



Development of heterocyclic analogs of curcumin for Alzheimer's disease

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Abstract:

Amyloid β ($A\beta$) peptide monomers polymerizes to form insoluble amyloid fibril aggregates and accumulates as senile plaques which eventually leads to cognitive impairment. Modulating abnormal amyloid aggregation can be considered as a therapeutic target for Alzheimer's disease. Recent studies supports that Curcumin interferes with larger protein aggregate formation by destabilizing the salt bridge (Asp 23-Lys 28) of $A\beta$ protein. Anti-amyloid compounds must inhibit such accumulation by stabilizing soluble $A\beta$ oligomers by forming hydrogen bonds and π - π stacking. Docking scores of such modifications mostly ranged in between -5.9 to -7.1 Kcal/mol which is even more than that of standard curcumin (-5.5 Kcal/mol). In silico docking studies of compound (1) with both $A\beta$ protein and β -secretase enzyme (BACE1) was found to be -6.4 Kcal/mol and -8.7 Kcal/mol respectively which is higher than that of standard. Compound 1 interacts with KLVFFAE fragment (Lys16-Glu22) which is essential for dimerization of the monomers by π - π stacking with Phe A:19. Ala21 in the salt bridge also exerts π -made interactions with the central isoxazole ring as well as the terminal phenyl ring. The compound (1) exhibit hydrogen bonding interaction with Thr232 which is located in S3 pocket of BACE1 making compound binding stable within the pocket. De novo ligand design generated best suitable derivative of the selected lead by iterations. Both compound (1) and de novo designed lead offspring reached the binding pocket of both the proteins, passed Lipinski's rule of five and in silico toxicity testing by admetSAR.

Biography:

Ms. Puja Mishra has completed her Master's degree in Pharmacy from IIT BHU. She is pursuing PhD from MAKAUT university and working as an Assistant professor in Durgapur, W.B.



Publication of speakers:

1. Mishra, Pooja & Singh, K. & Singh, Dharmendra & Rajput, Navin. (2015). Pattern analysis of MiniSAR data for differentiation of icy craters in lunar surface. 3219-3222. 10.1109/IGARSS.2015.7326503.
2. Mishra, Pooja & Singh, Dharmendra. (2015). An Approach for Finding Possible Presence of Water Ice Deposits on Lunar Craters Using MiniSAR Data. IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing. 8. 30-38. 10.1109/JSTARS.2014.2374236.
3. Mishra, Pooja & Singh, Keshava & Singh, Dharmendra & Rajput, Navin. (2014). Critical analysis of deorientation effect on various land covers: An application of POLSAR data. International Geoscience and Remote Sensing Symposium (IGARSS). 2746-2749. 10.1109/IGARSS.2014.6947044.
4. Mittal, Gunjan & Mishra, Pooja & Singh, Dharmendra. (2014). Fusion of polarimetric channel information of PALSAR data for land cover classification. Geomatics. 5. 10.1080/19475705.2013.802260.

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