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# Crystal structure and Hirshfeld surface analysis of methyl 1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxylate

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## RESEARCH ARTICLE



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## ABSTRACT

The title compound, C<sub>13</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>, crystallizes with six molecules in the asymmetric unit, such that, the 1H-pyrazole rings are essentially planar. The six molecules are stabilized by intramolecular C-H···N and C-H···Cl interactions and the crystal structure is stabilized by intermolecular C-H···O hydrogen bonds, forming molecular sheets into parallel to the (-1 1 0) plane. These sheets are connected to each other by C-H···O hydrogen bonds and C-H···π interactions. In the Hirshfeld surface analysis, the H···H, Cl···H/H···Cl, C···H/H···C, O···H/H···O, N···H/H···N, Cl···Cl, Cl···O/O···Cl interactions add to 95.8% of the intermolecular contacts of the Hirshfeld surface area. The remaining contributions (2.9%) correspond to Cl···C/C···Cl, C···O/O···C, O···O and N···N interactions. Crystal Data for C<sub>13</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> (*M* = 299.15 g/mol): Triclinic, space group *P*-1 (no. 2), *a* = 12.0505(10) Å, *b* = 12.3189(11) Å, *c* = 29.184(3) Å, *α* = 88.565(4)°, *β* = 89.296(4)°, *γ* = 76.833(4)°, *V* = 4217.0(7) Å<sup>3</sup>, *Z* = 12, *T* = 296(2) K, *μ*(MoK $\alpha$ ) = 0.460 mm<sup>-1</sup>, *D*<sub>calc</sub> = 1.414 g/cm<sup>3</sup>, 83073 reflections measured (2.8° ≤ 2 $\theta$  ≤ 47°), 12426 unique (*R*<sub>int</sub> = 0.0411, *R*<sub>sigma</sub> = 0.0235) which were used in all calculations. The final *R*<sub>1</sub> was 0.0662 (*I* > 2 $\sigma$ (*I*)) and *wR*<sub>2</sub> was 0.2481 (all data).

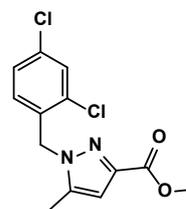
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## 1. Introduction

Pyrazole ring is a commonly found structural motif in bioactive compounds, and a large number of pyrazole derivatives with diverse pharmacological activities such as anti-inflammatory, antiplatelet, anticancer, antimycobacterial, antidepressant and anticonvulsant activities have appeared in the literature [1-5].

In the last decade, we have reported a large series of pyrazole derivatives with promising anti-inflammatory and anticancer activities, indicating the use of pyrazole core as a versatile tool for development of novel drug candidates with diverse biological activities [6-11]. In this work, we report the crystallographic characterization and Hirshfeld surface analysis of the methyl 1-[(2,4-dichlorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate (**1**), which is regioselectively formed by benzylation of methyl 5-methyl-1H-pyrazole-3-carboxylate (Scheme 1).



Scheme 1

## 2. Experimental

### 2.1. Instrumentation

Starting materials were purchased from commercial suppliers and used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Fourier 300 (Billerica, MA, USA) using tetramethylsilane as the internal standard. All chemical shifts were recorded as  $\delta$  (ppm).

**Table 1.** Crystal data and structure refinement for the title compound.

CCDC no	1843087
Empirical formula	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
Formula weight	299.15
Temperature (K)	296(2)
Crystal system	Triclinic
Space group	P-1
a (Å)	12.0505(10)
b (Å)	12.3189(11)
c (Å)	29.184(3)
α (°)	88.565(4)
β (°)	89.296(4)
γ (°)	76.833(4)
Volume (Å <sup>3</sup> )	4217.0(7)
Z	12
ρ <sub>calc</sub> (g/cm <sup>3</sup> )	1.414
μ (mm <sup>-1</sup> )	0.46
F(000)	1848
Crystal size (mm <sup>3</sup> )	0.83 × 0.74 × 0.48
Radiation	MoKα (λ = 0.71073)
2θ range for data collection (°)	2.80 to 47.00
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -32 ≤ l ≤ 32
Reflections collected	83073
Independent reflections	12426 [R <sub>int</sub> = 0.0411, R <sub>sigma</sub> = 0.0235]
Data/restraints/parameters	12426/0/1039
Goodness-of-fit on F <sup>2</sup>	1.098
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0662, wR <sub>2</sub> = 0.2217
Final R indexes [all data]	R <sub>1</sub> = 0.1253, wR <sub>2</sub> = 0.2481
Largest diff. peak/hole (e.Å <sup>-3</sup> )	0.76/-0.63

All coupling constants are reported as Hertz. High resolution mass spectra data (HRMS) were collected using Waters (Milford, MA, USA) LCT Premier XE Mass Spectrometer (high sensitivity orthogonal acceleration time-of-flight instrument) operating in ESI(+) or ESI(-) method, also coupled to an AQUITY Ultra Performance Liquid Chromatography system using a UV detector monitoring at 254 nm. Purity for the final compound was >95%, according to the UPLC-MS method using (A) water + 0.1% formic acid and (B) acetonitrile + 0.1% formic acid; flow rate = 0.3 mL/min, Column: Aquity BEH C18 column (2.1 × 100 mm, 1.7 mm). Flash column chromatography on silica gel was performed on Interchim prepacked disposable silica gel columns using Interchim Puriflash 4250 (Montlucon, France). Melting point (M.P.) was determined on Mettler Toledo-MP90 (Columbus, OH, USA) Melting Point System and was uncorrected. IR spectra was obtained using a Perkin Elmer (Waltham, MA, USA) Spectrum 400 FTIR/FTNIR spectrometer equipped with a Universal ATR Sampling accessory.

## 2.2. Synthesis of methyl 1-(2,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxylate (I)

A solution of methyl 5-methyl-1H-pyrazole-3-carboxylate (350 mg, 2.49 mmol) in DMF, K<sub>2</sub>CO<sub>3</sub> (1034 mg, 7.49 mmol) and 2,4-dichlorobenzylchloride (382 μL, 2.74 mmol) were added, and the resulting mixture was heated at 80 °C for 4 hours. The reaction mixture was cooled to room temperature, poured onto ice-water and extracted with ethyl acetate. The collected organic layer was dried, filtered and evaporated to give the crude, which was purified with automated-flash chromatography, eluting with a gradient of 0-50% ethyl acetate in hexane to separate two regioisomers. The product methyl 1-[(2, 4-dichlorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate was obtained as solid. The obtained product was recrystallized from hexane and ethyl acetate. Color: Translucent light white. Yield: 40.4%. M.p.: 90.1-90.6 °C. FTIR (ATR, ν, cm<sup>-1</sup>): 3094 (=C-H), 2946 (C-H), 1728 (C=O), 1587, 1229 (C-O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ, ppm): 7.42 (d, 1H, J = 2.1 Hz, Ar-H), 7.15 (dd, 1H, J = 8.4, 2.1 Hz, Ar-H), 6.67 (s, 1H, Ar-H), 6.56 (d, 1H, J = 8.4 Hz, Ar-H), 5.43 (s, 2H, -CH<sub>2</sub>-), 3.93 (s, 3H, -OCH<sub>3</sub>), 2.21 (s, 3H, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, δ, ppm): 162.8, 143.0, 140.6, 134.4, 132.5, 132.4, 129.3, 128.7, 127.8, 109.0,

52.0, 50.5, 11.0. HRMS (m/z) calcd. for C<sub>13</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 299.0354; found: 299.0351.

## 2.3. X-ray crystallography

Data collection and cell refinement for compound **I** were carried out using a diffractometer Bruker APEX-II CCD [12] with graphite monochromated MoKα radiation at 296 K and Bruker SAINT [12], respectively. The absorption correction was applied using Multi-scan SADABS [12]. The structure was solved by using SHELXT-2014 [13] and refined by using SHELXL-2014 [14]. The structure was drawn with ORTEP-3 for Windows [15] and Software used to prepare material for publication with PLATON [16] and WinGX [15]. The crystal data, conditions of data collection and refinement are reported in Table 1.

## 2.4. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. All H atoms were positioned geometrically and treated as riding with C-H = 0.93-0.97 Å and U<sub>iso</sub>(H) = 1.2 or 1.5 U<sub>eq</sub>(C). The measured crystal was of poor quality. It has been unable to grow a suitable crystal. The (-2 9 3), (5 -6 9), (0 -1 11), (1 1 17), (4 -6 9), (3 10 0), (-3 -15 15), (6 1 9), (5 -4 10), (5 10 1), (5 -1 11), (11 1 14), (5 -2 10), (10 10 2), (-2 -1 9), (8 -6 5), (3 -3 14), (8 3 12), (0 1 24), (7 -2 31), (-2 2 1), (-2 -3 1), (2 5 1), (-5 -4 1), (-4 -5 1), (-6 6 4), (2 -8 7), (1 -2 5), (3 1 0), (4 -2 10), (7 3 10), (-7 -9 2), (0 -2 1), (5 -3 5), (-4 -12 5), (-8 9 3), (-7 1 20), (-8 -8 9), (-10 -8 1), (-9 -10 11), (5 5 1), (2 9 1) and (-4 5 1) reflections were omitted owing to bad disagreement.

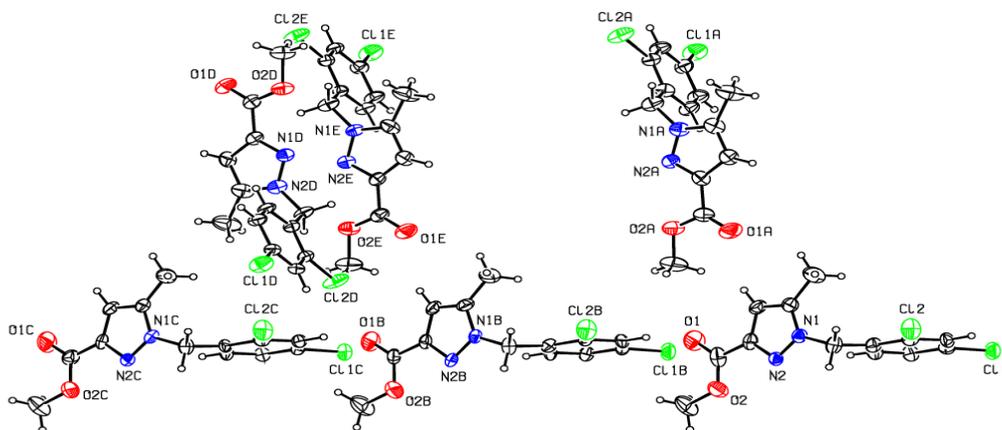
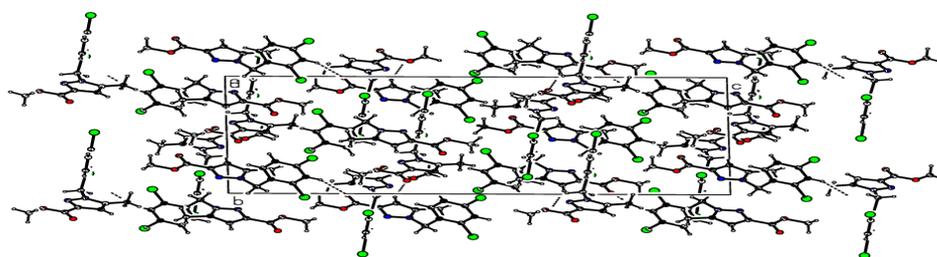
## 3. Result and discussion

### 3.1. Description of crystal structure of compound I

Figure 1 shows the asymmetric unit with the six molecules of the title compound. The 1H-pyrazole ring of each of these molecules are essentially planar. In all six molecules, the dichloro benzene ring and the 1H-pyrazole ring plane, which is essentially coplanar with the methyl-carboxylate group are nearly orthogonal, the dihedral angle between the C1-C6 and

**Table 2.** Selected geometric parameters (Å, °) for compound I.

C11—C3	1.736 (5)
C12—C5	1.752 (5)
O1—C12	1.225 (7)
N1—N2	1.325 (5)
N2—C11	1.328 (6)
C11—C3—C4	118.8 (4)
C12—C5—C4	118.2 (4)
N1—C7—C6	112.7 (4)
O1—C12—O2	124.9 (5)
C9—C8—C10	130.0 (5)
C13—O2—C12—C11	-178.9 (5)
N2—N1—C8—C9	-177.2 (5)
C11—C3—C4—C5	-177.8 (4)
C11—C5—C6—C1	178.3 (4)
N2—C11—C12—O2	-1.4 (7)

**Figure 1.** View of the title compound with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.**Figure 2.** Packing diagram of the title compound viewed down the *a* axis. Hydrogen bonds are indicated by broken lines.

C8-C10-C11-N1-N2 planes of the rings is  $87.5 (3)^\circ$  for the molecule with the atom C11,  $81.8 (3)^\circ$  for the one with the atom C11A,  $87.8 (2)^\circ$  for the one with the atom C11B,  $87.8 (2)^\circ$  for the one with the atom C11C,  $81.8 (2)^\circ$  for the one with the atom C11D and  $82.1 (2)^\circ$  for the one with the atom C11E.

All bond length and bond angle values for each molecule of the six molecules in the asymmetric unit (Table 2) are normal and comparable to those observed in the crystal structures of the related compounds, *via.*: Ethyl 1-(2,4-dichlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate [17] and dimethyl 1-{4-[4,5-*bis*(methoxycarbonyl)-1,2,3-triazol-1-ylmethylcarbonyl]-phenyl}-1*H*-pyrazole-3,4-dicarboxylate [18].

The six molecules in the asymmetric unit are stabilized by intramolecular C-H...N and C-H...Cl interactions (Table 3). In the crystal, molecules are linked by intermolecular C-H...O hydrogen bonds, forming molecular sheets into parallel to the (-1 1 0) plane (Table 3; Figures 2 and 3). These sheets are connected to each other by C-H...O hydrogen bonds and C-H... $\pi$  interactions.

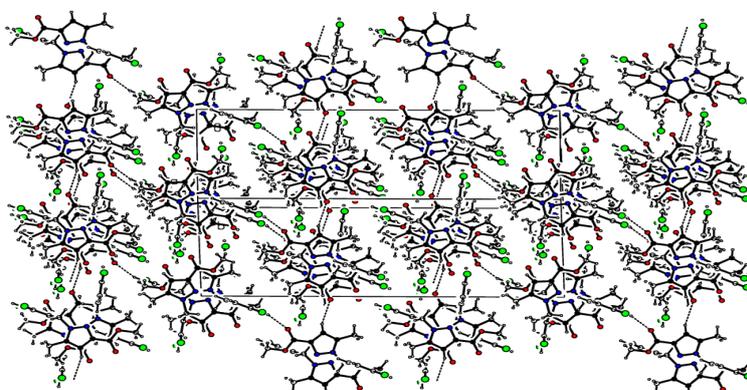
### 3.2. Hirshfeld surface analysis

Visualization and exploration of intermolecular close contacts in the crystal structure of the title complex is invaluable. Thus, a Hirshfeld surface analysis [19,20]; was carried out by using CrystalExplorer 17.5 [21] to investigate the locations of atom-atom short contacts with potential to form hydrogen bonds and the quantitative ratios of these interactions, using the coordinates of the atoms of the first one (with non-suffix) of the six molecules in the asymmetric unit. The Hirshfeld surface of a molecule in a crystal is constructed by calculating the spherical atom electron densities. In the Hirshfeld surface plotted over  $d_{\text{norm}}$  (Figure 4), the white surface indicates contacts with distances equal to the sum of van der Waals radii, and the red and blue colours indicate distances shorter (in close contact) or longer (distinct contact) than the van der Waals radii, respectively [22]. The contact distances to the closest atom inside ( $d_i$ ) and outside ( $d_e$ ) of the Hirshfeld surface analyze the intermolecular interaction *via*

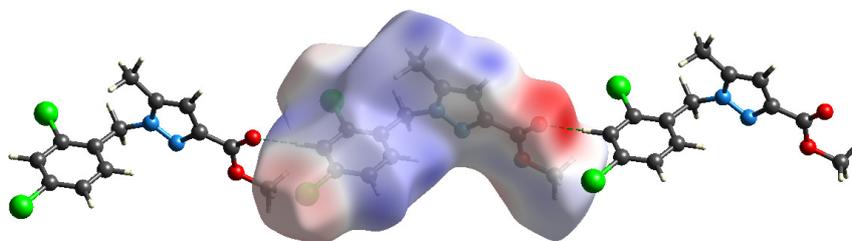
**Table 3.** Hydrogen-bond parameters (Å, °) for compound I\*.

D—H...A	D—H	H...A	D...A	D—H...A
C1—H1...N1	0.93	2.53	2.856(6)	101
C7A—H7A1...Cl2A	0.97	2.68	3.051(5)	104
C1A—H1A...N1A	0.93	2.51	2.847(6)	102
C1B—H1B...N1B	0.93	2.54	2.859(6)	100
C1C—H1C...N1C	0.93	2.54	2.858(5)	100
C1D—H1D...N1D	0.93	2.51	2.858(6)	102
C1E—H1E...N1E	0.93	2.51	2.855(6)	102
C4—H4...O1C <sup>i</sup>	0.93	2.32	3.189(6)	156
C4B—H4B...O1	0.93	2.30	3.186(6)	160
C4C—H4C...O1B	0.93	2.31	3.181(6)	156
C7B—H7B2...Cl2B	0.97	2.62	3.058(5)	108
C7—H7B...Cl2	0.97	2.61	3.052(5)	108
C10—H10...O1A	0.93	2.58	3.454(7)	157
C10B—H10B...O1E	0.93	2.58	3.457(6)	157
C7C—H7C2...Cl2C	0.97	2.60	3.055(5)	109
C7D—H7D2...Cl2D	0.97	2.67	3.037(5)	103
C7E—H7E1...Cl2E	0.97	2.69	3.049(5)	102
C4A—H4A...Cg2 <sup>ii</sup>	0.93	2.78	3.655(5)	158
C4D—H4D...Cg8 <sup>iii</sup>	0.93	2.74	3.630(5)	159
C4E—H4E...Cg6 <sup>ii</sup>	0.93	2.76	3.646(5)	159

\* Symmetry codes: (i)  $x-1, y-1, z-1$ ; (ii)  $x+1, y+1, z$ ; (iii)  $-x+1, -y+1, -z+1$ . Cg2, Cg6 and Cg8 are the centroids of the benzene rings (C1A–C6A), (C1D–C6D) and (C1E–C6E).



**Figure 3.** Packing diagram of the title compound viewed down the *b* axis. Hydrogen bonds are indicated by broken lines.



**Figure 4.** View of the three-dimensional Hirshfeld surface of the title complex plotted over  $d_{norm}$  in the range  $-0.3431$  to  $1.9396$  a.u., highlighting C—H...O hydrogen bonds by dashed lines..

the mapping of  $d_{norm}$ . In a  $d_{norm}$  surface, any intermolecular interactions will appear as a red spot. The shape-index of the Hirshfeld surfaces is a tool to visualize the  $\pi$ - $\pi$  stacking interactions by the presence of adjacent red and blue triangles; if there are no adjacent red and/or blue triangles, then there are no  $\pi$ - $\pi$  interactions. Figure 5 clearly suggests that there are no  $\pi$ - $\pi$  interactions in the title compound.

The Hirshfeld surfaces of the one with the atom Cl1 of six independent molecules in the asymmetric unit were obtained using a standard (high) surface resolution with the three-dimensional  $d_{norm}$  surfaces mapped over a fixed colour scale of  $-0.3431$  (red) to  $1.9396$  (blue). In the Hirshfeld surfaces plotted over  $d_{norm}$  and the fingerprint plots [23], shown in Figures 6 and 7, respectively, the points indicated by *b*, *c*, *d*, *e*, *f*, *g* and *h* correspond to H...H, Cl...H/H...Cl, C...H/H...C, O...H/H...O, N...H/H...N, Cl...Cl, Cl...O/O...Cl interactions with

relative contributions of 32.0, 20.9, 15.6, 13.9, 6.3, 5.0 and 2.1%, respectively. These types of interactions add to 95.8% of the intermolecular contacts of the Hirshfeld surface area. The remaining contributions (2.9%) correspond to Cl...C/C...Cl (1.3%), C...O/O...C (0.7%), O...O (0.5%) and N...N (0.4%), and other less-important interactions (< 1%).

#### 4. Conclusions

In this study, we have determined the crystal structure of methyl 1-[(2,4-dichlorophenyl)methyl]-5-methyl-1*H*-pyrazole-3-carboxylate using single crystal X-ray diffraction analysis. Also, we report Hirshfeld surface analysis of it. All bond length and bond angle values for each molecule in the asymmetric unit are normal and comparable to those observed in the crystal structures of the related compounds.

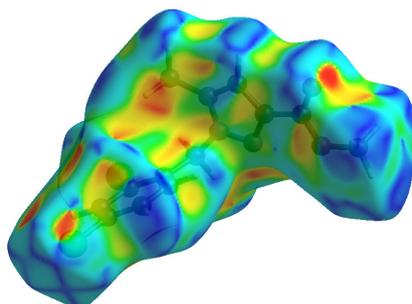


Figure 5. Hirshfeld surface of the title complex plotted over shape-index.

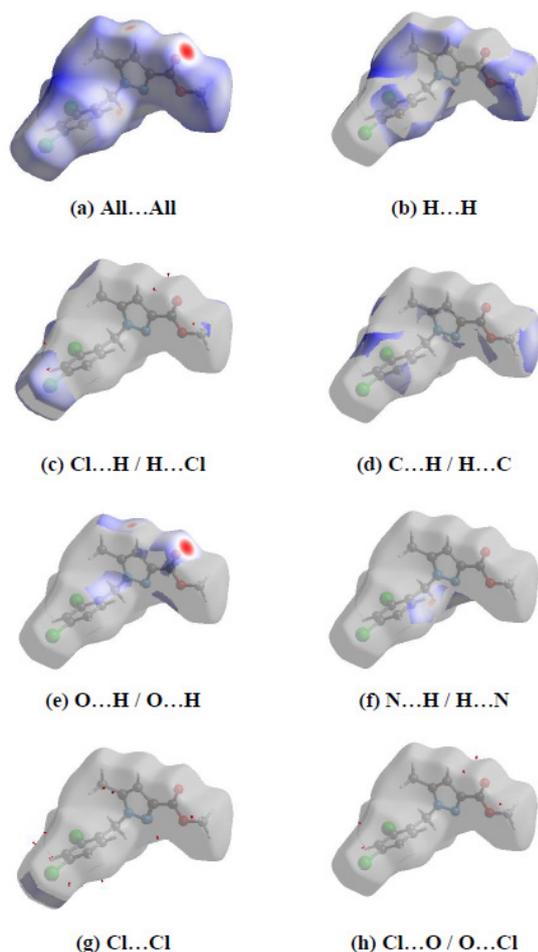


Figure 6. The full two-dimensional fingerprint plots for the title complex, showing (a) all interactions, and delineated into (b) H...H, (c) Cl...H/H...Cl, (d) C...H/H...C, (e) O...H/H...O, (f) N...H/H...N, (g) Cl...Cl, (h) Cl...O/O...Cl interactions. The  $d_i$  and  $d_e$  values are the closest internal and external distances (in Å) from given points on the Hirshfeld surface contacts.

The asymmetric unit of the title compound contains six molecules which the 1*H*-pyrazole rings are essentially planar. The crystal structure is stabilized by intermolecular C-H...O hydrogen bonds, forming molecular sheets into parallel to the (-1 1 0) plane. According to the Hirshfeld surface analysis, the H...H, Cl...H/H...Cl, C...H/H...C, O...H/H...O, N...H/H...N, Cl...Cl, Cl...O/O...Cl interactions add to 95.8% of the intermolecular contacts of the Hirshfeld surface area. The remaining contributions correspond to other less-important interactions.

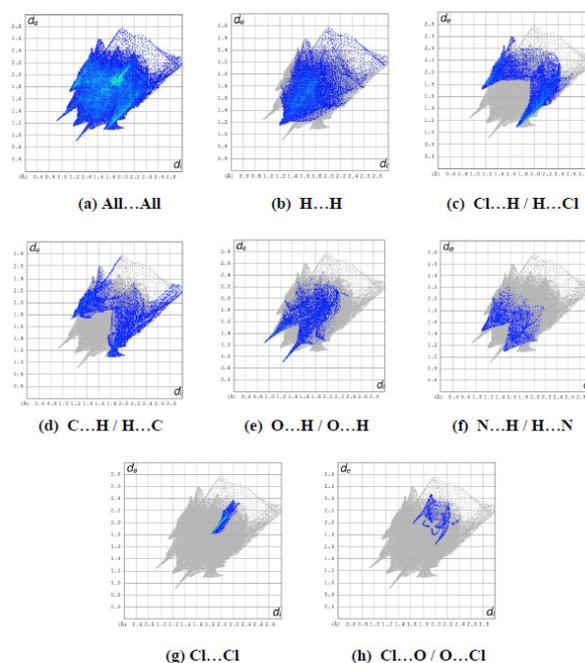


Figure 7. The Hirshfeld surface representations with the function  $d_{norm}$  plotted onto the surface for (a) all interactions, and (b) H...C/C...H, (c) H...H, (d) H...Cl, (e) O...H/H...O, (f) Cl...H, (g) Cl...Cl and (h) H...O interactions.

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#### Supplementary information

CCDC-1843087 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>, or by e-mailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

#### Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.

Author contributions: All authors contributed equally to this work.

Ethical approval: All ethical guidelines have been adhered.

Sample availability: Samples of the compounds are available from the author.

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