

Structural, Electronic and In Silico Biological Activity Evaluation of 5-methyl-3-phenyl-1H-1,2,4-triazole-5-carboxaldehyde Molecule

5-metil-3-fenil-1H-1,2,4-triazol-5-karboksaldehit Molekülünün Yapısal, Elektronik ve Bilgisayar Destekli Biyolojik Aktivite Değerlendirmesi

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ABSTRACT

In this study, the structural, electronic, and biological interaction properties of 5-methyl-3-phenyl-1H-1,2,4-triazole-5-carboxaldehyde (MPTrzCHO), a 1,2,4-triazole derivative, were investigated using density functional theory (DFT) and molecular docking approaches. To determine the most stable geometry of the molecule, conformational analysis was first performed using the MMFF force field approach, followed by geometry optimization at the DFT/B3LYP/6-311++G(d,p) theoretical level. To evaluate the reliability of the calculated results, comparative calculations were additionally carried out using the cc-pVDZ basis set and the IEFPCM model in a water solvent environment. The electronic structure of the molecule was investigated through frontier molecular orbital (HOMO–LUMO), molecular electrostatic potential (MEP), APT, Hirshfeld, and NBO atomic charge distribution, natural bond orbital (NBO), and reduced density gradient–non-covalent interaction (RDG–NCI) analyses. The obtained results revealed a stable and highly polarized electronic structure characterized by electron density concentration around the O and N heteroatoms. The similar distributions obtained from different basis sets and solvent environments in the HOMO–LUMO, MEP, and atomic charge analyses demonstrated the methodological consistency of the theoretical results. Molecular docking studies performed with the VEGFR-2 (PDB: 4ASD) enzyme showed that the MPTrzCHO molecule can establish hydrogen bonding and hydrophobic interactions within the active site. In addition, in silico toxicity estimations performed using the ProTox 3.0 platform revealed that the molecule exhibits inactive cytotoxicity and immunotoxicity profiles; however, possible hepatotoxic, carcinogenic, and mutagenic effects were also predicted. Overall, the obtained findings indicate that MPTrzCHO possesses remarkable interaction capability toward biological targets and may serve as a potentially biologically active 1,2,4-triazole derivative and a promising starting scaffold for the development of new pharmacological structures in future experimental studies.

Keywords: Triazole, DFT, Molecular docking, Cancer

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ÖZ

Bu çalışmada, bir 1,2,4-triazol türevi olan 5-metil-3-fenil-1H-1,2,4-triazol-5-karboksaldehit (MPTrzCHO) molekülünün yapısal, elektronik ve biyolojik etkileşim özellikleri yoğunluk fonksiyonel teorisi (DFT) ve moleküler kenetlenme yaklaşımları kullanılarak araştırılmıştır. Molekülün en kararlı geometrisini belirlemek amacıyla öncelikle MMFF kuvvet alanı yaklaşımı kullanılarak konformasyonel analiz gerçekleştirilmiş, ardından DFT/B3LYP/6-311++G(d,p) teorik seviyesinde geometri optimizasyonu yapılmıştır. Hesaplama sonuçlarının güvenilirliğini değerlendirmek amacıyla ek olarak cc-pVDZ baz seti ve su çözücü ortamında IEFPCM modeli kullanılarak karşılaştırmalı hesaplamalar gerçekleştirilmiştir. Molekülün elektronik yapısı; sınır moleküler orbital (HOMO–LUMO), moleküler elektrostatik potansiyel (MEP), APT, Hirshfeld ve NBO atomik yük dağılımları, doğal bağ orbitali (NBO) ve indirgenmiş yoğunluk gradyanı–kovalent olmayan etkileşim (RDG–NCI) analizleri aracılığıyla incelenmiştir. Elde edilen sonuçlar, özellikle O ve N heteroatomları çevresinde yoğunlaşan elektron yoğunluğu ile karakterize kararlı ve polarize bir elektronik yapı ortaya koymuştur. HOMO–LUMO, MEP ve atomik yük analizlerinde farklı baz setleri ve çözücü ortamında elde edilen benzer dağılımlar, teorik sonuçların metodolojik olarak tutarlı olduğunu göstermiştir. VEGFR-2 (PDB: 4ASD) enzimi ile gerçekleştirilen moleküler kenetlenme çalışmaları, MPTrzCHO molekülünün aktif bölge ile hidrojen bağları ve hidrofobik etkileşimler kurabildiğini göstermiştir. Ayrıca ProTox 3.0 platformu kullanılarak gerçekleştirilen in silico toksisite tahminleri, molekülün sitotoksisite ve immünotoksisite açısından inaktif bir profil sergilediğini; ancak olası hepatotoksik, karsinojenik ve mutajenik etkiler gösterebileceğini ortaya koymuştur. Genel olarak elde edilen bulgular, MPTrzCHO molekülünün biyolojik hedeflerle etkileşim kapasitesi açısından dikkat çekici özellikler taşıdığını ve gelecekte gerçekleştirilecek deneysel çalışmalar için potansiyel bir biyolojik aktif 1,2,4-triazol türevi ve yeni farmakolojik yapıların geliştirilmesinde değerlendirilebilecek bir başlangıç iskeleti olabileceğini göstermektedir.

Anahtar Sözcükler: Triazol, DFT, Moleküler kenetlenme, Kanser

INTRODUCTION

Triazoles are a class of compounds belonging to five-membered heterocyclic systems and are of great interest in scientific research due to their unique structural properties. Within this group, 1,2,4-triazoles stand out particularly for their characteristic spatial arrangement of three nitrogen and two carbon atoms, their ability to participate in weak molecular interactions, their distinctly basic character, and their capacity to exhibit multiple coordination modes (Zhang et al., 2014). These structural features also enable the emergence of pharmaceutically significant biological activities. 1,2,4-triazoles are widely used as scaffold structures in the design of numerous bioactive molecules exhibiting antibacterial, antifungal, antioxidant, antidiabetic, anticancer, and anti-inflammatory activities in the field of pharmacology (Abdelli et al., 2021; Hunashal et al., 2011; Öz Tuncay & Çakmak 2023). This is because all the nitrogen atoms in the triazole core are suitable for functionalization, allowing the structure to be effectively modulated with different substituents and consequently significantly broadening the spectrum of biological activity (Abdelli et al., 2021).

Diabetes and cancer are two major, multifactorial diseases with increasing prevalence worldwide, high mortality rates, and high treatment costs. A long-standing and bidirectional relationship exists between them, supported by current research. This relationship, particularly between pancreatic ductal adenocarcinoma (PDAC), which constitutes the vast majority of pancreatic cancers, and diabetes, reveals remarkable findings at both epidemiological and biological levels (Andersen et al., 2017). Epidemiological data show that the risk of pancreatic cancer is approximately 1.5–2 times higher in individuals with

diabetes compared to the general population. This increased risk is reported to be related to the duration of diabetes, with the highest risk observed in newly diagnosed diabetic patients (Ben et al., 2011). This suggests that the relationship between diabetes and pancreatic cancer may not only progress in the “diabetes → cancer” direction but also in the “cancer → diabetes” direction. Furthermore, it has been shown that not only diabetes but also impaired glucose metabolism at the prediabetic level can increase the risk of pancreatic cancer (Huang et al., 2024). These findings reveal that glycemic disorders are a persistent risk factor. Current clinical guidelines highlight the relationship between pancreatogenic diabetes and pancreatic cancer and recommend considering underlying pancreatic pathologies in cases of newly diagnosed diabetes at older ages (Bures et al., 2023). In conclusion, the relationship between diabetes and pancreatic cancer is of great importance both in terms of risk assessment and potential early diagnostic approaches. Evaluating the duration of diabetes, age of onset, and accompanying clinical findings together can contribute to identifying high-risk patient groups (Ali et al., 2024).

Density functional theory (DFT) is the most important quantum chemical computational method used to determine the electronic properties of molecules in order to understand their chemical reactivity and biological interactions (Akman et al., 2020). Calculating electronic properties such as the energy levels of HOMO–LUMO orbitals, the energy gap between these two orbitals, global hardness and softness, the electrophilicity index, the charge values of each atom in the structure, and the electrostatic potential surface (MEP) maps of molecules helps us predict the electron-donating and accepting tendencies of molecules, their charge distributions, and possible interaction regions, enabling the identification of active atomic regions

that may interact with biological targets (Sagaama & Issaoui, 2020; Noreen & Sumrra 2022; Jomaa et al., 2020). Molecular docking studies, on the other hand, are a computational approach that allows predicting at the atomic level how molecules interact with the active sites of biological target proteins (Agu et al., 2023). By determining the most likely binding positions of ligands on the target protein, they enable detailed analysis of interaction types. Furthermore, molecular docking studies guide scientists before experimental work, offering significant advantages in terms of time and cost (Sahoo et al., 2019; Pramanik et al. 2021)

The electronic reactivity and biological interaction behavior of 1,2,4-triazole derivatives can significantly vary depending on the nature of the attached aromatic ring and functional substituents, since these groups directly influence charge delocalization, orbital distribution, and intermolecular interaction capability. Therefore, detailed investigation of the electronic structure and interaction behavior of newly substituted triazole derivatives is important for understanding their potential biological activities and possible pharmacological applications. For these reasons, this study investigated the electronic properties of the 5-Methyl-3-phenyl-1H-1,2,4-triazole-5-carbaldehyde ligand, a derivative of the 1,2,4-triazole group, in detail; furthermore, molecular docking studies were conducted to evaluate its potential antidiabetic and anticancer (pancreatic cancer) activities.

COMPUTATIONAL MODELS and METHODS

Before proceeding with optimization calculations, a conformational analysis was performed using a molecular mechanics-based MMFF force field in Spartan 08 software (Shao et al., 2006) to determine possible conformers. The lowest-energy conformer obtained from this analysis was selected as the starting geometry for quantum chemical calculations. Geometry optimizations and the main electronic structure calculations were carried out at the DFT/B3LYP/6-311++G(d,p) level of theory (Becke, 1993; Lee et al., 1988; Kores et al., 2021) using the Gaussian 16W program (Frisch et al., 2016), since this level is widely preferred for reliably describing the electronic properties, charge distributions, and molecular reactivity parameters of heteroatom-containing organic molecules. The 6-311++G(d,p) basis set includes diffuse (+) and polarization (d,p) functions, allowing a more accurate representation of electron density distributions, particularly around heteroatoms and frontier molecular orbitals (Kores et al., 2021).

In addition, to evaluate the dependence of the obtained results on the computational level, the structure was also optimized using the cc-pVDZ basis set, and electronic properties such as HOMO–LUMO, molecular electrostatic potential (MEP), and atomic charge distributions were comparatively calculated. The cc-pVDZ basis set is a reliable and widely used theoretical approach in electronic structure calculations due to its correlation-consistent character and balanced valence description (Dunning 1989). Since the MPTrzCHO molecule was evaluated as a potentially biologically active structure, the calculations were not limited only to the gas phase, and addi-

tional calculations were performed in a water solvent environment to represent polar biological conditions more realistically. Therefore, solvent effects were included in the theoretical calculations using the IEFPCM (Integral Equation Formalism Polarizable Continuum Model) approach (Vinoth Kumar et al., 2018). The structures and electronic properties obtained from the calculations were visualized and analyzed using GaussView 6.1 software (Dennington et al., 2016). Molecular docking analyses were conducted utilizing Autodock 2.2.6 software (Morris et al., 1998) to examine ligand–protein interactions, while docking sites were visualized using Discover Studio software (Dassault Systèmes BIOVIA 2016).

RESULTS and DISCUSSION

Conformational Analysis and Molecular Geometry

Before geometry optimization, a conformational analysis is a crucial step for identifying the lowest-energy structure with the highest Boltzmann population, corresponding to the most thermodynamically stable conformer (Kucuk, 2025). Accordingly, a conformational search for the MPTrzCHO molecule was carried out using the molecular mechanics approach with the MMFF force field implemented in the Spartan 08 software package. As a result of this analysis, two conformers were obtained (see Figure 1). Both Conformer I and Conformer II exhibit identical energy values of 4.13 eV; however, Conformer I shows a higher Boltzmann population (0.518). Therefore, Conformer I was selected for geometry optimization, and all subsequent calculations were performed based on this conformer.

The structure of Conformer I, optimized at the DFT/B3LYP/6-311++G(d,p) theoretical level, is given in Figure 2, while the bond length and bond angle values are listed in Table 1. The bond lengths and bond angles obtained from the calculation results clearly reflect the electronic and geometric properties of the MPTrzCHO molecule. The O1–C14 bond length of the carbonyl group was calculated as 1.207 Å, and this result shows that this bond clearly carries a C=O double bond. The N2–N3 bond length of the triazole ring was calculated as 1.352 Å, and the N2–C6, N3–C10, and N4–C10 bond lengths were calculated as 1.377, 1.327, and 1.363 Å, respectively. Since these results are between single and double bond values, they confirm the aromatic character of the triazole ring with π -electron delocalization. The N2–C5 bond, connecting the triazole ring to the phenyl ring, was found to be 1.429 Å, while the C10–C14 bond length, connecting the triazole ring to the carbonyl group, was calculated as 1.478 Å. When the bond angles were examined, the N3–N2–C5, C5–N2–C6, N3–C10–N4, and C6–N4–C10 angles were calculated as 120.34°, 130.13°, 114.52°, and 103.75°, respectively. Additionally, the C10–C14–O1 angle was found to be 124.83°.

Frontier Molecular Orbital Analyses

The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) describe the electron-donating and electron-accepting abilities of a molecule and the energy difference between these two orbitals is the

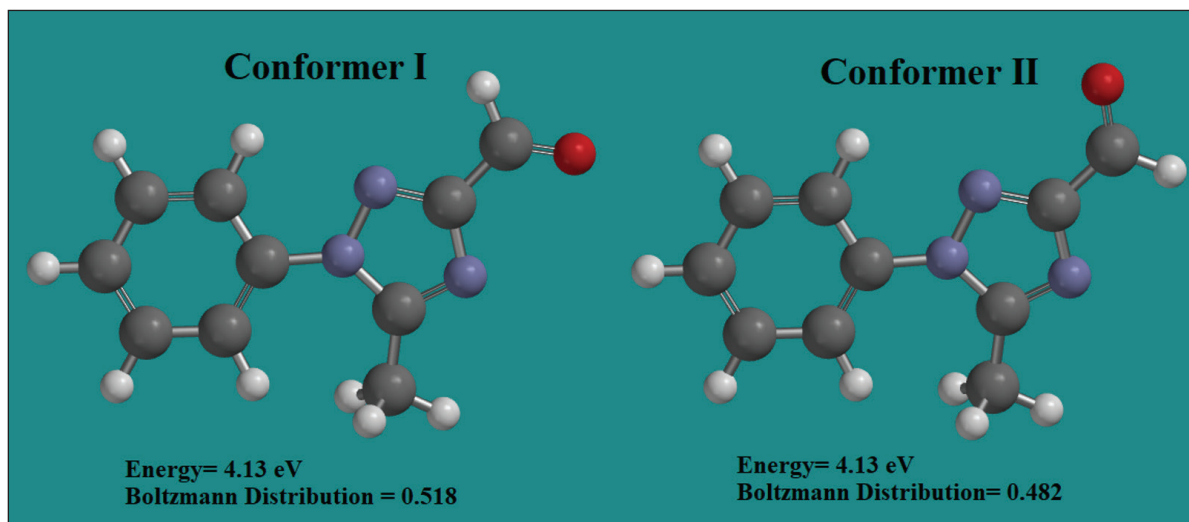


Figure 1. Conformer structures of the MPTrzCHO molecule.

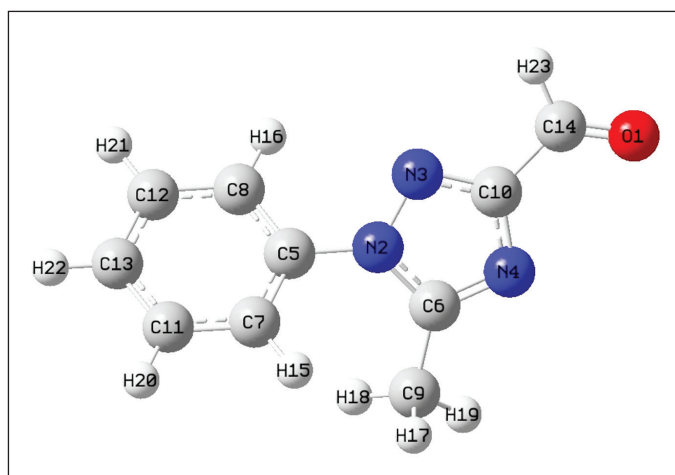


Figure 2. Optimized structure of the MPTrzCHO molecule calculated at the DFT/B3LYP/6-311++G(d,p) level of theory.

most important parameter determining the chemical reactivity and electronic transition behavior of the molecule (Abdou, 2022). HOMO is distributed on atoms and functional groups exhibiting nucleophilic character, while LUMO is more localized on atoms or functional groups exhibiting electrophilic character (Singh et al., 2023). The energy difference between HOMO and LUMO orbitals is also directly related to the chemical rigidity and electronic properties of the molecule. Molecules with a smaller energy gap exhibit softer and more reactive characteristics. As the energy difference between these two orbitals increases, the molecule becomes more stable and its chemical reactivity decreases (Rossi et al., 2024).

If the energy values of the HOMO and LUMO orbitals of a molecule are known, other quantum chemical properties that provide information about the molecule's reactivity can be calculated using the following equations (Abu-Dief et al., 2024):

Table 1. Geometric Parameters of the MPTrzCHO Molecule Calculated at the DFT/B3LYP/6-311++G(d,p) Level of Theory.

Bond lengths (Å)		Bond angles (°)	
Parameters	DFT	Parameters	DFT
O1—C14	1.207	N3—N2—C5	120.34
N2—N3	1.352	N3—N2—C6	109.45
N2—C5	1.429	C5—N2—C6	130.13
N2—C6	1.377	N2—N3—C10	102.94
N3—C10	1.327	C6—N4—C10	103.76
N4—C6	1.316	N2—C5—C7	120.30
N4—C10	1.363	N2—C5—C8	118.99
C6—C9	1.491	N3—C10—N4	114.52
C10—C14	1.478	N3—C10—C14	119.35
		N4—C10—N4	126.12
		N2—C6—N4	109.31
		C6—N4—C10	103.75
		N4—C6—C9	125.21
		N2—C6—C9	125.45
		C10—C14—O1	124.83

Å: Angstrom; °: degree.

$$I = -E_{HOMO} \quad \text{ionization potential} \quad (1)$$

$$A = -E_{LUMO} \quad \text{electron affinity} \quad (2)$$

$$\eta = (-E_{HOMO} + E_{LUMO})/2 \quad \text{global hardness} \quad (3)$$

$$\mu_c = (E_{HOMO} + E_{LUMO})/2 \quad \text{chemical potential} \quad (4)$$

$$\chi = -\mu_c \quad \text{electronegativity} \quad (5)$$

$$\sigma = 1/\eta \quad \text{global softness} \quad (6)$$

Ionization potential is defined as the minimum energy required to remove an electron from a molecule, while electron affinity is the molecule's ability to accept electrons and is represented by the negative values of the HOMO and LUMO orbitals, respectively. The resistance of a molecule's electronic structure to deformation is defined as global hardness. Chemical potential is the tendency of a molecular system to change its electron density. Electronegativity, directly related to chemical potential, is known as a measure of a molecule's electron-attracting power (Bhatia, 2024).

The quantum chemical calculations performed using two different basis sets and solvent environments revealed that all calculated electronic parameters were highly consistent with each other. The HOMO and LUMO energy values calculated at the B3LYP/6-311++G(d,p) level in the gas phase were found to be -7.25 and -1.97 eV, respectively, whereas these values shifted to -7.27 and -2.27 eV in the water phase. Similarly, for the cc-pVDZ basis set, the HOMO and LUMO energy values were calculated as -6.89 and -1.67 eV in the gas phase, while they were obtained as -6.96 and -1.88 eV in the water phase. The HOMO–LUMO energy gaps were determined as 5.28 and 5.01 eV for the 6-311++G(d,p) basis set in the gas and water phases, respectively, whereas the corresponding values for the cc-pVDZ basis set were calculated as 5.22 and 5.08 eV. The shift of the orbital energies toward more negative values in the solvent environment indicates that both the HOMO and LUMO orbitals become more stabilized under polar solvent effects. In addition, the slight decrease in the HOMO–LUMO energy gap suggests that electronic transitions may occur relatively more easily in the solvent environment (Sethi et al., 2016; Kucuk et al., 2025).

Similarly, for the cc-pVDZ basis set, the HOMO and LUMO energy values were calculated as -6.89 and -1.67 eV in the gas phase, while they were obtained as -6.96 and -1.88 eV in the water phase. The HOMO–LUMO energy gaps were determined as 5.28 and 5.01 eV for the 6-311++G(d,p) basis set in the gas

and water phases, respectively, whereas the corresponding values for the cc-pVDZ basis set were calculated as 5.22 and 5.08 eV. The shift of the orbital energies toward more negative values in the solvent environment indicates that both the HOMO and LUMO orbitals become more stabilized under polar solvent effects. In addition, the slight decrease in the HOMO–LUMO energy gap suggests that electronic transitions may occur relatively more easily in the solvent environment (Sethi et al., 2016; Kucuk et al., 2025).

The ionization potential and electron affinity values also exhibited only minor variations depending on the solvent effect. For the 6-311++G(d,p) basis set, the ionization potential values were calculated as 7.25 and 7.27 eV in the gas and water phases, respectively, while the electron affinity values were found to be 1.97 and 2.27 eV. Similarly, for the cc-pVDZ basis set, these values varied within the ranges of 6.89–6.96 eV and 1.67–1.88 eV, respectively. The slight decrease observed in the global hardness values under solvent conditions [2.64→2.50 eV and 2.61→2.54 eV] indicates that the molecule becomes more sensitive to electron density fluctuations in polar media. On the other hand, the global softness values remained nearly constant within the range of 0.38–0.40 eV⁻¹, while the electrophilicity index slightly increased in the solvent environment, indicating an enhanced electron-accepting tendency in polar media. Furthermore, the chemical potential and electronegativity values shifted toward more negative values in the solvent phase, suggesting that the electron density is more stably localized around the heteroatomic centers. Overall, the close agreement between the results obtained from different basis sets and solvent environments confirms the reliability and computational stability of the theoretical findings presented in this study.

The frontier molecular orbital visualizations obtained using both the 6-311++G(d,p) and cc-pVDZ basis sets in the gas phase and water solvent environment are presented in Figure 3. At all calculation levels, the HOMO orbital was found to be

Table 2. The Energy Values of the Quantum Chemical Properties of the MPTrzCHO Molecule

Parameters		6-311++G(d,p)		cc-pVDZ	
		Gas	Water	Gas	Water
E _{HOMO}		-7.25	-7.27	-6.89	-6.96
E _{LUMO}		-1.97	-2.27	-1.67	-1.88
Energy band gap		5.28	5.01	5.22	5.08
Ionization potential		7.25	7.27	6.89	6.96
Electron affinity	eV	1.97	2.27	1.67	1.88
Global hardness		2.64	2.50	2.61	2.54
Electronegativity		4.61	4.77	4.28	4.42
Chemical potential		-4.61	-4.77	-4.28	-4.42
Global electrophilicity		4.02	4.54	3.51	3.85
Global softness	eV ⁻¹	0.38	0.40	0.38	0.39

predominantly concentrated around the N2, N3, and N4 atoms of the heterocyclic triazole ring together with the aromatic π -conjugated phenyl system. The significant orbital density localized on the nitrogen-containing regions indicates that these centers may play an important role in electron donation processes, coordination behavior, and possible biological interactions. Moreover, the similar HOMO distributions observed in both the gas phase and water solvent environment suggest that the electron-donating character of the molecule is not significantly affected by either the basis set or solvent effect.

In contrast, the LUMO orbital was mainly localized around the O1 atom, the carbonyl group, and the adjacent π -conjugated region connected to the triazole ring. This distribution demonstrates that the electron-accepting character of the molecule is primarily associated with the carbonyl oxygen and neighboring heteroatomic π -systems. In both basis sets, the LUMO orbital density became more pronounced around the carbonyl oxygen in the water solvent environment, indicating stabilization of the electron-accepting centers under polar solvent conditions. Therefore, the HOMO→LUMO transition can be described as an intramolecular charge transfer process from the nitrogen-rich electron-donating regions toward the carbonyl-centered electron-accepting region. Furthermore, the strong similarity between the orbital distributions obtained from different basis sets and water solvent conditions confirms the consistency and reliability of the calculated electronic structure results.

Molecular Electrostatic Potential (MEP) Analysis

The molecular electrostatic potential (MEP) maps showing the spatial distribution of electron density and the nucleophilic–electrophilic reactivity regions of the optimized MPTrzCHO molecule were calculated using the 6-311++G(d,p)

and cc-pVDZ basis sets in both the gas phase and water solvent environment, and the results are presented in Figure 4. For the 6-311++G(d,p) basis set, the electrostatic potential values ranged from -6.687×10^{-2} to $+6.687 \times 10^{-2}$ a.u. in the gas phase, while these values expanded to -8.351×10^{-2} and $+8.351 \times 10^{-2}$ a.u. in the water solvent environment. Similarly, for the cc-pVDZ basis set, the potential ranges were calculated as -6.567×10^{-2} to $+6.567 \times 10^{-2}$ a.u. in the gas phase and -8.109×10^{-2} to $+8.109 \times 10^{-2}$ a.u. in the water solvent environment. In the generated MEP maps, the red and orange regions represent negative electrostatic potential and indicate nucleophilic regions, whereas the blue regions correspond to positive electrostatic potential and indicate electrophilic regions (Murray & Politzer, 2011; Zinatloo-Ajabshir et al., 2024).

Examination of the MEP maps revealed that the negative electrostatic potential was predominantly concentrated around the O1 atom in both basis sets and environments, indicating the strong nucleophilic character of the carbonyl oxygen. In addition, noticeable negative potential regions were also observed around the N3 and N4 atoms of the heterocyclic triazole ring, suggesting that these centers may actively participate in coordination interactions and hydrogen bonding processes. In contrast, the hydrogen atoms attached to the aromatic phenyl ring and methyl group were mainly located in positive electrostatic potential regions, indicating their possible hydrogen bond donor character.

A comparison between the gas phase and water solvent environment showed that the general electrostatic potential distribution pattern was preserved, while the negative potential around the carbonyl oxygen became more pronounced in the solvent environment. This observation indicates that the polar solvent stabilizes the electron-rich regions and enhances the polarization of the molecular surface. Furthermore, the in-

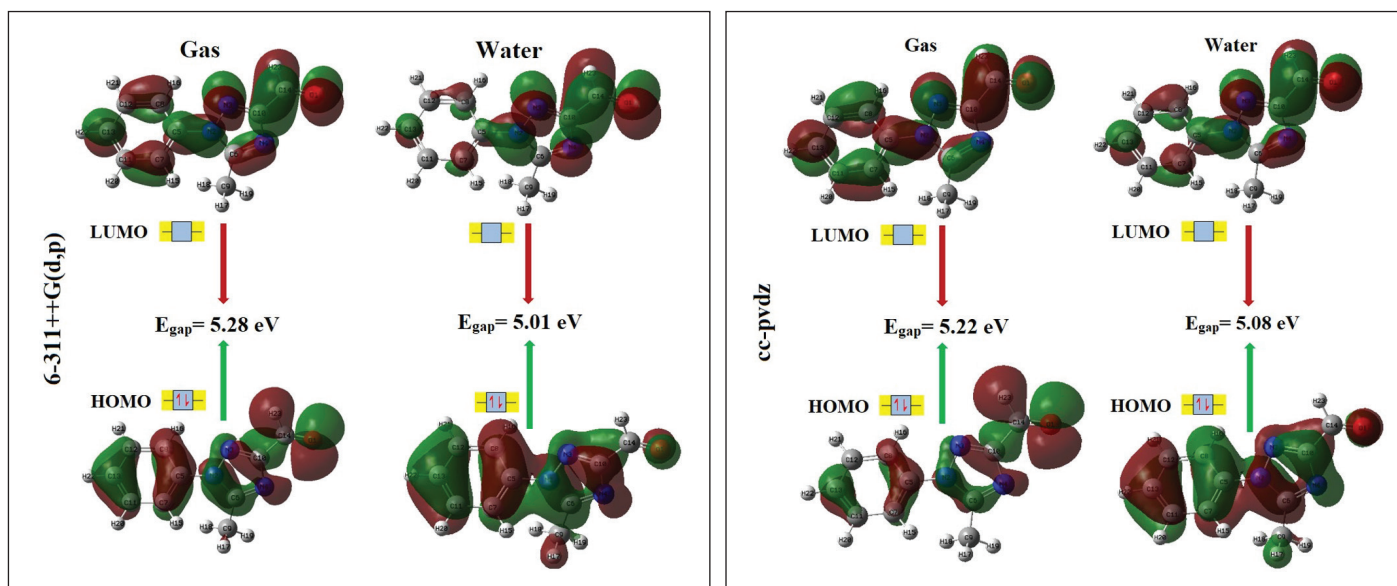


Figure 3. HOMO and LUMO orbital distributions of the MPTrzCHO molecule calculated using the 6-311++G(d,p) and cc-pVDZ basis sets in the gas phase and water solvent environment.

crease in the electrostatic potential magnitude under solvent conditions suggests that the molecule may exhibit stronger electrostatic interaction capability in polar media. Overall, the MEP analyses demonstrate that the MPTrzCHO molecule possesses a highly polarized electrostatic structure and, particularly through the negative potential regions localized around the O and N atoms, exhibits a strong tendency toward metal coordination and intermolecular interactions.

Charge Analyses

APT, Hirshfeld, and NBO atomic charge analyses clearly reveal how the electron density within the molecule is distributed depending on the calculation method, basis set, and solvent environment, as well as which atoms emerge as potential interaction centers. The obtained charge values are presented in Table 3. At all calculation levels, the O1 and N4 atoms were found to carry significant negative charges, indicating that these atoms represent the main nucleophilic centers of the molecule. In particular, for the 6-311++G(d,p) basis set, the APT, Hirshfeld, and NBO charges of the O1 atom were calculated as -0.760 , -0.237 , and -0.499 in the gas phase, whereas these values shifted to -1.055 , -0.285 , and -0.565 in the water solvent environment. Similarly, in the cc-pVDZ basis set, the

O1 atom preserved its negative character and became more pronounced under solvent conditions. This result indicates that the polar solvent stabilizes the electron density around the carbonyl oxygen.

The N4 atom also exhibited high negative charge values at all calculation levels, especially in the APT and NBO analyses, demonstrating a pronounced nucleophilic character. In addition, the negative charge values observed for the N2 and N3 atoms indicate that the triazole ring generally forms an electron-rich region. Although the narrower charge distribution obtained from the Hirshfeld analysis is an expected result, the preservation of the negative character of the O1, N3, and N4 atoms under all calculation conditions suggests that the electron density around these centers is structurally stable. The NBO analysis reflected bonding characteristics and electron delocalization effects more clearly, particularly showing that the C9 atom carries high negative charge values. For the 6-311++G(d,p) basis set, the NBO charge of the C9 atom was calculated as -0.624 in the gas phase and -0.638 in the water solvent environment, whereas the corresponding values for the cc-pVDZ basis set were found to be -0.692 and -0.700 , respectively. These results indicate that the electron density localized on the C9 atom is associated with resonance and

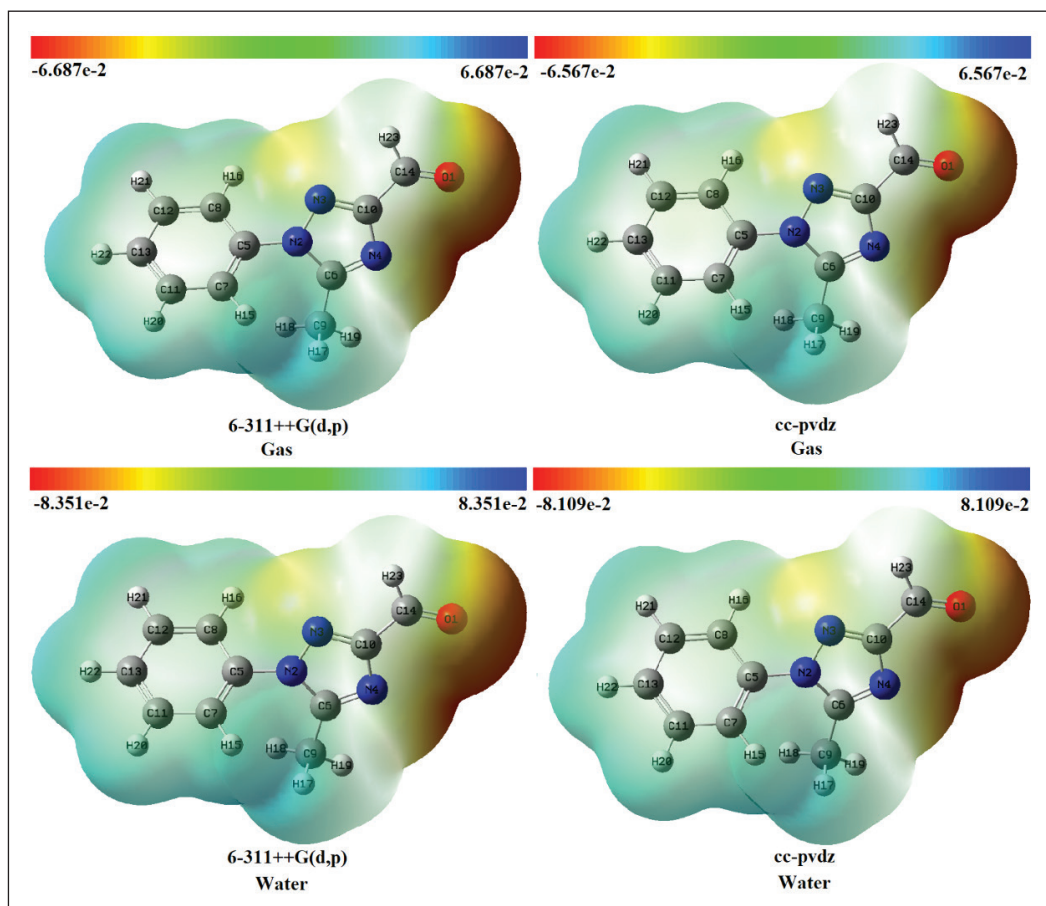


Figure 4. Molecular electrostatic potential (MEP) surface maps of the MPTrzCHO molecule calculated using the 6-311++G(d,p) and cc-pVDZ basis sets in the gas phase and water solvent environment.

conjugation interactions involving neighboring heteroatoms. In contrast, the C14 atom exhibited the highest positive charge values at all calculation levels, indicating that this center represents the most prominent electrophilic region within the molecule. The increase in positive charge density around the C14 atom under solvent conditions further suggests that the polar environment enhances intramolecular charge separation.

The obtained atomic charge distributions are also highly consistent with the MEP maps. In the MEP analyses, the most intense negative potential was concentrated around the O1 atom, whereas the positive potential was mainly localized in the C14 region, supporting the results obtained from the charge analyses. Furthermore, the electron-rich regions surrounding the nitrogen atoms suggest that these centers may act as hydrogen bond acceptors and electrostatic interaction

sites. Overall, the similar charge distributions obtained from different basis sets and water solvent environments demonstrate that the MPTrzCHO molecule possesses a highly polarized electronic structure and is prone to coordination, hydrogen bonding, and electrostatic interactions with biological targets, particularly through the O and N atoms.

Natural Bond Orbital (NBO) Analysis

Natural bond orbital analysis was utilized to demonstrate charge transfer and delocalization brought on by intra- and intermolecular interactions between bonds as well as other elements including stability, reactivity, and correlation between donor and acceptor (Dalal et al., 2023). Quantitatively analyzes bonding and anti-bonding interactions generated by second-order disturbance, quantifying the energy as $E^{(2)}$ (El-Laatef et al., 2023). The NBO study of the MPTrzCHO structure,

Table 3. APT, Hirshfeld, and NBO Charge Analyses of the MPTrzCHO Molecule Calculated Using the 6-311++G(d,p) and cc-pVDZ Basis Sets in the Gas Phase and Water Solvent Environment.

Atoms	6-311++G(d,p)						cc-pVDZ					
	Gas			Water			Gas			Water		
	APT	Hirshfeld	NBO	APT	Hirshfeld	NBO	APT	Hirshfeld	NBO	APT	Hirshfeld	NBO
O1	-0.760	-0.237	-0.499	-1.055	-0.285	-0.565	-0.704	-0.222	-0.504	-0.943	-0.265	-0.554
N2	-0.387	0.049	-0.230	-0.424	0.055	-0.211	-0.388	0.043	-0.233	-0.427	0.053	-0.217
N3	-0.108	-0.117	-0.269	-0.128	-0.135	-0.266	-0.099	-0.127	-0.298	-0.112	-0.120	-0.298
N4	-0.499	-0.182	-0.475	-0.649	-0.218	-0.508	-0.486	-0.185	-0.523	-0.623	-0.206	-0.551
C5	0.372	0.042	0.144	0.428	0.036	0.139	0.377	0.043	0.157	0.434	0.042	0.151
C6	0.442	0.104	0.416	0.581	0.111	0.442	0.440	0.100	0.457	0.572	0.113	0.480
C7	-0.097	-0.047	-0.209	-0.107	-0.033	-0.218	-0.097	-0.041	-0.238	-0.103	-0.043	-0.240
C8	-0.098	-0.040	-0.189	-0.107	-0.037	-0.204	-0.094	-0.036	-0.216	-0.097	-0.046	-0.229
C9	0.008	-0.072	-0.624	-0.023	-0.071	-0.638	0.014	-0.075	-0.692	-0.011	-0.070	-0.700
C10	-0.085	0.055	0.227	-0.147	0.043	0.225	-0.102	0.053	0.282	-0.173	0.050	0.278
C11	-0.017	-0.033	-0.190	-0.050	-0.028	-0.190	0.003	-0.032	-0.212	-0.018	-0.031	-0.211
C12	-0.004	-0.029	-0.187	-0.042	-0.029	-0.193	0.013	-0.029	-0.211	-0.013	-0.032	-0.214
C13	-0.049	-0.036	-0.195	-0.037	-0.029	-0.203	-0.049	-0.033	-0.221	-0.039	-0.036	-0.223
C14	1.005	0.123	0.391	1.372	0.130	0.400	0.977	0.127	0.382	1.289	0.128	0.387
H15	0.059	0.041	0.216	0.084	0.058	0.228	0.051	0.046	0.236	0.072	0.050	0.243
H16	0.077	0.043	0.230	0.087	0.052	0.239	0.073	0.048	0.253	0.078	0.042	0.257
H17	0.010	0.049	0.223	0.025	0.058	0.238	0.003	0.046	0.240	0.016	0.057	0.253
H18	0.020	0.047	0.224	0.036	0.052	0.238	0.016	0.042	0.243	0.030	0.055	0.253
H19	0.035	0.058	0.242	0.031	0.056	0.246	0.033	0.055	0.261	0.027	0.056	0.264
H20	0.037	0.047	0.211	0.051	0.055	0.221	0.025	0.047	0.234	0.034	0.054	0.242
H21	0.038	0.050	0.212	0.051	0.055	0.221	0.027	0.048	0.235	0.034	0.054	0.242
H22	0.042	0.045	0.211	0.055	0.054	0.218	0.030	0.047	0.234	0.037	0.050	0.238
H23	-0.040	0.041	0.120	-0.034	0.051	0.140	-0.063	0.034	0.136	-0.067	0.044	0.152

Table 4. Second-Order Perturbation Theory Analysis of Fock Matrix in NBO Corresponding to the Selected Charge Transfer Interactions of the Complex.

Donor	Acceptor	$E^{(2)}$ (kcal/mol) ^a	$\epsilon_i - \epsilon_j$ (a.u.) ^b	$F(i,j)$ (a.u.) ^c
$LP(1)(N_2)$	$\pi^*(N_4 - C_6)$	45.09	0.29	0.106
$\pi(N_4 - C_6)$	$\pi^*(N_3 - C_{10})$	30.93	0.31	0.092
$LP(1)(N_2)$	$\pi^*(N_3 - C_{10})$	27.76	0.28	0.080
$LP(2)(O_1)$	$\pi^*(C_{14} - H_{23})$	22.43	0.63	0.107
$\pi(C_8 - C_{12})$	$\pi^*(C_5 - C_7)$	21.60	0.27	0.069
$\pi(C_{11} - C_{13})$	$\pi^*(C_5 - C_7)$	21.12	0.27	0.069
$\pi(C_8 - C_{12})$	$\pi^*(C_{11} - C_{13})$	20.18	0.28	0.068
$\pi(C_{11} - C_{13})$	$\pi^*(C_5 - C_7)$	21.12	0.27	0.069
$\pi(C_{11} - C_{13})$	$\pi^*(C_8 - C_{12})$	19.98	0.28	0.068
$LP(2)(O_1)$	$\pi^*(C_{10} - C_{14})$	19.42	0.71	0.105
$\pi(C_5 - C_7)$	$\pi^*(C_8 - C_{12})$	19.19	0.30	0.068
$\pi(C_5 - C_7)$	$\pi^*(C_{11} - C_{13})$	19.19	0.30	0.067

σ : sigma bonds, LP: lone pairs, π^* : pi bonds

a $E^{(2)}$ means energy of hyper conjugative interactions.

b Energy difference between donor and acceptor i and j NBO orbitals.

c $F_{(i,j)}$ is the Fock matrix element between i and j NBO orbitals

shown in Table 4, revealed significant electron donor and acceptor orbitals with an interaction stabilization energy of $E^{(2)} \geq 15$ kcal/mol. As shown in Table 4, the most important interactions are the distinct $LP(N_2) \rightarrow \pi^*$ interactions, which reveal the strong electron donor character of the N2 atom and its effective participation in the conjugated system. On the other hand, the stability of the ligand is due to second perturbation energies associated with ligand hyperconjugation interactions, such as $LP(2)(O_1) \rightarrow \pi^*(C_{14} - H_{23})$.

The high stabilization energies appear to originate from $\pi \rightarrow \pi^*$ type donor-acceptor interactions, indicating extensive π -electron delocalization on the molecular framework. In particular, the 30.93 kcal/mol $E^{(2)}$ values associated with the N4-C6 and N3-C10 moieties clearly demonstrate a strong conjugation pathway within the heterocyclic skeleton. The strong intramolecular interactions of π electrons in the C-C and anti C-C bonds of the ring contribute to the stabilization of the ring.

NCI RDG Analysis

Molecular interactions contribute to the stability of the molecular structure. Both intramolecular and weak intermolecular interactions can be discerned through reduced density gradient (RDG) analysis, which is predicated on the examination of non-covalent interactions (NCI) within the system (Ramalingam et al., 2022). The RDG approach illustrates noncovalent interactions (NCIs) inside the examined system, including van der Waals forces, attractive bonds, and steric interactions, with 2D and 3D representations, as depicted in Figure 5. As illustrated in Figure 5, steric effects (repulsive interactions) are denoted by dotted red colors. The ring centers of the phenyl

and triazole rings exhibited the highest steric repulsive effects in the molecule. The π - π stacking interactions (Ramalingam et al., 2022) and the red region in the RDG plot are between 0.02 and 0.05. Also, the van der Waals interactions exhibit values of λ_2 and density that are nearly zero ($\rho \approx 0$, $\lambda_2 \approx 0$) (Gholivand et al. 2022). The presence of a weak non-covalent H...H interaction is indicated by the green color.

Molecular Docking

Molecular docking is a theoretical simulation method considered a useful tool in drug development and design (Chen et al., 2025). 1,2,4-Triazole scaffolds are widely used in medicinal chemistry because they can interact with biological targets such as enzymes and receptors and are found in many drug molecules. Also, studies have shown that some 1,2,4-triazole derivatives have shown promising effects in pancreatic cancer cell lines (Šermukšnytė et al., 2022). In our study, we evaluated the effect of the title compound on pancreatic cancer using an in silico method. In both healthy and diseased states, binding between vascular endothelial growth factor (VEGF) and its associated receptors is an essential stage in tumor spread and resistance (Mohamed et al., 2024). The FDA has authorized VEGFR inhibitors to treat a variety of malignancies (Wang et al., 2024), and 69% of pancreatic tumors have been shown to overexpress VEGFR-2. Thus, one possible therapy strategy for pancreatic cancer is to target VEGFR-2 (Doi et al., 2010). The docking of the ligand to the active sites of VEGFR-2 (PDB: 4ASD) was achieved using the molecular docking method. In the simulation, water molecules were excluded, and missing hydrogen atoms in the protein were added using Autodock

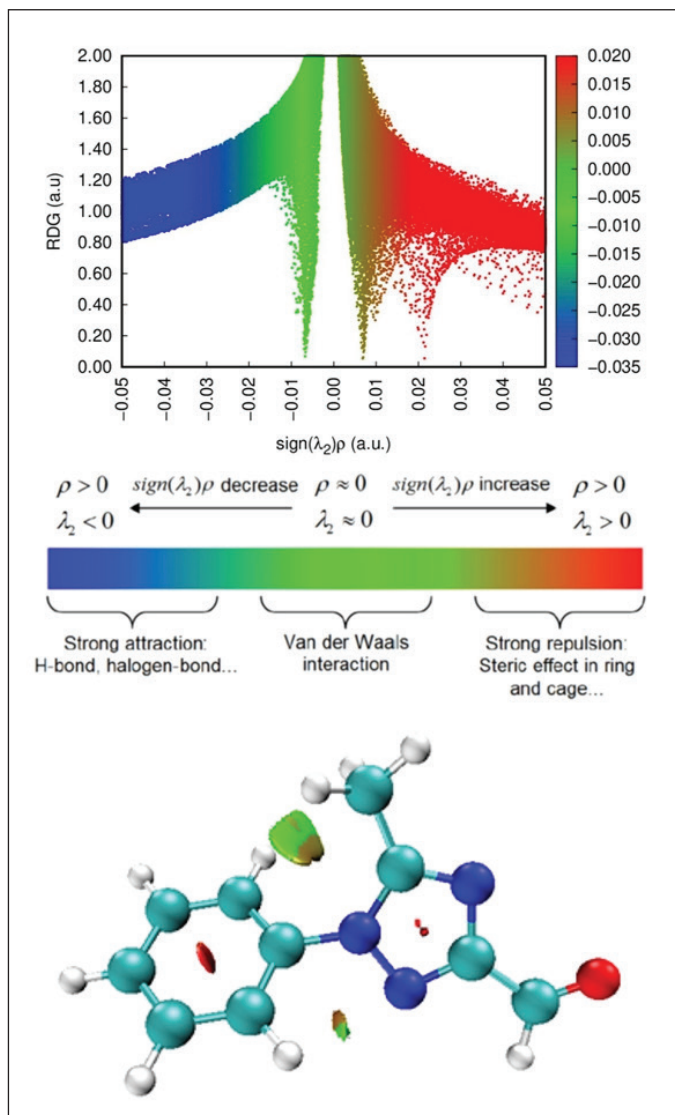


Figure 5. The 3D and 2D coloured scattered plot and RDG isosurface density plot of compound.

Tools. PDB structures of the ligand were generated in pdb format based on Gaussian optimized structures. Site map analysis was performed to determine the x, y, and z coordinates of the grid box for the selection of suitable binding or active sites for the VEGFR-2 enzyme. In addition, Biovia Discovery Studio was used to visualize the interactions between the protein and ligand (Figure 6).

The interactions resulting from the binding of the ligand to the active site of VEGFR-2 kinase are shown in Figure 6. To assess the efficiency of the coupling results between the chemical and the chosen protein, we compared the protein-ligand interaction results of a previously investigated (Dawood et al., 2020) sorafenib as standard VEGFR-2 inhibitor to our findings.

Molecular docking analyses, an affinity value of less than or near 5 kcal/mol indicates insignificant binding, while a value

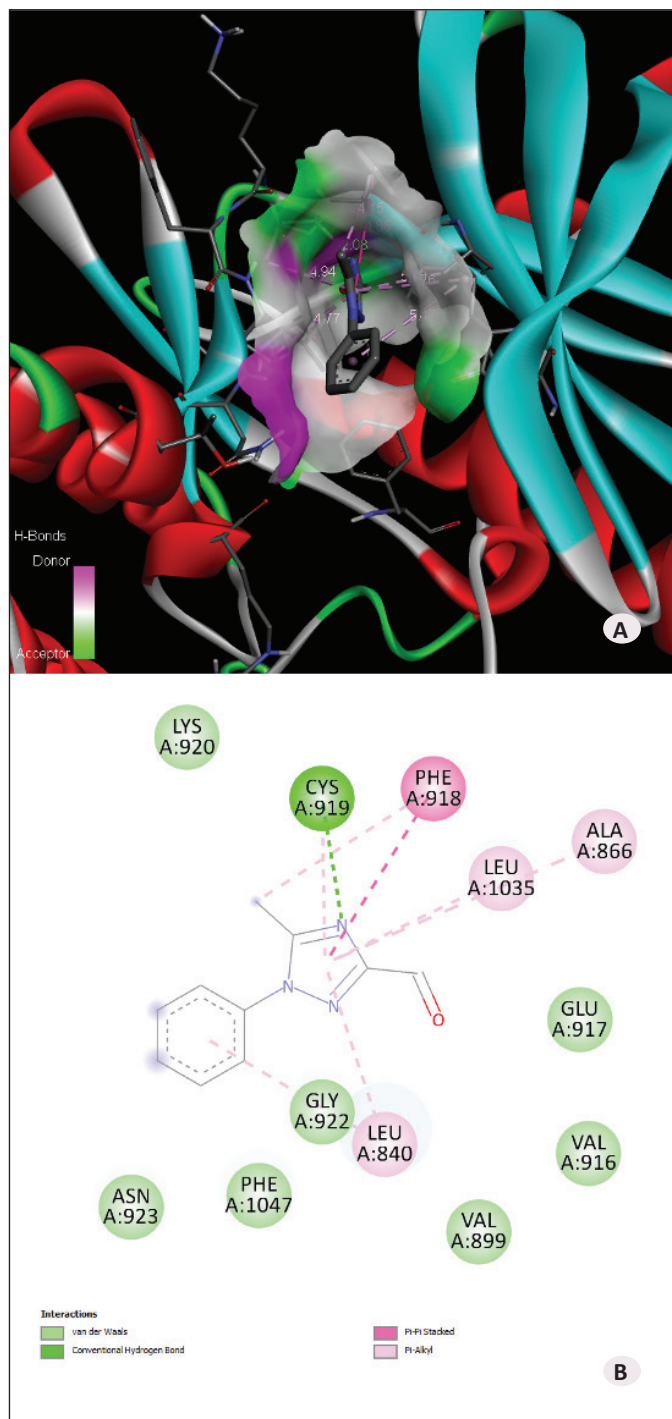


Figure 6. 3D (a) and 2D (b) Binding-interaction diagrams of ligand with the VEGFR-2 active site.

greater than 5 kcal/mol indicates effective binding, according to the software used (Çelik et al.; 2024). This interaction resulted in a binding energy of -6.32 kcal/mol at root mean square deviation (RMSD) value equal 22.60. The compound MPTrzCHO exhibits good binding energy due to ligand-enzyme interactions; however, it showed lower interaction energies

Table 5. Protox III Parameters of MPTrzCHO Compound.

Toxicity Class	LD ₅₀ (mg/kg)	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
IV	2000	Active (0.56)	Active (0.69)	Inactive (0.99)	Active (0.50)	Inactive (0.84)

- Class I: fatal if swallowed (LD50≤5)
- Class II: fatal if swallowed (5< LD50≤50)
- Class III: toxic if swallowed (50< LD50≤300)
- Class IV: harmful if swallowed (300< LD50≤2000)
- Class V: may be harmful if swallowed (2000< LD50≤5000)
- Class VI: non-toxic (LD50>5000)

compared to the sorafenib (-8.95 kcal/mol) (Dawood et al., 2020), suggesting that hydrogen bonding may play a minimal role in its interaction with the enzyme (Ullah et al. 2025).

The H atom is bonded to the nitrogen atom of the Cys919 amino acid in VEGFR-2, a hydrogen bond between the nitrogen atom in the triazole ring with a bond distance of 2.08 Å. On the other hand, it interacts with the hydrophobic side chains of the VEGFR-2 active site Leu840, Phe918, Asn923, Leu1035, and Phe1047 amino acids via hydrophobic interactions (see Figure 6).

Toxicity Prediction of the Compound

ProTox 3.0 predictions (Banerjee et al. 2024) indicate that the MPTrzCHO compound has a profile that suggests it may be detrimental when swallowed for the quaternary toxicity endpoint. The compound’s organ toxicity (carcinogenicity) is assessed toxicologically with a confidence score of 0.69. The results indicate that the chemical is carcinogenic, mutagenic, and hepatotoxic but has no impact on immunotoxicity or cytotoxicity (Table 5). While the absence of projected cytotoxic and immunotoxic effects is a positive discovery, it does not provide proof of overall safety. The compound’s potential biological application would be limited by its predicted hepatotoxic, carcinogenic, and mutagenic effects. As a result, MPTrzCHO’s safety profile may be substantiated by detailed in vitro and in vivo toxicological investigations, as well as extensive experimental confirmation of its biological compatibility.

CONCLUSION and SUGGESTIONS

In this study, the electronic structure and biological interaction potential of the MPTrzCHO molecule were comprehensively evaluated using DFT and molecular docking approaches. The obtained results showed that the triazole ring and carbonyl group establish effective electronic communication within the molecule, contributing significantly to its structural stability and polarized electronic character. Comparative calculations performed using different basis sets and solvent environments demonstrated that the calculated electronic parameters and orbital distributions are highly consistent and computationally reliable. The relatively high HOMO–LUMO energy gap indicates that the molecule possesses a generally stable electronic structure, while the localization of charge density around heteroatomic centers suggests its susceptibility toward selective intermolecular interactions. Frontier molecular orbital analyses revealed that the electron-donating regions are main-

ly concentrated on the nitrogen atoms of the triazole ring, whereas the electron-accepting character is predominantly localized around the carbonyl group. Similarly, MEP and atomic charge analyses confirmed that the O and N atoms represent the main nucleophilic interaction centers of the molecule. In addition, the enhancement of electrostatic polarization under water solvent conditions suggests that the molecule may exhibit stronger interaction capability in polar biological environments. NBO and NCI analyses further demonstrated that the molecular stability arises not only from covalent bonding but also from π -electron delocalization and weak non-covalent interactions.

Molecular docking studies showed that MPTrzCHO can bind effectively within the active site of the VEGFR-2 enzyme through hydrogen bonding and hydrophobic interactions. In particular, the interactions involving the nitrogen atoms of the triazole ring appear to contribute significantly to binding stability. These findings suggest that MPTrzCHO may be considered a potential scaffold for the design of biologically active compounds targeting VEGFR-2-related anticancer mechanisms. Furthermore, in silico toxicity predictions indicated inactive cytotoxicity and immunotoxicity profiles; however, potential hepatotoxic, carcinogenic, and mutagenic effects were also predicted. Therefore, although the molecule demonstrates promising electronic and biological interaction characteristics, further in vitro and in vivo studies are required to more accurately evaluate its biological compatibility and therapeutic potential.

Ethics Committee Approval: Ethics committee approval was not required for this study because the research was entirely computational and did not involve human participants, human-derived materials, or experimental animals.

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