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REGULAR ARTICLE

Biological Activity, Hydrogen Bonding and Natural Bonding Orbital Analyses of 2-fluoro L-histidine: A Computational Study

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Abstract: A theoretical study on a non-native amino acid, 2-fluoro-L-histidine at DFT- B3LYP/6-311++G** level has been carried out. The effect of substitution is discussed and it is found that all the changes can be accredited to the inductive effects of fluorine. AIM's topological analysis is performed for a confirmation of hydrogen bonding within the molecule. NBO analysis is used in order to understand various intra-molecular interactions and charge transfer due to hydrogen bonding interaction. Substituent effect is taken into account to discuss atomic charge distribution as well as electronic properties. Biological activity of the molecule is also calculated and discussed.

AMS subject classifications: 92EXX

Keywords: Histidine, fluorine substitution, hydrogen bond, DFT, NBO, SAR

1. Introduction

Proteins contain many amino acids of different types with a complex structure. The protein structure and its functions have been the subject of investigation for a long time [1]. The incorporation of unnatural amino acids leads to exploration of protein structure and functions [2, 3]. L-Histidine (L-His) is an essential amino acid found in protein. 2-Fluoro-L-Histidine (2-FHis) is an analog of L-His in which fluorine merely replaces one of the hydrogen in imidazole side chain as indicated in **Figure 1**. 2-FHis exhibits quite different properties with relatively isosteric change as fluorine closely mimics hydrogen. For example,

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fluorine reduces the pKa of the imidazole ring to 1.5 from its normal value of 6 [4]. This is why 2-FHis was the first compound used for antimalarial testing and found to have excellent antimalarial activity against Plasmodium falciparum parasites [5]. It also has been found to show antimetabolic activities in protein synthesis by inhibiting enzymatic induction [6, 7].

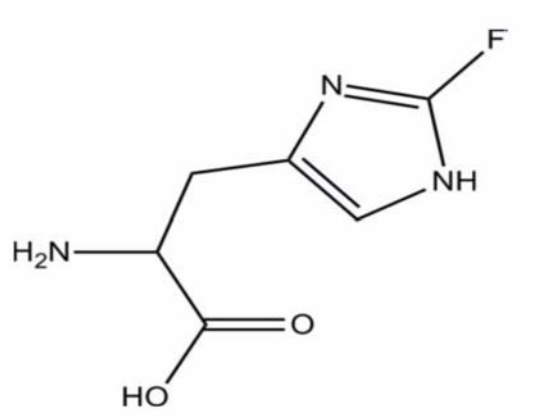

Figure 1: Schematic structure of 2-Fluoro-L-Histidine

Thus pharmacological importance of 2-FHis motivated us to perform a detailed theoretical study on this molecule. We have employed density functional theory (DFT) in order to explore distinct features of the title molecule. DFT is well recognized for its good compromise between computational accuracy and cost and has been extensively used for the study of biomolecules and medium sized molecular system [8]. Since various properties (electronic as well as chemical) of molecules are closely related to their geometry or structure. We have first attempt to discuss the effect of substitution on structural properties for 2-FHis. The analyses of HOMO-LUMO and MESP plots are then carried out in order to understand the relative stability. A confirmation of an intramolecular hydrogen bonding in 2-FHis is given using AIM analysis and its geometry is calculated by DFT. NBO analysis is also performed to explore interactions among different orbitals and lone-pairs taking place within the molecule. We have also discussed the substituent effect on atomic charge distribution as well as on the electronic properties of the molecule. The effect of fluorination on biological activities was evaluated and predicted by PASS online software.

2. Computational details

All the studies were carried out on Intel Core i3 2.20 GHz personal computer with the help of Gaussian 09 program package [9] in which Density Functional Theory (DFT) at B3LYP level [10] was used in conjunction with 6-311++G** basis set. The structure of molecule was

optimized to its minimum energy conformation. There was no imaginary frequency observed at this conformation. The Atoms In Molecule (AIM) analysis was performed using AIMAll program [11] at the same level of theory. This analysis is based on topological description of electron density and has become a powerful tool for understanding the properties of hydrogen bonds [12-15]. The natural bonding orbital (NBO) analysis was also performed by NBO 3.1 Program [16] as implemented in Gaussian 09 with the DFT method at B3LYP/6-311++G**. This analysis employs the second-order perturbation theory in order to give the energy of hyperconjugative interaction:

$$E^{(2)} = - n_i \langle i | F | j \rangle^2 / (\varepsilon_j - \varepsilon_i) \qquad (1)$$

where $\langle i | F | j \rangle$ is the Fock matrix element between the ith and jth NBOs having energies εi and εj respectively and ni is the population of ith donor orbital.

3. Results and Discussions

3.1. Effect of substitution on molecular geometry

The various structural parameters were calculated for optimized molecular geometry i.e. structure corresponding to minimum of energy as shown in **Figure 2**. The optimization was achieved by self-consistent field iterations at B3LYP/6-311++G** level. The calculated bond lengths and selected bond angles are listed in **Table 1**. The experimental values are adopted from X-ray crystallography on single crystal of 2-FHis [17]. The mere differences between the two are most likely due to calculation performed in the gas phase of molecule thus keeping intermolecular interaction aside. In condensed (crystal) phase, 2-FHis contains a number of intermolecular hydrogen bonding between various O and N atoms that certainly affect the structure and geometry of the molecule.

2-FHis is an isosteric analog of L-His [18] but the fluorination of imidazole ring causes the change in the geometric parameters. This is mainly attributed to the inductive effects of fluorine due to its highly electronegative character. The fluorine atom, F15 substituted at C6 of the ring pulls the shared electrons towards this atom from nitrogen atoms N17 and N18 resulting in a number of changes in bond lengths and bond angles. For example, the bond angle at C6 atom, N17-C6-N18 is enhanced to 114.2° with respect to the corresponding angle of 111.3° in L-His computed at the same level of theory. The major structural changes due to substitution of fluorine are listed in **Table 2**.

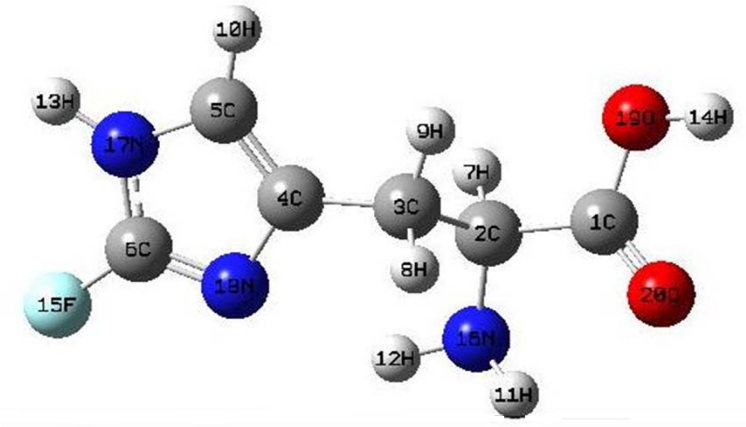

Figure 2: Molecular Geometry of 2-FHis optimized at B3LYP/6-311++G** level

Table 1 Bond-lengths (Å) and Bond-angles (degree) of 2-FHis calculated at B3LYP/6-311++G** level

Bond-length	Calculated	Experimental	Bond-angle	Calculated	Experimental
C1-C2	1.518	1.536	C2-C1-O19	111.9	116.6
C1-O19	1.355	1.256	O19-C1-O20	122.6	127.0
C1-O20	1.205	1.248	C1-C2-C3	107.7	110.0
C2-C3	1.564	1.545	C1-C2-N16	108.8	109.7
C2-H7	1.094	0.990	C3-C4-N18	121.7	120.7
C2-N16	1.453	1.492	C5-C4-N18	109.9	110.1
C3-C4	1.494	1.493	C4-C5-N17	105.6	106.6
C3-H8	1.095	1.000	H10-C5-N17	122.0	126.7
C3-H9	1.093	0.990	F15-C6-N17	119.8	118.7
C4-C5	1.368	1.354	F15-C6-N18	125.9	125.6
C4-N18	1.395	1.405	N17-C6-N18	114.2	115.7
C5-H10	1.076	0.950	C2-N16-H11	110.0	120.0
C5-N17	1.393	1.344	H11-N16-H12	108.6	120.0
C6-F15	1.326	1.317	C5-N17-C6	105.6	102.7
C6-N17	1.352	1.376	C5-N17-H13	127.8	127.6
C6-N18	1.291	1.292	C4-N18-C6	104.5	104.9
H11-N16	1.015	0.880	C1-O19-H14	107.1	109.5
H12-N16	1.015	0.880	C1-C2-H7	107.3	109.2
H13-N17	1.007	0.880	H7-C2-N16	109.4	109.2
H14-O19	0.969	0.840	H8-C3-H9	107.7	107.9

Table 2 Changes in structural parameters due to fluorination of L-His

Parameters	2-FHis (calc)[a]	2-FHis (expt)[b]	L-His (calc)[a]	L-His (expt)[c]
N17-C6-N18	114.2	115.7	111.3	112.2
C5-N17-C6	104.5	104.9	107.2	106.9
C4-N18-C6	105.6	102.7	106.1	104.9
N18-C4	1.395	1.405	1.383	1.382
N18-C6	1.291	1.292	1.313	1.327

Note: Bond lengths are in angstroms and bond angles in degrees.

[a]Calculated at B3LYP/6-311++G**

[b]Experimental value from Ref. [17]

[c]Experimental value from Ref. [18]

3.2. HOMO-LUMO and MESP Plots

The study of frontier molecular orbitals reveals important information about various chemical properties because these are the main orbitals that take part in chemical reactions and interactions. The highest occupied molecular orbital (HOMO) represents ability to donate an electron while lowest unoccupied molecular orbital (LUMO) denotes ability to accept it.

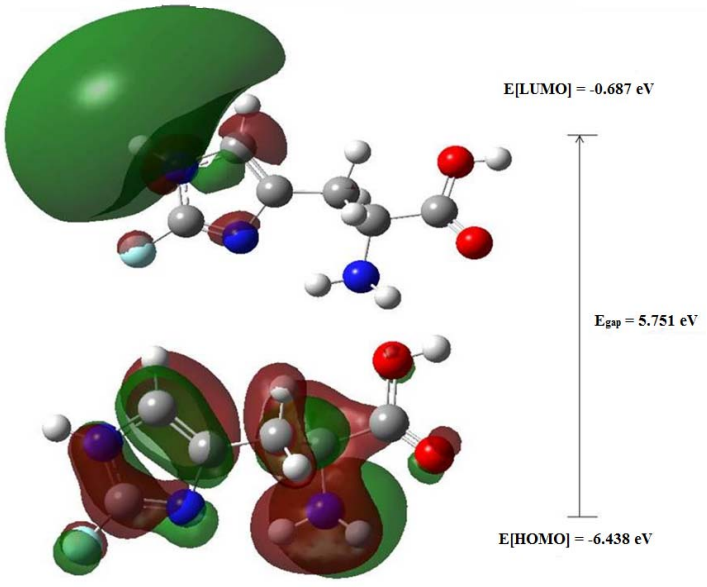

Figure 3: HOMO-LUMO plots for 2-FHis obtained at B3LYP/6-311++G** level

The HOMO-LUMO plots for 2-FHis with corresponding energy values are shown in **Figure 3**. Evidently, the HOMO with the energy of 6.4216 eV is located on the whole molecule while the LUMO with the energy of 0.6802 eV is contributed mainly by imidazole ring. The transition from HOMO→LUMO in 2-FHis indicates charge transfer to imidazole ring from methylene and amino group. The energy difference (E_{gap}) between HOMO and LUMO well describes the chemical reactivity of molecule. The lesser the energy difference, the greater the reactivity and vice versa [19]. In the present study, the energy gap is found to be 5.751 eV. For comparison, same computational procedure yields the energy gap of 5.654 eV in case of L-His. The increase in energy gap may indicate that 2-FHis is relatively more stable than L-His. Thus the substitution leads to the chemical stability of the molecule.

The molecular electrostatic potential (MESP) surface, a map of electrostatic potential on uniform electron density, is used to visualize charge or electron density distribution within the molecule. The importance of MESP lies in the fact that it simultaneously displays molecular size, shape as well as positive, negative and neutral electrostatic potential regions in terms of the colour grading (**Figure 4**). In the present context, colour code ranges between -0.07563 a.u. for deepest red and +0.07563 a.u. for deepest blue. The electronegative region lies in the vicinity of N of amine group with the isovalue of -0.05228 a.u. and the most positive one over the hydrogen attached with N of imidazole ring with the value of +0.07529 a.u. This possibly suggests that an electrophile will be attracted to the electron rich region of amine group while a nucleophilic attack will favour the positively charged region of imidazole ring.

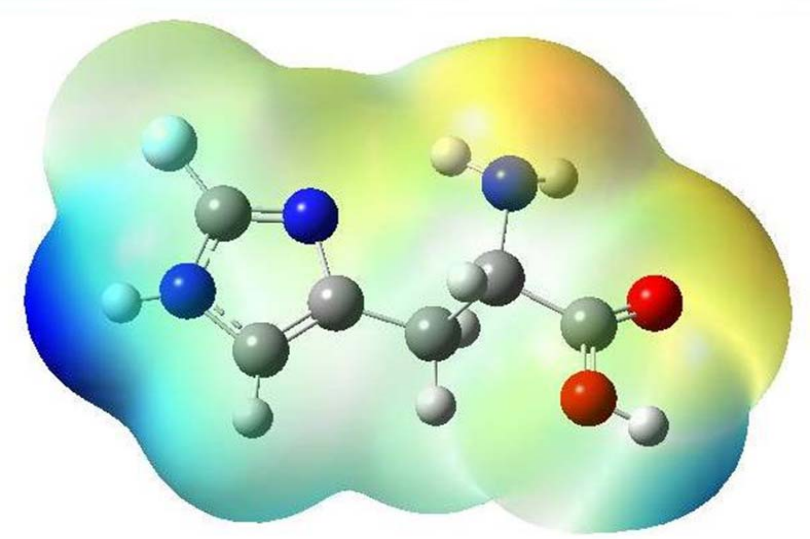

Figure 4: MESP plot for 2-FHis at B3LYP/6-311++G** level

3.3. Hydrogen bonding analysis

The various inter-molecular, intra-molecular and H–bonding interactions are characterized by the Quantum theory of Atoms in molecules (QTAIM) [20]. According to Rozas et al. [21], weak H–bonds characterized by Lapacian of ϱ at BCP > 0 and H_{BCP} > 0 are mainly electrostatic. Molecular graph of the title compound using AIMAll program at B3LYP/6–311++G** level is shown in **Figure 5**. Topological parameters viz. charge density (ϱ), Laplacian of ϱ, potential energy density (V), kinetic energy density (G) and total energy density (H) at the BCP of interacting atoms are listed in **Table 3**. As proposed by Espinosa et al., a proportionality between interaction energy (E) and potential energy density (V_{BCP}) at A··B contact exists as E = ½ (V_{BCP}) [22]. According to AIM calculations, the interaction energy of H12··N18 in 2-FHis is calculated as 2.485 kcal/mol. We have also repeated the same calculation on L-His which revealed the H-bond energy of 2.651 kcal/mol. This difference, however small, might suggest that the substitution weakens the bond.

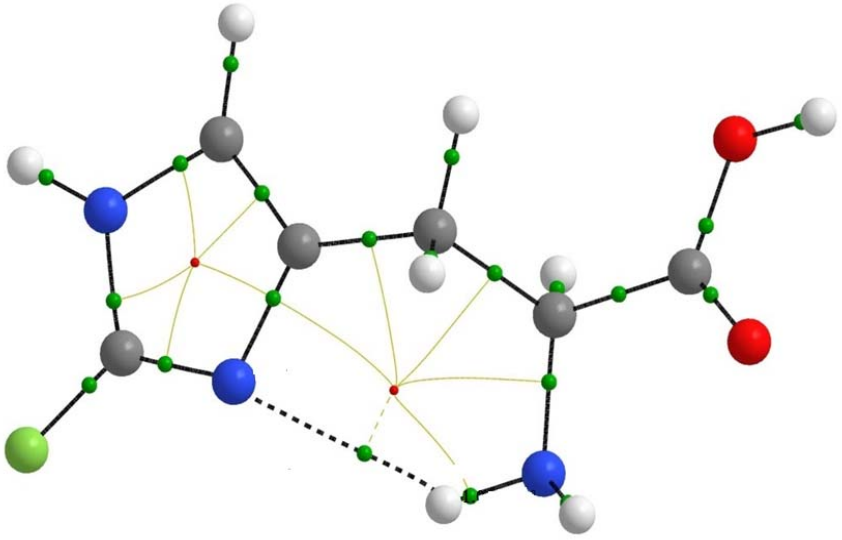

Figure 5: Molecular graph of 2-FHis showing hydrogen bonding interaction.

Thus the AIM analysis confirms a weak intramolecular hydrogen bonding interaction N16-H12···N18 between imidazole side chain and amine group. The geometrical parameters associated with this bond (**Table 3**) also suggest the interaction to be weak i.e. either electrostatic or dispersive [23]. The calculated length of this weak bond is 2.322 Å and the angle is greater than 90°. The bond distance between N18 of imidazole and N16 of amine is found to be 3.114 Å. The same distance is calculated to be 3.100 Å in L-His. Thus an increase

in the distance N··N again indicates the electron withdrawing behavior of the fluorine substitution.

Table 3 AIM calculated geometrical (in Å and degrees) and topological (in a.u.) parameters. Interaction energy E is given in kcal/mol.

Molecule	H12··N18	N16–H12··N18	ρ	$\nabla^2\rho$	G	V	H	E
2-FHis	2.322	134.0	0.01368	0.0458	0.00969	-0.00792	0.00177	-2.485
L-His	2.296	135.1	0.01460	0.0482	0.01026	-0.00845	0.00181	-2.651

3.4. NBO analysis

The NBO analysis is well appreciated for its strength to predict the hybridization of atomic lone-pairs as well as of the atoms involved in bonding orbitals. The analysis can further be extended for particularly H-bonded and other van-der Waal bonded complexes [24]. The donor (filled) NBO σ of the Lewis structure are well adopted to describe covalency effects while noncovalent delocalization effects are associated with σ→σ* interactions where σ* denotes acceptor (empty) NBO of the non-Lewis structure. The second order Fock matrix is used to describe the donor-acceptor interactions in NBO basis. The interactions result in charge transfer (CT) from Lewis into an empty non-Lewis orbital.

The second order perturbation theory analysis of Fock matrix for the molecule under study is given in **Table 4**. Only selected NBOs are shown in **Table 4** with the corresponding electron densities (ED). The hyperconjugative interactions formed by orbital overlap between bonding (C-C), (C-H) and antibonding (C-C), (C-N) stabilizes the system by intramolecular CT. The electron density of five conjugated single as well as double bonds of imidazole ring (~1.9 e) clearly demonstrate a strong delocalization for 2-FHis molecule. The interaction σ(C4-C5)→σ*(H13-N17) causes the stabilization by 3.95 kcal/mol which is enhanced to 11.69 kcal/mol for π(C4-C5)→π*(C6-N18). Another significant contribution comes from σ(C4 - N18)→σ*(C6 - F15) with the stabilization energy of 10.31 kcal/mol. The lone-pairs of fluorine n_1(F15) and n_2(F15)→σ*(C6 - N18) have stabilization energies of 1.34 and 7.95 respectively while the third lone-pair n3(F15) contributes 23.58 kcal/mol when it interacts with π*(C6 - N18). The interaction of first lone-pair of nitrogen N17 with the π-antibond (C6-N18) contributes to the greatest amount 53.50 kcal/mol in the stabilization. It is interesting to note that the lone pair N18 of imidazole ring involved in intramolecular hydrogen bonding N18···H12-N16 has ED value of 1.91e while non H-bonded N17 of the ring has 1.61e. A similar trend can be seen for ED of N-H antibonding in amine group, H-bonded H12-N16 with ED of 0.010e and non H-bonded H11-N16 with 0.009e and presumably it may explain small ED transfer from proton acceptor (N18) to the proton

donor H11-N16. The interaction between donor and acceptor causes stabilization of the molecule by an amount of 1.53 kcal/mol.

Table 4 Second order perturbation analysis of Fock matrix in NBO basis

Donor		Acceptor		$E^{(2)}$	$\varepsilon_j - \varepsilon_i$	$<i \mid F \mid j>$
NBO *(i)*	ED (e)	NBO *(j)*	ED (e)	*(Kcal/mol)*	*(a.u.)*	*(a.u.)*
σ(C1 - C2)	1.97161	σ*(H12 - N16)	0.01057	2.09	1.11	0.043
σ(C1 - C2)	1.97161	σ*(H14 - O19)	0.01125	2.19	1.03	0.042
σ(C2 - C3)	1.95656	π*(C1 - O20)	0.19910	3.94	0.60	0.045
σ(C2 - C3)	1.95656	π*(C4 - C5)	0.28862	2.56	0.61	0.038
σ(C2 - H7)	1.96554	σ*(C1 - O20)	0.02202	3.49	1.11	0.056
σ(C2 - H7)	1.96554	π*(C1 - O20)	0.19910	2.49	0.51	0.033
σ(C2 - H7)	1.96554	σ*(C3 - H8)	0.01764	2.45	0.90	0.042
σ(C2 - H7)	1.96554	σ*(H11 - N16)	0.00984	2.68	0.95	0.045
σ(C2 - N16)	1.98773	σ*(C1 - O19)	0.09852	2.08	1.06	0.043
σ(C3 - C4)	1.97893	σ*(C5 - N17)	0.00963	1.00	1.06	0.029
σ(C3 - H9)	1.97318	σ*(C2 - N16)	0.01393	3.62	0.87	0.050
σ(C3 - H9)	1.97318	σ*(C4 - N18)	0.02236	6.32	0.96	0.070
σ(C4 - C5)	1.98033	σ*(C6 - F15)	0.05382	0.83	1.00	0.026
σ(C4 - C5)	1.98033	σ*(H13 - N17)	0.01547	3.95	1.11	0.059
π (C4 - C5)	1.87895	π*(C6 - N18)	0.39755	11.69	0.27	0.054
σ(C4 - N18)	1.96400	σ*(C6 - F15)	0.05382	10.31	1.03	0.092
n1 (F15)	1.99028	σ*(C6 - N18)	0.02336	1.34	1.64	0.042
n2 (F15)	1.95853	σ*(C6 - N18)	0.02336	7.95	1.02	0.081
n3(F15)	1.92274	π*(C6 - N18)	0.39755	23.58	0.43	0.099
n1(N17)	1.61657	π*(C4 - C5)	0.28862	26.47	0.31	0.083
n1(N17)	1.61657	π*(C6 - N18)	0.39755	53.50	0.28	0.110
n1(N18)	1.91001	σ*(H12 - N16)	0.01057	1.53	0.86	0.033
n1(O19)	1.97711	σ*(C1 - O20)	0.02202	7.02	1.25	0.084
n2(O19)	1.82774	π*(C1 - O20)	0.19910	43.58	0.35	0.112
n2(O20)	1.84740	σ*(C1 - O19)	0.09852	33.54	0.61	0.130
n2(O20)	1.84740	σ*(C1 - C2)	0.06660	17.60	0.65	0.097

Note- $E^{(2)}$ is given by Eq. (1).

3.5. Substituent effects on molecular properties

3.5.1. Atomic charge distribution

The charge distribution on atoms in molecule is a feature that can be explored only theoretically. There is no corresponding experimental technique to perform this analysis. Atomic charges of 2-FHis and L-His were computed using natural population analysis (NPA) scheme at B3LYP/6-311++G** level. **Figure 6** plots the partial charges on the atom excluding F15/H15 for a visual indication. It is apparent from the plot that the substitution tends to modify charge distribution appreciably on C6, H13, N17 and N18 atomic sites.

The carbon atoms were found to carry both positive and negative charges. The maximum charge on N16 atom of methylene group was seen due to effect of negatively charged carbon. The nitrogen atoms of imidazole ring as well as of amine group all are negative and the same for oxygen atoms of carboxylic group. Thus all N and O atoms accept electrons. The more interesting is the charges on C6 atom. Substitution of fluorine causes charge transfer from carbon to fluorine atom (C6→F15) advocating its electron withdrawing capability. All the other changes are closely related to this fact. It is also interesting to note that charges on hydrogen atoms have only positive values. This clearly explains the charge transfer from H to N, C and O atoms (H10→C5, H13→N17, H14→O19, H11/H12→N16).

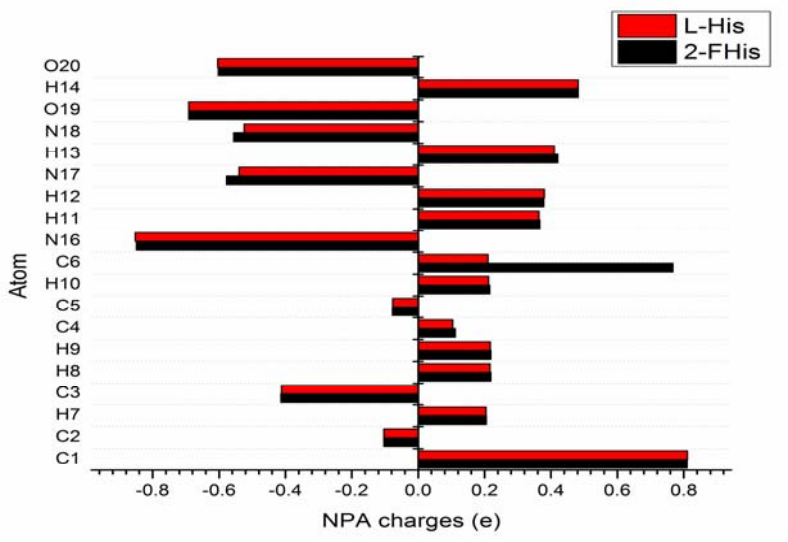

Figure 6: Partial atomic charges for 2-FHis and L-His by NPA scheme. Charges on F15/H15 are not shown.

3.5.2. Electronic properties

The frontier molecular orbitals energies are used to find useful global parameters describing reactivity of molecule. The popular Koopmans' theorem describes ionization potential (I) and electron affinity (A) as the negative of energy eigen values of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), respectively.

Other parameters viz. absolute electro-negativity (χ), chemical hardness (η) and electrophilic index (ω) can be found using finite-difference approximations [25-28]. The dipole moment (μ) of molecule gives a signature about charge distribution and geometry of the molecule. The calculated values for various parameters are listed in **Table 5** for 2-FHis as well as L-His.

Table 5 Electronic parameters calculated for 2-FHis and L-His at B3LYP/6-311++G**

Parameters	2-FHis	L-His
I (eV) $= -E[HOMO]$	6.438	6.296
A (eV) $= -E[LUMO]$	0.687	0.642
χ (eV) $= ½ (I + A)$	3.562	3.469
η (eV) $= ½ (I - A)$	2.875	2.827
ω (eV) $= ½\eta (\chi 2)$	2.206	2.128
μ (D)	5.871	5.984

3.6. Biological Activity

In order to explore and predict the pharmacological effects and biological activities of molecule, we have used PASS software [29]. PASS predicts 900 pharmacological effects, molecular mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity. This prediction is based on the analysis of Structure Activity Relationships (SAR) for the training set including more than 46,000 drugs, drug-candidates and lead compounds whose biological activity is determined experimentally. An average accuracy of prediction in leave-one-out cross-validation is about 85% [30]. Being an analogue of L-His, many biological activities of 2-FHis closely mimic that of L-His. The effect of substitution causes the change in activity values as well as results in some additional activities. For the sake of clarity in our discussion, we have listed only these additional activities predicted by PASS in Table 6 with $P_a > 70\%$. This clearly indicates that the molecule will most likely exhibit these activities experimentally. Furthermore, the probability that the molecule is a close analogue of the known drug is quite high.

Table 6 Some biological activities of 2-FHis predicted by PASS software

Activities	P_a	P_i
Lymphocytopoiesis inhibitor	0.997	0.000
Hematopoietic inhibitor	0.906	0.001
HIF1A expression inhibitor	0.882	0.007

Hematopoiesis is a recursive process of generation of blood cellular components and cell division [31]. Lymphocytopoiesis, also termed as lymphoid hematopoiesis, is related to

the generation of white blood cells viz. lymphocytes [32]. Thus the molecule may result in the inhibition of blood cell generation or division in general and it is more effective for white blood cells. Hypoxia-inducible factor 1-alpha is a protein encoded by HIF1A gene in humans [33]. The over expression of a natural antisense transcript (aHIF) of this gene is associated with a kidney cancer [34]. 2-FHis can be found to be active against inhibition of HIF1A expression.

4.Conclusions

On the basis of our studies, we can say that the inductive effects of fluorine greatly influence the equilibirium geometry and intra-molecular hydrogen bonding interaction of the title molecule. NBO analysis reveals that the greatest stabilization is caused by interaction of first lone-pair of nitrogen N17 with the π-antibond (C-N) and indicates clearly a small amount of electron density transfer due to hydrogen bonding interaction. The calculation also reveals the fact that the substitution increases the biological activity of the molecule.

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