Efficient Fluoride-Catalyzed Conversion of CO_2 to CO at Room Temperature

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Supporting Information

General Methods

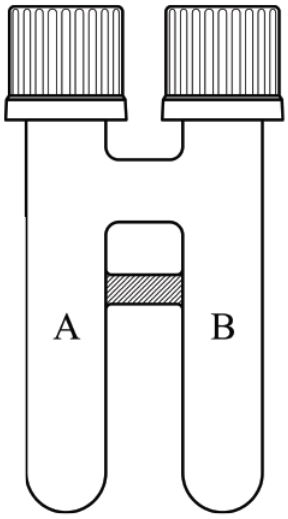
Solvents were dried according to standard procedures and reactions were monitored by thin-layer chromatography (TLC) analysis. All other chemicals were used as received without further purification. Flash chromatography was carried out on silica gel 60 (230-400 mesh). Pressure was measured using a Digital Manometer LEO Record (EI). The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400 MHz, 100 MHz and 376 MHz, respectively, on a 400 MHz spectrometer. The chemical shifts for the NMR spectra are reported in ppm relative to the solvent residual peak. NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sext = sextet, sep = septet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). HRMS were performed on a LC TOF (ES).

COware

Two glass vials (Chamber A and B) connected with a glass tube to allow gas-transfer.

Total volume = 20 mL.

The system is sealed using a screw cap lined with a PTFE/silicone seal.

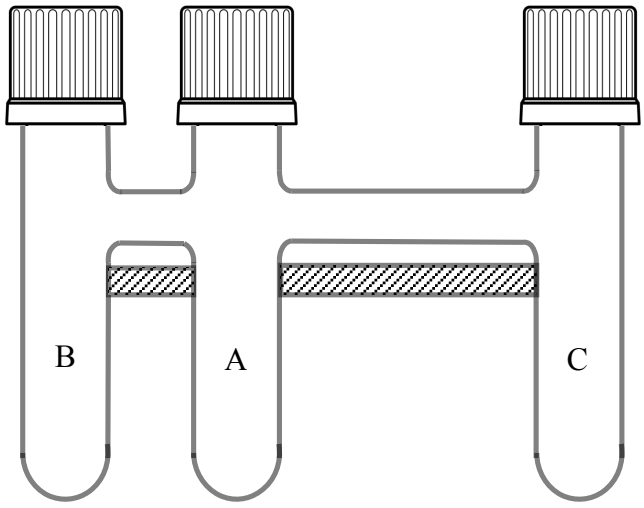


3-Chamber system

Three glass vials (chamber A, B and C) connected with glass tubes to allow gas-transfer. The connecting tube between chamber A and C measures 5 cm to allow heating of chamber C if needed.

Total volume = 33 mL.

Closed using H-Caps and screw caps lined with PTFE/silicone seals.



Tetraphenyldimethyldisilane

$(Ph_2MeSi)_2$ was prepared according to literature procedure.[1]

In an oven-dried round bottom flask under argon atmosphere was added freshly hexane-washed lithium (500 mg, 72.0 mmol), dry THF (50 mL) and chlorodiphenyl(methyl)silane (23.2 g, 100 mmol). The reaction mixture was stirred at 0 °C for 4 h under argon. 1,2-Dibromoethane (1 mL) and water (100 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried using Na_2SO_4 and the solvents were removed under reduced pressure. Recrystallization from EtOH afforded pure tetraphenyldimethyldisilane as colorless crystals (11.8 g, 60% yield).

Spectral data matched those reported in the literature.

Conditions for the $Cu(OAc)_2$ catalyzed reduction of CO_2 *via* injection

General procedure for chamber A in the two-chamber system for $Cu(OAc)_2$ catalyzed CO_2 reduction.

In a glovebox under argon, to chamber A of the two-chamber system was added $Cu(OAc)_2$ (14 mg, 0.075 mmol), 1,2-bis(diphenylphosphino)benzene (DPPBz) (37 mg, 0.083 mmol), tetraphenyldimethyldisilane (296 mg, 0.75 mmol) and NMP (3.0 mL). Chamber A was sealed using a screw cap lined with a PTFE/silicone seal. As the last reagent, CO_2 (21 mL, 0.85 mmol) was added with a syringe through the septum outside the glovebox. Reaction mixture in Chamber A was stirred at 150 °C for 18 h.

Conversion in chamber A was determined by crude ^{1}H NMR-analysis ($CDCl_3$) comparing the integrals of the peaks residing at 0.53 ppm for (**Me**$Ph_2Si)_2O$ and at 0.61 ppm for (**Me**$Ph_2Si)_2$

General procedure for chamber B (aminocarbonylation from *p*-iodoanisole with *n*-hexylamine).

In a glovebox under argon, in chamber B of the two-chamber system, $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol) and *p*-iodoanisole (117 mg, 0.50 mmol) were dissolved in dioxane (3.0 mL). *n*-Hexylamine (133 μL, 1.0 mmol) and Et_3N (135 μL, 1.0 mmol) were then added. Chamber B was sealed using a screw cap lined with a PTFE/silicone seal and the reaction mixture stirred at 80 °C for 18 hours. Conversion in chamber B was measured by crude ^{1}H NMR

[1] Fleming, I.; Roberts, R. S.; Smith, S. C. J. *Chem. Soc., Perkin Trans.* **1998**, 1209.

($CDCl_3$) analysis. The crude reaction mixture from chamber B was concentrated under reduced pressure and purified by silica gel column chromatography eluting with 20% EtOAc in pentane.

Conditions for the CsF catalyzed reduction of CO_2 *via* injection.

General procedure for chamber A in the two-chamber system for CsF catalysed CO_2 reduction.

In a glovebox under argon, to chamber A of the two-chamber system was added CsF (11 mg, 0.075 mmol), tetraphenyldimethyldisilane (296 mg, 0.75 mmol) and DMSO (3.0 mL). Chamber A was sealed using a screw cap lined with a PTFE/silicone seal. As the last reagent, CO_2 (21 mL, 0.85 mmol) was added with a syringe through the septum outside the glovebox. Reaction mixture in Chamber A was stirred at 20 °C for 18 hours.

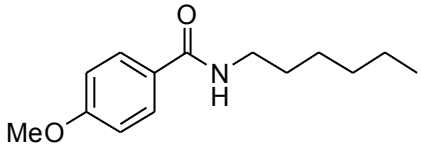
NB: For the optimization experiments, 0.050 mmol (7.6 mg) of CsF and 0.5 mmol (197 mg) of tetraphenyldimethyldisilane were used.

Conversion in chamber A was determined by crude ^{1}H NMR-analysis ($CDCl_3$) comparing the integrals of the peaks residing at 0.53 ppm for (**Me**$Ph_2Si)_2O$ and at 0.61 ppm for (**Me**$Ph_2Si)_2$.

Chamber B is loaded following the General procedure for Chamber B (aminocarbonylation from *p*-iodoanisole with *n*-hexylamine) as previously described.

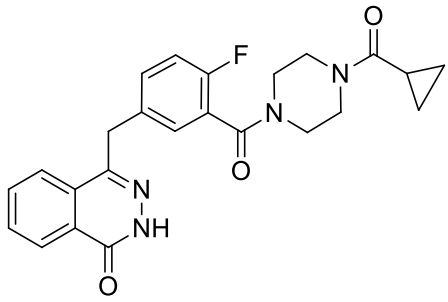
Experimental details

n-Hexyl-4-methoxybenzamide (2)[2]



2 was prepared following the general procedure for the reduction of CO_2 *via* injection for chamber A and chamber B. The title compound was isolated as a pale yellow solid (116 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H), 6.35 (bs, 1H), 3.81 (s, 3H), 3.39 (t, J = 6.0 Hz, 2H), 1.57 (quin, J = 7.2 Hz, 2H), 1.41-1.23 (m, 6H), 0.86 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 162.1, 128.4 (2C), 127.3, 113.7 (2C), 55.4, 40.2, 31.6, 29.8, 26.8, 22.7, 14.1. HRMS $C_{14}H_{21}NO_2$ [M+H$^+$]: calculated 236.1651, found 236.1648.

4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2*H*)-one (Olaparib) (3a)[3]



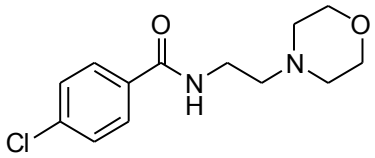
3a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In chamber B of the two-chamber system was added 4-(3-bromo-4-fluorobenzyl)phthalazin-1(2*H*)-one (166.6 mg, 0.50 mmol), cyclopropyl(piperazin-1-yl)methanone (154 mg, 1.0 mmol) $Pd(dba)_2$ (30 mg, 0.050 mmol), Xantphos (29 mg, 0.050 mmol), DIPEA (250 μL, 1.4 mmol) and dioxane (3 mL). Chamber B was stirred at 100 °C for 18 h. Column chromatography (0 to 2% MeOH in EtOAc) afforded **3a** as a light yellow solid (210 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91-11.75 (m, 1H), 8.48-8.40 (m, 1H), 7.78-7.67 (m, 3H), 7.38-7.28 (m, 2H), 7.01 (t, J = 8.9 Hz, 1H), 4.28 (s, 2H), 3.89-3.50 (m, 6H), 3.43-3.17 (m, 2H), 1.81-1.56 (m, 1H), 1.02-0.95 (m, 2H), 0.84-0.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 165.3, 161.1, 157.1 (d, J = 248.0 Hz), 145.6, 134.6 (d, J = 2.9 Hz), 133.7, 131.8 (d, J = 8.1 Hz), 131.6, 129.6, 129.3 (bs), 128.4, 127.2, 125.1, 123.8 (d, J = 16.9 Hz), 116.2 (d, J = 22.0 Hz),

[2]Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K. ; Lupp, D. and Skrydstrup, T. *J. Am. Chem. Soc.*, **2011**, *133*, 6061

[3] Lindhardt, A. T. ; Simonssen, R. ; Taaning, R. H.; Gøgsig, T. M.; Nilsson, G. N.; Stenhagen, G.; Elmore, C. S.; Skrydstrup, T. *J. Label. Compd. Radiopharm.* **2012**, *55*, 411

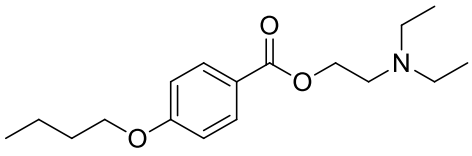
47.5-46.7 (m), 45.9-44.8 (m), 42.3 (bs, 2C), 37.8, 11.1, 7.8 (2C). ^{19}F NMR (367 MHz, $CDCl_3$) δ -117.8 HRMS $C_{24}H_{23}FN_4O_3$ [M+H$^+$]: calculated 435.1832, found 435.1829

4-Chloro-*N*-(2-morpholinoethyl)benzamide (Moclobemide) (4a)[4]



4a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In chamber B of the two-chamber system was added 1-chloro-4-iodobenzene (119 mg, 0.50 mmol), 2-morpholinoethanamine (130 mg, 1.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Et_3N (135 µL, 1.0 mmol) and dioxane (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (1 to 2% MeOH in CH_2Cl_2) afforded **4a** as a colorless solid (133 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.83 (bs, 1 H), 3.68 (t, J = 4.4 Hz, 4H), 3.50 (q, J = 5.6 Hz, 2H), 2.56 (t, J = 6.4 Hz, 2H), 2.46 (t, J = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 137.6, 133.0, 128.8 (2C), 128.4 (2C), 67.0 (2C), 56.9, 53.4 (2C), 36.2. HRMS $C_{13}H_{17}ClN_2O_2$ [M+H$^+$]: calculated 269.1057, found 269.1054.

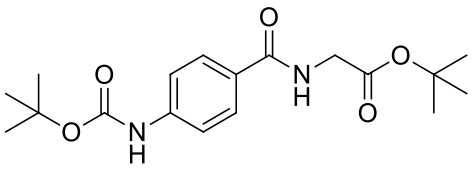
2-(Diethylamino)ethyl 4-butoxybenzoate (Butoxycaine) (5a)



5a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In Chamber B of the two-chamber system was added 1-bromo-4-butoxybenzene (115 mg, 0.50 mmol), 2-(diethylamino)ethan-1-ol (266 µL, 2.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), CataCXium A (18 mg, 0.050 mmol), Na_2CO_3 (160 mg, 1.5 mmol), DMAP (15.3 mg, 0.13 mmol) and toluene (3 mL). Chamber B was stirred at 100 °C for 18 h. Column chromatography (0 to 5% MeOH in EtOAc) afforded **5a** as a colorless oil (141 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.36 (t, J = 6.2 Hz, 2H), 4.01 (t, J = 6.5 Hz, 2H), 2.85 (t, J = 6.2, 2H), 2.63 (q, J = 7.1, 4H), 1.79 (quin, J = 7.4, 2H), 1.50 (sext, J = 7.4, 2H), 1.07 (t, J = 7.1, 6H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 163.1, 131.7 (2 C), 122.6, 114.2 (2 C), 68.0, 63.3, 51.2, 48.0 (2 C), 31.3, 19.3, 14.0, 12.3 (2 C). HRMS $C_{17}H_{27}NO_3$ [M+H$^+$]: calculated 294.2069, found 294.2070.

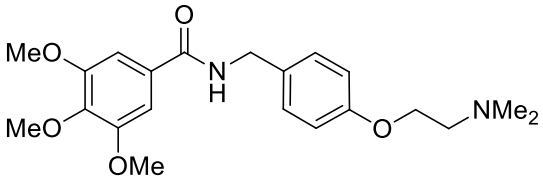
[4] Allen, C. L.; Chhatwal, A. R. ; Williams, J. M. J. *Chem. Commun.* **2012** , *48*, 666

***tert*-Butyl (4-((*tert*-butoxycarbonyl)amino)benzoyl)glycinate (Protected aminohippuric acid) (6a)**



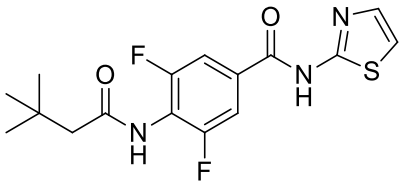
6a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In chamber B of the two-chamber system was added *tert*-butyl (4-bromophenyl)carbamate (136 mg, 0.50 mmol), *tert*-butyl glycinate (131 mg, 1.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), CataCXium A (18 mg, 0.05 mmol), Na_2CO_3 (160 mg, 1.5 mmol), DMAP (15.3 mg, 0.13 mmol) and toluene (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (0 to 3% MeOH in CH_2Cl_2) afforded **6a** as a colorless solid (162 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.66 (t, J = 5.9 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 3.86 (d, J = 5.9 Hz, 2H), 1.49 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 166.0, 152.6, 142.4, 128.1 (2 C), 127.1, 117.1 (2 C), 80.5, 79.5, 41.8, 28.1 (3 C), 27.7 (3 C). HRMS $C_{18}H_{26}N_2O_5$ [M+Na$^+$]: calculated 373.1739, found 373.1737.

***N*-(4-(2-(Dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide (Tigan) (7a)**



7a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In Chamber B of the two-chamber system was added 5-iodo-1,2,3-trimethoxybenzene (147 mg, 0.50 mmol), 2-(4-(aminomethyl)phenoxy)-*N*,*N*-dimethylethanamine (194 mg, 1.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Et_3N (135 μL, 1.0 mmol) and dioxane (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (CH_2Cl_2/EtOAc/MeOH 5:1:1) afforded **7a** as a light yellow solid (193 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 7.02 (s, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.46 (bs, 1H), 4.55 (d, J = 5.5 Hz, 2H), 4.14 (t, J = 5.5 Hz, 2H), 3.88 (s, 6H), 3.86 (s, 3H), 2.90-2.85 (m, 2H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.5, 153.3 (2 C), 141.0, 130.5, 130.0, 129.4 (2 C), 114.9 (2 C), 104.5 (2 C), 66.2, 61.0, 58.4, 56.4 (2 C), 46.0 (2 C), 43.8. HRMS $C_{21}H_{28}N_2O_5$ [M+H$^+$]: calculated 389.2076, found 389.2077.

4-(3,3-Dimethylbutanamido)-3,5-difluoro-*N*-(thiazol-2-yl)benzamide (Potent hA_{2A} receptor antagonist) (8a)[5]



8a was prepared following the general procedure for the reduction of CO_2 *via* injection to chamber A. In chamber B of the two-chamber system was added *N*-(4-bromo-2,6-difluorophenyl)-3,3-dimethylbutanamide (153 mg, 0.50 mmol), thiazol-2-amine (55 mg, 0.55 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), Xantphos (14.5 mg, 0.050 mmol), DIPEA (175 µL, 1.0 mmol) and toluene (3 mL). Chamber B was stirred at 100 °C for 18 h. Column chromatography (2 to 5 % MeOH in CH_2Cl_2) followed by recrystallization from CH_2Cl_2 afforded **8a** as a colorless solid (134 mg, 76% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 9.76 (s, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 2.20 (s, 2H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 162.8, 158.9 (bs), 157.1 (dd, J = 249.4 Hz, 5.1 Hz, 2C), 137.1 (bs), 131.4 (bs), 118.5 (t, J = 17.1 Hz), 114.1, 111.7 (d, J = 24.9 Hz, 2C), 48.4, 30.7, 29.5 (3C). ^{19}F NMR (376 MHz, DMSO-d_6) δ −115.5. HRMS $C_{16}H_{17}F_2N_3O_2S$ [M+H$^+$]: calculated 354.1088, found 354.1086.

Conditions for the reduction of $^{13}CO_2$ generated from $Ba^{13}CO_3$ in the three-chamber system

Chamber A

In a glovebox under argon, to chamber A of the three-chamber system was added CsF (11 mg, 0.075 mmol), tetraphenyldimethyldisilane (296 mg, 0.75 mmol) and DMSO (3.0 mL). Chamber A was fitted with a H-cap and stirred at 20 °C for 18 hours outside the glovebox.

Chamber B

The chamber B of the three-chamber system is loaded in a glovebox under argon and sealed with H caps. See below conditions in chamber B for each substrate.

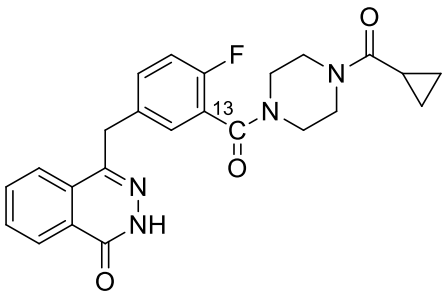
Chamber C

In a glovebox under argon, to chamber C of the three-chamber system was added $Ba^{13}CO_3$ (198.3 mg, 1.0 mmol) and camphorsulfonic acid (476 mg, 2.1 mmol). 1,2-Dichlorobenzene (0.7 mL) was added and at last water (0.6 mL) was added slowly and chamber C was fitted with a H-cap. The

[5] Korsager, S.; Skrydstrup, T.; Taaning, R. H. *J. Am. Chem.Soc.* **2013** , *135*, 2891

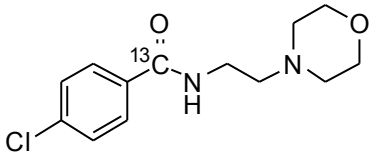
release of $^{13}CO_2$ starts when chamber C is stirred at 20 °C outside the glovebox. Chamber C is stirred at 20 °C for 18 hours **(**release of $^{13}CO_2$ is done after 10 minutes).

[^{13}C]-4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2*H*)-one (^{13}C-Olaparib) (3b)



3b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added 4-(3-bromo-4-fluorobenzyl)phthalazin-1(2*H*)-one (166.6 mg, 0.50 mmol), cyclopropyl(piperazin-1-yl)methanone (154 mg, 1.0 mmol), $Pd(dba)_2$ (30 mg, 0.050 mmol), Xantphos (29 mg, 0.050 mmol), DIPEA (250 µL, 1.4 mmol) and dioxane (3 mL). Chamber B was stirred at 100 °C for 18 h. Column chromatography (0 to 1% MeOH in EtOAc) afforded **3b** (179 mg, 82% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79-11.63 (m, 1H), 8.48-8.43 (m, 1H), 7.78-7.67 (m, 3H), 7.38-7.28 (m, 2H), 7.01 (t, J = 8.9 Hz, 1H), 4.28 (s, 2H), 3.89-3.50 (m, 6H), 3.43-3.17 (m, 2H), 1.81-1.56 (m, 1H), 1.02-0.95 (m, 2H), 0.84-0.66 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.4 (^{13}C-enriched), 160.9, 157.2 (d, J = 247.2 Hz), 145.7, 134.6 (t, J = 3.7 Hz), 133.8, 131.9 (d, J = 8.1 Hz), 131.7, 129.7, 129.4 (bs), 128.5, 127.4, 125.2, 124.4-123.3 (m), 116.4 (d, J = 20.5 Hz), 47.5-44.9 (m, 2C), 42.4 (bs, 2C), 37.9, 11.2, 7.9 (2C). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.7. HRMS $C_{23}{}^{13}CH_{23}FN_4O_3$ [M+H$^+$]: calculated 436.1866, found 436.1866.

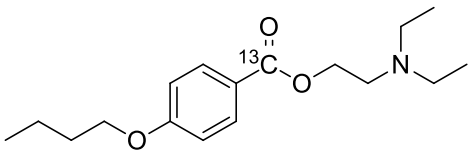
[^{13}C]-4-Chloro-*N*-(2-morpholinoethyl)benzamide (^{13}C-Moclobemide) (4b)



4b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added 1-chloro-4-iodobenzene (119 mg, 0.50 mmol), 2-morpholinoethanamine (130 mg, 1.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Et_3N (135 µL, 1.0 mmol) and dioxane (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (1 to 2 % MeOH in CH_2Cl_2) afforded **4b** as a colorless solid (132 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 8.4 Hz, J = 3.6 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.81 (bs, 1H), 3.70 (t, J = 4.4 Hz, 4H), 3.57-3.45 (m, 2H), 2.57 (t, J = 6.0 Hz, 2H), 2.53-2.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (^{13}C-enriched),

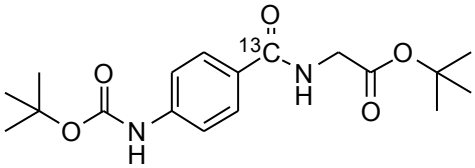
137.6, 133.1 (d, J = 64.6 Hz), 128.9 (d, J = 4.4 Hz), 128.4 (d, J = 2.5 Hz), 67.1 (2C), 56.9, 53.4 (2C), 36.2. HRMS $C_{12}{}^{13}CH_{17}ClN_2O_2$ [M+H$^+$]: calculated 270.1090, found 270.1088.

[^{13}C]-2-(Diethylamino)ethyl 4-butoxybenzoate (^{13}C-Butoxycaine) (5b)



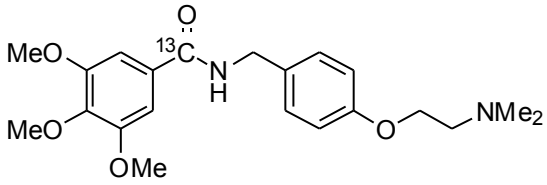
5b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added 1-bromo-4-butoxybenzene (115 mg, 0.50 mmol), 2-(diethylamino)ethanol (265 μL, 2.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), CataCXium A (17.9 mg, 0.050 mmol), DMAP (15.3 mg, 0.13 mmol), Na_2CO_3 (159 mg, 1.5 mmol) and toluene (3 mL). Chamber B was stirred at 100 °C for 18 h. Column chromatography (0 to 2% MeOH in EtOAc) afforded **5b** as a colorless oil (139 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.34 (td, J = 6.4 Hz, J = 3.2 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H), 2.61 (q, J = 7.2 Hz, 4H), 1.79 (quint, J = 7.4 Hz, 2H), 1.47 (sext, J = 7.4 Hz, 2H), 1.05 (t, J = 7.2 Hz, 6H), 0.97 (t, J = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (^{13}C-enriched), 162.9, 131.5 (d, J = 2.9 Hz, 2C), 122.4 (d, J = 77.0 Hz), 114.0 (d, J = 4.4 Hz, 2 C), 67.8, 63.0 (d, J = 2.2 Hz), 51.0, 47.8 (2 C), 31.1, 19.1, 13.8, 12.1 (2 C). HRMS $C_{16}{}^{13}CH_{27}NO_3$ [M+H$^+$]: calculated 295.2103, found 295.2104.

[^{13}C]-*tert*-Butyl 2-(4-((*tert*-butoxycarbonyl)amino)benzamido)acetate (^{13}C-Protected aminohippuric acid) (6b)



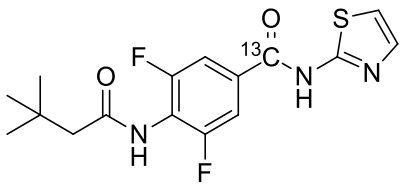
6b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added *tert*-butyl (4-bromophenyl)carbamate (136 mg, 0.50 mmol), *tert*-butyl glycinate HCl salt (167 mg, 1.0 mmol), CataCXium A (18 mg, 0.005 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), Na_2CO_3 (266 mg, 2.5 mmol), DMAP (15.3 mg, 0.13 mmol) and toluene (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (0.5 to 1% MeOH in CH_2Cl_2) afforded **5b** as a colorless solid (146 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, J = 8.8 Hz, J = 2.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.72 (bs, 1H), 6.58 (bs, 1H), 4.12 (dt, J = 4.8 Hz, J = 0.8 Hz, 2H), 1.52 (s, 9H), 1.50 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.8 (^{13}C-enriched), 152.4, 141.8, 128.4 (m, 2 C), 128.3 (d, J = 32.0 Hz, 1 C), 117.8 (m, 2 C), 82.7, 81.3, 42.6, 28.4 (3 C), 28.2 (3 C). HRMS $C_{17}{}^{13}CH_{26}N_2O_5$ [M+Na$^+$]: calculated 374.1773, found 374.1771.

[^{13}C]-*N*-(4-(2-(Dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide (^{13}C-Tigan) (7b)



7b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added 5-iodo-1,2,3-trimethoxybenzene (147 mg, 0.50 mmol), 2-(4-(aminomethyl)phenoxy)-*N,N*-dimethylethanamine (194 mg, 1.0 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Et_3N (135 μL, 1.0 mmol) and dioxane (3 mL). Chamber B was stirred at 80 °C for 18 h. Column chromatography (CH_2Cl_2/EtOAc/MeOH 5:1:1) afforded **7b** as a colorless solid (192 mg, 99% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.36 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.56 (d, J = 4.0 Hz, 2H), 4.26 (t, J = 5.2 Hz, 2H), 3.91 (s, 6H), 3.84 (s, 3H), 3.26 (t, J = 5.2 Hz, 2H), 2.73 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 169.2 (^{13}C-enriched), 158.7, 154.3 (d, J = 5.9 Hz, 2C), 142.0, 133.2, 130.8 (d, J = 64.5), 130.1 (2C), 115.7 (2C), 106.0 (d, J = 2.7 Hz, 2C), 64.8, 61.1, 58.3, 56.8 (2C), 44.9 (2C), 44.0. HRMS $C_{20}{}^{13}CH_{28}N_2O_5$ [M+H$^+$]: calculated 390.2110, found 390.2109.

[^{13}C]-4-(3,3-Dimethylbutanamido)-3,5-difluoro-N-(thiazol-2-yl)benzamide (8b)



8b was prepared in the three-chamber system according to the general procedure for chambers A and C. In a glovebox under argon, in chamber B of the three-chamber system was added *N*-(4-bromo-2,6-difluorophenyl)-3,3-dimethylbutanamide (153 mg, 0.50 mmol), 2-aminothiazole (55 mg, 0.55 mmol), $Pd(dba)_2$ (15 mg, 0.025 mmol), Xantphos (14.5 mg, 0.025 mmol), DIPEA (175 μL, 1.0 mmol) and toluene (3 mL). Chamber B stirred at 100 °C for 18 h. Column chromatography (0 to 5% MeOH in CH_2Cl_2) followed by recrystallization from CH_2Cl_2 afforded **8b** as a colorless solid (136 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (bs, 1H), 9.82 (s, 1H), 7.89 (dd, J = 8.4 Hz, J = 4.4 Hz, 2H), 7.58 (d, J = 3.7 Hz 1H), 7.31 (d, J = 3.7 Hz, 1H), 2.26 (s, 2H), 1.04 (s, 9H).^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 162.8 (^{13}C enriched), 157.2 (dt, J = 250.2, 6.6 Hz, 2C), 137.1, 131.4 (dt, J = 68.2 Hz, J = 8.8 Hz), 118.6 (t, J = 17.6 Hz), 114.1 (2C), 111.8 (d, J = 23.5 Hz, 2C), 48.4, 30.7, 29.5 (3C). ^{19}F NMR (DMSO-d_6, 376 MHz) δ -115.6. HRMS $C_{15}{}^{13}CH_{17}F_2N_3O_2S$ [M+H$^+$]: calculated 355.1121, found 355.1117.

Experiments with B_2pin_2 and pinBSiMe$_2$Ph

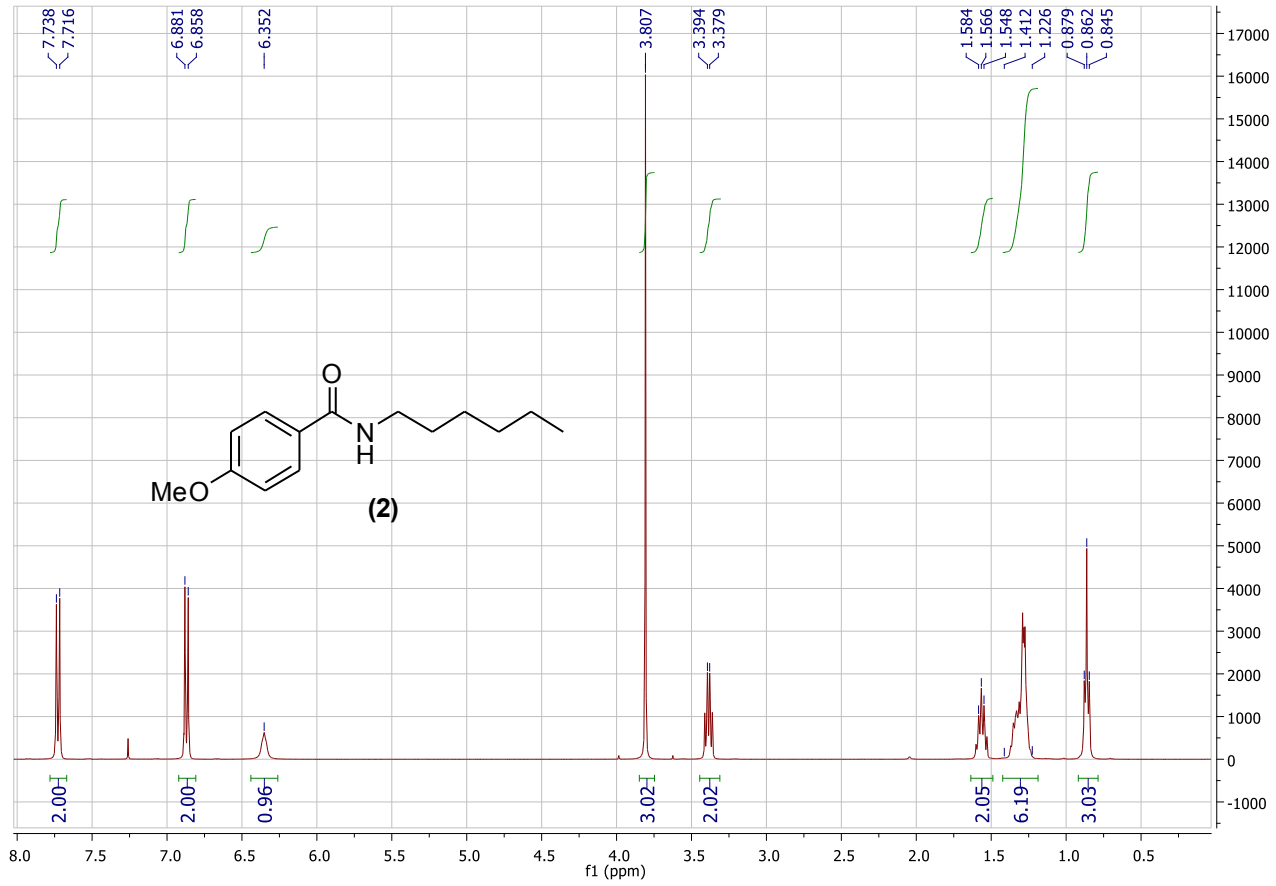
In a glovebox under argon, to chamber A of the two-chamber system was added CsF (7.6 mg, 0.050 mmol), B_2pin_2 (127 mg, 0.50 mmol) or pinBSiMe$_2$Ph (131 mg, 0.50 mmol) and DMSO (3.0 mL). Chamber A was sealed using a screw cap lined with a PTFE/silicone seal. In chamber B of the two-chamber system, $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol) and *p*-iodoanisole (117 mg, 0.50 mmol) were dissolved in dioxane (3.0 mL). *n*-Hexylamine (133 μL, 1.0 mmol) and Et_3N (135 μL, 1.0 mmol) were then added. Chamber B was sealed using a screw cap lined with a PTFE/silicone seal. As the last reagent, CO_2 (21 mL, 0.85 mmol) was added with a syringe through the septum outside the glovebox. The reactions mixtures were stirred overnight with chamber A at room temperature and chamber B at 80 °C. Conversion in Chamber A was measured by crude ^{1}H and ^{11}B NMR (a capillary with DMSO-d_6 added) analysis. Conversion in chamber B was measured by crude ^{1}H NMR ($CDCl_3$) analysis.

Experiments Set up in Air

In air outside a glovebox, to chamber A of the two-chamber system was added KHF_2 (3.9 mg, 0.050 mmol), $(MePh_2Si)_2$ (197 mg, 0.50 mmol) and DMSO (3.0 mL). Chamber A was sealed using a screw cap lined with a PTFE/silicone seal. In chamber B of the two-chamber system, $Pd(dba)_2$ (15 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol) and *p*-iodoanisole (117 mg, 0.50 mmol) were dissolved in dioxane (3.0 mL). *n*-Hexylamine (133 μL, 1.0 mmol) and Et_3N (135 μL, 1.0 mmol) were then added. Chamber B was sealed using a screw cap lined with a PTFE/silicone seal. As the last reagent, CO_2 (21 mL, 0.85 mmol) was added with a syringe through the septum. The reactions mixtures were stirred overnight with chamber A at room temperature or at 30 °C and chamber B at 80 °C. Conversion in Chamber B was measured by crude ^{1}H NMR ($CDCl_3$) analysis.

Pressure Measurement Experiment

In a glovebox under argon, to chamber A of the two-chamber system was added CsF (7.6 mg, 0.050 mmol), $(MePh_2Si)_2$ (197 mg, 0.50 mmol) and DMSO (3.0 mL). Chamber A was sealed using a screw cap lined with a PTFE/silicone seal and a manometer was attached to chamber B. CO_2 (21 mL, 0.85 mmol) was added with a syringe through the septum outside the glovebox. The reaction was followed by measuring the pressure of the system every 3 seconds.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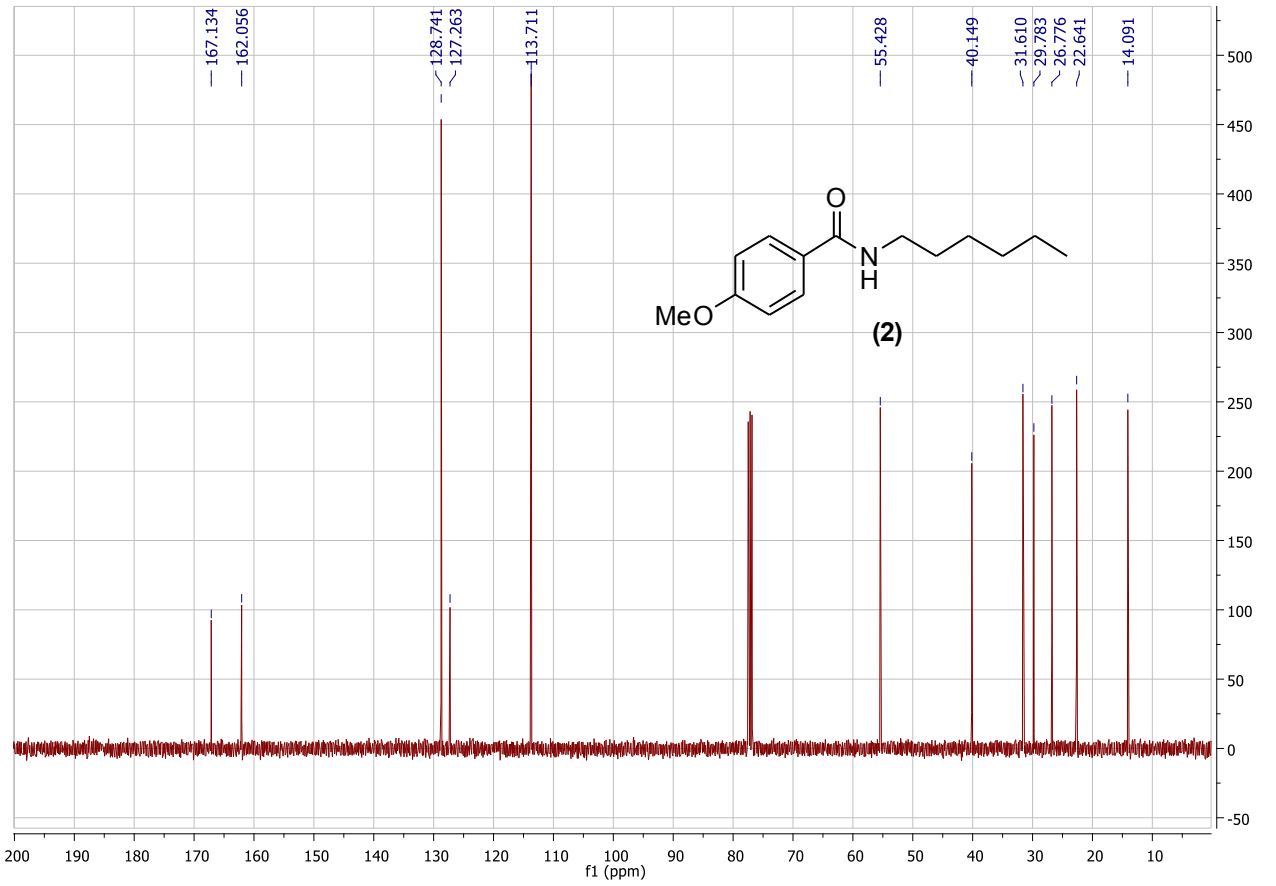
7.716
6.881
6.858
6.352
3.807
3.394
3.379
1.584
1.566
1.548
1.412
1.226
0.879
0.862
0.845
2.00
2.00
0.96
3.02
2.02
2.05
6.19
3.03
MeO
O
N
H
(2)
f1 (ppm)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128.741
127.263
113.711
55.428
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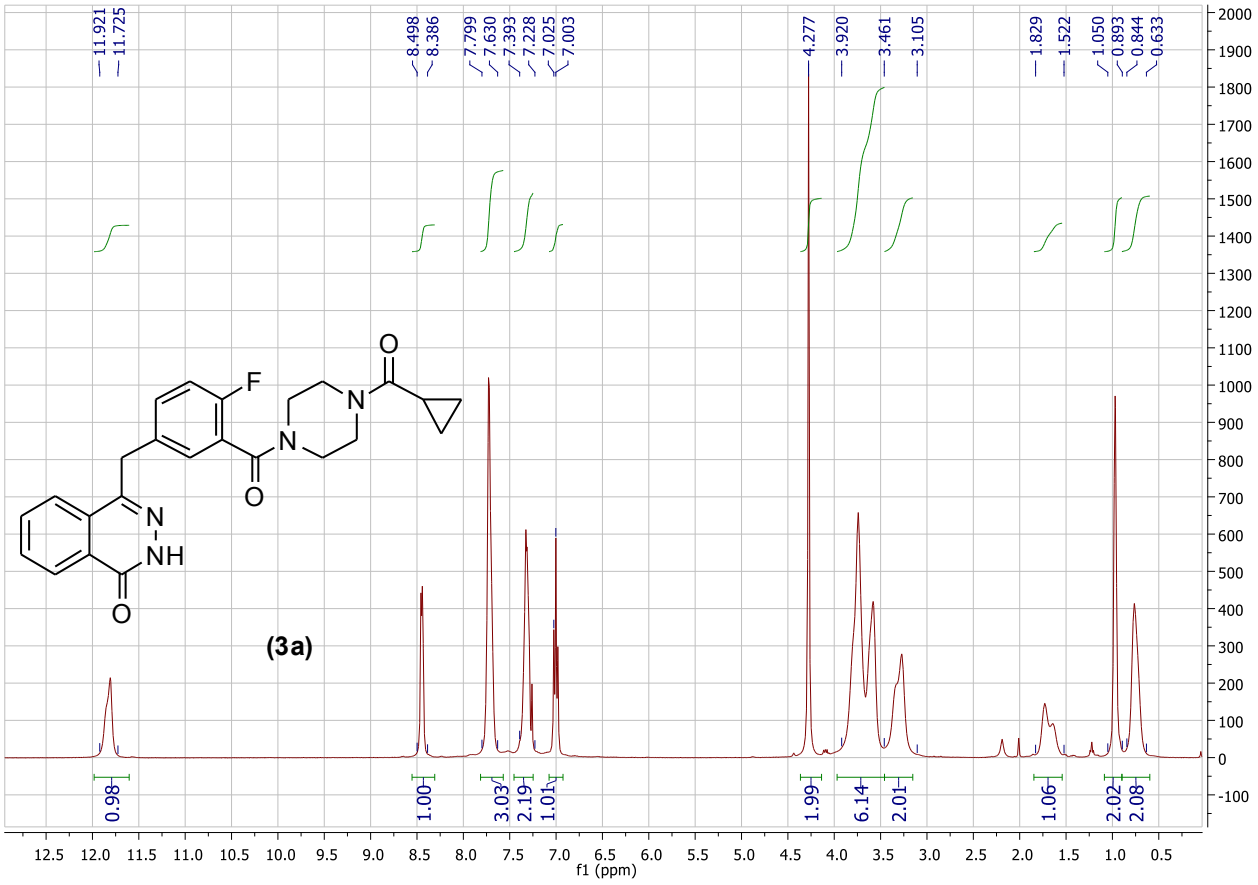
26.776
22.641
14.091
MeO
O
N
H
(2)
f1 (ppm)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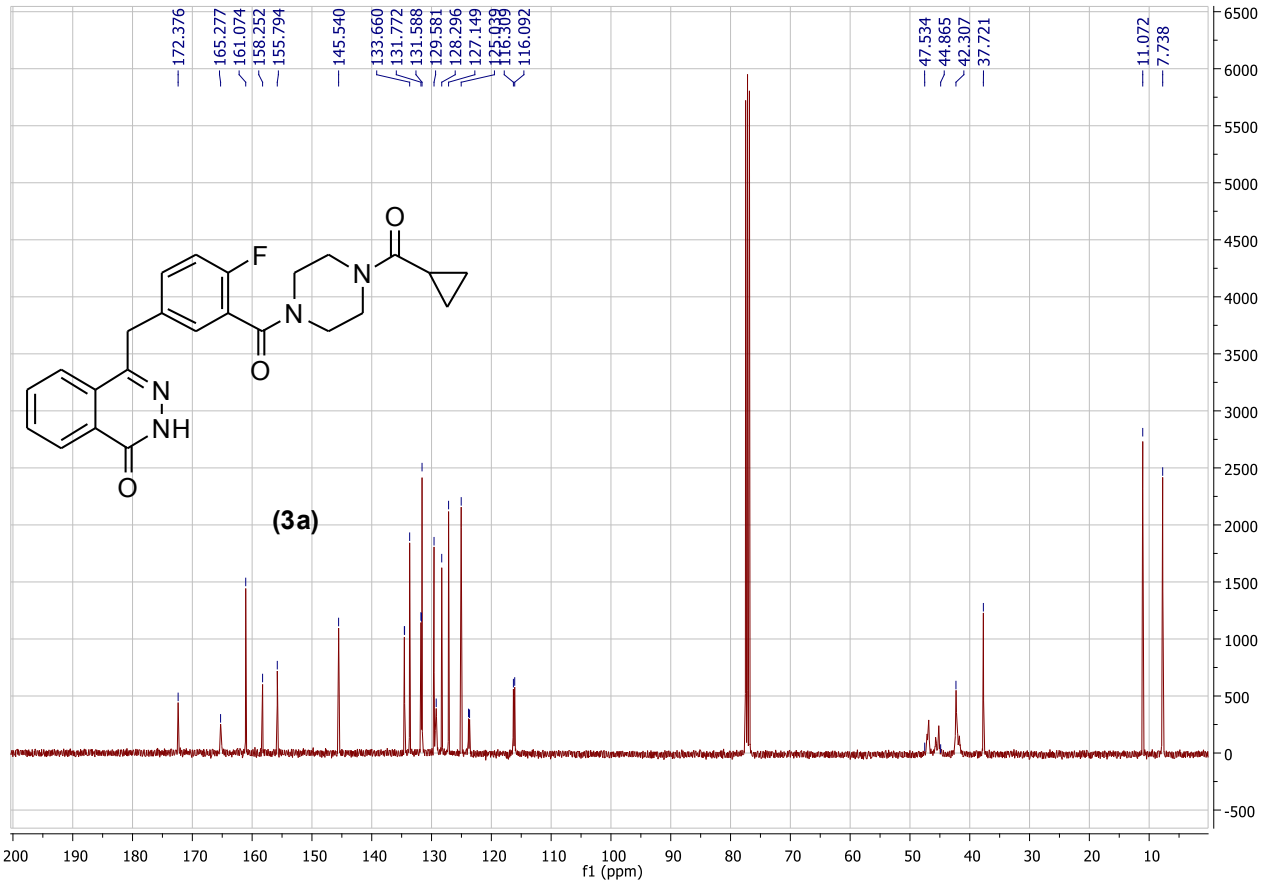
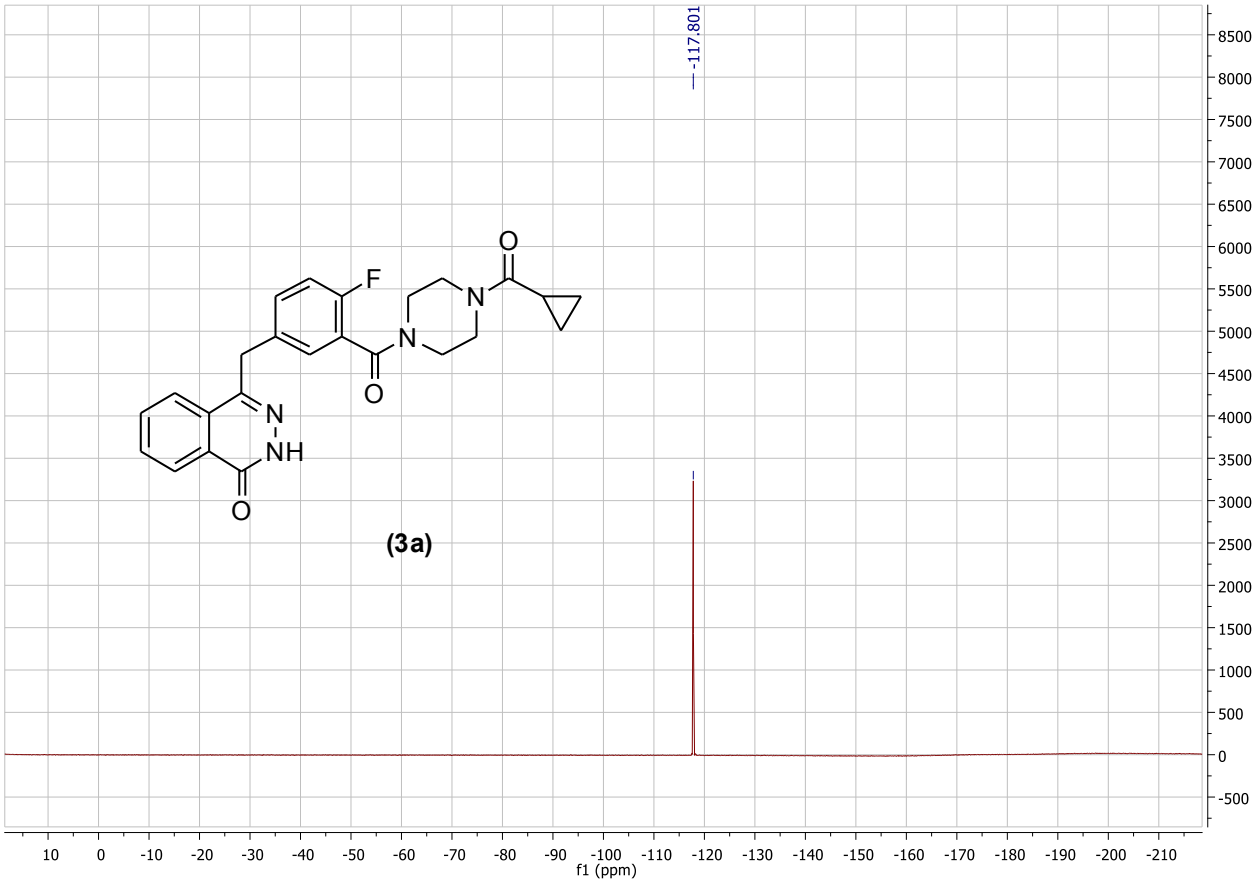
11.725
8.498
8.386
7.799
7.630
7.393
7.228
7.025
7.003
4.277
3.920
3.461
3.105
1.829
1.522
1.050
0.893
0.844
0.633
0.98
1.00
3.03
2.19
1.01
1.99
6.14
2.01
1.06
2.02
2.08
F
O
N
N
O
N
NH
O
(3a)
f1 (ppm)


172.376
165.277
161.074
158.252
155.794
145.540
133.660
131.772
131.588
129.581
128.296
127.149
116.309
116.092
47.534
44.865
42.307
37.721
11.072
7.738
F
O
N
N
O
N
NH
O
(3a)
f1 (ppm)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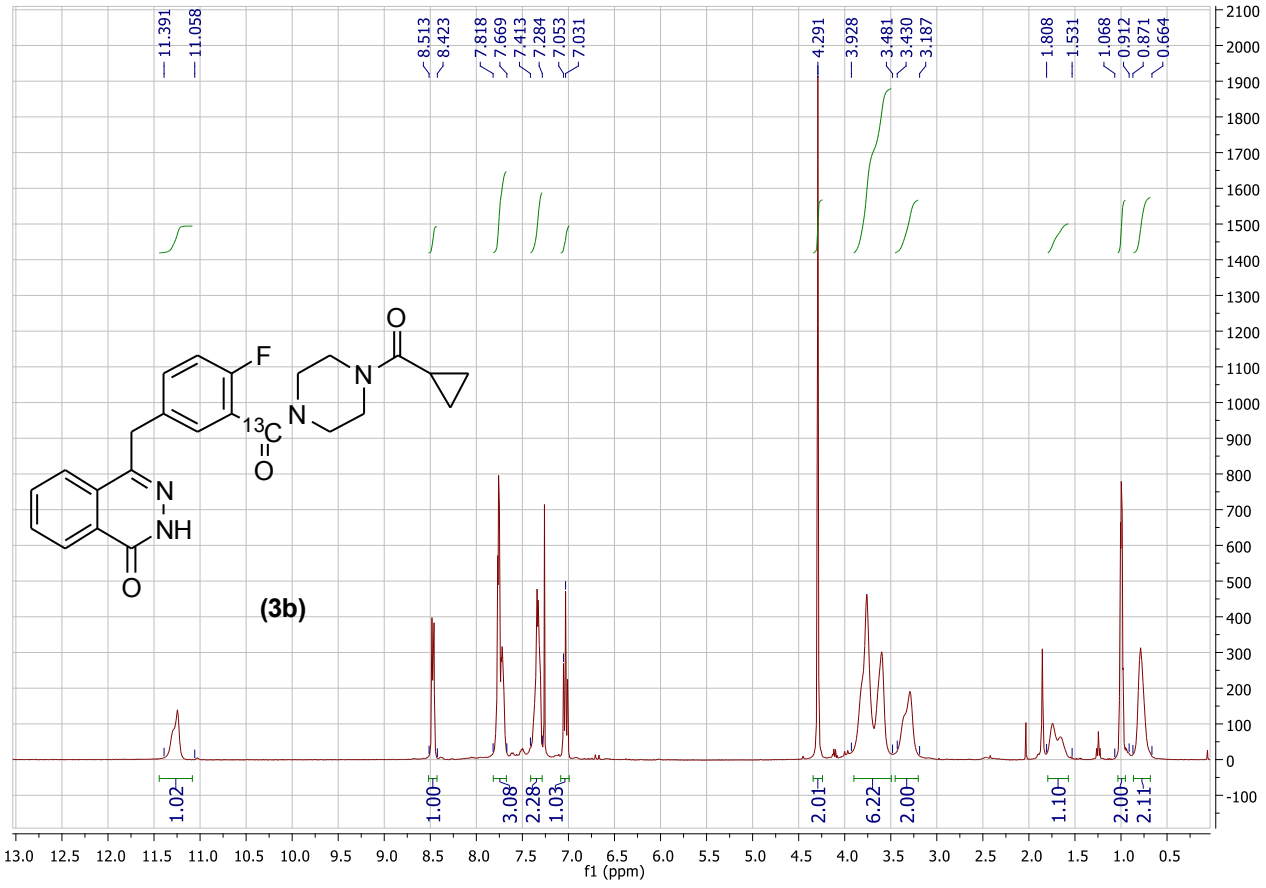
F
O
N
N
O
N
NH
O
(3a)
f1 (ppm)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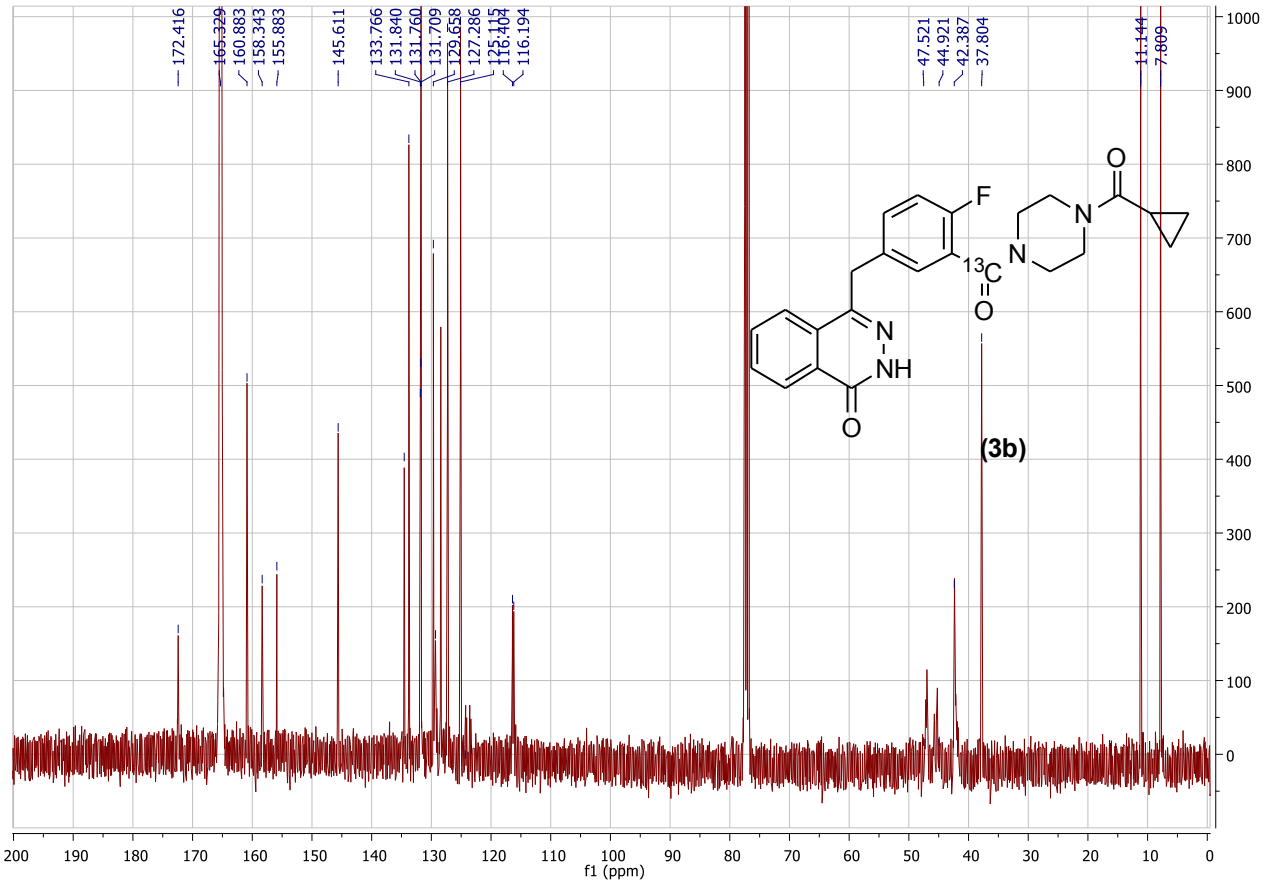
11.058
8.513
8.423
7.818
7.669
7.413
7.284
7.053
7.031
4.291
3.928
3.481
3.430
3.187
1.808
1.531
1.068
0.912
0.871
0.664
F
O
N
N
13C
O
N
NH
O
(3b)
1.02
1.00
3.08
2.28
1.03
2.01
6.22
2.00
1.10
2.00
2.11
f1 (ppm)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155.883
145.611
133.766
131.840
131.760
131.709
129.658
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116.194
47.521
44.921
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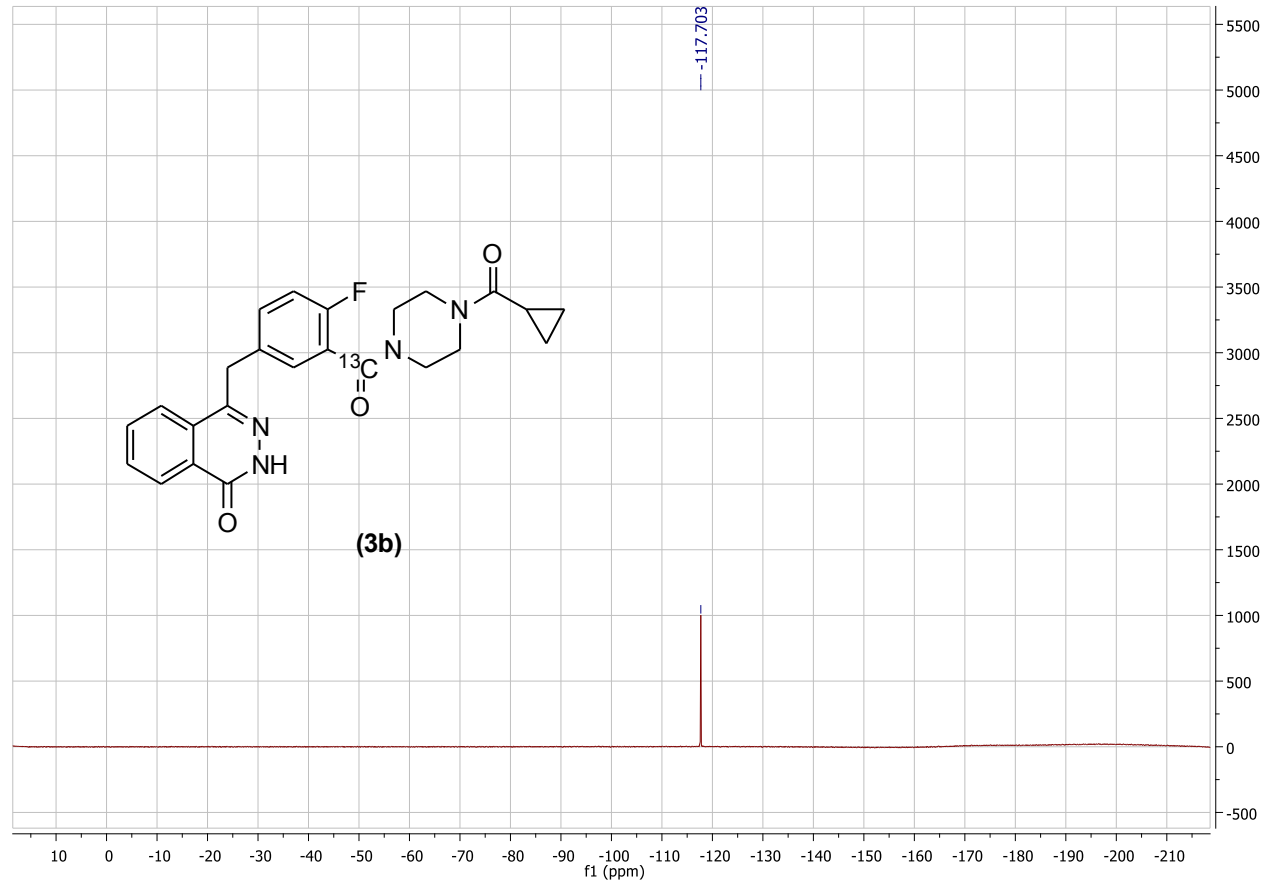
N
13C
O
N
NH
O
(3b)
f1 (ppm)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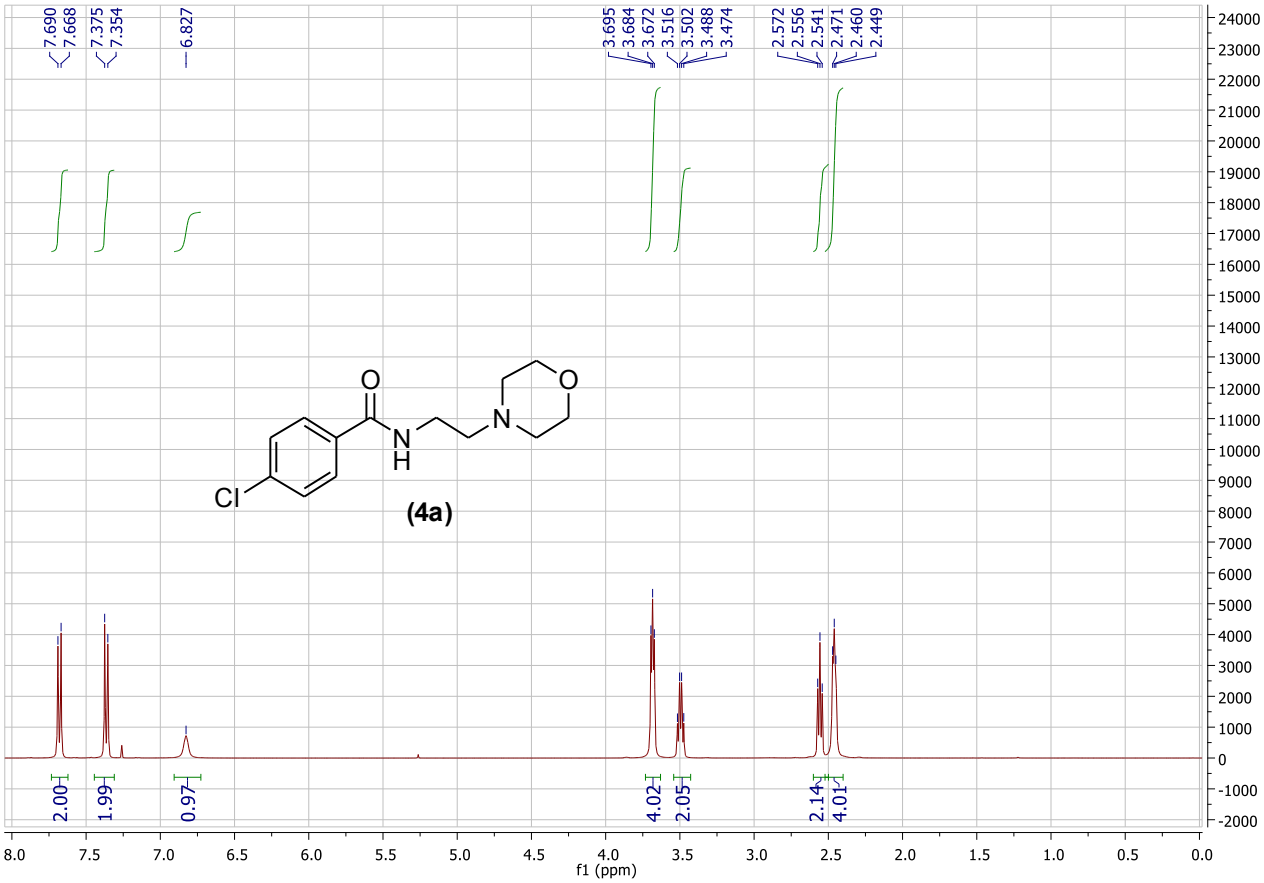
O
N
N
13C
O
N
NH
O
(3b)
f1 (ppm)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7.668
7.375
7.354
6.827
3.695
3.684
3.672
3.516
3.502
3.488
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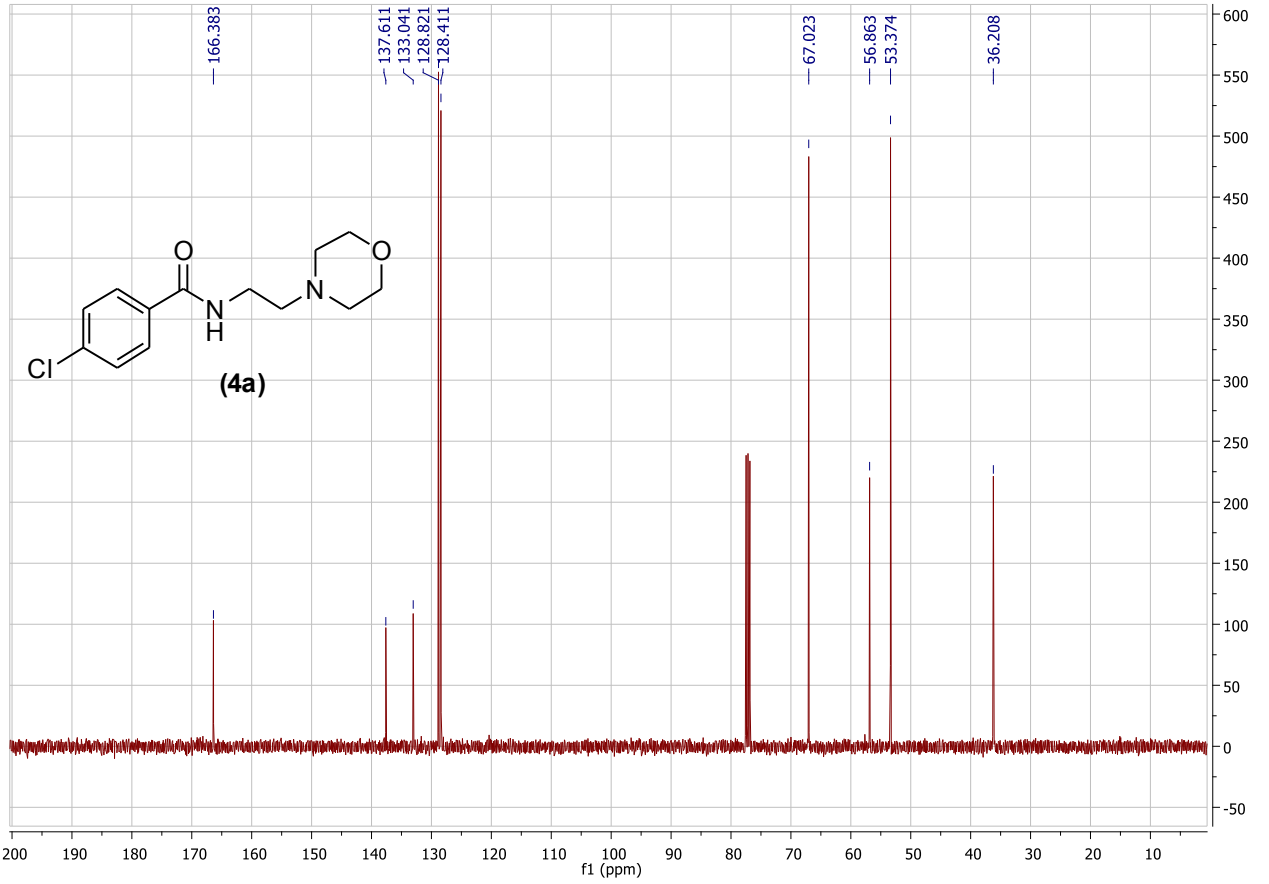
2.556
2.541
2.471
2.460
2.449
O
N
H
N
O
Cl
(4a)
2.00
1.99
0.97
4.02
2.05
2.14
4.01
f1 (ppm)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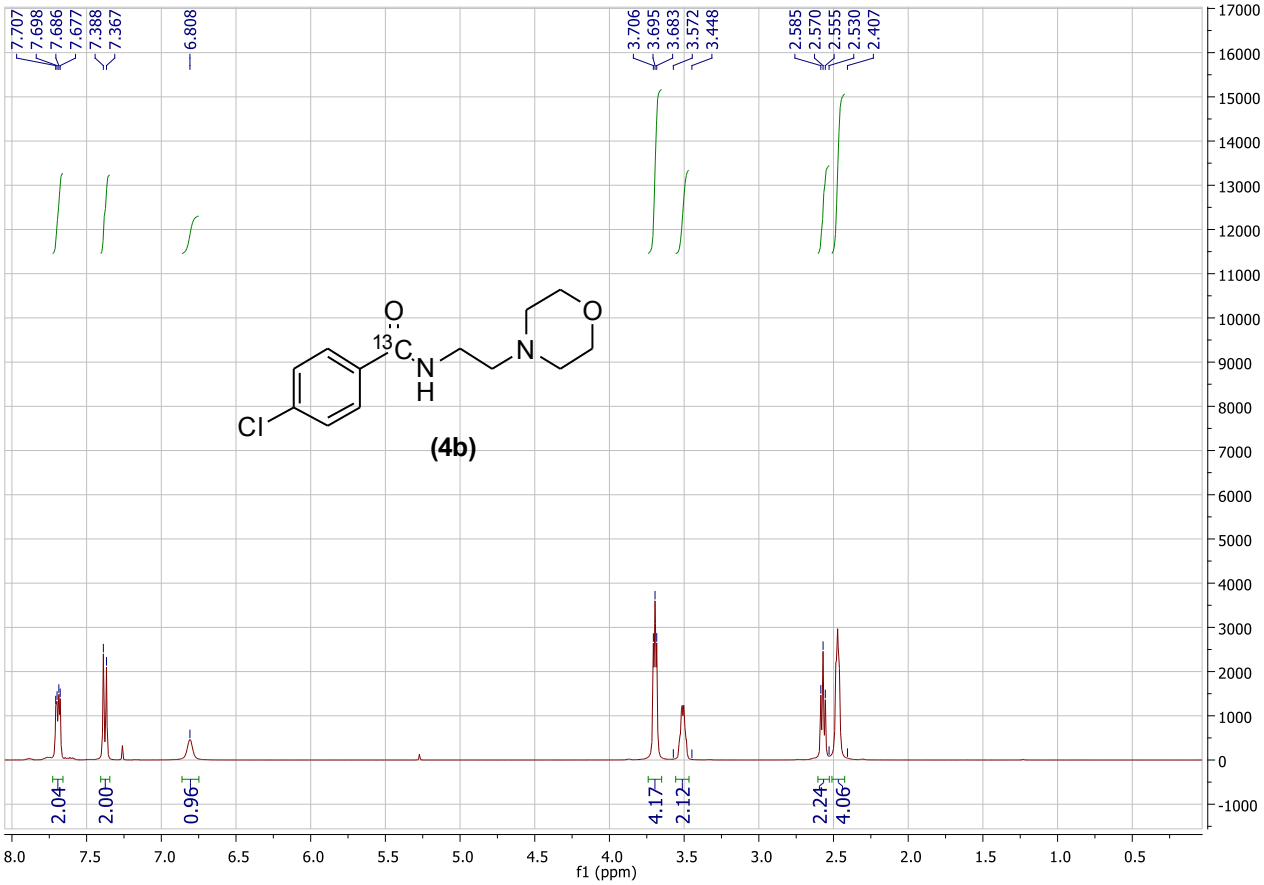
N
H
N
O
Cl
(4a)
f1 (ppm)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7.686
7.677
7.388
7.367
6.808
3.706
3.695
3.683
3.572
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2.585
2.570
2.555
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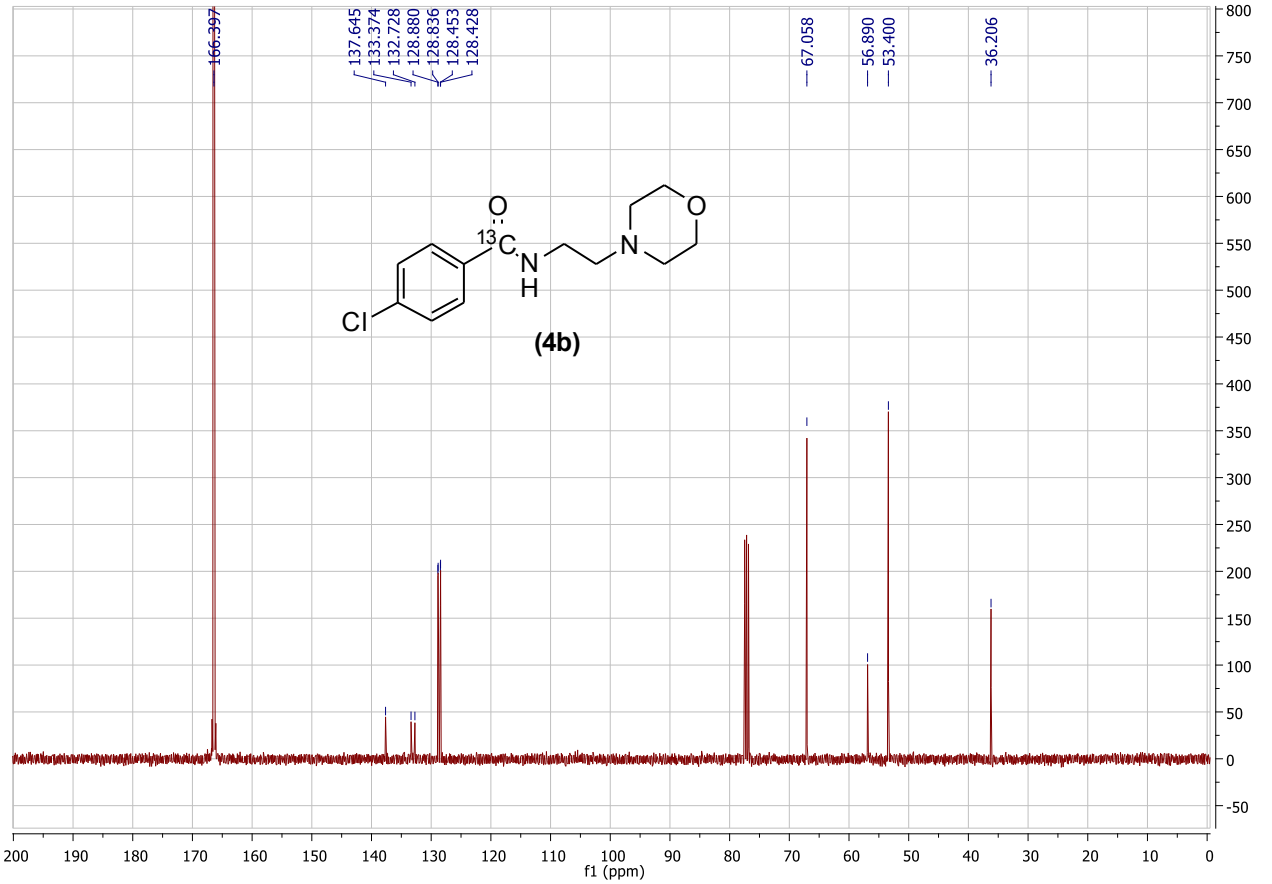
2.04
2.00
0.96
4.17
2.12
2.24
4.06
f1 (ppm)
(4b)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128.428
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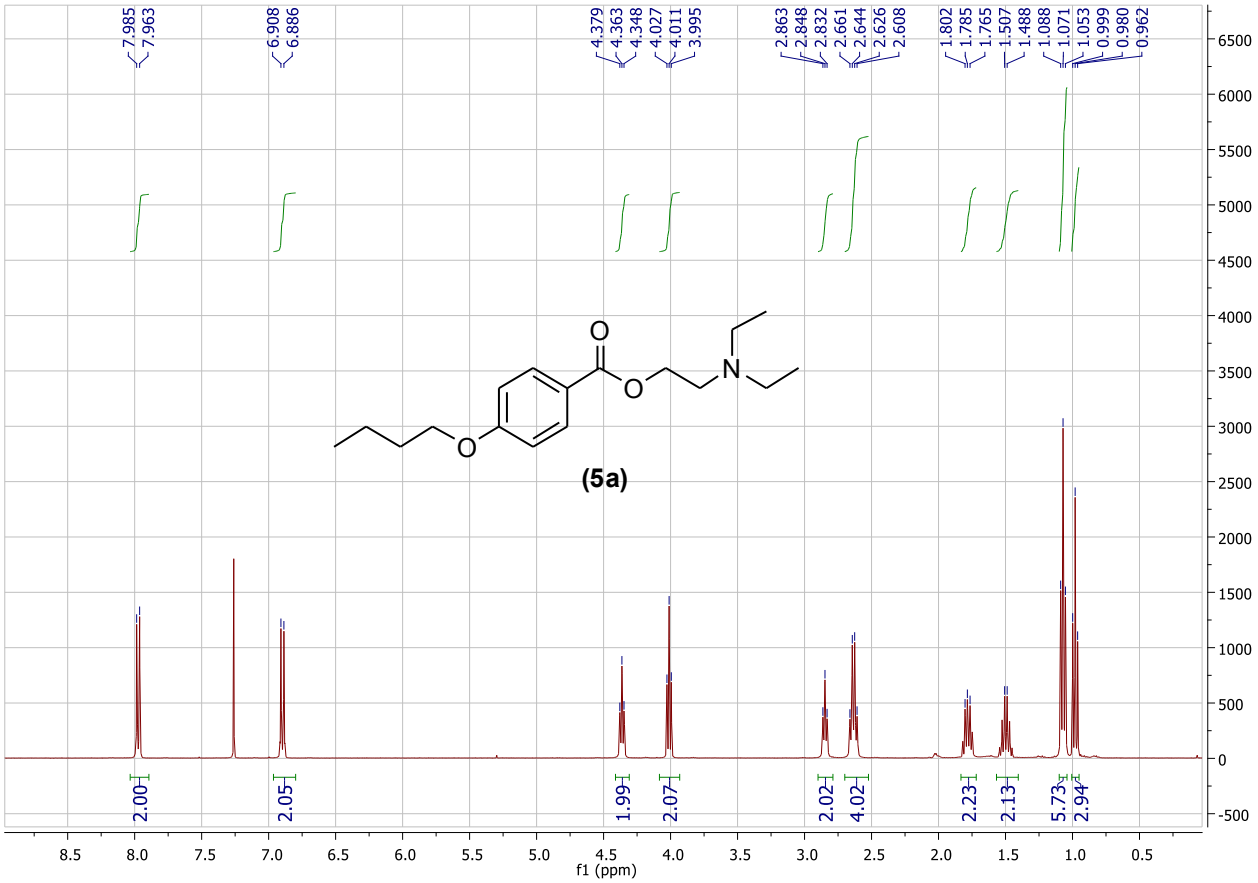
53.400
36.206
f1 (ppm)
(4b)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7.963
6.908
6.886
4.379
4.363
4.348
4.027
4.011
3.995
2.863
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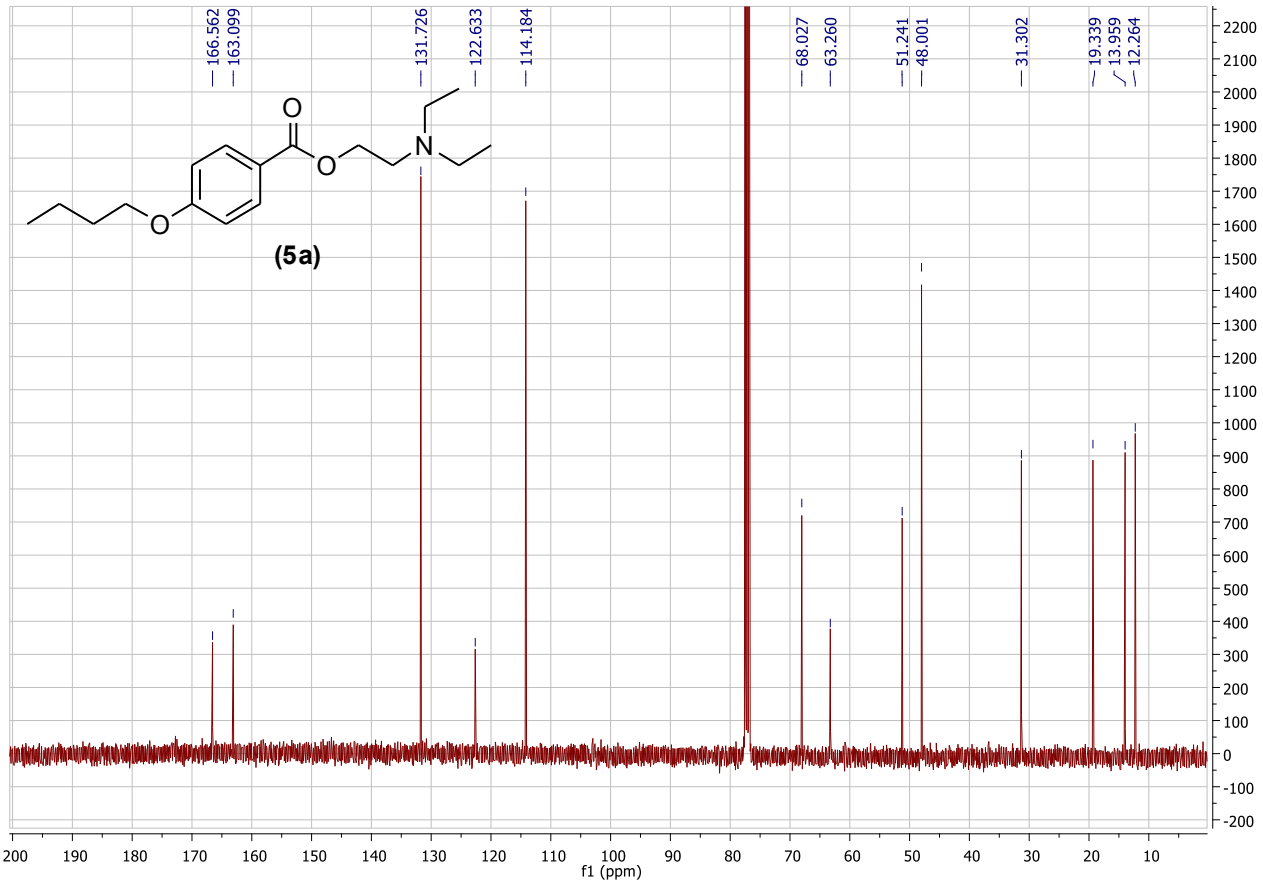
2.661
2.644
2.626
2.608
1.802
1.785
1.765
1.507
1.488
1.088
1.071
1.053
0.999
0.980
0.962
(5a)
2.00
2.05
1.99
2.07
2.02
4.02
2.23
2.13
5.73
2.94
f1 (ppm)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19.339
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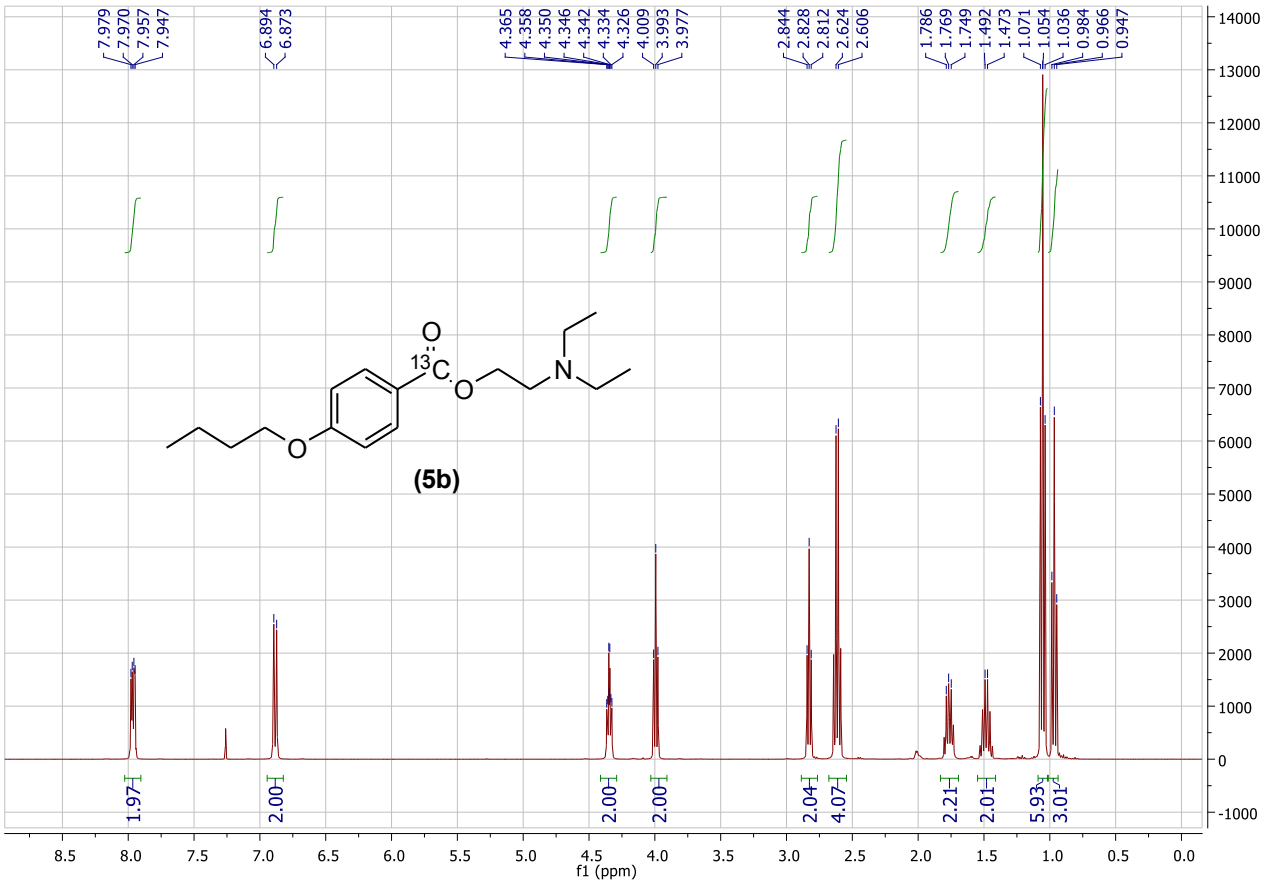
(5a)
f1 (ppm)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6.873
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4.342
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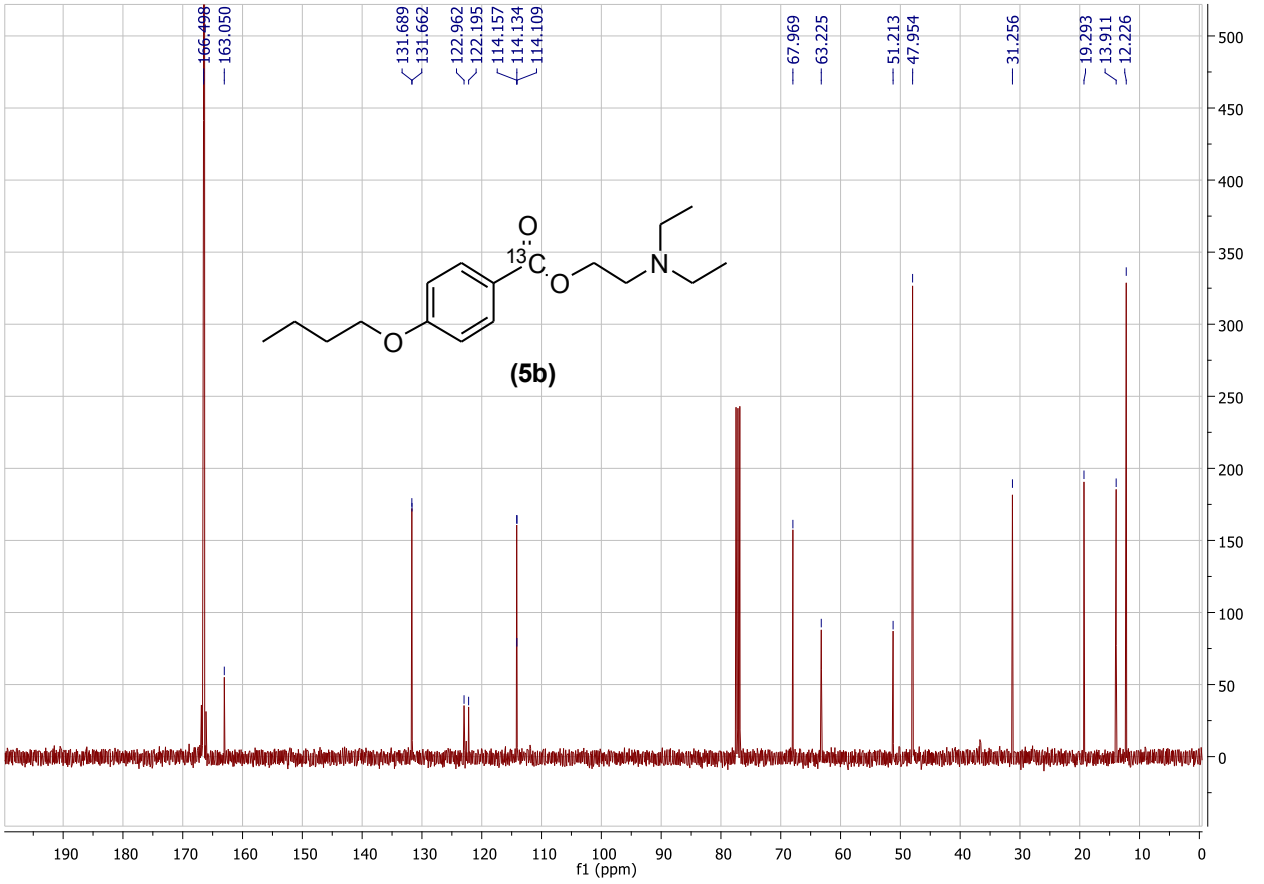
4.009
3.993
3.977
2.844
2.828
2.812
2.624
2.606
1.786
1.769
1.749
1.492
1.473
1.071
1.054
1.036
0.984
0.966
0.947
1.97
2.00
2.00
2.00
2.04
4.07
2.21
2.01
5.93
3.01
f1 (ppm)
(5b)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114.157
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114.109
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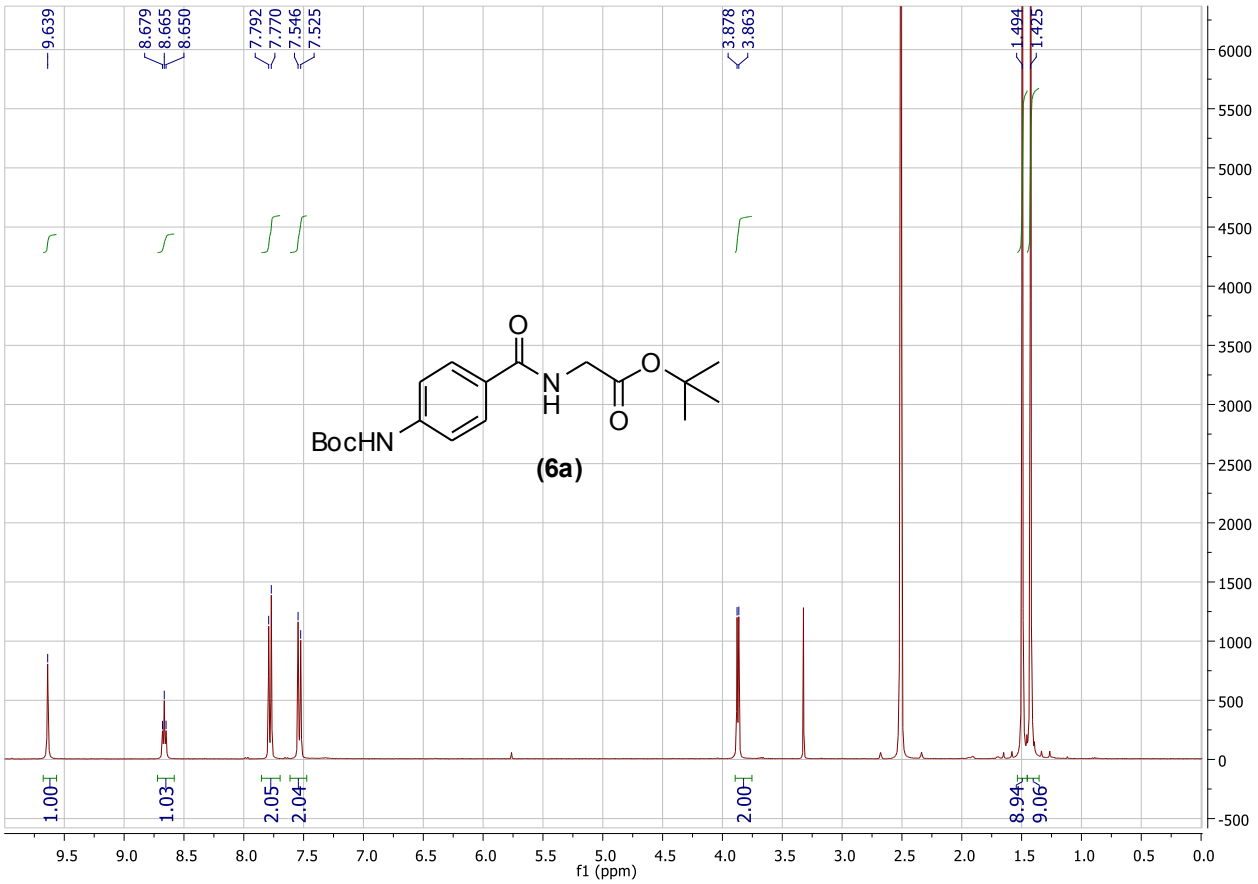
19.293
13.911
12.226
f1 (ppm)
(5b)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7.770
7.546
7.525
3.878
3.863
1.494
1.425
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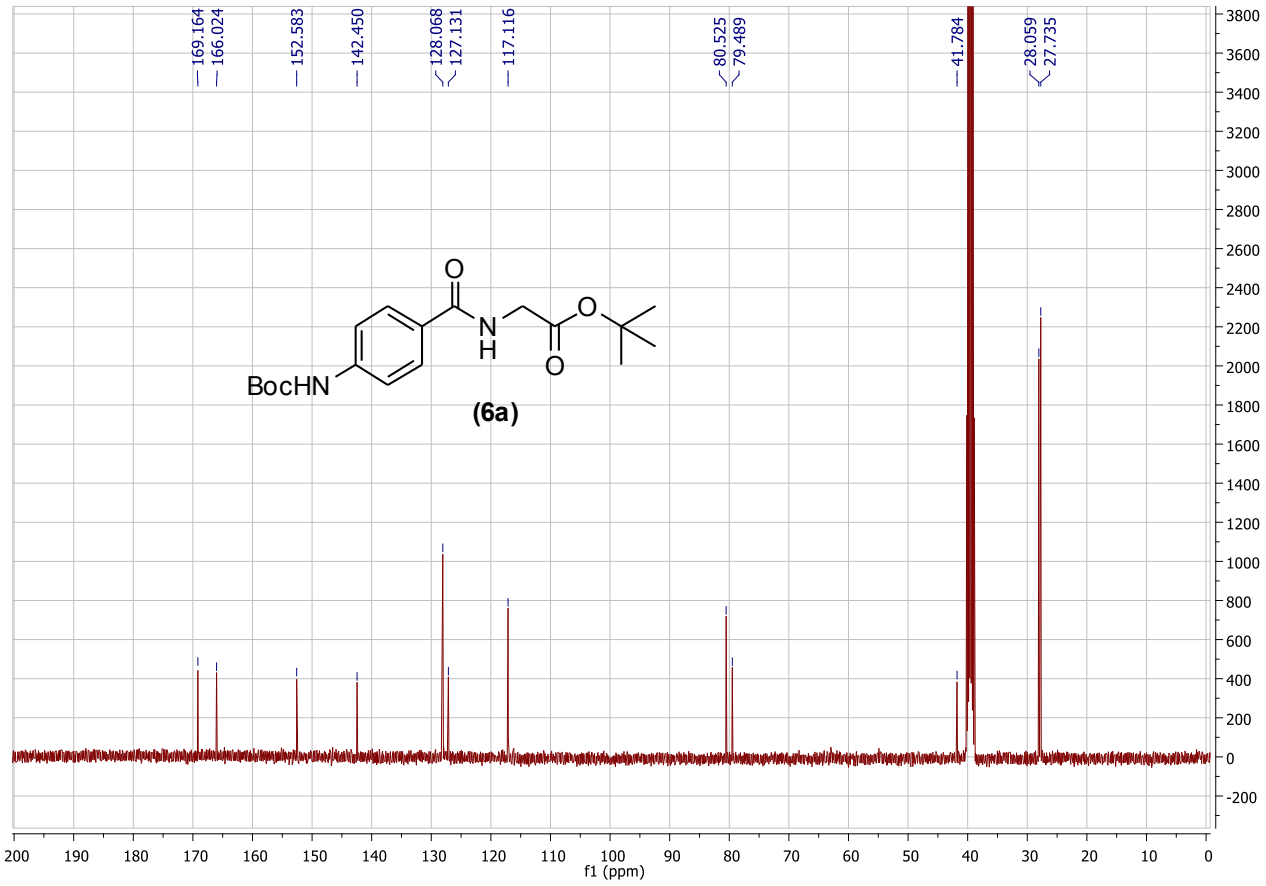
8.94
9.06
BocHN
(6a)
f1 (ppm)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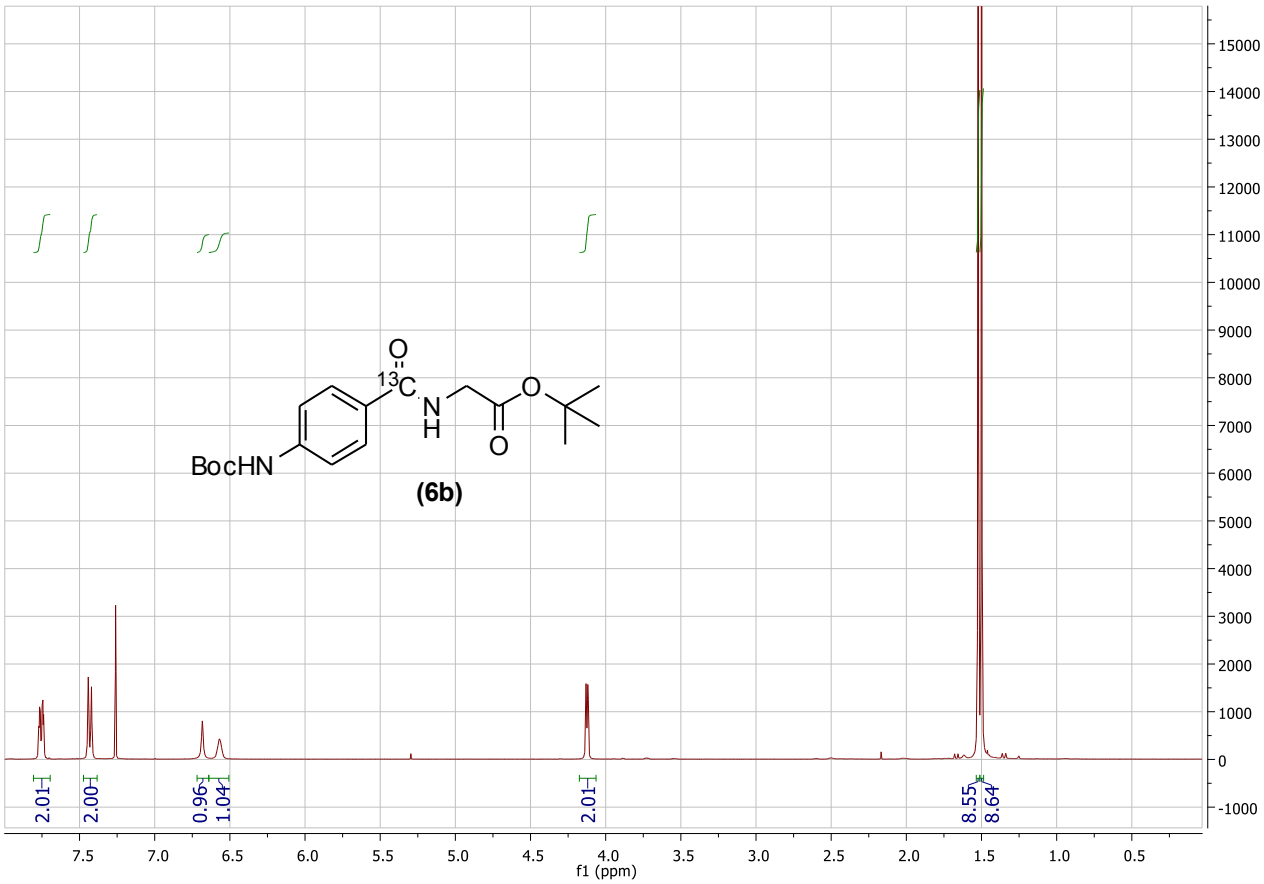
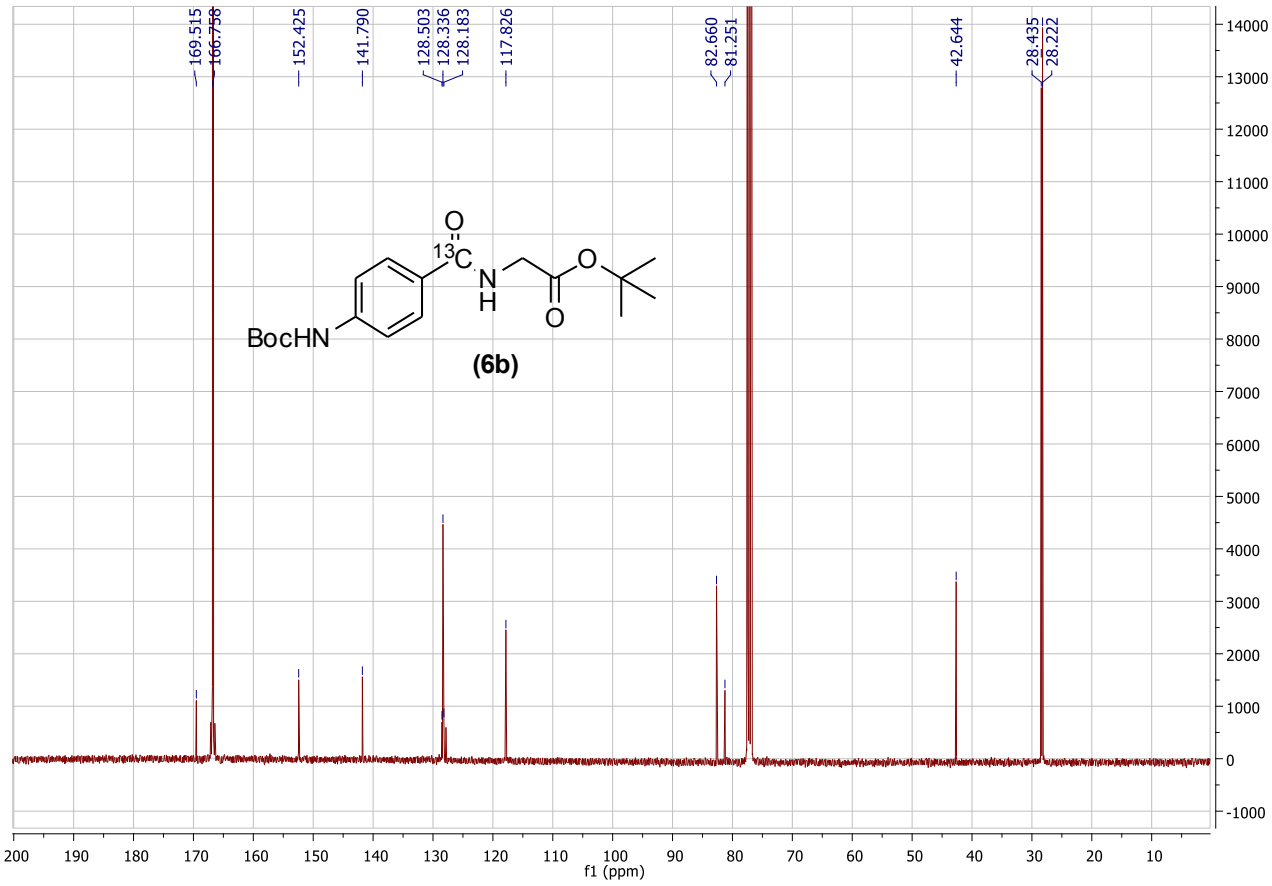
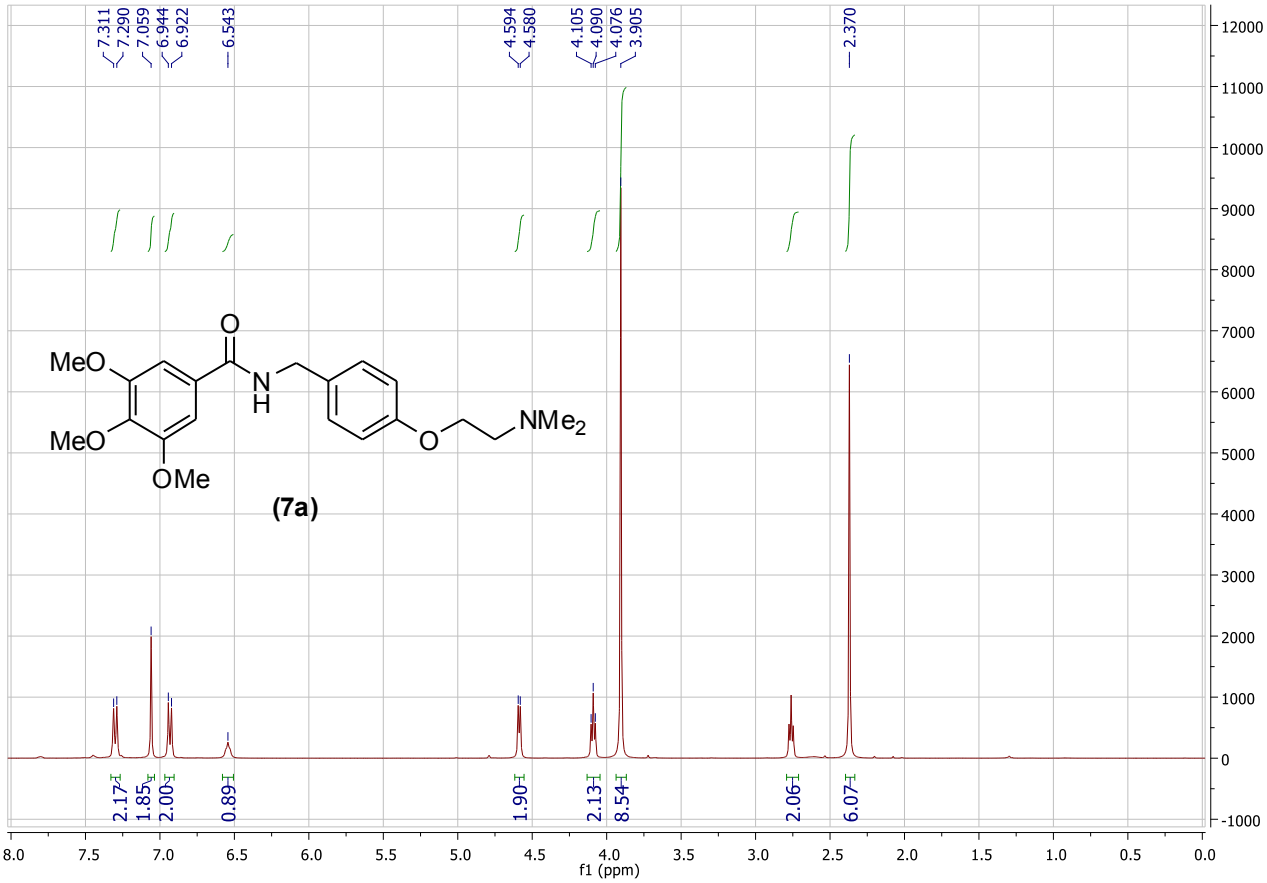
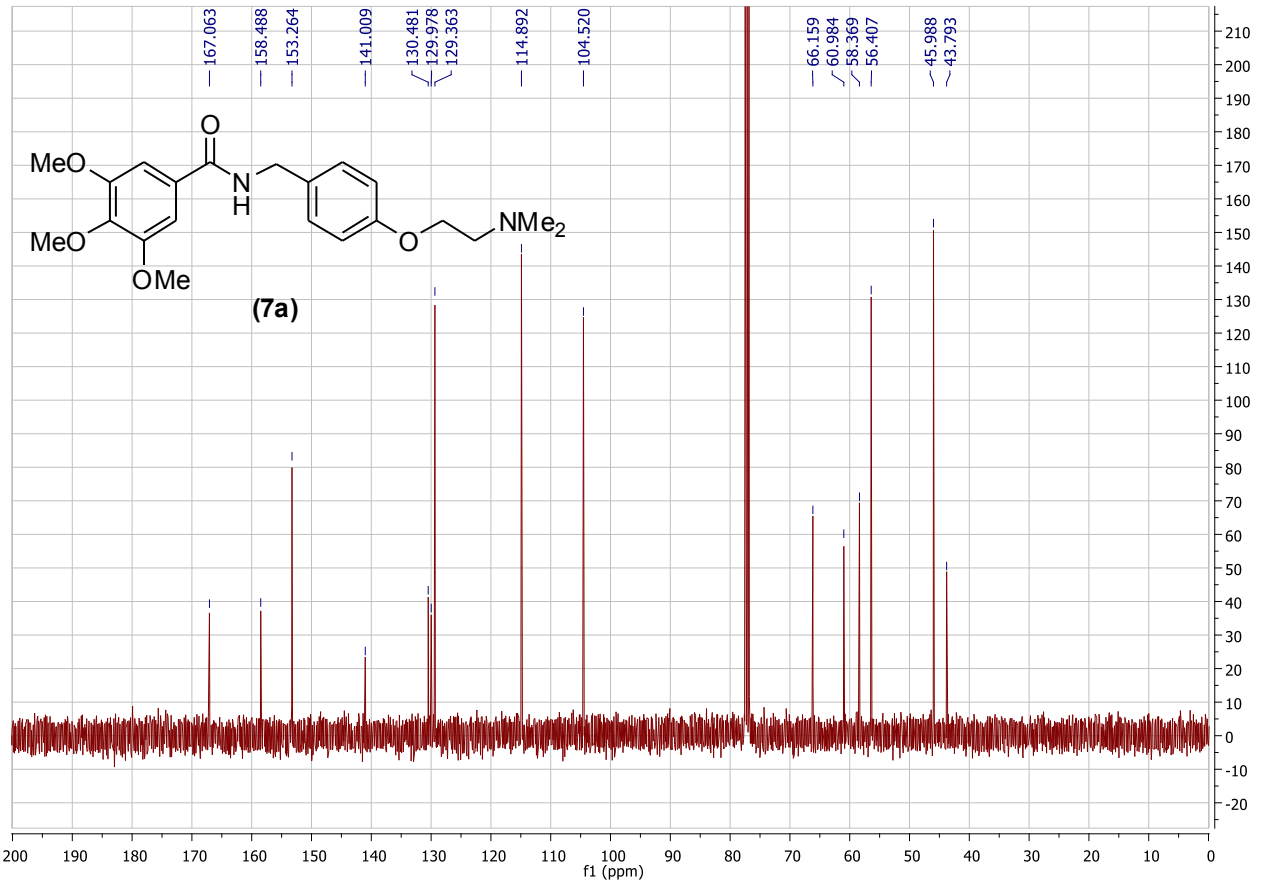
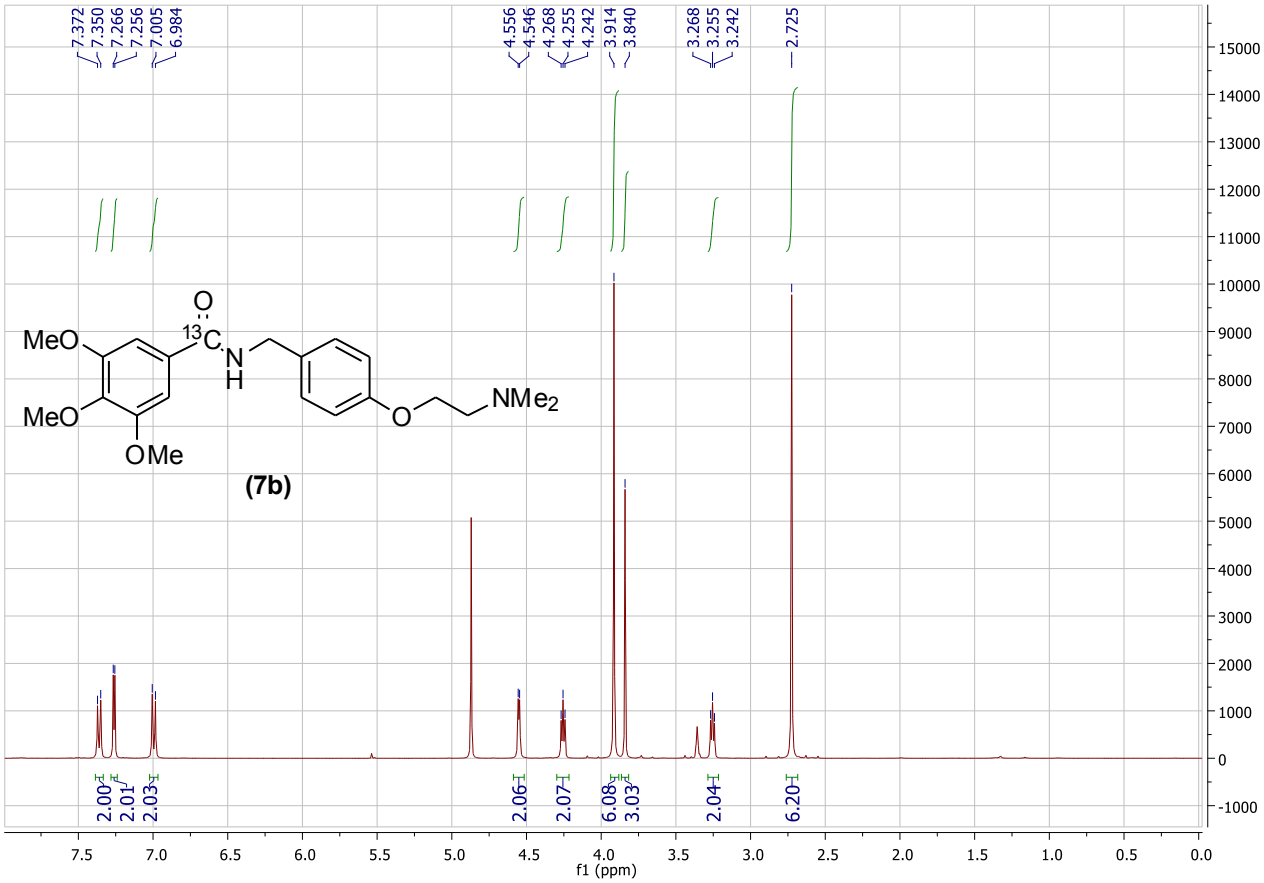
142.450
128.068
127.131
117.116
80.525
79.489
41.784
28.059
27.735
BocHN
(6a)
f1 (ppm)

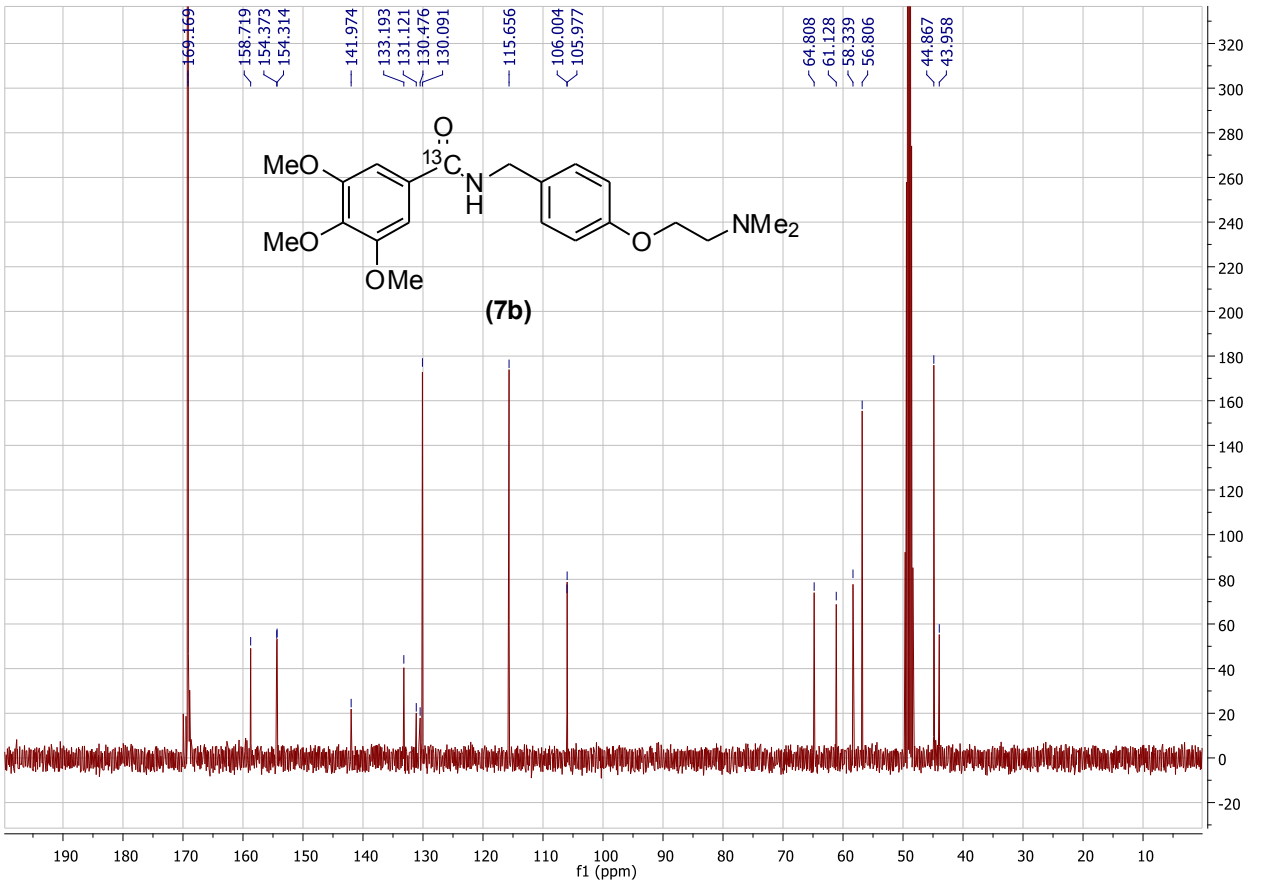

2.01
2.00
0.96
1.04
2.01
8.55
8.64
f1 (ppm)
BocHN
(6b)

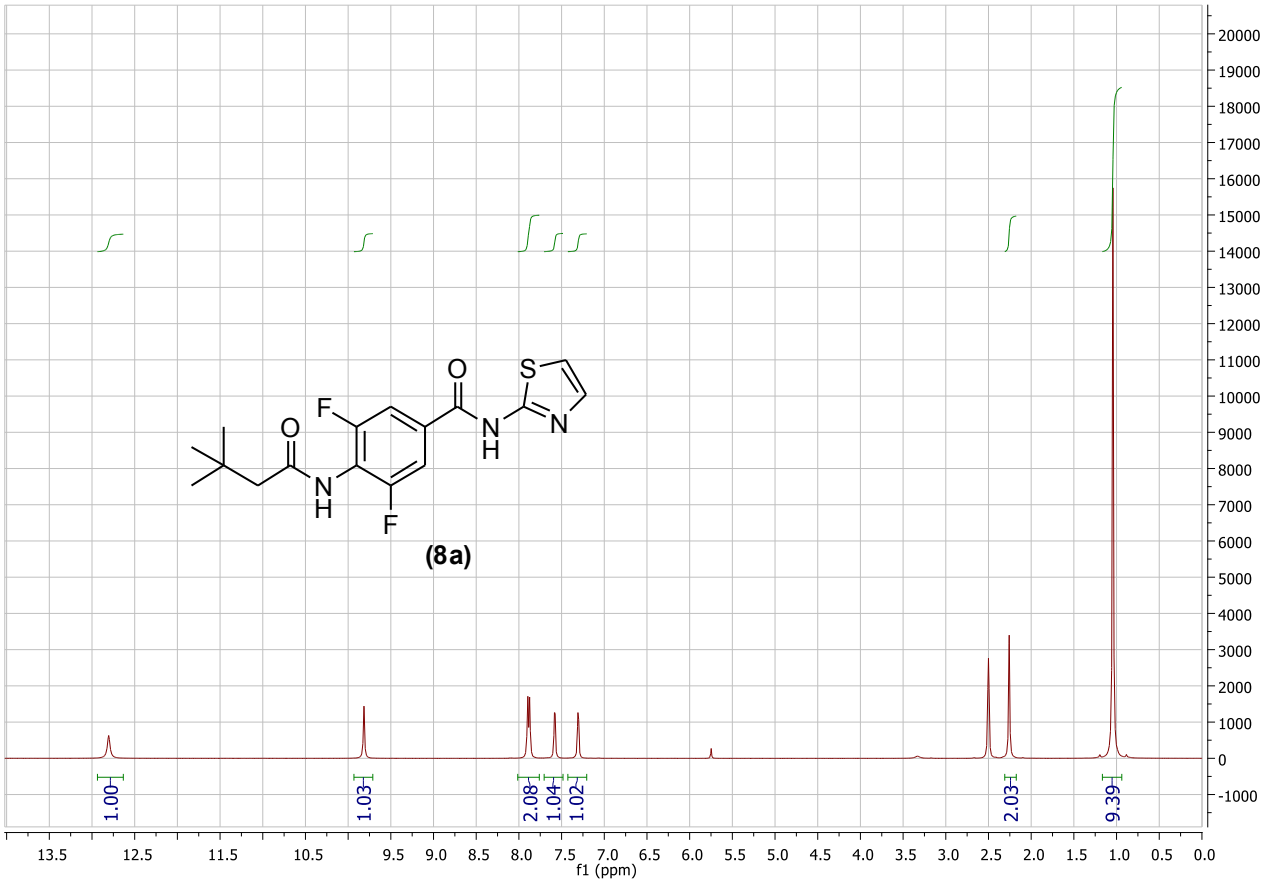

169.515
166.758
152.425
141.790
128.503
128.336
128.183
117.826
82.660
81.251
42.644
28.435
28.222
f1 (ppm)
BocHN
(6b)

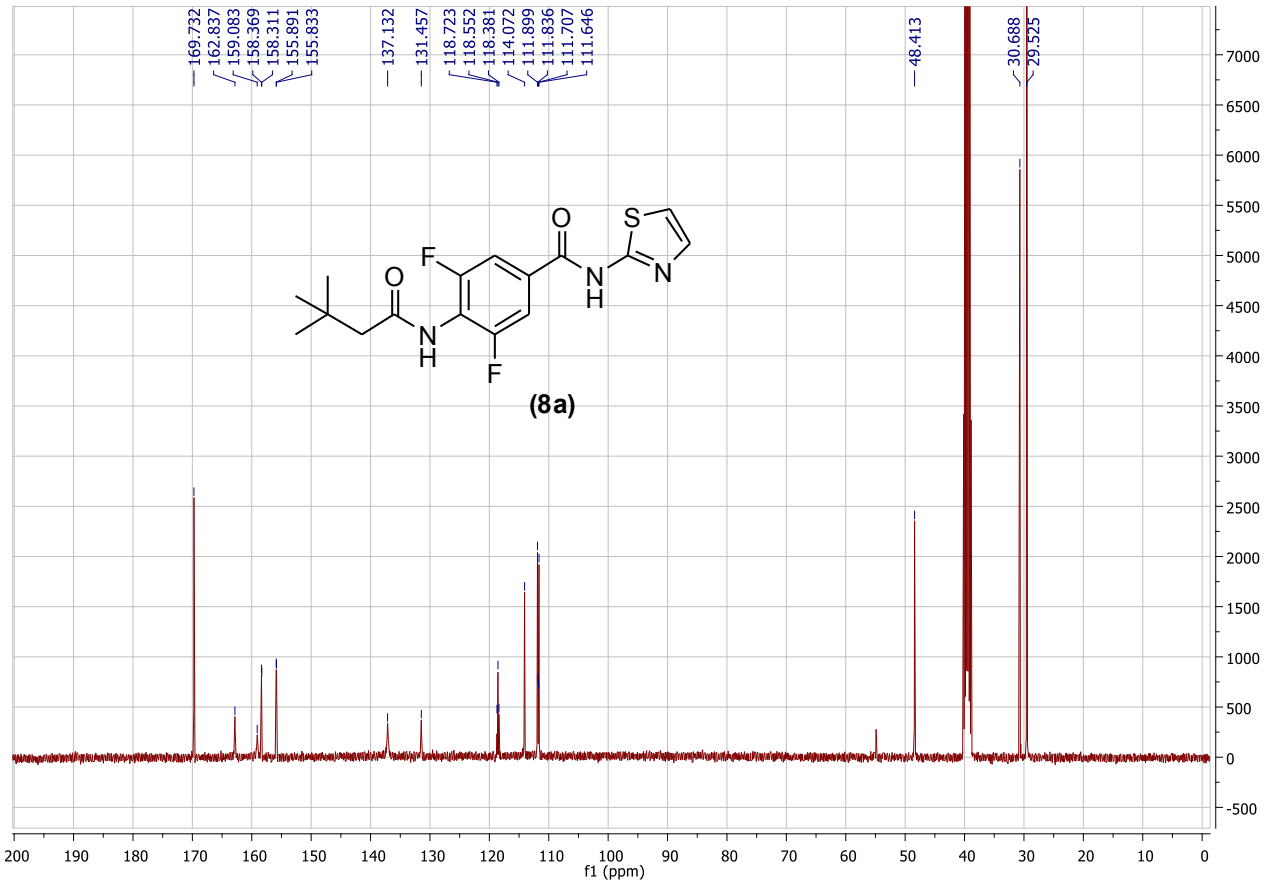

7.311
7.290
7.059
6.944
6.922
6.543
4.594
4.580
4.105
4.090
4.076
3.905
2.370
MeO
MeO
OMe
O
N
H
O
NMe2
(7a)
2.17
1.85
2.00
0.89
1.90
2.13
8.54
2.06
6.07
f1 (ppm)

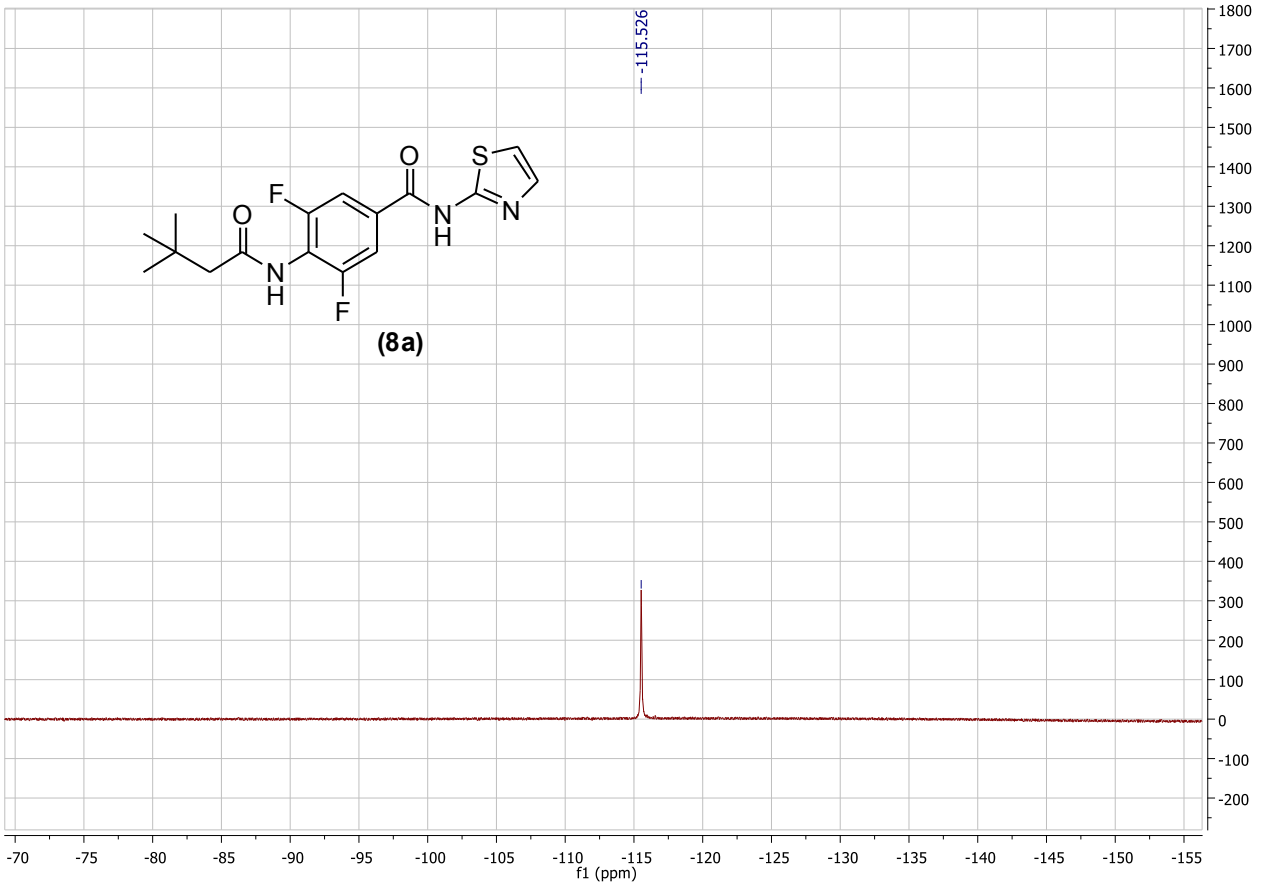

167.063
158.488
153.264
141.009
130.481
129.978
129.363
114.892
104.520
66.159
60.984
58.369
56.407
45.988
43.793
MeO
MeO
OMe
O
N
H
O
NMe2
(7a)
f1 (ppm)

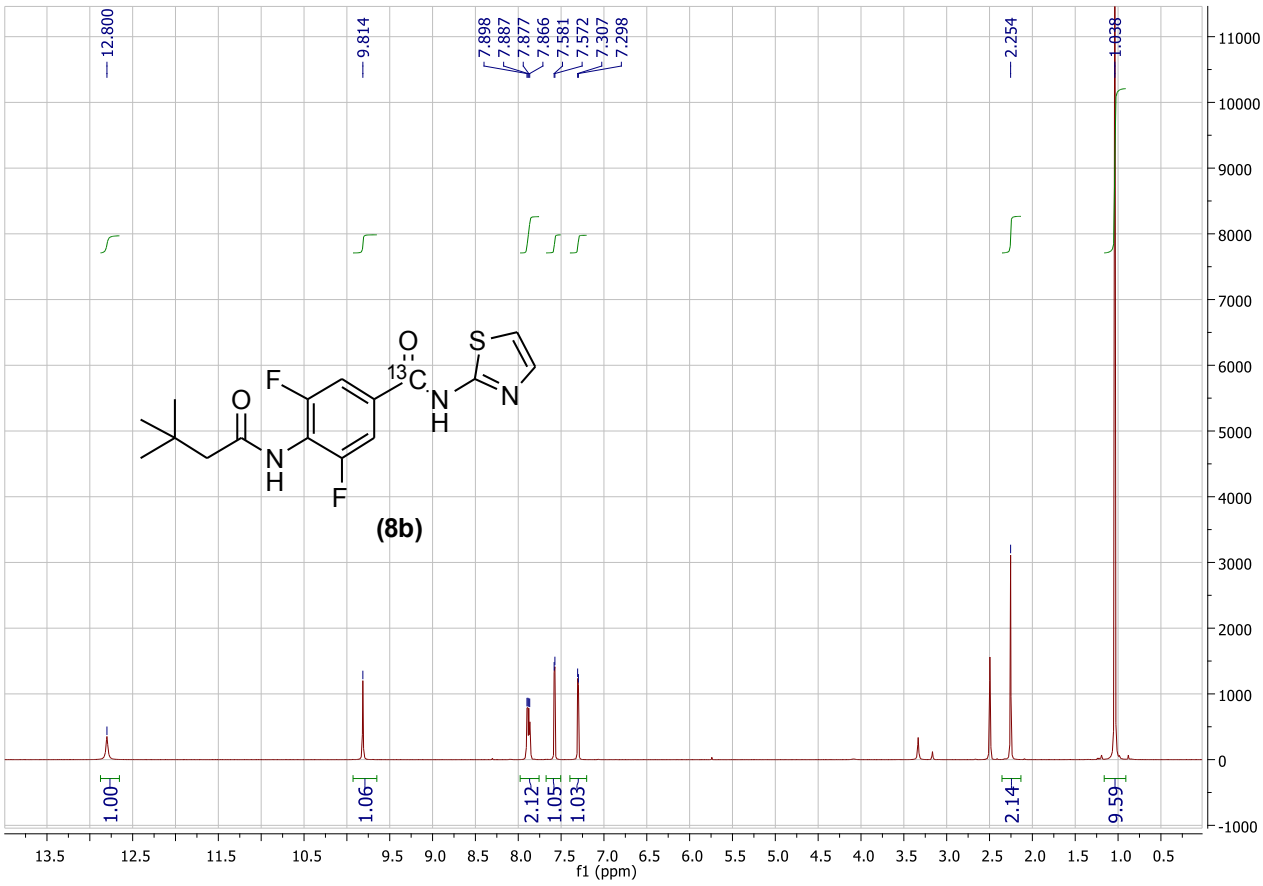

7.372
7.350
7.266
7.256
7.005
6.984
4.556
4.546
4.268
4.255
4.242
3.914
3.840
3.268
3.255
3.242
2.725
MeO
MeO
OMe
O
13C
N
H
O
NMe2
(7b)
2.00
2.01
2.03
2.06
2.07
6.08
3.03
2.04
6.20
f1 (ppm)

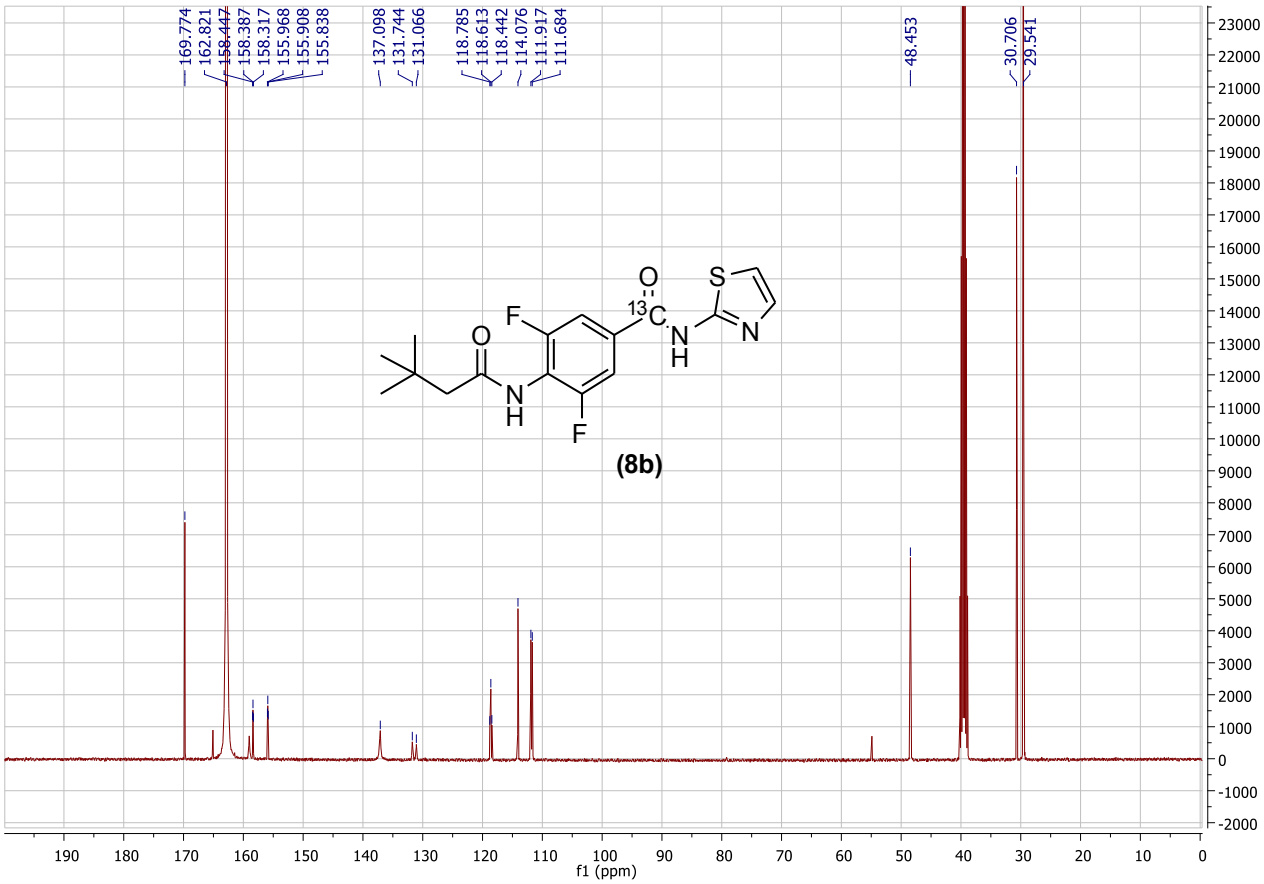

169.169
158.719
154.373
154.314
141.974
133.193
131.121
130.476
130.091
115.656
106.004
105.977
64.808
61.128
58.339
56.806
44.867
43.958
MeO
MeO
OMe
O
13C
N
H
O
NMe2
(7b)
f1 (ppm)

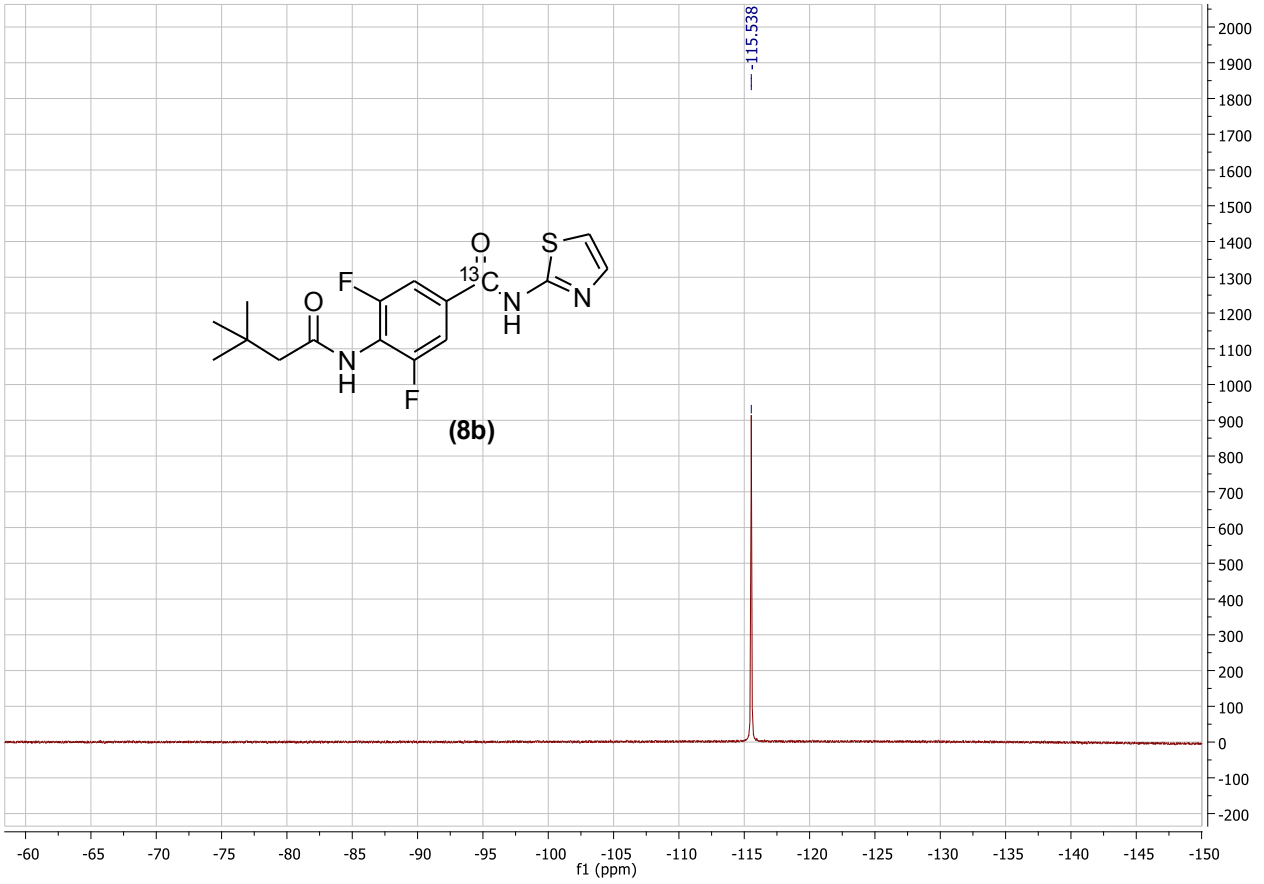

(8a)
1.00
1.03
2.08
1.04
1.02
2.03
9.39
f1 (ppm)


169.732
162.837
159.083
158.369
158.311
155.891
155.833
137.132
131.457
118.723
118.552
118.381
114.072
111.899
111.836
111.707
111.646
48.413
30.688
29.525
(8a)
f1 (ppm)


-115.526
(8a)
f1 (ppm)


12.800
9.814
7.898
7.887
7.877
7.866
7.581
7.572
7.307
7.298
2.254
1.038
1.00
1.06
2.12
1.05
1.03
2.14
9.59
(8b)
f1 (ppm)


169.774
162.821
158.447
158.387
158.317
155.968
155.908
155.838
137.098
131.744
131.066
118.785
118.613
118.442
114.076
111.917
111.684
48.453
30.706
29.541
(8b)
f1 (ppm)


115.538
(8b)
f1 (ppm)