



Synthesis, Crystal Structures Investigations and Hirshfeld Surface Analysis of Novel Molecule 2, 5-Dihydro [2]Benzopyrano [3,4-c] Pyrazole-water (1/4)

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Abstract

2,5-dihydro[2]benzopyrano[3,4-c]pyrazole-water (1/4) has been novel and newly synthesized nucleus has till date never been reported earlier, it has crystallized in reddish bipyramidal shape, further its need to determine the site of action of these kind of molecules, followed by its detailed X-ray crystal structure were studied. Crystal structure was solved by direct method and refined by full matrix least squares procedure. The crystal structure was stabilized by elaborate system of O-H...N, N-H...O, N-H...N and C-H...O hydrogen bonds along with π - π interactions. 3D Hirshfeld surfaces and allied 2D fingerprint plots were analyzed for molecular interactions.

Keywords: Synthesis; Crystal Structure; Intermolecular Hydrogen Bonding; Hirshfeld Surface Analysis

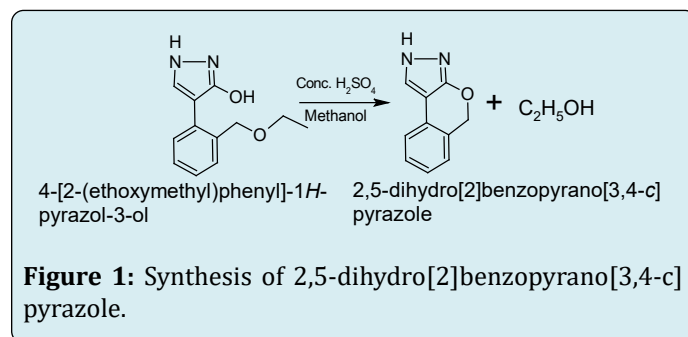
Introduction

The main aim is to introduce this novel combined tricyclic compound benzopyrano-pyrazol is a specific group having some specific biological properties which are not evaluated till the date. In the reaction mechanism with the removal of ethanol molecule the process of cyclization is approached from the parental compound. The final compound is having hexacyclic ring containing hetero oxygen atom. The data of the synthesized parental compound that is 4-[2-(ethoxymethyl)phenyl]-1H-pyrazol-3-ol is reported earlier [1]. This type of molecules usually shows anticancer, antioxidant, antitubercular and antimicrobial properties as per literature and structural similarities [2]. Also this type of compounds is showing some vasodilator properties.

Synthesis

Take a 0.218 gm 4-[2-(ethoxymethyl)phenyl]-1H-pyrazol-3-ol and dissolve in 10 ml methanol as a solvent to

added dropwise 5 drops of concentrated H₂SO₄. The whole reaction mixture is refluxing about 6 hr to get the final product. The final product is further filtered out and the solid compound is crystallized with them to further dissolved in methanol and by the process of slow evaporation reddish bipyramidal shaped crystals were separated out and it has to be used for further crystallographic study (Figure 1).



Crystal Structure Determination and Refinement

The molecular structure solution was obtained by direct method procedure as using SHELXT [3,4]. The cell dimensions were determined by least-squares fit of angular settings of 1723 reflections in the θ range 2.33° to 27.25°. The value of $R_{\text{int}} = 0.0484$ and $R_{\text{sigma}} = 0.0678$ shows satisfactory quality of the data. Five cycles of full-matrix least-squares refinement was carried out and it brought the final R-factor to 0.0563 and to GOOF value of 1.080. All non-hydrogen

atoms of the molecule were located in the best E-map and refined in anisotropic approximation using SHELXS [3,4]. The crystallographic data are summarized in Table 1. The position of all the Hydrogen atoms bonded to C atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms [C-H = 0.93-0.96 Å, and $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$ of the attached C atoms for methyl groups and $1.2 U_{\text{eq}}(\text{C})$ for other H atoms]. The residual electron density in the final difference Fourier map between $-0.25 < \Delta\rho < 0.23$. The geometry of the title molecule was calculated using WinGX [5], PARST [6] and PLATON [7] software.

Chemical formula	4(C ₁₀ H ₈ N ₂ O), H ₂ O
System, sp. gr., Z	Monoclinic, C 2/c, 4
a, b, c Å	34.929(2), 6.2889(5), 15.5975(9)
β deg	99.310(6)°
V, Å ³	3381.1(4)
D_x g.cm ⁻³	1.388
Radiation, λ , Å	MoK α , 0.71073
μ , mm ⁻¹	0.095
T, K	150.01(10)
Sample size, mm	0.30 X 0.20 X 0.20
Diffractionmeter	Rigaku Oxford CCD plate Diffractionmeter
Scan mode	ω scan
Absorption correction,	multi-scan
$T_{\text{min}}, T_{\text{max}}$	0.50638, 1.00000
$\theta_{\text{max}}, \text{deg}$	25.242
h, k, l ranges	-42 ≤ h ≤ 40
	-4 ≤ k ≤ 7
	-19 ≤ l ≤ 19
Number of reflections: measured/unique (N1)	5929/3296
R_{int} /with $I > 2\sigma(I)$ (N2)	0.0484/2346
Refinement method	Full matrix least squares on F ²
Number of refined parameters	240
R1/wR2 relative to N1	0.0806/0.1540
R1/wR2 relative to N2	0.0563/0.1338
S	1.08
$\Delta\rho_{\text{max}}/\Delta\rho_{\text{min}}, \text{e}/\text{Å}^3$	0.23/-0.25

Table 1: Crystallographic characteristics, details of X-ray data collection and structure refinement parameters for compound (1).

Crystallographic information has been deposited with Cambridge Crystallographic Data Centre, CCDC number 2282075. The data can be obtained from through www.ccdc.cam.ac.uk/data_request/cif by e-mailing data_request@ccdc.

cam.ac.uk, or by contacting The Cambridge Crystallography Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(0) 1223-336033.

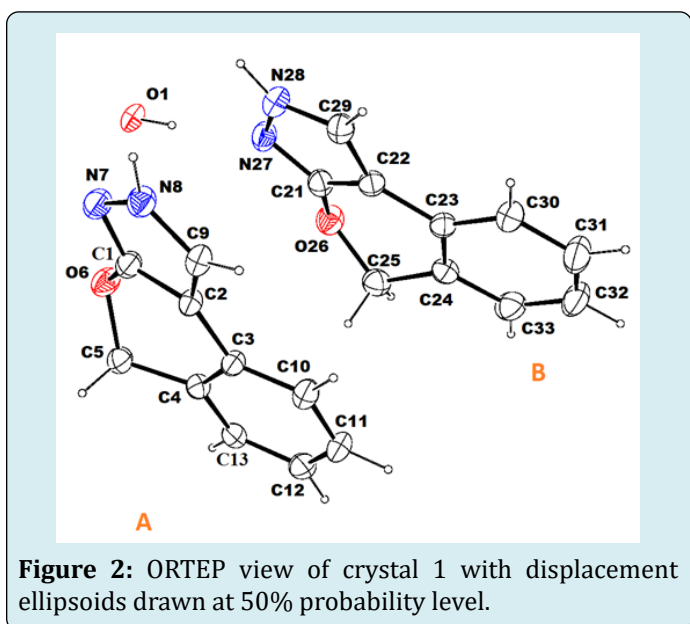
Hirshfeld Surfaces Calculations

The crystallographic information file (CIF) was utilised as input for the Crystal Explorer 17.5 programme [8] which performed the Hirshfeld surface analysis and generated fingerprint plots. The shape index, curvature, and standard (high) surface resolution of the 3D d_{norm} surfaces were used to create the molecular Hirshfeld surface of 1. The surfaces were demonstrated to be transparent to enable visualisation of the molecular moiety in a consistent orientation. Plotting 2D fingerprint graphs involves adding together (d_i, d_j) pairs.

Results and Discussion

Crystal Structure

The molecular structure containing atomic labeling of the asymmetric unit, '4(C₁₀H₈N₂O), H₂O' is shown in Figure 2 (ORTEP) [9]. The X-ray analyses showed that the asymmetric unit of the compound (1) contains two crystallographically independent molecules A and B along with a half water molecule. The central moieties of this compound are building from fusion of 1H-isochromene ring and a pyrazole ring.



The geometry of the title molecule is close to their normal geometry [10]. Moreover, there is very little difference between the bond lengths and angles of the title molecule and the structurally related molecule (C₂₀H₁₉N₃O₄) [11].

In pyrazole moiety, the bond lengths and angles around nitrogen atoms N7=N8 = 1.371(3)Å and N7-N8-C9 = 112.7(2)° in molecule A, and N27=N28 = 1.371(3)Å and N27-N28-C29 = 112.3(2)° are close to that are in related molecule (C₂₀H₁₉N₃O₄), respectively.

Bond	d, Å	Bond	d, Å
O6-C1	1.360(3)	O26-C21	1.359(3)
O6-C5	1.454(3)	O26-C25	1.445(3)
N7-C1	1.322(3)	N27-C21	1.311(3)
N7-N8	1.371(3)	N27-N28	1.371(3)
N8-C9	1.333(3)	N28-C29	1.333(3)
C1-C2	1.396(3)	C21-C22	1.401(3)
C2-C9	1.372(3)	C22-C29	1.382(3)
C2-C3	1.454(3)	C22-C23	1.451(3)
C3-C10	1.385(3)	C23-C30	1.393(4)
C3-C4	1.409(3)	C23-C24	1.401(4)
C4-C13	1.383(3)	C24-C33	1.390(4)
C4-C5	1.508(3)	C24-C25	1.505(4)
C10-C11	1.386(4)	C30-C31	1.379(4)
C11-C12	1.390(4)	C31-C32	1.387(4)
C12-C13	1.386(4)	C32-C33	1.382(4)
Angle	ω, deg	Angle	ω, deg
C1-O6-C5	111.07(19)	C21-O26-C25	112.29(19)
C1-N7-N8	102.4(2)	C21-N27-N28	103.1(2)
C9-N8-N7	112.7(2)	C29-N28-N27	112.3(2)
N7-C1-O6	121.3(2)	N27-C21-O26	121.0(2)
N7-C1-C2	113.9(2)	N27-C21-C22	114.0(2)
O6-C1-C2	124.6(2)	O26-C21-C22	124.7(2)
C9-C2-C1	103.3(2)	C29-C22-C21	102.8(2)
C9-C2-C3	136.4(2)	C29-C22-C23	136.8(2)
C1-C2-C3	120.0(2)	C21-C22-C23	119.6(2)
C10-C3-C4	119.4(2)	C30-C23-C24	119.4(2)
C10-C3-C2	125.7(2)	C30-C23-C22	124.7(2)
C4-C3-C2	114.8(2)	C24-C23-C22	115.7(2)
C13-C4-C3	119.7(2)	C33-C24-C23	119.6(3)
C13-C4-C5	121.4(2)	C33-C24-C25	121.4(3)
C3-C4-C5	118.8(2)	C23-C24-C25	119.0(2)
O6-C5-C4	113.43(19)	O26-C25-C24	114.5(2)
N8-C9-C2	107.7(2)	N28-C29-C22	107.8(2)
C3-C10-C11	120.5(3)	C31-C30-C23	120.2(3)
C10-C11-C12	120.2(3)	C30-C31-C32	120.4(3)
C13-C12-C11	119.7(2)	C33-C32-C31	119.8(3)
C4-C13-C12	120.6(3)	C32-C33-C24	120.5(3)

Table 2: Bond lengths d, Å and bond angles ω, deg for non-hydrogen atoms (e.s.d.'s are given in parentheses) for compound (1).

From the pluckering amplitude analysis of all the investigated molecules, the 1H-isochromene rings have distorted chair conformation where maximum deviation from plane of mean deviation are 0.02669(1) for atom C5 and 0.2439(1) for C25 in the molecule A and B, respectively [12]. All other component of ring moieties are individually planar as reflected from the small value of torsion angles. Furthermore, the dihedral angle value suggests that the pyrazole moiety is in plane to benzene moiety in both molecules A and B respectively. The bond lengths and bond angles for non-hydrogen atoms in compound 1 are shown in Table 2.

Analysis of the crystal packing showed that there exist intermolecular hydrogen bonds of O-H...N, N-H...O, N-H...N and C-H...O type, along with π - π and Van der Waal's forces; which play an important role in crystal structure stabilization. Packing view of molecules within the unit cell is generated using PLATON and viewed down to c-axis are shown in Figure 3. The active H atom H28 of the pyrazole moiety B attached at N28 atom participate with N7 nitrogen atom of molecule A, in formation of N-H...N intermolecular hydrogen bonds [13]. Figure 3 is the wire and frame image shown perpendicular along c direction forming chain like patterns.

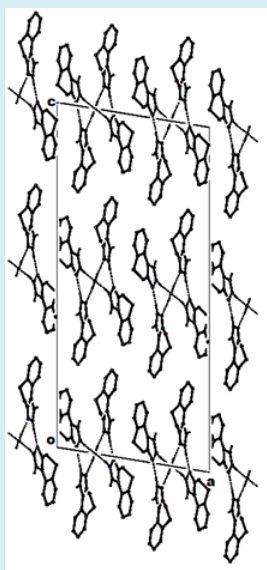


Figure 3: Packing view of molecules down to b-axis within the unit cell of 1.

Pyrazole rings are closely stacked through π - π interactions. The geometry of these interactions is presented in Tables 3 and 4. CgI represents the center of gravity of the ring (N27/N28/C29/C22/C21) and CgJ represents the center of gravity of the ring (N7/N8/C9/C2/C1). CgI...CgJ

represents the distance between the ring centroid; CgI...P represents the perpendicular distance of the centroid of one ring from the plane of the other; α is the dihedral angle between the planes of rings I and J; β is the angle between the normal to the centroid of the ring I and the line joining ring centroids; Δ is the displacement of the centroid of rings J relative to the intersection point of the normal to the centroid of ring I and the least-squares plane of ring J.

D-H...A	D-H, Å	H...A, Å	D...A, Å	θ (D-H...A), deg
O1-H1...N27 ⁱ	0.91	1.88	2.781(3)	171
N8-H8...O1 ⁱⁱ	0.98	1.77	2.737(3)	169
N28-H28...N7 ⁱⁱⁱ	0.92	1.96	2.871(3)	171
C9-H9...O26 ⁱⁱ	0.95	2.59	3.340(3)	136
C29-H29...O26 ⁱⁱ	0.95	2.57	3.280(3)	132

Table 3: Geometry of intermolecular interactions for compound (1).

Symmetry Codes: (i) x,y,z (ii) x,-1+y,z (iii) -x,-y,1/2-z.

CgI	CgJ	CgI...CgJ, Å	CgI...P, Å	α , deg	β , deg	Δ , Å
7	1 ⁱ	3.6674(15)	3.6017(10)	3.4579(10)	19.5	0.68

Table 4: Geometry of π - π interactions for compound 1.

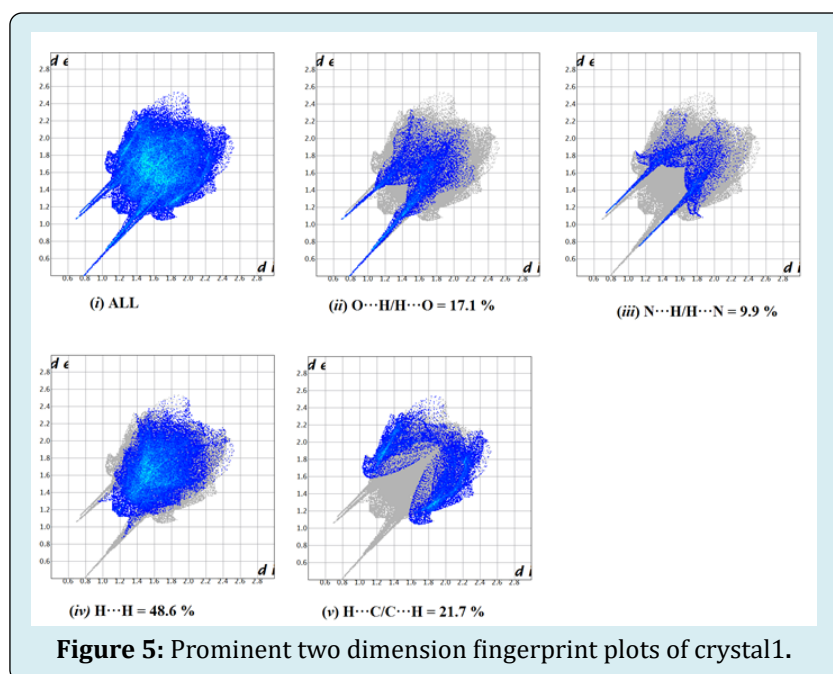
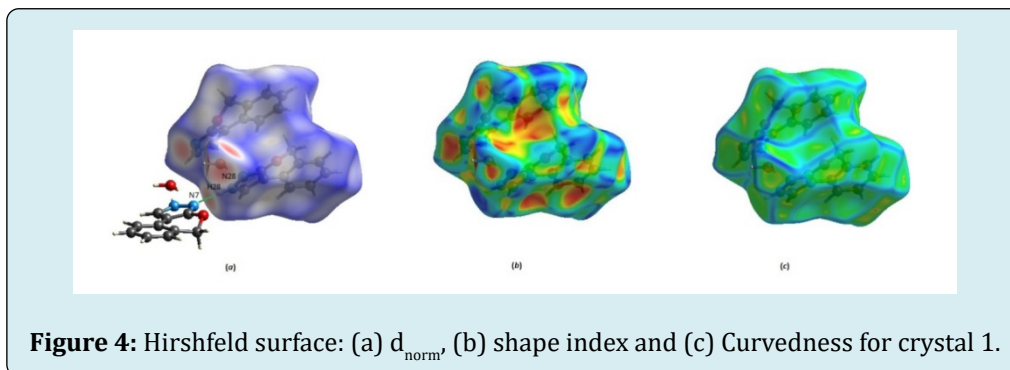
Symmetric code: (i) x, y, z.

Hirshfeld Surface Analysis

The mapping of intermolecular tight interactions in molecular crystals can be studied qualitatively and quantitatively using the Hirshfeld surface analysis. A set of points in 3D space where the contribution of the molecule of interest to the electron density is equal to the contribution of all other molecules make up the Hirshfeld surface that encloses that molecule [12]. Molecular Hirshfeld surfaces are constructed using an electron distribution model where the electron densities of all the spherical atoms are added together [14]. A standard (high) surface resolution was used to create the molecular Hirshfeld surface for the compound 1, and the 3D d_{norm} surfaces were mapped across a predetermined color scale of -1.2783 a. u. (red) to 1.2612 a. u. (blue). Figure 4(a) shows that a sizable red area on the molecule's d_{norm} surface is connected to the brief cyclic hydrogen bond connection between H28 and N7. The shape index was mapped in the -1.0 to 1.0 color space. Figure 4 (b) demonstrates the presence of self-complementary patches for the molecule that exhibits close stacking. The degree of

curvature was plotted between -4.0 and 0.4. Small, relatively flat green areas are separated by broad, positive curved dark

blue boundaries in Figure 4(c) showing that benzene rings are involved in the π - π sequence.



Plotting 2D fingerprint graphs involves adding together (d_i , d_e) pairs. Each collection's coloring is determined by the fraction of crystal 1 surface points, ranging from blue (few points) to green (average points) to red (many points). Figure 5 displays the associated 2D fingerprint plots [15] for the crystal 1 Hirshfeld surfaces, which highlight the primary intermolecular interactions and their proportional contribution to the total Hirshfeld surface area. The prominent symmetrical spike in the fingerprint map of crystal 1 emerges owing to $O\cdots H/H\cdots O$ contacts, is attributed to the existence of a strong ($C-H\cdots O$) hydrogen bond interaction with minimum ($d_i + d_e$) value of 2.80 Å. Table 5 shows that $H\cdots H$ interaction followed by $H\cdots C/C\cdots H$ interaction with 48.6 and 21.7 % respectively making a significant contribution among all common Hirshfeld surfaces, which are reflected in middle and upper half of scattered points in 2D fingerprint plots.

Intermolecular interaction	Contribution, %
$O\cdots O$	0.1
$O\cdots N/N\cdots O$	0.1
$O\cdots H/H\cdots O$	17.1
$O\cdots C/C\cdots O$	0.5
$N\cdots N$	0.1
$N\cdots H/H\cdots N$	9.9
$N\cdots C/C\cdots N$	0.9
$H\cdots H$	48.6
$H\cdots C/C\cdots H$	21.7
$C\cdots C$	0.4

Table 5: Summary of the various intermolecular contacts contributed to the Hirshfeld surface.

Conclusion

The entitled compound has 2,5-dihydro[2]benzopyrano[3,4-c]pyrazole-water (1/4) was synthesized with the elucidation of the reaction mechanism and further characterized by means of single X-ray crystallographic studies in order to elucidated the crystal structure and understand the behavior of the title molecule in presence of different hydrogen bond modes and $\pi\cdots\pi$ interactions stabilization and formation of supramolecular crystal structure. Hirshfeld surface analysis helped to identify and offer an insight into intermolecular interactions. The two-dimensional fingerprint plots indicated that H \cdots H and O \cdots H/H \cdots O are the major contributors towards these interactions.

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