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SUPPORTING INFORMATION

Title: Ultrasound-Promoted Reaction of 2-Chlorobenzoic Acids and Aliphatic Amines
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Ref. No.: O200700281

General Remarks

Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, which were visualized by CAMAG UV-CABINET II at 254 nm. Melting points were determinated in open capillaries with a GALLENKANMP melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F Spectrometer at 300^{o}K, using DMSO as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to residual deuterated solvent signal as an internal reference. The coupling constants (*J*) are given in Hz. Mass spectra were recorded by using Spectrometer Q-TOFII-Micromass, Manchester Ing. Elemental analyses were carried out by a Fisons EA 1108 CHNS-O apparatus at the Microanalytical Unit of the Instituto de Biorgánica de la Universidad de La Laguna, Tenerife, Spain. All reagents purchased from commercial sources were used without further purification. The yields reported in the publication represent an average of at least three independent runs.

Ultrasonic Irradiation Experiments

All ultrasonic irradiation experiments were carried out in a sonochemical apparatus SONIPRED-150. The frequency can be tuned between 18 and 35 kHz and the power can be varied up to a

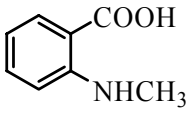
maximum output of 350 W. All the reactions were performed on an open flat-bottomed glass tube (diameter: 30 mm; thickness: 1mm; volume: 50 mL).

General Procedure for the condensation of 2-chlorobenzoic acids with primary or secondary amines (1a-16a and 1b-20b)

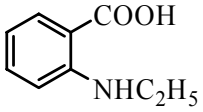
A) Under conventional heating: A mixture of 2-chlorobenzoic acid derivative (0.04 mol), alkylamine (0.08 mol), anhydrous potassium carbonate (0.02 mol), copper powder, (0.003 mol) was refluxed in DMF (25 mL) for 2 h (primary amines) or 4 h (secondary amines). The mixture was slowly added with shaking to a HCl:H_2O (1:1). The solid obtained was filtered off, washed with water and dissolved in 30 mL aqueous sodium hydroxide solution (10%). The basic solution acidified with 40 mL AcOH:H_2O (1:3) to pH 5. The 2-(alkylamino)benzoic acid (**1a**–**16a**) or 2-(dialkylamino) benzoic acid (**1b**–**20b**) crystallized and was filtered off and washed with water. Further purification was carried out by recrystallization from EtOH/H_2O.

B) Under ultrasonic irradiation: 2-chlorobenzoic acid derivative (0.04 mol), alkylamine (0.08 mol), anhydrous potassium carbonate (0.02 mol), copper powder, (0.003 mol) were added to the flat-bottomed glass tube. The mixture was sonicated for 15–25 min. at 20 kHz and 300 W using an immersion horn. The reactions were monitored by TLC using ethyl acetate:chloroform:acetic acid (8:6:1 v/v/v). After completion of the reaction the mixture was slowly added with shaking to a HCl:H_2O (1:1). The solid obtained was filtered off, washed with water and dissolved in 30 mL aqueous sodium hydroxide solution (10%). The basic solution acidified with 40 mL AcOH:H_2O (1:3) to pH 5. The 2-(alkylamino)benzoic acid (**1a**–**16a**) or 2-(dialkylamino) benzoic acid (**1b**–**20b**) crystallized and was filtered off and washed with water. Further purification was carried out by recrystallization from EtOH/H_2O.

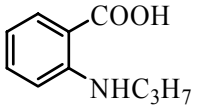
The structures of the products obtained were confirmed by melting point, elemental analyses, ^{1}HNMR, ^{13}CNMR and mass spectra corresponding to those reported in the literature.[1-6]



2-(methylamino)benzoic acid (Table 1, 1a). Yield: 73% (Method A), 85% (Method B). m. p. 181-182 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.33 (s, br, OH, NH), 7.80 (dd, ^{3}J=8.5 Hz, ^{4}J=1.2 Hz, 1 H, 6-H), 7.37 (dt, ^{3}J=8.2 Hz, ^{3}J=7.3 Hz, ^{4}J=1.2 Hz, 1 H, 4-H), 6.74 (dd, ^{3}J=8.2 Hz, ^{4}J=1.0 Hz, 1 H, 3-H), 6.58 (dt, ^{3}J=8.5 Hz, ^{3}J=7.3 Hz, ^{4}J=1.0 Hz, 1 H, 5-H), 2.81 (s, 3 H, C<u>H</u>$_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.5 (<u>C</u>OOH), 150.2 (2-C), 133.8, 131.6 (4-C, 6-C), 113.9, 110.7 (3-C, 5-C), 109.3 (1-C), 28.6 (<u>C</u>H$_3$). ESI-MS (m/z): 152.1156 $[M+H]^+$. Anal. Calcd. for $C_8H_9NO_2$ (151.16): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.68; H, 5.88; N, 9.41.

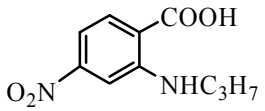


2-(ethylamino)benzoic acid (Table 1, 2a). Yield: 71% (Method A), 83% (Method B). m. p. 153-154 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.31 (s, br, OH, NH), 7.79 (dd, ^{3}J=8.3 Hz, ^{4}J=1.5 Hz, 1 H, 6-H), 7.35 (dt, ^{3}J=8.6 Hz, ^{3}J=7.7 Hz, ^{4}J=1.5 Hz, 1 H, 4-H), 6.71 (dd, ^{3}J=8.6 Hz, ^{4}J=1.1 Hz, 1 H, 3-H), 6.54 (dt, ^{3}J=8.3 Hz, ^{3}J=7.7 Hz, ^{4}J=1.1 Hz, 1 H, 5-H), 3.23 (q, ^{3}J=7.1 Hz, 2 H, C<u>H</u>$_2$-CH$_3$), 1.11 (t, ^{3}J=7.1 Hz, 3 H, CH$_2$-C<u>H</u>$_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.8 (<u>C</u>OOH), 150.4 (2-C), 134.2, 131.9 (4-C, 6-C), 113.7, 110.3 (3-C, 5-C), 109.6 (1-C), 39.7 (<u>C</u>H$_2$CH$_3$), 15.9 (CH$_2$<u>C</u>H$_3$). ESI-MS (m/z): 166.1734 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}NO_2$ (165.19): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.31; H, 6.89; N, 8.63.

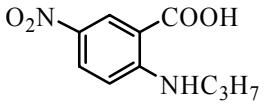


2-(propylamino)benzoic acid (Table 1, 3a). Yield: 72% (Method A), 84% (Method B). m. p. 110-111 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.22 (s, br, OH, NH), 7.78 (dd, ^{3}J=8.0 Hz, ^{4}J=1.4 Hz, 1 H, 6-H), 7.35 (dt, ^{3}J=8.5 Hz, ^{3}J=7.1 Hz, ^{4}J=1.4 Hz, 1 H, 4-H), 6.71 (d, ^{3}J=8.5 Hz, 1 H, 3-H), 6.54 (t, ^{3}J=8.0 Hz, ^{3}J=7.1 Hz 1 H, 5-H), 3.13 (t, ^{3}J=6.9 Hz, 2 H, C<u>H</u>$_2$-CH$_2$-CH$_3$), 1.60 (m, 2 H, CH$_2$-C<u>H</u>$_2$-CH$_3$), 0.95 (t, ^{3}J=7.4 Hz, 3 H, CH$_2$-CH$_2$-C<u>H</u>$_3$). ^{13}C NMR (63 MHz,

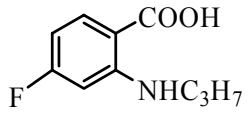
DMSO-d_6, 25 °C): δ= 169.7 (COOH), 150.4 (2-C), 134.1, 131.4 (4-C, 6-C), 113.6, 110.8 (3-C, 5-C), 109.4 (1-C), 43.4 ($CH_2CH_2CH_3$), 21.5 ($CH_2CH_2CH_3$), 11.1 ($CH_2CH_2CH_3$). ESI-MS (m/z): 180.0123 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{13}NO_2$ (179.22): C, 67. 02; H, 7.31; N, 7.82. Found: C, 67.29; H, 7.42; N, 7.53.



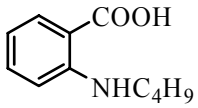
4-nitro-2-(propylamino)benzoic acid (Table 1, 4a). Yield: 75% (Method A), 86% (Method B). m. p. 198-200 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ=8.14 (s, br, OH, NH), 8.00 (d, ^3J=8.7 Hz, 1 H, 6-H), 7.40 (d, ^4J=2.3 Hz, 1 H, 3-H), 7.28 (dd, ^3J=8.7 Hz, ^4J=2.3 Hz, 1 H, 5-H), 3.23 (t, ^3J=6.9 Hz, 2 H, CH_2-CH_2-CH_3), 1.64 (m, 2 H, CH_2-CH_2-CH_3), 0.97 (t, ^3J=7.4 Hz, 3 H, CH_2-CH_2-CH_3). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 168.4 (COOH), 151.0, 150.6 (2-C, 4-C), 132.9 (6-C), 107.2, 104.7 (3-C, 5-C), 103.2 (1-C), 43.4 ($CH_2CH_2CH_3$), 21.1 ($CH_2CH_2CH_3$), 10.9 ($CH_2CH_2CH_3$). ESI-MS (m/z): 225.3857 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}N_2O_4$ (224.21): C, 53.57; H, 5.39; N, 12.49. Found: C, 53.43; H, 5.27; N, 12.62.



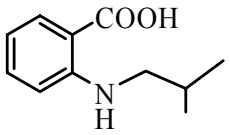
5-nitro-2-(propylamino)benzoic acid (Table 1, 5a). Yield: 77% (Method A), 89% (Method B). m. p. 188-190 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.20 (s, br, OH, NH), 8.74 (d, ^4J=3.0 Hz, 1 H, 6-H), 8.14 (dd, ^3J=9.6 Hz, ^4J=3.0 Hz, 1 H, 4-H), 6.86 (d, ^3J=9.6 Hz, 1 H, 3-H), 3.29 (t, ^3J=6.9 Hz, 2 H, CH_2-CH_2-CH_3), 1.66 (m, 2 H, CH_2-CH_2-CH_3), 0.97 (t, ^3J=7,3 Hz, 3 H, CH_2-CH_2-CH_3). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.9 (COOH); 156.5 (5-C), 136.7 (2-C), 130.9, 130.2 (4-C, 6-C), 112.6 (3-C), 108.1 (1-C), 45.7 ($CH_2CH_2CH_3$), 23.3 ($CH_2CH_2CH_3$), 12.1 ($CH_2CH_2CH_3$). ESI-MS (m/z): 225.1567 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}N_2O_4$ (224.21): C, 53.57; H, 5.39; N, 12.49. Found: C, 53.71; H, 5.24; N, 12.60.



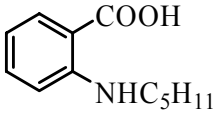
4-fluoro-2-(propylamino)benzoic acid (Table 1, 6a). Yield: 74% (Method A), 87% (Method B). m. p. 118-120 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.12 (s, br, OH, NH), 7.83 (dd, ^{3}J=8.7 Hz, $^{4}J_{H\text{-}F}$=7.3 Hz, 1 H, 6-H), 6.48 (dd, ^{4}J=2.3 Hz, $^{3}J_{H\text{-}F}$=10.5 Hz, 1 H, 3-H), 6.33 (dt, ^{3}J=8.7 Hz, ^{4}J=2.3 Hz, $^{3}J_{H\text{-}F}$=11.0 Hz, 1 H, 5-H), 3.12 (t, ^{3}J=6.9 Hz, 2 H, C$\underline{H}_2$-CH_2-CH_3), 1.60 (m, 2 H, CH_2-C$\underline{H}_2$-CH_3), 0.95 (t, ^{3}J=7.3 Hz, 3 H, CH_2-CH_2-C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 168.8 (<u>C</u>OOH), 168.0/164.1 (4-C, $J_{C\text{-}F}$=248 Hz), 152.8/152.6 (2-C, $J_{C\text{-}F}$=11 Hz), 134.2/134.0 (6-C, $J_{C\text{-}F}$=11 Hz), 106.4 (1-C), 101.1/100.7, 96.8/96.4 (3-C, 5-C, $J_{C\text{-}F}$=23 Hz, $J_{C\text{-}F}$=26 Hz), 43.4 (<u>C</u>$H_2CH_2CH_3$), 21.2 (CH_2<u>C</u>H_2CH_3), 10.9 (CH_2CH_2<u>C</u>H_3). ESI-MS (m/z): 198.1851 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}FNO_2$ (197.21): C, 60.90; H, 6.13; N, 7.10. Found: C, 61.01; H, 5.99; N, 7.29.



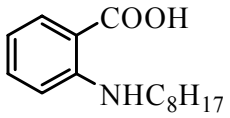
2-(buthylamino)benzoic acid (Table 1, 7a). Yield: 76% (Method A), 88% (Method B). m. p. 77-78 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.24 (s, br, OH, NH), 7.77 (dd, ^{3}J=7.5 Hz, ^{4}J=1.6 Hz, 1 H, 6-H), 7.33 (dt, ^{3}J=8.4 Hz, ^{3}J=7.0 Hz, ^{4}J=1.6 Hz, 1 H, 4-H), 6.75 (d, ^{3}J=8.4 Hz, 1 H, 3-H), 6.53 (t, ^{3}J=7.5 Hz, ^{3}J=7.0 Hz, 1 H, 5-H), 3.14 (t, ^{3}J=6.9 Hz, 2 H, C$\underline{H}_2$-CH_2-CH_2-CH_3), 1.56 (m, 2 H, CH_2-C$\underline{H}_2$-CH_2-CH_3), 1.36 (m, 2 H, CH_2-CH_2-C$\underline{H}_2$-CH_3), 0.92 (t, ^{3}J=7.3 Hz, 3 H, CH_2-CH_2-CH_2-C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 170.0 (<u>C</u>OOH), 150.9 (2-C), 134.4, 131.6 (4-C, 6-C), 113.9, 111.1 (3-C, 5-C), 109.7 (1-C), 41.6 (<u>C</u>$H_2CH_2CH_2CH_3$), 30.7 (CH_2<u>C</u>$H_2CH_2CH_3$), 19.7 (CH_2CH_2<u>C</u>H_2CH_3), 13.6 ($CH_2CH_2CH_2$<u>C</u>H_3). ESI-MS (m/z): 194.3619 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{15}NO_2$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.45; H, 7.93; N, 7.12.



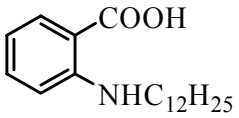
2-(isobuthylamino)benzoic acid (Table 1, 8a). Yield: 74% (Method A), 86% (Method B). m. p. 79-80 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.25 (s, br, OH, NH), 7.77 (dd, ^{3}J=7.7 Hz, ^{4}J=1.6 Hz, 1 H, 6-H), 7.33 (dt, ^{3}J=8.4 Hz, ^{3}J=7.2 Hz, ^{4}J=1.6 Hz, 1 H, 4-H), 6.70 (d, ^{3}J=8.4 Hz, 1 H, 3-H), 6.52 (t, ^{3}J=7.7 Hz, ^{3}J=7.2 Hz, 1 H, 5-H), 2.98 (d, ^{3}J=6.6 Hz, 2 H, C$\underline{H}_2$-CH-$(CH_3)_2$), 1.86 (m, 1 H, CH_2-C$\underline{H}$-$(CH_3)_2$), 0.94 (m, 6 H, CH_2-CH-(C$\underline{H}_3$)$_2$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 170.1 (C$\underline{O}$OH), 151.1 (2-C), 134.4, 131.7 (4-C, 6-C), 113.9, 111.2 (3-C, 5-C), 109.7 (1-C), 49.7 ($\underline{C}H_2CH(CH_3)_2$), 27.4 ($CH_2\underline{C}H(CH_3)_2$), 20.2 ($CH_2CH(\underline{C}H_3)_2$). ESI-MS (m/z): 194.1957 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{15}NO_2$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.49; H, 7.69; N, 7.10.



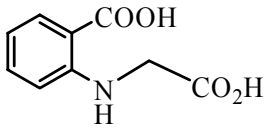
2-(penthylamino)benzoic acid (Table 1, 9a). Yield: 77% (Method A), 87% (Method B). m. p. 72-73 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.21 (s, br, OH, NH), 7.79 (dd, ^{3}J=7.9 Hz, ^{4}J=1.3 Hz, 1 H, 6-H), 7.31 (dt, ^{3}J=8.2 Hz, ^{3}J=7.0 Hz, ^{4}J=1.3 Hz, 1 H, 4-H), 6.71 (d, ^{3}J=8.2 Hz, 1 H, 3-H), 6.55 (t, ^{3}J=7.9 Hz, ^{3}J=7.0 Hz, 1 H, 5-H), 3.16 (t, ^{3}J=6.8 Hz, 2 H, C$\underline{H}_2$-CH_2-$(CH_2)_2$-CH_3), 1.59 (m, 2 H, CH_2-C$\underline{H}_2$-$(CH_2)_2$-CH_3), 1.37-1.29 (m, 4 H, CH_2-CH_2-(C$\underline{H}_2$)$_2$-CH_3), 0.91 (t, ^{3}J=7.3 Hz 3 H, CH_2-CH_2-$(CH_2)_2$-C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 170.1 (C$\underline{O}$OH), 151.2 (2-C), 134.2, 131.8 (4-C, 6-C), 114.1, 111.0 (3-C, 5-C), 109.5 (1-C), 44.8 ($\underline{C}H_2CH_2CH_2$ CH_2CH_3) 32.4 ($CH_2\underline{C}H_2CH_2CH_2CH_3$), 31.2 ($CH_2CH_2\underline{C}H_2$ CH_2CH_3), 23.9 ($CH_2CH_2CH_2\underline{C}H_2CH_3$), 15.3 ($CH_2CH_2CH_2CH_2\underline{C}H_3$). ESI-MS (m/z): 208.3589 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.63; H, 8.17; N, 6.84.



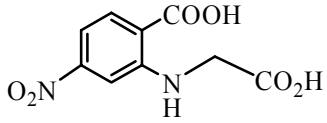
2-(octhylamino)benzoic acid (Table 1, 10a). Yield: 78% (Method A), 87% (Method B). m. p. 75-76 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.15 (s, br, OH, NH), 7.78 (dd, ^{3}J=7.9 Hz, ^{4}J=1.4 Hz, 1 H, 6-H), 7.34 (dt, ^{3}J=8.3 Hz, ^{3}J=6.9 Hz, ^{4}J=1.4 Hz, 1 H, 4-H), 6.70 (d, ^{3}J=8.3 Hz, 1 H, 3-H), 6.53 (t, ^{3}J=7.9 Hz, ^{3}J=6.9 Hz, 1 H, 5-H), 3.15 (t, ^{3}J=6.8 Hz, 2H, C$\underline{H}_2$-CH_2-$(CH_2)_5$-CH_3), 1.58 (m, 2 H, CH_2-C$\underline{H}_2$-$(CH_2)_5$-CH_3), 1.45-1.17 (m, 10 H, CH_2-CH_2-$(C\underline{H}_2)_5$-CH_3), 0.85 (m, 3 H, CH_2-CH_2-$(CH_2)_5$-C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.8 (C$\underline{O}$OH), 150.9 (2-C), 134.2, 131.5 (4-C, 6-C), 113.8, 110.9 (3-C, 5-C), 105.0 (1-C), 41.9 ($\underline{C}H_2CH_2(CH_2)_3CH_2$ CH_2CH_3), 31.0 ($CH_2\underline{C}H_2(CH_2)_3CH_2CH_2CH_3$), 28.5 ($CH_2CH_2(\underline{C}H_2)_3CH_2$ CH_2CH_3), 26.4 ($CH_2CH_2(CH_2)_3\underline{C}H_2CH_2CH_3$), 21.9 ($CH_2CH_2(CH_2)_3CH_2$ $\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2(CH_2)_3$-$CH_2CH_2\underline{C}H_3$). ESI-MS (m/z): 250.2641 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{23}NO_2$ (249.35): C, 72.25; H, 9.30; N, 5.62. Found: C, 72.38; H, 9.41; N, 5.78.



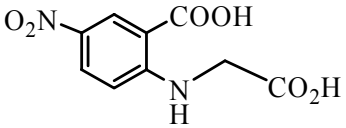
2-(dodecylamino)benzoic acid (Table 1, 11a). Yield: 80% (Method A), 91% (Method B). m. p. 80-81 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.19 (s, br, OH, NH), 7.77 (dd, ^{3}J=7.6 Hz, ^{4}J=1.4 Hz, 1 H, 6-H), 7.32 (dt, ^{3}J=8.2 Hz, ^{3}J=7.3 Hz, ^{4}J=1.4 Hz, 1 H, 4-H), 6.68 (d, ^{3}J=8.2 Hz, 1 H, 3-H), 6.51 (t, ^{3}J=7.6 Hz, ^{3}J=7.3 Hz, 1 H, 5-H), 3.13 (t, ^{3}J=6.8 Hz, 2 H, C$\underline{H}_2$-CH_2-$(CH_2)_9$-CH_3), 1.56 (m, 2 H, CH_2-C$\underline{H}_2$-$(CH_2)_9$-CH_3), 1.44-1.13 (m, 18 H, CH_2-CH_2-$(C\underline{H}_2)_9$-CH_3), 0.84 (m, 3 H, CH_2-CH_2-$(CH_2)_5$-C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.9 (C$\underline{O}$OH), 150.8 (2-C), 134.1, 131.5 (4-C, 6-C), 113.7; 110.9 (3-C, 5-C), 105.1 (1-C), 41.9 ($\underline{C}H_2CH_2(CH_2)_7$ $CH_2CH_2CH_3$), 31.1 ($CH_2\underline{C}H_2(CH_2)_7CH_2CH_2CH_3$), 28.8 ($CH_2CH_2(\underline{C}H_2)_7CH_2$ CH_2CH_3), 26.4 ($CH_2CH_2(CH_2)_7\underline{C}H_2CH_2CH_3$), 21.9 ($CH_2CH_2(CH_2)_7$ $CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2(CH_2)_3$ $CH_2CH_2\underline{C}H_3$). ESI-MS (m/z): 306.3490 $[M+H]^+$. Anal. Elem. Anal. Calcd. for $C_{19}H_{31}NO_2$ (305.46): C, 74.71; H, 10.23; N, 4.59. Found: C, 74.90; H, 10.08; N, 4.73.



2-[(carboxymethyl)amino]benzoic acid (Table 1, 12a). Yield: 85% (Method A), 94% (Method B). m. p. 185-186 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.18 (s, br, OH, NH), 7,80 (dd, ^{3}J=7.8 Hz, ^{4}J=1.7 Hz, 1 H, 6-H), 7.34 (dt, ^{3}J=8.0 Hz, ^{3}J=7.5 Hz, ^{4}J=1.7 Hz, 1 H, 4-H), 6.78 (d, ^{3}J=8.0 Hz, 1 H, 3-H), 6.62 (t, ^{3}J=7.8 Hz, ^{3}J=7.5 Hz, 1 H, 5-H), 4.11 (s, 2 H, C$\underline{H}_2$-COOH). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 171.1 (C$\underline{O}$OH), 169.9 (C$\underline{O}$OH), 150.2 (2-C), 133.7, 131.1 (4-C, 6-C), 114.1, 111.6 (3-C, 5-C), 109.6 (1-C), 46.2 (C$\underline{H}_2$COOH). ESI-MS (m/z): 196.0693 $[M+H]^+$. Anal. Calcd. for $C_9H_9NO_4$ (195.17): C, 55.39; H, 4.65; N, 7.18. Found: C, 55.52; H, 4.54; N, 7.31.

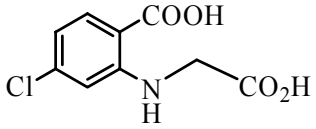


2-[(carboxymethyl)amino]-4-nitrobenzoic acid (Table 1, 13a). Yield: 86% (Method A), 95% (Method B). m. p. 245-247 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.88 (s, br, OH, NH), 8.03 (d, ^{3}J=8.5 Hz, 1 H, 6-H), 7.32 (dd, ^{3}J=8.5 Hz, ^{4}J=2.1 Hz, 1 H, 5-H), 7.26 (d, ^{4}J=2.1 Hz, 1 H, 3-H), 4.05 (s, 2 H, C$\underline{H}_2$-COOH). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 171.2 (C$\underline{O}$OH), 168.7 (C$\underline{O}$OH), 150.3 (4-C), 149.9 (2-C), 132.8 (6-C), 108.1, 104.9 (3-C, 5-C), 103.5 (1-C), 44.5 (C$\underline{H}_2$COOH). ESI-MS (m/z): 241.2825 $[M+H]^+$. Anal. Calcd. for $C_9H_8N_2O_6$ (240.17): C, 45.01; H, 3.36; N, 11.66. Found: C, 45.19; H, 3.25; N, 11.80.

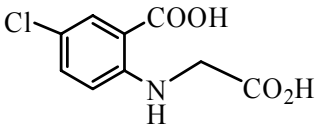


2-[(carboxymethyl)amino]-5-nitrobenzoic acid (Table 1, 14a). Yield: 88% (Method A), 97% (Method B). m. p. 222-223 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.98 (s, br, OH, NH), 8.65 (d, ^{4}J=2.7 Hz, 1 H, 6-H), 8.17 (dd, ^{3}J=9.4 Hz, ^{4}J=2.7 Hz, 1 H, 4-H), 6.78 (d, ^{3}J=9.4 Hz, 1 H, 3-H), 4.19 (s, 2 H, C$\underline{H}_2$-COOH). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 170.5 (C$\underline{O}$OH), 168.2 (C$\underline{O}$OH), 153.9 (5-C), 135.2 (2-C), 129.1, 128.3 (4-C, 6-C), 112.2 (3-C), 109.7 (1-C), 44.2

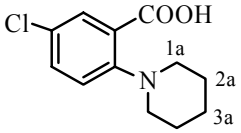
(CH$_2$COOH). ESI-MS (m/z): 241.2636 [M+H]$^+$. Anal. Calcd. for $C_9H_8N_2O_6$ (240.17): C, 45.01; H, 3.36; N, 11.66. Found: C, 44.99; H, 3.46; N, 11.75.



2-[(carboxymethyl)amino]-4-chlorobenzoic acid (Table 1, 15a). Yield: 82% (Method A), 91% (Method B). m. p. 112-113 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 °C): δ= 8.77 (s, br, OH, NH), 7.80 (d, ^3J=8.3 Hz, 1 H, 6-H), 6.49-6.45 (m, 2 H, 3-H, 5-H), 3.70 (s, 2 H, CH$_2$-COOH). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 °C): δ= 171.9 (COOH), 170.1 (COOH), 150.5 (2-C), 136.9 (4-C), 133.2 (6-C), 114.1, 113.0 (3-C, 5-C), 109.8 (1-C), 45.8 (CH$_2$COOH). ESI-MS (m/z): 230.0986/232.0632 [M+H]$^+$. Anal. Calcd. for $C_9H_8ClNO_4$ (229.62): C, 47.08; H, 3.51; N, 6.10. Found: C, 46.91; H, 3.39; N, 6.25.

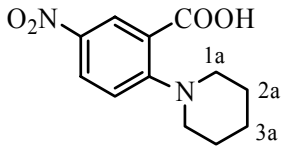


2-[(carboxymethyl)amino]-5-chlorobenzoic acid (Table 1, 16a). Yield: 87% (Method A), 96% (Method B). m. p. 212-215 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 °C): δ= 8.81 (s, br, OH, NH), 7.75 (d, ^4J=2.7 Hz, 1 H, 6-H), 7.16 (dd, ^3J=8.8 Hz, ^4J=2.7 Hz, 1 H, 4-H), 6.44 (d, ^3J=8.8 Hz, 1 H, 3-H), 3.71 (s, 2 H, CH$_2$-COOH). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 °C): δ= 171.7 (COOH), 169.8 (COOH), 148.2 (2-C), 131.0, 130.6 (4-C, 6-C), 121.4 (5-C), 116.8 (3-C), 112.1 (1-C), 45.7 (CH$_2$COOH). ESI-MS (m/z): 230.0977/232.1008 [M+H]$^+$. Anal. Calcd. for $C_9H_8ClNO_4$ (229.62): C, 47.08; H, 3.51; N, 6.10. Found: C, 47.22; H, 3.36; N, 6.27.

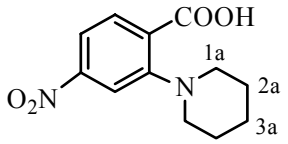


5-chloro-2-(1-piperidinyl)benzoic acid (Table 1, 1b). Yield: 60% (Method A), 86% (Method B). m. p. 179-180 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 °C): δ= 7.72 (d, ^4J=2.7 Hz, 1 H, 6-H), 7.21 (dd, ^3J=8.9 Hz, ^4J=2.7 Hz, 1 H, 4-H), 6.67 (d, ^3J=8.9 Hz, 1 H, 3-H), 3.31-3.18 (m, 4 H,

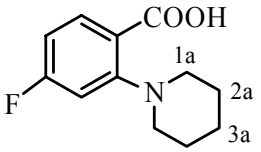
2XC$\underline{H}_2$-1a), 1.68-1.56 (m, 6 H, 3XC$\underline{H}_2$-2a, 3a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 168.1 (C$\underline{O}$OH), 146.1 (2-C), 131.5, 130.6 (4-C, 6-C), 120.0 (5-C), 118.1 (3-C), 114.6 (1-C), 52.1 (2X$\underline{C}H_2$-1a), 24.7 (2X$\underline{C}H_2$-2a), 23.4 ($\underline{C}H_2$-3a). ESI-MS (m/z): 240.6763/242.6078 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}Cl\,NO_2$ (239.70): C, 60.13; H, 5.89; N, 5.84. Found: C, 60.27; H, 5.72; N, 6.00.



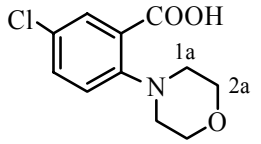
5-nitro-2-(1-piperidinyl)benzoic acid (Table 1, 2b). Yield: 61% (Method A), 90% (Method B). m. p. 198-199 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 ^{o}C): δ= 8.36 (d, ^{4}J=2.9 Hz, 1 H, 6-H), 8.16 (dd, ^{3}J=9.0 Hz, ^{4}J=2.9 Hz, 1 H, 4-H), 7.20 (d, ^{3}J=9.0 Hz, 1 H, 3-H), 3.31-3.21 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.62 (m, 6 H, 3XC$\underline{H}_2$-2a, 3a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 167.3 (C$\underline{O}$OH), 155.3 (5-C), 137.7 (2-C), 127.2, 127.0 (4-C, 6-C), 120.1 (1-C), 117.9 (3-C), 51.8 (2X$\underline{C}H_2$-1a), 25.0 (2X$\underline{C}H_2$-2a), 23.1 ($\underline{C}H_2$-3a). ESI-MS (m/z): 251.1488 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.43; H, 5.75; N, 11.32.



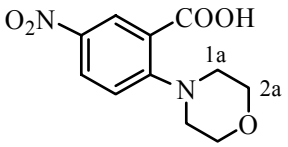
4-nitro-2-(1-piperidinyl)benzoic acid (Table 1, 3b). Yield: 58% (Method A), 83% (Method B). m. p. 218-220 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 ^{o}C): δ= 7.96 (d, ^{3}J=8.8 Hz, 1 H, 6-H), 7.44 (d, ^{4}J=2.8 Hz, 1 H, 3-H), 7.23 (dd, ^{3}J=8.8 Hz, ^{4}J=2.8 Hz, 1 H, 5-H), 3.30-3.24 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.72-1.66 (m, 6 H, 3XC$\underline{H}_2$-2a, 3a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 167.7 (C$\underline{O}$OH), 152.2 (4-C), 150.4 (2-C), 131.7 (6-C), 112.8, 110.2 (3-C, 5-C), 103.7 (1-C), 52.0 (2X$\underline{C}H_2$ 1a), 25.2 (2X$\underline{C}H_2$-2a), 23.6 ($\underline{C}H_2$-3a). ESI-MS (m/z): 251.1827 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.71; H, 5.77; N, 11.01.



4-fluoro-2-(1-piperidinyl)benzoic acid (Table 1, 4b). Yield: 57% (Method A), 86% (Method B). m. p. 172-174 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 ^{o}C): δ= 7.85 (dd, ^{3}J=8.9 Hz, $^{4}J_{H\text{-}F}$=6.8 Hz, 1 H, 6-H), 6.63 (dd, ^{4}J=2.2 Hz, $^{3}J_{H\text{-}F}$=10.2 Hz, 1 H, 3-H), 6.39 (dt, ^{3}J=8.9 Hz, ^{4}J=2.2 Hz, $^{3}J_{H\text{-}F}$=10.9 Hz, 1 H, 5-H), 3.35-3.20 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.70-1.60 (m, 6 H, 3XC$\underline{H}_2$-2a, 3a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 169.1 (C$\underline{O}$OH), 168.6/162.1 (4-C, $J_{C\text{-}F}$=260 Hz), 154.2/154.0 (2-C, $J_{C\text{-}F}$=10 Hz), 135.4/135.2 (6-C, $J_{C\text{-}F}$=11 Hz), 113.3 (1-C), 104.3/103.6, 101.0/100.3 (3-C, 5-C, $J_{C\text{-}F}$=30 Hz, $J_{C\text{-}F}$=28 Hz), 51.7 (2XC$\underline{H}_2$-1a), 25.0 (2XC$\underline{H}_2$-2a), 23.0 (C$\underline{H}_2$-3a). ESI-MS (m/z): 224.2645 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}FNO_2$ (223.24): C, 64.56; H, 6.32; N, 6.27. Found: C, 64.49; H, 6.38; N, 6.20.

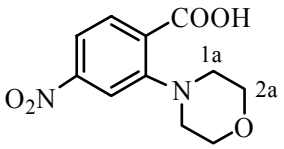


5-chloro-2-(4-morpholinyl)benzoic acid (Table 1, 5b). Yield: 62% (Method A), 83% (Method B). m. p. 186-187 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 ^{o}C): δ= 7.77 (d, ^{4}J=2.9 Hz, 1 H, 6-H), 7.24 (dd, ^{3}J=8.8 Hz, ^{4}J=2.9 Hz, 1 H, 4-H), 6.60 (d, ^{3}J=8.8 Hz, 1 H, 3-H), 3.75 (m, 4 H, 2XC$\underline{H}_2$-2a), 3.24 (m, 4 H, 2XC$\underline{H}_2$-1a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 168.6 (C$\underline{O}$OH), 145.3 (2-C), 132.2, 131.4 (4-C, 6-C), 121.5 (5-C), 119.8 (3-C), 115.5 (1-C), 65.1 (2XC$\underline{H}_2$-2a), 47.4 (2XC$\underline{H}_2$-1a). ESI-MS (m/z): 242.5215/244.5659 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}ClNO_3$ (241.67): C, 54.67; H, 5.00; N, 5.80. Found: C, 54.50; H, 5.12; N, 5.98.

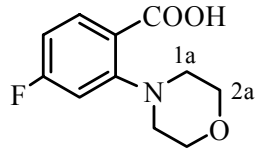


2-(4-morpholinyl)-5-nitrobenzoic acid (Table 1, 6b). Yield: 63% (Method A), 89% (Method B). m.p. 164-166 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 ^{o}C): δ= 8.40 (d, ^{4}J=2.9 Hz, 1 H, 6-H), 8.19 (dd, ^{3}J=9.3 Hz, ^{4}J=2.9 Hz, 1 H, 4-H), 7.18 (d, ^{3}J=9.3 Hz, 1 H, 3-H), 3.72 (m, 4 H, 2XC$\underline{H}_2$-2a), 3.27 (m, 4 H, 2XC$\underline{H}_2$-1a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 ^{o}C): δ= 166.9 (C$\underline{O}$OH), 154.7

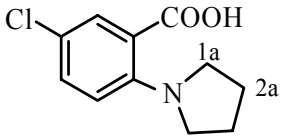
(5-C), 137.9 (2-C), 127.0, 126.8 (4-C, 6-C), 120.6 (1-C), 117.4 (3-C), 65.3 (2X<u>C</u>H_2-2a), 50.6 (2X<u>C</u>H_2-1a). ESI-MS (m/z): 253.1359 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}N_2O_5$ (252.22): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.43; H, 4.73; N, 11.01.



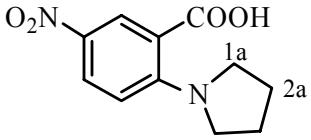
2-(4-morpholinyl)-4-nitrobenzoic acid (Table 1, 7b). Yield: 61% (Method A), 85% (Method B). m.p. 198-200 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.93 (d, ^3J=9.0 Hz, 1 H, 6-H), 7.45 (d, ^4J=2.6 Hz, 1 H, 3-H), 7.22 (dd, ^3J=9.0 Hz, ^4J=2.6 Hz, 1 H, 5-H), 3.84 (m, 4 H, 2XC<u>H</u>$_2$-2a), 3.74 (m, 4 H, 2XC<u>H</u>$_2$-1a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 167.6 (<u>C</u>OOH), 156.4 (4-C), 151.2 (2-C), 130.8 (6-C), 112.1, 109.2 (3-C, 5-C), 103.4 (1-C), 63.7 (2X<u>C</u>H_2-2a), 49.4 (2X<u>C</u>H_2-1a). ESI-MS (m/z): 253.3649 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}N_2O_5$ (252.22): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.41; H, 4.74; N, 11.21.



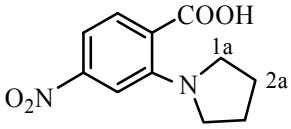
4-fluoro-2-(4-morpholinyl)-4-nitrobenzoic acid (Table 1, 8b). Yield: 61% (Method A), 82% (Method B). m. p. 175-177 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.89 (dd, ^3J=8.7 Hz, $^4J_{H\text{-}F}$=6.1 Hz, 1 H, 6-H), 6.78 (dd, ^4J=2.4 Hz, $^3J_{H\text{-}F}$=9.8 Hz, 1 H, 3-H), 6.41 (dt, ^3J=8.7 Hz, ^4J=2.4 Hz, $^3J_{H\text{-}F}$=10.3 Hz, 1 H, 5-H), 3.82 (m, 4 H, 2XC<u>H</u>$_2$-2a), 3.26 (m, 4 H, 2XC<u>H</u>$_2$-1a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 169.7 (<u>C</u>OOH), 168.9/164.9 (4-C, $J_{C\text{-}F}$=250 Hz), 154.3/154.1 (2-C, $J_{C\text{-}F}$=11 Hz), 135.8/135.6 (6-C, $J_{C\text{-}F}$=11 Hz), 113.9 (1-C), 106.1/105.7, 103.4/102.9 (3-C, 5-C, $J_{C\text{-}F}$=24 Hz; $J_{C\text{-}F}$=26 Hz), 63.1 (2X<u>C</u>H_2-2a), 48.6 (2X<u>C</u>H_2-1a). ESI-MS (m/z): 226.1490 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}FNO_3$ (225.22): C, 58.66; H, 5.37; N, 6.22. Found: C, 58.79; H, 5.42; N, 6.09.



5-chloro-2-(1-pyrrolidinyl)benzoic acid (Table 1, 9b). Yield: 69% (Method A), 91% (Method B). m. p. 169-170 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.72 (d, ^{4}J=2.4 Hz, 1 H, 6-H), 7.33 (dd, ^{3}J=8.8 Hz, ^{4}J=2.4 Hz, 1 H, 4-H), 6.64 (d, ^{3}J=8.8 Hz, 1 H, 3-H), 3.34 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.94 (m, 4 H, 2XC$\underline{H}_2$-2a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 168.4 ($\underline{C}$OOH), 148.2 (2-C), 133.0, 129.1 (4-C, 6-C), 121.6 (5-C), 119.0 (3-C), 116.7 (1-C), 51.9 (2X$\underline{C}H_2$-1a), 24.3 (2X$\underline{C}H_2$-2a). ESI-MS (m/z): 226.5481/228.4831 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}ClNO_2$ (225.67): C, 58.54; H, 5.36; N, 6.21. Found: C, 58.68; H, 5.31; N, 6.16.

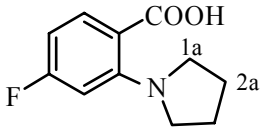


5-nitro-2-(1-pyrrolidinyl)benzoic acid (Table 1, 10b). Yield: 71% (Method A), 92% (Method B). m. p. 225-226 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.30 (d, ^{4}J=2.9 Hz, 1 H, 6-H), 8.09 (dd, ^{3}J=9.5 Hz, ^{4}J=2.9 Hz, 1 H, 4-H), 6.88 (d, ^{3}J=9.5 Hz, 1 H, 3-H), 3.36 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.94 (m, 4 H, 2XC$\underline{H}_2$-2a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 167.9 ($\underline{C}$OOH), 150.5 (5-C), 134.7 (2-C), 127.0, 126.4 (4-C, 6-C), 116.6 (1-C), 113.8 (3-C), 50.8 (2X$\underline{C}H_2$-1a), 25.1 (2X$\underline{C}H_2$-2a). ESI-MS (m/z): 237.3504 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}N_2O_4$ (236.22): C, 55.93; H, 5.12; N, 11.86. Found: C, 55.85; H, 5.23; N, 11.72.

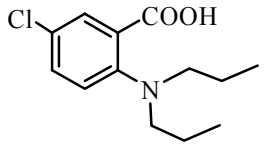


4-nitro-2-(1-pyrrolidinyl)benzoic acid (Table 1, 11b). Yield: 68% (Method A), 88% (Method B). m. p. 204-206 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.99 (d, ^{3}J=8.9 Hz, 1 H, 6-H), 7.45 (d, ^{4}J=2.6 Hz, 1 H, 3-H), 7.19 (dd, ^{3}J=8.9 Hz, ^{4}J=2.6 Hz, 1 H, 5-H), 3.33 (m, 4 H, 2XC$\underline{H}_2$-1a), 1.90 (m, 4 H, 2XC$\underline{H}_2$-2a). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 168.1 ($\underline{C}$OOH), 155.5 (4-C), 152.2 (2-C), 131.1 (6-C), 112.8, 109.7 (3-C, 5-C), 103.6 (1-C), 51.8 (2X$\underline{C}H_2$-1a), 24.2

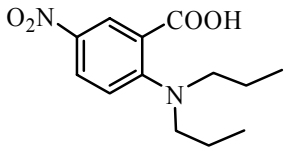
(2XCH$_2$-2a). ESI-MS (m/z): 237.1268 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}N_2O_4$ (236.22): C, 55.93; H, 5.12; N, 11.86. Found: C, 56.11; H, 5.27; N, 11.99.



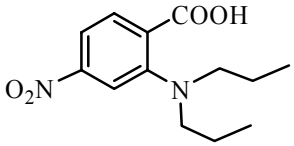
4-fluoro-2-(1-pyrrolidinyl)benzoic acid (Table 1, 12b). Yield: 66% (Method A), 89% (Method B). m. p. 181-182 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 °C): δ= 7.84 (dd, ^3J=8.6 Hz, $^4J_{H\text{-}F}$=6.3 Hz, 1 H, 6-H), 6.89 (dd, ^4J=2.1 Hz, $^3J_{H\text{-}F}$=10.0 Hz, 1 H, 3-H), 6.48 (dt, ^3J=8.6 Hz, ^4J=2.1 Hz, $^3J_{H\text{-}F}$=10.3 Hz, 1 H, 5-H), 3.37 (m, 4 H, 2XCH$_2$-1a), 1.92 (m, 4 H, 2XCH$_2$-2a). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 °C): δ= 169.3 (COOH), 169.1/163.6 (4-C, $J_{C\text{-}F}$=255 Hz), 151.7/151.5 (2-C, $J_{C\text{-}F}$=10 Hz), 134.4/134.2 (6-C, $J_{C\text{-}F}$=11 Hz), 110.3 (1-C), 105.6/105.1, 102.7/102.3 (3-C, 5-C, $J_{C\text{-}F}$=26 Hz, $J_{C\text{-}F}$=24 Hz), 51.8 (2XCH$_2$-1a), 24.2 (2XCH$_2$-2a). ESI-MS (m/z): 210.3308 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{12}FNO_2$ (209.22): C, 63.15; H, 5.78; N, 6.69. Found: C, 63.24; H, 5.69; N, 6.78.



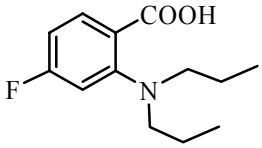
5-chloro-2-(dipropylamino)benzoic acid (Table 1, 13b). Yield: 52% (Method A), 78% (Method B). m. p. 138-140 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 °C): δ= 7.74 (d, ^4J=2.5 Hz, 1 H, 6-H), 7.33 (dd, ^3J=8.3 Hz, ^4J=2.5 Hz, 1 H, 4-H), 6.66 (d, ^3J=8.3 Hz, 1 H, 3-H), 3.29 (t, ^3J=7.0 Hz, 4 H, 2XCH$_2$ CH$_2$CH$_3$), 1.68 (m, 4 H, 2XCH$_2$CH$_2$CH$_3$), 1.07 (t, ^3J=7.7 Hz, 6 H, 2XCH$_2$ CH$_2$CH$_3$). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 °C): δ= 168.8 (COOH), 145.6 (2-C), 132.3, 131.7 (4-C, 6-C), 121.1 (5-C), 119.7 (3-C), 117.4 (1-C), 52.8 (2XCH$_2$CH$_2$CH$_3$), 21.1 (2XCH$_2$CH$_2$CH$_3$), 12.1 (2XCH$_2$CH$_2$CH$_3$). ESI-MS (m/z): 256.6260/258.7155 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}ClNO_2$ (255.74): C, 61.05; H, 7.09; N, 5.48. Found: C, 60.91; H, 7.22; N, 5.63.



2-(dipropylamino)-5-nitrobenzoic acid (Table 1, 14b). Yield: 53% (Method A), 79% (Method B). m. p. 212-214 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 8.34 (d, ^{4}J=2.7 Hz, 1 H, 6-H), 8.19 (dd, ^{3}J=9.1 Hz, ^{4}J=2.7 Hz, 1 H, 4-H), 7.21 (d, ^{3}J=9.1 Hz, 1 H, 3-H), 3.31 (t, 4 H, ^{3}J=7.1 Hz, 2XC$\underline{H}_2$ CH_2CH_3), 1.66 (m, 4 H, 2X$CH_2C\underline{H}_2CH_3$), 1.05 (t, ^{3}J=7.5 Hz 6 H, 2X$CH_2CH_2C\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 168.0 (C$\underline{O}$OH), 152.9 (5-C), 137.6 (2-C), 126.9, 126.1 (4-C, 6-C), 120.8 (1-C), 118.3 (3-C), 52.3 (2X$\underline{C}H_2CH_2CH_3$), 21.7 (2X$CH_2\underline{C}H_2CH_3$), 11.9 (2X$CH_2CH_2\underline{C}H_3$). ESI-MS (m/z): 267.1492 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}N_2O_4$ (266.29): C, 58.63; H, 6.81; N, 10.52. Found: C, 58.51; H, 6.89; N, 10.65.

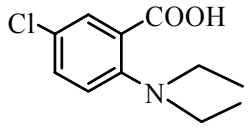


2-(dipropylamino)-4-nitrobenzoic acid (Table 1, 15b). Yield: 50% (Method A), 72% (Method B). m. p. 214-215 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.90 (d, ^{3}J=8.8 Hz, 1 H, 6-H), 7.46 (d, ^{4}J=2.4 Hz, 1 H, 3-H), 7.13 (dd, ^{3}J=8.8 Hz, ^{4}J=2.4 Hz, 1 H, 5-H), 3.26 (t, ^{3}J=7.0 Hz, 4 H, 2XC$\underline{H}_2$ CH_2CH_3), 1.65 (m, 4 H, 2X$CH_2C\underline{H}_2CH_3$), 1.03 (t, ^{3}J=7.3 Hz 6 H, 2X$CH_2CH_2C\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 167.9 (C$\underline{O}$OH), 156.1 (4-C), 153.6 (2-C), 131.3 (6-C), 112.6, 108.9 (3-C, 5-C), 103.8 (1-C), 51.7 (2X$\underline{C}H_2CH_2CH_3$), 20.9 (2X$CH_2\underline{C}H_2CH_3$), 11.3 (2X$CH_2CH_2\underline{C}H_3$). ESI-MS (m/z): 267.1234 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}N_2O_4$ (266.29): C, 58.63; H, 6.81; N, 10.52. Found: C, 58.56; H, 6.77; N, 10.64.

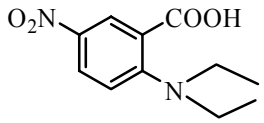


2-(dipropylamino)-4-fluorobenzoic acid (Table 1, 16b). Yield: 51% (Method A), 76% (Method B). m. p. 220-222 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.87 (dd, ^{3}J=8.5 Hz, $^{4}J_{H\text{-}F}$=6.0 Hz, 1 H, 6-H), 6.76 (dd, ^{4}J=2.7 Hz, $^{3}J_{H\text{-}F}$=9.6 Hz, 1 H, 3-H), 6.45 (dt, ^{3}J=8.5 Hz, ^{4}J=2.7 Hz, $^{3}J_{H\text{-}F}$=10.1 Hz, 1 H, 5-H), 3.28 (t, ^{3}J=7.2 Hz, 4 H, 2XC$\underline{H}_2CH_2CH_3$), 1.69 (m, 4 H,

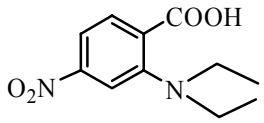
2XCH$_2$ C$\underline{H}_2$CH$_3$), 1.01 (t, ^3J=7.6 Hz, 6 H, 2XCH$_2$CH$_2$C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 ^{o}C): δ= 171.2 (C$\underline{O}$OOH), 169.4/164.4 (4-C, $J_{C\text{-}F}$=250 Hz), 153.4/153.2 (2-C, $J_{C\text{-}F}$=10 Hz), 136.9/136.7 (6-C, $J_{C\text{-}F}$=10 Hz), 112.6 (1-C), 103.8/103.1, 101.4/100.7 (3-C, 5-C, $J_{C\text{-}F}$=29 Hz, $J_{C\text{-}F}$=30 Hz), 51.6 (2X$\underline{C}$H$_2$CH$_2$CH$_3$), 20.4 (2XCH$_2\underline{C}$H$_2$CH$_3$), 11.8 (2XCH$_2$CH$_2\underline{C}$H$_3$). ESI-MS (m/z): 240.1397 [M+H]$^+$. Anal. Calcd. for $C_{13}H_{18}FNO_2$ (239.29): C, 65.25; H, 7.58; N, 5.85. Found: C, 65.09; H, 7.66; N, 5.99.



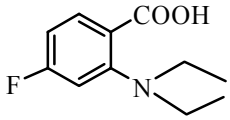
5-chloro-2-(diethylamino)benzoic acid (Table 1, 17b). Yield: 57% (Method A), 81% (Method B). m. p. 142-143 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 ^{o}C): δ= 7.76 (d, ^4J=2.8 Hz, 1 H, 6-H), 7.38 (dd, ^3J=8,6 Hz, ^4J=2.8 Hz, 1 H, 4-H), 6.60 (d, ^3J=8.6 Hz, 1 H, 3-H), 3.37 (q, ^3J=7.0 Hz, 4 H, 2XC$\underline{H}_2$CH$_3$), 1.12 (t, ^3J=7.0 Hz, 6 H, CH$_2$C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 ^{o}C): δ= 168.2 (C$\underline{O}$OOH), 144.9 (2-C), 131.8, 130.9 (4-C, 6-C), 120.4 (5-C), 119.2 (3-C), 116.9 (1-C), 46.7 (2X$\underline{C}$H$_2$CH$_3$), 11.8 (2XCH$_2\underline{C}$H$_3$). ESI-MS (m/z): 228.5735/230.5271 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{14}ClNO_2$ (227.69): C, 58.03; H, 6.20; N, 6.15. Found: C, 58.17; H, 6.12; N, 6.29.



2-(diethylamino)-5-nitrobenzoic acid (Table 1, 18b). Yield: 56% (Method A), 82% (Method B). m. p. 176-177 ^{o}C. ^{1}H NMR (250 MHz, DMSO-d$_6$, 25 ^{o}C): δ= 8.33 (d, ^4J=2.9 Hz, 1 H, 6-H), 8.16 (dd, ^3J=9.3 Hz, ^4J=2.9 Hz, 1 H, 4-H), 7.22 (d, ^3J=9.3 Hz, 1 H, 3-H), 3.38 (q, ^3J=7.1 Hz, 4 H, 2XC$\underline{H}_2$CH$_3$), 1.10 (t, ^3J=7.1 Hz, 6 H, CH$_2$C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d$_6$, 25 ^{o}C): δ= 167.6 (C$\underline{O}$OOH), 152.6 (5-C), 137.4 (2-C), 126.7, 126.6 (4-C, 6-C), 121.2 (1-C), 117.6 (3-C), 46.3 (2X$\underline{C}$H$_2$CH$_3$), 11.7 (2XCH$_2\underline{C}$H$_3$). ESI-MS (m/z): 239.1613 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{14}N_2O_4$: (238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 58.43; H, 6.03; N, 11.69.



2-(diethylamino)-4-nitrobenzoic acid (Table 1, 19b). Yield: 54% (Method A), 75% (Method B). m. p. 216-217 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.91 (d, ^{3}J=8.9 Hz, 1 H, 6-H), 7.49 (d, ^{4}J=2.6 Hz ,1 H, 3-H), 7.18 (dd, ^{3}J=8.9 Hz, ^{4}J=2.6 Hz, 1 H, 5-H), 3.36 (q, ^{3}J=6.9 Hz, 4 H, 2XC$\underline{H}_2$CH$_3$), 1.16 (t, ^{3}J=6.9 Hz, 6 H, CH$_2$C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 167.9 ($\underline{C}$OOH), 155.7 (4-C), 152.9 (2-C), 131.4 (6-C), 112.3, 109.6 (3-C, 5-C), 104.1 (1-C), 46.1 (2X$\underline{C}$H$_2$CH$_3$), 11.6 (2XCH$_2\underline{C}$H$_3$). ESI-MS (m/z): 239.1964 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{14}N_2O_4$ (238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 55.39; H, 6.08; N, 11.89.



2-(diethylamino)-4-fluorobenzoic acid (Table 1, 20b). Yield: 54% (Method A), 78% (Method B). m. p. 177-179 °C. ^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ= 7.90 (dd, ^{3}J=8.7 Hz, $^{4}J_{H\text{-}F}$=6.3 Hz, 1 H, 6-H), 6.78 (dd, ^{4}J=2.5 Hz, $^{3}J_{H\text{-}F}$=9.9 Hz, 1 H, 3-H), 6.49 (dt, ^{3}J=8.7 Hz, ^{4}J=2.5 Hz, $^{3}J_{H\text{-}F}$=10.2 Hz, 1 H, 5-H), 3.41 (q, ^{3}J=7.3 Hz, 4 H, 2XC$\underline{H}_2$CH$_3$), 1.16 (t, ^{3}J=7.3 Hz, 6 H, CH$_2$C$\underline{H}_3$). ^{13}C NMR (63 MHz, DMSO-d_6, 25 °C): δ= 170.8 ($\underline{C}$OOH), 169.3/163.8 (4-C, $J_{C\text{-}F}$=255 Hz), 153.1/152.9 (2-C, $J_{C\text{-}F}$=11 Hz), 136.2/136.0 (6-C, $J_{C\text{-}F}$=11 Hz), 111.8 (1-C), 105.9/105.2, 103.2/102.5 (3-C, 5-C, $J_{C\text{-}F}$=28 Hz, $J_{C\text{-}F}$=29 Hz), 46.4 (2X$\underline{C}$H$_2$CH$_3$), 11.1 (2X$\underline{C}$H$_2$CH$_3$). ESI-MS (m/z): 212.1636 [M+H]$^+$. Anal Anal. Calcd. for $C_{11}H_{14}FNO_2$ (211.23): C, 62.55; H, 6.68; N, 6.63. Found: C, 62.61; H, 6.76; N, 6.56.

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