Concise approach to mono- and disubstituted luotonin A analogs and their cytotoxicity test

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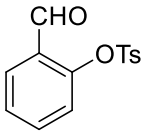
General Information

All reactions were run in oven-dried glassware under an argon atmosphere. All reactions were monitored by Thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plates, visualized by UV florescence quenching (254 nm), *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH), ammonium molybdate (in 10% H_2SO_4), potassium permanganate (in water containing NaOH and K_2CO_3), or Hanessian's staining solution. Ambient temperature refers to 18–26 °C. Flash column chromatography (EtOAc/Hexanes or EtOAc/CH_2Cl_2 or EtOAc/$CHCl_3$) was performed on Cica 60 (spherical/63–210 μm) silica gel. NMR spectra were measured on Varian 400 MR or JEOL AL–400 spectrometers at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra, or a JEOL JX–500 spectrometer at 500 MHz for ^{1}H spectra, or JEOL JNM–ECA600 or JNM–ECZ600 spectrometers at 600 MHz for ^{1}H spectra and 150 MHz for ^{13}C spectra. ^{1}H spectra were calibrated from internal standard TMS (δ 0.0) or solvent resonance ($CHCl_3$: 7.26, $(CD_3)_2SO$: 2.49). ^{13}C spectra were calibrated from solvent resonance ($CHCl_3$: 77.0, $(CD_3)_2SO$: 39.5). NMR data are reported as: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. Infrared spectra were recorded on a SHIMADZU FT–IR 8300 spectrophotometer and reported in frequency of absorption (cm^{-1}). High-resolution mass spectra using fast atom bombardment (FAB) was reported on a JEOL MStaion JMS-700.

Materials

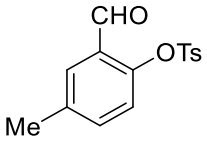
Anhydrous THF and methylene chloride (CH_2Cl_2) were purchased from Kanto Chemical Co., Inc. Dioxane was distilled from CaH_2 prior to use. DMF and DMSO were distilled from CaH_2 under reduced pressure. $POCl_3$ and PBr_3 were distilled and used immediately. TsCl was recrystallized from $CHCl_3$ prior to use. Unless otherwise mentioned, commercially obtained reagents were used as received.

Synthetic Procedures



17a

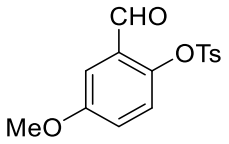
2-Formylphenyl 4-methylbenzenesulfonate (**17a**): To a stirred solution of salicylic aldehyde (**16a)** (1.01 g, 8.28 mmol) in CH_2Cl_2 (1.00 mL) and NaOH (291 mg, 7.26mmol) in water (3.00 mL) was added a solution of TsCl (1.82 g, 9.57 mmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred overnight at ambient temperature. After separation, the organic layer was acidified with aqueous HCl solution. The solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide an oil. The oil was purified by flash column chromatography (SiO_2, 50% EtOAc/Hexanes) to afford **17a** (2.12 g, 93%) as a white solid; mp 50–52 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.21 (dd, *J* = 1.0, 8.2 Hz, 1H), 7.33–7.35 (m, 1H), 7.38–7.42 (m, 2H), 7.59 (ddd, *J* = 1.0, 7.0, 8.6 Hz, 1H), 7.70–7.72 (m, 2H), 7.87 (dd, *J* = 1.6, 8.6 Hz, 1H), 9.99 (s, 1H).



17b

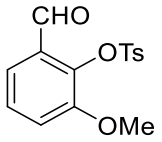
2-Formyl-4-methylphenyl 4-methylbenzenesulfonate (**17b**): To a stirred solution of 5-methylsalicylic aldehyde (**16b)** (554 mg, 4.07 mmol) in CH_2Cl_2 (1.00 mL) and NaOH (190 mg, 4.75 mmol) in water (3.00 mL) was added a solution of TsCl (840 mg, 4.41 mmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred overnight at ambient temperature. After separation, the organic layer was acidified with aqueous HCl solution. The solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide an oil. The oil was purified by flash column chromatography (SiO_2, 25% EtOAc/Hexanes) to afford **17b** (1.14 g, 97%) as a white solid; mp 120–123 ºC; IR (NaCl): 1698, 1171, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.45

(s, 3H), 7.07 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 2.4, 8.4 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 149.2, 146.2, 137.7, 136.0, 131.4, 130.1, 128.9, 128.7, 128.5, 123.5, 21.8, 20.8; HRMS (FAB) calcd for $C_{13}H_{15}O_4S$ $[M+H]^+$: 291.0691. Found: 291.0688.



17c

2-Formyl-4-methoxyphenyl 4-methylbenzenesulfonate (**17c**)[1]: To a stirred solution of 5-methoxysalicylic aldehyde **16c** (331 mg, 2.18 mmol) in CH_2Cl_2 (1.00 mL) and NaOH (143 mg, 3.59 mmol) in water (3.00 mL) was added a solution of TsCl (564 mg, 2.96 mmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred overnight at ambient temperature. After separation, the organic layer was acidified with aqueous HCl solution. The solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide an oil. The oil was purified by flash column chromatography (SiO_2, 25% EtOAc/Hexanes) to afford **17c** (752 mg, 100%) as a white solid; mp 90–94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.82 (s, 3H), 7.07 (m, 1H), 7.29 (dd, J = 1.0, 2.4 Hz, 1H), 7.33 (dd, J = 8.0 Hz, 2H), 7.68 (dd, J = 8.0 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 158.3, 146.2, 145.0, 131.2, 130.1, 129.9, 128.5, 125.0, 122.3, 110.5, 55.8, 21.8.

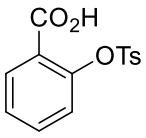


17d

2-Formyl-6-methoxyphenyl 4-methylbenzenesulfonate (**17d**)[1]: To a stirred solution of 3-methoxysalicylic aldehyde **16d** (1.05 g, 6.94 mmol) in CH_2Cl_2 (1.00 mL) and NaOH (300 mg, 7.50 mmol) in water (3.00 mL) was added a solution of TsCl (1.52 g, 8.00 mmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred overnight at ambient

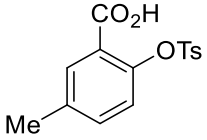
[1] W. B. Motherwell and S. Vázquez, *Tetrahedron Lett.,* 2000, **41**, 9667.

temperature. After separation, the organic layer was acidified with aqueous HCl solution. The solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide an oil. The oil was purified by flash column chromatography (SiO_2, 25% EtOAc/Hexanes) to afford **17d** (1.94 g, 91%) as a white solid; mp 91–95 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.59 (s, 3H), 7.11 (dd, *J* = 1.6, 6.4 Hz, 1H), 7.30–7.36 (m, 3H), 7.49 (dd, *J* = 3.2, 6.4 Hz, 1H), 7.77 (dd, *J* = 1.6, 6.8 Hz, 2H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0 152.7, 143.6, 132.6, 131.3, 129.6, 128.6, 127.9, 119.4, 117.9, 55.9, 21.7.



15a

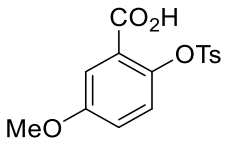
2-(Tosyloxy)benzoic acid (**15a**)[2]: To a solution of aldehyde **17a** (1.50 g, 5.44 mmol) in CH_3CN (1.00 mL) were added NaH_2PO_4 (1.03 g, 8.59 mmol), H_2O_2 (0.500 mL), $NaClO_2$ (1.52 g, 16.9 mmol), and water (3.00 mL) at 10 ºC. The reaction mixture was stirred at ambient temperature for 2 h. A small amount of Na_2SO_3 was added to quench unreacted HOCl and H_2O_2. The resulting mixture was acidified with aqueous HCl solution. The mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide a solid. The solid was recrystallized from EtOAc to give salicylic acid **15a** (1.51 g, 100%) as a white solid; mp 165–166 ºC (lit.[2] mp: 165–171 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.29 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.31–7.34 (m, 2H), 7.39 (ddd, *J* = 0.8, 7.8, 7.9 Hz, 1H), 7.58 (ddd, *J* = 1.6, 7.9, 7.9Hz, 1H), 7.73–7.76 (m, 2H), 7.97 (dd, *J* = 1.6, 7.8 Hz, 1H).



15b

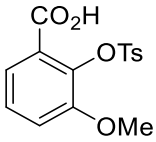
[2] S. V. Luis, P. Ferrer, and M. I. Burguete, *J. Org. Chem.,* 1990, **55**, 3808.

5-Methyl-2-(tosyloxy)benzoic acid (**15b**): To a solution of aldehyde **17b** (1.00 g, 3.44 mmol) in CH_3CN (6.00 mL) were added NaH_2PO_4 (1.18 g, 9.80 mmol), H_2O_2 (0.500 mL), $NaClO_2$ (936 mg, 10.4 mmol), and water (3.00 mL) at 10 ºC. The reaction mixture was stirred at ambient temperature for 2 h. A small amount of Na_2SO_3 was added to quench unreacted HOCl and H_2O_2. The resulting mixture was acidified with aqueous HCl solution. The mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide a solid. The solid was recrystallized from EtOAc to give salicylic acid **15b** (777 mg, 73%) as a white solid; mp 217–218 ºC; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.31 (s, 3H), 2.42 (s, 3H), 6.86 (d, J = 8.4 Hz, 1H), 7.35 (ddd, J = 0.4, 2.0, 5.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.67–7.69 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 165.9, 146.1, 145.2, 137.5, 132.2, 132.1, 130.5, 128.7, 126.6, 123.6, 21.6, 20.6.



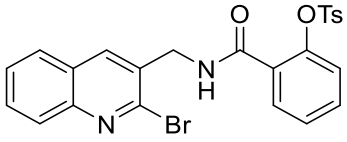
15c

5-Methoxy-2-(tosyloxy)benzoic acid (**15c**): To a solution of aldehyde **17c** (2.50 g, 8.15 mmol) in CH_3CN (6.00 mL) were added NaH_2PO_4 (2.02 g, 16.9 mmol), H_2O_2 (1.00 mL), $NaClO_2$ (2.26 g, 25.0 mmol) and water (3.00 mL) at 10 ºC. The reaction mixture was stirred at ambient temperature for 2 h. A small amount of Na_2SO_3 was added to quench unreacted HOCl and H_2O_2. The resulting mixture was acidified with aqueous HCl solution. The mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide a solid. The solid was recrystallized from EtOAc to give salicylic acid **15c** (2.13 g, 81%) as a white solid; mp 172–173 ºC; IR (NaCl): 2917, 1699, 1170, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.85 (s, 3H), 7.06 (dd, J = 3.2, 8.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 3.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 145.7, 132.0, 129.8, 128.7, 125.5, 124.7, 120.1, 116.3, 55.8, 21.7; HRMS (FAB) calcd for $C_{15}H_{14}O_6S$ $[M]^+$: 322.0511. Found: 322.0514.



15d

3-Methoxy-2-(tosyloxy)benzoic acid (**15d**): To a solution of aldehyde **17d** (1.87 g, 6.12 mmol) in CH_3CN (10.0 mL) were added NaH_2PO_4 (1.36 g, 11.3 mmol), H_2O_2 (1.00 mL), $NaClO_2$ (1.82 g, 20.2 mmol), and water (5.00 mL) at 10 ºC. The reaction mixture was stirred at ambient temperature for 2 h. A small amount of Na_2SO_3 was added to quench unreacted HOCl and H_2O_2. The resulting mixture was acidified with aqueous HCl solution. The mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide a solid. The solid was recrystallized from EtOAc to give salicylic acid **15d** (1.97 g, 100%) as a white solid; mp 170–171 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.62 (s, 3H), 7.12 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.28–7.33 (m, 3H), 7.50 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H).

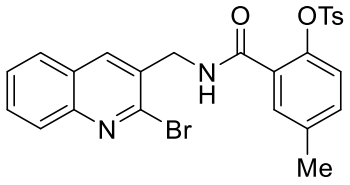


13a

2-(((2-Bromoquinolin-3-yl)methyl)carbamoyl)phenyl 4-methylbenzenesulfonate (**13a**)[3]: To a stirred of azide **18** (207 mg, 0.790 mmol) in THF (10.0 mL) were added PPh_3 (278 mg, 1.06 mmol) and water (1.00 mL) at ambient temperature. The mixture was heated at 55 ºC for l h. After removal of the solvent under reduced pressure, the residue was diluted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude amine. The amine was used in the next step without purification. To a stirred solution of the crude amine in CH_2Cl_2 (20.0 mL) were added BOP (349 mg, 0.790 mmol), 2-tosyloxybenzoic acid **15a** (277 mg, 0.950 mmol), and Et_3N (0.420 mL, 3.16 mmol) at ambient temperature. The mixture was allowed to stir for 6 h. After removal of the solvent under reduced pressure, the residue was purified

[3] K. Natsuki, T. Shindo, and M. Toyota, *Heterocycles,* 2012, **84**, 1301.

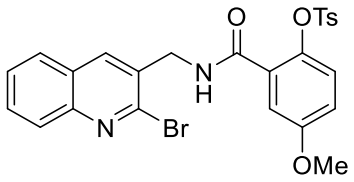
by flash column chromatography (SiO_2, 33% EtOAc/Hexanes) to afford amide **13a** (351 mg, 87% for two steps) as a white crystal; mp 163–165 ºC; IR (NaCl): 3327, 2992, 1649, 1438, 1171, 1119, 839, 835, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.73–4.77 (m, 2H), 7.14–7.19 (m, 3H), 7.27–7.31 (m, 1H), 7.37 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.53–7.58 (m, 1H), 7.62–7.64 (m, 2H), 7.72 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.81–7.83 (m, 1H), 7.91 (dd, *J* = 1.2, 7.6 Hz, 1H), 8.03 (dd, *J* = 7.6, 8.0 Hz, 1H), 8.25–8.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 150.1, 147.8, 147.1, 146.5, 146.4, 138.1, 137.5, 132.5, 131.8, 130.5, 130.1, 129.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 127.3, 123.1, 41.8, 21.8; HRMS (FAB) calcd for $C_{24}H_{20}O_4N_2BrS$ $[M+H]^+$: 511.0327. Found: 511.0339.



13b

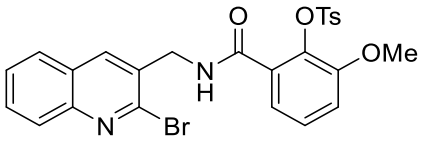
2-(((2-Bromoquinolin-3-yl)methyl)carbamoyl)-4-methylphenyl 4-methylbenzene-sulfonate (**13b**): To a stirred of azide **18** (48.1 mg, 0.180 mmol) in THF (5.00 mL) were added PPh_3 (53.3 mg, 0.200 mmol) and water (0.200 mL) at ambient temperature. The mixture was heated at 55 ºC for l h. After removal of the solvent under reduced pressure, the residue was diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude amine. The amine was used in the next step without purification. To a stirred solution of the crude amine in CH_2Cl_2 (20.0 mL) were added BOP (84.9 mg, 0.190 mmol), 3-methyl-6-tosyloxybenzoic acid **15b** (58.8 mg, 0.190 mmol), and Et_3N (50.0 μmL, 0.360 mmol) at ambient temperature. The mixture was allowed to stir for 6 h. After remova1 of the solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, 50% EtOAc/Hexanes) to afford amide **13b** (78.6 mg, 82% for two steps) as a white crystal; mp 155–158 ºC; IR (NaCl): 3283, 1654, 1656, 1529, 1373, 1172, 1091, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32–2.35 (m, 6H), 4.73 (dd, *J* = 4.4, 6.4 Hz, 2H), 7.00 (dd, *J* = 4.0, 4.8 Hz), 7.17–7.22 (m, 3H), 7.27–7.32 (m, 1H), 7.52–7.58 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.69–7.74 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 8.02 (dd, *J* = 7.2, 8.0 Hz, 1H), 8.26 (d, *J* = 20 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 146.1, 144.2, 137.9, 137.8, 132.9, 132.0, 131.7, 130.4, 130.0, 129.3, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.4, 127.2, 122.8, 41.7, 21.7, 20.8; HRMS (FAB) calcd for $C_{25}H_{22}O_4N_2BrS$ $[M+H]^+$: 525.0484. Found: 525.0455.



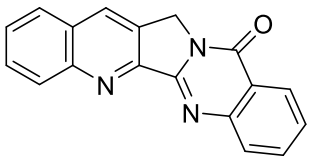
13c

2-(((2-Bromoquinolin-3-yl)methyl)carbamoyl)-4-methoxyphenyl 4-methylbenzene-sulfonate (**13c**): To a stirred of azide **18** (113 mg, 0.430 mmol) in THF (10.0 mL) were added PPh_3 (118 mg, 0.450 mmol) and water (0.500 mL) at ambient temperature. The mixture was heated at 55 ºC for l h. After removal of the solvent under reduced pressure, the residue was diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude amine. The amine was used in the next step without purification. To a stirred solution of the crude amine in CH_2Cl_2 (20.0 mL) were added BOP (314 mg, 0.710 mmol), 5-methoxy-2-(tosyloxy)benzoic acid **15b** (225 mg, 0.700 mmol), and Et_3N (0.120 mL, 0.860 mmol) at ambient temperature. The mixture was allowed to stir for 6 h. After remova1 of the solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, 50% EtOAc/Hexanes) to afford amide **13c** (200 mg, 86% for two steps) as a white crystal; mp 168–171 ºC; IR (NaCl): 3299, 2917, 1656, 1372, 1181, 1091, 893, 776, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.81 (s, 3H), 4.74 (dd, J = 4.0, 6.2 Hz, 2H), 6.92 (ddd, J = 1. 2, 4.0, 4.8 Hz, 1H), 7.01 (dd, J = 4.0, 4.8 Hz, 1H), 7.18 (br d, J = 8.4 Hz, 2H), 7.36 (d, J = 6.8 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7. 53–7. 58 (m, 1H), 7. 61 (d, J = 8. 4 Hz, 2H), 7.72 (dddd, J = 1.6, 1.6, 3.2, 7.2 Hz, 1H), 7.83 (br d, J = 8.0 Hz, 1H), 8.03 (br t, J = 8.0 Hz, 1H), 8.27 (br d, J = 20.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 146.1, 143.1, 139.1, 138.0, 137.4, 131.6, 130.4, 129.9, 129.2, 128.4, 128.2, 128.2, 127.9, 127.7, 127.3, 127.2, 124.2, 118.6, 115.0, 55.8, 43.6, 41.7, 21.7; HRMS (FAB) calcd for $C_{25}H_{22}O_5N_2BrS$ $[M+H]^+$: 541.0433. Found: 541.0391.



13d

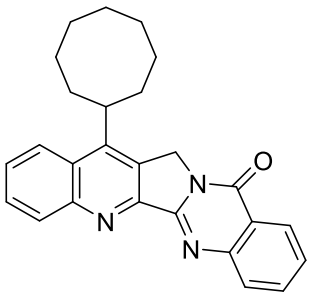
2-(((2-Bromoquinolin-3-yl)methyl)carbamoyl)-6-methoxyphenyl 4-methylbenzene-sulfonate (**13d**): To a stirred of azide **18** (409 mg, 1.55 mmol) in THF (30.0 mL) were added PPh_3 (612 mg, 2.33 mmol) and water (2.00 mL) at ambient temperature. The mixture was heated at 55 ºC for l h. After removal of the solvent under reduced pressure, the residue was diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude amine. The amine was used in the next step without purification. To a stirred solution of the crude amine in CH_2Cl_2 (20.0 mL) were added BOP (600 mg, 1.36 mmol), 3-methoxy-2-(tosyloxy)benzoic acid **15d** (524 mg, 1.63 mmol), and Et_3N (0.500 mL, 3.60 mmol) at ambient temperature. The mixture was allowed to stir for 6 h. After remova1 of the solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, 50% EtOAc/Hexanes) to afford amide **13d** (724 mg, 86% for two steps) as a white crystal; mp 166–167 ºC; IR (NaCl): 3296, 2918, 1656, 1372, 1179, 1091, 862, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.52 (s, 3H), 4.68 (dd, *J* = 6.0, 13.2 Hz, 2H), 6.99 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.17–7.22 (m, 1H), 7.28–7.34 (m, 3H), 7.49 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.52–7.57 (m, 1H), 7.70 (dddd, *J* = 2.0, 2.0, 3.2, 6.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.00 (dd, *J* = 7.2, 8.0 Hz, 1H), 8.29 (d, *J* = 21.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 152.4, 147.0, 145.6, 137.9, 137.4, 133.7, 130.4, 129.6, 129.4, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 127.3, 127.2, 122.5, 115.2, 55.9, 43.6, 41.7, 21.8; HRMS (FAB) calcd for $C_{25}H_{22}O_5N_2BrS$ $[M+H]^+$: 541.0433. Found: 541.0462.



2

Luotonin A (**2**)[3] : A mixture of amide **13a** (82.2 mg, 0.160 mmol), CuCN (63.1 mg, 0.640 mmol), $Pd_2(dba)_3$ (10.4 mg, 11.0 μmol), DPPF (18.5 mg, 33.0 μmol), K_2CO_3

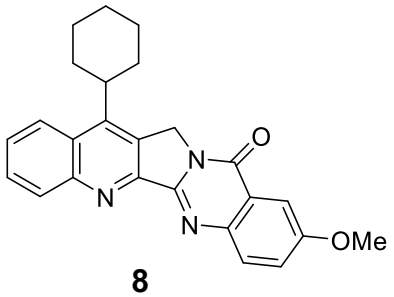
(22.1 mg, 0.160 mmol), and Et_4NCN (53.7 mg, 0.340 mmol) in 1,4-dioxane (3.00 mL) was heated at 130 ºC for 14 h. The resulting mixture was diluted with CH_2Cl_2, and the precipitates were filtered off through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 50% EtOAc/Hexanes) to afford luotonin A (**2**) (37.1 mg, 81%) as a pale yellow needle; mp 280–283 ºC (lit.[3] mp 281–283 ºC); IR (NaCl): 2923, 1652, 1558, 1540, 1507, 1079, 871, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (s, 2H), 7.60 (ddd, *J* = 0.8, 7.2, 7.2 Hz, 1H), 7.71 (ddd, *J* = 0.8, 7.2, 7.2 Hz, 1H), 7.87 (ddd, *J* = 1.2, 7.2, 7.2 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.45 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.45–8.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 152.8, 151.3, 149.6, 149.6, 134.8, 131.8, 130.9, 130.9, 129.6, 129.0, 128.3, 128.3, 128.1, 127.7, 126.6, 121. 5, 47.5; **HRMS** (FAB) calcd for $C_{18}H_{12}ON_3$ $[M]^+$: 285.0902. Found: 285.0904.



7

14-Cyclooctylquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**7**): To a solution of cyclooctane (1.00 mL, 7.43 mmol) and luotonin A (**2**) (13.3 mg, 47.0 μmol) in CH_2Cl_2 (1.00 mL) were added NaN_3 (20.9 mg, 0.321 mmol) and PIFA (101 mg, 0.234 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (5.40 mg, 83.0 μmol) and PIFA (36.2 mg, 84.0 μmol) were added to the reaction mixture. The resulting mixture was stirred for 7 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 93% Toluene/Acetone) to afford 14-cyclooctylluotonin A (**7**) (10.7 mg, 58%) as a yellow solid; mp 270–272 ºC; IR (NaCl): 3370, 2917, 2849, 1672,

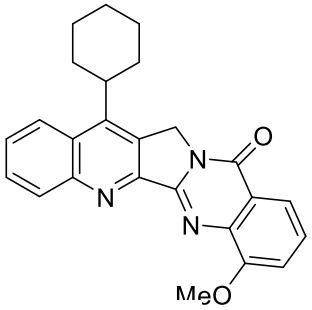
1465, 1254, 1035, 986, 750 cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2SO$, 80 ºC): δ 1.61–1.77 (m, 6H), 1.77–1.88 (m, 3H), 1.88–2.01 (m, 5H), 3.74 (br s, 1H), 5.40 (s, 2H), 7.62 (dt, *J* = 1.8 and 6.6 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.91–7.95 (m, 2H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.36 (br d, *J* = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, 80 ºC): δ 159.2, 152.9, 150.9, 149.2, 148.9, 134.0, 130.5, 129.4, 127.6, 127.4, 126.6, 126.1, 125.6, 120.8, 47.0, 40.0, 32.5, 26.3, 26.1, 25.5; **HRMS** (FAB) calcd for $C_{26}H_{26}ON_3$ $[M+H]^+$: 396.2076. Found: 396.2045.



8

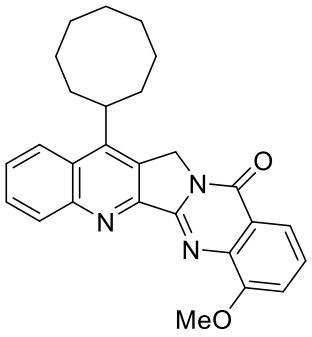
14-Cyclohexyl-9-methoxyquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**8**): To a solution of cyclohexane (1.00 mL, 9.26 mmol) and 9-methoxyluotonin A (**4**) (13.8 mg, 44.0 μmol) in CH_2Cl_2 (1.00 mL) were added NaN_3 (61.9 mg, 0.952 mmol) and PIFA (75.2 mg, 0.175 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (50.8 mg, 0.781 mmol) and PIFA (97.9 mg, 0.228 mmol) were added to the reaction mixture. The resulting mixture was stirred for 7 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 67% EtOAc/Hexanes) to afford 14-cyclohexyl-9-methoxyluotonin A (**8**) (7.50 mg, 43%) as a yellow solid; mp >300 ºC; IR (NaCl): 2923, 2850, 1673, 1622, 1568, 1486, 1269, 1077, 922, 767, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45–1.61 (m, 3H), 1.89–2.08 (m, 7H), 3.69 (br s, 1H), 4.08 (s, 3H), 5.46 (s, 2H), 7.28 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 6.8 Hz, 1H), 7.78 (dt, *J* = 1.2, 7.2 Hz, 1H), 8.00 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.25 (br s, 1H), 8.43 (dd, *J* = 1.2, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 155.5, 153.0, 148.6, 147.8, 146.0, 140.2, 132.0, 129.7, 128.0, 127.6, 127.5, 126.2, 122.3, 117.5, 114.1,

56.0, 48.1, 31.8, 27.0, 26.0; HRMS (FAB) calcd for $C_{25}H_{24}O_2N_3$ $[M+H]^+$: 398.1869. Found: 398.1905.



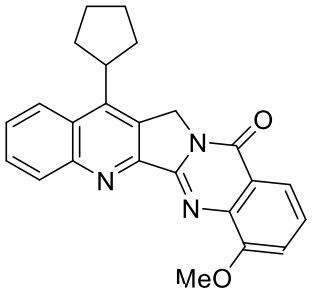
9

14-Cyclohexyl-7-methoxyquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**9**): To a solution of cyclohexane (0.500 mL, 4.63 mmol) and 7-methoxyluotonin A (**5**) (10.8 mg, 34.0 μmol) in CH_2Cl_2 (0.500 mL) were added NaN_3 (60.1 mg, 0.924 mmol) and PIFA (105 mg, 0.245 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (57.2 mg, 0.880 mmol) and PIFA (99.8 mg, 0.232 mmol) were added to the reaction mixture. The resulting mixture was stirred for 14 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 80% $CHCl_3$/EtOAc) to afford 14-cyclohexyl-7-methoxyluotonin A (**9**) (8.20 mg, 61%) as a yellow solid; mp >300 ºC; IR (NaCl): 3371, 2918, 2849, 1673, 1623, 1577, 1466, 1267, 1155, 1034, 745, 642 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 50 ºC): δ 1.43–1.66 (m, 3H), 1.86–2.09 (m, 7H), 3.64 (br s, 1H), 4.08 (s, 3H), 5.45 (s, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.67 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 8.01 (dd, *J* = 1.2, 9.0 Hz, 1H), 8.27 (br d, *J* = 9.0 Hz, 1H), 8.44 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 50 ºC): δ 160.6, 155.8, 152.0, 151.1, 150.1, 148.6, 140.5, 132.2, 129.7, 128.0, 127.6, 126.4, 123.8, 122.6, 117.7, 114.4, 56.1, 48.0, 41.0, 31.9, 27.1, 26.1; HRMS (FAB) calcd for $C_{25}H_{24}O_2N_3$ $[M+H]^+$: 398.1869. Found: 398.1856.



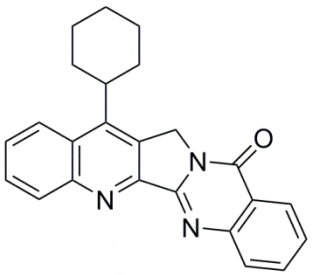
10

14-Cyclooctyl-7-methoxyquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**10**): To a solution of cyclooctane (0.500 mL, 3.72 mmol) and 7-methoxyluotonin A (**5**) (14.7 mg, 47.0 μmol) in CH_2Cl_2 (0.500 mL) were added NaN_3 (65.9 mg, 1.01 mmol) and PIFA (98.3 mg, 0.229 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (54.2 mg, 0.834 mmol) and PIFA (87.2 mg, 0.203 mmol) were added to the reaction mixture. The resulting mixture was stirred for 7 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three tiems with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 80% $CHCl_3$/EtOAc) to afford 14-cyclopentyl-7-methoxyluotonin A (**10**) (15.6 mg, 79%) as a yellow solid; mp >300 ºC; IR (NaCl): 3416, 2918, 2849, 1668, 1632, 1445, 1352, 1268, 1038, 758, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 50 ºC): δ 1.61–1.80 (m, 7H), 1.80–1.91 (m, 3H), 1.93–2.05 (m, 4H), 3.45–3.62 (br d, 1H), 4.08 (s, 3H), 5.37 (s, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.65 (br s, 1H), 7.77 (br t, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.22 (br s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 50 ºC): δ 160.6, 155.8, 152.2, 152.0, 150.5, 140.4, 132.2, 129.7, 127.6, 127.0, 122.6, 117.7, 114.4, 56.1, 47.5, 34.0, 33.3, 27.6, 27.1, 26.3; HRMS (FAB) calcd for $C_{27}H_{28}O_2N_3$ $[M+H]^+$: 426.2182. Found: 426.2161.



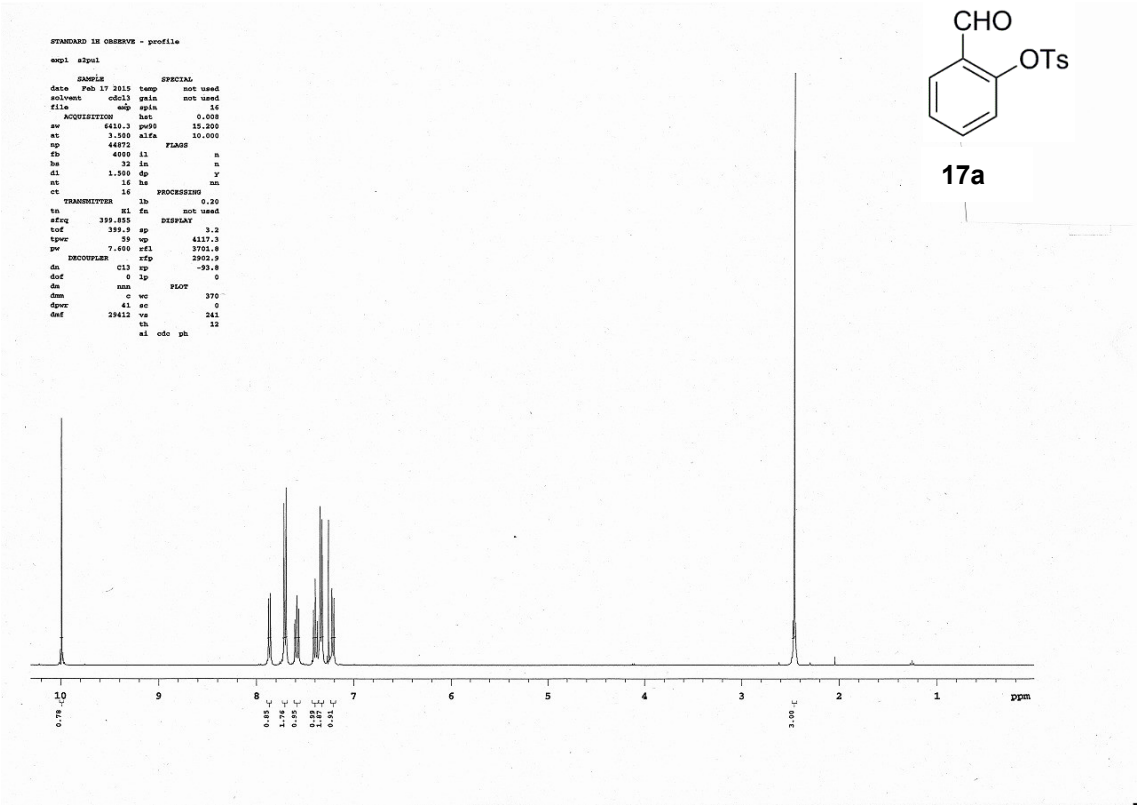
11

14-Cyclopentyl-7-methoxyquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**11**): To a solution of cyclopentane (1.00 mL, 10.7 mmol) and 7-methoxyluotonin A (**5**) (18.9 mg, 60.0 μmol) in CH_2Cl_2 (1.00 mL) were added NaN_3 (58.9 mg, 0.906 mmol) and PIFA (95.1 mg, 0.221 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (60.2 mg, 0.926 mmol) and PIFA (87.9 mg, 0.204 mmol) were added to the reaction mixture. The resulting mixture was stirred for 7 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 83% Toluene/Acetone) to afford 14-cyclopentyl-7-methoxyluotonin A (**11**) (4.60 mg, 20%) as a yellow solid; mp >300 ºC; IR (NaCl): 3394, 2929, 1674, 1631, 1443, 1123, 1034, 760, 616 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 50 ºC): δ 1.87–1.97 (m, 2H), 2.04–2.14 (m, 4H), 2.23–2.31 (m, 2H), 3.84–3.93 (m, 1H), 4.07 (s, 3H), 5.38 (s, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.63 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.77 (dd, *J* = 7.2, 7.8 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.5, 155.5, 152.0, 150.6, 149.9, 147.8, 140.1, 132.0, 129.7, 127.9, 127.7, 127.6, 127.0, 124.1, 122.3, 117.5, 114.1, 56.0, 47.6, 41.5, 32.6, 26.5; HRMS (FAB) calcd for $C_{24}H_{22}O_2N_3$ $[M+H]^+$: 384.1712. Found: 384.1718.



12

14-Cyclohexylquinolino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**12**): To a solution of cyclohexane (1.00 mL, 9.26 mmol) and luotonin A (**2**) (11.3 mg, 40.0 μmol) in CH_2Cl_2 (1.00 mL) were added NaN_3 (5.20 mg, 80.0μmol) and PIFA (35.4 mg, 82.0 μmol) at ambient temperature. The reaction mixture was stirred for 2 h, and then NaN_3 (5.40 mg, 83.0 μmol) and PIFA (36.2 mg, 84.0 μmol) were added to the reaction mixture. The resulting mixture was stirred for 7 h and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and evaporated to provide a crude product. The crude was purified by flash column chromatography (SiO_2, 80% $CHCl_3$/EtOAc) to afford 14-cyclohexylluotonin A (**12**) (8. 60 mg, 58%) as a yellow solid; mp 260–265 ºC; IR (NaCl): 3248, 2924, 2849, 1673, 1623, 1466, 1120, 733, 617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40–1.66 (m, 3H), 1.82–2.11 (m, 7H), 3.71 (br s, 1H), 5.48 (s, 2H), 7.58 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.80–7.88 (m, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.28 (br s, 1H), 8.45 (d, *J* = 1.2, 8.0 Hz, 1H), 8.49 (d, *J* = 1.2, 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 50 ºC): δ 160.7, 152.8, 151.2, 150.1, 149.8, 148.9, 134.5, 132.0, 129.9, 128.9, 128.1, 127.7, 127.2, 126.5, 123.8, 121.5, 47.9, 40.9, 31.9, 27.1, 26.1; HRMS (FAB) calcd for $C_{24}H_{22}ON_3$ $[M+H]^+$: 368.1763. Found: 368.1769.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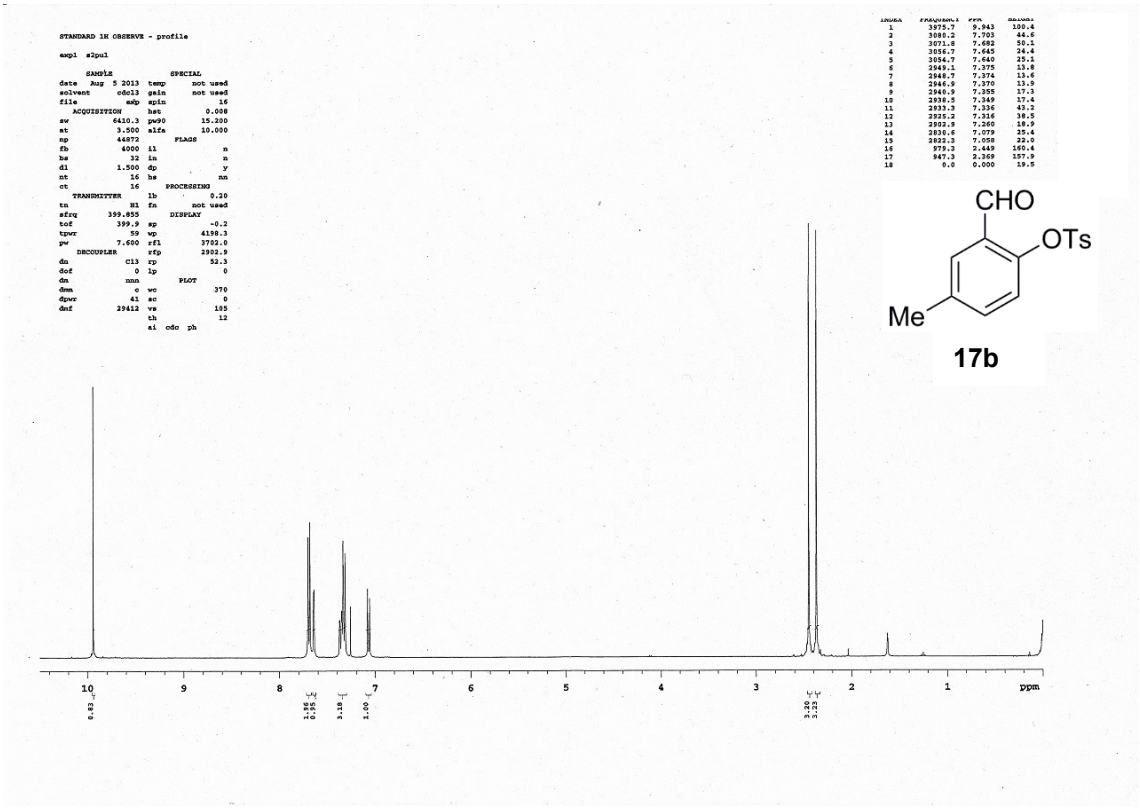
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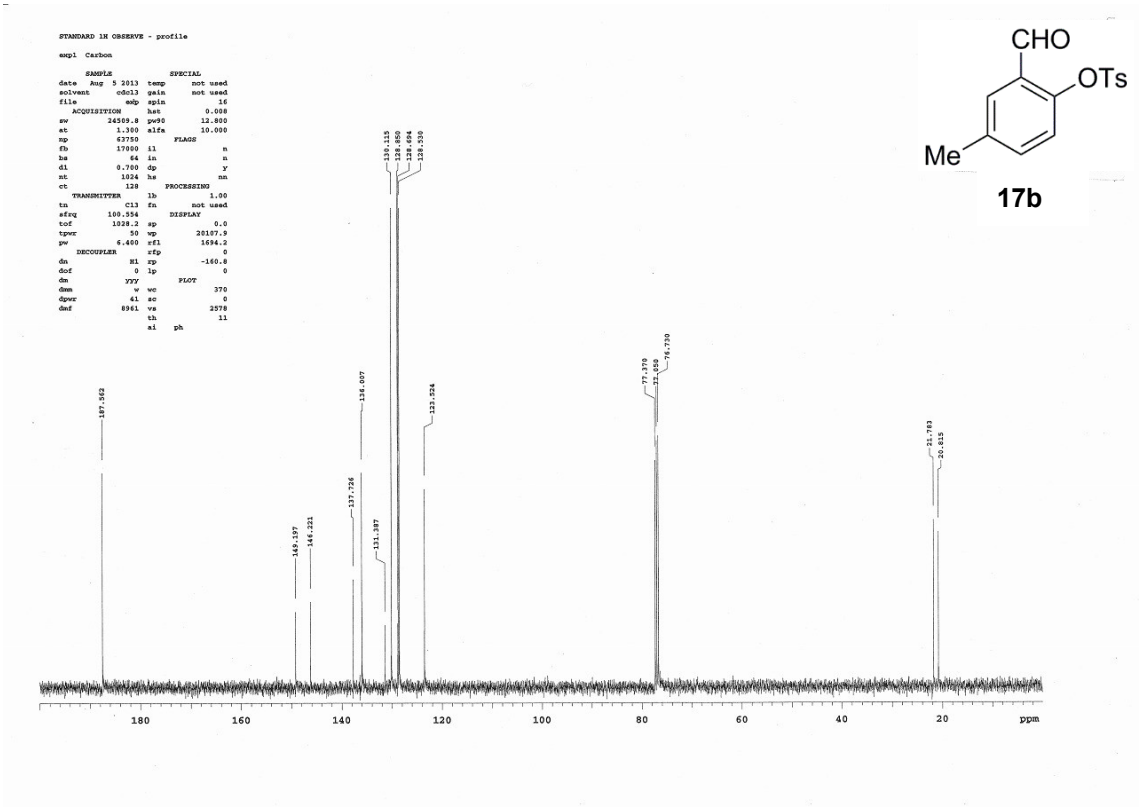
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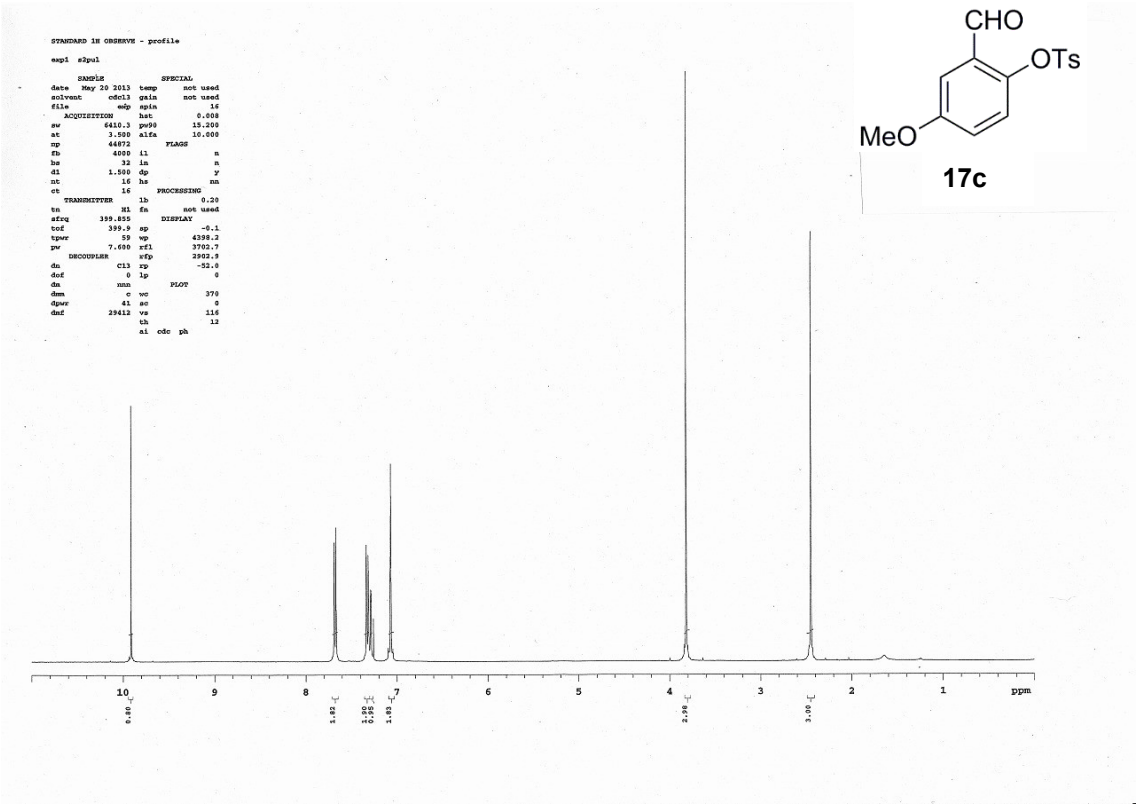
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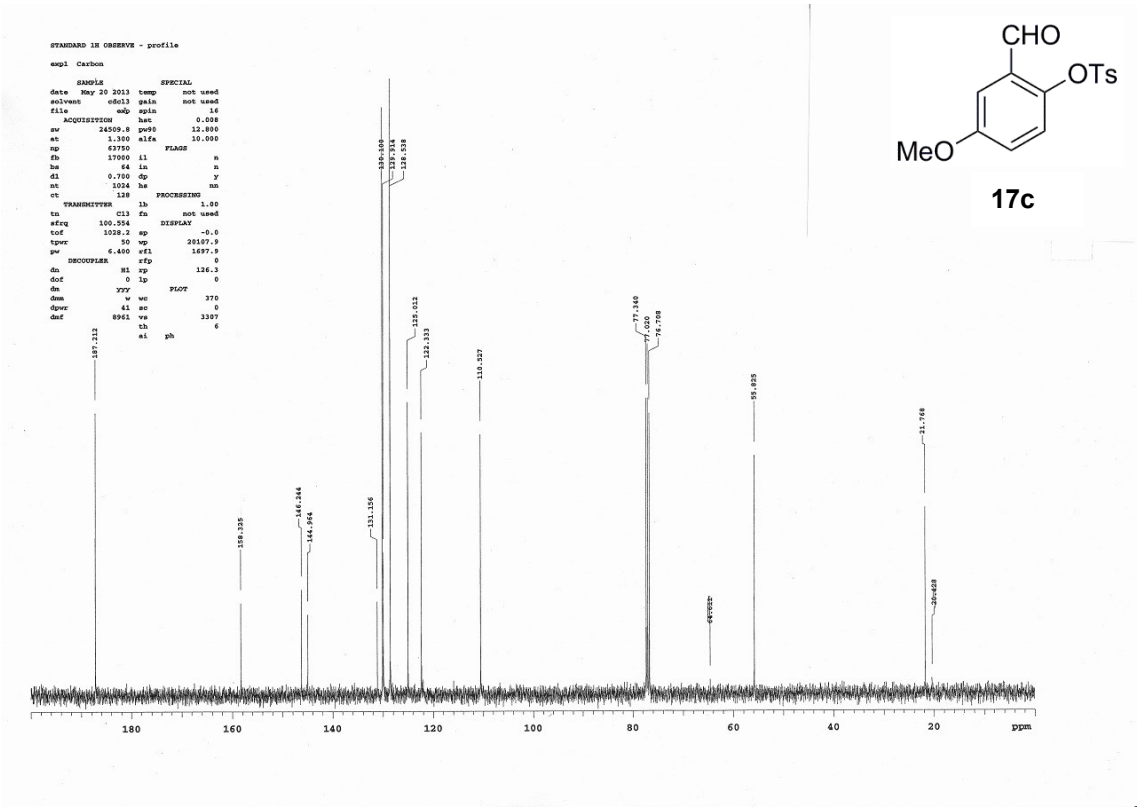
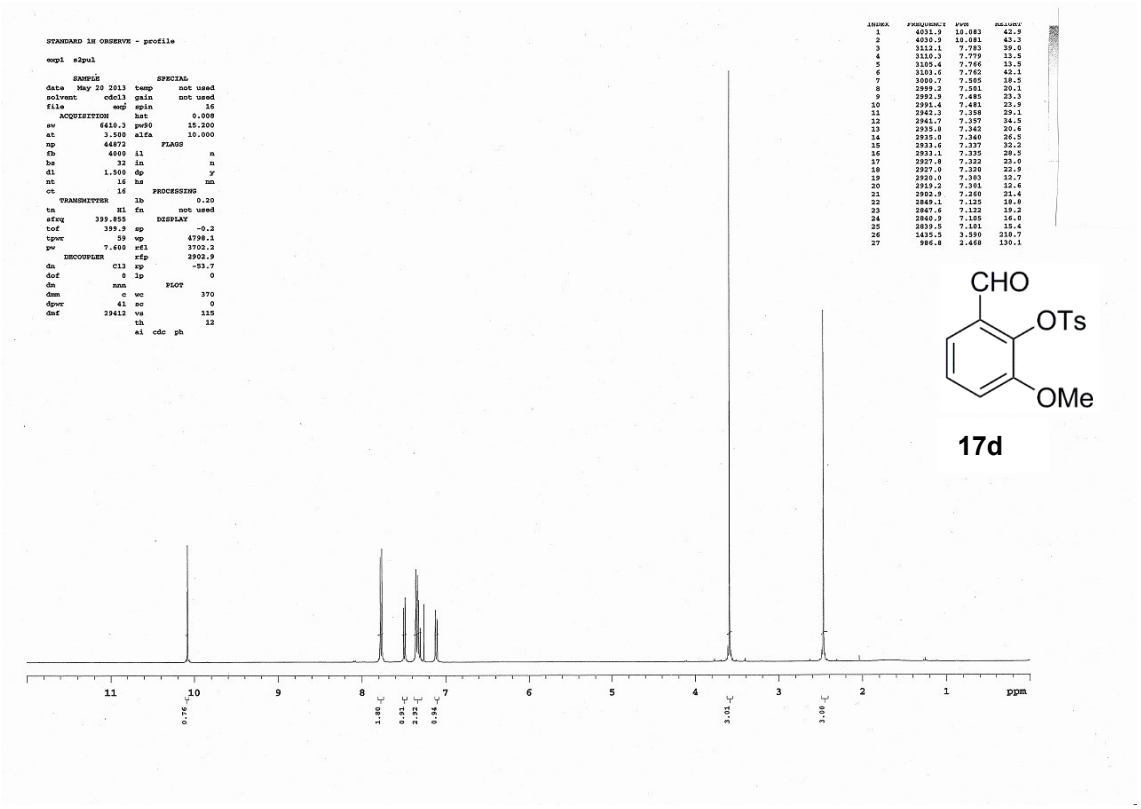
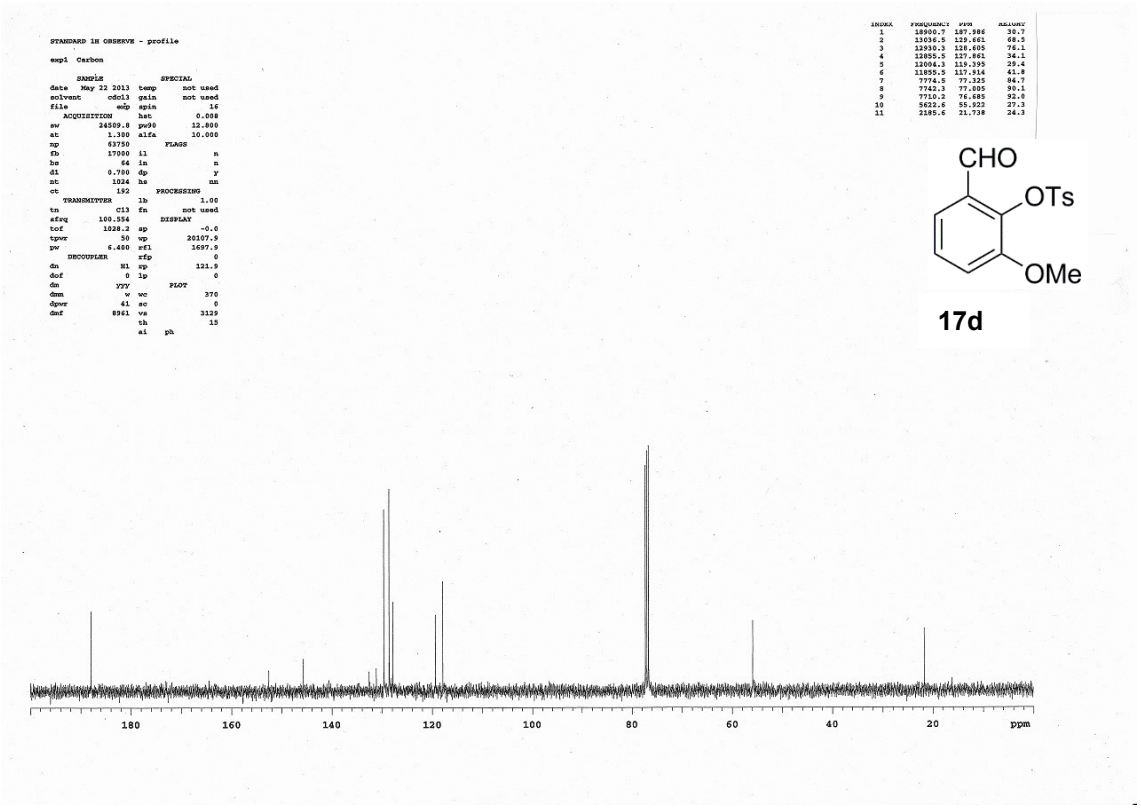
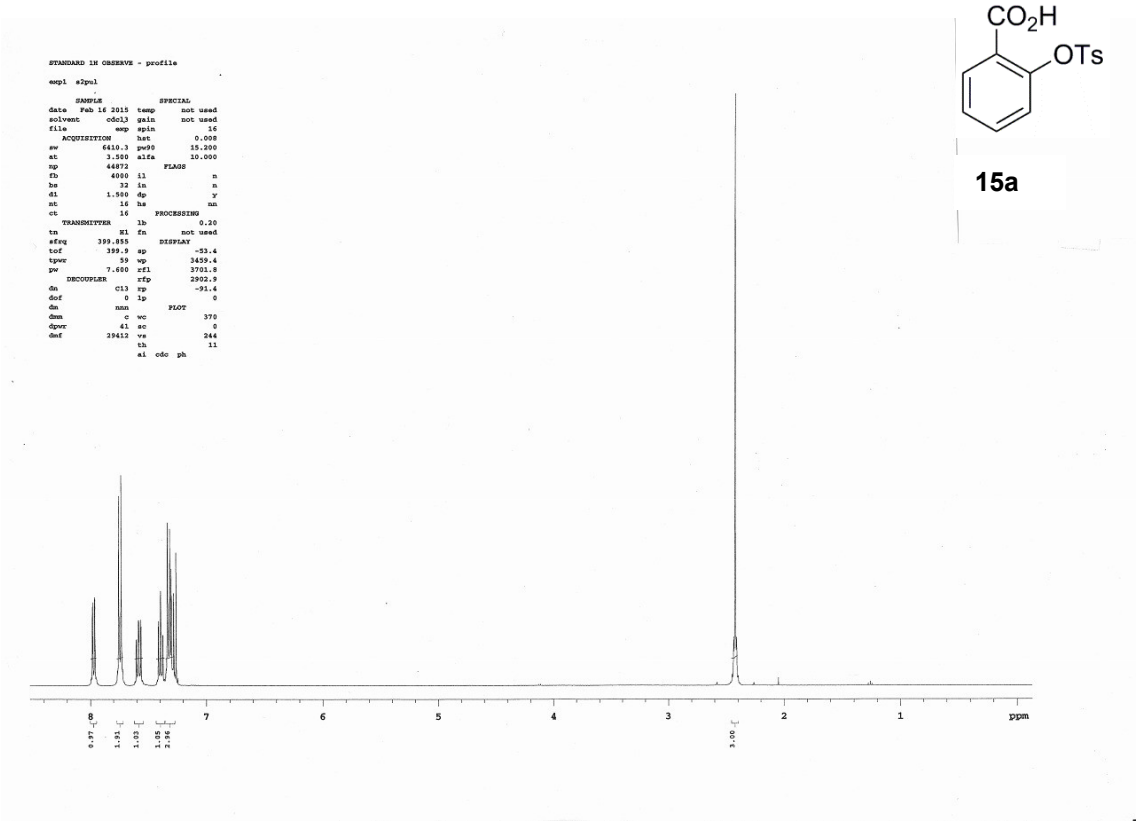
3.00


STANDARD 1H OBSERVE - profile
expl Carbon
SAMPLE
date May 20 2013
solvent cdcl3
file exp
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17050
bs 64
d1 0.700
nt 1024
ct 128
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.2
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -0.0
wp 20107.9
wfl 1697.9
rfp 0
rp 126.3
lp 0
PLOT
wc 370
sc 0
vs 3397
th 6
ai ph
187.212
159.235
146.244
144.994
131.156
129.403
129.314
128.538
125.011
122.333
110.527
77.240
77.020
76.708
55.825
31.766
30.428
180
160
140
120
100
80
60
40
20
ppm
CHO
OTs
MeO
17c

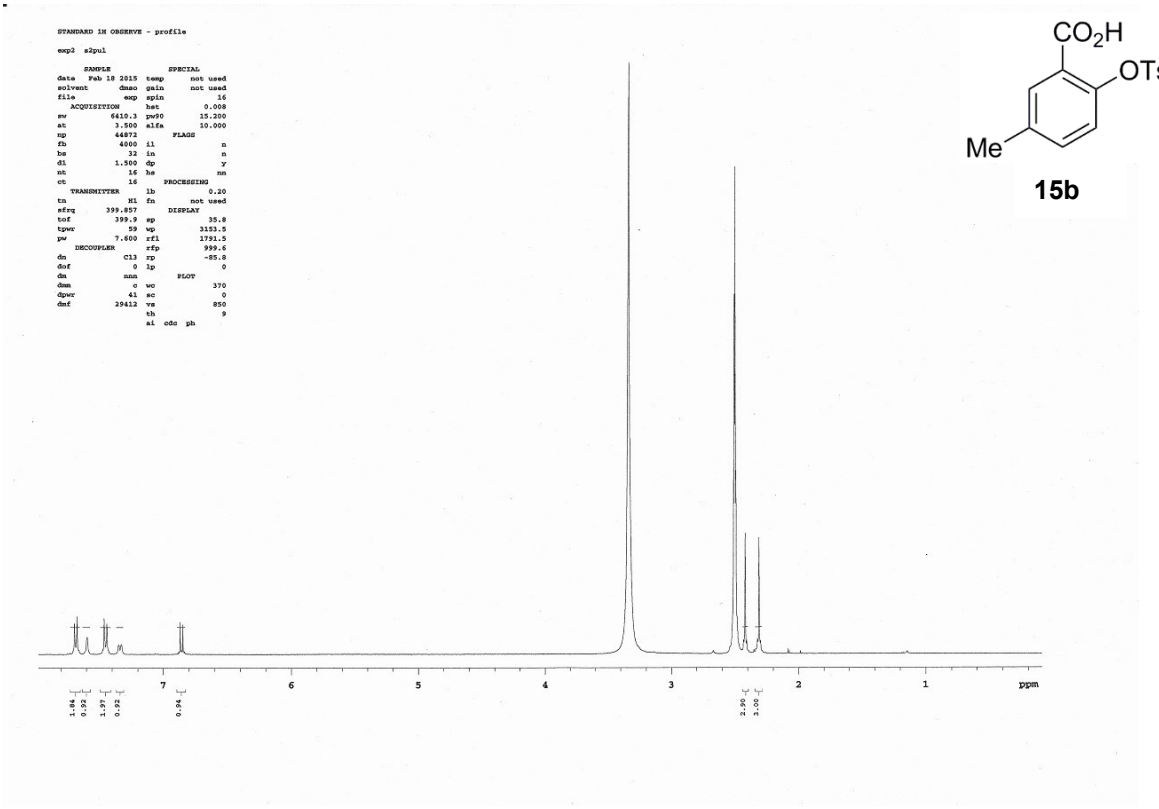

CHO
OTs
OMe
17d
ppm

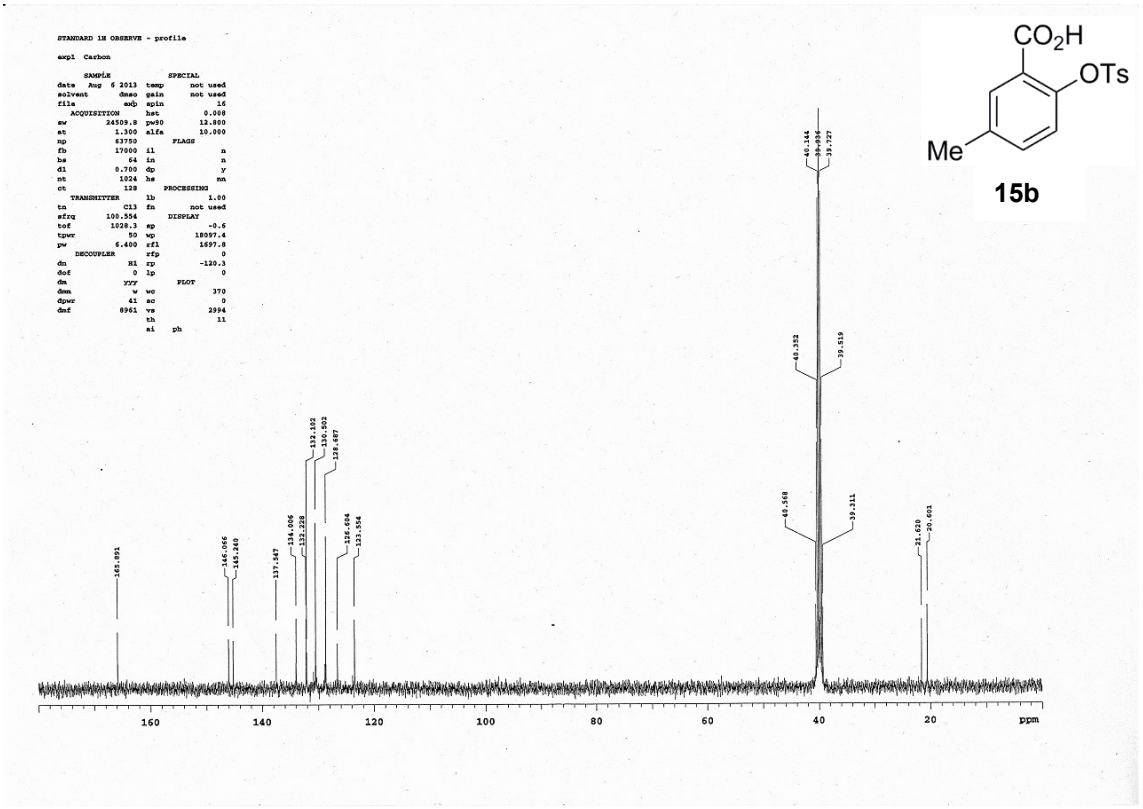

CHO
OTs
OMe
17d
ppm

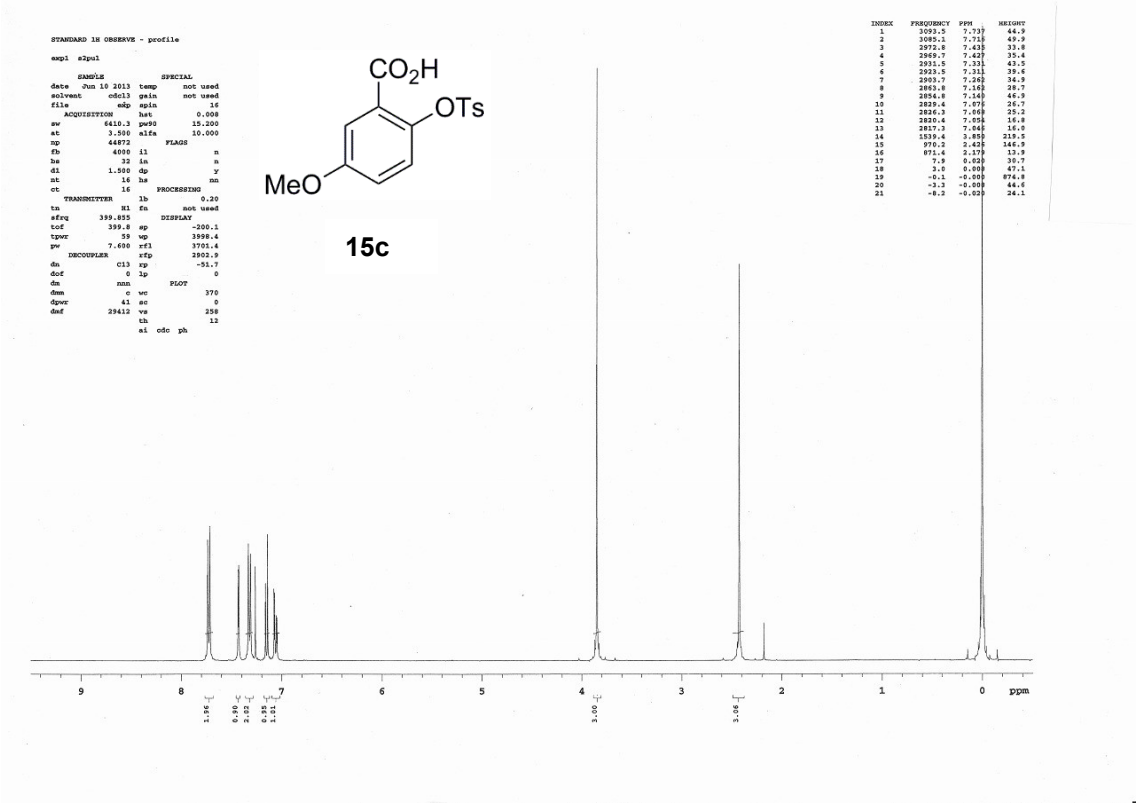

STANDARD 1H OBSERVE - profile
exp1 s2pul
SAMPLE
date Feb 16 2015
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.855
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -53.4
wp 3459.4
rfl 3701.8
rfp 2902.9
rp -91.4
lp 0
PLOT
wc 370
sc 0
vs 244
th 11
al cdc ph
8
7
6
5
4
3
2
1
ppm
0.97
1.91
1.03
1.05
2.98
3.00

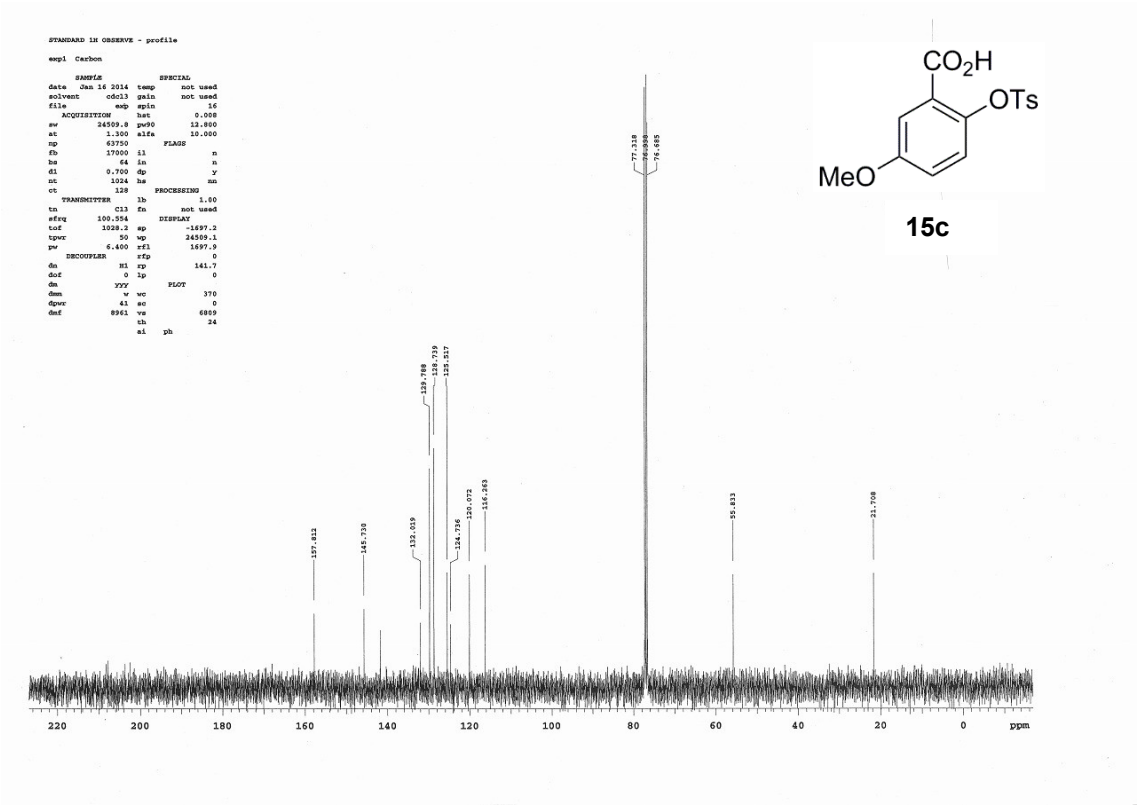
CO2H
OTs

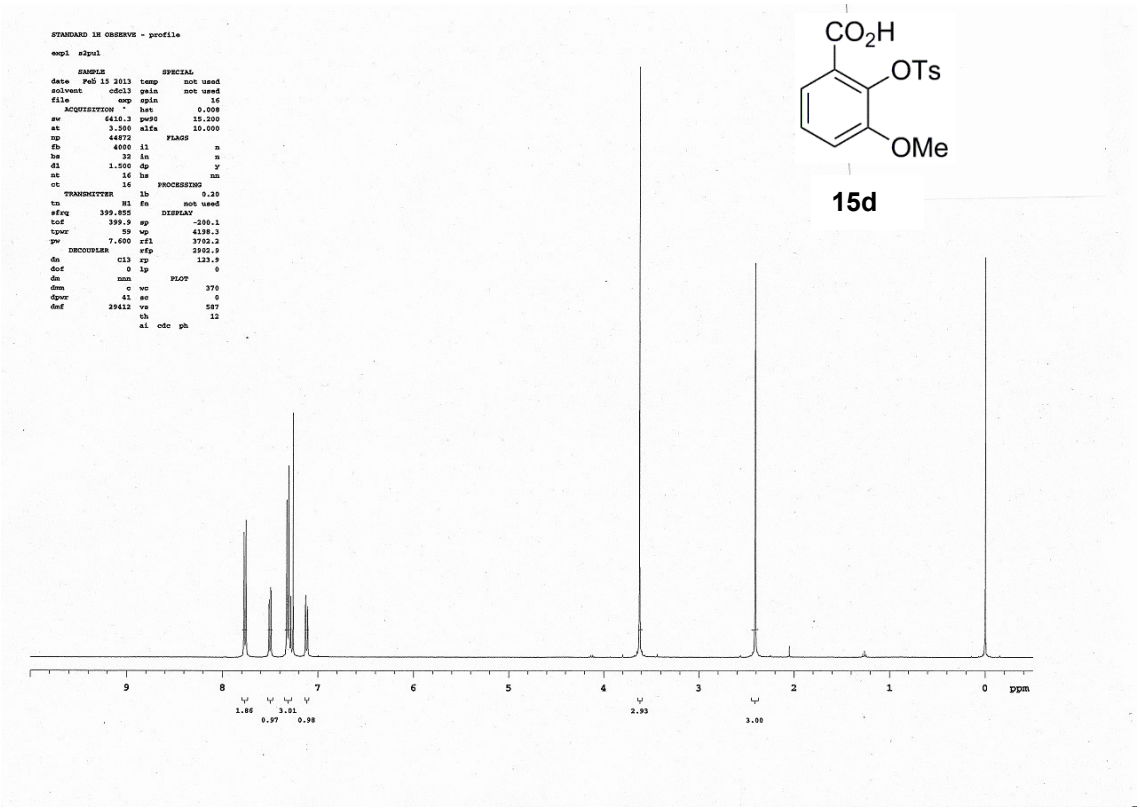
15a

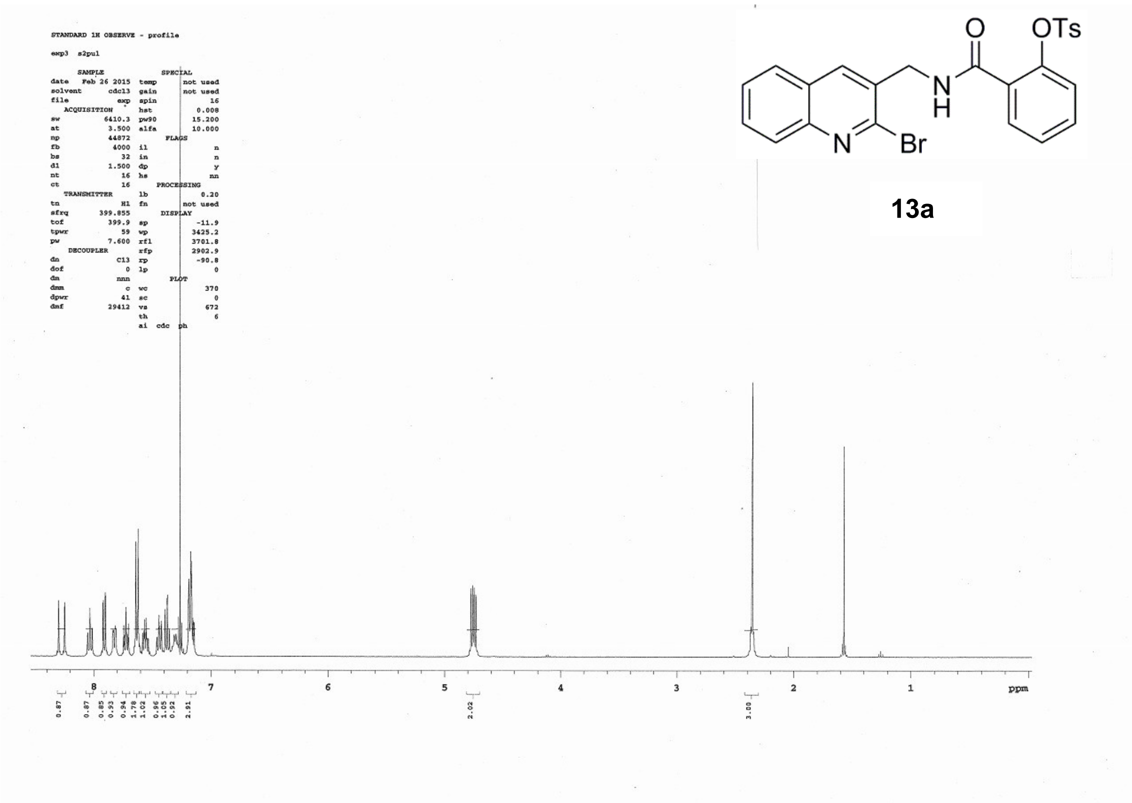

STANDARD 1H OBSERVE - profile
exp2 s2pul
SAMPLE
date Feb 18 2015
solvent dmso
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.857
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp 35.8
wp 3153.5
rfl 1791.5
rfp 999.6
rp -85.8
lp 0
PLOT
wc 370
sc 0
vs 850
th 9
ai cdc ph
1.04
0.92
1.97
0.92
0.94
2.90
3.00
7
6
5
4
3
2
1
ppm
CO2H
OTs
Me
15b


STANDARD 1H OBSERVE - profile
exp1 Carbon
SAMPLE
date Aug 6 2013
solvent dmso
file exp
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17000
bs 64
d1 0.700
nt 1024
ct 128
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.3
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -0.6
wp 18097.4
rfl 1697.8
rfp 0
rp -129.3
lp 0
PLOT
wc 370
sc 0
vs 2994
th 11
ai ph
165.891
146.066
145.240
137.347
134.006
132.228
132.102
130.502
126.497
126.494
123.554
40.144
39.936
39.727
40.352
39.519
40.560
39.311
21.620
20.601
160
140
120
100
80
60
40
20
ppm
CO2H
OTs
Me
15b

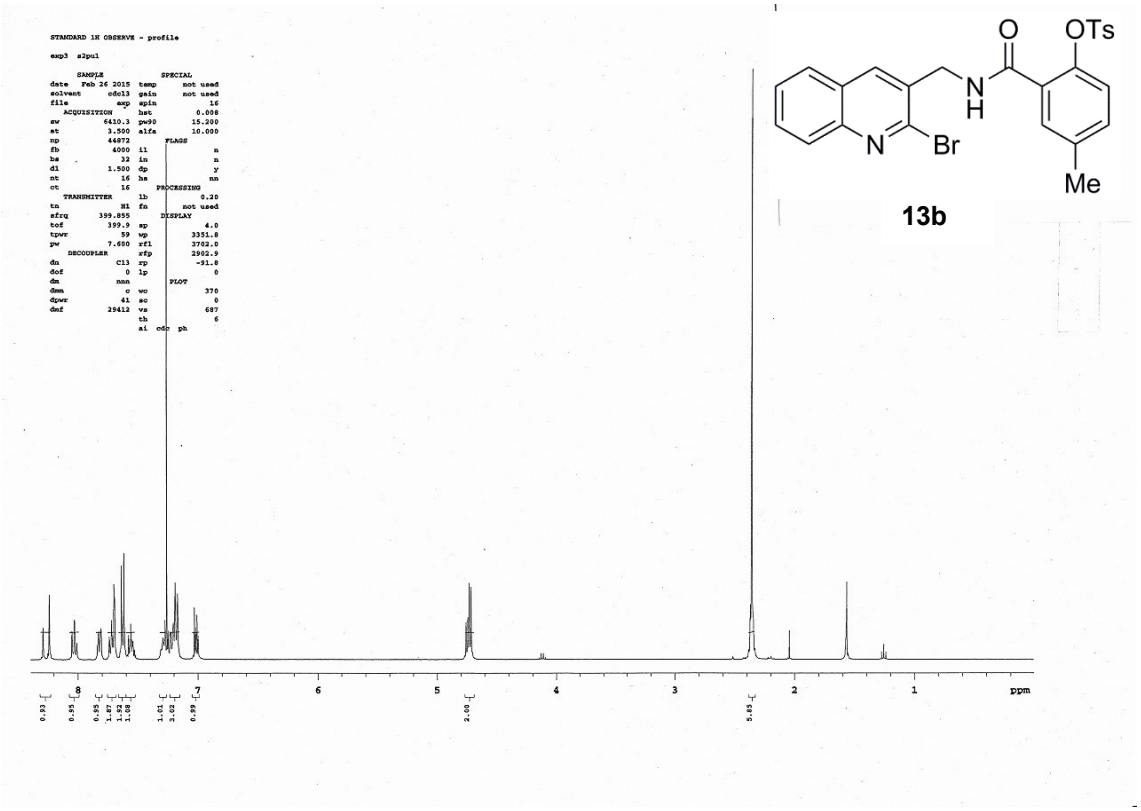

CO2H
OTs
MeO
15c
ppm

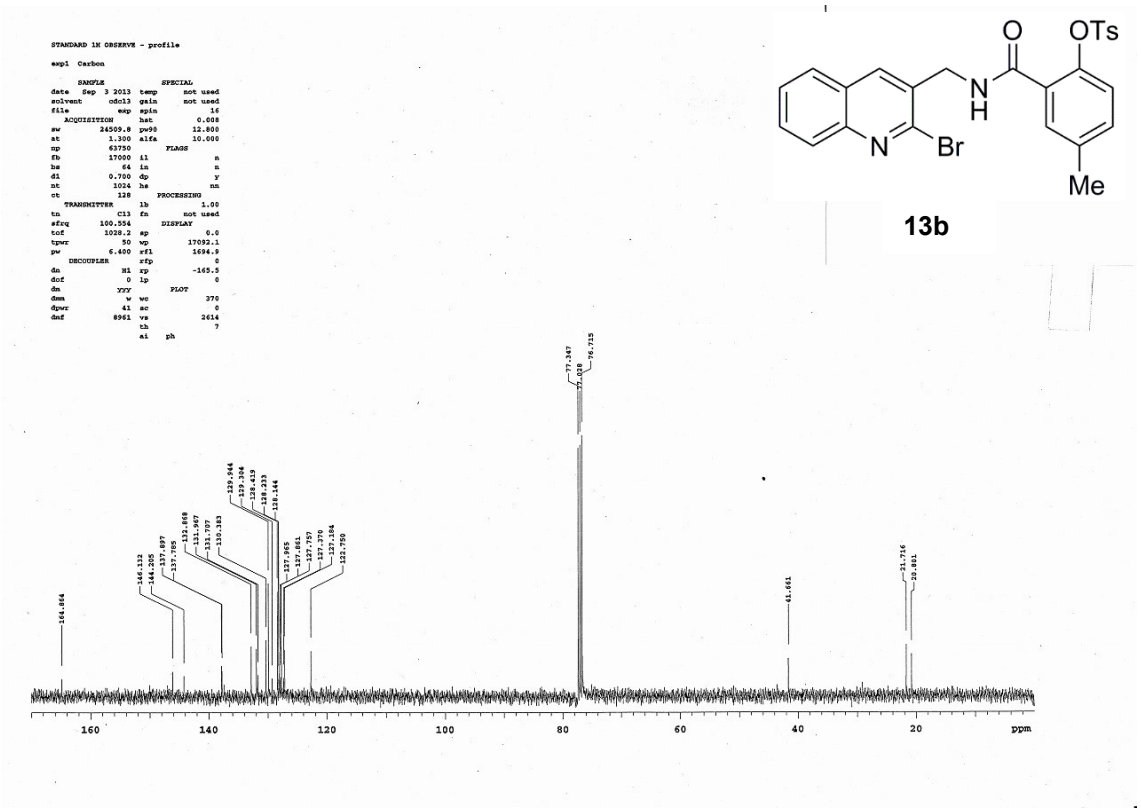

STANDARD 1H OBSERVE - profile
exp1 Carbon
SAMPLE
date Jan 16 2014
solvent cdcl3
file exp
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17000
bs 64
d1 0.700
nt 1024
ct 128
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.2
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.60
fn not used
DISPLAY
sp -1697.2
wp 24569.1
rfl 1697.9
rfp 0
rp 141.7
lp 0
PLOT
wc 370
sc 0
vs 6809
th 24
ai ph
157.812
145.730
132.019
129.788
128.739
126.527
124.736
120.072
116.263
77.318
77.000
76.685
55.833
21.708
220
200
180
160
140
120
100
80
60
40
20
0
ppm
CO2H
OTs
MeO
15c

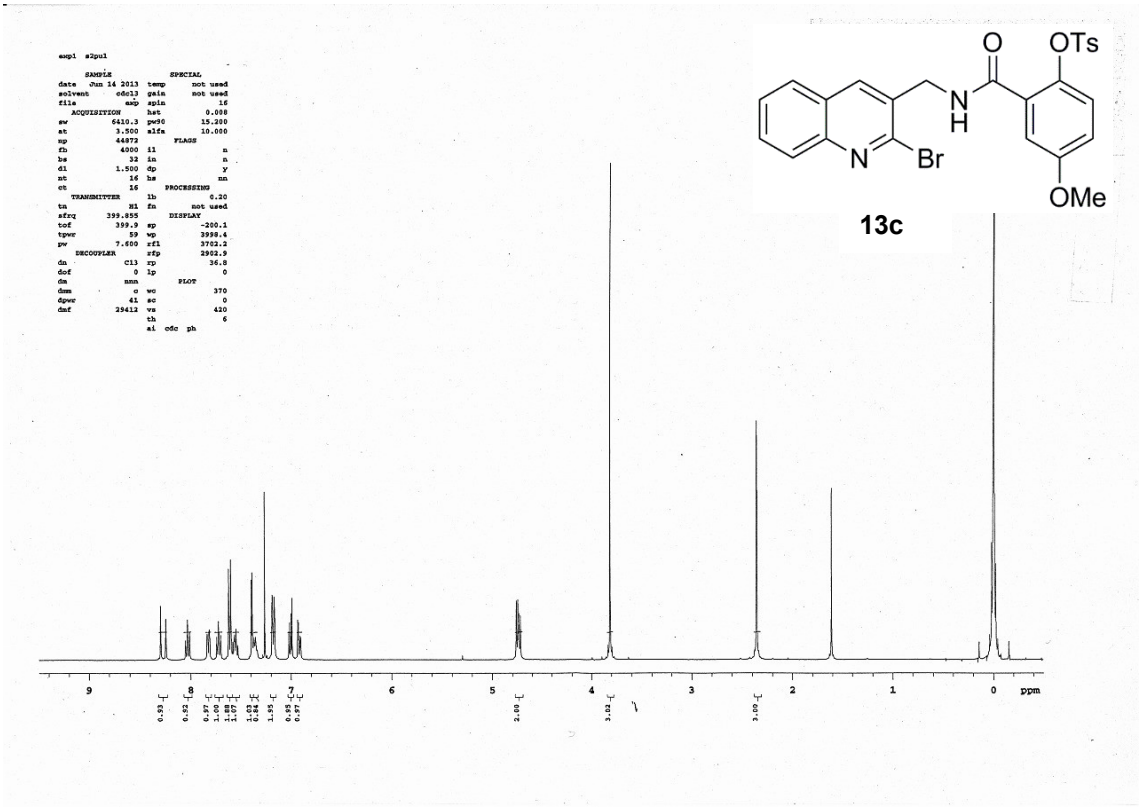

STANDARD 1H OBSERVE - profile
exp1 s2pul
SAMPLE
date Feb 15 2013
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.855
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -200.1
wp 4198.3
rfl 3702.2
rfp 2902.9
rp 123.9
lp 0
PLOT
wc 370
sc 0
vs 587
th 12
ai cdc ph
9
8
7
6
5
4
3
2
1
0
ppm
1.86
3.01
0.97
0.98
2.93
3.00
CO2H
OTs
OMe
15d

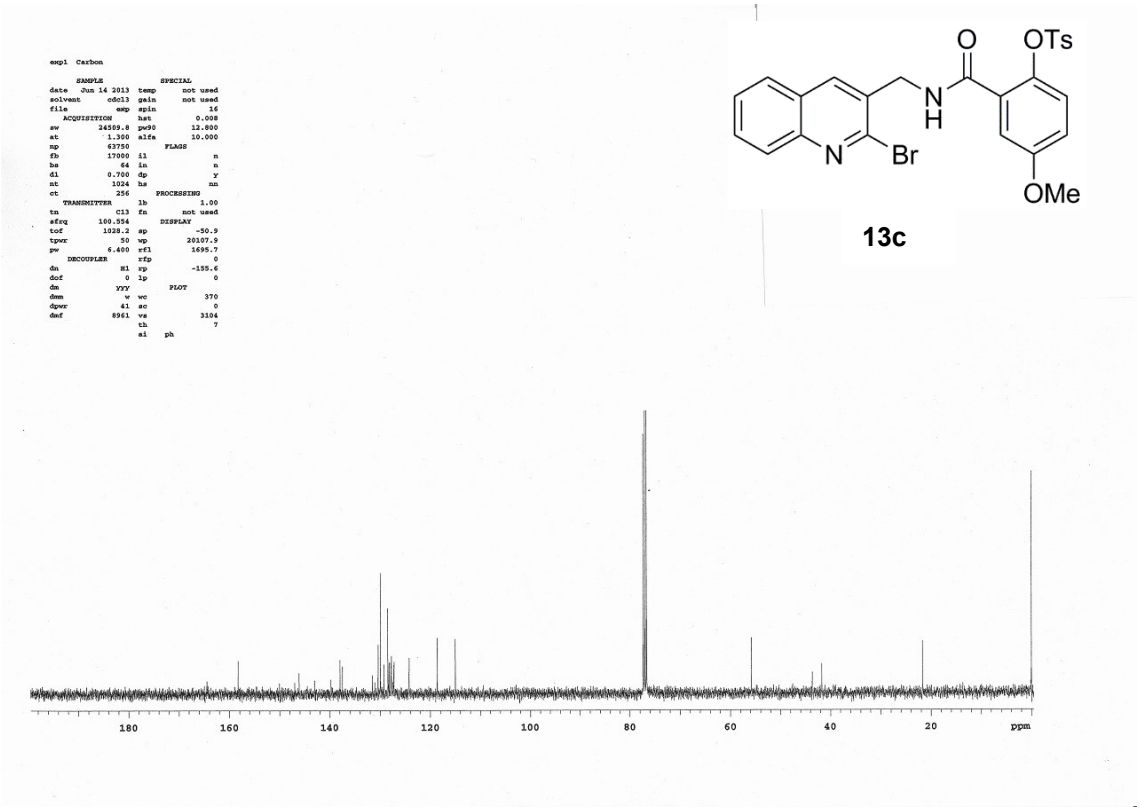


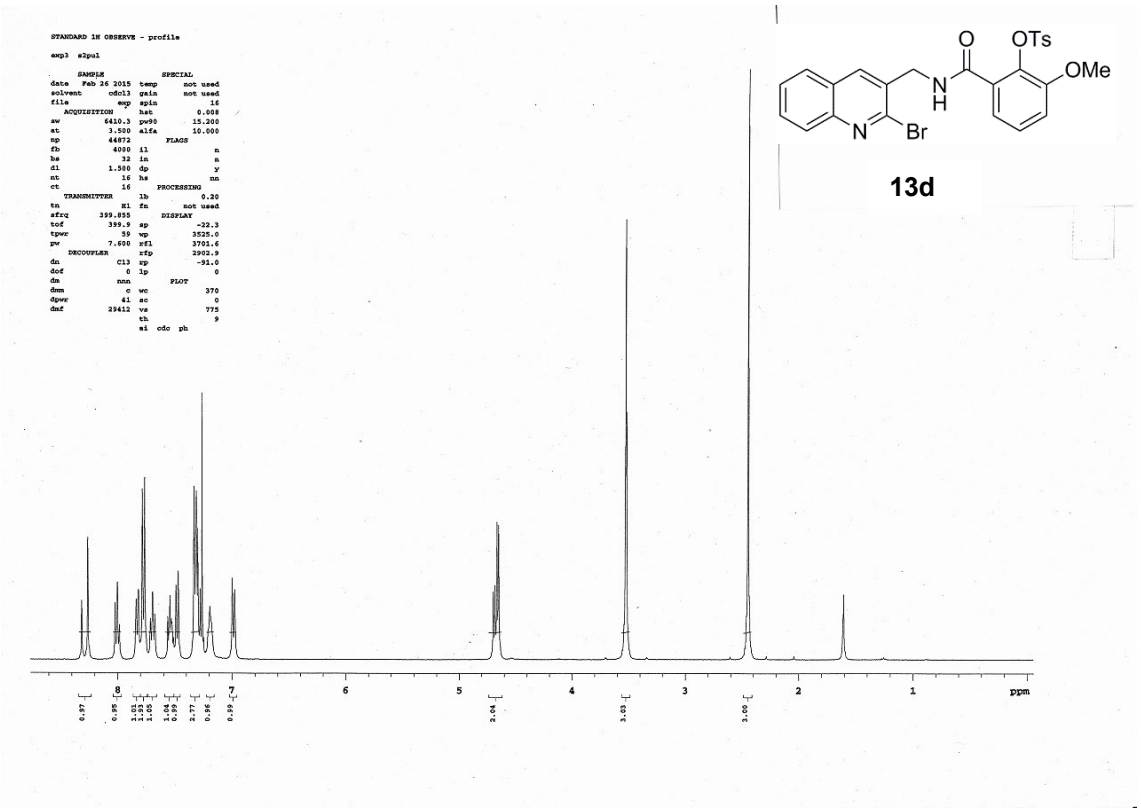
13a

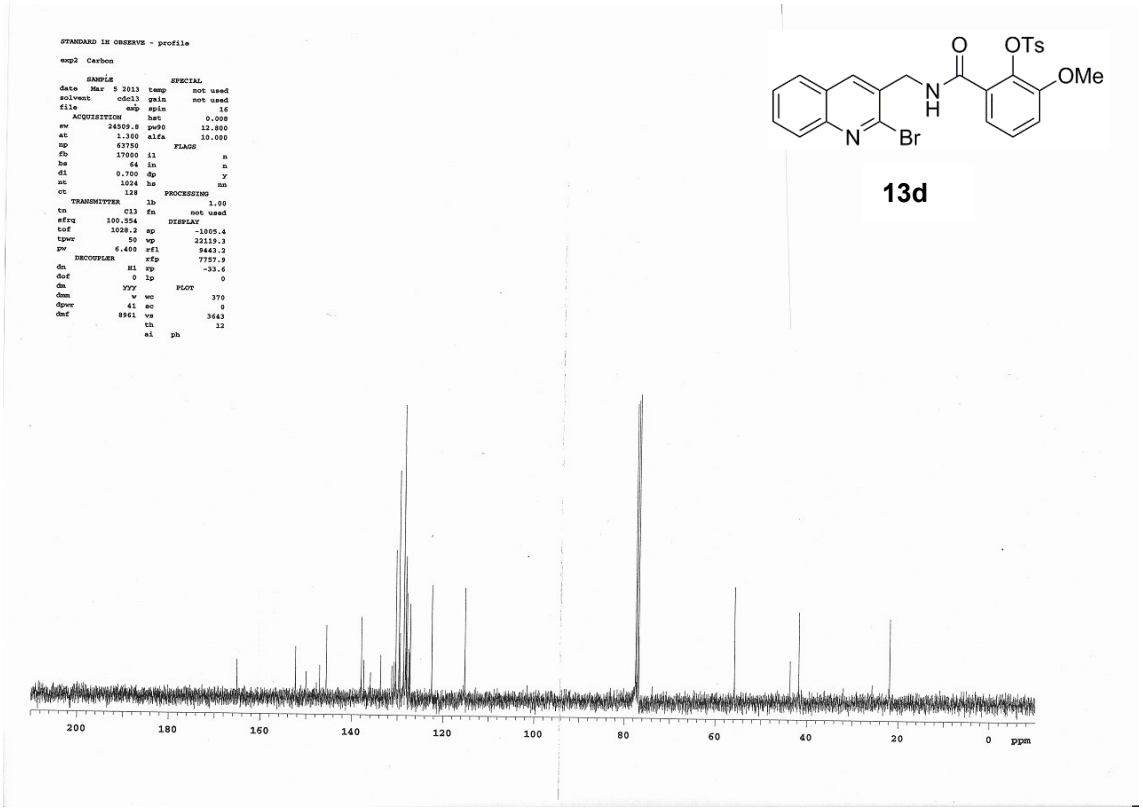

13b
ppm

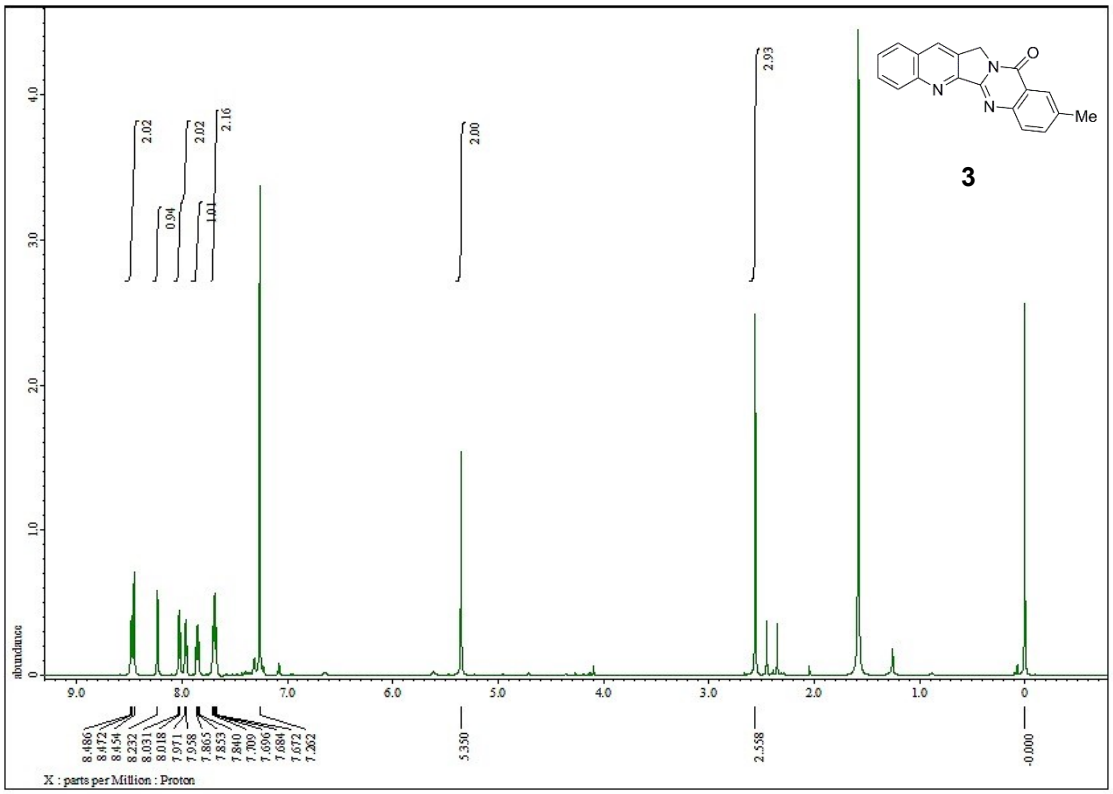

13b
ppm

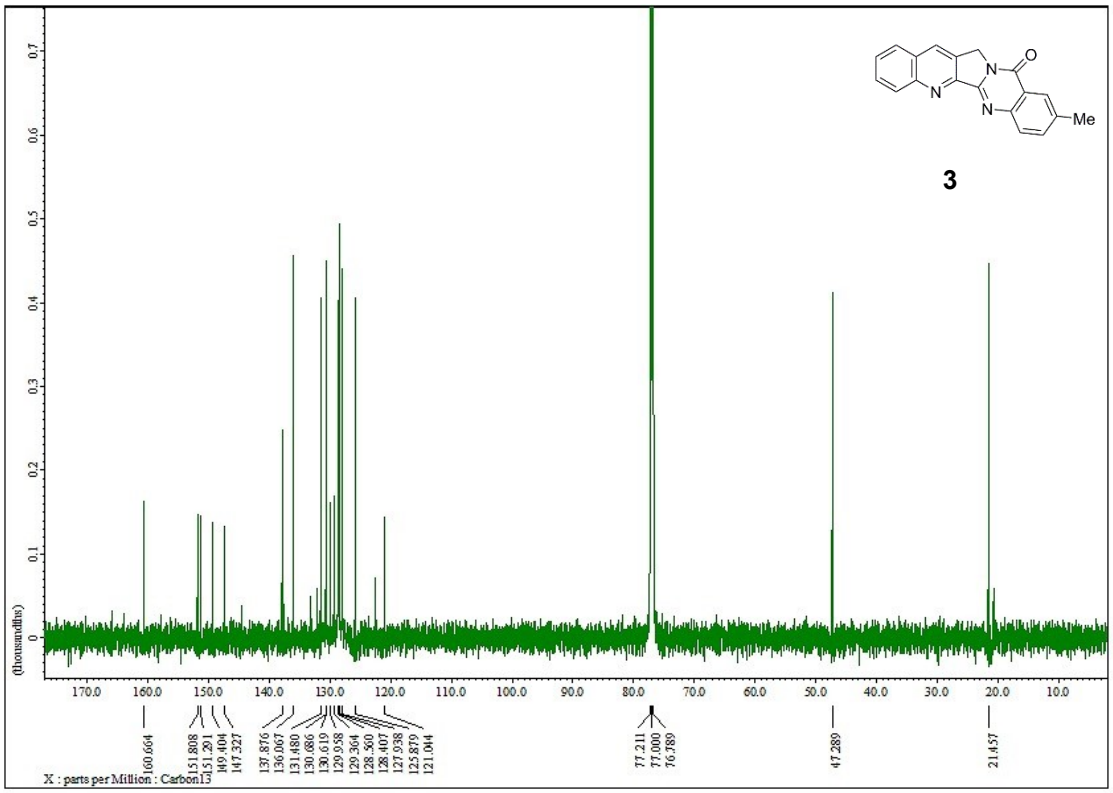

exp1 s2pul
SAMPLE
date Jun 14 2013
solvent cdcl3
file amb
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.895
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -200.1
wp 3998.4
rfl 3702.2
rfp 2902.9
rp 36.8
lp 0
PLOT
wc 370
sc 0
vs 420
th 6
ai cdc ph
O
OTs
N
H
N
Br
OMe
13c
9
8
7
6
5
4
3
2
1
0
ppm
0.93
0.92
0.97
1.06
1.00
1.03
0.84
1.95
0.98
0.97
2.00
3.02
3.00

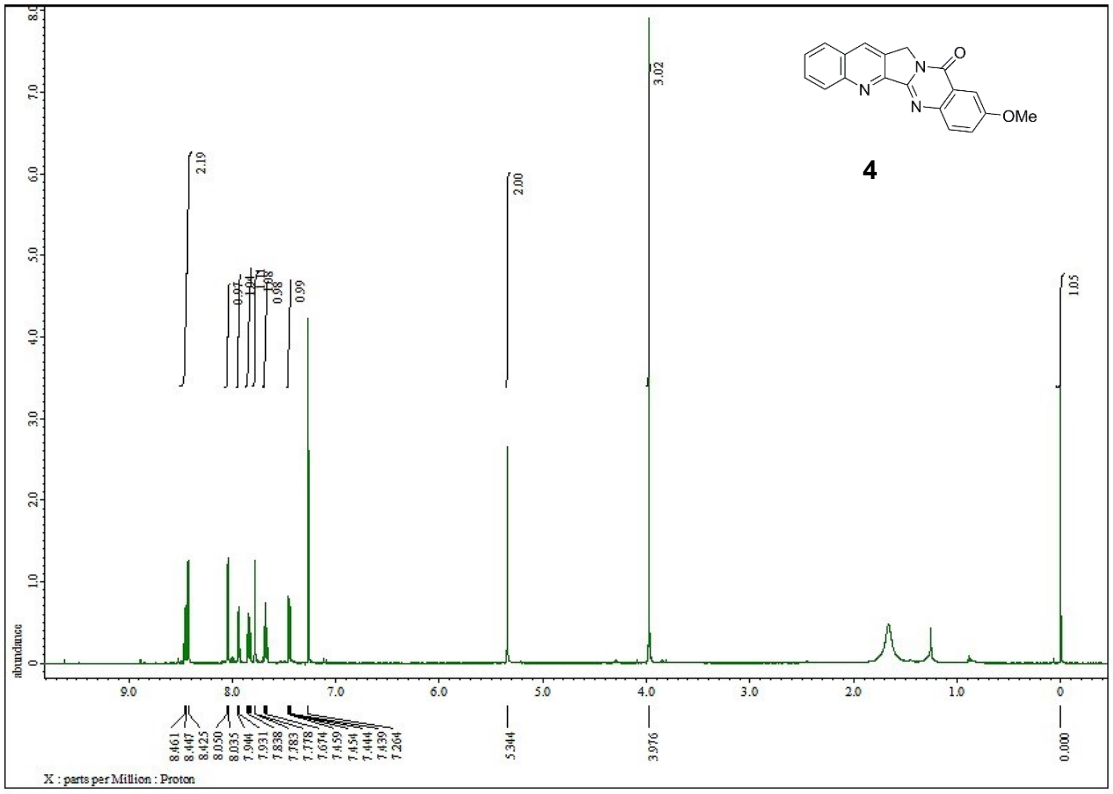

exp1 Carbon
SAMPLE
date Jun 14 2013
solvent cdcl3
file exp
ACQUISITION
sw 24589.8
at 1.300
np 63750
fb 17000
bs 64
d1 0.700
nt 1024
ct 256
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.2
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -50.9
wp 20107.9
rfl 1695.7
rfp 0
rp -155.6
lp 0
PLOT
wc 370
sc 0
vs 3104
th 7
ai ph
O
OTs
N
H
N
Br
OMe
13c
180
160
140
120
100
80
60
40
20
ppm

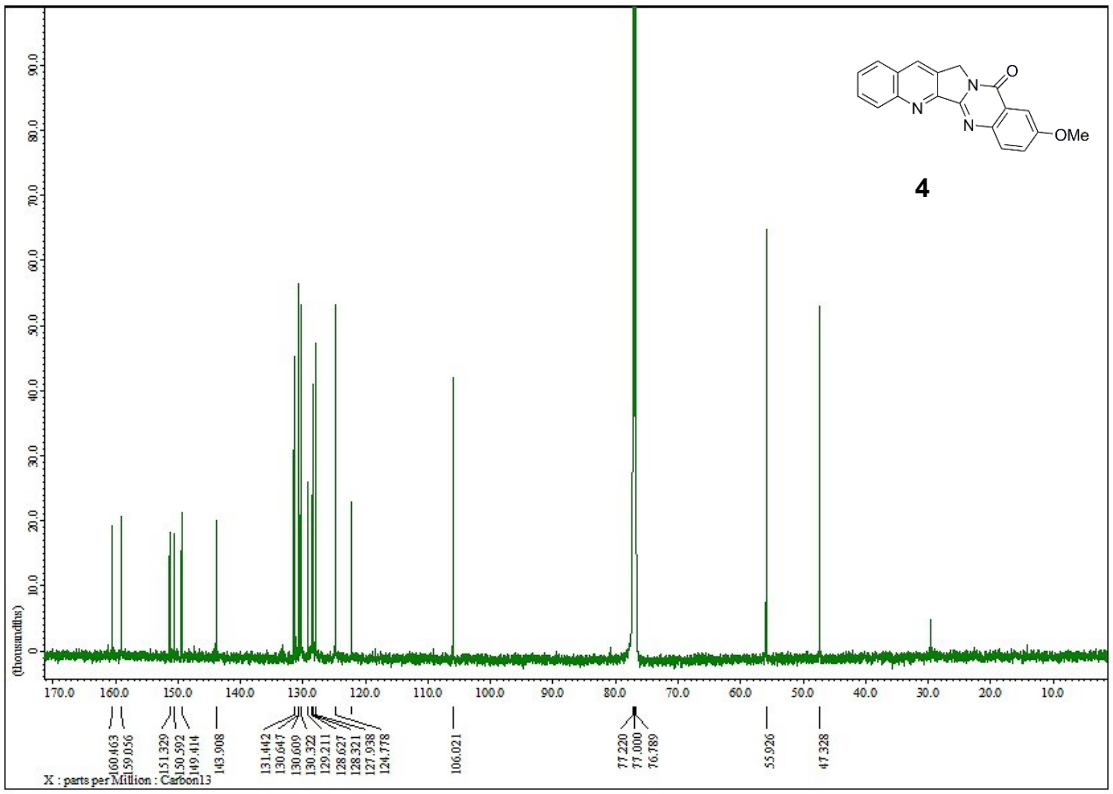

STANDARD 1H OBSERVE - profile
exp3 s2pul
SAMPLE
date Feb 26 2015
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.855
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -22.3
wp 3525.0
rfl 3701.6
rfp 2902.9
rp -91.0
lp 0
PLOT
wc 370
sc 0
vs 775
th 9
ai cdc ph
O
OTs
OMe
N
H
N
Br
13d
0.97
0.95
1.01
1.03
1.03
1.04
0.99
2.77
0.96
0.99
2.04
3.03
3.00
8
7
6
5
4
3
2
1
ppm

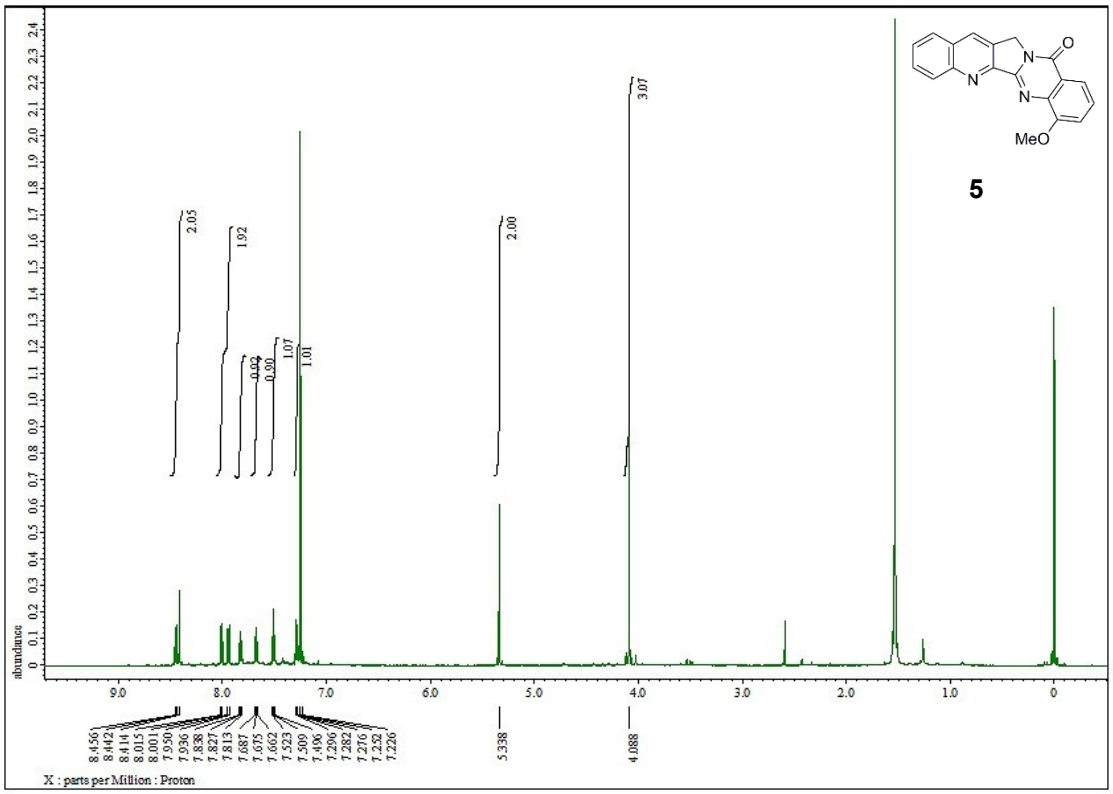

STANDARD 1H OBSERVE - profile
exp2 Carbon
SAMPLE
date Mar 5 2013
solvent cdcl3
file exp
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17000
bs 64
di 0.700
nt 1024
ct 128
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.2
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.000
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1005.4
wp 22119.3
rfl 9443.2
rfp 7757.9
rp -33.6
lp 0
PLOT
wc 370
sc 0
vs 3643
th 12
ai ph
O
OTs
OMe
N
H
N
Br
13d
200
180
160
140
120
100
80
60
40
20
0
ppm

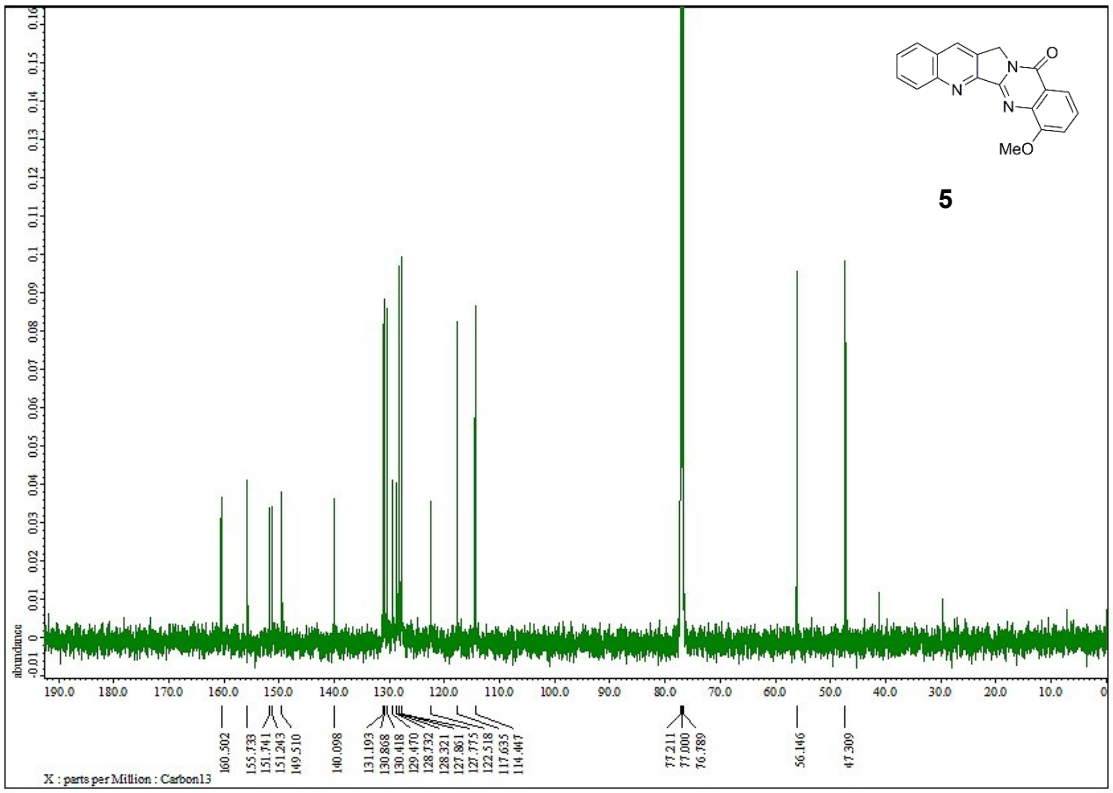

2.02
0.94
2.02
1.01
2.16
2.00
2.93
3
Me
abundance
X : parts per Million : Proton

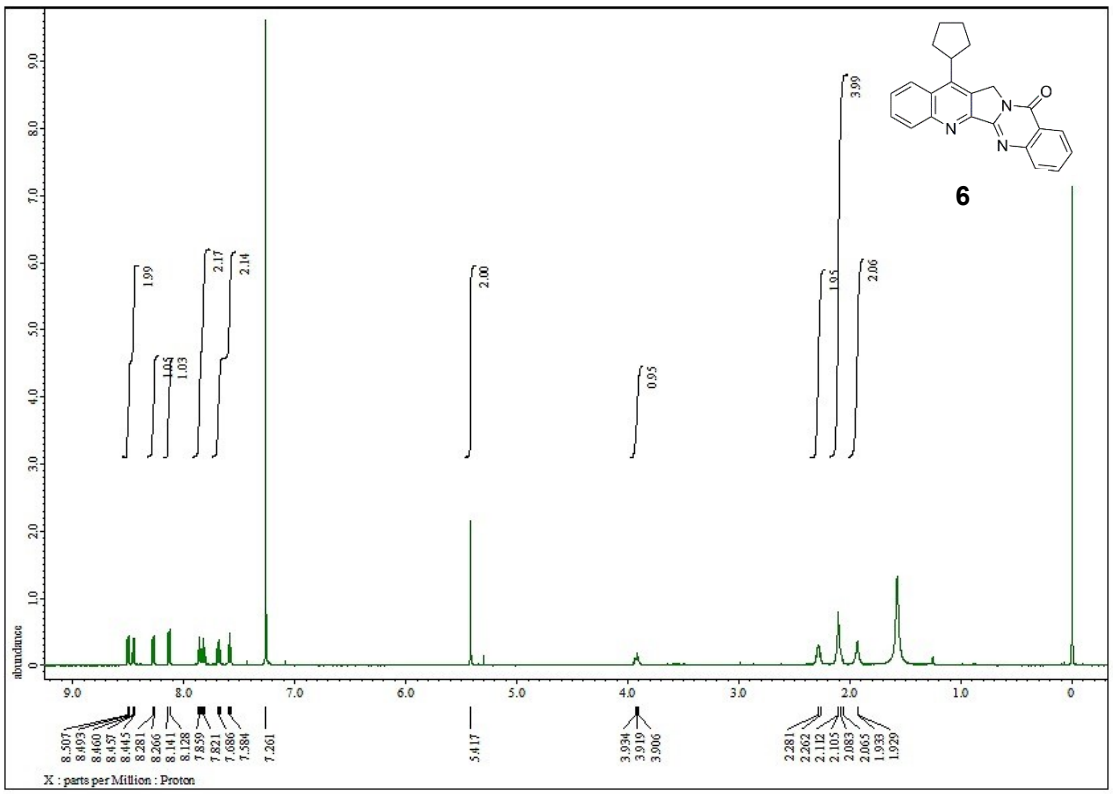

3
Me
(thousandths)
X : parts per Million : Carbon13

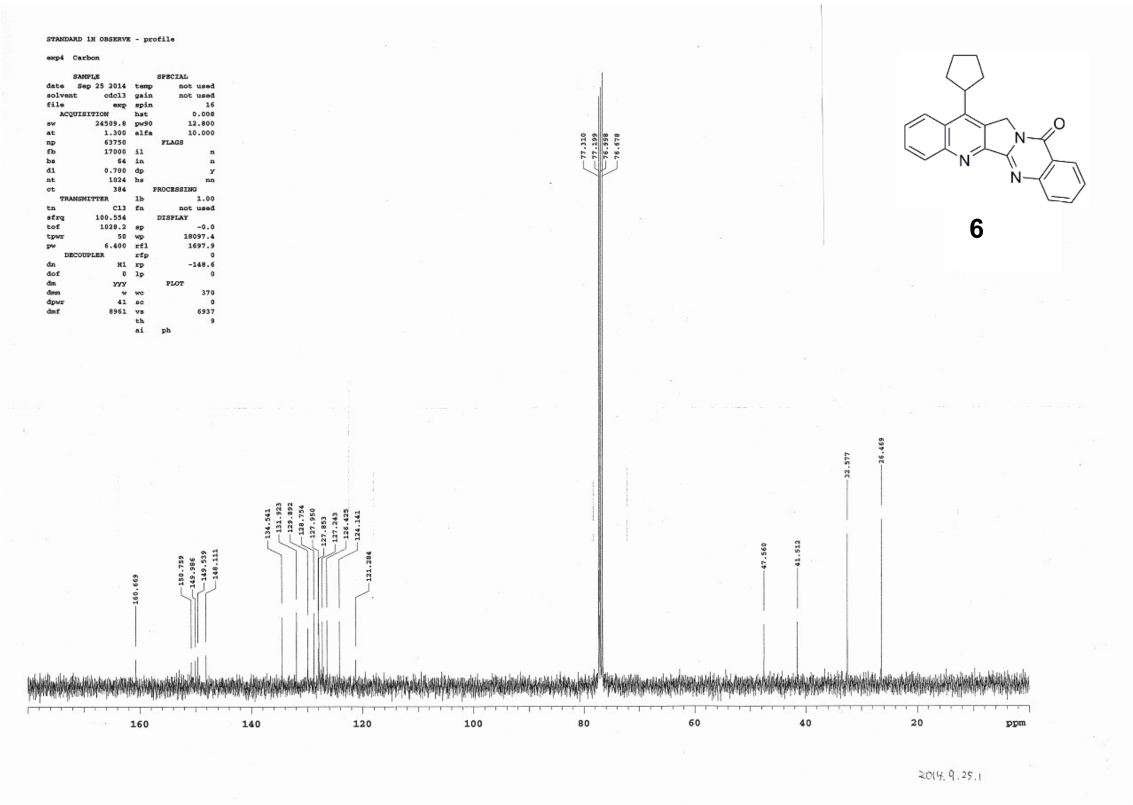

4
OMe
N
N
O
abundance
X : parts per Million : Proton
2.19
2.00
3.02
1.05
0.99
8.461
8.447
8.423
8.050
8.035
7.944
7.931
7.838
7.783
7.778
7.674
7.459
7.454
7.444
7.439
7.264
5.344
3.976
0.000


4
OMe
(thousandths)
X : parts per Million : Carbon13
160.463
159.056
151.329
150.592
149.414
143.908
131.442
130.647
130.609
130.322
129.211
128.627
128.321
127.938
124.778
106.021
77.220
77.000
76.789
55.926
47.328

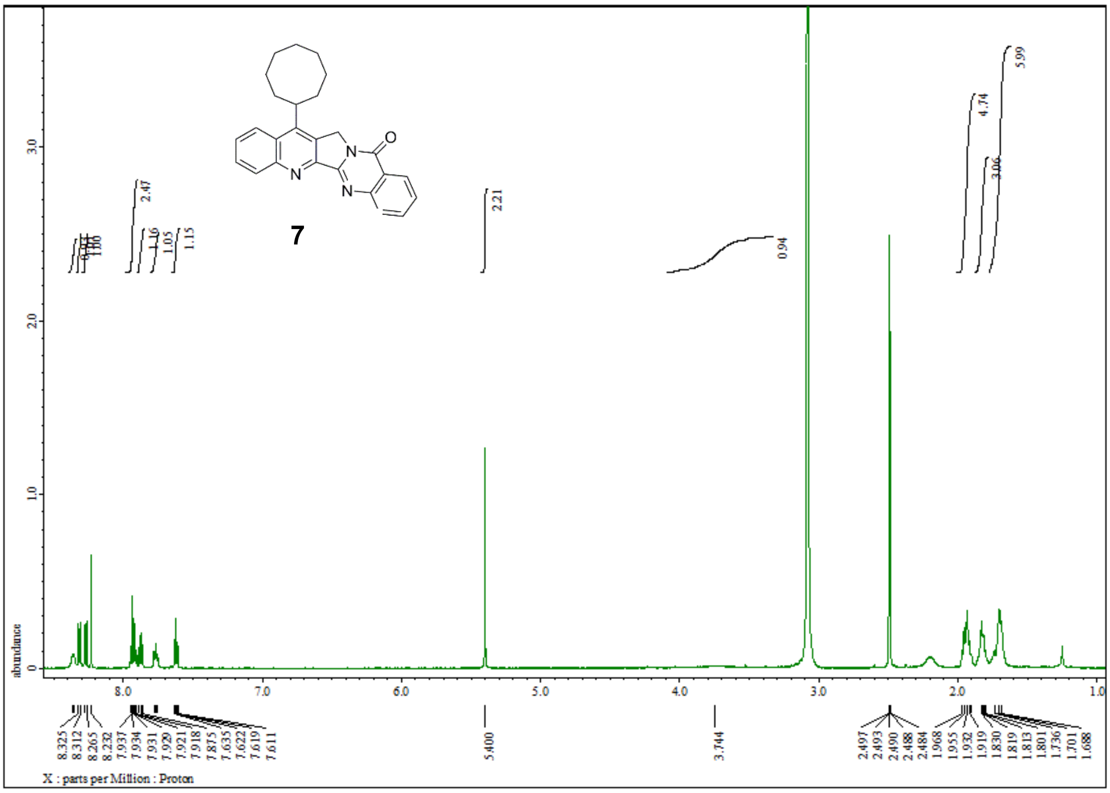

5
2.05
1.92
0.92
0.90
1.07
1.01
2.00
3.07
abundance
X : parts per Million : Proton


5
abundance
X : parts per Million : Carbon13

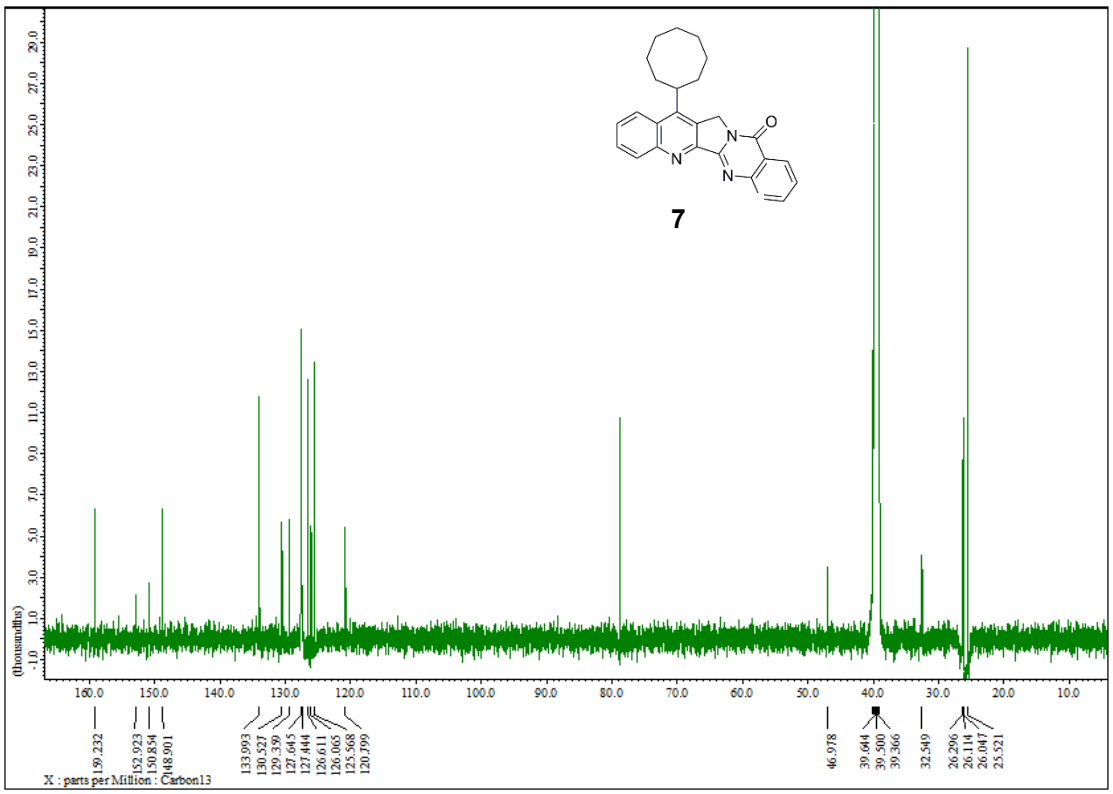

6
abundance
X : parts per Million : Proton
1.99
1.05
1.03
2.17
2.14
2.00
0.95
1.95
3.99
2.06
8.507
8.493
8.460
8.457
8.445
8.281
8.266
8.141
8.128
7.859
7.821
7.686
7.584
7.261
5.417
3.934
3.919
3.906
2.281
2.262
2.112
2.105
2.083
2.063
1.933
1.920

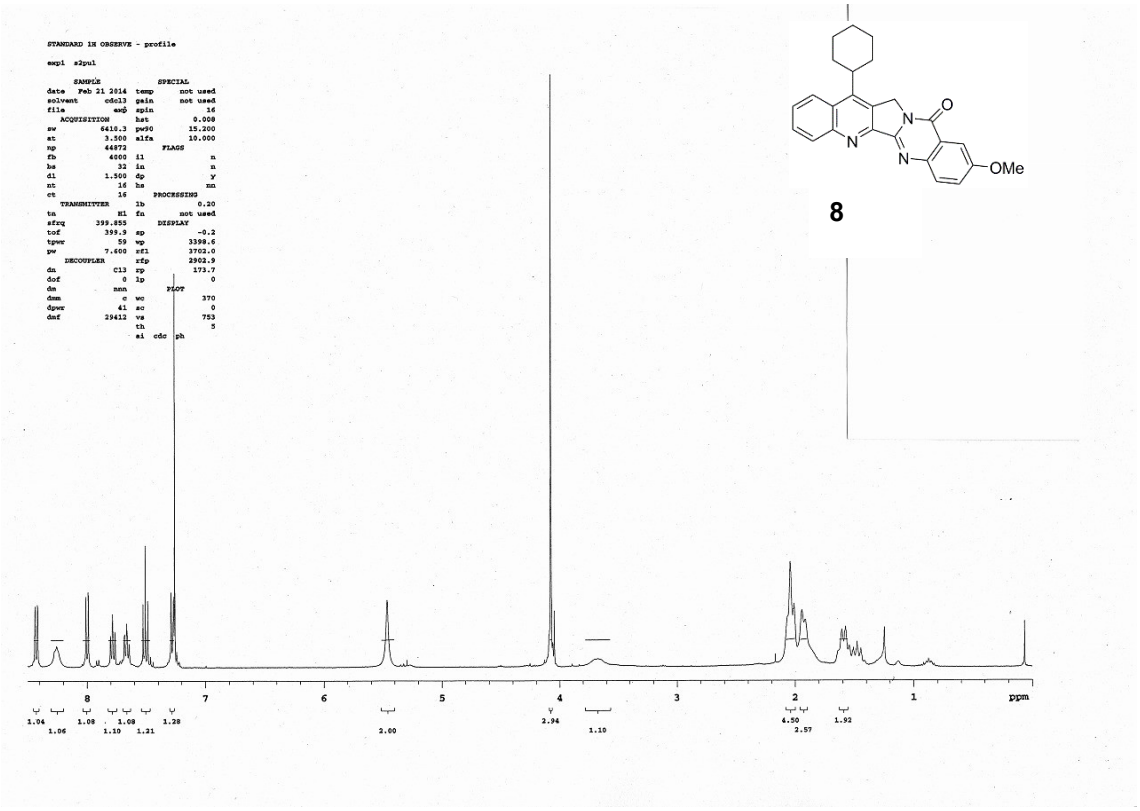


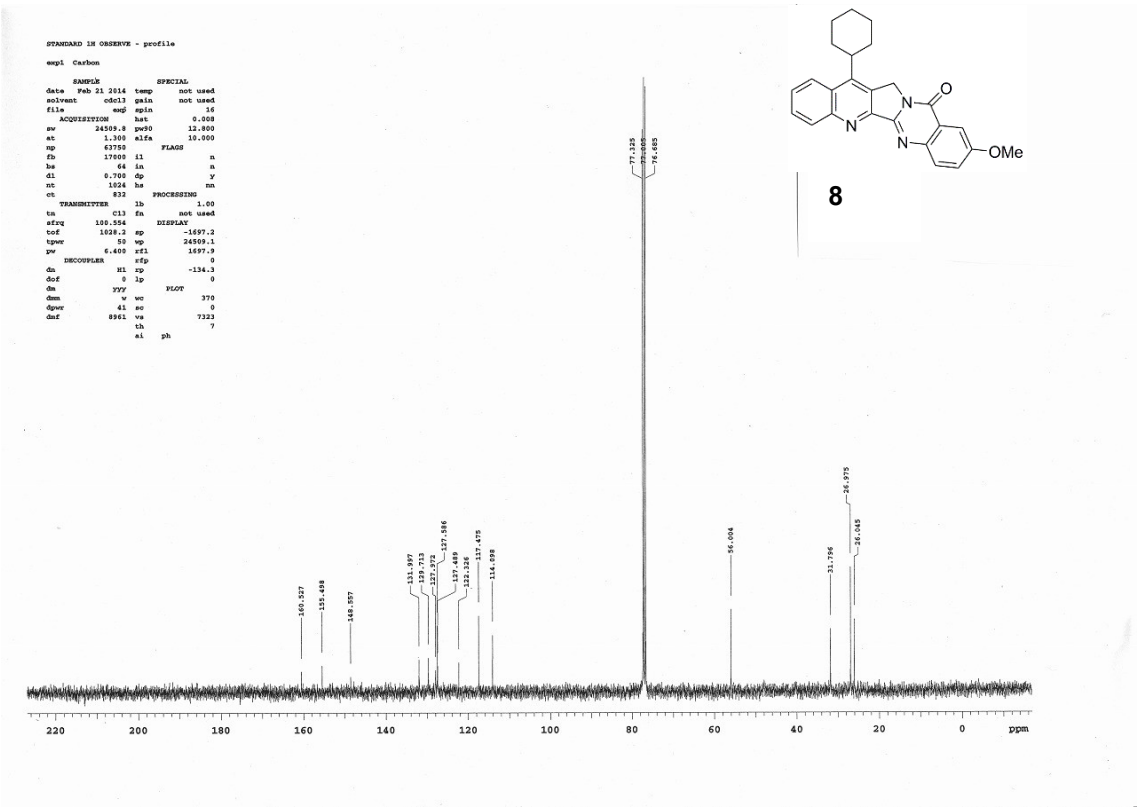
STANDARD 1H OBSERVE - profile
exp4 Carbon
6
160.669
150.759
149.986
149.539
148.111
134.641
131.923
129.892
128.754
127.950
127.853
127.243
126.425
124.141
121.284
47.560
41.512
32.577
26.469
160
140
120
100
80
60
40
20
ppm

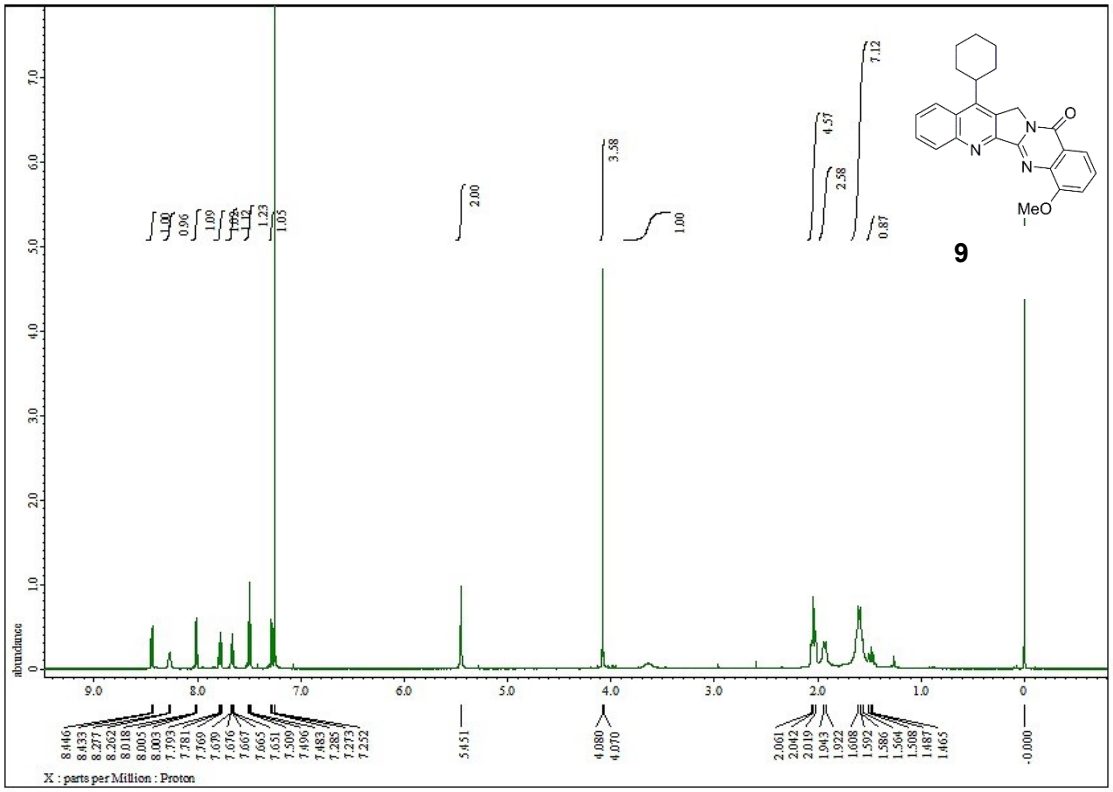


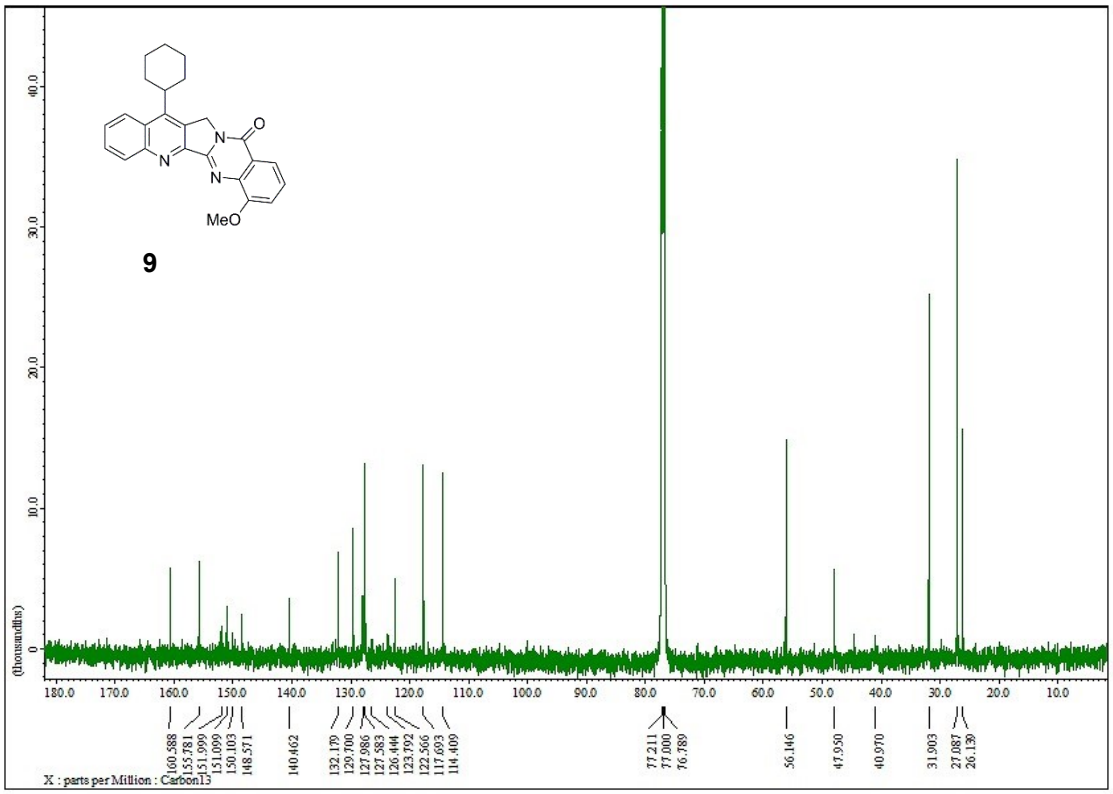
7
abundance
2.47
1.16
1.05
1.15
2.21
0.94
4.74
3.06
5.99
8.325
8.312
8.265
8.232
7.937
7.934
7.931
7.929
7.921
7.918
7.875
7.635
7.622
7.619
7.611
5.400
3.744
2.497
2.493
2.490
2.488
2.484
1.968
1.955
1.932
1.919
1.830
1.819
1.813
1.801
1.736
1.701
1.688
X : parts per Million : Proton

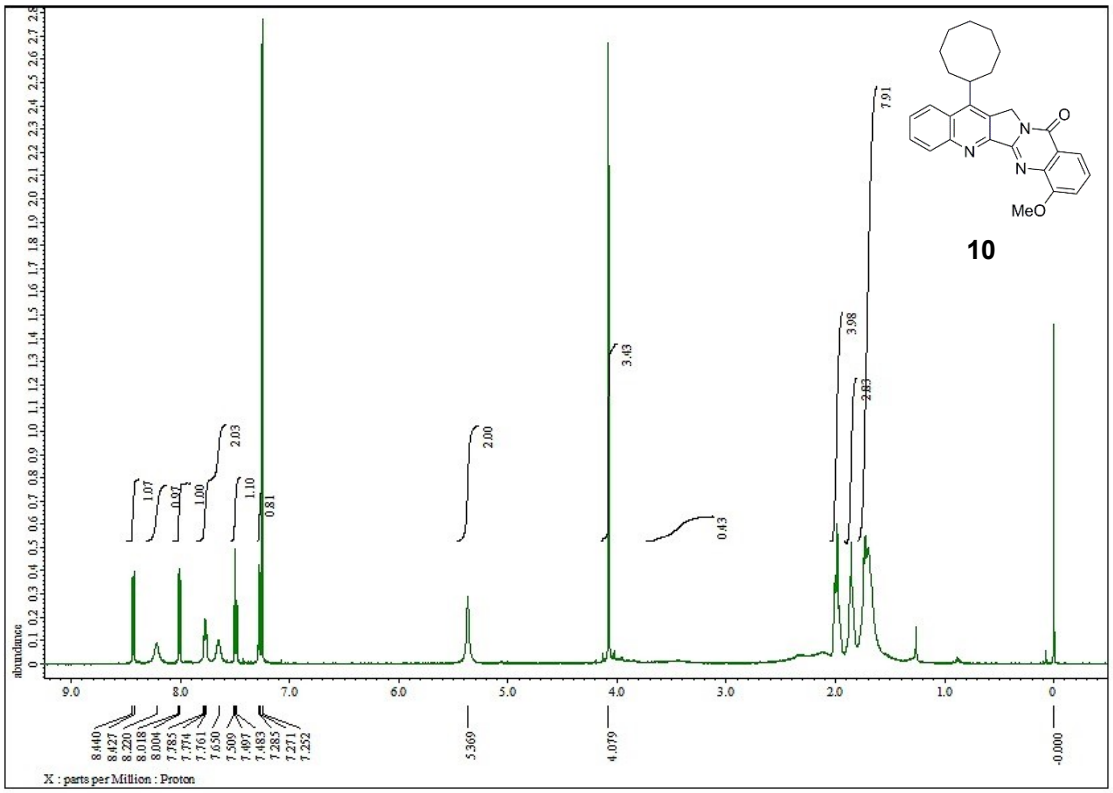

7
(thousandths)
X : parts per Million : Carbon13
159.232
152.923
150.854
148.901
133.993
130.527
129.339
127.645
127.444
126.611
126.065
125.568
120.999
46.978
39.664
39.500
39.366
32.549
26.296
26.114
26.047
25.521

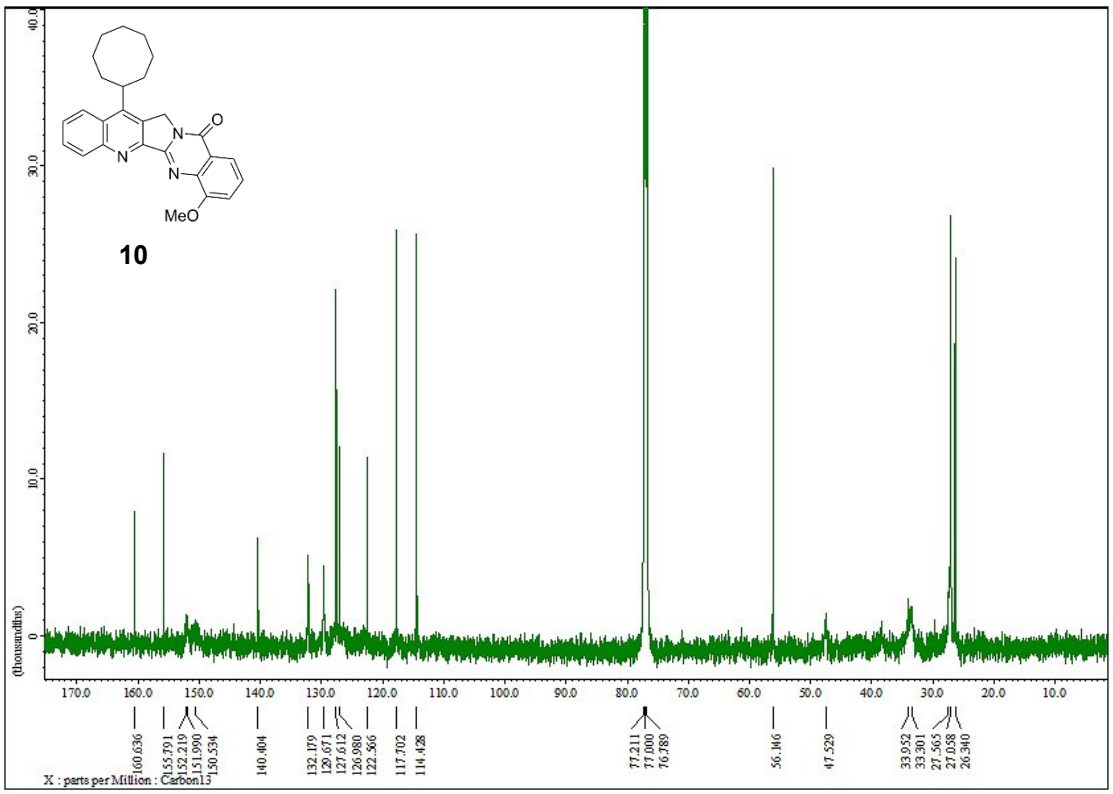

STANDARD 1H OBSERVE - profile
exp1 s2pul
SAMPLE
date Feb 21 2014
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44872
fb 4000
hs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.855
tof 398.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -0.2
wp 3398.6
rfl 3702.0
rfp 2902.9
rp 173.7
lp 0
PLOT
wc 370
sc 0
vs 753
th 5
ai cdc ph
OMe
8
ppm
1.04
1.06
1.08
1.10
1.08
1.21
1.28
2.00
2.94
1.10
4.50
2.57
1.92

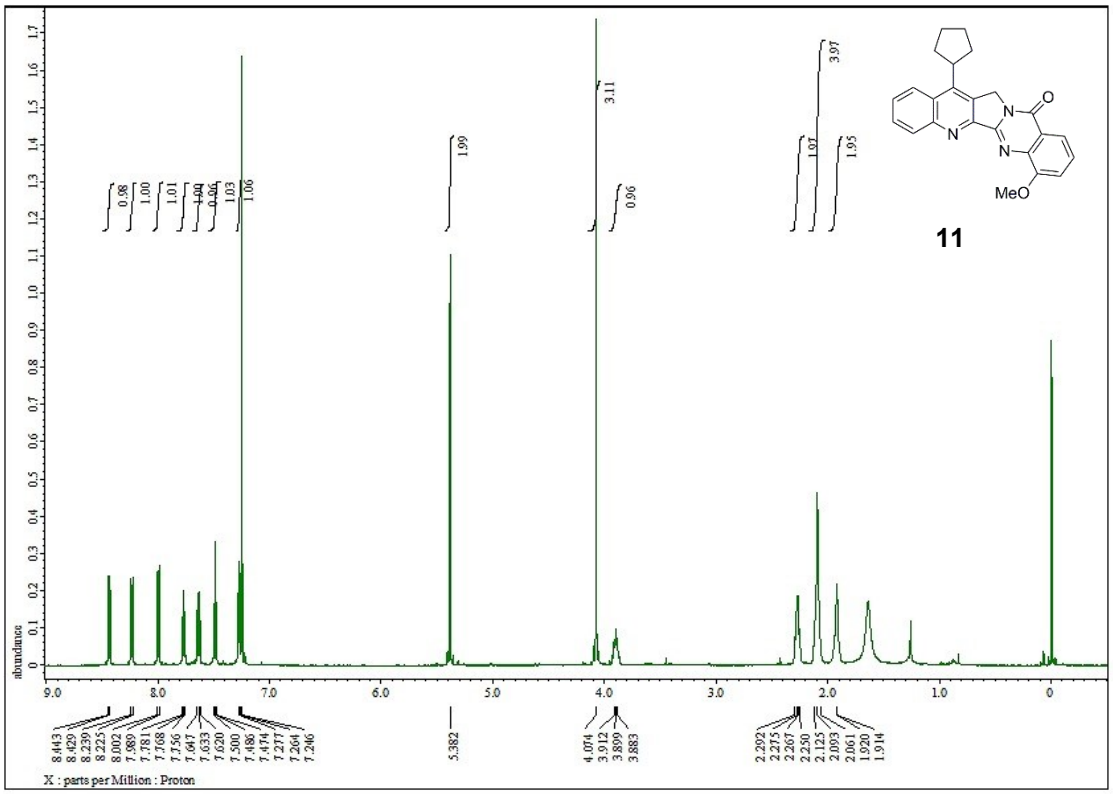

STANDARD 1H OBSERVE - profile
exp1 Carbon
SAMPLE
date Feb 21 2014
solvent cdcl3
file exp
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17800
hs 64
d1 0.700
nt 1024
ct 832
TRANSMITTER
tn C13
sfrq 100.554
tof 1028.2
tpwr 50
pw 6.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 8961
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 12.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1697.2
wp 24509.1
rfl 1697.9
rfp 0
rp -134.3
lp 0
PLOT
wc 370
sc 0
vs 7323
th 7
ai ph
OMe
8
160.527
155.498
149.557
131.997
129.713
127.586
127.489
122.326
117.475
114.098
77.325
77.000
76.685
56.004
31.756
26.975
26.045
ppm

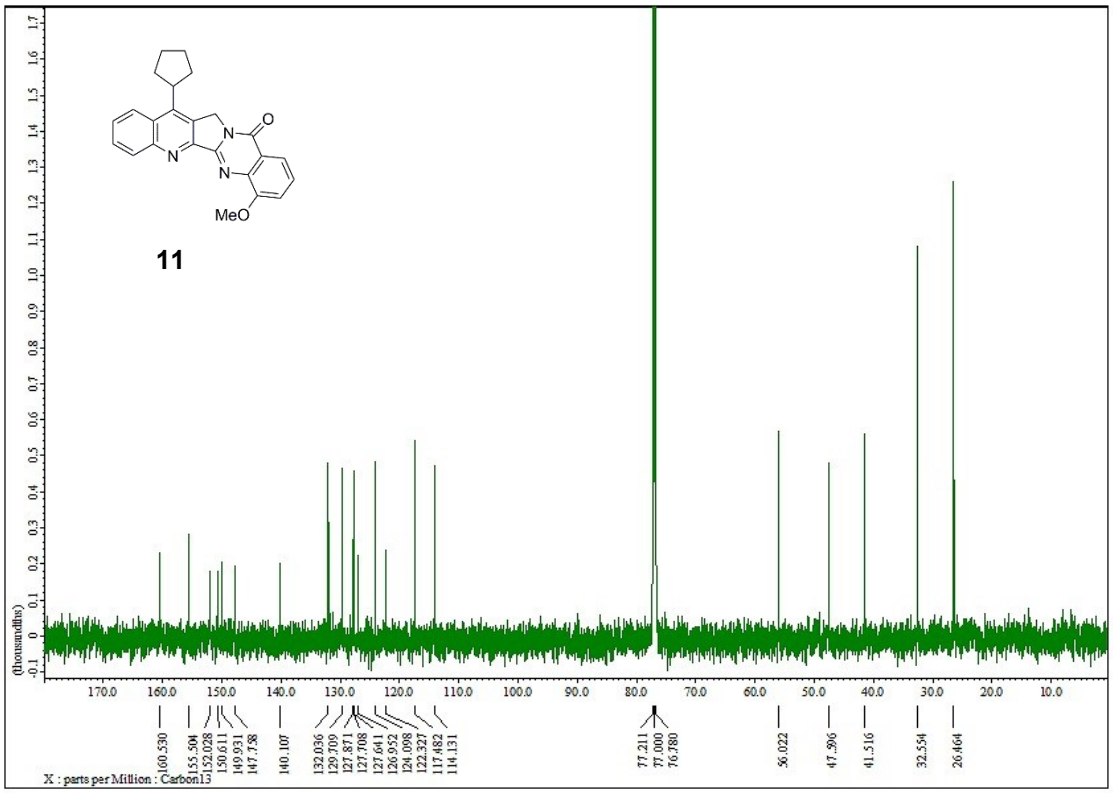

9
MeO
abundance
X : parts per Million : Proton

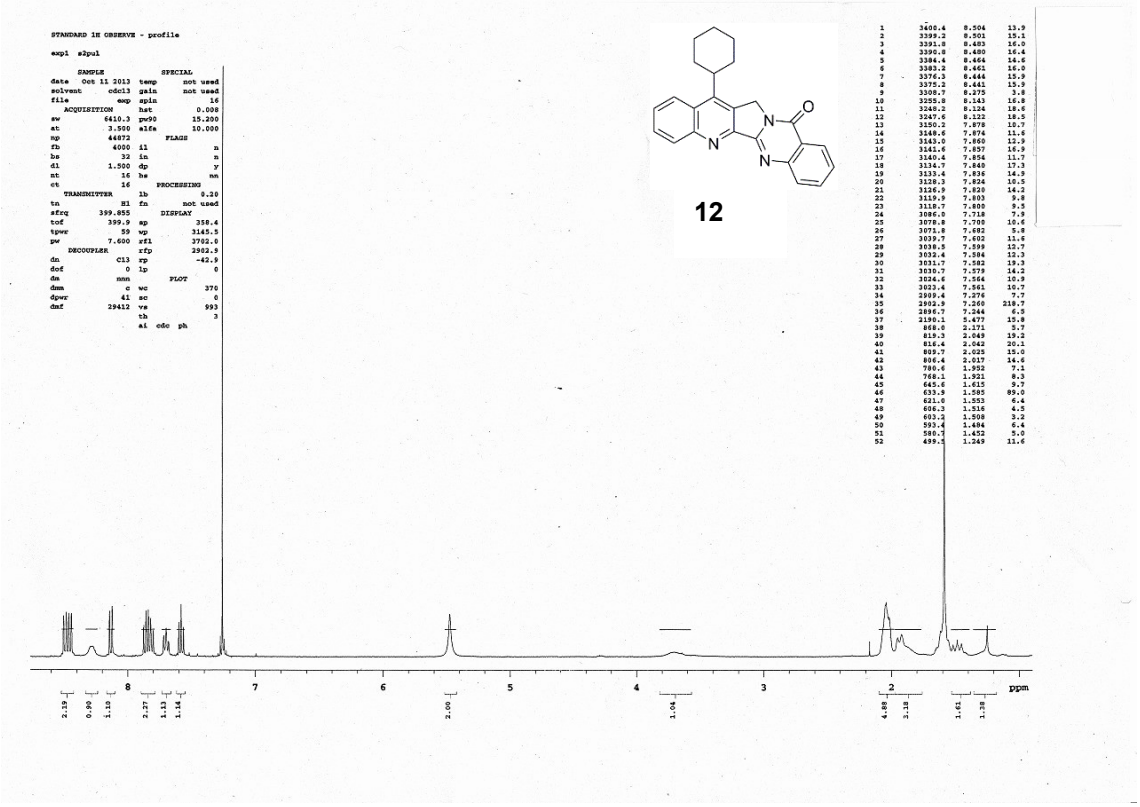

MeO
9
(thousandths)
X : parts per Million : Carbon13

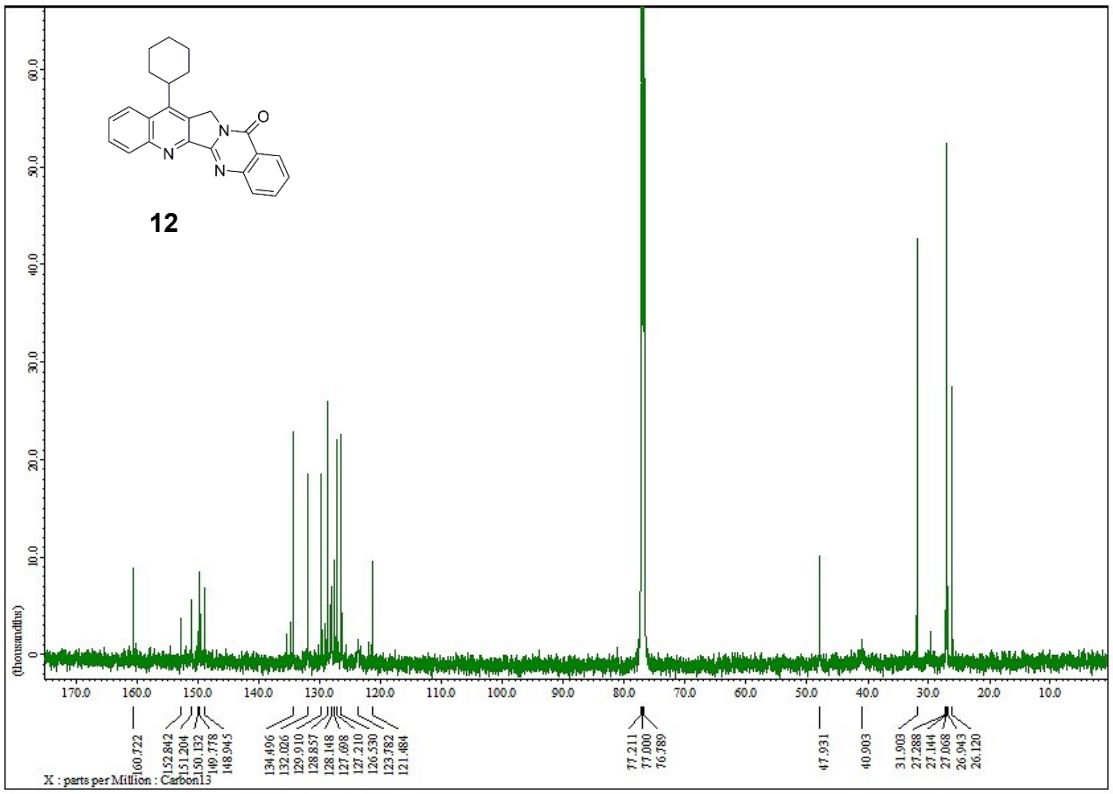

MeO
10
7.91
3.98
3.43
2.03
2.00
1.10
1.07
1.00
0.97
0.81
0.43
abundance
X : parts per Million : Proton


10
MeO
(thousandths)
X : parts per Million : Carbon13
160.636
155.791
152.219
151.990
150.534
140.404
132.179
129.671
127.612
126.980
122.566
117.702
114.428
77.211
77.000
76.789
56.146
47.529
33.952
33.301
27.565
27.058
26.340


11
MeO
X : parts per Million : Proton


11
MeO
X : parts per Million : Carbon13


STANDARD 1H OBSERVE - profile
expl s2pul
SAMPLE
date Oct 11 2013
solvent cdcl3
file exp
ACQUISITION
sw 6410.3
at 3.500
np 44072
fb 4000
bs 32
d1 1.500
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.855
tof 399.9
tpwr 59
pw 7.600
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 29412
SPECIAL
temp not used
gain not used
spin 16
hst 0.008
pw90 15.200
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp 358.4
wp 3145.5
rfl 3702.0
rfp 2902.5
rp -42.9
lp 0
PLOT
wc 376
sc 0
vs 993
th 3
ai cdc ph
12
ppm


12
(thousandths)
X : parts per Million : Carbon13
160.722
152.842
151.204
150.152
149.778
148.945
134.496
132.026
129.910
128.857
128.148
127.698
127.210
126.530
123.782
121.484
77.211
77.000
76.789
47.931
40.903
31.903
27.288
27.144
27.068
26.943
26.120

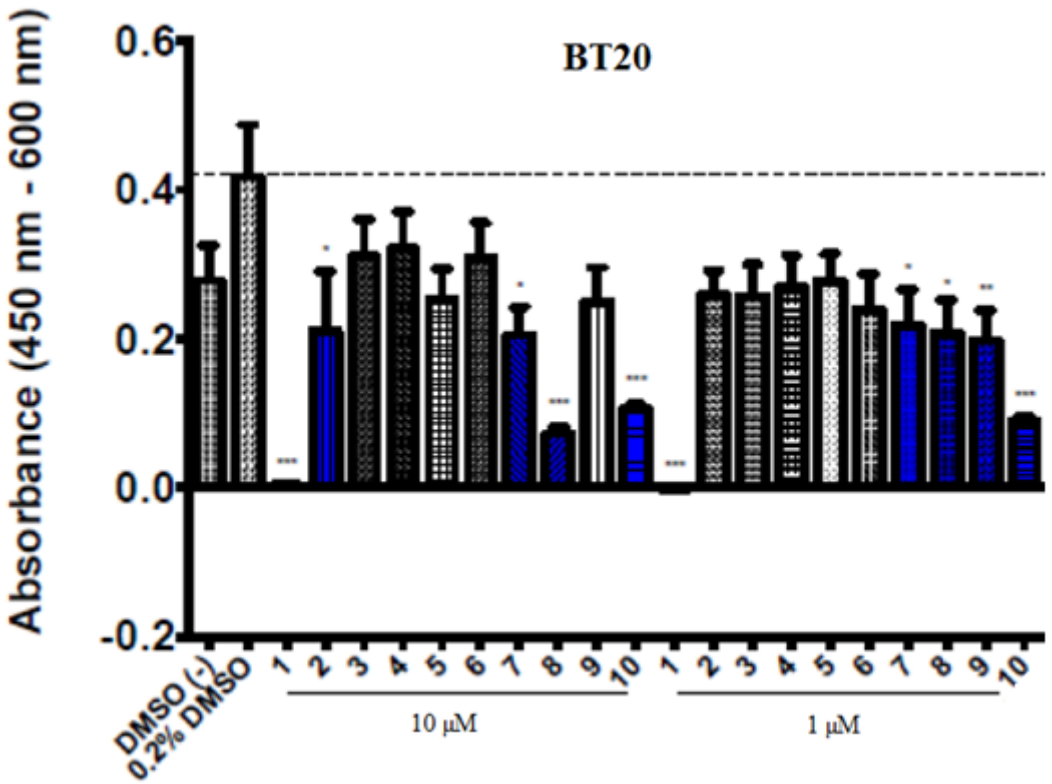
Cell proliferation assay (Typical procedure)

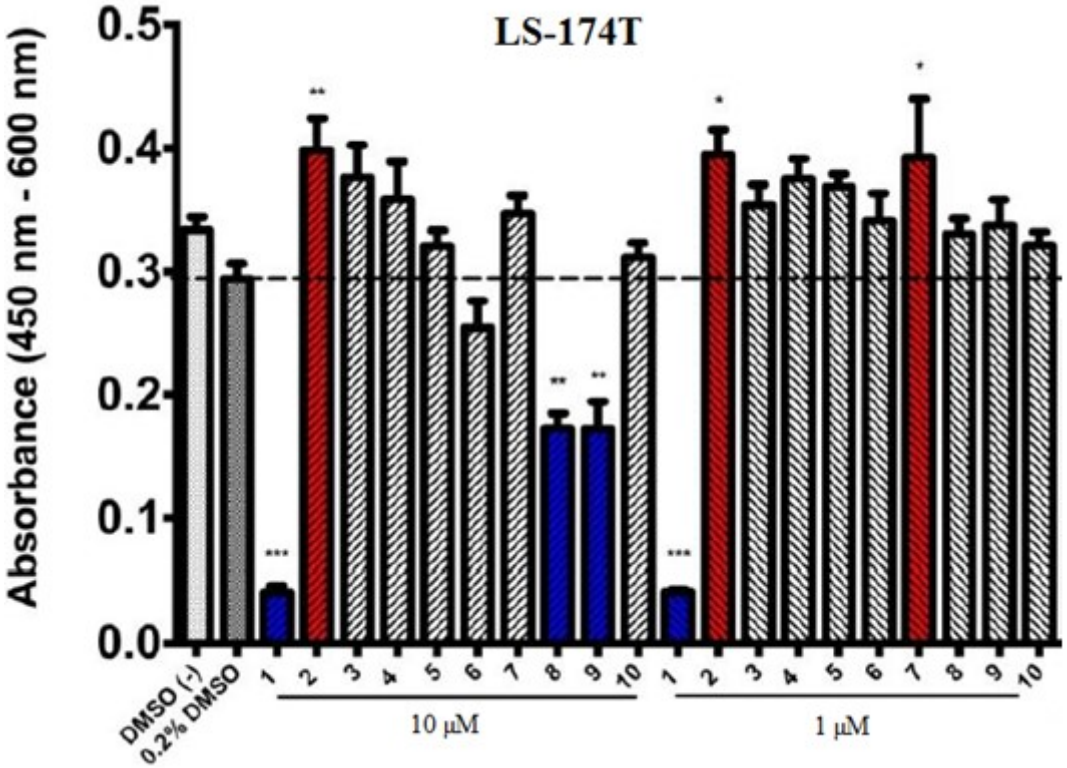
Daudi cancer cell culture containing 0.2% DMSO solution of the synthetic compound **3** (1 μM and 10 μM, respectively, at the final concentration) was incubated at 37 °C for 3 days. After addition of WST-8 reagent, it was incubated for an additional 4 h. The absorbance of the sample container was measured at 450-600 nm.

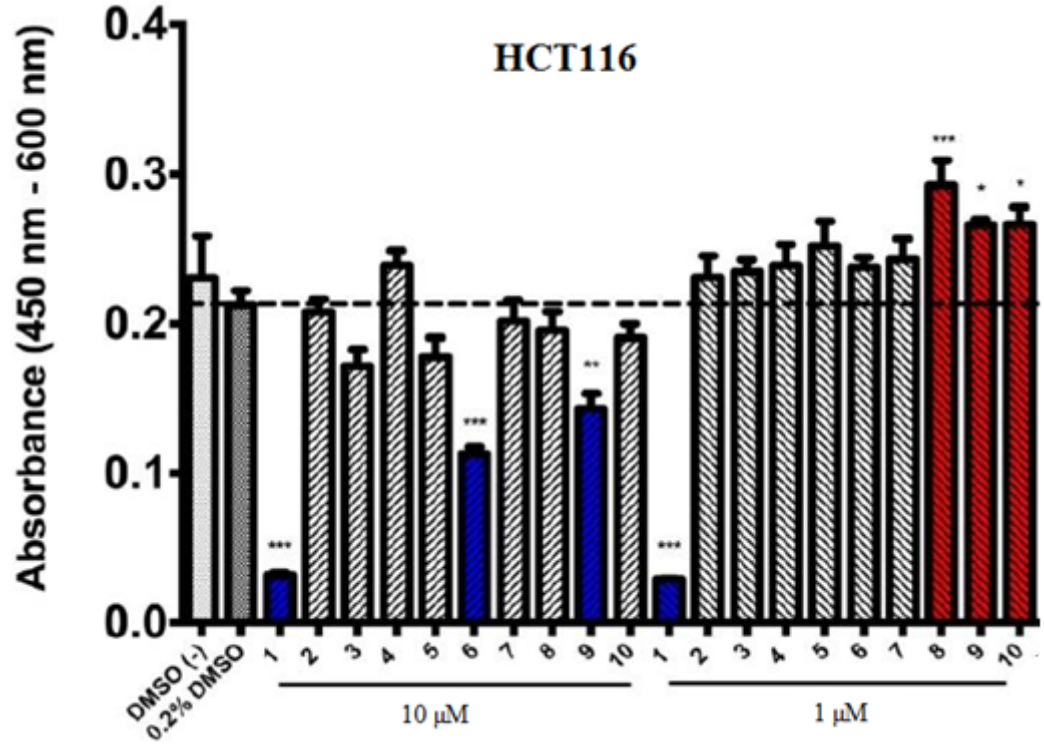
footnote

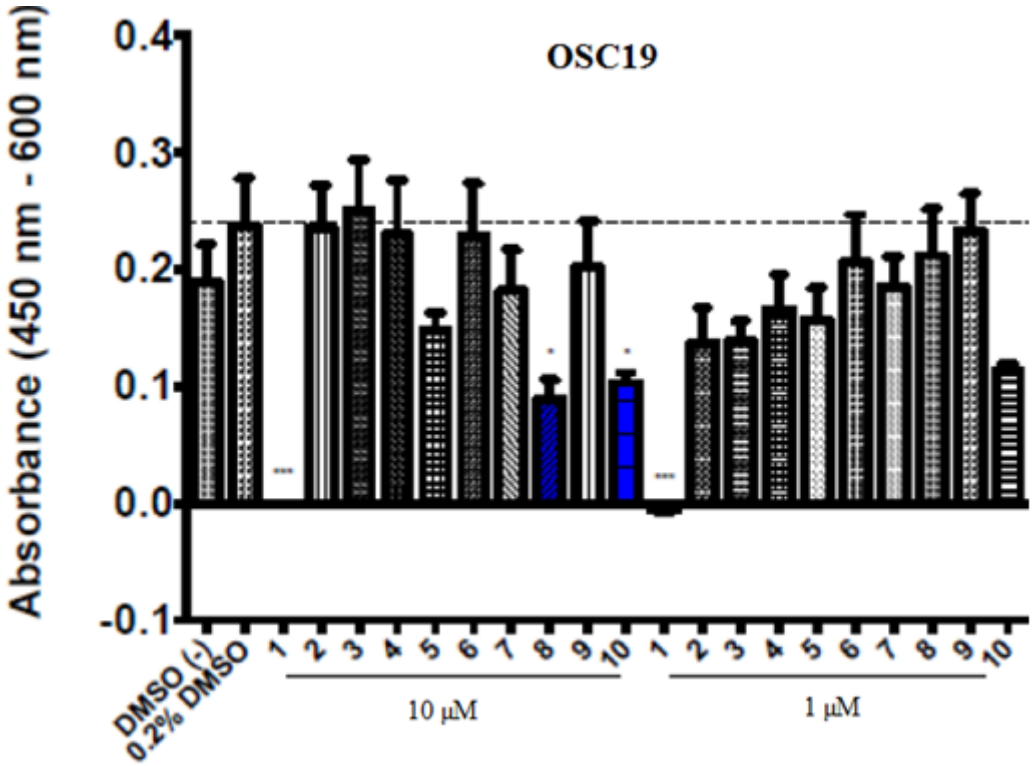
DMSO (-) in the graph is the culture which does not contain DMSO and the synthetic compound. Additionally, 0.2% DMSO in the graph means the culture which contains only DMSO.

Cytotoxicity Test




LS-174T
Absorbance (450 nm - 600 nm)
0.5
0.4
0.3
0.2
0.1
0.0
DMSO (-)
0.2% DMSO
1 2 3 4 5 6 7 8 9 10
10 µM
1 µM


HCT116
Absorbance (450 nm - 600 nm)
0.4
0.3
0.2
0.1
0.0
DMSO (-)
0.2% DMSO
1 2 3 4 5 6 7 8 9 10
10 µM
1 µM


OSC19
Absorbance (450 nm - 600 nm)
0.4
0.3
0.2
0.1
0.0
-0.1
DMSO (-)
0.2% DMSO
1
2
3
4
5
6
7
8
9
10
10 µM
1 µM