Computational Discovery of Potential NS3 Protease Inhibitors of Zika Virus

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Zika Virus (ZIKV) poses a considerable threat to human life, with over 100,000 cases confirmed. Since no treatments or drugs are available, a novel approach was created to expedite the identification of potential inhibitors to ZIKV using existing Dengue NS3 protease inhibitors. The virus NS3 protease is essential for viral replication and is highly conserved in Flavivirus. A process using a pharmacophore model, followed by molecular docking, was employed. Pre-existing inhibitors of the DENV NS3 Protease were docked to the DENV viral protein (PDB Code: 3U1I) to generate a pharmacophore model. Compound databases were amalgamated to generate a library of four million compounds. Lipinski's Rule of 3 was employed to reduce the library by 30%. The remaining compounds were then screened using the pharmacophore model, and the compounds with the lowest root mean square deviation were retained. These were then docked to the ZIKV protein (PDB Code: 5H4I), with fourteen compounds exhibiting significant potential for future research. Of the fourteen, CHEMBL 1516087, 272375, and 1878574 demonstrated the best docking results with more of their conformations showing better affinity for the ZIKV NS3 Protease than others in the entire library. The project identified these three compounds as strong potential inhibitors of ZIKV NS3 Protease. This demonstrates the effectiveness of using DENV NS3 protein docking as the basis of pharmacophore modeling, combined with molecular docking of the ZIKV NS3 Protease, to generate a viable subset from large compound databases. These inhibitors have the potential to stop a crisis affecting millions of people.

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