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Computational Analysis of 5-Aryl-3-(Napth-2-Yl)-1h-Pyrazole

J. Jenisha, J. Jeba Lenet and T. F. Abbs Fen Reji*

Department of Chemistry & Research Centre,
Nesamony Memorial Christian College,
(Affiliated to Manonmaniam Sundaranar University, Tirunelveli),
Marthandam, Tamilnadu-629165, India

Abstract

The compound 5-aryl-3-(napth-2-yl)-1H-pyrazole which was excepected to have anti-cancer activity, were synthesised from acetyl naphthalene. The title compound was computed by means of DFT chemical quantum calculations to obtain optimized molecular geometry using Gaussian 09 software package. Bond lengths, bond angles and dihedral angles of the 5-aryl-3-(napth-2-yl)-1H-pyrazole have been investigated. The Mulliken population analysis an atomic charges have been computed. The calculated energy gap between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of the molecules confirms the charge transfer occurring within the molecule. The molecular docking study is carried out using PyRx and visualised by PyMoL software. The docking aims to achieve the possible interactions between protein and ligand molecules.

Keywords: B3LYP, DFT, Gaussian09, HOMO, LUMO, Mulliken charges, Docking.

Introduction

Heterocyclic compounds have played a significant role in medicinal chemistry because of their biological actions. Anti-infective, anti-bacterial, and anti-fungal properties are achieved through the production of different heterocyclic compounds[1]. Nitrogen-containing heterocyclic compounds are widely used in medicinal chemistry[2], with indoles[3], pyrazole[4], thiazole[5], and pyridine being the most important. According to the literature, molecules containing the Naphthalene ring have a wide range of medicinal properties, including antioxidant, anti-inflammatory, anticancer, antiviral, antituberculosis, and antibacterial properties. In the realm of coordination chemistry,

DFT has evolved into a standard technique for understanding and guessing the activities of a wide range of chemical, physical, and biological processes that are important in chemical reactivity, linear and electronic characteristics, among other things.[6-8] The goal of this study was to design novel molecules by coupling the naphthalene ring with the thiazole ring and using DFT computation to derive information about their structure and bonding nature.

EXPERIMENTAL

Computational Method

The DFT computation was done with the Gaussian 09 programme for the compound 5-aryl-3-(napth-2-yl)-1H-pyrazole at the Becke-3Lee-Yang-Parr level with the standard 6-31G basis set for the compound 5-aryl-3-(napth-2-yl)-1H-pyrazole.

RESULT AND DISCUSSION

Molecular geometry

The Gaussian 09 package provides molecular geometry via an atom numbering method. The DFT structure of optimization utilising the 6-31G basis set yielded the lowest energy. **Figure 1** shows the optimised molecular structure as well as the numbering scheme for 5-aryl-3-(napth-2-yl)-1H-pyrazole.

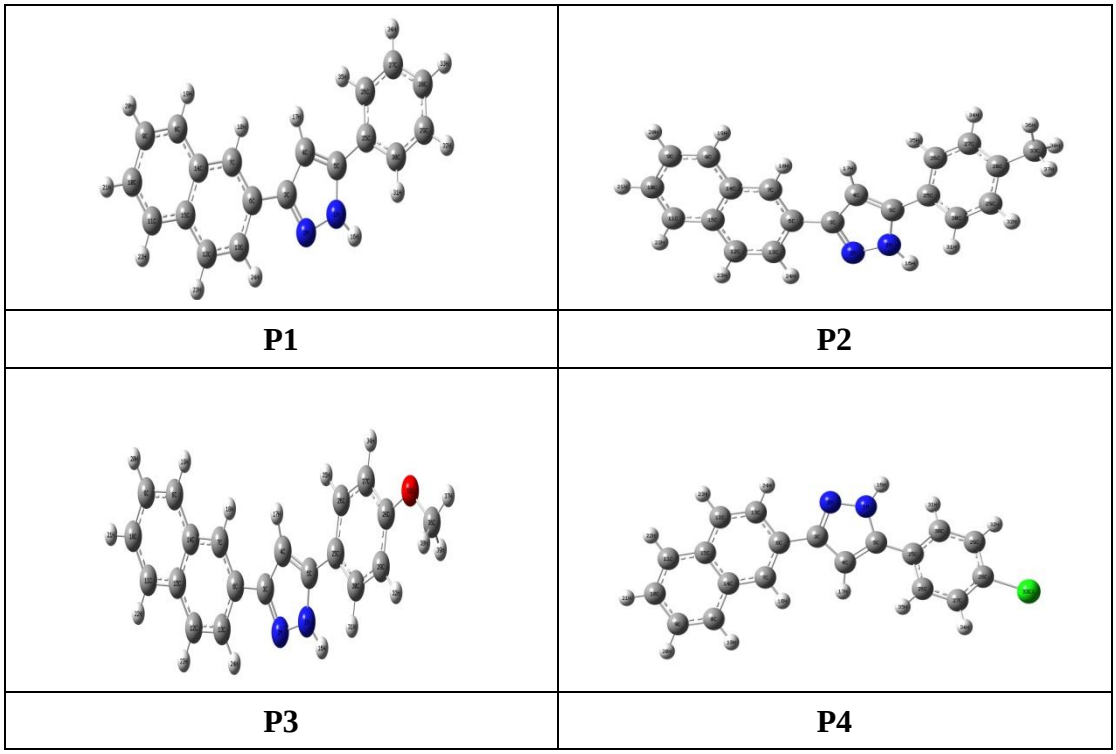


Figure 1: Optimized structure of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Table 1: Bond length data of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Position	Atoms	Bond Length			
		P1	**P2**	**P3**	**P4**
Pyrazole	N-N	1.3644	1.3646	1.3608	1.3647
Pyrazole	C – N	1.305	1.307	1.306	1.306
Pyrazole	C – C	1.367	1.367	1.367	1.367
Pyrazole	C – H	1.076	1.076	1.076	1.076
Naphthalene	C – C	1.388	1.388	1.388	1.388
Naphthalene	C – H	1.086	1.086	1.086	1.086
Phenyl	C - C	1.4649	1.4651	1.4643	1.4658
Phenyl	C-H	1.0865	1.0852	1.0845	1.0831
Phenyl	C-Cl	-	-	-	1.8250
Phenyl	C-O	-	-	1.3885	-

Mulliken Atomic charges

The atomic charges can be calculated using mulliken population analysis and molecular orbital calculations. **Figure 2** depicts the charge distribution structure of 5-aryl-3-(napth-2-yl)-1H-pyrazole. The electrical charge on the chelating atoms determines a molecule's bonding capacity[9]. The mulliken population investigation was calculated utilising the B3LYP/6-31G basis set to determine the results' credibility. Nitrogen and Oxygen atoms have a negative charge in all the compounds, and some carbon atoms have a negative charge as well, acting as electron acceptors. Carbon and hydrogens that remain have a positive charge and operate as electron donors

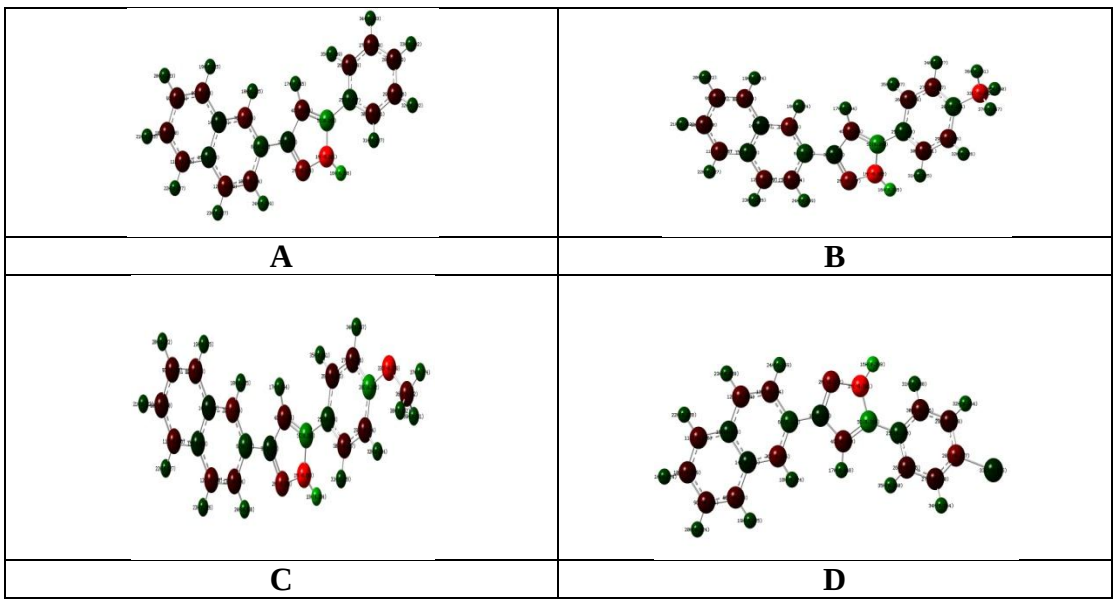


Figure 2: Mulliken atomic charges of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Table 2: Mulliken atomic charges of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Atom	Mulliken Atomic Charge			
	N1	**N2**	**N3**	**N4**
N1	-0.581	-0.44	-0.450	-0.453
N2	-0.274	-0.170	-0.175	-0.178
C_3	0.075	0.045	0.045	-0.119
C_4	-0.163	-0.087	-0.091	-0.092
C_5	0.268	0.220	0.220	0.220
C_6	0.117	0.120	0.121	0.119
C_7	-0.192	-0.192	-0.192	-0.192
C_8	-0.151	-0.150	-0.152	-0.153
C_9	-0.133	-0.133	-0.109	-0.109
C_{10}	-0.124	-0.124	-0.134	-0.135
C_{11}	-0.155	-0.155	-0.155	-0.153
C_{12}	-0.169	-0.168	-0.169	-0.169
C_{13}	-0.138	-0.137	-0.138	-0.138
C_{14}	0.056	0.056	0.056	0.056
C_{15}	0.078	0.080	0.081	0.081
H_{16}	0.336	-0.162	-0.158	-0.159
H_{17}	0.145	0.130	0.130	0.130
H_{18}	0.125	0.129	0.128	0.129
H_{19}	0.128	0.129	0.128	0.129
H_{20}	0.128	0.129	0.129	0.128
H_{21}	0.123	0.134	0.132	0.131
H_{22}	0.127	0.135	0.133	0.134
Cl	-	-	-	0.075
O	-	-	-0.559	-

Frontier molecular orbital analysis

To explain charge transfer within the molecule, HOMO-LUMO study was performed. **Figure 3** depicts the relative energy of the molecular orbitals and a graphical representation of HOMO-LUMO of 5-aryl-3-(napth-2-yl)-1H-pyrzole. HOMO-LUMO has energies of 0.15148, 0.22981, 0.23418, 0.10667. The reduced HOMO-LUMO energy gap explained the charge transfer interactions that occur within the molecule, which affects the molecule's bioactivity[10]. **Table 3** shows the calculated electronic characteristics of 5-aryl-3-(napth-2-yl)-1H-pyrazole. The HOMO-LUMO of 5-aryl-3-(napth-2-yl)-1H-pyrazole is depicted graphically in Figure 3. Among all the four compounds, compound **P4** showed the smallest HOMO-LUMO energy gap, *i.e.,* 0.10667eV. Hence, this compound may be biologically active.

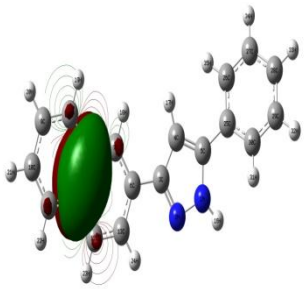
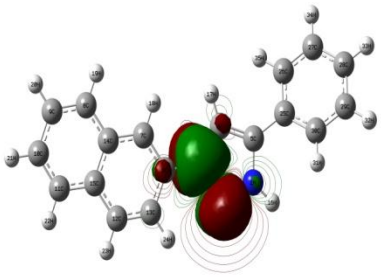
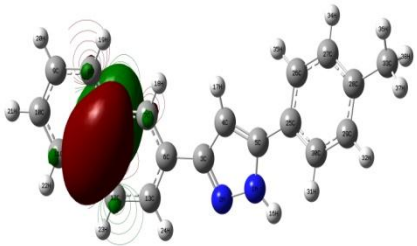
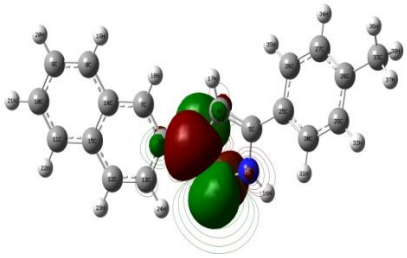
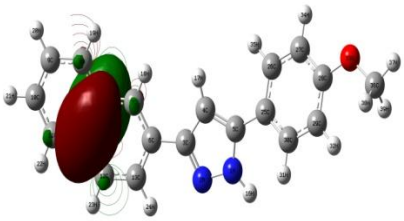
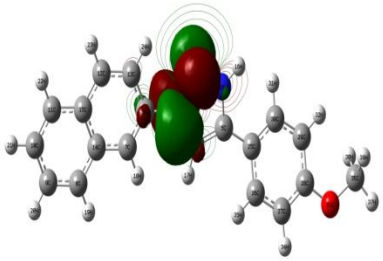
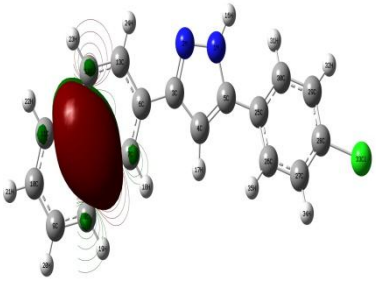
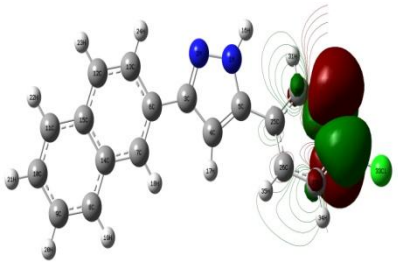
	
P1	**P1**
	
P2	**P2**
	
P3	**P3**
	
P4	**P4**

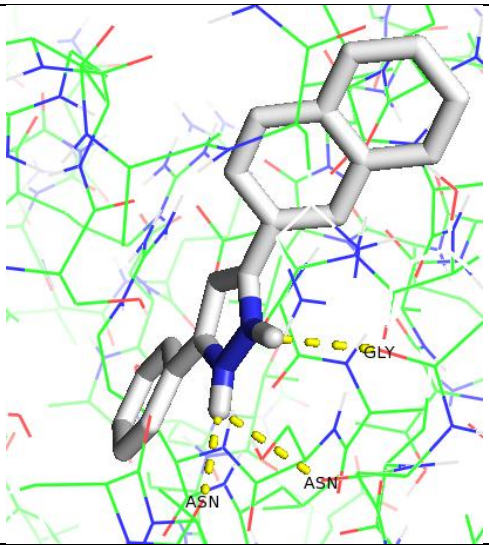
Figure 3: HOMO-LUMO structure of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Table 3: Electronic Parameters of 5-aryl-3-(napth-2-yl)-1H-pyrazole

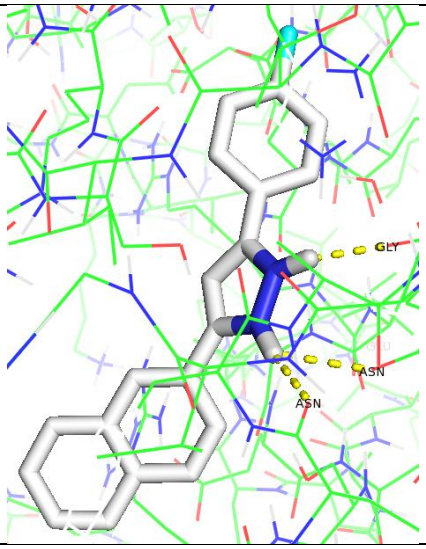
Parametres (a.u)	P1	P2	P3	P4
EHOMO	-0.22527	-0.22433	-0.22381	-0.22878
ELUMO	0.00165	0.00352	0.00464	-0.00787
ΔE	0.22362	0.22081	0.21917	0.22091
Ionization Potential (I)	0.22527	0.2243	0.2238	0.2278
Electron affinity (A)	0.00165	0.00352	0.00464	0.00787
Electronegativity (χ)	0.1134	0.1139	0.1142	0.1183
Hardness (η)	0.1118	0.11039	0.1095	0.1104
Softness (S)	4.4718	4.5293	4.5626	4.5269

Docking Study

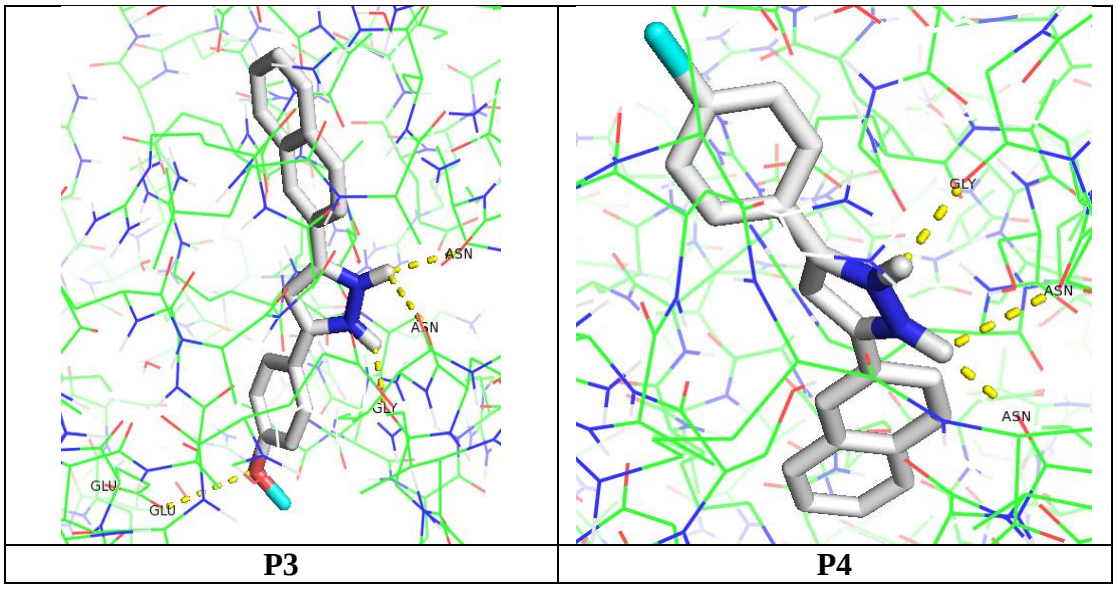
Molecular docking is a powerful approach in molecular structure based computer assisted drug design[11]. The docking aims to achieve the possible interactions between protein and ligand molecules. The ligands were loaded in the PDB format using Openbabel software. The geometry optimization of the compounds was done by Gaussian '09 software with density functional theory at the B3LYP/631G level of theory. The docking scores and H-bond between the proteins of 5-aryl-3-(napth-2-yl)-1H-pyrazole are given in **Table 4.** Pymol software was used to display the hydrogen bonding and hydrophobic interactions between pyrazoles and the protein. From the docking results, all four compounds have good docking scores and are very active. It may be deduced that they have strong agreements with cancer cells based on the docking results.



P1



P2



P3 **P4**

Figure 4: Docking images of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Table 4: Docking score of 5-aryl-3-(napth-2-yl)-1H-pyrazole

Compound	**Docking scoreKJmol^{-1}**	**H-bond**
	5CP6	5CP6
P1	-9.6	GLY37 ASN38 ASN38
P2	-10.3	GLY37 ASN38 ASN38
P3	-9.8	GLU68 ASN38 GLY37
P4	-10.2	ASN38 GLY37

Conclusion

The optimal structural parameters, molecular orbital energies, and Mulliken charge distribution were calculated using Gaussian 09 software. Mulliken charge distribution can be used to characterise the electronic charge distribution in a molecule. The HOMO and LUMO analysis made it abundantly evident which chemicals had lower HOMO-LUMO band gaps and which chemicals had stronger biological actives. The HOMO-LUMO energy gap reveals the activity of 5-aryl-3-(napth-2-yl)-1H-pyrazole. All the compounds have strong agreements with cancer cells based on the docking results. It might be useful for the development of novel, therapeutics in the future.

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