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Original Article

Remdesivir Analogues as Promising SARS-CoV-2 RNA-Dependent RNA Polymerase Inhibitors: A Molecular Docking Study

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Abstract

Background: Coronavirus RNA-dependent RNA polymerase (RdRp) is vital for viral replication and serves as a major therapeutic target. During the early stages of the COVID-19 pandemic, remdesivir (RDV), a well-characterized RdRp inhibitor, represented an effective therapeutic agent against SARS-CoV-2 infection.

Method: Structurally similar RDV analogues were retrieved from the ZINC, CACTUS, and ChEMBL databases through ligand-based similarity searching. The corresponding triphosphate forms were modeled based on the active remdesivir metabolite, remdesivir triphosphate (RDV-TP), and evaluated by molecular docking against SARS-CoV-2 RdRp using AutoDock Vina implemented in PyRx.

Results: Among nucleotide analogues and their corresponding triphosphate forms, compound 2A (5-(7-amino-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-tetrahydro-2-(hydroxymethyl)furan-3-ol) exhibited the most favorable predicted binding affinity in its triphosphate form.

Conclusion: These findings suggest that novel nucleotide analogues hold promise as potential drug candidates for the treatment of SARS-CoV-2 infection.

Keywords: COVID-19, Drug Discovery, Molecular Docking, RdRp, Virtual Screening

Introduction

There are global health concerns about a new SARS-like coronavirus (SARS-CoV-2) which is closely related to severe acute respiratory syndrome [1]. All scientists and research groups are struggling to combat this serious problem. The development of an effective drug against coronaviruses is an ideal goal in the current situation. Understanding the viral life cycle and selectively targeting essential viral processes without adversely affecting host-cell function represents an important therapeutic strategy [2]. Remdesivir (RDV, formerly GS-5734) as a broad-spectrum antiviral nucleotide analogue had shown *in vitro* and *in vivo* antiviral activity against coronaviruses [3]. Evaluation of its mechanism of action demonstrates inhibition of RNA-dependent RNA polymerase (RdRp) complex which is a critical viral enzyme for coronavirus genome replication [4].

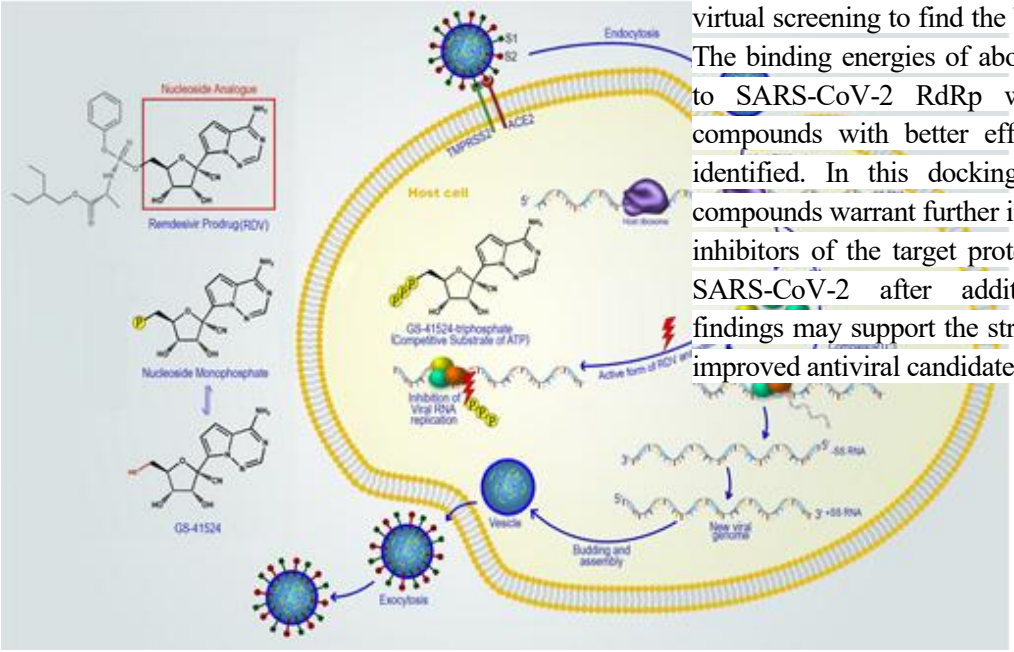
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There are some reports about inhibition of the viral RNA synthesis by RDV for all coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-*2*) RdRp proteins [5]. Recently, remdesivir has been confirmed as a drug candidate for treating COVID-19 patients [6]. This effective antiviral therapeutic can reduce hospitalizations and mortality as a preventive and therapeutic agent.

RDV, a monophosphoramidate prodrug, could readily cross the cell membrane, be metabolized to nucleoside monophosphate and eventually to the active nucleoside triphosphate form (RDV-TP). This active form can be utilized as a substrate for most viral RdRp complexes (**Figure 1**). In fact, RDV-TP is an adenosine triphosphate (ATP) molecule analogue which can compete with the nucleotide during viral RNA synthesis (Figure 1). Remdesivir causes delayed chain termination during viral RNA synthesis, which blocks transcription after addition of the next incoming nucleotide by forming a phosphodiester bond [3]. Probable inhibition of RdRp by new RDV analogues against this emerging disease could provide a starting point for a structure-guided approach to the design of new drugs [7].



In this report, the docking studies were performed on RDV, its metabolite (GS-41524), and new RDV analogues retrieved from various databases based on virtual screening to find the best inhibitors of RdRp. The binding energies of about 200 RDV analogues to SARS-CoV-2 RdRp were investigated, and compounds with better efficacy than RDV were identified. In this docking study, the identified compounds warrant further investigation as potential inhibitors of the target protein of RdRp present in SARS-CoV-2 after additional studies. These findings may support the structure-guided design of improved antiviral candidates.

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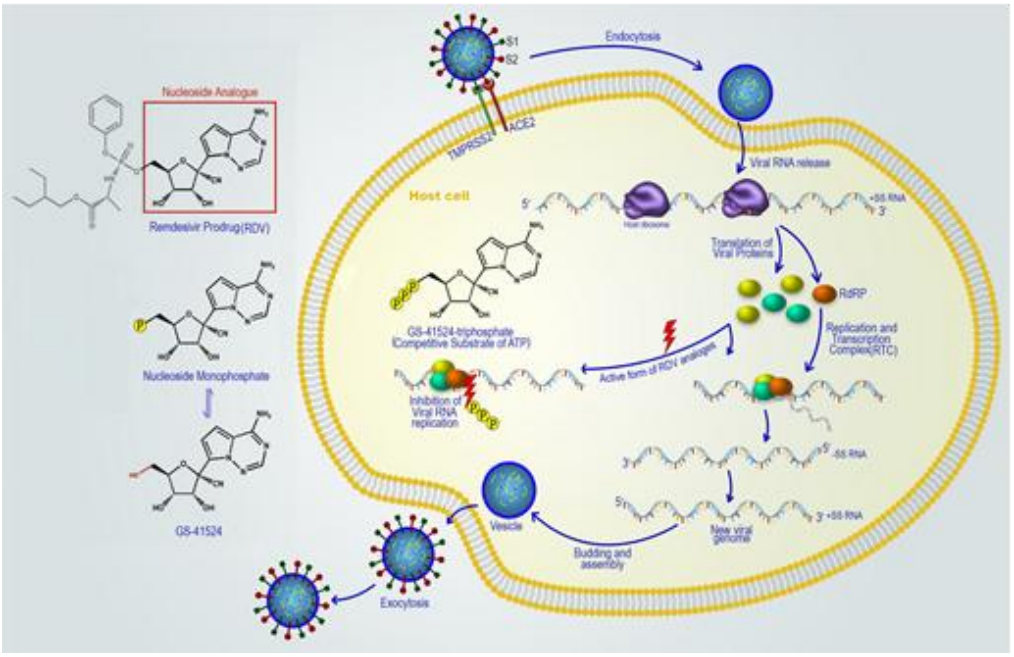


Figure 1. Mechanism of remdesivir against SARS-CoV-2. The figure shows remdesivir and its metabolites (GS-41524, GS-41524-monophosphate, and GS-41524-triphosphate); SARS-CoV-2 entry into the cell and its RNA synthesis, which can be blocked by the active form of remdesivir (GS-41524-triphosphate).

Experimental

Virtual screening

The dataset of RDV analogues was selected and downloaded from the ZINC database (similarity 60%) [8], Cactus (pass prediction range for antiviral activity, drug-likeness prediction, Tanimoto index 80%) [9], and Chemical Entities of Biological Interest; ChEBI (similarity 60%) [10]. Over 200 compounds were identified by the virtual screening strategies. All compounds were prepared and optimized in their main forms and three phosphate forms.

Molecular docking procedure

PyRx-Vina software was used in all docking experiments [11], with the optimized SARS-CoV-2 RdRp (PDB ID: 6BV2) model as the docking target. Before docking the compounds on the target, the protein was edited. The water molecules were removed; the polar hydrogen atoms were added to the amino acid residues, and Gasteiger charges were assigned to all atoms of the protein. Then the protein in PDBQT format was used as an input for the PyRx program. Prior to docking, binding pocket residues was performed as center (x=92.2110812568, y=82.8591589959, z=100.950867622), size (x=50.5460942617, y=37.4432794079, z=48.0054690025). The docking grid was set up around the predicted binding site residues, covering the key residues to reduce the search space for ligand optimization. An automated docking engine was utilized to screen the composed docking library, and the compounds were ranked based on a scoring function that approximates the ligand binding affinity in kcal/mol. The top hits from the first round of docking were selected after extensive post-docking analysis by comparing their predicted binding energies.

Analysis of Protein-Ligand Interaction

Interactions of ligand-receptor complexes were examined by Discovery Studio Visualizer 2020 (BIOVIA, 2017). Compounds with the most favorable binding energies (≤ –7.5 kcal/mol for the remdesivir active form) were selected for further analysis.

ADMET Profiling

To evaluate the potential pharmacokinetic properties of the top compounds, preliminary computational screening was performed using SWISS ADMET profiling to estimate their toxicity and drug-likeness [12-14].

Results and Discussion

Prior to performing ligand docking against RdRp, the structures of small molecules were ensured to be in the optimized active (triphosphate) form [15, 16]. During all of the docking experiments, the active site

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(ALA688, THR687, ASN691, ASP623, CYS622, SER682, VAL557, LYS545, ARG555) and ligands were treated as flexible.

Table 1 shows the docking score values of the top three ligands for the SARS-CoV-2 RdRps. The chemical structures of these inhibitors are shown in

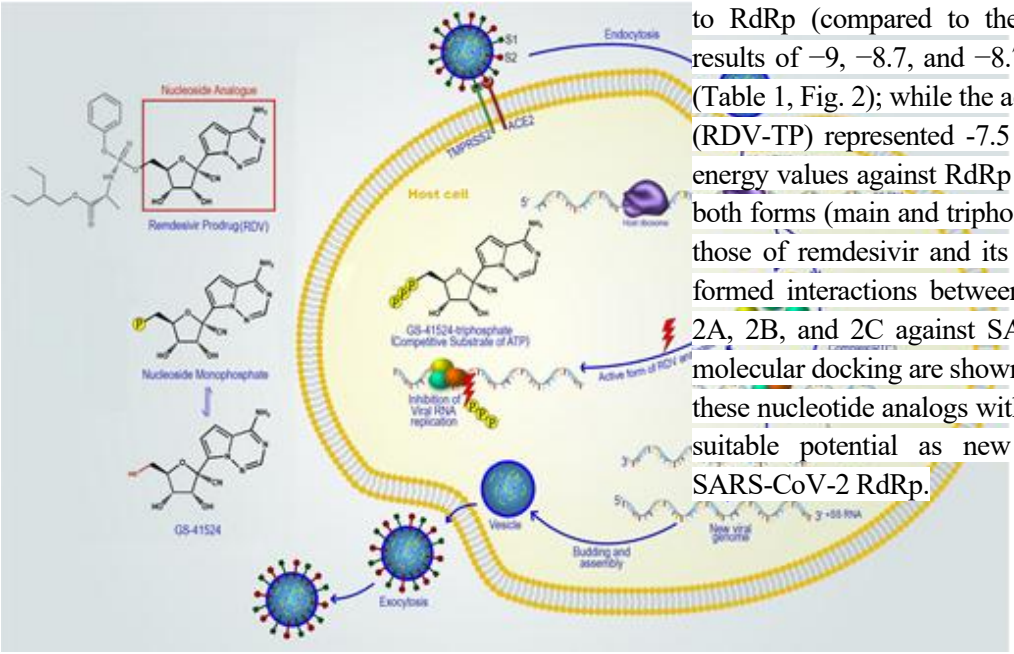


Figure 1.

The compounds 1A, 1B, and 1C are RDV analogues obtained from virtual screening of data sets (Figure 2), presenting the lower binding energies to RdRp among search results. The compounds 2A, 2B, and 2C are the triphosphate forms of the top three compounds displaying the lowest binding energies to RdRp (compared to the main structure), with results of −9, −8.7, and −8.7 kcal/mol, respectively (Table 1, Fig. 2); while the active form of remdesivir (RDV-TP) represented -7.5 Kcal/mol. The binding energy values against RdRp for these compounds in both forms (main and triphosphate) were superior to those of remdesivir and its triphosphate form. The formed interactions between RDV-TP and ligands 2A, 2B, and 2C against SARS-CoV-2 RdRp after molecular docking are shown in Fig. 2. Interestingly, these nucleotide analogs with simple structures have suitable potential as new candidates to inhibit SARS-CoV-2 RdRp.

Table 1. Data analysis of the flexible docking of compounds A, B, C and remdesivir in the active site of SARS-CoV-2 RdRp receptor

Compounds	Binding Affinity (Kcal/mol)	Intermolecular interactions
1A	-6.6	THR:556, ARG:555, THR:680, MET:542,
2A-TP	-9	ALA:688, THR:687,SER:759,ASN:691,THR:680, ARG:555,SER:682, TYR:456, ARG:624, THR:556, ASP:623
1B	-6.6	ALA:547, LYS:545, PHB:442
2B-TP	-8.7	ASN:691,CYS:622,THR:556, TYR:456, SER:682
1C	-6.5	ARG:555, GLN:444, LYS:551, ALA:547, PHE:442
2C -TP	-8.7	SER:759, SER:682, ASN:691, THR:680, SER:681, THR:687, ALA:688
RDV	-6.5	TYR:619, ARG:555, ASP:623
RDV-TP	-7.5	ASP:623, LYS:621, TYR:619, ARG:555,ASN:691

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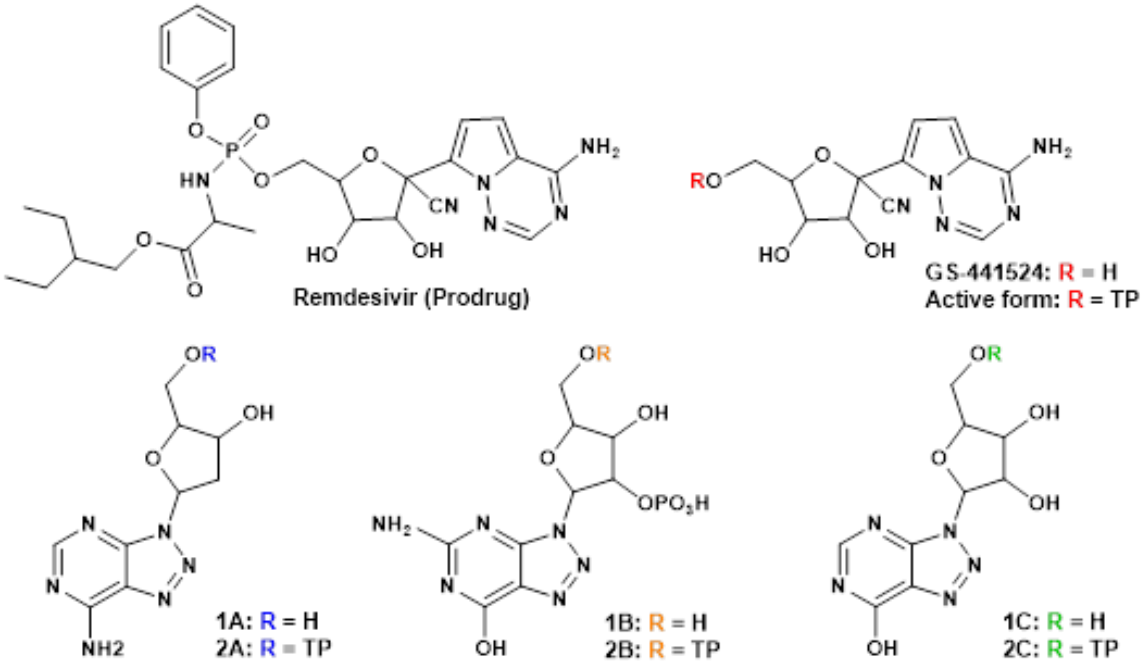


Figure 2. Chemical structures of the prodrug remdesivir, GS-41524, active form of GS-41524, and identified remdesivir analogues (A-C) based on a molecular docking study. TP: triphosphate

A comparative overview of interactions between the binding-site residues of the receptor protein RdRp and the identified inhibitors (RDV, RDV-TP, 1A-1C, and 2A-2C) is also represented in Table 1. Among the binding residues, those involved in making hydrogen bonds with ligands are shown, mentioning the type of hydrogen bond formed (in the context of hydrogen bond donor and acceptor), and the distance between the atoms forming them. RDV-TP organized 6H-bonds (ASP623, LYS 621, TYR 619, ARG 555, ASN 691, TYR 456) and eight hydrophobic interactions with the SARS-CoV-2 RdRp, which is reflected in its binding energy values (−7.5 kcal/mol) (Table 1, Figure 3).

Among the best RDV analogues shown in Figure 3, compound 2A was found to form 7H-bonds with RdRp residues. Additionally, 2B and 2C make 6H-bonds and 8H-bonds with the SARS-CoV-2 RdRp, respectively. Moreover, the compounds can tightly bind to the newly emerged coronavirus RdRp, hence interfering with the protein's function, leading to viral extinction. In addition, the physicochemical properties of the best ligands are presented in Table 2. All compounds are able to pass through the biological membrane based on Lipinski's drug-likeness.

In summary, the approved drug (remdesivir) and its selected analogues (1A-1C) form specific interactions with SARS-CoV-2 RdRp, with less favorable predicted binding energies than their active form (2A-2C). However, these new RDV analogs may require prodrug optimization (as RDV) to improve pharmacokinetic properties in comparison with the parent drug, mainly to cross the cell membrane. Probably, further optimizations may improve the efficacy of the selected analogues to inhibit SARS-CoV-2 RdRp and overcome to the newly emerged infection. However, further studies, including synthesis of these analogues and *in vitro* and *in vivo* evaluations, are necessary.

Table 2. Predicted physicochemical and drug likeness properties of potential SARS-CoV-2 ligands

Properties	1A	1B	1C
Formula	$C_9H_{12}N_6O_3$	$C_9H_{13}N_6O_8P$	$C_9H_{11}N_5O_5$
Molecular weight (g/mol)	252.23	364.21	269.21
Hydrogen bond donor	3	6	4
Hydrogen bond acceptor	7	12	9
CLogP	-1.11	-2.88	-1.61

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LogS	-1.03	-0.88	-0.66
Rotatable bonds	2	4	2
Bioavailability (10%)	0.55	0.11	0.55

Note: LogP: molecular lipophilicity; LogS: aqueous solubility

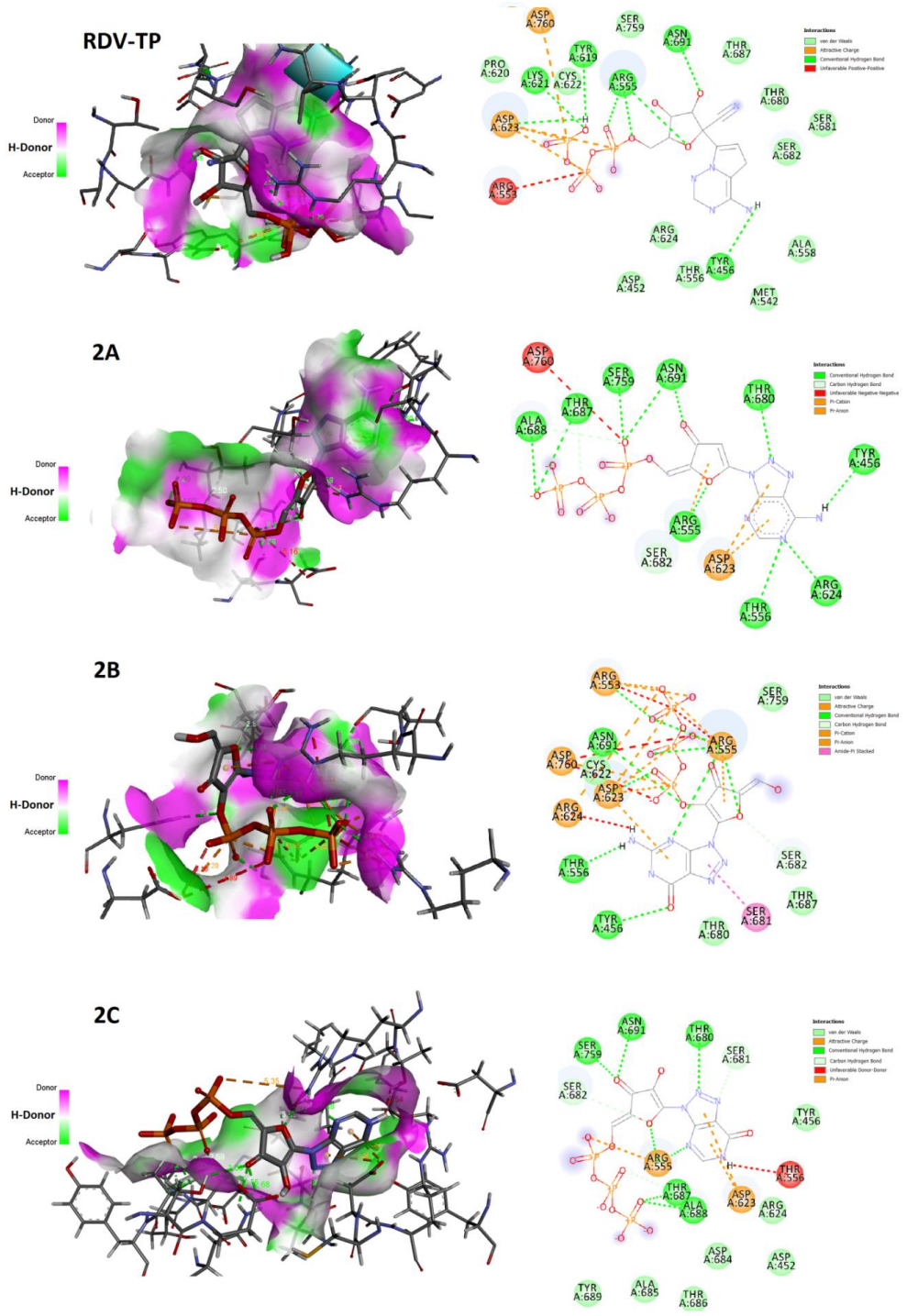


Figure 3. The contact model between compounds 2A, 2B, and 2C and SARS-CoV-2 RdRp in 2D and 3D forms, based on hydrogen-bond style visualized by Discovery Studio Visualizer

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Conclusion

COVID-19 pandemic is a public health crisis that needs to be managed effectively and quickly. About 2000000 deaths from this infection are reported up to the writing of this manuscript. In the current study, three compounds were identified as new inhibitors of the SARS-CoV-2 RdRp using molecular docking and binding energy calculations. The results showed the most favorable interaction of compounds (2A-2C) with the target protein, even better than the approved drug remdesivir. However, their biological activity has not been experimentally verified. These compounds have potential for further studies as novel drugs to overcome this new pandemic worldwide.

Competing Interests

The authors declare that they have no conflict of interest.

Author contributions

M.M: Investigation, Methodology, Software, Formal analysis, Editing.

K.R.S: Investigation, Software, Methodology, Formal analysis, Writing-original draft.

M.Z: Investigation, Methodology.

P.A: Review & editing.

A.T: Project administration, Conceptualization, Visualization, Supervision, Formal analysis, Writing-review & critical editing.

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