EuroSciCon

9th Edition of International Conference on

Mass Spectrometry

March 04-05, 2019
Berlin, Germany

Amir Zeb, Int J Drug Dev & Res 2019, Volume 11
DOI: 10.21767/0975-9344-C1-005

Understanding inhibitory mechanism of the selective inhibitors of CdK5/p25 complex by molecular modelling studies

Amir Zeb, Shailima Rampogu, Minky Son, Ayoung Baek, Sang Hwa Yoon and **Keun Woo Lee**

Gyeongsang National University, Republic of Korea

Neurotoxic insults activate calpain, which in turn produces truncated p25 from p35. p25 forms hyperactivated CdK5/p25 complex, and thereby induces severe neuropathological aberrations including hyperphosphorylated tau, neuroinflammation, apoptosis, and neuronal death. Inhibition of Cdk5/p25 complex alleviates aberrant phosphorylation of tau to mitigate AD pathology. PHA-793887 and Roscovitine have been investigated as selective inhibitors of Cdk5/p25 with IC50 values 5nM and 160nM, respectively, but their mechanistic studies remain unknown. Herein, computational simulations have explored the binding mode and interaction mechanism of PHA-793887 and Roscovitine with Cdk5/p25. Docking results suggested that PHA-793887 and Rsocovitine have occupied the ATP-binding site of Cdk5 and obtained highest docking (GOLD) score of 66.54 and 84.03, respectively. Furthermore, molecular dynamics (MD) simulation demonstrated that PHA-793887 and Roscovitine established stable RMSD of 1.09 Å and 1.48 Å with Cdk5/p25, respectively. Profiling of polar interactions suggested that each inhibitor formed hydrogen bonds (H-bond) with catalytic residues of Cdk5 and could remain stable throughout the molecular dynamics simulation. Additionally, binding free energy calculation by molecular mechanics/Poisson–Boltzmann surface area (MM/PBSA) suggested that PHA-793887 and Roscovitine had lowest binding free energies of -150.05 kJ/mol and -113.14 kJ/mol, respectively with Cdk5/p25. Free energy decomposition demonstrated that polar energy by H-bond between the Glu81 of Cdk5 and PHA-793887 is the essential factor to make PHA-793887 highly selective towards Cdk5/p25. Overall, this study provided substantial evidences to explore mechanistic interactions of the selective inhibitors of Cdk5/p25 and could be used as fundamental considerations in the development of structure-based selective inhibitors of Cdk5/p25.

Biography

Amir Zeb is PhD student at Geyongsang National University, South Korea. His research interest is Computer Aided Drug Designing and Molecular Modelling. Mr. Zeb has been exposed to a number of proteins modelling projects and achieved excellent output. Currently, Mr. Zeb is trying to unveil the mechanistic studies of therapeutics targets in neurological disorders and their computational inhibition. He has published more than 15 papers in reputed journals.

zebamir85@gmail.com