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Crystal Structure Analysis of 5-*tert*-Butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one

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*The compound 5-*tert*-Butyl-8-methyl-2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-1-one, (3) was synthesized and characterized by ^{1}H NMR, IR, and mass spectroscopy. Its molecular structure was solved by single crystal X-ray diffraction method. The crystal structure analysis revealed that two different conformers of compound 3 are present in the crystal. The difference in two conformational structures was found in the arrangement of C=O group to the plane of the molecule. The hydrogen bonding of the two conformers was not similar. The Hirshfeld surface analyses and two-dimensional finger plots showed that the two conformers are completely different.*

*[Supplemental materials are available for this article. Go to the publisher's online edition of Molecular Crystals and Liquid Crystals to view the free supplemental file: Spectral data (MS, NMR, PXRD, DSC, and TGA) of the compound **3** are available in the supporting information in .pdf format. Crystallographic information file (.cif) of compound **3** is available in the electronic format.]*

Keywords Conformational isomerism; hirshfeld surface analyses; hydrogen bonding; single crystal; 5-*tert*-Butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one; X-ray diffraction

Introduction

Quinoline- and pyrrole-based structural frameworks are found to be integral part of many natural products. Compounds containing a combined form of this two *N*-hetercycles, e.g., pyrroloquinolines also exhibit a wide range of biological activities such as anticancer, antifungal, antibacterial, and antiproliferative properties along with inhibition of HIV integrase, PI3-kinase-related kinases, caspase-3, and vasorelaxing, antileukemic activities [1–9]. Hexahydro pyrrolo quinolines are considered as important scaffolds in the design and construction of bacterial topoimerase (II) inhibitors [10]. As part of our ongoing studies on novel pyrroloquinoline derivatives of potential pharmacological interest [11], we

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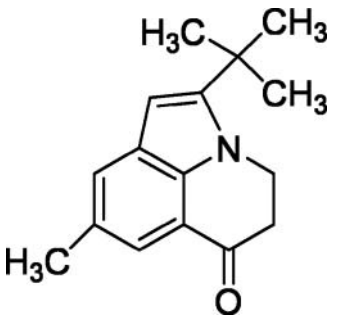


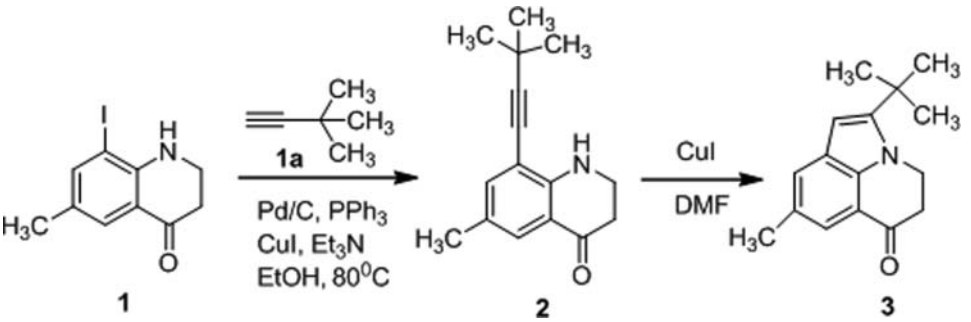
Figure 1. Molecular structure of the compound 3.

report in this communication, the title compound, 5-*tert*-Butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one the structure (Fig. 1) of which was determined by using the X-ray diffraction method. The Hirshfeld surface analysis associated with two-dimensional (2D) fingerprint plots of compound 3 are presented. The synthesis of 5-*tert*-butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one is shown in Scheme 1.

Materials and Methodology

General Procedures and Materials

All reactions were carried out under nitrogen atmosphere. Melting points were determined on a Buchi B-540 melting point apparatus and are uncorrected. All compounds were routinely checked by thin layer chromatography (TLC) and ^{1}H NMR. TLC was performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F254) with spots visualized by UV light. All chemicals and reagents (purity >99.8%) were purchased from Aldrich Co. Ltd.



Scheme 1. Synthesis of 5-*tert*-butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one, (**3**).

^{1}H and ^{13}C NMR Spectroscopy

^{1}H and ^{13}C NMR spectrum was determined in $CDCl_3$ solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane ($\delta =$ 0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as *s* (singlet), *d* (doublet), *t* (triplet), and *m* (multiplet) as well as *b* (broad). Coupling constants (*J*) are given in hertz.

Infrared Spectroscopy

Jasco FT–IR 4200 (Easton, Maryland) type-A Fourier transform infrared spectrophotometer was used to record the infrared (IR) spectra of the samples (sample concentration is 2 mg in 20 mg of KBr). The spectra were recorded over the range of 4000–600 cm^{-1}. Data were analyzed using spectrum version 2 software (JASCO, Easton, Maryland, USA).

High-Resolution Mass Spectra

High-resolution mass spectra (HRMS) were measured on a Waters LCT Premier XE instrument.

Differential Scanning Calorimetry (DSC)

Thermal analysis of this sample was performed on a Thermal Advantage differential scanning calorimetry (DSC) Q2000 V9.8 Build 296 (TA Instrument, USA) module which was calibrated for temperature and cell constants using indium and sapphire. The instrument was equipped with refrigerator cooling system (RCS). The crystals (3–5 mg) were crimped in aluminum pans (nonhermetic) (30 μL) scanned at a heating rate of 10°C/min in the range 30–300°C under a dry nitrogen atmosphere (flow rate 50 mL/min). The data were collected by TA Instruments Universal Analysis 2000 V4.3A software.

Thermogravimetric Analysis (TGA)

Thermal analyses of these samples were carried out by TA Instrument (USA) thermogravimetric analysis (TGA) Q5000 module with RCS. The crystals (5–10 mg) were placed in aluminum crucibles (30 μL) under a dry nitrogen atmosphere (flow rate is 25 mL/min). The data were collected by TI Universal Analysis software.

Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) patterns were collected on a Rigaku D/MAX 2200 (The Woodlands, Texas) powder diffractometer with a Cu Kα radiation (1.54056 Å). The tube voltage and amperage were set at 50 kV and 34 mA, respectively. The divergence slit and antiscattering slit settings were variable for the illumination on the 20 mm sample size. Each sample was scanned 3° and 45° in 2θ with a step size of 0.02°. The instrument had previously been calibrated using a silicon standard.

Single Crystal X-ray Diffraction

The single-crystal XRD of the crystal was collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 296(2) K using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL [12]. The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97 [13]. The positions of all aromatic and aliphatic C–H hydrogen atoms were calculated geometrically, and a riding model was used in the refinement, with C–H distances in the range of 0.93–0.98 Å and Uiso(H) = 1.5 Ueq(C). The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3,

Table 1. Salient crystallographic data and structure refinement parameters of compound 3

	3
Empirical formula	$C_{16}H_{19}NO$
Formula weight	241.32
Crystal system	Orthorhombic
Space group	*Pbcn*
T/K	273(2)
a/Å	40.4228(15)
b/Å	11.0618(4)
c/Å	11.6197(4)
α/°	90.00
β/°	90.00
γ/ °	90.00
Z	16
V/Å^3	5,195.7(3)
D_{calc}/g/cm^3	1.234
F(000)	2,080
μ/mm^{-1}	0.076
θ/°	1.91–27.00
Index ranges	$-51 \leq h \leq 47$
	$-14 \leq k \leq 12$
	$-14 \leq l \leq 6$
N total	24,310
N independent	5,674
N observed	4,886
Parameters	333
R_1 ($I > 2\sigma(I)$)	0.0407
wR_2 (all data)	0.1009
GOF	1.017

and X-Seed [14–16]. Table 1 gives the pertinent crystallographic data, and Table 2 gives hydrogen bond parameters.

Results and Discussion

Procedure for the Preparation of 8-(3,3-dimethylbut-1-ynyl)-6-methyl-2,3-dihydroquinolin-4(1H)-one (2)

A mixture of compound 1 (300 mg, 1.04 mmol), 10% Pd/C (11.12 mg, 0.01 mmol), PPh_3 (10.91 mg, 0.04 mmol), CuI (19.8 mg, 0.10 mmol), and Et_3N (2.60 mmol) in ethanol (8 mL) was stirred at 25°C for 1 h under nitrogen. The acetylenic compound 1a (1.56 mmol) was added and the mixture was stirred at 80°C for 4 h. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (120 mL) and filtered through a celite bed. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate to afford the desired product.

Table 2. Geometrical parameters of hydrogen bonds in compound 3

Compound	D–H···A[a]	D···A (Å)	H···A (Å)	D–H···A (°)	Symmetry code
1	C(14)–H(14B)···O(2)	3.6714 (15)	2.63	161	1/2−x,1/2+y,z
	C(14)–H(14C)···O(2)	4.0008 (17)	2.93	171	x,1−y,1/2+z
	C(15)–H(15C)···O(2)	3.3969 (17)	2.32	172	—
	C(29)–H(29B)···O(1)	3.8709 (15)	2.97	141	−x,1−y,-z
	C(30)–H(30A)···O(1)	3.6402 (16)	2.57	168	x,−1+y,z
	C(30)–H(30B)···O(1)	3.4945 (15)	2.46	159	−x,1−y,−z
	C(31)–H(31B)···O(1)	3.7633 (15)	2.84	143	−x,1−y,−z
	C(32)–H(32C)···O(2)	3.5465 (17)	2.88	120	x,−y,1/2+z

[a]All of the C–H distances are neutron normalized to 1.083 Å.

Procedure for the Preparation of 5-tert-Butyl-8-methyl- 2,3-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-1-one (3)

To a clear solution of 2 (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added CuI (36.47 mg, 0.191 mmol) at room temperature under nitrogen. The reaction mixture was heated at 100°C for 12 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (nhexane/EtOAc) to yield the desired product as a light yellow solid (75 mg, yield 65%); mp 96–98 °C; R*f* 0.35 (25% ethyl acetate/*n*-hexane); m.p. 115–118°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (*s*, 1H), 7.49 (*s*, 1H), 6.27(*s*, 1H), 4.51 (*t*, $J = 6.8$ Hz, 2H), 3.03 (*t*, $J = 6.8$ Hz, 2H), 1.46 (*s*, 3H), 1.38 (*s*, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3, 29.9, 32.4, 38.5, 44.8, 98.6, 117.4, 118.6, 126.4, 127.7, 129.3, 140.0, 150.8, and 192.9; IR (KBr): 2966, 2872, and 1683 cm^{-1}; mass (ES) m/z: 242.20 (M+1,100%); and HRMS (ESI): calcd for $C_{16}H_{20}NO$ (M+H) 242.1545, found 242.1557.

Preliminary Characterization

The shape of the crystals of the compound 3 was observed under the LEICA DFC295 polarizing microscope.

DSC and TGA Analyses

DSC and TGA thermograms show the thermal behavior of the compound 3. DSC thermogram of the compound shows that a sharp endothermic peak at 100.56°C (melting point: 115°C–118°C) attributed to its melting point and no endothermic peak below the melting point shows that there was no inclusion of solvent in the crystal. TGA shows that there was no weight loss in the compound and found that the crystals are anhydrous in nature. It was finally confirmed by single crystal X-ray diffraction.

PXRD Analysis

The PXRD pattern of compound 3 was shown crystalline nature solid.

Crystal Structure Analysis

Compound 3 crystallizes in the orthorhombic *Pbcn* space group with two molecules in the asymmetric unit ($Z' = 2$). It was found that two molecules in the asymmetric unit are

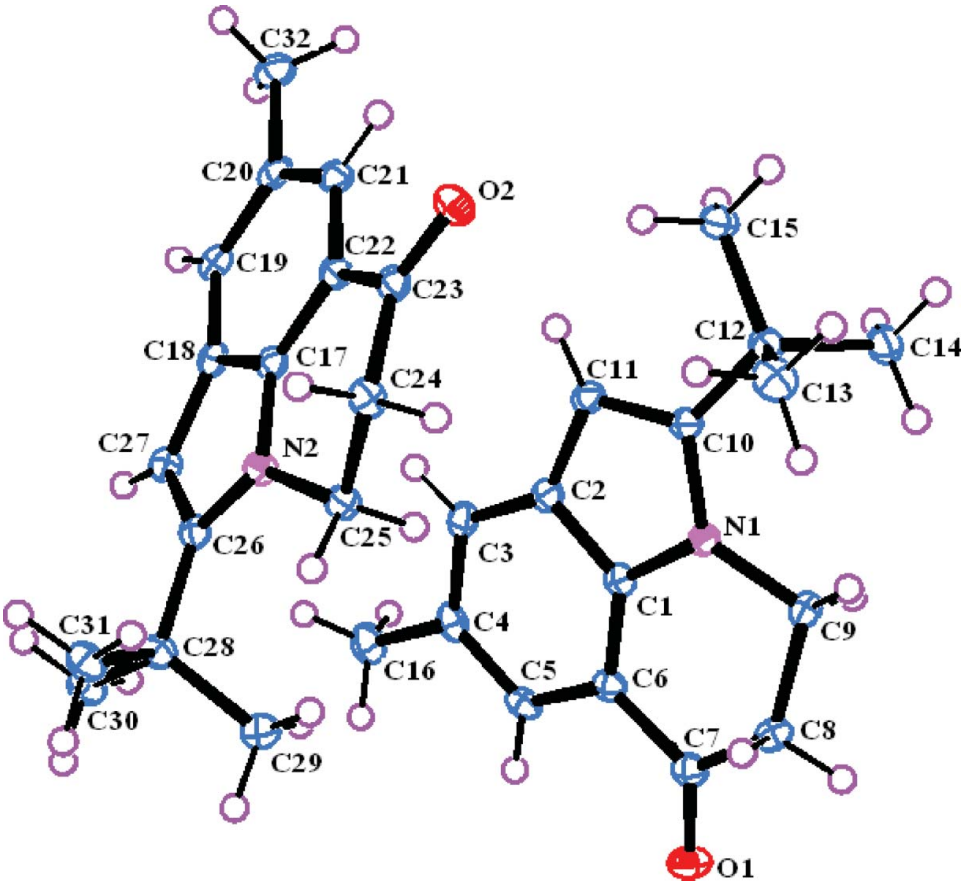


Figure 2. ORTEP representation of conformers-A and B of compound 3. Thermal ellipsoids are drawn at 50% probability level.

conformers (Fig. 2). These two molecules form almost similar hydrogen bonding in the crystal structure. In these conformers the 2,3-dihydro-quinolin-1-one moiety is in envelope shape. The projection of the $-CH_2$ groups in these conformers are in above and below the planes (the torsion angles of 2,3-dihydro-quinolin-1-one moieties in two conformers are: N1-C9-C7-C8 = 47.31°; N2-C25-C24-C23 = −48.23°). Moreover, the torsion angles of tertiary butyl methyl groups to pyrrole ring are also different (N1-C10-C12-C14 = 61.66°; N2-C26-C28-C31 = 58.73°). So, the two conformers are designated as A and B (Fig. 3).

The crystal structure analysis reveals that the molecules form 2D-layered structure. Two molecules of one conformer and two molecules of second conformer form a supramolecular tetramer synthon with C–H···O hydrogen bonds (Figs 4 and 5). This tetramer synthon is formed by the interaction of tertiary-butyl group methyl C–H of a pair of inversion related conformers of B with the C=O group of another pair of inversion-related conformers of A. These supramolecular tetramer synthons are interconnected by the methyl C–H group of tert-butyl moiety of conformer-A with C=O group of conformer B via C–H···O hydrogen bonds. The overall structure is a 2D-layered structure (Fig. 6).

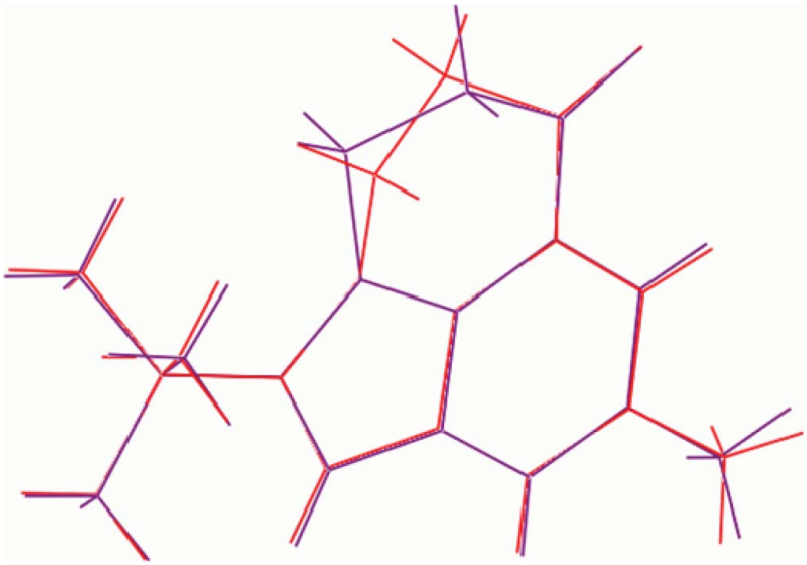


Figure 3. Shows the overlay diagram of conformer-A (violet) and conformer-B (red) of compound 3.

Hirshfeld Surface Analysis

Hirshfeld surface analysis associated with 2D fingerprint plots was carried out to differentiate the two conformers. The 2D fingerprint plots show that the two molecules in the asymmetric unit are completely different and hence these two are conformational isomers. The 2D fingerprint plots of compound 3 were derived from the Hirshfeld surface by plotting the fraction of points on the surface as a function of the pair (*d*i, *d*e). Each point on the standard 2D graph represents a bin formed by discrete intervals of *d*i and *d*e (0.01 × 0.01

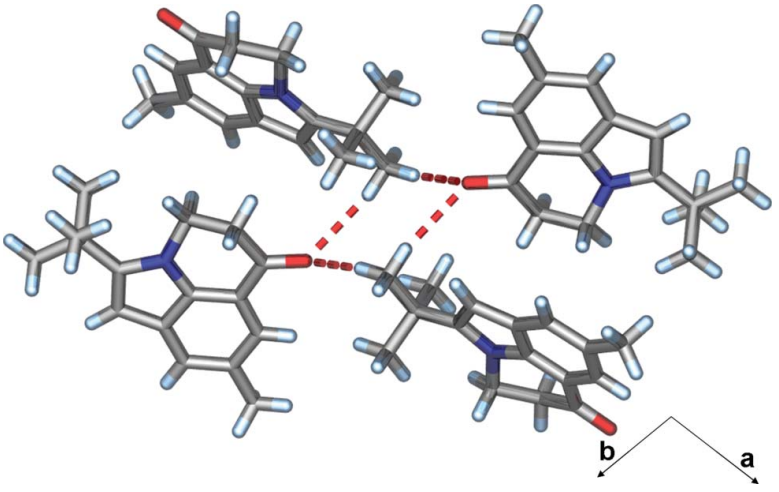


Figure 4. A supramolecular tetramer synthon is formed by the two conformers (A and B) of compound 3 with C–H···O hydrogen bonds.

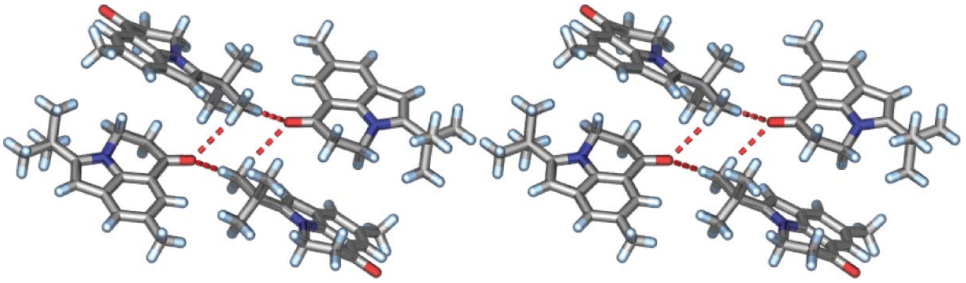


Figure 5. Stereovision of supramolecular tetramer synthon formed by the two conformers (A and B) of compound 3.

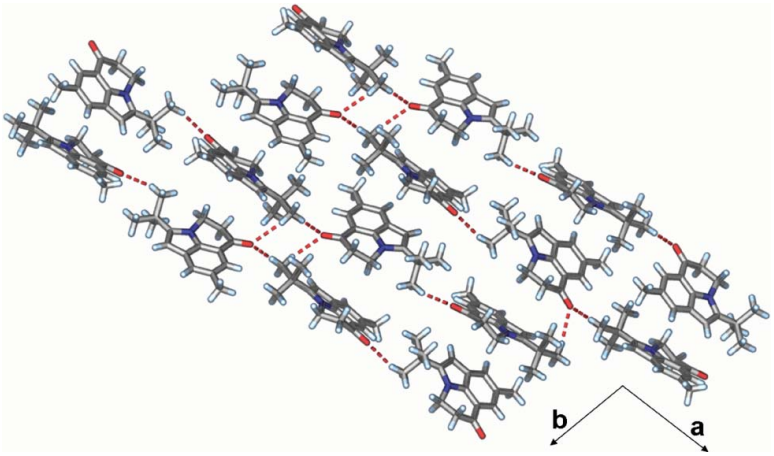


Figure 6. A 2D layered structure is formed by the C–H···O hydrogen bonds.

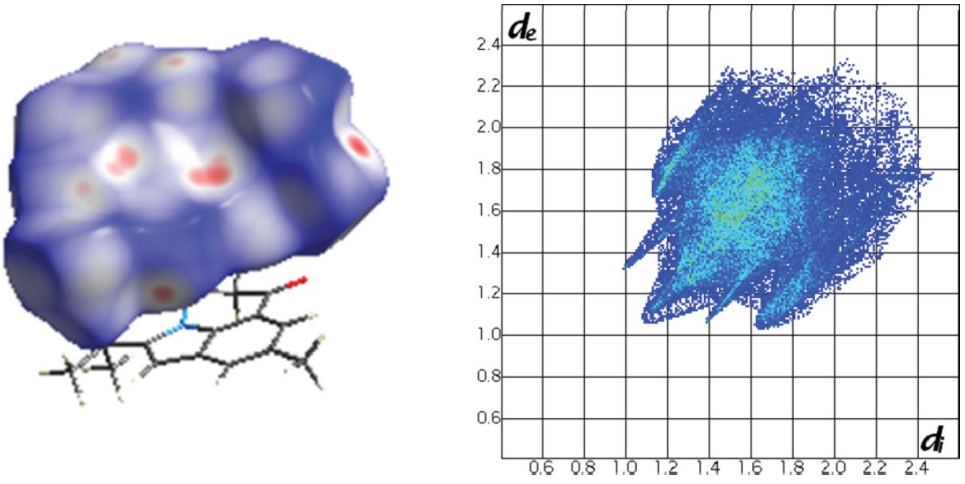


Figure 7. Hirshfeld surface and 2D finger plots of conformer A.

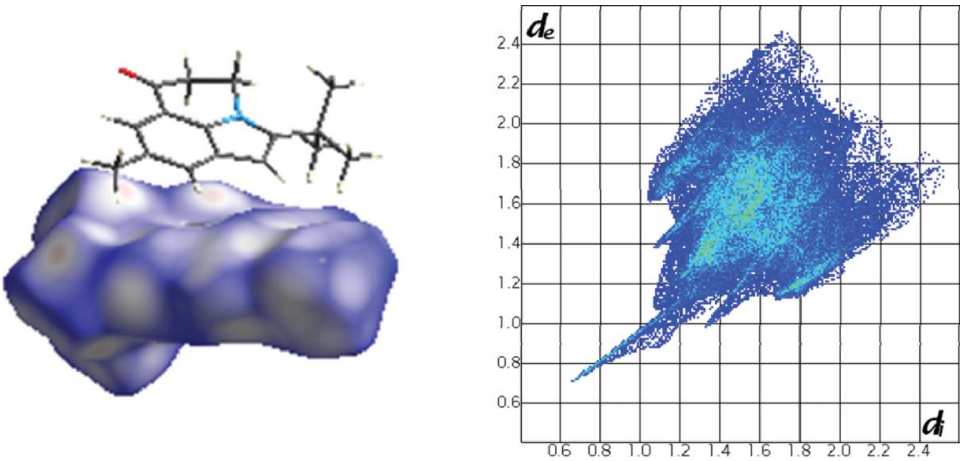


Figure 8. Hirshfeld surface and 2D finger plots of conformer B.

Å), and the points are colored as a function of the fraction of surface points in that bin, with a range from blue (relatively few points) through green (moderate fraction). The Hirshfeld surfaces and 2D fingerprint plots are given in Figs. 7 and 8. It is clear from this analysis that the two conformers-A and B of compound 3 are completely different and exhibits the conformational isomerism. Inspection of the fingerprint plots in Figs. 7 and 8 highlights the major differences between the two conformers. The conformer-A features the diffuse region of the blue points between the hydrogen bond spikes, while this feature is extended in the fingerprint plot of conformer-B till 0.6 *d*i.

Conclusions

The compound 5-*tert*-Butyl-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one, (3) was synthesized and characterized by spectral data. The molecular structure of this compound was determined by single crystal XRD method. It was found that the compound has two conformers and these are forming a supramolecular tetramer synthon in the crystal structure. The Hirshfeld analyses and 2D finger plots showed that the two conformers are completely different.

Acknowledgments

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