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Theoretical and Hirshfeld Surface Study of Pharmacologically Active Dihydropyrimidine based Compound

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Abstract: *The crystal structures of methyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate were determined and analysis of their molecular conformations was carried out. A comparative study of the intermolecular interactions and the degree of iso-structurality was quantified. The intermolecular interactions were characterized in terms of the periodic system electron density and the topological investigation highlighted the role of N–H···O C hydrogen bonds in the stabilization of the different supramolecular architectures. The interaction energies for molecular pairs involving N–H···O C hydrogen bonds indicated a dominant contribution to packing stabilization coming from the Coulombic components. Hirshfeld surfaces and fingerprint plots allowed us to visualize different intermolecular contacts and their relative contributions to the entire surface for each compound. Study of the electrostatic potentials (ESP) correlated well with the computed energies, thus characterizing the strengths of the different interactions.*

Keywords: Conformations, Fingerprint, Electrostatic Potentials

I. INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. The search and discovery for new MCRs on one hand and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. One such MCR that belongs in the latter category is the honored Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acidcatalyzed cyclocondensation reaction of ethyl acetoacetate (1), benzaldehyde (2), and urea (3). The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1H)-one (1).

The multifunctionalized dihydropyrimidine scaffold (DHPMs,"Biginelli compounds") represents a heterocylic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial and anti-inflammatory activities, has been attributed to these partly reduced pyrimidine derivatives. More recently, appropriately functionalized DHPMs have emerged as, e.g. orally active antihypertensive agents or R1a adrenoceptor-selective antagonists.

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Compound name:
methyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
Scheme 1: Schematic representation of reported dihydropyrimidine based derivative

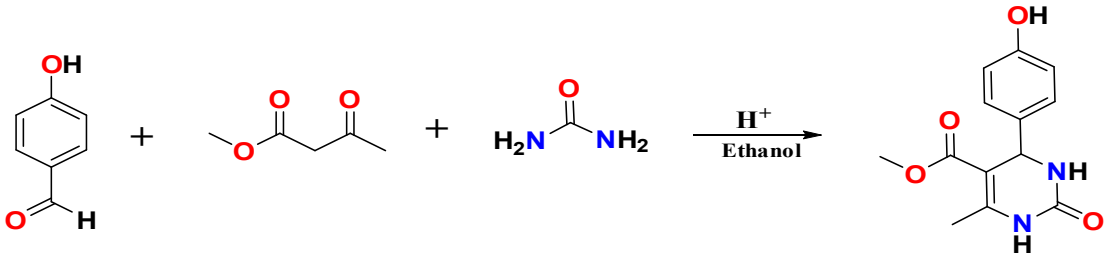

Figure: 1

Cambridge Crystallographic Data Centre (CCDC)
The **Cambridge Crystallographic Data Centre (CCDC)** is a non-profit organization. In 1965, with the aim of to available crystal structure data in a systematic manner to everyone, Dr. Olga Kennard OBE FRSand 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 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 submit their data obtained from X-RAY crystallography, electron and neutron diffraction to CSD. This is freely accessible to us on CCBC website. Currently, 1126815 crystal structure are available and this number increases year by year (2). There are certain software developed by CCDC such as Mercury, Con Quest, Mogul. We will discuss about Mercury in details.

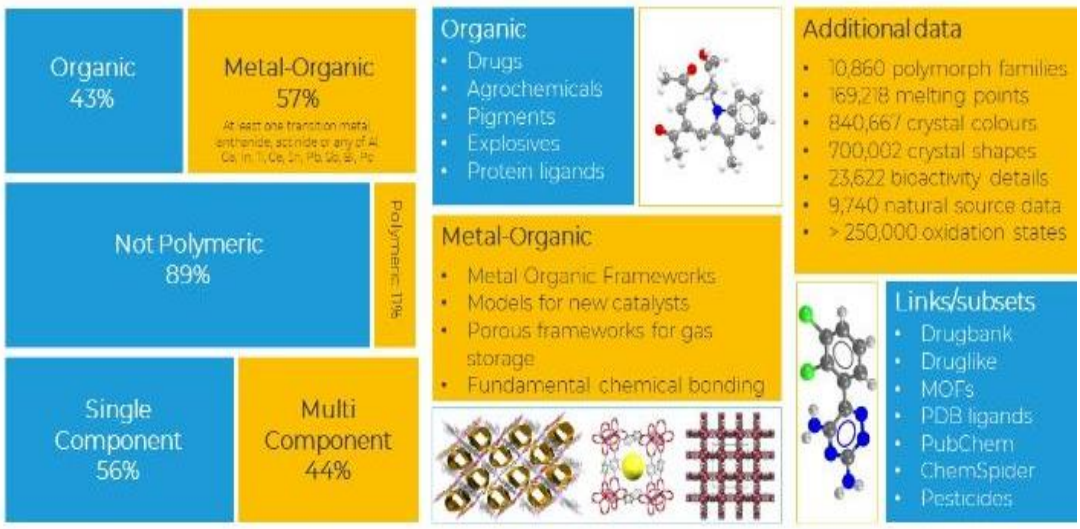

Figure 2: Content of CSD

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Mercury Software Analysis:

The program Mercury, developed at the Cambridge Crystallographic Data Centre, was originally designed primarily as a crystal structure visualization tool. Over the years the fields and scientific communities of chemical crystallography and crystal engineering have developed to require more advanced structural analysis software. Mercury has evolved alongside these scientific communities and is now a powerful analysis, design and prediction platform which goes a lot further than simple structure visualization (3).

The program Mercury was first launched by the Cambridge Crystallographic Data Centre (CCDC) in 2001 as a focused crystal structure visualization tool. Mercury has since become established as a prominent crystal structure visualizer with a free-to-access version available for any researcher and many thousands of citations of its first two versions at the time of writing 4608 for Mercury 1.0 (Macrae et al., 2006) and 5459 for Mercury 2.0 (Macrae et al., 2008)]. In the 18 years since the launch of Mercury 1.0, the fields of chemical crystallography (Watkin, 2010) and crystal engineering (Nangia & Desiraju, 2019) have changed dramatically, with much more sophisticated analysis of crystal structures now usual, alongside both knowledge-based and quantum chemical analysis of structures (4). Over this time period, and very much driven by the requests of these communities, Mercury has become much more than a visualizer. Mercury is now a powerful platform delivering analysis, design and prediction functionality alongside visualization. The Mercury interface also acts as a hub for wider capabilities of the software suite built around the Cambridge Structural Database (CSD) (Allen, 2002; Groom et al., 2016). In the past decade in particular, the capabilities of Mercury have developed significantly, with a focus towards pharmaceutical and agrochemical solid-form informatics. These new components collectively referred to as CSD-Materials, have been significantly driven by the CCDC's industrial Crystal Form Consortium, which was first introduced in August 2008. The discussions and direction provided by the CFC members over the years, which continue today, help to ensure both scientific value and clear industrial applicability in this area. Mercury is used by a very broad community, both geographically and by subject area and the CCDC continues to be directed by the needs of the scientific communities in how sew plan the next iterations of the software. This paper in particular will illustrate the evolution of Mercury over the past decade from version 2.0, described by Macrae et al. (2008), up to the recently released version 4.0. (5)

Hirshfeld surface analysis:

The major themes of modern crystal engineering can all be found in Desiraju's 1989 monograph on the subject: Crystal Engineering- The Design of Organic Solids. That definitive work aimed to bring together organic chemists, materials scientists, physical and theoretical chemists and crystallographers and, among other things, it set out the rationale for designing crystal structures of organic molecules, summarised computational methods and databases with a view to crystal structure prediction, reviewed dominant intermolecular interactions and touched on polymorphism (6). It also provided the now standard definition of the topic: "the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties". However this definition begs two important questions: (i) By what means can we achieve the required understanding? and (ii) In what ways can we exploit that understanding? This Highlight focuses on a novel way of addressing the first of these questions.

Aakeröy and Beatty in a recent review noted that "predicting and controlling the competition between intermolecular forces such as weak and strong hydrogen bonds, halogen-halogen interactions, π-π contacts, vanderwaals forces, etc., are part of every crystal engineering effort. The challenge comes down to the following: how do we unravel the bundle of often inter-related interactions and identify strong, directional, reliable non-covalent interactions?"

This brings us to the concept of a toolkit for crystal engineering, first discussed in 1999 by Seddon who identified synthetic vectors (hydrogen bonding, inter-ring interactions, covalent bonds, Coulombic forces), computational chemistry, visualization tools, and the Cambridge Structural Database (CSD) as the tools available at that time. Although the four basic types of tools remain essentially unchanged, the capabilities of computational chemistry and visualization have been greatly enhanced in the ensuing decade. There are a small number of key intermolecular

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interactions, as well as many others that will also be significant. How can we rationalize even the known crystal structures in terms of these interactions in order to make useful predictions? The magnitude of the problem is considerable, as there are a vast number of known organic molecular crystal structures (~436 000 in the CSD at January 1 2008).

In order to be most successful, and with the least bias possible, a method must satisfy the needs outlined by Desiraju in 1997: "Another compelling need is to be able to visualise a crystal structure in its entirety, not just look at selected intermolecular interactions that have been deemed to be important". A successful approach might also be able to address specific questions, such as those raised by Nangia and Desiraju: "A detailed understanding of crystal packing and crystal design depends very substantially on viewing the molecule as an organic whole. Given such realities, an immediate need in crystal engineering is to be able to compare crystal structures. Many will appreciate that the structure of, say, naphthalene resembles that of anthracene more than it resembles benzene. Is it possible to quantify such comparisons? If so, such quantification would amount to pattern matching and becomes important because crystals that are structurally similar are also likely to have similar properties".

The 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 (7). At the time we of course knew that Bader's quantum theory of atoms in molecules (QTAM) (9) provided a well-defined solution to this problem, but the zero-flux boundary surfaces are piecewise smooth, with abrupt discontinuities which make numerical integration far from trivial. We also explored a partitioning based on a generalization of the Wigner-Seitz cell, but these surfaces consisted of a union of planar or hyperbolic sections with odd irregularities. As a part of this work we quite literally stumbled on Hirshfeld surfaces, and realized that they possessed a number of attributes that make them highly attractive for an exploration of intermolecular interactions in crystals.

II. RESULT AND DISCUSSION

Cambridge Structural Database (CSD) Analysis:

The Cambridge Structural Database (CSD) (Conquest version 1.17; CCDC version 2.0.0) [1] shows that the crystal structures of the title molecules (Scheme 1) were reported by G.C. Rovnyak et al., [2]. The crystal structure and crystallographic details are explained here.

Crystallographic Analysis:

The reported title compound crystallizes in triclinic crystal system with two molecules in the asymmetric unit and form P-1 space group. The dihedral angle in one molecule between phenyl ring (C2-C1-C4-C3-N1-N2) plane and hydropyrimidine plane (C10-C9-C11-C8-C12-C13) are observed 88.80 and that of hydropyrimidine ring and ester part are shown as 16.46°. 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 79.09° and that of hydropyrimidine ring and ester part are shown as 13.23°. The torsional angle for one ester part (C6-O3-C5-C3) shows 173.87° and that of other ester part (C25-O8-C26-C27) are shows 178.07°. In the crystal structure the hydrogen bonds N_2-$H_2\cdots O_4$ form dimer which lead to formation of chain in their crystal packing and propagate it in *b*-axis (8-10) (Figure-2). Further, the molecules 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 C_1-$O_1\ldots H_3$and O_1.$H_3\ldots O_5$ boding interactions. The crystal packing for the molecules are shown in the figure 3 and 4. The crystallographic details and prominent hydrogen bonding for the molecule are shown in table.1 and table.2 respectively.

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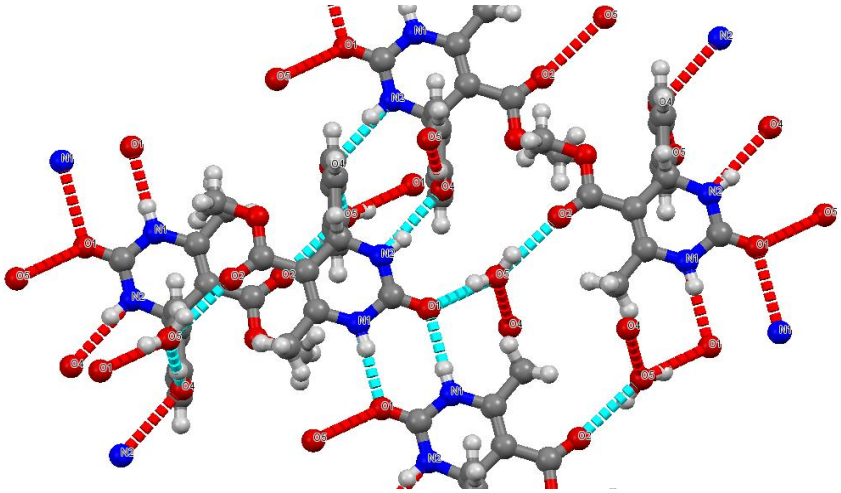

Figure 3: The molecule form various hydrogen bonding in their crystal packing structure

Table 1: Crystallography details of compound methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Crystal Data	**Compound code**
Formula	$C_{13}H_{13}O_3N_2Cl$
Formula weight	280.7
a(Å)	5.7934
b(Å)	10.5193
c(Å)	11.8476
α (°)	67.8290(10)
β (°)	88.076(2)
γ (°)	76.9240(10)
V ($Å^3$)	650.225
Z'	1
Z	2
Crystal system	Triclinic
Density (g cm^{-3})	1.49

Table 2: Prominent hydrogen bonding interactions

D-X⋯A	**D-X(Å)**	**X⋯A(Å)**	**D⋯A(Å)**	**<D-X⋯A(°)**
N_1-H_1…O_1	0.862	2.023	2.893	177.12
N_2-H_2…O_4	0.876	2.058	2.922	167.91
O_1-H_3…O_5	1.372	0.908	2.761	165.09
C_1-O_1…H_3	1.246	1.872	2.801	126.68
C_5-O_2…H_2	1.211	2.022	3.221	173.37
O_2-O_5…O_1	2.797	2.761	5.376	150.59

Simulated powder pattern image:

The Simulated Powder X-ray pattern for the title compound was obtained from single-crystal x-ray diffraction technique and analysis using Mercury software. The plot of diffraction intensity against 2theta for the wavelength 1.54056 is shown in figure 3. The sharp peak indicate that substance is crystalline in nature (11).

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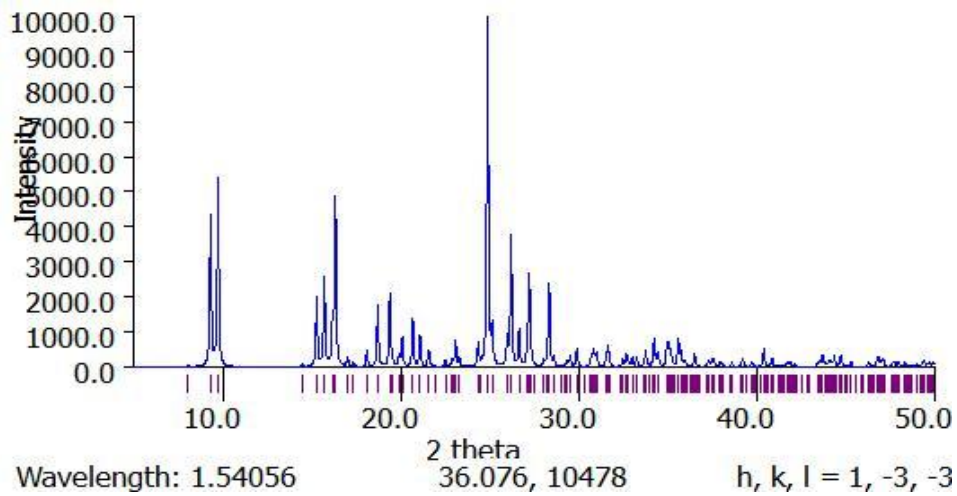

Figure 4: Simulated powder X-ray pattern for the title compound obtained from single- crystal x-ray diffraction technique.

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 (d,e,f) and 6 (g,h,i).

The intermolecular interaction of the compound is strongly evidenced by the two-dimensional fingerprint plot (12-13). 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···O interaction shown in Figure-6(d). The finger-print plots shown in figure-6(b) show the H···H intermolecular contacts contribute relatively high (49.9%) compared to the other intermolecular interactions. The percentage contribution of other intermolecular interactions in the title compound is as follows:

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

Sr. No.	Type of intermolecular interaction	Percentage contribution (%)
1.	Total	100
2.	H···H	49.9
3.	O···H	17.3
4.	N···H	0.5
5.	C···H	7.6
6.	C···O	0.9
7.	N···C	0.3
8.	C…C	3.3
9.	N···O	0.3

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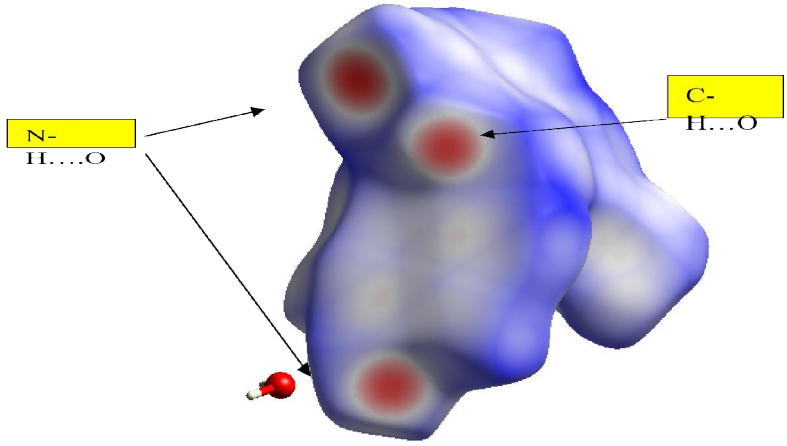
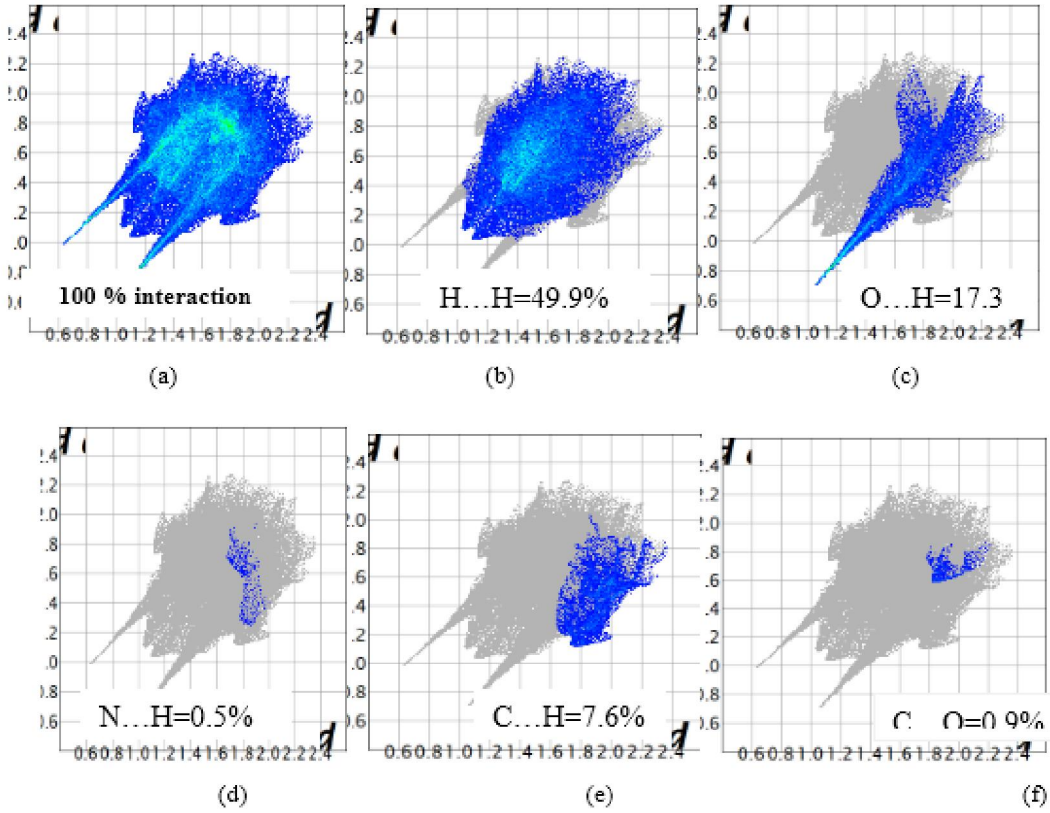


Figure 5: The dnorm Hirsgfeld surface generated on the molecule for title compound



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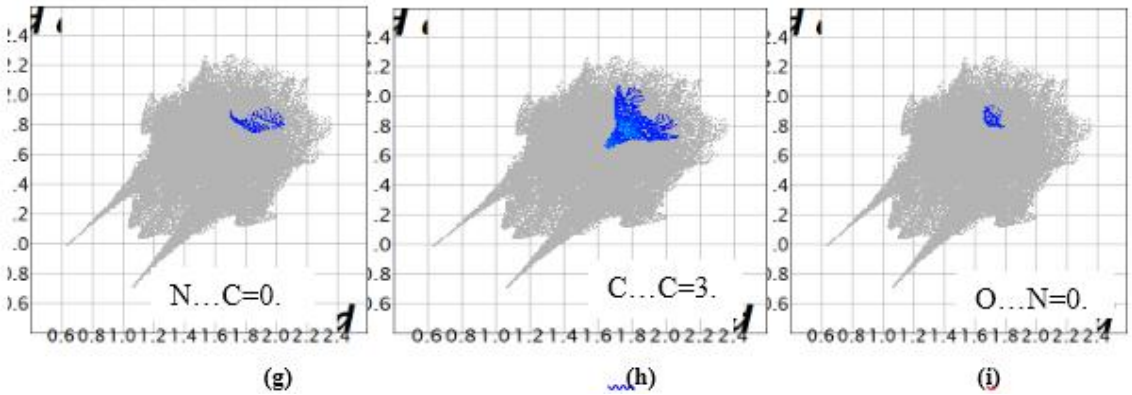

Figure 6: Two dimentional (2d) fingerprint plot with percentage contribution of interaction present in the compound

III. CONCLUSION

The supramolecular studies of surface analysis of pharmacologically active dihydropyrimidine based compound 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···O interactions which form ring motif in their crystal packing. Further Hirshfeld surface analysis shows that O···H (17.3%) interactions contributes more after H···H (49.9%) interactions.

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