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Rational Design of Potent Compounds for Inhibiting Ca2+ -Dependent Calmodulin Kinase IIa, a Target of Alzheimer's Disease

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Abstract : Ca2+ - dependent calmodulin kinase IIa (CaMKIIa) has recently been found to associate with protein tau missorting and polymerization in Alzheimer's Disease (AD). However, there has yet inhibitors targeting CaMKIIa to investigate the correlation between CaMKIIa activity and protein tau polymer formation. Combining virtual screening and our statistics in binding contribution scoring function (BCSF), we rationally identified potential compounds that bind to specific CaMKIIa active site and specificity-affinity distribution of the ligand within the active site. Using molecular dynamics simulation, we identified structural stability of CaMKIIa and potent inhibitors, and site-directed bonding, separating non-specific and specific molecular interaction features. Despite of variation in confirmation of simulation time, interactions of the potent inhibitors were found to be strongly associated with the unique chemical features extracted from molecular binding poses. In addition, competitive inhibitors within CaMKIIa showed an important molecular recognition pattern toward specific ligand features. Our approach combining virtual screening with BCSF may provide an universally applicable method for precise identification in the discovery of compounds.

Keywords : Alzheimer's disease, Ca 2+ -dependent calmodulin kinase IIa, protein tau, molecular docking
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