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HIRSHFELD SURFACE AND SUPRAMOLECULAR ANALYSIS OF ELECTRON WITHDRAWING GROUP ON DIHYDROPYRIMIDINE COMPOUND

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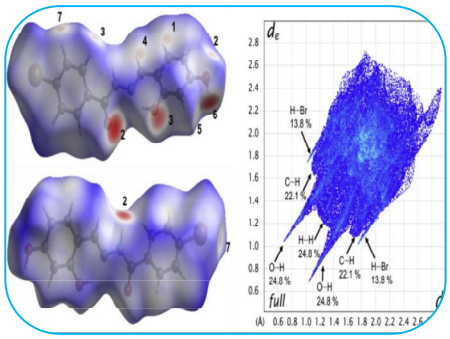
ABSTRACT



The dihydropyrimidine is a pharmaceutically active compound which was first prepared by Pietro Biginelli in 1893. It is simple multicomponent product of aryl aldehyde, betaketoester and urea or thiourea. In the present study we done the CSD analysis and reported dihydropyrimidine compound were analyzed for their crystallographic, and interaction study. From Mercury software analysis it is observed that the N-H···O interaction play important role to form dimer in their crystal packing which further form ring motif. Further, the crystal packing were consolidate through C-H···O, O-H···O type of interactions. The short molecular interactions and its contribution in the crystal structure were calculated using Hirshfeld surface analysis. Which suggest that after H···H interactions the O···H contributed more. The significant interactions were analyzed in the main result part section.

KEYWORDS : *dihydropyrimidine , pharmaceutically , multicomponent product.*

INTRODUCTION:

Heterocyclic compounds are an important class of molecules in organic chemistry, as they are present in natural products and their use in pharmaceuticals chemistry. Heterocyclic compounds shows biological activity in many small drugs molecules, due to their ability to hydrogen bond, alter polarity, and modulate lipophilicity at specific sites in the pathogen or host .One of the hetrocyclic compound with molecular formula C4H6N2 is dihydropyrimidine. Dihydropyrimidines (DHPMs) are well-known scaffolds that are easily prepared through condensation reaction of urea/thiourea, β-ketoester, and aryl aldehyde. It was first reported by Italian chemist Pietro Biginelli in 1891. The various substituents on the DHPMs nucleus make it biologically active nucleus (1).

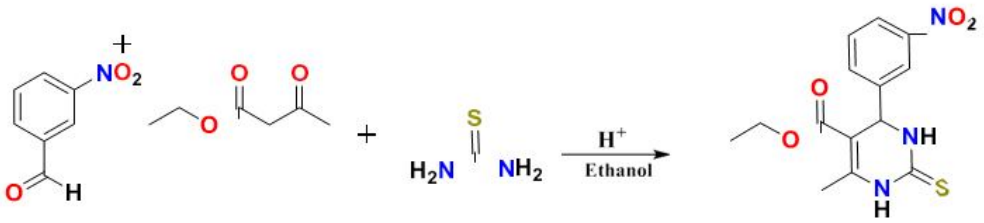
DHPM derivatives have a significant role in medicinal chemistry for various pharmacological activities, such as anticancer, antibacterial, antifungal, antihypertensive, antitubercular, antimalarial, antiviral, and anti-inflammatory activities Also, cardio- vascular drugs such as potent calcium channel inhibitor, pancreatic neuroendocrine neoplasm therapy and topoisomerase inhibitors have used compounds from DHPM for treatment. In the current study we have done the supramolecular analysis of reported dihydropyrimidine based molecule for their better understanding of structural property relationship. The details of analysis part are added in the result and discussion section.

The compound shown in scheme 1 is the dihydropyrimidine derivative (molecular formula C14H15N3O4S) with electron withdrawing nitro group on phenyl ring.

COMPOUND NAME:

Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Scheme 1: Schematic representation of reported dihydropyrimidine based derivative



Cambridge Crystallographic Data Centre (CCDC)

The **Cambridge Crystallographic Data Centre (CCDC)** is a non-profit organization. In 1965, with the aim of available crystal structure data in a systematic manner to everyone, Dr. Olga Kennard OBE FRS and her group started collecting published bibliographies, for all small molecules studied by X-RAY and neutron diffraction technique. At the starting, this data was in printed form as in published journals and it manually retyped. Later, with development it took in electronics form and today standard format .cif file.

The **Cambridge Structural Database (CSD)** is a repository and a validated and curated resource for the three-dimensional structural data of organic, metal-organic and organometallic molecules. The CSD is overseen by the not-for-profit incorporated company the Cambridge Crystallographic Data Centre, CCDC. The scientists around the World can sumbbit their data obtained from X-RAY crystallography, electron and neutron diffraction to CSD. This is freely accessible to us on CCBC website. Currently more than one million crystal structure data available in the CSD database and this number increases day by day. There are certain software developed by CCDC such as Mercury, Con Quest, Mogul (2). We will discuss about Mercury in detail in next section.

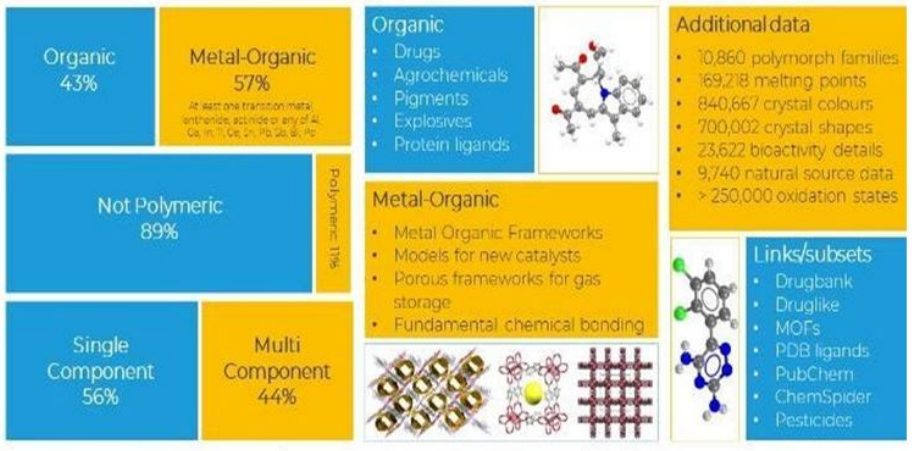


Figure 1: Content of CSD

Mercury Software Analysis:

Crystals are solid materials where atoms and molecules are arranged in a highly ordered (periodic) microscopic structure. Unit cell is the smallest repeating unit of the crystal. To interpret the crystal structure and types of interactions present in the molecule, we perform different diffraction techniques and analyse them with the help of computer software. The Cambridge Crystallographic Data Centre (CCDC) developed and launched two programs, named ConQuest and Mercury that run under Windows and various types of Unix, including Linux. ConQuest as a search interface to the Cambridge Structural Database (CSD), with Fortran code, where we can search number of two dimensional and three-dimensional sub structures.

The program Mercury was first launched by the Cambridge Crystallographic Data Centre (CCDC) in 2001 as a crystal structure visualization tool. The mercury program entirely written in object-oriented C++. Current version Mercury can read ".cif", ".mol", ".mol2", ".pdb", ".res", ".sd" and ".xyz" types of files. Mercury has its own file format with filename extension ".mryx". Mercury has free-to-access version available for any researcher so become popular among the scientists. With the time and demand Mercury Software get updated and came with newer and newer version with more functions. Mercury helps three-dimensional visualization of crystal structure and assists in drawing and analysis of crystal packing and intermolecular interactions. Along with visualization, Mercury is a platform for delivering analysis, design and prediction functionality of a crystal structure (3-7).

Following are the Application of Mercury software:-

- We can rotate and translate the 3D crystal-structure display, and view down cell axes, reciprocal cell axes, and the normals to least-squares and Miller planes.
- We can see the structure in different 3D styles such as Wireframe, Capped Stick, Ball and Stick, Spacefill, Ellipsoid and Polyhedral.
- With the help of Mercury we can measure and display distances, angles and torsion angles involving atoms, centroids and planes.
- One can create and display centroids, least-squares mean planes and Miller planes.
- We can display unit cell axes, the contents of any number of unit cells in any direction, or a slice through a crystal in any direction.
- We can observe free space in crystal structures, or voids, can be calculated and displayed as coloured surfaces.
- We can display space-group symmetry elements.
- Useful to build and visualise a network of intermolecular contacts.
- Can perform graph set analysis of hydrogen-bonding patterns.
- We can manually edit structures including the addition of hydrogen atoms, the addition of bonds, the editing of bond types, the removal of atoms, bonds and molecules, the addition of atoms and the editing of atom types or labels.
- We can automatically assign bond-types, standardise bond-types to Cambridge Structural Database conventions and to add missing hydrogen atoms.
- Useful to calculate, display and save the powder diffraction pattern for the structure.
- .We can generate structure representations as high-resolution graphics, movies or 3D printable model files.

Hirshfeld Surface Analysis:

Knowledge about intermolecular interaction in molecule is important in the design of new solids with desirable physical and chemical properties. Intermolecular forces such as weak and strong hydrogen bonds, halogen-halogen interactions, π···π contacts, Van der Waals forces and identify strong, directional, reliable non-covalent interactions, in a crystal give valuable information to us.

The concept of Hirshfeld surface emerged from an attempt to define the space occupied by a molecule in a crystal for the purpose of partitioning the crystal electron density into molecular fragments (3). Hirshfeld surface was named after F.L Hirshfeld. A Hirshfeld surface is defined as the density weight function of the specific molecule of interest (i.e. the pro- molecule) over the same sum of density of its nearest neighbour (i.e. the pro-crystal), thereby resulting in a 0.5 arbitrary units iso surface, which is similar to that of a van der Waals surface but, unlike the latter, takes into consideration neighbouring molecules and hence provides information about intermolecular interaction (4).

The Hirshfeld surfaces can be mapped with different properties namely, dnorm, electrostatic potential, shape-index and curvedness. These are useful to accumulate additional information on weak intermolecular interactions. The Hirshfeld surfaces mapped over dnorm utilize the function of normalized distances de and di, where de and di are the distances from a given point on the surface to the nearest atom outside and inside, respectively. A surface with low curvedness represent a flat region and may be indicative of π–π stacking in the crystal. On the other hand, a Hirshfeld surface with high curvedness is highlighted as dark-blue edges, which is indicative of an absence of π–π stacking. The shape-index is a qualitative measure of shape and is sensitive to subtle changes in surface shape, particularly in a flat region. Two shape indices differing by sign represent complementary `bumps and hollows. The blue bump-shape and shape-index > 1 belongs to the donor, and that representing a red hollow with index < 1 corresponds to the acceptor of an intermolecular interaction (5-6).

The two-dimensional fingerprint plot derived from a Hirshfeld surface provides a convenient visual summary of the frequency of each combination of de and di across the surface of a molecule. It is a highly useful method to summarize complex information contained in a crystal. The color of each point corresponding to the relative area of a (de and di) pair is recognized as the contribution from different interatomic contacts: blue, green and red correspond to small, moderate and greatest contributions whereas an uncoloured region indicates no contribution to the Hirshfeld surface.

To conduct the above calculations, one should employ the final validated CIF as the input to Crystal Explorer Software. Crystal Explorer or CE is a freeware designed to analysis the crystal structure with cif file format. In 2006, M. A. Spackman's student Dylan Jayatilaka and coworkers developed a crystallographic software Crystal Explorer. It is helpful to investigate different areas of solid-state chemistry such as Hirshfeld surface analysis, intermolecular interactions, polymorphism, effect of pressure and temperature on crystal structure, single-crystal to single-crystal reactions, analyzing the voids present in crystal, and structure-property relationships.

Result and Discussion

Cambridge Structural Database (CSD) Survey:

The Cambridge Structural Database (CSD) (Conquest version 1.17; CCDC version 2.0.0) shows that the crystal structures of the title molecules (Scheme 1) were reported by G. C. Rovnyak. The crystal structure and crystallographic details are explained here.

Crystallographic Analysis:

The reported title compound crystallizes in triclinic crystal system with two molecule in the asymmetric unit and form P-1 space group. The dihedral angle in one molecule between phenyl ring (C5-C6-C7-C8-C9-C10) plane and hydropyrimidine plane (C1-N1-N2-C2-C3-C4) are observed 85.87° and that of hydropyrimidine ring and ester part are shown as 11.85°. However for second molecule the dihedral angles between phenyl ring (C21-C22-C23-C24-C19-C20) and hydropyrimidine plane (C17-C18-N4-C15-N5- C16) are observed 83.65° and that of hydropyrimidine ring and ester part are shown as 11.77°. The torsional angle for one ester part (C11-O4-C12-C13) shows 178.35° and that of other ester part (C25-O8-C26-C27) are shows 177°. In the crystal structure the hydrogen bonds N2-H2···S2 form dimer which lead to formation of chain in their crystal packing and propagate it in *b*-axis (8-10) (Figure-2.1). Further the molecule also form various hydrogen bonding in their crystal packing. The bifurcated type of hydrogen bond also observed in the molecule through same hydrogen bond acceptor

atom via C14-H14···O1 and C10- H7···O1 boding interactions. The crystal packing for the molecule are shown in the figure

3 The crystallographic details and prominent hydrogen bonding for the molecule are shown in table 1 and table 2 respectively.

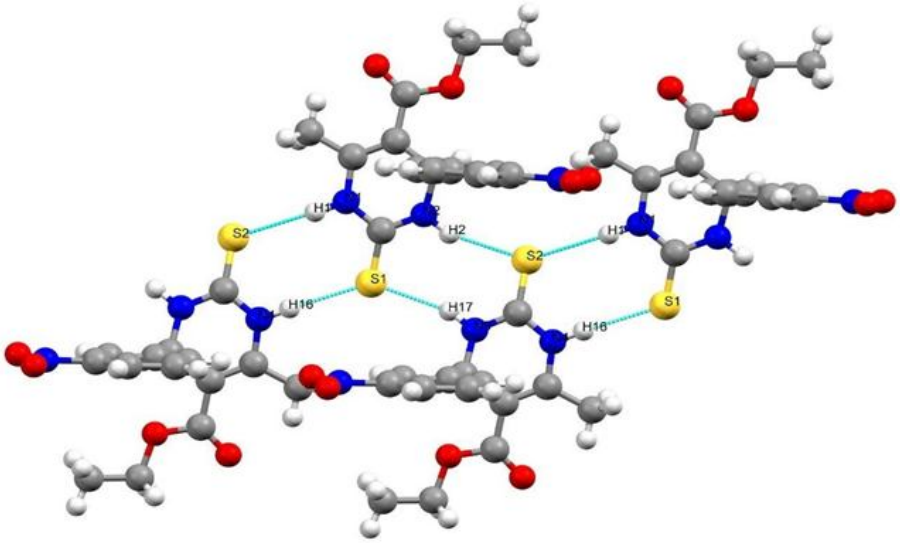


Figure 2: The molecule form dimer through N-H...S hydrogen bonding in the crystal packing.

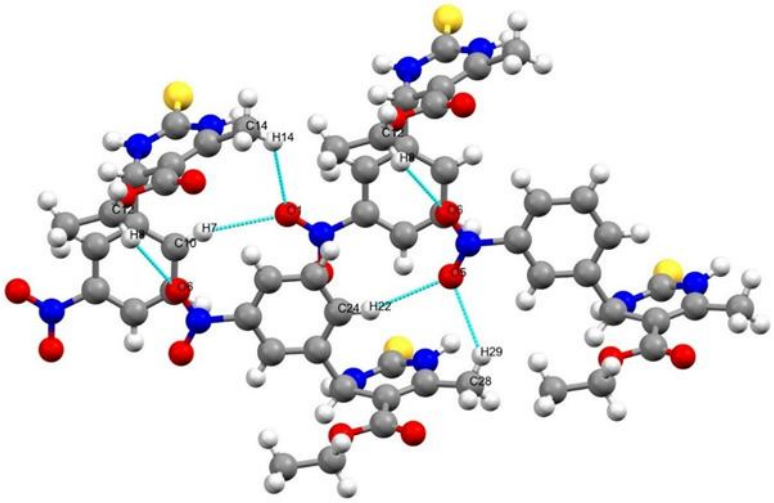


Figure 3: The molecule form various hydrogen bonding in their crystal packing structure.

Table 1: Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine- 5-carboxylate

Crystal Data	Compound code
Formula	C14H15N3O4S
Formula weight	321.35
a(Å)	8.45(1)
b(Å)	13.56(1)
c(Å)	14.47(2)
α (°)	101.35(9)
β (°)	98.23(8)
γ (°)	104.34(9)
V (Å³)	1542.46
Z'	2
Z	4
Crystal System	Triclinic

Table 2: Prominent hydrogen bonding interactions

D-X···A	D-X(Å)	X···A(Å)	D···A(Å)	<D-X···A(°)
N4-H16···S1	0.956	2.469	3.405	165.85
N1-H1···S2	0.955	2.602	3.508	158.4
C10-H7···O1	0.966	2.606	3.54	163.6
C14-H14···O1	0.950	2.609	3.30	130.8
C13-C10···O5	0.954	2.606	3.545	168.17
C28-H29···O5	0.951	2.618	3.387	138.29
C12-H8···O6	0.950	2.532	3.258	133.40

Simulated Powder Pattern Image

The Simulated Powder X-ray pattern for the title compound was obtained from single- crystal x-ray diffraction technique and analyse using Mercury 3.8 software.

The plot of diffraction intensity against 2-theta for the wavelength 1.54056 is shown in figure 2.3. The sharp peak indicate that substance is crystalline in nature.

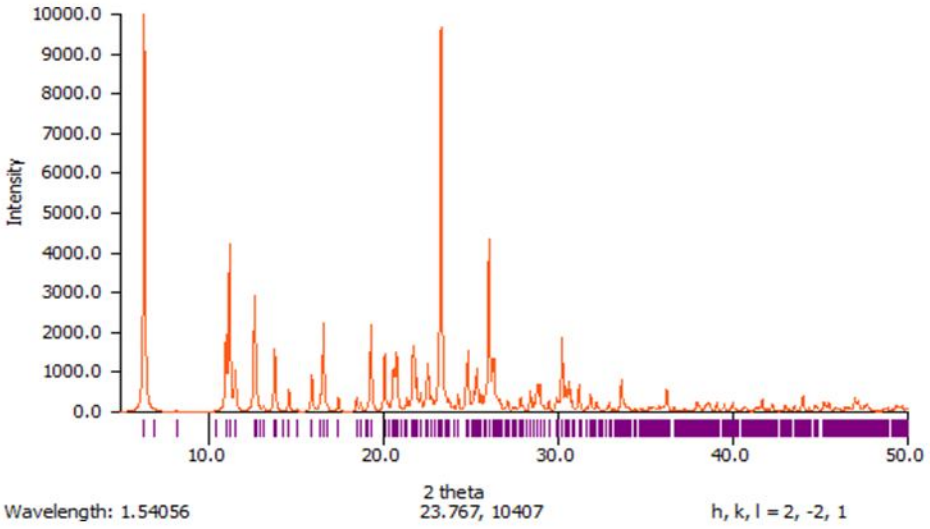


Figure 4: Simulated Powder X-ray pattern for the title compound obtained from single- crystal x-ray diffraction technique.

Hirshfeld surface Analysis:

Hirshfeld surface is a visualizing tool which quantifies the intermolecular interactions using a two-dimensional finger-print plot. The Hirshfeld surface of the molecule is mapped over dnorm which compasses two values, di which represents the distance of the surface nearest to the exterior atoms and de which represents a distance of the surface from nearest to the internal atoms. Here, the Hirshfeld surface and two-dimensional finger-print plots using *Crystal Explorer*-17.5 software have been developed as shown in Figure 6 and 7

The intermolecular interaction of the compound is strongly evidenced by the two- dimensional fingerprint plot. The red spot on the Hirshfeld surface shows the presence of strong intermolecular interactions and blue color shows free from contacts. The title compound shows a red spot due to strong N-H···S interaction shown in Figure-5. The finger-print plots shown in figure-6(b) show the H···H intermolecular contacts contribute relatively high (39.9%) compared to the other intermolecular interactions. The percentage contribution of other intermolecular interactions in the title compound is as follows: O···H/H···O(24.3%), S···H/H···S(16.7%), C···H/H···C(6.9%), C···O/O···C(5.6%), N···H/H···N(2.4%),, N···C/C···N(2.4%) C···S/S···C(0.8%) N···O/O···N(0.5%) and C···C(0.5%). It has been observed from this analysis that, the O···H (24.3%) intermolecular interactions are the significant interactions after H···H interactions (9-11)

Table 3: Types of intermolecular interaction and it's percentage contribution

Sr.No	Type of intermolecular interaction	Percentage contribution
1.	H···H	39.9%
2.	O···H	24.3%
3.	S···H	16.7%
4.	C···H	6.9%
5.	C···O	5.6%
6.	N···H	2.4%
7.	N···C	2.4%
8.	C···S	0.8%
9.	N···O	0.5%
10.	C···C	(0.5%)

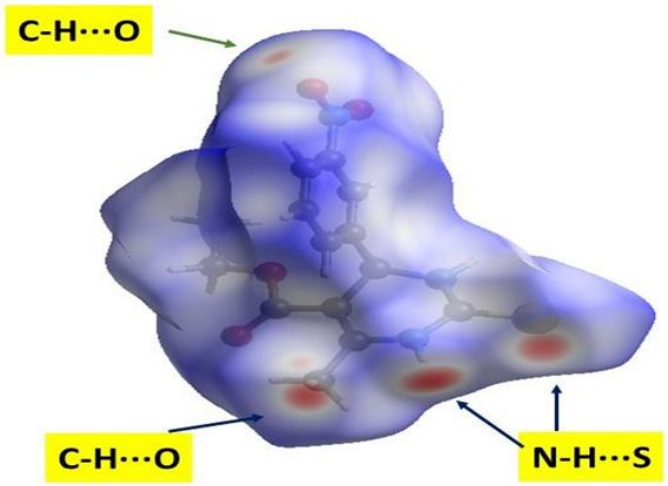


Figure 5: The dnorm Hirshfeld surface generated on the molecule for title compound

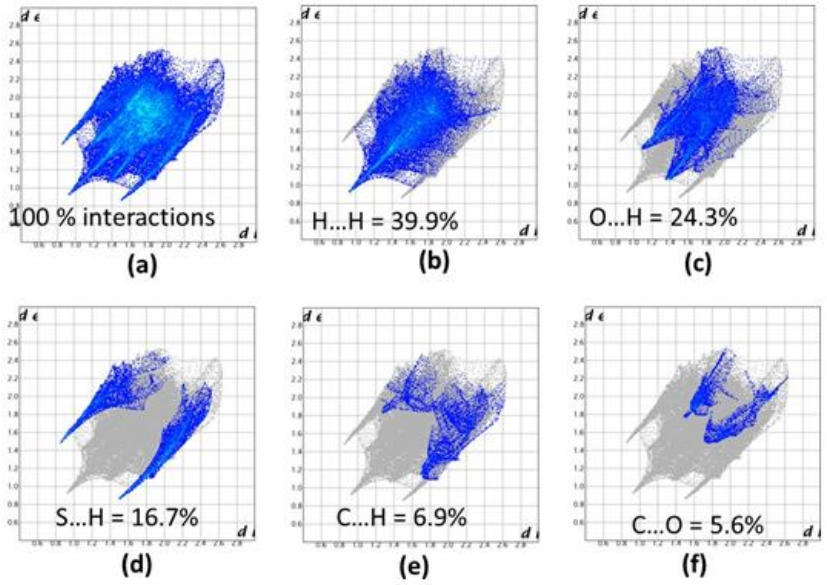


Figure 6: Two dimensional (2d) fingerprint plot with percentage contribution of interactions present in the compound.

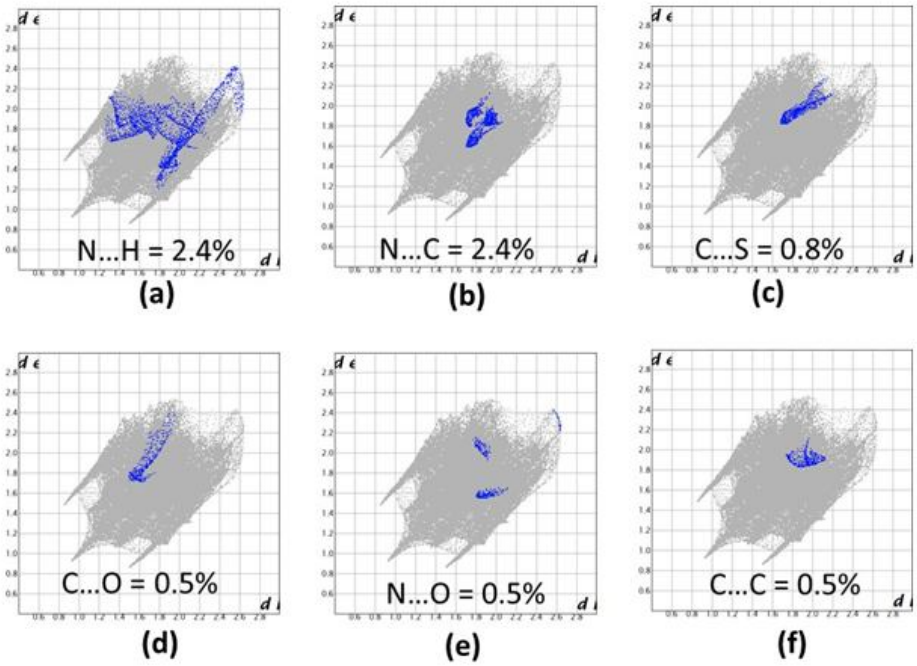


Figure 7: Two dimensional fingerprint plot with percentage contribution of interactions present in the compound.

CONCLUSION:

The supramolecular study of nitro based dihydropyrimidine molecule were analyzed using mercury software. It is observed that the title compound has crystallizes in triclinic system in the crystal packing. The peak observed in powder pattern clearly shows that the compound is highly

crystalline in nature. The compound prefer to form dimer through N-H···S interactions which form ring motif in their crystal packing. Further Hirshfeld surface analysis shows that O···H (24.3%) interactions contributes more after H···H (39.9%) interactions.

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