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SINTESIS DAN KARAKTERISASI SUATU SERI *p*-ALKOKSIASETOFENON MENGGUNAKAN METODE SPEKTROSKOPI (Synthesis and Characterization A Series of *p*-Alkoxyacetophenone using Spectroscopy Method)

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ABSTRACT

A series of *p*-Alkoxy Acetophenone have been synthesized using *para*-hydroxyacetophenone as starting material to give the target compounds (**3a**-**g**) with good yields ranging from 68.2% to 87.8%. The target compounds were fully characterized by infrared, ^{1}H NMR and ^{13}C NMR spectra.

Keywords: Synthesis, p-alkoxyacetophenone, para-hydroxyacetophenone

ABSTRAK

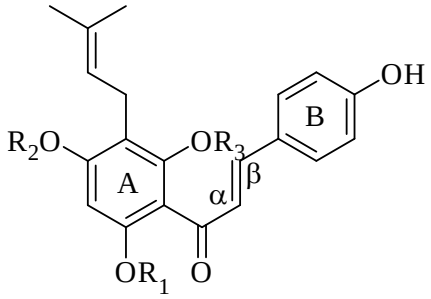
Suatu seri senyawa *p*-alkoksiasetofenon telah berhasil disintesis dengan menggunakan *para*-hidroksiasetofenon sebagai material awal dan memberikan senyawa target (**3a**-**g**) dengan rendemen yang baik antara 68,2% sampai 87,8%. Senyawa-senyawa target yang diperoleh telah dikarakterisasi menggunakan metode-metode spektroskopi seperti spektroskopi infra merah, ^{1}H NMR dan ^{13}C NMR.

Katakunci: Sintesis, p-alkoksiasetofenon, *para*-hidroksiasetofenon

1. INTRODUCTION

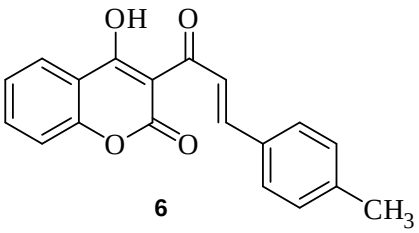
In recent years, design and synthesize a medicine or a pharmaceutical agent which will benefit humanity have been attempted by many researchers. Chalcone along with their analogues have drawn considerable attention of synthetic chemists, due to their potential use in medicinal chemistry. The natural and synthetic chalcone derivatives display a variety of biological activities against bacteria, fungi, viruses and tumours. The physiological, bacteriostatic and anti-tumour activities of chalcones lead to modification and screening of their analogues in search for novel therapeutic agents.

Xanthohumol **1** is the most naturally abundant prenylated chalcone. This compound has been isolated from hop cones of *Humulus lupulus* [1] and showed an interesting spectrum of pharmacological activities, such as apoptotic activity against different cell lines, anti-HIV agent, and inhibitor of prostate cancer [2],[3],[4],[5]. Xanthohumol and its derivatives **2**-**5** were also successfully synthesised by Vogel *et al.* (2008) and were evaluated the cytotoxicity and anti-oxidative activities [6]. All the tested derivatives showed remarkable cytotoxicity and antioxidant properties. Additionally, the results indicated that the variation of the hydroxyl group of ring A (concerning number and position) in xanthohumol derivatives effected the strength of the cytotoxicity in comparison to **1**.



1 $R_1 = CH_3$, $R_2 = H$; $R_3 = H$
2 $R_1 = H$, $R_2 = H$; $R_3 = H$
3 $R_1 = H$, $R_2 = CH_3$; $R_3 = H$
4 $R_1 = CH_3$, $R_2 = CH_3$; $R_3 = H$
5 $R_1 = H$, $R_2 = CH_3$; $R_3 = CH_3$

Hamdi *et al.* (2010), has synthesised a series of chalcone associated with the coumarin moiety and screened them against *Staphylococcus aureus* bacteria [7]. The coumarin-chalcone **6** was the most active derivative with IC_{50} value of 2.07 µM.



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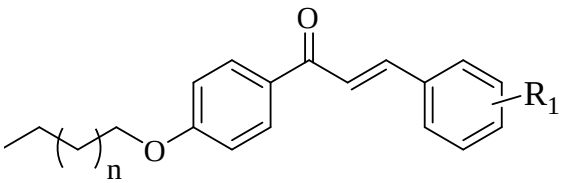

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The effect of natural or synthetic alkyl chains in these type of compounds has also been investigated thoroughly by many researchers [8], [9]. Due to the ability of lipophilic alkyl chains to disrupt microorganism cell wall [10], [11].

Recently, the synthesis of hydroxylated chalcone derivatives **7** with variable chain length (C_6, C_{10}, C_{12} and C_{14}) by treating benzaldehyde with 4-hydroxyacetophenone in the presence of potassium carbonate was investigated by Ngaini *et al.* (2012) [12]. All these derivatives were screened for antibacterial activity against *Escherichia coli* and were found to inhibit the growth of this strain in relevant concentrations. The results also

indicated that the presence of hydroxyl groups at *meta* position with C_6 alkyl chains has considerable effect on antimicrobial activities observed.

The synthesis of chalcone derivatives can be carried out *via* various synthetic procedures, including Claisen-Schmidt reaction, Baker-Venkataraman rearrangement method, Algar-Flynn-Oyamada and Suzuki coupling reaction. The Claisen–Schmidt condensation is a general method to synthesize chalcone derivatives and their analogues, which was used to synthesize novel chalcone derivatives in this study. It is a simple, straight-forward and fast procedure to prepare chalcones derivatives, *via* the condensation aromatic aldehydes with acetophenone derivatives in the presence of aqueous alkali media [13]. The base-catalyzed Claisen-Schmidt condensation have also been attempted by many synthetic chemists to synthesize chalcones. Detsi *et al.* (2009) have successfully synthesised chalcone and aurone derivatives with a Claisen-Schmidt reaction between appropriately substituted 2'-hydroxy-acetophenones and benzaldehydes in basic condition to give 41-88% yield of the final product [14]. In this research, we will prepare a series of *p*-alkoxyacetophenone with variable chain length (C_7, C_8, C_9, C_{10}, C_{12}, C_{14} and C_{19}) as starting material of chalcone derivatives. The assignments of the structures were analysed by spectroscopy IR, ^{1}H NMR as well as the ^{13}C NMR spectral data.

2. RESEARCH METHOD

2.1. General

All of the chemicals, including 5-bromosalicylaldehyde and 5- nitrosalicylaldehyde, used in this study were purchased from Sigma-Aldrich, USA without further purification. Stuart Scientific SMP1 apparatus were used to determine the melting point of synthesized compounds. The synthesized compounds purity were check by using TLC, performed on pre-coated Merck 60 GF_{254} silica gel plates (absorbent thickness, 0.25 mm). Nuclear Magnetic Resonance (NMR) spectra were recorded in acetone-d_6, with TMS as internal standard at 25^{o}C, using a Bruker Avance 500 and 300 MHz spectrometer. Chemical shifts were reported in ppm (δ) and coupling constant (*J*) are expressed in part per million and hertz, respectively. Column chromatographic separations were performed using silica gel (Merck Kieselgel 60, 70–230 mesh ASTM). HRESIMS spectra were performed using a Micro TOF-Q mass spectrometer. IR (KBr) spectra were recorded using a Perkin-Elmer system 2000 FT-IR spectrometer.

2.2 General procedure for the synthesis of p- alkyloxyphenyl-ethanone 3a-g

Various type of *n*-bromoalkane were reacted with *para*-hydroxyacetophenone in hot dimetylformamide with constant stirring. The reaction mixture was refluxed for 5 hours in the presence of sodium carbonate. The crude products obtained were poured into cold water to get 1-[4-(alkoxy)phenyl]-ethanone) and recrystallized from EtOAc/EtOH to get the pure crystalline compounds, **3a**-**g**.

2.2.1 Synthesis of 1-[4-(heptoxy)phenyl]-ethanone (3a)

Sodium carbonate **1** (1.3 g, 12.5 mmol) was slowly added to a solution of 4-hydroxyacetophenone **2** (0.7 g, 5 mmol) in dimethylformamide (100 mL). The solution was stirred at room temperature for 15 minutes. Bromoheptane (2 mL, 5 mmol) was then added dropwise to this mixture while stirring and the reaction was heated at reflux for 5 hours. The reaction mixture was then allowed to cool to room temperature for 40 minutes. The solution was then poured into 500 mL of an ice water mixture to get brownish precipitates. These precipitates were filtered and washed with cold water. Workup and recrystallization from EtOAc/EtOH (3:1) afforded **3a.**

2.2.2 Synthesis of 1-[4-(octyloxy)phenyl]-ethanone (3b)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (13.2 g, 125 mmol),bromooctane (9 mL, 50 mmol), and 4-hydroxyacetophenone **2** (6.8 g, 50 mmol) in dimethylformamide (250 mL), after purification, gave the title compound **3b**

2.2.3 Synthesis of 1-[4-(nonyloxy)phenyl]-ethanone (3c)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (13.2 g, 125 mmol), bromononane (10 mL, 50 mmol) and 4-hydroxyacetophenone **2** (6.8 g, 50 mmol) in dimethylformamide (250 mL), after purification, gave the title compound **3c**

2.2.4 Synthesis of 1-[4-(decyloxy)phenyl]-ethanone (3d)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (13.2 g, 125 mmol), bromodecane (10 mL, 50 mmol) and 4-hydroxyacetophenone **2** (6.8 g, 50 mmol) in dimethylformamide (250 mL), after purification, gave the title compound **3d**

2.2.5 Synthesis of 1-[4-(dodecyloxy)phenyl]-ethanone (3e)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (4.2 g, 40 mmol), bromododecane (4.8 mL, 17 mmol) and 4-hydroxyacetophenone **2** (2.3 g, 17 mmol) in dimethylformamide (125 mL), after purification, gave the title compound **3e**

2.2.6 Synthesis of 1-[4-(tetradecyloxy)phenyl]-ethanone (3f)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (13.2 g, 125 mmol), bromotetradecane (18 mL, 50 mmol) and 4-hydroxyacetophenone **2** (6.8 g, 50 mmol) in dimethylformamide (250 mL), after purification, gave the title compound **3f**

2.2.7 Synthesis of 1-[4-(nonadecyloxy)phenyl]-ethanone (3g)

Using the procedure described for the synthesis of **3a**, sodium carbonate **1** (0.8 g, 7.5 mmol), bromononadecane (1.0 g, 3 mmol) and 4-hydroxyacetophenone **2** (0.4 g, 3 mmol) in dimethylformamide (75 mL), after purification, gave the title compound **3g.**

3. RESULT AND DISCUSSION

3.1. Result

3.1.1 1-[4-(heptyloxy)phenyl]-ethanone (3a)

Colourless crystal. Yield: 77.4%. IR KBr (v cm^{-1}): 2928 (CH-aliphatic), 1673 (C=O), 1603, 1576 (C=C-aromatic), 1249, 1175 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.91 (2H, *d*, *J* = 9.0 Hz), 6.91 (2H, *d*, *J* = 9.0 Hz), 4.01 (2H, *t*, *J* = 6.5 Hz), 2.54 (3H, *s*), 1.77-1.82 (2H, *m*), 1.42-1.48 (2H, *m*), 1.29-1.38 (6H, *m*), 0.89 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.1 (C=O), 163.5 (C-4'), 130.6 (C-2',6'), 130.1 (C-1'), 114.5 (C-3',5'), 68.6 (C-1''), 31.7 (C-5''), 29.1 (C-2''), 29.0 (C-4''), 26.3 (C-2), 25.9 (C-3''), 22.1 (C-6''), 14.4 (C-7'').

3.1.2. 1-[4-(octyloxy)phenyl]-ethanone (3b)

Colourless crystal. Yield: 70.9%. IR KBr (v cm^{-1}): 2928 (CH-aliphatic), 1676 (C=O), 1603, 1577 (C=C-aromatic), 1250, 1172 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.87 (2H, *d*, *J* = 9.0 Hz), 6.87 (2H, *d*, *J* = 9.0 Hz), 3.95 (2H, *t*, *J* = 6.5 Hz), 2.48 (3H, *s*), 1.78-1.82 (2H, *m*), 1.39-1.44 (2H, *m*), 1.27-1.32 (8H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 196.7 (C=O), 163.4 (C-4'), 130.8 (C-2',6'), 130.1 (C-1'), 114.4 (C-3',5'), 68.5 (C-1''), 32.1 (C-6''), 30.0 (C-2''), 29.7 (C-4''), 29.4 (C-5''), 26.3 (C-2), 25.9 (C-3''), 23.0 (C-7''), 14.4 (C-8'').

3.1.3. 1-[4-(nonyloxy)phenyl]-ethanone (3c)

Colourless crystal (1.1 g, 84.7%). IR KBr (v cm^{-1}): 2926 (CH-aliphatic), 1671 (C=O), 1601, 1574 (C=C-aromatic), 1248, 1177 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.90 (2H, *d*, *J* = 9.0 Hz), 6.90 (2H, *d*, *J* = 9.0 Hz), 4.00 (2H, *t*, *J* = 6.5 Hz), 2.53 (3H, *s*), 1.77-1.83 (2H, *m*), 1.42-1.47 (2H, *m*), 1.30-1.36 (2H, *m*), 1.26-1.32 (8H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.2 (C=O), 163.5 (C-4'), 130.9 (C-2',6'), 130.5 (C-1'),

114.5 (C-3',5'), 68.6 (C-1''), 32.3 (C-7''), 29.9 (C-2''), 29.7 (C-4''), 29.6 (C-5''), 29.5 (C-6''), 26.7 (C-2), 26.4 (C-3''), 23.1 (C-8''), 14.5 (C-9'').

3.1.4. 1-[4-(decyloxy)phenyl]-ethanone (3d)

Orange pale solid (0.9 g, 75.0%). IR KBr (v cm^{-1}): 2921 (CH-aliphatic), 1675 (C=O), 1605, 1578 (C=C-aromatic), 1248, 1174 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.91 (2H, *d*, *J* = 8.5 Hz), 6.91 (2H, *d*, *J* = 8.5 Hz), 4.01 (2H, *t*, *J* = 6.5 Hz), 2.54 (3H, *s*), 1.78-1.82 (2H, *m*), 1.43-1.47 (2H, *m*), 1.32-1.37 (2H, *m*), 1.23-1.29 (8H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.2 (C=O), 163.5 (C-4'), 131.0 (C-2',6'), 130.9 (C-1'), 114.5 (C-3',5'), 68.7 (C-1''), 32.3 (C-8''), 29.9 (C-2'',4''), 29.7 (C-5''), 29.6 (C-6''), 29.5 (C-7''), 26.4 (C-3''), 26.2 (C-2), 23.1 (C-9''), 14.5 (C-10'').

3.1.5. 1-[4-(dodecyloxy)phenyl]-ethanone (3e)

Yellow pale solid (1.3 g, 87.8%). IR KBr (v cm^{-1}): 2920 (CH-aliphatic), 1676 (C=O), 1601, 1576 (C=C-aromatic), 1251, 1170 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.92 (2H, *d*, *J* = 9.0 Hz), 6.91 (2H, *d*, *J* = 9.0 Hz), 4.01 (2H, *t*, *J* = 6.5 Hz), 2.55 (3H, *s*) 1.78-1.83 (2H, *m*), 1.44-1.47 (2H, *m*), 1.31-1.36 (2H, *m*), 1.25-1.30 (14H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.2 (C=O), 163.5 (C-4'), 131.0 (C-2',6'), 130.5 (C-1'), 114.5 (C-3',5'), 68.7 (C-1''), 32.3 (C-10''), 30.1 (C-2''), 30.0 (C-4''), 29.9 (C-5'',6''), 29.7 (C-7'',8''), 29.5 (C-9''), 26.4 (C-3''), 26.3 (C-2), 23.1 (C-11''), 14.5 (C-12'').

3.1.5. 1-[4-(tetradecyloxy)phenyl]-ethanone (3f)

Yellow pale solid (1.4 g, 84.9%). IR KBr (v cm^{-1}): 2917 (CH-aliphatic), 1676 (C=O), 1606, 1578 (C=C-aromatic), 1253, 1174 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.92 (2H, *d*, *J* = 9.0 Hz), 6.92 (2H, *d*, *J* = 9.0 Hz), 4.01 (2H, *t*, *J* = 6.5 Hz), 2.55 (3H, *s*), 1.76-1.82 (2H, *m*), 1.43-1.47 (2H, *m*), 1.31-1.36 (2H, *m*), 1.25-1.30 (14H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.1 (C=O), 163.5 (C-4'), 130.9 (C-2',6'), 130.3 (C-1') 114.5 (C-3',5'), 68.6 (C-1''), 32.3 (C-12''), 30.1 (C-2''), 30.0 (C-4''), 29.9 (C-5''-8''), 29.8 (C-9''-10''), 29.5 (C-11''), 26.6 (C-2), 26.4 (C-3''), 23.1 (C-13''), 14.5 (C-14'').

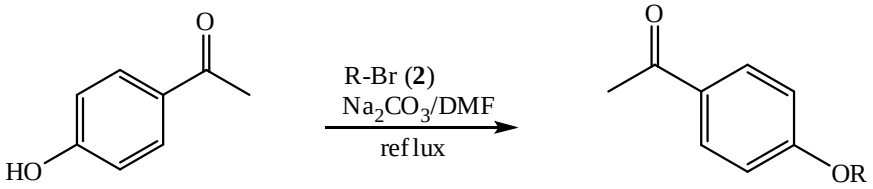
3.1.6. 1-[4-(nonadecyloxy)phenyl]-ethanone (3g)

White pale solid (1.4 g, 68.2%). IR KBr (v cm^{-1}): 2919 (CH-aliphatic), 1676 (C=O), 1604, 1575 (C=C-aromatic), 1247, 1172 (C-O); ^{1}H NMR (δ, ppm, 500 MHz, $CDCl_3$): 7.92 (2H, *d*, *J* = 9.0 Hz), 6.92 (2H, *d*, *J* = 9.0 Hz), 4.01 (2H, *t*, *J* = 6.5 Hz), 2.55 (3H, *s*), 1.77-1.82 (2H, *m*), 1.42-1.46 (2H, *m*), 1.30-1.35 (2H, *m*), 1.22-1.27 (28H, *m*), 0.88 (3H, *t*, *J* = 6.5 Hz); ^{13}C NMR (δ, ppm, 75 MHz, $CDCl_3$): 197.3 (C=O), 163.5 (C-4'), 131.0 (C-2',6'), 130.4 (C-1'),

114.5 (C-3',5'), 68.7 (C-1''), 32.3 (C-17''), 30.1 (C-2''-10''), 30.0 (C-11'',12''), 29.9 (C-13'',14''), 29.7 (C-15''), 29.5(C-16''), 26.7 (C-2), 26.4 (C-3''), 23.1 (C-18''), 14.5 (C-19'').

3.2. Discussion

A series of seven *p*-Alkoxyacetophenone (**3a–g**) were prepared by condensing substituted benzaldehydes and appropriately substituted acetophenone in equimolar ratio to form the expected compounds, using potassium hydroxide as a catalyst (Scheme 1). In this study, *p*-alkoxy acetophenones **3a**-**g** were prepared by reacting *p*-hydroxy acetophenones with *n*-bromoalkane in good yields (68.2-87.8%). The synthesized compounds **3a-g** were characterized by infrared, ^{1}H NMR and ^{13}C NMR spectra. The IR absorption (Fig. 1) of representative *p*-alkoxy acetophenone from *p*-hydroxy acetophenone, 1-[4-(heptoxy)phenyl]-ethanone **3a** clearly indicated the presence of aliphatic (CH), carbonyl (C=O), C-C double bonds aromatics (C=C), and alkoxy (C-O-C) groups in the structure due to their characteristic bands at 2928, 2852, 1673, 1603, 1576, 1249 and 1175 cm^{-1} respectively. The ^{1}H NMR spectrum of **3a** (Fig. 2; Table 1) displayed the presence of long alkyl chains in the structure, as revealed by resonances at 0.89, 1.32-2.54 and 4.01 ppm.



p-hydroxyacetophenone (**1**)

3a-g

a R=C_7H_{15} ; **b** R=C_8H_7;
c R=C_9H_{19} ; **d** R=$C_{10}H_{21}$;
e R=$C_{12}H_{25}$; **f** R=$C_{14}H_{29}$;
g R=$C_{19}H_{39}$

Scheme 1 Synthesis of *p*-alkoxy acetophenone **3a**-**g**

These assignments were complemented by the ^{13}C NMR spectra which exhibited signals at 14.4–68.6 ppm indicating the presence of carbon chains. Selected IR, ^{1}H NMR and ^{13}C NMR spectral data are presented in Table 2.

Table 1. Comparative yields, important IR, ^{1}H NMR and ^{13}C NMR signals of *p*-alkoxy acetophenone **3a**-**g**

Compd.	R	Yield (%)	IR (v, cm^{-1})	^{1}H NMR[a] δ_H (ppm); mult; *J* (Hz)	^{13}C NMR[b] δ_C (ppm)
3a	C_7H_{15}	77.4	2928 (CH_3) 1673 (C=O) 1603, 1576 (C=C) 1249, 1175 (C-O)	0.89 *t* (6.5, H-7''), 2.54 *s* (H-2) and 4.01 *t* (6.5, H-1'')	14.4 (C-7''), 68.6 (C-1''), 163.5 (C-4'), 197.1 (C-1)
3b	C_8H_{17}	70.9	2928 (CH_3) 1676 (C=O) 1603, 1577 (C=C) 1250, 1172 (C-O)	0.88 *t* (6.5, H-8''), 2.48 *s* (H-2) and 3.95 *t* (6.5, H-1'')	14.4 (C-8''), 68.5 (C-1''), 163.4 (C-4'), 196.7 (C-1)
3c	C_9H_{19}	84.7	2926 (CH_3) 1671 (C=O) 1601, 1574 (C=C) 1248, 1177 (C-O)	0.88 *t* (6.5, H-9''), 2.53 *s* (H-2) and 4.00 *t* (6.5, H-1'')	14.5 (C-9''), 68.6 (C-1''), 163.5 (C-4'), 197.2 (C-1)
3d	$C_{10}H_{21}$	75.0	2921 (CH_3) 1675 (C=O) 1605, 1578 (C=C) 1248, 1174 (C-O)	0.88 *t* (6.5, H-10''), 2.54 *s* (H-2) and 4.01 *t* (6.5, H-1'')	14.5 (C-10''), 68.7 (C-1''), 163.5 (C-4'), 197.2 (C-1)
3e	$C_{12}H_{25}$	87.8	2920 (CH_3) 1676 (C=O) 1601, 1576 (C=C) 1251, 1170 (C-O)	0.88 *t* (6.5, H-12''), 2.55 *s* (H-2) and 4.01 *t* (6.5, H-1'')	14.5 (C-12''), 68.7 (C-1''), 163.5 (C-4'), 197.2 (C-1)
3f	$C_{14}H_{29}$	84.9	2917 (CH_3) 1676 (C=O) 1606, 1578 (C=C) 1253, 1174 (C-O)	0.88 *t* (6.5, H-14''), 2.55 *s* (H-2) and 4.01 *t* (6.5, H-1'')	14.5 (C-14''), 68.6 (C-1''), 163.5 (C-4'), 197.1 (C-1)
3g	$C_{19}H_{39}$	68.2	2919 (CH_3) 1676 (C=O) 1604, 1575 (C=C) 1247, 1172 (C-O)	0.88 *t* (6.5, H-19''), 2.55 *s* (H-2) and 4.01 *t* (6.5, H-1'')	14.5 (C-19''), 68.7 (C-1''), 163.5 (C-4'), 197.3 (C-1)

[a]500 MHz, $CDCl_3$; [b] 125 MHz, $CDCl_3$

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