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Combined 2D- / 3D-QSAR, molecular docking, accelerated molecular dynamics simulation and QM/MM calculation studies on pepstatin A analogues as cathepsin D inhibitors

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Introduction/Aim: Cathepsin D, one of the attractive targets for the treatment of breast cancer, has been implicated in HIV neuropathogenesis since it increases intracellular viral replication. However, its mechanism of action has neither been fully explored nor well understood. This study aims at developing a predictive quality approach to understanding the mechanism of action of cathepsin D in the treatment of HIV and breast cancer.

Methods: Herein, we employed diverse computational methodologies including 2D-QSAR, 3D-QSAR, hybrid QM/MM, accelerated molecular dynamics, MM-PBSA, Principal component analysis, residue interaction network, cross-correlation, potential energy analysis, RMSD, RMSF to investigate the stability, fluctuation and detailed binding modes between Cathepsin D and 78 pepstatin A analogues.

Results: The 3D-QSAR model shows good predictive ability with R^2 of 0.780 and Q2 of 0.574 while 2D-QSAR model has R^2 of 0.821 and Q^2 of 0.365. Cross-correlation provided insight into atomic motions with respect to their biological function. RMSD and potential energy analyses showed the stability of the 5 compounds in the enzyme and RMS deviation of C-alpha were not more than 1Å. PCA analysis showed that the two eigenvectors account for >37.1% of all motions in all the complexes analysed in this study.

Conclusions: The insight gained from this study offer theoretical references, which could provide an incentive to understanding the mechanism of action of Cathepsin D. It could also aid in the designing of potent, clinically relevant drugs with improved pharmacokinetic and pharmacodynamics properties that could aid the treatment of HIV-1 and breast cancer co-infection in Africa.

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