Supporting Information

Quorum Sensing Inhibition Attenuates the Virulence of the Plant Pathogen *Ralstonia solanacearum* Species Complex

Ayaka Yoshihara,[†,a] Mika Shimatani,[a] Megumi Sakata,[a] Chika Takemura,[b] Wakana Senuma,[b] Yasufumi Hikichi,[b] and Kenji Kai[†,*,a]

[†] These authors contributed equally to this work.

[a] Graduate School of Life and Environmental Sciences, Osaka Prefecture University, 1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531, Japan
[b] Laboratory of Plant Pathology and Biotechnology, Kochi University, 200 Otsu, Monobe, Nanko-ku, Kochi 783-8502, Japan

E-mail: kai@biochem.osakafu-u.ac.jp

Contents

1. SI Figures

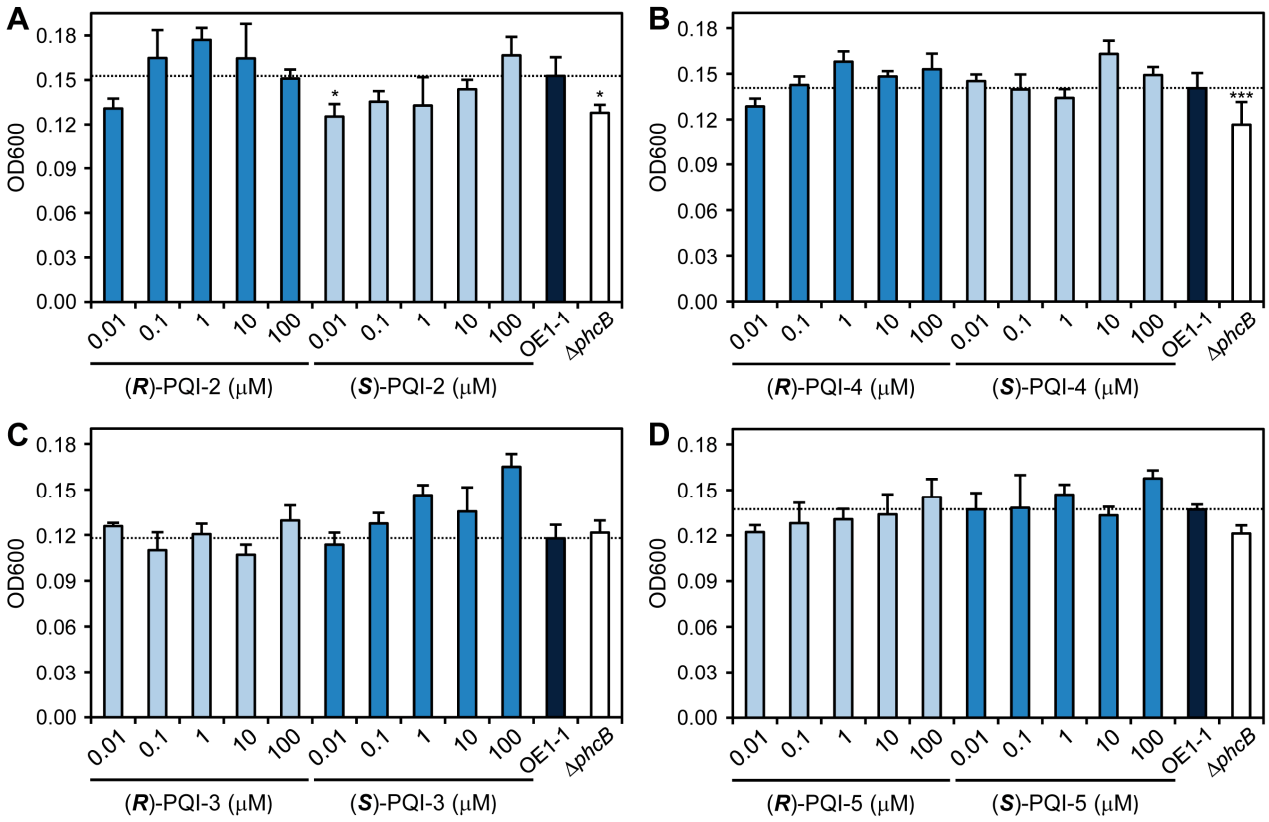


Figure S1. Effects of enantiopure (A) PQI-2, (B) PQI-4, (C) PQI-3, and (D) PQI-5 on OE1-1 growth. Error bars are the mean ±SD (n = 5). *p < 0.05, ***p < 0.001 versus OE1-1 control (Dunnett's test).

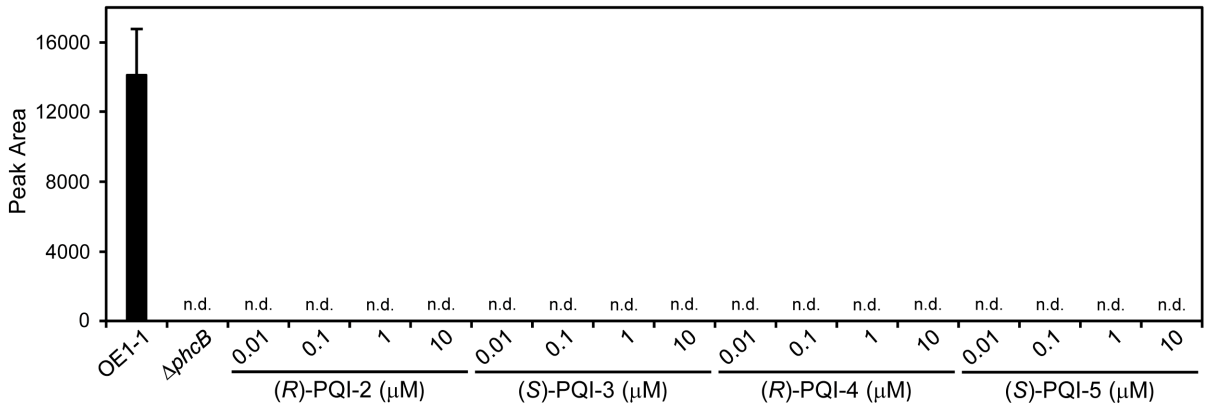


Figure S2. Evaluation of the agonistic effects of PQIs on ralfuranone A production in Δ*phcB*. n.d.: not detected. OE1-1 was used as a positive control. Error bars are the mean ±SD (n = 3).

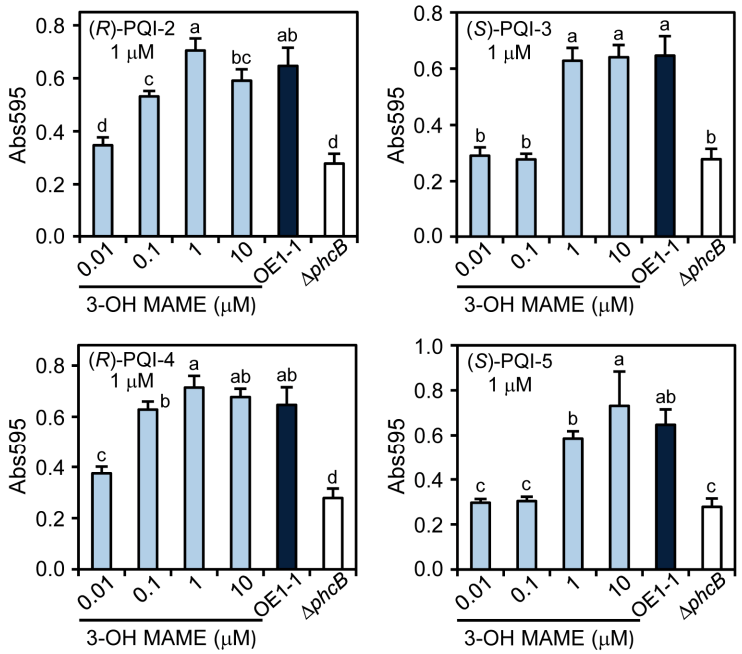


Figure S3. Competitive evaluation of the QS inhibition activity of 1 μM PQIs-2–5 with 0–10 μM 3-OH MAME. The *phc* QS-dependent biofilm formation was used to assess the PQI competiveness. Error bars are the mean ±SD (n = 3). Different letters above the bars indicate significant differences ($p < 0.05$, Tukey's test).

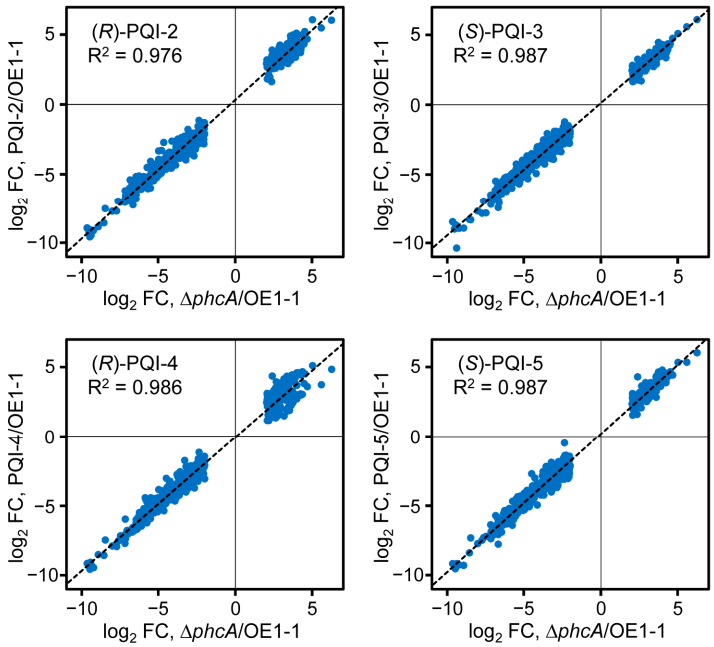


Figure S4. Scatterplots of $\log_2$ FC (fold change) of gene expression between PQI-treated OE1-1 and Δ*phcA*. Log_2 FC is computed by averaging FPKM values from the replicate samples with those from the OE1-1 control (n = 4).

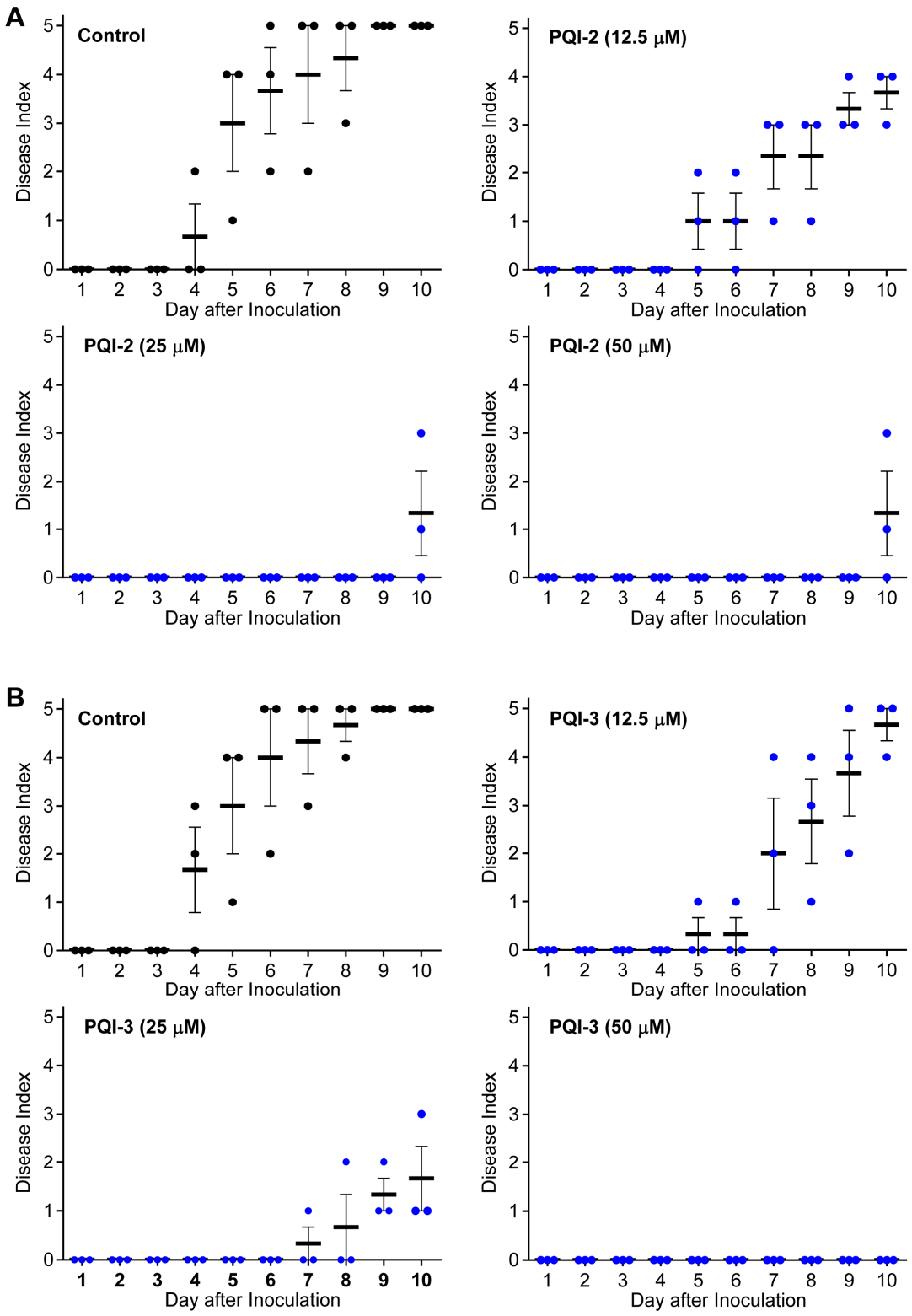


Figure S5. Effects of (A) PQI-2 and (B) PQI-3 on disease progression in tomato plants infected with strain OE1-1. Disease index scale: 0, no wilting; 1, 1–25% wilting; 2, 26–50% wilting; 3, 51–75% wilting; 4, 76–100% wilting; 5, dead. Error bars are the mean ±SEM (n = 3).

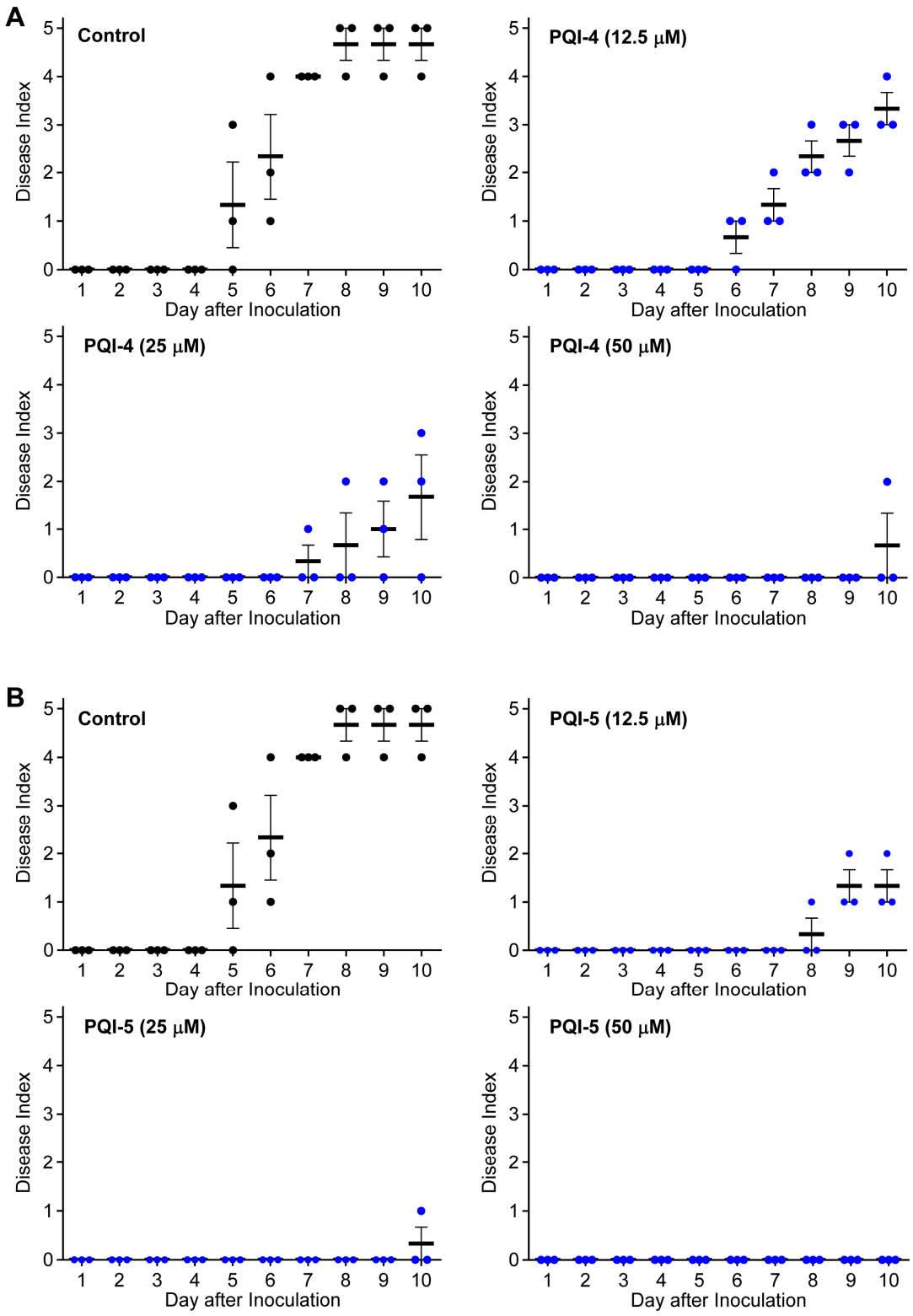


Figure S6. Effects of (A) PQI-4 and (B) PQI-5 on disease progression in tomato plants infected with strain OE1-1. Disease index scale: 0, no wilting; 1, 1–25% wilting; 2, 26–50% wilting; 3, 51–75% wilting; 4, 76–100% wilting; 5, dead. Error bars are the mean ±SEM (n = 3).

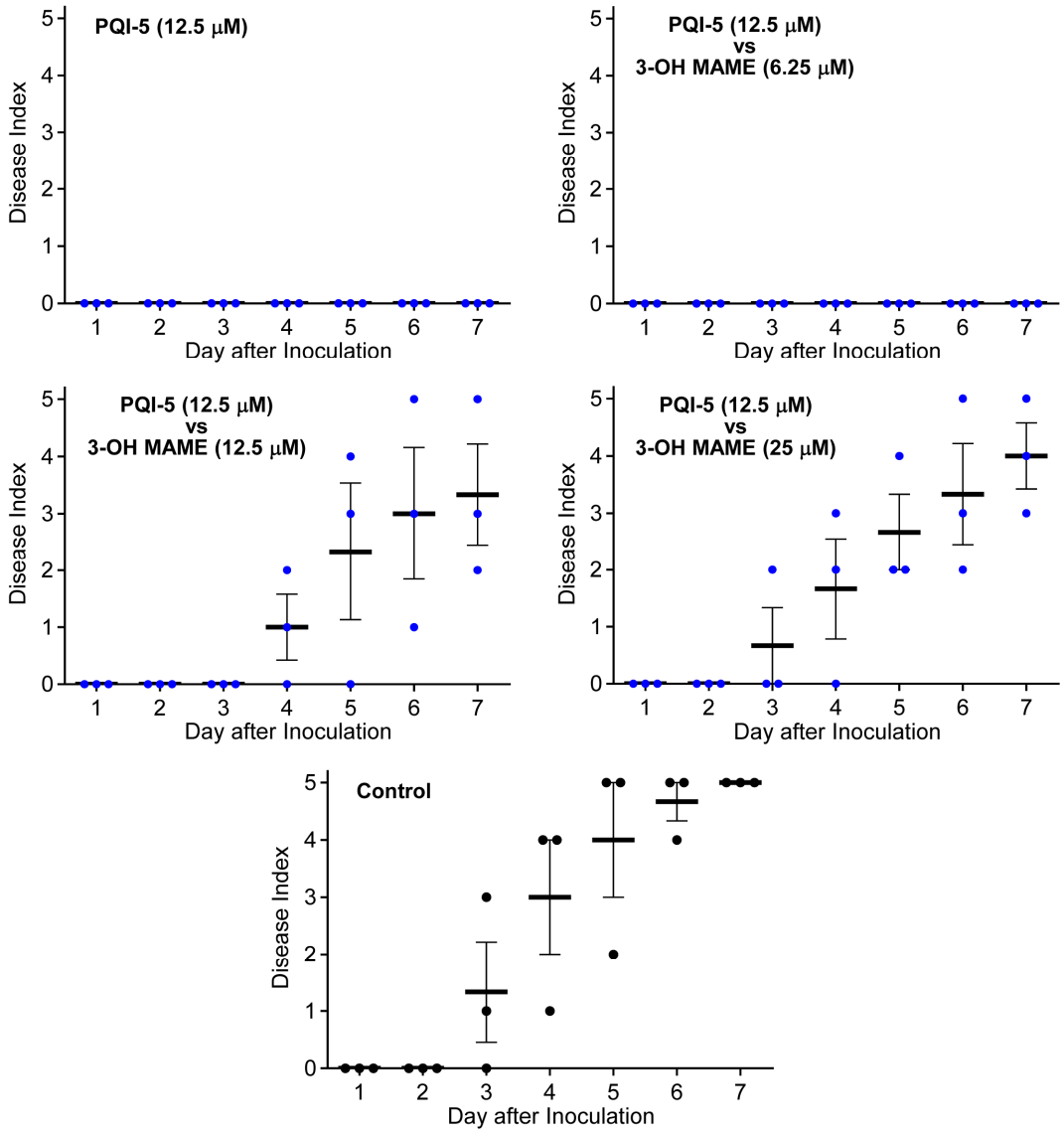
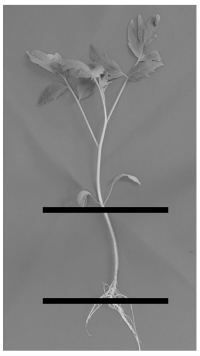


Figure S7. Time-course competitive evaluation of virulence attenuation of PQI-5 versus the natural ligand 3-OH MAME. Tomato plants inoculated with strain OE1-1 were grown for 3 days in the presence of 12.5 μM PQI-5 and 0–25 μM 3-OH MAME, and for a further 4 days in the presence of 3-OH MAME. Error bars are the mean ±SEM (n = 3).



	OE1-1	Δ*phcB*	PQI-5
shoot	detect	not detected	not detected
root	detect	detect	detect

Figure S8. Plate-printing assay of tomato plants to assess RSSC spread *in planta*. The behavior of bacterial cells in tomato roots and stems at 8 days post-inoculation by a root-dipping method was assessed.

2. SI Methods

General Information. All purchased chemicals were used without further purification. Silica gel column chromatography was performed on a Wakogel C-200 gel (Wako Pure Chemical Industries). Chemical reactions were carried out under a nitrogen atmosphere with dry solvents (Wako Pure Chemical Industries) unless otherwise indicated. The yields of synthetic reactions were not optimized. NMR spectra were recorded on a JNM-ECZ500R/S1 spectrometer (JEOL) and JNM-AL400 spectrometer (JEOL). Chemical shifts are reported as δ values (ppm); tetramethylsilane ($\delta_H = 0$, $\delta_C = 0$) or $CDCl_3$ ($\delta_H = 7.26$, $\delta_C = 77.0$) were used as internal references. HRESIMS data were obtained using an Orbitrap Elite FT mass spectrometer (Thermo Fisher Scientific). HPLC experiments were performed on a LaChrom Elite HPLC system (Hitachi High-Technologies) and Prominence HPLC system (Shimadzu). LC/MS data were obtained using an LCMS-2020 spectrometer (Shimadzu). Solvents for HPLC and LC/MS were purchased from Wako Pure Chemical Industries.

Synthesis of PQI-1. *Methyl 3-oxo-8-phenyloctanoate:* The solution of 6-phenylhexanoic acid (200 μL, 1.04 mmol), DMAP (140 mg, 1.14 mmol), Meldrum's acid (150 mg, 1.04 mmol), and DCC (236 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) was stirred for 16 h at rt. The formed DCU was removed by filtration and the filtrate was evaporated to remove the solvent. The residue was dissolved in EtOAc (30 mL), washed with 2 M HCl and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in MeOH (5 mL) and heated at reflux with stirring for 5 h. The concentrate was used for the next reaction without purification. *Methyl 3-hydroxy-8-phenyloctanoate:* The solution of methyl 3-oxo-8-phenyloctanoate in MeOH (5 mL) was cooled to 0°C and then $NaBH_4$ (51.1 mg, 1.35 mmol) was added to the solution. The mixture was stirred for 30 min at rt and then diluted with EtOAc (20 mL). The EtOAc layer was washed with water and brine, and dried over Na_2SO_4. The concentrate was purified by silica gel chromatography to give PQI-1 as a colorless oil (125 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.28–7.25 (m, 2H), 7.18–7.16 (m, 3H), 3.99 (m, 1H), 3.71 (s, 3H), 2.90 (d, J = 2.9 Hz, 1H), 2.60 (m, 2H), 2.50 (dd, J = 16.4, 3.2 Hz, 1H), 2.40 (dd, J = 16.4, 9.2 Hz, 1H), 1.63 (m, 2H), 1.55–1.32 (m, 6H).^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 173.5, 142.7, 128.4 (2), 128.2 (2), 125.6, 67.9, 51.8, 41.1, 36.4, 35.9, 31.4, 29.1, 25.4. HRESIMS: m/z 279.1955 $[M+H]^+$ (calcd for $C_{17}H_{27}O_3^+$, 279.1955).

Synthesis of PQI-2. *5-(4-Chlorophenyl)pent-4-yl-1-ol:* The solution of 1-chloro-4-iodobenzene (1.00 g, 4.19 mmol), bis(triphenylphosphine)palladium(II) dichloride (29.4 mg, 41.9 μmol), and CuI (15.9 mg, 83.8 μmol) in Et_3N (10 mL) was stirred for 5 min at rt, and then 4-pentyl-1-ol (390 μL, 4.19 mmol) was added to the solution. After stirring for 14 h, the mixture was evaporated to remove Et_3N. The residue was dissolved in EtOAc (100 mL), and washed with sat. $NaHCO_3$ and brine. The EtOAc layer was dried over Na_2SO_4 and the concentrate was subjected to silica gel chromatography to give the title compound as a brown oil (727 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33–7.30 (m, 2H), 7.27–7.24 (m, 2H), 3.82 (m, 2H), 2.54 (t, J = 7.0 Hz, 2H), 1.86 (m, 2H), 1.50 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 133.6, 132.8 (2), 128.5 (2), 122.2, 90.4, 80.0, 61.8, 31.2, 16.0.

ESI-MS: *m*/*z* 195 $[M+H]^+$ (calcd for $C_{11}H_{12}ClO^+$, 195.1). *5-(4-Chlorophenyl)pentan-1-ol:* The mixture of 5-(4-chlorophenyl)pent-4-yl-1-ol (727 mg, 3.73 mmol) and Pd/C (10% Pd, 145 mg) in MeOH (5 mL) was stirred for 14 h at rt under H_2 atmosphere. After filtration to remove Pd/C and evaporation, the residue was subjected to silica gel chromatography to give the title compound as a colorless oil (629 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28–7.22 (m, 2H), 7.12–7.09 (m, 2H), 3.65 (m, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.66–1.56 (m, 4H), 1.43–1.35 (m, 2H), 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.9, 131.3, 129.7 (2), 128.3 (2), 62.9, 35.2, 32.6, 31.2, 25.3. ESI-MS: *m*/*z* 199 $[M+H]^+$ (calcd for $C_{11}H_{16}ClO^+$, 199.1). *5-(4-Chlorophenyl)pentanoic acid:* The solution of 5-(4-chlorophenyl)pentan-1-ol (629 mg, 3.16 mmol) in acetone (5 mL) was cooled to 0°C, and then Jones reagent prepared from CrO_3 (948 mg, 9.48 mmol), conc. H_2SO_4 (2 mL), and water (6 mL) was added to the solution. The mixture was stirred for 2 h at 0°C and for 18 h at rt. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL ×2). The combined EtOAc layer was washed with brine and dried over Na_2SO_4. The concentrate was purified by silica gel chromatography to give the title compound as a colorless oil (513 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26–7.22 (m, 2H), 7.12–7.08 (m, 2H), 2.60 (m, 2H), 2.37 (m, 2H), 1.69–1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.5, 140.4, 131.2, 129.7 (2), 128.4 (2), 34.9, 33.7, 30.6, 24.1. ESI-MS: *m*/*z* 211 $[M-H]^-$ (calcd for $C_{11}H_{12}ClO_2^-$, 211.1). *Methyl 7-(4-chlorophenyl)-3-oxoheptanoate:* The solution of 5-(4-chlorophenyl)pentanoic acid (513 mg, 2.41 mmol), DMAP (324 mg, 2.65 mmol), Meldrum's acid (347 mg, 2.41 mmol), and DCC (547 mg, 2.65 mmol) in CH_2Cl_2 (10 mL) was stirred for 19 h at rt. The formed DCU was removed by filtration and the filtrate was evaporated to remove the solvent. The residue was dissolved in EtOAc (50 mL), washed with 2 M HCl and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in MeOH (10 mL) and heated at reflux with stirring for 6 h. The mixture was evaporated and the residue was purified by silica gel chromatography to give the title compound as a colorless oil (606 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26–7.22 (m, 2H), 7.10–7.08 (m, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.61–2.54 (m, 4H), 1.64–1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.5, 167.6, 140.4, 131.5, 129.7 (2), 128.4 (2), 52.4, 49.0, 42.7, 35.0, 30.6, 22.9. ESI-MS: *m*/*z* 269 $[M+H]^+$ (calcd for $C_{14}H_{18}ClO_3^+$, 269.1). *Methyl 7-(4-cholorophenyl)-3-hydroxyheptanoate (PQI-2):* The solution of methyl 7-(4-chlorophenyl)-3-oxoheptanoate (606 mg, 2.25 mmol) in MeOH (10 mL) was cooled to 0°C and then $NaBH_4$ (110 mg, 2.93 mmol) was added to the solution. The mixture was stirred for 30 min at rt and then diluted with EtOAc (50 mL). The EtOAc layer was washed with water and brine, and dried over Na_2SO_4. The concentrate was purified by silica gel chromatography to give PQI-2 as a colorless oil (336 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26–7.22 (m, 2H), 7.11–7.09 (m, 2H), 3.99 (m, 1H), 3.71 (s, 3H), 2.91 (d, *J* = 3.9 Hz, 1H), 2.59 (t, *J* = 7.7 Hz, 3H), 2.50 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.64–1.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 140.9, 131.4, 129.7 (2), 128.4 (2), 67.8, 51.8, 41.0, 36.2, 35.2, 31.2, 25.0. HRESIMS: *m*/*z* 271.1094 $[M+H]^+$ (calcd for $C_{14}H_{20}ClO_3^+$, 271.1095).

Synthesis of PQI-3. *6-(4-Chlorophenyl)hex-5-yn-1-ol:* Sonogashira cross-coupling of

1-chloro-4-iodobenzene (1.00 g, 4.19 mmol) with 5-hexyn-1-ol (462 μL, 4.19 mmol) was performed to produce the title compound as a brown oil (831 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33–7.29 (m, 2H), 7.27–7.23 (m, 2H), 3.75–3.69 (m, 2H), 2.45 (m, 2H), 1.79–1.65 (m, 4H), 1.40 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 133.5, 132.7 (2), 128.5 (2), 122.4, 90.9, 79.9, 62.4, 31.9, 24.9, 19.2. ESI-MS: *m*/*z* 209 $[M+H]^+$ (calcd for $C_{12}H_{14}ClO^+$, 209.1). *6-(4-Chlorophenyl)hexan-1-ol:* Hydrogenation of 6-(4-chlorophenyl)hex-5-yn-1-ol (831 mg, 3.98 mmol) with Pd/C (166 mg) was performed to produce the title compound as a colorless oil (710 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30–7.06 (m, 4H), 3.63 (m, 2H), 2.58 (m, 2H), 1.65–1.53 (m, 4H), 1.42–1.28 (m, 4H), 1.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.1, 131.3, 129.7 (2), 128.3 (2), 62.9, 35.2, 32.6, 31.3, 28.9, 25.5. ESI-MS: *m*/*z* 213 $[M+H]^+$ (calcd for $C_{12}H_{18}ClO^+$, 213.1). *6-(4-Chlorophenyl)hexanoic acid:* Jones oxidation of 6-(4-chlorophenyl)hexan-1-ol (710 mg, 3.34 mmol) was performed to produce the title compound as a colorless oil (521 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30–7.20 (m, 2H), 7.13–7.06 (m, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.71–1.58 (m, 4H), 1.43−1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 196.4, 140.8, 131.4, 129.7 (2), 128.4 (2), 35.0, 33.7, 30.9, 28.5, 24.4. ESI-MS: *m*/*z* 225 $[M–H]^-$ (calcd for $C_{12}H_{14}ClO_2^-$, 225.1). *Methyl 6-(4-chlorophenyl)hexanoate:* 6-(4-Chlorophenyl)hexanoic acid (521 mg, 2.30 mmol) was dissolved in 0.5 M HCl/MeOH (5 mL) and the solution was stirred for 1.5 h at rt. After evaporation of HCl/MeOH, the residue was purified by silica gel chromatography to give the title compound as a colorless oil (489 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29–7.21 (m, 2H), 7.11–7.07 (m, 2H), 3.66 (s, 3H), 2.57 (m, 2H), 2.30 (t, *J* = 8.0 Hz, 2H), 1.69–1.55 (m, 4H), 1.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 174.1, 140.9, 131.4, 129.7 (2), 128.3 (2), 51.5, 35.0, 33.9, 31.0, 28.6, 24.7. ESI-MS: *m*/*z* 241 $[M+H]^+$ (calcd for $C_{13}H_{18}ClO_2^+$, 241.1). *Methyl 7-(4-chlorophenyl)-2-oxoheptanoate:* The solution of NaH (45.1 mg, 1.88 mmol) and MeOH (19.0 μL, 0.470 mmol) in THF (2 mL) was stirred for 5 min at 0°C. Dimethyl oxalate (200 mg, 1.69 mmol) and methyl 6-(4-chlorophenyl)hexanoate (407 mg, 1.69 mmol) were added to the solution, and the mixture was refluxed with stirring for 3 h. After cooling to rt, the reaction was quenched with H_2O and the solution was evaporated. The residue was dissolved in conc. HCl/AcOH (1:3, 1 mL) and refluxed with stirring for 4 h. The reaction mixture was poured into ice water (30 mL) and extracted with EtOAc (10 mL ×3). After drying with Na_2SO_4, the sample was evaporated to remove solvents. The residue was dissolved in MeOH (4 mL) containing *p*-toluenesulfonic acid (3 mg) and refluxed for 2 h. After evaporation of MeOH, the residue was dissolved in EtOAc (20 mL) and washed with 20% K_2CO_3 (20 mL ×3). After drying with Na_2SO_4, the concentrate was purified by silica gel chromatography to give the title compound as a colorless oil (14.3 mg, 3.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29–7.22 (m, 2H), 7.10–7.08 (m, 2H), 3.87 (s, 3H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 1.70–1.54 (m, 4H), 1.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 194.1, 177.9, 140.7, 129.7, 128.4 (2), 128.3 (2), 52.9, 39.2, 35.0, 31.0, 28.4, 22.7. ESI-MS: *m*/*z* 269 $[M+H]^+$ (calcd for $C_{14}H_{18}ClO_3^+$, 269.1). *Methyl 7-(4-chlorophenyl)-2-hydroxyheptanoate (PQI-3):* Reduction of methyl 7-(4-chlorophenyl)-2-oxoheptanoate (13.6 mg, 53.2 μmol) with $NaBH_4$ (2.60

mg, 69.0 μmol) was performed to produce PQI-3 as a colorless oil (8.80 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.25–7.22 (m, 2H), 7.10–7.08 (m, 2H), 4.20–4.17 (m, 1H), 3.78 (s, 3H), 2.72–2.70 (m, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.18 (s, 1H), 1.80–1.75 (m, 1H), 1.66–1.57 (m, 2H), 1.51–1.30 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 175.8, 141.0, 131.3, 129.7 (2), 128.3 (2), 70.3, 52.5, 35.1, 34.2, 31.2, 28.8, 24.6. HRESIMS: *m/z* 271.1096 $[M+H]^+$ (calcd for $C_{14}H_{20}ClO_3^+$, 271.1095).

Synthesis of PQI-4. *5-(p-Tolyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 4-iodotoluene (1.00 g, 4.59 mmol) with 4-pentyn-1-ol (427 μL, 4.59 mmol) was performed to produce the title compound as an orange oil (708 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29 (dd, *J* = 7.9, 2.0 Hz, 2H), 7.09 (dd, *J* = 8.5, 0.5 Hz, 2H), 3.83 (dd, *J* = 6.6, 5.9 Hz, 2H), 2.53 (t, *J* = 6.3 Hz, 2H), 2.33 (s, 3H), 1.89–1.83 (m, 2H), 1.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 137.7, 131.4 (2), 129.0 (2), 120.6, 88.4, 81.2, 61.9, 31.4, 21.4, 16.0. ESI-MS: *m/z* 175 $[M+H]^+$ (calcd for $C_{12}H_{15}O^+$, 175.1). *5-(p-Tolyl)pentan-1-ol:* Hydrogenation of 5-(*p*-tolyl)pent-4-yn-1-ol (708 mg, 4.06 mmol) with Pd/C (142 mg) was performed to produce the title compound as a colorless oil (627 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.06 (m, 4H), 3.64 (m, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.67–1.56 (m, 4H), 1.43–1.35 (m, 2H), 1.26 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 139.5, 135.1, 128.9 (2), 128.3 (2), 62.9, 35.4, 32.6, 31.4, 25.4, 21.0. ESI-MS: *m/z* 179 $[M+H]^+$ (calcd for $C_{12}H_{19}O^+$, 179.1). *5-(p-Tolyl)pentanoic acid:* Jones oxidation of 5-(*p*-tolyl)pentan-1-ol (627 mg, 3.52 mmol) was performed to produce the title compound as a colorless oil (495 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.72–1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.1, 138.9, 135.2, 129.0 (2), 128.2 (2), 35.1, 33.6, 30.9, 24.3, 21.0. ESI-MS: *m/z* 191 $[M–H]^–$ (calcd for $C_{12}H_{15}O_2^–$, 191.1). *Methyl 3-oxo-7-(p-tolyl)heptanoate:* 5-(*p*-Tolyl)pentanoic acid (495 mg, 2.60 mmol) was converted to the title compound as a colorless oil (471 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.03 (m, 4H), 3.72 (s, 3H), 3.42 (s, 2H), 2.59–2.53 (m, 4H), 2.31 (s, 3H), 1.75–1.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.6, 167.7, 138.9, 135.2, 129.0 (2), 128.2 (2), 52.3, 49.0, 42.9, 35.2, 30.8, 23.0, 21.0. ESI-MS: *m/z* 249 $[M+H]^+$ (calcd for $C_{15}H_{21}O_3^+$, 249.1). *Methyl 3-hydroxy-7-(p-tolyl)heptanoate (PQI-4):* Reduction of methyl 3-oxo-7-(*p*-tolyl)heptanoate (471 mg, 1.90 mmol) with $NaBH_4$ (93.0 mg, 2.50 mmol) was performed to produce PQI-4 as a colorless oil (442 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 4.00 (m, 1H), 3.71 (s, 3H), 2.88 (d, *J* = 3.0 Hz, 1H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.50 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.32 (s, 3H), 1.66–1.33 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 139.4, 135.1, 128.9 (2), 128.2 (2), 67.9, 51.7, 41.0, 36.3, 35.4, 31.5, 25.1, 21.0. HRESIMS: *m/z* 251.1645 $[M+H]^+$ (calcd for $C_{15}H_{23}O_3^+$, 251.1642).

Synthesis of PQI-5. *6-(p-Tolyl)hex-5-yn-1-ol:* Sonogashira cross-coupling of 4-iodotoluene (1.00 g, 4.59 mmol) with 5-hexyn-1-ol (506 μL, 4.59 mmol) was performed to produce the title compound as a brown oil (669 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.72 (m, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 1.79–1.65 (m, 4H), 1.30 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 137.8, 131.4 (2), 128.9 (2), 120.8, 89.0, 81.0, 62.5, 31.9, 25.0,

21.4, 19.2. ESI-MS: *m*/*z* 189 $[M+H]^+$ (calcd for $C_{13}H_{17}O^+$, 189.1). *6-(p-Tolyl)hexan-1-ol:* Hydrogenation of 6-(*p*-tolyl)hex-5-yn-1-ol (669 mg, 3.55 mmol) with Pd/C (134 mg) was performed to produce the title compound as a colorless oil (644 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 3.64 (m, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 1.65–1.53 (m, 4H), 1.38–1.35 (m, 4H), 1.22 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 139.6, 135.0, 128.9 (2), 128.3 (2), 63.0, 53.4, 32.7, 31.5, 29.0, 25.6, 21.0. ESI-MS: *m*/*z* 193 $[M+H]^+$ (calcd for $C_{13}H_{21}O^+$, 193.2). *6-(p-Tolyl)hexanoic acid:* Jones oxidation of 6-(*p*-tolyl)hexan-1-ol (644 mg, 3.34 mmol) was performed to produce the title compound as a colorless oil (521 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.35 (t, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 1.70–1.58 (m, 4H), 1.42–1.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.3, 139.3, 135.1, 129.0 (2), 128.3 (2), 35.2, 33.9, 31.2, 28.6, 24.5, 21.0. ESI-MS: *m*/*z* 205 $[M-H]^-$ (calcd for $C_{13}H_{17}O_2^-$, 205.1). *Methyl 6-(p-tolyl)hexanoate:* Methylation of 6-(*p*-tolyl)hexanoic acid (521 mg, 2.53 mmol) was performed with 0.5 M HCl/MeOH to produce the title compound as a colorless oil (507 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 3.66 (s, 3H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.32–2.28 (m, 4H), 1.69–1.56 (m, 4H), 1.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 174.2, 139.4, 135.1, 128.9 (2), 128.3 (2), 51.6, 35.2, 34.0, 31.2, 28.7, 24.8, 21.0. ESI-MS: *m*/*z* 221 $[M+H]^+$ (calcd for $C_{14}H_{21}O_2^+$, 221.2). *Methyl 2-oxo-7-(p-tolyl)heptanoate:* Methyl 6-(*p*-tolyl)hexanoate (507 mg, 2.60 mmol) was converted to the title compound as a colorless oil (396 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.04 (m, 4H), 3.86 (s, 3H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 1.70–1.50 (m, 4H), 1.40–1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 194.2, 161.5, 139.3, 135.1, 129.0 (2), 128.3 (2), 53.1, 39.2, 35.2, 31.2, 28.5, 22.8, 21.0. ESI-MS: *m*/*z* 249 $[M+H]^+$ (calcd for $C_{15}H_{21}O_3^+$, 249.1). *Methyl 2-hydroxy-7-(p-tolyl)heptanoate (PQI-5):* Reduction of methyl 2-oxo-7-(*p*-tolyl)heptanoate (396 mg, 1.59 mmol) with $NaBH_4$ (78.0 mg, 2.06 mmol) was performed to produce PQI-5 as a colorless oil (173 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 4.18 (m, 1H), 3.78 (s, 3H), 2.70 (d, *J* = 5.6 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.75 (m, 1H), 1.64–1.32 (7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 175.8, 139.5, 135.0, 128.9 (2), 128.3 (2), 70.5, 52.3, 35.3, 34.3, 31.4, 28.9, 24.6, 21.0. HRESIMS: *m*/*z* 251.1643 $[M+H]^+$ (calcd for $C_{15}H_{23}O_3^+$, 251.1642).

Synthesis of compound 7. *Methyl 3-oxo-9-phenylnonanoate:* 7-Phenylheptanoic acid (202 mg, 0.978 mmol) was converted to the title compound (quant). The product was used for the next reaction without purification. *Methyl 3-hydroxy-9-phenylnonanoate:* Reduction of methyl 3-oxo-9-phenylnonanoate (0.978 mmol) with $NaBH_4$ (48.1 mg, 1.27 mmol) was performed to produce compound **7** as a colorless oil (159 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29–7.24 (m, 2H), 7.19–7.16 (m, 3H), 4.01 (m, 1H), 3.69 (s, 3H), 2.88 (d, *J* = 3.0 Hz, 1H), 2.60 (m, 2H), 2.50 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.63–1.17 (10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 142.8, 128.4 (2), 128.2 (2), 125.6, 68.0, 51.8, 41.0, 36.4, 35.9, 31.4, 29.3, 29.2, 25.4. ESI-MS: *m*/*z* 265 $[M+H]^+$ (calcd for $C_{16}H_{25}O_3^+$, 265.2).

Synthesis of compound 8. *Methyl 3-oxo-10-phenyldecanoate:* 8-Phenyloctanoic acid (200 mg,

0.908 mmol) was converted to the title compound (quant). The product was used for the next reaction without purification. *Methyl 3-hydroxy-10-phenyldecanoate:* Reduction of methyl 3-oxo-10-phenyldecanoate (0.908 mmol) with $NaBH_4$ (44.6 mg, 1.18 mmol) was performed to produce compound **8** as a colorless oil (100 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30–7.26 (m, 2H), 7.19–7.17 (m, 3H), 4.00 (m, 1H), 3.72 (s, 3H), 2.88 (d, *J* = 3.0 Hz, 1H), 2.61 (m, 2H), 2.52 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.62–1.25 (12H). ESI-MS: *m*/*z* 279 $[M+H]^+$ (calcd for $C_{17}H_{27}O_3^+$, 279.2).

Synthesis of compound 9. *Methyl 7-(naphthalen-2-yl)-3-oxoheptanoate:* 5-(Naphthalen-2-yl)pentanoic acid (156 mg, 0.683 mmol) was converted to the title compound (quant). The product was used for the next reaction without purification. *Methyl 3-hydroxy-7-(naphthalen-2-yl)heptanoate:* Reduction of methyl 7-(naphthalen-2-yl)-3-oxoheptanoate (65.5 mg, 0.229 mmol) with $NaBH_4$ (11.3 mg, 0.298 mmol) was performed to produce compound **9** as a colorless oil (10.8 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.49 (m, 1H), 8.05–7.89 (m, 4H), 7.63–7.56 (m, 2H), 4.05 (m, 1H), 3.72 (s, 3H), 3.52–3.41 (m, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 3.10 (d, *J* = 3.0 Hz, 1H), 2.52 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.69–1.62 (m, 2H), 1.40–1.25 (m, 2H). ESI-MS: *m*/*z* 282 $[M+H]^+$ (calcd for $C_{18}H_{23}O_3^+$, 282.2).

Synthesis of compound 10. *Methyl 4-([1,1'-biphenyl]-4-yl)-3-oxobutanoate:* 4-Biphenylacetic acid (200 mg, 0.942 mmol) was converted to the title compound (quant). The product was used for the next reaction without purification. *Methyl 4-([1,1'-biphenyl]-4-yl)-3-hydroxybutanoate:* Reduction of methyl 4-([1,1'-biphenyl]-4-yl)-3-oxobutanoate (0.942 mmol) with $NaBH_4$ (46.3 mg, 1.22 mmol) was performed to produce compound **10** as a colorless oil (10.8 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.59–7.53 (m, 4H), 7.46–7.42 (m, 2H), 7.36–7.29 (m, 3H), 4.31 (m, 1H), 3.71 (s, 3H), 2.92 (d, *J* = 3.9 Hz, 1H), 2.91 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.82 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.56 (dd, *J* = 16.5, 3.7 Hz, 1H), 2.49 (dd, *J* = 16.5, 8.8 Hz, 1H). ESI-MS: *m*/*z* 271 $[M+H]^+$ (calcd for $C_{17}H_{19}O_3^+$, 271.1).

Synthesis of compound 11. *Methyl 7-benzamido-3-hydroxyheptanoate:* The solution of methyl 7-amino-3-hydroxyheptanoate (103 mg, 0.586 mmol), benzoic acid (71.5 mg, 0.586 mmol), DCC (133 mg, 0.644 mmol), and DMAP (78.7 mg, 0.644 mmol) in CH_2Cl_2 (4.5 mL) was stirred for 8 h at rt. After filtration to remove DCU, the filtrate was concentrated and the residue was dissolved in CH_3Cl/MeOH (95:5, 20 mL). The solution was washed with 2 M HCl and brine, and dried over Na_2SO_4. The concentrate was purified by silica gel chromatography to give compound **11** as a colorless oil (26.4 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.77–7.75 (m, 2H), 7.50–7.41 (m, 3H), 6.23 (br, 1H), 4.03 (m, 1H), 3.72 (s, 3H), 3.48 (dt, *J* = 6.8, 6.8 Hz, 2H), 3.03 (d, *J* = 3.9 Hz, 1H), 2.52 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.44 (dd, *J* = 16.5, 8.9 Hz, 1H), 1.71–1.44 (m, 6H). ESI-MS: *m*/*z* 280 $[M+H]^+$ (calcd for $C_{15}H_{22}NO_4^+$, 280.2).

Synthesis of compound 12. *5-Hydroxy-7-methoxy-7-oxoheptyl benzoate:* The solution of methyl 3,7-dihydroxyheptanoate (100 mg, 0.568 mmol), benzoic acid (69.3 mg, 0.568 mmol), DCC (129 mg, 0.624 mmol), and DMAP (76.3 mg, 0.624 mmol) in CH_2Cl_2 (5 mL) was stirred for 8 h at rt. After

filtration to remove DCU, the filtrate was concentrated and the residue was dissolved in EtOAc (20 mL). The solution was washed with 2 M HCl and brine, and dried over Na_2SO_4. The concentrate was purified by silica gel chromatography to give compound **12** as a colorless oil (72.2 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.05–8.03 (m, 2H), 7.56 (tt, J = 7.4, 1.5 Hz, 1H), 7.46–7.42 (m, 2H), 4.33 (t, J = 6.6 Hz, 2H), 4.03 (m, 1H), 3.72 (s, 3H), 2.97 (d, J = 3.9 Hz, 1H), 2.53 (dd, J = 16.4, 3.2 Hz, 1H), 2.44 (dd, J = 16.4, 8.9 Hz, 1H), 1.85–1.77 (m, 2H), 1.66–1.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.4, 166.7, 132.9, 130.3, 129.5 (2), 128.3 (2), 67.8, 34.8, 51.8, 41.1, 36.0, 28.6, 22.1. ESI-MS: m/z 281 $[M+H]^+$ (calcd for $C_{15}H_{21}O_5^+$, 281.1).

Synthesis of compound 13. *7-(4-Chlorophenyl)hept-6-yn-1-ol:* Sonogashira cross-coupling of 1-chloro-4-iodobenzene (1.00 g, 4.19 mmol) with 6-heptyn-1-ol (522 μL, 4.19 mmol) was performed to produce the title compound as an orange oil (854 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.32–7.30 (m, 2H), 7.26–7.24 (m, 2H), 3.68 (q, J = 5.7 Hz, 2H), 2.42 (t, J = 6.6 Hz, 2H), 1.67–1.50 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 133.4, 132.8 (2), 128.5 (2), 122.5, 91.1, 79.7, 62.9, 32.3, 28.4, 25.1, 19.4. ESI-MS: m/z 223 $[M+H]^+$ (calcd for $C_{13}H_{16}ClO^+$, 223.1). *7-(4-Chlorophenyl)heptan-1-ol:* Hydrogenation of 7-(4-chlorophenyl)hept-6-yn-1-ol (848 mg, 3.74 mmol) with Pd/C (170 mg) was performed to produce the title compound as a colorless oil (684 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29–7.22 (m, 2H), 7.18–7.17 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 3.63 (t, J = 6.6 Hz, 2H), 2.62–2.55 (m, 2H), 1.63–1.54 (m, 5H), 1.35–1.24 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 141.2, 131.2, 129.7 (2), 128.3 (2), 63.0, 35.9, 32.7, 31.3, 29.2, 29.1, 25.7. ESI-MS: m/z 227 $[M+H]^+$ (calcd for $C_{13}H_{20}ClO^+$, 227.1). *7-(4-Chlorophenyl)heptanoic acid:* Jones oxidation of 7-(4-chlorophenyl)heptan-1-ol (678 mg, 3.00 mmol) was performed to produce the title compound as a colorless oil (623 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29–7.22 (m, 2H), 7.19–7.16 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 2.56 (t, J = 7.7 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 1.64–1.58 (m, 4H), 1.38–1.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 179.6, 141.0, 131.3, 129.7 (2), 128.4 (2), 35.9, 33.9, 31.1, 28.9, 28.7, 24.5. ESI-MS: m/z 239 $[M–H]^–$ (calcd for $C_{13}H_{16}ClO_2^–$, 239.1). *Methyl 9-(4-chlorophenyl)-3-oxononanoate:* 7-(4-Chlorophenyl)heptanoic acid (617 mg, 2.56 mmol) was converted to the title compound as a colorless oil (536 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29–7.22 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H), 3.44 (s, 2H), 2.59–2.51 (m, 4H), 1.63–1.57 (m, 4H), 1.33–1.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 202.8, 167.7, 141.0, 131.3, 129.7 (2), 128.3 (2), 52.4, 49.0, 43.0, 35.2, 31.1, 28.9, 28.8, 23.3. ESI-MS: m/z 297 $[M+H]^+$ (calcd for $C_{16}H_{22}ClO_3^+$, 297.1). *Methyl 9-(4-chlorophenyl)-3-hydroxynonanoate:* Reduction of methyl 9-(4-chlorophenyl)-3-oxononanoate (530 mg, 1.79 mmol) with $NaBH_4$ (88.0 mg, 2.33 mmol) was performed to produce compound **13** as a colorless oil (512 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.25–7.22 (m, 2H), 7.11–7.08 (m, 2H), 4.01–3.97 (m, 1H), 3.71 (s, 3H), 2.89 (d, J = 4.0 Hz, 1H), 2.56 (t, J = 7.7 Hz, 2H), 2.51 (dd, J = 16.6, 2.9 Hz, 1H), 2.41 (dd, J = 16.6, 9.2 Hz, 1H), 1.60–1.32 (10H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 173.5, 141.2, 131.2, 129.7 (2), 128.3 (2), 67.9, 51.8, 41.0, 36.4, 35.2, 31.3, 29.3, 29.1, 25.4. ESI-MS: m/z 299 $[M+H]^+$ (calcd for $C_{16}H_{24}ClO_3^+$, 299.1).

Synthesis of compound 14. *Methyl 8-(4-chlorophenyl)-3-oxooctanoate:* 6-(4-Chlorophenyl)hexanoic acid (695 mg, 2.56 mmol) was converted to the title compound as a colorless oil (715 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.24 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 3.74 (s, 3H), 3.44 (s, 2H), 2.59–2.51 (m, 4H), 1.66–1.56 (m, 4H), 1.35–1.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.7, 167.7, 140.1, 131.3, 131.3 (2), 128.3 (2), 52.4, 49.0, 42.9, 35.0, 31.1, 28.4, 23.1. ESI-MS: m/z 283 $[M+H]^+$ (calcd for $C_{15}H_{20}ClO_3^+$, 283.1). *Methyl 8-(4-chlorophenyl)-3-hydroxyoctanoate:* Reduction of methyl 8-(4-chlorophenyl)-3-oxooctanoate (715 mg, 2.53 mmol) with $NaBH_4$ (124 mg, 3.29 mmol) was performed to produce the title compound as a colorless oil (272 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.23 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 4.03–3.95 (m, 1H), 3.72 (s, 3H), 2.90 (d, J = 4.1 Hz, 1H), 2.57 (t, J = 7.7 Hz, 2H), 2.51 (dd, J = 16.6, 3.2 Hz, 1H), 2.41 (dd, J = 16.6, 9.0 Hz, 1H), 1.64–1.33 (8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 141.0, 131.3, 129.7 (2), 128.3 (2), 67.9, 51.8, 41.0, 36.3, 35.1, 31.2, 29.0, 25.3. ESI-MS: m/z 285 $[M+H]^+$ (calcd for $C_{15}H_{22}ClO_3^+$, 285.1).

Synthesis of compound 16. *4-(4-Chlorophenyl)but-3-yn-1-ol:* Sonogashira cross-coupling of 1-chloro-4-iodobenzene (1.00 g, 4.19 mmol) with 3-butyn-1-ol (317 μL, 4.19 mmol) was performed to produce the title compound as an orange oil (692 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.35–7.33 (m, 2H), 7.28–7.26 (m, 2H), 3.82 (dt, J = 6.3, 6.3 Hz, 2H), 2.69 (t, J = 6.2 Hz, 2H), 1.81 (t, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 133.9, 132.9 (2), 128.6 (2), 121.8, 87.4, 81.3, 61.1, 23.8. ESI-MS: m/z 181 $[M+H]^+$ (calcd for $C_{10}H_{10}ClO^+$, 181.0). *4-(4-Chlorophenyl)butan-1-ol:* Hydrogenation of 4-(4-chlorophenyl)but-3-yn-1-ol (692 mg, 3.83 mmol) with Pd/C (138 mg) was performed to produce the title compound as a colorless oil (636 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.25–7.23 (m, 2H), 7.13–7.10 (m, 2H), 3.66 (dt, J = 5.9, 5.9 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 1.72–1.55 (m, 4H), 1.25 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.7, 131.4, 129.7 (2), 128.4 (2), 62.7, 35.0, 32.2, 27.5. ESI-MS: m/z 185 $[M+H]^+$ (calcd for $C_{10}H_{14}ClO^+$, 185.1). *4-(4-Chlorophenyl)butanoic acid:* Jones oxidation of 4-(4-chlorophenyl)butan-1-ol (636 mg, 3.44 mmol) was performed to produce the title compound as a colorless oil (538 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.27–7.24 (m, 2H), 7.11 (d, J = 8.5 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 1.97–1.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.8, 139.6, 131.8, 129.8 (2), 128.5 (2), 34.2, 33.0, 26.1. ESI-MS: m/z 197 $[M-H]^-$ (calcd for $C_{10}H_{10}ClO_2^-$, 197.0). *Methyl 6-(4-chlorophenyl)-3-oxohexanoate:* 4-(4-Chlorophenyl)butanoic acid (538 mg, 2.70 mmol) was converted to the title compound as a colorless oil (628 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.25 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 3.73 (s, 3H), 3.43 (s, 2H), 2.60–2.54 (m, 4H), 1.94–1.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.2, 167.6, 139.8, 131.7, 129.8 (2), 128.5 (2), 52.4, 49.0, 41.9, 34.1, 24.7. ESI-MS: m/z 255 $[M+H]^+$ (calcd for $C_{13}H_{16}ClO_3^+$, 255.1). *Methyl 6-(4-chlorophenyl)-3-hydroxyhexanoate:* Reduction of methyl 6-(4-chlorophenyl)-3-oxohexanoate (628 mg, 2.46 mmol) with $NaBH_4$ (121 mg, 3.20 mmol) was performed to produce compound **16** as a colorless oil (415 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.24 (dd, J = 8.5, 2.1 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 4.04–4.00 (m, 1H), 3.71 (s, 3H), 2.97 (d, J = 3.9 Hz, 1H), 2.61 (t, J = 7.6 Hz,

2H), 2.50 (dd, J = 16.6, 3.2 Hz, 1H), 2.41 (dd, J = 16.6, 9.0 Hz, 1H), 1.85–1.74 (m, 1H), 1.70–1.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.4, 140.5, 131.5, 129.7 (2), 128.4 (2), 67.7, 51.8, 41.0, 35.8, 35.0, 27.1. ESI-MS: m/z 257 $[M+H]^+$ (calcd for $C_{13}H_{18}ClO_3^+$, 257.1).

Synthesis of compound 17. *7-(4-Bromophenyl)hept-6-yn-1-ol:* Sonogashira cross-coupling of 1-bromo-4-iodobenzene (2.00 g, 7.07 mmol) with 6-heptyn-1-ol (969 μL, 7.78 mmol) was performed to produce the title compound as a brown oil (1.70 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.42–7.40 (m, 2H), 7.26–7.23 (m, 2H), 3.68 (dt, J = 6.0, 6.0 Hz, 2H), 2.41 (t, J = 7.0 Hz, 2H), 1.68–1.50 (m, 6H), 1.26 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 133.0 (2), 131.4 (2), 122.9, 121.6, 91.4, 79.8, 62.8, 32.3, 28.4, 25.1, 16.4. ESI-MS: m/z 267 $[M+H]^+$ (calcd for $C_{13}H_{16}BrO^+$, 267.0). *7-(4-Bromophenyl)heptan-1-ol:* Hydrogenation of 7-(4-bromophenyl)hept-6-yn-1-ol (1.70 g, 6.36 mmol) with Pd/C (340 mg) was performed to produce the title compound as a colorless oil (1.47 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.37 (m, 2H), 7.04 (d, J = 8.3 Hz, 2H), 3.64 (dt, J = 6.0, 6.0 Hz, 2H), 2.55 (t, J = 7.7 Hz, 2H), 2.05−1.53 (m, 6H), 1.37–1.25 (m, 4H), 1.21 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.7, 131.3 (2), 130.2 (2), 119.3, 63.0, 35.3, 32.7, 31.2, 29.2, 29.1, 25.6. ESI-MS: m/z 271 $[M+H]^+$ (calcd for $C_{13}H_{20}BrO^+$, 271.1). *7-(4-Bromophenyl)heptanoic acid:* Jones oxidation of 7-(4-bromophenyl)heptan-1-ol (1.47 g, 5.42 mmol) was performed to produce the title compound as a colorless oil (1.23 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.37 (m, 2H), 7.04 (d, J = 8.3 Hz, 2H), 2.55 (t, J = 7.7 Hz, 2H), 2.35 (d, J = 7.4 Hz, 2H), 1.65–1.55 (m, 4H), 1.40–1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.1, 141.5, 131.3 (2), 130.2 (2), 119.3, 35.2, 33.8, 31.0, 28.8, 28.7, 24.5. ESI-MS: m/z 283 $[M–H]^–$ (calcd for $C_{13}H_{16}BrO_2^–$, 283.0). *Methyl 9-(4-bromophenyl)-3-oxononanoate:* 7-(4-Bromophenyl)heptanoic acid (1.23 g, 4.31 mmol) was converted to the title compound as a colorless oil (866 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.38 (dd, J = 8.4, 1.7 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.52 (t, J = 7.3 Hz, 2H), 1.64–1.52 (m, 6H), 1.33–1.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.8, 167.7, 141.5, 131.3 (2), 130.2 (2), 119.3, 52.4, 49.0, 43.0, 35.2, 31.0, 28.8, 28.7, 23.3. ESI-MS: m/z 341 $[M+H]^+$ (calcd for $C_{16}H_{22}BrO_3^+$, 341.1). *Methyl 9-(4-bromophenyl)-3-hydroxynonanoate:* Reduction of methyl 9-(4-bromophenyl)-3-oxononanoate (866 mg, 2.54 mmol) with $NaBH_4$ (125 mg, 3.30 mmol) was performed to produce compound **17** as a colorless oil (296 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.38 (dd, J = 8.6, 2.2 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 4.00 (m, 1H), 3.71 (s, 3H), 2.90 (d, J = 3.9 Hz, 1H), 2.55 (t, J = 7.6 Hz, 2H), 2.51 (dd, J = 16.6, 3.0 Hz, 1H), 2.41 (dd, J = 16.6, 9.0 Hz, 1H), 1.61–1.39 (10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 141.7, 131.2 (2), 130.2 (2), 119.3, 67.9, 51.8, 41.0, 36.4, 35.3, 31.2, 29.3, 29.0, 25.4. ESI-MS: m/z 343 $[M+H]^+$ (calcd for $C_{16}H_{24}BrO_3^+$, 343.1).

Synthesis of compound 18. *5-(4-Bromophenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-bromo-4-iodobenzene (2.00 g, 7.07 mmol) with 4-pentyn-1-ol (724 μL, 7.78 mmol) was performed to produce the title compound as an orange oil (1.30 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.41 (dd, J = 8.8, 2.1 Hz, 2H), 7.26–7.23 (m, 2H), 3.82 (dt, J = 6.0, 6.0 Hz, 2H), 2.53 (t, J = 7.0 Hz, 2H), 1.89–1.83 (m, 2H) 1.44 (t, J = 5.4 Hz, 1H). ESI-MS: m/z 239 $[M+H]^+$ (calcd for $C_{11}H_{12}BrO^+$, 239.0).

5-(4-Bromophenyl)pentan-1-ol: Hydrogenation of 5-(4-bromophenyl)pent-4-yn-1-ol (1.30 g, 5.41 mmol) with Pd/C (130 mg) was performed to produce the title compound as a colorless oil (1.13 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.38 (m, 2H), 7.05 (d, J = 8.5 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H), 1.65–1.59 (m, 4H), 1.44–1.35 (m, 2H). ESI-MS: m/z 243 $[M+H]^+$ (calcd for $C_{11}H_{16}BrO^+$, 243.0). *5-(4-Bromophenyl)pentanoic acid:* Jones oxidation of 5-(4-bromophenyl)pentan-1-ol (1.13 g, 4.65 mmol) was performed to produce the title compound as a colorless oil (682 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.38 (m, 2H), 7.05 (d, J = 8.5 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.39–2.37 (m, 2H), 1.69–1.65 (m, 4H). ESI-MS: m/z 255 $[M–H]^–$ (calcd for $C_{11}H_{12}BrO_2^–$, 255.0). *Methyl 7-(4-bromophenyl)-3-oxoheptanoate:* 5-(4-Bromophenyl)pentanoic acid (682 mg, 4.31 mmol) was converted to the title compound as a colorless oil (805 mg, 97%). ESI-MS: m/z 313 $[M+H]^+$ (calcd for $C_{14}H_{18}BrO_3^+$, 313.0). *Methyl 7-(4-bromophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(4-bromophenyl)-3-oxoheptanoate (805 mg, 2.57 mmol) with $NaBH_4$ (126 mg, 3.34 mmol) was performed to produce compound **18** as a colorless oil (484 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.37 (m, 2H), 7.05–7.03 (m, 2H), 4.00 (m, 1H), 3.71 (s, 3H), 2.91 (d, J = 3.9 Hz, 1H), 2.57 (t, J = 7.6 Hz, 2H), 2.50 (dd, J = 16.6, 3.2 Hz, 1H), 2.41 (dd, J = 16.6, 9.0 Hz, 1H), 1.66–1.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 141.4, 131.3 (2), 130.1 (2), 119.4, 67.8, 51.8, 41.0, 36.2, 35.2, 31.2, 25.0. ESI-MS: m/z 315 $[M+H]^+$ (calcd for $C_{14}H_{20}BrO_3^+$, 315.1).

Synthesis of compound 19. *5-(4-Fluorophenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-fluoro-4-iodobenzene (518 μL, 4.51 mmol) with 4-pentyn-1-ol (420 μL, 4.51 mmol) was performed to produce the title compound as an orange oil (559 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.38–7.35 (m, 2H), 6.99–6.97 (m, 2H), 3.83 (dt, J = 5.9, 5.9 Hz, 2H), 2.53 (t, J = 7.0 Hz, 2H), 1.89–1.83 (m, 2H), 1.48 (t, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 163.3 (0.5), 160.87 (0.5), 133.4, 133.3, 119.7, 115.5, 115.3, 88.9, 80.1, 61.8, 31.3, 15.9. ESI-MS: m/z 179 $[M+H]^+$ (calcd for $C_{11}H_{12}FO^+$, 179.1). *5-(4-Fluorophenyl)pentan-1-ol:* Hydrogenation of 5-(4-fluorophenyl)pent-4-yn-1-ol (559 mg, 3.14 mmol) with Pd/C (55.9 mg) was performed to produce the title compound as a colorless oil (530 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.14–7.11 (m, 2H), 6.97–6.95 (m, 2H), 3.66–3.63 (m, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.66–1.56 (m, 4H), 1.45–1.35 (m, 2H), 1.29 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 162.4 (0.5), 159.9 (0.5), 138.1, 129.7, 129.6, 115.1, 114.9, 62.9, 35.1, 32.6, 31.3, 25.3. ESI-MS: m/z 183 $[M+H]^+$ (calcd for $C_{11}H_{16}FO^+$, 183.1). *5-(4-Fluorophenyl)pentanoic acid:* Jones oxidation of 5-(4-fluorophenyl)pentan-1-ol (530 mg, 2.91 mmol) was performed to produce the title compound as a colorless oil (444 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.13–7.11 (m, 2H), 6.97–6.95 (m, 2H), 2.61 (t, J = 7.1 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.68–1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.5, 162.4 (0.5), 160.0 (0.5), 137.5, 129.7, 129.6, 115.1, 114.9, 34.7, 33.7, 30.9, 24.1. ESI-MS: m/z 195 $[M–H]^–$ (calcd for $C_{11}H_{12}FO_2^–$, 195.1). *Methyl 7-(4-fluorophenyl)-3-oxoheptanoate:* 5-(4-Fluorophenyl)pentanoic acid (444 mg, 2.24 mmol) was converted to the title compound as a colorless oil (390 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H =

7.12–7.10 (m, 2H), 6.97–6.94 (m, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.59–2.56 (m, 4H), 1.66–1.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.5, 167.6, 162.4 (0.5), 160.0 (0.5), 137.6, 129.7, 129.6, 115.1, 114.9, 52.4, 49.0, 42.8, 34.8, 30.8, 22.9. ESI-MS: *m*/*z* 253 $[M+H]^+$ (calcd for $C_{14}H_{18}FO_3^+$, 253.1). *Methyl 7-(4-fluorophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(4-fluorophenyl)-3-oxoheptanoate (390 mg, 1.54 mmol) with $NaBH_4$ (76.0 mg, 2.01 mmol) was performed to produce compound **19** as a colorless oil (27.8 mg, 7.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.13–7.09 (m, 2H), 6.97–6.94 (m, 2H), 4.00 (m, 1H), 3.71 (s, 3H), 2.91 (d, *J* = 3.9 Hz, 1H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.50 (dd, *J* = 16.6, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.6, 9.0 Hz, 1H), 1.66–1.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 162.4 (0.5), 160.0 (0.5), 138.0, 129.7, 129.6, 115.1, 114.9, 67.8, 51.2, 41.0, 36.3, 35.0, 31.5, 25.0. ESI-MS: *m*/*z* 255 $[M+H]^+$ (calcd for $C_{14}H_{20}FO_3^+$, 255.1).

Synthesis of compound 21. *4-(p-Tolyl)but-3-yn-1-ol:* Sonogashira cross-coupling of 4-iodotoluene (1.00 g, 4.59 mmol) with 3-butyn-1-ol (347 μL, 4.59 mmol) was performed to produce the title compound as an orange oil (721 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31–7.30 (m, 2H), 7.10 (dd, *J* = 8.4, 0.6 Hz, 2H), 3.81 (dt, *J* = 6.3, 6.3 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 3H), 1.86–1.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 138.0, 131.5 (2), 129.0 (2), 120.2, 85.4, 82.6, 61.2, 23.8, 21.4. ESI-MS: *m*/*z* 161 $[M+H]^+$ (calcd for $C_{11}H_{13}O^+$, 161.1). *4-(p-Tolyl)butan-1-ol:* Hydrogenation of 4-(*p*-tolyl)but-3-yn-1-ol (721 mg, 4.50 mmol) with Pd/C (144 mg) was performed to produce the title compound as a colorless oil (654 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.07 (m, 4H), 3.66 (dt, *J* = 6.2, 6.2 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 1.72–1.58 (m, 4H), 1.20 (t, *J* = 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 139.2, 135.2, 129.0 (2), 128.3 (2), 62.9, 35.2, 32.3, 27.6, 21.0. ESI-MS: *m*/*z* 165 $[M+H]^+$ (calcd for $C_{11}H_{17}O^+$, 165.1). *4-(p-Tolyl)butanoic acid:* Jones oxidation of 4-(*p*-tolyl)butan-1-ol (654 mg, 3.98 mmol) was performed to produce the title compound as a colorless oil (529 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.11–7.06 (m, 4H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 1.98–1.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.8, 138.1, 135.5, 129.1 (2), 128.4 (2), 34.5, 33.1, 26.3, 21.0. ESI-MS: *m*/*z* 177 $[M-H]^-$ (calcd for $C_{11}H_{13}O_2^-$, 177.1). *Methyl 3-oxo-6-(p-tolyl)hexanoate:* 4-(*p*-Tolyl)butanoic acid (529 mg, 2.97 mmol) was converted to the title compound as a colorless oil (548 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.11–7.04 (m, 4H), 3.73 (s, 3H), 3.42 (s, 2H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 1.95–1.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.5, 167.7, 138.2, 135.5, 129.1 (2), 128.3 (2), 52.3, 49.0, 42.2, 34.3, 24.9, 21.0. ESI-MS: *m*/*z* 235 $[M+H]^+$ (calcd for $C_{14}H_{19}O_3^+$, 235.1). *Methyl 3-hydroxy-6-(p-tolyl)hexanoate:* Reduction of methyl 3-oxo-6-(*p*-tolyl)hexanoate (548 mg, 2.34 mmol) with $NaBH_4$ (115 mg, 3.00 mmol) was performed to produce compound **21** as a colorless oil (225 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.10–7.05 (m, 4H), 4.02 (m, 1H), 3.71 (s, 3H), 2.88 (d, *J* = 3.9 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.50 (dd, *J* = 16.3, 3.2 Hz, 1H), 2.40 (dd, *J* = 16.3, 9.0 Hz, 1H), 2.31 (s, 3H), 1.81–1.75 (m, 1H), 1.67–1.64 (m, 1H), 1.59–1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 139.0, 135.2, 129.0 (2), 128.3 (2), 67.8, 51.7, 41.0, 36.0, 35.2, 27.3, 21.0.

ESI-MS: *m*/*z* 237 $[M+H]^+$ (calcd for $C_{14}H_{21}O_3^+$, 237.1).

Synthesis of compound 22. *5-(4-Ethylphenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 4-iodotoluene (625 μL, 4.31 mmol) with 4-pentyn-1-ol (401 μL, 4.31 mmol) was performed to produce the title compound as an orange oil (quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32–7.29 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.83 (dt, *J* = 5.9, 5.9 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 1.89–1.83 (m, 2H), 1.54 (br, 1H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 144.0, 131.5 (2), 127.8 (2), 120.8, 88.4, 81.2, 61.9, 31.4, 28.7, 16.0, 15.4. ESI-MS: *m*/*z* 189 $[M+H]^+$ (calcd for $C_{13}H_{17}O^+$, 189.1). *5-(4-Ethylphenyl)pentan-1-ol:* Hydrogenation of 5-(4-ethylphenyl)pent-4-yn-1-ol (4.31 mmol) with Pd/C (179 mg) was performed to produce the title compound as a colorless oil (565 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.13–7.08 (m, 4H), 3.63 (br, 2H), 2.65–2.57 (m, 4H), 1.65–1.56 (m, 4H), 1.42–1.38 (m, 2H), 1.25 (br, 1H), 1.22 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.5, 139.7, 128.3 (2), 127.7 (2), 63.0, 35.5, 32.6, 31.3, 28.4, 25.4, 15.6. ESI-MS: *m*/*z* 193 $[M+H]^+$ (calcd for $C_{13}H_{21}O^+$, 193.2). *5-(4-Ethylphenyl)pentanoic acid:* Jones oxidation of 5-(4-ethylphenyl)pentan-1-ol (565 mg, 2.94 mmol) was performed to produce the title compound as a colorless oil (180 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.13–7.08 (m, 4H), 2.64–2.56 (m, 4H), 2.40–2.37 (m, 2H), 1.71–1.61 (m, 4H), 1.22 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.4, 141.7, 139.2, 128.3 (2), 127.8 (2), 35.1, 33.8, 30.9, 28.4, 24.3, 15.6. ESI-MS: *m*/*z* 205 $[M-H]^-$ (calcd for $C_{13}H_{17}O_2^-$, 205.1). *Methyl 7-(4-ethylphenyl)-3-oxoheptanoate:* 5-(4-Ethylphenyl)pentanoic acid (332 mg, 1.61 mmol) was converted to the title compound as a colorless oil (311 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.11–7.08 (m, 4H), 3.73 (s, 3H), 3.43 (s, 2H), 2.65–2.54 (m, 6H), 1.66–1.58 (m, 4H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.6, 167.7, 141.7, 139.2, 128.3 (2), 127.8 (2), 52.3, 49.0, 42.9, 35.2, 30.8, 28.4, 23.1, 15.6. ESI-MS: *m*/*z* 263 $[M+H]^+$ (calcd for $C_{16}H_{23}O_3^+$, 263.2). *Methyl 7-(4-ethylphenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(4-ethylphenyl)-3-oxoheptanoate (311 mg, 1.19 mmol) with $NaBH_4$ (115 mg, 3.00 mmol) was performed to produce compound **22** as a colorless oil (108 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.11–7.09 (m, 4H), 4.00 (m, 1H), 3.71 (s, 3H), 2.88 (d, *J* = 3.9 Hz, 1H), 2.64–2.57 (m, 4H), 2.51 (dd, *J* = 16.5, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.67–1.36 (m, 6H) 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 141.5, 139.6, 128.3 (2), 127.7 (2), 67.9, 51.8, 41.0, 36.3, 35.4, 31.4, 28.4, 25.2, 15.6. ESI-MS: *m*/*z* 265 $[M+H]^+$ (calcd for $C_{16}H_{25}O_3^+$, 265.2).

Synthesis of compound 23. *5-(4-Propylphenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-iodo-4-propylbenzene (1.00 g, 4.06 mmol) with 4-pentyn-1-ol (378 μL, 4.06 mmol) was performed to produce the title compound as an orange oil (quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31–7.30 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 3.83 (dt, *J* = 5.9, 5.9 Hz, 2H), 2.57–2.53 (m, 4H), 1.88–1.84 (m, 2H), 1.63–1.60 (m, 2H), 1.53 (br, 1H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 142.5, 131.4 (2), 128.4 (2), 120.8, 88.5, 81.2, 61.9, 37.9, 31.4, 24.4, 16.0, 13.7. ESI-MS: *m*/*z* 203 $[M+H]^+$ (calcd for $C_{14}H_{19}O^+$, 203.1). *5-(4-Propylphenyl)pentan-1-ol:* Hydrogenation of 5-(4-propylphenyl)pent-4-yn-1-ol (4.06 mmol) with Pd/C (188 mg) was performed to produce the

title compound as a colorless oil (827 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.09 (s, 4H), 3.64 (dt, J = 6.6, 6.6 Hz, 2H), 2.59–2.55 (m, 4H), 1.68–1.57 (7H), 1.44–1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.0, 139.7, 128.3 (2), 128.2 (2), 63.0, 37.7, 35.5, .32.7, 31.3, 25.4, 24.6, 13.9. ESI-MS: *m*/*z* 207 $[M+H]^+$ (calcd for $C_{14}H_{23}O^+$, 207.2). *5-(4-Propylphenyl)pentanoic acid:* Jones oxidation of 5-(4-propylphenyl)pentan-1-ol (827 mg, 4.00 mmol) was performed to produce the title compound as a colorless oil (452 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.09 (s, 4H), 2.59–2.56 (m, 4H), 2.37 (t, J = 7.0 Hz, 2H), 1.66–1.62 (m, 6H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.3, 140.1, 139.2, 128.4 (2), 128.2 (2), 37.7, 35.1, 33.8, 30.9, 24.6, 24.3, 13.9. ESI-MS: *m*/*z* 219 $[M–H]^–$ (calcd for $C_{14}H_{19}O_2^–$, 219.1). *Methyl 3-oxo-7-(4-propylphenyl)heptanoate:* 5-(4-Propylphenyl)pentanoic acid (452 mg, 2.05 mmol) was converted to the title compound as a colorless oil (462 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.09–7.06 (m, 4H), 3.73 (s, 3H), 3.43 (s, 2H), 2.58–2.54 (m, 6H), 1.67–1.57 (m, 6H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.6, 167.7, 140.1, 139.2, 128.4 (2), 128.2 (2), 52.3, 49.0, 42.9, 37.6, 35.2, 30.8, 24.6, 23.1, 13.9. ESI-MS: *m*/*z* 277 $[M+H]^+$ (calcd for $C_{17}H_{25}O_3^+$, 277.2). *Methyl 3-hydroxy-7-(4-propylphenyl)heptanoate:* Reduction of methyl 3-oxo-7-(4-propylphenyl)heptanoate (433 mg, 1.57 mmol) with $NaBH_4$ (77.2 mg, 2.00 mmol) was performed to produce compound **23** as a colorless oil (134 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.08 (s, 4H), 4.00 (m, 1H), 3.71 (s, 3H), 2.87 (d, J = 3.9 Hz, 2H), 2.60–2.37 (m, 6H), 1.67–1.36 (7H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 140.0, 139.6, 128.4 (2), 128.2 (2), 67.9, 51.8, 41.0, 37.7, 36.4, 35.4, 31.4, 25.2, 24.6, 13.9. ESI-MS: *m*/*z* 279 $[M+H]^+$ (calcd for $C_{17}H_{27}O_3^+$, 279.2).

Synthesis of compound 24. *5-(4-Nitrophenyl)pentanoic acid:* The solution of 5-phenylvaleric acid (2.00 g, 11.2 mmol) in conc. HNO_3 (14 mL) was stirred for 18 h at rt. The reaction was quenched with ice water (40 mL) and a precipitate was formed. The precipitate was collected by filtration, washed with water, and dried under a vacuum. The title compound was obtained as a yellowish solid (353 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.16–8.14 (m, 2H), 7.33 (d, J = 8.5 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.40 (t, J = 7.0 Hz, 2H), 1.74–1.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.5, 149.8, 146.4, 129.1 (2), 123.7 (2), 35.4, 33.7, 30.2, 24.1. ESI-MS: *m*/*z* 222 $[M–H]^–$ (calcd for $C_{11}H_{12}NO_4^–$, 222.1). *Methyl 7-(4-nitrophenyl)-3-oxoheptanoate:* 5-(4-Nitrophenyl)pentanoic acid (353 mg, 1.58 mmol) was converted to the title compound as a colorless oil (109 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.16–8.13 (m, 2H), 7.34–7.31 (m, 2H), 3.74 (s, 3H), 3.45 (s, 2H), 2.75–2.71 (m, 2H), 2.61–2.57 (m, 2H), 1.66–1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.2, 167.6, 149.9, 146.4, 129.1 (2), 123.7 (2), 52.4, 49.0, 42.6, 35.6, 30.2, 22.8. ESI-MS: *m*/*z* 280 $[M+H]^+$ (calcd for $C_{14}H_{18}NO_5^+$, 280.1). *Methyl 3-hydroxy-7-(4-nitrophenyl)heptanoate:* Reduction of methyl 7-(4-nitrophenyl)-3-oxoheptanoate (50.0 mg, 0.179 mmol) with $NaBH_4$ (8.80 mg, 0.230 mmol) was performed to produce compound **24** as a colorless oil (28.1 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.14 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.00 (m, 1H), 3.72 (s, 3H), 2.94 (d, J = 3.9 Hz, 1H), 2.73 (t, J = 7.7 Hz, 2H), 2.50

(dd, J = 16.6, 3.0 Hz, 1H), 2.41 (dd, J = 16.6, 8.9 Hz, 1H), 1.71–1.65 (m, 2H), 1.57–1.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.4, 150.4, 146.3, 129.1 (2), 123.6 (2), 67.7, 51.8, 41.0, 36.1, 35.8, 30.8, 25.1. ESI-MS: m/z 279 $[M+H]^+$ (calcd for $C_{14}H_{20}NO_5^+$, 279.2).

Synthesis of compound 25. *4-(5-Hydroxypent-1-yn-1-yl)benzonitrile:* Sonogashira cross-coupling of 4-iodobenzonitrile (1.00 g, 4.37 mmol) with 4-pentyn-1-ol (406 μL, 4.37 mmol) was performed to produce the title compound as an orange oil (593 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58–7.56 (m, 2H), 7.47–7.45 (m, 2H), 3.83–3.80 (m, 2H), 2.58 (t, J = 7.1 Hz, 2H), 1.91–1.84 (m, 2H), 1.51 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 132.1 (2), 131.9 (2), 128.8, 118.6, 110.9, 94.5, 79.8, 61.5, 31.1, 16.0. ESI-MS: m/z 186 $[M+H]^+$ (calcd for $C_{12}H_{12}NO^+$, 186.1). *4-(5-Hydroxypentyl)benzonitrile:* Hydrogenation of 4-(5-hydroxypent-1-yn-1-yl)benzonitrile (593 mg, 3.20 mmol) with Pd/C (119 mg) was performed to produce the title compound as a yellowish oil (526 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58–7.56 (m, 2H), 7.28 (d, J = 8.3 Hz, 2H), 3.66–3.63 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 1.70–1.57 (m, 4H), 1.42–1.39 (m, 2H), 1.30 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 148.2, 132.1 (2), 129.2 (2), 119.1, 109.6, 62.7, 36.0, 32.4, 30.7, 25.3. ESI-MS: m/z 190 $[M+H]^+$ (calcd for $C_{12}H_{16}NO^+$, 190.1). *5-(4-Cyanophenyl)pentanoic acid:* Jones oxidation of 4-(5-hydroxypentyl)benzonitrile (526 mg, 2.78 mmol) was performed to produce the title compound as a colorless oil (507 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58–7.57 (m, 2H), 7.28 (d, J = 8.5 Hz, 2H), 2.71–2.69 (m, 2H), 2.40–2.38 (m, 2H), 1.69–1.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 177.6, 147.6, 132.2 (2), 129.2 (2), 119.1, 109.8, 35.7, 33.3, 30.2, 24.1. ESI-MS: m/z 202 $[M–H]^–$ (calcd for $C_{12}H_{12}NO_2^–$, 202.1). *Methyl 7-(4-cyanophenyl)-3-oxoheptanoate:* 5-(4-Cyanophenyl)pentanoic acid (526 mg, 2.78 mmol) was converted to the title compound as a colorless oil (526 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58–7.55 (m, 2H), 7.28–7.26 (m, 2H), 3.74 (s, 3H), 3.44 (s, 2H), 2.68–2.67 (m, 2H), 2.59–2.57 (m, 2H), 1.66–1.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.2, 167.6, 147.7, 132.2 (2), 129.2 (2), 119.1, 109.7, 52.4, 49.0, 42.6, 35.8, 30.1, 22.8. ESI-MS: m/z 260 $[M+H]^+$ (calcd for $C_{15}H_{18}NO_3^+$, 260.1). *Methyl 7-(4-cyanophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(4-cyanophenyl)-3-oxoheptanoate (100 mg, 0.386 mmol) with $NaBH_4$ (19.0 mg, 0.500 mmol) was performed to produce compound **25** as a colorless oil (60.3 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58–7.56 (m, 2H), 7.28–7.27 (m, 2H), 4.00 (m, 1H), 3.72 (s, 3H), 2.94 (d, J = 3.9 Hz, 1H), 2.68 (t, J = 7.7 Hz, 2H), 2.50 (dd, J = 16.6, 3.2 Hz, 1H), 2.41 (dd, J = 16.6, 9.0 Hz, 1H), 1.72–1.37 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.4, 148.1, 132.1 (2), 129.2 (2), 119.1, 109.6, 67.7, 51.8, 41.0, 36.1, 36.0, 30.8, 25.1. ESI-MS: m/z 262 $[M+H]^+$ (calcd for $C_{15}H_{20}NO_3^+$, 262.2).

Synthesis of compound 26. *5-(4-(Trifluoromethyl)phenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-iodo-4-(trifluoromethyl)benzene (1.00 g, 3.68 mmol) with 4-pentyn-1-ol (342 μL, 3.68 mmol) was performed to produce the title compound as an orange oil (quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.54 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 3.83 (dt, J = 5.9, 5.9 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 1.91–1.85 (m, 2H), 1.48 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 131.8 (2), 125.2 (0.5), 125.1 (0.5), 92.2, 80.0, 61.7, 31.2, 16.0. ESI-MS: m/z 229 $[M+H]^+$ (calcd for

$C_{12}H_{12}F_3O^+$, 229.1). *5-(4-(Trifluoromethyl)phenyl)pentan-1-ol:* Hydrogenation of 5-(4-(trifluoromethyl)phenyl)pent-4-yn-1-ol (1.15 g, 5.02 mmol) with Pd/C (229 mg) was performed to produce the title compound as a colorless oil (1.02 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.65 (dt, *J* = 6.3, 6.3 Hz, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 1.71–1.57 (m, 4H), 1.45–1.37 (m, 2H), 1.24 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 128.7 (2), 125.2 (0.5), 125.1 (0.5), 62.8, 35.7, 32.5, 31.0, 25.4. ESI-MS: *m*/*z* 233 $[M+H]^+$ (calcd for $C_{12}H_{16}F_3O^+$, 233.1). *5-(4-(Trifluoromethyl)phenyl)pentanoic acid:* Jones oxidation of 5-(4-(trifluoromethyl)phenyl)pentan-1-ol (1.02 g, 4.37 mmol) was performed to produce the title compound as a colorless oil (862 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.40–2.38 (m, 2H), 1.70–1.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.2, 128.7 (2), 125.3, 35.4, 33.5, 30.4, 24.2. ESI-MS: *m*/*z* 245 $[M–H]^–$ (calcd for $C_{12}H_{12}F_3O_2^–$, 245.1). *Methyl 3-oxo-7-(4-(trifluoromethyl)phenyl)heptanoate:* 5-(4-(Trifluoromethyl)phenyl)pentanoic acid (800 mg, 3.25 mmol) was converted to the title compound as a colorless oil (666 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.68 (br, 2H), 2.59–2.56 (m, 2H), 1.65–1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.3, 167.6, 128.7 (2), 125.3 (0.5), 125.2 (0.5), 52.4, 49.0, 42.7, 35.5, 30.4, 22.9. ESI-MS: *m*/*z* 303 $[M+H]^+$ (calcd for $C_{15}H_{18}F_3O_3^+$, 303.1). *Methyl 3-hydroxy-7-(4-(trifluoromethyl)phenyl)heptanoate:* Reduction of methyl 3-oxo-7-(4-(trifluoromethyl)phenyl)heptanoate (665 mg, 2.20 mmol) with $NaBH_4$ (108 mg, 2.90 mmol) was performed to produce compound **26** as a colorless oil (131 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.00 (m, 1H), 3.71 (s, 3H), 2.92 (d, *J* = 3.9 Hz, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.50 (dd, *J* = 16.6, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.6, 9.0 Hz, 1H), 1.72–1.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 128.7 (2), 125.2, 67.8, 51.8, 41.0, 36.2, 35.7, 31.0, 25.1. ESI-MS: *m*/*z* 305 $[M+H]^+$ (calcd for $C_{15}H_{20}F_3O_3^+$, 305.1).

Synthesis of compound 27. *5-(3-Chlorophenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-chloro-3-iodobenzene (1.00 g, 4.19 mmol) with 4-pentyn-1-ol (390 μL, 4.19 mmol) was performed to produce the title compound as an orange oil (653 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.38 (t, *J* = 1.7 Hz, 1H), 7.29–7.19 (m, 3H), 3.82 (dt, *J* = 5.9, 5.9 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.90–1.83 (m, 2H), 1.47 (t, *J* = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 134.0, 131.5, 127.0, 129.4, 128.0, 125.4, 90.8, 79.8, 61.7, 31.2, 15.9. ESI-MS: *m*/*z* 195 $[M+H]^+$ (calcd for $C_{11}H_{12}ClO^+$, 195.1). *5-(3-Chlorophenyl)pentan-1-ol:* Hydrogenation of 5-(3-chlorophenyl)pent-4-yn-1-ol (653 mg, 3.35 mmol) with Pd/C (131 mg) was performed to produce the title compound as a colorless oil (519 mg, 78%). ESI-MS: *m*/*z* 199 $[M+H]^+$ (calcd for $C_{11}H_{16}ClO^+$, 199.1). *5-(3-Chlorophenyl)pentanoic acid:* Jones oxidation of 5-(3-chlorophenyl)pentan-1-ol (519 mg, 2.61 mmol) was performed to produce the title compound as a colorless oil (199 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.23–7.15 (m, 3H), 7.06–7.04 (m, 1H), 2.63–2.61 (m, 2H), 2.40–2.37 (m, 2H), 1.69–1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.6, 144.0, 134.1, 129.6, 128.5, 126.6, 126.0, 35.2, 33.6, 30.5, 24.2. ESI-MS: *m*/*z* 211 $[M–H]^–$ (calcd for $C_{11}H_{12}ClO_2^–$, 211.1). *Methyl*

7-(3-chlorophenyl)-3-oxoheptanoate: 5-(3-Chlorophenyl)pentanoic acid (199 mg, 0.934 mmol) was converted to the title compound as a colorless oil (163 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.21–7.17 (m, 3H), 7.05–7.03 (m, 1H), 3.74 (s, 3H), 3.44 (s, 2H), 2.62–2.55 (m, 4H), 1.64–1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.4, 167.6, 144.0, 134.1, 129.6, 128.5, 126.6, 126.0, 52.4, 49.0, 42.7, 35.3, 30.4, 22.9. ESI-MS: *m*/*z* 269 $[M+H]^+$ (calcd for $C_{14}H_{18}ClO_3^+$, 269.1). *Methyl 7-(3-chlorophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(3-chlorophenyl)-3-oxoheptanoate (163 mg, 0.607 mmol) with $NaBH_4$ (29.9 mg, 0.789 mmol) was performed to produce compound **27** as a colorless oil (118 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.22–7.14 (m, 3H), 7.06–7.04 (m, 1H), 4.00 (m, 1H), 3.71 (s, 3H), 2.91 (d, *J* = 4.1 Hz, 1H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.51 (dd, *J* = 16.6, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.6, 8.9 Hz, 1H), 1.66–1.37 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 144.5, 134.0, 129.5, 128.5, 126.6, 125.9, 67.8, 51.8, 41.0, 36.2, 35.5, 31.1, 25.1. ESI-MS: *m*/*z* 271 $[M+H]^+$ (calcd for $C_{14}H_{20}ClO_3^+$, 271.1).

Synthesis of compound 28. *5-(3-Ethylphenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1-ethyl-3-iodobenzene (1.00 g, 4.31 mmol) with 4-pentyn-1-ol (401 μL, 4.31 mmol) was performed to produce the title compound as an orange oil (715 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.24 (br, 1H), 7.21–7.20 (m, 2H), 7.12–7.11 (m, 1H), 3.83 (dt, *J* = 5.7, 5.7 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 1.90−1.84 (m, 2H), 1.52 (br, 1H), 1.22 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 144.2, 131.0, 128.8, 128.2, 127.5, 123.5, 88.8, 81.4, 61.9, 31.4, 28.6, 16.0, 15.4. ESI-MS: *m*/*z* 189 $[M+H]^+$ (calcd for $C_{13}H_{17}O^+$, 189.1). *5-(3-Ethylphenyl)pentan-1-ol:* Hydrogenation of 5-(3-ethylphenyl)pent-4-yn-1-ol (715 mg, 3.80 mmol) with Pd/C (143 mg) was performed to produce the title compound as a colorless oil (661 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.20 (t, *J* = 7.8 Hz, 1H), 7.02–7.00 (m, 3H), 3.66–3.63 (m, 2H), 2.65–2.58 (m, 4H), 1.66–1.60 (m, 5H), 1.43–1.39 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 144.2, 142.5, 128.2, 128.0, 125.6, 125.2, 63.0, 35.9, 32.6, 31.3, 28.8, 25.5, 15.6. ESI-MS: *m*/*z* 193 $[M+H]^+$ (calcd for $C_{13}H_{21}O^+$, 193.2). *5-(3-Ethylphenyl)pentanoic acid:* Jones oxidation of 5-(3-ethylphenyl)pentan-1-ol (661 mg, 3.44 mmol) was performed to produce the title compound as a colorless oil (347 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.20 (t, *J* = 7.4 Hz, 1H), 7.02–6.99 (m, 3H), 2.63–2.61 (m, 4H), 2.39–2.37 (m, 2H), 1.69–1.68 (m, 4H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 179.3, 144.3, 142.0, 128.3, 128.0, 125.6, 125.3, 35.5, 33.8, 30.8, 28.8, 24.4, 15.6. ESI-MS: *m*/*z* 205 $[M–H]^–$ (calcd for $C_{13}H_{17}O_2^–$, 205.1). *Methyl 7-(3-ethylphenyl)-3-oxoheptanoate:* 5-(3-Ethylphenyl)pentanoic acid (347 mg, 1.68 mmol) was converted to the title compound as a colorless oil (202 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.19 (t, *J* = 7.4 Hz, 1H), 7.02–6.99 (m, 3H), 3.73 (s, 3H), 3.43 (s, 2H), 2.65–2.54 (m, 6H), 1.65–1.61 (m, 4H), 1.23 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.6, 167.7, 144.3, 142.0, 128.3, 128.0, 125.6, 125.3, 52.3, 49.0, 42.9, 35.7, 30.8, 28.8, 23.1, 15.6. ESI-MS: *m*/*z* 263 $[M+H]^+$ (calcd for $C_{16}H_{23}O_3^+$, 263.2). *Methyl 7-(3-ethylphenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(3-ethylphenyl)-3-oxoheptanoate (202 mg, 0.770 mmol) with $NaBH_4$ (37.9 mg, 1.00 mmol) was performed to produce compound **28** as a colorless oil (102 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$):

δ_H = 7.21–7.17 (m, 1H), 7.02–6.99 (m, 3H), 4.00 (m, 1H), 3.71 (s, 3H), 2.88 (d, *J* = 4.1 Hz, 1H), 2.65–2.58 (m, 4H), 2.51 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.5, 9.0 Hz, 1H), 1.68–1.35 (m, 6H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 144.2, 142.5, 128.2, 128.0, 125.6, 125.2, 67.9, 51.8, 41.1, 36.4, 35.9, 31.4, 28.8, 25.2, 15.6. ESI-MS: *m*/*z* 265 $[M+H]^+$ (calcd for $C_{16}H_{25}O_3^+$, 265.2).

Synthesis of compound 29. *5-(3,4-Dichlorophenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 1,2-dichloro-4-iodobenzene (1.00 g, 3.66 mmol) with 4-pentyn-1-ol (341 μL, 3.66 mmol) was performed to produce the title compound as an orange oil (661 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.48 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.81 (dt, *J* = 6.1, 6.1 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 1.89–1.83 (m, 2H), 1.25 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 133.2, 132.3, 132.0, 130.7, 130.2, 123.7, 91.6, 79.0, 61.6, 31.2, 15.9. ESI-MS: *m*/*z* 229 $[M+H]^+$ (calcd for $C_{11}H_{11}Cl_2O^+$, 229.0). *5-(3,4-Dichlorophenyl)pentan-1-ol:* Hydrogenation of 5-(3,4-dichlorophenyl)pent-4-yn-1-ol (661 mg, 2.88 mmol) with Pd/C (132 mg) was performed to produce the title compound as a colorless oil (533 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.66–3.63 (m, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.63–1.59 (m, 4H), 1.43–1.35 (m, 2H), 1.26 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 142.7, 132.0, 130.3, 130.2, 129.5, 127.9, 62.8, 35.0, 32.5, 30.9, 25.3. ESI-MS: *m*/*z* 230 $[M+H]^+$ (calcd for $C_{11}H_{15}Cl_2O^+$, 230.0). *5-(3,4-Dichlorophenyl)pentanoic acid:* Jones oxidation of 5-(3,4-dichlorophenyl)pentan-1-ol (533 mg, 2.28 mmol) was performed to produce the title compound as a colorless oil (430 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.34 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.1, 2.1 Hz, 1H), 2.61–2.59 (m, 2H), 2.40–2.36 (m, 2H), 1.68–1.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.0, 142.2, 132.2, 130.3, 130.2, 129.7, 127.9, 34.6, 33.4, 30.4, 24.1. ESI-MS: *m*/*z* 245 $[M-H]^-$ (calcd for $C_{11}H_{11}Cl_2O_2^-$, 245.0). *Methyl 7-(3,4-dichlorophenyl)-3-oxoheptanoate:* 5-(3,4-Dichlorophenyl)pentanoic acid (430 mg, 1.74 mmol) was converted to the title compound as a colorless oil (419 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.74 (s, 3H), 3.44 (s, 2H), 2.58–2.56 (m, 4H), 1.64–1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.3, 167.6, 142.2, 132.2, 130.3, 130.2, 129.7, 127.9, 52.4, 49.0, 42.7, 34.8, 30.3, 22.8. ESI-MS: *m*/*z* 303 $[M+H]^+$ (calcd for $C_{14}H_{17}Cl_2O_3^+$, 303.1). *Methyl 7-(3,4-dichlorophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(3,4-dichlorophenyl)-3-oxoheptanoate (419 mg, 1.38 mmol) with $NaBH_4$ (68.0 mg, 1.80 mmol) was performed to produce compound **29** as a colorless oil (121 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 8.3, 2.0 Hz, 1H), 4.00 (m, 1H), 3.72 (s, 3H), 2.93 (d, *J* = 3.9 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.50 (dd, *J* = 16.5, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.5, 8.2 Hz, 1H), 1.66–1.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 142.7, 132.1, 130.3, 130.2, 129.6, 127.9, 67.8, 51.8, 41.0, 36.2, 35.0, 31.0, 25.0. ESI-MS: *m*/*z* 305 $[M+H]^+$ (calcd for $C_{14}H_{19}Cl_2O_3^+$, 305.1).

Synthesis of compound 30. *5-(2,4-Dichlorophenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of

2,4-dichloro-1-iodobenzene (1.00 g, 3.66 mmol) with 4-pentyn-1-ol (341 μL, 3.66 mmol) was performed to produce the title compound as an orange oil (quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 8.3, 2.2 Hz, 1H), 3.85 (dt, J = 5.8, 5.8 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 1.91–1.87 (m, 2H), 1.51 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 136.5, 133.9, 133.8, 129.1, 126.8, 122.2, 96.0, 77.2, 61.6, 31.1, 16.2. ESI-MS: *m*/*z* 229 $[M+H]^+$ (calcd for $C_{11}H_{11}Cl_2O^+$, 229.0). *5-(2,4-Dichlorophenyl)pentan-1-ol:* Hydrogenation of 5-(2,4-dichlorophenyl)pent-4-yn-1-ol (3.66 mmol) with Pd/C (232 mg) was performed to produce the title compound as a yellow oil (687 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.35 (d, J = 2.2 Hz, 1H), 7.16 (dd, J = 8.5, 2.2 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 3.66 (t, J = 6.6 Hz, 2H), 2.72−2.69 (m, 2H), 1.65–1.59 (m, 4H), 1.46–1.41 (m, 2H) 1.26 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 138.6, 134.5, 132.0, 131.1, 129.2, 126.9, 62.9, 33.0, 32.5, 29.4, 25.4. ESI-MS: *m*/*z* 233 $[M+H]^+$ (calcd for $C_{11}H_{15}Cl_2O^+$, 233.0). *5-(2,4-Dichlorophenyl)pentanoic acid:* Jones oxidation of 5-(2,4-dichlorophenyl)pentan-1-ol (687 mg, 2.94 mmol) was performed to produce the title compound as a colorless oil (588 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.35 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.2, 2.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 2.72 (t, J = 7.4 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 1.74–1.62 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 178.5, 138.1, 134.5, 132.2, 131.1, 129.2, 127.0, 33.5, 32.7, 28.9, 24.2. ESI-MS: *m*/*z* 245 $[M–H]^–$ (calcd for $C_{11}H_{11}Cl_2O_2^–$, 245.0). *Methyl 7-(2,4-dichlorophenyl)-3-oxoheptanoate:* 5-(2,4-Dichlorophenyl)pentanoic acid (579 mg, 2.34 mmol) was converted to the title compound as a colorless oil (428 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.35 (d, J = 1.9 Hz, 1H), 7.16 (dd, J = 8.2, 1.9 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 3.74 (s, 3H), 3.45 (s, 2H), 2.70 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 1.68–1.57 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 202.4, 167.6, 138.1, 134.5, 132.2, 131.1, 129.2, 127.0, 52.4, 49.0, 42.7, 32.8, 28.9, 22.9. ESI-MS: *m*/*z* 303 $[M+H]^+$ (calcd for $C_{14}H_{17}Cl_2O_3^+$, 303.1). *Methyl 7-(2,4-dichlorophenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(2,4-dichlorophenyl)-3-oxoheptanoate (414 mg, 1.36 mmol) with $NaBH_4$ (67.1 mg, 1.77 mmol) was performed to produce compound **30** as a colorless oil (361 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.34 (d, J = 1.9 Hz, 1H), 7.16 (dd, J = 8.2, 1.9 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 4.04–3.98 (m, 1H), 3.72 (s, 3H), 2.94 (d, J = 4.0 Hz, 1H), 2.70 (t, J = 7.7 Hz, 2H), 2.51 (dd, J = 16.5, 3.2 Hz, 1H), 2.42 (dd, J = 16.5, 9.2 Hz, 1H), 1.65–1.39 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 173.5, 138.6, 134.5, 132.0, 131.1, 129.2, 127.0, 67.8, 51.8, 41.1, 36.2, 33.0, 29.5, 25.2. ESI-MS: *m*/*z* 305 $[M+H]^+$ (calcd for $C_{14}H_{19}Cl_2O_3^+$, 305.1).

Synthesis of compound 31. *5-(4-Chloro-2-methylphenyl)pent-4-yn-1-ol:* Sonogashira cross-coupling of 4-chloro-1-iodo-2-methylbenzene (275 μL, 1.98 mmol) with 4-pentyn-1-ol (184 μL, 1.98 mmol) was performed to produce the title compound as an orange oil (227 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.27 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 2.0, 0.5 Hz, 1H), 7.08 (ddd, J = 8.0, 2.0, 0.5 Hz, 1H), 3.83 (dt, J = 5.8, 5.8 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.91–1.84 (m, 2H), 1.47 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.7, 133.2, 133.0, 129.4, 125.7, 122.1, 94.2, 79.0, 61.8, 31.5, 20.6, 16.1. ESI-MS: *m*/*z* 209 $[M+H]^+$ (calcd for $C_{12}H_{14}ClO^+$, 209.1).

5-(4-Chloro-2-methylphenyl)pentan-1-ol: Hydrogenation of 5-(4-chloro-2-methylphenyl)pent-4-yn-1-ol (227 mg, 1.09 mmol) with Pd/C (45.0 mg) was performed to produce the title compound as a colorless oil (193 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26 (m, 1H), 7.12–7.02 (m, 2H), 3.66 (br, 2H), 2.63–2.55 (m, 2H), 2.30 (s, 3H), 1.63–1.57 (m, 4H), 1.49–1.41 (m, 2H), 1.24 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 130.1, 130.0, 129.9, 128.8, 125.8 (2), 63.0, 33.2, 32.6, 30.0, 25.8, 19.3. ESI-MS: *m*/*z* 213 $[M+H]^+$ (calcd for $C_{12}H_{18}ClO^+$, 213.1). *5-(4-Chloro-2-methylphenyl)pentanoic acid:* Jones oxidation of 5-(4-chloro-2-methylphenyl)pentan-1-ol (193 mg, 0.920 mmol) was performed to produce the title compound as a colorless oil (160 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.12–7.02 (m, 3H), 2.63–2.61 (m, 2H), 2.41–2.39 (m, 2H), 2.30 (s, 3H), 1.71–1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 178.8, 131.3, 130.2, 130.0, 129.9, 128.7, 125.9, 33.68, 32.3, 29.5, 24.5, 19.2. ESI-MS: *m*/*z* 225 $[M–H]^–$ (calcd for $C_{12}H_{14}ClO_2^–$, 225.1). *Methyl 7-(4-chloro-2-methylphenyl)-3-oxoheptanoate:* 5-(4-Chloro-2-methylphenyl)pentanoic acid (160 mg, 0.710 mmol) was converted to the title compound as a colorless oil (25.0 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.08–7.05 (m, 3H), 3.73 (s, 3H), 3.44 (s, 2H), 2.60–2.54 (m, 4H), 2.26 (s, 3H), 1.72–1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 202.4, 167.6, 138.7, 137.7, 131.2, 130.0, 129.9, 125.8, 52.4, 49.0, 42.8, 32.4, 29.4, 23.2, 19.2. ESI-MS: *m*/*z* 283 $[M+H]^+$ (calcd for $C_{15}H_{20}ClO_3^+$, 283.1). *Methyl 7-(4-chloro-2-methylphenyl)-3-hydroxyheptanoate:* Reduction of methyl 7-(4-chloro-2-methylphenyl)-3-oxoheptanoate (25.0 mg, 88.0 μmol) with $NaBH_4$ (4.30 mg, 110 μmol) was performed to produce compound **31** as a colorless oil (15.7 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.11 (s, 1H), 7.09–7.08 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.01 (m, 1H), 3.72 (s, 3H), 2.91 (d, *J* = 3.9 Hz, 1H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.51 (dd, *J* = 16.6, 3.3 Hz, 1H), 2.42 (dd, *J* = 16.6, 9.0 Hz, 1H), 2.27 (s, 3H), 1.59–1.39 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 173.5, 139.1, 137.7, 131.1, 130.0, 129.9, 125.8, 67.9, 51.8, 41.1, 36.3, 32.6, 30.0, 25.4, 19.2. ESI-MS: *m*/*z* 285 $[M+H]^+$ (calcd for $C_{15}H_{22}ClO_3^+$, 285.1).

Synthesis of compound 33. *Methyl 5-(4-chlorophenyl)pentanoate:* Methylation of 5-(4-chlorophenyl)pentanoic acid (585 mg, 2.96 mmol) was performed with 0.5 M HCl/MeOH to produce the title compound as a colorless oil (477 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.24–7.23 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 3.66 (s, 3H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.34–2.32 (m, 2H), 1.69–1.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 174.0, 140.5, 131.5, 129.7 (2), 128.4 (2), 51.5, 34.9, 33.8, 30.7, 24.4. ESI-MS: *m*/*z* 227 $[M+H]^+$ (calcd for $C_{12}H_{16}ClO_2^+$, 227.1). *Methyl 6-(4-chlorophenyl)-2-oxohexanoate:* Methyl 5-(4-chlorophenyl)pentanoate (400 mg, 1.77 mmol) was converted to the title compound as a yellowish oil (182 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.25–7.23 (m, 2H), 7.10–7.09 (m. 2H), 3.86 (s, 3H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.66–2.59 (m, 2H), 1.68–1.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 193.9, 158.7, 144.6, 129.9, 128.6 (2), 128.2 (2), 52.6, 39.0, 34.9, 30.5, 22.5. ESI-MS: *m*/*z* 255 $[M+H]^+$ (calcd for $C_{13}H_{16}ClO_3^+$, 255.1). *Methyl 6-(4-chlorophenyl)-2-hydroxyhexanoate:* Reduction of methyl 6-(4-chlorophenyl)-2-oxohexanoate (182 mg, 0.710 mmol) with $NaBH_4$ (33.0 mg, 0.880 mmol) was performed to produce compound **33**

as a colorless oil (127 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.25–7.22 (m, 2H), 7.10–7.09 (m, 2H), 4.22–4.17 (m, 1H), 3.78 (s, 3H), 2.70 (d, *J* = 5.8 Hz, 1H), 2.62 (t, *J* = 7.3 Hz, 2H), 1.85–1.41 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 175.7, 140.7, 129.9, 128.6 (2), 128.0 (2), 69.9, 52.9, 35.0, 34.1, 31.0, 24.3. ESI-MS: *m*/*z* 257 $[M+H]^+$ (calcd for $C_{13}H_{18}ClO_3^+$, 257.1).

Synthesis of compound 34. *Methyl 7-(4-chlorophenyl)heptanoate:* Methylation of 7-(4-chlorophenyl)heptanoic acid (648 mg, 2.69 mmol) was performed with 0.5 M HCl/MeOH to produce the title compound as a colorless oil (648 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.66 (s, 3H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.64–1.56 (m, 4H), 1.37–1.32 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 174.2, 141.1, 131.3, 129.7 (2), 128.4 (2), 51.4, 35.1, 34.0, 31.1, 28.9, 28.7, 24.8. ESI-MS: *m*/*z* 255 $[M+H]^+$ (calcd for $C_{14}H_{20}ClO_2^+$, 255.1). *Methyl 8-(4-chlorophenyl)-2-oxooctanoate:* Methyl 7-(4-chlorophenyl)heptanoate (648 mg, 2.54 mmol) was converted to the title compound as a yellowish oil (312 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 2H), 3.87 (s, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 1.64–1.58 (m, 4H), 1.35–1.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 194.2, 161.5, 141.0, 131.3, 129.7 (2), 128.4 (2), 52.9, 39.2, 35.1, 31.1, 28.7 (2), 22.8. ESI-MS: *m*/*z* 283 $[M+H]^+$ (calcd for $C_{15}H_{20}ClO_3^+$, 283.1). *Methyl 8-(4-chlorophenyl)-2-hydroxyoctanoate:* Reduction of methyl 8-(4-chlorophenyl)-2-oxooctanoate (305 mg, 1.08 mmol) with $NaBH_4$ (53.0 mg, 1.40 mmol) was performed to produce compound **34** as a colorless oil (188 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.24–7.22 (m, 2H), 7.10–7.08 (m, 2H), 4.18–4.17 (m, 1H), 3.78 (s, 3H), 2.69 (d, *J* = 3.9 Hz, 1H), 2.58–2.55 (m, 2H), 1.77–1.58 (m, 4H), 1.44–1.34 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 175.8, 141.1, 131.3, 129.7 (2), 128.3 (2), 70.4, 52.5, 35.2, 34.3, 31.2, 29.1, 28.9, 24.6. ESI-MS: *m*/*z* 285 $[M+H]^+$ (calcd for $C_{15}H_{22}ClO_3^+$, 285.1).

Optical Resolution. The optical resolution of racemic PQI compounds was performed as follows: PQI-2: CHIRALPAK IA (250×10 mm, 5 μm, Daicel), 75% MeOH/H_2O, 4 mL/min, (*R*)-PQI-2 (t_R 19.1 min, $[\alpha]_D^{25}$ = –12.6, *c* = 0.973, chloroform), (*S*)-PQI-3 (t_R 23.0 min, $[\alpha]_D^{25}$ = +12.2, *c* = 1.03, chloroform). PQI-3: CHIRALPAK IA (250×10 mm), 67% MeOH/H_2O, 4 mL/min, (*R*)-PQI-3 (t_R 33.6 min, $[\alpha]_D^{25}$ = –3.26, *c* = 0.259, chloroform), (*S*)-PQI-3 (t_R 36.8 min, $[\alpha]_D^{25}$ = +4.05, *c* = 0.346, chloroform). PQI-4: CHIRALPAK IA (250×10 mm), 67% MeOH/H_2O, 4 mL/min, (*R*)-PQI-4 (t_R 31.0 min, $[\alpha]_D^{25}$ = –14.3, *c* = 0.440, chloroform), (*S*)-PQI-4 (t_R 36.6 min, $[\alpha]_D^{25}$ = +15.7, *c* = 0.427, chloroform). PQI-5: CHIRALPAK IA (250×10 mm), 65% MeOH/H_2O, 4 mL/min, (*R*)-PQI-5 (t_R 32.1 min, $[\alpha]_D^{25}$ = –6.77, c = 0.399, chloroform), (*S*)-PQI-5 (t_R 35.6 min, $[\alpha]_D^{25}$ = +4.15, c = 0.337, chloroform).

Biofilm Formation Assay. To measure biofilm formation of *R. solanacearum*, we used a standard PVC assay. Strain OE1-1 cells from overnight bacterial cultures in CPG were diluted to an OD_{600} of 0.1 in new medium. A sample (5 μL) of the cell suspension was seeded into each well of a PVC 96-well microtiter plate (Thermo Fisher Scientific) containing CPG media (95 μL) and PQIs. Plates were sealed with Breathe-Easy membrane (Sigma-Aldrich) and incubated statically at 30°C. After 24

h, each well was stained with 25 μL of 1% crystal violet for 25 min at rt. PVC plates were washed twice with MilliQ water (200 μL) and the remaining liquid was aspirated from the bottom of the plate. Adhering crystal violet was dissolved in 95% EtOH (200 μL), transferred to a new polystyrene plate, and measured as absorbance at 595 nm. The IC_{50} values of PQIs-2–5 were calculated by fitting the data points to a logistic curve using GraphPad Prism 6J software.

Ralfuranone A Production Assay. OE1-1 cells grown in B medium at 30°C for 4−6 h were diluted to an OD_{600} of 0.01 in MGRLS medium. Each 2-mL cell suspension was transferred to test tubes and incubated for 48 h at 30°C with shaking. After 24 h incubation, the supernatants were prepared by centrifugation and the samples (800 μL) were applied to the solid-phase extraction with MonoSpin C18 (GL Science). The mini columns were washed with MilliQ water (300 μL) and then eluted with MeOH (100 μL). The eluates were analyzed by the following LC/MS: column Cosmosil 2.5πNAP (100×2.0 mm, 2.5 μm, Nacalai), column oven at 40°C, flow rate of 0.2 mL/min, and eluent of 20–95% MeCN in H_2O (0–15 min) and 95% MeCN (15–20 min). The IC_{50} values of PQIs-2–5 were calculated by fitting the data points to a logistic curve using GraphPad Prism 6J software.

EPS I Production Assay. OE1-1 cells grown in B medium at 30°C for 4–6 h were diluted to an OD_{600} of 1.0 in new medium. A sample (50 μL) of the cell suspension was pipetted onto a BG agar plate and the plate was incubated for 24 h at 30°C. Bacterial cells and EPS I produced were collected in MilliQ water (5 mL), and the OD_{600} values were measured. EPS I was quantified using anti-*R. solanacearum* EPS I antibodies by an enzyme-linked immunosorbent assay per 100 μL of cell suspension according to the manufacturer's instructions (Agdia). EPS I productivity was quantified by absorbance at 620 nm.

RNA-Seq Assay. Total RNA was isolated from *R. solanacearum* strains grown in 1/4 M63 medium (OD_{600}: from 0.0001 to 0.3) in the presence of 10 μM PQIs using the High Pure RNA Isolation Kit (Roche Diagnostics). Ribosomal RNA was removed from the extracted total RNA using the Ribo-Zero rRNA Removal Kit (Gram-Negative Bacteria) (Illumina). Oriented paired-end RNA sequencing (2×100 bp) was performed by Hokkaido System Science (Sapporo, Japan) using an Illumina HiSeq 2000 system and the procedures recommended by Illumina. The adaptors and primers were designed by Hokkaido System Science. The selected inserts were 100 bp. We performed paired-end sequencing of libraries. Reads were trimmed using Cutadapt (version 1.1) and Trimmomatic (version 0.32), and then mapped with TopHat (version 2.0.10). Read counts obtained for each of the samples are presented as FPKM, which were calculated by Cufflinks (version 2.2.1). These experiments were carried out in quadruplicate; however, the data of Δ*phcB* were obtained from sextuplicate experiments.

Virulence Assay. Tomato plants (cv. Oogata-Fukuju) were grown in pots containing commercial soil (Takii Seed) and watered with five-fold-diluted Hoagland's solution in a growth room at 25°C under 10000 lx for 16 h per day. The roots of 5-week-old tomato plants were soaked in bacterial suspension at 1.0×10^8 CFU/mL for 30 min and then washed in running water. The inoculated plants were grown in water-culture pots (Yamato Plastic) with five-fold-diluted Hoagland's solution in a

growth room at 25°C under 10000 lx for 16 h per day. Within each trial, three plants were used. Plants were coded and inspected for wilting symptoms daily after inoculation. Plants were rated on a 0–5 disease index scale: 0, no wilting; 1, 1%–25% wilting; 2, 26%–50% wilting; 3, 51%–75% wilting; 4, 76%–99% wilting; 5, dead.

AHL Reporter Assays. *A. tumefaciens* NTL4(pZLR) was grown in ABM medium overnight on a shaker at 30°C (OD_{600} = 0.2). Culture (2 mL) was suspended in warm ABM (5 mL, containing 0.8% agar). X-Gal (60 μL, 20 mg/mL in DMF) was added to the soft agar bacterium suspension. The agar suspension was poured onto the surface of standard ABM agar (15 mL, 90 mm dish), and paper discs (6 mm, Toyo Roshi Kaisha) containing appropriate concentrations of test samples were placed on the surface of the solidified agar. The agar plate was incubated for 24 h at 30°C.

C. violaceum CV026 was grown in LB medium overnight on a shaker at 30°C (OD_{600} = 1.0). Culture (2 mL) was suspended in warm LB (5 mL, containing 0.8% agar). The agar suspension was poured onto the surface of LB agar (15 mL, 90 mm dish), and paper discs containing appropriate concentrations of test samples were placed on the surface of the solidified agar. The agar plate was incubated for 24 h at 30°C.