TheoreticalStudyoftheStabilityandChemicalReactivityofaSeriesof Dihydropyrazoles with Antiproliferative Activities

ABSTRACT

In recent years, there has been a marked increase in the number of cases of cancer, particularly prostate cancer. In this work, we were interested in the theoretical study of the stability and chemical reactivity of a seriesofantiproliferative dihydropyrazoles. Thistheoretical study of stability andreactivity wascarried out on six molecules from a series of antiproliferative dihydropyrazoles (DP) substituted by halogens andcyclic molecules, using density functional theory at the B3LYP/6-31+G (d,p) level. Verification of the thermodynamic formation quantities provided confirmation of the formation and existence of the series of molecules studied. Examination of the boundary molecular orbitals, including the energy gap (ΔE), electronegativity(χ),chemicalhardness(η)andelectrophilicityindex(ω),providedadeeperperspectiveon molecular properties. As a result, among the compounds studied, 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 those examined. Analysis of the local descriptors andtheisodensityandelectrostatic potentialmaps identified the twonitrogen atoms as the preferred sites for electrophilic and nucleophilic attack. One is the nucleophilic site and the other is the electrophilic site.

Key words: antiproliferative activity, local descriptors, global descriptors, dihydropyrazole, chemical stability

1. INTRODUCTION

Cancer is a complex and devastating disease that represents a major globalhealth issue. Cancer 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 survival of living beings [2]. In 2020, cancer was responsible for almost 10 million deaths, making it one of the leading causes of death worldwide. Today, there are several types of cancer, including breast, ovarian, colorectal, skin and prostate. However, our work will focus specificallyon prostate cancer, as it is one of the most devastating cancers in men. In fact, prostate cancer is the most common form of cancer in men and is the second most common cause of cancer-related death [3] and the fourth most common cause of cancer-related death in men and women combined [4]. In 2020, there were more than 19.3 million cases of cancer worldwide [5], including nearly 2,747 cases in Côte d'Ivoire [6]. Prostatecanceroccursmainlyintheelderly,withaverylowincidencebeforetheageof50(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 unevenly across the world. This incidence is rising steadily due to increased life expectancy and advances in screening techniques [7]. Several factors have been identified as being involved in the development of prostate cancer, including age, race, family predisposition and environmental factors, which are considered to be risk factors [8]. Prevention of cancer, particularlyprostate cancer, is based on regular physical activity and a healthy, balanced diet. Studies have shown that phenyl-substituted dihydropyrazoles are an important pharmacophore and have led to the discovery of new derivatives [9]. These dihydropyrazole derivatives exhibit a broad spectrum of biological activities, including antimicrobial, antioxidant, anticancer, antimalarial and antituberculosis properties [10-13]. Currently, the density functional theory (DFT) method is known as a popular approach for calculating the structuralcharacteristicsandenergiesofmoleculesbythescientificcommunity[14].Fortheaccurate

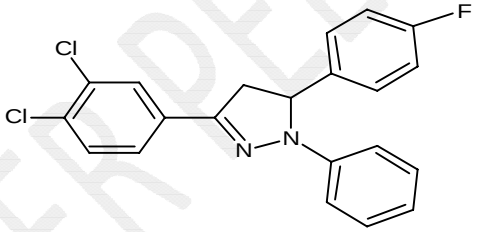
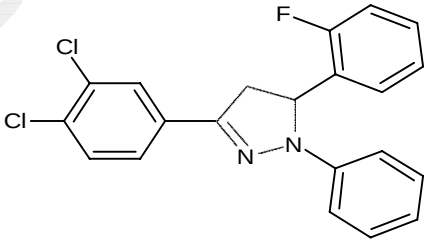
evaluation of a number of molecular properties [15], Parr and Yang adopted the idea that well-known chemical properties such as electronegativity, chemical potential and affinity could be accurately described and calculated by manipulating electron density as a fundamental quantity [16, 17]. Furthermore, based on the work of Fukui and the theory of frontier molecular orbitals (FMOs) [18], the same authors generalised the concept and proposed the Fukui function as a tool for describing local reactivity in molecules [19, 20]. 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 thestabilityandreactivityofaseriesof dihydropyrazoleswithantiproliferativeactivitiesandtoidentifythe nucleophilic/electrophilic attack sites capable of explaining the antiproliferative activities. This study could be decisive in understanding the biological properties and design of new molecules in the pharmaceutical field.

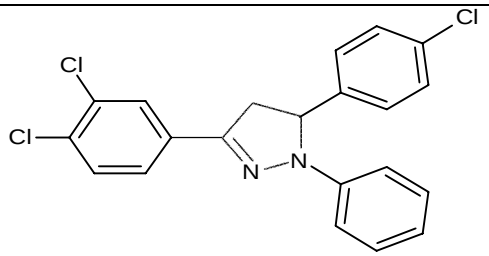
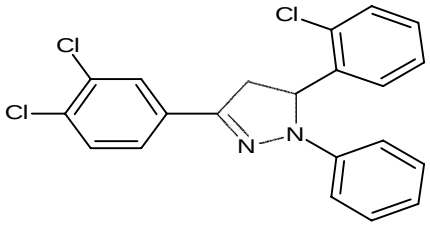
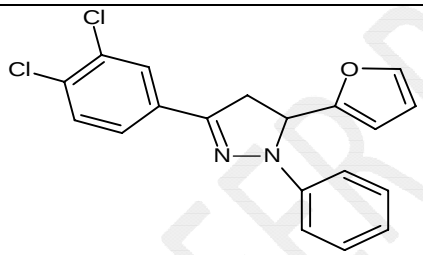
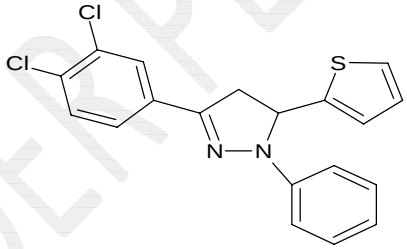
2. MATERIALSANDMETHODS

TheoreticalMethodology

Dihydropyrazoles are heterocycles belonging to the pyrazole family. Their distinctive feature is that they possess a double bond between the carbon and nitrogen atoms. 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 [21]. 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 inhibitoryconcentration (IC_{50}) is a measure of the effectiveness of a given compound in inhibiting a specific biological or biochemical function.

Table1:Moleculesinthedatabaseandtheirrespectivecharacteristics.

Codes	Molecularstructures	(µM)
DP-1	 3-(3,4-dichlorophenyl)-5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	119
DP-2	 3-(3,4-dichlorophenyl)-5-(2-fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	327

DP-3	 5-(4-chlorophenyl)-3-(3,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	149
DP-4	 5-(2-chlorophenyl)-3-(3,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	134
DP-5	 3-(3,4-dichlorophenyl)-5-(furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole	162
DP-6	 3-(3,4-dichlorophenyl)-1-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole	84

ComputationTheoryLevel

In this work, the B3LYP/6-31+G(d, p) levelof theoryand a series of six dihydropyrazolemolecules (DP-1, DP-2, DP-3, DP-4, DP-5 and DP-6) were used. The geometries of these six (6) molecules were optimisedat the DFT calculation level with the B3LYP functional [22, 23] in the 6-31+ G(d,p) basis using Gaussian 09 software [24]. This hybrid functional gives better energies and is in agreement with high-level ab initio methods [25, 26]. As for the split-valence and double-dzeta basis (6-31+G (d, p)), it is sufficientlyextensive and the polarisation functions taken into account are important for explaining the presence of the free doublets of the heteroatoms.

ReactivityDescriptors

GlobalDescriptors

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 verysimple waywithintheKoopmansapproximation[27].The LUMOenergycharacterisesthemolecule'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):

$$\begin{aligned} \square &= -\square_{\square\square\square\square} \\ \square &= -\square_{\square\square\square\square} \\ \square &= -\square = -1/2(\square_{\square\square\square\square} + \square_{\square\square\square\square}) \\ \square &= (\square_{\square\square\square\square} - \square_{\square\square\square\square})/2 \\ \square &= \frac{\square^2}{2\square} \\ \square &= 1/\square \end{aligned} \qquad (1)$$

LocalReactivityDescriptors

FukuiIndices

Thesearelocalreactivityindicesanddualdescriptors.Toexplaintheselectivityofelectrophilicand nucleophilicattacksonthemolecule,theFukuifunction[28]($\square^+$,$\square^-$)and$\square_{\square}$localreactivitydescriptorshave been proposed. It is important to remember that the Fukui function$\square_{\square}^+$indicates reactivity when the moleculeisattackedbyanucleophilicreagent,whiletheFukuifunction$\square_{\square}^-$indicateselectrophilicattack onaspecificsite.Themostactivesitereceivesthehighestfukuifunctionvalue.Thedualdescriptorisa good tool for predicting reactivity and identifying the problem of regioselectivity. A site with a higher electrondensityisindicatedbyapositivedualdescriptor.Ontheotherhand,anegativedualdescriptor indicatesasitelikelytoloseelectrondensity,makingitmorenucleophilic.Asitewhoseabilitytoreceive andgiveupelectrondensityisconsideredtohaveadualdescriptorvalueclosetozero.Equations(2)are usedtocalculatethedifferentvaluesofthelocaldescriptors[29,30,31,32]:

$$\begin{aligned} \square_{\square}^+ &= \square_{\square}(\square+1) - \square_{\square}(\square) \\ \square_{\square}^- &= \square_{\square}(\square) - \square_{\square}(\square-1) \end{aligned} \qquad (2)$$

Where:$\square_{\square}(\square)$:electronicpopulationofatomkintheneutralmolecule.
$\square_{\square}(\square+1)$:electronicpopulationofatomkintheanionicmolecule.
$\square_{\square}(\square-1)$:electronicpopulationofatomkinthecationicmolecule.

2.3.2.2.NaturalPopulationAnalysis(NPA)andSurfaceMolecularElectrostaticPotential(MEP)

In quantum chemistry, the calculation of the natural atomic charge is crucial for the study of molecular systems. 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 in proportion to their free atom densities at the corresponding distances from the nuclei is a common and natural option [33]. This work used natural population analysis to calculate atomic charge values.
The colours range 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 [34, 35]. 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. RESULTSANDDISCUSSION

AnalysisofThermodynamicFormationQuantities

The thermodynamic parameters of 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**.

Table2:ThermodynamicformationquantitiesforoptimisedPDsattheB3LYP/6-31+G(d,p)level.

Molécules	$\Delta_f H^\circ_{298}$(kcal/mol)	$\Delta_f S^\circ_{298}$(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

Examination of **Table 2** shows that all the values of the standard thermodynamic quantities for the formation of the molecules are negative. These negative values for enthalpy and free enthalpy respectively reflect an exothermic reaction and a spontaneous reaction under the conditions studied. 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 quantities determined at the 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.

AnalysisofBoundaryMolecularOrbitals

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

Table 3: Energies of the HOMO and LUMO molecular boundary orbitals 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

It can be seen that the various HOMO and LUMO energy values from **Table 3** are negative. These values make it possible to classify these molecules in order of stability according to the gap energy values of the molecules studied. Furthermore, the results obtained in Table 1 show that the 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 theleast stable. We also note that the stability of the first four molecules substitutedby halogen atoms depends

on the position and 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.

Hencetheorderofdecreasing stability:

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

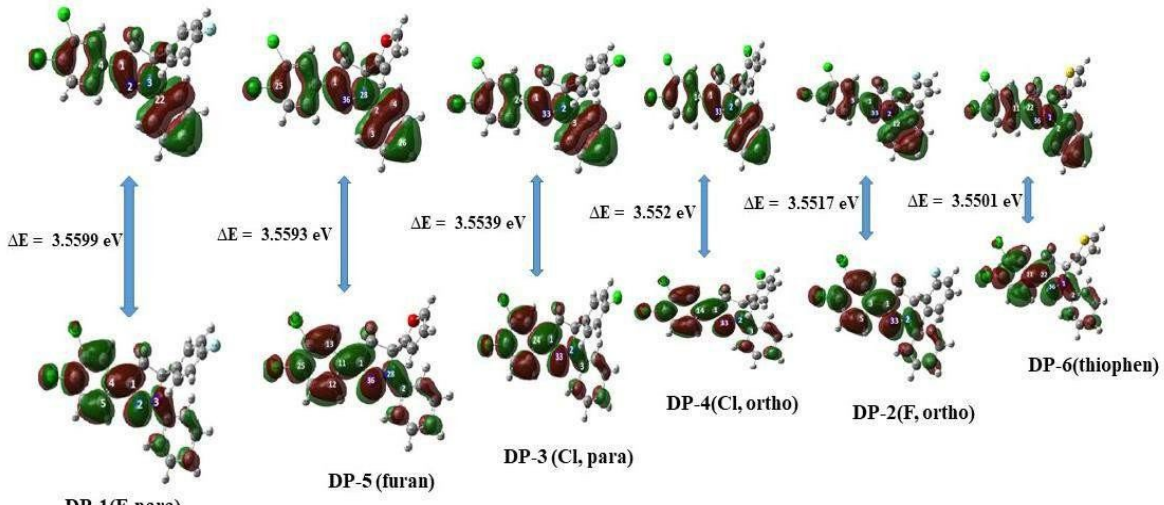
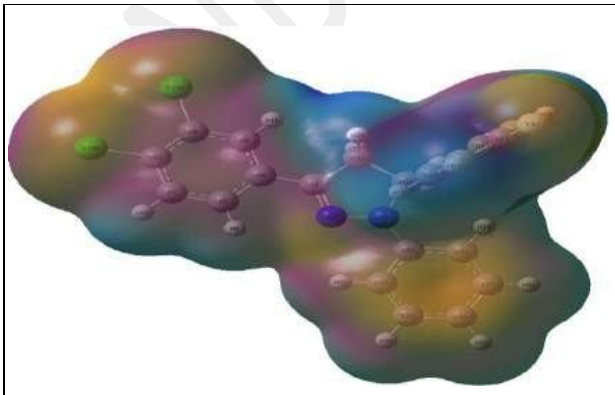
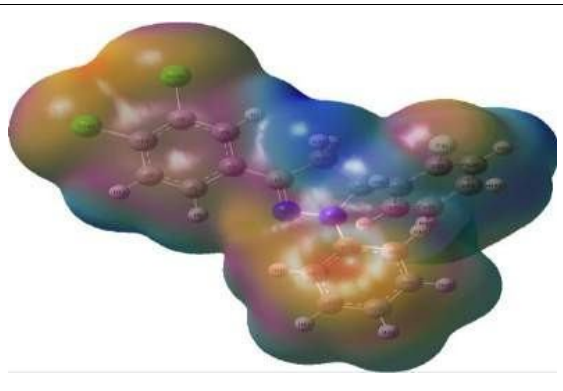


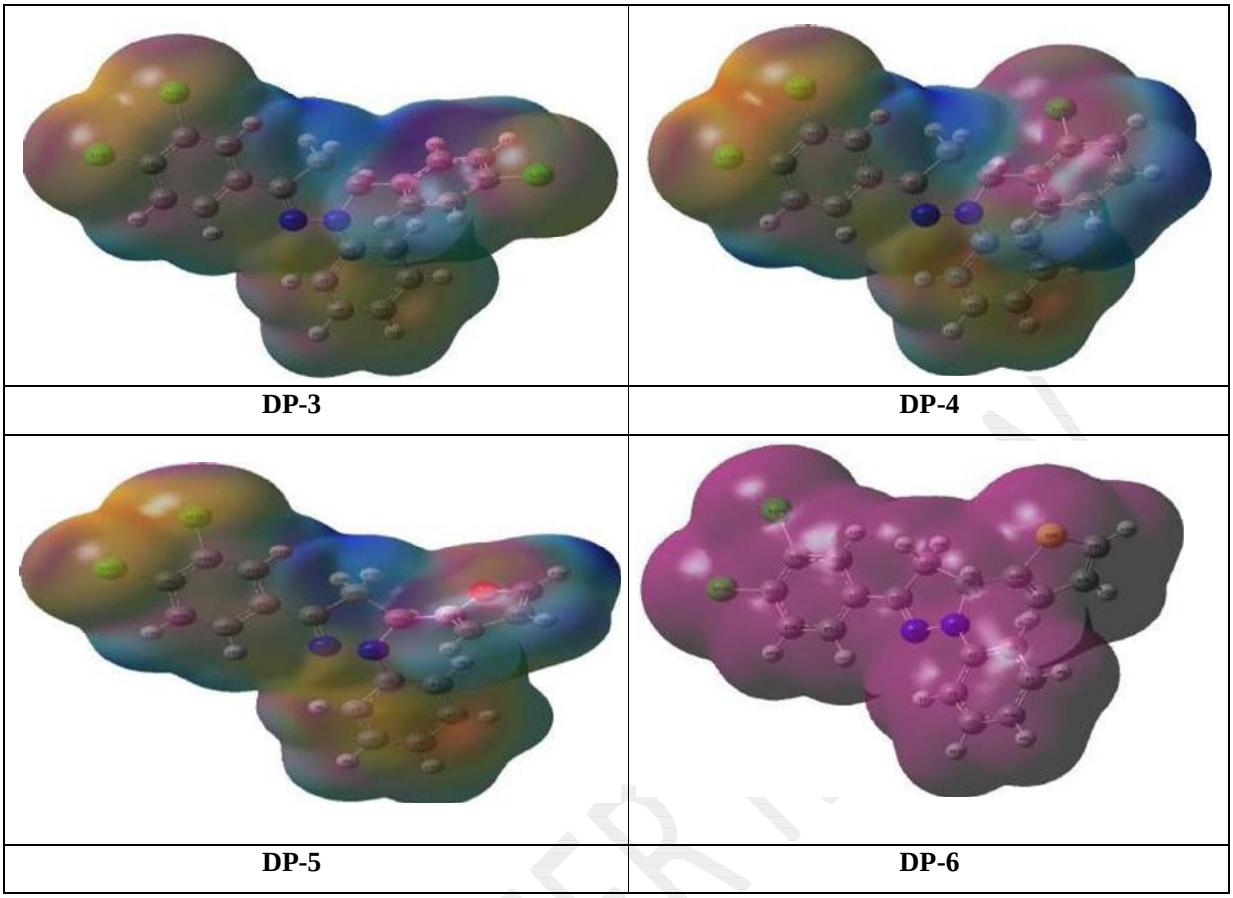
Figure 1: Decreasing order of stability of the series of halogen-substituted dihydropyrazoles studied from the energy gap.

Examination of the overall descriptors revealed that compounds DP-1 and DP-6 were the most stable and reactive, respectively. In addition, DP-1 was identified as the best electron donor and the hardest of the compounds examined. In the rest of our work, we will study the local and dual descriptors of these two (2) molecular structures, namely DP-1 and DP-6.

3.3MolecularElectrostaticPotentials(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.

	
DP-1	**DP-2**



DP-3	DP-4
DP-5	DP-6

Figure2: ElectrostaticpotentialmapsfromDP-1toDP-6

- In the case of the electrostatic potential map of DP-1, the **N2** atom (**NSP^2**hybridised) is located in an area coloured yellow while the**N3** atom (**NSP^3**hybridised) is located in an area coloured cyan(a mixture of blue and green). The **N2** atom (**Nsp^2**)is therefore a probable electrophilic site and the 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. The **N2** atom (**NSP^3**hybridised)islocatedinacyanzoneandisthereforeaprobablenucleophilicsitefortheDP- 2, DP-3 and DP-4 molecules.
- In the case of the electrostatic potential map of DP-5, atom **N36** (**NSP^2**hybridised) is located in a yellow zone while atom **N28** (**NSP^3**hybridised) is located in a cyan region. So atom **N36** (**Nsp^2**) is a likely electrophilic site and atom **N28** (**Nsp^3**) is a likely nucleophilic site.

By studying the electrostatic potential map of the molecules studied, we were able to show that the **N** atom (**NSP^2**hybridised) is the probable electrophilic site, while the **N** atom (**NSP^3**hybridised) is the probable nucleophilic site.

AnalysisofLocalReactivityDescriptorsandIsodensityMaps

In the isodensity map study, if a site belongs to a large lobe, it can be either nucleophilic or electrophilic [36]. Isodensity maps of potential nucleophilic electrophilicattacksites usingthelarge lobesof compounds DP-1 and DP-6.

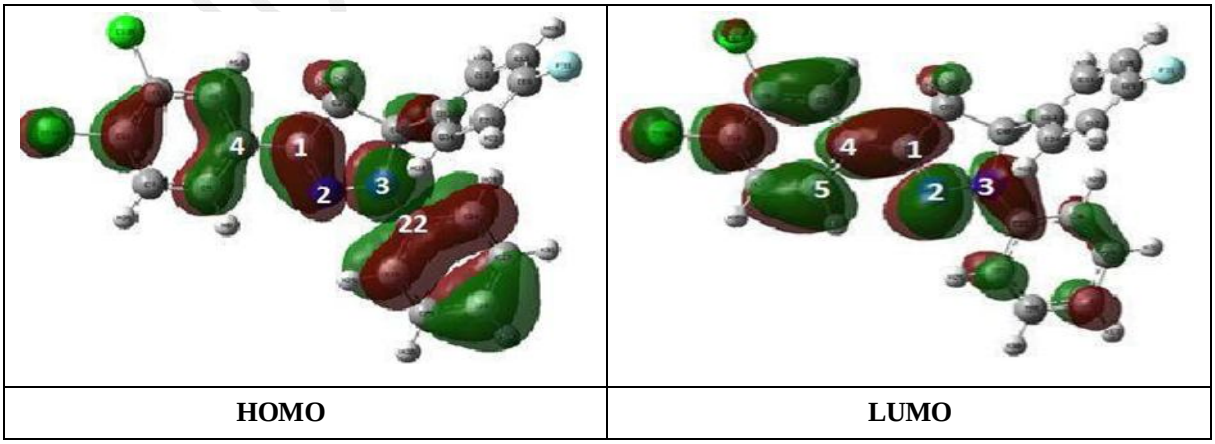
FukuiIndicesandIsodensityMapsoftheDP-1Molecule

CalculationoftheFukuiindexoftheDP-1moleculegivesthevalueslistedin **Table4**.

Table4:ValuesoflocalFukuiindices,calculatedattheB3LYP/6-31G+(d,p)level,usingNPA 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 theresults inthis table shows that the **N2** (**Nsp^2**) atom has the highest electrophilic Fukui index for the population analysis used, while the**N3** (**Nsp^3**) atom has the highest nucleophilic Fukui index. Thisis because any electrophilic attack will preferentially be made on the **N3** (**Nsp^3**) atom while a nucleophilic attack will be made on the **N2** (**Nsp^2**) atom. Analysis of the DP-1 isodensity map is shown in **Figure 3**.



HOMO | **LUMO**

Figure3:HOMOandLUMOisodensitymapsofDP-1

Observationofthemapsshowsthat:

- For HOMO (the busiest molecular orbital), we see that one of the bulky lobes of this orbitalcompletely encompasses the **N3** atom (hybridised **NSP^3**). This observation suggests that the **N3** atom (**Nsp^3**) could be one of the potential nucleophilic sites in the DP-1 molecule, i.e. it tends to attract electrons.
- Concerningthe LUMO (lowest unoccupiedmolecular orbital), we note that a large lobe of this orbital is entirely occupied by the **N2** atom (hybridised **NSP^2**). This observation suggests that the **N2** atom (**Nsp^2**) could be one of the potentially electrophilic sites in the DP-1 molecule, i.e. it generally accepts electrons.

FukuiIndicesandIsodensityMapsoftheDP-6Molecule

ThecalculationoftheFukuiindexoftheDP-6moleculegivesusthevaluesrecordedin **Table5**.

Table 5: Values of local Fukui indices, calculated at the B3LYP/6-31G+ (d, p) level, using NPApopulation 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 for the population analysis used, while the **N1** (**Nsp3**) atom has the highest nucleophilic Fukui index. This is because any electrophilic attack will preferentially bemade on atom **N1** (**Nsp^3**) while a nucleophilic attack will be made on atom **N36** (**Nsp^2**). Analysis of the DP-6 isodensity map is shown in **Figure 4**.

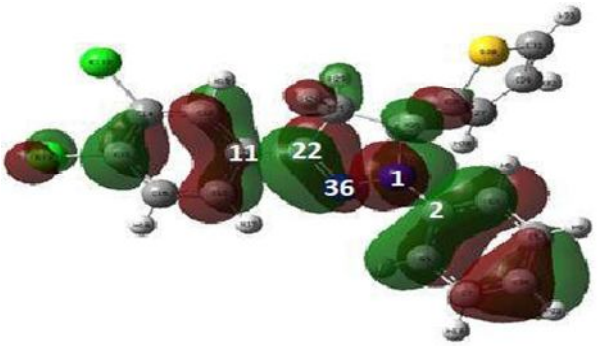
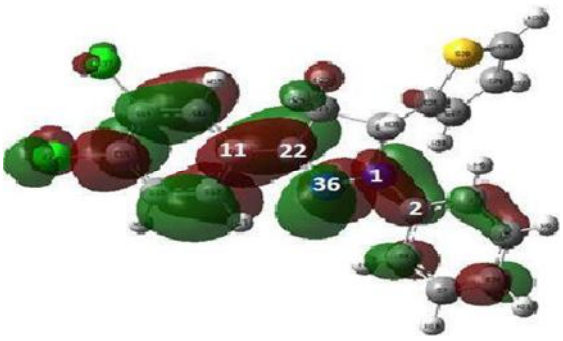
	
HOMO	**LUMO**

Figure 4: HOMO and LUMO isodensity maps of DP-6

Lookingatthemaps,thefollowingobservationscanbe made:

- In the case of HOMO, it can be seen that one of the bulky lobes is completely localised around the **N1** atom (**hybridised NSP^3**). This observation suggests that the **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 the **N36** 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 site.

4. CONCLUSION

In this work, Quantum Chemistry and Molecular Modeling methods were used on six (6) molecules belongingtothe dihydropyrazolefamily. This theoretical study was carriedout using the DFTmethod 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 molecules studied. 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 the compounds examined. Furthermore, the analysis of local descriptors as well as isodensity and electrostatic potential maps allowed us to identify the probable sites of electrophilic and nucleophilic attacks. For a precise determination of the attack sites, Fukui indices were calculated from the charges of the NPA population. These indices revealed that, in the series of molecules studied, 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:

- ✓ Conductastudyontheinfluenceofpressureon stability;
- ✓ Determinethelipophilicityofdihydropyrazolesinordertoexplaintheirtherapeuticproperties

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