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ARTICULO DE REVISIÓN

In silico approach in treatment of alzheimer disease of apolipoprotein e4 inhibitor discovery

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Abstract

A significant genetic risk factor for Alzheimer's disease is the presence of apolipoprotein E4 (Apoe) (AD). Maintaining a steady supply of neuronal lipids for quick and dynamic membrane production is essential for brain function. The development of beta amyloid plaques (A) and neurofibrillary tangles in the brain is what causes AD. The goal of the current research is to foresee a treatment against excessive apoE4 activity. The current investigation included 22 natural chemicals, including marine, microbial, and plant derivatives.These substances were utilized as inhibitors to block the action of the apoE4 protein. Six synthetic compounds were also docked with the target protein in order to compare and evaluate the outcomes with natural chemicals.Teleglobe, a synthetic chemical, exhibited the highest binding affinity for the target protein but did not exhibit hydrogen bonding with any of the amino acid residues. Moreover, a natural substance called Digitoxin digitoxoside had the highest binding affinity while failing to form hydrogen bonds with any amino acid residue.Based on binding affinity and hydrogen bonding to decrease AD development, our investigation identified digitoxin digit oxide as a possible lead chemical.

Keywords: Apo lipoprotein ,Alzheimer’s disease, docking, bioinformatics,Digit toxin digitoxoside

Introduction

Millions of individuals worldwide are afflicted by Alzheimer's disease (AD), a neurological condition. Alois Alzheimer first gave the condition a description in 1906. He noticed in patients' vascular abnormalities, neurofibrillary tangles, and amyloid plaques(Jönsson, 2013).One of the genetic risk factors for Alzheimer's disease (AD) has been established through linkage studies of the apolipoprotein E (ApoE) gene variants(Ahmed, 2017).The gene coding for the apoE protein has three distinct isoforms: apoE2 (epsilon 2), apoE3 (epsilon 3), and apoE4 (epsilon 4). On chromosome 19q13.2, there is the gene for apoE.Numerous potential genes have been discovered, but only the E4 allele is being evaluated as a significant risk factor for both early and late-onset AD(Huang, 2014).

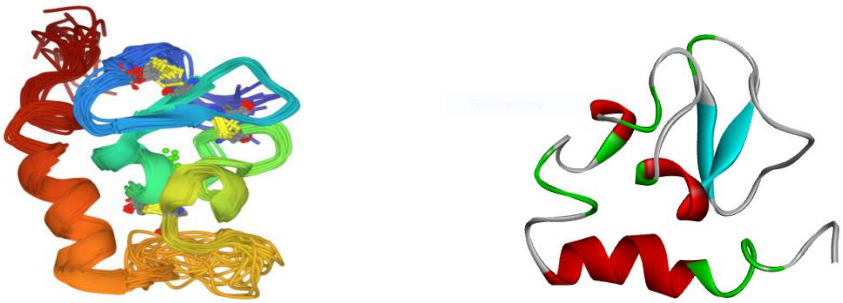
The goal of drug design is to identify chemical compounds that match a certain protein target or that may strengthen or weaken the protein depending on the situation(Gómez-Isla, 1997). By using computational tools, Computer Assisted Drug Designing (CADD) may quickly and cheaply find chemical compounds that are compatible with potential protein targets.In this work, we employed a variety of CADD approaches to find prospective lead compounds that may block ApoE4's harmful function.Natural substances that are produced from plants, bacteria, and marine microorganisms can be utilized to combat the ApoE4 gene with the fewest possible negative effects(Jia, 2017). Curcumin, rebellions, manzamine, and rhizome are some of these substances(Corder, 1993).

Drug research and development utilise a computer technique called molecular docking to ascertain the interaction and binding affinity between a small molecule (ligand) and a target protein. Molecular docking is essential for understanding the biology of Alzheimer's disease (AD), finding viable drug candidates, and creating innovative therapeutic strategies. The following key points emphasise how crucial molecular docking is to the study of Alzheimer's disease.The use of molecular docking facilitates the identification and evaluation of potential treatment targets for Alzheimer's disease. Researchers can simulate the interaction between small compounds and target proteins implicated in AD in order to prioritise targets and quantify their binding affinity for the goal of guiding the drug discovery process (Conway 1998). In order to identify potential treatments for Alzheimer's disease, large databases of already marketed drugs may be analysed using molecular docking. By docking current medicines against target proteins implicated in AD pathogenesis, researchers can discover approved treatments that may interact with these targets, accelerating the therapeutic development process.

Material and Method

Protein Structure and Refinement Retrieval:

The structure of ApoE4 was already predicted.The structure was obtained using RCSB PDB (http://www.rcsb.org/pdb) from the Protein Databank (PDB ID 2KNY).Using a Ramachandran plot, the effectiveness of a structure was verified(Pericak-Vance, 1991). The protein underwent further processing using Discovery Studio to remove water molecules and minimize energy in preparation for docking analysis(Johnson, 2014).



A) b)

Figure1 (a)3D structure of protein 2KNY (b) protein prepared by discovery studio**.**

Retrieval of Ligand 3D Structures:

After doing a literature study, the natural substances were discovered. These substances showed activity in tau-related screenings. Tau-based medicines have been proposed as being more suited for anti-A therapy(Strittmatter, 1993). Tau is also becoming a more popular target as a possible option for treating AD(Roses, 1998). PubChem (https://pubchem.ncbi.nlm.nih.gov) was used to get the 3D structures of the legends.The collection consists of 6 synthetic and 22 natural chemicals. To compare our findings, clinical trials using synthetic drugs to treat AD at various stages of development were employed(van der Flier, 2011).

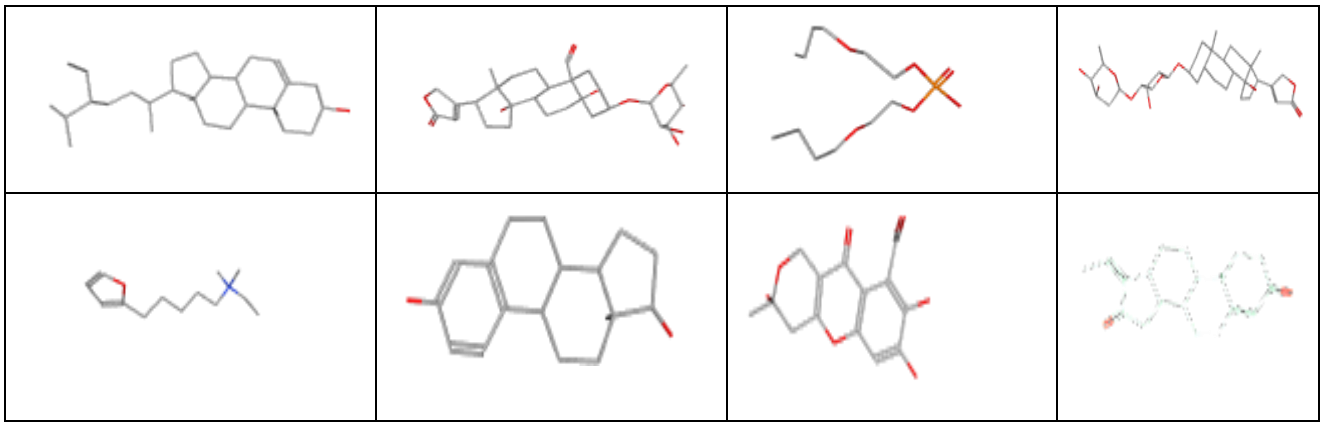


Table1 3D structure of some selected ligand compounds from pubchem.

Docking of Protein-Ligands and Interactions:

The docking study was carried out following the recovery of the protein structure and ligands. In order to identify the optimal protein-ligand conformation with a high binding affinity, the compounds were docked against the target protein(Dong, 1994). Pyrex, a free virtual screening tool, was used for the docking. It combines Auto Dock Vina, Mayavi, and Open Babel. It docks using Auto Dock 4.2.Discovery studio was used to visualize the ligands that have a high affinity for the target protein(Tanzi & Bertram, 2005). Using legplot plus, the investigation of hydrophilic and hydrophobic interactions was carried out(Risner, 2006).

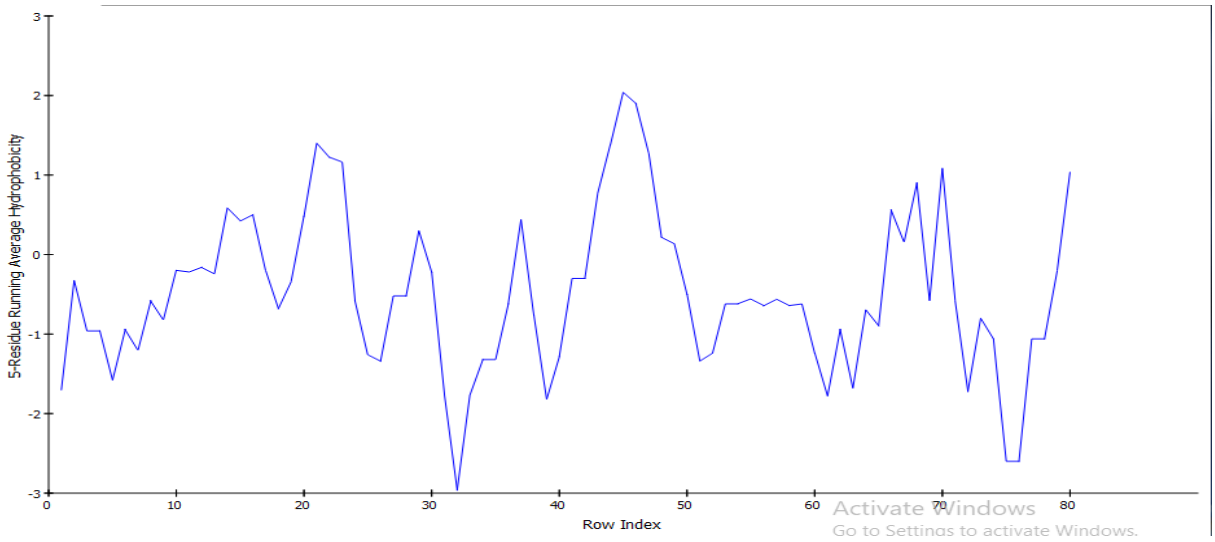


Figure 3 Hydrophobicity chart

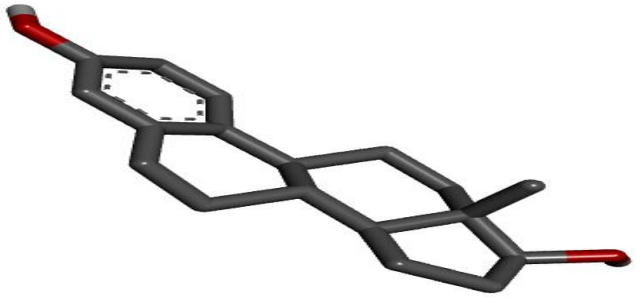


Figure4 Ligand selected with high binding Affinity

Toxicity Analysis of Chemical Compounds:

To learn more about the features of chemical compounds' Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET), toxicity analyses were conducted on them(Kalita & S, 2014). The chemical compounds' ADMET characteristics were calculated using admetSAR (http://www. admetexp.org) for the study(Stahl, 2006).

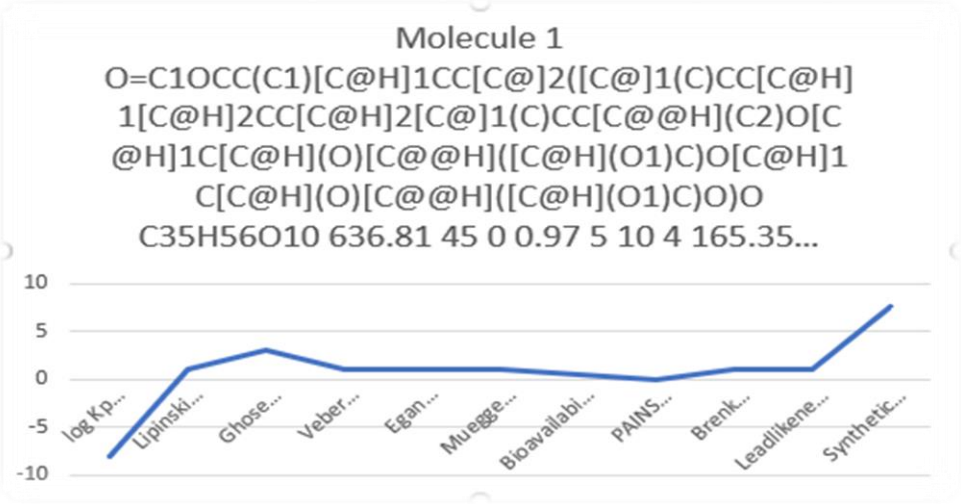


Figure5 ADMET analysis through swiss admet

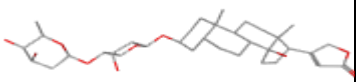
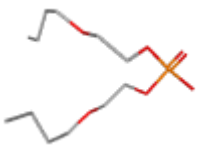
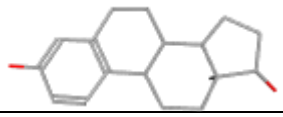
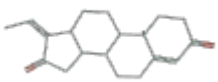
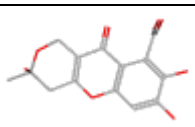
Dynamic Simulation Analysis

I MODE simulations are regarded as an important step in the investigation of protein-ligand complex interactions in computer-aided drug development. They also give comprehensive details on the binding affinity of the complex structure. Only two compounds obtained docking scores that were equal to or lower than -8.75 kcal mol1, according to the results of a molecular docking study.A simulation using IMODE was run for 50 and 100 ns. During the simulation process, it was demonstrated that the MM/GBSA methodology is one of the most effective methods for calculating the numerical values of binding affinity. The docking scores and

binding energies of the studied drugs are consistently ordered in the same order. The maximum binding energy of the serotinine J3QKP3 active site compound andboth achieved the docking score

Resultsand Discussion

A docking study of the protein ApoE4 revealed three important binding sites. There are 22 naturally derived chemicals in the collection. Moreover, the collection included includes 6 synthesized substances(Conway, 1998). Several stages of clinical studies to treat AD are being conducted using these synthesized medicines. The major polypeptide chain of the protein molecule's conformation angles, phi and psi, were displayed on the Ramachandran plot. The plot made clear that 99.3% of the leftovers were in the preferred area. Also, there were no outliers and 0.7% of the residues were in the permitted area(Goyal, 2013). To assess the differences in binding affinities and interacting amino acid residues, docking findings of synthetic and natural drugs were compared. Table shows display the top 5 natural compounds' structures, molecular weights, and binding affinities(Kalita & S, 2014)(Mayeux, 1999).

No	Compound name	Structure	Molecular weight(g/mol)	Binding affinity(kcal/mol)
1	Digitoxin digitoxoside		634.8	-7.7
2	Diethyl ammonium bis(2-butoxyethyl)phosphate		371.45	-7.1
3	Convallotoxin		550.6	-7
4	Estradiol		272.4	-7
5	Guggul Strone		312.4	-6.9
6	Fulvic acid		308.24	-6.5

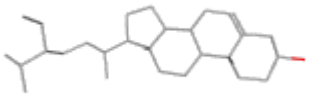
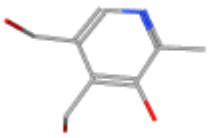
7	Beta-sitosterol		414.7	-6.2
8	Di methyl ethyl(5-(2-furyl)pentyl) ammonium		337.24	-5.6
9	Pyridoxine		169.18	-4.5

Table2Molecular weight, binding affinity, and the top 9 most dominant molecules. Analyzing the differences in binding affinities and interacting amino acid residues required comparing the docking data of synthetic and natural drugs. In order of binding affinity, the top 9 natural and synthesized chemicals are listed.

Hydrogen bonding is the most significant connection between biological molecules. A protein's three-dimensional structure is stabilized by it. Hydrogen bonding is crucial for biological recognition and directly affects molecular mobility for the biological process through the quick creation and breaking of bonds.A current topic of research is identifying the substrate/ligand in macromolecules using hydrogen bonding(Burley, 2018). We observe hydrogen bonding in the protein-ligand complexes' active regions.While they improve the binding affinity of protein and ligand, hydrophobic interactions are also highly important. In this investigation, we examined the weak intermolecular forces to comprehend the ideal shape and stability of the protein-ligand complex(Lovell, 2003).

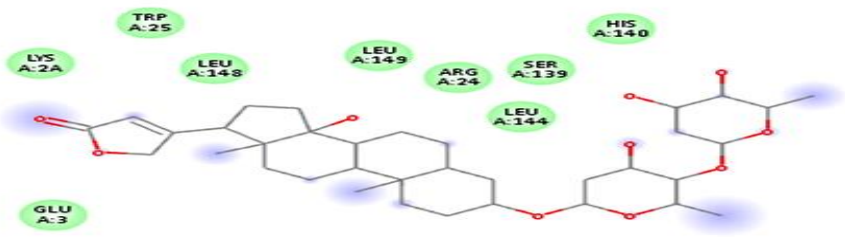


Figure62D structure of protein 2KNY with high binding affinity ligand

The greatest binding affinities were demonstrated by the naturally occurring molecules digitoxin digitoxoside and diethyl ammonium bis(2-butoxyethyl)phosphate, with -7.7 and -7.1 kcal/mol, respectively.Remarkably, Digitoxin digitoxoside transforms seeding-competent A oligomers into offpathway seeding-incompetent(Li & Gotz, 2017). A assemblies, which significantly lessens the cytotoxicity of the AD -amyloid peptide.Teleglobe did not exhibit hydrogen bonding with any amino acids when we docked synthetic molecules being tested in clinical trials with the target protein(Kim & T, 2015).

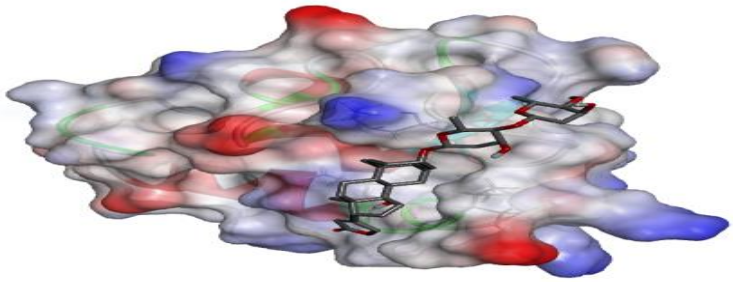


Figure8 Pose of the leading candidate docked

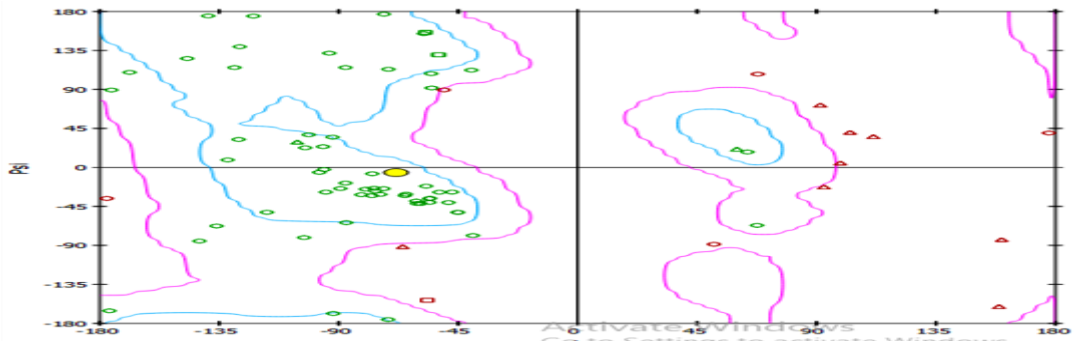


Figure9Ramchandan plot

Analyzing ADMET characteristics is crucial for the process of finding and developing new drugs. Evaluations conducted in vivo and in vitro are pricy and time-consuming(Trott, 2010). Hence, in silico approaches are frequently employed today to ascertain the ADMET features of chemical compounds. The top three natural substances' toxicity was calculated for negative consequences(Cheng, 2012). The findings of the toxicity analysis are displayed in. Moreover, proteins have a wide variety of covert ways to coordinate and regulate one another. They may have an impact on one another's output or jointly support particular organ systems. These direct and indirect interactions make up the protein's functional relationship(Gopalakrishnan, 2007).In the process of analysing protein-ligand complex interactions in computer-aided drug development, MD simulations are seen as a key step. In addition, they offer comprehensive

details on the binding affinity of the complex structure. Only two substances obtained molecular docking scores that were equal to or less than -8.75 kcal mol1, according to the findings of the study.Over 50 and 100 ns, an MD simulation was performed. One of the most effective methods for determining the numerical values of binding affinity during the simulation process has been demonstrated to be the MM/GBSA method. Table 2 shows that the docking scores and binding energies of the investigated drugs are consistently listed in the same order. Aferin increases the maximum binding energy of the serotinine J3QKP3 active site compound andthe docking scores and binding energies of the investigated drugs are consistently ordered in the same order. The greatest binding energy and docking score of the serotinine J3QKP3 active site compound were achieved with aferin.

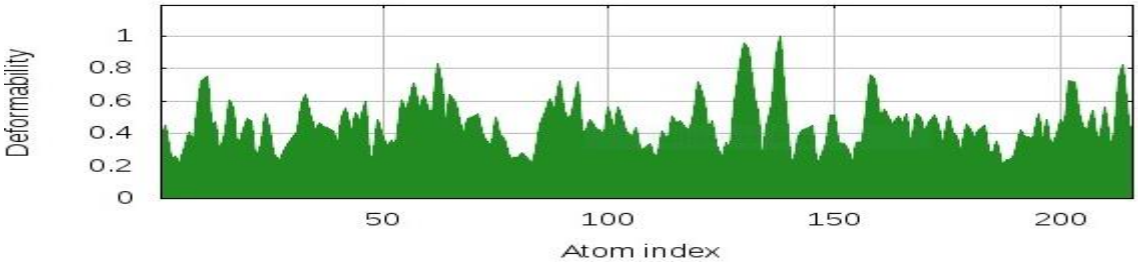


Figure10 A molecule's capacity to deform at each of its residues is measured by its main-chain deformability. Regions with high deformability can be used to determine where the chain "hinges" will be.

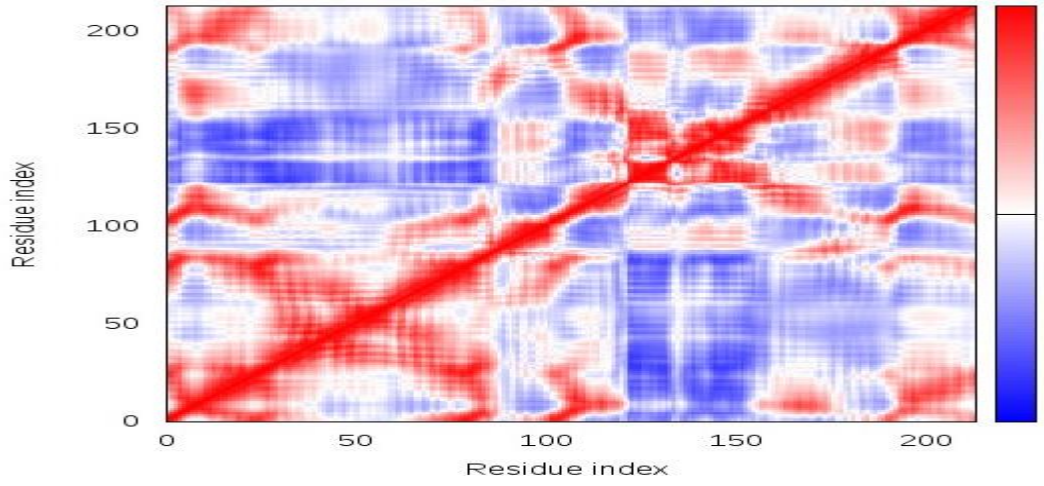


Figure11 The covariance matrix shows how closely two residue pairs are coupled, i.e., whether they move in correlated (red), uncorrelated (white), or anti-correlated (blue) ways.Using equation 2 and the C Cartesian coordinates, the correlation matrix is calculated in: Karplus M. and Ichiye T. Molecular Dynamics and Normal Mode Simulations: A Covariance Analysis of

Atomic Fluctuations in Collective Motions in Proteins.

Conclusion

To identify the most effective ApoE4 inhibitors, we used docking analysis. Digitoxin digitoxoside was chosen as a possible lead chemical with the use of docking and analytical tools because it is projected to have high binding affinity and hydrogen bonding(Corder, 1993)(Desiraju & Steiner, 2001). A molecule that may be employed as an inhibitor is further made important by its hydrophilic qualities and lower toxicity when compared to other chemicals. Future AD treatments may restrict the disease's progression using this inhibitor(Panigrahi & Desiraju, 2007).

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