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Synthesis of ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate by an unusual protocol: Crystal and molecular structure, Hirshfeld surface analysis

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ABSTRACT

The compound, ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate was synthesized by the reaction of ethyl 2-(4-chlorobenzylidene)-3-oxobutanoate and phenylhydrazine hydrochloride. The synthesized compound was characterized by ^{1}H NMR and mass spectral analysis and finally the structure was confirmed by single crystal X-ray diffraction studies. The compound $C_{19}H_{17}ClN_2O_2$ crystallizes in the triclinic crystal system, in $\rho\bar{1}$ space group. The structure exhibits intramolecular hydrogen bonds of the type C–H...O and contributes to the structural stability. The molecular structure is also stabilized by the $\pi\ldots\pi$ interactions. The antimicrobial activities of the compound have been studied for their pharmacological importance. Further, the Hirshfeld surface analysis reveals the nature of molecular interactions; the fingerprint plot provides information about the percentage contribution from each individual molecular contact to the surface.

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Specifications table

Subject area	Synthesis, crystallography, antimicrobial activity
Compound	Ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate
Data category	Spectral, synthesized, crystallographic,
Data acquisition format	*CIF*
Data type	Analyzed
Procedure	The title compound, ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate was synthesized and pale yellow block shaped crystals of the compound were obtained by slow evaporation technique. A single crystal of dimension 0.28 × 0.30 × 0.30 mm of the title compound was selected for data collection and X-ray intensity data were collected with χ fixed at 54° and φ, from 0° to 360°, scan width at 0.5°, exposure time of 3 s and the sample to detector distance of 50.0 mm at a temperature 293 K.
Data accessibility	CCDC 1518801: URL: https://www.ccdc.cam.ac.uk/conts/retrieving.html

1. Rationale

Development of novel and accessible procedure for the transformation of a simple molecule in to heterocycles is a worthwhile contribution in organic synthesis. α, β-unsaturated ketones were treated as the useful synthons for the construction of bioactive molecules such as benzothiazepines [1,2], pyrazolines [3], and isoxazolines [4]. Among the five membered nitrogen heterocycles, pyrazoles attracted the greater interest due to their broad spectrum of synthetic utilities and biological applications [5].

Pyrazole and their derivatives are reported to exhibit as anticancer [6,7], amine oxidases inhibition [8], antimicrobial and antioxidant [9], potential PDE4 inhibitors [10], and acaricidal and insecticidal [11] properties. In view of the wide range of biological activities associated with pyrazoles, we herein report the synthesis, spectral characterization and single crystal X-ray diffraction studies of ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate by an unusual procedure.

2. Experimental procedure

2.1. Materials and methods

In a typical reaction, a solution of (*E*)-ethyl 2-(4-chlorobenzylidene)-3-oxobutanoate (**1**), phenylhydrazine hydrochloride (**2**) in ethyl alcohol and catalytic amount of piperidine was refluxed on a water bath for 3 h. After completion of the reaction followed by work-up procedure, the reaction yielded ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**3**) in 90% yield. The reaction pathway is illustrated in Fig. 1.

2.2. Synthesis of ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate

The solution of (*E*)-ethyl 2-(4-chlorobenzylidene)-3-oxobutanoate (**1**) (0.01 mol) and phenylhydrazine hydrochloride (**2**) (0.01 mol) in ethyl alcohol (20 mL), to this 3–4 drops of piperidine was added. The mixture was refluxed on a water bath for 3 h. The progress of the reaction was monitored by TLC. After completion, the mixture was poured into ice cold water and the solid separated was filtered, washed with ice cold water to obtain the crude product. The solid obtained was crystallized from methyl alcohol by slow evaporation to obtain pale yellow rectangular shaped crystals of ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**4**) in 92% yield, m.p. 182 °C.

Spectral data: ^{1}H NMR spectra was recorded on Agilent-NMR 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrometer TOF mode. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 CHN analyzer. ^{1}H NMR ($CDCl_3$): δ 1.147–1.182 (t, 3H, CH_3), 2.574 (s, 3H, CH_3), 4.140–4.194 (q, 2H, OCH_2), 7.140–7.293 (m, 9H, Ar-H), (Fig. S1). MS (*m/z*) for $C_{19}H_{17}ClN_2O_2$: 343 (MH+, ^{37}Cl, 33), 341 (MH+, ^{35}Cl, 100) (Fig. S2). Anal. Calcd. (%): C, 66.96; H, 5.03; N, 8.22; Found (%): C, 66.81; H, 4.89; N, 8.13.

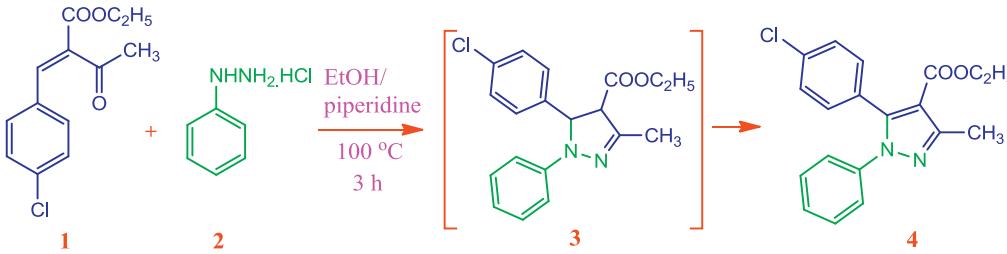

Fig. 1. Schematic diagram for the synthesis of ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate.

2.3. Data collections

A block shaped colorless defect free single crystal of approximate dimension 0.28 × 0.26 × 0.22 mm was chosen for X-ray diffraction studies. X-ray intensity data for the title compound were collected at temperature 296 K on a Bruker Proteum2 CCD diffractometer with X-ray generator operating at 45 kV and 10 mA, using CuK_α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of φ (0° and 90°), keeping the scan width of 0.5°, exposure time of 5 s, the sample to detector distance of 45.10 mm. The compound $C_{19}H_{17}ClN_2O_2$ crystallized in the triclinic crystal system, in $\rho^{\bar{1}}$ space group. The complete intensity data sets were processed using *SAINT PLUS* [12]. All the frames could be indexed by using a primitive triclinic lattice. The crystal structure was solved by direct method and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [13]. 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 $U_{iso}(H) = 1.2\ U_{eq}(C)$, $U_{iso}(H) = 1.5\ U_{eq}\ (C_{methyl})$. A total of 219 parameters are refined with 2714 unique reflections of 10,585 observed reflections. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residue is saturated to 0.0475. The geometrical calculations were carried out using the program *PLATON* [14]. The molecular and packing diagrams were generated using the software *MERCURY* [15].

3. Data, value and validation

The precursor ethyl 2-(4-chlorobenzylidene)-3-oxobutanoate was synthesized according to the reported procedure [16]. Acid catalysis reaction of α, β-unsaturated carbonyl compounds with phenylhydrazines to produce corresponding pyrazolines is well established [17]. In the presence of mild bases α, β-unsaturated carbonyl compounds reacted with phenylhydrazines to produce directly pyrazoles instead of expected pyrazolines as under acidic conditions [18]. The reaction of ethyl 2-(4-chlorobenzylidene)-3-oxobutanoate with phenylhydrazine hydrochloride in presence of catalytic amount of piperidine in ethanol yielded directly the title compound ethyl 5-(4-chlorophenyl)3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**4**) directly in 92% yield through an intermediate (**3**). The expected molecule ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (**3**) was not isolated and characterized. The direct formation of compound (4) was supported by the literature [18]. In ^{1}H NMR spectra, compound showed a triplet at δ 1.147–1.182 ppm for an ester CH_3 protons, a singlet at δ 2.574 ppm for CH_3 protons, a quartet at δ 4.140–4.194 ppm for an ester OCH_2 protons. A multiplet for nine protons absorbed at δ 7.140–7.293 ppm was assigned to aromatic protons. In mass spectra, compound showed an M+ peak at m/e 243 with a relative abundance of 33% corresponding to isotope ^{37}Cl, and a base peak at *m/z* 241 corresponding to a molecular mass of ^{35}Cl. Further, satisfactory elemental analyses data obtained supports the structure of the product.

X-ray diffraction analysis revealed that the title compound $C_{19}H_{17}ClN_2O_2$ crystallizes in the triclinic crystal system in $\rho^{\bar{1}}$ space group with unit cell parameters $a = 8.6235(3)$ Å, $b = 10.0092(3)$ Å, $c = 10.4708(4)$ Å, $\alpha = 77.296(1)^o$, $\beta = 72.676(1)^o$, $\gamma = 75.912(1)^o$ and $Z = 2$ with unit cell volume 826.16(5) Å^3. The ORTEP of the molecule with displacement ellipsoids drawn at 50% probability level is shown in Fig. 2. The details of the crystal data and structure refinement are as given in Table 1.

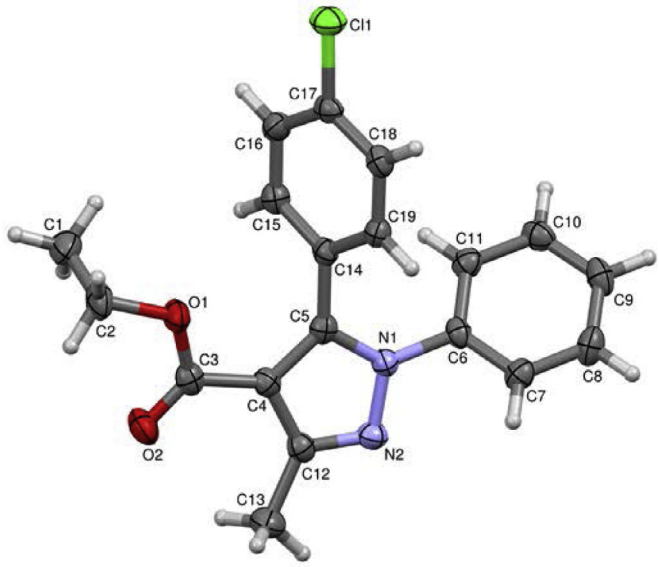

Fig. 2. ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 1
Crystal data and structure refinement details.

Parameter	Value
CCDC deposit No.	CCDC 1518801
Empirical formula	$C_{19}H_{17}ClN_2O_2$
Formula weight	340.80
Temperature	296 K
Wavelength	1.54178 Å
Crystal system, Space group	Triclinic, $\rho\bar{1}$
Unit cell dimensions	$a = 8.6235(3)$ Å
	$b = 10.0092(3)$ Å
	$c = 10.4708(4)$ Å
	$\alpha = 77.296(1)^o$
	$\beta = 72.676(1)^o$
	$\gamma = 75.912(1)^o$
Volume	826.16(5) Å^3
Z	2
Density(calculated)	1.370 Mg m^{-3}
Absorption coefficient	2.158 mm^{-1}
F_{000}	356
Crystal size	0.28 × 0.26 × 0.22 mm
θ range for data collection	5.90°–64.50°
Index ranges	$-10 \le h \le 9$
	$-11 \le k \le 11$
	$-12 \le l \le 10$
Reflections collected	10,585
Independent reflections	2714 [R int = 0.0394]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	2714/0/219
Goodness-of-fit on F^2	1.190
Final [$I > 2\sigma(I)$]	R1 = 0.0475, wR2 = 0.1407
R indices (all data)	R1 = 0.0485, wR2 = 0.1411
Largest diff. peak and hole	0.299 and −0.277 e Å^{-3}

Table 2
Bond lengths (Å).

Atoms	Length	Atoms	Length
Cl1–C17	1.741(3)	C6–C7	1.385(5)
O1–C2	1.459(4)	C6–C11	1.390(5)
O1–C3	1.343(4)	C7–C8	1.384(5)
O2–C3	1.214(4)	C8–C9	1.383(5)
N1–N2	1.373(4)	C9–C10	1.387(5)
N1–C5	1.357(4)	C10–C11	1.384(4)
C1–C2	1.499(6)	C14–C19	1.400(5)
C3–C4	1.465(4)	C15–C16	1.384(4)
C4–C5	1.396(4)	C16–C17	1.386(5)

Table 3
Bond angles (°).

Atoms	Angles	Atoms	Angles
C2–O1–C3	117.4(2)	C6–C7–C8	118.9(3)
N2–N1–C5	112.5(3)	C7–C8–C9	120.6(3)
N2–N1–C6	118.1(3)	C8–C9–C10	119.9(3)
O1–C2–C1	110.0(3)	N2–C12–C4	111.4(3)
O1–C3–O2	123.8(3)	N2–C12–C13	119.8(3)
O1–C3–C4	112.2(2)	C4–C12–C13	128.8(3)
O2–C3–C4	124.0(3)	C5–C14–C15	121.1(3)
N1–C5–C4	106.0(3)	C15–C16–C17	119.4(3)
N1–C5–C14	122.2(3)	Cl1–C17–C16	119.8(3)
N1–C6–C7	118.6(3)	C16–C17–C18	121.4(3)
N1–C6–C11	120.2(3)	C17–C18–C19	118.8(3)
C7–C6–C11	121.3(3)	C14–C19–C18	120.6(3)

Table 4
Torsion angles (°).

Atoms	Angles	Atoms	Angles
C2–O1–C3–O2	−9.8(5)	C5–C4–C12–C13	178.1(4)
C2–O1–C3–C4	171.3(3)	N1–C5–C14–C15	126.5(4)
C6–N1–N2–C12	−179.0(3)	C4–C5–C14–C15	−58.5(5)
N2–N1–C5–C14	175.7(3)	N1–C6–C7–C8	−179.6(3)
C6–N1–C5–C4	178.8(3)	C11–C6–C7–C8	0.2(5)
C6–N1–C5–C14	−5.0(6)	N1–C6–C11–C10	179.8(3)
N1–N2–C12–C13	−178.6(3)	C5–C14–C15–C16	178.3(3)
O1–C3–C4–C12	167.0(3)	C5–C14–C19–C18	−179.2(3)
C3–C4–C5–N1	176.9(4)	C15–C16–C17–Cl1	−177.6(2)
C3–C4–C12–N2	−176.8(3)	C17–C18–C19–C14	0.8(5)

3.1. Results and discussion

The single crystal X-ray diffraction analysis confirms the molecular structure of the title compound $C_{19}H_{17}ClN_2O_2$. The bond lengths and bond angles are in good agreement with the standard values, and the list of selected bond lengths and bond angles is given in Tables 2 and 3. The observed bond distance of C3–O2 is 1.214(4) Å and C2–O1 is 1.459(4) Å which are evident for the carbonyl form and consistent with the C=O and C–O bonds and are comparable with the standard bond distances of 1.21 Å and 1.42 Å respectively [19]. Similarly the bond distance 1.373(4) Å of N1–N2 is consistent with the N–N single bond, which is comparable with the standard bond distance value of 1.35 Å. The C4-C5 has the bond distance of 1.396(4), which is also well comparable with the standard bond value and consistent with the C=C double bond. The conformation of the molecule can be described by the torsion angles between the rings. The list of torsion angles is shown in Table 4. The molecular structure consists of five membered pyrazole ring which is attached by the six membered phenyl and

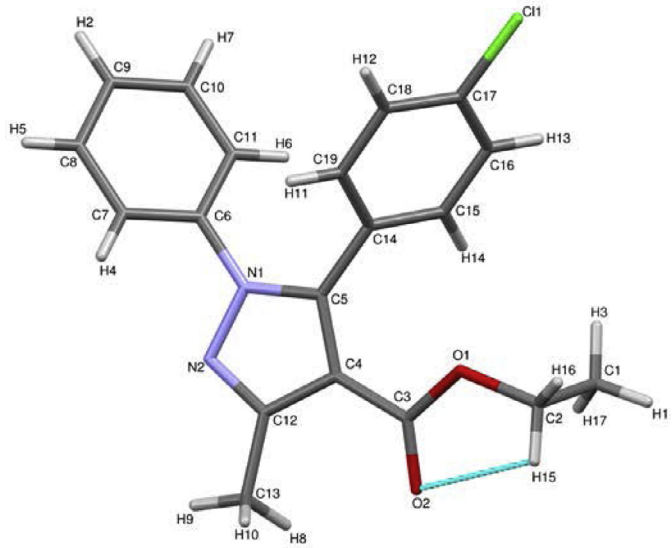

Fig. 3. The intra molecular hydrogen bonding interaction.

chlorophenyl ring at the 1, 5-position. The methyl group and carbonyl ethyl chain are directly attached to the 3, 4-position of the pyrazole ring.

Both phenyl and chlorophenyl rings adopts *+syn-periplanar* conformation, which is indicated by the torsion angle value of 1.22° and 0.40°. The ring planes of both the phenyl and chlorophenyl ring are twisted with respect to the plane of the pyrazole ring, which is indicated by their dihedral angle values 45.64(18)º and 55.39(18)° with the pyrazole ring. The methyl group adopts *+anti-periplanar* conformations, which is indicated by the torsion angle value of 178.1(4)° for C5–C4–C12–C13. The pendant ethyl chain has an extended conformation as indicated by the torsional angle value of 171.3(3)° for C2-O1-C3-C4. The methyl chain is almost planar to the five membered pyrazole ring plane which is specified by the torsion angle values of 167.0(3)º and −8.9(6)° for O1–C3–C4–C12 and O1–C3–C4–C5 respectively. Similarly torsion angle values of 172.2(4)º and −11.9(6)° for O2–C3–C4–C5 and O2–C3–C4–C12 show that the carbonyl group is in the same plane of the pyrazole ring.

The structure exhibits intramolecular hydrogen bonds of the type C—H...O. The C2—H15...O2 hydrogen bond has a length of 2.713(4) Å and an angle of 103°, which is accountable for the stability of the molecule. The structure also exhibits the $\pi\cdots\pi$ interaction [20,21]; *Cg*(1)···*Cg*(3) (*Cg(1)* is the centroid of the ring N1/N2/C12/C4/C5 and *Cg3* is the centroid of the ring C14/C15/C16/C17/C18/C19) with a *Cg-Cg* distance of 5.022(2) Å, $\alpha = 55.39(18)°$, $\beta = 28.3°$, $\gamma = 56.8°$, a perpendicular distance of *Cg*1(centroid) on ring C14/C15/C16/C17/C18/C19 is −2.7522(14) Å, a perpendicular distance of *Cg3*(centroid) on ring N1/N2/C12/C4/C5 is −4.4223(15) Å and a symmetry code of 2-x, 1-y, -z. The intra molecular hydrogen bonding C2—H15...O2 interaction is as shown in Fig. 3.

4. Hirshfeld surface studies

Hirshfeld surface analysis is an excellent tool to generate unit cell packing diagrams of the molecules. It also helps us to study the intermolecular contacts of the molecule in a crystalline environment. Analysis and calculations of the Hirshfeld surface were carried out and finger print plots were plotted using the software CrystalExplorer version 3.0 [22]. The d_{norm} plots were mapped with a color scale in between −0.556 au (blue) and 1.453 au (red) respectively. Expanded 2D fingerprint plots [23,24] were displayed in the range of 0.6–2.8 Å views with the d_e and d_i distance scales displayed on the graph axes. Here d_e and d_i are the distances to the nearest nuclei outside and inside the surface from the Hirshfeld surface respectively. The intermolecular interactions between the atoms

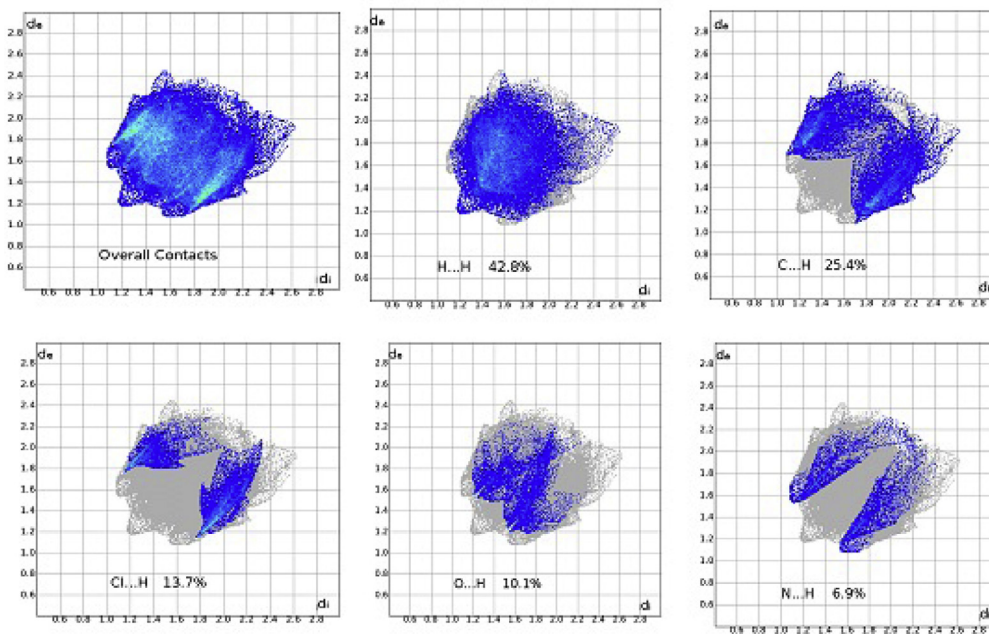

Fig. 4. Fingerprint plots of the title compound showing the individual contribution of each interaction. d_i is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

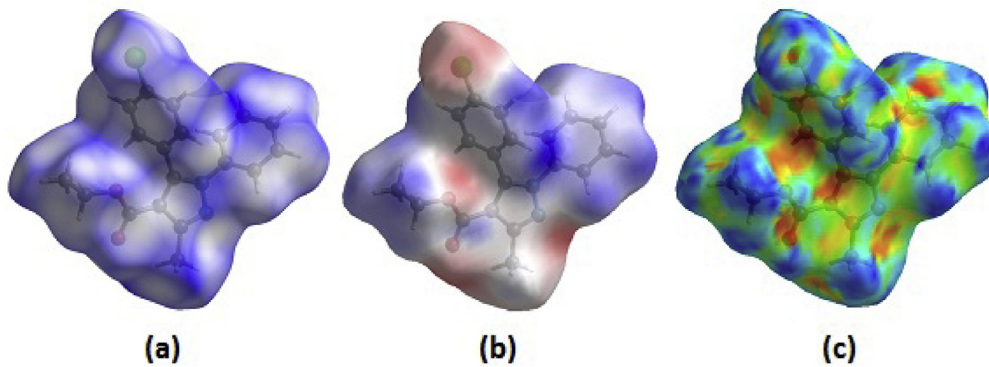

Fig. 5. d_{norm} (**a**), electrostatic potential (**b**) and the shape index (**c**) mapped on Hirshfeld surface for visualizing the molecular contacts. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

on the Hirshfeld surface can be represented in terms of color codes. The percentage contribution of intermolecular contacts to the surface is revealed by fingerprint plots. The H...H (42.8%) contacts have maximum and C...C (0.7%) has minimum contributions. Similarly the C...H (25.4%), Cl...H (13.7%), O...H (10.1%) and N...H (6.9%) contacts contribute to the total area of the surface as shown in Fig. 4. These contacts are highlighted on the molecular surface using conventional mapping of d_{norm}, electrostatic potential and shape index as shown in the Fig. 5. The regions with red and blue color represent the shorter and longer inter contacts [25–27].

5. Conclusions

The title compound $C_{19}H_{17}ClN_2O_2$ 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, IR and mass spectrum. The molecular structure of the compound was confirmed by the single crystal X-ray diffraction studies. The synthesized compound crystallizes in the triclinic crystal system, in $\rho^{\bar{1}}$ space group. The molecule was evaluated in vitro for its antimicrobial and anti-fungal activities. The crystal and molecular structure of the compound is stabilized by weak C-H...O interactions. The structure also involves $\pi\cdots\pi$ interactions. The molecular Hirshfeld surface analysis and fingerprint plots reveal the nature of molecular interactions and their contributions to the molecular surface respectively.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.cdc.2017.04.002.

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