Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2018, 7 (1): 77-84

(International Peer Reviewed Journal)

Synthesis and Crystal structure Analysis of 2-(6-dimethyl)3,5-dicarboxamide 4-(4-methoxyphenyl) N3,N5-bis(3-chloro-4-fluorophenyl) pyridine using Hirshfeld Surface Analysis

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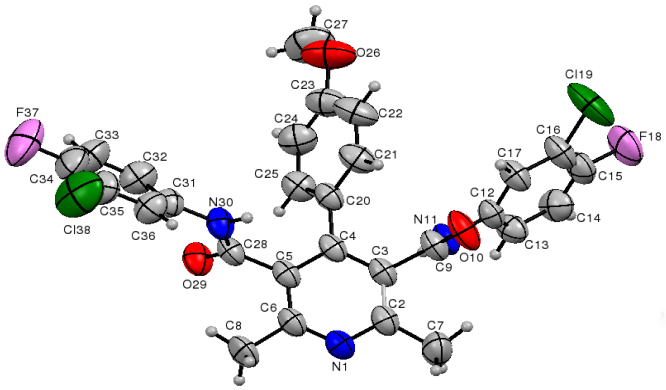
Accepted on 16th January 2018, Published online on 27th January 2018

ABSTRACT

The title compound, $C_{28}H_{22}Cl_2F_2N_3O_3$, crystallizes in the triclinic crystal system and space group $P\bar{1}$ with cell parameter, a = 9.5780(10) Å, b = 10.3730(18) Å, c = 4.493(2) Å, α = 89.739(4)°,β= 70.940(7)°, γ = 82.402(9)°, V = 1347.9(3) Å^3 for Z = 2. The structure exhibits intra and inter-molecular hydrogen bonds of the type C-H· · · O and N-H...O.

Graphical Abstract:



The ORTEP diagram of the compound

Keywords: Synthesis, Crystal structure Analysis, Hirshfeld Surface Analysis.

INTRODUCTION

Pyridine is structurally related to benzene, wherein one CH group in the aromatic six-membered ring is replaced by a nitrogen atom. This simple aromatic heterocyclic organic compound used as a precursor to agro-chemicals and pharmaceutical. It exists as a colorless liquid with a distinctive, unpleasant fish like odor. Pyridines and some pyridine fused ring systems have attracted great attention as potential chemotherapeutic agents [1–7]. Pyridine acts as reagent for detection of acid on paper chromatograms [8]. It is also used as a solvent or intermediary in numerous industries including producing piperidine, rubber products, polycarbonate resins, medicines, vitamins, food flavorings, herbicides, pesticides, explosives, paints, dyes, adhesives and waterproofing for fabrics, antihistamine steroids, sulfa antibiotics. In addition, it is a denaturant for antifreeze mixtures and is sometimes used as a ligand in coordination chemistry. Acute ingestion or inhalation impacts on nervous system including headaches, giddiness, a desire to sleep, quickening of the pulse, rapid breathing and nausea. Pyridine derivatives possess exciting antibacterial, anti-viral and anti-diabetic activities. The compound was synthesized and crystallized as dihydropyridine, but due to aromatization, dihydropyridine loses the proton and converts into pyridine structure.

MATERIALS AND METHODS

Synthesis and Method of Crystallization: Acetoacetanilide (0.02mol) and 4-methoxybenzaldehyde (0.01mol) were dissolved in 25 mL methanol and heated on water bath till the solid disappeared in the reaction mass. 3 mL ammonium carbonate was added to the reaction and it was refluxed on a water bath for a period of 10-12 h. The completion was monitored by TLC (Merck 60 F_{254}). After completion of the reaction it was cooled to room temperature and a solid mass was obtained. The product was filtered and washed with ether and recrystallized from ethanol and acetone.

4-(4-methoxyphenyl)-N3, N5-bis (3-chloro, 4-fluorophenyl)-2, 6-dimethyl-1,4-dihydropyridine-3, 5-dicarboxamide (2.5 g) was taken in 30 mL solvent mixture (Ethanol+DMF, 7.5:2.5). 1 g ofcharcoal was added and heated on a heating device for 6 min. The solution was filtered while hot through Whatman 41 filter paper. The solution was kept in a stopper conical flask slightly opened. The crystals were grown up due to thin film evaporation.

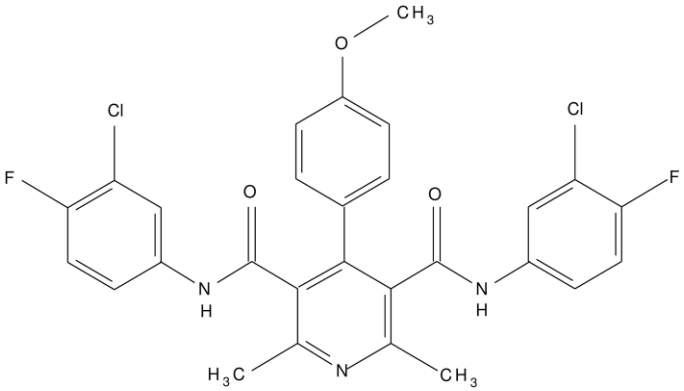


Fig 1. The Schematic diagram of the compound

Table 1. Crystal data and structure refinement table

CCDC	691262
Empirical formula	$C_{28}H_{21}Cl_2F_2N_3O_3$
Formula weight	556.38

Temperature	293(2)K
Wavelength	0.71073Å
Crystal system	Triclinic
Space group	P $\bar{1}$
Cell dimensions	a= 9.5780(10)Å b= 10.3730(18)Å c= 14.493(2)Å α= 89.739(4)° β= 70.940(7)° γ = 82.402(9)°
Volume	1488.7(9)Å^3
Z	2
Density(calculated)	1347.9(3) Mg/m^3
Absorption coefficient	0.289 mm^{-1}
F_{000}	572
Crystal size	0.3 x 0.25 x 0.25 mm
Theta range for data collection	2.27°to 25°
Index ranges	−10≤ h≤ 10 -12≤ k≤ 12 -17≤ l≤ 17
Reflections collected	6244
Independent reflections	4135 [R_{int}= 0.0364]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4135 / 0 / 347
Goodness-of-fit on F^2	1.093
Final R indices [I>2 σ(I)]	R1 = 0.0600, wR2 =0.1703
R indices (all data)	R1 = 0.0825, wR2 = 0.1971
Extinction coefficient	0.055(7)
Largest diff. peak and hole	0.560 and -0.336 e.Å^{-3}

RESULTS AND DISCUSSION

Crystal Structure Determination: A single crystal of the title compound with dimensions 0.30x0.25x0.25 mm was chosen for the X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3 kW sealed X-ray source (graphite monochromated MoK_α). The crystal to detector distance was fixed at 120 mm with the detector area of 441 x 240 mm^2. Thirty-six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to 400s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [9]. The reflections were merged with Scalepack [10]. All the frames could be indexed using a primitive triclinic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [11]. Least-squares refinement using SHELXL-97 [11] with isotropic temperature factors for all the non-hydrogen atoms converged the residual R1 to 0.0825. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen

atoms which were placed at chemically acceptable positions. The hydrogen atoms were allowed to ride on their parent atoms. After eight cycles of refinement the residual converged to 0.0600. The details of crystal data and refinement are given in Table 1.

Tables 2 and 3 gives list of the atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms and anisotropic thermal parameters of the non-hydrogen atoms. Tables 4 and 5 give the list of bond lengths and bond angles respectively which are in good agreement with the standard values. The ORTEP of the molecule with thermal ellipsoids is shown in Fig. 2.

Table 2. Selected bond lengths and bond angles (Å, °)

Atoms	Length	Atoms	Angle
C9-O10	1.221(3)	O10-C9-N11	123.8(2)
C15-F18	1.352(4)	F18-C15-C14	119.6(3)
C16-Cl19	1.722(3)	F18-C15-C16	119.7(3)
C23-O26	1.380(5)	C22-C23-O26	115.4(4)
C28-N30	1.331(4)	N30-C28-C5	113.8(2)
C28-O29	1.226(3)	C31-C32-C33	119.8(4)
N30-C31	1.412(4)	F37-C34-C35	119.2(4)
C34-F37	1.346(5)	F37-C34-C33	119.8(4)

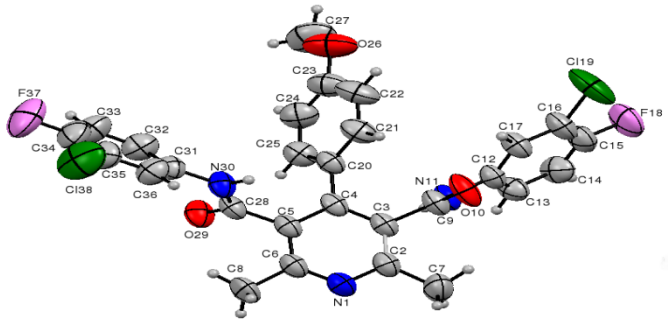


Figure 2. The ORTEP diagram of the compound

The dihedral angles between the least squares planes of pyridine ring and the two phenyl rings bridged by C-N group are 73.38(16)°and 54.66(18)° respectively, while that of pyridine ring and the phenyl ring is 59.95(16)°. The atom C12 deviates from Cremer and Pople plane by -0.012(3) Å, defined by C12-C13-C14-C15-C16-C17. Pyridine ring and the three phenyl rings exhibits planar conformation. The torsion angles about C5-C4-C20-C21 and C3-C4-C20-C25 are 122.3(3)° and 119.1(3)° respectively, indicating *ant-clinal* and *-syn-periplanar* conformation. The value being close to 60° or 120° indicates that the methoxy phenyl ring bisects pyridine ring. The torsion angles C2-C3-C9-O10 and C6-C5-C28-N30 being -74.5(4)° and 95.4(3)° give *-syn-clinal* and *ant-clinal* conformation, respectively.

Table 3. Selected Torsion Angles (deg)

Atoms	Torsion Angles	Atoms	Torsion Angles
N1-C2-C3-C9	175.4(3)	C4-C3-C9-O10	102.1(4)
C4-C5-C28-O29	101.3(4)	C5-C4-C20-C21	122.3(4)
C13-C14-C15-F18	179.0(4)	C28-C5-C6-N1	-178.9(3)
C32-C33-C34-F37	179.7(3)	C14-C15-C16-Cl19	-178.9(3)

The molecule exhibits both intra and inter-molecular hydrogen bonds of the type C-H...O and N-H...O . The intra-molecular hydrogen bond C17-H17...O10 has a length of 2.848(4) Å with an angle of 112°. The inter-molecular hydrogen bonds N11-H11...O29 and N30-H30...O10 have lengths of 2.811(3) Å and 2.808(4) Å with angles of 155° and 173°, with symmetry codes 1-x, -y, -z and 2-x, -y, -z respectively. The stability of the crystal structure can be accounted for by these hydrogen bonds. Packing of the molecules down *b* axis is shown in Fig. 3.

Table 4. Hydrogen bond geometry (Å, deg.)

D-H...A	D-H	H...A	D...A (Å)	D-H...A (°)
N11-H11-O29	0.86	2.01	2.811(3)	155
N30-H30-O10	0.86	1.95	2.808(4)	173
C17-H17-O10	0.93	2.36	2.848(4)	112

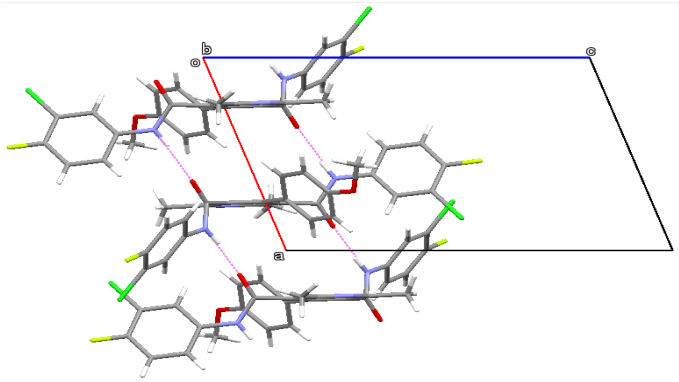


Figure 3. The packing view of the molecules down the b axis. The red lines indicate hydrogen bonds

Hirshfeld Surface Analysis: The intermolecular interaction of the title compound is quantified using Hirshfeld surface analysis [12-14]. The shape of the Hirshfeld surface is characteristic of the molecule and its crystalline environment.

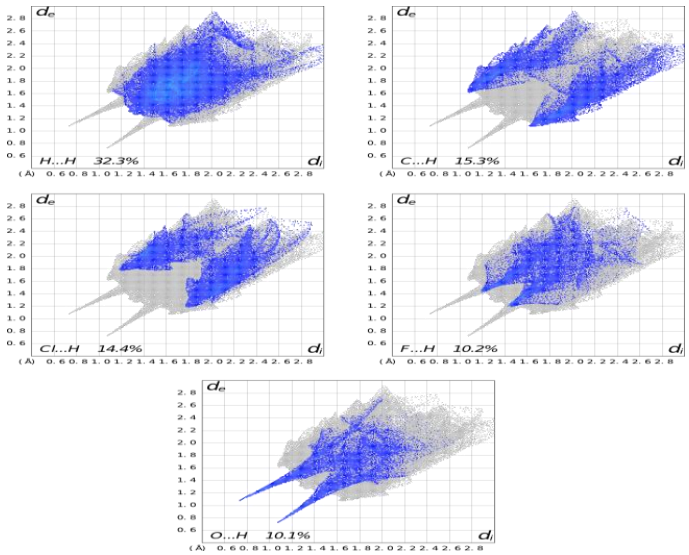


Figure 4. Fingerprint plot of the title compound

The intermolecular interaction of the title compound is quantified using Hirshfeld surface analysis[12]. The shape of the Hirshfeld surface is characteristic of the molecule and its crystalline environment. The distances $d_{e,}$ is the closest external contacts with percentage of various intermolecular contacts and $d_{i,}$ the closest internal distance from given point on the Hirshfeld surface mapped provide a three-dimensional picture of intermolecular close contacts in a crystal. They are also used to generate a fingerprint plot fig 4, a concise two-dimensional summary of intermolecular interactions and the relative contributions to the Hirshfeld surface (in percentage) for major intermolecular contacts associated with the title compound. The contribution of the intercontacts to the Hirshfeld surfaces are, H...H (32.3%), C...H (15.3%), Cl...H (14.4%), F...H (10.2%), O...H (10.1%) and others (17.7%). These intercontacts are highlighted by conventional mapping of d_{norm} on molecular Hirshfeld surfaces are shown in Fig. 5. The red spots over the surface indicate the intercontacts involved in hydrogen bond, while H...H bonding is the major contributor in crystal packing. In Fig.6 the curvedness and shape index show characteristic packing arrangement and the ways in which adjacent molecules contact one another. The shape index surface clearly shows that the two sides of the molecules are involved in same contacts with neighboring molecules and curvedness plots show flat surface patches characteristic of planar stacking.

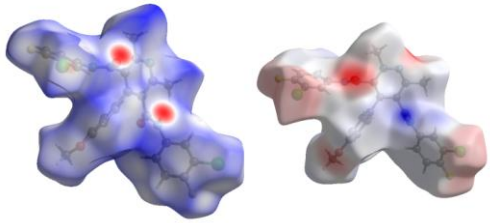


Fig 5. d_{norm} and electrostatic potential mapped on Hirshfeld surface for visulaising the intercontacts of the title compound. Color scale is in between -0.18 au(blue) to 1.4au (red)

APPLICATIONS

Literature survey shows that the pyridine derivatives have numerous applications. This research work is useful for the creation of a library. Whenever there is a need for molecule with these properties, we can make use of the title compound.

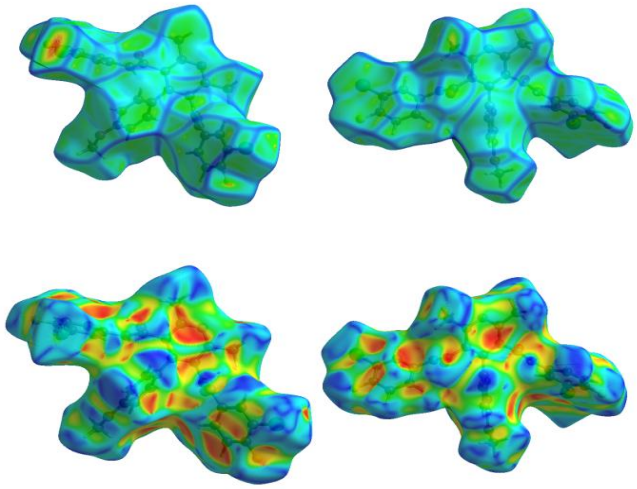


Fig 6. Front and back views of the Hirshfeld surface for title compound mapped with curvedness and shape index

CONCLUSIONS

The present work helps us to understand the molecular structure and the intermolecular interactions of the synthesized compound. The structure was confirmed by X-ray diffraction. Further, from the Hirshfeld surface analysis and its associated fingerprint plot it can be concluded that the major contribution to the total surface area is from H...H interactions.

ACKNOWLEDGEMENTS

The authors would like to thank Department of Studies in Physics, Manasagangotri, University of Mysore, Mysuru and Department of Chemistry, Saurashtra University, Rajkot for providing the laboratory facility.

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