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A Heterocyclic Compound Hispidulin: Theoretical Investigation by DFT/TD-DFT Methods and Molecular Docking Studies

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Abstract: Flavonoids are polyphenolic plant secondary metabolites with biological properties including Alzheimer's disease (AD) inhibition activities. Numerous studies have been conducted on naturally occurring flavonoids modified to obtain effective drugs for the management of AD. In this study, DFT/B3PW91, TD-DFT/B3LYP methods of target molecule hispidulin 4′,5,7-Trihydroxy-6-Methoxyflavone (THMF) and LANL2DZ (d,p), 6-311G (d,p) basic HOMO-LUMO energy calculations, optimized molecular geometry, molecular electrostatic potential surface (MEPS), non-linear optics (NLO), charge transfer within the molecule and mulliken atomic charges structure were determined and the results were displayed. Moreover the identification of the mechanism of action of the tested compound based on the structure-activity relationship with the molecular docking process is to provide important information to be considered for further research, and thus to design new, more efficient and selective systems.

Bir Heterosiklik Bileşik Hispidulin: DFT/TD-DFT Metotları ile Teorik Olarak İncelenmesi ve Moleküler Yerleştirme Çalışmaları

Anahtar Kelimeler
Hispidulin,
DFT,
TD-DFT,
Moleküler Yerleştirme

Öz: Flavonoidler, Alzheimer hastalığı (AD) inhibisyon aktiviteleri de dahil olmak üzere biyolojik özelliklere sahip polifenolik bitki ikincil metabolitleridir. AH yönetimi için etkili ilaçlar elde etmek için modifiye edilmiş doğal olarak oluşan flavonoidler üzerinde çok sayıda araştırma yapılmıştır. Bu çalışmada, hedef molekül hispidulin 4′,5,7-Trihidroksi-6-Metoksiflavon (THMF)'in DFT/B3PW91, TD-DFT/B3LYP yöntemleri ve LANL2DZ (d,p), 6-311G (d,p) temel setleri kullanılarak HOMO-LUMO enerji hesaplamaları, optimize edilmiş moleküler geometri, moleküler elektrostatik potansiyel yüzey (MEPS), doğrusal olmayan optik (NLO), molekül içindeki yük transferi ve mulliken atomik yükleri yapısı belirlendi ve sonuçlar görüntülendi. Ayrıca, moleküler yerleştirme işlemiyle yapı-aktivite ilişkisine dayalı olarak test edilen bileşiğin etki mekanizmasının tanımlanması, daha sonraki araştırmalar için dikkate alınması gereken önemli bilgiler sağlamak ve bu sayede yeni, daha verimli ve seçici sistemleri tasarlamaktır.

1. Introduction

Alzheimer's disease (AD) is classically the most common type of dementia, a multifaceted neurodegenerative disease with typical cognitive symptoms and neuroanatomical changes. AD, the most common neurodegenerative brain disease causes dementia and death in the elderly population [1,2]. The preliminary studies have demonstrated beneficial effects of flavone-based compounds in various cell cultures against AD [3]. Flavonoids are polyphenolic heterocyclic compounds found in abundance in plants. Flavonoids are an important class of heterocyclic natural organic compounds. Hispidulin which has AD activity is a natural flavone. Today, natural products are gaining more and more attention due to their AD activity and low toxicity. Hispidulin, a natural flavone; It has many biological activities such as antiplatelet, anticonvulsant, anti-inflammatory, antifungal and anti-osteoporotic, especially in AD [4]. Based on the available literature, it can be seen that hispidulin is an important complementary medicine for the treatment and prevention of AD [5].

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In addition to experimental studies involving the effects of flavonoids in AD, the well-known electronic structure principle is of great importance in the development of drugs. For this purpose, DFT / TD-DFT should be considered as powerful tools. Theoretical tools such as DFT and molecular docking provide important information about the AD behavior and drug properties of molecular systems. Theoretical tools such as DFT and molecular docking provide useful information about drug properties of molecular systems. The electronic parameters of this molecule depend on the charge distribution on the hispidulin molecular rings. The electronic properties of naturally occurring flavonoids such as hispidulin were investigated based on quantum chemical calculations. The electronic properties of hispidulin, a natural flavonoid were investigated according to quantum chemical calculations [6].

In the field of new applications, we predicted the drug design of hispidulin as a research on this subject. Pharmaceutical technology allows the use of hispidulin in many fields such as nonlinear optics and energy storage. There are theoretical computational studies to investigate the electronic parameter properties of the conjugated π system (HOMO-LUMO, stimulation energies) [7-10] in the hispidulin compound. DFT and TD-DFT methods are the leading methods used in modeling the molecule in hispidulin compound [11]. Molecular docking, binding mechanism of ligand-protein interactions was carried out.

2. Material and Method

2.1. Computer calculations for DFT/TD-DFT methods

Quantum calculations were made for the structural and chemical properties of hispidulin using DFT and TD-DFT methods. All quantum chemical calculations of the molecule were determined using DFT/TD-DFT methods, B3PW91 / LANL2DZ (d, p) and B3LYP /6-311G (d, p) basic set and Gaussian 09 package program [12] and its electronics, geometry and structural properties were determined. The plotted molecule data was displayed in GaussView 6.0 [13].

2.2. Computer simulations for molecular docking

Molecular docking study for ligand-enzyme interactions and the compound's potential to bind to protein as an inhibitor was performed with Schrödinger's Maestro Molecular Modeling platform (version 11.8) (The Ligand-protein docking approach was realized with the glide docking module) [14]. The crystal structures of β-Secretase 1 (BACE-1) (PDB:4FM7), glutaminyl cyclase (QC) (PDB: 6YI1) enzymes were downloaded from PDB database [15,16]. Preparation and ligand docking placement studies were carried out using ligprep module, protein prep, receptor grid box modules. Inhibition performance, docking score, and binding conformations were determined. Docking study results were visualized with the Discovery Studio 2016 client (Visualizer 2005) [17].

3. Results

3.1. Geometry optimization

It is a variable function consisting of parameters in a molecular system, and this function is called Potential Energy Surface (PES). PES has many maximum and minimum points [18]. Geometry optimization is the state of the molecule where the energy is minimum and most stable. The optimized geometric structure of hispidulin is given in Figure 1.

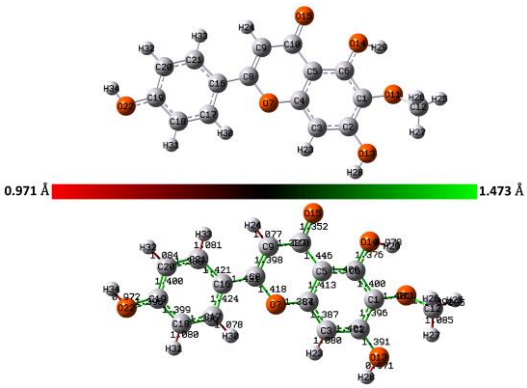

Figure 1. Optimized molecular structure of hispidulin.

Optimizations and energy calculations were made separately in a single calculation with the same basis set. Its optimized structure for the hispidulin molecule is shown in Figure 1 and all parameters are listed in Table 1. Here there are very minor differences between the B3PW91 / LANL2DZ (d, p) and B3LYP /6-311G (d, p) base set values. This optimized structure showed that it has minimum potential energy.It was studied by comparing two optimized base sets of hispidulin. The optimized bond lengths and bond angles obtained in the aromatic ring are within normal values. C-C bond lengths for B3LYP are 1.385 – 1.446 Å and C-O bond lengths for B3PW91 are 0.975 – 1.467 Å and for the oxygen atom in the aromatic ring 1.386 – 1.410 Å. C-H lengths in the aromatic ring 1.080 – 1.084 Å. All C-C-C angles are between 117° and 122°. The C-C-H angle in the compound is 119° - 121°, C-C-O 117° - 122° and O-C-H 104-110°.

3.2. Molecular reactivity analyzes

The DFT method offers important information in investigating the structural properties of the molecule. The position and energy of the HOMO-LUMO orbitals of the molecule are vital in reactivity, and active sites based on electron exchange are involved in reactions. [19]. The HOMO orbitals of the hispidulin molecule are located in the benzene part of the molecule, while the LUMO orbitals are located in the aromatic region of the

Table 1. The theoretically obtained some parameters and values of hispidulin molecule.

	Bond Lengths (Å)			Bond Angles (°)	
Atom Groups	**B3PW91**	**B3LYP**	**Atom Groups**	**B3PW91**	**B3LYP**
C1-C2	1.40	1.39	C1-C2-C3	119.96	120.17
C1-C6	1.41	1.39	C1-C2-O13	117.54	117.58
C1-O11	1.40	1.40	C1-C6-C5	121.32	121.46
C2-C3	1.39	1.40	C2-C3-C4	118.85	119.35
C2-O13	1.38	1.39	C2-C1-C6	120.17	119.70
C3-C4	1.39	1.38	C2-C3-H23	121.95	121.58
C3-H23	1.08	1.08	C2-O13-H28	112.13	111.89
C4-C5	1.41	1.41	C3-C2-O13	122.48	122.23
C4-O7	1.39	1.38	C4-C5-C6	116.12	117.15
C5-C6	1.41	1.40	C4-C3-H23	119.18	119.06
C5-C10	1.48	1.44	O7-C8-C9	120.11	117.97
C6-O14	1.36	1.37	O7-C8-C16	112.20	113.57
O7-C8	1.39	1.41	C8-C9-C10	123.77	122.38
C8-C9	1.36	1.39	C8-C9-H24	120.69	119.13
C8-C16	1.47	1.43	O11-C12-H25	105.24	104.93
C9-C10	1.46	1.38	O11-C12-H26	110.35	110.20
O11-C12	1.46	1.47	C16-C21-H33	120.44	120.31
C12-H25	1.09	1.08	C17-C18-C19	119.68	120.18
C12-H26	1.09	1.09	C17-C18-H31	121.42	121.20
C12-H27	1.09	1.08	C18-C19-O22	116.98	117.11
O13-H28	0.97	0.97	C19-C20-C21	119.71	120.15
O14-H29	0.98	0.97	C19-C18-H31	118.88	118.61
C16-C17	1.41	1.42	C19-O22-H34	112.59	111.85
C16-C21	1.41	1.42	C19-C20-H32	120.46	120.16
C18-C19	1.40	1.39	C20-C21-H33	118.51	118.45
C18-H31	1.08	1.08	C20-C19-O22	122.88	122.96
C19-C20	1.40	1.39	C21-C20-H32	119.82	119.68
	Dihedral Angles (°)			**Dihedral Angles (°)**	
Atom Groups	**B3PW91**	**B3LYP**	**Atom Groups**	**B3PW91**	**B3LYP**
C1-C2-C3-C4	1.29	1.47	C5-C6-O14-H29	-176.58	-175.67
C1-C2-O13-H28	-176.05	-177.53	C18-C19-C20-C21	-0.005	0.01
C3-C4-O7-C8	-179.40	-179.66	H30-C17-C18-H31	0.01	0.005
O7-C8-C9-H24	-179.80	179.85	H32-C20-C21-H33	-0.05	0.01
C1-O11-C12-H27	65.25	100.68	C18-C19-O22-H34	-179.92	-179.90

Table 2. Calculated global chemical reactivity parameters of hispidulin molecule.

	E_{HOMO}	E_{LUMO}	ΔE	I	A	η	s	μ	χ	ω
B3PW91	-6.1956	-1.9717	4.2239	6.1956	1.9717	2.1119	1.0559	-4.0836	4.0836	3.9480
B3LYP	-5.8911	-2.2610	3.6301	5.8911	2.2610	1.8150	0.9075	-4.0760	4.0760	4.5767

*IP: Ionization Potential ($-E_{HOMO}$); EA: Electron Affinity ($-E_{LUMO}$); ΔE: Energy Gap, χ: Electronegativity;
η: Chemical Softness; δ: Chemical Hardness; ω: Electrophilicity Index

Table 3. For the hispidulin compound; calculated dipole moments (μ), polarizability (α) and initial hyperpolarizability (β) components.

Parameter	**B3PW91**	**B3LYP**	**Parameter**	**B3PW91**	**B3LYP**
μ_x	-1.7021	-2.3754	β_{XXX}	-32.9209	-38.1515
μ_y	-5.2213	-5.3701	β_{XXY}	86.6308	85.7021
μ_z	1.1592	1.1692	β_{XYY}	-2.1561	-0.7157
$\mu_{(D)}$	5.6128	5.9873	β_{YYY}	-126.3533	-121.5803
α_{xx}	-88.7194	-88.9430	β_{XXZ}	47.0164	46.6971
α_{yy}	-129.3166	-131.6313	β_{XYZ}	-5.7841	-5.9735
α_{zz}	-130.1194	-130.6571	β_{YYZ}	-4.5679	-3.6232
α_{XY}	-25.9039	-25.2835	β_{XZZ}	24.5948	22.8018
α_{XZ}	7.1129	6.4845	β_{YZZ}	0.8623	0.7933
α_{YZ}	0.0039	0.1898	β_{ZZZ}	1.0215	0.3141
α (au)	-116.0518	-117.0771	β (esu)	$5.9x10^{-31}$	$5.8x10^{-31}$

molecule. These results mean that molecules perform electron acceptor through aromatic, while electron donor via benzene. The localized state of the HOMO-LUMO energies for the hispidulin molecule is given in Figure 2. The HOMO and LUMO values of hispidulin obtained using DFT / TD-DFT methods are -6.1956 - -1.9717 eV and -5.8911 - -2.2610 eV, respectively. HOMO-LUMO orbitals play an important role in the chemical behavior and reactivity of the molecule.

Global reactivity descriptors are criteria used in the reactivity of the molecule, including many parameters

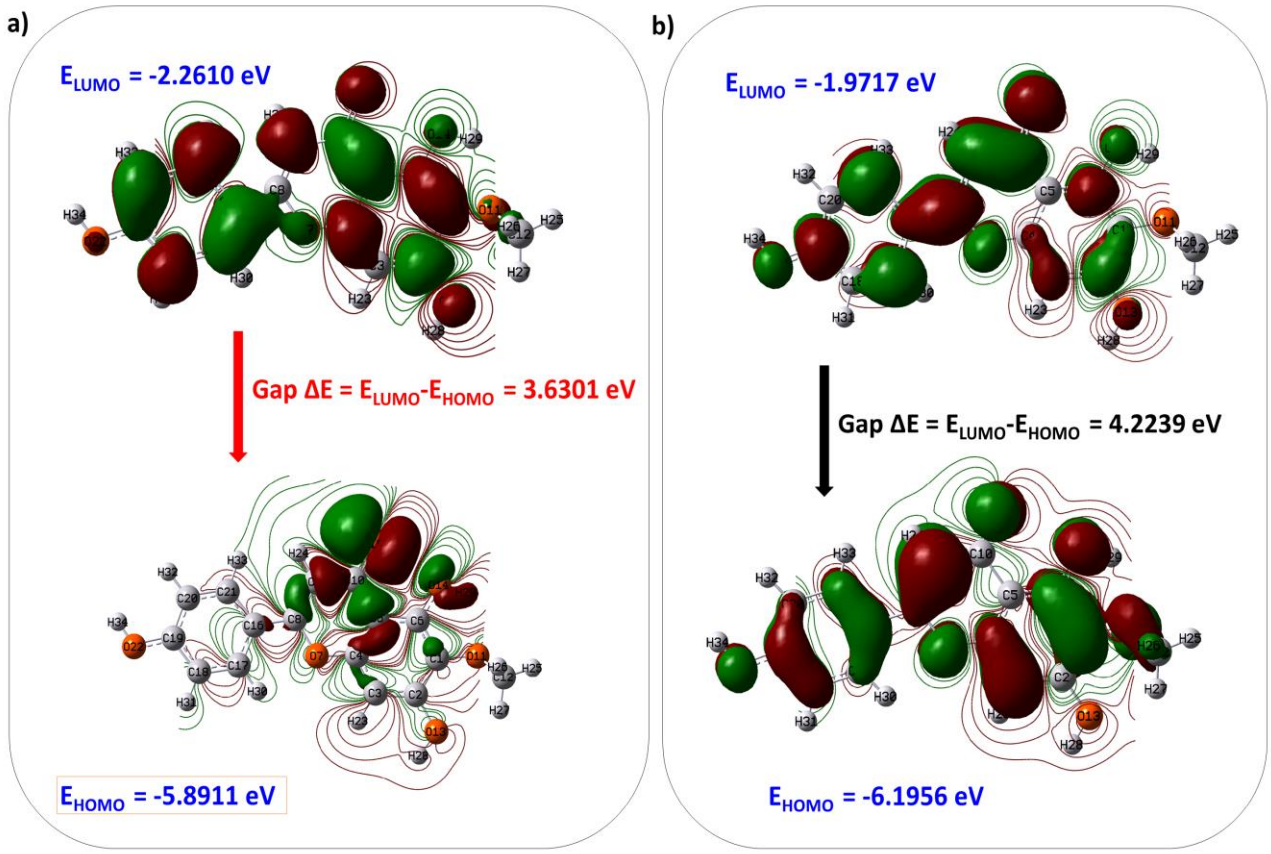

Figure 2. HOMO-LUMO energy diagrams of Hispidulin

such as IP, ΔE and χ. Chemical reactivity indices are given in Table 2.

The dipole moment, an important property of the molecule, is the energy between structural strength and chemical reactivity [20].

The dipole moment, polarizability (α) and first hyperpolarizability (β) calculations of the hispidulin molecule are given in Table 3.

3.3. Molecular electrostatic potential surface (MEPS)

MEPS is a powerful tool that provides information about a molecule's electrostatic potential, electronegativity, and partial charges on different atoms. The MEPS map shows many reactive regions of the compound, such as shape, size, and identifies these areas with color codes [18]. The surface map is defined by colors ranging from red to blue, that is, from electron-rich to lesser regions [21].

In the MEPS map of Hispidulin, the red colored parts are concentrated around the negative electrostatic potential regions of the oxygen atoms, while the blue colored parts are concentrated around the positive electrostatic potential regions of the carbon and hydrogen atoms (Figure 3).

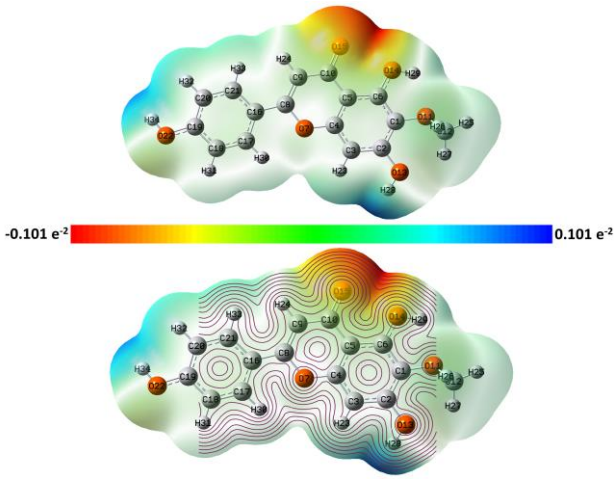

Figure 3. MEPS mappings for hispidulin

3.4. Mulliken atomik charges

Mulliken atomic charges depend on the electronic charge on the atoms forming the bonding ability of a molecule and play an important role in characterizing the electronic charge distribution in the molecule [22]. Mulliken atoms of hispidulin have been calculated using LANL2DZ (d, p) and 6-311G (d, p) basis sets. The charge distribution of carbon and oxygen atoms in the hispidulin molecule calculated by the DFT / TD-DFT method is directly observed in Figure 4 with the color of the spheres. (color index and range given),

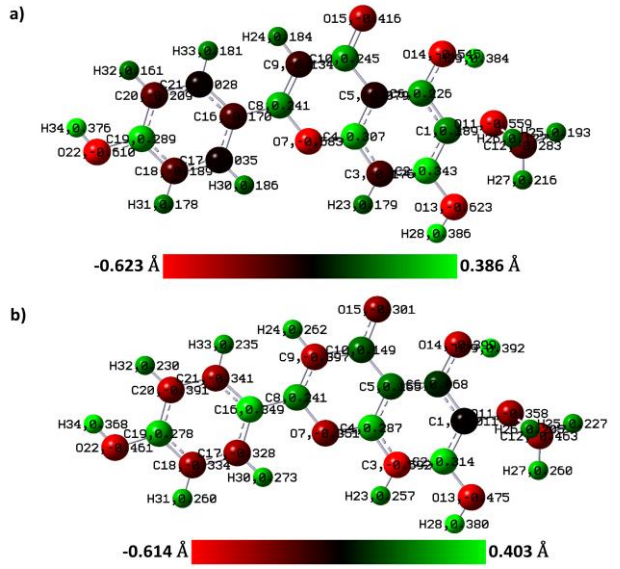

Figure 4. The Mulliken atomic charges in DFT/TD-DFT optimized geometry of hispidulin.

3.5. Molecular docking studies

Molecular docking is essential to investigate the ligand-receptor interaction mechanism and to understand their binding states. [23]. The enzyme structure was added with codes from the Research Collaboratory for Structural Bioinformatics (RCSB) protein database (PDB). (http // www.rcsb.org/pdb). [24] While dementia is currently diagnosed in more than 50 million people worldwide, it is estimated to increase to over 150 million by 2050 [25].

Post-mortem analyzes of AD patient brains revealed that amyloidogenic plaques are composed of N-terminal modified Aβ peptides that are highly inhibited due to cyclization of glutamate residues that make up each part of a pyroglutamic acid. [25].

They are amyloid-β (Aβ) peptides and are insoluble. In the hypothesis, elevated Aβ production and reduced clearance are a molecular problem and cause AD. There is proteolytic cleavage within the endosome mediated by the β-domain of amyloid precursor protein (APP), β-Secretase 1 (BACE-1). Characterization in in vitro studies expressed the enzyme BACE-1, which is the rate limiter for the production of Aβ peptides and a good choice for inhibition of AD [26].

The formation of pyroglutamic acid (pGlu) of Aβ peptides is catalyzed enzymatically (in the pathophysiological side reaction of monoZn(II). According to the literature, gastrin or orexin in the secretory pathway is part of hormone maturation, namely glutaminyl cyclase (QC), the neurotensin enzyme that is physiologically amenable to peptides. It is speculated that overexpression of QC is what causes the increased formation of toxic Aβ peptide species. To reduce cellular toxicity, QC needs to be lowered or inhibited. That is, human QC plays a vital role in the pathogenesis of AD in the early onset steps. Hence, it is presented as a meet the expectation drug candidate in the quest to reduce aging [25].

In fact, molecular docking was applied here to find preferred binding sites of ligands with the receptor. This practice has adequately validated empirical research. The interaction of 3D (Figure 6) and 2D (Figure 5a) is shown as a result of the hispidulin - BACE-1 molecular docking study. The glide score for

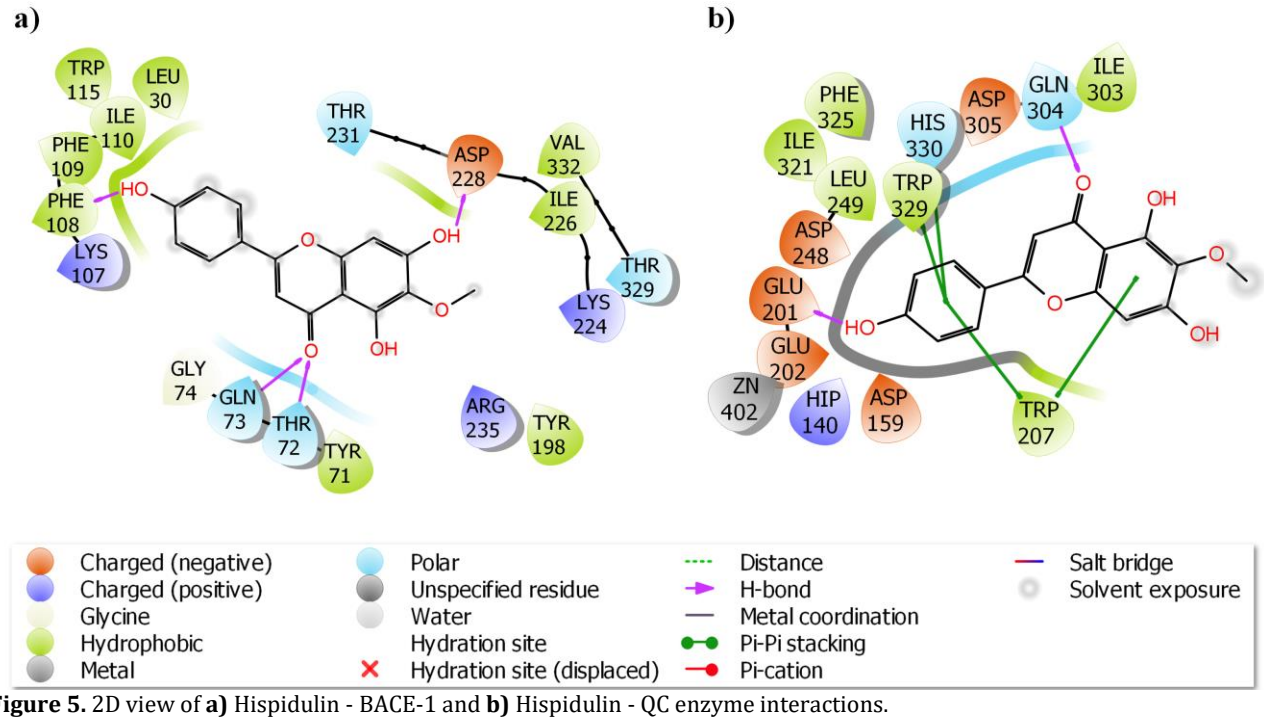

Figure 5. 2D view of **a)** Hispidulin - BACE-1 and **b)** Hispidulin - QC enzyme interactions.

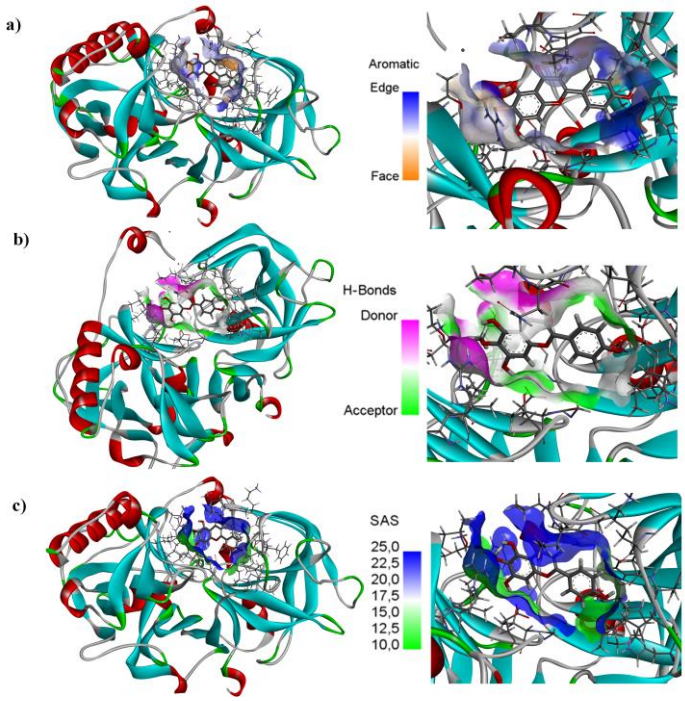

Figure 6. a) 3D view of the aromatic surface on the receptor b) 3D view of hydrogen bond donor/acceptor surface on the receptor and c) 3D view of the SAS surface on the receptor of hispidulin-BACE-1 enzyme interactions.

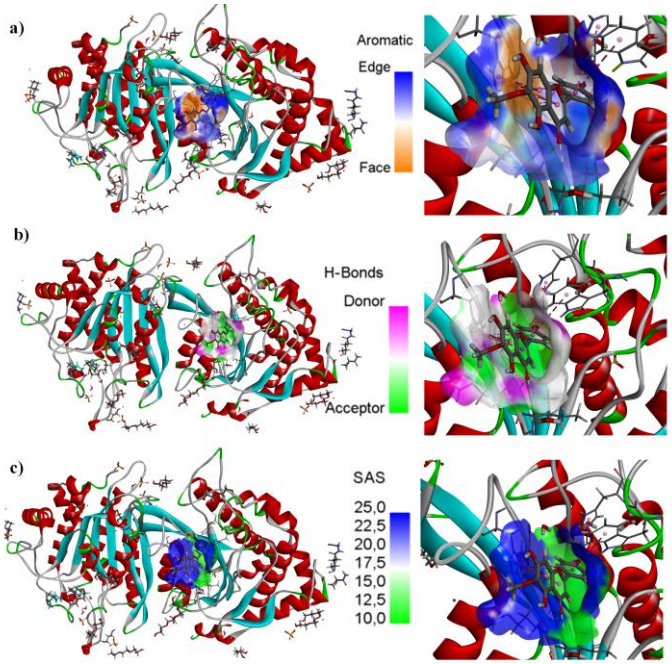

Figure 7. 3D view of a) The aromatic surface on the receptor b) Hydrogen bond donor/acceptor surface on the receptor and c) The SAS surface on the receptor of hispidulin-QC enzyme interactions.

binding affinity with hispidulin - BACE-1 was calculated as -5.318 kcal/mol. Here, considering the bonding mechanism, conventional hydrogen bond ASP A:228 1.90 Å and PHE A:108 1.78 Å in hydrogen bonded to hydroxyl, conventional hydrogen bonds bonded to oxygen ARG A:235 2.91 Å, THR A:72 2.57 Å, GLN A:73 is 2.38 Å.

The interaction of 3D (Figure 7) and 2D (Figure 5b) is presented as a result of the hispidulin-QC molecular docking study. Hispidulin-QC glide score was determined as -9.096 kcal/mol. It is understood from this value that the docking compatibility is high. Here, if we look at the bonding mechanism, Pi-Pi T-shaped TRP A:207 5.07Å, TRP A:329 5.99 Å and HIS A:330 5.19 Å, also Pi-Pi stacked TRP A:207 4.98 Å and Pi-Pi stacked TRP A:207 4.98 Å and It is 5.57 Å. Carbon hydrogen bond bonded to oxygen and hydrogen of hydroxyl is ILE A:303 2.58 Å and GLN A:304 2.57 Å, also concentional hydrogen bond GLN A:304 1.90 Å and GLU A:201 1.69 Å. Finally, the metal-acceptor ZN A:402 attached to the hydrogen of the hydroxyl is 2.09 Å.

4. Discussion and Conclusion

With this study, it is aimed to discover new drug active ingredient candidate compounds for the fight against AD or to reveal the necessary studies to reach precursor compounds. DFT and TD-DFT quantum calculations (energy properties, dipole moment calculations, MEPS maps and Mulliken atomic charges) of the molecule whose geometry is minimized in the gas phase have been made. As a result of this study, which included one compound and 2 sets of enzymes, good placement results were achieved. Ligands were placed in the catalytic active site of the enzymes analyzed according to their binding affinity and docking results in the interaction mode. At the molecular level, the best interaction in the ligand-protein structure and docking affinity score was observed in the QC enzyme. According to all these results, it may be promising as well as making an important contribution to new studies..

Declaration of Ethical Code

In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

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