

Insilico and invitro investigation of the molecular mechanisms of antiviral compounds for potentially inhibiting dengue virus Ns2b-Ns3 protease

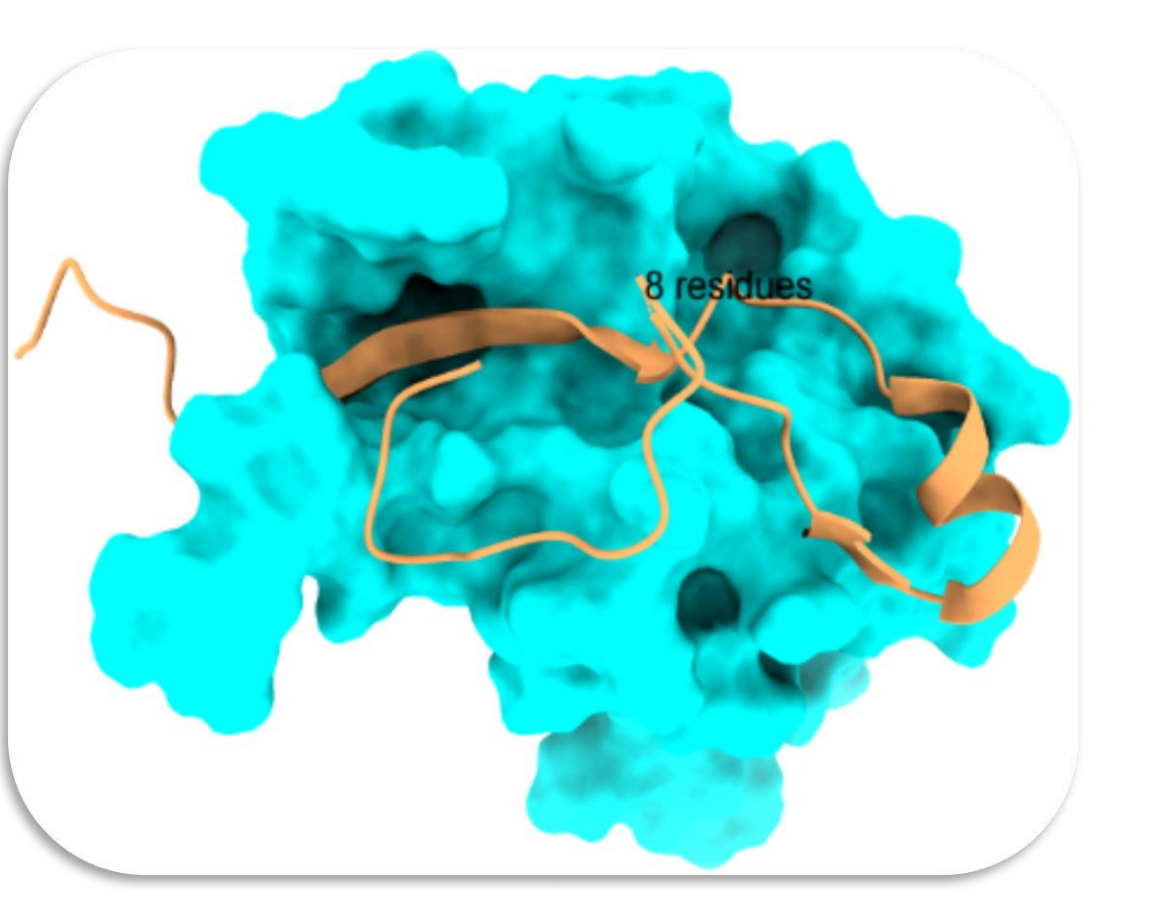


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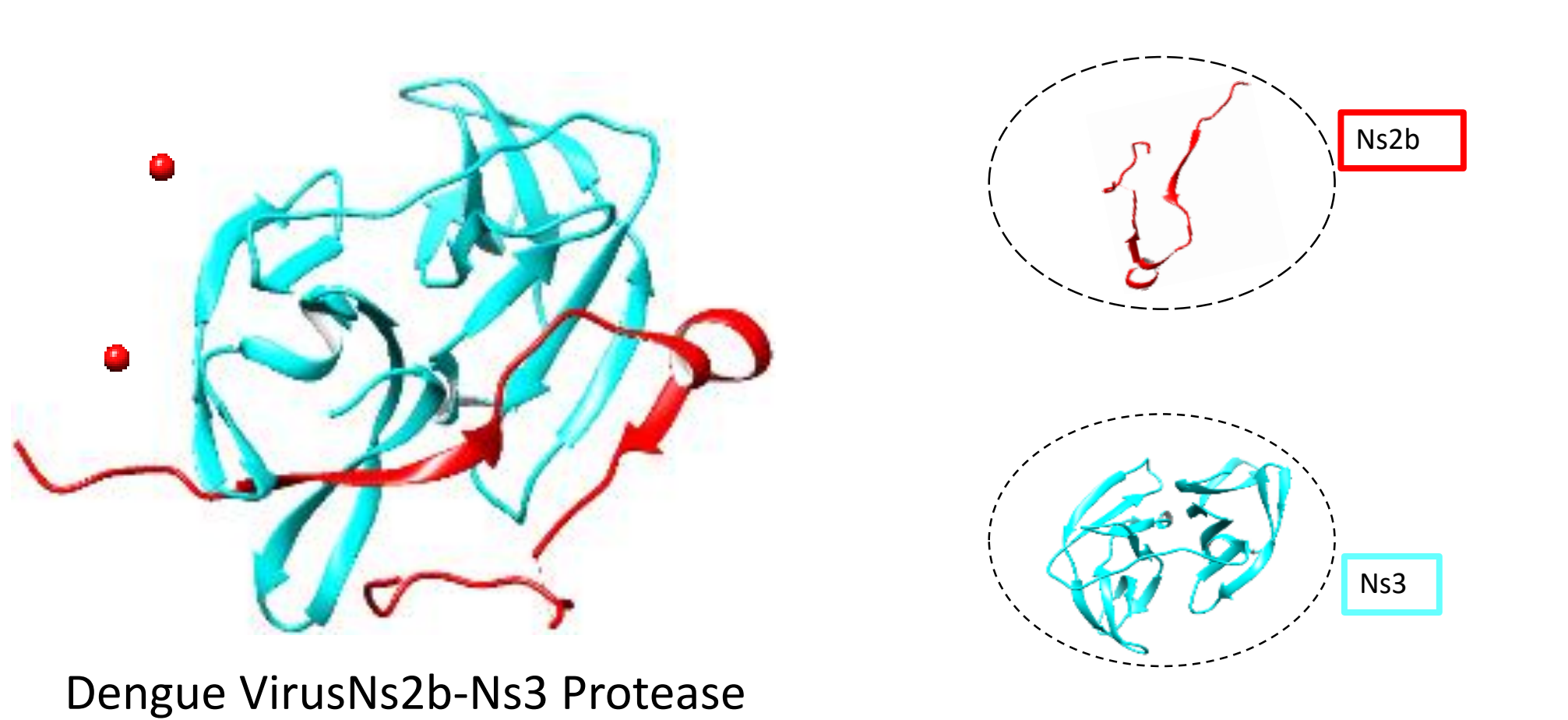
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Abstract : The Ns2b-Ns3 protease plays a crucial role in replicating the dengue virus, yet no effective treatment has been found to completely block its activity and prevent viral replication. To address this, we employed a multidisciplinary approach, combing pharmacophore modeling, molecular docking, molecular dynamics simulation, and in-vitro studies to identify potential antiviral compounds. Our research revealed three promising compounds that successfully bound to key sites on the protease, offering new avenues for inhibiting dengue virus infection.

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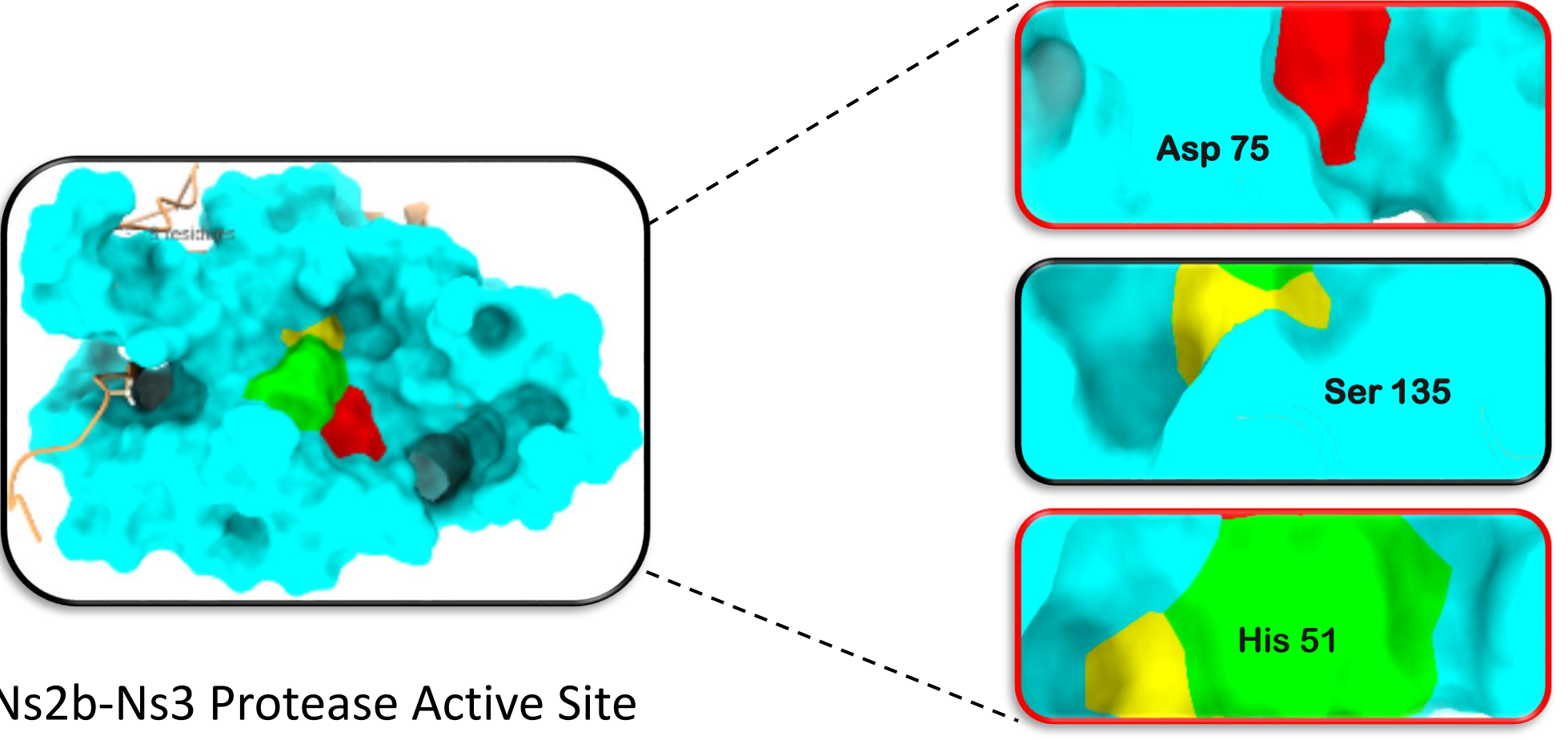


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Dengue VirusNs2b-Ns3 Protease

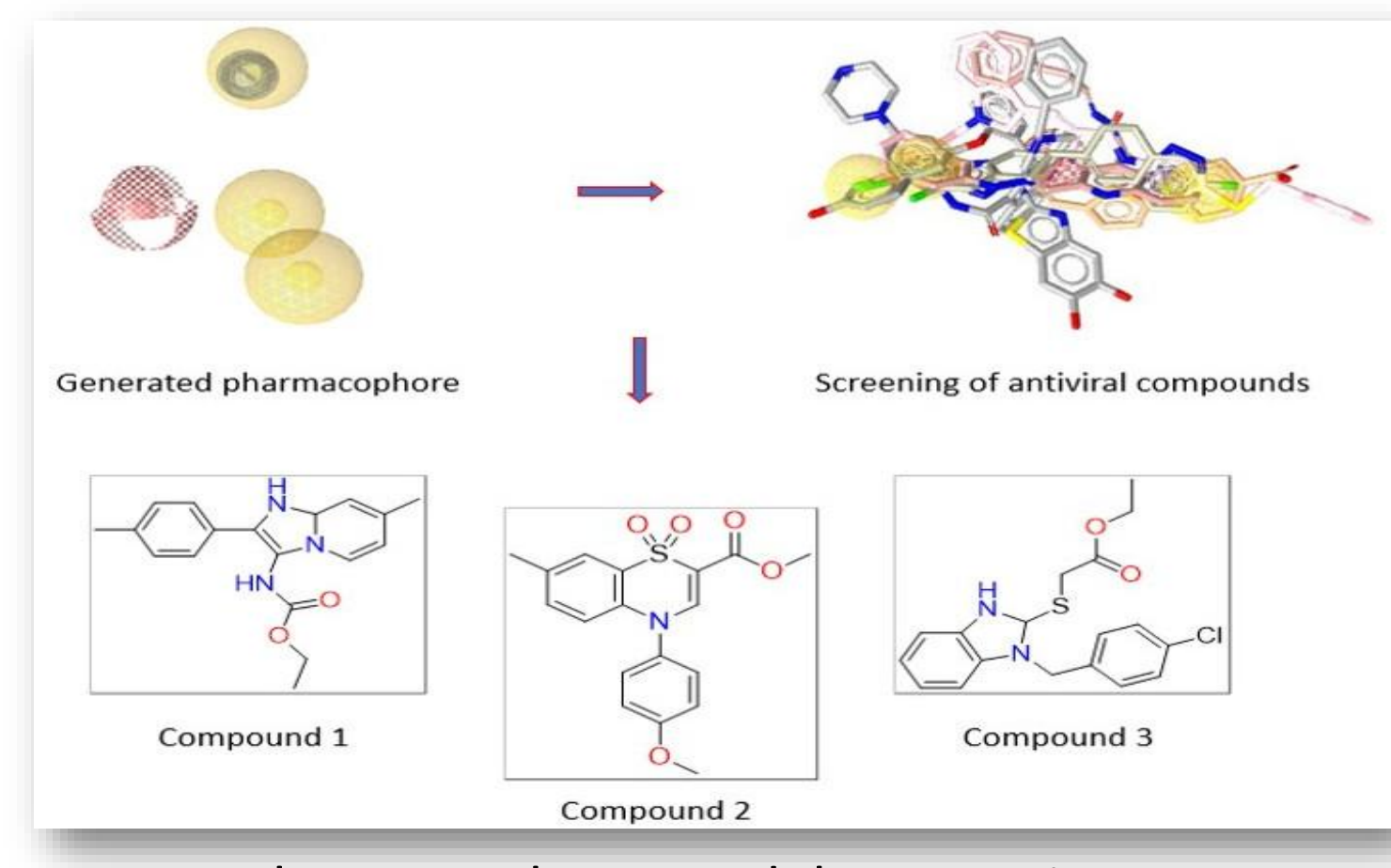
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Ns2b-Ns3 Protease Active Site

- The Ns2b-Ns3 protease is responsible for the replication of the dengue virus. The Ns3 part of protease contains a catalytic triad.
- Having a compound that can act on the catalytic triad will be essential for viral inhibition.

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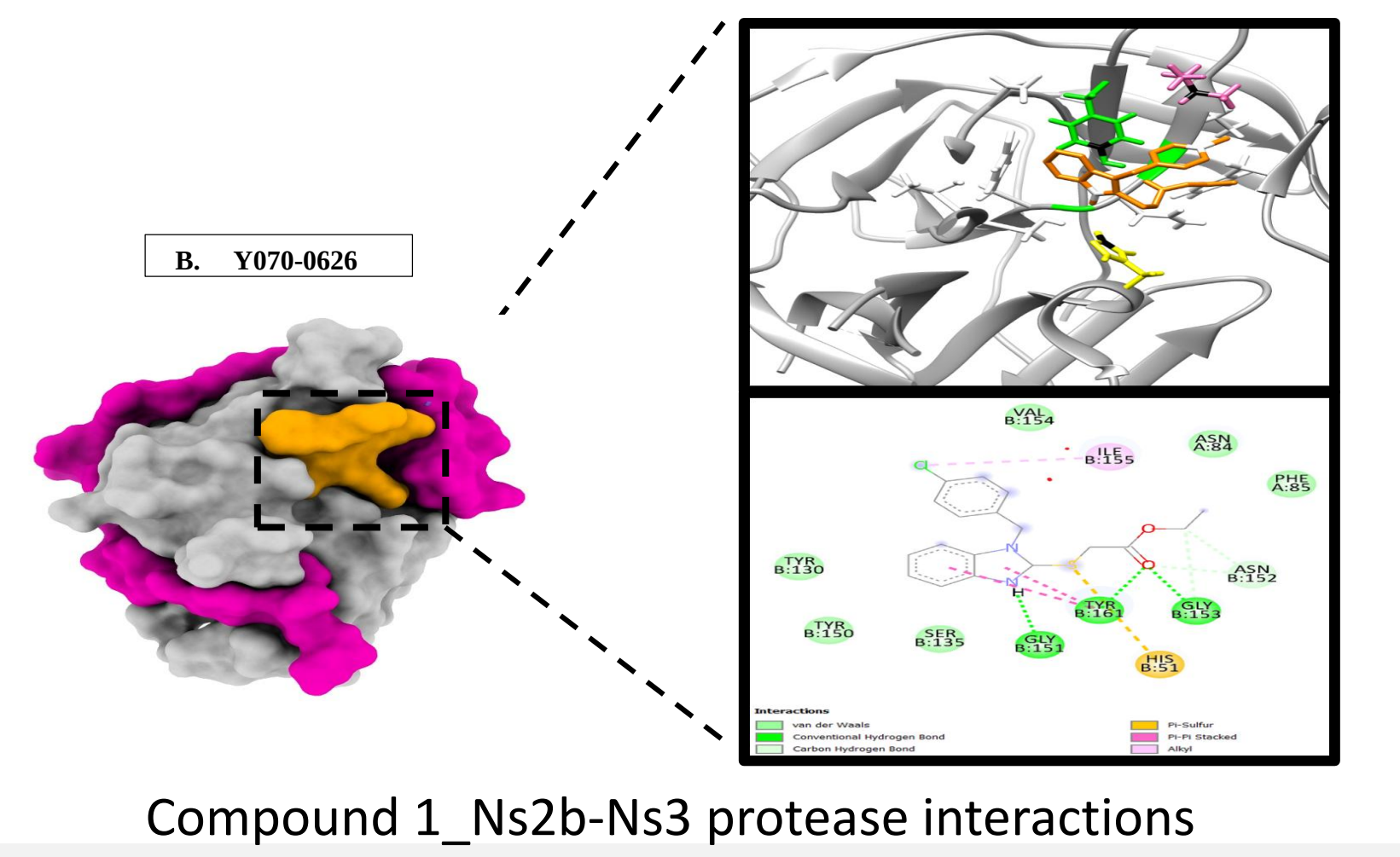
Pharmacophore Model Generation

Results

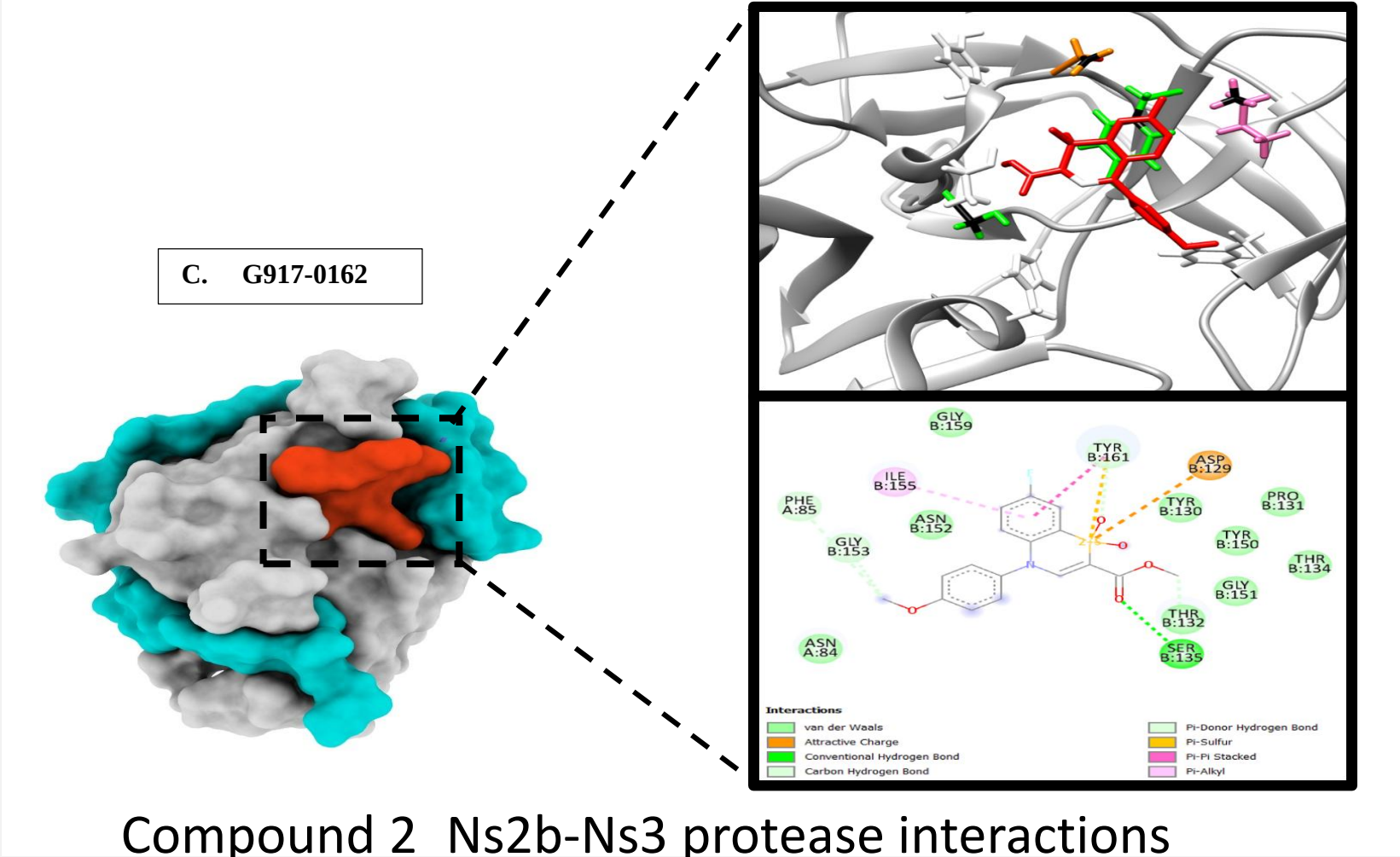
A pharmacophore model was employed to guide the screening process, and a threshold of 55 was set for the pharmacophore fit.

Following this criterion, three compounds emerged as top candidates, having successfully met the specified threshold and demonstrating a strong alignment with the pharmacophore model.

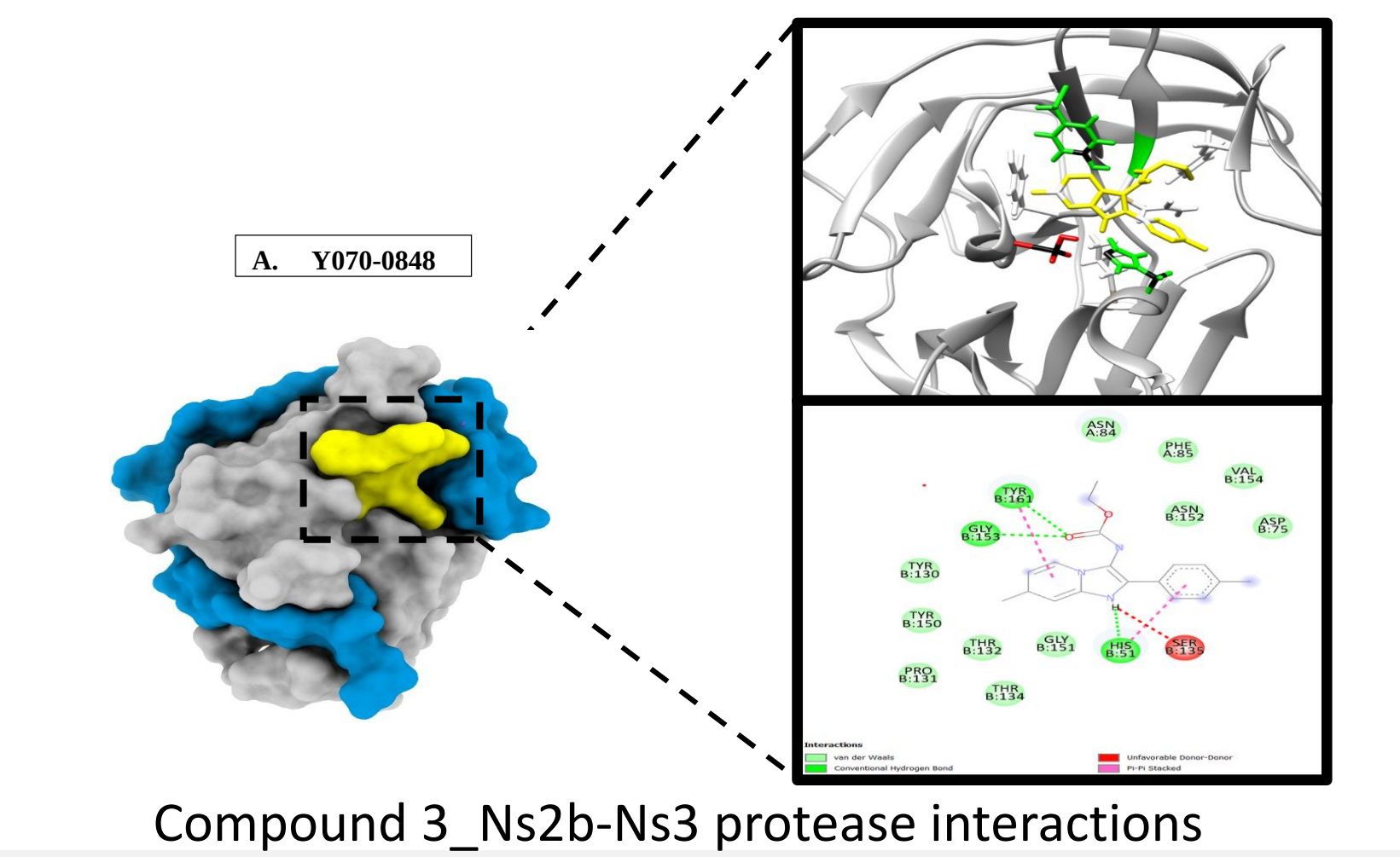
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Compound 1_Ns2b-Ns3 protease interactions

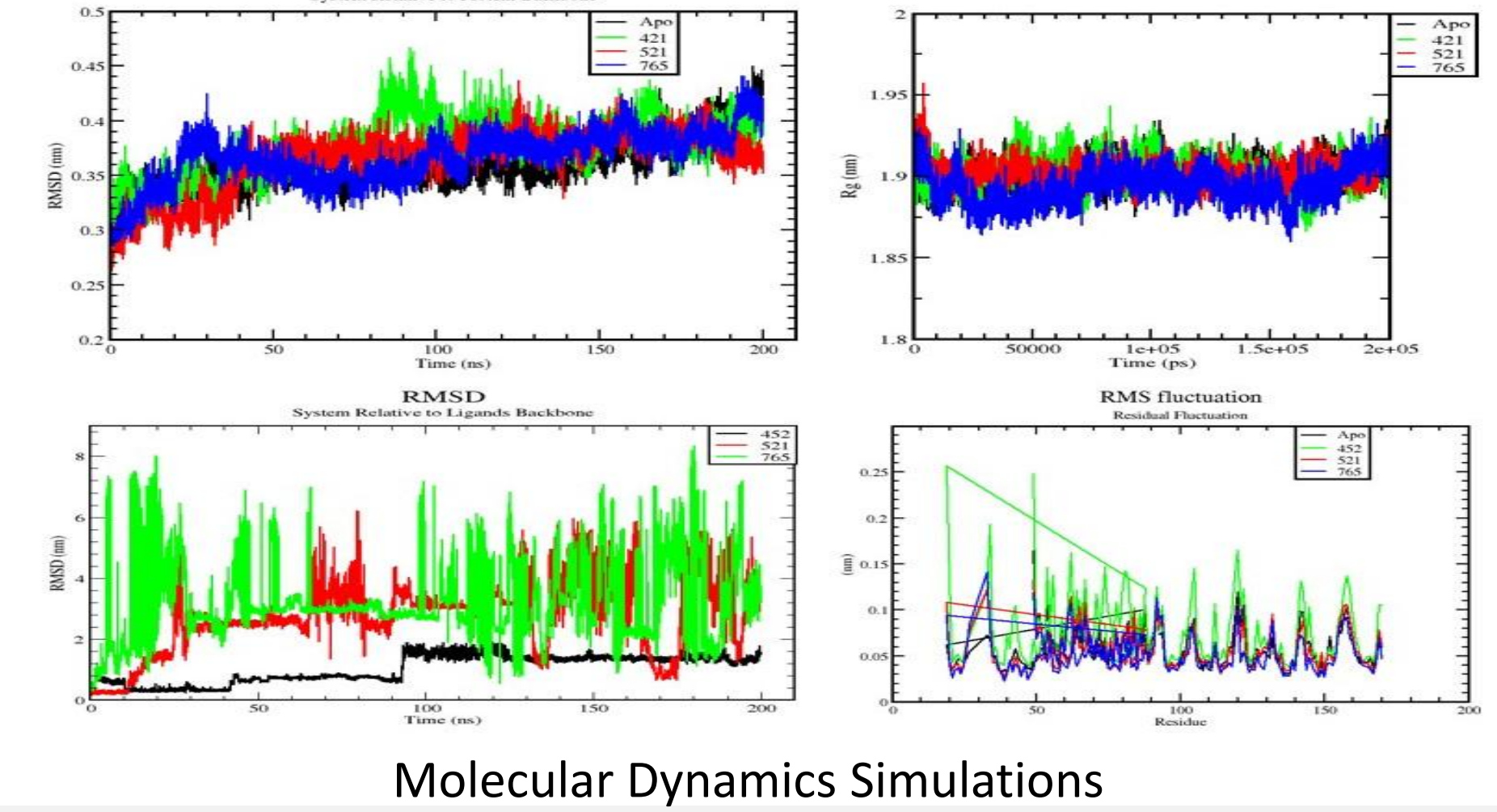


Compound 2_Ns2b-Ns3 protease interactions



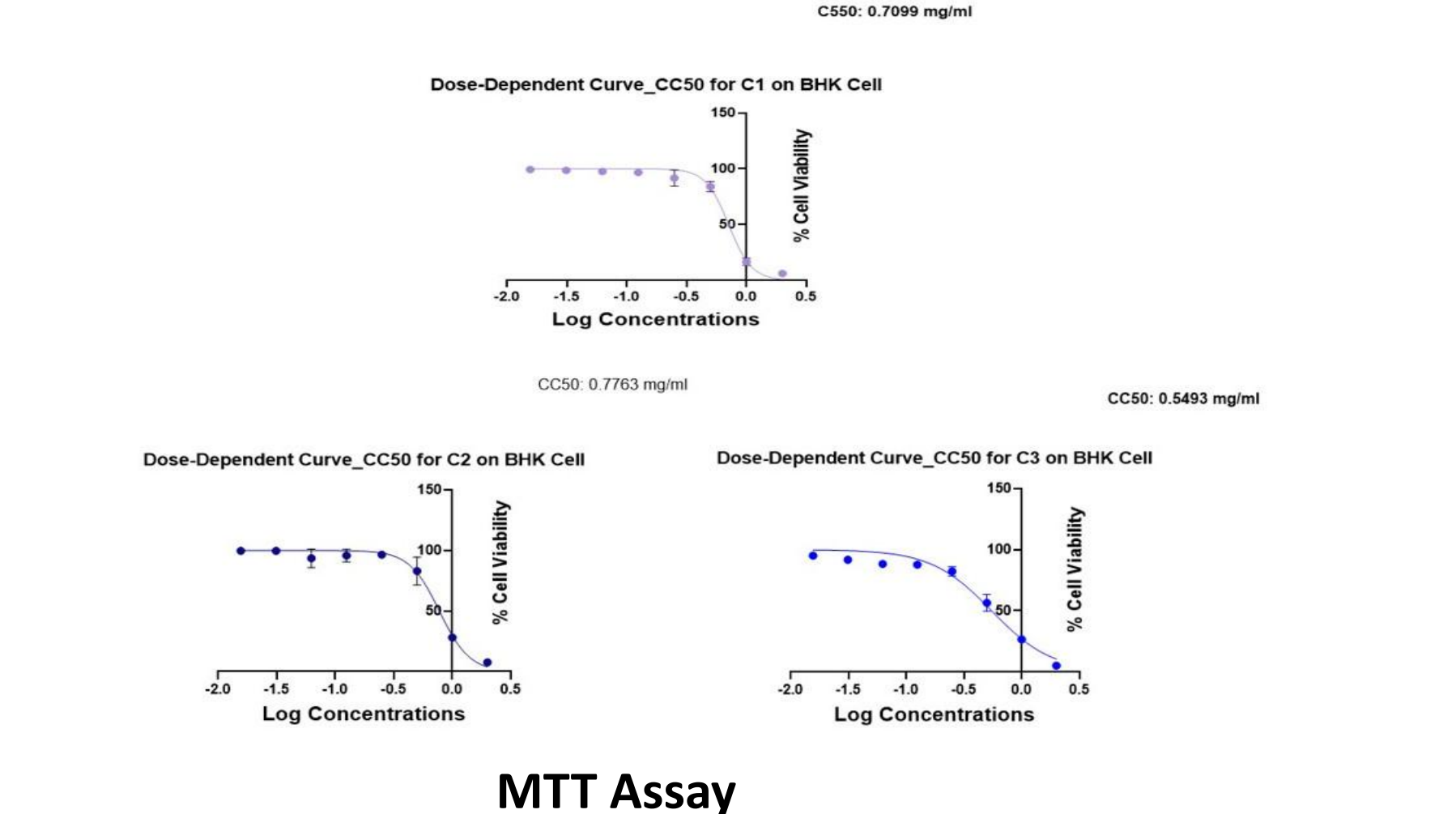
Compound 3_Ns2b-Ns3 protease interactions

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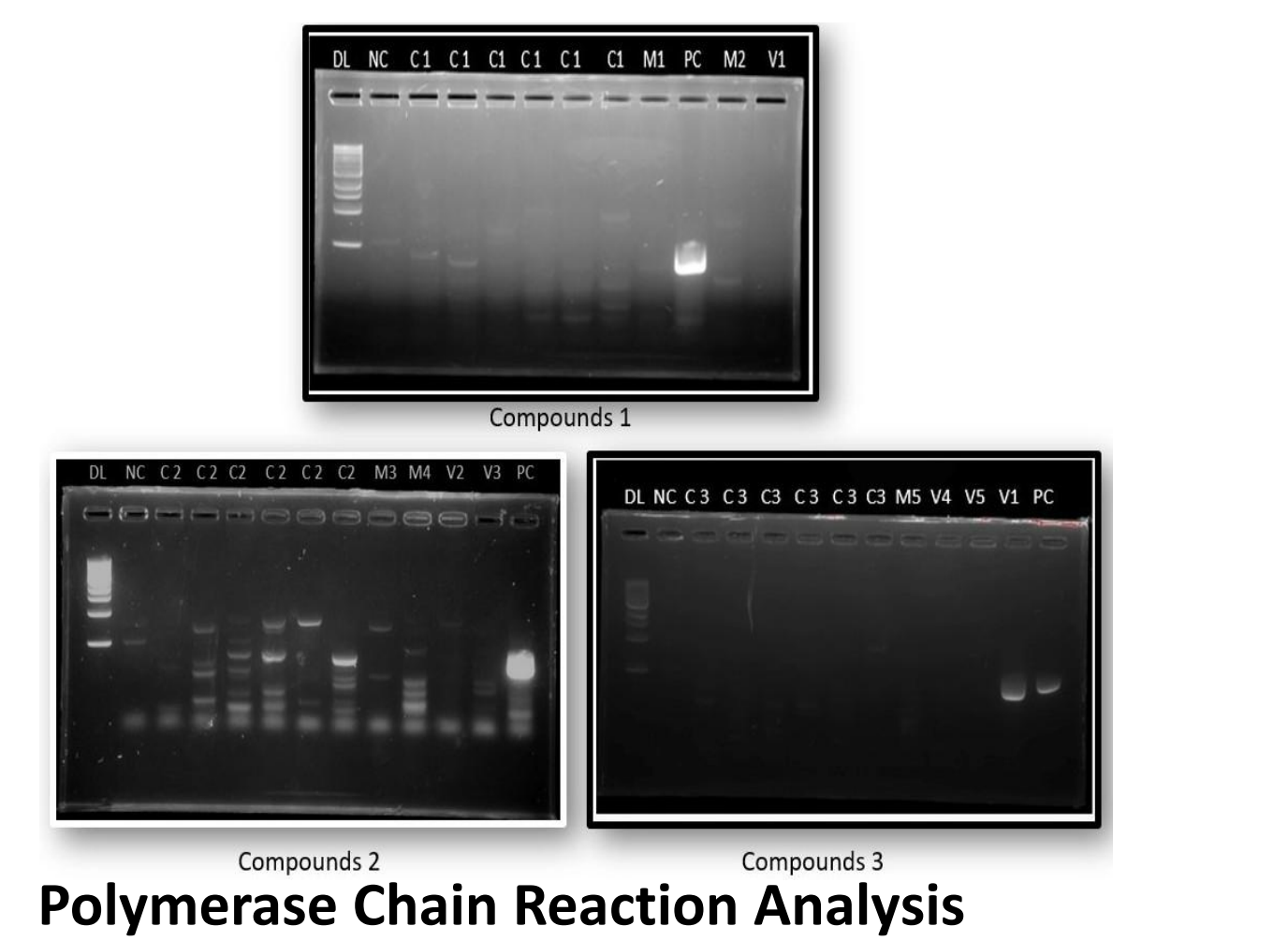
Molecular Dynamics Simulations

7



MTT Assay

4



Polymerase Chain Reaction Analysis

Conclusion

- A comprehensive, rigorous, systematic and exhaustive high-throughput screening of 65,345 diverse and structurally unique antiviral compounds against the dengue virus.
- The effort yielded highly promising, encouraging, and significant results. Notably, it identified three exceptionally potent, efficacious, and selective compounds.
- These compounds have the potential to effectively inhibit the dengue protease. This enzyme is crucial, essential, and vital for the virus’s replication, survival, and transmission.
- Consequently, this discovery offering new avenues for the development of innovative and effective therapeutic interventions.

