

# Teriflunomide and COVID-19: A Friend or Foe?!

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**Abstract:** Unfortunately, the coronavirus disease 2019 (COVID-19) pandemic has become an irritating universal crisis. Thus, the discovery/identification of prospective drug candidates to disband the branched health issues caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become urgent. This current research sheds light on the repositioning possibility of the potent antirheumatic drug teriflunomide to act as an efficient anti-SARS-CoV-2/anti-COVID-19 remedy. Herein, a motivating *in silico* molecular docking/modeling study of teriflunomide explores its potential inhibitory actions on the novel coronaviral-2 RNA-dependent RNA polymerase (nCoV-RdRp) enzyme/protein was reported. Interestingly, the computational analysis of the teriflunomide superior inhibitory binding mode in the binding cavity of one of the active sites of the nCoV-RdRp detected that teriflunomide molecule shows considerably stronger inhibitory binding interactions and better inhibitory binding affinities (it shows lower binding energies which reached -9.70 kcal/mol) than both used references. It was reported that teriflunomide potently impairs viral replication/reproduction by employing two distinct action mechanisms. Thus, the existing study's findings surprisingly uphold teriflunomide's double mode of action. In conclusion, the presented research work paves the way to biologically and clinically begin exploring the promising properties of teriflunomide to strongly hit the SARS-CoV-2 particles of the different strains and inhibit their pathogenic replication in an integrative triple mode of action. Hopingly, the potential sextet COVID-19 attacker teriflunomide can be rapidly subjected to the various *in vitro/in vivo*/clinical anti-COVID-19 assays/trials in a serious attempt to assess its comprehensive bioactivities against COVID-19 to be effectively used in SARS-CoV-2 infections therapy soon.

**Keywords:** Anti-SARS-CoV-2 drug; COVID-19 therapy; coronaviral/coronaviral-2; RNA-dependent RNA polymerase (RdRp); cytokine storm; teriflunomide; leflunomide; remdesivir; GS-441524; *in silico* molecular docking/modeling

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## 1. Introduction

On the latest days of 2019, a novel type of coronaviruses (2019-nCoV), known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dramatically appeared in Wuhan (China) [1]. Transmission of this occult single-stranded positive nonsegmented RNA viral microbe is continuous, resulting in the prevalence of the virus-specific illness, coronavirus disease 2019 (COVID-19), with its prominent signs/symptoms mainly existent in the human respiratory system (reach to severe pneumonia and death in many cases) [1,2]. The SARS-CoV-2 has sheaths that enfold around the RNA genome (virion, which is the whole virus, is

round/oval, usually polymorphic, with a diameter of approximately 50-200 nm) [3]. Despite the presence of some known agents and new compounds that are undergoing extensive investigations and clinical trials for their expected promising anti-SARS-CoV-2 and/or anti-COVID-19 pharmacological activities (e.g., molnupiravir, cyanorona-20, CoViTris2020, and ChloViD2020), there is no specific and effective potent drug therapy successfully 100% approved and used for the comprehensive COVID-19 therapy to date at the last quarter of 2021 [4–7]. The old drugs are known for their antiviral activities or any activities that may hinder any stage(s) of the coronaviral life cycle are of special interest for medicinal chemists for the repurposing strategies against the COVID-19. Antirheumatic medicines, such as chloroquine, hydroxychloroquine, leflunomide, and teriflunomide, are among the drugs under the microscope in this regard because of their possible antiviral activities [6,8–10]. To the best of my knowledge, there is no reported comprehensive, evidence-based study exploring and proving the possibility of repurposing leflunomide and/or its active metabolite teriflunomide against the untreatable COVID-19 to date.

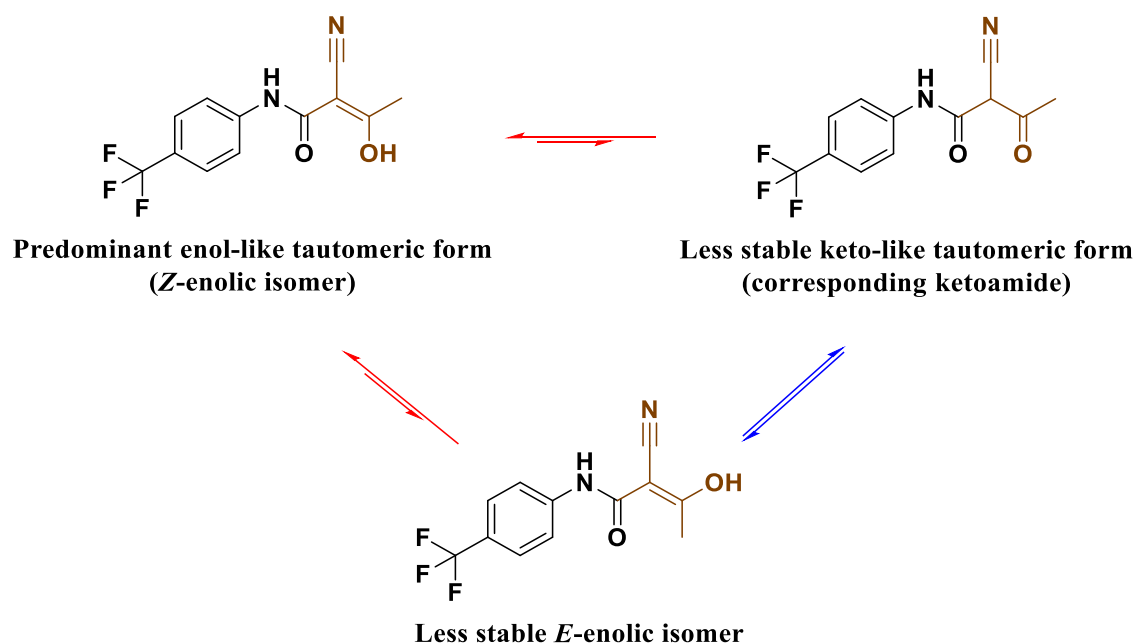
Teriflunomide (chemically, the IUPAC name of its molecular structure is 2-cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]-2-butenamide), a once-daily orally-administered potent immunosuppressive/immunomodulatory agent, gained its regulatory approvals in most countries (including the United States and the European Union) for the effective treatment of the moderate-to-severe multiple sclerosis and some other rheumatic conditions [11]. It was initially identified as the major active metabolite of its parent antirheumatic drug leflunomide [12]. Leflunomide is converted by the action of the *in vivo* metabolic activation into teriflunomide, which is specifically responsible for almost the parent drug's complete biological and therapeutic actions (Figure 1) [12]. The single chemical distinction between the two molecules is the opening of the isoxazole nucleus to free and generate the two biologically-important moieties, cyanide, and hydroxyl groups, in the pharmacologically-active teriflunomide molecule instead of being inclosed as less-active heteroatoms in the heterocyclic nucleus (the isoxazole ring) of the leflunomide molecule [12,13]. The previous molecular pharmacokinetic studies revealed that the teriflunomide molecule subsists in two different tautomeric structures, enol/keto forms, in the aqueous media like blood and biologic fluids; the enol form, in turn, exists either in the *Z*- or *E*-configuration (*Z-E* interconversion), with the *Z* enolic form being the preferable structure as it is the most stable form among all the three isomers as schemed in Figure 2 [13,14].

It is worth mentioning that there are two principal concerns in the infection of SARS-CoV-2 particles, the viral load (almost the first phase of the infection, which is mainly characterized by the rapid SARS-CoV-2 multiplication) and the immune response (the second phase of the infection, which is characterized by the severe immune-mediated damage) [15]. If both critical phases are effectively suppressed and sufficiently managed, the disease will be significantly controlled and treated. Additionally, the success in managing any following secondary and marginal health issues after the coronaviral-2 attack should also be considered. In principle, teriflunomide, with its exceptional synergistic antiviral/immunomodulatory dual mode of action, can expectedly fulfill the managing strategy for COVID-19 [9–11]. First, it can significantly decrease and control the SARS-CoV-2 viral load, and second, it can effectively combat and overcome the massive cytokine immune outbreak. The main goal of the current research study is to find any supplemental anti-SARS-CoV-2 activities (anti-COVID-19 mechanisms of action) of teriflunomide to evaluate the potentials of its clinical medical use as

an available choice to be combined in the ideal therapeutic regimens and protocols designed and recommended for the effective treatment of COVID-19.



**Figure 1.** Teriflunomide *in vivo* generation in the human body from its parent drug leflunomide.

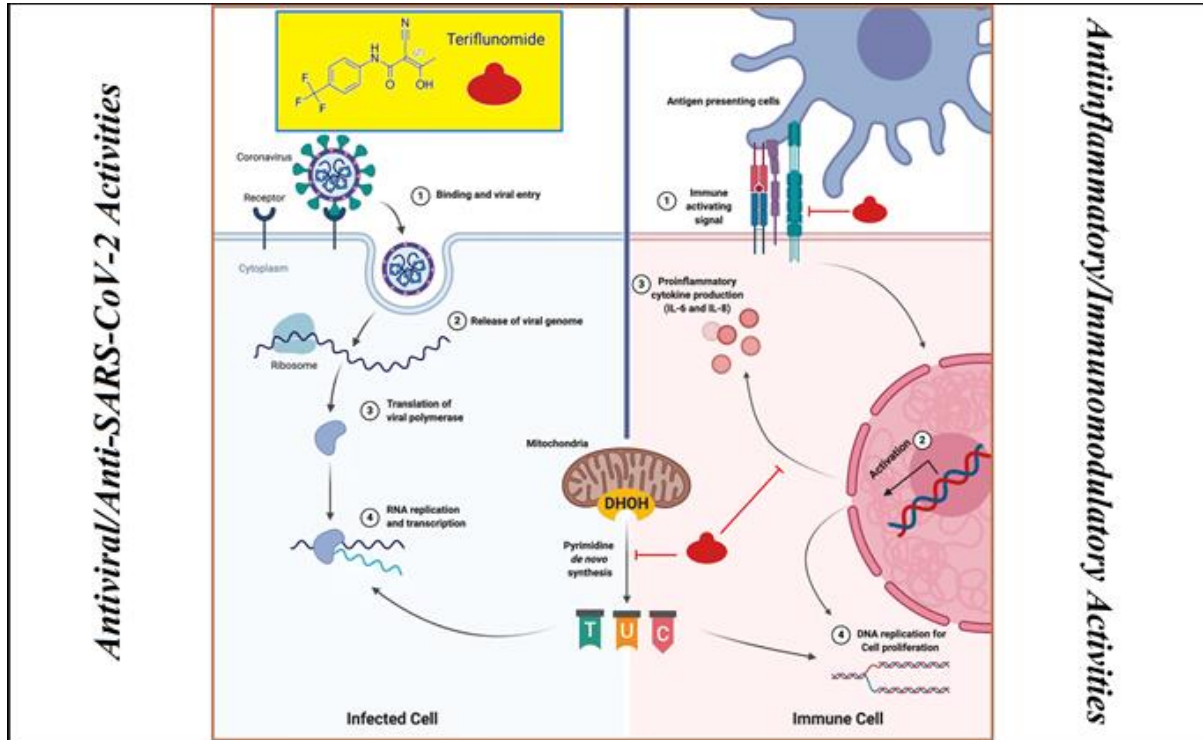


**Figure 2.** Teriflunomide *in vivo* isomerization cycle in aqueous media.

RNA-dependent RNA polymerase (RdRp) is certainly considered one of the most interesting and effective targets for designing/exploring new therapies against the scary SARS-CoV-2 [6,7]. Structurally, RdRp is the nonstructural protein 12/7/8 (nsp12/7/8); nsp12 is the polymerase that binds to its critical co-factors, nsp7 and nsp8 [16]. It is a very pivotal enzyme in the necessary replication and transcription of the coronaviral genome. As a consequence, the strong inhibition of the bioactivities of this enzyme will significantly impair the replication of SARS-CoV-2 [6,7,16]. The close similarity between the teriflunomide chemical structure and the nucleoside analogs chemical structures motivated me to expect and suggest the possibility that teriflunomide can act as a potent inhibitor of the novel coronaviral-2 RdRp (nCoV-RdRp or CoV-RdRp). To precisely assess this possibility, a computational molecular docking and modeling study was done using the new and credible molecular docking webserver COVID-19 Docking Server [17]. The known remdesivir comparator protocol was used for the comparison purpose using both remdesivir and its major active metabolite (GS-441524) as the reference ligands [18]. The obtained results were promising and encouraging since they disclosed the strong inhibitory binding affinities of teriflunomide with the active amino acid residues of one of the recognized binding pockets of the nCoV-RdRp active site (either in its complicated state with RNA or in its free state). Surprisingly, teriflunomide significantly surpasses both the

reference ligand remdesivir and the active metabolite GS-441524 in their estimated binding energies with the nCoV-RdRp.

According to these new findings and all the prior literature data and information [9-12,15,19–21], my present comprehensive hypothesis can be interestingly established and presented, declaring that teriflunomide can supposedly act as a very effective therapeutic candidate for the treatment of COVID-19 infection *via* two broad integrative effective modes of action (i.e., a dual-mode of action), each of which has three different, synergistic mechanisms of action (Figure 3).



**Figure 3.** Expected dual mode of action of teriflunomide for the effective treatment of COVID-19 (six synergistic mechanisms of anti-COVID-19 action, which are complementary to each other).

The first triple pathway is the new anticoronaviral (anti-SARS-CoV-2) mode of action, which involves: 1. inhibiting the coronaviral replication through interfering with the nucleocapsid tegumentation of SARS-CoV-2, which results in disturbed SARS-CoV-2 virion assembly; 2. interfering with the coronaviral multiplication in the different infected host cells through inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which takes an important key role in the *de novo* synthesis of natural pyrimidine and uridine monophosphate (rUMP), resulting in impaired pyrimidine *de novo* synthesis and depletion of the available pyrimidine pools, this, in turn, causes a significant decrease in the nucleoside/nucleotide availability needed for the viral RNA generation and SARS-CoV-2 reproduction (i.e., antimultiplicative effect); and 3. blocking the coronaviral replication through acting as a strong direct nCoV-RdRp inhibitor (a new potential effect explored in the present work). On the other hand, the second triple pathway is the potent immunomodulatory (anti-cytokine) mode of action (complementary to the first triple pathway), which includes: 1. reducing the cytokines generation, especially the interleukin 6 (IL-6), which is found to significantly contribute to the human acute respiratory distress syndrome (ARDS) in the SARS-CoV-2 infection; 2. inhibiting the activation of the immune cells (mainly, inhibiting the autoimmune lymphocytic activities, adhesion molecules expression, and immunoglobulin production) through disrupting the interactions with the antigen-presenting cells (by the integrin

activation impairment and reduced protein aggregation); and 3. impairing the cellular (mainly, the activated autoimmune cell) reproduction and proliferation through the previously-mentioned strong action of blocking the pyrimidine *de novo* biosynthesis and, therefore, significantly depleting the intracellular pyrimidine pools. The first mode of action is concerned with the SARS-CoV-2 particles, while the second is especially concerned with the human cells. Both effective modes of action are supposed to synergistically act in a complementary way in the therapeutic battle against COVID-19.

In short, an interesting *in silico* molecular docking research study of teriflunomide as a potential nCoV-RdRp inhibitor (anti-SARS-CoV-2 therapeutic candidate) was reported. Thus it paved the way to establish the theoretical base for the clinical investigation of the promising actions of teriflunomide to cure the COVID-19 via attacking the SARS-CoV-2 effectively and efficiently inhibiting its replication in a triple mode of antiviral action (it acts as a potential triple attacker of the virus, and as a sextet attacker of the COVID-19 in general) through combining the recently-discovered nCoV-RdRp-inhibiting properties herein with the preceding-known two antiviral mechanisms of action (along with the original three potent mechanisms of immunoregulatory action).

## 2. Materials and Methods

To specifically evaluate the nCoV-RdRp-inhibiting properties among the overall potential anti-COVID-19 activities of the antirheumatic drug teriflunomide before performing its planned experimental anti-COVID-19 biological evaluation (through the *in vitro/in vivo* studies and preclinical/clinical trials), accurate computational docking of the ligand teriflunomide molecule in the nCoV-RdRp enzyme has been primarily accomplished through utilizing the most known and credible molecular docking engines in the cheminformatics/bioinformatics field (e.g., the docking engines of GemDock, Discovery Studio, and GOLD). Trying out various programs of docking software was to make sure of the results and guarantee the data reproducibility. The comprehensive integration of the expected key pharmacophoric features with the analytical data of interaction energies detected functionally crucial amino acid residues in the active binding pockets of the SARS-CoV-2 RdRp and the *in silico*-predicted prevalent inhibitory binding modes with the very potent standard reference compounds (e.g., remdesivir and GS-441524). Computationally, the molecular docking outcomes were very promising and encouraged me to use the newly-designed web docking servers (especially programmed and founded after the COVID-19 pandemic has occurred, in 2020, for the sake of immediate assessment of the potential anti-COVID-19 activities of the recommended and potential ligands) for the specific and direct docking of the SARS-CoV-2 RdRp structure. Therefore, the COVID-19 Docking Server was specifically used [17].

The used COVID-19 Docking Server application (AutoDock Vina is employed as the main molecular docking engine in this new computational server) is web-based software for interactively docking small molecules/peptides/antibodies against the possible COVID-19 protein targets to predict the binding modes between the SARS-CoV-2 targets and the potential ligands together with screening and estimating the anti-SARS-CoV-2 activities of these ligands (i.e., the program furnishes an open and free interactive, up-to-date tool using a highly accurate information-based scoring function for evaluating the candidate binding poses for the particular prediction of the COVID-19 target-ligand interactions and the following drug discovery for the COVID-19 therapy) [17]. According to this interactive server, the structures of all the

functional and structural protein targets (enzymes, receptors, etc.) involved in the replication/reproduction life cycle of the coronavirus 2 were either directly collected or indirectly constructed based on their known homologs of the entire family of coronaviruses (by employing the homology modeling module of Maestro 10, website: [www.schrodinger.com](http://www.schrodinger.com)), and got ready for direct and perfect docking on this web-based software [17]. The 3D protein structure of the nCoV-RdRp (nsp12/7/8) cocrystallized in a complex with RNA, and the triphosphate form of remdesivir (RTP) was downloaded from the Protein Data Bank (PDB) database with the code of 7BV2 [16,22]. Therefore, two major active sites for small/simple molecule docking of nCoV-RdRp were identified: the RTP binding site (RTP site, i.e., for RdRp-RNA or RdRp with RNA), and the RNA binding site (RNA site, i.e., for RdRp alone or without RNA) [17]. For docking of only a single small molecule each time, the "Docking" mode box as the computational type must be particularly chosen for each specific target (this is the user selection in the current state). To get the most precise results as much as possible, an average exhaustiveness selection of "12" has opted. Teriflunomide was the tested ligand, while remdesivir and GS-441524 were used as the positive reference control ligands. The obtained binding complexes were visualized in 3D models by JSmol. The data outputs of the COVID-19 Docking Server include both the binding free energy score values (in kcal/mol) and rescoring binding affinity random forest (RF) score values (expressed as pKd " $= -\log(Kd)$ ") (Kd is the dissociation constant which is commonly used to quantify the strength with which a ligand binds with a specific protein. This important equilibrium constant measures the tendency of a specific protein-ligand complex to separate into its constituent components; it is used herein to characterize the degree of tightness of proteins to their binding ligands. That is, by interpreting complexes whose components are more likely to dissociate "high dissociation constants" as loosely bound "low binding affinities" and vice versa. In brief, higher pKd values reflect exponentially greater binding affinities).

### 3. Results and Discussion

The recognition of the SARS-CoV-2 protein-ligand interactions represents a very crucial challenge in drug discoveries for the management and treatment of COVID-19.

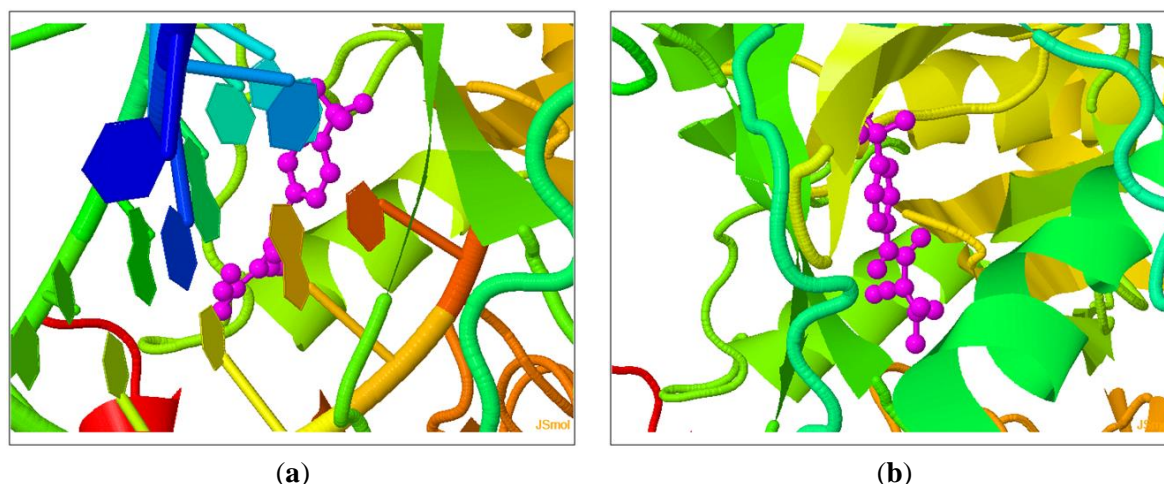
**Table 1.** Score values of the two computationally-assessed biological anti-COVID-19 activities (against SARS-CoV-2 RdRp-RNA and SARS-CoV-2 RdRp, respectively) of the target teriflunomide and the two bioactive references (remdesivir and GS-441524), respectively, using the COVID-19 Docking Server methodology (the table displays the top docking model score value "ranked 1", i.e., the best binding mode score value or the least predicted binding free energy value, in kcal/mol, together with its corresponding highest binding affinity RF score value, expressed as pKd value, for each compound with each targeted RdRp site of the two ones).

Classification	Compound Name	Top Pose Score Values for Docking of SARS-CoV-2 RdRp			
		nCoV-RdRp-RNA (RTP Site)		nCoV-RdRp (RNA Site)	
		Score Value (kcal/mol)	RF Score Value (pKd)	Score Value (kcal/mol)	RF Score Value (pKd)
<i>Tested Drug</i>	Teriflunomide	-9.70	6.99	-7.80	5.66
<i>Reference Drugs</i>	Remdesivir	-8.30	5.38	-7.10	5.27
	GS-441524	-9.10	6.47	-7.00	4.86

The primary theoretical prediction of the anti-nCoV-RdRp properties of the presently-repurposed antirheumatic drug teriflunomide will assist us in taking a step forward, among all the needed steps to explore the comprehensive anti-COVID-19 bioactivities of this target compound. This computational modeling prediction will also significantly help us obtain a fundamental understanding of the major mode of anti-SARS-CoV-2 action of teriflunomide

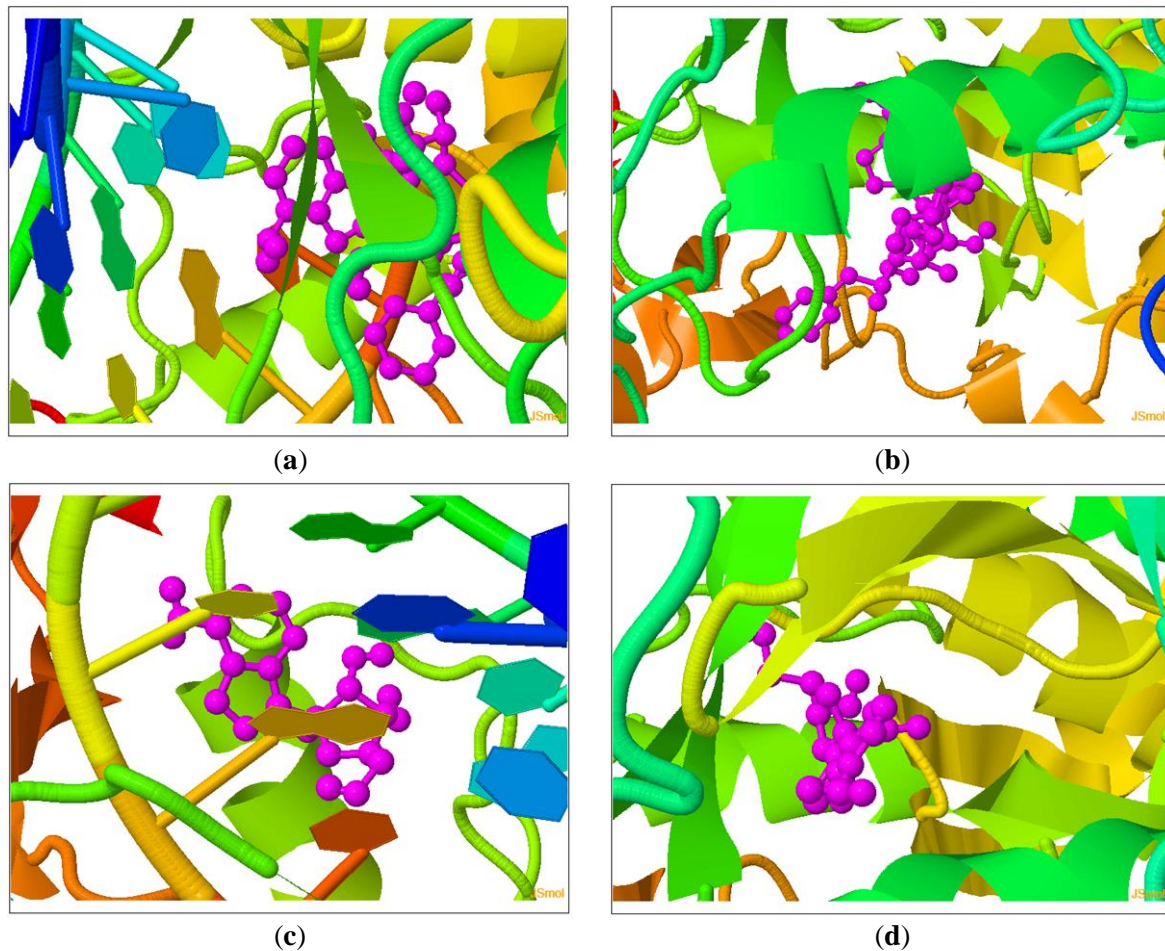
and the drug's expected degrees of effectiveness and potency. The accurate docking procedures were relatively sufficient for these purposes since they were performed in the nCoV-RdRp in each of its two statuses, the complex-with-RNA status and the free one. The detailed results of all the calculations for the top model in each case are shown in Table 1.

On close checking of the score values of docking of nCoV-RdRp-RNA and nCoV-RdRp using the COVID-19 Docking Server (shown in Table 1), it is obviously noticed that teriflunomide is specifically ranked first in its *in silico* inhibitory binding affinities and potencies with binding free energies of -9.70 and -7.80 kcal/mol and with corresponding rescoring RF values of pKd of 6.99 and 5.66, respectively. The binding affinities of teriflunomide considerably surpass those of the active references remdesivir (it has binding free energies of -8.30 and -7.10 kcal/mol, and RF score values "expressed as pKd" of the inhibitory binding affinities of 5.38 and 5.27, respectively) and GS-441524 (it has binding free energies of -9.10 and -7.00 kcal/mol, and RF score values "expressed as pKd" of the inhibitory binding affinities of 6.47 and 4.86, respectively). Teriflunomide strongly binds to the SARS-CoV-2 RdRp (with RNA) in their complex (i.e., teriflunomide molecule forms a stable complex with the SARS-CoV-2 RdRp-RNA) with a relatively low binding free energy, which is the lowest among all the three examined ligands (i.e., significantly smaller than the binding free energies of both remdesivir and GS-441524 in their complexes with RdRp-RNA).



**Figure 4.** Screenshots of COVID-19 Docking Server outputs of the top predicted binding model of the docking of teriflunomide molecule (colored pink) in (a) nCoV-RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other different colors; Cartoon Style); (b) nCoV-RdRp "RNA site" (PDB code: 7BV2; colored with other different colors; Cartoon Style).

GS-441524 and its parent potent antiviral remdesivir come second and third, respectively, in their relative inhibitory binding/potency/efficacy on nCoV-RdRp. Therefore, the results clearly express the higher superiority of the antirheumatic teriflunomide over both of them as a potent anti-COVID-19 candidate agent. For more explanation, Figure 4a,b, and Figure 5a-d show the outputs of the COVID-19 Docking Server top (best) predicted binding mode and model of docking of SARS-CoV-2 RdRp-RNA and SARS-CoV-2 RdRp with the potential inhibitor teriflunomide and the two potent references remdesivir and GS-441524, respectively. These promising data of the expected binding modes of teriflunomide with the protein enzyme SARS-CoV-2 RdRp (with/without RNA) considerably comply with and support the formerly-suggested mechanism of the anti-COVID-19 effect of teriflunomide (Figure 3).

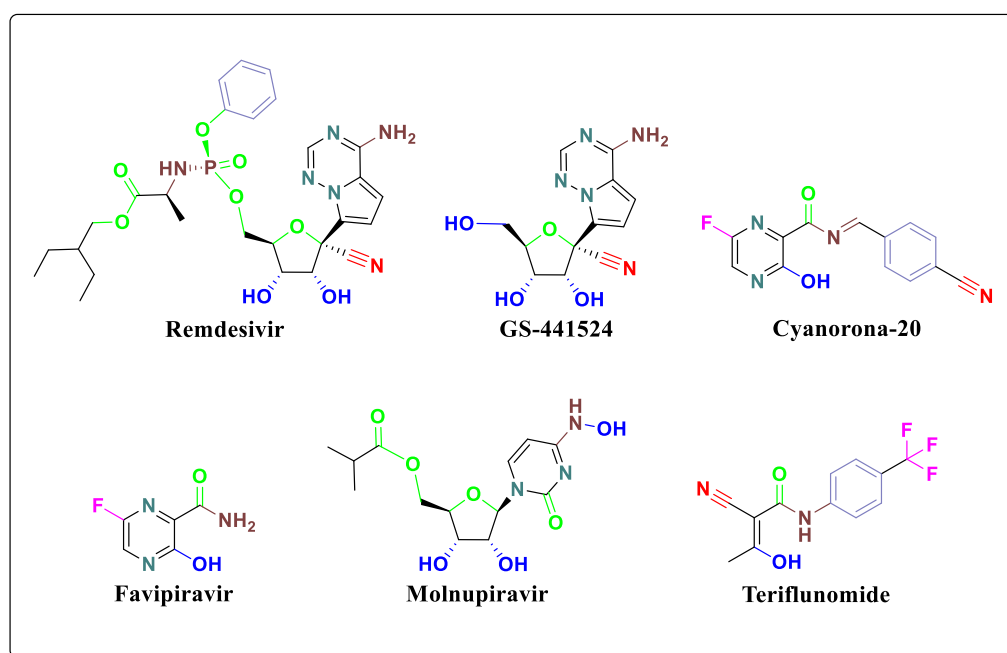


**Figure 5.** Screenshots of COVID-19 Docking Server outputs of the top predicted binding model of the docking of: (a) Remdesivir molecule (colored pink) in nCoV-RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other different colors; Cartoon Style); (b) Remdesivir molecule (colored pink) in nCoV-RdRp "RNA site" (PDB code: 7BV2; colored with other different colors; Cartoon Style); (c) GS-441524 molecule (colored pink) in nCoV-RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other different colors; Cartoon Style); (d) GS-441524 molecule (colored pink) in nCoV-RdRp "RNA site" (PDB code: 7BV2; colored with other different colors; Cartoon Style).

Interestingly, the significant binding activity of the teriflunomide molecule makes it more stabilized and firm in the relevant enzymatic binding pocket of nCoV-RdRp (based on the promising results of the current molecular docking research, teriflunomide molecule potently interacts with some pivotal amino acid residues in one of the active binding pockets of the SARS-CoV-2 RdRp enzyme with a considerable number of hydrogen bonds, i.e., with significant blocking binding strength), and therefore, more efficient in blocking and hindering the RdRp performance/bioactivity than the two reference molecules. In Addition, the chance that teriflunomide molecule may undergo intracellular metabolism into less active forms by human cellular enzymes is extremely limited or even totally excluded since, biologically and clinically, teriflunomide is almost the final active metabolite that can be biogenerated from the parent antirheumatic leflunomide. Therefore, teriflunomide has an extra advantage, over remdesivir and most other under-investigation anti-COVID-19 drug candidates, of being nonconvertible to other inactive or less active forms *in vivo*. It is worth mentioning that teriflunomide has significant chemical structural similarity with many investigational anti-COVID-19 drug candidates, like remdesivir, GS-441524, cyanorona-20 [6], favipiravir [23], and molnupiravir [5], as it has the same key anti-SARS-CoV-2 RdRp structural elements (e.g.,



cyano group, hydroxyl group(s), fluoro group(s), nitrogenous moieties, ketonic moiety/moieties, phenyl moiety, and aliphatic side chains) as almost all of them (Figure 6).



**Figure 6.** The significant similarity of the key anti-nCoV-RdRp functional moieties of the chemical structures of teriflunomide and many investigational potential anti-COVID-19 drugs.

The chemical structure of teriflunomide specifically shows higher degrees of balanced conformational and orientational flexibilities when compared to the structures of the two reference drugs, remdesivir, and GS-441524. These exceptional flexibilities of teriflunomide chemical structure are evidently observed in the resulted top docking poses in the target proteins nCoV-RdRp-RNA and nCoV-RdRp as formerly shown in Figure 4a,b, respectively. The Teriflunomide molecule has a much simpler chemical structure with lower molecular weight/volume when compared to the structures of both used references. The highly-balanced flexibility of the uncomplicated structure of teriflunomide is crucially needed for outstanding and perfect positioning of the drug molecule to be extremely superimposable in the active binding pocket and cavity of the COVID-19 polymerase protein (i.e., required for the extreme lock-and-key positioning) [24]. This, in turn, results in more adequate (i.e., potent) inhibition and impairment of the replication activities interceded and controlled by the SARS-CoV-2 RdRp. Foreseeably, the highly-balanced flexibility of the teriflunomide molecule significantly increases its ability to be a very potent anti-SARS-CoV-2 candidate agent. The collective results of the present work are expected to pave the way for medicinal chemists, pharmacologists, clinical researchers, and physicians to start their deep and extensive biological and clinical studies and trials to investigate and assess the significant and effective capabilities of teriflunomide to inhibit and hinder the targeted coronavirus-2 replication/reproduction processes and treat the COVID-19 condition as a whole.

#### 4. Conclusions

In total, in the light of the proven potent antiviral/immunomodulatory activities of teriflunomide, along with the promising computational docking results of the present study, we can build a strong starting base for the encouraging abilities of the drug teriflunomide to effectively hit the SARS-CoV-2 particles and fight their accompanying cytokine storm in the

human body, and therefore, providing effective dual treatment for COVID-19. Teriflunomide significantly inhibits SARS-CoV-2 RdRp (in its complex state with RNA) with a very promising low inhibitory binding energy of -9.70 kcal/mol. The current research study supports the hypothesis that teriflunomide may inhibit SARS-CoV-2 replication in a triple mode of action by combining the newly-discovered mechanism of nCoV-RdRp-inhibiting with the previously-known two mechanisms of anticoronaviral-2 action. Moreover, teriflunomide attacks the COVID-19 inflammatory immune storm in a triple mode of very strong immunomodulatory action. Hopefully, the triple SARS-CoV-2 assailant (or the sextet COVID-19 attacker) teriflunomide can be further subjected to several *in vitro/in vivo* anti-SARS-CoV-2 examinations together with the properly-designed preclinical/clinical anti-COVID-19 trials in a serious step to extensively evaluate and successfully confirm its comprehensive pharmacological bioactivities against SARS-CoV-2/COVID-19 to be efficiently used as an available choice in the COVID-19 therapy soon. In brief, teriflunomide is computationally and hypothetically proposed to be a potential effective anti-COVID-19 drug (i.e., a potent anticoronaviral-2 candidate agent), as it can potentially take comprehensive roles in the treatment of COVID-19 *via* its integrative dual-mode of six synergistic mechanisms of action.

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## Conflicts of Interest

The author of this new work declares no conflicts of interest.

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