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Repurposing of Selected Antivirals and Anthelmintics for Treatment of COVID-19 (In Silico Study)

Salma Elmallah

Arab Academy for Science, Technology and Maritime Transport (AASTMT), Division of Pharmaceutical Sciences (Pharmaceutical Chemistry Department), College of Pharmacy, Abu Qir Campus, Egypt

Email: salmamallah@aast.edu

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ABSTRACT:

The 2019 Coronavirus Disease (COVID-19) is a highly contagious viral illness that has infected a lot of people, causing high rates of morbidity worldwide, turning mostly into a pandemic. The disease is caused by the SARS-CoV-2 virus, resulting in severe respiratory and hyper-inflammatory responses. Finding an immediate, effective cure for the recently discovered disease has drawn the interest of researchers to repurpose existing drug candidates, including different pharmacological classes such as antiviral and anti-inflammatory medicines. Numerous therapy modalities have been investigated for COVID-19 treatment. Niclosamide and Nitazoxanide, the FDA-approved anthelminthic medications, have been shown to be effective against several viral infections. This finding suggests the drugs' potential as antiviral agents. Also, many antiviral drugs with different mechanisms have shown great efficacy in treating COVID-19, such as Molnupiravir and Remdesivir. The primary objective of this brief study is to enhance the pharmacokinetics of the FDA-approved anthelmintic drugs Niclosamide and Nitazoxanide through in silico structural modification, aiming to confirm their repurposing as antiviral candidates against COVID-19. Computer-aided drug design (CADD) has contributed to the acceleration of drug discovery and the development of new analogs. Using molecular docking simulations (CDocker algorithm) and ADMET predictions, several analogs of both drugs were generated and assessed. Among the tested analogs, Niclosamide modification 2 demonstrated the most promising profile, with the least C-docker interaction energy, superior binding affinity compared to the parent Niclosamide and Nitazoxanide analogs, and comparable results to the benchmark antiviral Molnupiravir. This analog also exhibited improved hydrophilic interactions (and favorable pharmacokinetic properties, including enhanced solubility and absorption. These findings suggest that Niclosamide modification three and Nitazoxanide modification one could serve as a promising lead candidate for further synthesis and experimental validation in the development of new COVID-19 therapies.

KEYWORDS:

COVID-19 treatment, drug optimization, drug repurposing, in silico modeling, Molnupiravir and Remdesivir, Niclosamide and Nitazoxanide.

INTRODUCTION

At the end of 2019, the world encountered the most challenging pandemic of the modern era. A novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. [The COVID-19 outbreak has posed a serious threat to public health worldwide. Coronaviruses are a family of positive ribonucleic acid (RNA) viruses, leading to severe acute respiratory syndrome (SARS) and a variety of other respiratory infections.

Vaccines have reduced the transmission and severity of COVID-19, but there remains a lack of efficacious treatment for drug-resistant strains and more susceptible individuals. The aim of this study is to repurpose existing FDA-approved drug alternatives. Drug repurposing is the process of identifying new therapeutic uses for existing drugs. This strategy significantly reduces the time, cost, and risk associated with traditional drug discovery, as repurposed drugs have already undergone extensive safety and toxicity testing. In the context of the COVID-19 pandemic, where urgent therapeutic solutions are needed, repurposing offers an efficient and scientifically robust approach for accelerating drug development. The FDA-approved anthelmintics, Niclosamide and Nitazoxanide, have shown a promising ability to inhibit viral infections, including SARS-CoV, MERS-CoV, ZIKV, HCV, and human adenovirus, in nanomolar to micromolar potency with activity comparable to

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the currently used medications.[,]

Niclosamide and Nitazoxanide have been associated with some pharmacokinetic drawbacks, such as poor water solubility and, consequently, low oral bioavailability.[2] The aim of this study is to execute computer-aided structural modification on both drugs in order to maximize their antiviral efficacy and overcome their structure-related setbacks. The activity and efficacy of the selected agents have been evaluated and compared to their proposed structural alterations and benchmark antiviral agents, Molnupiravir and Remdesivir, in terms of testing the improvement in their efficacy, enhancement of their absorption, with the aim of developing new optimized drug candidates.

Methods

Construction of 3D drug molecules using BIOVIA Discovery Studio software. The structure of SARS-CoV-2 main protease (PDB ID: 6LU7, resolution: 2.16 Å) and RNA-dependent RNA polymerase (PDB ID: 7BV2, resolution: 2.5 Å) were retrieved from the protein data bank (www.rcsb.org). Virtual screening was implemented by the docking module of the BIOVIA Discovery Studio, Dassault Systèmes, Academic Standard Base, PR14361, San Diego: Dassault Systèmes, 2024, using the CDocker technique. The docking was performed using the full potential CDocker algorithm and the CHARMm forcefield for the highest accuracy and minimal result biases. The binding sites were defined according to the co-crystallized ligands. For 6LU7, the binding pocket was centered at (-10.75, 12.39, 68.98 Å) with a radius of 15.7 Å. For 7BV2, the binding sphere was centered at (96.50, 117.04, 83.03 Å) with a radius of 5 Å. Ten random conformations per ligand were generated, followed by simulated annealing dynamics (2000 heating steps and 5000 cooling steps). The top docking poses were ranked according to their CDOCKER-Interaction energy. Validation of the docking protocol was pursued by redocking the co-crystallized ligands into their respective binding pockets. The reproduced poses aligned well with the crystallographic conformations, yielding a Root Mean Square Deviation (RMSD) of 1.88 Å (6LU7) and 1.14 Å (7BV2), confirming excellent reliability of the docking procedure (Fig. 1). The pharmacokinetic properties (ADMET, Absorption, Distribution, Metabolism, Elimination and Toxicity) of all drug candidates have been calculated using the BIOVIA, Dassault Systèmes software.

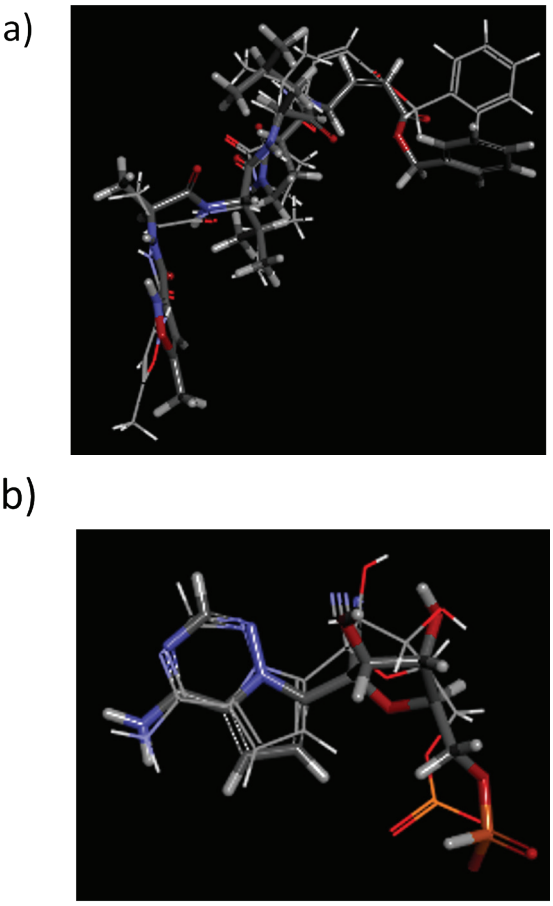

Figure 1: RMSD overlay images of the co-crystallized ligand (line) and the redocked ligand (ball and stick) in the binding sites of a) 6LU7, b) 7BV2

Results and Discussion

Remdesivir is the first approved antiviral agent, but due to its limited oral bioavailability and extensive side effects, the search for a more potent agent has been pivotal.[Molnupiravir was then developed, showing improved binding affinity to the target protein and better oral bioavailability. In this study, molecular docking simulations of both antiviral agents, Remdesivir and Molnupiravir (Fig. 2a, Fig. 3a, respectively), were performed against RNA-dependent RNA polymerase SARS-CoV-2 proteins, and their binding interactions were evaluated for ongoing comparison with other agents under repurposing investigation (Fig. 2b, Fig. 3b, respectively). The negative interaction energy of Remdesivir and Molnupiravir was calculated (50.24 and 51.29, respectively) along with their ADMET properties. From the extracted ADMET diagram, it can be concluded that both drugs have moderate pharmacokinetic properties, while Molnupiravir, as previously discussed, may have improved characteristics.

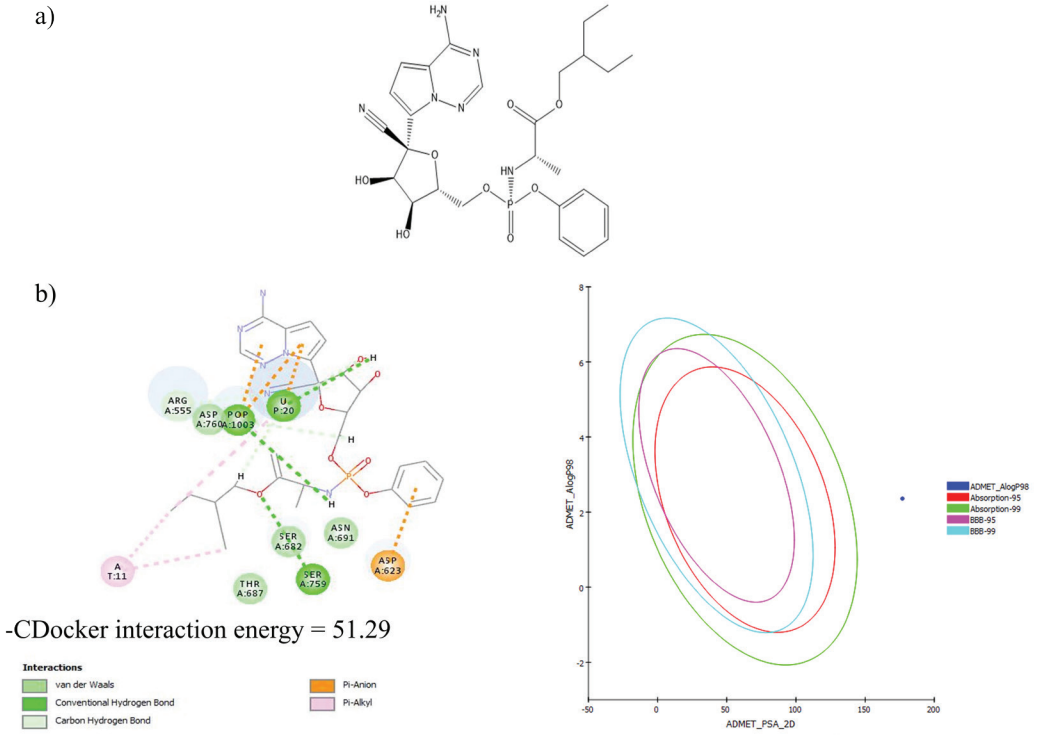

Figure 2: Remdesivir a) chemical structure, b) Molecular docking 3D interaction against 7BV2, c) ADMET calculation

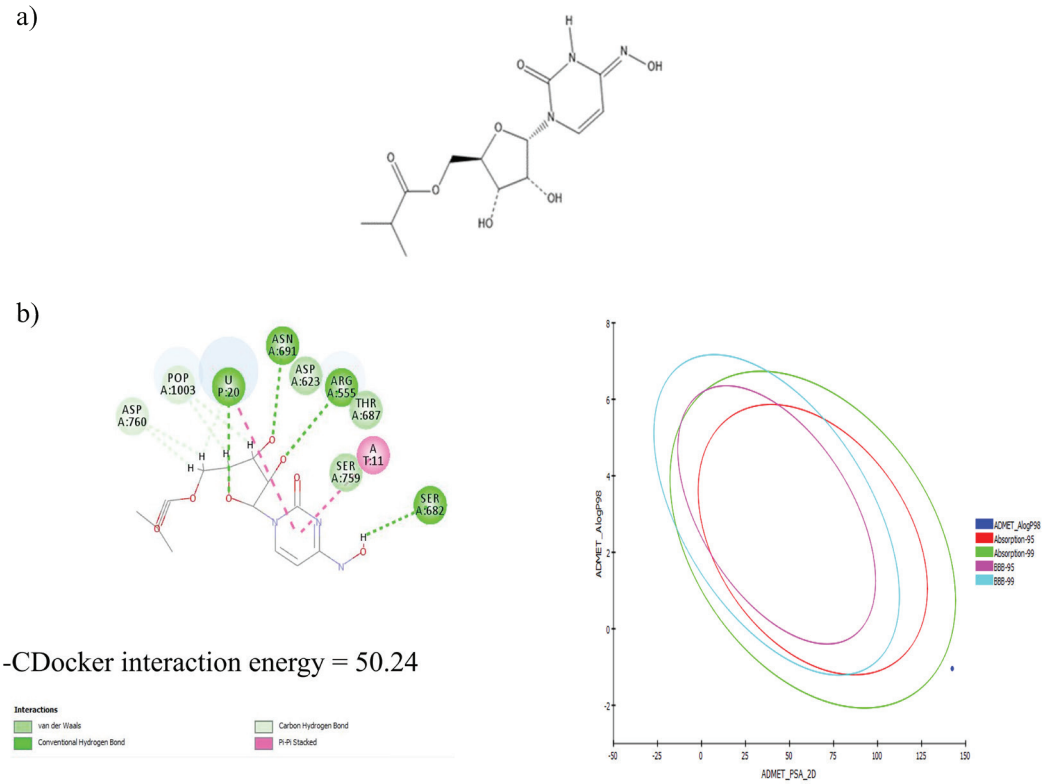

Figure 3: Malnupiravir a) chemical structure, b) Molecular docking 3D interaction against 7BV2, c) ADMET calculation

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Taking the antiviral agents' generated results into consideration, anthelmintic drug candidates, Niclosamide and Nitazoxanide, were examined to investigate their antiviral activity. The novel input of this study is the implementation of structural modifications on anthelmintic agents and comparing their binding affinity and pharmacokinetic properties to both the parent compounds and existing antiviral agents, Remdesivir and Molnupiravir. Niclosamide and Nitazoxanide (Fig. 4a, Fig. 5a, respectively) have been successfully repurposed for the eradication of coronavirus infection.[1, 2]

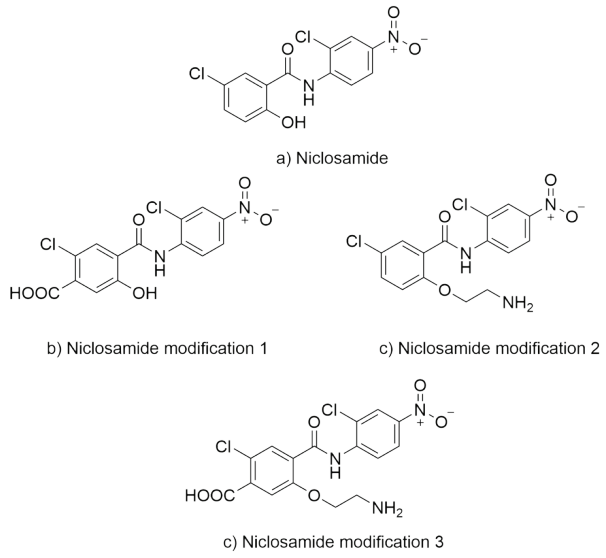

Figure 4: Niclosamide and its proposed structural modifications

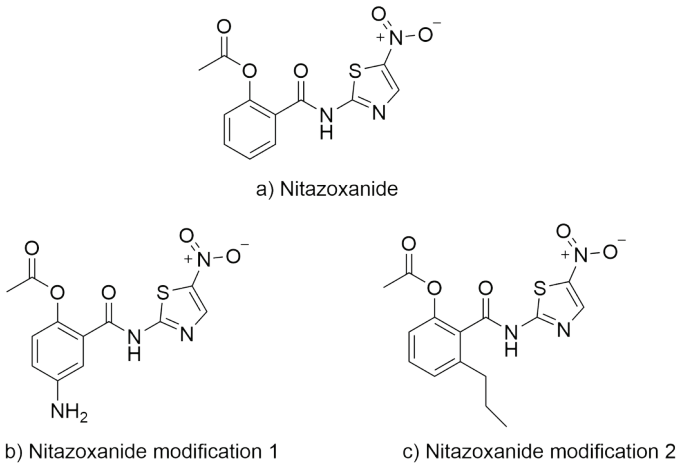

Figure 5: Nitazoxanide and its proposed structural modifications

Niclosamide has faced challenges progressing to clinical therapy due to its poor water solubility, lowering its bioavailability.[2] In this study, the main goal is to implement chemical modifications, such as the addition of ionizable groups like carboxylic acid or amino groups (Fig. 4b, c, d), on the parent compound to render it more water-soluble and examine their effect on the activity of the drug. In silico modeling of the three modified Niclosamide analogs has been established and compared to the parent compound (Fig. 6).

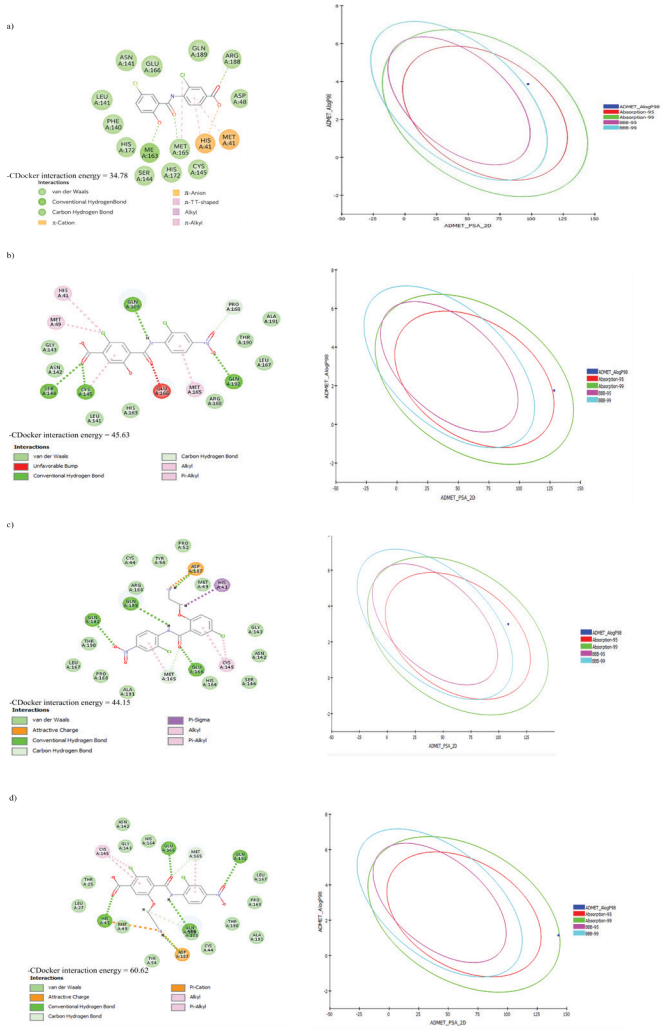

Figure 6: Molecular docking 3D interaction with 6LU7 and ADMET calculation respectively of: a) Niclosamide, b) Niclosamide modification 1, c) Niclosamide modification 2, d) Niclosamide modification 3

Analysis of docking interactions revealed that all Niclosamide analogs showed improved binding affinity compared to their parent compounds. Importantly, Niclosamide modification 3 achieved the most favorable binding profile, with a C-docker score of −60.62 kcal/mol, surpassing the parent Niclosamide and the benchmark antivirals. Interaction mapping indicated multiple hydrogen bonds and stabilizing hydrophobic contacts with key residues of the SARS-CoV-2 main protease, enhancing its binding stability. From these findings and the almost comparable pharmacokinetic calculations, it can be concluded that rendering

Niclosamide more water soluble to overcome its limited bioavailability had a positive effect on the activity of the drug.

On the other hand, Nitazoxanide has almost no water solubility, which has drawn the attention of researchers to enhance its aqueous solubility by finding a suitable organic solvent for dissolution. [] Recognizing that the drug's dissolution and solubility is an important factor for absorption and bioavailability, two structural modifications of Nitazoxanide have been suggested to enhance its hydrophilicity through the addition of an amino group (Fig. 5b) or its lipophilicity through the addition of a propyl chain (Fig. 5c). To validate the study's findings, it is crucial that the proposed modifications do not diminish the drug's effectiveness. Molecular docking simulation and ADMET calculations have been performed (Fig. 7).

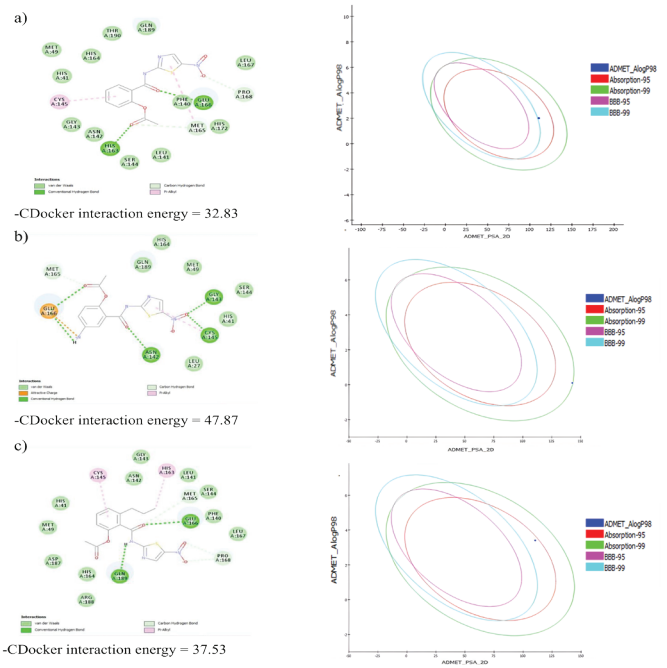

Figure 7: Molecular docking 3D interaction with 6LU7 and ADMET calculation respectively of: a) Nitazoxanide, b) Nitazoxanide modification 1, c) Nitazoxanide modification 2

Among Nitazoxanide analogs, modification 1 was the best-performing candidate with a C-docker score of −47.87 kcal/mol. It formed a favorable number of hydrophilic and hydrophobic interactions. The analogs also showed comparable pharmacokinetic properties.

These findings highlight Niclosamide modification three as the top-performing analog overall, while Nitazoxanide modification one also shows potential as a viable repurposed candidate.

Conclusion

Anthelmintic agents, Niclosamide and Nitazoxanide, have been previously repurposed as antivirals for the treatment of COVID-19. In this research study, it was aimed to prove their repurposing and propose different structural analogs with different hydro-lipophilicity to overcome the parent drugs' limited bioavailability, resulting from their poor dissolution. This study demonstrates that structural modification of Niclosamide and Nitazoxanide can significantly enhance their pharmacokinetic and binding properties for potential repurposing as COVID-19 therapeutics. Among the tested analogs, Niclosamide modification 3 emerged as the most promising candidate, with favorable hydrophilic and hydrophobic interactions and an improved ADMET profile. Its pharmacological performance was superior to that of its parent compound and comparable to benchmark antivirals. Nitazoxanide modification one also demonstrated improved binding affinity and favorable pharmacokinetic properties, making it a viable candidate. These results suggest that Niclosamide modification 3, in particular, could serve as a valuable lead for further synthesis, in vitro validation, and potential clinical development.

Declarations

Availability of Data and Materials:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

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Authors Contributions:

All authors contributed to the study conception and design. The experimental part, data collection, analysis, and discussion, was carried out by SE. All authors read, edited, and approved the final manuscript.

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