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Review article

Potential RNA-dependent RNA polymerase (RdRp) inhibitors as prospective drug candidates for SARS-CoV-2

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ABSTRACT

The SARS-CoV-2 pandemic is considered as one of the most disastrous pandemics for human health and the world economy. RNA-dependent RNA polymerase (RdRp) is one of the key enzymes that control viral replication. RdRp is an attractive and promising therapeutic target for the treatment of SARS-CoV-2 disease. It has attracted much interest of medicinal chemists, especially after the approval of Remdesivir. This study highlights the most promising SARS-CoV-2 RdRp repurposed drugs in addition to natural and synthetic agents. Although many in silico predicted agents have been developed, the lack of in vitro and in vivo experimental data has hindered their application in drug discovery programs.

1. Introduction

Infectious diseases are still one of the major public health challenges. Diverse microorganisms including viruses, bacteria, fungi, and parasites are the main cause of infectious diseases [1]. Many epidemics and pandemics due to HIV/AIDS, avian flu, swine flu, Ebola, Zika, SARS-CoV-2, and monkeypox viruses have occurred in the last few decades [2,3]. The entire global population is still suffering from emergent and recurring infectious diseases caused by many microorganisms [4]. About two years ago, the WHO (World Health Organization) announced COVID-19 (coronavirus disease 2019) as a public health concern (March 11, 2020) due to the widespread global impact of an infectious SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) parasite. More than 6.6 million deaths and 639 million infected patients have been reported till the beginning of December 2022 [5,6]. The first identified case of SARS-CoV-2 was reported in the local fish and wild animal market in Wuhan City, China [7]. SARS-CoV-2 is a RNA zoonotic virus (family: *Coronaviridae*, order: *Nidovirales*, genus: *Betacoronavirus*). It is mainly found in bats. After this virus was transferred to humans in China, it then widely spread to all other countries, leading to a global pandemic [8–10]. Four genera (α, β, δ, and ϒ) of coronavirus are known [11]. Several waves of SARS-CoV-2 infections have been recognized due to viral mutations. The most important variants of the virus are Beta, Gamma, Delta, and Omicron variants. The new Omicron variant indicates that the epidemic/pandemic is far from its end due to its efficient human-to-human transmission [12]. The main symptoms due to the infection from this variant are fever, dry cough, diarrhea, and shortness of breath besides blood clotting and stroke in severe conditions [10,13]. Repurposed drugs and vaccination substantially helped to overcome the pandemic and retain the socioeconomic status and human life to normal [14].

SARS-CoV-2 belongs to a positive-sense single-stranded RNA viral group (ssRNA(+)). It can infect humans and largely spreads through close contact and by breathing droplets generated by coughing/sneezing. Its genetic material can directly act as a viral messenger RNA (mRNA) and translate into viral proteins in the host cell [15–17]. Several enzymes are involved in coronaviral replication. Thus, targeting these enzymes in drug discovery efforts might lead to promising antiviral drugs [18]. The SARS-CoV-2 nonstructural proteins including RNA-dependent RNA polymerase (RdRp) and main protease (M^{pro}) are crucial for viral genomic transcription and replication [17,19]. The crystal structures of both RdRP and M^{pro} are available in the Protein Data Bank (PDB) [20–22].

The enzyme RdRp is encoded in all RNA viruses. Viral RdRp is the main target for developing potent antiviral agents against SARS-CoV-2, not only due to its ability to accelerate the replication of RNA but also

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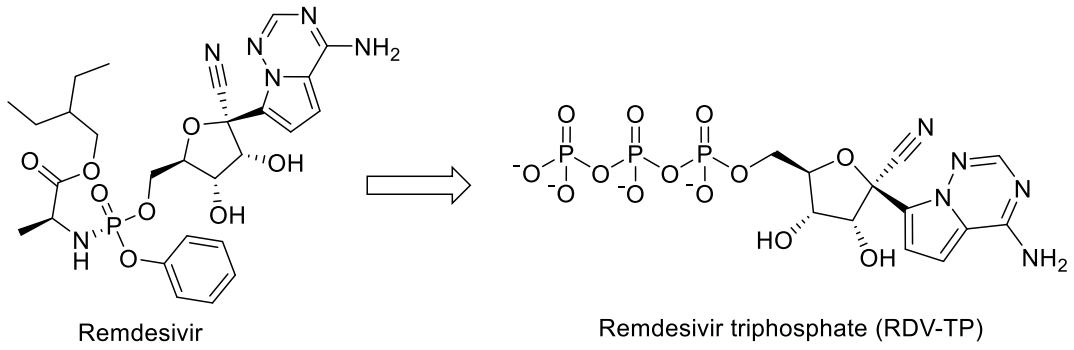


Fig. 1. Strucure of Remdesivir prodrug and its active triphosphate derivatives (RDV-TP).

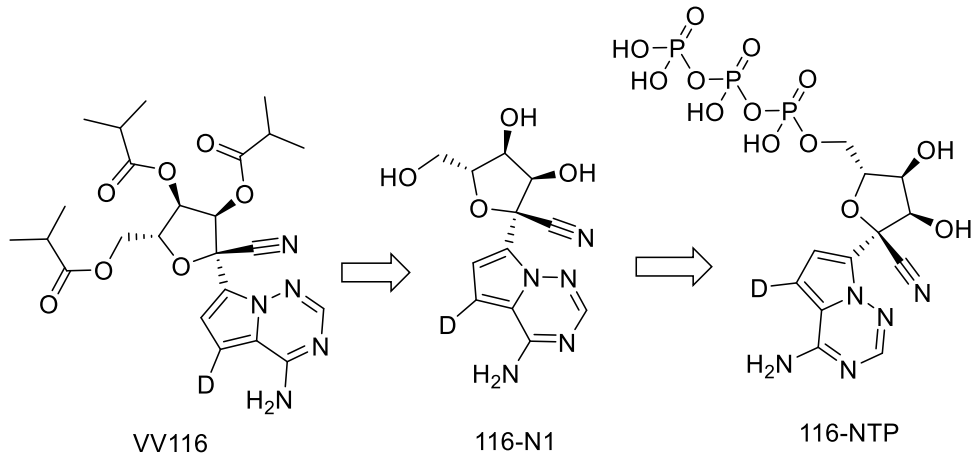


Fig. 2. Structures of W116, 116-N1 and 116-NTP.

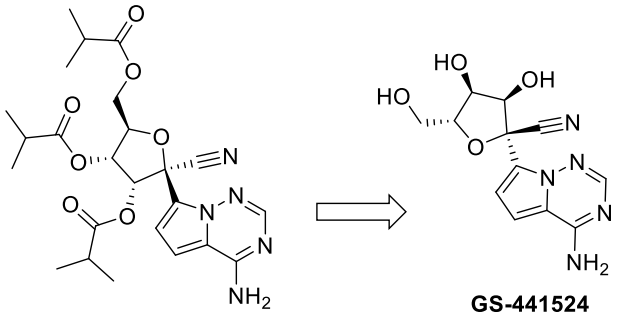


Fig. 3. Structures of GS-621763 and GS-441524.

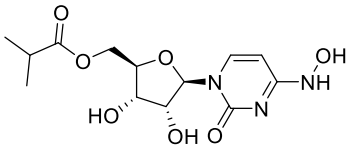


Fig. 5. Molnupiravir, COVID-19 therapeutical agent.

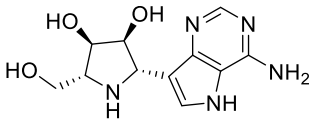


Fig. 6. Galidesivir(BCX4430) RdRNAp replication inhibitor.

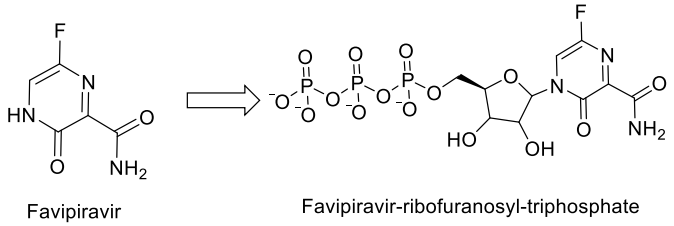


Fig. 4. Structures of Favipiravir and its ribofuranosyl-triphosphate analogue.

due to the lack of RdRp closely related host cell counterparts. Theoretically, the designed agent will selectively target the viral RdRp with no off-target side effects [23].

RdRp inhibitors are categorized into two classes based on their structure and location for binding to RdRp: nucleoside analog inhibitors (NIs) and non-nucleoside analog inhibitors (NNIs). Structurally, NIs are known to bind the RdRp protein at the enzyme active site, NNIs bind to the allosteric sites of RdRp. Several studies on RdRp inhibitors with various applications have been reported. Tian et al. reported a recent review for RdRp inhibitors however, most of the mentioned analogs are for pyrimidine-containing compounds (either NIs and NNIs) [24]. This current review adopts wider scope summarizing the natural and synthetic compounds as well as the repurposed drugs/active agents with RdRp inhibitory properties for treating SARS-CoV-2, with various heterocyclic scaffolds. Notably, the screening techniques for coronavirus RdRp are not as simple as those for proteases [25]. With increasing interest, a few studies on RdRp screening for coronavirus have been reported.

Table 1
The anti-SARS-CoV-2 properties of Galidesivir against different cell cultures.

Cell line	SARS-CoV-2 strains	Assay	Incubation period	EC_{50} (μM)	EC_{90} (μM)	CC50 (μM)	SI
Caco-2	WA1/2020	VYR[a]	24 h	n.d.[b]	14.19	82.8	5.8
Vero-76	WA1/2020	VYR[a]	24 h	n.d.[b]	10.94	>295.7	>27
		CPE[c]			50.3		5.8
Calu-3	WA1/2020	Imaging	2 h	14.15	n.d.	>50	>3.5

[a] VYR = Viral Yield Reduction.
[b] n.d. = not determined.
[c] CPE = cytopathic effect.

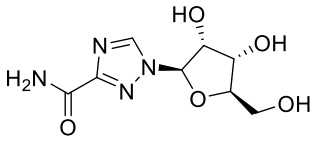


Fig. 7. Ribavirin, a broad spectrum antiviral agent.

2. Drug repurposing

Development of new drug(s) usually involves many successive stages which are: design, synthesis, bio-properties investigation, formulation of prototypes, and pre-clinical and clinical trials. Due to the pandemic outbreak, drug repurposing is considered the most accessible and appealing approach for urgent identifying potential therapeutics to control the disaster and save human lives. Drug repurposing means the adoption of an existing broad-spectrum therapeutical entity of potential efficacy and minimal adverse effects for clinical application of the infected patients supported by pre-clinical establishments. Drug repurposing strategy is superior to traditional drug discovery in terms of cost and time reduction. In addition to a lower failure rate compared with the traditional approaches owing to its well-established efficacy, metabolic characteristics, dose determination, and safety or toxicity issues [26–28]. FDA (food and drug administration) approved several drugs of other pathophysiological under the emergency use authorization of which antiviral drugs (remdesivir, penciclovir and favipiravir) and antimalarial drugs (chloroquine, hydroxychloroquine) as anti-COVID-19 agents. Meanwhile, adverse effects humbled the clinical applicability of some of them [29–31].

2.1. Remdesivir (RDV, formerly GS-5734)

Yin et al. investigated the inhibition of the RdRp from SARS-CoV-2 by remdesivir. The complex structure of SARS-CoV-2 RdRp and remdesivir reveals that the partial double-stranded RNA template is inserted into the central channel of the RdRp, where remdesivir is covalently incorporated into the primer strand at the first replicated base pair and terminates chain elongation [32]. Remdesivir (RDV) is the first FDA-authorized drug to treat COVID-19 patients with severe conditions (on Oct. 22, 2020) [33,34]. Remdesivir is a phosphoramidite prodrug of a 1′-cyano-substituted adenosine nucleotide analog, which acts as an RNA polymerase inhibitor (regulate genomic replication) developed initially by Gilead Sciences for Ebola viral infections treatment in 2014 [35]. It has been mentioned as a broad-spectrum antiviral property against various acute viral infections caused by different ssRNA viruses including Hendra virus, Lassa fever virus, Junin virus, Nipah virus, and coronaviruses (SARS-CoV and MERS-CoV) in addition to the efficacy in the therapeutical composition against HCV (hepatitis C virus) and HIV (human immunodeficiency virus) [36–38]. Remdesivir is the first candidate as an anti-COVID-19 drug owing to its broad spectrum as an antiviral agent, especially on coronaviruses (SARS-CoV and MERS-CoV), this encourages Gilead Sciences to repurpose it to treat patients infected with SARS-CoV-2 and approved by FDA in 2020 for treatment patient with COVID-19 infection [34,39].

The broad-spectrum antiviral properties of Remdesivir are attributed to its ability to be metabolized in the host cell as nucleoside triphosphate (RDV-TP). Consequently, it can be integrated within the nascent viral

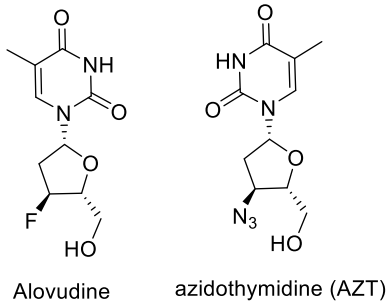


Fig. 9. Structural of Alovudine and azidothymidine (AZT).

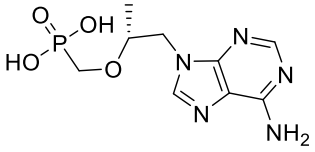


Fig. 10. Structure of tenofovir.

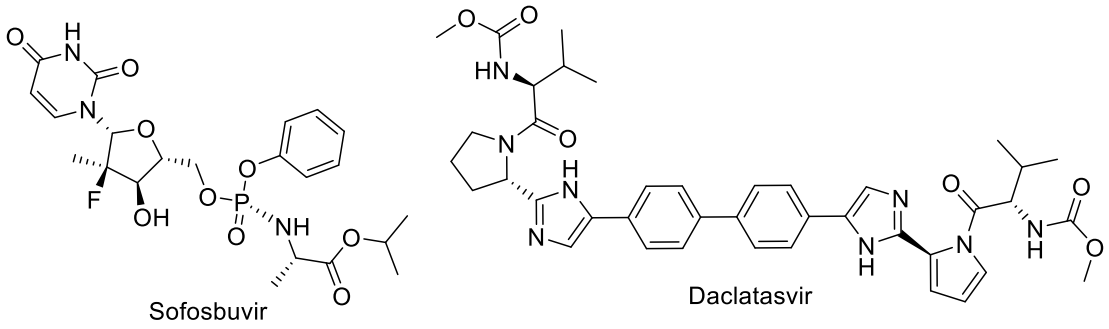


Fig. 8. Sofosbuvir and, Daclatasvir, repurposed drugs fir COVID-19.

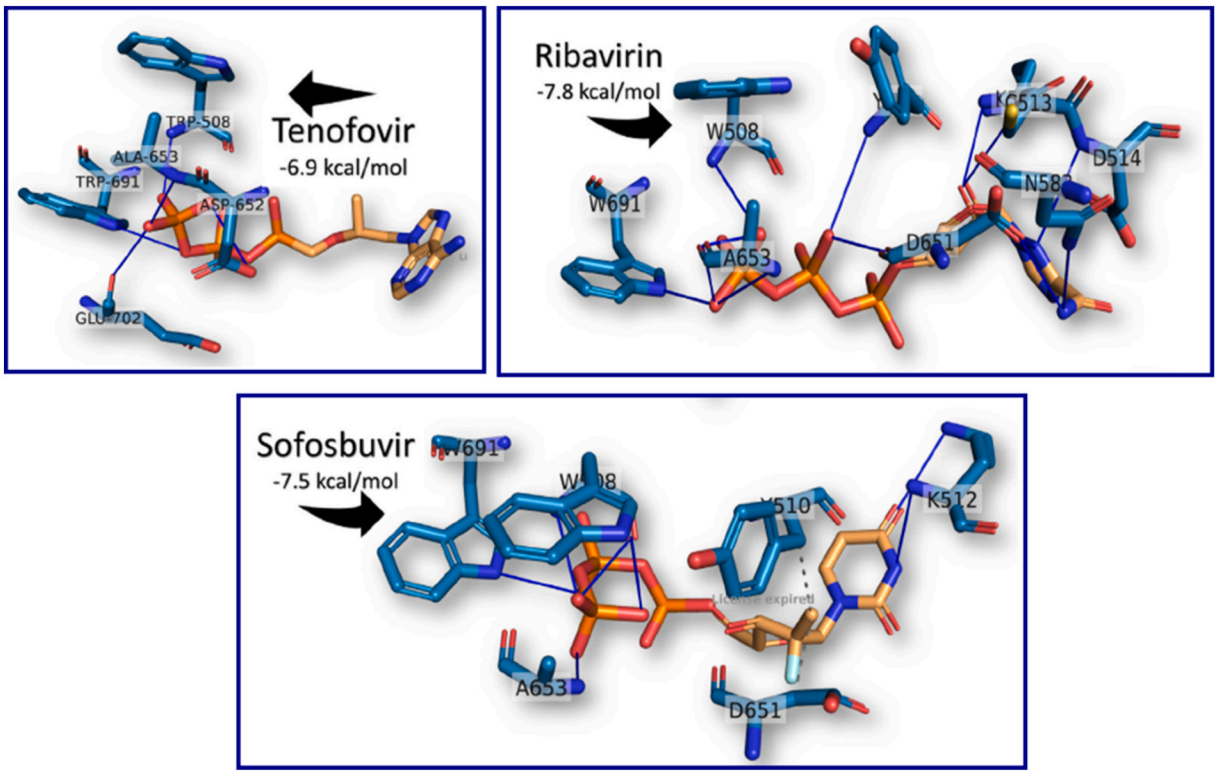


Fig. 11. Docking poses of Tenofovir, Ribavirin and Sofosbuvir in SARS HCoV RdRp (PDB ID: 6NUR), using AutoDock Vina software [80].

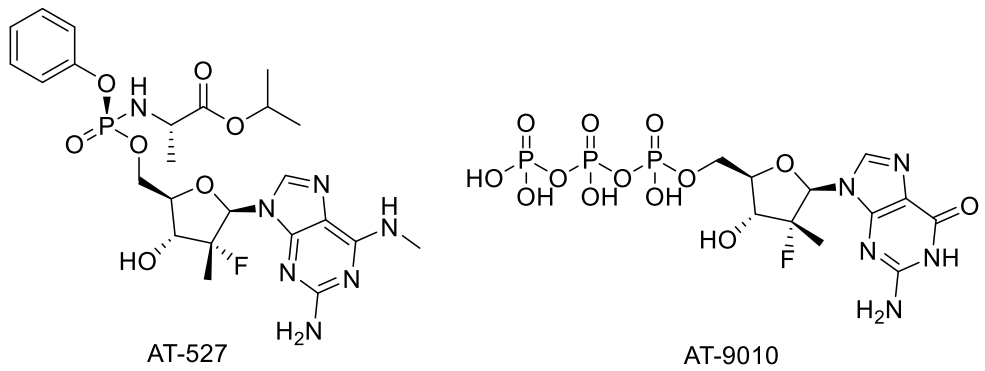


Fig. 12. Structures of AT-527 and AT-9010.

RNA chains due to the RdRp action. Thus, viral RNA synthesis is terminated (Fig. 1) [34,40]. In the VERO-E6 assay, the EC_{50} of Remdesivir is 0.77 μM, and the CC_{50} = >100 μM (SI, selectivity index = >129.87) [41].

To improve the $t_{1/2}$ and in-vivo metabolism of the Remdesivir, Wen et al. replaced the hydrogen in the active molecular group with isotope deuterium as the carbon-deuterium bonds (C–D) are more stable than carbon-hydrogen bonds(C–H) [24,42,43].

New oral RDV derivatives were found to demonstrate SARS-CoV-2 RdRp inhibitors such as VV116 and GS-621763. VV116 (JT001) is a tri-isobutyrate ester RDV prodrug derivative. VV116 is rapidly metabolized into the parent nucleoside (116-N1) in vivo which is intracellularly converted to the active form nucleoside triphosphate that incorporates with RdRp, thus inhibiting SARS-CoV-2 replication [44] (Fig. 2). VV116 exhibited potent activity against a panel of SARS-CoV-2 variants [45,46] with satisfactory safety in phase I studies [44].

Another oral RDV derivative is GS-621763 metabolized in plasma to GS-441524 (Fig. 3). In the lung the triphosphate effectively controls the SARS-CoV2 replication. Both metabolites GS-621763 and GS-441524 possess anti-SARS-CoV-2 properties against different variants. Viral proliferation was completely terminated by oral GS-621763 [47].

2.2. *Favipiravir*

Another nucleotide analog inhibitor of RdRp is Favipiravir (FPV, favilavi, or Avigan). Favipiravir was originally developed by Toyama Chemicals, Japan, and approved as anti-influenza in 2014 in Japan [48,49]. Favipiravir is a RdRp inhibitor that has demonstrated antiviral activity against influenza virus H1N1 infection [48]. During the Ebola virus outbreak in West Africa, Favipiravir has been evaluated against human Ebola virus infection. It reveals a promising activity against Ebola virus infection in the mouse model however, poor activity was observed in human Ebola infections [50].

Favipiravir showed effectiveness in controlling the progression of the SARS-COV-2 virus. Patients with mild COVID-19 had a potential clinical recovery rate [51]. While treating severe COVID-19 patients with Favipiravir, an improvement in the lymphocyte count was recorded [52]. Therefore, the clinical tackle was recommended for

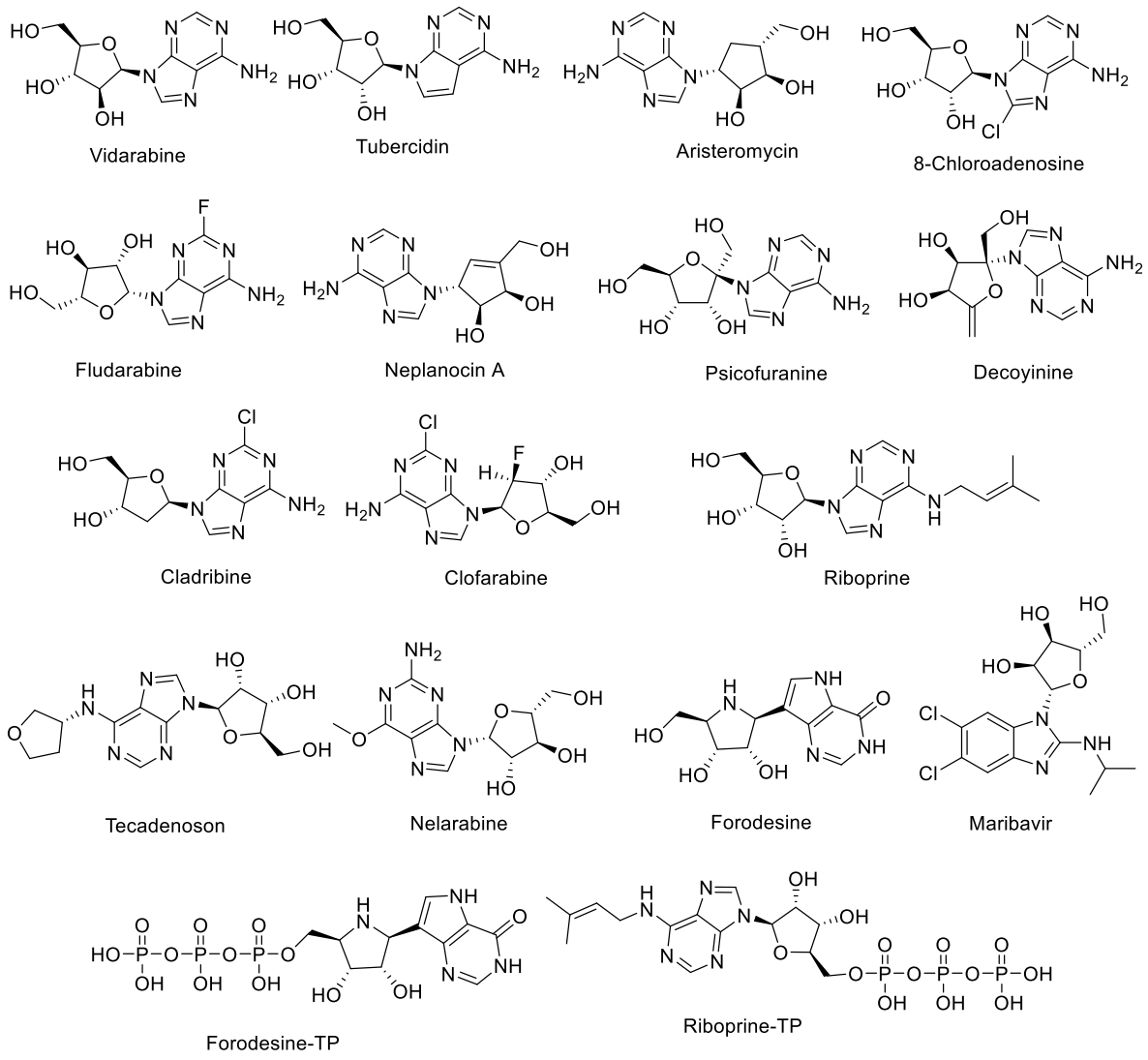


Fig. 13. Strucure of promising nucleosides as anti-RdRNAP, anti-ExoN, and anti-SARS-CoV-2 relative to Riboprine-TP and Forodesine-TP.

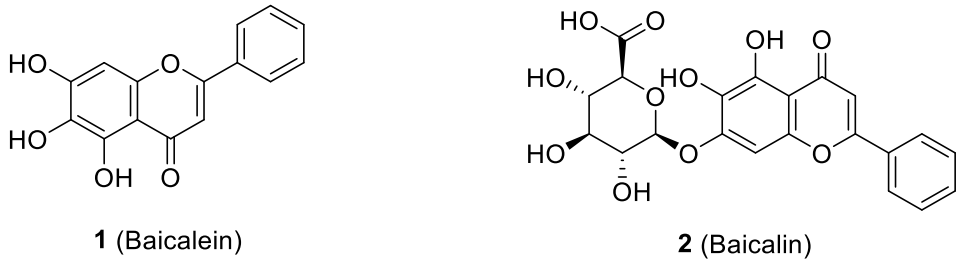


Fig. 14. Baicalein (1) and Baicalin (2) polyphenolic flavonoids of potential anti-SARS-CoV-2 RdRp.

mild-to-moderate COVID-19 patients with Favipiravir [53].

Favipiravir (pro-drug) metabolized in the body to the active favipiravir-ribofuranosyl-5′-triphosphate (FPV-RTP) via ribosylation and phosphorylation which binds to the active site of the viral RdRp thus terminates the replication of viral RNA (Fig. 4) [54]. In Vero-E6 assay, Favipiravir reveals $EC_{50} = 61.88$ and $CC_{50} = >400$ μM (SI = 6.46) [41].

2.3. Molnupiravir

Molnupiravir (EIDD-1931 or NHC) is the isopropyl ester pro-drug of the ribonucleoside analog β-D-N4-hydroxycytidine [55]. It can inhibit SARS-CoV-2 replication in human airway epithelial cell cultures and various animal models [56,57]. Clinical trial studies supported the effectiveness of Molnupiravir against SARS-CoV-2 relative to Placebo (inert medication with no therapeutical value) [58]. Molnupiravir was granted emergency use authorization by FDA and MRHA (medicines and healthcare products regulatory agency) for the treatment COVID-19 patients (Fig. 5) [59].

The inhibitory mechanism of Molnupiravir is quite similar to that of Favipiravir. The oral administration of molnupiravir rapidly appears in plasma and is converted to its triphosphate form in cells. The active NHC triphosphate form is incorporated into viral RNA in place of cytosine or

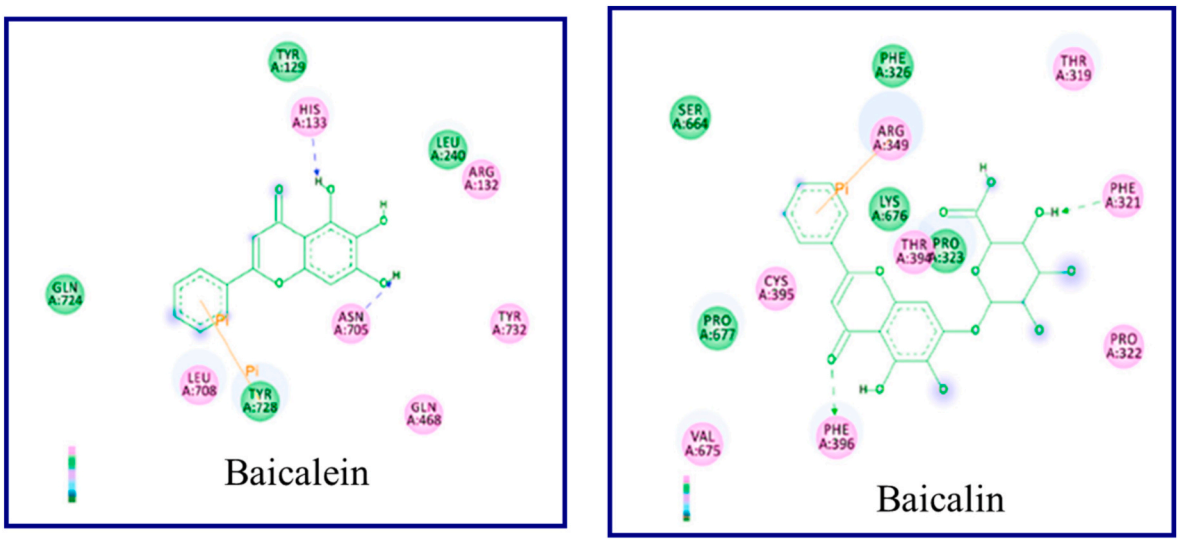


Fig. 15. Baicalein and baicalin in the active site of PDB, ID: 6XQB [99].

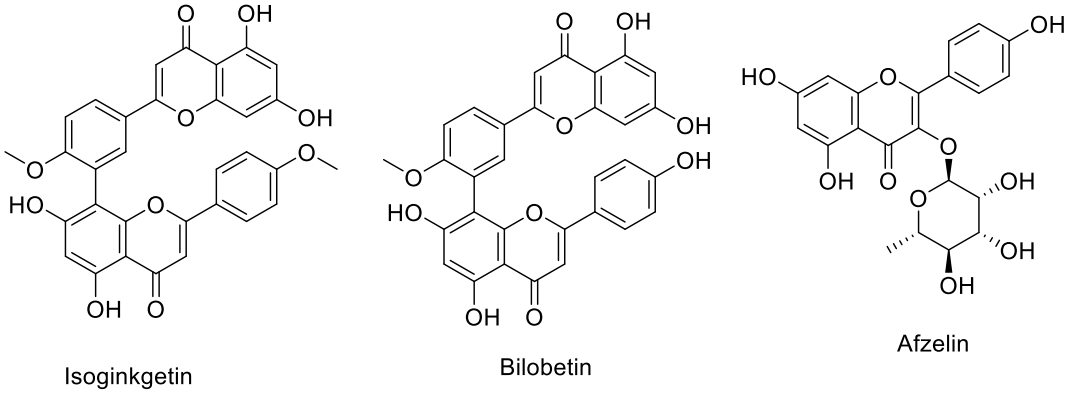


Fig. 16. Strucures for Isoginkgetin, Bilobetin and, Afzelin.

uracil by RdRp, causing a break of viral replication [56,60,61]. The IC_{50} = 1.965, 0.7556 μM of Molnupiravir are against WT and Omicron SARS-CoV-2 variants, respectively in Calu-3 cells [62].

2.4. Galidesivir

Galidesivir (BCX4430) (Fig. 6) is an adenosine analog with RdRp replication inhibitory activities against many RNA viruses including Ebola, Zika, Marburg, and yellow fever (in vitro and in animal models) [63,64]. In Syrian golden hamster models, it was tested as anti-SARS-CoV-2 reducing the lung pathology upon the treatment initiated 24 h before the viral infection, compared with untreated controls [65]. The Galidesivir triphosphate is the active substrate responsible for binding to the active site of the viral RdRp and terminates the replication of viral RNA [66]. Table 1 exhibits the anti-SARS-CoV-2 activity of Galidesivir in different cell cultures [65].

2.5. Ribavirin

Ribavirin (RBV,1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a guanosine analog (Fig. 7). Ribavirin has a broad antiviral spectrum against in vitro human cell line and several animal models [67]. It was repurposed to treat COVID-19, and reflected a promising activity against SARS-CoV-2 [68,69]. RBV was reported to have a high survival rate in severe patients due to its ability for viral clearance (observational study) [70]. Another clinical trial (Phase II) demonstrated that a combination of RBV, interferon beta-1b, and lopinavir-ritonavir, is a potential treatment for mild to moderate COVID-19 patients [71]. Hemolytic anemia in addition to the reduction of calcium and magnesium in the elder besides the restriction for pregnant women are the serious adverse effects of RBV [72]. The active substrate RBV triphosphate (RBV-TP) is formed via the host cell kinases, which pairs with the uridine triphosphate or cytidine triphosphate in the RNA template resulting in lethal mutagenesis and so prevents viral RNA replication [73]. The EC_{50} = 7.1, CC_{50} = 160 μM (SI = 16) are of Ribavirin in Calu-3 assay [74].

2.6. Sofosbuvir and daclatasvir

The replication process of HCV is similar to that of coronavirus, especially at the start of the disease. Anti-HCV therapies such as Sofosbuvir (HCV polymerase inhibitor) [75] and Daclatasvir (RNA replication and virion assembly inhibitor) [76] were suggested to have promising potential in the treatment of COVID-19 (Fig. 8) [74]. Randomized clinical trials on moderate or severe COVID-19 patients demonstrated that sofosbuvir and daclatasvir reducing the hospital stay duration relative to the standard care alone. This is attributed to the daclatasvir/sofosbuvir antiviral efficacy on SARS-CoV-2 replication in respiratory cells [74,77]. The EC_{50} = 7.3, 1.1 and CC_{50} = 512, 38 μM are for Sofosbuvir and Daclatasvir, respectively in Calu-3 assay [74].

Alovudine and AZT which are nucleotide-related structures to Sofosbuvir (2′-fluoro-2′-methyl-UTP) were investigated as anti-SARS-CoV RdRp-inhibitors (Fig. 9). They terminate RNA synthesis and

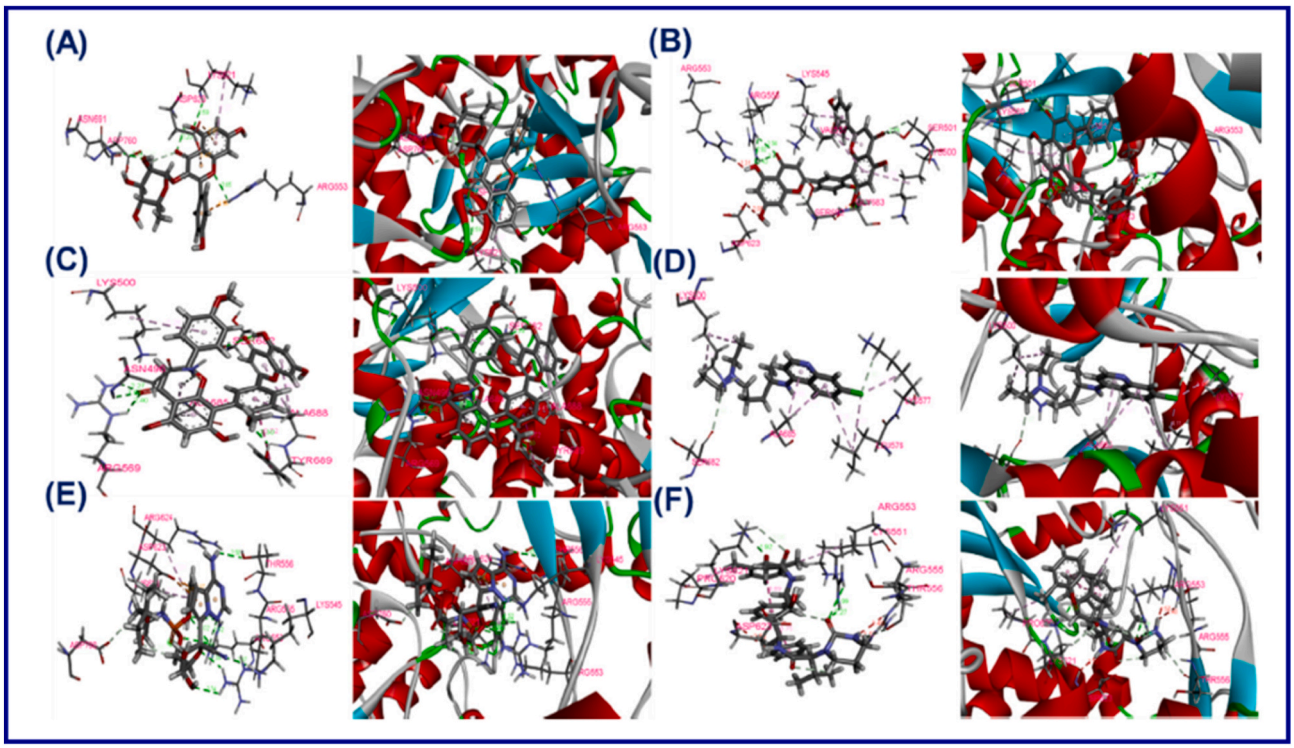


Fig. 17. 3D-conformations of (A) afzelin, (B) bilobetin, (C) isoginkgetin, (D) chloroquine, (E) remdesivir, and (F) lopinavir in PDB: 6 M71 [100].

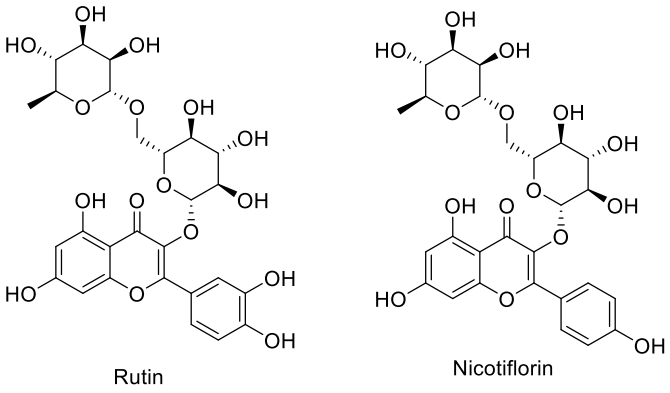


Fig. 18. Rutin and Nicotiflorin, promising anti-SARS-CoV-2 based on in silico studies.

replication of the virus in model polymerase extension experiments [78].

2.7. Tenofovir

Tenofovir is a broad-spectrum antiviral drug active against the HIV and hepatitis B virus (HBV). The active triphosphate form of the tenofovir diphosphate acts as a terminator of viral RNA subsequent polymerase synthesis (Fig. 10) [79,80]. Few in vitro studies on tenofovir or its prodrug formulations have been reported. The results are not promising and are contradictory [81,82]. Although these reports, in silico studies mentioned that tenofovir binds strongly to SARS-CoV-2 RdRp, with binding energies close to other successful drugs (Remdesivir, Galidesivir, Ribavirin, and Sofosbuvir) with no supporting biochemical observations (Fig. 11) [83].

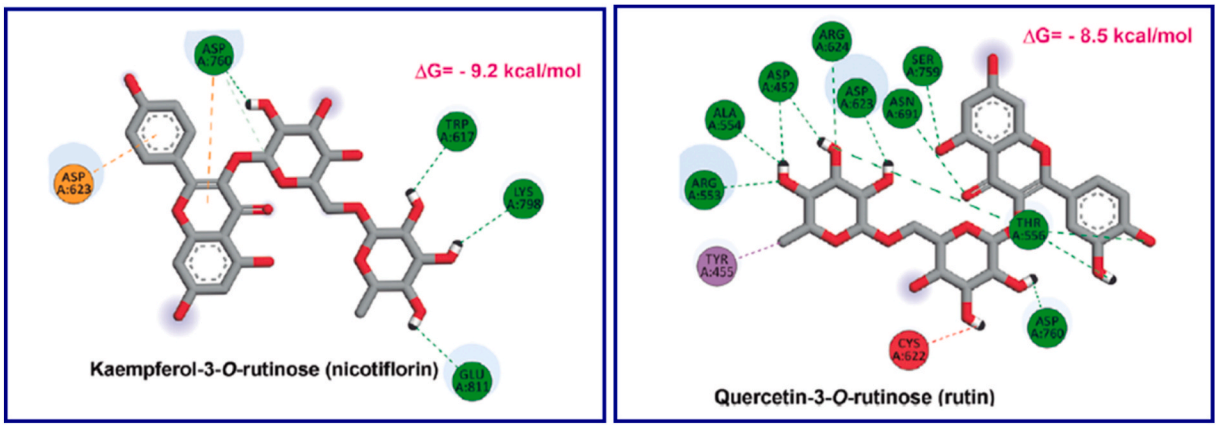


Fig. 19. Nicotiflorin and rutin in the active site of PDB: 6M71 [101].

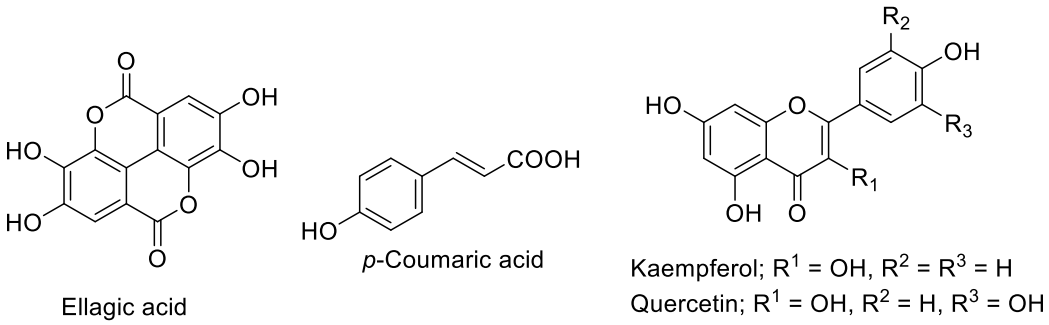


Fig. 20. Ellagic acid, p-Coumaric acid, Kaempferol, and Quercetin, promising anti- SARS-CoV-2 supported by in silico studies.

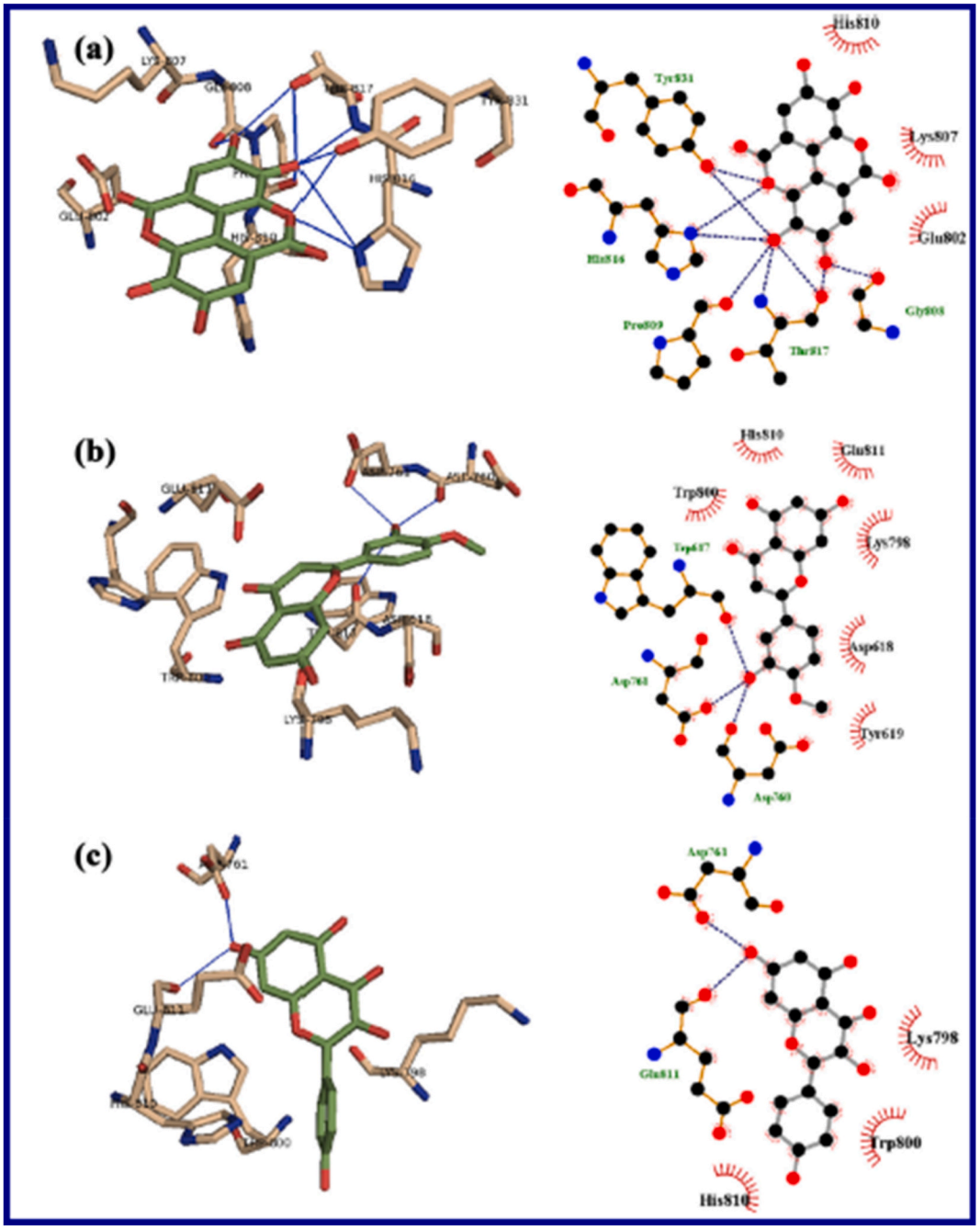
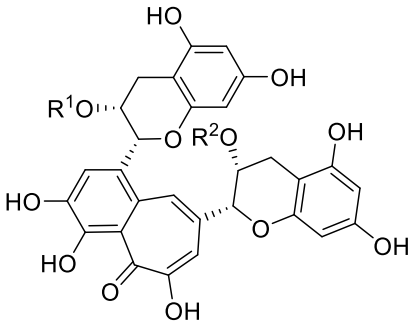


Fig. 21. Docking confirmations of (a) ellagic acid, (b) hesperetin, and (c) kaempferol in PDB: 6M71 [103].



Theaflavin, $R^1 = R^2 = H$

Theaflavin-3,3'-di-O-gallate, $R^1 = R^2$ = galloyl

Fig. 22. Theaflavin and theaflavin-3,3′-di-O-gallate.

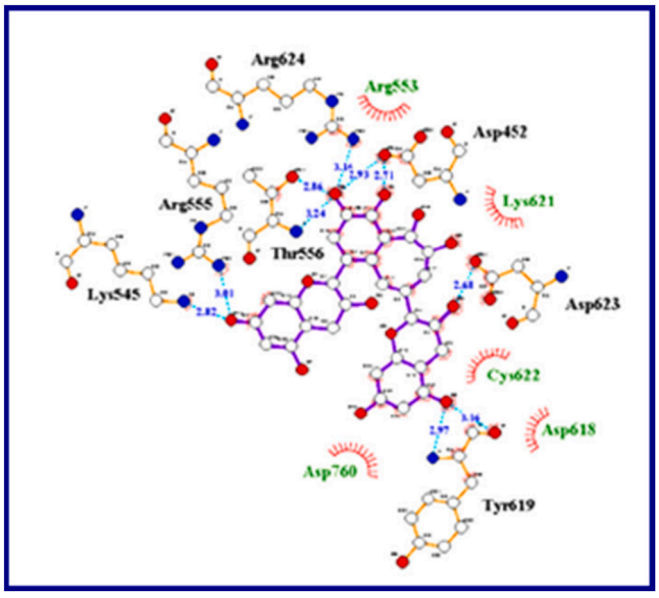


Fig. 23. 2D-interaction diagram of Theaflavin and SARS-CoV-2 RdRp by the Blind Dock server [106].

2.8. AT-527

AT-527 is an orally available prodrug of a guanosine nucleotide analog that acts as a potent broad-spectrum anti-coronavirus inhibitor in a variety of cell lines by targeting the RdRp activity (Fig. 12) [84]. AT-527 is converted by cellular enzymes to the active triphosphate metabolite, AT-9010. AT-527 recently entered phase III clinical trials to treat COVID-19 [85]. AT-9010 can bind to the active site of RdRp exhibiting promising efficacy against COVID-19 [86].

Nucleoside analogs were used in searching for potent anti-SARS-CoV-2 inhibitors with both SARS-CoV-2-RdRp and SARS-CoV-2 exonuclease (ExoN) dual inhibitory enzyme effects as a strategy to combat COVID-19 [87]. Based on the pharmacodynamic/pharmacokinetic results and predicted anti-SARS-CoV-2 activities, analogs were selected for docking studies (Fig. 13). Blind docking was performed via MOE (molecular operating environment) software using SARS-CoV-2 RdRp (PDB, ID: 7BV2) and ExoN (PDB, ID: 7MC6) proteins from PDB (protein data bank). The molecular docking results revealed that some of the compounds were with promising binding energies in both enzymes relative to Riboprine-TP and Forodesine-TP (triphosphates). The assumptions were supported by in vitro testing as anti-RdRp, anti-ExoN, and anti-SARS-CoV-2 [88].

3. Natural RdRp inhibitors

Natural isolate compounds have a significant impact on drug development and pharmacotherapy due to their tremendous structural, and chemical variety, and relatively low toxicity. Numerous natural products were discovered to have medicinal potential, including morphine, quinine, paclitaxel, penicillin, lovastatin, and doxorubicin. Natural compounds were and still are one of the major sources for new medications, with an estimated 34% of approved new chemical entities between 2000 and 2014 coming from natural compounds isolated from plants, microorganisms, and other resources. Many analogs of potential bio-properties are mimicked based on the chemical scaffold of promising natural biologically active entities [89–91]. A famous example is Artemisinin, one of the recent naturally isolate compounds with high potential as anti-malarial (*Plasmodium falciparum*) properties described by Tu Youyou (Noble Prize winner in 2015). Artemisinin is extracted from the plant *Artemisia annua* (sweet wormwood, a herb used in traditional medicine in Chinese) [92]. Several review articles reported the antiviral properties of some natural isolate compounds [93–95].

3.1. Benzopyrans

Flavonoids and their glycosides or their bioisosteres displayed antiviral properties inhibiting different stages of the virus infective cycle (inhibition of viral protease, RNA polymerase, and mRNA). Different reports mentioned the efficacy against some RNA viruses (SARS-CoV, MERS-CoV, and influenza A virus) [96–98].

Zandi et al. reported the antiviral properties of baicalein **1** and baicalin **2** (polyphenolic flavonoids accessible in traditional Chinese medicine extracted from *Scutellaria baicalensis* root) against SARS-CoV-2 through cell-based and biochemical studies (Fig. 14). Both compounds inhibited activity against SARS-CoV-2 RdRp with higher efficacy for baicalein than that of baicalin. Antiviral evaluation assay of baicalein and baicalin exhibited 99.8% and 98% inhibition of SARS-CoV-2, respectively (at 20 μM). Baicalein also showed more potency against SARS-CoV-2 relative to baicalin with an $EC_{50} = 4.5$ μM and $EC_{90} = 7.6$ μM. Both compounds also demonstrated anti-SARS-CoV-2 activity when tested in Vero-E6 and human Calu3 cells with safe cytotoxicity ($EC_{50} =$ 4.5, 9.0; 1.2, 8.0; $CC_{50} = 8.6$, >100; 91, >100 μM for baicalein and baicalin in Vero-E6 and Calu3 cells, respectively). In the SARS-CoV-2 RdRp testing of the compounds using Remdesivir-triphosphate (RDV-TP, reference standard), baicalein significantly revealed higher potency against RNA polymerase than that of RDV-TP and baicalin. In silico studies (PDB, ID: 6XQB) using AutoDock Vina 1.5.6 and Discovery Studio 2.5 software showed that both compounds were with higher affinity to SARS-CoV-2 RdRp compared with Remdesivir (Fig. 15) [99].

A series of 4*H*-chromen-4-one containing compounds were subjected to virtual screening studies with the coronavirus main protease (M^{pro}, also called $3CL^{pro}$ "3-chymotrypsin-like cysteine protease", PDB: 6LU7) using AUTO-DOCK and VINA software. The top hits (isoginkgetin, bilobetin, and afzelin molecules, Fig. 16) were subjected to in vitro testing (SARS-CoV-2–infected Vero cell drug screening assay). Isoginkgetin was the most potent active agent discovered with $IC_{50} =$ 22.81 μM, relative to $IC_{50} = 7.18$, 11.63, and 11.49 μM for the standard references Remdesivir, Chloroquine, and Iopinavir, respectively. Isoginkgetin was also docked in RdRp (PDB: 6M71) (Fig. 17). Good binding affinities were noticed in both SARS-CoV-2 M^{pro} and RdRp docking studies supporting its efficacy [100].

In silico studies adopting the docking technique (AutoDock Vina software) of quercetin-3-*O*-rutinoside (rutin) and kaempferol-3-*O*-rutinoside (nicotiflorin) "flavonoid glycosides found in *Dysphania ambrosioides*" in the SARS-CoV-2 M^{PRO} (PDB: 6W63) and RdRp (PDB: 6M71), support the possibility as promising agents against SARS-CoV-2. However, intensive in vitro and in vivo studies are still needed for these assumptions (Figs. 18 and 19) [101].

Similarly, various flavonoids and triterpenes were considered in

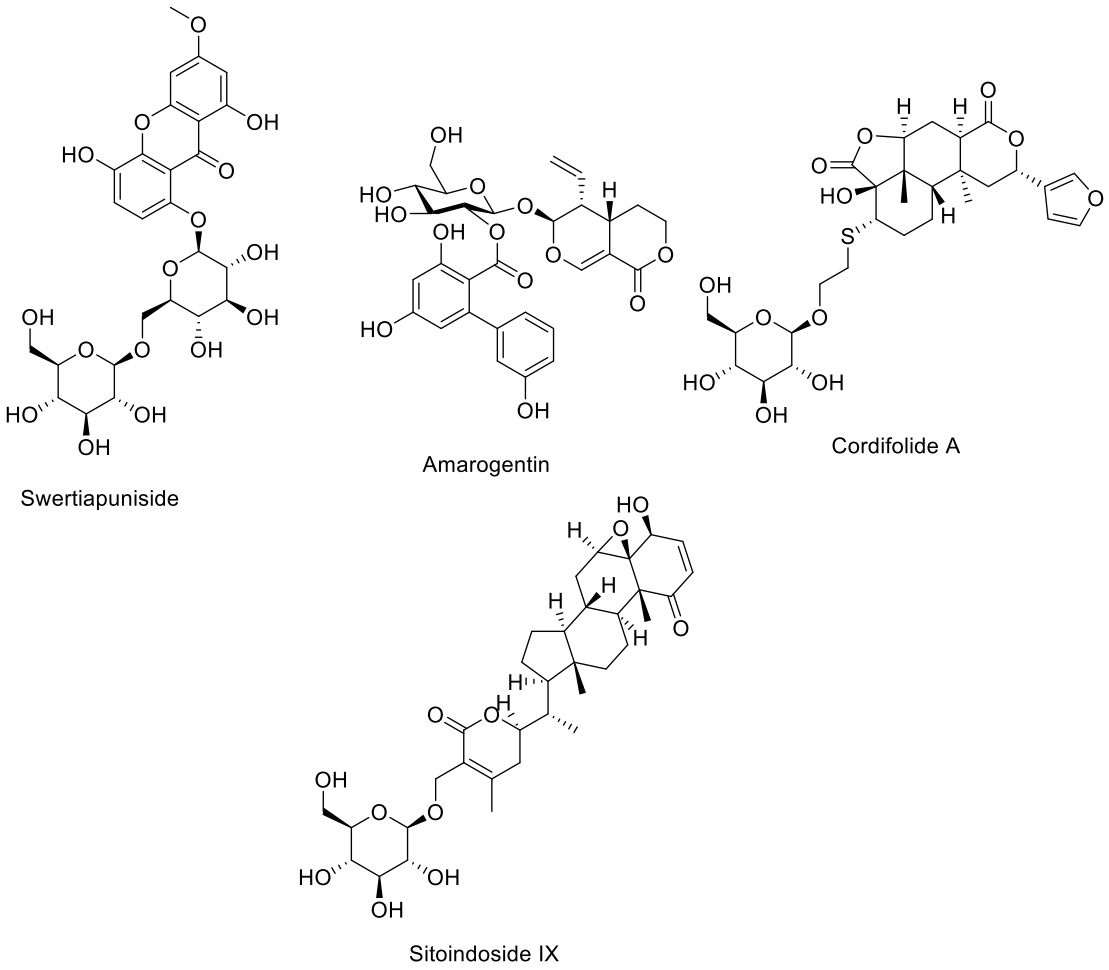


Fig. 24. Phytochemicals from Indian medicinal plants of potential RdRp inhibitors.

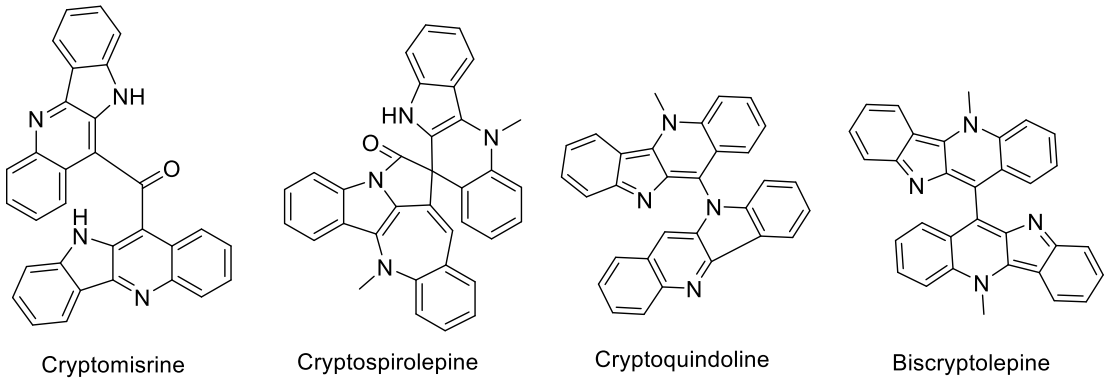


Fig. 25. Cryptomisrine, cryptospirolepine, cryptoquindoline and biscryptolepine of potentional inhibitory properties against MPro and RdRp through in silico studies.

docking studies against RdRp (PDB: 7BV2) utilizing Schrödinger software revealing promising docking scores with no experimental supporting (in vitro/in vivo) observations [102]. Ellagic acid, *p*-Coumaric acid, kaempferol, and quercetin (Fig. 20) were also mentioned as anti-SARS-CoV-2 agents due to docking studies in M^{pro} (PDB: 6LU7) and RdRp (PDB: 6M71) utilizing AutoDock Vina software (Fig. 21) [103].

Theaflavin extracted from *Camellia sinensin*, is a polyphenolic compound found in black tea with a considerable medicinal value useable in Chinese traditional medicine (Fig. 22). Theaflavin and theaflavin gallate derivatives exhibit broad-spectrum antiviral properties against several viruses, influenza A and B and hepatitis C virus [104,105]. In silico studies utilizing theaflavin revealed promising efficacy against RdRp of SARS-CoV-2. Similar observations were also noticed for SARS-CoV, and MERS-CoV, using the UCSF Chimera and SWISS-MODEL (Fig. 23) [106].

In-silico studies, including molecular docking (DOCK 6 software) and molecular dynamics simulations, identified four phytochemicals, from Indian medicinal plants, swertiapuniside, and amarogentin (from *Swertia chirayita*), cordifolide A (from *Tinospora cordifolia*) and sitoindoside IX (from *Withania Somnifera)* as RdRp inhibitors of SARS-CoV-2 (Fig. 24) [107].

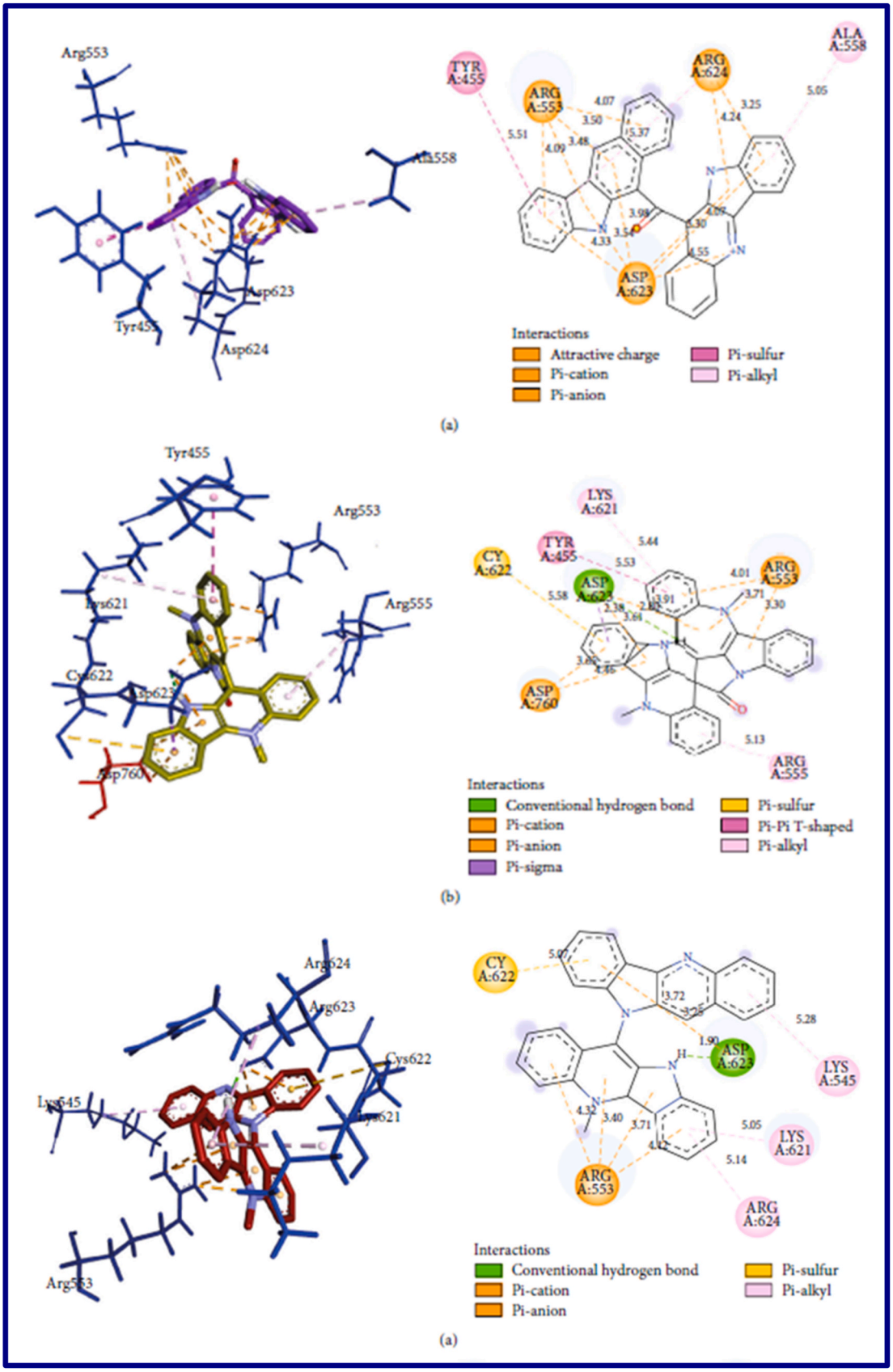


Fig. 26. View of 3D- (left) and 2D-interactions (right) of (a) cryptomisrine, (b) cryptospirolepine and (c) cryptoquindoline with RdRp enzyme active pocket [109].

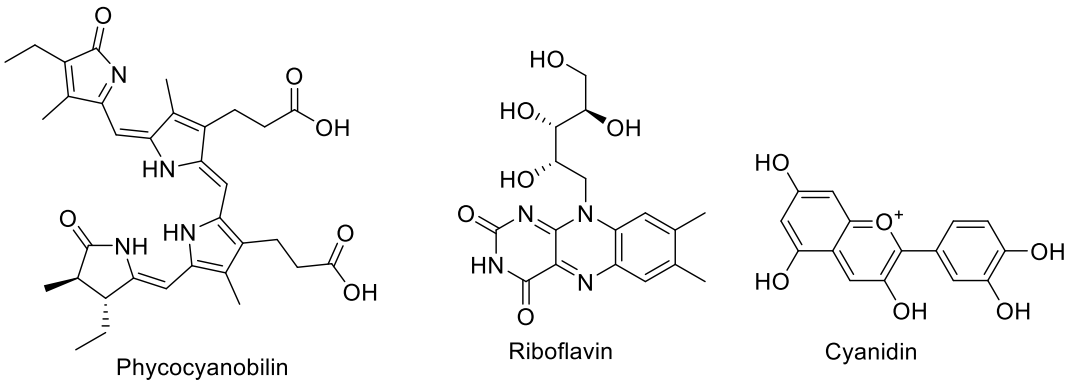


Fig. 27. Phycocyanobilins, riboflavin and cyanidin of potential inhibitory properties against Mpro and RdRp enzymes through in silico studies.

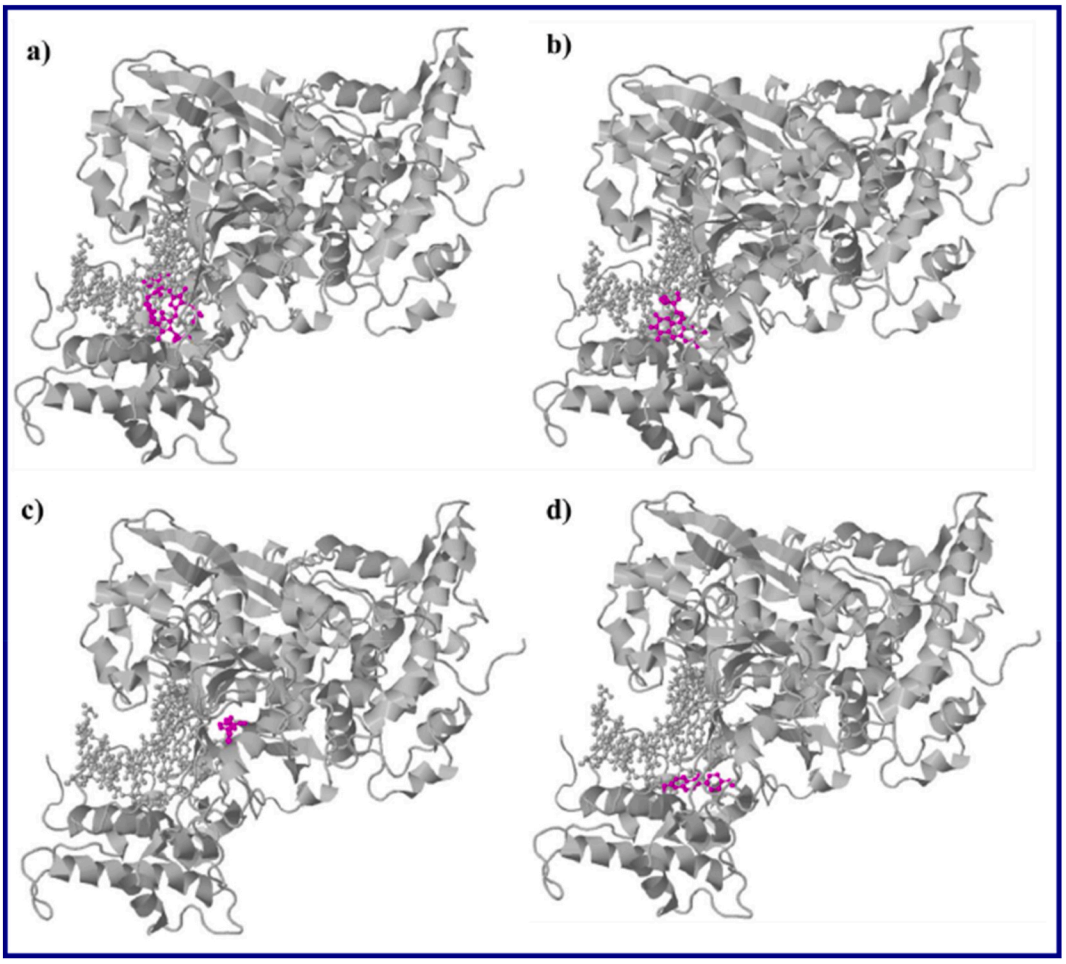


Fig. 28. Docked compounds "(a) Phycocyanobilin, (b) Riboflavin, (c) Cyanidin and (d) Daidzein" in RdRp [110].

3.2. Alkaloid

Alkaloids are found in *Cryptolepis sanguinolenta* (West African herb with antiviral, antiplasmodial and anti-inflammatory properties) [108]. In silico studies for the potential anti-SARS-CoV-2, the main protease (M^{pro}, PDB: 6LU7) and RdRp (PDB: 6M71) were considered for the alkaloid analogs. Cryptomisrine, cryptospirolepine, cryptoquindoline, and biscryptolepine showed promising affinity towards RdRp enzyme, suggesting their potential inhibitory properties towards both proteins (Figs. 25 and 26) [109].

In another in silico molecular docking study for some of the food bioactive compounds, three alkaloids phycocyanobilin (found in Spirulina), riboflavin (found in eggs, meat, fruits), cyanidin (found in grapes and berries) revealed high binding affinity towards SARS-CoV-2 M^{pro} and RdRp enzymes relative to the antiviral drugs Remdesivir, Nelfinavir, and Lopinavir utilizing AutoDock Vina software (Figs. 27 and 28) [110].

3.3. Polycyclic aromatic

The potential inhibitory effects of phytocompounds derived from *Clerodendrum* spp (with the application against respiratory disorders problems) [111,112] against SARS-CoV-2 RdRp (PDB: 7BV2) were

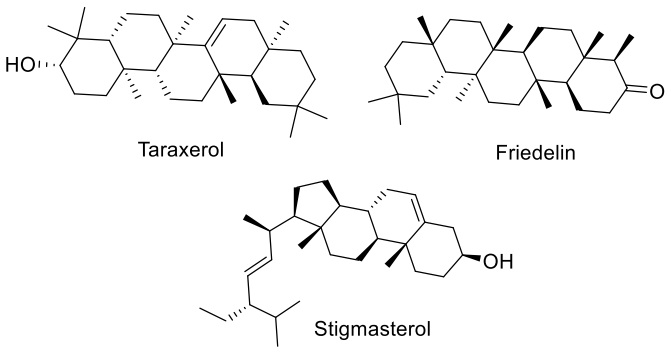


Fig. 29. Phytocompounds of potential inhibitory properties aganst SARS-CoV-2Mpro and RdRp through in silico studies.

studied by molecular docking (AutoDock Vina software). Taraxerol, friedelin, and stigmasterol displayed the highest binding potential relative to Remdesivir and Favipiravir. They also exhibited promising inhibitory affinity against the M^{pro} (SARS-CoV-2 spike protein) (Figs. 29 and 30) [113].

4. Synthetic non-nucleoside RdRp inhibitors

4.1. Indole

A series of 2-[(indol-3-yl)thio)]-*N*-benzyl-acetamides **7** were synthesized through the reaction of the Bunte salt ethyl acetate-2-sodium thiosulfate **3**, and indole derivatives **4** to afford the indolyl thioacetates **5**. The hydrolysis of **5** yielded the corresponding acids **6**. Finally, the coupling reaction of **6** with different substituted benzylamines afforded the target products **7**. Compound **8** was also generated

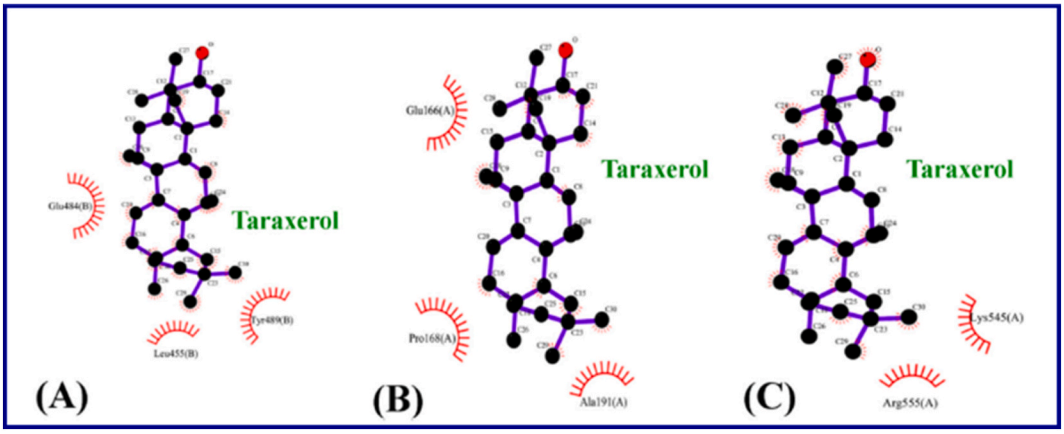
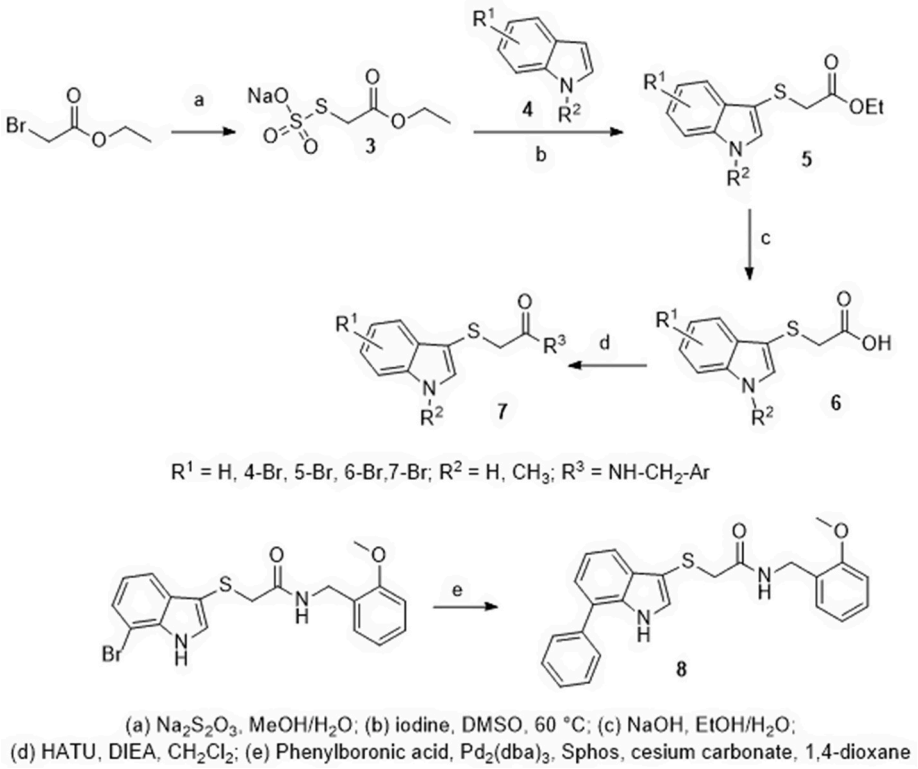


Fig. 30. Interaction of Taraxerol in (A) SARS-CoV-2 spike protein, (B) SARS-CoV-2 M^{pro} and (C) SARS-CoV-2 RdRp [113].



Scheme 1. Synthesis of 2-[(indol-3-yl)thio]-N-benzyl-acetamides **7** and **8**.

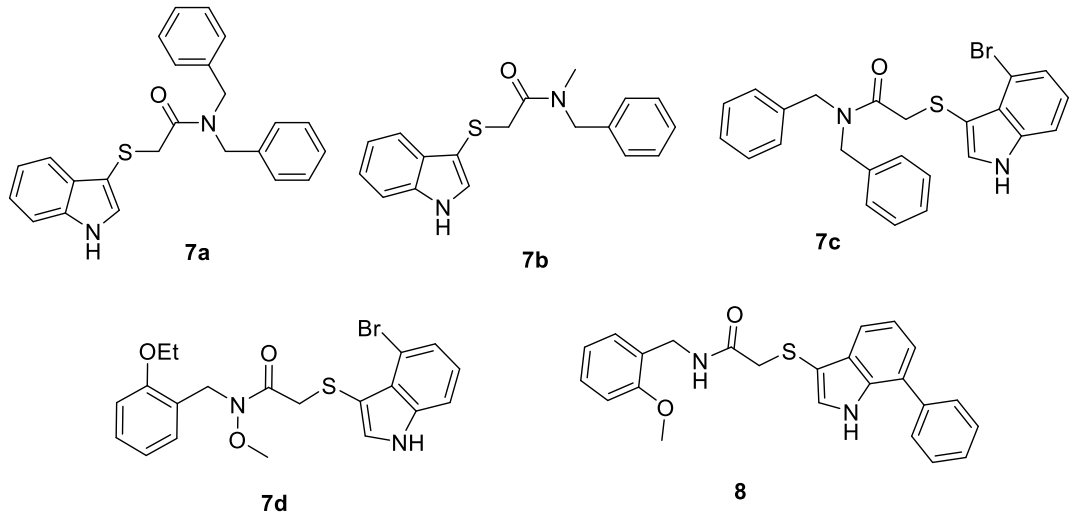
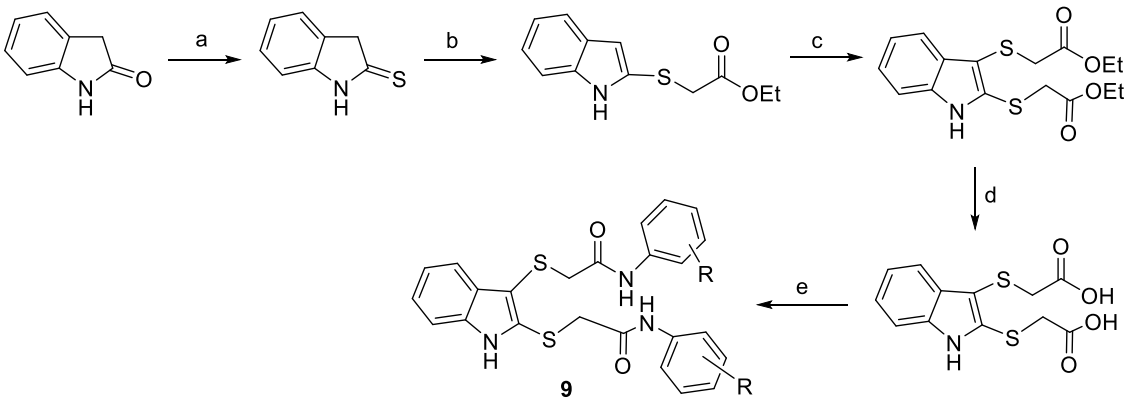


Fig. 31. Effective candidates in the CoV-RdRp-Gluc reporter assay.



a) P_2S_5, THF, Reflux; b) ethyl 2- bromoacetate, K_2CO_3, DMF;
c) sodium S-(2-ethoxy-2-oxoethyl) sulfurothioate, iodine, DMSO, 60 °C;
d) Na, EtOH/H_2O; e) substituted aniline, HATU, DIEA, CH_2Cl_2

Scheme 2. Synthesis of 2,3-dithioindoles **9**.

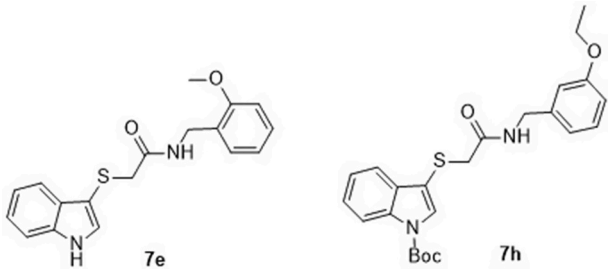
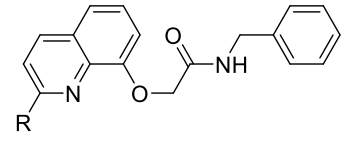


Fig. 32. Compounds **7e** and **7h** with high potency against SARS-CoV-2 RdRp.



10a, R = 4-bocpiperazin-1-yl
10b, R = (*S*)-boc-3-amino-pyrrolidinyl
10c, R = (*R*)-boc-3-amino-pyrrolidinyl

Fig. 33. Quinolines **10a-c** of promising SARS-CoV-2-RdRp inhibitory properties.

via Suzuki-Miyaura cross-coupling of its corresponding analog **7** with phenylboronic acid (Scheme 1) [114].

CoV-RdRp-Gluc reporter assay was considered for evaluation of SARS-CoV-2 RdRp inhibitory properties of the synthesized agents. Five compounds (**7a-7d, 8**) showed dose-dependent inhibition of SARS-CoV-2 RdRp with IC_{50} values of 1.11–4.55 μM while the IC_{50} of the positive control (Remdesivir) was 1.19 μM (Fig. 31). The most potent five compounds (**7a-7d, 8**) were further evaluated for their ability to inhibit the RNA synthesis by SARS-CoV-2 RdRp. All of them decreased the levels of viral plus- and minus-strand Gluc RNA in a dose-dependent manner (at 5 and 10 μM concentrations). Three compounds **7b**, **7d**, and **8** diminished the levels of both plus- and minus-strand Gluc RNA more potently than the Remdesivir. The antiviral effect of the most potent compound **7d** was evaluated against the human coronavirus strains HCoV-OC43 (β-coronavirus as SARS-CoV-2) and HCoVNL63 (α-coronavirus as SARS-CoV-2) in a cell-based assay in vitro. It was found that compound **7d** inhibits the replication of HCoV-OC43 more effectively than Remdesivir in a dose-dependent manner [114].

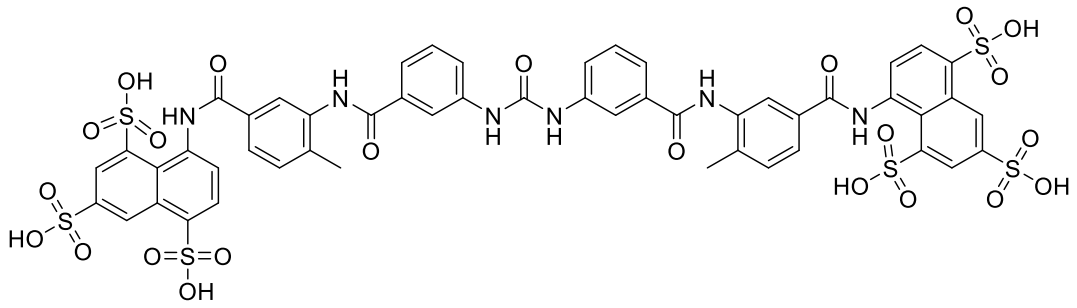


Fig. 34. Suramin, a promising RdRp inhibitor.

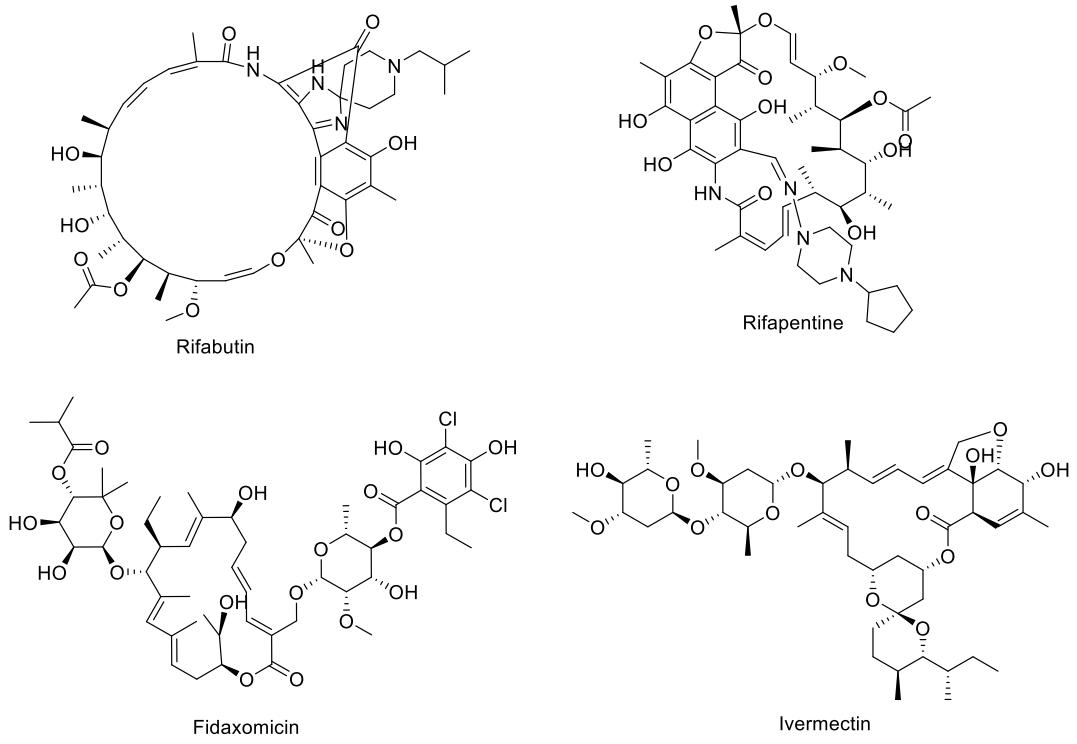


Fig. 35. Rifapentine, Rifabutin, Fidaxomicin and Ivermectin of potential interaction with SARS-COV-2 RdRNAP protein.

The 2-[(1*H*-indol-3-yl)thio]-*N*-phenyl-acetamide, 2-[(indol-3-yl) thio)-*N*-benzyl-acetamide (Scheme 1), and 2,3-dithioindole derivatives (synthesized according to Scheme 2) were screened through CoV-RdRp-Gluc assay. Compound **7h** (R^1 = H, R^2 = Boc, R^3 = 3-EtOC_6H_4) represented the most promising agent (EC_{50} = 1.41 μM, selectivity index = >70.92). However, the other compounds showed good to mild RdRp inhibition effect with an EC_{50} = 1.70, 2.75, 2.53, 3.07, 1.05 μM for **7e** ($R^1 = R^2$ = H, R^3 = 2-MeOC_6H_4), **7f** ($R^1 = R^2$ = H, R^3 = 3,4-$Cl_2C_6H_3$), **7g** (R^1 = R^2 = H, R^3 = 3-$H_3CC_6H_4$), **9a** (R = 3,4-Cl_2), and Remdesivir respectively [115].

High potency against SARS-CoV-2 RdRp was revealed by compounds **7e** and **7h** (EC_{50} = 1.58, 1.18 μM, respectively measured in HEK293T cells with CCK-8 kits) relative to Remdesivir (EC_{50} = 0.73 μM, measured in A549 cells with CCK-8 kits) [115] (Fig. 32).

4.2. Quinoline

Quinoline derivatives **10a–c** (Fig. 33), that considered previously against the influenza A virus, were repurposed as SARS-CoV-2-RdRp inhibitors. The assumed compounds revealed promising inhibitory properties relative to Remdesivir at 10 μM (95.03%, 92.85%, and 74.94% for **10a–10c**, respectively). The CC_{50} values for **10a–10c** were 70.79, 72.44, and 79.43 μM, respectively, with therapeutic indexes 65.55, 34.83, and 20.26, respectively reflecting their low cytotoxicity. Compound **10a** showed antiviral activity against human coronavirus strains HCoV-OC43 and HCoVNL63 determine by the cell-based assay (HCT-8 and LLC-MK2 cell lines infected with HCoV-OC43 "β-coronavirus as SARS-CoV-2" and HCoV-NL63 (α-coronavirus as SARS-CoV-2″) [116].

4.3. Suramin

A 100 year-old-drug, Suramin (Fig. 34) is identified as a potent inhibitor of the SARS-CoV-2 RdRp and acts by blocking the binding of RNA to the enzyme. Biochemical studies suggest Suramin and its derivatives are at least 20-fold more potent than Remdesivir. The 2.6 Å cryo-electron microscopy structure of the viral RdRp bound to Suramin uncovers two binding sites of which one directly blocks the binding of the RNA template strand and the other clashes with the RNA primer strand near the RdRp catalytic site, thus inhibiting RdRp activity. The IC_{50} values obtained from the solution-based assays of RdRp inhibition for Suramin is 0.26 μM, and for Remdesivir in its triphosphate form (RDV-TP) is 6.21 μM under identical assay conditions, suggesting that Suramin is at least 20-fold more potent than RDV-TP [117].

Table 2
Predicted ADME-Tox properties.

Compd.	MW	logP	HBD	HBA	RB	TPSA	BBB	HIA	P-gp substrate	hERG pIC_{50}	BS
Remdesivir	602.6	1.77	4	14	15	203.5	–	–	yes	4.60	0.17
VV116	501.5	2.59	1	12	12	168.1	–	+	no	4.16	0.17
GS-621763	501.5	2.59	1	12	12	168.1	–	+	no	4.17	0.17
Favipiravir	157.1	−1.25	2	5	1	88.84	–	+	no	3.28	0.55
Molnupiravir	329.3	−0.34	4	10	6	143.1	–	–	no	3.85	0.55
Galidesivir	265.3	−1.20	6	8	2	140.3	–	+	yes	3.69	0.55
Ribavirin	244.2	−1.85	4	9	3	143.7	–	–	no	3.26	0.55
Sofosbuvir	529.5	1.19	3	12	11	158.2	–	+	yes	4.51	0.17
Daclatasvir	734.8	4.00	4	14	17	176.3	–	+	yes	4.57	0.17
Alovudine	244.32	−0.44	2	6	2	84.32	–	+	no	4.21	0.55
Azidothymidine	267.2	−0.02	2	9	3	134.1	–	+	no	4.09	0.55
Tenofovir	287.2	−0.005	3	9	5	136.4	–	–	yes	4.61	0.55
AT-527	581.5	2.03	4	14	12	185	–	–	yes	4.96	0.17
Vidarabine	267.2	−1.05	4	9	2	139.5	–	+	no	4.19	0.55
Tubercidin	266.3	−0.77	4	8	2	126.7	–	+	no	4.24	0.55
Aristeromycin	265.3	−0.53	4	8	2	130.3	–	–	yes	4.47	0.55
8-Chloroadenosine	301.7	−0.49	4	9	2	139.5	–	+	no	4.29	0.55
Fludarabine	285.2	−1.04	4	9	2	139.5	–	+	no	4.44	0.55
Neplanocin A	263.3	−0.77	4	8	2	130.3	–	+	yes	4.61	0.55
Psicofuranine	297.3	−1.7	5	10	3	159.8	–	+	yes	3.96	0.55
Decoyinine	279.3	−1.22	4	9	2	139.5	–	+	yes	4.15	0.55
Cladribine	285.7	0.02	3	8	2	119.3	–	–	no	4.45	0.55
Clofarabine	303.7	−0.19	3	8	2	119.3	–	+	no	4.47	0.55
Riboprine	335.4	0.23	4	9	5	125.6	–	–	yes	5.19	0.55
Tecadenoson	337.3	−0.20	4	10	4	134.8	–	–	yes	7.83	0.55
Nelarabine	297.3	−0.98	4	10	3	148.8	–	+	no	4.20	0.55
Forodesine	266.3	−1.59	6	8	2	134.3	–	+	no	3.72	0.55
Maribavir	376.2	2.09	4	7	4	99.77	–	+	yes	5.17	0.55
Forodesine-TP	506.2	−0.40	9	17	8	273.9	–	–	yes	2.35	0.11
Riboprine-TP	575.3	0.58	7	18	11	265.1	–	–	yes	3.55	0.11
Baicalein	270.2	0.31	3	5	1	90.9	–	+	no	4.54	0.55
Baicalin	446.4	2.94	6	11	4	187.1	–	+	no	3.03	0.11
Isoginkgetin	566.5	4.24	4	10	5	159.8	–	+	no	5.11	0.55
Bilobetin	552.5	3.81	5	10	4	170.8	–	+	yes	5.01	0.55
Afzelin	432.4	0.40	6	10	3	170.1	–	–	no	4.41	0.55
Rutin	610.5	−0.82	10	16	6	269.4	–	–	yes	3.89	0.17
Nicotiflorin	594.5	−0.69	9	15	6	249.2	–	–	yes	4.04	0.17
Ellagic acid	302.2	1.57	4	8	0	141.3	–	+	yes	5.16	0.55
p-Coumaric acid	164.2	1.47	2	3	2	57.53	+	+	no	3.58	0.55
Kaempferol	286.2	2.55	4	6	1	111.1	–	+	no	4.65	0.55
Quercetin	302.2	1.54	5	7	1	131.4	–	+	no	4.41	0.55
Theaflavin	564.5	1.65	9	12	2	217.6	–	–	yes	4.90	0.17
Swertiapuniside	598.5	−1.18	9	16	7	258.4	–	–	no	4.22	0.17
Amarogentin	586.5	0.81	6	13	8	201.7	–	–	yes	4.08	0.11
Cordifolide A	598.7	0.34	5	12	7	185.3	–	+	yes	4.00	0.17
Sitoindoside IX	632.7	0.57	5	11	6	175.5	–	+	yes	4.29	0.17
Cryptomisrine	462.5	4.98	2	5	2	74.43	–	+	yes	5.65	0.17
Cryptospirolepine	504.6	5.70	1	5	0	44.27	–	+	no	6.17	0.55
Cryptoquindoline	448.5	6.74	0	4	1	35.64	+	+	yes	7.01	0.55
Biscryptolepine	462.5	7.93	0	4	1	35.64	+	+	yes	6.65	0.55
Phycocyanobilin	588.7	3.79	5	10	11	164.7	–	–	yes	2.64	0.11
Riboflavin	376.4	−0.86	5	10	5	161.6	–	+	no	4.40	0.55
Cyanidin	287.2	2.09	5	6	1	112.4	–	+	no	4.72	0.55
Taraxerol	426.7	5.80	1	1	0	20.23	+	+	no	5.41	0.55
Friedelin	426.7	5.53	0	1	0	17.07	+	+	no	5.08	0.55
Stigmasterol	412.7	7.16	1	1	5	20.23	+	+	yes	6.28	0.55
7a	386.5	4.56	1	3	8	36.1	+	+	no	5.40	0.55
7b	310.4	3.16	1	3	6	36.1	+	+	no	4.91	0.55
7c	465.4	5.37	1	3	8	36.1	+	+	yes	5.51	0.55
7d	449.4	4.08	1	5	9	54.56	–	+	yes	5.07	0.55
7e	326.4	2.84	2	4	7	54.12	+	+	no	4.27	0.55
7f	440.6	4.57	1	6	11	69.56	–	+	yes	5.18	0.55
10a	476.6	3.75	1	8	10	84	–	+	yes	5.41	0.55
10b	461.1	3.75	1	7	10	80.76	–	+	yes	5.31	0.55
10c	461.1	3.74	1	7	10	80.76	–	+	yes	5.31	0.55
Suramin	1297	1.97	12	29	22	483.8	–	–	yes	3.96	0.11
Rifabutin	847	2.90	5	15	5	205.6	–	+	yes	4.24	nd
Rifapentine	877	4.05	6	16	6	220.1	–	+	yes	6.24	nd
Fidaxomicin	1058	3.76	7	18	15	266.7	–	–	yes	4.82	nd
Ivermectin	875.1	3.33	3	14	8	170.1	–	–	yes	4.96	nd

Ideal values for oral drug candidates: MW ≥ 500; logP ≥5; HBD ≥5; HBA ≥10; RB ≥ 10; TPSA ≥140; BBB (−); HIA (+); P-gp substrate (yes); hERG $pIC_{50} \geq 5$; BS ≥ 0.55.

5. In silico proposed compounds

In silico techniques help design bioactive agents and identify anti-SARS-CoV-2 hits [118,119]. Diverse acyclic [120] and heterocycles [121–123] of different scaffolds (triazole [124], oxadiazole [125], thiadiazole [126], indole [127], pyridine [128], pyrimidine [129] and coumarin [130]) were predicated as effective inhibitory agents for SARS-CoV-2 RdRp. However, the lack of experimental in vitro and in vivo observed results hindered the usefulness of these proposed prospective compounds. Recently, Saha et al. explored the impact of natural products (Tellimagrandin I, SaikosaponinB2, Hesperidin (−)-Epigallocatechin Gallate) on SARS-COV-2 RdRp protein [131].

In addition to the nucleoside and non-nucleoside based RdRp inhibitors, many lead candidates were identified through molecular docking and homolog model-based screening. Parvez et al. revealed that antibacterial drugs (fidaxomicin, ivermectin, rifabutin, and rifapentine) show potential interaction with SARS-COV-2 RdRp protein (Fig. 35). These drugs could be further investigated and considered as leads for further development of potential RdRp inhibitors for SARS-COV-2 [132].

6. Predicted ADME-Tox Properties

Drug development is always a tedious and challenging task. Several strategies have been used in recent years to expertise the process which includes molecular hybridization, molecular docking, and consideration of ADME-Tox properties. As many drug candidates fail to reach their drug target because of their poor ADME-Tox profile. It is essential to pay attention for having balanced pharmacokinetic properties while developing new RdRp inhibitors for SARS-CoV-2. The descriptor and drug-likeness properties of the compounds included in this article were calculated with the Swiss ADME server [133] and STARDROP software [134]. Among the various parameters, we considered to include molecular weight (MW), logP, hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), number of rotatable bonds (RB), topological polar surface area (TPSA), ability to cross the blood-brain barrier (BBB), human intestine absorption (HIA), inhibition of P-glycoprotein (P-gp), human ether-a-go-go-related gene (hERG) potassium channel inhibition and bioavailability score (BS) as these properties play critical role (see Table 2). These data could serve as additional information for the new drug development process.

7. Conclusion

SARS-CoV-2 is considered one of the most severe pandemics facing the global population. The development of efficient anti-SARS-CoV-2 drugs over a short time is associated with many challenges, considerable obstacles, and unknown difficulties. Among various modern approaches to adopt for developing potential drug candidates for SARS-CoV-2, rational drug design and drug repurposing strategies are key. In the past two years, RdRp is found to be a prime target as this enzyme has capable to combat viral replication. Some drugs have been identified as anti-SARS-CoV-2 RdRp accessible for mild and weak infectious patients. Numerous natural and synthetic molecules have also been investigated. However, drug candidates with higher potency are still in demand. In silico studies have been exploring the most in the search for potential drug candidates but without supporting in vitro and in vivo observations their accessibilities will be hindered for any drug discovery program. We believe the compiled information will develop an interest in this field among the research community and provide them with a deeper understanding of the requirements and importance of chemical scaffolds for designing potential RdRp inhibitors for SARS-CoV-2.

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.

Data availability

No data was used for the research described in the article.

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