

In silico Studies of Novel Synthetic Compounds as Potential Drugs to Inhibit Coronavirus (SARS-CoV-2): A Systematic Review

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Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), detected first in China, spread out fast to other parts of the world, and was soon recognized as a pandemic in March 2020. According to WHO, 179.686.071 confirmed cases and 3.899.172 deaths due to new coronavirus were reported worldwide on 26th June 2021. Despite countless efforts in searching for repositioned drugs to treat this disease, the results are still modest. Thus, the search for new molecular entities in the treatment of COVID-19 is an essential field in medicinal chemistry. Since the pandemic's beginning, several studies have reported the synthesis of novel organic compounds and their *in silico* interactions with the new coronavirus. Such computational studies are currently being applied to unveil the complexities of drug-target molecule interaction and also helping in developing new pharmacological treatments. This systematic review aims to provide an overview of studies describing the utilization of novel compounds as prospective drugs in the treatment of COVID-19.

Keywords: COVID-19; molecular docking; synthesis.

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1. Introduction

The COVID-19 has emerged as an infectious disease that spreads rapidly worldwide and is transmitted mainly by contact with contaminated saliva droplets or nasal discharge while the patient coughs or sneezes [1,2]. While efforts to develop pharmaceutical interventions for COVID-19 are underway, alternatives to avoid virus spread, such as social distancing and the use of masks, have been widely used and encouraged by the authorities [3]. Additionally, worldwide vaccination is still a challenge [4]. So far, no specific antiviral agent has been approved for the novel coronavirus, the causative agent of COVID-19, except for remdesivir [5]. This repositioned broad-spectrum RNA-dependent RNA polymerase inhibitor was recently approved against SARS-CoV-2 [6]. Drug repositioning works as an alternative and systematic method of drug discovery that can help determine new indications for existing drugs [7].

Novel synthetic compounds, sometimes referred to as new molecular entities (NME), are innovative molecules that serve previously unmet medical needs or significantly help advance patient care and public health [8,9]. NME has chemical structures that have never been approved before. Along with the drug repositioning approach, NME research is an essential branch in drug discovery and development. As a result, 378 new drugs and 27 biosimilars were approved by the US Food and Drug Administration (FDA) between 2010 and 2019 [10]. In the

search for novel compounds, developing more economical and eco-friendly synthetic routes is highly significant [11,12]. In this context, increasingly cleaner reactions, ultrasound and microwave assistance, recoverable catalysts, and purification efficiency are desirable. Additionally, considering the industrial synthesis, reproducible and scaling-up chemical reactions are required.

In silico drug design techniques play a critical role in developing new drugs since they limit the use of animal models in clinical research and perform an economic identification of promising drug candidates [13]. Computational methods such as molecular docking generate ligand conformations and orientations so that the most appropriate ones are later selected for further interactions study in the protein binding site. Conversely, molecular dynamics help to predict the stability of a particular ligand [14]. *In silico* ADME predictions have also emerged as potential tools to predict drug absorption based on physicochemical and pharmacokinetic parameters [15]. Together, these computational approaches have been widely applied as additional tools in drug design and development.

The worldwide crisis generated by the pandemic associated with the lack of drugs for the treatment of COVID-19 contributed to the emergence of several studies aimed at synthesizing new compounds and their molecular interaction with the coronavirus proteins by computational tools. The present systematic review aims to provide an overview of these studies since some of them may soon reveal new chemical entities to treat this global disease.

2. Material and Methods

A systematic review was performed through a literature search conducted in June 2021 and included articles published and indexed from 01/01/2020 to 06/10/2021. This literature search was carried out over specialized search databases (PubMed, SCOPUS, and SciFinder) using distinct combinations of the following keywords: synthesis, coronavirus, COVID-19, and docking. Search terms were selected based on our aim to find everything published about molecular docking interactions of synthetic compounds with coronavirus proteins, given that molecular docking may be considered the most used tool in drug development. Parameters of inclusion criteria were defined as follows: 1. Articles written in English; 2. Studies describing molecular docking interaction of novel synthetic compounds; 3. Studies describing molecular dynamics or ADME/T predictions. Articles were excluded with the following properties: 1. Studies are reporting drugs against targets other than the new coronavirus; 2. Studies describing metal complexes preparation and; 3. Studies not describing conventional synthesis (e.g., combinatorial synthesis, polymer synthesis).

For the manuscript choices, articles were selected according to the title, then to abstract, and then through an analysis of the full-text publication. Finally, the resulting papers were manually reviewed to identify and exclude the works as stated in the criteria described above.

3. Results

The primary search resulted in 1155 articles, of which 797 remained after the removal of duplicates (Figure 1). Overall, 60 studies fitted the inclusion criteria. Then, the full text of each article was reviewed. Articles that matched the exclusion criteria were withdrawn from the study, resulting in 25 original articles describing newly synthesized molecules through conventional synthetic routes and their molecular docking interactions with the new coronavirus proteins.

As we can see in table 1, different classes of compounds, targets, software for molecular docking, and additional paper features are described. Concerning compound classes, the great majority of the studies (68%) describe nitrogen heterocyclic synthesis. Despite the classification shown in the table, most of the synthesized compounds are hybrid or multifunctional compounds. With regard to targets, the main protease was the compound's target is 76% of the studies, followed by nucleocapsid protein and RNA polymerase (16% and 12%, respectively). Furthermore, 84% of the studies explored compounds as mono-target drug candidates, while 16% evaluated them as potential multi-target drugs. Molecular docking interactions were mainly accomplished by Autodock vina, representing 56% of the studies.

Additional features of the selected articles are presented in table 1. Although we did not consider these features in the initial search, they can indicate studies' quality assessment. ADME/T predictions were evaluated in 40% of the studies. In 32% of the studies, an X-ray crystal structure was obtained and analyzed. The same percentage was observed for studies that appraised density functional theory (DFT). In addition, 20% of the studies accomplished molecular dynamics simulations. Finally, sonochemical synthesis was performed in 16% of the studies.

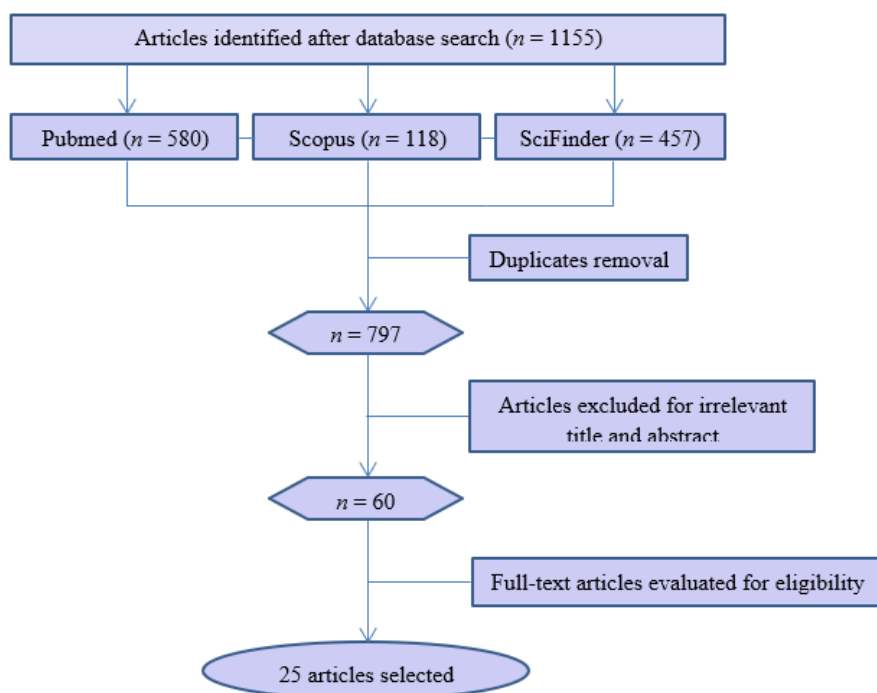


Figure 1. Study selection diagram.

Table 1. Characteristics of studies included in the systematic review.

Study	Compound Class	Target (PDB ID)	Software	Additional Features
Abu-Melha <i>et al.</i> , 2020 [16]	triazolopyrimidine	Main protease (6Y84)	AutoDock Vina	Clean Grinding Technique & Molecular Dynamics
Ahmed-Belkacem <i>et al.</i> , 2020 [17]	adenine dinucleosides	Nsp14 (5C8T & 5NFY)	Autodock Vina	<i>in vitro</i> evaluation
Alsafi <i>et al.</i> , 2020 [18]	chalcone	Main protease (7BYQ)	Autodock Vina	X-ray crystal structure analysis
Alshammari <i>et al.</i> , 2021 [19]	quinolonyl acetohydrazides	Main protease (6LU7) RNA polymerase (6M71)	Autodock 4.2	NMR, mass, IR & elemental analysis characterization
Aly <i>et al.</i> , 2021 [20]	bis-quinolinones	Main protease (6LU7)	AutoDock 4.2	X-ray crystal structure analysis
Asha <i>et al.</i> , 2021 [21]	piperidines	Spike (6VSB) Main protease (6Y84)	AutoDock Vina	X-ray crystal structure analysis, DFT studies & ADMET predictions

Study	Compound Class	Target (PDB ID)	Software	Additional Features
Benbouguerra <i>et al.</i> , 2021 [22]	Hydrazino-phosphonic acid	Main protease (6LU7) RNA polymerase (7BV2)	Autodock 4.2	one-pot multicomponent reaction, DFT & Spectral studies
Chemboli <i>et al.</i> , 2021 [23]	quinoxalines	Nucleocapsid (6M3M)	GemDock DockThor SwissDock	Sonochemical synthesis, <i>in vitro</i> evaluation & ADMET predictions
Chhetri <i>et al.</i> , 2021 [24,25]	Azo-imidazoles	Main protease (6LU7)	Autodock Vina	ADME predictions, NMR & IR characterization
Chidambaram <i>et al.</i> , 2021 [26]	coumarins	Main protease (5N5O)	Autodock Vina	ADME predictions, NMR, mass, IR & elemental analysis characterization
Domínguez-Villa <i>et al.</i> , 2021 [27]	indolones	Main protease (6LU7)	Autodock tools	ADMET predictions
Douche <i>et al.</i> , 2021 [28]	quinolinols	Main protease (6Y84)	AutoDock Vina	X-ray crystal structure analysis & DFT studies
Kalai <i>et al.</i> , 2021 [29]	Pyridazinone	Nsp3 (6WEY), Main protease (6XHU), Papain-like protease (6YVA), Nucleocapsid (6WKP), Co-factor Complex (6WQD)	SwissDock	X-ray crystal structure analysis, DFT studies & TGA/DTA studies
Khorsandi <i>et al.</i> , 2021 [30]	Lopinavir analogs	Main protease (6LU7)	AutoDock 4.2	Hoveyda-Grubbs' catalyst Molecular Dynamics
Kreutzer <i>et al.</i> , 2020 [31]	cyclic peptide	Main protease (6YB7)	AutoDock Vina	Solid phase synthesis <i>in vitro</i> evaluation & Molecular Dynamics
Kusumaningsih <i>et al.</i> , 2021 [32]	phloroglucinol	Main protease (6LU7)	AutoDock wizard	Sonochemical synthesis, DFT studies & ADMET predictions
Lauro <i>et al.</i> , 2021 [33]	Lactam-Steroid	Main protease (6LU7)	Chimera Achilles-Blind	Mild conditions synthesis & NMR characterization
Özkan <i>et al.</i> , 2020 [34]	Norcantharimides	Main protease (6LU7)	Molegro	ADME predictions, NMR, IR & elemental analysis characterization
Sarfraz <i>et al.</i> , 2021 [35]	thiobarbituric acids	Main protease (6Y84, 6LU7)	Autodock tools	one-pot multicomponent reaction Molecular Dynamics & ADMET predictions
Satyanarayana <i>et al.</i> , 2021 [36]	pyrazines	Nucleocapsid (6M3M)	Autodock Vina	Sonochemical synthesis & ADME predictions
Shahinshavali <i>et al.</i> , 2020 [37]	quinoxalines	Nucleocapsid (6M3M)	AutoDock Vina	Sonochemical synthesis
Topal <i>et al.</i> , 2021 [38]	hydrazone-pyridine	Main protease (6LU7)	AutoDock Vina	X-ray crystal structure analysis, DFT studies, IR & Raman spectroscopic analysis
Venkateshan <i>et al.</i> , 2020 [39]	Azaphenanthrenes	Main protease (6LU7)	AutoDock Vina	X-ray crystal structure analysis, DFT studies & QTAIM analysis
Venkateshan <i>et al.</i> , 2020 [40]	Azafluorenes	RNA polymerase (6NUR)	AutoDock Vina	X-ray crystal structure analysis, DFT studies, ADMET predictions & binding free energy calculations

4. Discussion

4.1. Synthesis.

The emergence of new diseases and the increase in the incidence of those already known aroused the interest of researchers in the development and synthesis of new pharmacologically active substances [41,42]. For example, regarding the new coronavirus pandemic, in addition to the importance of worldwide vaccination and the repositioning of

existing drugs, the synthesis of new potential drug candidates in the treatment of COVID-19 is highly relevant [43,44].

In general, studies included in this review use conventional chemical reactions and short synthetic routes, with moderate to high overall yields. One-pot multicomponent reactions were applied as well [22,35]. It is an excellent tool for rapidly generating small molecules with broad chemical diversity and molecular complexity [45].

As ultrasound irradiation has dramatically accelerated organic reactions, sonochemical synthesis has gained considerable attention in recent years [46], and diverse transformations have been performed using ultrasound [47,48]. For example, Kusumaningsih *et al.* prepared dimeric 2,4-diacetyl phloroglucinol in a 95% yield after sonication for 30 min at 60° [32]. The same reaction, utilizing conventional stirring, yielded the product in 87% after 3 hours. The gram-scale synthesis was also efficient under ultrasound irradiation, providing the phloroglucinol derivative in 94% after 20 min of reaction. Under optimized conditions, quinoxaline derivatives [22, 37] and pyrazine derivatives [36] were prepared using an ultrasound-assisted methodology. Compared to their previously reported synthesis, the new sonochemical method was performed in shorter times and avoided using solvents that are not environmentally friendly.

Progress in solid-phase synthesis has stimulated great interest in protein design and synthesis of structurally diverse peptide libraries that can be screened against biological targets. Kreutzer *et al.* designed and synthesized a cyclic peptide containing a [4-(2-aminoethyl)phenyl]-acetic acid (AEPA) linker, named UCI-1, by Fmoc-based solid synthesis [31]. Treatment of the Fmoc-AEPA-OH intermediate with 2-chlorotriyl chloride resin followed by linear peptide synthesis and resin cleavage provided the desired cyclic peptide used by authors for *in vitro* and *in silico* studies. The Grindstone technique has also been used as a green and fast process to synthesize organic compounds [49]. This method, first used by Toda [50], has proven that different reactions can be performed in high yield by grinding solids together using a mortar and pestle. Abu-Melha *et al.* prepared some triazolopyrimidine derivatives by grinding precursor reagents in the presence of a few drops of acetic acid at room temperature [15]. The products were obtained in 88-92% yield. Chidambaram *et al.* synthesized some coumarin analogs through a grinding technique, in which the reagents were placed in the ground well, and few drops of concentrated HCl were added [51]. In this case, yields varied from 82-92%.

4.2. Computational studies.

Molecular docking is a computational method that predicts the preferred binding position of a molecule into the binding site of a macromolecular target. In addition, it indicates the strength of the connection or binding affinity between the ligand and protein by using scoring functions. Molecular docking has been widely employed as an essential tool in drug design and development [52].

As mentioned before, the main protease (M^{PRO}) from SARS-CoV-2 was the primary target for molecular docking in 76% of the studies (19 studies) described here. This protease is essential for processing polyproteins translated from virus RNA and critical for virus replicating and spreading [53]. Recent studies have shown that M^{PRO} of SARS-CoV-2 consisted of three domains, and similar to other coronaviruses, SARS-CoV-2 M^{PRO} also has a catalytic Cys-145-His-41 dyad located in a groove between domain I and domain II [54]. Table 2 shows the docking scores of selected compounds with SARS-CoV-2 M^{PRO} . From the table,

we can notice that all the docked compounds were promising in binding to the M^{PRO}, with higher docking scores than reference drugs. Furthermore, most compounds successfully interacted with the M^{PRO} catalytic dyad or at least one amino acid. They thus showed auspicious protease activity, thereby being attractive drug candidates for the new coronavirus.

The nucleocapsid protein is a relevant structural protein for the coronavirus, which participates in the RNA package and virus particle delivery [55]. It is, therefore, a potential target for antiviral drugs and was the unique target in 3 studies [23, 36, 37] (Table 1). Pyrrolo[2,3-*b*]-quinoxaline [8] and 3-alkynyl substituted 2-chloroquinoxaline derivatives [37] were docked against the *N*-terminal RNA binding domain. In both studies, the novel synthetic compounds showed greater binding affinity than reference compound DA-3003-1. In addition, 2-alkynyl 3-chloropyrazines prepared by Satyanarayana *et al.* [36] also presented good docking scores when targeted the nucleocapsid of SARS-CoV-2. In this case, binding affinities were lower than DA-3003-1 but higher than favipiravir.

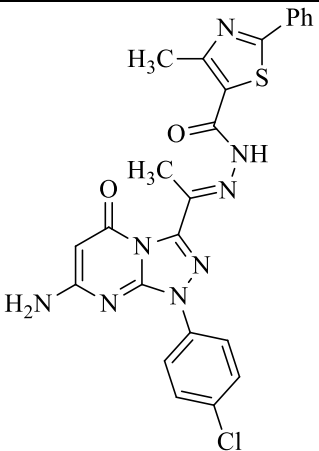
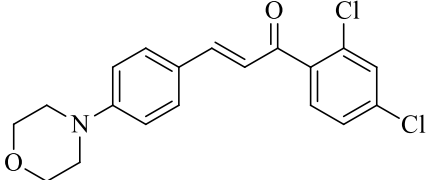
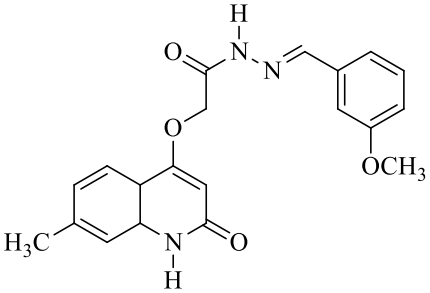
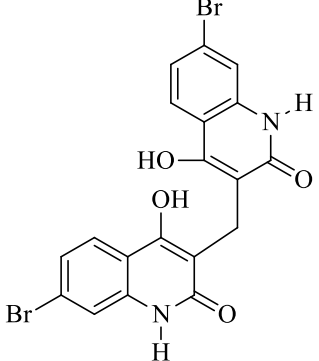
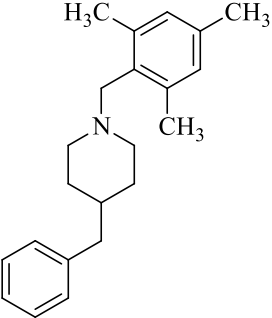
Potential multi-target drugs are more advantageous than mono-target ones in better pharmacokinetics prediction and reduced risk of drug synergism [7]. Only 4 studies (16% of the studies) evaluated the novel synthetic compounds as multi-target potential drugs [19, 21, 22, 29]. In this regard, we can mention the work of Kalay *et al.* [29]. These authors prepared a novel synthetic styrylpyridazin-3(2H)-one, considered a promising candidate for multi-target therapy. From the 7 targets assessed, 5 presented negative binding affinity values. These include nsp3 macro X domain, main protease, papain-like protease, nucleocapsid, and the co-factor complex between nsp7 and the C-terminal domain of nsp8.

Molecular Dynamics (MD) is the most widely used computational technique to study biological systems' equilibration structures and dynamic interactions [56,57]. It simulates the dynamic behavior of molecular systems as a function of time, treating all the entities in the simulation box as flexibles. 4 studies (16% of the studies) used MD simulation to monitor and evaluate the conformational behaviors of the atoms and molecules, to validate the outcomes of the molecular docking [15, 30, 31, 35]. The RMSD profile results showed that, in these studies, selected compounds exhibited significant stability in the active site during MD simulations.

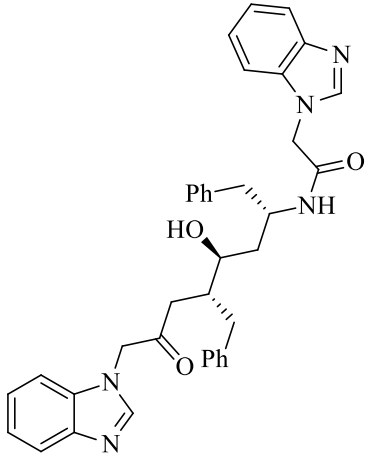
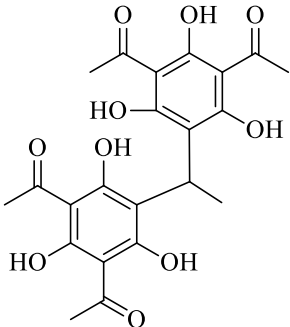
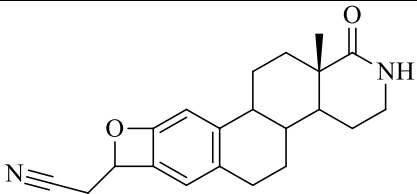
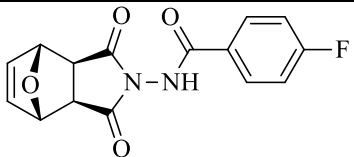
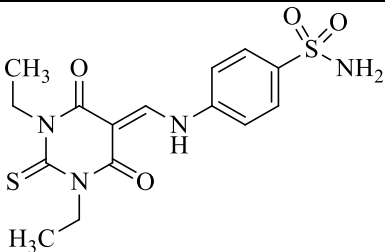
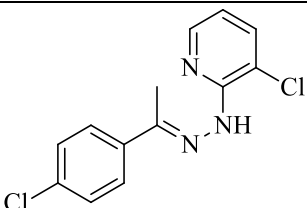
Aside from previously discussed pharmacodynamic properties, effective and safe medications displayed favorable pharmacokinetics that combines adequate absorption, distribution, metabolism, excretion, as well as tolerable toxicity (ADMET). Costly drug failures are found in late development or clinical trials due to poor pharmacokinetics and toxicity issues. 9 out of 25 studies performed ADME/T predictions for the synthesized compounds [21, 23-27, 32, 34-36, 40]. Tools such as SwissADME [58], admetSAR [59] and pkCSM-pharmacokinetics [60] were used to calculate this predictive parameters. Most of these studies describe amine-containing compounds. Because they are weak bases, amines respond to balancing the dual requirements of water and fat solubility. By having a pKa value in the range of 6–8, they are partially ionized at the slightly acidic and alkaline pHs present in the gut and blood, respectively. They can easily balance their ionized and non-ionized forms, allowing them to cross cell membranes in the unionized form.

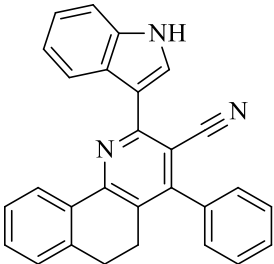
In contrast, the presence of the ionized form gives the molecule good water solubility and allows good binding interactions with its target link site [61]. Thus, with few exceptions, the compounds showed good drug-likeness properties, with no Lipinski or Veber rules violations. Where applicable, the molecules also appeared to be safe from the standpoint of predicted acute and chronic toxicities.

Table 2. Docking scores of selected compounds with SARS-CoV-2 M^{PRO}.

Comp.	Structure	Docking Score	Interact w/ catalytic dyad (His-41 and Cys-145)	Ref.
1		-8.3 (Nelfinavir = -6.7)	No	[15]
2		-7.0 (Remdesivir = -4.9)	yes	[18]
3		-9.7 (Remdesivir = -8.5)	No	[19]
4		-8.63 (Darunavir = -8.19)	No	[20]
5		-6.2 (Remdesivir = -5.4)	No	[21]

Comp.	Structure	Docking Score	Interact w/ catalytic dyad (His-41 and Cys-145)	Ref.
6		-6.0 (Remdesivir = -4.96)	His-41	[22]
7		-8.1 (Remdesivir = -5.8)	Yes	[24]
8		-7.9 (Remdesivir = -5.8)	Yes	[25]
9		-7.9 (Hydroxychloroquine = -5.8)	No	[26]
10		-7.2 (Remdesivir = -5.4)	No	[28]

Comp.	Structure	Docking Score	Interact w/ catalytic dyad (His-41 and Cys-145)	Ref.
11		-9.61 (Remdesivir = -7.81)	yes	[30]
12		-8.1 (Remdesivir = -7.8)	yes	[32]
13		-7.6 (Favipiravir = -5.3)	No	[33]
14		-128.2 (Nelfinavir = -146.76)	Yes	[34]
15		-7.28 (Remdesivir = -6.33)	Cys-145	[35]
16		-6.4 (hydroxychloroquine = -5.0)	Yes	[38]

Comp.	Structure	Docking Score	Interact w/ catalytic dyad (His-41 and Cys-145)	Ref.
17		-9.4 (Remdesivir = -8.5)	No	[39]

5. Conclusions

This review has considered the perspectives in applying novel synthetic compounds as potential drugs in treating COVID-19 disease. Computational methods such as molecular docking, molecular dynamics, and ADME/T predictions have been demonstrated as useful for pharmacodynamics and pharmacokinetics evaluations. As most synthetic strategies use classical and well-studied organic reactions, this approach can contribute to the rapid development of new drugs to treat this pandemic respiratory disease that has devastated many lives. Despite significant improvements described here, it is essential to mention that synthesis optimization in large-scale and clinical tests will be crucial to develop a new and efficient drug to treat COVID-19.

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Conflicts of Interest

The authors declare no conflict of interest.

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