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Quantum Chemical Calculation And Molecular Docking Studies Of Coumarin Based Curcumins As α-Glucosidase Inhibitors

Kumarin Bazlı Kurkuminlerin α-Glukozidaz İnhibitörleri Olarak Kuantum Kimyasal Hesaplamaları ve Moleküler Yerleştirme Çalışmaları

Semiha Köprü[1,2]*

[1*]Department of Chemistry, Faculty of Sciences, Erciyes University, 38039, Kayseri, Türkiye, semihaaydin@erciyes.edu.tr, https://orcid.org/ 0000-0002-2269-6980

[2] Technology Research and Application Center, Erciyes University, 38039, Kayseri, Türkiye

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Yapay Zeka Etik Beyanı: Yazar bu makalenin hazırlanma sürecinin hiç bir aşamasında yapay zekadan faydalanılmadığını; bu konuda tüm sorumluluğun kendisine(kendilerine) ait olduğunu beyan etmektedir.

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Quantum Chemical Calculation and Molecular Docking Studies of Coumarin Based Curcumins as α-Glucosidase Inhibitors

ABSTRACT

This study aimed to investigate the physicochemical, structural, and electronic properties, and in silico assessment of molecular docking studies of six coumarin-based ethylcurcumin derivatives (C1-C6) as α-glucosidase inhibitors. The ground state geometries and chemical reactivity parameters of the compounds were calculated using the Lee–Yang–Parr, B3LYP hybrid functional with 6-311^{++}G(2d, 2p) basis set through Density Functional Theory (DFT) approach using the Gaussian 09 W. In addition, HOMO-LUMO energy levels and molecular electrostatic potential (MEP) analysis were performed to identify electrophilic and nucleophilic reactive sites. The ADMET (absorption, distribution, metabolism, elimination, and toxicity) profiles and pharmacokinetic parameters of all compounds were predicted through in silico calculations using the SwissADME and Pro Tox-3.0 web servers. Molecular docking analysis was performed for all compounds against the target protein (PDB ID: 3A4A) using AutoDock Vina (version 1.5.7). The docking results revealed that all compounds (**C1-C6)** exhibited strong interactions with the 3A4A receptor. Computational studies showed that compound C5 had the highest binding energy (-9.9 kcal/mol) in the molecular docking. Curcumin compounds, identified as having potential antidiabetic properties, exhibited higher binding energies against the 3A4A receptor than the reference compound acarbose, based on molecular docking analysis. The antidiabetic effects of curcumin-derived compounds are promising for future drug candidate molecules.

Keywords- Curcumin, Density Functional Theory, α-glucosidase, Molecular Docking.

Highlights

- Quantum chemical calculations of coumarin-based curcumin derivatives were performed using the Density Functional Theory (DFT) method.
- In silico ADMET (absorption, distribution, metabolism, elimination, and toxicity) profiles were determined.
- Molecular docking studies were conducted towards the PDB ID:3A4A protein.
- Curcumin-based compounds have been identified as anti-diabetic agents.

Kumarin Bazlı Kurkuminlerin α-Glukozidaz İnhibitörleri Olarak Kuantum Kimyasal Hesaplamaları ve Moleküler Yerleştirme Çalışmaları

ÖZ

Bu çalışmada altı kumarin bazlı etil kurkumin türevlerinin (C1-C6) fizikokimyasal, yapısal ve elektronik özelliklerinin araştırılması ve in silico moleküler yerleştirme çalışmalarıyla α-glukozidaz inhibitörü olarak değerlendirilmesi amaçlanmıştır. Bileşiklerin temel durum geometrileri ve kimyasal reaktivite parametreleri, Gaussian 09 W'da, Yoğunluk Fonksiyonel Teorisi (DFT) yaklaşımı kullanılarak, standart baz seti 6-311^{++}G(2d,2p) sahip B3LYP hibrit fonksiyoneli kullanılarak hesaplanmıştır. Buna ek olarak, elektrofilik ve nükleofilik reaktif bölgeleri belirlemek için HOMO-LUMO enerji seviyeleri ve moleküler elektrostatik potansiyel (MEP) analizi gerçekleştirilmiştir. ADMET (emilim, dağıtım, metabolizma, eliminasyon ve toksisite) profili ve farmakokinetik parametreler, SwissADME ve ProTox-3.0 web sunucusu kullanılarak tüm bileşikler için tahmin edilmiştir. AutoDock Vina 1.5.7 kullanılarak, tüm bileşikler için PDB ID: 3A4A'ya karşı moleküler yerleştirme analizi gerçekleştirilmiştir. Yapılan moleküler yerleştirme çalışmaları sonucunda, C1-C6 bileşikleri 3A4A reseptörü ile güçlü etkileşimler ortaya koymuştur. Hesaplamalı çalışmalar, C5 bileşiğinin moleküler yerleştirmede en yüksek bağlanma enerjisine (-9,9 kcal/mol) sahip olduğunu göstermiştir. Potansiyel antidiyabetik özelliklere sahip olduğu tespit edilen kurkumin bileşikleri, moleküler yerleştirme analizine göre 3A4A reseptörüne karşı referans bileşik

akarboza göre daha yüksek bağlanma enerjisi göstermiştir. Kurkumin türevi bileşiklerin antidiyabetik etkileri, gelecekteki ilaç adayı moleküller için umut vericidir.

Anahtar Kelimeler- Kurkumin, Yoğunluk Fonksiyonel Teorisi, α-glukozidaz, Moleküler Yerleştirme

Öne Çıkanlar

- Kumarin bazlı kurkumin türevlerinin kuantum kimyasal hesaplamaları Yoğunluk Fonksiyonel Teorisi (DFT) yöntemi kullanılarak gerçekleştirildi.
- In silico ADMET (emilim, dağılım, metabolizma, eliminasyon ve toksisite) profilleri belirlendi.
- PDB ID:3A4A proteini kullanılarak moleküler yerleştirme çalışmaları yürütüldü.
- Kurkumin bazlı bileşiklerin anti-diyabetik ajanlar olduğu belirlenmiştir.

I. INTRODUCTION

Diabetes results from the abnormal metabolism of carbohydrates, lipids, and proteins in body tissues, resulting from a lack of insulin secretion and insulin resistance. It is classified into two types: Type 1 and Type 2. Type 2 diabetes is a metabolic disorder characterized by impaired pancreatic beta-cell function, peripheral tissue insulin resistance, and increased pancreatic alpha-cell activity [1,2]. It is projected that this number could reach 850 million worldwide by 2050 [3]. The most commonly used treatment for type 2 diabetes is to regulate blood sugar levels by reducing hyperglycemia, which occurs as a result of high blood sugar levels caused by insufficient insulin production [4].

α-Glucosidase and α-amylase, which are effective in controlling the carbohydrate hydrolysis mechanism and regulating postprandial glucose levels, are the main enzymes investigated in diabetes treatment studies. Consequently, inhibiting α-Glucosidase delays glucose production and reduces post-meal blood sugar spikes, helping to control type II diabetes [5]. α-Glucosidase inhibitors, including acarbose, miglitol, and voglibose, are widely used to regulate blood sugar levels in patients with diabetes. Acarbose, the most commonly prescribed agent, also inhibits the action of α-amylase. Because it inhibits salivary and pancreatic α-amylase to a greater extent than α-glucosidase, it may cause side effects such as abdominal pain and bloating. In this context, various α-glucosidase inhibitors are being investigated for their potential to regulate type 2 diabetes [6]. In the drug discovery process, structural modifications have enhanced the therapeutic potential and played an important role in treating or preventing diseases. Generally, through modern tools of molecular biochemistry, biology, and chemistry, it has played a significant role in drug discovery and development processes [7]-9]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) is a yellow hydrophobic polyphenol that is one of the main components of the rhizome extract of turmeric. It has an unsaturated diketone moiety, a seven-carbon linker, and two aromatic rings with o-methoxy phenolic groups. The turmeric plant, Curcuma longa, has been widely used in traditional Indian and Chinese medicines. The most abundant naturally occurring extract is curcumin (Fig 1a), followed by demethoxycurcumin (Fig.1b) and bisdemethoxycurcumin, which contains common secondary metabolites (Figure 1.c) [10].

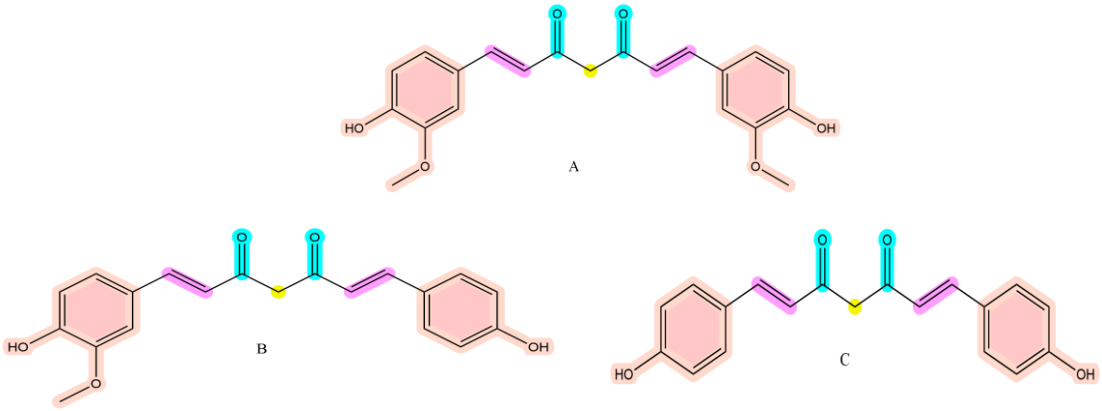


Figure 1. Chemical structure of **a**) curcumin, **b**) demethoxycurcumin, **c**) bisdemethoxycurcumin

Despite low bioavailability and poor aqueous solubility, various curcumin analogues have been synthesized to achieve biologically active levels in animals and humans. Recent studies have revealed various compounds and techniques aimed at increasing the bioavailability of curcumin. In addition to its biological and pharmacological properties, such as anti-inflammatory [11], antibacterial [12], antioxidant [13], anticancer [14], antiarthritic, anti-Alzheimer's [15], antimicrobial, and antimalarial [16] activities.

Curcumin hybrids are important lead molecules in medicinal chemistry studies [17,18]. β-unsaturated carbonyl group, methoxy, diketone, and hydroxyl groups are the sources of such activities. (Scheme 1) [19], [20]. Numerous studies have demonstrated that curcumin is safe even at relatively high doses in both humans and animal models, indicating its favorable pharmacological safety profile and potential efficacy in the treatment of various diseases [21]. Curcumin is an ideal therapeutic agent due to its non-toxic structure, but its limited bioavailability may be a concern for clinical applications. In general, curcumin is less soluble in water at both acidic and neutral pH media, while it is soluble in acetone, DMSO, and ethanol. Due to its poor absorption and rapid excretion, it is present in low concentrations in plasma and tissues. Recently, studies have been conducted to increase the bioavailability of curcumin. [10].

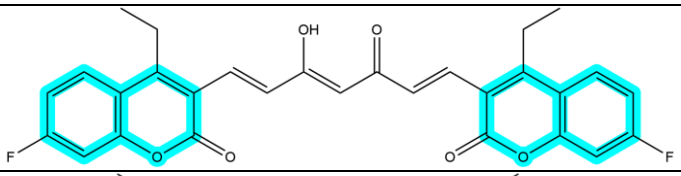
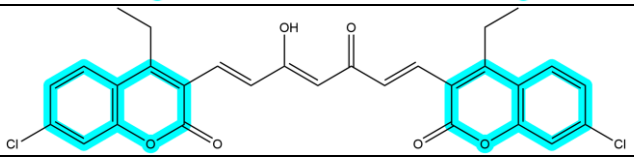
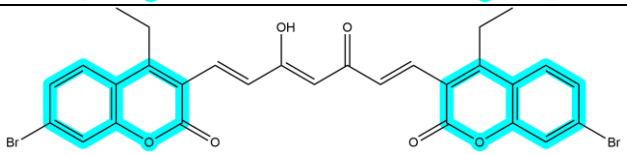
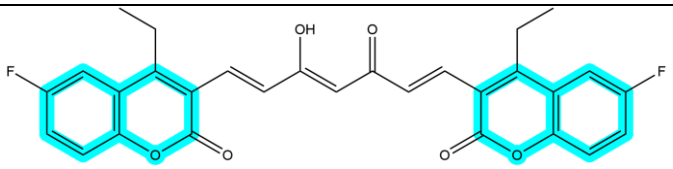
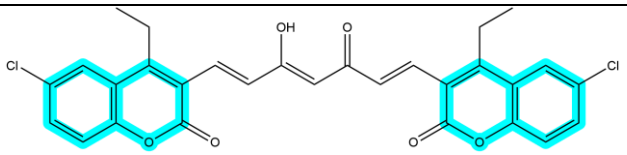
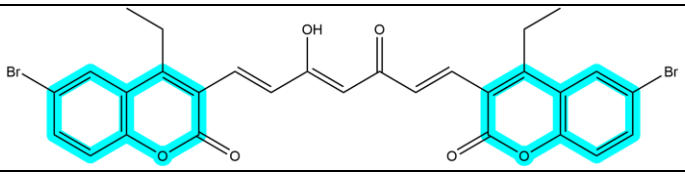
Coumarin, the name comes from the species *Coumarouna odorata Aube* from which it was isolated, is one of the widely used organic compounds known for its diverse pharmacological and biological effects. Coumarin curcumin derivatives, which have pharmacological effects, including anti-inflammatory, anticoagulant, antihypertensive, anticonvulsant, antioxidant, and antimicrobial activities, thereby expanding their therapeutic potential. Additionally, coumarin derivatives regulate signaling pathways that affect various cell processes. Substitutions attached to the coumarin ring have been reported to have therapeutic effects against various types of cancer, including lung, colorectal, liver, and kidney cancer [9].

Six coumarin-based curcumin derivatives **(C1-C6)** synthesized in the literature have been investigated for their antioxidant, antitumor, and antibacterial properties [22]. In this study, druggability and physicochemical properties of these compounds were evaluated using the SwissADME, Pro-Tox 3.0 web tool, and DFT approaches. DFT, ADMET, and Molecular Docking approaches were applied for the first time to coumarin-based curcumin compounds in this work. Molecular docking studies of compounds **C1-C6** with the α-glucosidase enzyme revealed binding energies in the range of -9.5 to -9.9 kcal/mol. The highest binding energy was obtained for compound C5 (-9.9 kcal/mol). The reference compound, acarbose, had a docking score of -9.0 kcal/mol, and coumarin-based curcumin compounds exhibited higher binding energy results.

II. MATERIAL AND METHOD

Theoretical calculations using the DFT method have been conducted at the B3LYP/6-311^{++}G(2d,2p) level to optimise the geometries of curcumin compounds. The representations of the optimized structures, HOMO-LUMO, and MEP plots were drawn with the GaussView 6.0 program and optimized by the Gaussian 09 W program [23], [24]. The SwissADME web tool (http://www.swissadme.ch) and Pro-Tox 3.0 programs were employed to evaluate pharmacokinetic properties and drug-likeness. Parameters such as bioavailability and bioavailability radar play a significant role in assessing the suitability of compounds as drug candidates from a pharmacological perspective. [25]. ChemDraw Ultra 16.0 was used to draw the 2D structure of all coumarin-based curcumin derivatives (Table 1).

Table 1. Chemical structure of coumarin-based curcumin (**C1-C6**) analogues

Cmpnd	Structure
C1	
C2	
C3	
C4	
C5	
C6	

III. RESULTS AND DISCUSSION

A. Molecular Docking

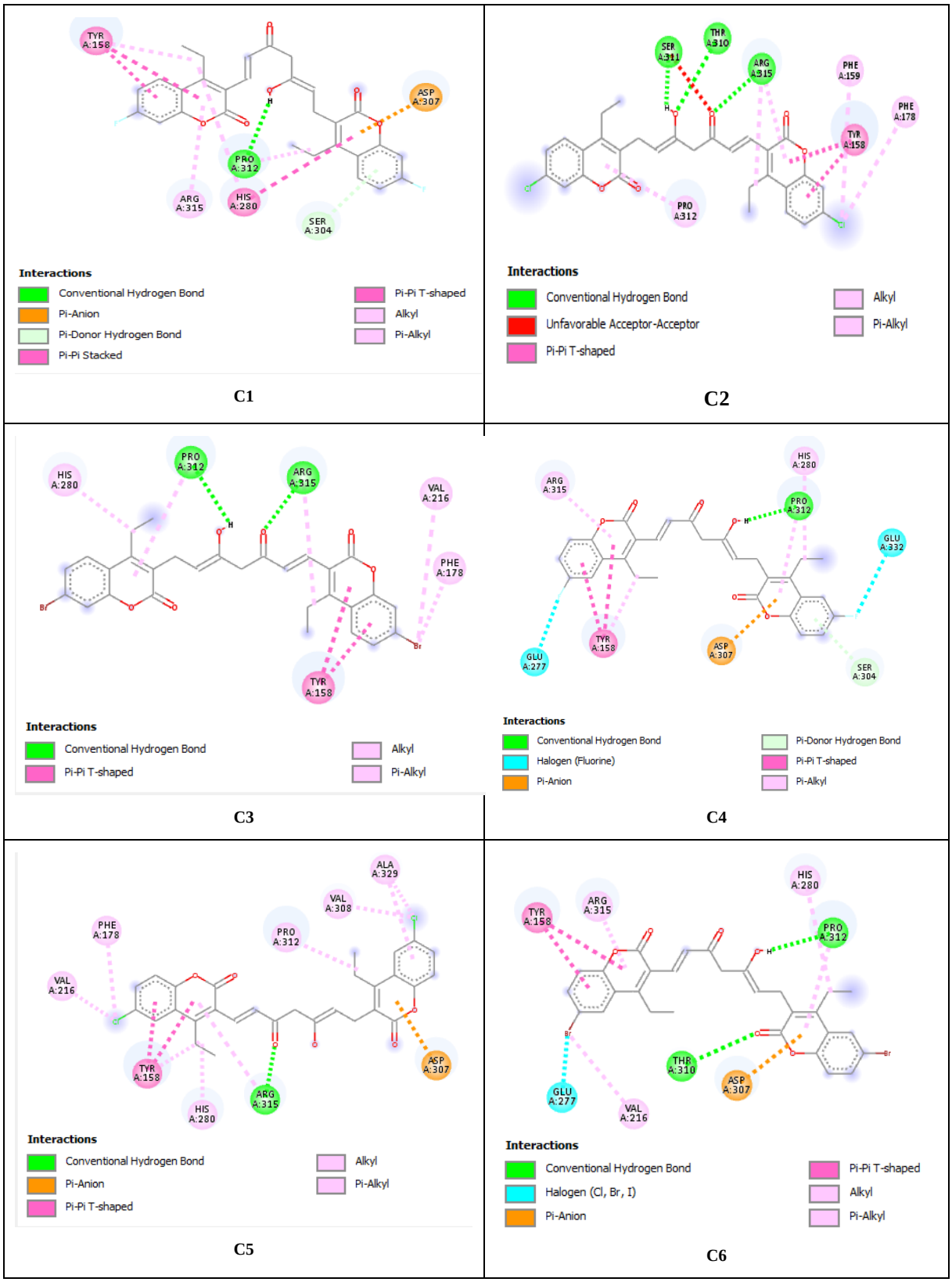
In the early stages of drug discovery, molecular docking enables the rapid and efficient identification of promising drug candidates, thereby significantly accelerating the overall process. This approach has contributed to reducing drug development timelines. When combined with ADME and toxicity prediction results, molecular docking improves lead optimization and drug safety [26]. The Docking scores of ligand compounds (C1-C6 and acarbose) towards PDB ID: 3A4A, Rmsd values, and hydrogen bond distances (Å) are given in Table 2. The 3D structure of the α-glucosidase enzyme was obtained from the RCSB Protein Data Bank for this study (http://www.rcsb.org/pdb). AutoDock Tools 1.5.7 was used to prepare the 3D structures of the target protein (PDB ID: 3A4A). The protein file was uploaded into. pdbqt format, and the binding pose reporting the best binding energy was selected as the ligand. Subsequently, 3D interactions were recorded, followed by 2D visualization of amino acid interactions, including hydrogen bonds and hydrophobic interactions, intermolecular distances, and the interacting amino acid residues. Biovia Discovery Studio 2021 was used to visualize molecular interactions. ChemDraw 16.0 was employed to generate the chemical structures of the ligands. The energy minima of the ligand molecules were recorded, and docking was performed with AutoDock Vina 1.5.7. The center of the binding site was defined using Cartesian coordinates (x = 21.273, y = −0.744, and z = 18.636). Binding and interaction types were obtained from docking analyses. 2D ligand interactions of compounds (C1-C6) toward PDB ID: 3A4A are presented in table 3. Molecular docking studies of compounds **C1-C6** using the α-glucosidase enzyme revealed values in the range of -9.5 to -9.9 kcal/mol. The highest binding energy was obtained for compound C5 (-9.9 kcal/mol). The reference compound, acarbose, had a docking score of -9.0 kcal/mol, and coumarin-based curcumin

compounds exhibited higher binding energy results. The results suggest that coumarin-containing curcumin derivatives hold promise as potential anti-diabetes drug candidates. PRO A:312 residue, showed conventional hydrogen bond (CHB) interaction with the coumarin ring in C1, C3, C4, and C6 compounds and with the -OH group at the centre of the curcumin compound. There is a conventional hydrogen bond interaction with the ARG A:315 residue and the carbonyl group at the center of the curcumin compound in the C2, C3, and C5 compounds. All compounds with TYR A:158 residue are in a hydrophobic Pi-Pi T shape interaction with the coumarin ring. Halogen interactions with -F, Cl, and Br atoms were observed with the GLU A:277 residue. Electrostatic Pi-Anion interactions were observed between the ASP A:307 residue and the coumarin ring. HIS A:280 residue is in a hydrophobic alkyl, Pi-alkyl interaction with the coumarin ring ethyl group.

Table 2. Docking Scores (kcal/mol), Rmsd values, and hydrogen bond distance (Å) of C1-C6 compounds toward PDB ID: **3A4A**

Cmpnd	Docking Score (kcal/mol)	Rmsd	HydrogenBond Distance (Å)	Interactions with amino acids
C1	-9.5	1.291	2.158	***Conventional Hydrogen Bond (CHB)*:** PRO A:312. ***Hydrophobic:*** TYR A:158, ARG A:315, HIS A:280, SER A:304, ASP A:307
C2	-9.6	1.233	2.811, 2.577, 2.035	***CHB*:** SER A: 311, THR A:310, ARG A:315.***Hydrophobic:*** PHE A:159, PHE A:178**,** TYR A:158, PRO A:312
C3	-9.8	1.531	2.348, 2.597	***CHB*:** PRO A:312, ARG A:315 ***Hydrophobic:*** TYR A:158, HIS A:280, PHE A:178, VAL A:216.
C4	-9.8	1.383	2.391	***CHB*:** PRO A:312 ***Pi-Donor Hydrogen Bond:*** SER A:304. ***Hydrophobic:*** HIS A:280, TYR A:158, ARG A:315. ***Halogen (Fluorine):*** GLU A:277, GLU A:332.
C5	-9.9	1.130	2.390	***CHB*:** ARG A:315. ***Hydrophobic:*** PHE A:178, VAL A:216, TYR A:158, HIS A:280, ALA A:329, VAL A:308, PRO A:312. ***Electrostatic:*** ASP A:307
C6	-9.5	1.526	3.377, 2.674	***CHB*:** PRO A:312, THR A:310. ***Hydrophobic:*** HIS A:280, VAL A:216, TYR A:158, ARG A:315, ***Halogen:*** GLU A:277, ***Electrostatic:*** ASP A:307
Acarbose	-9.0	1.343	3.313, 2.894, 3.154	***CHB*:** THR A:310, HIS A:280, GLN A:279, ***Hydrophobic:*** PHE A:303, ***Electrostatic:*** ASP A:307

Table 3. 2D ligand interactions of compounds (C1-C6) toward PDB ID: **3A4A**



B. Computational Details

The aim of drug development is to determine a chemical molecule that can fit into a specific cavity, both geometrically and chemically, of the target protein. Computational approaches serve as powerful tools in the drug development process, facilitating molecular design, screening, comparison, modeling, binding energy estimation, pharmacokinetic prediction, and optimization [27]. The calculated electronic parameters of coumarin-based curcumin analogues (C1-C6) are presented at the B3LYP/6-311G^{++} (2d,2p) level in Table 4. The highest occupied molecular orbital (HOMO) represents the electron-donating ability, whereas the lowest unoccupied molecular orbital (LUMO) indicates the electron-accepting capacity [28]. These frontier molecular orbitals are essential for understanding the chemical stability and reactivity of organic compounds. The HOMO-LUMO and $\mathbf{\Delta E_{Gap}}$ diagrams of the C1-C6 compounds were presented in Figure 2. The energy difference (ΔEg) is an indicator of molecular stability. A larger HOMO-LUMO energy difference corresponds to greater chemical hardness and lower reactivity due to reduced electron mobility. Conversely, systems with lower energy gaps are more reactive, as fewer electrons are required for electronic transitions to occur. The energy difference value for C1 is the highest, 3.0612, and the lowest value is 3.0178 for the C3 compound. In this case, the C3 compound shows high reactivity. Energy gap (ΔE_{gap}) values greater than 1.5 eV indicate that the molecules are thermodynamically steady and resistant [29]. According to the calculation results, it was concluded that the energy difference of curcumin derivatives was in the range of 3.0178-3.0612. The small value of the energy difference in the molecule indicates that the electron distribution can be easily directed, resulting in large polarization. As seen in Table 4, the polarizability value is the highest for the C3 molecule with the smallest HOMO-LUMO difference value compared to other molecules. Electronegativity is the power of an atom in a molecule to attract electrons. Since the electrophilicity of the C6 molecule is greater than that of the other molecules, C6 is the most electrophilic [30]. Accordingly, the softest and most reactive compound is seen as the C3 compound in Table 4. By using molecular electrostatic potential maps, important information is obtained about the regions in the molecule where electrophilic and nucleophilic reactions can occur, and the formation of intramolecular hydrogen bonds. MEP maps of coumarin-based ethyl curcumin compounds are presented in Table 5. The electrostatic potential increases in the order of red, orange, yellow, green, and blue, respectively. The highest electron density (negative potential) is shown in the red region, while the most positive potential (partially positively charged region) is shown in blue. Yellow represents regions with fewer electrons than other regions, and green represents neutral regions with zero potential. Positive regions indicate nucleophilic reactivity, while negative regions indicate electrophilic reactivity. MEP maps provide important clues in determining active regions in the chemical synthesis of the molecule [31]. As shown in Table 5, the highest nucleophilic potential is observed in the blue region, aliphatic ethyl group and aromatic ring hydrogen atoms, while the highest electrophilic potential is found in the red region, hydroxyl groups and oxygen atoms.

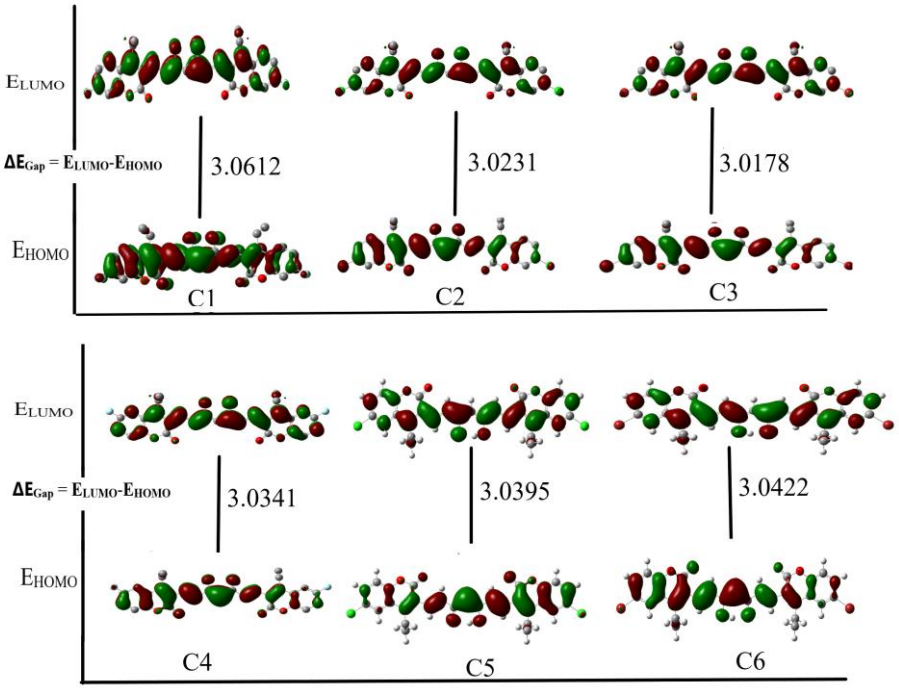
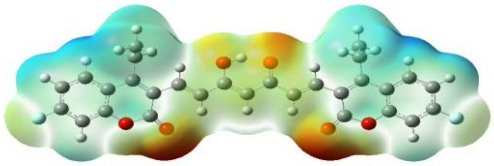
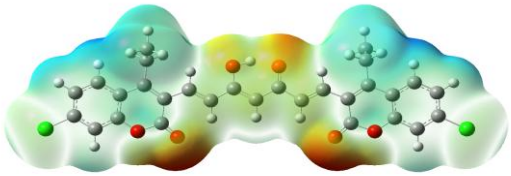
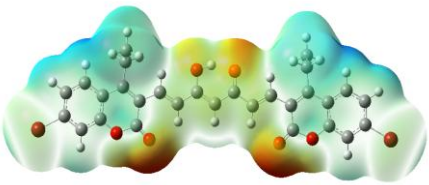
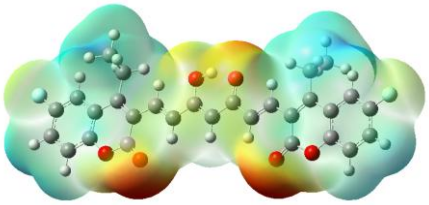
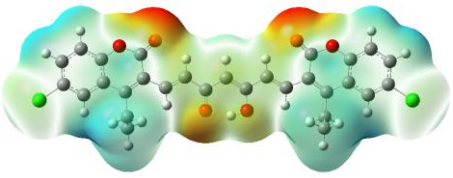
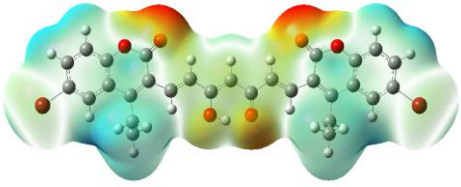


Figure 2. HOMO-LUMO energy levels and ΔE_{Gap} (E_{LUMO}-E_{HOMO}) graph of the C1-C6 compounds at the B3LYP/6-311++G (2d,2p) level https://gaussian.com/gaussview6/

Table 4. Electronic parameters of the coumarin-based curcumins (C1-C6) with B3LYP/6-311G^{++} (2d, 2p) level

	C1	C2	C3	C4	C5	C6
I=-E_{HOMO} (eV)	6.1470	6.1851	6.1906	6.2260	6.2532	6.2586
A=-E_{LUMO} (eV)	3.0858	3.1620	3.1728	3.1919	3.2137	3.2164
Energy gap (ΔE_{Gap}=I-A) (eV)	3.0612	3.0231	3.0178	3.0341	3.0395	3.0422
Polarizability (α) (a.u.)	532.846	586.104	612.101	531.332	572.181	594.757
Dipol Moment (Debye)	6.508	6.496	6.459	3.367	3.316	3.328
Chemical potential (μ) (eV)=$-\frac{I+A}{2}$	-4.6164	-4.6735	-4.6817	-4.7089	-4.7334	-4.7375
Hardness (η) (eV)=$\frac{I-A}{2}$	1.5306	1.5115	1.5089	1.5170	1.5197	1.5211
Softness (σ) (eV)=$\frac{1}{2\eta}$	0.3267	0.3308	0.3313	0.3296	0.3290	0.3287
Electronegativity (χ) (eV)=$\frac{I+A}{2}$	4.6164	4.6735	4.6817	4.7089	4.7334	4.7375

Table 5. MEP maps of coumarin-based ethyl curcumin compounds (**C1-C6)**

 **C1**	 **C2**
 **C3**	 **C4**
 **C5**	 **C6**

C. In silico ADME screening, Druglikeness Properties and Toxicity Evaluation

In the early stages of drug delivery, ADME properties for drug candidates before synthesis guide the selection of potential candidates. Concurrently, ADME parameters were evaluated through the online server available at (http://www.swissadme.ch), and toxicity parameters were assessed using the online web server Pro-Tox 3.0 at (https://tox.charite.de/protox3).

The estimated ADME properties and drug-likeness profiles for coumarin-based ethyl curcumins are presented in Table 6. The iLOGP values, which indicate lipophilicity, were found to range from 3.99 to 4.47. The Log S (ESOL) was in the range of -6.46 to -7.96, and all compounds were found to be in the low level group in terms of water solubility. Lipinski's 5 criteria must be met: molecular weight < 500 Da, log P < 5, HBD < 5, HBA < 10, and TPSA (topological polar surface area) is greater than 20 $Å^2$ and less than 130 $Å^2$ [32],[33]. The TPSA values of the C1-C6 compounds (97.2 $Å^2$) fall within the acceptable range. According to these results, all compounds presented in Table 6 were determined to satisfy all criteria except the molecular weight rule. The molecular mass of compounds is greater than 500 Da. The number of H-bond donors (HBD) value is 1 for all compounds, remaining below the threshold value of 5. The number of H-bond acceptors (HBA) is between 6 and 8, which is also within acceptable limits. The blood-brain barrier (BBB) is a diffusion barrier necessary for the normal function of the central nervous system (CNS) [34]. The BBB is a complex and dynamic interface between the blood and the central nervous system, and it also plays an important role in transporting nutrients necessary for the normal metabolism of brain cells and preventing many toxic compounds from entering the CNS [35]. None of the compounds synthesized in the study passed through the brain barrier. Therefore, there is no harm to the CNS, and they do not cause CNS depression or drowsiness. Gastrointestinal absorption is low for all compounds. Druglikeness properties and bioavailability scores of curcumin compounds (C1-C6) are shown in Table 7. When the results were examined in Table 7, it was determined that C1 and C4 compounds containing a fluorine atom obeyed the Lipinski and Veber rule but violated the Egan, Muege, and Ghose rule, while compounds C2, C3, C5, and C6 obeyed only the Veber rule. Furthermore, the bioavailability value for all compounds was 0.56. It was concluded that the curcumin derivatives examined exhibited moderate bioavailability and permeability according to Lipinski's rule. ADMET results show that the molecules exhibit drug-like properties. Furthermore, analysis using the Pro-Tox 3.0 web tool found the compounds to pose no toxicological risks.

Table 6. Radar chart, physicochemical, and druggability properties of coumarin-based ethyl curcumin derivatives (**C1-C6**) from the SwissADME database

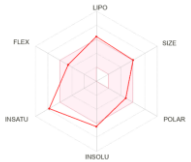
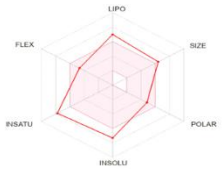
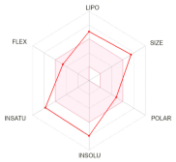
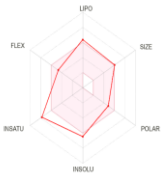
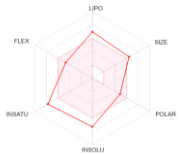
Compound	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**
Formula	$C_{29}H_{22}F_2O_6$	$C_{29}H_{22}Cl_2O_6$	$C_{29}H_{22}Br_2O_6$	$C_{29}H_{22}F_2O_6$	$C_{29}H_{22}Cl_2O_6$	$C_{29}H_{22}Br_2O_6$
Molecular weight (g/mol)	504.48	537.39	626.29	504.48	537.39	626.29
Number heavy atoms	37	37	37	37	37	37
Number arom. heavy atoms	20	20	20	20	20	20
Num. H-bond acceptors	8	6	6	8	6	6
Num. H-bond donors	1	1	1	1	1	1
TPSA (Å²)	97.72	97.72	97.72	97.72	97.72	97.72
Log Po/w (iLOGP)	4.19	4.20	4.47	3.99	4.32	4.13
Log S (ESOL)	-6.46	-7.32	-7.96	-6.46	-7.32	-7.96
GI absorption	Low	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No	No
RADAR						

Table 7. Druglikeness properties and bioavailability scores of curcumin compounds

No	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
C1	Yes	No	Yes	No	No	0.56
C2	No	No	Yes	No	No	0.56
C3	No	No	Yes	No	No	0.56
C4	Yes	No	Yes	No	No	0.56
C5	No	No	Yes	No	No	0.56
C6	No	No	Yes	No	No	0.56

IV. CONCLUSIONS

Curcumin is a polyphenol derived from turmeric and has various anti-inflammatory and anti-cancer properties. In addition to its strong antioxidant capacity at neutral and acidic pH, curcumin has multiple mechanisms of action in the body. In this study, druggability and physicochemical properties of six coumarin-based curcumin derivatives (**C1-C6**) were researched with SwissADME, Pro-Tox 3.0 web tool, and DFT approaches. According to ADMET results, the curcumin compounds exhibit drug-like properties. Finally, it was concluded that the compounds in question do not pose an irritant, tumor-forming, mutagenic, or reproductive risk. Since the compounds studied did not pass the BBB, there is no harm to the CNS, and they do not cause depression or drowsiness. As shown in Table 7, although not all compounds met the Ghose, Egan, and Muegge criteria, only compounds C1 and C4 met the Lipinski rule. Gastrointestinal absorption is low for all compounds. The bioavailability of the compounds is 0.56, indicating moderate bioavailability and permeability according to Lipinski's five rules. Moreover, a molecular docking study showed that all curcumin derivative compounds in the study interacted with α-glucosidase through hydrogen bonds and hydrophobic interactions with key residues in the active site of the enzyme, compared to the standard drug acarbose docking results. Therefore, the results suggest that coumarin-containing curcumin derivatives hold promise as potential anti-diabetes drug candidates.

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