

# A Density Functional Theory Study of Electronic Populations, Reactivity and Stability Descriptors of Four Hydroxamic Acids: Comparative Analysis

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## Abstract

Many studies have been conducted on the structure of hydroxamic acids as anticancer compounds. The metal chelating property of hydroxamic acids has been used extensively to develop inhibitors for zinc containing enzymes and proteins such as histone deacetylase (HDAC). In this work, we aim to determine the atom that is most willing to form a bond with zinc. On the basis of quantum chemistry, calculations have been made and the reactivity of the hydroxamic acids has been studied. Density functional theory (DFT) can be used to calculate a precise electronic structure, HOMO and LUMO energies, orbital energy levels, global hardness, chemical potential, electrophilic systems, and also Hirshfeld's charges of the compounds. These parameters were determined to predict the relative stability and reactivity of the hydroxamic acids. The work was conducted at computational level B3LYP/6-311G(d,p). The compound 2 with the lowest energy gap (3.933 eV) is the most polarizable of these compounds. The analysis of the local indices of reactivity as well as the dual descriptors revealed that oxygen O<sub>35</sub> is the most favorable site with respect to an electrophilic attack. The study of orbitals locates oxygen O<sub>35</sub> in the HOMO and O<sub>35</sub> would be the most favored for a binding with Zn<sup>2+</sup>. The results of this study can be used for a study of zinc complex with hydroxamic acid.

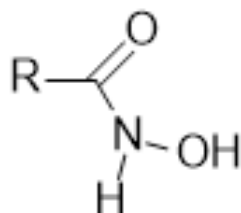
## Keywords

Conceptual DFT; Fukui Function; Hirshfeld Charge Analysis; Hydroxamic Acids

## 1. Introduction

Hydroxamic acids are chemical compounds with multiple biological activities. They contain the oxime (-N-OH) and carbonyl (C=O) groups and have the following structure:

Figure 1: General Structure of Hydroxamic Acids



Indeed, they are effective and selective inhibitors of a large number of enzymes, such as urease [1], matrix metalloproteinases [2], histones deacetylases [3], etc. The detailed role of hydroxamic acid derivatives as enzyme inhibitors has been well described by Muri et al. [4]. They

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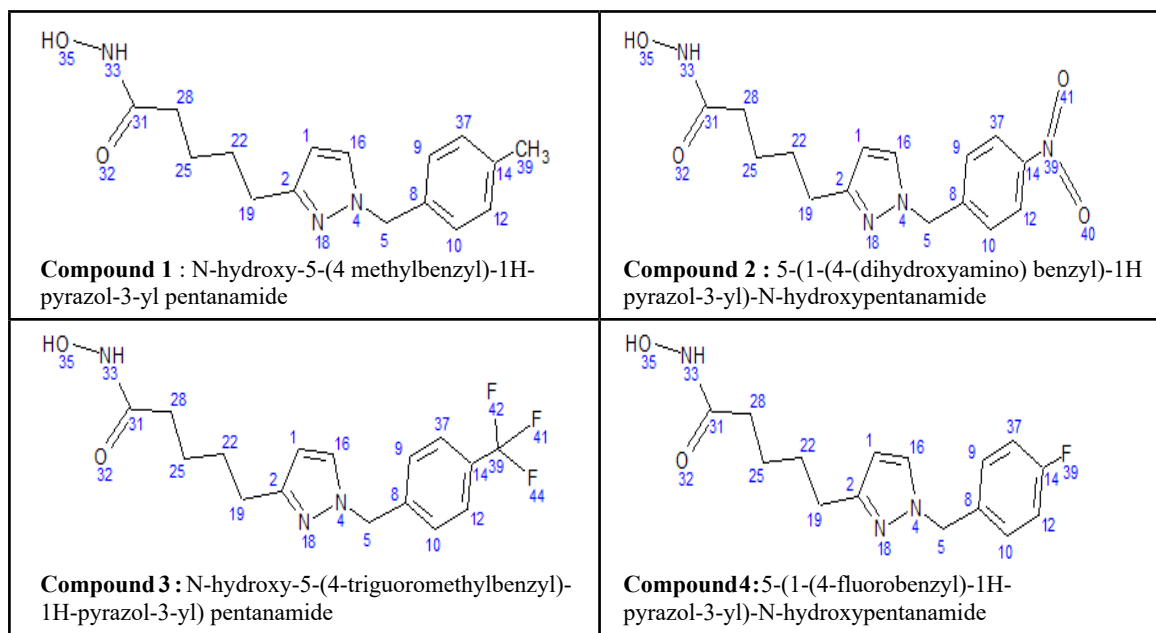
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have been developed as drugs against all these diseases that can arise by overactivation of these enzymes. In addition to acting as enzyme inhibitors, hydroxamic acids have also been described as acting against cancer [5], malaria, tuberculosis and fungi [6], HIV [7], the disease Alzheimer's and cardiovascular disorders [8]. All these biological activities of hydroxamic acids are due to their core structure, which allows them to form multiple hydrogen bonds with the enzyme. However, a good knowledge of their structures is very important because most applications of hydroxamic acids come from their chelating capacity. For this, the correct understanding of chelating atoms is essential. Theoretical methods can help in this direction, to provide information on the electronic population around each atom constituting the molecule.

Thus, we focused on the stability and reactivity of four hydroxamic acid compounds. The density functional theory (DFT) method is a popular approach for the calculation of the structural characteristics and energies of molecules [9] and for the efficiency and accuracy of the evaluation of a number of molecular properties [10]. The understanding of chemical reactivity and site selectivity of the molecular systems has been effectively handled by the conceptual density functional theory (DFT). 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 [11]. Moreover, based on Fukui's work and his theory of frontier molecular orbitals (FMO) [12],

the same authors generalized the concept and proposed Fukui's function as a tool for describing local reactivity in molecules [13]. In this work, the goal is to determine the most favorable atom for an electrophilic attack during a chemical reaction. By implementing quantum chemistry methods, we determined Fukui indices using Hirshfeld's population analysis (HPA). According literature, this method provides good information on electron populations compared to the Mulliken analysis. It is interesting to note that the accuracy of these results depends on the choice of atomic bases [14]. Indeed, the use of the extended basis sets 6-31+G(d), 6-31+G(d,p) and 6-311G(d,p) allow, in certain cases, to establish conclusive results concerning the powers of electrophilic and nucleophilic attacks. It is interesting to note that the exact precision of these results depends on the choice of atomic bases. A number of experimental and theoretical studies to elucidate the structures and properties of hydroxamic acids have appeared in the literature in recent years. In this paper, a theoretical study was conducted to determine the atom responsible for chelation of the ion  $Zn^{2+}$ . This study was conducted on four (4) compounds from the hydroxamic acid family shown in Figure 1. These molecules were synthesized by Yao et al. [5]. This author has observed that these compounds have anti-cancer activities in vitro against several cancer cell lines. The study of their binding effect in the active site of histone deacetylases HDAC containing the  $Zn^{2+}$  ion is the next step to propose new and more effective hydroxamic acid molecules.

**Figure 2:** Numbered Molecular Structures of Hydroxamic Acids Compounds 1- 4



## 2. Material and Methods

### 2.1. Hirshfeld Population Analysis

The calculation of Hirshfeld's atomic charge plays an important role in the study of molecular systems in quantum chemistry. For the quantitative description of a molecular charge distribution, the molecule is dissected into well-defined atomic fragments. 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 of the nuclei [15]. In this work, the atomic charge values were obtained by the Hirshfeld population analysis. The geometry of the molecules was optimized by the DFT calculation method with the B3LYP functional [16] in the 6-311G basis (d, p) using the Gaussian 09 [17]. This Hybrid functional gives better energies and is in line with high-level ab initio methods [18]. The geometries are conserved for cationic and anionic systems at computational level B3LYP/6-311G (d,p) to which a calculation of energy has been made.

### 2.2. Frontier Molecular Orbitals Theory

The frontier molecular orbital play a fundamental role in the qualitative interpretation of chemical reactivity [19]. The highest occupied molecular orbital (HOMO), which is considered to be the outer electron-containing orbital, tends to give these electrons as an electron donor. On the other hand, the lowest vacant molecular orbital (LUMO) is perceived as the lowest orbital containing free places to accept electrons. While the energy of the HOMO is directly related to the ionization potential, that of the LUMO is directly related to the electronic affinity. The difference in energy between the HOMO and the LUMO, called the energy gap, is an important stability factor for structures. The HOMO-LUMO energy gap helps characterize the chemical reactivity and kinetic stability of the molecule [19]. A molecule with a high energy gap ( $\Delta E$ ) is less polarizable and is generally associated with low chemical reactivity and high kinetic stability [20].

### 2.3. Reactivity Descriptors

#### 2.3.1. Global Descriptors

Some theoretical descriptors related to conceptual DFT have been determined to predict chemical reactivity. These are ionization potential (I), electron affinity (A), the electronegativity ( $\chi$ ), global Softness (s), global hardness ( $\eta$ ) and global electrophilicity ( $\omega$ ) [21]. These descriptors are all determined from the optimized molecules. It should be noted that the descriptors related

to the molecular frontier orbitals have been calculated as part of the Koopmans approximation [22]. The LUMO energy which characterizes the sensitivity of the molecule to a nucleophilic attack, and as for the HOMO energy, it characterizes the susceptibility of a molecule to an electrophilic attack. Electronegativity ( $\chi$ ) is the parameter that reflects the ability of a molecule not to let its electrons escape. Global softness (s) expresses the resistance of a system to the change in its number of electrons. The overall electrophilicity index characterizes the electrophilic power of the molecule. These different parameters are calculated from equations (1):

$$\begin{aligned} I &= -E_{HOMO} \\ A &= -E_{LUMO} \\ \chi &= -\mu = -1/2(E_{LUMO} + E_{HOMO}) \\ \eta &= (E_{LUMO} - E_{HOMO})/2 \quad (1) \\ \omega &= \frac{\chi^2}{2\eta} \\ s &= 1/\eta \end{aligned}$$

The chemical potential ( $\mu$ ) is defined as the escaping tendency of electron from equilibrium while ( $\chi$ ) describes the ability of a molecule to attract electrons towards itself in a covalent bond. With regard to the global hardness, it measures the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction. Parr and et al. introduced the concept of Electrophilicity as a global reactivity index similar to the chemical hardness and chemical potential.

#### 2.3.2. Local and Dual Descriptors

Fukui indices of a molecule inform about the local reactivity in a molecule. The atom with the largest Fukui index is more reactive than the other constituent atoms of the molecule [23]. These indices represent the qualitative description of the reactivity of the atoms in the molecule. Fukui's function successfully predicts the relative reactivity for most chemical systems. The determination of the Fukui indices for the selectivity of electrophilic and nucleophilic atoms in the hydroxamic acid compounds has been made. Ayers and Parr [24] explained that molecules tend to react where Fukui's function is greatest when attacked by soft reagents and in places where Fukui's function is smaller when attacked by hard reagents. Using

the Hirshfeld atomic charges of the ground state optimized compounds, the Fukui function ( $f_k^+$ ,  $f_k^-$ ), the local softness ( $s_k^+ = s_k^-$ ) and the local electrophilia indices ( $\omega_k^+$ ,  $\omega_k^-$ ) [15, 12] have been determined. The functions of Fukui are calculated using equation (2):

$$f_k^+ = q_k(N+1) - q_k(N) \quad (2)$$

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

$f_k^+$ : for nucleophilic attack

$f_k^-$ : for electrophilic attack

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

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

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

Local softness and electrophilicity indices are calculated using (3)

$$s_k^+ = s_k^-$$

$$(s_k^+ = s_k^-) \quad (3)$$

$$\omega_k^+ = \omega_k^-$$

$$\omega_k^- = \omega_k^+$$

The values of the dual descriptors [25] are obtained from the equations (4)

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

$$\Delta s = s_k^+ - s_k^- \quad (4)$$

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

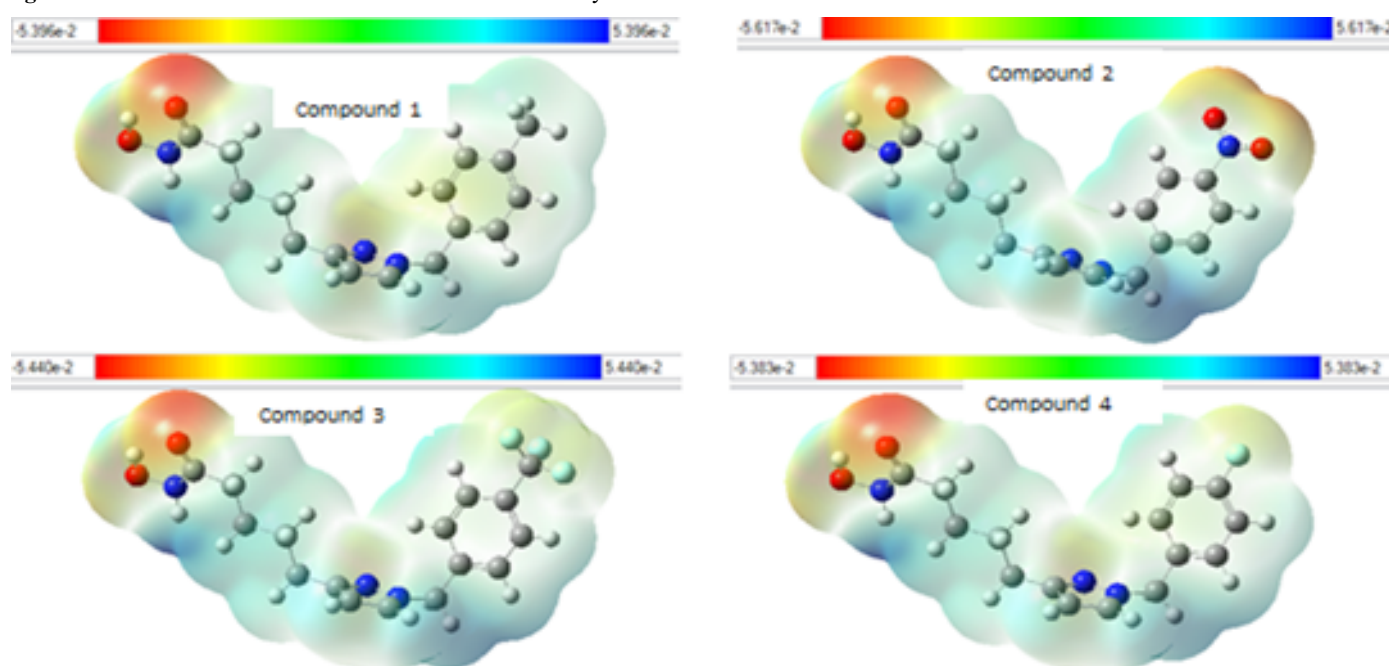
## 3. Results and Discussion

### 3.1. Molecular Electrostatic Potentials

The different areas of the electrostatic surface potential are represented by colors ranging from red to blue. The potential increases in order red < orange < yellow < green < blue, where red indicates the most negative potentials and blue the most positive potentials [26] passing successively through orange, yellow and green. The surfaces of the electrostatic potentials of the studied molecules were represented after optimization at the B3LYP / 6-311G (d, p) level. They are presented in Figure 3 obtained from Gaussian 09 [17].

These maps indicate that the oxygen atoms (O<sub>35</sub> and O<sub>32</sub>) would be sites of electrophilic attack by the presence of the red neighborhood of negative potential around the hydroxamic acid function. With regard to nucleophilic attack, carbon atoms are the most available in view of their approach environment which is blue.

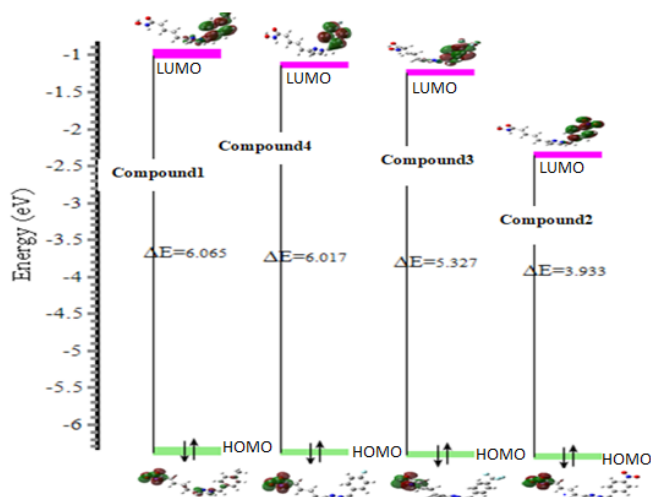
**Figure 3:** Surfaces of Molecular Electrostatic Potentials of Hydroxamic Acids



### 3.2. Analysis of Frontier Molecular Orbital

below shows the HOMO and LUMO boundary molecular orbital patterns of the hydroxamic acids obtained using the B3LYP/6-311G(d,p) method.

**Figure 4:** Highest and Lowest Occupied Molecular Orbital of Compounds 1-4



The analysis of the frontier orbital indicates that the HOMO covering the hydroxamic acid function in which the O<sub>35</sub> and O<sub>32</sub> oxygen are, while the LUMO covers most of the carbon atoms. This study of frontier orbital both confirms the analysis done with molecular electrostatic potential surfaces. The energy parameters obtained from

**Table 1:** Energy Parameters of the Compounds Studied

| Compounds | E <sub>HOMO</sub> (eV) | E <sub>LUMO</sub> (eV) | I (eV) | A (eV) |
|-----------|------------------------|------------------------|--------|--------|
| 1         | -6.569                 | -0.504                 | 6.569  | 0.504  |
| 2         | -6.657                 | -2.725                 | 6.657  | 2.725  |
| 3         | -6.632                 | -1.305                 | 6.632  | 1.305  |
| 4         | -6.603                 | -0.586                 | 6.603  | 0.586  |

**Table 2:** Global Descriptors of Chemical Reactivity of Hydroxamic Acids 1-4

| Compounds | χ (eV) | μ (eV) | η (eV) | ω (eV) | s (eV <sup>-1</sup> ) |
|-----------|--------|--------|--------|--------|-----------------------|
| 1         | 3.537  | -3.537 | 3.032  | 2.062  | 0.33                  |
| 2         | 4.691  | -4.691 | 1.966  | 5.595  | 0.509                 |
| 3         | 3.969  | -3.969 | 2.664  | 2.957  | 0.375                 |
| 4         | 3.594  | -3.594 | 3.008  | 2.147  | 0.332                 |

the energies of the frontier orbital are grouped in Table 1.

These results show that Compound 2 has the smallest energy gap ( $\Delta E_{\text{gap}} = 3.933$  eV), so it is the most polarizable, has the highest chemical reactivity and the lowest kinetic stability with respect to all studied molecules. In contrast, compound 1 has the largest value of the energy gap of 6.065 eV. The molecule 1 is therefore the least polarizable, with low chemical reactivity and high kinetic stability on four (04) molecules studied.

### 3.3 Reactivity Descriptors

#### 3.3.1 Global Reactivity Descriptors

The study of the global reactivity of molecules is based on the calculation of global indices deduced from electronic properties. The overall indices of the reactivity of the hydroxamic acids studied were calculated from Equations (1) and recorded in Table 2.

The value of the overall hardness of compound 2 ( $\eta = 1.966$  eV) is the lowest of all molecules. Thus, it appears that the compound 2 is more reactive than all the compounds studied. Also, we note that compound 2 has a significantly higher electronegativity value ( $\chi = 4.691$  eV) than other compounds; it is the best acceptor of electrons. In addition, the value of the electrophilic index of compound 2 ( $\omega = 5.595$  eV) indicates that it is the most electrophilic.

#### 3.3.2 Local and Dual Reactivity Descriptors

Local indices and dual descriptors of reactivity were also determined for each molecule according to equations (2), (3) and (4). All the atoms of compounds are concerned in this study except the hydrogen atoms. These different local indices and descriptors of reactivity are grouped in Tables 3 to 6.

The values of the local descriptors and dual descriptors of compound 1 calculated at B3LYP/6-311G (d, p) show that the oxygen atom O<sub>35</sub> is the preferred site of electrophilic attack. According to this same level of calculation, a nucleophilic attack will preferably take place on the C<sub>39</sub> atom having a value in the Table 3.

The results in Table 4 predict that the O<sub>35</sub> oxygen atom is most favored for electrophilic attacks. As regards

the nucleophilic attack, it occurs preferentially on oxygen O<sub>40</sub>.

In the Table 5, the O<sub>35</sub> oxygen atom is most favored for electrophilic attack. As regards the nucleophilic attack, it occurs preferentially on C<sub>37</sub> carbon.

Table 6 predicts that the O<sub>35</sub> oxygen atom is most favored against electrophilic attacks. As regards the nucleophilic attack, it occurs preferentially on C<sub>37</sub> carbon.

The analysis of these results noted in these tables, oxygen O<sub>35</sub> appears to be the preferred electrophilic attack site in this family of compounds. As regards the sites of nucleophilic attacks in this same family of compounds, we retain the carbon atoms C<sub>37</sub>, C<sub>39</sub> and oxygen O<sub>40</sub>.

**Table 3:** Compound 1 Reactivity Descriptors Calculated Using Hirshfeld Population Analysis (HPA)

| sites | Local descriptors |                |                |                |                |                |                |                | Dual descriptors |        |        |
|-------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|------------------|--------|--------|
|       | f                 | f <sup>+</sup> | s <sup>-</sup> | s <sup>+</sup> | η <sup>-</sup> | η <sup>+</sup> | ω <sup>-</sup> | ω <sup>+</sup> | Δf               | Δs     | Δω     |
| C1    | 0.070             | 0.041          | 0.023          | 0.014          | 0.211          | 0.125          | 0.144          | 0.085          | -0.028           | -0.009 | -0.058 |
| C2    | 0.050             | 0.022          | 0.017          | 0.007          | 0.152          | 0.067          | 0.104          | 0.045          | -0.028           | -0.009 | -0.058 |
| N4    | 0.041             | 0.004          | 0.014          | 0.001          | 0.125          | 0.012          | 0.085          | 0.008          | -0.037           | -0.012 | -0.077 |
| C5    | 0.048             | 0.079          | 0.016          | 0.026          | 0.144          | 0.239          | 0.098          | 0.162          | 0.031            | 0.010  | 0.064  |
| C8    | 0.038             | 0.063          | 0.013          | 0.021          | 0.116          | 0.190          | 0.079          | 0.129          | 0.024            | 0.008  | 0.050  |
| C9    | 0.045             | 0.071          | 0.015          | 0.023          | 0.138          | 0.216          | 0.094          | 0.147          | 0.026            | 0.008  | 0.053  |
| C10   | 0.035             | 0.071          | 0.012          | 0.023          | 0.106          | 0.216          | 0.072          | 0.147          | 0.036            | 0.012  | 0.075  |
| C12   | 0.042             | 0.063          | 0.014          | 0.021          | 0.129          | 0.190          | 0.088          | 0.129          | 0.020            | 0.007  | 0.041  |
| C14   | 0.049             | 0.070          | 0.016          | 0.023          | 0.150          | 0.213          | 0.102          | 0.145          | 0.021            | 0.007  | 0.043  |
| C16   | 0.046             | 0.039          | 0.015          | 0.013          | 0.139          | 0.118          | 0.095          | 0.080          | -0.007           | -0.002 | -0.014 |
| N18   | 0.024             | 0.017          | 0.008          | 0.005          | 0.072          | 0.050          | 0.049          | 0.034          | -0.007           | -0.002 | -0.015 |
| C19   | 0.039             | 0.026          | 0.013          | 0.009          | 0.117          | 0.078          | 0.080          | 0.053          | -0.013           | -0.004 | -0.027 |
| C22   | 0.021             | 0.012          | 0.007          | 0.004          | 0.063          | 0.035          | 0.043          | 0.024          | -0.009           | -0.003 | -0.019 |
| C25   | 0.018             | 0.018          | 0.006          | 0.006          | 0.053          | 0.054          | 0.036          | 0.037          | 0.000            | 0.000  | 0.001  |
| C28   | 0.030             | 0.044          | 0.010          | 0.015          | 0.090          | 0.135          | 0.061          | 0.092          | 0.015            | 0.005  | 0.030  |
| C31   | 0.024             | 0.049          | 0.008          | 0.016          | 0.073          | 0.148          | 0.049          | 0.101          | 0.025            | 0.008  | 0.051  |
| O32   | 0.062             | 0.049          | 0.020          | 0.016          | 0.188          | 0.149          | 0.128          | 0.101          | -0.013           | -0.004 | -0.026 |
| N33   | 0.080             | 0.043          | 0.026          | 0.014          | 0.243          | 0.129          | 0.165          | 0.088          | -0.037           | -0.012 | -0.077 |
| O35   | 0.108             | 0.039          | 0.036          | 0.013          | 0.329          | 0.119          | 0.223          | 0.081          | -0.069           | -0.023 | -0.143 |
| C37   | 0.060             | 0.081          | 0.020          | 0.027          | 0.183          | 0.246          | 0.125          | 0.167          | 0.021            | 0.007  | 0.043  |
| C39   | 0.070             | 0.100          | 0.023          | 0.033          | 0.212          | 0.304          | 0.144          | 0.207          | 0.030            | 0.010  | 0.063  |

**Table 4:** Compound 2 Reactivity Descriptors Calculated Using Hirshfeld Population Analysis (HPA)

| sites | Local descriptors |                |                |                |                |                |                |                | Duals descriptors |        |        |
|-------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|--------|--------|
|       | f                 | f <sup>+</sup> | s <sup>-</sup> | s <sup>+</sup> | η <sup>-</sup> | η <sup>+</sup> | ω <sup>-</sup> | ω <sup>+</sup> | Δf                | Δs     | Δω     |
| C1    | 0.093             | 0.034          | 0.047          | 0.017          | 0.183          | 0.066          | 0.520          | 0.188          | -0.059            | -0.030 | -0.332 |
| C2    | 0.060             | 0.016          | 0.031          | 0.008          | 0.118          | 0.031          | 0.336          | 0.089          | -0.044            | -0.022 | -0.247 |
| N4    | 0.062             | -0.008         | 0.031          | -0.004         | 0.122          | -0.017         | 0.346          | -0.048         | -0.070            | -0.036 | -0.393 |
| C5    | 0.044             | 0.062          | 0.022          | 0.031          | 0.086          | 0.121          | 0.245          | 0.345          | 0.018             | 0.009  | 0.101  |
| C8    | 0.006             | 0.078          | 0.003          | 0.040          | 0.011          | 0.153          | 0.032          | 0.435          | 0.072             | 0.037  | 0.403  |
| C9    | 0.023             | 0.080          | 0.012          | 0.041          | 0.045          | 0.157          | 0.128          | 0.447          | 0.057             | 0.029  | 0.320  |
| C10   | 0.010             | 0.081          | 0.005          | 0.041          | 0.019          | 0.158          | 0.054          | 0.450          | 0.071             | 0.036  | 0.396  |
| C12   | 0.018             | 0.080          | 0.009          | 0.041          | 0.036          | 0.158          | 0.103          | 0.448          | 0.062             | 0.031  | 0.346  |
| C14   | 0.023             | 0.043          | 0.012          | 0.022          | 0.045          | 0.085          | 0.127          | 0.241          | 0.020             | 0.010  | 0.114  |
| C16   | 0.059             | 0.011          | 0.030          | 0.006          | 0.115          | 0.021          | 0.328          | 0.061          | -0.048            | -0.024 | -0.267 |
| N18   | 0.030             | -0.002         | 0.015          | -0.001         | 0.060          | -0.004         | 0.170          | -0.011         | -0.032            | -0.016 | -0.181 |
| C19   | 0.046             | 0.017          | 0.024          | 0.009          | 0.091          | 0.034          | 0.260          | 0.097          | -0.029            | -0.015 | -0.163 |
| C22   | 0.029             | -0.003         | 0.015          | -0.002         | 0.057          | -0.007         | 0.161          | -0.019         | -0.032            | -0.016 | -0.180 |
| C25   | 0.020             | 0.009          | 0.010          | 0.004          | 0.039          | 0.017          | 0.111          | 0.049          | -0.011            | -0.006 | -0.062 |
| C28   | 0.040             | -0.001         | 0.020          | -0.001         | 0.079          | -0.003         | 0.224          | -0.007         | -0.041            | -0.021 | -0.231 |
| C31   | 0.032             | 0.000          | 0.016          | 0.000          | 0.062          | 0.000          | 0.176          | -0.001         | -0.032            | -0.016 | -0.177 |
| O32   | 0.081             | 0.006          | 0.041          | 0.003          | 0.158          | 0.012          | 0.451          | 0.034          | -0.074            | -0.038 | -0.416 |
| N33   | 0.106             | 0.001          | 0.054          | 0.000          | 0.209          | 0.002          | 0.596          | 0.005          | -0.106            | -0.054 | -0.591 |
| O35   | 0.139             | 0.010          | 0.071          | 0.005          | 0.274          | 0.020          | 0.780          | 0.058          | -0.129            | -0.066 | -0.722 |
| C37   | 0.035             | 0.090          | 0.018          | 0.046          | 0.068          | 0.176          | 0.194          | 0.501          | 0.055             | 0.028  | 0.307  |
| N39   | 0.004             | 0.093          | 0.002          | 0.048          | 0.008          | 0.183          | 0.023          | 0.522          | 0.089             | 0.045  | 0.499  |
| O40   | 0.018             | 0.153          | 0.009          | 0.078          | 0.035          | 0.301          | 0.100          | 0.857          | 0.135             | 0.069  | 0.757  |
| O41   | 0.024             | 0.152          | 0.012          | 0.078          | 0.047          | 0.299          | 0.133          | 0.852          | 0.129             | 0.065  | 0.720  |

**Table 5:** Compound 3 Reactivity Descriptors Calculated Using Hirshfeld Population Analysis (HPA)

| sites | Local descriptors |                |                |                |                |                |                |                | Duals descriptors |        |        |
|-------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|--------|--------|
|       | f                 | f <sup>+</sup> | s <sup>-</sup> | s <sup>+</sup> | η <sup>-</sup> | η <sup>+</sup> | ω <sup>-</sup> | ω <sup>+</sup> | Δf                | Δs     | Δω     |
| C1    | 0.084             | 0.038          | 0.031          | 0.014          | 0.223          | 0.102          | 0.247          | 0.113          | -0.045            | -0.017 | -0.134 |
| C2    | 0.060             | 0.019          | 0.023          | 0.007          | 0.161          | 0.052          | 0.178          | 0.057          | -0.041            | -0.015 | -0.121 |
| N4    | 0.057             | -0.004         | 0.022          | -0.002         | 0.153          | -0.012         | 0.170          | -0.013         | -0.062            | -0.023 | -0.183 |
| C5    | 0.046             | 0.080          | 0.017          | 0.030          | 0.123          | 0.213          | 0.137          | 0.236          | 0.033             | 0.013  | 0.099  |
| C8    | 0.014             | 0.085          | 0.005          | 0.032          | 0.037          | 0.225          | 0.041          | 0.250          | 0.071             | 0.027  | 0.209  |
| C9    | 0.029             | 0.089          | 0.011          | 0.033          | 0.077          | 0.237          | 0.085          | 0.263          | 0.060             | 0.023  | 0.178  |
| C10   | 0.015             | 0.086          | 0.006          | 0.032          | 0.040          | 0.229          | 0.045          | 0.254          | 0.071             | 0.027  | 0.209  |
| C12   | 0.024             | 0.087          | 0.009          | 0.033          | 0.065          | 0.232          | 0.072          | 0.258          | 0.063             | 0.024  | 0.186  |
| C14   | 0.030             | 0.083          | 0.011          | 0.031          | 0.081          | 0.222          | 0.090          | 0.247          | 0.053             | 0.020  | 0.157  |
| C16   | 0.057             | 0.021          | 0.021          | 0.008          | 0.152          | 0.057          | 0.169          | 0.063          | -0.036            | -0.013 | -0.105 |
| N18   | 0.031             | 0.006          | 0.012          | 0.002          | 0.083          | 0.016          | 0.092          | 0.018          | -0.025            | -0.009 | -0.074 |

| sites | Local descriptors |                |                |                |                |                |                |                | Duals descriptors |        |        |
|-------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|--------|--------|
|       | f                 | f <sup>+</sup> | s <sup>-</sup> | s <sup>+</sup> | η <sup>-</sup> | η <sup>+</sup> | ω <sup>-</sup> | ω <sup>+</sup> | Δf                | Δs     | Δω     |
| C19   | 0.046             | 0.022          | 0.017          | 0.008          | 0.121          | 0.060          | 0.135          | 0.066          | -0.023            | -0.009 | -0.068 |
| C22   | 0.028             | 0.005          | 0.011          | 0.002          | 0.075          | 0.013          | 0.083          | 0.015          | -0.023            | -0.009 | -0.068 |
| C25   | 0.020             | 0.014          | 0.007          | 0.005          | 0.052          | 0.038          | 0.058          | 0.042          | -0.005            | -0.002 | -0.016 |
| C28   | 0.038             | 0.027          | 0.014          | 0.010          | 0.101          | 0.071          | 0.112          | 0.079          | -0.011            | -0.004 | -0.033 |
| C31   | 0.030             | 0.031          | 0.011          | 0.011          | 0.079          | 0.082          | 0.088          | 0.091          | 0.001             | 0.000  | 0.003  |
| O32   | 0.076             | 0.033          | 0.029          | 0.012          | 0.203          | 0.088          | 0.225          | 0.098          | -0.043            | -0.016 | -0.127 |
| N33   | 0.100             | 0.026          | 0.037          | 0.010          | 0.266          | 0.070          | 0.295          | 0.078          | -0.073            | -0.028 | -0.217 |
| O35   | 0.132             | 0.028          | 0.049          | 0.011          | 0.351          | 0.075          | 0.390          | 0.084          | -0.104            | -0.039 | -0.306 |
| C37   | 0.042             | 0.100          | 0.016          | 0.038          | 0.113          | 0.267          | 0.125          | 0.296          | 0.058             | 0.022  | 0.171  |
| C39   | 0.006             | 0.029          | 0.002          | 0.011          | 0.016          | 0.076          | 0.018          | 0.085          | 0.022             | 0.008  | 0.067  |
| F40   | 0.010             | 0.031          | 0.004          | 0.012          | 0.026          | 0.083          | 0.029          | 0.092          | 0.021             | 0.008  | 0.063  |
| F41   | 0.013             | 0.035          | 0.005          | 0.013          | 0.035          | 0.095          | 0.039          | 0.105          | 0.022             | 0.008  | 0.066  |
| F42   | 0.012             | 0.027          | 0.004          | 0.010          | 0.031          | 0.073          | 0.034          | 0.081          | 0.016             | 0.006  | 0.047  |

**Table 6:** Compound 4 Reactivity Descriptors Calculated Using Hirshfeld Population Analysis (HPA)

| sites | Local descriptors |                |                |                |                |                |                |                | Duals descriptors |        |        |
|-------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|--------|--------|
|       | f                 | f <sup>+</sup> | s <sup>-</sup> | s <sup>+</sup> | η <sup>-</sup> | η <sup>+</sup> | ω <sup>-</sup> | ω <sup>+</sup> | Δf                | Δs     | Δω     |
| C1    | 0.076             | 0.034          | 0.025          | 0.011          | 0.227          | 0.103          | 0.162          | 0.074          | -0.041            | -0.014 | -0.089 |
| C2    | 0.052             | 0.015          | 0.017          | 0.005          | 0.156          | 0.046          | 0.112          | 0.033          | -0.037            | -0.012 | -0.079 |
| N4    | 0.046             | -0.003         | 0.015          | -0.001         | 0.138          | -0.008         | 0.098          | -0.006         | -0.048            | -0.016 | -0.104 |
| C5    | 0.047             | 0.062          | 0.015          | 0.021          | 0.140          | 0.187          | 0.100          | 0.133          | 0.016             | 0.005  | 0.033  |
| C8    | 0.032             | 0.038          | 0.011          | 0.013          | 0.097          | 0.114          | 0.069          | 0.081          | 0.006             | 0.002  | 0.012  |
| C9    | 0.042             | 0.087          | 0.014          | 0.029          | 0.125          | 0.262          | 0.090          | 0.187          | 0.045             | 0.015  | 0.097  |
| C10   | 0.029             | 0.138          | 0.010          | 0.046          | 0.088          | 0.414          | 0.063          | 0.296          | 0.108             | 0.036  | 0.233  |
| C12   | 0.042             | 0.100          | 0.014          | 0.033          | 0.126          | 0.301          | 0.090          | 0.215          | 0.058             | 0.019  | 0.125  |
| C14   | 0.043             | 0.046          | 0.014          | 0.015          | 0.130          | 0.138          | 0.093          | 0.099          | 0.003             | 0.001  | 0.005  |
| C16   | 0.049             | 0.026          | 0.016          | 0.009          | 0.147          | 0.079          | 0.105          | 0.057          | -0.022            | -0.007 | -0.048 |
| N18   | 0.025             | 0.003          | 0.008          | 0.001          | 0.074          | 0.010          | 0.053          | 0.007          | -0.021            | -0.007 | -0.046 |
| C19   | 0.040             | 0.022          | 0.013          | 0.007          | 0.121          | 0.067          | 0.086          | 0.048          | -0.018            | -0.006 | -0.039 |
| C22   | 0.023             | 0.009          | 0.008          | 0.003          | 0.069          | 0.028          | 0.050          | 0.020          | -0.014            | -0.005 | -0.030 |
| C25   | 0.018             | 0.017          | 0.006          | 0.006          | 0.055          | 0.052          | 0.039          | 0.037          | -0.001            | 0.000  | -0.002 |
| C28   | 0.033             | 0.045          | 0.011          | 0.015          | 0.100          | 0.135          | 0.071          | 0.096          | 0.012             | 0.004  | 0.025  |
| C31   | 0.027             | 0.050          | 0.009          | 0.017          | 0.080          | 0.150          | 0.057          | 0.107          | 0.023             | 0.008  | 0.050  |
| O32   | 0.068             | 0.050          | 0.023          | 0.017          | 0.206          | 0.150          | 0.147          | 0.107          | -0.019            | -0.006 | -0.040 |
| N33   | 0.089             | 0.044          | 0.030          | 0.015          | 0.269          | 0.132          | 0.192          | 0.094          | -0.046            | -0.015 | -0.098 |
| O35   | 0.119             | 0.040          | 0.040          | 0.013          | 0.359          | 0.119          | 0.256          | 0.085          | -0.080            | -0.027 | -0.171 |
| C37   | 0.059             | 0.138          | 0.019          | 0.046          | 0.176          | 0.416          | 0.126          | 0.297          | 0.080             | 0.027  | 0.172  |
| F39   | 0.041             | 0.038          | 0.014          | 0.013          | 0.123          | 0.113          | 0.088          | 0.081          | -0.003            | -0.001 | -0.007 |

## 4. Conclusion

The study of electrostatic potential maps, frontier orbitals and Fukui indices has shown that the high electron density zone is located around the hydroxamic acid function, especially on O<sub>35</sub> oxygen. Thus oxygen O<sub>35</sub> would be the most reactive site for electrophilic attack. The global and local indices as well as the dual descriptors of reactivity were determined. The local index of reactivity ( $f_{-K}^{A-}$ ) gives the highest value to the O<sub>35</sub> site in all these studied compounds. Thus, this oxygen should be the most favorable site for an electrophilic attack. 5-(1-(4-(dihydroxyamino) benzyl)-1H-pyrazol-3-yl)-N-hydroxypentanamide (compound 2) is the most polarizable with the highest chemical reactivity and the lowest kinetic stability with respect to all studied molecules. For these compounds, the oxygen atom O<sub>35</sub> is the preferred binding site for the zinc in histone deacetylases. From these results, a study of zinc complexes with hydroxamic acids will be conducted.

## References

1. Arnold M, Brown D, Deeg O (1998) Hydroxamate-Bridged Dinuclear Nickel Complexes as Models for Urease Inhibition. *Inorg Chem* 1669: 2920-2925.
2. Tegoni M, Dallavalle F, Amélia Santos M (2004) Succinylhydroxamic derivatives of alpha-amino acids as MMP inhibitors. Study of complex-formation equilibria with Cu<sup>2+</sup>, Ni<sup>2+</sup> and Zn<sup>2+</sup>. *J Inorg Biochem* 98: 209-218.
3. Mogal A, Abdulkadir SA (2006) Effects of Histone Deacetylase Inhibitor (HDACi); Trichostatin-A (TSA) on the expression of housekeeping genes 20: 81-86.
4. Muri EMF, Nieto MJ, Sindelar RD, et al. (2002) Hydroxamic acids as pharmacological agents. *Curr Med Chem* 17: 1631-1653.
5. Yao Y, et al. (2014) European Journal of Medicinal Chemistry Design, synthesis, and biological evaluation of 1,3-disubstituted-pyrazole derivatives as new class I and IIb histone deacetylase inhibitors. *Eur J Med Chem* 86: 639-652.
6. Holland KP, Elford HL, Bracchi V, et al. (1998) Antimalarial activities of polyhydroxyphenyl and hydroxamic acid derivatives. *Antimicrob Agents Chemother* 42: 2456-2458.
7. Miller MJ (1989) Syntheses and therapeutic potential of hydroxamic acid based siderophores and analogs. *Chem Rev* 89:1563-1579.
8. JEY, Pang YP (1999) Novel Stable Configurations and Tautomers of the Neutral and Deprotonated Hydroxamic Acids Predicted from High-Level ab Initio Calculations.
9. Abdel-Rahman LH, Abu-Dief AM, Moustafa H, et al. (2017) Ni(II) and Cu(II) complexes with ONNO asymmetric tetradentate Schiff base ligand: synthesis, spectroscopic characterization, theoretical calculations, DNA interaction and antimicrobial studies. *Appl Organomet Chem* 31: e3555.
10. Ravikumar C, Joe IH, Jayakumar VS (2008) Charge transfer interactions and nonlinear optical properties of push-pull chromophore benzaldehyde phenylhydrazone: A vibrational approach. *Chem Phys Lett* 460: 552-558.
11. Parr RG, Yang W (1995) Density-Functional Theory of the Electronic Structure of Molecules. *Annu Rev Phys Chem* 46:701-728.
12. Fukui K, Yonezawa T, Shingu H (1952) A Molecular Orbital Theory of Reactivity in Aromatic Hydrocarbons. *J Chem Phys* 20: 722-725.
13. Parr RG, Yang W (1984) Density functional approach to the frontier-electron theory of chemical reactivity. *J Am Chem Soc* 106: 4049-4050.
14. Vargas-Sánchez RD, Mendoza-Wilson AM, Balandrán-Quintana RR, et al. (2015.) Study of the molecular structure and chemical reactivity of pinocembrin by DFT calculations. *Comput. Theor Chem* 1058: 21-27.
15. Hirshfeld FL (1977) Bonded-atom fragments for describing molecular charge densities. *Theor Chim Acta* 44: 129-138.
16. Becke AD (1993) Density-functional thermochemistry. iii. the role of exact exchange. *J Chem Phys* 98: 5648-5652.
17. Frisch MJ, et al. (2009) Spectroscopic Evaluation of the Molecular Structures of di-μ-Chlorobis(1,5-Cyclooctadiene) Iridium (I) and Rhodium (I) Complexes. *J Appl Math Phys* 03: 140-144.
18. Johnson BG, Gill PMW, Pople JA (1993) The performance of a family of density functional methods. *J Chem Phys* 98: 5612-5626.
19. Hoffmann R, Woodward RB (1968) The Conservation of Orbital Symmetry. *J Am Chem Soc* 1: 17-22.
20. Gouasmia A, Villemin D (2016) Molecular Structure, HOMO-LUMO, MEP and Fukui Function Analysis of Some TTF- donor Substituted Molecules Using DFT (B3LYP) Calculations Synthesis of new ILs and their spectroscopy analysis, View project Synthesis of New 4-Substituted Aminopyrido [2,3-d] pyrimidine Derivatives View project.

21. Ndri JS, Koné MG, Kodjo CG, et al. (2018) Theoretical Study of the Chemical Reactivity of Five Schiff Bases Derived From Dapsone by the DFT Method 22: 1-11.
22. Koopmans T (1934) Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den einzelnen Elektronen eines Atoms. Physica 1: 104-113.
23. Dheivamalar S, Sugi L, Ambigai K (2016) Density Functional Theory Study of Exohedral Carbon Atoms Effect on Electrophilicity of Nicotine : Comparative Analysis 17-31.
24. Ayers PW, Parr RG (2000) Variational Principles for Describing Chemical Reactions: The Fukui Function and Chemical Hardness Revisited. J Am Chem Soc 122: 2010-2018.
25. Morell C, Grand A, Toro-Labbé A (2006) Theoretical support for using the  $\Delta f(r)$  descriptor. Chem Phys Lett 425: 342-346.
26. Mekky ABH, Elhaes HG, El-Okr MM, et al. (2015) Ibrahim, Molecular Electrostatic Potential Analysis of Nano-Scale Fullerene (C60) Crystals and Some Specific Derivatives: DFT Approach. J Nanomater Mol Nanotechnol 4.

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