Exploring Molnupiravir (EIDD-2801) by Molecular Docking, Temperature-Dependent Dynamics Simulations, and DFT Calculations on the RNA-Dependent RNA Polymerase (RdRp) from SARS-CoV-2

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INTRODUCTION

The RNA-dependent RNA polymerase (RdRp, Fig. 1) of the SARS-CoV-2 is currently an important target in drug discovery for the treatment of COVID-19.[1,2] Molnupiravir (Fig. 1), a broad-spectrum antiviral originally produced by Merck to treat influenza, was found to reduce hospitalizations by 50%, according to phase three clinical trials.[1] Also, no deaths were reported in patients who received the "COVID-19 pill". It is an orally bioavailable prodrug of the nucleoside analog *β-D*-N4-hydroxycytidine (NHC, Fig. 1), which increases G to A and C to U transition mutations in replicating coronaviruses.[3] Finally, we decided to understand how different temperatures could affect the interactions of NHC into RdRp by using *in silico* methodologies.

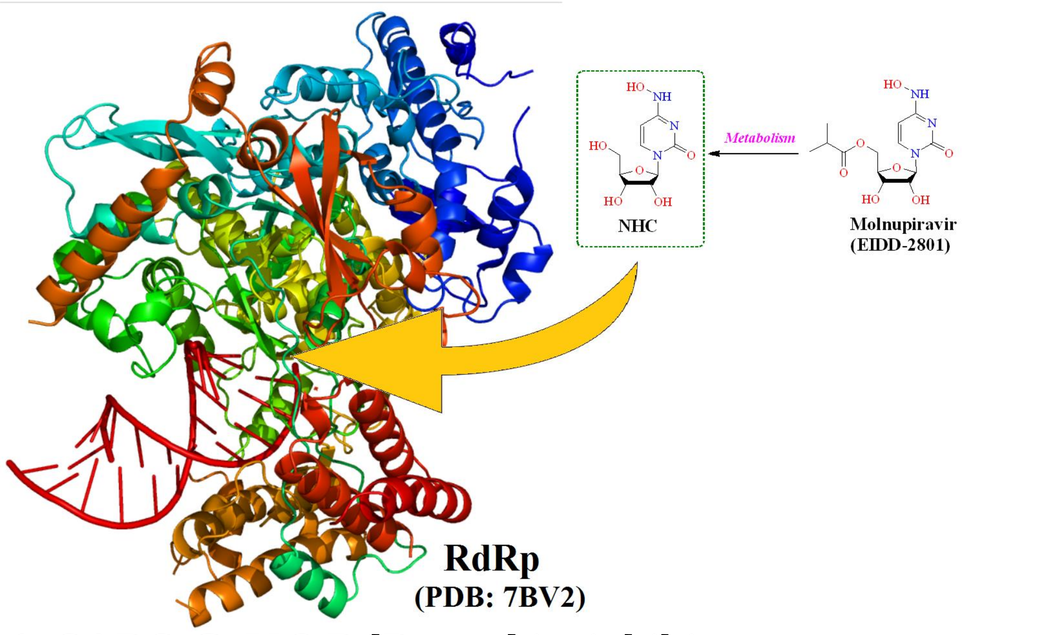

Fig. 1. SARS-CoV-2 RdRp and its inhibitors.

METHODS

The workflow of this study is shown in Fig. 2 below.

Fig. 2. Workflow used in this study.

RESULTS AND DISCUSSION

NHC shows a similar binding mode than remdesivir (RMSD: 0.51Å). MD simulations displayed that complexes at 300 and 310K exhibits similar profiles (RMSD: 0.2-0.25Å). In contrast, the complex at 313K presents higher RMSD values (0.18-0.35Å) up to 5.5 ns and, then it stabilizes similarly to the other two complexes (Fig. 3A). Finally, DFT calculations revealed that NHC presents the most stable binding at 313K, with −47.86 kcal/mol (Fig. 3B).

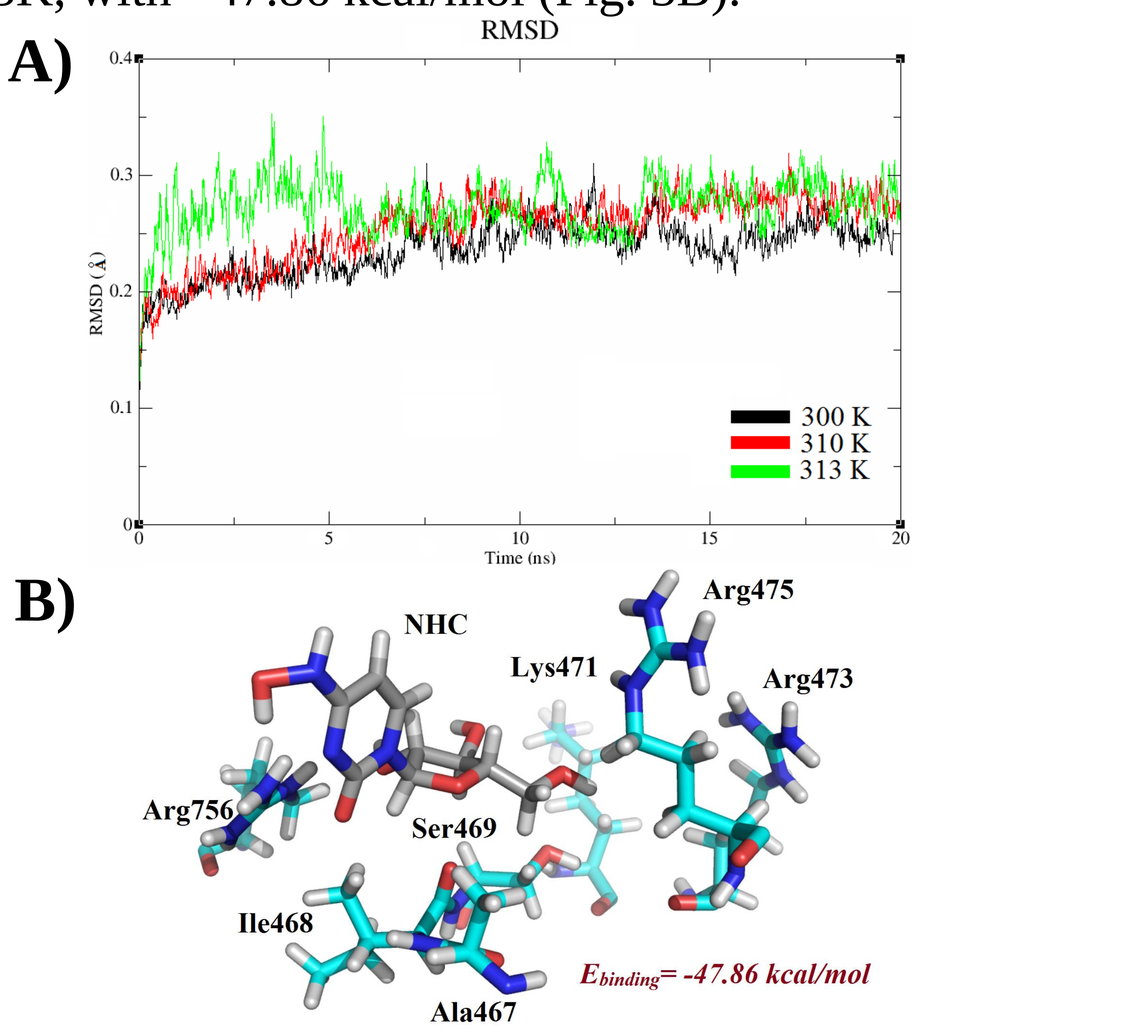

Fig. 3. RMSD values (A) and NHC interactions at 313K(B).

Conclusions

All complexes produced by MD are stable. However, the complex at 313K needs more time to stabilize. Interactions of NHC depends on temperature, but it remains at the RdRp active site. Finally, the better stability of NHC at 313K suggests that it is truly effective in febrile patients, as observed in phase III studies.

References

1. https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/
2. Silva-Júnior *et al.* **Bioorg Med Chem**. 2020, 28: 115745.
3. Kabinger *et al.* **Nat Struct Mol Biol**. 2021, 28(9): 740-746.

Acknowledgment

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