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Crystal Structure and Hirshfeld Surface Analysis of a *β*-Carboline Derivative

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ABSTRACT

The title compound was synthesized in redox neutral C–H functionalization method. The resultant compound was characterized by ^{1}H NMR and X-ray diffraction. The X-ray diffraction study reveals that the sample has crystallized in the triclinic crystal system with the space group $P\bar{1}$. The asymmetric unit cell contains two molecules. The lattice parameters are a = 9.6544(3) Å, b = 11.1048(4) Å, c = 14.1787(5) Å, α = 87.2370(10)°, β = 70.5310(10)°, γ = 65.3700(10)° and V = 1295.48(8) Å^3. The molecule is stabilized by both intra and intermolecular interactions of the type C-H...O, C-H...N and N-H...O hydrogen bonds.

Keywords: *β*-carbolines, *P. Harmala*, Hirshfeld surface analysis, Fingerprint plots.

INTRODUCTION

The title compound $C_{30}H_{26}BrClN_2O_3$ belongs to the class of the *β*-carbolines. *β*- Carboline alkaloids are a group of natural and synthetic indole alkaloids. They are commonly present in various plants, bacteria, fungi, marine microorganisms, and in human tissues and body fluids [1]. These alkaloids have great biological and pharmacological applications such as sedative, hypnotic, anxiolytic, and anticonvulsant, antitumor, antiparasitic, antimicrobial and antiviral activities. Some of the *β*-carbolines and its derivatives have been considered as inhibitors of CDK's (cyclin-dependendent kinases) [2].

Literature survey reveals that, the *β*-carbolines are one of the important chemical compositions of the Herbal (*Peganum harmala L.* family *Zygophyllaceae*) plant [3]. This plant is commonly found in Iran and is used as a medicinal plant in Central Asia, North Africa and Middle East [2, 3]. Various pharmacological studies show that the *P. Harmala* extracts and their main active alkaloids, harmine, harmaline have different cardiovascular effects such as bradycardia, decreasing systemic arterial blood pressure and total peripheral vascular resistance and angiogenic inhibitory effects [3]. From the previous studies it is revealed that harmine and harmaline are promising candidates to inhibit 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) mediated induction of Cyp1a1 (*cytochrome* P450, family 1, subfamily a, *polypeptide* 1) in mice hepatic and extra hepatic tissues [4].

With this background, the compound ((6bR,14bR,15R,15aR)-ethyl 5-bromo-14b-phenyl-1,6b, 8,9,14, 14b,15,15a-octahydrochromeno[3',4':2,3] indolizino [8,7-b] indole-15-carboxylate) was synthesized and

characterized. The study of X-ray diffraction and Hirshfeld surface analysis along with fingerprint plots confirm the structure of the compound and nature of the intermolecular interactions respectively.

MATERIALS AND METHODS

Chemicals were purchased from Sigma Aldrich Chemical Corporation. Proton nuclear magnetic resonance spectra ^{1}H NMR spectra were recorded on an Agilent Bruker DRX - 500 spectrometer at 400 MHz using DMSO as a solvent and are reported in ppm using $CDCl_3$ /DMSO-d6 as the internal standard (7.24/2.50 ppm) [5]. X-ray diffraction data were collected on a Bruker CCD instrument.

Synthesis of the title compound: The compound ((6bR,14bR,15R,15aR)-ethyl 5-bromo-14b-phenyl-1,6b,8,9,14,14b,15,15a-octahydrochromeno[3',4':2,3] indolizino [8,7-b] indole-15-carboxylate) was synthesized in redox neutral C–H functionalization method. The detailed synthesis procedure is reported in [5]. In order to get the suitable crystal for X-ray diffraction, the compound was dissolved in minimum amount of dichloromethane followed by the addition of non-polar solvent (hexane) and the solution was kept for slow evaporation. The schematic diagram of the synthesized compound is shown in **figure 1**.

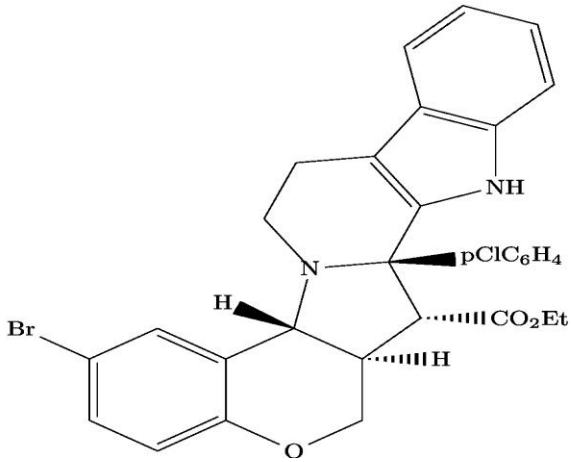


Fig 1. The Schematic diagram of the compound

RESULTS AND DISCUSSION

X-ray crystal structure determination: A white colored solid block single crystal of the title compound with appropriate dimensions of 0.27 x 0.26 x 0.25 mm was chosen for the X-ray diffraction. The compound ($C_{30}H_{26}BrClN_2O_3$) crystallizes in the triclinic crystal system in the space group $P\bar{1}$ and Z = 2. The unit cell parameters are a = 9.6544(3) Å, b = 11.1048(4) Å, c = 14.1787(5) Å, α = 87.2370(10) ˚, β = 70.5310(10) ˚, γ = 65.3700(10) ˚.

Data were collected on the Bruker CCD equipped with CuK_α radiation. Using BRUKER *SADABS* program [6] data reduction and absorption corrections were carried out with multi-scan method. The structure of the molecule was solved by direct methods using *SHELXS-97* and refined by full matrix least squares refinement against F^2 using *SHELXL-97* [7]. Crystal data and structure refinement details are summarized in **table 1**. Hydrogen atoms attached to the carbon atoms were placed in geometrically idealized positions and all the non-hydrogen atoms were refined anisotropically. The bond lengths and bond angles values are within the expected range and are listed in **table 2**. A total of 335 parameters were refined with 4269 unique reflections. After final refinement, the residual value converged to R = 0.04. The geometrical calculations were carried out using the program *PLATON* [8].

Table 1. Crystal data and structure refinement details

CCDC deposit number	1054104
Empirical formula	$C_{30}H_{26}BrClN_2O_3$
Formula weight	577.89
Temperature	293 K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Cell parameters	a = 9.6544(3) Å, b = 11.1048(4) Å, c = 14.1787(5) Å, α = 87.237(1) ˚, β = 70.531(1) ˚, γ = 65.370(1) ˚.
Volume	1295.48(8) Å ^{3}
Z	2
Density (calculated)	1.481 Mg m $^{-3}$
Absorption coefficient	3.398 mm^{-1}
F_{000}	592
Crystal dimension	0.27 × 0.26 × 0.25 mm
θ range for data collection	3.32˚ to 64.52˚
Index ranges	$-11 \le h \le 11$ $-12 \le k \le 12$ $-16 \le l \le 15$
Reflections collected	12227
Independent reflections	4269 [R_{int} = 0.0662]
Refinement method	Full matrix least-squares on F ^{2}
Data / restraints / parameters	4269 / 0 / 335
Goodness of fit on F^2	1.025
Final [I > 2σ(I)]	R1 = 0.04, *wR2* = 0.1104
Largest diff. Peak and hole	0.451 and -0.868 eÅ $^{-3}$

Figure 2 shows the *ORTEP* diagram of the molecule with thermal ellipsoids drawn at 50% probability. **Table 3** lists out the selected torsion angles. Hydrogen bond geometry is given in **table 4** with symmetry code $2-x, 1-y, -1-z$.. The molecular graphics were generated using *Mercury* [9]. **Figures 3** and **4** shows the packing diagrams viewed down *b* and *c* axes respectively.

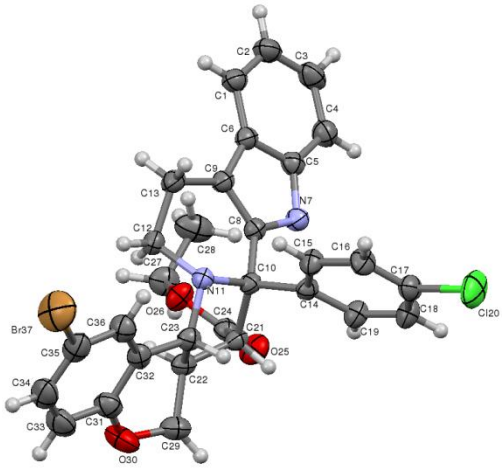


Figure 2. The *ORTEP* diagram of the compound.

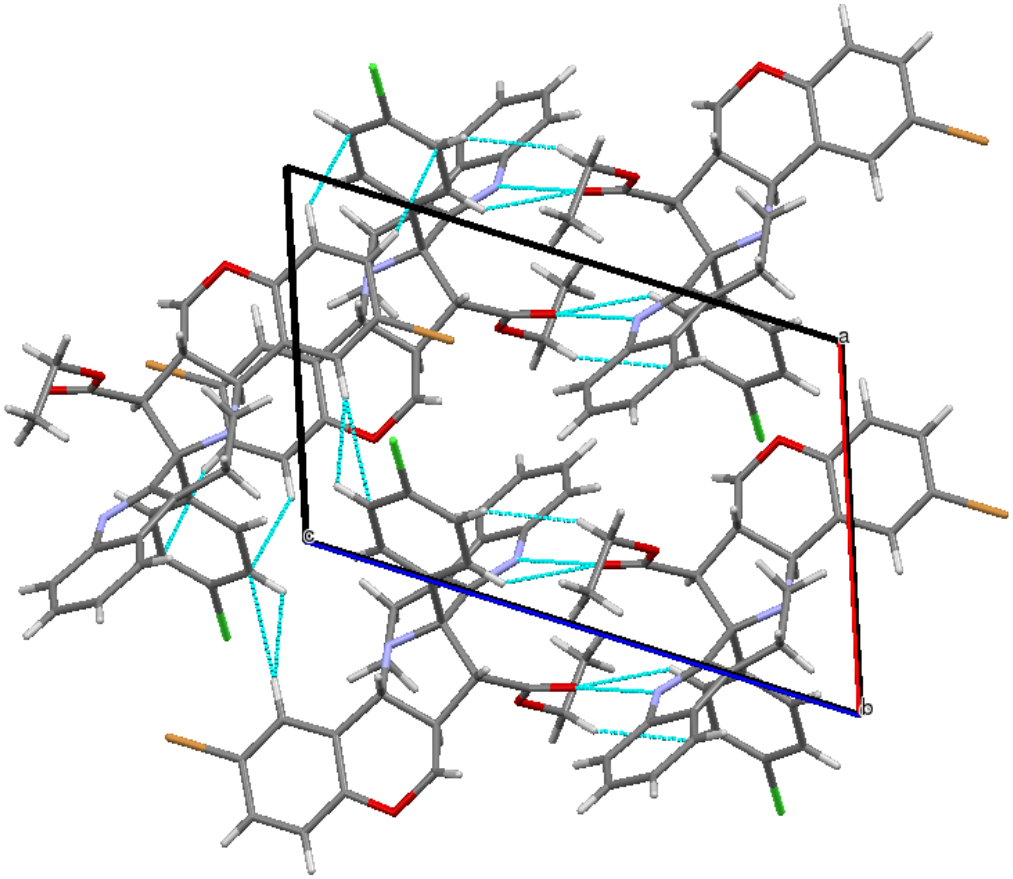


Figure 3.The packing view of the molecules down the *b* axis. The cyan lines indicate hydrogen bonds.

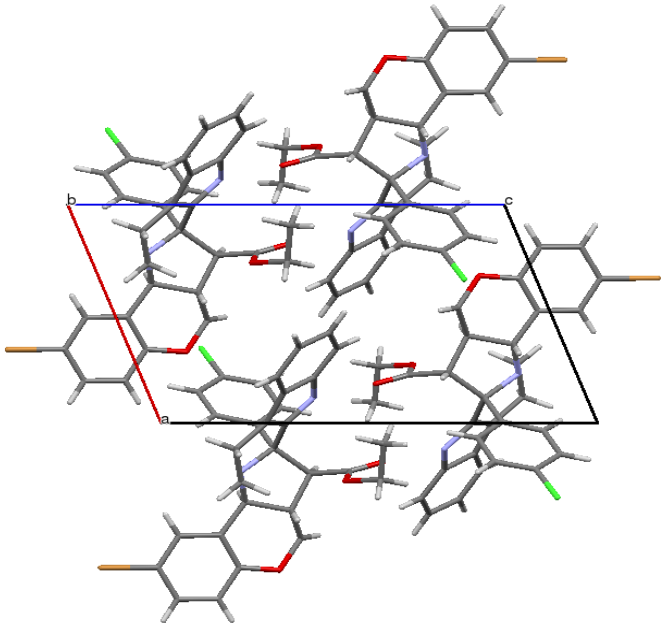


Figure 4. The packing view of the molecules down the *c* axis.

In the structure the five membered ring (C5-C6-N7-C8-C9) is highly planar with the maximum deviation of 0.006(2) Å for C9 atom, and the ring is *sp2* hybridized. The five membered ring (C10-N11-C21-C22-C23) adopts an envelope conformation on C23 atom with an r.m.s deviation of 0.326(2) Å and is *sp3* hybridized. The carboxylate group attached to the five membered ring (C10-N11-C21-C22-C23) is in *-syn-periplanar* conformation as indicated by the torsion angle value of -3.6(4)˚.

The molecular conformation is stabilized by a weak intramolecular $\pi - \pi$ stacking interaction between the rings (C1-C2-C3-C4-C5-C6) and (C5-C6-N7-C8-C9) with centroid-centroid distances of 3.523(3) Å and 3.689(3) Å respectively. The dihedral angle between the least-squares planes of the chlorophenyl ring and the *β*-carboline ring is 60.2(2)˚ implying that the chlorophenyl ring is in *synclinal* conformation.

The structure exhibits intramolecular hydrogen bonds of the type C-H..O and C-H...N with bond lengths of 3.015(2) Å and 3.015(2) Å respectively. There are also intermolecular interactions of the type C-H...O and N-H..O involving atoms with symmetry code $2 - x, 1 - y, -1 - z$.

In the crystal, N-H..O and C-H...O hydrogen bonds connect the molecules into inversion dimers. These are further connected by C-H...O and C-H...N hydrogen bonds forming a three-dimensional framework.

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

Atoms	**Bond lengths (**Å)	**Atoms**	**Bond angles (deg)**
O30-C29	1.437(3)	C24-O26-C27	118.58(17)
N11-C23	1.476(4)	C10-N11-C12	114.37(16)
C10-C14	1.550(3)	C2-C1-C6	119.3(2)
C34-H34	0.9300	N11-C23-C32	120.8(2)
Br37-C35	1.900(3)	Br37-C35-C36	120.0(3)
C23-C32	1.489(4)	O25-C24-C21	124.68(19)

N11-C12	1.487(2)	C8-C9-C13	121.0(2)
C1-C2	1.377(4)	N7-C8-C10	123.79(17)
O26-C27	1.450(3)	C22-C21-H21	109.00
N7-C8	1.380(3)	C14-C15-C16	121.4(2)

Table 3. selected torsion angles (deg)

Atoms	**Torsion Angles (deg)**	**Atoms**	**Torsion Angles (deg)**
N7-C8-C10-C14	60.2(2)	Br37-C35-C36-C32	177.38(16)
O25-C24-O26-C27	-3.6(4)	C1-C6-C9-C13	3.5(5)
C29-O30-C31-C33	-171.2(2)	C10-C21-C22-C29	-144.67(18)
C8-N7-C5-C4	-179.6(2)	C23-C22-C29-O30	63.7(2)
C10-N11-C12-C13	−63.5(2)	C12-N11-C10-C21	-92.9(2)
C10-C8-C9-C13	-8.6(3)	C22-C23-C32-C31	22.8(3)

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

D-H...A	**D-H**	**H...A**	**D...A**	**D-H..A**
N(7)−H(7)...O(25)	0.86	2.16	3.015(2)	172
C(15)−H(15)...N(11)	0.93	2.39	2.753(3)	103
C(19)−H(19)...O(25)	0.93	2.59	3.323(3)	136
C(22)−H(22)...O(26)	0.98	2.40	2.851(3)	108

Hirshfeld Surface Analysis: Hirshfeld surface generator is an useful tool for describing the surface interactions of the molecules. Hirshfeld surfaces and their associated fingerprint plots were generated using the program CrystalExplorer [10]. The close intermolecular contacts can be shown on the Hirshfeld surface by calculating a normalised contact distance d_{norm} ; where d_{norm} gives the distance between two atoms across the surface to the combined van der Waals radii of the atoms [10]. The value of d_{norm} is negative or positive depending upon the shorter or longer intermolecular contacts than the van der Waals radii respectively. The red regions represent shorter contacts with negative d_{norm} value; blue regions represent longer contacts with positive d_{norm} value and white regions represent the distance of contacts is exactly the van der Waals separation with a d_{norm} value of zero [11].

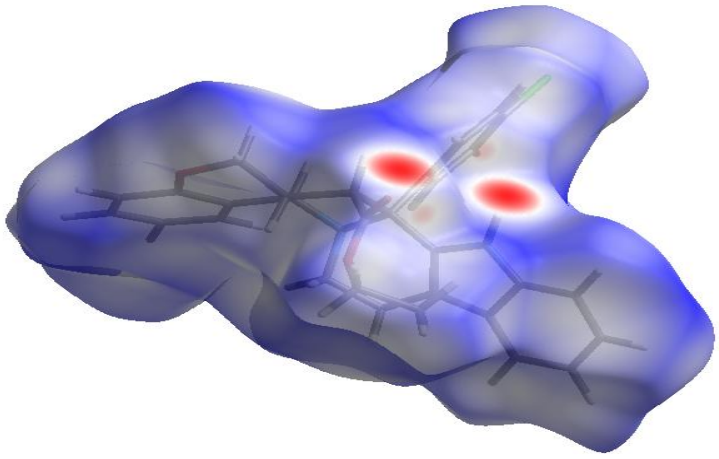
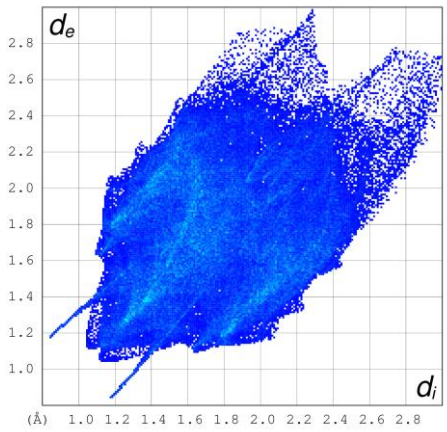


Figure 5. Hirshfeld surface of the compound $C_{30}H_{26}BrClN_2O_3$

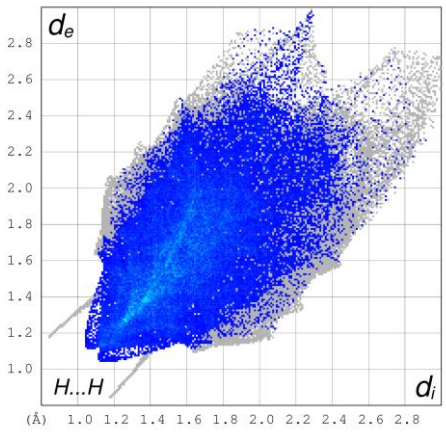
The 2-D fingerprint plots quantitatively give the nature and type of intermolecular contacts experienced by the molecules in the crystal. It plots the distance (d_i) from the nearest atom inside the surface against the distance (d_e) to the nearest atom external to the surface [12].

Table 5 shows the individual contribution of the intermolecular contacts to the total Hirshfeld surface. Among all the various contacts H...H accounts for the major contribution (44.1%) while C...H (21.0%), Br...H (11.2%), Cl...H (10.2%) and O...H (8.5%) contacts are the other significant contributors to the total Hirshfeld surface area. The minor contribution is from O...Cl contacts (0.2%). **Figure 5** shows the mapping of d_{norm} on the molecular Hirshfeld surface the compound. The bright red spots in the figure arises from the hydrogen bonds N7-H7...O25 and C19-H19...O25 intermolecular interactions. Their presence is also confirmed by the single crystal x-ray diffraction. The 2-D fingerprint plots are shown in **figure 6.**

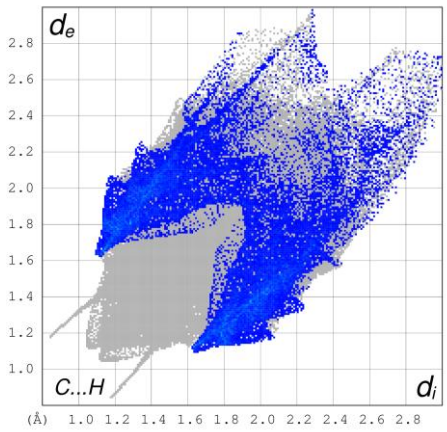
(a)



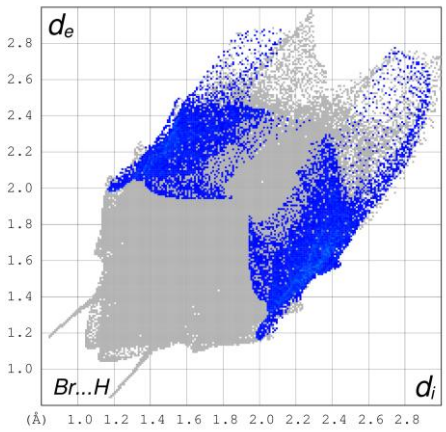
(b)



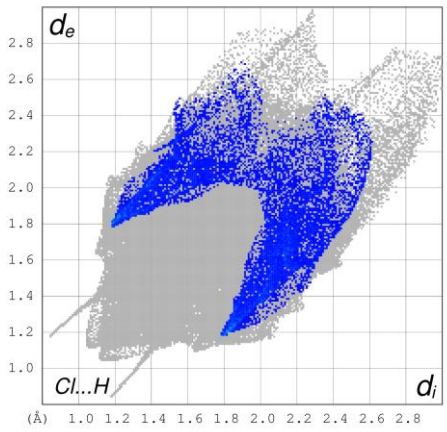
(c)



(d)



(e)



(f)

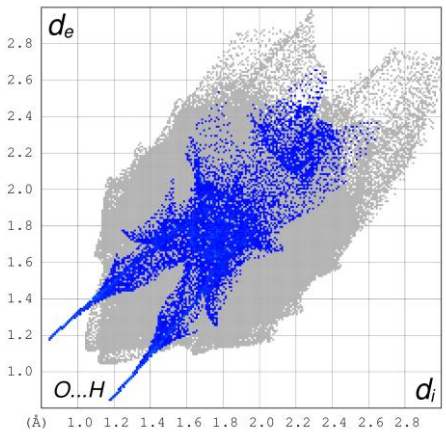


Figure 6. Fingerprint plots of the compound **a)** The total contribution from all the interactions **b)** H...H **c)** C...H **d)** Br...H **e)** Cl...H **f)** O...H showing the percentage of contacts contributed to the total Hirshfeld surface area for the molecule.

Table 5. 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	44.1	C – Cl	1.0
C – H	21.0	C – O	0.8
Br – H	11.2	Cl – Br	0.7
Cl – H	10.2	N – H	0.4
O – H	8.5	O – Cl	0.2
C – Br	1.3	O – Cl	0.2

APPLICATIONS

Literature survey shows that the *β*-carboline and its derivatives are biologically more active. They find numerous applications in medical field such as antitumor, antiparasitic and antimicrobial activities. Indole alkaloids are the potent inhibitors of cardiovascular related problems.

CONCLUSIONS

The present work helps us to understand the molecular structure and the intermolecular interactions of the synthesized compound. The structure was confirmed by ^{1}H NMR and X-ray diffraction. The compound has been crystallized in triclinic crystal system with space group $P\bar{1}$. The final residual value is *R = 0.04.* Further, from the Hirshfeld surface analysis, it can be concluded that the major contribution to the total surface area is from H...H interactions.

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