J. Mater. Environ. Sci. 5 (1) (2014) 281-292
ISSN : 2028-2508
CODEN: JMESCN

Synthesis and Cytotoxicity Studies of 4-Alkoxychalcones as New Antitumor Agents

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Received 03 Oct 2013, Revised 26 Oct 2013, Accepted 26 Oct 2013
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Abstract
A series of new 36 B-ring 4-alkoxychalcones have been prepared and characterized on the basis of their spectral data and microanalysis. All the synthesized compounds were further screened for their cytotoxic activity against *Artemia salina* (Brine shrimp) and one tumor cell line, namely human Prostate Cancer (PC-3) cell line. The results of these studies revealed that 4-alkoxychacones (**3c-7c**, **11c, 13c**) bearing 4-flouro group on ring A were highly toxic to brine shrimp with LD_{50} values ranging from 0.003-0.4 µg/mL as compared to Etoposide (LD_{50} = 7.5 µg/mL) used as reference standard drug, whereas 4-alkoxychalcones (**3c**, **5b, 5c**, **6b**) exhibited moderate *in vitro* antiproliferative activity against PC-3 with the IC_{50} values ranging from 20-40 µM. The present series of 4-alkoxychalcones with high level of toxicity against *Artemia salina* and moderate antiproliferative activity against PC-3 may prove to be potential cell selective antitumor agents.

Keywords: Alkoxy chalcones, Cytotoxicity, Prostate cancer (PC-3), Potential cell selectivity

Introduction
Cancer, being one of the most serious clinical problems, is still threatening in developing as well as developed countries. The general toxicity to proliferating cells together with some normal cells limits the therapeutic potential of most anticancer drugs in clinical use [1]. Therefore, the chemists are continuously trying to develop novel antiproliferating agents with higher level of cancerous cell selectivity. The lack of tumor cells selectivity of anticancer drugs and the development of multidrug resistance are the key factors playing their role in search of new classes of target-specific cytotoxic compounds that may be able to overcome multidrug resistance [2, 3]. Among these classes of compounds, derivatives containing α, β-unsaturated Michael acceptor functionalities, namely chalcones have attracted considerable attention as potential anticancer agents. As previous evidences indicate that alkylating agents (potential anticancer compounds) bind directly to various cellular nucleophiles, thus lacking tumoral selectivity. Whereas, structurally modified Michael acceptors can react selectively with target nucleophiles [4].

Chalcones (1,3-diaryl-2-propen-1-ones or phenyl styryl ketone) being precursors of flavonoids are common natural pigments and have wide-spread distribution in fruits, vegetables and tea [5]. These are abundant in edible plants and are considered to be one of the important intermediates in the biosynthesis of flavonoids and isoflavonoids. Both natural and synthetic chalcones are important bioactive agents with diverse pharmacological applications [6-15]. Flavonoids are naturally occurring polyphenols which also possess a wide range of biological activities [16]. In recent years, the anticancer potential of flavonoids and their biogenetic precursors have thoroughly been investigated [17-18]. Claisen–Schmidt condensation of acetophenones and Benzaldehydes provide an attractive drug scaffold and precursors for the synthesis of a wide variety of organic compounds including heterocyclic compounds. Recent literature on structure-activity-relationship (SAR) [19, 20] shows that a number of biological activities are dependent on the substitution pattern of methoxy and hydroxyl groups in both A and B rings [21, 22]. For example, the substitution of 2′,4′,5′-trimethoxy groups on the ring A of chalcones favour antimalarial activity [23, 24] and 3′,4′,5′-trimethoxy groups inhibits the transport activity of glycoprotein

and showed reversal of multidrug resistance (MDR) activity [25]. Similarly, nitric oxide scavenging and anti-proliferation activity was observed for 2′,4′,6′-trimethoxy chalcones [26]. Substitution at 2′ and 4′ positions of ring A was found crucial for breast cancer resistance protein inhibition [13, 27]. Stilbene and trimethoxy substituted chalcone hybrids showed antiplasmodial activity [15]. Fluorine and methoxy substituted chalcones were found to inhibit nitric oxide production [28].

The interesting role of chalcones in the induction of apoptosis [29,30] and their ability to change mitochondrial membrane potential is recently recognized [31]. The presence of fewer hydroxyl groups on ring A and B of chalcone was found more effective as compared to chalcones containing more hydroxyl groups. This difference was connected with the acidity of the phenolic hydroxyl groups. The intervention with the mitotic phase of the cell cycle is the main reason by which chalcones exert their cytotoxic activity. A hypothetical basis for the anti-mitotic activity of chalcones was proposed by Edwards *et al* [32] against HeLa cells where a large number of methoxylated chalcones showed anti-mitotic activity. In an effort to search for novel antitumor agents with potential cell selectivity, herein we report the synthesis of a series of B-ring 4-alkoxy chalcones as antitumor agents.

Experimental Section

All reagents were purchased from Merck (Germany) and Sigma-Aldrich (Germany) and were used without further purification. All organic solvents were dried and distilled before use according to the reported procedures. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer using deuterated solvents and TMS as internal standard operating at 300 and 75.5 MHz, respectively. The splitting of proton resonances in the reported ^{1}H NMR spectra are defined as s = singlet, d = doublet, dd = doublet of doublet, qn = quintet, t = triplet and m = multiplet. IR spectra were recorded on a Bio-Rad FTS 3000 MX spectrophotometer (400-4000 cm^{-1}). The elemental analyses were conducted using a LECO-183 CHNS analyzer. The GC-MS spectra were performed with Agilent 5973 inert mass selective detector in combination with Agilent 6890N gas chromatograph. Helium was used as a carrier gas; a 30 m DB5MS column with 0.25 µm film was used. The measuring program for inlet was at 250 °C and the ramping rate of 10 °C/minute was adjusted 300 °C for final phase. Melting points were determined using capillary tubes and an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo, Japan, and the values are uncorrected. R_f values were calculated by thin layer chromatography (TLC), using aluminium-backed plates coated with silica gel 60 with F_{254} indicator, in ethyl acetate:pet-ether solvent system and compounds were visualized by UV light (254 nm and 365 nm) or iodine.

Syntheis of 4-Alkoxybenzaldehydes

A series of 4-alkoxybenzaldehydes **(2a-2I)** was synthesized by already reported method [33] by reacting 4-hydroxybenzaldehyde with bromoalkanes.

General Procedure for the Synthesis of 4-alkoxychalcones (3-14)

To a solution of compound **(1a-1c)** in ethanol (20 mL) was added an ice cooled 10% NaOH solution (200 mL) with stirring. The mixture was kept stirring for about 30 minutes at room temperature. 4-Alkoxybenzaldehyde **(2a−2I)** was then added and stirred the reaction mixture for another 6-8 hours at room temperature till the appearance of pale yellow precipitates. Crushed ice was then added to the solid mass and the solution was neutralized with dilute HCl. The pure products **(3-14)** were obtained as yellow crystalline solids after filtration and recrystallization from ethanol. To explain the coupling constants for various protons in the experimental data, the following labeling scheme is used for convenience (Figure 1).

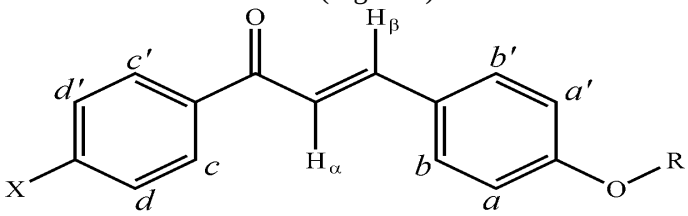


Figure. 1 Labelling scheme of protons.

3a: (*E*)-1-(4-bromophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Yield 93%; pale yellow solid; m. p. 144−146˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1645, 1618, 1250, 1047, 1071, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H, −O−C***H***$_3$), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.64 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.80 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 114.4 (2C), 119.0, 127.4, 127.6, 129.9 (2C), 130.37 (2C), 131.8 (2C), 137.2, 145.2, 161.8, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 317, Base Peak 237). Anal. calcd. for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13; Found: C, 60.56; H, 4.10%

3b: (*E*)-1-(4-cholorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Yield 96%; pale yellow solid; m. p. 120−122˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1648, 1621, 1255, 1049, 1044, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H, −O−C***H***$_3$), 6.96 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.39 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.63 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.82 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 114.4 (2C), 119.1, 127.4, 128.9, (2C), 129.8 (2C), 130.37 (2C), 136.7, (2C), 138.9, 145.2, 161.8, 189.2, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 272). Anal. calcd. for $C_{16}H_{13}BrO_2$: C, 70.46; H, 4.80; Found: C, 70.44; H, 4.78%.

3c: (*E*)-1-(4-fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one
Yield 95%; pale yellow solid; m. p. 103−104˚C; R_f = 0.81 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1644, 1625, 1251, 1045, 1123, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H, −O−C***H***$_3$), 6.96 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.19 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 114.4 (2C), 115.5, 115.8 (2C), 119.1, 127.4, 130.3 (2C), 130.9 (2C), 131.5, 144.9, 161.7, 188.8, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 256). Anal. calcd. for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11; Found: C, 74.97; H, 5.10%

4a: (*E*)-1-(4-bromophenyl)-3-(4-ethoxyphenyl)prop-2-en-1-one
Yield 96%; pale yellow solid; m. p. 126−128˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1642, 1620, 1259, 1039, 1069, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, 3H, *J* = 7.2 Hz, −O−CH_2−C***H***$_3$), 4.01 (q, 2H, *J* = 7.0 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 63.7, 114.9 (2C), 118.9, 127.2, 127.6, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.3, 161.3, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 331, Base Peak 330) Anal. calcd. for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56; Found: C, 61.62; H, 4.53%

4b: (*E*)-1-(4-cholorophenyl)-3-(4-ethoxyphenyl)prop-2-en-1-one
Yield 94%; pale yellow solid; m. p. 109−111˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1645, 1623, 1256, 1041, 1035, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, 3H, *J* = 7.0 Hz, −O−CH_2−C***H***$_3$), 4.01 (q, 2H, *J* = 7.0 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.48 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.97 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 63.7, 114.9 (2C), 118.9, 127.2, 128.8, 129.8 (2C), 130.3 (2C), 136.8 (2C), 138.9, 145.3, 161.2, 189.2, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 286). Anal. calcd. for $C_{17}H_{15}BrO_2$: C, 71.20; H, 5.27; Found: C, 71.17; H, 5.25%

4c: (*E*)-1-(4-fluorophenyl)-3-(4-ethoxyphenyl)prop-2-en-1-one
Yield 93%; pale yellow solid; m. p. 98−99˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1648, 1623, 1254, 1045, 1125, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, 3H, *J* = 7.0 Hz, −O−CH_2−C***H***$_3$), 4.10 (q, 2H, *J* = 6.9 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.19 (t, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 63.6, 114.9 (2C), 115.5, 115.8 (2C), 119.0, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.2, 188.8, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 270). Anal. calcd. for $C_{17}H_{15}FO_2$: C, 75.54; H, 5.59; Found: C, 75.51; H, 5.57%

5a: (*E*)-1-(4-bromophenyl)-3-(4-propylxyphenyl)prop-2-en-1-one
Yield 94%; pale yellow solid; m. p. 106−108˚C; R_f = 0.85 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1647, 1624, 1255, 1043, 1065, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.5 Hz,−O−$(CH_2)_2$−C***H***$_3$), 1.85 (sextet, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−CH_3), 3.99 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.5, 69.6, 114.9 (2C), 118.9, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 345, Base Peak 223). Anal. calcd. for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96; Found: C, 62.60; H, 4.93%

5b: (*E*)-1-(4-cholorophenyl)-3-(4-propylxyphenyl)prop-2-en-1-one
Yield 95%; pale yellow solid; m. p. 101−103˚C; R_f = 0.85 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1641, 1624, 1258, 1048, 1042, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_2$−C***H***$_3$), 1.85 (sextet,

2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−CH_3), 3.99 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$),7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$),7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 10.5, 22.5, 69.6, 114.9 (2C), 118.9, 127.1, 128.8 (2), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 300, Base Peak 223). Anal. calcd. for $C_{18}H_{17}BrO_2$: C, 71.88; H, 5.70; Found: C, 71.86; H, 5.68%

5c: (*E*)-1-(4-fluorophenyl)-3-(4-propylxyphenyl)prop-2-en-1-one

Yield 92%; pale yellow solid; m. p. 90−92˚C; R_f = 0.85 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1649, 1628, 1255, 1044, 1128, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.07 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_2$−C***H***$_3$), 1.85 (sextet, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−CH_3), 3.98 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 10.5, 22.5, 69.6, 114.9 (2C), 115.5, 115.8 (2C), 119.0, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.8, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 284). Anal. calcd. for $C_{18}H_{17}FO_2$: C, 76.04; H, 6.03; Found: C, 76.01; H, 6.00%

6a: (*E*)-1-(4-bromophenyl)-3-(4-butyloxyphenyl)prop-2-en-1-one

Yield 95%; pale yellow solid; m. p. 103−105˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1649, 1625, 1251, 1045, 1068, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.00 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_3$−C***H***$_3$), 1.52 (sextet, 2H, *J* = 7.5 Hz, −O−CH_2−CH_2−C***H***$_2$−CH_3), 1.81 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−CH_2−CH_3), 4.03 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.3 Hz, H_α), 7.60 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.3 Hz, H_β),7.90 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 13.8, 19.2, 31.1, 67.9, 114.9 (2C), 118.9, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 359, Base Peak 223). Anal. calcd. for $C_{19}H_{19}BrO_2$: C, 63.52; H, 5.33; Found: C, 63.49; H, 5.30%

6b: (*E*)-1-(4-cholorophenyl)-3-(4-butyloxyphenyl)prop-2-en-1-one

Yield 94%; pale yellow solid; m. p. 98−98˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1642, 1627, 1254, 1046, 1044, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.00 (t, 3H, *J* = 7.5 Hz,−O−$(CH_2)_3$−C***H***$_3$), 1.52 (sextet, 2H, *J* = 7.5 Hz, −O−CH_2−CH_2−C***H***$_2$−CH_3), 1.81 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−CH_2−CH_3), 4.03 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.3 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.3 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 13.8, 19.2, 31.9, 67.9, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.4 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 314, Base Peak 223). Anal. calcd. for $C_{19}H_{19}BrO_2$: C, 72.49; H, 6.08; Found: C, 72.47; H, 6.06%

6c: (*E*)-1-(4- fluorophenyl)-3-(4-butyloxyphenyl)prop-2-en-1-one

Yield 91%; pale yellow solid; m. p. 88−89˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1646, 1621, 1258, 1042, 1124, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.00 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_3$−C***H***$_3$), 1.52 (sextet, 2H, *J* = 7.5 Hz, −O−CH_2−CH_2−C***H***$_2$−CH_3), 1.81 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−CH_2−CH_3), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 13.8, 19.2, 31.1, 67.8, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.8, MS (EI) *m/z* ($M^{+\bullet}$, Base Peak 298). Anal. calcd. for $C_{19}H_{19}FO_2$: C, 76.49; H, 6.42; Found: C, 76.47; H, 6.41%

7a: (*E*)-1-(4-bromophenyl)-3-(4-pentyloxyphenyl)prop-2-en-1-one

Yield 92%; pale yellow solid; m. p. 88−90˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1640, 1621, 1257, 1048, 1072, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.96 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_4$−C***H***$_3$), 1.38−1.50 (m, 4H, −O−CH_2−CH_2−(C***H***$_2$)$_2$−CH_3), 1.83 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−C_3H_7), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 14.0, 22.4, 28.1, 28.8, 68.2, 114.9 (2C), 118.9, 127.1, 127.6, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 373, Base Peak 223). Anal. calcd. for $C_{20}H_{21}BrO_2$: C, 64.35; H, 5.67; Found: C, 64.32; H, 5.65%

7b: (*E*)-1-(4-cholorophenyl)-3-(4-pentyloxyphenyl)prop-2-en-1-one

Yield 93%; pale yellow solid; m. p. 93−95˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1646, 1625, 1259, 1041, 1048, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.96 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_4$−C***H***$_3$), 1.38−1.50 (m, 4H, −O−CH_2−CH_2−(C***H***$_2$)$_2$−CH_3), 1.83 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−C_3H_7), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 14.0, 22.4,

28.1, 28.8, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 328, Base Peak 223). Anal. calcd. for $C_{20}H_{21}BrO_2$: C, 73.05; H, 6.44; Found: C, 73.03; H, 6.42%

7c: (*E*)-1-(4- fluorophenyl)-3-(4-pentyloxyphenyl)prop-2-en-1-one

Yield 93%; pale yellow solid; m. p. 67−68˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1640, 1626, 1256, 1047, 1128, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.2 Hz,−O−$(CH_2)_4$−C***H***$_3$), 1.38−1.50 (m, 4H, −O−CH_2−CH_2−(C***H***$_2)_2$−CH_3), 1.83 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−C_3H_7), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.4, 28.1, 28.8, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 119.0, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$, 312, Base Peak 241). Anal. calcd. for $C_{20}H_{21}FO_2$: C, 76.90; H, 6.78; Found: C, 76.87; H, 6.76%

8a: (*E*)-1-(4-bromophenyl)-3-(4-hexyloxyphenyl)prop-2-en-1-one

Yield 95%; pale yellow solid; m. p. 95−97˚C; R_f = 0.81 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1648, 1628, 1255, 1051, 1075, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_5$−C***H***$_3$), 1.36−1.51 (m, 6H, −O−CH_2−CH_2−(C***H***$_2)_3$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−C_4H_9), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.3 Hz, H_α), 7.60 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.63 (d, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.3 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.6, 29.1, 31.5, 68.2, 114.9 (2C), 118.9, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 387, Base Peak 223). Anal. calcd. for $C_{21}H_{23}BrO_2$: C, 65.12; H, 5.99; Found: C, 65.09; H, 5.96%

8b: (*E*)-1-(4-cholorophenyl)-3-(4-hexyloxyphenyl)prop-2-en-1-one

Yield 91%; pale yellow solid; m. p. 95−97˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1644, 1629, 1251, 1053, 1046, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_5$−C***H***$_3$), 1.34−1.51 (m, 6H, −O−CH_2−CH_2−(C***H***$_2)_3$−CH_3), 1.82 (qn, 2H, *J* = 7.8 Hz, −O−CH_2−C***H***$_2$−C_4H_9), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.7, 29.1, 31.5, 68.2, 114.9 (2C), 118.8, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 342, Base Peak 223). Anal. calcd. for $C_{21}H_{23}BrO_2$: C, 73.57; H, 6.76; Found: C, 73.55; H, 6.75%

8c: (*E*)-1-(4- fluorophenyl)-3-(4-hexyloxyphenyl)prop-2-en-1-one

Yield 95%; pale yellow solid; m. p. 63−64˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1647, 1623, 1257, 1050, 1122, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_5$−C***H***$_3$), 1.34−1.51 (m, 6H, −O−CH_2−CH_2−(C***H***$_2)_3$−CH_3), 1.82 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−C_4H_9), 4.03 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.7, 29.1, 31.5, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 326, Base Peak 241). Anal. calcd. for $C_{21}H_{23}FO_2$: C, 77.27; H, 7.10; Found: C, 77.25; H, 7.09%

9a: (*E*)-1-(4-bromophenyl)-3-(4-heptyloxyphenyl)prop-2-en-1-one

Yield 93%; pale yellow solid; m. p. 99−101˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1644, 1630, 1245, 1047, 1069, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_6$−C***H***$_3$), 1.33−1.51 (m, 8H, −O−CH_2−CH_2−(C***H***$_2)_4$−CH_3), 1.82 (qn, 2H, *J* = 7.8 Hz, −O−CH_2−C***H***$_2$−C_5H_{11}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 29.0, 29.1, 31.7, 68.2, 114.9 (2C), 118.8, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 401, Base Peak 223). Anal. calcd. for $C_{22}H_{25}BrO_2$: C, 65.84; H, 6.28; Found: C, 65.81; H, 6.26%

9b: (*E*)-1-(4-cholorophenyl)-3-(4-heptyloxyphenyl)prop-2-en-1-one

Yield 94%; pale yellow solid; m. p. 92−94˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1640, 1622, 1249, 1049, 1040, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_6$−C***H***$_3$), 1.33−1.51 (m, 8H, −O−CH_2−CH_2−(C***H***$_2)_4$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−C_5H_{11}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.97 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 29.0, 29.1, 31.7, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 356, Base Peak 223). Anal. calcd. for $C_{22}H_{25}BrO_2$: C, 74.04; H, 7.06; Found: C, 74.01; H, 7.04%

9c: (*E*)-1-(4- fluorophenyl)-3-(4-heptyloxyphenyl)prop-2-en-1-one

Yield 96%; pale yellow solid; m. p. 72−73˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1643, 1622, 1255, 1047, 1126, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_6$−C***H***$_3$), 1.33−1.51 (m, 8H, −O−CH_2−CH_2−(C***H***$_2)_4$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−C_5H_{11}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 29.0, 29.1, 31.7, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 340, Base Peak 241). Anal. calcd. for $C_{22}H_{25}FO_2$: C, 77.62; H, 7.40; Found: C, 77.60; H, 7.39%

10a: (*E*)-1-(4-bromophenyl)-3-(4-octyloxyphenyl)prop-2-en-1-one

Yield 95%; pale yellow solid; m. p. 92−94˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1647, 1625, 1258, 1040, 1070, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_7$−C***H***$_3$), 1.31−1.50 (m, 10H, −O−CH_2−CH_2−(C***H***$_2)_5$−CH_3), 1.82 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−C_6H_{13}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 68.2, 114.9 (2C), 118.8, 127.1, 127.6, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 415, Base Peak 223). Anal. calcd. for $C_{23}H_{27}BrO_2$: C, 66.51; H, 6.55; Found: C, 66.48; H, 6.51%

10b: (*E*)-1-(4-cholorophenyl)-3-(4-octyloxyphenyl)prop-2-en-1-one

Yield 96%; pale yellow solid; m. p. 93−95˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1645, 1626, 1255, 1047, 1047, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_7$−C***H***$_3$), 1.31−1.50 (m, 10H, −O−CH_2−CH_2−(C***H***$_2)_5$−CH_3), 1.82 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−C_6H_{13}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.48 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 68.2, 114.9 (2C), 118.8, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 370, Base Peak 223). Anal. calcd. for $C_{23}H_{27}BrO_2$: C, 74.48; H, 7.34; Found: C, 74.45; H, 7.33%

10c: (*E*)-1-(4- fluorophenyl)-3-(4-octyloxyphenyl)prop-2-en-1-one

Yield 92%; pale yellow solid; m. p. 80−81˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1646, 1625, 1252, 1045, 1129, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_7$−C***H***$_3$), 1.31−1.50 (m, 10H, −O−CH_2−CH_2−(C***H***$_2)_5$−CH_3), 1.82 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−C_6H_{13}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 119.0, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.8, MS (EI) *m/z* ($M^{+\bullet}$ 354, Base Peak 242). Anal. calcd. for $C_{23}H_{27}FO_2$: C, 77.93; H, 7.68; Found: C, 77.90; H, 7.66%

11a: (*E*)-1-(4-bromophenyl)-3-(4-nonyloxyphenyl)prop-2-en-1-one

Yield 92%; pale yellow solid; m. p. 90−92˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1641, 1629, 1262, 1044, 1068, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_8$−C***H***$_3$), 1.30−1.50 (m, 12H, −O−CH_2−CH_2−(C***H***$_2)_6$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−C_7H_{15}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.60 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 29.5, 31.8, 68.2, 114.9 (2C), 118.9, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 429, Base Peak 223). Anal. calcd. for $C_{24}H_{29}BrO_2$: C, 67.13; H, 6.81; Found: C, 67.11; H, 6.79%

11b: (*E*)-1-(4-cholorophenyl)-3-(4-nonyloxyphenyl)prop-2-en-1-one

Yield 93%; pale yellow solid; m. p. 90−92˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1647, 1627, 1266, 1042, 1045, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_8$−C***H***$_3$), 1.31−1.50 (m, 12H, −O−CH_2−CH_2−(C***H***$_2)_6$−CH_3), 1.82 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−C_7H_{15}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.49 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.4, 29.5, 31.8, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8 (2C), 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 384, Base Peak 223). Anal. calcd. for $C_{24}H_{29}BrO_2$: C, 74.88; H, 7.59; Found: C, 74.86; H, 7.57%

11c: (*E*)-1-(4- fluorophenyl)-3-(4-nonyloxyphenyl)prop-2-en-1-one
Yield 95%; pale yellow solid; m. p. 86−87˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1649, 1629, 1260, 1049, 1128, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_8$−C***H***$_3$), 1.30−1.50 (m, 12H, −O−CH_2−CH_2−(C***H***$_2)_6$−CH_3), 1.82 (qn, 2H, J = 7.2 Hz, −O−CH_2−C***H***$_2$−C_7H_{15}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, J = 8.4 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, J = 15.6 Hz, H_α), 7.61 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 8.07 (d, 2H, J = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.9, 26.0, 29.1, 29.2, 29.4, 29.5, 31.8, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 368, Base Peak 242). Anal. calcd. for $C_{24}H_{29}FO_2$: C, 78.23; H, 7.93; Found: C, 78.20; H, 7.91%

12a: (*E*)-1-(4-bromophenyl)-3-(4-decyloxyphenyl)prop-2-en-1-one
Yield 95%; pale yellow solid; m. p. 94−95˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1646, 1621, 1257, 1052, 1065, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_9$−C***H***$_3$), 1.30−1.51 (m, 14H, −O−CH_2−CH_2−(C***H***$_2)_7$−CH_3), 1.82 (qn, 2H, J = 7.8 Hz, −O−CH_2−C***H***$_2$−C_8H_{17}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, J = 15.6 Hz, H_α), 7.60 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, J = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 7.90 (d, 2H, J = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.3, 29.4, 29.5, 31.9, 68.2, 114.9 (2C), 118.9, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.3, MS (EI) *m/z* ($M^{+\bullet}$ 443, Base Peak 223). Anal. calcd. for $C_{25}H_{31}BrO_2$: C, 67.72; H, 7.05; Found: C, 67.70; H, 7.02%

12b: (*E*)-1-(4-cholorophenyl)-3-(4-decyloxyphenyl)prop-2-en-1-one
Yield 95%; pale yellow solid; m. p. 92−94˚C; R_f = 0.82 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1640, 1622, 1252, 1050, 1041, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_9$−C***H***$_3$), 1.29−1.50 (m, 14H, −O−CH_2−CH_2−(C***H***$_2)_7$−CH_3), 1.82 (qn, 2H, J = 7.5 Hz, −O−CH_2−C***H***$_2$−C_8H_{17}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, J = 15.6 Hz, H_α), 7.49 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, J = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 7.98 (d, 2H, J = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.4, 29.5, 31.9, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 398, Base Peak 223). Anal. calcd. for $C_{25}H_{31}BrO_2$: C, 75.26; H, 7.83; Found: C, 75.24; H, 7.81%

12c: (*E*)-1-(4- fluorophenyl)-3-(4-decyloxyphenyl)prop-2-en-1-one
Yield 93%; pale yellow solid; m. p. 78−79˚C; R_f = 0.85 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1640, 1621, 1259, 1052, 1125, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_9$−C***H***$_3$), 1.29−1.50 (m, 14H, −O−CH_2−CH_2−(C***H***$_2)_7$−CH_3), 1.82 (qn, 2H, J = 7.5 Hz, −O−CH_2−C***H***$_2$−C_8H_{17}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, J = 8.4 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, J = 15.6 Hz, H_α), 7.61 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 8.07 (d, 2H, J = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.9, 26.0, 29.0, 29.1, 29.3, 29.3, 29.5, 31.9, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 382, Base Peak 242). Anal. calcd. for $C_{25}H_{31}FO_2$: C, 78.50; H, 8.17; Found: C, 78.47; H, 8.15%

13a: (*E*)-1-(4-bromophenyl)-3-(4-undecyloxyphenyl)prop-2-en-1-one
Yield 93%; pale yellow solid; m. p. 96−98˚C; R_f = 0.85 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1644, 1624, 1254, 1047, 1072, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_{10}$−C***H***$_3$), 1.29−1.50 (m, 16H, −O−CH_2−CH_2−(C***H***$_2)_8$−CH_3), 1.82 (qn, 2H, J = 7.8 Hz, −O−CH_2−C***H***$_2$−C_9H_{19}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, J = 15.6 Hz, H_α), 7.60 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, J = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 7.90 (d, 2H, J = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 68.2, 114.9 (2C), 118.8, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 457, Base Peak 223). Anal. calcd. for $C_{26}H_{33}BrO_2$: C, 68.27; H, 7.27; Found: C, 68.24; H, 7.25%

13b: (*E*)-1-(4-cholorophenyl)-3-(4-undecyloxyphenyl)prop-2-en-1-one
Yield 92%; pale yellow solid; m. p. 86−88˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1649, 1627, 1259, 1045, 1044, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz,−O−$(CH_2)_{10}$−C***H***$_3$), 1.30−1.51 (m, 16H, −O−CH_2−CH_2−(C***H***$_2)_8$−CH_3), 1.82 (qn, 2H, J = 7.8 Hz, −O−CH_2−C***H***$_2$−C_9H_{19}), 4.02 (t, 2H, J = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, J = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, J = 15.6 Hz, H_α), 7.49 (d, 2H, J = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, J = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, J = 15.6 Hz, H_β), 7.98 (d, 2H, J = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.2, 29.3, 29.4, 29.4, 29.5, 31.9, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8,

138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 412, Base Peak 223). Anal. calcd. for $C_{26}H_{33}BrO_2$: C, 75.61; H, 8.05; Found: C, 75.59; H, 8.03%

13c: (*E*)-1-(4- fluorophenyl)-3-(4-undecyloxyphenyl)prop-2-en-1-one

Yield 94%; pale yellow solid; m. p. 85−86˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1649, 1625, 1256, 1043, 1129, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_{10}$−C***H***$_3$), 1.29−1.50 (m, 16H, −O−CH_2−CH_2−(C***H***$_2)_8$−CH_3), 1.82 (qn, 2H, *J* = 7.0 Hz, −O−CH_2−C***H***$_2$−C_9H_{19}), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.18 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 396, Base Peak 242). Anal. calcd. for $C_{26}H_{33}FO_2$: C, 78.75; H, 8.39; Found: C, 78.73; H, 8.38%

14a: (*E*)-1-(4-bromophenyl)-3-(4-dodecyloxyphenyl)prop-2-en-1-one

Yield 94%; pale yellow solid; m. p. 95−97˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1643, 1625, 1253, 1049, 1067, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_{11}$−C***H***$_3$), 1.28−1.51 (m, 18H, −O−CH_2−CH_2−(C***H***$_2)_9$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−$C_{10}H_{21}$), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.37 (d, 1H, *J* = 15.6 Hz, H_α), 7.60 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.65 (d, 2H, *J* = 8.4 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.90 (d, 2H, *J* = 8.4 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 31.9, 68.2, 114.9 (2C), 118.8, 127.1, 127.5, 129.9 (2C), 130.3 (2C), 131.8 (2C), 137.2, 145.4, 161.5, 189.4, MS (EI) *m/z* ($M^{+\bullet}$ 471, Base Peak 223). Anal. calcd. for $C_{27}H_{35}BrO_2$: C, 68.78; H, 7.48; Found: C, 68.75; H, 7.46%

14b: (*E*)-1-(4-cholorophenyl)-3-(4-dodecyloxyphenyl)prop-2-en-1-one

Yield 91%; pale yellow solid; m. p. 88−90˚C; R_f = 0.83 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1641, 1624, 1256, 1041, 1042, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_{11}$−C***H***$_3$), 1.28−1.50 (m, 18H, −O−CH_2−CH_2−(C***H***$_2)_9$−CH_3), 1.82 (qn, 2H, *J* = 7.5 Hz, −O−CH_2−C***H***$_2$−$C_{10}H_{21}$), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.94 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.38 (d, 1H, *J* = 15.6 Hz, H_α), 7.48 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 7.98 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 31.9, 68.2, 114.9 (2C), 118.9, 127.1, 128.8 (2C), 129.8 (2C), 130.3 (2C), 136.8, 138.9, 145.3, 161.5, 189.2, MS (EI) *m/z* ($M^{+\bullet}$ 426, Base Peak 223). Anal. calcd. for $C_{27}H_{35}BrO_2$: C, 75.94; H, 8.26; Found: C, 75.91; H, 8.24%

14c: (*E*)-1-(4- fluorophenyl)-3-(4-dodecyloxyphenyl)prop-2-en-1-one

Yield 93%; pale yellow solid; m. p. 82−83˚C; R_f = 0.84 (petroleum ether:ethyl acetate, 4:1), FT−IR (KBr, cm^{-1}): 1644, 1628, 1253, 1047, 1124, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz,−O−$(CH_2)_{11}$−C***H***$_3$), 1.29−1.50 (m, 18H, −O−CH_2−CH_2−(C***H***$_2)_9$−CH_3), 1.82 (qn, 2H, *J* = 7.2 Hz, −O−CH_2−C***H***$_2$−$C_{10}H_{21}$), 4.02 (t, 2H, *J* = 6.6 Hz, −O−C***H***$_2$−), 6.95 (d, 2H, *J* = 8.7 Hz, Ar$H_{a=a'}$), 7.19 (t, 2H, *J* = 8.7 Hz, Ar$H_{d=d'}$), 7.40 (d, 1H, *J* = 15.6 Hz, H_α), 7.61 (d, 2H, *J* = 8.7 Hz, Ar$H_{b=b'}$), 7.81 (d, 1H, *J* = 15.6 Hz, H_β), 8.07 (d, 2H, *J* = 8.7 Hz Ar$H_{c=c'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 31.9, 68.2, 114.9 (2C), 115.5, 115.8 (2C), 118.9, 127.2, 130.3 (2C), 130.9 (2C), 131.0, 145.0, 161.4, 188.9, MS (EI) *m/z* ($M^{+\bullet}$ 410, Base Peak 242). Anal. calcd. for $C_{27}H_{35}FO_2$: C, 78.99; H, 8.59; Found: C, 78.95; H, 8.56%

Brine shrimp Lethality Bioassay

The hatching tray was half filled with filtered bromine solution and then 50 mg eggs of brine shrimp Artemia salina (Leach) were sprinkled, lid was placed and incubation for hatching at 27 °C was allowed for two days. 4-Alkoxychalcones (**3a-14c**) test sample (20 mg) were dissolved in 2 ml of DMSO to prepare the stock solution. From the stock solution 500 µL, 50 µL and 5 µL were transferred to vials corresponding to 1000, 100 and 10 µg/mL respectively. 30 larvae were placed in each vial using a pasture pipette. The volume was adjusted to 5 ml by sea water. Incubation under illumination was done at 25−27 °C for 24 hours. The number of survivors were recounted and compared with other vials containing solvent and reference cytotoxic drug. The date was analyzed with the help of Finney computer program to determine LD_{50} values with 95% confidence intervals [38].

Prostate Cancer PC-3 Cell Line

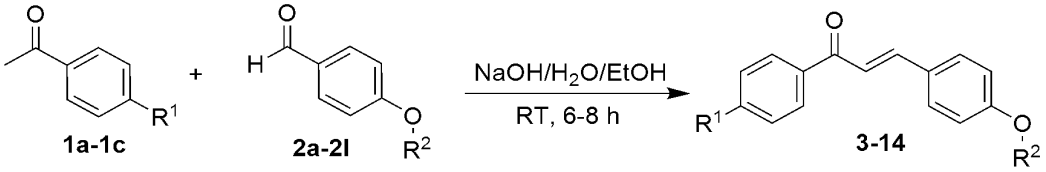
Cytotoxic activity of the synthesized compounds was evaluated in 96-well flat-bottomed micro plates by using the standard MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyl-tetrazolium bromide) colorimetric assay [39]. For this purpose, PC-3 cells (Prostate Cancer) were cultured in Dulbecco's Modified Eagle's Medium, supplemented with 5%

of fetal bovine serum (FBS), 100 IU/mL of penicillin and 100 µg/mL of streptomycin in 25 mL flask, and kept in 5% CO_2 incubator at 37 ^oC. Exponentially growing cells were harvested, counted with haemocytometer and diluted with a particular medium. Cell culture with the concentration of $1x10^5$ cells/mL was prepared and introduced (100 µL/well) into 96-well plates. After overnight incubation, medium was removed and 200 µL of fresh medium was added with different concentrations of compounds (1−100 µM). After 48 h, 50 µL MTT (2 mg/mL) was added to each well and incubated further for 4 hrs. Subsequently, 100 µL of DMSO was added to each well. The extent of MTT reduction to formazan within cells was calculated by measuring the absorbance at 570 nm, using a micro plate reader (Spectra Max plus, Molecular Devices, CA, USA). The cytotoxicity was recorded as concentration causing 50% growth inhibition (IC_{50}) for PC3.

Results and Discussion

The B-ring 4-alkoxychalcones (**3a-14c**) were synthesized by reacting 4′-substituted acetophenones (**1a-1c**) with 4-alkoxybenzaldehydes (**2a-2I**) [33] in the presence of ethanol/aq. NaOH at room temperature for about 6-8 hours (Scheme 1).

The target compounds were obtained in 91-96% yield. The structures of these chalcones were confirmed by their physical, spectral (IR, ^1H and ^{13}C NMR, Mass) and elemental analysis data. The electronic properties of the substituents at the 4-position of both the reactants did not affect the efficiency of the reaction. All the compounds were purified by simple recrystallization using ethanol as solvent and were found geometrically pure with *E*-configuration (J_{trans} = ~16 Hz) around double bond by ^{1}HNMR spectroscopy.



R^1 = Br, Cl, F; $R^2 = C_nH_{2n+1}$ with n = 1-12

3a: (R^1,R^2) = Br, CH_3	**7a**: (R^1,R^2) = Br, C_5H_{11}	**11a**: (R^1,R^2) = Br, C_9H_{19}
3b: (R^1,R^2) = Cl, CH_3	**7b**: (R^1,R^2) = Cl, C_5H_{11}	**11b**: (R^1,R^2) = Cl, C_9H_{19}
3c: (R^1,R^2) = F, CH_3	**7c**: (R^1,R^2) = F, C_5H_{11}	**11c**: (R^1,R^2) = F, C_9H_{19}
4a: (R^1,R^2) = Br, C_2H_5	**8a**: (R^1,R^2) = Br, C_6H_{13}	**12a**: (R^1,R^2) = Br, $C_{10}H_{21}$
4b: (R^1,R^2) = Cl, C_2H_5	**8b**: (R^1,R^2) = Cl, C_6H_{13}	**12b**: (R^1,R^2) = Cl, $C_{10}H_{21}$
4c: (R^1,R^2) = F, C_2H_5	**8c**: (R1,R^2) = F, C_6H_{13}	**12c**: (R^1,R^2) = F, $C_{10}H_{21}$
5a: (R^1,R^2) = Br, C_3H_7	**9a**: (R^1,R^2) = Br, C_7H_{15}	**13a**: (R^1,R^2) = Br, $C_{11}H_{23}$
5b: (R^1,R^2) = Cl, C_3H_7	**9b**: (R^1,R^2) = Cl, C_7H_{15}	**13b**: (R^1,R^2) = Cl, $C_{11}H_{23}$
5c: (R^1,R^2) = F, C_3H_7	**9c**: (R^1,R^2) = F, C_7H_{15}	**13c**: (R^1,R^2) = F, $C_{11}H_{23}$
6a: (R^1,R^2) = Br, C_4H_9	**10a**: (R^1,R^2) = Br, C_8H_{17}	**14a**: (R^1,R^2) = Br, $C_{12}H_{25}$
6b: (R^1,R^2) = Cl, C_4H_9	**10b**: (R^1,R^2) = Cl, C_8H_{17}	**14b**: (R^1,R^2) = Cl, $C_{12}H_{25}$
6c: (R^1,R^2) = F, C_4H_9	**10c**: (R^1,R^2) = F, C_8H_{17}	**14c**: (R^1,R^2) = F, $C_{12}H_{25}$

Scheme 1. Synthesis of new chalcones **3-14**

Cytotoxicity Studies

Brine Shrimp Lethality Bioassay

Brine shrimp lethality assay has extensively been used as a simple and useful tool for preliminary screening of toxicity of synthesized compounds as well as physiologically active plant extracts [34-36]. This general bioassay is not only rapid, it is also reliable. The results of this bioassay can be extrapolated for cell line toxicity and anti-tumor activity because a positive relationship between brine shrimp lethality and human carcinoma has been demonstrated [37]. Therefore, the cytotoxicity of the synthesized compounds (**3a-14c**) was determined by *in vivo* lethality to brine shrimp larvae. In the present study, Etoposide was used as standard cytotoxic drug. The results

revealed that fluoro substituted compounds **3a-7c**, **11c** and **13c** were highly toxic to brine shrimp larvae with LD_{50} values much lower than the LD_{50} values of the standard drug used as reference (Table 1). This highest degree of cytotoxicity is attributed to electromeric effect contributed by the fluoro group being situated at the *para*-position to the carbonyl group on aromatic ring. However, the remaining compounds demonstrated lower degree of cytotoxic activity (Table 1).

Table 1. Cytotoxicity, Brine Shrimp Lethality and PC3 cell lines of the 4-Alkoxychalcones **3−14**.

Compound		Substituents		Brine Shrimp Lethality	Cytotoxicity PC3 cell lines
		R^1	R^2	LD_{50} (µg/mL)	IC_{50} (µM)
3	**3a**	Br	CH_3	67	>100
	3b	Cl	CH_3	218	69
	3c	F	CH_3	0.01	29
4	**4b**	Br	C_2H_5	133	73
	4c	Cl	C_2H_5	47	>100
	4d	F	C_2H_5	0.056	72
5	**5a**	Br	C_3H_7	374	81
	5b	Cl	C_3H_7	12	39
	5c	F	C_3H_7	0.003	39
6	**6a**	Br	C_4H_9	1082	>100
	6b	Cl	C_4H_9	29	40
	6c	F	C_4H_9	0.042	57
7	**7a**	Br	C_5H_{11}	42179	>100
	7b	Cl	C_5H_{11}	221	67
	7c	F	C_5H_{11}	0.400	>100
8	**8a**	Br	C_6H_{13}	711	>100
	8b	Cl	C_6H_{13}	19	>100
	8c	F	C_6H_{13}	6.75	62
9	**9a**	Br	C_7H_{15}	112774	>100
	9b	Cl	C_7H_{15}	12.53	>100
	9c	F	C_7H_{15}	37.43	>100
10	**10b**	Br	C_8H_{17}	11	>100
	10c	Cl	C_8H_{17}	9.94	>100
	10d	F	C_8H_{17}	28.63	>100
11	**11a**	Br	C_9H_{19}	908	>100
	11b	Cl	C_9H_{19}	7.27	>100
	11c	F	C_9H_{19}	0.34	>100
12	**12a**	Br	$C_{10}H_{21}$	36	75
	12b	Cl	$C_{10}H_{21}$	4.5	>100
	12c	F	$C_{10}H_{21}$	16	>100
13	**13a**	Br	$C_{11}H_{23}$	71	>100
	13b	Cl	$C_{11}H_{23}$	28710	>100
	13c	F	$C_{11}H_{23}$	4.4	>100
14	**14a**	Br	$C_{12}H_{25}$	1237	74
	14b	Cl	$C_{12}H_{25}$	14	>100
	14c	F	$C_{12}H_{25}$	59	>100
ETO[a]				7.5	0.912
DOX[b]				-	

[a]ETO: Etoposide, [b] DOX: Doxorubinin.

***In vitro* Anticancer Screening**

All the newly synthesized compounds **3a-14c** were initially screened at the single concentration of 100 μM using the colorimetric MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] to test their *in vitro* cytotoxicity against human Prostate Cancer (PC-3) cell line. Doxorubinin was used as the reference drug in this study. The cytotoxicity of all the tested compounds was evaluated in terms of percent growth inhibition compared to untreated control cells. All the test compounds showed ≥70% inhibition and were retested by serial dilution from 100-20 μM. The results were expressed as IC_{50} (inhibitory concentration 50%), the concentration of the compound which inhibits the tumor cell growth by 50% of three independent experiments and the data are presented in Table 1. Careful inspection of the acquired cytotoxic data revealed that four compounds out of 36 tested compounds showed promising antiproliferative activity against the tested PC-3 cell line. This observation could be attributed to the missing synergistic effect that may result from combining the hydroxyl group at C-2 of phenol with the ketone structural feature. Most of the compounds showed low efficacy against human Prostate Cancer (PC-3) cell line with IC_{50} values range of 100-40 μM compared to IC_{50} value of standard drug DOX (0.912 μM) Table 1. However, human PC-3 cell line, proved to be sensitive toward compounds **3c**, **5b, 5c** and **6b** with IC_{50} concentration range of 29-40 μM compared to standard drug DOX (IC_{50} = 0.912 μM, respectively). Evidently, compounds having more electronegative halogen substituent at *para*-position of phenyl (R^1) and small alkoxy side chain at *para*-position of phenyl (R^2), retained the highest activity against the PC-3 cell line. This is attributed to the less power of more electronegative halogen substituents to donate the electrons mesomerically which makes the Michael acceptor functionality slightly more reactive towards cellular nucleophiles. Interestingly, increase in the alkyl side chain for increasing the lipophilic character of the synthesized compounds did not affect the activity too much. The results indicate that compounds **3a-14c,** although showed low efficacy against human Prostate Cancer (PC-3) cell line with IC_{50} value 29-40 μM compared to DOX IC_{50} (0.9 μM) are promising antitumor agents and excellent candidates for further research to solve the problems of tumor cell selectivity.

Conclusions

In conclusion, we have efficiently synthesized a series of 36 new 4-alkoxychalcones, evaluated their cytotoxic activity against *Artemia salina* and human Prostate Cancer (PC-3) cell line and found that compounds bearing strong electron withdrawing and moderately lipophilic alkoxy substituents exhibited higher cytotoxic activity. Among them flouro substituted compounds (**3c-7c**, **11c, 13c**) showed highest cytotoxic activity against brine shrimp with LD_{50} values much lower than the LD_{50} values of the standard drug and compounds (**3c**, **5b, 5c**, **6b**) showed good *in vitro* antiproliferative activity against PC-3 cell line with the IC_{50} values ranging from 29-40 μM. However, most of the other halogenated alkoxy chalcones were found to be less active/not active. The results demonstrate that novel halogenated alkoxy chalcones may be promising candidates for future anticancer research.

Acknowledgements-The authors AA and MMN are grateful to Higher Education Commission (HEC) of Pakistan for financial support. We are also thankful to Panjwani Center for Molecular Medicine and Drug Research, HEJ research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Pakistan for biological studies.

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