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Solute-solvent interactions, electrostatic & covalent surface analysis, and pharmacokinetic studies via in-silico simulation on diethyl 3-hydroxyglutarate: Anti-hypercholesterolemia activity

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Highlights

- Anti-hypercholesterolemia activity on 4-(Bis(2-chloroethyl)amino)-L-phenylalanine was predicted with docking.
- Solvatochromic correlations were used to find the solute-solvent interaction center of D3HG.
- Covalent and electrostatic interactions were assessed by AIM, ELF, LOL & RDG,
- Microscopic-level interactions in solutions were performed with UV–Vis, MEP and FMOs.

- In silico ADME toxicity measurements for the D3HG were also performed.

Abstract

In this study, theoretical investigations of the anti-hypercholesterolemia molecule diethyl 3-hydroxyglutarate (D3HG) have been carried out using DFT techniques. Vibrational spectral analyses were utilized for the structural determination after the compound's stability was identified through DFT optimization. As per the QTAIM findings, the highest electron density and electron distribution asymmetry were found at O4═C9 and O5═10 in the molecule D3HG. Under the topological evaluation, the covalent and electrostatic interactions were assessed by Laplacian electron density ($\nabla^2\rho(r)$) and reduced density gradient (RDG). Studies of solvent effects on electronic absorptions, molecular electrostatic potentials, global reactive descriptors, and Fukui functions have been analysed to understand better the mechanism causing chemical responsiveness. First-order hyperpolarizability (β) and natural bond orbital (NBO) stability calculations were also included. Solvatochromic correlations are used to approximate the referred molecule's reactions to polar and non-polar solutions as well as the solute-solvent interactions. Using Lipinski's rule, the molecule's drug-likeness study was carried out; pharmacokinetics and the D3HG molecule's interactions with iso-enzymes were also explored. A molecular docking study also demonstrates the efficacy of the title molecule to have anti-hypercholesterolemia activity.

Introduction

Hypercholesterolemia is a significant cardiovascular risk factor that increases the prevalence of atherosclerotic diseases. Millions of people worldwide suffer a range of issues related to high cholesterol (hypercholesterolemia) [1], [2]. The effectiveness of drugs in pharmacologically treating these disorders has improved in recent years. Diethyl 3-hydroxyglutarate (D3HG) is an extensively used chemical in pharmaceutical delivery systems and one of the most efficient intermediates in producing drugs for hypercholesterolemia [3], [4], [5]. Optically active D3HG is an important primary component for producing a variety of medicinally significant chemicals, such as pimaricin, statins, and l-carnitine [6], and it also completes the gap between the demands of the health industry and the practical efficacy of fluorine chemistry [7]. It is an effective bioconversion to several biosynthesis products for medicines, especially hypercholesterolemia [6], [7], [8]. This substance played a major role in developing and

producing several HMG-CoA reductase inhibitors of pyrrole-based used to treat hypercholesterolemia [9], [10], [11]. When titanium is present, polyesters of hyperbranched aliphatic made from the D3HG monomers were reported [12]. The effective biocatalytic synthesis of an intermediate, recorded in various studies, significantly contributes to the environmentally friendly synthesis of medications [4]. Using polar aprotic solvents and high substrate concentrations, the efficiency of Novozymwas improved in the asymmetrical hydrolysis of a substrate containing the D3HG [13].

Using a variety of theoretical methodologies, the study of theoretical modelling of drug molecules for hypercholesterolemia with medical significance has recently benefitted greatly from the development of computer simulators [14], [15]. As a result, it is now possible to evaluate the crucial chemical and physical qualities of the compounds of drugs for hypercholesterolemia treatment that have been approved [16], [17]. Due to its superior precision and low processing cost compared to conventional methodologies, density functional theory (DFT) has improved by developing a considerably more precise exchange-correlation function. Numerous studies on organic drug molecules have demonstrated that the DFT can effectively replicate experimental results [18], [19], [20], [21], [22]. There is growing interest in developing more environmentally friendly methods for producing medications to treat hypercholesterolemia because chemically synthesised processes in solvents are required for reaction conditions and commonly use water as a reaction medium [23].

The present investigation aimed to achieve the following main objectives by expanding on previous research of hypercholesterolemia activity of the title molecule with reported results. The local and global reactive descriptors, UV spectra, and computational results from the DFT approach were used to assess the reactivity behaviour in the various solvents. Geometrical, IR, Raman, and topological characteristics (AIM, ELF, and LOL) were estimated in the ground state for the structural properties. Studies on molecular docking and ADMET predictions of D3HG were major aspects of this study. The literature review and OnlinePASS tool were utilised to predict the targeted proteins (PDB code: 1A4L, 1HWK and 4GKB) of 1,4-Lactonase inhibitors and their relationship with human hypercholesterolemia was performed for the current investigations. The docking study aimed to identify the best docking score with the least binding energy among the three hypercholesterolemia protein targets with the most residues in non-covalent (ligand-protein) interactions.

Section snippets

Computational details

Gaussian 09W was used for all theoretical computations utilising the hybrid B3LYP functional [24] and Chemcraft 1.6 based on the LANL2DZ basis set. For this investigation, triple-zeta basis sets with two polarisation functions were selected since they are more affordable and produce better significance for molecular bond interactions. The vibrational frequencies were assessed at the same theoretical level, and the scaled wavenumbers 0.958 and 0.983 [25] with the VEDA tool using PED prediction …

Molecular structure and geometry

The **D3HG** key structural information, including the bond lengths and angles, was attained using the DFT method, as shown in Table 1. D3HG is a chemical compound with the point group C1 and the formula $C_9H_{16}O_5$. With a dipole moment of 4.612310 Debye and the minimal lower bound energy of −728.964148 Hartree, this ideally optimised structure is depicted in Fig. 1. The compound has major functional groups, including two C═O, three CO and one OH group. Because of these functional groups' (C═O, CO and…

Conclusion

DFT techniques have been used in this study to conduct theoretical examinations of the anti-hypercholesterolemia compound diethyl 3-hydroxyglutarate (D3HG). The AIM result shows that O4═C9 and O5═10 had the highest determined electron densities and the highest levels of asymmetry in the electron distribution (BCP's; = 0.0847 & 0.0847 a.u.). This may be due to the most robust covalent interactions between the molecule's double-bond attachments (C═O). The RDG study concluded that there are no…

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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