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Synthesis, Characterization and Antibacterial Study of Cinnamic Acid Derivatives

Farah Amirah Azmi[1], Asnuzilawati Asari[1,2*], Maisara Abdul Kadir[1,2], Yosie Andriani[3], Fauziah Abdullah[4] and Habsah Mohamad[3]

[1]Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[2]Advanced Nano Materials (ANoMa) Research Group, Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[3]Institute of Marine Biotechnology, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[4]Phytochemistry Programme Natural Product Division, Forest Research Institute of Malaysia, 52109 Kepong, Selangor, Malaysia
*Corresponding author (e-mail: asnu@umt.edu.my)

Cinnamic acids are a group of aromatic carboxylic acids found naturally in the plant kingdom. This group of molecules can be found in coffee beans, tea, cocoa, apples, citruses, and potatoes. Cinnamic acids possess outstanding biological and pharmacological activities. In this study, a series of known and new cinnamic acid ester derivatives (**3-10**) were synthesized by employing acyl halide esterification reactions. All the ester derivatives were characterized using analytical spectroscopic techniques including ^{1}H & ^{13}C Nuclear Magnetic Resonance (NMR) and Fourier Transform Infrared (FTIR). The synthesized compounds were evaluated *in-vitro* for their antibacterial activity against five different bacteria test strains, which were Gram-positive (*Bacillus cereus, Staphylococcus epidermidis*, and *Staphylococcus aureus)* and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria using the disk diffusion method. Among all of the synthesized compounds, derivative **3** exhibited the highest inhibitory activity against all the Gram-positive and Gram-negative bacteria. Most of the synthesized molecules in this study have not yet been reported in the literature, and thus may have biological activities worth investigating.

Key words: Cinnamic acid derivatives; acyl halide esterification; disk diffusion method; antibacterial activity

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Bacterial infections are caused by harmful strains of bacteria either on or inside the human body. These infections range from acne and food poisoning to severe forms such as pneumonia and tuberculosis [1-2]. These bacterial diseases have become a global health threat especially for developing and low-income countries [3-4], which only rely on antibiotics such as penicillin, ampicillin, methicillin, and tetracycline [5]. However, misuse and overconsumption of these drugs has caused antibiotic resistance by selected bacterial strains [6, 7]. *Staphylococcus aureus*, for example, is resistant to ampicillin, penicillin, methicillin, and vancomycin [8], while *Escherichia coli* is resistant to chloramphenicol, tetracycline, and fluoroquinolones [1]. This has become a major concern for hospitals and other health care services [9]. Therefore, there is an urgent need to search for new compounds which are safe and selective against selected bacterial strains to treat this type of disease.

The interest in the exploration of drugs based on natural compounds have been increasing during the past few years. The characterization of such compounds has high priority within pharmacology and medicine in the search of new and more efficient compounds to treat various diseases. Cinnamic acid and its derivatives, one of the naturally occurring phenolic compounds that usually can be found in plants and food products, have drawn a great attention from researchers due to their outstanding biological and pharmacological activities such as antibacterial [10], antioxidant [11-12], antiviral [13], anticancer [14-17], anti-inflammatory [18-19], and antifungal [20-22] activities. Many studies reported that cinnamic acid derivatives have excellent inhibitory effects against several bacteria strains [23-25]. Thus, this study aimed to synthesize, characterize, and evaluate the cinnamic acid derivatives (**3-10**) against selected Gram-positive and Gram-negative bacteria.

MATERIALS AND METHODS

1. Chemicals

All the chemicals used in this study were obtained from Sigma-Aldrich Co., Merck Chemical Co., Acros Organics Co., and R&M Chemical, and used without

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further additional purification. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on Bruker Spectrospin-400 Spectrometer. FTIR spectra were recorded using Perkin Elmer 100 FT-IR spectrometer with KBr pellets. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck). Analytical thin layer chromatography (TLC) was done on precoated silica gel 60 (F_{254}, Merck) plates and visualized under UV 254 nm without treatment.

2. General Procedure for the Synthesis of Cinnamic Acid Ester Derivatives (3-10)

Cinnamic acid (1.30 mmol, 1.0 eq) was dissolved in 10 mL of anhydrous dichloromethane under inert atmosphere. 0.25 mL of triethylamine was added to the solution and stirred for 30 minutes at 0-5 ºC. An excess of acyl chloride (2.60 mmol, 2.0 eq) was added to the solution and stirred for another 30 minutes. Then, the solution was continuously stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. After completion, the solvent was removed using a rotary evaporator. The purification of the residue was done using column chromatography with hexane and ethyl acetate (4:1).

3(2-((3-methylbutanoyl)oxy)phenyl)acrylic acid (3): Light yellow solid; Yield: 31%; IR (KBr, ν_{max}, cm^{-1}) 3069, 2962, 1749, 1685, 1626, 1458, 1200, 1096, 758; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 1.03 (d, *J* = 6.4 Hz, 6H, H-1), 2.10-2.18 (m, 1H, H-2), 2.56 (d, *J* = 7.2 Hz, 2H, H-3), 6.58 (d, *J* = 16.0 Hz, 1H, H-4), 7.20 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H, CH_{ar}), 7.33 (t, *J* = 7.6 Hz, 1H, CH_{ar}), 7.48 (td, *J* = 8.0 Hz, 1.2 Hz, 1H, CH_{ar}), 7.57 (d, *J* = 16.4 Hz, 1H, CH_{ar}), 7.90 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H, H-9); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 22.56, 25.80, 42.79, 122.01, 123.75, 126.97, 127.3, 128.2, 131.8, 137.0, 149.4, 167.7, 171.5 ppm.

3(2-((4-methylbenzoyl)oxy)phenyl)acrylic acid (4): Light yellow crystal; Yield: 40%; IR (KBr, ν_{max}, cm^{-1}) 3036, 2924, 1732, 1690, 1628, 1485, 1265, 1096, 745; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 2.45 (s, 3H, H-1), 6.61 (d, *J* = 16.0 Hz, 1H, H-2), 7.34-7.40 (m, 2H, CH_{ar}), 7.47 (d, *J* = 8.0 Hz, 2H, CH_{ar}), 7.51-7.57 (m, 2H, CH_{ar}), 7.96 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, H-3), 8.10 (d, *J* = 8.0 Hz, CH_{ar}); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 20.7, 120.9, 122.9, 124.9, 126.1, 126.3, 127.3, 129.2, 129.4, 130.8, 135.9, 144.5, 148.5, 163.8, 166.6 ppm.

3(2-(heptanoyloxy)phenyl)acrylic acid (5): Light yellow solid; Yield: 15%; IR (KBr, ν_{max}, cm^{-1}) 3100, 2932, 1763, 1690, 1624, 1416, 1219, 1107, 771; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 0.87 (t, *J* = 8.0 Hz, 3H, H-1), 1.28-1.32 (m, 4H, H-2), 1.34-1.40 (m, 2H, H-3), 1.64-1.71 (m, *J* = 12.0 Hz, 2H, H-4), 2.65 (t, *J* = 8.0 Hz, 2H, H-5), 6.57 (d, *J* = 16.0 Hz, 1H, H-6), 7.20 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H, CH_{ar}), 7.32 (t, *J* = 8.0 Hz, 1H, CH_{ar}), 7.48 (td, *J* = 7.6 Hz, 1.2 Hz, 1H, CH_{ar}), 7.56 (d, *J* = 16.0 Hz, 1H, CH_{ar}), 7.89 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, H-7); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 14.4, 22.4, 24.9, 28.6, 28.7, 31.4, 33.9, 121.9, 123.8, 126.9, 127.3, 128.2, 131.8, 137.1, 149.5, 167.7, 172.2 ppm.

3(2-(propionyloxy)phenyl)acrylic acid (6): Light yellow solid; Yield: 72%; IR (KBr, ν_{max}, cm^{-1}) 3080,2990, 1767, 1686, 1632, 1423, 1130, 1092, 760; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 1.19 (t, *J* = 7.2 Hz, 3H, H-1), 2.71 (q, *J* = 7.2 Hz, 2H, H-2), 6.58 (d, *J* = 16.0 Hz, 1H, H-3), 7.22 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H, CH_{ar}), 7.32 (td, *J* = 7.6 Hz, 0.4 Hz, 1H, CH_{ar}), 7.48 (td, *J* = 8.0 Hz, 1.6 Hz, 1H, CH_{ar}), 7.56 (d, *J* = 16.0 Hz, 1H, CH_{ar}), 7.89 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, H-4); ^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 8.4, 26.3, 120.8, 122.7, 125.8, 126.1, 127.2, 130.7, 136.0, 148.4, 166.7, 171.9 ppm.

3(3,4-bis(butyryloxy)phenyl)acrylic acid (7): Yellow solid; Yield: 32%; IR (KBr, ν_{max}, cm^{-1}) 3487, 2967, 1759, 1686, 1628, 1431, 1250, 1146, 829; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 0.98 (t, *J* = 5.6 Hz, 6H, H-1), 1.63-1.67 (m, 4H, H-2), 2.56 (td, *J* = 7.2 Hz, 0.8 Hz, 4H, H-3), 6.57 (d, *J* = 16.0 Hz, 1H, H-4), 7.33 (d, *J* = 8.4 Hz, 1H, CH_{ar}), 7.60 (d, *J* = 16.0 Hz, 1H, CH_{ar}), 7.65 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H, H-5), 7.68 (sd, *J* = 2.0 Hz, 1H, CH_{ar}); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 13.8, 18.3, 35.4, 120.9, 123.5, 124.6, 127.2, 133.6, 142.6, 142.8, 143.7, 167.9, 171.0, 171.1 ppm.

3(3,4-bis(propionyloxy)phenyl)acrylic acid (8): Yellow solid; Yield: 70%; IR (KBr, vmax, cm-1) 3489, 2984, 1761, 1688, 1630, 1431, 1256, 1074, 824; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 1.27-1.31 (m, *J* = 7.2 Hz, 6H, H-1), 2.58-2.64 (m, *J* = 4.4 Hz, 4H, H-2), 6.44 (d, *J* = 16.0 Hz, 1H, H-3), 7.27 (t, *J* = 6.0 Hz, 1H, CH_{ar}), 7.41 (d, *J* = 2.0 Hz, 1H, CH_{ar}), 7.46 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H, CH_{ar}), 7.75 (d, *J* = 16.0 Hz, 1H, H-4); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 9.1, 27.5, 118.6, 123.0, 124.0, 126.6, 132.8, 142.6, 144.0, 145.0, 171.5, 171.6 ppm.

3(2-((3-bromobenzoyl)oxy)phenyl)acrylic acid (9): White crystal; Yield: 40%; IR (KBr, ν_{max}, cm^{-1}) 3090, 2976, 1736, 1690, 1628, 1420, 1211, 1096, 739; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 6.62 (d, *J* = 16.0 Hz, 1H, H-1), 7.41 (t, *J* = 5.6 Hz, 2H, CH_{ar}), 7.55 (td, *J* = 9.2 Hz, 3.2 Hz, 2H, CH_{ar}), 7.63 (t, *J* = 8.0 Hz, 1H, CH_{ar}), 7.97 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, CH_{ar}), 8.04 (d, *J* = 12.0 Hz, 1H, CH_{ar}), 8.20 (d, *J* = 8.0 Hz, 1H, H-2), 8.30 (s, 1H, CH_{ar}); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 121.1, 121.6, 122.7, 126.2, 126.3, 127.3, 127.7, 128.3, 129.9, 130.3, 130.9, 131.1, 131.6, 135.0, 135.8, 136.6, 148.3, 162.6, 165.4, 166.6 ppm.

3(2-((4-butylbenzoyl)oxy)phenyl)acrylic acid (10): White solid; Yield: 27%; IR (KBr, ν_{max}, cm^{-1}) 3040, 2955, 1724, 1690, 1628, 1420, 1273, 1096, 764; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 0.92 (t, *J* = 7.2 Hz, 3H, H-1), 1.29-1.38 (m, *J* = 7.2 Hz, 2H, H-2), 1.58-1.63 (m, J = 7.6 Hz, 2H, H-3), 2.72 (t, *J* = 7.6 Hz, 2H, H-4), 7.34-7.40 (m, 2H, CH_{ar}), 7.48 (d, *J* = 8.4 Hz, 2H, CH_{ar}), 7.51-7.59 (m, 2H, CH_{ar}), 7.96 (dd, *J* = 7,6 Hz, 1.2 Hz, 1H, CH_{ar}), 8.10 (d, *J* = 8.0 Hz, 2H, CH_{ar}); ^{13}C-

NMR (100 MHz, DMSO-d_6) δ 13.2, 21.2, 120.9, 122.9, 125.1, 126.1, 126.3, 127.3, 128.5, 129.4, 130.8, 135.9, 148.6, 149.1, 163.8, 166.6 ppm.

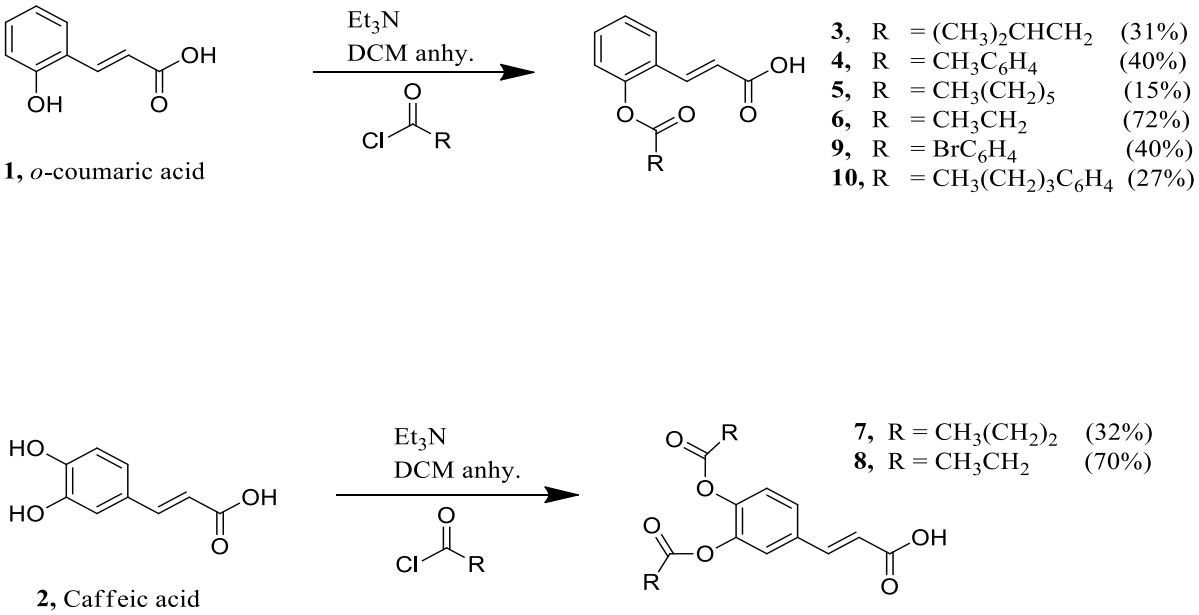
3. Antibacterial Assay

The antibacterial activity of the derivatives was determined by the disk diffusion method [27]. The selected Gram-positive (*B. cereus, S. epidermidis,* and *S. aureus*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacteria were subcultured overnight on Mueller-Hinton agar plates at 37ºC. The cultured bacteria were then diluted in sterilized distilled water and the concentration was adjusted to 0.5 McFarland standard by using a spectrophotometer. Then, the bacterial inocula were seeded uniformly using sterile cotton swabs on MHA plates. 1 mg/mL of each derivative was dissolved in methanol and 40 µL of each sample was loaded onto paper disks. A disk of each sample was put on the surface of the each agar plate using forceps sterilized by flaming. The antibiotic tetracycline was used as the positive control while methanol was used as the negative control.

RESULTS AND DISCUSSION

The synthesis routes for the formation of the cinnamic acid derivatives (**3-10**) are summarized in **Scheme 1**. The reactions were based on a single step reaction between *o*-coumaric acid or caffeic acid with various acyl chlorides in the presence of triethylamine to produce the ester derivatives. Five new compounds (**3-5**, **9-10**) and three known compounds (**6-8**) have been successfully synthesized at varied yields (15-72%). The structures of all synthesized compounds were confirmed by ^{1}H and ^{13}C-NMR and FTIR spectroscopies.

In this study, all of the synthesized compounds (**3-10**) were evaluated against the selected bacteria using the disk diffusion method. **Table 1** shows the inhibition zone diameter of all the compounds. From the results obtained, all the compounds were active against two bacteria, *B. cereus* and *S. aureus* which are both Gram-positive bacteria. For *S. epidermidis*, almost all the compounds exhibited antibacterial activities towards the strain. Compounds **5-6** and **8-10** did not possess any antibacterial activity against all the Gram-negative bacteria, probably due to the presence of double membranes, which are the inner and outer membranes surrounding the Gram-negative bacteria, hence making the bacteria more resistant towards the antibacterial agents [26]. However, compounds **3, 4,** and **7** showed moderate to good antibacterial activities against *E. coli* and *P. aeruginosa*. According to [1], compounds with short chain, long chain or branching chain of alkyl substituent resulted in decreased antibacterial activities probably due to the poor lipophilic short chain groups and steric hindrance caused by the presence of bulky groups. Compound **3** displayed good results of antibacterial activities for both Gram-positive and Gram-negative bacteria, which was in agreement with previous studies [1, 27, 28] that reported a median carbon chain possessed the best results of antibacterial testing compared to other compounds.



Scheme 1. Synthetic routes for compounds **3-10**

Table 1. Antibacterial activities of cinnamic acid derivatives against some pathogenic bacteria

Compound	Zone of inhibition (mm)				
	Gram-positive bacteria			Gram-negative bacteria	
	B. cer	*S. aur*	*S. epi*	*E. coli*	*P. aer*
1	**7**	**8**	**-**	**-**	**-**
3	**7**	**8**	**9**	**11**	**15**
4	**7**	**8**	**8**	**12**	**12**
5	**7**	**9**	**9**	**-**	**-**
6	**7**	**9**	**8**	**-**	**-**
7	**7**	**10**	**8**	**-**	**12**
8	**7**	**10**	**8**	**-**	**-**
9	**7**	**10**	**8**	**-**	**-**
10	**7**	**10**	**-**	**-**	**-**
Tetracycline	**19**	**24**	**13**	**22**	**32**

B. cer: Bacillus cereus, S. aur: Streptococcus aureus, S. epi: Streptococcus epidermidis, E. coli: Escherichia coli, P.aer: Pseudomonas aeruginosa,.(-) No Inhibition

CONCLUSION

A series of new and known cinnamic acid ester derivatives were successfully synthesized by a simple esterification reaction. Derivative **3** showed the most potent antibacterial activities for both the Gram-positive and Gram-negative bacteria, indicating a broad spectrum activity. These results indicated that cinnamic acid ester derivatives have the potential to be further studied for the development of new antibacterial agents.

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