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Theoretical Study of the Stability and Chemical Reactivity of a Series of Dihydropyrazoles with Antiproliferative Activities

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In recent years, the number of cancer cases are increasing particularly that of prostate. In this work, we were interested in anticipating dihydropyrazole-cancer cell interactions and their anti-prostatic activity by studying the chemical reactivity and stability of a series of six dihydropyrazole compounds. This study was carried out on six molecules from a series of antiproliferative dihydropyrazoles (DP) substituted by halogens and cyclic molecules, using density functional theory at the B3LYP/6-31+G (d,p) level. Obtained at 298 K thermodynamic formation parameters confirm the formation and existence of the series of studied molecules. Boundary molecular orbitals examination, including the energy gap (ΔE), electronegativity (χ), chemical hardness (η) and electrophilicity index (ω), provided a deeper perspective on molecular properties. As a result, among studied compounds, DP-1 and DP-5 stand out for having the highest energy gaps between boundary orbitals, making them more stable and less reactive. In addition, DP-1 was found to be the best electron donor and the hardest compound among examined ones. Analysis of local descriptors, isodensity and electrostatic potential maps identified the two nitrogen atoms as the preferred sites for electrophilic and nucleophilic attack. However, the two nitrogen atoms contained in the pyrazole ring of dihydropyrazoles (DP) with one in sp3 and the other sp2 hybridization state are the preferred sites for electrophilic and nucleophilic attacks, respectively.

Keywords: Antiproliferative activity; local descriptors; global descriptors; dihydropyrazole; chemical stability.

1. INTRODUCTION

“ Cancer is a complex and devastating disease that represents a major global health challenge. It is defined as the uncontrolled and abnormal proliferation of cells in the body, which can lead to the formation of cancerous tumours ” [1]. “ When normal cells are damaged or unable to repair themselves, they automatically undergo a process of programmed cell death called apoptosis. Cancer cells have the ability to invade surrounding tissues and detach themselves from the original tumour. They can then migrate through blood vessels and lymphatic vessels, resulting in the formation of metastases, tumours in other parts of the body. Widespread metastases are the main cause of cancer-related deaths. By destroying its environment, cancer can become a real threat to the human beings survival [2]. In 2020, cancer was responsible for almost 10 million deaths, making it one of the leading causes of death worldwide [3]. “ There are several types of cancer, including breast, ovarian, colorectal, skin and prostate. However, our work will focus specifically on prostate one, as it is one of the most devastating cancers in men. In fact, prostate cancer is the most common form of cancer and is the second most common cause of death from cancer in men ” [4] and the fourth most common cause of death from all type of cancer [5]. In 2020, there were more than 19.3 million cases of cancer worldwide [6], including nearly 2,747 cases in Côte d'Ivoire [7]. “ Prostate cancer occurs mainly in the old people, with a very low incidence before the age of 50 (0.3%). Around 66% of prostate cancer cases are diagnosed after the age of 70, and 45% after the age of 75. The incidence of prostate cancer appears to vary unequally across the world. This incidence is rising steadily due to the increasing life expectancy and advances in screening techniques ” [8]. “ Several factors have been identified as being involved in the development of prostate cancer, including age, colour of skin, family predisposition and environmental factors, which are considered to be risk factors ” [9]. “ Prevention of cancer, particularly prostate cancer, is based on regular physical activity and a healthy, balanced diet. Studies have shown that phenyl-substituted dihydropyrazoles are an important pharmacophore's family which have led to the discovery of new derivatives ” [10]. These dihydropyrazole derivatives exhibit a broad spectrum of biological activities, including antimicrobial, antioxidant, anticancer, antimalarial and antituberculosis properties [11-14]. Currently, “ the density functional theory (DFT) method is known as a popular approach for calculating the structural characteristics and energies of molecules by the scientific community ” [15]. For the accurate evaluation of a number of molecular properties [16], Parr and Yang adopted the idea that well-known chemical properties such as electronegativity, chemical potential and affinity could be accurately described and calculated by manipulating electron density as a fundamental

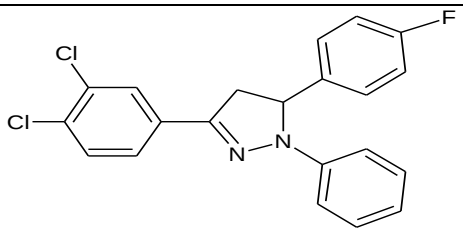
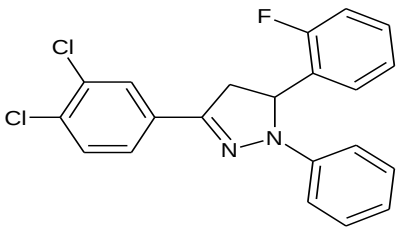
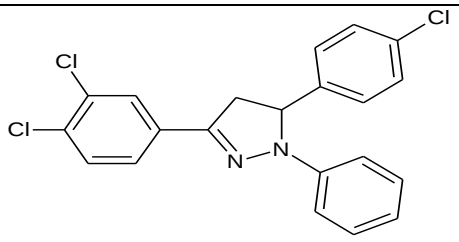
quantity [17,18]. Furthermore, based on the work of Fukui and the theory of frontier molecular orbitals (FMOs) [19], the same authors generalised the concept and proposed the Fukui function as a tool for describing local reactivity in molecules [20,21]. In this work, the B3LYP/6-31+G (d, p) level of theory and a series of six dihydropyrazole molecules (DP-1, DP-2, DP-3, DP-4, DP-5 and DP-6) were used. Thermodynamic quantities, global and local reactivity descriptors, the isodensity map and the molecular electrostatic potential map were also used to assess the reactivity of antiproliferative dihydropyrazoles. The general objective of this work is to study theoretically the stability and reactivity of a series of dihydropyrazoles with antiproliferative activities and to identify the nucleophilic/electrophilic attack sites capable of explaining the antiproliferative activities. Specifically, the analysis of global descriptors obtained by Koopmans approximation, local descriptors such as Fukui Indices and Natural Population Analysis (NPA) and Molecular Surface Electrostatic Potential (MEP) were evaluated to characterize the stability and reactivity of dihydropyrazoles (DP). This study could be decisive in understanding the biological properties and design of new molecules in the pharmaceutical field.

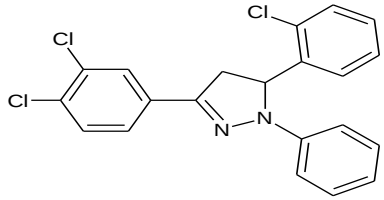
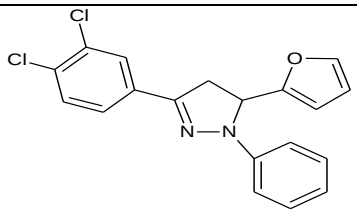
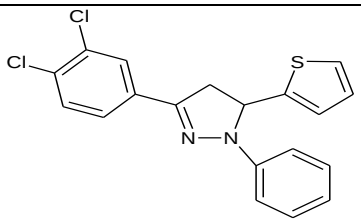
2. MATERIALS AND METHODS

2.1 Theoretical Methodology

Dihydropyrazoles are heterocycles belonging to the pyrazole family. Their distinctive feature is that they possess a double bond between the carbon and nitrogen atoms [22]. To carry out our work, we based ourselves on a series of six (6) dihydropyrazole-derived molecules synthesised and biologically tested on the DU145 prostate cancer strain by Shaik et al [23]. The molecular structures and their Inhibitory Concentration ranging from 84 to 327 µM are listed in Table 1. It should be noted that the median inhibitory concentration (IC_{50}) is a measure of the effectiveness of a given compound in inhibiting a specific biological or biochemical function.

Table 1. Molecules and their respective characteristics

Codes	Molecular structures	IC_{50}^{exp} (µM)
DP-1		119
	3-(3,4-dichlorophenyl)-5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	
DP-2		327
	3-(3,4-dichlorophenyl)-5-(2-fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	
DP-3		149
	5-(4-chlorophenyl)-3-(3,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	

Codes	Molecular structures	IC_{50}^{exp} (μM)
DP-4		134
	5-(2-chlorophenyl)-3-(3,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	
DP-5		162
	3-(3,4-dichlorophenyl)-5-(furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	
DP-6		84
	3-(3,4-dichlorophenyl)-1-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole	

2.2 Computation Theory Level

In this work, the B3LYP/6-31+G(d, p) level of theory and a series of six dihydropyrazole molecules (DP-1, DP-2, DP-3, DP-4, DP-5 and DP-6) were used. The geometries of studied molecules were optimised at the DFT calculation level with the B3LYP functional [24,25] in the 6-31+ G(d,p) basis using Gaussian 09 software [26]. This hybrid functional gives better energies and is in agreement with high-level ab initio methods [27,28]. As for the split-valence and double-dzeta basis (6-31+G (d, p)), it is sufficiently extensive and the polarisation functions taken into account are important for explaining the presence of the free doublets of the heteroatoms.

2.3 Reactivity Descriptors

2.3.1 Global descriptors

To predict chemical reactivity, certain theoretical descriptors linked to the conceptual DFT have been determined. In particular, the energy of the lowest vacant molecular orbital (ELUMO), the energy of the highest occupied molecular orbital (EHOMO), 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 Koopmans approximation [29]. The LUMO energy characterises the molecule's sensitivity to nucleophilic attack, while the HOMO energy characterises the molecule's susceptibility to electrophilic attack. Electronegativity (χ) is the parameter that expresses the ability of a molecule not to let its electrons escape. The overall softness (σ) expresses a system's resistance to changes in its number of electrons. The overall electrophilicity index characterises the electrophilic power of the molecule. These different parameters are calculated from equations (1):

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

2.3.2 Local reactivity descriptors

Fukui indices: For selectivity of electrophilic and nucleophilic attacks explaining in the molecule,

Fukui functions [30] (f_k^+, f_k^-) and local reactivity descriptors have been proposed. It is important to know that f_k^+ indicates reactivity when the molecule is attacked by a nucleophilic reagent, while f_k^- indicates electrophilic attack on a specific site. The most active site receives the highest Fukui function value. The dual descriptor is a good tool for predicting reactivity and allows to solve the problem of regioselectivity. A site with a higher electron density is indicated by a positive dual descriptor. On the other hand, a negative dual descriptor indicates a site susceptible to lose electron density, making it more nucleophilic. A site which is able to receive and give up electron density is considered to have a dual descriptor value close to zero. Equations (2) are used to calculate the different values of the local descriptors [31-34]:

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

Where: $q_k(N)$: 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.

Natural population analysis (NPA) and surface molecular electrostatic potential (MEP): In quantum chemistry, the calculation of the natural atomic charge is crucial for molecular systems study. The molecule is divided into well-defined atomic fragments for the quantitative description of a molecular charge distribution. Sharing the charge density between the different atoms at each point proportionally to their free atom densities at the corresponding distances from the nuclei is a common and natural option [35]. This work used natural population analysis to calculate atomic charge values.

The colours are ranging from red to blue to describe areas of the molecular electrostatic potential (MEP) surface. The green colour represents areas with zero potential. The potential develops in the following order: red, orange, yellow, green, cyan and blue [36,37]. The negative areas (red and yellow) of the MEP surface are sites of electrophilic attack, while the positive areas (cyan and blue) are sites of nucleophilic attack.

3. RESULTS AND DISCUSSION

3.1 Analysis of Thermodynamic Formation Quantities

The thermodynamic parameters such as enthalpy of formation **Δ_f H°** (kcal/mol), entropy of formation **Δ_f S°** (kcal/molK), and free enthalpy of formation **Δ_f G°** (kcal/mol) were explored. It should be noted that a variation in enthalpy indicates the thermicity of a chemical reaction, while a variation in entropy indicates the level of disorder in the system. Furthermore, a variation in free enthalpy reflects the spontaneity with which a chemical reaction occurs. These thermodynamic quantities in our study were obtained after optimisation and frequency calculation, at the B3LYP/6-31+G (d, p) level. The values of the thermodynamic parameters are given in Table 2.

Examination of Table 2 shows that all the values of the standard thermodynamic quantities for the formation of studied molecules are negative. These negative values for enthalpy and free enthalpy respectively reflect an exothermic reaction and a spontaneous reaction under the conditions of the study. As far as entropy is concerned, a negative value indicates a decrease in disorder. Thus, the formation of all the compounds occurs spontaneously with a release of heat and a decrease in disorder. At this level, we note that the determined quantities at B3LYP/6-31+G level of theory (d, p) confirm the formation and existence of the series of hydropyrazoles explored at temperature 298.15K and 1 atm.

Table 2. Thermodynamic formation quantities for optimised PDs at the B3LYP/6-31+G(d,p) level

Molécules	$\Delta_f H^0_{298}$(kcal/mol)	$\Delta_f S^0_{298}$(kcal/mol.k)	$\Delta_f G^0_{298}$(kcal/mol)
DP-1	-866.857	-1131.687	-529.445
DP-2	-866.830	-1132.148	-529.280
DP-3	-823.650	-1130.272	-486.659
DP-4	-823.146	-1132.201	-485.581
DP-5	-834.010	-1043.184	-522.985
DP-6	-765.044	-1042.746	-454.149

Table 3. Energies of HOMO and LUMO and the energy gap calculated at the B3LYP/6-31G+ level (d, p)

MOLECULES	E_{HOMO}(eV)	E_{LUMO}(eV)	ΔE(eV)
DP-1	-5.4850	-1.9251	3.5599
DP-2	-5.4455	-1.8938	3.5517
DP-3	-5.4932	-1.9393	3.5539
DP-4	-5.4485	-1.8965	3.5520
DP-5	-5.4523	-1.8930	3.5593
DP-6	-5.4436	-1.8935	3.5501

3.2 Analysis of Boundary Molecular Orbitals

Boundary orbitals play an important role in chemical reactions. The values of the energies of HOMO and LUMO boundary molecular orbitals and the energy gap are shown in Table 3.

It can be seen that different values of HOMO and LUMO energy from Table 3 are all negative. These values allow to classify these molecules in order of stability according to energy gap values of studied molecules. Furthermore, obtained results in Table 1 show that DP-1 molecule is the least reactive and the most stable, as it has the highest gap energy value **(ΔE=3.5599 eV**), while the DP-6 compound has the lowest gap energy value **(ΔE=5.5501 eV**), and is therefore the most reactive and the least stable among studied compound. We also note that the first four stable molecules are substituted by halogen atoms. Their stability depends on the position and the nature of the halogens. Molecules substituted by halogens (fluorine(F) or chlorine(Cl)) in the meta position are more stable than those substituted by halogens in the para position. Hence the order of decreasing stability:

ΔE : DP-1(F: para) > DP-5 (furan)> DP-3 (Cl: para)> DP-4(Cl: ortho) > DP-2(F: ortho) > DP-6(thiophen)

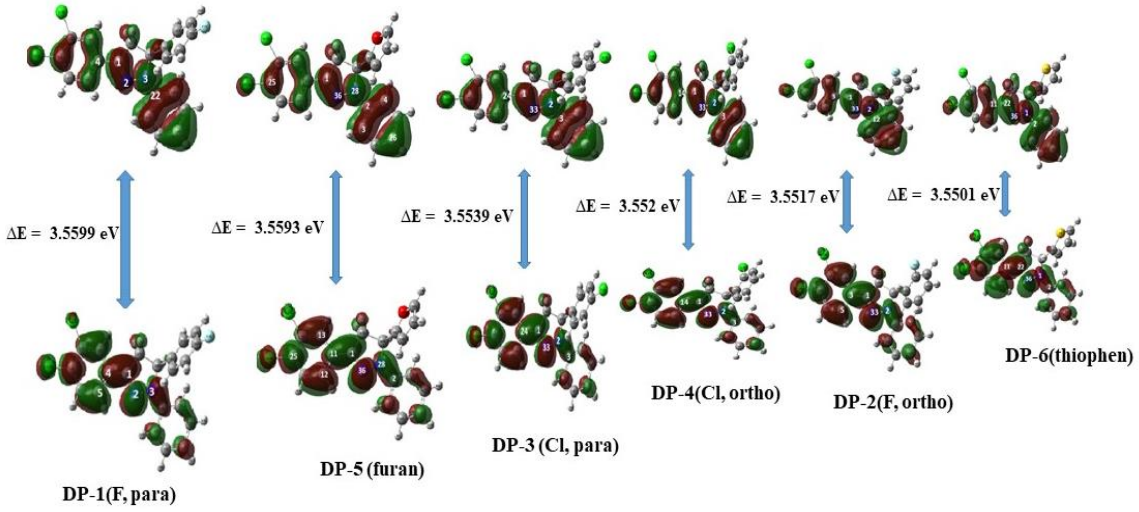


Fig. 1. Decreasing order of stability of halogen-substituted dihydropyrazoles according to the energy gap

Examination of the overall descriptors revealed that compounds DP-1 and DP-6 were the most stable and most reactive, respectively. In addition, DP-1 was identified as the best electron donor and the hardest of the examined compounds. For the continuation of our work, we will study the global descriptors through the maps of the molecular electrostatic potential of the six (6) compounds on the one hand. And on the other hand, the study of the local descriptors will be carried out by the analysis of the Fukui indices, the Natural Population Analysis (NPA) and the isodensity surfaces on the two (2) molecular structures, namely DP-1 and DP-6, respectively the most stable and the most reactive.

3.3 Molecular Electrostatic Potentials (MEP)

The MEP surface analysis of the compounds was determined by DFT calculation using the optimised structure with the B3LYP/6-31G+(d,p) basis set. The electrostatic potential maps for DP-1 to DP-6 are shown below.

- In the case of the electrostatic potential map of DP-1, the **N2** atom (N_{SP2} hybridised) is located in an area coloured yellow while **N3** atom (**NSP^3** hybridised) is located in an area coloured cyan (a mixture of blue and green). **N2** atom (**Nsp^2**) is therefore a probable electrophilic site and N3 atom (Nsp^3) is a probable nucleophilic site.
- Analysis of the electrostatic potential maps shows that atom **N33** (**NSP^2** hybridised) is located in a yellow region, so it is a likely electrophilic site for molecules DP-2, DP-3 and DP-4. **N2** atom (N_{SP3} hybridised) is located in a cyan zone and is therefore a probable nucleophilic site for the DP-2, DP-3 and DP-4 molecules.
- In the case of the electrostatic potential map of DP-5, atom **N36** (N_{SP2} hybridised) is located in a yellow zone while atom **N28** (N_{SP3} hybridised) is located in a cyan region. So atom **N36** (**Nsp^2**) is a likely electrophilic site and atom **N28** (**Nsp^3**) is a susceptible nucleophilic site.

By studying the electrostatic potential map of the studied molecules, we are able to show that the **Nitrogen** atom hybridised (N_{SP2}) is the probable electrophilic site, while the **Nitrogen** atom hybridised ($N_{SP}{}^3$) is the probable nucleophilic site.

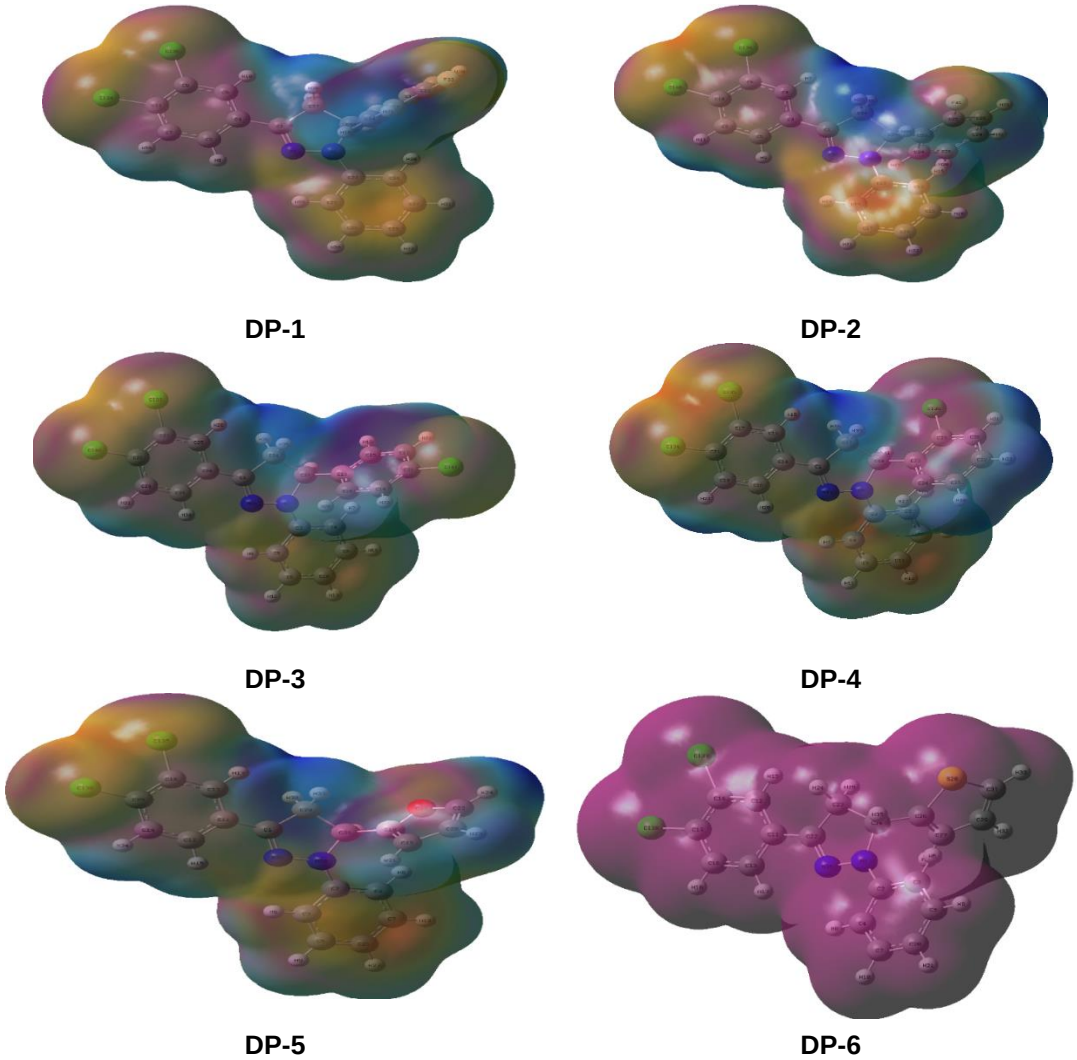


Fig. 2. Electrostatic potential maps from DP-1 to DP-6

Table 4. Values of local Fukui indices, calculated at the B3LYP/6-31G+ (d, p) level, using NPA population analyses for the DP-1 molecule

Atome	NPA	
	f^+	f^-
C1	0.08094	0.12269
N2	**0.12992**	-0.01691
N3	0.01597	**0.14737**
C4	0.05492	-0.03482
C5	0.05120	0.02981
C6	0.04295	0.02856
C7	0.01911	0.01245
C9	0.01180	0.00769
C11	0.09616	0.04469
C12	-0.01872	0.01732
C13	0.01111	0.00671
C14	-0.00644	0.00425
C15	0.01370	0.02400
C17	0.01669	0.02532
C19	0.01709	0.04523
C22	-0.00105	-0.06784
C23	0.02717	0.07095
C24	0.01404	-0.02089
C25	0.00886	0.01772
C27	0.02088	0.04179
C29	0.05350	0.07473
F33	0.01479	0.03727
Cl34	0.07509	0.05260
Cl35	0.05896	0.03936
C37	-0.01563	-0.01560
C40	0.00579	-0.05418

Analysis of the results in this table shows that the N2 (Nsp^2) atom has the highest electrophilic Fukui index , while the N3 (Nsp^3) atom has the highest nucleophilic Fukui index. indeed any electrophilic attack will preferentially be done on the N3 (Nsp^3) atom while a nucleophilic attack will be done on the N2 (Nsp^2) atom. Analysis of the DP-1 isodensity map is shown in Fig. 3.

3.4 Analysis of Local Reactivity Descriptors and Isodensity Maps

In the isodensity map study, if a site belongs to a large lobe, it can be either nucleophilic or electrophilic [38]. Isodensity maps of potential nucleophilic or electrophilic attack sites used the largest lobes of compounds DP-1 and DP-6.

3.4.1 Fukui Indices and Isodensity Maps of the DP-1 Molecule

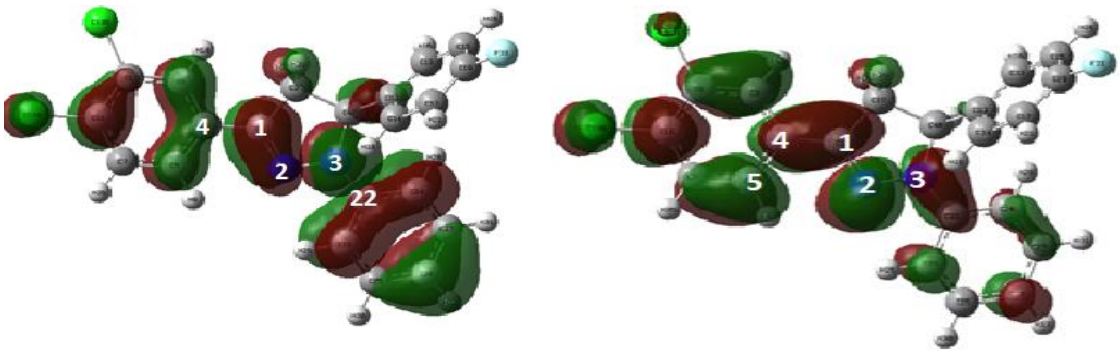
Calculation of the Fukui index of the DP-1 molecule gives the following values listed in Table 4.

Observation of the maps shows that :

- For HOMO (the highest occupied molecular orbital), we see that one of the bulky lobes of this orbital completely encompasses **N3** atom (hybridised $\mathbf{N_{SP3}}$). This observation suggests that **N3** atom ($\mathbf{Nsp^3}$) could be one of the potential nucleophilic sites in the DP-1 molecule, in other words, it tends to attract electrons.
- Concerning the LUMO (lowest unoccupied molecular orbital), we note that a large lobe of this orbital is entirely occupied by **N2** atom (hybridised $\mathbf{NSP^2}$). This observation suggests that **N2** atom ($\mathbf{Nsp^2}$) could be one of the potentially electrophilic sites in the DP-1 molecule, in other words, it generally accepts electrons.

3.4.2 Fukui indices and isodensity maps of the DP-6 molecule

The calculation of the Fukui index of the DP-6 molecule gives us the following values recorded in Table 5.



HOMO **LUMO**

Fig. 3. HOMO and LUMO isodensity maps of DP-1

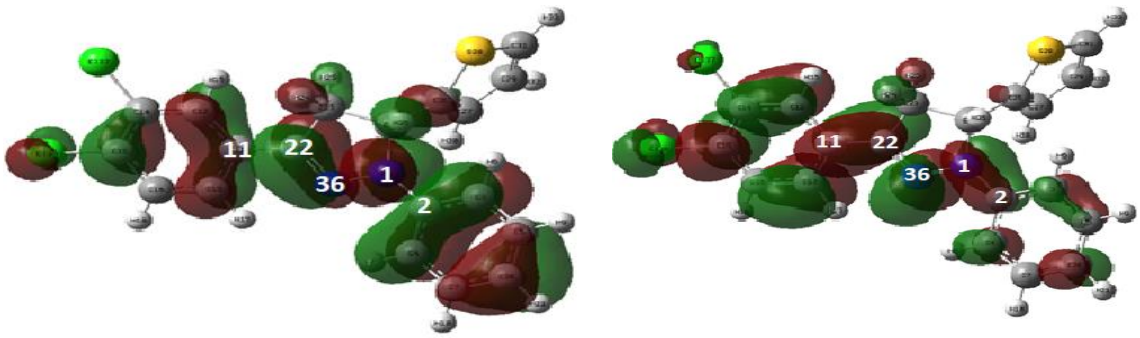
Table 5. Values of local Fukui indices, calculated at the B3LYP/6-31G+ (d, p) level, using NPA population analyses for the DP-6 molecule

Atome	NPA	
	f^+	f^-
N1	0.01469	**0.18136**
C2	-0.00030	-0.01374
C3	0.01422	0.06839
C4	0.02597	0.06487
C5	0.02006	0.00516
C7	0.00891	0.00391
C11	0.05410	-0.03046
C12	0.04236	0.04113
C13	0.05175	0.03350
C14	0.01218	-0.00058
C16	0.01890	0.00473
C19	0.09632	0.05159
C20	0.05359	0.11175
C22	0.08163	0.11716
C23	-0.01572	-0.01528
C26	-0.02127	-0.04185
C27	0.00934	0.00794
S28	0.02949	0.03192
C29	0.00438	0.00492
C31	0.02747	0.02697
C34	0.00690	-0.01063
N36	**0.13034**	-0.01500
Cl37	0.05919	0.04532
Cl38	0.07530	0.06910

Analysis of the results in this table shows that the N36 (Nsp^2) atom has the highest electrophilic Fukui index, while the N1 (Nsp3) atom has the highest nucleophilic Fukui index. This is because any electrophilic attack will preferentially be done on atom N1 (Nsp^3) while a nucleophilic attack will be done on atom N36 (Nsp^2). Analysis of the DP-6 isodensity map is shown in Fig. 4.

Looking at the maps, the following observations can be made:

- In the case of HOMO, it can be seen that one of the bulky lobes is completely localised around **N1** atom (**hybridised NSP^3**). This observation suggests that **N1** atom (**Nsp^3**) could be one of the probable nucleophilic sites in the DP-6 molecule. A nucleophilic site is a site in a molecule that has a strong affinity for electronic species (such as ions or electrons) and can participate in nucleophilic substitution reactions.
- As for LUMO, we can see that one of the large lobes is located entirely around **N36**



HOMO **LUMO**

Fig. 4. HOMO and LUMO isodensity maps of DP-6

atom (**hybridised NSP^2**). This observation suggests that the **N36** atom (**Nsp^2**) could be one of the probable electrophilic sites in the DP-6 molecule. An electrophilic site is a site in a molecule that has a tendency to attract or accept electrons during a chemical reaction, generally due to a positive partial charge or an electron deficit.

Analysis of the isodensity maps and Fukui indices of the six molecules studied showed that nitrogen atoms constitute the electrophilic and nucleophilic sites in these six molecules. The **N** atom (**hybridised NSP^2**) is the electrophilic site and the N atom (**NSP^3**) is the nucleophilic one.

4. CONCLUSION

In this work, Quantum Chemistry and Molecular Modeling methods were used on six (6) molecules belonging to the dihydropyrazole family. This theoretical study was carried out using the DFT method with the B3LYP/6-31+G (d, p) level. By analyzing the thermodynamic quantities of formation, we were able to confirm the formation and presence of the series of studied molecules. We also note that the stability of molecular structures substituted by halogen atoms depends on the position and nature of the halogens. Indeed, molecules substituted by halogens (fluorine (F) or chlorine (Cl)) in the meta position are more stable than those substituted by halogens in the para position. The study of global descriptors revealed that compounds DP-1 and DP-6 were respectively the most stable and the most reactive. In addition, compound DP-1 was identified as the best electron donor and the hardest among examined compounds. Furthermore, the analysis of local descriptors as well as isodensity and electrostatic potential maps allowed us to show that the nitrogen atoms contained in the pyrazole nucleus of dihydropyrazoles constitute the sites. For a precise determination of the attack sites, Fukui indices were calculated from the charges of NPA population. These indices revealed that, in the series of studied molecules, the sp3 hybridized nitrogen atom is the preferred site for electrophilic attacks, while the sp2 hybridized nitrogen atom is the preferred site for nucleophilic attacks. As perspectives for the continuation of this work, we could:

- ✓ Conduct a study on the influence of pressure on stability;
- ✓ Determine the lipophilicity of dihydropyrazoles in order to explain their therapeutic properties
- ✓ Study the effect of halogen on the chemical and biological properties of compounds

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DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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