Synthesis and Spectral Characterization of a Novel Series of Methylcinnamate Derivatives of 15-Crown-5

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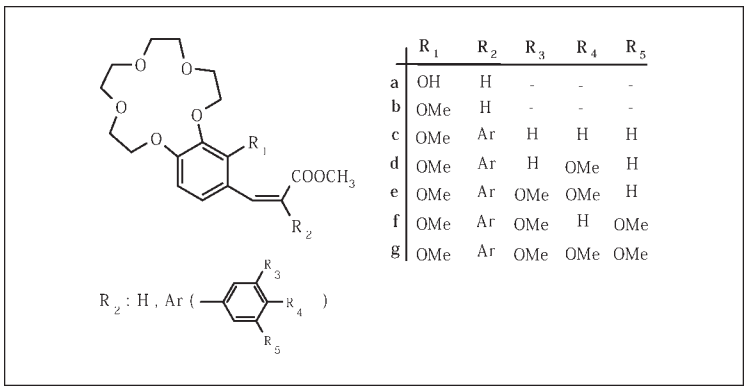

	R_1	R_2	R_3	R_4	R_5
a	OH	H	-	-	-
b	OMe	H	-	-	-
c	OMe	Ar	H	H	H
d	OMe	Ar	H	OMe	H
e	OMe	Ar	OMe	OMe	H
f	OMe	Ar	OMe	H	OMe
g	OMe	Ar	OMe	OMe	OMe

A series of novel methylcinnamate derivatives of 15-crown-5 have been synthesized. The derivatives of methylcinnamate have been prepared by a synthesis from the corresponding chromenone-crown ether with MeONa/MeOH or KOH, CH_3I, and DMSO as solvent. Novel compounds were characterized by elemental analysis, IR, ^{1}H NMR, and MALDI-TOF.

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INTRODUCTION

Cinnamic (3-phenylpropenoic) acid analogues are a fundamental part of plant chemistry. The hydroxylated cinnamic acids possess antifungal, antibacterial, and parasite fighting abilities [1]. In the cinnamic acid molecule, the carboxylic acid group is separated from the aromatic ring by a double bond. Conjugation between the —C=C— bond gives very interesting electronic structure to cinnamic acid derivatives.

The flavonoid class compound coumarin (2*H*-chromenone) derivatives exist in many plants as free or glucosides. Because of biological activities, which gain importance in recent years, many coumarin derivatives have been synthesized and took place in literature. Most important coumarins are the ones that have substituted in third position. Some coumarins show a perfect fluorescens characteristic in addition to their anticoagulant, anti-inflammatory, anti-oxidative, anti-aging, and anticancer effects [2,3]. Methyl and acetyl substituents destroy the activities of coumarins. The beneficial effects of phenolic antioxidants on health have been attributed to their antioxidant capacity, particularly their ability to protect low-density lipoproteins from oxidative attack [4]. As a result of this, hydroxy coumarin derivatives gain more importance. Particularly, *o*-dihydroxy-3-phenylcoumarin shows antioxidant property and the 18-crown-6, 15-crown-5, 12-crown-4 derivatives form complexes with alkali metal cations [5–8]. δ-Lacton ring of alkyloxy coumarin compounds can be opened using sodium alkoxide in dry respective alcohol yielding cinnamate derivatives. Then, the phenolic hydroxyl group can be alkylated [9,10].

Because the cinnamic acid analogues show biological activity, we might expect that the crown ether derivatives of methylcinnamate could also have biological activity.

This work introduces the preparation and characterization of some novel crown ether derivatives of methylcinnamate compounds obtained from respective chromenone-crown ethers.

RESULTS AND DISCUSSION

Recent work from our laboratory described general method for the synthesis of chromenone-crown ethers [5–8]. 7,8-Dihydroxy-2*H*-chromenone crown ether derivatives **4a–f** were synthesized from the polyethylene glycol ditosylate or dichloride with corresponding 7,8-dihydroxy-2*H*-chromenone derivatives **3a–f**, which were prepared from pyrogallol and D,L-malic acid **2a** in the presence of H_2SO_4 or 2,3,4-trihydroxybenzaldehyde and corresponding methoxyphenylacetic acid in NaOAc/Ac_2O mixture **3b–f** [5–8]. All these compounds were purified using column chromatography (silica gel) with

chloroform. The structures of all synthesized compounds were identified by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry [6–8].

We report herein a general method for the synthesis of methylcinnamate derivatives of 15-crown-5 from the respective chromenone-crown ethers. The phenylacrylic acids have been prepared by a synthesis from the corresponding chromenone-crown ethers with MeONa solution in MeOH refluxed for 4 h to afford **5a** [11–13] or KOH and DMSO as solvent at 60°C for 3–6 h. The phenolic hydroxyl group was methylated with CH_3I to give desired compounds **5b–g** in quantitative yield [14,15]. The structures of all synthesized compounds were identified by elemental analysis, IR, ^{1}H NMR, and mass spectrometry. All spectral data confirm the proposed structures of all of the new compounds **5a–g**.

The IR spectra of novel methylcinnamate derivatives of 15-crown-5 **5a–g** showed C—H stretching bands at about 2940 and 2858 cm^{-1}, an α,β-unsaturated ester carbonyl and double bond in the region 1680–1700, 1600 cm^{-1}, respectively. The bending peaks around 1040–1260 cm^{-1} showed the structure of C—O—C ether chain for all new methylcinnamate derivatives.

The cinnamate skeleton was also elucidated by ^{1}H NMR spectra. The ^{1}H NMR spectrum of compound **5a–g**, which showed triplets for the methylene protons [—OCH_2CH_2O—] at δ 3.66–4.39, a pair of doublet with ortho-coupling constants at δ 6.54–7.40 ppm (d, J = 8.50 Hz, H-6) and δ 7.10–7.90 ppm (d, J = 8.50 Hz, H-5) implied the presence of methylcinnamate derivatives of 15-crown-5. When the ^{1}H NMR spectra of compounds 7,8-dihydroxy-2*H*-chromenone derivatives of 15-crown-5 **4a–f** and methylcinnamate derivatives of 15-crown-5 **5a–g** were compared, one marked difference lay in the aromatic proton region with a singlet (s, H-3) was observed in the spectrum of **5a–g** at lower field than **4a–f**. And, also peaks at 3.68–3.92 ppm indicated the presence of —OCH_3 groups.

The IR spectrum of compound **5a**, the absorption band at 3400 cm^{-1} corresponding to hydroxyl stretching vibration disappears after its conversion into compound **5b**. The rest of spectral data of compound **5a** are very similar to **5b**. The IR spectrum of compound **5a** and **5b** including the stretching bands around 2947–2858 cm^{-1} of the C—H stretching frequency, 1701–1681 $cm^{-1}$of the carbonyl group, 1623–1604 cm^{-1} of the benzene ring, and 1261–1041 cm^{-1} of the ether chain, respectively. The structural assignments are based on the ^{1}H NMR coupling constants of the olefinic protons, and stereochemistry of the **5a** and **5b** was assigned as *trans*-on the basis of the coupling constant value ($J_{H—H}$ = 15.99 Hz) with reference to previous data [11].

The structures of newly synthesized compounds **5a–g** were checked using MS spectrometry. Also MALDI-TOF mass spectra confirmed the formation of novel methylcinnamate derivatives of 15-crown-5 **5a–g** (Scheme 1).

EXPERIMENTAL

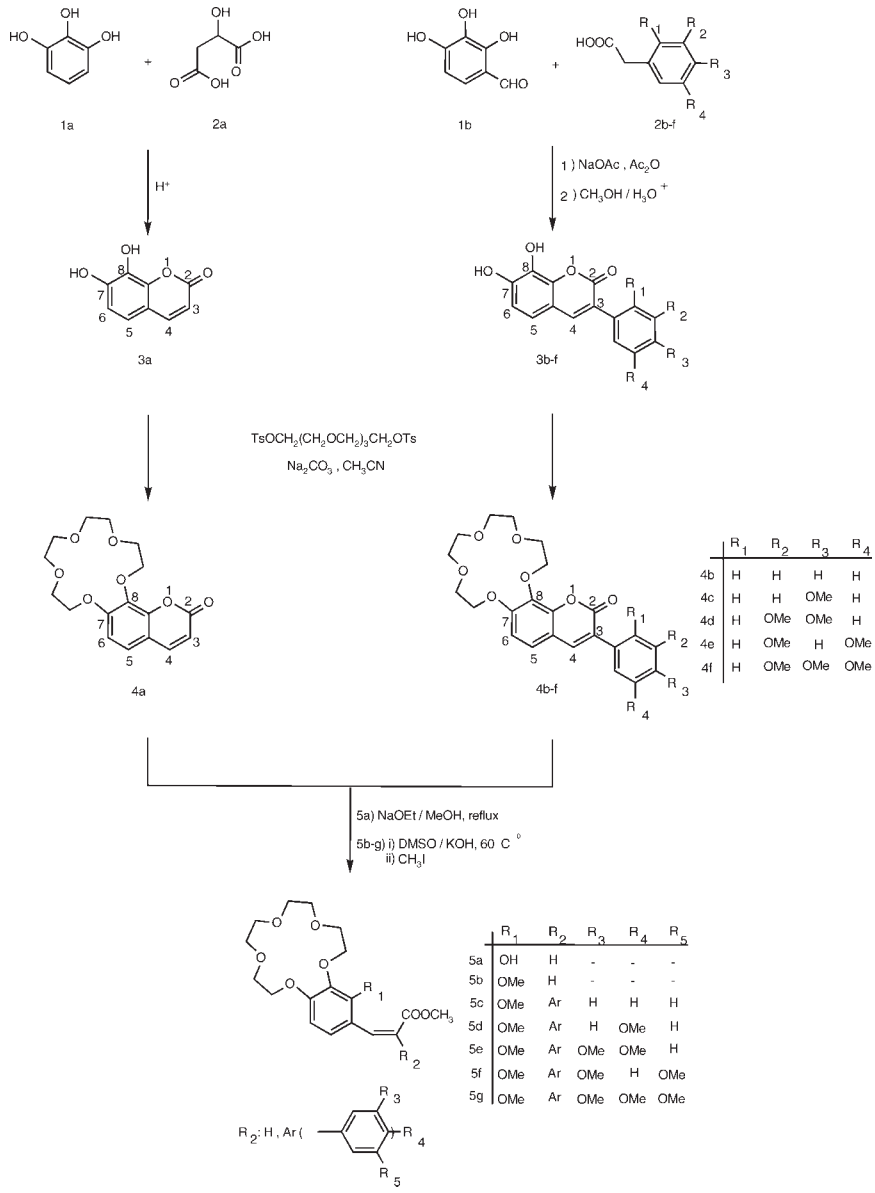
The starting chemicals used were of reagent grade. Melting points were obtained on a Gallenkamp apparatus. Elemental analysis was performed on a LECO CHNS 92 instrument. ^{1}H NMR spectra were determined with a Brucker DPX-400, 400 MHz High Performance Digital FT-NMR spectrometer. IR spectra were recorded as KBr disks in the range of 400–4000 cm^{-1} on a Schimadzu FTIR-8300 spectrometer. Mass spectra have been obtained with MALDI-TOF Instruments, model Bruker Autoflex III.

General procedure for the synthesis of methylcinnamate derivatives of 15-crown-5 5a–g. The crown ethers **4a–f** were prepared according to the known procedure [5–8]. The typical procedure for the reaction leading to a series of novel substituted methylcinnamate 15-crown-5 **5a–g** is as follows: A solution of sodium methoxide (28% in MeOH) (4 mmol) was added to a solution of the crown ether **4a** (2 mmol) in dry MeOH, and the mixture refluxed for 4 h and then the reaction mixture concentrated and extracted with AcOEt. The organic layer washed with brine and dried over $MgSO_4$ and evaporated to give product **5a** [11–13]. The crown ethers **4b–f** and methylcinnamate 15-crown-5 **5a** (1 mmol) were dissolved in DMSO, and then the KOH (2 mmol) was added to the reaction mixture and stirred at 60°C for 3–6 h. The reaction could also be monitored by thin-layer chromatography. CH_3I (2.5 mmol) was then added to the cooled reaction mixture. The reaction mixture was stirred at ambient room temperature for 2–6 h. The reaction was followed by thin-layer chromatography. The resulting mixture was poured into 30–50 mL icy water. The precipitate was collected by filtration, washed with water, and dried to give product **5b–g** [14,15].

(E)-Methyl-3-(14-hydroxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5a: $C_{18}H_{24}O_8$). A solution of sodium methoxide (28% MeOH) (0.77 mL, 4 mmol) was added to compound **4a** (0.672 g, 2 mmol) in MeOH (10 mL), which was reacted as described earlier to afford **5a**. Yield: 0.42 g (57%), mp 188–189°C; IR (KBr): 3402, 2939, 2873, 2858, 1681, 1604, 1504, 1458, 1261, 1041 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.66 (t, 4H, J = 4.29 Hz), 3.68 (s, 3H, OCH_3), 3.70 (t, 2H, J = 4.29 Hz), 3.79 (t, 2H, J = 4.29 Hz), 3.88 (t, 2H, J = 4.29 Hz), 4.00 (t, 2H, J = 5.46 Hz), 4.20 (t, 2H, J = 4.29 Hz), 4.30 (t, 2H, J = 5.46 Hz), 6.48 (d, 1H, J = 8.97 Hz), 6.55 (d, 1H, J = 15.99 Hz), 7.15 (d, 1H, J = 8.58 Hz), 7.90 (d, 1H, J = 15.99 Hz). *Anal*. Calcd. for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57. Found: C, 58.45; H, 6.78.

(E)-Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5b: $C_{19}H_{26}O_8$). A mixture of compound **5a** (0.40 g, 1.09 mmol) and CH_3I (0.138 mL, 2.7 mmol) in DMSO was treated as described earlier to give **5b**. Yield: 0.18 g (43%) mp 84–85°C; IR (KBr): 2947, 2904, 2858, 1701, 1623, 1593, 1496, 1461, 1296, 1261, 1041 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.74 (t, 8H, J = 5.46 Hz), 3.79 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (t, 4H, J = 4.68 Hz), 4.16 (t, 2H, J = 4.29 Hz), 4.18 (t, 2H, J = 5.07 Hz), 6.41 (d, 1H, J = 16.38 Hz), 6.64 (d, 1H, J = 8.58 Hz), 7.23 (d, 1H, J = 8.58 Hz), 7.87 (d, 1H, J = 15.99

Scheme 1



Hz); ms: *m*/*z* 382 (M^+), 405 ($M^+ + Na^+$), 421 ($M^+ + K^+$). *Anal*. Calcd. for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.45; H, 6.78.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-phenylacrylate (5c: $C_{25}H_{30}O_8$). A mixture of compound **4c** (0.206 g, 0.5 mmol) and KOH (0.056 g, 1 mmol) in DMSO (5 mL) was heated, then treated with CH_3I (0.068 mL 1.25 mmol), reacted, and then worked up as described earlier to afford **5c**. Yield: 0.044 g (19%) mp 82°C; IR (KBr): 2947, 2904, 2858, 1701, 1623, 1593, 1461, 1261, 1041 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$) :δ 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.98 (t, 8H, J = 4.68 Hz), 4.08 (t, 4H, J = 4.60 Hz), 4.18 (t, 4H, J = 4.60 Hz), 6.90 (dd, 2H, J = 8.97 and 2.34 Hz), 6.97 (dd, 1H, J = 8.97 and 2.34 Hz), 7.10 (d, 1H, J = 8.58 Hz), 7.40 (dd, 2H, J = 8.58), 7.90 (d, 1H, J = 8.58 Hz), 7.98 (s, 1H); ms: *m*/*z* 458 (M^+), 481 ($M^+ + Na^+$), 497 ($M^+ + K^+$). *Anal*. Calcd. for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 64.85; H, 6.75.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-(4-methoxyphenyl)acrylate (5d: $C_{26}H_{32}O_9$). Compound **4d** (0.221 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were reacted as described earlier to give **5d**. Yield: 0.058 g (24%) mp 76–77°C; IR (KBr): 2923, 2858, 1728, 1600, 1454, 1292, 1110, 1033 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.72 (t, 8H, J = 5.04 Hz), 3.73 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 3.90 (t, 4H, J = 5.50 Hz), 4.21 (t, 4H, J = 5.07 Hz), 6.59 (d, 1H, J = 8.58 Hz), 7.00 (d, 1H, J = 8.58 Hz), 7.20 (d, 2H, J = 7.80 Hz), 7.36 (d, 2H, J = 7.80 Hz), 8.05 (s, 1H); ms: *m*/*z* 488 (M^+), 511 ($M^+ + Na^+$), 527 ($M^+ + K^+$). *Anal*. Calcd. for $C_{26}H_{32}O_9$: C, 63.92; H, 6.60. Found: C, 62.78; H, 6.45.

Methyl-2-(3,4-dimethoxyphenyl)-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxa-cyclopentadecin-15-yl)acrylate (5e: $C_{27}H_{34}O_{10}$). Compound **4e** (0.236 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5e**. Yield: 0.044 g (17%) mp 91–92°C; IR (KBr): 2923, 2858, 1728, 1600, 1454, 1292, 1110, 1033 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 (t, 4H, J = 4.29 Hz), 3.98 (t, 4H, J = 4.29 Hz), 4.14 (t, 2H, J =4.29 Hz), 4.20 (t, 2H, J = 5.46 Hz), 4.23 (t, 2H, J = 4.29 Hz), 4.38 (t, 2H, J = 4.68 Hz), 6.59 (d, 1H, J = 8.97 Hz), 6.85 (dd, 1H, J = 8.77 and 2.73 Hz), 6.92 (br d, 1H, J = 8.19 Hz), 7.19 (d, 1H, J = 8.58 Hz), 7.28 (d, 1H, J = 1.95 Hz), 7.69 (s, 1H); ms: m/z 518 (M^+), 541 ($M^+ + Na^+$), 557 ($M^+ + K^+$). *Anal*. Calcd. for $C_{27}H_{34}O_{10}$: C, 62.54; H, 6.61. Found: C, 61.45; H, 6.88.

Methyl-2-(3,5-dimethoxyphenyl)-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5f: $C_{27}H_{34}O_{10}$). Compound **4f** (0.236 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5f**. Yield: 0.040 g (15%) mp 97–98°C; IR (KBr): 2939, 2873, 2858, 1681, 1604, 1458, 1261, 1041 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.76 (s, 3H, OCH_3), 3.83 (s, 9H, OCH_3), 3.95 (t, 4H, J = 4.40 Hz), 3.98 (t, 4H, J = 4.40 Hz), 4.24 (t, 4H, J = 4.40 Hz), 4.39 (t, 4H, J = 4.90 Hz), 6.49 (t, 1H, J = 2.40 Hz), 6.83 (d, 2H, J = 2.40 Hz), 6.86 (d, 1H, J = 9.20 Hz), 7.19 (d, 1H, J = 8.40 Hz), 7.73 (s, 1H); ms: m/z 518 (M^+). *Anal*. Calcd. for $C_{27}H_{34}O_{10}$: C, 62.54; H, 6.61. Found: C, 62.95; H, 6.42.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo-[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-(3,4,5-trimethoxyphenyl)acrylate (5g: $C_{28}H_{36}O_{11}$). Compound **4g** (0.251 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5g**. Yield: 0.048 g (18%) mp 89°C; IR (KBr): 2978, 2825 (C—H), 1676 (C=O), 1247, 1040 (C—O) cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.75 (t, 8H, J = 4.29 Hz), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3), 3.96 (t, 4H, J = 4.29 Hz), 4.23 (t, 2H, J = 4.29 Hz), 4.398 (t, 2H, J = 4.68 Hz), 6.85 (d, 1H, J = 8.97 Hz), 6.90 (br s, 2H), 7.19 (d, 1H, J = 8.58 Hz), 7.70 (s, 1H); ms: m/z 573 ($M^+ + Na^+$). *Anal*. Calcd. for $C_{28}H_{36}O_{11}$: C, 61.30; H, 6.61. Found: C, 61.01; H, 6.75.

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