# Synthesis of Some Novel Cytotoxic Di- and tri-substitutedbenzyl Gamma-ketohexanoates

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**Summary:** Present study describes diethyl cadmium mediated preparation of sixteen (**3a-3p**) new di- and tri-substitutedbenzyl gamma-ketohexanoates from corresponding sixteen (**2a-2p**) di- and tri-substitutedbenzyl 4-chloro-4-ketobutanoates. Their formation was proved through structural characterization by modern spectroscopic techniques. The prepared gamma keto esters were subjected to brine shrimp lethality test for cytotoxic activity and all of the gamma keto esters displayed cytotoxic activity. Trichlorobenzyl 4-ketohexanoate (**3n**) and tribromobenzyl 4-ketohexanoate (**3o**) displayed highest cytotoxic activity.

Keywords: Benzyl gamma-ketohexanoate, Cytotoxic activity, Thionyl chloride, Diethyl cadmium, Brine shrimp

## Introduction

Gamma keto esters are esters of 4-ketoacids with various alcohols. Gamma keto esters reported in the literature differ structurally in size and complexity of acid as well as alcohol parts [1, 2]. Hooz and Layton et al., have reported the preparation of gamma-ketohexanoates from propargylic esters, *beta*-keto esters are other useful precursors of gamma-ketohexanoates [3, 4]. Ronsheim and Zercher, and Lin applied chain extension strategies for their preparation [5, 6]. Prakash et al., prepared gmma-ketohexanoates by umpolung technique [1]. Cason reported the synthesis of long chain gamma-ketohexanotes [7, 8].

Esters of gamma-ketohexanoic acids with different alcohols have enjoyed much application in synthesis [4, 9-11]. Moreover, their use as medicinal, cytotoxic, antimicrobial and anticancer is well documented [12, 13]. Some of the precursors of these gamma keto esters have been investigated for their antibacterial and antifungal activities [14-16]. The properties of the gamma keto esters prompted us to carry out work on their synthesis [8, 17]. In the present study sixteen (**3a-3p**) new gamma keto esters have been synthesized from corresponding acid chlorides (**2a-2p**) via Cason's approach [7] Table-1. Brine shrimp cytotoxic activity of the sixteen (**3a-3p**) gamma keto esters has also been explored.

## Experimental

*General*

All the required chemicals were purchased from Sigma-Aldrich (St. Louis, New York, USA). The UV spectra of **2a-2p** were recorded in $CHCl_3$ while of compounds **3a-3p** in absolute EtOH employing IRMECO UV/VIS Model U-2020 spectrophotometer. IR spectra were obtained on a TENSOR 27 FT-IR spectrophotometer supplied by Bruker, Ettiligen, Germany. $^1$H- and $^{13}$C-NMR spectra were procured in $CDCl_3$ at ($^1$H) 300 MHz, ($^{13}$C) 75 MHz using Bruker Biospin, AMX 300 MHz FT NMR spectrometer. Elemental analyses were performed by Midwest Microlab (USA). Column chromatography was carried out using silica gel ($PF_{254}$, mesh size 60-70), E. Merck, Darmstadt Germany; thin layer chromatography was performed on pre-coated silica gel plate (20 × 20 cm, 0.2 mm thickness) with UV fluorescence indicator ($PF_{254}$), E. Merck, Darmstadt, Germany.

*Preparation of diethyl cadmium reagent* [18, 19]

The diethyl cadmium reagent was prepared by adding dry $CdCl_2$ (11.8 mmol) to the Grignard reagent [prepared from ethyl bromide (11.8 mmol) and magnesium metal (11.8 mmol) cooled to 0 °C in dry diethyl ether (60 mL)] over a period of 10 min with vigorous stirring. Stirring was continued for a further hour and the diethyl cadmium reagent thus obtained was used as such without further purification.

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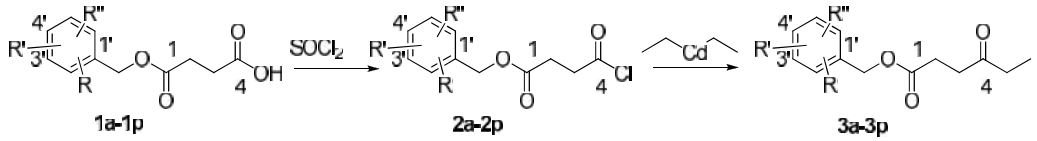


Table-1: Structure of Synthesized Compounds **1a**-**3p.**

| Compd # | R | R' | R'' | Compd # | R | R' | R'' | Compd # | R | R' | R'' |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | **H** | **3'-Me** | **4'-Me** | **2a** | **H** | **3'-Me** | **4'-Me** | **3a** | **H** | **3'-Me** | **4'-Me** |
| **1b** | **H** | **3'-Me** | **5'-Me** | **2b** | **H** | **3'-Me** | **5'-Me** | **3b** | **H** | **3'-Me** | **5'-Me** |
| **1c** | **H** | **3'-$NO_2$** | **4'-$NO_2$** | **2c** | **H** | **3'-$NO_2$** | **4'-$NO_2$** | **3c** | **H** | **3'-$NO_2$** | **4'-$NO_2$** |
| **1d** | **H** | **3'-$NO_2$** | **5'-$NO_2$** | **2d** | **H** | **3'-$NO_2$** | **5'-$NO_2$** | **3d** | **H** | **3'-$NO_2$** | **5'-$NO_2$** |
| **1e** | **H** | **2'-OEt** | **6'-OEt** | **2e** | **H** | **2'-OEt** | **6'-OEt** | **3e** | **H** | **2'-OEt** | **6'-OEt** |
| **1f** | **H** | **3'-OEt** | **4'-OEt** | **2f** | **H** | **3'-OEt** | **4'-OEt** | **3f** | **H** | **3'-OEt** | **4'-OEt** |
| **1g** | **H** | **3'-OH** | **5'-OH** | **2g** | **H** | **3'-OH** | **5'-OH** | **3g** | **H** | **3'-OH** | **5'-OH** |
| **1h** | **2'-OMe** | **3'-OMe** | **4'-OMe** | **2h** | **2'-OMe** | **3'-OMe** | **4'-OMe** | **3h** | **2'-OMe** | **3'-OMe** | **4'-OMe** |
| **1i** | **2'-OMe** | **4'-OMe** | **5'-OMe** | **2i** | **2'-OMe** | **4'-OMe** | **5'-OMe** | **3i** | **2'-OMe** | **4'-OMe** | **5'-OMe** |
| **1j** | **3'-Me** | **4'-Me** | **5'-Me** | **2j** | **3'-Me** | **4'-Me** | **5'-Me** | **3j** | **3'-Me** | **4'-Me** | **5'-Me** |
| **1k** | **H** | **3'-OMe** | **4'-$NO_2$** | **2k** | **H** | **3'-OMe** | **4'-$NO_2$** | **3k** | **H** | **3'-OMe** | **4'-$NO_2$** |
| **1l** | **H** | **4'-OMe** | **3'-$NO_2$** | **2l** | **H** | **4'-OMe** | **3'-$NO_2$** | **3l** | **H** | **4'-OMe** | **3'-$NO_2$** |
| **1m** | **H** | **2'-OMe** | **5'-$NO_2$** | **2m** | **H** | **2'-OMe** | **5'-$NO_2$** | **3m** | **H** | **2'-OMe** | **5'-$NO_2$** |
| **1n** | **2'-Cl** | **4'-Cl** | **6'-Cl** | **2n** | **2'-Cl** | **4'-Cl** | **6'-Cl** | **3n** | **2'-Cl** | **4'-Cl** | **6'-Cl** |
| **1o** | **2-Br** | **4'-Br** | **5'-Br** | **2o** | **2-Br** | **4'-Br** | **5'-Br** | **3o** | **2-Br** | **4'-Br** | **5'-Br** |
| **1p** | **2'-Me** | **4'-Me** | **6'-Me** | **2p** | **2'-Me** | **4'-Me** | **6'-Me** | **3p** | **2'-Me** | **4'-Me** | **6'-Me** |

*General procedure for preparation of acid chlorides* (**2a-2p**) *and gamma keto esters* (**3a-3p**) [18, 19]

Acid chlorides (**2a-2p**) required in the preparation of gamma keto esters (**3a-3p**) were prepared by the reaction of di-/tri-substitutedbenzyl hydrogen succinates (8 mmol)) and thionyl chloride (22.5 mmol). The acid halides (**2a-2p**) were purified over silica gel short column employing ethyl acetate: hexane (9:1→2:8). The di-/tri-substitutedbenzyl 4-chloro-4-ketobutanoates (acid chlorides, 5 mmol) on treatment with diethyl cadmium in ether solvent (50 mL) over a period of 6-8 hours gave desired gamma keto esters (**3a-3p**). All of the compounds (**3a-3p**) were purified over silica gel short column using ethyl acetate: hexane (9:1→3:7).

*3′,4′-Dimethylbenzyl 4-chloro-4-ketobutanoate* (**2a**)

Yield 70%, 1.89 g (5.6 mmol); Viscous oil; Anal. Calcd. for $C_{13}H_{15}ClO_3$ (254.71**)**: C, 61.30; H, 5.94; Cl, 13.92; Found: C, 61.29; H, 5.93; Cl, 13.93%; FT-IR (Neat, $cm^{-1}$): 3088, 1775, 1721, 1601, 1478, 1259, 1125, 1010; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.37 (6H, s, 2×Me), 2.91 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.86-7.16 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.0, 171.2, 136.7, 134.5, 132.3, 132.3, 123.1, 66.9, 38.4, 28.3, 20.5, 19.4; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 268.3 (3.8).

*3′,5′-Dimethylbenzyl 4-chloro-4-ketobutanoate* (**2b**)

Yield: 72%, 1.46 g (5.76 mmol); Viscous oil; Anal. Calcd. for $C_{13}H_{15}ClO_3$ (254.71**)**: C, 61.30; H, 5.94; Cl, 13.92; Found: C, 61.32; H, 5.93; Cl, 13.92%; FT-IR (Neat, $cm^{-1}$): 3098, 1774, 1724, 1632, 1494, 1256, 1123, 1018; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.38 (6H, s, 2×Me) 2.90 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.65 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.21 (2H, s, -O-C$\underline{H}_2$), 7.12-7.34 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.0, 171.2, 135.9, 134.7, 131.6, 129.4, 127.9, 123.1, 66.9, 38.7, 28.4, 20.5, 19.6; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 264.4 (3.8).

*3′,4′-Dinitrobenzyl 4-chloro-4-ketobutanoate* **(2c)**

Yield 63%, 1.59 g (5.04 mmol); Pale yellow viscous oil; Anal. Calcd. for $C_{11}H_9ClN_2O_7$ (316.65**)**: C, 41.72; H, 2.86; Cl, 11.20; N, 8.85; Found: C, 41.71; H, 2.87; Cl, 11.21; N, 8.84%; FT-IR (Neat, $cm^{-1}$): 3114, 1779, 1732, 1517, 1450, 1364, 1242, 1120, 1020; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.93 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.23 (2H, s, -O-C$\underline{H}_2$), 7.97-8.58 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 176.2, 171.4, 149.0, 147.8, 142.3, 133.4, 124.1, 123.4, 66.8, 39.3, 29.8; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 272.3 (3.5).

*3′,5′-Dinitrobenzyl 4-chloro-4-ketobutanoate* **(2d)**

Yield 65%, 1.64 g (5.2 mmol); Pale yellow viscous oil; Anal. Calcd. for $C_{11}H_9ClN_2O_7$ (316.65**)**: C, 41.72; H, 2.86; Cl, 11.20; N, 8.85; Found: C, 41.73; H, 2.87; Cl, 11.19; N, 8.87%; FT-IR (Neat, $cm^{-1}$): 3104, 1776, 1730, 1605, 1582, 1413, 1373, 1248, 1122, 1025; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.93 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.23 (2H, s, -O-C$\underline{H}_2$), 7.97-8.58 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 176.3, 171.5, 148.9, 148.9,

142.2, 128.7, 128.7, 116.7, 64.7, 39.4, 29.6; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 271.8 (3.7).

*2′,6′-Diethoxybenzyl 4-chloro-4-ketobutanoate* **(2e)**

Yield 67%, 1.68 g (5.36 mmol); Viscous oil; Anal. Calcd. for $C_{15}H_{19}ClO_5$ (314.76**)**: C, 57.24; H, 6.08; Cl, 11.26; Found: C, 57.25; H, 6.03; Cl, 11.25%; FT-IR (Neat, $cm^{-1}$): 3105, 1778, 1733, 1612, 1491, 1253, 1125, 1020; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.88 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.06 (2H, s, -O-C$\underline{H}_2$), 6.42-7.24 (3H, m, Aromaic); 1.26 (6H, t, *J* = 7.6 Hz, 2× C$\underline{H}_3$-$CH_2$-), 4.25 (4H, q, 7.6 Hz, 2× $CH_3$-C$\underline{H}_2$-); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.8, 171.7, 153.2, 153.2, 127.6, 117.8, 103.4, 103.4, 65.4, 55.8, 38.6, 28.5, 15.9; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 272.5 (4.07).

*3′,4′-Diethoxybenzyl 4-chloro-4-ketobutanoate* **(2f)**

Yield 69%, 1.74 g (5.52 mmol); Viscous oil; Anal. Calcd. for $C_{15}H_{19}ClO_5$ (314.76**)**: C, 57.24; H, 6.08; Cl, 11.26; Found: C, 57.23; H, 6.06; Cl, 11.27%; FT-IR (Neat, $cm^{-1}$): 3077, 1777, 1732, 1606, 1475, 1249, 1124, 1022; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.89 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.19 (2H, s, -O-C$\underline{H}_2$), 6.62-7.09 (3H, m, Aromaic); 1.25 (6H, t, *J* = 7.6 Hz, 2×C$\underline{H}_3$-$CH_2$-), 4.28 (4H, t, *J* = 7.6 Hz, 2×$CH_3$-C$\underline{H}_2$-);$^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.9, 171.6, 146.7, 145.8, 122.3, 119.4, 112.4, 111.8, 66.8, 65.5, 38.3, 29.4, 15.8; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 272.2 (4.4).

*3′,5′-Dihydroxybenzyl 4-chloro-4-ketobutanoate* **(2g)**

Yield 74%, 1.55 g (6.0 mmol); Viscous oil; Anal. Calcd. for $C_{11}H_{11}ClO_5$ (258.66**)**: C, 51.08; H, 4.29; Cl, 13.71; Found: C, 51.08; H, 4.29; Cl, 13.71%; FT-IR (Neat, $cm^{-1}$): 3250, 3066, 1779, 1731, 1515; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.88 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.27-6.75 (3H, m, Aromaic); 11.5 (2H, br, s, 2×O$\underline{H}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.2, 170.7, 157.4, 157.4, 137.8, 106.8, 106.8, 104.6, 67.1, 38.4, 29.3; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 273.6 (3.9).

*2′,3′,4′-Trimethoxybenzyl 4-chloro-4-ketobutanoate* **(2h)**

Yield 72%, 1.85 g (5.84 mmol); Viscous oil; Anal. Calcd. for $C_{14}H_{17}ClO_6$ (316.73): C, 53.09; H, 5.41; Cl, 11.19; Found: C, 53.10; H, 5.40; Cl, 11.20%; FT-IR (Neat, $cm^{-1}$): 3097, 1774, 1731, 1618, 1499, 1267, 1131, 1012; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.87 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.67 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 6.39-6.84 (2H, m, Aromaic); 3.98, (9H, s, 3×O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.5, 171.3, 153.6, 147.5, 140.4, 119.8, 119.8, 105.7, 62.5, 61.5, 39.2, 29.5; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 275.3 (3.98).

*2′,4′,5′-Trimethoxbenzyl 4-chloro-4-ketobutanoate* **(2i)**

Yield 74%, 1.90 g (6.0 mmol); Viscous oil; Anal. Calcd. for $C_{14}H_{17}ClO_6$ (316.73): C, 53.09; H, 5.41; Cl, 11.19; Found: C, 53.11; H, 5.42; Cl, 11.18%; FT-IR (Neat, $cm^{-1}$): 3087, 1778, 1731, 1604, 1493, 1266, 1154, 1020; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.88 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 6.44-6.95 (2H, m, Aromaic); 3.94 (9H, s, 3×O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.4, 172.9, 149.8, 148.5, 141.3, 119.6, 112.6, 96.9, 63.1, 57.2, 38.8, 29.7; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 273.9 (4.16).

*3′,4′,5′-Trimethoxybenzyl 4-chloro-4-ketobutanoate* **(2j)**

Yield 75%, 1.92 g (6.08 mmol); Viscous oil; Anal. Calcd. for $C_{14}H_{17}ClO_6$ (316.73): C, 53.09; H, 5.41; Cl, 11.19; Found: C, 53.08; H, 5.39; Cl, 11.21%; FT-IR (Neat, $cm^{-1}$): 3076, 1777, 1731, 1504, 1488, 1257, 1155, 1023; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.87 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.71 (2H, t, 6.8 Hz, 5.22 C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.66 (2H, m, Aromaic); 3.95 (9H, s, 3×O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.1, 171.2, 154.6, 154.6, 137.9, 129.2, 108.4, 108.4, 67.5, 61.2, 57.3, 38.9, 29.1; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 276.8 (4.22).

*3′-Methoxy-4′-nitrobenzyl 4-chloro-4-ketobutanoate* **(2k)**

Yield 66%, 1.61 g (5.36 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{12}H_{12}ClNO_6$ (301.68): C, 47.78; H, 4.01; Cl, 11.75; N, 4.64; Found: C, 47.77; H, 4.03; Cl, 11.74; N, 4.65%; FT-IR (Neat, $cm^{-1}$): 3083, 1778, 1730, 1621, 1575, 1392, 1374, 1134, 1250, 1022; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.91 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.71 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.21 (2H, s, -O-C$\underline{H}_2$), 7.22-8.15 (3H, m, Aromaic); 3.91(3H, s, O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.7, 171.4, 153.2, 143.4, 136.5, 124.7, 118.9, 113.8, 65.9**,** 55.3, 38.5, 29.6; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 268.7 (3.86).

*4'-Methoxy-3'-nitrobenzyl 4-chloro-4-ketobutanoate* **(2l)**

Yield 64%, 1.54 g (5.12 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{12}H_{12}ClNO_6$ (301.68): C, 47.78; H, 4.01; Cl, 11.75; N, 4.64; Found: C, 47.76; H, 3.99; Cl, 11.79; N, 4.63%; FT-IR (Neat, $cm^{-1}$): 3077, 1783, 1726, 1618, 1584, 1386, 1372, 1251, 1132, 1016; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.89 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.19 (2H, s, -O-C$\underline{H}_2$), 7.24-8.23 (3H, m, Aromaic); 3.97 (3H, s, O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.7, 171.3, 149.5, 139.6, 133.7, 133.2, 123.8, 112.4, 65.7, 55.4, 37.6, 28.9; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 269.8 (3.84).

*2'-Methoxy-5'-nitrobenzyl 4-chloro-4-ketobutanoate* **(2m)**

Yield 68%, 1.64 g (5.44 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{12}H_{12}ClNO_6$ (301.68): C, 47.78; H, 4.01; Cl, 11.75; N, 4.64; Found: C, 47.79; H, 3.98; Cl, 11.76; N, 4.65%; FT-IR (Neat, $cm^{-1}$): 3069, 1785, 1724, 1512, 1482, 1370, 1245, 1123, 1010; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.91 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 7.25-8.18 (3H, m, Aromaic); 3.97 (3H, s, O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.6, 172.8, 157.5, 140.7, 127.4, 125.8, 123.6, 112.7, 61.8, 57.4, 37.6, 28.4; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 268.7 (3.96).

*2',4',6'-Trichlorobenzyl 4-chloro-4-ketobutanoate* **(2n)**

Yield 63%, 1.66 g (5.04 mmol); Viscous oil; Anal. Calcd. for $C_{11}H_8Cl_4O_3$ (329.99): C, 40.04; H, 2.44; Cl, 42.97; Found: C, 40.08; H, 2.43; Cl, 42.96%; FT-IR (Neat, $cm^{-1}$): 3086, 1779, 1729, 1616, 1395, 1250, 1126, 1015, 733; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.92 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.67 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.03 (2H, s, -O-C$\underline{H}_2$), 7.77- 7.81(2H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 174.3, 171.6, 138.4, 134.9, 127.9, 127.5, 57.8, 39.2, 29.4; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 267.8 (3.95).

*2',4',5'-Tribromobenzyl 4-chloro-4-ketobutanoate* **(2o)**

Yield 64%, 2.37 g (5.12 mmol); Viscous oil; Anal. Calcd. for $C_{11}H_8Br_3ClO_3$ (463.34): C, 28.51; H, 1.74; Br, 51.74; Cl, 7.65; Found: C, 28.52; H, 1.73; Br, 51.76; Cl, 7.63%; FT-IR (Neat, $cm^{-1}$): 3090, 1781, 1728, 1516, 1493, 1256, 1132, 1018, 529; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.91 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.05 (2H, s, -O-C$\underline{H}_2$), 7.33-7.98 (2H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.8, 171.9, 136.7, 136.2, 135.4, 125.8, 124.6, 122.5, 63.7, 38.7, 28.5; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 268.6 (4.21).

*2',4',6'-Trimethylbenzyl 4-chloro-4-ketobutanoate* **(2p)**

Yield 71%, 1.52 g (5.68 mmol); Viscous oil; Anal. Calcd. for $C_{14}H_{17}ClO_3$ (268.74): C, 62.57; H, 6.38; Cl, 13.19; Found: C, 62.58; H, 6.37; Cl, 13.20%; FT-IR (Neat, $cm^{-1}$): 3084, 1778, 1726, 1614, 1397, 1258, 1135, 1010; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 2.93 (2H, t, *J* = 6.8 Hz, Cl-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.12 (2H, s, -O-C$\underline{H}_2$), 6.92 (3H, m, Aromaic), 2.47 (9H, s, 3×O$\underline{Me}$; $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 175.2, 171.4, 135.8, 132.5, 132.3, 132.6, 127.6, 127.4, 63.5, 37.9, 28.6, 22.6, 20.3; UV-VIS ($CHCl_3$) ($\lambda_{max/}$nm (log ε): 267.6 (3.43).

*3',4'-Dimethylbenzyl γ-ketohexanoate* **(3a)**

Yield 77%, 0.95 g (3.85 mmol); Viscous oil; Anal. Calcd. for $C_{15}H_{20}O_3$ (248.32**)**: C, 72.55; H, 8.12; Found: C, 72.56; H, 8.13%; FT-IR (Neat, $cm^{-1}$): 3089, 1772, 1724, 1608, 1476, 1255, 1124, 1016; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.91 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.86-7.16 (3H, m, Aromaic), 2.37 (6H, s, 2×$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.9, 172.2, 138.0, 136.2, 134.7, 131.2, 129.4, 124.5, 66.9, 36.9, 33.3, 30.2, 20.4, 19.3, 7.8; UV-VIS (EtOH) ($\lambda_{max/}$nm (log ε): 267.8 (3.84).

*3',5'-Dimethylbenzyl γ-ketohexanoate* **(3b)**

Yield 78%, 0.97 g (3.90 mmol); Viscous oil; Anal, Calcd. for $C_{15}H_{20}O_3$ (248.32**)**: C, 72.55; H, 8.12; Found: C, 72.57; H, 8.10%; FT-IR (Neat, $cm^{-1}$): 3087, 1773, 1726, 1621, 1492, 1251, 1124, 1017; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.05 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.44 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.90 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.65 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.21 (2H, s, -O-C$\underline{H}_2$), 7.12-7.34 (3H, m, Aromaic), 2.38 (2H, s, 2×Me); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.2, 171.9, 139.5, 136.7, 128.9, 127.2, 67.3, 37.1, 32.9, 29.8, 22.6, 7.7; UV-VIS (EtOH) ($\lambda_{max/}$nm (log ε): 267.2 (3.76).

*3′,4′-Dinitrobenzyl γ-ketohexanoate* **(3c)**

Yield 68%, 1.05 g (3.40 mmol); Pale yellow viscous oil; Anal. Calcd for $C_{13}H_{14}N_2O_7$ (310.26**)**: C, 50.33; H, 4.55; N, 9.03; Found: C, 50.34; H, 4.56; N, 9.05%; FT-IR (Neat, $cm^{-1}$): 3117, 1778, 1734, 1518, 1456, 1368, 1245, 1123, 1024; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.05 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.45 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.93 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.23 (2H, s, -O-C$\underline{H}_2$), 7.97-8.58 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.3, 172.2, 151.6, 149.5, 145.3, 134.9, 125.8, 123.7, 65.8, 36.7, 32.5, 29.1, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 271.2 (3.56).

*3′,5′-Dinitrobenzyl γ-ketohexanoate* **(3d)**

Yield 69%, 1.07 g (3.45 mmol); Pale yellow viscous oil; Anal. Calcd. for $C_{13}H_{14}N_2O_7$ (310.26**)**: C, 50.33; H, 4.55; N, 9.03; Found: C, 50.32; H, 4.56; N, 9.08%; FT-IR (Neat, $cm^{-1}$): 3107, 1771, 1729, 1612, 1581, 1412, 1372, 1249, 1124, 1022; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.44 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.92 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.67 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.23 (2H, s, -O-C$\underline{H}_2$), 8.55-8.72 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.8, 171.8, 148.5, 144.2, 130.2, 130.2, 116.4, 64.8, 36.5, 32.2, 29.7, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 275.1 (3.95).

*2′,6′-Diethoxybenzyl γ-ketohexanoate* **(3e)**

Yield 67%, 1.03 g (3.35 mmol); Viscous oil; Anal. Calcd. for $C_{17}H_{24}O_5$ (308.37**)**: C, 66.21; H, 7.84; Found: C, 66.22; H, 7.83%; FT-IR (Neat, $cm^{-1}$): 3123, 1775, 1734, 1615, 1494, 1255, 1124, 1022; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.43 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.88 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.06 (2H, s, -O-C$\underline{H}_2$), 6.42-7.24 (3H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.5, 171.2, 155.6, 127.6, 117.2, 106.5, 55.7, 36.1, 33.1, 29.2, 7.7; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 274.2 (4.11).

*3′,4′-Diethoxybenzyl γ-ketohexanoate* **(3f)**

Yield 74%, 1.14 g (3.70 mmol); Viscous oil; Anal. Calcd. for $C_{17}H_{24}O_5$ (308.37**)**: C, 66.21; H, 7.84; Found: C, 66.20; H, 7.85%; FT-IR (Neat, $cm^{-1}$): 3323, 3074, 1776, 1731, 1608, 1472, 1246, 1122, 1026; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.03 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.89 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.19 (2H, s, -O-C$\underline{H}_2$), 6.62-7.09 (3H, m, Aromaic); 1.25 (3H, t, *J* = 7.6 Hz, C$\underline{H}_3$-$CH_2$-O), 4.28 (2H, q, 7.6 Hz, $CH_3$-C$\underline{H}_2$-O); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.4, 172.2, 151.2, 149.8, 124.5, 122.4, 113.5, 112.6, 67.1, 65.5, 37.3, 33.0, 29.4, 15.6, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 273.6 (4.27).

*3′,5′-Dihydroxybenzyl γ-ketohexanoate* **(3g)**

Yield 75%, 0.95 g (3.75 mmol); Viscous oil; Anal. Calcd. for $C_{13}H_{16}O_5$ (252.26**)**: C, 61.90; H, 6.39; Found: C, 61.91; H, 6.38%; FT-IR (Neat, $cm^{-1}$): 3250; 3064, 1774, 1732, 1516, 1493, 1268, 1136, 1027; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.02 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.88 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.27-6.75 (3H, m, Aromaic), 11.5 (2H, br, s, Phenolic OH); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.3, 171.7, 157.8, 137.4, 106.5, 104.3, 67.5, 36.9, 33.2, 29.5, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 275.3 (3.91).

*2′,3′,4′-Trimetxoxybenzyl γ-ketohexanoate* **(3h)**

Yield 76%, 1.18 g (3.80 mmol); Viscous oil; Anal. Calcd. for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.15; Found: C, 61.91; H, 7.16%; FT-IR (Neat, $cm^{-1}$): 3091, 1772, 1736, 1616, 1490, 1262, 1133, 1014; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.43 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.87 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.67 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 6.39-6.84 (2H, m, Aromaic), 3.98 (9H, s, 3×OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.6, 172.4, 153.2, 148.5, 143.6, 123.7, 119.6, 106.3, 62.9, 62.6, 62.2, 57.2, 36.8, 32.9, 29.3, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 276.5(3.89).

*2′,4′,5′-Trimethoxbenzyl γ-ketohexanoate* **(3i)**

Yield 75%, 1.16 g (3.75 mmol); Viscous oil; Anal. Calcd. for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.15; Found: C, 61.93; H, 7.14%; FT-IR (Neat, $cm^{-1}$): 3088, 1777, 1730, 1606, 1482, 1268, 1155, 1028; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.05 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.88 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 6.44-6.95 (2H, m, Aromaic), 3.94 (9H, s, 3×OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.9, 172.3, 152.2, 151.3, 141.2, 119.7, 112.6, 98.4, 62.8, 57.3, 36.4, 32.7, 32.7, 7.7; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 277.3 (4.13).

*3′,4′,5′-Trimethoxybenzyl γ-ketohexanoate* **(3j)**

Yield 78%, 1.21 g (3.90 mmol); Viscous oil; Anal. Calcd. for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.15; Found: C, 61.91; H, 7.16%; FT-IR (Neat, $cm^{-1}$): 3078, 1776, 1732, 1508, 1485, 1252, 1157, 1023; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.43 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.87 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.71 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.22 (2H, s, -O-C$\underline{H}_2$), 6.66 (2H, m, Aromaic), 3.95 (9H, s, 3×OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 209.1, 172.2, 154.7, 139.6, 108.3, 67.6, 62.5, 57.4, 37.2, 32.1, 29.4, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 275.6 (4.2).

*3′-Methoxy-4′-nitrobenzyl γ-ketohexanoate* **(3k)**

Yield 71%, 1.05 g (3.55 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.29): C, 56.94; H, 5.80; N, 4.74; Found: C, 56.95; H, 5.81; N, 4.75%; FT-IR (Neat, $cm^{-1}$): 3084, 1774, 1733, 1625, 1572, 1390, 1373, 1252, 1131, 1027; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.05 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.41 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.91 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.71 (2H, t, 6.8 Hz, $CH_2$-CO-O), 5.21 (2H, s, -O-C$\underline{H}_2$), 7.22-8.15 (3H, m, Aromaic), 3.91 (3H, s, O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.6, 171.9, 155.3, 145.2, 141.6, 126.2, 121.4, 113.6, 67.2, 57.7, 36.5, 32.6, 29.2, 7.7; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 269.8 (3.87).

*4′-Methoxy-3′-nitrobenzyl γ-ketohexanoate* **(3l)**

Yield 72%, 1.06 g (3.60 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.29): C, 56.94; H, 5.80; N, 4.74; Found: C, 56.93; H, 5.82; N, 4.76%; FT-IR (Neat, $cm^{-1}$): 3094, 3094, 1728, 1622, 1575, 1383, 1371, 1254, 1133, 1015; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.89 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.19 (2H, s, -O-C$\underline{H}_2$), 7.24-8.23 (3H, m, Aromaic), 3.97 (3H, s, O$\underline{Me}$); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.7, 172.1, 153.2, 142.3, 136.7, 135.6, 125.8, 115.4, 55.2, 36.5, 32.3, 29.5, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 270.9 (3.85).

*2′-Methoxy-5′-nitrobenzyl γ-ketohexanoate* **(3m)**

Yield 69%, 1.02 g (3.45 mmol); Light yellow viscous oil; Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.29): C, 56.94; H, 5.80; N, 4.74; Found: C, 56.96; H, 5.81; N, 4.75%; FT-IR (Neat, $cm^{-1}$): 3066, 1782, 1725, 1725, 2.91; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (3H, t, *J* = 7.5 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.43 (2H, q, *J* = 7.5 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.91 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.68 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.26 (2H, s, -O-C$\underline{H}_2$), 7.25-8.18 (3H, m, Aromaic), 3.97 (3H, s, OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.5, 172.5, 163.5, 142.3, 129.5, 126.7,126.5, 112.4, 62.2, 56.8, 36.1, 32.9, 29.1, 7.7; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 269.4 (3.92).

*2′,4′,6′-Trichlorobenzyl γ-ketohexanoate* **(3n)**

Yield 67%, 1.08 g (3.35 mmol); Viscous oil; Anal. Calcd. for $C_{13}H_{13}Cl_3O_3$ (323.60): C, 48.25; H, 4.05; Cl, 32.87; Found: C, 48.24; H, 4.08; Cl, 32.86%; FT-IR (Neat, $cm^{-1}$): 3084, 1776, 1728, 1615-1394, 1248, 1127, 1012 732; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.03 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.41 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.92 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.67 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.03 (2H, s, -O-C$\underline{H}_2$), 7.77-7.65 (2H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.6, 172.6, 140.7, 137.9, 136.6, 136.4, 129.8, 129.6, 58.4, 36.2, 32.8, 29.2, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 268.5 (3.91).

*2′,4′,5′-Tribromobenzyl γ-ketohexanoate* **(3o)**

Yield 61%, 1.39 g (3.05 mmol); Viscous oil; Anal. Calcd. for $C_{13}H_{13}Br_3O_3$ (456.95): C, 34.17; H, 2.87; Br, 52.46; Found: C, 34.17; H, 2.87; Br, 52.46%; FT-IR (Neat, $cm^{-1}$): 3092, 1776, 1727, 1518, 1494, 1250, 1137, 1016, 526; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.04 (2H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.43 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.91 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-C$\underline{H}_2$), 2.66 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.05 (2H, s, -O-C$\underline{H}_2$), 7.33-7.98 (2H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.4, 172.4, 141.2, 138.6, 137.4, 128.3, 126.8, 124.5, 64.4, 36.3, 32.4, 29.1, 7.8; UV-VIS (EtOH) ($\lambda_{max}$/nm (log ε): 273.7 (4.24).

*2′,4′,6′-Trimethylbenzyl γ-ketohexanoate* **(3p)**

Yield 64%, 0.84 g (3.20 mmol); Viscous oil; Anal. Calcd. for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45; Found: C, 73.26; H, 8.44%; FT-IR (Neat, $cm^{-1}$): 3087, 1774, 1725, 1616, 1394 1256, 1138, 1014; $^1$H-NMR (300 MHz, $CDCl_3$,δ/ppm): 1.05 (2H, t, *J* = 7.4 Hz, C$\underline{H}_3$-$CH_2$-CO-$CH_2$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3$-C$\underline{H}_2$-CO-$CH_2$), 2.93 (2H, t, *J* = 6.8 Hz, $CH_3$-$CH_2$-CO-$CH_2$), 2.69 (2H, t, 6.8 Hz, C$\underline{H}_2$-CO-O), 5.12 (2H, s, -O-C$\underline{H}_2$), 6.92 (2H, m, Aromaic); $^{13}$C-NMR (75 MHz, $CDCl_3$, δ/ppm): 208.7, 172.3, 138.5, 135.2,

129.4, 128.9, 63.7, 37.1, 33.4, 29.4, 22.7, 20.3, 7.4; UV-VIS (EtOH) ($\lambda_{max/}$nm (log ε): 268.8 (3.48).

*Cytotoxic activity*

Cytotoxic activity test was performed according to a known procedure [20]. Briefly, to a beaker (3000 mL) containing 2500 mL of distilled water was added 4 tablespoon of marine salts to get a solution of specific gravity 1.03. The pH of the solution was adjusted to 8 by the addition of Epson salt. The solution was divided into two portions of 300 & 2200 mL. To 300 mL of the salt solution contained in a beaker (1000 mL) a pinch (1/4 teaspoon) of brine shrimp eggs were added. The beaker was covered with a polyethylene sheet and placed at a ventilated place near an electric bulb of 200 watts such that the temperature of water did not exceed 25-30 °C. Overnight-hatched brine shrimps were used in the cytotoxic test of the gamma keto esters (**3a-3p**).

The remaining 2200 mL of the salt solution were used to prepare solutions of gamma keto esters. To 25 mL of the salt solutions with 1% DMSO (v/v) contained in beakers (150 mL) were added 500, 250, 125, 62.25 and 31.12 µg of gamma keto esters. To each concentrations of gamma-ketoester were transferred with help of a lens and tweezers 20 overnight-hatched brine shrimps. The beakers were covered with polyethylene sheets and left overnight in light. After 24 hours the numbers of survivors in each concentration were found and subjected to Probit Software Analysis (PSA) to determine $LC_{50.}$

**Results and Discussion**

Brine Shrimps Lethality Assay (BSLA) is one of the several techniques which are primarily used to evaluate cytotoxic activity of the novel synthesized compounds. So the cytotoxic activity of the compounds (**3a-3p**) has been investigated using Brine Shrimps Lethality Assay (BSLA). Statistical analysis was carried out making use of Probit Analysis Software (PAS) and values reported in Table-2 correspond to Least Squares Normal Distribution (LSND) and has been rounded off to four decimal places. LC50 value, which are the minimum concentration of the tested drug/compound to kill half of the organisms were calculated for all compounds (**3a-3p**) and are in the range 193.5369 to 235.4863 µg. Moreover, the cytotoxic structure activity relationship (SAR) could be understood by looking on the values in table 2. Compound **1i**, a 2′,4′,5′-trimthoxy derivative displayed the lowest activity i.e. highest LC50 value of 241.8421 with LCL (Lower Confidence Level) vale of 283.1060 and LC50 UCL (Upper Confidence Level) value of 200.5783. Compound **1e**, a 2′,6′-diethoxy derivative ranked second to display the lowest activity i.e. LC50 value of 235.4863 with LCL (Lower Confidence Level) vale of 283.2735) and LC50 UCL (Upper Confidence Level) value of 187.6992. Substitution of halogens substantially increased the cytotoxicity. Compounds **3n** & **3o** showed highest activity (lowest LC50 values) indicating that these are more cytotoxic. The LC50 LCL (Lower Confidence Level) and LC50 UCL (Upper Confidence Level) of compounds (**3a-3p**) have also been reported in table 2. All of the tested compounds displayed 100 % mortality (no survivor) at concentration equal or > 500 µg and zero mortality (100 % survivor) at concentrations equal or < 31.12 µg. Lowest cytotoxic activity was observed for compound 5b. In the control consisting of 25 mL of saline water, 1% DMSO (v/v), 20 brine shrimp & without any added gamma-ketoester, all brine shrimp were found alive.

Table-2: $LC_{50}$, values (µg) of **1b-16b** obtained via Probit Analysis- Least squares [Normal Distribution].

| Cmpd # | Concentrations in µg/Survivors | | | | | $LC_{50}$ | $LC_{50}$ (LCL) | $LC_{50}$ (UCL) |
|---|---|---|---|---|---|---|---|---|
| | 500 | 250 | 125 | 62.25 | 31.12 | | | |
| **3a** | **0** | **8** | **14** | **19** | **20** | **219.4536** | **271.2815** | **167.6257** |
| **3b** | **0** | **5** | **17** | **18** | **20** | **212.3725** | **250.7048** | **174.0403** |
| **3c** | **0** | **7** | **18** | **19** | **20** | **234.1899** | **279.8341** | **188.5458** |
| **3d** | **0** | **8** | **15** | **18** | **20** | **220.6302** | **263.5899** | **177.6704** |
| **3e** | **0** | **8** | **17** | **19** | **20** | **235.4863** | **283.2735** | **187.6992** |
| **3f** | **0** | **7** | **16** | **18** | **20** | **219.3182** | **260.3025** | **178.3339** |
| **3g** | **0** | **9** | **15** | **18** | **20** | **227.2859** | **271.4213** | **183.1505** |
| **3h** | **0** | **8** | **17** | **18** | **20** | **230.6515** | **271.7786** | **189.5244** |
| **3i** | **0** | **9** | **18** | **18** | **20** | **241.8421** | **283.1060** | **200.5783** |
| **3j** | **0** | **10** | **17** | **18** | **20** | **230.6515** | **271.7786** | **189.5244** |
| **3k** | **0** | **8** | **12** | **19** | **20** | **208.7914** | **263.3047** | **154.2779** |
| **3l** | **0** | **5** | **16** | **19** | **20** | **212.4292** | **258.4350** | **166.4234** |
| **3m** | **0** | **7** | **13** | **18** | **20** | **204.0399** | **247.6211** | **160.4587** |
| **3n** | **0** | **6** | **14** | **18** | **20** | **203.0547** | **244.6224** | **161.4870** |
| **3o** | **0** | **7** | **11** | **18** | **20** | **193.5369** | **238.9032** | **148.1705** |
| **3p** | **0** | **9** | **14** | **19** | **20** | **225.9650** | **279.1207** | **172.8093** |

$LC_{50}$: Minimum concentration of the compound required to kill half of the organisms
$LC_{50}$ (LCL): Lower Confidential Limit of the tested compounds
$LC_{50}$ (UCL): Upper Confidential Limit of the tested compounds
Total number of Brine shrimps added to each solution = 20
Total number of Brine shrimps added to control = 20

## Conclusion

In the present study sixteen (**3a-3p**) new di-,tri-substituted-benzyl 4-chloro-4-oxobutanoates have been successively converted into sixteen (**3a-3p**) new di-,tri-substituted-benzyl gamma-ketohexanoates. To ascertain bioactivity of new compounds, (**3a-3p)**, these were screened for Brine Shrimp Lethality Assay (BSLA). All of the di-,tri-substituted-benzyl gamma-ketohexanoates (**3a-3p** ) displayed cytotoxic activity.

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