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 antiviral 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 threo-phenylalanine 17 [44]. Peptidomimetics have shown high potential against SARS-CoV-2, because the coronavirus 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 antiviral 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], flavonone 39 [58], flavan 40 [52], coumarin 41 [59], naphthoquinones shikonin 42 [60] and plumbagin 43 [61], and anthraquinone 44 [62]. Transflavanones 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-N7-methyltransferase nsp14. Carmofur 55 [60, 69] is the only to exhibit
Fig. 1. Structures of peptidomimetics 1–10.

1 [30] SARS-CoV 3CLpro IC$_{50}$ = 0.051 uM
2 [31] SARS-CoV-2 Mpro IC$_{50}$ = 0.31 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

SARS-CoV Mpro IC$_{50}$ = 0.27 uM
SARS-CoV-2 Mpro IC$_{50}$ = 0.31 uM
Fig. 2. Structures of peptidomimetics 11–23.
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.
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**Fig. 3.** Structures of polyphenols 24–37.

- **24** [49]
  - SARS-CoV NTPase/helicase EC$_{50}$ = 2.7 uM

- **26** [50]
  - SARS-CoV helicase IC$_{50}$ = 2.7 uM

- **28** [52]
  - SARS-CoV PLpro IC$_{50}$ = 3.7 uM

- **29** Scutellarein [51]
  - SARS-CoV nsp13 IC$_{50}$ = 2.71 uM

- **30** [54]
  - SARS-CoV 3CLpro IC$_{50}$ = 8.3 uM

- **31** Luteolin [54]
  - SARS-CoV 3CLpro IC$_{50}$ = 20.2 uM

SARS-CoV NTPase/helicase EC$_{50}$ = 2.7 uM
SARS-CoV NTPase IC$_{50}$ = 4 uM
helicase IC$_{50}$ = 11 uM
SARS-CoV nsp13 IC$_{50}$ = 2.71 uM
SARS-CoV nsp13 IC$_{50}$ = 0.86 uM
SARS-CoV 3CLpro IC$_{50}$ = 8.3 uM
SARS-CoV 3CLpro IC$_{50}$ = 20.2 uM
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] (IC₅₀<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 hydroxychloroquine 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],...
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.
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 132–131 [48, 57, 99] and HIV protease inhibitor nelfinavir 132 [112]. Basically, the activity of these compounds was assessed.
Fig. 6. Structures of nucleoside analogs 54–64.
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\textsubscript{50} 0.03 \textmu M), 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\textsubscript{50} 0.04 \textmu M) 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 \textmu M) and dimeric benzimidazole derivative 157 [128] (0.003 \textmu M!) (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
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\textsubscript{50} = 5.47 uM

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

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

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

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

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

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

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

89 [93]
SARS-CoV 3CLpro IC\textsubscript{50} = 17.2 uM

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

91 Montelukast [95]
MERS-CoV S IC\textsubscript{50} = 3 uM

Fig. 9. Structures of quinoline derivatives 81–91.
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**Fig. 10.** Structures of six-membered heterocycles 92–104.
Fig. 11. Structures of six-membered heterocycles 105–120.


**Fig. 11.** (Contd.)

**Fig. 12.** Structures of six-membered heterocycles 121–127.
Fig. 13. Structures of hydrogenated isoquinolines 128–135.
**MAIN CHEMOTYPES OF SARS-COV-2 REPRODUCTION INHIBITORS**

**Fig. 14.** Structures of five-membered heterocycles 136–148.
SARS-CoV 3CLpro IC\textsubscript{50} = 7.0 \textmu M

Dronedarone [57, 85]
SARS-CoV-2 repl. IC\textsubscript{50} = 3.92 \textmu M

Raloxifene [85]
SARS-CoV-2 repl. IC\textsubscript{50} = 0.02 \textmu M

Celecoxib [85]
SARS-CoV-2 repl. IC\textsubscript{50} = 0.04 \textmu M

SARS-CoV 3CLpro IC\textsubscript{50} = 5.8 \textmu M

MERS-CoV 3CLpro IC\textsubscript{50} = 5.8 \textmu M

Eltrombopag [86, 127]
SARS-CoV-2 repl. IC\textsubscript{50} = 8.27 \textmu M
S-ACE2 complex

Fig. 15. Structures of five-membered heterocycles 149–157.
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-2 chymotrypsin-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
MERS-CoV ATPase IC$_{50}$ = 0.47 uM
helicase IC$_{50}$ = 2.5 uM

Terconazole [86]
SARS-CoV-2 repl. IC$_{50}$ = 11.92 uM

Tideglusib [60]
SARS-CoV-2 Mpro IC$_{50}$ = 2.1 uM

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

SARS-CoV-2 E inh. 77% inh. at 10 mmol
Orf10 65% inh. at 10 mmol

Iodobananin [135, 136]
SARS-CoV nsp13 IC$_{50}$ = 7.0 uM

Vanillinbananin [135, 136]
SARS-CoV nsp13 IC$_{50}$ = 2.7 uM

Eubananin [135, 136]
SARS-CoV nsp13 IC$_{50}$ = 5.4 uM

Fig. 17. Structures of cage compounds 166–171.
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Fig. 18. Structures of phenothiazine antipsychotics 172–177 and methylene blue 178.

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

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

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

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

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

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

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.
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Fig. 21. (Contd.)

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

193 [141]
SARS-CoV-2 PLpro IC₅₀ = 2.2 uM

194 [142]
SARS-CoV PLpro IC₅₀ = 2.9 uM
SARS-CoV-2 PLpro IC₅₀ = 7.6 uM
SARS-CoV-2 repl. EC₅₀ = 7.85 uM

195 [142]
SARS-CoV PLpro IC₅₀ = 6.5 uM
SARS-CoV-2 PLpro IC₅₀ = 15 uM
SARS-CoV-2 repl. EC₅₀ = 1.77 uM

196 [142]
SARS-CoV PLpro IC₅₀ = 14 uM
SARS-CoV-2 PLpro IC₅₀ = 42 uM
SARS-CoV-2 repl. EC₅₀ = 4.74 uM

197 Toremifene [86]
SARS-CoV-2 repl. IC₅₀ = 4.77 uM

198 Clomiphene [57]
SARS-CoV-2 repl. IC₅₀ = 5.36

199 Droloxifene [57]
SARS-CoV-2 repl. IC₅₀ = 6.60 uM

200 Tamoxifen [86]
SARS-CoV-2 repl. IC₅₀ = 34.12 uM

201 Triparanol [86]
SARS-CoV-2 repl. IC₅₀ = 4.68 uM
Niclosamide [57]  
SARS-CoV-2 repl. IC_{50} = 8.86 uM

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

SARS-CoV-2 repl. IC_{50} = 0.04 uM

SARS-CoV-2 Mpro IC_{50} = 0.2 uM

SARS-CoV-2 repl. IC_{50} = 0.64 uM

SARS-CoV 3CLpro IC_{50} = 1.06 uM

SARS-CoV repl. EC_{50} < 2 uM

HCoV-OC34 repl. EC_{50} < 2.5 uM

Fig. 22. (Contd.)

Fig. 23. Structures of aromatic compounds 204–215.
Fig. 23. (Contd.)

**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

**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

**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.
Fig. 25. Structures of triterpenoids 225–234.
**Fig 25.** (Contd.)

- **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 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.)
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 against 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 anticonoviral 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.

REFERENCES

1. Planas, D., Bruel, T., Grzelak, L., Guivel-Benhassine, F., Staropoli, I., Porrot, F., Planchais, C., Buchrieser, J., Rajah, M.M., Bishop, E., Albert, M., Donati, F., Behillil, S., Enouf, V., Maquart, M., Gonzalez, M., De Sèze, J., Péré H., Veyer, D., Sève, A., Simon-Lorière, E., Fafi-Kremer, S., Stefic, K., Mouquet, H., Hocqueldom, L., van der Werf, S., Prazuck, T., and Schwartz, O., bioRxiv, 2021. https://doi.org/10.1101/2021.02.12.430472
2. Silva, L.R., da Silva Santos-Júnior, P.F., de Andrade Brandão, J., Anderson, L., Bassi, E.J., de Araújo-Júnior, J.X., Cardoso, S.H., and da Silva-Júnior, E.F., Bioorg. Med. Chem., 2020, vol. 28, p. 115745. https://doi.org/10.1016/j.bmc.2020.115745
3. Naveja, J.J., Madariaga-Mazón, A., Flores-Murrieta, F., Granados-Montiel, J., Maradiaga-Ceceña, M., Alainz, V.D., Maldonado-Rodriguez, M., García-Morales, J., Senosiain-Peláez, J.P., and Martinez-Mayorga, K., Drug Disc. Today, 2021, vol. 26, p. 229. https://doi.org/10.1016/j.drudis.2020.10.018
4. Ojha, P.K., Kar, S., Krishna, J.G., Roy, K., and Leszczyńska, J., Mol. Divers., 2021, vol. 25, p. 625. https://doi.org/10.1007/s11030-020-10134-x
5. Chowdhury, K.H., Chowdhury, M.R., Mahmud, S., Tarreq, A.M., Hanif, N.B., Banu, N., Reza, A.S.M.A., Enran, T.B., and Simal-Gandara, J., Biol., 2021, vol. 10, p. 2. https://doi.org/10.3390/biology10010002
6. Caruso, F.P., Scala, G., Cerulo, L., and Ceccarelli, M., Brief. Bioinform., 2020, vol. 22, p. 701. https://doi.org/10.1093/bib/bbaa328
7. Santibanez-Moran, M.G., Lopez-Lopez, E., Prieto-Martínez, F.D., Sanchez-Cruz, N., and Medina-Franco, J.L., RSC Adv., 2020, vol. 10, p. 25089. https://doi.org/10.1039/d0ra04922k
8. Ahamad, S., Branch, S., Harrelson, S., Hussain, M.K., Saquib, M., and Khan, S., Eur. J. Med. Chem., 2021, vol. 209, p. 112862. https://doi.org/10.1016/j.ejmech.2020.112862
9. de Almeida, S.M.V., Soares, J.C.S., dos Santos, K.L., Alves, J.E.F., Ribeiro, A.G., Jacob, I.T.T., da Silva, Ferreira, C.J., dos Santos, J.C., de Oliveira, J.F., de Carvalho, Junior, L.B., and de Lima, M.C.A., Bioorg. Med. Chem., 2020, vol. 28, p. 115757. https://doi.org/10.1016/j.bmc.2020.115757
10. Butterworth, R.F., J. Pharmaceut. Pharmacol., 2020, vol. 8, p. 4. https://doi.org/10.13188/2327-204x.1000035
11. Choudhry, N., Zhao, X., Xu, D., Zanin, M., Chen, W., Yang, Z., and Chen, J., J. Med. Chem., 2020, vol. 63, p. 13205. https://doi.org/10.1021/acs.jmedchem.0c00626
12. Hosseini-Zare, M.S., Thilagavathi, R., and Selvam, C., RSC Adv., 2020, vol. 10, p. 28287. https://doi.org/10.1039/d0ra04395h
38. Fu, L., Ye, F., Feng, Y., Yu, F., Wang, O., Wu, Y., Zhao, C., Sun, H., Huang, B., Niu, P., Song, H., Shi, Y., Li, X., Tan, W., Qi, J., and Gao, G.F., *Nat. Commun.*, 2020, vol. 11, p. 4417.
39. St. John, S.E. and Mesecar, A.D., US Patent Appl. no. US 9 975 885 B2.
40. Kanka namalage, A.C.G., Kim, Y., Damalanka, V.C., Rathnayake, A.D., Fehr, A.R., Mehzabeen, N., Battaile, K.P., Lovell, S., Lushington, G.H., Perlman, S., Chang, K.-Y., and Groutas, W.C., *Eur. J. Med. Chem.*, 2018, vol. 150, p. 334.
41. Yang, S., Chen, S.-J., Hsu, M.-F., Wu, J.-D., Tseng, C.-T.K., Liu, Y.-F., Chen, H.-C., Kuo, C.-W., Wu, C.-S., Chang, L.-W., Chen, W.-C., Liao, S.-Y., Chang, T.-Y., Hung, H.-H., Shih, H.-J., Liu, C.-Y., Huang, Y.-A., Chang, L.-Y., Hsu, J.-C., Peters, C.J., Wang, A.H.-J., and Hsu, M.-C., *Med. Chem.*, 2006, vol. 49, p. 4971.
42. Sacco, M.D., Ma, C., Lagarias, P., Gao, A., Townsend, J.A., Meng, X., Dube, P., Zhang, X., Hu, Y., Kamamura, N., Hurst, B., Tarbet, B., Marty, M.T., Kolar, A., Xiang, Y., Chen, Y., and Wang, J., *Sci. Adv.*, 2020, vol. 6, p. eabe0751.
43. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauermann, L., Becker, S., Rox, K., and Hilgenfeld, R., *Science*, 2020, vol. 368, p. 409.
44. Zhang, L., Lin, D., Kusov, Y., Nian, Y., Ma, Q., Wang, J., von Brunn, A., Leysen, P., Lanko, K., Neyts, J., de Wilde, A., Snijder, E.J., Liu, H., and Hilgenfeld, R., *J. Med. Chem.*, 2020, vol. 63, p. 4562.
45. Wang, J., Liang, B., Chen, Y., Chan, J.F.-W., Yuan, S., Ye, H., Nie, L., Zhou, J., Wu, Y., Wu, M., Huang, L.S., An, J., Warshel, A., Yuen, K.-Y., Ciechanover, A., Huang, Z., and Xu, Y., *Eur. J. Med. Chem.*, 2021, p. 113267.
46. Ghahremanpour, M.M., Tirado-Rives, J., Deshmukh, M., Ippolito, J.A., Zhang, C.-H., de Vaca, I.C., Liosi, M.-E., Anderson, K.S., and Jorgensen, W.L., *ACS Med. Chem. Lett.*, 2020, vol. 11, p. 2526.
47. Botyanszki, J., Catalano, J.G., Chong, P.Y., Dickson, H., Jin, Q., Leivers, A., Maynard, A., Liao, X., Miller, J., Shottwell, J.B., Tai, V.W.-F., and Thalji, R., *J. Med. Chem.*, 2018, vol. 61, p. 7015.
48. Choy, K.-T., Wong, A.Y.-L., Kaewpreedee, P., Sia, S.F., Chen, D., Hui, K.P.Y., Chu, D.K.W., Chan, M.C.W., Cheung, P.P.-H., Huang, X., Peiris, M., and Yen, H.L., *Antivir. Res.*, 2020, vol. 178, p. 104786.
49. Lee, C., Lee, J.M., Lee, N.-R., Kim, D.-R., Jeong, Y.-L., and Chong, Y., *Bioorg. Med. Chem. Lett.*, 2009, vol. 19, p. 4538.
50. Chung, Y.H., Jeong, Y.J., and Lee, C.W., *Kor. Patent Appl. no. KR2011000683A*, 2011.
51. Yu, M.-S., Lee, J., Lee, J.M., Kim, Y., Chin, Y.-W., Jee, J.-G., Keung, Y.-S., and Jeong, Y.-J., *Bioorg. Med. Chem. Lett.*, 2012, vol. 22, p. 4049.
52. Park, J.-Y., Yuk, H.J., Ryu, H.W., Lim, S.H., Kim, K.S., Park, K.H., Ryu, Y.B., and Lee, W.S., *J. Enzyme Inhib. Med. Chem.*, 2017, vol. 32, p. 504.
53. Kim, M.K., Yu, M.-S., Park, H.R., Kim, K.B., Lee, C., Cho, S.Y., Kang, J., Yoon, H., Kim, D.-E., Choo, H., Jeong, Y.-J., and Chong, Y., *Eur. J. Med. Chem.*, 2011, vol. 46, p. 5698.
54. Ryu, Y.B., Jeong, H.J., Kim, J.H., Kim, Y.M., Park, J.-Y., Kim, D., Naguyen, T.T.H., Park, S.-J., Chang, J.S., Park, K.H., Rho, M.-C., and Lee, W.S., *Bioorg. Med. Chem.*, 2010, vol. 18, p. 7940.
55. Jo, S., Kim, S., Shin, D.H., and Kim, M.-S., *J. Enzyme Inhib. Med. Chem.*, 2020, vol. 35, p. 145.
56. Jo, S., Kim, S., Kim, D.Y., Kim, M.-S., and Shin, D.H., *J. Enzyme Inhib. Med. Chem.*, 2020, vol. 35, p. 1539.
76. Zheng, Z., Groaz, E., Snoeck, R., De Jonghe, S., Herde
67. Park, J.-Y., Kim, J.H., Kwon, J.M., Kwon, H.-J., Jeong, H.J.,
69. Jin, Z., Zhao, Y., Sun, Y., Zhang, B., Wang, H., Wu, Y.,
70. Zandi, K., Amblard, F., Musall, K., Downs-Bowen, J.,
72. Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X.,
75. Wang, Z. and Yang, L.,
77. Ikejiri, M., Saijo, M., Morikawa, S., Fukushi, S.,
80. Sara
81. Adedeji, A.O., Singh, K., Calcaterra, N.E., DeDiego, M.L.,
MAIN CHEMOTYPES OF SARS-COV-2 REPRODUCTION INHIBITORS

2006, vol. 49, p. 3485.
https://doi.org/10.1021/jm050852f

104. Ramajayam, R., Tan, K.-P., Liu, H.-G., and Liang, P.-H., Bioorg. Med. Chem. Lett., 2010, vol. 20, p. 3569.
https://doi.org/10.1016/j.bmcl.2010.04.118

105. Lee, H., Ren, J., Pesavento, R.P., Ojeda, I., Rice, A.J., Lv, H., Kwon, Y., and Johnson, M.E., Bioorg. Med. Chem., 2019, vol. 27, p. 1981.
https://doi.org/10.1016/j.bmcc.2019.03.050

106. Mukherjee, P., Shah, F., Desai, P., and Avery, M., J. Chem. Inf. Model., 2011, vol. 51, p. 1376.
https://doi.org/10.1021/ci1004916

107. Holwerda, M., Vkovski, P., Wider, M., Thiel, V., and Dijkman, R., Microorganisms, 2020, vol. 8, p. 1872.
https://doi.org/10.3390/microorganisms8121872

108. Lee, H., Mittal, A., Patel, K., Gatuz, J.L., Truong, L., Torres, J., Mulhearn, D.C., and Johnson, M.E., Bioorg. Med. Chem., 2014, vol. 22, p. 167.
https://doi.org/10.1016/j.bmc.2013.11.028

109. Wiliam, L., Gage, P., and Ewart, G., Virology, 2006, vol. 353, p. 294.
https://doi.org/10.1016/j.virol.2006.05.028

110. Shin, Y.S., Lee, J.Y., Noh, S., Kwak, Y., Jeon, S., Kwon, S., Jin, Y., Jang, M.S., Kim, S., Song, J.H., Kim, H.R., and Park, C.M., Bioorg. Med. Chem., 2020, vol. 31, p. 127667.
https://doi.org/10.1016/j.bmc.2020.127667

111. Yamamoto, N., Matsuyama, S., Hoshino, T., and Yama-moto, N., bioRxiv, 2020.
https://doi.org/10.1101/2020.04.06.02647

112. Ohnishi, K., Hattori, Y., Kobayashi, K., and Akaji, K., Bioorg. Med. Chem., 2019, vol. 27, p. 425.
https://doi.org/10.1016/j.bmcc.2018.12.019

113. Yoshizawa, S., Hattori, Y., Kobayashi, K., and Akaji, K., Bioorg. Med. Chem., 2020, vol. 28, p. 115273.
https://doi.org/10.1016/j.bmcc.2019.115273

114. Shimamoto, Y., Hattori, Y., Kobayashi, K., Teruya, K., Sanjoh, A., Nakagawa, A., Yamashita, E., and Akaji, E., Bioorg. Med. Chem., 2015, vol. 23, p. 876.
https://doi.org/10.1016/j.bmcc.2014.12.028

115. Taylor, R.D., MacCoss, M., and Lawson, A.D.G., J. Med. Chem., 2014, vol. 57, p. 5845.
http://doi.org/10.1021/jm4017625

116. Lee, J.-M., Cho, J.-B., Ahn, H.-C., Jung, W., and Jeong, Y.-J., J. Microbiol. Biotechnol., 2017, vol. 27, p. 2070.
https://doi.org/10.4014/jmb.1707.07073

117. Nguyen, T.T.H., Ryu, H.-J., Lee, S.-H., Hwang, S., Breton, V., Rhee, J.H., and Kim, D., Bioorg. Med. Chem. Lett., 2011, vol. 21, p. 3088.
https://doi.org/10.1016/j.bmcl.2011.03.034

118. Yang, N., Tanner, A., Wang, Z., Huang, J.-D., Zheng, B.-J., Zhua, N., and Sun, H., Chem. Commun., 2007, p. 4413.
https://doi.org/10.1039/B709515E

119. Ghosh, A.K., Gong, G., Grum-Tokars, V., Mulhearn, D.C., Baker, S.C., Coughlin, M., Prabhakar, B.S., Sleeman, K., Johnson, M.E., and Mesecar, A.D., Bioorg. Med. Chem. Lett., 2008, vol. 18, p. 5684.
https://doi.org/10.1016/j.bmcl.2008.08.082

120. Zhou, L., Liu, Y., Zhang, W., Wei, P., Huang, C., Pei, J., Yuan, Y., and Lai, L., J. Med. Chem., 2006, vol. 49, p. 3440.
https://doi.org/10.1021/jm0602357

121. Liu, W., Zhu, H.-M., Niu, G.-J., Shi, E.-Z., Chen, J., Sun, B., Chen, W.-Q., Zhou, H.-G., and Yang, C., Bioorg. Med. Chem. Lett., 2014, vol. 22, p. 292.
https://doi.org/10.1016/j.bmcl.2013.11.028

122. Wang, X., Cao, R., Zhang, H., Liu, J., Xu, M., Hu, H., Li, Y., Zhao, L., Li, W., Sun, X., Yang, X., Shi, Z., Deng, F., Hu, Z., Zhong, W., and Wang, M., Cell. Discov., 2020, vol. 6, p. 28.
https://doi.org/10.1038/s41421-020-0169-8

123. Khamitov, R.A., Loginova, S.Ya., Shchukina, V.N., Borisievich, S.V., Maksimov, V.A., and Shuster, A.M., Vopr. Virusol., 2008, vol. 53, p. 9.

124. Kumar, V., Tan, K.P., Wang, Y.M., Lin, S.W., and Liang, P.H., Bioorg. Med. Chem., 2016, vol. 24, p. 3035.
https://doi.org/10.1016/j.bmcc.2016.05.013

125. Ramajayam, R., Tan, K.-P., Liu, H.-G., and Liang, P.-H., Bioorg. Med. Chem., 2010, vol. 18, p. 7849.
https://doi.org/10.1016/j.bmcl.2010.09.050

126. Feng, S., Luan, X., Wang, Y., Wang, H., Zhang, Z., Wang, Y., Tian, Z., Liu, M., Xiao, Y., Zhao, Y., Zhou, R., and Zhang, S., Infect. Gen. Evol., 2020, vol. 85, p. 04419.
https://doi.org/10.1016/j.meegid.2020.104419

127. Zhu, O., Zhang, Y., Wang, L., Yao, X., Wu, D., Cheng, J., Pan, X., Liu, H., Yan, Z., and Gao, L., Antivir. Res., 2021, vol. 187, p. 105015.
https://doi.org/10.1016/j.antiviral.2021.105015
129. Węglarz-Tomczak, E., Tomczak, J.M., Talma, M., and Brul, S., bioRxiv, 2020. https://doi.org/10.1101/2020.05.17.100768

130. Zaher, N.H., Mostafa, M.I., and Altaher, A.Y., Acta Pharm., 2020, vol. 70, p. 145. https://doi.org/10.2478/acph-2020-0024

131. Sarafanios, S.G. and Adedeji, A.O., WO Patent Appl. no. WO 2013 188887 A1, 2013.

132. Konstantinidi, A., Chountoulesi, M., Naziris, N., Sartori, B., Amenitsch, H., Mali, G., Čendak, T., Plakantonaki, M., Triantafyllakou, I., Tselios, T., Demetzos, C., Busath, D.D., Mavromoustakos, T., and Kolocouris, A., Biochim. Biophys. Acta Biomembr., 2019, vol. 1862, p. 183156. https://doi.org/10.1016/j.bbamem.2019.183156

133. Eleftheratos, S., Spearpoint, P., Ortore, G., Kolocouris, A., Martinelli, A., Martin, S., and Hay, A., Bioorg. Med. Chem. Lett., 2010, vol. 20, p. 4182. https://doi.org/10.1016/j.bml.2010.05.049

134. Mandala, V.S., McKay, M.J., Shcherbakov, A.A., Dregni, A.J., Kolocouris, A., and Hong, M., Nat. Struct. Mol. Biol., 2020, vol. 27, p. 1202. https://doi.org/10.1038/s41594-020-00536-8

135. Kesel, A.J., Anti-Infect. Agents Med. Chem., 2006, vol. 5, p. 161. https://doi.org/10.2174/187152106776359039

136. Tanner, J.A., Zheng, B.J., Zhou, J., Watt, R.M., Jiang, J.Q., Wong, K.L., Lin, Y.P., Lu, L.Y., He, M.L., Kung, H.F., Kesel, A.J., and Huang, J.D., Chem. Biol., 2005, vol. 12, p. 303. https://doi.org/10.1016/j.chemb.2005.01.006

137. Syvatchenko, V.A., Nikonov, S.D., Mayorov, A.P., Gel'fond, M.L., and Loktev, V.B., Photodiagn. Photodyn. Ther., 2021, vol. 33, p. 102112. https://doi.org/10.1016/j.pdpdt.2020.102112

138. Báez-Santos, Y.M., Barraza, S.J., Wilson, M.W., Agius, M.P., Mielech, A.M., Davis, N.M., Baker, S.C., Larsen, S.D., and Mesecar, A.D., J. Med. Chem., 2014, vol. 57, p. 2393. https://doi.org/10.1021/jm401712t

139. Ghosh, A.K., Takayama, J., Rao, K.V., Ratia, K., Chaudhuri, R., Mulhearn, D.C., Lee, H., Nichols, D.B., Bali-ji, S., Baker, S.C., Johnson, M.E., and Mesecar, A.D., J. Med. Chem., 2010, vol. 53, p. 4968. https://doi.org/10.1021/jm1004489

140. Ghosh, A.K., Takayama, J., Aubin, Y., Ratia, K., Chaudhuri, R., Baez, Y., Sleeman, K., Coughlin, M., Nichols, D.B., Mulhearn, D.C., Prabhakar, B.S., Baker, S.C., Johnson, M.E., and Mesecar, A.D., J. Med. Chem., 2009, vol. 52, p. 5228. https://doi.org/10.1021/jm900611t

141. Gao, X., Qin, B., Chen, P., Zhu, K., Hou, P., Wojdyla, J.A., Wang, M., and Cui, S., Acta Pharm. Sin. B, 2021, vol. 11, p. 237. https://doi.org/10.1016/j.apsb.2020.08.014

142. Welker, A., Kersten, C., Müller, C., Madhugiri, R., Zimmer, C., Müller, P., Zimmermann, R., Hammerschmidt, S., Maus, H., Ziebuhr, J., Sotriffer, C., and Schirmeister, T., ChemMedChem, 2021, vol. 16, p. 340. https://doi.org/10.1002/cmdc.202000548

143. Bacha, U., Barrila, J., Velazquez-Campoy, A., Leavitt, S.A., and Freire, E., Biochemistry, 2004, vol. 43, p. 4906. https://doi.org/10.1021/bi0361766

144. Hoffmann, M., Schroeder, S., Kleine-Weber, H., Müller, M.A., Drosten, C., and Pöhlmann, S., Antimicrob. Agents Chemother., 2020, vol. 64, p. e00754. https://doi.org/10.1128/AAC.00754-20

145. Yang, O., Chen, L., He, X., Gao, Z., Shen, X., and Bai, D., Chem. Pharm. Bull., 2008, vol. 56, p. 1400. https://doi.org/10.1248/cpb.56.1400

146. Gage, P.W., Ewart, G.D., Wilson, L.E., Best, W., and Premkumar, A., US Patent Appl. no. US 20150313909, 2015.

147. Lee, C., Lee, J.M., Lee, N.-R., Jin, B.-S., Jang, K.J., Kim, D.-E., Jeong, Y.-J., and Chong, Y., Bioorg. Med. Chem. Lett., 2009, vol. 19, p. 1636. https://doi.org/10.1016/j.bml.2009.02.010

148. Lee, C.-C., Kuo, C.-J., Hsu, M.-F., Liang, P.-H., Fang, J.-M., Shie, J.-J., and Wang, A.H.-J., FEBS Lett., 2007, vol. 581, p. 5454. https://doi.org/10.1016/j.febslet.2007.10.048

149. Yang, N., Tanner, J., Zheng, B.-J., Watt, R., He, M.-L., Lu, L.-Y., Jiang, J.-Q., Shum, K.-T., Lin, Y.-P., Wong, K.-L., Lin, M., Kung, H.-F., Sun, H., and Huang, J.-D., Angew. Chem. Int. Ed., 2007, vol. 46, p. 6464. https://doi.org/10.1002/anie.200701021

150. Shu, T., Huang, M., Wu, D., Ren, Y., Zhang, X., Han, Y., Mu, J., Wang, R., Qiu, Y., Zhang, D.-Y., and Zhou, X., Virol. Sin., 2020, vol. 35, p. 321. https://doi.org/10.1007/s12250-020-00242-1

151. Krasiqi, B., Stevaert, A., Loy, B.V., Nguyen, T., Thomas, J., Vandeput, J., Jochnams, D., Thiel, V., Dijkman, R., Dehaen, W., Voet, A., and Naesens, L.,
bioRxiv, 2020.
https://doi.org/10.1101/2020.12.10.418996

152. Ryu, Y.B., Park, S.-J., Kim, Y.M., Lee, J.-Y., Seo, W.D., Chang, J.S., Park, K.H., Rho, M.-C., and Lee, W.-S., *Bioorg. Med. Chem. Lett.*, 2010, vol. 20, p. 1873.
https://doi.org/10.1016/j.bmcl.2010.01.152

153. Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., and Cintali, J., *J. Med. Chem.*, 2005, vol. 48, p. 1256.
https://doi.org/10.1021/jm0493008

154. Yu, S., Zhu, Y., Xu, J., Yao, G., Zhang, P., Wang, M., Zhao, Y., Lin, G., Chen, H., Chen, L., and Zhang, J., *Phytomedicine*, 2020, p. 153364.
https://doi.org/10.1016/j.phymed.2020.153364

155. Zarubaev, V.V., Anikin, V.B., and Smirnov, V.S., *Infek. Immun.*, 2016, vol. 6, p. 199.
https://doi.org/10.15789/2220-7619-2016-3-199-206

156. Tripathi, P.K., Upadhyay, S., Singh, M., Raghavendhar, S., Bhardwaj, M., Sharma, P., and Patel, A.K., *Int. J. Biol. Macromol.*, 2020, vol. 164, p. 2622.
https://doi.org/10.1016/j.ijbiomac.2020.08.166

157. Svenningsen, E.B., Thyrrsted, J., Blay-Cadanet, J., Liu, H., Lin, S., Moyano-Villameriel, J., Olagnier, D., Idorn, M., Paludan, S.R., Holm, C.K., and Poulsen, T.B., *Antivir. Res.*, 2021, vol. 185, p. 104988.
https://doi.org/10.1016/j.antiviral.2020.104988

158. Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., and Wagstaff, K.M., *Antivir Res.*, 2020, vol. 178, p. 104787.
https://doi.org/10.1016/j.antiviral.2020.104787

159. Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., Yang, X., Bai, F., Liu, H., Liu, X., Guddat, L.W., Xu, W., Xiao, G., Qin, C., Shi, Z., Jiang, H., Rao, Z., and Yang, H., *Nature*, 2020, vol. 582, p. 289.
https://doi.org/10.1038/s41586-020-2223-y

160. Lockbaum, G.J., Reyes, A.C., Lee, J.M., Tilvawala, R., Nalivaika, E.A., Ali, A., Kurt, Yilmaz, N., Thompson, P.R., and Schiffer, C.A., *Viruses*, 2021, vol. 13, p. 174.
https://doi.org/10.3390/v13020174

161. Yin, W., Mao, C., Luan, X., Shen, D.D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y.C., Tian, G., Jiang, H.W., Tao, S.C., Shen, J., Jiang, Y., Jiang, H., Xu, Y., Zhang, S., Zhang, Y., and Xu, H.E., *Science*, 2020, vol. 368, p. 1499.
https://doi.org/10.1126/science.abc1560

162. Sheehan, J.C. and Henery-Logan, K.R., *J. Am. Chem. Soc.*, 1957, vol. 79, p. 1262.
https://doi.org/10.1021/ja01562a063