Supporting Information

Design, Synthesis, and Structure-Activity Relationship of a Novel Series of GluN2C-Selective Potentiators

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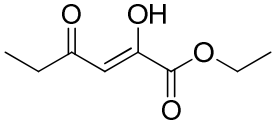
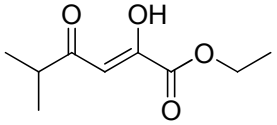
CHEMISTRY EXPERIMENTAL

Compounds for which synthesis is not described were purchased from a commercial vendor. Purchased compounds were greater than 90% pure as determined by the suppliers.

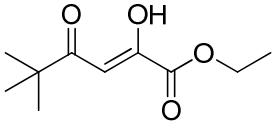
All dry solvents were obtained from a Glass Contour System. Reagents used were acquired from commercial suppliers and utilized without additional purification. Pre-coated glass plates (silica gel 60 F254, 0.25 mm) were used to monitor the progress of reactions by thin layer chromatography (TLC). Purification by flash column chromatography was performed on a Teledyne ISCO Combiflash Companion using prepackaged Teledyne RediSep disposable normal phase silica columns. ^{1}H and ^{13}C NMR experiments were each carried out on an INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-600 (600 MHz), Unity-600 (600 MHz), or Mercury 300 Vx (300 MHz). All chemical shifts are reported in parts per million and referenced to the residual solvent peak. All coupling constants are reported in Hertz (Hz). The IR spectra were acquired with a Nicolet Avatar 370 DTGS. Mass spectra were performed by the Emory University Mass Spectrometry Center on a VG 70-S Nier Johnson or JEOL instrument. Purity of all final compounds was established by LCMS (Agilent) and was found to be > 95% (85% ACN with 0.1% formic acid and 85% MeOH with 0.1% formic acid).



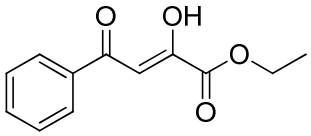
(Z)-Ethyl 2-hydroxy-4-oxohex-2-enoate (3). Compound **3** was prepared via Procedure II from butan-2-one (1.2 mL, 14 mmol) to yield a yellow oil (0.58 g, 24 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.31 (q, J = 5.4 MHz, 2H), 2.50 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 9.0 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.2, 181.2, 162.2, 101.4, 62.5, 34.3, 14.1, 8.7; HRMS (APCI) Calcd for $C_8H_{12}O_4$ 173.0808; found 173.0805 $[M+H]^+$.



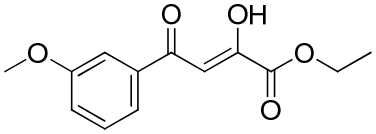
(Z)-Ethyl 2-hydroxy-5-methyl-4-oxohex-2-enoate (4). Compound **4** was prepared via Procedure II from 3-methylbutan-2-one (1.0 g, 12 mmol) to yield a black oil (1.8 g, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.62 (sept, J = 7.2 Hz, 1H), 1.32 (t, J = 6.4 Hz, 3H), 1.13 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 167.1, 162.3, 100.2, 62.6, 39.1, 18.7, 14.1, 14.0; HRMS (APCI) Calcd for $C_9H_{14}O_4$ 187.0965; found 187.0963 $[M+H]^+$.



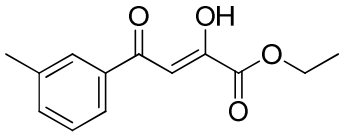
(Z)-Ethyl 2-hydroxy-5,5-dimethyl-4-oxohex-2-enoate (5). Compound **5** was prepared via Procedure II from 3,3-dimethylbutan-2-one (1.0 g, 10 mmol) to yield a yellow oil (0.62 g, 31 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 4.30 (q, J = 6.8 Hz, 2H), 1.32 (t, J = 6.8 Hz, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 167.4, 162.0, 97.7, 62.2, 41.4, 26.5, 13.9; HRMS (APCI) Calcd for $C_{10}H_{16}O_4$ 201.1121; found 201.1119 $[M+H]^+$.



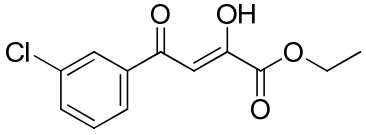
(Z)-Ethyl 2-hydroxy-4-oxo-4-phenylbut-2-enoate (6). Compound **6** was prepared via Procedure II from acetophenone (1.0 g, 8.3 mmol) to yield an orange oil (0.80 g, 44 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 7.8 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.03 (s, 1H), 4.35 (q, J = 6.6 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.7, 169.8, 162.1, 134.8, 133.8, 128.9, 127.9, 97.9, 62.6, 14.1; HRMS (APCI) Calcd for $C_{12}H_{12}O_4$ 221.0808; found 221.0806 $[M+H]^+$.



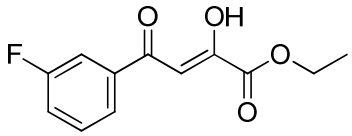
(Z)-Ethyl 2-hydroxy-4-(3-methoxyphenyl)-4-oxobut-2-enoate (7). Compound **7** was prepared via Procedure II from 1-(3-methoxyphenyl)ethanone (1.0 g, 6.7 mmol) to yield a brown-yellow oil (0.96 g, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.03 (s, 1H), 4.38 (q, J = 7.6 Hz, 2H), 3.85 (s, 3H), 1.39 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 169.4, 162.3, 160.1, 136.4, 130.0, 120.6, 120.3, 112.4, 98.3, 62.7, 55.6, 14.2; HRMS (APCI) Calcd for $C_{13}H_{14}O_5$ 251.0914; found 251.0911 $[M+H]^+$.



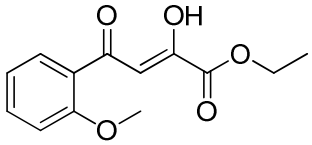
(Z)-Ethyl 2-hydroxy-4-oxo-4-(m-tolyl)but-2-enoate (8). Compound **8** was prepared via Procedure II from 1-*m*-tolylethanone (1.0 mL, 7.5 mmol) to yield a brown-yellow oil (0.26 g, 15 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.77 (mult, 2H), 7.41-7.35 (mult, 2H), 7.05 (s, 1H), 4.39 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.40 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 169.7, 162.4, 138.9, 135.0, 134.8, 128.9, 128.5, 125.3, 98.2, 62.7, 21.5, 14.2; HRMS (APCI) Calcd for $C_{13}H_{14}O_4$ 235.0965; found 235.0963 $[M+H]^+$.



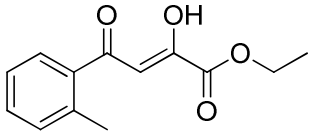
(Z)-Ethyl 4-(3-chlorophenyl)-2-hydroxy-4-oxobut-2-enoate (9). Compound **9** was prepared via Procedure II from 1-(3-chlorophenyl)ethanone (1.0 g, 6.5 mmol) to yield a brown-green solid (1.1 g, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 7.96 (t, J = 1.6 Hz, 1H), 7.87 (dt, J = 1.2 Hz, J = 7.6 Hz, 1), 7.58 (ddd, J = 1.2 Hz, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.04 (s, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 170.3, 162.1, 126.7, 135.4, 133.8, 130.3, 128.0, 126.1, 98.1, 62.9, 14.2; HRMS (APCI) Calcd for $C_{12}H_{11}ClO_4$ 255.0419; found 255.0416 $[M+H]^+$.*(Z)-Ethyl 4-(3-fluorophenyl)-*



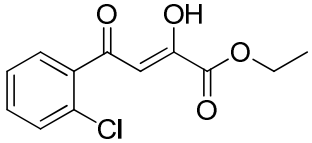
(Z)-Ethyl 4-(3-fluorophenyl)-2-hydroxy-4-oxobut-2-enoate (10). Compound **10** was prepared via Procedure II from 1-(3-fluorophenyl)ethanone (1.0 g, 7.2 mmol) to yield a light brown solid (1.1 g, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (br s, 1H), 7.78 (dt, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.68 (dt, J = 1.6 Hz, J = 9.2 Hz, 1H), 7.49 (td, J = 6.0 Hz, J = 8.4 Hz, 1H), 7.31 (ddd, J = 1.2 Hz, J = 2.8 Hz, J = 8.4 Hz, 1H), 7.04 (s, 1H), 4.41 (q, J = 7.6 Hz, 2H), 1.42 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (d, J = 2.2 Hz), 170.3, 163.0 (d, J = 24.7 Hz), 162.1, 137.2 (d, J = 7.4 Hz), 130.7 (d, J = 7.4 Hz), 123.7 (d, J = 2.2 Hz), 120.9 (d, J = 20.8 Hz), 114.8 (d, J = 22.3 Hz), 98.1, 62.9, 14.2; HRMS (APCI) Calcd for $C_{12}H_{11}FO_4$ 239.0714; found 239.0710 $[M+H]^+$.



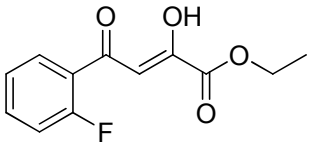
(Z)-Ethyl 2-hydroxy-4-(2-methoxyphenyl)-4-oxobut-2-enoate (11). Compound **11** was prepared via Procedure II from 1-(2-methoxyphenyl)ethanone (1.0 g, 6.7 mmol) to yield a yellow solid (0.89 g, 53 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.87 (mult, 1H), 7.52-7.48 (mult, 1H), 7.31 (s, 1H), 7.06-6.98 (mult, 2H), 4.41-4.34 (mult, 2H), 3.93 (s, 3H), 1.42-1.38 (mult, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.4, 169.1, 162.6, 159.2, 134.7, 130.7, 124.2, 120.9, 111.8, 103.2, 62.4, 55.7, 14.1; HRMS (APCI) Calcd for $C_{13}H_{14}O_5$ 249.0769; found 249.0769 $[M-H]^-$.



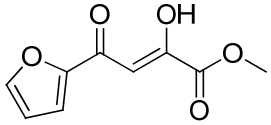
(Z)-Ethyl 2-hydroxy-4-oxo-4-(o-tolyl)but-2-enoate (12*).* Compound **12** was prepared via Procedure II from 1-*o*-tolylethanone (0.98 mL, 7.5 mmol) to yield an orange oil (1.8 g, >99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.2 Hz, 1H), 7.30-7.24 (mult, 3H), 6.84 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 1.39 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 168.2, 162.2, 138.4, 135.7, 132.2, 132.0, 129.1, 126.1, 101.8, 62.6, 21.1, 14.1; HRMS (APCI) Calcd for $C_{13}H_{14}O_4$ 235.0965; found 235.0963 $[M+H]^+$.



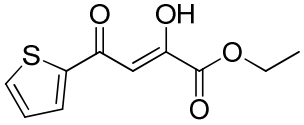
(Z)-Ethyl 4-(2-chlorophenyl)-2-hydroxy-4-oxobut-2-enoate (13). Compound **13** was prepared via Procedure II from 1-(2-chlorophenyl)ethanone (1.0 g, 6.5 mmol) to yield a yellow oil (0.58 g, 35 %). ^{1}H NMR (600 MHz, $CDCl_3$, 60 °C) δ 7.65 (t, J = 6.6 Hz, 1H), 7.47-7.44 (mult, 2H), 7.37 (d, J = 6.6 Hz, 1H), 6.95 (d, J = 6.6 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8, 168.1, 161.9, 135.8, 132.9, 132.2, 131.1, 130.3, 127.2, 103.1, 62.7, 14.1; HRMS (APCI) Calcd for $C_{12}H_{11}ClO_4$ 255.0419; found 255.0417 $[M+H]^+$.



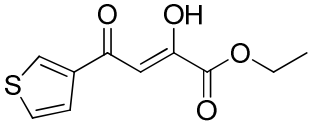
(Z)-Ethyl 4-(2-fluorophenyl)-2-hydroxy-4-oxobut-2-enoate (14). Compound **14** was prepared via Procedure II from 1-(2-fluorophenyl)ethanone (0.88 mL, 6.7 mmol) to yield a yellow solid (0.48 g, 29 %). ^{1}H NMR (600 MHz, $CDCl_3$, 60 °C) δ 7.98-7.94 (mult, 1H), 7.56-7.54 (mult, 1H), 7.30-7.26 (mult, 1H), 7.19-7.15 (mult, 1H), 7.10-7.09 (mult, 1H), 4.42-4.38 (mult, 2H), 1.43-1.40 (mult, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 170.4, 162.2, 161.9 (d, J = 255.8 Hz), 135.4 (d, J = 8.3 Hz), 130.7, 125.0, 123.7, 117.1 (d, J = 24.8 Hz), 102.5 (d, J = 12.3 Hz), 62.9, 14.3; HRMS (APCI) Calcd for $C_{12}H_{11}FO_4$ 239.0714; found 239.0718 $[M+H]^+$.



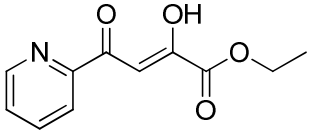
(Z)-Methyl 4-(furan-2-yl)-2-hydroxy-4-oxobut-2-enoate (15). Compound **15** was prepared via Procedure II from 1-(furan-2-yl)ethanone (1.0 g, 9.1 mmol) in MeOH (4.1 mL, 2.2 M) to yield a yellow solid (1.1 g, 61 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 1.2 Hz, 1H), 7.33 (d, J = 3.6 Hz, 1H), 6.93 (s, 1H), 6.61-6.61 (mult, 1H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.2, 165.6, 162.6, 151.0, 148.0, 118.8, 113.3, 99.3, 53.3; HRMS (APCI) Calcd for $C_9H_8O_5$ 197.0445; found 197.0443 $[M+H]^+$.



(Z)-Ethyl 2-hydroxy-4-oxo-4-(thiophen-2-yl)but-2-enoate (16). Compound **16** was prepared via Procedure II from 1-(thiophen-2-yl)ethanone (0.89 mL, 7.9 mmol) to yield a yellow oil (0.71 g, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 1.2 Hz, J = 4.0 Hz, 1H), 7.74 (dd, J = 0.8 Hz, J = 4.8 Hz, 1H), 7.18 (dd, J = 4.0 Hz, J = 5.2 Hz, 1H), 6.91 (s, 1H), 4.38 (q, J = 7.6 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 164.8, 162.2, 142.2, 135.4, 132.8, 128.9, 99.6, 62.8, 14.2; HRMS (APCI) Calcd for $C_{10}H_{10}O_4S$ 227.0370; found 227.0370 $[M+H]^+$.

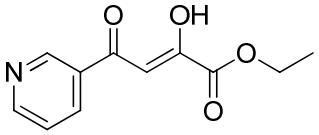


(Z)-Ethyl 2-hydroxy-4-oxo-4-(thiophen-3-yl)but-2-enoate (17). Compound **17** was prepared via Procedure II from 1-(thiophen-3-yl)ethanone (1.0 g, 7.9 mmol) to yield a cream colored solid (1.2 g, 68 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, J = 3.0 Hz, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.37 (dd, J = 3.0 Hz, J = 5.4 Hz, 1H), 6.86 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 168.7, 162.3, 139.6, 132.7, 127.3, 126.4, 99.3, 62.7, 14.2; HRMS (APCI) Calcd for $C_{10}H_{10}O_4S$ 227.0373; found 227.0377 $[M+H]^+$.

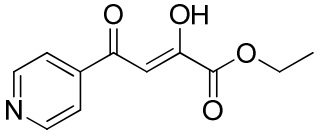


(Z)-Ethyl 2-hydroxy-4-oxo-4-(pyridin-2-yl)but-2-enoate (18). Compound **18** was prepared via Procedure II from 1-(pyridin-2-yl)ethanone to yield a dark red solid (0.61 g, 33 %). ^{1}H NMR

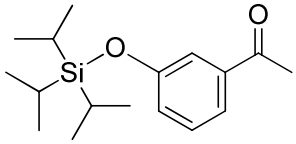
(600 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.8 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 1H), 7.92 (td, *J* = 1.8 Hz, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.53 (ddd, *J* = 1.8 Hz, *J* = 4.8 Hz, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 6.6 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 218.3, 181.2, 173.1, 151.9, 149.3, 137.7, 127.7, 123.2, 98.9, 62.8, 14.3; HRMS (APCI) Calcd for $C_{11}H_{11}NO_4$ 222.0761; found 222.0759 $[M+H]^+$.



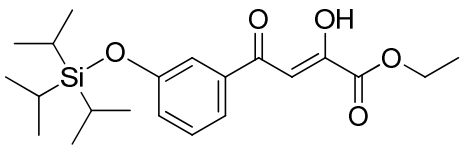
(Z)-Ethyl 2-hydroxy-4-oxo-4-(pyridin-3-yl)but-2-enoate (19). Compound **19** was prepared via Procedure II from 1-(pyridin-3-yl)ethanone (9.0 mL, 83 mmol) to yield a pale yellow solid (7.3 g, 40 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.19 (t, *J* = 1.2 Hz, 1H), 8.81 (d, *J* = 4.8 Hz, 1H), 8.26 (dt, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 4.8 Hz, *J* = 7.8 Hz, 1H), 7.07 (s, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.8, 181.1, 171.0, 161.9, 154.1, 149.3, 135.3, 130.7, 123.9, 63.0, 14.2; HRMS (APCI) Calcd for $C_{11}H_{11}NO_4$ 222.0761; found 222.0759 $[M+H]^+$.



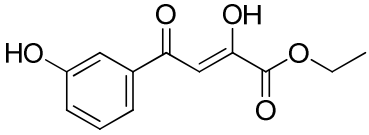
(Z)-Ethyl 2-hydroxy-4-oxo-4-(pyridin-4-yl)but-2-enoate (20). Compound **20** was prepared via Procedure II from 1-(pyridine-4-yl)ethanone (0.55 mL, 8.3 mmol) to yield an orange solid (0.29 g, 16 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 6.0 Hz, 2H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.07 (s, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 173.4, 161.7, 151.1, 141.4, 120.8, 98.0, 63.1, 14.2; HRMS (APCI) Calcd for $C_{11}H_{11}NO_4$ 222.0761; found 222.0759 $[M+H]^+$.



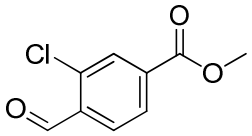
1-(3-((Triisopropylsilyl)oxy)phenyl)ethanone (143). To a solution of 1-(3-hydroxyphenyl)ethanone (3.0 g, 22 mmol) in DCM (59 mL, 0.38 M) was added 1*H*-imidazole (2.4 mL, 44 mmol, 2.0 equiv) and chlorotriisopropylsilane (8.7 mL, 41 mmol, 1.8 equiv). The resulting mixture was stirred at rt for 6 hrs before being diluted with water and extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (6.4 g, >99 %), which was taken on without further attempts at purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 1H), 7.47 (s, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 0.8 Hz, *J* = 2.4 Hz, 1H), 2.57 (s, 3H), 1.26 (sept, *J* = 8.0 Hz, 3H), 1.11 (d, *J* = 8.0 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 156.5, 138.6, 129.6, 124.9, 121.4, 119.3, 26.7, 18.0, 17.82, 17.76; HRMS (APCI) Calcd for $C_{17}H_{28}O_2Si$ 293.1931; found 293.1932 $[M+H]^+$.



(Z)-Ethyl 2-hydroxy-4-oxo-4-(3-((triisopropylsilyl)oxy)phenyl)but-2-enoate (144*)*. Compound **144** was prepared via Procedure II from **143** (8.8 g, 30 mmol) to yield a yellow oil (3.3 g, 28 %), which was taken on without further attempts at purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 4.40 (q, *J* = 6.8 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.28 (sept, *J* = 6.4 Hz, 3H), 1.12 (d, *J* = 4.0 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 169.5, 162.3, 156.8, 136.5, 130.0, 125.5, 120.8, 118.9, 98.3, 62.7, 18.0, 17.8, 17.6, 14.2; HRMS (APCI) Calcd for $C_{21}H_{32}O_5Si$ 393.2092; found 393.2091 $[M+H]^+$.

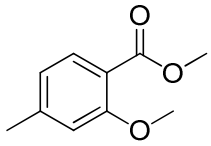


(Z)-Ethyl 2-hydroxy-4-(3-hydroxyphenyl)-4-oxobut-2-enoate (21). To a solution of **144** (3.3 g, 8.5 mmol) in THF (150 mL, 0.06 M) at 0 °C was added a solution of TBAF (25 mL, 1.0 M in THF, 3.0 equiv). The reaction mixture was stirred for 30 min at 0 °C before being warmed to rt and stirred for an additional 35 min. At this time the resulting solution was diluted with water and extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 1/1) to afford a pale yellow solid (0.86 g, 43 %), which was taken on without further attempts at purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.50 (mult, 2H), 7.37-7.31 (mult, 1H), 7.15-7.12 (mult, 1H), 7.06 (s, 1H), 4.40 (q, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 169.6, 162.8, 156.8, 136.2, 130.3, 121.3, 120.3, 114.7, 98.4, 63.2, 14.2; HRMS (APCI) Calcd for $C_{12}H_{12}O_5$ 237.0758; found 237.0758 $[M+H]^+$.

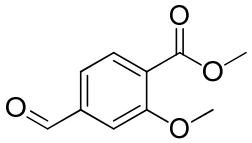


Methyl 3-chloro-4-formylbenzoate (32). To a solution of methyl 3-chloro-4-methylbenzoate (1.0 g, 5.4 mmol) in carbon tetrachloride (54 mL, 0.1 M) was added *N*-bromosuccinimide (2.2 g, 12 mmol) and benzoic peroxyanhydride (0.05 g, 0.22 mmol). The reaction mixture was refluxed for 4 hrs. At this time the resulting solution was cooled to rt and filtered. The filtrate was collected, quenched with water and washed with saturated sodium thiosulfate (2x). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give methyl 4-(dibromomethyl)-3-chlorobenzoate as a yellow oil. The crude material was then dissolved in acetone:water (5:1, 0.35 M) and silver nitrate (1.6 g, 9.7 mmol) was added. The flask was covered with foil before being allowed to stir at rt for 3 hrs. The reaction mixture was then filtered through celite, diluted with EtOAc and extracted with saturated sodium bicarbonate (2x). The combined organic layers were washed with water and brine before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc) to give a white solid (0.61 g, 63 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.13 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 7.2

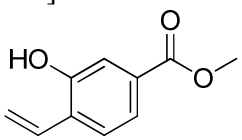
Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.4, 173.1, 165.2, 136.1, 135.3, 132.0, 129.6, 128.3, 53.1; HRMS (APCI) Calcd for $C_9H_7ClO_3$ 197.0000; found 197.0000 $[M-H]^-$.



Methyl 2-methoxy-4-methylbenzoate (181). To a solution of 2-hydroxy-4-methylbenzoic acid (1.0 g, 6.6 mmol) in acetone (12 mL) was added finely ground potassium carbonate (2.4 g, 20 mmol) and dimethyl sulfate (1.9 mL, 20 mmol, 3.0 equiv). The solution stirred at rt for 18 hrs before being brought to reflux and heated for one additional hour. The resulting mixture was then filtered and concentrated *in vacuo*. The crude residue was dissolved in EtOAc (35 mL) and triethylamine (2.7 mL, 6.6 mmol, 1.0 equiv) was added. After stirring at rt for 30 min, the mixture was washed with water, 2N HCl, and brine before being dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes:EtOAc, 6:1) to give a clear oil (0.91 g, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 1.6 Hz, J = 7.2 Hz, 1H), 6.80-6.78 (mult, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 159.5, 144.9, 132.1, 121.1, 117.0, 112.9, 56.1, 52.1, 22.2; HRMS (APCI) Calcd for $C_{10}H_{12}O_3$ 181.0859; found 181.0857 $[M+H]^+$.

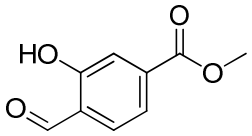


Methyl 4-formyl-2-methoxybenzoate (33). To a solution of **181** (0.5 g, 2.8 mmol) in carbon tetrachloride (28 mL, 0.1 M) was added *N*-bromosuccinimide (1.1 g, 6.2 mmol) and benzoic peroxyanhydride (0.03 g, 0.11 mmol). The reaction mixture was refluxed for 4 hrs. At this time the resulting solution was cooled to rt and filtered. The filtrate was collected, quenched with water and washed with saturated sodium thiosulfate (2x). The combined organic layers were then dried over MgSO4, filtered and concentrated *in vacuo* to give methyl 4-(dibromomethyl)-2-methoxybenzoate as a yellow oil. The crude material was then dissolved in acetone:water (5:1, 0.35 M) and silver nitrate (0.97 g, 5.7 mmol) was added. The flask was covered with foil before being allowed to stir at rt for 3 hrs. The reaction mixture was then filtered through celite, diluted with EtOAc and extracted with saturated sodium bicarbonate (2x). The combined organic layers were washed with water and brine before being dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (0.21 g, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.49-7.47 (mult, 2H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.7, 166.2, 159.3, 139.9, 132.1, 125.9, 122.9, 110.8, 56.4, 52.7. HRMS (APCI) Calcd for $C_{10}H_{10}O_4$ 193.0495; found 193.0495 $[M-H]^-$.

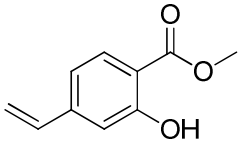


Methyl 3-hydroxy-4-vinylbenzoate (182). To a solution of methyl 3-hydroxy-4-iodobenzoate (0.5 g, 1.8 mmol) in THF:H_2O (4:1, 0.13 M) was added dibutyl vinylboronate (0.50 g, 2.7 mmol), sodium carbonate (1.3 g, 13 mmol) and 5 mol % dichloro-bis(triphenylphosphine)palladium. The reaction mixture was purged with $N_{2(g)}$ for 5 min before

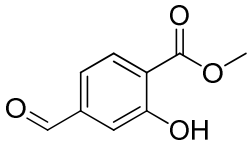
being refluxed for 2 hrs. The resulting mixture was concentrated *in vacuo*, diluted with EtOAc and washed with water and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a pale yellow solid (0.22 g, 68 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.2 Hz, J = 7.8 Hz, 1H), 7.55 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 10.8 Hz, J = 18.0 Hz, 1H), 5.88 (d, J = 18.0 Hz, 1H), 5.59 (br s, 1H), 5.47 (d, J = 11.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 153.3, 131.0, 130.2, 129.9, 127.2, 122.1, 117.8, 117.2, 52.6; HRMS (APCI) Calcd for $C_{10}H_{10}O_3$ 179.0703; found 179.0703 $[M+H]^+$.



Methyl 4-formyl-3-hydroxybenzoate (34). 182 (0.22 g, 1.2 mmol) was dissolved in DCM (7.5 mL, 0.4 M) in a flask open to air. The reaction mixture was cooled to −78 °C and a stream of $O_{2(g)}$ was passed through it for 5 min. At this time, $O_{3(g)}$ was bubbled into the mixture until the color turned blue. The resulting solution was then purged with $O_{2(g)}$ for an additional 5 min before being treated with dimethylsulfane (0.27 mL, 3.7 mmol, 3.0 equiv) and allowed to warm to rt overnight. The mixture was concentrated *in vacuo* and purified using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a pale yellow solid (0.19 g, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 10.00 (s, 1H), 7.67-7.66 (mult, 3H), 3.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.7, 165.9, 161.4, 137.5, 133.8, 123.1, 120.6, 119.3, 52.9; HRMS (APCI) Calcd for $C_9H_8O_4$ 181.0495; found 181.0496 $[M+H]^+$.

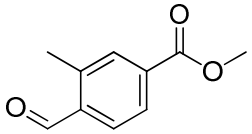


Methyl 2-hydroxy-4-vinylbenzoate (183). To a solution of methyl 2-hydroxy-4-iodobenzoate (1.0 g, 3.6 mmol) in THF:H_2O (4:1, 0.13 M) was added dibutyl vinylboronate (0.99 g, 5.4 mmol), sodium carbonate (2.7 g, 25 mmol) and 5 mol % dichloro-bis(triphenylphosphine)palladium. The reaction mixture was purged with $N_{2(g)}$ for 5 min before being refluxed for 2 hrs. The resulting mixture was concentrated *in vacuo*, diluted with EtOAc and washed with water and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a clear oil (0.51 g, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.95 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 6.68 (dd, J = 10.8 Hz, J = 17.6 Hz, 1H), 5.87 (d, J = 17.6 Hz,1H), 5.40 (d, J = 10.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 161.9, 145.0, 136.1, 130.2, 117.5, 117.3, 115.1, 111.7, 52.5; HRMS (APCI) Calcd for $C_{10}H_{10}O_3$ 179.0703; found 179.0701 $[M+H]^+$.

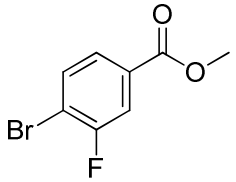


Methyl 4-formyl-2-hydroxybenzoate (35). Compound **183** (0.49 g, 2.8 mmol) was dissolved in DCM (7.5 mL, 0.4 M) in a flask open to air. The reaction mixture was cooled to −78 °C and a

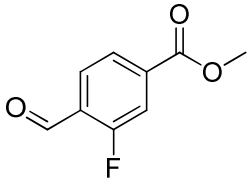
stream of $O_{2(g)}$ was passed through it for 5 min. At this time, $O_{3(g)}$ was bubbled into the mixture until the color turned blue. The resulting solution was then purged with $O_{2(g)}$ for an additional 5 min before being treated with dimethylsulfane (0.61 mL, 8.3 mmol, 3.0 equiv) and allowed to warm to rt overnight. The mixture was concentrated *in vacuo* and purified using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a white solid (0.30 g, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 10.02 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.41 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 170.1, 162.1, 141.6, 131.0, 119.6, 119.0, 117.0, 53.1; HRMS (APCI) Calcd for $C_9H_8O_4$ 181.0495; found 181.0493 $[M+H]^+$.



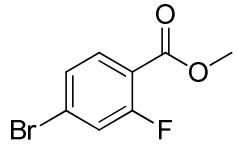
Methyl 4-formyl-3-methylbenzoate (36). To a solution of methyl 4-iodo-3-methylbenzoate (1.0 g, 3.6 mmol) in THF (24 mL, 0.15 M) at -15 °C was added *iso*-propylmagnesium chloride (7.2 mL, 14.5 mmol, 4.0 equiv). The reaction mixture was allowed to continue stirring at -15 °C for 2 hrs before *N,N*-dimethylformamide (1.4 mL, 18 mmol, 5.0 equiv) was added. The mixture was warmed to room temperature over a period of 1 hr. At this time the reaction was quenched with HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a white solid (0.45 g, 70 %) which was taken on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.10-8.00 (mult, 1H), 7.95-7.87 (mult, 2H), 3.96 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 166.5, 140.8, 137.1, 134.3, 133.1, 131.9, 127.5, 52.8, 19.7; HRMS (APCI) Calcd for $C_{10}H_{10}O_3$ 177.0546; found 177.0541 $[M+H]^+$.



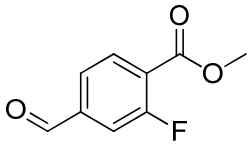
Methyl 4-bromo-3-fluorobenzoate (184). Compound **184** was prepared via Procedure III from 4-bromo-3-fluorobenzoic acid (2.0 g, 9.1 mmol) to give a yellow oil (2.1 g, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.67 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.63-7.59 (mult, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 159.0 (d, J = 247.4 Hz), 138.8, 131.5 (d, J = 6.4 Hz), 126.3 (d, J = 1.9 Hz), 117.5 (d, J = 12.0 Hz), 114.9 (d, J = 21.3 Hz), 52.7; HRMS (APCI) Calcd for $C_8H_6BrFO_2$ 232.9608; found 232.9609 $[M+H]^+$.



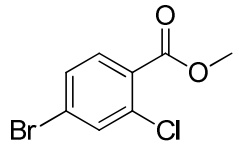
Methyl 3-fluoro-4-formylbenzoate (37). Compound **37** was prepared via Procedure IV from **184** (2.0 g, 8.7 mmol) to yield a clear oil (0.12 g, 8%), which was carried on immediately. HRMS (APCI) Calcd for $C_9H_7FO_3$ 181.02955; found 181.02929 $[M-H]^-$.



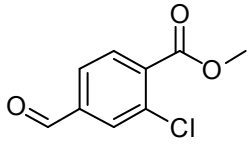
Methyl 4-bromo-2-fluorobenzoate (185). Compound **185** was prepared via Procedure III from 4-bromo-2-fluorobenzoic acid (1.0 g, 4.6 mmol) to give an off-white solid (0.93 g, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (mult, 1H), 7.39-7.34 (mult, 2H), 3.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2 (d, J = 6.3 Hz), 163.5 (d, J = 269.7 Hz), 133.3, 128.1 (d, J = 8.3 Hz), 127.7, 120.8 (d, J = 26.9 Hz), 117.8 (d, J = 10.2 Hz), 52.7; HRMS (APCI) Calcd for $C_8H_6BrFO_2$ 232.9608; found 232.9609 $[M+H]^+$.



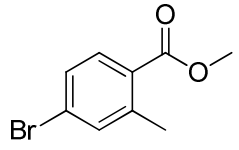
Methyl 2-fluoro-4-formylbenzoate (38). Compound **38** was prepared via Procedure IV from **185** (0.91 g, 3.9 mmol) to yield a white solid (0.080 g, 11 %) which was taken on immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.12 (td, J = 0.8 Hz, J = 7.6 Hz, 1H), 7.74 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.66 (dd, J = 1.6 Hz, J = 10.0 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 164.1, 162.1 (d, J = 261 Hz), 141.0 (d, J = 6.7 Hz), 133.2 (d, J = 9.7 Hz), 125.1 (d, J = 4.4 Hz), 120.8 (d, J = 25.3 Hz), 117.3 (d, J = 23.1 Hz), 53.0; HRMS (APCI) Calcd for $C_9H_7FO_3$ 183.0353; found 183.0352 $[M+H]^+$.



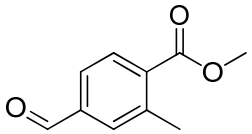
Methyl 4-bromo-2-chlorobenzoate (186). Compound **186** was prepared via Procedure III from 4-bromo-2-chlorobenzoic acid (2.0 g, 8.5 mmol) to give an orange oil (2.1 g, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 135.2, 134.0, 132.8, 130.2, 128.9, 126.7, 52.8; HRMS (APCI) Calcd for $C_8H_6BrClO_2$ 248.9312; found 248.9313 $[M-H]^-$.



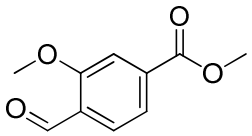
Methyl 2-chloro-4-formylbenzoate (39). Compound **39** was prepared via Procedure IV from **186** (1.0 g, 4.0 mmol) to yield a yellow oil (0.19 g, 24 %) which was taken on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.97-7.94 (mult, 2H), 7.84-7.81 (mult, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 162.7, 139.0, 135.3, 134.7, 132.0, 131.9, 127.4, 53.1; HRMS (APCI) Calcd for $C_9H_7ClO_3$ 197.0000; found 197.0000 $[M-H]^-$.



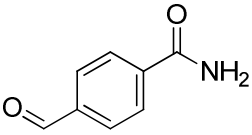
Methyl 4-bromo-2-methylbenzoate (187). Compound **187** was prepared via Procedure III from 4-bromo-2-methylbenzoic acid (1.0 g, 4.7 mmol) to give a yellow oil (0.98 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.39 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 142.6, 134.8, 132.3, 129.2, 128.5, 126.9, 52.2, 21.8; HRMS (APCI) Calcd for $C_9H_9BrO_2$ 228.9859; found 228.9860 $[M-H]^-$.



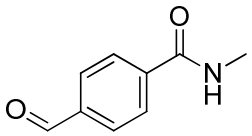
Methyl 4-formyl-2-methylbenzoate (40). Compound **40** was prepared via Procedure IV from **187** (1.0 g, 4.4 mmol) to yield a clear oil (0.15 g, 19 %) which was taken on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.76-7.75 (mult, 2H), 3.94 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 167.5, 141.0, 138.3, 132.8, 131.3, 130.7, 126.9.52.5, 21.7; HRMS (APCI) Calcd for $C_{10}H_{10}O_3$ 179.0703; found 179.0703 $[M+H]^+$.



Methyl 4-formyl-3-methoxybenzoate (41). To a solution of 4-formyl-3-hydroxybenzoic acid (0.5 g, 3.0 mmol) in DMSO (5.2 mL, 0.60 M) was added finely ground potassium carbonate (2.6 g, 19 mmol) and methyl iodide (0.65 mL, 3.0 mmol, 1.0 equiv). The reaction mixture was allowed to stir at rt for 3 hrs before being diluted with water and extracted into EtOAc. The organic layer was washed with water (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified using flash column chromatography on SiO_2 (5% MeOH/DCM) to yield a white solid (0.34 g, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.88 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 1H), 7.70-7.67 (mult, 2H), 4.00 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 166.3, 161.6, 136.6, 128.7, 127.7, 121.8, 113.0, 56.2, 52.8; HRMS (APCI) Calcd for $C_{10}H_{10}O_4$ 195.0652; found 195.0650 $[M+H]^+$.

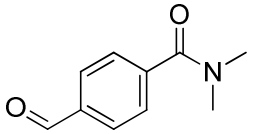


4-Formyl-benzamide (42). To a solution of Vilsmeier reagent (0.86 g, 6.7 mmol) in THF (5.9 mL, 1.1 M) at 0 °C was added 4-formylbenzoic acid (1.0 g, 6.7 mmol). The resulting mixture continued stirring at 0 °C for 16 hrs before being poured onto cold aqueous ammonia (6.1 mL, 15 M), concentrated *in vacuo*, filtered and washed with cold water to give a white solid (0.29 g, 30 %). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.07 (s, 1H), 8.20 (br s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 7.6 Hz, 2H), 7.64 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 193.0, 167.1, 139.4, 137.8, 129.4, 128.2; HRMS (APCI) Calcd for $C_8H_7NO_2$ 150.05496; found 150.05511 $[M+H]^+$.

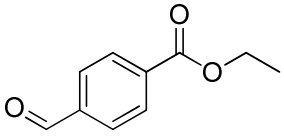


4-Formyl-N-methylbenzamide (43). To a solution of 4-formylbenzoic acid (1.0 g, 6.7 mmol) in DMF (11 mL, 0.61 M) at 0 °C was added DMAP (0.90 g, 7.3 mmol) and EDCI (1.3 g, 6.7

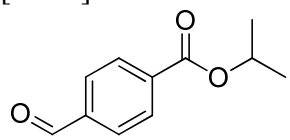
mmol). The reaction mixture was stirred at 0 °C for 45 minutes. At this time methanamine (3.3 mL, 2.0 M in MeOH, 6.7 mmol) was added and the mixture was warmed to room temperature and stirred overnight. The resulting mixture was concentrated *in vacuo*, partitioned between 1.0 M HCl and EtOAc and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 1/1) to afford a white solid (0.15 g, 14 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.96-7.92 (mult, 4H), 6.28 (br s, 1H), 3.06 (d, J = 4.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.7, 167.3, 140.0, 138.3, 130.1, 127.8, 27.2; HRMS (APCI) Calcd for $C_9H_9NO_2$ 164.0706; found 164.0708 $[M+H]^+$.



4-Formyl-N,N-dimethylbenzamide (44). To a solution of 4-formylbenzoic acid (1.0 g, 6.7 mmol) in DMF (11 mL, 1.2 M) at 0 °C was added DMAP (1.8 g, 15 mmol) and EDCI (2.6 g, 13 mmol). The reaction mixture was stirred at 0 °C for 45 minutes. At this time dimethylamine (6.7 mL, 2.0 M in THF, 13 mmol) was added and the mixture was warmed to room temperature and stirred overnight. The resulting mixture was concentrated *in vacuo*, partitioned between 1.0 M HCl and EtOAc and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 1/1) to afford an opaque oil (1.2 g, 51 %). ^{1}H NMR (400 MHz, $CDCl_3$, 60°C) δ 10.01-9.99 (s, 1H), 7.89-7.85 (mult, 2H), 7.54-7.50 (mult, 2H), 3.07 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 142.1, 136.9, 129.9, 127.7, 39.4, 35.4; HRMS (APCI) Calcd for $C_{10}H_{11}NO_2$ 178.0863; found 178.0864 $[M+H]^+$.

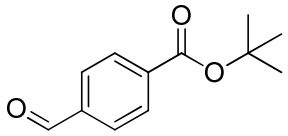


Ethyl 4-formylbenzoate (45). To a solution of 4-formylbenzoic acid (1.0 g, 6.7 mmol) in DMF (26 mL, 0.26 M) was added finely ground potassium carbonate (1.8 g, 13 mmol) and iodoethane (1.3 mL, 17 mmol, 2.5 equiv). The reaction stirred at rt until completion was indicated by TLC before being diluted with water and extracted with Et_2O (2x). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to afford a yellow oil (1.0 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.21 (d, J = 8.4 Hz, 2H), 7.96 (dd, J = 1.8 Hz, J = 7.2 Hz, 2H), 4.43 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.9, 165.8, 139.3, 135.7, 130.4, 129.7, 61.8, 14.5; HRMS (APCI) Calcd for $C_{10}H_{10}O_3$ 179.0703; found 179.0703 $[M+H]^+$.

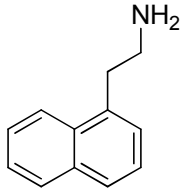


Isopropyl 4-formylbenzoate (46). To a solution of 4-formylbenzoic acid (1.0 g, 6.7 mmol) in DMF (26 mL, 0.26 M) was added finely ground potassium carbonate (1.8 g, 13 mmol) and 2-iodopropane (1.7 mL, 17 mmol, 2.5 equiv). The reaction stirred at rt until completion was indicated by TLC before being diluted with water and extracted with Et_2O (2x). The combined

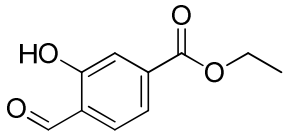
organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to afford a yellow oil (0.30 g, 24 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 5.28 (sept, J = 6.6 Hz, 1H), 1.39 (d, J = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.0, 165.2, 139.2, 136.1, 130.3, 129.6, 69.4, 22.1; HRMS (APCI) Calcd for $C_{11}H_{12}O_3$ 193.0859; found 193.0860 $[M+H]^+$.



tert-Butyl-4-formylbenzoate (47). To a solution of 4-formylbenzoic acid (1.0 g, 6.7 mmol) in refluxing benzene (12.6 mL, 0.50 M) was added 1,1-di-*tert*-butoxy-*N,N*-dimethylmethanamine (6.4 mL, 26.6 mmol, 4.0 equiv) over a period of 1 hr. The reaction was then allowed to continue refluxing for 30 min before being cooled to rt and diluted with water. After washing with saturated sodium bicarbonate (2x), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified using flash column chromatography on SiO_2 (Hexanes/EtOAc: 6/1) to yield a white solid (1.1 g, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.14 (dd, J = 1.6 Hz, J = 6.8 Hz, 2H), 7.93 (dt, J = 1.6 Hz, J = 7.6 Hz, 2H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 164.9, 139.0, 137.2, 130.2, 129.6, 82.2, 28.3; HRMS (APCI) Calcd for $C_{12}H_{14}O_3$ 207.1016; found 207.1016 $[M+H]^+$.

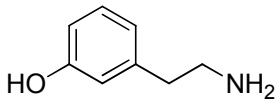


2-(Naphthalen-1-yl)ethanamine (188). 2-(Naphthalen-1-yl)acetonitrile (0.89 mL, 6.0 mmol) in diethyl ether (5.0 mL, 1.2 M) was added dropwise to a solution of lithium aluminum hydride (12 mL, 12 mmol, 2.0 equiv) in diethyl ether (20 mL, 0.30 M). The suspension was then allowed to stir at rt for 12 hrs. Water was added dropwise until no more gas was given off, at which point 1.0 M NaOH was added to pH = 9. The mixture was extracted with Et_2O (2x) and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was achieved via flash column chromatography on SiO_2 (10% MeOH/DCM) to yield a yellow oil (0.41 g, 40 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.50-7.44 (mult, 2H), 7.37 (t, J = 6.6 Hz, 1H), 7.30 (d, J = 6.6 Hz, 1H), 3.18 (t, J = 7.2 Hz, 2H), 3.04 (t, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 134.0, 131.9, 128.8, 127.2, 126.8, 126.0, 125.6, 125.5, 123.6, 42.4, 36.6; HRMS (APCI) Calcd for $C_{12}H_{13}N$ 172.1121; found 172.1119 $[M+H]^+$.



Ethyl 4-formyl-3-hydroxybenzoate (189). To a solution of 4-formyl-3-hydroxybenzoic acid (0.43 g, 2.6 mmol) in DMF (0.52 mL, 5.0 M) was added cesium fluoride (0.59 g, 3.9 mmol) and iodoethane (0.23 mL, 2.9 mmol, 1.1 equiv). The reaction mixture stirred at rt for 6 days before being concentrated *in vacuo*, diluted with water and extracted with DCM (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification was

achieved via flash column chromatography on SiO_2 (Hexanes/EtOAc: 1/1) to afford a white solid (0.19 g, 39 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.95 (s, 1H), 9.99 (s, 1H), 7.68-7.65 (mult, 3H), 4.41 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.2, 165.4, 161.4, 137.9, 133.8, 133.0, 120.6, 119.362.0, 14.4; HRMS (APCI) Calcd for $C_{10}H_{10}O_4$ 195.0652; found 195.0649 $[M+H]^+$.



3-(2-Aminoethyl)phenol (190). To a solution of 2-(3-methoxyphenyl)ethanamine (1.0 g, 6.6 mmol) in acetic acid (3.97 mL, 1.7 M) was added 48% 48% hydrogen bromide solution (4.0 mL, 35 mmol, 5.3 equiv). The resulting mixture was brought to reflux and stirred for 4 hrs. The mixture was then cooled to rt and concentrated *in vacuo*. The residue was dissolved in MeOH and concentrated down 4 times to afford a brown crystalline solid. The solid was dissolved in minimal DCM and triethylamine (2.8 mL, 20 mmol, 3.0 equiv) was added. After stirring for 2 hrs the mixture was washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an orange oil (0.46 g, 51 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 1H), 6.71-6.68 (mult, 2H), 6.65 (s, 1H), 4.01 (br s, 3H), 3.02 (t, J = 6.4 Hz, 2H), 1.15 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 140.6, 130.2, 119.8, 116.3, 114.3, 42.7, 38.5; HRMS (APCI) Calcd for $C_8H_{11}NO$ 138.0913; found 138.0913 $[M+H]^+$.

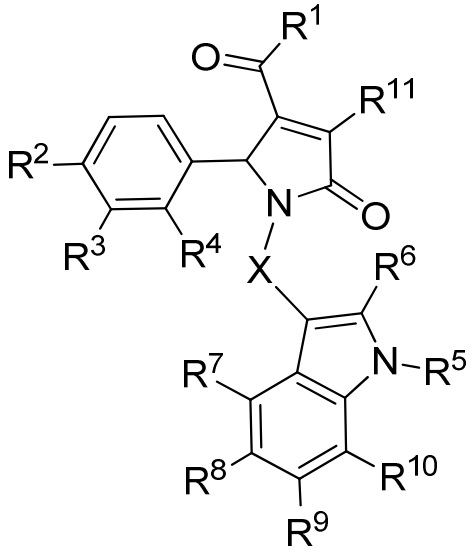


Figure S1: Generic formula for SAR development.