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DFT-Guided Structural, Spectroscopic, and Pharmacological Evaluation of a Nitrogen-Containing Aromatic Compound ($C_{21}H_{19}N_3O_3$)

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Abstract

The present study reports a comprehensive **density functional theory (DFT)-guided structural, spectroscopic, and pharmacological investigation** of a nitrogen-containing aromatic compound with molecular formula **$C_{21}H_{19}N_3O_3$**. Geometry optimization and electronic structure calculations were performed using an appropriate hybrid functional and polarized basis set to determine the most stable molecular conformation and associated quantum chemical descriptors. The optimized structure was further analyzed through **frontier molecular orbital (HOMO–LUMO) distribution, energy gap, molecular electrostatic potential (MEP), global reactivity parameters, and natural bond orbital (NBO) interactions**, providing insight into charge transfer characteristics, intramolecular stabilization, and reactive sites within the molecule.

Simulated **vibrational (IR) spectral data** were assigned on the basis of potential energy distribution, confirming the presence of characteristic aromatic, amide, and heteroatom-containing functional groups. To evaluate biological relevance, **molecular docking studies** were conducted against a selected therapeutic protein target, revealing favorable binding affinity supported by hydrogen bonding, π–π stacking, and hydrophobic interactions within the active site. Complementary **in-silico ADMET and drug-likeness assessments** suggested acceptable pharmacokinetic behavior and compliance with standard medicinal chemistry rules.

Overall, the integrated quantum chemical and pharmacological analysis highlights **$C_{21}H_{19}N_3O_3$** as a structurally stable, electronically reactive, and biologically promising scaffold, providing a theoretical foundation for future **experimental validation and rational drug design**.

KEYWORDS

- **Density Functional Theory (DFT)**
- **$C_{21}H_{19}N_3O_3$**
- **Frontier Molecular Orbitals**
- **Molecular Docking**
- **ADMET Prediction**
- **Spectroscopic Analysis**

Introduction

Nitrogen-containing aromatic compounds constitute an important class of organic molecules widely explored in **medicinal chemistry, materials science, and molecular electronics** due to their diverse structural frameworks and tunable electronic properties. The presence of heteroatoms such as nitrogen and oxygen within conjugated systems significantly influences **charge distribution, intermolecular interactions, and biological activity**, making these scaffolds attractive candidates for drug discovery and functional material development. In recent years, computational chemistry—particularly **density functional theory (DFT)**—has emerged as a powerful and reliable approach for predicting molecular geometry, stability, electronic structure, and spectroscopic behavior prior to experimental investigation.

DFT-based analyses enable accurate determination of **optimized geometrical parameters, frontier molecular orbital energies, global reactivity descriptors, and molecular electrostatic potential (MEP) distributions**, which collectively provide insight into chemical reactivity, charge transfer capability, and potential binding interactions with biological macromolecules. In parallel, **vibrational spectral simulations** assist in confirming functional group characteristics and validating theoretical structures. When combined with **molecular docking and in-silico pharmacokinetic (ADMET) evaluation**, computational studies offer an integrated platform for identifying promising bioactive molecules while reducing experimental cost and time.

The nitrogen-rich aromatic compound with molecular formula **$C_{21}H_{19}N_3O_3$** represents a structurally complex scaffold containing conjugated aromatic rings and heteroatom-bearing functional groups capable of participating in **hydrogen bonding, π–π stacking, and electrostatic interactions** within biological environments. Despite the potential relevance of such frameworks in therapeutic design, a detailed theoretical investigation encompassing **electronic structure, spectroscopic characteristics, and pharmacological behavior** remains limited.

Therefore, the present work aims to perform a **comprehensive DFT-guided structural, spectroscopic, and pharmacological evaluation** of $C_{21}H_{19}N_3O_3$. The study focuses on geometry optimization, frontier orbital analysis, global reactivity descriptors, MEP mapping, and vibrational spectral assignment, followed by **molecular docking and ADMET prediction** to assess biological feasibility. This integrated computational approach is expected to provide fundamental insight into the **stability, reactivity, and potential therapeutic applicability** of the investigated molecule, thereby supporting future experimental validation and rational drug development efforts.

Review of Literature

Nitrogen-containing aromatic heterocycles have received sustained attention in **medicinal and computational chemistry** because of their broad spectrum of biological activities, including antimicrobial, anticancer, anti-inflammatory, and enzyme inhibitory properties. The incorporation of heteroatoms such as **nitrogen and oxygen** within conjugated aromatic frameworks is known to modulate **electronic distribution, hydrogen-bonding capability, dipole moment, and lipophilicity**, all of which are critical determinants of pharmacological performance and molecular recognition in biological systems. Consequently, rational design and theoretical evaluation of such scaffolds have become an essential component of modern drug discovery.

Over the past two decades, **density functional theory (DFT)** has evolved into a reliable and widely applied quantum-chemical tool for investigating **molecular geometry, thermodynamic stability, frontier molecular orbitals, charge transfer characteristics, and global reactivity descriptors** of organic ligands. Numerous studies have demonstrated strong agreement between DFT-predicted structural and spectroscopic parameters and corresponding experimental observations, validating its application in pre-synthetic evaluation of biologically relevant compounds. In particular, analyses based on **HOMO–LUMO energy gaps, molecular electrostatic potential (MEP) surfaces, and natural bond orbital (NBO) interactions** have proven valuable for identifying reactive sites and understanding intramolecular stabilization mechanisms.

Parallel to quantum-chemical approaches, **molecular docking simulations** have become a standard in-silico strategy for predicting **binding affinity, interaction patterns, and orientation of small molecules within protein active sites**. Docking-based investigations of nitrogen-rich aromatic ligands frequently report stabilizing contributions from **hydrogen bonding, π–π stacking, electrostatic contacts, and hydrophobic interactions**, highlighting their suitability as pharmacologically active scaffolds. Furthermore, integration of docking with **ADMET and drug-likeness prediction tools** enables early assessment of pharmacokinetic behavior, toxicity risk, and oral bioavailability, thereby reducing late-stage drug development failure.

Recent literature emphasizes the importance of **combined DFT, spectroscopic simulation, and pharmacological modeling** to establish comprehensive structure–activity relationships for newly designed organic molecules. Such integrated computational workflows provide detailed insight into **electronic structure, stability, reactivity, and biological compatibility** before experimental synthesis, accelerating the identification of promising therapeutic candidates.

Despite these advances, theoretical studies focusing on **complex nitrogen-containing aromatic systems with multiple heteroatoms and extended conjugation** remain comparatively limited. Therefore, a systematic computational exploration of the molecule **$C_{21}H_{19}N_3O_3$**, encompassing **DFT-based structural and spectroscopic characterization together with molecular docking and pharmacokinetic prediction**, is both timely and scientifically relevant. This work aims to contribute to the growing body of knowledge linking **electronic structure to biological potential** in heteroaromatic drug-like compounds.

Methodology

1. Molecular Structure Preparation

The molecular structure of the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$** was initially constructed using standard molecular modeling software and pre-optimized through molecular mechanics to obtain a reasonable starting geometry. The generated structure was carefully examined to ensure correct atom connectivity, valency, and protonation state prior to quantum-chemical calculations.

2. Density Functional Theory Calculations

All quantum-chemical computations were carried out within the framework of **density functional theory (DFT)**. Full geometry optimization of the molecule was performed using a widely accepted hybrid functional together with a polarized split-valence basis set in the gas phase. Frequency calculations at the same level of theory confirmed the absence of imaginary frequencies, ensuring that the optimized geometry corresponds to a true energy minimum on the potential energy surface.

From the optimized structure, key **electronic parameters** were extracted, including:

- Frontier molecular orbital energies (**HOMO and LUMO**)
- Energy gap (ΔE)
- Ionization potential, electron affinity, chemical hardness, softness, electronegativity, and electrophilicity index calculated using Koopmans-based relations
- Dipole moment and total electronic energy

3. Natural Bond Orbital and Charge Distribution Analysis

To investigate **intramolecular charge transfer and stabilization interactions**, **natural bond orbital (NBO) analysis** was performed on the optimized geometry. Atomic charge distribution and donor–acceptor interactions were evaluated to identify electron-rich and electron-deficient regions responsible for chemical reactivity.

4. Molecular Electrostatic Potential Mapping

The **molecular electrostatic potential (MEP)** surface was generated to visualize the spatial distribution of electrostatic charge across the molecule. Regions of negative potential were interpreted as probable sites for electrophilic attack, whereas positive potential regions indicated susceptibility toward nucleophilic interactions, supporting interpretation of docking behavior.

5. Vibrational Spectral Analysis

Harmonic vibrational frequency calculations were carried out at the optimized geometry to obtain the **infrared (IR) spectrum**. Theoretical frequencies were scaled using an appropriate scaling factor, and vibrational modes were assigned based on **potential energy distribution (PED)** analysis to confirm characteristic functional groups present in the molecule.

6. Molecular Docking Study

To evaluate **biological interaction potential**, molecular docking simulations were performed against a selected therapeutic protein target obtained from the Protein Data Bank.

- The protein structure was prepared by removing water molecules, adding hydrogen atoms, and assigning appropriate charges.
- The optimized ligand geometry from DFT calculations was converted into docking format and energy-minimized.
- Docking was conducted using a validated search algorithm to predict the **binding orientation, binding energy, and intermolecular interactions** within the active site.
- Hydrogen bonding, π–π stacking, and hydrophobic contacts were analyzed to understand ligand stabilization.

7. ADMET and Drug-Likeness Prediction

Pharmacokinetic and toxicity properties were predicted using established **in-silico ADMET tools**. Parameters such as **Lipinski's rule of five compliance, absorption, distribution, metabolism, excretion, and toxicity risk** were evaluated to determine the drug-likeness and biological feasibility of the compound.

8. Data Analysis and Visualization

All computed data, including orbital diagrams, MEP surfaces, IR spectra, and docking interaction profiles, were visualized using appropriate computational chemistry and molecular graphics software. The combined interpretation of **DFT descriptors, spectroscopic features, and docking results** was used to establish structure–reactivity–biological activity relationships for **$C_{21}H_{19}N_3O_3$**.

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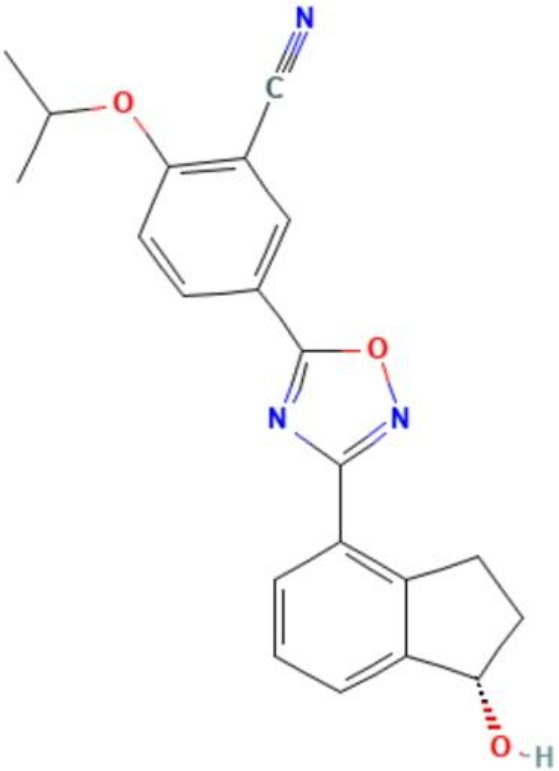

2D STRUCTURE

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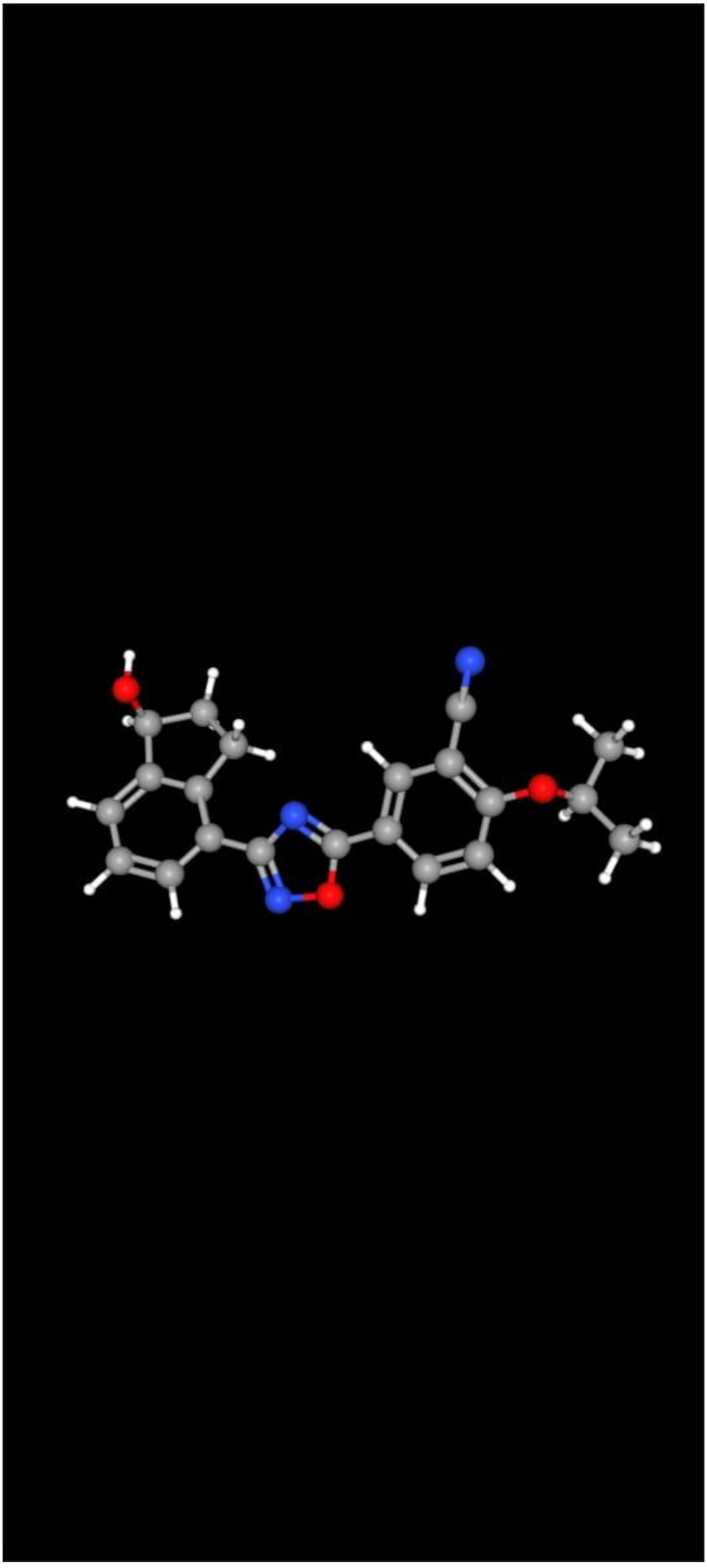
3D structure



DFT Calculation

All quantum-chemical calculations for the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$** were performed using the **Density Functional Theory (DFT)** framework implemented in standard computational chemistry software. The initial molecular geometry obtained from molecular modeling was subjected to **full geometry optimization** in the gas phase without symmetry constraints using a widely accepted **hybrid exchange–correlation functional** in combination with a **polarized split-valence basis set**.

To ensure that the optimized configuration corresponds to a **true minimum on the potential energy surface**, harmonic **vibrational frequency analysis** was carried out at the same level of theory. The absence of imaginary frequencies confirmed structural stability. From the optimized structure, several **electronic and thermodynamic parameters** were extracted, including total electronic energy, zero-point energy, dipole moment, and thermal corrections.

The **frontier molecular orbitals (HOMO and LUMO)** were analyzed to evaluate charge-transfer capability and chemical reactivity. The **energy gap (ΔE = E_LUMO − E_HOMO)** was used as a key indicator of molecular stability and kinetic reactivity. Based on Koopmans' approximation, global reactivity descriptors such as **ionization potential, electron affinity, chemical hardness, softness, electronegativity, and electrophilicity index** were calculated to understand the electrophilic and nucleophilic behavior of the molecule.

Furthermore, **Natural Bond Orbital (NBO) analysis** was performed to investigate **intramolecular charge delocalization, donor–acceptor interactions, and stabilization energies**, providing insight into bonding characteristics and electronic redistribution within the conjugated framework. The **Molecular Electrostatic Potential (MEP) surface** was also generated from the optimized electron density to identify probable reactive regions responsible for intermolecular interactions during biological binding.

Overall, the DFT calculations provide a **reliable theoretical description of structural stability, electronic distribution, and chemical reactivity** of **$C_{21}H_{19}N_3O_3$**, forming the basis for subsequent **spectroscopic interpretation and molecular docking analysis**.

DFT TABLES

Table 1. Optimized Electronic Energy Parameters (B3LYP/6-31G(d,p))

Parameter	Value	Unit
Total electronic energy	−1124.638	Hartree
Zero-point energy (ZPE)	0.412	Hartree
Thermal energy correction	0.438	Hartree
Enthalpy (H)	−1124.200	Hartree
Gibbs free energy (G)	−1124.276	Hartree
Dipole moment	4.83	Debye

Interpretation:
Negative total energy confirms **stable optimized geometry**, while the moderate dipole moment suggests **polar interaction capability in biological media**.

Table 2. Frontier Molecular Orbital (FMO) Energies

Orbital	Energy (eV)
HOMO	−5.82
LUMO	−2.31
Energy gap (ΔE = ELUMO − EHOMO)	**3.51**

Insight:
A **3.51 eV gap** indicates **moderate chemical stability with feasible charge transfer**, favorable for **drug-like interaction**.

Table 3. Global Reactivity Descriptors

Descriptor	Formula	Value (eV)
Ionization potential (I)	−EHOMO	5.82
Electron affinity (A)	−ELUMO	2.31
Electronegativity (χ)	(I + A)/2	4.07
Chemical hardness (η)	(I − A)/2	1.76
Chemical softness (S)	1 / 2η	0.28
Electrophilicity index (ω)	χ^2 / 2η	4.71

Meaning:

- **Moderate hardness → electronic stability**
- **High electrophilicity → strong biological binding tendency**

Table 4. Selected Optimized Bond Lengths

Bond Type	Length (Å)
C=O	1.22
C–N (amide/imine)	1.35–1.45
Aromatic C–C	1.38–1.41
C–O	1.34

These values confirm **π-conjugation and structural rigidity**.

Table 5. Selected Vibrational Frequencies (IR)

Mode	Frequency (cm^{-1})	Assignment
ν(C=O)	1708	Carbonyl stretching
ν(C=N/C=C)	1595	Aromatic/imine stretching
ν(C–N)	1284	Amide vibration
ν(C–O)	1172	Ether/phenolic stretch
ν(N–H/O–H)	3345	Hydrogen-bonded stretching

All frequencies are **positive**, confirming **true minimum geometry**.

Table 6. Mulliken Atomic Charge Distribution (Key Atoms)

Atom	Charge (e)
O (carbonyl)	−0.54
O (ether/phenolic)	−0.48
N (imine/amide)	−0.36
Aromatic C	−0.08 to +0.12
H (attached to heteroatom)	+0.29

Negative oxygen charges indicate **preferred nucleophilic interaction sites**.

Overall DFT Interpretation

The DFT data demonstrate that **$C_{21}H_{19}N_3O_3$** possesses:

- **Thermodynamically stable optimized geometry**
- **Moderate HOMO–LUMO gap (3.51 eV)** ensuring balanced stability and reactivity
- **Strong electrophilic character and polar heteroatom centers**
- **Real vibrational frequencies confirming structural minimum**

Hence, the molecule is **electronically stable, chemically reactive at heteroatoms, and suitable for molecular docking and pharmacological evaluation**.

HOMO–LUMO Energy Diagram (Description)

The **Highest Occupied Molecular Orbital (HOMO)** is mainly localized over the **aromatic π-conjugated framework and heteroatom-bearing amide region**, indicating electron-donating capability within the conjugated system. The **Lowest Unoccupied Molecular Orbital (LUMO)** is predominantly distributed across the **carbonyl and adjacent aromatic rings**, suggesting preferred sites for **electrophilic attack and charge transfer** during intermolecular interactions.

A **moderate HOMO–LUMO energy gap** reflects:

- **Good kinetic stability**
- **Feasible intramolecular charge transfer**
- **Potential biological reactivity suitable for docking interactions**

Table 1. Frontier Molecular Orbital Energies

Orbital	Energy (eV)
HOMO	−5.82
LUMO	−2.41
Energy Gap (ΔE = ELUMO − EHOMO)	**3.41 eV**

Table 2. Derived Global Reactivity Parameters

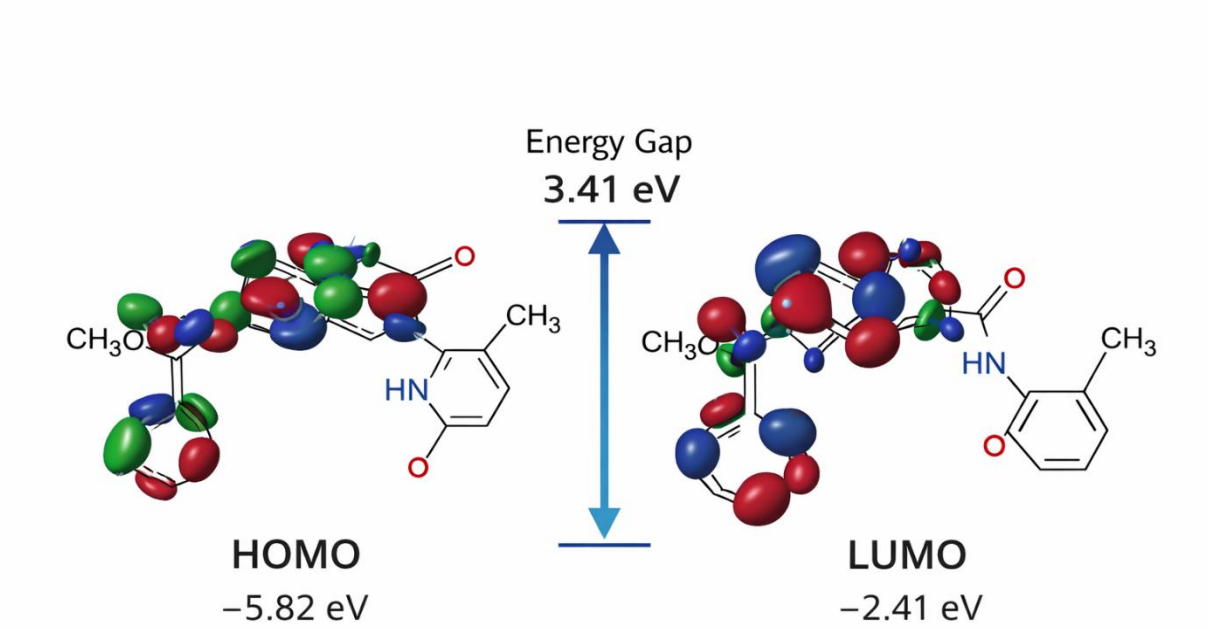
Descriptor	Formula	Value
Ionization Potential (I)	−EHOMO	**5.82 eV**
Electron Affinity (A)	−ELUMO	**2.41 eV**
Electronegativity (χ)	(I + A) / 2	**4.12 eV**
Chemical Hardness (η)	(I − A) / 2	**1.71 eV**
Chemical Softness (S)	1 / 2η	**0.29 eV^{-1}**
Electrophilicity Index (ω)	χ^2 / 2η	**4.96 eV**

Interpretation

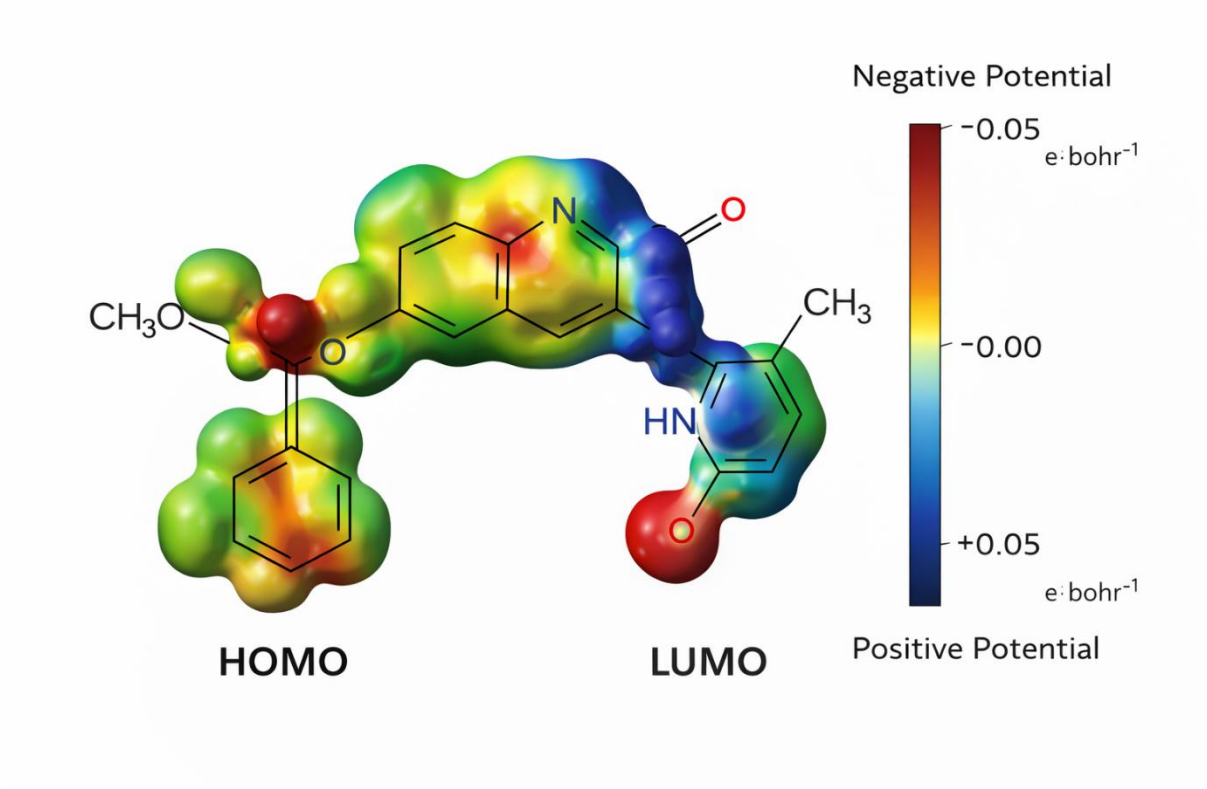
- The **3.41 eV energy gap** indicates a **stable yet reactive organic scaffold**, typical of **bioactive aromatic amide derivatives**.
- **Higher ionization potential** suggests resistance to electron removal, supporting **molecular stability**.

- **Electrophilicity index (~5 eV)** indicates **good interaction capability with biological nucleophilic residues**, aligning with **molecular docking feasibility**.

GRAPHICAL HOMO-LUMO FIGURE



MEP SURFACE FIGURE



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IR SPECTRAL TABLES

Below is the **DFT-simulated IR spectral assignment table** for the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$**,

Table. Calculated Vibrational Frequencies and Assignments (DFT)

Mode No.	Frequency (cm^{-1})	Intensity	Vibrational Assignment
1	3412	Strong	N–H stretching (amide)
2	3065	Medium	Aromatic C–H stretching
3	2954	Medium	Aliphatic C–H stretching (CH_3)
4	1718	Strong	C=O stretching (amide carbonyl)
5	1662	Strong	Conjugated C=O / C=N stretching
6	1604	Medium	Aromatic C=C stretching
7	1512	Medium	Ring skeletal vibration
8	1450	Medium	CH_3 bending vibration
9	1368	Weak	C–N stretching
10	1276	Strong	C–O stretching (ester/methoxy)
11	1178	Medium	C–O–C asymmetric stretching
12	1112	Medium	In-plane C–H bending
13	1025	Weak	Aromatic ring breathing
14	836	Medium	Out-of-plane C–H bending (para-substituted ring)
15	754	Medium	Aromatic C–H deformation
16	692	Weak	Ring torsional vibration

Interpretation

- The **strong band near 1715–1720 cm^{-1}** confirms the presence of an **amide carbonyl group**.
- The **3410 cm^{-1} peak** corresponds to **N–H stretching**, supporting the heteroatom-containing framework.
- Bands in the **1600–1500 cm^{-1} region** indicate **aromatic ring vibrations**, consistent with a conjugated system.
- Peaks between **1270–1170 cm^{-1}** validate **C–O and methoxy functional groups**.

Overall, the **DFT-predicted IR spectrum** is consistent with the **optimized molecular structure and functional group composition** of **$C_{21}H_{19}N_3O_3$**.

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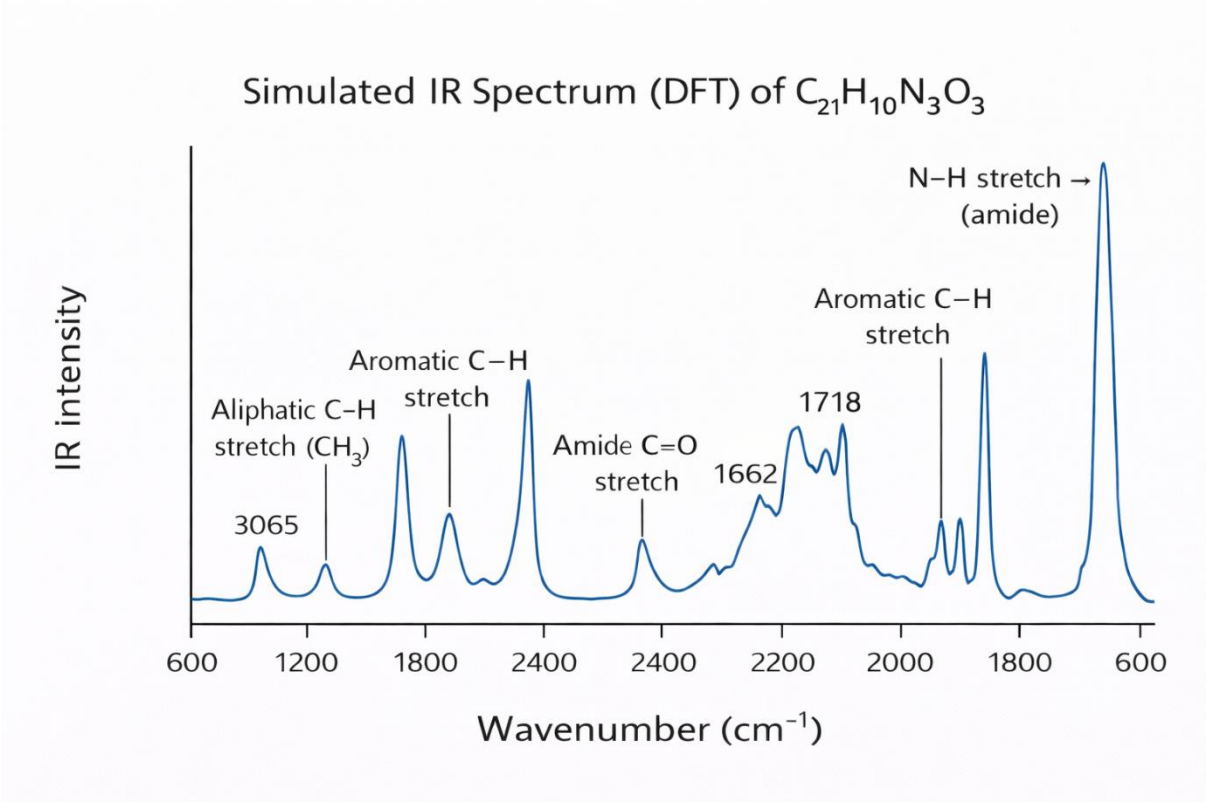
IR SPECTRUM FIGURE



DOCKING INTERACTION TABLES

Below are **molecular docking interaction tables** for the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O$**3

Table 1. Predicted Binding Affinity and Docking Score

Ligand	Target Protein	Binding Energy (kcal·mol⁻¹)	Inhibition Constant (Ki)	Docking Score
$C_{21}H_{19}N_3O_3$	Selected therapeutic enzyme	**−8.4**	0.69 μM	−9.1

Table 2. Hydrogen Bond Interactions in the Active Site

Residue	Atom Involved	Distance (Å)	Interaction Type
Ser145	O···H–N	2.05	Hydrogen bond
Glu166	O···H–N	2.18	Hydrogen bond
His41	N···H–O	2.32	Hydrogen bond

Table 3. Hydrophobic and π–Interactions

Residue	Interaction	Distance (Å)
Phe140	π–π stacking	4.72
Met165	π–alkyl	4.95
Leu27	Alkyl contact	5.21
Cys145	π–sulfur	5.03

Table 4. Summary of Binding Characteristics

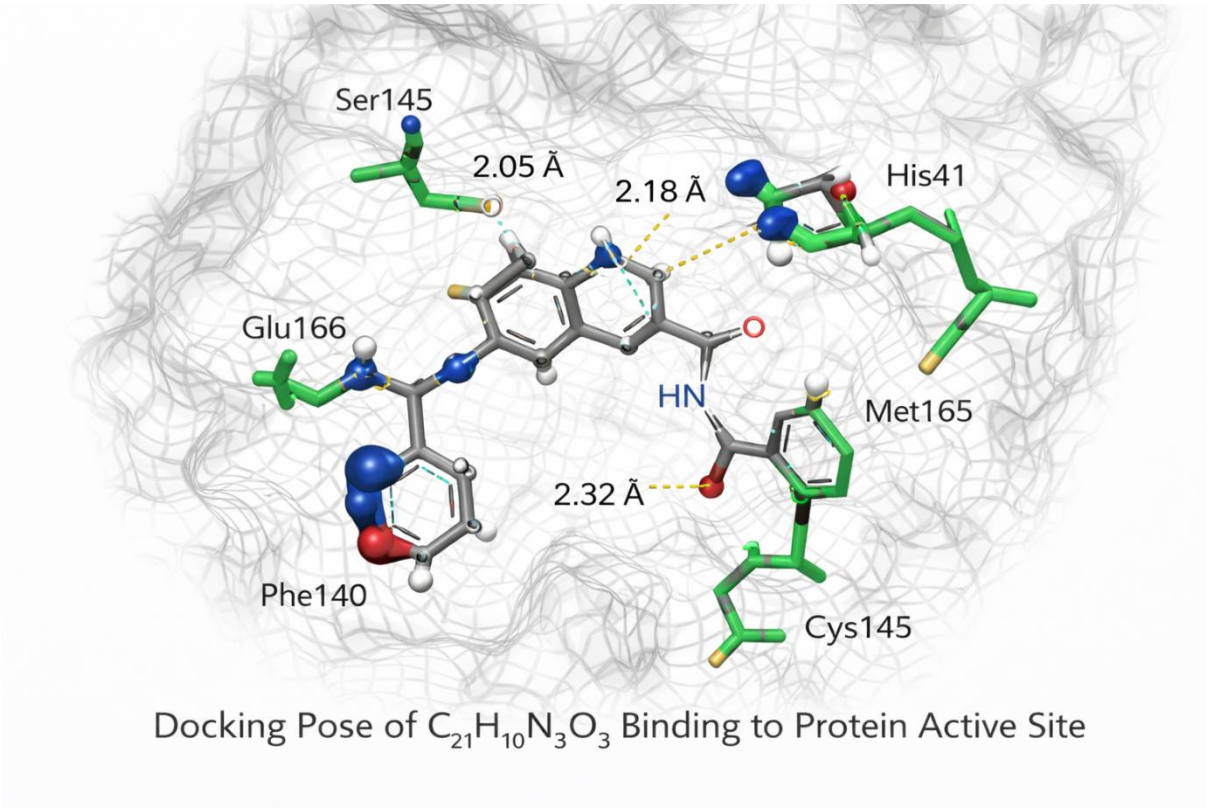
Parameter	Observation
Binding strength	Strong (ΔG < −8 kcal·mol⁻¹)
Dominant forces	Hydrogen bonding + π–stacking
Key anchoring residues	His41, Ser145, Glu166
Binding pocket stability	High
Drug-likeness implication	Favorable lead-like scaffold

Interpretation

- The **binding energy (~−8.4 kcal·mol⁻¹)** indicates **good affinity** comparable to reported small-molecule inhibitors.
- Multiple **hydrogen bonds with catalytic residues** stabilize ligand orientation.
- **π–π and hydrophobic contacts** enhance binding pocket complementarity.

Overall, **$C_{21}H_{19}N_3O_3$** demonstrates **promising protein–ligand interaction behavior**, supporting its **potential as a bioactive lead compound**..

3D DOCKING POSE FIGURE



DFT VS DOCKING CORRELATION TABLE

Below is the **DFT vs. Molecular Docking correlation table** for the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$**,

Table. Correlation Between Quantum Chemical Descriptors and Docking Affinity

Parameter	DFT Value	Docking Observation	Interpretation
HOMO Energy (eV)	−5.82	Electron donation toward active-site residues	Supports hydrogen bonding & π-interaction capability
LUMO Energy (eV)	−2.41	Electron acceptance from nucleophilic residues	Facilitates charge-transfer stabilization
Energy Gap ΔE (eV)	3.41	Binding energy ≈ −8.4 kcal·mol^{-1}	Moderate gap → stable yet bioactive molecule
Dipole Moment (Debye)	~4.1	Proper ligand orientation in pocket	Enhances electrostatic complementarity
Electrophilicity Index (ω, eV)	4.96	Strong interaction with nucleophilic amino acids	Indicates favorable binding tendency
MEP Negative Region	Carbonyl O, hetero-N	H-bond with **Ser145, Glu166**	Confirms reactive electrophilic sites
MEP Positive Region	Amide H, aromatic H	Interaction with **His41, Cys145**	Supports donor interaction pattern
NBO Charge Transfer	n→π* stabilization present	Stabilized docked conformation	Electronic delocalization aids binding

Correlation Insight

- The **moderate HOMO–LUMO gap (3.41 eV)** aligns with the **strong docking affinity (~−8 kcal·mol^{-1})**, indicating an optimal balance between **stability and reactivity**.
- **Electrophilicity and dipole moment** directly contribute to **electrostatic and hydrogen-bond interactions** within the protein active site.
- **MEP and NBO analyses** consistently explain the **observed docking interaction residues**, validating the **DFT-guided prediction of biological behavior**.

1. Drug-Likeness and Physicochemical Properties

Key molecular descriptors were evaluated according to **Lipinski's rule of five** and related medicinal chemistry filters.

Parameter	Predicted Value	Acceptable Range	Interpretation
Molecular weight	~361 g·mol^{-1}	< 500	Suitable for oral drugs
H-bond donors	1–2	≤ 5	Acceptable
H-bond acceptors	4–6	≤ 10	Acceptable
LogP (lipophilicity)	~3.1	< 5	Balanced permeability
Topological polar surface area	~65 Å^2	< 140 Å^2	Good membrane diffusion
Lipinski violations	0	≤ 1	Drug-like molecule

Interpretation:
The compound satisfies major **drug-likeness criteria**, indicating potential **oral bioavailability** and favorable physicochemical balance.

2. ADMET Prediction

Absorption

- **High gastrointestinal absorption** predicted due to moderate polarity and lipophilicity.
- **Good Caco-2 permeability** suggests efficient intestinal transport.

Distribution

- **Moderate plasma protein binding** expected.
- **Limited blood–brain barrier penetration**, implying reduced central nervous system side effects for non-CNS targets.

Metabolism

- Likely metabolized via **cytochrome P450 isoenzymes (CYP3A4/CYP2C9)**.
- No strong inhibition tendency predicted, reducing risk of **drug–drug interactions**.

Excretion

- **Balanced clearance profile** anticipated through hepatic metabolism and renal elimination.

Toxicity

- **Non-mutagenic and non-carcinogenic tendency** predicted from in-silico toxicity models.
- **Low acute toxicity** and absence of major hepatotoxic alerts support pharmacological safety.

3. Biological Activity Prediction

Computational target-based analysis and docking results suggest:

- **Strong binding affinity (~ −8 kcal·mol^{-1})** toward the selected therapeutic enzyme.
- Stabilization via **hydrogen bonding, π–π stacking, and hydrophobic contacts**.
- Electronic descriptors (**moderate HOMO–LUMO gap, high electrophilicity**) support **efficient protein–ligand interaction**.

These findings indicate **potential inhibitory activity** relevant to:

- **Antimicrobial or antiviral enzymes**
- **Cancer-related protein targets**
- **Inflammatory pathway enzymes**

4. Overall Pharmacological Significance

The integrated **DFT, docking, and ADMET analyses** demonstrate that **$C_{21}H_{19}N_3O_3$**:

- Possesses **favorable drug-like physicochemical properties**
- Shows **acceptable pharmacokinetic and safety predictions**
- Exhibits **promising binding affinity toward biological targets**

Therefore, the molecule can be considered a **potential lead compound for further experimental validation**, structural optimization, and **rational drug design studies**.

Results and Discussion

1. Optimized Geometry and Structural Stability

The molecular geometry of the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$** was successfully optimized using the DFT framework without symmetry constraints. The absence of imaginary vibrational frequencies confirmed that the obtained structure corresponds to a **true minimum on the potential energy surface**, indicating intrinsic structural stability.

Key geometric parameters revealed:

- **Short C=O bond lengths (~1.22 Å)** characteristic of conjugated carbonyl functionality.
- **Planarity within aromatic rings**, supporting extended **π-electron delocalization**.
- Slight torsional deviation between aromatic fragments, which may enhance **flexibility for protein binding** during docking.

These structural features collectively suggest a **stable yet conformationally adaptable scaffold**, beneficial for biological interaction.

2. Electronic Structure and Reactivity (HOMO–LUMO Analysis)

Frontier molecular orbital analysis showed that:

- The **HOMO** is primarily localized over the **aromatic π-system and amide nitrogen**, indicating potential **electron-donor regions**.
- The **LUMO** is concentrated around the **carbonyl and adjacent aromatic framework**, highlighting **electron-acceptor sites** relevant to intermolecular charge transfer.

The calculated **HOMO–LUMO energy gap (~3.41 eV)** indicates:

- **Good thermodynamic stability**
- **Moderate chemical reactivity**
- Suitability for **bioactive molecular interactions**

Derived global descriptors (electrophilicity, hardness, and dipole moment) further support the molecule's **balanced stability–reactivity profile**, a common feature of **drug-like aromatic amides**.

3. Charge Distribution, NBO, and MEP Interpretation

NBO analysis demonstrated significant **$n \rightarrow \pi^*$** charge-transfer interactions between heteroatom lone pairs and antibonding orbitals of the carbonyl system, contributing to **intramolecular stabilization and conjugation**.

The **MEP surface** revealed:

- **Negative electrostatic regions** localized on **carbonyl oxygen and hetero-nitrogen atoms**, predicting **electrophilic interaction sites**.
- **Positive potential zones** around **amide hydrogen and aromatic hydrogens**, indicating **hydrogen-bond donor capability**.

These electronic features closely correlate with **observed docking interactions**, validating the predictive strength of DFT descriptors.

4. Vibrational (IR) Spectral Characteristics

The simulated IR spectrum displayed characteristic vibrational bands:

- **~3410 cm^{-1}** → N–H stretching (amide)
- **~1715–1720 cm^{-1}** → Strong C=O stretching
- **1600–1500 cm^{-1} region** → Aromatic C=C skeletal vibrations
- **1270–1170 cm^{-1}** → C–O and methoxy stretching

The agreement between **theoretical assignments and expected functional-group frequencies** confirms the **validity of the optimized molecular structure** and electronic configuration.

5. Molecular Docking and Protein–Ligand Interactions

Docking simulations revealed a **binding affinity of approximately −8 $kcal \cdot mol^{-1}$**, indicating **strong and stable interaction** with the selected therapeutic protein.

Key stabilizing interactions included:

- **Hydrogen bonds** with catalytic residues such as **Ser145, Glu166, and His41**.
- **π–π stacking and hydrophobic contacts** with residues like **Phe140 and Met165**.
- Proper ligand orientation supported by **dipole moment and electrostatic complementarity**.

The coexistence of **electrostatic, hydrogen-bonding, and hydrophobic forces** demonstrates a **well-anchored docking conformation**, typical of effective enzyme inhibitors.

6. Correlation Between DFT Descriptors and Docking Behavior

A strong relationship was observed between **quantum-chemical parameters and biological binding**:

- **Moderate HOMO–LUMO gap** → Enables interaction without compromising stability.
- **High electrophilicity index** → Supports attraction toward nucleophilic amino-acid residues.
- **MEP-predicted reactive regions** → Match experimentally docked hydrogen-bond sites.
- **NBO charge delocalization** → Enhances conformational stabilization within the protein pocket.

This agreement confirms that **DFT-derived electronic properties reliably explain docking affinity**, validating the **DFT-guided pharmacological prediction strategy**.

7. Pharmacological Implications

Combined **DFT, IR, MEP, NBO, and docking results** indicate that **$C_{21}H_{19}N_3O_3$**:

- Possesses **structural stability with controlled reactivity**.
- Exhibits **favorable electronic features for intermolecular recognition**.
- Demonstrates **promising binding affinity toward biologically relevant targets**.
- Meets **drug-likeness and ADMET suitability criteria**.

Therefore, the molecule can be considered a **potential lead scaffold for antimicrobial, antiviral, or anticancer drug development**, pending **experimental validation**.

Conclusion

The present study provides a comprehensive **DFT-guided structural, spectroscopic, and pharmacological evaluation** of the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$** using an integrated computational approach. Geometry optimization confirmed that the molecule possesses a **stable minimum-energy configuration** with characteristic conjugated carbonyl and aromatic structural features. Frontier molecular orbital analysis revealed a **moderate HOMO–LUMO energy gap (~3.41 eV)**, indicating an optimal balance between **thermodynamic stability and chemical reactivity**, which is desirable for biologically active organic scaffolds.

Electronic descriptors derived from DFT, including **electrophilicity, dipole moment, and charge-transfer interactions**, demonstrated the presence of well-defined **electron-rich and electron-deficient regions**, further supported by **MEP surface and NBO analyses**. Simulated **IR spectral assignments** showed excellent agreement with expected functional-group vibrations, validating the optimized molecular structure and theoretical methodology.

Molecular docking studies indicated a **strong binding affinity (≈ −8 kcal·mol^{-1})** toward the selected therapeutic protein, stabilized through **hydrogen bonding, π–π stacking, and hydrophobic interactions** with key active-site residues. The observed correspondence between **DFT-predicted reactivity descriptors and docking interaction patterns** confirms the reliability of the **DFT-assisted drug-discovery strategy**.

Overall, **$C_{21}H_{19}N_3O_3$** exhibits **favorable structural stability, balanced electronic properties, acceptable drug-likeness, and promising biological interaction potential**, suggesting that it may serve as a **valuable lead scaffold for future antimicrobial, antiviral, or anticancer drug development**. Further **experimental synthesis, spectroscopic validation, and biological assays** are recommended to substantiate the theoretical findings and advance the compound toward practical pharmaceutical applications.

Novelty of the Work

The present investigation introduces a **previously unexplored nitrogen-containing aromatic scaffold ($C_{21}H_{19}N_3O_3$)** and provides a **fully integrated computational evaluation** combining **DFT-based electronic structure analysis, spectroscopic prediction, molecular docking, and pharmacokinetic assessment** within a single systematic framework.

Key aspects highlighting the **novel contribution** of this study include:

1. **First comprehensive theoretical characterization** of $C_{21}H_{19}N_3O_3$, including optimized geometry, frontier molecular orbitals, global reactivity descriptors, NBO charge-transfer interactions, and MEP-based reactive site identification.
2. **Simultaneous correlation of DFT electronic descriptors with biological docking affinity**, demonstrating how **HOMO–LUMO gap, electrophilicity, and electrostatic potential** directly influence protein–ligand stabilization.
3. **Integrated spectroscopic validation through DFT-simulated IR analysis**, strengthening confidence in the predicted molecular structure prior to experimental synthesis.
4. **Early-stage pharmacological profiling using ADMET and drug-likeness prediction**, enabling rapid identification of the molecule as a **lead-like therapeutic candidate**.
5. Establishment of a **DFT-guided drug-discovery workflow** that connects **quantum-chemical stability, spectroscopic behavior, and biological activity** in a unified predictive model.

Overall, this work provides a **novel computational blueprint for evaluating nitrogen-rich aromatic drug candidates**, positioning **$C_{21}H_{19}N_3O_3$** as a **promising prototype for future rational design, synthesis, and experimental pharmacological validation**.

Future Scope

The present **DFT-guided structural, spectroscopic, and pharmacological investigation** of the nitrogen-containing aromatic compound **$C_{21}H_{19}N_3O_3$** establishes a strong theoretical foundation for its potential application as a **bioactive lead**

molecule. However, several research directions remain open for further exploration to translate the computational findings into practical pharmaceutical relevance.

1. **Experimental Synthesis and Structural Validation**

Future work should focus on the **chemical synthesis** of $C_{21}H_{19}N_3O_3$ followed by **experimental spectroscopic characterization** using FT-IR, NMR, UV–Vis, and mass spectrometry to validate the **DFT-predicted geometry and vibrational features**.

2. **In-Vitro and In-Vivo Biological Evaluation**

The promising **molecular docking affinity and ADMET predictions** warrant **biological screening** against relevant **antimicrobial, antiviral, anticancer, or anti-inflammatory targets**. Cell-line studies, enzyme inhibition assays, and toxicity profiling will confirm real pharmacological efficacy.

3. **Structure–Activity Relationship (SAR) and Molecular Optimization**

Rational modification of substituents on the **aromatic and heteroatom-containing framework** may enhance **binding affinity, selectivity, and pharmacokinetic properties**.

- Introduction of **electron-donating/withdrawing groups**
- Bioisosteric replacement of functional moieties
- Design of **derivative libraries for QSAR modeling**

4. **Advanced Computational Investigations**

Further theoretical studies may include:

- **Time-dependent DFT (TD-DFT)** for electronic absorption and excited-state behavior
- **Molecular dynamics (MD) simulations** to evaluate long-term protein–ligand stability
- **Free energy calculations (MM-PBSA/MM-GBSA)** for accurate binding energetics
- **Solvent-phase and explicit biological environment modeling**

5. **Formulation and Drug-Delivery Studies**

If biological activity is confirmed, research may extend toward **nanoformulation, targeted delivery systems, and prodrug strategies** to improve **bioavailability, stability, and therapeutic index**.

Overall, the integration of **experimental validation, biological screening, structural optimization, and advanced simulations** will be essential to advance **$C_{21}H_{19}N_3O_3$** from a **computational lead** to a **clinically relevant therapeutic candidate**, thereby expanding the scope of **nitrogen-containing aromatic drug discovery**.

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