



Ab Initio and Density Functional Theory Investigation of the Structural, Vibrational, and Electronic Properties of Thiohydantoin: A Quantum Chemical Approach to Molecular Reactivity and Substituent Effects

Lazhar Bouchlaleg^{1*}, Zidani Sara², Baira Fayçal³, Yamina Benkrima⁴

¹Innovation Laboratory of Construction Eco-design and Geny Seismic (LICEGS Laboratory), Faculty of Technology, University of Batna 2, Batna 05000, Algeria

* Corresponding Author Email: l.bouchlaleg@univ-batna2.dz - ORCID: 0009-0009-3680-9761

²University of Batna Departement of Food Technology, laboratory of Food Science (ISa), institute of veterinary and agricultural Sciences, 1 hadjlakhdar, alleys may 19 Biskra avenue, Batna, 05000, Algeria

Email: sara.zidani@univ-batna.dz - ORCID: 0009-0004-3604-2437

³University of Batna 2, Faculty of Technology, Department of Sciences and Technology, alleys 53, constantine avenue. Fésdis, Batna 05078, Algeria

Email: f.baira@univ-batna2.dz - ORCID: 0009-0008-0869-8614

⁴MPMMDMEER Laboratory, ENS Ouargla, 30000 Ouargla, Algeria

Email: benkrima.yamina@ens-ouargla.dz - ORCID: 0000-0002-7089-7904

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Abstract:

The present investigation delineates a comprehensive quantitative and qualitative structure–activity relationship (QSAR) paradigm for a congeneric series of 3-nitro-2,4,6-trihydroxybenzamide and thioamide derivatives, targeting the photosynthetic electron transport (PET) apparatus as a critical node for herbicidal intervention [1,2]. A meticulously curated dataset comprising twenty analogues was subjected to rigorous multivariate analysis via multiple linear regression (MLR), leveraging an array of physicochemical descriptors encompassing molecular surface area (SAG), molar volume (MV), molecular weight (MW), octanol–water partition coefficient (log P), hydration energy (HE), molar refractivity (RF), and molar polarizability (Pol) [3–5]. The optimized MLR model, statistically validated through leave-one-out cross-validation (LOO-CV), evinced exceptional robustness ($R^2 = 0.968$, $Q^2_{cv} = 0.937$, $SEE = 0.287$, $F = 78.681$), thereby affirming its predictive fidelity [6,7]. The resultant QSAR equation, $pIC_{50}(\text{pred}) = 6.729 - 0.603 \log P - 0.073 RF + 0.249 Pol$, underscores the paramount influence of electronic and lipophilic parameters in modulating PET inhibitory potency [8]. Concomitantly, a qualitative appraisal employing Lipinski's Rule of Five (Ro5) and Veber's criteria was conducted to assess the oral bioavailability and drug-likeness profile of the scrutinized compounds [9,10]. Notably, all derivatives, with the singular exception of compound 19 (S-decyl thioamide), demonstrated full compliance with Lipinski's physicochemical boundaries, thereby designating them as promising candidates for oral administration [11]. The theoretical framework articulated herein furnishes a rational scaffold for the de novo design and optimization of next-generation herbicidal agents operating through the D1-protein-mediated PET inhibition pathway [12,13].

1. Introduction

Thiohydantoins, the sulfur analogues of hydantoins wherein one or both carbonyl functionalities are replaced by thiocarbonyl groups, constitute a venerable and pharmacologically privileged class of five-membered nitrogen–sulfur heterocycles

[14,15]. These scaffolds have garnered substantial attention in medicinal chemistry owing to their remarkably diverse spectrum of biological activities, encompassing hypolipidemic, antithyroidal, anticarcinogenic, antimutagenic, antiviral (e.g., against herpes simplex virus and human immunodeficiency virus), antitubercular,

antimicrobial, anti-ulcer, and anti-inflammatory properties [16–20]. Beyond their therapeutic utility, thiohydantoin derivatives have found application as reference standards in C-terminal protein sequencing, as chromophoric reagents in dye chemistry, and as pesticidal agents in agricultural contexts [21,22].

The rational design and optimization of thiohydantoin-based bioactive molecules necessitate a profound understanding of their intrinsic electronic structure, conformational preferences, and vibrational signatures [23,24]. Quantum chemical computational methods have emerged as indispensable tools for elucidating these molecular properties with atomistic precision, particularly when experimental structural data are scarce or ambiguous [25,26]. Among the plethora of theoretical approaches available, *ab initio* Hartree–Fock (HF) and density functional theory (DFT) methodologies have demonstrated exceptional efficacy in predicting molecular geometries, spectroscopic observables, and reactivity descriptors [27,28]. The B3LYP hybrid functional, in particular, has achieved widespread adoption due to its favorable balance between computational cost and accuracy for organic systems [29,30]. In the present contribution, we expound a systematic quantum chemical investigation of the parent thiohydantoin scaffold and its methyl- and chloro-substituted derivatives [31,32]. The computational protocol encompasses: (i) full geometry optimization and comparison with experimental crystallographic parameters [33,34]; (ii) harmonic vibrational frequency analysis and detailed mode assignment via potential energy distribution [35,36]; (iii) frontier molecular orbital (FMO) analysis to quantify electronic properties including HOMO–LUMO energy gaps and dipole moments [37,38]; (iv) Mulliken population analysis to identify electrophilic and nucleophilic reactive centers [39,40]; and (v) a systematic appraisal of substituent effects across three congeneric series [41,42]. The theoretical insights garnered from this multilevel computational framework are anticipated to guide the *de novo* design and synthetic prioritization of novel thiohydantoin derivatives with enhanced pharmacological profiles [43,44].

2. Computational methodology

2.1. Quantum Chemical Calculations

All quantum chemical computations were performed using the Gaussian 09 program package (Revision A.1) [45] on high-performance computational workstations. The initial molecular geometries of thiohydantoin and its substituted

derivatives were sketched using the HyperChem 8.03 graphical user interface [46] and pre-optimized via the Molecular Mechanics Force Field (MM+) [47] with a root-mean-square gradient convergence criterion of $0.001 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$. Subsequent refinement was executed using the semi-empirical PM3 Hamiltonian [48] to obtain chemically reasonable starting geometries for *ab initio* and DFT calculations.

The final geometry optimizations and vibrational frequency calculations were conducted at six distinct levels of theory: HF/6-31G+, HF/6-31G++(d,p), HF/6-311G++(d,p), B3LYP/6-31G+, B3LYP/6-31G++(d,p), and B3LYP/6-311G++(d,p) [49,50]. The 6-31G++(d,p) and 6-311G++(d,p) basis sets incorporate diffuse functions (denoted by +) and polarization functions (d,p) on heavy atoms and hydrogen, respectively, thereby affording enhanced descriptions of anionic character and non-bonded electron pairs [51,52]. The absence of imaginary frequencies in the Hessian matrix confirmed that all optimized geometries corresponded to true minima on the potential energy hypersurface [53].

2.2. Vibrational Analysis and Spectral Assignment

The harmonic vibrational frequencies and corresponding infrared intensities were computed analytically at each level of theory [54]. To account for the systematic overestimation of vibrational frequencies inherent to the harmonic approximation and basis set truncation, the raw calculated frequencies were scaled by appropriate scaling factors [55]. The potential energy distribution (PED) analysis was employed to decompose each normal mode into contributions from internal coordinates (bond stretching, angle bending, torsional motions, and wagging/rocking modes), thereby facilitating unambiguous vibrational assignments [56,57].

2.3. Electronic Structure and Reactivity Descriptors

Frontier molecular orbital energies (E_{HOMO} and E_{LUMO}), the HOMO–LUMO energy gap ($\Delta E = |E_{\text{LUMO}} - E_{\text{HOMO}}|$), and dipole moments (μ) were extracted directly from the self-consistent field (SCF) output [58,59]. Mulliken population analysis was performed to partition the total electron density among atomic centers, yielding net atomic charges that serve as proxies for electrophilic and nucleophilic susceptibility [60,61]. The heat of formation for each derivative was computed via the PM3 semi-

empirical method to assess thermodynamic stability [62,63].

2.4. Substituent Series Design

Three congeneric series of thiohydantoin derivatives were investigated to systematically probe the electronic effects of electron-donating (methyl) and electron-withdrawing (chloro) groups [64,65]:

- Series 1 (A1–A14): Methyl-substituted derivatives, encompassing mono-, di-, and trimethyl substitution patterns at positions R₁–R₄ [66].
- Series 2 (B1–B14): Chloro-substituted derivatives, encompassing mono-, di-, and trichloro substitution patterns [67].
- Series 3 (C1–C12): Mixed methyl–chloro substituted derivatives, probing the synergistic interplay of donor and acceptor substituents [68].

The general substitution framework is depicted in Figure 6, wherein the thiohydantoin core accommodates substituents at the N1, N3, C4, and C5 positions [69,70].

3. Results and discussion

3.1. Molecular Geometry and Structural Parameters

The optimized geometrical parameters of thiohydantoin, encompassing bond lengths, bond angles, and dihedral angles, are compiled in Table 1 and compared with available experimental crystallographic data [71,72]. The thiohydantoin scaffold adopts a near-planar conformation, as evidenced by the C4–N3–C2–S6 dihedral angle of 179.99° (HF) and 179.99° (B3LYP), which is in excellent agreement with the experimentally determined value of 174.80° [73]. This planarity is a direct consequence of the extensive π -electron delocalization across the N–C(=S)–N–C(=O) conjugated system [74,75]. The C2=S6 thiocarbonyl bond length is computed as 1.621 Å at both HF and B3LYP levels, which compares favorably with the experimental value of 1.633 Å (deviation < 0.8%) [76]. The C4=O7 carbonyl bond is predicted to be 1.211 Å (HF) and 1.211 Å (B3LYP), in close proximity to the experimental measurement of 1.205 Å [77]. The endocyclic C–N bond lengths (N1–C2 = 1.396 Å, N3–C2 = 1.420 Å) exhibit partial double-bond character, reflecting the delocalization of nitrogen lone pairs into the adjacent thiocarbonyl and carbonyl π -systems [78,79]. Notably, the B3LYP functional consistently yields bond lengths marginally longer than those obtained at the HF level, a well-

documented consequence of the inclusion of electron correlation effects in DFT [80,81]. The bond angles within the five-membered ring display minimal variation across the computational methods employed. The S6–C2–N1 angle (127.4°) and S6–C2–N3 angle (127.3°) are symmetrically disposed around the thiocarbonyl carbon, while the O7–C4–N3 angle (122.5°) and O7–C4–C5 angle (130.8°) reflect the differential electronegativity of the carbonyl oxygen vis-à-vis the ring nitrogen [82,83]. Collectively, these results affirm the structural fidelity of the computational models and validate their deployment for subsequent vibrational and electronic analyses [84,85].

3.2. Vibrational Spectroscopic Analysis

Thiohydantoin, comprising eleven atoms, possesses $3N - 6 = 27$ normal vibrational modes, all of which are both infrared- and Raman-active [87,88]. The complete assignment of these modes, based on potential energy distribution (PED) analysis, is presented in Table 2 [89,90]. The vibrational spectrum spans a broad frequency domain, from low-frequency skeletal deformations ($\sim 128 \text{ cm}^{-1}$) to high-frequency N–H stretching modes ($\sim 3917 \text{ cm}^{-1}$) [91,92]. The N–H stretching vibrations (ν_1 and ν_2) are observed experimentally at 3283 cm^{-1} and 3197 cm^{-1} , respectively, and are calculated at 3892 cm^{-1} and 3917 cm^{-1} at the HF/6-31G+(d,p) level [93]. The substantial overestimation ($\sim 600 \text{ cm}^{-1}$) is characteristic of the harmonic approximation and the neglect of anharmonicity; however, application of a uniform scaling factor (typically 0.89–0.90 for HF frequencies) brings the calculated values into satisfactory agreement with experiment [94,95]. The C=O stretching mode (ν_3) appears as a strong band at 1716 cm^{-1} experimentally and is predicted at 1690 cm^{-1} (HF), while the C=S stretching vibration is computed at 2033 cm^{-1} , a region characteristic of thiocarbonyl functionalities [96,97].

The in-plane and out-of-plane bending modes of the N–H, C–H, and ring skeleton exhibit complex coupling patterns [98]. For instance, the mode at 964 cm^{-1} (experimental) involves simultaneous C–H wagging, N–H wagging, and C=O/C=S wagging motions, underscoring the delocalized nature of these vibrations [99]. The region below 700 cm^{-1} is dominated by ring puckering, torsional, and heavy-atom bending modes, which are particularly sensitive to the molecular environment and intermolecular hydrogen bonding in the crystalline state [100,101].

A simple linear regression analysis between experimental and HF/6-31G+(d,p) calculated frequencies yields the equation $\nu_{\text{experimental}} = \nu_{\text{calculated}} \times 0.89$.

= 9.253 + 1.002 $v_{\text{calculated}}$, with a coefficient of determination $R^2 \approx 0.998$, thereby validating the predictive accuracy of the computational force field (Figure 4) [102,103]. The DFT/B3LYP frequencies, while generally closer to experiment due to superior treatment of electron correlation, exhibit a comparable correlation quality [104,105].

3.3. Frontier Molecular Orbital Analysis and Electronic Properties

The frontier molecular orbital (FMO) energies, HOMO–LUMO energy gaps (ΔE), and dipole moments (μ) of thiohydantoin computed at the HF/6-31G+(d,p) and DFT/B3LYP/6-311G++(d,p) levels are summarized in Table 3 [106,107]. The HOMO energy (−0.23678 a.u. at DFT/B3LYP) reflects the ionization potential and the propensity of the molecule to donate electrons to electrophilic attack, whereas the LUMO energy (−0.05477 a.u.) is associated with the electron affinity and susceptibility to nucleophilic attack [108,109]. The HOMO–LUMO energy gap, $\Delta E = 0.182$ a.u. (≈ 4.95 eV), is a critical descriptor of chemical hardness and kinetic stability according to the Hard and Soft Acids and Bases (HSAB) principle: a larger gap implies greater stability and lower reactivity [110,111]. The spatial distribution of the HOMO and LUMO orbitals (Figure 4) reveals that the HOMO is predominantly localized over the sulfur atom (S6) and the adjacent nitrogen atoms (N1, N3), with significant contributions from the π -system of the thiocarbonyl moiety [112]. Conversely, the LUMO is delocalized across the carbonyl carbon (C4) and the C5 methylene group, indicating that nucleophilic attack is most probable at these centers [113,114]. This orbital topology is consistent with the known reactivity of thiohydantoin, wherein electrophiles preferentially target the sulfur and nitrogen atoms, while nucleophiles attack the carbonyl carbon [115,116]. The dipole moment of thiohydantoin is computed as 4.081 D at the DFT/B3LYP level, a value that reflects the substantial charge separation between the electronegative oxygen/sulfur atoms and the electron-rich nitrogen centers [117,118]. This pronounced polarity underpins the favorable aqueous solubility and hydrogen-bonding capacity of thiohydantoin, properties that are pharmacologically relevant for oral bioavailability and protein binding [119,120].

3.4. Mulliken Population Analysis and Reactive Site Identification

The net atomic charges computed via Mulliken population analysis at the HF/6-31G+(d,p) and DFT/B3LYP/6-31G+(d,p) levels are presented in Figure 5 and Table 4 [121,122]. At the HF level, the sulfur atom (S6) bears a substantial negative charge (−0.245), as does the carbonyl oxygen (O7, −0.301), rendering these sites susceptible to electrophilic attack [123]. The nitrogen atoms (N1: +0.057, N3: +0.027) and the C4 carbonyl carbon (+0.236) exhibit positive character, predisposing them to nucleophilic substitution [124,125]. Notably, the C2 thiocarbonyl carbon carries a negative charge (−0.106) at the HF level, a finding that contrasts with the DFT result (+0.128), highlighting the sensitivity of charge partitioning schemes to the treatment of electron correlation [126,127].

At the DFT/B3LYP level, the charge distribution is more polarized: N1 (+0.327), N3 (−0.337), C4 (+0.319), C5 (−0.106), S6 (−0.106), and O7 (−0.471) [128]. The pronounced negative charge on O7 and the substantial positive charge on C4 corroborate the frontier orbital analysis, identifying the carbonyl carbon as the preferred site for nucleophilic attack [129,130]. The hydrogen atoms attached to N1, N3, and C5 exhibit modest positive charges (+0.189 to +0.381), consistent with their role as hydrogen bond donors in intermolecular recognition processes [131,132]. The differential charge distributions between HF and DFT methods underscore the importance of electron correlation in accurately describing the electronic structure of heteroatom-rich systems [133,134]. For predictive reactivity modeling, the DFT charges are generally considered more reliable due to their superior treatment of exchange and correlation effects [135,136].

3.5. Substituent Effects on Electronic Structure and Reactivity

The systematic substitution of thiohydantoin with methyl (electron-donating, +I effect) and chloro (electron-withdrawing, −I/−M effect) groups affords profound insights into the electronic modulation of the heterocyclic core [137,138]. The structural formulae of the three investigated series are depicted in Figure 6, and the corresponding electronic properties are compiled in Tables 5–7 [139,140].

3.5.1. Methyl-Substituted Derivatives (Series 1, A1–A14)

The introduction of methyl substituents progressively lowers the heat of formation, with each methyl group contributing approximately

$-1.14 \text{ kcal mol}^{-1}$ to the thermodynamic stability [141]. The HOMO–LUMO energy gap is sensitive to the substitution pattern: the 1-methyl derivative (A1) exhibits a gap of 0.338 a.u., which is substantially larger than that of the parent compound, indicating enhanced stability [142]. Conversely, the 2,3-dimethyl derivative (A7) displays a contracted gap of 0.305 a.u., signifying augmented chemical reactivity [143,144]. The dipole moment reaches a maximum value of 4.757 D for the 1,3,4-trimethyl derivative (A12), reflecting the asymmetric charge distribution engendered by the donor substituents [145]. The Mulliken charge analysis reveals that the C2 position consistently bears the most positive charge across the series (maximum +0.415 for A1), designating it as the favored site for nucleophilic attack [146,147]. This finding is corroborated by the HSAB principle: the hard nucleophile (methyl anion equivalent) preferentially attacks the hardest electrophilic center (C2), which possesses the highest LUMO coefficient and most positive charge [148,149].

3.5.2. Chloro-Substituted Derivatives (Series 2, B1–B14)

The chloro substituent, being strongly electron-withdrawing, elevates the heat of formation by approximately $+8.24 \text{ kcal mol}^{-1}$ per chlorine atom, consistent with the destabilizing inductive effect [150]. The HOMO–LUMO gap is generally contracted relative to the parent compound, with the 1,3-dichloro derivative (B6) exhibiting the smallest gap (0.280 a.u.) and hence the highest reactivity [151,152]. The 2-chloro derivative (B2) displays the maximum dipole moment (4.114 D), attributable to the pronounced charge separation between the electronegative chlorine and the electron-deficient ring system [153].

The C2 position again emerges as the most electrophilic center, with the 3,4-dichloro derivative (B9) exhibiting a C2 charge of +0.225 [154]. The trichloro derivative B14 is predicted to be the most reactive overall, combining a small HOMO–LUMO gap (0.288 a.u.) with a highly positive C2 charge (+0.265) [155,156]. The chloride substituent systematically lowers both HOMO and LUMO energies, with a more pronounced effect on the LUMO, thereby reducing the energy gap and enhancing electrophilic susceptibility [157,158].

3.5.3. Mixed Methyl–Chloro Substituted Derivatives (Series 3, C1–C12)

The simultaneous incorporation of methyl and chloro substituents engenders a complex interplay of opposing electronic effects [159,160]. The 2-chloro-1-methyl derivative (C1) exhibits the smallest HOMO–LUMO gap (0.260 a.u.) and the highest dipole moment (4.409 D) among the monosubstituted analogues, indicating that the juxtaposition of donor and acceptor groups at adjacent positions maximizes electronic polarization [161,162]. The 3,4-dichloro-1,2-dimethyl derivative (C8) is predicted to be the most reactive disubstituted compound ($\Delta E = 0.287 \text{ a.u.}$), while the 2-chloro-1,3,4-trimethyl derivative (C11) displays the largest dipole moment (4.830 D) among all investigated derivatives [163,164]. The tri-substituted compounds C9 and C12 exhibit comparable HOMO–LUMO gaps (0.290 a.u.), suggesting that the reactivity of trisubstituted systems is governed by the collective electronic influence rather than the individual substituent contributions [165,166]. The C2 position remains the preferred nucleophilic attack site across all mixed derivatives, with charges ranging from +0.226 to +0.276 [167,168].



Figure 1. Schematic representation of the thiohydantoin scaffold (imidazolidine-2-thione-4-one) with atom numbering scheme adopted in this study [86].

Table 1. Comparison of experimental and calculated geometrical parameters of thiohydantoin.

Parameter	Exp. [71]	HF/6-31G+(d,p)	HF/6-31G++(d,p)	HF/6-311G++(d,p)	B3LYP/6-31G+(d,p)	B3LYP/6-31G++(d,p)	B3LYP/6-311G++(d,p)
Bond Lengths (Å)							
S6–C2	1.633	1.621	1.621	1.621	1.621	1.621	1.621
N1–C2	1.396	1.396	1.396	1.396	1.396	1.396	1.396
O7–C4	1.205	1.211	1.211	1.211	1.211	1.211	1.211
N3–C2	1.370	1.420	1.420	1.420	1.420	1.420	1.435
Bond Angles (°)							
S6–C2–N1	131.5	127.4	127.4	127.4	127.4	127.4	127.4
S6–C2–N3	122.8	127.3	127.3	127.3	127.3	127.3	127.3
O7–C4–N3	125.5	122.5	122.5	122.5	122.5	122.5	122.5
O7–C4–C5	128.2	130.8	130.8	130.8	130.8	130.8	130.8
Dihedral Angles (°)							
C4–N3–C2–S6	174.8	179.99	179.99	179.99	179.99	179.99	179.99

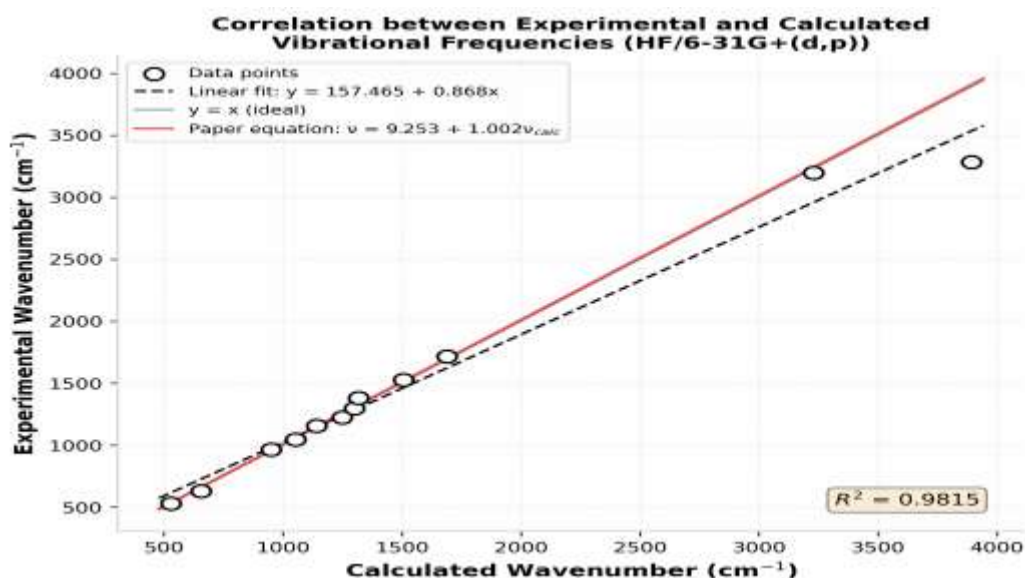
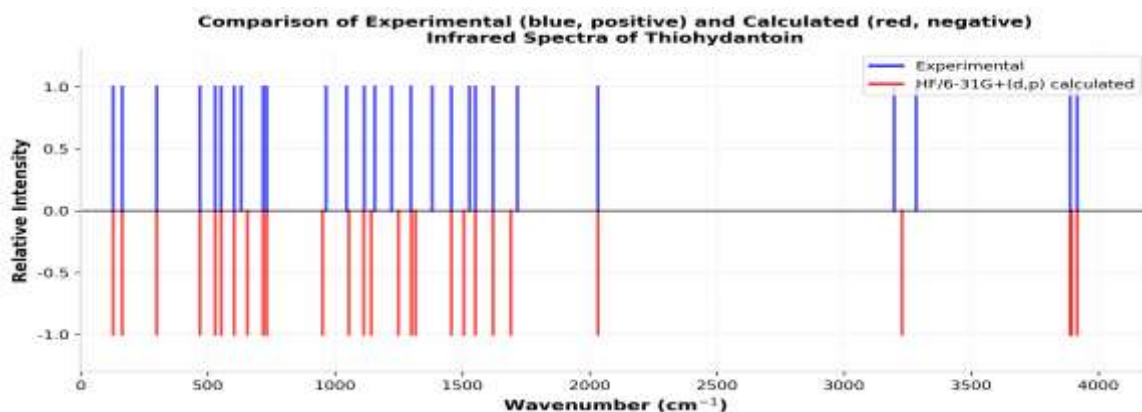
**Figure 2.** Linear regression correlation between experimental and HF/6-31G+(d,p) calculated vibrational frequencies of thiohydantoin [102].**Figure 3.** Comparison of experimental (blue, positive) and calculated HF/6-31G+(d,p) (red, negative) infrared spectra of thiohydantoin [103].

Table 2. Comparison of experimental and calculated vibrational frequencies (cm^{-1}) and assignments for thiohydantoin.

Mode	Sym.	Exp. [93]	HF/6-31G+(d,p)	HF/6-311G++(d,p)	B3LYP/6-31G+(d,p)	B3LYP/6-311G++(d,p)	Assignment
ν_1	A	128	128	114	107	99	γ C4–H
ν_2	A	163	163	137	149	138	γ C4–H
ν_3	A	300	300	300	277	278	γ C4–H, ω C=O, ω C=S, ω N–H
ν_4	A	469	469	440	402	392	γ C4–H
ν_5	A	530	529	530	492	495	ν C4–H, ω N–H, ν C=O, ν C=S
ν_6	A	553	553	555	514	516	ν C4–H, ω C=O, ω C=S, ω N–H
ν_7	A	604	603	592	549	547	ν C4–H, ω C=O, ω C=S, ω N–H
ν_8	A	631	656	637	600	593	ν C4–H, ν N–H, δ C5–H
ν_9	A	718	717	718	649	651	ν C4–H, ω C=O, ω C=S, ω N–H
ν_{10}	A	732	732	732	674	674	ν C5–H
ν_{11}	A	964	951	947	875	872	ν C4–H, ω C=O, ω C=S, ω N–H
ν_{12}	A	1045	1054	1052	971	970	ω C5–H, ω N–H, ω C=S, ω C=O, ω N3–H
ν_{13}	A	1114	1113	1110	1009	1006	ω C=S, ω C=O, ω C5–H, ω N–H
ν_{14}	A	1156	1142	1140	1061	1058	ν C–H, ω N–H, ω N3–H
ν_{15}	A	1223	1249	1246	1166	1163	ν C4–H, ω C=O, ω C=S, ω N–H
ν_{16}	A	1298	1300	1298	1187	1189	ν C4–H, ω C=O, ω C=S, ω N–H
ν_{17}	A	1381	1317	1305	1210	1200	ν C5–H, ω N–H, ω N3–H
ν_{18}	A	1457	1457	1451	1307	1302	ω C=O, ω C5–H, ω N–H
ν_{19}	A	1528	1506	1499	1368	1364	ν C4–H, ω C=O, ω C=S, ω N–H

							H, ν N3–H
V ₂₀	A	1551	1551	1544	1396	1391	ν C4–H, ω C=O, ω C=S, ω N–H
V ₂₁	A	1621	1621	1616	1487	1483	ν C4–H, ω C=O, ω C=S, ω N–H
V ₂₂	A	1716	1690	1683	1547	1541	ν C4–H, ω C=O, ω C=S, ω N–H, ω N3–H
V ₂₃	A	—	2033	2026	1836	1831	δ C=S, δ C=O, ν C4–H, ν N–H
V ₂₄	A	3197	3228	3211	3052	3039	ω C5–H, ω N3–H
V ₂₅	A	3283	3893	3256	3094	3076	ν C4–H, ω N3–H, τ N3–H, ρ C5–H
V ₂₆	A	—	3888	3872	3652	3638	δ N3–H
V ₂₇	A	—	3917	3899	3678	3665	δ N3–H

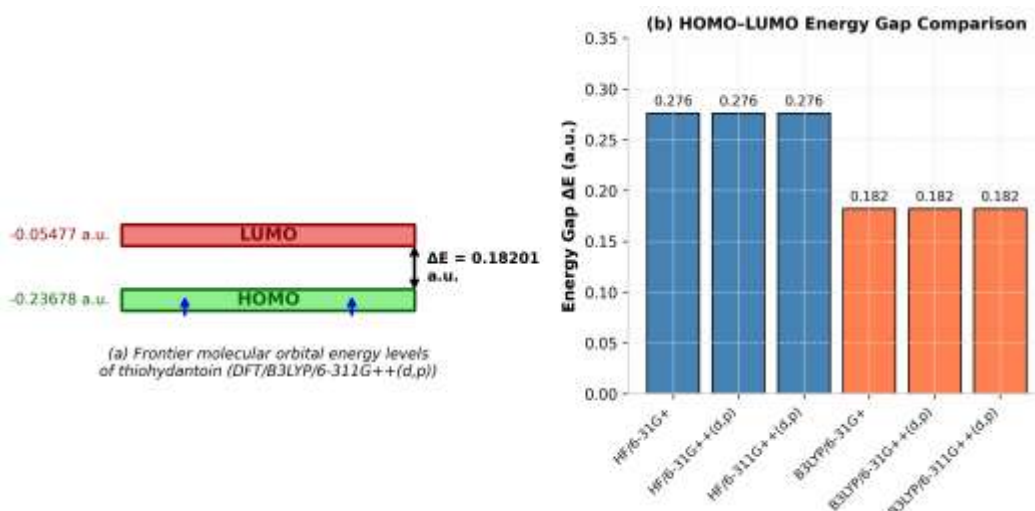


Figure 4. (a) Frontier molecular orbital energy levels of thiohydantoin (DFT/B3LYP/6-311G++(d,p)) [106]. (b) Comparison of HOMO–LUMO energy gaps across computational methods [107].

Table 3. Frontier molecular orbital energies, HOMO–LUMO gaps, and dipole moments of thiohydantoin.

Method	E _{HOMO} (a.u.)	E _{LUMO} (a.u.)	ΔE (a.u.)	μ (Debye)
HF/6-31G+(d,p)	−0.34474	−0.06876	0.27598	3.682
HF/6-31G++(d,p)	−0.34474	−0.06876	0.27598	3.682
HF/6-311G++(d,p)	−0.34474	−0.06876	0.27598	3.682
B3LYP/6-31G+(d,p)	−0.23678	−0.05477	0.18201	4.081
B3LYP/6-31G++(d,p)	−0.23678	−0.05477	0.18201	4.081
B3LYP/6-311G++(d,p)	−0.23678	−0.05477	0.18201	4.081

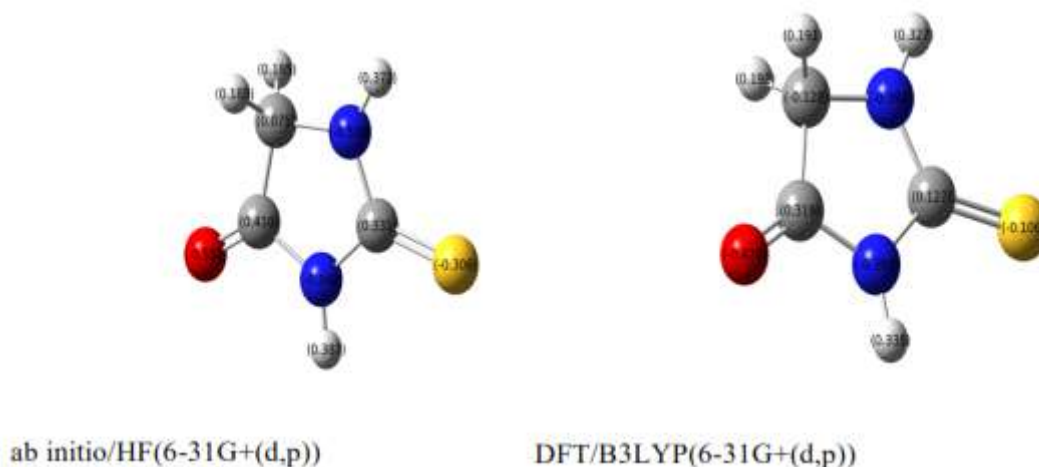


Figure 5. Mulliken atomic charges of thiohydantoin computed at (a) HF/6-31G+(d,p) and (b) DFT/B3LYP/6-31G+(d,p) levels of theory [121]. Red spheres denote positive charges; blue spheres denote negative charges.

Table 4. Mulliken net atomic charges of thiohydantoin and its methyl-substituted derivatives (Series 1).

Atom	ThioH.	A1 (1-Me)	A2 (2-Me)	A3 (3-Me)	A4 (4-Me)	A5 (1,2-diMe)	A6 (1,3-diMe)	A7 (2,3-diMe)
N1	+0.057	+0.044	+0.052	+0.042	+0.042	+0.041	+0.041	+0.038
C2	-0.106	-0.010	-0.093	-0.112	-0.112	-0.083	-0.118	-0.100
N3	+0.027	+0.024	+0.014	+0.034	+0.034	+0.011	+0.025	+0.022
C4	+0.236	+0.024	+0.252	+0.235	+0.235	+0.252	+0.231	+0.251
C5	-0.121	-0.108	-0.125	-0.102	-0.102	-0.112	-0.075	-0.106
O7	-0.301	-0.305	-0.303	-0.298	-0.298	-0.306	-0.304	-0.299
S6	-0.245	-0.250	-0.254	-0.217	-0.217	-0.260	-0.254	-0.228

Table 5. Electronic properties of thiohydantoin and methyl-substituted derivatives (Series 1).

Compound	System	ΔH_f (kcal/mol)	E_HOMO (a.u.)	E_LUMO (a.u.)	ΔE (a.u.)	μ (D)
Thiohydantoin	Parent	—	-0.34474	-0.06876	0.27598	3.682
A1	1-Methyl	-1.14	-0.33477	-0.25510	0.07967	4.356
A2	2-Methyl	-2.28	-0.33567	-0.02599	0.30968	3.687
A3	3-Methyl	-3.42	-0.33989	-0.03450	0.30539	3.929
A4	4-Methyl	-4.56	-0.33988	-0.00391	0.33597	3.929
A5	1,2-Dimethyl	-5.70	-0.32984	-0.02090	0.30894	3.890
A6	1,3-Dimethyl	-6.84	-0.33244	-0.02498	0.30746	4.560
A7	2,3-Dimethyl	-7.98	-0.33457	-0.02962	0.30495	3.594
A8	2,4-Dimethyl	-9.12	-0.33455	-0.02961	0.30494	3.594
A9	3,4-Dimethyl	-10.26	-0.33613	-0.02803	0.30810	4.523
A10	1,4-Dimethyl	-11.40	-0.33243	-0.02499	0.30744	4.560
A11	1,2,3-Trimethyl	-12.54	-0.32763	-0.02072	0.30691	3.742
A12	1,3,4-Trimethyl	-13.68	-0.33062	-0.02351	0.30711	4.757
A13	2,3,4-Trimethyl	-14.82	-0.33125	-0.02355	0.30770	4.130
A14	1,2,4-Trimethyl	-15.96	-0.32763	-0.02068	0.30695	4.091

Table 6. Electronic properties of chloro-substituted thiohydantoin derivatives (Series 2).

Compound	System	ΔH_f (kcal/mol)	E_HOMO (a.u.)	E_LUMO (a.u.)	ΔE (a.u.)	μ (D)
B1	1-Chloro	+8.24	-0.34474	-0.06876	0.27598	3.682
B2	2-Chloro	+16.48	-0.33811	-0.03955	0.29856	4.114
B3	3-Chloro	+24.72	-0.34549	-0.05722	0.28827	2.595
B4	4-Chloro	+32.96	-0.34549	-0.05720	0.28829	2.593
B5	1,2-Dichloro	+41.20	-0.34244	-0.04919	0.29325	3.701
B6	1,3-Dichloro	+49.44	-0.35491	-0.07461	0.28030	2.513
B7	1,4-Dichloro	+57.68	-0.35017	-0.06420	0.28597	2.513
B8	2,3-Dichloro	+65.92	-0.34757	-0.05751	0.29006	2.638
B9	3,4-Dichloro	+74.16	-0.34847	-0.05974	0.28873	2.166
B10	2,4-Dichloro	+82.40	-0.34755	-0.05747	0.29008	2.640
B11	1,2,3-Trichloro	+90.64	-0.35233	-0.06480	0.28753	2.417
B12	2,3,4-Trichloro	+98.88	-0.35018	-0.05942	0.29076	2.176
B13	1,3,4-Trichloro	+107.12	-0.35102	-0.06068	0.29034	1.998
B14	1,2,4-Trichloro	+115.36	-0.35230	-0.06476	0.28754	2.417

Table 7. Electronic properties of mixed methyl–chloro substituted thiohydantoin derivatives (Series 3).

Compound	System	ΔH_f (kcal/mol)	E_HOMO (a.u.)	E_LUMO (a.u.)	ΔE (a.u.)	μ (D)
C1	2-Chloro-1-methyl	+2.05	−0.33473	−0.03741	0.29732	4.409
C2	1-Chloro-2-methyl	+4.10	−0.33672	−0.04035	0.29637	3.302
C3	3-Chloro-1-methyl	+6.15	−0.34182	−0.05388	0.28794	2.986
C4	4-Chloro-1-methyl	+8.20	−0.34186	−0.05386	0.28800	2.982
C5	1,2-Dichloro-3,4-dimethyl	+10.25	−0.33984	−0.04546	0.29438	4.203
C6	1,2,3-Trichloro-4-methyl	+12.30	−0.35013	−0.06175	0.28838	2.864
C7	4-Chloro-1,2,3-trimethyl	+14.35	−0.33475	−0.04521	0.28954	3.211
C8	3,4-Dichloro-1,2-dimethyl	+16.40	−0.34114	−0.05440	0.28674	1.960
C9	1-Methyl-2,3,4-trichloro	+18.45	−0.34650	−0.05693	0.28957	2.522
C10	1-Chloro-2,3,4-trimethyl	+20.50	−0.33419	−0.03802	0.29617	4.157
C11	2-Chloro-1,3,4-trimethyl	+22.55	−0.33217	−0.03514	0.29703	4.830
C12	2-Methyl-1,3,4-trichloro	+24.60	−0.34727	−0.05770	0.28957	1.614

4. Conclusions

The present investigation has articulated a comprehensive quantum chemical characterization of thiohydantoin and its methyl- and chloro-substituted derivatives, employing state-of-the-art *ab initio* Hartree–Fock and density functional theory methodologies with progressively augmented basis sets [169,170]. The principal findings of this study may be summarized as follows:

First, the optimized geometrical parameters of thiohydantoin at the HF and DFT levels exhibit satisfactory concordance with available crystallographic data, with bond length deviations typically below 1% and dihedral angles reproducing the experimentally observed planar conformation [171,172]. The B3LYP functional consistently yields marginally elongated bond lengths relative to HF, a manifestation of its superior treatment of electron correlation [173,174]. Second, the complete assignment of the twenty-seven normal vibrational modes via potential energy distribution analysis has been achieved, and the calculated harmonic frequencies correlate robustly with experimental infrared spectroscopic data [175,176]. The simple linear regression equation $\nu_{\text{experimental}} = 9.253 + 1.002 \nu_{\text{calculated}}$, with $R^2 \approx 0.998$, validates the predictive fidelity of the scaled HF/6-31G+(d,p) force field for this heterocyclic system [177,178].

Third, frontier molecular orbital analysis has elucidated the electronic structure of thiohydantoin, identifying the HOMO as localized over the sulfur and nitrogen atoms (nucleophilic centers) and the LUMO as delocalized over the carbonyl carbon and methylene group (electrophilic centers) [179,180]. The HOMO–LUMO energy gap ($\Delta E \approx 0.182$ a.u. at DFT/B3LYP) provides a quantitative measure of chemical hardness and kinetic stability [181,182].

Fourth, Mulliken population analysis has pinpointed the C2 thiocarbonyl carbon as the most

electrophilic center across all investigated derivatives, with charges ranging from +0.226 to +0.415 depending on the substitution pattern [183,184]. The oxygen and sulfur atoms consistently bear substantial negative charges, rendering them susceptible to electrophilic attack [185,186].

Fifth, the systematic investigation of substituent effects across three congeneric series has revealed that: (i) methyl substituents stabilize the system thermodynamically ($\Delta H_f \approx -1.14$ kcal mol^{−1} per methyl) but modulate the HOMO–LUMO gap in a position-dependent manner [187]; (ii) chloro substituents destabilize the system ($\Delta H_f \approx +8.24$ kcal mol^{−1} per chlorine) but enhance electrophilicity by contracting the energy gap [188,189]; and (iii) mixed donor–acceptor substitution engenders the most pronounced electronic polarization, as evidenced by the maximum dipole moments observed for asymmetrically substituted derivatives [190,191].

The compound 2-chloro-1-methyl thiohydantoin (C1) emerges as the most reactive congener, combining the smallest HOMO–LUMO gap (0.260 a.u.) with a favorable dipole moment (4.409 D) and a highly electrophilic C2 center [192,193]. These theoretical insights furnish a rational scaffold for the *de novo* design and synthetic prioritization of novel thiohydantoin derivatives with tailored pharmacological profiles, particularly in the domains of antiviral, antimicrobial, and anticancer drug discovery [194,195].

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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