

DFT, Molecular Docking and In-Silico ADME Studies of 2-(2-(4- Chlorophenyl)Benzo[D]-Oxazol-5- Yl)Propanoic Acid Compound

Research Article

10.65520/erciyesfen.1791980

Imprint:


Volume: 42(1)

Year: 2026

Page: 123-140

 Barış Kartal^a

 Mehmet Bağlan^b

 Kenan Gören^{c*}

^a Asst. Prof., Adıyaman University,
baris.j.kartal@gmail.com

^b Dr., Kafkas University,
mehmetbaglan36@gmail.com

^c Dr., Kafkas University,
kenangoren49@gmail.com

* Corresponding Author

Received: 9/26/2025

Accepted: 2/3/2026

Citation:

Barış Kartal, Mehmet Bağlan, Kenan
Gören, (2026). DFT, Molecular
Docking and In-Silico ADME Studies
of 2-(2-(4-Chlorophenyl)Benzo[D]-
Oxazol-5-Yl)Propanoic Acid

Compound. *Erciyes University Journal
of Institute Of Science and Technology*,
42(1), 123-140.

[https://doi.org/10.65520/erciyesfen.
1791980](https://doi.org/10.65520/erciyesfen.1791980)

Screened by

 iThenticate[®]
for Authors & Researchers



Except where otherwise noted, content
in this article is licensed under a
Creative Commons 4.0 International
license. Icons by Font Awesome.

Abstract

As crucial building blocks of several chemical compounds, benzoxazole derivatives are currently garnering increased interest from chemists and biochemists for the creation of novel medications and pharmaceutical research. In this research, density functional theory (DFT) and B3PW91/B3LYP methods with 6-31G(d,p) basis set were used to optimize the molecular electrostatic potential (MEP), molecular orbital (HOMO-LUMO gap, hardness and softness), Nonlinear optical (NLO) and Mulliken charges properties of 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)propanoic acid (BOXP), a benzoxazole derivative. Additionally, the molecule conforms with Lipinski's rule and has promise in terms of bioavailability, according to pharmacokinetic parameters analyzed by ADME (absorption, distribution, metabolism, excretion) analysis utilizing Schrödinger Admetlab 2.0 software. Finally, molecular docking analysis was performed for 2HQ6 (colon cancer) and 4JPS (lung cancer), which are known target enzymes in cancer therapy. In the docking analysis, a score of -9.30 kcal/mol was obtained for the 2HQ6 enzyme code, while a score of -8.60 kcal/mol was obtained for the 4JPS enzyme code. These findings indicate that BOXP is a valuable molecule candidate for pharmaceutical development.

Keywords: DFT, Molecular Docking, ADME, MEP, Benzoxazole



2-(2-(4-Klorofenil)Benzo[D]Oksazol-5- İl)Propanoik Asit Bileşiminin DFT, Moleküler Doking ve İn-Silico ADME Çalışmaları

Öz

Benzoxazole türevleri birçok organik maddenin önemli iskeletleridir ve artık kimyager ve biyokimyacıların yeni ilaçların sentezi ve farmasötik geliştirmeleri için giderek daha fazla ilgisini çekmektedir. Bu araştırmada, Benzoxazole türevi olan 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)propanoic acid (BOXP) bileşiminin optimizasyonu, moleküler orbital (HOMO-LUMO boşluğu, sertlik ve yumuşaklık) ve moleküler elektrostatik potansiyel (MEP), Doğrusal Olmayan optik (NLO) and Mulliken charges özelliklerini açıklamak için B3PW91/B3LYP metotları ve 6-31G(d,p) temel seti ile yoğunluk fonksiyonel teorisi (DFT) kullanılmıştır. Ayrıca, Farmakokinetik özellikler, Schrödinger Admetlab 2.0 yazılımı kullanılarak ADME (absorpsiyon, dağılım, metabolizma, atılım) analizleri ile incelenmiş ve bileşimin Lipinski'nin kuralına uygun olduğu, biyoyararlanım açısından potansiyel taşıdığı gözlemlenmiştir. Son olarak, moleküler doking analizi, kanser tedavisinde hedef enzimler olarak bilinen 2HQ6 (kolon kanseri) ve 4JPS (akciğer kanseri) için gerçekleştirilmiştir. Doking analizinde, 2HQ6 enzim kodu için -9,30 kcal/mol puanı elde edilirken, 4JPS enzim kodu için -8,60 kcal/mol puanı elde edildi. Bu bulgular, BOXP'nin farmasötik geliştirme için değerli bir molekül adayını işaret etmektedir.

Anahtar kelimeler: DFT, Moleküler Doking, ADME, MEP, Benzoksazol



1. Introduction

Cancer remains one of the leading causes of death worldwide despite advances in diagnostic techniques and modern therapeutic strategies [1]. Among cancers, colon and lung cancers are particularly concerning due to their high incidence and mortality rates [2]. Colon cancer is one of the most commonly diagnosed cancers globally, with over one million new cases each year [3]. Its development is influenced by various risk factors such as obesity, high-fat diet, alcohol consumption, chronic inflammation, and genetic predisposition. Lung cancer, in contrast, is strongly associated with smoking; although its incidence has decreased in some developed countries among men due to anti-smoking measures, it continues to pose a significant threat, especially for women [4].

In the search for more effective cancer therapies, scientists focus on the synthesis of new chemical entities (NCEs) and the investigation of their pharmacological properties [5]. Heterocyclic compounds have attracted particular attention in this field due to their structural diversity and biological relevance. Among these, benzoxazole derivatives are especially prominent because of their broad spectrum of biological activities, including antibacterial, anticancer, anti-inflammatory, and antimycobacterial effects [6]. The benzoxazole scaffold is also present in several clinically used drugs (e.g., chloroxazone, flunoxaprofen), demonstrating its potential as a drug-like structure [7]. Importantly, benzoxazole derivatives have shown promising anticancer activity in various studies, suggesting their potential as novel anticancer agents [8]. These properties make benzoxazole-based molecules valuable candidates for further exploration, particularly in the treatment of colon and lung cancers.

Drug discovery processes are often long, expensive, and experimentally demanding. Therefore, computer-aided drug design approaches, including molecular modeling and in silico analyses, are widely used to accelerate development and reduce costs [9]. Density Functional Theory (DFT) and other quantum chemical techniques enable detailed examination of the electronic, chemical, and molecular properties of new compounds, while molecular docking studies help predict their interactions with target proteins [10].

In this study, 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)propanoic acid [11] (BOXP) compound carrying a benzoxazole ring in its structure was investigated theoretically and its chemical properties were optimized using DFT with B3LYP and B3PW91 methods. The pharmacokinetic profile of BOXP was evaluated by ADME analyses and its potential interactions with both colon cancer (PDB: 2HQ6) and lung cancer (PDB: 4JPS) proteins were investigated by molecular docking analyses. By investigating BOXP's possible anticancer properties, this study seeks to aid in the assessment of this novel therapeutic candidate.

2. Material and Methods

In this study, comprehensive analyses of the biological activity of the BOXP molecule were performed using a combination of theoretical calculations and molecular modeling techniques. Using Gaussian 09 software, theoretical computations were performed within the framework of DFT [12], and in these calculations, 6-31G(d,p) basis set and B3LYP, B3PW91 methods were preferred. To reflect a more realistic behavior of molecules in a biological environment, the solvent effect was modeled using the Polarizable Continuum Model (PCM). Water (H₂O) was chosen as the solvent. Tüm geometri optimizasyonları ve frekans hesaplamaları bu ortamda yapılmıştır. This theoretical level was effectively used in obtaining the optimized geometry of the molecule, examining its electronic characteristics and determining its reactivity parameters. The Protein Data Bank (PDB) was used to download the target proteins' three-dimensional structures needed for molecular docking investigations [13] and structural preparations were performed using Schrödinger Maestro software [14]. Docking operations were done to reveal the binding affinity of the BOXP molecule with the active site of the target proteins and the types of interactions. Detailed interaction analyses and visualizations

of the complex structures obtained were performed using the Discovery Studio program [15]. Furthermore, ADME parameters were analyzed to assess the suitability of the BOXP molecule for drug candidacy, and the Admetlab 2.0 online platform [16] was used in these analyses. Thus, predictions were made about the pharmacokinetic properties of the molecule, and its bioavailability potential and possible toxicity profile were evaluated.

3. Results and Discussion

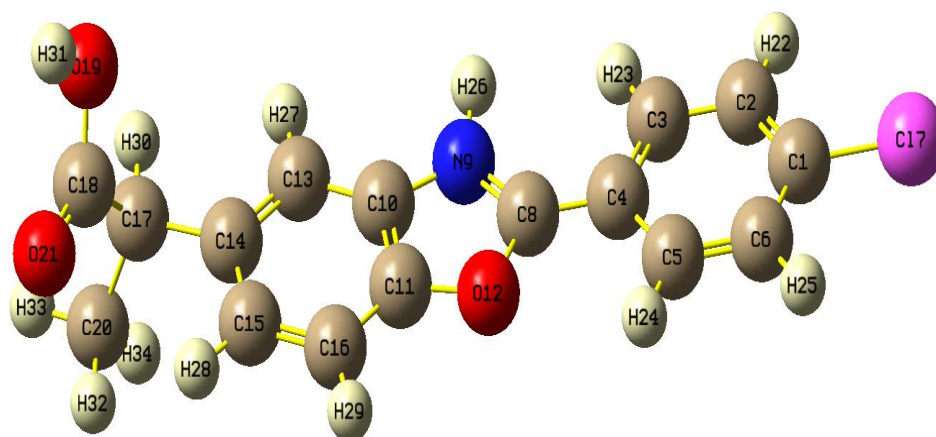
3.1. Structure Details and Analysis

Theoretical investigation of the structural properties of the BOXP molecule provides in-depth information on the chemical stability and potential biological interactions of the compound [17, 18]. In this context, the geometry optimization of the compound was done utilizing two different DFT methods, and the calculated bond lengths and bond angles were compared. Some structural properties (bond angles, bond lengths) of the BOXP compound optimized using two different methods were calculated and the results have been listed in Table 1. Especially the fact that the basic bond lengths such as C1–C2 and C3–H23 have very similar values in both methods (1.398–1.400 Å and 1.086 Å, respectively) reveals the consistency of the computational methods used and the reliability of the optimized structure of the molecule. These small differences depend on the sensitivity of the theoretical models and do not lead to a significant deterioration in the overall geometric structure of the molecule. These obtained parameters show that the BOXP compound has a well-defined and stable molecular skeleton; In addition, this structure suggests that it provides a suitable three-dimensional framework that can establish specific interactions with target biomolecules. Indeed, it is known in the literature that organic molecules with similar structural properties bind with high affinity, especially to enzyme or receptor sites, and exhibit effective biological activities. Therefore, the theoretical structural parameters of the BOXP molecule are significant and remarkable enough to require the evaluation of the compound in terms of pharmacophore properties. The geometric representation of the BOXP compound optimized using the B3LYP approach is displayed in Figure 1.

The theoretical bond lengths and bond angles given in Table 1 show high agreement between the B3PW91 and B3LYP methods, demonstrating the reliability of the optimized structure. In particular, the aromatic C–C bond lengths (1.39–1.43 Å) and bond angles of approximately 120° indicate conserved aromaticity, a critical structural feature in terms of π – π stacking and hydrophobic interactions, which play an important role in ligand-receptor interactions in biological systems. Aromatic rings are widely reported in the literature as fundamental structural units frequently found in pharmacophore models [19]. In addition, the C8–N9 and C8–O12 bond lengths indicate the presence of a conjugated system in the BOXP molecule, and it is understood that the molecule can act as both a hydrogen bond acceptor and donor thanks to the appropriate geometric positions of these heteroatoms. Hydrogen bonding capacity is considered one of the fundamental pharmacophore properties in determining biological activity [20]. Furthermore, the O19–C18–O21 bond angle (122°) and the C18=O bond length indicate that the carbonyl group is favorable for strong hydrogen bonding interactions, increasing the potential for interaction of this functional group with biological targets. The fact that most dihedral angles show values close to planar indicates that prolonged conjugation is maintained throughout the molecule. This planarity contributes to the stabilization of the electronic distribution and more effective molecular recognition processes with biological targets. Considering that biologically active benzoxazole derivatives reported in the literature exhibit similar planarity, aromaticity, and hydrogen bonding properties [21], it can be said that the structural parameters of the BOXP molecule are consistent with known pharmacophore motifs. In conclusion, the geometric data presented in Table 1 not only reveal a theoretically consistent structure but also support the evaluation of the BOXP molecule as a potential pharmacophore when compared with active benzoxazole derivatives reported in the literature.

Table 1. The theoretically calculated bond lengths (Å) and bond angles (o) for the BOXP molecule

Bond Lengths		B3PW91	B3LYP	Bond Lengths		B3PW91	B3LYP
C1-C2		1.398	1.400	C18-O19		1.348	1.353
C4-C5		1.426	1.429	C18-O21		1.210	1.212
C4-C8		1.396	1.398	C8-N9		1.387	1.393
C14-C17		1.524	1.529	C1-C17		1.746	1.759
C17-C20		1.531	1.537	C3-H23		1.086	1.086
C8-O12		1.376	1.382	N9-H26		1.006	1.008
Bond Angles		B3PW91	B3LYP	Bond Angles		B3PW91	B3LYP
C1 -C2-C3		119.990	119.925	C2-C1-C17		119.785	119.721
C5-C4-C8		120.791	120.867	O12-C8-N9		113.772	108.101
C10-C13-C14		117.699	117.805	O19-C18-O21		122.643	122.580
C14-C17-C20		112.421	110.434	C18-O19-H31		106.050	106.160
Planar	Bond	B3PW91	B3LYP	Planar	Bond	B3PW91	B3LYP
Angles				Angles			
C2-C3-C4-C8		178.971	178.864	C13-C14-C17-C20		110.871	110.074
C5-C4-C8-N9		177.574	177.349	O21-C18-C17-H30		151.909	152.463
C3-C2-C1-C17		-179.985	179.995	O12-C8-N9-H26		162.870	159.149
C16-C15-C14-C17		178.676	178.638	C2-C1-C6-H25		179.685	179.683

**Figure 1.** Optimized molecular geometry of the BOXP compound at the B3LYP level

3.1. Mulliken Atomic Charge

One of the first and most often used population analysis techniques for figuring out the electron density between atoms in molecular systems is the Mulliken charge distribution [22]. The main reason for the wide use of this method is that it is integrated by default in many quantum chemistry software and its high applicability. Mulliken analysis relies on the equal distribution of electron densities among the atoms in the areas where two orbitals overlap and the idea that molecule orbitals are created by a linear combination of atomic orbitals [23]. However, this approach has some limitations because it does not sufficiently take into account electronegativity differences, which are an important factor affecting the electron distribution in chemical bonds. Especially when large or diffuse basis sets are used, the Mulliken method may give results that are far from physical meaning; for example, unrealistic situations such as negative charge density in some atoms or calculation of more than two electrons in an orbital may occur [24]. Table 2 shows the calculated Mulliken charges for the BOXP molecule, revealing an imbalance in the positive-negative charge distribution between the carbon atoms. The optimized structure was found to have a total negative charge due to the electron-donating behavior of the oxygen atom. The closeness of the Mulliken charges obtained from two different functionals

demonstrates intermethod consistency. Although it has limitations, Mulliken charge analysis provides useful information for comparative studies.

Table 2. The theoretically calculated Mulliken Atomic Charges of the BOXP molecule

ATOM	B3PW91	B3LYP	ATOM	B3PW91	B3LYP
C1	-0.148	-0.111	C17	-0.013	-0.038
C3	-0.151	-0.130	N9	-0.728	-0.683
C5	-0.137	-0.116	O12	-0.548	-0.543
C8	0.511	0.477	O19	-0.500	-0.489
C10	0.328	0.327	O21	-0.472	-0.468
C13	-0.169	-0.155	H22	0.138	0.103
C14	0.079	0.102	H24	0.139	0.102
C15	-0.159	-0.134	H26	0.299	0.276
C16	-0.172	-0.140	H29	0.148	0.110
C17	-0.251	-0.191	H31	0.336	0.322
C18	0.606	0.591	H33	0.138	0.112
C20	-0.366	-0.298	H34	0.136	0.109

3.3. HOMO and LUMO Analysis

The energy difference (ΔE) between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) is one of the most significant parameters determining a molecule's optical, electronic, stability, and chemical reactivity characteristics within the framework of molecular orbital theory [25]. HOMO and LUMO energy levels define the electron donation and acceptance tendencies of the molecule; HOMO is the highest energy orbital from which the molecule can donate an electron, while LUMO is the lowest energy orbital to which it can accept an electron [26]. As the energy gap increases, the molecule generally exhibits greater stability, lower chemical reactivity, and reduced polarizability [27]. In this context, quantum chemical calculations performed for the BOXP compound provide important information about its electronic properties. Table 3 lists the HOMO and LUMO energies obtained using two different methods. Using the B3PW91 functional, the HOMO energy was calculated as -5.1200 eV and the LUMO energy as -0.0598 eV, yielding an energy gap of 5.1798 eV. Similarly, the B3LYP method gave HOMO and LUMO energies of -5.0246 eV and -0.0713 eV, respectively, resulting in an energy gap of 5.0959 eV. The close agreement between the two methods indicates consistent and reliable results. The obtained HOMO–LUMO gap of approximately 5.1 eV represents a relatively wide energy separation, suggesting that the BOXP molecule has high chemical stability, low reactivity, and low polarizability under external electric fields. Therefore, BOXP may be a promising candidate for applications requiring high stability, such as materials science and optoelectronic research. The HOMO-LUMO orbitals of the compound in question are graphically depicted in Figures 2, 3. As can be seen in Figures 2, 3, the HOMO orbitals are spread over the N9-C8-O12 and C4-C3-H23, while the LUMO orbitals are shifted and spread over O19-C18-O21 and C4-C3-H23, providing convincing evidence for intramolecular charge transfer within the compound.

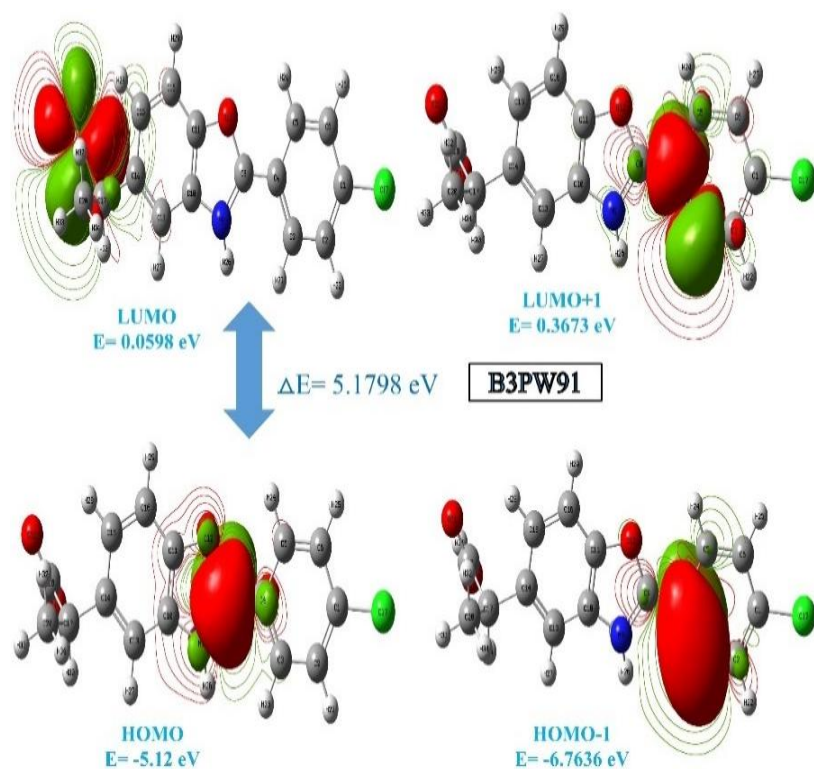


Figure 2. The boundary molecular orbitals (HOMO and LUMO) of the BOXP molecule calculated using the B3PW91/6-31G(d,p) method

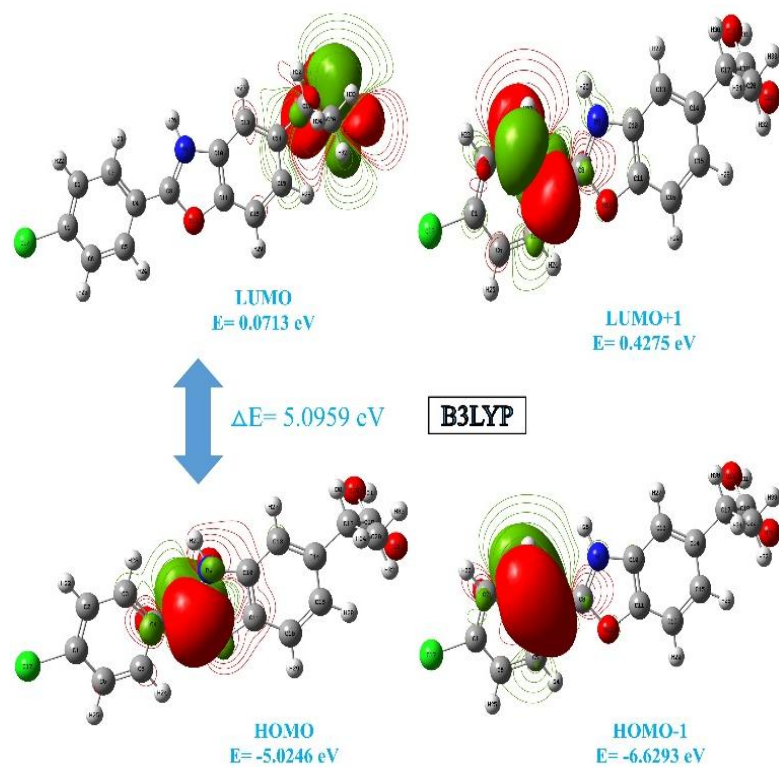


Figure 3. The boundary molecular orbitals (HOMO and LUMO) of the BOXP molecule calculated using the B3LYP/6-31G(d,p) method

Table 3. The HOMO and LUMO quantum chemical characteristics determined by the B3PW91 and B3LYP methods for the BOXP molecule

Molecules Energy		B3PW91	B3LYP
E_{LUMO}		-0.0598	-0.0713
E_{HOMO}		-5.1200	-5.0246
E_{LUMO+1}		0.3673	0.4275
E_{HOMO-1}		-6.7636	-6.6293
Energy Gap	$(\Delta E) E_{HOMO}-E_{LUMO} $	5.1798	5.0959
Ionization Potential	$(I=-E_{HOMO})$	5.1200	5.0246
Electron Affinity	$(A=-E_{LUMO})$	0.0598	0.0713
Chemical hardness	$(\eta=(I-A)/2)$	2.5301	2.4766
Chemical softness	$(s=1/2\eta)$	1.2651	1.2383
Chemical Potential	$(\mu=-(I+A)/2)$	-2.5899	-2.5479
Electronegativity	$(\chi=(I+A)/2)$	0.5299	0.5356
Electrophilicity index	$(\omega=\mu^2/2\eta)$	1.3256	1.3106

3.4. Molecular Electrostatic Potential (MEP)

In several fields of study, MEP has been extensively employed as a molecular indicator of chemical reactivity. These include analyzing molecule electrical structure, studying reactivity patterns, studying noncovalent complexes and biological interactions, and characterizing events in condensed phases [28]. Furthermore, as a source for the derivation of partial charges needed to assess electrostatic interactions in classical calculations, MEP has emerged as a popular technique in force field parameterization. Information on electrophilic (negative) and nucleophilic (positive) sites for chemical reactions and hydrogen bonding interactions is provided by MEP surface analysis [29-31]. BOXP molecule is a molecule carrying a 4-chlorophenyl group and bonded with a propanoic acid functional group. This structural feature plays a vital role in assessing the biological and chemical characteristics of BOXP. The compound has a distinct electron structure resulting from the combination of aromatic ring structures, which direct its electrophysical behavior and potential interactions. The benzo[d]oxazole ring is a structure located in the center of the molecule and increases its chemical reactivity with its electron richness. In addition, the presence of the 4-chlorophenyl group is an important factor that differentiates this structure electrochemically. The chloro group can change the electron density of the molecule, affecting its behavior, especially in electrophilic and nucleophilic interactions. The MEP map for the BOXP molecule calculated by the methods of the gas phase study has been shown in Figure 4. In the surface diagram, red indicates regions of negative electrostatic potential (electron-rich), while blue indicates regions of positive electrostatic potential (electron-poor). The blue color (nucleophilic site) indicates the header molecule above the nitrogen atom. The blue shade of the header molecule also reflects the nucleophilic potential of the hydrogen and carbon atoms. The biological activity of a molecule is indicated by the presence of an active nitrogen site.

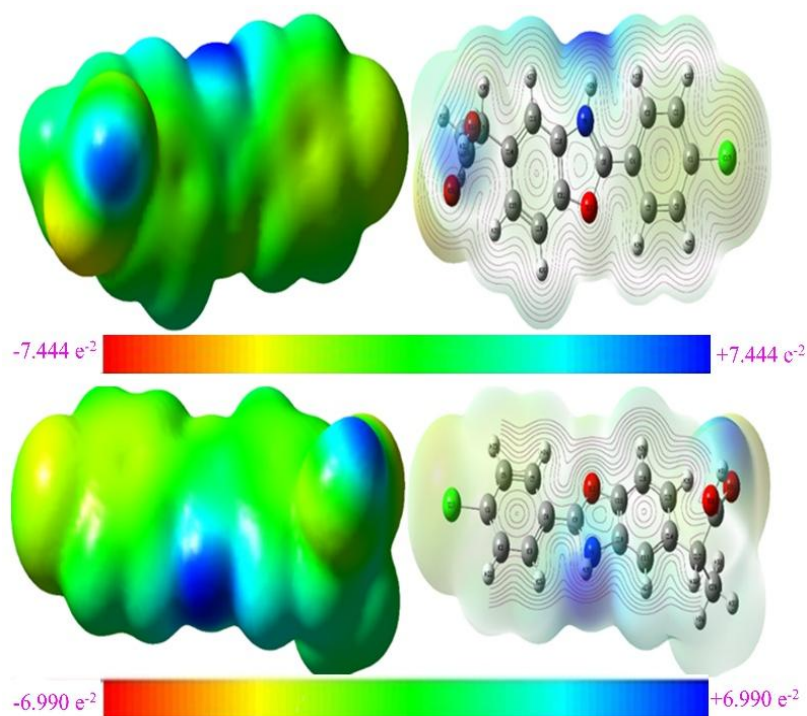


Figure 4. MEP maps of the BOXP molecule calculated using the B3PW91/6-31G(d,p) and B3LYP/6-31G(d,p) methods

3.5. Nonlinear Optical Properties (NLO)

Nonlinear optical (NLO) behavior is the basis of research on the interaction of molecules and materials with light, and understanding this behavior plays a significant part in the development of modern optical technologies [32]. NLO activities are usually studied using quantum chemical calculations, which allow us to deeply understand the interactions of molecules with electromagnetic fields [33, 34]. Fundamental optical characteristics such as electric dipole moment, polarizability, and hyperpolarizability are critical parameters in the characterization of nonlinear optical processes. Especially hyperpolarizability is an important indicator of nonlinear optical phenomena and plays an active role in applications such as second harmonic generation of light or optical parameterized oscillators. Table 4 displays the μ -electric dipole moment, α -polarizability, and β -hyperpolarizability values for the BOXP compound that were determined using two distinct approaches. As a result of the calculations, the dipole moment of a compound calculated as 8.5999 and 8.5364 indicates that the electrical properties of the molecule are quite strong and can play a significant part in nonlinear optical interactions. Furthermore, the high values of first-order hyperpolarizability for the gas phase, such as 1.36×10^{-30} and 1.35×10^{-30} , reveal that the NLO activities of this compound are quite pronounced. When compared to a comparative compound such as urea, these values are approximately seven times higher in the gas phase, indicating that this compound has a great potential in terms of nonlinear optical properties.

Table 4. DFT-based calculation of the BOXP molecule's NLO parameters utilizing B3PW91 and B3LYP functionals

Parameters	B3PW91	B3LYP	Parameters	B3PW91	B3LYP
μ_x	-8.0178	-7.9614	β_{XXX}	-489.2122	-487.4135
μ_y	-1.3889	-1.3772	β_{YYY}	8.5832	8.8543
μ_z	-2.7827	-2.7549	β_{ZZZ}	-6.0786	-6.1097
$\mu_{(D)}$	8.5999	8.5364	β_{XYY}	-14.3693	-14.5455
α_{XX}	-118.2587	-120.0360	β_{XXY}	43.9649	44.0617
α_{YY}	-110.8901	-112.3195	β_{XXZ}	-54.1177	-53.6125
α_{ZZ}	-137.6758	-137.4811	β_{XZZ}	7.6756	8.5706
α_{XY}	-10.9941	-3.8582	β_{YZZ}	-0.0067	0.0222
α_{XZ}	11.5867	11.3650	β_{YYZ}	-5.5881	-5.2476
α_{YZ}	3.9917	3.9507	β_{XYZ}	-25.3280	-24.2116
$\alpha(\text{au})$	-139.1339	-149.3467	$\beta(\text{esu})$	1.36×10^{-30}	1.35×10^{-30}

Urea (Reference)= $\mu_{(D)} = 1.3197$, $\beta(\text{esu}) = 0.1947 \times 10^{-30}$

3.6. ADME Analysis

To expedite the conversion of hits and promising candidates into qualified development candidates, physicochemical and pharmacological property evaluation is being carried out at very early stages of drug discovery [35]. To lower the loss rate of these possible drug candidates as they advance through the development process, in vitro ADME analyses are specifically carried out at every stage of the discovery process, from hit generation to potency optimization [36-38]. The analytical community needs to produce quicker and better analytical techniques to boost the "developability" of drug potentials since the tendency in drug development is to acquire ADME information earlier and earlier in the process [39]. Similar to structure-activity relationships, the pharmaceutical industry has adopted the strategy of identifying potential liabilities early in the discovery process, which has replaced the late-stage optimization of ADME properties. This has led to the addition of the structure-ADME relationship dimension as a crucial component of the iterative drug discovery process. The Admetlab 2.0 web tool was used to calculate the molecular characteristics of Lipinski's rule of five, which are displayed in Table 5. Consequently, physicochemical characteristics were predicted using Lipinski's rule of five. The compounds under investigation did not fail to meet the established standards, as shown in Table 5. As a result, these substances fully abide with Lipinski's rule. The gut is often the main site of absorption when medications are taken orally. Determining the proportion of chemicals absorbed via the small intestine (>30%) is the goal of human intestinal absorption (HIA). High intestinal membrane absorption was demonstrated by the BOXP molecule (0.004). In terms of distribution qualities, the roflumilast chemical demonstrated the ability to penetrate the blood-brain barrier (BBB: 0.37), which is required to lessen toxicity and adverse effects or to boost the effectiveness of medications that target the brain. Figure 5 shows the physicochemical parameter maps and color areas of the compounds being studied.

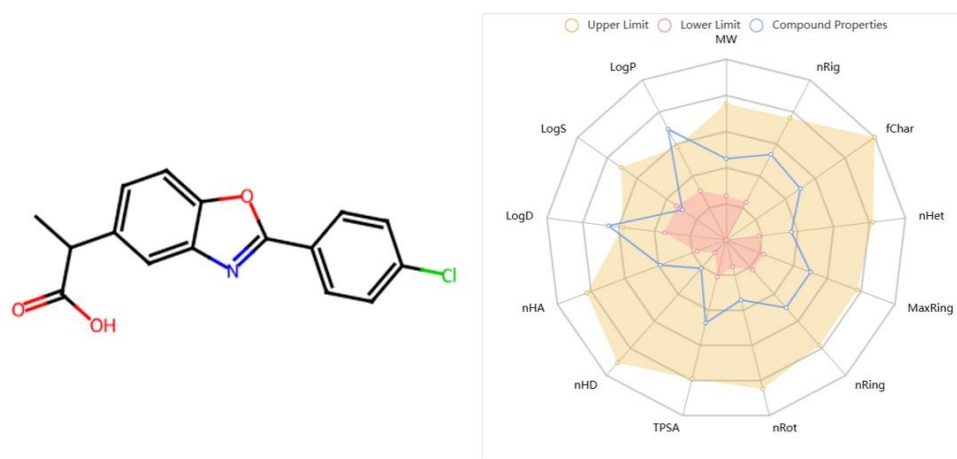


Figure 5. Physicochemical parameters and color regions of BOXP molecule

Table 5. BOXP molecule's physicochemical and lipophilicity

Property	BOXP	Comment
Molecular Weight	301.05	Molecular Weight< 500
nHA	4	Hydrogen bond acceptors<12
nHD	1	Hydrogen bond donors<7
MR	80.81	molar refraction values between 4-130
logP	4.193	Log of the octanol/water partition coefficient: 0-5
TPSA	63.33	Topological Polar Surface Area:0-140
HIA	0.004	Category 1: HIA+(HIA<30%); Category 0: HIA-(HIA>=30%);
BBB	0.37	The output value is the probability of being HIA+ The output value is the probability of being BBB+

3.7. Molecular Docking Studies

Molecular docking methods are at the core of structure-based drug design approaches and play an important role in modern drug discovery processes [40]. With this computational technique, the binding affinities and binding positions of potential drug candidates with target proteins can be modeled in a three-dimensional plane, thus identifying compounds with biological activity can be achieved more systematically and rapidly [41]. Compared to laboratory-based screening processes, which are particularly costly and time-consuming, molecular docking studies conducted on in silico platforms provide significant time and resource contributions to early-stage drug development processes [42, 43]. Cancer has become a critical public health problem due to its increasing incidence and mortality rates worldwide. However, most of the current conventional treatment methods show limited efficacy, and there is still a lack of specific pharmacological agents for many types of cancer [44]. In this context, the identification of new therapeutic targets and the design of small molecules that can bind to these targets with high affinity are of great importance. In this study, molecular docking analyses were performed to determine the interaction potential of BOXP molecule with target enzymes associated with colorectal and lung cancers. Crystal structures of 2HQ6, known to play a role in colon cancer, and 4JPS, associated with lung cancer, were selected as target proteins. Molecular docking simulations were conducted utilizing the Schrödinger Maestro program [14] to evaluate the binding affinity of BOXP molecule to these target proteins. In this study, Discovery Studio Client 2017 [15] software was used to perform detailed analysis of interactions between proteins and ligands. As a result of examining Figure 6, it was observed that various amino acid residues were located in the regions where the ligands bind and that these residues had different physicochemical properties. The best binding locations found through molecular docking studies were identified, and Figures 7 and 8 clearly depict these locations. The binding properties of the BOXP compound on the target protein

were focused on and the key amino acid residues that interacted as a result of the docking analyses were reported in Table 7 together with their interaction types. The binding energies obtained revealed that BOXP exhibited binding scores of -9.30 kcal/mol with 2HQ6 enzyme and -8.60 kcal/mol with 4JPS enzyme, and these values have been given in Table 6. These values indicate that the molecule interacts strongly and stably with both targets. Especially the high binding affinity obtained with 2HQ6 enzyme indicates that BOXP may be a promising inhibitor candidate in colorectal cancer therapy. The fact that BOXP also exhibited significant binding with 4JPS suggests that this molecule may also be evaluated within the scope of multi-target agent development studies for lung cancer treatment. These findings suggest that BOXP may be a valuable lead compound in pharmaceutical development processes for cancer treatment. These amino acid residues directly affect binding affinity and conformational stability by establishing versatile and specific interactions with the ligand. The data obtained reveal that there are significant differences between the structural binding sites of different protein targets, thus each target has unique interaction motifs. This shows that drug candidates such as BOXP should be designed specifically for target proteins and that detailed examination of the interaction profile is critical for pharmacological efficacy.

Table 6. Molecular docking interaction scores for the BOXP compound's PDBID: 2HQ6 and PDBID: 4JPS enzymes

Compound	Docking Score	
	(PDB: 2HQ6)	(PDB: 4JPS)
BOXP	-9.30	-8.60

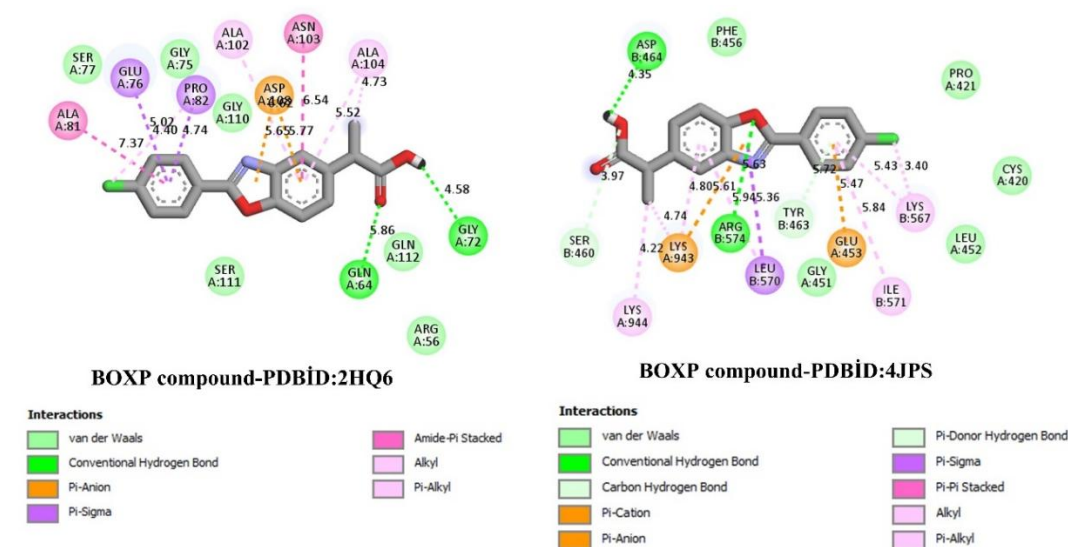


Figure 6. 2D Mode view of BOXP Compound and PDBID: 2HQ6, PDBID:4JPS enzymes

Table 7. The interaction parameters between BOXP compound and 2HQ6, 4JPS enzymes

Important Interactions	2HQ6 Enzyme			4JPS Enzyme		
	Full Name	Type	Bond Length (Å)	Full Name	Type	Bond Length (Å)
Van der Waals	SER111	Serine	-	PRO42	Proline	-
	ARG51	Arginine	-	1	Cysteine	-
	GLN112	Glutamine	-	CYS42	Leucine	-
	GLY110	Glycine	-	0	Glycine	-
	SER77	Serine	-	LEU45 2 GLY45 1		-
Conventional Hydrogen Bond	GLN64	Glutamine	5.86	ASP46	AsparticAcid	4.35
	GLY72	Glycine	4.58	4 ARG57 4	Arginine	5.94
Pi-Anion	ASP102	AsparticAcid	5.65	GLU45 3	GlutamicAcid	5.47
Pi-Sigma	GLU76	GlutamicAcid	5.02	LEU57 0	Leucine	5.36
Pi-Cation				LYS94 3	Lysine	5.61
Amide-Pi stacked	ALA81	Alanine	7.87	TYR12	Tyrosine	5.76
Alkyl	ALA104	Alanine	4.73	LYS94	Lysine	4.22
	ALA104	Alanine	5.52	4 LYS56 7	Lysine	3.40
Pi-Alkyl	ALA102	Alanine	5.65	ILE571	Isoleucine	5.84
				LYS56 7	Lysine	5.43
Carbon Hydrogen Bond	-	-	-	SER46 0	Tyrosine	5.72
Pi-Pi Stacked	-	-	-	LEU57 0	Leucine	5.63
Pi-Donor Hydrogen Bond	-	-	-	TYR46 3	Tyrosine	5.72

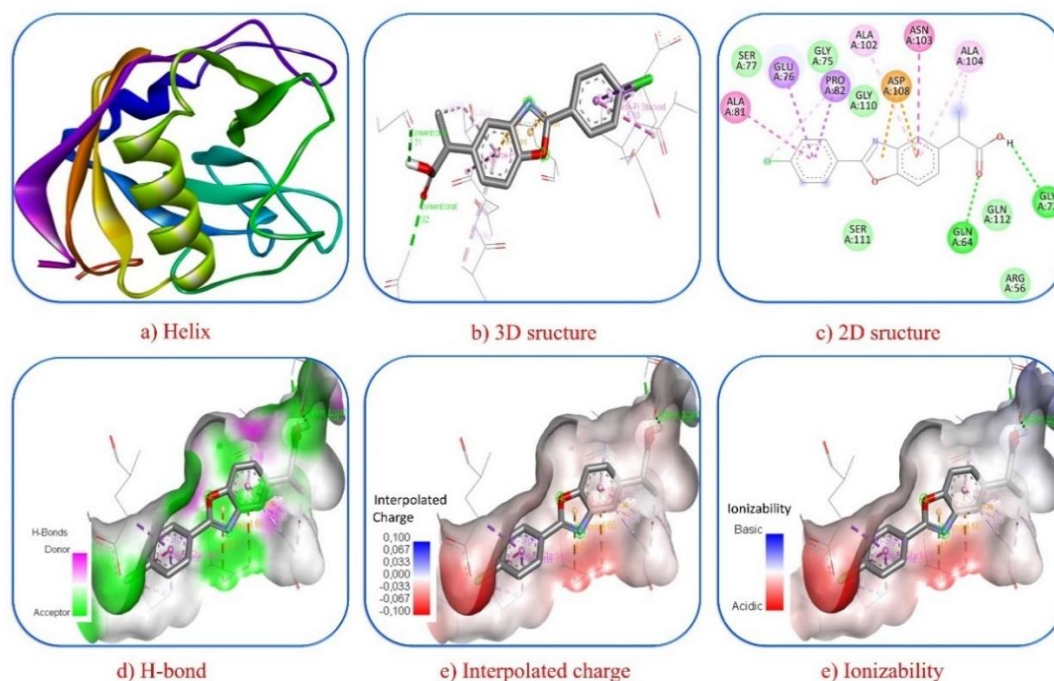


Figure 7. Molecular docking visual results of BOXP compound with 2HQ6 enzyme

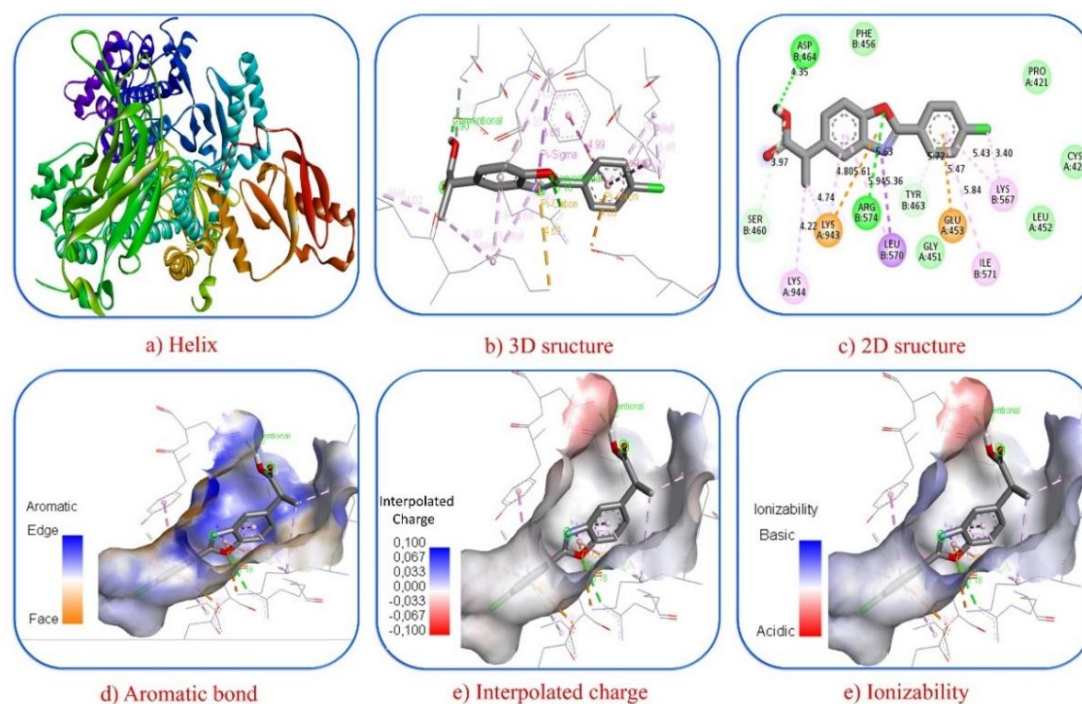


Figure 8. Molecular docking visual results of BOXP compound with 4JPS enzyme

4. Conclusion

In this study, the structural, electronic, pharmacokinetic and biological properties of 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)propanoic acid (BOXP) molecule were investigated in detail by multi-dimensional theoretical approaches. Quantum chemical parameters of the molecule were optimized with 6-31G(d,p) basis set using B3LYP and B3PW91 methods and the stability of the

obtained structural data was evaluated by various theoretical indicators such as HOMO-LUMO energy difference, molecular electrostatic potential (MEP) distributions, natural bond orbital (NBO) analysis, nonlinear optical (NLO) properties and Mulliken charge distribution. The results obtained with both functionals were found to be consistent with each other, confirming the reliability of the calculations and the chemical stability of the molecule. The HOMO-LUMO energy difference is an important parameter to determine the chemical reactivity and stability of a molecule, and the HOMO-LUMO gap of BOXP shows a wide value. This suggests that the molecule has high chemical stability and can potentially show low reactivity in interaction with biological targets. In addition, the hardness and softness values of the molecule indicate that BOXP may exhibit a softer approach to chemical reactions while binding to targets in biological systems and therefore has high biocompatibility. Molecular electrostatic potential (MEP) analysis also provides important findings. MEP shows the electrical charge distribution of the molecule and the interaction between electrophilic and nucleophilic regions. While the BOXP molecule exhibits strong interactions, especially in its nucleophilic regions, this feature may facilitate the interaction of the molecule with biological targets. Such properties may be one of the determining factors of the biological activity of the molecule. Pharmacokinetic evaluations focused on the ADME properties of BOXP. Analysis using Schrödinger Admetlab 2.0 software revealed that BOXP complies with Lipinski's Rule of Five. This indicates that the compound may be bioavailable and potentially enter the systemic circulation. Factors such as the molecule's high bioavailability, strong binding energies and compliance with Lipinski's rule mean that BOXP may work effectively and safely in biological systems. This makes it a worthy candidate for further pharmaceutical development. Molecular docking analysis was conducted to evaluate the activity of BOXP against important target enzymes in cancer treatment. In the analyses performed with 2HQ6 enzyme code for colon cancer and 4JPS enzyme code for lung cancer, it was determined that BOXP showed high binding energy to these proteins and had strong binding potential. Binding energies of -9.30 kcal/mol with 2HQ6 enzyme and -8.60 kcal/mol with 4JPS enzyme indicate that BOXP has high affinity for these targets and can effectively interact with these targets. These binding energies indicate the potential of BOXP to be used as a targeting molecule in cancer treatment. Theoretical analyses and molecular docking studies show that BOXP is a potential molecule candidate in cancer treatment. Theoretical binding capacity of the compound to strong biological targets provides a significant advantage for pharmaceutical development. Especially for comm opticon and fatal diseases such as colon and lung cancer, BOXP may offer a potential treatment option.



Peer-review: External, Independent.

Acknowledgements:

-

Declarations:

1. Statement of Originality:

This work is original.

2. Author Contributions:

Concept: BK,MB,KG; **Conceptualization:** BK,MB,KG; **Literature Search:** BK,MB,KG; **Data Collection:** BK,MB,KG; **Data Processing:** BK,MB,KG; **Analysis:** BK,MB,KG; **Writing – original draft:** BK,MB,KG; **Writing – review & editing:** BK,MB,KG.

3. Ethics approval:

Not applicable.

4. Funding/Support:

This work has not received any funding or support.

5. Competing Interests:

The authors declare no competing interests.

6. GenAI Usage Statement:

No GenAI tools were used at any stage of the study.

7. Sustainable Development Goals:



REFERENCES

- [1] Bayar, İ., Çağlar Yavuz, S., Akkoç, S. 2024. In Vitro And In Silico Studies on Lignan Secoisolariciresinol Diglucoside. *Journal of Faculty of Pharmacy of Ankara University*, 48(1), 127-137.
- [2] Kökbudak, Z., Türkmenoğlu, B., Akkoç, S. 2022. A New Schiff Base Molecule Prepared from Pyrimidine-2-thione: Synthesis, Spectral Characterization, Cytotoxic Activity, DFT, and Molecular Docking Studies. *Adıyaman University Journal of Science*, 12(1), 9-25.
- [3] Çağlar Yavuz, S. 2023. Molecular Docking and Reactive Sites Identification (Homo–Lumo, Mep) of Allicin and Diallyl Disulfide: Potential Anticancer Inhibitor. *Karadeniz Fen Bilimleri Dergisi*, 13(4), 1523-1539.
- [4] Şahin, N., Üstün, E. 2021. Molecular Docking Analysis of Benzimidazolium Type Molecules with VEGFR-2 and TrxR Crystal Structures for Evaluating Anti-Cancer Activity. *Ordu Üniversitesi Bilim ve Teknoloji Dergisi*, 11(1), 36-44.
- [5] Şahin, N., Üstün, E. 2021. Molecular Docking and DFT Analysis of Methallyl Substituted N-Heterocyclic Carbene Salts for Potential Anticancer Activity. *Ordu Üniversitesi Bilim ve Teknoloji Dergisi*, 11(2), 186-192.
- [6] Şener, N., Çavuş, M. 2023. Synthesis and Analysis of Some Azo Dyes Obtained from Benzothiazole by Density Functional Theory. *Süleyman Demirel University Faculty of Arts and Science Journal of Science*, 18(2), 181-194.
- [7] Abbas, A. M., Aboelmagd, A., Kishk, S. M., Nasrallah, H. H., Boyd, W. C., Kalil, H., Orabi, A. S. 2022. A Novel Ibuprofen Derivative and Its Complexes: Physicochemical Characterization, DFT Modeling, Docking, In Vitro Anti-Inflammatory Studies, and DNA Interaction. *Molecules*, 27(21), 7540.
- [8] Abdellaoui, F., Haouas, A., Samud, A. M., Belaid, A. K., Al-Ghulikah, H., Taher, Y. A., Guerfel, T., Bannur, Z. M., Hajji, M. 2024. Unravelling the structure and reactivity of N,O-heterocycles: a multifaceted quantum chemical approach using a benzoxazole derivative as a case study. *Journal of Chemical Sciences*, 136(4), 76.
- [9] Siddiqui, B., Yadav, C. S., Akil, M., Faiyyaz, M., Khan, A. R., Ahmad, N., Hassan, F., Azad, M. I., Owais, M., Nasibullah, M., Azad, I. 2025. Artificial Intelligence in Computer-Aided Drug Design (CADD) Tools for the Finding of Potent Biologically Active Small Molecules: Traditional to Modern Approach. *Combinatorial Chemistry & High Throughput Screening*.
- [10] Akhtar, M. N., AlDamen, M. A., Zierkiewicz, W., Michalczyk, M., Khalid, M., Idrisi, M., Shahid, M.

2020. Synthesis, crystal structure, DFT calculations, molecular docking study and Hirshfeld surface analysis of alkoxido-bridged dinuclear iron(III) complex. *Research on Chemical Intermediates*, 46(9), 4155-4171.
- [11] Kakkar, S., Tahlan, S., Lim, S. M., Ramasamy, K., Mani, V., Shah, S. A. A., Narasimhan, B. 2018. Benzoxazole derivatives: design, synthesis and biological evaluation. *Chemistry Central Journal*, 12(1), 92.
- [12] M.J. Frisch, G. W. T., H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, . Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09. 2009.
- [13] Burley, S. K., Berman, H. M., Bhikadiya, C., Bi, C., Chen, L., Di Costanzo, L., Christie, C., Dalenberg, K., Duarte, J. M., Dutta, S., Feng, Z., Ghosh, S., Goodsell, D. S., Green, R. K., Guranovi, V., Guzenko, D., Hudson, B. P., Kalro, T., Liang, Y., Lowe, R., Namkoong, H., Peisach, E., Periskova, I., Prli, A., Randle, C., Rose, A., Rose, P., Sala, R., Sekharan, M., Shao, C., Tan, L., Tao, Y.-P., Valasatava, Y., Voigt, M., Westbrook, J., Woo, J., Yang, H., Young, J., Zhuravleva, M., Zardecki, C. 2018. RCSB Protein Data Bank: biological macromolecular structures enabling research and education in fundamental biology, biomedicine, biotechnology and energy. *Nucleic Acids Research*, 47(D1), D464-D474.
- [14] Release, S., 1: Maestro, Schrodinger, LLC, New York. 2019.
- [15] Studio, B. D. 2016. Dassault Systmes Biovia Corporation. San Diego, USA.
- [16] ADMETlab2.0. A platform for systematic ADMET evaluation. [cited 2026 05.02.2026]; Available from: <https://admetmesh.scbdd.com/>.
- [17] Gren, K., Bađlan, M., Yildiko, . 2025. Analysis by DFT, ADME and Docking Studies of N'-(4-hydroxy-3-methoxybenzylidene)naphtho[2,3-b]furan-2-carbohydrazide. *Eskiehir Teknik niversitesi Bilim ve Teknoloji Dergisi B - Teorik Bilimler*, 13(1), 7-23.
- [18] Bađlan, M., Gren, K., akmak, İ. 2022. Theoretical Investigation of 1H and 13C NMR Spectra of Diethanol Amine Dithiocarbamate RAFT Agent. *Journal of the Institute of Science and Technology*, 12(3), 1677-1689.
- [19] Kakkar, S., Kumar, S., Narasimhan, B., Lim, S. M., Ramasamy, K., Mani, V., Shah, S. A. A. 2018. Design, synthesis and biological potential of heterocyclic benzoxazole scaffolds as promising antimicrobial and anticancer agents. *Chemistry Central Journal*, 12(1), 96.
- [20] Ghoshal, T., Patel, T. M. 2020. Anticancer activity of benzoxazole derivative (2015 onwards): a review. *Future Journal of Pharmaceutical Sciences*, 6(1), 94.
- [21] Abdullahi, A., Yeong, K. Y. 2024. Targeting disease with benzoxazoles: a comprehensive review of recent developments. *Medicinal Chemistry Research*, 33(3), 406-438.
- [22] Wang, X., Yao, J. 2017. Improvement of the self-consistent-charge density-functional-tight-binding theory by a modified Mulliken charge. *Theoretical Chemistry Accounts*, 136(10), 124.
- [23] Tahirođlu, V., Gren, K., Yildiko, ., Bađlan, M. 2024. Investigation, Structural Characterization and Evaluation of the Biological Potency by Molecular Docking of Amoxicillin Analogue of a

- Schiff Base Molecule. *International Journal of Chemistry and Technology*, 8(2), 190-199.
- [24] Gümüş, H. 2020. Spectroscopic (Vibrational and NMR) Characterizations and Molecular Docking Analysis of Zn(II), Cd(II) and Hg(II) Complexes with Alkyl-Aryl Dithiocarbamates. *Arabian Journal for Science and Engineering*, 45(6), 4929-4937.
- [25] Gören, K., Bağlan, M., Tahiroğlu, V., Yıldiko, Ü. 2024. Theoretical Calculations and Molecular Docking Analysis of 4-(2-(4-Bromophenyl)Hydrazineylidene)-3,5-Diphenyl-4H-Pyrazole Molecule. *Journal of Advanced Research in Natural and Applied Sciences*, 10(4), 786-802.
- [26] Sarikavakli, N., Genç, O., Çalışkan, Ş. G., Erol, F. 2023. Molecular docking, HOMO-LUMO and quantum chemical computation analysis of anti-glyoximehydrazone derivatives containing pyrazolone moiety and their transition metal complexes. *Journal of the Indian Chemical Society*, 100(5), 100981.
- [27] Singh, J. S., Khan, M. S., Uddin, S. 2023. A DFT study of vibrational spectra of 5-chlorouracil with molecular structure, HOMO-LUMO, MEPs/ESPs and thermodynamic properties. *Polymer Bulletin*, 80(3), 3055-3083.
- [28] Soliva, R., Luque, F. J., Orozco, M. 1997. Reliability of MEP and MEP-derived properties computed from DFT methods for molecules containing P, S and CL. *Theoretical Chemistry Accounts*, 98(1), 42-49.
- [29] Gören, K., Bağlan, M., Yıldiko, Ü. 2024. Antimicrobial, and Antitubercular Evaluation with ADME and Molecular Docking Studies and DFT Calculations of (Z)-3-((1-(5-amino-1,3,4-thiadiazol-2-yl)-2-Phenylethyl)imino)-5-nitroindolin-2-one Schiff Base. *Karadeniz Fen Bilimleri Dergisi*, 14(4), 1694-1708.
- [30] Tahiroğlu, V., Gören, K., Çimen, E., Yıldiko, Ü. 2024. Molecular Docking and Theoretical Analysis of the (E)-5-((Z)-4-methylbenzylidene)-2-(((E)-4-methylbenzylidene)hydrazineylidene)-3-phenylthiazolidin-4-one Molecule. *Bitlis Eren Üniversitesi Fen Bilimleri Dergisi*, 13(3), 659-672.
- [31] Gören, K., Bağlan, M., Yıldiko, Ü. 2024. Melanoma Cancer Evaluation with ADME and Molecular Docking Analysis, DFT Calculations of (E)-methyl 3-(1-(4-methoxybenzyl)-2,3-dioxindolin-5-yl)-acrylate Molecule. *Journal of the Institute of Science and Technology*, 14(3), 1186-1199.
- [32] Krawczyk, P. 2010. DFT study of linear and nonlinear optical properties of donor-acceptor substituted stilbenes, azobenzenes and benzilideneanilines. *Journal of Molecular Modeling*, 16(4), 659-668.
- [33] Gören, K., Yıldiko, Ü. 2024. Aldose Reductase Evaluation against Diabetic Complications Using ADME and Molecular Docking Studies and DFT Calculations of Spiroindoline Derivative Molecule. *Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü Dergisi*, 28(2), 281-292.
- [34] Tahiroğlu, V., Gören, K., Bağlan, M., Yıldiko, Ü. 2024. Molecular Docking and DFT Analysis of Thiazolidinone-Bis Schiff Base for anti-Cancer and anti-Urease Activity. *Journal of the Institute of Science and Technology*, 14(2), 822-834.
- [35] Arshad, R., Asim, K. M., Sadaf, M., Sufyan, H., H., A.-H. G., and Refat, M. S. 2023. DFT, Molecular Docking and ADME Studies of Thiazolidinones as Tyrosinase Inhibitors. *Polycyclic Aromatic Compounds*, 43(8), 6750-6765.
- [36] Bağlan, M., Gören, K., Yıldiko, Ü. 2023. HOMO-LUMO, NBO, NLO, MEP analysis and molecular docking using DFT calculations in DFPA molecule. *International Journal of Chemistry and Technology*, 7(1), 38-47.
- [37] Bağlan, M., Gören, K., Yıldiko, Ü. 2023. DFT Computations and Molecular Docking Studies of 3-(6-(3-aminophenyl)thiazolo[1,2,4]triazol-2-yl)-2H-chromen-2-one(ATTC) Molecule. *Hittite*

- Journal of Science and Engineering, 10(1), 11-19.
- [38] Bağlan, M., Yıldiko, Ü., Gören, K. 2023. DFT Calculations And Molecular Docking Study in 6-(2"-pyrrolidinone-5"-yl)-(-)epicatechin Molecule from Flavonoids. Eskişehir Teknik Üniversitesi Bilim ve Teknoloji Dergisi B - Teorik Bilimler, 11(1), 43-55.
- [39] Rossi, A., Stagno, C., Piperno, A., Iraci, N., Panseri, S., Montesi, M., Feizi-Dehmayebi, M., Bassi, G., Di Pietro, M. L., Micale, N. 2024. Anticancer activity and morphological analysis of Pt (II) complexes: Their DFT approach, docking simulation, and ADME-Tox profiling. Applied Organometallic Chemistry, 38(5), e7403.
- [40] Yıldiko, Ü., Türkan, F., Tanriverdi, A. A., Ata, A. C., Atalar, M. N., Cakmak, İ. 2021. Synthesis, enzymes inhibitory properties and characterization of 2- (bis (4-aminophenyl) methyl) butan-1-ol compound: Quantum simulations, and in-silico molecular docking studies. Journal of the Indian Chemical Society, 98(11), 100206.
- [41] Bağlan, M., Yıldiko, Ü., Gören, K. 2022. Computational Investigation of 5.5",7"-trihydroxy-3,7-dimethoxy-4'-4'''-O-biflavone from Flavonoids Using DFT Calculations and Molecular Docking. Adiyaman University Journal of Science, 12(2), 283-298.
- [42] Abdelsattar, A. S., Alyaa, D., and Helal, M. A. 2021. Interaction of nanoparticles with biological macromolecules: a review of molecular docking studies. Nanotoxicology, 15(1), 66-95.
- [43] Ardahanli, H., Derin, Y., Yilmaz, R. F., Gül, H., Sertçelik, M., Tutar, A. 2025. New thiosemicarbazones: synthesis, structural characterization, in vitro, and in silico evaluation of antiproliferative effects. Future Medicinal Chemistry, 17(21), 2583-2590.
- [44] Callil-Soares, P. H., Biasi, L. C. K., Pessoa Filho, P. d. A. 2023. Effect of preprocessing and simulation parameters on the performance of molecular docking studies. Journal of Molecular Modeling, 29(8), 251.

