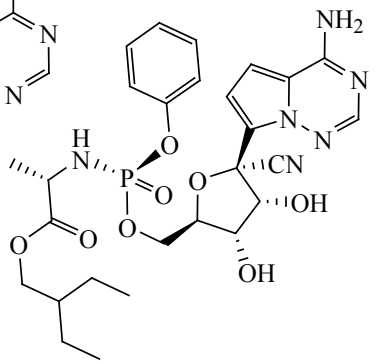
59 Favipiravir [72]
SARS-CoV-2 repl. EC_{50} = 61.88 uM



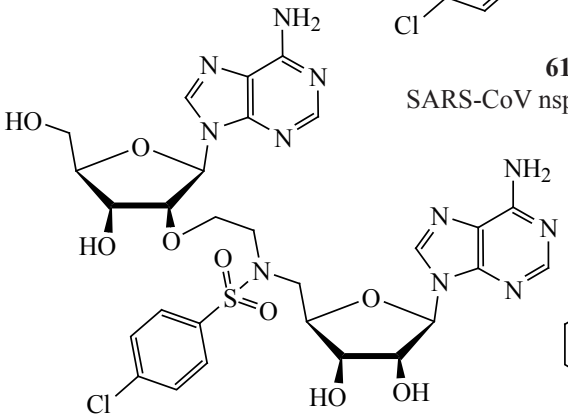
60 [73]
MERS-CoV repl. EC_{50} = 0.2 uM
SARS-CoV repl. EC_{50} = 0.5 uM



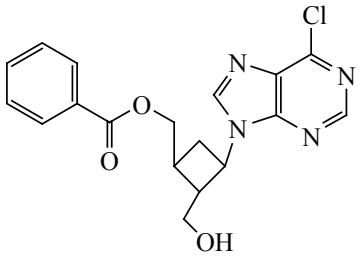
61 [74]
SARS-CoV nsp14 IC_{50} = 0.6 uM



62 Remdesivir [75, 76]
SARS-CoV-2 repl. EC_{50} = 0.77 uM

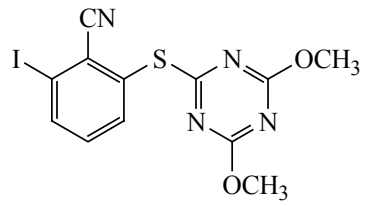


63 [74]
SARS-CoV nsp14 IC_{50} = 1.5 uM

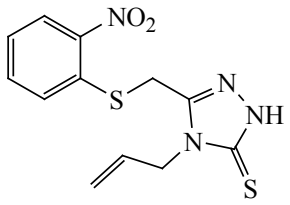


64 [77]
SARS-CoV repl IC_{50} = 14.5 uM

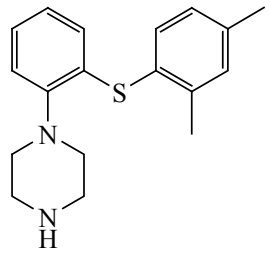
Fig. 6. Structures of nucleoside analogs **54–64**.



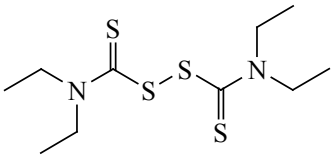
65 [78]
SARS-CoV MPro IC_{50} = 3.30 uM



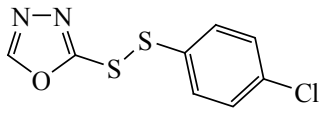
66 [79, 80, 81]
SARS-CoV nsp13 IC_{50} = 5.9 uM



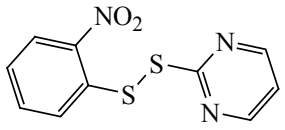
67 Vortioxetine [82]
SARS-CoV-2 repl. IC_{50} = 8.03 uM



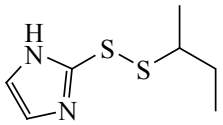
68 Disulfiram [83]
MERS-CoV 3CLpro IC_{50} = 14.6 uM
SARS-CoV 3CLpro IC_{50} = 24.1 uM



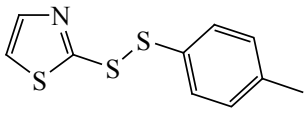
69 [84]
SARS-CoV Mpro IC_{50} = 0.516 uM



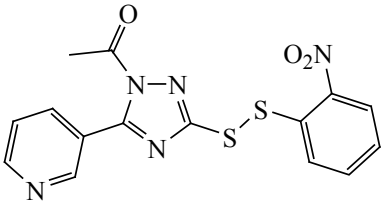
70 [85]
SARS-CoV Mpro IC_{50} = 0.883 uM



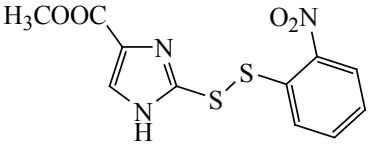
71 [60]
SARS-CoV-2 Mpro IC_{50} = 0.9 uM



72 [84]
SARS-CoV Mpro IC_{50} = 1.250 uM



73 [84]
SARS-CoV Mpro IC_{50} = 1.762



74 [84]
SARS-CoV Mpro IC_{50} = 2.075 uM

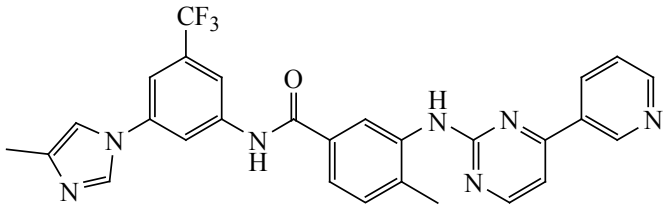
Fig. 7. Structures of sulfides and disulfides **65–74**.

using cell models. However, the target of compounds **133–135** [113–115] is the chymotrypsin-like protease 3CLpro/Mpro.

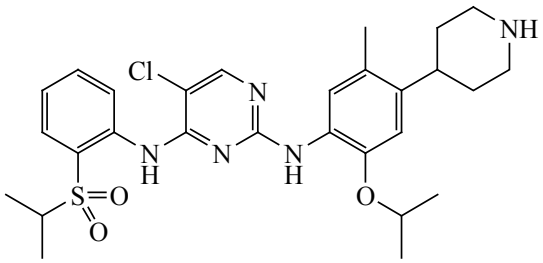
Since five-membered heterocyclic systems are among the most common components of known drugs [116], it is not surprising that this structural type is one of the most abundant among compounds active against coronaviruses. This group includes heterocycles containing one **136–148** [57, 61, 85, 90, 91, 100, 118–124] (Fig. 14), two **149–160** [57, 85, 86, 89, 90, 100, 125, 127–129] (Fig. 15), and three heteroatoms **161–165** [60, 86, 94, 130, 131] (Fig. 16), including fused bicyclic systems.

Virus-inhibiting properties were found in porphyrins **139–140** [61–119], indole derivatives, including **141** [120] (IC_{50} 0.03 μM), and umifenovir (Arbidol) **145** [90, 123, 124], which was recommended as a COVID-19 therapeutic. An appreciable antiviral activity of the selective COX-2 inhibitor celecoxib **149** [85] (IC_{50} 0.04 μM) and antiulcer drug omeprazole **158** [90]. The highest activity in this group of compounds was found to be characteristic of raloxifene **148** [85] (0.02 μM) and dimeric benzimidazole derivative **157** [128] (0.003 μM!) (Fig. 15).

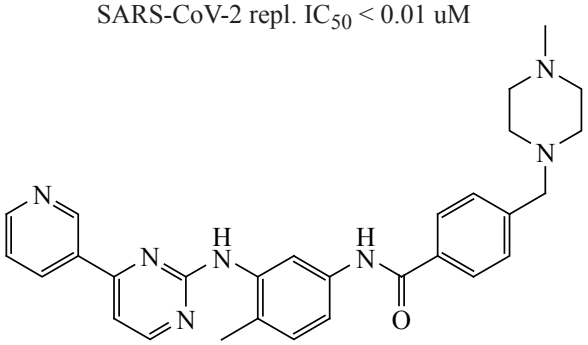
Cage compounds **166** [134] and **167** [62], whose activity against the M2 ion channels of the influenza virus is well known [132, 133], showed activity against SARS-CoV-2, too (Fig. 17). It was found that amantadine **166** and 3-fluoroamantadine **167** are capable of binding with the E ion channel. However, bananin derivatives **168–171** [135–136], which have a trioxaadamantane



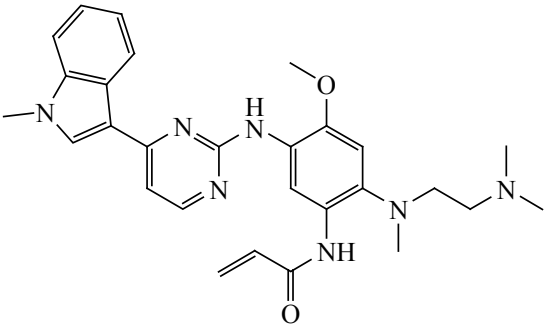
75 Nilotinib (AMN-107) [85]
SARS-CoV-2 repl. IC_{50} < 0.01 uM



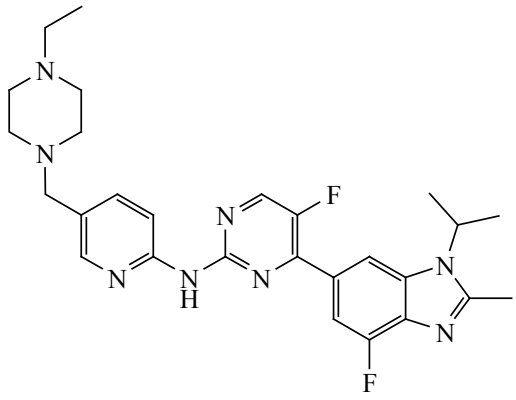
76 Ceritinib [57]
SARS-CoV-2 repl. IC_{50} = 2.86 uM



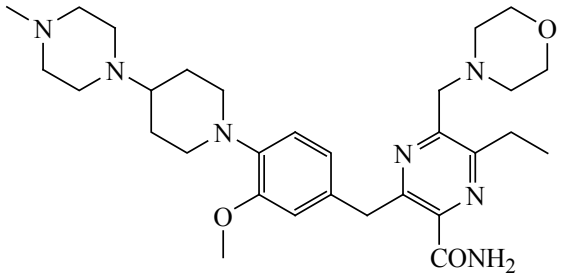
77 Imatinib [86]
SARS-CoV-2 repl. IC_{50} = 3.24 uM



78 Osimertinib [57]
SARS-CoV-2 repl. IC_{50} = 3.26 uM



79 Abemaciclib [57]
SARS-CoV-2 repl. IC_{50} = 6.62



80 Gilteritinib [57]
SARS-CoV-2 repl. IC_{50} = 6.76 uM

Fig. 8. Structures protein kinase inhibitors (tinibs) **75–80**.

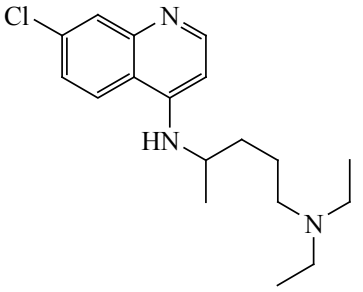
core, inhibit another coronavirus target, specifically helicase nsp13.

Phenothiazine antipsychotics **172–177** [57, 86, 137] in micromolar concentrations inhibit coronavirus replication (Fig. 18). Russian scientists have revealed a high virus-inhibiting activity of methylene blue **178** [137] (IC_{50} 0.22 μM) under conditions of photodynamic activation.

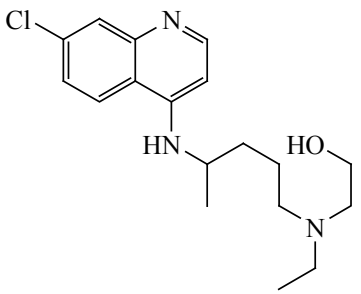
Drugs, the active pharmaceutical ingredients of which contain di- and triannulated seven-membered heterocycles, such as azepine **179** [90], di- and tetrahydroazepines **180–182** [48, 85, 86], and dihydrooxepine **183** [82] inhibit SARS-CoV-2 replication in the micromolar range (Fig. 19).

A number of diphenylmethyl-containing drugs **184–189** [46, 57, 85, 86] exhibit a pronounced activity against coronaviruses (Fig. 20).

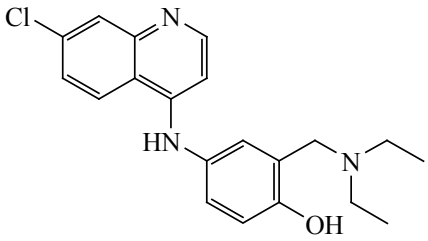
1-(Naphthalen-1-yl)ethyl derivatives **190–196** [138–142] (Fig. 21) have been studied in sufficient detail. They proved to be highly active both against the papain-like protease PLpro SARS-CoV and SARS-CoV-2, and inhibit the replication of viral particles in cell models in the micro and submicromolar ranges.



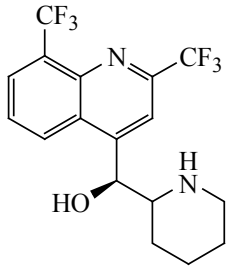
81 Chloroquine [87, 88, 89]
SARS-CoV-2 repl. EC_{50} = 5.47 uM



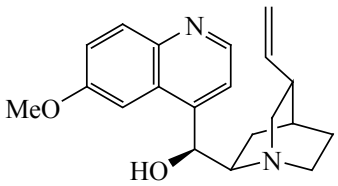
82 Hydroxychloroquine [87, 88, 89]
SARS-CoV-2 repl. EC_{50} = 0.72 uM



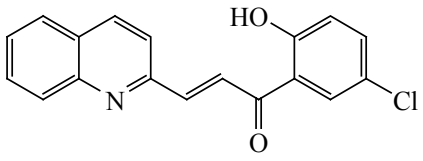
83 Amodiaquine [86]
SARS-CoV-2 repl. IC_{50} = 2.59 uM



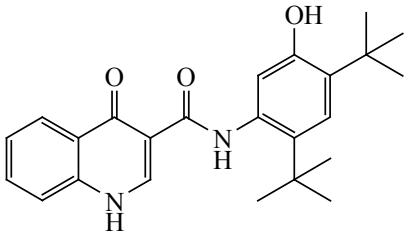
84 Mefloquine [86]
SARS-CoV-2 repl. IC_{50} = 7.11 uM



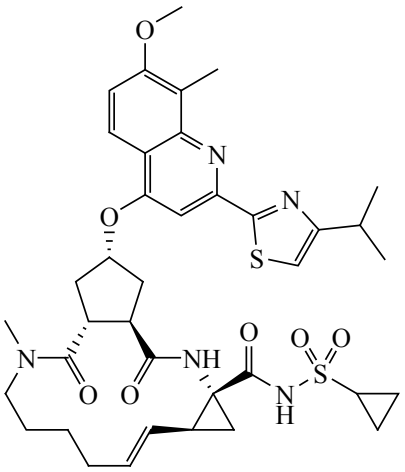
85 Quinidine [90]
SARS-CoV-2 repl. EC_{50} = 5.11 uM



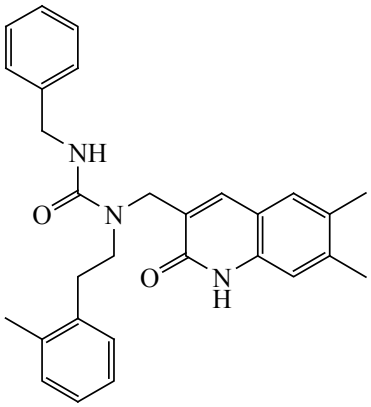
86 [91]
SARS-CoV-2 3CLpro IC_{50} = 13.8 uM



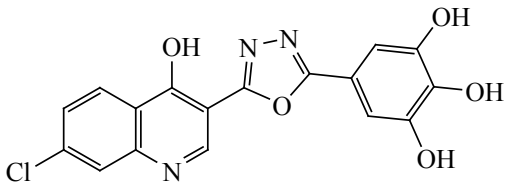
87 Ivacaftor [57]
SARS-CoV-2 repl. IC_{50} = 6.57 uM



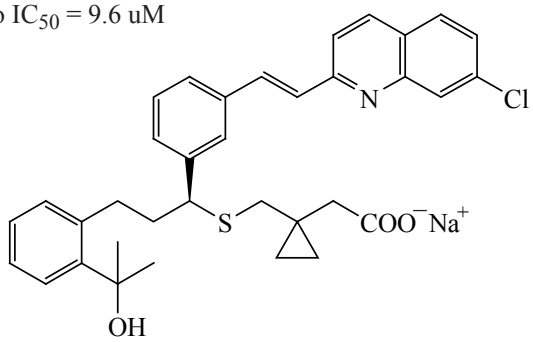
88 Simeprevir [92]
SARS-CoV-2 Mpro IC_{50} = 9.6 uM



89 [93]
SARS-CoV 3CLpro IC_{50} = 17.2 uM

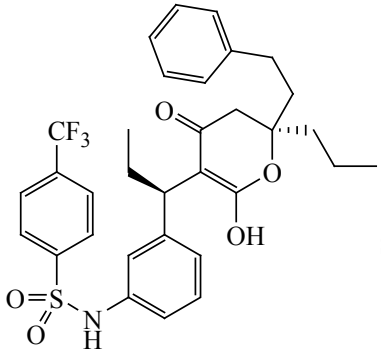


90 [94]
SARS-CoV-2 repl. EC_{50} = 1.01 uM

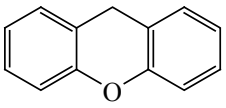


91 Montelukast [95]
MERS-CoV S IC_{50} = 3 uM

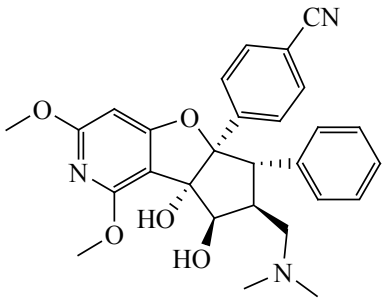
Fig. 9. Structures of quinoline derivatives **81–91**.



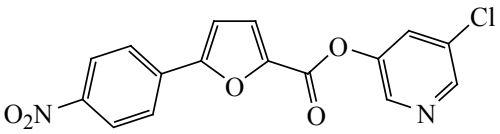
92 Tipranavir [96]
SARS-CoV-2-Nluc repl. IC_{50} = 8.65 uM



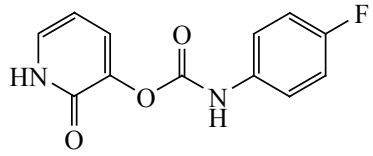
93 [62]
SARS-CoV-2 E - 80% inh. at 10 mmol
3a - 20% inh. at 10 mmol
Orf7b - 50% inh. at 10 mmol



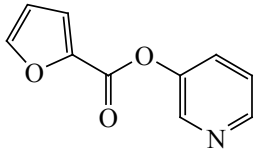
94 Zotatifin [21]
SARS-CoV-2 repl. IC_{90} = 0.037 uM



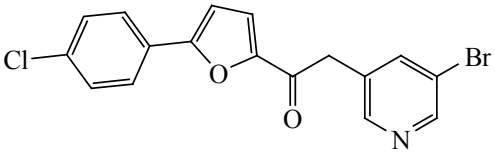
95 [97]
SARS-CoV 3CLpro IC_{50} = 0.06 uM



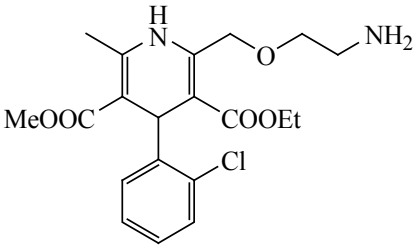
96 [91]
FCoV 3CLpro IC_{50} = 3.56 uM
SARS-CoV 3CLpro IC_{50} = 7.00 uM
SARS-CoV-2 3CLpro IC_{50} = 12.72 uM



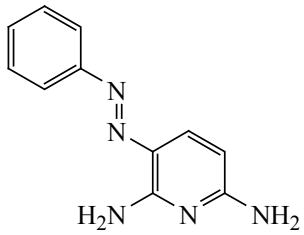
97 [98]
SARS-CoV 3CLpro IC_{50} = 7.9 uM



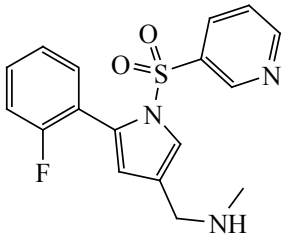
98 [98]
SARS-CoV 3CLpro IC_{50} = 13 uM



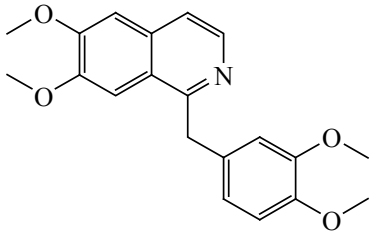
99 Amlodipine [85]
SARS-CoV-2 repl. IC_{50} = 10.28 uM



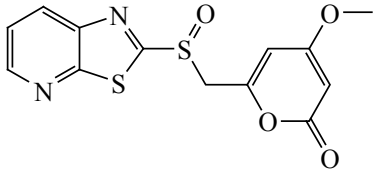
100 Phenazopyridine [57]
SARS-CoV-2 repl. IC_{50} = 28.0



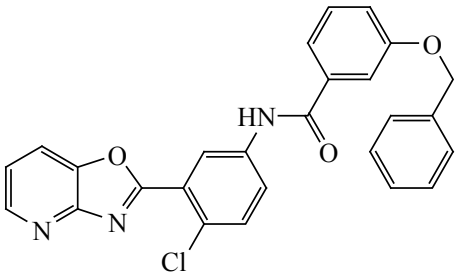
101 Vonoprazan [90]
SARS-CoV-2 repl. EC_{50} = 35.38 uM



102 Papaverine [99]
SARS-CoV-2 repl. IC_{50} = 1.1 uM

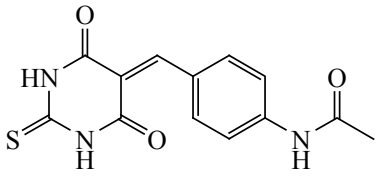


103 [100]
SARS-CoV 3CLpro IC_{50} = 7.2 uM

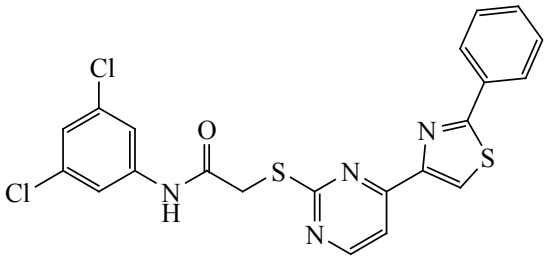


104 [101]
SARS-CoV Mpro EC_{50} = 6 uM

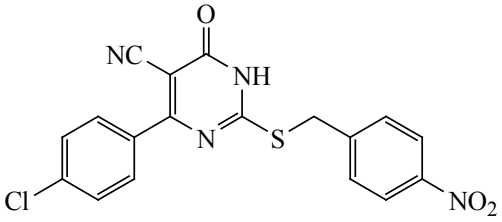
Fig. 10. Structures of six-membered heterocycles **92–104**.



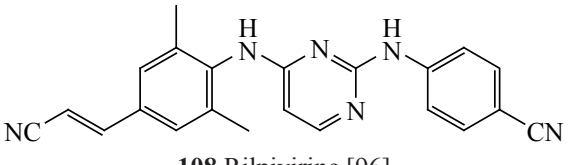
105 [102]
SARS-CoV ATPase IC_{50} = 1.19 uM
helicase IC_{50} = 32.9 uM



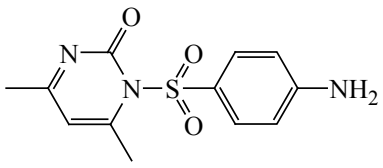
106 [103]
SARS-CoV 3CLpro IC_{50} = 3 uM



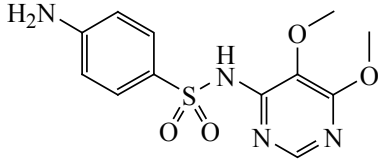
107 [104]
3CLpro SARS-CoV IC_{50} = 6.1 uM



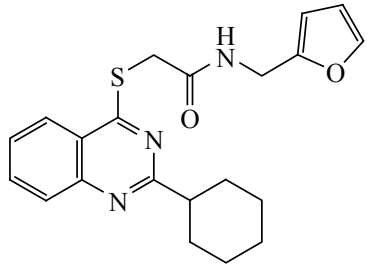
108 Rilpivirine [96]
SARS-CoV-2-Nluc repl. IC_{50} = 7.8 uM



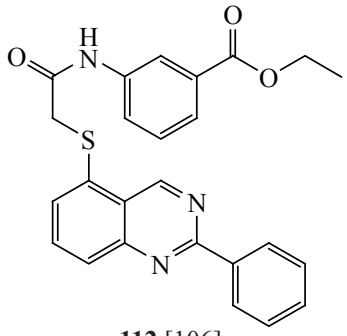
109 [105]
MERS-CoV 3CLpro IC_{50} = 20.0 uM



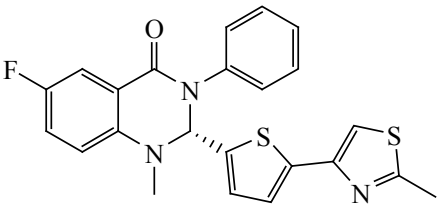
110 Sulfadoxine [90]
SARS-CoV-2 repl. EC_{50} = 35.37 uM



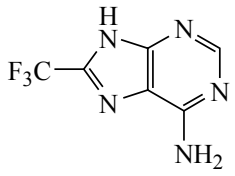
111 [93]
SARS-CoV 3CLpro IC_{50} = 18.2 uM



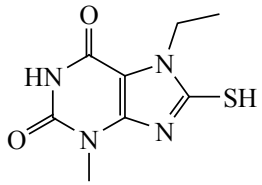
112 [106]
SARS-CoV 3CLpro IC_{50} = 5.8 uM



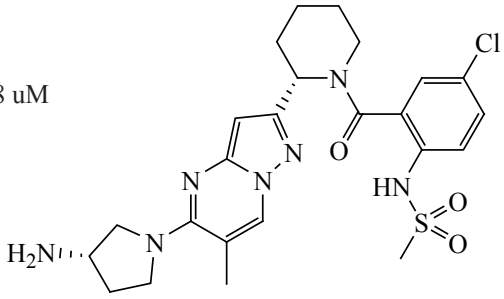
113 [107]
SARS-CoV-2 repl IC_{50} = 0.08 uM



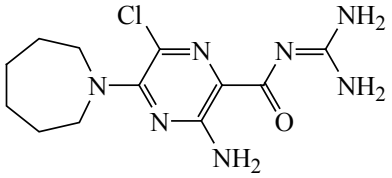
114 [96]
SARS-CoV 3CLpro IC_{50} = 13.9 uM



115 [109]
SARS-CoV ATPase IC_{50} = 8.66 uM
helicase IC_{50} = 41.6 uM

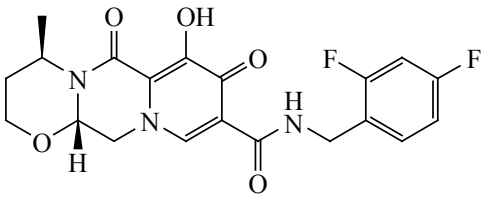


116 Presatovir [96]
SARS-CoV-2-Nluc repl. IC_{50} = 2.53 uM

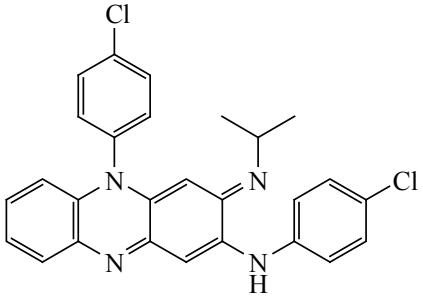


117 Hexamethyleneamiloride [110]
HCoV-229E repl. EC_{50} = 1.34 uM

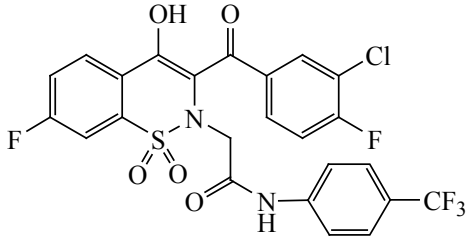
Fig. 11. Structures of six-membered heterocycles **105–120**.



118 Dolutegravir [90]
SARS-CoV-2 repl. EC_{50} = 22.04 uM

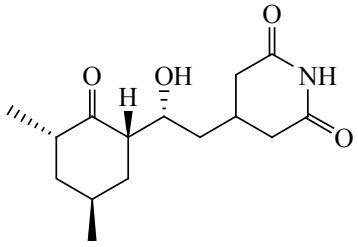


119 Clofazimine [85]
SARS-CoV-2 repl. IC_{50} = 0.01 uM

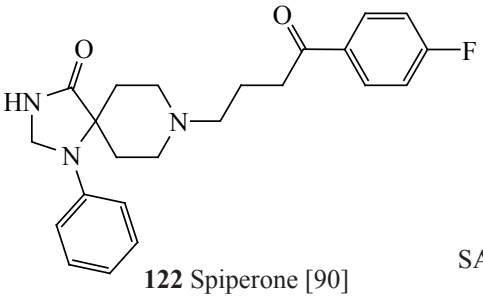


120 [111]
SARS-CoV-2 repl. IC_{50} = 0.88 uM

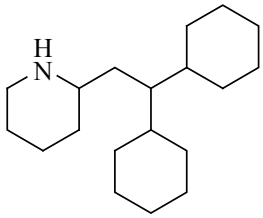
Fig 11. (Contd.)



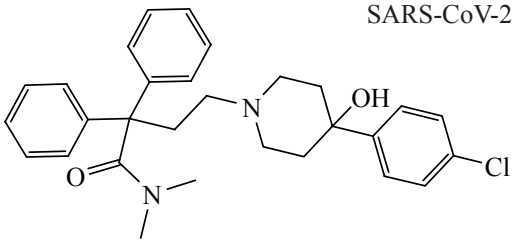
121 Cycloheximide [99]
SARS-CoV-2 repl. IC_{50} = 0.58 uM



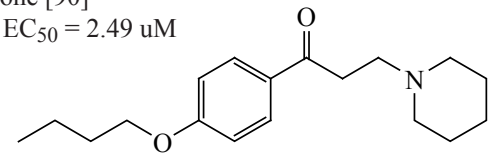
122 Spiperone [90]
SARS-CoV-2 repl. EC_{50} = 2.49 uM



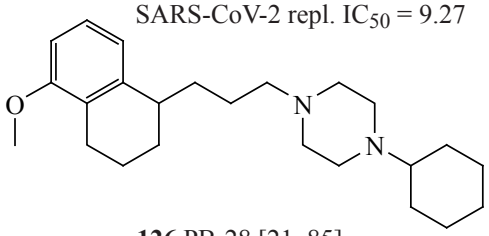
123 Perhexiline [57]
SARS-CoV-2 repl. IC_{50} = 6.38 uM



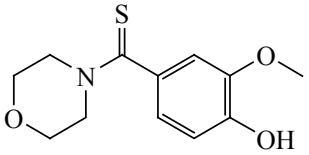
124 Loperamide [57]
SARS-CoV-2 repl. IC_{50} = 9.27



125 Dyclonine [90]
SARS-CoV-2 repl. EC_{50} = 10.00 uM

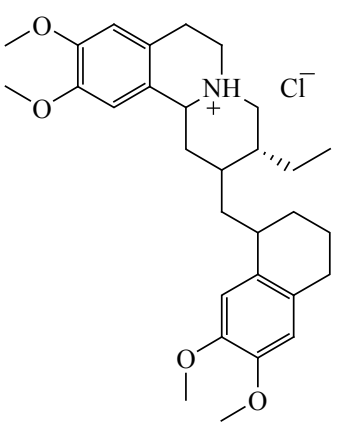


126 PB-28 [21, 85]
SARS-CoV-2 repl. IC_{90} = 0.278 uM

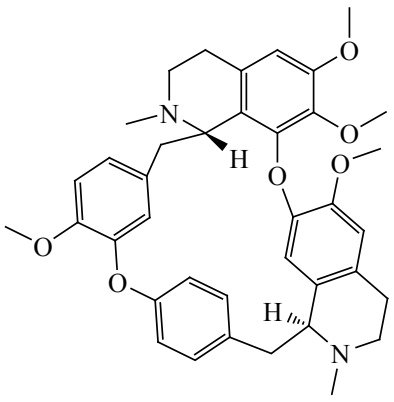


127 Vanitiolide [61]
SARS-CoV-2 Mpro IC_{50} = 4.6 uM

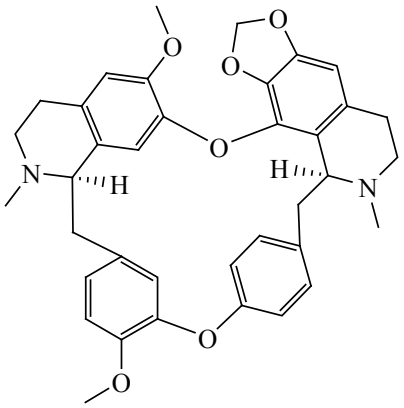
Fig. 12. Structures of six-membered heterocycles **121–127**.



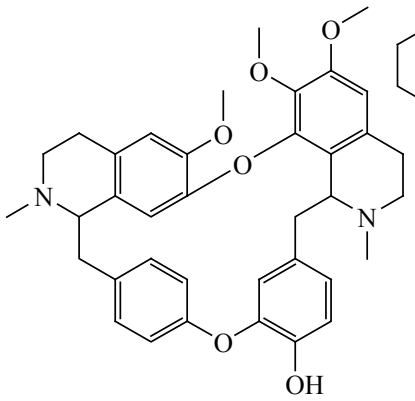
128 Emetine [48, 99]
SARS-CoV-2 repl. EC_{50} = 0.46 uM



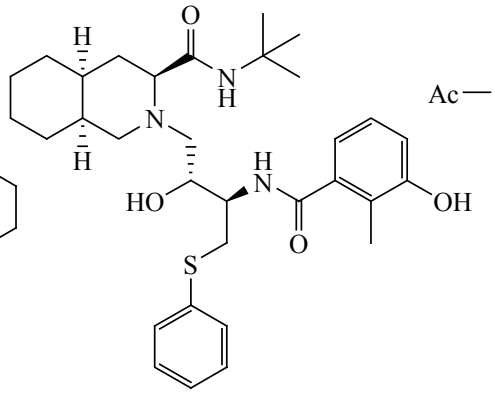
129 Tetrandrine [57]
SARS-CoV-2 repl. IC_{50} = 3.00 uM



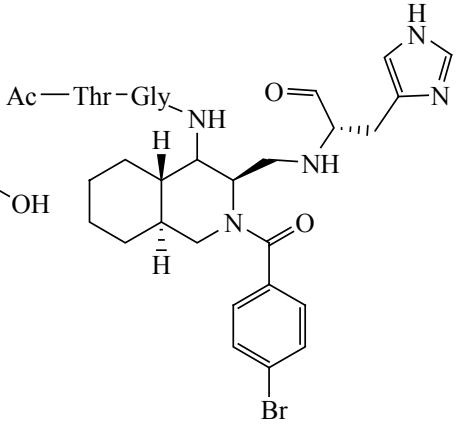
130 Cefaransine [57]
SARS-CoV-2 repl. IC_{50} = 4.47 uM



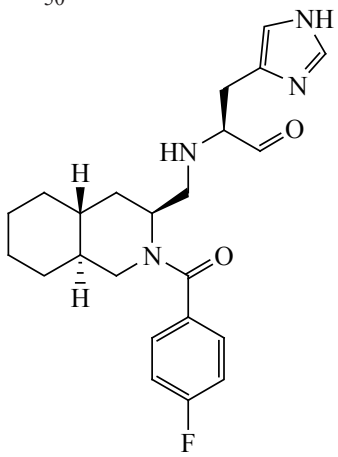
131 Berbamine [57]
SARS-CoV-2 repl. IC_{50} = 7.87 uM



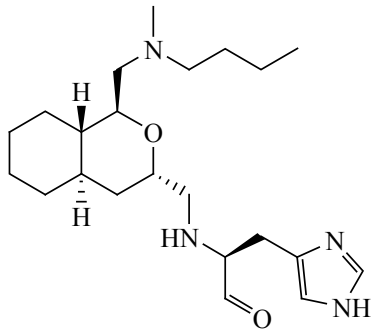
132 Nelfinavir [112]
SARS-CoV-2 repl. EC_{50} = 1.3 uM



133 [113, 114]
SARS-CoV 3CLpro IC_{50} = 20.0 uM

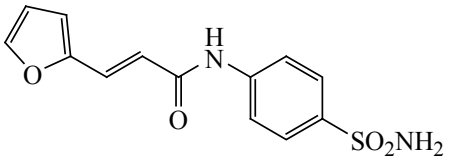


134 [115]
SARS-CoV-2 3CLpro IC_{50} = 57 uM

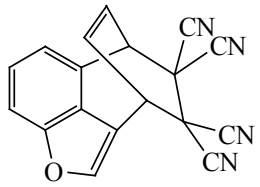


135 [113, 114]
SARS-CoV 3CLpro IC_{50} = 95 uM

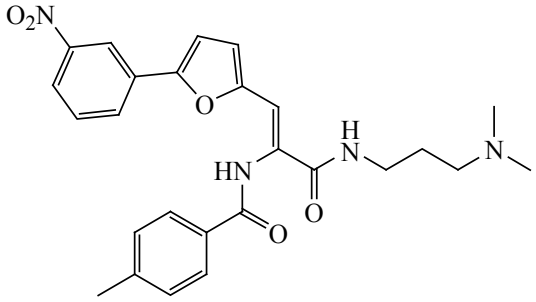
Fig. 13. Structures of hydrogenated isoquinolines **128–135**.



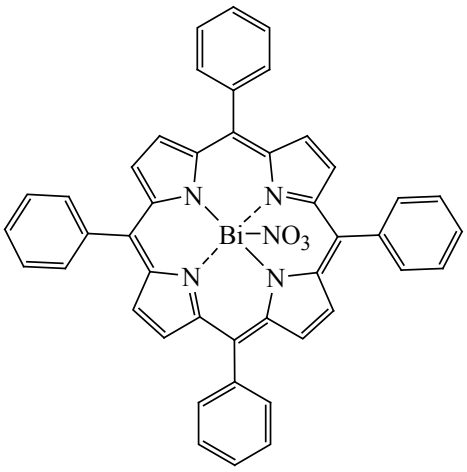
136 [117]
SARS-CoV ATPase IC_{50} = 2.09 uM
helicase IC_{50} = 13.2 uM



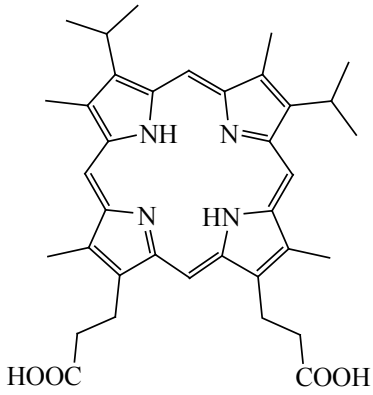
137 [91]
SARS-CoV-2 3CLpro IC_{50} = 16.14 uM



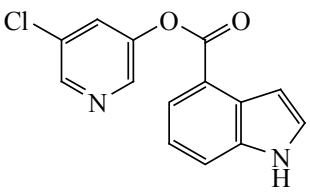
138 [118]
SARS-CoV 3CLpro IC_{50} = 38.6 uM



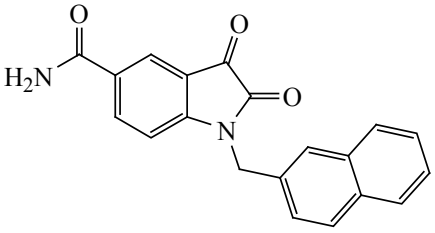
139 [119]
SARS-CoV helicase EC_{50} = 3 uM



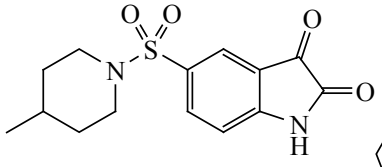
140 Hematoporphyrin [61]
SARS-CoV-2 Mpro IC_{50} = 3.9 uM



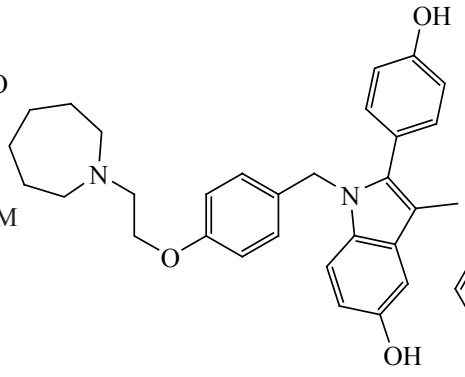
141 [120]
SARS-CoV 3CLpro IC_{50} = 0.03 uM
EC_{50} = 6.9 uM



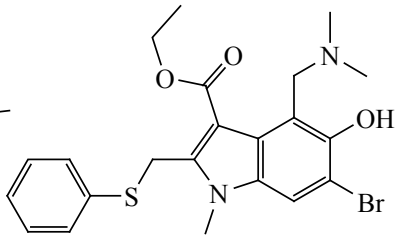
142 [121]
SARS-CoV 3CLpro IC_{50} = 0.37 uM



143 [122]
SARS-CoV 3CLpro IC_{50} = 1.18 uM

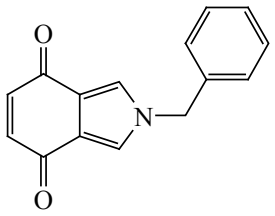


144 Bazedoxifene [57]
SARS-CoV-2 repl. IC_{50} = 3.44 uM

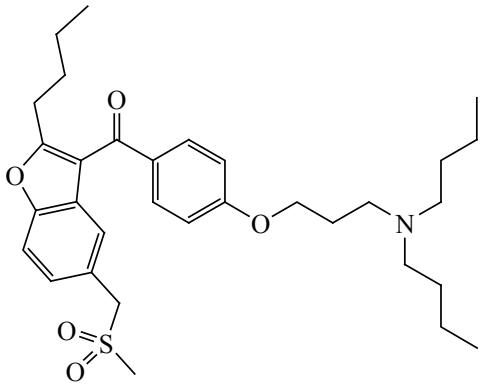


145 Umifenovir [90, 123, 124]
SARS-CoV-2 repl. EC_{50} = 10.7 uM

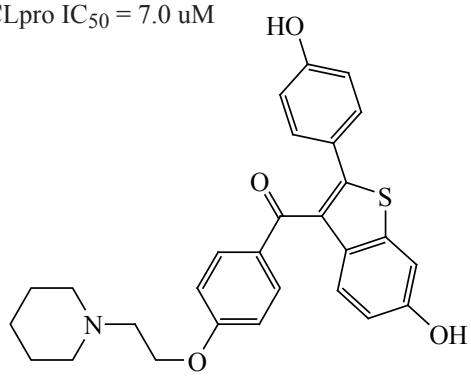
Fig. 14. Structures of five-membered heterocycles **136–148**.



146 [100]
SARS-CoV 3CLpro IC_{50} = 7.0 uM

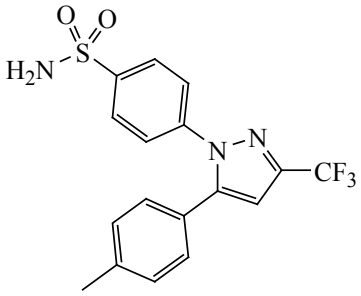


147 Dronedarone [57, 85]
SARS-CoV-2 repl. IC_{50} = 3.92 uM

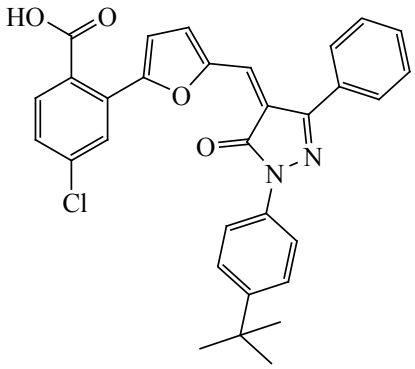


148 Raloxifene [85]
SARS-CoV-2 repl. IC_{50} = 0.02 uM

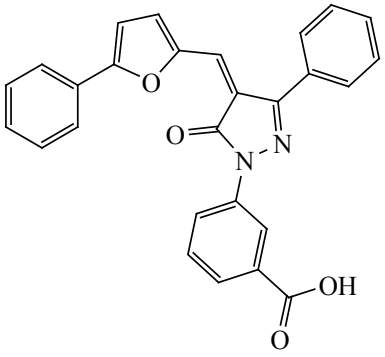
Fig 14. (Contd.)



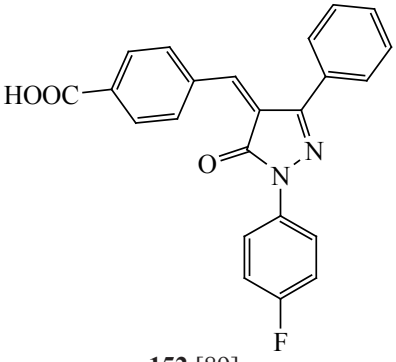
149 Celecoxib [85]
SARS-CoV-2 repl. IC_{50} = 0.04 uM



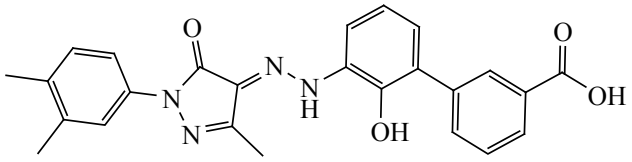
150 [125]
SARS-CoV 3CLpro IC_{50} = 5.8 uM



151 [125]
MERS-CoV 3CLpro IC_{50} = 5.8 uM



152 [89]
SARS-CoV 3CLpro IC_{50} = 6.8 uM



153 Eltrombopag [86, 127]
SARS-CoV-2 repl. IC_{50} = 8.27 uM
S-ACE2 complex

Fig. 15. Structures of five-membered heterocycles **149–157**.

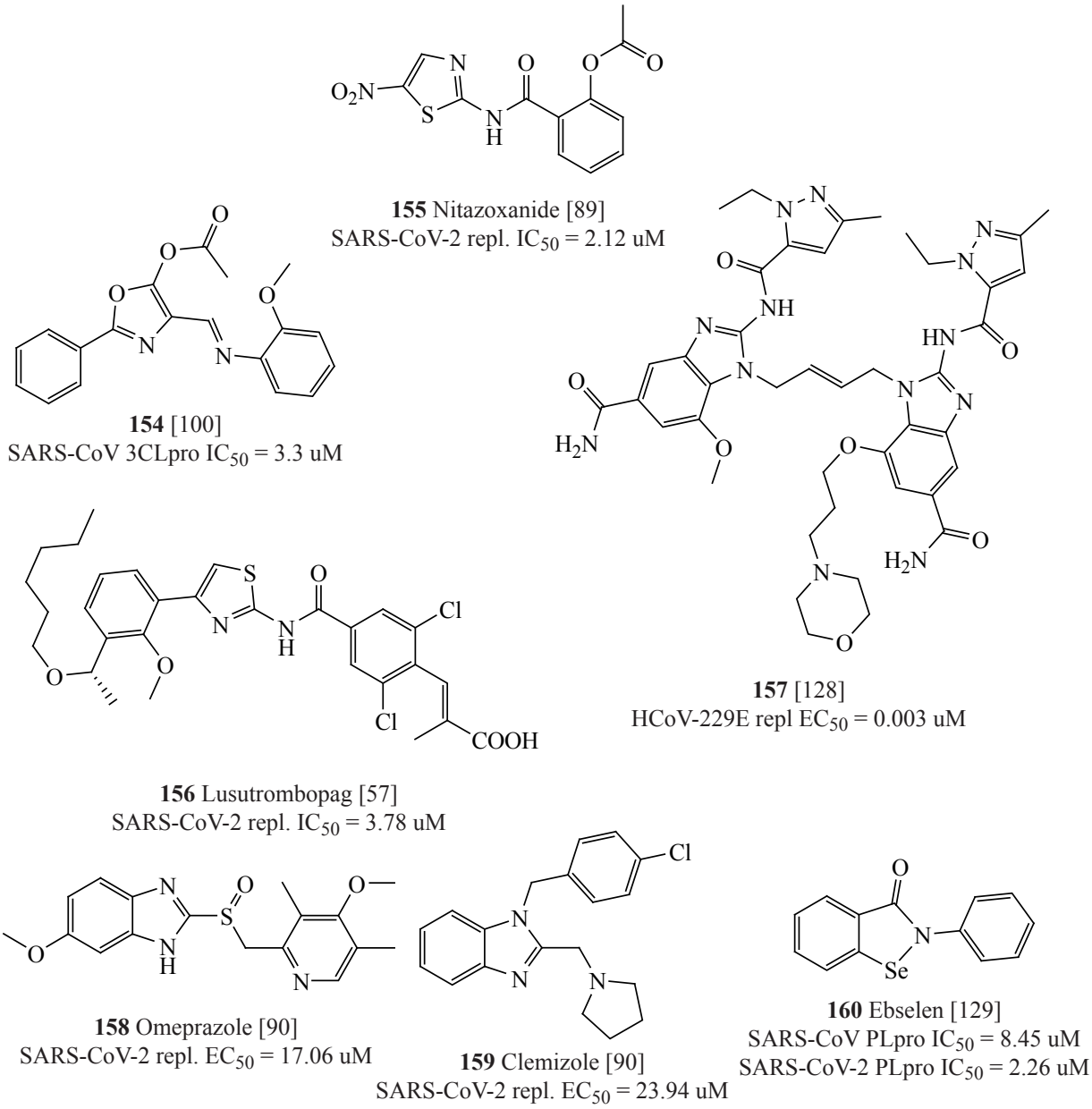
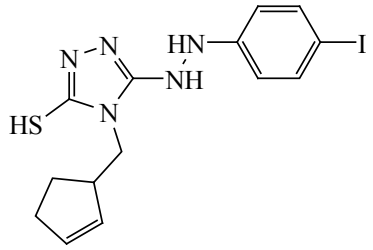


Fig 15. (Contd.)

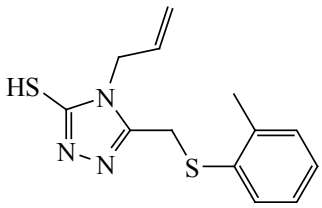
A great number of aromatic compounds **197–216** [57, 61, 85, 86, 90, 99, 143–147], including some estrogen antagonists **197–201** [57, 86], in particular tamoxifen **200** [86], as well as anthelmintic drugs **202–204** [57–85], are capable of inhibiting the reproduction of SARS-CoV-2 in vitro (Fig. 22). Compounds such as nafamostat **206** [99, 144], Evans blue **207** [61], camostat **208** [99], and hexachlorophene **209** [57] exhibit high activity in the submicromolar range (Fig. 23).

Organomercury compounds **217** [61, 148] and **218** [61], organic sulfides and zinc complexes **219–222** [148], bismuth complex **223** [149, 150], as well as bronopol **224** [148] effectively inhibit the SARS-CoV and SARS-CoV-2chymotrypsin-like protease 3CLpro/Mpro (Fig. 24).

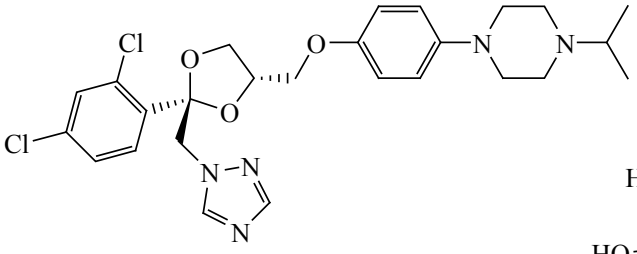
Natural and semisynthetic tetra- and pentacyclic triterpenoids (compounds **225–234** [57, 90, 151–155]) were found capable of inhibiting SARS-CoV-2 replication (Fig. 25). The members of the Research Institute of Influenza under the Ministry of Health of the Russian Federation and the Ufa Research Center of the Russian Academy of Sciences evaluated the



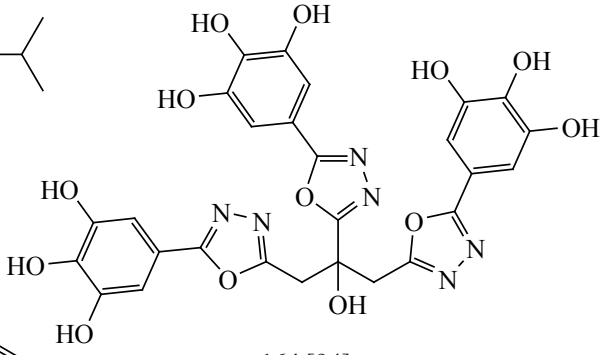
161 [130]
MERS-CoV ATPase IC_{50} = 0.47 uM
helicase IC_{50} = 2.5 uM



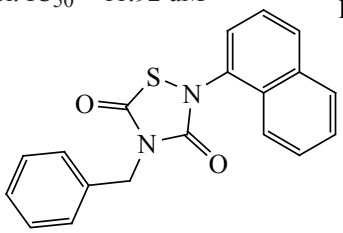
162 [131]
SARS-CoV helicase IC_{50} = 5.6 uM



163 Terconazole [86]
SARS-CoV-2 repl. IC_{50} = 11.92 uM

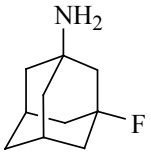


164 [94]
SARS-CoV-2 repl. EC_{50} = 0.31 uM

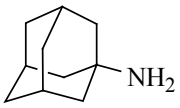


165 Tideglusib [60]
SARS-CoV-2 Mpro IC_{50} = 2.1 uM

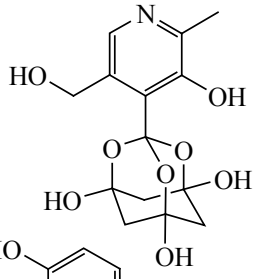
Fig. 16. Structures of five-membered heterocycles **161–165**.



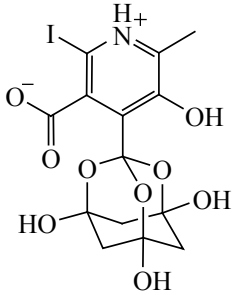
166 [134]
SARS-CoV-2 E



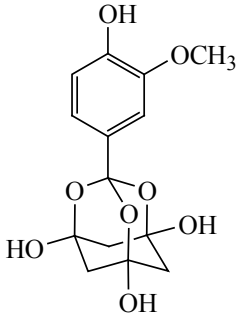
167 [62]
SARS-CoV-2 E inh. 77% inh. at 10 mmol
Orf10 65% inh. at 10 mmol



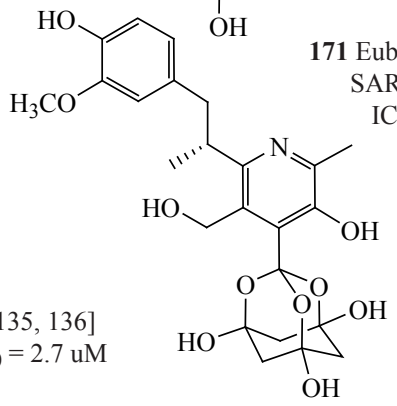
168 Bananin [135, 136]
SARS-CoV nsp13
IC_{50} = 3.0 uM



169 Iodobananin [135, 136]
SARS-CoV nsp13 IC_{50} = 7.0 uM

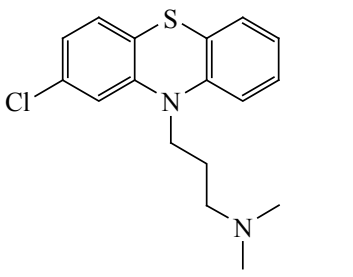


170 Vanillinbananin [135, 136]
SARS-CoV nsp13 IC_{50} = 2.7 uM

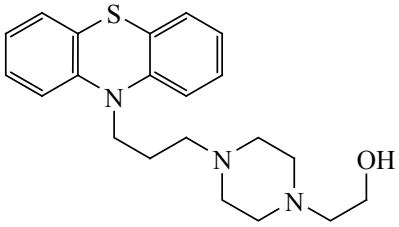


171 Eubananin [135, 136]
SARS-CoV nsp13
IC_{50} = 5.4 uM

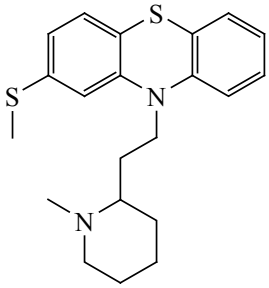
Fig. 17. Structures of cage compounds **166–171**.



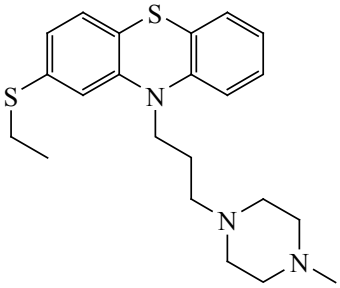
172 Chlorpromazine [86]
SARS-CoV-2 repl. IC_{50} = 3.14 uM



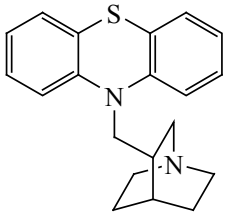
173 Fluphenazine [86]
SARS-CoV-2 repl. IC_{50} = 6.36 uM



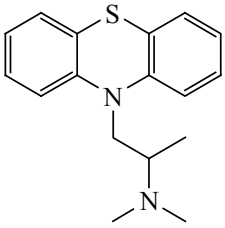
174 Thioridazine [57]
SARS-CoV-2 repl. IC_{50} = 6.69 uM



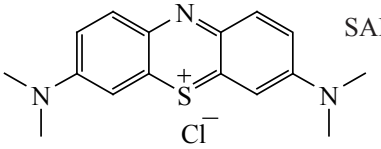
175 Thiethylperazine [86]
SARS-CoV-2 repl. IC_{50} = 7.09 uM



176 Mehitazin [57]
SARS-CoV-2 repl. IC_{50} = 7.28 uM

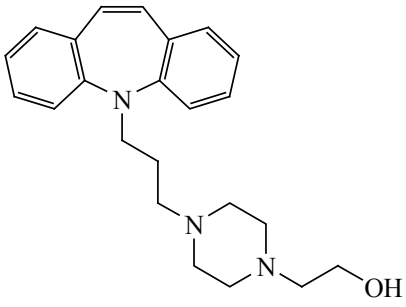


177 Promethazine [86]
SARS-CoV-2 repl. IC_{50} = 9.21 uM

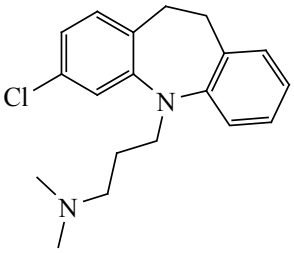


178 Methylene blue [137]
SARS-CoV-2 repl. IC_{50} = 0.22 uM

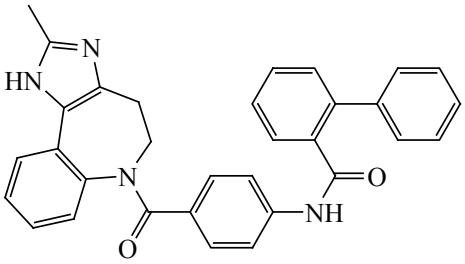
Fig. 18. Structures of phenothiazine antipsychotics **172–177** and methylene blue **178**.



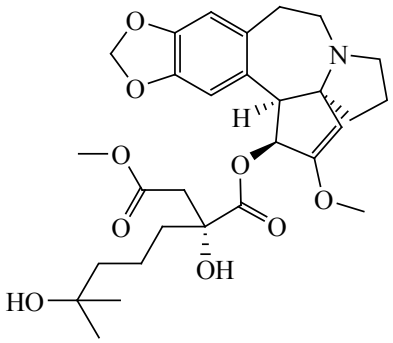
179 Opipramol [90]
SARS-CoV-2 repl. EC_{50} = 5.05 uM



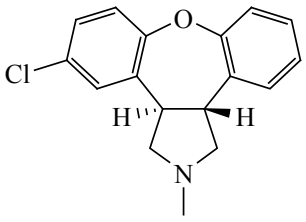
180 Clomipramine [86]
SARS-CoV-2 repl. IC_{50} = 5.63 uM



181 Conivaptan [85]
SARS-CoV-2 repl. IC_{50} = 10.34

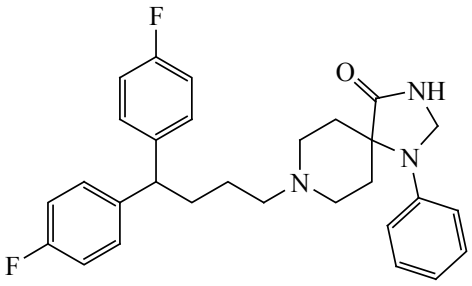


182 Omacetaxine
(homoharringtonine) [48]
SARS-CoV-2 repl.
EC_{50} = 2.55 uM

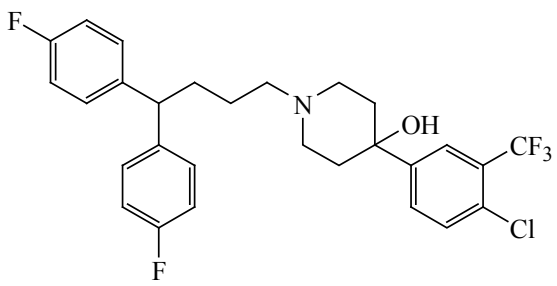


183 Asenapine [82]
SARS-CoV-2 repl. IC_{50} = 16.70 uM

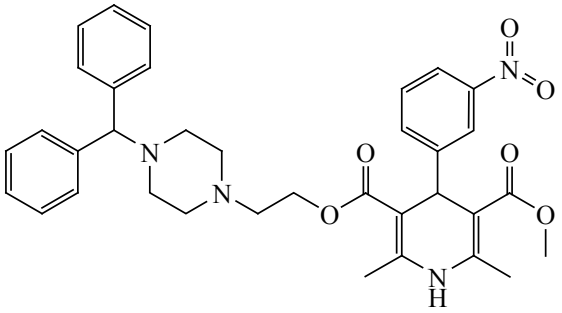
Fig. 19. Structures of di- and triannulated seven-membered heterocycles **179–183**.



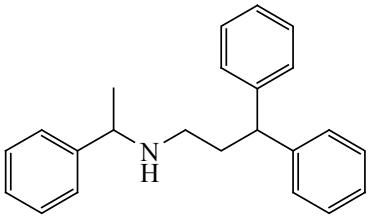
184 Fluspirilene [86]
SARS-CoV-2 repl. IC_{50} = 3.16 uM



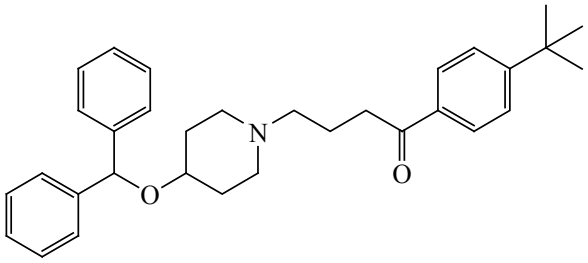
185 Penfluridol [57]
SARS-CoV-2 repl. IC_{50} = 5.01 uM



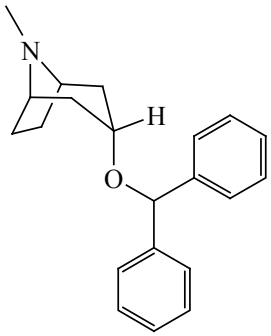
186 Manidipine [46]
SARS-CoV-2 Mpro IC_{50} = 4.81 uM



187 Fendiline [85]
SARS-CoV-2 repl. IC_{50} = 10.23 uM

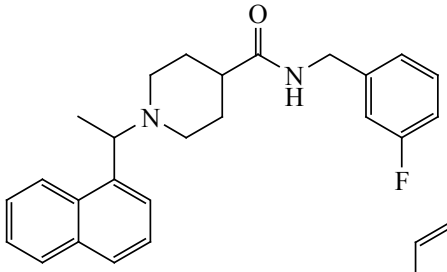


188 Ebastin [57]
SARS-CoV-2 repl. IC_{50} = 6.92 uM

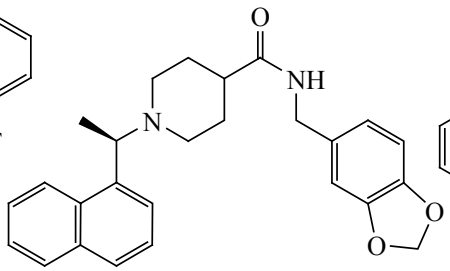


189 Benztropine [86]
SARS-CoV-2 repl. IC_{50} = 13.8 uM

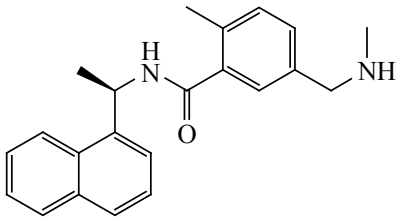
Fig. 20. Structures of diphenylmethyl derivatives **184–189**.



190 [138]
SARS-CoV PLpro IC_{50} = 0.15 uM

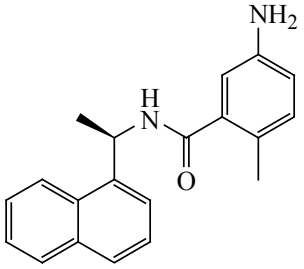


191 [139]
SARS-CoV PLpro IC_{50} = 0.32 uM
repl. EC_{50} = 9.1 uM

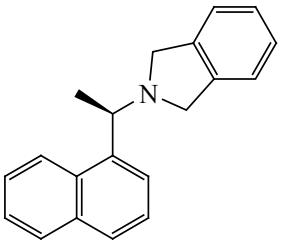


192 [140]
SARS-CoV PLpro IC_{50} = 1.3 uM
repl. EC_{50} = 2.5 uM

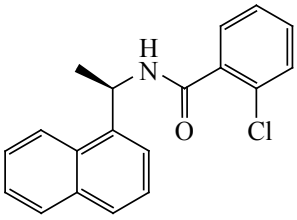
Fig. 21. Structures of 1-(naphthalen-1-yl)ethyl derivatives **190–196**.



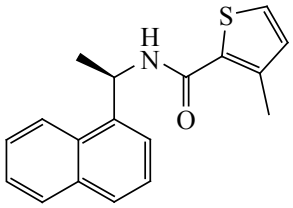
193 [141]
SARS-CoV-2 PLpro IC_{50} = 2.2 uM



194 [142]
SARS-CoV PLpro IC_{50} = 2.9 uM
SARS-CoV-2 PLpro IC_{50} = 7.6 uM
SARS-CoV-2 repl. EC_{50} = 7.85 uM

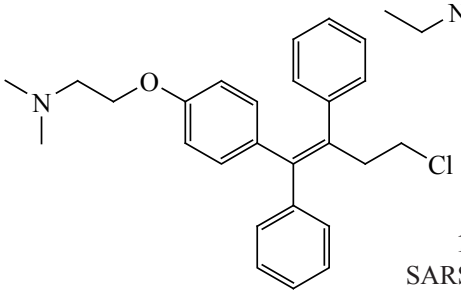


195 [142]
SARS-CoV PLpro IC_{50} = 6.5 uM
SARS-CoV-2 PLpro IC_{50} = 15 uM
SARS-CoV-2 repl. EC_{50} = 1.77 uM

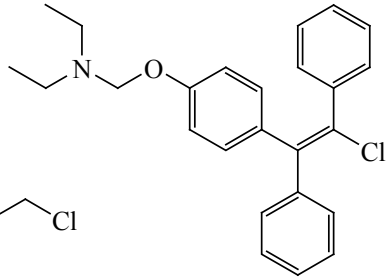


196 [142]
SARS-CoV PLpro IC_{50} = 14 uM
SARS-CoV-2 PLpro IC_{50} = 42 uM
SARS-CoV-2 repl. EC_{50} = 4.74 uM

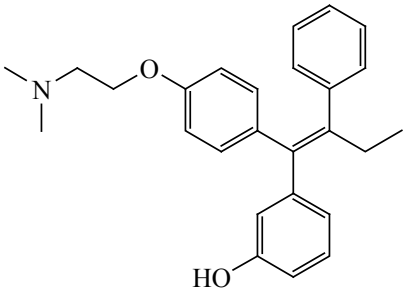
Fig 21. (Contd.)



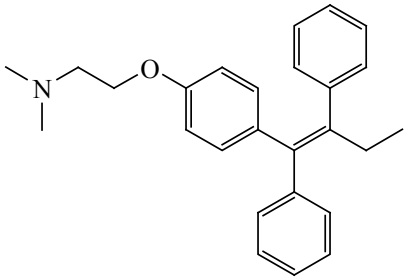
197 Toremifene [86]
SARS-CoV-2 repl. IC_{50} = 4.77 uM



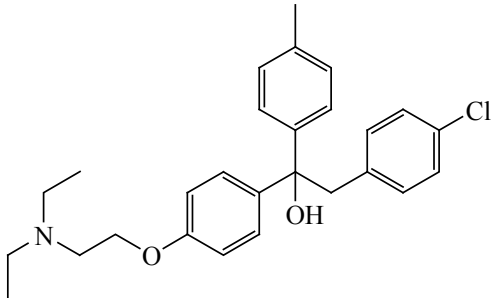
198 Clomiphene [57]
SARS-CoV-2 repl. IC_{50} = 5.36



199 Droloxifene [57]
SARS-CoV-2 repl. IC_{50} = 6.60 uM

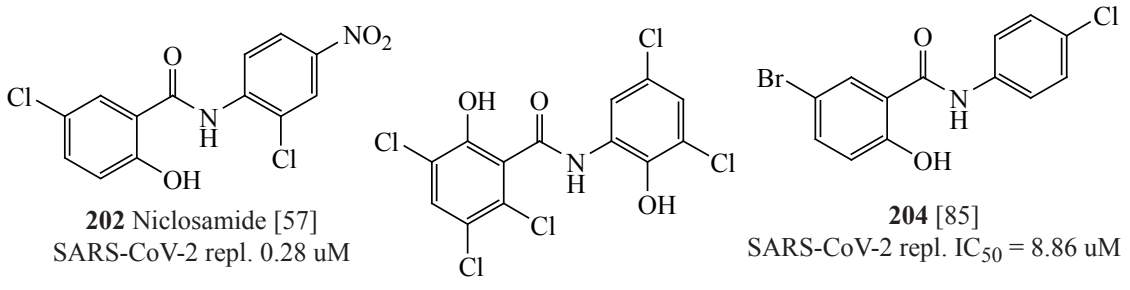


200 Tamoxifen [86]
SARS-CoV-2 repl. IC_{50} = 34.12 uM



201 Triparanol [86]
SARS-CoV-2 repl. IC_{50} = 4.68 uM

Fig. 22. Structures of aromatic compounds **197–204**.

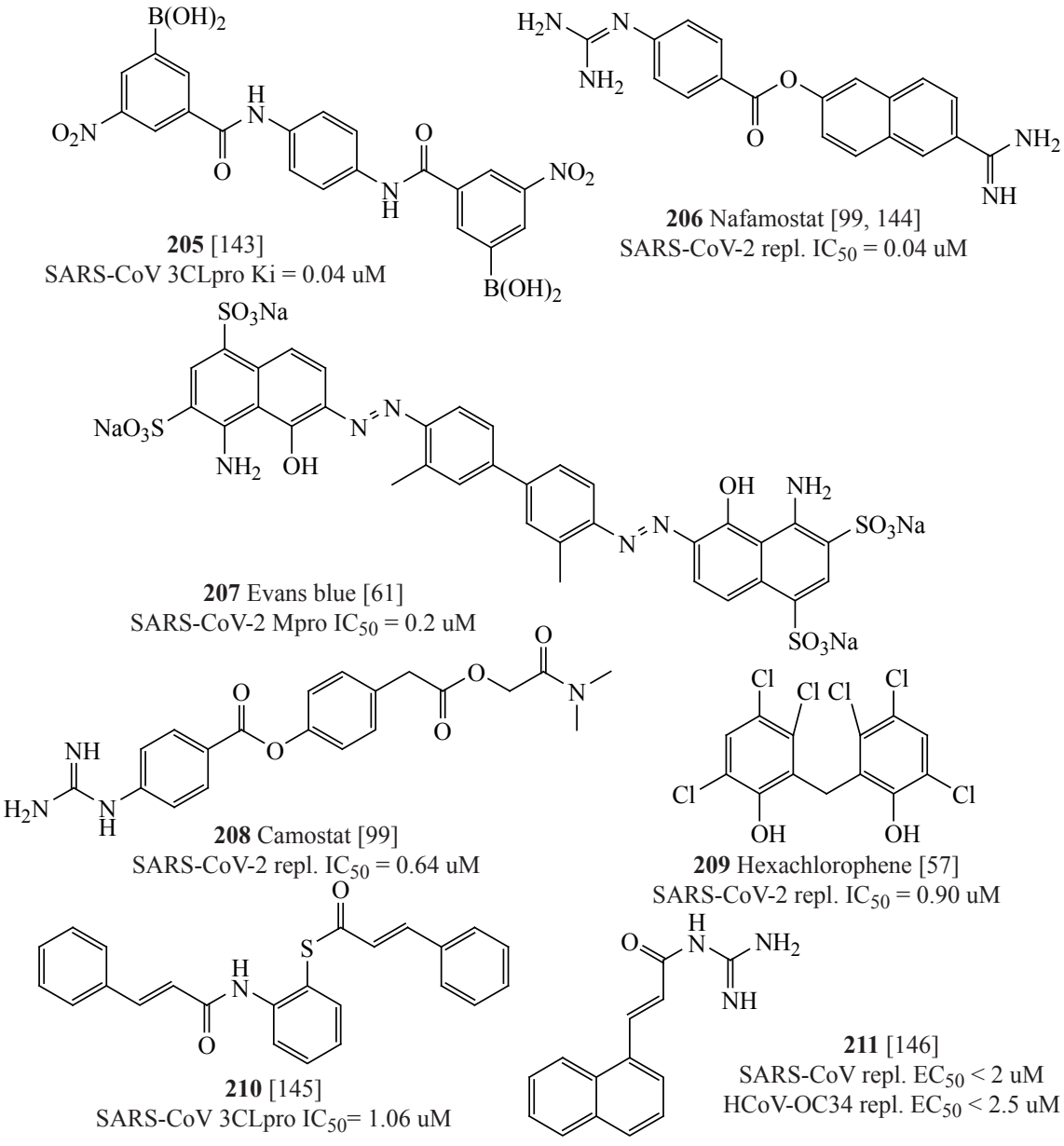


202 Niclosamide [57]
SARS-CoV-2 repl. 0.28 uM

203 Oxyclozanide [57]
SARS-CoV-2 repl. IC_{50} = 3.71 uM

204 [85]
SARS-CoV-2 repl. IC_{50} = 8.86 uM

Fig 22. (Contd.)



205 [143]
SARS-CoV 3CLpro Ki = 0.04 uM

206 Nafamostat [99, 144]
SARS-CoV-2 repl. IC_{50} = 0.04 uM

207 Evans blue [61]
SARS-CoV-2 Mpro IC_{50} = 0.2 uM

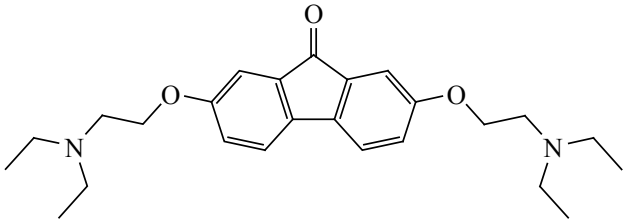
208 Camostat [99]
SARS-CoV-2 repl. IC_{50} = 0.64 uM

209 Hexachlorophene [57]
SARS-CoV-2 repl. IC_{50} = 0.90 uM

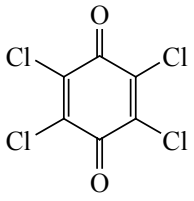
210 [145]
SARS-CoV 3CLpro IC_{50}= 1.06 uM

211 [146]
SARS-CoV repl. EC_{50} < 2 uM
HCoV-OC34 repl. EC_{50} < 2.5 uM

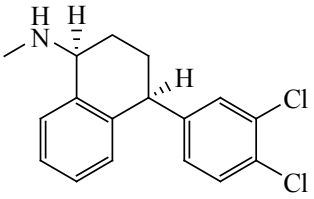
Fig. 23. Structures of aromatic compounds **204–215**.



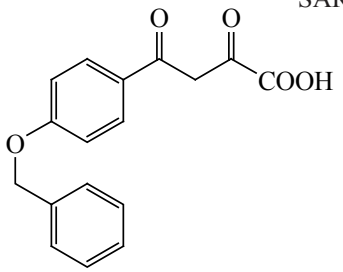
212 Tiloron [57]
SARS-CoV-2 repl. IC_{50} = 4.09 uM



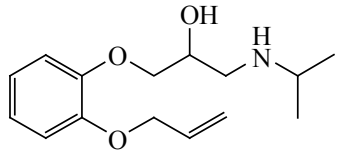
213 [61]
SARS-CoV-2 Mpro IC_{50} = 4.1 uM



214 Sertraline [85]
SARS-CoV-2 repl. IC_{50} = 9.34 uM

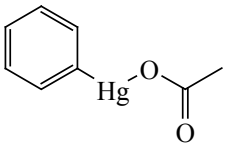


215 [147]
SARS-CoV helicase EC_{50} = 13.6 uM

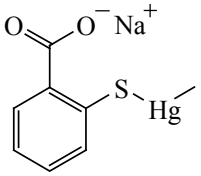


216 Oxprenolol [90]
SARS-CoV-2 repl. EC_{50} = 20.22 uM

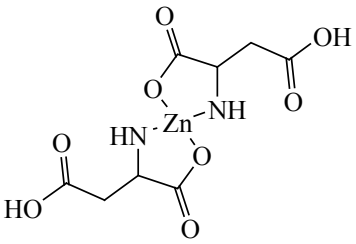
Fig 23. (Contd.)



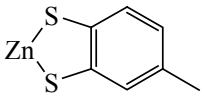
217 [61, 148]
SARS-CoV 3CLpro K_i = 0.7 uM
SARS-CoV-2 Mpro IC_{50} = 0.4 uM



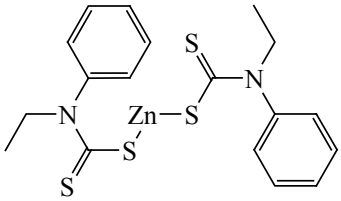
218 Thiomersal [61]
SARS-CoV-2 Mpro IC_{50} = 0.6 uM



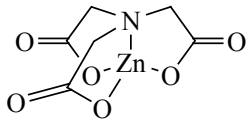
219 [148]
SARS-3CLpro K_i = 0.05 uM



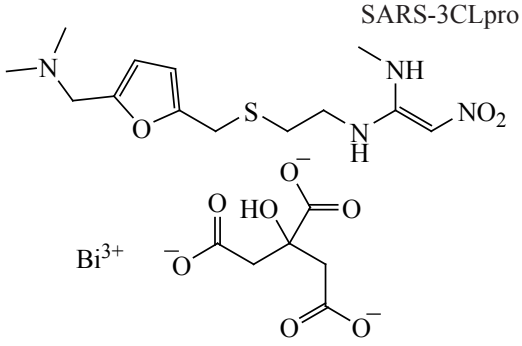
220 [148]
SARS-3CLpro K_i = 1.4 uM



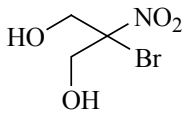
221 [148]
SARS-3CLpro K_i = 1 uM



222 [148]
SARS-3CLpro K_i = 0.32 uM

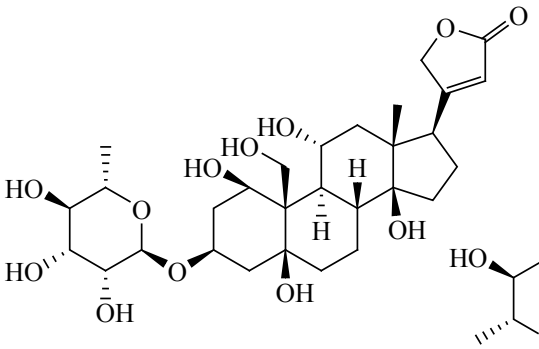


223 Ranitidine bismuth citrate [149, 150]
SARS-CoV helicase IC_{50} = 0.3 uM
EC_{50} = 5.9 uM

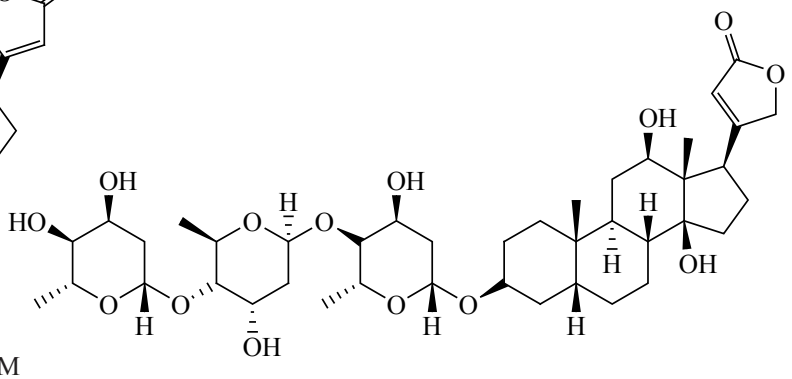


224 Bronopol [148]
SARS-CoV-2 Mpro IC_{50} = 4.4 uM

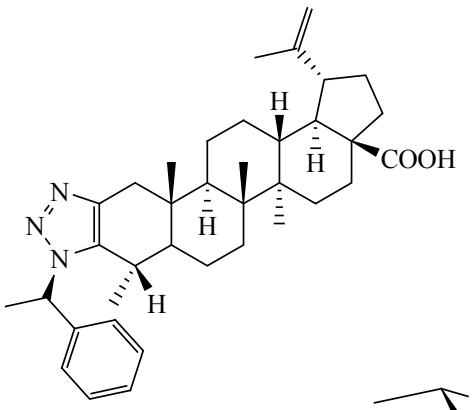
Fig. 24. Structures of salts and metal complexes **217–223** and bronopol **224**.



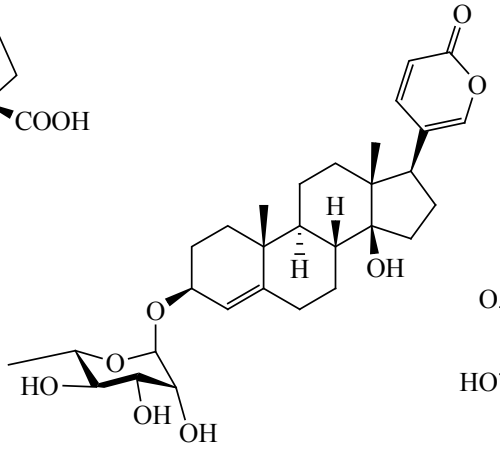
225 Ouabain [57]
SARS-CoV-2 repl. IC_{50} < 0.097 uM



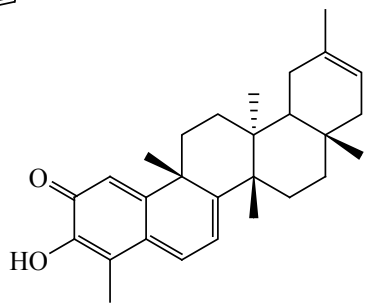
226 Digitoxin [57]
SARS-CoV-2 repl. IC_{50} = 0.23



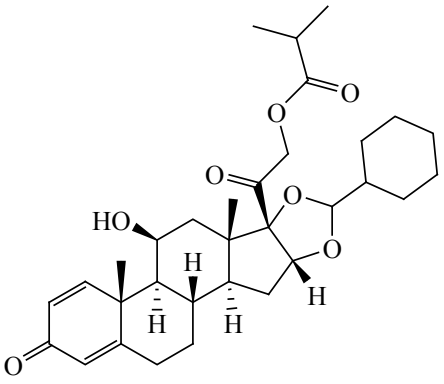
227 [151]
HCoV-229E nsp15 EC_{50} = 0.6 uM



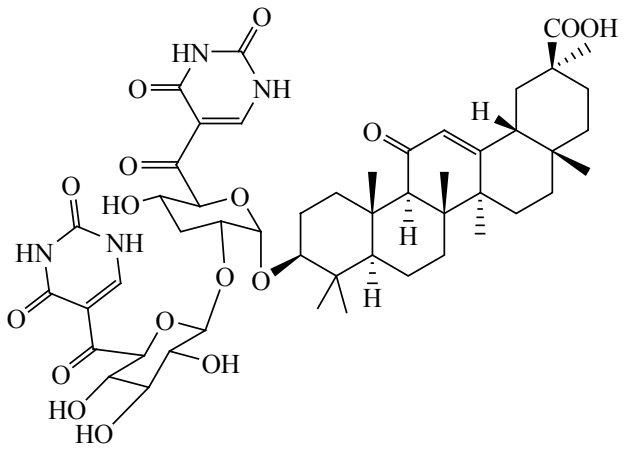
228 Proscilaridin [57]
SARS-CoV-2 repl. IC_{50} = 2.04 uM



229 [152]
SARS-CoV 3CLpro IC_{50} = 2.6 uM

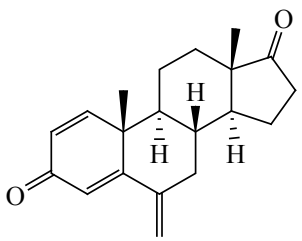


230 Ciclesonide [57]
SARS-CoV-2 repl. IC_{50} = 4.33 uM

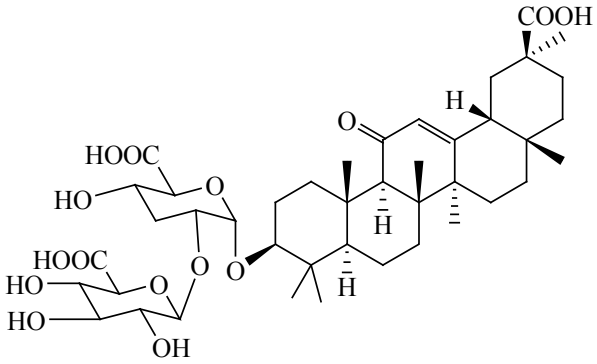


231 [153]
SARS-CoV repl. IC_{50} = 5 uM

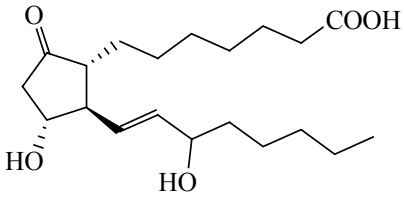
Fig. 25. Structures of triterpenoids **225–234**.



232 Exemestane [90]
SARS-CoV-2 repl. EC_{50} = 7.51 uM

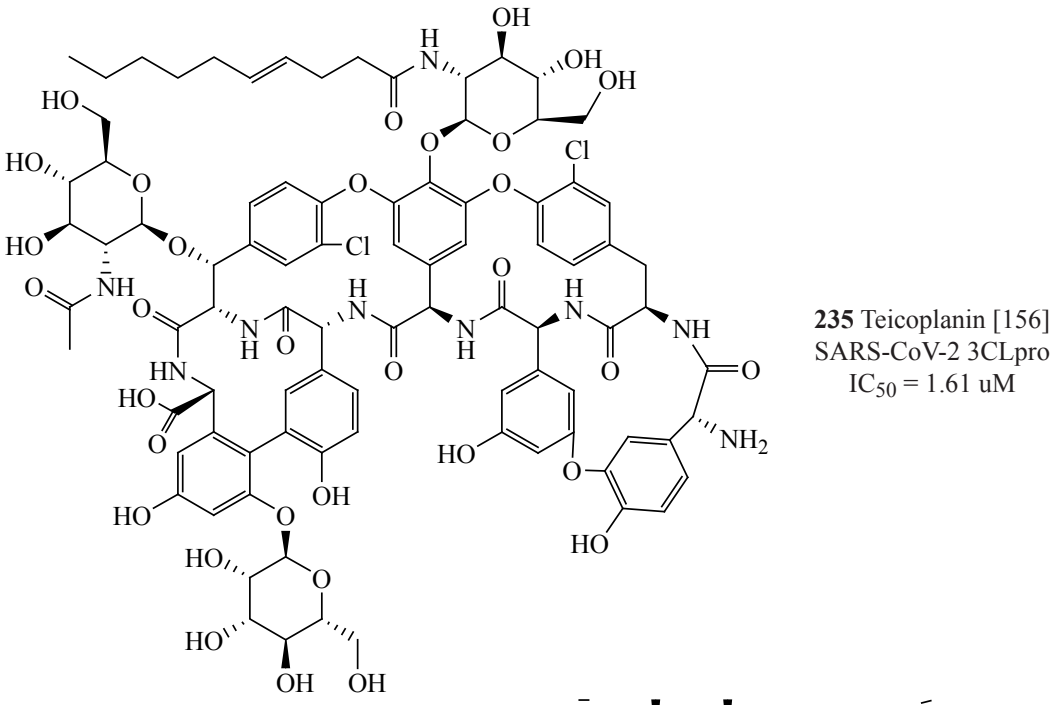


233 Glycyrrhizic acid [153, 154, 155]
SARS-CoV-2 S/ACE IC_{50} = 22 uM

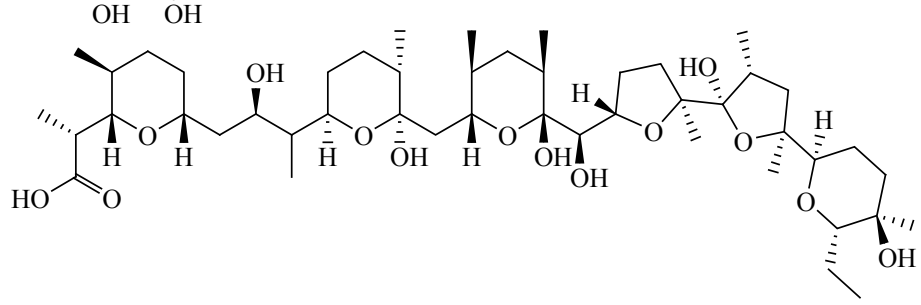


234 Alprostadil [90]
SARS-CoV-2 repl. EC_{50} = 5.39 uM

Fig 25. (Contd.)

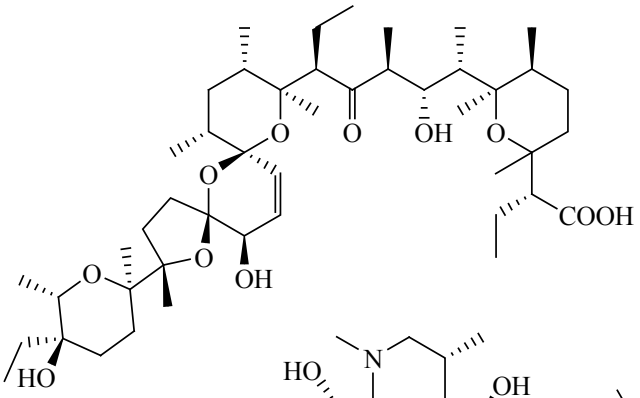


235 Teicoplanin [156]
SARS-CoV-2 3CLpro
IC_{50} = 1.61 uM

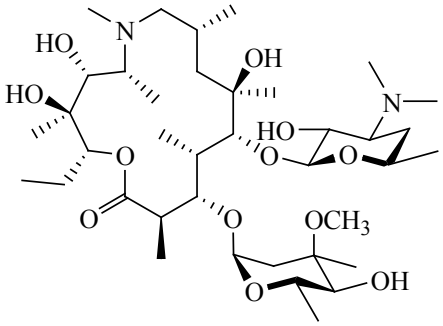


236 X-206 [157]
SARS-CoV-2 repl.
IC_{50} = 8.2 uM

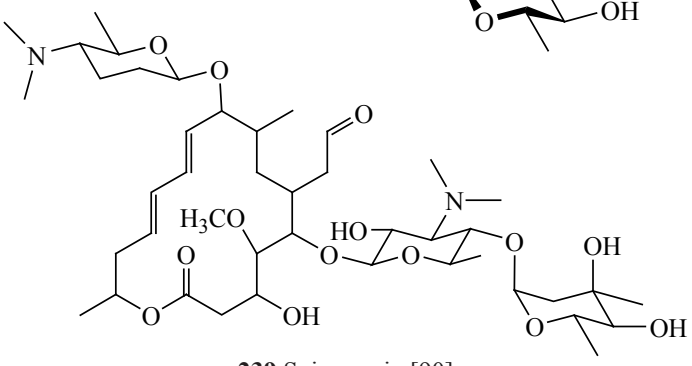
Fig. 26. Structures of antibiotics **235–240**, anidulafungin **241**, cyclosporine **242**, and ivermectin B_{1a} **243**.



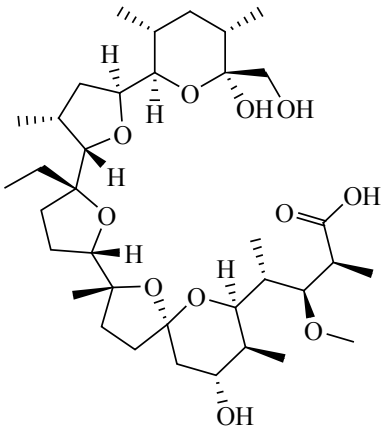
237 Salinomycin [57]
SARS-CoV-2 repl. IC_{50} = 0.24 uM



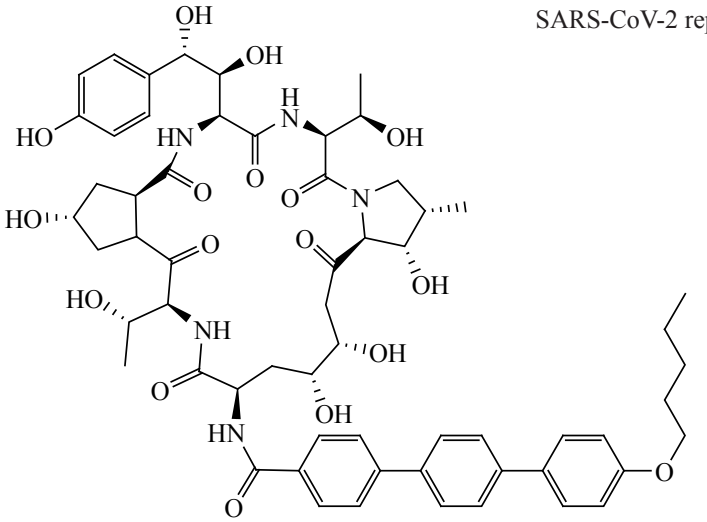
238 Azithromycin [90]
SARS-CoV-2 repl. EC_{50} = 2.12 uM



239 Spiramycin [90]
SARS-CoV-2 repl. EC_{50} = 7.95 uM

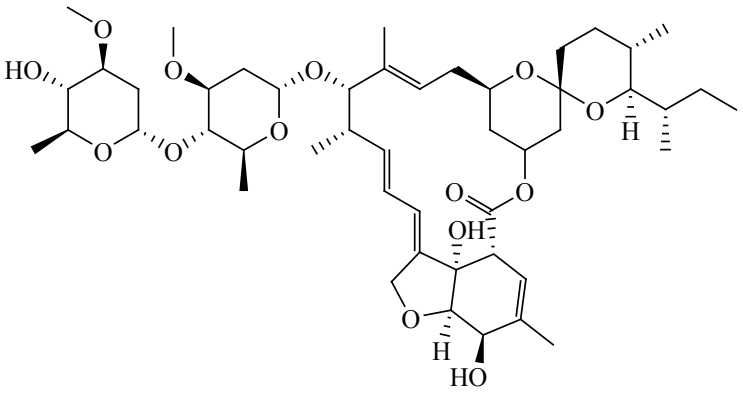


240 Monensin [85]
SARS-CoV-2 repl. IC_{50} = 0.60 uM

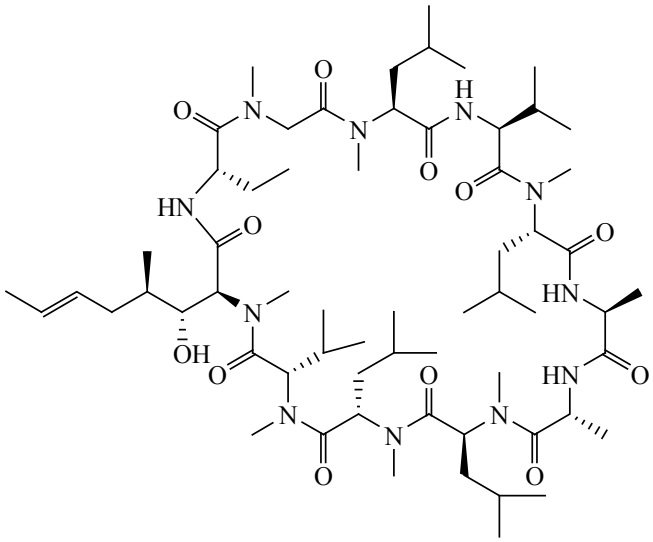


241 Anidulafungin [57]
SARS-CoV-2 repl. IC_{50} = 4.64 uM

Fig 26. (Contd.)



243 Ivermectin B_{1a} [158]
SARS-CoV-2 repl.
IC_{50} = 2 uM



242 Cyclosporine [57]
SARS-CoV-2 repl.
IC_{50} = 5.82 uM

Fig 26. (Contd.)

activity of glycyrrhetic and glycyrrhizic acid derivatives against SARS-CoV. The highest activity was found in compound **231** (IC_{50} 5 μM). The viral targets of this class of compounds were identified only for betulonic acid derivative **227** (endoribonuclease nsp15) and glycyrrhizic acid **233** (spike protein).

Natural and semisynthetic antibiotics **235–240** [57, 85, 90, 156, 157] showed quite a high in vitro activity aganst coronaviruses. The fungicide anidulafungin **241** [57], immunosuppressant cyclosporine **242** [158], and a series of antiparasitic ivermectins, the most active of which is ivermectin B_{1a} **243** [158] (IC_{50} 2 μM), in vitro (Fig. 26).

CONCLUSIONS

The great body of accumulated evidence on the anticoronaviral activity of low-molecular-weight compounds is described primarily in terms of their targets (mainly 3CLpro/Mpro and PLpro proteases). This approach is undoubtedly very convenient, especially considering the recently reported experimental 3D structures of target proteins of coronaviruses and their complexes with ligands [38, 69, 134, 141, 159, 160, 161], which facilitates computer simulation of interactions of virtual structures with targets.

However, in this case, the synthetic chemist often falls into the "trap" of the target protein and focuses on the search for compounds active against specific proteins, without considering the possibility of interfering with other stages of the reproductive cycle of the virus. In this case, activity is tested on models that provide information exclusively on direct ligand–target interaction, but are useless for assessing the effect of the test compound on the biochemical processes in the infected cell. On the contrary, knowledge of features of the chemical structure of active compounds provides a general direction for the search for new potential drug candidates, without regard to their "points of application".

The above analysis of the literature does not pretend to exhaustively cover all compounds tested for activity against SARS-CoV, MERS-CoV, or SARS-CoV-2 (about 2500) but provides sufficient insight into the chemotypes of the most active compounds known at the present time. Even though a fairly large number of types of active molecules have already been discovered, many leading molecules are still awaiting their discovery.

In the past, the community of organic chemists has generally been successful in combating human health threats posed by infectious diseases. The creation of sulfa drugs, semisynthetic and synthetic antibiotics, antimalarial and antituberculosis drugs, modified antiviral nucleosides, antiretroviral drugs, and viral protease inhibitors only partly reflects the contribution of organic synthetic chemists to solving critical problems of global health protection.

On this way, both the development of new synthetic methods (for example, the use of dicyclohexylcarbodiimide or protective groups [162]) and creation of models for coordinating the effort of basic scientists and specialists in the medical industry. The new challenges should lead to rethinking the relationship between synthetic chemists, medicinal chemists, biomedical researchers, and organic chemists working in the pharmaceutical industry.

The authors hope that combining genius of these people in the light of the unsolved problems will allow humanity to gain confidence in successfully overcoming the current crisis of global health service by creating in the near future a wide range of new effective drugs against coronavirus infections.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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