

Article

Synthesis and Antibacterial Activities of Novel 4-Hydroxy-7-hydroxy- and 3-Carboxycoumarin Derivatives

Pen-Yuan Lin ¹, Kuang-Sheng Yeh ², Chien-Ling Su ³, Shiow-Yunn Sheu ¹, Tiffany Chen ⁴, Keng-Liang Ou ⁵, Mei-Hsiang Lin ¹ and Lin-Wen Lee ^{6,*}

¹ School of Pharmacy, College of Pharmacy, Taipei Medical University, 250 Wuxing St., Taipei 11031, Taiwan

² Department of Veterinary Medicine, School of Veterinary Medicine, College of Bioresources and Agriculture, National Taiwan University, No. 1, Sec. 4, Roosevelt Rd., Taipei 10617, Taiwan

³ School of Respiratory Therapy, Taipei Medical University, Taipei Medical University, 250 Wuxing St., Taipei 11031, Taiwan

⁴ Department of Biochemistry and Chemistry, University of Washington, 4311 11th Ave. NE, Seattle, WA 98105-4068, USA

⁵ Research Center for Biomedical Devices and Prototyping Production, Taipei Medical University, 250 Wuxing St., Taipei 11031, Taiwan

⁶ Department of Microbiology and Immunology, School of Medicine, College of Medicine, Taipei Medical University, 250 Wuxing St., Taipei 11031, Taiwan

* Author to whom correspondence should be addressed; E-Mail: lucie@tmu.edu.tw; Tel.: +886-227-361-661 (ext. 3917); Fax: +886-229-278-316.

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Abstract: Coumarin derivatives are used as fluorescent dyes and medicines. They also have some notable physiological effects, including the acute hepatotoxicity and carcinogenicity of certain aflatoxins, the anticoagulant action of dicoumarol, and the antibiotic activity of novobicin and coumerymycin A1. Because the number of drug resistant strains is increasing at present, the synthesis of new antibacterial compounds is one of the critical methods for treating infectious diseases. Therefore, a series of coumarin-substituted derivatives, namely 4-hydroxy- and 7-hydroxycoumarins, and 3-carboxycoumarins were synthesized. 4-Hydroxycoumarin derivatives **4a–c** underwent rearrangement reactions. Both 4- and 7-hydroxycoumarins were treated with activated aziridines which produced series of ring-opened products **7, 8, 10, and 11**. 3-Carboxy-coumarin amide dimer derivatives **14–21** were prepared by reacting aliphatic alkylamines and

alkyldiamines with PyBOP and DIEA. In this study, we use a new technique called modified micro-plate antibiotic susceptibility test method (MMAST), which is more convenient, more efficient, and more accurate than previous methods and only a small amount of the sample is required for the test. Some of the compounds were produced by reactions with acid anhydrides and demonstrated the ability to inhibit Gram-positive microorganisms. The dimer derivatives displayed lower antibacterial activities.

Keywords: 4-hydroxy-; 7-hydroxy-; 3-carboxycoumarin derivatives; antibacterial activities

1. Introduction

Coumarin is a lactone compound which is widely distributed in plants and can be extracted, among others, from *Anthoxanthum odoratum*, *Melilotus officinalis*, *Dipterix oppositifolia* and *Dipterix oppositifolia* [1]. Its derivatives are used as daylight fluorescent pigments [2], brighteners [3], fluorescent dyes [4], fluorescent sensors [5], laser dyes [6], drug carriers [7], and drug delivery agents [8]. Recently, various medicinal effects, such as anticoagulant [9,10], analytical fluorescence indicator, anti-inflammatory [11] and antioxidant [12–15] properties have been reported. Many authors have reported the convenient and effective synthesis of the dimers from salicylaldehydes and by biomimetic synthesis. Acetoxycoumarins, polycyclic 7-hydroxycoumarins and other coumarin derivatives display anticarcinogenic properties [16–22]. Roma also reported that tricyclic or bicyclic coumarin derivatives with amino groups showed antiplatelet activity [23]. 4-Heteroaryl-amino-, triazolopyridine, imidazolopyridine, *N*-substituted-3-carboxamido- and other groups incorporate a coumarin moiety displaying new coumarin derivative structures which showed antibacterial [24–29] and antifungal [30] activities. Several novel coumarin analogs possess antimycobacterial activity [31–33]. Modification of the chemical structure of the coumarin parent skeleton showed unit enzyme inhibition *in vitro* and *in vivo* [34–37]. Coumarin also combines with sugar units to form C-glycosyl compounds. In this study, we report the characteristics of several chemicals including 4-hydroxycoumarin derivatives **1a–c**, **5**, and 7-hydroxycoumarin **9** and 3-carboxycoumarin derivatives **12**. By using acid anhydrides, activated aziridines **6**, benzotriazol-1-yloxytri-(pyrrolidinol)phosphonium hexafluorophosphate (PyBOP, **13**), diisopropylethylethylamine (DIEA), dimethylformamide (DMF), alkylamines, and alkyldiamines to react with 3-carboxycoumarin, instead of dicyclohexylcarbodiimide (DCC) as a coupling reagent high yields of 3-carboxycoumarin amide dimers were obtained.

Microbiological trials using the minimal inhibitory concentration (MIC) on penicillin G, amikin and the new modified micro-plate antibiotic susceptibility test (MMAST) were carried out on different bacterial strains to test the activities of the new compounds [38].

2. Results and Discussion

Acylation of **1a–c** with acid anhydride in a suitable solvent at ca. 150 °C caused the substitution to produce **3a–c**, **3a₁–c₁** and **3a₂–c₂**. The acyl groups were removed via rearrangement to produce compounds **4a–c**, **4a₁–c₁**, and **4a₂–c₂** under heating conditions. 4-Acyloxycoumarins experienced a

greater extent of rearrangement than 7-acyloxycoumarins. The effects might have been due to an electron deficiency inductive effect plus the different distances between position 7-acyloxy and the non-aromatic double-bond electron density at positions 3 and 4 of the 4-acyloxycoumarins. In this study, only the aliphatic acid anhydride acylation of 4-hydroxycoumarin caused rearrangements, while aromatic acid anhydrides failed to react. For 7-hydroxycoumarin, its acylation product was not observed, even when aliphatic or aromatic acid anhydrides with NaOMe in methanol were used. When 7-hydroxycoumarin treated with base will become more resonance anion and more difficult to react with anhydride by weak base MeOH and even by strong base NaOMe. Therefore both of bases are unable to carry out the reaction. We also tried to use other diketone and amide compounds to react with the hydroxycoumarins, unfortunately, the expected acylation rearrangement did not occur. This might be explained by the greater number of methylene groups and the increase in the distance between the two C=O bonds which makes it more difficult to attack the other carbonyl position. Synthesis of coumarin derivatives via the ring-opening reaction with activated aziridines has not been reported and characterized previously. The reaction of the coumarin anion with *N*-benzoyl- or *N*-sulfonylaziridines **6** yielded amidoethylated 7- or 4-hydroxycoumarins **7**, **8**, **9** and **10**. The final results depend on the substitution of the *N*-acyl or *N*-sulfonyl groups on the acyl group, such as benzoyl and the coumarin anions will attack from an abnormal position to provide the major products **7d–f**, **10n**, and **10q**. Only trace amounts of products are produced from normal ring-openings of aziridines. However, with the *N*-sulfonyl group, we obtained both products (in 4:1 ratio), but the main products resulted from normal ring-opening of the activated aziridines **7h**, **8i**, **8j**, **10k–l**, and **11k**. It was assumed that compounds **7**, **8**, **10**, **11**, and their analogues were formed by the nucleophilic attack of acylaziridines via an S_N2-like ring opening mechanism. The comparison of the proton NMR of the NH group in **7** and **8** revealed the cleavage of the ring position.

In our previous work [35], we reported that when PyBOP (**13**) was used as a coupling reagent to synthesize natural amide dimers, relatively high yields was obtained. The reaction did not perturb the formation of amide dimers even when a sugar moiety is attached to the parent compounds. In general, for the formation of amide or dimer chains, the reaction temperatures had a great influence on the structural conformation. From NMR spectroscopic analysis, the intermediate, coumarin-triazobenzene, displayed rearranged characteristics. We hypothesize that it might depend on the two factors of the solvent system introduced and the duration of the reaction. The reaction was carried out under mild conditions, by mixing the reagents with DMF at ca. 0 °C, followed by the addition of DIEA. The resulting solution was allowed to warm to room temperature for 1–3 days, then alkyldimines were added dropwise to produce high yields of coumarin amide dimers.

All of the above synthetic products were further tested for their antibacterial effects. The MICs of the compounds tested against the reference strains are shown in Table 1. The antimicrobial tests performed on coumarin derivatives **3c**, **3c₁**, **4a₂**, **4b**, **4c**, and **7f** confirmed the better activities of these compounds against Gram-positive rather than Gram-negative bacteria and some were especially active against *Bacillus subtilis* and *Staphylococcus aureus*. Compound **7f** was the most potent of the tested compounds against *B. subtilis*, with an MIC value of 8 µg/mL. Compounds **3c**, **3c₁**, **4a₂**, **4b**, **4c**, and **7d** only inhibit bacterial growth moderately, with lower MICs of 32, 16, and 64 µg/mL, respectively, when compared to penicillin G. The MICs of coumarin amide dimers **14–21** ranged from 128 to 256. Prior to these studies, the available information on coumarin-aziridins and the dimerization moiety of

SAR indicated that molecular recognition involved specific receptor interactions. We propose that the various aziridines and dimer chain lengths might change the binding characteristics of ligands or the conformational direction to their respective receptors and, thereby, improve the biological activities.

Table 1. MICs of compounds **3**, **4**, **7**, **8**, **10**, **11**, and **14–21** against the reference strains.

Compds.	MIC ($\mu\text{g/mL}$) ^a			
	Gram (+) bacteria ^b		Gram (–) bacteria ^b	
	<i>B. s.</i>	<i>S. a.</i>	<i>E. c.</i>	<i>P. a.</i>
3a	>256	>256	>256	>256
3a₁	>256	>256	>256	>256
3a₂	128	>256	>256	>256
3b	128	>256	128	>256
3b₁	128	256	256	>256
3b₂	>256	>256	>256	>256
3c	32	32	>256	>256
3c₁	32	>256	>256	>256
3c₂	>256	>256	>256	>256
4a	128	>256	>256	>256
4a₁	>256	>256	>256	>256
4a₂	64	>256	>256	>256
4b	64	128	256	>256
4b₁	>256	>256	>256	>256
4b₂	128	>256	>256	>256
4c	16	16	128	>256
4c₁	>256	>256	>256	>256
4c₂	64	32	>256	>256
7d	64	64	>256	>256
7e	>256	>256	>256	>256
7f	8	8	>256	>256
7g	>256	>256	>256	>256
7h	>256	>256	>256	>256
8i	>256	>256	>256	>256
8j	>256	>256	>256	>256
10k	>128	>128	128	>128
10l	>128	>128	>128	>128
10m	>128	>128	128	>128
10n	>128	>128	>128	>128
10o	>128	>128	>128	>128
10p	>128	>128	>128	>128
10q	>128	>128	>128	>128
10r	>128	>128	>128	>128
11k	>128	>128	>128	>128
14	>128	>128	>128	>128
15	>128	>128	>128	>128
16	>128	>128	>128	>128
17	>128	>128	>128	>128

Table 1. Cont.

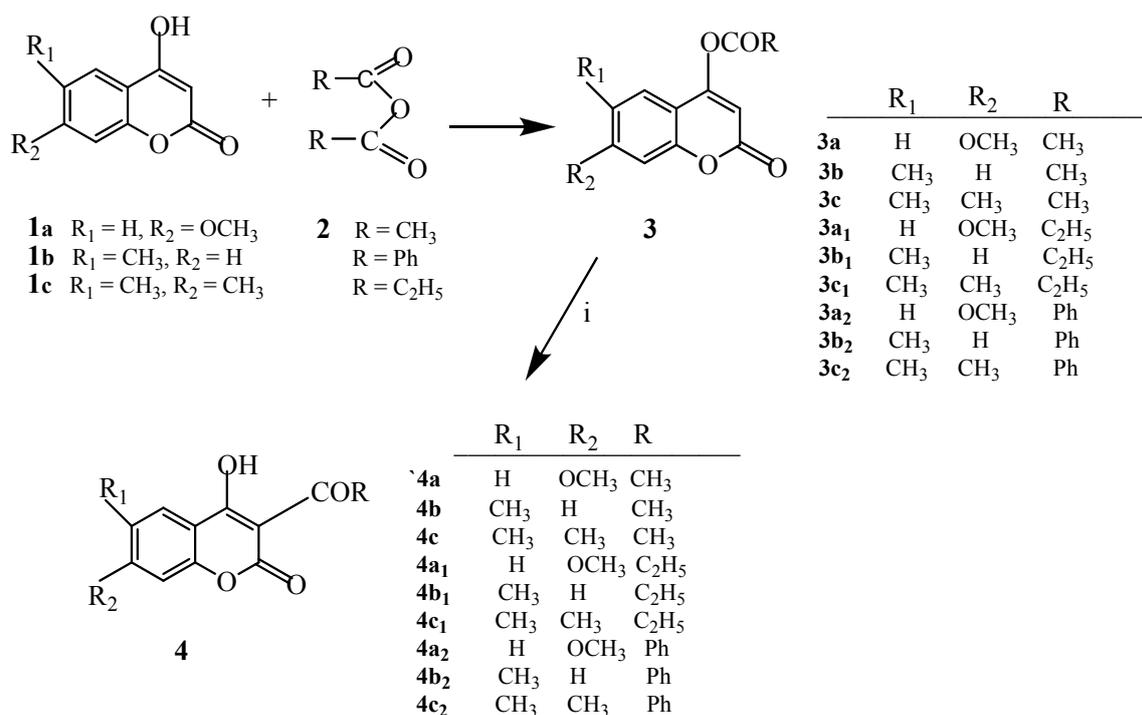
Comps.	MIC ($\mu\text{g/mL}$) ^a			
	Gram (+) bacteria ^b		Gram (-) bacteria ^b	
	<i>B. s.</i>	<i>S. a.</i>	<i>E. c.</i>	<i>P. a.</i>
18	>128	>128	>128	>128
19	>128	>128	>128	>128
20	>128	>128	>128	>128
21	>128	>128	>128	>128
PenicillinG ^c	8	0.0625	-	-
Amikin	-	-	1	0.125

^a MIC, minimal inhibitory concentration. ^b Bacteria: *B. s.*, *Bacillus subtilis* (BCRC 10029); *S. a.*, *Staphylococcus aureus* (BCRC 11863); *E. c.*, *Escherichia coli* (BCRC 11758); *P. a.*, *Pseudomonas aeruginosa* (BCRC 11733). ^c Penicillin G potassium salt, Sigma p8721, lot 102K0483, 1,589 units/mg.

2.1. Chemistry

Regarding the synthetic route applied to 4-hydroxycoumarin derivatives, 4-hydroxycoumarin and its analogues **1a–c** were used as starting materials to react with acid anhydrides, acetic anhydride, e.g., propionic anhydride, and benzoic anhydride, to produce the corresponding O-acyloxyl products **3a–c**. It was observed that a proton on the hydroxyl group of coumarin was substituted by an acyl group when we elevated the temperature to ca. 150 °C. Similar conditions were adopted to produce the O-acyloxyl and benzoyloxyl derivatives as the main reaction products. High yields were achieved when methyl groups were introduced at the 6 and 7 positions of the parent coumarin structure (Scheme 1).

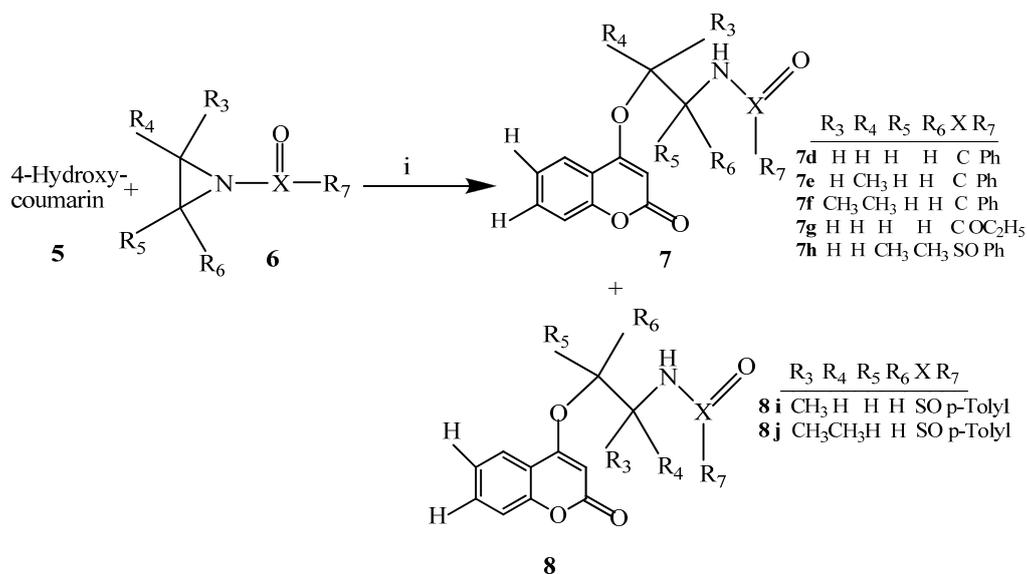
Scheme 1. 4-Hydroxycoumarin reacted with acid anhydride.



Reaction Conditions: i. reflux.

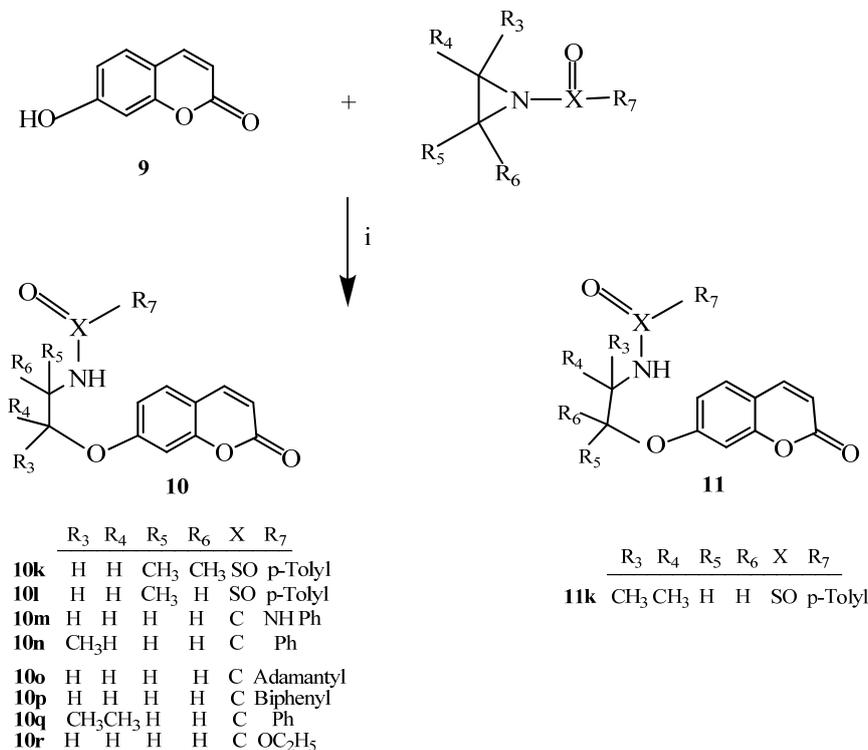
The subsequent reaction involving heating over 170 °C in a sealed tube led to the rearrangement products **4a–c** in yields comparable to compounds **3a–c**. Methyl group substitution produced greater yields of 52%–64%. Excess acid anhydrides were finally removed by column chromatography on silica gel. Furthermore, 4-hydroxy- and 7-hydroxycoumarin derivatives were found to undergo ring-opening reactions with various activated aziridines (Schemes 2 and 3).

Scheme 2. 4-Hydroxycoumarin reacted with activated aziridines **6**.



Reagents: *i.* NaOCH₃/THF.

Scheme 3. Reactions of 7-hydroxycoumarin with activated aziridines **6**.

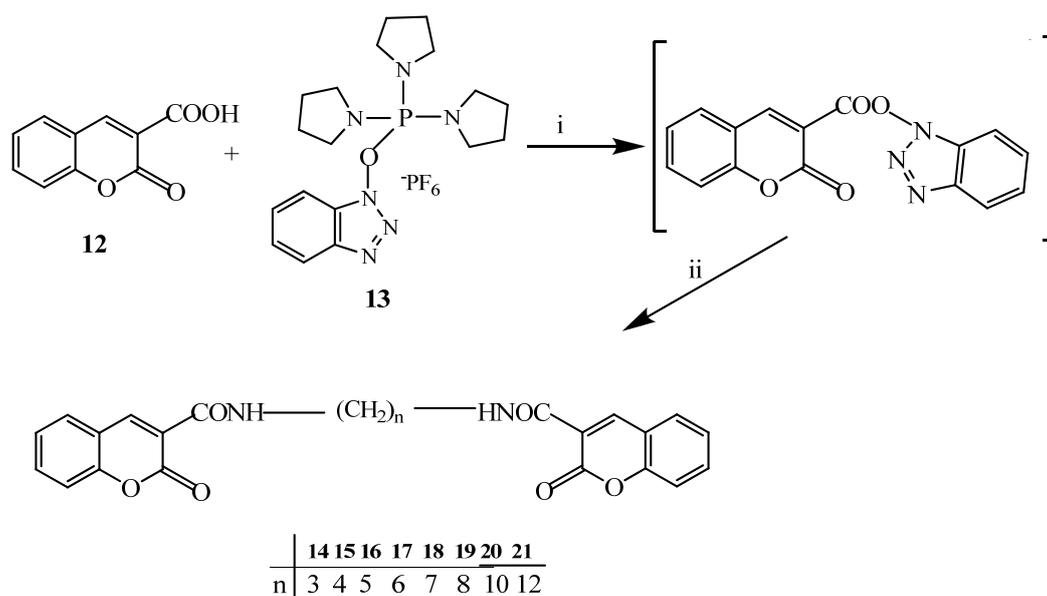


Reagents: *i.* K₂CO₃/acetone.

These new and convenient approaches to the synthesis of 4-hydroxy-, 7-hydroxycoumarins or other hydroxycoumarin derivatives were apparently caused by the nucleophilic attack on the activated aziridine rings. We used two hydroxycoumarins as starting materials in refluxing tetrahydrofuran (THF) and acetone in the presence of a base (NaOCH_3 or K_2CO_3) for 2–3 h to form “coumarin 5-O” and “coumarin 9-O” [the anions of 4-hydroxycoumarin (**5**) and 7-hydroxycoumarin (**9**)], and then reacted them with various activated aziridines. It was found that two isomers **7**, **8** or **10**, **11** were produced from each hydroxycoumarin in yields of 28%–88%. The main products generated from *N*-benzoylaziridines ($X = \text{C}$) were produced by abnormal regioselective ring-opening reactions producing **7d–g**, **10m–n**, and **10q** with strongly preferred cleavage of the N– CH_2 bond. In the similar reactions with tolylaziridines ($X = \text{SO}$), a mixture of normal regioselectivity ring-opening products **7h**, **8i–j**, **10k–l**, and **11k** were observed to predominate.

The syntheses of some coumarin dimers using Mn(III) or Fe(III) in the presence of a strong acid to obtain high yields were reported. We reacted coumarin acid **12** with diamines ($n = 3–12$) in the presence of PyBOP, DIEA, and dimethylformamide at room temperature or 60 °C with stirring for 18 h. The excess solvent, DIEA, and alkyldiamines were removed by column chromatography on silica gel to provide coumarin amide dimers **14–21** in excellent yields (82%–87%). The products were recrystallized from ether and methanol (Scheme 4). The yields of dimers seem not to be affected by the bulky PyBOP reagent and essentially no steric hindrance between diamines and coumarins was observed. The chemical structures of these products were established using spectroscopic methods including IR, ^1H -, ^{13}C -NMR, FAB-MS, HR-FAB-MS, and LC/MS/MS (ESI). The IR spectra of these amide dimers showed the C=O absorption peaks around 1647–1665 cm^{-1} . In the ^1H -NMR (in CDCl_3) the amide N–H absorption appeared at δ 8.79–8.92 ppm as a broad singlet. The ethylene amide dimers of coumarins revealed doublet of doublet signals at δ 3.47 ppm (–NH– CH_2 –). ^{13}C -NMR showed the amide (NH–C) signal at δ 161.4–161.8 ppm in the parent compounds.

Scheme 4. 3-Carboxycoumarin reactions with alkyldiamines.



Reagents: i, DIEA/THF; ii, 3-coumaric acid/THF, alkyldiamine.

2.2. Antibacterial Activity Test

Acyl coumarins **3a–4c**, 4-hydroxy-, and 7-hydroxycoumarins **7–11** and coumaric amide dimers **14–21** were tested against reference strains of *Bacillus subtilis* (BCRC 10029), *Staphylococcus aureus* (BCRC 11863), *Escherichia coli* (BCRC 11758), and *Pseudomonas aeruginosa* (BCRC 11733) obtained from The Bioresources Collection & Research Center (BCRC), Taiwan. Penicillin G potassium salt (CAS 113-98-4, USP grade) was used as a reference and purchased from Sigma-Aldrich (St. Louis, MO, USA). Bacteria were grown overnight in Müller-Hinton broth (Difco, Detroit, MI, USA) and trypticase soy broth (TSB, Oxoid, Basingstoke, Hampshire, UK).

The minimal inhibitory concentrations (MICs) of all synthesized compounds were determined using the reference method of broth dilution measurements. Each test compound and penicillin G was dissolved in DMSO/EtOH/phosphate buffer or phosphate buffer before a serial two-fold dilution to the desired test concentration ranges. DMSO/EtOH/phosphate buffer and phosphate buffer were used for the solvent control test. The seed was cultured with trypticase soy broth containing 10^7 colony forming units (cfu)/mL. Müller-Hinton broth was sterilized by autoclaving at 120 °C for 15 min, and microorganism were suspended in 96-well microplate. The final concentration of microorganism in each well was 10^5 cfu/mL. Modified 96-well plates were used with a two-fold micro-dilution method of the MTT assay in Müller-Hinton broth. Microorganism suspensions containing 10^5 cfu/mL were inoculated onto the 96-well microplates and mixed with the test compounds. The MIC was defined as the lowest concentration of test compounds, allowing no visible growth of test strain bacteria after incubation at 37 °C for 3 h. Then SDS in 0.1 N HCl was added. The absorbance was measured by ELISA reader (Bio-Tek Instruments, Microplate Autoreader, EL 311) at 595 nm.

3. Experimental

3.1. General

The IR spectra were recorded on a Thermo Mattson IR300 and Nicolet 510 PET spectrometers. Optical rotations were measured with a JASCO p-1020 digital polarimeter. NMR spectra were recorded at 500 (^1H -NMR) and 125 MHz (^{13}C -NMR) on a Bruker DRX-500 spectrometer in CDCl_3 or DMSO solution with respect to the corresponding solvent peak used as the internal standard. Mass spectra were measured on a Finnigan/Thermo Quest NAT 95XL, JEOL JMX-HX 110, JEOL JMSHX 110 FAB-MS, and LC/MS/MS Micromass Quattro II. The compounds were prepared according to similar procedures, and reactions took place in high-pressure tubes (Büchiglasuster, bursting disc, 0032). For the chromatographic analysis, Merck silica gel 60 was used. The chemical reagents used in the synthesis were purchased from Sigma-Aldrich and Merck. The crude products were purified by column chromatography and recrystallized using ether/methanol or *n*-hexane/methanol. Biological data were recorded on a Microplate Autoreader EL 311.

3.2. Preparation of Acylcoumarins

4-Hydroxycoumarin and its derivatives **1a–c** were added to a high-pressure tube (Bursting disc, Büchiglasuster) containing of acid anhydride **2**. The solution was stirred for 2 h at 150 °C. The dried

mass was separated by column chromatography (CHCl₃/EA/n-hexane = 8:1:1) to give compounds **3a–c**. Next the solution was stirred at 180 °C and purified by column chromatography to obtain the rearranged compounds **4a–c**.

3.3. Preparation of 4-hydroxy-, and 7-hydroxycoumarin Derivatives via Ring Opening of Activated Aziridines

Synthesis of 4-hydroxy-, and 7-hydroxycoumarin derivatives with activated aziridines are shown in Schemes 2 and 3. Compound **5** was dissolved in dry acetone, CH₃ONa and then added activated aziridine. The mixture was stirred at 130 °C, and dry mass was purified by column chromatography (CHCl₃/EA = 9:1) for compounds **7** and **8**. Compound **9** was dissolved in dry acetone then added K₂CO₃ with same procedure for compounds **10** and **11**.

3.4. Preparation of Coumarin Amide Dimers

Synthesis of the desired amide dimer derivatives of coumarin acid with alkyldiamines is shown in scheme 4. The PyBOP coupling reagent was used to prepare a series of coumarin acid amide dimers under mild conditions. Compound **12** was dissolved in dry dimethylformamide (DMF) then added various alkyldiamines. When the mixtures were cooled PyBOP solution DMF and diisopropylethylamine (DIEA) was added. After the mixture was allowed to warm to room temperature and stirred for 18 h the residues were purified by column chromatography (CHCl₃/acetone = 10:1) for compounds **14–21**.

4-O-Acetyl-7-methoxycoumarin (3a). M.p. 131–134 °C. ¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 3.86 (3H, s), 6.82 (1H, d, *J* = 2.1 Hz), 6.84 (1H, dd, *J* = 7.6, 2.1 Hz), 7.47 (1H, d, *J* = 7.6 Hz), IR (KBr, cm⁻¹) 1656 (C = O), 1721 (lactone).

4-O-Acetyl-6-methylcoumarin (3b). M.p. 128–130 °C. ¹H-NMR (CDCl₃) δ: 2.45 (3H, s), 2.47 (3H, s), 6.32 (1H, s), 7.26 (1H, d, *J* = 7.5 Hz), 7.46 (1H, dd, *J* = 7.5, 2.1 Hz), IR (KBr, cm⁻¹) 1645, 1680 (C=O).

4-O-Acetyl-6,7-dimethylcoumarin (3c). M.p. 157–159 °C. ¹H-NMR (CDCl₃) δ: 2.35 (3H, s), 2.36 (3H, s), 2.42 (3H, s), 6.27 (1H, s), 7.13 (1H, s), 7.67 (1H, s). IR (KBr, cm⁻¹) 1657, 1720 (C=O).

4-O-Propionyl-7-methoxycoumarin (3a₁). M.p. 176–177 °C. ¹H-NMR (CDCl₃) δ: 1.53 (3H, t, *J* = 7.6 Hz), 2.45 (2H, q, *J* = 7.6 Hz), 3.86 (3H, s), 6.50 (1H, dd, *J* = 8.3, 2.4 Hz), 7.69 (1H, *J* = 8.3 Hz). IR (KBr) 1645, 1748 (C=O) cm⁻¹.

4-O-Propionyl-6-methylcoumarin (3b₁). M.p. 154–156 °C. ¹H-NMR (CDCl₃) δ: 1.22 (3H, t, *J* = 7.6 Hz), 2.43 (3H, s), 3.22 (2H, q, *J* = 7.6 Hz), 7.04 (1H, s), 7.20 (1H, d, *J* = 7.9 Hz), 7.47 (1H, dd, *J* = 7.9, 1.9 Hz), 7.84 (1H, s). IR (KBr, cm⁻¹) 1634, 1701 (C=O).

4-O-Propionyl-6,7-dimethylcoumarin (3c₁). M.p. 167–168 °C. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J* = 7.5 Hz), 2.31 (3H, s), 2.35 (3H, s), 2.72 (2H, q, *J* = 7.5 Hz), 6.41 (1H, s), 7.14 (1H, s), 7.30 (1H, s). IR (KBr, cm⁻¹) 1646, 1711 (C=O). MS *m/z* (rel. int %): 246 (M)⁺ (14), 190 (51), 148 (78), 91 (20), 57 (100).

4-O-Benzoyl-7-methoxycoumarin (3a₂). M.p. 147–148 °C. ¹H-NMR (CDCl₃) δ: 3.87 (3H, s), 6.42 (1H, s), 6.84 (1H, d, *J* = 2.2 Hz), 6.84 (1H, dd, *J* = 7.5, 2.2 Hz), 7.54 (1H, d, *J* = 7.5 Hz), 7.54 (2H, t, *J* = 7.5 Hz), 7.68 (1H, t, *J* = 7.5 Hz), 8.20 (2H, d, *J* = 7.5 Hz). IR (KBr, cm⁻¹) 1640, 1710 (C=O). MS *m/z* (rel. int %): 296 (M)⁺ (2), 105 (1), 77 (40), 51 (20).

4-O-Benzoyl-6-methylcoumarin (3b₂). M.p. 126–128 °C. ¹H-NMR (CDCl₃) δ: 2.41 (3H, s), 6.56 (1H, s), 7.29 (1H, d, *J* = 8.4 Hz), 7.39 (1H, dd, *J* = 8.4, 2.1 Hz), 7.44 (1H, d, *J* = 2.1 Hz), 7.58 (2H, t, *J* = 7.7 Hz), 7.72 (1H, t, *J* = 7.7 Hz), 8.24 (2H, d, *J* = 7.7 Hz). IR (KBr, cm⁻¹) 1645, 1720 (C=O).

4-O-Benzoyl-6,7-dimethylcoumarin (3c₂). M.p. 163–164 °C. ¹H-NMR (CDCl₃) δ: 2.26 (3H, d, *J* = 7.1 Hz), 2.33 (3H, d, *J* = 7.1 Hz), 6.46 (1H, s), 7.16 (1H, s), 7.35 (1H, s), 7.55 (2H, t, *J* = 7.9 Hz), 7.69 (1H, t, *J* = 7.9 Hz), 8.21 (2H, d, *J* = 7.9 Hz). IR (KBr, cm⁻¹) 1665, 1728 (C=O).

3-Acetyl-4-hydroxy-7-methoxycoumarin (4a). M.p. 194–196 °C. ¹H-NMR (CDCl₃) δ: 2.73 (3H, s), 3.89 (3H, s), 6.72 (1H, d, *J* = 2.1 Hz), 6.85 (1H, dd, *J* = 8.9, 2.1 Hz), 7.92 (1H, d, *J* = 8.9 Hz). IR (KBr, cm⁻¹) 1661, 1753 (C=O), 3442 (OH). LC/MS/MS (ESI) *m/z*, (rel. int. %): 234.9(M)⁺ (20), 217.3 (–OH, 100), 192.9 (–acetyl, 62), 151.1 (74).

3-Acetyl-4-hydroxy-6-methylcoumarin (4b). M.p. 156–159 °C. ¹H-NMR (CDCl₃) δ: 2.43 (3H, s), 2.78 (3H, s), 7.19 (1H, d, *J* = 8.4 Hz), 7.48 (1H, dd, *J* = 8.4, 1.5 Hz), 7.84 (1H, s). IR (KBr) 1661, 1753 (C=O), 3410 (OH). LC/MS/MS (ESI) *m/z*, (rel. int. %) 243.2 (M+Na) (80), 203.1 (M+Na–OH, 90), 135.1 (100).

3-Acetyl-4-hydroxy-6, 7-dimethylcoumarin (4c). M.p. 168–170 °C. ¹H-NMR (CDCl₃) δ: 2.36 (3H, s), 2.41 (3H, s), 2.79 (3H, s), 7.11 (1H, s), 7.50 (1H, s). IR (KBr, cm⁻¹) 1631, 1723 (C=O), 3419 (OH). LC/MS/MS (ESI) *m/z*, (rel. int. %) 233.2 (M+H) (30), 215.1 (M+H–H₂O), (100), 149.2 (60).

3-Acetyl-4-hydroxy-7-methoxycoumarin (4a₁). M.p. 197–199 °C. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J* = 7.6 Hz), 2.72 (2H, q, *J* = 7.6 Hz), 3.86 (3H, s), 6.79 (1H, d, *J* = 2.2 Hz), 6.90 (1H, dd, *J* = 7.8, 2.2 Hz), 7.83 (1H, d, *J* = 7.8 Hz). IR (KBr, cm⁻¹) 1653, 1763 (C=O), 3438 (OH). LC/MS/MS (ESI) *m/z*, (rel. int. %) 287.0 (M+K) (60), 272.1 (M+K–CH), (100), 257.3 (M+K–OCH₃) (33), 244.1 (M+K–C₃H₇) (90).

3-Propionyl-4-hydroxy-6-methylcoumarin (4b₁). M.p. 191–192 °C. ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.5 Hz), 2.47 (3H, s), 2.77 (2H, q, *J* = 7.1 Hz), 7.46 (1H, dd, *J* = 7.1, 2.1 Hz), 7.73 (1H, s), IR (KBr, cm⁻¹) 1652, 1759 (C=O). LC/MS/MS (ESI) *m/z*, (rel. int. %) 271.2 (M+K)⁺ (40), 256.0 (M+K–CH₃)⁺ (60), 203.2 (70), 135.0(100).

3-Propionyl-4-hydroxy-6,7-dimethylcoumarin (4c₁). M.p. 201–202 °C. ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.6 Hz), 2.35 (3H, s), 2.37 (3H, s), 2.74 (2H, q, *J* = 7.6 Hz), 7.12 (1H, s), 7.65 (1H, s). IR (KBr, cm⁻¹) 1652, 1730 (C=O), 3400 (OH). LC/MS/MS (ESI) *m/z*, (rel. int. %) 285.1 (M+K)⁺ (80), 270.3 (M+K–CH₃)⁺, 255.1 (23), 227.0 (18), 217.2 (70), 149.1 (100), 105.0 (18).

3-Benzoyl-4-hydroxy-7-methoxycoumarin (4a₂). M.p. 182–183 °C. ¹H-NMR (CDCl₃) δ: 3.89 (3H, s), 6.86 (1H, d, *J* = 2.3 Hz), 6.88 (1H, dd, *J* = 7.7, 2.3 Hz), 7.56 (1H, t, *J* = 7.7 Hz), 7.54 (2H, t, *J* = 7.8 Hz), 7.72 (1H, t, *J* = 7.8 Hz), 8.22 (2H, d, *J* = 7.8 Hz). IR (KBr, cm⁻¹) 1650, 1714 (C=O), 3425 (OH).

3-Benzoyl-4-hydroxy-6-methylcoumarin (4b₂). M.p. 176–178 °C. ¹H-NMR (CDCl₃) δ: 2.41 (3H, s), 7.29 (1H, d, *J* = 7.6 Hz), 7.40 (1H, dd, *J* = 7.6, 1.8 Hz), 7.46 (1H, s), 7.58 (2H, t, *J* = 7.7 Hz), 7.72 (1H, t, *J* = 7.7 Hz), 8.24 (2H, d, *J* = 7.7 Hz). IR (KBr, cm⁻¹) 1655, 1724 (C=O), 3445 (OH).

3-Benzoyl-4-hydroxy-6,7-dimethylcoumarin (4c₂). M.p. 197–198 °C. ¹H-NMR (CDCl₃) δ: 2.30 (3H, d, *J* = 7.1 Hz), 2.37 (3H, d, *J* = 7.1 Hz), 7.16 (1H, s), 7.38 (1H, s), 7.57 (2H, t, *J* = 7.7 Hz), 7.71 (1H, t, *J* = 7.7 Hz), 8.24 (2H, d, *J* = 7.7 Hz). IR (KBr, cm⁻¹) 1665, 1728 (C=O), 3480 (OH).

4-(N-Benzoylamino)ethoxycoumarin (7d). M.p. 172–173 °C. ¹H-NMR (CDCl₃) δ: 4.01 (2H, t, *J* = 5.2 Hz), 4.32 (2H, t, *J* = 5.2 Hz), 5.71 (1H, s), 6.53 (1H, s), 7.28 (1H, d, *J* = 7.7 Hz), 7.32 (1H, t, *J* = 7.7 Hz), 7.43 (2H, t, *J* = 8.2 Hz), 7.44 (1H, t, *J* = 7.7 Hz), 7.52 (1H, t, *J* = 8.2 Hz), 7.78 (1H, d, *J* = 7.7 Hz), 7.83 (2H, d, *J* = 8.2 Hz). IR (KBr, cm⁻¹) 1653, 1730 (C=O), 3223 (NH). MS *m/z* (rel. int. %) 309 (2), 148 (91), 105 (100), 77 (95). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₁₈H₁₅NO₄ 309.1001, found 309.1000.

4-[(N-Benzoylamino)-2-propoxyl]coumarin (7e). M.p. 193–194 °C. ¹H-NMR (CDCl₃) δ: 1.41 (3H, d, *J* = 6.1 Hz), 3.79 (1H, dd, *J* = 6.4, 10.2 Hz), 3.94 (1H, dd, *J* = 3.8, 6.3, 10.2 Hz), 4.88 (1H, dd, *J* = 6.4, 10.2 Hz), 5.78 (1H, s), 7.25 (1H, d, *J* = 7.3 Hz), 7.27 (1H, t, *J* = 7.3 Hz), 7.39 (1H, t, *J* = 7.3 Hz), 7.42 (2H, t, *J* = 7.8 Hz), 7.78 (2H, d, *J* = 7.8 Hz). IR (KBr, cm⁻¹) 1635, 1735 (C=O), 3214 (NH). MS *m/z*, (rel. int. %) 323 (1), 174 (25), 148 (48), 59 (100).

4-[(N-Benzoylamino)-2-methyl-2-propoxy]coumarin (7f). M.p. 198–200 °C. ¹H-NMR (CDCl₃) δ: 1.38 (3H, s), 3.88 (2H, d, *J* = 6.3 Hz), 5.87 (1H, s), 6.52 (1H, t-like), 7.27 (1H, *J* = 7.6 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 7.41 (1H, t, *J* = 7.6 Hz), 7.44 (2H, t, *J* = 7.9 Hz), 7.75 (1H, d, *J* = 7.6 Hz), 7.78 (1H, t, *J* = 7.9 Hz), 7.79 2H, d, *J* = 7.9 Hz). IR (KBr, cm⁻¹) 1648, 1742 (C=O), 3300 (NH). MS *m/z*, (rel. int. %) 337 (M)⁺ (1), 212 (21), 141 (25), 77 (100), 70 (90). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₂₀H₁₉NO₄ 337.1314, found 337.1322.

4-[(N-Ethylcarbamyl)ethyl]coumarin (7g). M.p. 123–124 °C. ¹H-NMR (CDCl₃) δ: 1.24 (3H, t, *J* = 6.5 Hz), 3.71 (2H, d, *J* = 5.1 Hz), 4.14 (2H, t, *J* = 5.1 Hz), 4.17 (2H, q, *J* = 6.5 Hz), 5.03 (1H, s), 5.68 (1H, s), 7.28 (1H, d, *J* = 7.9 Hz), 7.31 (1H, t, *J* = 7.9 Hz), 7.54 (1H, t, *J* = 7.9 Hz), 7.80 (1H, d, *J* = 7.9 Hz). IR (KBr, cm⁻¹) MS *m/z*, (rel. int. %) 277 (10), 116 (80), 88 (100).

4-[(N-Benzosulfonyl)-1,1-dimethylethyl]coumarin (7h). M.p. 169–171 °C. ¹H-NMR (CDCl₃) δ: 1.61 (6H, s), 3.31 (2H, d, *J* = 6.8 Hz), 5.72 (1H, s), 7.23–7.29 (2H, dd, *J* = 8.1, 8.2 Hz), 7.54 (3H, dd, *J* = 1.3, 7.4 Hz), 7.62 (2H, ddd, *J* = 1.2, 7.4, 7.8 Hz), 7.86 (2H, dd-like, *J* = 1.1, 7.2 Hz). IR (KBr, cm⁻¹) 1638, 1692 (C=O), 3200 (NH). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₁₉H₁₉NO₅S 373.0984, found 373.0986.

4-[(*N-p-Tolylsulfonyl*)-2-methylethyl]coumarin (**8i**). M.p. 154–156 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, d, $J = 6.8$ Hz), 2.39 (3H, s), 3.83 (1H, m), 3.96 (2H, d, $J = 3.8$ Hz), 4.93 (1H, d, $J = 7.7$ Hz), 5.48 (1H, s), 7.21 (1H, d, $J = 7.6$ Hz), 7.23 (1H, t, $J = 7.6$ Hz), 7.29 (2H, d, $J = 8.2$ Hz), 7.53 (1H, t, $J = 7.6$ Hz), 7.65 (1H, d, $J = 7.6$ Hz), 7.72 (2H, d, $J = 8.2$ Hz). IR (KBr, cm^{-1}) 1620, 1693 (C=O), 3172 (NH). MS m/z , (rel. int. %) 373 (10), 218 (25), 155 (46), 91 (100). HR-FAB-MS (EI, 80 eV) m/z , calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_5\text{S}$ 373.0984, found 373.0986.

4-[(*N-p-Tolylsulfonyl*)-1,1-dimethylethyl]coumarin (**8j**). M.p. 187–190 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (3H, s), 2.23 (3H, s), 3.89 (2H, s), 4.97 (1H, s), 5.85 (1H, s), 7.07 (1H, d, $J = 7.3$ Hz), 7.28 (1H, t, $J = 7.3$ Hz), 7.53 (1H, t, $J = 7.3$ Hz), 7.65 (2H, d, $J = 7.5$ Hz), 7.68 (1H, d, $J = 7.3$ Hz), 7.73 (2H, d, $J = 7.5$ Hz). IR (KBr, cm^{-1}) 1620, 1683 (C=O), 3425 (NH). MS m/z , (rel. int. %) 387 (M^+) (2), 212 (25), 155 (30), 91 (100), 70 (70).

7-[(*N-p-Tosyl*)-2,2-dimethylethyloxy]coumarin (**10k**). M.p. 220–221 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (6H, s), 2.45 (3H, s), 3.76 (2H, s), 4.91 (1H, s), 6.72 (1H, d, $J = 9.5$ Hz), 6.62 (1H, bs), 6.76 (1H, dd, $J = 8.5, 1.8$ Hz), 7.18 (2H, d, $J = 7.9$ Hz), 7.36 (1H, d, $J = 7.9$ Hz), 7.63 (1H, d, $J = 9.5$ Hz), 7.74 (2H, d, $J = 8.0$ Hz). IR (KBr, cm^{-1}) 1692 (C=O), 3406 (NH).

7-[(*N-p-Tosyl*)-2-methylethyloxy]coumarin (**10l**). M.p. 110–111 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.15 (3H, s), 2.26 (3H, s), 3.62 (1H, t-like, $J = 5.5$ Hz), 3.73 (1H, dd, $J = 5.1, 9.3$ Hz), 3.81 (1H, dd, $J = 4.9, 9.2$ Hz), 5.87 (1H, d, $J = 7.6$ Hz), 6.12 (1H, d, $J = 9.2$ Hz), 6.50 (1H, bs), 6.58 (1H, d, $J = 8.3$ Hz), 7.13 (2H, d, $J = 7.7$ Hz), 7.21 (1H, d, $J = 8.5$ Hz), 7.56 (1H, d, $J = 9.5$ Hz), 7.67 (2H, d, $J = 8.0$ Hz). IR (KBr, cm^{-1}) 1718 (C=O), 3421 (NH).

7-[(*N-Phenylaminylcarboxamido*)ethyloxy]coumarin (**10m**). M.p. 164–165 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 3.53 (2H, t, $J = 5.5$ Hz), 4.07 (2H, t, $J = 5.3$ Hz), 6.14 (1H, d, $J = 9.5$ Hz), 6.24 (1H, t, $J = 5.6$ Hz), 6.78 (1H, d, $J = 2.3$ Hz), 6.82 (1H, dd, $J = 2.8, 8.6$ Hz), 6.83 (1H, ddd, $J = 1.7, 2.7, 6.9$ Hz), 7.13 (2H, dd, $J = 2.3, 8.0$ Hz), 7.30 (2H, d, $J = 8.0$ Hz), 7.39 (1H, d, $J = 8.6$ Hz), 7.68 (1H, d, $J = 8.1$ Hz), 8.23 (1H, s). IR (KBr, cm^{-1}) 1660, 1701 (C=O), 3312 (NH).

7-[(*N-Benzoyl*)-1-methylethyloxy]coumarin (**10n**). M.p. 135–136 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (3H, d, $J = 6.8$ Hz), 4.15 (2H, ddd, $J = 4.5, 9.3, 12.4$ Hz), 4.65 (1H, dd, $J = 3.5, 7.1$ Hz), 6.25 (1H, d, $J = 9.5$ Hz), 6.85 (1H, d, $J = 2.2$ Hz), 6.89 (1H, dd, $J = 7.8, 2.3$ Hz), 7.38 (1H, d, $J = 8.6$ Hz), 7.44 (2H, dd, $J = 7.8, 2.1$ Hz), 7.50 (1H, d, $J = 7.3$ Hz), 7.62 (1H, d, $J = 9.5$ Hz), 7.77 (2H, d, $J = 7.5$ Hz). IR (KBr, cm^{-1}) 1662, 1708 (C=O), 3330 (NH).

7-[(2-Adamantanecarboxamido)ethyloxy]coumarin (**10o**). Oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (3H, s), 1.72 (6H, dd, $J = 12.3, 26.9$ Hz), 1.86 (6H, d, $J = 2.4$ Hz), 2.05 (3H, s), 3.69 (2H, dd, $J = 5.5, 10.8$ Hz), 4.10 (2H, t, $J = 5.1$ Hz), 6.03 (1H, s), 6.26 (1H, d, $J = 9.5$ Hz), 6.82 (1H, d, $J = 2.2$ Hz), 6.85 (1H, dd, $J = 8.6, 2.4$ Hz), 7.38 (1H, d, $J = 8.5$ Hz), 7.63 (1H, d, $J = 9.5$ Hz). IR (KBr, cm^{-1}) 1663, 1705 (C=O), 3282 (NH).

7-[(*N-p-Phenylbenzoyl*)-ethyloxy]coumarin (**10p**). M.p. 216–217 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 3.95 (2H, dd, $J = 5.5, 10.8$ Hz), 4.24 (2H, t, $J = 5.1$ Hz), 6.86 (1H, d, $J = 2.3$ Hz), 6.88 (1H, dd, $J = 8.4, 2.3$ Hz),

7.39 (2H, d, $J = 8.4$ Hz), 7.46 (2H, t, $J = 7.6$ Hz), 7.61 (2H, t, $J = 4.5$ Hz), 7.63 (1H, d, $J = 9.5$ Hz), 7.67 (2H, d, $J = 8.3$ Hz), 7.87 (2H, d, 8.3 Hz). IR (KBr, cm^{-1}) 1656, 1697 (C=O), 3356 (NH).

7-[(*N*-Benzoyl)-1,1-dimethylethyloxy]coumarin (**10q**). M.p. 104–105 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (6H, s), 3.71 (2H, d, $J = 6.0$ Hz), 6.27 (1H, d, $J = 9.5$ Hz), 6.76 (1H, d, $J = 4.2$ Hz), 6.88 (1H, d, $J = 2.2$ Hz), 6.89 (1H, dd, $J = 8.3, 2.2$ Hz), 7.36 (1H, d, $J = 8.4$ Hz), 7.43 (2H, t, $J = 7.5$ Hz), 7.49 (1H, t, $J = 7.3$ Hz), 7.63 (1H, d, $J = 9.5$ Hz), 7.81 (2H, d, $J = 7.4$ Hz). IR (KBr, cm^{-1}) 1651, 1692 (C=O), 3366 (NH).

7-[(*N*-Ethylcarbamyloxy)ethyloxy]coumarin (**10r**). M.p. 115–116 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (3H, t, $J = 6.8$ Hz), 3.62 (2H, d, $J = 5.1$ Hz), 4.09 (1H, t, $J = 5.0$ Hz), 4.14 (1H, t, $J = 6.8$ Hz), 5.10 (1H, bs), 6.26 (1H, d, $J = 9.6$ Hz), 6.80 (1H, d, $J = 1.8$ Hz), 6.84 (1H, dd, $J = 8.6, 2.2$ Hz), 7.38 (1H, d, $J = 8.6$ Hz), 7.63 (1H, d, $J = 9.5$ Hz). IR (KBr, cm^{-1}) 1677, 1733 (C=O), 3292 (NH).

7-[(*N*-*p*-Tosyl)-1,1-dimethylethyloxy]coumarin (**11k**). M.p. 177–178 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (6H, s), 2.45 (3H, s), 3.12 (2H, d, $J = 6.4$ Hz), 4.88 (1H, t, $J = 5.8$ Hz), 6.32 (1H, d, $J = 9.5$ Hz), 6.80 (2H, d, $J = 7.3$ Hz), 7.35 (3H, dd, $J = 7.4, 5.5$ Hz), 7.64 (1H, d, $J = 9.5$ Hz), 7.76 (2H, d, $J = 8.1$ Hz). IR (KBr, cm^{-1}) 1721 (C=O), 3416 (NH)

Bis(3-coumarin)propylenediamide (**14**). M.p. 264–265 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.98 (2H, dd, $J = 6.5, 13.3$ Hz), 3.58 (2H, dd, $J = 6.4, 12.8$ Hz), 7.38 (2H, dd, $J = 7.9, 7.6$ Hz), 7.67 (2H, ddd, $J = 1.1, 7.4, 8.4$ Hz), 8.92 (1H, bs), 9.01 (1H, s). $^{13}\text{C-NMR}$ δ 29.61 (CH_2CN), 37.40 ($2 \times \text{CCH}_2\text{N}$), 116.62 (C-4,4'), 118.55 (C-8,8'), 118.68 (C-5,5'), 125.22 (C-6,6'), 129.77 (C-7,7'), 133.94 (C-9,9'), 148.31 (C-3,3'), 154.46 (C-10,10'), 161.38 (OCN), 161.82 (O=CO). IR (KBr, cm^{-1}) 1658, 1705 (C=O), 3341 (NH). HR-FAB-MS (EI, 80 eV) m/z , calculated for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_6$ 418.1165, found 418.1163.

Bis(3-coumarin)butamethylenediamide (**15**). M.p. 250–251 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.75 (2H, t, $J = 2.8$ Hz), 3.52 (2H, d, $J = 5.8$ Hz), 7.39 (2H, dd, $J = 8.8, 7.5$ Hz), 7.68 (2H, ddd, $J = 8.8, 7.7, 1.4$ Hz), 8.86 (1H, bs, NH), 8.91 (1H, s, H-4). $^{13}\text{C-NMR}$ δ : 27.02 ($2 \times \text{NCCH}_2$), 39.47 ($2 \times \text{NCH}_2\text{C}$), 116.61 (C-4,4'), 118.51 (C-8,8'), 118.67 (C-5,5'), 125.25 (C-6,6'), 129.79 (C-7,7'). 133.96 (C-9,9'), 148.31 (C-3,3'), 154.41 (C-10,10'), 161.41 (OCN), 161.48 (O=CO). IR (KBr, cm^{-1}) 1658, 1710 (C=O), 3337 (NH). HR-FAB-MS (EI, 80 eV) m/z , calculated for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_6$ 432.1321, found 432.1471.

Bis(3-coumarin)pentamethylenediamide (**16**). M.p. 221–222 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.52 (2H, ddd, $J = 6.9, 8.4, 12.1$ Hz), 1.70 (4H, dd, $J = 7.3, 14.7$ Hz), 3.49 (4H, dd, $J = 13.1, 6.9$ Hz, 2N- CH_2), 7.38 (4H, dd, $J = 7.7, 8.8$ Hz), 7.67 (4H, dd, $J = 7.7, 8.4$ Hz), 8.82 (2H, bs, NH), 8.90 (2H, s, H-4,4'). $^{13}\text{C-NMR}$ δ : 24.38 (NCCCH_2), 29.08 ($2 \times \text{NCCH}_2$), 39.67 ($2 \times \text{CH}_2$), 116.61 (C-4,4'), 118.63 (C-8,8'), 118.72 (C-5,5'), 125.22 (C-6,6'), 129.77 (C-7,7'), 133.88 (C-9,9'), 148.19 (C-3,3'), 154.43 (C-10,10'), 161.45 (OCN), 161.47 (OCO). IR (KBr, cm^{-1}) 1654, 1702 (C=O). HR-FAB-MS (EI, 80 eV) m/z , calculated for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_6$ 446.1478, found 446.1477.

Bis(3-coumarin)hexamethylenediamide (**17**). M.p. 212–213 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (4H, t-like, $J = 7.1, 12.2$ Hz), 1.66 (4H, t-like $J = 6.7, 13.5$ Hz), 3.47 (4H, dd, $J = 6.8, 13.1$ Hz), 7.38 (4H, dd, $J = 7.6, 8.5$ Hz), 7.68 (4H, dd, $J = 7.2, 8.5$ Hz), 8.81 (2H, bs, NH), 8.91 (2H, s, H-4,4'). $^{13}\text{C-NMR}$ δ :

26.71 (2×NCCCCH₂), 29.31 (2×NCCH₂), 39.80 (2×NCH₂), 116.61 (C-4,4'), 118.65 (C-8,8'), 118.72 (C-5,5'), 125.22 (C-6,6'), 129.76 (C-7,7'), 133.88 (C-9,9'), 148.17 (C-3,3'), 154.42 (C-10,10'), 161.41 (OCN), 161.48 (OCO). IR (KBr, cm⁻¹) 1668, 1712 (C=O), 3341 (NH). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₂₆H₂₄N₂O₆ 460.1634, found 460.1640.

Bis(3-coumarin)heptamethylenediamide (18). M.p. 198–199 °C. ¹H-NMR (CDCl₃) δ: 1.42 (6H, s, NCC(CH₂)₃), 1.64 (4H, t-like, *J* = 6.2, 12.9 Hz, NC(CH₂)₂), 3.47 (4H, dd, *J* = 7.0, 13.1 Hz, N(CH₂)₂), 7.38 (4H, dd, *J* = 7.5, 9.2 Hz, H-6,6',8,8'), 7.66 (4H, dd, *J* = 1.1, 7.7, 9.0 Hz, H-5,5',7,7'), 8.80 (2H, bs, 2×NH), 8.91 (2H, s, H-4,4'). ¹³C-NMR δ: 26.90 (NCCCCH₂), 28.94 (NCCCH₂), 29.32 (NCCH₂), 39.85 (NCH₂), 116.0 (C-4,4'), 118.65 (C-8,8'), 118.72 (C-5,5'), 125.21 (C-6,6'), 129.75 (C-7,7'), 133.87 (C-9,9'), 148.16 (C-3,3'), 154.41 (C-10,10'), 161.37 (CON), 161.47 (COO). IR (KBr, cm⁻¹) 1662, 1704 (C=O), 3368 (NH). MS (rel.int. %) 475.384 (M⁺+H) (40), 191.041 (100), 173.029 (80). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₂₇H₂₆N₂O₆ 474.1791, found 474.2761.

Bis(3-coumarin)octamethylenediamide (19). M.p. 199–200 °C. ¹H-NMR (CDCl₃) δ: 1.31 (8H, t-like, *J* = 3.8, 7.1 Hz), 1.63 (4H, dd, *J* = 7.1, 14.0 Hz), 3.46 (4H, dd, *J* = 7.0, 13.1 Hz, 2×NCH₂), 7.38 (4H, dt, *J* = 1.4, 7.5, 8.4 Hz, H-6,6',8,8'), 7.67 (4H, dddd, *J* = 1.0, 1.2, 8.6, 8.9 Hz, H-5,5',7,7'), 8.80 (2H, bs, 2×NH), 8.91 (2H, s, H-4,4'). ¹³C-NMR δ: 26.94 (NCCCCH₂), 29.16 (NCCCH₂), 29.36 (NCCH₂), 39.90 (NCH₂), 116.61 (C-4,4'), 118.67 (C-8,8'), 118.72 (C-5,5'), 125.22 (C-6,6'), 129.76 (C-7,7'), 133.88 (C-9,9'), 148.14 (C-3,3'), 154.42 (C-10,10'), 161.37 (OCN), 161.49 (OCO). IR (KBr, cm⁻¹) 1665, 1710 (C=O), 3342 (NH). HR-FAB-MS (EI, 80 eV) *m/z*, calculated for C₂₈H₂₈N₂O₆ 488.1947, found 488.1951.

Bis(3-coumarin)decamethylenediamide (20). M.p. 203–204 °C. ¹H-NMR (CDCl₃) δ: 1.37 (12H, t-like, *J* = 5.9, 8.9 Hz), 1.63 (4H, dt, *J* = 7.4, 14.3 Hz), 3.46 (4H, dd, *J* = 6.9, 13.2 Hz, NCH₂), 7.38 (4H, *J* = 7.5, 8.1 Hz, H-6,6',8,8'), 7.67 (4H, dd, *J* = 7.7, 8.6 Hz, H-5,5',7,7'), 8.80 (2H, bs, NH), 8.91 (2H, s, H-4,4'). ¹³C-NMR δ: 27.01, 29.26, 29.38, 29.43, 39.96 (NCH₂), 116.61 (C-4,4'), 118.68 (C-8,8'), 118.73 (C-5,5'), 125.22 (C-6,6'), 129.76 (C-7,7'), 133.88 (C-9,9'), 148.14 (C-3,3'), 154.42 (C-10,10'), 161.39 (OCN), 161.49 (OCO). IR (KBr, cm⁻¹) 1647, 1688 (C=O), 3310 (NH). LCMS 517.305 (M⁺+H), HR-FAB-MS (EI, 80eV) *m/z*, calculated for C₃₀H₃₂N₂O₆ 512.2260, found 516.2051.

Bis(3-coumarin)dodecamethylenediamide (21). M.p. 172–173 °C. ¹H-NMR (CDCl₃) δ: 1.36 (16H, ddd, *J* = 6.6, 7.5, 13.5 Hz), 1.63 (4H, dt, *J* = 7.5, 14.4 Hz), 3.45 (4H, dd, *J* = 7.0, 13.1 Hz, 2×NCH₂), 7.38 (4H, dt, *J* = 7.5, 8.4 Hz, H-6,6',8,8'), 7.68 (4H, dddd, *J* = 1.3, 5.7, 7.6, 8.7 Hz, H-5,5',7,7'), 8.79 (2H, bs, NH), 8.91 (2H, s, H-4,4'). ¹³C-NMR δ: 27.03, 29.30, 29.38, 29.51, 29.54, 39.96 (NCH₂), 116.61 (C-4,4'), 118.68 (C-8,8'), 118.73 (C-5,5'), 125.22 (C-6,6'), 129.76 (C-7,7'), 133.88 (C-9,9'), 148.14 (C-3,3'), 154.42 (C-10,10'), 161.39 (OCN), 161.49 (OCO). IR (KBr, cm⁻¹) 1664, 1707 (C=O), 3362 (NH). HR-FAB-MS (EI, 80eV) *m/z*, calculated for C₃₂H₃₆N₂O₆ 544.2573, found 544.2572.

4. Conclusions

Synthesis of coumarin derivatives via the ring-opening reaction with activated aziridines has not been reported previously. The reaction of the coumarin anion with *N*-benzoyl- or *N*-sulfonylaziridines

6 yielded amidoethylated 7- or 4-hydroxycoumarins **7**, **8**, **9** and **10**. The final results depend on the substitution of the *N*-acyl or *N*-sulfonyl groups on the acyl group, so the benzoyl and the coumarin anions will attack from an abnormal position to provide the major products **7d–f**, **10n**, and **10q**. The main products resulted from normal ring-opening of the activated aziridines **7h**, **8i**, **8j**, **10k–l**, and **11k**. It was assumed that compounds **7**, **8**, **10**, **11**, and their analogues were formed by the nucleophilic attack of acylaziridines via an S_N2-like ring opening mechanism. In our previous work, when PyBOP (**13**) used as a coupling reagent to synthesize natural amide dimers, relatively high yields were obtained. In general, for the formation of amide or dimer chains, the reaction temperature had a great influence on the structural conformation. From NMR spectroscopic analysis, the intermediate, coumarin-triazobenzene, displayed rearrangement characteristics. The antimicrobial tests performed on coumarin derivatives **3c**, **3c₁**, **4a₂**, **4b**, **4c**, and **7f** confirmed the better potential activities of these compounds against Gram-positive rather than Gram-negative bacteria. Compound **7f** was the most potent of these tested compounds against *B. subtilis*, with a MIC value of 8 µg/mL, while the coumarin amide dimers **14–21** displayed lower antibacterial activities (the MICs are >128 to 256).

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Sample Availability: Samples of the compounds **14–21** are available from the authors.

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