Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Research Article

Studies of the Chemical Reactivity of a Series of Benzimidazolyl-Chalcone by Quantum Chemical Approaches

Mamadou Guy-Richard KONÉ[1,2,3]*, Affoué Lucie BÉDÉ [2,5], Bafétigué OUATTARA[4], Georges Stéphane DEMBÉLÉ[1,2], Panaghiotis KARAMANIS[3] and Nahossé ZIAO[1,2]

[1] *Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, Université NANGUI ABROGOUA, Abidjan, Côte-d'Ivoire*
[2] *Groupe Ivoirien de Recherches en Modélisation des Maladies (GIR2M), Université NANGUI ABROGOUA, Abidjan, Côte-d'Ivoire*
[3] *E2S UPPA, CNRS, IPREM, Université de Pau et des Pays de l'Adour, 64053 Pau, France*
[4] *Laboratoire de Physique Fondamentale et Appliquée, UFR SFA, Université NANGUI ABROGOUA, Abidjan, Côte-d'Ivoire*
[5] Laboratoire de Constitution et Réaction de la Matière (LCRM), Université Félix Houphouët-Boigny, Côte d'Ivoire

Article Info:

Article History:

Received 26 July 2023
Reviewed 02 Sep 2023
Accepted 10 Sep 2023
Published 15 Oct 2023

Cite this article as:

Koné MGR, Bédé AL, Ouattara B, Dembélé GS, Karamanis P, Ziao N, Studies of the Chemical Reactivity of a Series of Benzimidazolyl-Chalcone by Quantum Chemical Approaches, Journal of Drug Delivery and Therapeutics. 2023; 13(10):46-53

DOI: http://dx.doi.org/10.22270/jddt.v13i10.5970

*Address for Correspondence:

Mamadou Guy-Richard KONE, Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, Université NANGUI ABROGOUA, Abidjan, Côte-d'Ivoire

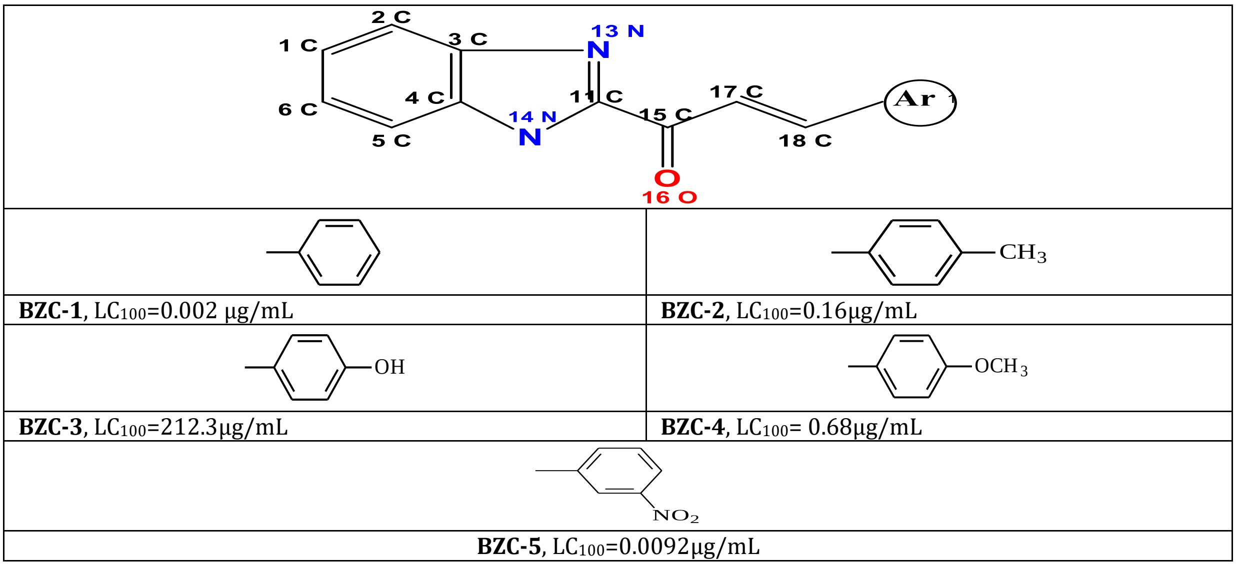
Abstract

This theoretical chemical reactivity study was conducted using the Density Functional Theory (DFT) method at the B3LYP/6-311G(d,p) level of calculation. It involved a series of five (05) Benzimidazolyl-Chalcone (BZC) and allowed the prediction of the chemical reactivity of these compounds. The DFT global chemical reactivity descriptors (HOMO and LUMO energies, chemical hardness, energy, electronic chemical potential and electrophilicity) were examined to predict the relative stability and reactivity of BZCs. Thus BZC-4 which has a boundary orbital energy gap of ΔE_{gap} = 3.650 eV is the most polarisable, most reactive, good nucleophile.and it is a soft molecule. The values of the global reactivity descriptors confirmed the high chemical reactivity of BZC-4. Local reactivity indices as well as dual descriptors were calculated to indicate the likely sites of electrophilic and nucleophilic attack of the different compounds studied. The analysis of the local indices and the dual descriptors revealed that the nitrogen heteroatom N13 is the preferential site of electrophilic attack and the carbon atom C1 should be the most reactive site with respect to a nucleophilic attack. the Hierarchical Ascending Classification analysis allowed us to group all five (5) compounds studied into three categories. The most active which are BZC-1 and BZC-5, the moderately active BZC-2, and the compounds BZC-3 and BZC-4, the least active. Moreover, this classification is consistent with the value of the Larvicide concentrations (LC_{100} (µg/mL)).

Keywords : Benzimidazolyl-Chalcone (BZC), Global descriptors, Local descriptors, Dual descriptors

1. INTRODUCTION

Nematodes are a large group of worms found in all living environments. They live as parasites of plants, animals and humans. They are the cause of most parasitic diseases in humans (elephantiasis, filariasis) [1, 2], gastrointestinal infections and loss of productivity in animals [3, 4]. Anthelmintics have been developed with benzimidazoles, imidazothiazoles, tetrahydropyrimidines, to control these parasites. However, for more than two decades, the permanent appearance of new, resistant races of nematodes has been of increasing concern to the agricultural, medical and health communities. By studying these molecules, we want to contribute to the preservation of African livestock, which implies a contribution to the fight against food insecurity. As we know, the economy of most African countries is essentially agro-pastoral. One of the worms that poses a threat to ruminant livestock is the helminth known as Haemonchus contortus. This parasite, for example, causes anaemia, oedema and death in infected sheep and goats, mainly during the summer in hot and humid climates [5-7]. In such a context the further development of new anthelmintic molecules is a vital necessity. To this end, work on chalcones and the benzimidazole heterocycle as potential pharmacochemical precursors of new anthelmintics has been initiated [8]. Benzimidazolyl-Chalcone derivatives are of considerable pharmacological interest due to their therapeutic properties in many diseases. Several studies have shown that benzimidazolyl derivatives possess antihistaminic [9], antifungal [10], antiallergic [11], antibacterial [12-14] and antiviral [15] properties. Studies on heterocyclic compounds have long been an area of interest in medicinal chemistry. A number of heterocyclic derivatives containing heteroatoms (nitrogens, oxygens) serve as unique and versatile scaffolds for experimental drug design [16]. Therapeutic properties are linked to the conformation of the molecules and the interactions they can establish with each other. The knowledge of molecular conformation and interactions requires the determination of physicochemical descriptors through theoretical chemistry. With the development of computational techniques and computational chemistry, quantum chemistry provides insight into the electronic structures of molecules and strongly propels the development of traditionally experimental chemistry [17]. Currently, the density functional theory (DFT) method has been accepted as a popular approach for the calculation of structural features and energies of molecules by the scientific community [18] and for the efficiency and accuracy in evaluating a number of molecular properties [19]. Parr and Yang followed the idea that well-known chemical properties such as electronegativity, chemical potentials and affinities could be accurately described and calculated by manipulating the electron density as the fundamental quantity [20, 21]. Furthermore, based on the work of Fukui and his theory of molecular boundary orbitals (MBO) [22], the same authors generalised the concept and proposed the Fukui function as a tool for describing local reactivity in molecules [23, 24]. The present study focuses on five (05) benzimidazolyl-chalcone derivatives presented in Figure 1.



BZC-1, LC_{100}=0.002 µg/mL

BZC-2, LC_{100}=0.16µg/mL

BZC-3, LC_{100}=212.3µg/mL

BZC-4, LC_{100}= 0.68µg/mL

BZC-5, LC_{100}=0.0092µg/mL

Figure 1: Molecular structures and numbering of the atoms in the benzimidazolyl-chalcone ring of the studied compounds

These benzimidazolyl-chalcone or 1-(1H-benzimidazol-2-yl)-3-aryl-2-propen-1-one derivatives are chalcone hybrid compounds associated with the benzimidazole ring and the arylpropenone moiety. Ouattara et *al.* [8] synthesised these compounds by a Michael reaction and tested them in vitro against Haemonchus contortus larvae [6] to evaluate their nematocidal activities. The anthelmintic activities obtained were compared to those of Fenbendazole and Ivermectin, the dewormers used in the study as reference drugs. The study of the different larvicidal concentrations (LC_{100}) allowed the identification of the compounds shown in Figure 1, which have nematocidal activities ranging from 0.002 to 212.3 µg/mL. The aim of this work is to determine theoretically, the preferred sites of electrophilic and nucleophilic attack on the aromatic carbon atoms and heteroatoms contained in the benzimidazolyl ring, by different quantum chemical methods.

2. MATERIALS AND METHODS

2.1. Level of computational theory

The theoretical study of chemical reactivity was carried out on the basis of three theoretical approaches. The first one concerns the analysis of molecular electrostatic potential surfaces. The second approach is related to molecular boundary orbitals. The last approach is concerned with local indices of reactivity and dual descriptors. The geometries of the molecules were optimised at the DFT level with the B3LYP functional [25, 26] in the 6-311 G(d,p) basis using the Gaussian 09 software [27]. This hybrid functional gives better energies and is in agreement with high-level ab initio methods [28, 29]. As for the split-valence and triple-dzeta basis (6-311G (d, p)), it is sufficiently large and the consideration of polarisation functions are important for the explanation of the presence of free doublets of heteroatoms. The geometries are kept constant for both cationic and anionic systems. The overall reactivity indices were obtained from the conceptual DFT model [20]. The Hierarchical Ascending Classification (HAC) analysis was conducted using XLSTAT software [30]. As for the chemical reactivity space indices, they were determined using the electronic populations calculated with the Mulliken population analysis (MPA) [31].

2.2. Reactivity Descriptors

2.2.1. Global Descriptors

To predict chemical reactivity, some theoretical descriptors related to the conceptual DFT have been determined. In particular, the energy of the Lowest Vacant Molecular Orbital (LUMO), the energy of the Highest Occupied Molecular Orbital (HOMO), the electronegativity (χ), the global softness (σ) and the global electrophilicity index (ω). These descriptors are all determined from the optimised molecules. It should be noted that, the descriptors related to the boundary molecular orbitals have been calculated in a very simple way within the Koopmans approximation [32]. The LUMO energy characterises the sensitivity of the molecule to nucleophilic attack, and the HOMO energy characterises the susceptibility of a molecule to electrophilic attack. The electronegativity (χ) is the parameter that expresses the ability of a molecule not to let its electrons escape. The overall softness (σ) expresses the resistance of a system to the change in its electron number. The overall electrophilicity index characterises the electrophilic power of the molecule. These different parameters are calculated from equations (1):

$$I = -E_{HOMO} \qquad A = -E_{LUMO}$$

$$\chi = -\mu = -1/2\,(E_{LUMO} + E_{HOMO})$$

$$\eta = (E_{LUMO} - E_{HOMO})/2 \qquad (1)$$

$$\omega = \frac{\chi^2}{2\eta} \qquad \sigma = 1/\eta$$

2.2.2. Local and Dual Descriptors

In order to differentiate the reactive behaviour of atoms forming a molecule, different indices have been used. These are precisely the local indices and dual descriptors of reactivity. The local descriptors of reactivity, in this case the Fukui function [33], are used to differentiate the reactive behaviour of the atoms forming a molecule. (f_k^+, f_k^-), local softness (σ_k^+, σ_k^-), the local electrophilic power (ω_k^+, ω_k^-), and dual descriptors have been proposed to explain the selectivity of electrophilic and nucleophilic attacks of the molecule. It should be recalled that the Fukui function f_k^+expresses the reactivity when the molecule is attacked by a nucleophilic reagent, while the Fukui f_k^- The Fukui function teaches about the electrophilic attack on a given site. The highest Fukui function value is assigned to the most active site. Condensed indices $\sigma_k^+$and ω_k^+ express the capacity of a site to receive electron density by nucleophilic attack, on the other hand, the σ_k^- and ω_k^- express the ability of a site to give up electron density by electrophilic attack. The dual descriptor is a good tool for predicting reactivity and identifying the problem of regioselectivity. Indeed, a positive dual descriptor corresponds to a site likely to receive electron density, and therefore more electrophilic. Conversely, a negative dual descriptor corresponds to a site capable of giving up electron density, and therefore more nucleophilic. A site with a value of the dual descriptor close to zero corresponds to a site whose capacity to receive and that to give up electron density are equivalent. The different values of the local descriptors are calculated from equations (2) [34-37]:

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

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

$$\sigma_k^+ = \sigma f_k^+$$

$$\sigma_k^- = \sigma f_k^- \qquad (2)$$

$$\omega_k^+ = \omega f_k^+$$

$$\omega_k^- = \omega f_k^-$$

Où : $q_k(N)$: electronic population of atom k in the neutral molecule.

$q_k(N+1)$: electronic population of atom k in the anionic molecule.

$q_k(N-1)$: electronic population of atom k in the cationic molecule.

The values of the dual descriptors [38-40] are obtained from equations (3):

$$\Delta f = f_k^+ - f_k^-$$

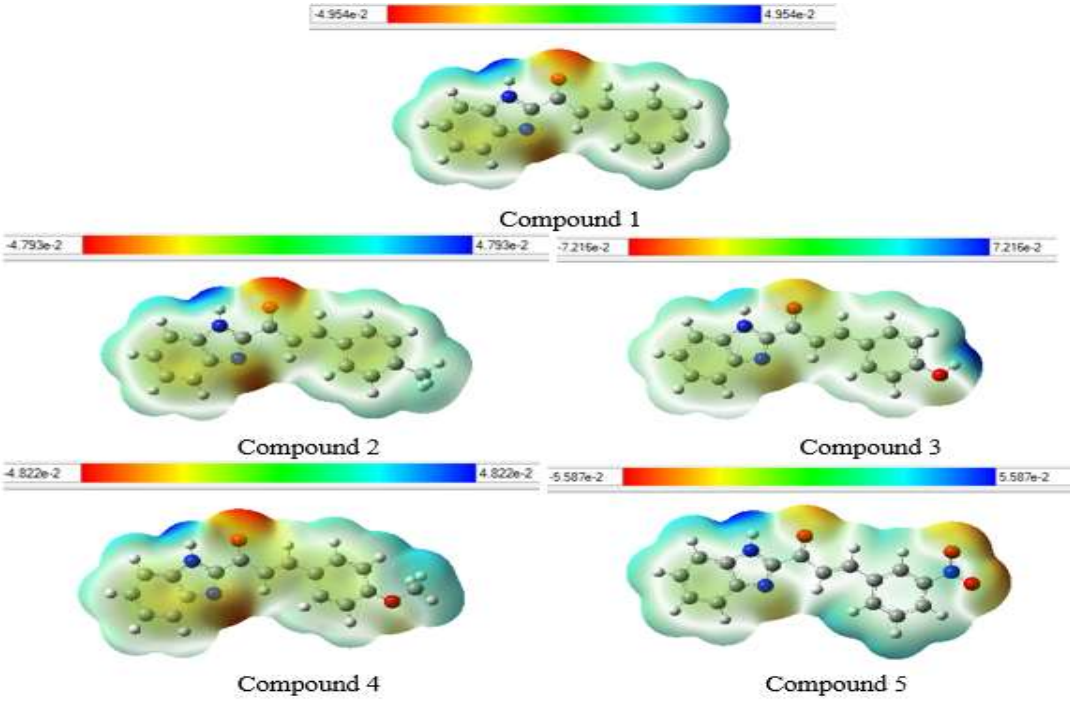
$$\Delta\sigma = \sigma_k^+ - \sigma_k^- \qquad (3)$$

$$\Delta\omega = \omega_k^+ - \omega_k^-$$

3. RESULTS AND DISCUSSION

3.1. Molecular Electrostatic Potentials (MEP)

The different values of the electrostatic surface potential are represented by different colours. The potential increases in the order red < orange < yellow < green < blue. The colour code of these maps ranges from - 7,216e-2 a.u. (bright red) to 7,216e-e-2 a.u. (dark blue) in compounds BZC-1 to BZC-5, where red indicates the most negative potentials and blue the most positive potentials [41] passing successively through orange, yellow and green [42]. The surfaces of the electrostatic potentials of the studied molecules were represented after optimisation at the B3LYP/ 6-311 G(d,p) level. They are presented in Figure 2.



Compound 1

Compound 2

Compound 3

Compound 4

Compound 5

Figure 2: Benzimidazolyl-Chalcone molecular electrostatic potential surfaces of the compounds studied

These maps indicate on the one hand, that the heteroatoms (O16, N14,N13) are the sites of electrophilic or nucleophilic attack. The N13 nitrogen and oxygen heteroatoms have a red neighbourhood of negative potential with a high electronic concentration around the oxygen (O16) reflecting an electrophilic attack site of the benzimidazolyl-chalcone ring. As for the N14 nitrogen atom, it presents a strongly blue coloured zone of positive potential translating a nucleophilic attack zone of the benzimidazolyl-chalcone nucleus. On the other hand, the carbon atoms, with the exception of those involved in the benzimidazolyl fusion (- C4=C3-), are more favourable to a nucleophilic attack given their approach zone which is light blue with a positive potential.

3.2. Analysis of Boundary Molecular Orbitals

The highest occupied (HOMO) and lowest vacant (LUMO) frontier orbitals play a fundamental role in the qualitative interpretation of chemical reactivity [43]. The highest occupied molecular orbital (HOMO), which can be considered as the outer orbital containing electrons, tends to give these electrons as an electron donor. On the other hand, the lowest vacant molecular orbital (LUMO) is seen as the lowest orbital containing free places to accept electrons [44]. Therefore, while the energy of the HOMO is directly related to the ionisation potential, that of the LUMO is directly related to the electron affinity. The energy difference between HOMO and LUMO, called the energy gap, is an important stability factor for structures [45]. The HOMO-LUMO energy gap helps to characterise the chemical reactivity and kinetic stability of the molecule [46]. A molecule with a high energy gap (ΔE) is less polarisable and is generally associated with low chemical reactivity and high kinetic stability [47]. Figure 3 below represents the HOMO and LUMO boundary molecular orbital diagrams of the Benzimidazolyl-Chalcone derivatives of the compounds studied using the B3LYP/6-311 G(d,p) method.

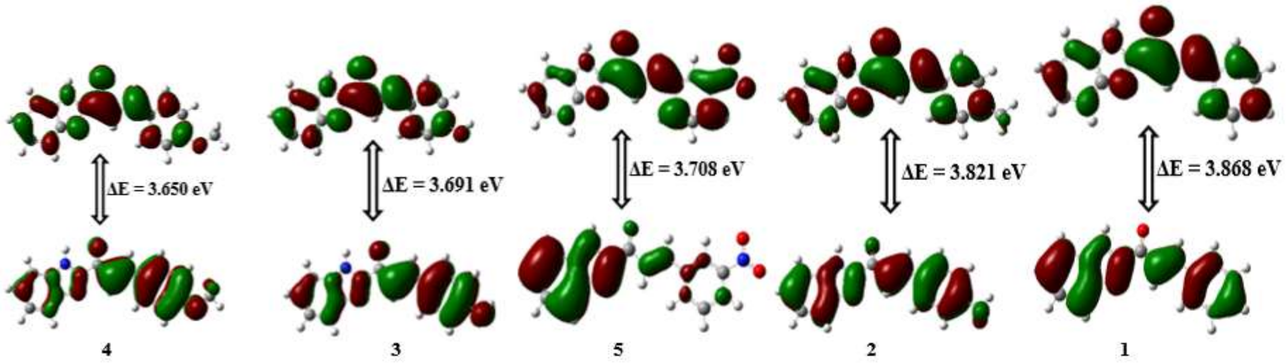


Figure 3: highest occupied and lowest vacant molecular orbitals of compounds 1-5.

The energy parameters of the boundary orbitals are listed in Table 1.

Table 1: Energy descriptors of the studied compounds**.**

compounds	E_{HOMO} (eV)	E_{LUMO}(eV)	ΔE_{gap}(eV)	I (eV)	A (eV)
BZC-1	-6.455	-2.587	**3.868**	6.455	2.587
BZC-2	-6.332	-2.512	3.821	6.332	2.512
BZC-3	-6.129	-2.438	3.691	6.129	2.438
BZC-4	-6.049	-2.400	**3.650**	6.049	2.400
BZC-5	-6.734	-3.026	3.708	6.734	3.026

These results show that BZC-4 has the smallest energy gap (ΔE_{gap} = 3.650 eV) and therefore is the most polarisable, has the highest chemical reactivity and the lowest kinetic stability of all the molecules studied. In contrast, BZC-1 has the highest energy gap value of 3.868 eV. BZC-1 is therefore the least polarisable, with low chemical reactivity and high kinetic stability out of all the five (05) molecules studied.

3.3. Analysis Reactivity Descriptors

3.3.1. Analysis Global Reactivity Descriptors

The study of the global reactivity of the molecules is based on the calculation of global indices deduced from the electronic properties. The global reactivity indices of the studied BZCs(1-5) were calculated from equations (1) and reported in Table 2.

Table 2 : Global chemical reactivity descriptors for BZCs from 1-5.

compounds	μ (eV)	χ (eV)	η (eV)	σ (eV)	ω (eV)
BZC-1	-4.521	4.521	1.934	0.517	5.284
BZC-2	-4.422	4.422	1.910	0.523	5.118
BZC-3	-4.284	4.284	1.846	0.542	4.971
BZC-4	-4.225	4.225	**1.825**	0.548	**4.890**
BZC-5	-4.880	4.880	1.854	0.539	6.424

The chemical reactivity varies with the structure of the molecules. The chemical hardness value of the compound BZC-4 is the lowest (η = 1.825eV) among all molecules. Thus, BZC-4 is found to be more reactive than all the compounds. Furthermore, the electrophilicity (ω) gives an idea of the stabilisation energy when the system is saturated with electrons from the external environment. This reactivity information shows that a molecule is a good nucleophile for low values of the electrophilicity (ω), while it is a good electrophile for high values of the electrophilicity (ω). Our results indicate that BZC-4 has the lowest value (ω = 4.890 eV), this indicates that BZC-4 is a good nucleophile. However, BZC-4 has the smallest energy gap, so it is more polarizable and is associated with high chemical reactivity, low kinetic stability and is also considered a soft molecule. And finally, a good nucleophile.

3.3.2. Analysis Local Descriptors and Dual Descriptors of Reactivity

The local indices and dual descriptors of reactivity were also determined for each molecule according to equations (2). The sites concerned are the carbon atoms linked to a hydrogen atom and the two nitrogen heteroatoms N13 and N14 in the different Benzimidazolyl rings of each molecule. These different indices and descriptors of reactivity are grouped in Tables 3 to 7.

Table 3: BZC-1 reactivity descriptors calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f-	f+	σ-	σ+	η-	η+	ω-	ω+	Δf	Δσ	Δω
C2	0.047	0.029	0.025	0.015	0.092	0.057	0.251	0.155	-0.018	-0.009	-0.095
C1	**0.040**	**0.022**	**0.021**	**0.011**	**0.078**	**0.042**	**0.212**	**0.115**	**-0.019**	**-0.010**	**-0.098**
C6	0.020	0.012	0.010	0.006	0.039	0.023	0.106	0.062	-0.008	-0.004	-0.045
C5	0.049	0.038	0.025	0.020	0.095	0.074	0.260	0.203	-0.011	-0.006	-0.057
N13	**0.025**	**0.028**	**0.013**	**0.015**	**0.048**	**0.054**	**0.132**	**0.149**	**0.003**	**0.002**	**0.017**
N14	0.016	0.008	0.008	0.004	0.031	0.016	0.084	0.043	-0.008	-0.004	-0.041

The values of the local and dual descriptors of BZC-1 calculated at the B3LYP/ 6 311G(d,p) level, show that the C1 carbon atom with the value Δω = -0.098, is the preferred site for electrophilic attack. According to this same level of calculation, a nucleophilic attack will preferentially take place on the N_{13} heteroatom with the value Δω = 0.017.

Table 4: BZC-2 reactivity descriptors calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f-	f+	σ-	σ+	η-	η+	ω-	ω+	Δf	Δσ	Δω
C2	0.040	0.029	0.021	0.015	0.077	0.056	0.206	0.150	-0.011	-0.006	-0.056
C1	**0.035**	**0.022**	**0.018**	**0.011**	**0.067**	**0.041**	**0.179**	**0.111**	**-0.013**	**-0.007**	**-0.068**
C6	0.018	0.011	0.009	0.006	0.035	0.022	0.093	0.059	-0.007	-0.003	-0.034
C5	0.042	0.038	0.022	0.020	0.080	0.073	0.214	0.196	-0.004	-0.002	-0.018
N13	**0.018**	**0.028**	**0.009**	**0.015**	**0.034**	**0.054**	**0.090**	**0.145**	**0.011**	**0.006**	**0.055**
N14	0.012	0.008	0.006	0.004	0.023	0.016	0.063	0.043	-0.004	-0.002	-0.020

The results in Table 4 predict that the C1 site is the most favoured for electrophilic attack. With regard to nucleophilic attack, it occurs preferentially at the N_{13}.

Table 5: Reactivity descriptors of BZC-3 calculated using Mulliken population analysis (MPA).

Sites	Local descriptors								Dual descriptors		
	f-	f+	σ-	σ+	η-	η+	ω-	ω+	Δf	Δσ	Δω
C2	0.035	0.030	0.019	0.016	0.064	0.056	0.173	0.151	-0.004	-0.002	-0.022
C1	**0.031**	**0.022**	**0.017**	**0.012**	**0.057**	**0.041**	**0.153**	**0.110**	**-0.008**	**-0.005**	**-0.042**
C6	0.017	0.011	0.009	0.006	0.031	0.021	0.083	0.057	-0.005	-0.003	-0.026
C5	0.036	0.040	0.020	0.022	0.067	0.073	0.180	0.198	0.004	0.002	0.018
N13	**0.012**	**0.030**	**0.006**	**0.016**	**0.022**	**0.056**	**0.059**	**0.150**	**0.018**	**0.010**	**0.091**
N14	0.009	0.009	0.005	0.005	0.017	0.017	0.047	0.045	0.000	0.000	-0.001

Table 5 shows the results of the calculations of local indices and dual reactivity descriptors, using the MPA population analysis at the B3LYP/6-311G (d,p) design level. This indicates that electrophilic attack is likely to occur at the C1 carbon atom, since the dual descriptors take on negative values for the latter site. However, the N13 site is the most favourable for nucleophilic attacks.

Table 6: Reactivity descriptors of BZC-4 calculated using Mulliken population analysis (MPA).

Sites	**Local descriptors**								**Dual descriptors**		
	f-	**f+**	**σ-**	**σ+**	**η-**	**η+**	**ω-**	**ω+**	**Δf**	**Δσ**	**Δω**
C2	0.031	0.030	0.017	0.016	0.056	0.055	0.151	0.147	-0.001	0.000	-0.004
C1	**0.027**	**0.022**	**0.015**	**0.012**	**0.050**	**0.040**	**0.134**	**0.107**	**-0.005**	**-0.003**	**-0.027**
C6	0.015	0.011	0.008	0.006	0.028	0.021	0.075	0.055	-0.004	-0.002	-0.020
C5	0.032	0.039	0.018	0.022	0.058	0.072	0.157	0.193	0.007	0.004	0.036
N13	**0.008**	**0.030**	**0.004**	**0.017**	**0.015**	**0.055**	**0.039**	**0.148**	**0.022**	**0.012**	**0.108**
N14	0.008	0.009	0.004	0.005	0.014	0.017	0.037	0.044	0.002	0.001	0.008

As shown in the previous tables, the local indices as well as the dual descriptors derived from the MPA analysis predict a maximum value for the C_1 atom favouring it for electrophilic attack. Furthermore, based on the values of the different indices, we can conclude that nucleophilic attack occurs primarily on the N_{13} nitrogen.

Table 7: Reactivity descriptors of BZC-5 calculated using Mulliken population analysis (MPA).

Sites	**Local descriptors**								**Dual descriptors**		
	f-	**f+**	**σ-**	**σ+**	**η-**	**η+**	**ω-**	**ω+**	**Δf**	**Δσ**	**Δω**
C2	**0.058**	**0.022**	**0.031**	**0.012**	**0.107**	**0.042**	**0.372**	**0.144**	**-0.035**	**-0.019**	**-0.228**
C1	0.048	0.018	0.026	0.009	0.089	0.033	0.307	0.113	-0.030	-0.016	-0.194
C6	0.023	0.011	0.012	0.006	0.042	0.020	0.146	0.070	-0.012	-0.006	-0.076
C5	0.059	0.028	0.032	0.015	0.110	0.053	0.382	0.183	-0.031	-0.017	-0.199
N13	0.037	0.016	0.020	0.008	0.069	0.029	0.239	0.101	-0.021	-0.012	-0.138
N14	0.022	0.005	0.012	0.003	0.041	0.009	0.144	0.032	-0.017	-0.009	-0.112

From these results, we note that the local and dual reactivity descriptors calculated using the B3LYP method with the 6-311G(d,p) base suggest that carbon C2 is the most favourable site for electrophilic attack for compound BZC-5. For compounds BZC-1, BZC-2, BZC-3 and BZC-4, carbon C1 is the preferred site for electrophilic attack. The local reactivity indices (f_k^+, σ_k^+ et ω_k^+) and the dual descriptors ($\Delta f_k, \Delta\sigma_k$ et $\Delta\omega_k$), provide the highest value for the C1 site. Thus the latter should be the most reactive site towards nucleophilic attack. Furthermore, through these same local reactivity indices and the dual descriptors, the N13 nitrogen heteroatom is the preferred site for nucleophilic attack. It should be noted that in a previous study by Koné et *al.* **48** based on hydrogen bonding that the N_{13} nitrogen heteroatom in an sp2 hybridization state is the site of reactivity for Benzimidazolyl-Chalcones.

3.4. Hierarchical Cluster Analysis (HCA)

Figure 4 shows the Hierarchical Ascending Classification (HAC) analysis of the studied molecules. The horizontal lines represent the compounds. The vertical lines represent the similarity values between pairs of compounds, a compound and a group of compounds and among groups of compounds.

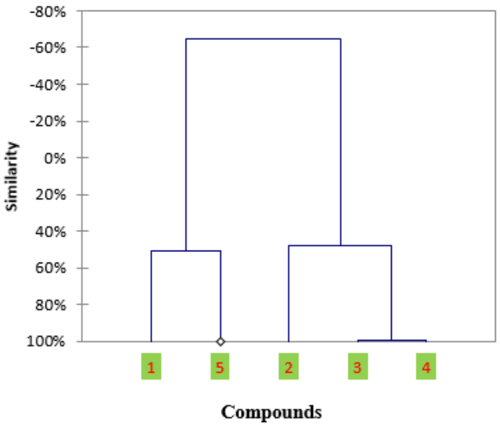


Figure 4: Dendrogram obtained for the BZCs studied

We can note from this analysis that the compounds studied were grouped into three categories: the most active which are BZC-1 and BZC-5, BZC-2, moderately active and the less active compounds BZC-3 and BZC-4. It should be noted that this classification is in accordance with the value of the larvicide concentrations (LC_{100} (µg/mL)) (Figure 1).

4. CONCLUSION

In conclusion, based on the B3LYP/6-311G (d, p) functional density method, global and local descriptors were used to study the reactivity of different nucleophilic, electrophilic and radical sites and their influence on the molecular interaction in a qualitative and quantitative way. The descriptors obtained could also provide more information and contribute to a better understanding of the electronic structure of benzimidazolyl chalcones. The electrostatic potential maps showed that the areas of high electron density are located around the heteroatoms. The carbon atoms, with the exception of those involved in the benzimidazolyl fusion (-C4=C3-), are more favourable to nucleophilic attack. The compound BZC-4 is more polarisable and is associated with high chemical reactivity and is also called a soft molecule. Furthermore, the local reactivity descriptors of BZCs obtained by the Mulliken population analysis method, indicate that the C1 atom is the nucleophilic attack site and the N13 nitrogen heteroatom is the electrophilic attack site. Therefore, the C1 atom can be used as a precursor for the synthesis of new heterocyclic compounds such as dimers. Finally, we hope that these results will be useful in the search for experimental and theoretical evidence for new BZCs through molecular bonding.

ACKNOWLEDGMENTS

We would like to thank Professor OUATTARA Mahama for making this series of Benzimidazolyl-Chalcone Molecules available to us.

CONFLICTS OF INTEREST

We declare there is no conflict of interest for the publication of this paper

REFERENCES

[1]-J. Horton, Global anthelmintic chemotherapy programs: learning from history, Tendances Parasitol.; 9 (9): pp. 403-409, (2003). https://doi.org/10.1016/S1471-4922(03)00171-5 PMid:12957517

[2]-P. J. Hotez, P. J. Brindley, C. H. King, E. J. Pearce, and J. M. Bethony, Helminth infections: the great neglected tropical diseases, J Clin Invest.; 118 (4): pp. 1311-1321; (2008). https://doi.org/10.1172/JCI34261 PMid:18382743 PMCid:PMC2276811

[3]-S. Geerts, B. Gryseels, Drug resistance in human helminths: current situation and lessons from livestock, Clin Microbiol Rev, 13 (3): pp. 207-222; (2000). https://doi.org/10.1128/CMR.13.2.207 PMid:10755998 PMCid:PMC100151

[4]-P. J. Waller. (a), The future of anthelmintics in sustainable parasite control programs for livestock, Helminthologia; 40: pp. 97-102; (2003).

[5]-Burke, Joan, scientifique animal de recherches. Gestion du ver de Barber chez les moutons et les chèvres dans le sud des États-Unis USDA, ARS, Centre de recherche des petites fermes Dale Bumpers, Booneville, Small Farms Research Update, février 2005, publié par Dale Bumpers Centre de recherche sur les petites fermes, SPA, ARS, USDA

[6]- B. D. Perry; T. F. Randolph; J. J. McDermott, K. R. Sones, P. K. Thornton, Investing in animal health research to alleviate poverty, International Livestock Research Institute, Nairobi, Kenya, pp:148, (2002).

[7]- Haemonchus, Ostertagia, et Trichostrongylus spp, Le manuel vétérinaire Merck. 2006 Récupéré le -07/01/ 2007

[8]- M. Ouattara, D. Sissouma, M. W. Koné, H. E. Menan, S. A. Touré and L. Ouattara, Synthesis and anthelmintic activity of some hybrid Benzimidazolyl-Chalcone derivatives, Tropical Journal of Pharmaceutical Research; 10 (6): pp. 767-775, (2011). https://doi.org/10.4314/tjpr.v10i6.10

[9]-E. Souness; D. Aldous; C. Sargent, Immunosuppressive and anti-inflammatory effects of. cyclic AMP phosphodiesterase (PDE) type 4 inhibitors, Immunopharmacology, 47(2-3): pp. 127-162, (2004). https://doi.org/10.1016/S0162-3109(00)00185-5 PMid:10878287

[10]-O. Sanja, K. Podunavac, D.C. Dragoljub, Lipophilicity and antifungal activity of some 2-Substituted benzimidazole derivatives, Chemical industry and Chemical Engineering Quarterly. 17(1): pp. 9-15, (2011). https://doi.org/10.2298/CICEQ100329044P

[11]-G. Ayhan-Kilcigil; C. Kus; B. Can-Eke; M. Iscan, Synthesis and antioxidant properties of some, Arch. Pharm. Res., 27: pp. 156-163, (2004). https://doi.org/10.1007/BF02980099 PMid:15022715

[12]-A. Carta, M. Loriga, S. Zanetti, L. A. Sechi, Quinoxalin-2-ones: Part 5. Synthesis and antimicrobial evaluation of 3-alkyl-, 3-halomethyl- and 3-carboxyethylquinoxaline-2-ones variously substituted on the benzo-moiety, Farmaco, 58(12): pp. 1251-1255, (2003). https://doi.org/10.1016/S0014-827X(03)00198-8 PMid:14630235

[13]-V. T. Andriole, The Quinolones. Third Edition, Elsevier Academic Press. pp. 517, (2000). https://doi.org/10.1016/B978-012059517-4/50017-9

[14]-S. Emami, A. Shafiee, A. Foroumadi, Quinolones: Recent Structural and Clinical Developments, Iranian Journal of Pharmaceutical Research. 3: pp. 123-136, (2005).

[15]-A. Mertens; B. Muller-Beckmann; W. Kampe; J. P Holck; W. Von der Saal, Synthesis of benzimidazol-2-thiones from dimedone, J. Med. Chem., 30: pp. 1279-1287, (1987). https://doi.org/10.1021/jm00391a004 PMid:3612681

[16]- N. B Patel, F. M Shaikh, New 4-thiazolidinones of nicotinic acid with 2-amino-6-methylbenzothiazole and their biological activity, Sci Pharm., 78:753-765, (2010). https://doi.org/10.3797/scipharm.1009-15 PMid:21179315 PMCid:PMC3007608

[17]-J. B. Foresman, A. Frisch, Exploring Chemistry with Electronic Structure Methods, Gaussian Inc., Pittsburgh, USA, (1996).

[18]-M. Kurt, T. R. Sertbakan, M. Ozduran, Spectrochim, An experimental and theoretical study of molecular structure and vibrational spectra of 3-and 4-pyridineboronic acid molecules by density functional theory calculations. Acta Part A: Mol. Biomol. Spectrosc, 70(3):pp. 664-673 (2008). https://doi.org/10.1016/j.saa.2007.08.019 PMid:17933583

[19]-C. Ravikumar, I. H. Joe, V. S. Jayakumar, Charge transfer interactions and nonlinear optical properties of push- pull chromophore benzaldehyde phenylhydrazone: A vibrational approach, Chemical Physics Letters 460 (4-6), pp. 552-558, (2008) https://doi.org/10.1016/j.cplett.2008.06.047

[20]-R. G. Parr, W. Yang, Density-functional theory of the electronic structure of molecules, Annu. Rev. Phys. Chem. 46, pp. 701-728, (1995). https://doi.org/10.1146/annurev.pc.46.100195.003413 PMid:24341393

[21]-R. G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules; Oxford University Press: Oxford, UK. (1989)

[22]-K Fukui; Y Yonezawa; H Shingu, A molecular orbital theory of reactivity in aromatic hydrocarbons, J. Chem, Phys, 20, pp. 722-725, (1952) https://doi.org/10.1063/1.1700523

[23]-R. G. Parr, W. Yang, Density functional approach to the frontier-electron theory of chemical reactivity, J. Am. Chem. Soc., 106, pp. 4049-4050, (1984) https://doi.org/10.1021/ja00326a036

[24]-P.W. Ayers; M Levy, Density Functional Approach to the. Frontier-Electron Theory of Chemical Reactivity. Theor. Chem. Acc, 103 (3-4), pp. 353-360, (2000). https://doi.org/10.1007/s002149900093

[25]-W.Yang Lee and R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, Phys. Rev. B, 37(2): pp. 785-789, (1988) https://doi.org/10.1103/PhysRevB.37.785 PMid:9944570

[26]-A. D. Becke, Density-functional thermochemistry. III. The role of exact exchange, J. Chem. Phys. 98(7): pp.5648-5652 (1993) https://doi.org/10.1063/1.464913

[27] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, Gaussian, Inc., Wallingford CT, (2009).

[28] J. Kapp, M. Remko, P. v. R. Schleyer, H2XO and (CH3)2XO Compounds (X= C, Si, Ge, Sn, Pb): Double bonds vs carbene-like structures can the metal compounds exist at all?, Journal of the American Chemical Society, 118(24), pp. 5745-5751, (1996). https://doi.org/10.1021/ja953846p

[29]-B. G. Johnson, P. M. Gill, J. A. Pople, The performance of a family of density functional methods, The Journal of Chemical Physics , 98(7), pp. 5612-5626., 1993. https://doi.org/10.1063/1.464906

[30] XLSTAT Version 2014.5.03 Copyright Addinsoft 1995-2014 (2014) XLSTAT and Addinsoft are Registered Trademarks of Addinsoft. https://www.xlstat.com

[31]-R. S. Mulliken, Criteria for the construction of good self-consistent-field molecular orbital wave functions, and the significance of LCAO-MO population analysis, J. Chem. Phys. 36(12),pp. 3428-3439 (1962) https://doi.org/10.1063/1.1732476

[32]-T. Koopmans, Über die Zuordnung von Wellenfunktiomen und Eigenwerten zu den einzelnen Elektronen eines Atoms, Physica, 1: pp. 104-113, (1934) https://doi.org/10.1016/S0031-8914(34)90011-2

[33]-W. Yang, R. G. Parr, R. Pucci, Electron density, Kohn-Sham frontier orbitals, and Fukui functions. J. Chem. Phys. 81(6), pp. 2862-2863, (1984). https://doi.org/10.1063/1.447964

[34]-W.Yang, W. Mortier, The use of global and local molecular parameters for the analysis of the gas-phase basicity of amines. J. Am. Chem. Soc. 108 (19), pp 5708-5711, (1986) https://doi.org/10.1021/ja00279a008 PMid:22175316

[35]-W. Yang, R. G. Parr, Chemistry. Hardness, softness, and the Fukui function in the electronic theory of metals and catalysis, Proc. Natl. Acad. Sci. USA, 82, pp. 6723-6726, (1985)https://doi.org/10.1073/pnas.82.20.6723 PMid:3863123 PMCid:PMC390758

[36]-P. K. Chattaraj, B. Maiti et U. Sarkar, Philicity: A unified treatment of chemical reactivity and selectivity, J. Phys. Chem., 107, pp. 4973-4975, (2003). https://doi.org/10.1021/jp034707u

[37]-P. Fuentealba, R. Contreras. In ReViews in Modern Quantum Chemistry: A celebration of the contributions of R. G. Parr; K. D Sen., Ed.; World Scientific: River Edge, NJ, 2002; p 1013. L. R Domingo; M. J. Aurell, P. Perez, R. Contreras, J. Phys. Chem., 106 (29), pp 6871-6875, (2002) https://doi.org/10.1142/9789812775702_0034

[38]-J. Padmanabhan, R. Parthasarathi, M. Elango, V. Subramanian, B. S. Krishnamoorthy, S. Gutierrez-Oliva, A. Toro-Labbe, D. R. Roy et P. K. Chattaraj, Multiphilic Descriptor for Chemical Reactivity and Selectivity , J. Phys. Chem., 111, pp. 9130-9138, (2007). https://doi.org/10.1021/jp0718909 PMid:17715901

[39]-C. Morell, A. Grand, A. Toro-Labbé, New dual descriptor for chemical reactivity, J. Phys. Chem., 109 (1), pp 205-212, (2005). https://doi.org/10.1021/jp046577a PMid:16839107

[40]-C. Morell, A. Grand, A. Toro-Labbé, Theoretical support for using the Delta f(r). descriptor. Chem. Phys. Lett., in Press, 425, 342-346 (2006). https://doi.org/10.1016/j.cplett.2006.05.003

[41]-H. M. Abdel-Baset, G. E. Hanan, Mohamed M El-Okr, Medhat A Ibrahim/J Nanomater Mol Nanotechnol, 4:2, (2015).

[42]-L. X-Hong, C. H-Ling, Z. R-Zhou, Z. X-Zhou, Molecular and Biomolecular Spectroscopy Spectrochimica Acta Part A.137, pp. 321-327, (2015). https://doi.org/10.1016/j.saa.2014.08.036 PMid:25228040

[43]-R. B.Woodward, R. Hoffmann, The conserVation of Orbital Symmetry Chemie : Weinhein ; Germany, (1970). https://doi.org/10.1016/B978-1-4832-3290-4.50006-4

[44]-G. Gece, The use of quantum chemical methods in corrosion inhibitor studies. Corros Sci. 50(11): pp. 2981-2992, (2008). https://doi.org/10.1016/j.corsci.2008.08.043

[45]-D. F. V. Lewis, C. Ioannides, D.V Parke. Interaction of a series of nitriles with the alcohol-inducible isoform of P450: Computer analysis of structure-activity relationships. Xenobiotica. 24(5): pp. 401-408, (1994). https://doi.org/10.3109/00498259409043243 PMid:8079499

[46]-Y. Uesugi, M. Mizuno, A. Shimojima, H. Takahashi, Transient resonance raman and ab-initio mo calculation studies of the structures and vibrational assignments of the t1 state and the anion radical of coumarin and its isotopically substituted analogues. J. Phys. Chem. 101(3): pp. 268-274, (1997). https://doi.org/10.1021/jp9626881

[47]-L. Sinha, O. Prasad, V. Narayan, S. Shukla, R. Raman, FT-IR spectroscopic analysis and first-order hyperpolarisability of 3-benzoyl-5-chlorouracil by first principles. Molecular Simulation. 37, pp. 153-163, (2011). https://doi.org/10.1080/08927022.2010.533273

[48] M. G-R. Koné, S. T. Affi, N. Ziao, K. Bamba and E. F. Assanvo, Hydrogen bonding sites in Benzimidazolyl-chalcones molecules: An ab initio and DFT investigation, Journal of Chemical and Pharmaceutical Research, 7(12): pp. 805-812, (2015)