

Research Article

# Benzothiazole-derived Compound with Antitumor Activity: Molecular Structure Determination Using Density Functional Theory (Dft) Method

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## Abstract

The Gaussian computational chemistry software package was employed to investigate the molecular structure and energetics of benzothiazole, a compound known for its anti-tumor properties. Density functional theory (DFT) calculations were conducted using the Becke, 3-parameter, Lee-Yang-Parr (B3LYP) method, coupled with the LanL2DZ basis set. Molecular structure optimization was carried out to determine the most stable configurations of the benzothiazole compound. Furthermore, thorough analyses of molecular orbital energies, molecular properties, and molecular electrostatic potential surface maps were performed on the optimized molecular system. Our current research suggests that the compound 2-(4-aminophenyl) benzothiazole, containing benzothiazole, maybe a potential drug candidate for free radical species on cells due to its anti-cancer properties.

## Introduction

The pursuit of effective anti-cancer agents has intensified in recent years due to the escalating global cancer burden [1]. Traditional cancer therapies often entail debilitating side effects and limited efficacy, underscoring the need for innovative treatments that can selectively target malignant cells while sparing healthy tissue. In this context, benzothiazoles have emerged as promising candidates for anti-cancer drug development [2-4].

Benzothiazole-containing compounds have garnered considerable interest in the field of medicinal chemistry for their potential anti-tumor properties. Notably, these compounds have exhibited significant anti-inflammatory effects, positioning them as intriguing candidates for cancer therapy [5]. Their capacity to selectively target cancer cells, while minimizing harm to normal tissues, highlights their potential as efficacious and well-tolerated treatments [6].

Of particular interest is the ligand 2-(4-aminophenyl) benzothiazole, which has demonstrated [7-9] efficacy against various cancer types including ovarian, breast, lung, kidney, and colon cancers. Its selective anti-tumor activity [10] renders it a compelling candidate for further investigation and potential clinical development [11].

In drug design, computational methods play a pivotal

role in elucidating molecular properties and guiding the development of potential therapeutics. Density Functional Theory (DFT) calculations offer valuable insights into the structural and electronic characteristics of compounds, facilitating the identification of promising drug candidates. By employing DFT calculations, researchers can delve into the molecular intricacies of compounds like 2-(4-aminophenyl) benzothiazole, shedding light on their anti-cancer mechanisms and informing further experimental studies.


In this study, we utilized DFT calculations to explore the molecular structure and properties of 2-(4-aminophenyl) benzothiazole. Through structural optimization and analysis of electronic properties, we aimed to deepen our understanding of its anti-tumor activity and potential mechanisms of action. Our findings contribute to the growing body of knowledge surrounding benzothiazole-based compounds and lay the groundwork for future experimental investigations aimed at validating their therapeutic potential.

## Details of computational analysis

The molecular simulation of the molecule in its ground state was meticulously conducted using the renowned Gaussian 09W program package [12]. Employing the sophisticated density functional theory (DFT) method, the intricate interplay of molecular forces and electronic structure

### More Information

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was meticulously unraveled. Subsequently, the rich data obtained from these calculations were meticulously analyzed and visually represented using the powerful visualization tools offered by the Gaussian View 5 software [13], enabling a comprehensive understanding of molecular dynamics.

All computational endeavors were meticulously executed using the esteemed B3LYP method, a hybrid functional meticulously crafted by Becke with the incorporation of the LYP correlation functional. This methodological choice was further fortified by the utilization of the LANL2DZ (Los Alamos National Laboratory 2 Double Zeta) [14-16] basis set, renowned for its accuracy and versatility in capturing the intricate nuances of molecular interactions. Originating from the esteemed Los Alamos National Laboratory, the LANL2DZ [17] basis set boasts a dual-layered architecture, meticulously designed to model the core and diffusion layers of molecular orbitals. This meticulous design ensures a more accurate representation of higher-energy orbital interactions, consequently elevating the fidelity of computational predictions.

In summary, the meticulous selection of computational methodologies [18] and basis sets [19] underscores the precision and rigor employed in this study. By harnessing the power of cutting-edge computational tools and methodologies, we aim to unravel the intricate molecular mechanisms underlying the observed anti-tumor activity of the investigated compound, thereby paving the way for the development of novel therapeutic strategies in cancer treatment.

## Results and Discussion

### Analysis of molecular geometry structure in benzothiazole-derived compound

The crystal structure of the molecule containing benzothiazole [C<sub>14</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>5</sub>] with anti-tumor activity was synthesized by I. Caleta and colleagues [20]. The X-ray single crystal structure of this synthesized molecule is available in the Cambridge Crystallographic Data Centre (CCDC) with the code CCDC 224459. The molecular weight of the benzothiazole derivative molecule is 378.32 g/mol, and its unit cell belongs to the triclinic system with the space group P1. The experimental structure and atom numbers of the benzothiazole derivative molecule are depicted in Figure 1.

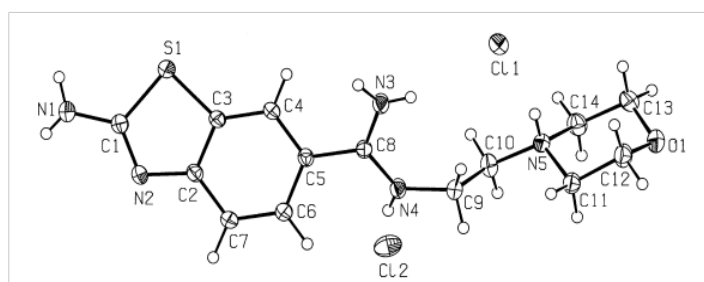


Figure 1: Experimental Structure of the Benzothiazole-Derived Molecule [20].

The experimental crystal structure provides crucial insights into the spatial arrangement of atoms within the benzothiazole derivative molecule, facilitating a deeper understanding of its chemical properties and potential biological interactions.

To examine the geometric structure of the molecule containing benzothiazole theoretically and compare it with experimental data, crystal structure data obtained from the CSD were calculated using Density Functional Theory (DFT) in the B3LYP method with the Gaussian 09 program. The optimized structure was determined using the DFT/B3LYP/LanL2DZG(d,p) method, known for its accuracy in predicting molecular geometries. This method accounts for both electronic and steric effects, providing a comprehensive understanding of the molecule's structural properties. The optimized structure is depicted in Figure 2.

Computational packages like Gaussian 09, employing density functional theory (DFT) methods, are predominantly utilized for calculating the properties of molecular structures in the gas phase and vacuum environments. These computational environments allow for the investigation of molecular systems under more isolated conditions, largely independent from their real-world surroundings. Such calculations play a pivotal role in elucidating the theoretical properties of molecular systems and facilitating comparisons with experimental data. Thus, in the present study, the geometric parameters, including bond length and bond angle, of the benzothiazole derivative molecule were meticulously examined. Utilizing the DFT/B3LYP/LANL2DZ method, optimizations were conducted in both the gas phase and stable state, as well as in vacuum conditions. Additionally, the experimental result files obtained from single-crystal X-ray diffraction, sourced from the literature, were meticulously scrutinized. The resulting optimized theoretical bond lengths and bond angles were compiled and are presented in Table 1 for comprehensive analysis.

The bond length between S1-C1 atoms of the benzothiazole-derived molecule, as listed in Table 1, exhibits an experimental value of 1.765 Å, while the theoretically calculated value using the DFT method is 1.76525 Å. Similarly, the bond angle between the C4-C3-S1 atoms has an experimental value of 128.2°, whereas the theoretically calculated value using the

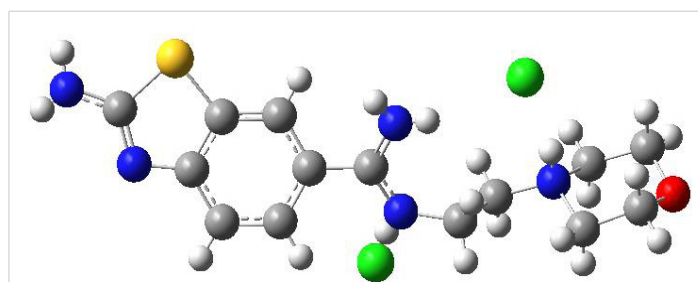


Figure 2: Optimized Geometry of the Benzothiazole-Derived Molecule Calculated Using the B3LYP/LANL2DZ Method.

**Table 1:** Geometric Parameters of the Benzothiazole-Derived Molecule.

| Bond Lengths (Å) | Bond Angles (°) |         |            |          |           |
|------------------|-----------------|---------|------------|----------|-----------|
|                  | X-ray           | B3LYP   |            | X-ray    | B3LYP     |
| S1-C3            | 1.742(1)        | 1.74203 | C3-S1-C1   | 88.2(1)  | 88.18996  |
| S1-C1            | 1.765(2)        | 1.76525 | C1-N2-C2   | 109.9(1) | 109.87221 |
| N1-C1            | 1.345(2)        | 1.34491 | C8-N4-C9   | 124.9(1) | 124.85369 |
| N2-C1            | 1.313(2)        | 1.31262 | C14-N5-C11 | 109.6(1) | 109.57555 |
| N2-C2            | 1.384(2)        | 1.38358 | N2-C1-N1   | 124.4(1) | 124.37129 |
| N3-C8            | 1.320(2)        | 1.32032 | N2-C1-S1   | 116.5(1) | 116.51831 |
| N4-C8            | 1.327(2)        | 1.32693 | N1-C1-S1   | 119.1(1) | 119.10507 |
| N4-C9            | 1.452(2)        | 1.45244 | N2-C2-C7   | 125.6(1) | 125.61936 |
| C2-C7            | 1.407(2)        | 1.40695 | N2-C2-C3   | 115.6(1) | 115.63915 |
| C2-C3            | 1.411(2)        | 1.41095 | C7-C2-C3   | 118.7(1) | 118.74109 |
| C3-C4            | 1.381(2)        | 1.38122 | C4-C3-C2   | 122.1(1) | 122.08309 |
| C4-C5            | 1.403(2)        | 1.40256 | C4-C3-S1   | 128.2(1) | 128.14280 |
| C5-C6            | 1.412(2)        | 1.41174 | C2-C3-S1   | 109.8(1) | 109.77328 |
| C5-C8            | 1.476(2)        | 1.47601 | C3-C4-C5   | 118.9(1) | 118.88365 |
| C6-C7            | 1.388(2)        | 1.38797 | C4-C5-C6   | 119.8(1) | 119.75215 |
| C9-C10           | 1.534(2)        | 1.53392 | C4-C5-C8   | 119.0(1) | 118.99756 |
| C10-N5           | 1.498(2)        | 1.49765 | C6-C5-C8   | 121.2(1) | 121.20934 |
| N5-C11           | 1.505(2)        | 1.50487 | C7-C6-C5   | 121.0(1) | 120.95631 |
| N5-C14           | 1.504(2)        | 1.50420 | C6-C7-C2   | 119.6(1) | 119.56898 |
| C11-C12          | 1.514(2)        | 1.51420 | N3-C8-N4   | 121.4(1) | 121.41092 |
| C12-O1           | 1.422(2)        | 1.42218 | N3-C8-C5   | 119.2(1) | 119.23023 |
| O1-C13           | 1.423(2)        | 1.42312 | N4-C8-C5   | 119.3(1) | 119.33564 |
| C13-C14          | 1.517(2)        | 1.51747 | N4-C9-C10  | 111.6(1) | 111.58760 |

DFT method is 128.77°. Upon examination of all the data in Table 1, it is observed that there is a good agreement between the experimental [20] and theoretically calculated data for the molecular geometric parameters of bond length and bond angle of the benzothiazole-derived molecule. This close agreement not only highlights the reliability and accuracy of the DFT method in predicting molecular geometric parameters but also underscores the utility of computational methods in complementing experimental techniques. While experimental methods provide invaluable direct measurements, computational approaches offer detailed insights into molecular structures and properties, often inaccessible through experimentation alone. This synergy between experimental and theoretical techniques enhances our understanding of molecular behavior and facilitates the design of novel compounds with tailored properties for diverse applications.

### Electronic properties in Benzothiazole-derived compound

Density Functional Theory (DFT) serves as a versatile tool for calculating the energy levels of molecular structures across various electronic configurations and molecular systems. Among these, the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) play pivotal roles. The HOMO orbital governs the chemical reactivity and electronic properties of the molecule, while the LUMO orbital participates in electron-deficient regions within the molecule and contributes to chemical bond formation. These orbitals, situated at specific energy levels as per molecular orbital theory, dictate the electron distribution and chemical bonds within a molecule. Notably,

the HOMO level signifies the molecule's propensity to engage in chemical interactions with other molecules, whereas the LUMO level indicates its readiness to participate in chemical reactions. When the HOMO of one molecule aligns with the LUMO of another, it enhances the likelihood of a chemical reaction between the two, thereby influencing the nature and probability of such reactions.

Moreover, the energy gap between HOMO and LUMO, known as the HOMO-LUMO energy gap, serves as a critical parameter in predicting the occurrence and characteristics of chemical reactions. The  $E_{\text{HOMO}}$  denotes the energy of the highest occupied molecular orbital, reflecting the molecule's tendency to donate electrons ( $\pi$ -donor), while the  $E_{\text{LUMO}}$  represents its inclination to accept electrons ( $\pi$ -acceptor). Extracted from computations employing the B3LYP method with the LANL2DZ basis set, electronic structure parameters ( $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$ ) facilitate the determination of ionization potential (I), electron affinity (A), electronegativity ( $\chi$ ), chemical softness (S), and chemical hardness ( $\eta$ ) values. This comprehensive analysis, as outlined in Table 2, illuminates the intricate electronic properties of the benzothiazole-derived molecule and its potential implications across various chemical processes and applications.

In the realm of theoretical gas-phase calculations, understanding the behavior of molecules at the atomic and subatomic levels is paramount. One fundamental aspect is the ionization potential energy, which denotes the energy required to remove an electron from a molecule. This process, known as ionization, is crucial in elucidating the stability and reactivity of chemical species. The ionization potential serves as a yardstick, indicating the ease or difficulty with which electrons can be stripped away from a molecular system. This metric is indispensable in various fields, including spectroscopy, where it aids in identifying molecular structures and elucidating electronic transitions.

Conversely, electron affinity represents the energy change when an additional electron is added to a neutral atom or molecule. This property sheds light on the tendency of a species to accept electrons and form negative ions. Electron affinity is a key determinant of chemical reactivity, influencing phenomena such as redox reactions and the formation of chemical bonds. Understanding electron affinity is crucial in fields like materials science and catalysis, where the manipulation of electron transfer processes is pivotal.

**Table 2:** Molecular Orbital Energy Calculations for the Benzothiazole-Derived Molecule.

|   | B3LYP /LANL2DZ |
|---|----------------|
| $E_{\text{HOMO}}$ (eV)                              | -6,23935       |
| $E_{\text{LUMO}}$ (eV)                              | -1,08629       |
| $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ (eV) | 0,18937        |
| Ionization Potential (eV)                           | 6,23935        |
| Electron Affinity (eV)                              | 1,08629        |
| Electronegativity (eV)                              | 3,66282        |
| Chemical Hardness (eV)                              | 2,57653        |
| Chemical Softness (eV <sup>-1</sup> )               | 0,080137       |
| $E_{\text{TOTAL}}$ (a.u)                            | -934.96075     |

Electronegativity, on the other hand, is a measure of an atom's ability to attract electrons toward itself when participating in a chemical bond within a molecule. It is a fundamental concept in understanding the nature of chemical bonds, particularly in polar covalent bonds where electrons are unevenly shared between atoms. Electronegativity values help predict the polarity of molecules and their overall chemical behavior. For instance, in organic chemistry, electronegativity differences between atoms dictate the direction of electron flow in reactions such as nucleophilic or electrophilic substitutions.

Chemical hardness is a concept that delves into the resistance of a molecule to changes in its electronic structure, particularly regarding charge transfer phenomena. It quantifies the energy required to induce infinitesimal changes in the electron density of a molecule, reflecting its stability and reactivity. Chemical hardness is closely related to concepts such as softness and electrophilicity, providing valuable insights into molecular interactions and reaction mechanisms.

Now, let's apply these concepts to a specific example molecule derived from benzothiazole. Benzothiazole, a heterocyclic compound consisting of benzene and thiazole rings, exhibits diverse chemical properties due to its unique molecular structure. By analyzing the selected boundary molecular orbitals and their electronic transitions, as depicted in Figure 3, we gain a deeper understanding of the electronic structure and reactivity of this molecule. Such analyses are instrumental in fields ranging from organic synthesis to drug design, where a comprehensive understanding of molecular properties is crucial for the rational design and optimization of chemical compounds.

Based on electrostatic potential mappings, atoms highlighted in red typically exhibit a heightened electron density. This phenomenon signifies an accumulation of

electrons around the atom's nucleus, indicative of regions with increased electron density. These areas are commonly regarded as electron-rich sites or reactive centers, pivotal in chemical interactions and reactivity pathways [21].

Analyzing the electrostatic potential distributions of Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) orbitals reinforces theoretical insights, aligning with experimental observations. Consequently, it is anticipated that regions characterized by elevated electron density correspond to HOMO and LUMO orbitals, reflecting their potential roles in electron transfer processes and chemical transformations [22]. Such correlations between orbital characteristics and electrostatic potential provide valuable mechanistic insights into molecular reactivity and intermolecular interactions, facilitating the rational design of functional materials and pharmaceutical compounds.

Furthermore, the localization of HOMO orbitals serves as a significant predictor of a compound's chemical reactivity and biological activity [23]. Notably, the proximity between a molecule's HOMO orbitals and reactive centers or target molecules underscores its potential as a candidate for drug discovery or as a key participant in chemical reactions. This holistic understanding of molecular properties, informed by electrostatic potential analyses and orbital characteristics, enriches our comprehension of molecular behavior and guides the development of novel chemical entities with tailored functionalities and applications.

### **Molecular electrostatic potential surface (MEPS) Map in Benzothiazole-derived compound**

Expanding upon the discussion, Molecular Electrostatic Potential (MEP) emerges as a pivotal tool in elucidating a myriad of molecular behaviors, ranging from intricate structure-activity relationships to the subtle nuances of chemical reactivity and the formation of crucial intermolecular interactions like hydrogen bonding. The MEP concept is instrumental in discerning the electrostatic landscape surrounding a molecule, offering invaluable insights into its electronic structure and behavior in chemical environments [24].

For instance, when considering benzothiazole derivative molecules, researchers often turn to MEP analysis to unravel the intricate interplay of electron density within these compounds. By employing advanced computational methods such as the B3LYP/LANL2DZ approach, three-dimensional MEP maps, as showcased in Figure 4, are meticulously crafted. These maps serve as cartographic guides, delineating the topography of electron density distribution across the molecular surface. Regions of high electron density are depicted in contrasting hues to those of low electron density, providing a visual representation of the molecular charge distribution.

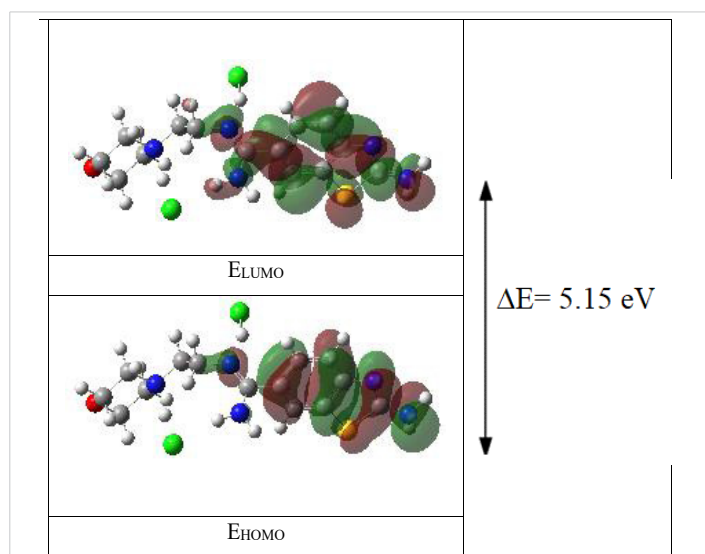
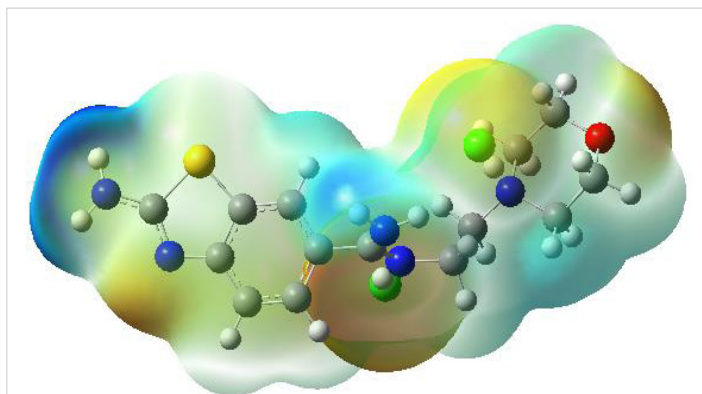


Figure 3: The calculated (with B3LYP/LANL2DZ level) 3D orbital energies of the benzothiazole derivative molecule.





**Figure 4:** Molecular Electrostatic Potential Surface Map of the Benzothiazole Derivative Molecule.

The significance of MEP visualization transcends mere depiction; it acts as a gateway to understanding the reactivity patterns and structural features of benzothiazole derivatives. By discerning regions of electron abundance and scarcity, researchers can anticipate sites prone to nucleophilic or electrophilic attack, guiding the rational design of novel compounds with tailored properties. Moreover, MEP analysis facilitates the identification of potential binding sites for molecular recognition and the prediction of pharmacological activity in drug design endeavors.

Furthermore, the utility of MEP extends to elucidating the mechanisms underlying intermolecular interactions, particularly hydrogen bonding—an essential aspect governing molecular recognition and supramolecular assembly. By overlaying MEP maps of interacting molecules, researchers can pinpoint regions conducive to hydrogen bond formation, thereby facilitating the rational design of molecular scaffolds with enhanced binding affinity and specificity [25].

In essence, Molecular Electrostatic Potential analysis stands as a cornerstone in modern computational chemistry, offering a holistic perspective on molecular properties and behaviors. Its integration with advanced computational techniques not only enriches our understanding of chemical phenomena but also paves the way for the innovative design and development of molecular entities with diverse applications in fields ranging from pharmaceuticals to materials science.

In the realm of molecular chemistry, understanding the distribution of electron density within molecules is foundational. Molecular Electrostatic Potential (MEP) maps serve as indispensable tools in this endeavor, providing visual representations of electron density distribution. These maps not only elucidate molecular size and shape but also offer insights into electrostatic potential values, essential for comprehending chemical interactions and reactivities.

In a neutral molecule, MEP maps typically reveal electron-rich regions highlighted in shades of red, while electron-poor areas appear in shades of blue. Notably, high electron density

concentrations are often observed around electronegative atoms like oxygen, reflecting their ability to attract electron pairs. Conversely, regions with the lowest electron density are commonly found near C-H bonds, underscoring the relatively lower electronegativity of carbon-hydrogen bonds.

The significance of MEP maps extends beyond mere visualization; they are instrumental in unraveling molecular reactivity and intermolecular interactions. By examining these maps, researchers can discern structural features influencing chemical behaviors, thus guiding the design of novel compounds with tailored functionalities.

Moreover, advancements in computational chemistry have facilitated the generation of highly detailed MEP maps, enabling researchers to explore intricate molecular landscapes with unprecedented precision. Through sophisticated computational algorithms and high-performance computing, MEP analysis has evolved into a versatile tool for predicting chemical reactivity, molecular recognition, and catalytic mechanisms [26]. This integration of computational methods with experimental techniques has propelled molecular electrostatic potential mapping to the forefront of modern molecular sciences, driving innovation in drug discovery, materials design, and catalysis research [27].

In conclusion, Molecular Electrostatic Potential maps continue to play a pivotal role in understanding molecular properties and behaviors, offering profound insights into the intricate world of chemical interactions and paving the way for transformative discoveries in various fields of science and technology [28,29].

## Conclusion

The utilization of computational methodologies, notably density functional theory (DFT) calculations employing the B3LYP method with the LanL2DZ basis set, has yielded invaluable insights into the molecular architecture and attributes of compounds containing benzothiazole, renowned for their potential antitumor efficacy. This approach enabled the optimization of molecular structures, thereby elucidating stable conformations crucial for an exhaustive examination of their molecular attributes.

Furthermore, the scope of investigation transcended structural refinement to encompass analyses of molecular orbital energies and molecular electrostatic potential surface maps. These comprehensive assessments provided a nuanced comprehension of the electronic configuration and reactivity tendencies inherent in the compounds, thereby illuminating their plausible pharmacological attributes.

The outcomes derived from this scholarly inquiry underscore the efficacy of computational methodologies in unraveling the intricate molecular nuances of bioactive compounds. By harnessing sophisticated computational tools,



scholars can glean pivotal insights into the intricate structure-activity relationships and therapeutic potentials embodied by compounds incorporating benzothiazole moieties.

Moreover, the ramifications of this study extend beyond theoretical elucidation, promising substantial advancements in the realm of cancer therapeutics. Benzothiazole-derived compounds, characterized by their diverse structural motifs and pharmacological properties, emerge as auspicious candidates for the innovation of novel antineoplastic agents.

The insights garnered from computational analyses not only illuminate the structural and electronic attributes of these compounds but also furnish crucial intelligence about their interactions with biological targets. This holistic comprehension serves as a springboard for the judicious design and refinement of benzothiazole derivatives endowed with heightened anticancer efficacy and refined pharmacokinetic profiles.

A pivotal avenue of exploration, facilitated by these findings, lies in unraveling structure-activity relationships (SAR), wherein subtle alterations to the molecular framework can impart significant alterations in biological potency. Through the synthesis of computational data with empirical observations, researchers can fine-tune the chemical architecture of benzothiazole derivatives to optimize their efficacy against specific malignancies whilst mitigating off-target effects.

Furthermore, the identification of key pharmacophoric attributes within benzothiazole-derived compounds facilitates the tailored formulation of therapies aimed at exploiting precise molecular vulnerabilities inherent in cancerous cells. For instance, molecules exhibiting heightened affinities for select protein targets implicated in tumor proliferation or metastasis may be prioritized for further developmental endeavors as antineoplastic agents.

Moreover, the advent of personalized medicine underscores the imperative of tailoring therapeutics to target the unique molecular signatures of individual tumors. Computational methodologies, complemented by empirical validation, offer an expedited avenue for screening expansive compound libraries, thereby identifying lead candidates with the potential for personalized anticancer interventions.

In addition to their direct cytotoxic effects, benzothiazole-derived compounds may engender synergistic interactions with extant chemotherapeutic agents, thereby augmenting treatment efficacy whilst attenuating the risk of drug resistance. Rational combinatorial strategies, informed by computational modeling, hold promise for surmounting the heterogeneity and adaptability inherent in neoplastic tissues.

In summation, the findings emanating from this scholarly endeavor herald a significant stride toward the realization of

more efficacious and targeted modalities for cancer treatment. By harnessing the computational prowess inherent in contemporary chemistry, scholars stand poised to unlock the full therapeutic potential harbored by benzothiazole-derived compounds in combating this debilitating malady, thereby engendering tangible enhancements in patient outcomes and quality of life.

**Author contributions:** Hacer Gumus contributed to the conception, design, and execution of the study, as well as data analysis and interpretation.

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