

Article

Crystal and Molecular Structure Studies of Ethyl 4-(4-Hydroxyphenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate and Ethyl 4-(3-Bromophenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate

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Abstract: The crystal and molecular structures of the title compounds, ethyl 4-(4-hydroxyphenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate (**I**) and ethyl 4-(3-bromophenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate (**II**), are reported and confirmed by single crystal X-ray diffraction data. Compound (**I**), C₂₆H₂₄O₅, crystallizes from a methanol solution in the monoclinic *C2/c* space group with eight molecules in the unit cell. The unit cell parameters are: $a = 25.4114(5) \text{ \AA}$, $b = 8.47440(10) \text{ \AA}$, $c = 20.6921(4) \text{ \AA}$, $\beta = 108.328(2)^\circ$ and $V = 4229.92(13) \text{ \AA}^3$. Disorder is observed throughout the entire molecule with an occupancy ratio 0.690(2):0.310(2). Compound (**II**), C₂₆H₂₃O₄Br, crystallizes from an ethyl acetate solution in the monoclinic *P2₁/c* spacegroup with four molecules in the unit cell. The unit cell parameters are $a = 17.8991(9) \text{ \AA}$, $b = 11.4369(6) \text{ \AA}$, $c = 10.8507(5) \text{ \AA}$, $\beta = 92.428(4)^\circ$ and $V = 2219.25(19) \text{ \AA}^3$. Disorder is observed in the cyclohexenone ring and the carboxylate group with an

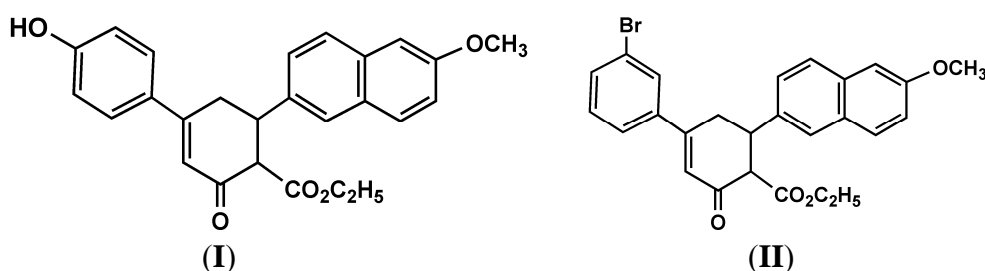
occupancy ratio 0.830(6):0.170(6). Weak O–H...O (**I**) or C–H...O (**II**) intermolecular interactions are observed which influence crystal packing stability. These chalcone derivative types of molecules are important in their ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts which exhibit a multitude of biological activities.

Keywords: cyclohexenecarboxylates; X-ray crystal structure; disorder; weak intermolecular interactions

1. Introduction

Chalcones and their corresponding heterocyclic analogs are valuable intermediates in organic synthesis [1]. This scaffold is found in various medicinally useful compounds and is known to exhibit a multitude of biological activities [2]. From a chemical point of view, an important feature of the chalcones scaffold is the ability to act as activated unsaturated systems in conjugate *i.e.*, 1,4-addition reactions of carbanions in the presence of bases [3]. This reactivity may be exploited for obtaining highly functionalized derivatives [4]. The more common application is found in preparation of 3,5-diaryl-6-carbethoxycyclohexanones, efficient synthons in building spiro compounds [5], or intermediates in the synthesis of benzisoxazoles, or carbazole derivatives [6,7], via 1,3-Michael addition of ethyl acetoacetate. Crystal structures of (8RS, 9SR)-ethyl 4-(3-bromothien-2-yl)-6-(2-furyl)-2-oxocyclohex-3-ene-1-carboxylate [8], ethyl 4-(3-bromo-2-thienyl)-2-oxo-6-phenylcyclohex-3-ene-1-carboxylate [9], (*R*, *S*)-methyl 3-methyl-5-oxo-1-phenylcyclohex-3-ene-1-carboxylate [10], rac-ethyl 3-(3-bromo-2-thienyl)-2-oxo-6-(4-propoxyphenyl)cyclohex-3-ene-1-carboxylate [11], (±)-ethyl 6-(6-methoxy-2-naphthyl)-4-(4-methylphenyl)-2-oxocyclohex-3-ene-1-carboxylate [12], ethyl 6-(6-methoxy-2-naphthyl)-2-oxo-4-(2-thienyl)cyclohex-3-ene-1-carboxylate [13], (1RS,6SR)-ethyl 4-(4-chlorophenyl)-6-(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate toluene hemisolvate [14], ethyl 4-(2,4-dichlorophenyl)-6-(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate [15], ethyl 4,6-bis(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate [16] and methyl 4,6-bis(4-fluorophenyl)-2-oxocyclohex-3-ene-1-carboxylate [17] have been reported. In view of the pharmacological importance of these derivatives, crystal and molecular structure studies of two new derivatives of cyclohex-3-ene-1-carboxylates, (**I**) and (**II**) (Figure 1), are reported, and expected to be useful for the docking studies.

Figure 1. The molecular structures of (**I**) C₂₆H₂₄O₅; and (**II**) C₂₆H₂₃O₄Br.



2. Results and Discussion

The molecule in **(I)** is totally disordered. The disordered cyclohexene ring (C7A/C8A/C9A/C10A/C11A/C12A and C7B/C8B/C9B/C10B/C11B/C12B: occupancy ratio 0.690(2)/0.310(2)) adopts a slightly distorted half-chair conformation with puckering parameters Q , θ and φ of 0.436(5) Å, 129.4(7)°, 48.6(9)° and 0.522(11) Å, 50.4(14)°, 227.5(18)°, respectively [18], in their molecular structures (Figure 2). For an ideal half-chair θ has a value of 50.4(7)° or 180° – θ . Weak O–H...O intermolecular interactions contribute to crystal packing stability (Table 1). The dihedral angle between the least squares planes of the benzene and naphthalene rings is 71.7(8)° (A).

Figure 2. Molecular structure of **(I)** showing the atom labeling scheme and 30% probability displacement ellipsoids. Only the 0.690(2) occupancy disordered atoms are shown. The dihedral angle between the least squares planes of the benzene and naphthalene rings is 71.7(8)°.

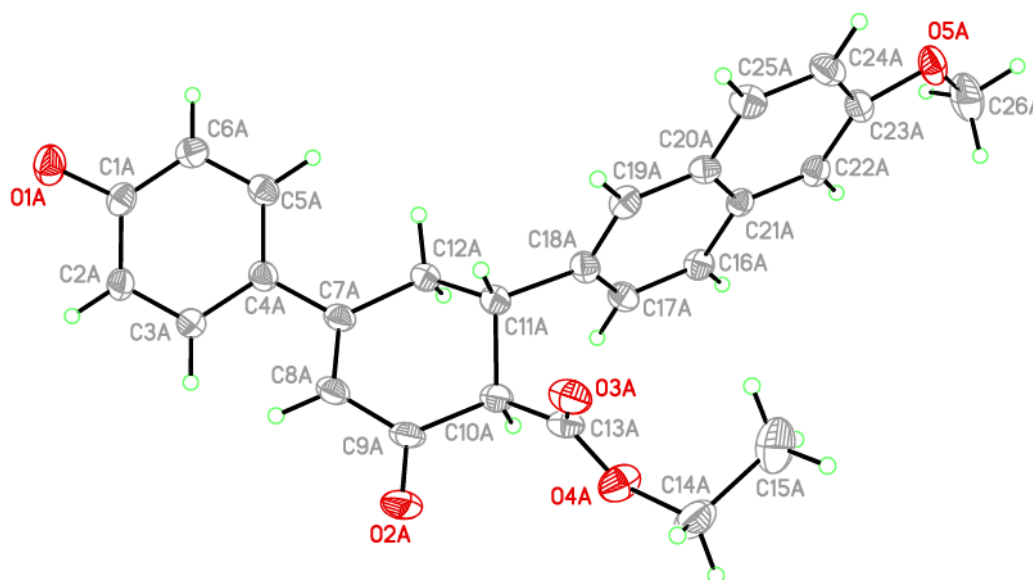


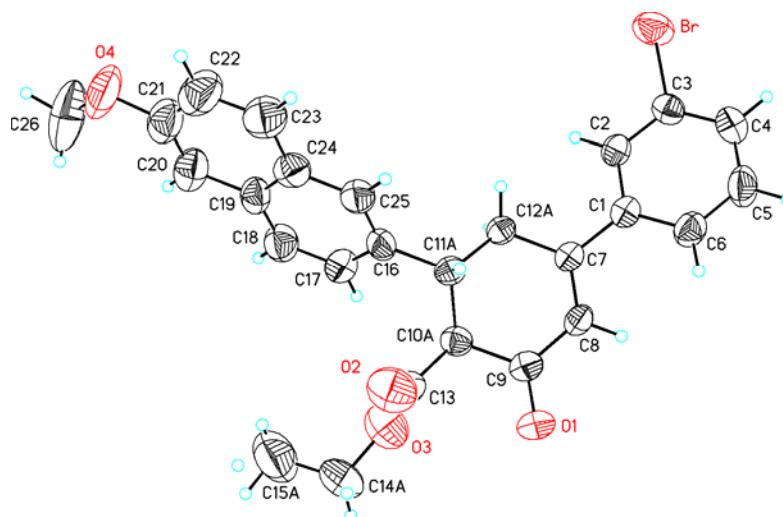
Table 1. Hydrogen bonds for **(I)** C₂₆H₂₅O₅, [Å and °].

D–H...A	d (D–H)	d (H...A)	d (D...A)	< (DHA)
O1A—H1A...O5A ^{#1}	0.84	2.44	3.219(7)	154(1)
1B—H1B...O5B ^{#2}	0.84	2.30	3.135(2)	177(1)
O2B—H2B1...O2B	0.84	2.55	3.36(3)	162(1)

Symmetry transformations used to generate equivalent atoms: ^{#1} $x + 1/2, -y + 1/2, z + 1/2$; ^{#2} $-x + 1, y, -z + 3/2$.

In **(II)**, the disordered cyclohexene ring (C7/C8/C9/C10A/C11A/C12A and C7/C8/C9/C10B/C11B/C12B: occupancy ratio 0.819(5)/0.181(5)) also adopts a slightly distorted half-chair conformation with puckering parameters Q , θ and φ of 0.463(4) Å, 47.5(4)°, 229.7(6)° and 0.646(15) Å, 125.7(9)°, 13.7(10)°, respectively [18], in their molecular structures (Figure 3). In addition, disorder is observed in the carboxylate group (C13/O2/O3/C14A/C15A and C13/O2/O3/C14B/C15B) with an occupancy ratio 0.819(5)/0.181(5). The dihedral angle between the least squares planes of the benzene and naphthalene rings is 65.0(2)°.

Figure 3. Molecular structure of (**II**) showing the atom labeling scheme and 30% probability displacement ellipsoids. Only the 0.830(6) occupancy disordered atoms are shown. The dihedral angle between the least squares planes of the benzene and naphthalene rings is 64.9(9)°.

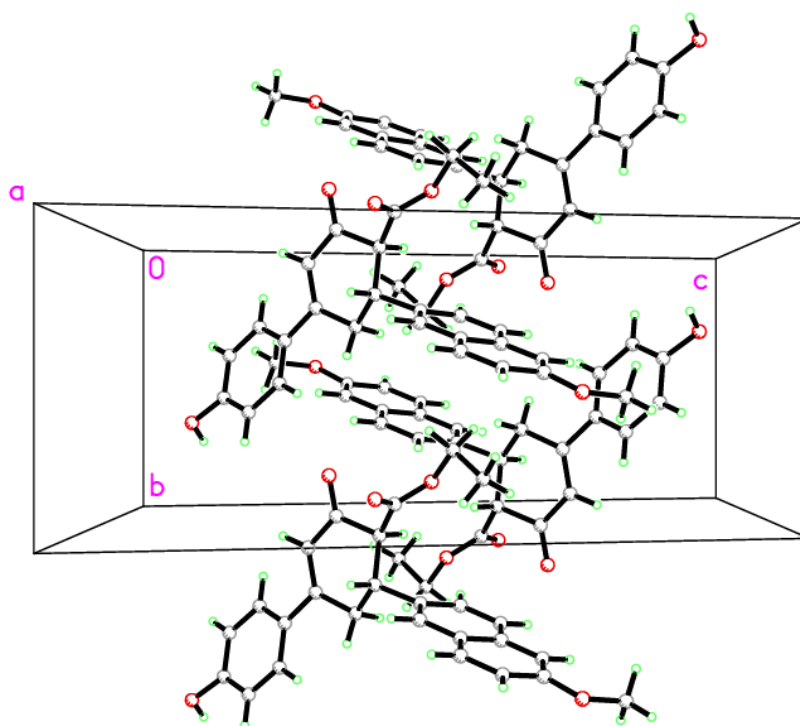


Bond lengths are in normal ranges for both (**I**) and (**II**) [19]. Selected bond lengths for both molecules (disordered A atoms in (**I**) and (**II**)) are listed in Table 2.

Table 2. Selected atom distances [\AA] for (**I**) and (**II**) (disordered A atoms).

Atoms (I)	Distance (I)	Atoms (II)	Distance (II)
C1A—O1A	1.365(4)	C3—Br	1.895(3)
C9A—O2A	1.211(5)	C9—O1	1.212(3)
C9A—C10A	1.492(5)	C9—C10A	1.524(4)
C10A—C11A	1.520(5)	C10A—C11A	1.523(4)
C10A—C13A	1.525(6)	C10A—C13	1.520(5)
C13A—O3A	1.182(8)	C13—O2	1.191(4)
C13A—O4A	1.308(7)	C13—O3	1.310(4)
C14A—O4A	1.430(6)	C14A—O3	1.444(5)
C14A—C15A	1.602(9)	C14A—C15A	1.440(7)
C23A—O5A	1.386(4)	C21—O4	1.384(4)
O5A—C26A	1.422(7)	O4—C26	1.432(6)

In (**I**) weak O—H...O intermolecular interactions (Table 1) are observed which contribute to crystal packing stability (Figure 4).

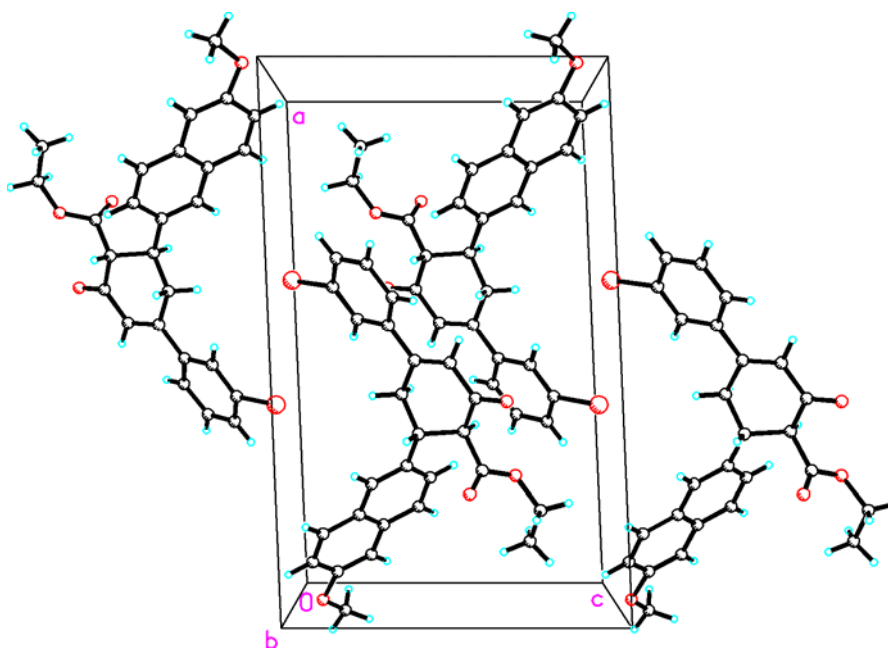
Figure 4. Packing diagram of **(I)** viewed along the *a* axis.

In **(II)** weak C—H...O intermolecular interactions are observed (Table 3) which influence crystal packing in the unit cell (Figure 5).

Table 3. Hydrogen bonds for **(II)** C₂₆H₂₃O₄Br, [Å and °].

D—H...A	d (D—H)	d (H...A)	d (D...A)	< (DHA)
C12B—H12D...O1 ^{#1}	0.97	2.33	3.110(4)	136(2)

Symmetry transformations used to generate equivalent atoms: ^{#1} $x, -y + 3/2, z - 1/2$.

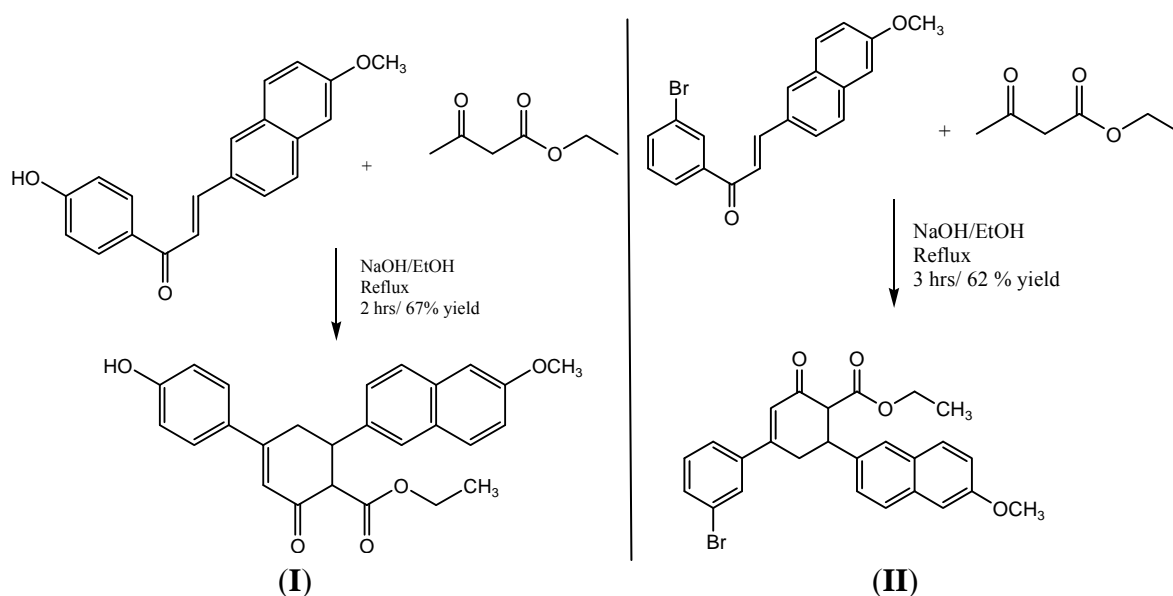
Figure 5. Packing diagram of **(II)** viewed along the *a* axis.

3. Experimental Section

3.1. General

The two cyclohexene carboxylates (**I**) and (**II**) were prepared by the method of Mayekar *et al.* [19], Scheme 1.

Scheme 1. The synthesis of (**I**) and (**II**).



3.2. Synthesis of Ethyl 4-(4-Hydroxyphenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate

(*E*)-1-(4-Hydroxyphenyl)-3-(6-methoxynaphthalen-2-yl)prop-2-en-1-one (1.52 g, 5 mmol) and ethyl acetoacetate (0.65 g, 5 mmol) were refluxed for 2 h in 10–15 mL ethanol in presence of 0.8 mL 10% NaOH. The reaction mixture was cooled to room temperature and the reaction mass was filtered. The compound was recrystallized from methanol (Yield = 67%; m.p.: 461–463 K; Scheme 1). X-ray quality crystals of (**I**) were obtained from slow evaporation of methanol solution. Composition for $C_{26}H_{24}O_5$: Found (Calculated): C: 74.88 (74.98%); H: 5.77 (5.81%).

3.3. Synthesis of Ethyl 4-(3-Bromophenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate

(*E*)-1-(3-Bromophenyl)-3-(6-methoxynaphthalen-2-yl)prop-2-en-1-one (1.84 g, 5 mmol) and ethyl acetoacetate (0.65 g, 5 mmol) were refluxed for 3 h in 10–15 mL ethanol in presence of 0.8 mL 10% NaOH. The reaction mixture was cooled to room temperature and the reaction mass was filtered. Recrystallization of the compound was done using methanol (Yield: 62%; m.p.: 419–421 K; Scheme 1). X-ray quality crystals of (**II**) were grown from slow evaporation of ethyl acetate solution. Composition for $C_{26}H_{23}O_4Br$: Found (Calculated): C: 65.08 (65.14%); H: 4.79 (4.84%).

3.4. Data Collection and Refinement

Crystallographic data for both **(I)** and **(II)** were collected on an Oxford Diffraction CCD-Diffractometer with monochromatic Cu-K α ($\lambda = 1.54178 \text{ \AA}$) **(I)** or Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) **(II)** and a Gemini R detector [20]. The structures were solved by direct methods [21], full-matrix least-squares refinement [21] on F^2 and 306 **(I)** or 299 **(II)** parameters. In **(I)**, the molecule was totally disordered with an occupancy ratio 0.690(2)/0.310(2). All of the H atoms were placed in their calculated positions and then refined using the riding model with C—H lengths of 0.95 \AA (CH), 0.99 \AA (CH₂) or 0.98 \AA (CH₃). The isotropic displacement parameters for these atoms were set to 1.18 to 1.21 (CH, CH₂), or 1.49 to 1.50 (OH, CH₃), times U_{eq} of the parent atom. In **(II)** the cyclohexenone ring (C10A/C10B, C11A/C11B, C12A/C12B) and the carboxylate group (C14A/C14B, C15A/C15B) were disordered with a occupancy ratio 0.819(5)/0.181(5). All of the H atoms were placed in their calculated positions and then refined using the riding model with C—H lengths of 0.93 or 0.98 \AA (CH), 0.97 \AA (CH₂) or 0.96 \AA (CH₃). The isotropic displacement parameters for these atoms were set to 1.19 to 1.20 (CH, CH₂), or 1.5 (CH₃), times U_{eq} of the parent atom.

Crystal data for **(I)**: colorless chunk, $0.44 \times 0.31 \times 0.27 \text{ mm}$, C₂₆H₂₄O₅, $M_r = 416.45$, monoclinic $C2/c$, $a = 25.4114(5) \text{ \AA}$, $b = 8.47440(10) \text{ \AA}$, $c = 20.6921(4) \text{ \AA}$, $\beta = 108.328(2)^\circ$ and $V = 4229.92(13) \text{ \AA}^3$, $Z = 8$, $F(000) = 1760$, $T = 123(2) \text{ K}$, $\rho_{\text{calc}} = 1.308 \text{ g}\cdot\text{cm}^{-3}$, $\mu = 0.733 \text{ mm}^{-1}$, 13998 reflections measured ($-29 \leq h \leq 31$, $-10 \leq k \leq 10$, $-25 \leq l \leq 14$; $3.66 \leq \theta \leq 75.71^\circ$), $R_{\text{int}} = 0.0243$, 4326 merged reflections, $I > 2\sigma(I)$, 306 parameters, 82 restraints, $\text{GOF} = 1.096$, $R(F) = 0.0938$, $wR(F^2) = 0.2328$, $w = 1/\sigma^2(F_o^2) + 0.0541P^2$], where $P = (F_o^2 + 2F_c^2)/3$, min./max. $\Delta\rho = -0.651, +0.566 e \text{ \AA}^3$. Cambridge Database deposition number: CSD-888539.

Crystal data for **(II)**: colorless chunk, $0.51 \times 0.38 \times 0.15 \text{ mm}$, C₂₆H₂₃O₄Br, $M_r = 479.35$, monoclinic $P2_1/c$, $a = 17.8991(9) \text{ \AA}$, $b = 11.4369(6) \text{ \AA}$, $c = 10.8507(5) \text{ \AA}$, $\beta = 92.428(4)^\circ$ and $V = 2219.25(19) \text{ \AA}^3$, $Z = 4$, $F(000) = 984$, $T = 295 \text{ K}$, $\rho_{\text{calc}} = 1.435 \text{ g}\cdot\text{cm}^{-3}$, $\mu = 1.882 \text{ mm}^{-1}$, 21008 reflections measured ($-26 \leq h \leq 26$, $-16 \leq k \leq 17$, $-15 \leq l \leq 16$; $5.18 \leq \theta \leq 32.47^\circ$), $R_{\text{int}} = 0.0638$, 7380 merged reflections, $I > 2\sigma(I)$, 299 parameters, 10 restraints, $\text{GOF} = 0.973$, $R(F) = 0.0533$, $wR(F^2) = 0.1082$, $w = 1/\sigma^2(F_o^2) + 0.0541P^2$], where $P = (F_o^2 + 2F_c^2)/3$, min./max. $\Delta\rho = -0.597, +0.398 e \text{ \AA}^3$. Cambridge Database deposition number: CSD-888540.

4. Conclusions

The crystal and molecular structures ethyl 4-(4-hydroxyphenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate **(I)** and ethyl 4-(3-bromophenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate **(II)** are reported. This data represents the structural confirmation of two new derivatives of chalcone molecules which exhibit a multitude of biological activities.

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