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Crystal Structure and Hirshfeld Surface Analysis of a Tosyl group Substituent Indole Derivative

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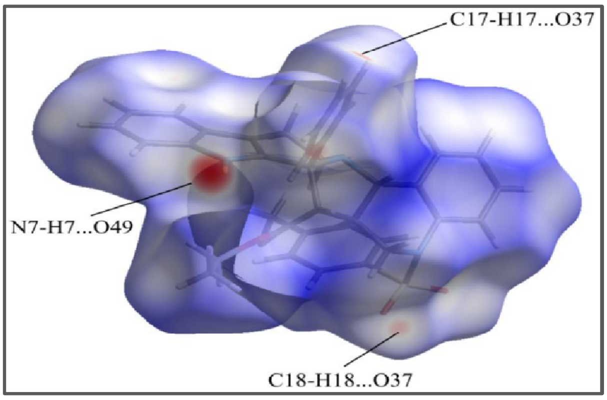
ABSTRACT

The crystal structure of (6bR,14bR,15R,15aS)-ethyl 14b-phenyl-2-tosyl-2,6b,8,9,14,14b,15,15a-octahydro-1H-indolo[3',2':7]indolizino[2,3-c]quinoline-15-carboxylate is determined by single crystal X-ray diffraction technique. The compound crystallizes in the triclinic crystal system in the space group $P\bar{1}$. *The unit cell parameters are:* $a = 11.4998(7)$ Å, $b = 12.4129(7)$ Å, $c = 13.5102(8)$ Å, $\alpha = 75.678(2)°$, $\beta = 79.099(2)°$, $\gamma = 74.438(2)°$. *Two molecules comprise the asymmetric unit. In the structure C-H...N, C-H...O and N-H...O hydrogen bond interactions are observed. Hirshfeld surface analysis was carried out to understand the intermolecular interactions.*

Graphical Abstract



Hirshfeld surface mapped with the normalized contact distance d_{norm}.

Keywords: Crystal structure, Indole, Cytotoxic, Graph-set motif, Hirshfeld surface.

INTRODUCTION

Indole is nitrogen containing bicyclic heterocyclic compound which shows many characteristic biological activities. Indole derivatives act as therapeutical agents. A few indole derivatives, such as melatonin and serotonin, influence major biochemical processes [1]. Serotonin is a bioregulating neuro transmitting key in animals, which plays a vital role in human mental health [2]. Indole derivatives are very good scaffolds for designing many drugs [3]. They act as anticancer [4], antibacterial, antifungal [5], cytotoxic, antitumor, and anti-HIV agents [6]. They are found to act against hepatitis *B* virus, and exhibit antibacterial activities. Several investigations revealed that the indole derivatives act as potent inhibitors of human immunodeficiency virus [7]. The diverse range of biological applications of indole derivatives piqued us to synthesize and study the structure of an indole derivative.

MATERIALS AND METHODS

All the chemicals were purchased from Sigma Aldrich Corporation. The compound was synthesized by the method of diastereo selective intramolecular [3+2]-cycloaddition of benzylic amines. A solution of aldehyde (1 mmol, 1 equi.) and toluene (10 mL) was prepared. To this mixture 3 Å molecular sieve (200 mg), amine (1.2 mmol, 1.2 equi.) and benzoic acid (0.2 mmol, 0.2 equi.) were added and stirred at 50 °C for 18 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was filtered through a celite plug rinsed with 20 mL EtOAc, when no aldehyde content was detected. Using saturated aqueous $NaHCO_3$ (3 x 15 mL) the filtrate was washed and the combined aqueous layers were extracted with EtOAc (3 x 15 mL). These layers were dried over anhydrous Na_2SO_4. The solvent was removed and residue was purified by silica gel chromatography. The final product yield was 92 % as a white solid. The obtained compound was dissolved in minimum amount of dimethyl sulfoxide followed by the addition of non-polar solvent (hexane). The solution was kept for slow evaporation to get suitable crystals for X-ray diffraction studies. The schematic diagram of the synthesized compound $C_{39}H_{41}N_3O_5S_2$ is shown in figure 1. The melting point of the compound was found to be 156-158°C.

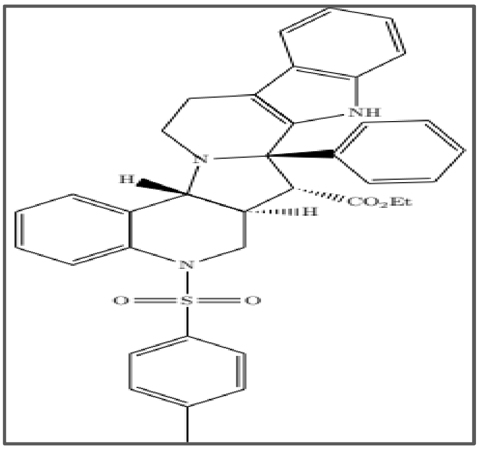


Figure 1. The schematic diagram of the compound.

^1H NMR spectrum was recorded on Bruker-400 MHz using DMSO-d_s as the internal solvent. ^{13}C NMR spectrum was recorded on Bruker-100 MHz using DMSO-d_6. The spectral details and elemental analysis are reported in [8].

X-ray crystallography: A block of white colored single crystal of approximate dimensions 0.23 x 0.22 x 0.21 mm was chosen for X-ray diffraction study. Data were collected on a Bruker CCD diffractometer equipped with CuK_α radiation of wavelength 1.54178 Å. *APEX*2 package [9] was used for data reduction of all the measured reflections, and absorption corrections. Crystal structure was solved by direct methods using *SHELXS*-97. They were refined by full matrix least squares refinement against F^2 using *SHELXL*-97 [10]. All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon atoms were placed at geometrically acceptable positions. A total of 446 parameters were refined with 5939 unique reflections. After the final refinement, the residual value R converged to 0.0405. The crystal data, data collection and structure refinement details are given in table 1. The geometrical calculations were carried out using *PLATON* [11]. *MERCURY* [12] software was employed to generate the molecular graphics. A few selected geometrical parameters are listed in table 2.

Table 1. Crystal data and structure refinement details

CCDC number	1550554	Empirical formula	$C_{39}H_{41}N_3O_5S_2$
Formula weight	695.87	Temperature	293 K
Wavelength	1.54178 Å	θ range	3.78° to 64.68°
Crystal system	Triclinic	Space group	$P\bar{1}$
Cell dimensions	a = 11.4998(7) Å,	Volume	1784.45(18) $Å^3$
	b = 12.4129(7) Å,	Z	2
	c = 13.5102(8) Å,	Density(calculated)	1.295 Mg m^{-3}
	α = 75.678(2)°,	Absorption coefficient	1.739 mm^{-1}
	β = 79.099(2)°,	F_{000}	736
	γ = 74.438(2)°	Crystal size	0.23 x 0.22 x 0.21 mm
Index ranges	$-13 \le h \le 13$		
	$-13 \le k \le 14$	Reflections collected	29146
	$-15 \le l \le 15$	Independent reflections	5939 [R_{int} =0.0389]
Absorption correction	Multi-scan	Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5939 / 0 / 446	Goodness-of-fit	1.034
Final [$I > 2\sigma(I)$]	R_1 = 0.0405, wR_2 = 0.1072	R indices (all data)	R_1 = 0.0439, wR_2 = 0.1105
Extinction coefficient	1.739	Largest diff. peak and hole	0.493 and −0.377 e $Å^{-3}$

Table 2. Selected geometrical parameters in Å and °

Atoms	Bond lengths (Å)	Atoms	Bond angles and torsion angles (°)
S36-O37	1.425(2)	O37-S36-O38	119.6(1)
S36-N29	1.662(2)	N29-S36-C39	108.8(1)
N11-C22	1.472(2)	S36-C39-C40	119.9(2)
C10-C14	1.537(2)	O24-C23-O25	124.5(2)
N29-C30	1.450(2)	S36-N29-C30-C32	−62.6(2)
S46-C47	1.763(3)	N7-C8-C10-C20	63.1(2)
N7-C5	1.376(2)	O38-S36-C39-C40	145.8(2)
O25-C23	1.332(2)	O37-S36-N29-C28	−32.2(2)
S36-C39	1.766(2)	C14-C10-C20-C23	119.0(2)

RESULTS AND DISCUSSION

The compound ($C_{39}H_{41}N_3O_5S_2$) crystallizes in the triclinic crystal system in the space group $P\bar{1}$. The unit cell parameters are a = 11.4998(7) Å, b = 12.4129(7) Å, c = 13.5102(8) Å, α = 75.678(2)°, β = 79.099(2)°, γ = 74.438(2)°, Z = 2. The asymmetric unit has two molecules.

The carboxylate group attached to the five membered ring C20-C21-C22-N11-C10 deviates from the mean plane with a maximum r.m.s deviation of -0.072(2) for C10 atom. The *ORTEP* diagram of the compound is shown in the figure 2. Five membered ring N11-C10-C20-C21-C22 adapts an envelope conformation on C22 atom with puckering parameters Q = 0.4786(17) Å and φ = 322.4(2)°. The dihedral angle between the benzene and pyrrole ring in the indole system is 177.9(2)° (C8-N7-C5-C4) , which indicates that they are nearly coplanar. The bond angle around C8 in the five membered rings C6-C5-N7-C8-C9 is 358.3° indicates that the ring is sp^2 hybridized.

The intra and intermolecular contacts are given in table 3. The association of phenyl ring with the six membered ring C10-N11-C12-C13-C9-C8 is described by the torsion angles N11-C10-C14-C15 = 24.9(2)° and N11-C10-C14-C19 = -160.2(2)°. This orientation is influenced by the intramolecular C-H...N interactions. Similarly, the orientation of tosyl group with the six membered ring C21-C28-N29-C30-C31-C22 is described by the torsion angles C28-N29-S36-O37 = -32.2(2)°, C28-N29-S36-O38 = -160.7(1)° and C40-C39-S36-O37 = 15.6(2)°. This orientation is influenced by C-H...O

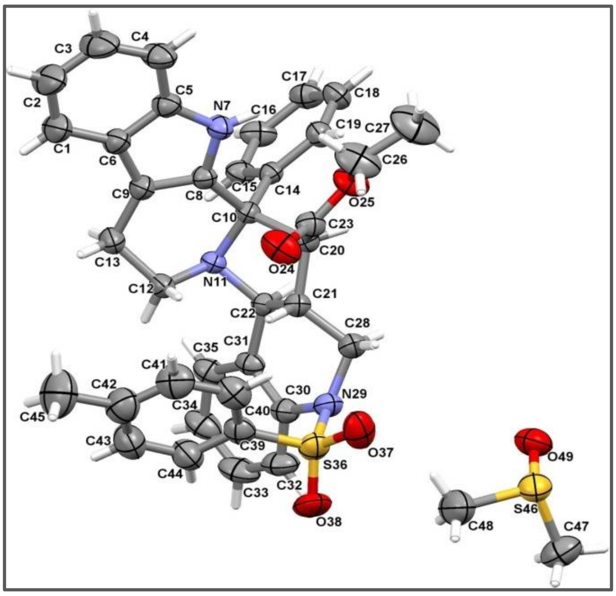


Figure 2. *ORTEP* diagram of the compound with 50% probability displacement ellipsoids.

intramolecular interactions. The syn-clinal conformation of carboxylate group as indicated by the torsion angle value -35.9(3)° for C21-C20-C23-O24 atoms from the pyridine ring is also influenced by intramolecular C-H...O interactions.

Table 3. Hydrogen bond geometry in Å and °

D-H...A	D-H	H...A	D...A	D-H...A
N7-H7...O49[a]	0.86	2.10	2.864(2)	148
C15-H15...N11	0.93	2.44	2.798(2)	103
C17-H17...O37[b]	0.93	2.52	3.233(3)	134
C18-H18...O37[c]	0.93	2.58	3.372(3)	144
C21-H21...O24	0.98	2.52	2.906(2)	103
C28-H28B...O37	0.97	2.33	2.820(2)	111
C32-H32...O38	0.93	2.40	2.896(3)	113
C40-H40...O37	0.93	2.57	2.931(3)	103

Note: [a], [b], and [c] indicates an intermolecular interactions with Symmetry codes *x*,1-*y*,1-*z*,*x*,-1+*y*,*z* and *x*,1-*y*,1-*z* respectively. In the structure the presence dimethyl sulfoxide solvent molecule is observed.

The terminal tosyl group substituent is in -syn-clinal conformation as indicated by the torsion angle of -62.6(2)° for S36-N29-C30-C32 atoms. The atom S36 in the tosyl group has nearly tetrahedral conformation with bond angles of N29-S36-O38 = 107.51(9)°, N29-S36-O37 = 105.19(9)°, C39-S36-O37 = 108.4(1)° and C39-S36-O38 = 107.0(1)°. The variation of bond angle for C22-N11-C12 atoms (112.4(1)°) is small as compared to previously reported indole derivatives [13, 14].

Supramolecular features: The molecular packing in the crystal structure is governed by N-H...O and C-H...O hydrogen bond interactions. Figure 3 shows the packing of the molecules down the *b* axis; N-H...O intermolecular interactions are also shown. The supramolecular architecture in the crystal structure (Figure 4) involves C26-H26B...O24 interactions, which link the pair of molecules to form inversion dimers generating R_2^2(10) graph-set motif [15]. Molecular packing is further reinforced by C-H...cg interactions.

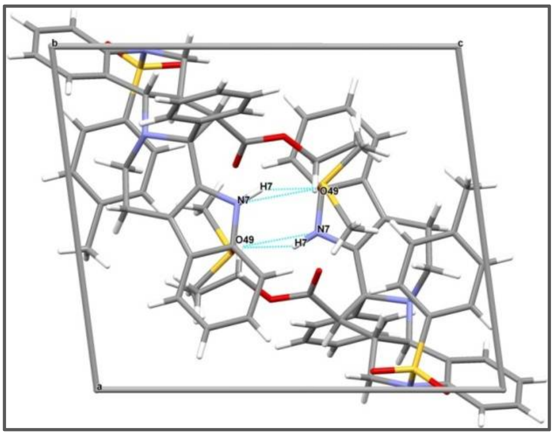


Figure 3. Packing of the molecules viewed down *b* axis with cyan color dotted lines showing N-H...O intermolecular hydrogen bonds.

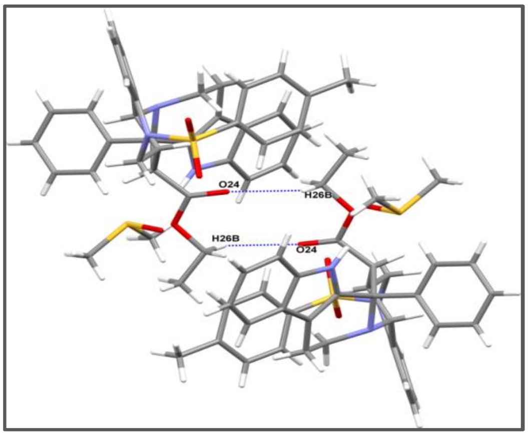


Figure 4. Molecules showing the formation of $R_2^2(10)$ graph-set motif via C-H...O hydrogen bonds (blue color dotted lines).

Hirshfeld surface analysis: To explore the packing modes and intermolecular interactions of the molecules in a crystal, Hirshfeld surface analysis was carried out using Crystal Explorer [16]. It highlights the atomic contacts which are involved in the significant interactions that are responsible for the molecular arrangement in the crystal. The mapping of normalized contact distance d_{norm} value onto the Hirshfeld surface employs red, blue, and white color scheme, where red color represents shorter contacts, blue color indicates longer contacts, and white color represents contacts around the van der Waal's separation (Figure 5). The value of d_{norm} is positive or negative when intermolecular interactions are shorter or longer than van der Waals radii respectively [17]. The bright red region on the surface is due to N7-H7...O49 intermolecular contacts. The other faint regions reflected on the surface are from C17-H17...O37 and C18-H18...O37 intermolecular interactions.

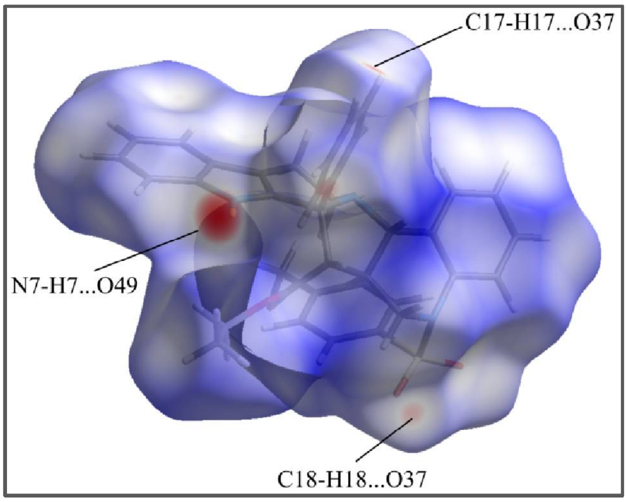
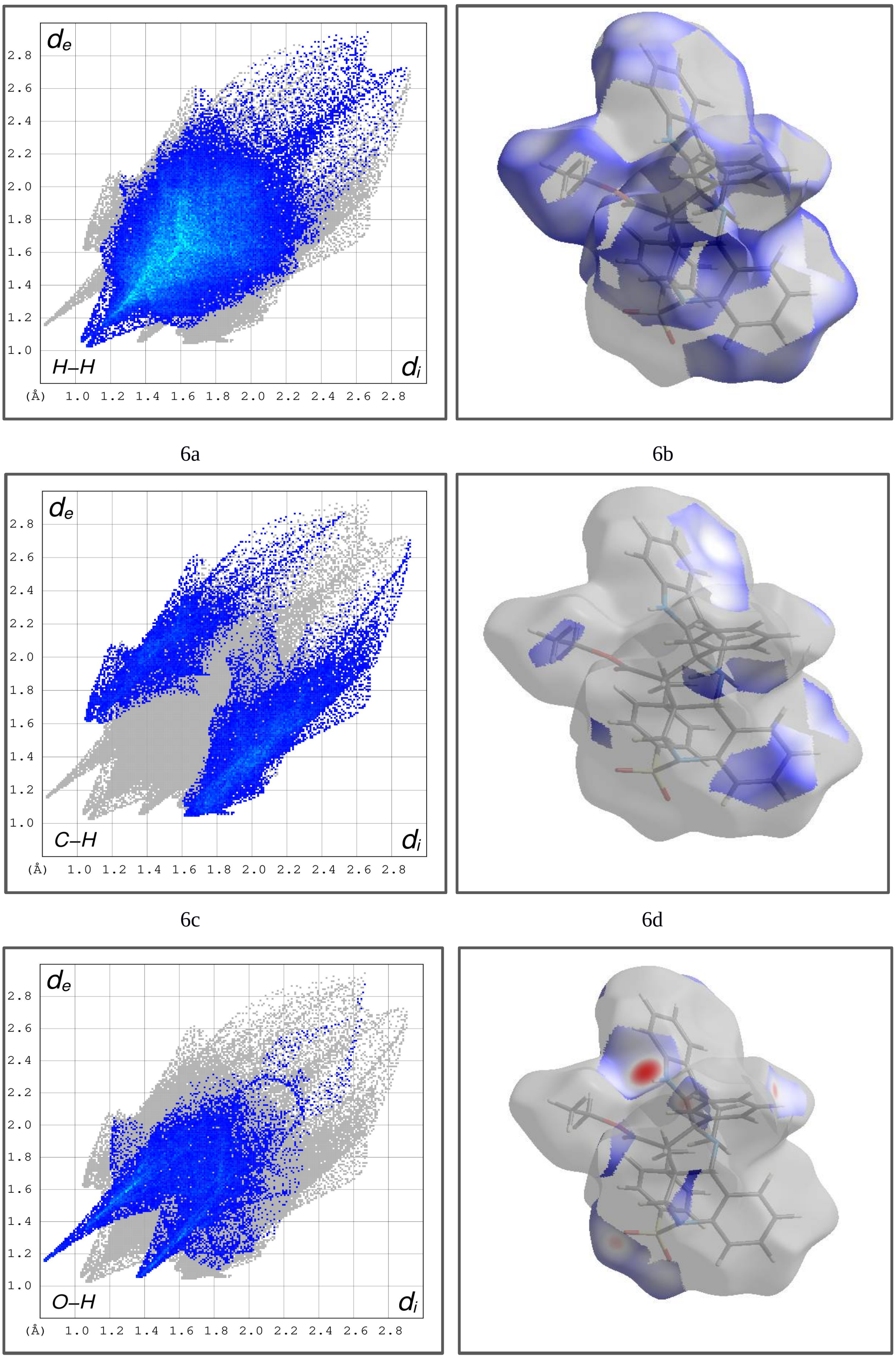


Figure 5. Hirshfeld surface mapped with the normalized contact distance d_{norm}.

Fingerprint plots: Fingerprint plots are visual representations of all the intermolecular interactions experienced by the molecules in the crystal. They give a concise two-dimensional summary of the intermolecular interactions in the crystal. Figure 6 displays the decomposed fingerprint plots and the contribution of corresponding contacts to the total Hirshfeld surface. They were generated by calculating the distance from a point on the Hirshfeld surface to the nearest atom inside the surface (d_i), and the distance from the surface to the nearest atom outside the surface (d_e) [16].



6a 6b

6c 6d

6e 6f

Figure 6. The resolved fingerprint plots and the associated Hirshfeld surfaces.

APPLICATION

Literature survey reveals that indole derivatives find applications in biochemical processes. They are more useful in medical filed to design many drugs.

CONCLUSION

In the structure intramolecular interactions of the type C-H...N and C-H...O are observed. Intermolecular interactions were analyzed using Hirshfeld surface analysis. Intermolecular hydrogen bonds of the type C-H...O connect the molecules to form inversion dimers. Hirshfeld surface analysis shows that N-H...O intermolecular interactions dominate.

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