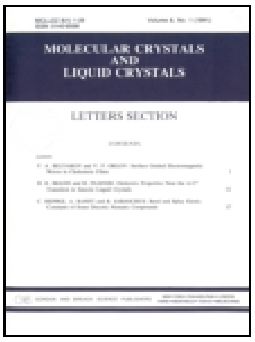

Molecular Crystals and Liquid Crystals

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Hirshfeld surface analysis and crystal structure of [2-Bromo-4-(4-fluoro-benzoyl)-phenoxy]-acetic acid ethyl ester

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ABSTRACT

The title compound $C_{17}H_{14}BrFO_4$ was synthesized using 3-Bromo-4-hydroxy-phenyl-(4-fluoro-phenyl)-methanone, ethyl chloroacetate, and anhydrous potassium carbonate. Its structure was established using elemental analysis, NMR, and single crystal X-ray diffraction techniques. The compound crystallizes in orthorhombic crystal system and space group Pbca. The cell parameters are a = 10.1444(13) Å, b = 8.2781(10) Å, c = 38.423(5) Å, Z = 8, V = 3226.6(7) Å^3. The dihedral angle between two least squares planes of two phenyl rings bridged by keto carbonyl group is −28.2(5)°. The molecule exhibits intermolecular interactions of the type C–H …F and C–H …O. The intercontacts in the crystal structure are studied using Hirshfeld surface analysis.

KEYWORDS
Allergen of the year; benzophenones; electrostatic potential; finger print plot; hirshfeld surface analysis

Introduction

Benzophenone has been named as 2014 Contact "Allergen of the Year" by the American Contact Dermatitis Society, because of its chemical ultraviolet (UV) light absorption. It is used in sunscreens, hair sprays, and plastic lens filters for color photography. They were initially used as preservers of industrial products [1]. Benzophenones are also used for packing purposes; addition of benzophenones to the plastic packages acts as an UV blocker.

The competence of benzophenone analogs as chemotherapeutic agents especially as anti-inflammatory is well recognized [2]. Photochemical DNA damage can occur when DNA directly interacts with UV. Upon direct exposure to sunlight the photosensitizers increase the probability of developing skin cancer. Benzophenone is a classical and paradigmatic sensitizer in photochemical studies. Irradiation of this chromophore in the presence of DNA leads to the formation of nucleobase modifications [3].

With this background here is an attempt to synthesize [2-Bromo-4-(4-fluoro-benzoyl)-phenoxy]-acetic acid ethyl ester compound. Its structure is determined using elemental analysis, ^{1}H NMR (nuclear magnetic resonance) and XRD (X-Ray Diffraction). Its intermolecular interactions are studied using Hirshfeld surface analysis.

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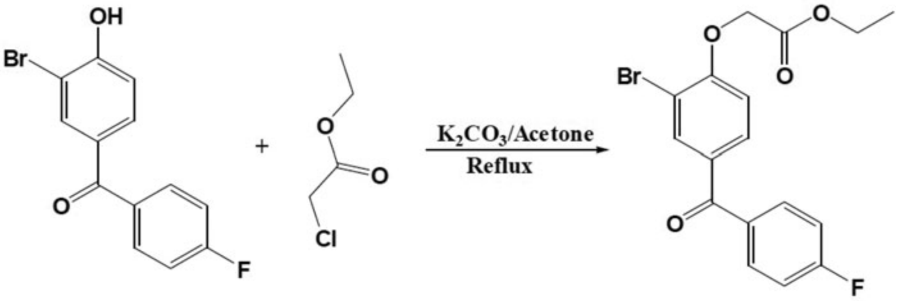
Experimental

Materials and methods

Chemicals were purchased from Sigma Aldrich Chemical Corporation. Thin layer chromatography was performed on aluminum-backed silica plates from Merck & Co., and visualized under UV light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrophotometer in DMSO-d_6 solvent and the chemical shifts were recorded in ^{TM} (ppm) downfield from tetramethylsilane. Elemental analysis was done using the Perkin Elmer 2400 elemental analyzer and results are within 0.4% of the calculated value.

Synthesis of [2-bromo-4-(4-fluoro-benzoyl)-phenoxy]-acetic acid ethyl ester

Compound [2-Bromo-4-(4-fluoro-benzoyl)-phenoxy]-acetic acid ethyl ester was obtained by refluxing a mixture of compound (3-Bromo-4-hydroxy-phenyl)-(4-fluoro-phenyl)-methanone (0.013 mol) and ethyl chloroacetate (0.026 mol) in dry acetone (50 mL) and anhydrous potassium carbonate (0.019 mol) for 10 hr. The reaction mixture was cooled and the solvent was removed by distillation and the reaction was monitored by TLC (Thin-layer chromatography) using benzene:ethyl acetate (10:1) as an eluent. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (3 × 50 mL). The ether layer was washed with 10% sodium hydroxide solution (3 × 50 mL). It was dried over anhydrous sodium sulfate and evaporated to dryness to obtain crude solid, which on recrystallization with ethanol afforded desired compound (3) in good yield 89%, m.p. 60°C–62°C (Scheme 1).



Scheme 1. Scheme of [2-Bromo-4-(4-fluoro-benzoyl)-phenoxy]-acetic acid ethyl ester.

Results and discussions

Elemental analysis

In order to confirm the chemical composition of the synthesized compound, carbon (C), hydrogen (H) analysis was carried out. The experimental and calculated percentages of C and H are given in Table 1. The differences between experimental and calculated percentages of C and H were very small and are within the experimental errors. This confirms the formation of the product in the stoichiometric proportion.

Table 1. Elemental analysis for the title compound.

Element	Experimental (%)	Calculated (%)
Carbon	53.58	53.56
Hydrogen	3.72	3.70

^{1}HNMR spectral analysis

The ^{1}H NMR data of the crystal structure are: The NMR peak at δ 1.2 triplet is for three hydrogens in CH_3 of ester, the quartet peak at δ 4.1 is for the CH_2 ester group, the singlet peak at δ 4.9 is for two hydrogen of -OCH_2, and the peaks at δ 6.8–7.8 clearly indicates the seven aromatic hydrogens of the compound, thus confirms the structure.

Single crystal X-ray diffraction

A white colored, prismatic single crystal of the synthesized compound with approximate dimensions of 0.23 × 0.22 × 0.21 mm was used for X-ray diffraction study. Data were collected on a Bruker CCD diffractometer equipped with Cu K_α radiation. Data reduction and applying of absorption corrections were carried out using the *APEX 2* package [4]. Crystal structure was solved by direct methods using *SHELXS-97* and was refined by full-matrix least squares refinement against F^2 using *SHELXL-97* [5]. All nonhydrogen atoms were refined anisotropically and hydrogen atoms were placed in chemically acceptable positions. A total

Table 2. The crystal data and structure refinement details.

CCDC deposit number	1023409
Empirical formula	$C_{17}\,H_{14}\,Br\,F\,O_4$
Formula weight	381.19
Temperature	293 K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	*P bca*
Cell dimensions	$a = 10.1444(13)$ Å $b = 8.2781(10)$ Å $c = 38.423(5)$ Å
Volume	3226.6(7) Å^3
Z	8
Density(calculated)	1.569 Mgm$^{-\cdot}$
Absorption coefficient	3.732 mm$^{-\cdot}$
F_{000}	1536
Crystal size	0.180 × 0.180 × 0.180 mm
θ range for data collection	4.60° to 63.78°
Index ranges	$-$ndex$h \leq 11$ $-$ 11x$k \leq 7$ $- \leq 7$x $l \leq 43$
Reflections collected	11846
Independent reflections	2628 [$R_{int} = 0.0309$]
Refinement method	Full matrix least-squares on F^2
Data/restraints/parameters	2628/0/209
Goodness-of-fit on F^2	1.095
Final [I > 2σ(I)]	R1 = 0.0398, wR2 = 0.1024
Largest diff. peak and hole	0.482 and $-$0.911 e Å^{-3}

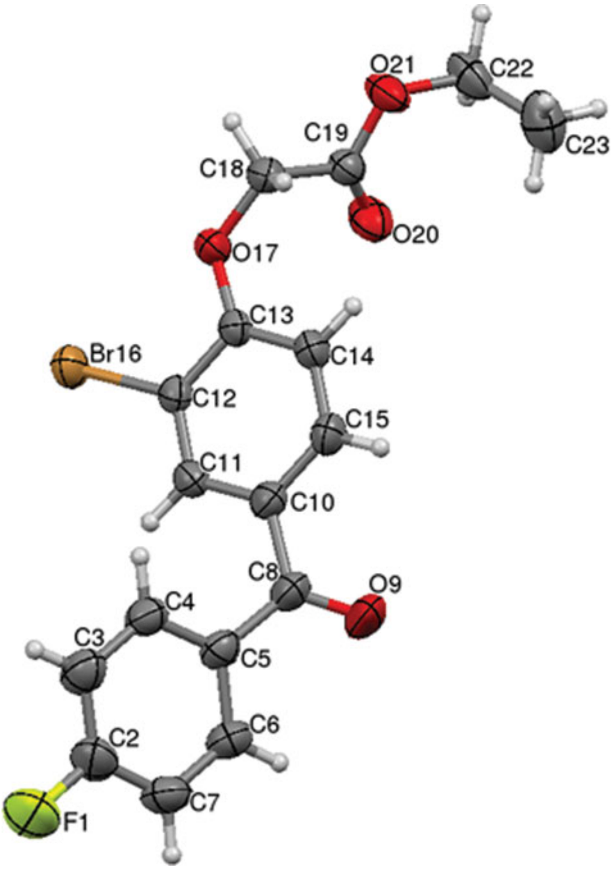


Figure 1. *ORTEP* diagram of the molecule with thermal ellipsoids drawn at 50% probability.

of 217 parameters were refined with 3069 unique reflections, which converged the residual to $R = 0.0495$. The bond lengths and bond angles values are within the expected range.

The compound $C_{17}H_{14}BrFO_4$ crystallizes in orthorhombic crystal system, with space group *Pbca*. The unit cell parameters are $a = 10.1444(13)$ Å, $b = 8.2781(10)$ Å, $c = 38.423(5)$ Å. The details of the crystal data and structure refinement are given in Table 2. The geometrical calculations were carried out using the program *PLATON* [6]. The molecular and packing diagrams were generated using *Mercury* [7]. Figure 1 shows the *ORTEP* diagram of the

Table 3. Selected bond lengths and bond angles (Å, deg.).

Atoms	Bond lengths/angles	Atoms	Bond lengths/angles
O20-C19	1.201(4)	C6-C7	1.377(5)
C2-C7	1.378(5)	O17-C18	1.423(3)
C10-C15	1.394(4)	C10-C11	1.395(4)
F1-C2	1.359(4)	C3-C4	1.383(5)
O9-C8	1.216(4)	C18-C19	1.510(4)
C13-O17-C18	119.1(2)	C8-C10-C15	119.0(3)
C19-O21-C22	117.2(2)	C11-C10-C15	118.6(3)
F1-C2-C3	118.4(3)	C10-C11-C12	120.1(2)
F1-C2-C7	118.5(3)	Br16-C12-C11	119.50(19)
O9-C8-C5	120.6(3)	O20-C19-O21	125.0(3)

Table 4. Selected torsion angles (deg.).

Atoms	Torsion angles	Atoms	Torsion angles
C18-O17-C13-C14	− 7.0(4)	C5-C8-C10-C15	144.0(3)
C12-C13-C14-C15	0.3(4)	O9-C8-C10-C15	− 34.7(6)
C18-O17-C13-C12	172.5(2)	C4-C5-C8-C10	− 28.2(5)
C7-C2-C3-C4	1.8(6)	C8-C10-C11-C12	− 177.8(3)
C4-C5-C6-C7	1.4(5)	C13-C14-C15-C10	− 0.7(5)
F1-C2-C7-C6	179.8(3)	C10-C11-C12-Br16	− 179.9(2)

molecule with thermal ellipsoids drawn at 50% probability. The bond distances and angles are listed in the Table 3. Torsion angles are listed in the Table 4.

The dihedral angle between two least square planes of two phenyl rings bridged by keto carbonyl group (C4-C5-C8-C10) is −28.2(5)°. The phenyl rings of benzophenone are planar (C2−C7) (r.m.s. deviation 0.01(3) Å), with a maximum deviation of 0.010(4) Å for C3; (C10−C15) (r.m.s. deviation 0.005(3) Å), with a maximum deviation of 0.004(3) Å for C11 and C14. The torsion angle for O9-C8-C10-C15 is −34.7(6)°, which indicates that carbonyl group is oriented in – synclinal conformation.

The phenyl rings (C2−C7) and (C10−C15) of benzophenone are *sp2* hybridized. They are well described by the torsion angles 1.03° and 0.50°, respectively; which suggest that they adopt +syn-periplanar (+sp). The bond lengths and angles are in fairly good agreement with those of previously reported benzophenone derivatives. The bond length of C=O of the ester group (O20–C19) is 1.201(4) Å , which is greater than the corresponding values of 1.198(2) Å and 1.197(3) Å reported for $C_{23}H_{20}O_3$ and $C_{21}H_{14}C_{l2}O_3$, respectively [8].

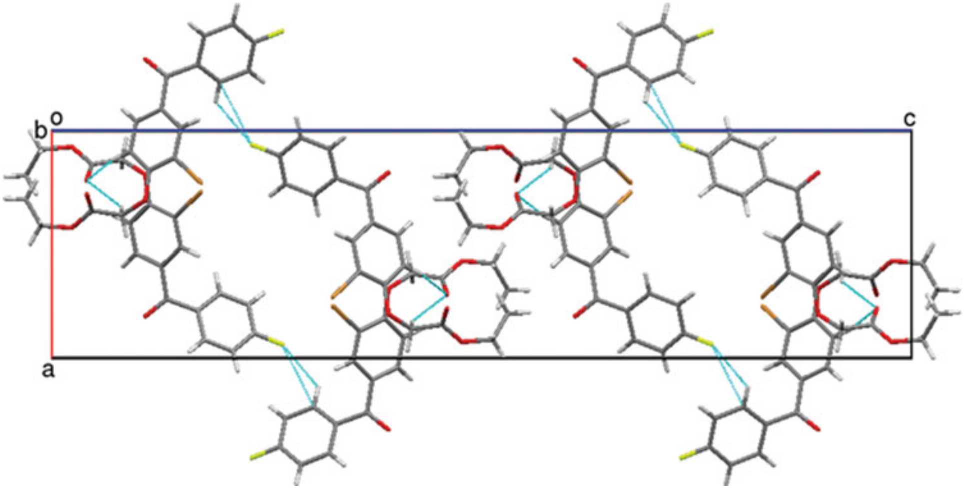


Figure 2. Packing of molecules when viewed down *b*-axis.

Table 5. Hydrogen-bond geometry (Å , deg.).

D–H ...A	D–H	H ...A	D ...A	D–H ...A
C(4)-H(4) ...F(1) (a)	0.93	2.53	3.135(4)	123
C(14)-H(14) ...O(20) (b)	0.93	2.49	3.340(4)	151
C(18)-H(18A) ...O(20) (b)	0.97	2.57	3.386(4)	142
C(18)-H(18B) ...O(9) (c)	0.97	2.40	3.349(4)	168

Note. Symmetry codes (a) 1/2+x,y,1/2-z, (b) 3/2-x,1/2+y,z, (c) 1+x,y,z.

The structure exhibits intermolecular interactions of the type C–H ...F and C–H ...O, which holds the molecules in the crystal lattice. Figure 2 shows the packing of molecules when viewed along *b*-axis. The intermolecular hydrogen bond between the phenyl group and fluorine moiety has a length of 3.135(4) Å and an angle of 123°. Its symmetry group is $1/2 + x, y, 1/2 - z$. Table 5 shows the hydrogen-bond geometry.

Hirshfeld surface analysis

Hirshfeld surface analysis was made using a graphical tool “CrystalExplorer” [9]. Hirshfeld surface analysis is an approach wherein we study the intermolecular contacts in a crystal structure. Figure 3 shows a surface that has been mapped over d_{norm}. The red highlighted region on the d_{norm} surface shows the intermolecular contacts closer than the sum of the van der Waals radii; whereas the blue region shows the longer contacts [10].

Table 6 shows the contributions of various intermolecular contacts to the Hirshfeld surface. The major contributions are from H ...H (28%) and H ...O (24.5%) contacts. Figure 4 shows the fingerprint plots. Figure 4(a) shows H ...H (28.1%) contribution of intercontact to the Hirshfeld surfaces. Figures 4(b)–(d) show the intercontacts of H ...O (24.5%), C ...H (17.9%), and H ...F (9.2%), respectively. Features along the diagonal occur due to H–H contacts. Blue color points indicate smaller contribution to the surface; whereas uncolored points

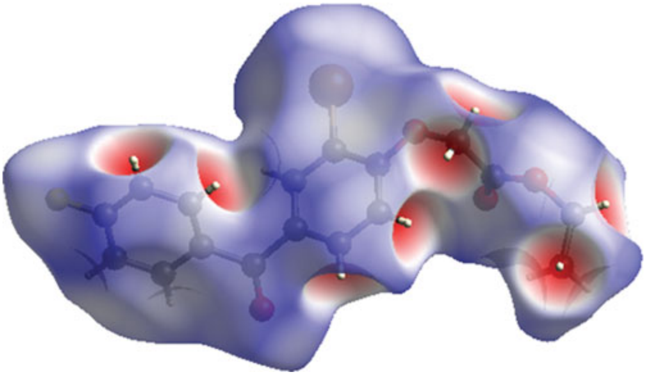


Figure 3. d_{norm} mapped on Hirshfeld surface for the visualization of the intercontacts of the title compound.

Table 6. Hirshfeld surface: Percentage of various intermolecular contacts contributed to Hirshfeld surface.

Intercontacts	Contribution (%)
H - H	28.1
H - O	24.5
C - H	17.9
H - F	9.2

on the plot indicate no contribution to the surface [11]. Figure 5 shows the electrostatic potential indicating the distribution of positive and negative potential over the Hirshfeld surfaces. Blue region corresponds to positive electrostatic potential and red region indicates negative electrostatic potential [12].

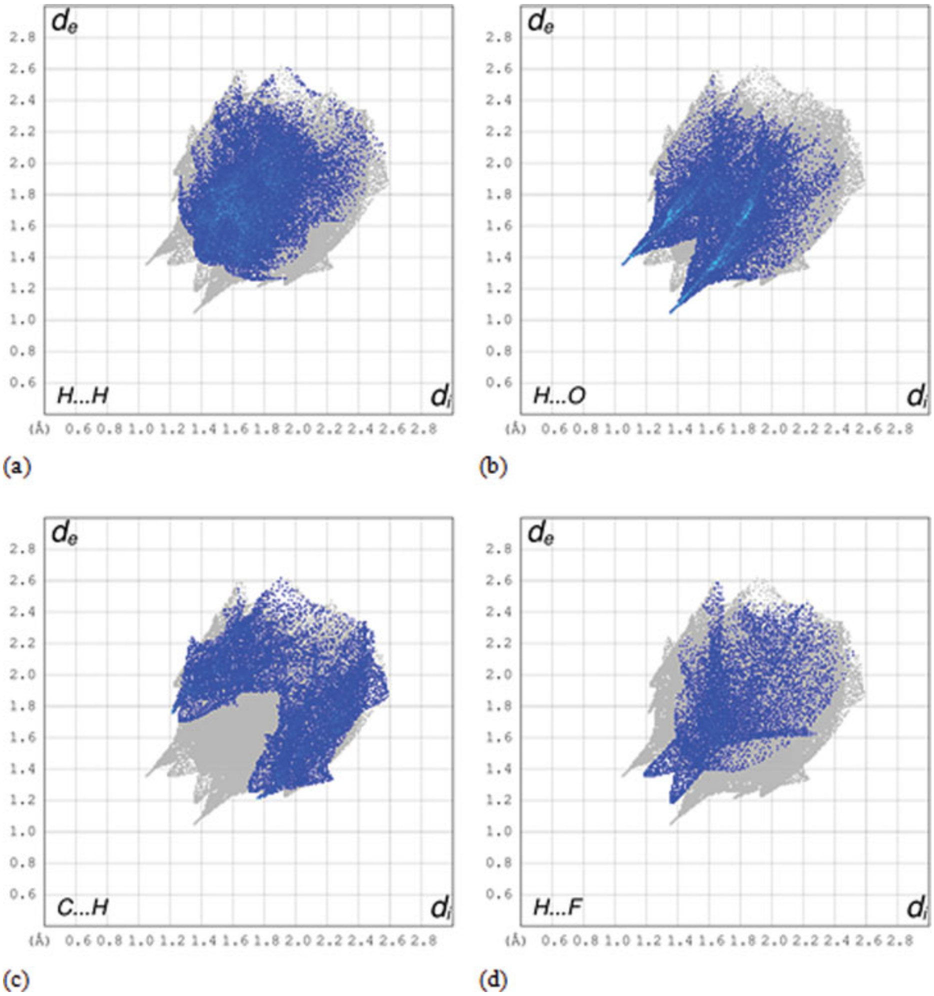


Figure 4. Fingerprint plots of the title compound (a) H ...H, (b) H ...O, (c) C ...H, and (d) H ...F showing the percentage contribution of the contacts to the total Hirshfeld surface area of the molecule.

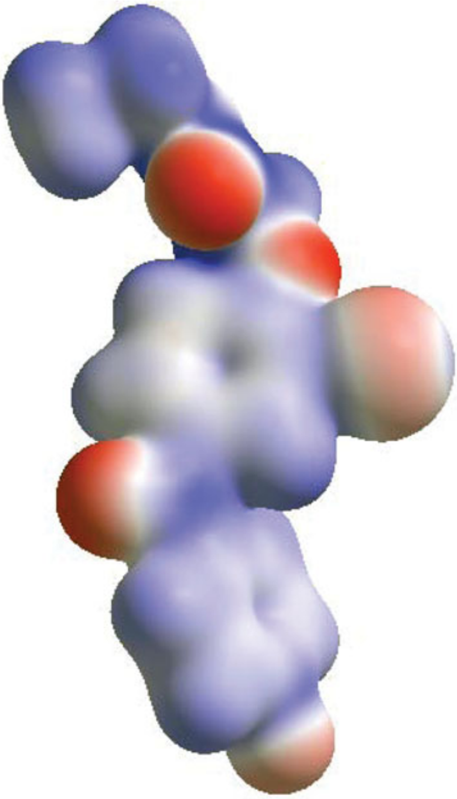


Figure 5. Electrostatic potential mapped on Hirshfeld surface.

Acknowledgments

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