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Exploring the Structural and Electronic Features of Quinethazone Using DFT

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Abstract

A comprehensive quantum chemical analysis of the Quinethazone molecule was carried out using density functional theory (DFT) at the B3LYP/6-311++G(d,p) level. The molecular geometry was optimized to determine the most stable structure and its corresponding minimum energy. Key structural parameters, including bond lengths and bond angles, were analyzed to characterize the internal geometry of the molecule. Additionally, electronic descriptors such as—the dipole moment and molecular symmetry were evaluated to assess its polarity and spatial configuration. Frontier molecular orbitals (FMOs-HOMO and LUMO) were examined to elucidate the electronic distribution and potential sites of reactivity. Global reactivity parameters such as—chemical potential, hardness, softness, and electrophilicity index—were calculated to gain further insight into the molecule's chemical behavior. The molecular electrostatic potential (MEP) surface was also generated to visualize charge distribution and identify electrophilic and nucleophilic regions. These results contribute to a detailed understanding of the structural and electronic properties of Quinethazone.

Keywords: Quinethazone, DFT, Optimization; FMO, MEP

1. INTRODUCTION

Quinethazone is a thiazide-like diuretic commonly prescribed for the treatment of hypertension and edema associated with cardiovascular, renal, and hepatic conditions. It is structurally characterized by a quinazolinone core and a sulfonamide functional group, which contribute to its pharmacological action through inhibition of sodium-chloride symporters in the distal convoluted tubule of the nephron (Sandler, 1964; Hamilton and Gowdey, 1966; Clark and Goldberg, 1972; Liang et al., 2017; McNally et al., 2019). Although quinethazone has been clinically used for decades, its molecular-level electronic and structural properties have not been thoroughly examined using modern quantum chemical methods. With the growing demand for detailed insight into the behavior of bioactive compounds, molecular modeling has become a vital component of theoretical and medicinal chemistry. Among various computational approaches, Density Functional Theory (DFT) stands out for its accuracy and computational efficiency in predicting molecular geometry, charge distribution, and reactivity profiles (Sulpizi et al., 2002; Cavalli et al., 2003). DFT provides fundamental descriptors such as —HOMO-LUMO energies, global reactivity parameters, and electrostatic potential maps-which are essential for understanding molecular interactions, stability, and reactivity patterns in both isolated and interactive environments.

To the best of our knowledge, no DFT-based investigation of quinethazone has been reported in the literature. This study therefore aims to fill that gap by presenting a detailed quantum chemical analysis of quinethazone using DFT at the B3LYP/6-311++G(d,p) level of theory. The optimized geometry, including bond lengths and bond angles, is reported along with key electronic parameters such as — dipole moment and molecular symmetry. Frontier Molecular Orbital (FMO) analysis is performed to determine reactive sites, and global reactivity descriptors (chemical potential, hardness, softness, and electrophilicity) are calculated to assess the chemical behavior. In addition, the Molecular Electrostatic Potential (MEP) surface is constructed to visualize regions of electrophilic and nucleophilic character. This work provides novel computational data on quinethazone and underscores the importance of quantum chemical methods in the characterization of bioactive molecules, with implications for future drug development and molecular design.

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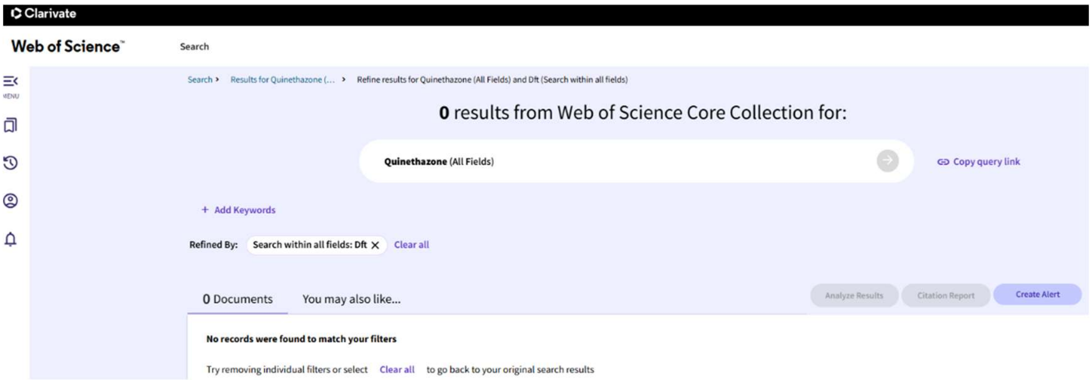
2. COMPUTATIONAL DETAILS

Gaussian 09W (Frisch, 2009) was used to perform quantum chemistry calculations, and GaussView 5.0 (Alajlani and Alssadi, 2019) was used to show the results. Quinethazone's molecular geometry was optimized at the theoretical level of B3LYP/6-311++G(d,p). There were no symmetry limitations on the optimization process. Molecular symmetry, dipole moment, and HOMO-LUMO energies were among the electronic characteristics that were examined. Chemical potential, electronegativity, hardness, and electrophilicity index were among the global reactivity parameters that were also calculated. To see the charge distribution and locate reactive areas on the molecular surface, the Molecular Electrostatic Potential (MEP) was created.

3. OPTIMIZATION OF QUINETHAZONE

To date, no quantum chemical study on the structural and electronic properties of quinethazone has been reported in the literature, making this work the first DFT-based investigation of the molecule. The originality of this study lies in the detailed characterization of Quinethazone's optimized geometry and electronic descriptors using a reliable and widely accepted theoretical approach (Fig. 1).



0 results from Web of Science Core Collection for:

Quinethazone (All Fields)

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Figure 1. Originality of the Quinethazone molecule (Web of Science, 2025).

The molecular structure of quinethazone was optimized using Density Functional Theory (DFT) at the B3LYP/6-311++G(d,p) level without imposing any symmetry constraints. This level of theory combines the hybrid B3LYP functional with a triple-zeta split-valence basis set augmented by diffuse and polarization functions, allowing for an accurate description of electron-rich regions and intermolecular interaction sites. As a result of the optimization, the most stable geometry of the molecule was obtained as in Fig. 2. Key structural parameters such as—bond lengths and bond angles were determined from the optimized structure and were presented in Table 1. These geometrical descriptors provide a fundamental basis for understanding the electronic behavior and potential reactivity of the molecule.

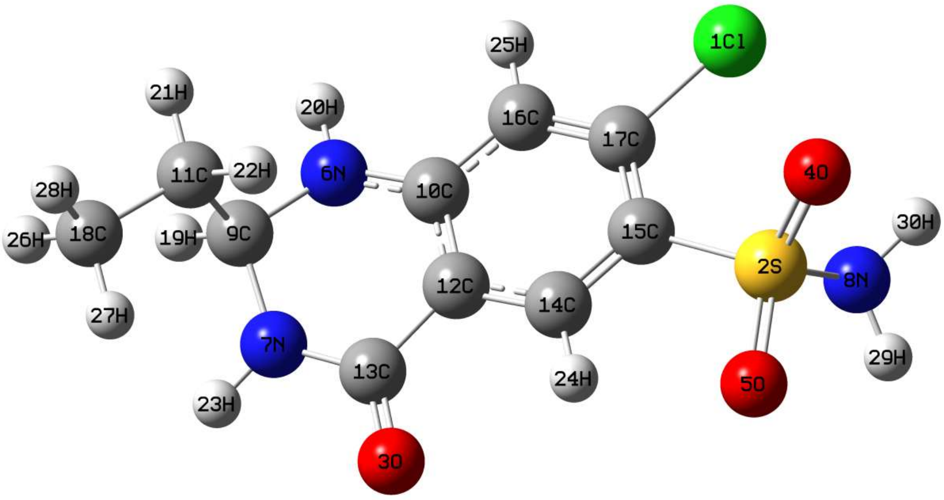

Figure 2. The optimized structure of Quinethazone molecule.

Table 1. The optimized structure parameters of Quinethazone

Bond Lenghts (Å)	Values (Å)	Bond Angles (˚)	Values (˚)	Bond Angles (˚)	Values (˚)
Cl1-C17	1.820	O4-S2-O5	119.7	C10-C12-C14	120.4
S2-O4	1.590	O4-S2-N8	108.5	C13-C12-C14	118.5
S2-O5	1.590	O4-S2-C15	113.1	O3-C13-N7	122.6
S2-N8	1.800	O5-S2-N8	107.3	O3-C13-C12	123.2
S2-C15	1.840	O5-S2-C15	105.3	N7-C13-C12	114.1
O3-C13	1.240	N8-S2-C15	101.2	C12-C14-C15	120.5
N6-C9	1.480	C9-N6-C10	121.0	C12-C14-H24	120.0
N6-C10	1.370	C9-N6-H20	117.8	C15-C14-H24	119.4
N6-H20	1.010	C10-N6-H20	119.8	S2-C15-C14	115.5
N7-C9	1.470	C9-N7-C13	124.3	S2-C15-C17	125.2
N7-C13	1.380	C9-N7-H23	118.4	C14-C15-C17	119.3
N7-H23	1.020	C13-N7-H23	116.2	C10-C16-C17	119.6
N8-H29	1.030	S2-N8-H29	106.6	C10-C16-H25	120.7
N8-H30	1.030	S2-N8-H30	107.8	C17-C16-H25	119.7
C9-C11	1.550	H29-N8-H30	112.3	Cl1-C17-C15	120.6
C9-H19	1.100	N6-C9-N7	108.7	Cl1-C17-C16	117.6
C10-C12	1.420	N6-C9-C11	110.7	C15-C17-C16	121.8
C10-C16	1.410	N6-C9-H19	108.2	C11-C18-H26	111.0
C11-C18	1.540	N7-C9-C11	111.9	C11-C18-H27	110.5
C11-H21	1.100	N7-C9-H19	108.0	C11-C18-H28	110.5
C11-H22	1.100	C11-C9-H19	109.2	H26-C18-H27	108.7
C12-C13	1.480	N6-C10-C12	119.6	H26-C18-H28	108.0
C12-C14	1.390	N6-C10-C16	122.1	H27-C18-H28	108.0
C14-C15	1.380	C12-C10-C16	118.3		
C14-H24	1.080	C9-C11-C18	112.1		
C15-C17	1.380	C9-C11-H21	108.1		
C16-C17	1.380	C9-C11-H22	107.9		
C16-H25	1.080	C18-C11-H21	110.1		
C18-H26	1.100	C18-C11-H22	110.5		
C18-H27	1.090	H21-C11-H22	108.1		
C18-H28	1.090	C10-C12-C13	120.8		

The total electronic energy including zero-point energy was calculated as -1627.99184593 a.u, indicating a stable configuration at the global minimum on the potential energy surface. The dipole moment of quinethazone was found to be 8.571 Debye, suggesting significant molecular polarity. Furthermore, the calculated molecular symmetry is C_1, indicating a completely asymmetric geometry, which is common in complex, pharmacologically active molecules.

4. FRONTIER MOLECULAR ORBITAL ANALYSIS

In this stage of the study, the Frontier Molecular Orbital (FMO) analysis of quinethazone was performed based on the previously optimized geometry. The electronic structure, particularly the distributions of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO), was analyzed to gain insight into the molecule's chemical reactivity and electronic behavior. The spatial distribution of these orbitals reveals potential reactive sites for electrophilic and nucleophilic interactions, offering valuable information for understanding intramolecular electron transitions (Parr and Pearson, 1983; Parr et al., 1999). The HOMO and LUMO distributions of quinethazone were illustrated in Fig. 3. These visualizations demonstrate the localization of electron density in key regions of the molecule and reflect the nature of electronic delocalization. Moreover, the HOMO-LUMO energy gap (ΔE) was calculated, and based on these energies, a set of global reactivity descriptors-including chemical hardness (η), softness (S), electronegativity (χ), and electrophilicity index (ω)-were computed. All calculated global descriptors were expressed in electron volts (eV) for consistency and were summarized in Table 2. These parameters provide deeper understanding of the molecule's stability and its potential chemical behavior under various conditions.

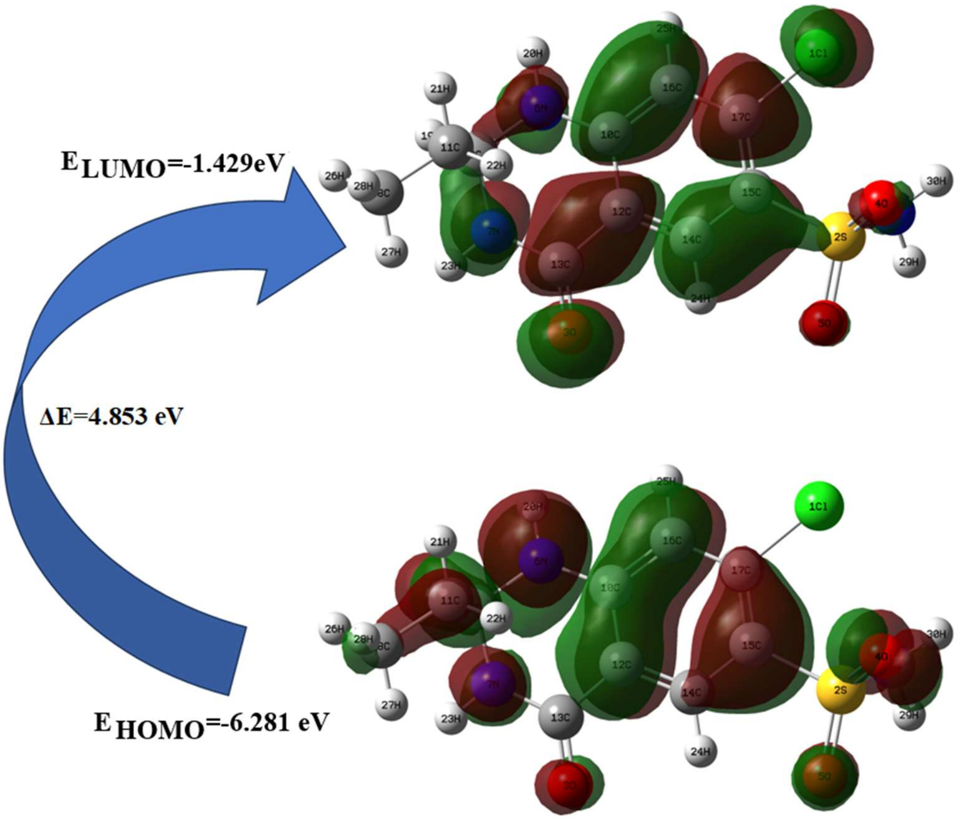

Figure 3. The HOMO-LUMO distributions of Quinethazone molecule.

Table 2. Some global reactivity descriptors the computed for the title compound.

Parameters (eV)	**Values**
E_{LUMO}	-1.429
E_{HOMO}	-6.281
Energy bandgap $\lvert E_{\mathrm{HOMO}}-E_{\mathrm{LUMO}}\rvert$	4.853
Ionization potential ($I = -E_{\mathrm{HOMO}}$)	6.281
Electron affinity ($A = -E_{\mathrm{LUMO}}$)	1.429
Chemical hardness ($h = (I-A)/2$)	2.426
Chemical softness ($z = 1/2h$)	0.206
Electronegativity ($\chi = (I+A)/2$)	3.855
Chemical potential ($\mu = -(I+A)/2$)	-3.855
Electrophilicity index $w = \mu^2/2h$	3.062
Maximum charge transfer index ($\Delta N_{max.} = -\mu/h$)	1.589

5. MOLECULAR ELECTROSTATIC POTENTIAL ANALYSIS

The Molecular Electrostatic Potential (MEP) analysis of quinethazone was performed based on the optimized molecular geometry to visualize the charge distribution and identify potential sites for electrophilic and nucleophilic interactions. As shown in Fig. 4, the MEP map clearly illustrates regions of electron-rich and electron-deficient character across the molecular surface. According to the results, the MEP values range from -7.0905×10^{-2} to 7.905×10^{-2} atomic units, indicating a moderate polarity and the presence of localized charge concentrations. This distribution supports the findings from frontier orbital analysis and provides complementary insight into the molecule's reactive potential in various chemical environments.

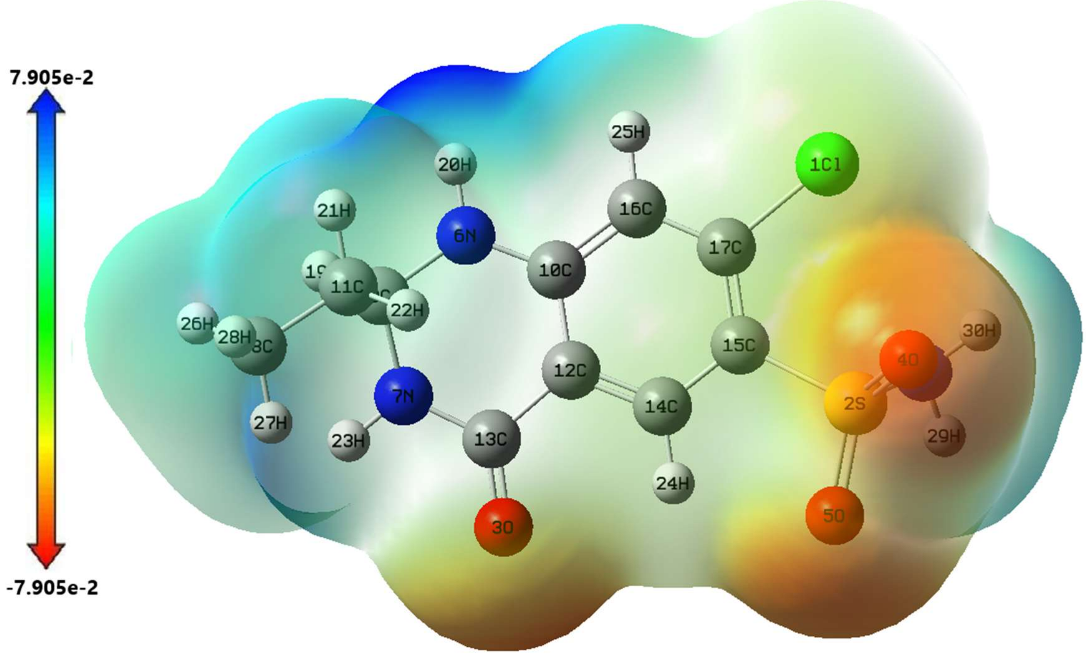

Figure 4. The MEP surface of Quinethazone molecule.

6. CONCLUSION

In this study, the structural and electronic properties of the quinethazone molecule were investigated for the first time using density functional theory (DFT) at the B3LYP/6-311++G(d,p) level. Geometry optimization yielded a stable, asymmetric structure with a significant dipole moment, indicating high polarity. Frontier molecular orbital (FMO) analysis revealed well-separated HOMO and LUMO distributions, and the computed energy gap suggested moderate chemical reactivity. Global reactivity descriptors provided further insight into the molecule's electrophilic and nucleophilic tendencies. Additionally, the molecular electrostatic potential (MEP) map supported the presence of distinct charge distribution regions. Overall, these findings contribute novel theoretical data to the literature and offer a foundational understanding of quinethazone's molecular behavior, potentially supporting future studies in drug interaction and design.

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REFERENCES

Alajlani, R., & Alssadi, A. (2019). Dipole Moments of the Bioactive Constituents Present in Flutab Drug by Ab-Initio Calculations. *Open Journal of Physical Chemistry*, *9*(4), 216-220.

Cavalli, A., Folkers, G., Recanatini, M., & Scapozza, L. (2003). Density-functional Theory Applications in Computational Medicinal Chemistry. *Quantum Medicinal Chemistry*, 41-71.

Clark, D. W., & Goldberg, L. I. (1972). Guancydine: a new antihypertensive agent: use with quinethazone and guanethidine or propranolol. *Annals of Internal Medicine*, *76*(4), 579-585.

Frisch, M. J. E. A. (2009). gaussian 09, Revision d. 01, Gaussian. *Inc, Wallingford CT*, *201*.

Hamilton, J. T., & Gowdey, C. W. (1966). A comparison of the effects of chlorothiazide, quinethazone and placebo on student volunteers and on rats: a teaching exercise. *Canadian Medical Association Journal*, *95*(2), 62.

McNally, R. J., Morselli, F., Farukh, B., Chowienczyk, P. J., & Faconti, L. (2019). A review of the prescribing trend of thiazide-type and thiazide-like diuretics in hypertension: A UK perspective. *British journal of clinical pharmacology*, *85*(12), 2707-2713.

Liang, W., Ma, H., Cao, L., Yan, W., & Yang, J. (2017). Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-analysis. *Journal of cellular and molecular medicine*, *21*(11), 2634-2642.

Parr, R. G., & Pearson, R. G. (1983). Absolute hardness: companion parameter to absolute electronegativity. *Journal of the American chemical society*, *105*(26), 7512-7516.

Parr, R. G., Szentpály, L. V., & Liu, S. (1999). Electrophilicity index. *Journal of the American Chemical Society*, *121*(9), 1922-1924.

Sandler, G. (1964). Quinethazone, a new oral diuretic. *British Medical Journal*, *2*(5404), 288.

Sulpizi, M., Folkers, G., Rothlisberger, U., Carloni, P., & Scapozza, L. (2002). Applications of density functional theory-based methods in medicinal chemistry. *Quantitative Structure-Activity Relationships*, *21*(2), 173-181.

Web of Science, (2025). [Access Date: 07-Feb-2025].