Exploring effects of temperature on the catalytic site of non-structural protease 2 (nsP2) from Chikungunya virus by using molecular dynamics simulations and DFT calculations

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INTRODUCTION

Chikungunya virus (CHIKV) is an emerging arthropod-borne virus transmitted to humans by the bite of infected *Aedes* mosquitoes, responsible for more than 1 million illnesses worldwide.[1,2] The nsP2 is an essential CHIKV protease with a catalytic dyad (Cys^{1013}/His^{1083}), which processes viral polyproteins.[2] Interestingly, some authors suggested that this dyad is interchangeable with a proximal serine, making it a non-papain-like cysteine protease.[3] Thusly, effects of different temperatures (300 to 400K) on the distances between Ser-His-Cys residues were investigated *in silico*. Lastly, non- and covalent mechanisms of inhibition were investigated by DFT calculations.

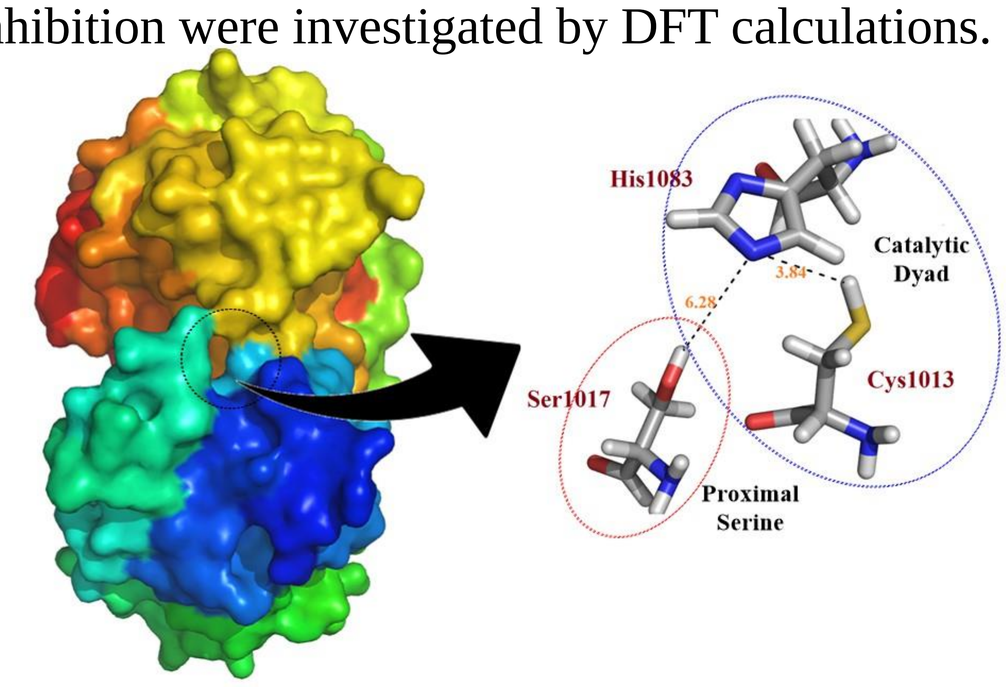

Fig. 1. CHIKV nsP2 and its catalytic dyad along with a proximal serine residue.

METHODS

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

Fig. 2. Workflow used in this study.

RESULTS AND DISCUSSION

Molecular dynamics (MD) revealed that the distances between the catalytic residues increased with an increase in temperature (Fig. 3A), therefore, decreasing the probability of generating an ion-pair. The lowest RMSD variation was observed at 325K. DFT calculations predicted Cys^{-}/His^{+} (Fig. 3B) as the major ion-pair (at a distance of 3.03Å), and barrier values ($\Delta G^{\ddagger}$) of 12.44-14.3 kcal/mol. The nucleophilic attack of Cys^{-} at the Michaels' acceptor moiety of acylhydrazone inhibitor is not plausible, suggesting non-covalent mode (Fig. 3C).

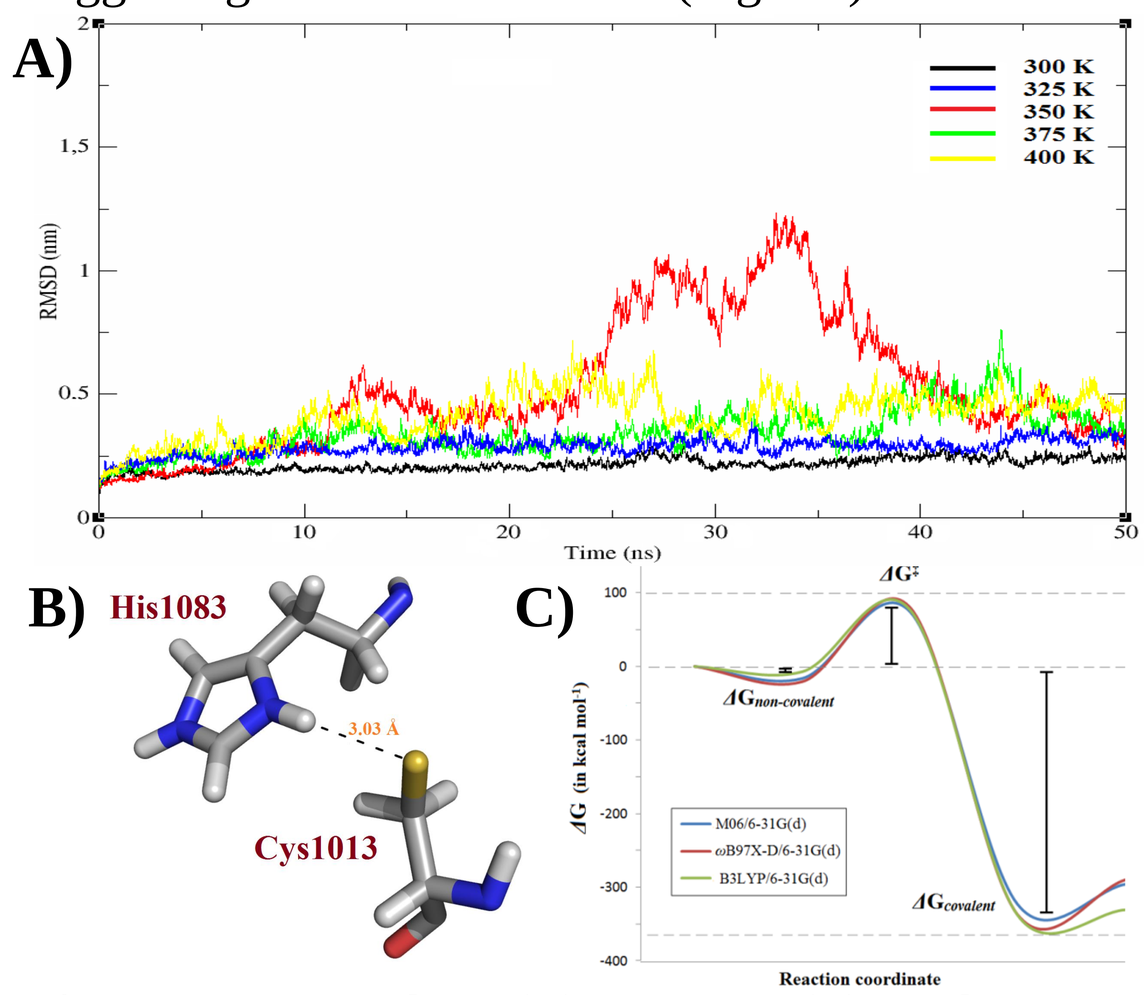

Fig. 3. RMSD values (A), ion-pair (B), and reaction coordinate for the nsP2 inhibitor (C).

CONCLUSIONS

The nsP2 catalytic site presents different structural variations with increasing temperature. However, it at 325K allowed to generate the His-Cys ion-pair. Finally, it was revealed that the nsP2 inhibitor may develops its mechanism of action by performing a non-covalent interacts with nsP2 binding site.

References

1. Passos *et al.* **Pharmaceuticals,** 2020, 13: 141.
2. Silva-Júnior *et al.* **Bioorg Med Chem.** 2017, 25(16): 4219-4244.
3. Saisawang *et al.* **Scientific Reports**, 2015, 5: 17125.

Acknowledgment

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