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Computational Insights into Trypsin–Benzamidine Interactions: Implications for Protein Degradation in Huntington's Disease

Abstract:
Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by abnormal protein aggregation and selective neuronal death, primarily caused by an expanded CAG repeat in the huntingtin (HTT) gene. This mutation leads to the accumulation of mutant huntingtin protein, which disrupts cellular homeostasis and impairs normal protein degradation pathways, including the ubiquitin–proteasome and autophagy systems. Among therapeutic strategies, small-molecule inhibitors targeting protease activity have gained attention as they can modulate protein processing and reduce aggregation-associated toxicity.

In this study, trypsin, a representative serine protease, was investigated for its interaction with benzamidine, a well-established competitive inhibitor, using molecular docking. Benzamidine serves as a prototypical model ligand to understand protease inhibition, providing insight into how small molecules may stabilize enzyme-inhibitor complexes relevant to protein degradation pathways implicated in HD. The docking simulations revealed a lowest binding energy of –4.29 kcal/mol, indicating a moderate and favorable interaction between benzamidine and the catalytic site of trypsin. Cluster analysis highlighted that the stability of this interaction is mediated by hydrogen bonding, electrostatic contacts, and aromatic stacking with key residues within the active site pocket.
These findings emphasize the relevance of computational docking in exploring protease-ligand interactions as part of therapeutic development strategies for neurodegenerative disorders. While benzamidine itself is a model compound, the study underscores the potential of rational inhibitor design in targeting protein degradation dysfunctions in Huntington's disease and related conditions.
Keywords: Huntington's disease, Trypsin, Benzamidine, Molecular Docking, Protein Degradation, Neurodegeneration

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