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Research Article

Synthesis and theoretical study of the stability and reactivity of some 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives using the density functional theory (DFT) method

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Abstract

The stability and reactivity of the five (5) 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives were studied using density functional theory at the B3LYP/6-31+ G (d, p) level. Analysis of the molecular electrostatic potential (MEP) map and determination of the dual descriptor showed that nitrogen N13, sulfur S5 and carbons C19 and C21 are nucleophilic. They are therefore susceptible to electrophilic attack. The nitrogens N2, N3 and N14 are shared between electrophilic and nucleophilic sites. The study of the chemical reactivity of our compounds was carried out based on the analysis of molecular frontier orbitals (HOMO and LUMO), energy gap ($\Delta\varepsilon$), chemical hardness (η), electrophilicity (ω) and chemical softness (S). Compound 1 was found to be the most stable, the least reactive and electron-donating. This study also opens up a new way of synthesizing biologically active molecules by modulating the C19 carbon with inductive electroattractant groups.

Keywords: Benzimidazole, Imidazole, DFT, ESP, reactivity, stability.

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I. INTRODUCTION

Infectious diseases represent a major public health problem nowadays, due to the emergence and spread of new strains of bacteria [1] and the widespread emergence of drug resistance [2]. Faced with this problem, the development of new types of anti-infective drugs, particularly those with a new target and/or which are capable of overcoming drug resistance, is essential [3]. In this study, we are interested in 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives, which are heterocyclic compounds resulting from the juxtaposition of two bioactive entities (imidazole and benzimidazole) through a chemical link (methylthio). From five compounds studied, two showed biological activity on Staphyloccocus aureus and Enterococcus faecalis [4].

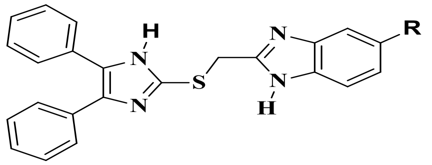
The aim of this study is to theoretically determine the stability, reactivity and nucleophilic/electrophilic attack sites using various quantum chemical methods, in order to optimize their inhibitory properties. All calculations were performed in the gas phase at the B3LYP/6-31+ G (d, p) level of theory. Reactivity and stability were established through the calculation of descriptors such as energy gap (**$\Delta\varepsilon$**), chemical hardness (**η**), electrophilicity (**ω**) and chemical softness (**S**). Nucleophilic/electrophilic attack sites were determined through analysis of the electrostatic potential map (ESP) and the dual descriptor.

II. MATERIALS AND METHODS

II.1 Materials

The compounds studied are presented in Table 1 below:

Table 1: Structures of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives



COMPOUNDS		R
1		H
2		CH_3
3		NO_2
4		Cl
5		CF_3

II.2 Theory level

Calculations were performed using Gaussian 09 software [5]. Density functional theory (DFT) [6] is the method used. Previous theoretical work on the calculation of molecular properties has shown that hybrid functions such as B3LYP and others, combined with an extended base of functions, lead to values in good agreement with experimental results [7]. The level of theory chosen for this study was B3LYP/6-31+G(d,p). For each 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivative, a molecular geometry optimization calculation was followed by a frequency calculation. Certain stability and reactivity parameters have been determined.

II.2.1 Reactivity descriptors

The electrostatic surface potential (ESP) corresponds to the interaction energy of a proton with the nuclei and electrons of a molecule. It is defined by equation (1) below.

$$V(r) = \sum_{A}^{\text{Nuclei}} \frac{Z_A}{|R_A - r|} - \int \frac{\rho(\mathrm{r'})\mathrm{dr'}}{|\mathrm{r'} - r|}$$

In this equation, Z_A is the charge of nucleus A, $R_A - r$ and $r' - r$ are the proton-nucleus and proton-electron distances respectively, and ρ(r') is the electron density. The electrostatic potential and its map are effective tools for analyzing and predicting molecular reactive behavior. Electrostatic potential surface analysis is based on colors and highlights areas likely to be nucleophilic or electrophilic attack sites. Potential increases in the following order: red < orange < yellow < green < cyan < blue [8,9]. In the electrostatic potential surface, areas with zero potential are represented by the color green, negative areas (red and yellow) are electrophilic attack sites, and positive areas (cyan and blue) are electrophilic attack sites.

II.2.1.2 Global molecular descriptors

Global descriptors are quantities independent of chemical space. They take the same value at any point in the system to which they refer. They correspond to the response of a global quantity to a global perturbation. As such, they can be used to describe the overall stability and reactivity of a molecule [10].

The first derivative of the chemical potential with respect to the electron number N leads to the hardness **η** and its inverse the chemical softness **S** [11,12,13].

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{V(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \frac{1}{S}$$

According to the theory of acids and bases developed by Pearson [14], these quantities can be expressed in terms of ionization potential (**IP**) and electron affinity (**EA**).

$$\eta = \frac{1}{S} = (\mathrm{IP} - \mathrm{EA})/2$$

The ionization potential (**IP**) and electron affinity (**EA**) are simply obtained in the Koopmans approximation [15], according to which:

$$\mathrm{IP} = -\,\varepsilon_{\mathrm{HOMO}} \text{ et } \mathrm{EA} = -\,\varepsilon_{\mathrm{LUMO}}$$

$\boldsymbol{\varepsilon_{\mathrm{HOMO}}}$ and $\boldsymbol{\varepsilon_{\mathrm{LUMO}}}$ are respectively the energies of the highest occupied orbital (HOMO) and the lowest vacant orbital (LUMO). It's the theory of frontier molecular orbitals [16]. The energy gap (**ΔƐ**) is an important index of stability. It serves as a measure of a molecule's excitability. The lower the energy range, the more the molecule can interact with the environment. A large HOMO-LUMO gap implies high stability for the molecule in the sense of low reactivity in chemical reactions, while a small gap implies high reactivity for the molecule.

$$\Delta\varepsilon = \varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}$$

II.2.1.3 Local and dual descriptors

In 2004, Morell and al. [17] proposed a new descriptor for chemical reactivity, called the "dual descriptor". It is defined as the difference between the Fukui functions ($f_k^+$and f_k^-) for nucleophilic and electrophilic attack respectively. The value of the dual descriptor is calculated according to the following relationship:

$$f_k^+ = q_k(N+1) - q_k(N) \quad and$$

$$f_k^- = q_k(N) - q_k(N-1)$$

$$\Delta f(r) = f_k^+ - f_k^-$$

This new index is called the "dual descriptor". It simultaneously detects electrophilic and nucleophilic regions in the molecule. For a particular region in a molecule, the type of favorable attack can be determined from the sign of the dual descriptor.

When Δf(r)>0, this indicates an electrophilic region, thus favorable to nucleophilic attack.

When Δf(r)<0, the region is nucleophilic, so favorable to electrophilic attack.

II.2.1.4 Hirshfeld populations

Hirshfeld charges are qualitatively compatible with general chemical concepts and can quantify the electrophilicity and nucleophilicity of molecular surfaces [18,19]. A general and natural choice is to share the charge density at each point between the different atoms in proportion to their free atom densities at the corresponding distances from the nuclei [20]. In this work, atomic charge values were obtained by analysis of the Hirshfeld population.

III. RESULTS AND DISCUSSION

A general numbering system has been adopted for the results analysis.

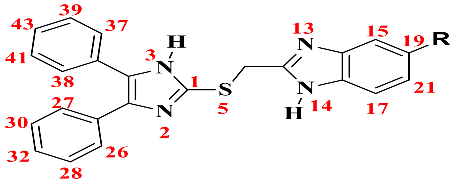


Figure 1: Numbering of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives

III.1 Energy stability and global reactivity

III.1.1 Energy stability

The stability parameters examined in this series of compounds the HOMO energy (ε_{HOMO}), the LUMO energy (ε_{LUMO}) and the frontier orbital energy gap ($\Delta\varepsilon$) expressed in eV.

The calculated values of said parameters are reported in Table 2 below.

Table 2: Energy descriptors for the compounds studied

COMPOUNDS	ε_{LUMO}	ε_{HOMO}	$\Delta\varepsilon$
1	2.62	-7.91	**10.53**
2	-1.49	-5.84	4.35
3	-2.37	-6.14	**3.77**
4	-1.58	-5.98	4.40
5	-1.62	-6.04	4.42

Analysis of the data in Table 2 shows that the energy gap ($\Delta\varepsilon$) ranges from 3.77 eV to 10.53 eV. Smaller the gap is, more the compound can transfer electrons from the HOMO to the LUMO level and more reactive it is. A large gap difference ($\Delta\varepsilon$) between HOMO and LUMO is synonymous with stability. With the largest energy gap (10.53 eV), compound 1 is the most stable. Compound 3 is the most reactive with the smallest energy gap (3.77 eV). A ranking from least stable (most reactive) to most stable (least reactive) gives us:

Compound 3 < Compound 2< Compound 4< Compound 5< Compound 1

III.1.2 Global reactivity

The reactivity parameters examined in this series of compounds are: hardness (**η**), electrophilicity (**ω**), expressed in (eV) and chemical softness (**S**) expressed in (eV)$^{-1}$. The calculated values of said parameters are reported in Table 3 below

.**Table 3**: Global descriptors of the chemical reactivity of the compounds studied.

COMPOUNDS	η	S	ω
1	**5.26**	**0.19**	**2.63**
2	2.18	0.46	1.09
3	**1.89**	**0.53**	**0.94**
4	2.20	0.45	1.10
5	2.21	0.45	1.10

Looking at Table 3, analysis of the data shows that electrophilicity values (ω) range from 0.94 eV to 2.63 eV. Compound 3 has the lowest electrophilicity value (ω = 0.94 eV) of all our compounds. Consequently, it is the compound that receives the fewest electrons, and therefore the most reactive. As for hardness (η), it ranges from 1.89 eV to 5.26 eV. The smaller the value, the more reactive the compound. Compound 3 has the lowest value (1.89 eV), making it the most reactive. Ranking in ascending order of stability according to hardness gives us:

Compound 3 < Compound 2 < Compound 4 < Compound 5 < Compound 1

The chemical softness values (**S**) reported in Table 3 range from 0.19 eV^{-1} to 0.53 eV^{-1}. The higher the value, the less stable (more reactive) the compound. They also give us the same order of increasing stability.

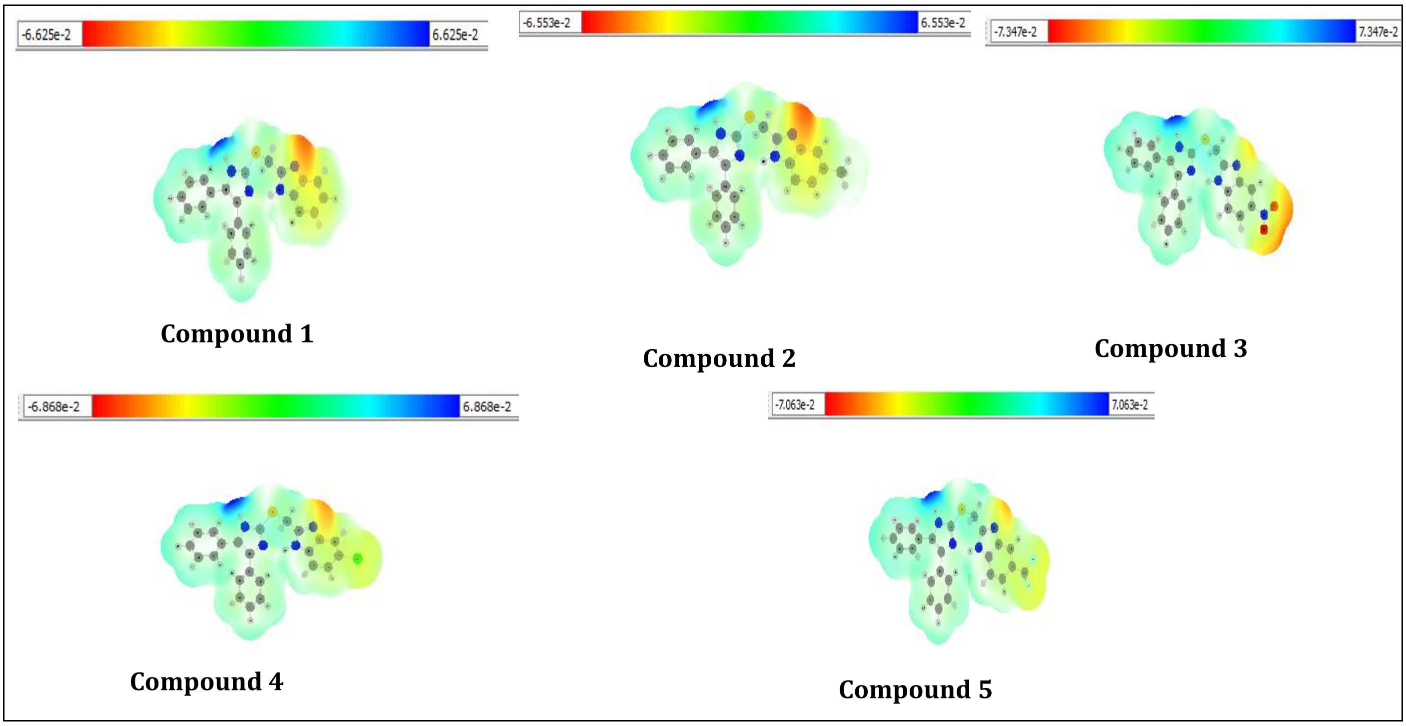
Compound 3 < Compound 2 < Compound 4 < Compound 5 < Compound 1

These three descriptors confirm that compound 3 is the most reactive.

III.2 Local reactivity

III.2.1 Electrostatic surface potential (ESP) map

In order to get a more general idea of the electrophilic and nucleophilic sites of a compound, an analysis of the electrostatic potential map is made from figure 2. Negative areas (colored red or yellow) are nucleophilic sites, and positive areas (colored cyan or blue) are electrophilic sites.



Compound 1

Compound 2

Compound 3

Compound 4

Compound 5

Figure 2: Electrostatic potential map of 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives

Analysis of the electrostatic potential maps of the different 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives shows us that nitrogen N13, carbons C15, C19 and C21 are nucleophilic sites, thus favorable to electrophilic attack for the compounds. Nitrogens N2, N3 and N14 are electrophilic sites, making them suitable for nucleophilic attack. Sulfur S5, on the other hand, is prone to electrophilic attack.

III.2.2 Dual descriptors

The values of the various dual descriptors for certain atoms are given in the following tables:

Table 4: Local reactivity descriptors for compound 1 using Hirschfeld charges at the Theory 6-31+G(d,p) level

ATOMES	q_k(N)	q_k(N+1)	q_k(N-1)	f_k^+	f_k^-	Δf (r)
1	2.9592	2.9450	2.9703	-0.0142	-0.0111	-0.0031
2	3.6024	3.5938	3.6106	-0.0086	-0.0083	**-0.0003**
3	3.5402	3.5307	3.5498	-0.0095	-0.0096	**0.0001**
5	8.0005	7.9469	8.0293	-0.0535	-0.0288	**-0.0247**
13	3.6204	3.6040	3.6301	-0.0164	-0.0097	**-0.0068**
14	3.5465	3.5444	3.5455	-0.0021	0.0010	**-0.0031**
15	3.0252	3.0098	3.0358	-0.0154	-0.0105	**-0.0049**
17	3.0321	3.0227	3.0367	-0.0094	-0.0046	**-0.0048**
19	3.0314	3.0184	3.0400	-0.0130	-0.0086	**-0.0045**
21	3.0290	3.0062	3.0385	-0.0227	-0.0095	**-0.0132**

Table 5: Local reactivity descriptors for compound 2 using Hirschfeld charges at the Theory 6-31+G(d,p) level

ATOMES	q_k(N)	q_k(N+1)	q_k(N-1)	f_k^+	f_k^-	Δf (r)
1	2.9593	2.9475	2.9731	-0.0118	-0.0138	0.0019
2	3.6023	3.5958	3.6110	-0.0065	-0.0088	**0.0023**
3	3.5402	3.5312	3.5529	-0.0089	-0.0127	**0.0038**
5	8.0012	7.9517	8.0315	-0.0495	-0.0304	**-0.0191**
13	3.6210	3.6082	3.6289	-0.0128	-0.0078	**-0.0050**
14	3.5468	3.5401	3.5447	-0.0067	0.0021	**-0.0088**
15	3.0282	3.0167	3.0353	-0.0116	-0.0071	**-0.0045**
17	3.0320	3.0225	3.0342	-0.0095	-0.0022	**-0.0073**
19	3.0051	2.9834	3.0108	-0.0217	-0.0057	**-0.0160**
21	3.0306	3.0131	3.0378	-0.0175	-0.0072	**-0.0103**

Table 6: Local reactivity descriptors for compound 3 using Hirschfeld charges at the Theory 6-31+G(d,p) level

ATOMES	q_k(N)	q_k(N+1)	q_k(N-1)	f_k^+	f_k^-	Δf (r)
1	2.9597	2.9413	2.9650	-0.0184	-0.0053	-0.0132
2	3.6011	3.5895	3.6030	-0.0116	-0.0018	**-0.0098**
3	3.5390	3.5284	3.5461	-0.0105	-0.0071	**-0.0034**
5	7.9973	7.9395	8.0169	-0.0578	-0.0196	**-0.0382**
13	3.6151	3.6036	3.6257	-0.0115	-0.0106	**-0.0009**
14	3.5433	3.5453	3.5487	0.0020	-0.0054	**0.0074**
15	3.0145	3.0057	3.0346	-0.0088	-0.0201	**0.0113**
17	3.0259	3.0226	3.0372	-0.0033	-0.0113	**0.0080**
19	2.9872	2.9808	2.9943	-0.0065	-0.0071	**0.0006**
21	3.0213	3.0098	3.0308	-0.0115	-0.0095	**-0.0020**

Table 7: Local reactivity descriptors for compound 4 using Hirschfeld charges at the Theory 6-31+G(d,p) level

ATOMES	q_k(N)	q_k(N+1)	q_k(N-1)	f_k^+	f_k^-	Δf (r)
1	2.9595	2.9462	2.9692	-0.0133	-0.0097	-0.0035
2	3.6018	3.5944	3.6092	-0.0074	-0.0074	**0.0000**
3	3.5396	3.5304	3.5484	-0.0093	-0.0087	**-0.0005**
5	7.9994	7.9498	8.0296	-0.0496	-0.0302	**-0.0195**
13	3.6190	3.6072	3.6299	-0.0119	-0.0108	**-0.0010**
14	3.5456	3.5398	3.5460	-0.0058	-0.0003	**-0.0055**
15	3.0248	3.0131	3.0377	-0.0118	-0.0128	**0.0011**
17	3.0280	3.0188	3.0363	-0.0093	-0.0083	**-0.0009**
19	2.9884	2.9718	2.9954	-0.0166	-0.0070	**-0.0096**
21	3.0285	3.0155	3.0397	-0.0129	-0.0113	**-0.0017**

Table 8: Local reactivity descriptors for compound 5 using Hirschfeld charges at the Theory 6-31+G(d,p) level

ATOMES	q_k(N)	q_k(N+1)	q_k(N-1)	f_k^+	f_k^-	Δf (r)
1	2.9596	2.9426	2.9713	-0.0169	-0.0117	-0.0052
2	3.6017	3.5910	3.6086	-0.0106	-0.0070	**-0.0036**
3	3.5394	3.5292	3.5513	-0.0102	-0.0118	**0.0017**
5	7.9986	7.9418	8.0332	-0.0568	-0.0346	**-0.0222**
13	3.6173	3.6043	3.6282	-0.0131	-0.0109	**-0.0022**
14	3.5445	3.5450	3.5448	0.0005	-0.0003	**0.0008**
15	3.0199	3.0094	3.0341	-0.0105	-0.0142	**0.0037**
17	3.0272	3.0223	3.0359	-0.0048	-0.0087	**0.0039**
19	3.0205	3.0117	3.0292	-0.0088	-0.0087	**-0.0001**
21	3.0242	3.0087	3.0341	-0.0154	-0.0100	**-0.0055**

The dual descriptor gives us precise information on the character of the different atoms. Analysis of the different values of the dual descriptor reported in tables (4,5,6,7 and 8) shows that nitrogen N13, sulfur S5, carbons C19 and C21 are nucleophilic sites, thus favorable to electrophilic attack. A modulation on carbon C19 induced by the electroattractant group (-NO_2) confers a positive value on the dual descriptor for compound 3 (see table 6). On the other hand, modulations generated by electroattractant groups (-Cl and -CF_3) give a negative value to the dual descriptor for compounds 4 (see table 7) and 5 (see table 8). The -NO_2 group is electroattractant by mesomeric effect and the -Cl and -CF_3 groups electroattractant by inductive effect. Considering those compounds 1, 2 and 3 showed no activity, modulation on C19 or C21 by inductively attracting groups could lead to the molecule series becoming biologically active.

Dual descriptor values for N2 nitrogen are positive for compounds 2 and 4, thus prone to nucleophilic attack, and negative for compounds 1, 3 and 5, thus prone to electrophilic attack. Nitrogen N3 has positive dual descriptor values for compounds 1, 2 and 5, i.e. prone to nucleophilic attack, and negative values for compounds 3 and 4. Nitrogen N14 has negative dual descriptor values for compounds 1, 2 and 4. It is therefore favorable to electrophilic attack. However, it is favorable to nucleophilic attack in compounds 3 and 5, as it has positive dual descriptor values.

IV. CONCLUSION

Theoretical studies carried out on the five (5) 2-[(benzimidazolyl)methylthio]-4,5-diphenylimidazole derivatives synthesized showed that compound 1 is the one with the greatest number of stability characteristics and the one that yields electrons with difficulty, thanks to the use of global reactivity descriptors. The electrostatic potential map (ESP) and the dual descriptor were used to precisely determine the attack sites. The latter showed that the N13 nitrogen atom, the S5 sulfur and the C19 and C21 carbons are nucleophilic sites. Nitrogens N2, N3 and N14 are shared between electrophilic and nucleophilic sites. The C19 carbon plays a decisive role in the biological activity of the molecules through modulation by electron-withdrawing groups via inductive effects. This study opens the way to the synthesis of new biologically active molecules.

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