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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].

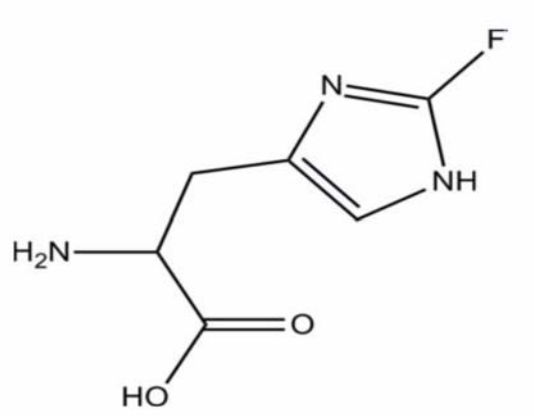


**Figure 1:** Schematic structure of 2-Fluoro-L-Histidine

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