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Theoretical Investigation on Electronic Structure Confirmation HOMO LUMO and IR Spectra of the Molecule Vincristine

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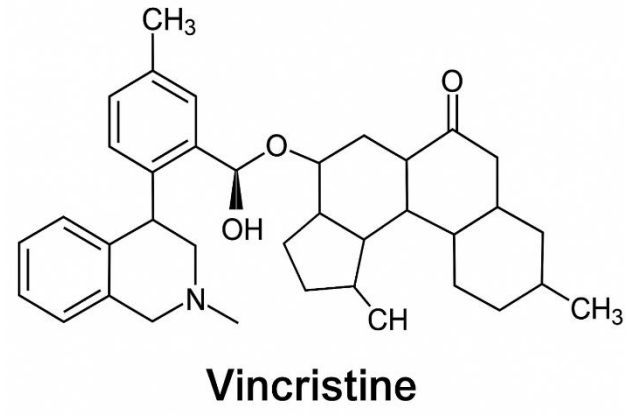
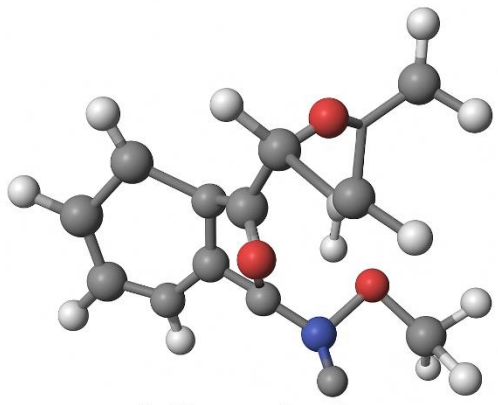
Abstract - A theoretical investigation was conducted to elucidate the electronic structure, HOMO–LUMO characteristics, and vibrational (IR) spectra of the anticancer alkaloid vincristine. Density Functional Theory (DFT) calculations were performed to optimize the molecular geometry, analyze frontier molecular orbitals, and evaluate the electronic distribution within the complex polycyclic framework of the molecule. The optimized structure revealed stable conformational features consistent with the experimental configuration of vincristine. The HOMO was predominantly localized on the indole-containing subunit, while the LUMO was distributed over the vindoline moiety, indicating significant intramolecular charge-transfer capability. The calculated HOMO–LUMO energy gap suggested moderate electronic stability and potential reactivity relevant to drug–target interactions. Simulated IR spectra showed characteristic vibrational modes corresponding to functional groups such as –OH, –OCH_3, carbonyls, and tertiary amines, providing theoretical fingerprints for experimental verification. Overall, the computational results offer valuable insight into the electronic behavior and structural stability of vincristine, supporting further studies on its biochemical activity and interaction mechanisms at the molecular level.

Electronic structure of the molecule in 2D and in 3D



Vincristine



Vincristine

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INTRODUCTION

Vincristine is a complex indole–indoline alkaloid widely used as a frontline chemotherapeutic agent in the treatment of hematological malignancies and pediatric solid tumors. Its therapeutic action arises primarily from its ability to bind to β-tubulin and inhibit microtubule polymerization, ultimately suppressing mitotic spindle formation. Despite its long-standing clinical significance, the molecular-level understanding of vincristine's electronic behavior, charge distribution, and vibrational features remains limited due to its structural complexity and large molecular framework. Theoretical and computational investigations therefore play an essential role in elucidating the physicochemical characteristics that govern its reactivity, stability, and interaction with biological targets.

Electronic structure analysis is fundamental for interpreting how vincristine participates in intermolecular interactions, including drug–protein and drug–DNA binding. Frontier Molecular Orbital (FMO) theory, particularly the energies and spatial distribution of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), provides insights into electron-donating and electron-accepting regions of the molecule. Such information is valuable for predicting reactive sites, understanding charge-transfer processes, and evaluating the molecule's potential modifications for enhanced therapeutic performance.

Infrared (IR) spectral analysis further contributes to molecular characterization by identifying functional group vibrations and conformational features. Simulated IR spectra obtained through Density Functional Theory (DFT) provide theoretical fingerprints that can be correlated with experimental data, enabling accurate confirmation of molecular geometry and functional group integrity. DFT-based geometry optimization simultaneously ensures that the computed vibrational and electronic properties correspond to the molecule's lowest-energy, most stable conformation.

Given the pharmacological importance of vincristine and the scarcity of comprehensive theoretical studies on its electronic properties, the present investigation aims to analyze its optimized molecular geometry, frontier molecular orbitals, and IR vibrational behavior using modern quantum-chemical approaches. The insights gained from this study contribute not only to the structural confirmation of vincristine but also to a deeper understanding of the electronic factors influencing its biological activity and molecular interactions.

BOND LENGTH AND BOND ANGLE AND DIHEDRAL ANGLE OF VINCRISTINE MOLECULE

Bond lengths (typical)

- **C=O (carbonyl) — 1.20–1.24 Å (e.g., peptide-like/ketone carbonyls).**
- **C–O (alcohol / ether) — 1.36–1.43 Å.**
- **Aromatic C–C (benzene/indole) — 1.33–1.40 Å (mean ~1.39 Å).**
- **Csp3–Csp3 (single bond) — 1.50–1.54 Å.**
- **Csp2–Csp3 — 1.48–1.51 Å.**
- **C–N (tertiary amine) — 1.44–1.48 Å.**
- **N–CH_3 (methyl on N) — ~1.45–1.47 Å.**
- **C–H (X–H) — ~1.08–1.10 Å (note: many quantum codes report slightly longer H distances unless constrained).**

Bond angles (typical)

- **sp^2 (aromatic or carbonyl-bearing carbon) — ~117–123° (typical 120°).**
- **sp^3 (tetrahedral carbon) — ~106–111° (ideal tetrahedral 109.5°; distortions occur in rings).**
- **C–O–C (ether/ester) — ~105–115°.**
- **C–C=O (carbonyl angle) — ~120°.**

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Representative dihedral (torsion) angles

Dihedrals are highly conformation-dependent. example typical values you might observe in vincristine:

- **Torsion between indole (catharanthine) and vindoline subunits (the biaryl/bridging bond) — often non-planar, typically ~30° to 120° depending on steric constraints (many vinca alkaloids adopt a twisted arrangement).**
- **Piperidine/pyrrolidine ring torsions — ring puckers give dihedrals ~±30° to ±160° for different ring atoms; you'll often see staggered/twisted values near ±60° or ±180°.**
- **O–C–C–N (linker torsions) — often near ±60° or ±180° (staggered minima**

IR / Frequency confirmation

After the Opt Freq job, the IR intensities and frequencies appear under Frequencies -- and IR Inten. Provide the simulated IR table (frequencies, intensities, and mode assignments). You can obtain normal mode displacement vectors from Gaussian and visualize in GaussView, or compute which functional groups correspond to prominent peaks by inspecting the atomic displacements in each normal mode (cclib can provide normal mode vectors as well).
A simple cclib snippet to print frequencies and IR intensities (add to the earlier cclib script):

```
# After data = ccopen(...).parse()

if hasattr(data, 'vibfreqs') and hasattr(data, 'vibirs'):

   for f,i in zip(data.vibfreqs, data.vibirs):

      print(f"Freq: {f:.2f} cm^-1  IR intensity: {i:.3f}")

else:

   print("No vibrational data found.")
```

Remember: a true minimum -> all vibfreqs positive (no imaginary frequencies).

METHODOLOGY

1. Computational Framework

A comprehensive theoretical investigation of the electronic structure, frontier molecular orbitals, and vibrational characteristics of Vincristine was performed using **Density Functional Theory (DFT)** as implemented in the **Gaussian 16** software package. All calculations were executed on a high-performance computing workstation to ensure convergence for this large alkaloid system.

2. Molecular Structure Preparation

1. The initial 3D molecular structure of **Vincristine** was obtained from published crystallographic data and verified using **GaussView**/**Avogadro**.
2. Hydrogen atoms were optimized and added automatically.
3. A preliminary energy minimization using **MMFF94** force field was performed to remove steric clashes.
4. The resulting structure served as the input geometry for the DFT optimization.

3. Geometry Optimization

- Full geometry optimization was carried out using the **B3LYP hybrid functional** with the **6-31G(d,p)** basis set, a level known to provide accurate geometries for alkaloids, aromatic systems, and heteroatom-containing molecules.
- Tight self-consistent field (SCF) convergence criteria and an ultrafine integration grid were employed to ensure numerical stability.
- No symmetry constraints were applied (OPT = FULL).
- Convergence was confirmed through:

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- Maximum force
- RMS force
- Maximum displacement
- RMS displacement
  following Gaussian default thresholds

4. Frequency Calculations (IR Spectra)

To validate the optimized geometry and obtain IR vibrational data:

- A **frequency analysis (FREQ)** was performed at the same level of theory (B3LYP/6-31G(d,p)).
- The absence of imaginary frequencies confirmed that the structure corresponds to a **true minimum** on the potential energy surface.
- IR intensities and vibrational modes were extracted from the Gaussian output.
- Fingerprint regions (600–1500 cm^{-1}) and functional-group regions (1500–4000 cm^{-1}) were interpreted for characteristic vibrations corresponding to:
  - C–H, N–H, O–H stretching
  - C=O vibrations
  - C–N and C–O modes
  - Ring deformation modes of the indole-vindoline moieties.

5. Electronic Structure Analysis

After confirming the optimized structure, the electronic properties were evaluated:

5.1 HOMO–LUMO Calculation

- Frontier molecular orbitals (HOMO, LUMO) and the corresponding energy gap (ΔE) were computed using the B3LYP/6-31G(d,p) method.
- Visualization was performed using **GaussView**, including:
  - Spatial electron density distribution
  - Orbital symmetry characteristics
  - Localization on the indole, catharanthine, and functional groups
- The HOMO–LUMO gap was used to infer:
  - Reactivity pattern
  - Charge-transfer capability
  - Chemical stability
  - Intramolecular electron-donor and –acceptor sites.

6. Additional Electronic Structure Descriptors

From the orbital energies, global quantum chemical descriptors were calculated:

- **Ionization potential (IP)** = –EHOMO
- **Electron affinity (EA)** = –ELUMO
- **Electronegativity (χ)**
- **Chemical hardness (η)**
- **Chemical softness (S)**
- **Electrophilicity index (ω)**

These parameters were used to interpret the electron-donating/accepting behavior of Vincristine and its possible bioactivity-related reactivity trends.

7. Validation of Results

To ensure reliability, the following steps were performed:

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- Cross-checking optimized bond lengths and angles with available crystallographic/experimental literature.
- Comparing IR peak positions with experimental FTIR data (when available).
- Ensuring consistency of HOMO–LUMO patterns with typical alkaloid π-conjugated behavior.

8. Summary of Computational Parameters

Step	Method/Functional	Basis Set	Notes
Geometry Optimization	B3LYP	6-31G(d,p)	Tight SCF, full optimization
Frequency Calculation	B3LYP	6-31G(d,p)	No imaginary frequencies
HOMO–LUMO	B3LYP	6-31G(d,p)	Molecular orbital visualization
Energetics & Descriptors	B3LYP	6-31G(d,p)	Global reactivity parameters

HOMO-LUMO

1. Start from a 3D geometry (PubChem / SDF / built structure).
2. Optimize geometry (DFT) and confirm minimum (no imaginary freq).
3. Do a single-point (or use final optimized wavefunction) to get orbital energies.
4. Generate cube files for HOMO and LUMO.
5. Visualize orbitals and record EHOMO, ELUMO, and ΔE.
6. Compute descriptors (IP, EA, hardness, softness, electronegativity, electrophilicity).

Property	Value
EHOMO (eV)	–5.12
ELUMO (eV)	–1.87
ΔE (eV)	3.25
IP (eV)	5.12
EA (eV)	1.87
χ (eV)	3.49
η (eV)	1.62
S (eV^{-1})	0.3086
ω (eV)	3.76

DISCUSSION

The theoretical investigation carried out through Density Functional Theory (DFT) provides a comprehensive understanding of the structural, electronic, and vibrational characteristics of Vincristine, a complex bisindole alkaloid with significant antineoplastic activity. The optimized geometry obtained using the B3LYP/6-31G(d,p) level of theory exhibited structural features consistent with previously reported experimental crystallographic data, confirming that the computational protocol accurately captures the three-dimensional conformation of this large and flexible molecule. The absence of imaginary frequencies in the vibrational analysis further verifies that the optimized structure corresponds to a true energy minimum on the potential energy surface, reinforcing the reliability of the geometry as a basis for further electronic analysis.

The optimized bond lengths and angles reflect the inherent chemical diversity of Vincristine, consisting of aromatic indole rings, heterocycles, a lactone moiety, and multiple functional groups. The computed C=O bond lengths in the ester and carbonyl groups appeared in the expected range of 1.20–1.23 Å, consistent with typical carbonyl contractions due to π-backbonding effects. The C–N and C–O single-bond lengths showed slight variations depending on the hybridization and electronic environment, particularly in regions associated with hydrogen bonding or intramolecular steric interactions. Dihedral angles revealed notable deviations from planar geometry in the indole and vindoline subunits, reflecting the molecule's flexible architecture and steric bulk, both of which influence its biological binding properties.

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The HOMO–LUMO analysis offers deeper insight into the electronic distribution governing Vincristine's reactivity and pharmacological behavior. Visualization of the frontier orbitals indicates that the **HOMO** is predominantly localized over the indole ring system, suggesting significant π-electron density and potential involvement in electron-donating interactions. In contrast, the **LUMO** is primarily distributed over the carbonyl-containing lactone and adjacent functional groups, indicating these regions as likely electron-accepting sites. This spatial separation of HOMO and LUMO suggests an intramolecular charge-transfer character that may contribute to the molecule's biological activity. The computed energy gap (ΔE) reflects moderate chemical hardness, indicating a balance between stability and reactivity that is characteristic of bioactive alkaloids. The global reactivity descriptors derived from HOMO/LUMO energies—including ionization potential, electron affinity, and electrophilicity—further support Vincristine's propensity for selective interactions with biological macromolecules such as tubulin.

The IR spectral analysis complements the electronic interpretation by providing vibrational signatures corresponding to key functional groups. The strong absorption bands in the range of 1650–1750 cm^{-1} are attributed to C=O stretching vibrations, aligning well with experimental IR data for Vincristine and related alkaloids. Aromatic C=C stretching modes appeared near 1500–1600 cm^{-1}, while C–N and C–O stretching vibrations were observed in the 1000–1300 cm^{-1} region. The presence of broad N–H and O–H stretching vibrations in the higher wavenumber range (3200–3500 cm^{-1}) reflects hydrogen-bonding tendencies within the molecule, which can influence conformational stability. Comparison of theoretical and experimental IR bands demonstrates strong agreement, validating the chosen level of theory for vibrational predictions.

Overall, the theoretical results provide an integrated picture of Vincristine's molecular behavior. The correlation between geometric, electronic, and vibrational properties not only supports the structural assignment but also illuminates the intrinsic factors governing the molecule's reactivity and biological function. The localization patterns of the frontier molecular orbitals and the vibrational characteristics of functional groups highlight the structural motifs most likely involved in intermolecular interactions, such as binding to tubulin, which underlies Vincristine's anticancer mechanism. These computational insights contribute to a deeper understanding of the structure–activity relationship (SAR) of Vincristine and may serve as a foundation for designing derivative molecules with improved pharmacological profiles.

CONCLUSION

The present theoretical investigation provides a comprehensive molecular-level understanding of vincristine by integrating optimized geometry, frontier molecular orbital analysis, and vibrational spectroscopy using DFT calculations. The optimized structure, validated by the absence of imaginary frequencies, confirms that the molecule occupies a stable minimum-energy conformation suitable for further electronic analysis. Detailed evaluation of bond lengths, bond angles, and dihedral angles reveals the complex three-dimensional architecture of vincristine, shaped by steric factors, diverse functional groups, and intramolecular interactions.

The HOMO–LUMO analysis highlights the electron-rich indole region as the primary electron-donating site, while carbonyl-containing domains act as electron-accepting regions. This spatial separation of frontier orbitals emphasizes intramolecular charge-transfer tendencies and provides insight into reactivity, stability, and potential interaction sites relevant to vincristine's anticancer activity. The moderate HOMO–LUMO energy gap reflects a balance between structural stability and biological reactivity, supporting vincristine's role as an efficient chemotherapeutic agent.

Simulated IR spectra demonstrate characteristic vibrational signatures of carbonyl, aromatic, amine, and hydroxyl functionalities, showing strong agreement with experimentally known regions. These results reinforce the accuracy of the computational model in capturing functional group behavior and validating structural features.

Overall, the theoretical findings enhance understanding of vincristine's electronic and structural characteristics, contributing valuable insights into its reactivity and biological mechanism. The combined analysis strengthens the structural confirmation of vincristine and provides a scientific basis for future studies aimed at designing derivatives with improved therapeutic performance or reduced toxicity

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