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Synthesis, Crystal and Molecular Structure Studies and Hirshfeld Surface Analysis of a 6-amino-1,4-dihydro-3-methyl-4-(5,7-dimethyl-2-oxo-2H-chromen-4-yl)pyrano[2,3-c]pyrazole-5-carbonitrile

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ABSTRACT

The title compound was synthesized via green, efficient and ecofriendly protocol using DMAP catalyzed one-pot four-component reaction, and characterized by ¹H NMR and the crystal structure was confirmed by using single crystal X-ray diffraction method. The X-ray diffraction study reveals that the compound (C₂₀H₂₀O₄N₄) has crystallized in the orthorhombic crystal system with the space group P2₁2₁2₁. And the lattice parameters are a = 7.4374(5) Å, b = 13.4666(9) Å, c = 18.6416(12) Å, α = β = γ = 90°, Z = 4 and V = 1867.1(2) Å³. The molecular structure exhibits intermolecular hydrogen bonds of the type N–H---O, N–H---N and contributes to the crystal packing. The structure is also stabilized by C–H---π and π---π stacking interactions. And it exhibits intermolecular hydrogen bond of the O–H---N with the solvent methanol molecule. Further, the molecular Hirshfeld surface analysis was carried out to understand the nature of intermolecular contacts, the fingerprint plot provide the information about the percentage contribution from the intermolecular contacts to the molecular surface.

Keywords: 1,4-dihydropyrano[2,3-c]pyrazole, Crystal structure, X-ray diffraction, Hirshfeld surface analysis, fingerprint plot, C–H---π, π---π interactions.

INTRODUCTION

The title compound C₂₀H₂₀O₄N₄ belongs to the class of the 1,4-dihydropyrano[2,3-c]pyrazole. 1,4-Dihydropyrano[2,3-c]pyrazole scaffolds represents a privileged structural motif well distributed in bioactive natural products and medicinally important synthetic heterocycles possessing a wide range of activities [1]. Pyrazolones fused pyran rings compose a very important class potential biological and pharmacological properties such as antimicrobial [2], anti-inflammatory [3], anticancer [4], insecticidal [5] and inhibitors of human Chk1 kinase [6]. Hence, investigation of the structural features of biologically potent pyrano[2,3-c]pyrazole molecules is of both scientific and practical interest [7].

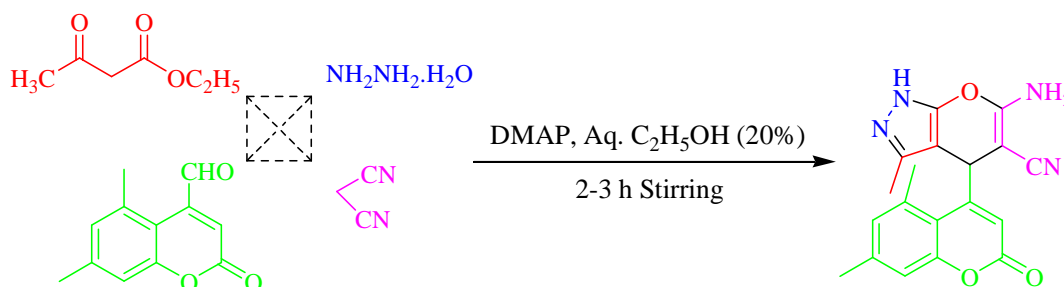
Literature survey reveals that the therapeutic importance of coumarin, pyrazole, pyran scaffolds and clean chemistry, the present investigation pertaining to the hybridization of these three pharmacophoric motifs in a single molecule. In continuation of our efforts to develop useful green synthetic protocols for biologically important molecules, we herein report the synthesis, characterization, single crystal X-ray diffraction and Hirshfeld surface analysis of the

novel pyrazole derivative, 6-amino-1,4-dihydro-3-methyl-4-(5,7-dimethyl-2-oxo-2H-chromen-4-yl)pyrano[2,3-c]pyrazole-5-carbonitrile.

MATERIALS AND METHODS

All the chemicals were purchased by commercial source and used without further purification unless otherwise stated. The progress of the reaction were monitored by thin-layer chromatography (TLC) analysis with Merck Kieselgel 60 F254 plates and visualized using UV light at 254 nm and KMnO_4 staining or iodine vapour and also purity of the compound was checked by TLC. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker 400 MHz and 100 MHz, respectively using $\text{DMSO-}d_6$ as solvent and TMS as an internal standard. The X-ray diffraction study was performed on a BRUKER AXS SMART APEX CCD diffractometer.

Synthesis of 6-amino-1,4-dihydro-3-methyl-4-(5,7-dimethyl-2-oxo-2H-chromen-4-yl)pyrano[2,3-c]pyrazole-5-carbonitrile: The synthesis of 1,4-dihydropyrano[2,3-c]pyrazole compound was carried out *via* one-pot four component reaction in aqueous ethanol using low cost and environmentally benign DMAP as catalyst at room temperature. To a mixture of hydrazine hydrate 96% (1 mmol) and ethyl acetoacetate (1 mmol) in aqueous ethanol (20%) was stirred for 5-10 minutes. Then aldehyde (1 mmol), malononitrile (1 mmol) and base (5 mmol %) were added to it successively at ambient temperature under an open atmosphere with vigorous stirring for 2-3 hrs. The progress of the reaction was monitored by TLC. The precipitated solid was filtered and repeatedly washed with water to obtained a pure desired title compound 6-amino-1,4-dihydro-3-methyl-4-(5,7-dimethyl-2-oxo-2H-chromen-4-yl)pyrano[2,3-c]pyrazole-5-carbonitrile.

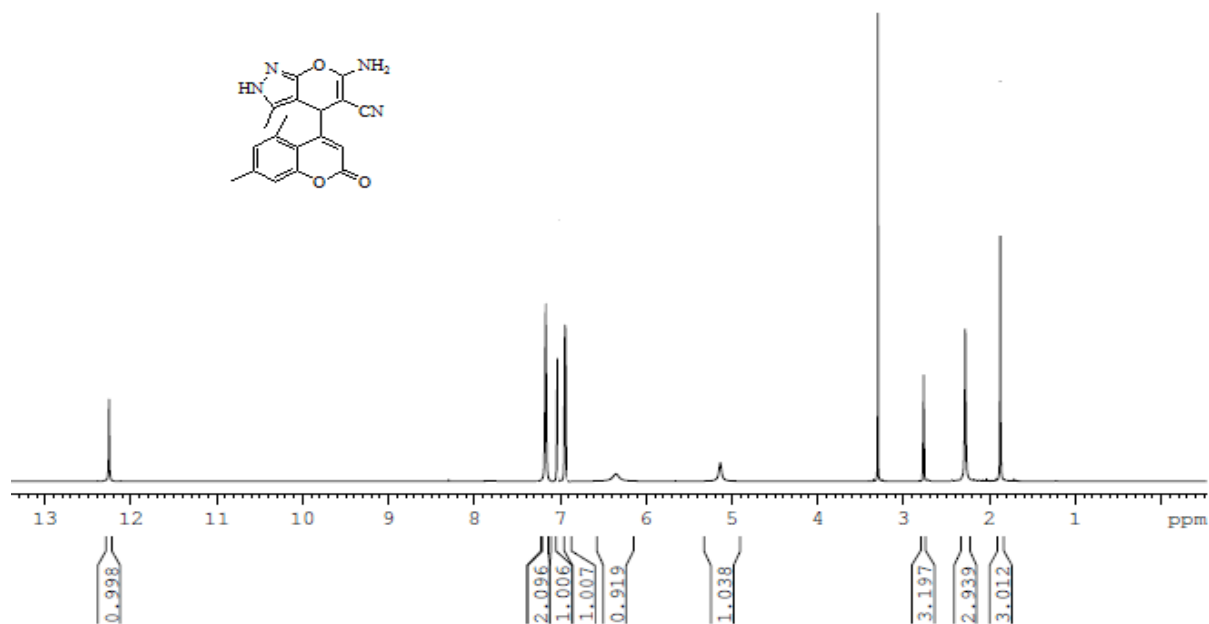
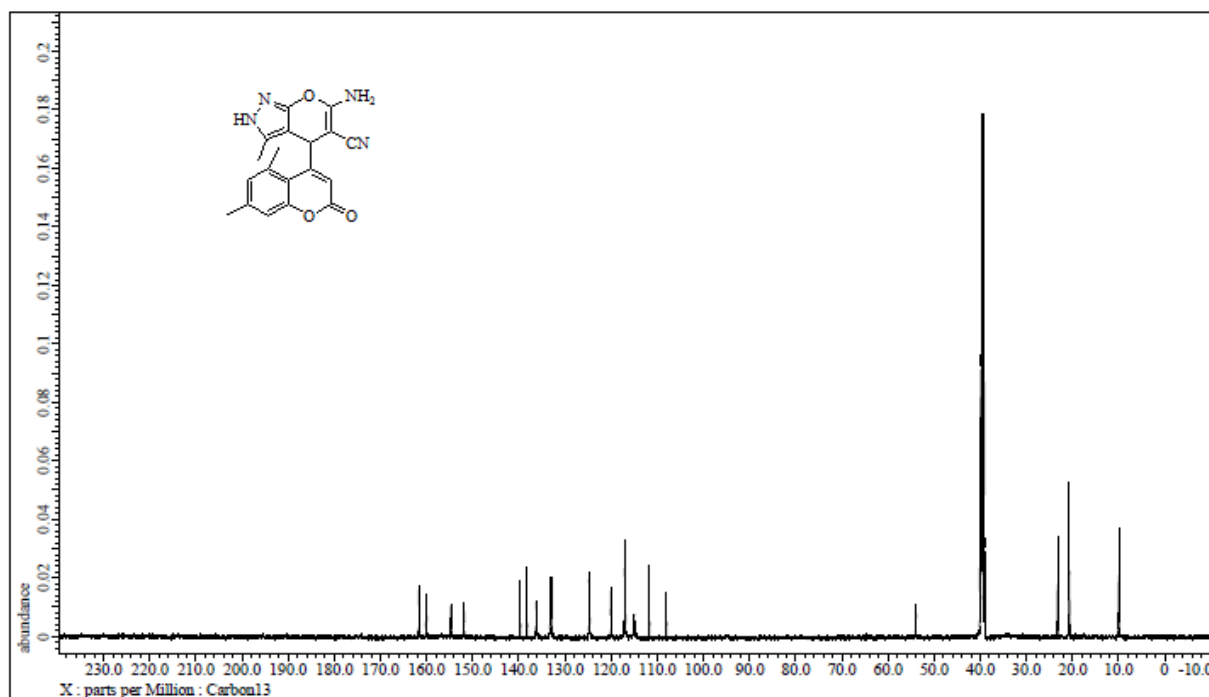


Scheme 1: Schematic representation of reaction pathway of the title compound

Results of spectroscopic characterization

The structure of the 1,4-dihydropyrano[2,3-c] pyrazole compound was confirmed by spectral studies, including ^1H NMR, ^{13}C NMR, and mass spectroscopy. NMR spectrums of the title compound are shown in **Figure 1a** and **1b** respectively. Good single crystals were obtained using methanol as a solvent through slow evaporation method. For crystallization, 100 mg of the compound was dissolved in 35 mL solvent and left for several days at ambient temperature.

White; Yield 60%; m.p: 231-232 °C; IR (KBr) cm^{-1} 3339, 3311, 2201, 1707; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 12.25 (s, 1H), 7.15 (s, 2H), 7.06 (s, 1H), 6.98 (s, 1H), 6.51 (s, 1H), 6.34 (s, 1H), 5.13 (s, 1H), 2.78 (s, 3H), 2.27 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ (ppm): 161.62, 160.07, 154.71, 151.89, 139.42, 138.68, 136.19, 133.17, 132.98, 124.71, 120.01, 116.96, 114.96, 112.98, 108.16, 53.95, 23.71, 20.67, 9.90; MS (m/z): 348.

Figure 1a: ¹H-NMR Spectrum of the title compoundFigure 1b: ¹³C-NMR Spectrum of the title compound**Single Crystal X-ray Diffraction Studies:**

A needle shaped colorless defect free single crystal of dimension 0.26×0.20×0.12 mm was chosen for X-ray diffraction studies. X-ray intensity data were collected at a temperature of 293 K on a Bruker SMART APEX CCD diffractometer with X-ray generator operating at 45 kV and 10 mA, using MoK α radiation of wavelength 0.71073 Å. Data collection was carried out for 24 frames with exposure time of 5 s and scan width of 0.5° in different settings of

ϕ (0° and 90°) range. The sample to detector distance was fixed at 45.10 mm. The experimental analysis discloses that the synthesized compound $C_{20}H_{20}O_4N_4$ crystallizes in the orthorhombic crystal system, in $P2_12_12_1$ space group with unit cell parameters $a = 7.4374(5)$ Å, $b = 13.4666(9)$ Å, $c = 18.6416(12)$ Å, $\alpha = \beta = \gamma = 90^\circ$, $Z = 4$ and $V = 1867.1(2)$ Å³. The data reduction was achieved using *XPREP* [8]. The crystal structure was solved by direct methods and refined by full matrix least squares refinement against F^2 using *SHELXS-97* and *SHELXL-97* [9]. All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were positioned geometrically, with C-H = 0.93 Å and refined using a riding model with $U_{iso}(H) = 1.2 U_{eq}(C, N)$, $U_{iso}(H) = 1.5 U_{eq}(C_{methyl})$ and $U_{iso}(H) = 1.5 U_{eq}(O)$. A total of 258 parameters are refined with 2414 unique reflections of 5336 observed reflections. The geometrical calculations were carried out using the program *PLATON* [10]. The molecular and packing diagrams were generated using *MERCURY* [11] software. The ORTEP of the title compound is shown in **Figure 2**. The crystallographic data and refinement parameters are given in **Table 1**.

RESULTS AND DISCUSSION

The structure of the title compound $C_{20}H_{20}O_4N_4$ was confirmed by single crystal X-ray diffraction analysis. The bond lengths and bond angles are in good agreement with the standard values, and the list of selected bond lengths and bond angles are given in **Table 2** and **3** respectively. The conformation of the molecules can be described by the torsion angles between the rings. The list of torsion angles is shown in **Table 4**.

The crystal structure revealed that the five membered pyrazole ring N1—C5 and six membered pyrano ring O10—C9 are sp² hybridized. They are well described by the torsion angle values 0.41° and 0.80° respectively indicating *+syn-periplanar* conformation. The bond lengths and angles agree well with those of previously reported pyrazole derivatives. The six membered rings O17—C18 and C18—C21 adopts *+syn-periplanar* conformation with sp² hybridization which is indicated by the torsion angle values of 5.26° and 2.25° respectively. The observed bond distance of C16—O20 is $1.210(3)$ Å is evident for the carbonyl form and consistent with the C=O double bonds [12]. The dihedral angle between the pyrazole and pyrano ring is 1.59° which indicates that they have planar in nature. Similarly the mean plane of the coumarin ring O17—C19 forming a dihedral angle of 85.40° with the pyrazole ring shows that the coumarin ring lies in the equatorial position with respect to the pyrazole ring. The pyran moiety adopts a flattened bent conformation with one mirror plane passing through the atoms C7 and O10 and the other bisecting the bonds C5—C4 and C8—C9. The six membered ring O17—C18 adopts *+syn-periplanar* conformation with the Cremer and Pople [13] puckering parameters $Q = 0.0948$ Å, $\theta = 91.87^\circ$ and $\phi = 232.26^\circ$. The ring puckering analysis reveals that the ring has a weighted average ring bond distance of $1.399(999,166)$ Å and weighted average torsion angle of $5.26(41,133)^\circ$.

The nine membered O10—C9 ring adopts *+Syn-clinal* conformation with the torsion angle value of 79.60° and with the total puckering amplitude of $Q = 0.0340$ Å. In the crystal structure the molecules are linked by the intermolecular hydrogen bonds of the type N—H...O, N—H...N into infinite two-dimensional network. The N2—H2...O28 hydrogen bond has a length of 2.8510 Å and an angle of 157° . Similarly the hydrogen bond N3—H13A...N1 has a length of 2.0521 Å and an angle of 159° . The hydrogen bond interactions are as given in **Table 5**. The structure also exhibits the C—H...Cg interaction; C21—H21...Cg4 (Cg4 is the centroid of the ring C18/C19/C24/C23/C22/C21) with C—Cg distance of 3.5685 Å, H...Cg distance of 2.92 Å, C—H...Cg angle of 128° , and with a symmetry code $-1/2+x, 1/2-y, 1-z$. Similarly C25—H24B...Cg1 (Cg1 is the centroid of the ring N1/N2/C24/C3/C4/C5) with C—Cg distance of 3.5672 Å, H...Cg distance of 2.85 Å, C—H...Cg angle of 132° , and with a symmetry code $2-x, -1/2+y, 1/2-z$. The molecular structure is also stabilized by π ... π stacking interaction of the type C16—O20...Cg2 (Cg2 is the centroid of the ring C18/C19/C24/C23/C22/C21) with C—Cg distance of 4.7563 Å, H...Cg distance of 3.9920 Å, C—H...Cg angle of 123° , and with a symmetry code $2-x, 1/2+y, 1/2-z$. The packing of the molecule viewed down along the *a*-axis is as shown in **Figure 3**.

Table 1: Crystal data and structure refinement details

Parameter	value
CCDC deposit No.	1482379
Empirical formula	C ₂₀ H ₂₀ O ₄ N ₄
Formula weight	380.40
Temperature	293 K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, <i>P</i> 212121
Unit cell dimensions	a = 7.4374(5) Å b = 13.4666(9) Å c = 18.6416(12) Å α = 90° β = 90° γ = 90°
Volume	1867.1(2) Å ³
Z	4
Density(calculated)	1.353 Mg m ⁻³
Absorption coefficient	0.097 mm ⁻¹
F 000	800
Crystal size	0.26 × 0.20 × 0.12 mm
θ range for data collection	1.87° to 22.92°
Index ranges	-7 ≤ h ≤ 8 -8 ≤ k ≤ 14 -20 ≤ l ≤ 18
Reflections collected	5336
Independent reflections	2414 [R int = 0.0218]
Refinement method	Full matrix least-squares on F ²
Data / restraints / parameters	2414 / 0 / 258
Goodness-of-fit on F ²	1.025
Final [I > 2σ(I)]	R1 = 0.0374, wR2 = 0.0932
R indices (all data)	R1 = 0.0428, wR2 = 0.0970
Extinction coefficient	0.0093(17)
Largest diff. peak and hole	0.169 and -0.170 e Å ⁻³

Table 2: Bond lengths (Å)

Atoms	Length	Atoms	Length
O10-C5	1.367(3)	C7-C8	1.531(4)
O10-C9	1.364(3)	C7-C14	1.531(3)
O17-C16	1.372(3)	C8-C9	1.372(3)
O17-C18	1.377(3)	C8-C11	1.407(4)
O20-C16	1.210(3)	C14-C19	1.462(3)
O28-C27	1.367(5)	C14-C15	1.351(4)
N1-C5	1.318(3)	C15-C16	1.424(4)
N1-N2	1.369(3)	C18-C19	1.408(4)
N2-C3	1.343(3)	C18-C21	1.382(4)
N12-C11	1.145(4)	C19-C24	1.426(4)
N13-C9	1.336(4)	C21-C22	1.366(5)
C3-C4	1.372(3)	C22-C26	1.510(4)
C3-C6	1.499(4)	C22-C23	1.394(4)
C4-C5	1.377(3)	C23-C24	1.379(4)
C4-C7	1.495(3)	C24-C25	1.506(4)

Table 3: Bond angles (°)

Atoms	Angle	Atoms	Angle
C5-O10-C9	115.69(18)	N12-C11-C8	176.0(3)
C16-O17-C18	122.2(2)	C7-C14-C15	117.4(2)
N2-N1-C5	101.37(19)	C7-C14-C19	123.7(2)
N1-N2-C3	113.3(2)	C15-C14-C19	118.7(2)
N2-C3-C6	122.9(2)	C14-C15-C16	124.5(2)
N2-C3-C4	106.5(2)	O17-C16-C15	115.7(2)
C4-C3-C6	130.4(2)	O20-C16-C15	127.5(2)
C3-C4-C5	103.6(2)	O17-C16-O20	116.8(2)
C5-C4-C7	123.3(2)	O17-C18-C19	122.3(2)
C3-C4-C7	133.0(2)	C19-C18-C21	123.8(3)
O10-C5-C4	125.8(2)	O17-C18-C21	113.9(3)
N1-C5-C4	115.2(2)	C14-C19-C24	128.4(2)
O10-C5-N1	119.0(2)	C18-C19-C24	115.8(2)
C4-C7-C8	106.84(18)	C14-C19-C18	115.9(2)
C4-C7-C14	113.5(2)	C18-C21-C22	120.0(3)
C8-C7-C14	109.56(19)	C21-C22-C26	121.5(3)
C7-C8-C11	117.1(2)	C23-C22-C26	121.1(3)
C7-C8-C9	124.9(2)	C21-C22-C23	117.4(2)
C9-C8-C11	117.9(3)	C22-C23-C24	124.3(3)
N13-C9-C8	127.6(3)	C23-C24-C25	116.5(2)
O10-C9-C8	123.4(3)	C19-C24-C25	124.9(2)
O10-C9-N13	109.0(2)	C19-C24-C23	118.6(2)

Table 4: Torsion angles (°)

Atoms	Angle	Atoms	Angle
C5-O10-C9-N13	179.0(2)	C8-C7-C14-C15	-84.5(3)
C5-O10-C9-C8	-1.6(4)	C8-C7-C14-C19	90.3(3)
C9-O10-C5-N1	179.3(2)	C11-C8-C9-N13	-2.7(4)
C9-O10-C5-C4	1.5(4)	C7-C8-C9-N13	-179.8(3)
C18-O17-C16-C15	8.5(4)	C7-C8-C9-O10	1.0(4)
C16-O17-C18-C19	-1.9(4)	C11-C8-C9-O10	178.0(2)
C16-O17-C18-C21	177.4(3)	C7-C14-C15-C16	174.4(3)
C18-O17-C16-O20	-173.2(3)	C15-C14-C19-C24	-174.1(2)
N2-N1-C5-O10	-177.8(2)	C7-C14-C19-C18	-167.5(2)
C5-N1-N2-C3	0.3(3)	C7-C14-C19-C24	11.2(4)
N2-N1-C5-C4	0.2(3)	C19-C14-C15-C16	-0.6(4)
N1-N2-C3-C4	-0.6(3)	C15-C14-C19-C18	7.2(3)
N1-N2-C3-C6	-177.4(2)	C14-C15-C16-O17	-7.3(4)
C6-C3-C4-C5	177.1(3)	C14-C15-C16-O20	174.6(3)
C6-C3-C4-C7	-5.1(5)	O17-C18-C19-C14	-6.2(4)
N2-C3-C4-C5	0.6(3)	O17-C18-C19-C24	175.0(2)
N2-C3-C4-C7	178.5(3)	C21-C18-C19-C14	174.6(3)
C3-C4-C7-C14	61.7(4)	C21-C18-C19-C24	-4.3(4)
C5-C4-C7-C8	0.0(3)	O17-C18-C21-C22	-177.5(3)
C3-C4-C5-O10	177.3(2)	C19-C18-C21-C22	1.8(5)
C7-C4-C5-O10	-0.8(4)	C14-C19-C24-C23	-175.1(2)
C7-C4-C5-N1	-178.6(2)	C14-C19-C24-C25	7.4(4)
C3-C4-C5-N1	-0.5(3)	C18-C19-C24-C23	3.5(3)
C5-C4-C7-C14	-120.8(3)	C18-C19-C24-C25	-174.0(2)
C3-C4-C7-C8	-177.4(3)	C18-C21-C22-C23	1.4(4)
C4-C7-C14-C15	34.9(3)	C18-C21-C22-C26	-179.5(3)
C4-C7-C8-C9	-0.1(3)	C21-C22-C23-C24	-2.0(4)
C4-C7-C8-C11	-177.2(2)	C26-C22-C23-C24	178.9(3)
C14-C7-C8-C9	123.2(3)	C22-C23-C24-C19	-0.6(4)
C14-C7-C8-C11	-53.9(3)	C22-C23-C24-C25	177.1(3)

Table 5: Intermolecular Hydrogen bonds and symmetry table

D—H...A	D—H	H...A	D...A	D—H...A	Symmetry code
N(2) --H(2) ..O(28)	0.86	2.04	2.8510	157	1+x,y,z
N(3) --H(13A) ..N(1)	0.86	2.23	2.0521	159	-1/2+x,1/2-y,-z
N(13) --H(13B) ..O(20)	0.86	2.17	2.0135	166	1-x,-1/2+y,1/2-z
O(28) --H(28) ..N(2)	0.82	2.24	2.8510	132	-1+x,y,z

Hirshfeld surface calculations

Analysis and calculations of the Hirshfeld surface were carried out and finger print plots were plotted using the software Crystal Explorer version 3.0 [14]. The d_{norm} plots were mapped with colour scale in between -0.542 au

(blue) to 1.432 au (red) respectively. The 2D fingerprint plots [15,16] in an expanded format were displayed in the range of 0.6 – 2.8 Å view with the d_e and d_i distance scales displayed on the graph axes.

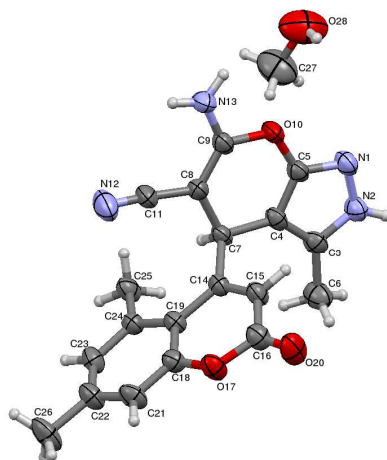


Figure 2: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

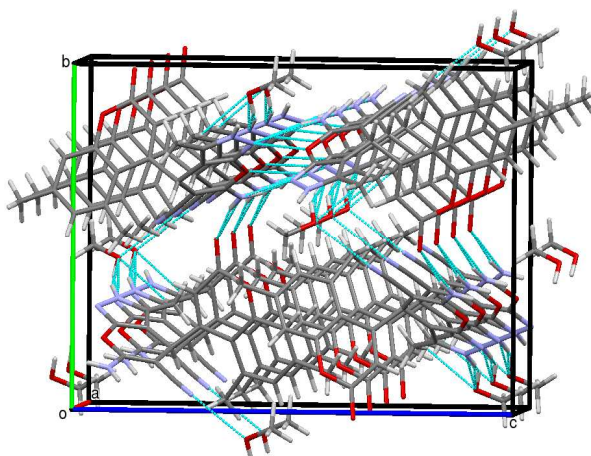


Figure 3: Packing of the molecules when viewed down along the 'a' axis. The dotted line represents hydrogen bond interactions

Hirshfeld surface studies

Hirshfeld surface analysis is used to describe the surface interactions of the atoms of the molecule and to generate unit cell packing diagrams. It also helps us to study the intermolecular contacts of the molecule in a crystalline environment. The close proximity of the intermolecular contacts can be shown on the Hirshfeld surface by calculating a normalized contact distance d_{norm} ; where d_{norm} gives the distance between two atoms across the surface to the atomic radii of the atoms [15]. Further the 2D fingerprint plots provide us information about the intermolecular interaction between the atoms and which can be represents in terms of d_e and d_i . Here d_e and d_i are the distances to the nearest nuclei outside and inside the surface from the Hirshfeld surface respectively. The contribution of the intermolecular interaction between the atoms to the Hirschfeld surface can be represented in terms of colour codes. Depending upon the shorter or longer intermolecular contacts the value of the d_{norm} varies from

negative to positive value. The red regions represent shorter contacts with negative and blue regions represent longer contacts with positive d_{norm} value. The white regions represent the distance of contacts with zero d_{norm} value [16].

The percentage contribution of individual intermolecular contacts to the surface revealed by fingerprint plot is given in **Table 6**. The H...H contacts shows maximum contribution, and other contacts are shown in **Figure 4**. These contacts are highlighted on the molecular surface using conventional mapping of d_{norm} and electrostatic potential as shown in the **Figure 5**. The bright red spots on the d_{norm} surface represents the presence of N(2)--H(2) ..O(28) and O(28) --H(28) ..N(2) hydrogen bond interactions.

Table 6: Percentage contributions to the Hirshfeld surface area from the various close intermolecular contacts of molecules in the crystal

Inter-contacts	Contributions (%)	Inter-contacts	Contributions (%)
H – H	40.9	C – C	0.6
C – H	17.7	N – O	4.4
N – H	14.8	O – O	0.2
O – H	20.8	C – O	0.5

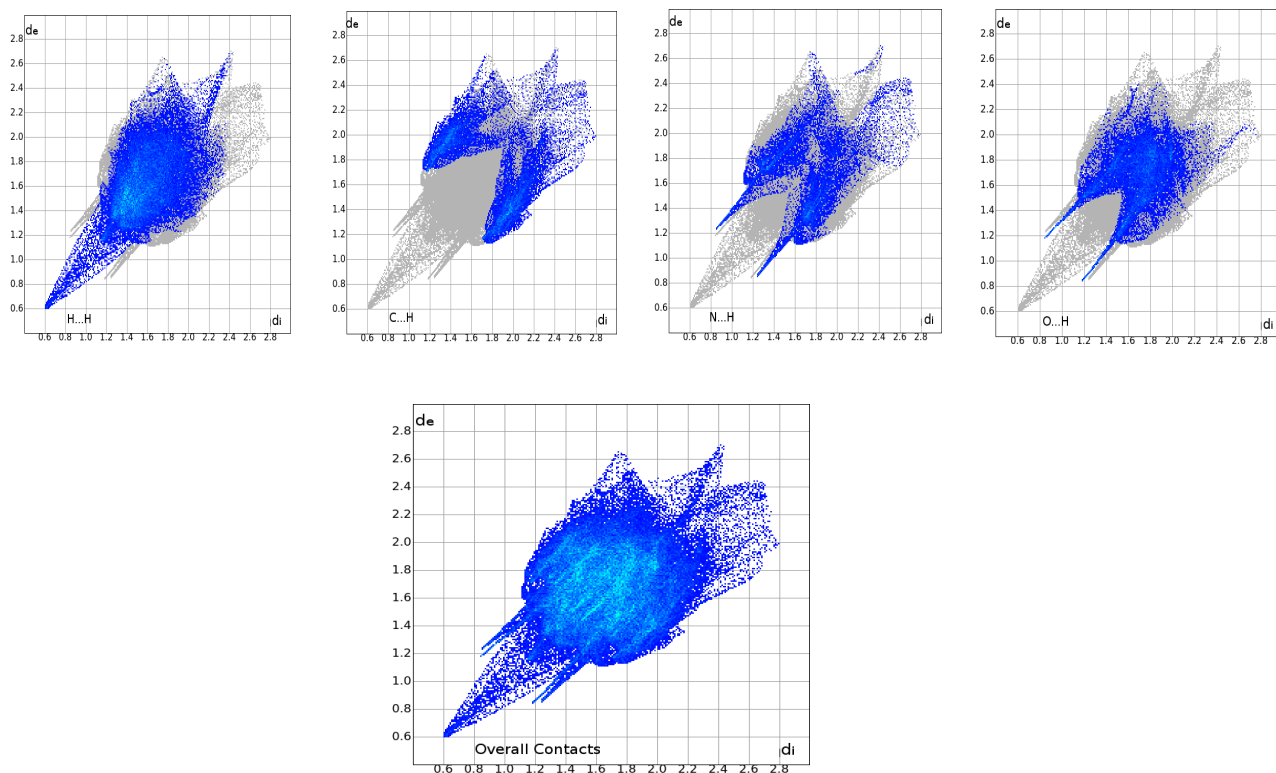


Figure 4: Fingerprint plots of the title compound showing H...H, C...H, N...H and O...H interactions. d_i is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts

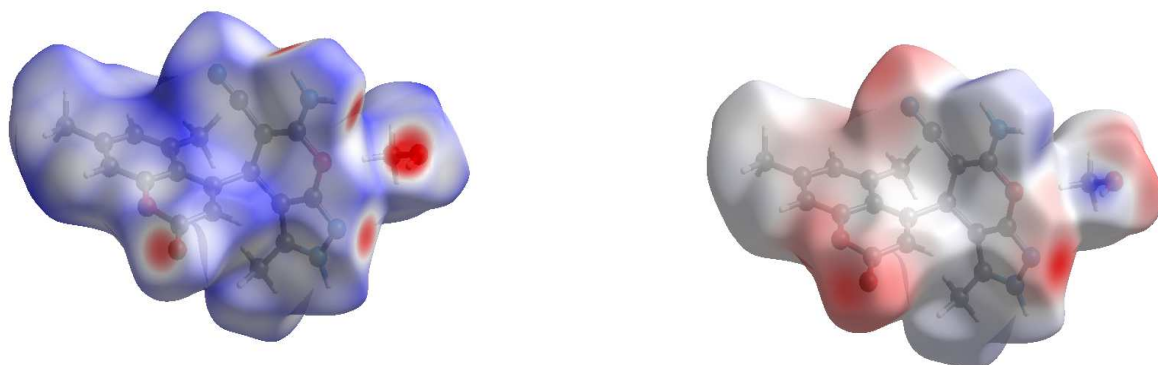


Figure 5: d_{norm} and electrostatic potential mapped on Hirshfeld surface for visualizing the intermolecular contacts

CONCLUSION

The title compound $\text{C}_{20}\text{H}_{20}\text{O}_4\text{N}_4$ has been synthesized and the single crystals were grown by the slow evaporation method using methanol as a solvent. The compound was characterized using the NMR and mass spectrum. The molecular structure of the compound was confirmed by the single crystal X-ray diffraction studies. The compound crystallizes in the orthorhombic crystal system, in $P2_12_12_1$ space group. The final residual value is $R = 0.0374$. The molecular structure exhibits intermolecular hydrogen bonds of the type $\text{N-H}\cdots\text{O}$, $\text{N-H}\cdots\text{N}$. The structure is also stabilized by $\text{Cg}\cdots\text{Cg}$ and $\pi\cdots\pi$ stacking interactions. The molecular Hirshfeld surface analysis and fingerprint plots reveal the nature of intermolecular interactions and their contributions to the molecular surface respectively.

SUPPLEMENTARY MATERIALS

CCDC **1482379** provides the supplementary crystallographic data of the title compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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