Reagent controlled domino synthesis of skeletally diverse compound collections

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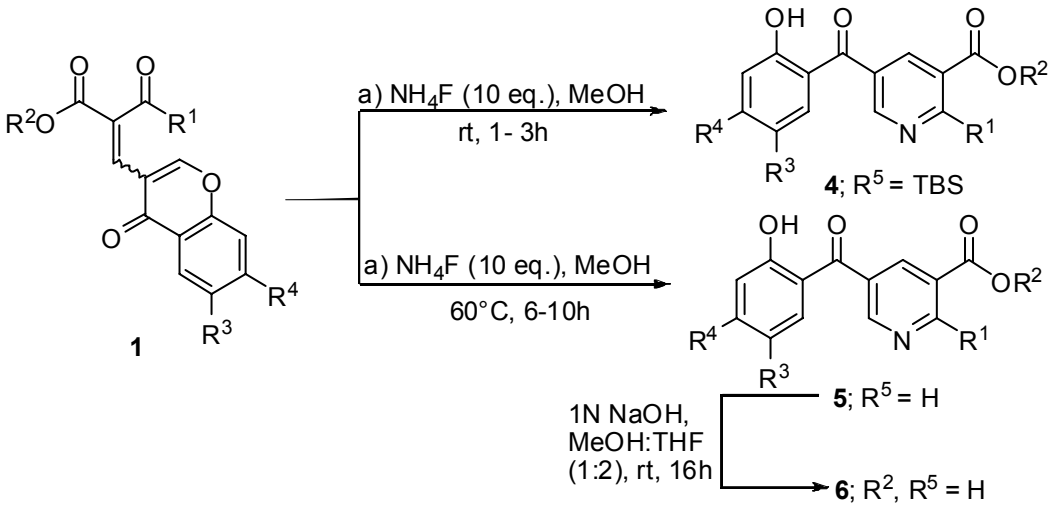
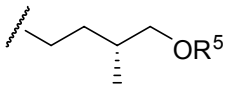
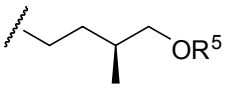
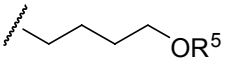
1 Supporting information

1.1 General

^{1}H NMR and ^{13}C spectra were recorded on a Varian Mercury 600 or a Bruker DRX 500 spectrometer. NMR spectra were calibrated to the solvent signal of $CDCl_3$ (7.26 ppm and 77.0 ppm) and DMSO (2.49 ppm and 39.5 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad. GC-MS(EI) were measured on a Hewlett-Packard 6890 Series gas chromatograph connected to a Hewlett-Packard 5973 series mass spectrometer; column: H&W 19091σ-102 HP-5MS capillary: 25.0 m × 201 μm × 0.33 μm nominal. LC-MS was performed on a 1100 series from Hewlett-Packard connected to a Finnigan LCQ ESI-Spectrometer; column: VP 50 / 10 Nucleosil C18PPN-column (Macherey-Nagel); gradient: 90 / 10 (v / v) H_2O / acetonitrile (0.1% formic acid) to 10 / 90 (v / v) in 30 min, flow 1.00 ml / min. High resolution mass spectra (HR-MS) were measured on a finnigan MAT 8200 spectrometer. IR spectra were measured on a Bruker Vector 22 spectrometer with a diffuse reflectance head A527 from Spectra Tech. The optical rotation was determined with Perkin Elmer Polarimeter 241. TLC was performed on Merck silica gel 60F254 aluminium sheets using UV as a visualizing agent and a 0.5% aqueous potassium permanganate solution or an ethanolic solution of phosphomolybdic acid and heat as developing agents. For flash chromatography silica gel (40-60 μm) from Merck was used. All reactions were performed under an argon atmosphere with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise noted, reagents were obtained from Aldrich, Acros, Fluka, Lancaster and Strem and used without further purification.

1.2 Synthesis of substituted pyridines without cleaving the TBS group

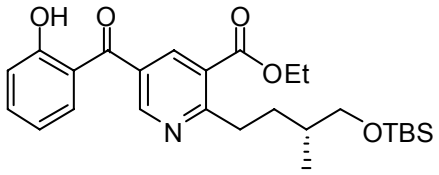


R¹ = **i)**  **ii)**  **iii)** 

Substance	R¹	R²	R³	R⁴	4 Yield[%][a]	5 Yield[%][a]	6 Yield[%][a,b]
a	i)	Et	H	H	87	71	67
b	ii)	Me	H	H	83	87	79
c	iii)	Et	H	H	79	76	81
d	iii)	Et	*i*-Pr	H	85	89	82

a) isolated yields; b) yield from **5**.

Representative procedure for the domino reactions leading to substituted pyridines:

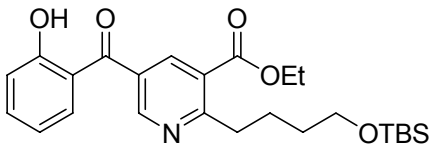


(3*R*)-Ethyl 2-(4-(tert-butyldimethylsilyloxy)-3-methylbutyl)-5-(2-hydroxy-benzoyl) nicotinate (4a)

To a solution of chromonylidene-*β*-ketoester **1a** (33.3 mg, 0.070 mmol) in MeOH (5 ml) was added ammonium fluoride (26.0 mg, 0.70 mmol, 10.0 eq.). The reaction mixture was stirred for 1h (TLC-control) at room temperature. The methanol was removed in *vacuo*, water was

added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 27.8 mg (0.059 mmol, 87%); R_f = 0.42 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = -3.1 ° (c =1.81, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.81 (s, 1H), 8.91 (d, J = 2.3 Hz, 1H), 8.45 (d, J = 2.3 Hz, 1H), 7.14-7.05 (m, 1H), 7.59-7.43 (m, 2H), 6.92 (ddd, J = 8.1 Hz, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.54 (dd, J = 9.8 Hz, J = 5.7 Hz, 1H), 3.43 (dd, J = 9.9 Hz, J = 6.5 Hz, 1H), 3.28 (ddd, J = 22.1 Hz, J = 10.7 Hz, J = 5.5 Hz, 1H), 1.94-1.81 (m, 1H), 1.78-1.64 (m, 1H), 1.60-1.46 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 198.3, 166.9, 165.7, 163.2, 151.2, 139.0, 137.0, 132.8, 130.8, 125.6, 119.1, 118.8, 118.7, 68.2, 61.7, 36.1, 34.8, 33.3, 25.9, 18.3, 16.6, 14.2, -5.3; LC-MS(ESI): t_R = 9.69 min; calcd. for $C_{26}H_{37}O_5Si$ 471.24, found 358.19 $[M\text{-}SiMe_2tBu]^+$.

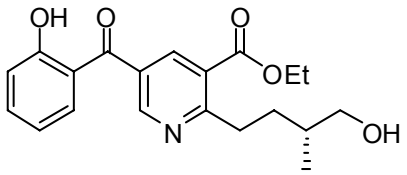


Ethyl 2-(4-(*tert*-butyldimethylsilyloxy)-butyl)-5-(2-hydroxybenzoyl) nicotinate (4c)

Yield = 23.91 mg (0.052 mmol, 79%); R_f = 0.41 (cyclohexane / EtOAc = 2 / 1); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.79 (s, 1H), 8.90 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H), 7.61-7.46 (m, 2H), 7.09 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.71-3.58 (m, 1H), 3.26 (t, J = 7.7 Hz, 2H), 1.88-1.74 (m, 2H), 1.71-1.58 (m, 2H), 1.39 (t, J = 7.2 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 198.3, 166.5, 165.7, 163.2, 151.2, 138.9, 137.0, 132.8, 130.9, 125.6, 119.1, 118.8, 118.7, 63.0, 61.7, 36.8, 32.8, 26.1, 25.9, 18.3, 14.1, -5.2; LC-MS(ESI): t_R = 9.20 min; calcd. for $C_{25}H_{35}NO_5Si$ 457.23, found 344.20 [$[M\text{-}SiMe_2tBu]^+$.

1.3 Procedure for the synthesis of substituted pyridines with TBS deprotection

Representative procedure for the domino reactions leading to substituted pyridines:

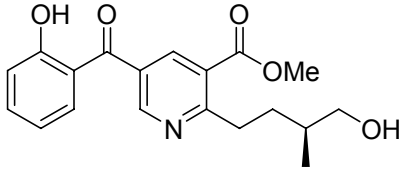


(3*R*)-Ethyl 2-(4-hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinate (5a)

To a solution of chromonylidene-β-ketoester **1a** (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

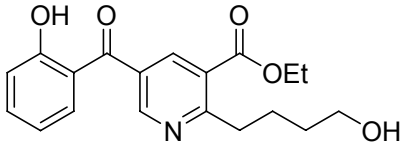
Yield = 24.7 mg (0.069 mmol, 71%); R_f = 0.40 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = -4.9 ° (*c* =2.01, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.76 (s, 1H), 8.89 (d, *J* = 2.2 Hz, 1H), 8.47 (d, *J* = 2.2 Hz, 1H), 7.61-7.44 (m, 2H), 7.08 (dd, *J* = 8.4, *J* = 0.8 Hz, 1H), 6.96-6.85 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.57 (dd, *J* = 5.6 Hz, *J* = 4.4 Hz, 2H), 3.32-3.21 (m, 2H), 1.82-1.73 (m, 2H), 1.74-1.61 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ(ppm) = 198.1, 166.8, 165.5, 163.2, 151.2, 139.2, 137.1, 132.7, 131.0, 125.3, 119.1, 118.8, 118.7, 67.2, 61.9, 35.6, 34.1, 32.8, 16.7, 14.1; LC-MS (ESI): t_R = 10.93 min; calcd. for $C_{20}H_{23}NO_5$ 357.16, found 358.23 $[M+H]^+$.

Derivates were synthesizes by following the procedure for **5a**



(3*S*)-Methyl 2-(4-hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinate (5b)

Yield = 17.3 mg (0.050 mmol, 87%); R_f = 0.41 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = -1.7 ° (c = 1.78, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.76 (s, 1H), 8.94-8.88 (m, 1H), 8.50-8.46 (m, 1H), 7.60-7.48 (m, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.94-6.87 (m, 1H), 3.93 (d, J = 5.8 Hz, 3H), 3.65-3.51 (m, 2H), 3.33-3.23 (m, 2H), 1.91-1.74 (m, 3H), 1.75-1.62 (m, 1H), 1.01 (d, J = 7.2 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ(ppm) = 198.0, 167.0, 165.9, 163.2, 151.4, 139.3, 137.1, 132.7, 131.0, 124.8, 119.1, 118.7, 118.7, 67.2, 52.7, 35.6, 34.2, 32.8, 16.7; LC-MS (ESI): t_R = 9.08 min; calcd. for $C_{19}H_{21}NO_5$ 343.1420, found 344.18 $[M+H]^+$.

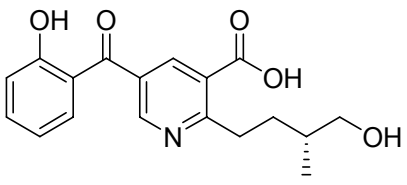


Ethyl 5-(2-hydroxybenzoyl)-2-(4-hydroxybutyl) nicotinate (5c)

Yield = 19.6 mg (0.057 mmol, 76%); R_f = 0.40 (cyclohexane / EtOAc = 2 / 1); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.77 (s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.50-8.41 (m, 1H), 7.61-7.47 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 0.7 Hz, 1H), 4.46-4.30 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 6.1 Hz, 2H), 3.34-3.23 (m, 2H), 1.92-1.66 (m, 5H), 1.39 (dt, J = 7.1 Hz, J = 0.7 Hz, 3H), ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ(ppm) = 198.1, 166.4, 165.6, 163.2, 151.2, 139.1, 137.0, 132.7, 131.0, 125.4, 119.1, 118.8, 118.7, 62.1, 61.8, 36.2, 32.2, 25.6, 14.1; LC-MS (ESI): t_R = 9.08 min; calcd. for $C_{19}H_{21}NO_5$ 343.14, found 344.20 $[M+H]^+$.

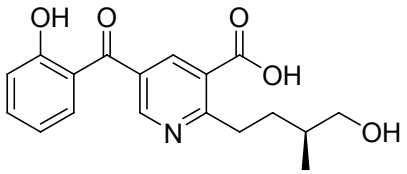
1.4 General procedure for hydrolysis of substituted pyridines

To a solution of ester **5** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC-control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude acid. The residue was purified by column chromatography.



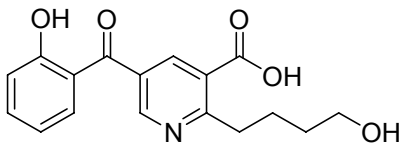
(3*R*)-2-(4-Hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinic acid (6a)

Yield = 13.5 mg (0.041 mmol, 67%); R_f = 0.32 (EtOAc / MeOH = 5 / 3); $[\alpha]_D^{20}$ = -6.7 °(c = 1.56, DMSO); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.56 (brs, 1H), 8.86 (d, J = 2.2 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 8.8 Hz, J = 2.6 Hz, 1H), 7.52 (d, J = 2.6 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.31-3.16 (m, 3H), 3.10 (ddd, J = 12.8 Hz, J = 10.5 Hz, J = 5.8 Hz, 1H), 1.75 (ddd, J = 10.6 Hz, J = 7.4 Hz, J = 5.3 Hz, 1H), 1.52 (dd, J = 12.8 Hz, J = 6.7 Hz, 1H), 1.45-1.33 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) = 192.7, 167.1, 166.5, 155.2, 151.4, 138.6, 135.8, 132.1, 130.0, 126.8, 125.8, 119.0, 110.4, 66.1, 35.5, 33.9, 33.0, 16.5.



(3*S*)-2-(4-Hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinic acid (6b)

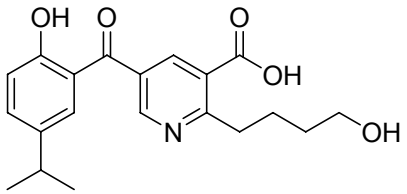
Yield = 7.5 mg (0.023 mmol, 79%); R_f = 0.35 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = 4.5 ° (c = 0.98, DMSO); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.42 (brs, 1H), 8.86 (d, J = 2.2 Hz, 1H), 8.33 (d, J = 2.2 Hz, 1H), 7.50-7.45 (m, 1H), 7.42 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 6.98 (dd, J = 7.8 Hz, J = 4.6 Hz, 2H), 3.29 (dd, J = 10.4 Hz, J = 5.9 Hz, 1H), 3.24-3.17 (m, 2H), 3.16-3.07 (m, 1H), 1.76 (dd, J = 7.5 Hz, J = 5.4 Hz, 1H), 1.54 (d, J = 6.1 Hz, 1H), 1.47-1.34 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) =196.1, 170.1, 164.4, 157.0, 147.9, 137.2, 134.9, 133.3, 130.1, 124.6, 118.9, 116.8, 65.9, 35.4, 33.4, 33.0, 16.8; LC-MS (ESI): t_R = 8.80 min; calcd. for $C_{18}H_{19}NO_5$ 329.13, found 330.17 $[M+H]^+$.



5-(2-Hydroxybenzoyl)-2-(4-hydroxybutyl) nicotinic acid (6c)

Yield = 14.6 mg (0.046 mmol, 79%); R_f = 0.35 (cyclohexane / EtOAc = 2 / 1); ^{1}H–NMR (400 MHz, DMSO-d_6): δ(ppm) = 10.42 (brs, 1H), 8.87 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 7.52-7.38 (m, 2H), 7.04-6.89 (m, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.22-3.11 (m,

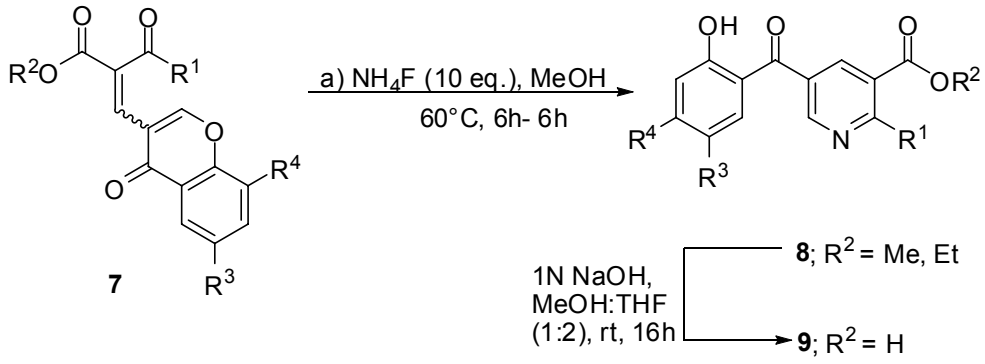
2H), 1.76-1.64 (m, 2H), 1.52-1.40 (m, 2H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) = 194.6, 167.1, 165.6, 156.8, 151.1, 138.7, 134.0, 130.7, 130.6, 125.9, 124.0, 119.4, 116.8, 60.5, 35.8, 32.4, 25.7; LC-MS (ESI): t_R = 8.34 min; calcd. for $C_{17}H_{17}NO_5$ 315.1107, found 316.19 M+H]$^+$.



5-(2-Hydroxy-5-isopropylbenzoyl)-2-(4-hydroxybutyl) nicotinic acid (6d)

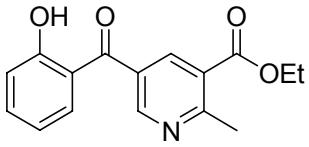
Yield = 14.6 mg (0.41 mmol, 74%); R_f = 0.33 (cyclohexane / EtOAc = 2 / 1); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.20 (s, 1H), 8.86 (d, J = 2.2 Hz, 1H), 8.33 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.5 Hz, J = 2.3 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 3.39 (t, J = 6.5 Hz, 2H), 3.18-3.12 (m, 2H), 2.90-2.78 (m, 1H), 1.74-1.65 (m, 2H), 1.46 (dd, J = 14.8 Hz, J = 6.8 Hz, 2H), 1.16 (d, J = 6.9 Hz, 6H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) = 194.8, 167.2, 165.7, 155.0, 151.3, 139.2, 138.6, 132.1, 130.6, 127.8, 125.7, 123.5, 116.8, 60.5, 35.9, 32.4, 32.3, 25.7, 23.8; LC-MS (ESI): t_R = 9.46 min; calcd. for $C_{20}H_{23}NO_5$ 357.15, found 358.22 [M+H]$^+$.

1.5 Synthesis of substituted pyridines with shorter alkyl chains



Substance	R^1	R^2	R^3	R^4	**8** Yield [%][a]	**9** Yield [%][a,b]
a	Me	Et	H	H	78	94
b	Me	Et	Me	H	73	97
c	Me	Et	Cl	Cl	75	100
d	Et	Me	H	H	67	97
e	Et	Me	Me	H	78	99

a) isolated yields; b) yield from **8**.



Ethyl-5-(2-hydroxybenzoyl)-2-methylnicotinate (8a)

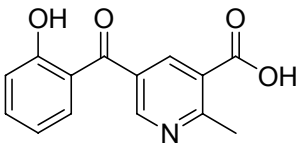
To a solution of chromonylidene-β-ketoester **7a** (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 233.0 mg (0.817 mmol, 78%); R_f = 0.39 (cyclohexane / EtOAc = 2 / 1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.79 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 7.63-7.45 (m, 2H), 7.09 (dd, J = 8.4 Hz, J = 1.0 Hz, 1H), 6.91 (ddd, J = 8.2, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.93 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 198.2, 165.5, 163.2, 163.1, 151.2, 138.8, 137.0, 132.8,

131.0, 125.5, 119.1, 118.8, 118.7, 61.7, 24.9, 14.2; GC-MS(EI): t_R = 8.58 min; m / z (rel. Int. [%]): 285 (75) [M^+], 268 (3), 256 (26), 239 (34), 211 (26), 121 (100), 93 (20), 65 (31).

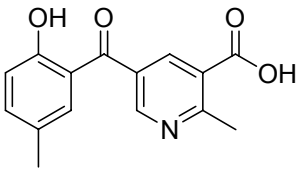
1.6 General procedure for hydrolysis of substituted pyridines with shorter alkyl chains

To a solution of ester **8** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude acid. The residue was purified by column chromatography.



5-(2-Hydroxybenzoyl)-2-methylnicotinic acid (9a)

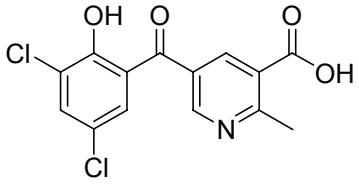
Yield = 14.3 mg (0.056 mmol, 94%); R_f = 0.34 (EtOAc / MeOH = 5 / 3); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.52 (br s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.52-7.38 (m, 2H), 6.98 (m, 2H), 2.80 (s, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 194.7, 167.0, 162.4, 156.8, 151.3, 138.4, 133.9, 130.7, 130.5, 125.6, 124.0, 119.4, 116.8, 24.6; LC-HRMS (ESI): t_R = 2.07 min; calcd. for $C_{14}H_{12}NO_4$ 258.07608, found 258.07605 $[M+H]^+$.



5-(2-Hydroxy-5-methylbenzoyl)-2-methylnicotinic acid (9b)

Yield = 12.1 mg (0.045 mmol, 97%); R_f = 0.37 (EtOAc / MeOH = 5 / 3); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.52 (br s, 1H), 8.82 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H), 7.28 (ddd, J = 8.3 Hz, J = 2.3 Hz, J = 0.6 Hz, 1H), 7.23-7.19 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 2.80 (s, 3H), 2.24 (s, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 194.7, 167.0, 162.3, 154.7, 151.3, 138.5, 134.7, 130.8, 130.4, 128.1,

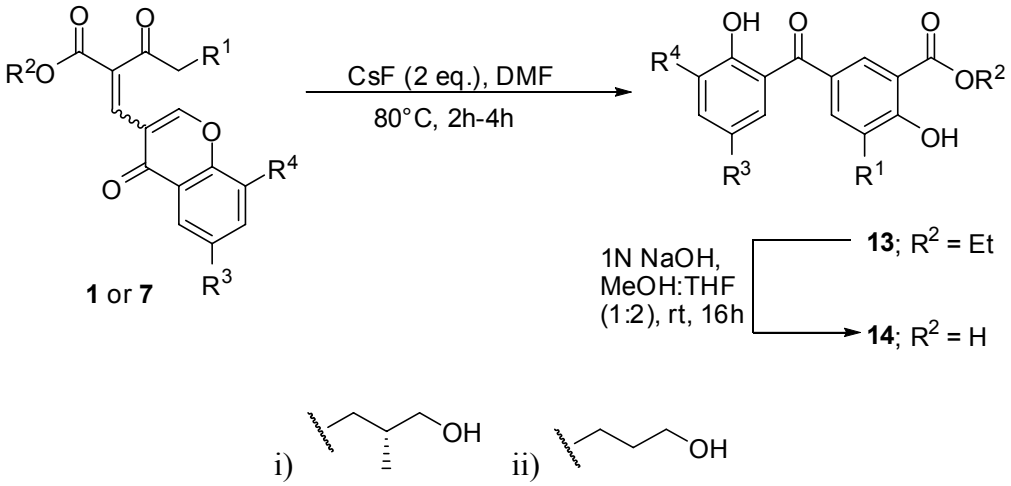
125.6, 123.7, 116.7, 24.6, 19.8; LC-HRMS (ESI): t_R = 2.37 min; calcd. for $C_{15}H_{14}NO_4$ 272.09173, found 272.09170 $[M+H]^+$.



5-(3,5-Dichloro-2-hydroxybenzoyl)-2-methylnicotinic acid (9c)

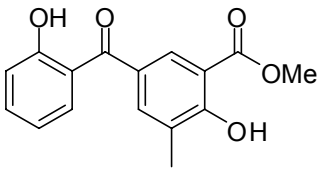
Yield = 13.7 mg (0.042 mmol, 100%); R_f = 0.47 (EtOAc / MeOH = 5 / 3); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.60 (br s, 1H), 8.84 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 2.3 Hz, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 2.81 (s, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 192.5, 166.9, 163.1, 151.6, 150.8, 138.4, 132.5, 129.9, 128.4, 127.8, 125.8, 123.6, 123.2, 24.7; LC-HRMS (ESI): t_R = 2.74 min; calcd. for $C_{14}H_{10}{}^{35}Cl_2NO_4$ 325.99814, found 325.99847 $[M+H]^+$.

1.7 Procedure for synthesis of substituted phenols



Substance	R^1	R^2	R^3	R^4	13 Yield [%][a]	14 Yield [%][a,b]
a	Me	Me	H	H	67	89
b	Me	Me	Me	H	71	92
c	Me	Me	Cl	H	63	90
d	i)	Et	H	H	56	NA

a) isolated yield; b) yield from **13**.

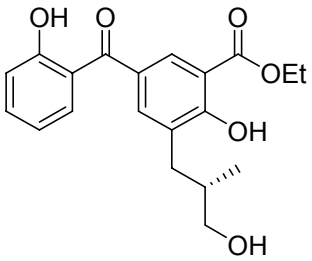


Methyl 2-hydroxy-5-(2-hydroxybenzoyl)-3-methylbenzoate (13a)

To a solution of chromonylidene-β-ketoester **7a** (516.4 mg, 1.804 mmol) in DMF (5 ml) was added caesium fluoride (548.0 mg, 0.097 mmol, 2.0 eq.) at room temperature and the reaction mixture was stirred for 2-4h (TLC-control) at 80°C. After addition of EtOAc and brine, the biphasic mixture was several times extracted with brine. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude phenol. The residue was purified by column chromatography.

Yield: = 346.0 mg (1.209 mmol, 67%); R_f = 0.34 (cyclohexane / EtOAc = 2 / 1); ^{1}HNMR (400 MHz, $CDCl_3$): δ(ppm) = 11.85 (s, 1H), 11.47 (s, 1H), 8.09 (dd, J = 2.2 Hz, J = 0.5 Hz, 1H), 7.74-7.68 (m, 1H), 7.58 (dd, J = 8.1 Hz, J = 1.6 Hz, 1H), 7.49 (ddd, J = 8.8 Hz,

J = 7.2 Hz, *J* = 1.7 Hz, 1H), 7.06 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 6.93-6.86 (m, 1H), 3.95 (s, 3H), 2.32 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ(ppm) = 199.2, 170.3, 163.1, 162.9, 136.8, 135.9, 132.9, 130.0, 128.2, 127.3, 119.0, 118.6, 118.3, 111.1, 52.5, 15.6; GC-MS(EI): t_R = 8.79 min; m / z (rel. Int. [%]): 286 (75) [M^+], 271 (21), 253 (32), 239 (6), 226 (11), 197 (18), 161 (30), 134 (84), 121 (100).

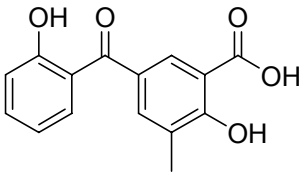


(2*S*)-Ethyl 2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-(2-hydroxybenzoyl)benzoate (13d)

Yield: = 17.1 mg (0.047 mmol, 56%); R_f = 0.25 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = 6.2 ° (c = 1.51, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.87 (s, 1H), 11.79 (s, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.59 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.52 (ddd, *J* = 8.7 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz, 1H), 7.09 (dd, *J* = 8.4 Hz, *J* = 0.9 Hz, 1H), 6.91 (ddd, *J* = 8.1 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.48 (dd, *J* = 6.4 Hz, *J* = 5.7 Hz, 2H), 2.91-2.85 (m, 1H), 2.61 (dd, *J* = 13.5 Hz, *J* = 7.0 Hz, 1H), 2.05 (m, 1H), 1.45-1.38 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ(ppm) = 199.4, 170.1, 163.0, 162.9, 137.6, 136.1, 132.9, 130.3, 129.4, 128.5, 119.1, 118.6, 118.5, 112.6, 66.8, 62.1, 36.3, 32.8, 16.6, 14.1; LC-MS (ESI): t_R = 11.93 min; calcd. for $C_{20}H_{22}O_6$ 358.14, found 359.12 [M+H]$^+$.

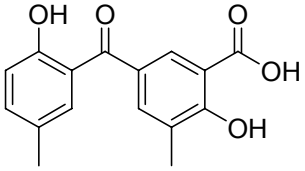
1.8 General procedure for hydrolysis of substituted phenols

To a solution of ester **6** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude acid. The residue was purified by column chromatography.



2-Hydroxy-5-(2-hydroxybenzoyl)-3-methylbenzoic acid (14a)

Yield: = 24.6 mg (0.090 mmol, 89%); R_f = 0.45 (EtOAc / MeOH = 5 / 2); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.23 (brs, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 2.2 Hz, J = 0.9 Hz, 1H), 7.39 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.7 Hz, 1H), 7.30 (dd, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.07-6.79 (m, 1H), 2.23 (s, 3H), ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) = 194.9, 171.9, 163.3, 156.1, 136.1, 132.6, 130.7, 129.8, 128.0, 126.2, 125.1, 119.0, 116.5, 111.6, 15.2; LC-HRMS (ESI): t_R = 2.86 min; calcd. for $C_{15}H_{13}O_5$ 273.07575, found 273.07581 $[M+H]^+$.

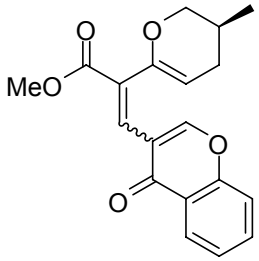


2-Hydroxy-5-(2-hydroxy-5-methylbenzoyl)-3-methylbenzoic acid (14b)

Yield: = 17.8 mg (0.062 mmol, 92%); R_f = 0.46 (EtOAc / MeOH = 5 / 2); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.91 (brs, 1H), 8.02-7.97 (m, 1H), 7.80 (dd, J = 2.3 Hz, J = 0.9 Hz, 1H), 7.22-7.16 (m, 1H), 7.08 (d, J = 2.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 2.22 (s, 6H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ(ppm) = 195.0, 171.9, 163.3, 153.8, 136.1, 133.1, 130.7, 129.7, 128.1, 127.6, 126.1, 125.0, 116.3, 111.7, 19.8, 15.2; LC-HRMS (ESI): t_R = 3.03 min; calcd. for $C_{16}H_{15}O_5$ 287.09140, found 287.09143 $[M+H]^+$.

1.9 Procedures for synthesis of intermediate in benzopyran formation

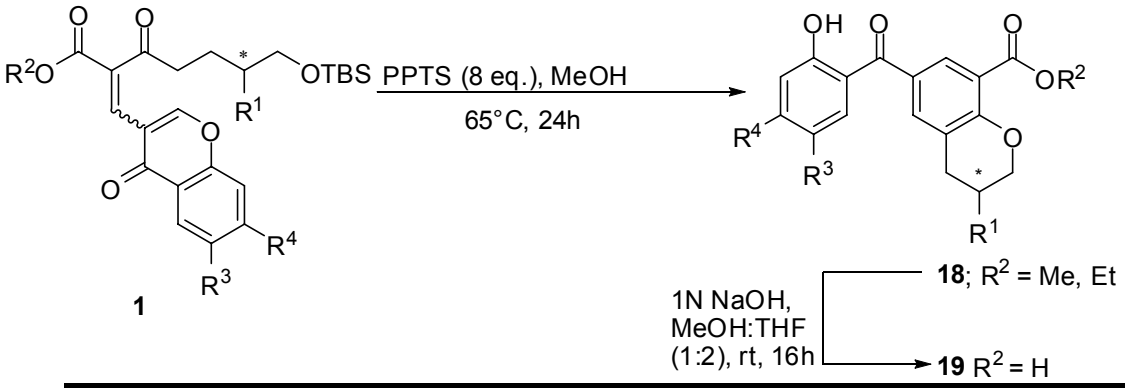
To a solution of chromonylidene-β-ketoester **1** (1.0 eq.) in MeOH (5 ml) was added PPTS (8.0 eq.) at room temperature and the reaction mixture was stirred for 1 h (TLC-control) at 65°C. The methanol was removed in *vacuo,* water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude chromane. The residue was purified by column chromatography.



(3*S*,*E*)-Methyl
2-(3-methyl-3,4-dihydro-2*H*-pyran-6-yl)-3-(4-oxo-4*H*-chromen-3-yl)acrylate (17a)

R_f = 0.30 (cyclohexane / EtOAc = 2 / 1); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.41 (d, J = 1.0 Hz, 1H), 8.27-8.23 (m, 1H), 7.82 (d, J = 1.0 Hz, 1H), 7.73-7.63 (m, 1H), 7.48-7.39 (m, 2H), 4.83 (dd, J = 4.8 Hz, J = 2.9 Hz, 1H), 4.10 (ddd, J = 10.4 Hz, J = 3.4 Hz, J = 1.8 Hz, 1H), 3.79 (s, 3H), 2.31-2.13 (m, 1H), 2.10-2.00 (m, 1H), 1.85-1.72 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 175.7, 166.6, 155.9, 153.4, 146.9, 133.8, 133.6, 132.3, 129.4, 126.3, 126.2, 125.6, 125.3, 118.1, 118.0, 117.7, 102.7, 101.9, 71.9, 52.3, 52.2, 29.4, 28.7, 26.8, 26.8, 17.2, 17.0.

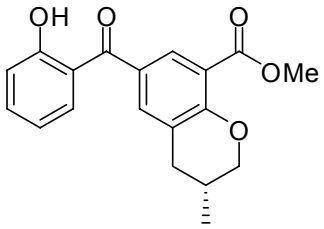
1.10 Procedures for the synthesis of benzopyrans



Substance	R^1	R^2	R^3	R^4	18 Yield[%][a]	19 Yield[%][a,b]
b	(*R*)-Me	Me	H	H	78	NA
a	(*S*)-Me	Me	H	H	63	90
c	(*S*)-Me	Me	Br	H	56	89
d	H	Et	H	H	60	94
e	H	Et	*i*-Pr	H	77	98
f	(*R*)-Me	Et	Br	H	59	NA

a) isolated yield; b) yield from **18**

Representative procedure for the domino reactions leading to benzopyrans with *trans* esterification:



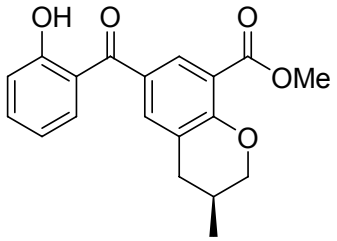
Methyl 3,4-Dihydro-(3*R*)-methyl-6-(2-hydroxybenzoyl)-2*H*-chromene-8-carboxylate (18b)

To a solution of chromonylidene-*β*-ketoester **I** (33.3 mg, 0.070 mmol) in MeOH (5 ml) was added PPTS (140.7 mg, 0.56 mmol, 8.0 eq.) at room temperature and the reaction mixture was stirred for 36 h (TLC-control) at 65°C. The methanol was removed in *vacuo,* water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases

were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude product which was further purified by column chromatography.

Yield: = 17.9 mg (0.055 mmol, 78%); R_f = 0.39 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = 17.4 °, (c = 1.74, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.85 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 6.2 Hz, J = 1.8 Hz, 2H), 7.54-7.46 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.94-6.85 (m, 1H), 4.42 (ddd, J = 10.8 Hz, J = 3.4 Hz, J = 2.2 Hz, 1H), 3.85 (s, 3H), 2.93 (ddd, J = 16.4 Hz, J = 4.9 Hz, J = 1.7 Hz, 1H), 2.54 (dd, J = 16.2 Hz, J = 10.2 Hz, 1H), 2.33-2.16 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 199.2, 165.7, 162.9, 157.7, 136.0, 134.8, 133.0, 131.6, 128.9, 123.6, 119.1, 118.8, 118.6, 118.3, 72.8, 52.1, 33.4, 26.2, 16.7; LC-MS(ESI): t_R = 10.47 min; calcd. for $C_{19}H_{18}O_5$ 326.12, found 327.12 $[M+H]^+$.

Representative procedure for the domino reactions leading to benzopyrans:



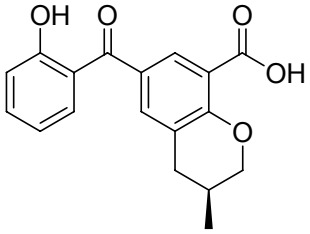
Methyl 3,4-Dihydro-(3*S*)-methyl-6-(2-hydroxybenzoyl)-2*H*-chromene-8-carboxylate (18a)

To a solution of chromonylidene-β-ketoester (1.0 eq.) in MeOH (5 ml) was added PPTS (8.0 eq.) at room temperature and the reaction mixture was stirred for 24 h at 65°C. The methanol was removed in *vacuo,* water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude chromane. The residue was purified by column chromatography.

Yield: = 16.3 mg (0.050 mmol, 63%); R_f = 0.38 (cyclohexane / EtOAc = 2 / 1); $[\alpha]_D^{20}$ = -79.3 ° (c = 2.46, $CHCl_3$); ^{1}H–NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.85 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.62-7.56 (m, 2H), 7.52-7.46 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.92-6.82 (m, 1H), 4.41 (ddd, J = 10.8 Hz, J = 3.4 Hz, J = 2.2 Hz, 1H), 3.90-3.80 (m, 4H), 2.97-2.87 (m, 1H), 2.53 (dd, J = 16.2 Hz, J = 10.1 Hz, 1H), 2.29-2.14 (m, 1H), 1.08 (d, J = 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 199.2, 165.7, 162.9, 157.7, 135.9, 134.8, 133.0, 131.6, 128.9, 123.6, 119.0, 118.7, 118.6, 118.3, 72.8, 52.1, 33.4, 26.2, 16.6; LC-MS(ESI): t_R = 10.71 min; calcd. for $C_{19}H_{18}O_5$ 326.16, found 327.12 $[M+H]^+$.

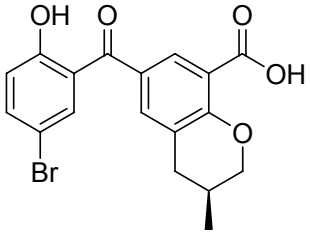
1.11 General procedure for hydrolysis of substituted benzopyrans

To a solution of ester **18** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude acid. The residue was purified by column chromatography.



3,4-Dihydro-(3*S*)-methyl-6-(2-hydroxybenzoyl)-2*H*-chromene-8-carboxylic acid (19a)

Yield: = 5.8 mg (0.019 mmol, 90%); R_f = 0.38 (EtOAc / MeOH = 5 / 2); $[\alpha]_D^{20}$ = 17.4 ° (c = 0.69, DMSO); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.18 (s, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.39 (dd, J = 11.1 Hz, J = 4.5 Hz, 1H), 7.31-7.24 (m, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.31 (d, J = 10.4 Hz, 1H), 3.82 (t, J = 10.0 Hz, 1H), 2.89 (dd, J = 16.2 Hz, J = 4.2 Hz, 1H), 2.55-2.43 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 195.0, 166.5, 157.2, 156.1, 133.9, 132.5, 131.0, 129.8, 128.5, 125.1, 123.4, 119.8, 119.0, 116.5, 71.9, 32.4, 25.6, 16.3; LC-MS(ESI): t_R = 9.74 min; calcd. for $C_{18}H_{16}O_5$ 312.10, found 313.11 $[M+H]^+$.



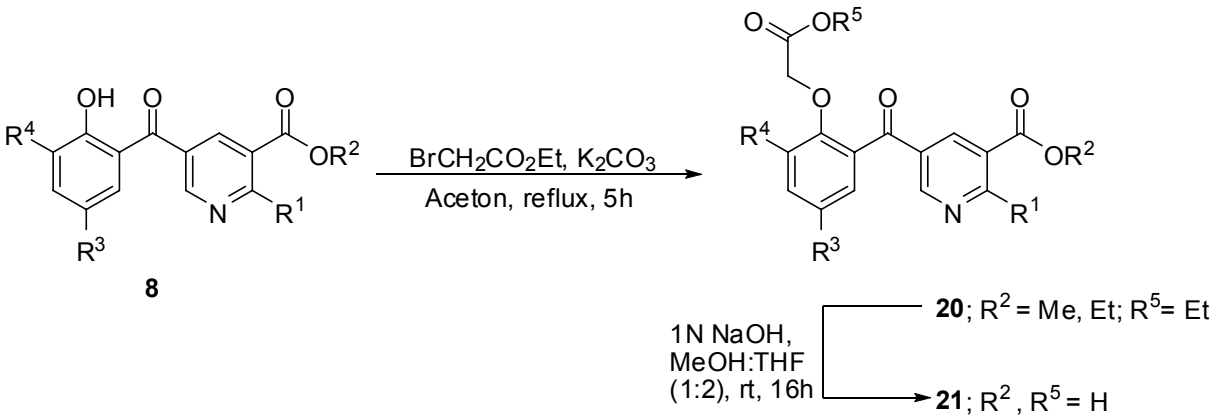
3,4-Dihydro-(3*S*)-methyl-6-(5-bromo-2-hydroxybenzoyl)-2*H*-chromene-8-carboxylic acid (19c)

Yield: = 9.1 mg (0.025 mmol, 89%); R_f = 0.32 (EtOAc / MeOH = 5 / 2); $[\alpha]_D^{20}$ = 9.0 ° (c = 2.16, DMSO); ^{1}H–NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.26 (s, 1H), 7.78 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.7 Hz, J = 2.6 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 4.34-4.23 (m, 1H), 3.88-3.75 (m, 1H), 2.88 (dd,

J = 16.2 Hz, *J* = 4.5 Hz, 1H), 2.55-2.40 (m, 1H), 2.06 (dd, *J* = 2.4 Hz, *J* = 1.5 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 192.8, 166.5, 157.6, 154.4, 134.3, 133.9, 131.2, 131.1, 128.4, 128.0, 123.5, 120.0, 118.6, 110.0, 72.0, 32.4, 25.6, 16.3; LC-MS(ESI): t_R = 10.15 min; calcd. for $C_{18}H_{15}BrO_5$ 390.01, found 391.06 $[M+H]^+$.

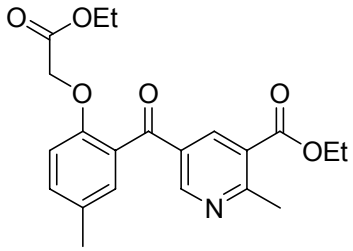
1.12 General procedure for the conversion of ethyl bromoacetic ester with pyridine derivates

Pyridine derivate **8** (1.0°eq.), K_2CO_3 (1.0 eq.) and ethyl 2-bromoacetate (1.0 eq.) were dissolved in acetone (5 ml) and heated under an argon atmosphere for 10h at 50 °C. The acetone was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude pyridine. The residue was purified by column chromatography.



Substance	R^1	R^2	R^3	R^4	20 Yield[%]	21 Yield[%][a,b]
a	Me	Et	Me	H	88	98
b	Me	Et	Br	H	86	99
c	Et	Me	H	H	89	93
d	Et	Me	*i*-Pr	H	88	97

a) isolated yield; b) yield from **20**.

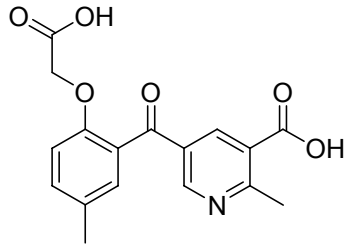


Ethyl-5-(2-(2-ethoxy-2-oxoethoxy)-5-methylbenzoyl)-2-methyl nicotinate (20a)

Yield = 37.2 mg (0.097 mmol, 88%); R_f = 0.37 (PE / EtOAc = 2 / 1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.85 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 7.29-7.11 (m, 2H), 6.68 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.81 (s, 3H), 2.27 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 193.6, 167.9, 166.0, 163.3, 153.6, 152.7, 138.8, 133.4, 131.6, 131.0, 130.8, 127.6, 125.4, 112.3, 65.6, 61.4, 61.2, 24.9, 20.2, 14.1, 13.9; GC-MS(EI): t_R = 10.08 min; m / z (rel. Int. [%]): 385 (20) [M^+], 340 (29), 312 (79), 284 (76), 251 (70), 179 (100), 135 (96).

1.13 General procedure for hydrolysis to diacids

To a solution of ester **20** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude acid. The residue was purified by column chromatography.



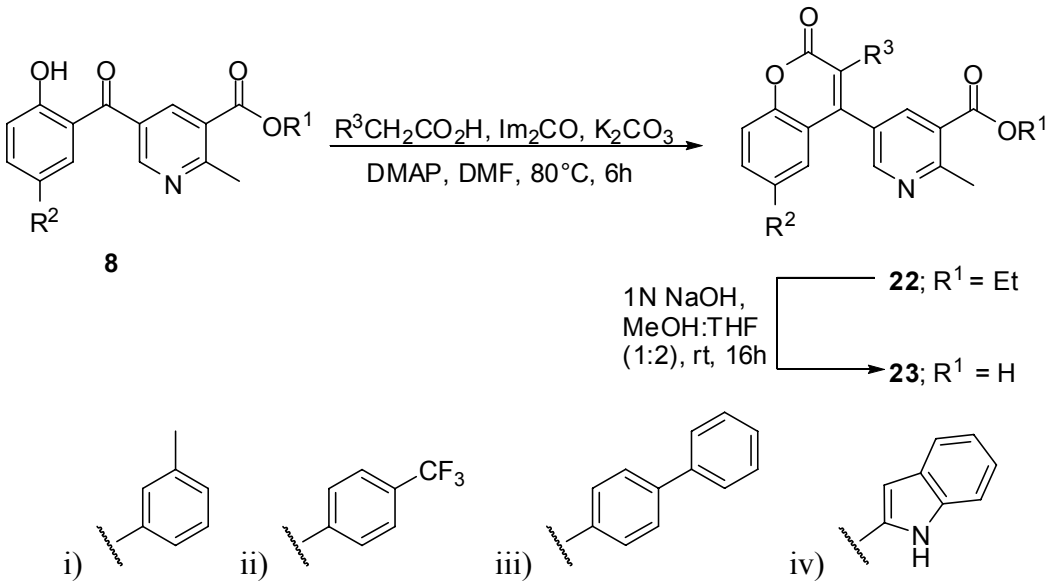
5-(2-(Carboxymethoxy)-5-methylbenzoyl)-2-methylnicotinic acid (21a)

Yield = 18.6 mg (0.056 mmol, 100%); R_f = 0.43 (EtOAc / MeOH = 5 / 2); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.85 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 7.35 (ddd, J = 8.6 Hz, J = 2.3 Hz, J = 0.6 Hz, 1H), 7.26-7.23 (m, 1H), 6.97 (d, J = 8.6 Hz, 1H),

4.58 (s, 2H), 2.78 (s, 3H), 2.29 (s, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 193.6, 169.5, 167.0, 162.7, 153.3, 151.7, 138.3, 133.3, 130.4, 130.4, 129.7, 127.0, 125.8, 112.8, 64.8, 24.7, 19.8; LC-HRMS (ESI): t_R = 2.06 min; calcd. for $C_{17}H_{17}NO_6$ 330.09721, found 330.09718 $[M+H]^+$.

1.14 General procedure for the synthesis of coumarin-derivates

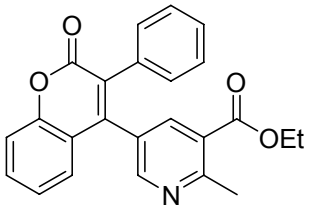
Pyridine derivate **8** (1.0 eq.), carbonyl diimidazole (2.0 eq.), K_2CO_3 (1.0 eq.), DMAP (0.1 eq.), and 2-substituted-acetic acid (2.0 eq.) were dissolved in DMF (5 ml) and heated under an argon atmosphere for 6h at 80 °C. After addition of EtOAc and brine, the biphasic mixture was several times extracted with brine. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude phenol. The residue was purified by column chromatography.



Entry	R^1	R^2	R^3	22 Yield[%]	23 Yield[%][a,b]
a	Et	H	Ph	100	97
b	Et	*i*-Pr	Ph	71	97
c	Et	*i*-Pr	i)	78	93
d	Et	Br	i)	92	99
e	Et	H	ii)	86	94
f	Et	Cl	ii)	88	100

Entry	R^1	R^2	R^3	22 Yield[%]	23 Yield[%][a,b]
g	Et	H	iii)	92	97
h	Et	Br	iii)	94	96
i	Et	Br	iv)	78	91
j	Et	Cl	iv)	100	95

a) isolated yield; b) yield from **22**.

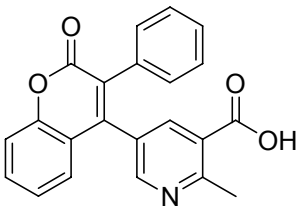


Ethyl 2-methyl-5-(2-oxo-3-phenyl-2*H*-chromen-4-yl)nicotinate (22a)

Yield = 67.9 mg (0.176 mmol, 100%); R_f = 0.42 (PE / EtOAc = 2 / 1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.37 (d, J = 2.3 Hz, 1H), 8.05-7.95 (d, J = 2.3 Hz，1H), 7.59-7.55 (m, 1H), 7.46-7.44 (m, 1H), 7.26-7.21 (m, 4H), 7.15–7.10 (m, 3H), 4.41-4.22 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 165.7, 160.6, 159.9, 153.2, 151.4, 146.9, 139.2, 133.0, 131.9, 130.4, 128.5, 128.2, 127.9, 126.9, 125.0, 124.5, 119.8, 117.1, 61.5, 24.7, 14.2; LC-HRMS (ESI): t_R = 2.80 min; calcd. for $C_{24}H_{20}NO_4$ 386.13868, found 386.13904 $[M+H]^+$.

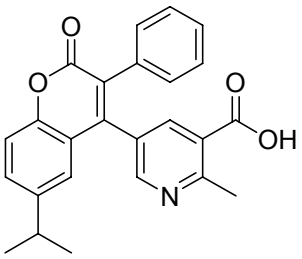
1.15 General procedure for hydrolysis of coumarins

To a solution of ester **13** in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to give crude acid. The residue was purified by column chromatography.



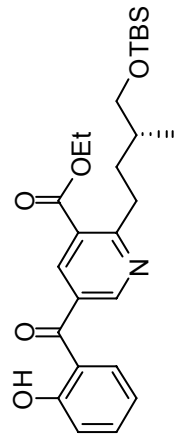
2-Methyl-5-(2-oxo-3-phenyl-2*H*-chromen-4-yl)nicotinic acid (23a)

Yield = 13.1 mg (0.037 mmol, 97%); R_f = 0.37 (EtOAc / MeOH = 7 / 2); ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ (ppm) = 8.22 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.56 (ddd, J = 8.4 Hz, J = 7.3 Hz, J = 1.6 Hz, 1H), 7.40 (dd, J = 8.3 Hz, 0.8 Hz, 1H), 7.25-7.19 (m, 1H), 7.18-7.11 (m, 3H), 7.08 (ddd, J = 7.3 Hz, J = 4.7 Hz, J = 1.6 Hz, 3H), 2.67 (s, 3H); ^{13}C-NMR (100.6 MHz, CH_3OH-d_4): δ (ppm) = 167.2, 159.8, 158.1, 152.4, 150.7, 146.8, 138.6, 133.6, 131.8, 130.3, 127.7, 127.7, 127.5, 126.9, 124.6, 119.8, 116.4, 24.1; LC-HRMS (ESI): t_R = 2.07 min; calcd. for $C_{22}H_{16}NO_4$ 358.10738, found 358.10736 $[M+H]^+$.

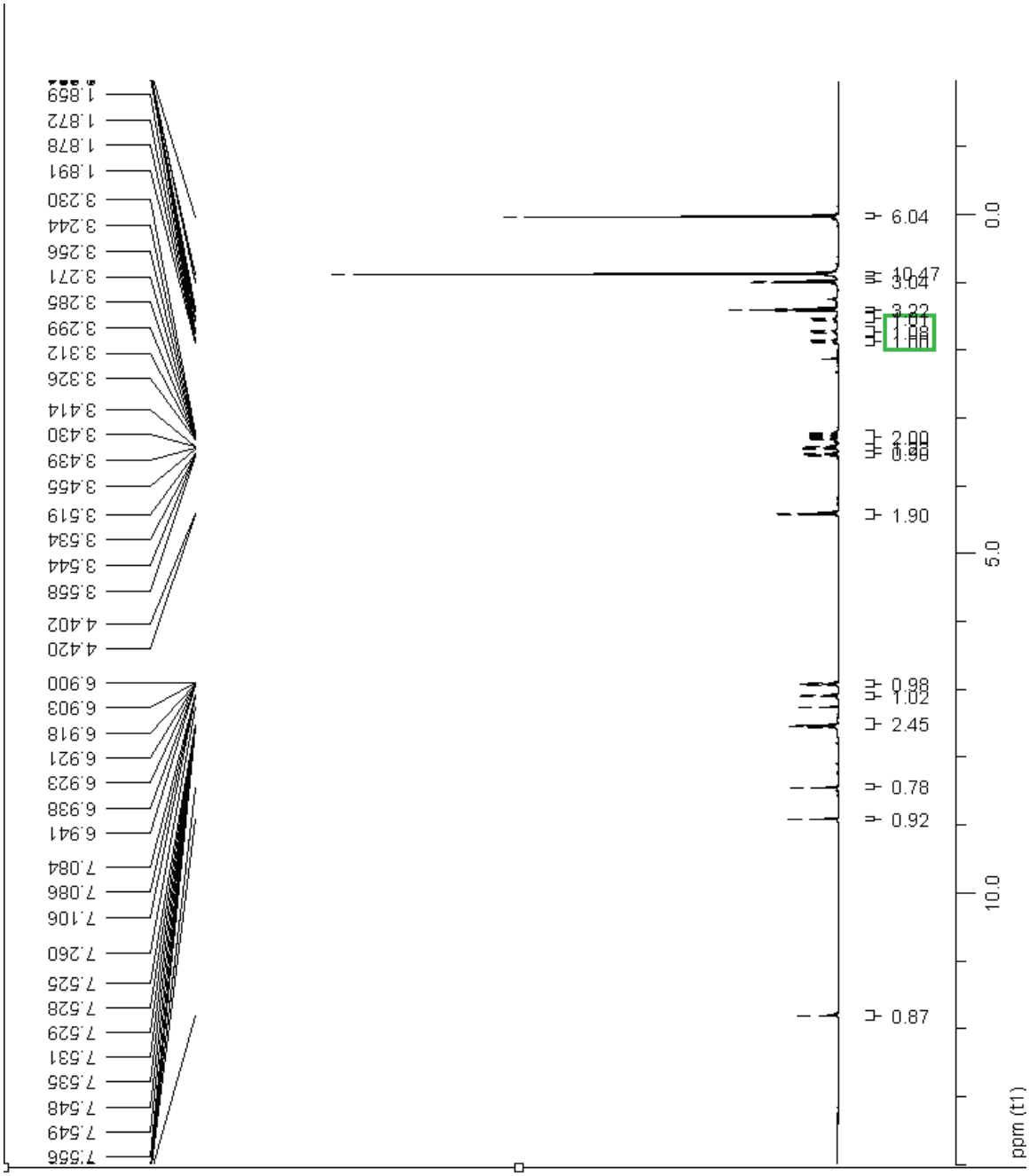


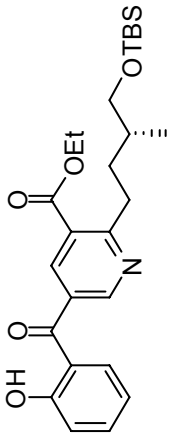
5-(6-isopropyl-2-oxo-3-phenyl-2*H*-chromen-4-yl)-2-methylnicotinic acid (23b)

Yield = 11.2 mg (0.028 mmol, 97%); R_f = 0.39 (EtOAc / MeOH = 7 / 2); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.39 (d, J = 2.2 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 8.6 Hz, J = 2.1 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.26-7.10 (m, 5H), 6.88 (d, J = 2.1 Hz, 1H), 2.95-2.80 (m, 1H), 2.67 (s, 3H), 1.10 (d, J = 6.9 Hz, 6H); ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 167.1, 159.9, 158.2, 150.9, 150.9, 146.8, 144.6, 138.8, 133.7, 130.4, 129.9, 127.7, 127.7, 127.5, 125.0, 124.0, 119.4, 116.5, 32.7, 24.1, 23.6; LC-HRMS (ESI): t_R = 2.57 min; calcd. for $C_{25}H_{22}NO_4$ 400.15433, found 400.15287 $[M+H]^+$.

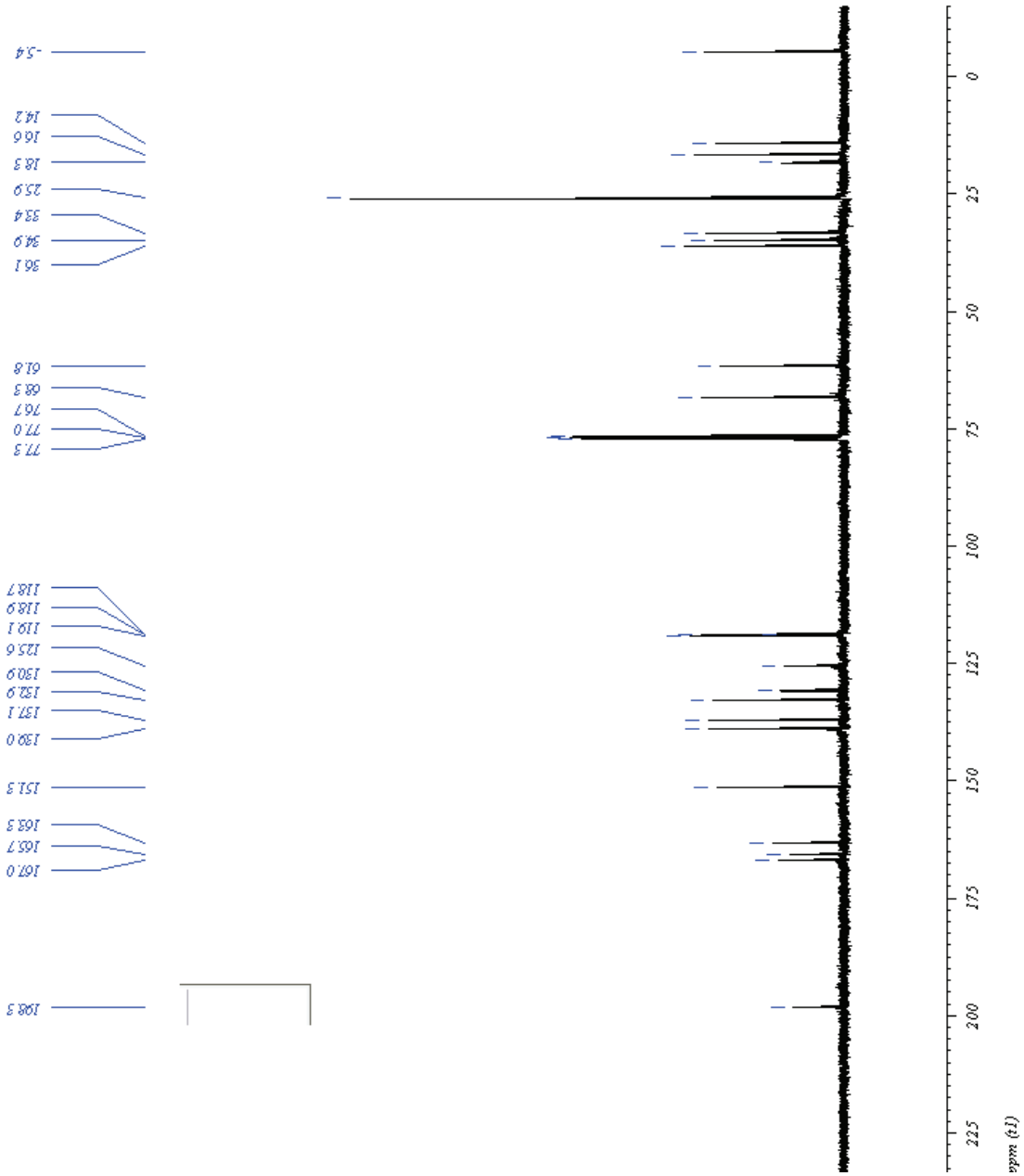


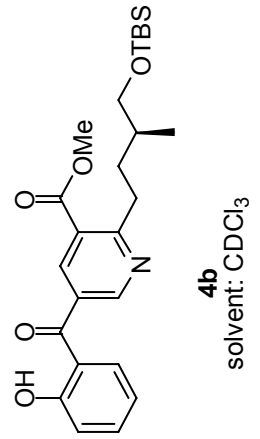
4a
solvent: $CDCl_3$



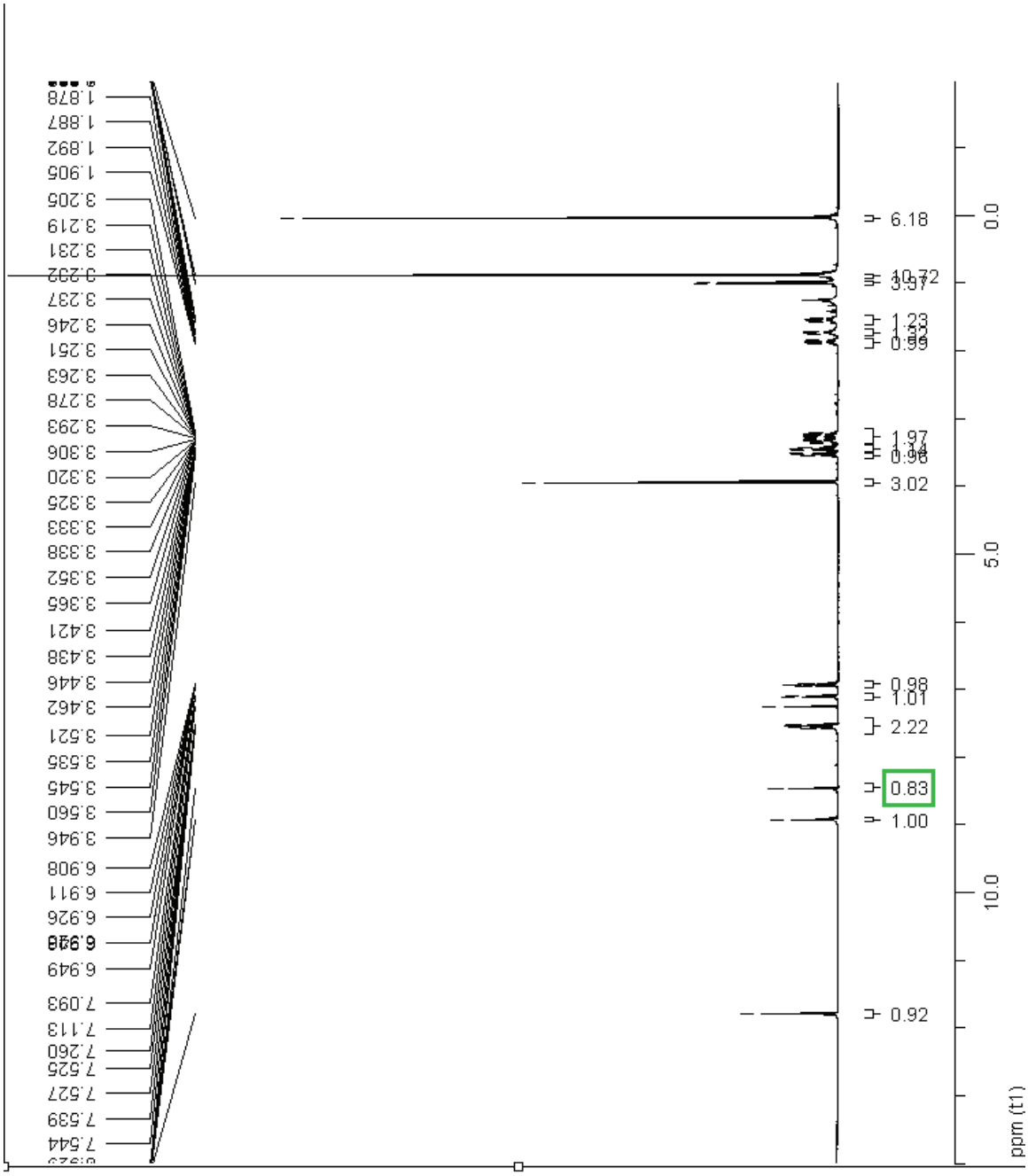


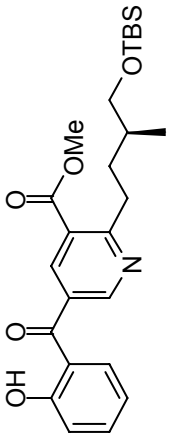
4a
solvent: $CDCl_3$



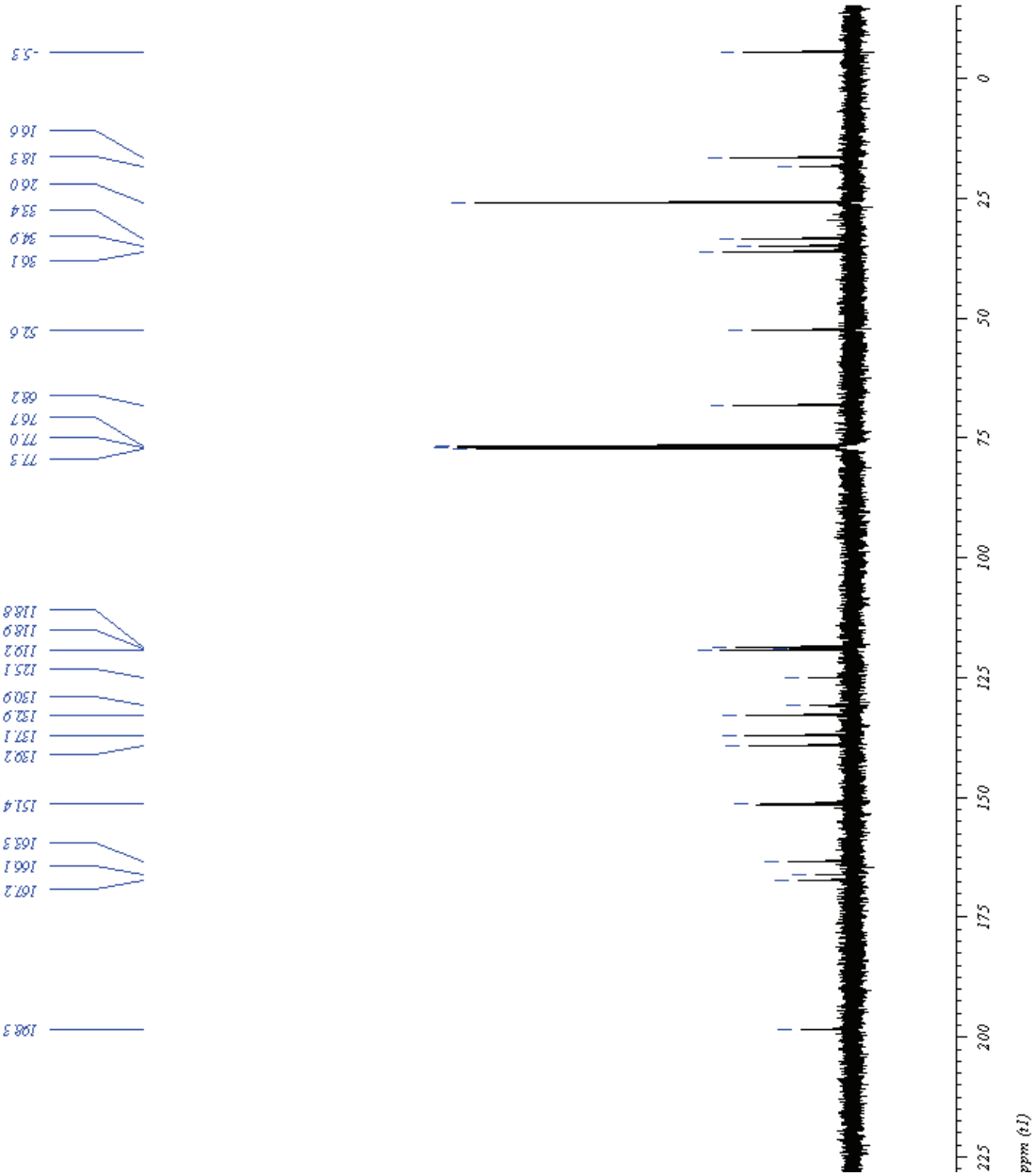


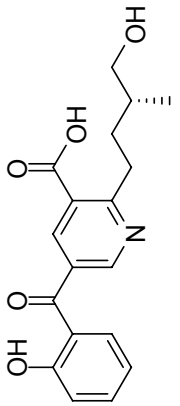
4b
solvent: $CDCl_3$



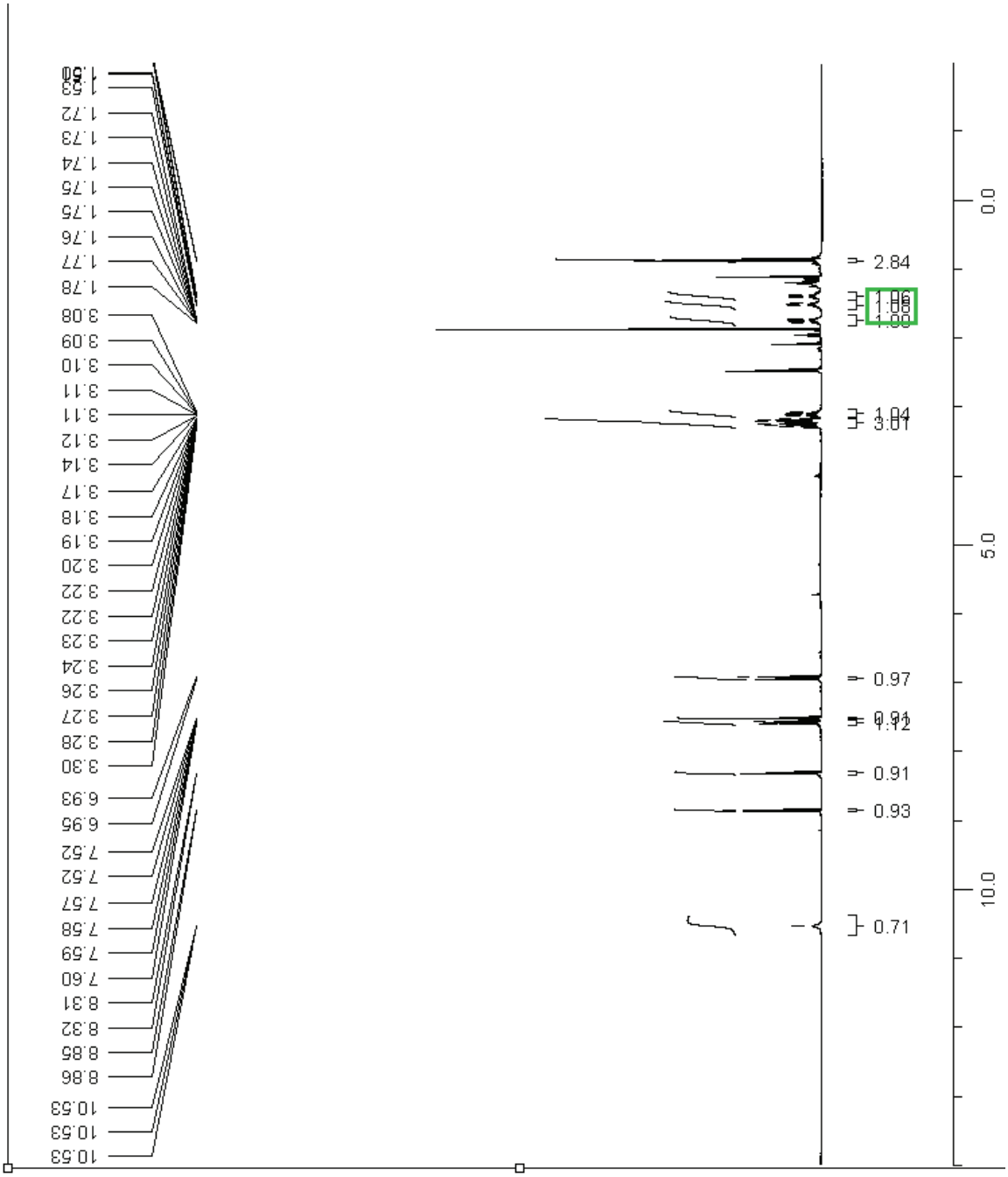


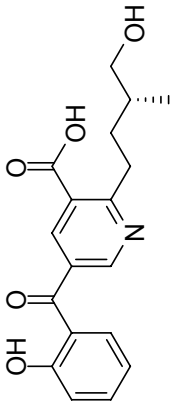
4b
solvent: $CDCl_3$



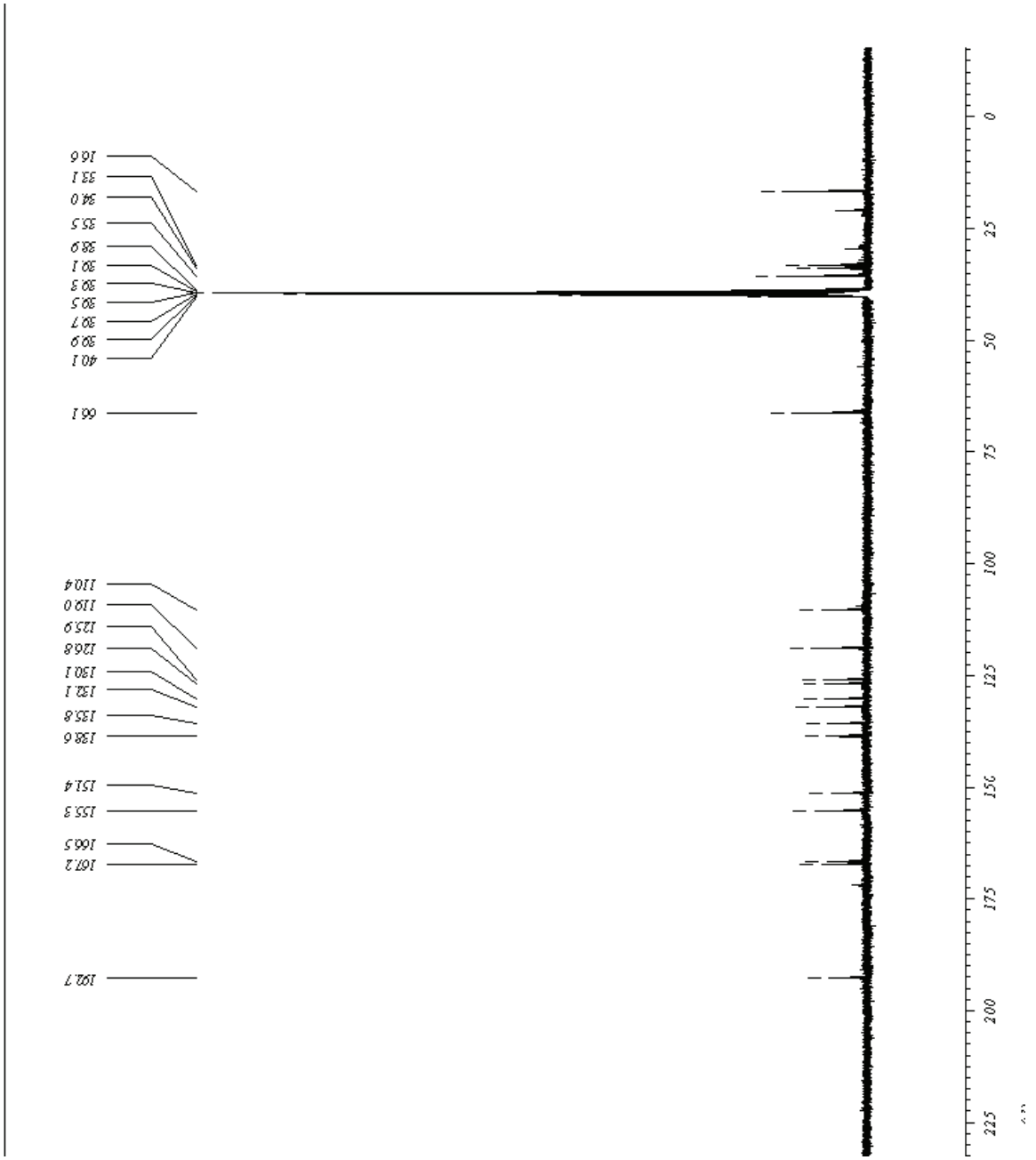


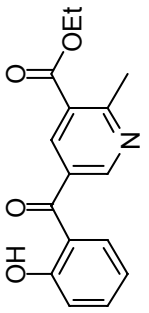
6a
solvent: DMSO



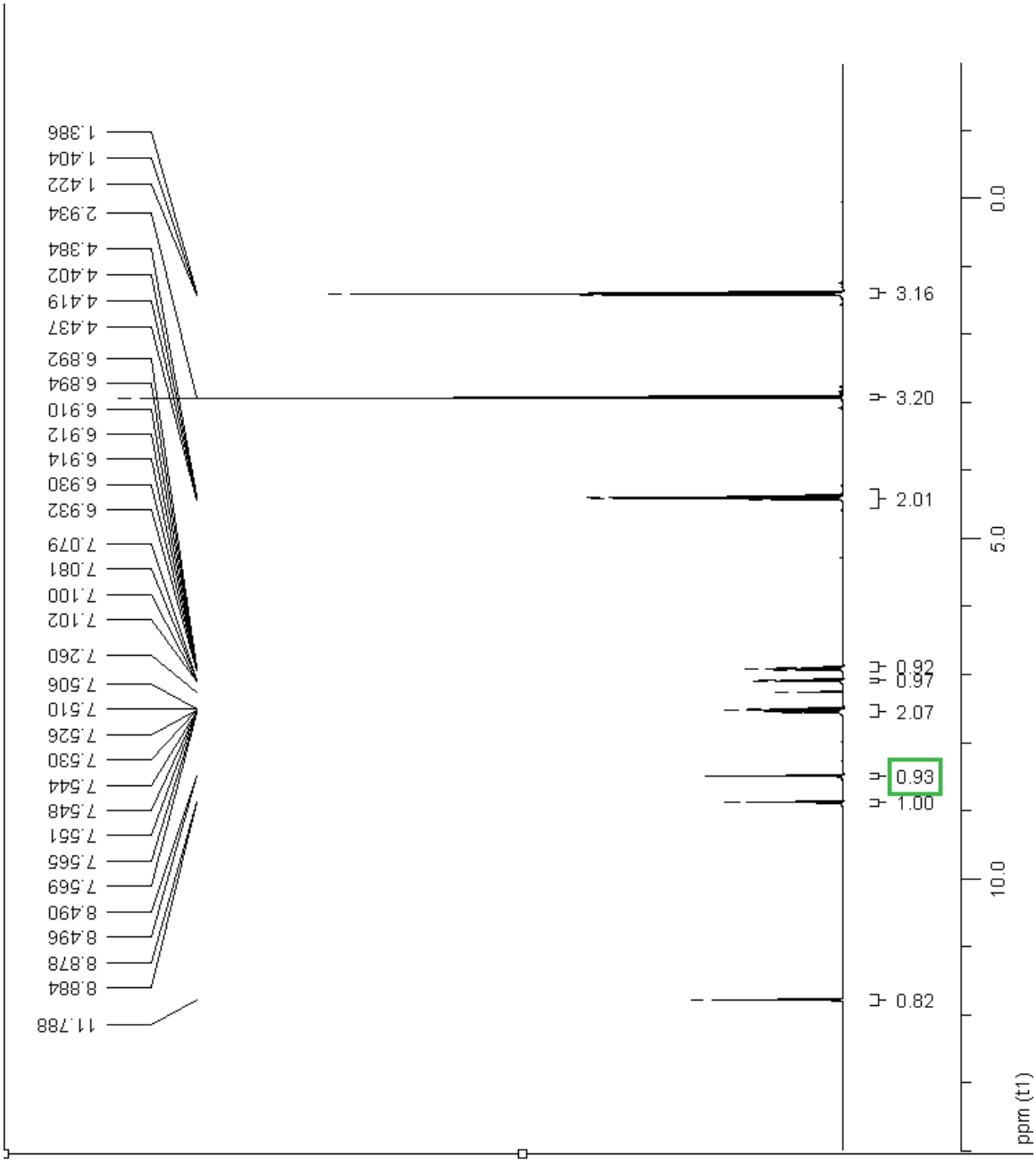


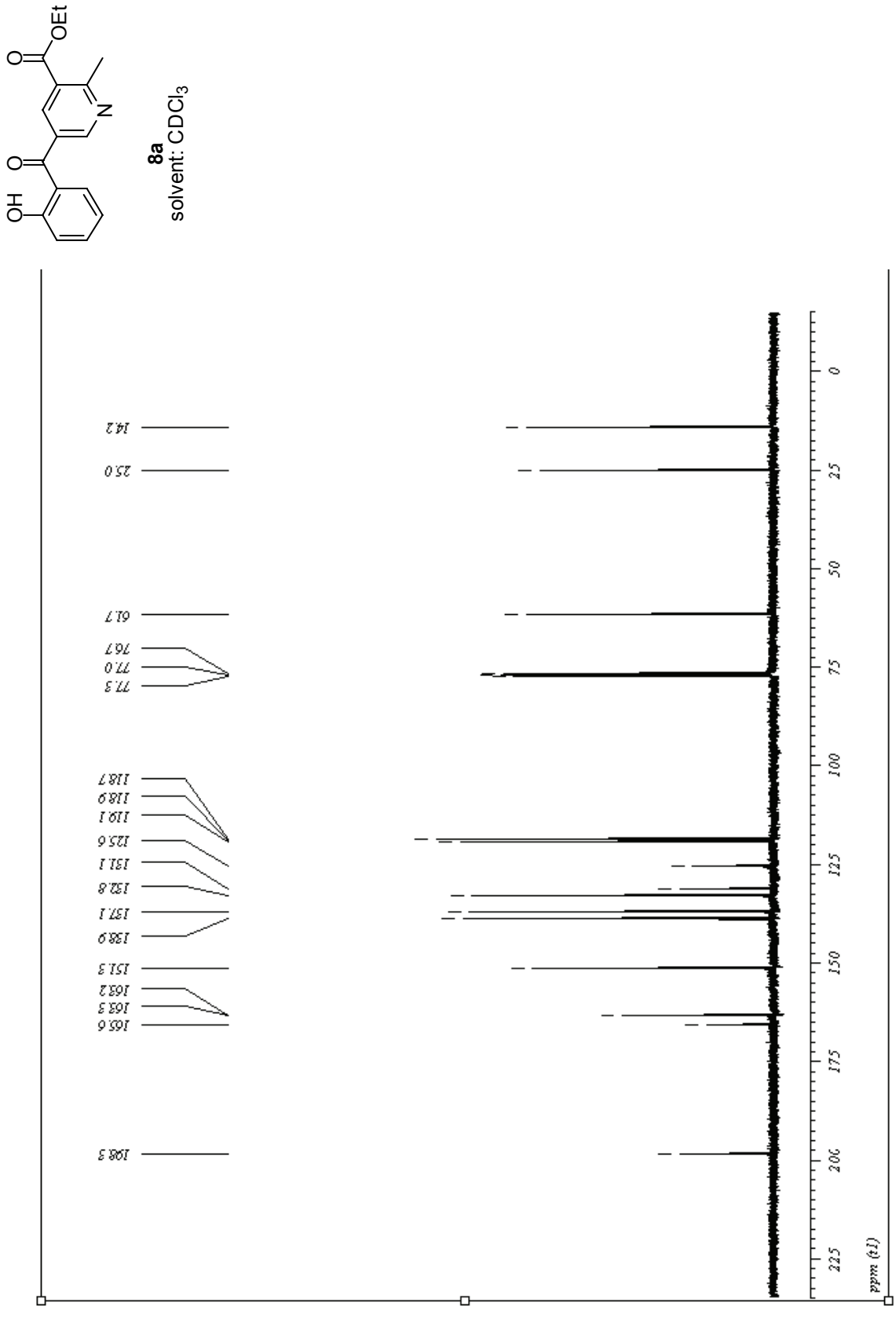
6a
solvent: DMSO





8a
solvent: $CDCl_3$




OEt
O
N
O
OH
8a
solvent: CDCl3
14.2
25.0
61.7
76.7
77.0
77.3
118.7
118.9
119.1
125.6
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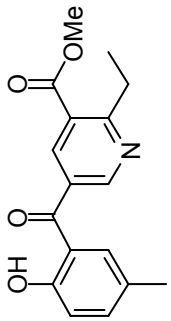
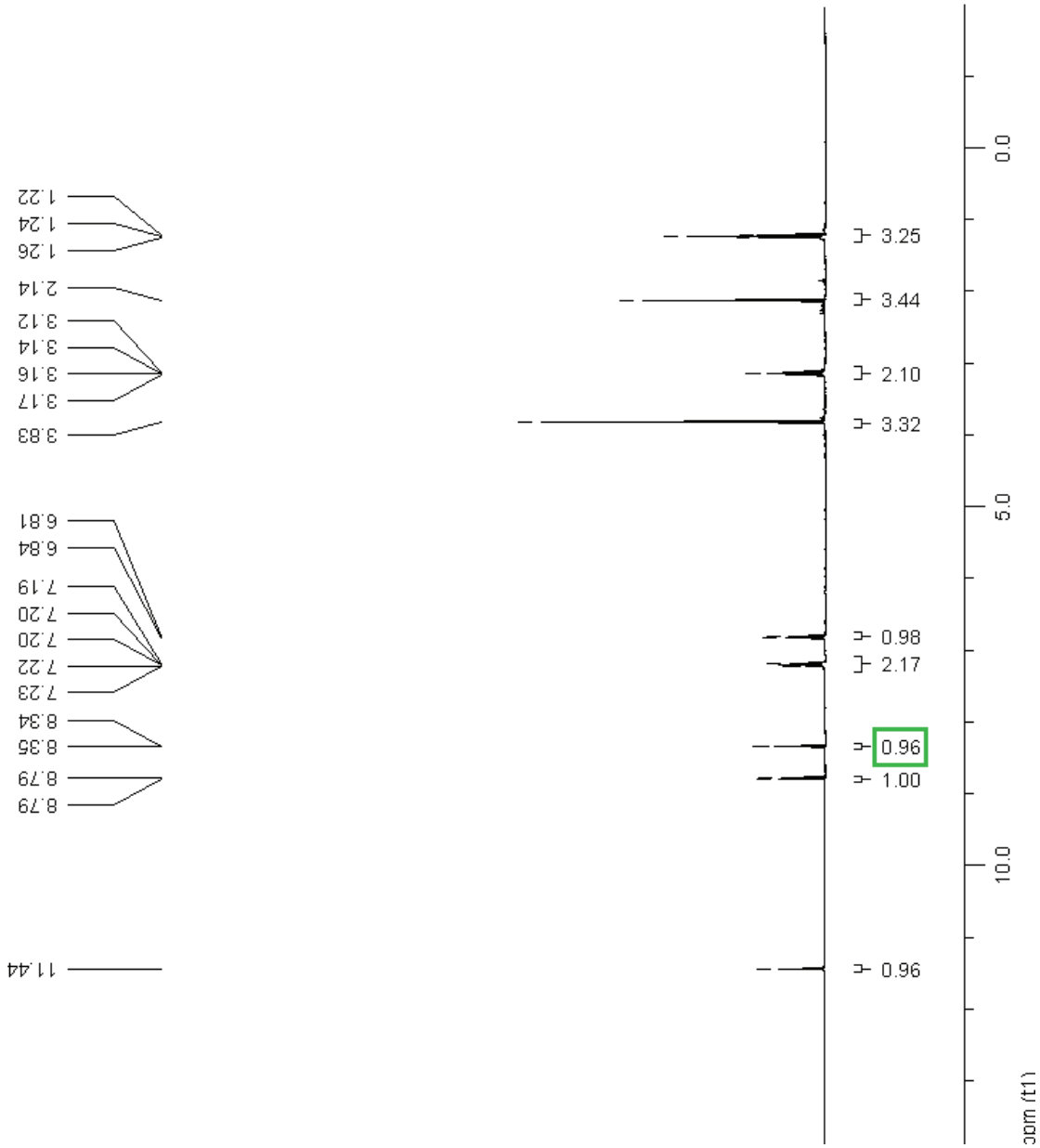
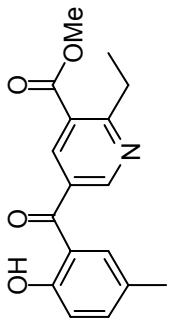
132.8
137.1
138.9
151.3
163.2
163.3
165.6
198.3
ppm (t1)



8e
solvent: $CDCl_3$





8e
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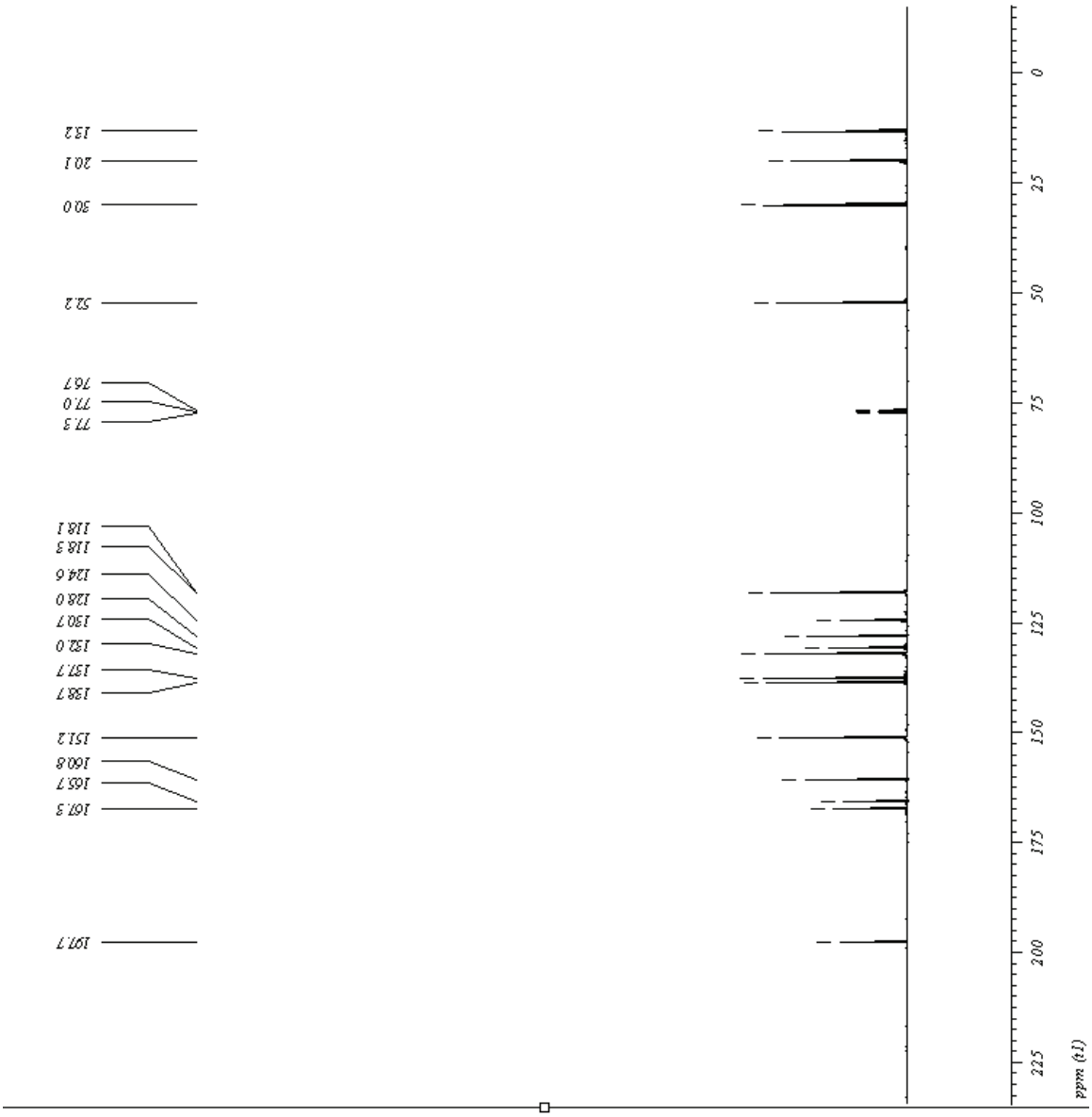
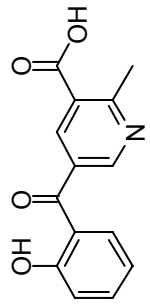
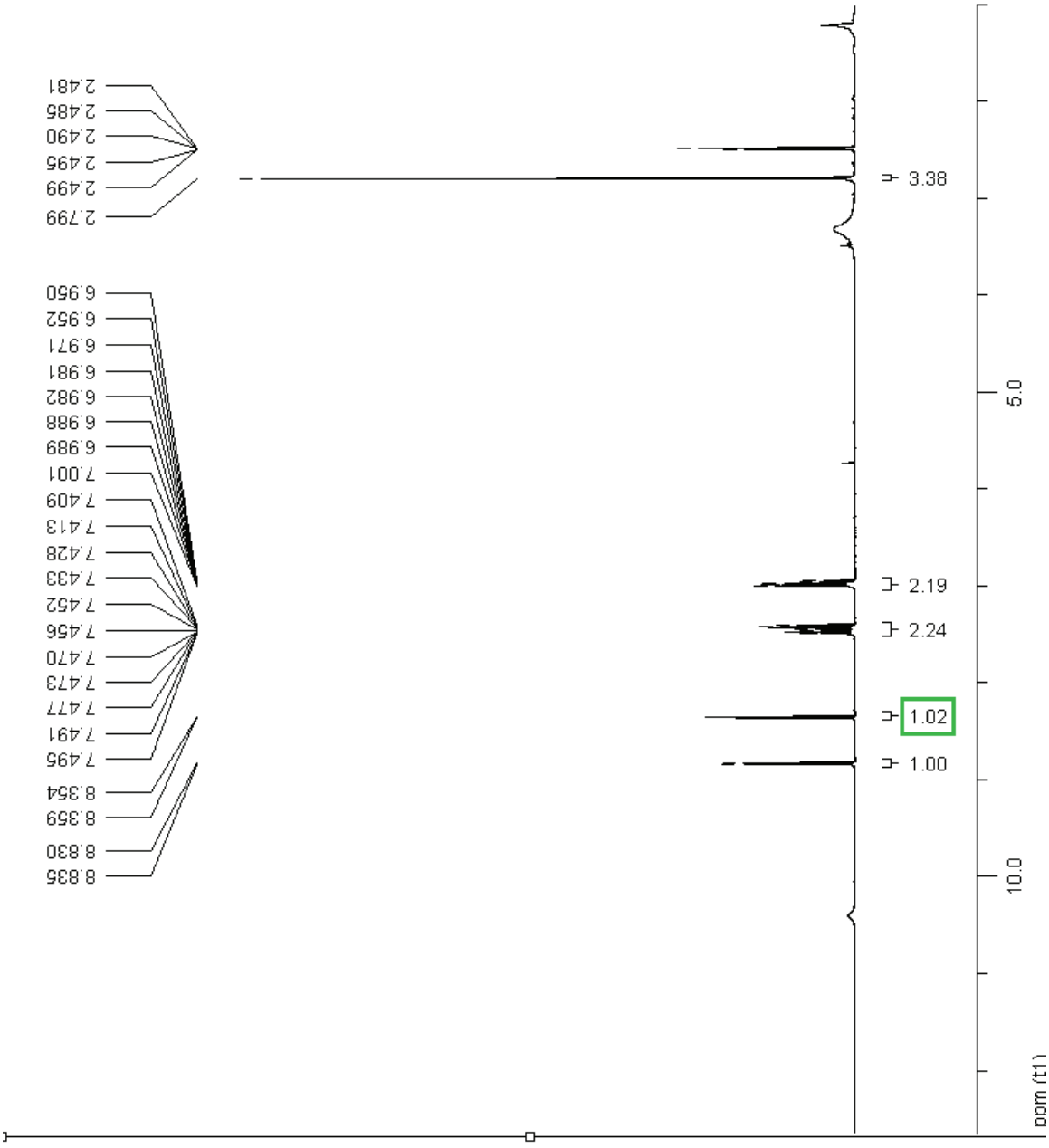
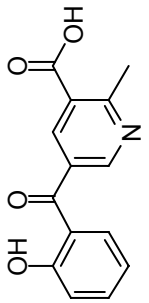


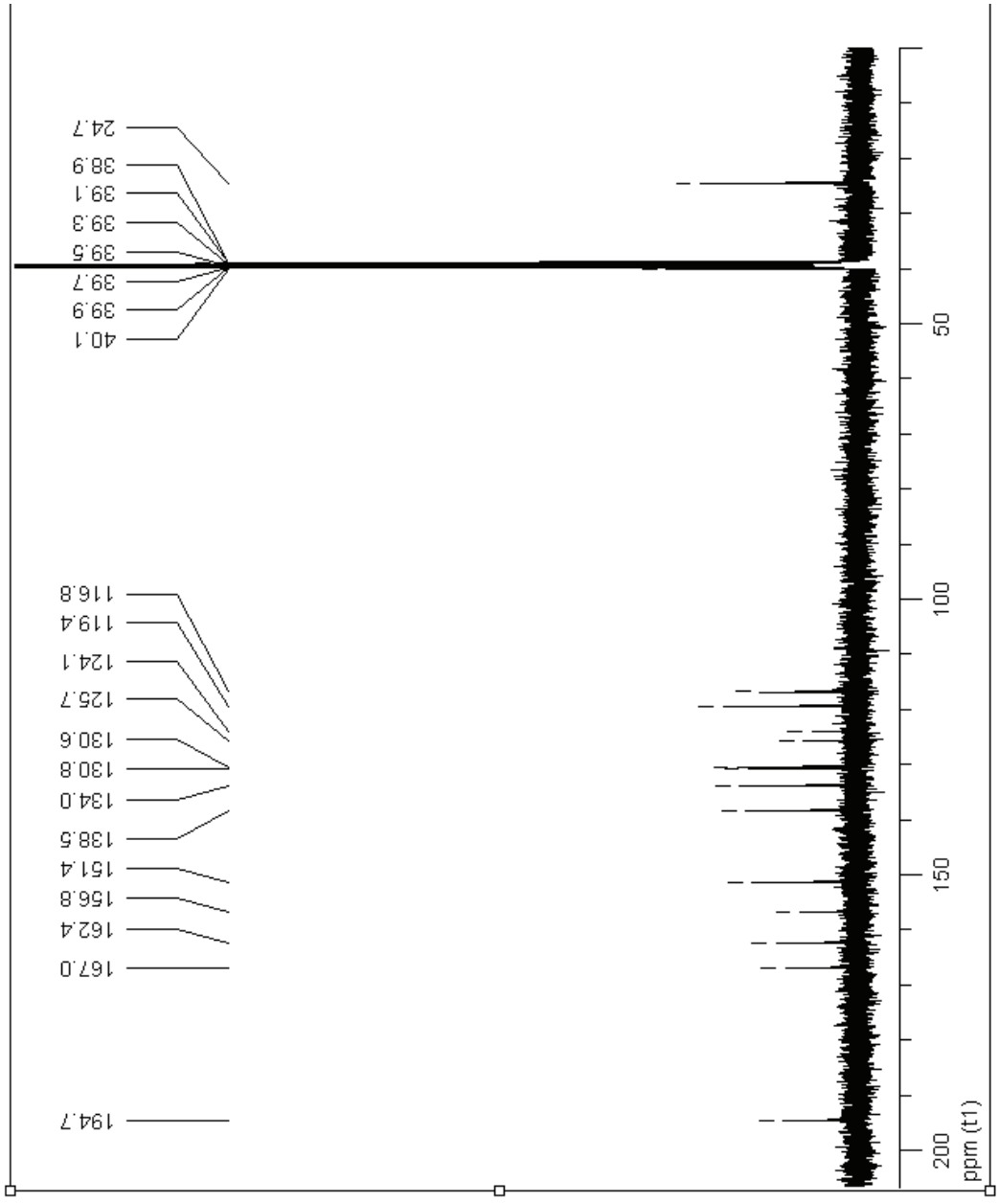


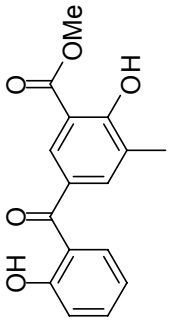
9a
solvent: DMSO



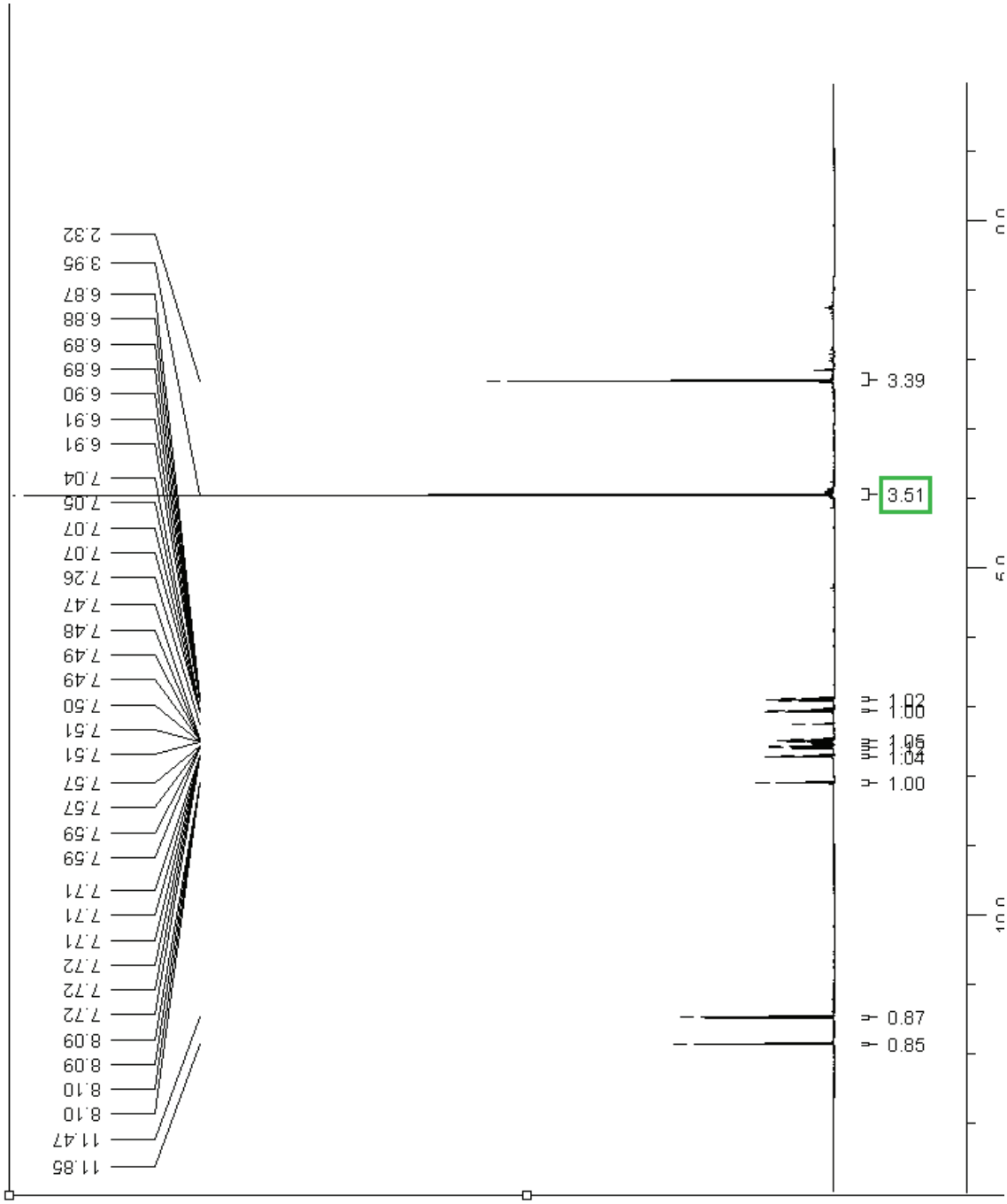


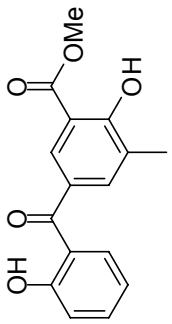
9a
solvent: DMSO



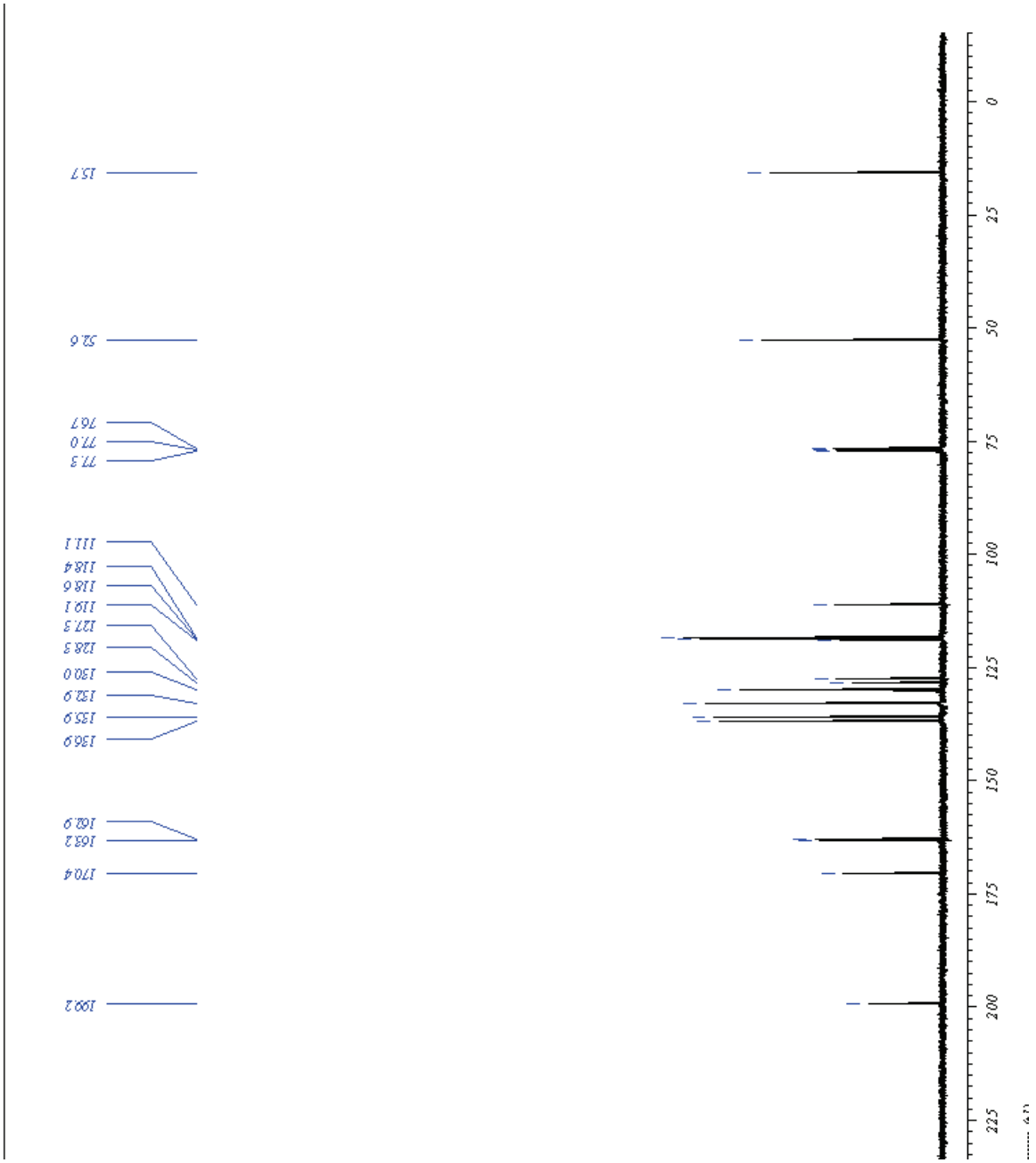


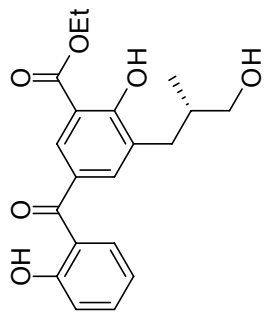
13a
solvent: CDCl3



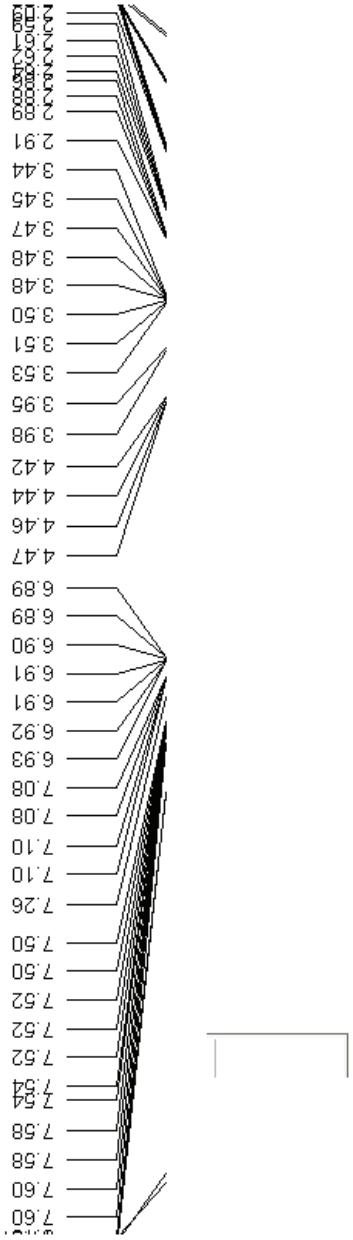


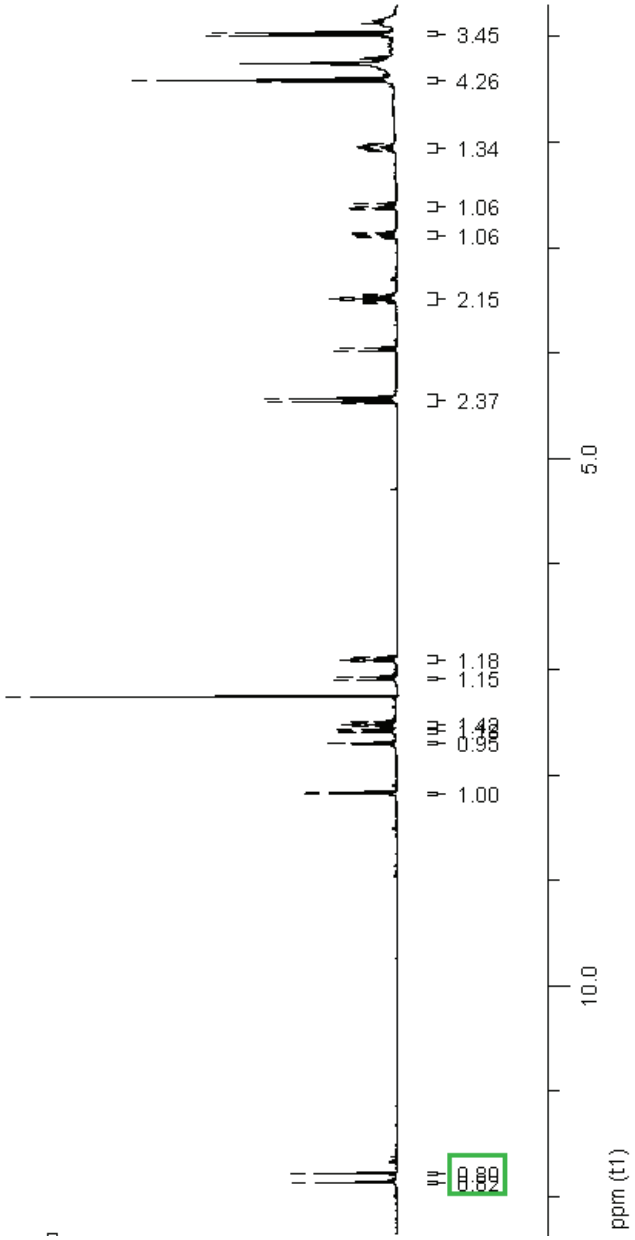
13a
solvent: CDCl3

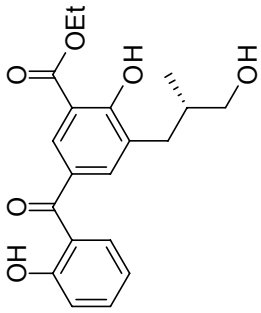




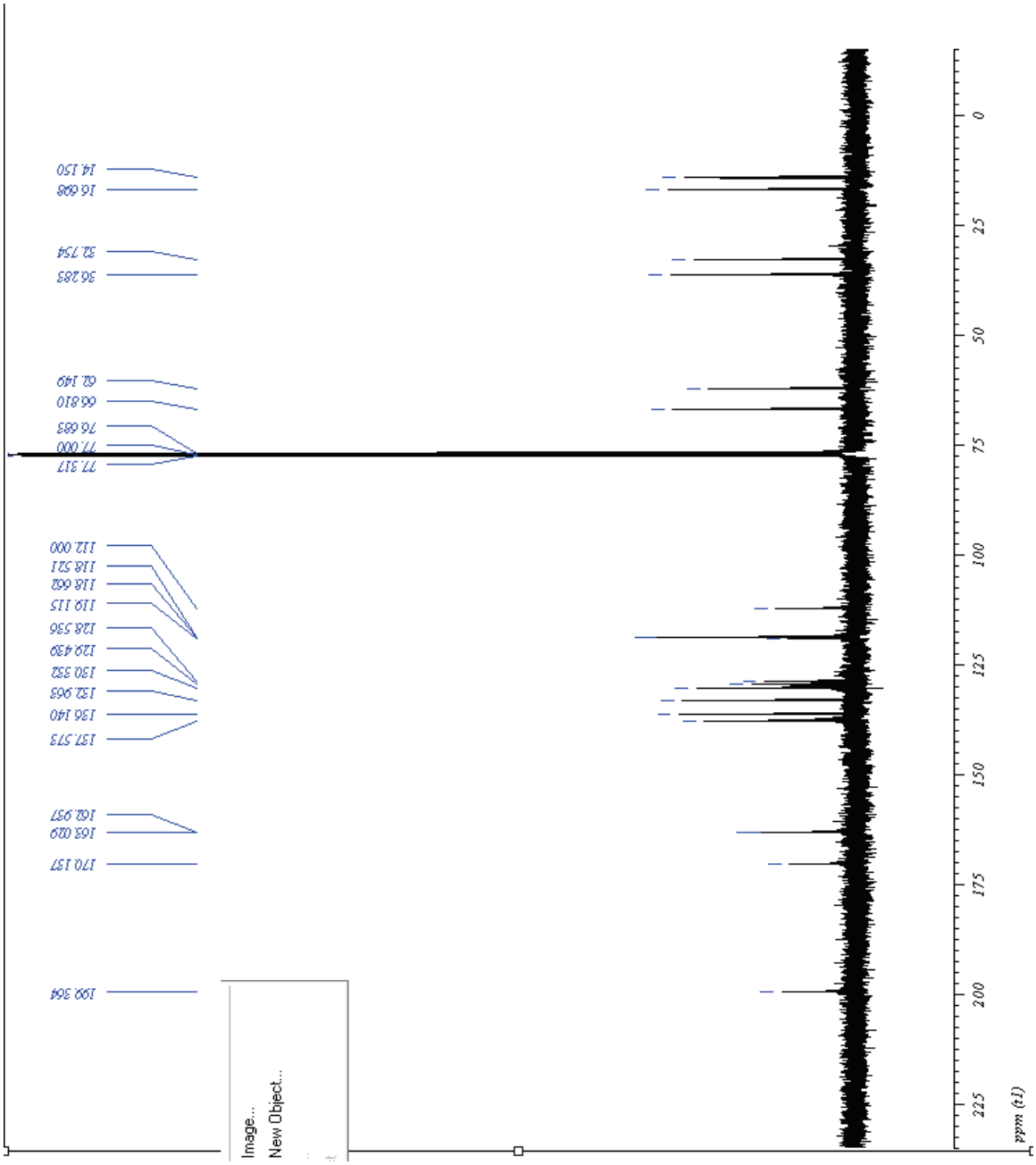
13d
solvent: $CDCl_3$

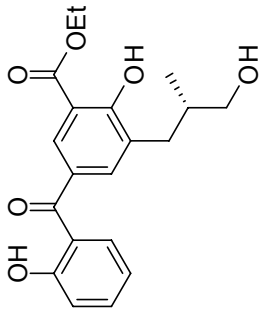




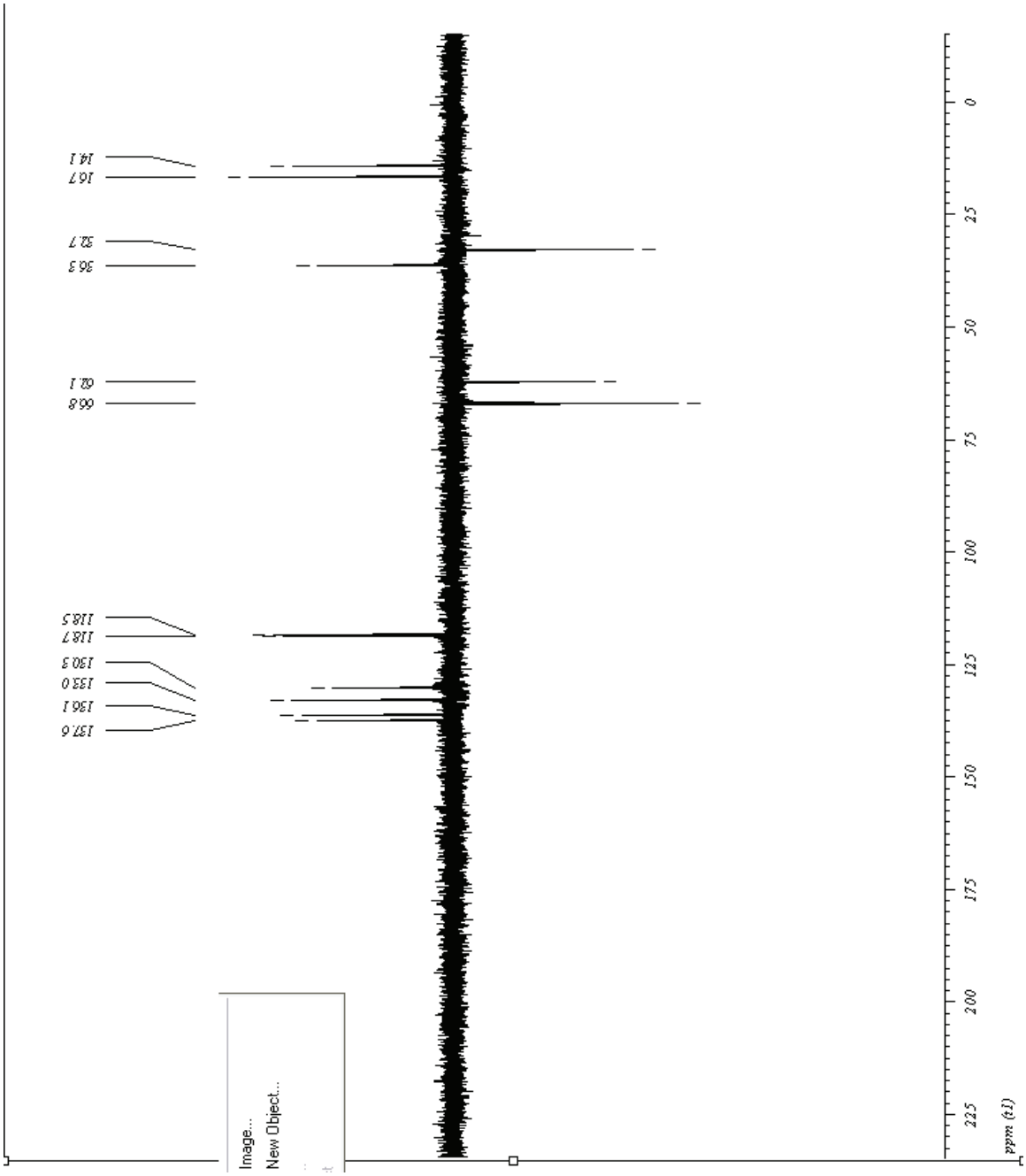


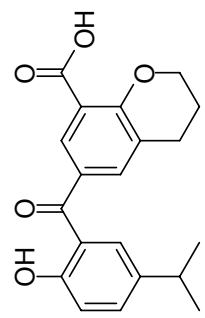
13d
solvent: $CDCl_3$



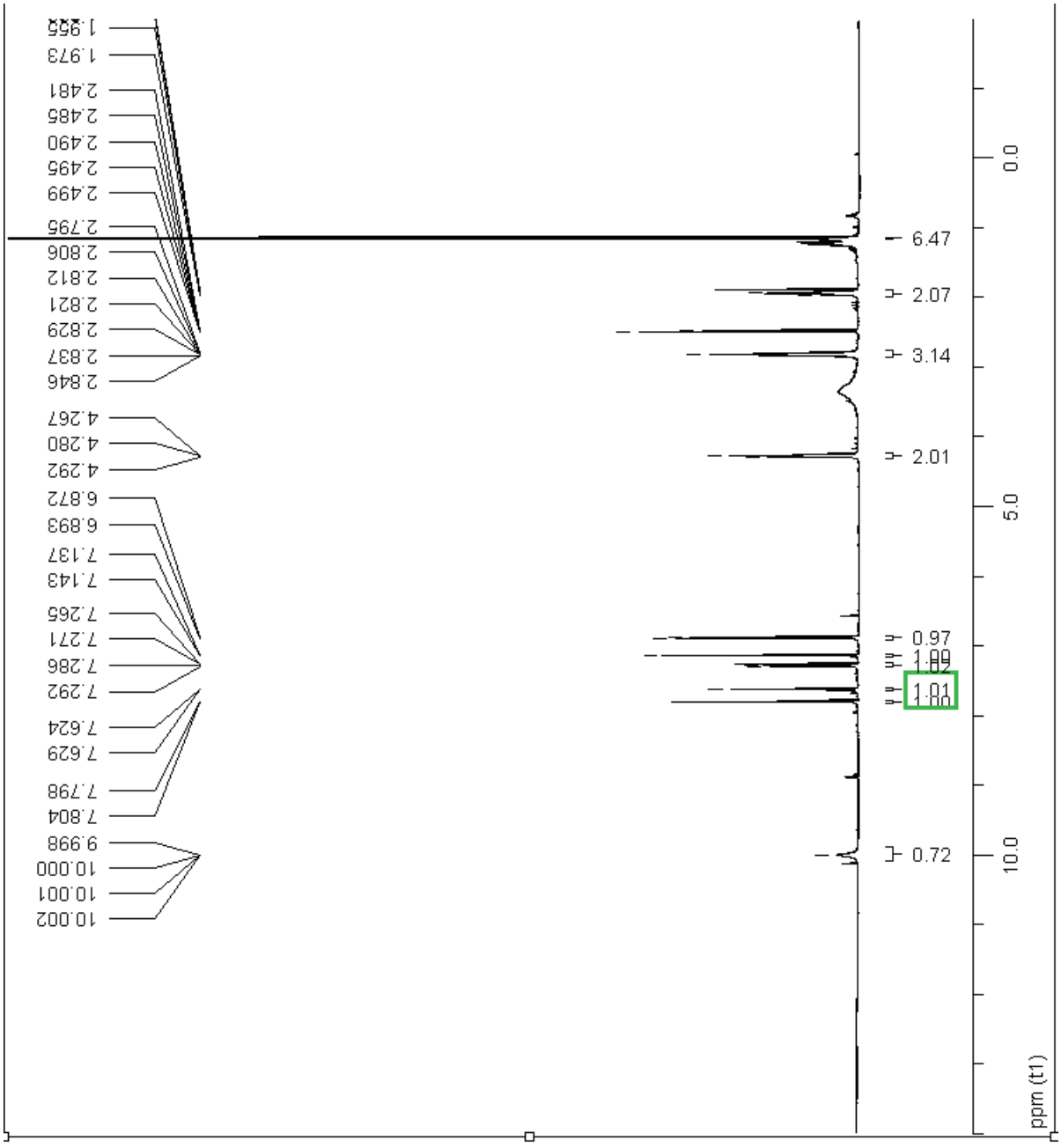


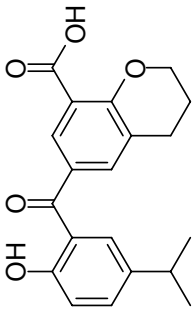
13d
solvent: $CDCl_3$



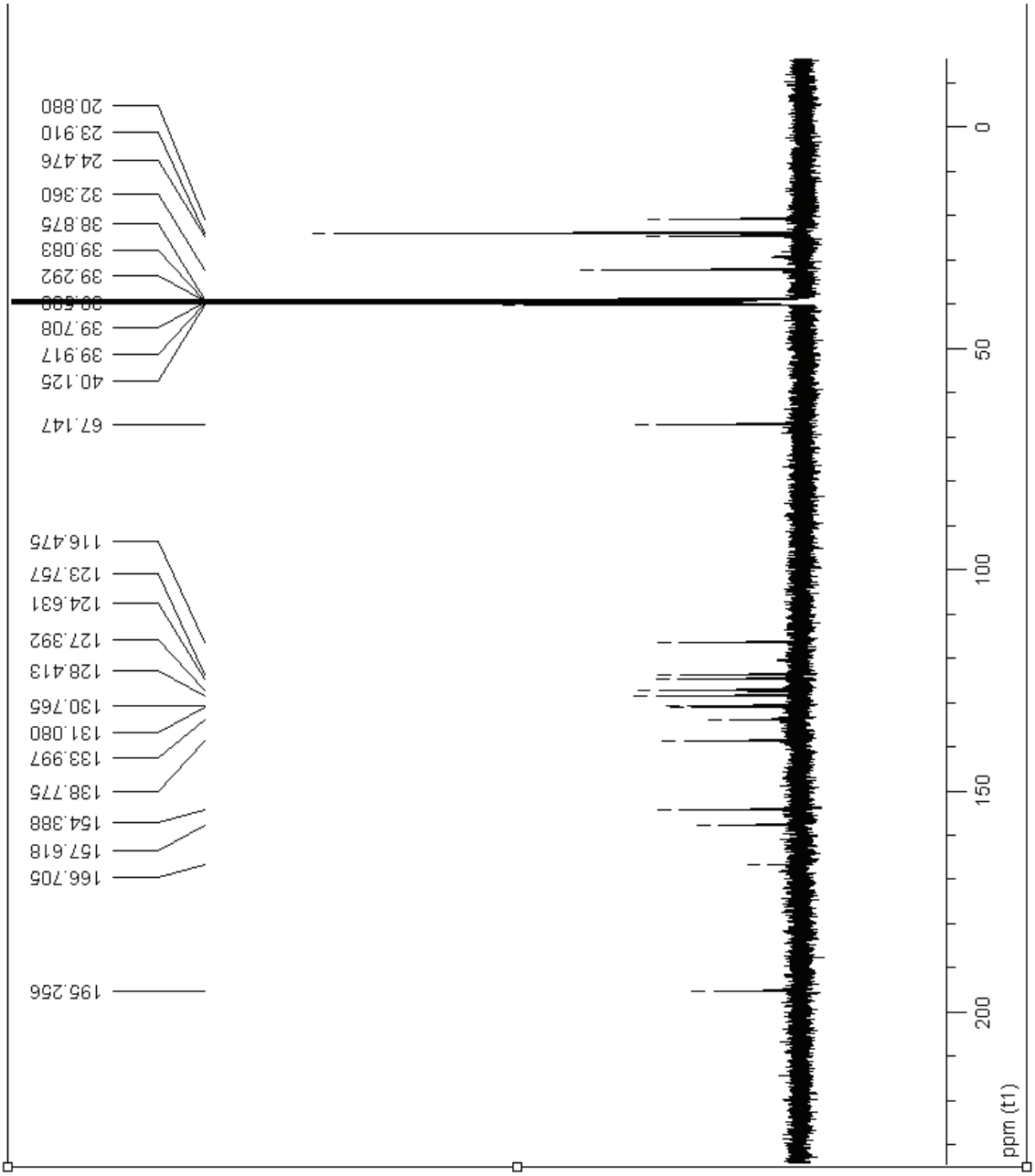


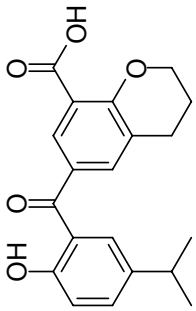
19e
solvent: DMSO



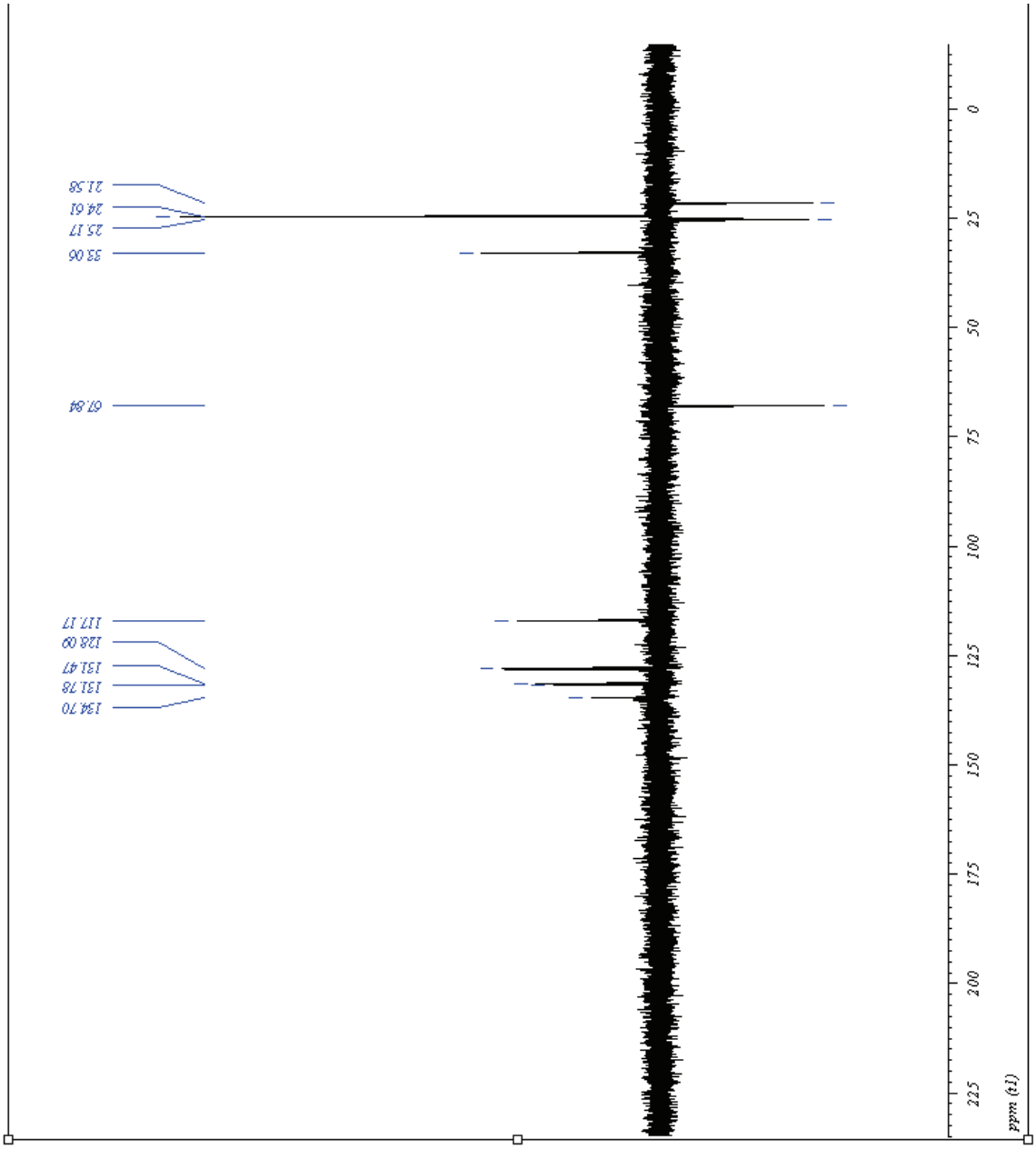


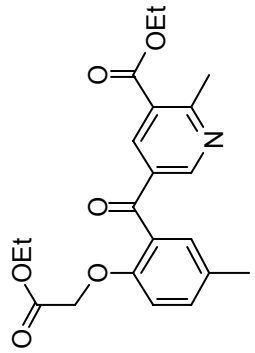
19e
solvent: DMSO



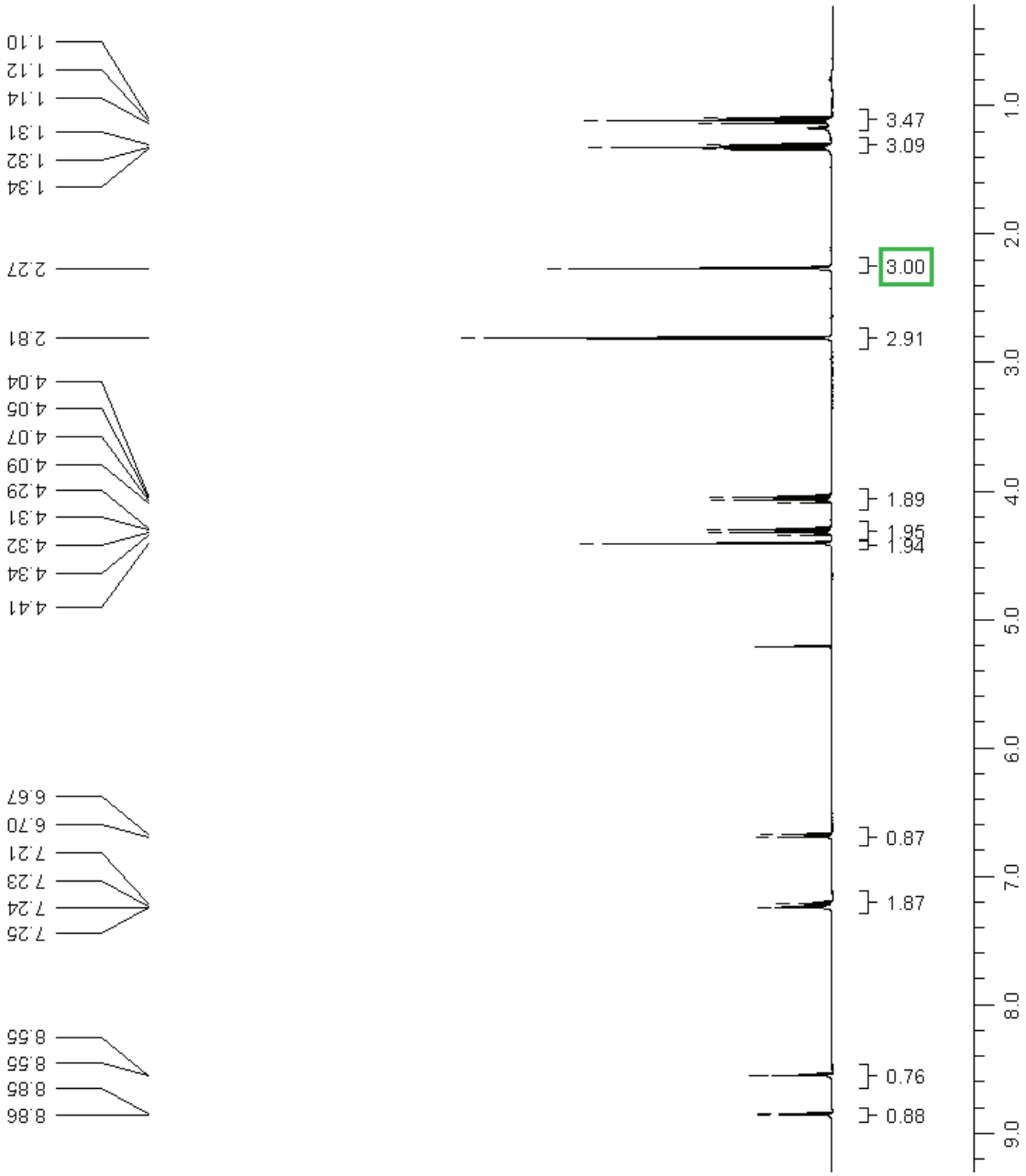


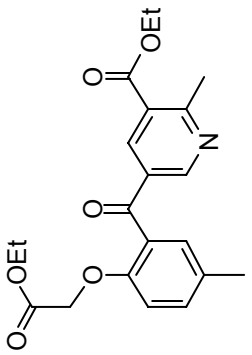
19e
solvent: DMSO



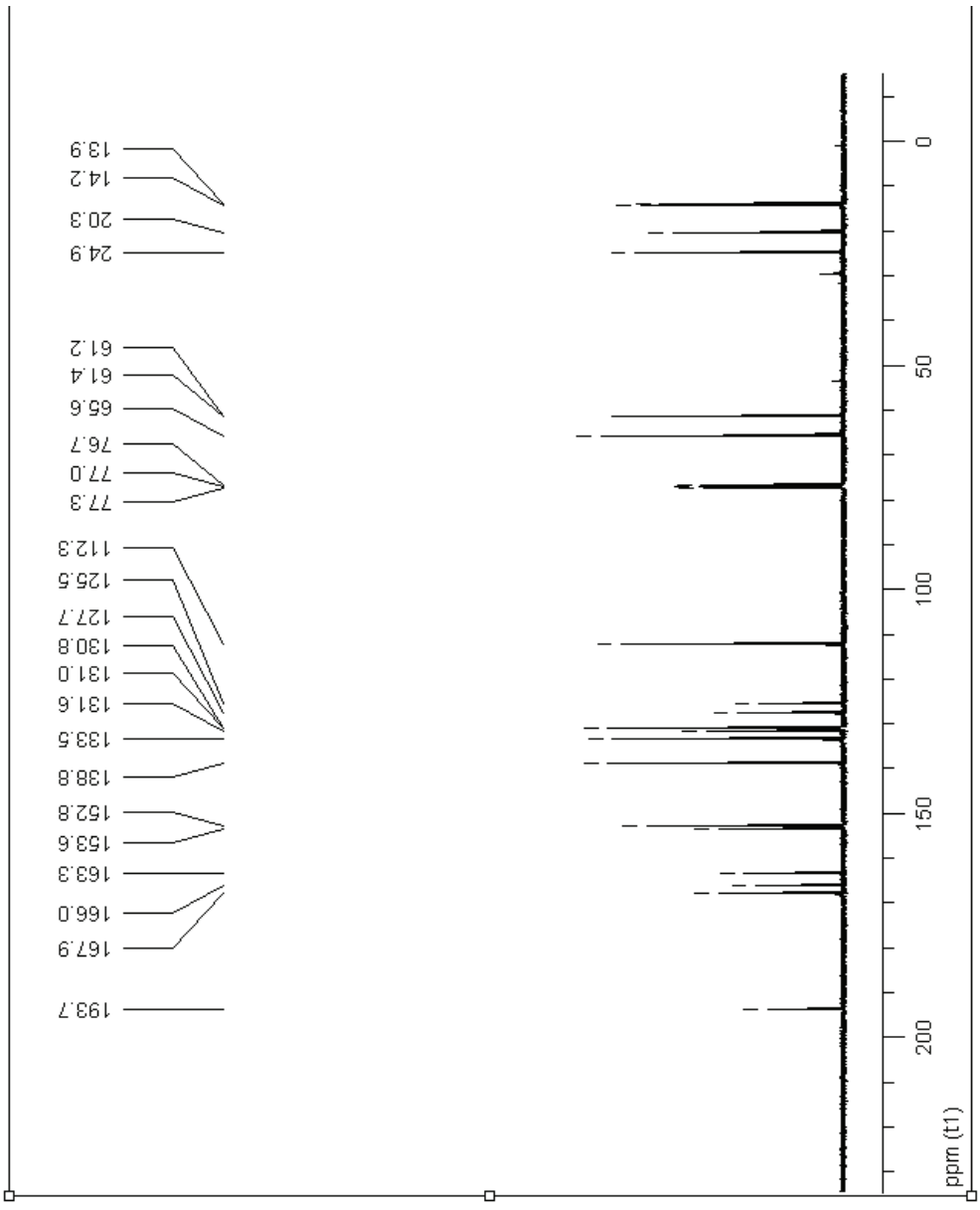


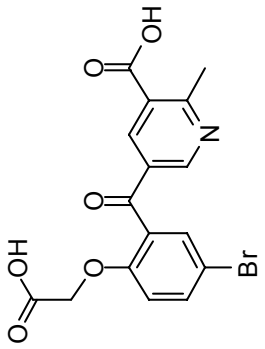
20a
solvent: $CDCl_3$



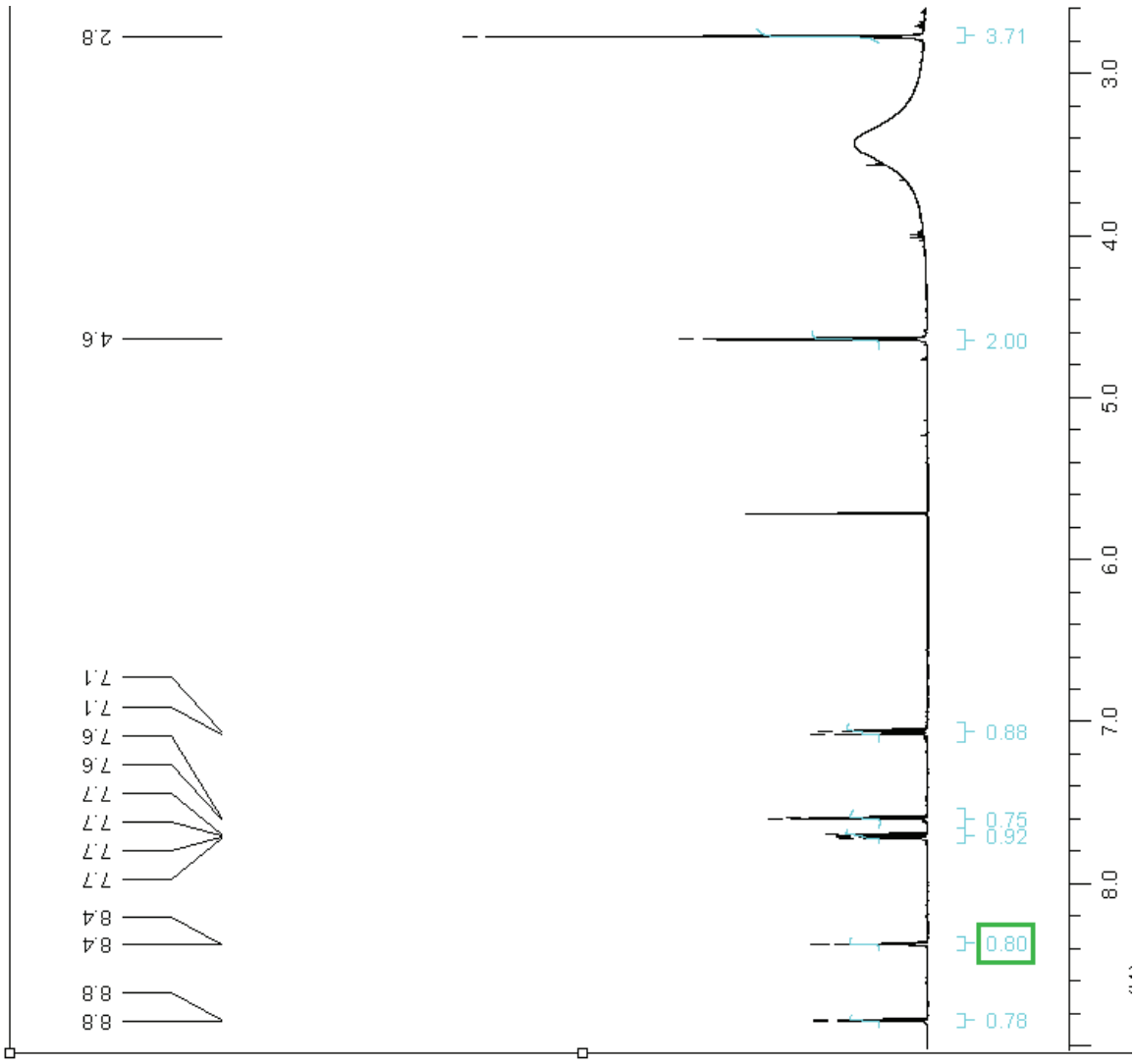


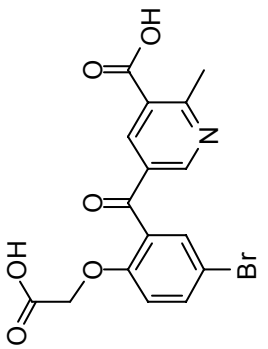
20a
solvent: $CDCl_3$



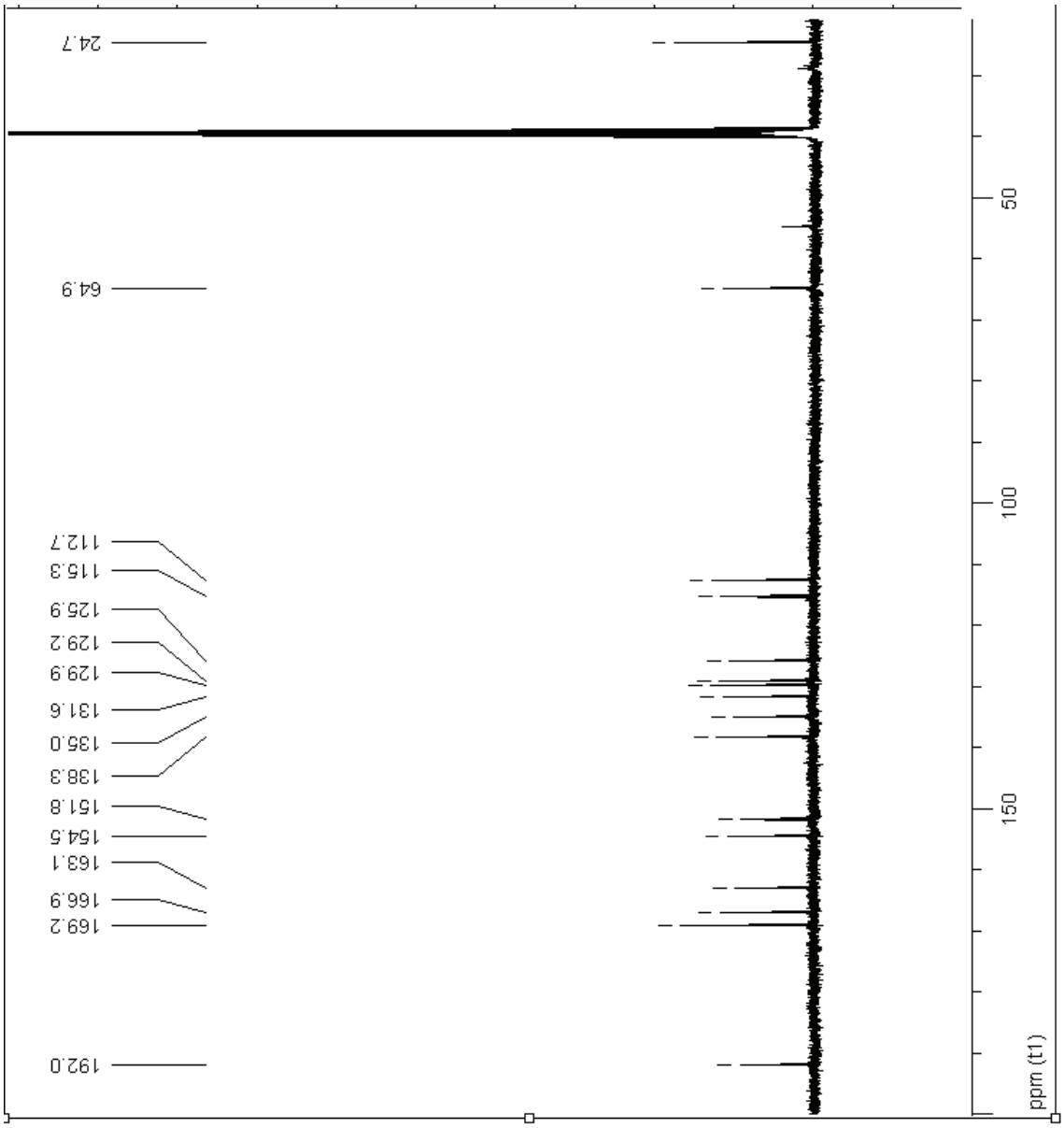


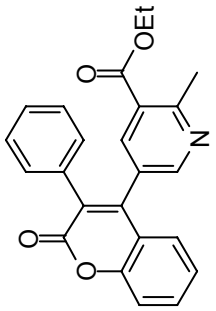
21b
solvent: DMSO



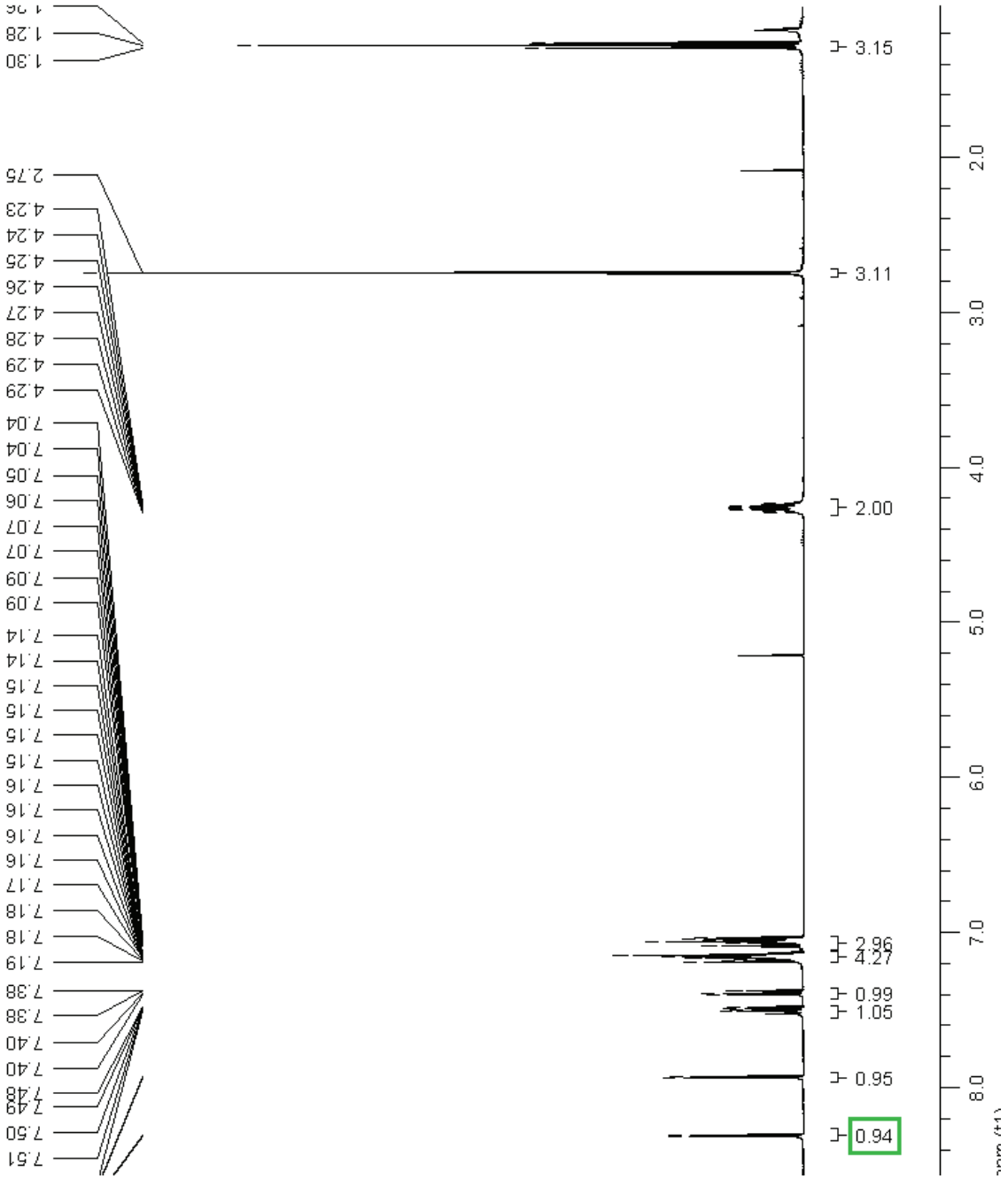


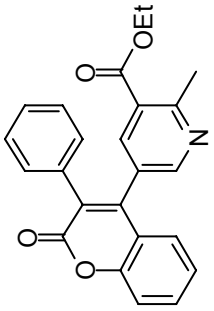
21b
solvent: DMSO



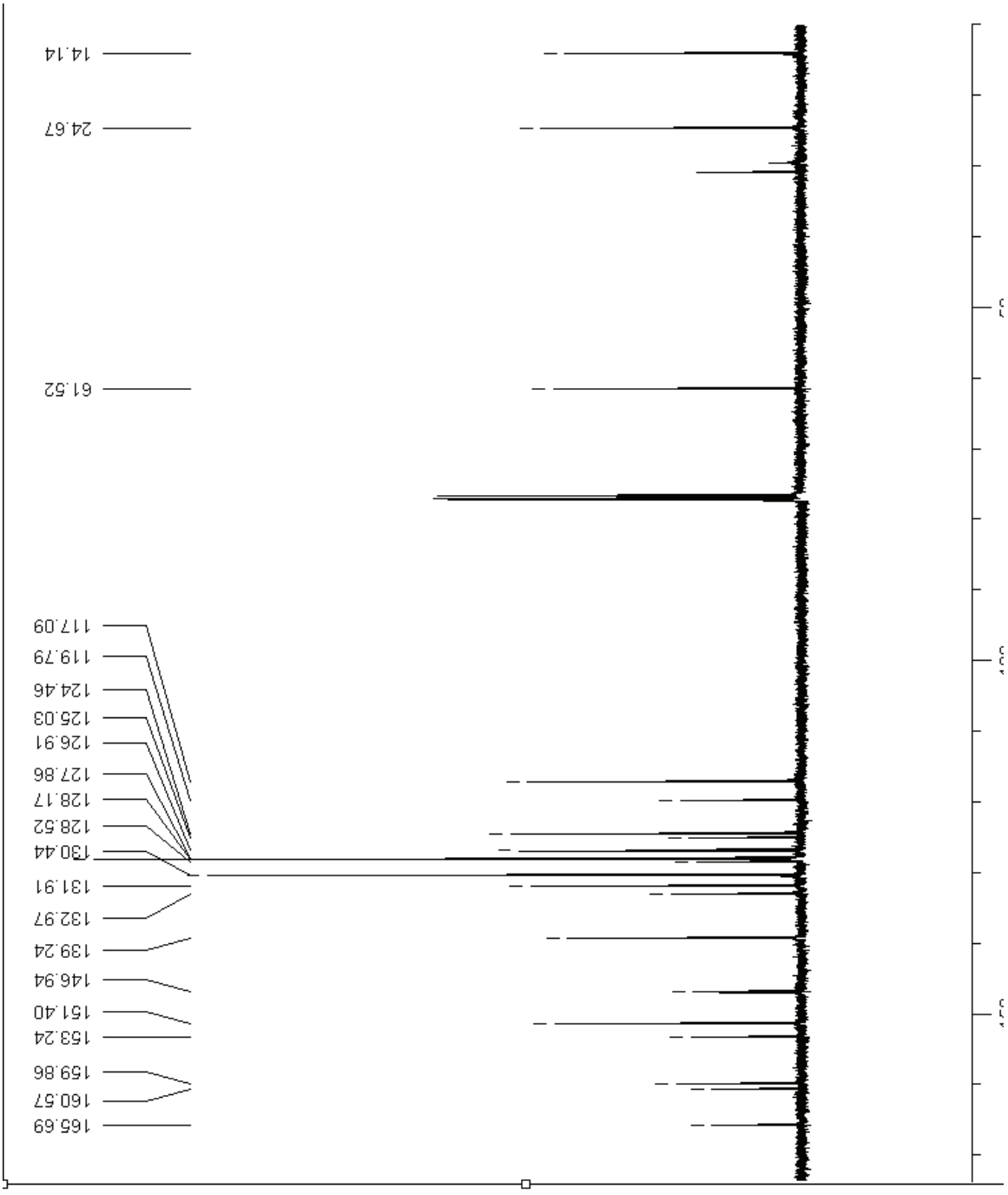


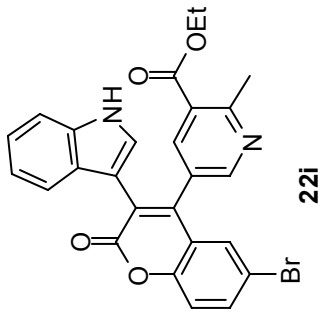
22a
solvent: $CDCl_3$



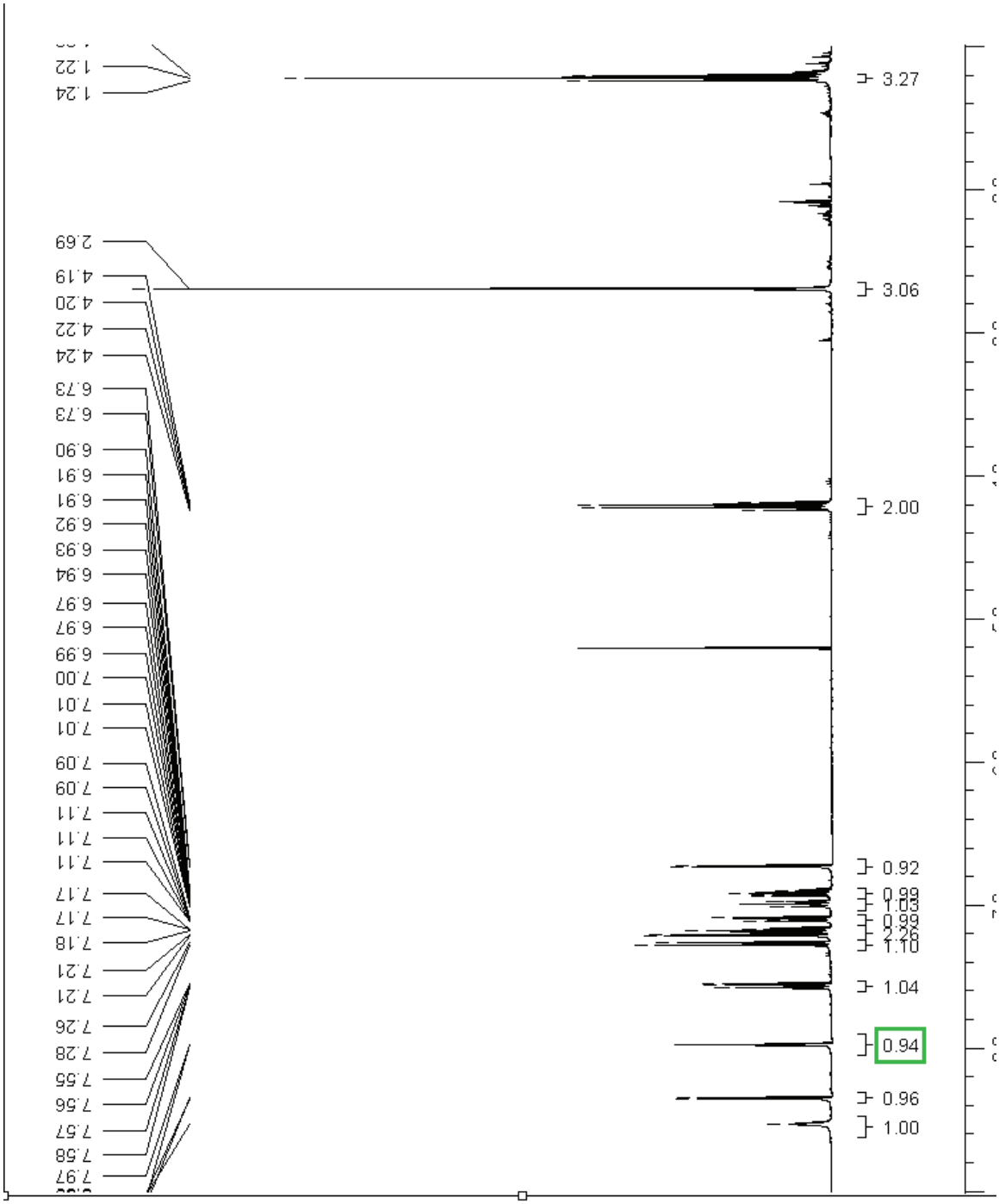


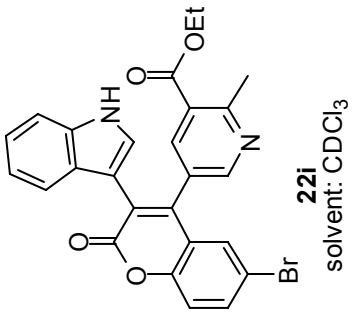
22a
solvent: $CDCl_3$



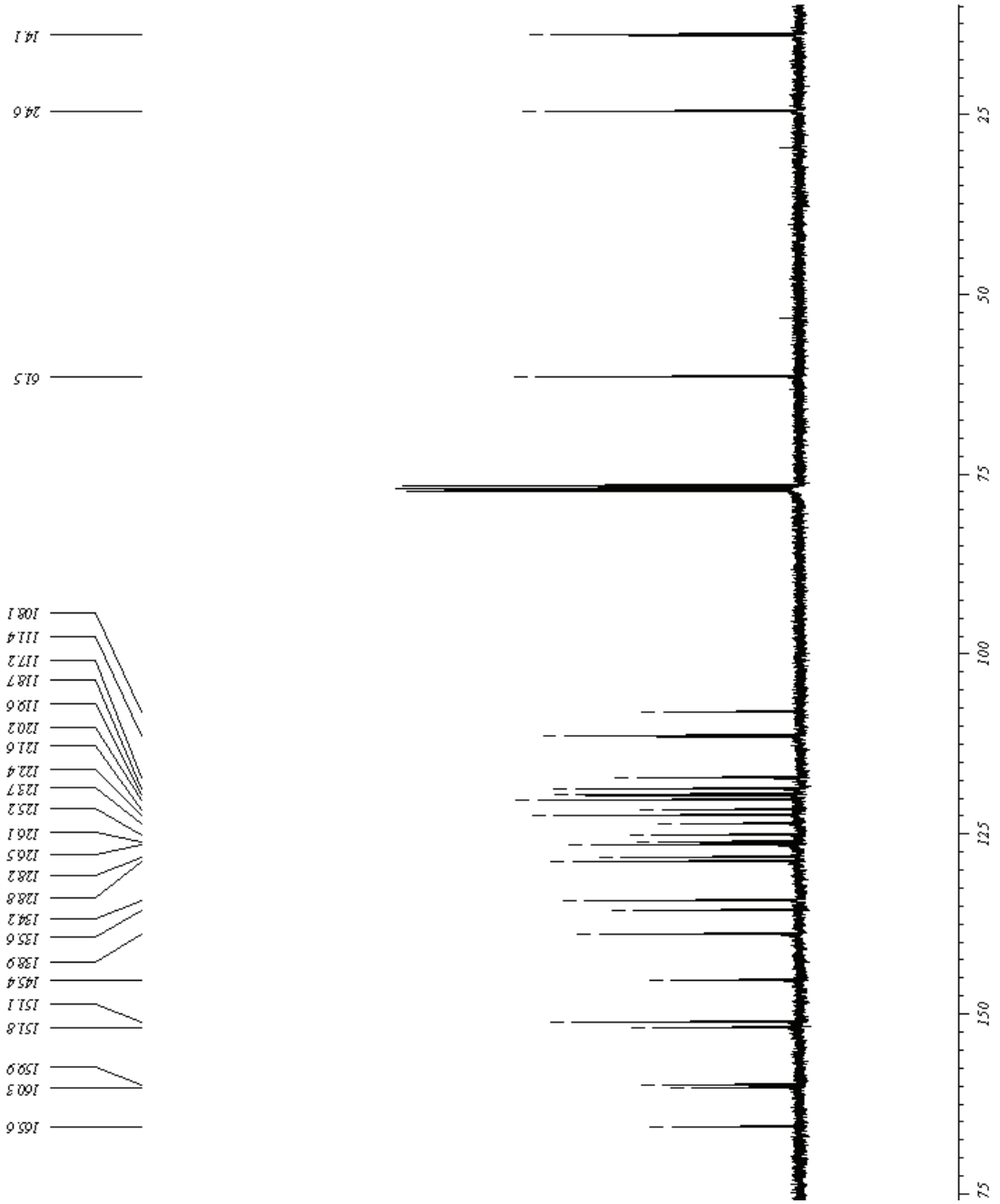


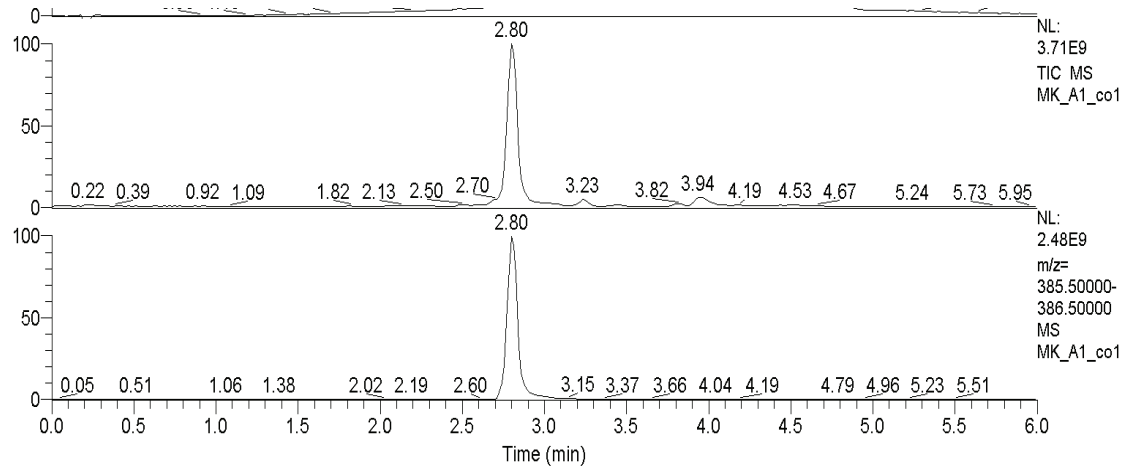
22i
solvent: $CDCl_3$



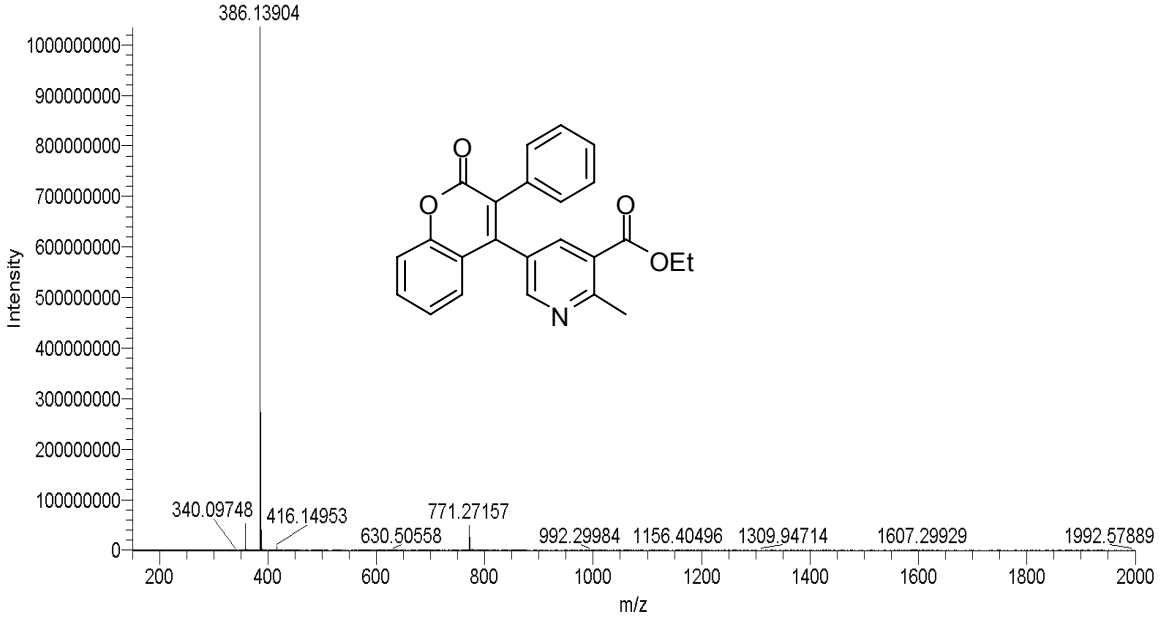


22i
solvent: $CDCl_3$

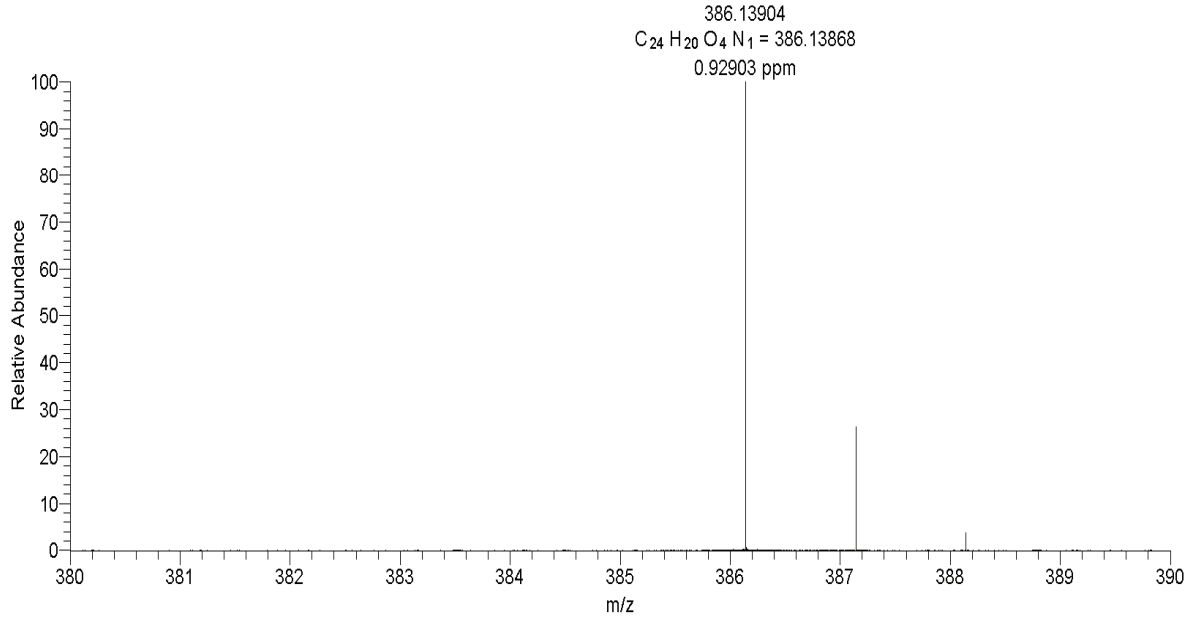


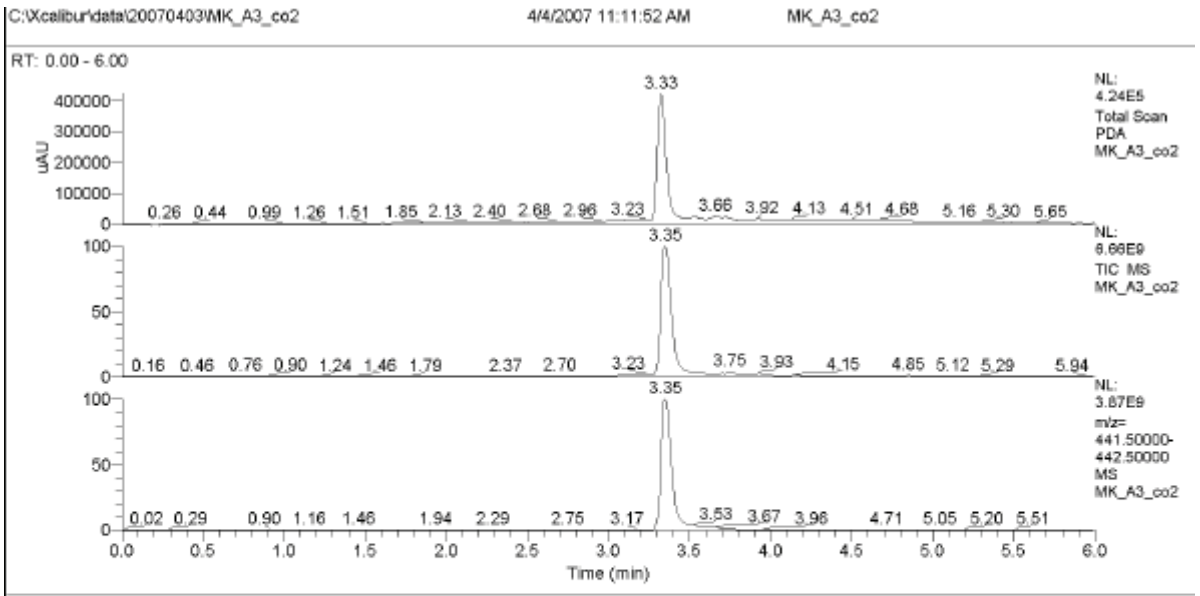


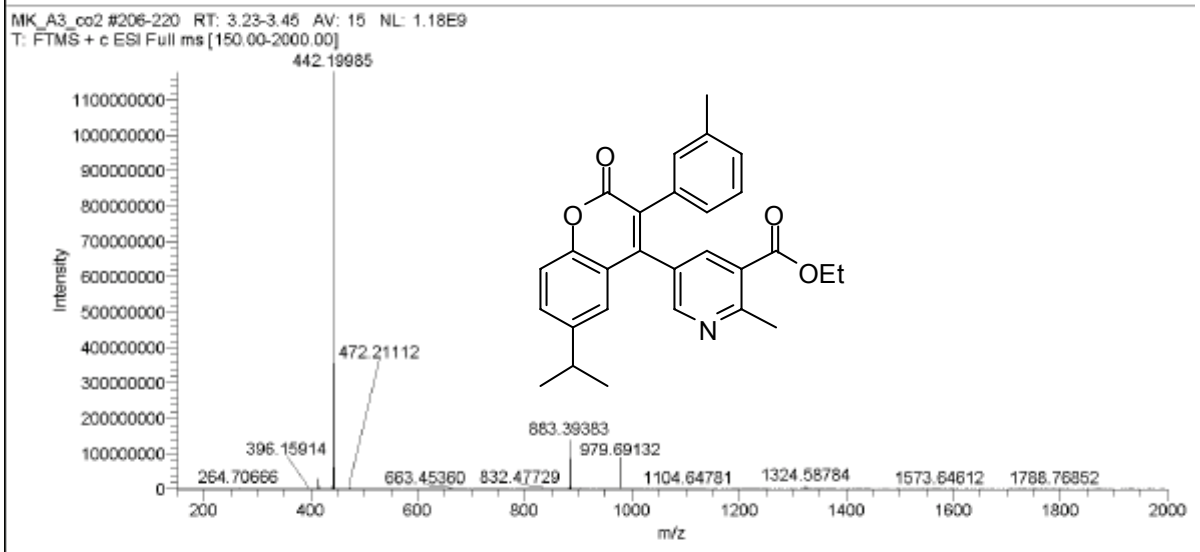
MK_A1_co1 #178-188 RT: 2.72-2.88 AV: 11 NL: 1.03E9
T: FTMS + c ESI Full ms [150.00-2000.00]

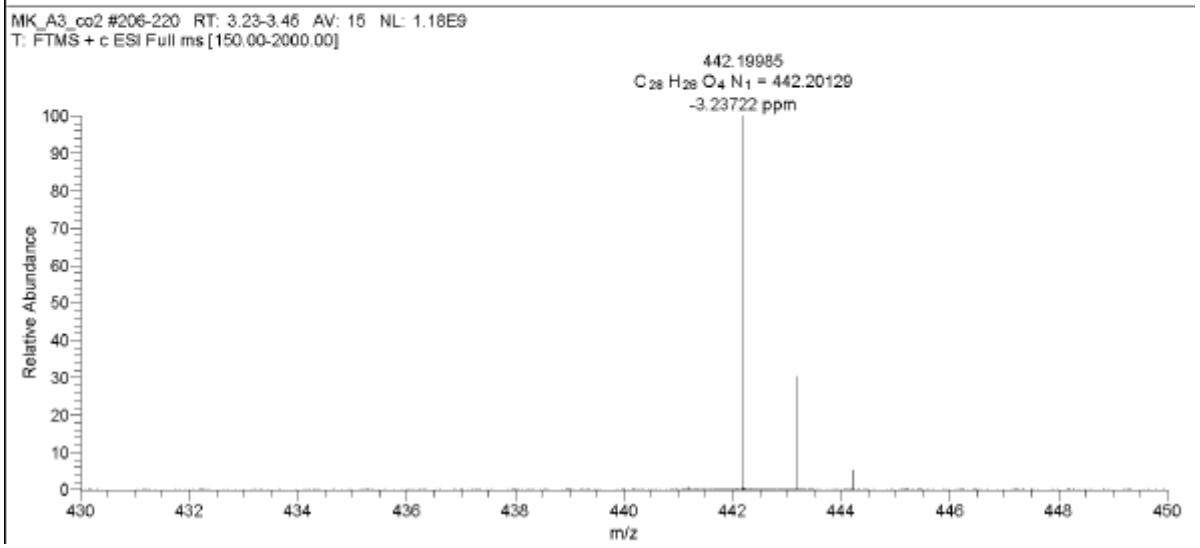


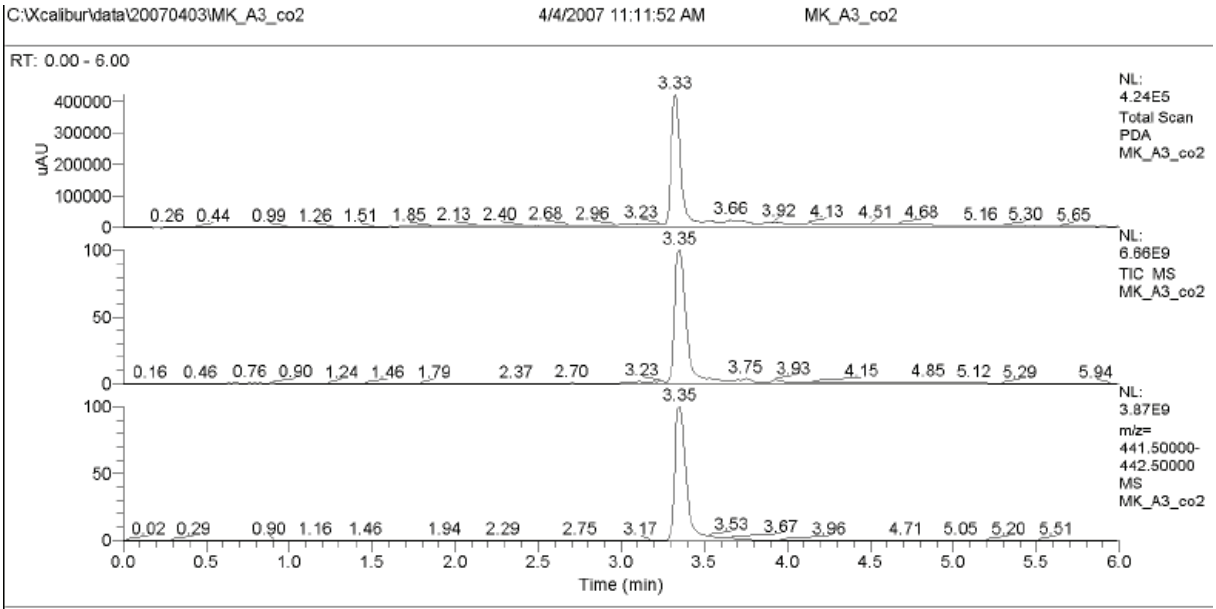
MK_A1_co1 #178-188 RT: 2.72-2.88 AV: 11 NL: 1.03E9
T: FTMS + c ESI Full ms [150.00-2000.00]

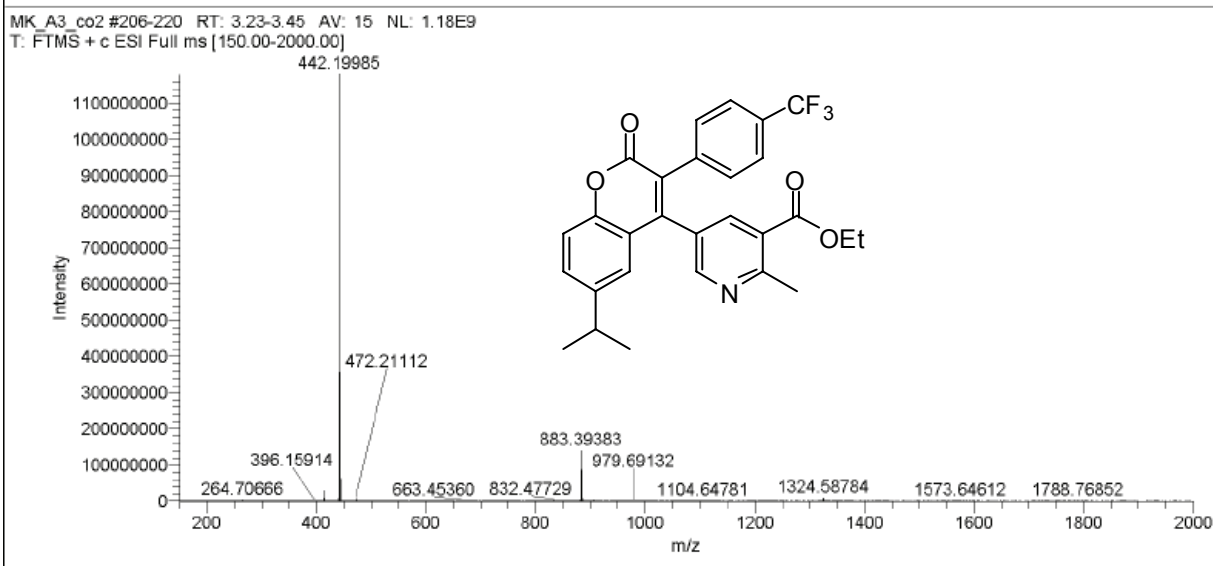


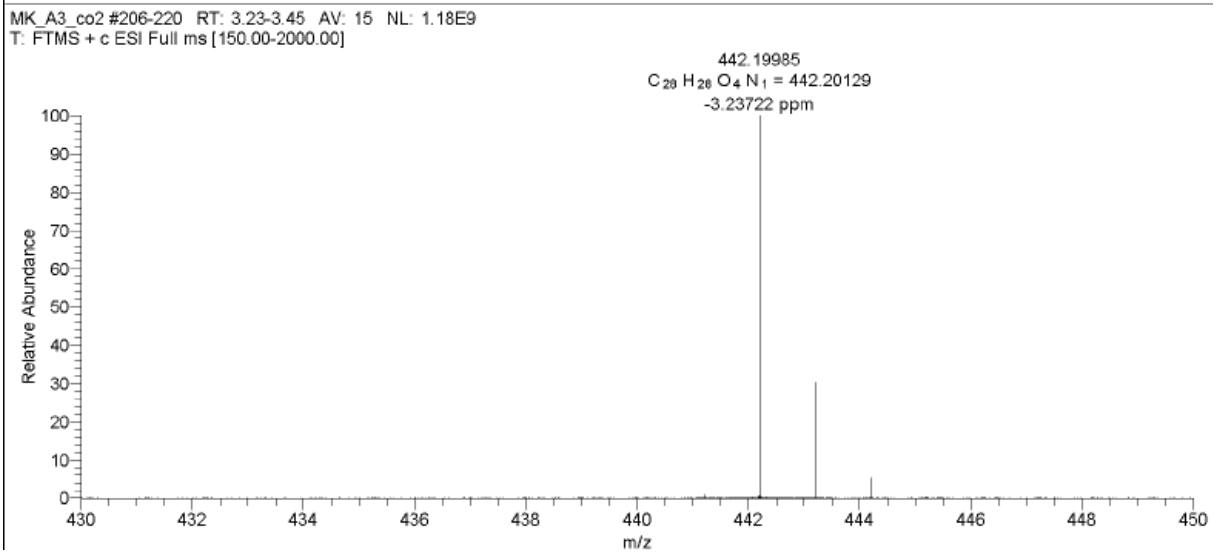




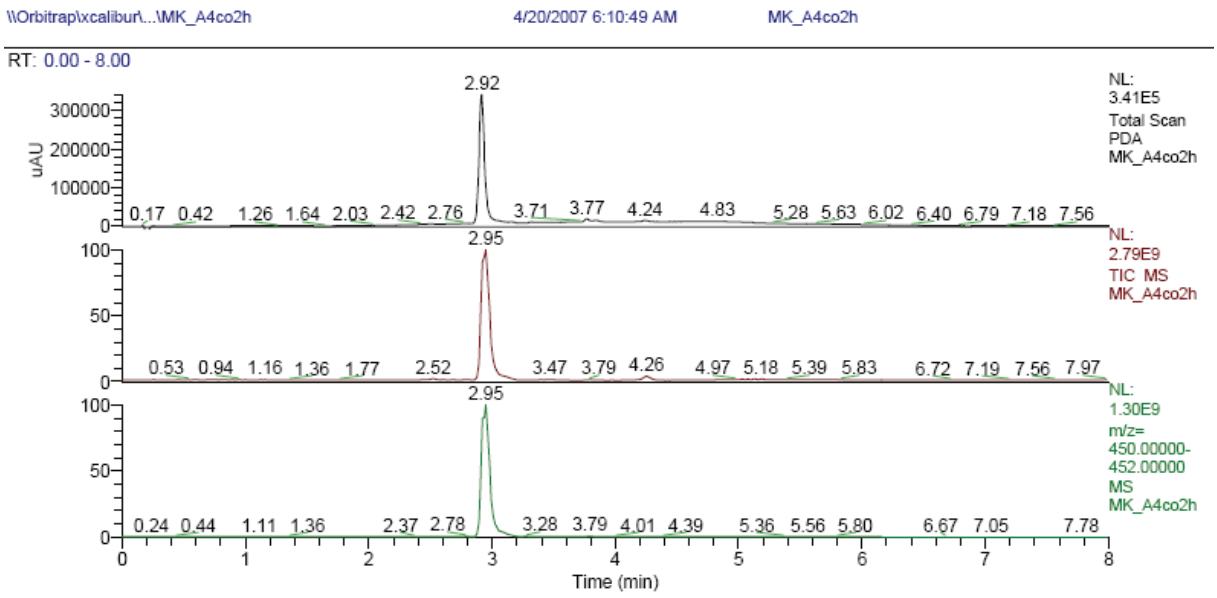


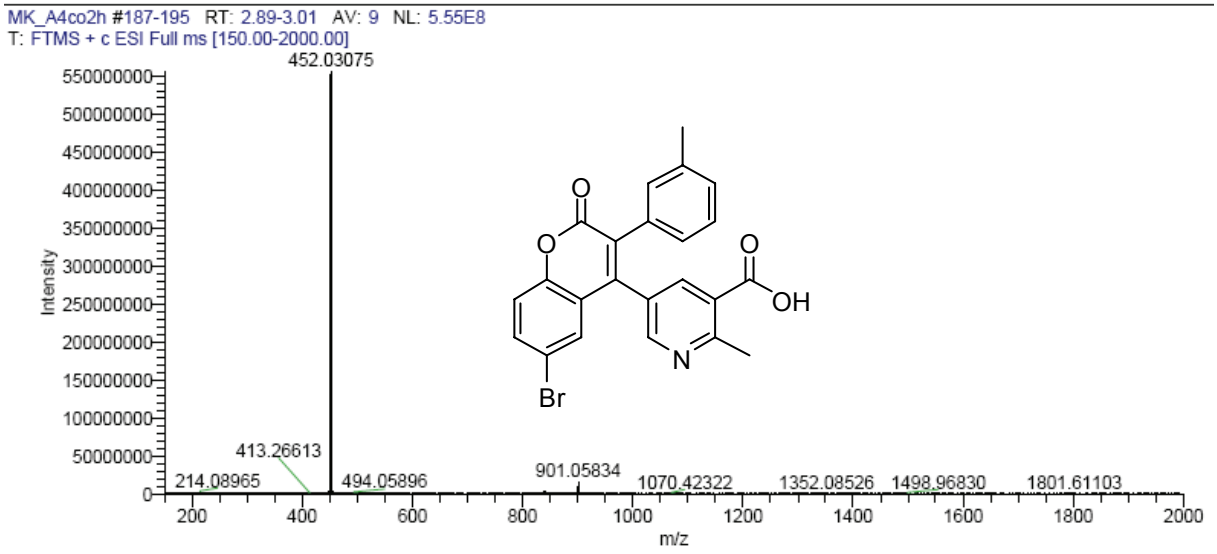

C:\Xcalibur\data\20070403\MK_A3_co2
4/4/2007 11:11:52 AM
MK_A3_co2
RT: 0.00 - 6.00
uAU
NL:
4.24E5
Total Scan
PDA
MK_A3_co2
NL:
6.66E9
TIC MS
MK_A3_co2
NL:
3.87E9
m/z=
441.50000-
442.50000
MS
MK_A3_co2
Time (min)

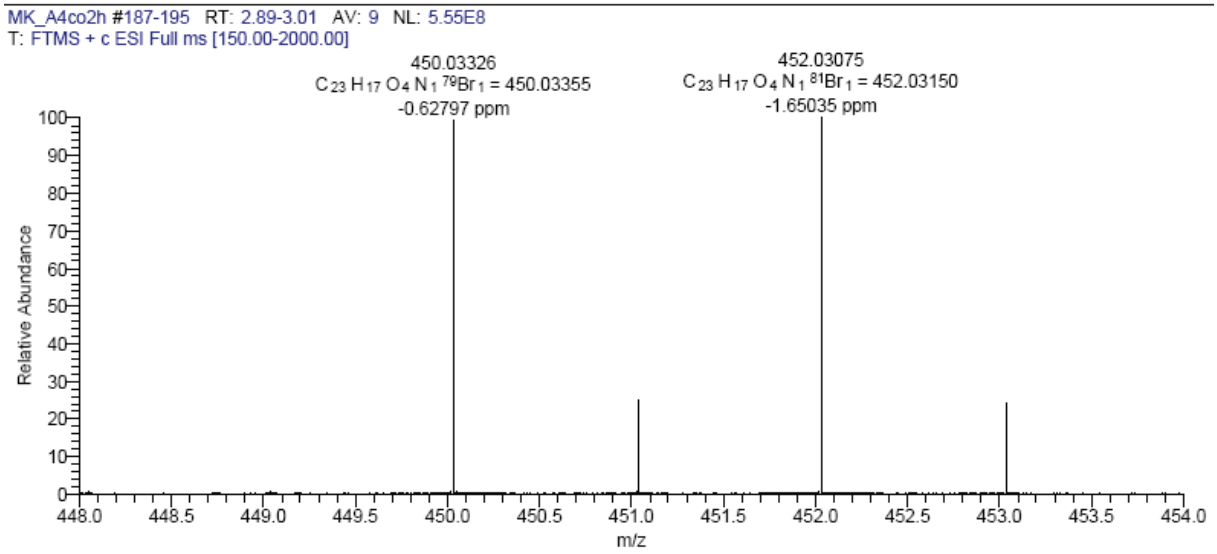

MK_A3_co2 #206-220 RT: 3.23-3.45 AV: 15 NL: 1.18E9
T: FTMS + c ESI Full ms [150.00-2000.00]
Intensity
m/z
442.19985
472.21112
396.15914
883.39383
979.69132
264.70666
663.45360
832.47729
1104.64781
1324.58784
1573.64612
1788.76852
CF3
O
OEt
N

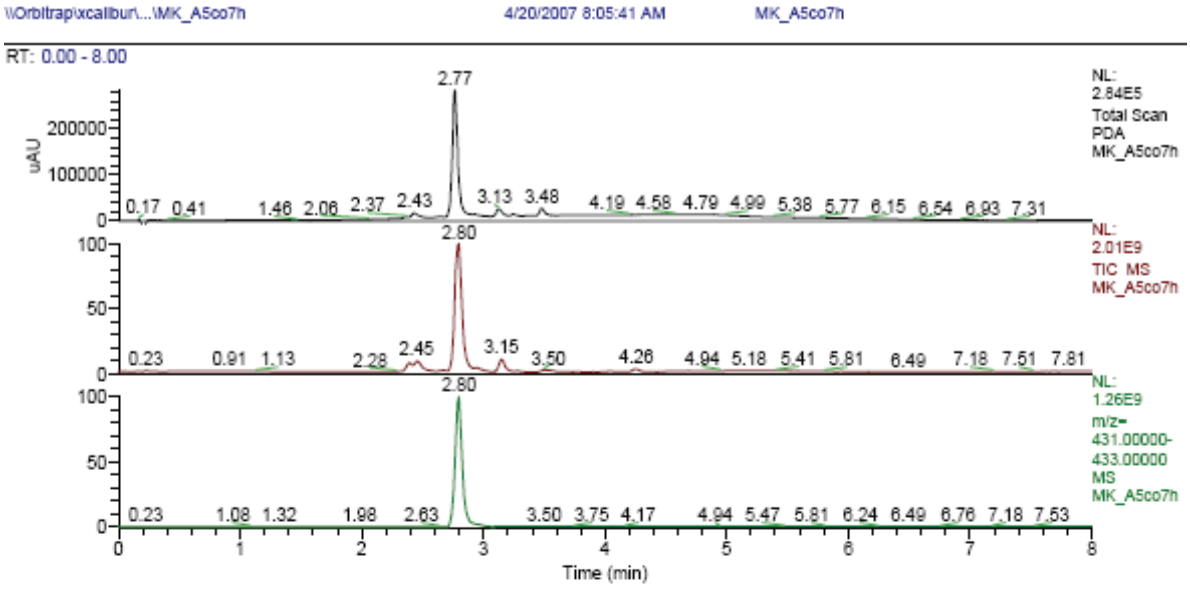

MK_A3_co2 #206-220 RT: 3.23-3.45 AV: 15 NL: 1.18E9
T: FTMS + c ESI Full ms [150.00-2000.00]
442.19985
C29 H28 O4 N1 = 442.20129
-3.23722 ppm
Relative Abundance
m/z

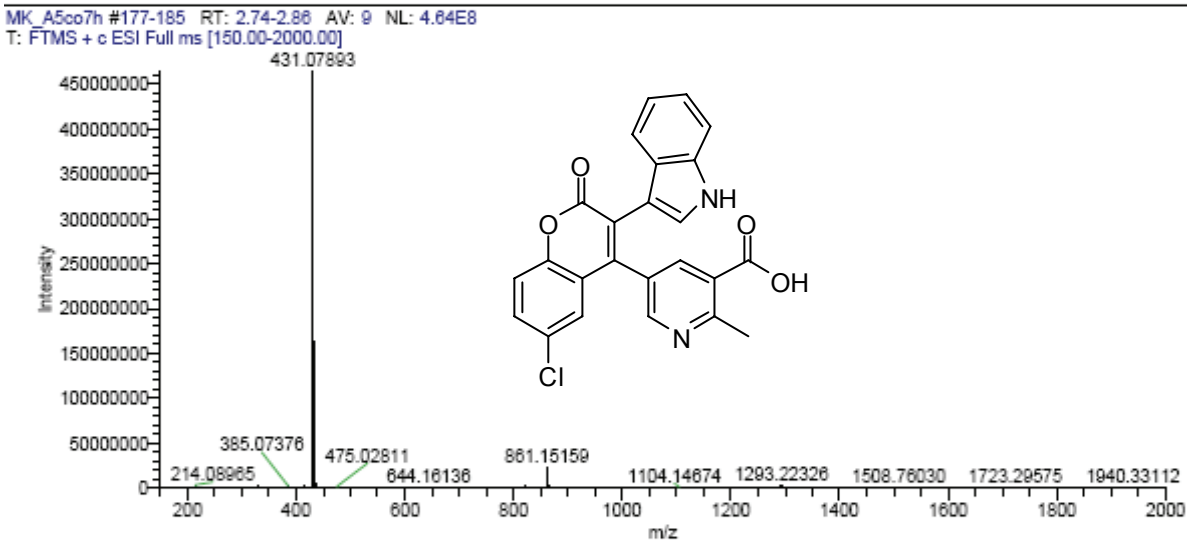
.

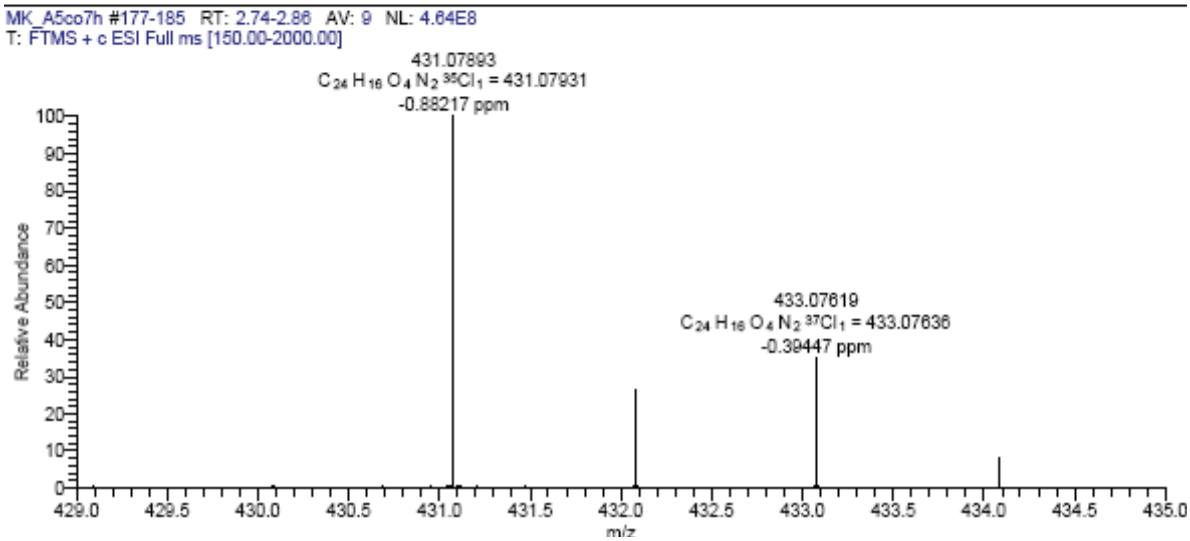

\\Orbitrap\xcalibur\...\MK_A4co2h
4/20/2007 6:10:49 AM
MK_A4co2h
RT: 0.00 - 8.00
2.92
NL:
3.41E5
Total Scan
PDA
MK_A4co2h
uAU
2.95
NL:
2.79E9
TIC MS
MK_A4co2h
2.95
NL:
1.30E9
m/z=
450.00000-
452.00000
MS
MK_A4co2h
Time (min)

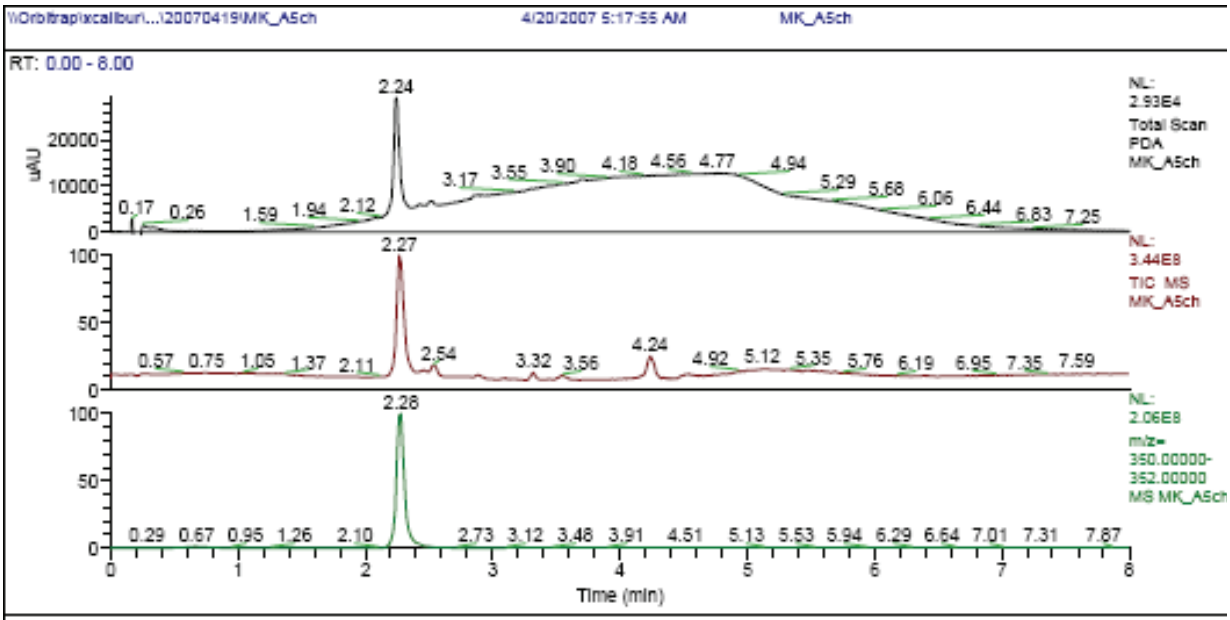

MK_A4co2h #187-195 RT: 2.89-3.01 AV: 9 NL: 5.55E8
T: FTMS + c ESI Full ms [150.00-2000.00]
452.03075
Intensity
413.26613
214.08965
494.05896
901.05834
1070.42322
1352.08526
1498.96830
1801.61103
m/z
O
O
O
OH
N
Br

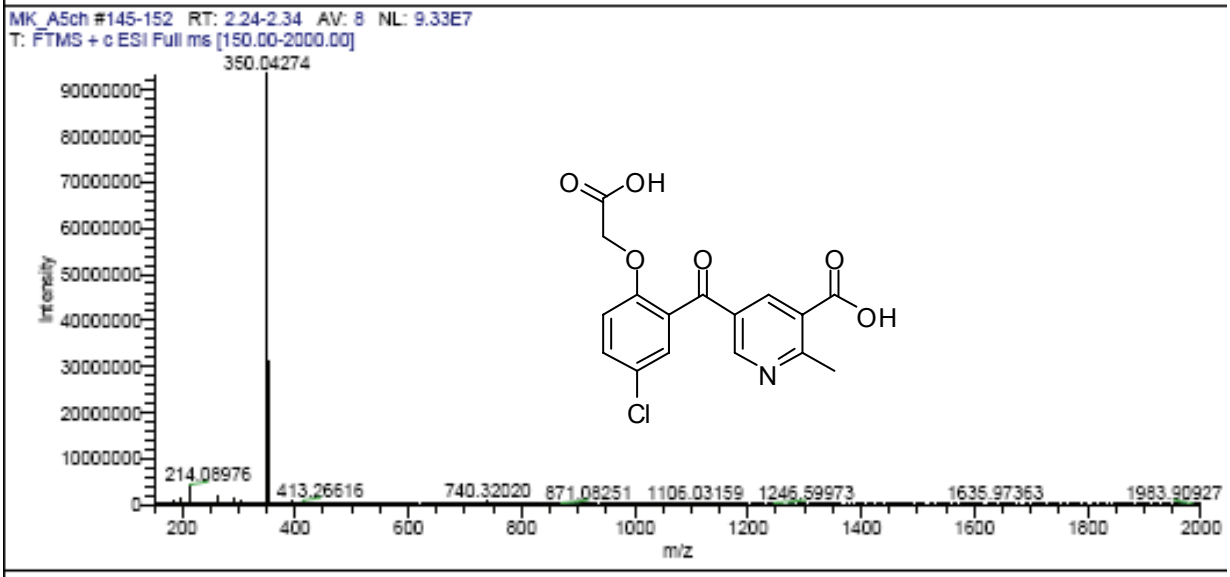

MK_A4co2h #187-195 RT: 2.89-3.01 AV: 9 NL: 5.55E8
T: FTMS + c ESI Full ms [150.00-2000.00]
450.03326
C23 H17 O4 N1 79Br1 = 450.03355
-0.62797 ppm
452.03075
C23 H17 O4 N1 81Br1 = 452.03150
-1.65035 ppm
Relative Abundance
m/z

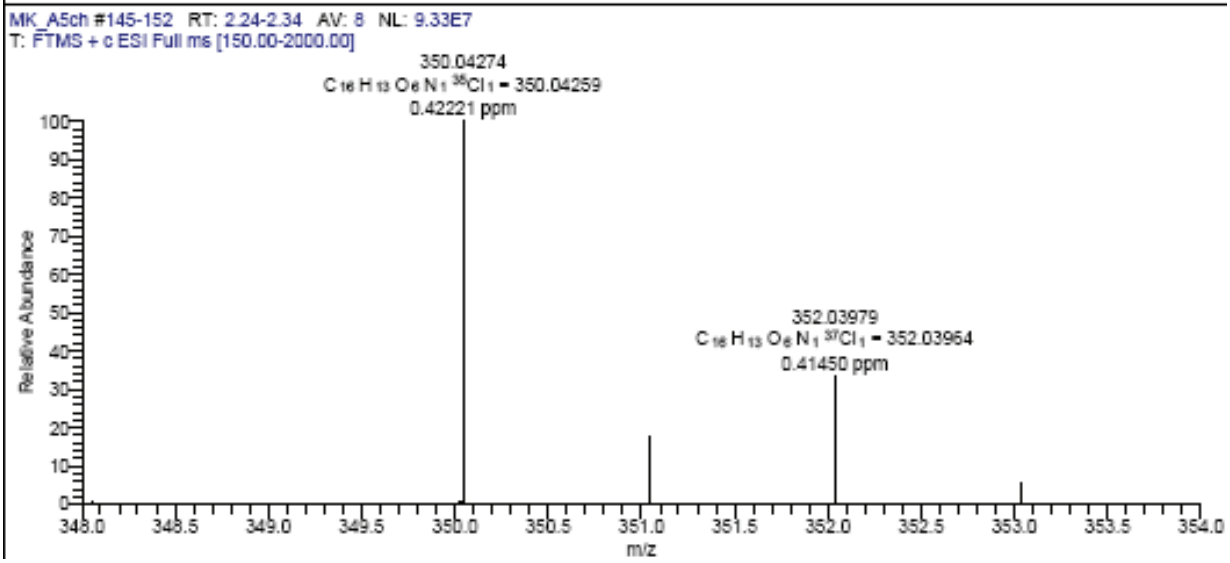


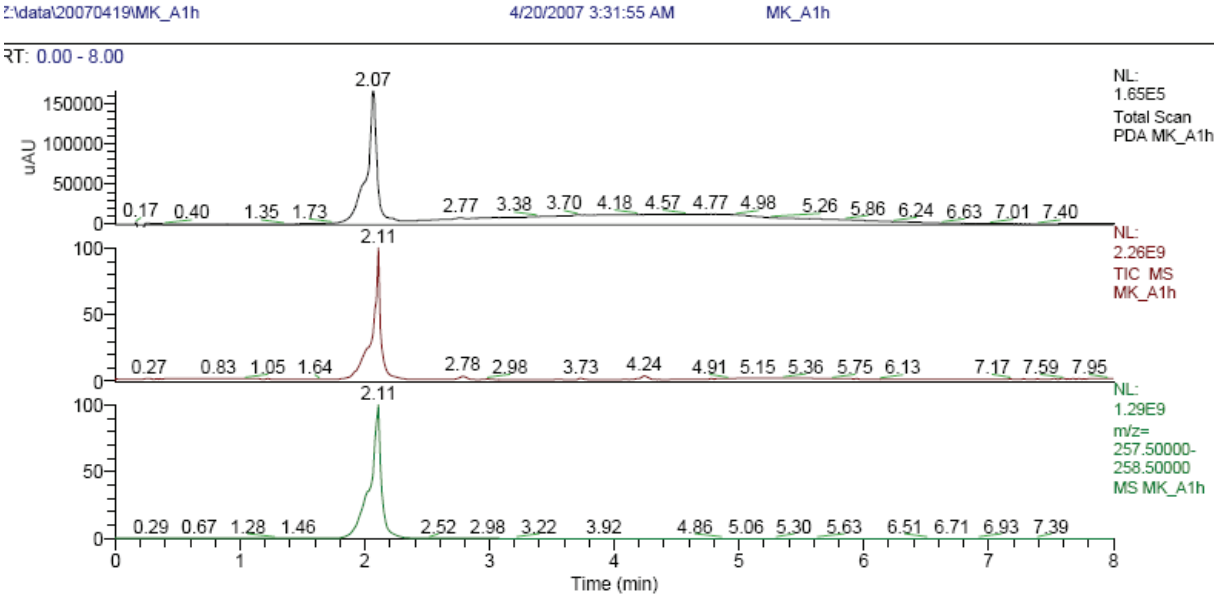




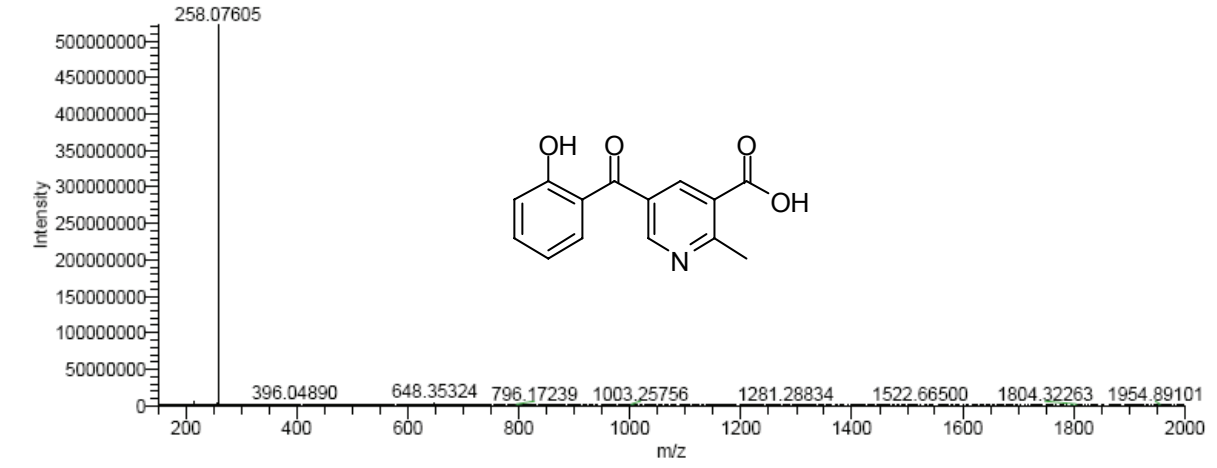




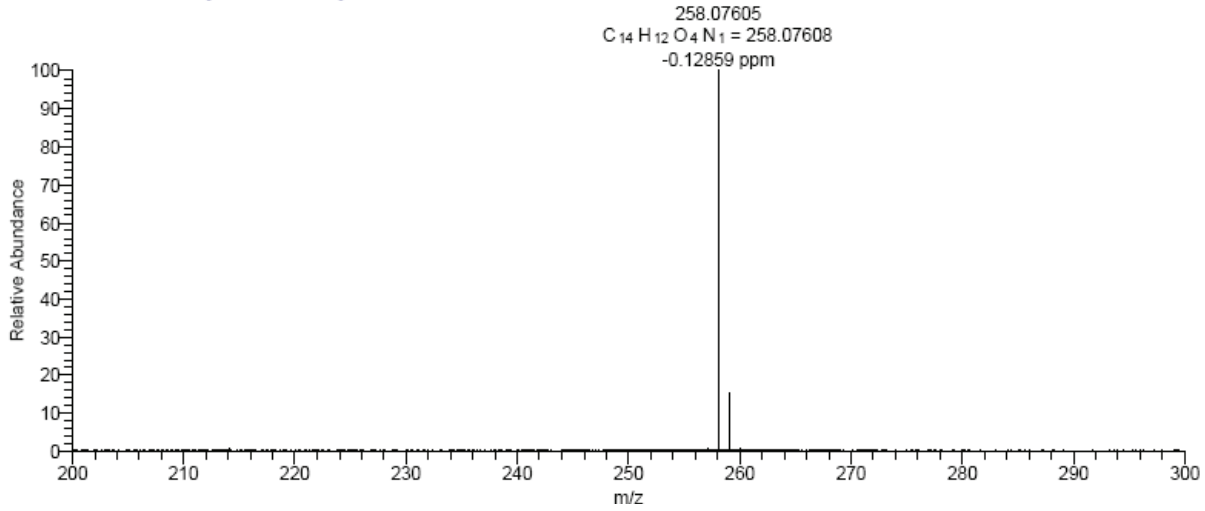


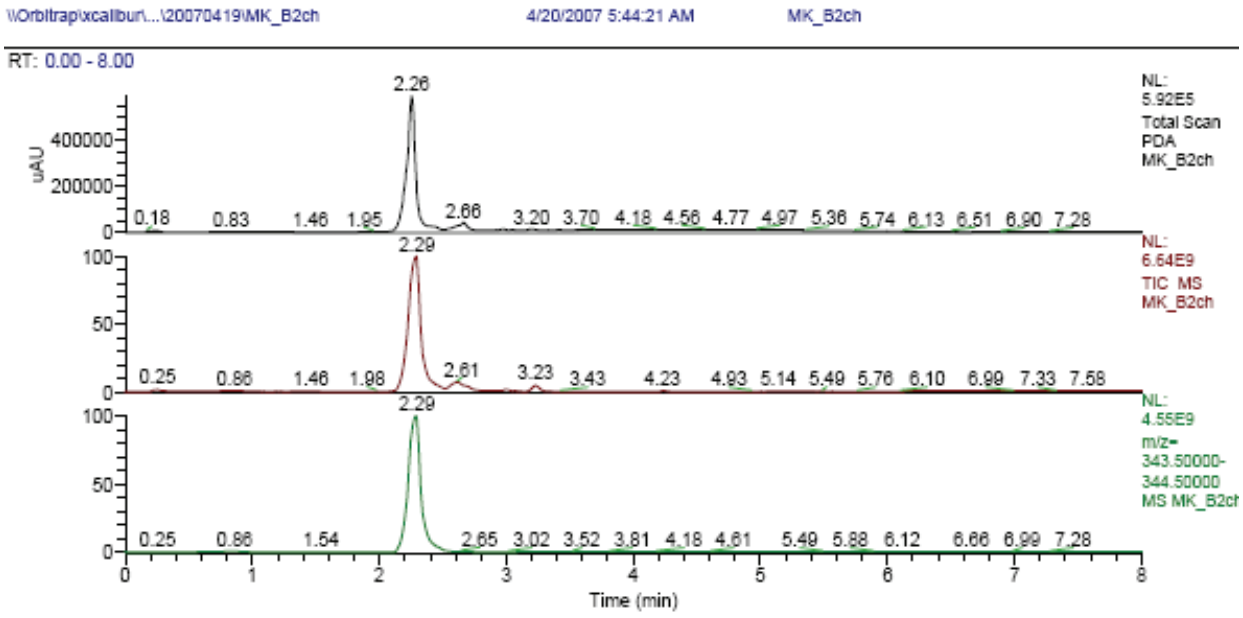


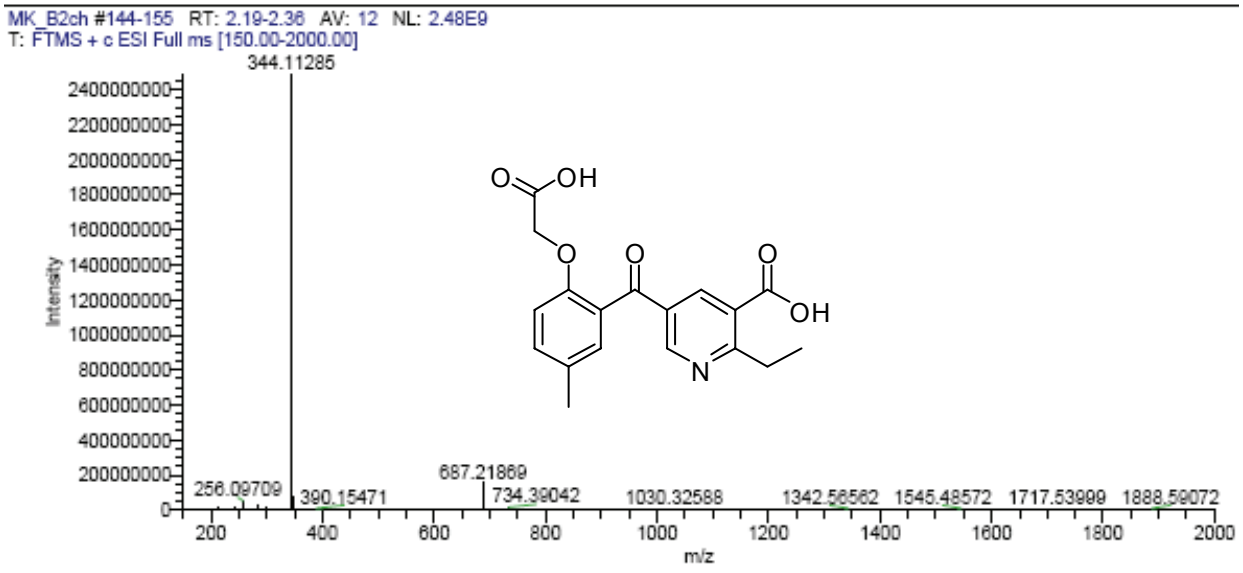
MK_A1h #128-141 RT: 1.96-2.15 AV: 14 NL: 5.21E8
T: FTMS + c ESI Full ms [150.00-2000.00]

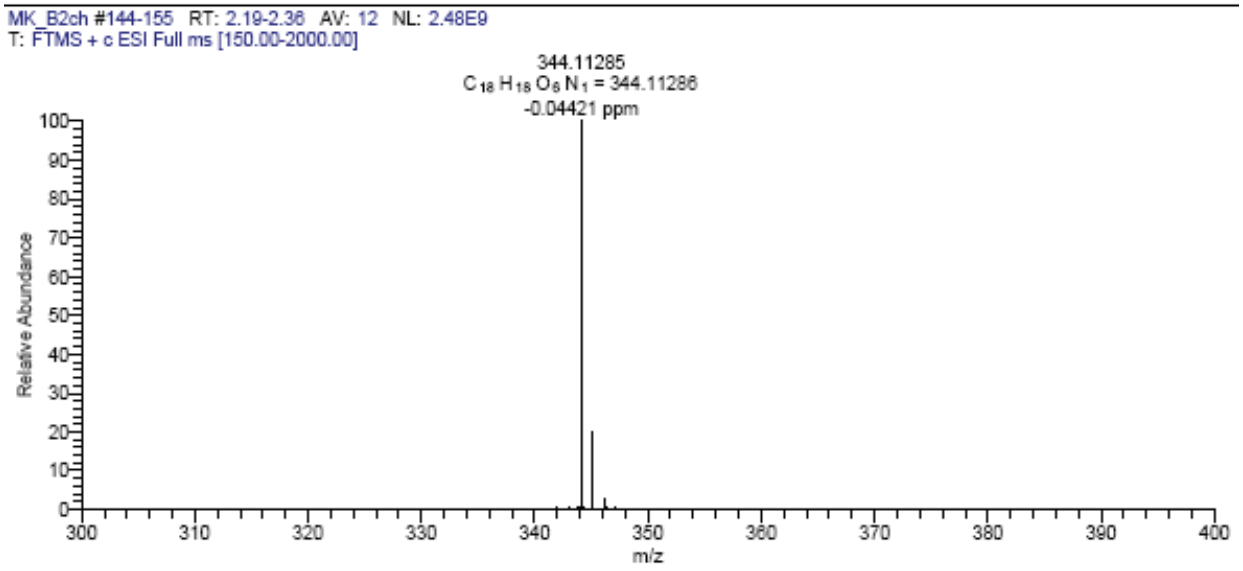


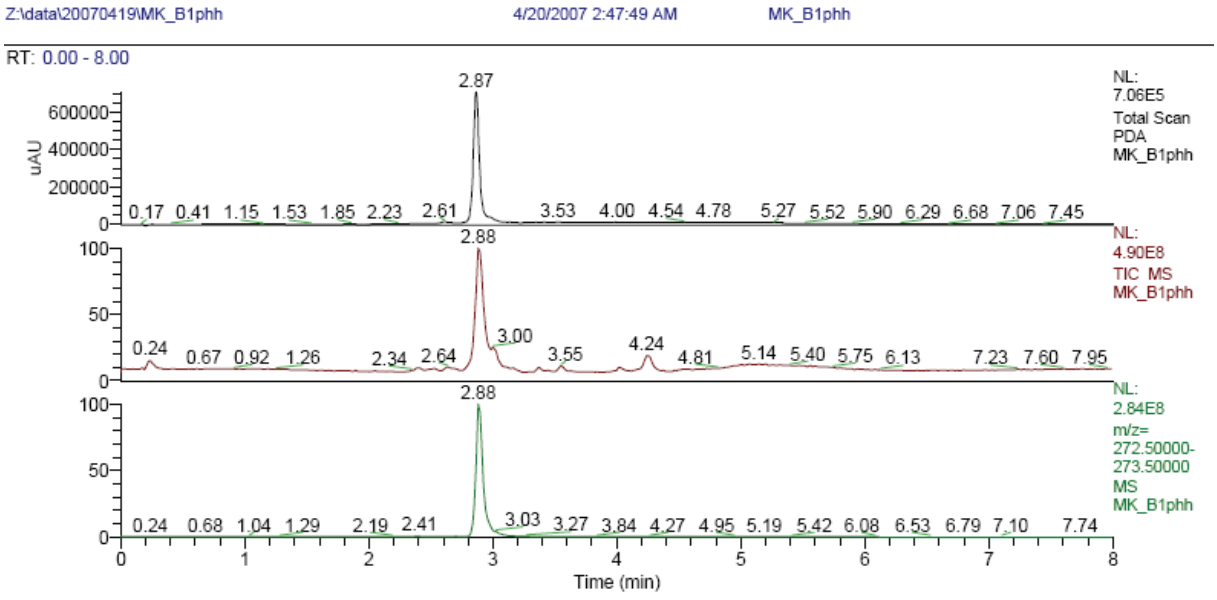
MK_A1h #128-141 RT: 1.96-2.15 AV: 14 NL: 5.21E8
T: FTMS + c ESI Full ms [150.00-2000.00]

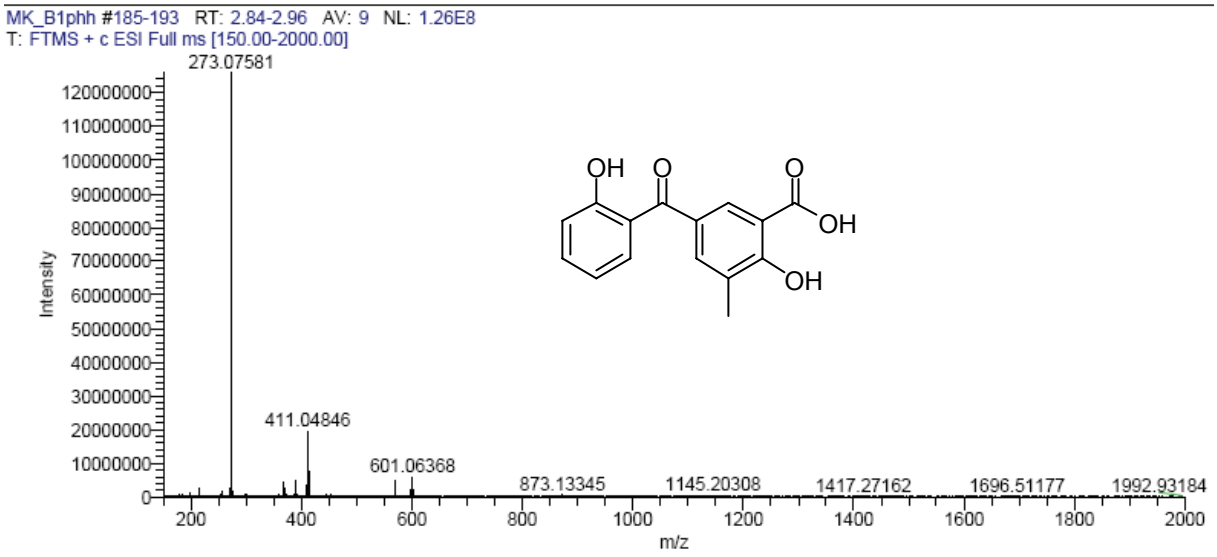


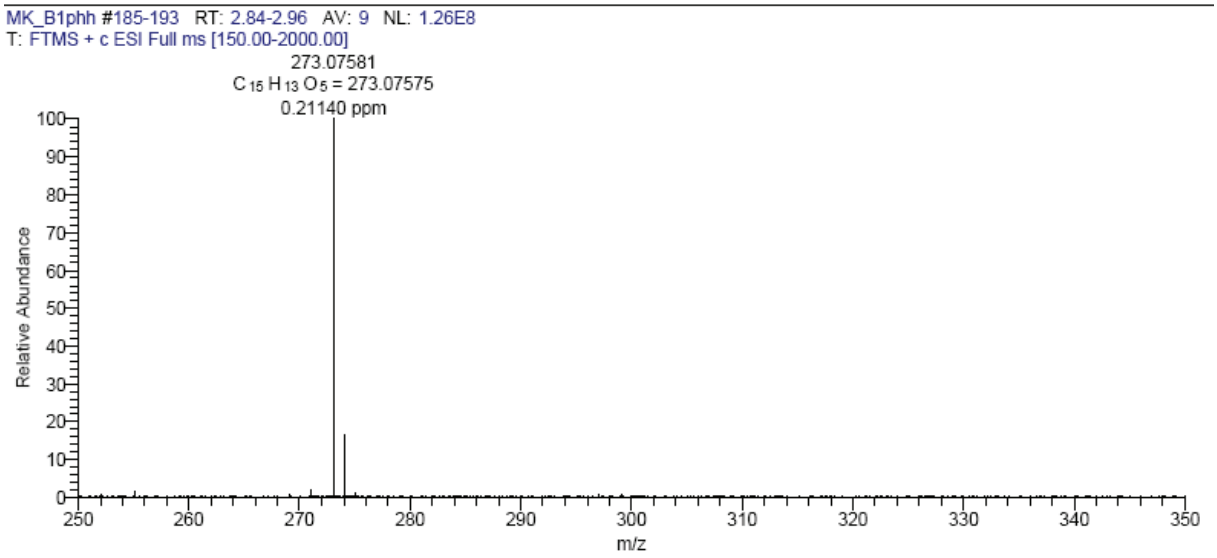

\\Orbitrap\xcalibur\...\20070419\MK_B2ch 4/20/2007 5:44:21 AM MK_B2ch
RT: 0.00 - 8.00
uAU
NL: 5.92E5 Total Scan PDA MK_B2ch
NL: 6.64E9 TIC MS MK_B2ch
NL: 4.55E9 m/z= 343.50000-344.50000 MS MK_B2ch
Time (min)


MK_B2ch #144-155 RT: 2.19-2.36 AV: 12 NL: 2.48E9
T: FTMS + c ESI Full ms [150.00-2000.00]
344.11285
Intensity
m/z


MK_B2ch #144-155 RT: 2.19-2.36 AV: 12 NL: 2.48E9
T: FTMS + c ESI Full ms [150.00-2000.00]
344.11285
C18 H18 O6 N1 = 344.11286
-0.04421 ppm
Relative Abundance
m/z


Z:\data\20070419\MK_B1phh
4/20/2007 2:47:49 AM
MK_B1phh
RT: 0.00 - 8.00
NL: 7.06E5 Total Scan PDA MK_B1phh
NL: 4.90E8 TIC MS MK_B1phh
NL: 2.84E8 m/z= 272.50000-273.50000 MS MK_B1phh
uAU
Time (min)


MK_B1phh #185-193 RT: 2.84-2.96 AV: 9 NL: 1.26E8
T: FTMS + c ESI Full ms [150.00-2000.00]
273.07581
411.04846
601.06368
873.13345
1145.20308
1417.27162
1696.51177
1992.93184
Intensity
m/z
OH
O
O
OH
OH


MK_B1phh #185-193 RT: 2.84-2.96 AV: 9 NL: 1.26E8
T: FTMS + c ESI Full ms [150.00-2000.00]
273.07581
C 15 H 13 O 5 = 273.07575
0.21140 ppm
Relative Abundance
m/z