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Preliminary communication

Synthesis and antinociceptive activity of capsinoid derivatives

G.-J. He [a,b], X.-L. Ye [c], X. Mou [a], Z. Chen [a], X.-G. Li [a,*]

[a] Chemistry Institute of Pharmaceutical Resources, School of Pharmaceutical Science, Southwest University, Chongqing 400716, China
[b] Department of Biology and Environment Engineering, Guiyang School, Guizhou 550005, China
[c] School of Life Sciences, Southwest University, Chongqing 400715, China

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ABSTRACT

According to the data of structural identification, six capsinoids or their derivatives were successfully synthesized to test for their analgesic activity. Three of them were capsinoids with different acyl chain compared with capsaicin after substitution of ester for amide at C_1 position. The other three could be described as capsinoid derivatives with different alkoxy chain, compared with capsaicin after substitution of ester for amide at C_1 position and alkoxy for hydroxy at C_4 position and synthesis of them was reported first. Compared with capsaicin, experiment results about pungency showed that capsinoids and their derivatives synthesized were all no or only slight pungent; that is, capsinoid derivates synthesized still have the same advantage of nonpungency with capsinoid. Relation between analgesic activity and molecular structure of compounds synthesized was also reported first, which would facilitate finding capsinoid derivatives owning excellent analgesic activity. The experiment results about analgesic activity showed that capsinoids displayed moderate analgesia effect and their antinociceptive activity decreased with the elongation of acyl chain at C_1 position; that antinociceptive activities of capsinoid derivatives synthesized were much stronger not only than those of indomethacin but also than those of their precursor (vanillyl decanoate), which increased with elongation of alkoxyl chain at C_4 position. Especially 4-hexyloxyl-3-methoxybenzyl decanoate showed the best antinociceptive activity in synthesized compounds, which was 9-fold higher than its precursor (vanillyl decanoate) and 6-fold higher than that of indomethacin.

1. Introduction

Capsaicinoid (CAP) is a pungent principal of capsicum plants [1,2] and it has various physiological activities [3,4], such as analgesia, weight loss and detoxification, etc. However, its strong pungency and nociceptive activity limit its application in food or medicine fields. A novel group of compounds, capsinoids including capsiate, dihydrocapsiate, and nordihydrocapsiate, have been isolated from the fruits of a sweet cultivar of pepper, CH-19 Sweet (*Capsicum annuum* L.) [5,6]. The fundamental chemical structure of capsinoids is an aliphatic hydroxyl group in vanillyl alcohol with a fatty acid. Capsinoids bear a marked structural resemblance to capsaicinoids, except for the central linkage; that is, an amide moiety is found in capsaicinoids, and ester moiety is in capsinoids. Despite the structural similarity between capsinoid and capsaicinoid, the former has no or only slight pungency and less harmful stimulation [6]. Capsinoids own physiological functions similar to those of capsaicinoids. Ohnuki [7] have reported that the intake of a nonpungent pepper containing natural capsinoids raised human skin temperature and promoted human energy metabolism, and suppressed fat accumulation without marked perspiration or languidness. Such characteristics make it potential to be widely used in food or medicine [8]. The yield of CH-19 Sweet and the content of capsinoid in it are too low to meet with the market need, so chemical synthesis becomes a main way to obtain materials owning function similar to capsinoids.

A capsinoid was synthesized by the lipase-catalyzed esterification of vanillyl alcohol with fatty acid derivatives in an organic solvent [9]. However, there was no report about the alkoxyl modification for capsinoid and the relationship between the structure and analgesic activity of capsinoid or capsinoid derivatives at present.

In the following study, several homologues of capsinoid or their derivates having various acyl chain length at C_1 position or alkoxyl chain length at C_4 position were synthesized chemically to evaluate the effect of substituted group on the pungency and the analgesic activity.

Abbreviations: C.L., confidence limits; MPP, the concentrations having a moderate pain-producing potency; RPP, relative pain-producing potency.

* Corresponding author. Tel./fax: +86 23 68250728.
E-mail addresses: xuegangli2000@yahoo.com.cn, heguoju78@163.com (X.-G. Li).

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2. Chemistry

With vanillyl alcohol as lead compound, caprylyl chloride, decanoyl chloride or lauroyl chloride as acylating agent, under strict control of reaction conditions, capsinoid compared with capsaicin after substitution of ester for amide at C_1 position, i.e. vanillyl caprylate (A in Fig. 1), vanillyl decanoate (B in Fig. 1), vanillyl laurate (C in Fig. 1), were synthesized according to Fig. 1. In addition, the chemistry reaction between vanillyl alcohol and corresponding alkyl bromide took place and their product was intermediate of 4-alkoxy-3-methoxybenzyl alcohol, then capsinoid derivatives compared with capsaicin after substitution of ester for amide at C_1 position and alkoxy for hydroxy at C_4 position were obtained by acylation reaction of intermediate with decanoyl chloride, i.e. 4-ethoxy-3-methoxybenzyl decanoate (D in Fig. 1), 4-butoxy-3-methoxybenzyl decanoate (E in Fig. 1), 4-hexyloxy-3-methoxybenzyl decanoate (F in Fig. 1) according to Fig. 1. Synthesis of D–F was reported first.

3. Pharmacology

Healthy Kunming mice of both genders (20 ± 2 g, 7 weeks old) were purchased from Laboratory Animal Centre of Chongqing Medical University. Animal certificate No. was 0001802, and license No. was scxk (Yu) 20020004. Mice were housed in stainless cages in a room with controlled temperature ($23 \pm 2\,^{\circ}C$) and humidity (40–60%) and a 12 h light/dark cycle. The protocol complied with the guidelines of Chongqing City Laboratory Animal Administration Committee of China for the care and use of laboratory animals. Then animals were kept under observation for 7 days to detect the effect of capsinoids and their derivatives on analgesic activity and pungent potency.

3.1. Evaluation of the potency of pungency

The wiping test [10] was performed to evaluate the pungency potency. Briefly, capsaicin and six compounds synthesized were dissolved by 10% Tween-80 aqueous solution in successive twofold dilutions. Each dilution was dropped into the right eye (vehicle being administered to the left eye as negative control) of KM rats, and the total number of protective movements (scratching, wiping of the eye with the foreleg) was counted for 30 min. Each concentration was applied to a total of 6 rats (half male and half female), and a dose–response curve was obtained from the mean value of each group. MPP (the concentrations having a moderate pain-producing potency) were calculated from the dose–response curve; that is, the concentration inducing equal reactions of 32 scratches (the median response induced by CAP) was recorded. On the basis of the MPP values obtained, RPP (relative pain-producing potency) values were determined with respect to the pain-producing potency of CAP, which was taken as 1000.

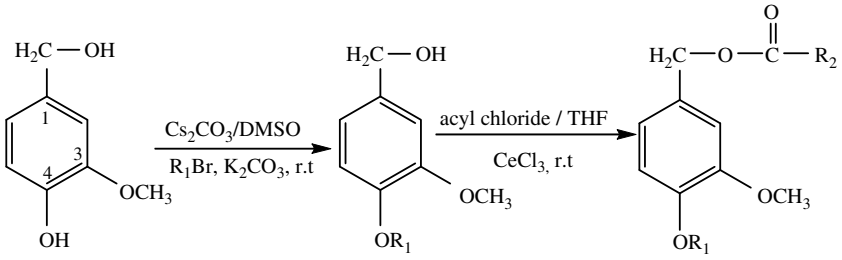
3.2. Evaluation of antinociceptive effects

According to the method [11], antinociceptive tests were carried out in half male and half female mice. Capsaicin and six compounds synthesized were dissolved by 10% Tween-80 aqueous solution in successive twofold dilutions. Each group included eight mice fed with food and water randomly. The test solution was administered by subcutaneous injection with single dose of 0.2 mL (indomethacin and vehicle administered as control). After 20 min, 0.2 mL of 0.7% acetic acid was injected intraperitoneally to induce writhing. Then the mice were placed in separate clear glass cages and the number of writhes was counted for 30 min after acetic acid injection, a writhe being defined as a sequence of arching of the back, followed by pelvic rotation and hind limb extension. According to the experiment results, ED_{50} values were obtained at last.

4. Results and discussion

4.1. Synthesis of compounds

The spectral data and other characteristic parameters of compounds A–F are shown in Section 6.2. From the IR data, we could see that diagnostic IR absorbance of phenolic hydroxyl bond, ester bond emerged in the IR spectra of compounds A–C and only



		R_1	R_2
A	Vanillyl caprylate	H	$^{7}\,^{6\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_4CH_2CH_3$
B	Vanillyl decanoate	H	$^{9}\,^{8\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_6CH_2CH_3$
C	Vanillyl laurate	H	$^{11}\,^{10\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_8CH_2CH_3$
D	4-ethoxy-3-methoxybenzyl decanoate	$^{2'}\,^{1'}$ -CH_2CH_3	$^{9}\,^{8\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_6CH_2CH_3$
E	4-butoxy-3-methoxybenzyl decanoate	$^{4'\sim2'}\,^{1'}$ -$(CH_2)_3CH_3$	$^{9}\,^{8\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_6CH_2CH_3$
F	4-hexyloxy-3-methoxybenzyl decanoate	$^{6'\sim2'}\,^{1'}$ -$(CH_2)_5CH_3$	$^{9}\,^{8\sim3}\,^{2}\,^{1}$ -$CH_2(CH_2)_6CH_2CH_3$

Fig. 1. Synthesis of capsinoid derivatives.

ester bond in the IR spectra of compounds D–F. Compared with compounds A–C's ^{1}H NMR data, the peak data of Ph-OH disappeared and the peak data of alkoxy hydrogen emerged in the ^{1}H NMR data of compounds D–F. All spectral data could be analyzed reasonably by their molecular structures. So, we concluded that compounds A–F were synthesized successfully.

4.2. Evaluation of the pungency for compounds synthesized

Relative pungent potency of compounds synthesized was listed in Table 1. According to evaluation method of pungency potency, those concentrations inducing equal reactions of 32 scratchings must be found, before MPP values were obtained during the experiment. The MPP value of capsaicin was 0.099 mg/mL, and its RPP value was defined as 1000; that is, 0.099 mg/mL of capsaicin could make mice scratch 32 times in 30 min. During the experiment, six compounds synthesized were undiluted by solvent and dropped directly into rats' eyes, the total number of protective movements of rats for six compounds could not reach 32 times. According to the results of Table 1, the MPP value of compounds synthesized was 10 000-fold higher than that of capsaicin. It indicated that compounds synthesized were no or only slight pungent compared with capsaicin after substitution of ester for amide at C_1 position.

For compounds A–C, the scratching times in 30 min decreased with the elongation of the acyl chain lengths at C_1 position. It indicated that the pungency was weakened correspondingly.

For compounds D–F, the scratching times were only 4, 8 and 11, respectively, while those of their precursor (compound B) were 25 times. Therefore, the pungency of D–F would be weaker than that of compound B. It suggested the substitution of alkoxy for hydroxy at C_4 position make the scratching times decrease greatly. As a result, 4-alkoxyl-3-methoxybenzyl decanoates had no pungency, compared with capsaicin; that is, capsinoid derivates synthesized still remain with the same nonpungent property with capsinoid. Yet there was an increasing trend in pungency relatively for compounds D–F with elongation of alkoxyl chain at C_4 position.

4.3. Experiment result of antinociceptive effect for synthesized compounds

Using indomethacin as a reference compound, the antinociceptive effects of compounds synthesized are listed in Table 2. All mice treated with these compounds showed a dose-related decrease in writhing counts induced by acetic acid. Writhing was most pronounced for 30 min following the administration of acetic acid, gradually subsiding after having reached a peak in the first 10–15 min.

In general, ED_{50} values of compounds A–C were slightly higher than those of indomethacin, and displayed moderate analgesia effect. And their antinociceptive activity decreased with the elongation of acyl chain at C_1 position.

Table 1
The relative pungent potency of substances synthesized.

Compound	Scratching times in 30 min ($x \pm s$)	MPP (mg/mL)	RPP
Capsaicin	$32 \pm 4.8^{**}$	0.099	1000
A	$28 \pm 2.5^{**}$	[a]	–
B	$25 \pm 1.9^{**}$	[a]	–
C	$22 \pm 1.2^{**}$	[a]	–
D	$4 \pm 0.4^{**}$	[a]	–
E	$8 \pm 0.8^{**}$	[a]	–
F	$11 \pm 1.2^{**}$	[a]	–

[a] Treatment with pure compounds (purity of more than 97%); $^{**}p < 0.01$ compared with capsaicin; –: relative nonpungency compared with capsaicin.

Table 2
Antinociceptive effects of synthesized compounds on acetic acid-induced writhing in mice.

Compound	ED_{50} (95% C.L.)[a] (mg/kg)	Potency ratio
Indomethacin	10.08 ± 0.86	1.00
A	12.61 ± 1.24	0.80
B	15.60 ± 1.40	0.65
C	19.42 ± 1.08	0.52
D	3.92 ± 0.25	2.57
E	3.16 ± 0.18	3.19
F	1.84 ± 0.11	5.89

[a] ED_{50} and 95% confidence limits were calculated by means of SPSS 10.0 statistical software.

While ED_{50} values of compounds D-CF were much lower than not only their precursor (compound B) but also that of indomethacin; that is, their antinociceptive effect is better than not only their precursor but also indomethacin, so they showed excellent antinociceptive activity. With the alkoxyl chain of derivates prolonging, the ED_{50} would be declined. Especially, the ED_{50} of 4-hexyloxyl-3-methoxybenzyl decanoate was one sixth of that of indomethacin and one ninth of that of compound B. It indicated that the antinociceptive activity of capsinoid derivates increased with the elongation of alkoxyl chain at C_4 position, which was stronger than that of indomethacin and that of their precursor.

5. Conclusion

According to the data of structural identification, capsinoids and their derivates were synthesized successfully. Pungent results showed that capsinoid and its derivatives were no or only slight pungent compared with capsaicin after substitution of ester for amide at C_1 position. Antinociceptive experiment suggested that capsinoid derivatives had a stronger antinociceptive activity after the substitution of alkoxy for hydroxy at C_4 position compared with capsinoid, which increased with elongation of alkoxyl chain. 4-Hexyloxyl-3-methoxybenzyl decanoate showed the best antinociceptive activity in synthesized compounds and its antinociceptive activity was 6-fold higher than that of indomethacin and 9-fold higher than its precursor (vanillyl decanoate).

6. Materials and methods

6.1. Chemicals and apparatus

Capsaicin (purity of more than 99%) was provided by Chemistry Institute of Pharmaceutical Resources of Southwest University in China (Chongqing, China); vanillyl alcohol was purchased from Sigma–Aldrich Japan K.K. (Japan). Other reagents were of A.R. grade, purchased from Chongqing Chemical Reagent Company (Chongqing, China).

UV, IR, ^{1}H NMR and TLC were used to identify the structures of compounds A–F. ^{1}H NMR was recorded on a Bruker DPX400 spectrometer with TMS as internal standard. IR data were obtained through Model Perkin Elmer IR spectrometer and UV data through Model Hitachi U-1800 UV spectrometer. Elemental analysis was performed on Model Perkin Elmer 240 element analyzer within ±0.4% of the theoretical values. TLC with mixtures of petroleum (60–90 °C) and ethyl acetate as developer was used to identify the compounds synthesized, performed on silica gel-GF_{254} thin layer with separated compounds visualized at 254 nm under a UV lamp.

6.2. Synthesis of capsinoids and capsinoid derivates

The synthesis route of capsinoids and capsinoid derivatives is shown in Fig. 1.

6.2.1. Vanillyl caprylate (A in Fig. 1)

The synthesis method made reference to literature [12]. Under a nitrogen atmosphere, to a solution of vanillyl alcohol (1.62 mM) in dry THF (8 mL), caprylyl chloride (1.62 mM) and $CeCl_3$ (0.081 mM) were added. After stirring at room temperature for 12 h, the reaction was worked up by removal of the solvent, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ (ca. 50 mL each). The organic phase was washed with anhydrous Na_2SO_4 and evaporated. Then the residue was purified by gravity column chromatography on silica gel (petroleum ether–ethyl acetate, 7:2, V/V) to give 350 mg (77%) of vanillyl caprylate as a colourless oil. UV (CH_3OH) λ_{max} (log ε): 281 (2.22), 238 (2.77) nm; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, $J = 7$ Hz, 3H, 1-CH_3), 1.22–1.33 (m, 8H, 3–6-$(CH_2)_4$), 1.63 (m, 2H, 2-CH_2), 2.33 (t, $J = 7.6$ Hz, 2H, 7-CH_2), 3.90 (s, 3H, $ArOCH_3$), 5.03 (s, 2H, $ArCH_2O$), 5.70 (s, 1H, ArOH), 6.86–6.90 (m, 3H, 3ArH). IR (primary absorption apex, KBr pellet, cm^{-1}) ν: 3445, 2925, 2857, 1733, 1614, 1520, 1464, 1434, 1382, 1275, 1234, 1036, 853, 819, 743, 724; Anal. Calcd for $C_{16}H_{24}O_4$: C 68.54, H 8.63; found C 68.46, H 8.61.

6.2.2. Vanillyl decanoate (B in Fig. 1)

Compound B was prepared using the similar method as used for A, yet difference from the latter was that reactant caprylyl chloride was substituted by decanoyl chloride and the residue containing vanillyl decanoate was purified by gravity column chromatography on silica gel (petroleum ether–ethyl acetate, 3:1) to give 357 mg (71%) of vanillyl caprylate as a colourless oil. UV (CH_3OH) λ_{max} (log ε): 281 (2.34), 240 (2.59) nm; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, $J = 7.0$ Hz, 1-CH_3), 1.25–1.27 (m, 12H, 3–8-$(CH_2)_6$), 1.63 (q, $J = 7.2$ Hz, 2H, 2-CH_2), 2.32 (t, $J = 7.6$ Hz, 2H, 9-CH_2), 3.88 (s, 3H, OCH_3), 5.05 (s, 2H, $ArCH_2O$), 5.70 (s, 1H, ArOH), 6.86–6.91 (m, 3H, 3ArH); IR (primary absorption apex, KBr pellet, cm^{-1}) ν: 3445, 2926, 2856, 1733, 1614, 1560, 1516, 1464, 1435, 1381, 1277, 1230, 1036, 853, 819, 744, 723; Anal. Calcd for $C_{18}H_{28}O_4$: C 70.09, H 9.15; found C 69.97, H 9.16.

6.2.3. Vanillyl laurate (C in Fig. 1)

Compound C was also prepared using the similar method as used for A, yet difference from the latter was that reactant caprylyl chloride was substituted by lauroyl chloride; that the residue containing vanillyl laurate was purified by gravity column chromatography on silica gel (petroleum ether–ethyl acetate, 2:1) to give 388 mg (72%) products as a colourless oil. UV (CH_3OH) λ_{max} (log ε): 280 (2.39), 239 (2.77) nm; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, $J = 7.0$ Hz, 3H, 1-CH_3), 1.24–1.29 (m, 16H, 3–10-$(CH_2)_8$), 1.62 (m, 2H, 2-CH_2), 2.33 (t, $J = 7.6$ Hz, 2H, 11-CH_2), 3.88 (s, 3H, $ArOCH_3$), 5.03 (s, 2H, $ArCH_2$), 5.70 (s, 1H, ArOH), 6.86–6.90 (m, 3H, 3ArH); IR (primary absorption apex, KBr pellet, cm^{-1}) ν: 3445, 2926, 2855, 1733, 1615, 1516, 1464, 1434, 1383, 1275, 1233, 1036, 854, 817, 742, 723; Anal. Calcd for $C_{20}H_{32}O_4$: C 71.39, H 9.59; found C 71.33, H 9.61.

6.2.4. 4-Ethoxy-3-methoxybenzyl decanoate (D in Fig. 1)

Under a nitrogen atmosphere, the following substances were added to a round-bottomed flask in the sequence: anhydrous DMSO (5.0 mL), Cs_2CO_3 (0.1 mM), K_2CO_3 (2.0 mM), vanillyl alcohol (1.0 mM), ethyl bromide (1.5 mM), molecular sieve (200 mg). After stirring at room temperature for 15 h, isopropyl ether (100 mL) was added to play a role in dilution. Mixture in flask was filtered and was washed in water and dehydrated with anhydrous Na_2SO_4. After evaporation, the reside was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 5:2) to get a colourless oil (87%) of 4-ethoxy-3-methoxybenzyl alcohol. ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, $J = 7$ Hz, 3H, 1′-CH_3), 3.42 (q, $J = 6.9$ Hz, 2H, 2′-CH_2), 3.78 (s, 3H, OCH_3), 3.91 (s, 2H, $ArCH_2O$), 4.40 (s, 1H, ArCOH), 6.80–6.91 (m, 3H, 3ArH); Anal. Calcd for $C_{10}O_3H_{14}$: C 65.91, H 7.74; found: C 65.96, H 7.71. And those data proved the intermediate product was synthesized successfully to a great extent.

Then under a nitrogen atmosphere, to a solution of 4-ethoxy-3-methoxybenzyl alcohol (1.62 mM) in dry THF (8 mL), caprylyl chloride (1.62 mM) and $CeCl_3$ (0.081 mM) were added. After stirring at room temperature for 12 h, the reaction was worked up by removal of the solvent. The residue was partitioned between EtOAc and saturated $NaHCO_3$ (ca. 50 mL each). The organic phase was washed with anhydrous Na_2SO_4 and evaporated, and the residue was purified by gravity column chromatography on silica gel (petroleum ether–ethyl acetate, 3:1) to give 446 mg (82%) of compound D as a colourless oil. Spectral data of D were as follows: UV (CH_3CH_2OH) λ_{max} (log ε): 255 (3.86), 292 (3.33) nm; ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, $J = 6.8$ Hz, 3H, 1-CH_3), 1.27 (t, $J = 8$ Hz, 12H, 3–8-$(CH_2)_6$), 1.46 (t, $J = 7$ Hz, 3H, 1′-CH_3), 1.62 (m, 2H, 2-CH_2), 2.34 (t, $J = 7.8$ Hz, 2H, 9-CH_2), 3.88 (s, 3H, OCH_3), 4.10 (q, $J = 6.9$ Hz, 2H, 2′-CH_2), 5.04 (s, 2H, $ArCH_2O$), 6.83–6.91 (m, 3H, 3ArH); IR (primary absorption peak, KBr pellet, cm^{-1}) ν: 2925, 1736, 1592, 1516, 1265, 1162, 803; Anal. Calcd for $C_{20}H_{32}O_4$: C 71.41, H 9.59; found C 71.33, H 9.62.

6.2.5. 4-Butoxy-3-methoxybenzyl decanoate (E in Fig. 1)

Compound E was prepared using the similar method as used for compound D, yet difference from the latter was that reactant of ethyl bromide was replaced by 1-butyl bromide. Then 4-butoxy-3-methoxybenzyl alcohol of intermediate product (86%) was synthesized and its spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, $J = 7.3$ Hz, 3H, 1′-CH_3), 1.39 (m, 2H, 2′-CH_2), 1.63 (m, 2H, 3′-CH_2), 2.47 (t, $J = 6.8$ Hz, 2H, 4′-CH_2), 3.70 (s, 3H, OCH_3), 3.90 (s, 2H, $ArCH_2O$), 4.38 (s, 1H, ArCOH), 6.53–6.88 (m, 3H, 3ArH); Anal. Calcd for $C_{12}O_3H_{18}$: C 68.54, H 8.63; found: C 68.47, H 8.65.

In the end 466 mg (79%) of Compound E was obtained as a kind of colourless oil. Its spectra data were as follows: UV (CH_3CH_2OH) λ_{max} (log ε): 254 (3.87), 293 (3.34) nm; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, $J = 7$ Hz, 3H, 1-CH_3), 0.97 (t, $J = 7.4$ Hz, 3H, 1′-CH_3), 1.25–1.28 (m, 12H, 3–8-$(CH_2)_6$), 1.49 (m, 2H, 2′-CH_2), 1.63 (m, 2H, 2-CH_2), 1.83 (m, 2H, 3′-CH_2), 2.33 (t, $J = 7.6$ Hz, 2H, 9-CH_2), 3.87 (s, 3H, OCH_3), 4.02 (t, $J = 6.8$ Hz, 2H, 4′-CH_2), 5.04 (s, 2H, $ArCH_2O$), 6.84–6.89 (m, 3H, 3ArH); IR (primary absorption apex, KBr pellet, cm^{-1}) ν (cm^{-1}): 2927, 2857, 1738, 1608, 1515, 1267, 1163, 803; Anal. Calcd for $C_{22}H_{36}O_4$: C 72.49, H 9.95; found C 72.45, H 9.91.

6.2.6. 4-Hexyloxy-3-methoxybenzyl decanoate (F in Fig. 1)

Compound F was also prepared using the similar method as D, yet the difference from the latter was that reactant of ethyl bromide was replaced by bromic 1-hexane. Then 4-hexyloxy-3-methoxybenzyl alcohol of intermediate product (84%) was synthesized and its spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, $J = 7.1$ Hz, 3H, 1′-CH_3), 1.31–1.34 (m, 4H, 3′–4′-$(CH_2)_2$), 1.45 (m, 2H, 2′-CH_2), 1.82 (m, 2H, 5′-CH_2), 3.80 (s, 3H, OCH_3), 3.90 (s, 2H, $ArCH_2$), 4.01 (t, $J = 7$ Hz, 2H, 6′-CH_2), 4.38 (s, 1H, ArCOH), 6.63–6.88 (m, 3H, 3ArH); Anal. Calcd for $C_{14}O_3H_{22}$: C 70.56, H 9.30; found: C 70.63, H 9.33.

At last 489 mg offspring (78%) of compound F was obtained as a colourless oil and its spectra data were as follows: UV (CH_3CH_2OH) λ_{max} (log ε): 255 (3.86), 291 (3.34) nm; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, $J = 6.9$ Hz, 3H, 1-CH_3), 0.90 (t, $J = 7.1$ Hz, 3H, 1′-CH_3), 1.24–1.28 (m, 12H, 3–8-$(CH_2)_6$), 1.31–1.35 (m, 4H, 3′–4′-$(CH_2)_2$), 1.45 (m, 2H, 2′-CH_2), 1.64 (m, 2H, 2-CH_2), 1.84 (m, 2H, 5′-CH_2), 2.33 (t, $J = 7.6$ Hz, 2H, 9-CH_2), 3.87 (s, 3H, OCH_3), 4.00 (t, $J = 7$ Hz, 2H, 6′-CH_2), 5.03 (s, 2H, $ArCH_2$), 6.83–6.90 (m, 3H, 3ArH); IR (primary absorption apex, KBr pellet, cm^{-1}) ν (cm^{-1}): 2927, 2857, 1738, 1608, 1515, 1267, 1163, 804; Anal. Calcd for $C_{24}H_{40}O_4$: C 73.43, H 10.27; found C 73.37, H 10.24.

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