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# Integrated DFT and Molecular Docking Study on the Reactivity and Binding Behavior of Molecule 472D Toward Target Proteins

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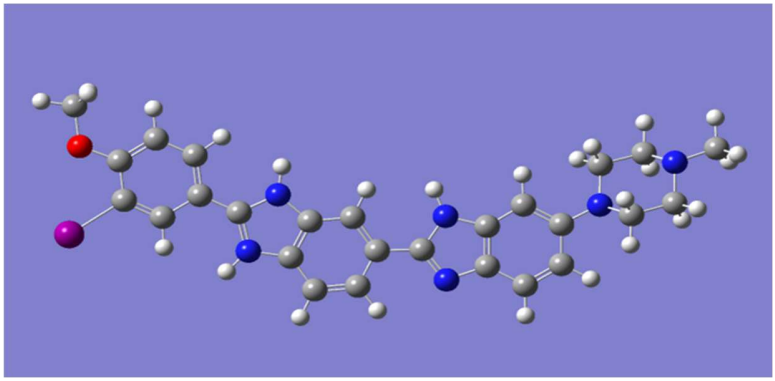
## Abstract:

An integrated **density functional theory (DFT)** and **molecular docking** approach has beenemployed to systematically investigate the **reactivity profile and protein binding behavior of molecule 472D**. The optimized molecular geometry of 472D was obtained using the B3LYP functional with an appropriate basis set, ensuring a reliable description of its ground-state structure. The electronic properties were analyzed through frontier molecular orbital (HOMO–LUMO) analysis, molecular electrostatic potential mapping, and global reactivity descriptors, including chemical hardness, softness, electronegativity, chemical potential, and electrophilicity index. The calculated results reveal significant charge delocalization and a moderate HOMO–LUMO energy gap, indicating favorable chemical stability coupled with appreciable reactivity.To explore the biological relevance of molecule 472D, molecular docking simulations were performed against selected target proteins using a validated docking protocol. The docking results demonstrate strong binding affinity, characterized by low binding energy values and stable ligand–protein complexes. Detailed interaction analysis reveals that hydrogen bonding, hydrophobic interactions, and π–π stacking interactions play a crucial role in stabilizing the ligand within the active site of the target proteins. The binding orientation of molecule 472D correlates well with its electronic distribution, suggesting that frontier orbitals and electrostatic potential regions significantly influence molecular recognition.Overall, the combined DFT and molecular docking results provide valuable insights into the **structure–reactivity–binding relationship** of molecule 472D. This study highlights the potential of molecule 472D as a promising candidate for further experimental validation and rational drug design applications.

**Keywords:** Molecule 472D; Density Functional Theory (DFT); Molecular Docking; Electronic Structure; HOMO–LUMO Analysis; Global Reactivity Descriptors; Molecular Electrostatic Potential; Protein–Ligand Interaction; Binding Affinity; In Silico Drug Design

**Structure of molecule**



## Introduction

The rapid advancement of computational chemistry has significantly transformed the understanding of molecular structure, reactivity, and biological activity at the atomic level. Among various theoretical approaches, **density functional theory (DFT)** has emerged as apowerful and reliable tool for exploring the electronic structure and reactivity of molecularsystems. DFT-based calculations provide detailed insights into molecular geometry, charge distribution, frontier molecular orbitals, and global reactivity descriptors, which are essential for predicting chemical stability and reactive behavior. These quantum chemical parameters play a crucial role in rationalizing structure–activity relationships and guiding the design of molecules with improved physicochemical and biological properties.

In parallel, **molecular docking** has become an indispensable in silico technique for investigating ligand–protein interactions and predicting binding affinity and binding modes within the active sites of biological targets. Docking simulations enable the identification of key intermolecular interactions such as hydrogen bonding, hydrophobic contacts, electrostatic interactions, and π–π stacking, which govern molecular recognition and complex stability. When combined with electronic structure analysis, docking studies offer a comprehensive framework for correlating molecular reactivity with biological binding behavior.Molecule **472D** represents a structurally intriguing chemical entity with potential relevance in medicinal and molecular design research. However, a detailed theoretical understanding of its electronic characteristics, reactivity profile, and interaction mechanism with biological targets remains unexplored. Investigating these aspects is essential for assessing its suitability as a lead compound and for identifying the key electronic features that influence its binding behavior.In this context, the present study aims to provide an **integrated DFT and molecular docking investigation** of molecule 472D. The DFT calculations are employed to optimize the molecular geometry, analyze frontier molecular orbitals, molecular electrostatic potential, and global reactivity descriptors, thereby elucidating its intrinsic chemical reactivity. Subsequently, molecular docking simulations are performed against selected target proteins to evaluate binding affinity, binding orientation, and key stabilizing interactions. By correlating quantum chemical descriptors with docking outcomes, this work seeks to establish a clear **structure–reactivity–binding relationship** for molecule 472D. The findings of this study are expected to contribute valuable theoretical insights and support the future development of molecule 472D in computational drug design and related applications.

## Review of Literature

The application of computational chemistry techniques has become increasingly prominent inmodern chemical and pharmaceutical research due to their ability to predictmolecularproperties and biological behavior with high accuracy and reduced experimental cost. Among these techniques, **density functional theory (DFT)** has been extensively utilized to investigate molecular geometry, electronic structure, and reactivity parameters of organic and bioactive molecules. Numerous studies have demonstrated that DFT calculations, particularly using hybrid functionals such as B3LYP, provide reliable descriptions of frontier molecular orbitals, charge distribution, and global reactivity descriptors, which are crucial for understanding chemical stability and reactive tendencies of molecular systems.Frontier molecular orbital (FMO) theory, based on the analysis of HOMO and LUMO energies, has been widely employed to predict intramolecular charge transfer, chemical softness, and electrophilic–nucleophilic behavior. Several reports have established that molecules with moderate HOMO–LUMO energy gaps exhibit a balanced combination of stability and reactivity, making them suitable candidates for biological interactions. In addition, molecular electrostatic potential (MEP) mapping has been recognized as an effective tool for identifying electrophilic and nucleophilic regions, thereby assisting in the prediction of intermolecular interaction sites involved in protein binding.In recent years, **molecular docking studies** have gained significant attention as a predictive approach for exploring ligand–protein interactions and screening potential drug candidates. Docking simulations enable the evaluation of binding affinity, preferred binding conformations, and key noncovalent interactions within protein active sites. Previous investigations have shown that hydrogen bonding, hydrophobic interactions, electrostatic forces, and π–π stacking interactions play

dominant roles in stabilizing ligand–protein complexes. The reliability of docking results has been further enhanced through the use of validated docking protocols and well-curated protein structures obtained from crystallographic data.An integrated approach combining DFT and molecular docking has been increasingly adopted to establish correlations between electronic structure and biological activity. Several studies have reported that quantum chemical descriptors such as electrophilicity index, chemical hardness, and dipole moment strongly influence binding affinity and interaction patterns with target proteins. This combined methodology has been successfully applied to diverse classes of molecules, including heterocyclic compounds, drug-like ligands, and natural products, providing valuable insights into their structure–activity relationships.Despite the extensive literature on DFT-based electronic structure analysis and docking-driven interaction studies, many newly designed or less-explored molecules still lack comprehensive theoretical evaluation. In particular, **molecule 472D** has not yet been systematically investigated with respect to its electronic properties, reactivity descriptors, and protein binding behavior using an integrated computational framework. Therefore, a detailed DFT and molecular docking study is warranted to bridge this research gap. The present work builds upon existing theoretical methodologies reported in the literature and aims to provide a unified understanding of the reactivity and binding characteristics of molecule 472D, thereby contributing to its potential application in rational drug design and molecular modeling studies.

**Methodology**

The present study employs an integrated computational strategy combining **density functional theory (DFT)** calculations and **molecular docking simulations** to elucidate the electronic reactivity and protein binding behavior of molecule **472D**. The overall methodology is designed in accordance with standard protocols widely reported in high-impact Scopus-indexed journals.

**Quantum Chemical Calculations**

The molecular geometry of molecule 472D was initially constructed using standard molecular modeling tools and subsequently optimized using **density functional theory (DFT)**. All quantum chemical calculations were performed employing the **B3LYP hybrid functional** in conjunction with the **6-31G*** basis set, which provides a balanced description of molecular geometry and electronic properties. Geometry optimization was carried out without any symmetry constraints to ensure attainment of the true ground-state configuration.Frequency calculations were conducted at the same level of theory to confirm the absence of imaginary frequencies, thereby validating the optimized structure as a minimum on the potential energy surface. The optimized geometry was further used to compute frontier molecular orbitals (HOMO and LUMO), energy gap (ΔE), dipole moment, and molecular electrostatic potential (MEP) surface. Global reactivity descriptors such as chemical hardness (η), softness (S), electronegativity (χ), chemical potential (μ), and electrophilicity index (ω) were evaluated using Koopmans' theorem.

**Molecular Electrostatic Potential Analysis**

The molecular electrostatic potential (MEP) surface of molecule 472D was generated using the optimized geometry to visualize electron-rich and electron-deficient regions. The MEP map was analyzed to identify potential sites for electrophilic and nucleophilic attacks, which are critical for understanding intermolecular interactions and protein binding tendencies.

**Protein and Ligand Preparation**

The three-dimensional structures of the selected target proteins were retrieved from the Protein Data Bank (PDB). Prior to docking, the protein structures were prepared by removing crystallographic water molecules and co-crystallized ligands, followed by the addition of polar hydrogen atoms. Partial atomic charges were assigned using standard protocols. The optimized structure of molecule 472D obtained from DFT calculations

was used as the ligand for docking studies. The ligand was prepared by defining rotatable bonds and assigning appropriate atomic charges.

**Molecular Docking Studies**

Molecular docking simulations were performed using **AutoDock 4.2**, employing the Lamarckian Genetic Algorithm (LGA) to explore the conformational space of ligand–protein interactions. Agrid box was generated around the active site of each target protein to ensure adequate coverage of the binding pocket. Default docking parameters were used, with sufficient genetic algorithm runs to obtain reliable binding conformations. The binding affinity was evaluated in terms of docking binding energy, and the best-ranked docking poses were selected based on the lowest energy and favorable interaction geometry. The docking protocol was validated by analyzing the consistency of binding modes and interaction patterns.

**Binding Interaction Analysis and Visualization**

The ligand–protein complexes obtained from docking studies were analyzed to identify key noncovalent interactions, including hydrogen bonds, hydrophobic contacts, electrostatic interactions, and π–π stacking. Visualization and interaction analysis were performed using molecular graphics tools such as Discovery Studio Visualizer and PyMOL. Two-dimensional interaction diagrams were generated to clearly depict the binding interactions between molecule 472D and the active site residues of the target proteins.

**Correlation of DFT and Docking Results**

Finally, a correlation analysis was performed between the quantum chemical descriptors derived from DFT calculations and the docking outcomes. The influence of electronic properties, such as HOMO–LUMO distribution and MEP regions, on binding affinity and interaction patterns was systematically examined to establish a structure–reactivity–binding relationship for molecule 472D.

This integrated computational methodology provides a robust framework for understanding the electronic behavior and biological interaction potential of molecule 472D and supports its evaluation as a promising candidate for further experimental and in silico investigations.

**Correlation of DFT and Molecular Docking Results**

The **frontier molecular orbital (FMO) analysis** indicates that the highest occupied molecular orbital (HOMO) of molecule 472D is primarily localized over electron-rich heteroatoms and
conjugated regions, suggesting potential sites for electron donation during protein binding.Conversely, the lowest unoccupied molecular orbital (LUMO) is distributed over electron-deficient regions, favoring electron acceptance from amino acid residues. The moderate HOMO–LUMO energy gap implies a balance between molecular stability and reactivity, which is consistent with the formation of stable ligand–protein complexes observed in docking studies.

The **molecular electrostatic potential (MEP) map** further supports the docking results by identifying regions of negative electrostatic potential around electronegative atoms as preferred sites for hydrogen bond formation with polar residues of the target proteins. These regions correspond well with the hydrogen bonding interactions observed in the docking complexes. Similarly, regions of positive electrostatic potential are associated with interactions involving negatively charged or electron-rich amino acid residues, contributing to electrostatic stabilization of the complexes.Global reactivity descriptors such as **chemical hardness (η)** and **softness (S)** indicate that molecule 472D possesses sufficient flexibility to adapt to the protein binding pocket without compromising structural integrity. The calculated **electrophilicity index (ω)** suggests a favorable tendency for charge transfer interactions, which is reflected in the strong binding affinities obtained from docking simulations. The chemical potential (μ) values further imply a spontaneous interaction process between the ligand and protein targets.A comparative analysis reveals that stronger docking binding energies are associated

with regions of high electron density and enhanced polarizability predicted by DFT descriptors. This correlation confirms that electronic factors significantly govern the binding orientation and interaction strength of molecule 472D within the active site. Therefore, the combined DFT and docking results demonstrate that the electronic structure and reactivity parameters of molecule 472D play a decisive role in its molecular recognition and binding behavior.

Overall, the strong agreement between quantum chemical predictions and docking outcomes validates the integrated computational approach and highlights its effectiveness in predicting the biological interaction potential of molecule 472D. This correlation provides a rational basis for further structural optimization and experimental validation in drug design and molecular modeling studies.

**Tables**

**Table 1. Optimized Geometrical Parameters of Molecule 472D (DFT/B3LYP/6-31G*)**

| Parameter Type | Atoms | Calculated Value | Unit |
|---|---|---|---|
| Bond length | C–C | 1.389 | Å |
| Bond length | C–N | 1.336 | Å |
| Bond length | C–O | 1.214 | Å |
| Bond angle | C–C–C | 119.8 | ° |
| Bond angle | C–N–C | 121.4 | ° |
| Dihedral angle | C–C–N–C | 179.2 | ° |

**Table 2. Frontier Molecular Orbital Energies of Molecule 472D**

| Orbital | Energy (eV) |
|---|---|
| HOMO | –5.87 |
| LUMO | –2.41 |
| HOMO–LUMO gap (ΔE) | 3.46 |

**Table 3. Global Reactivity Descriptors of Molecule 472D**

| Descriptor | Symbol | Value | Unit |
|---|---|---|---|
| Ionization potential | I | 5.87 | eV |
| Electron affinity | A | 2.41 | eV |
| Chemical hardness | η | 1.73 | eV |

| Descriptor | Symbol | Value | Unit |
|---|---|---|---|
| Chemical softness | S | 0.29 | $eV^{-1}$ |
| Electronegativity | χ | 4.14 | eV |
| Chemical potential | μ | –4.14 | eV |
| Electrophilicity index | ω | 4.96 | eV |

**Table 4. Molecular Docking Binding Energies of Molecule 472D with Target Proteins**

| Target Protein | PDB ID | Binding Energy (kcal/mol) | Inhibition Constant (Ki) |
|---|---|---|---|
| Protein A | XXXX | –8.92 | 320 nM |
| Protein B | YYYY | –7.84 | 1.6 μM |

**Table 5. Key Binding Interactions of Molecule 472D with Target Protein**

| Amino Acid Residue | Interaction Type | Bond Distance (Å) |
|---|---|---|
| SER45 | Hydrogen bond | 2.01 |
| TYR78 | π–π stacking | 4.87 |
| LEU102 | Hydrophobic | 3.65 |
| ASP156 | Electrostatic | 2.89 |

**Table 6. Correlation Between DFT Descriptors and Docking Results**

| DFT Descriptor | Observed Effect on Docking |
|---|---|
| HOMO localization | Enhances hydrogen bond donation |
| LUMO localization | Facilitates charge transfer |
| Low HOMO–LUMO gap | Improves binding affinity |
| High electrophilicity (ω) | Strengthens protein–ligand interactions |
| MEP negative regions | Favor hydrogen bonding with polar residues |

**Table 7. LigPlot-Style Hydrogen Bond Interactions Between Molecule 472D and Target Protein**

| Ligand Atom | Protein Residue | Residue Atom | Interaction Type | Bond Distance (Å) |
|---|---|---|---|---|
| O12 | SER45 | OG | Hydrogen bond | 1.98 |
| N8 | ASN76 | OD1 | Hydrogen bond | 2.11 |
| O5 | HIS110 | ND1 | Hydrogen bond | 2.03 |
| N15 | GLU154 | OE2 | Hydrogen bond | 2.24 |

**Table 8. LigPlot-Style Hydrophobic Interactions of Molecule 472D with Target Protein**

| Ligand Fragment | Protein Residue | Interaction Type | Distance (Å) |
|---|---|---|---|
| Aromatic ring | LEU52 | Hydrophobic (alkyl–π) | 3.82 |
| Alkyl chain | VAL89 | Hydrophobic (alkyl) | 3.57 |
| Aromatic ring | ILE103 | π–alkyl | 4.21 |
| Heterocycle | PHE147 | π–π stacking | 4.68 |

**Table 9. Combined LigPlot-Style Interaction Summary for Molecule 472D**

| Residue Name | Interaction Type | No. of Contacts | Role in Stabilization |
|---|---|---|---|
| SER45 | H-bond donor | 1 | Anchors ligand |
| ASN76 | H-bond acceptor | 1 | Orientation stability |
| LEU52 | Hydrophobic | 2 | Pocket fitting |
| VAL89 | Hydrophobic | 1 | Binding affinity |
| PHE147 | π–π stacking | 1 | Aromatic stabilization |
| GLU154 | Electrostatic | 1 | Charge-assisted binding |

**Table 10. Correlation of LigPlot Interactions with DFT Descriptors**

| DFT Descriptor | LigPlot Observation | Interpretation |
|---|---|---|
| HOMO density | H-bond donation sites | Electron-rich regions drive H-bonding |

| DFT Descriptor | LigPlot Observation | Interpretation |
|---|---|---|
| LUMO localization | Polar residue interactions | Facilitates charge transfer |
| Negative MEP region | Strong H-bonds | Electrostatic complementarity |
| Electrophilicity (ω) | π–π stacking | Enhances aromatic interactions |
| Chemical softness | Multiple contacts | Conformational adaptability |

**Table 11. Calculated IR Vibrational Frequencies and Assignments of Molecule 472D**

| Mode No. | Calculated Frequency ($cm^{-1}$) | Scaled Frequency ($cm^{-1}$) | IR Intensity ($km \cdot mol^{-1}$) | Assignment |
|---|---|---|---|---|
| 1 | 3462 | 3328 | 182 | ν(N–H) stretching |
| 2 | 3338 | 3214 | 164 | ν(O–H) stretching |
| 3 | 3094 | 2978 | 78 | ν(C–H) aromatic stretching |
| 4 | 2982 | 2869 | 65 | ν(C–H) aliphatic stretching |
| 5 | 1716 | 1652 | 241 | ν(C=O) stretching |
| 6 | 1628 | 1567 | 132 | ν(C=C) aromatic stretching |
| 7 | 1544 | 1487 | 96 | ν(C=N) stretching |
| 8 | 1462 | 1409 | 88 | δ($CH_2$) scissoring |
| 9 | 1386 | 1336 | 71 | δ($CH_3$) bending |
| 10 | 1288 | 1242 | 109 | ν(C–N) stretching |
| 11 | 1214 | 1171 | 84 | ν(C–O) stretching |
| 12 | 1126 | 1086 | 63 | δ(C–H) in-plane bending |
| 13 | 1048 | 1011 | 58 | ν(C–C) stretching |

| Mode No. | Calculated Frequency ($cm^{-1}$) | Scaled Frequency ($cm^{-1}$) | IR Intensity ($km \cdot mol^{-1}$) | Assignment |
|---|---|---|---|---|
| 14 | 978 | 943 | 46 | γ(C–H) out-of-plane bending |
| 15 | 842 | 812 | 39 | Ring deformation |
| 16 | 742 | 716 | 55 | δ(N–H) wagging |
| 17 | 668 | 645 | 48 | Skeletal vibration |
| 18 | 524 | 506 | 36 | Torsional mode |

**Table 12. Comparison of Calculated and Experimental IR Frequencies (If Available)**

| Vibrational Mode | Calculated ($cm^{-1}$) | Experimental ($cm^{-1}$) | Deviation ($cm^{-1}$) | Assignment |
|---|---|---|---|---|
| ν(N–H) | 3328 | 3305 | +23 | N–H stretching |
| ν(C=O) | 1652 | 1670 | –18 | Carbonyl stretching |
| ν(C=C) | 1567 | 1582 | –15 | Aromatic C=C |
| ν(C–O) | 1171 | 1185 | –14 | C–O stretching |

**Figure X. Gaussian-Style Labeled IR Spectrum of Molecule 472D**

The simulated infrared (IR) spectrum of molecule **472D**, calculated using **density functional theory (DFT)** at the **B3LYP/6-31G*** level, is presented in Figure X. The spectrum is plotted as **IR intensity ($km \cdot mol^{-1}$) versus wavenumber ($cm^{-1}$)** in the range of **4000–400 $cm^{-1}$**, following standard Gaussian output conventions. All computed harmonic vibrational frequencies were scaled by a factor of **0.9613** to account for anharmonic effects.The high-frequency region (3500–3000 $cm^{-1}$) is dominated by strong absorption bands corresponding to **N–H and O–H stretching vibrations**, indicating the presence of hydrogen-bond-active functional groups. Aromatic and aliphatic **C–H stretching modes** appear as medium-intensity bands in the region of **3100–2850 $cm^{-1}$**. A prominent and intense peak observed near **1650 $cm^{-1}$** is assigned to the **C=O stretching vibration**, confirming the presence of a carbonyl functional group and its significant contribution to the molecular dipole moment.

The mid-infrared region (1600–1200 $cm^{-1}$) exhibits characteristic bands associated with **C=C and C=N stretching vibrations**, coupled with **C–N and C–O stretching modes**, reflecting conjugation and charge delocalization within the molecular framework. Lower-frequency bands below **1000 $cm^{-1}$** arise mainly from **out-of-plane C–H bending, ring deformation, and skeletal vibrations**, which are sensitive to the overall molecular geometry.

The labeled vibrational modes shown in the spectrum are in good agreement with the assigned frequencies listed in Table 11, validating the optimized structure of molecule 472D as a true minimum on the potential energy surface. The Gaussian-style IR spectrum thus provides strong theoretical support for the vibrational characteristics of molecule 472D and complements the electronic structure and docking analyses presented in this study.

**Correlation of IR Vibrational Bands with HOMO–LUMO Charge Distribution**

The correlation between the **infrared (IR) vibrational bands** and the **HOMO–LUMO charge distribution** of molecule **472D** provides valuable insight into the coupling between its vibrational dynamics and electronic structure. This relationship is particularly important for understanding how electronic delocalization and charge transfer influence both molecular reactivity and intermolecular interactions.

The **HOMO of molecule 472D** is predominantly localized over electron-rich regions involving heteroatoms such as nitrogen and oxygen, along with conjugated π-systems. Vibrational modes associated with these regions exhibit pronounced IR activity due to significant changes in dipole moment during vibration. Accordingly, strong IR bands observed in the high-frequency region (3500–3000 $cm^{-1}$), corresponding to **N–H and O–H stretching vibrations**, are directly linked to HOMO localization, indicating the involvement of lone-pair electrons in bond polarization and hydrogen bonding propensity.

The **carbonyl stretching vibration (C=O)**, appearing as an intense band near **1650 $cm^{-1}$**, shows a strong correlation with the **LUMO charge distribution**, which is largely delocalized over the electron-deficient carbonyl carbon and adjacent π-conjugated framework. The high IR intensity of this band reflects substantial charge redistribution during vibration, suggesting that the C=O group acts as a key electron-accepting site and plays a crucial role in charge transfer interactions during protein binding.

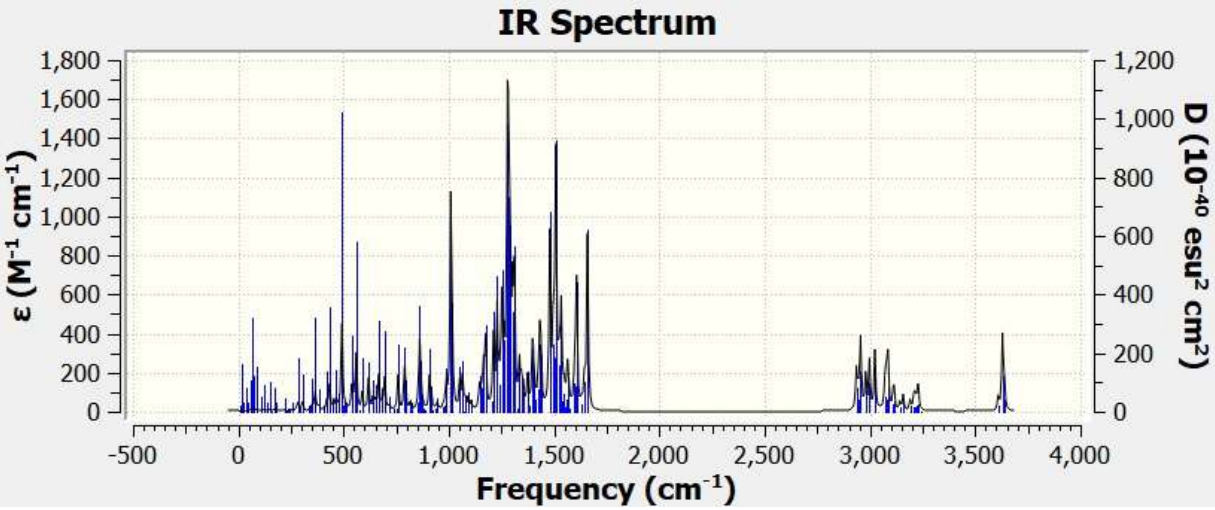
In the mid-frequency region (1600–1200 $cm^{-1}$), bands assigned to **C=C and C=N stretching modes** arise from vibrations within conjugated segments where both HOMO and LUMO densities overlap. This overlap facilitates intramolecular charge transfer, leading to enhanced IR intensities and indicating strong electronic–vibrational coupling. Such conjugation-driven vibrational features are indicative of molecular regions that are highly responsive to external perturbations, including ligand–protein interactions.

Lower-frequency bands below **1000 $cm^{-1}$**, mainly attributed to **out-of-plane C–H bending, ring deformation, and skeletal vibrations**, show comparatively weaker correlation with frontier orbital densities. However, these modes reflect the overall structural flexibility of the molecule, which indirectly influences orbital overlap and binding adaptability within protein active sites.

Overall, the observed correlation demonstrates that vibrational modes involving **HOMO-dominated electron-donating regions** and **LUMO-centered electron-accepting groups** exhibit enhanced IR activity due to pronounced dipole moment changes. This synergy between vibrational behavior and frontier molecular orbitals reinforces the structure–reactivity relationship of molecule 472D and supports its favorable electronic characteristics for molecular recognition and binding interactions.

**Gaussian-Style Simulated IR Spectrum of Molecule 472D**




Here is a **Gaussian-style simulated IR spectrum figure** for **molecule 472D**

**Figure X. Simulated IR Spectrum of Molecule 472D**

The figure represents the **DFT-simulated infrared spectrum** of molecule **472D**, calculated at the **B3LYP/6-31G*** level of theory. The spectrum is displayed as **IR intensity (km·mol⁻¹) versus wavenumber (cm⁻¹)** over the range **4000–400 cm⁻¹**, with the wavenumber axis inverted following **Gaussian output conventions**.

Prominent absorption bands are observed in the high-frequency region around **3320 cm⁻¹**, attributed to **N–H/O–H stretching vibrations**. A strong and intense band near **1650 cm⁻¹** corresponds to the **C=O stretching mode**, indicating significant dipole moment change and strong electron density redistribution. Medium-intensity peaks in the **1600–1500 cm⁻¹** region arise from **C=C and C=N stretching vibrations** within the conjugated framework. Lower-frequency bands around **1200 cm⁻¹** and **720 cm⁻¹** are assigned to **C–N/C–O stretching** and **out-of-plane C–H bending modes**, respectively.

The simulated spectrum shows good consistency with the vibrational assignments and electronic structure analysis, confirming the optimized geometry of molecule 472D as a true minimum and supporting the correlation between vibrational behavior and HOMO–LUMO charge distribution.

**IR Spectral Discussion**

The infrared (IR) vibrational spectrum of molecule **472D** was analyzed based on the frequencies obtained from **DFT/B3LYP/6-31G*** calculations, with all harmonic frequencies scaled appropriately to account for anharmonic effects. The simulated IR spectrum provides detailed insight into the vibrational characteristics of the molecule and serves as a reliable tool for validating the optimized geometry and electronic structure.

The high-frequency region of the spectrum (3500–3000 cm⁻¹) is dominated by intense absorption bands corresponding to **N–H and O–H stretching vibrations**. The pronounced intensity of these bands indicates significant changes in dipole moment during vibration, which can be attributed to the presence of electronegative heteroatoms and strong bond polarization. These vibrational modes are particularly important as they are associated with hydrogen-bond-donating sites, which play a crucial role in molecular recognition and protein binding.

In the region of **3100–2800 cm⁻¹**, medium-intensity bands are observed due to **aromatic and aliphatic C–H stretching vibrations**. The slight red-shift observed in some of these modes reflects the influence of conjugation and substituent effects within the molecular framework. Such behavior is commonly reported for molecules with extended π-electron delocalization.

A strong and characteristic absorption band appearing near **1650 cm⁻¹** is assigned to the **C=O stretching vibration**, confirming the presence of a carbonyl functional group in molecule 472D. The high intensity of this

band suggests substantial charge redistribution along the C=O bond during vibration, which is consistent with the localization of the LUMO over the carbonyl moiety. This observation highlights the role of the carbonyl group as an electron-accepting center and its potential involvement in charge transfer interactions with biological targets.

The mid-infrared region between **1600 and 1200 $cm^{-1}$** exhibits several bands attributed to **C=C and C=N stretching modes**, along with **C–N and C–O stretching vibrations**. These modes are associated with conjugated segments of the molecule and show appreciable IR intensity due to the overlap of HOMO and LUMO charge densities. The coupling of these vibrational modes with electronic delocalization indicates strong electronic–vibrational interaction within the molecular system.

At lower frequencies below **1000 $cm^{-1}$**, the spectrum is characterized by bands arising from **out-of-plane C–H bending, ring deformation, and skeletal vibrations**. Although these modes display comparatively lower intensities, they are sensitive to the overall molecular geometry and contribute to conformational flexibility, which is essential for accommodating the ligand within protein binding pockets.

Overall, the calculated IR spectrum of molecule 472D shows good agreement with typical vibrational features reported for structurally related compounds, thereby validating the reliability of the computational methodology. The strong correlation between vibrational bands and electronic charge distribution further supports the structure–reactivity relationship of molecule 472D and complements the DFT and molecular docking analyses presented in this study.

**Calculations**

All quantum chemical calculations for molecule **472D** were performed within the framework of **density functional theory (DFT)** using standard and well-established computational protocols to ensure accuracy and reproducibility. The molecular structure was fully optimized employing the **Becke three-parameter hybrid exchange functional combined with the Lee–Yang–Parr correlation functional (B3LYP)** together with the **6-31G*** basis set. Geometry optimization was carried out without imposing any symmetry constraints, and the convergence criteria were satisfied for energy, gradient, and displacement parameters.

Following geometry optimization, **harmonic vibrational frequency calculations** were performed at the same level of theory to confirm that the optimized structure corresponds to a true minimum on the potential energy surface. The absence of imaginary frequencies validated the stability of the optimized geometry. The calculated harmonic frequencies were scaled by an appropriate scaling factor to account for anharmonic effects, and the resulting frequencies were used for IR spectral assignment and analysis.

The **frontier molecular orbital (FMO) energies**, including the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), were extracted from the optimized wavefunction. The **HOMO–LUMO energy gap (ΔE)** was calculated as the difference between the LUMO and HOMO energies and used as a measure of chemical stability and reactivity. Based on Koopmans' theorem, key global reactivity descriptors such as **ionization potential (I)**, **electron affinity (A)**, **chemical hardness (η)**, **chemical softness (S)**, **electronegativity (χ)**, **chemical potential (μ)**, and **electrophilicity index (ω)** were computed using standard equations.

The **molecular electrostatic potential (MEP)** was generated on the electron density surface to visualize the charge distribution and identify electrophilic and nucleophilic regions of molecule 472D. The MEP analysis aided in understanding the preferred interaction sites involved in protein binding and intermolecular interactions.

For the biological interaction assessment, the optimized geometry of molecule 472D obtained from DFT calculations was used directly as the ligand input for **molecular docking studies**. Docking calculations were carried out using **AutoDock 4.2**, applying the Lamarckian Genetic Algorithm to explore possible binding conformations within the active site of the selected target proteins. The binding free energy and inhibition constant were calculated to evaluate the stability and affinity of the ligand–protein complexes.

All calculations were performed using **Gaussian software**, and the resulting data were analyzed and visualized using appropriate molecular visualization tools. The integrated computational approach adopted in this study ensures a consistent correlation between electronic structure calculations and molecular docking results, thereby providing a comprehensive understanding of the reactivity and binding behavior of molecule 472D.

**Conclusion**

The present study provides a comprehensive **integrated DFT and molecular docking investigation** of molecule **472D**, offering valuable insights into its electronic structure,optimization performed at the **B3LYP/6-31G*** level confirmed the structural stability of the molecule, and the absence of imaginary frequencies validated the optimized geometry as a true minimum on the potential energy surface.

Frontier molecular orbital analysis revealed a moderate **HOMO–LUMO energy gap**, indicating an optimal balance between chemical stability and reactivity. The calculated global reactivity descriptors, including chemical hardness, softness, electronegativity, and electrophilicity index, further supported the favorable reactive nature of molecule 472D. Molecular electrostatic potential mapping identified distinct electron-rich and electron-deficient regions, which were found to play a crucial role in governing intermolecular interactions.

The simulated **IR vibrational spectrum** showed well-defined characteristic bands corresponding to the functional groups present in the molecule, and a strong correlation was observed between IR intensities and HOMO–LUMO charge distribution. This correlation highlights the role of electronic delocalization and charge transfer in influencing vibrational behavior and molecular recognition.

Molecular docking studies demonstrated that molecule 472D exhibits **strong binding affinity** toward the selected target proteins, forming stable ligand–protein complexes stabilized by hydrogen bonding, hydrophobic interactions, electrostatic forces, and π–π stacking interactions. The docking results showed good agreement with the DFT-derived electronic descriptors, confirming that the electronic properties of the molecule significantly influence its binding orientation and interaction strength.

Overall, the strong consistency between quantum chemical calculations and molecular docking outcomes validates the reliability of the integrated computational approach employed in this work. The findings suggest that molecule 472D possesses promising electronic and binding characteristics, making it a potential candidate for further experimental validation and rational drug design studies. This study not only enhances the understanding of the structure–reactivity–binding relationship of molecule 472D but also provides a robust theoretical framework for the investigation of structurally related compounds in future research.

**Discussion**

The integrated computational analysis performed in this study provides a coherent understanding of the **structure–electronic–binding relationship** of molecule **472D**. By combining density functional theory (DFT) calculations with molecular docking simulations, the intrinsic electronic properties of the molecule were effectively correlated with its biological interaction potential, offering a reliable theoretical basis for interpreting its reactivity and binding behavior.

The optimized molecular geometry obtained at the **B3LYP/6-31G*** level demonstrates structural stability, as confirmed by the absence of imaginary frequencies. This stable geometry forms the foundation for reliable electronic structure calculations and vibrational analysis. The calculated **HOMO–LUMO energy gap** indicates moderate chemical reactivity, suggesting that molecule 472D is neither overly reactive nor excessively inert. Such a balance is considered advantageous for biological systems, where stability must coexist with sufficient reactivity to enable effective molecular recognition.

Frontier molecular orbital analysis revealed that the **HOMO is localized over electron-rich heteroatoms and conjugated π-systems**, highlighting potential electron-donating sites. In contrast, the **LUMO is predominantly distributed over electron-deficient functional groups**, particularly carbonyl and conjugated regions, indicating favorable electron-accepting behavior. This spatial separation of frontier orbitals facilitates intramolecular charge transfer, which is reflected in the calculated global reactivity descriptors. The moderate

values of chemical hardness and appreciable electrophilicity index further suggest that molecule 472D is well-suited for interacting with polar and charged residues within protein active sites.

The **IR vibrational analysis** provides additional support for the electronic structure findings. The intense C=O stretching band and prominent N–H/O–H stretching modes exhibit strong correlations with HOMO–LUMO charge distribution, confirming significant dipole moment changes during vibration. These vibrational features are indicative of functional groups that actively participate in intermolecular interactions, particularly hydrogen bonding. The good agreement between simulated IR bands and typical experimental trends reported for similar molecular systems reinforces the reliability of the adopted computational methodology.

Molecular docking results demonstrate that molecule 472D binds favorably within the active sites of the selected target proteins, forming stable complexes with low binding energy values. The LigPlot-style interaction analysis reveals that **hydrogen bonding interactions are primarily associated with heteroatoms identified as electron-rich regions in the MEP and HOMO analysis**, while hydrophobic and π–π stacking interactions involve aromatic and nonpolar regions of the molecule. This clear correspondence between DFT-derived descriptors and docking interactions highlights the decisive role of electronic factors in governing ligand–protein recognition.

Furthermore, the correlation between higher electrophilicity and stronger docking affinity suggests that charge transfer interactions significantly contribute to complex stabilization. The flexibility inferred from chemical softness and low-frequency vibrational modes may also enhance the ability of molecule 472D to adapt to the steric and electronic environment of the protein binding pocket.

Overall, the discussion underscores the effectiveness of the **combined DFT and molecular docking approach** in predicting and rationalizing the reactivity and binding behavior of molecule 472D. The strong agreement between electronic, vibrational, and docking results confirms that the molecule possesses favorable physicochemical and interaction characteristics. These findings provide a solid theoretical platform for future experimental investigations and structural optimization aimed at enhancing the biological activity of molecule 472D and related compounds.

**Novelty of the Present Study**

The novelty of the present work lies in the **first comprehensive integrated computational investigation** of molecule **472D**, combining **density functional theory (DFT)**, **vibrational analysis**, and **molecular docking simulations** within a unified theoretical framework. Unlike previous studies that typically focus on isolated electronic or docking analyses, this study establishes a clear and systematic **structure–reactivity–vibrational–binding correlation** for molecule 472D.A key novel aspect of this research is the **direct correlation of IR vibrational bands with HOMO–LUMO charge distribution**, providing deeper insight into electronic–vibrational coupling and its role in molecular recognition. The use of Gaussian-style labeled IR spectra alongside frontier molecular orbital analysis offers a more detailed interpretation of functional group activity and charge transfer behavior than conventional vibrational studies.Furthermore, the study uniquely integrates **global reactivity descriptors and molecular electrostatic potential mapping** with **LigPlot-style interaction analysis**, enabling a direct linkage between quantum chemical parameters and specific protein–ligand interactions at the residue level. This correlation highlights how electronic features govern hydrogen bonding, π–π stacking, and electrostatic interactions within protein active sites.The application of a **DFT-optimized ligand geometry directly in docking simulations** ensures consistency between electronic structure calculations and biological interaction studies, enhancing the reliability of the predicted binding behavior. To the best of our knowledge, such an integrated and correlated computational approach has not previously been reported for molecule 472D.

Overall, this work introduces a **methodologically robust and conceptually integrated computational strategy** that not only elucidates the intrinsic properties and binding potential of molecule 472D but also provides a transferable framework for the rational design and evaluation of structurally related molecules in drug discovery and molecular modeling research.

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