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Structural studies of a novel bioactive benzophenone derivative: (4-Chloro-2-hydroxy-phenyl)-phenyl-methanone

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ABSTRACT

The title compound (4-Chloro-2-hydroxy-phenyl)-phenyl-methanone was synthesized and the product obtained was characterized by spectroscopic techniques, and finally the structure was confirmed by X-ray diffraction studies. The compound crystallizes in the orthorhombic crystal system with the space group *Pbca* with unit cell parameters, $a = 14.0359(5)$ Å, $b = 6.8084(3)$ Å, $c = 23.1097(8)$ Å, and $Z = 4$. The structure exhibits an intramolecular hydrogen bond which closes an *S(6)* ring. No directional interactions beyond the van der Waals packing contacts were identified in the crystal structure.

KEYWORDS

Benzophenones; crystal structure; hydrogen bond

1. Introduction

Benzophenones are a class of compounds obtained from natural sources [1] or by synthetic methods [2]. Benzophenone and substituted benzophenone derivatives have been found to possess diverse biological activities such as antimicrobial [3], anti-inflammatory [4], antioxidant [5], and anticancer [6] activities. These are of great importance fundamentally due to their diverse biological and chemical properties. Benzophenones exhibit significant antitumor activity both in vitro and in vivo [7]. In addition, synthetic benzophenones, such as 2-aminobenzophenone [8] and dihydroxy-4-methoxy benzophenone [9] have proven to be antimitotic and anticancer agents respectively. Recently, para-methoxy-substituted benzophenones were evaluated as p38a inhibitors with high efficacy and selectivity (IC50: 14 nM) [10]. Amino- and methoxy-substituted benzophenones have been reported to be potent cytotoxic agents against a panel of human cancer cell lines, including multi-drug resistant cell lines [11]. Analogs of benzophenone exhibit a selective toxicity for proliferating endothelial cells by induction of apoptosis [12], and polyprenylated benzophenone derivatives are also able to induce caspasemediated apoptosis [13]. In view of their broad spectrum of medicinal properties and as a part of our ongoing work on benzophenone derivatives [14], the title compound was synthesized. The compound obtained was characterized spectroscopically, and finally confirmed by X-ray diffraction studies.

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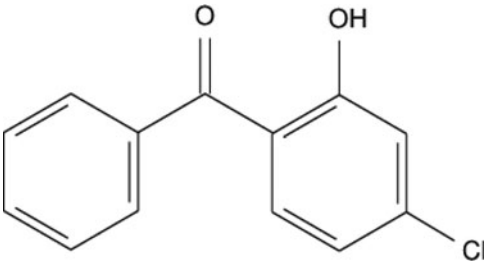

Figure 1. Schematic diagram of the title compound.

2. Experimental

2.1. *Preparation of (4-Chloro-2-hydroxy-phenyl)-phenyl-methanone*

The starting material benzoate was synthesized by benzoylation of *p*-chloro phenol with benzoyl chlorides (1:1) in the presence of 10% sodium hydroxide solution. The reaction mass was stirred for 2–3 hr at 0°C. After the completion of reaction, the oily product was extracted with ether layer and dried over anhydrous sodium sulphate, and the solvent was evaporated under pressure. (4-Chloro-2-hydroxy-phenyl)-phenyl-methanone were synthesized by the Fries rearrangement. Benzoate (0.001 mol) and aluminium chloride (0.002 mol) were blended and the mixture was heated to 150–170°C under without-solvent condition for about 2–3 hr. Then the reaction mixture was cooled to 0°C and quenched with 6 N hydrochloric acid in the presence of ice water. The reaction mixture was stirred for about 2–3 hr, filtered, and the solid obtained was recrystallized with methanol by the slow evaporation method to obtain green colored crystals. A schematic diagram of the molecule is shown in Fig. 1; yield: 80%; m.p.: 272–274°C.

Table 1. Crystal data and structure refinement table.

Parameter	Value
CCDC deposit No.	1025093
Empirical formula	$C_{18}H_{16}Cl_2F_2N_2O_3S$
Formula weight	426.52 Da
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	$a = 8.1657(16)$ Å $b = 11.3721(18)$ Å $c = 21.314(3)$ Å
Volume	1979.2(6) Å^3
Z, calculated density	4, 1.508 mg m^{-3}
Absorption coefficient	4.311 mm^{-1}
$F_{(000)}$	960
Crystal size	0.3 × 0.27 × 0.25 mm
Theta (θ) range for data collection	7.43° to 63.85°
Limiting indices	$-15 \leq h \leq 16$, $-7 \leq k \leq 5$, $-26 \leq l \leq 25$
Reflections collected/unique	11576/1739 [R(int) = 0.0418]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1739/0/146
Goodness-of-fit on F^2	1.077
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0326$, $wR2 = 0.0866$
R indices (all data)	$R1 = 0.0330$, $wR2 = 0.0870$
Largest diff. peak and hole	0.300 and −0.238 e. Å^{-3}

Table 2. Bond lengths (Å).

Atoms	Length	Atoms	Length
C1-C2	1.385(2)	C9-C14	1.408(2)
C1-C6	1.387(2)	C9-C10	1.415(2)
C2-C3	1.387(2)	C10-O16	1.348(2)
C3-C4	1.386(2)	C10-C11	1.395(2)
C4-C5	1.392(2)	C11-C12	1.373(2)
C5-C6	1.397(2)	C12-C13	1.394(2)
C5-C7	1.494(2)	C13-C14	1.372(2)
C7-O8	1.2404(19)	C13-Cl15	1.7446(16)
C7-C9	1.470(2)		

Infrared (IR) (KBr) νmax (cm^{-1}): 1635 (C=O), 3520–3640 cm^{-1} (OH)

^{1}H NMR (400 MHz) ($CDCl_3$): δ 6.7–7.8 (m, 8H, Ar–H), 9.1 (bs, 1H, OH).

Liquid chromatography–mass spectrometry (LC-MS) *m/z*: 232 (M^{+1}, 233), 266 (100), 154.5 (57), 111.5 (50).

Anal. Calcd. for $C_{13}H_9ClO_2$ C, 67.11; H, 3.90; Cl, 15.24%. Found: C, 67.05; H, 3.83; Cl, 15.20%

2.2. *Crystal Structure Determination*

A green color, rectangle-shaped single crystal of dimensions 0.3 × 0.27 × 0.25 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 [15]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using SHELXS and SHELXL programs [16]. 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 [17]. The molecular and packing diagrams were generated using the software MERCURY [18]. The details of the crystal structure and data refinement

Table 3. Bond angles (º).

Atoms	Angle (°)	Atoms	Angle (°)
C2-C1-C6	120.26(15)	C14-C9-C7	121.90(14)
C1-C2-C3	120.11(15)	C10-C9-C7	119.70(14)
C4-C3-C2	120.19(15)	O16-C10-C11	117.40(13)
C3-C4-C5	119.83(15)	O16-C10-C9	122.58(15)
C4-C5-C6	119.92(14)	C11-C10-C9	120.01(15)
C4-C5-C7	118.42(13)	C12-C11-C10	120.72(15)
C6-C5-C7	121.55(13)	C11-C12-C13	119.46(15)
C1-C6-C5	119.66(14)	C14-C13-C12	121.22(15)
O8-C7-C9	120.43(14)	C14-C13-Cl15	119.99(12)
O8-C7-C5	118.32(14)	C12-C13-Cl15	118.77(12)
C9-C7-C5	121.26(13)	C13-C14-C9	120.24(14)
C14-C9-C10	118.32(14)		

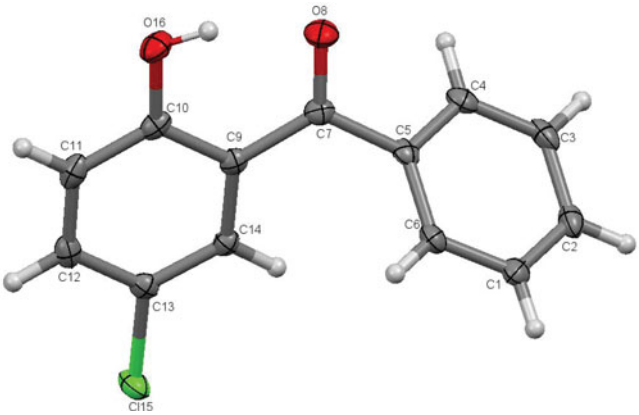

Figure 2. ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

are given in Table 1. The list of bond lengths and bond angles of non-hydrogen atoms are given in Tables 2 and 3 respectively. Figure 2 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

3. Results and discussion

The molecule is non-planar. The two phenyl rings are bridged via a carbonyl group. The bond lengths and bond angles are normal and the molecular conformation is characterized by a dihedral angle of 56.42(10)° between the mean planes of two aromatic rings, and is greater than the corresponding value of 51.98(11)° reported for (4-Chlorophenyl)(2-hydroxy-5-methylphenyl)-methanone [19]. The rotation of aromatic rings is characterized by the torsion angles relative to the carbonyl plane. Another indicator of conformation are the values of

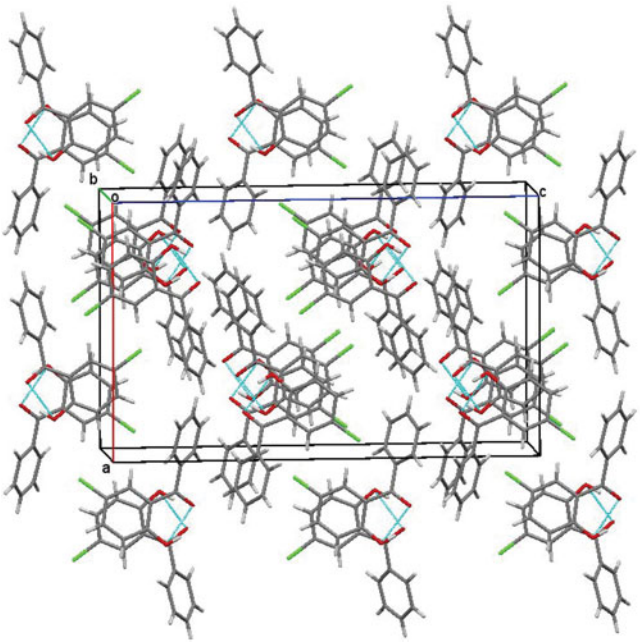

Figure 3. Packing diagram of the molecule when viewed down along the *b*-axis.

the torsion angles C4-C3-C9-O10 = 8.0(3)° and C16-C11-C9-C10 = 47.1(3)°. For benzophenones, these torsion angles take the same sign and are each reported to be 30° in energy-minimized benzophenone. The carbonyl O atom of the benzoyl group lies nearly on the hydroxychlorophenyl ring plane, as indicated by the torsion angle value of 8.0(3)° for C4-C3-C9-O10, and this value is comparable with the value reported earlier [19]. This small torsion angle is due to the intramolecular hydrogen bonding between the hydroxy group and the carbonyl moiety and is very small compared with the reported value of 30°. The molecular conformation is stabilized by a strong intramolecular O–H …O hydrogen bonding between the hydroxy group and the carbonyl moiety. The intra-molecular hydrogen bond O8–H8 …O10 has a length of 1.85 Å and an angle of 145°, which closes to form a *S(6)* ring. No directional interactions beyond the van der Waals packing contacts were identified in the crystal structure. The molecules exhibit layered stacking when viewed down along the *b*-axis (Fig. 3).

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