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Theoretical study of the thermodynamic, electronic, and pharmacokinetic stability of 2-[(benzimidazolyl) methylthio]-4,5-diphenylimidazole derivatives: implications for the development of new antibacterial agents

Anoh Valentin Ablé [1], Neantien Thilerien Yao Bi [1, *], Bamoro Coulibaly [2], Esme Roxane Edjème Inès Sié [1], Soleymane Koné [1] and Bamba El Hadj Sawaliho [1]

[1] *Department of Sciences of Structure and Matter (SSMT), Laboratory of Constitution and Reaction of Matter (LCRM).*
[2] *Department of Agro-Industrial Sciences and Technologies (AIST), UFR Agriculture, Halieutic Resources and Agro-Industry (AHRAI), University of San Pedro, San Pedro, Ivory Coast.*

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Abstract

Infectious diseases remain a major challenge for public health, reinforcing the need for new effective antimicrobial agents. In this context, five derivatives of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole were studied using theoretical calculations based on density functional theory (DFT, B3LYP/6-31+G(d,p)) to evaluate their thermodynamic stability, electronic properties, and pharmacokinetic potential. The results show that all compounds exhibit good energy stability, with negative values for enthalpy of formation ($\Delta_f H$), Gibbs free energy (ΔG^0), and total energy (E_T), reinforced in the aqueous phase by the solvation effect. Frontier orbital analysis reveals a small HOMO – LUMO gap for compound 3, indicating increased electronic reactivity and enhanced electron transfer capacity. At the same time, the dipole moment in aqueous phase is highest for this same compound (μ = 16.420 D), highlighting high polarity and an ability to interact with polar biomolecules. The physicochemical and pharmacokinetic properties (molar mass, LogP, TPSA, HBD/HBA) confirm that compound 3 combines high polarity, moderate lipophilicity, and favorable hydrogen bonding potential. These results suggest that this derivative has a promising profile for biological and pharmaceutical applications, in line with the principles of rational design of bioactive molecules.

Keywords: DFT; Heterocyclic Derivatives; Thermodynamic Stability; Frontier Orbitals; Dipole Moment; ADME; Antibacterial.

1. Introduction

Infectious diseases remain a major global public health problem due to the continuous emergence of new pathogenic strains and the rapid spread of antimicrobial resistance. This situation compromises the effectiveness of conventional treatments and highlights the urgent need to develop new anti-infective agents with improved efficacy and alternative mechanisms of action [1]; World Health Organization [2]. In this context, heterocyclic compounds occupy a central place in medicinal chemistry due to their great structural diversity and numerous biological activities [3].

Among these compounds, imidazole and benzimidazole derivatives are widely recognized for their antibacterial, antifungal, and anticancer properties [4]. The combination of these two pharmacophores within the same molecular structure can lead to favorable synergistic effects, particularly through modulation of electronic and structural properties, thereby enhancing their biological potential [5]. Recently, a series of five derivatives of 2-[(benzimidazolyl)methylthio] -4,5-diphenylimidazole was the subject of an initial theoretical study focused on analyzing overall reactivity, electronic stability, and the identification of nucleophilic and electrophilic attack sites using

* Corresponding author: Neantien Thilerien Yao Bi

density functional theory (DFT) calculations [6]. This study highlighted the influence of substituents on electronic distribution and their potential role in the observed biological activity.

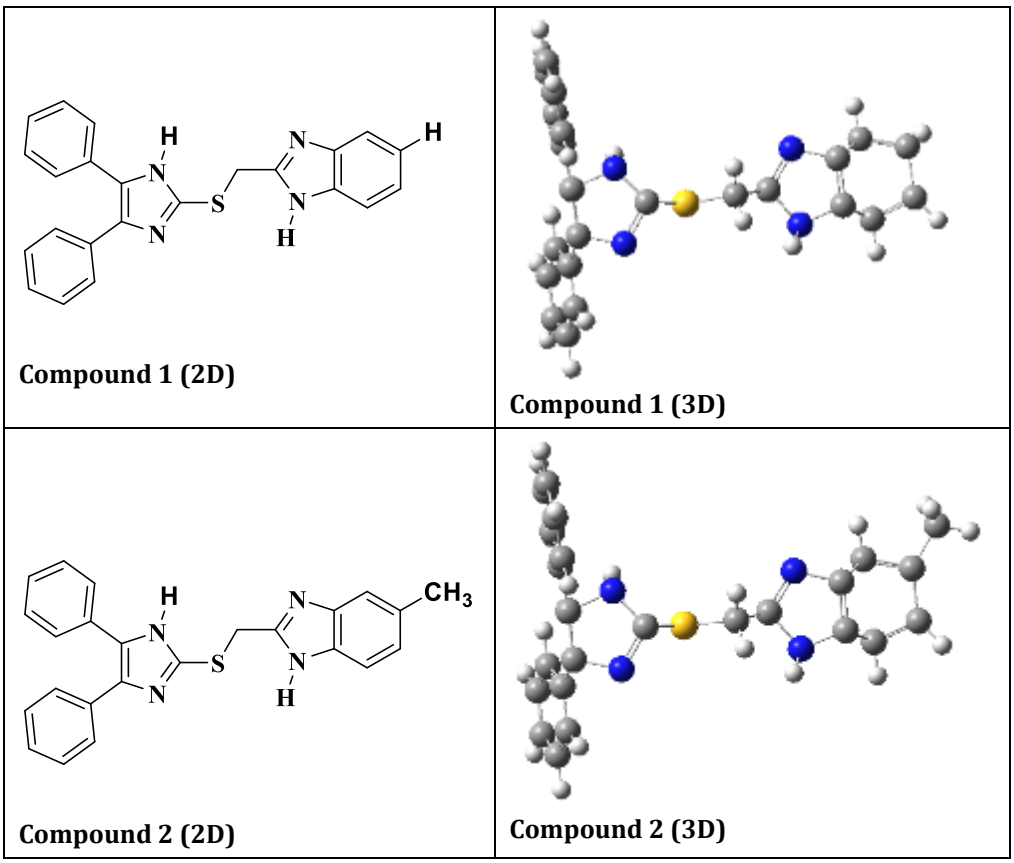
However, beyond intrinsic reactivity, the biological behavior of drug candidates depends heavily on their thermodynamic stability, the effect of the solvent on their electronic properties, and their pharmacokinetic characteristics [7]. In particular, the aqueous environment, representative of physiological conditions, can induce significant changes in molecular polarity, frontier orbital energy levels, and HOMO–LUMO energy gap, which may influence chemical reactivity and interactions with biological targets [8]. Furthermore, early evaluation of ADME parameters and drug-likeness criteria is an essential step in identifying promising compounds and rationally optimizing new therapeutic agents [9].

In this context, the present work aims to conduct an in-depth theoretical study of the thermodynamic, electronic, and pharmacokinetic properties of five derivatives of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole. DFT calculations were performed at the B3LYP/6-31+G(d,p) level in the gas phase and in the aqueous phase to evaluate the enthalpy of formation, Gibbs free energy, entropy, total energy, frontier molecular orbitals, and dipole moment. In addition, an in silico analysis of ADME parameters was conducted to estimate the pharmacokinetic potential and drug development suitability of these compounds. This complementary study provides a deeper understanding of structure-property relationships and the influence of the solvent, contributing to the rational design of new heterocyclic derivatives with antibacterial potential.

2. Materials and Calculation Methodology

2.1. Materials

The various compounds that make up our study material are grouped together in Figure 1 below.



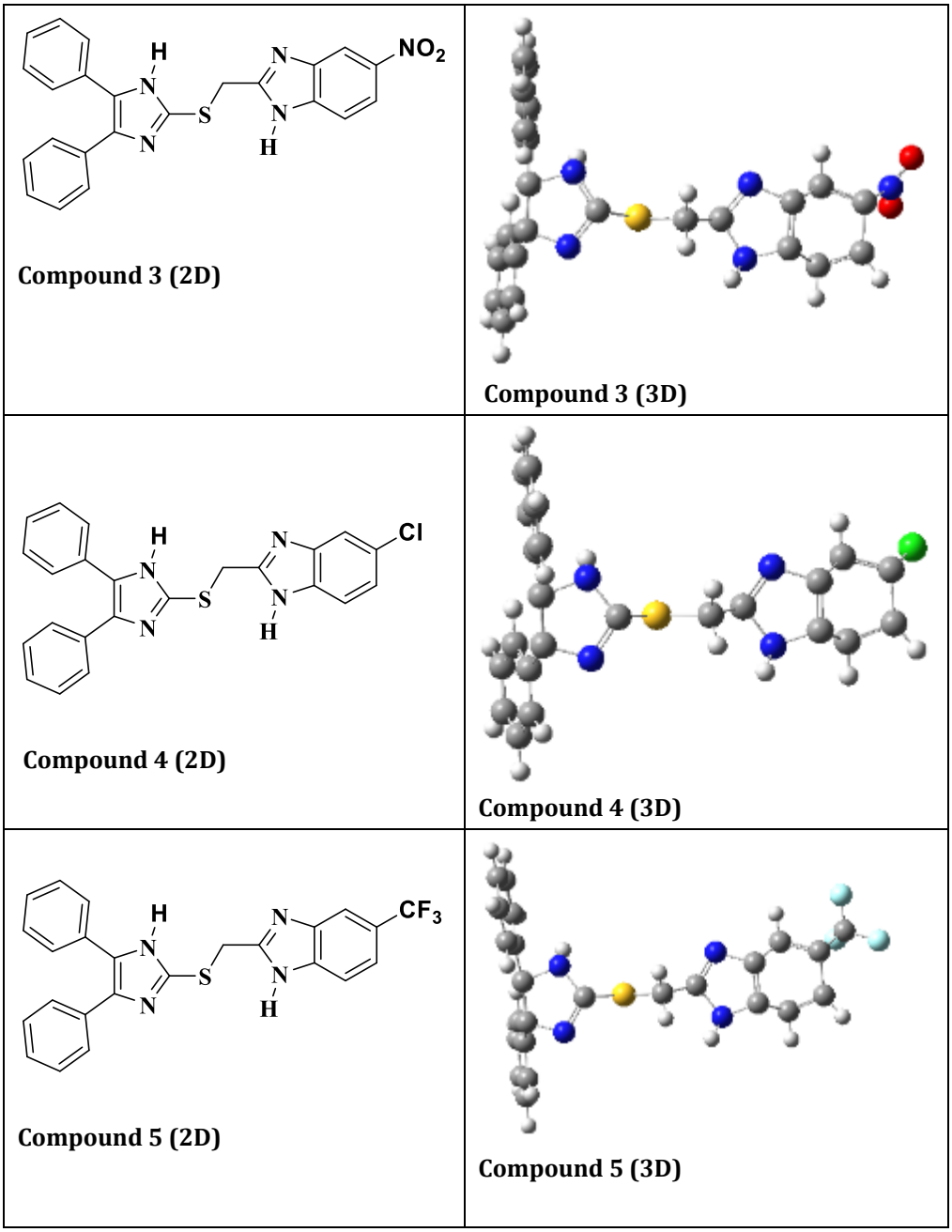


Figure 1 2D and 3D structures of the five derivatives of 2-[(benzimidazolyl)methylthio]-4,5-diphénylimidazole

2.2. Calculation methodology

In this study, five derivatives of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole were analyzed to evaluate their thermodynamic, electronic, and pharmacokinetic properties. First, the molecular structures were drawn and converted into SMILES notations on the SwissADME platform, which enabled the analysis of various ADME parameters, such as molar mass, lipophilicity (LogP), topological polar surface area (TPSA), and the number of hydrogen bond donors and acceptors (HBD/HBA). This step also made it possible to assess compliance with Lipinski's rules, with the aim of estimating the oral bioavailability potential of the compounds.

Next, using Gaussian 09 software, the thermodynamic and electronic properties were calculated using density functional theory (DFT) **[10]** with the B3LYP functional and the 6-311++G(d,p) basis set, after complete geometric optimization of the structures. These calculations were performed in both the gas phase and in aqueous media in order to evaluate the effect of solvation on thermodynamic stability ($\Delta_f H$, ΔG^0, E_T), molecular polarity (dipole moment), and electronic reactivity (E_{HOMO}, E_{LUMO}, ΔE_{gap}).

3. Results and discussion

3.1. Thermodynamic properties of compounds

The enthalpy of formation ($\Delta_f H$) and free enthalpy of formation ($\Delta G°$) were calculated using the theory mentioned above. These quantities are useful for evaluating the stability of structures. The calculations were performed in the gaseous and aqueous media presented in Tables 1 and 2.

Table 1 Enthalpy of formation ($\Delta_f H$) and free enthalpy of formation ($\Delta G°$) and total energy (E_T), calculated in aqueous and gaseous media. These energies are expressed in kcal/mol.

COMPOUNDS		$\Delta_f H$ (kcal/mol)	ΔG° (kcal/mol)	E_T (kcal/mol)
Compound 1	Gaseous	-943890.448	-943939.384	-944131.729
Compound 1	Aqueous	-943900.878	-943950.077	-944141.969
Compound 2	Gaseous	-968545.372	-968597.039	-968804.913
Compound 2	Aqueous	-968555.836	-968607.476	-968815.189
Compound 3	Gaseous	-1072219.215	-1072272.309	-1072463.550
Compound 3	Aqueous	-1072232.883	-1072285.823	-1072476.970
Compound 4	Gaseous	-1232291.118	-1232342.103	-1232527.076
Compound 4	Aqueous	-1232301.658	-1232352.570	-1232537.447
Compound 5	Gaseous	-1155391.198	-1155446.667	-1155637.460
Compound 5	Aqueous	-1155402.194	-1155457.451	-1155648.162

Examination of the thermodynamic parameters calculated for the five compounds reveals marked energy stability in both the gas phase and the aqueous phase, as illustrated by the highly negative values of the enthalpy of formation ($\Delta_f H$), standard Gibbs free energy (ΔG^0), and total energy (E_T). In the gas phase, compound 1, for example, has a $\Delta_f H$ of −943,890.448 kcal/mol and a ΔG^0 of −943,939.384 kcal/mol, while its total energy reaches −944,131.729 kcal/mol. These values already indicate good thermodynamic stability of the system. However, when transitioning to the aqueous phase, these parameters become slightly more negative ($\Delta_f H$ = −943,900.878 kcal/mol; ΔG^0 = −943,950.077 kcal/mol; E_T = −944,141.969 kcal/mol), highlighting the stabilizing effect of the solvent.

This trend is consistently observed for all of the compounds studied. For example, compound 2 sees its Gibbs free energy change from −968,597.039 kcal/mol in the gas phase to −968,607.476 kcal/mol in the aqueous phase, while its total energy changes from −968,804.913 to −968,815.189 kcal/mol. Similarly, compound 3, which has the most negative energy values, has a ΔG^0 of −1,072,272.309 kcal/mol in the gas phase, which further decreases to −1,072,285.823 kcal/mol in an aqueous medium, accompanied by a total energy change from −1,072,463.550 to −1,072,476.970 kcal/mol. These results suggest a particularly high thermodynamic stability for this compound, possibly linked to better electron delocalization and enhanced solvent–solute interactions.

Furthermore, compounds 4 and 5 follow the same energy evolution. In the gas phase, compound 4 has a ΔG^0 of −1,232,342.103 kcal/mol and a total energy of −1,232,527.076 kcal/mol, values that become −1,232,352.570 kcal/mol and −1,232,537.447 kcal/mol, respectively, in the aqueous phase. Similarly, for compound 5, the ΔG^0 changes from −1,155,446.667 kcal/mol to −1,155,457.451 kcal/mol, confirming that the aqueous environment systematically contributes to additional energy stabilization.

Overall, the slight decrease in the values of $\Delta_f H$, ΔG^0, and E_T during the transition from the gas phase to the aqueous phase confirms that solvation plays a decisive role in the thermodynamic stabilization of these systems. This behavior is consistent with the principles of chemical thermodynamics and continuous solvation models, according to which a polar medium such as water promotes the stabilization of molecular species through electrostatic interactions and polarization effects **[11]**. Thus, these results reinforce the hypothesis that these compounds exhibit increased stability under conditions close to the biological environment, which is a major advantage for their potential pharmacological applications.

3.2. Analysis of frontier orbitals and electronic stability

The energies of molecular frontier orbitals (E_{HOMO} and E_{LUMO}), as well as the HOMO–LUMO energy gap (ΔEgap), are key indicators of the electronic stability and chemical reactivity of molecules.

Table 2 Energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}), as well as the HOMO–LUMO energy gap (ΔEgap)

COMPOUNDS	PHASES	E_{HOMO}(eV)	E_{LUMO} (eV)	ΔE_{gap} (eV)
Compound 1	Gaseous	-5.866	-1.501	4.365
Compound 1	Aqueous	-5.820	-1.335	4.485
Compound 2	Gaseous	-5.840	-1.489	4.351
Compound 2	Aqueous	-5.815	-1.333	4.482
Compound 3	Gaseous	-6.143	-2.370	3.773
Compound 3	Aqueous	-5.864	-2.941	2.923
Compound 4	Gaseous	-5.980	-1.580	4.401
Compound 4	Aqueous	-5.837	-1.340	4.498
Compound 5	Gaseous	-6.042	-1.625	4.417
Compound 5	Aqueous	-5.842	-1.350	4.492

The study of frontier molecular orbitals, through the energies of the highest occupied molecular orbital (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}), as well as the HOMO–LUMO energy gap (ΔEgap), is a widely used approach for evaluating the electronic stability and chemical reactivity of molecular systems [12]. In the gas phase, the E_{HOMO} values of the compounds studied range from −5.840 eV for compound 2 to −6.143 eV for compound 3, reflecting notable differences in their ability to donate electrons. A more negative E_{HOMO} is generally associated with greater electronic stability and a lower tendency to oxidize [13]. Thus, compound 3, characterized by the lowest E_{HOMO} (−6.143 eV), exhibits increased resistance to electron donation, suggesting a more electronically stabilized structure.

At the same time, E_{LUMO} values range from −1.489 eV to −2.370 eV in the gas phase, with compound 3 exhibiting the lowest vacant orbital (E_{LUMO} = −2.370 eV). This characteristic indicates an enhanced ability to accept electrons, favoring interactions with donor species and, consequently, increased electronic reactivity [14]. Consistent with these observations, the HOMO–LUMO gap of compound 3 is the smallest in the series (ΔEgap = 3.773 eV), while the other compounds have higher values, ranging from 4.351 eV for compound 2 to 4.417 eV for compound 5. According to frontier orbital theory, a low ΔEgap is generally correlated with greater ease of electron transfer and more pronounced chemical reactivity [15].

When the effect of the solvent is taken into account, a significant change in orbital energies is observed for all compounds. In the aqueous phase, the E_{HOMO} values become less negative overall, as illustrated by compound 1, whose E_{HOMO} changes from −5.866 eV in the gas phase to −5.820 eV in the aqueous phase, reflecting the influence of polarization induced by the solvated medium. At the same time, the E_{LUMO} values are also affected by solvation, which directly modifies the HOMO–LUMO energy gap.

In the aqueous phase, the ΔEgap values of compounds 1, 2, 4, and 5 increase slightly to 4.485 eV, 4.482 eV, 4.498 eV, and 4.492 eV, respectively, suggesting increased electronic stabilization and moderate reactivity in a polar environment. In contrast, compound 3 exhibits unusual behavior, with a marked decrease in ΔEgap from 3.773 eV in the gas phase to 2.923 eV in the aqueous phase. This significant reduction indicates an increase in electronic reactivity in an aqueous medium, probably linked to preferential stabilization of the LUMO orbital by solvent-solute interactions and enhanced electronic delocalization [8].

Overall, these results highlight the decisive influence of molecular structure and solvent environment on the electronic properties of the compounds studied. The combination of a low ΔEgap, high sensitivity to solvation, and increased electron transfer capacity gives compound 3 a particularly favorable profile for interactions with biological targets, in accordance with the principles of quantum chemistry applied to the design of bioactive molecules.

3.3. Dipole moment and solvent effect

The dipole moment (μ) is an essential parameter for evaluating molecular polarity and the behavior of compounds in biological environments.

Table 3 Dipole moment (μ) of compounds in the gas and aqueous phases in Debye (D)

COMPOUNDS	μ (Gaz, D)	μ (Aqueux, D)	Variation Δμ
Compound 1	6.450	8.560	+2.110
Compound 2	6.085	8.007	+1.922
Compound 3	12.902	16.420	+3.518
Compound 4	8.905	11.365	+2.460
Compound 5	10.392	12.910	+2.518

The dipole moment (μ) is a fundamental parameter for characterizing molecular polarity and predicting the behavior of compounds in polar environments such as biological media **[16]**. Thus, in the gas phase, the dipole moment values of the compounds studied range from 6.085D for compound 2 to 12.902D for compound 3, indicating moderate to high polarity overall, depending on the nature and distribution of the substituents. This variability reflects marked differences in the asymmetry of the electron density and in the relative contribution of the polarizable heteroatoms present within the molecular structures.

The increasing order of polarity in the gas phase with their substituents is as follows:

Compound 2 ($-CH_3$) < Compound 1 (H) < Compound 4 (−Cl) < Compound 5 ($-CF_3$) < Compound 3 ($-NO_2$).

Compound 3 stands out clearly with the highest dipole moment in the gas phase (μ = 12.902 D), reflecting a strong separation of partial charges. This behavior can be explained by the presence of the $-NO_2$ group, which combines a strong inductive attractor effect (–I) and a mesomeric attractor effect (–M), generating significant electronic asymmetry **[17]**. In contrast, compound 2, with a μ value of 6.085D, has the lowest polarity. The methyl group ($-CH_3$) exerts a moderate donor inductive effect (+I) that slightly enriches the system in electron density without creating a strong separation of charges, explaining this moderate polarity **[18]**.

Compound 1 (H), which has no significant inductive or mesomeric effect, is the structural reference and has an intermediate value (6.450 D), reflecting the inherent asymmetry of the molecular skeleton. Compounds 4 (–Cl) and 5 ($-CF_3$) have intermediate values of 8.905 D and 10.392 D, respectively. Chlorine exerts an attractive inductive effect (–I) partially offset by a weak donor mesomeric effect (+M), while the $-CF_3$ group exhibits a strong attractive inductive effect (–I) due to the high electronegativity of the fluorine atoms. These characteristics explain their significant polarity, which is nevertheless lower than that of compound 3.

When the aqueous environment is taken into account, a notable increase in dipole moment is observed for all compounds. The values reach 8.007 D for compound 2, 8.560 D for compound 1, 11.365 D for compound 4, 12.910 D for compound 5, and 16.420 D for compound 3. The order of polarity remains strictly conserved in the aqueous phase:

Compound 2 ($-CH_3$) < Compound 1 (H) < Compound 4 (−Cl) < Compound 5 ($-CF_3$) < Compound 3 ($-NO_2$).

The Δμ variations also follow a trend consistent with the nature of the substituents:

Compound 2 (+1.922) < Compound 1 (+2.110) < Compound 4 (+2.460) < Compound 5 (+2.518) < Compound 3 (+3.518).

This evolution can be attributed to the polarization induced by the solvent, which stabilizes the partial charges and amplifies the electronic asymmetry of the molecules **[8]**. More specifically, compound 3 shows the greatest variation in dipole moment (Δμ = +3.518 D), confirming its increased sensitivity to solvation due to the highly attractive and polar nature of the substituent ($-NO_2$). Compound 5 also shows a notable variation related to its powerful –I effect, while compounds 4, 1, and 2 show more moderate increases, in line with their respective electronic effects.

In summary, the order of polarity observed directly reflects the intensity of the electronic effects of the substituents: strongly attractive groups ($-NO_2$, $-CF_3$) induce the strongest charge separations, –Cl occupies an intermediate position due to its –I effect partially compensated by a weak +M, $-CH_3$ confers the lowest polarity due to its moderate +I effect, and hydrogen serves as a neutral reference. The systematic increase in dipole moment in the aqueous phase thus confirms the decisive role of the solvent in modulating the electronic properties of the compounds studied. These results indicate that the most polar molecules, particularly compound 3, could exhibit more favorable behavior in physiological environments, both in terms of solubility and affinity for biological targets, thereby reinforcing their potential as bioactive candidates **[18]**.

3.4. Analysis of pharmacokinetic properties (ADME)

The evaluation of the physicochemical properties of compounds, such as molar mass, octanol/water partition coefficient (LogP), total polar surface area (TPSA), and the number of hydrogen bond donors and acceptors (HBD and HBA), is an essential step in estimating their pharmacological behavior and their potential for absorption, distribution, metabolism, and excretion (ADME) **[19]**. These parameters are summarized in Table 4 below:

Table 4 Physicochemical properties of the compounds studied

Codes	Masse molaire(g/mol)	LogP	TPSA ($Å^2$)	HBA	HBD
Compound 1	382.48	4.61	82.66	2	2
Compound 2	396.51	5.00	82.66	2	2
Compound 3	429.49	3.88	126.36	4	4
Compound 4	416.93	5.17	82.66	2	2
Compound 5	450.48	5.66	82.66	5	2

Thus, the molar masses of the five derivatives studied range from 382.48 g/mol for compound 1 to 450.48 g/mol for compound 5, reflecting the increasing complexity of the structures and the gradual introduction of bulky and polarizable substituents. This variation is likely to influence the diffusion and membrane permeability of the compounds **[20]**.

In terms of lipophilicity, LogP values range from 3.88 for compound 3 to 5.66 for compound 5. A LogP between 1 and 5 is generally considered favorable for oral absorption, while higher values may limit aqueous solubility but promote membrane permeability **[21]**. Notably, compound 3 has a lower LogP (3.88) despite its high molar mass (429.49 g/mol), suggesting a favorable balance between solubility and lipophilicity, likely related to the presence of additional polar groups.

Furthermore, the total polar surface area (TPSA) of compound 3 (126.36 $Å^2$) is significantly higher than that of the other derivatives (≈ 82.66 $Å^2$), indicating increased polarity and a higher potential for hydrogen bond formation with biological targets **[22]**. Concomitantly, the number of hydrogen bond donors and acceptors (HBD/HBA) for compound 3 is also higher (4/4), confirming its ability to establish stable interactions with polar biomolecules. Conversely, compounds 1, 2, and 4 have more moderate values (2/2), while compound 5, although highly lipophilic (LogP = 5.66), retains a limited number of HBDs (2) and a high number of HBAs (5), which may influence its solubility and biological interactions.

Thus, analysis of these physicochemical properties suggests that compound 3 combines high polarity, moderate lipophilicity, and significant hydrogen-bonding potential, which could explain the distinct behaviors observed in previous analyses (high dipole moment and low ΔEgap). In contrast, the more lipophilic compounds (4 and 5) exhibit lower polarity and may have limited aqueous solubility, although they retain promising potential for membrane permeability. These observations confirm that the combination of molecular weight, polarity, and lipophilicity is critical for the bioavailability and overall pharmacokinetic profile of these compounds, influencing both their solubility, their ability to diffuse through biological membranes, and their interactions with the molecular target.

4. Conclusion

The theoretical study of the five derivatives of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole has revealed structural and electronic characteristics that are decisive for their pharmacological potential. Firstly, all of the

compounds exhibit notable thermodynamic stability, which improves in aqueous phase due to solvation, illustrating the importance of the polar environment in modeling biological behavior. Second, analysis of the HOMO and LUMO orbitals, as well as the energy gap ΔEgap, revealed that compound 3 has a unique electronic profile, characterized by a low ΔEgap and increased reactivity, which promotes electronic interactions with biological targets. Third, the dipole moment and physicochemical properties, including molar mass, lipophilicity, and hydrogen bonding ability, confirmed that compound 3 exhibits the best combination of solubility, polarity, and binding potential. Finally, the evaluation of ADME parameters suggests that this compound may have a favorable pharmacokinetic profile. Overall, these results highlight the decisive role of molecular structure and solvation on stability, reactivity, and biological potential, providing a solid basis for the rational design of new antibacterial derivatives with optimized activity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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