Tandem Achmatowicz-Knoevenagel protocol: Diastereoselective synthesis and anticancer evaluation of cyclopenta[b]pyrane derivatives

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Supporting information

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Experimental Section

All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed graduated vessels. Solvents were dried and purified by conventional methods prior use. Flash column chromatography was performed with Silica gel 60, 0.040-0.063 mm (230-400 mesh). Aluminium backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography. ^{1}H, ^{13}C spectra were recorded on 250 MHz / 63 MHz or 400/ 100.7 MHz spectrometers. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (7.27 ppm, 1H; 77.16 ppm, the middle peak, ^{13}C). Elemental analysis was performed on elemental analyzer. The FD mass spectra were recorded using a mass spectrometer connected to a PDO 11/34 (DEC) computer system. All compounds were determined to be >95% pure by high-performance liquid chromatography (HPLC). Purity of compounds

were determined on a Phenomenex Luna C18- (2), 3 mm column, 4.6 mm i.d.× 30 mm length, with 30-75% acetonitrile/water/0.1% trifluoroacetic acid, 1.0 mL/min elution at rt using 210, 254, or 280 nm wavelength.

General procedure of the synthesis of compounds 5a and 5b. A suspension of NaH (174 mg, 4.4 mmol, 65% dispersion in mineral oil) in 10 mL of THF at 0 °C was cautiously treated with *tert*-butyl acetoacetate (0.66 mL, 4 mmol) under argon over a 15 min period. After stirring at this temperature for 30 min, a solution of *n*-BuLi (2.75 mL, 4.4 mmol, 1.6 M in *n*-hexane) was added dropwise over 10 min. The mixture was stirred at 0 °C for 30 min. The resultant milky solution was cooled to -78 °C then 4 mmoles of either furfural (384 m) or 2-acetylfuran (440 mg) in 10 ml of THF was added. The reaction was then stirred at the same tempreture for 1 h, after which the mixture was quenched with a saturated solution of NH_4Cl (15 mL), extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4 and concentrated under vacuum to give a yellowish crude oil. The crude was purified through a short silica gel column using hexane/ EtOAc (9:1) as eluent to afford compounds **5a** (917 mg, 95% yield) and **5b** (977 mg, 91% yield) as a yellowish oils.

***tert*-Butyl 5-(2-furyl)-5-hydroxy-3-oxopentanoate** (**5a**). ^{1}H NMR (250 MHz, $CDCl^3$) δ 7.31 (dd, *J* = 0.8, 1.8 Hz, 1H, H-5'), 6.30 (dd, *J* = 1.8, 3.2 Hz, 1H, H-4'), 6.22 (d, *J* = 3.2 Hz, 1H, H-3'), 5.13 (dd, *J* = 3.3, 8.3 Hz, 1H, H-5), 3.37 (s, 2H, H-2a, H-2b), 3.10 (dd, *J* = 8.3, 17.5 Hz, 1H, H-4a), 2.97 (dd, *J* = 3.3, 17.5 Hz, 1H, H-4b), 1.39 ($CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 202.7 (C-2), 166.1 ($CO_2C(CH_3)_3$), 154.8 (C-2'), 110.3 (C-5'), 110.2 (C-4'), 106.3 (C-3'), 82.3 ($CO_2C(CH_3)_3$), 63.5 (C-5), 51.1 (C-2), 47.8 (C-4), 27.9 ($CO_2C(CH_3)_3$); FD-MS m/z = 255 $(M + 1)^+$, Anal. Calcd for $C_{13}H_{18}O_5$ (254.28); C, 61.40; H, 7.14. Found: C, 61.20; H, 7.31.

***tert*-Butyl 5-(2-furyl)-5-hydroxy-3-oxohexanoate** (**5b**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 0.9, 1.8 Hz, 1H, H-5'), 6.02 (dd, *J* = 1.8, 3.2 Hz, 1H-4'), 6.15 (dd, *J* = 0.9, 3.3 Hz, 1H, H-3'), 3.25 (bs, 2H, H-2a, H-2b), 3.18 (d, *J* = 16.5 Hz, 1H, H-4a), 2.82 (d, *J* = 16.5 Hz, 1H, H-4b), 1.43 (CH_3), 1.63 ($CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, CDCl3) δ 203.0 (C-3), 165.0 ($CO_2C(CH_3)_3$), 158.5 (C-2'), 110.3 (C-5'),

110.2 (C-4'), 104.7 (C = 3'), 82.0 ($CO_2C(CH_3)_3$), 70.0 (C-5), 51.7 (C-2), 51.5 (C-4), 28.2 ($CO_2C(CH_3)_3$), 27.6 (CH_3); FD-MS m/z = 269 $(M + 1)^+$, Anal. Calcd for $C_{14}H_{20}O_5$ (268.31); C, 62.67; H, 7.51. Found: C, 62.51; H, 7.42.

General procedure for the synthesis of compounds 7a and 7b. A solution of **5a** (1270 mg, 5 mmol) or **5b** (1341.5 mg, 5 mmol) in dicholomethane (40 mL) at 0 °C was treated with *m*-chloroperbenzoic acid (1376 mg, 8.0 mmol of 80% aqueous slurry) which was dissolved in 30 ml DCM, dried over Na_2SO_4, filtered, diluted with 50 ml toluene and dried under reduced pressure) and stirred at 0 °C for 6 h. Sodium sulfite solution (30 mL of 10%) was introduced, and the layers were separated after 1 h of rapid mixing. The aqueous phase was washed with saturated sodium bicarbonate solution (30 mL), brine and water (30 mL) prior to drying and solvent evaporation. The crude viscous yellowish oils (**6a** and **6b**) was used in the next step without further purification.

A solution of the crude anomeric mixture of **6a** (852 mg, 3 mmol) or **6b** (810 mg, 3 mmol) in dry toluene (30 ml), freshly prepared piperidinium acetate (3.9 mmol) and 4 °A molecular sieves (250 mg) was stirred at 50 °C for 4 h. The hot mixture was filtered and evaporated under reduced pressure. The brown viscous oil was dissolved in EtOAc and extracted with saturated solution of $NaHCO_3$, brine, water and dried over Na_2SO_4. The crude was purified on a silica gel column using hexane/ EtOAc (7:3) as eluent to afford compounds **7a** (350 mg, 68% yield) and **7b** (425 mg, 73% yield) as amorphous solids.

***tert*-Butyl (7a*S*)-2-hydroxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5-carboxylate** (**7a**). ^{1}H NMR (250 MHz, CDCl3) δ 7.25 (bt, *J* = 10.1 Hz, 1H, H-3), 6.42 (dd, *J* = 3.3, 10.1 Hz, 1H, H-4), 5.60 (bs, 1H, H-2), 5.16 (dd, *J* = 4.7, 6.8 Hz, 1H, H-7a), 2.84 (dd, *J* = 6.8, 17.6 Hz, 1H, H-7), 2.51 (dd, *J* = 4.6, 17.6 Hz, 1H, H-7'), 15.3 (s, 9H, ^{t}BuO); ^{13}C NMR (63 MHz, $CDCl_3$) δ 199.1, 199.2 (C-6), 170.5, 170.7 (C-4a), 166.2 ($CO_2C(CH_3)_3$), 142, 138.2 (C-3), 125.0, 123.0 (C-4), 92.7, 89.1 (C-2), 82.0, 71.5 ($CO_2C(CH_3)_3$), 65.5 (C-7a), 42.5, 42.3 (C-7), 28.2 ($CO_2C(CH_3)_3$); FD-MS m/z = 252 (M)+, Anal. Calcd for $C_{13}H_{16}O_5$ (252.10); C, 61.90; H, 6.39. Found: C, 61.85; H, 6.43.

***tert*-Butyl (7a*S*)-2-hydroxy-7a-methyl-6-oxo-2,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5-carboxylate** (**7b**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.13 (m, 2H, H-3), 6.32 (m, 2H, H-4), 5.59, 5.51 (bs, 2H, H-2), 2.57 (m, 4H, H-7,7'), 1.42 (bs, 12H, CH_3-7a, $CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 198.8, 198.5 (C-6), 170.5, 170.4 (C-4a), 161.1 ($CO_2C(CH_3)_3$), 141.5, 138.5 (C-3), 125.7, 125.3 (C-5), 122.5, 121.3 (C=4), 89.6, 88.7 (C-2), 82.5 ($CO_2C(CH_3)_3$),77.5, 73.9 (C-7a) 52.2, 51.9 (C-7), 28.9, 24.2 (CH_3 = 7a), 28.1, 27.8 ($CO_2C(CH_3)_3$); FD-MS m/z = 266 (M)+, Anal. Calcd for $C_{13}H_{16}O_5$ (266.12); C, 63.15; H, 6.81. Found: C, 63.09; H, 6.87.

General procedure for the synthesis of compounds 8a, 8b and 9. A solution of the anomeric mixture of **7a** (756 mg, 3 mmol) or **7b** (798 mg, 3 mmol) in MeI (15 mL) at rt was treated with 3.0 mmol of Ag_2O. The progress of reaction was monitored by TLC (12 h). When complete, the reaction mixture was filtered over celite. The filtrate was washed with saturated solutions of sodium sulfite, sodium bicarbonate, brine, dried and evaporated. The residue was purified on silica gel column using hexane/EtOAc (9:1) as an eluent.

***tert*-Butyl (2*S*,7a*S*)-2-methoxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5-carboxylate** (**8a**). Yiel: 540 mg, 80%; Significant NMR NOEs are 2-H to 7a-H, 36%; 7a-H to 2-H, 32%. ^{1}H NMR (250 MHz, CDCl3) δ 7.20 (dd, *J* = 0.4, 10.1 Hz, 1H, H-3), 6.30 (dd, *J* = 3.3, 10.1 Hz, 1H, H-4), 5.00 (dd, *J* = 3.3 Hz , 1H, H-2), 4.96 (dd, *J* = 4.8, 6.9 Hz, 1H, H-7a), 3.45 (s, 3H, OMe),2.80 (dd, *J* = 7.0, 17.6 Hz, 1H, H-7), 2.48 (dd, *J* = 4.5, 17.6 Hz, 1H, H-7'), 1.48 (s, 9H, ^{t}BuO); ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.8 (C-6), 166.1 (C-4a), 160.8 ($CO_2C(CH_3)_3$), 137.2 (C-3), 123.0 (C-4), 127.0 (C-5), 95.6 (C-2), 82.5 ($CO_2C(CH_3)_3$), 65.5 (C-7a), 56.4 (OMe), 42.3 (C-7), 28.0 ($CO_2C(CH_3)_3$); FD-MS m/z = 266 (M)+, Anal. Calcd for $C_{14}H_{18}O_5$ (266.16); C 63.12, H 6.82. Found: C 63.51, H 6.55.

***tert*-Butyl (2*S*,7a*S*)-2-methoxy-7a-methyl-6-oxo-2,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5-carboxylate** (**8b**). Yiel: 742 mg, 94%; Significant NMR NOEs are 2-H to 7a-CH_3, 31%; 7a-CH_3 to 2-H, 33%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 1.7, 10.0 Hz, 1H, H-3), 6.62 (dd, *J* = 1.6, 10.0 Hz, 1H, H-4), 5.10 (bd, *J* = 3.1 Hz, 1H, H-2), 3.44 (s, 3H, OMe), 2.74 (d, *J* = 17.1 Hz, 1H, H-7), 2.57 (d, *J* = 17.1 Hz, 1H, H-7'), 1.48 (s, 3H, 7a-CH_3), 1.47 (s, 9H, ($CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.7 (C-6), 169.4 (C-4a), 160.9

($CO_2C(CH_3)_3$), 139.0 (C-2), 123.8 (C-3), 123.7 (C-5), 95.6 (C-2), 82.3 ($CO_2C(CH_3)_3$), 76.7 (C-7a), 55.1 (OMe), 52.1 (C-7), 28.2 ($CO_2C(CH_3)_3$), 24.3 (7a-CH_3); FD-MS m/z =280 $(M)^+$, Anal. Calcd for $C_{15}H_{20}O_5$ (280.32); C 64.27, H 7.19; Found: C 63.95, H 7.32.

***tert*-Butyl (2*R*,7a*S*)-2-methoxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5-carboxylate** (**9**). Yield: 138 mg, 20%; Significant NMR NOEs are 2-OMe to 7a-H, 37%; 7a-H to 2-OMe, 29%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 2.1, 10.1 Hz, 1H, H-3), 6.32 (dd, *J* = 1.4, 10.1 Hz, 1H, H-4), 5.34 (dd, *J* = 0.6, 2.0 Hz, 1H, H-2), 4.74 (dd, *J* = 4.7, 6.9 Hz, 1H, H-7a), 3.47 (s, 3H, OMe), 2.83 (dd, *J* = 6.8, 17.7 Hz, 1H, H-7), 2.55 (dd, *J* = 4.6, 17.7 Hz, 1H, H-7'), 1.47 (s, 9H, ($CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.5 ($CO_2C(CH_3)_3$), 169.7 (C-4a), 141.6 (C-3), 124.8 (C-4), 98.7 (C-2), 82.0 ($CO_2C(CH_3)_3$), 71.4 (C-7a), 56.0 (OMe), 42.6 (C-7), 28.2 ($CO_2C(CH_3)_3$); FD-MS m/z = 266 (M)+, Anal. Calcd for $C_{14}H_{18}O_5$ (266.12); C 63.15, H 6.81; Found: C 62.98, H 7.11.

***tert*-Butyl (2*S*,4a*S*,5*R*,7a*S*)-2-methoxy-7a-methyl-6-oxooctahydrocyclopenta[*b*]pyran-5-carboxylate** (**10**). To a stirred solution of **8b** (560 mg**,** 2.0 mmol) in dry EtOAc/MeOH (1:1, 20 mL) was added Pd/C (56 mg, 15% Pd/C w/w). The mixture was placed under 1.0 atm of H_2 pressure, and the progress of reaction was monitored by TLC. After 2 h, the solid was removed by filtration through a celite pad, which was washed repeatedly with EtOAc. After concentration of the filtrate, the residue was purified on silica gel column (elution with 5% ethyl acetate in hexane) to give **10** as amorphous solid (430 mg, 87%). Significant NMR NOEs are 4a-H to 5-H, 37%; 7a-CH_3 to 2-H, 31%; 7a-CH_3 to 2-H, 35%; 4aH to 2-OMe, 21%. ^{1}H NMR (250 Mz, $CDCl_3$) δ 4.73 (dd, *J* = 2.4, 9.8 Hz, 1H, H-2), 3.29 (d, *J* = 6.2 Hz; 1H, H-5), 3.24 (s, 3H, OMe), 2.79 (d, *J* = 18.4 Hz, ; H-7), 2.45 (ddd, *J* = 2.3, 4.6, 6.2 Hz, 1H, H-4a), 2.31 (d, *J* = 18.4 Hz, 1H, H-7'), 1.97 (m, 2H), 1.74 (dm, *J* = 17.0 Hz, 1H) 1.65 (dm, *J* = 13.0 Hz, 1H), 1.49 (s, 3H, CH_3-7a), 1.41 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.3 (C-6), 171.0 ($CO_2C(CH_3)_3$), 95.7 (C-2), 82.2 ($CO_2C(CH_3)_3$), 81.7 (C-7a), 60.2 (C-5), 56.8 (OMe), 55.0 (C-7), 51.5 (C-4a), 34.0 (C-3), 28.4($CO_2C(CH_3)_3$), 25.4 (C-4), 24.7 (CH_3-7a); FD-MS m/z = 284 $(M)^+$, Anal. Calcd for $C_{15}H_{24}O_5$ (284.35); C 63.40, H 8.51; Found: C 63.52, H 8.46.

General procedure for the synthesis of compounds 11a-f. The bicyclic β-ketoester **10** derived from the reduction product of **8b** (142 mg, 0.5 mmol) and the desired hydrazine derivative (0.52 mmol) in 20 ml absolute ethanol was refluxed, and the progress of reaction was monitored by TLC. After 6 h, the reaction mixture was concentrated on a rotary evaporator, the residue was purified on silica gel column (elution with 10% ethyl acetate in hexane) to give **11a-f** as amorphous solids.

(3b*S*,6*S*,7a*S*)-6-Methoxy-7a-methyl-2-(4-methylphenyl)-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11a**). Yield: 122 mg, 88%; ^{1}H NMR (400 Mz, $CDCl_3$) δ 7.70 (d, J = 7.3 Hz, 2H, Ar-H), 7.17 (d, *J* = 7.3 Hz, 2H, Ar-H), 4.64 (dd, *J* = 2.7, 7.9 Hz, 1H, H-2), 3.04 (bd, *J* = 6.2 Hz; 1H), 3.30 (s, 3H, OMe), 2.25 (dd, *J* = 4.6, 11.3 Hz, 1H), 2.20 (m, 3H), 2.17 (s, 3H, Ar-CH3), 1.90 (m, , 3H), 1.45 (s, 3H, CH_3-7a); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 159.6, 143.0, 141.7, 137.4, 133.4, 132.6, 125.9, 115.6, 94.2, 84.1, 60.2, 56.8, 55.0, 34.1, 25.4, 24.7, 20.9; FD-MS m/z = 314 (M)+, Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38); C, 68.77; H, 7.05; N, 8.91. Found: C, 68.56; H, 7.24; N, 9.07.

4-[(3b*S*,6*S*,7a*S*)-6-Methoxy-7a-methyl-3-oxo-1,3,3b,4,5,6,7a,8-octahydro-2*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-2-yl]benzonitrile (**11b**). Yield: 91.5 mg, 75% ^{1}H NMR (400 Mz, $CDCl_3$) δ 7.81 (dd, *J* = 1.2, 7.4 Hz, 2H, Ar-H), 7.73 (dd, *J* = 1.1, 7.4 Hz, 2H, Ar-H), 4.90 (dd, *J* = 3.1, 8.2 Hz, 1H, H-2), 3.01 (bd, *J* = 6.4 Hz; 1H), 3.41 (s, 3H, OMe), 2.62 (m, 2H), 2.46 (dd, *J* = 4.3, 10.1 Hz, 1H), 2.23 (m, 2H), 1.92 (m, , 2H), 1.49 (s, 3H, CH_3-7a); FD-MS m/z = 325 (M)+, Anal. Calcd for $C_{18}H_{19}N_3O_3$ (325.14); C, 66.45; H, 5.89; N, 12.91. Found: C, 66.27; H, 5.95; N, 12.70.

(3b*S*,6*S*,7a*S*)-6-Methoxy-7a-methyl-2-(4-nitrophenyl)-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11c**). Yield: 104 mg, 78%; ^{1}H NMR (400 Mz, $CDCl_3$) δ 8.34 (dd, *J* = 0.9, 6.9 Hz, 2H, Ar-H), 8.18 (dd, 1.0, *J* = 6.9 Hz, 2H, Ar-H),

4.85 (dd, *J* = 2.9, 7.0 Hz, 1H, H-2), 3.01 (m, 1H), 3.53 (s, 3H, OMe), 3.01 (dd, *J* = 2.1, 4.5 Hz, 1H), 2.71-2.79 (m, 2H), 2.45(dt, *J* = 3.3, 10.1 Hz, 1H), 2.20 (m, 2H), 1.89 (m, 2H), 1.47 (s, 3H, CH_3-7a); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 161.6, 144.3, 142.1, 133.0, 122.7, 119.5, 115.0, 94.9, 84.7, 55.7, 49.2, 44.1, 30.8, 22.4, 22.0; FD-MS m/z = 345 (M)+, Anal. Calcd for $C_{17}H_{19}N_3O_5$ (345.13); C, 59.12; H, 5.55; N, 12.1. Found: C, 59.22; H, 5.67; N, 12.31.

(3b*S*,6*S*,7a*S*)-6-Methoxy-2-(4-methoxyphenyl)-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11d**). Yield: 110 mg, 82%; ^{1}H NMR (400 Mz, $CDCl_3$) δ 7.61 (dd, *J* = 0.9, 6.5 Hz, 2H, Ar-H), 6.95 (dd, 1.0, *J* = 6.5 Hz, 2H, Ar-H), 4.93 (dd, *J* = 2.2, 6.2 Hz, 1H, H-2), 3.77 (s, 3H, Ar-OMe), 3.00 (m, 1H), 3.40 (s, 3H, OMe), 2.75 (dd, *J* = 2.3, 4.4 Hz, 1H), 1.88 (m, 1H), 2.42(dt, *J* = 3.3, 9.5 Hz, 1H), 2.20 (m, 1H), 1.50 (s, 3H, CH_3-7a); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 161.75, 132.5, 132.4, 115.1, 112.6, 94.2, 84.6, 55.7, 55.6, 46.1, 39.8, 32.8, 25.7, 25.2; FD-MS m/z = 330 (M)+, Anal. Calcd for $C_{18}H_{22}N_2O_4$ (330.16); C, 65.44; H, 6.71; N, 8.48, 12.1. Found: C, 65.53; H, 6.65; N, 8.52.

(3b*S*,6*S*,7a*S*)-2-(4-Chlorophenyl)-6-methoxy-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11e**). Yield: 120.7 mg, 85%; ^{1}H-NMR (400 Mz, $CDCl_3$) δ 7.85 (dd, *J* = 0.8, 6.1 Hz, 2H, Ar-H), 7.30 (dd, 0.9, *J* = 6.1 Hz, 2H, Ar-H), 5.00 (dd, *J* = 2.3, 5.7 Hz, 1H, H-2), 3.03 (m, 1H), 3.99 (s, 3H, OMe), 2.76 (dd, *J* = 2.2, 4.1 Hz, 1H), 2.22-2.46 (m, 3H), 1.89 (m, 3H), 1.47 (s, 3H, CH_3-7a); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 160.9, 151.8, 151.3, 139.0, 132.4, 116.8, 115.1, 94.7, 84.6, 55.7, 49.3, 46.1, 30.2, 21.8, 21.4; FD-MS m/z = 334 (M)+, Anal. Calcd for $C_{17}H_{19}ClN_2O_3$ (334.11); C, 60.99; H, 5.72; Cl, 10.59; N, 8.37. Found: C, 60.85; H, 5.79; Cl, 10.61; N, 8.42.

(3b*S*,6*S*,7a*S*)-2-(1*H*-Indol-2-yl)-6-methoxy-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11f**). Yield: 98 mg, 76%; ^{1}H NMR (400 Mz, $CDCl_3$) δ 10.62 (bs, 1H), 10.26 (s, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.52 (s, 1H), 7.37 (d,

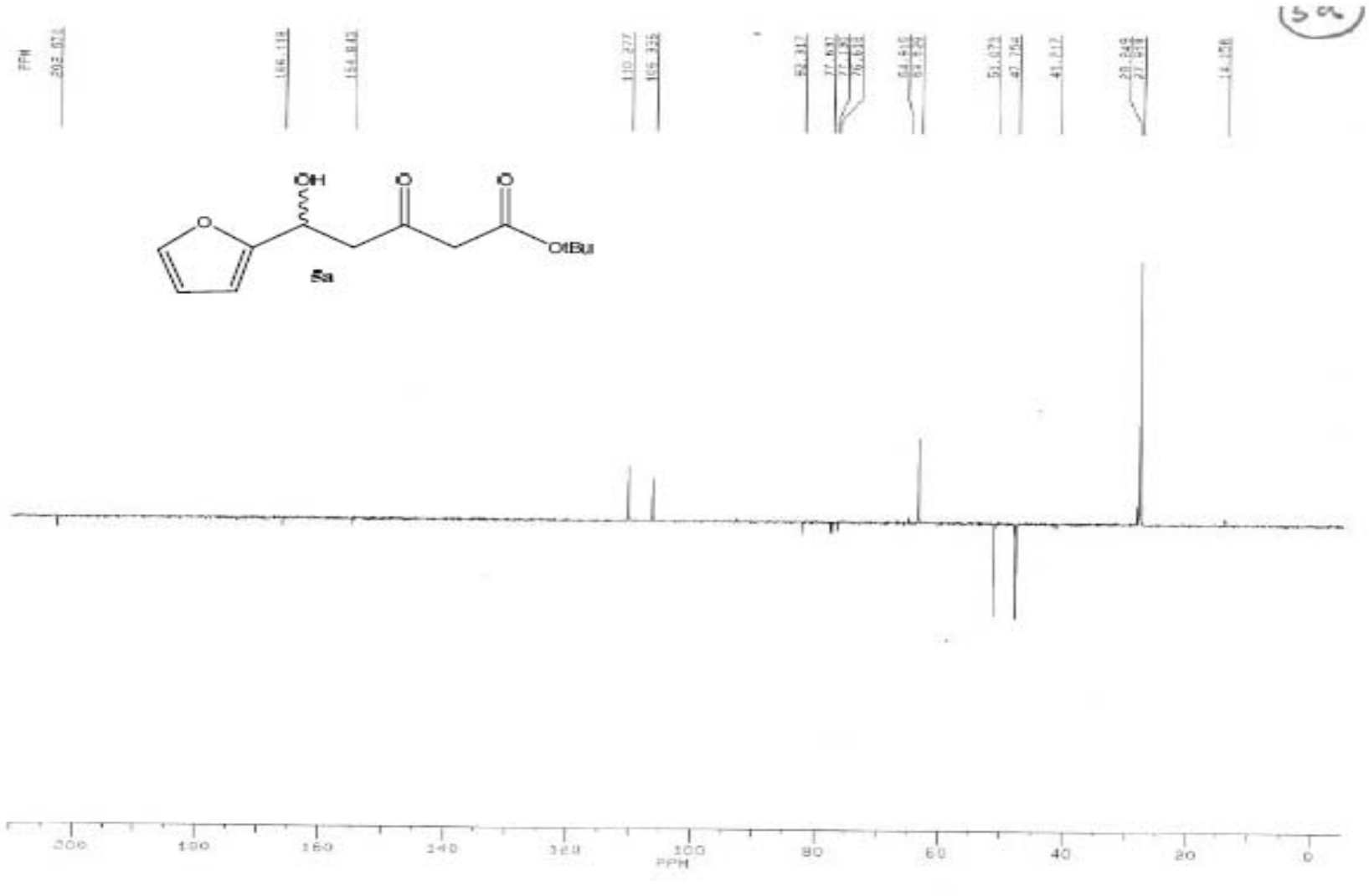
J = 2.0 Hz, 1H), 7.16 (t, *J* = 1.8, 3.2 Hz, 1H), 6.50 (t, *J* = 1.8, 3.3 Hz, 1H), 4.84 (dd, *J* = 2.1, 5.2 Hz, 1H, H-2), 3.00 (m, 1H), 3.49 (s, 3H, OMe), 2.77 (m, 1H), 2.21-2.46 (m, 2H), 1.88 (m, 2H), 1.47 (s, 3H, CH_3-7a); FD-MS m/z = 334 (M)+, Anal. Calcd for $C_{19}H_{21}N_3O_3$ (339.16); C, 67.24; H, 6.24; N, 12.38. Found: C, 67.33; H, 6.13 N, 12.45.

(3b*S*,6*S*,7a*S*)-6-Methoxy-7a-methyl-2-pyridin-2-yl-1,2,3b,4,5,6,7a,8-octahydro-3*H*-pyrano[3',2':3,4]cyclopenta[1,2-*c*]pyrazol-3-one (**11g**). Yield: 119 mg, 79%; ^{1}H NMR (400 Mz, $CDCl_3$) δ 8.41 (d, *J* = 1.1 Hz, 1H), 7.92 (d, *J* = 0.9 Hz, 1H), 7.63 (t, *J* = 1.3 Hz, 1H), 6.98 (t, *J* = 1.2 Hz, 1H), 5.19 (t, *J* = 4.4 Hz, 1H, H-2), 3.08 (m, 1H), 3.77 (s, 3H, OMe), 2.65 (m, 2H), 2.21-2.38 (m, 3H), 1.85 (m, 2H), 1.42 (s, 3H, CH_3-7a); FD-MS m/z = 301 (M)+, Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.14); C, 63.77; H, 6.36; N, 13.94. Found: C, 63.65; H, 6.42; N, 13.81.

Molecular Modeling. ChemBio3D Ultra 11 was used to calculate the thermodynemicall more preferred conformations of compounds **10** and **10a** using force field MM2 method.[18]

***In vitro* cytotoxicity assay.** The cytotoxic activity of the cyclopenta[b]pyrane derivatives **11a-11g** was determined using a standard (MTT)-based colorimetric assay.[12] This assay quantifies viable cells by observing the reduction of tetrazolium salt, MTT, to formazan crystals by the cells. Based on the absorbance of the cell samples after the test is carried out, cell viability can be measured. Cells were plated with nutritional medium in 96 well plates (2000 and 5000 cells/well for HCT116, SK-N-SH and the non-tumorigenic cell line derived from breast tissue (MCF10A)). After 24 hours, cells were treated with different concentrations (0.1, 0.5, 1, 3 and 10 μM) of the new compounds, each concentration in 3 repetitions. The plates were incubated with the pyrazolone derivatives for 72 hours. At the end of treatment, cells were washed with PBS solution. Then, 100 µl of fresh medium and 50 µl from a stock solution of MTT (3mg/ml PBS)

were added to each well. After 4 hours of incubation at 37 °C, the medium was discarded and 100 µl of DMSO solution were added to each well, in order to dissolve the crystals that were formed. After a 30 minute period, the absorbance of the samples was measured by an Elisa reader. The absorbance data were converted to % cell viability. The IC50 were calculated using Graphpad Prism software.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O
OtBu
5a
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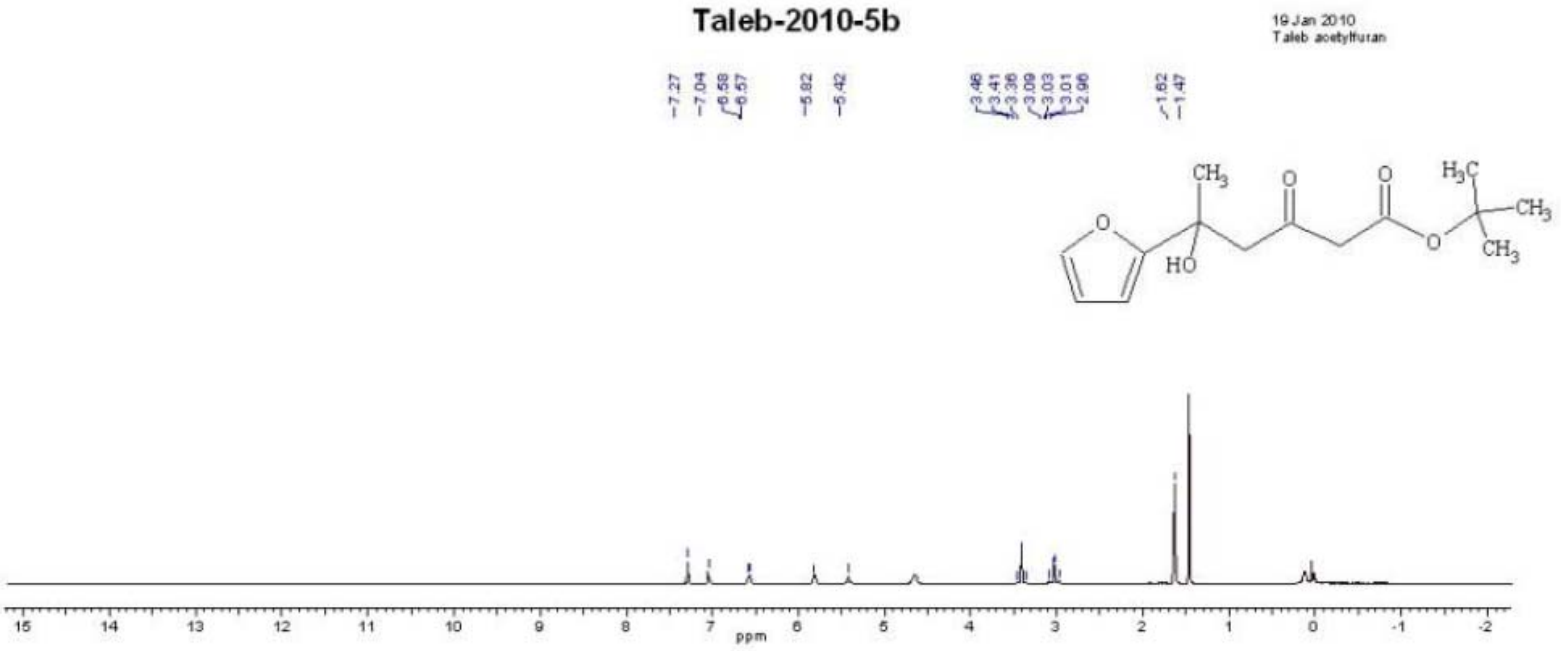
160
140
120
100
80
60
40
20
0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19 Jan 2010
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6.57
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5.42
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3.36
3.09
3.03
3.01
2.96
1.62
1.47
CH3
O
O
O
H3C
CH3
CH3
O
HO
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7
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3
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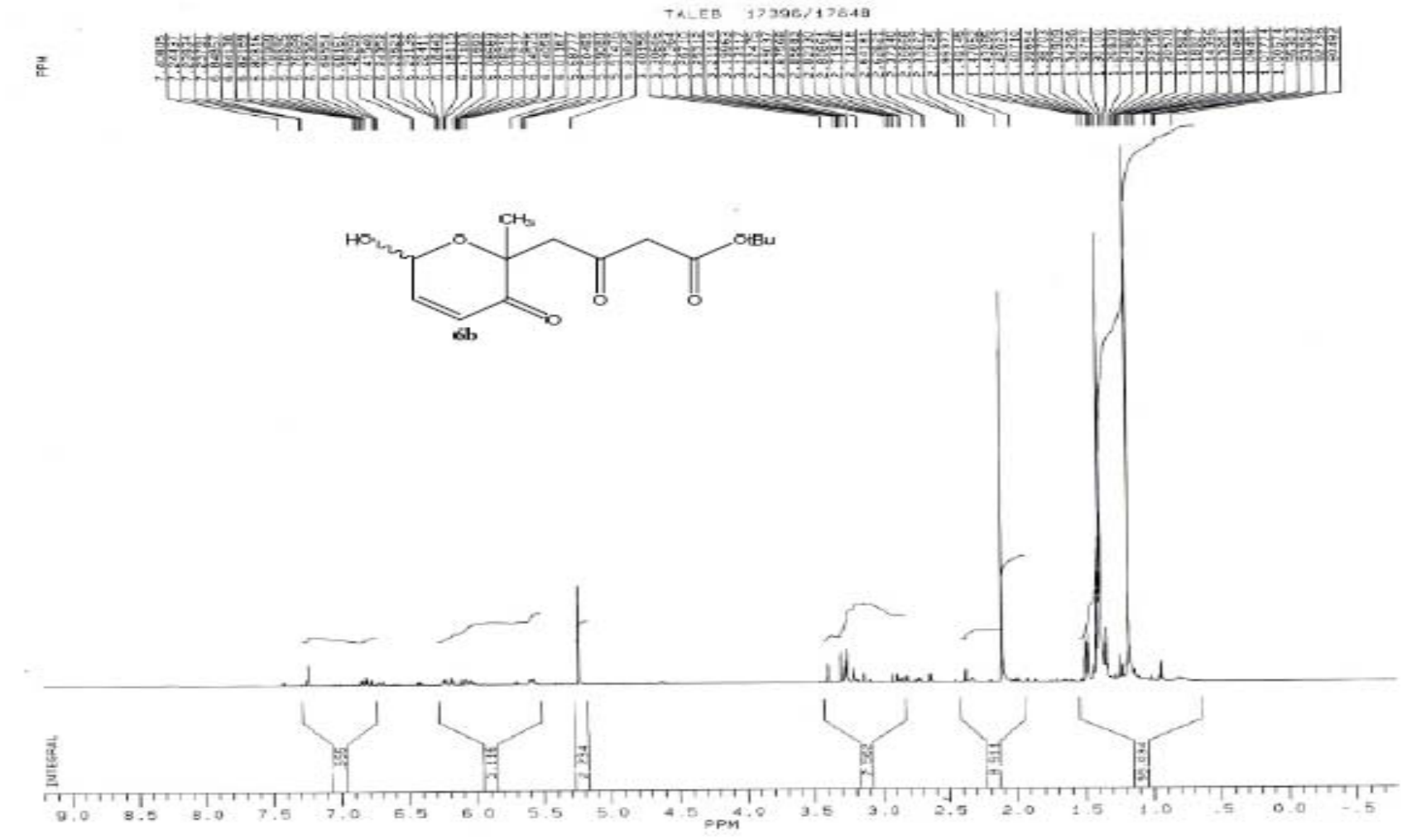
-2
ppm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OtBu
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6b
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6.0
5.5
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3.5
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1.5
1.0
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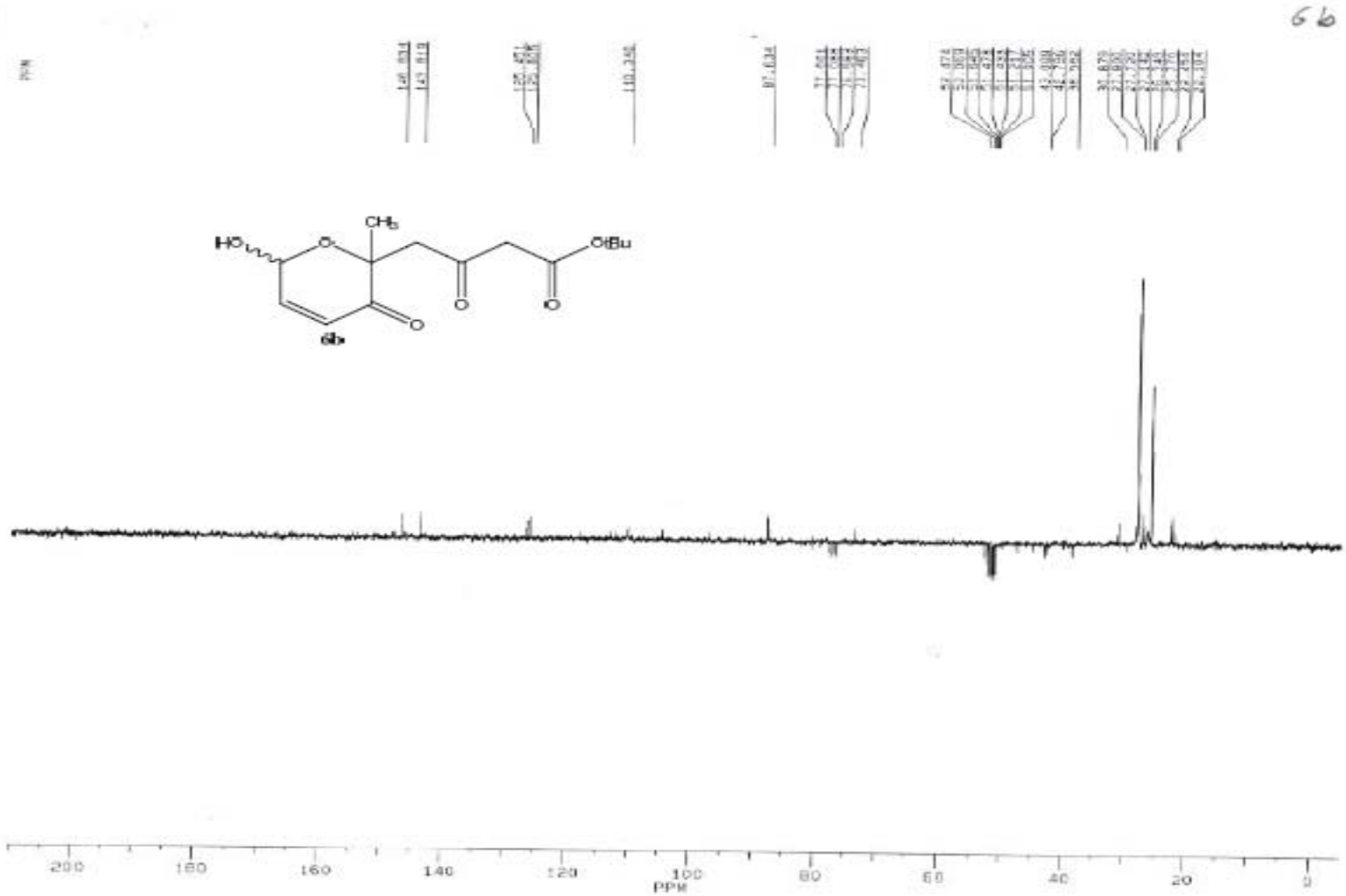
-.5
PPM


6b
HO
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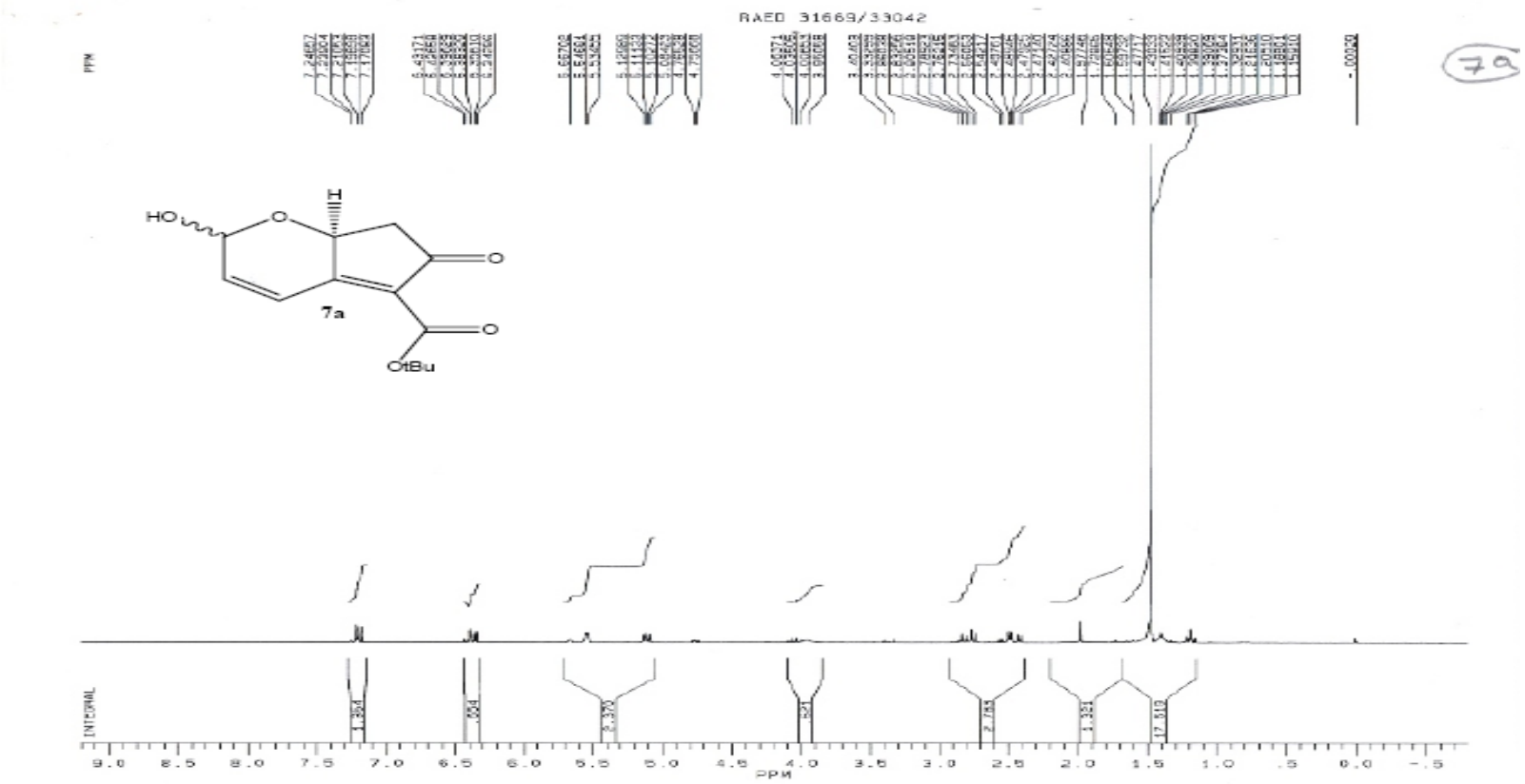
CH3
OtBu
O
O
O
6b
200
180
160
140
120
100
80
60
40
20
0
PPM


RAED 31669/33042
PPM
HO
O
H
O
O
OtBu
7a
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.921
2.755
1.381
17.812
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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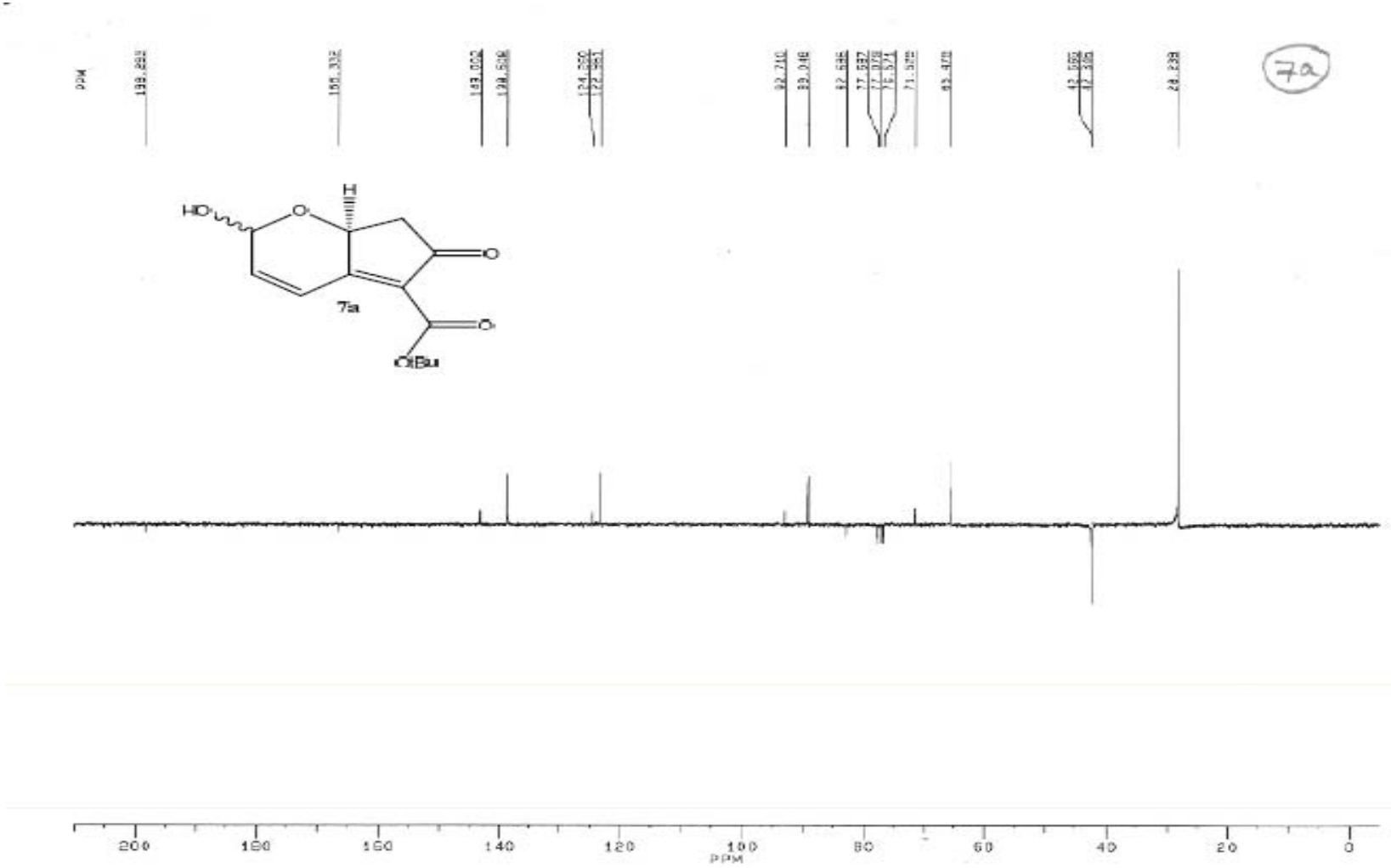
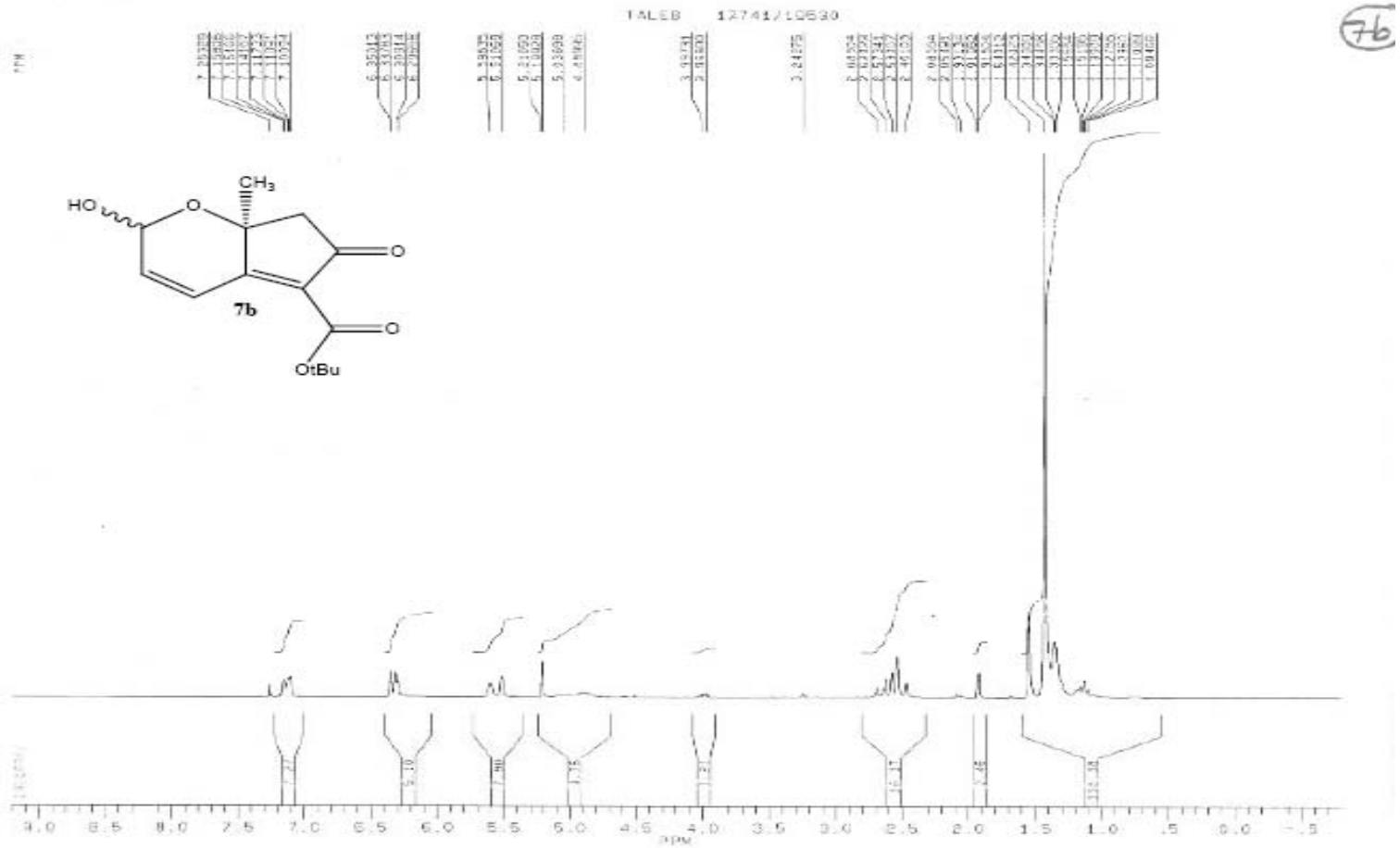
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM


7a
HO
O
H
O
O
OtBu
200
180
160
140
120
100
80
60
40
20
0
PPM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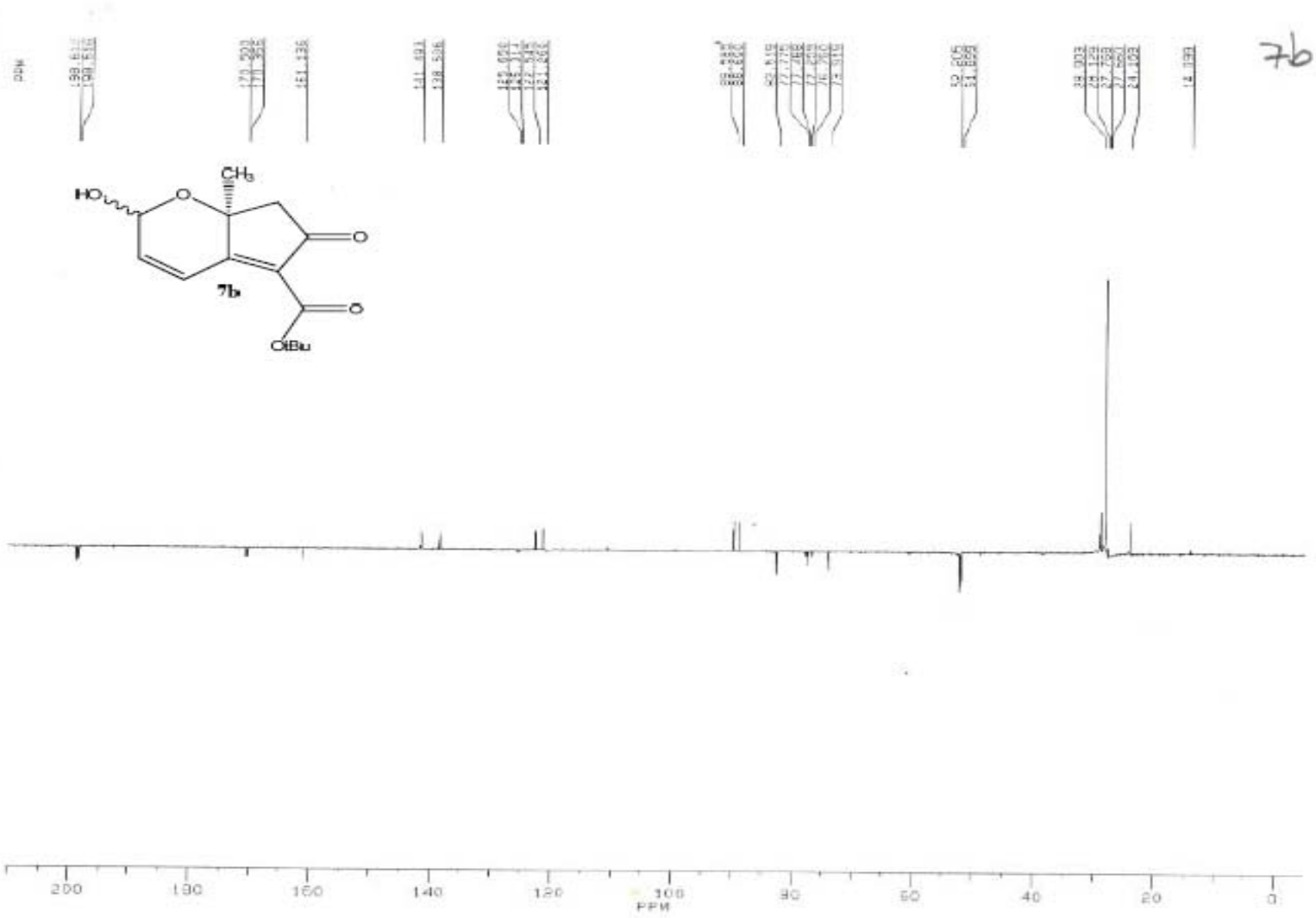
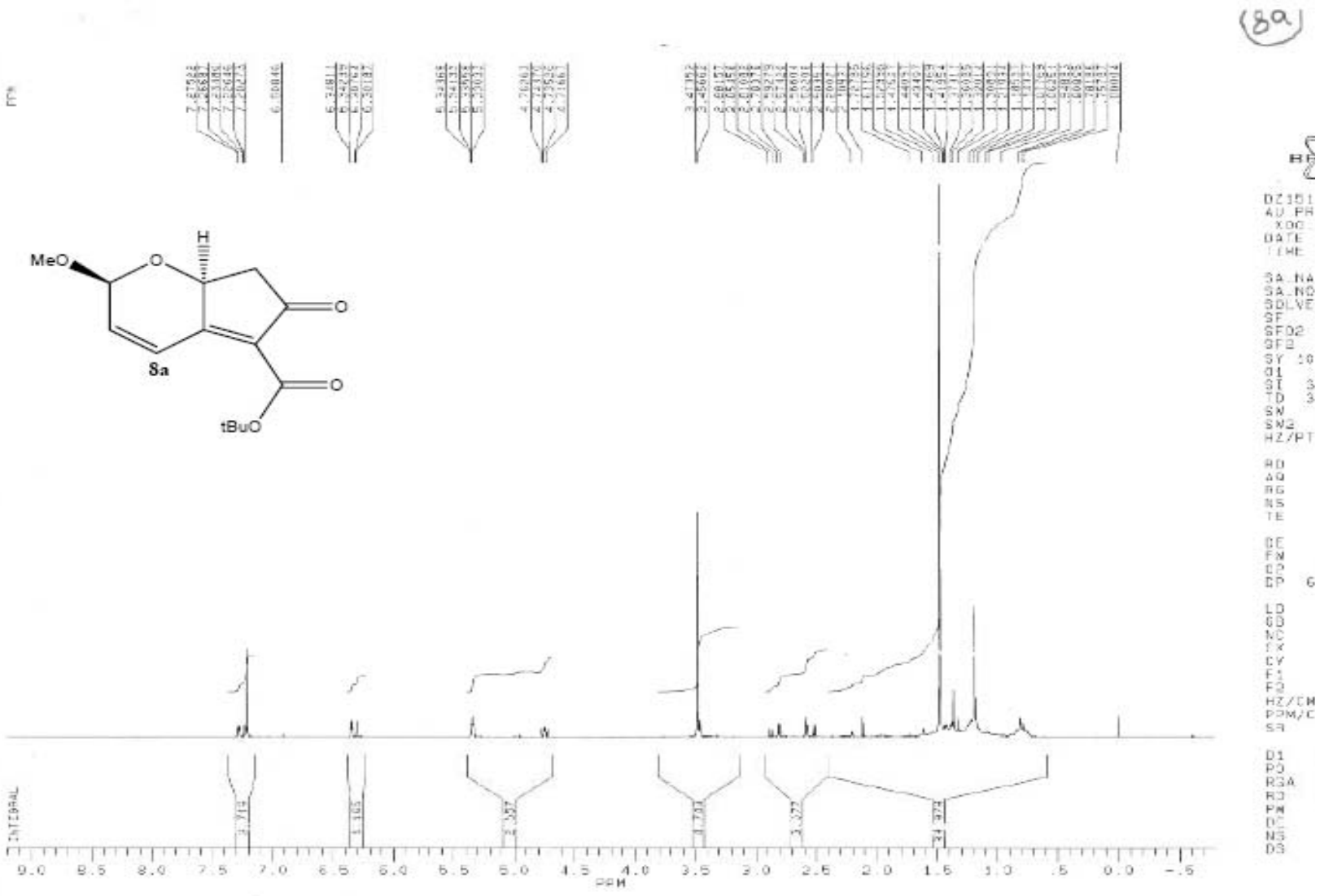
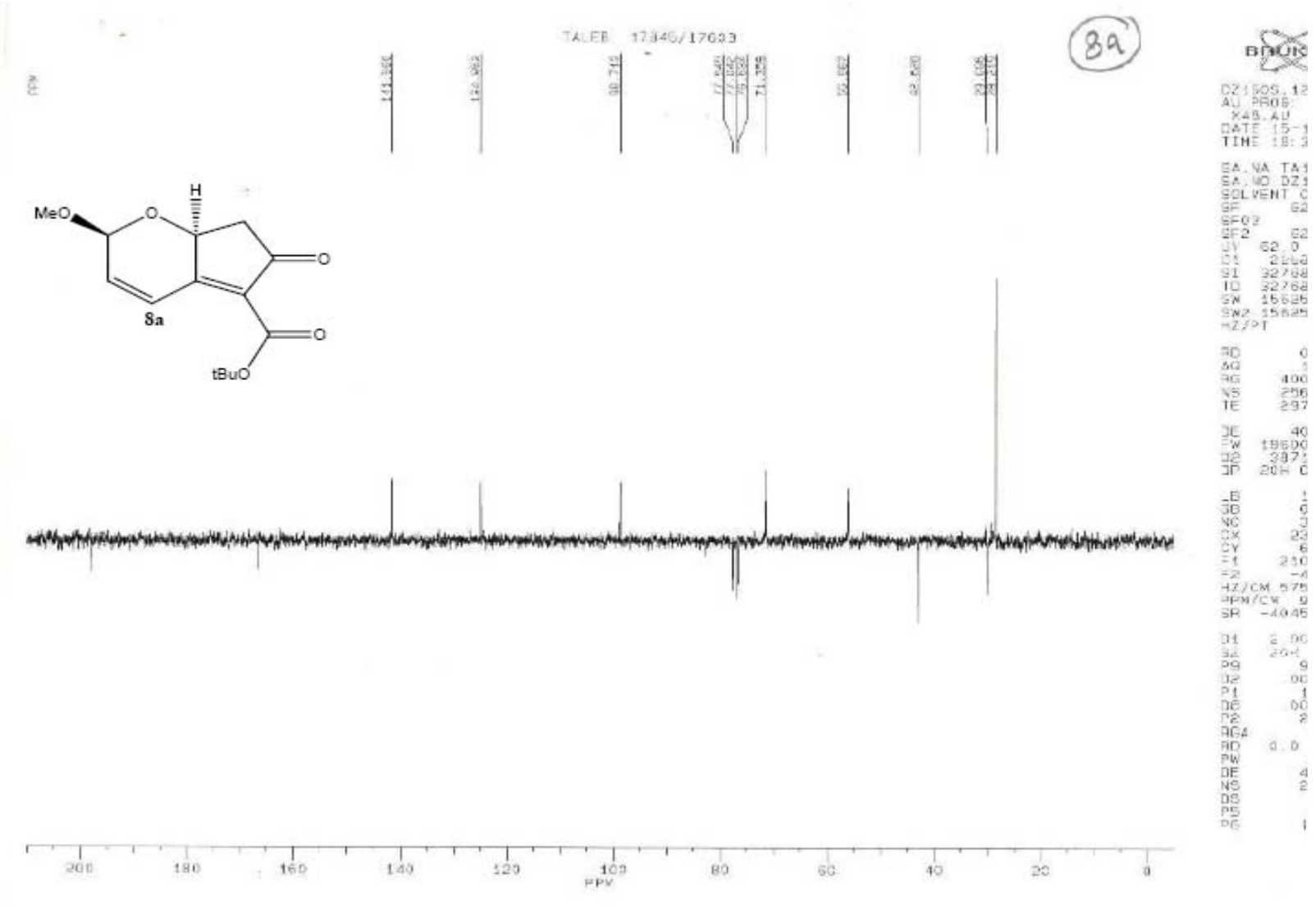
7b
HO
O
CH3
O
O
O
OtBu
PPM


7b
HO
O
CH3
O
O
OtBu
7b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


(8a)
MeO
O
H
O
O
O
tBuO
8a
INTEGRAL
PPM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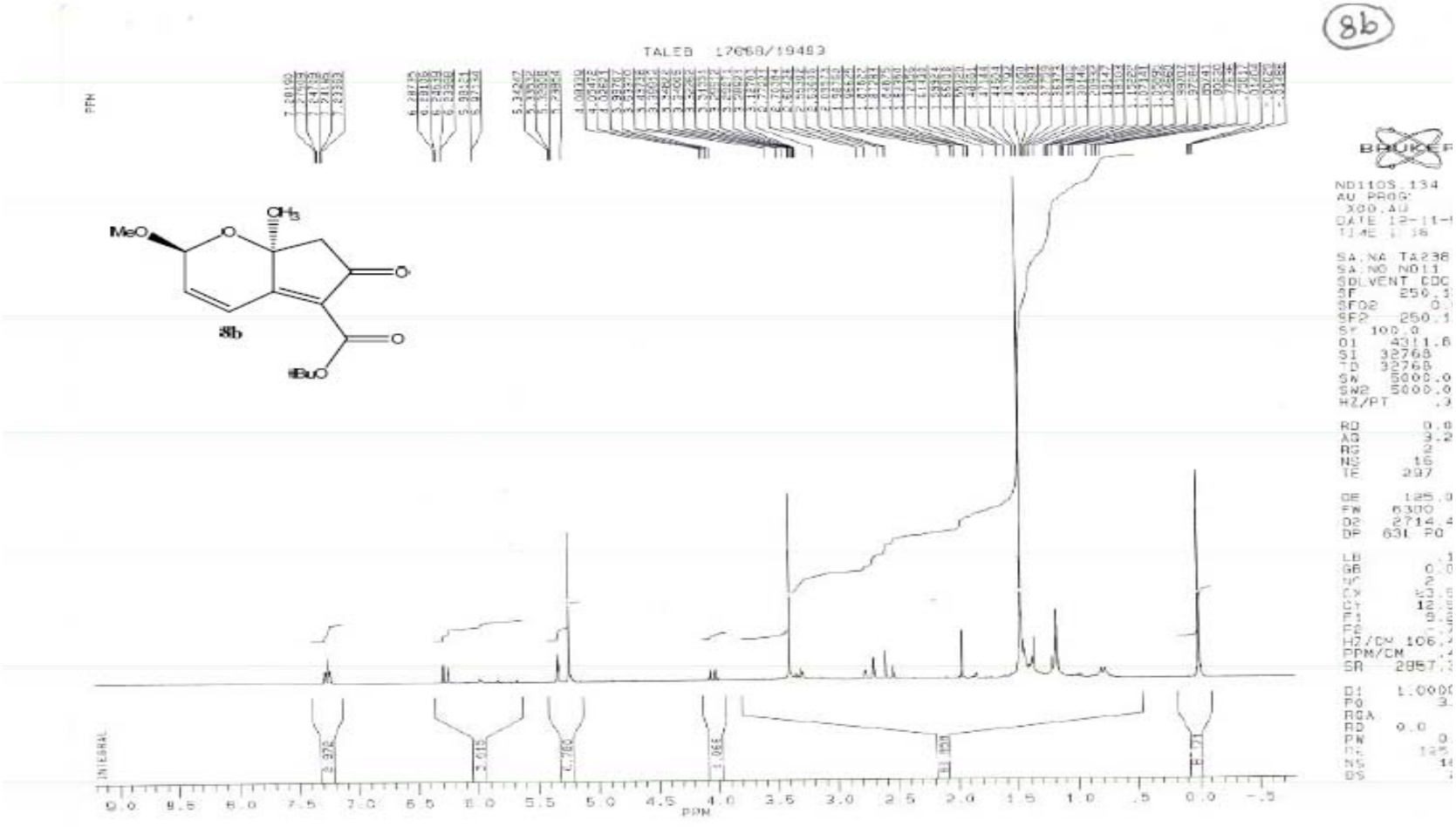
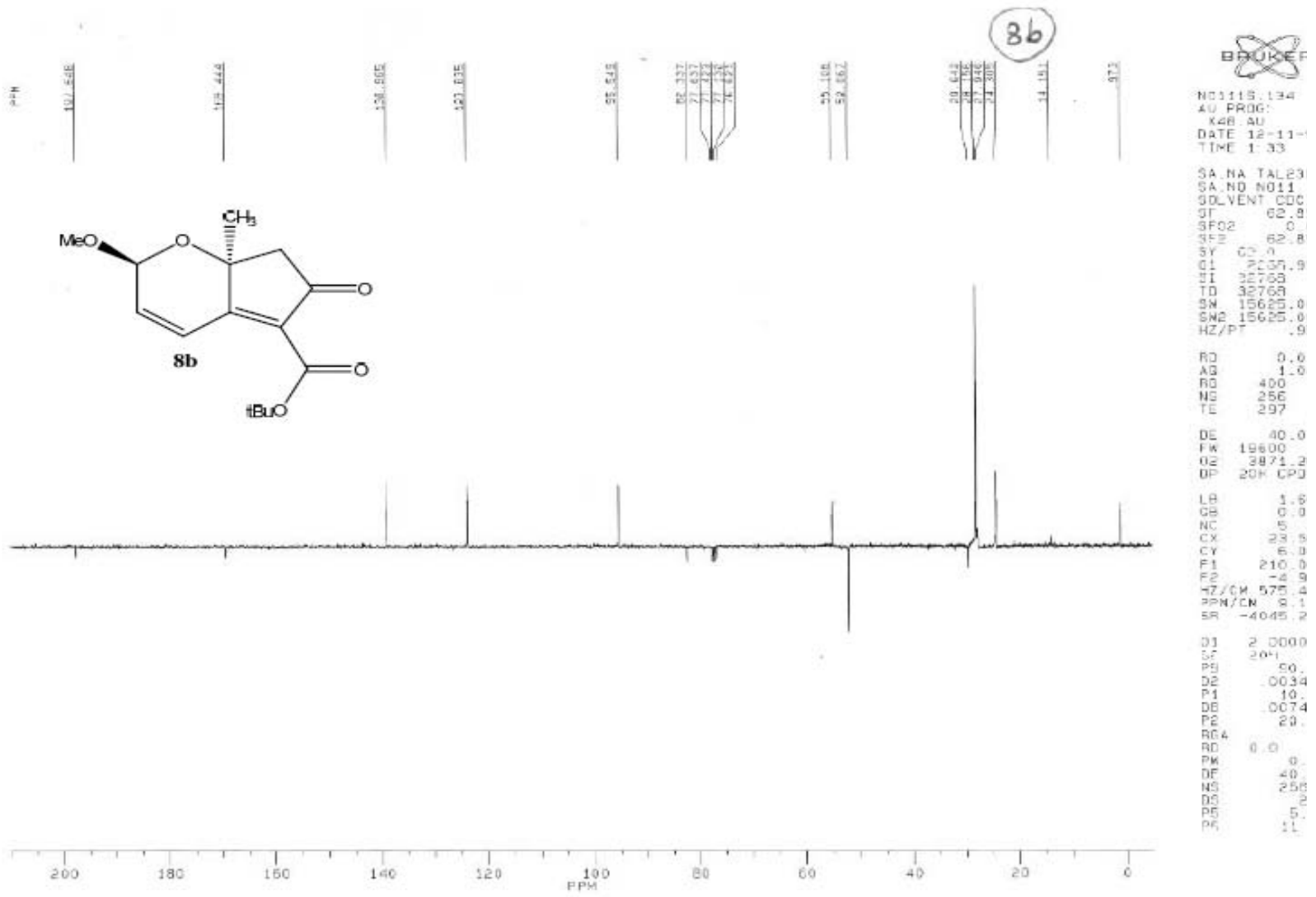
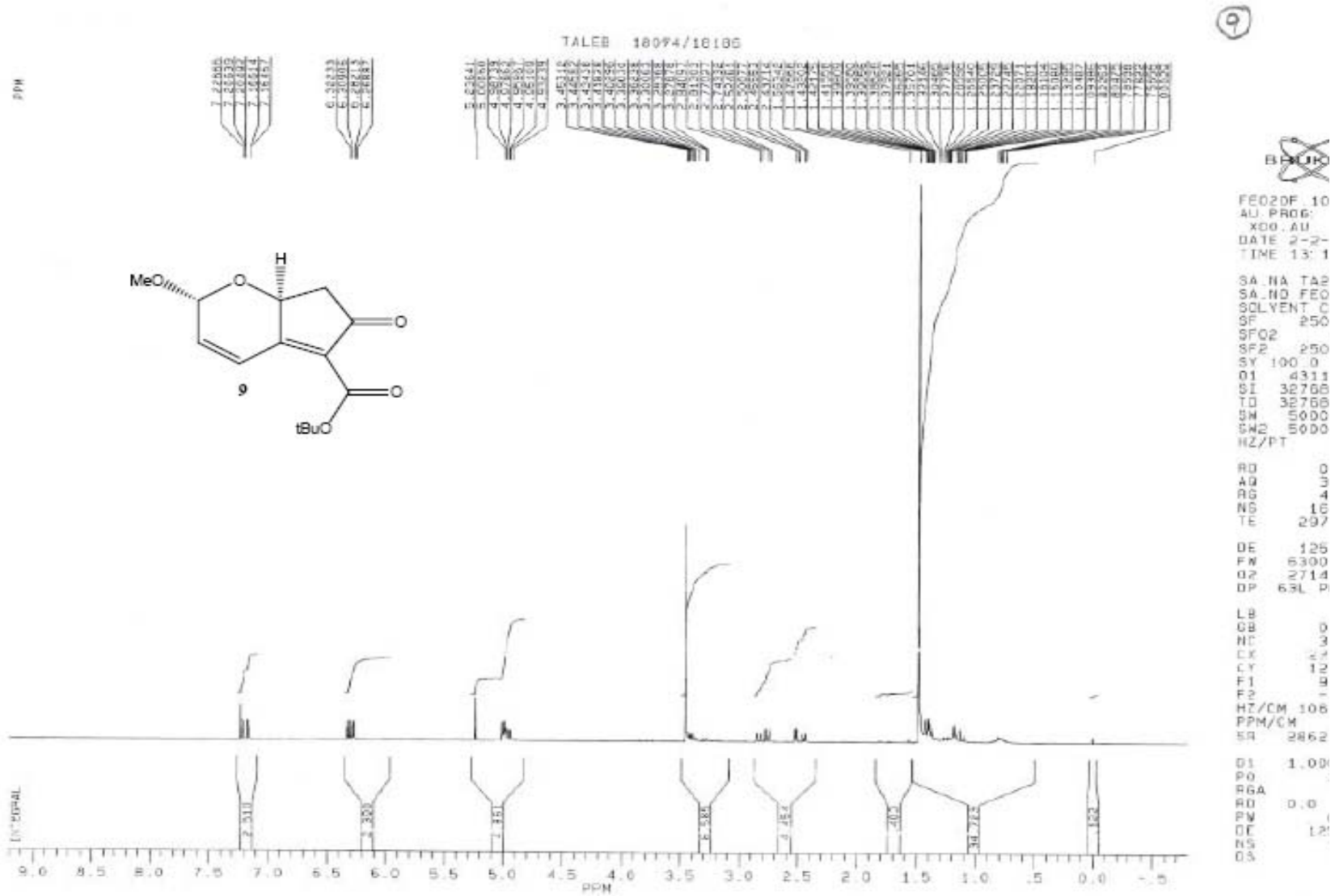
MeO
H
O
O
O
tBuO
PPM


8b
TALEB 17068/19493
MeO
CH3
O
O
O
8b
tBuO
INTEGRAL
PPM


86
MeO
CH3
O
O
O
O
tBuO
8b
200
180
160
140
120
100
80
60
40
20
0
PPM


TALEB 18094/18186
PPM
MeO
O
H
O
O
tBuO
9
INTEGRAL
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2.320
2.351
6.384
2.454
2.052
34.722
1.000
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 .5 0.0 -.5
PPM
FE020F.10
AU PROG:
XDO.AU
DATE 2-2-
TIME 13:1
SA.NA TA2
SA.NO FEO
SOLVENT C
SF 250
SFO2
SF2 250
SY 100.0
O1 4311
SI 32768
TD 32768
SW 5000
SW2 5000
HZ/PT
RD 0
AQ 3
RG 4
NS 16
TE 297
DE 125
FW 6300
O2 2714
DP 63L P
LB
GB 0
NC 3
CX
CY 12
F1 9
F2
HZ/CM 106
PPM/CM
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PO
RGA
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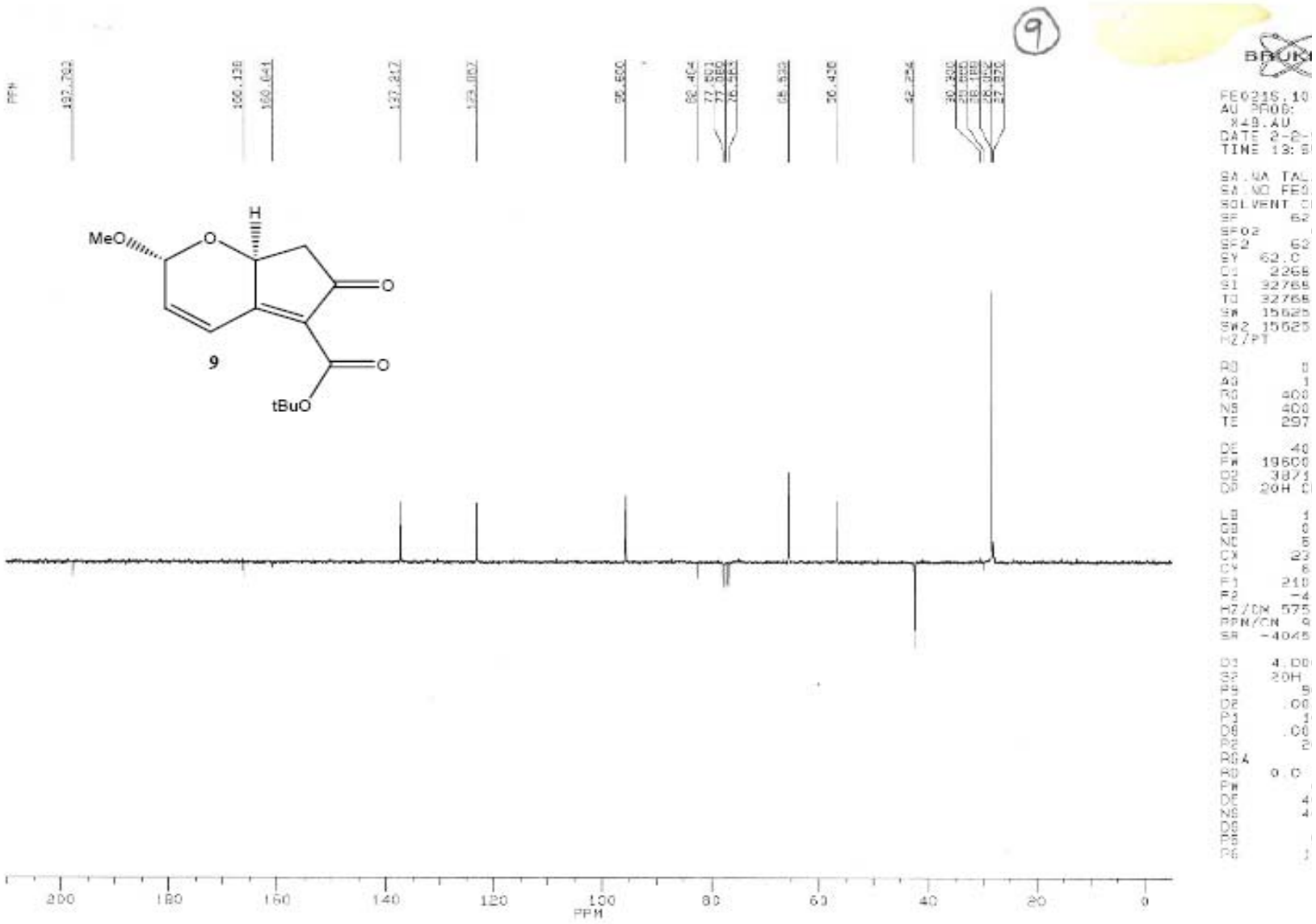
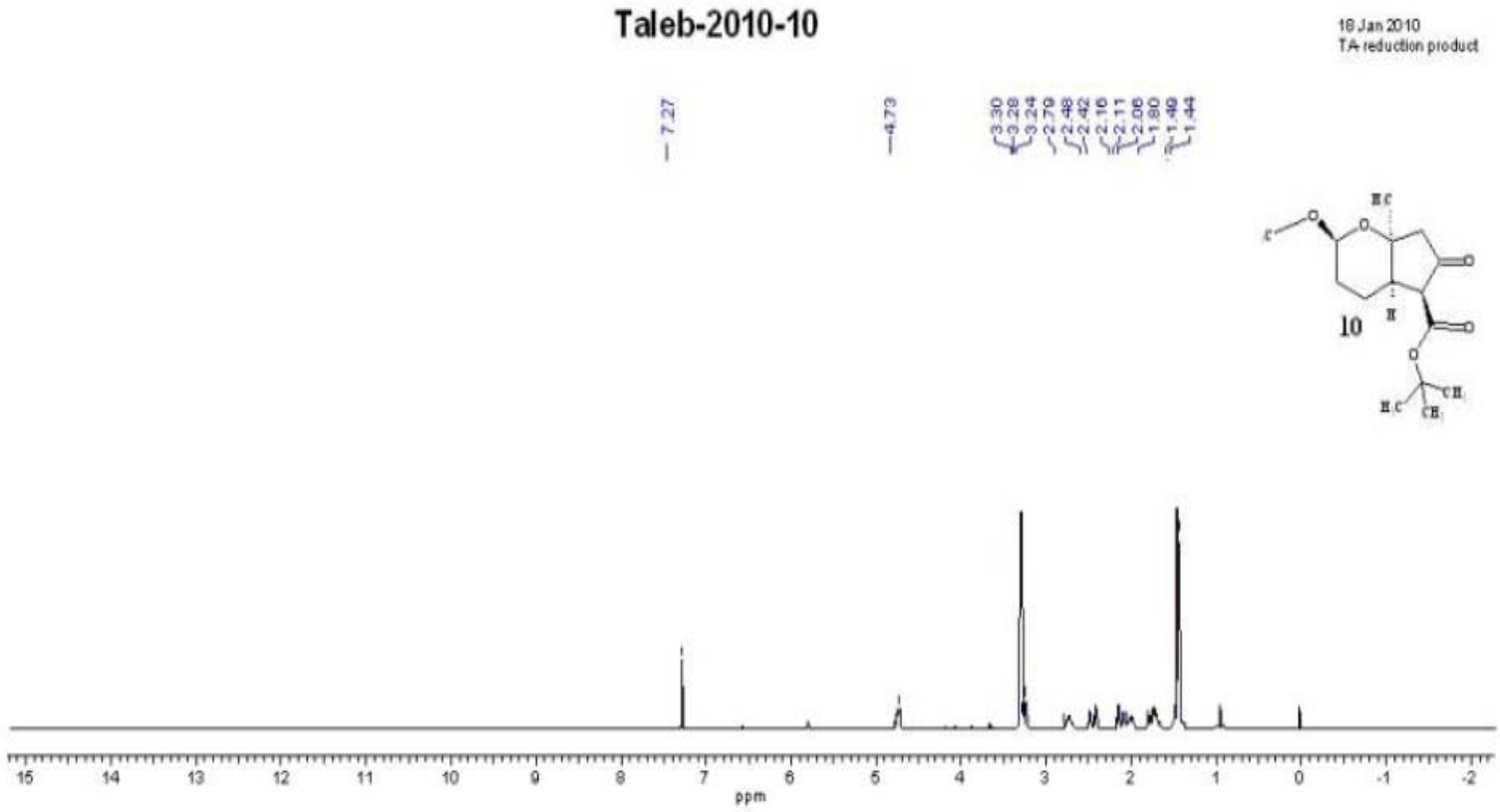
PW
DE 12
NS
DS


9
MeO
O
H
O
O
tBuO
9
PPM
200
180
160
140
120
100
80
60
40
20
0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18 Jan 2010
TA reduction product
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4.73
3.30
3.28
3.24
2.79
2.48
2.42
2.16
2.11
2.06
1.80
1.49
1.44
10
ppm

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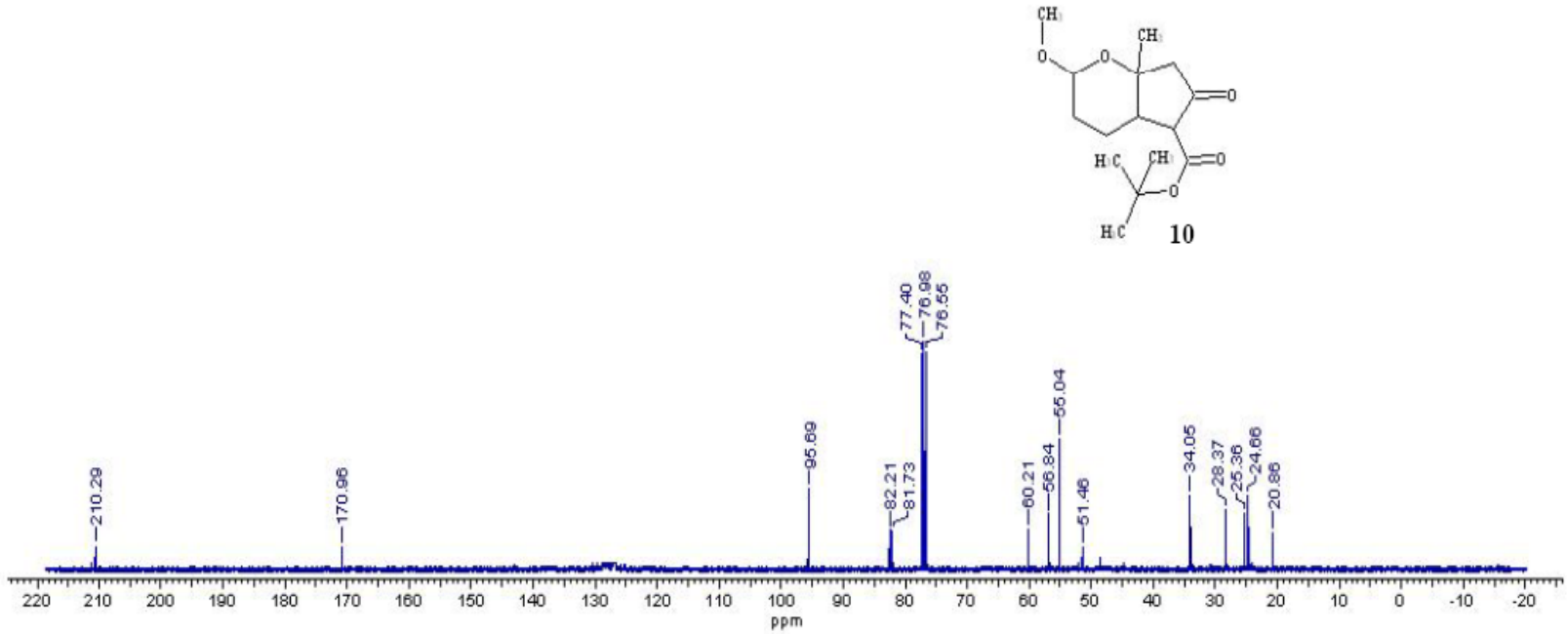
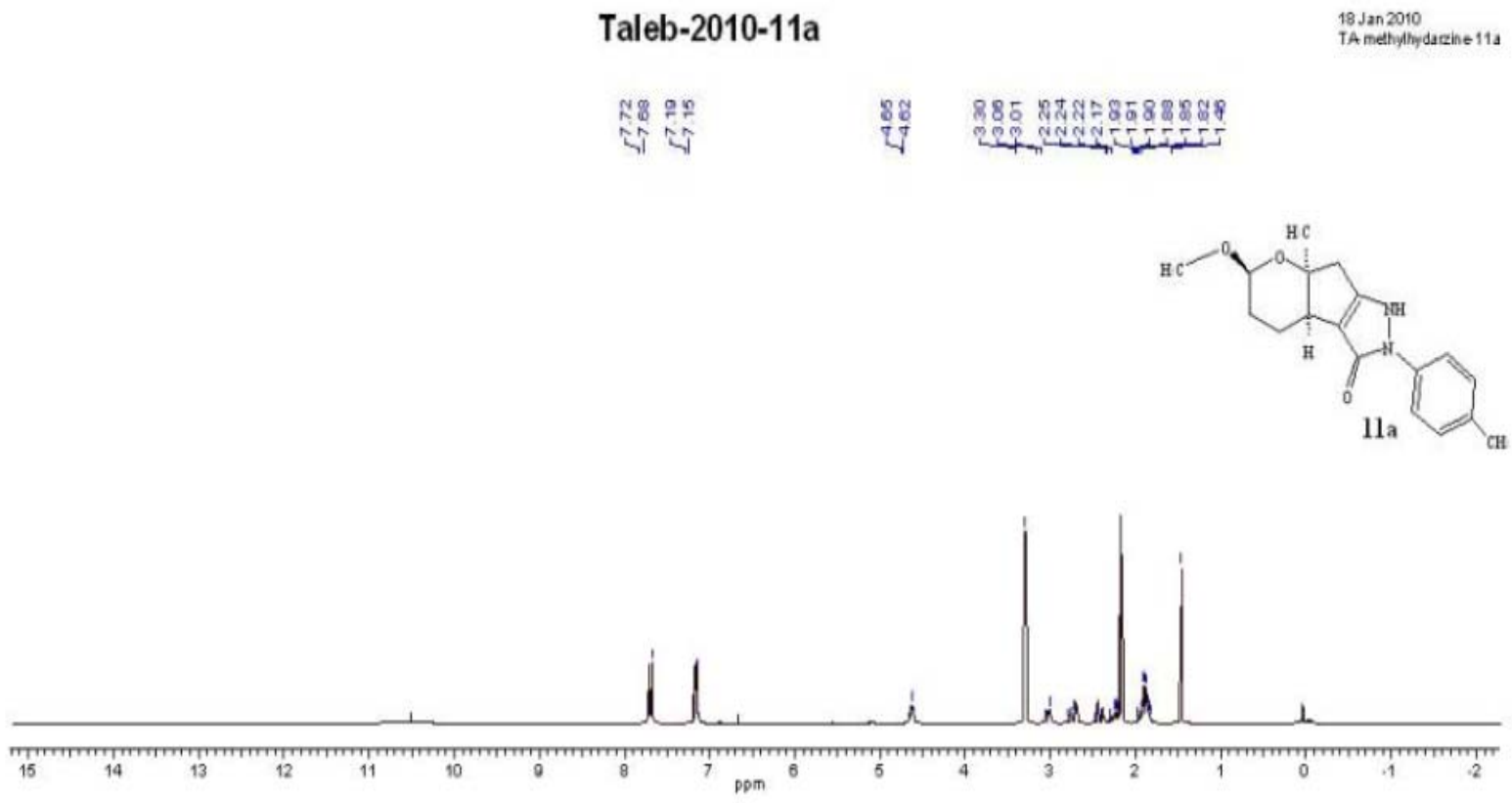
Temperature (degree C)	27.000						

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18 Jan 2010
TA methylhydrazine-11a
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7.68
7.19
7.15
4.65
4.62
3.30
3.06
3.01
2.25
2.24
2.22
2.17
1.93
1.91
1.90
1.88
1.85
1.82
1.46
HC
O
HC
O
NH
N
H
O
11a
CH
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

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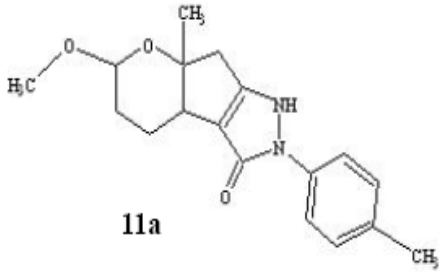
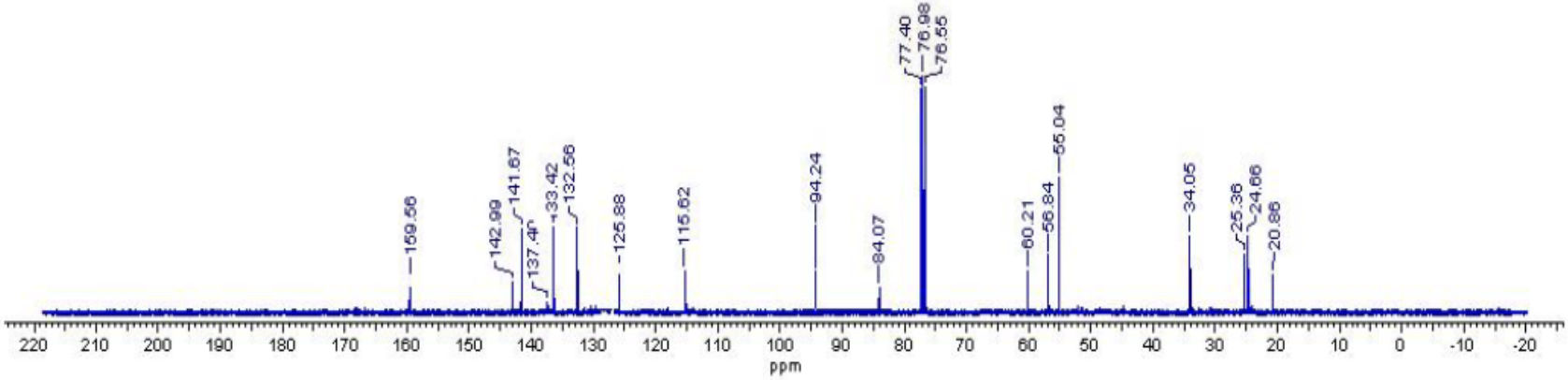
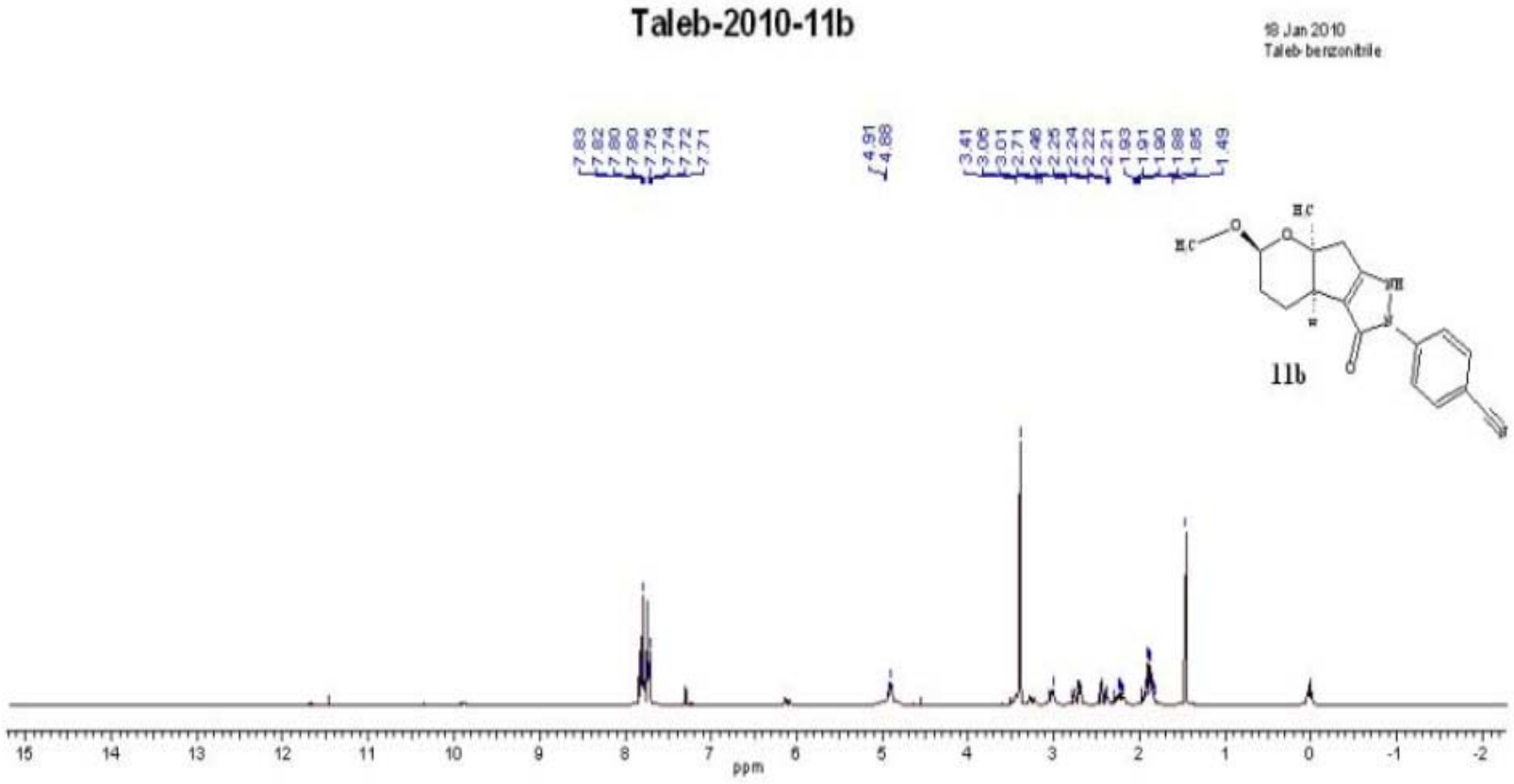
Temperature (degree C)	27.000						



11a

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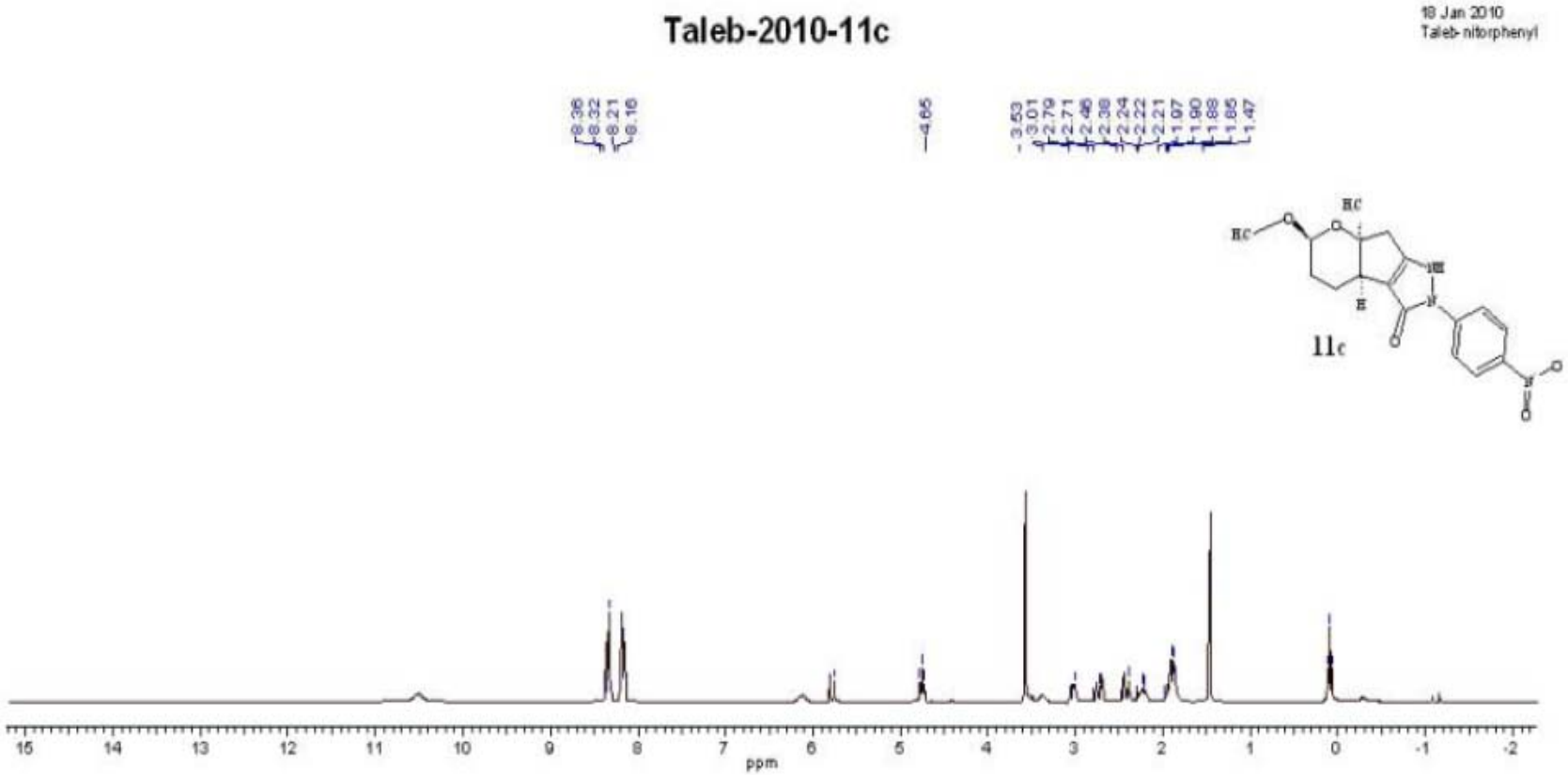
19 Jan 2010
Taleb benzonitrile
7.83
7.82
7.80
7.80
7.75
7.74
7.72
7.71
4.91
4.88
3.41
3.06
3.01
2.71
2.46
2.25
2.24
2.22
2.21
1.93
1.91
1.90
1.88
1.85
1.49
11b
ppm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18 Jan 2010
Taleb- nitorphenyl
8.36
8.32
8.21
8.16
4.65
3.53
3.01
2.79
2.71
2.46
2.38
2.24
2.22
2.21
1.97
1.90
1.88
1.85
1.47
11c
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

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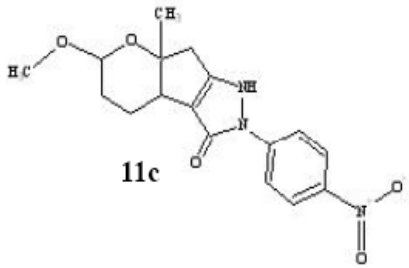
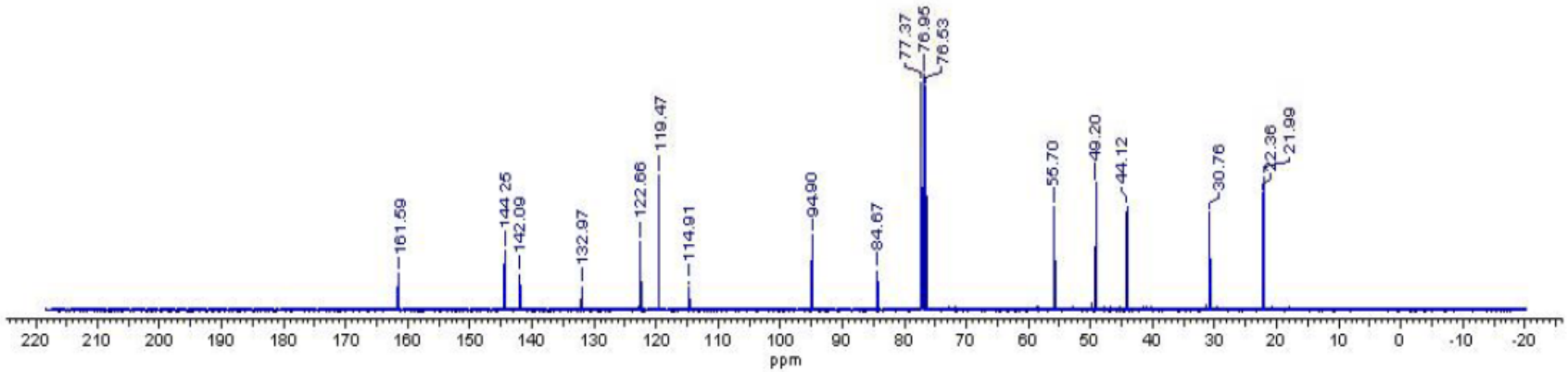
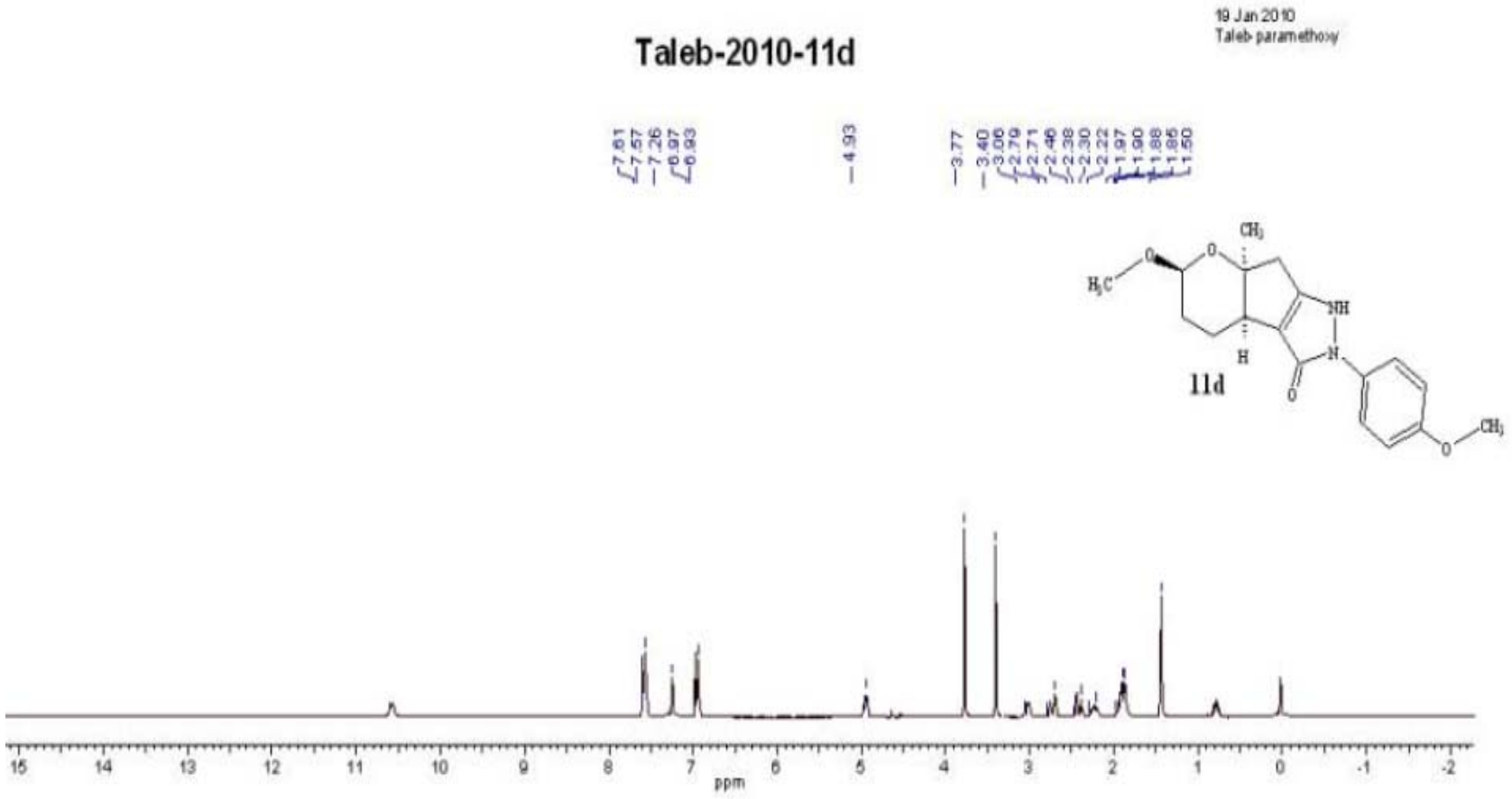


11c

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19 Jan 2010
Taleb-paramethoxy
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7.26
6.97
6.93
4.93
3.77
3.40
3.06
2.79
2.71
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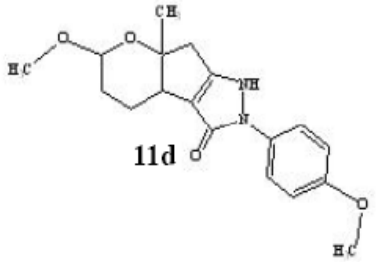
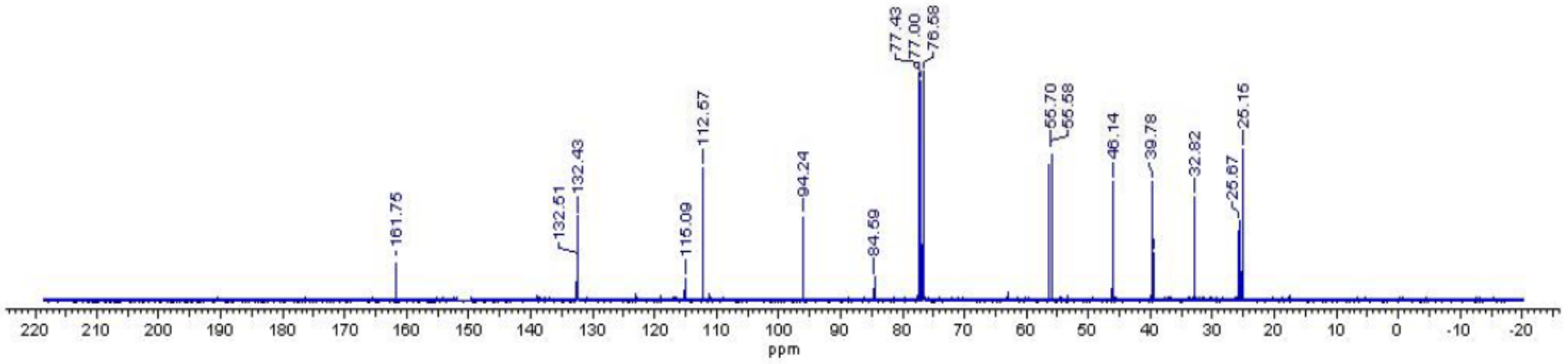
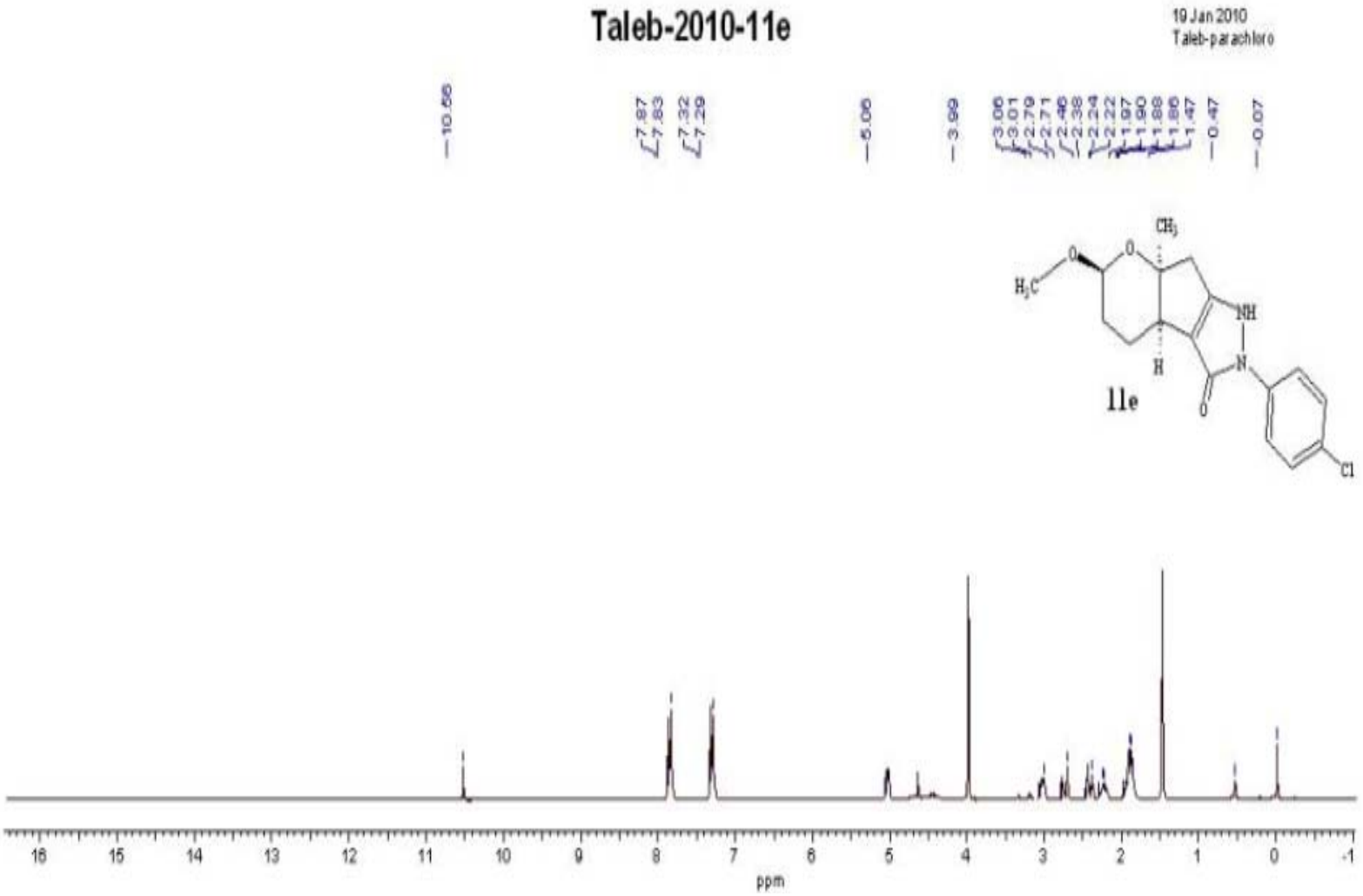
2.22
1.97
1.90
1.88
1.86
1.50
11d
ppm

Nucleus	13C	*Number of Transients*	2400	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	zgdc30	*Solvent*	CHLOROFORM-D	*Sweep Width (Hz)*	18028.85	*Temperature (degree C)*	27.000

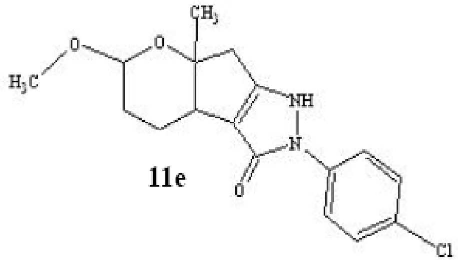


11d

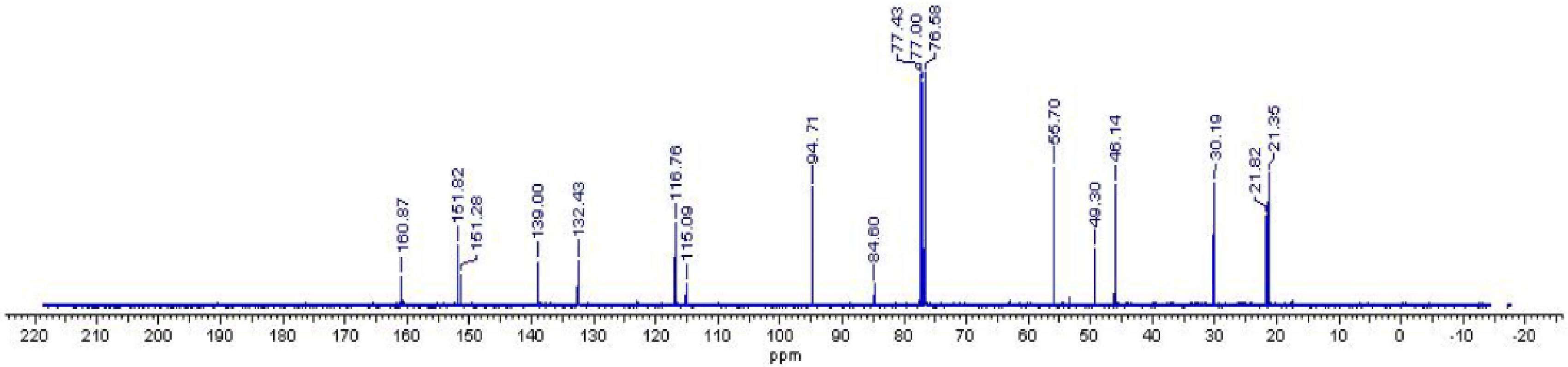


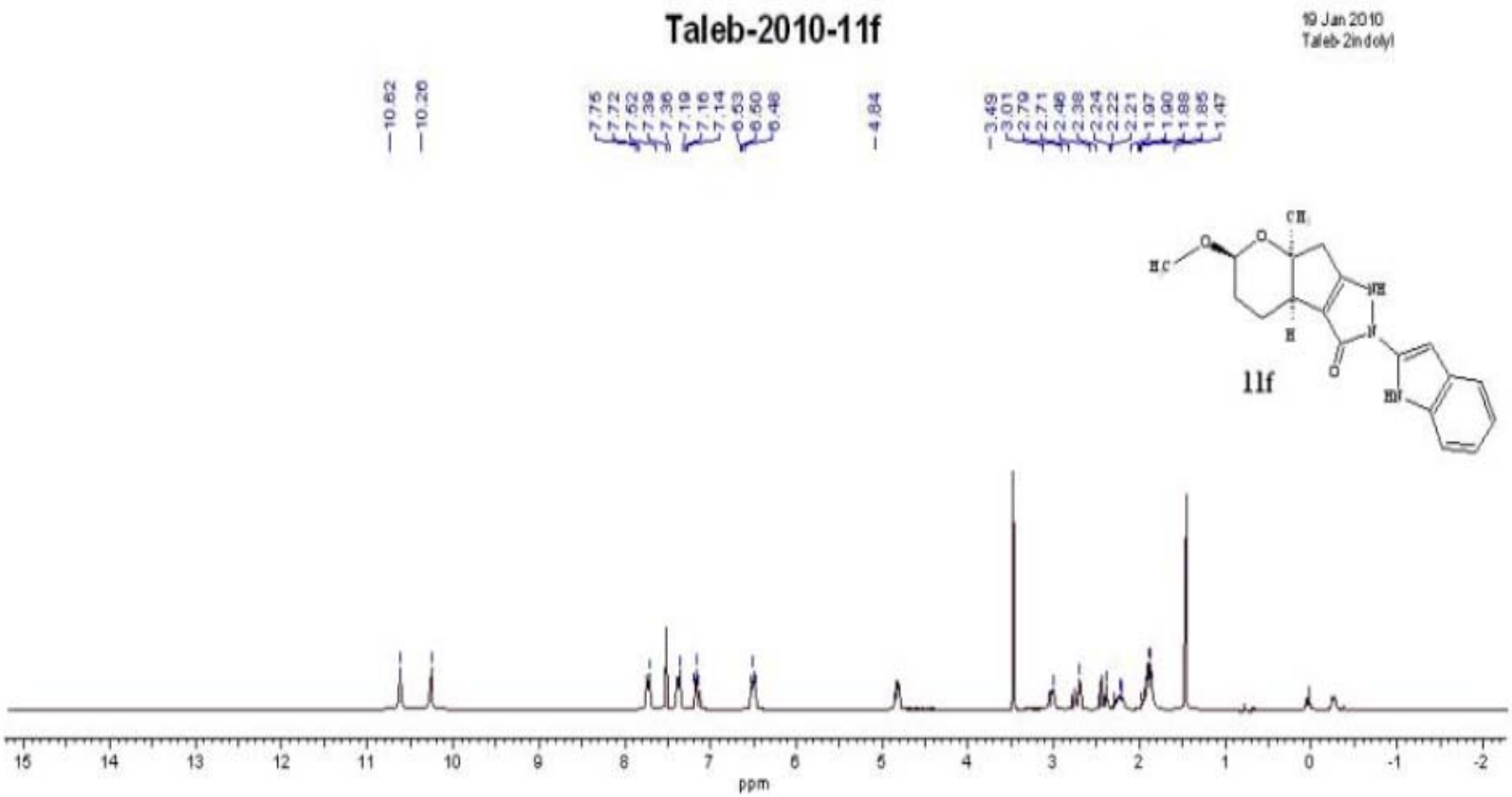

Taleb-2010-11e
19 Jan 2010
Taleb-parachloro
10.56
7.97
7.83
7.32
7.29
5.06
3.99
3.06
3.01
2.79
2.71
2.46
2.38
2.24
2.22
1.97
1.90
1.88
1.86
1.47
0.47
0.07
CH3
H3C
O
O
NH
N
H
O
Cl
11e
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

File Name	C:\Documents and Settings\user\Desktop\TA-RA-08\TA-Ampyr-Citranon-Solid\TA-Ampyr-Citranon-Solid_01\1000\fid					Frequency (MHz)	75.48
Nucleus	13C	Number of Transients	2400	Original Points Count	32768	Points Count	32768
Pulse Sequence	zgdc30	Solvent	CHLOROFORM-D	Sweep Width (Hz)	18028.85	Temperature (degree C)	27.000



11e

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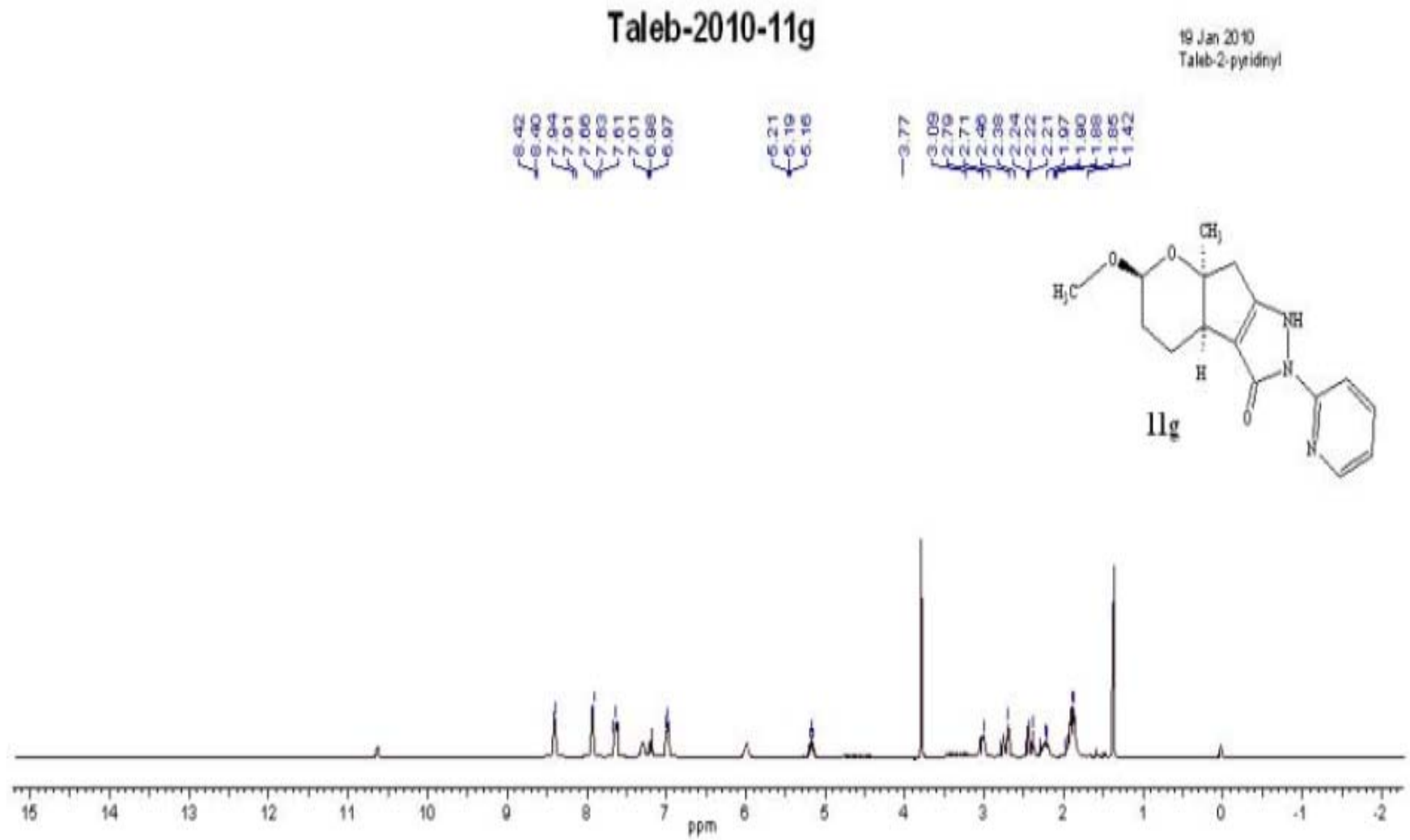
19 Jan 2010
Taleb-2indolyl
10.62
10.26
7.75
7.72
7.52
7.39
7.36
7.19
7.16
7.14
6.53
6.50
6.48
4.84
3.49
3.01
2.79
2.71
2.46
2.38
2.24
2.22
2.21
1.97
1.90
1.88
1.85
1.47
11f
ppm


Taleb-2010-11g
19 Jan 2010
Taleb-2-pyridinyl
8.42
8.40
7.94
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7.66
7.63
7.61
7.01
6.98
6.97
6.21
6.19
6.16
3.77
3.09
2.79
2.71
2.46
2.38
2.24
2.22
2.21
1.97
1.90
1.88
1.85
1.42
CH3
O
O
H3C
NH
N
H
O
N
11g
15
14
13
12
11
10
9
8
7
ppm
6
5
4
3
2
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-1
-2