Synthesis of Conformationally Constrained Benzoylureas as BH3-mimetics

General Procedure A: Amide Synthesis

To a stirred solution of the carboxylic acid in anhydrous DCM (10 mL per mmol) was added EDCI (1.5 eq) and HOBt (1.5 eq). The amine (1.5 eq) was then added and the reaction stirred under N_2 at room temperature. After 12 h, the reaction mixture was quenched with a saturated sodium bicarbonate ($NaHCO_3$) solution and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo.* The resulting residue was purified *via* flash chromatography.

General Procedure B: Sonogashira Cross-Coupling

An oven dried schlenk tube purged with N_2 was charged with $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) and anhydrous DMF (1 mL/mmol). After 15 mins, CuI (10 mol %), 2,4-difluorophenyl acetylene (1.5 eq) and piperidine (1.5 eq) were added and the mixture was stirred for 12 h at 60 ˚C. The mixture was then diluted with EtOAc and poured onto 1N HCl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$ and concentrated. The dark brown oil was purified *via* column chromatography, eluting with EtOAc/pet.ether.

General Procedure C: Phenol Alkylation

Under a N_2 atmosphere, the phenol was dissolved in anhydrous DMF (1 mL/mmol), and treated with Cs_2CO_3 (5 eq). The alkylating agent (1.2 eq) was added and the reaction stirred at 50 ˚C for 4-8 h. After this time the reaction was diluted with EtOAc and poured onto 1N HCl. The aqueous phase was then extracted three times with EtOAc. The combined organic layers were washed with brine, H_2O, dried with $MgSO_4$ and concentrated. The residue was purified *via* column chromatography eluting with EtOAc/pet.ether to obtain the pure product.

2-Formyl-3-iodophenol (10)

Compound **10** was synthesised according to a literature procedure.[1] $MgCl_2$ beads and $(CH_2O)_n$ were dried over P_2O_5 for 12 h prior to use. To a stirred solution of 2-iodophenol **8** (1.0 g, 4.5 mmol) in anhydrous THF (30 mL) was added $MgCl_2$ (0.866 g, 9.1 mmol) beads, Et_3N (1.3 mL, 9.0 mmol) and $(CH_2O)_n$ (0.405, 13.5 mmol). The reaction was refluxed under argon for 12 h. The mixture was then diluted with Et_2O and washed with 2 N HCl (3 x 25 mL), H_2O (25 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated in *vacuo*. The resultant yellow oil was crystallised from EtOAc/hexane to afford **10** as a yellow solid (0.945 g, 84% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1H, OH), 9.74 (s, 1H, CHO), 7.97 (dd, J = 7.7 and 1.6 Hz, 1H, CH), 7.56 (dd, J = 7.6 and 1.6 Hz, 1H, CH). 6.81 (appt. t, J = 7.7 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) 195.9 (C), 160.4 (C), 146.1 (CH), 133.9 (CH), 121.6 (CH), 120.6 (CH), 85.4 (CH); IR (ATR cm-1) 3371, 2979, 1712, 1602, 1511, 1487, 1240, 789; MP 78-79 ^{o}C

Methyl 2-hydroxy-3-iodobenzoate (11)

The ester **11** was prepared according to a literature procedure.[2] To a stirred solution of **10** (0.800 g, 3.2 mmol) in anhydrous MeOH (0.4 mL) was added NaCN (0.030 g, 0.6 mmol), MnO_2 (0.209 g, 2.4 mmol) and AcOH (0.036 mL, 0.6 mmol). The reaction was stirred at room temperature for 12 h, after which time it was filtered through celite to remove the MnO_2 and then concentrated. The brown residue was then purified *via* column chromatography, eluting with EtOAc/pet.ether (10:90) to yield a white solid (0.685 g, 77 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (dd, J = 7.7 and 1.6 Hz, 1H, CH), 7.82 (dd, J = 7.9, and 1.6 Hz, 1H, CH), 6.65 (appt. t, J = 7.8 Hz, 1H, CH), 3.95 (s, 3H, CH_3);^{13}C NMR ($CDCl_3$, 75 MHz) 170.1(C), 160.3 (C), 145.2 (CH), 130.2 (CH), 120.8 (CH), 112.6 (C), 85.2 (C), 52.7 (CH_3); MP 60 – 64 °C; IR (ATR, cm^{-1}) 2952, 1673, 1600, 1434, 1319, 1148, 753.

***tert*-Butyl-3-(2-(methoxycarbonyl)-6-iodophen-oxy)propylcarbamate (12)**

Compound **12** was prepared from the phenol **11** (1.2 g, 4.3 mmol) according to general procedure F. Purification *via* flash column chromatography eluting with EtOAc/pet.ether

(20:80) furnished a clear oil (1.38 g, 76 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (dd, J = 7.6 and 1.6 Hz, 1H, CH), 7.79 (dd, J = 7.8 and 1.6 Hz, 1H, CH), 6.88 (t, J = 7.8 Hz, 1H, CH), 5.43 (s, 1H, NH), 4.05 (t, J = 5.4 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 3.55 (q, J = 5.1 Hz, 2H, CH_2), 1.44 (s, 9H, 3 x CH_3);^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3 (C), 157.6 (C), 156.2 (C), 143.6 (CH), 132.0 (CH), 125.8 (CH), 125.4 (C), 93.9 (C), 79.1 (C), 73.5 (CH_2), 52.5 (CH_3), 40.8 (CH_2), 28.9 (3 x CH_3); IR (ATR, cm^{-1}) 3620, 2359, 2293, 1437, 1039; MS (ES^+), *m/z* 322 (M-Boc); HRMS (ES^+) Calculated for $C_{15}H_{21}INO_5$ (M + H): 422.0464; found 422.0465

tert-butyl-3-(2-(Methoxycarbonyl)-6-iodophenoxy)-propyl carbamate (13)

The phenol **11** (0.503 g, 1.8 mmol) was alkylated as described in general procedure F. Flash column chromatography eluting with EtOAc/pet.ether (10:90 then 20:80), yielded a clear oil (0.504 g, 64 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (dd, J = 7.8 and 1.6 Hz, 1H, CH), 7.80 (dd, J = 7.8 1.7 Hz, 1H, CH), 6.90 (app.t, J = 7.8 Hz, 1H, CH), 5.31 (br. s, 1H, NH), 3.97 (t, J = 5.7 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.38 (pent, J = 6.1 Hz, 2H, CH_2), 2.03 (t, J = 5.9 Hz, 2H, CH_2), 1.40 (s, 9H, 3 x CH_3);^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4 (C), 158.1 (C), 156.1 (C), 143.5 (C), 131.9 (CH), 125.6 (CH), 125.5 (C), 94.4 (C), 78.9 (C), 72.5 (CH_2), 52.4 (CH_3), 37.7 (CH_2), 30.1 (CH_2), 28.4 (3 x CH_3); MS (ES^+) m/z, 436, (M+H); IR (ATR cm-1) 3399, 2976, 1700, 1433, 1208, 730; HRMS (ES^+) Calculated for $C_{16}H_{22}INO_2Na$ (M + Na): 458.0440; found 458.0440

3,4 – Dihydro-9-iodobenzo[f][1,4]oxazepin-5(2H)-one (14)

12 (0.652 g, 1.5 mmol) was dissolved in anhydrous DCM (1.68 mL) and treated with TFA (1.68 mL). The mixture was stirred for 4 h, diluted with toluene (5 mL) and concentrated. This process was repeated three times. The residue was dissolved in anhydrous *n*BuOH (3 mL) and to this solution was added Na_2CO_3 (0.198 g, 1.9 mmol). The suspension was stirred under N_2 at 80 ºC for 12 h. The reaction was then diluted with EtOAc (15 mL) and poured onto 10 % citric acid (10 mL). The aqueous was extracted three times with EtOAc (10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried with $MgSO_4$ and concentrated under reduce pressure. The yellow oil was purified *via* a silica plug, eluting with EtOAc/pet.ether to yield a slightly

yellow solid (0.335 g, 75 %). ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J = 7.7 and 1.6 Hz, 1H, CH), 7.74 (br.s, 1H, NH), 7.82 (dd, J = 7.7 and 1.6 Hz, 1H, CH), 6.93 (app. t, J = 7.7 Hz, 1H, CH), 4.44 (t, J = 5.3 Hz, 2H, CH_2), 3.56 – 3.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.8 (C), 156.2 (C), 142.2 (CH), 131.2 (CH), 125.8 (C), 125.0 (C), 70.5 (CH), 40.0 (CH_2), 31.1 (CH_2); MP 150-155°C; MS (ES^+) *m/z* 289 (M + H); HRMS (ES^+) Calculated for $C_9H_8INO_2$ (M + H): 288.9600; found 288.9606

2,3,4,5-Tetrahydro-10-iodobenxo[b][1,5]oxazocin-6-one (15)

The stirred solution of **13** (0.421 g, 1.0 mmol) in DCM (1 mL) was added TFA (1 mL). The dark brown mixture was stirred at room temperature for 6 h. After this time, the reaction was diluted with toluene (3 mL) and concentrated. This process was repeated three times, affording a brown oil. The oil was dissolved in anhydrous DCM (15 mL) and treated with DIPEA (52 µL, 3 mmol). At 0 °C, this solution was added to a solution of EDCI (0.864 g, 5 mmol) and HOBT (0.608 g, 5 mmol) in DCM (15 mL). The reaction mixture was warmed to room temperature and stirred under a N_2 atmosphere for 48 h. The mixture was then diluted with EtOAc (15 mL) and washed with 5 % HCl (30 mL), $NaHCO_3$ (30 mL), brine (30 mL), dried with $MgSO_4$ and concentrated. The residue was dissolved in a 1:1 mixture of DCM:MeOH and passed through a silica plug, eluting DCM/MeOH (100:0 to 90:10) to yield **19** as a white solid (0.108 g, 37 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (dd, J = 7.8 and 1.6 Hz, 1H, CH), 7.52 (dd, J = 7.7, 1.7 Hz, 1H, CH), 7.16 (br. s, 1H, NH), 6.86 (app. t, J = 7.7 Hz, 1H, CH), 4.31 (t, J = 5.5 Hz, 2H, CH_2), 3.35-3.30 (m, 2H), 1.99-1.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9 (C), 156.2 (C), 142.2 (C), 131.24 (CH), 125.87 (CH), 125.0 (CH), 91.0 (C), 70.5 (CH_2), 40.0 (CH_2), 31.1 (CH_2); MS (ES^+) *m/z* 304 (M+H); MP 168-172°C; HRMS (ES^+) Calculated for $C_{10}H_{11}INO_2$ (M+H): 303.9834; found 303.9835

9-(2-(2,4-Difluorophenyl)ethynyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (16)

The alkyne **16** was prepared from the aryl iodide **14** (0.100 g, 0.35 mmol) according to general procedure B. The crude oil was purified *via* flash column chromatography eluting with EtOAc/pet.ether (5:95), yielding a yellow solid (0.092 g, 89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (dd, J = 7.9 and 1.7, 1H, CH), 7.71-7.63 (m, 2H), 7.55-7.44 (m, 2H), 7.14 (t, J = 7.7, 1H, CH), 6.87 (br. s, 1H, NH), 4.55-4.51 (m, 2H), 3.55-3.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (C), 164.6 (C), 162.5 (C), 155.6 (C), 136.9 (CH), 134.4 (CH), 132.1 (C), 128.5 (CH), 124.3 (C), 122.9 (CH), 111.7 (CH), 107.6 (C), 104.4 (CH), 90.1 (C), 85.5 (C), 73.4 (CH_2), 41.3 (CH_2); MP 166-170°C; MS (ES^+) *m/z* 300 (M + H); HRMS (ES^+) Calculated for $C_{17}H_{12}F_2NO_2$ (M+H): 300.0836; found 300.0836

10-(2-(2,4-Difluorophenyl) ethynyl)-2,3,4,5-tetrahydrobenzo [b][1,5]oxazocin-6-one (17)

The alkyne **17** was synthesised from the aryl iodide **15** (0.045 g, 0.15 mmol) according to general procedure B. Flash column chromatography eluting with DCM/MeOH (100:0 DCM, then 95:5) afforded an off white powder (0.033 g, 71 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63-7.47 (m, 3H), 7.12 (app.t, J = 7.6 Hz, 1H, CH), 6.93-6.84 (m, 2H), 6.43 (br.s, 1H, NH), 4.44 (t, J = 5.4 Hz, 2H, CH_2), 3.40-3.33 (m, 2H), 2.04-1.98 (m, 2H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4 (C), 164.7 (C), 161.4 (C), 158.3 (C), 135.8 (CH), 134.3 (CH), 134.1 (CH), 133.5 (C), 131.3 (CH), 123.3 (CH), 116.1 (C), 111.7 (CH), 107.7 (C), 104.3 (CH), 90.1 (C), 86.6 (C), 70.3 (CH_2), 40.2 (CH_2), 31.0 (CH_2).

MS (ES^+) m/z, 314, (M+H); MP 193-197°C; HRMS (ES^+) Calculated for $C_{19}H_{14}F_2NO_2$ (M+H): 314.0993; found 314.0993

Ethyl 2-hydroxy-5-iodobenzoate (20)

Compound **20** was prepared *via* a literature procedure.[3] To a stirred solution of NaI (10.7 g, 0.07 mol) and ethyl salicylate **9** (10.0 g, 0.06 mol) in anhydrous DMF (50 mL) under a N_2 atmosphere, was added Chloramine T (16.4 g, 0.072 mol) portion wise over five minutes at 0 ˚C. The solution was warmed to room temperature and allowed to stir for a further 3 h. The solution was then poured onto H_2O (300 mL) and acidified with 2 N HCl to pH 3. The solution was filtered and the solid was washed with H_2O (100 mL) and 10 % NaS_2SO_4.The off-white solid was dried in a vacuum oven over night. Further purification *via* column chromatography eluting with EtOAc/pet.ether (95:5) gave **24** as a white solid (16.7 g, 82 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.7 (s, 1H, OH), 8.03 (d, J =

2.3 Hz, 1H, CH), 7.60 (dd, *J* = 8.7, 2.3 Hz, 1H, CH), 6.68 (d, *J* = 8.8 Hz, 1H, CH), 4.40 (q, *J* = 7.1 Hz, 2H, CH_2), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (CDCl3, 75 MHz) 168.9 (C), 161.3 (C), 143.9 (CH), 138.2 (CH) 119.9 (CH), 114.8 (C), 79.9 (C) 61.8 (CH2), 14.2 (CH3); MP 73-74 ºC; IR (ATR cm-1) 3371, 2979, 1712, 1602, 1511, 1487, 1240, 789.

***tert*-Butyl 2-(2(methoxycarbonyliodophenoxy)ethylcarbamate (21)**

The phenol **20** (2.0 g, 6.80 mmol) was alkylated according to general procedure C. Purification *via* column chromatography eluting with EtOAc/pet.ether (95:5) afforded a clear oil (1.93 g, 65 %).^{1}H NMR ($CDCl_3$) δ 8.06 (d, *J* = 2.3 Hz, 1H, CH), 7.69 (dd, *J* = 8.7 and 2.4 Hz, 1H, CH), 6.70 (d, *J* = 8.8 Hz, 1H, CH), 5.44 (br. s. 1H, NH), 4.35 (q, *J* = 7.1 Hz, 2H, CH_2), 4.06 (t, *J* = 5.1 Hz, 2H, CH_2), 5.24 (q, *J* = 5.2 Hz, 2H, CH_2), 1.42 (s, 9H, 3 x CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.6 (C), 158.1 (C), 155.9 (C), 141.99 (C), 140.1 (CH), 122.9 (CH), 116.1 (CH), 82.6 (C), 68.8 (CH_2), 61.3 (CH_2), 39.8 (CH_2), 28.4 (3 x CH_3), 14.3 (2 x CH_3); MS (ES^+) *m/z* 336 (M-Boc); IR (ATR cm-1) 3399, 2976, 1700, 1433, 1208, 730; HRMS (ES^+) Calculated for $C_{16}H_{23}INO_5$ (M + H): 436.0621; found 436.0621

3,4-Dihydro-7-iodobenzo[f][1,4]oxazepin-5(2H)-one (22)

To a stirred solution of **25** (1.6 g, 3.67 mmol) in DCM (4 mL) was added TFA (4 mL). The mixture was allowed to stir for 5 h, after which time the reaction was diluted, the residue dissolved in toluene (10 mL) and concentrated. This process was repeated three times. The residue was dissolved in anhydrous nBuOH (10 mL), under a N_2 atmosphere. Na_2CO_3 (0.585, 5.51 mmol) was added and the suspension was stirred at 80 ˚C for 16 h. The reaction was then diluted with EtOAc (15 mL) and poured onto 10% citric acid (15 mL). The aqueous was extracted three times with EtOAc (3 x 10 mL) and the combined organic layers were washed with $NaHCO_3$ (15 mL), brine (15 mL), H_2O (15 mL), dried with $MgSO_4$ and concentrated. The brown residue was dissolved in 1:1 DCM:MeOH and passed through a silica plug, eluting with DCM/MeOH (0:100 to 10:90). The lactam **26** was isolated as an off white solid (0.488 g, 46 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, *J* = 2.3 Hz, 1H, CH), 8.04 (br. s, 1H, NH), 7.66 (dd, *J* = 8.6and 2.3 Hz, 1H, CH), 6.77 (d,

J = 8.6 Hz, 1H, CH), 4.40-4.37 (m, 2H, CH_2), 3.53-3.48 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4 (C), 155.5 (C), 142.1 (CH), 140.5 (CH), 125.2 (C), 123.5 (CH), 85.1 (C), 73.0 (CH_2), 41.5 (CH_2); IR (ATR cm-1) 3550, 3090, 2855, 1650, 1537, 1422, 1143, 809; MS (ES^+) *m/z*, 290, (M+H); HRMS (ES^+) Calculated for $C_9H_9INO_2$ (M+H): 289.9678; found 289.9678

7-(2-(2,4-Difluorophenyl)ethynyl)-3,4- dihydrobenzo[f][1,4]oxazepin-5(2H)-one (23)

23 was prepared from the aryl iodide **22** (0.100 g, 0.34 mmol) following general procedure B. Flash column chromatography eluting with EtOAc/pet.ether (90:10) yielded the alkyne as a brown solid (0.086 g, 83 %).^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, *J* = 2.1 Hz, 1H, CH), 7.77 (br. s, 1H, NH), 7.67 (ddd, *J* = 12.1, 8.1 and 1.4 Hz, 1H, CH), 7.56 (dd, *J* = 8.5 and 2.2 Hz, 1H, CH), 7.50-7.43 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H, CH), 4.43 (dd, *J* = 5.5 and 4.5 Hz, 2H, CH_2), 3.55 (dd, *J* = 9.2 and 5.3 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9 (C), 162.3 (C), 163.4 (C), 155.7 (C), 136.2 (CH), 134.3 (C) 132.0 (CH), 128.5 (CH), 122.8 (C), 121.5 (CH), 117.1 (C), 112.2 (CH), 104.3 (CH), 94.2 (C), 82.3 (C), 72.8 (CH_2), 41.8 (CH_2); MS ($ESMS^+$) *m/z* 300 (M + H); MP 137-138 ^oC; HRMS (ES^+) Calculated for $C_{17}H_{12}F_2NO_2$ (M+H): 300.0836; found 300.0836

***tert*-Butyl-3-(2-(methoxycarbonyl)-4-iodophenoxy)propylcarbamate (25)**

Compound **25** was prepared from the phenol **20** (1.09 g, 3.72 mmol) according to general procedure C. Purification *via* flash column chromatography, eluting with EtOAc/hexane (95:5 then 90:10), furnished a clear oil (0.972 g, 58 %);^1H NMR ($CDCl_3$, 300 MHz) *d* 8.06 (d, *J* = 2.3 Hz, 1H, CH), 7.69 (dd, *J* = 8.7 and 2.4 Hz, 1H, CH), 6.70 (d, *J* = 8.8 Hz, 1H, CH), 5.44 (br. s, 1H, NH), 4.35 (q, *J* = 7.1 Hz, 2H, CH_2), 4.06 (t, *J* = 5.1 Hz, 2H, CH_2), 3.34 (q, *J* = 5.2 Hz, 2H, CH_2), 1.99 (m, 2H), 1.42 (s, 9H, 3 x CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) *d* 164.4 (C), 158.36 (C), 156.3 (C), 142.0 (C), 140.1 (CH), 122.1 (CH), 115.1 (CH), 81.9 (C), 78.8 (C), 67.9 (CH_2), 61.1 (CH_2), 38.7 (CH_2), 29.1 (CH), 28.5 (3 x CH_3), 14.3 (CH_3); MS (ES^+) *m/z* 472 (M + Na); IR (ATR cm-1) 3399, 2976, 1700, 1433, 1208, 730; Elemental Calculated for $C_{17}H_{24}INO_5$: C 45.45, H, 5.38, N 3.12; found C 45.77, H 5.63, N 3.28

Ethyl 5-(2-(2,4-difluorophenyl)ethynyl)-2-hydroxybenzoate (30)

The alkyne **30** was prepared from the aryl iodide **20** (2.4 g, 8.2 mmol) as describe in general procedure B. The crude product was purified *via* flash column chromatography, eluting with toluene/pet.ether (50:50) to give a yellow solid (1.9 g, 77 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.02 (s, 1H, OH), 8.0 (dd, *J* = 2.1 and 0.3 Hz, 1H, CH), 7.58 (ddd, *J* = 8.9 and 2.1 Hz, 1H, CH), 7.49-7.42 (m, 1H), 6.95 (dd, *J* = 8.6 and 0.4 Hz, 1H, CH), 6.94-6.82 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H, CH_2), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) d 169.6 (C), 164.3 (C), 161.9 (C), 161.4 (C), 138.5 (C), 134.1 (CH), 133.5 (CH), 118.1 (CH), 113.7 (CH), 112.8 (CH), 111.6 (CH), 107.8 (C), 104.3 (CH), 93.1 (CH), 80.5 (C), 61.8 (CH_2), 14.2 (CH_3); IR (ATR cm-1) 3556, 3283, 3077, 2850, 1631, 1541, 1430, 1224, 1010; MP 69-70 °C; HRMS (ES^-) Calculated for $C_{17}H_{11}F_2O_3$ (M – H): 301.0676; found 301.0679

Ethyl 2-allyl-5-(2-(2,4-difluorophenyl)ethynyl)benzoate (31)

To a stirred solution of the phenol **30** (1.30 g, 4.3 mmol) in anhydrous DCM (11 mL) was added collidine (0.689 mL, 5.2 mmol) and DMAP (0.011 g, 0.09 mmol) under a N_2 atmosphere. The mixture was cooled to -78 °C and Tf_2O (0.868 mL, 5.2 mmol) was added drop-wise. The reaction mixture was warmed to room temperature and stirred for 1 h. The solution was diluted with EtOAc (30 mL) and poured onto $NaHCO_3$ (30 mL). The aqueous was extracted three times with EtOAc (3 x 20 mL) and the combined organics were washed with H_2O (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated. The triflate (0.400 g, 0.92 mmol), along with $Pd(PPh_3)_4$ (0.107 g, 0.092 mmol) was dissolved in anhydrous DMF (2.76 mL) under a N_2 atmosphere. Tribuytlallyltin (0.342 mL, 1.10 mmol) was added and the reaction stirred at 90 °C for 12 h. The mixture was diluted with EtOAc (10 mL) and poured onto 1N HCl (10 mL). The aqueous was extracted three times with EtOAc (3 x 10 mL) and the combined organics washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated. The crude was subjected to column chromatography eluting with EtOAc/pet.ether (0:100 to 5:95) to give **35** as a slightly yellow solid (0.234 g, 78 %); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.04 (d, *J* = 1.8 Hz, 1H, CH), 7.56 (dd, *J* = 7.9 and 1.8 Hz, 1H, CH), 7.51-7.44 (m, 1H), 7.26-7.24 (m, 1H), 6.89-6.82 (m, 2H), 6.06-5.93 (m, 1H), 5.10-4.98 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H, CH_2), 3.76

(ddd, J = 7.7, 2.7 and 1.4 Hz, 2H, CH_2), 1.40 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9 (C), 164.5 (C), 161.2 (C), 142.0 (C), 134.6 (CH), 134.3 (C), 134.2 (CH), 133.4 (CH), 131.1 (CH), 130.4 (C), 120.8 (CH), 116.0 (CH_2), 111.5 (CH), 108.0 (C), 104.3 (CH), 93.1 (C), 82.1 (C), 61.1 (CH_2), 38.2 (CH_2), 14.3 (CH_3); MP 93-98 °C; HRMS (ES$^+$) Calculated for $C_{20}H_{16}F_2O_2Na$ (M + Na): 349.1016; found 349.1016

_N_,2-Diallyl-5-(2-(2,4-difluorophenyl)ethynyl)benzamide (32)

The ester **31** (0.550 g, 1.7 mmol) was dissolved in DCM (1.5 mL) and treated with a 2M NaOH solution in MeOH (1.5 mL). After 3 h, the mixture was quenched with 10 % citric acid (5 mL) and extracted with EtOAc (10 mL). The aqueous was extracted three times with EtOAc (3 x 10 mL) and the combined organic layers washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated. The carboxylic acid (0.450 g, 1.5 mmol) was then converted to the amide **36** *via* general procedure A. Flash column chromatography, eluting with EtOAc/pet.ether (30:70), afforded 4.81 as a slightly yellow solid (0.341 g, 67 %).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.18 (m, 3H), 7.21-7.18 (m, 1H), 6.87-6.79 (m, 2H), 5.97-5.81 (m, 3H), 5.24-4.95 (m, 4H), 4.02-3.96 (m, 2H), 3.53 (d, J = 6.4 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8 (C), 164.6 (C), 161.2 (C), 138.5 (C), 136.9 (CH), 136.5 (C), 134.3 (CH), 133.7 (CH), 132.9 (CH), 130.7 (CH), 130.3 (CH), 120.9 (C), 116.9 (CH_2), 116.5 (CH_2), 111.7 (CH), 108.1 (C), 104.5 (CH), 93.1 (C), 82.2 (C), 42.4 (CH_2), 37.3 (CH_2); MS (ES+) m/z 339 (M+H); MP 117-120 °C; HRMS (ES$^+$) Calculated for $C_{21}H_{18}F_2NO$ (M+H): 338.1356; found 338.1356.

Ethyl 2-(allyloxy)-5-(2-(2,4-difluorophenyl) ethynyl) benzoate (36)

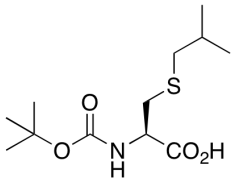
Compound **36** was prepared from the phenol **30** (1.82 g, 6.0 mmol) according to general procedure C. Flash column chromatography, eluting with EtOAc/pet.ether (10:90), gave a clear oil (1.81 g, 88 %); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, J = 2.2 Hz, 1H, CH), 7.49 (dd, J = 8.6 and 2.2 Hz, 1H, CH), 7.42-7.34 (m, 1H), 6.85-6.74 (m, 3H), 6.03-5.91 (m, 1H), 5.45 (ddd, J = 17.2, 3.3, and 1.7 Hz, 1H, CH), 5.23 (ddd, J = 10.6, 3.1 and 1.5 Hz, 1H, CH), 4.53 (ddd, J = 6.5, 3.3 and 1.9 Hz, 2H, CH_2), 4.31 (q, J = 7.1 Hz, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4 (C), 163.4 (C), 160.1 (C), 157.1 (C), 135.2 (CH), 133.9 (CH), 133.1 (C), 131.2 (CH), 120.3 (CH), 116.7 (CH_2),

113.8 (CH), 112.5 (C), 110.5 (CH), 107.2 (C), 103.2 (CH), 92.0 (C), 80.1 (C), 68.5 (CH_2), 60.0 (CH_2), 13.3 (CH_3); IR (ATR cm-1) 3253, 2959, 2348, 1698, 1508, 1143; HRMS (ES^+) Calculated for $C_{20}H_{17}F_2O_3Na$ (M + H): 343.1146; found 343.1152.

***N*-allyl-2-(allyloxy)-5-(2-(2,4-difluorophenyl)ethynyl)benzamide (37)**

The ester **36** (1.91 g, 5.6 mmol) was dissolved in MeOH (6 mL) and treated with an 8 M aqueous solution of LiOH (2.0 mL, 16.7 mmol). The suspension was left to stir for 12 h, after which time it was quenched with 10% citric acid (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The acid (1.4 g, 4.5 mmol) was then converted to the amide *via* general procedure A. Flash column chromatography, eluting with EtOAc/pet.ether (30:70), afforded **37** as a slightly yellow solid (0.604 g, 38 %); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (dd, J = 2.3 and 0.9 Hz, 1H, CH), 7.88-7.85 (m, 1H), 7.50-7.37 (m, 2H), 6.87-6.76 (m, 3H), 6.02-5.85 (m, 2H), 5.42-5.10 (m, 4H), 4.62 (dd, J = 5.5 and 1.1 Hz, 2H, CH_2), 4.07-4.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6 (C), 164.4 (C), 161.0 (C), 156.5 (C), 135.7 (CH), 135.5 (CH), 134.1 (CH), 134.2 (CH), 134.1 (C), 131.6 (CH), 122.1 (C), 119.4 (CH_2), 116.0 (CH_2), 112.8 (CH), 111.5 (CH), 108.2 (C), 104.2 (CH), 93.2 (C), 81.1 (C), 70.0 (CH_2), 42.2 (CH_2); MP 103-105^{o}C; MS (ES^+) m/z 354 (M+H); HRMS (ES^+) Calculated for $C_{21}H_{17}F_2NO_2$ 354.1306 (M+H): found 354.1306

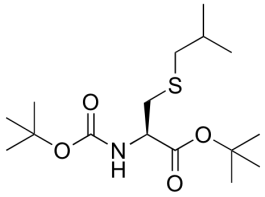
***N*-Boc-(L)-*iso*-butylcysteine**



L-Cysteine (10 g, 0.056 mol) was dissolved in ethanol (56 mL) and treated with 2N NaOH (84 mL, 0.168 mol), tetrabutylammonium iodide (0.621 g, 1.7 mmol) and 2-methyl-3-bromopropane (7.07 mL, 0.057 mol). The mixture was allowed to stir at room temperature for 3 days. After this time Boc_2O (18.83 g, 0.084 mol) was added and the reaction stirred for a further 24 h. The reaction mixture was then concentrated and the residue treated with cold 1N HCl (60 mL), followed by EtOAc (60 mL) and water (40

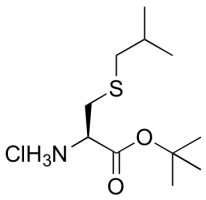
mL). The aqueous phase was extracted three times with EtOAc (3 x 40 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. Concentration of the organic phase afforded the title compound as a clear oil (15 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) (Rotamers) δ 8.96 (s, 1H, CO_2H), 5.68 – 5.49 (m, 1H, NH), 4.48 – 4.44 (m, 1H), 3.10 – 2.91 (m, 2H), 2.47 – 2.36 (m, 2H), 1.75 – 1.64 (m, 1H), 1.43 – 1.40 (m, 9H, 3 x CH_3), 0.89 (d, J = 6.6 Hz, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5 (C), 155.5 (C), 85.3 (C), 53.3 (CH), 41.9 (CH_2), 34.7 (CH_2), 28.6 (CH), 28.2 (3 x CH_3), 21.8 (2 x CH_3); IR (ATR cm-1) 3340, 2931, 2337, 1681, 1504, 1165, 910; MS (ES$^+$) mz 278 (M+H); HRMS (ES-) Calculated for $C_{12}H_{22}NO_4S$ (M -H): 276.1270; found 276.1270

_N_-Boc-(L)-isobuytlcysteine-_tert_-butyl ester



To a stirred solution of *N*-Boc-(L)-*iso*-butylcysteine (3.0 g, 0.011 mol) in *tert*-BuOH (20 mL), was added $(Boc)_2O$ (4.73 g, 0.021 mol) and DMAP (0.269 g, 0.002 mol). The mixture was stirred at room temperature for 16 h. The brown solution was diluted with EtOAc (15 mL), and quenched with 10% citric acid (15 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers washed with saturated $NaHCO_3$ (15 mL), H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated. The brown oil was purified *via* flash column chromatography, eluting with EtOAc/Hexane (20:80) to yield the title compound as a clear oil (1.50 g, 45%).^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.28 (br.s, 1H, NH), 4.31 – 4.28 (m, 1H), 2.89 – 2.87 (m, 2H), 2.37 – 2.31 (m, 2H), 1.66 (sept, J = 6.7 H, 1H, CH), 1.43 – 1.38 (m, 18H), 0.93 (d, J = 6.6 Hz, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (C), 155.0 (C), 82.3 (C), 79.7 (C), 54.0 (CH), 42.2 (CH_2), 35.2 (CH_2), 28.6 (CH), 28.6 – 27.8 (2 x CH_3), 21.9 – 21.8 (6 x CH_3); IR (ATR cm-1) 3368, 2957, 1709, 1500, 1366, 1161, 731; MS (ES$^+$) *mz* 233 (M-Boc); HRMS (ES$^+$) Calculated for $C_{16}H_{31}NO_4SNa$ (M + Na): 356.1871; found 356.1872

L-isobuytlcysteine hydrochloride methyl ester

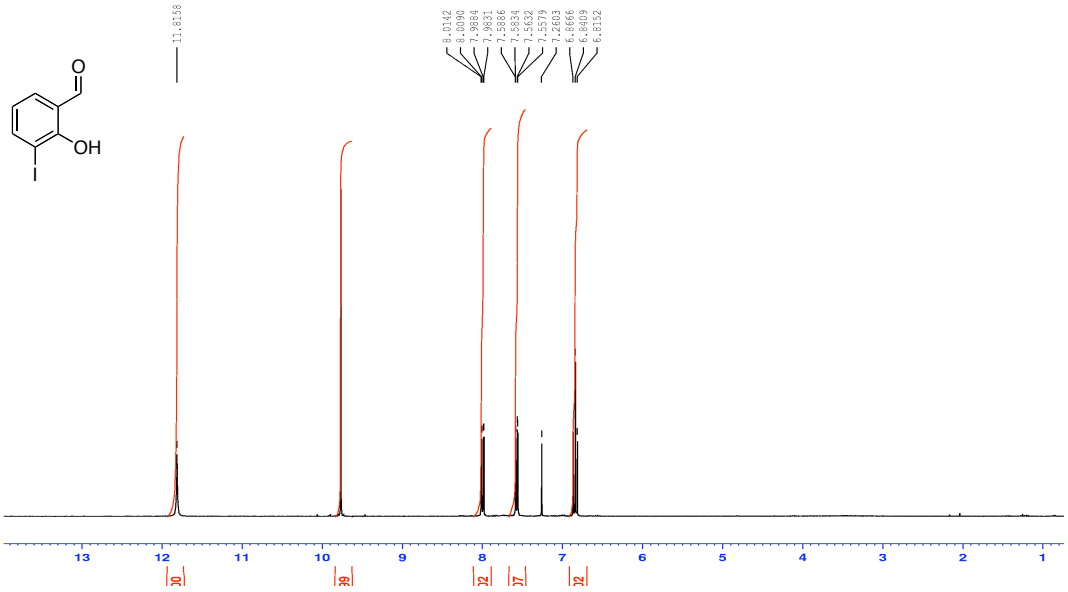


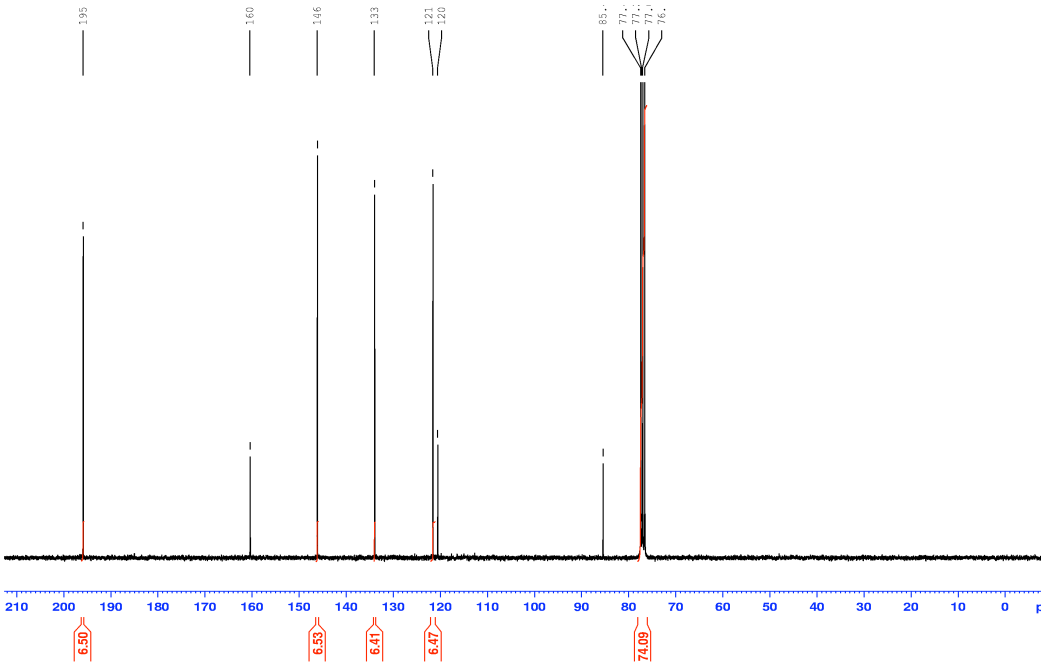
HCl gas was bubbled through a solution of *N*-boc(L)-isobuytlcysteine-*tert*-butyl ester (0.450 g, 1.60 mmol) in anhydrous dioxane (0.8 ml). After 30 mins the hydrochloride salt precipitated and was filtered and washed with EtOAc (10 mL) to afford the title compound as a white solid (0.378 g, 88%).^{1}H NMR (D_2O, 300 MHz) δ 4.20 (app. t, J = 5.5 Hz, 1H, CH), 3.10 (app.t, J = 4.7 Hz, 2H, CH_2), 2.48 (d, J = 6.8 Hz, 2H, CH_2), 1.77 (sept, J = 6.6 Hz, 1H, CH), 1.47 (s, 9H, CH_3), 0.92 (d, J = 6.6 Hz, 6H, 2 x CH_3); ^{13}C NMR (D_2O, 75 MHz) δ 167.7 (C), 86.3 (C), 53.1 (CH), 41.2 (CH_2), 31.9 (CH_2), 28.0 (CH), 27.1 (CH_3), 21.0 (2 x CH_3); MP 227-229 ^{o}C; MS (ES+) *mz* 234 (M+H) HRMS (ES^+) Calculated for $C_{11}H_{24}NO_2S$ (M + H): 234.1528; found 234.1528

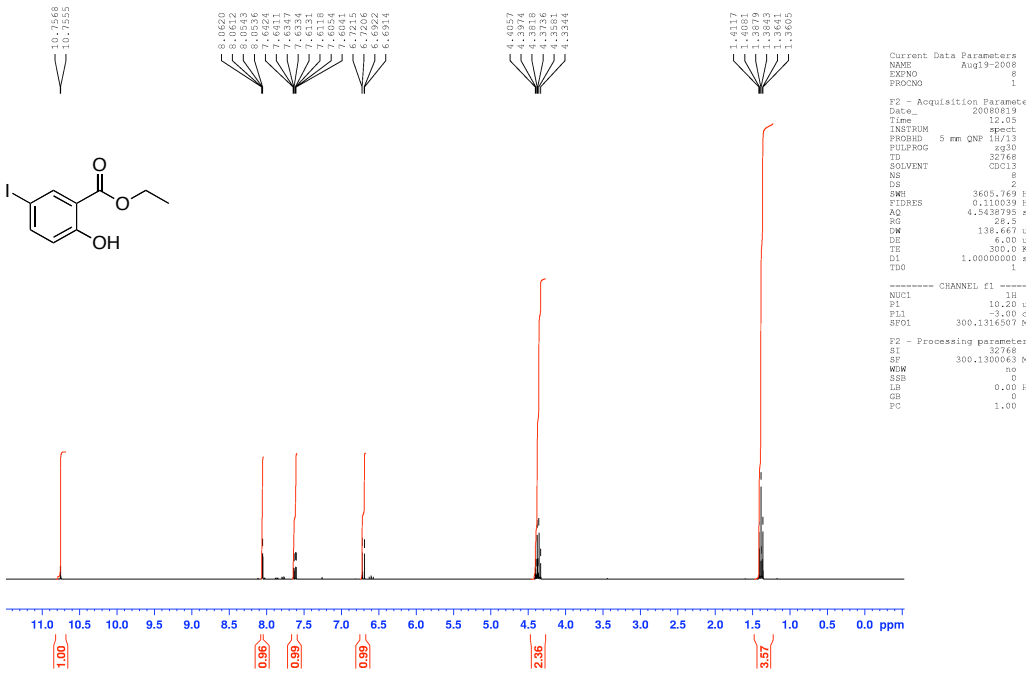
AlphaScreen Assay

Compounds were biologically evaluated using the AlphaScreen GST (glutathione S-transferase) detection kit system (Perkin-Elmer Lifesciences). Briefly, test compounds were titrated into the assay, which consisted of GST-tagged Bcl-x_L ΔC25 protein (0.6 nM final concentration) and biotinylated Bim BH3-26 peptide, Biotin-DLRPEIRIAQELRRIGDEFNETYTRR (5.0 nM final concentration), anti-GST-coated acceptor beads, and streptavidin-coated donor beads (both bead types at a final concentration of 15μg/mL) and a room temperature incubation time of 4 h before reading. More specifically, (i) a 384 well-plate was prepared with 4.75 μL of buffer and 0.25 μL of compound stock (20 mM in DMSO) per well; (ii) binding partners were mixed—in one tube, Bcl-x_L was added with the acceptor beads, while in the second tube biotinylated BH3 peptide was added with the donor beads; (iii) these two pairs of binding partners were preincubated for 30 min; (iv) 10 μL of the acceptor beads/Bcl-x_L protein complex was then added to each of the 384 wells; (v) plates were sealed and incubated at room temperature for a further 30 min; (vi) 10 μL of the donor bead/BH3 peptide complex was then added to each of the 384 wells; (vii) plates were sealed, covered with foil, and

incubated for a further 4 h and then read. The assay buffer contained 50 mM HEPES, pH 7.4, 10 mM DTT, 100 mM NaCl, 0.05% Tween 20, and 0.1 mg/mL casein. Bead dilution buffer contained 50 mM Tris-HCl, pH 7.5, 0.01% Tween 20, and 0.1 mg/mL casein. The final DMSO concentration in the assay was 1.0% (v/v). Assays were performed in 384-well white Optiplates (Perkin-Elmer Lifesciences) and analyzed on the PerkinElmer Fusion Alpha plate reader (Ex680, Em520-620 nM).





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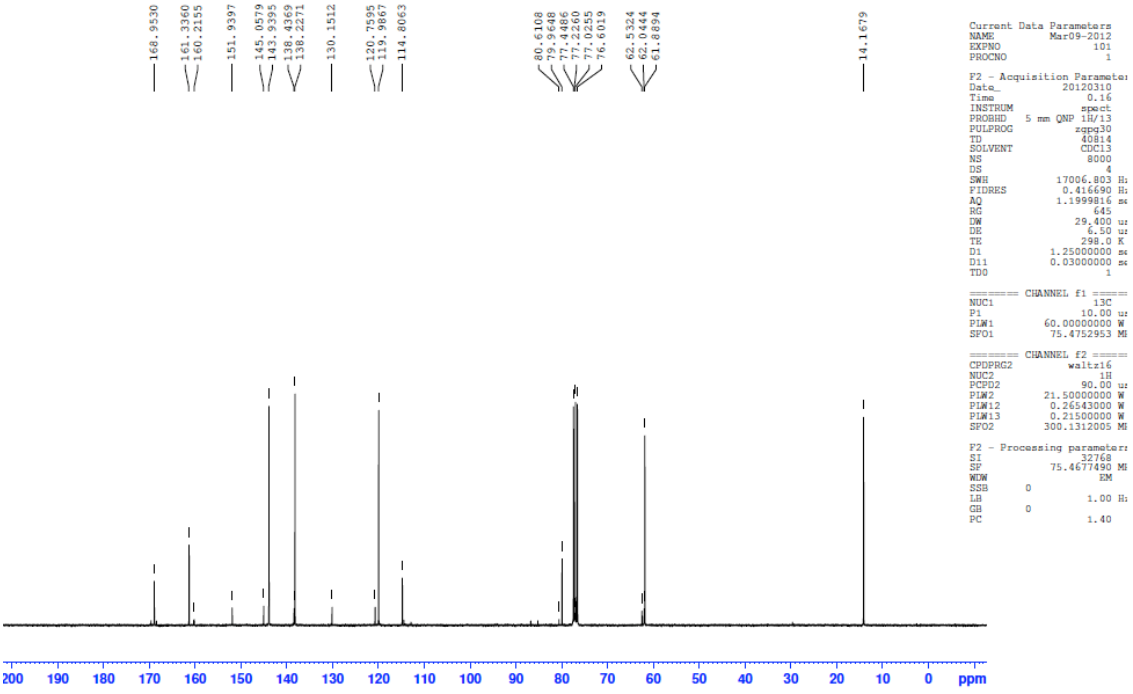


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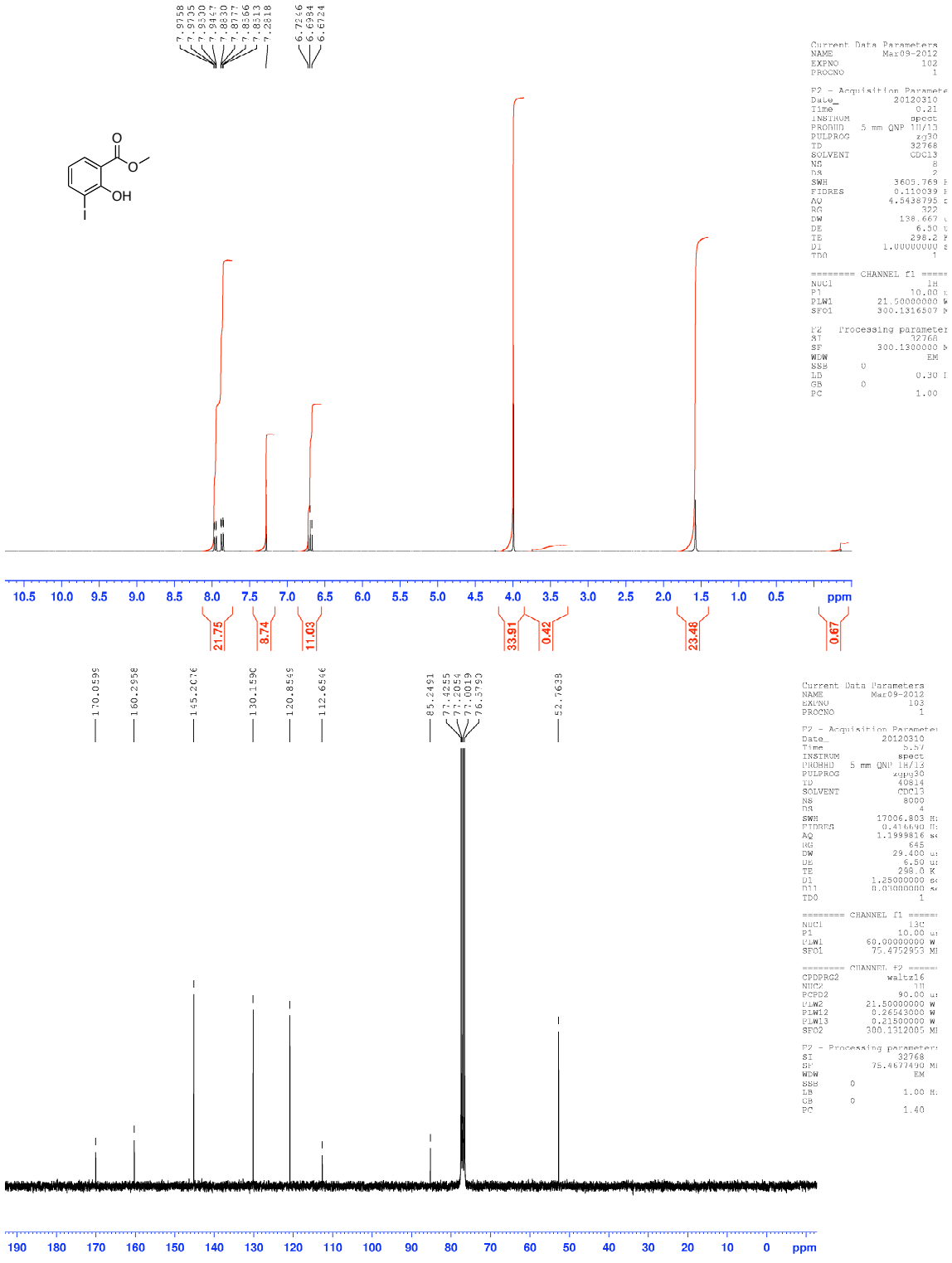

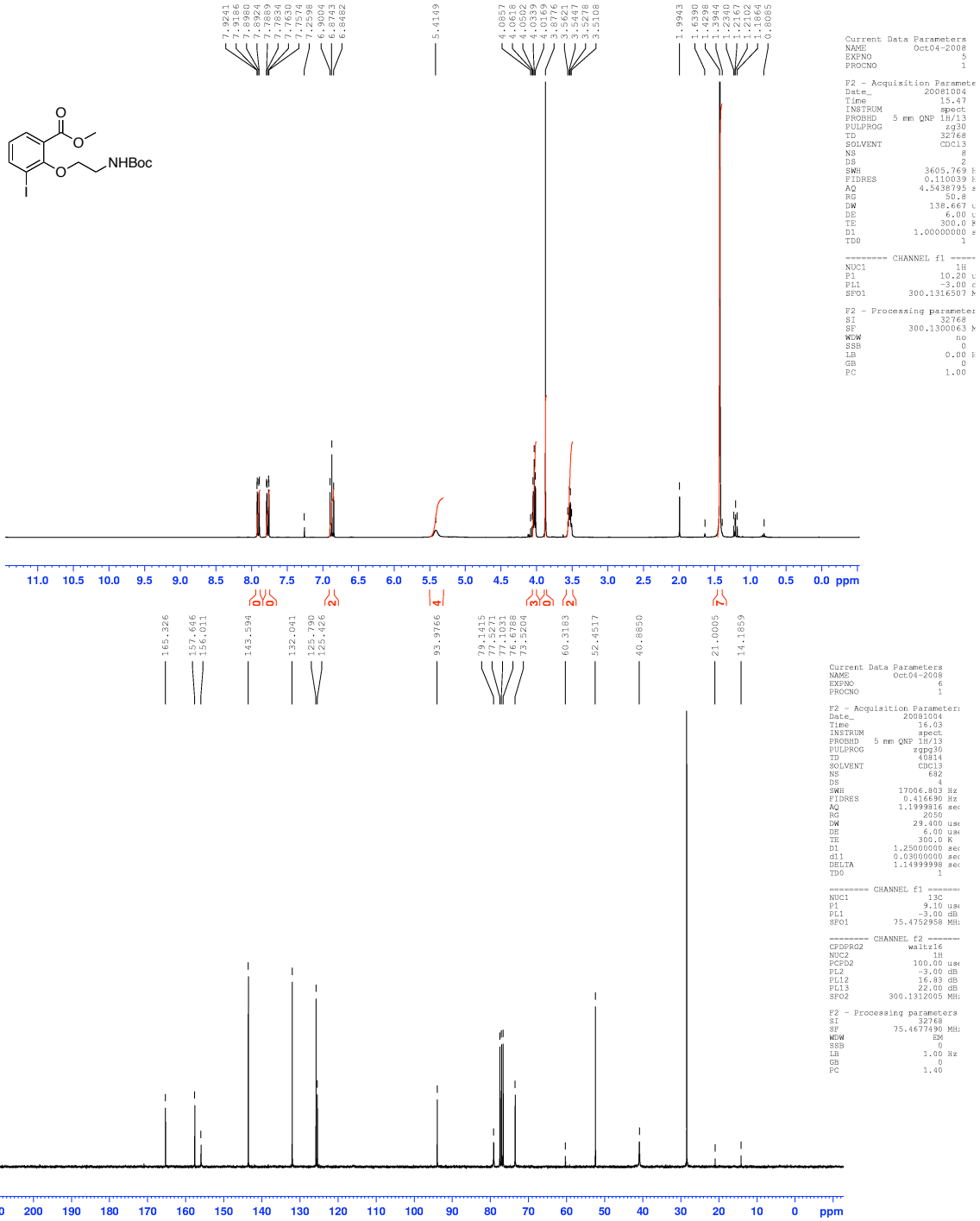
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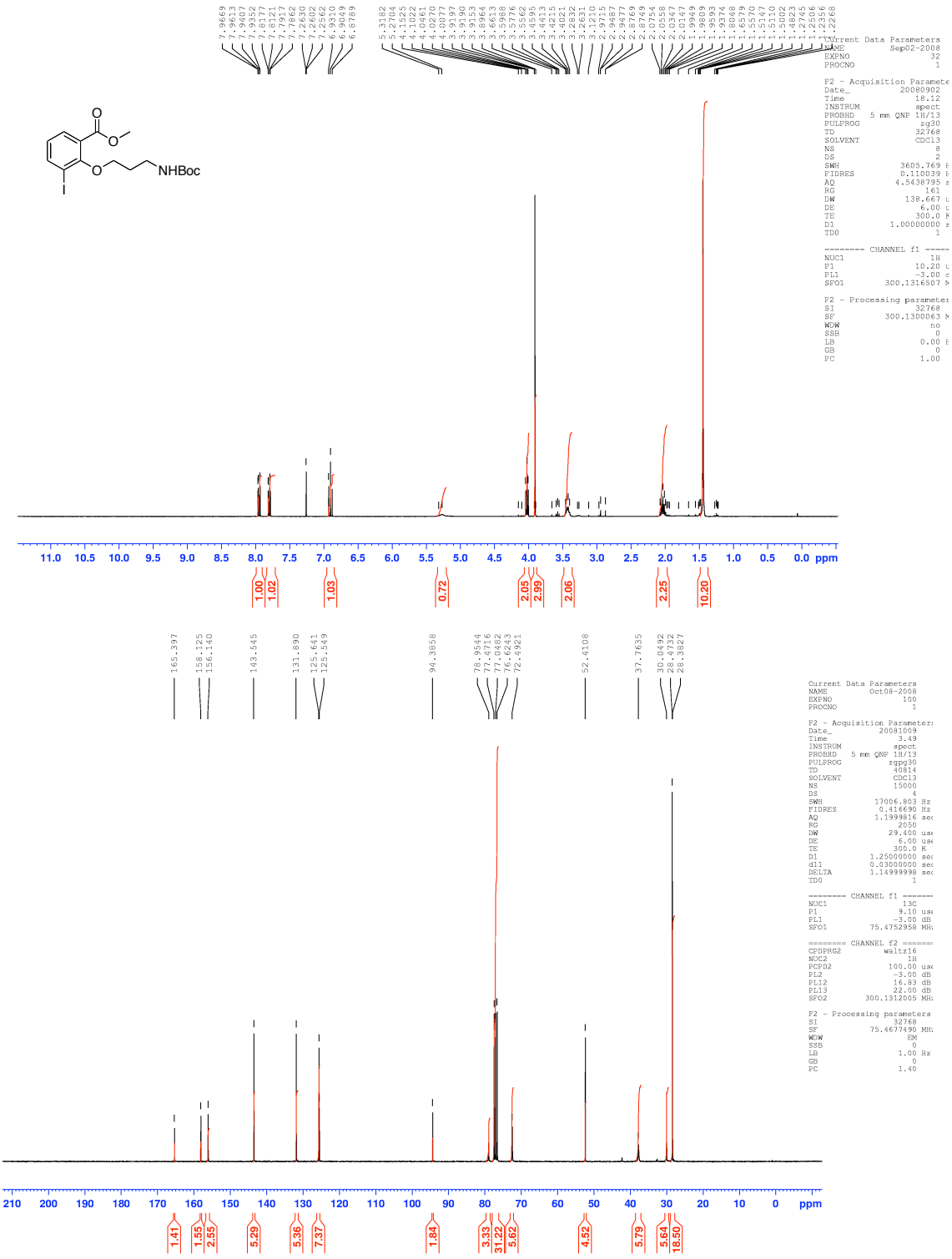

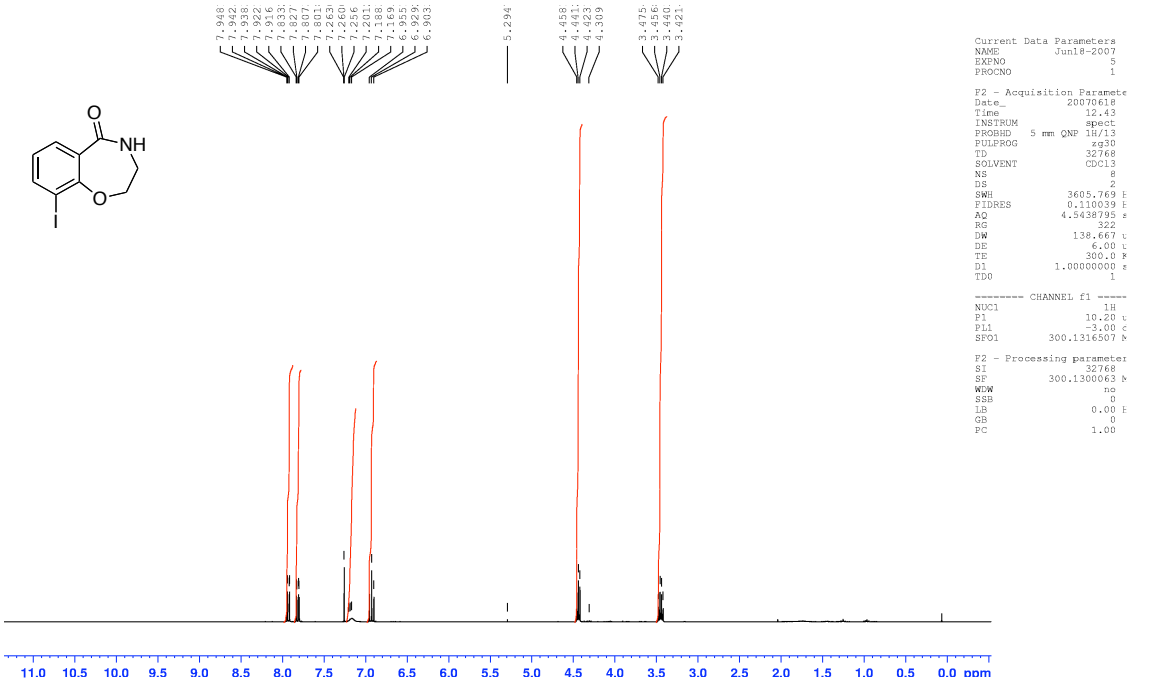


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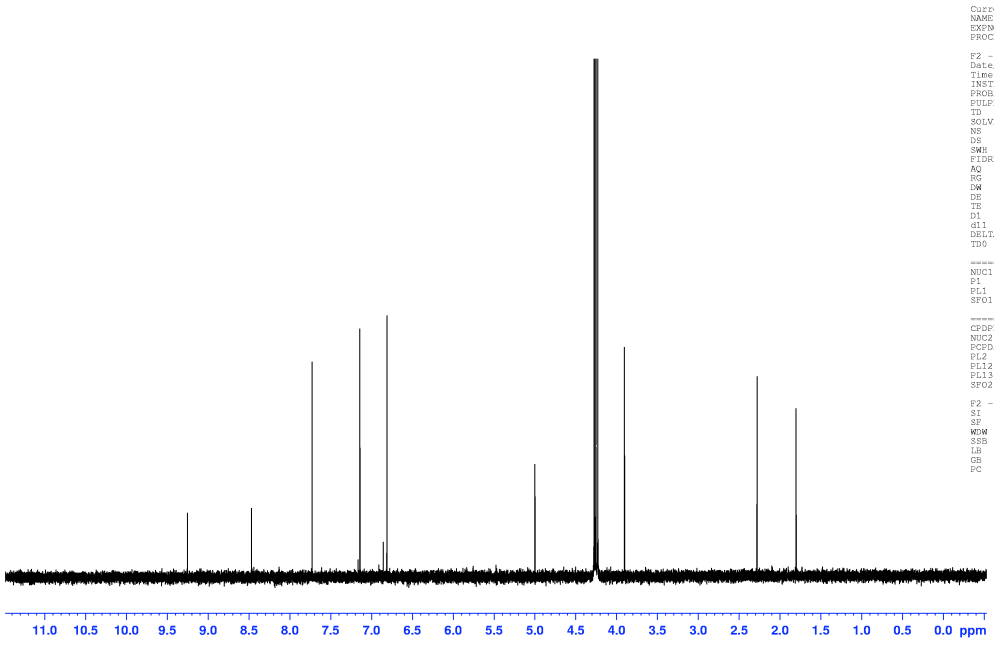


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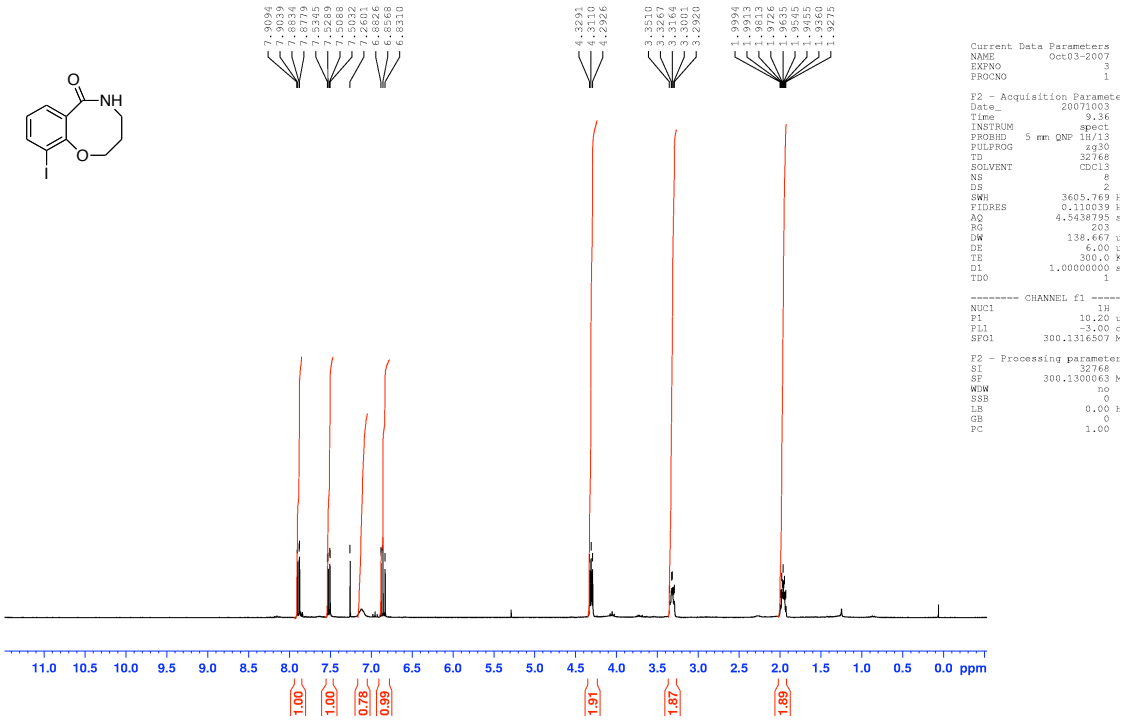
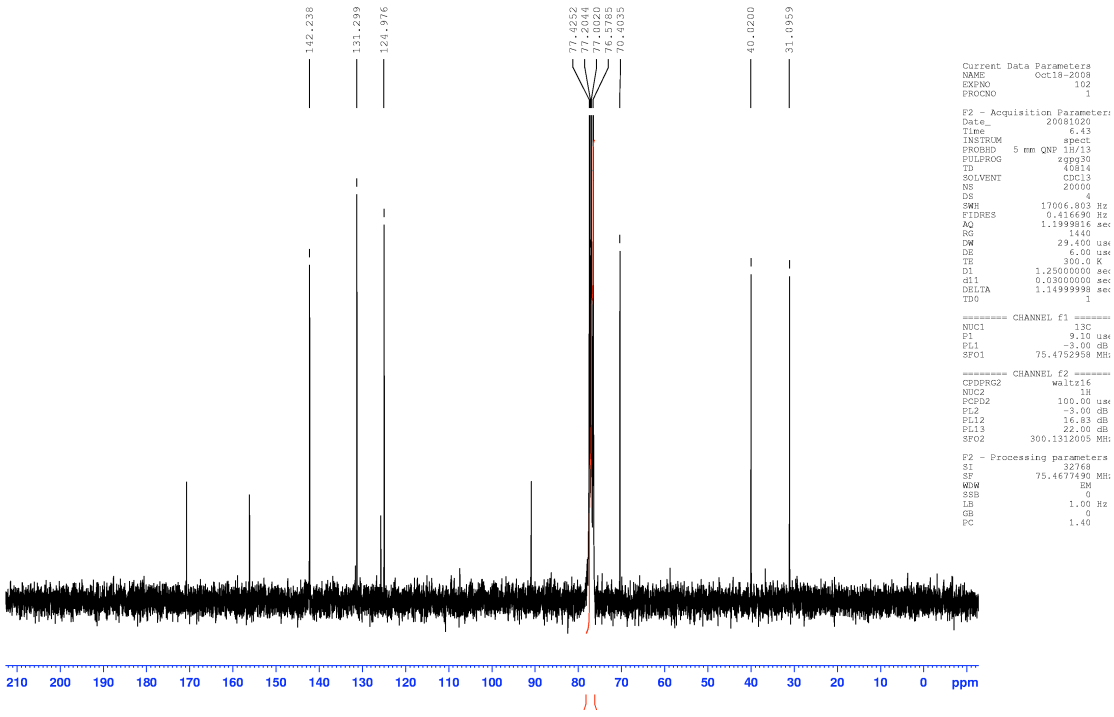
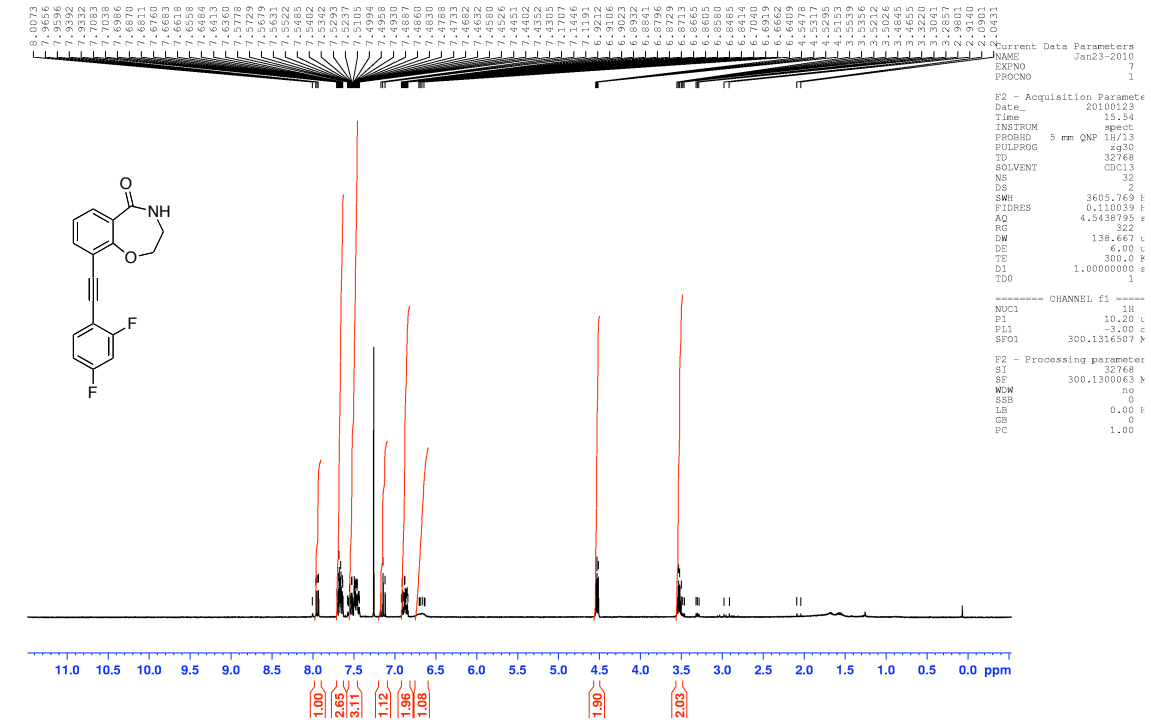
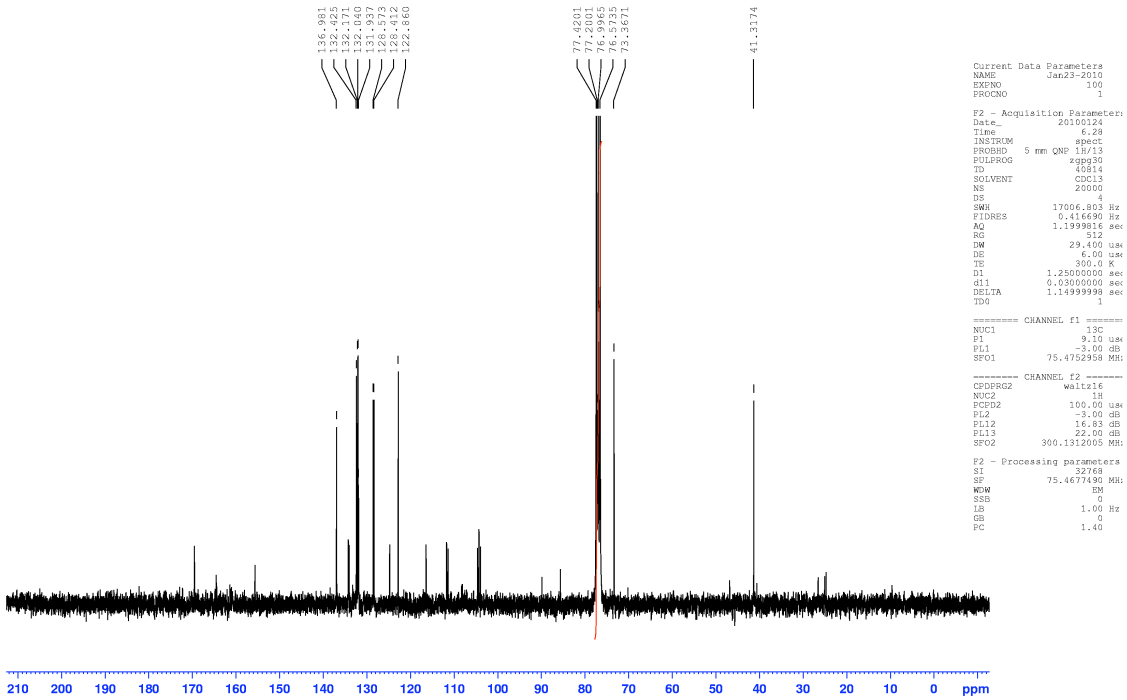
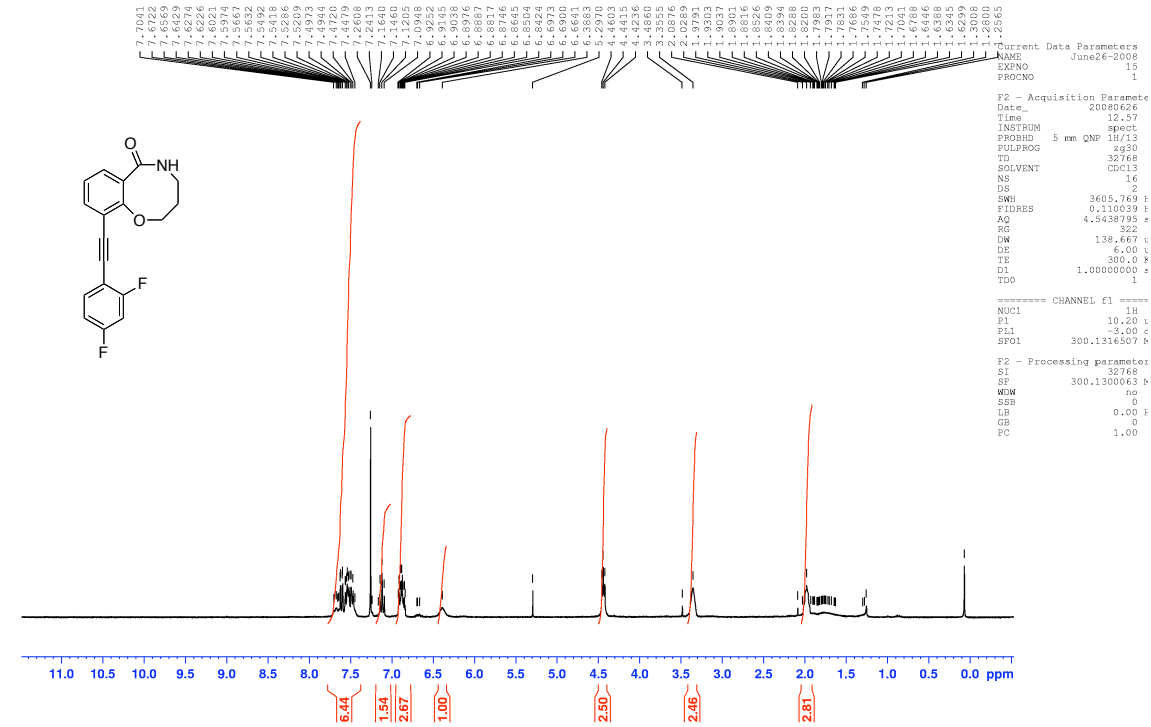
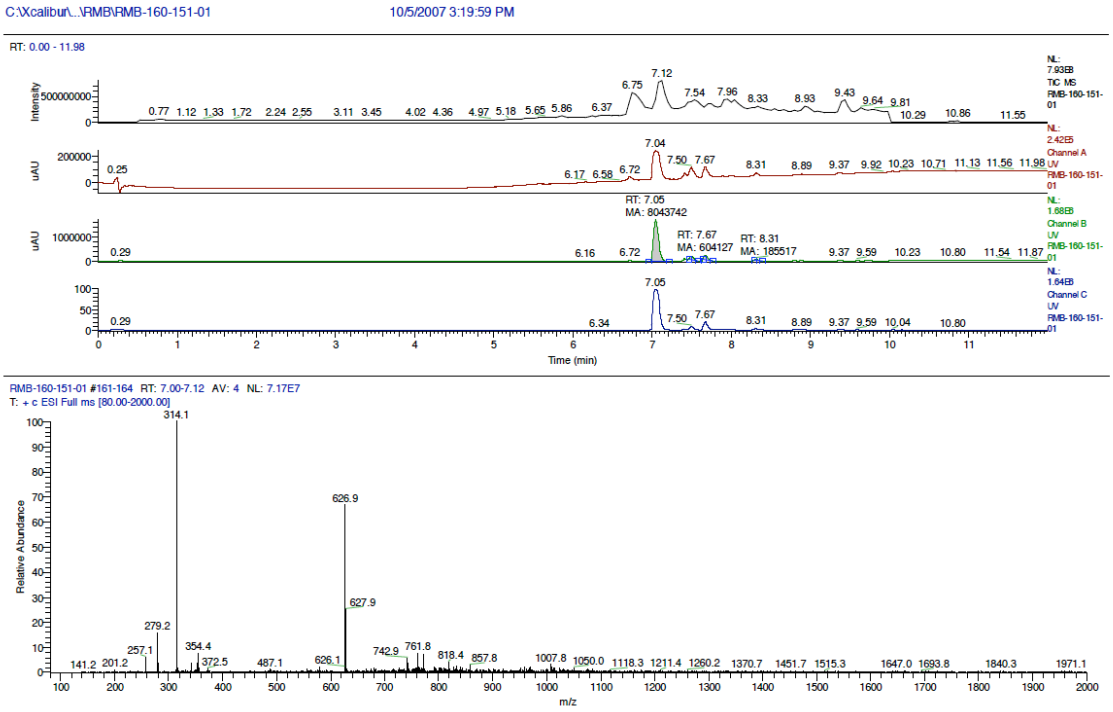




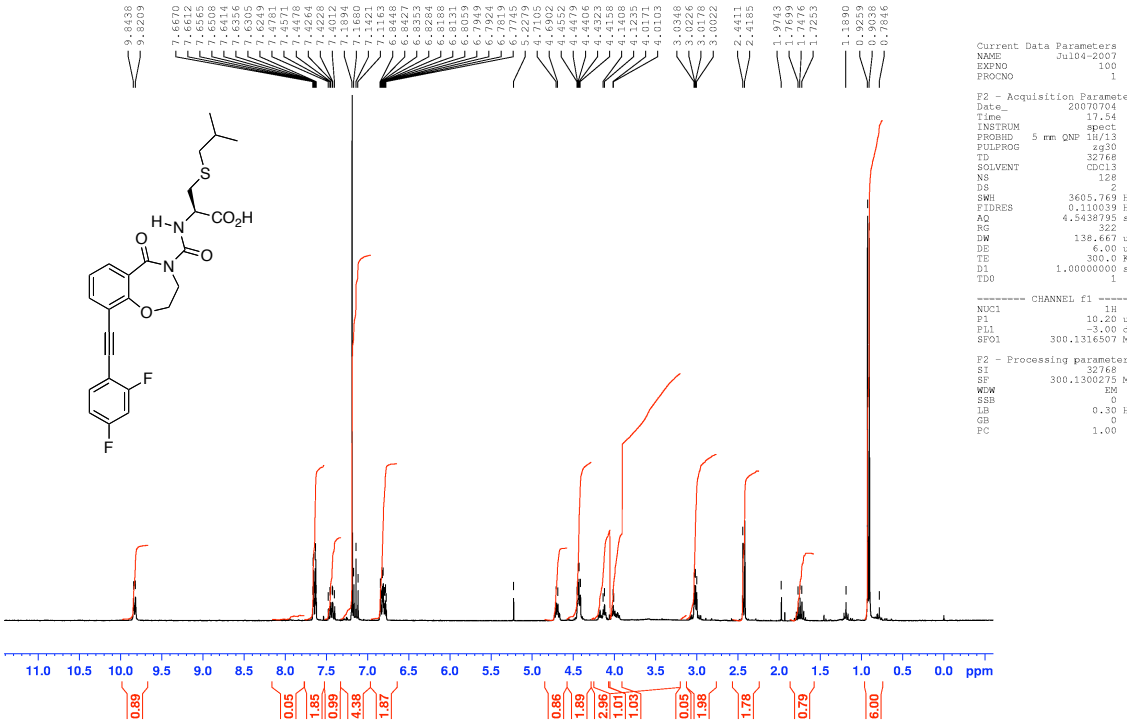

NH
O
O
F
F
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
2.65
3.11
1.12
1.96
1.08
1.90
2.03

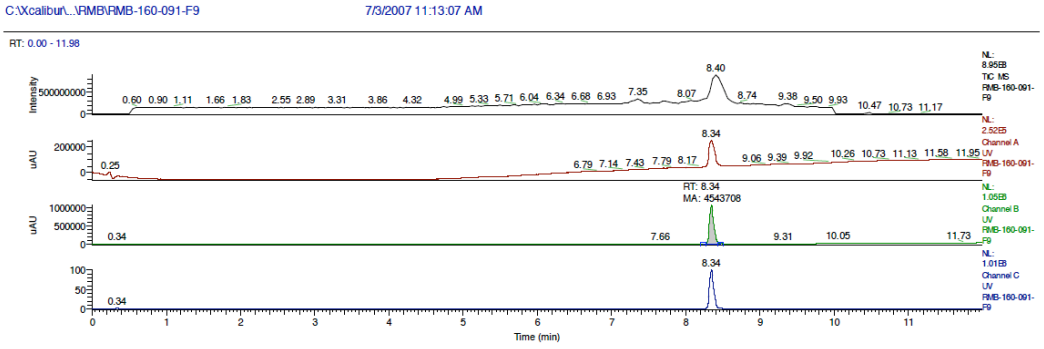

136.981
132.425
132.171
132.040
131.937
128.573
128.412
122.860
77.4201
77.2001
76.9965
76.5735
73.3671
41.3174
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

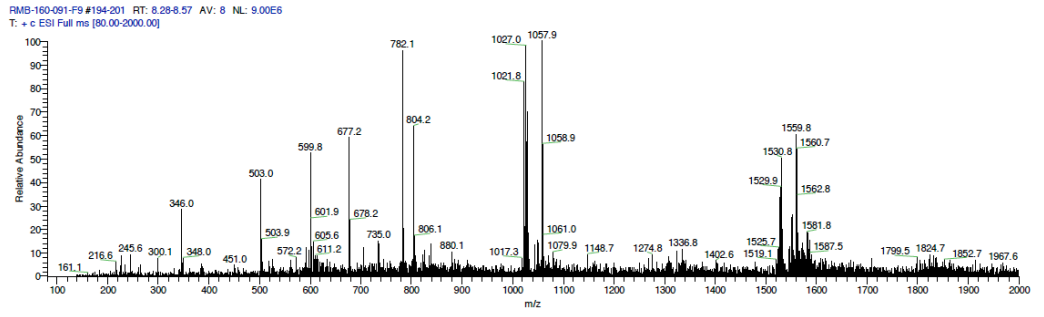




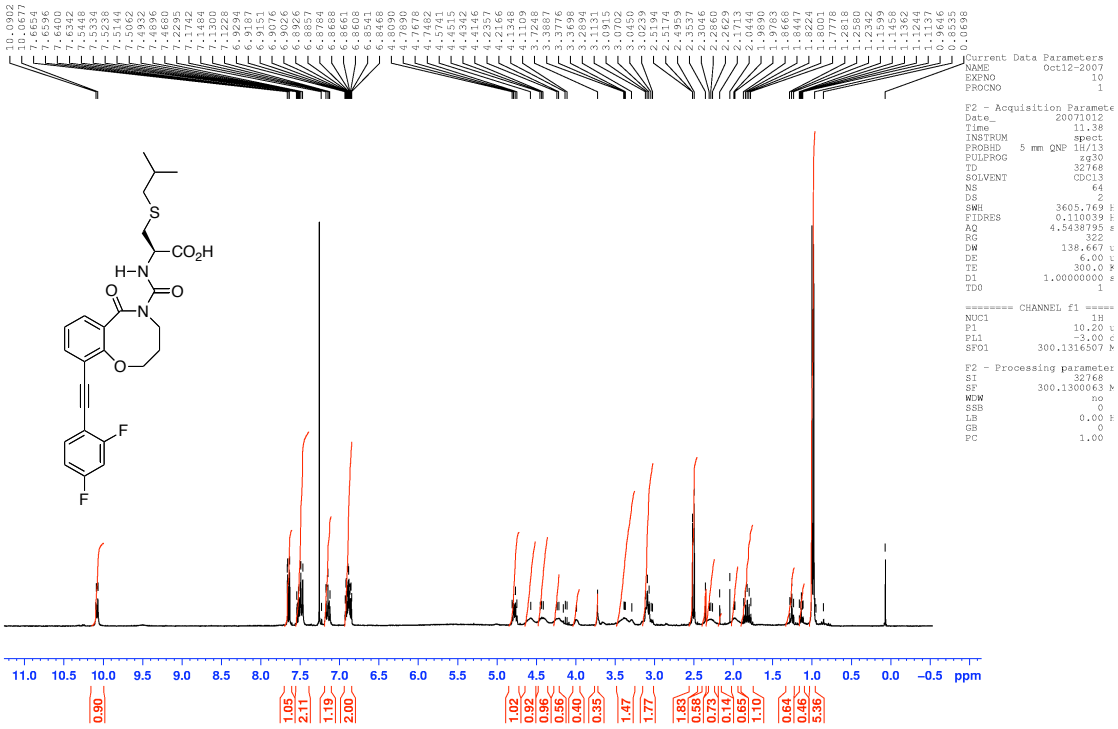
HPLC-RP: (254nm) : 91.6% : rt; 7.03

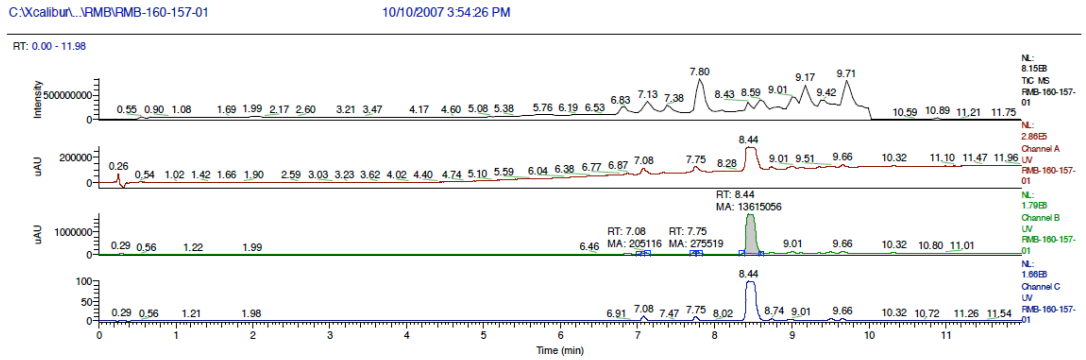


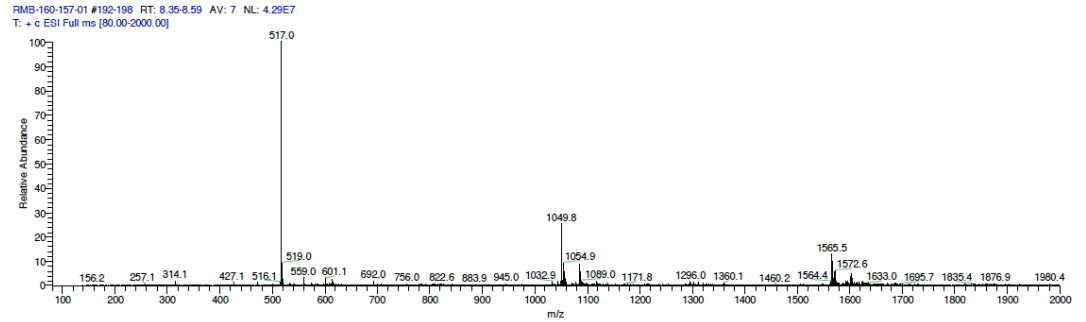




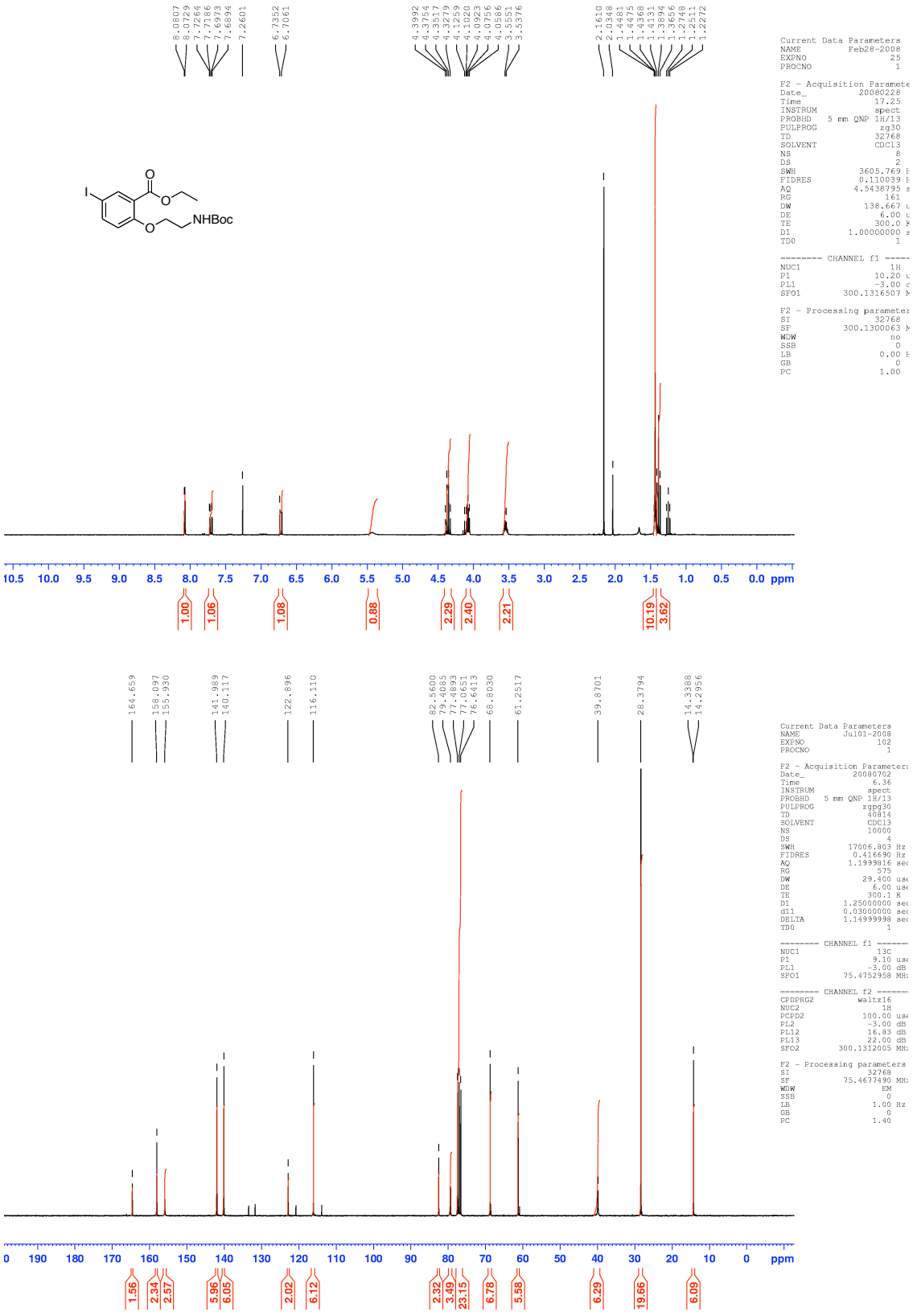
HPLC-RP: (254nm) : 99.0% : rt; 8.34

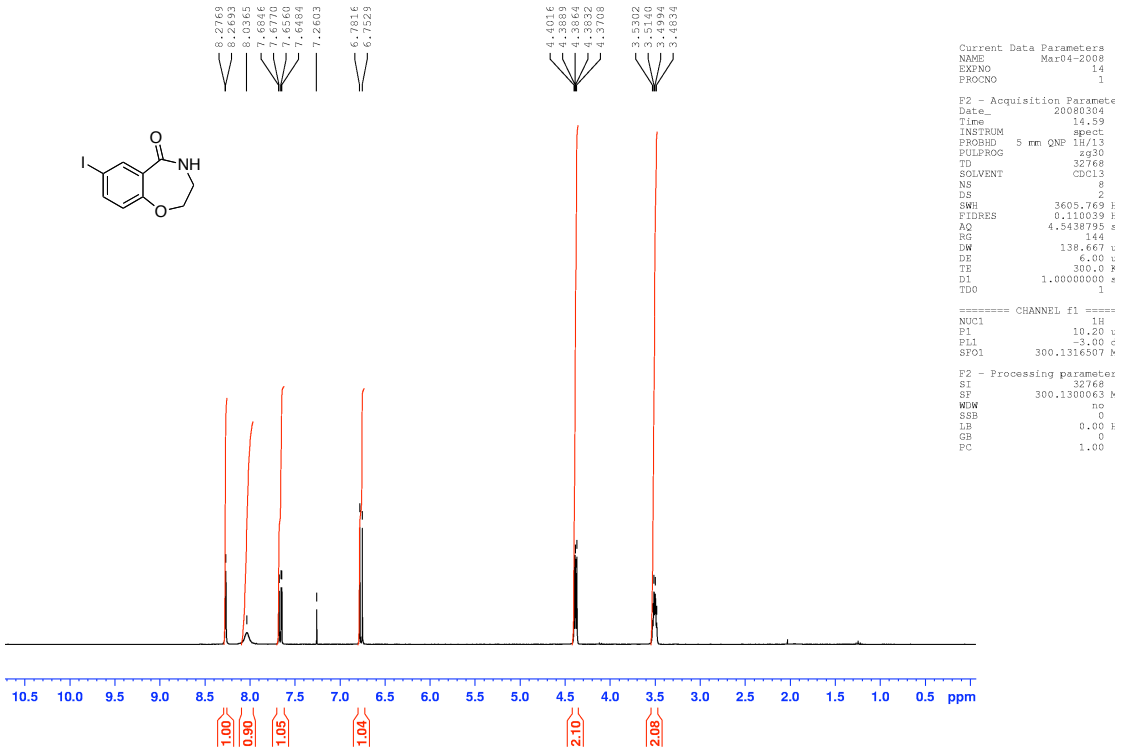


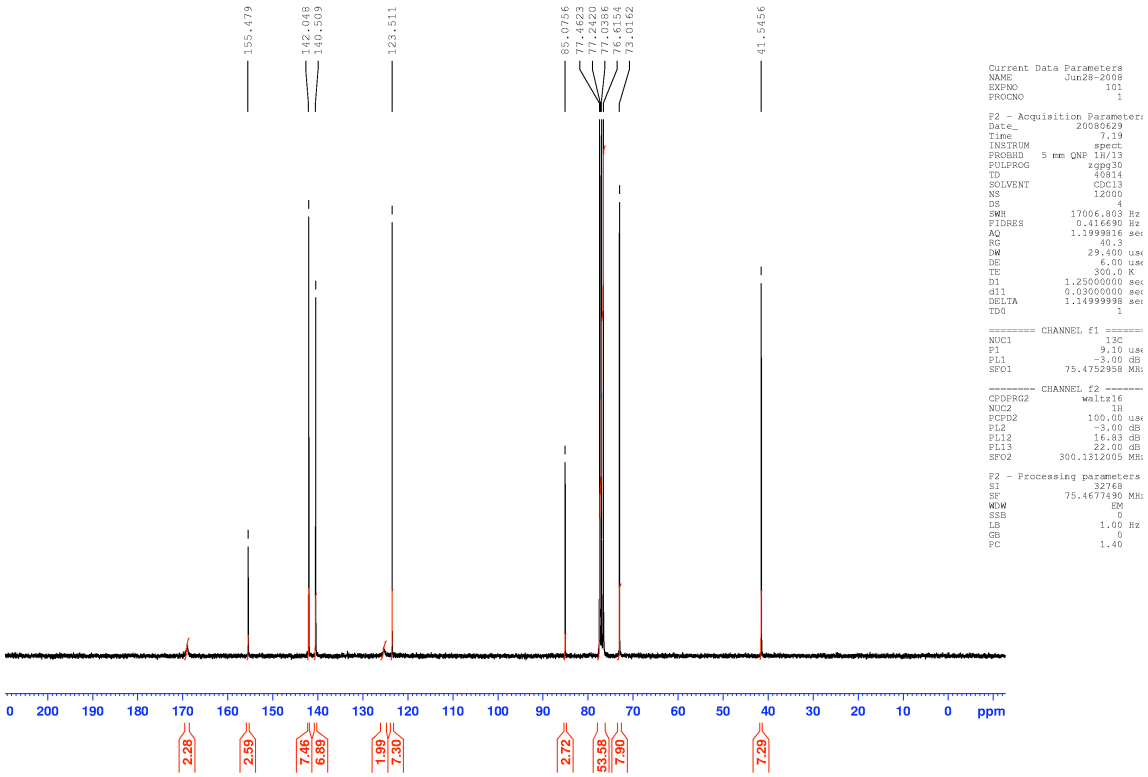


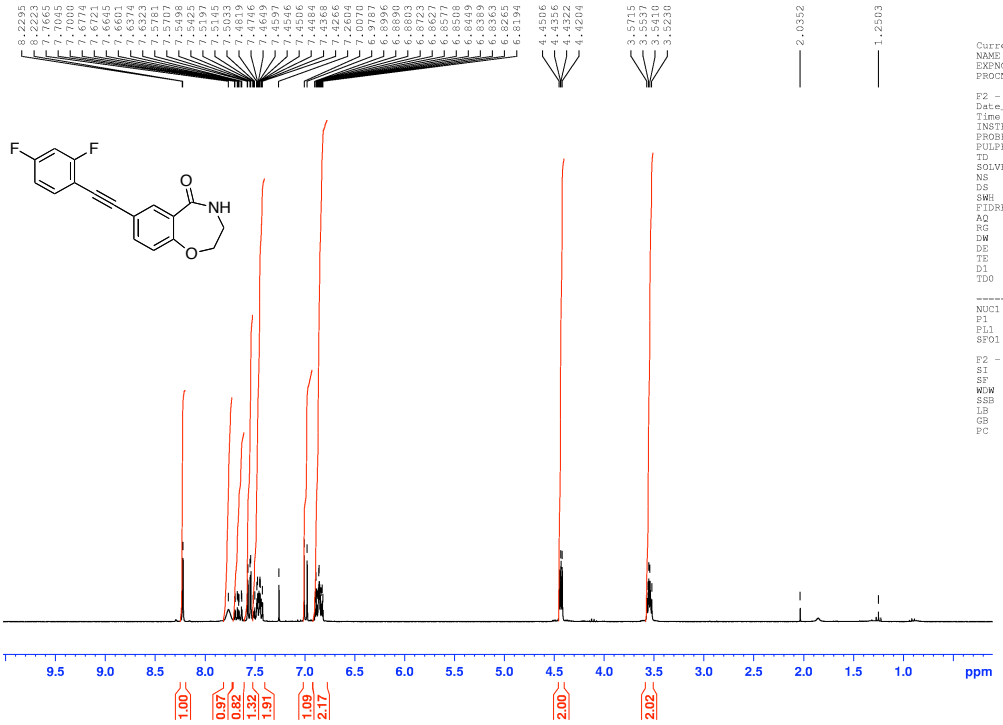


HPLC-RP: (254nm) : 96.6% : rt; 8.14


8.0807
8.0729
7.7264
7.7186
7.6973
7.6894
7.2601
6.7352
6.7061
4.3992
4.3754
4.3517
4.3279
4.1259
4.1020
4.0923
4.0756
4.0586
3.5551
3.5376
2.1610
2.0348
1.4481
1.4475
1.4368
1.4131
1.3894
1.3656
1.2748
1.2511
1.2272
I
O
O
O
NHBoc
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.06
1.08
0.88
2.29
2.40
2.21
10.19
3.62
Current Data Parameters
NAME Feb28-2008
EXPNO 25
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080228
Time 17.25
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 3605.769 Hz
FIDRES 0.110039 Hz
AQ 4.5438795 sec
RG 161
DW 138.667 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
PL1 -3.00 dB
SFO1 300.1316507 MHz
F2 - Processing parameters
SI 32768
SF 300.1300063 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
164.659
158.097
155.930
141.989
140.117
122.896
116.110
82.5600
79.4085
77.4893
77.0651
76.6413
68.8030
61.2517
39.8701
28.3794
14.3388
14.2956
0 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
1.56
2.34
2.57
5.96
6.05
2.02
6.12
2.32
3.49
23.15
6.78
5.58
6.29
19.66
6.09
Current Data Parameters
NAME Jul01-2008
EXPNO 102
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080702
Time 6.36
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 40814
SOLVENT CDCl3
NS 10000
DS 4
SWH 17006.803 Hz
FIDRES 0.416690 Hz
AQ 1.1999816 sec
RG 575
DW 29.400 usec
DE 6.00 usec
TE 300.1 K
D1 1.25000000 sec
d11 0.03000000 sec
DELTA 1.14999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.10 usec
PL1 -3.00 dB
SFO1 75.4752958 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 16.83 dB
PL13 22.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40





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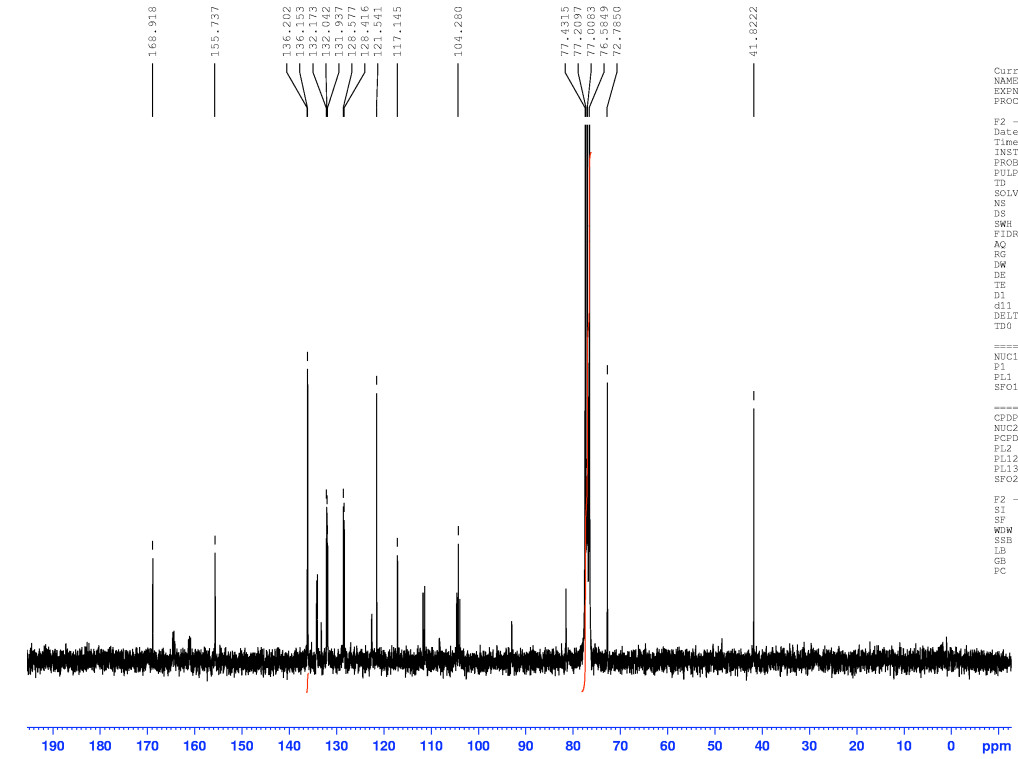
Current Data Parameters
NAME                  Mar10-2008
EXPNO                         13
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20080310
Time                       12.12
INSTRUM                    spect
PROBHD    5 mm QNP 1H/13
PULPROG                    zg30
TD                        32768
SOLVENT                   CDCl3
NS                             8
DS                             2
SWH                    3605.769 H
FIDRES                 0.110039 H
AQ                     4.5438795 s
RG                           161
DW                       138.667 u
DE                          6.00 u
TE                         300.0 K
D1                    1.00000000 s
TD0                            1

======== CHANNEL f1 =====
NUC1                         1H
P1                        10.20 u
PL1                       -3.00 d
SFO1                300.1316507 M

F2 - Processing parameters
SI                        32768
SF                  300.1300063 M
WDW                          no
SSB                           0
LB                         0.00 H
GB                            0
PC                         1.00
```



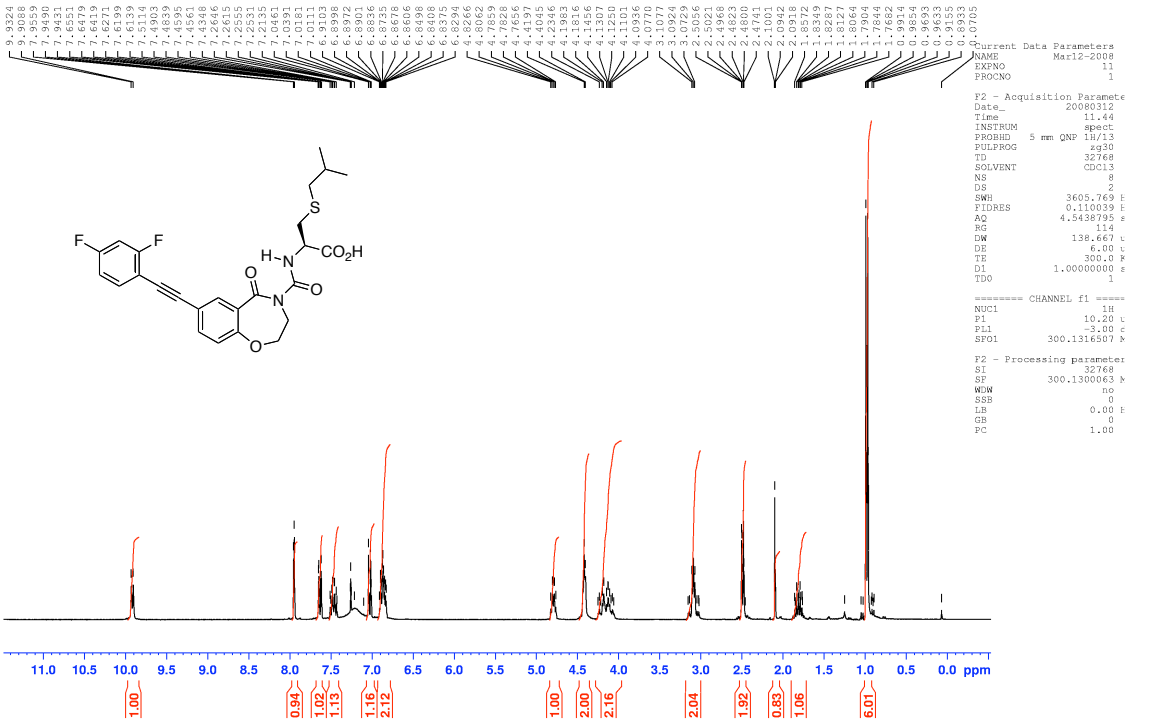

```
Current Data Parameters
NAME                  Jun28-2008
EXPNO                        100
PROCNO                         1

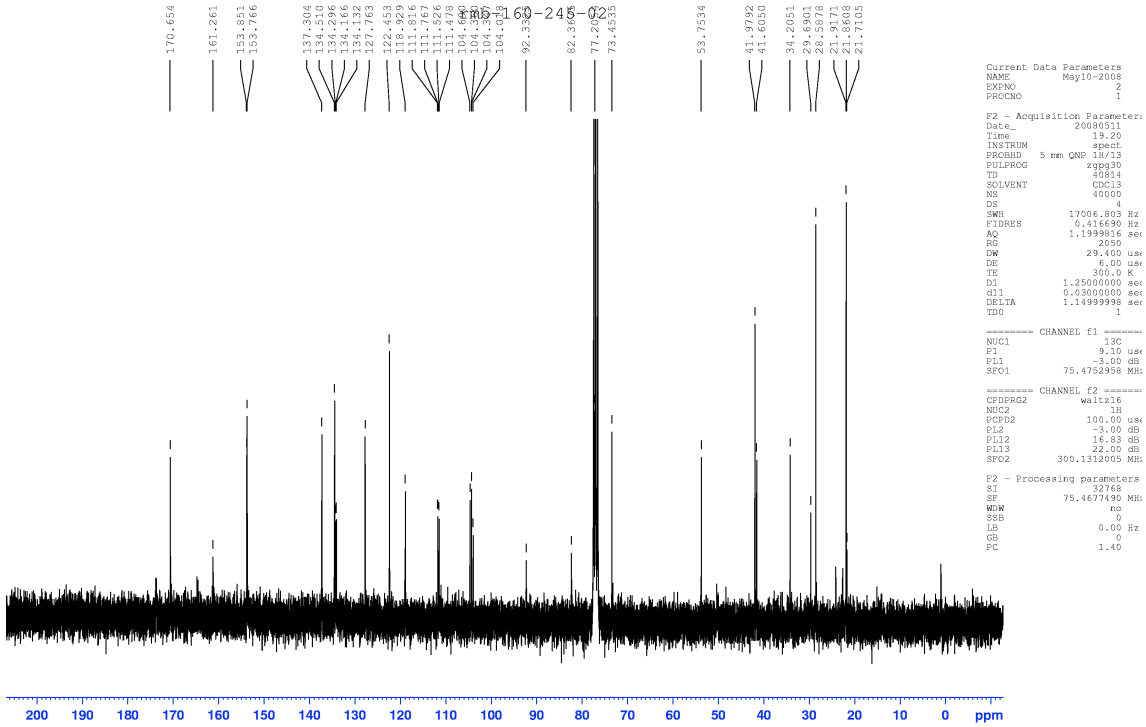
F2 - Acquisition Parameters
Date_                   20080628
Time                       22.51
INSTRUM                    spect
PROBHD    5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        40814
SOLVENT                   CDCl3
NS                        12000
DS                             4
SWH                17006.803 Hz
FIDRES              0.416690 Hz
AQ                  1.1999816 sec
RG                           645
DW                      29.400 use
DE                          6.00 use
TE                         300.0 K
D1                  1.25000000 sec
d11                 0.03000000 sec
DELTA               1.14999998 sec
TD0                            1

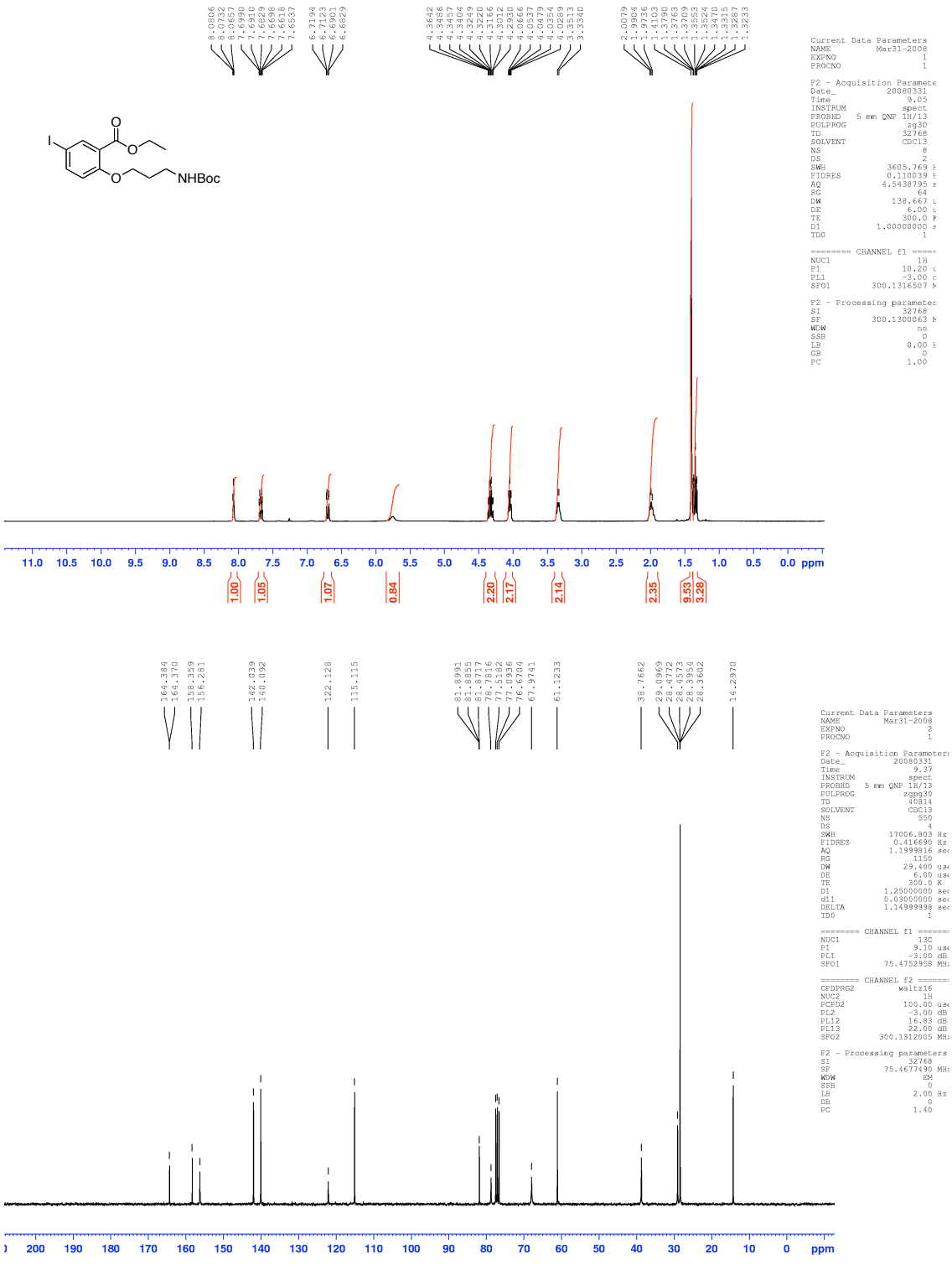
======== CHANNEL f1 ======
NUC1                         13C
P1                         9.10 use
PL1                       -3.00 dB
SFO1               75.4752958 MH

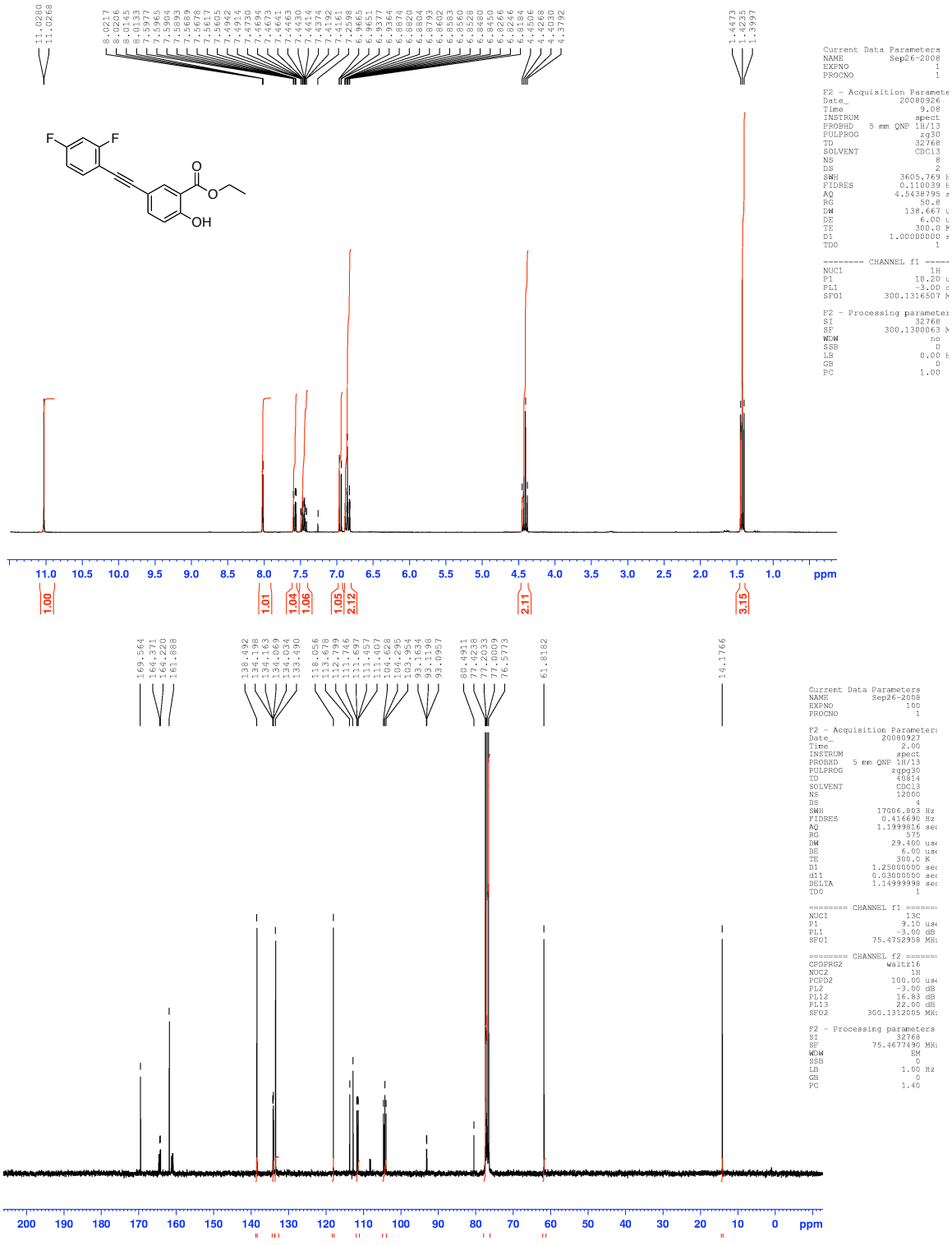
======== CHANNEL f2 ======
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                    100.00 use
PL2                       -3.00 dB
PL12                      16.83 dB
PL13                      22.60 dB
SFO2               300.1312005 MH

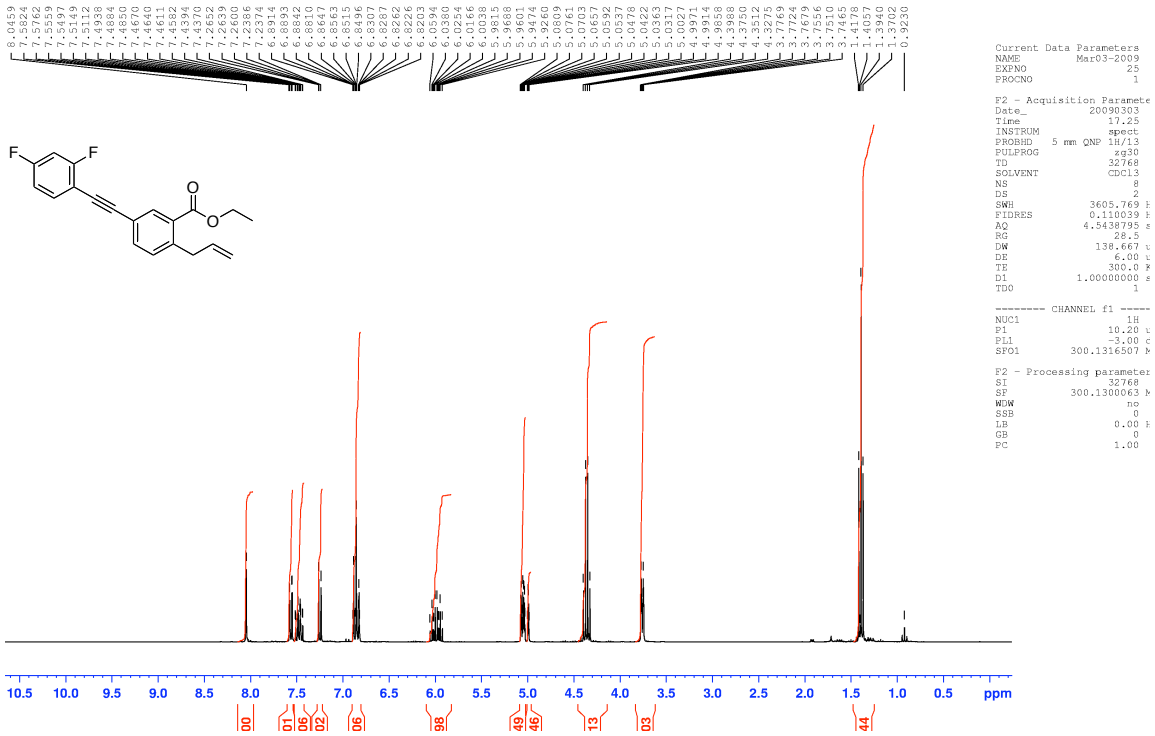
F2 - Processing parameters
SI                        32768
SF                 75.4677490 MH
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

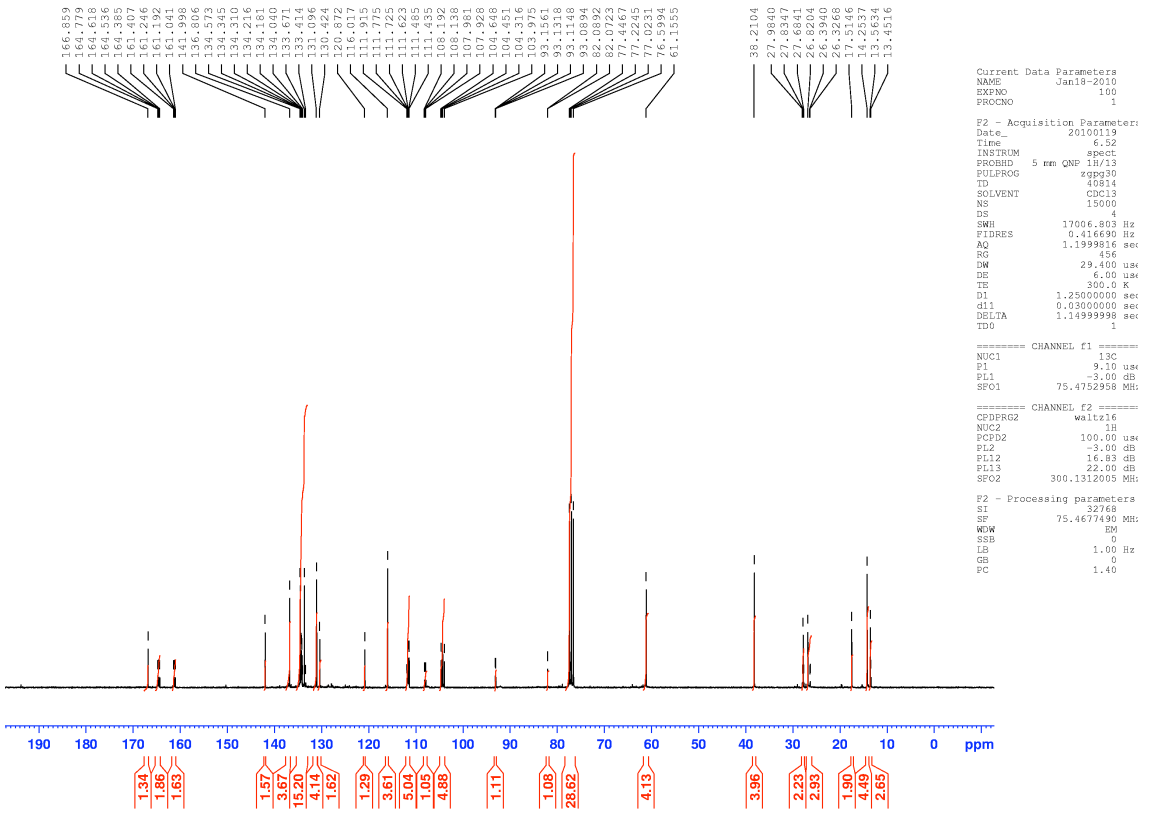

F
F
S
H-N
CO2H
O
N
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 0.94 1.02 1.13 1.16 2.12 1.00 2.00 2.16 2.04 1.92 0.83 1.06 6.01

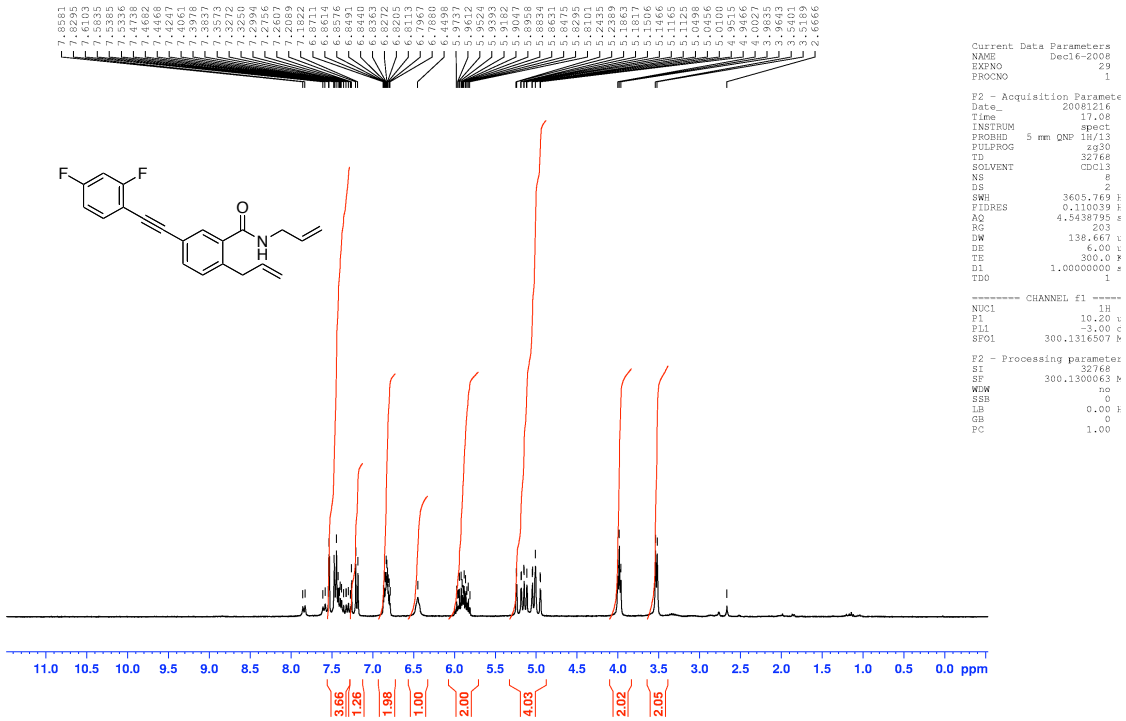

rmb-160-245-02
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

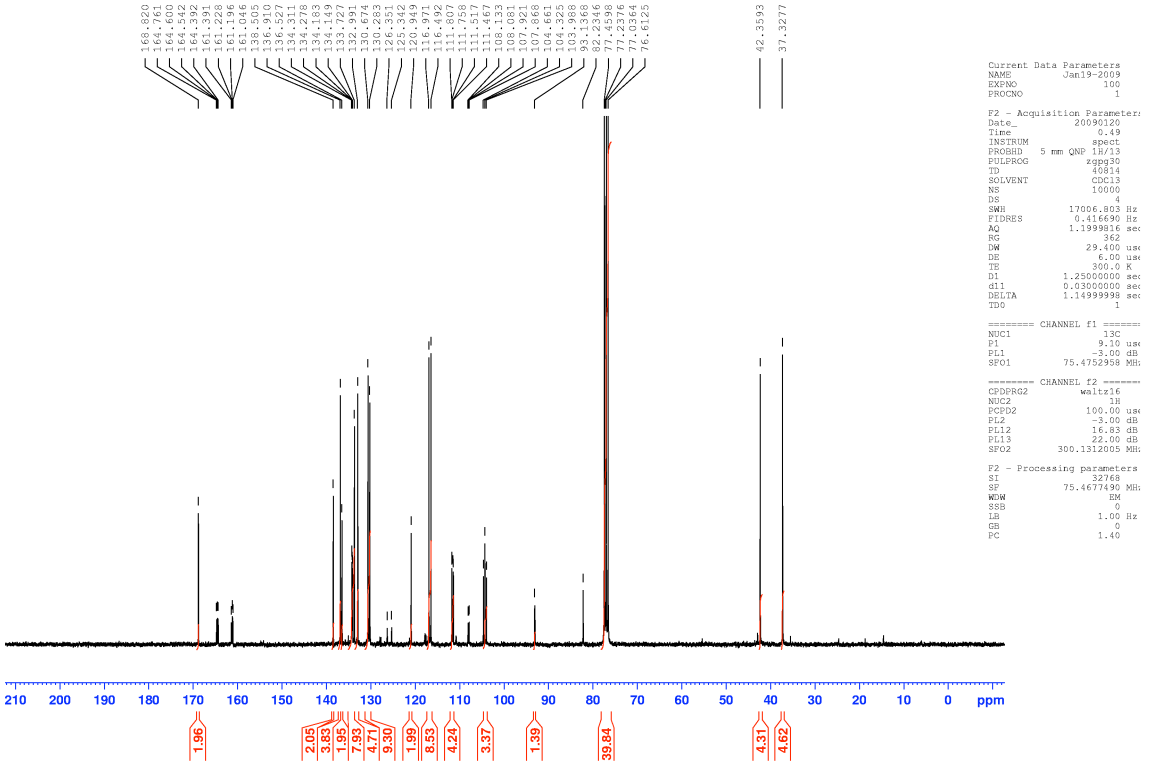


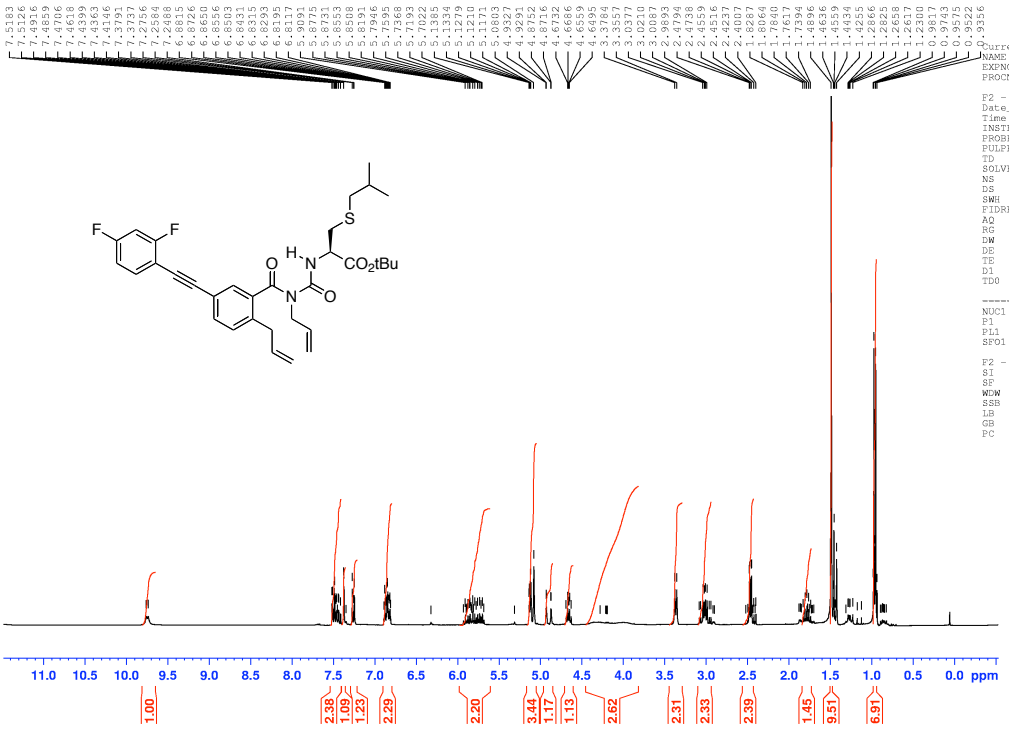

F
F
O
O
OH
ppm
ppm

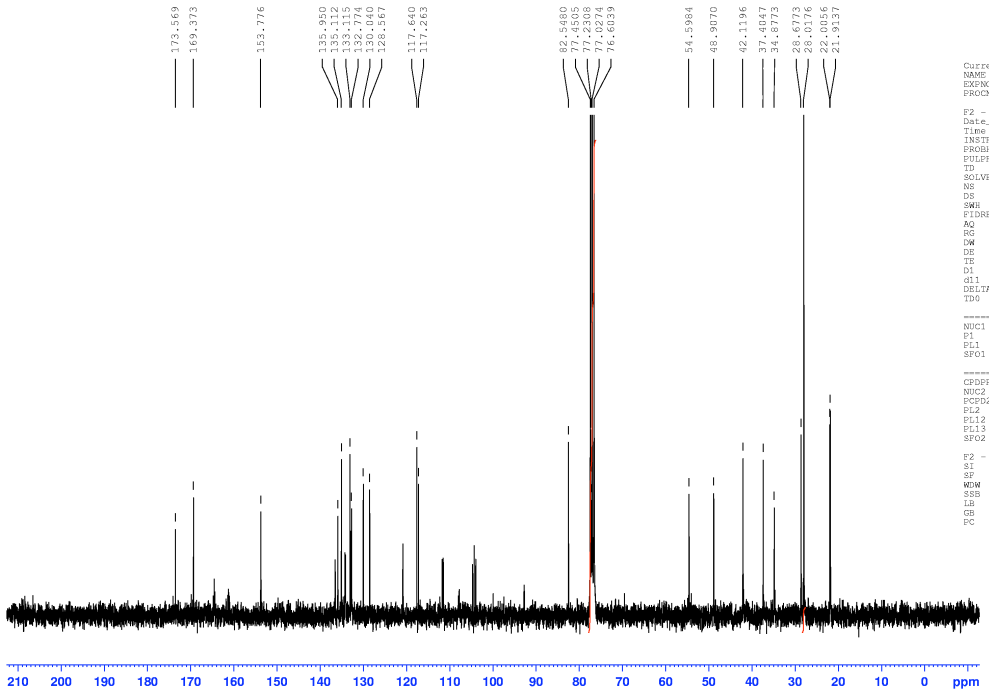

F
F
O
O
Current Data Parameters
NAME Mar03-2009
EXPNO 25
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090303
Time 17.25
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 3605.769 Hz
FIDRES 0.110039 Hz
AQ 4.5438795 sec
RG 28.5
DW 138.667 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.20 usec
PL1 -3.00 dB
SFO1 300.1316507 MHz
F2 - Processing parameters
SI 32768
SF 300.1300063 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
00 01 06 02 06 98 49 46 13 03 44

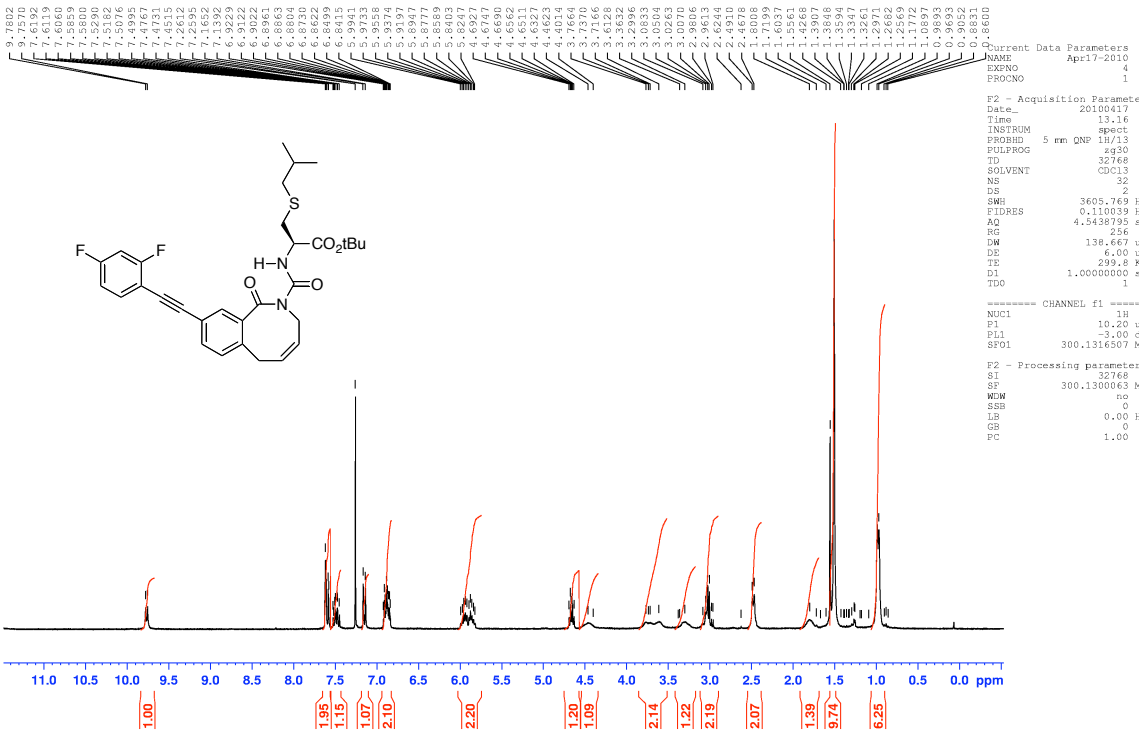

Current Data Parameters
NAME Jan18-2010
EXPNO 100
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100119
Time 6.52
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 40814
SOLVENT CDCl3
NS 15000
DS 4
SWH 17006.803 Hz
FIDRES 0.416690 Hz
AQ 1.1999816 sec
RG 456
DW 29.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.25000000 sec
d11 0.03000000 sec
DELTA 1.14999998 sec
TD0 1
======== CHANNEL f1 ======
NUC1 13C
P1 9.10 usec
PL1 -3.00 dB
SFO1 75.4752958 MHz
======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 16.83 dB
PL13 22.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
1.34 1.86 1.63 1.57 3.67 15.20 4.14 1.62 1.29 3.61 5.04 1.05 4.88 1.11 1.08 28.62 4.13 3.96 2.23 2.93 1.90 4.49 2.65

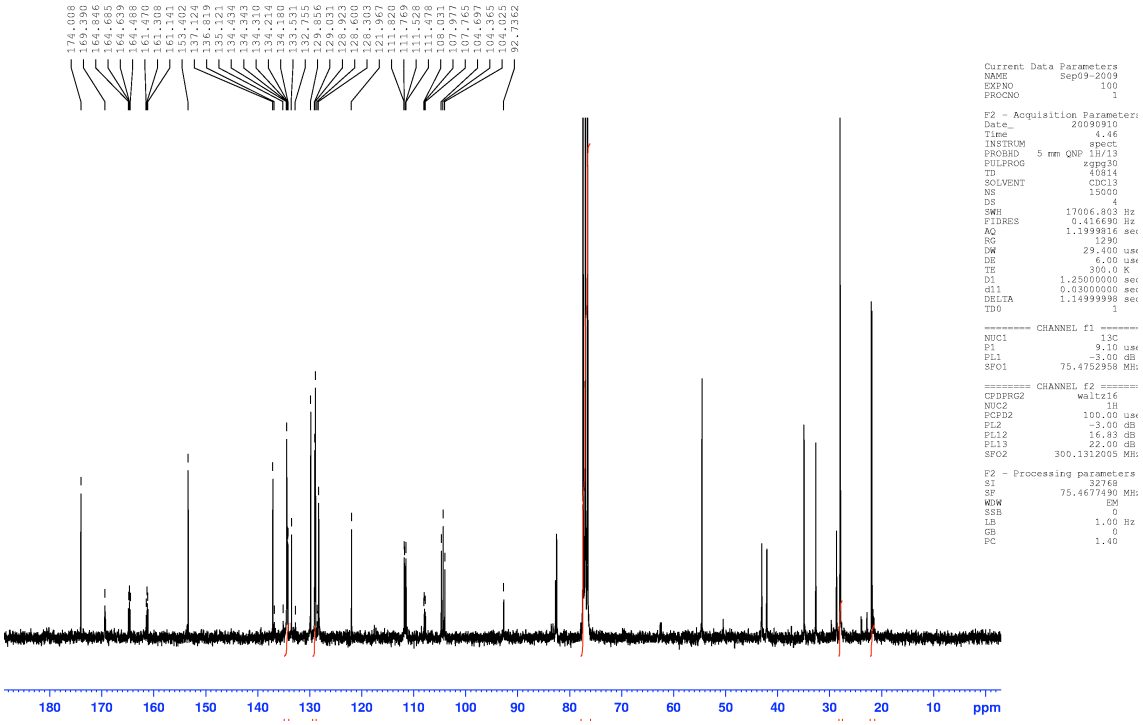


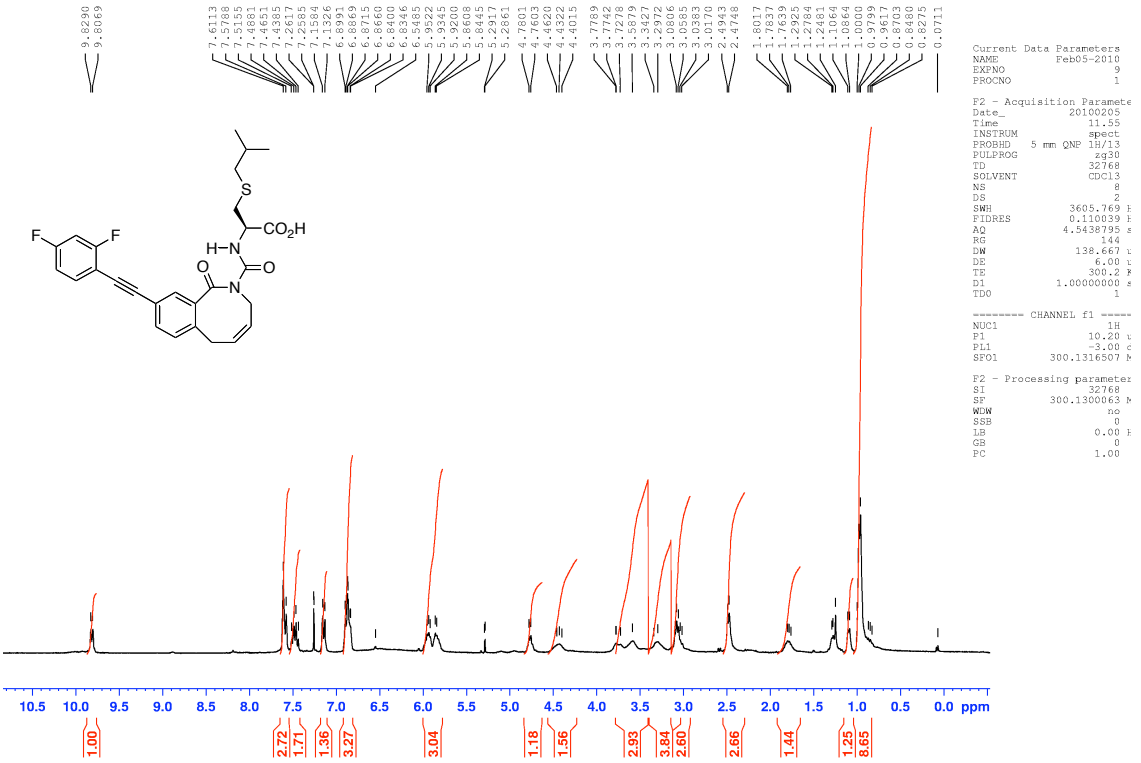


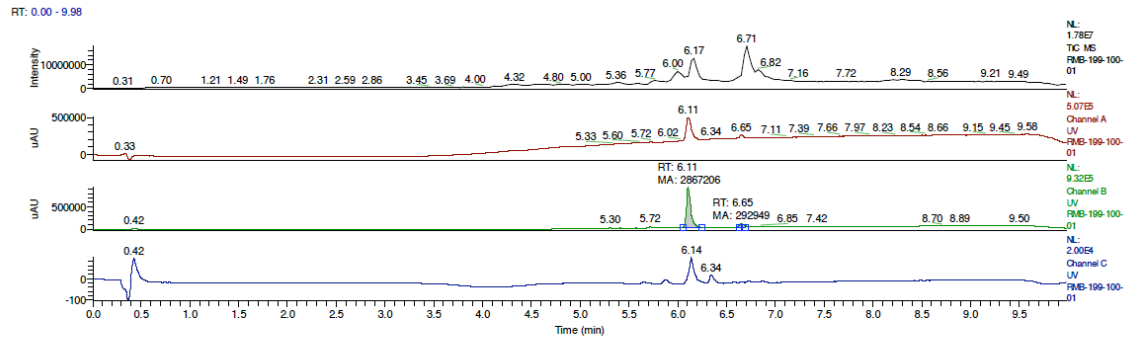


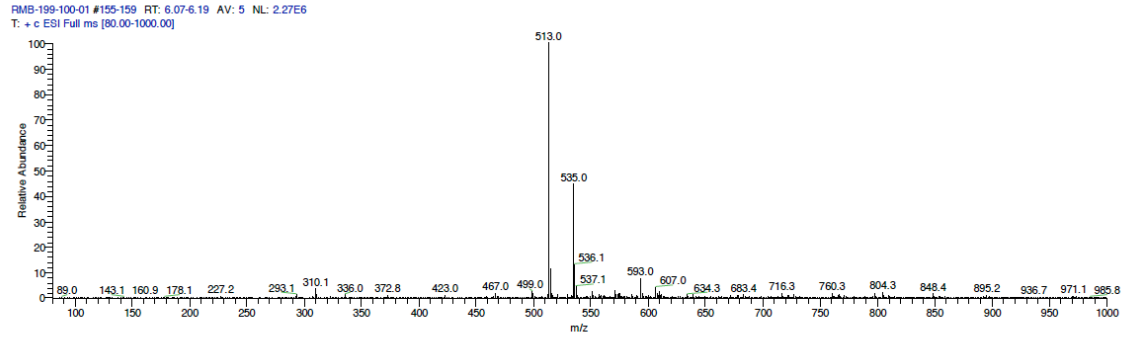



F
F
S
CO2tBu
H–N
O
O
N
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 1.95 1.15 1.07 2.10 2.20 1.20 1.09 2.14 1.22 2.19 2.07 1.39 9.74 6.25

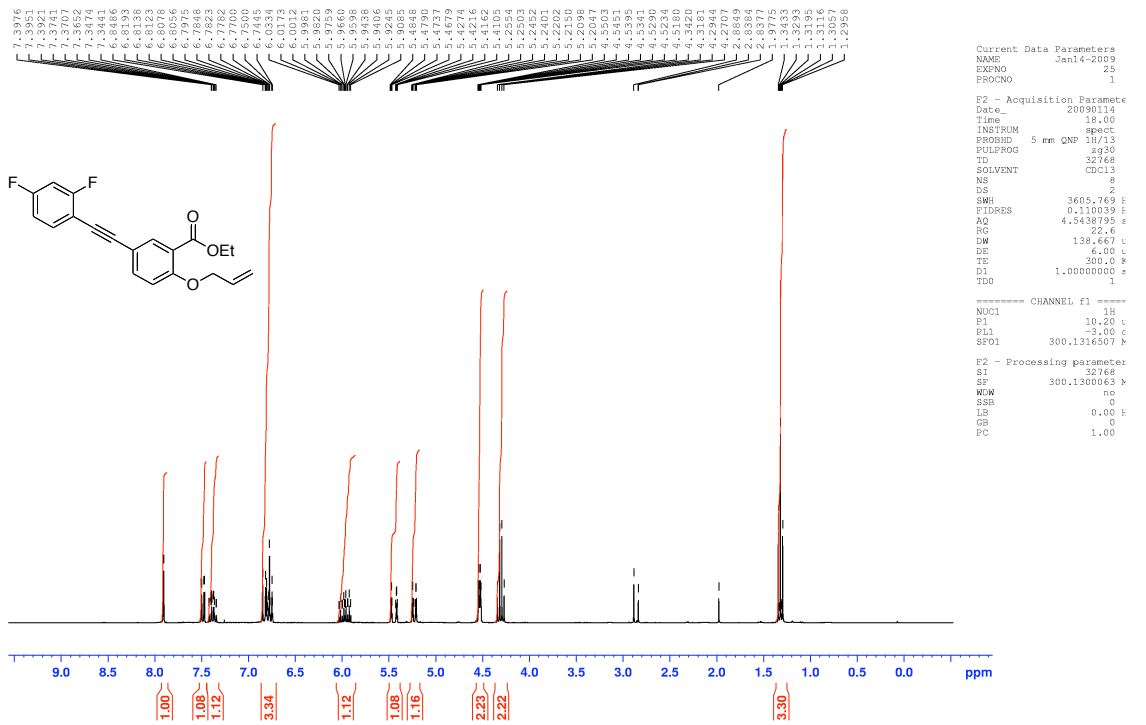

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

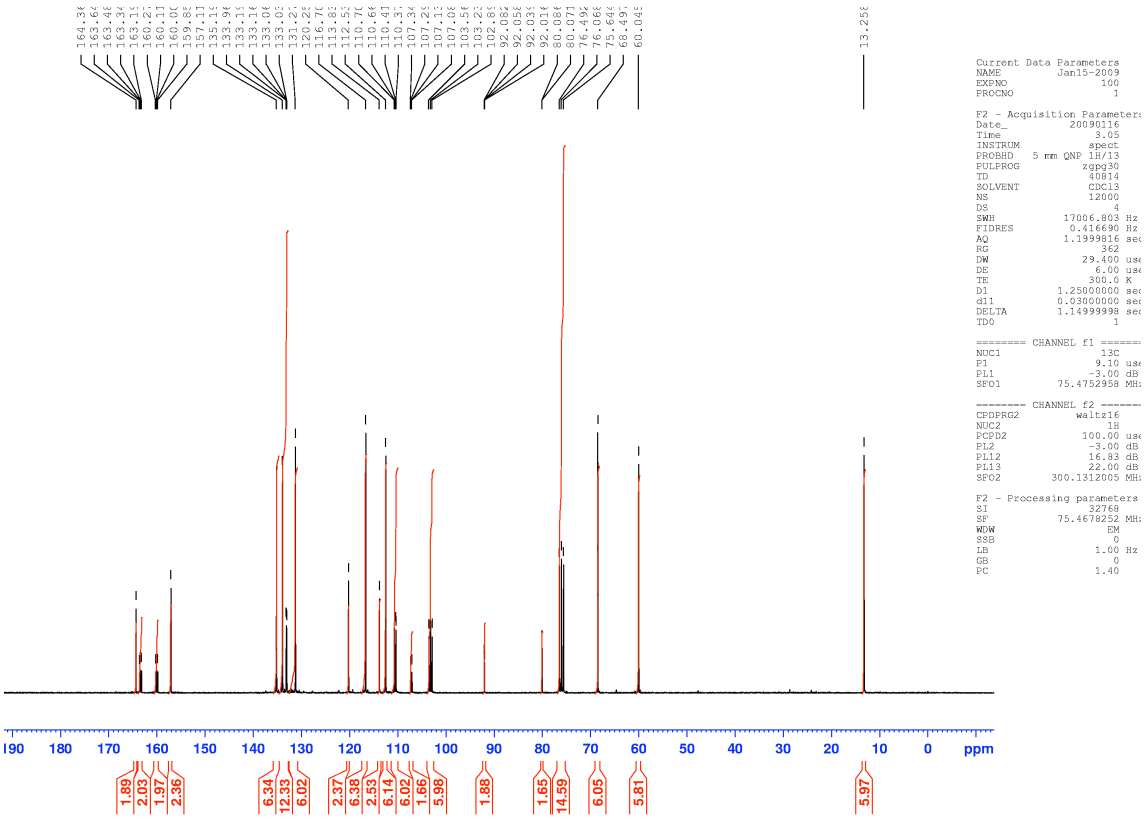






HPLC-RP: (254nm) : 98.0% : rt: 6.11


F
F
O
OEt
O
ppm
1.00
1.08
1.12
3.34
1.12
1.08
1.16
2.23
2.22
3.30


ppm
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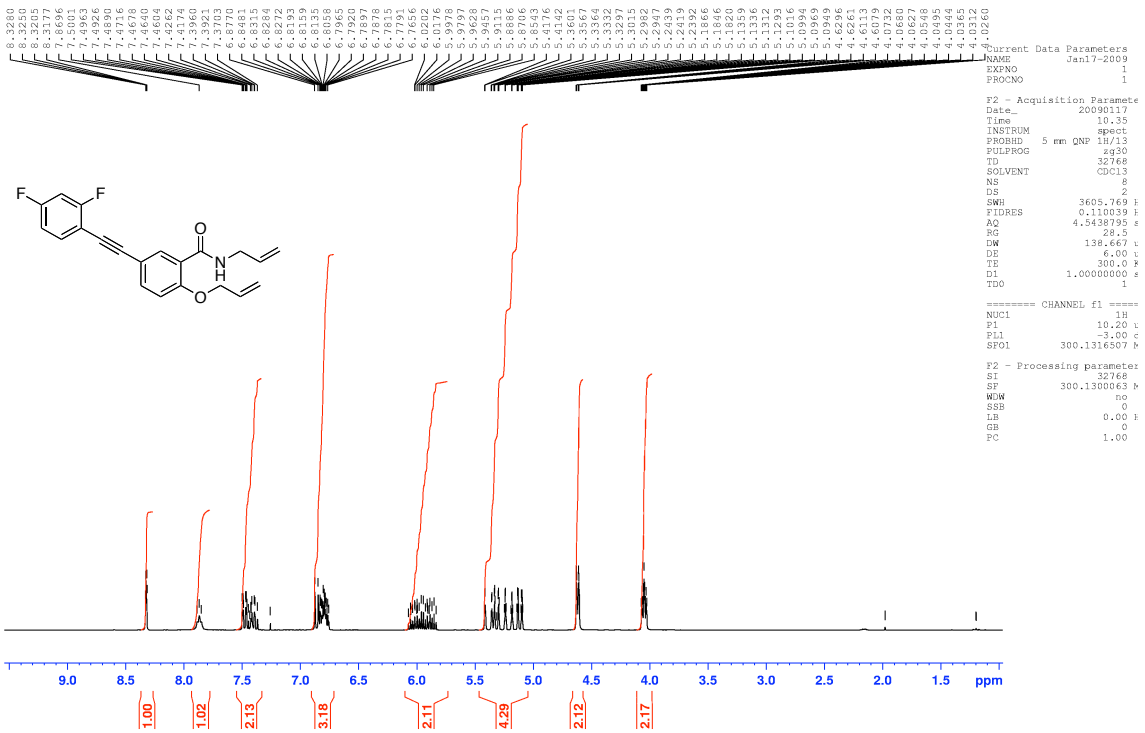
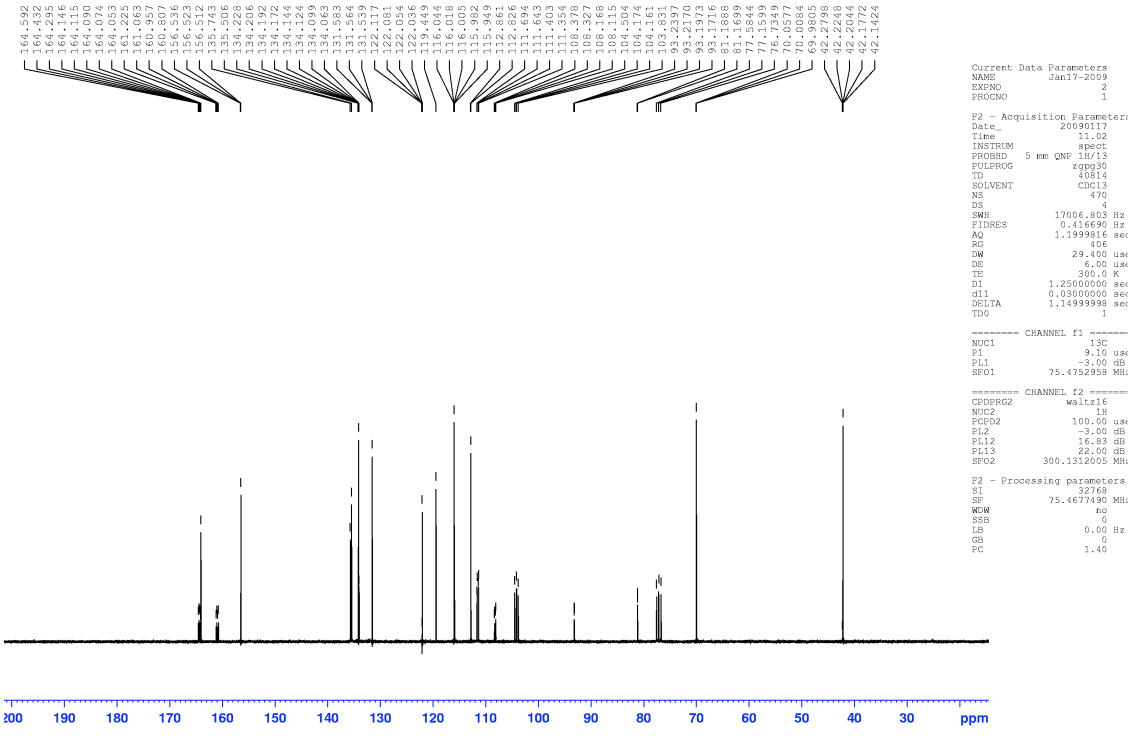
2.03
1.97
2.36
6.34
12.33
6.02
2.37
6.38
2.53
6.14
6.02
1.66
5.98
1.88
1.65
14.59
6.05
5.81
5.97


F
F
O
N
H
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.02
2.13
3.18
2.11
4.29
2.12
2.17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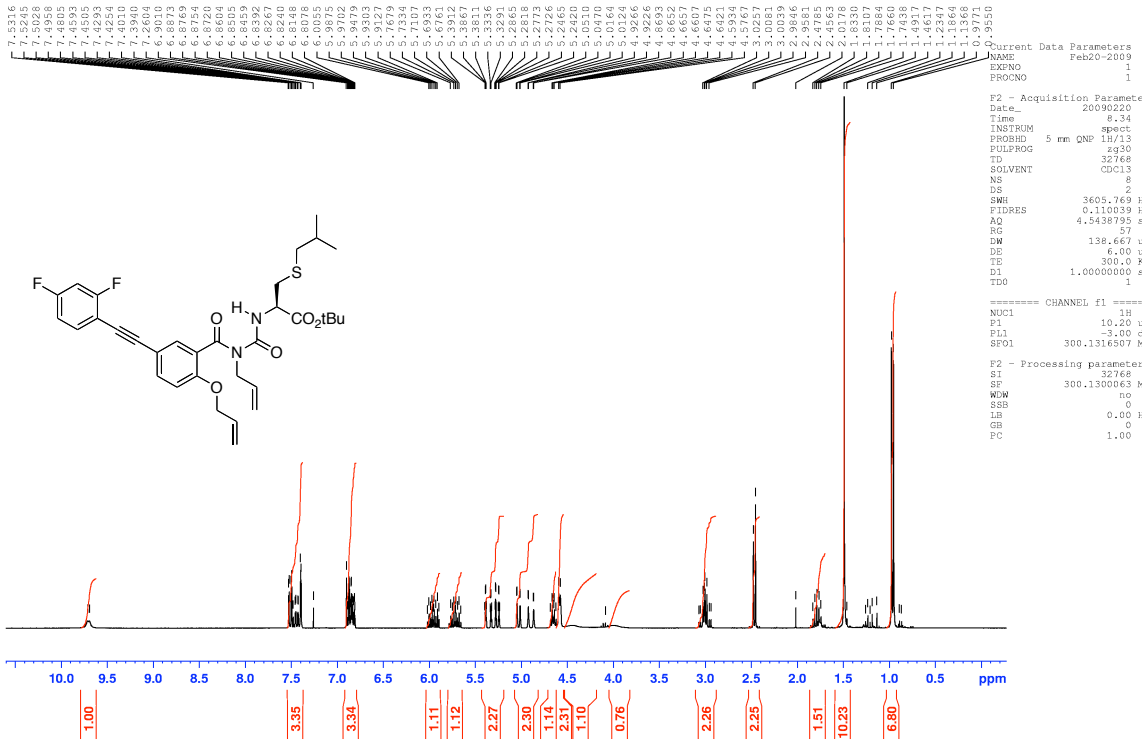
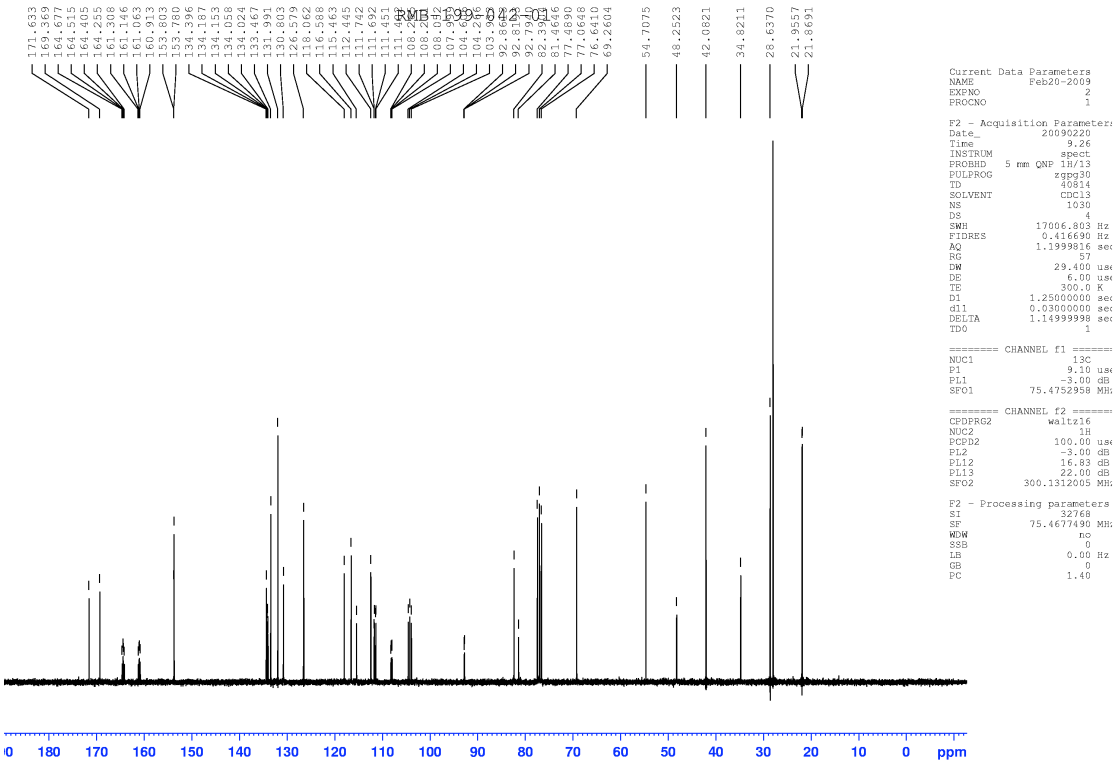
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


F
F
O
H
N
S
CO2tBu
N
O
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 3.35 3.34 1.11 1.12 2.27 2.30 1.14 2.31 1.10 0.76 2.26 2.25 1.51 10.23 6.80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161.146
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160.903
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134.396
134.187
134.153
134.058
134.024
133.467
131.991
130.803
126.579
118.062
116.588
115.463
112.745
112.492
111.692
111.451
111.442
108.212
108.042
108.012
107.950
104.698
104.246
103.965
92.844
92.810
92.794
92.778
82.246
77.466
77.490
77.064
76.641
69.260
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42.082
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28.637
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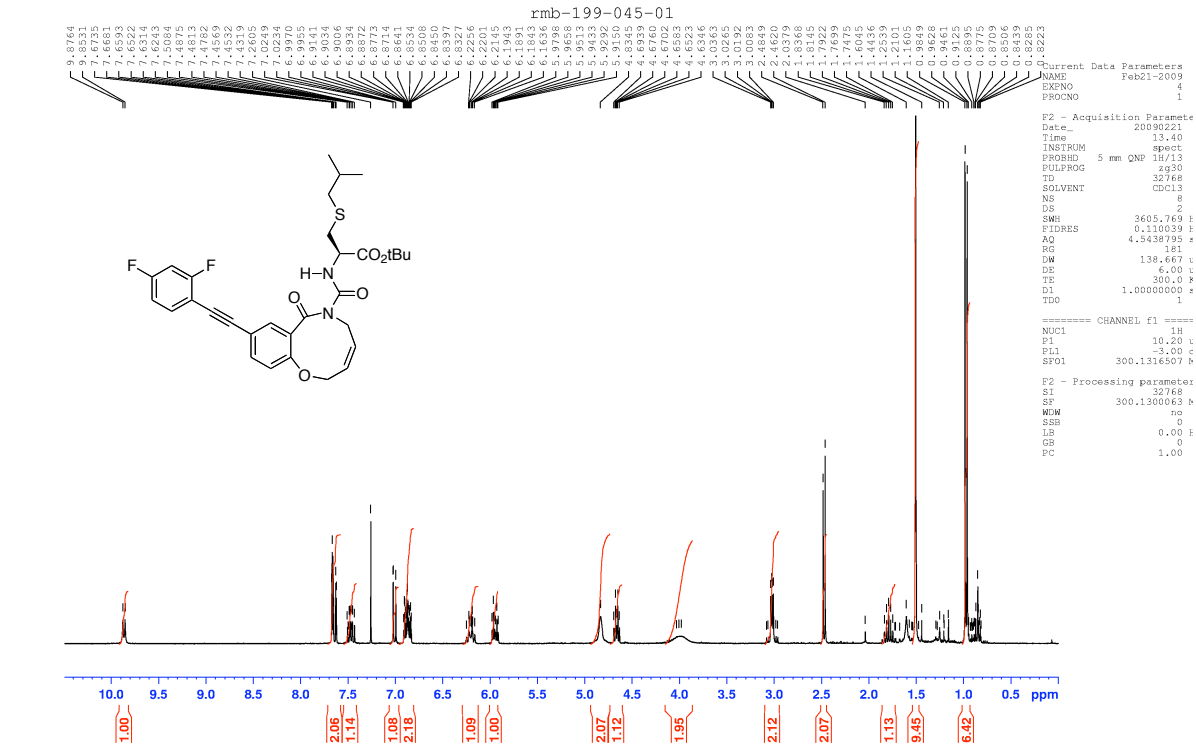
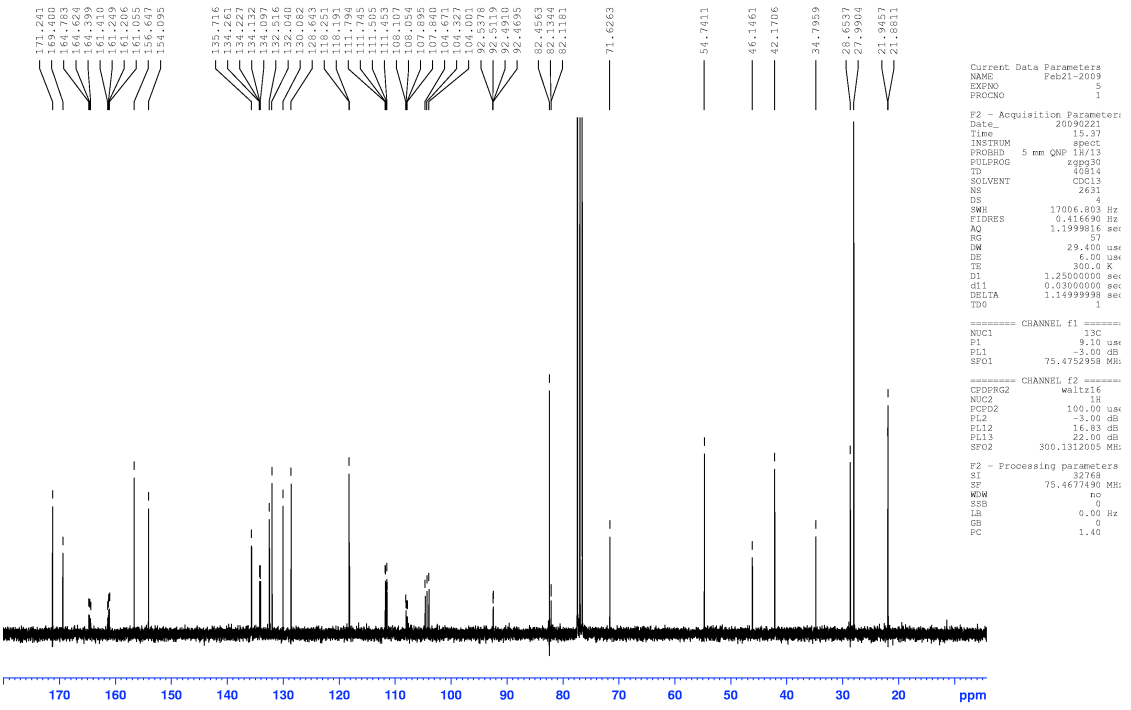
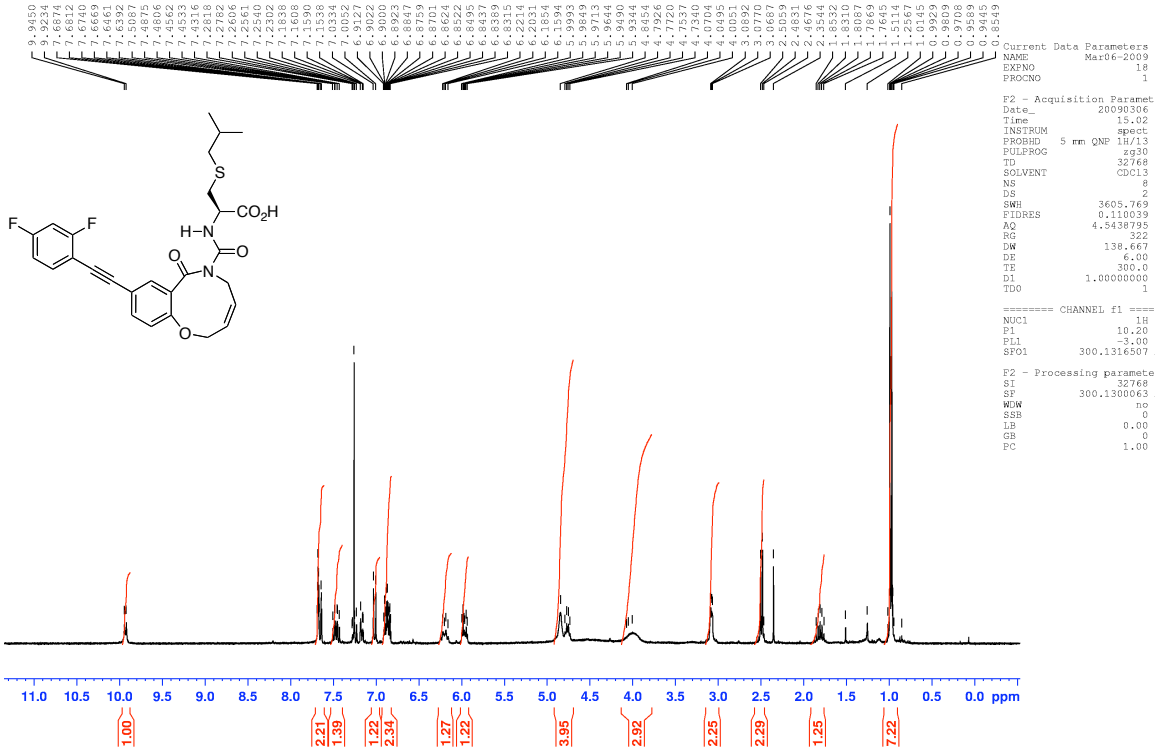
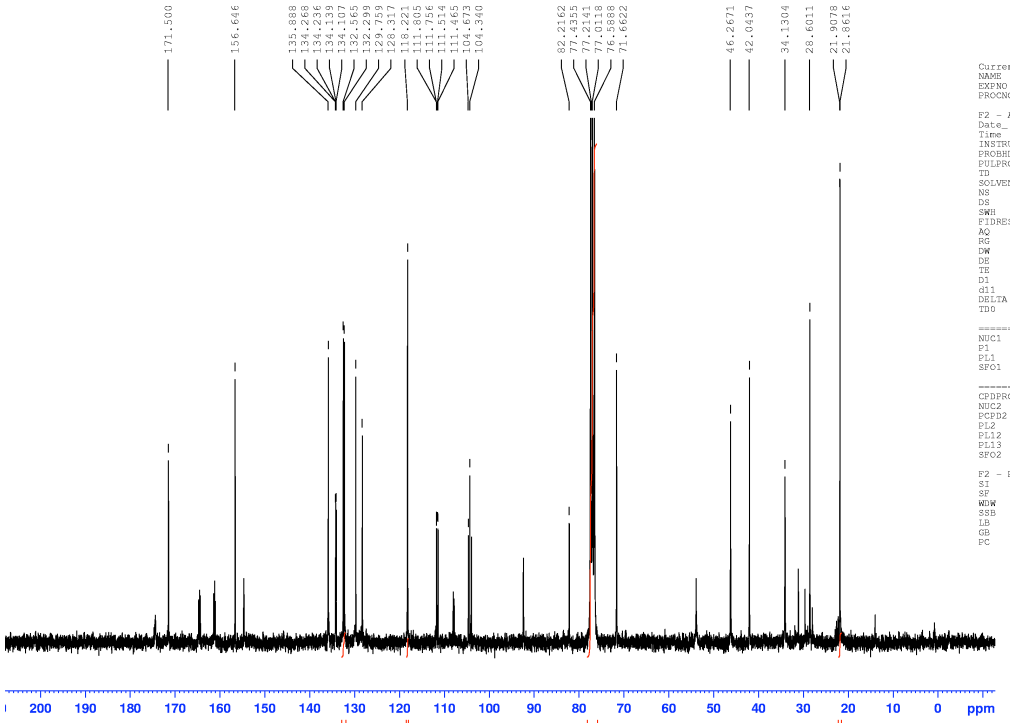
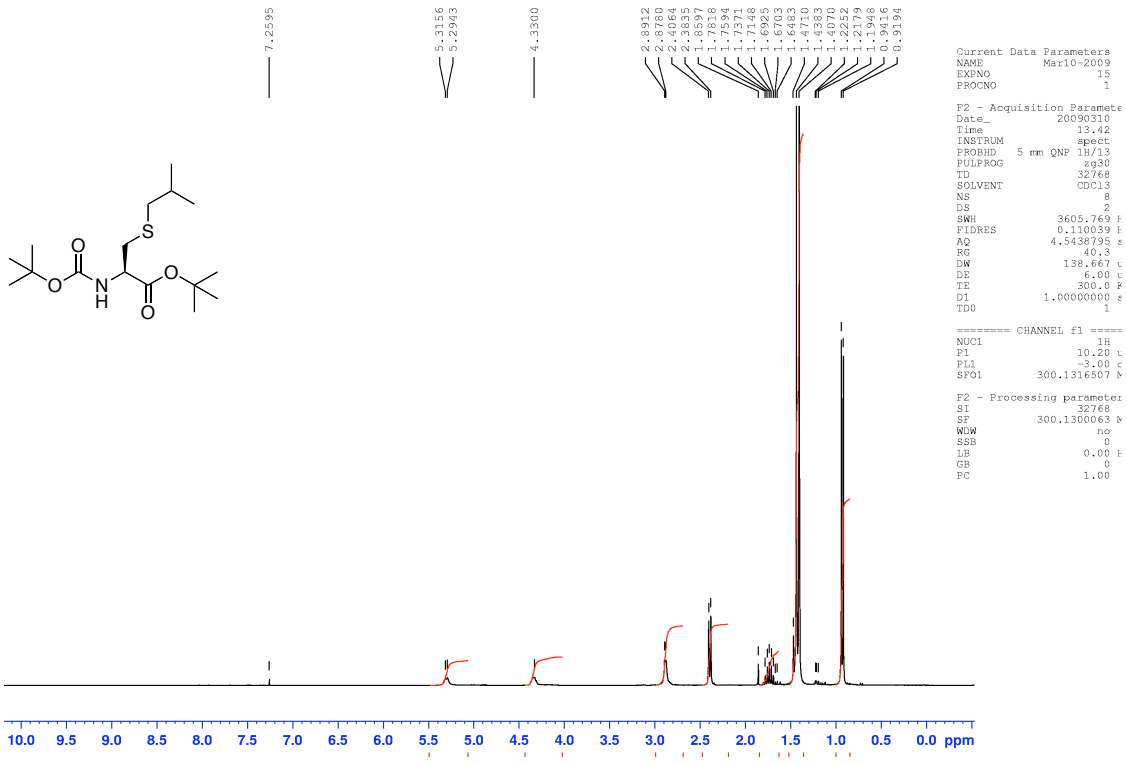
21.869
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

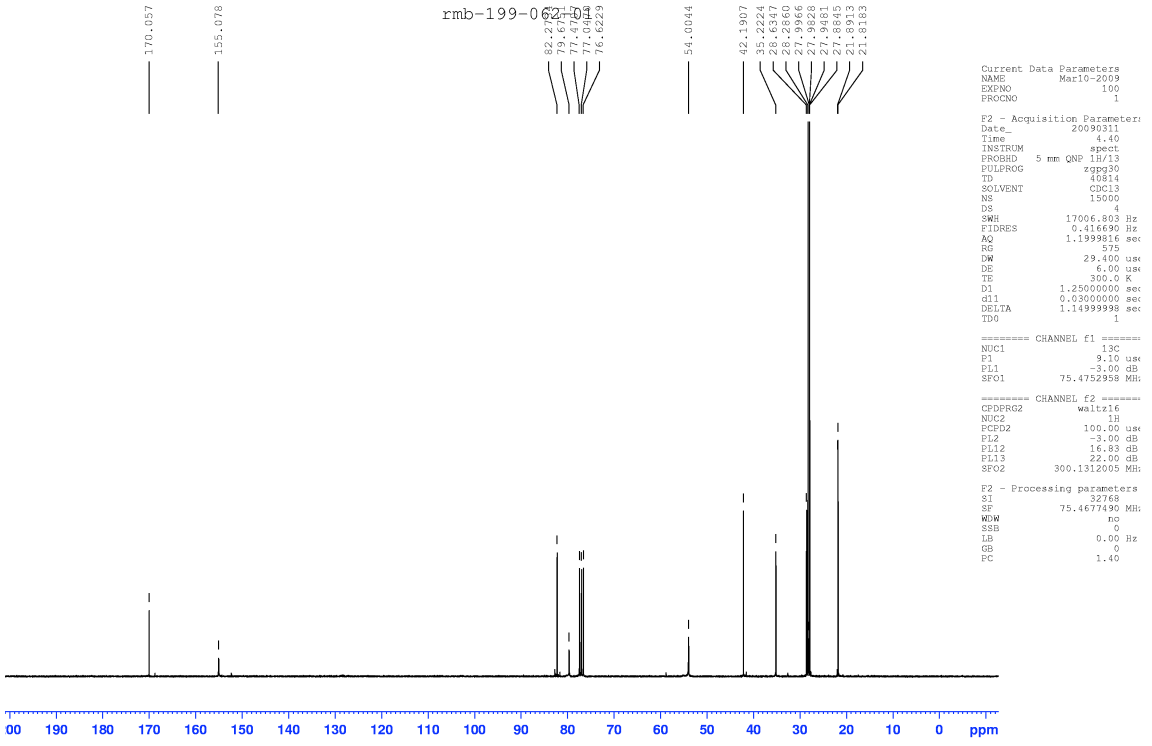


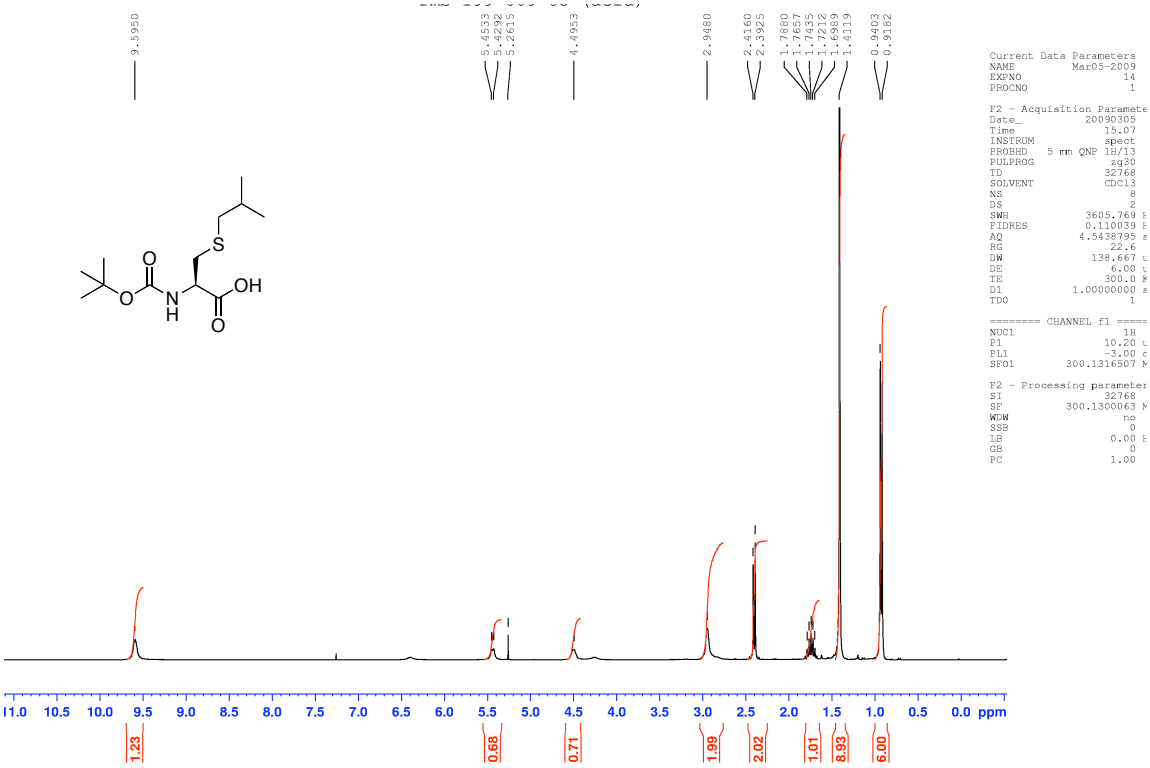


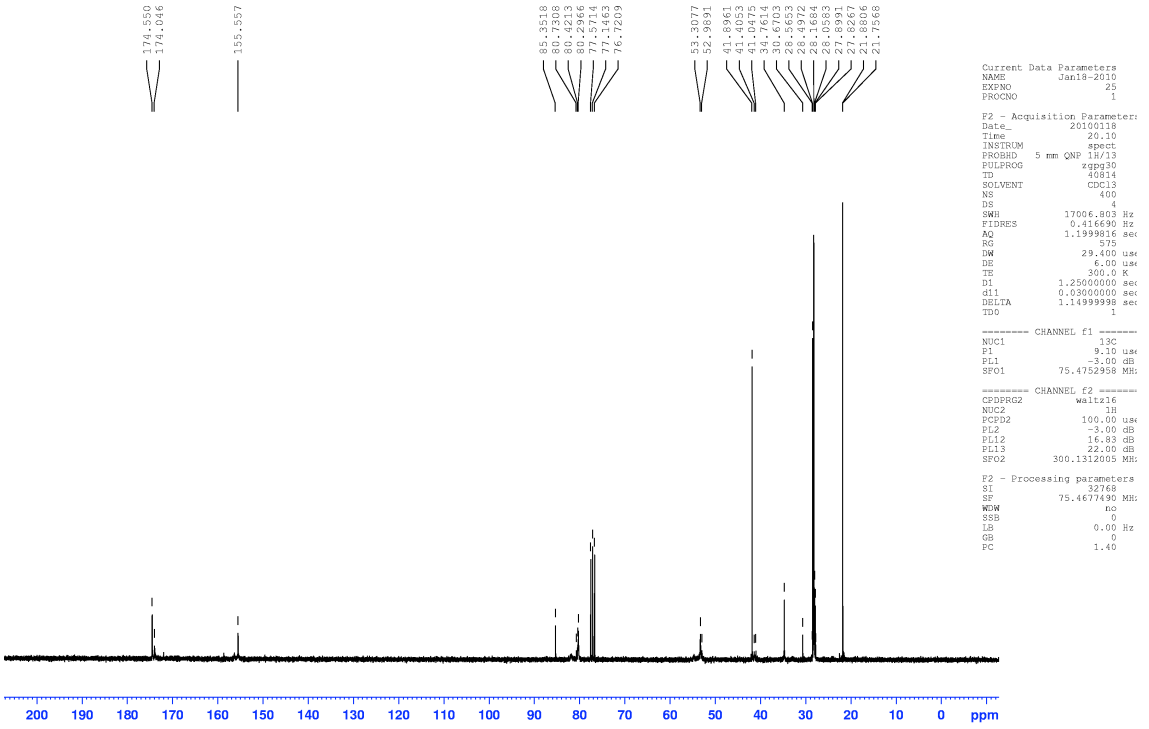


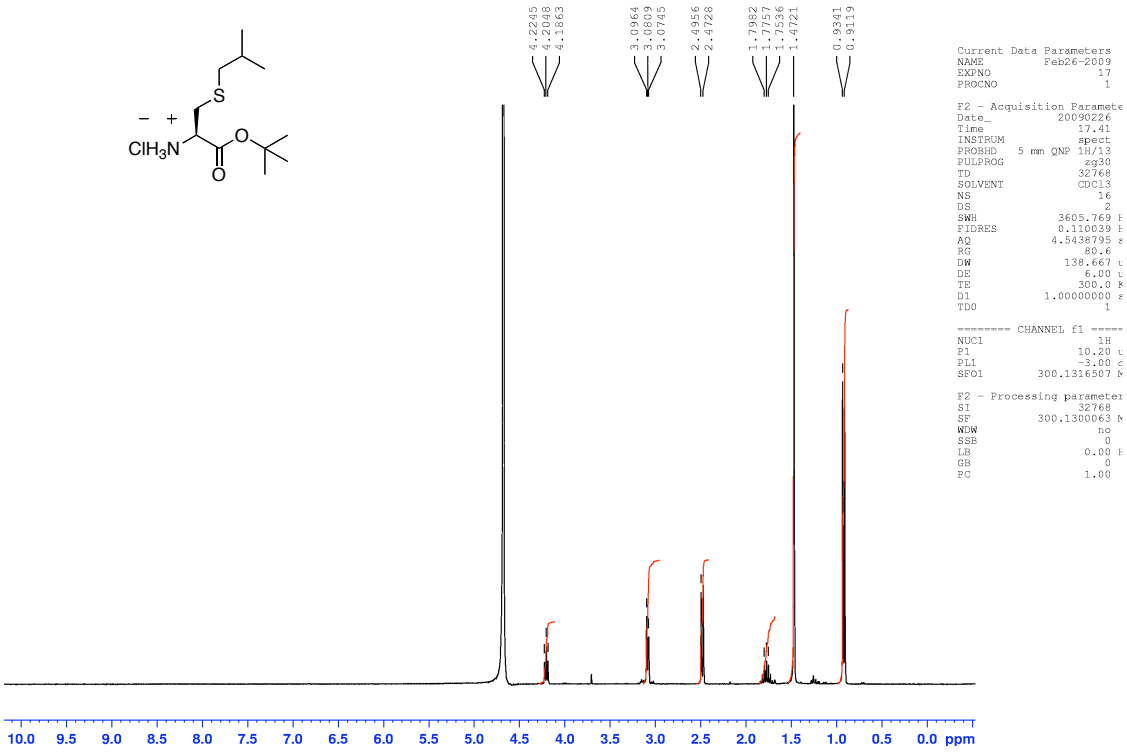


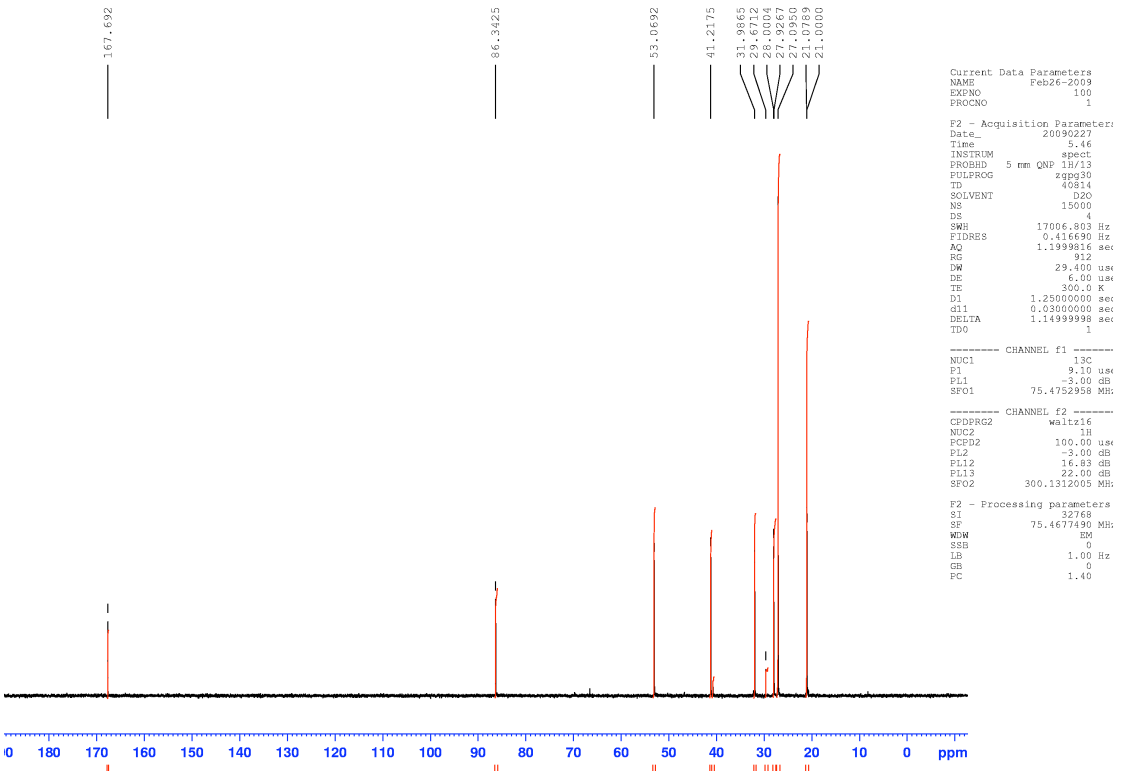












1. H. F. Anwar, L. Skattebol, J. Skramstad and T. V. Hansen, *TETRAHEDRON. LETT.*, 2005, **46**, 5285-5287.
2. K. S. Feldman, K. J. Eastman and G. Lessene, *Organic Letters*, 2002, **4**, 3525-3528.
3. T. Kometani, D. S. Watt and T. Ji, *TETRAHEDRON. LETT.*, 1985, **26**, 2043-2046.