The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)
01–30 NOVEMBER 2021 | ONLINE

3-APS against BACE-1 target in Alzheimer's disease; DFT calculations and molecular docking

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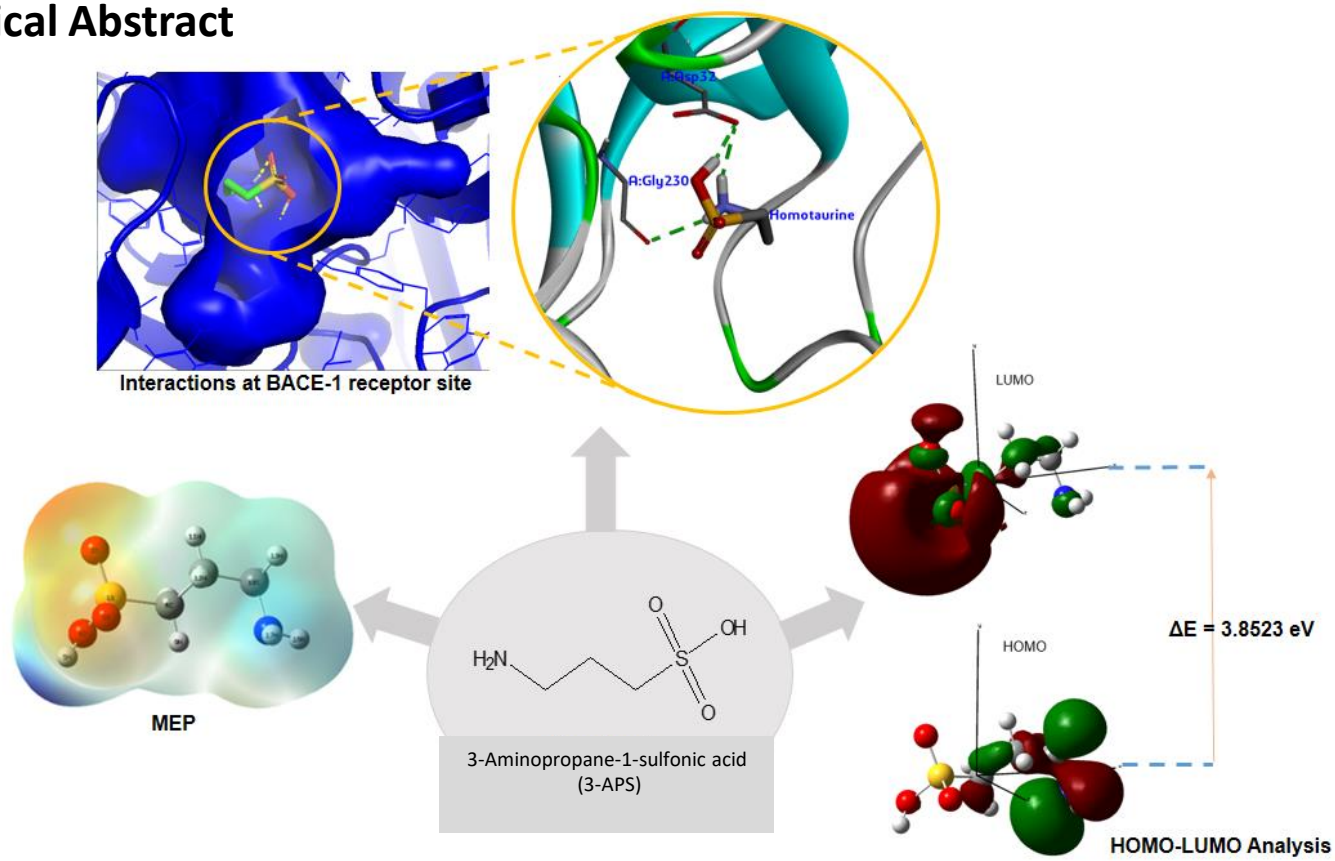
Graphical Abstract



Abstract:

Pathogenesis of Alzheimer's is mainly preceded by aggregation of β-amyloids (Aβ). Beta-site amyloid precursor protein Cleaving Enzyme-1 (BACE-1) is a rate-limiting enzyme in the production of Aβ. DFT calculations based on deduced from time dependent self-consistent field method show that 3-Aminopropane-1-sulfonic acid (3-APS) has a tendency for polar interactions and reactivity in binding pocket of BACE-1 based on the energies of the highest occupied and the lowest unoccupied molecular orbitals. Energy gap of frontier molecular orbitals was calculated to be 3.8523 eV reasonably describing global reactivity descriptors. Molecular electrostatic potential and Mulliken population charge analysis show electronegative behaviour and nucleophilic dominance of 3-APS. Drug-likeness predictions exposed the best agreement to Lipinski's rule of five and ADMET properties. Post-docking results analysis indicates that, most stable binding pose of ligand with no root mean square deviation has the binding affinity of -3.6 kcal/mol. Least stable conformation shows an affinity of -3.2 kcal/mol. Conventional hydrogen bonds were found to be dominant interactions where the participating residues were aspartic acid (ASP) and glycine (GLY) of chain A of BACE-1. Hydrogen bonding between amino group of ligand and GLY of receptor site recorded the longest distance of 2.5128 Å. Maximum dihedral angle of 158.485° was observed in between sulfonyl group of ligand and ASP. This is attributed to steric effect around sulfonyl group within pocket. Calculated DFT parameters and docking interactions could share with varying degree to significantly affect the binding affinity of 3-APS with BACE-1 receptor.

Keywords: Alzheimer's; Homotaurine; DFT; molecular docking

Introduction

- Alzheimer's disease (AD) is the most common form of dementia clinically characterized with cognitive decline or impairment. Accumulation of β-amyloids (Aβ) causes neurotoxic circumstances leading to AD. Previous pathological studies reveal that the cellular deposition of Aβ protein fibrils forming senile plaques effect on neurodegeneration.

- Formation and clearance of Aβ are enzyme-mediated processes. BACE-1 (Beta-site amyloid precursor protein (APP) Cleaving Enzyme-1, β-secretase) is a rate-limiting enzyme in the production of Aβ. Marine life phytochemicals establishing inhibition of BACE-1 activity are investigated in recent years for their potential drug-likeness properties.

- 3-APS extracted from *Grateloupia livida* (marine red alga) has been investigated for inhibiting Aβ aggregation in in vivo experiments [3]. Simulation-based aspects offer wide potential hypotheses for novel phytocompounds and their inhibiting interactions at target receptor sites. Present computational investigation employing quantum mechanical density functional theory (DFT) calculations and molecular docking tools aims to determine molecular properties of Homotaurine for drug candidacy and to profile binding energetics of different conformations of the Homotaurine at the BACE-1 receptor sites.

DFT Calculations

Quantum mechanical density functional estimations were carried out for Homotaurine ligand by Gaussian 09 software. B3LYP 6-311 + G (d,p) basis set was nominated for the DFT calculations. Molecular structure has been drawn using Gauss View. Structural geometry was optimized by minimizing its energies. Time dependent self-consistent field (TDSCF) method with integral equation formalism polarizable continuum solvent model (IEFPCM) was employed for ultraviolet energy calculations at the Gaussian 09.

Molecular Docking Procedure

Preparations of BACE-1 protein target (RCSB PDB ID: 4IVS) and Homotaurine ligand (CID: 1646) and docking grid generation were performed using AutoDockTools version 1.5.6 (ADT 1.5.6). Drug-likeness properties were predicted using Drug Likeness Tool (DruLiTo) and variable nearest neighbour (vNN) method-based ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) server. Molecular docking was performed using AutoDock Vina.

Results and discussion

Table 1 DFT calculations of FMO energy gap and reactivity descriptors in eV.

$\Delta E = E_{LUMO} - E_{HOMO}$	χ	η	δ	ω	I	A
3.8523	4.9875	1.9262	0.5192	6.4571	6.9136	3.0613

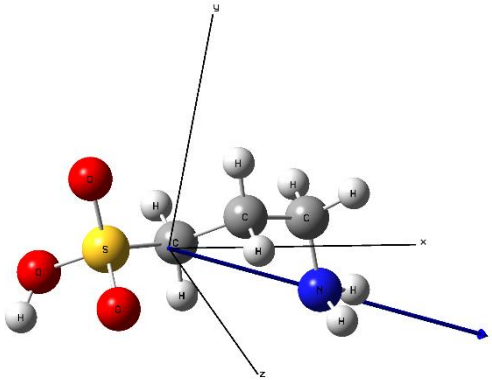


Figure 1 Dipole vector of geometry optimized Homotaurine

Table 1 BACE-1 - Homotaurine interactions

Interactions	Residues	Ligand sites	Distance (Å)	Dihedral angle
Conventional H bonds	ASP A:32	$-SO_3H$	2.18235	158.485
		$-NH_2$	2.25561	157.847
	GLY A:230	$-NH_2$	2.5128	115.861

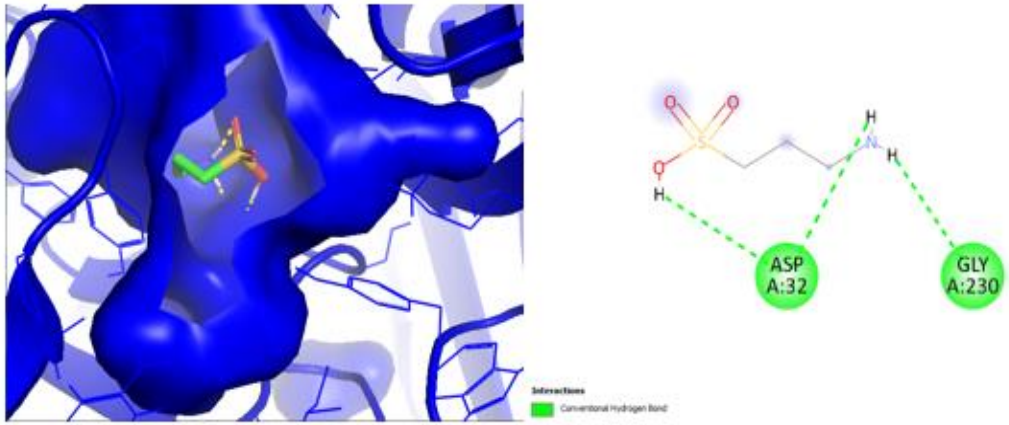


Figure 2 Most stable binding pose within pocket and hydrogen bond interactions

Conclusions

- 3-APS has been investigated as inhibitor against BACE-1 activity in AD. Homotaurine showed best agreement to drug-likeness predictions.
- The results revealed the best binding pose with -3.6 kcal/mol. The DFT results showed polarity and nucleophilic distributions confirming polar contacts of the ligand.
- The binding pose within the pocket is supported with net dipole vector calculated. These parameters affect the binding affinity of the drug at the active sites.
- From these in silico studies, it is very promising to conduct in vitro and in vivo studies against BACE-1 activity.