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Investigation of the misfolding of  
 $\beta$ -amyloid induced by phenyl pyridinium  
derivatives and heavy metals :  
A Computational Study

A thesis submitted for the degree of Doctor of Philosophy

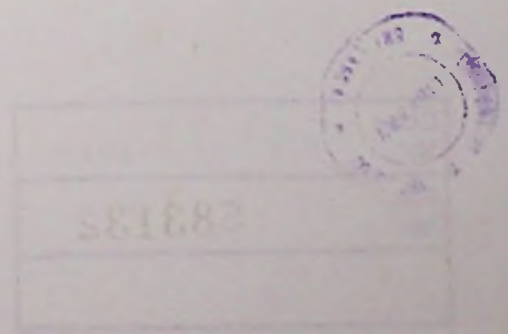
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## Abstract

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The intention of this work is to understand the structural changes occurring in  $\beta$ -amyloids at the early stages of misfolding. The study uses molecular dynamics (MD) simulations to describe specific observations made in published, experimental and theoretical work. A series of MD simulations were carried out to study the structural changes in the  $\beta$ -amyloid 1-42 protein, which is implicated in the pathology of Alzheimer's disease. The  $\beta$ -amyloid 1-42 is known to go through structural changes (misfold) and aggregate. The proteins aggregate into a soluble proteinaceous aggregate called amyloid oligomers, which are toxic to the human brain. The molecule 1-Methyl-4-phenylpyridinium and its derivatives are known to induce structural changes in proteins and four phenylpyridinium derivatives were chosen to study their effect on the misfolding of  $\beta$ -amyloid 1-42 monomer with respect to their inhibition kinetics. According to the results the 4'-trifluoromethyl-phenyl pyridinium derivative can induce structural changes that trigger misfolding of  $\beta$ -amyloid 1-42 protein.

Heavy metals play a vital role in amyloid toxicity. Thus a single heavy metal ion ( $\text{Cu}^{2+}$ ) was first chosen and the effect of the  $\text{Cu}^{2+}$  ion on amyloid misfolding is also studied. The  $\text{Cu}^{2+}$  is bound to  $\beta$ -amyloid 1-42 protein at the methionine residue (position 35 of the  $\beta$ -amyloid 1-42 sequence) and structural changes in the complete protein is studied through MD simulations. This study has identified a new binding site for  $\text{Cu}^{2+}$  at MET-35. Furthermore the effect of  $\text{Cu}^{2+}$  on amyloid oligomers is also studied by simulating penta-peptide systems of  $\beta$ -amyloid 1-42. This part of the study indicated physiological conditions where  $\text{Cu}^{2+}$  can initiate  $\beta$ -sheet formations in  $\beta$ -amyloid oligomers.