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Computational Study of Decapeptides Acting as MPACs Against Alzheimer's Disease

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Alzheimer's Disease (AD) is the leading cause of dementia worldwide. In this disease, metal ions are associated with the formation of oligomers along with the beta-amyloid protein (Aβ) and the generation of reactive oxygen species (ROS) in the brain. This study proposes an analysis of the ligand C-Asp, suggested by Caballero et al. (2020)[1], with the aim of computationally evaluating its stability and selectivity with copper, intending to minimize the interaction between Aβ and Cu(II). Initially, a conformational analysis of the ligand was performed through molecular dynamics simulations (MD) in solution using the Amber16 software, with the RMSD result illustrated in Figure 1(A). The conformational analysis of the ligand revealed the presence of two stable conformations, which were subsequently subjected to quantum calculations. Additionally, to examine its stability through quantum mechanics approaches, Density Functional Theory (DFT) was applied, for which a benchmarking was performed using the Gaussian09 software, with the LANL2DZ basis set for all atoms and applying several functionals, some highlighted in Figure 1(B). The copper coordination site was modeled based on the Cu(II)-Aβ structure available in the Protein Data Bank (PDB) under code 8b9q (model 1)[2]. Thus, the functionals were compared based on structural data. It was observed that the WB97XD functional resulted in an approximately tetrahedral geometry, while M11 and M06HF led to pentacoordinated geometries, with one of the histidines (His) acting as a bidentate ligand. On the other hand, the B3LYP and B3PW91 functionals presented a square planar geometry, like the initial structure, and were selected to evaluate the stability of C-Asp. Additionally, the conformational analysis of the ligands demonstrated that the main amino acid chain confers conformational stability to the cyclic compounds, making them promise for the proposed application.

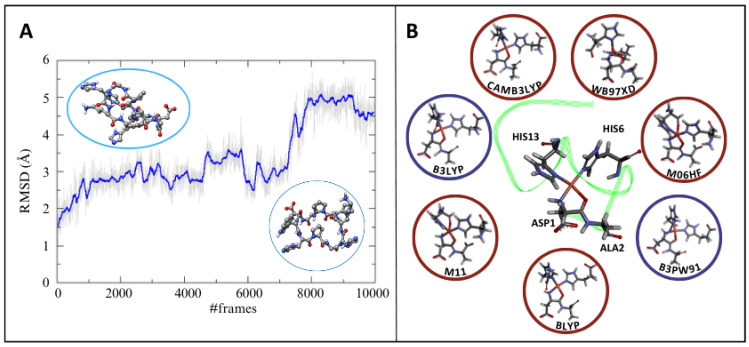

Figure 1 - **(A)** Average RMSD of the C-Asp structure in solution, highlighting its most stable conformations throughout the trajectory (100 frames = 1 ns). **(B)** Mimicked system of the Cu(II)-Aβ structure obtained from PDB:8B9Q[2], optimized through various functionals applied to benchmarking.

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References

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