انجمن بیوشیمی فیزیک ایران
ISOBC
دانشگاه هرمزگان
University of Hormozgan

18th National and 3rd International Conference of Iranian Biophysical chemistry
هجدهمین همایش ملی و سومین همایش بین المللی بیوشیمی فیزیک ایران

25-26 Des, 2024, University of Hormozgan
۶-۵ دی ماه ۱۴۰۳، دانشگاه هرمزگان

Clustering the Generalized Binding Region of Beta-Secretase for Alzheimer's Drug Design

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Abstract

Introduction

Beta-secretase-1 (BACE-1), a type I transmembrane aspartic protease, is a critical enzyme involved in the pathology of Alzheimer's disease, making it a prime target for therapeutic intervention. The identification and characterization of its Generalized Binding Region (GBR) provide crucial insights into ligand-protein interactions, aiding in drug design. By leveraging structural data and computational approaches, this study aims to define the GBR of BACE-1, analyze its structural conformations, and cluster these conformations for efficient ligand-binding studies [1,2].

Methods and Materials

Thirteen BACE-1 protein-ligand complexes were obtained from the Protein Data Bank (PDB) and processed using VMD software to clean and extract relevant structural data. The GBR was defined as residues within 4.5 Å of the ligands, and structural superposition was performed to minimize RMSD between equivalent residues. An RMSD-based dissimilarity matrix was calculated, and k-means clustering was applied to group the conformations into structurally homogeneous clusters. Representative complexes for each cluster were identified, and hydrogen atoms were added using Reduce software. All analyses were conducted using TCL scripts in VMD and statistical tools in R.

Results and Discussion

The GBR analysis identified seven key residues (GLY11, GLN12, GLY13, LEU30, ASP32, GLY34, SER35) frequently interacting with ligands, predominantly located in beta-sheet and turn secondary structures. Clustering the complexes based on the RMSD matrix resulted in three distinct clusters, each represented by a conformationally unique structure. These representative structures provide a comprehensive view of the GBR, facilitating the reduction of docking experiments and offering a robust framework for targeted drug design. Further exploration of alternate conformations and contact thresholds could enhance the accuracy of GBR characterization, contributing to more effective inhibitor development for Alzheimer's treatment.

Key words: Beta-secretase-1, Alzheimer's disease, Generalized Binding Region, structural clustering, RMSD, drug design.

References

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