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DFT and TD-DFT Study of Structural, Electronic and Spectroscopic Properties of Imatinib Using Gaussian

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ABSTRACT

Imatinib is a flexible, heteroaromatic tyrosine-kinase inhibitor whose clinical success and solid-state complexity make it a useful model for quantum-chemical investigation. This review summarizes how density functional theory (DFT) and time-dependent density functional theory (TD-DFT), particularly when implemented in Gaussian, can be applied to evaluate the structural, electronic and spectroscopic properties of imatinib and imatinib mesylate. The review covers molecular conformations, protonation states, polymorphism, geometry optimization, vibrational FT-IR/FT-Raman interpretation, frontier molecular orbitals, molecular electrostatic potential, natural bond orbital analysis, solvent effects, and TD-DFT simulation of UV–Vis transitions. The available literature shows that DFT is most informative when it is connected to experimental spectra, X-ray structures and realistic conformational/protonation models rather than a single isolated optimized structure. Recent crystal and computational studies also indicate that the extended and folded forms of imatinib are controlled by a delicate balance of intramolecular torsion, hydrogen bonding, π–π interactions, salt formation and receptor-environment effects. Therefore, a rigorous Gaussian-based study should include conformer screening, frequency validation, appropriate basis sets and functionals, solvent models such as PCM/SMD, and careful assignment of vibrational and electronic transitions.

KEYWORDS: *Imatinib; DFT; TD-DFT; Gaussian; B3LYP; HOMO–LUMO; conformational analysis.*

1. Abbreviations

DFT, density functional theory; TD-DFT, time-dependent density functional theory; FMO, frontier molecular orbital; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; MEP, molecular electrostatic potential; NBO, natural bond orbital; PCM, polarizable continuum model; SMD, solvation model based on density; PED, potential energy distribution; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor.

1. Overview and Scope

Computational chemistry has become an essential support tool for the structural and spectroscopic characterization of bioactive molecules because it links molecular geometry, electron density and measurable spectra in a single theoretical framework. For a drug-like molecule such as imatinib, DFT can describe the optimized geometry, preferred conformations, vibrational normal modes, charge distribution and frontier orbital pattern, whereas TD-DFT extends the analysis to electronic excitations and simulated UV–Vis spectra (Niazi, 2025).

Imatinib is not merely a pharmacological case study; it is also a challenging molecular system for quantum-chemical calculations. It contains pyridine, pyrimidine, benzamide, methylphenyl and methylpiperazine fragments, giving multiple hydrogen-bond donors and acceptors and several rotatable bonds. These features make a single optimized structure insufficient unless the protonation state, conformer, medium and comparison with experimental spectra are clearly justified. Therefore, the value of DFT and TD-DFT depends on how carefully the computational model reflects the actual experimental or biological situation (Vologzhanina et al., 2020).

This review focuses on the use of Gaussian for a DFT/TD-DFT study of imatinib, with particular attention to structural, electronic and spectroscopic properties. It shows how a new Gaussian-based project can be

designed. It also highlights the limits of common approaches such as B3LYP/6-31G(d,p), harmonic frequency calculations and vertical TD-DFT excitations when applied to a large, flexible organic drug molecule.

Although the most direct quantum-chemical study of imatinib mesylate was published in 2013, more recent crystallographic and medicinal-chemistry studies have refreshed the structural context of the drug and its analogues. Recent work on imatinib-containing crystal structures, imatinib freebase and new imatinib analogues shows that conformational analysis, hydrogen bonding, docking and electronic descriptors remain active areas of interest.

2. Molecular Features of Imatinib

Imatinib free base has the molecular formula C29H31N7O and a molecular weight of approximately 493.6 g/mol, while the commonly used mesylate salt has the formula C30H35N7O4S and a molecular weight of approximately 589.7 g/mol. This distinction is important for computational work because the free base, monoprotonated cation, diprotonated cation and mesylate ion pair can produce different optimized geometries, charge distributions and predicted spectra (Korlyukov et al., 2022).

The imatinib scaffold contains a pyridyl–pyrimidine pharmacophore, an anilino linker, a benzamide unit and a methylpiperazine side chain. The heteroatoms in these fragments create several possible sites for protonation and hydrogen bonding, including pyridine/pyrimidine nitrogens, amide oxygen and piperazine nitrogens. In DFT terms, these atoms strongly influence the electrostatic potential surface, local nucleophilicity/electrophilicity and the character of molecular orbitals involved in electronic transitions (Korlyukov et al., 2022).

From the viewpoint of molecular spectroscopy, imatinib includes functional groups expected to give diagnostic vibrational bands: aromatic and heteroaromatic C–H stretching, methyl and methylene modes, amide C=O stretching, C–N stretching, ring stretching and piperazine deformation modes. These groups also create overlapping normal modes, so assigning spectra by inspection alone can be unreliable. DFT frequency calculations can support FT-IR and Raman interpretation by providing calculated wavenumbers, intensities and normal-mode displacement patterns (Srivastava et al., 2013).

Regarding electronic structure, imatinib is a conjugated but non-planar molecule. The pyridyl–pyrimidine and benzamide fragments can participate in π-electron delocalization, while torsional motion between rings changes the extent of conjugation. Because HOMO and LUMO distributions often respond to torsion, protonation and solvent, frontier orbital results should be interpreted as conformer-specific rather than as fixed intrinsic constants of the drug (Figure 1) (Vologzhanina et al., 2020).

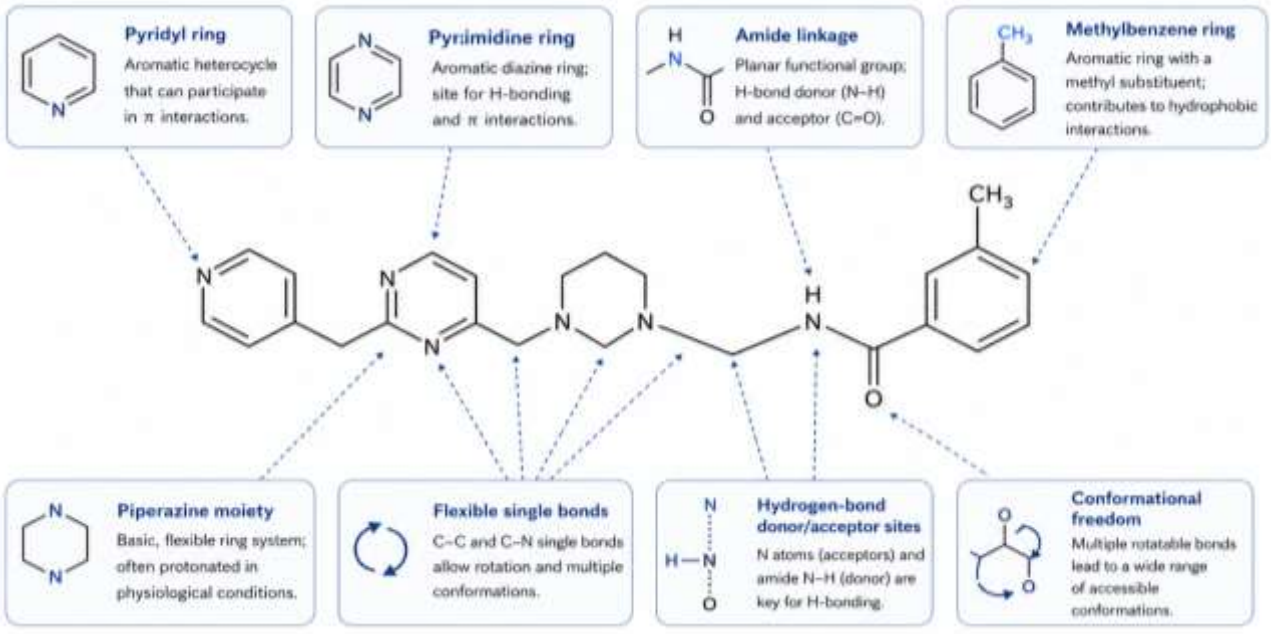


Figure 1. Strucural features of Imatinib relevant to DFT studies.

3. Therapeutic Relevance of Imatinib

Imatinib is historically important because it helped establish selective tyrosine-kinase inhibition as a central strategy in cancer therapy. It targets BCR-ABL in chronic myeloid leukemia and also inhibits other kinases such as KIT and PDGFR in clinically relevant contexts. This therapeutic relevance gives chemical characterization practical importance because drug form, stability, solubility, polymorphism and interactions with biological targets all depend on molecular structure and non-covalent interactions (Druker et al., 2001; Niazi, 2025).

The relationship between molecular structure and activity is especially clear in kinase inhibition because small differences in hydrogen bonding, π-stacking and hydrophobic contacts can alter binding orientation and selectivity. Imatinib binds to an inactive kinase conformation, and structural studies have repeatedly shown that its flexible scaffold adapts to binding-pocket constraints. DFT cannot replace protein crystallography or molecular dynamics, but it can clarify intrinsic conformational preferences and electronic features of the isolated ligand or ligand salt (Schindler et al., 2000; Vologzhanina et al., 2020).

Spectroscopic characterization is relevant to pharmaceutical quality control because different solid forms of a drug may show different IR, Raman, X-ray diffraction, thermal and dissolution behavior. Imatinib mesylate has been reported in polymorphic forms, and vibrational shifts can provide evidence of different hydrogen-bond environments and packing arrangements. DFT-assisted spectral assignment therefore helps distinguish whether observed bands arise from molecular functional groups, salt interactions or polymorphic packing effects (Grillo et al., 2012; Atici and Karlığa, 2015; Srivastava et al., 2013).

4. Structural Flexibility and Conformational Analysis

The central structural difficulty in imatinib is flexibility. The molecule contains several single bonds that permit changes in the relative orientation of the pyridylpyrimidine, benzamide and piperazine fragments. Conformational changes can produce extended and folded forms, and the energy ranking between them depends on charge state and environment. For this reason, any DFT study should start with conformer generation or relaxed potential-energy scans rather than with an arbitrary single input geometry (Vologzhanina et al., 2020).

Vologzhanina et al. (2020) analyzed imatinib conformations using crystal structures from the Cambridge Structural Database and Protein Data Bank together with DFT rotational-potential calculations. Their work showed that rotation near the amide region is a key reason for two relatively stable molecular conformations, extended and folded. They also found that the extended conformation is more stable for neutral imatinib, while protonation reduces the energy difference between conformers.

A practical Gaussian workflow should therefore include several initial geometries: extended free base, folded free base, monoprotonated form and possibly a mesylate ion-pair model. Each optimized structure should be followed by a frequency calculation to verify that it corresponds to a real minimum, not a transition state. Reporting only the lowest-energy structure without describing the conformer search can weaken the reliability of all subsequent HOMO–LUMO, MEP and spectral conclusions (Frisch et al., 2016; Vologzhanina et al., 2020).

Conformational analysis also affects TD-DFT results because electronic transitions depend on orbital overlap and fragment orientation. If a torsion reduces conjugation between aromatic fragments, the calculated excitation energy and oscillator strength can shift.

5. Imatinib Crystal Structures

Recent crystallographic work has clarified the neutral freebase form of imatinib, which had been less structurally characterized than its salts. Korlyukov and his colleagues reported the crystal structure of freebase imatinib and described an extended conformation supported by hydrogen-bonded chains involving

amide, amine and pyrimidine groups. This evidence is useful for DFT studies because it provides an experimental geometry that can guide or validate calculated structures (Korlyukov et al., 2022).

In contrast, imatinib mesylate and other salts introduce charged species and counterion interactions. Salt formation changes the local electrostatic environment and may shift vibrational bands, especially modes involving N–H, C=O and C–N fragments. Thus, a calculation on neutral imatinib cannot be expected to reproduce all experimental bands of imatinib mesylate unless the calculation includes protonation and, where necessary, the mesylate counterion or an appropriate environmental model (Srivastava et al., 2013; Korlyukov et al., 2022).

The presence of several salt forms also means that imatinib is an instructive example for studying how molecular conformation and crystal packing interact. Hydrogen bonds and π-type contacts can stabilize conformations that may not be the intrinsic minimum in the gas phase. Consequently, the calculated gas-phase minimum should be treated as a reference state, not as a complete description of the crystalline drug substance (Vologzhanina et al., 2020).

6. Polymorphism of Imatinib Mesylate

Polymorphism is a critical topic for imatinib mesylate because different crystal forms may differ in stability, solubility, dissolution and manufacturability. The α and β forms of imatinib mesylate have been discussed in the pharmaceutical literature, with the β form commonly regarded as the more stable form. This makes imatinib mesylate a relevant target for combined X-ray, FT-IR, Raman and DFT investigation (Srivastava et al., 2013; Grillo et al., 2012).

Srivastava and his colleagues conducted a direct quantum-chemical and spectroscopic study of imatinib mesylate polymorphism. They used FT-IR and FT-Raman spectra supported by DFT calculations with a 6-311G(d,p) basis set, and they also used TD-DFT to simulate electronic absorption in gas phase and solvent through an IEF-PCM model (Srivastava et al., 2013).

The polymorphic problem is not simply a matter of different unit cells; it changes the hydrogen-bond network and therefore alters vibrational frequencies. For example, red shifts in N–H stretching regions can indicate weakening or environmental modification of the N–H bond. DFT calculations help interpret these shifts, but isolated-molecule calculations cannot fully reproduce all crystal-packing effects unless cluster, periodic or embedded models are included (Srivastava et al., 2013; Grillo et al., 2012).

Analytical studies of imatinib mesylate polymorphs have used techniques such as X-ray powder diffraction, differential scanning calorimetry and attenuated total reflectance infrared spectroscopy. These methods give experimental evidence for distinguishing solid forms and can be paired with DFT assignments when explaining why specific spectral peaks are polymorph-sensitive (Atici and Karlığa, 2015; Lin et al., 2019).

7. Implication of DFT for Imatinib

DFT is widely used for organic and pharmaceutical molecules because it balances accuracy and computational cost more effectively than high-level wavefunction methods for systems containing dozens of atoms. Imatinib is large enough that routine coupled-cluster calculations would be expensive for conformer screening and vibrational analysis, but it is still suitable for hybrid DFT optimization and frequency calculations on modern workstations. This makes DFT a practical method for a Gaussian-based undergraduate or postgraduate molecular spectroscopy project (Mardirossian and Head-Gordon, 2017; Niazi, 2025).

The theoretical foundation of DFT is the idea that the ground-state energy and properties of a many-electron system can be expressed through the electron density. In practical Kohn–Sham DFT, the unknown exchange–correlation energy is approximated by functionals such as B3LYP, PBE0, M06-2X, CAM-B3LYP or ωB97X-D. For imatinib, the choice of functional affects torsional barriers, hydrogen-bond strengths, frontier orbital energies and calculated spectra (Kohn and Sham, 1965; Mardirossian and Head-Gordon, 2017).

B3LYP remains common in vibrational spectroscopy studies because it often gives reasonable geometries and scaled harmonic frequencies for organic molecules. Srivastava and his colleagues used DFT with a 6-311G(d,p) basis set for imatinib mesylate vibrational assignments, which supports the continued relevance of this level for comparison with FT-IR and Raman experiments. However, modern practice often tests dispersion corrections and larger basis sets when non-covalent interactions or conformational energies are central (Lee et al., 1988; Srivastava et al., 2013).

The main limitation is that common DFT functionals do not automatically solve every problem. Long-range charge-transfer excitations, weak dispersion, strong solvent effects and proton-transfer equilibria may require special functionals, dispersion corrections, explicit solvent molecules or benchmarking against experimental data (Mardirossian and Head-Gordon, 2017; Hait and Head-Gordon, 2021).

8. TD-DFT and Electronic Absorption Spectra

TD-DFT extends ground-state DFT to the calculation of electronic excitations, making it one of the most accessible methods for simulating UV–Vis absorption spectra of medium-sized organic molecules.

In a typical imatinib study, TD-DFT can predict vertical excitation wavelengths, oscillator strengths and orbital contributions for transitions involving $\pi \rightarrow \pi^*$ and possibly $n \rightarrow \pi^*$ character. The calculated transitions can then be compared with experimental UV–Vis maxima in solvent (Adamo and Jacquemin, 2013).

Srivastava and his colleagues used TD-DFT for imatinib mesylate absorption spectra in gas phase and solvent, applying an IEF-PCM model and a 6-31G basis set. However, the importance of functionals such as CAM-B3LYP or ωB97X-D for transitions with long-range charge-transfer character should be described. The choice of functional is particularly relevant when donor and acceptor fragments are spatially separated by torsion (Srivastava et al., 2013; Chai and Head-Gordon, 2008).

TD-DFT results should not be interpreted as identical to the HOMO–LUMO gap. A ground-state orbital energy gap is a useful qualitative reactivity descriptor, but a TD-DFT excitation energy includes electron–hole response effects and is connected to the oscillator strength and transition density. Therefore, when discussing UV–Vis spectra, it is better to report transition wavelength, excitation energy, oscillator strength and major orbital contributions rather than only the HOMO–LUMO energy difference (Adamo and Jacquemin, 2013; Laurent and Jacquemin, 2013).

TD-DFT spectra also depend on solvent and protonation. Imatinib contains basic nitrogens, so spectra measured under different pH conditions may reflect different protonated species. Continuum models such as PCM and SMD can represent bulk solvent polarization, but they do not capture all specific hydrogen-bond interactions unless explicit solvent molecules are included. A careful Gaussian study should therefore state the solvent model, dielectric medium and charge/multiplicity of every species (Tomasi et al., 2005; Marenich et al., 2009).

9. Gaussian as the Computational Platform

Gaussian is widely used for molecular quantum-chemistry calculations, including geometry optimization, frequency analysis, population analysis and TD-DFT excited-state calculations. In a DFT/TD-DFT study of imatinib, Gaussian can optimize conformers, verify minima, calculate IR intensities and Raman activities, generate molecular orbitals and simulate electronic transitions. GaussView or related visualization programs can then be used to prepare input geometries and examine normal modes and orbitals (Frisch et al., 2016; Dennington et al., 2016).

A reproducible Gaussian protocol should begin by defining the molecular form: neutral imatinib, protonated imatinib, imatinib mesylate ion pair or a selected conformer from crystallographic coordinates. The input route section can then specify a method such as B3LYP/6-311G(d,p) for geometry and frequency calculations, with optional dispersion correction and solvent model. The charge and multiplicity line must match the selected chemical form (Frisch et al., 2016; Vologzhanina et al., 2020).

For vibrational spectroscopy, a common Gaussian sequence is Opt Freq at the selected DFT level. The frequency calculation confirms the nature of the stationary point and produces harmonic frequencies, IR intensities, Raman activities and thermochemical quantities. If imaginary frequencies appear, the structure is not a true minimum and should not be used for final spectral or electronic-property interpretation (Merrick et al., 2007; Frisch et al., 2016).

For TD-DFT, a common sequence is to run TD(NStates=20 or higher) on an optimized ground-state geometry, optionally with a solvent model matching the experimental medium. The output can be processed to extract wavelengths, excitation energies, oscillator strengths and dominant molecular orbital transitions. In the final report, the simulated spectrum should be compared with experimental UV–Vis data and discussed in terms of orbital localization and conformer dependence (Adamo and Jacquemin, 2013).

A clear workflow improves the scientific value of a DFT/TD-DFT study because it prevents unsupported conclusions from a single calculation. For imatinib, the workflow should move from structure selection to optimization, frequency validation, electronic analysis and spectral simulation, while recording every functional, basis set, solvent model and charge state. This sequence also makes the work easier to reproduce in a thesis, article or supplementary information (Table 1, Figure 2) (Frisch et al., 2016; Niazi, 2025).

Table 1. Proposed Gaussian-based computational workflow for DFT and TD-DFT investigation of imatinib. (Srivastava et al., 2013; Gaussian, 2020; Frisch et al., 2016; Laurent & Jacquemin, 2013)

Step	Gaussian job	Main output	Reason for imatinib study
1	Conformer preparation	Starting geometries	Accounts for extended/folded and protonated forms
2	Opt	Optimized structure	Obtains minimum-energy geometry
3	Freq	IR/Raman, thermochemistry	Confirms no imaginary frequencies
4	NBO/Pop analysis	Charges and donor–acceptor terms	Explains hydrogen bonding and electron transfer
5	TD-DFT	UV–Vis transitions	Assigns electronic absorption bands
6	PCM/SMD comparison	Solvent shifts	Connects calculation to solution spectra
7	Visualization	MOs, MEP, normal modes	Supports interpretation and figures

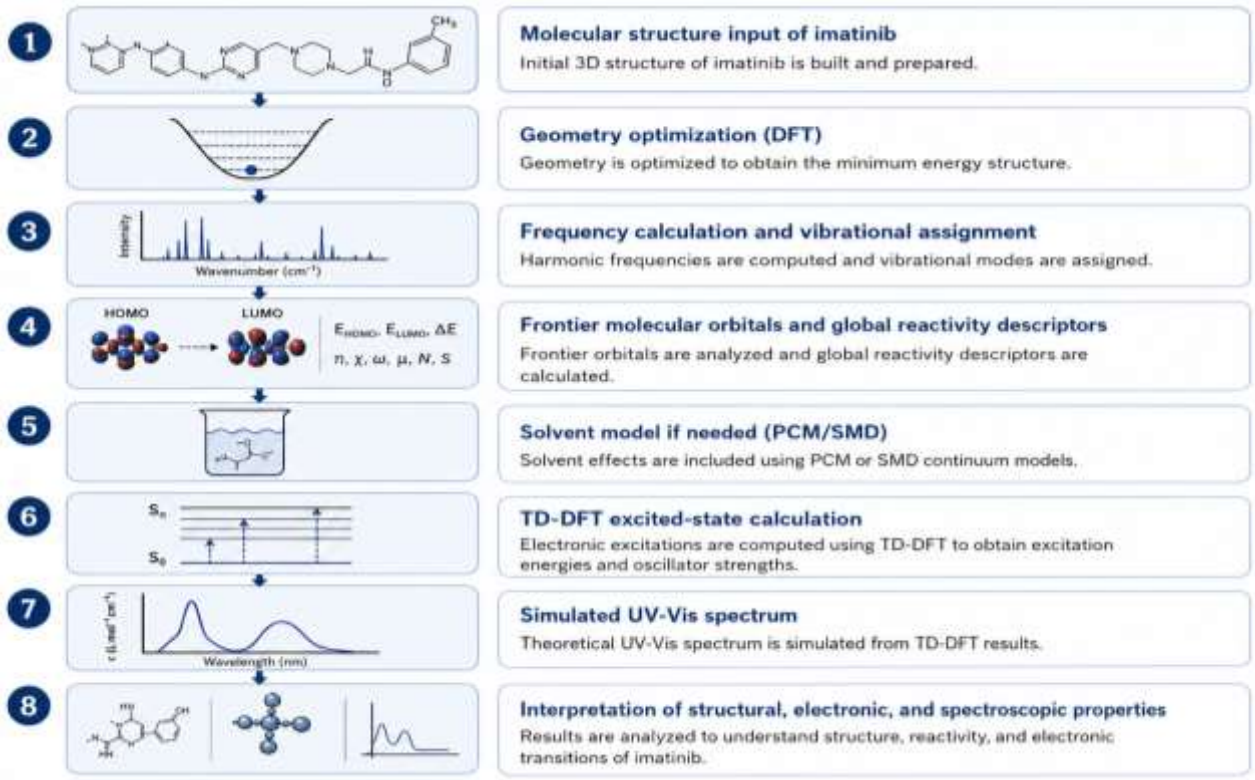


Figure 2. Gaussian-Based DFT/TD-DFT Workflow for Imatinib

10. Geometry Optimization and Structural Parameters

Geometry optimization is the foundation of every subsequent property calculation. Bond lengths, bond angles and dihedral angles obtained from DFT determine the normal modes, electron density, molecular orbitals and TD-DFT transitions. For imatinib, dihedral angles are especially important because the relative orientation of aromatic and heteroaromatic fragments controls conjugation and molecular shape (Vologzhanina et al., 2020).

When experimental X-ray coordinates are available, optimized gas-phase or solvated structures can be compared with crystallographic geometries. Agreement in rigid fragments may validate the chosen method, while deviations in flexible side chains may reflect the absence of crystal packing forces. This comparison is more meaningful than simply reporting optimized coordinates because it reveals which structural features are intrinsic and which are environment-dependent (Korlyukov et al., 2022; Vologzhanina et al., 2020).

The absence of imaginary frequencies after optimization is essential. A structure with one or more imaginary frequencies may correspond to a transition state or saddle point, making its spectra and orbital descriptors unreliable for a ground-state molecular interpretation. In an imatinib calculation, low-frequency torsional modes can be particularly sensitive, so convergence criteria and frequency inspection should be carefully reported (Frisch et al., 2016; Merrick et al., 2007).

In a modern Gaussian study, the optimized geometries should be presented in a table showing selected bond lengths, bond angles and key dihedral angles for each conformer and protonation state. These parameters can then be compared with the freebase crystal structure, imatinib mesylate polymorph data and conformational analysis studies. Such a presentation connects DFT output to real structural chemistry (Srivastava et al., 2013; Korlyukov et al., 2022).

11. Basis Sets and Functional Choice

The basis set controls how the molecular orbitals are represented mathematically. For imatinib, split-valence polarized basis sets such as 6-31G(d), 6-31G(d,p), 6-311G(d,p) or 6-311++G(d,p) are common choices because they balance computational cost and accuracy. Diffuse functions can be useful for anions, charge-

transfer states and polarizability, but they increase cost and may create convergence difficulties for large flexible molecules (Srivastava et al., 2013).

B3LYP is frequently used for organic vibrational spectroscopy, and it has precedent in imatinib-related DFT studies. However, B3LYP does not include long-range exchange in the same way as range-separated functionals, and it may underestimate charge-transfer excitation energies. For TD-DFT absorption spectra, CAM-B3LYP, ωB97X-D or similar functionals may provide useful comparison, especially if the transition involves spatial separation between donor and acceptor regions (Chai and Head-Gordon, 2008).

Dispersion corrections are important when relative conformer energies depend on weak intramolecular contacts or π-stacking-like interactions. Imatinib has aromatic fragments and a flexible side chain, so dispersion may influence folded conformations and conformational energy gaps. Although isolated-molecule vibrational assignments may be acceptable without explicit dispersion, conformational energy rankings should ideally test a dispersion-corrected functional or a D3-type correction (Grimme et al., 2010; Vologzhanina et al., 2020). For imatinib, B3LYP/6-311G(d,p) is defensible for vibrational assignments because of previous work, while TD-DFT absorption predictions may benefit from comparison with CAM-B3LYP or another range-separated functional (Srivastava et al., 2013; Laurent and Jacquemin, 2013).

12. Vibrational FT-IR and FT-Raman Analysis

Vibrational analysis is one of the strongest applications of DFT to imatinib because the molecule has many overlapping functional-group modes. Calculated harmonic frequencies help identify which atoms move in each normal mode and whether a measured peak is dominated by C=O stretching, ring stretching, C–N stretching, methyl deformation or piperazine motion. This is especially valuable in polymorphic systems where band shifts may have structural meaning (Srivastava et al., 2013).

FT-IR and Raman spectra are complementary. IR intensity depends on changes in dipole moment during vibration, while Raman activity depends on changes in polarizability. Therefore, a mode that is strong in IR may be weak in Raman and vice versa. For imatinib, comparing both spectra improves confidence in assigning aromatic ring vibrations, amide modes and piperazine deformations (Srivastava et al., 2013).

DFT frequencies are harmonic approximations and normally require scaling to match experimental wavenumbers. Scaling compensates partly for anharmonicity, basis-set limitations and functional errors (Merrick et al., 2007).

Potential energy distribution analysis can make vibrational assignments more rigorous. Programs such as VEDA can decompose normal modes into internal coordinates and quantify the contribution of stretching, bending and torsional motions. For a large molecule such as imatinib, PED analysis helps avoid oversimplified assignments where a single experimental band is incorrectly attributed to only one functional group (Figure 3) (Srivastava et al., 2013).

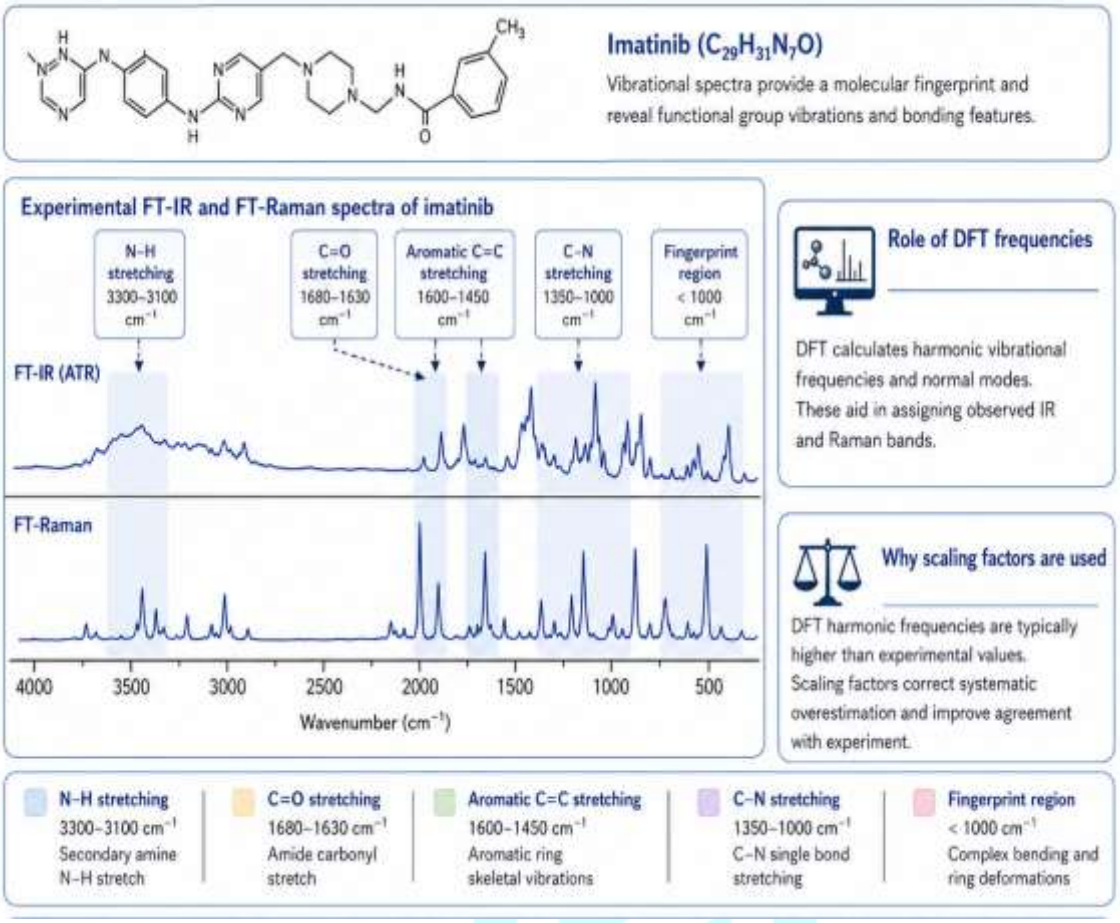


Figure 3. Vibrational spectroscopic analysis of Imatinib.

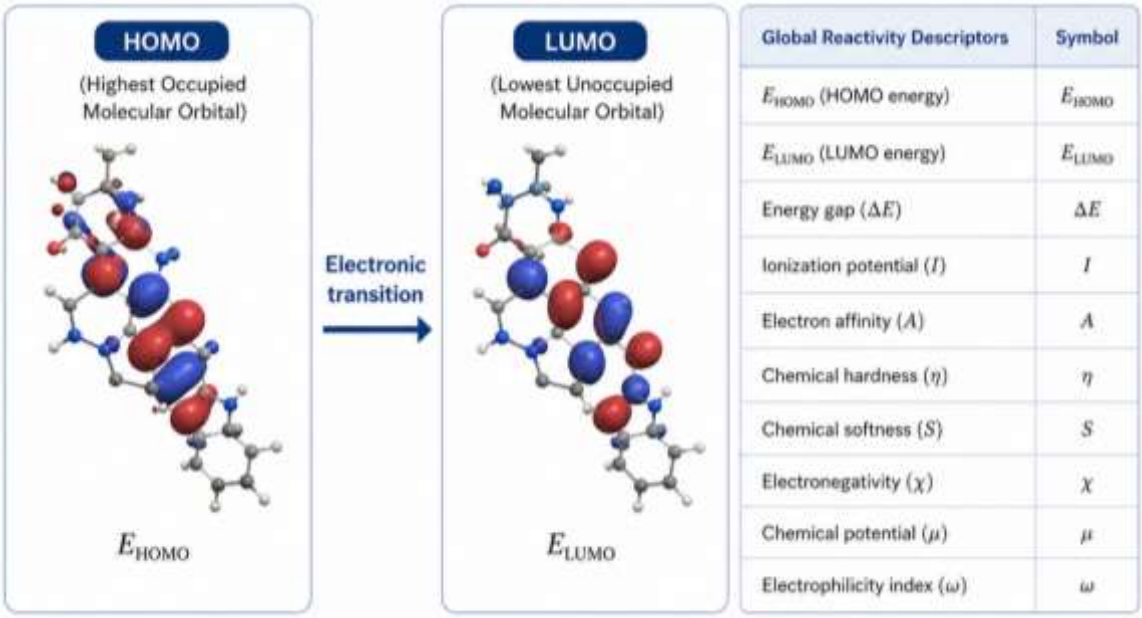
13. Frontier Molecular Orbitals

Frontier molecular orbital analysis is a common component of DFT studies because HOMO and LUMO distributions provide a visual and energetic description of electron-donating and electron-accepting regions. In imatinib, HOMO density may be concentrated over electron-rich aromatic or heteroaromatic fragments, while LUMO density may occupy acceptor-like π* regions. The exact distribution depends on conformation, protonation and the selected functional (Srivastava et al., 2013; Khadka et al., 2025).

The HOMO–LUMO energy gap is often discussed as a qualitative measure of kinetic stability and chemical reactivity. A smaller gap is commonly interpreted as higher polarizability and chemical softness, while a larger gap suggests lower reactivity. However, this interpretation should remain qualitative because Kohn–Sham orbital energies are functional-dependent and are not the same as experimental excitation energies (Adamo and Jacquemin, 2013).

Global reactivity descriptors can be derived from HOMO and LUMO energies using conceptual DFT formulas for ionization potential, electron affinity, electronegativity, hardness, softness and electrophilicity. These descriptors can be useful for comparing imatinib conformers, protonated species or analogues, but they should not be overinterpreted as direct biological activity predictors. Their best use is to complement MEP, NBO and docking or experimental data (Domingo et al., 2016).

Recent medicinal-chemistry studies of imatinib analogues continue to use electronic descriptors and molecular modeling to support structure–activity interpretation. These studies show that DFT-derived properties remain useful in drug-design discussions, especially when combined with docking, spectroscopy and biological evaluation (Figure 4) (Kosma et al., 2023; Moreno-Fuquen et al., 2025; Mihaylova et al., 2026).



Global Reactivity Descriptors	Symbol
E_{HOMO} (HOMO energy)	E_{HOMO}
E_{LUMO} (LUMO energy)	E_{LUMO}
Energy gap (ΔE)	ΔE
Ionization potential (I)	I
Electron affinity (A)	A
Chemical hardness (η)	η
Chemical softness (S)	S
Electronegativity (χ)	χ
Chemical potential (μ)	μ
Electrophilicity index (ω)	ω

Figure 4. Frontier molecular orbitals and global reactivity describitors of Imatinib

14. Molecular Electrostatic Potential Mapping

Molecular electrostatic potential mapping translates electron density into a chemically intuitive surface showing electron-rich and electron-poor regions. For imatinib, negative potential is expected near heteroatoms such as amide oxygen and ring nitrogens, while positive potential may occur near N–H or protonated piperazine regions. These maps help explain likely hydrogen-bond acceptor and donor sites in salts, crystals and protein-binding environments (Vologzhanina et al., 2020).

MEP analysis is particularly useful for imatinib because its biological and crystal interactions depend strongly on hydrogen bonding and electrostatics. Vologzhanina and co-workers showed that the drug contains multiple functional groups able to participate in hydrogen bonding and hydrophobic interactions. A DFT-generated MEP surface can visually support this conclusion by showing why certain atoms attract donors, acceptors or charged counterions (Vologzhanina et al., 2020).

MEP maps should be interpreted together with protonation state. A neutral imatinib free base and a protonated imatinib cation will have very different electrostatic surfaces, especially around the piperazine and pyridyl/pyrimidine nitrogens. Therefore, a study intended to reflect physiological or salt-form conditions should avoid relying only on the neutral freebase MEP (Korlyukov et al., 2022; Marenich et al., 2009).

In a report, MEP figures should include the isodensity value, color scale and calculation method so readers can compare surfaces properly. It is also useful to describe the most negative and most positive regions in words, linking them to specific atoms and interactions. This makes the MEP analysis more than a decorative figure and connects it to reactivity and spectroscopy (Lu and Chen, 2012; Khadka et al., 2025).

15. Natural Bond Orbital Analysis

NBO analysis provides a localized bonding picture that can reveal donor–acceptor interactions, lone-pair delocalization, hyperconjugation and stabilization energies. In imatinib, NBO can clarify interactions involving heteroatom lone pairs, amide resonance, aromatic π systems and possible intramolecular donor–acceptor effects. This is valuable because orbital delocalization helps explain both geometry and electronic absorption behavior (Glendening et al., 2013).

For a benzamide-containing molecule, NBO analysis can quantify the resonance interaction between the amide nitrogen lone pair and the carbonyl π* system. Changes in this interaction may influence C=O bond order, C–N bond character and vibrational frequency. In imatinib, this is relevant to the amide region that contributes to both molecular conformation and hydrogen-bonding ability (Glendening et al., 2013; Srivastava et al., 2013).

NBO can also support protonation-state analysis. Protonation of piperazine or heteroaromatic nitrogen changes lone-pair availability and redistributes electron density through the molecule. Comparing NBO charges and donor–acceptor interactions for neutral and protonated imatinib can therefore provide a mechanistic explanation for differences in MEP maps, HOMO–LUMO gaps and vibrational bands (Vologzhanina et al., 2020; Glendening et al., 2013).

Recent imatinib-analogue work has used DFT and NBO-type descriptors to support medicinal-chemistry interpretation. These studies demonstrate that localized electronic analysis remains relevant for tyrosine-kinase-inhibitor scaffolds, although biological conclusions require docking and experimental activity data (Kosma et al., 2023; Mihaylova et al., 2026).

16. Solvent Effects and Continuum Models

Solvent strongly influences imatinib because the molecule contains multiple polar and basic sites. A gas-phase calculation provides an intrinsic reference, but experimental UV–Vis spectra, solution conformer distributions and protonation equilibria occur in condensed media. Therefore, solvent effects should be included when the calculated result is compared with a solution-phase measurement (Tomasi et al., 2005; Marenich et al., 2009).

Gaussian offers continuum solvation models such as PCM and related variants that represent the solvent as a polarizable dielectric environment. These models can shift orbital energies and excitation wavelengths by stabilizing polar ground or excited states. Srivastava and co-workers used an IEF-PCM model for TD-DFT spectra of imatinib mesylate, making solvent modeling a clear part of the imatinib-specific computational literature (Srivastava et al., 2013; Tomasi et al., 2005).

SMD is another widely used continuum model that incorporates electrostatic and non-electrostatic solvation terms. It can be useful when comparing relative solvation of different protonation states or conformers, although explicit solute–solvent hydrogen bonds may still require microsolvated cluster models. For imatinib, this limitation matters because heteroatoms and protonated nitrogens can engage in specific hydrogen bonding with water or alcohol solvents (Marenich et al., 2009).

A practical recommendation is to report gas-phase and solvent-phase results side by side, but to interpret experimental solution spectra using the solvent-phase calculation. If different solvents are used experimentally, the dielectric constant and solvent model should be stated in every TD-DFT job. This improves reproducibility and prevents confusion between intrinsic electronic effects and solvent-induced shifts (Tomasi et al., 2005; Frisch et al., 2016).

17. Protonation State and pH Considerations

Protonation state is one of the most important modeling choices for imatinib. The molecule contains multiple basic nitrogens, and the experimentally relevant form may be neutral, monoprotonated, diprotonated or associated with a counterion depending on pH and salt form. Calculated geometry, MEP, NBO interactions, vibrational frequencies and TD-DFT transitions can change substantially when a proton is added (Vologzhanina et al., 2020; Korlyukov et al., 2022).

In the solid state, imatinib often appears in protonated salt forms, including mesylate. In biological environments, protonation can influence solubility, transport and binding interactions. A DFT therefore treat protonation not as a minor technical detail but as a central chemical variable that must be specified before comparing calculated values with experimental data (Korlyukov et al., 2022; Niazi, 2025).

Vologzhanina and his colleagues found that protonation can reduce the energy difference between extended and folded conformers. This means that the conformer preferred by neutral imatinib may not be the only relevant form under protonating conditions. Consequently, a rigorous Gaussian study should calculate at least the neutral and plausible protonated forms when discussing conformational stability and molecular interactions (Vologzhanina et al., 2020).

TD-DFT absorption spectra can also be protonation-dependent because protonation changes orbital energies, electron density distribution and allowed transitions. If experimental UV–Vis spectra are recorded at acidic, neutral or alkaline pH, the computational model should match the dominant species. Otherwise, disagreement between calculated and observed spectra may reflect an incorrect chemical form rather than failure of the TD-DFT method (Adamo and Jacquemin, 2013; Tomasi et al., 2005).

18. TD-DFT Assignment of UV–Vis Bands

UV–Vis absorption in imatinib is expected to involve transitions associated with aromatic and heteroaromatic π systems, with possible contributions from lone-pair to π* character in heteroatom-containing fragments. TD-DFT can assign calculated bands by listing major orbital transitions, their percentages and oscillator strengths. This makes the method valuable for explaining whether an observed absorption maximum is localized or involves charge redistribution across the molecule (Srivastava et al., 2013; Adamo and Jacquemin, 2013).

The oscillator strength is important because not every calculated excitation will produce a strong experimental absorption band. A transition with very low oscillator strength may be spectroscopically weak even if its wavelength falls within the measured range. Therefore, simulated spectra should weight transitions by oscillator strength rather than simply listing all excitation energies (Laurent and Jacquemin, 2013).

TD-DFT output should be visualized through frontier and near-frontier orbitals, but orbital pictures must be interpreted carefully. A transition labeled HOMO→LUMO can be misleading if several orbital configurations contribute significantly. For large molecules such as imatinib, it is often better to describe transitions in terms of donor and acceptor fragments rather than only molecular orbital numbers (Adamo and Jacquemin, 2013; Lu and Chen, 2012). Comparison with experimental UV–Vis spectra should consider peak broadening, solvent effects and conformer mixtures. A calculated vertical excitation is not a complete vibronic spectrum, so exact peak matching should not be expected. The strongest conclusion is obtained when TD-DFT reproduces the general absorption region and explains the electronic character of the transition consistently with the molecular structure (Figure 5) (Laurent and Jacquemin, 2013; Srivastava et al., 2013).

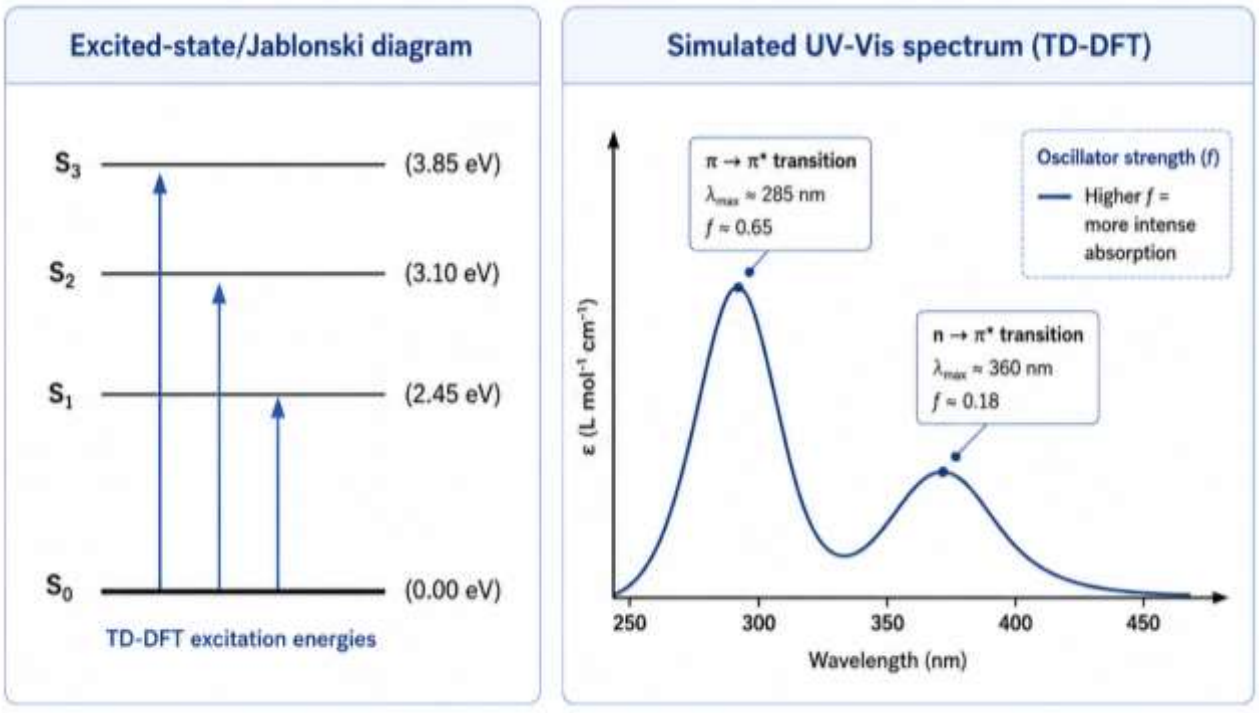


Figure 5. TD-DFT Interpretation of the Electronic Spectrum of Imatinib

19. Imatinib Analogues

Recent studies of imatinib analogues show that the parent scaffold continues to inspire medicinal-chemistry research. Kosma et al. (2023) designed and synthesized imatinib analogues and used DFT calculations alongside biological evaluation, illustrating how quantum descriptors can support interpretation of new analogues.

Moreno-Fuquen et al. (2025) reported a novel imatinib analogue for chronic myeloid leukemia and combined synthesis, characterization, docking and computational interpretation of conformation. Their work shows that conformational explanation remains central when modifying the imatinib scaffold. This supports the argument that DFT-based structural analysis remains useful for understanding analogues and not only the approved drug.

Mihaylova et al. (2026) reported terpene analogues of imatinib and investigated their effects on BCR-ABL-related signaling using synthesis, docking and biological evaluation. Their study demonstrates the contemporary interest in modifying the terminal region of imatinib-like molecules to tune interaction profiles and downstream signaling. Biological activity depends on protein binding, solubility, permeability, metabolism, efflux and cellular signaling, not only HOMO–LUMO gaps or MEP maps (Niazi, 2025).

20. Non-Covalent Interactions and Kinase Binding

Imatinib's binding to kinases depends on a network of hydrogen bonds, hydrophobic contacts and aromatic interactions. Structural studies have shown that the drug stabilizes inactive kinase conformations and uses multiple functional groups to fit the binding pocket. DFT calculations on the isolated ligand cannot fully model the protein environment, but they can identify the intrinsic electrostatic and conformational features that make these interactions possible (Vologzhanina et al., 2020).

Vologzhanina et al. (2020) compared imatinib interactions in crystal structures and ligand–receptor complexes, showing that hydrogen bonding is more numerous in receptor complexes than in salts because the binding pocket offers many donors and acceptors. They also noted the role of π-type interactions and molecular shape. This helps connect small-molecule DFT descriptors with the larger structural context of kinase recognition.

MEP and NBO analyses are especially relevant to binding interpretation because they identify electron-rich and electron-poor regions that can participate in hydrogen bonding and electrostatic contacts. For example, heteroaromatic nitrogens and amide oxygen are plausible acceptor sites, while protonated nitrogens can become donor or cationic interaction centers. These features should be linked to crystallographic and docking evidence rather than discussed in isolation (Glendening et al., 2013).

When extending a DFT study toward biological interpretation, molecular docking or molecular dynamics can be used as complementary methods. DFT can refine ligand charges or explain local electronic effects, while docking and dynamics address receptor geometry and conformational flexibility (Niazi, 2025; Ayaz et al., 2023).

21. Quality Control and Common Errors

A common error in student DFT reports is to calculate a single optimized structure and treat all derived results as universal properties of the molecule. For imatinib, this is particularly problematic because conformer and protonation differences can change geometry, orbitals and spectra. A quality-controlled study should show that relevant structures were screened and that the final reported structures are true minima (Vologzhanina et al., 2020; Frisch et al., 2016).

Another common error is to compare unscaled harmonic frequencies directly with experimental IR bands without acknowledging scaling and anharmonicity. While DFT frequencies often correlate well with experiment, they are not exact. The report should state whether scaling was used and should discuss band shifts caused by hydrogen bonding, salt formation or crystal packing (Merrick et al., 2007).

A third error is to equate the HOMO–LUMO gap with the UV–Vis absorption maximum. This is scientifically inaccurate because TD-DFT excitation energy is not simply the Kohn–Sham gap. A correct UV–Vis interpretation should use TD-DFT transitions, oscillator strengths and orbital contributions, while HOMO–LUMO analysis should remain a ground-state descriptor (Adamo and Jacquemin, 2013; Laurent and Jacquemin, 2013).

A fourth error is to ignore solvent and protonation when comparing with experimental spectra. Since imatinib is a basic molecule and often studied as a mesylate salt, neutral gas-phase calculations may not reproduce solution or solid-state data. The calculation should match the experimental condition as closely as possible, or the mismatch should be clearly explained (Korlyukov et al., 2022).

Conclusion

DFT and TD-DFT provide a powerful framework for studying the structural, electronic and spectroscopic properties of imatinib, especially when the calculations are designed around the molecule's real chemical complexity. Imatinib is flexible, protonatable and polymorphic, so a rigorous study must consider conformers, charge states, solvent and experimental comparison.

Gaussian offers the tools needed for geometry optimization, frequency analysis, electronic descriptors, NBO/MEP interpretation and UV–Vis simulation.

The literature indicates that DFT-assisted FT-IR and Raman analysis is particularly strong for assigning imatinib mesylate vibrational spectra and interpreting polymorphic effects. TD-DFT adds value by simulating electronic absorption and explaining transitions in terms of orbital contributions. However, spectral agreement depends on the chosen functional, basis set, solvent model and chemical form.

Recent imatinib structural studies show that extended and folded conformations, hydrogen bonding and π-type interactions are central to the molecule's behavior in crystals and receptor environments. This reinforces the need to treat DFT not as an isolated numerical exercise, but as part of a broader structural-chemical interpretation. A modern study should connect optimized geometries to X-ray structures, spectra and biological relevance.

Overall, a Gaussian-based DFT/TD-DFT review of imatinib should conclude that the best results come from methodological transparency, conformational awareness and careful comparison with real experimental data. When used in this way, DFT and TD-DFT can explain why imatinib shows particular vibrational bands, electronic transitions, reactive sites and non-covalent interaction patterns, while also guiding future studies of imatinib salts and analogues.

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