Supplementary Material (ESI) for Organic and Biomolecular Chemistry

A Highly Effective One-Pot Synthesis of Quinolines from *o*-Nitroarylcarbaldehydes

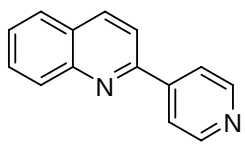
An-Hu Li,* Eilaf Ahmed, Xin Chen, Matthew Cox, Andrew P. Crew, Han-Qing Dong, Meizhong Jin, Lifu Ma, Bijoy Panicker, Kam W. Siu, Arno G. Steinig, Kathryn M. Stolz, Paula A. R. Tavares, Brian Volk, Qinghua Weng, Doug Werner, and Mark J. Mulvihill*

Department of Cancer Chemistry, OSI Pharmaceuticals, Inc., 1 Bioscience Park Drive, Farmingdale, NY 11735, USA

Corresponding authors: ali@osip.com; mmulvihill@osip.com

Supplementary Information

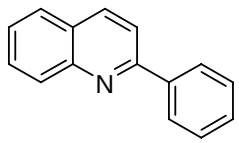
General Experimental Methods: Commercially available reagents, anhydrous solvents, and HPLC grade solvents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F254 (0.2 mm) precoated aluminum foil/plastic. Flash chromatography was performed with silica gel (400–230 mesh). IR spectra were recorded on a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as thin films using diffuse reflectance. ^{1}H NMR and ^{13}C NMR spectra were recorded with Varian or Bruker instruments (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) at ambient temperature with TMS or the residual solvent peak as internal standards. The line positions or multiplets are given in ppm (δ) and the coupling constants (*J*) are given as absolute values in Hertz. LC/MS analysis was performed using Hewlett Packard HP1100 (OpenLynx LC-MS: Detection: UV at 254 nM; Column: XTerra MS C18, 5μ particle size, 4.6×50mm; Mobile phase: 5-minute gradient of a mixture of acetonitrile and 0.01% formic acid in water; Flow rate: 1.3 mL/min). Mass spectra were obtained on MicromassZQ200 (OpenLynx LC-MS) mass spectrometers, using electrospray ionization (ES^{+}). Melting points were determined with a Mel-Temp II apparatus and are uncorrected. Elemental analyses were carried out at Atlantic Microlab, Inc., Norcross, GA.



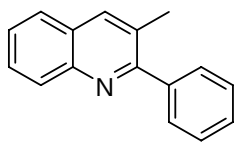
Synthesis of 2-(4-Pyridinyl)quinoline (**4**, Scheme 1): To a solution of *o*-nitrobenzaldehyde (**1**, 151 mg. 1.0 mmol) in ethanol (5 mL) was added iron powder (<10 μm, Aldrich, 560 mg, 10.0 mmol) followed by 0.1 N aq HCl (2 mL, 0.20 mmol) and the resulting mixture was vigorously stirred at 95 ºC (oil bath) for 30 min. TLC showed that the reduction reaction was complete. After cooling to room temperature, the reaction

mixture was filtered through a Celite pad. To the filtrate was added 4-acetylpyridine (**3**, 121.1 mg, 1.0 mmol) and powdered KOH (168 mg, 3.0 mmol) successively in portions (***Caution!*** Potential exotherm; add KOH slowly). The resulting mixture was stirred at 95 ºC for 40 min. then cooled to rt, diluted with CH_2Cl_2 (50 mL) and water (3 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel (MeOH/ CH_2Cl_2: 3/97) to afford 205.5 mg of 2-(4-pyridinyl)quinoline (**4**, yield: 100%). R_f = 0.1 (EtOAc:hexanes = 1:4). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.74 (d, *J* = 5.2 Hz, 2 H), 8.16 (dd, *J* = 2.0, 8.4 Hz, 2 H), 7.99 (d, *J* = 5.2 Hz, 2 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 154.29, 150.49, 148.22, 146.51, 137.20, 130.08, 129.96, 127.79, 127.55, 127.19, 118.32, 114.51. MS (ES^+): *m*/*z* 207.23 (MH^+). HPLC: t_R = 2.58 min (OpenLynx).

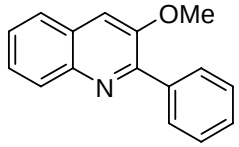
General procedure (Table 1): To a solution of *o*-nitroarylcarbaldehyde (**1** or **5**–**8**, 1.0 mmol) in ethanol (3 mL) was added iron powder (<10 μm, Aldrich, 223 mg, 4.0 mmol) followed by 0.1 N aq HCl (0.5 mL, 0.05 mmol) and the resulting mixture was vigorously stirred at 95 ºC (oil bath) for 40 min-5 h (See footnotes under Table 1). TLC analysis revealed that the reduction reaction was complete so respective ketones or aldehyde (**9**–**19**, 1.0 mmol) and powdered KOH (67.3 mg, 1.2 mmol) were added successively in portions (***Caution!*** Potential exotherm; add KOH slowly). The reaction mixture was stirred at 95 ºC for 30 min-48 h (See footnotes under Table 1), then cooled to rt, diluted with CH_2Cl_2 (50 mL), and filtered through a Celite pad. The filtrate was washed with water (10 mL) and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by chromatography over silica gel (eluted with EtOAc/hexane or MeOH/CH_2Cl_2) to afford the desired quinoline product **20**–**34**.



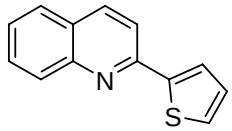
2-Phenylquinoline (**20**): Yield: 99%. m.p.: 84-85 ºC. IR (thin film, KBr, cm-1): 3057, 1615, 1596, 1582, 1153, 1508, 1490, 1319, 1074. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.46-7.51 (m, 1 H), 7.53-7.57 (m, 3 H), 7.70-7.78 (m, 1 H), 7.85 (d, *J* = 8.08 Hz, 1 H), 7.43 (d, *J* = 8.59 Hz, 1 H), 8.15-8.28 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 157.39, 136.84, 129.75, 129.71, 129.36, 128.88, 127.62, 127.49, 127.22, 127.20, 126.33, 119.04. MS (ES^+): *m*/*z* 206.20 (MH^+). HPLC: t_R = 3.68 min (OpenLynx).



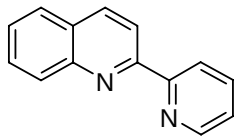
3-Methyl-2-phenylquinoline (**21**): Yield: 92%. R_f = 0.57 (EtOAc:Hexanes=1:10). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 8.6 Hz, 1 H), 8.03 (s, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.65-7.71 (m, 1 H), 7.58-7.64 (m, 2 H), 7.42-7.56 (m, 4 H), 2.48 (s, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 161, 147, 141, 137, 129.24, 129.17, 128.8, 128.7, 128.3, 128.2, 127.6, 126.7, 126.4, 26. MS (ES^+): *m*/*z* 220.20 (MH^+). HPLC: t_R = 2.46 min (OpenLynx).



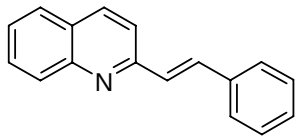
3-Methoxy-2-phenylquinoline (**22**): Yield: 66%; R_f = 0.39 (EtOAc/hexanes = 1:4); IR (thin film, KBr, cm^{-1}): 3056.1, 2923.5, 2851.9, 1685.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91-3.98 (m, 3 H), 7.47-7.49 (m, 1 H), 7.50 (t, *J* = 1.5 Hz, 1 H), 7.52 (d, *J* = 1.0 Hz, 1 H), 7.53-7.55 (m, 1 H), 7.55 (t, *J* = 2.0, 1.5 Hz, 1 H), 7.57-7.64 (m, 1 H), 7.76 (dd, *J* = 1.3 Hz, 1 H), 8.00-8.06 (m, 2 H), 8.15-8.21 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 151.7, 143.1, 137.9, 129.8, 129.6, 129.5, 129.4, 128.9, 128.7, 128.3, 128.1, 126.9, 126.8, 126.3, 112.9, 77.5, 77.2, 76.9, 55.5; MS (ES^+): *m*/*z* 236.18 (MH^+); HPLC: t_R = 1.86 min (OpenLynx).



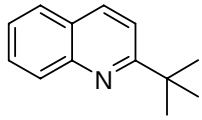
2-(2-Thiophenyl)quinoline (**23**): Yield: 80%. R_f = 0.44 (EtOAc:Hexanes = 1:4). m.p.: 130-132 ºC. IR (thin film, KBr, cm^{-1}): 3100, 3059, 1613, 1592, 1551, 1526, 1498, 1426, 1316, 1242, 1227, 1143, 1121, 1057, 905, 820, 719. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.70–7.77 (m, 2 H), 7.68 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1 H), 7.47 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 7.46 (dd, *J* = 5.2, 1.2 Hz, 1 H), 7.15 (dd, *J* = 5.2, 4.8 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 152.43, 148.20, 145.47, 136.76, 129.94, 129.37, 128.72, 128.20, 127.59, 127.31, 126.23, 126.12, 117.78. MS (ES^+): *m*/*z* 212.14 [MH^+]. HPLC: t_R = 3.74 min (OpenLynx).



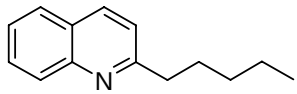
2-(2-Pyridinyl)quinoline (**24**): Yield: 92%. m.p.: 95.5 - 97.0 ºC. IR (thin film, KBr, cm^{-1}): 3054, 1595, 1555, 1502, 1419, 1237, 1123, 1088, 993, 957, 944, 741, 713, 623. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37 – 7.38 (m, 1 H), 7.56 – 7.59 (m, 1 H), 7.74 – 7.76 (m, 1 H) 7.86 – 7.90 (m, 2 H) 8.21 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H), 8.58 (d, *J* = 8.8 Hz, 1 H), 8.68 (d, *J* = 8.4 Hz, 1 H), 8.74 – 8.76 (m, 1 H). ^{13}C ($CDCl_3$, 100 MHz) 118.9, 121.8, 124.0, 126.7,127.6, 128.3, 129.6, 129.8, 136.8, 136.9, 147.9, 149.2, 156.2, 156.3. MS (ES^+): *m/z*: 207.14 [MH^+]. HPLC: t_R = 3.28 min (OpenLynx).



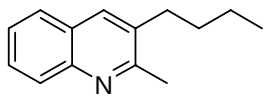
2-[(*E*)-Styryl]quinoline (**25**): Yield: 77%. R_f = 0.43 (20% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.72-7.62 (m, 5 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.47-7.37 (m, 4 H), 7.34-7.30 (m, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.98, 148.30, 136.56, 136.32, 134.45, 129.76, 129.25, 129.06, 128.84, 128.67, 127.56, 127.37, 127.33, 126.18, 119.30.



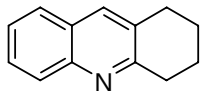
2-(*tert*-Butyl)quinoline (**26**): Yield: 90%; R_f = 0.73 (EtOAc/hexanes = 1:4); IR (thin film, KBr, cm^{-1}): 3059.9, 2957.6, 1618.5, 1599.9, 1502.9, 1363.0, 1137.7; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.67 (dt, *J* = 2.0, 8.8 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.27, 147.49, 135.87, 129.49, 129.00, 127.26, 126.49, 125.65, 118.24, 38.17, 30.20; MS (ES^+): *m*/*z* 186.24 (MH^+); HPLC: t_R = 2.18 min (OpenLynx).



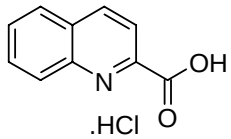
2-(*n*-Pentyl)quinoline (**27a**): Yield: 44%, separable from **27b**. R_f = 0.29 (EtOAc:hexanes = 3:97). IR (thin film, KBr, cm^{-1}): 3057, 2953, 2926, 2856, 1600, 1505, 1425, 1116, 822, 748. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.05 (d, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 1.3, 8.1 Hz, 1H), 7.67 (dt, *J* = 1.5, 6.5 Hz, 1H), 7.47 (dt, *J* = 1.0, 7.9 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 2.97 (t, *J* = 8.0 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.42 – 1.35 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 163.2, 147.9, 136.2, 129.3, 128.9, 127.5, 126.7, 125.6, 121.3, 39.4, 31.8, 29.8, 22.6, 14.0. MS (ES^+): *m*/*z* 200.36 (MH+). HPLC: t_R = 2.75 min (OpenLynx).



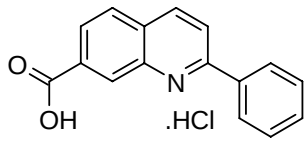
3-(*n*-Butyl)-2-methylquinoline (**27b**): Yield: 47%, separable from **27a**. R_f = 0.16 (EtOAc:hexanes = 3:97). IR (thin film, KBr, cm^{-1}): 3009, 2951, 2925, 2868, 1604, 1496, 1421, 1343, 1227, 1130, 894, 758. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.98 (d, *J* = 8.6 Hz, 1H), 7.83 (s, 1H), 7.72 (dd, *J* = 1.3 Hz, 1H), 7.62 (dt, *J* = 1.6, 8.3Hz, 1H), 7.45 (dt, *J* = 1.3, 8.1 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.73 (s, 3H), 1.72 – 1.64 (m, 2H), 1.51 – 1.42 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 158.6, 146.4, 134.5, 134.4, 128.4, 128.3, 127.4, 126.9, 125.6, 32.6, 31.8, 23.2, 22.6, 14.0. MS (ES^+): *m*/*z* 200.69 (MH+). HPLC: t_R = 2.39 min (OpenLynx).



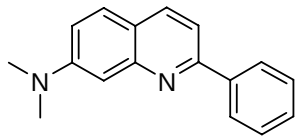
1,2,3,4-Tetrahydroacridine (**28**): Yield: 95%. R_f = 0.43 (EtOAc:hexanes = 1:4). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.97 (d, *J* = 8.4 Hz, 1 H), 7.70 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.57 (dt, *J* = 2.4, 7.2 Hz, 1 H), 7.39 (dt, *J* = 1.2, 7.2 Hz, 1 H), 3.10 (t, *J* = 5.8 Hz, 2 H), 2.92 (t, *J* = 6.4 Hz, 2 H), 1.99-1.92 (m, 2 H), 1.87-1.82 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 159.27, 146.66, 134.92, 130.92, 128.46, 128.32, 127.22, 126.90, 125.50, 33.62, 29.26, 23.26, 22.93. MS (ES^+): *m*/*z* 184.21 (MH+). HPLC: t_R = 1.86 min (OpenLynx).



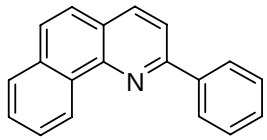
Quinoline-2-carboxylic acid hydrochloride (**29**): Yield: 95%. mp: 150-153 ºC (decompose). ^{1}H-NMR (CD_3OD, 400 MHz): δ = 7.72-7.76 (m, 1 H), 7.85-7.89 (m, 1 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 8.21-8.25 (m, 2 H), 8.53 (d, *J* = 8.3 Hz, 1 H). ^{13}C-NMR (CD_3OD, 100 MHz): δ = 167.7, 149.6, 148.1, 139.8, 132.1, 131.1, 130.3, 130.1, 129.2, 121.9. MS (ES^+): *m*/*z* 174 [MH^+]. HPLC: t_R = 1.80 min (OpenLynx).



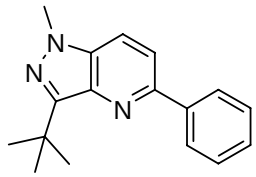
2-Phenylquinoline-7-carboxylic acid hydrochloride (**30**): Yield: 91%; mp: 255 °C; IR (thin film, KBr, cm^{-1}): 2924, 1682, 975, 760; ^{1}H NMR (400 MHz, CD_3OD) δ 8.67–8.70 (m, 1 H), 8.35 (d, *J* = 8.8 Hz, 1 H), 7.96–8.08 (m, 4 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.37–7.48 (m, 1 H) ^{13}C NMR (100 MHz, CD_3OD) δ 160.7, 149.3, 141.0, 139.2, 134.5, 133.0, 131.7, 131.6, 130.7, 129.8, 129.5, 127.8, 122.9; MS (ES+): *m/z* 250.15 [MH^+]; HPLC: t_R = 3.2 min (OpenLynx).



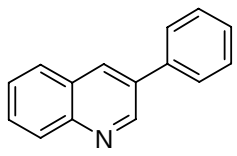
***N,N'*-Dimethyl-(2-phenylquinolin-7-yl)amine** (**31**): Yield: 67%, a yellow/orange oil; R_f = 0.49 (EtOAc/$CHCl_3$ = 1:5); IR (thin film, KBr, cm^{-1}): 3058, 3030, 1617, 1595; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.14 (s, 6 H), 7.18 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.42-7.49 (m, 1 H), 7.49-7.56 (m, 3 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 7.68 (d, *J* = 9.1 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 8.13 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.81, 107.65, 115.48, 116.35, 120.17, 127.76, 128.23, 128.92, 129.14, 136.41, 151.75, 157.95; MS (ES^+): *m*/*z* 249.16 (MH+); HPLC: t_R = 1.97 min (OpenLynx); Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28; Found C, 81.96; H, 6.55; N, 11.24.



2-Phenylbenzo[*h*]quinoline (**32**): Yield: 95%. R_f = 0.76 (EtOAc:hexanes = 1:4). m.p.: 66 – 67 ºC. IR (thin film, KBr, cm^{-1}): 3050, 2360. ^1H-NMR (DMSO-d_6, 400 MHz): δ = 9.37 (d, *J* = 7.2 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 2 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.90 – 7.97 (m, 2H), 7.76 – 7.83 (m, 2 H), 7.61 (t, *J* = 7.4 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H). ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 137.2, 133.5, 130.9, 129.5, 128.9, 128.4, 128.0, 127.3, 127.1, 127.0, 125.3, 125.0, 123.9, 119.1. MS (ES^+): *m*/*z* 256.11 (MH+). HPLC: t_R = 4.52 min (OpenLynx).



3-(*tert*-Butyl)-1-methyl-5-phenyl-1*H*-pyrazolo[4,3-*b*]pyridine (**33**): Yield: 82%; m.p.: 103-104 ºC; R_f = 0.76 (EtOAc/hexanes = 5:95); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dt, *J* = 1.2, 7.4 Hz, 2 H), 7.73 (d, *J* = 7.3 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 7.46 (dt, *J* = 1.8, 7.4 Hz, 2 H), 7.37 (tt, *J* = 1.2, 7.4 Hz, 1 H), 3.99 (s, 3 H), 1.62 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.27, 150.42, 139.57, 139.34, 132.75, 128.28, 127.98, 126.56, 117.27, 116.50, 35.09, 33.22, 29.33; MS (ES+): *m*/*z* 266.23 (MH^+); HPLC: t_R = 3.98 min (OpenLynx); Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84; Found C, 76.75; H, 7.17; N, 16.11.



3-Phenylquinoline (**34**): Yield: 87%. R_f = 0.16 (dichloromethane:hexanes 1:1). m.p.: 177–180 ºC (hydrochloride salt). IR (thin film, KBr, cm^{-1}): 3058, 3031, 1597, 1568, 1493, 1460, 1448, 1363, 1341, 1126, 1026, 954, 903, 786, 762, 696. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.19 (d, *J* = 2.2 Hz, 1 H), 8.31 (d, *J* = 2.2 Hz, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H), 7.89 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.75–7.69 (m, 3 H), 7.58 (ddd, *J* = 1.2, 6.8, 8.2 Hz, 2 H), 7.56–7.51 (m_c, 2 H), 7.47–7.42 (m_c, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.89, 147.30, 137.84, 133.78, 133.16, 129.32, 129.20, 129.12, 128.05, 127.97, 127.95, 127.37, 126.94. MS (ES^+): *m/z* 206.14 [MH^+]. HPLC: t_R = 2.78 min (OpenLynx).