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Synthesis of Geranyloxycoumarin Derivatives under Mild Conditions Using Cs_2CO_3

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Abstract: In this study, the synthesis of various geranyloxycoumarin derivatives from hydroxycoumarin was obtained in good yield under mild conditions using Cs_2CO_3. In the synthesis of geranyloxycoumarin derivatives, when 4-hydroxycoumarin reacts with geranyl bromide under mild conditions due to tautomeric keto-enol forms, 4-geranyoxycoumarin (3a), C-alkylated coumarin (3aa) and structure 3ab formed by hydrolysis and decarboxylation from 3aa were formed products. In addition, the alkylation reaction of 3-OH, 5-OH, 6-OH, 7-OH, and 8-OH coumarin except 4-OH group produced a high yield.

Keywords: Geranyloxycoumarin derivatives; 4-hydroxycoumarin; tautomeric keto-enol forms; coumarin compounds; geranyl bromide.

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INTRODUCTION

Coumarin and its derivatives are widely used in the synthesis of bioactive molecules (1). The derivatives also show a broad spectrum of beneficial effects, such as anti-inflammatory (2–6), anti-HIV (7–9), anticancer (10–15), antimicrobial (16–18), antitumor (19–23), anti-platelet (24), COX inhibitors (25), antioxidant (26–33), and antibacterial (34,35) activities.

Among them, hydroxylated coumarin secondary metabolites are essential in the synthesis of various derivatives, such geranyloxycoumarins, with outstanding bioactivities. Well known naturally occurred geranyloxycoumarins are 7-geranyloxycoumarin (auraptene) isolated from *Poncirus trifoliata Rafinesque* and 5-geranyloxy-7-methoxycoumarin, bergamottin (geranyloxypsoralen) isolated from *Citrus aurantifolia* (36).

Coumarin secondary metabolites with hydroxy group are critical in the synthesis of various derivatives with outstanding bioactivity. 4-Hydroxycoumarin and the synthesis of its derivatives first attracted the attention of Shah V.R. et al. in 1960 (36) and 4-hydroxycoumarin has since been used for producing a variety of coumarin derivatives based on its keto-enol tautomeric properties (37). The alkylation of the coumarin without the 4-OH group has also been investigated as a general method of synthesis. The alkylation reaction of the hydroxycoumarins has been investigated as a general method of synthesis of geranyloxycoumarins but, on the best of our view, the reaction strongly depended on the position of the hydroxy group, base additive, and reaction conditions. Interestingly, 4-hydroxycoumarin has since been used for producing a variety of O-4 and C-3 coumarin derivatives based on its keto-enol

tautomeric properties (38).

In this study, the reaction between hydroxycoumarins (1) and geranyl bromide (2) was studied in the synthesis of geranyloxycoumarin derivatives (3), using both weak and strong basic additives such as K_2CO_3, Cs_2CO_3, and Ag_2CO_3, respectively. The C-3 and O-4 alkylation of the 4-hydroxycoumarin under mild optimized reaction condition has also been investigated.

EXPERIMENTAL

General Experimental Procedures

The silica gel 60 (230-400 mesh ASTM, 0.040-0.063 mm) for open chromatography and GF_{254} for TLC were purchased from Merck Ltd. (Darmstadt, Germany). All solvents and chemicals used in this study were of analytical grade. For the hydroxycoumarin derivatives with a different substituent (4-hydroxycoumarin, 4-hydroxy-3-nitrocoumarin, 3-hydroxycoumarin, 6-hydroxycoumarin, 7-hydroxycoumarin, 3-phenylumbelliferone, 3-chloro-7-hydroxy-4-methylcoumarin and 6-chloro-7-hydroxy-4-methylcoumarin), the commercially available, 97%–98% pure TCI (Japan) and Alfa Aesar (USA) products were used. The established methods of synthesis were used to obtain 4-methyl-7-hydroxycoumarin (39,41), 6-hydroxy-4-methylcoumarin (39,41), 7-hydroxy-4-trifluoromethylcoumarin (39,41) and 4-methyl-6,7-dihydroxycoumarin (39,41). The alkenyl chain used in the synthesis of geranyloxycoumarin derivatives was 95% geranyl bromide (Aldrich, USA). For the base, NaOH, K_2CO_3, Cs_2CO_3, Ag_2CO_3 and triethylamine (Et_3N) were used, whereas the solvents used in this study were ethyl acetate (EtOAc), acetonitrile, n-hexane, dichloromethane (DCM), ethanol (EtOH), and acetone. Nuclear magnetic resonance spectrometer (NMR spectrometer; BRUKER AVANCE 400 MHz, BRUKER, Germany) was used for analysis. $CDCl_3$ containing tetramethylsilane (TMS), which is an internal standard, was used as analytical solvent. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are in hertz (Hz). Residual central signals of $CDCl_3$ were recorded as follows: δ H = 7.26, δ C = 77.00. Infrared spectroscopy was performed, in the form of KBr pellets, on FT/IR-4200 (JASCO, Japan) spectrophotometer, to confirm the functional groups in the compound. High-resolution mass spectra were recorded on an SCIEX (Qtrap 3200) liquid–chromatography-mass spectrometer (USA). In addition, the melting point was measured without calibrating the temperature. A thermometer was mounted under a paraffin oil container, and the open glass capillary method was used.

Common synthesis method of geranyloxycoumarin derivative

To a stirred mixture of hydroxycoumarin 1a (1.0 mmol) and powdered cesium carbonate (1.1 mmol) in acetonitrile (30 mL), geranyl bromide with 95% purity (1.2 mmol) was added, and the stirring was continued at RT for 3 hours. The reaction progress was monitored using TLC. When the reaction finished the solvent was removed under reduced pressure, then DCM (20 mL) was added to the mixture which was filtered off. After the evaporation of the solvent, crude products were purified by column chromatography on silica gel eluted with the mixture of n-hexane:DCM (1:1, v/v) to obtain pure geranyloxycoumarins (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-2Hchromen-2-one (3a), 3,3-bis((E)-3,7-dimethylocta-2,6-dien-1-yl)chromane-2,4-dione (3aa), and (E)-2-((E)-3,7-dimethylocta-2,6-dien-1-yl)-1-(2-hydroxyphenyl)-5,9-dimethyldeca-4,8-dien-1-one (3ab).

Characterization of (3a) (44)

White powder, Yield: 18%; m.p. 47–48 °C; **IR** (KBr, cm^{-1}): v 2923 (Aliphatic C-H), 1718 (C=O), 1620, 1371, 1235 (C-O), 1182 (C-O), 1104 (C-O), 923, 817, 764, 751, 500; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.62 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.08–2.18 (m, 4H, -CH_2CH_2-), 4.71 (d, *J* = 6.7 Hz, 2H, -CH_2-), 5.08–5.12 (m, 1H, =CH), 5.51 (t, *J* = 6.7 Hz, 1H, =CH), 5.69 (s, 1H, H-3), 7.25–7.33 (m, 2H, H-6 and H-8), 7.53–7.57 (m, 1H, H-7), 7.84 (dd, *J* = 2.2 Hz, 5.8Hz, 1H, H-5) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.82 (CH_3), 17.75 (CH_3), 25.70 (CH_3), 26.19 (CH), 39.50 (CH), 66.27 (CH), 90.64 (CH), 115.92 (C), 116.75 (CH), 117.06 (CH), 123.19 (CH), 123.46 (CH), 123.83 (CH), 132.13 (CH), 132.31 (C), 143.74 (C), 153.35 (C), 163.15 (C), 165.61 (C) ppm; **MS (EIMS)**: m/z 298 $[M]^+$; Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, Found: C, 76.49; H, 7.40.

Characterization of (3aa) (43)

Colorless liquid, Yield: 11%; **IR** (KBr, cm^{-1}): v 2966 (Aliphatic C-H), 2917 (Aliphatic C-H), 2854 (Aliphatic C-H), 1772 (C=O), 1689 (C=O), 1611, 1461, 1288 (C-O), 1142, 755; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.47 (s, 6H, $2CH_3$), 1.55 (s, 6H, $2CH_3$), 1.59 (s, 6H, $2CH_3$), 1.79 (s, 8H, 2(-CH_2CH_2-)), 2.70–2.80 (m, 2H, -CH_2-), 2.82–2.89 (m, 2H, -CH_2-), 4.86–4.95 (m, 4H, 4 (=CH)), 7.15 (dd, *J* = 2.5 Hz, 8.0 Hz, 1H, H-8), 7.21–7.25 (m, 1H, H-5), 7.58–7.63 (m, 1H, H-7), 7.91 (dd, *J* = 2.5 Hz, 8.0 Hz,1H, H-5) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.21 (CH_3), 17.52 (CH_3), 25.49 (CH_3), 26.33 (CH), 37.62 (CH), 39.65 (CH), 62.24 (C), 116.89 (CH), 117.49 (C), 119.53 (CH), 123.78 (CH), 124.66 (CH), 126.55 (CH), 131.32 (C), 136.82 (C), 140.59 (C), 154.89 (C), 170.56 (C), 194.66 (C) ppm; **MS (EIMS)**: m/z 434 $[M]^+$; Anal. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81, Found: C, 80.09; H, 8.76.

Synthesis method of (3ab)
To a stirred mixture of 3aa (2.3 mmol) and powdered cesium carbonate (2.5 mmol) in acetonitrile (30 mL), distilled water (2.6 mmol6mmol) was added, and the stirring was continued at RT for 9 hours. The reaction progress was monitored using TLC. When the reaction finished the solvent was removed under reduced pressure, then DCM (20 mL) was added to the mixture which was filtered up. After evaporation of the solvent crude products were filtered by column chromatography on silica gel eluted with the mixture of n-hexane:DCM (3:1, v/v) to obtain pure 3ab.

Characterization of (3ab)
Colorless liquid, Yield : 35%; IR (KBr, cm^{-1}): v 1712 (-C=O); ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.54 (s, 6H, $2CH_3$), 1.58 (s, 6H, $2CH_3$), 1.62 (s, 6H, $2CH_3$), 1.84–1.98 (m, 8H, 2(-CH_2CH_2-)), 2.25–2.32 (m, 2H, -CH_2-), 2.41–2.48 (m, 2H, -CH_2-), 3.47–3.54 (m, 1H, -C-H), 4.98–5.03 (m, 2H, 2(=C-H)), 5.06–5.11(m, 2H, 2(=C-H)), 6.86–6.90 (m, 1H), 6.95–6.98 (m, 1H), 7.42–7.46 (m, 1H), 7.76–7.79 (dd, *J* = 1.8 Hz, 8.2 Hz, 1H), 12.66 (s, 1H, OH, D_2O exch.) ppm; ^{13}C-NMR (100MHz, $CDCl_3$): δ 16.10 (CH_3), 17.67 (CH_3), 25.65 (CH_3), 26.54 (CH_2), 30.60 (CH_2), 39.74 (CH_2), 46.39 (CH), 118.56 (CH), 118.68 (CH), 119.65 (C), 121.10 (CH), 124.11 (CH), 130.24 (CH), 131.45 (C), 136.20 (CH), 137.59 (C), 162.93 (C), 210.28 (-C=O) ppm; MS (EIMS): m/z 408 $[M]^+$; Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.30; H, 9.87, Found: C, 82.27; H, 8.88.

Common synthesis method of geranyloxycoumarin derivatives
To a stirred mixture of hydroxycoumarin 1b-1l (1.0 mmol) and powdered cesium carbonate (1.1 mmol) in acetonitrile (30 mL), 95% geranyl bromide (1.2 mmol was added, and the stirring was continued at RT for 2.5-34 hours. The reaction progress was monitored using TLC. When the reaction finished the solvent was removed under reduced pressure, then DCM (20 mL) was added to the mixture which was filtered up. After evaporation of the solvent crude products were filtered by column chromatography on silica gel eluted with the mixture of n-hexane:DCM (1:1, v/v) to obtain pure geranyloxycoumarin 3c-3l.

Characterization of (3c)
White solid, Yield: 90%; m.p. 62–63 °C; **IR** (KBr, cm^{-1}): v 3077 (Aromatic C-H), 3030 (Aromatic C-H), 2974 (Aliphatic C-H), 2914 (Aliphatic C-H), 2894 (Aliphatic C-H), 1730 (Carbonyl (ester -C=O)), 1609 (C=C bond), 1556, 1516, 1452, 1427, 1400, 1351, 1275, 1215, 1192, 1166, 1137, 1014, 999, 958, 872, 818, 781, 715, 649, 626 ; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.57 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.03–2.13 (m, 4H, -CH_2CH_2-), 4.59 (d, *J* = 4.0 Hz, -OCH_2-), 5.01–5.06 (m, 1H, =CH), 5.40–5.45 (m, 1H, =CH), 6.57 (s, 1H, H-3), 6.83 (d, *J* = 2.5 Hz, 1H, H-8), 6.88 (dd, *J* = 2.5 Hz, 9.0 Hz, 1H, H-6), 7.56–7.59 (m, 1H, H-5) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.79 (CH_3), 17.70 (CH_3), 25.65 (CH_3), 26.20 (CH_2), 39.50 (CH_2), 65.67 (CH_2), 102.13 (CH), 106.88 (CH), 112.04 (q, $^{3}J_{CF}$ = 5.7 Hz), 113.98 (C), 120.25 (CH), 123.00 (CH), 123.54 (CH), 126.24 (q, $^{3}J_{CF}$ = 2.0 Hz, CH), 132.02 (C), 141.61 (q, $^{2}J_{CF}$ = 32.7 Hz, CCF_3), 142.78 (C), 156.31 (C), 159.49 (C), 162.86 (C) ppm; **^{19}F-NMR** (470 MHz, DMSO-d_6): δ 63.62 (s, 3F) ppm; **MS (EIMS)**: m/z 366 $[M]^+$; Anal. Calcd for $C_{20}H_{21}F_3O_3$: C, 65.57; H, 5.78, Found: C, 65.54; H, 5.76.

Characterization of (3d) (44)
White solid, Yield: 93%; m.p. 66–67 °C; **IR** (KBr, cm^{-1}): v 3082 (Aromatic C-H), 3053 (Aromatic C-H), 2972 (Aliphatic C-H), 2896 (Aliphatic C-H), 2879 (Aliphatic C-H), 2849 (Aliphatic C-H), 2833 (Aliphatic C-H), 1728 (Carbonyl (ester -C=O)), 1611 (C=C bond), 1507, 1452, 1430, 1403, 1369, 1348, 1280, 1234, 1201, 1165, 1126, 1103, 1022, 990, 889, 852, 830, 776, 760; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.06–2.15 (m, 4H, -CH_2CH_2-), 4.59 (d, *J* = 6.7 Hz, 2H, -CH_2-), 5.05–5.09 (m, 1H, =CH), 5.44–5.48 (m, 1H, =CH), 6.24 (d, *J* = 9.5 Hz, 1H, H-3), 6.81 (d, *J* = 2.5 Hz, 1H, H-6), 6.84 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H, H-8), 7.36 (d, *J* = 8.6 Hz, 1H, H-5), 7.63 (d, *J* = 9.5 Hz, 1H, H-4) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.37 (CH_3), 17.31 (CH_3), 25.26 (CH_3), 25.82 (CH_2), 39.11 (CH_2), 65.08 (CH_2), 101.18 (CH), 112.01 (CH), 112.56 (C), 112.84 (CH), 117.99 (CH), 123.20 (CH), 128.26 (CH), 131.57 (C), 141.98 (C), 143.04 (CH), 155.47 (C), 160.90 (C), 161.74 (C) ppm; **MS (EIMS)**: m/z 296 $[M]^+$; Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, Found: C, 76.45; H, 7.41.

Characterization of (3e) (45)
White solid, Yield: 91%; m.p. 54–55 °C; **IR** (KBr, cm^{-1}): v 3078 (Aromatic C-H), 3028 (Aromatic C-H), 2964 (Aliphatic C-H), 2917 (Aliphatic C-H), 2856 (Aliphatic C-H), 1726 (Carbonyl (ester -C=O)), 1617 (C=C bond), 1508, 1441, 1420,1390, 1345, 1278, 1257, 1199, 1154, 1134, 1070, 992, 982, 843, 825; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.57 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.03–2.13 (m, 4H, -CH_2CH_2-), 2.37 (d, *J* = 1.1 Hz, 3H, CH_3), 4.57 (d, *J* = 6.5 Hz, 2H, -CH_2-), 5.03–5.07 (m, 1H, =CH), 5.42–5.46 (m, 1H, =CH), 6.10 (q, *J* = 1,2 Hz, 2.4 Hz, 1H, H-3), 6.79 (d, *J* = 2.5 Hz, 8.8 Hz, 1H, H-8), 6.84 (d, *J* = 2.5 Hz, 1H, H-6), 7.46 (dd, *J* = 2.6 Hz, 8.8 Hz, 1H, H-5) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.79 (CH_3), 17.73 (CH_3), 18.70 (CH_3), 25.68 (CH_3), 26.24 (CH_2), 39.53 (CH_2), 65.44 (CH_2), 101.59 (CH), 111.85 (CH), 112.94 (C), 113.47 (CH), 118.45 (CH), 123.63 (CH), 125.46 (CH), 131.97 (C), 142.35 (C), 152.61 (C), 155.25 (C), 161.41 (C), 161.95 (C) ppm ; **MS (EIMS)**: m/z

312 $[M]^+$; Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74, Found: C, 76.88; H, 7.72.

C*haracterization of* (3f) (46)
Light yellow solid, Yield: 93%; m.p. 136–137 °C; **IR** (KBr, cm^{-1}): v 3076 (Aromatic C-H), 3027 (Aromatic C-H), 2960 (Aliphatic C-H), 2909 (Aliphatic C-H), 2851 (Aliphatic C-H), 1720 (Carbonyl (ester -C=O)), 1604 (C=C bond), 1600 (C=C bond), 1548, 1505, 1453, 1378, 1354, 1262, 1257, 1208, 1169, 1142, 1077, 1008, 946, 873, 818, 753, 583; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.06–2.17 (m, 4H, -CH_2CH_2-), 2.54 (s, 3H, CH_3), 4.60 (d, *J* = 6.6 Hz, -CH_2-), 5.05–5.09 (m, 1H, =CH), 5.43–5.48 (m, 1H, =CH), 6.82 (d, *J* = 2.5 Hz, 1H, H-8), 6.90 (dd, *J* = 2.5 Hz, 8.9 Hz, 1H, H-6), 7.51 (d, *J* = 8.9 Hz, 1H, H-5) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.12 (CH_3), 16.74 (CH_3), 17.66 (CH_3), 25.62 (CH_3), 26.18 (CH_2), 39.46 (CH_2), 65.50 (CH_2), 101.44 (CH), 113.10 (CH), 113.56 (C), 117.60 (CH), 118.24 (CH), 123.54 (CH), 125.74 (CH), 131.93 (C), 142.46 (C), 147.96 (C), 153.04 (C), 157.47 (C), 161.82 (C) ppm ; **MS (EIMS)**: m/z 346 $[M]^+$; Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68, Found: C, 68.70; H, 6.62.

C*haracterization of* (3g)
White solid, Yield: 90%; m.p. 95–96 °C; **IR** (KBr, cm^{-1}): v 3078 (Aromatic C-H), 3003 Aromatic C-H), 2965 (Aliphatic C-H), 2916 (Aliphatic C-H), 2856 (Aliphatic C-H), 2854 (Aliphatic C-H), 1728 (Carbonyl (ester -C=O)), 1609 (C=C bond), 1494, 1414, 1388, 1378, 1320, 1274, 1205, 1157, 1083, 1047, 982, 883, 829; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.06–2.15 (m, 4H, -CH_2CH_2-), 2.38 (d, *J* = 1.2 Hz, 3H, CH_3), 4.69 (d, *J* = 6.4Hz, 2H, -CH_2-), 5.04–5.08 (m, 1H, =CH), 5.44–5.48 (m, 1H, =CH), 6.16 (dd, *J* = 1.4 Hz, 2.6 Hz, 1H, H-3), 6.83 (s, 1H), 7.56 (s, 1H) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.89 (CH_3), 17.73 (CH_3), 18.65 (CH_3), 25.65 (CH_3), 26.19 (CH_2), 39.50 (CH_2), 66.63 (CH_2), 101.57 (CH), 112.74 (CH), 113.65 (C), 118.03 (CH), 119.34 (C), 123.54 (CH), 125.32 (CH), 132.01 (C), 142.66 (C), 151.70 (C), 153.52 (C), 156.93 (C), 160.79 (C) ppm; **MS (EIMS)**: m/z 346 $[M]^+$; Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68, Found: C, 69.00; H, 6.64.

C*haracterization of* (3h)
White solid, Yield: 92%; m.p. 104–105 °C; **IR** (KBr, cm^{-1}): v 3054 (Aromatic C-H), 3036 (Aromatic C-H), 2965 (Aliphatic C-H), 2909 (Aliphatic C-H), 2851 (Aliphatic C-H), 1707 (Carbonyl (ester -C=O)), 1606 (C=C bond), 1503, 1450, 1443, 1429, 1365, 1272, 1220, 1178, 1123, 1105, 1012, 990, 941, 827, 784, 691, 630; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05–2.15 (m, 4H, -CH_2CH_2-), 4.60 (d, *J* = 8.0 Hz, 2H, -CH_2-), 5.05–5.09 (m, 1H, =CH), 5.44–5.48 (m, 1H, =CH), 6.84–6.87 (m, 2H, H-6 and H-8), 7.34-7.44 (m, 4H), 7.65-7.68 (m, 2H), 7.74 (s, 1H, H-4) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.76 (CH_3), 17.69 (CH_3), 25.64 (CH_3), 26.20 (CH_2), 39.48 (CH_2), 65.47 (CH_2), 101.12 (CH), 113.19 (CH), 113.39 (CH), 118.38 (CH), 123.58 (C), 124.63 (CH), 128.36 (CH), 128.39 (CH), 128.74 (CH), 131.94 (C), 135.03 (C), 140.06 (C), 142.34 (CH), 155.23 (C), 160.95 (C), 161.88 (C) ppm; **MS (EIMS)**: m/z 374 $[M]^+$; Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00, Found: C, 80.16; H, 6.99.

C*haracterization of* (3i) (44,47)
White solid, Yield: 92%; m.p 95–96 °C; **IR** (KBr, cm^{-1}): v 3067 (Aromatic C-H), 3050 (Aromatic C-H), 2958 (Aliphatic C-H), 2911 (Aliphatic C-H), 2870 (Aliphatic C-H), 2840 (Aliphatic C-H), 1704 (Carbonyl (ester -C=O)), 1566 (C=C bond), 1490, 1443, 1385, 1276, 1175, 1171, 1110, 1017, 922, 882, 816, 706; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.06–2.16 (m, 4H, -CH_2CH_2-), 4.56 (d, *J* = 6.6 Hz, 2H, -CH_2-), 5.05–5.10 (m, 1H, =CH), 5.45–5.50 (m, 1H, =CH), 6.42 (d, *J* = 9.4 Hz, 1H, H-3), 6.92 (d, *J* = 2.9 Hz, 1H, H-5), 7.12 (dd, *J* = 2.9 Hz, 9.0 Hz, 1H, H-7), 7.26 (d, *J* = 9.0 Hz, 1H, H-8), 7.64 (d, *J* = 9.5 Hz, 1H, H-4) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.74 (CH_3), 17.73 (CH_3), 25.70 (CH_3), 26.25 (CH_2), 39.53 (CH_2), 65.57 (CH_2), 111.08 (CH), 117.02 (CH), 117.83 (CH), 118.90 (CH), 119.15 (CH), 120.15 (C), 123.65, 131.95 (C), 141.96 (C), 143.28 (CH), 148.41 (C), 155.34 (C), 161.05 (C) ppm; **MS (EIMS)**: m/z 298 $[M]^+$; Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, Found: C, 76.46; H, 7.42.

C*haracterization of* (3j)
White solid, Yield: 89%; m.p. 57–58 °C; **IR** (KBr, cm^{-1}): v 3040 (Aromatic C-H), 2965 (aliphatic C-H), 2925 (aliphatic C-H), 2884 (aliphatic C-H), 1712 (C=O), 1673, 1571, 1493, 1428, 1386, 1275, 1238 (C-O), 1167, 990, 926, 838; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.06–2.17 (m, 4H, -CH_2CH_2-), 2.41 (d, *J* = 1.2 Hz, 3H, CH_3), 4.59 (d, *J* = 6.6 Hz, 2H, -CH_2-), 5.06–5.10 (m, 1H, =CH), 5.47–5.51 (m, 1H, =CH), 6.30 (q, *J* = 1.4 Hz, 2.6 Hz, 1H, H-3), 7.04 (d, *J* = 2.9 Hz, 1H, H-5), 7.13 (dd, *J* = 2.9 Hz, 9.0 Hz, 1H, H-7), 7.27 (d, *J* = 9.0 Hz, 1H, H-8) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.74 (CH_3), 17.72 (CH_3), 18.74 (CH_3), 25.68 (CH_3), 26.27 (CH_2), 39.55 (CH_2), 65.56 (CH_2), 108.82 (CH), 115.44 (CH), 117.89 (CH), 119.00 (CH), 119.32 (C), 120.43 (CH), 123.64 (CH), 131.96 (C), 141.96 (C), 147.84 (C), 152.02 (C), 155.20 (C), 161.03 (C) ppm; **MS (EIMS)**: m/z 312 $[M]^+$; Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74, Found: C, 76.86; H, 7.75.

C*haracterization of* (3k)
White solid, Yield: 86%; m.p. 63–64 °C; **IR** (KBr,

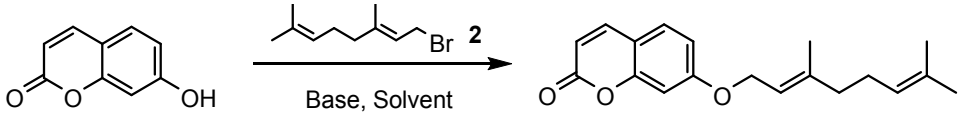
cm^{-1}): v 3065 (Aromatic C-H), 2937 (Aliphatic C-H), 2917 (Aliphatic C-H), 2854 (Aliphatic C-H), 1708 (Carbonyl (ester -C=O)), 1612 (C=C bond), 1562, 1520, 1430, 1384, 1280, 1231, 1164, 984, 822; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.59 (s, 6H, $2CH_3$), 1.64 (s, 6H, $2CH_3$), 1.77 (s, 6H, $2CH_3$), 2.06–2.15 (m, 8H, 2(-CH_2CH_2-)), 2.37 (d, *J* = 1.2 Hz, 3H, CH_3), 4.67 (d, *J* = 6.4 Hz, 4H, 2(-CH_2-)), 5.04–5.08 (m, 2H, 2(=CH)), 5.44–5.48 (m, 2H, 2(=CH)), 6.15 (dd, *J* = 1.4 Hz, 2.64 Hz, 1H, H-3), 6.83 (s, 1H, H-5), 7.55 (s, 1H, H-8) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 17.04 (CH_3), 17.17 (CH_3), 18.01 (CH_3), 19.14 (CH_3), 25.95 (CH_3), 26.52 (CH_3), 26.59 (CH_3), 39.81 (CH_2), 39.86 (CH_2), 66.63 (CH_2), 67.16 (CH_2), 101.75 (CH), 108.76 (CH), 112.37 (C), 112.65 (CH), 119.06 (CH), 119.92 (C), 123.96 (CH), 132.22 (C), 141.50 (C), 141.91 (C), 145.76 (C), 149.76 (C), 152.70 (C), 153.07 (C), 161.95 (C) ppm; **MS (EIMS)**: m/z 464 $[M]^+$; Anal. Calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68, Found: C, 77.54; H, 8.66.

Characterization of (3l) (44)
White solid, Yield: 87%; m.p. 72–73 °C; **IR** (KBr, cm^{-1}): v 3086 (Aromatic C-H), 3052 (Aromatic C-H), 2975 (Aliphatic C-H), 2917 (Aliphatic C-H), 2885 (Aliphatic C-H), 1745 (Carbonyl (ester -C=O)), 1638 (C=C bond), 1585, 1503, 1468, 1446, 1413, 1390, 1331, 1319, 1225, 1218, 1164, 1122, 996, 950, 938, 900, 864, 790, 761, 603; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.57 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.03–2.13 (m, 4H, -CH_2CH_2-), 4.61 (d, *J* = 8.0 Hz, 2H, -CH_2-), 5.02–5.06 (m, 1H, =CH), 5.46–5.51 (m, 1H, =CH), 6.79 (s, 1H, H-4), 7.20–7.28 (m, 2H, H6 and H-8), 7.32–7.37 (m, 2H, H-5 and H-7) ppm; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 16.82 (CH_3), 17.72 (CH_3), 25.66 (CH_3), 26.17 (CH), 39.50 (CH), 66.24 (CH), 113.69 (CH), 116.29 (CH), 117.96 (C), 119.82 (CH), 123.59 (C), 124.64 (CH), 126.37 (CH), 128.33 (CH), 132.00 (CH), 142.51 (C), 143.69 (C), 149.53 (C), 157.77 (C) ppm; **MS (EIMS)**: m/z 298 $[M]^+$; Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, Found: C, 76.44; H, 7.42.

RESULTS AND DISCUSSION

In this study, our first goal was to identify the optimal conditions for obtaining *O*-alkylated geranyloxycoumarin derivatives by reaction between hydroxycoumarin and geranyl bromide (Table 1). At first, the reaction between 7-hydroxycoumarin (1d) and geranyl bromide (2) was performed in the presence of Et_3N in acetone at RT to give tarry mixture unidentified degradation products (Table 1, Entry 1). Secondly, when changing to K_2CO_3 instead of TEA, the desired product 3d was obtained in a low 35% yield with 5 hours reaction time (Table 1, Entry 2). Prolonged the reaction time to 26 hours give higher 62% yield of the product 3d, but at solvent reflux temperature we isolated desired product at promising 73% yield (Table 1, Entries 3–4). Then we change solvent to CH_3CN, at solvent reflux temperature we obtained higher purity product with a little better 74% yield (Table 1, Entry 5). As such, the optimized CH_3CN solvent was tested using Cs_2CO_3 additive at 3 hours or 30 min. times, and at RT or under CH_3CN reflux temperature and geranyloxycoumarin 3d was formed with 93% or 87% yields, respectively (Table 1, Entries 6–7). The change base to more expensive silver(I) carbonate (Ag_2CO_3) give also good but low promising 85% yield of the product 3d (Table 1, Entry 8).

Table 1: Optimization of the reaction conditions for 7-geranyloxycoumarin (3d) preparation.



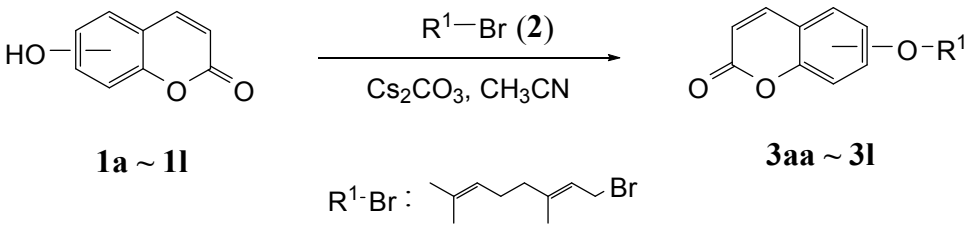
1d **3d**

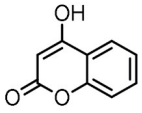
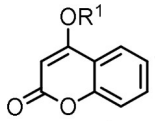
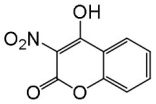
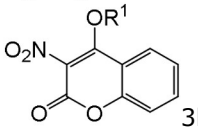
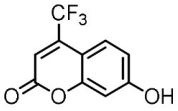
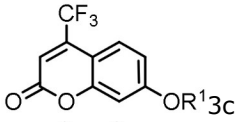
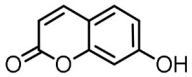
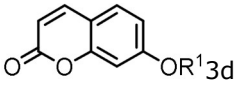
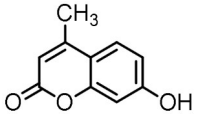
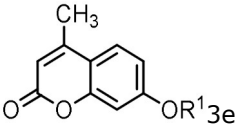
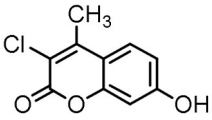
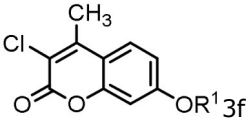
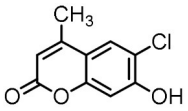
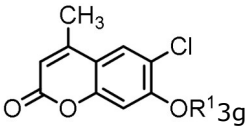
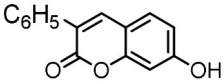
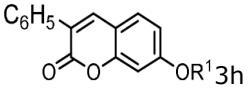
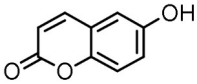
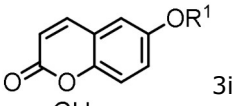
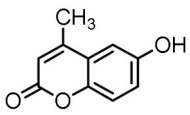
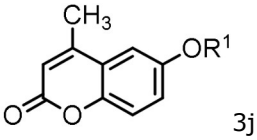
Entry	Conditions	Yield (%)
1	Et_3N, acetone, RT, 12 h	degradation
2	K_2CO_3, acetone, RT, 5 h	35
3	K_2CO_3, acetone, RT, 26 h	62
4	K_2CO_3, acetone, reflux, 1 h	73
5	K_2CO_3, CH_3CN, reflux, 1 h	74
6	Cs_2CO_3, CH_3CN, RT, 3 h	93
7	Cs_2CO_3, CH_3CN, reflux, 30 min	87
8	Ag_2CO_3, CH_3CN, RT, 3 h	85

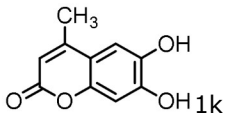
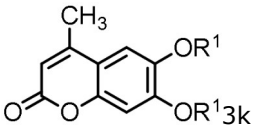
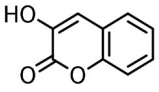
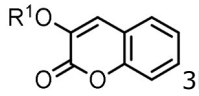
Geranyloxycoumarin was synthesized in good yield by the reaction of hydroxycoumarin excluding 4-OH group and geranyl bromide under weak base and CH_3CN condition. In the cases where the OH group was positioned on the 3rd, 5th, 6th, 7th, or 8th carbon of the coumarin structure, the reaction of

hydroxycoumarin (ex, 6-hydroxycoumarin) and geranyl bromide with cesium carbonate and acetonitrile at RT produced a high yield of *O*-alkylated compounds. In this result, the reaction of the different types of hydroxycoumarin and geranyl bromide under the given conditions produced various novel coumarin derivatives (Table 2).

Table 2: Synthesized geranyloxycoumarin derivatives.



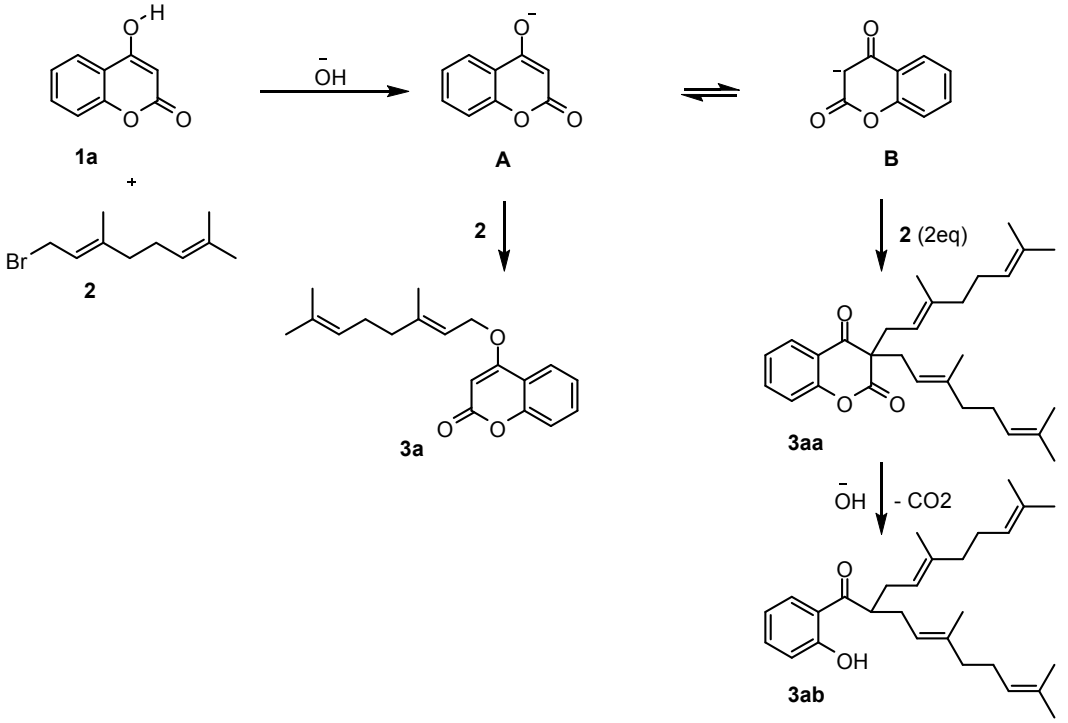
Entry	Coumarin	Time (h)	Product	Yield (%)
1	 1a	3	 3a	18
2	 1b	72	 3b	-
3	 1c	3.5	 3c	90
4	 1d	3	 3d	94
5	 1e	3	 3e	91
6	 1f	4	 3f	93
7	 1g	2.5	 3g	90
8	 1h	3	 3h	92
9	 1i	3	 3i	92
10	 1j	3	 3j	89

11	 1k	34	 3k	86[a]
12	 1l	3	 3l	87

[a.]When 2 equivalents of geranyl bromide(2) are used.

Next, we studied the reaction of 4-hydroxycoumarin (1a) with geranyl bromide (2) to produce *O*-4 and C-3 alkylated products. Under optimized reaction conditions for *O*-alkylation, the desired 4-geranyloxycoumarin (3a) was obtained in low 18% yield. This reaction takes place on the tautomer A with the anion located on the oxygen atom in the C-4 position.

On the other hand, C-3 alkylated coumarin 3aa was formed in the reaction with 2 equivalents of geranyl bromide (2) started on the keto form tautomer B, with anion localized at C-3 carbon atom, with 11% yield. Moreover, compound 3ab was obtained in 35% yield by hydrolysis and decarboxylation from 3aa. We also confirmed that 3ab was obtained by adding 3aa to acetonitrile to which water was added and stirring at RT for 9 hours. These results are reported by Yi-Jen Shue et al. to obtain a C-alkylated coumarin and a diallylated product, which was hydrolyzed and then decarboxylated, by reacting 4-hydroxycoumarin and cinnamyl alcohol with water and palladium catalyst (Scheme 1) (37-40).



Scheme 1: Reactivity of 4-hydroxycoumarin.

No reaction occurred between 4-hydroxy-3-nitrocoumarin (**1b**) and geranyl bromide (**2**) in Cs_2CO_3, CH_3CN for 72 hours at RT or in reflux condition. It is expected that the desired product was not obtained by the reversible structure of 4-hydroxy-3-nitrocoumarin of the nitro and nitrous types.

As can be seen, the alkylation reaction of hydroxycoumarin and geranyl bromide under mild conditions led to a good yield; however, a new method of synthesis is required to achieve a higher yield of 4-geranyloxycoumarin. In addition, as the *O*-alkylated derivatives of geranyloxycoumarin are predicted to exhibit diverse bioactivities, further studies should be conducted on their synthesis.

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