Dual RXR Agonists and RAR Antagonists Based on the Stilbene Retinoid Scaffold

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Experimental Procedures[1]

Methyl 5,8-Diiodo-2-naphthoate (12). To a solution of methyl 2-naphthoate **11** (1.50 g, 8.1 mmol) in CH_2Cl_2 (215 mL) were added Ipy_2BF_4 (6.0 g, 24.2 mmol) and TfOH (1.82 mL, 2.42 mmol) and the mixture was stirred at 25 ºC for 22h. A saturated aqueous solution of $Na_2S_2O_3$ was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, 90:10 hexane/AcOEt), to afford 2.71 g (71%) of **12** as a white solid. **m.p.:** 160 ºC (hexane/EtOAc). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.77 (d, *J* = 1.4 Hz, 1H), 8.13 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 4.02 (s, 3H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 166.3 (s), 140.2 (d), 138.9 (d), 136.9 (s), 135.7 (d), 134.2 (s), 133.6 (d), 130.0 (s), 127.9 (d), 100.9 (s), 100.2 (s), 52.6 (q) ppm. **HRMS** (ESI^+): Calcd. for $C_{12}H_9I_2O_2$, 438.8686 ($[M + H]^+$); found, 438.8706. **IR** (NaCl): υ 3062 (w, C-H), 2993 (w, C-H), 2946 (w, C-H), 2841 (w, C-H), 1690 (s, C=O) cm^{-1}.

Methyl 5,8-Diphenyl-2-naphthoate (13). To a solution of methyl 5,8-diiodo-2-naphthoate **12** (0.6 g, 1.37 mmol), in THF-H_2O (12 mL, 1:1 v/v) were added $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol), $PhB(OH)_2$ (0.37 g, 3.1 mmol) and Na_2CO_3 (0.3 g, 2.74 mmol) and the mixture was heated under microwave irradiation (60W, 5 min, 110 ºC). Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 97:3 hexane/EtOAc), to afford 0.43 g (91%) of **13** as a yellow solid. **m. p.:** 130 ºC (hexane/AcOEt). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 8.0-7.9 (m, 2H), 7.58 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.6-7.5 (m, 9H), 7.5-7.4 (m, 2H), 3.90 (s, 3H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 167.1 (s), 141.2 (s), 140.1 (s), 139.9 (s), 139.6 (s), 133.9 (s), 131.0 (s), 130.5 (s), 130.0 (d, 2x), 129.9 (d, 2x), 129.4 (d), 128.6 (d), 128.4 (d, 2x), 128.3 (d, 2x), 127.5 (d), 127.4 (d), 127.2 (d), 126.6 (d), 125.1 (d), 57.8 (q) ppm. **MS** (EI): *m*/*z* (%) 338 (M^+, 100), 279 (43), 278 (31), 277 (26), 276 (25). **HRMS** (EI): Calcd. for $C_{24}H_{18}O_2$, 338.1307; found, 338.1310. **IR** (NaCl): υ 3056 (w, C-H), 3027 (w, C-H), 2950 (w, C-H), 1719 (s, C=O), 1280 (s) cm^{-1}.

5,8-Diphenyl-2-naphthoic Acid (14). ***General procedure for saponification of esters***. A solution of methyl 5,8-diphenyl-2-naphthoate **13** (0.4 g, 1.18 mmol) and KOH (20 mL, 2M in H_2O, 40 mmol) in MeOH (80 mL) was heated to 50 ºC for 3h. After cooling down to room temperature, CH_2Cl_2 and brine were added and the layers were separated. The aqueous layer was treated with a 10% aqueous HCl solution until acidic pH and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH), to provide 0.38 g (99%) of **14** as a white solid. **m.p.:** 102 ºC (MeOH). **^{1}H-NMR** (400.13 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.00 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 6.9 Hz, 2H), 7.57 (d, *J* = 2.1 Hz, 2H), 7.6-7.5 (m, 8H) ppm. **^{13}C-NMR** (100.16 MHz, DMSO-d_6): δ 167.7 (s), 140.4 (s), 139.7 (s), 139.6 (s), 139.1 (s), 132.8 (s), 130.5 (s), 130.2 (s), 129.9 (d, 2x), 129.8 (d, 2x), 129.6 (d), 128.7 (d, 2x), 128.6 (d, 2x), 128.1 (d), 128.0 (d), 127.7 (d), 127.6 (d), 127.0 (d), 125.9 (d) ppm. **MS** (EI): *m*/*z* (%) 324 (M^+, 100), 280 (17), 279 (70), 278 (40), 276 (37), 248 (30), 203 (37), 202 (42), 201 (20), 200 (15). **HRMS** (EI): Calcd. for $C_{23}H_{16}O_2$, 324.1150; found, 324.1154. **IR** (NaCl): υ 3600-3000 (br, O-H), 3056 (w, C-H), 3026 (w, C-H), 2961 (w, C-H), 2876 (w, C-H), 1697 (s, C=O) cm^{-1}.

5,8-Diphenyl-2-naphthamide (15). To a solution of 5,8-diphenyl-2-naphthoic acid **14** (0.35 g, 1.08 mmol) in DMF (23 mL) was added HOBt (0.19 g, 1.19 mmol) and EDC (0.23 g, 1.19 mmol) and the mixture was stirred for 3h at 25 ºC. The residue was cooled down to 0 ºC, a solution of NH_3 (0.56 mL, 2M in MeOH) was added and the mixture was stirred at 25 ºC for 2.5h. A saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with AcOEt (3x). The combined organic layers were washed with water (3x) and brine (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 97:3 CH_2Cl_2/MeOH), 0.21 g (60%) of **15** as a white solid. **m.p.:** 165 ºC (MeOH). **^{1}H-NMR** (400.13 MHz, DMSO-d_6): δ 8.47 (d, *J* = 1.4 Hz, 1H), 8.09 (s, 1H), 7.95 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), 7.6-7.4 (m, 11H) ppm. **^{13}C-NMR** (100.16 MHz, DMSO-d_6): δ 167.9 (s), 140.3 (s), 139.6 (s), 139.5 (s), 138.9 (s), 132.3 (s), 131.9 (s), 130.5 (s), 129.8 (d, 2x), 129.7 (d, 2x), 128.5 (d, 2x), 128.4 (d, 2x), 128.3 (d), 127.8 (d), 127.6 (d), 127.2 (d), 126.4 (d), 125.7 (d), 124.2 (d) ppm. **MS** (EI): *m*/*z* (%) 323 (M^+, 97), 322 (15), 306 (29), 305 (100), 304 (39), 280 (20), 279 (75), 278 (60), 277 (51), 276 (51), 228 (24), 227 (16), 214 (15), 203 (14), 202 (27), 201 (23). **HRMS** (EI): Calcd. for $C_{23}H_{17}NO$, 323.1310; found, 323.1322. **IR** (NaCl): υ 3325 (s, N-H), 3057 (s, C-H), 1647 (s, C=O) 1394 (s) cm^{-1}.

4-{[(5,8-Diphenyl-2-naphthalenyl)carbonyl]-3-fluorobenzoic Acid 10b. ***General procedure for the Cu-catalyzed amidation of aryliodides***. In a sealed tube were added 5,8-diphenyl-2-naphthamide **15** (0.03 g, 0.093 mmol), ethyl 3-fluoro-4-iodobenzoate **16b** (0.024 g, 0.08 mmol), (1*S*,2*S*)-cyclohexane-1,2-diamine (0.002 g, 0.016 mmol), K_2CO_3 (0.022 g, 0.16 mmol) and CuI (0.002 g, 0.0093 mmol) in dioxane (3 mL) and the mixture was stirred at 140 ºC for 17h. The mixture was filtered though Celite® and the residue was purified by column chromatography (85:15 hexane/EtOAc), to produce 0.034 g (75%) of **17b** as a white solid.

Following the general procedure for the hydrolysis of esters, the reaction of ethyl 4-{[(5,8-diphenyl-2-naphthalenyl)carbonyl]-3-fluorobenzoic **17b** (0.029 g, 0.06 mmol) and KOH (0.99 mL, 2M inH_2O, 1.98 mmol) in MeOH (5 mL) afforded, after purification by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH), 0.014 g (51%) of **10b** as a white solid. **m.p.:** 250 ºC (MeOH). **^{1}H-NMR** (400.13 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.54 (br s, 1H), 8.07 (d, *J* = 8.9 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.77 (br s, 1H), 7.8-7.7 (m, 2H), 7.6-7.5 (m, 12H) ppm. **^{13}C-NMR** (100.16 MHz, DMSO-d_6): δ 171.9 (s), 165.6 (s), 154.4 (s) ($^1J_{C\text{-}F}$ = 247.9 Hz), 140.3 (s), 139.5 (s), 139.4 (s), 139.1 (s), 132.6 (s), 131.3 (s), 130.4 (s), 129.9 (d, 2x), 129.7 (d, 2x), 128.6 (d, 2x), 128.5 (d, 2x), 128.3 (d), 127.7 (d), 127.6 (d), 127.4 (d), 126.9 (d), 126.1 (d), 125.5 (d), 125.2 (d), 125.1 (d), 124.4 (d), 116.2 (s), 116.0 (s) ppm. **HRMS** (ESI^+): Calcd. for $C_{30}H_{21}FNO_3$, 462.1427; found, 462.1503. **IR** (NaCl): υ 3600-3000 (br, O-H), 3055 (w, C-H), 2956 (w, C-H), 2924 (w, C-H), 2867 (w, C-H), 1682 (s, C=O), 1617 (s, C=O) cm^{-1}. **Purity:** 92% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 25 min).

4-{[(5,8-Diphenyl-2-naphthalenyl)carbonyl]benzoic Acid 10a. Following the general procedure, the reaction of 5,8-diphenyl-2-naphthamide **15** (0.03 g, 0.093 mmol), ethyl 4-iodobenzoate **16a** (0.025 mL, 0.08 mmol), (1*S*,2*S*)-cyclohexane-1,2-diamine (0.002 g, 0.016 mmol), K_2CO_3 (0.022 g, 0.16 mmol) and CuI (0.002 g, 0.0093 mmol) in dioxane (3 mL) afforded, after purification by column chromatography (silica gel, 90:10 hexane/EtOAc), 0.031 g (74%) of **17a** as a white solid.

Following the general procedure for the hydrolysis of esters, the reaction of ethyl 4-{[(5,8-diphenyl-2-naphthalenyl)carbonyl]benzoate **17a** (0.023 g, 0.05 mmol) and KOH (0.83 mL, 2M in H_2O, 1.65 mmol) in MeOH (4

mL) afforded, after purification by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH), 0.016 g (72%) of **10a** as a white solid. **m.p.:** 183 ºC (MeOH). **^{1}H-NMR** (400.13 MHz, CD_3OD): δ 8.57 (d, *J* = 1.6 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.92 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.6-7.4 (m, 12H) ppm. **^{13}C-NMR** (100.16 MHz, CD_3OD): δ 170.2 (s), 169.2 (s), 144.5 (s), 142.2 (s), 141.6 (s), 141.5 (s), 141.3 (s), 134.8 (s), 133.4 (s), 132.6 (s), 131.7 (d), 131.3 (d, 2x), 131.2 (s), 131.1 (d, 2x), 129.7 (d, 2x), 129.6 (d, 2x), 129.5 (d), 129.4 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.3 (d), 127.9 (d), 124.9 (d), 121.1 (d, 2x) ppm. **HRMS** (ESI^+): Calcd. for $C_{30}H_{22}NO_3$, 444.1521; found 444.1597. **IR** (NaCl): υ 3600-3000 (br, O-H), 3288 (s, N-H), 3055 (w, C-H), 3019 (w, C-H), 2926 (w, C-H), 2855 (w, C-H), 1685 (s, C=O), 1651 (s, C=O), 1603 (s, C=C) cm^{-1}. **Purity:** 93% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 24 min).

3-Chloro-4-{[(5,8-Diphenyl-2-naphthalenyl)carbonyl]benzoic Acid 10c. Following the general procedure, the reaction of 5,8-diphenyl-2-naphthamide **15** (0.03 g, 0.093 mmol), ethyl 3-chloro-4-iodobenzoate **16c** (0.029 g, 0.093 mmol), (1*S*,2*S*)-cyclohexane-1,2-diamine (0.002 g, 0.019 mmol), K_2CO_3 (0.026 g, 0.19 mmol) and CuI (0.002 g, 0.0093 mmol) in dioxane (3 mL) afforded, after purification by column chromatography (silica gel, 95:5 hexane/EtOAc), 0.03 g (64%) of **17c** as a white solid.

Following the general procedure for the hydrolysis of esters, the reaction of ethyl 3-chloro-4-{[(5,8-diphenyl-2-naphthalenyl)carbonyl]benzoic **17c** (0.017 g, 0.034 mmol) and KOH (0.56 mL, 2M in H_2O, 1.12 mmol) in MeOH (4 mL) afforded, after purification by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH), 0.007 g (43%) of **10c** as a white solid. **m.p:** 210 ºC (MeOH). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.03 (s, 2H), 7.6-7.5 (m, 15H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 171.7 (s), 171.6 (s), 141.5 (s), 141.1 (s), 140.1 (s), 139.9 (s), 139.8 (s), 139.7 (s), 134.5 (s), 131.1 (s), 130.6 (d), 130.2 (d), 130.1 (d, 2x), 130.0 (d, 2x), 129.1 (d), 128.8 (d), 128.7 (s), 128.6 (d, 2x), 128.5 (d), 128.4 (d, 2x), 127.7 (d), 127.6 (d), 127.3 (d), 126.9 (d), 126.4 (s), 125.3 (d) ppm. **HRMS** (ESI): Calcd. for $C_{30}H_{21}{}^{35}ClNO_3$, 478.1208; found 478.1205. **IR** (NaCl): υ 3600-3000 (br, O-H), 3362 (w, N-H), 3057 (w, C-H), 3021 (w, C-H), 2925 (w, C-H), 2854 (w, C-H), 2643 (m), 2552 (m), 1687 (s, C=O) cm^{-1}. **Purity:** 96% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 25 min).

5,8-Diphenyl-2-naphthaldehyde 19. To a solution of methyl 5,8-diphenyl-2-naphthoate **13** (0.24 gr, 0.71 mmol) in THF (10 mL) at -78 °C was added Dibal-H (2.13 mL, 1M solution in THF, 2.13 mmol) and the reaction was stirred for at 0 °C for 4 hours. An aqueous solution of HCl (10 % aq) was added to the reaction mixture and extracted with AcOEt (3x), the combined organic phase was dried with Na_2SO_4 and the solvet was evaporated. The crude was purified by column chromatography (silicagel, 80:20 hexane/EtOAc) to afford 0.18 g (78 %) of **18** as a white solid.

A solution of 5,8-diphenyl-2-naphthalenemethanol **18** (0.18 g, 0.55 mmol) in CH_2Cl_2 (13 mL) was treated with MnO_2 (0.87 g, 10.0 mmol) at 0 °C for 3 hours. After filtration with Celite® and evaporation of the solvent the residue was purified by column chromatography (silica gel, 95:5 hexane/AcOEt) to afford 0.14 g (84%) of **19** as a white solid. **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.49 (s, 1H), 8.09 (d, *J*= 8.8 Hz, 1H), 7.93 (d, *J*= 8.9 Hz, 1H), 7.8-7.4 (m, 12H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 192.5 (d), 141.5 (s), 140.1 (s), 140.0 (s), 139.8 (s), 134.9 (s), 133.9 (d), 133.6 (d), 131.4 (s), 130.1 (d, 2x), 130.1 (d, 2x), 129.6 (d), 128.7 (d. 2x), 128.5 (d, 2x), 128.5 (s), 127.9 (d), 127.2 (d),

127.6 (d), 122.4 (d) ppm. **HRMS** (ESI): Calcd. for $C_{23}H_{17}O$, 309.1274; found 309.1273. **IR** (NaCl): υ 3055 (m), 3025 (m), 2815 (w), 1697 (s, C=O) cm^{-1}.

(*E*)-4-[(5,8-(diphenyl)-naphthalene-2-yl)-ethenyl]-benzoic Acid 11a. ***General procedure for the Horner-Wadsworth-Emmons reaction.*** To a cooled solution of methyl 4-(diethoxyphosphoryl)benzoate **20a** (0.19 g, 0.68 mmol) at 0 ºC in THF (5 mL) were added DMPU (1.5 mL) and *n*-BuLi (0.49 mL, 1.43 M in hexane, 0.68 mmol), and the mixture was stirred for 30 min. The reaction was cooled down to -78 ºC, a solution of 5,8-(diphenyl)-2-naphthaldehyde **19** (0.1 g, 0.32 mmol) in THF (5 mL) was added, and the mixture was stirred at 25 ºC for 12h. A saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with H_2O (3x) and brine (3x), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 95:5 hexane/EtOAc) to afford 0.094 g (67%) of **21a** as a white solid.

Following the general procedure for the hydrolysis of esters, the reaction of methyl (*E*)-4-[2-(5,8-(diphenyl)naphthalen-2-yl]-ethenyl]-benzoate **21a** (0.080 g, 0.18 mmol) and KOH (3 mL, 2M in H_2O, 5.94 mmol) in MeOH (18 mL) afforded, after purification by column chromatography (silica gel, 90:10 CH_2Cl_2/MeOH), 0.068 g (89%) of **11a** as a white solid. **^{1}H-NMR** (400.13 MHz, DMSO): δ 7.97-7.90 (m, 4H), 7.75-7.65 (m, 2H), 7.60-7.50 (m, 14H), 7.36 (d, *J*= 16.1 Hz, 1H) ppm. **^{13}C-NMR** (100.16 MHz, DMSO): δ 167.5 (s), 141.7 (s), 140.3 (s, 2x), 139.9 (s), 139.7 (s), 134.9 (s), 131.9 (s), 131.5 (d), 131.4 (s), 130.3 (d, 2x), 130.2 (d, 3x), 130.1 (d, 2x), 130.0 (s), 129.1 (d, 2x), 129.0 (d, 2x), 128.7 (d), 128.1 (d), 127.7 (d), 127.3 (d), 127.1 (d), 126.9 (d), 126.5 (d), 123.6 (d) ppm. **MS** (EI): m/z 426.2 (100), 425.2 (3), 303.1 (12), 302.1 (11), 289.1 (12). **HRMS** (EI): Calcd. for $C_{31}H_{22}O2$, 426.1620; found 426.1616. **IR** (NaCl): υ 3600-3000 (br, O-H), 2539 (w, C-H), 2164 (w, C-H), 1684 (s, C=O), 1603 (s, C=C) cm^- cm^{-1}. **Purity:** 94% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 14.99 min).

(*E*)-3-Fluoro-4-[(5,8-(diphenyl)-naphthalene-2-yl)-ethenyl]-benzoic Acid 11b. Following the general procedure for the Horner-Wadsworth-Emmons reaction, the reaction of methyl 3-fluor-4-(diethoxyphosphoryl)benzoate **20b** (0.19 g, 0.64 mmol) with DMPU (1.5 mL), *n*-BuLi (0.49 mL, 1.43 M in hexane, 0.68 mmol) and 5,8-(diphenyl)-2-naphthaldehyde **19** (0.1 g, 0.32 mmol) in THF (10 mL) afforded, after purification by column chromatography (silica gel, 95:5 hexane/EtOAc), 0.10 g (70%) of **21b** as a white solid.

Following the general procedure for the hydrolysis of esters, the reaction of methyl (*E*)-3-fluoro-4-[2-(5,8-(diphenyl)naphthalen-2-yl]-ethenyl]-benzoate **21b** (0.05 g, 0.10 mmol) and KOH (3 mL, 2M in H_2O, 3.3 mmol) in MeOH (10 mL) afforded, after purification by column chromatography (silica gel, 90:10 CH_2Cl_2/MeOH), 0.038 g (87%) of **11b** as a white solid. **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.05-7.9 (m, 3H), 7.91 (d, *J* = 9.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.70-7.50 (m, 14H), 7.38 (d, *J* = 16.4 Hz, 1H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 166.5 (s), 159.6 (s, $^1J_{C-F}$ = 248.8 Hz), 140.3 (s), 140.0 (s), 139.7 (s), 134.6 (s), 133.9 (s), 133.7 (s), 131.9 (s, $^3J_{C-F}$ = 7.4 Hz), 131.6 (s), 130.4 (d, 2x), 130.3 (d, 3x), 129.3 (s), 129.1 (d, 2x), 129.0 (d, 2x), 128.1 (d), 127.8 (d, $^3J_{C-F}$ = 3.6 Hz), 127.9 (d), 127.5 (d), 127.1 (d), 126.8 (d), 125.8 (d, $^4J_{C-F}$ = 2.5 Hz), 123.6 (d), 120.1 (d), 116.7 (d, $^2J_{C-F}$ = 23.5 Hz) ppm. **MS** (EI): m/z 445.2 (22), 444.2 (100), 400.2 (17). **HRMS** (EI): Calcd. for C31H21FO2, 444.1526; found 444.1519. **IR** (NaCl): υ 3400-3200 (br, O-H), 2968 (w,

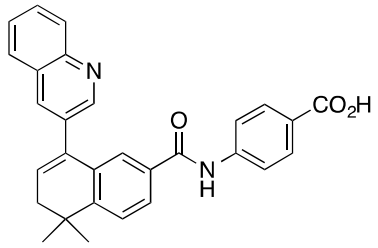
C-H), 2924 (w, C-H), 1685 (s, C=O) cm^{-1}. **Purity:** 98% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 14.9 min).

(*E*)-3-Bromo-4-[(5,8-(diphenyl)-naphthalene-2-yl)-ethenyl]-benzoic Acid 11d. Following the general procedure for the Horner-Wadsworth-Emmons reaction, the reaction of methyl 3-bromo-4-(diethoxyphosphoryl)benzoate **20d** (0.23 g, 0.64 mmol) with DMPU (1.5 mL), *n*-BuLi (0.49 mL, 1.43 M in hexane, 0.68 mmol) and 5,8-(diphenyl)-2-naphthaldehyde **19** (0.1 g, 0.32 mmol) in THF (10 mL) afforded, after purification by column chromatography (silica gel, 95:5 hexane/EtOAc), 0.12 g (73%) of **21d** as a white solid.

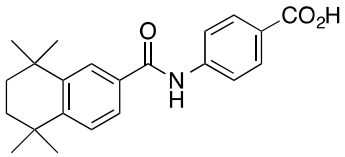
Following the general procedure for the hydrolysis of esters, the reaction of methyl (*E*)-3-bromo-4-[2-(5,8-(diphenyl)naphthalen-2-yl]-ethenyl]-benzoate **21d** (0.060 g, 0.11 mmol) and KOH (3 mL, 2M in H_2O, 3.3 mmol) in MeOH (10 mL) afforded, after purification by column chromatography (silica gel, 90:10 CH_2Cl_2/MeOH), 0.045 g (81%) of **11d** as a white solid. **^{1}H-NMR** (400.13 MHz, DMSO): δ 8.11-8.05 (m, 3H), 7.94 (s app, 2H), 7.88 (d, J = 8.2 Hz, 1H), 7.63-7.42 (m, 14H) ppm. **^{13}C-NMR** (100.16 MHz, DMSO): δ 166.5 (s), 140.6 (s), 140.2 (s, 2x), 140.1 (s), 139.7 (s), 134.6 (d), 134.5 (s), 134.0 (s), 131.9 (d), 131.6 (d), 130.4 (d, 2x), 130.3 (d, 2x), 129.1 (d, 2x), 129.1 (d, 3x), 129.0 (s), 128.1 (d, 2x), 127.8 (d), 127.6 (d, 2x), 127.2 (d), 126.9 (d), 126.6 (d), 123.7 (d), 123.4 (s) ppm. **MS** (EI): *m/z* 506.1 (47), 504.1 (47), 462.1 (32), 427.2 (33), 426.2 (100), 424.1 (23), 380.2 (44), 303.1 (50), 302.1 (52). **HRMS** (EI): Calcd. for $C_{31}H_{21}{}^{79}BrO_2$, 504.0725; found 504.0742. Calcd. for $C_{31}H_{21}{}^{81}BrO_2$, 506.0704; found 506.0724. **IR** (NaCl): υ 3500-3200 (br, O-H), 2966 (w, C-H), 2923 (w, C-H), 2853 (w, C-H), 1685 (s, C=O) cm^{-1} **Purity:** 92% (HPLC-UV, Sunfire C18, 1 mL/min, 95:5 CH_3CN/H_2O, t_R = 18.1 min).

Molecular Modeling

AMBER force field[2] parameters (parm99) were assigned to, or consistently derived for,[3,4] ligands atoms, and atom-centered B3LYP/6-31G* charges were calculated using the Gaussian 98 program[5] and the RESP methodology.[6] Both complexes of the LBD of RARα-BMS614 (PDB code: 1dkf) and RARα-**11a** were energy refined using the second generation AMBER force field[2] and 3000 steps of steepest descent energy minimization and 6000 steps of conjugate gradient of only sidechain of the protein and those atoms belonging to the bound ligand. This procedure allowed readjustment of covalent bonds and van der Waals contacts without changing the overall conformation of the complex. See Figure S1.



(BMS614)



(Am580)

The molecular systems were neutralized by addition of the appropriate number of sodium ions, placed in positions of negative electrostatic potential and immersed in a rectangular box of ~8100 transferable intermolecular potential three-point model water molecules. Each water box extended 8 Å away from any solute atom, and the cutoff distance for the nonbonded interactions was 9 Å. Periodic boundary conditions were used, and electrostatic interactions were represented using the smooth particle mesh Ewald method with a grid spacing of ~1 Å. Unrestrained molecular dynamics (MD) simulations at 300 K and 1 atm were then run for 6 ns using the SANDER module in AMBER 8.[7] The coupling for the temperature and pressure baths was 1.0 and 0.2 ps, respectively. SHAKE was applied to all bonds involving hydrogens, and an integration step of 2 fs was used throughout. The nonbonded pair list was updated every 10 steps. The simulation protocol involving a series of progressive energy minimizations followed by a 20 ps heating phase and a 70 ps equilibration period before data collection. System coordinates were saved every 2 ps for further analysis.

A structural comparison between the complexes of human RARα LBD in complex with antagonist BMS614 (PDB code: 1dkf) and with agonist Am580 and compound **11a** is shown in Figure S1.

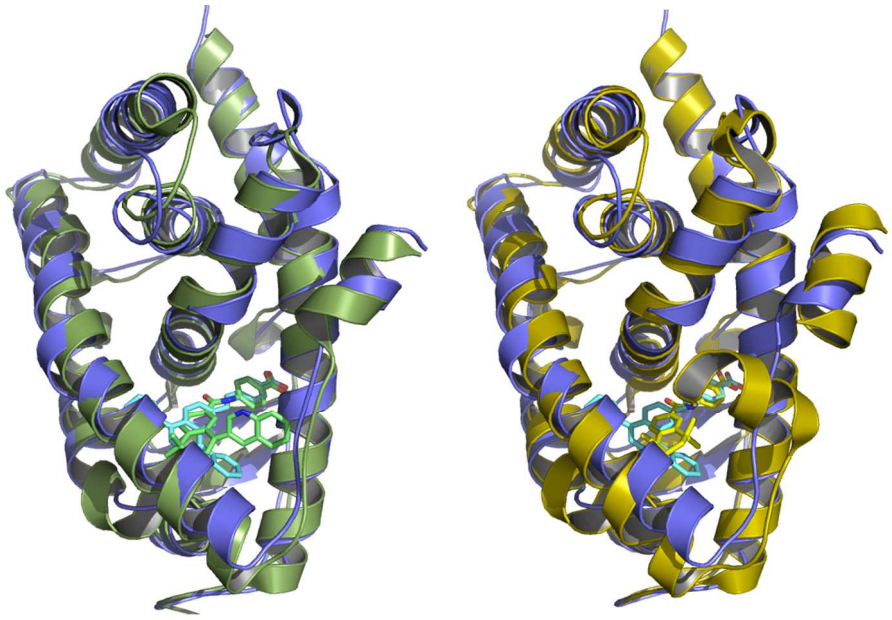


Figure S1*: Left: Superposition of human RAR□□LBD in complex with BMS614* (PDB code: 1dkf) *and ligand* ***11a*** *(green and blue, respectively). Right: Superposition of human RAR□□LBD in complex with Am580* (PDB code: 3kmr) *and ligand* ***11a*** *(yellow and blue, respectively).*

Molecular Dynamics and Energy Analysis of the LBD RARα·11a complex.

To assess the feasibility of the proposed binding orientation and to study the mutual adaptation between RARα□LBD and the ligand, the complex was refined using energy minimization and its dynamic behavior was simulated using unrestrained MD. After the equilibration period, the progression of the root-mean-square deviations (rmsd) of the coordinates of the Cα atoms with respect to the initial structure showed a notably stable behavior reflecting that the overall architecture of the protein was preserved for the whole length of the simulation. When were monitored by measuring the evolution of the rms deviation (rmsd) of **11a** with respect to the initial structure, it can be clearly seen that the rmsd value was maintained around 0.5 Å. (Figure S2)

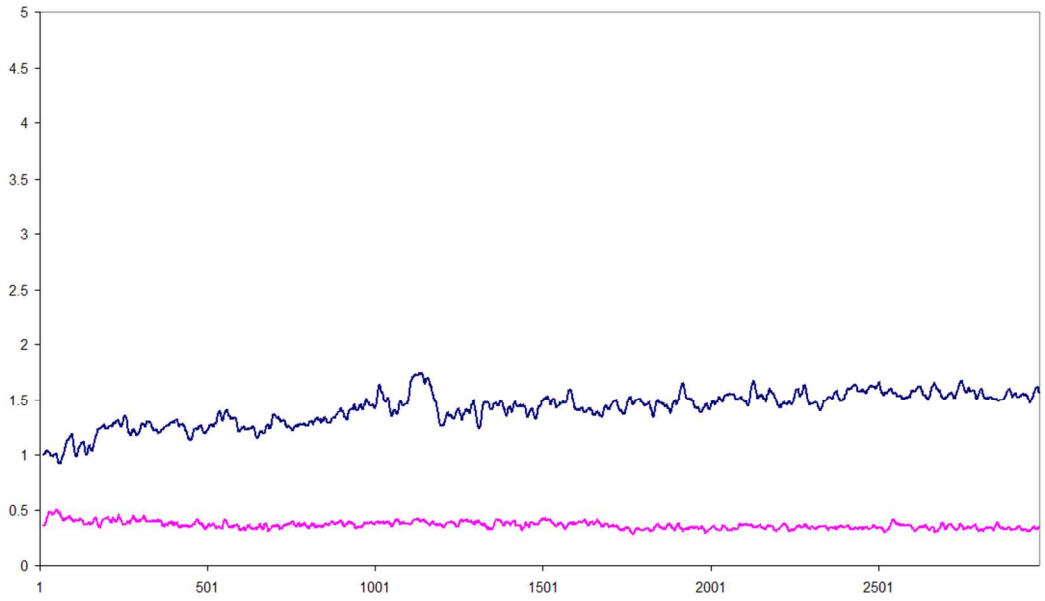
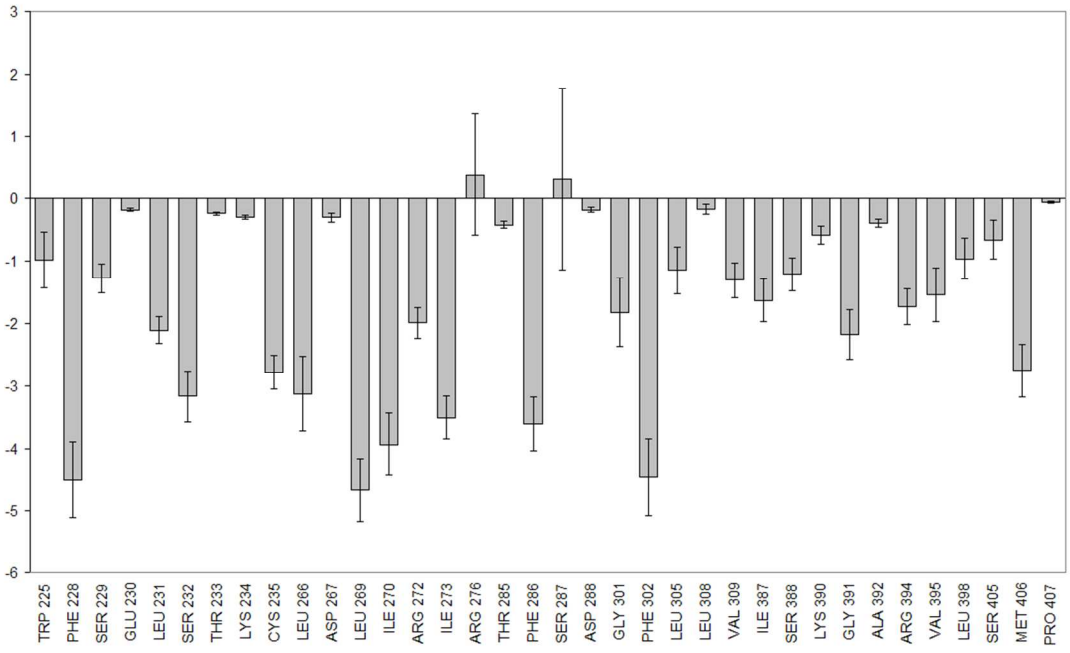


Figure S2*: Evolution of the root-mean-square deviations (rmsd) of the Cα atoms of human RAR□□LBD in complex with* ***11a*** *and rmsd of the retinoid atoms with respect to the initial structure (magenta and blue respectively).*

The binding mode of the ligand can be appreciated when the trajectories were analyzed in terms of intermolecular energy components (Figure S3). There were four consistently favorable and large van der Waals interactions with Phe228, Leu269, Ile 270, Ile 273, Phe 286 and Phe 302. On the other hand, the favorable electrostatic interactions were with Lys 234, Arg272 and Arg 276 whereas the unfavorable were with Glu230, Asp 267 and Asp288.

(A)



(B)

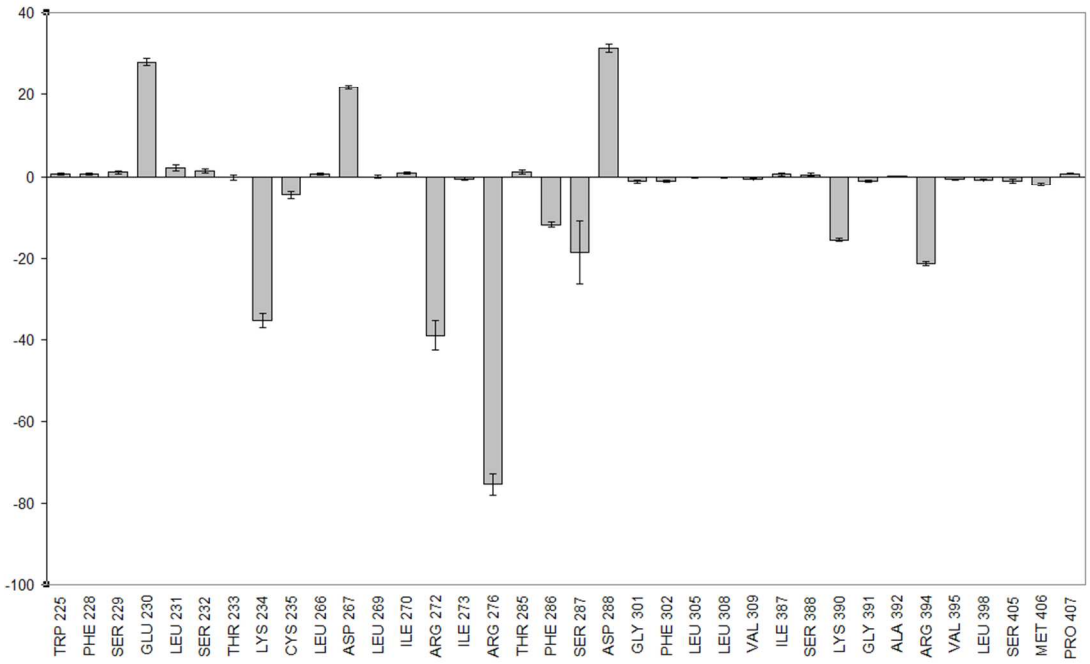


Figure S3*: Residue-based van der Waals (A) and electrostatic (B) contributions (kcal mol-1) to the binding of* ***11a*** *to LBD of human RAR*.

Figure S4 depicts one of the docking poses of compound **11a** in the LBP of RXR superimposed to the crystal structure of RXR bound to 9-*cis*-retinoic acid (PDB code: 1fby).

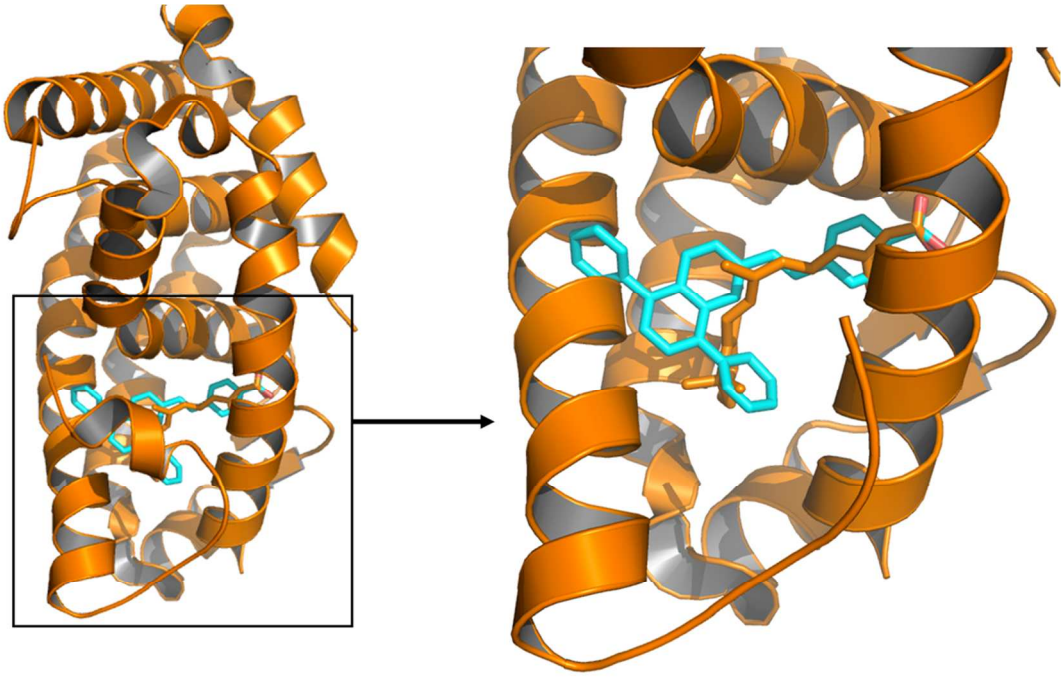


Figure S4*: Superposition of the complexes of 9-cis-retinoic acid (crystal structure) and compound* ***11a*** *docked in the RXR LBP (left) and close view after removing H12 to facilitate viewing (right).*

Determination of RAR and RXR agonistic and antagonistic activity of ligands.

HeLa reporter cells were stably transfected with an $(17m)_5$-βG-Luc-Neo reporter and with Gal4-mRARα (resp. β, γ) or Gal4-hRXRβ plasmids. They were maintained in DMEM that contained 5% fetal calf serum (FCS), supplemented with geneticin G418 (0.8 mg mL^{-1}), puromycin (0.3 μg mL^{-1}), hygromycin (0.2 mg mL^{-1}; added additionally only for the Gal4-hRXRβ-engineered HeLa cell line), and gentamycin (40 μg mL^{-1}). The assays were performed in DMEM without red phenol with 5% charcoal-treated FCS. To determine the RARα, RARβ, and RARγ induction potential of the ligands, equal aliquots (160,000 cells/well) of the corresponding cell line were seeded in a 24-well plate, and 12 h later the medium was replaced by a solution of the corresponding ligand in medium. The cells were incubated at 37 ºC in 5% CO_2 for 12 h. After that, the cells were washed (PBS) and lysed (50 μL of lysis buffer: 25 mM Tris phosphate (pH 7.8), 2 mM EDTA, 1 mM DTT, 10% glycerol, and 1% Triton X-100) for 15 minutes. Equal aliquots (50 μL) of the cell lysates were transferred in an Optiplate-96, and the luminescence in RLU (relative luminescence units) was determined on a MicroLumat LB96P luminometer ("Berthold") after automatic injection of 50 μL of luciferin buffer (20 mM Tris phosphate (pH 7.8), 1.07 mM $MgCl_2$, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT, 0.53 mM ATP, 0.47 mM luciferin, and 0.27 mM coenzyme A). The receptor activation potential of each compound was presented as fold induction measured as ratio of RLU of the compound over the RLU of the vehicle control.

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(7) http://amber.scripps.edu/doc8, U. AMBER8.

Spectroscopic data

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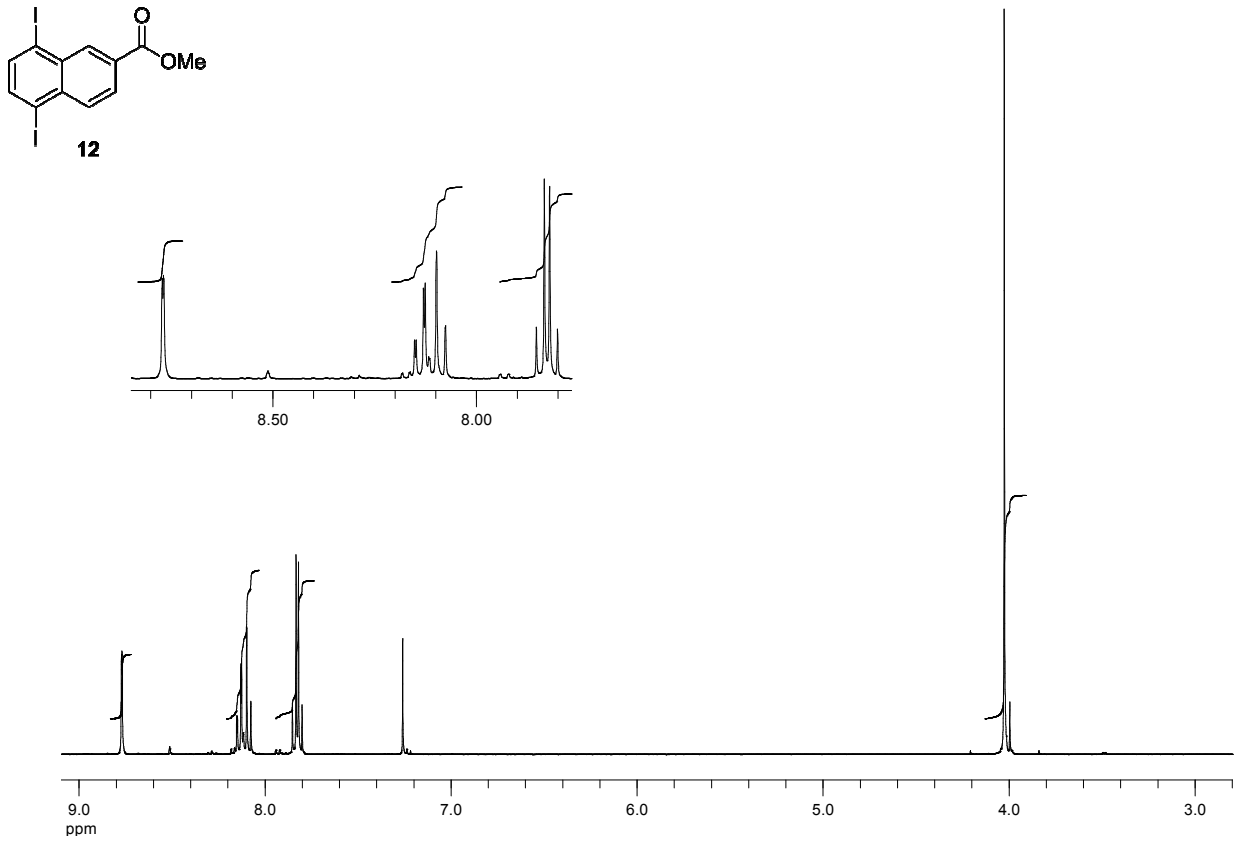

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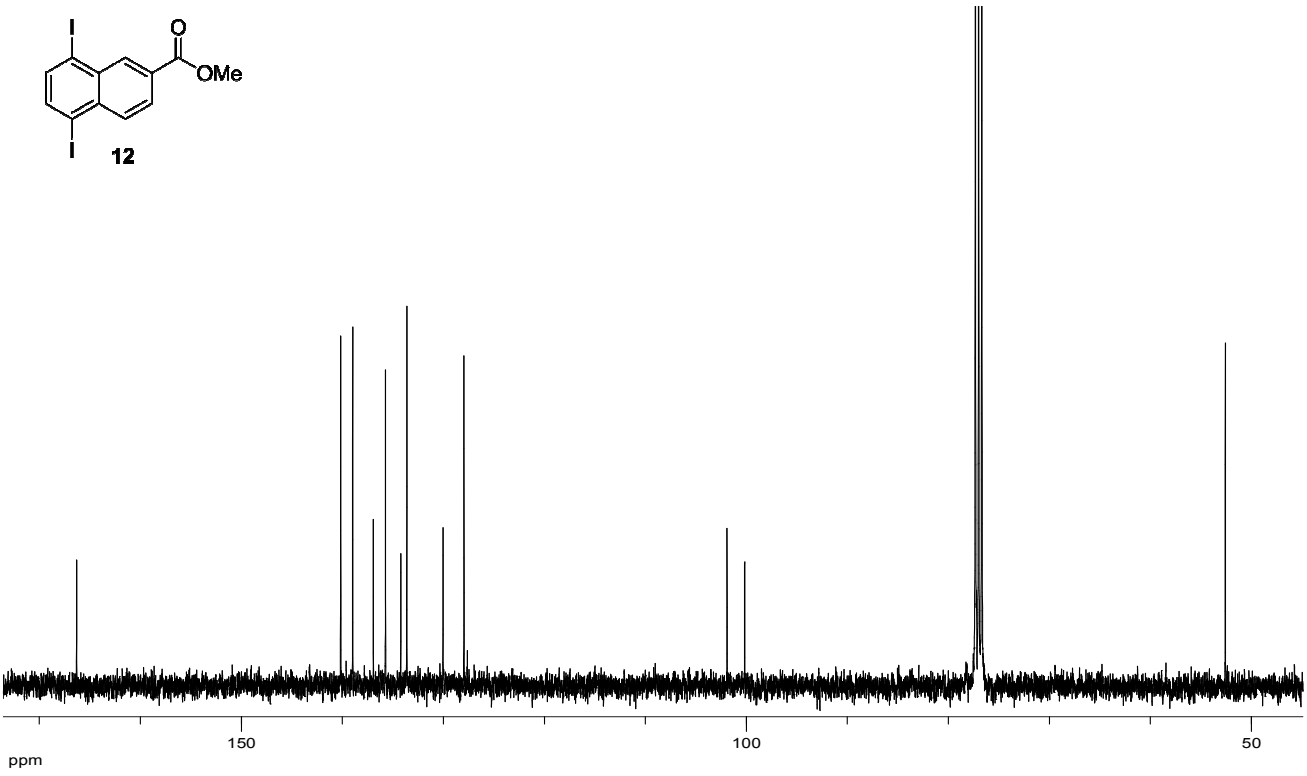

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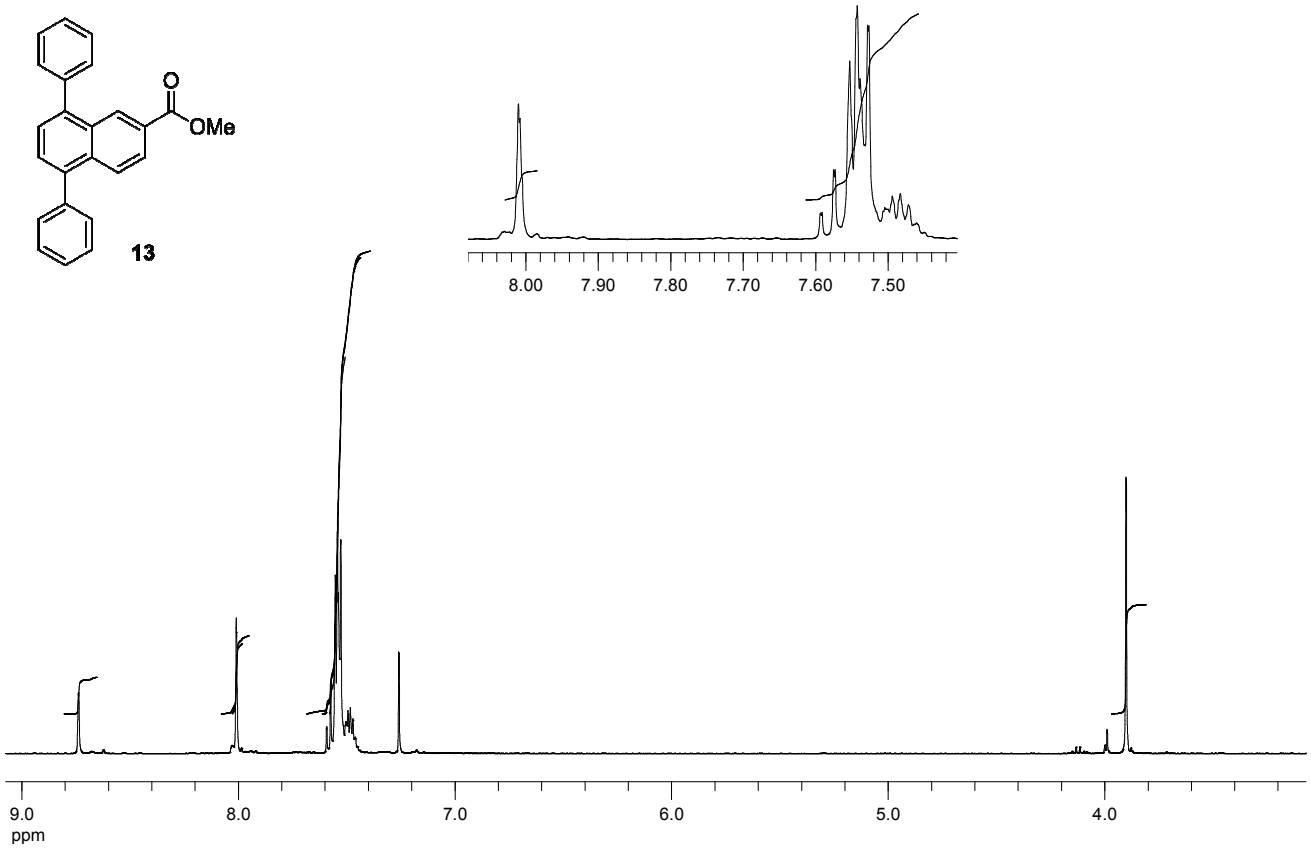

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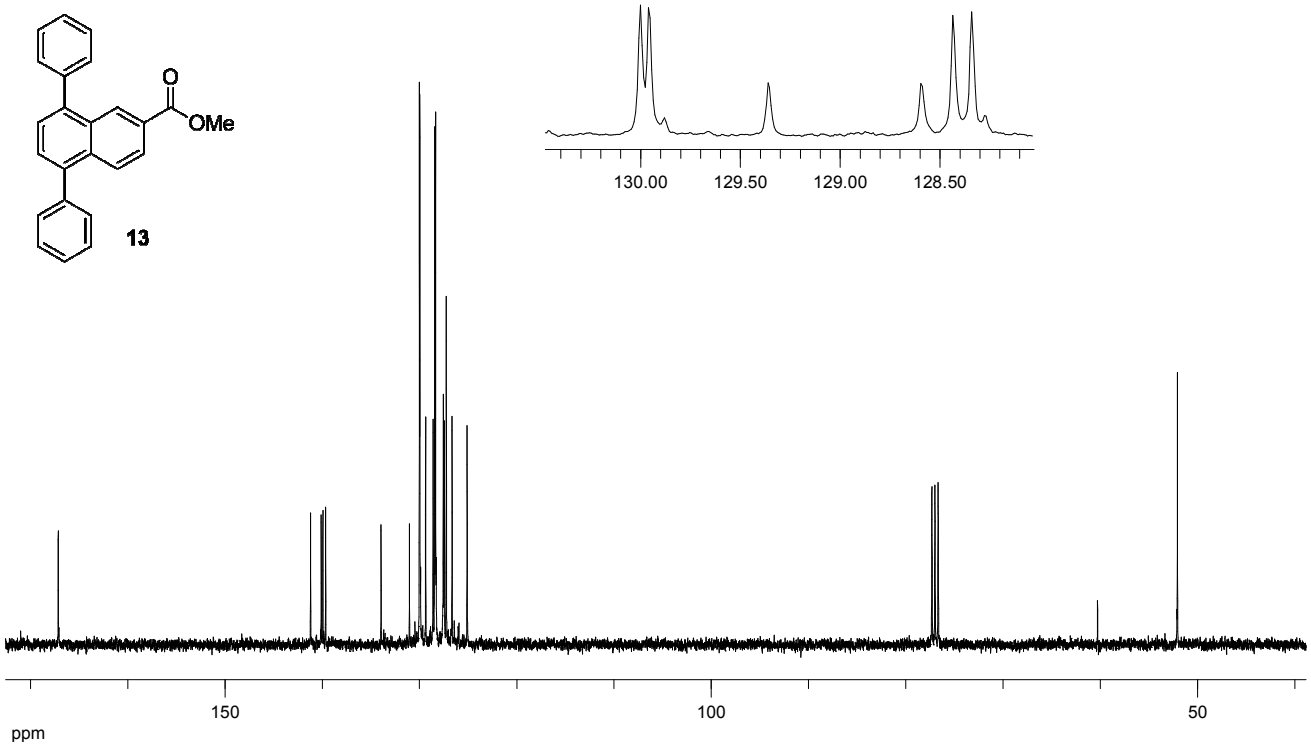

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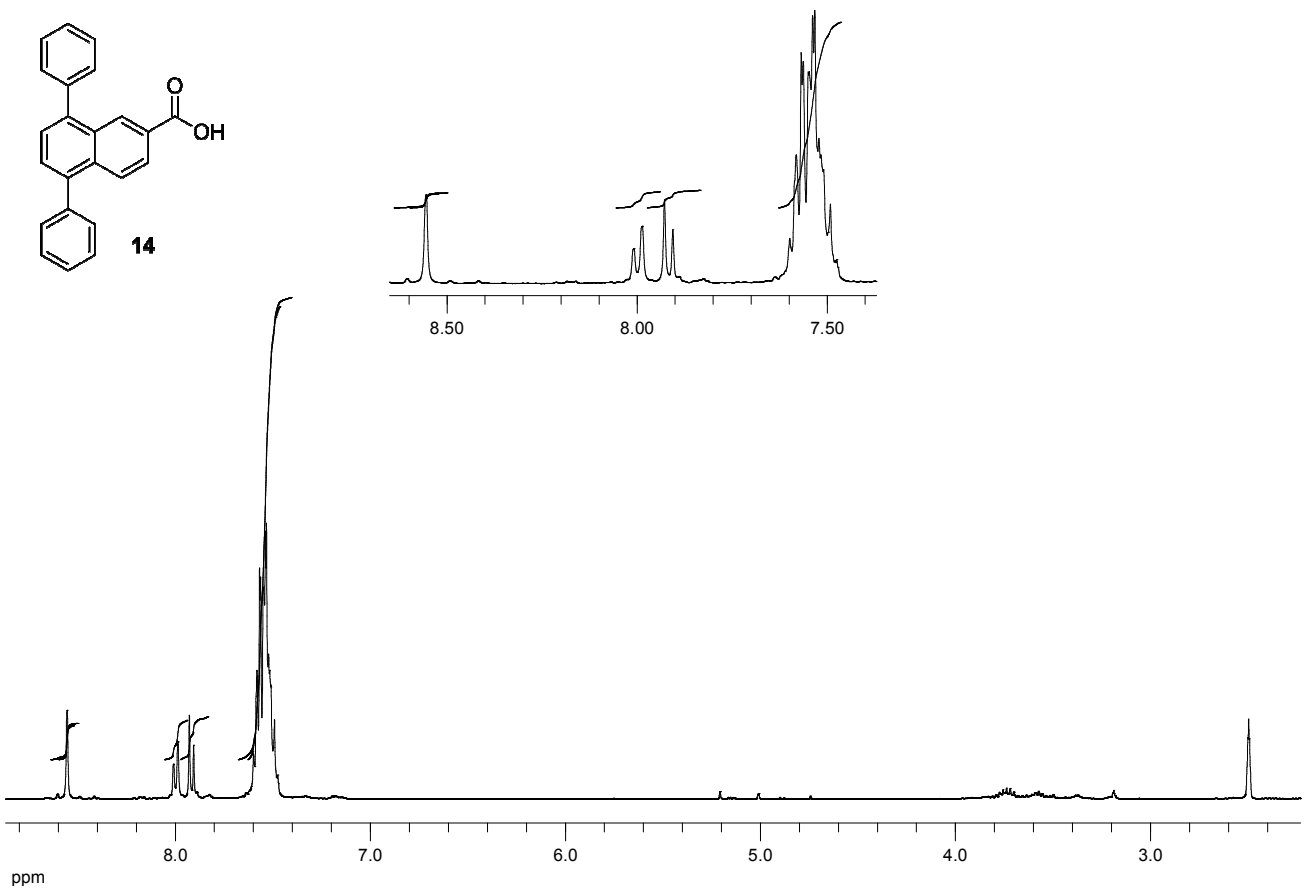

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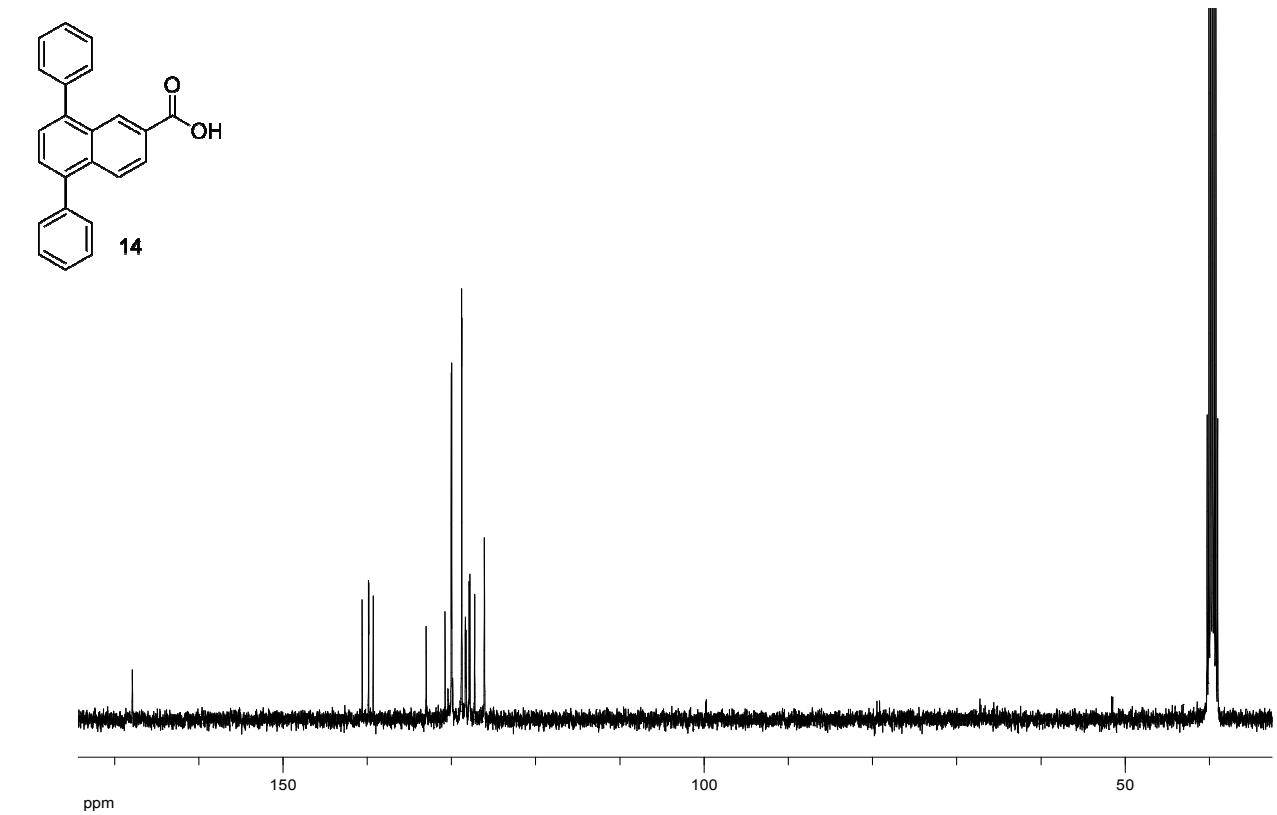

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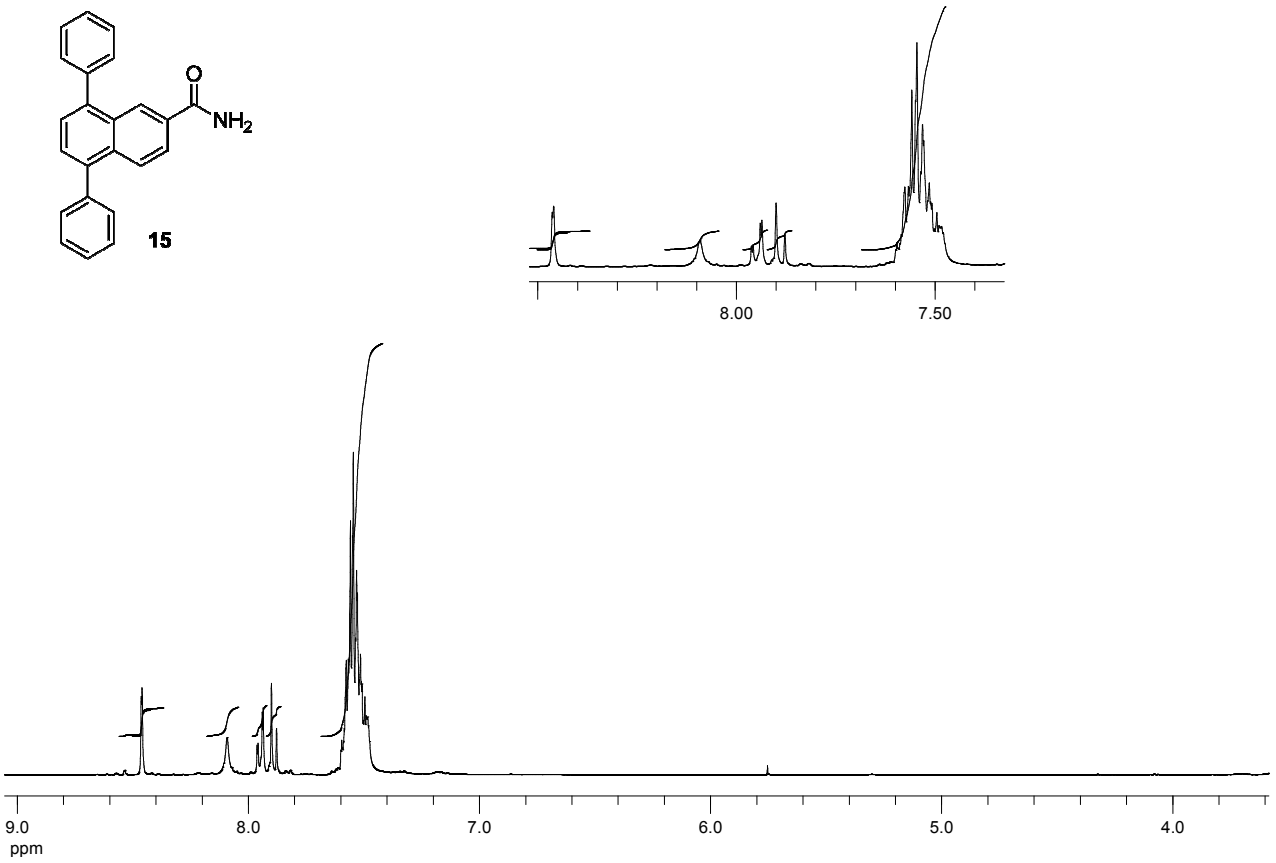

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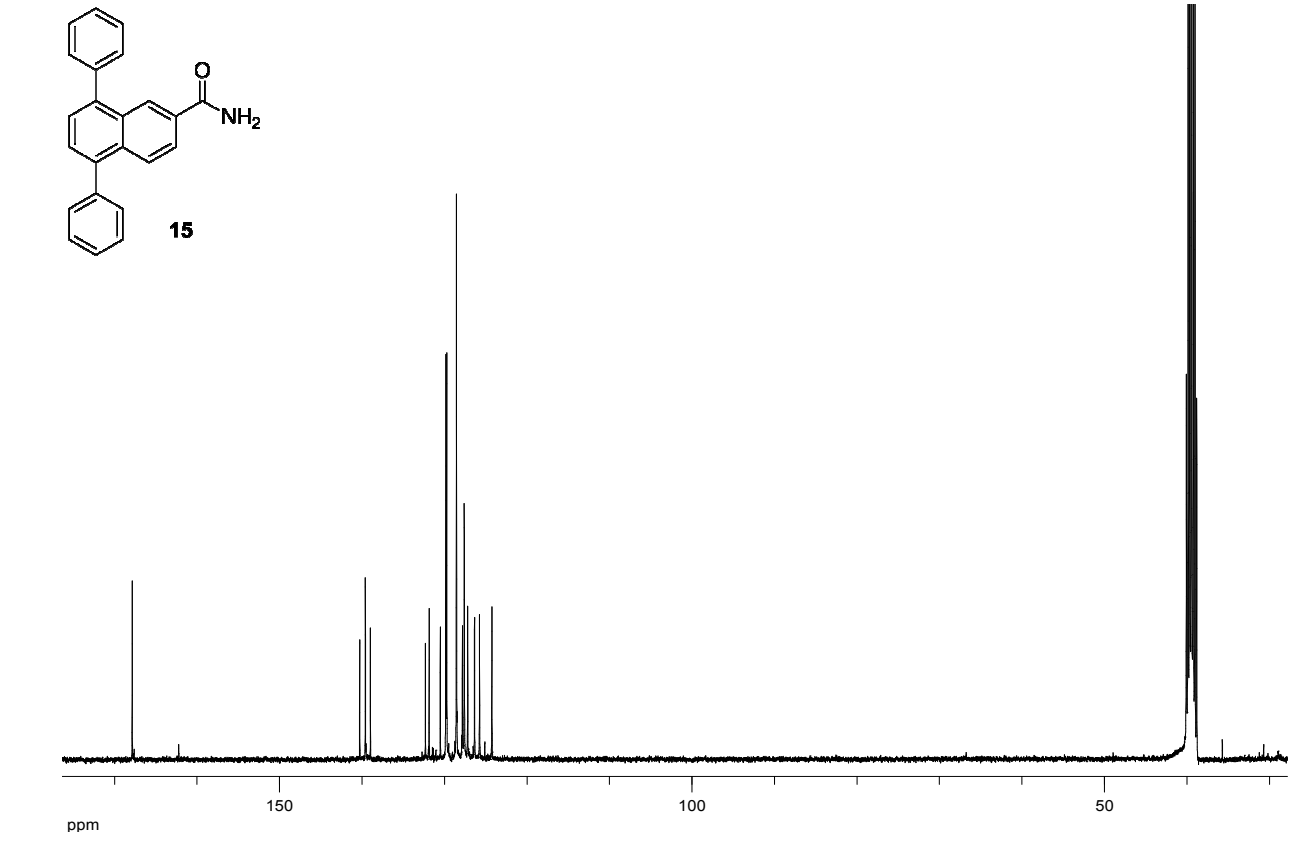

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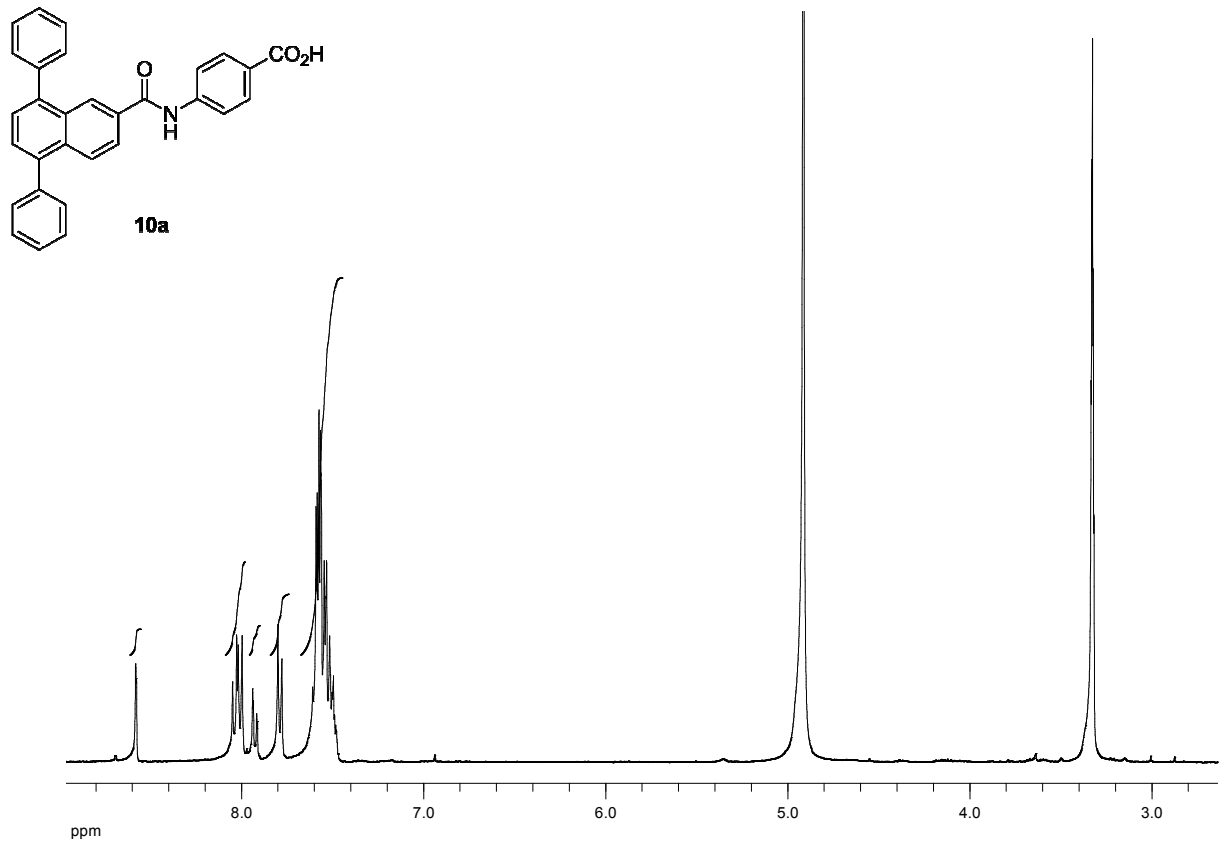

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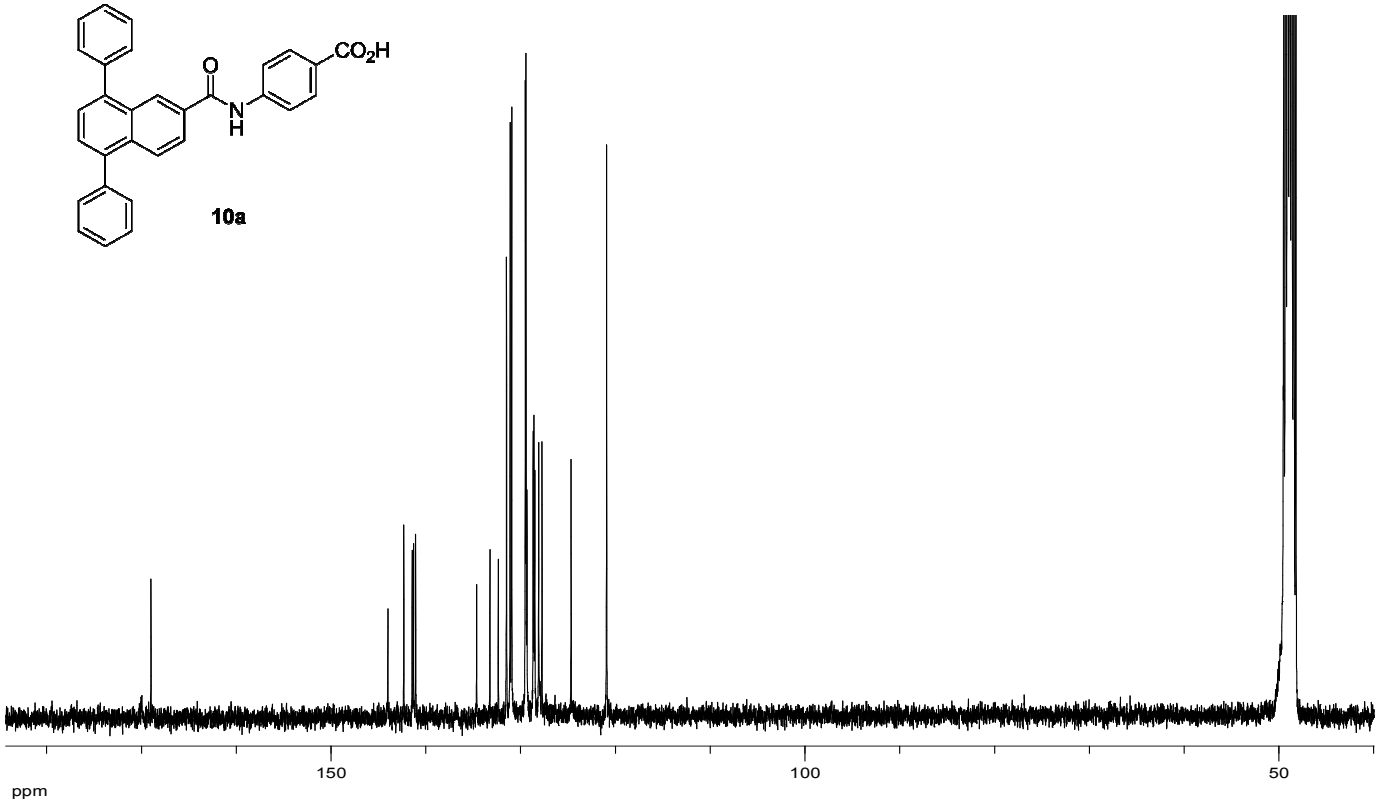

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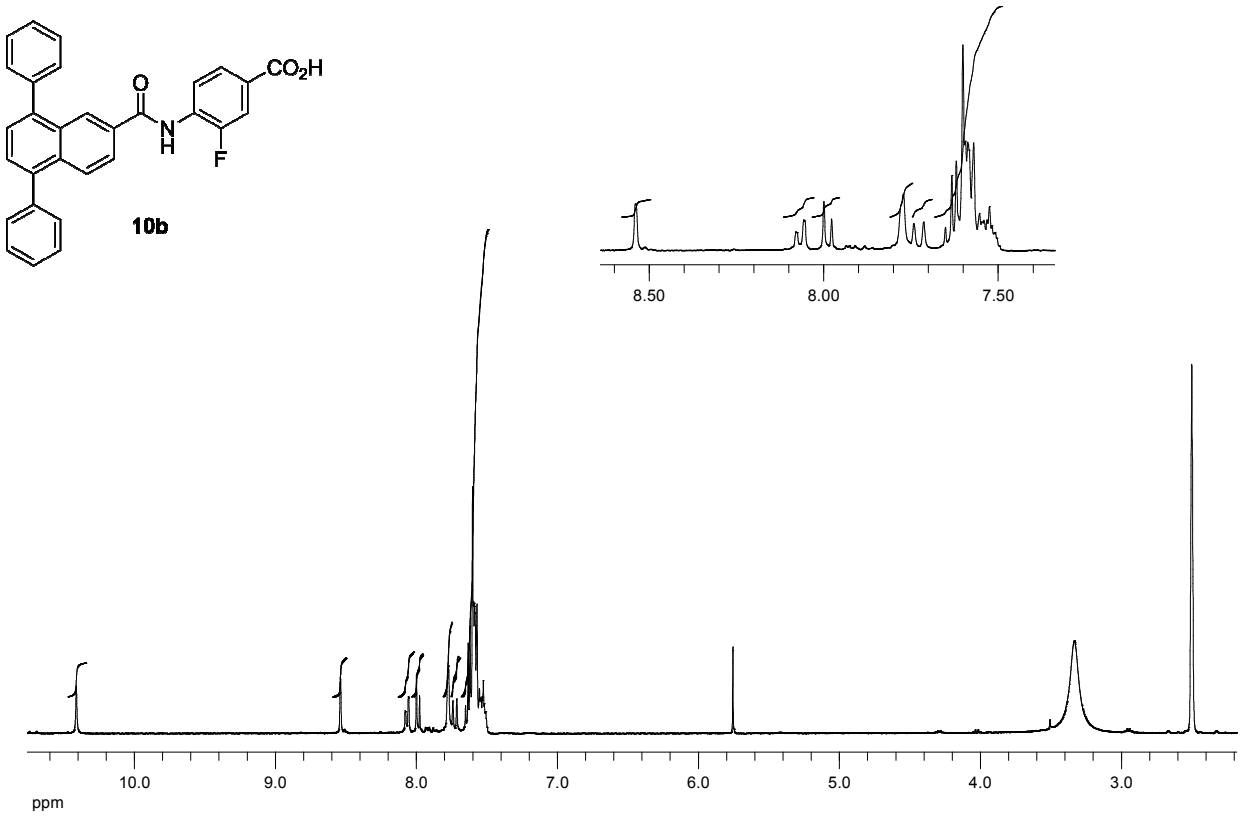

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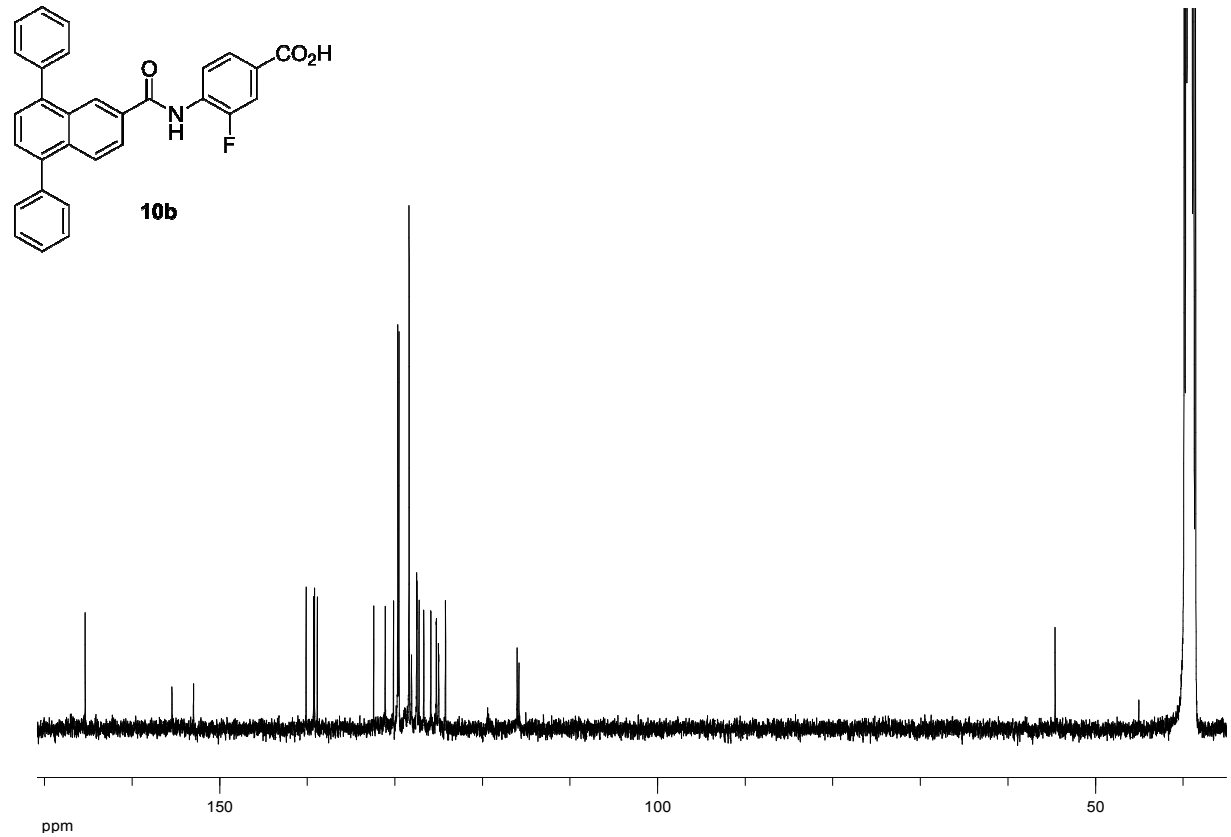

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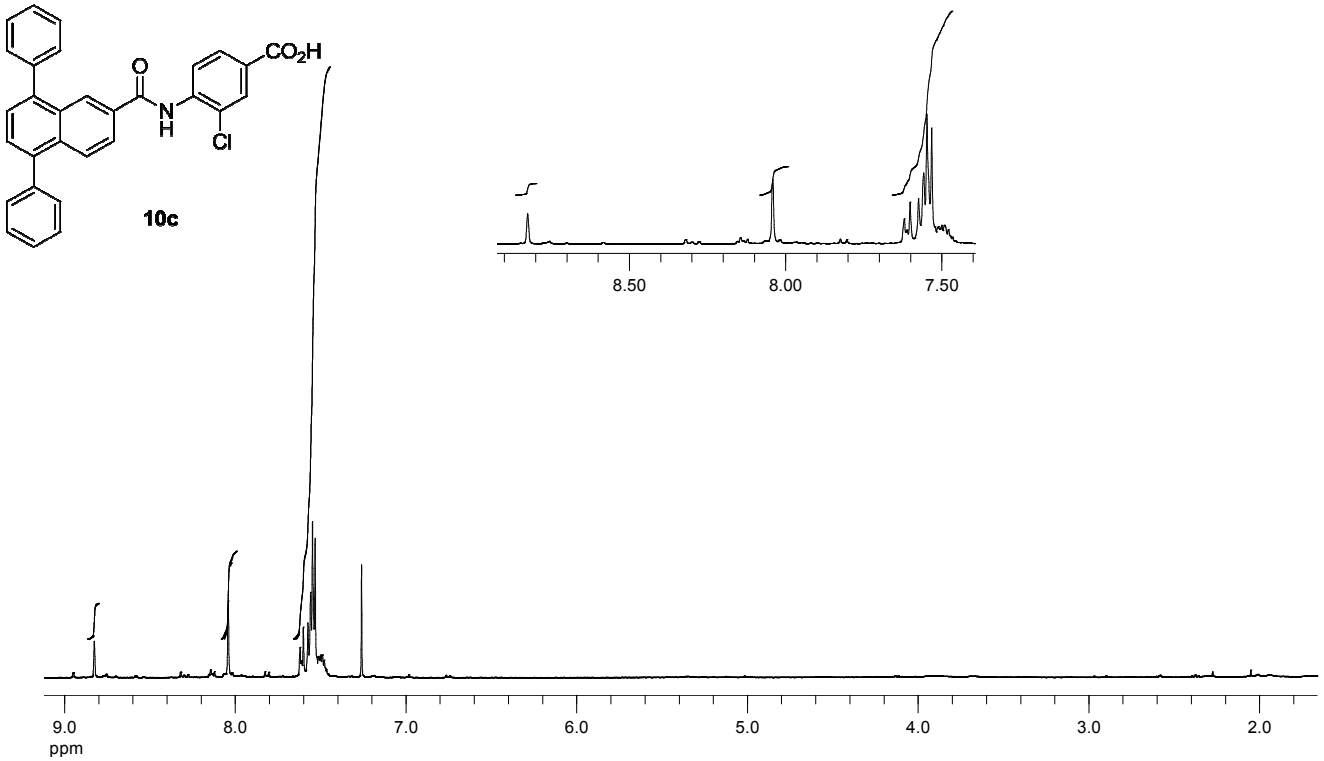

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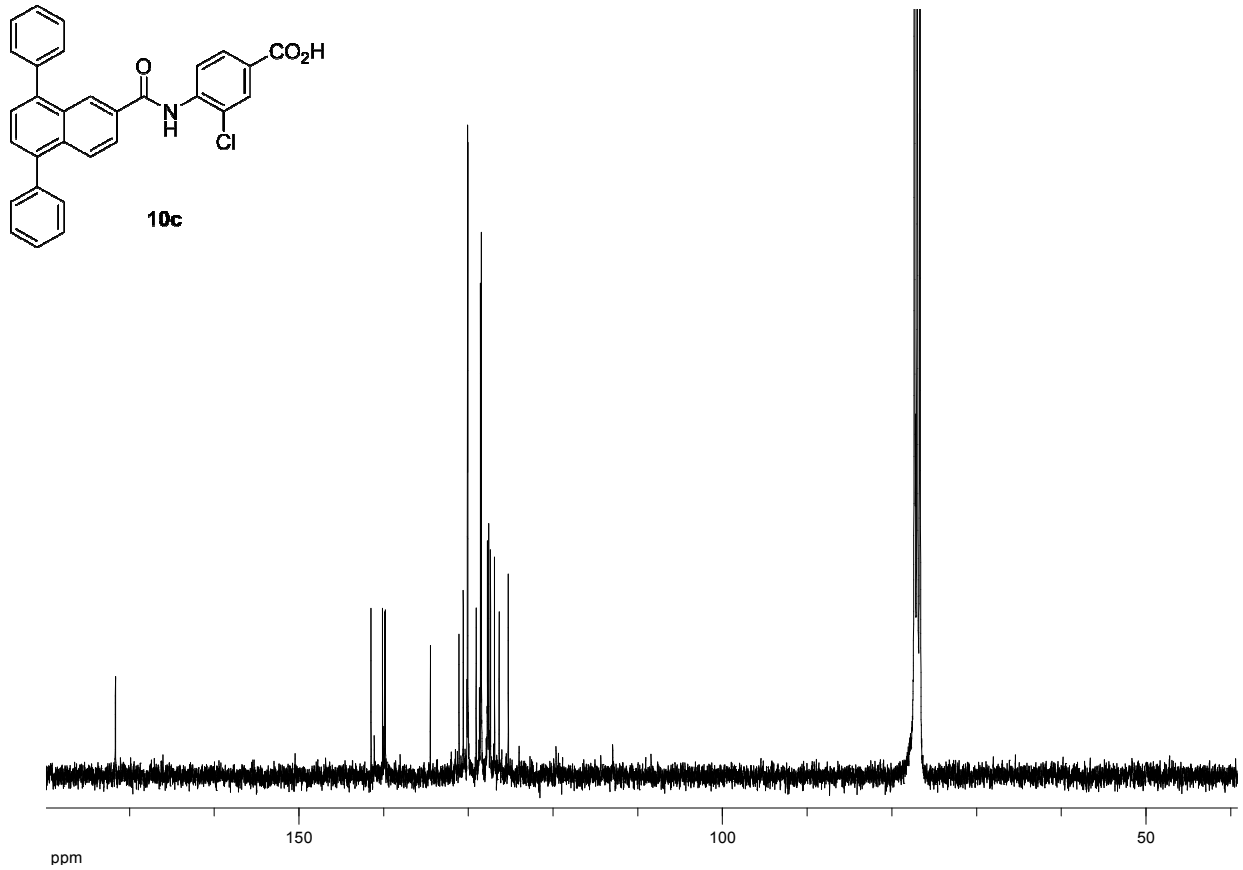

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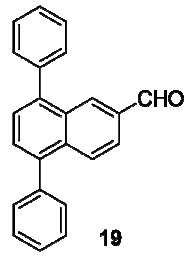

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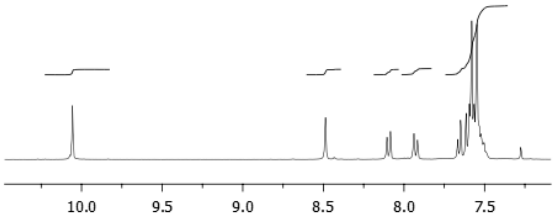

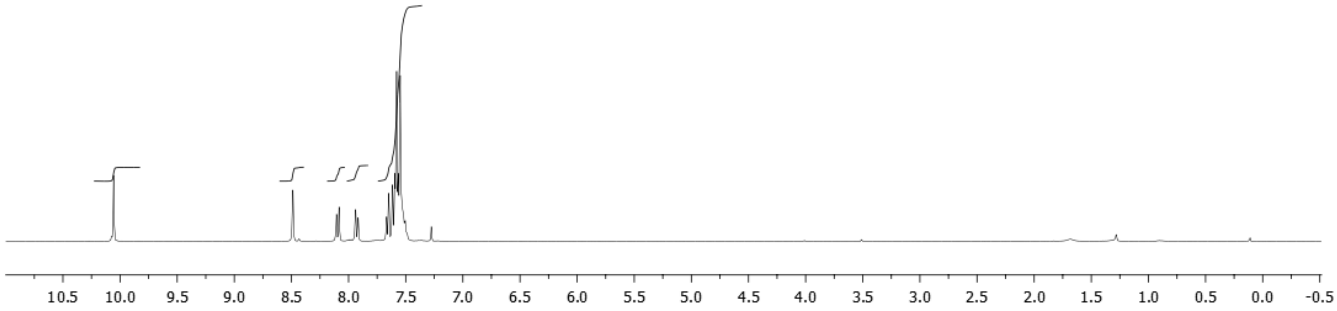

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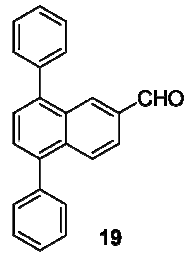

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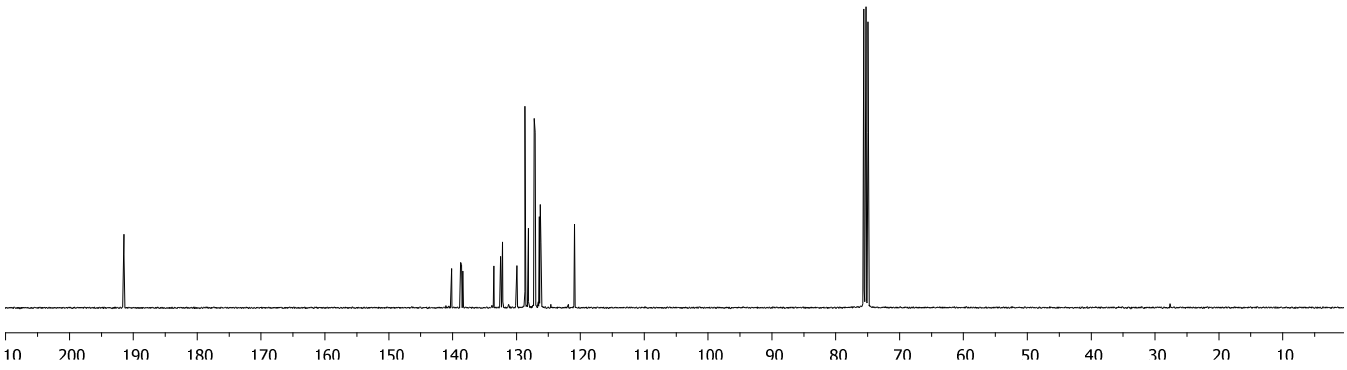

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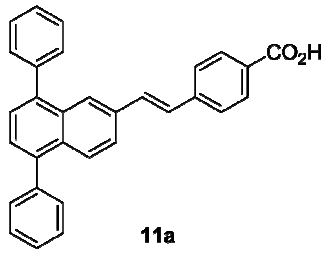
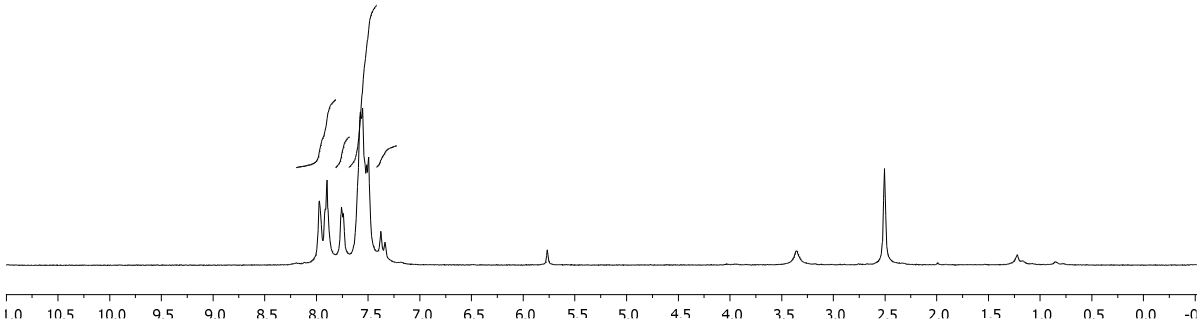


11a



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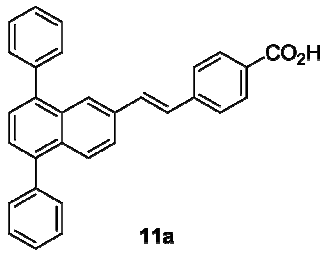

11a

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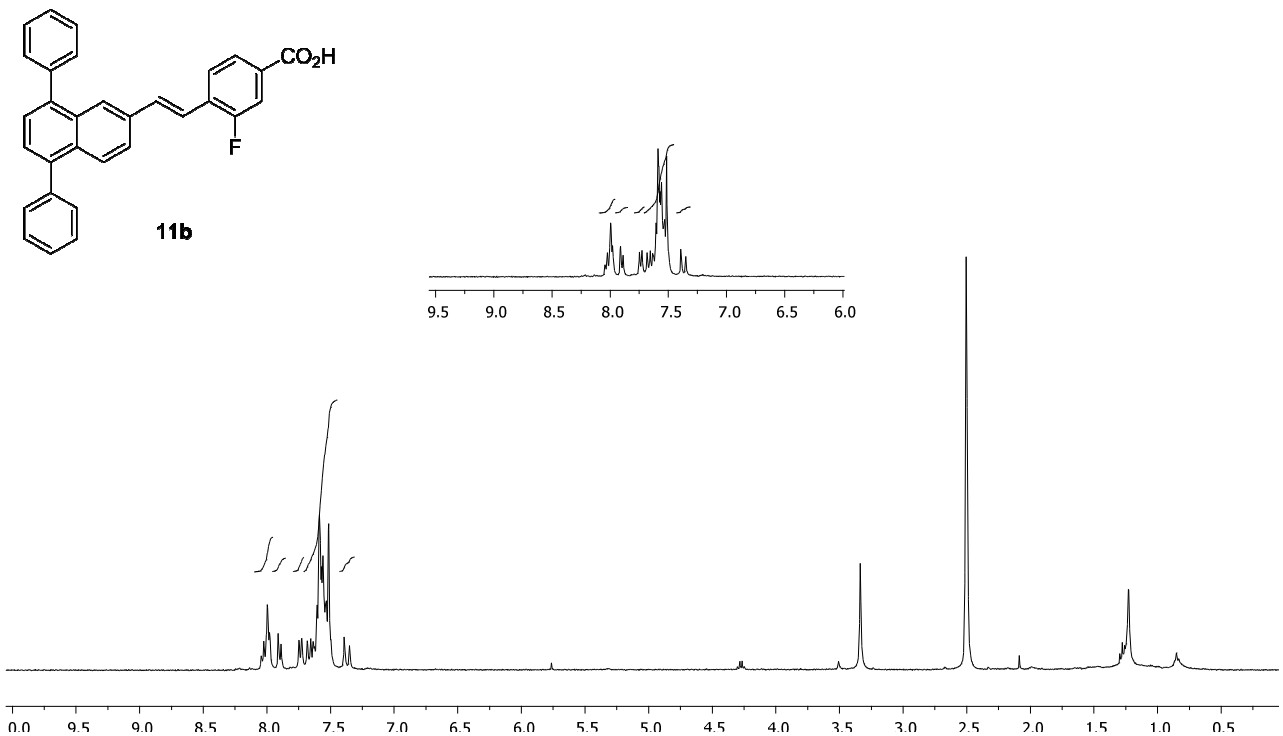

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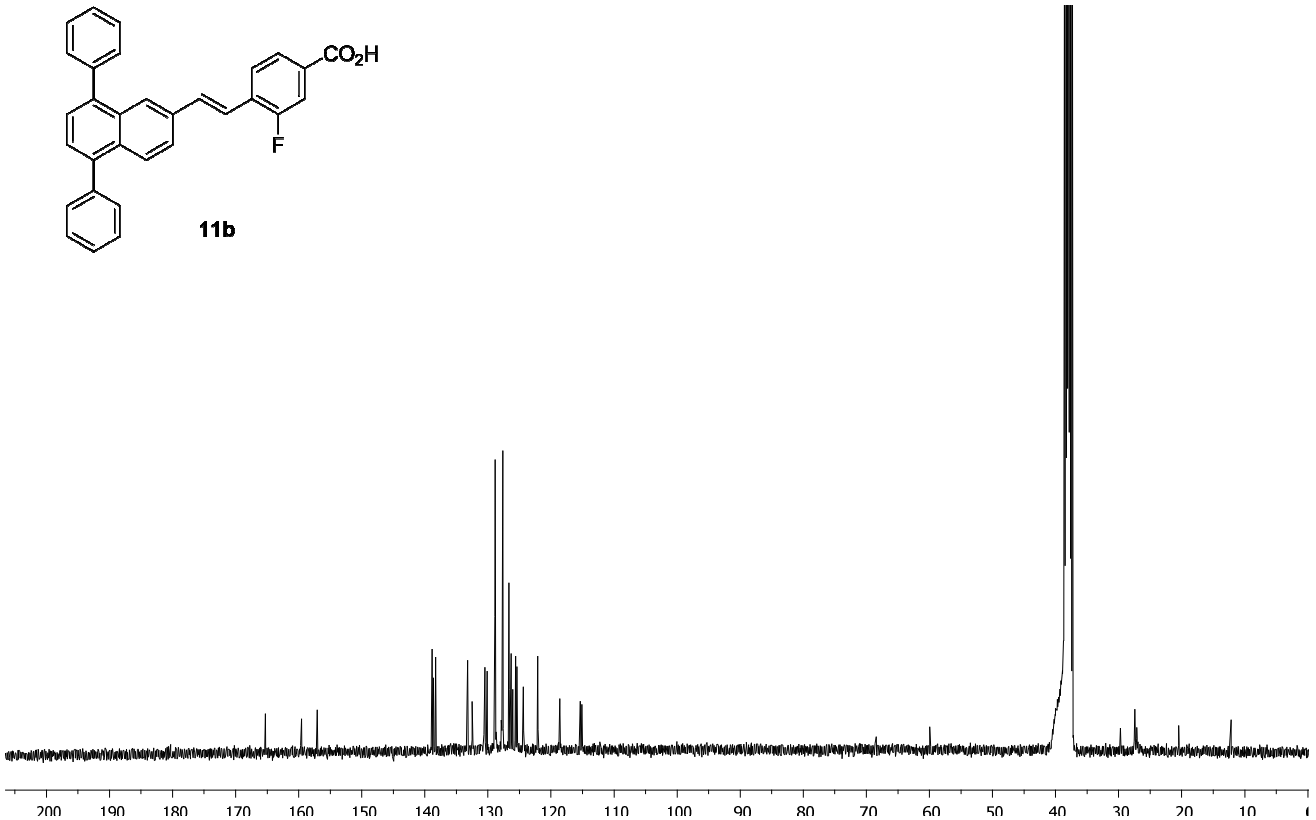

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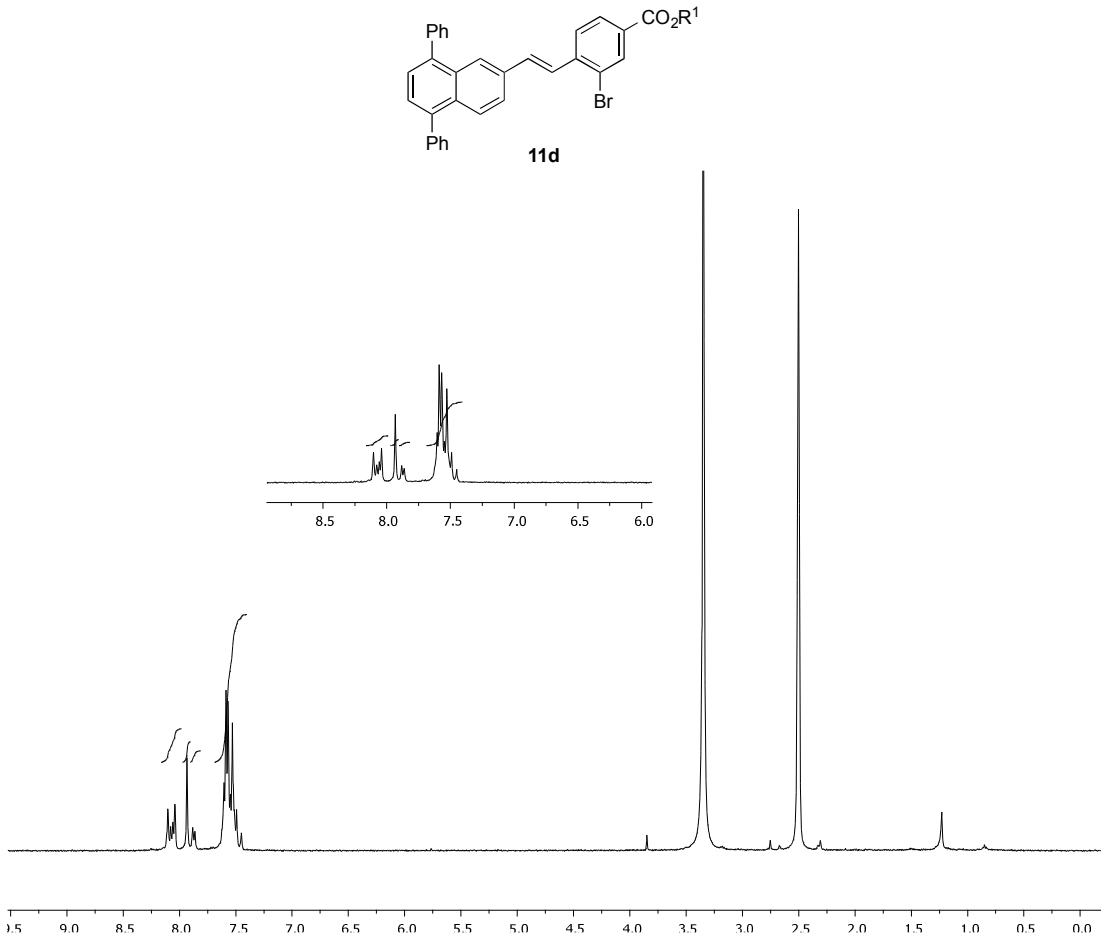
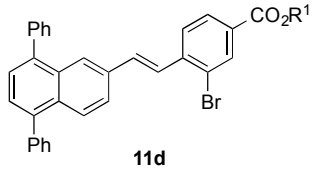
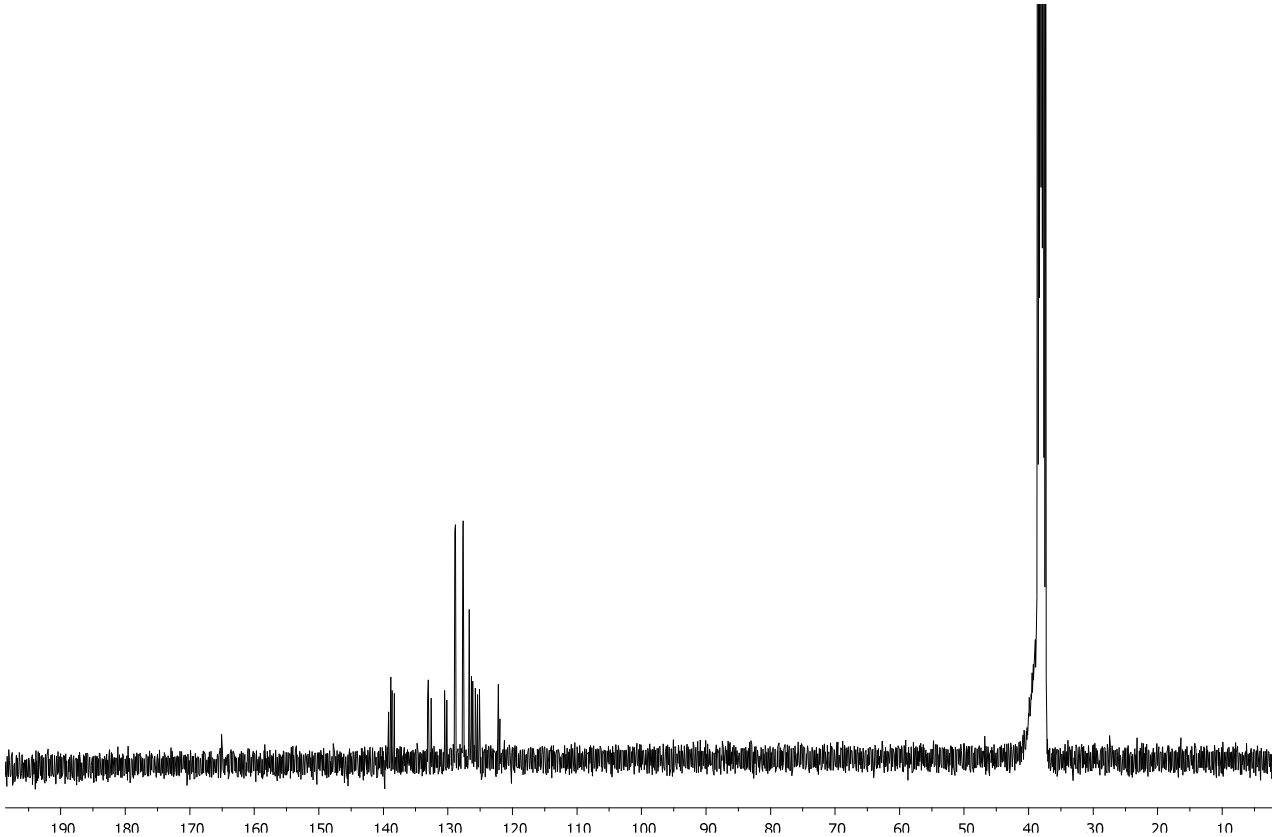


^{13}C NMR (100 MHz, DMSO-d_6)


Ph
CO2R1
Br
Ph

11d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10