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Synthesis, Characterization and DFT studies of 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine

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Abstract

The molecular structure of 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine was studied by ^{1}H, ^{13}C NMR, IR and mass spectra. ^{1}H-^{13}C COSY spectrum has also been recorded for the title compound. The ground state molecular geometry was calculated using Density Functional Theory (DFT/B3LYP) method with 6-31G(d,p) as basis set. From the optimized structure, the geometrical parameters such as bond angle, bond length and torsion angle have been derived. The electronic properties such as HOMO-LUMO energies, absolute electro negativity, absolute hardness and molecular electrostatic potential (MEP) were also calculated.

Keywords: *Aminopyrimidine, DFT, HOMO-LUMO, MEP*

I. INTRODUCTION

Pyrimidine and their derivatives are a type of N-containing heterocyclic scaffolds which comprise of life supporting substances, such as vitamins, coenzymes and uric acid, as well as in many synthetic drugs [1,2].The most important components of living cells like DNA and RNA contain aminopyrimidine ring as a part of its structure [3]. In addition, they possess a wide range of biological effectiveness such as antimicrobial [4], calcium channel blockers [5], antitubercular, anticancer [6], antibacterial [7] and anti-inflammatory [8] activities. Especially 2-amino substituted pyrimidine has frequently been studied during the recent decades as they act as synthetic precursors in a variety of organic conversions and in coordination chemistry [9]. Moreover, many fluorinated scaffolds are known to exhibit a broad range of biological activities in medicinal and agricultural scientific fields [10]. Thus, fluorine substitution remains an attractive means in the development of more efficient and selective pharmaceutical drug molecules.

Due to the important features of aminopyrimidine derivatives, the title compound was synthesized and the biological evaluation was previously reported [11].Further, with the development in the computational chemistry, investigation on the electronic structure of the molecule was carried out by using density functional theory (DFT). The present work is aimed to get more insight about the molecular geometry of 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine by using DFT/B3LYP method with 6-31g (d,p) basis set.

II. Experimental

All reagents and solvents were of analytical grade and used without further purification. Melting point was measured in open glass capillary and was uncorrected. The FT-IR spectrum was recorded on an AVATAR-330 FT-IR spectrophotometer using KBr pellet. The NMR spectra were recorded in $CDCl_3$ on a BRUKER Avance III 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Mass spectrum was recorded on a SCIEX-API 2000 spectrometer.

2.1. Synthesis of 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine

A mixture of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-phenylprop-2-en-1-one (0.01 mol) and guanidine nitrate (0.01 mol) was dissolved in ethanol (30 mL). The reaction mixture is then refluxed with the addition of small portion of aqueous sodium hydroxide (10%, 2 mL). To the refluxing mixture the remaining sodium hydroxide was added and refluxed for 5-6 h. The completion of the reaction was monitored by TLC. After the completion of the reaction, the resultant mixture was cooled and transferred into crushed ice. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

III. Results and discussion

3.1. Chemistry

The 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine (**5**) was synthesized as shown in **Scheme 1** [12,13]. The key intermediate (**3**) was prepared by Claisen-Schmidt condensation method as previously reported [14]. The structure of the compound was established by various spectroscopic techniques like IR, ^{1}H and ^{13}C NMR and mass spectrometry.

The IR spectrum of the compound (**5)** show a characteristic absorption band of N-H and C=N at 3495 cm^{-1} and 1631 cm^{-1} respectively (**Fig. 1**). The aromatic C-H stretching vibration appeared as collection of bands around 2845-3047 cm^{-1}. The absorption band at 1103 cm^{-1} and 1141 cm^{-1} were corresponding to the presence of C-F stretching. In addition, the mass spectra of the compounds showed molecular ion peak at 360 $[M+1]^{+}$ which is consistent with the proposed molecular formula ($C_{22}H_{15}F_2N_3$) (**Fig. 2**).

The signals of the NMR spectra were assigned depending upon their integrals, positions, and multiplicities. A broad singlet observed at 6.78 ppm with integral value of two protons was due to the primary amino group which confirmed the formation of the product. The H(5) proton of the pyrimidine ring was observed as singlet at 7.77 ppm. The signals observed around 7.20-8.34 ppm belong to the aromatic protons (**Fig. 3**).

In the ^{13}C NMR spectrum, the C(5) carbon appeared at 101.9 ppm. The signals around 164.2 and 164.9 ppm were due to C(4) and C(6) carbons of the pyrimidine moiety in which the difluoro biphenyl group and aryl group were substituted. In addition, a signal at 163.9 ppm was assigned to the amino group bearing carbon C(2) of the pyrimidine ring. The less intense peaks appeared as double doublets around 159.2 C(4') and 162.1 C(2') ppm were due to fluorine substituted carbon atoms. The other signals around 104.3-137.3 ppm were characteristic of the aromatic carbons (**Fig. 4**).

The tentative assignments made from ^{1}H and ^{13}C were further confirmed by ^{1}H-^{13}C COSY spectrum (**Fig. 5**). The proton signal at 6.78 ppm has no correlation with any of the carbon signal which clearly explains that it was due to NH_2 protons. The C(5) carbon at 101.9 ppm has correlation with 7.77 ppm H(5). The other correlations between ^{1}H and ^{13}C were corresponding to the aromatic protons and carbons.

3.2. Geometrical structure analysis

Computational calculations were carried out by Guassian 03 W package. Geometry optimizations were carried out at DFT level using 6-31 G (d, p) basis set [15]. All the calculations were carried out within the complete geometry optimizations at precise level.

The optimized structure and the atom numbering scheme for the title compound **5** was given in **Fig. 6.** As the crystal data of the compound 5 was not yet received, the geometrical parameters were compared with the similar system which was previously reported by Thangarasu *et al.*[16]. The selected geometrical parameters such as bond lengths, bond angles and dihedral angles were summarized in **Table 1**. The optimized bond lengths were in agreement with the experimental values. The calculated bond distance of C1-C4: 1.402 Å and C1-C2: 1.403 Å were positively deviated from the experimental bond distance C1-C4: 1.386 Å and C1-C2: 1.352 Å. The predicted and experimental bond length of C3-N38, C3-N36, C3-N37, C14-N36, C2-N37 in the pyrimidine ring were around 1.324-1.372 Å. All the C-C and C-N bond lengths of pyrimidine ring clearly specify that the substitution on C4 and C2 does not influence on the aromatic character of the compound. The calculated N38-H40 and N38-H39 (1.01 Å) bond lengths were elongated than the experimental value (0.86 Å).

The bond angle of C3-N37-C2 (116.5°) and C4-C1-C2 (117.8°) had negative deviation and N36-C3-N37 (126.8°) had positive deviation from their characteristic hexagonal angle of 120°. The other bond angles were satisfactory with the experimental values. From the torsion angles of C4-N36-C3-N38 (178.3°) and C2-N37-C3-N38 (178.4°) it is clear that the nitrogen atom of the amino group lie in the molecular plane whereas the hydrogen atoms of the amino group were deviated appreciably from the plane of the molecule. The torsion angles of N36-C3-N38-H40 and N36-C3-N38-H39 were found to be 15.1° and 166.3° respectively. This large discrepancy in N-C-N-H bond is because of the strong charge delocalization. From the above discussions we can conclude that the molecule is not planar.

3.3. Frontier molecular orbital analysis

In order to investigate energetic behavior of the title compound the frontier molecular orbital analysis was carried out (**Fig. 7)**. Highest occupied molecular orbital (HOMO) is correlated with the ability to donate an electron and lowest unoccupied molecular orbital (LUMO) is associated with the ability to accept electrons. So, higher values of E_{HOMO} indicates the greater ease of donating electrons and lower values of E_{LUMO} represents the higher accepting tendency of electrons. Furthermore, the energy gap between HOMO-LUMO gave an insight about the charge transfer within the molecule which is correlated with the biological activity of the molecule. From the E_{HOMO}-E_{LUMO} energy gap the chemical reactivity descriptors were calculated. As it is seen from figure, the energy value of HOMO and LUMO were –5.807 eV and –1.631 eV respectively. The calculated energy separation ($\Delta E = E_{HOMO}–E_{LUMO}$) of 4.176 eV indicates an eventual charge transfer interaction within the molecule. The ΔE also concludes that the molecule has better biological activity. In LUMO, the molecular delocalization takes place on the entire molecule whereas the HOMO is located over amino group, C-N and in

some of C-C bonds. The calculated chemical reactivity descriptors are as follows,
Chemical potential, $\mu = E_{HOMO} + E_{LUMO}/2 = -3.719$ eV
Global hardness, $\eta = E_{LUMO} - E_{HOMO}/2 = 2.088$ eV
Global Softness, $\zeta = 1/2\eta = 0.239$ eV
Electrophilicity index, $\omega = \mu^2/2\eta = 3.312$ eV
Electronegativity, $\chi = -\mu = 3.719$ eV

From the calculated hardness and softness values it is clear that the molecule was hard with high chemical stability and less polarizability.

3.4. Molecular electrostatic potential

The reactive sites for electrophilic and nucleophilic attack for the compound **5** were predicted by MEP analysis from the optimized geometry. The variable charged regions at the surface were represented by different colors. As it is well known that the positive regions (blue) are related to nucleophilic attack and the negative regions (red) are related to electrophilic attack. The 3-D electrostatic potential map of the compound **5** was shown in **Fig. 8**. From the figure, it is seen that there is maximum positive regions on the hydrogen atoms with electrophilic attack (red) on the nitrogen atom while the other regions represent intermediary electrostatic potential.

IV. Conclusion

In the present work, the synthesized 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2 amine was characterized by various spectral studies. The optimized structure was depicted using DFT studies. The HOMO-LUMO energy gap clearly explains the presence of intramolecular energy transfer within the molecule.

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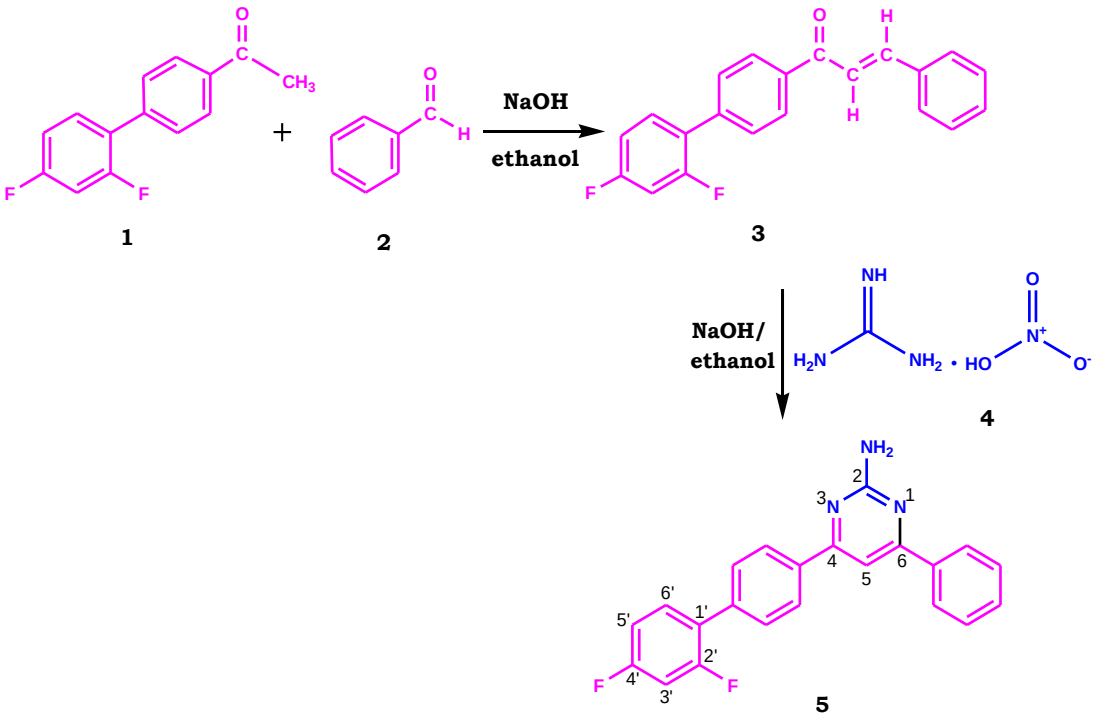

Scheme 1 Schematic representation of synthesis of 4-(2',4'-difluorobiphenyl-4-yl)-6-phenylpyrimidin-2-amine

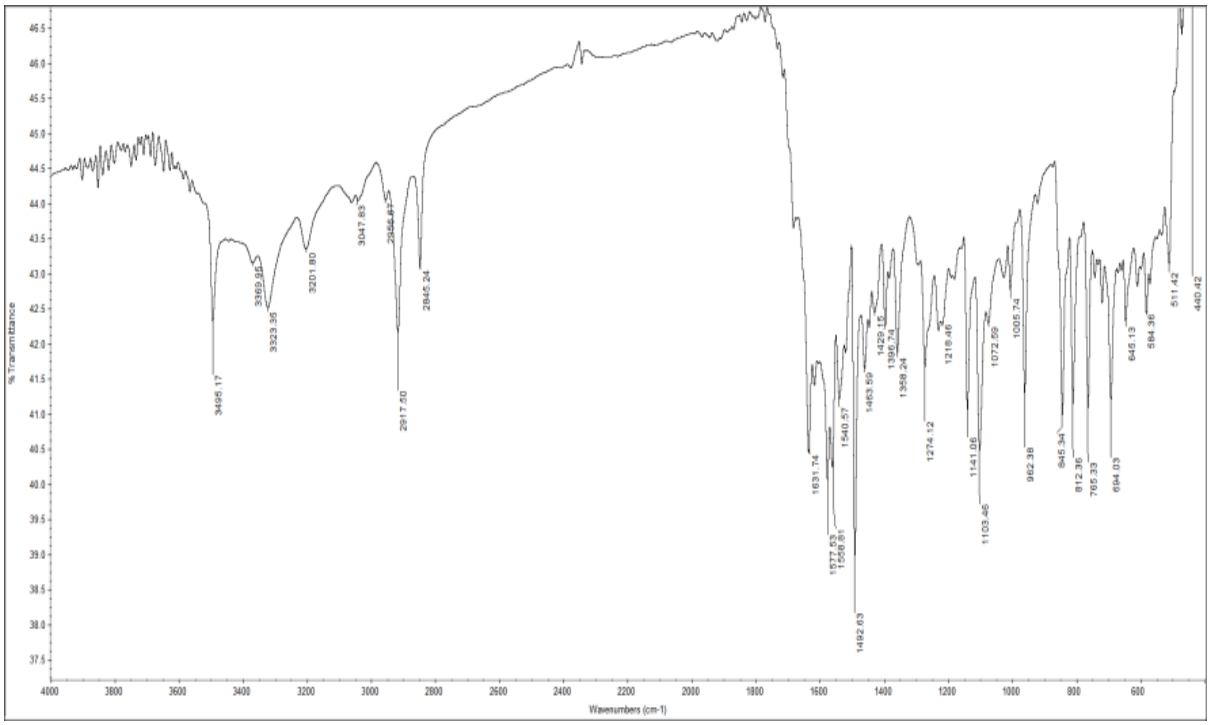

Fig. 1 IR spectrum of compound 5

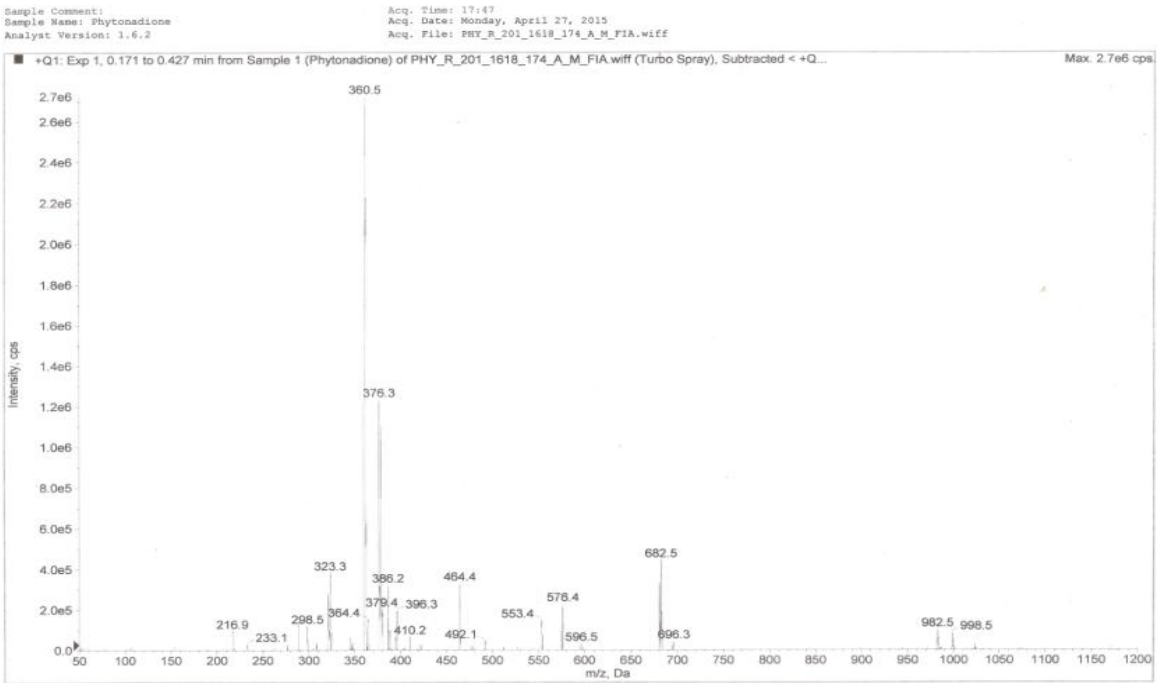

Fig. 2 Mass spectrum of compound 5

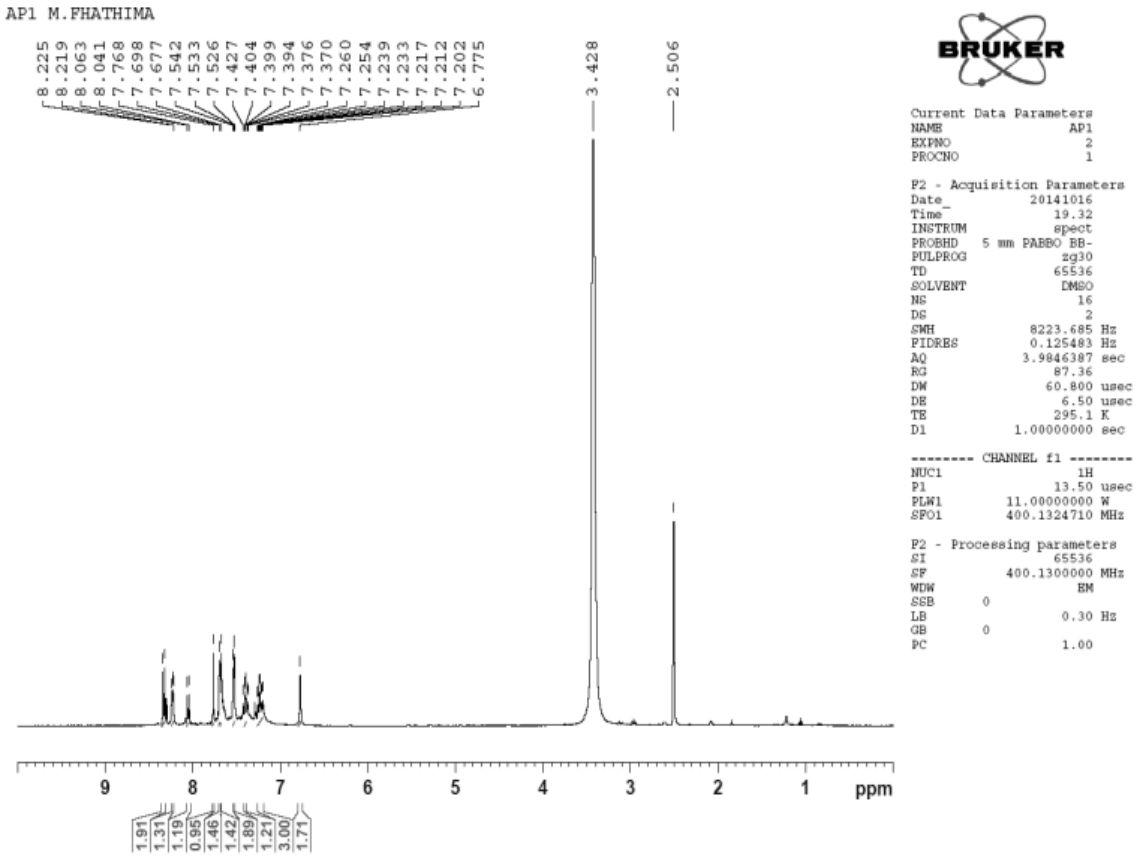

Fig. 3 ^{1}HNMR spectrum of compound 5

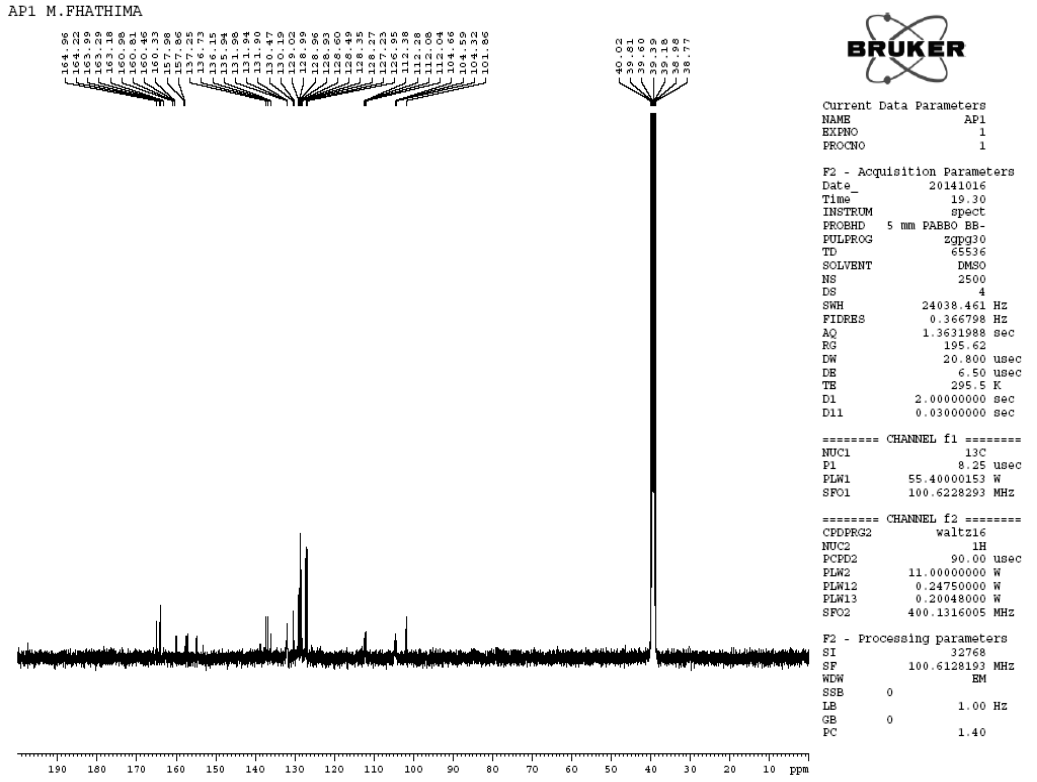

Fig. 4 ^{13}CNMR spectrum of compound 5

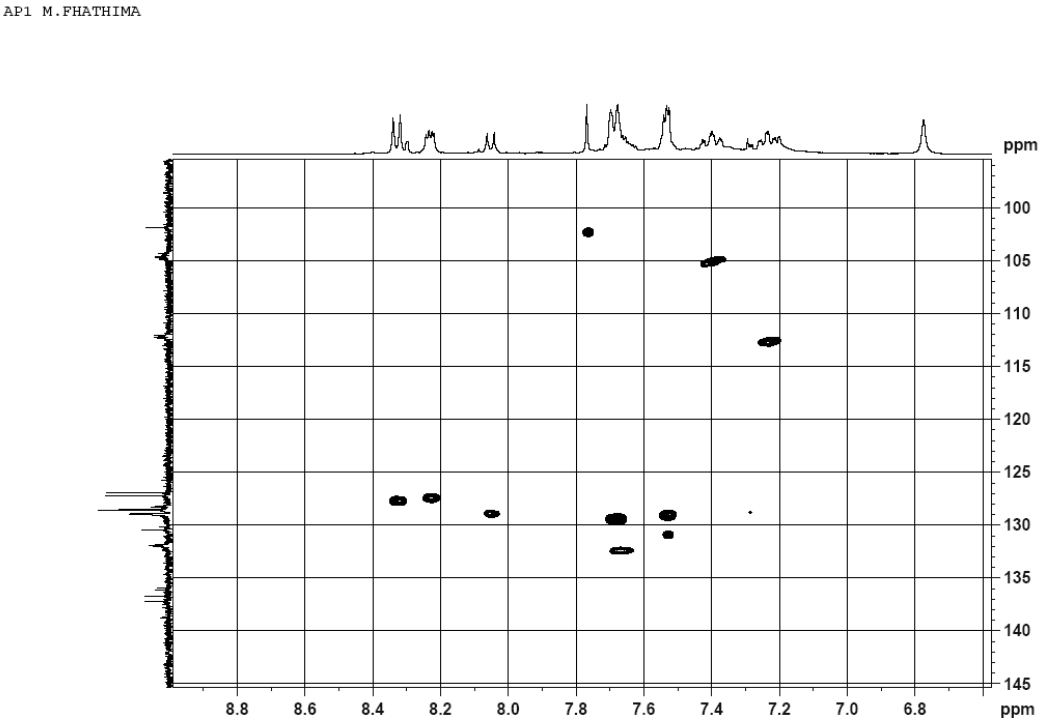

Fig. 5 Expanded ^{1}H-^{13}C spectrum of compound 5

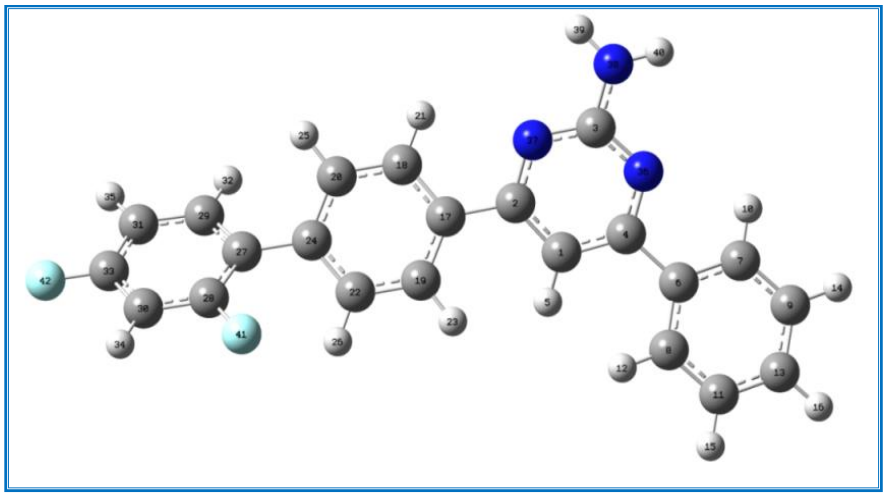

Fig. 6 Optimized structure of 5

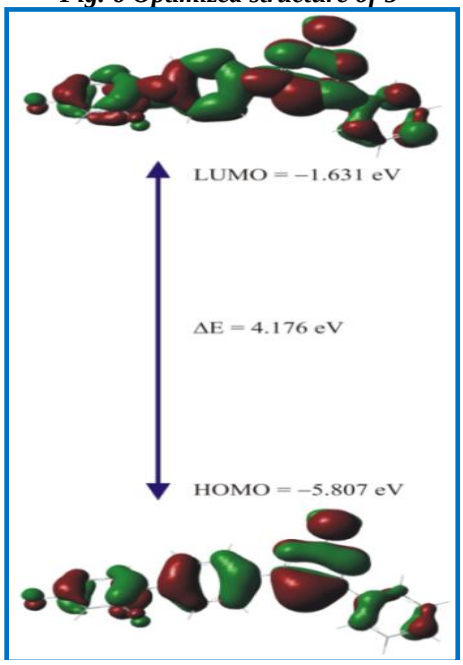

Fig. 7 Frontier molecular orbitals of 5

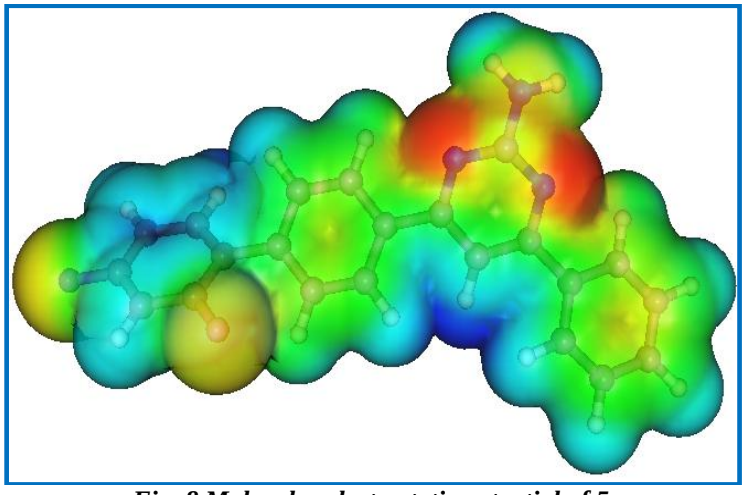

Fig. 8 Molecular electrostatic potential of 5

Table 1 Selected geometric parameters [bond lengths (Å), bond angles (°) and torsion angles (°)] for 5

Atoms	Bond length		Atoms	Bond angle		Atoms	Torsional angle
	XRD[a]	Theoretical		XRD[a]	Theoretical		Theoretical
N38-C3	1.324	1.372	C3-N38-H40	119.9	117.3	C4-C1-C2-C17	179.6
N38-H40	0.860	1.010	C3-N38-H39	118.2	117.3	C4-C1-C2-N37	0.749
N38-H39	0.860	1.010	H40-N38-H39	121.1	118.8	H5-C1-C2-N37	-175.7
C3-N36	1.347	1.371	N38-C3-N36	119.7	116.5	C2-C1-C4-C6	-179.7
C3-N37	1.351	1.346	N38-C3-N37	118.9	116.6	C2-C1-C4-N36	0.846
N36-C14	1.326	1.348	C3-N36-C4	116.9	116.5	N37-C3-N36-C4	0.096
C1-C4	1.386	1.402	N36-C4-C6	-	116.6	N38C3-N36-C4	178.3
C1-H5	0.932	1.076	N36-C4-C1	124.3	121.2	N36-C3-N37-C2	-0.188
C1-C2	1.352	1.403	C6-C4-C1	117.8	122.2	N38-C3-N37-C2	-178.5
C2-N37	1.343	1.345	N36-C3-N37	121.3	126.8	N36-C3-N38-H39	166.3
C4-C6	-	1.486	C4-C1-H5	121.7	120.9	N36-C3-N38-H40	15.1
C2-C17	-	1.477	C4-C1-C2	116.6	117.8	N37-C3-N38-H39	-15.2
C28-F41	-	1.346	H5-C1-C2	121.7	121.2	N37-C3-N38-H40	-166.5
C33-F42	-	1.346	C1-C2-C17	-	122.3		
			C1-C2-N37	119.8	121.2		
			C17-C2-N37	-	116.5		
			C3-N37-C2	121.2	116.5		

[a] *– taken from reference [16]*

