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Triazole, imidazole, and thiazole-based compounds as potential agents against coronavirus



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ABSTRACT

The expansion of the novel coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), COVID-19 (coronavirus disease 2019), or 2019-nCoV (2019 novel coronavirus) is a global concern over its pandemic potential. The need for therapeutic alternatives to stop this new pandemic is urgent. Nowadays, no efficacious therapy is available, and vaccines and drugs are underdeveloped to cure or prevent SARS-CoV-2 infections in many countries. Some vaccines candidates have been approved; however, a number of people are still skeptical of this coronavirus vaccines. Probably because of issues related to the quantity of the vaccine and a possible long-term side effects which are still being studied. The previous pandemics of infections caused by coronavirus, such as SARS-CoV in 2003, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, HCoV-229E, and HCoV-OC43 were described in the 1960 s, HCoV-NL63 isolated in 2004, and HCoV-HKU1 identified in 2005 prompted researchers to characterize many compounds against these viruses. Most of them could be potentially active against the currently emerging novel coronavirus. Five membered nitrogen heterocycles with a triazole, imidazole, and thiazole moiety are often found in many bioactive molecules such as coronavirus inhibitors. This present work summarizes to review the biological and structural studies of these compound types as coronavirus inhibitors.

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Introduction

The recent unprecedented coronavirus pandemic caused a dramatic change in the days of humans that increases the scientific interest in coronaviruses globally. Coronaviruses (CoVs) belong to Nidovirales order, Coronaviridae family, and the subfamily of *Coronavirinae*

contain 4 kinds: alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus (Fig. 1A) and are large (genome size 26–32 kb) [1], enveloped, positive-sense single-stranded ribonucleic acid (RNA) viruses that can infect both humans and animals. They are six human coronaviruses such as HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS (Middle East Respiratory

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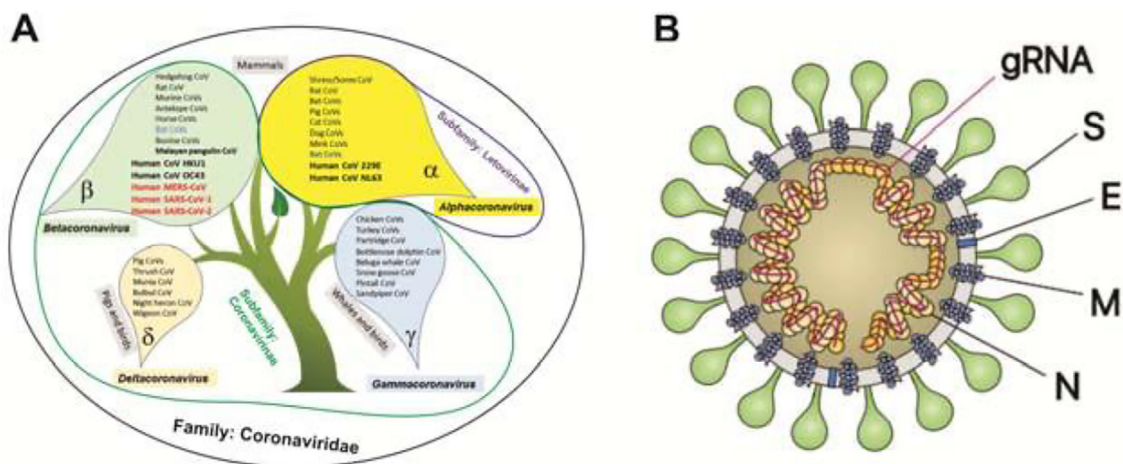


Fig. 1. (A) Taxonomy of the family Coronaviridae, Human coronaviruses are shown in bold type. Highly pathogenic human coronaviruses are shown in red type. Human coronaviruses belong to two different genera: Betacoronavirus and Alphacoronavirus [8]. (B) Structure of the SARS-CoV-2 virion gRNA: genomic RNA; N: nucleocapsid protein; S: spike; E: envelope; and M: membrane [9]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Syndrome)-CoV, and SARS (severe acute respiratory syndrome)-CoV that are of zoonotic origin [2]. Coronaviruses (CoVs) are widespread in domestic and wild mammals, in various bird species and are the source of significant economic losses, particularly in pig and poultry farming [3]. Moreover, CoVs were found to be the causative agents of MERS-CoV and SARS-CoV. With the emergence of SARS-CoV in 2002 and the emergence of MERS-CoV in 2012 in the Arabian Peninsula, they have become important human pathogens. Among the six different coronaviruses are now described in humans, SARS-CoV and MERS-CoV are the most lethal, with 10% and 40% mortality rates, respectively. Additionally, these two viruses are the result of interspecies transmission. SARS-CoV was derived from the adaptation of a bat coronavirus, and MERS-CoV was transmitted to humans through contact with dromedaries themselves probably infected with a bat coronavirus. Now it is evidence that MERS-CoV can be transmitted person-to-person [4,5]. In 2019, a novel coronavirus (SARS-CoV-2) has been newly identified in humans, which caused millions of deaths from January 2020 to March 2021. As of March 09, 2021, the total number of confirmed SARS-CoV-2 infections worldwide is 117,907,247, deaths 2,614,842, and recovered 93,594,978 [6]. Coronavirus virions are enveloped and form spherical structures (Fig. 1 B) [7].

The viral genome is made up of a single strand of positive RNA. Unfortunately, this SARS-CoV-2 spread with different RNA sequences and raised the question of drug efficiency against different Coronavirus variants [7]. To find new therapy against coronavirus, we focus on molecules containing scaffold triazole, imidazole, and thiazole as potential agents. These heterocycle and organic compounds are the most important and most active principles in medicinal chemistry. Heteroatoms including nitrogen [10,11], sulfur [12,13], oxygen [14], and others [15] containing in heterocyclic bioactive compounds are the main source of the reactivity of the target skeleton, the activity of the compounds, and interactions between target drugs. Triazoles (pyrroldiazoles) are a versatile class of heterocycle compounds. Many applications in drug discovery target triazole because it is considered as a good amide bioisostere that readily associates with biological targets via hydrogen bonding and dipole-dipole interactions [16].

Triazoles containing drugs exhibit wide therapeutic potential and are used in the treatment of many diseases such as cancer [17,18], malaria [19], viral and bacterial infections [20,21], tuberculosis [22], HIV-1 protease [23], leishmaniasis [24], trypanosomiasis [25], anti-inflammatory [26], Alzheimer [27], antioxidant [28], diabetes

[29], and hepatitis C [30]. Imidazole compounds are heterocyclic compounds or diazole compounds. Many of them come from natural product compounds like alkaloids or chemically synthesized. Imidazole and its derivatives are reported to possess physiological and pharmacological properties and used in the treatment of several diseases. Many of them including anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic, and antimalaria are known [31]. Thiazole ring is mostly found in microbial and marine sources and was firstly described by Hantzsch and Weber in 1887 [32]. It can be found in natural products such as peptides [33], vitamins (thiamine), alkaloids [34], epothilone [35] and chlorophyll [36]. It has been shown containing various biological activities like antioxidant, analgesic, antibacterial, anticancer, antiallergic, antihypertensive, anti-inflammatory, antimalarial, antifungal, and antipsychotic [37]. Thiazole scaffold is found also in more than 18 Food and Drug Administration (FDA) approved drugs including sulfathiazole, ritonavir, abafungin, dasatinib, tiazofurin, cinalukast [38].

For therapeutic options, these five-membered heterocycle scaffolds have as targets: coronavirus proteases such as 3CL-like protease (3CLpro), papain-like protease (PLpro), and coronavirus helicase due to their essential implications for coronaviral replication. The main function of 3CLpro and PLpro is to process the viral polyprotein in a coordinated manner. SARS-CoV 3C like protease, plays an important role in viral polyprotein processing and controls the activity of the replicase complex [39]. The enzymatic activity of 3CLpro is an essential target for antiviral drug discovery against SARS-CoV and other coronavirus infections because of its importance for the viral life cycle [40]. In the literature, peptidomimetics were focused on 3CLpro inhibition. These compounds contain reaction groups, such as aldehydes, halo-methyl ketones, or Michael acceptors at the terminus with a covalent interaction with the active site Cys145 residue [41–44].

In this review, we focus on the current progress in the research and development of triazole, imidazole, and thiazole-containing molecule coronavirus inhibitors.

1,2,3-triazole

The major Coronavirus protease that cleaves the replicase polyproteins during viral replication is 3CLpro. This protease is targeted by numerous classes of protease inhibitors, such as zinc, mercury conjugates, C2-symmetric diols, peptidomimetic- α,β -unsaturated esters, ani-

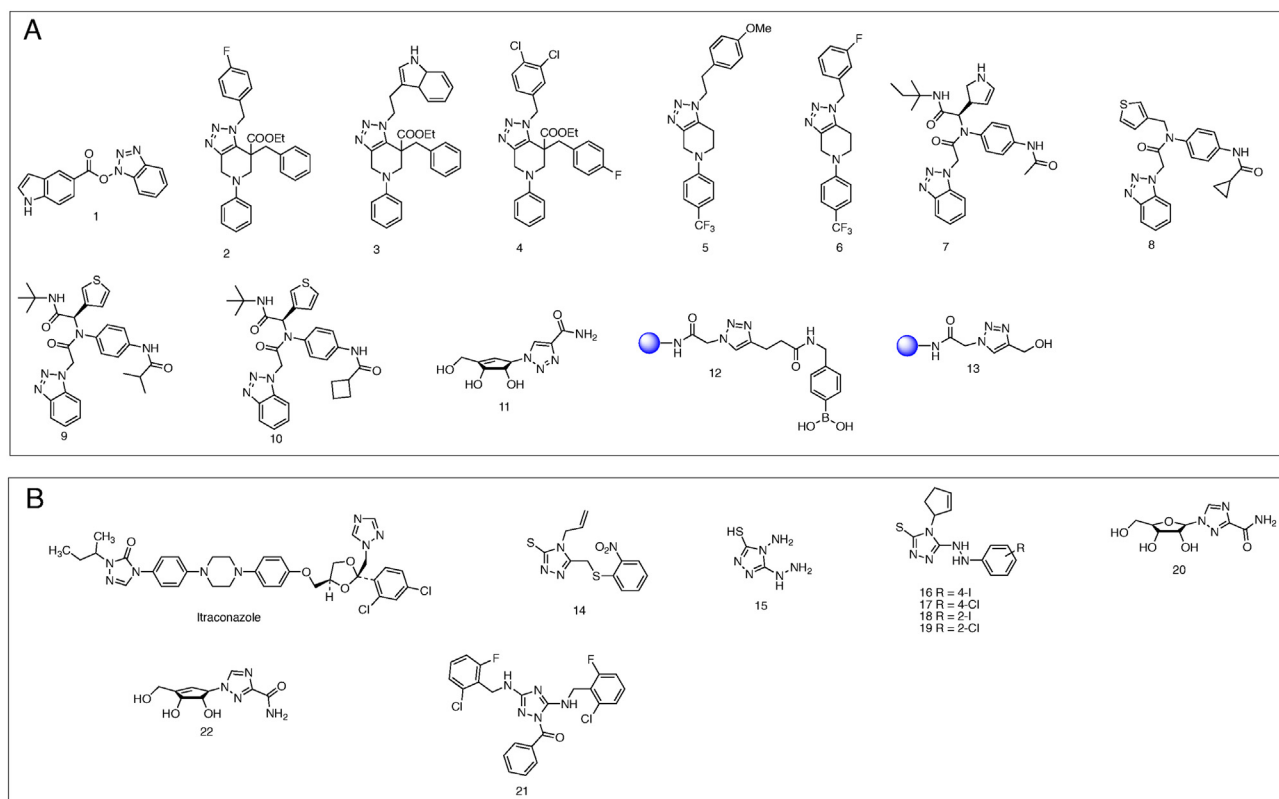


Fig. 2. 1,2,3-(A) 1,2,4-(B) triazole-based as potential anticoronavirus respectively [46,48,50,52,55,63,65,66,70,71].

lides, N-phenyl-2-acetamide, biphenyl sulfone, glutamic acid, glutamine peptide with a trifluoromethyl ketone group, pyrimidinone, and pyrazole analog [45]. Benzotriazole showed as a new class of potent 3CLpro inhibitors. The most potent inhibitor among the benzotriazole esters is compound 1 ($IC_{50} = 0.2 \mu M$) [46]. The mode of inhibition was studied by docking experiments based on computer modeling (Autodock version 3.0.5) [47] for illustrating the binding compound with 3CLpro. Results indicated that the benzotriazole moiety was disposed of within the active site forming a pocket with Cys145, Ser144, and Gly143 [46]. Karypidou et al. reported that five 1,2,3-triazoles such as 2 ($EC_{50} = 8.95 \mu M$), 3 ($EC_{50} = 9.45 \mu M$), 4 ($EC_{50} = 9.455 \mu M$), 5 ($EC_{50} = 8.90 \mu M$), and 6 ($EC_{50} = 11.95 \mu M$) (Fig. 2-A) showed moderate activity against HCoV-229E but all are approximately 50 fold lower than the activity of the reference *Urtica dioica* agglutinin (UDA) ($EC_{50} = 0.2 \mu M$) [48]. At the same time, using these triazoles through their structure–activity relationship (SAR), it was demonstrated that the active site is located within domains I and II, in which a catalytic dyad consisting of residues Cys145 and His41 [49]. The docking of bioactive derivatives of compounds 2 and 3 showed that they establish two HB interactions with Glu166 and His163, allowing also the position of the triazole ring in the proximity of the catalytic dyad [48]. Analyzed of compounds 4 and 5 gave a similar behavior, with the derivatives exhibiting antiviral activity, which able to establish two stable HB interactions within the catalytic site of 3CL pro. Compound 4 is anchored in the catalytic site through interaction with His163 and two interactions established with Glu166 and Thr25. Concerning the interactions of compound 5, it establishes stable HB contacts with both Glu166 and His163, while further anchoring to residue Gln189 [48].

Turlington et al. demonstrated potential non-covalent SARS-3CLpro inhibitors of the chemical class of triazoles [50]. Compounds

7 and 8 in (Fig. 2 A) were identified as a potential 3CLpro inhibitor with $IC_{50} = 6.2 \mu M$ and $IC_{50} = 4.11 \mu M$ respectively good selectivity versus PLpro ($IC_{50} > 60 \mu M$) used as a control for cysteine-protease activity [50]. This study revealed through crystallography data of compound 8 and related triazoles, inhibition of 3CLpro via a novel mechanism of action and provide a new direction for additional noncovalent inhibitor design and refinement. Replacement of the N-methyl pyrrole moiety with a thiophene ring and substitution on the acetamide moiety with isopropyl amide 9 and cyclobutylamide 10 (Fig. 2 A) improved the inhibitory profile with IC_{50} of 4.1 and 3.8 μM respectively [51]. Activity of 1-(4,5-dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1H-1,2,3-triazole-4-carboxylic acid amide (compound 11) against SARS-CoV was demonstrated with $EC_{50} = 47 \mu M$ [52]. Another kind of molecules, carbon quantum dots (CQDs) with a diameter below 10 nm and excellent water dispersion, are targeted for nanomedical applications because of a lack of visible signs of toxicity in animals [53]. Aleksandra and co-workers investigated the antiviral activity of CQDs for the treatment of HCoV-229E infection [54]. Results showed that the compound 12 concentration-dependent virus inactivation observed was estimated to $EC_{50} = 52 \pm 8 \mu g mL^{-1}$. Combination of mannose and compound 12 showed a complete loss of antiviral activity of the latter at low particle concentrations, with antiviral activity above 50 $\mu g mL^{-1}$. These highlight that boronic acid functions, where the mode of action is the selective and reversible formation of tetravalent complexes with *cis*-diols and thus glycan units [54], are interacting with HCoV-229E. Compound 12, considered as pseudo-lectin, targeted the S protein of HCoV-229E via a lectin-carbohydrate binding mechanism, similar to the oligomannose-specific lectin Griffithsin [55]. The presence of antiviral activity of the mannose saturated compound 12 might be due to the presence of the triazole scaffold on the particle's surface.

Compound **13** bears no boronic acid function but a triazole scaffold, displays some antiviral activity, even though largely decreased compared to compound **12**.

1,2,4-triazole

1,2,4-triazoles are structural isomers of 1,2,3-triazoles. They are versatile heterocyclic moieties with a broad spectrum of biological activities [56]. Triazole derivatives have shown as potential antiviral agents against the H1N1 influenza virus [57]. Zhao and coworkers showed that 1,2,4-triazole derivative had the most effective activity against influenza B [58]. Some triazole derivatives are shown to possess bioavailability [59]. Helicase inhibitors are attractive anti-coronavirus treatment options thanks to the high homologous of helicases of various coronaviruses [60]. Supported by their modes of action, CoV-helicase inhibitors are often categorized into two groups. The primary one inhibits the unwinding and ATPase activity of SARS-CoV helicase, leading to inhibition of viral replication *in vitro* [61,62]. The second group of CoV-helicase inhibitors includes compounds that selectively inhibit the unwinding activity but not the ATPase activity of CoV helicase for instance compound **14**. Adedeji et al. reported a variety limited of possible inhibitors of nsp13. It absolutely was shown that SSYA10-001 3-[(2-nitrophenyl)sulfanylmethyl]-4-prop-2-enyl-1-H-1,2,4-triazole-5-thione (**14**) (Fig. 2 A) a triazole derivative as an nsp13 non-inhibitor through the blockage of SARS-CoV and MERS-CoV replication but inhibited SARS-CoV via nsp13 with $IC_{50} = 6 \mu M$ [63]. The cleavage activity of 3CL-pro and PL-pro leads to the release of nonstructural proteins (nsp) which include nsp13 (NTPase/Helicase). It was supposed that also the compound **14** binding pocket of SARS-CoV nsp13 is preserved among different coronavirus helicases, revealing the discovery of broad-spectrum coronavirus inhibitors. The SARS-CoV nsp13 indeed, we noted high homology between SARS-CoV helicase and other coronavirus helicases (about 70%), which means that compound **14** may also inhibit several coronaviruses that cause human disease, including but not limited to HCoV-229E and HCoV-NL63. It was reported that SSYA10-001 is a potential inhibitor of viral replication in MERS-CoV replication [64]. Zaher et al. investigated the inhibition of helicase MERS-CoV enzymatic activity of newly halogenated 1,2,4-triazole derivatives against MERS-CoV [65]. Results showed that 4-amino-5-hydrazino-4H-1,2,4-triazole-3-thiol (**15**) inhibited the M-nsp 13 helicase and ATPase activity with an IC_{50} value of 12.4 and 8.9 $\mu mol L^{-1}$ respectively. Some halogenated 1,2,4-triazole derivatives showed significant anti-MERS-CoV activity. Compounds **16** and **17** (Fig. 2 B) were the foremost effective MERS-CoV helicase inhibitors with ATPase IC_{50} values of 0.47 and 0.51 $\mu mol L^{-1}$ respectively [65]. Besides, *ortho*-iodo derivative (compound **18**) and *ortho*-chloro (compound **19**) (Fig. 2B) derivatives were moderate inhibitors with ATPase IC_{50} values of 2.73 and 3.9 $\mu mol L^{-1}$ respectively. A known nonspecific antiviral, ribavirin has been used for treating SARS-CoV [66]. Ribavirin (compound **20**) (Fig. 2B), is a guanine derivative, which is known for treating human coronavirus and respiratory syncytial virus (RSV) that has been evaluated in patients with SARS-CoV and MERS-CoV. However, it contains some side effects such as anemia, which must be severe at high doses [60] and its potency against SARS-CoV-2 is uncertain. Mechanistically, ribavirin inhibits RNA synthesis by viral RdRp also as well as inhibits mRNA capping [67]. The combination of interferon- $\alpha 2b$ and ribavirin can reduce MERS-CoV replication *in vitro* and *in vivo* [68]. A typical cleavage recognition site is, therefore, (Ser, Ala)-(Val, Thr)-(Leu, Glu)-(Ser, Ala, Gly), which is conserved among all coronavirus 3CLpro [69]. These features were exploited for designing lead triazole compounds with a potential broad spectrum [70]. The molecular docking of compound **21** conformation revealed that it binds to the active site and forms similar key interactions throughout all five proteases (3D23, 2ZU2, 3V3M, 3TLO, and OC43). It had been shown that the

1,2,4-triazole scaffold formed a linker within the center of the structure and mediated the formation of a hydrogen bond between N2 and the backbone of Glu165/6, which formed a third hydrogen bond via the backbone carbonyl and ligand NH. HCoV-OC43 3CLpro exhibited a fourth hydrogen bond between N4 of the 1,2,4-triazole and Gln189. This latter is conserved in 3D23 and 3V3M structures, however, it was oriented towards the solvent-exposed exterior of the pocket. Concerning 2ZU2 and 3TLO, the Gln position is replaced by Pro188/9, which did not contribute to the formation of a bond [70]. 1,2,4-triazole analog (**22**) (Fig. 2B) exhibited moderate antiviral activity with $EC_{50} = 21 \mu M$, selectivity index $SI > 4.8$ against SARS virus [52]. Takano et al. showed the activity of Itraconazole (ICZ) inhibiting type I FCoV (Feline coronavirus) infection [71]. It was demonstrated that type I FCoV is associated with cholesterol throughout the viral life cycle [72]. Previous studies demonstrated that U18666A, is a cholesterol transport inhibitor, inhibits type I FCoV infection [71]. Based on these results, U18666A has been identified as a drug target for type I FCoV [73,74]. The inhibition of intracellular cholesterol transport by ICZ was confirmed [75]. Itraconazole induces cholesterol accumulation within the cytoplasm, but the mechanism has not been clarified [76,77]. Another study reported that ICZ induces cholesterol accumulation in the lysosome by acting on NPC1. For that, ICZ may inhibit type I FCoV replication via the identical mechanism as U18666A [75].

It was reported also that ICZ acts on the oxysterol-binding protein (OSBP) and inhibits the formation of viral replication organelles in enteroviruses [47]. However, it was supposed that the replication of coronavirus is associated with endoplasmic reticulum (ER)-derived structures referred to as double-membrane vesicles (DMVs) [78], but it's not clear that OSBP is involved during the formation of the viral replication organelle in coronavirus.

Imidazole

Imidazole and its derivatives are some of the most important bioactive compounds. The study of their biological activities can be done by theoretical or experimental methods. Many articles targeted the inhibition of coronavirus theoretically (Table 1) [79]. Abdallah et al. reported this study theoretically the possibility of using twenty-eight bioactive imidazole compounds against coronavirus [63,80]. Results showed that compounds **23**, **24**, and **25** (Figs. 3–5) are the best inhibitors with the best docking score. The common characters between these compounds are aromatic rings with one or more

Table 1
Imidazole-based compounds SARS-CoV inhibitors.

Compound	SARS-CoV	
	IC_{50} ($\mu g/ml$)	CC_{50} ($\mu g/ml$)
26	30	31
27	20	> 75
28	23	> 75
29	17	> 75
30	15	56
31	48	> 75
32	46	64
33	32	> 75
34	18	> 75
35	28	> 75
36	46	> 75
37	40	75
38	23	75
39	17	29
40	28	> 75
41	49	75
42	35	> 75
43	26	> 75
Ribavirin	n.t.	n.t.

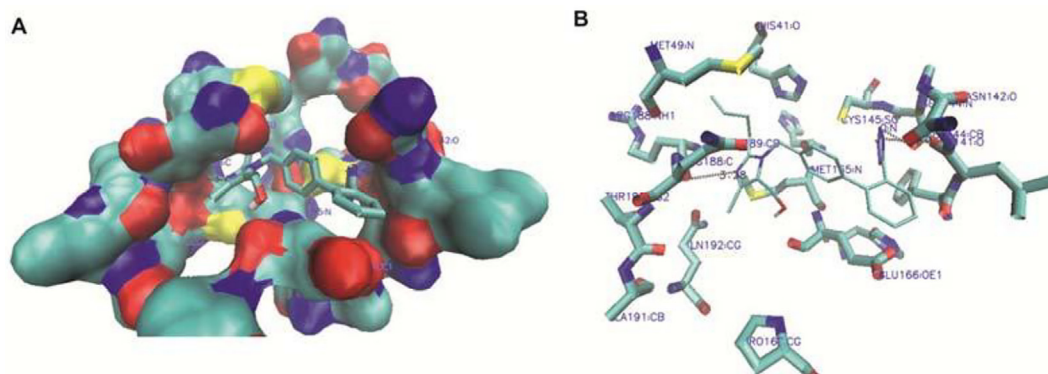


Fig. 3. Compound 23 at the active site of the protein (A) and in the active site of the protein making HB and pi-pi interactions (B) [80].

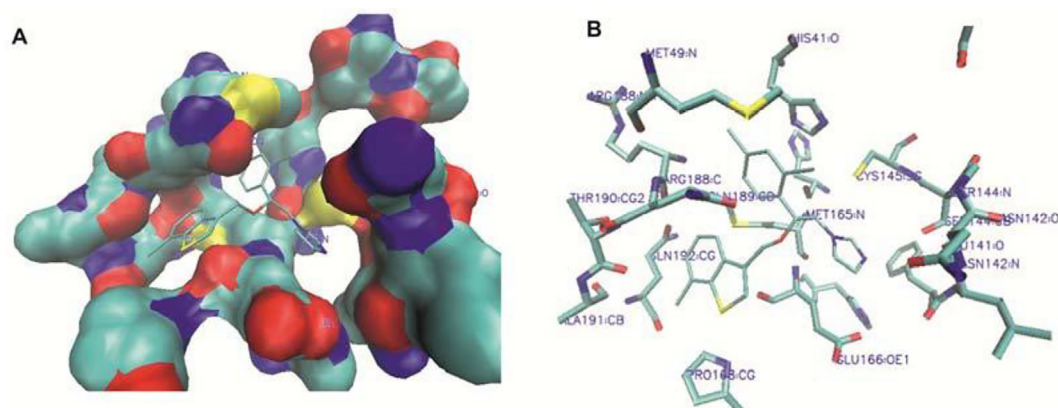


Fig. 4. Compound 24 at the active site of the protein (A) and in the active site of the protein making HB and pi-pi interactions (B) [80]

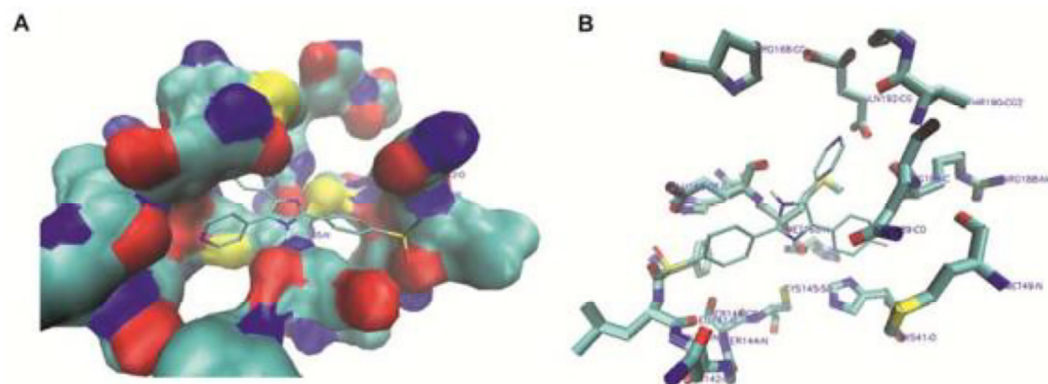


Fig. 5. Compound 25 at the active site of the protein (A) and of the active site of the protein making HB and pi-pi interactions (B) [80].

heteroatoms such as O or F or N or Cl branched. There are different interactions between protein (active sites) and compounds such as hydrogen bonds, *pi-pi* interactions, electrostatic interactions, hydrophobic, and hydrophilic interactions. The more interactions with the active site, the more binding forces made to the protein, the more stable the complex formed between the protein and the inhibitor, and the more inhibition ability. The characters, size, and conformation of the amino acids may be important in the interactions between the inhibitor and active site throughout the substituted groups. Compound 23 inhibits the virus by connecting with the active site through two types

of interactions, hydrogen bonds between OH groups and Arg188, Leu141 and Ser144, and *pi-pi* interactions and an aromatic ring. Compound 24 has an aromatic ring with Cl, O, and S heteroatoms. Its interactions with the active site are the hydrogen bond formed with amino acids Ser144 and Leu141. Compound 25 has made a hydrogen bond interaction with amino acids Ser144 and Leu141.

Günther et al. reported the results of 18 imidazole nucleoside/nucleotide analogs tested against SARS-CoV [81]. With compounds 27, 33, 40, 28, 29, and 34 (Fig. 6) virus-specific effects were observed. There was no evidence for the SARS-CoV virus-specific effect of com-

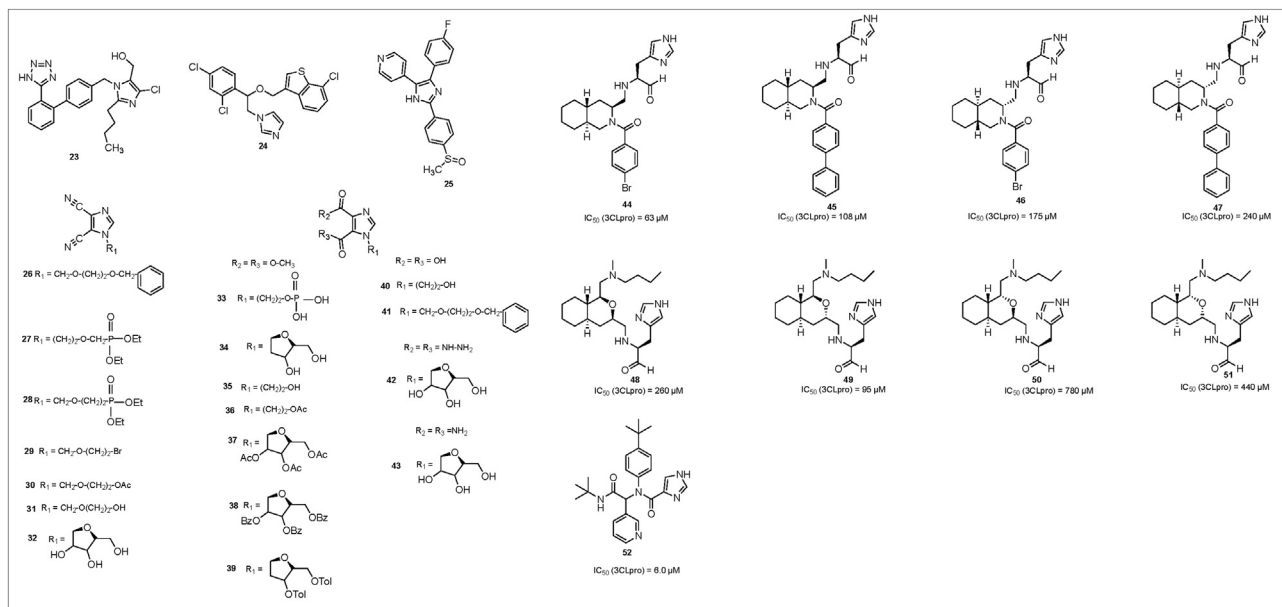


Fig. 6. Imidazole-based as potential SARS-CoV inhibitors [51,80,81,84].

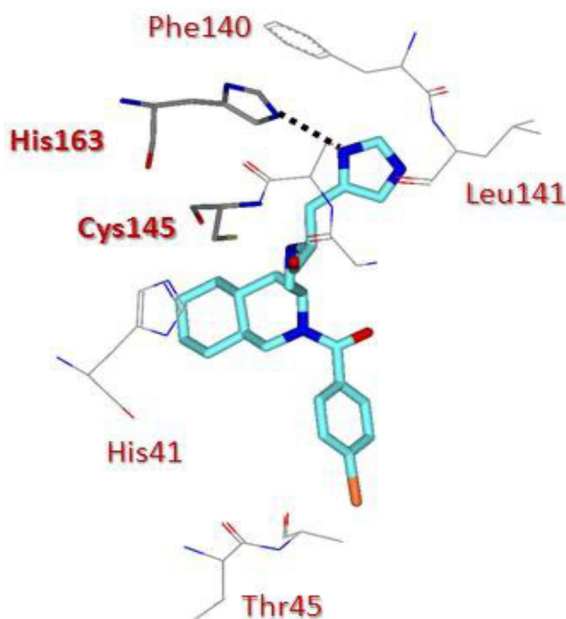


Fig. 7. X-ray crystal structure of compound 44 in SARS-CoV 3CLpro active site (PDB code: 4TWW) [82]

compound 26. The mode of action is speculative and may be different depending on the chemical characteristics of the given compound. Direct inhibition of the virus replication machinery is one possibility. Besides, the analogs might affect cellular pathways of nucleotide metabolism, which could also account for the toxicity associated with some compounds [81]. To investigate the role of the stereochemistry of the decahydroisoquinoline ring as well as different substitutions at the benzamide and imidazole moieties, Shimamoto and co-workers designed compounds 44–47 (Fig. 6). The X-ray structure of 3CLpro in complex with compound 44 inhibitor with IC₅₀ of 63 μ M revealed that the decahydroisoquinoline scaffold gets into the S2 pocket, while the imidazole ring occupied S1 pocket (Fig. 7) [82].

The potential of an octahydroisochromene scaffold as a unique hydrophobic core to interact with the S2 pocket of the protease was investigated. The diastereoisomers (48–51) (Fig. 6) were tested and the results revealed that a specific configuration of compound 49 (1S, 3S), which could guarantee the correct position of the P1 imidazole and the aldehyde moiety within the protease active site. However, it has been demonstrated that the n-butyl chain at 1-position of the fused-ring system was also found to be important for hydrophobic interactions [83].

The compound 52 bearing imidazole showed a potent profile with IC₅₀ of 6.0 μ M [51].

Thiazole

In the literature, among various biological activities, we have also anticoronavirus of compounds containing thiazole ring (compounds 53–85, Fig. 8). They reported that thiazolyl ketone-containing peptidic compounds as severe acute respiratory syndrome coronavirus protease (SARS-CoV 3CLpro) inhibitors with compound 53 as the most potent compound (Ki value of 2.20 μ M and IC₅₀ of 9.5 μ M) [80]. Konno et al. optimized the structure of compound 53 based on molecular docking studies using dimeric chymotrypsin-like proteases. Phenoxy-methyl carbonyl substitution 54 showed a slight activity with an IC₅₀ of 6.8 μ M. 4,5-dimethylthiazole (55) substitution at P1' increased the activity with IC₅₀ of 2 μ M. Benzothiazole substitution (56 and 57) showed four- to five-fold more active with IC₅₀ of 1.7 μ M and 2.3 μ M respectively. These benzothiazoles substituted with electron-donating groups on the phenyl ring of P4 increased the activity (58–65) (Fig. 8) with IC₅₀s of 0.6 μ M. Replacing the phenyl group with pyridinyl 66 at P4 reduced the activity to IC₅₀ of 2.9 μ M. Besides, replacement with phenylamino 67 recovered the activity to IC₅₀ of 1.5 μ M. Increasing the chain length 68 reduced the activity to IC₅₀ of 7.5 μ M. Substitution with polar groups did not increase the activity (69–71) (Fig. 8) IC₅₀s > 1600 μ M, while substitution with hydrophobic chain increased solubility. Cyclic amide at P1 was found to be essential for activity, but its replacement with imidazolyl did not increase the activity (72–74) (Fig. 8) IC₅₀s of 210 μ M to 1600 μ M [84].

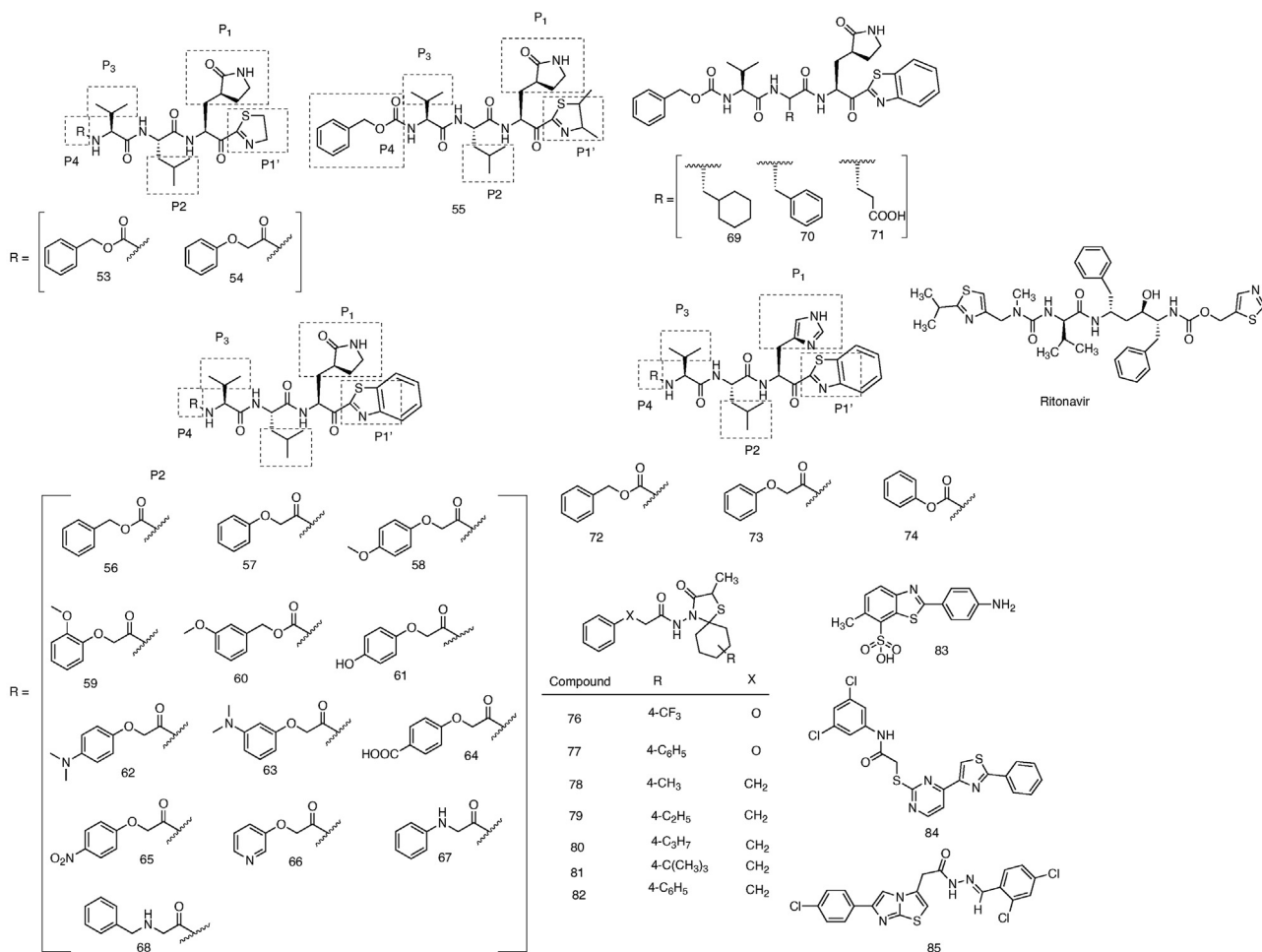


Fig. 8. Thiazole-based as potential coronavirus [51,84,86,87,88].

Apaydin et al. reported the synthesis and evaluation of a series of 1-thia-4-azaspiro [4.5]decan-3-ones against human coronavirus [85]. They showed that seven compounds (**76**, **77**, **78**, **79**, **80**, **81**, and **82**) (Fig. 8) were found to inhibit HCoV-229E replication. The most active compound was compound **81**, with an EC₅₀ of 5.5 μM comparable to the known coronavirus inhibitor, (Z)-N-[3-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-3-phenylprop-1-en-2-yl] benzamide as reference (EC₅₀ = 3.3 μM). The compounds showing activity carrying out all a methyl group at the c-2 position of the azaspiro (4.5) decane scaffold (R₁). For compounds **78**, **79**, **80**, **81**, and **82**, the coronavirus activity depended on the bulkiness of the C-8 substituted of azaspiro (4.5) decane (R). Compounds **78** and **79** showed intermediate activity with EC₅₀ values of 28 and 18 μM, which carry a 4-methyl and 4-ethyl group, respectively. The activity increased with compounds **80**, **81**, and **82** with EC₅₀ values 5.5–8.1 μM, carrying a 4-propyl, 4-tert-butyl, and 4-phenyl group respectively. Compound **83** (Fig. 8) showed a promising potential SARS-CoV 3CLpro inhibitor with IC₅₀ of 4.3 μM with significant selectivity over four proteases (HAV 3Cpro, NS3pro, chymotrypsin, and papain) [86]. Tsai and co-workers used structure-based virtual screening to identify novel SARS-CoV 3CLpro inhibitors. The best performing derivative is shown with compound **84** with IC₅₀ value of 3 μM [87]. Zhang et al. exhibited close interactions between SARS-CoV main proteinase and inhibitors (Table 2). The results showed that for ritonavir, the thiazole group (P1) and benzene group (P2) are inserted into S1 and S2 specificity pockets, while another benzene side chain (P3) might be too long to fit the substrate-binding pocket perfectly (Fig. 9) [88]. Ulusoy et al. evaluated a series of aryl-

Table 2

Binding pockets for SARS-CoV main proteinase with Ritonavir.

Ritonavir	
GLN 19	SER 123
VAL 20	PHE 140
THR 21	LEU 141
CYS 22	ASN 142
GLY 23	GLY 143
THR 24	SER 144
THR 25	CYS 145
THR 26	GLY 146
LEU 27	SER 147
ASN 28	HIS 163
PRO 39	HIS 164
ARG 40	MET 165
HIS 41	GLU 166
VAL 42	LEU 167
ILE 43	PRO 168
CYS 44	VAL 171
MET 49	HIS 172
LEU50	ALA 173
ASN51	GLY 174
PRO52	PHE 181
ASN 53	PHE 185
TYR 54	VAL 186
LEU 57	ASP 187
CYS 117	ARG 188
TYR 118	GLN 189
ASN 119	THR 190
GLY 120	ALA 191
SER 121	GLN 192
	ALA 193

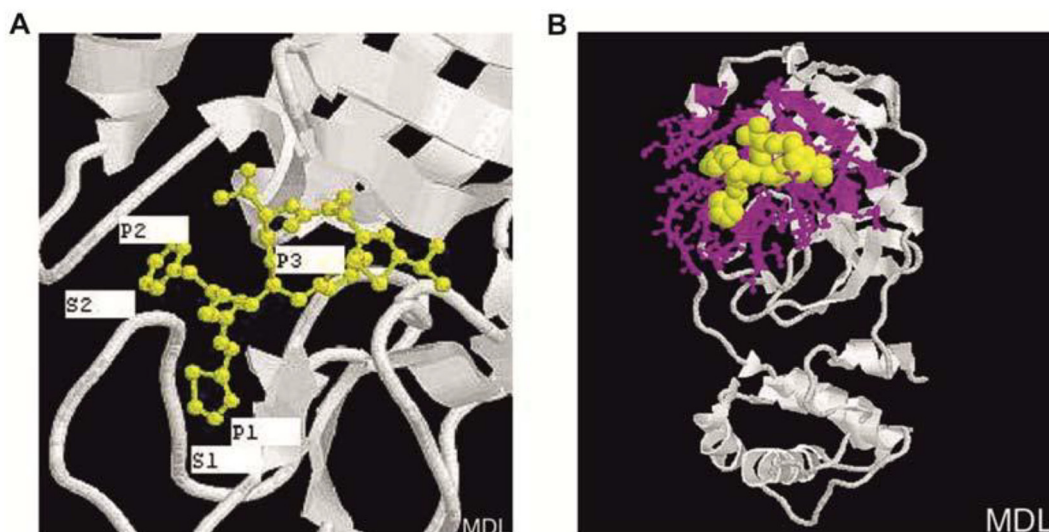


Fig. 9. A) a close view of the interactions between SARS-associated coronavirus main protease (white cartoon) with ritonavir (yellow-ball stick). B) The binding pockets (pink-ball stick) of SARS-associated coronavirus main protease with ritonavir (yellow space fill) [88].

dene hydrazide derivatives bearing imidazo[2,1-*b*]thiazole moieties. Results revealed that some compounds like compound 85 (Fig. 8) was the most active compound and inhibited FCoV with EC_{50} of 7.5 μ M [89].

Conclusion

This review was carried out to identify potential anti-SARS-CoV drug candidates from a known drug containing triazole, imidazole, and thiazole. The drug candidates presented in this study are not thorough and could be further broadened and examined for anti-coronavirus activity. Combinations of experimental tests and structure-based docking simulations are used to identify therapies for viral infections. In some cases, the mechanism of action depends on the heterocycle

scaffold. Mode of action of different compounds could be used as a basis for improving their properties and for developing and proposing specific anti-SARS-CoV-2 drugs.

CRediT authorship contribution statement

Insa Seck: Conceptualization, Investigation, Writing - original draft. **Filomain Nguemo:** Investigation, Supervision, Validation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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