Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(4):219-225
(http://derpharmachemica.com/archive.html)

Structural Elucidation, Synthesis, Characterization and Hirshfeld Surface Analysis of ethyl 2-(2-bromophenoxy)acetate

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ABSTRACT

The title compound, ethyl 2-(2-bromophenoxy)acetate was synthesized in good yield by refluxing O-bromophenol with ethyl chloroacetate in the presence of K_2CO_3 in anhydrous acetone. The product obtained was characterized by spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The compound crystallizes in the monoclinic crystal system with the space group $P2_1/n$ with unit cell parameters a = 5.3473(3) Å, b = 26.7605(15) Å, c = 7.9862(5) Å, β = 107.796(4)° and Z=4. The crystal packing exhibits intermolecular C—H...O hydrogen bonds forming a infinite linear chain propagating along [100] direction with graph set notation C(4). Hirshfeld surface analysis for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots have been used to examine molecular shapes.

Keywords: Bromophenoxy acetate, Crystal structure, Infinite linear chain, Hirshfeld Surfaces, C-H…O interaction**.**

INTRODUCTION

Analogues of phenoxy ethanoic acid are considered to be very important compounds in the field of medicinal chemistry and the compounds were found to have good antifungal activity against pathogenic fungi and possess moderate activity against gram negative bacteria in comparison to standard ciprofloxacin [1]. Recent studies shows the changes in the chemical and stereoisomeric structures of phenoxy ethanoic acid alter peroxisome proliferation [2]. Ethyl phenoxy acetate derivatives have potential antimicrobial, anticancer, antitumor antioxidant antiinflammatory and plant growth regulation activity properties [3–6]. These compounds are widely used as herbicides and pesticides. The ethyl phenoxy acetate analogues also showed very good antiulcerogenic activity, cyclooxygenase activity, anticonvulsant activity [7, 8]. In view of their broad spectrum of biological properties and as a part of our ongoing work on synthesis and characterization of novel compounds [9,10], the title compound was synthesized. The compound obtained was characterized spectroscopically and finally the structure was confirmed by X-ray diffraction studies. An investigation of close intermolecular contacts between the molecules *via* Hirshfeld surface analysis is also presented in order to quantify the interactions within the crystal structure.

MATERIALS AND METHODS

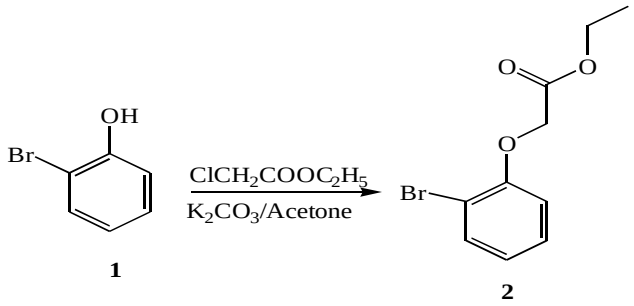
All the chemicals were purchased from Sigma Aldrich Chemical Co. ^{1}H NMR spectra was recorded on a Bruker 400 MHz in $CDCl_3$ and the chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a VG70-70H spectrophotometer. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ±0.4% of the

theoretical values.

Synthesis of ethyl 2-(2-bromophenoxy)acetate

A mixture of *O*-bromophenol (**1**, 0.025 mol), ethyl chloroacetate (0.037 mol) and anhydrous potassium carbonate (0.037 mol) in dry acetone (50 ml) was refluxed for 10 hrs. The reaction mixture was cooled and the solvent was removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (3 × 30 ml). The ether layer was washed with 10% sodium hydroxide solution (3 × 30 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulfate and evaporated to afford ethyl 2-(2-bromophenoxy)acetate (**2**). Yield (91%), M.P = 49-52º C

^{1}H NMR ($CDCl_3$): σ: 1.20 (t, 3H, CH_3), 4.16 (q, 2H, OCH_2 of ester), 4.76 (s, 2H, OCH_2), 6.87-7.2 (m, 4H, Ar-H); LC–MS m/z 244 (M+1). Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 46.36; H, 4.28; Br, 30.84. Found: C, 46.15; H, 3.97; Br, 30.55%.



Scheme 1 Synthesis of ethyl 2-(2-bromophenoxy) acetate

2.2 Crystal Structure Determination

A white coloured rectangle shaped single crystal of dimensions 0.28×0.26×0.24 mm of the title compound was chosen for an X-ray diffraction study. The X-ray intensity data were collected at a temperature of 296 K on a Bruker Proteum2 CCD diffractometer equipped with an 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 2 s, the sample to detector distance of 45.10 mm and 2θ value at 46.6°. A complete data set was processed using *SAINT PLUS* [11]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [12]. All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All the hydrogen atoms were positioned geometrically (C–H = 0.93 Å, O–H = 0.82 Å) and refined using a riding model with U_{iso}(H) = 1.2 U_{eq} and 1.5 U_{eq} (O). After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0326. The geometrical calculations were carried out using the program *PLATON* [13]. The molecular and packing diagrams were generated using the software *MERCURY* [14]. The details of the crystal structure and data refinement are given in **Table 1**. **Figure 1** represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

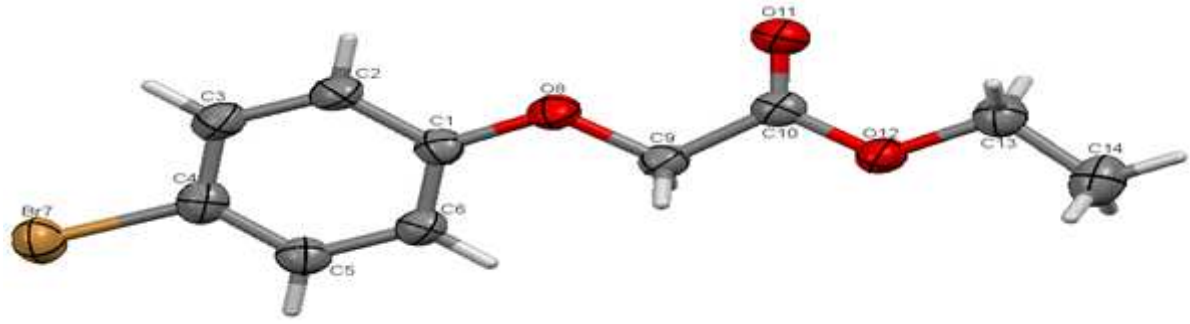


Figure 1: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

Hirshfeld surface calculations

Molecular Hirshfeld surface in the crystal structure was created based on the electron distribution calculated as the sum of spherical atom electron densities. The normalized contact distance (d_{norm}) based on both d_e, d_i and the van Der Waals radii of the enables identification of the regions of particular importance to intermolecular interactions. The Hirshfeld surfaces and fingerprint plots presented here were plotted using the software CrystalExplorer 3.0 [15]. The d_{norm} plots were mapped with colour scale in between −0.18 au (blue) and 1.4 au (red). The 2D fingerprint plots [16, 17] were displayed by using the expanded 0.6–2.8 Å view with the d_e and d_i distance scales displayed on the graph axes. When the cif file was uploaded into the CrystalExplorer software, all bond lengths to hydrogen were

automatically modified to typical standard neutron values i.e., C–H = 1.083Å.

Table 1: Crystal data and structure refinement table

Parameter	Value
CCDC deposit No.	CCDC 1451821
Empirical formula	$C_{10}H_{11}BrO_3$
Formula weight	259.10
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	A = 5.3473(3) Å b = 26.7605(15) Å c = 7.9862(5) Å β = 107.796(4)°
Volume	1088.11(11) $Å^3$
Z, Calculated density	4, 1.582 Mg/m^3
Absorption coefficient	5.006 mm^{-1}
$F_{(000)}$	520
Crystal size	0.28 x 0.26 x 0.24 mm
Theta range for data collection	6.05° to 82.53°
Limiting indices	$-6 \leq h \leq 6$, $-31 \leq k \leq 34$, $-9 \leq l \leq 9$
Reflections collected / unique	5758/ 1826 [R(int) = 0.0691]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1826 / 0 / 128
Goodness-of-fit on F^2	1.108
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0976, $wR2$ = 0.2200
R indices (all data)	$R1$ = 0.1921, $wR2$ = 0.2912
Largest diff. peak and hole	1.515 and −1.001 e. $Å^{-3}$

RESULTS AND DISCUSSION

The bromo-phenyl ring is planar. The pendant ethyl chain is in an extended conformation and almost lies in the plane of the bromophenyl ring as indicated by the dihedral angle value of 8.9(1)°. The structure exhibits intermolecular hydrogen bonds of the type C—H...O. The inter-molecular hydrogen bond C9—H9A...O8 has a length of 3.361(7) Å and an angle of 151° with a symmetry code *-1/2+x,1/2-y,-1/2+z* and the other hydrogen bond C9—H9B...O11, which has a length of 3.454(10) Å and an angle of 168° with symmetry code *-1+x, y, z.* These hydrogen bonds forms a infinite linear chain propagating along [100] direction with graph set notation *C(4)* **Figure 2**.

Hirshfeld surface studies

Hirshfeld surface analysis is an effective tool for exploring packing modes and intermolecular interactions in molecular crystals, as they provide a visual picture of intermolecular interactions and of molecular shapes in a crystalline environment. Surface features characteristic of different types of intermolecular interactions can be identified, and these features can be revealed by colour coding distances from the surface to the nearest atom exterior (d_e plots) or interior (d_i plots) to the surface. This gives a visual picture of different types of interactions present and also reflect their relative contributions from molecule to molecule. Further, 2D fingerprint plots (FP), in particular the breakdown of FP into specific atom…atom contacts in a crystal, provide a quantitative idea of the types of intermolecular contacts experienced by molecules in the bulk and presents this information in a convenient colour plot. Hirshfeld surfaces comprising d_{norm} surface and Finger Print plots were generated and analysed for the title compound in order to explore the packing modes and intermolecular interactions. The two dimensional fingerprint plots from Hirshfeld surface analyses **Figure 3**, illustrates the difference between the intermolecular interaction patterns and the relative contributions to the Hirshfeld surface (in percentage) for the major intermolecular contacts associated with the title compound. The fingerprint plots can be decomposed to highlight particular atoms pair close contacts. There are two sharp spikes pointing toward the lower left of the plots and are typical C--H□O hydrogen bonds. Importantly, H...H (35.1%) bonding appears to be a major contributor in the crystal packing, whereas the O...H/H...O (23.5%), Br...H/H...Br (22.2%), C...H/H...C(15.4%) plots also reveal the information regarding the intermolecular hydrogen bonds thus supporting for C--H...O intermolecular interactions.

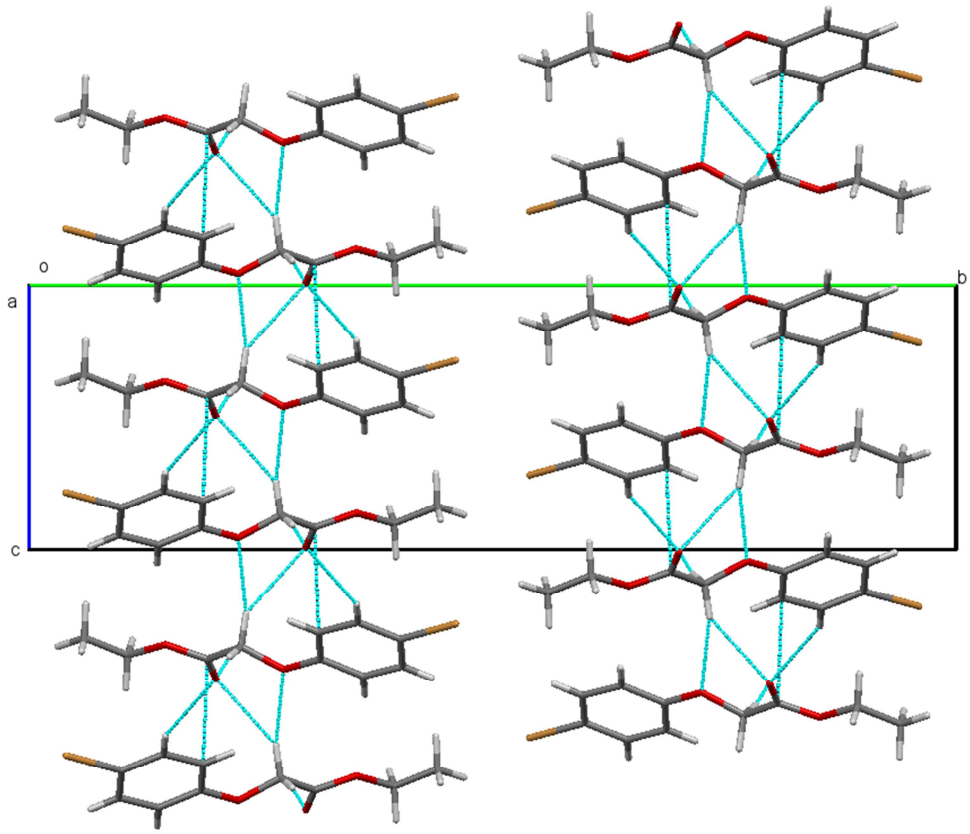


Figure 2: Packing of the molecules when viewed down along the [100] axis. The dotted lines represents hydrogen bonds forming a infinite linear chain with graph set notation C(4)

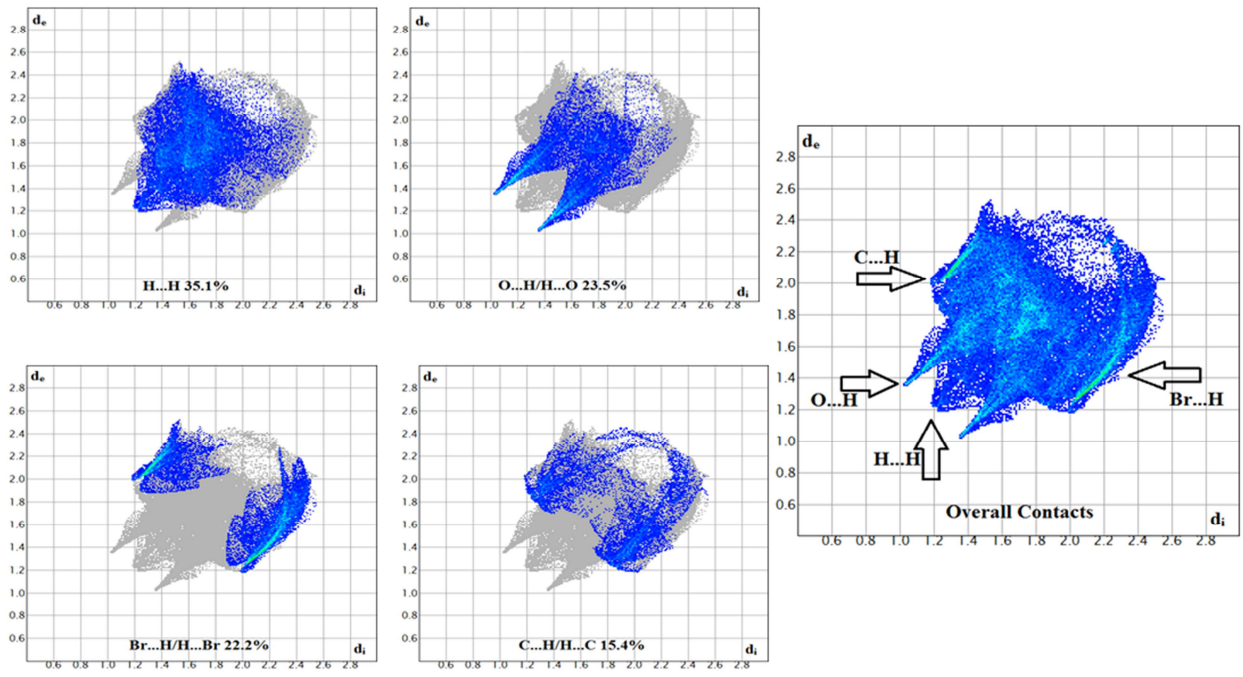


Figure 3: Fingerprint plots of the title compound showing H...H, O…H, Br...H and C...H interactions. d_i is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts

This intermolecular contact is highlighted by conventional mapping of d_{norm} on molecular Hirshfeld surfaces and is

shown in **Figure 4**. The red spots over the surface indicate the intercontacts involved in hydrogen bond. The dark-red spots on the d_{norm} surface arise as a result of the short interatomic contacts, i.e., strong hydrogen bonds, while the other intermolecular interactions appear as light-red spots.

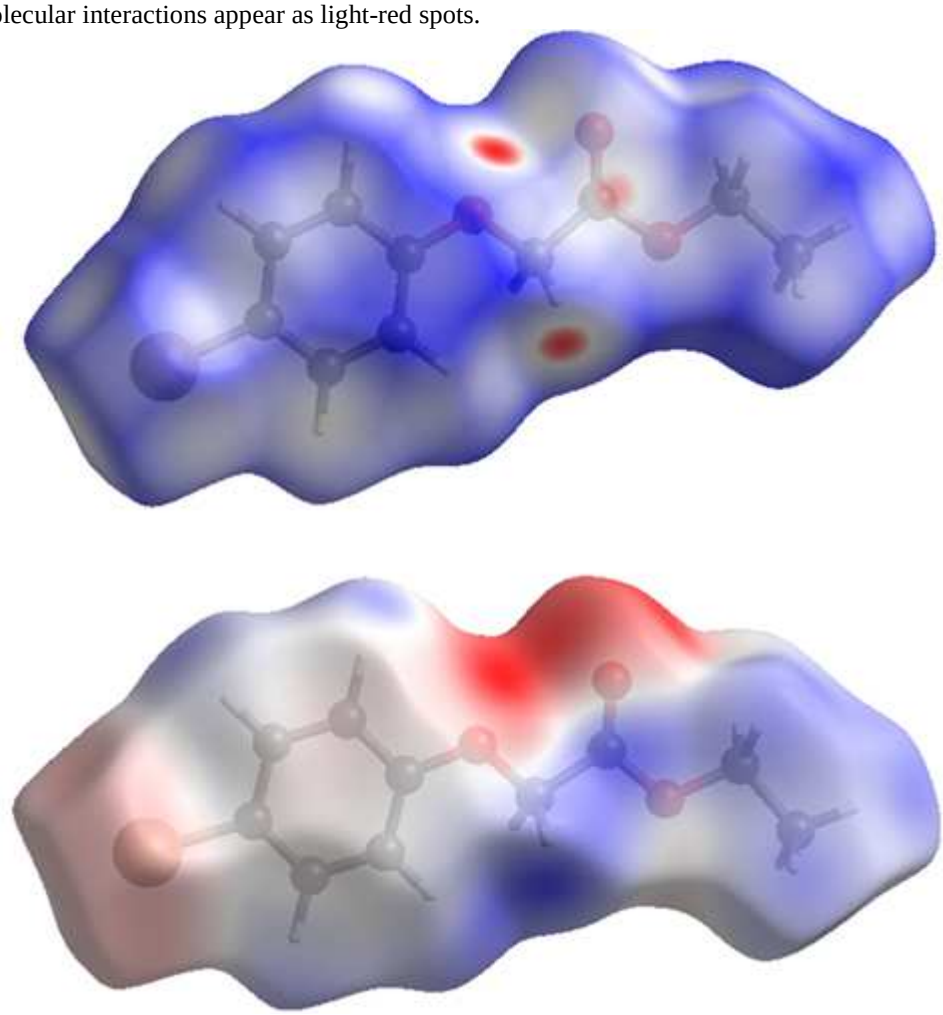


Figure 4: d_{norm} and electrostatic potential mapped on Hirshfeld surface for visualizing the intermolecular contacts

Figure 5 shows the curvedness and shape index mapped on Hirshfeld surface indicating the largest regions of flat curvedness appearing for the title compound. The shape index surface clearly shows that the two sides of the molecules are involved in same contacts with neighbouring molecules and curvedness plots show flat surface patches characteristic of planar stacking.

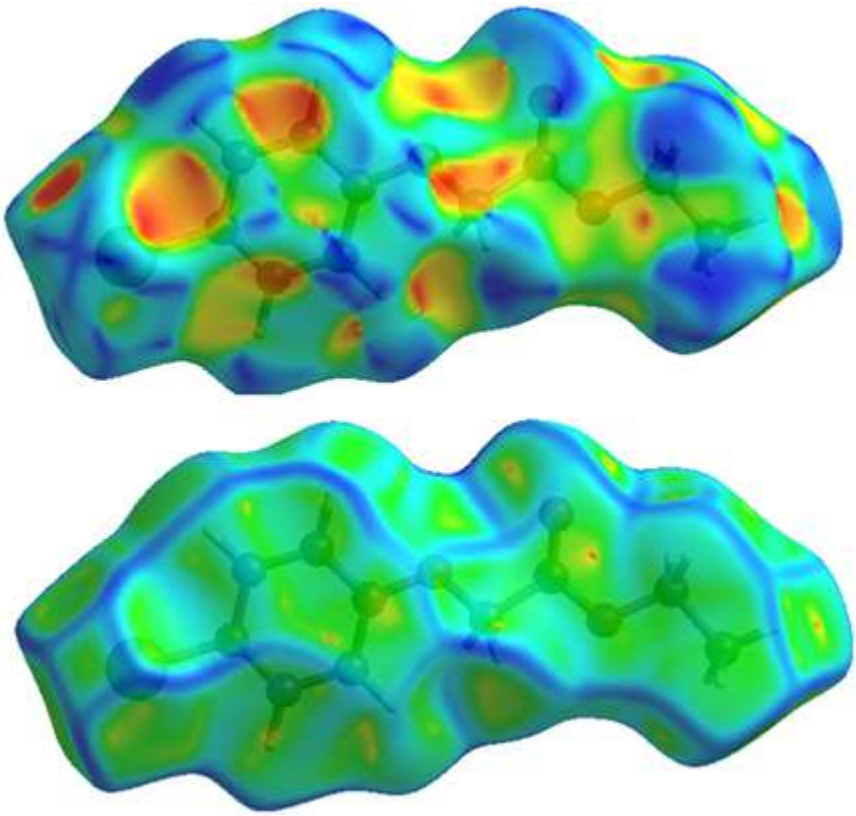


Figure 5: Shape index and curvedness index mapped on Hirshfeld surface. The surfaces are shown as transparent to allow visualization of the orientation and conformation of the functional groups in the molecules

Acknowledgments

The authors are grateful to the Institution of Excellence, Vijnana Bhavana, University of Mysore, India, for providing the single-crystal X-ray diffractometer facility. Yasser Hussain Issa Mohammed thanks University of Hajah, Yemen for the financial support. S.A. Khanum gratefully acknowledges the financial support provided by the Vision Group of Science and Technology, Government of Karnataka under the scheme CISEE, Department of Information Technology, Biotechnology and Science & Technology, Bangalore.

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