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In-silico Strategies for Developing Antiretroviral Drugs: Qualitative Structure-activity Relationship Model, Activity Prediction, Enumeration and Molecular Dynamics of Non-Nucleotide Reverse Transcriptase Inhibitors.

ABSTRACT

The rising incidence of HIV-1 drug resistance poses a significant challenge to the efficacy of combination antiretroviral therapy (cART), particularly in Southern Africa and other regions globally [1]. The emergency of resistance to non-nucleotide reverse transcriptase inhibitors (NNRTIs) is especially concerning, as it threatens the long-term success of antiretroviral treatment strategies [2]. In this study, we employed an in-silico approach to investigate NNTRI drugs and their derivates. Using Density Functional Theory (DFT), we optimized NNRTIs and analyzed their interaction with HIV-1 protein [3] .

A Quantitative Structure-Activity Relationship (QSAR) model was developed to predict the biological activity of the six NNRTIs under investigation. The QSAR model, based on 94 pyrimidine derivatives, achieved an R2 of 0.822 and a Q2 of 0.815, demonstrating high predictive accuracy. Molecular Dynamics simulations (MDS) were conducted to evaluate the stability of various ligands and their newly developed alternatives, confirming their sustained binding to the protein's active site over a 200-nanosecond simulation timeframe. Etravirine exhibited root mean square deviation (RMSD) fluctuations of approximately 4.5 Å, while its enumerated derivatives showed RMSD fluctuations of 3.5 Å.

Our findings were further validated using MDS and Molecular Mechanic Generalized Born Surface Area (MMGBSA) methods [4], which identified Enumerated Etravirine as a promising NNRTI candidate. Enumerated Etravirine demonstrated the best performance through molecular docking, MDS, and free energy calculations, with an activity value of 7.373 and a docking score of -10.517 kcal/mol. Additionally, the free energy of binding for Enumerated Etravirine was -89.684 kcal/mol, outperforming other ligands considered, including the co-crystalized ligand. These significant results suggest that the modified Etravirine holds considerable promise as a novel agent in antiretroviral therapy.

To perform the data-intensive simulations, we leveraged the Centre for High-Performance Computing (CHPC), conducting calculations at the DFT level using Gaussian 16 revision C01 and Minnesota 15-L functional with the 6-31++G(d,p) basis set [5]. These simulations were executed on a single node using the symmetric multiprocessing (SMP) queue. The jobs utilized 24 CPU cores per node and memory of 10GB with wall times of 10 – 11 hours for geometry optimization and frequency calculations. Docking was done on our local desktop machines as the dataset was not large enough to efficiently make use of the HPC resources. The molecular dynamics simulations used the Nvidia V100 graphical processing units (GPUs), generating 70 nanoseconds of simulation within the 12-hour wall time permitted GPU queue. MMGBSA simulations had to be conducted on the serial long queue as they ran within a 144-hour wall time. This study highlighted the crucial role of high-performance computing and computational drug discovery in designing improved drug candidates.

Keywords: Antimicrobial Resistance, HIV-1 Drug Resistance, Computational Chemistry, CHPC, DFT, MD, QSAR Model, GPU, MMGBSA.

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Student or Postdoc?

PhD or DTech4

Email address

Co-Authors

CHPC User

CHPC Research Programme

Workshop Duration

Primary authors: Dr GOVENDER, Krishna (University of Johannesburg); Mr MBAYO, Vitalis (University of Johannesburg, South Africa); MARONDEDZE, ephraim (University of Johannesburg); Prof. GOVENDER, Penny (University of Johannesburg)

Presenter: Mr MBAYO, Vitalis (University of Johannesburg, South Africa)

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