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A Hirshfeld Surface Analysis and Crystal Structure of 2'-[1-(2-Fluoro-Phenyl)-1H-tetrazol-5-Yl]-4-Methoxy-Biphenyl-2-Carbaldehyde

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ABSTRACT

The title compound, $C_{21}H_{15}FN_4O_2$ is synthesized and characterized by ^{1}H NMR, LC-MS and finally confirmed by single crystal X-ray diffraction method. This molecule crystallizes in the monoclinic crystal system and space group $P2_1/c$, with crystal parameters a = 9.4386(5) Å, b = 20.8082(1) Å, c = 9.4338(6) Å, β = 99.566(2)^0, Z = 4 and V = 1826.98(19) Å^3. The mean planes of fluro-phenyl moiety makes a dihedral angle of 21.51 (7)^0 with biphenyl moiety. The molecules are connected by hydrogen bonds of the type C---H...O and C---H...F. In addition, crystal structure is stabilized with π … π (exhibits intramolecular interaction) and C---O... π interactions. The intercontacts in the crystal structure are analyzed using Hirshfeld surfaces computational method.

Keywords: Crystal Structure; Intermolecular Interactions; Hirshfeld Surfaces

1. Introduction

Tetrazoles and its derivatives are the most important in the field of medicinal chemistry and found wide spectrum of applications in coordination chemistry because of their multiple coordination status, acting as ligands to metal ions and for the construction of novel metal-organic frameworks [1-3]. And they exhibit biological activities like antibacterial [4,5], antifungal and anticonvulsant [6], analgesic [7], antitubercular activity [8] and anti-cancer activity [9]. Also, 1,5-disubstituted tetrazoles used as anti-inflammatory and anti-hypertensive agents [10,11], such as Losartan [12,13]. Biphenyl tetrazoles have also demonstrated activities as stimulators of growth hormone release [14], metallo-protease inhibitors [15,16] and chloride channel blockers [17]. And, the 5-substituted 1H-tetrazole moiety has been used in the drug discovery as a bioisotere for the corboxylic acid group [18]. In addition, tetrazole compounds are used as new energetic materials because of their good thermal stability due to the presence of aromatic ring system (5-Azido-1*H*-tetrazole) [19]. Synthesizing the organic compounds in the Suzuki-Miyaura cross-coupling is one of the powerful methods for aromatic C-C bond formation [20]. We report here, the synthesis, spectroscopic studies, structural studies by X-ray diffraction method and analysis of intercontacts by Hirshfeld surfaces computational method of 2'-[1-(2-Fluoro-phenyl)-1H-tetrazol-5-yl]-4-methoxy- biphenyl-2-carbaldehyde.

2. Experimental

All reagents were purchased as reagent grade and used without further purification. The reaction was monitored and determination of product was accomplished by TLC technique. The melting point was determined on SELACO-650 hot stage apparatus. Elemental analysis (C, H, N) were determined with Vario-EL instrument. ^{1}H NMR spectra were recorded on a bruker DRX 300 MHz spectrometer using DMSO-d6 as solvent and TMS as internal standard. Chemical shifts are given in δ (ppm).

3. Synthesis and Crystallization of the Title Compound

The title compound is obtained using the Suzuki-Miyaura

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coupling (**Figure 1**) of the compound 1-(2-Flurophenyl)-1*H*-tetrazole (1mmol), 1), with 2-formyl-4-methoxy phenyl boronic acid (1 mmol) in presence of sodium carbonate (15 mmol) and palladium catalyst in a mixture of dimethyl ether (DME) and water in the ratio 3:1. Then the mixture was degasified by bubbling with nitrogen for 15 minutes. After degasify $PdCl_2$ $(PPh_3)_2$ [dikis] (0.05 mmol) was added. The resultant mixture was heated at 80˚C under nitrogen atmosphere for 5 hours. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to remove DME. Then residue was dissolved with ethyl acetate (25 mL), washed with 0.1 N hydrochloric acid (2 * 25 mL), followed by brine solution (2 * 25 mL). Then, the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude 2'-[1-(2-Fluorophenyl)-1H-tetrazol-5-yl]-4-methoxy-biphenyl-2-carbaldehyde. 2), which was purified by column chromatography over silica gel (60 - 120 mesh) using Hexane: Ethyl acetate mixture in 8:2 ratios as eluent. The pure compound 2 was crystallized in ethyl acetate and hexane to obtain colorless single crystals.

4. Spectral Analysis

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.90 (s, 1H), 7.57 - 7.52 (m, 2H), 7.35 - 7.32 (m, 2H), 7.20 (s, 1H), 7.14 (t, J = 6.0 Hz, 2H), 6.98 (t, J = 7.8 Hz, 2H), 6.69 - 6.60 (m, 2H), 3.80 (s, 3H) (**Figure 2**). Mass, calculated: 374.36 found: 375 (M^+ + 1) Elemental analyses, calculated: C, 67.37; H, 4.04; F, 5.07; N, 14.97; O, 8.55. Found: C, 67.57; H, 4.28; F, 5.02; N, 14.773; O, 8.76 (**Figure 3**). Melting point (˚C): 103 - 105 (Uncorrected).

5. Crystal Structure Determination

A good single crystal of the title compound with dimension 0.30 × 0.35 × 0.35 mm was chosen for X-ray diffraction study. Data collection and cell refinement were carried out using Bruker Kappa ApexII CCD diffractometer [21] with Mo$K\alpha$ radiation. The absorption correction was applied using multi-scan technique for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma$ (F^2). The structure was solved by the direct methods using SHELXS-97 [22,23]. All the non-hydrogen atoms were revealed in the Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [22,23] with isotropic temperature factors for all the atoms was done. Refinement of non-hydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on their parent atoms. About 165 parameters were refined with 3213 unique reflections which saturated the residuals to R1 = 0.0375 and wR2 = 0.1071. The details of the crystal data and refinement are given in **Table 1**. **Table 2** lists the hydrogen bonds. All the figures (*ORTEP*, packing and hydrogen bonding) were plotted using *MERCURY* [24]. Hirshfeld surface analyses were carried out and finger print plots were plotted using *CRYSTALEXPLORER* [25]. Electrostatic potentials were calculated using *TONTO* [26,27].

6. Results and Discussion

The dihedral angle between mean planes of fluoro-phenyl moiety and benzeze ring (C2/C3/C4/C5/C6/C7 attached with methoxy and carbaldehyde species) is $8.03(8)^0$. And, the mean planes of rings making dihedral angle with each other is as follows; the tetrazole ring (N1/N2/N3/N4/C15) makes $49.16(11)^0$ with benzene ring (C14/C13/C12/C11/C10/C9), $57.38(10)^0$ with fluro-phenyl moiety and $54.86(10)^0$, with phenyl moiety [(C2/C3/C4/C5/C6/C7) attached with methoxy and carbaldehyde species]. Similarly, the benzene ring (C14/C13/C12/C11/C10/C9) makes a dihedral angle of $64.67(10)^0$ with fluoro-phenyl moiety. Also, it makes an angle of $56.86(10)^0$ with phenyl moiety (C2/C3/C4/C5/C6/C7) attached with methoxy and carbaldehyde species. The overall geometry of the title compound is similar to 1-(4-nitrophenyl)-1*H*-tetrazol-5-amine and {(*E*)-[1-(4-ethoxyphenyl)-1*H*-tetrazol-5-yl] iminomethyl} dimethylamine [28].

Figure 4 represents the *ORTEP* diagram of the title molecule. The molecules in the unit cell are connected by hydrogen bonds C10-H10...F1, C12-H12...O2 and C20-H20...O2 (**Table 2**). And, **Figure 5** shows the packing of the molecules are arranged in the fishing net pattern. The observed weak interactions π...π and C---O...π helps in crystal structure stabilization. The intramolecular π...π interactions exists between centroid (*Cg*4: C16/C17/C18/C19/C20/C21) of fluoro-phenyl moiety and benzene ring (*Cg*2: C2/C3/C4/C5/C6/C7) with a distance 3.7806(10) Å [x, y, z] (**Figure 6**). And, inter molecular π…π exists between face to face (*Cg*4 and *Cg*4) interactions with a distance of 3.6875(11) Å [$2 - x$, $-y$, $1 - z$]. In addition to this C---O...π (*Cg*4) interaction exists between carbaldehyde moiety (C8-O2) and *Cg*4 with a distance of 3.9551(15) Å [x, y, z].

7. Hirshfeld Surface Analysis

The intermolecular interactions of the title compound are quantified using Hirshfeld surface analysis. This approach is a graphical tool for visualization and understanding of intermolecular interactions [25]. Here, we estimate the intermolecular contacts, which are shown in **Figure 7**. The chart indicates that the contribution of inter-contacts to the Hirshfeld surfaces, H...H (36%), N...H (19%), C...H (16%), O...H (14%), F...H (7%) and others (C...C, N...N, C...O, N...F; 8%). These inter-contacts

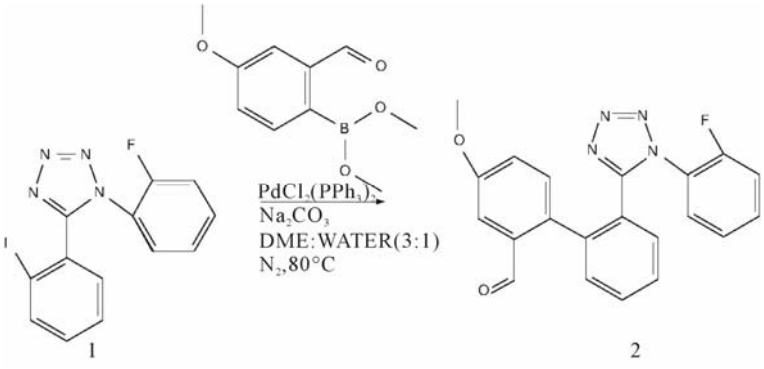


Figure 1. Schematic diagram and synthesis pathway of the title compound.

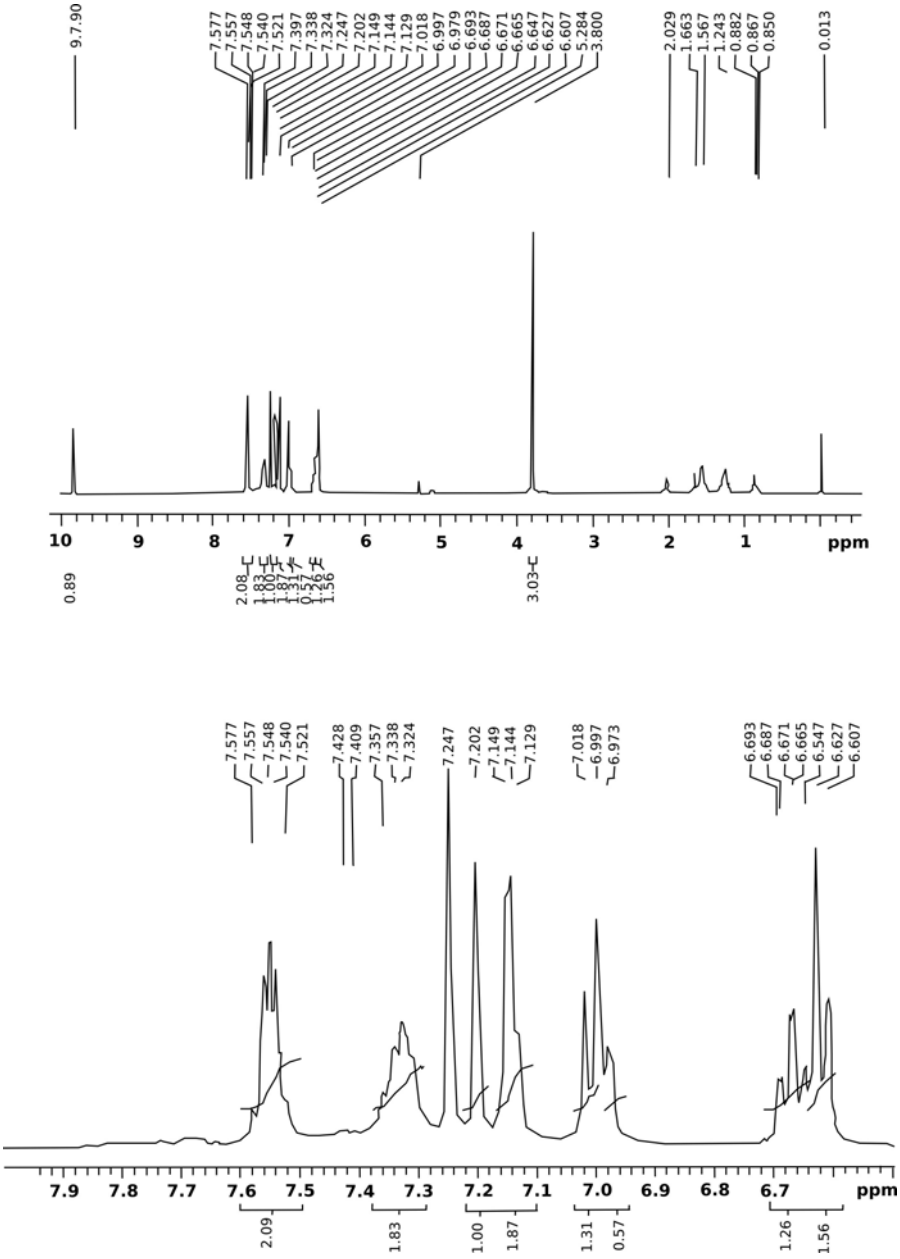
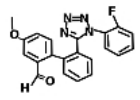


Figure 2. ^{1}H NMR spectra of the title compound.



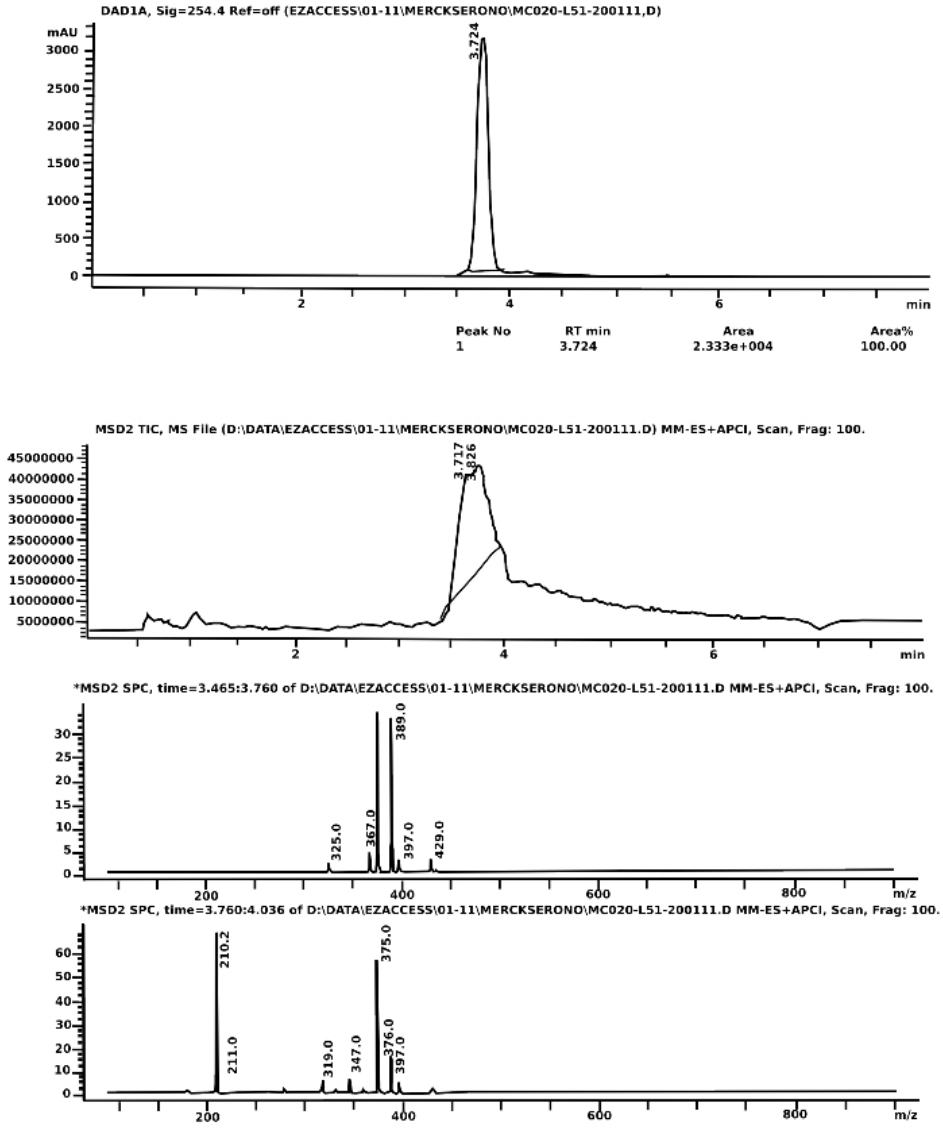


Figure 3. LC-MS spectra of the title compound.

are highlighted by conventional mapping of d_{norm} on molecular Hirshfeld surfaces are shown in **Figure 8**. The red spots over the surface indicate the intercontacts involved in the hydrogen bonds. Further, intercontacts were plotted with fingerprint plots (**Figure. 9**). H...H intercontacts, (**Figure 9(a)**) shows large surfaces, whereas the O...H plot (**Figure 9(d)**) shows the presence of O...H contact with the two characteristic wings. The N...H contact plot is shown in **Figure 9(b)**. The intercontacts F...H **(Figure 9(e))** showing two narrow pointed wings provide evidence for C-H...F non-classical hydrogen bonds. And, C...H plot reveals the information of inter molecular hydrogen bonds.

The electrostatic potential is mapped on Hirshfeld surface using STO-3G basis set at the Hartree-Fock theory over the range of ± 0.025 au (**Figure 10**). The positive electrostatic potential (blue region) over the surface indicates hydrogen donor potential, whereas the hydrogen bond acceptors are represented by negative electrostatic potential (red region) [27]. The crystal geometries were

Table 1. Crystal data, data collection and structure refinement.

CCDC 933058
Empirical formula $C_{21}H_{15}N_4O_2$
Formula weight 374.37
Temperature 293 K
Wavelength 0.71073Å
Crystal system monoclinic
Space group *P*21/*c*
Unit cell dimensions *a* = 9.4348(5) Å b = 20.8082(1) Å c = 9.4338(6) Å *β* = 99.566(2) °
Volume 1826.98(19) Å^3
Z 4
Calculated density 1.361 Mg/m^3
Absorption coefficient 0.098 mm^{-1}
$F_{(000)}$ 776
Crystal size 0.30 × 0.35 × 0.35 mm
Theta range for data collection 2.4˚ to 25.0˚
Limiting indices −11 <= h <= 11, −24 <= k <= 24, −11 <= l <= 11
Reflections collected / unique 16483/3213 [$R_{(int)}$ = 0.029]
Refinement method Full-matrix least-squares on F^2
Data/restraints/parameters 3213/0/255
Goodness-of-fit on F^2 1.04
Final *R* indices [$I > 2\sigma(I)$]R_1 = 0.0375, wR_2 = 0.1071
Largest diff. peak and hole 0.16 and −0.18 e.Å^{-3}

Table 2. Hydrogen bonds [Å, 0].

D-H…A	D-H*	H-A*	D-A	D-H…A	Symmetry codes
C10-H10...F1	0.93	2.50	3.388(2)	160	*x*,1/2 − *y*,−1/2 + *z*
C12-H12...O2	0.93	2.57	3.352(2)	143	−1 + *x*,*y*,*z*
C20-H20...O2	0.93	2.52	3.430(2)	167	*x*,1/2 − *y*,1/2 + *z*

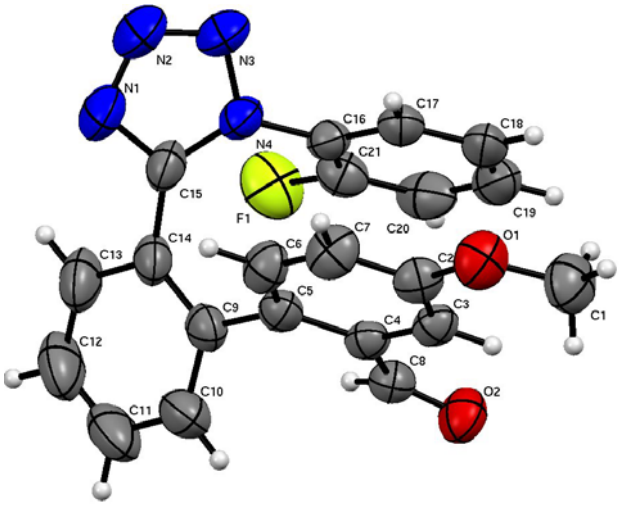


Figure 4. Molecular structure of the title compound showing the atomic numbering system. Displacement ellipsoids are drawn at the 50% probability.

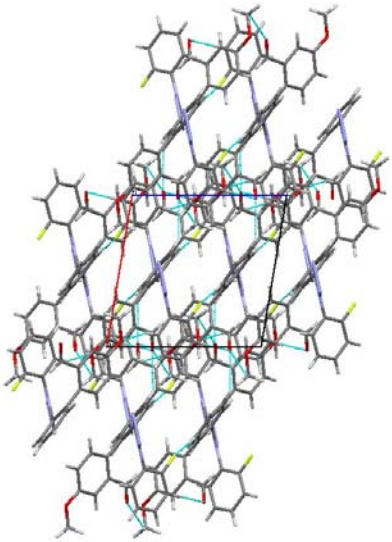


Figure 5. Packing diagram of the title molecule along b-axis. Dotted lines represents hydrogen bonds.

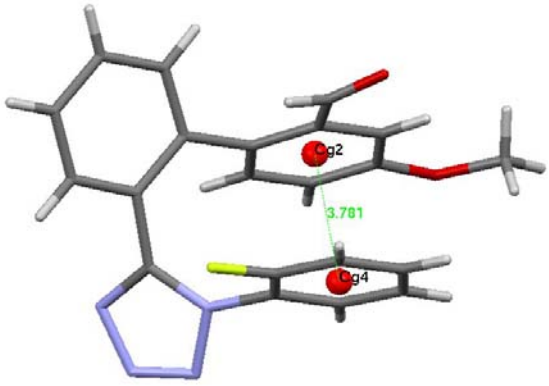


Figure 6. Intramolecular interaction between *Cg*2 and *Cg*4. Dotted lines (green) represents interaction.

Figure 7. Hirshfeld surface: Percentage of various intermolecular contacts contributed to the Hirshfeld surface.

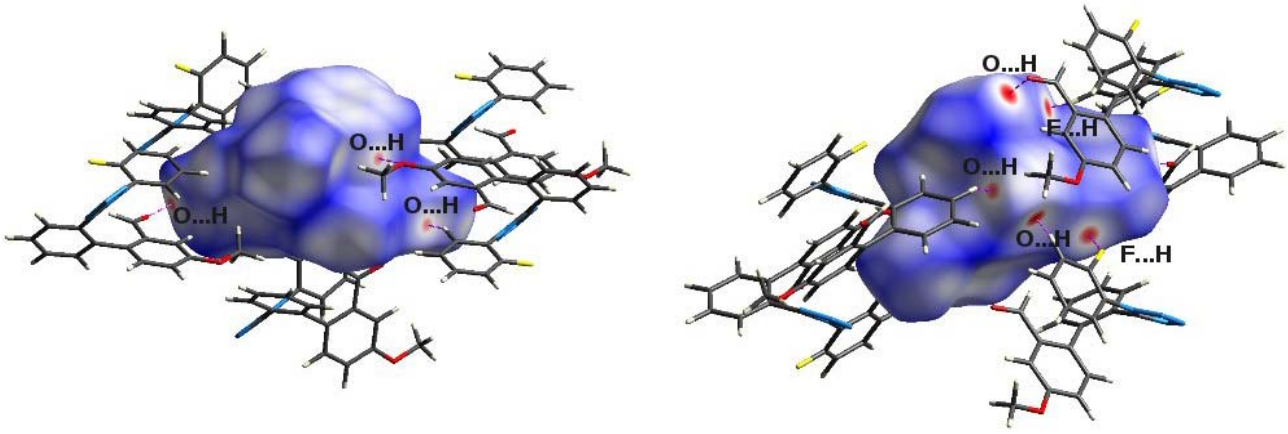


Figure 8. d_{norm} mapped on Hirshfeld surface for visualizing the intercontacts of the title compound. Color scale in between −0.18 au (blue) to 1.4 au (red). Dotted lines (magenta) represent hydrogen bonds.

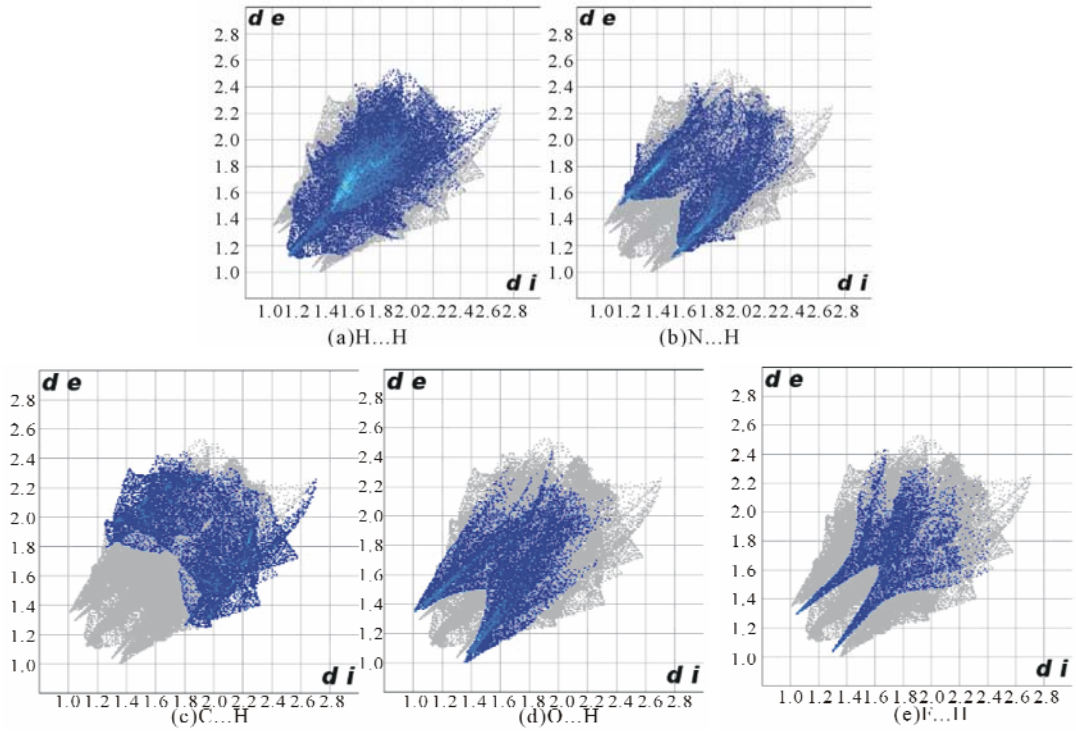


Figure 9. Fingerprint of the title compound, (a) H...H, (b) C...H, (c) C...H, (d) O...H and (e) F...H. The outline of the full fingerprint is shown in gray. d_i is the closest internal distance from a given point on the Hirshfeld surface and de is the closest external contacts.

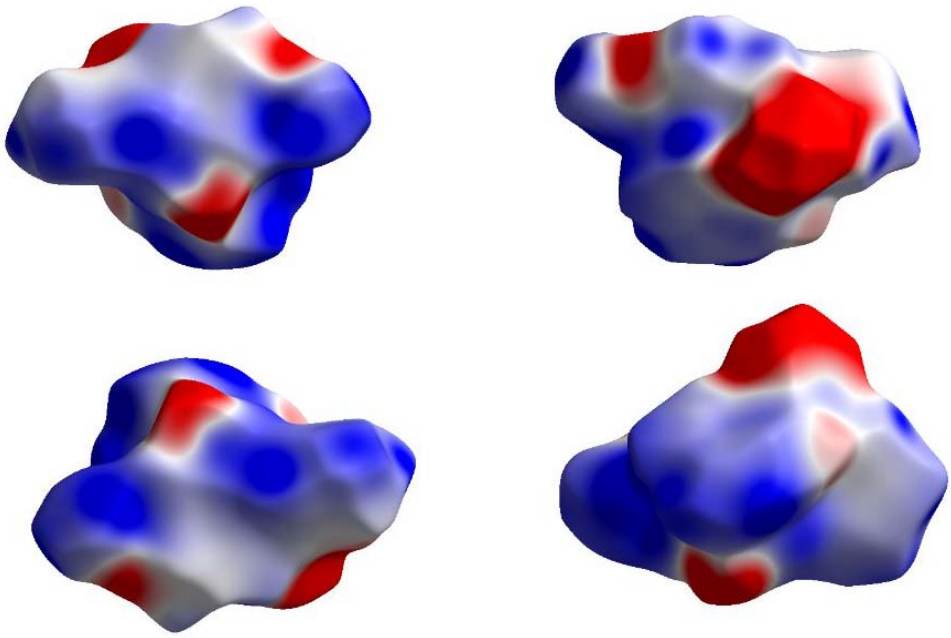


Figure 10. Electrostatic potential mapped on Hirshfeld surface (different orientation) with ± 0.25 au. Blue region corresponds to positive electrostatic potential and red region to negative electrostatic potential.

used as input to the *TONTO* [26] integrated with *Crystal explorer* [25].

8. Conclusion

The dihedral angle between fluro-phenyl moiety and biphenyl moiety is 21.51 $(7)^0$. The molecules are connected by C-H...O and C-H...F hydrogen bonds. In addition, the short contacts of the type π...π and C---O...π help in crystal stabilization. The Hirshfeld surface analysis with finger plots and electrostatic potential map reveals the percentage of intermolecular contacts and distribution of electrostatic potential of the title compound.

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