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Impact of GSK199 and GSK106 binding on protein arginine deiminase IV stability and flexibility: A computational approach

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Abstract

Protein arginine deiminase IV (PAD4) is a potential target for diseases including rheumatoid arthritis and cancers. Currently, GSK199 is a potent, selective yet reversible PAD4 inhibitor. Its derivative, GSK106, on the other hand, was reported as an inactive compound when tested against PAD4 assay. Although they had similar skeleton, their impact towards PAD4 structural and flexibility is unknown. In order to fill the research gap, the impact of GSK199 and GSK106 binding towards PAD4 stability and flexibility is investigated via a combination of computational methods. Molecular docking indicates that GSK199 and GSK106 are capable to bind at PAD4 pocket by using its back door with −10.6 kcal/mol and −9.6 kcal/mol, respectively. The simulations of both complexes were stable throughout 100 ns. The structure of PAD4 exhibited a tighter packing in the presence of GSK106 compared to GSK199. The RMSF analysis demonstrates significant changes between the PAD4-GSK199 and PAD4-GSK106 simulations in the regions containing residues 136, 160, 220, 438, and 606. The Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) analysis shows a marked difference in binding free energies, with −11.339 kcal/mol for the PAD4-GSK199 complex and 1.063 kcal/mol for the PAD4-GSK106 complex. The hydrogen bond analysis revealed that the GSK199 and GSK106 binding to PAD4 are assisted by six hydrogen bonds and three hydrogen bonds, respectively. The visualisation of the MD simulations revealed that GSK199 remained in the PAD4 pocket, whereas GSK106 shifted away from the catalytic site. Meanwhile, molecular dockings of benzoyl arginine amide (BAEE) substrate have shown that BAEE is able to bind to PAD4 catalytic site when GSK106 was present but not when GSK199 occupied the site. Overall, combination of computational approaches successfully described the behaviour of binding pocket of PAD4 structure in the presence of the active and inactive compounds.

Author Keywords

GSK106; GSK199; MD simulation and MMPBSA; PAD4

Index Keywords

Amides, Arginine, Binding energy, Complexation, Computational methods, Diseases, Molecular modeling, Proteins; Arginine deiminases, Computational approach, Gsk106, Gsk199, Inactive compounds, MD simulation, MD simulation and molecular mechanic poisson-boltzmann surface area, PAD4, Poisson-Boltzmann, Surface area; Hydrogen bonds

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