

Synthesis and Biological Activities of Jineol and Its Derivatives

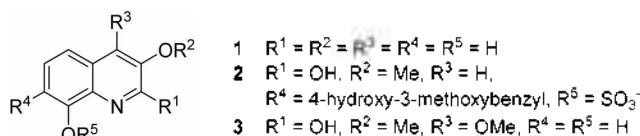
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Jineol (3,8-dihydroxyquinoline) (**1**), which exhibits cytotoxic and antifungal activities, has been isolated from the centipede *Scolopendra subspinipes mutilans* L. Koch.¹ Recently, the species was used in the isolation of scolopendrine (**2**)² and 2,8-dihydroxy-3,4-dimethoxyquinoline (**3**).³ Compound **3** exhibits radical scavenging and low-density lipoprotein (LDL) antioxidant activities.³ Jineol and its dialkylated derivatives were also synthesized from 2-methoxyaniline; however, their biological activities were not reported.⁴ Therefore, with regard to the biological activity of jineol derivatives, it might be interesting to introduce different functional groups at the two hydroxyl groups in compound **2**. Here, we report a method of synthesizing jineol and its derivatives along with a view to obtain antibacterial, antifungal, and cytotoxic activities.

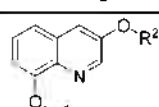


In this method, the reduction of 2-amino-3-methoxybenzoic acid (**4**) with lithium aluminum hydride followed by acetylation with acetic anhydride-triethylamine yielded 2-acetamido-3-methoxybenzyl acetate (**5**). Selective deacetylation with

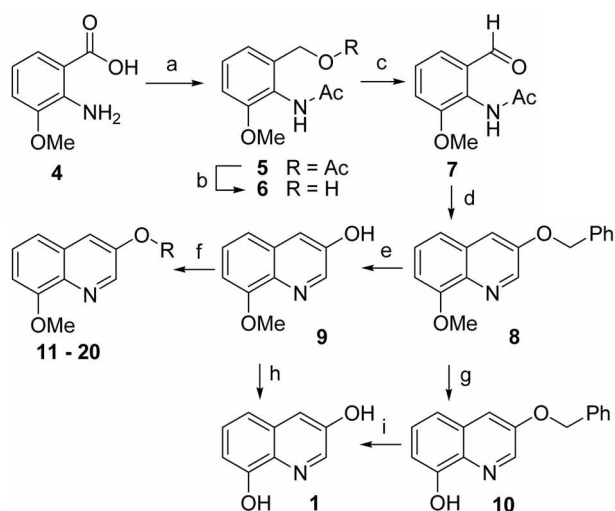
potassium carbonate in aqueous MeOH and subsequent oxidation with pyridium dichromate in dichloromethane afforded a key intermediate, 2-acetamido-3-methoxybenzaldehyde (**7**), which was unstable at room temperature. Modified Friedlander condensation⁵ of aldehyde **7** with benzyloxyacetaldehyde and sodium hydroxide in ethanol afforded quinoline **8** in 81% yield. Hydrogenation of compound **8** with hydrogen in the presence of Pd/C or demethylation of the methoxy group at C-8 of compound **8** with trimethylsilyl iodide in dry methylene chloride yielded jineol 8-methyl ether (**9**) or jineol 3-benzyl ether (**10**), respectively. Both demethylation of ether **9** with trimethylsilyl iodide and debenzilation of ether **10** with hydrogen gas afforded jineol (**1**, 3,8-dihydroxyquinoline) in 30% and quantitative yields, respectively. Spectroscopic data showed that the synthetic jineol was closely comparable to the natural product.¹ 3-O-Alkylated derivatives (**11-20**) of compound **1** were prepared from the reaction of **9** with various alkyl halides in basic dimethylsulfoxide in yields of 51-98%, as shown in Scheme 1.

The *in vitro* cytotoxicities of jineol and its derivatives were evaluated against human lung cancer cell A549 and mouse melanoma B16F1 cell lines, as shown in Table 1. Alkylation at 3-OH and 8-OH of compound **1** revealed no significant enhancement of activity as compared to the mother

Table 1. Antibacterial, antifungal, and cytotoxic activities of jineol and its derivatives^a

Compound No			Bacterial strain ^b				Fungal strain ^b		Cancer cell line ^c	
	R ¹	R ²	EC	SS	BS	SA	TM	CA	B16F1	A549
1	H	H	64	16	32	32	64	64	3.0	2.2
8	Me	benzyl	128	–	128	–	–	–	6.0	18
9	Me	H	–	–	–	–	–	–	–	–
10	H	benzyl	–	64	128	64	64	64	1.3	3.9
11	Me	2-methylbenzyl	–	–	–	–	–	–	9.6	–
12	Me	phenethyl	128	16	16	16	–	–	6.5	16
13	Me	cyclohexylmethyl	128	16	16	16	64	–	3.8	9.5
14	Me	2,3-dihydroxypropyl	–	–	–	–	–	–	–	–
15	Me	12-hydroxydodecyl	–	–	–	–	–	–	3.0	11
16	Me	ethyl	nt	nt	nt	nt	nt	nt	–	–
17	Me	isobutyl	nt	nt	nt	nt	nt	nt	26	30
18	Me	octadecyl	–	–	–	–	–	–	–	–
19	Me	hexadecyl	–	–	–	–	–	–	–	–
20	Me	2-ethylhexyl	–	8	8	8	–	–	11	14
Control ^d			1.0	0.5	0.5	0.5	4.0	4.0	7.5	10

^aData for antibiotic and cytotoxic activities are given in terms of minimum inhibitory concentrations (MIC, $\mu\text{g}/\text{mL}$) and 50% inhibitory concentrations (IC₅₀, $\mu\text{g}/\text{mL}$), respectively; “–” sign indicates no activity below 128 $\mu\text{g}/\text{mL}$ for bacterial and fungal strains and 40 $\mu\text{g}/\text{mL}$ for cancer cell lines; “nt” indicates that the sample was not tested. ^bEC, SS, BS, SA, TM, and CA represent *Escherichia coli*, *Shigella sonnei*, *Bacillus subtilis*, *Staphylococcus aureus*, *Trichophyton mentagrophytes*, and *Candida albicans*, respectively. ^cB16F1 and A549 cell lines originated from mouse melanoma and human lung cancer, respectively. ^dTetracycline, ketoconazole, and cisplatin were used as positive controls for antibacterial, antifungal, and cytotoxicity assays, respectively.



Scheme 1. Synthesis scheme of jineol and its derivatives. (a) LAH, THF, reflux, 2 h; Ac₂O, Et₃N, THF, rt, overnight, 71%; (b) K₂CO₃, 10% aq. MeOH, rt, 20 min, 95%; (c) PDC, CH₂Cl₂, rt, overnight, 89%; (d) benzyloxyethanal, NaOH, EtOH, reflux, 3 h, 81%; (e) H₂, Pd/C, MeOH, rt, quantitative; (f) alkyl halides, K₂CO₃, DMSO, 90 °C, overnight; (g) Me₃Si-I, CH₂Cl₂, rt, 24 h, 50%; (h) Me₃Si-I, CH₂Cl₂, rt, 24 h, 30%; (i) H₂, Pd/C, MeOH, rt, quantitative

compound (1). Furthermore, the synthetic compounds were tested against gram positive bacterial strains (*B. subtilis* and *S. aureus*), gram negative bacterial strains (*E. coli* and *S. sonnei*), and fungal strains (*T. mentagrophytes* and *C. albicans*). Compounds 12, 13, and 20 with phenethyl, cyclohexylmethyl, and 2-ethylhexyl groups at 3-OH, respectively, showed activity moderately higher or comparable to that of compound 1 against the bacterial strains (Table 1). On the other hand, other compounds like 15, 18, and 19, which bear long lipophilic alkyl groups showed no activity below 128 μg/mL against all the strains tested.

Experimental Section

Melting points were measured using a Fisher melting point apparatus and the values are reported uncorrected. NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer in deuterated methanol, acetone, or chloroform. Chemical shifts are expressed in ppm (δ) and referenced to methanol-*d*₄ (δ _H 3.31 and δ _C 49.15), acetone-*d*₆ (δ _H 2.05 and δ _C 29.92), and CDCl₃ (δ _H 7.27 and δ _C 77.23) as internal standards. IR spectra were recorded on a Perkin Elmer BX FT-IR spectrometer with KBr pellets; the spectra are reported in wave numbers (cm⁻¹). Mass spectra were measured on a JEOL HX110A Tandem HR mass spectrophotometer (electron impact mode) at the Korea Basic Science Institute. Routine monitoring of reactions was performed on a pre-coated silica gel plastic plate (Kieselgel 60, F₂₅₄, 20 × 20 cm, 0.25 mm thick, Merck). Column chromatography was accomplished using silica gel (Merck, 60) with the eluent indicated. The starting synthetic materials were purchased from Aldrich Chemical Co. Tetrahydrofuran (THF) was distilled from sodium/potassium in argon atmosphere prior to use. Methylene chloride (CH₂Cl₂) was distilled from calcium hydride.

All moisture-sensitive reactions were carried out in argon atmosphere using oven-dried glassware. The optical density for a 96-well microplate was measured on a Tecan Sunrise microplate reader (model A-5080) at 520 nm. Brucella broth (BB) and potato dextrose broth (PDB) were purchased from Becton Dickinson and Company. All bacterial and fungal strains were purchased from the Korean Collection for Type Cultures (KCTC). *Bacillus subtilis* (KCTC 1021), *Staphylococcus aureus* (KCTC 1621), *Escherichia coli* (KCTC 1039) and *Shigella sonnei* (KCTC 2009) were used for antibacterial assay. *Candida albicans* (KCTC 7121) and *Trichophyton mentagrophytes* (KCTC 6085) were used for antifungal assay. Human lung carcinoma A-549 and mouse melanoma B16-F1 cell lines were purchased from the Korean Cell Line Bank. Tetracycline, ketoconazole, and cisplatin were purchased from Sigma Aldrich Co.

2-Acetamido-3-methoxybenzyl acetate (5). 2-Amino-3-methoxybenzoic acid 4 (6.0 g, 36 mmol) was added in a small portion to a solution of lithium aluminum hydride (LAH) (2 g, 53 mmol) in dry THF (50 mL) in an ice bath for 10 min in argon atmosphere. The mixture was stirred for 2 h at room temperature. An additional amount of LAH (1 g, 26 mmol) was added and stirred for 2 h at room temperature followed by refluxing for 12 h. The reaction mixture was diluted with methanol (20 mL) and sodium hydroxide solution (1 M, 5 mL), and it was then filtered using celite. The filtrate was concentrated and extracted with ethyl acetate (50 mL × 4). The combined organic layers were dried over anhydrous magnesium sulfate. Concentration afforded 2-amino-3-methoxybenzyl alcohol as brown oil [5.17 g, TLC (5:5 hexane:ethyl acetate) *R*_f 0.41], which was subjected to acetylation without purification. The alcohol (5.17 g, 33.8 mmol) was added to a solution of acetic anhydride (8 mL, 78 mmol) and triethylamine (12 mL, 118 mmol) in THF (15 mL) and stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate (400 mL), washed with brine (40 mL × 2), and dried over anhydrous magnesium sulfate. Concentration afforded acetate 5 as a white solid. An authentic sample was obtained as a white crystalline solid by trituration with 8:2 hexane-EtOAc (6.4 g, 71% yield from 4); mp: 98°C; IR (KBr): ν_{\max} 3244, 1748, 1656, 1542, 1483, 1240, 1041, 770; ¹H NMR (acetone-*d*₆, 400 MHz): δ 7.23 (1H, t, *J* = 8.0 Hz), 7.00 (1H, d, *J* = 8.0 Hz), 6.98 (1H, d, *J* = 8.0 Hz), 5.03 (2H, s), 3.81 (3H, s), 2.10 (3H, s), 2.05 (3H, s); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 170.6, 169.1, 154.9, 135.7, 127.6, 125.3, 120.1, 111.2, 63.3, 56.1, 23.0, 20.8; EIMS: *m/z* 237 (*M*⁺, 45), 194 (50), 176 (21), 152 (98), 134 (55), 106 (100).

2-Acetamido-3-methoxybenzyl alcohol (6). Acetate 5 (6.4 g, 27 mmol) was added to a solution of K₂CO₃ (1.0 g, 7.2 mmol) in MeOH (25 mL) and H₂O (5 mL). The mixture was stirred at room temperature for 20 min and diluted with saturated ammonium chloride solution (150 mL). The solution was extracted with ethyl acetate (100 mL × 10). The combined organic layers was washed with brine (20 mL × 2) and dried over anhydrous magnesium sulfate. Concentration and trituration with EtOAc-hexane afforded alcohol 6 as a white solid (4.97 g, 95% yield); mp: 133°C; IR (KBr): ν_{\max}

3213, 3041, 1654, 1542, 1484, 1283, 1044, 777: ^1H NMR (acetone- d_6 , 400 MHz): δ 7.22 (1H, t, $J = 7.8$ Hz), 7.11 (1H, d, $J = 7.6$ Hz), 6.93 (1H, d, $J = 8$ Hz), 4.45 (2H, s), 3.80 (3H, s), 2.14 (3H, s); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 170.3, 154.7, 140.8, 127.7, 124.6, 121.2, 110.5, 61.6, 56.0, 23.1.

2-Acetamido-3-methoxy-benzaldehyde (7). Alcohol **6** (5.0 g, 26 mmol) and pyridium dichromate (15 g, 45 mmol) were dissolved in dry methylene chloride (100 mL). The mixture was stirred for 12 h at room temperature. The reaction mixture was passed through a short column of silica gel with the elution of ethyl acetate to obtain 2-acetamido-3-methoxy-benzaldehyde **7** as a colorless crystalline solid (4.4 g, 89% yield). The solid was subjected to subsequent reaction without further purification; IR (KBr): ν_{max} 3241, 1697, 1664, 1590, 1528, 1459, 1271, 1074, 771: ^1H NMR (acetone- d_6 , 400 MHz): δ 9.92 (1H, s), 7.40-7.38 (1H, m), 7.32-7.30 (2H, m), 3.89 (3H, s), 2.21 (3H, s); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 189.6, 170.6, 153.6, 132.2, 129.1, 127.0, 119.0, 116.5, 56.5, 23.2; TLC (1:9 hexane:ethyl acetate): R_f 0.3.

3-Benzoyloxy-8-methoxy quinoline (8). The aldehyde **7** (1.5 g, 7.8 mmol) and sodium hydroxide (1.8 g, 45 mmol) were dissolved in ethanol. Benzoyloxyethanal (1.8 mL, 12 mmol) was added dropwise to the aldehyde solution for 15 min at room temperature. The reaction mixture was stirred at 50 °C for 30 min and an additional amount of benzoyloxyacetaldehyde (1 mL, 6.7 mmol) was added and stirred for 3 h at the same temperature. The reaction mixture was diluted with EtOAc (500 mL), washed with brine (100 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration yielded a brown oil, which was purified by silica gel column chromatography (30 id \times 250 mm, 70-230 mesh) to obtain quinoline ether **8** as a brown crystalline solid (1.7 g, 81% yield); mp: 74 °C; ^1H NMR (acetone- d_6 , 400 MHz): δ 8.63 (1H, d, $J = 2.8$ Hz), 7.71 (1H, d, $J = 2.8$ Hz), 7.56-7.55 (2H, m), 7.46-7.41 (3H, m), 7.38-7.34 (2H, m), 7.00 (1H, dd, $J = 7.6, 1.2$ Hz), 5.28 (2H, s), 3.98 (3H, s); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 156.8, 153.5, 143.1, 137.5, 136.2, 131.1, 129.3 (2C), 128.8, 128.6 (2C), 128.3, 119.5, 114.3, 106.7, 70.7, 56.0; EIMS: m/z 265 (M^+ , 25), 116 (9), 91 (100).

3-Hydroxy-8-methoxyquinoline (9). Quinoline ether **8** (570 mg, 2.2 mmol) was dissolved in methanol (15 mL) and Pd/C (50 mg) was added. The mixture was flushed with hydrogen gas and stirred overnight in an atmosphere of hydrogen at room temperature. The reaction mixture was concentrated and diluted with EtOAc. It was then passed through a short column of celite with EtOAc elution. Concentration afforded alcohol **9** as a yellow solid in quantitative yield; mp: 198 °C; ^1H NMR (acetone- d_6 , 400 MHz): δ 8.59 (1H, d, $J = 2.8$ Hz), 7.52 (1H, d, $J = 2.8$ Hz), 7.40 (1H, t, $J = 8.0$ Hz, H-6), 7.28 (1H, dd, $J = 8.4, 1.2$ Hz), 6.95 (1H, d, $J = 7.6, 0.8$ Hz), 3.96 (3H, s, OMe); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 156.6, 152.2, 142.4, 135.7, 131.6, 128.0, 128.6, 119.0, 116.4, 105.9, 55.9; EIMS: m/z 175 (M^+ , 89), 146 (100), 116 (21).

3-Benzoyloxy-8-hydroxyquinoline (10). Trimethylsilyl iodide (0.4 mL, 1.65 mmol) was added dropwise to a solution of quinoline ether **8** (200 mg, 0.75 mmol) in dry CH_2Cl_2 (8 mL) in argon atmosphere and the mixture was stirred at room

temperature for 24 h. The mixture was then diluted with EtOAc (20 mL) and a saturated NaHCO_3 solution (20 mL) was added. The organic layer was washed with brine (10 mL \times 2) and dried over anhydrous MgSO_4 . After filtration and concentration, the residue was purified by silica gel column chromatography (30 id \times 250 mm, 70-230 mesh, 4:6 hexane:EtOAc) to obtain benzyl ether **10** as a brown solid (94.7 mg, 50% yield); mp: 104 °C; ^1H NMR (CD_3OD , 400 MHz): δ 8.56 (1H, d, $J = 2.8$ Hz), 7.66 (1H, d, $J = 2.8$ Hz), 7.50 (2H, d, $J = 7.2$ Hz), 7.33-7.42 (4H, m), 7.25 (1H, d, 8.0), 6.92 (1H, d, $J = 7.2$ Hz), 5.23 (2H, s); ^{13}C NMR (CD_3OD , 100 MHz): δ 154.39, 154.35, 143.2, 137.9, 135.2, 131.4, 129.6 (2C), 129.3, 129.2, 128.8 (2C), 118.4, 115.4, 109.9, 71.4.

Jineol (3,8-dihydroxyquinoline) (1)

Method (a): Trimethylsilyl iodide (0.2 mL, 0.83 mmol) was added dropwise to a solution of methyl ether **9** (80 mg, 0.46 mmol) in dry CH_2Cl_2 (8 mL) in argon atmosphere and the mixture was stirred at room temperature for 24 h. The mixture was then diluted with EtOAc (15 mL) and a saturated NaHCO_3 solution (15 mL) was added. The organic layer was washed with brine (5 mL \times 2) and dried over anhydrous MgSO_4 . After filtration and concentration, the residue was purified by silica gel column chromatography (30 id \times 250 mm, 70-230 mesh, 1:9 hexane:EtOAc) to obtain jineol **1** as a brown solid (22 mg, 30% yield).

Method (b): Benzyl ether **10** (95 mg, 0.38 mmol) was dissolved in MeOH and Pd/C (5 mg) was added. The mixture was flushed with hydrogen gas and stirred overnight in hydrogen atmosphere at room temperature. The reaction mixture was then passed through a short column of celite with EtOAc elution and concentrated to obtain alcohol **1** as a brown solid in quantitative yield; this solid was identical to the sample obtained by method (a).

General procedure for preparing 3-alkyloxy-8-methoxyquinolines (11-20). Compound **9** (50 mg, 0.28 mmol) was dissolved in DMSO (3 mL) and K_2CO_3 (38 mg, 0.28 mmol) was added. The mixture was stirred for 10 min. The following alkyl halides (1.5 eq. each) were then added: 2-methylbenzyl bromide; phenethyl bromide; cyclohexylmethyl bromide, 2,3-dihydroxypropyl bromide; 12-hydroxydodecyl bromide; ethyl bromide; isobutyl bromide; octadecyl bromide; hexadecyl bromide; and 2-ethylhexyl bromide for compounds **11** to **20**, respectively. The mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc (100 mL), washed with brine (100 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration followed by silica gel column chromatography (30 id \times 250 mm, 70-230 mesh) afforded the corresponding ethers **11-20** in specified yields for each compound.

3-(2-Methyl)benzyloxy-8-methoxy quinoline (11): A brown solid (51.8 mg, 65%); mp: 119 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 8.72 (1H, d, $J = 3.2$ Hz), 7.82 (1H, d, $J = 3.2$ Hz), 7.70 (1H, d, $J = 8.4$ Hz), 7.47 (1H, brd, $J = 7.2$ Hz), 7.24-7.30 (4H, m), 6.81 (1H, d, $J = 8.4$ Hz), 5.23 (2H, s), 4.07 (3H, s), 2.44 (3H, s); ^{13}C NMR (CDCl_3 , 100 MHz): δ 155.6, 154.1, 143.9, 137.3, 135.9, 133.7, 131.0, 130.9, 129.45, 129.41, 129.1, 126.4, 113.7, 111.0, 106.3, 69.3, 56.3, 19.2.

3-Phenethyloxy-8-methoxy quinoline (12): A light brown solid (48.6 mg, 61%); mp: 79 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.66 (1H, d, $J = 2.8$ Hz), 7.67 (1H, d, $J = 8.4$ Hz), 7.66 (1H, d, $J = 2.8$ Hz), 7.26-7.36 (6H, m), 6.79 (1H, d, $J = 8.4$ Hz), 4.36 (2H, t, $J = 7.2$ Hz), 4.06 (3H, s), 3.21 (2H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.6, 154.1, 143.9, 137.8, 135.8, 131.0, 129.4, 129.3 (2C), 128.9 (2C), 127.0, 113.3, 111.0, 106.2, 69.4, 56.3, 35.6.

3-Cyclohexylmethoxy-8-methoxy quinoline (13): A pale brown solid (75.9 mg, 98%); mp: 90 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.65 (1H, d, $J = 2.8$ Hz), 7.40 (1H, t, $J = 8.0$ Hz), 7.31 (1H, d, $J = 2.8$ Hz), 7.26 (1H, d, $J = 8.0$ Hz), 6.88 (1H, d, $J = 8.0$ Hz), 4.06 (3H, s), 3.86 (2H, d, $J = 6.0$ Hz), 1.69-1.92 (6H, m), 1.05-1.37 (5H, m); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.8, 153.5, 143.5, 135.2, 130.5, 127.6, 118.8, 113.2, 105.3, 73.9, 56.1, 37.8, 30.1, 26.6, 26.0.

3-(2,3-Dihydroxypropyl)oxy-8-methoxy quinoline (14): A pale brown solid (36.3 mg, 51%); mp: 181 °C; $^1\text{H NMR}$ (CD_3OD , 400 MHz): δ 8.55 (1H, d, $J = 3.2$ Hz), 7.69 (1H, d, $J = 3.2$ Hz), 7.47 (1H, d, $J = 7.6$ Hz), 7.39 (1H, d, $J = 7.6$ Hz), 7.04 (1H, d, $J = 7.6$ Hz), 4.24 (1H, dd, $J = 9.6, 4.4$ Hz), 4.15 (1H, $J = 9.6, 6.0$ Hz), 4.06 (1H, m), 4.03 (3H, s), 3.74 (1H, dd, $J = 11.2, 5.6$ Hz), 3.71 (1H, dd, $J = 11.2, 5.6$ Hz); $^{13}\text{C NMR}$ (CD_3OD , 100 MHz): δ 156.3, 154.6, 143.5, 135.7, 131.9, 129.0, 120.0, 115.4, 107.0, 71.5, 70.9, 64.0, 56.3.

3-(12-Hydroxydodecyl)oxy-8-methoxy quinoline (15): A white solid (102.7 mg, 91%); mp: 52 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.66 (1H, d, $J = 3.2$ Hz), 7.41 (1H, t, $J = 8.0$ Hz), 7.34 (1H, d, $J = 3.2$ Hz), 7.27 (1H, dd, $J = 8.0, 1.2$ Hz), 6.89 (1H, dd, $J = 8.0, 1.2$ Hz), 4.07 (2H, t, $J = 6.8$ Hz), 4.06 (3H, s), 3.63 (2H, t, $J = 6.8$ Hz), 1.86 (2H, m), 1.56 (2H, m), 1.50 (2H, m), 1.24-1.36 (14H, m); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.8, 153.4, 143.4, 135.2, 130.5, 127.6, 118.8, 113.3, 105.4, 68.6, 63.3, 56.1, 33.0, 29.80, 29.75 (3C), 29.63, 29.56, 29.3, 26.2, 25.9.

3-Ethoxy-8-methoxy quinoline (16): A brown oil (34.8 mg, 60%); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.69 (1H, d, $J = 2.8$ Hz), 7.43 (1H, t, $J = 8.0$ Hz), 7.38 (1H, d, $J = 2.8$ Hz), 7.29 (1H, dd, $J = 8.0, 1.2$ Hz), 6.91 (1H, dd, $J = 8.0, 1.2$ Hz), 4.17 (2H, quartet, $J = 7.2$ Hz), 4.07 (3H, s), 1.51 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.5, 153.2, 143.1, 135.0, 130.1, 127.8, 118.8, 113.9, 105.7, 64.2, 56.2, 14.8.

3-Isobutoxy-8-methoxy quinoline (17): A pale brown solid (62.7 mg, 95%); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.67 (1H, d, $J = 3.0$ Hz), 7.40 (1H, t, $J = 8.0$ Hz), 7.33 (1H, d, $J = 3.0$ Hz), 7.27 (1H, dd, $J = 8.0, 1.2$ Hz), 6.89 (1H, dd, $J = 8.0, 1.2$ Hz), 4.06 (3H, s), 3.84 (2H, d, $J = 6.0$ Hz), 2.17 (1H, septet, $J = 6.8$ Hz), 1.07 (6H, d, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.8, 153.5, 143.5, 135.2, 130.5, 127.6, 118.8, 113.3, 105.4, 74.9, 56.1, 28.4, 19.5 (2C).

3-Octadecyloxy-8-methoxy quinoline (18): A pale brown solid (88 mg, 74%); mp: 57 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.71 (1H, s), 7.43 (1H, t, $J = 8.0$ Hz), 7.40 (1H, d, $J = 2.8$ Hz), 7.30 (1H, d, $J = 8.4$ Hz), 6.93 (1H, d, $J = 8.0$ Hz), 4.09 (2H, t, $J = 6.8$ Hz), 4.08 (3H, s), 1.86 (2H, m), 1.50 (2H, m), 1.25-1.37 (28H, m), 0.87 (3H, t, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.3, 153.5, 143.1, 135.0, 130.6, 128.0, 118.7, 113.9, 105.9, 68.8, 56.2, 32.2, 29.92 (5C),

29.88 (3C), 29.82, 29.78, 29.6 (2C), 29.3, 26.2, 22.9, 14.3.

3-Hexadecyloxy-8-methoxy quinoline (19): A pale brown solid (73 mg, 67%); mp: 51 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.78 (1H, s), 7.48 (1H, t, $J = 8.0$ Hz), 7.34 (1H, d, $J = 2.8$ Hz), 7.31 (1H, dd, $J = 8.0$ Hz), 6.97 (1H, d, $J = 6.8$ Hz), 4.11 (2H, t, $J = 6.8$ Hz), 4.10 (3H, s), 1.87 (2H, m), 1.50 (2H, m), 1.25-1.34 (24H, m), 0.87 (3H, t, $J = 6.4$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 155.3, 153.5, 142.2, 135.2, 130.6, 128.0, 118.7, 113.9, 105.9, 68.8, 56.3, 32.2, 29.9 (4C), 29.88 (2C), 29.8, 29.77, 29.6 (2C), 29.2, 26.2, 22.9, 14.3.

3-(2-Ethyl)hexyloxy-8-methoxy quinoline (20): A pale brown oil (61.5 mg, 75%); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.66 (1H, d, $J = 2.8$ Hz), 7.41 (1H, t, $J = 8.0$ Hz), 7.35 (1H, d, $J = 2.8$ Hz), 7.27 (1H, brd, $J = 8.0$ Hz), 6.89 (1H, brd, $J = 8.0$ Hz), 4.06 (3H, s).

Antibacterial and antifungal activity. The antimicrobial activities of the synthetic compounds were determined by the broth dilution method.⁶ A solution of the synthetic compounds in methanol was added in 24-well plates containing 1 mL of culture broth (2.8 g BB in 100 mL water for bacteria and 2.4 g PDB in 100 mL water for fungi) for each microorganism and the wells were then two-fold serially diluted with culture broth. Overnight-precultured bacterial cells (10^6 CFU/mL) were inoculated in the wells and incubated at 37 °C for bacteria and 26 °C for fungi for 48 h. The lowest concentration that prevented the visible growth of microorganisms was reported as the minimum inhibitory concentration (MIC).

Cytotoxicity assay. Cytotoxicity of the cancer cell lines was measured by a colorimetric sulforhodamine B (SRB) assay.⁷ Exponentially growing cells were harvested and suspended in the culture media (100 μL , RPMI-1640) in a 96-well plate (seeding density for A-549 and B16F1: 1×10^5 and 2×10^4 cells/mL, respectively). After 24 h of incubation at 37 °C in humidified 5% CO_2 , serially diluted test solutions (100 μL in RPMI media) were added to the wells and incubated further for 48 h. The cells were fixed with 50% trichloroacetic acid and stained for 30 min with an SRB solution. The unbound dye was removed by 1% acetic acid (four times) and the protein-bound dye was extracted with 10 mM tris base (pH 10.5) for 5 min. The optical density of the released dye was measured at 520 nm using a microplate reader. The results were expressed as the concentration at which there was 50% inhibition (IC_{50}).

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