Supporting Information

Palladium-Catalyzed Carbon Isotope Exchange on Aliphatic and Benzoic Acid Chlorides

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1. General experimental details

All reactions were assembled in screw-cap vials or a 2 chamber COware with precautions to avoid air or moisture. ^{13}COgen and COware were purchased from Sigma Aldrich. ^{14}COgen was obtained as a toluene solution from Moravek.[1] Pd_2dba_3, $PdCl_2(cod)$, $[(t\text{-}Bu)_3PH]BF_4$, John-Phos, $Pd[(t\text{-}Bu)_3P]_2$ and $Pd[(o\text{-}tol)_3P]_2$ were purchased from Sigma Aldrich. $P(o\text{-}tol)_3$ was purchased from Strem. Commercially available acid chloride substrates were purchased from commercial suppliers. Other acid chloride substrates where prepared from the corresponding acids using the methods described below. Pharmaceutic substrates were obtained from Merck Process Chemistry, or commercial suppliers and referenced appropriately. Atorvastatin acetonide was obtained from Toronto Research Chemicals. (*S*)-2-Methyl-3-phenylpropanoic acid was obtained from Enamine, Ltd. All other reagents, substrates and solvents were purchased from commercial suppliers and used as received. Solvents used are anhydrous and thoroughly degassed by sparging with nitrogen prior to use.

HPLC MS analyses were performed on an Agilent1100 HPLC-MSD instrument in API-ES positive or negative ionization mode using an Ascentis® Express C18 column (2.7 μm, 4.6 × 100 mm, 5% to 95% ACN/2mM aqueous ammonium formate buffer, 1 ml/min flow rate. Isotope incorporation was determined based on the mass distribution using Isopat. software.[2]

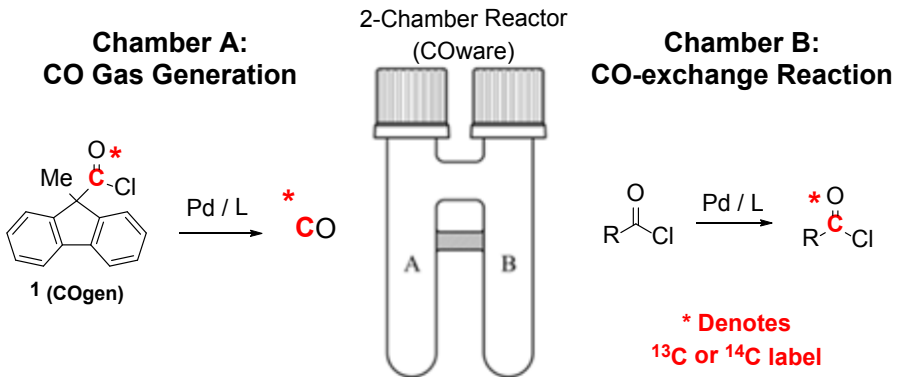
Carbon-14 reagents and compounds were handled by experimentalist uniquely trained in working with radioactive materials and operating in specialized laboratories. To minimize atmospheric release of [^{14}C]-Carbon monoxide, we suggest using the methods and apparatus described by Lindhardt and Skrydstrup.[3] C-14 radioactivity was measured in PerkinElmer Ultra Gold liquid scintillation cocktail with either a PerkinElmer 3110TR liquid scintillation analyzer. RadioHPLC and HPLC-UV comparison was conducted with an Agilent 1100 series HPLC connected in series to a PerkinElmer Radiomatic 625TR Flow Scintillation Analyzer.

Representative procedures for the conversion of acid to acid chloride:

Method A (Oxalyl chloride as chlorinating reagent). Synthesis of 3-(4-((4-chlorophenyl)sulfonyl)-4-(2,5-difluorophenyl)cyclohexyl)propanoyl chloride. To a 25 mL flask was added 3-(4-((4-chlorophenyl)sulfonyl)-4-(2,5 difluorophenyl)cyclohexyl)propanoic acid (100 mg, 0.226 mmol), dichloromethane (2.0 mL), oxalyl chloride (39.5 µl, 0.452 mmol), and DMF (0.874 µl, 0.011 mmol). The resulting solution was stirred at room temperature overnight. Conversion to the acid chloride was monitored by taking a small sample and quenching into an HPLC vial containing acetonitrile and $nBuNH_2$ and assaying as the nBuNH-amide derivative. The resulting acid chloride solution concentrated in vacuo and is used directly in the CO exchange reaction.

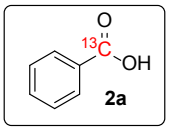
Method B (1-Chloro-N,N,2-trimethylprop-1-en-1-amine as chlorinating reagent).[4] Synthesis of (*S*)-2-methyl-3-phenylpropanoyl chloride. To a solution (*S*)-2-methyl-3-phenylpropanoic acid (50 mg, 0.305 mmol) in toluene (1.0 mL) was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (42.3 µl, 0.320 mmol) and stirred at room temperature for 1h. Conversion to the acid chloride was monitored by taking a small sample and quenching into an HPLC vial containing acetonitrile and $nBuNH_2$ and assaying as the nBuNH-amide derivative. The resulting acid chloride solution is used directly in the CO exchange reaction.

Representative procedure for CO exchange: Synthesis of ^{13}C-benzoic acid. A 2 chamber COware was brought into the glove box. To chamber B was added benzoyl chloride (41.0 µL, 0.356 mmol), Pd_2dba_3 (16.27 mg, 0.018 mmol), $P(o\text{-}tol)_3$ (21.63 mg, 0.071 mmol) and toluene (1 mL) then sealed. To chamber A was added 4-dimethylaminopyridine (109 mg, 0.889 mmol), $PdCl_2(cod)$ (10.14 mg, 0.036 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (20.63 mg, 0.071 mmol), ^{13}COgen (130 mg, 0.534 mmol; 1.5 equiv.). NMP (1 mL) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Chamber B was submerged into a 75 °C oil bath and stirred for 5 minutes (gas evolution observed). Both chambers were then submerged in the oil bath and stirred overnight at 75 °C. The reaction is then quenched with water (0.10 mL) and stirred for 2 h. Upon completion of hydrolysis of the acid chloride, the reaction was further diluted with water (2 mL) and extracted with EtOAc (5 mL). The organic layer was dried and concentrated and the resulting crude product was purified by column chromatography eluting with 0-10 % MeOH/DCM to give 37 mg of product (88 % yield).

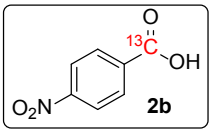


Scheme 1. Dual Closed Chamber Reactor

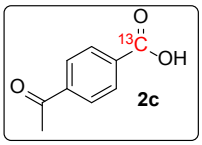
2. Experimental Procedures and Compound Characterization:



[^{13}C]Benzoic acid (2a): Benzoyl chloride was obtained from Sigma Aldrich and used without purification. CO exchange was performed as described in the experimental section. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 88 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.07 (m, 2H), 7.66 – 7.58 (m, 1H), 7.52 – 7.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.68, 134.03, 130.44, 129.57, 128.70. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 40.8 %.

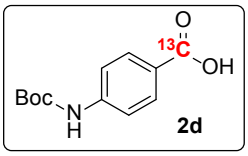


[^{13}C]4-Nitrobenzoic acid (2b): The acid chloride substrate was obtained from commercial source and used as is. CO exchange was performed as described in the experimental section. The product was crystallized from acetonitrile-toluene mixture, 84 % yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.66 (s, 1H), 8.33 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.25, 150.52, 136.84, 131.17, 124.21. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 25.5 %.

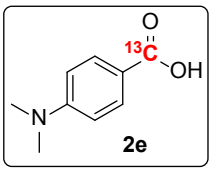


[^{13}C]4-Acetylbenzoic acid (2c): To a suspension of 4-acetylbenzoic acid (200 mg, 1.219 mmol) in 1,4-dioxane (2.0 mL) was added 1µL DMF and then oxalyl chloride (117 µl, 1.340 mmol). Assay by quenching a 20 µL sample into MeOH + Et_3N (100:1, 1mL). After 1 h, the solution was concentrated to an oil. All reagents and COware were transferred to the glove box. To COware chamber B was added the acid chloride dissolved in 1,4-dioxane (2.0 mL) and bis(tri-o-tolylphosphine)palladium(0) (0.087g, 0.122 mmol) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.445 g, 1.828 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.062 g, 0.122 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.714 g, 3.66 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with 0.1N NaOH (2 mL) and aged 15min. The aqueous layer was acidified with 0.1N

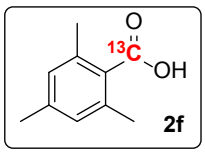
HCl (3 mL) and the product was extracted with EtOAc. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 180mg (90%) of a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.06 (s, 4H), 2.63 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.18, 167.09, 140.31, 135.23, 134.96, 134.67, 130.00, 128.79, 128.78, 128.76, 27.47. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 29.6 %



[^{13}C]4-((tert-Butoxycarbonyl)amino)benzoic acid (2d): The acid chloride substrate was prepared from commercially available 4-((tert-butoxycarbonyl)amino)benzoic acid in a similar fashion as described in the experimental section using 1-chloro-N,N,2-trimethylprop-1-en-1-amine as chlorinating reagent (Acid chloride formation Method B). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 5 % MeOH/DCM, 86 % yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 – 7.90 (m, 2H), 7.55 – 7.49 (m, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 169.87, 154.87, 145.50, 131.95, 125.54, 118.69, 81.48, 28.77. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 39.0 %

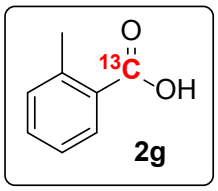


[^{13}C]4-(Dimethylamino)benzoic acid (2e): The acid chloride substrate was obtained from commercial source and used without purification. CO exchange was performed as described in the experimental section. The product was crystallized from acetonitrile-water mixture, 82% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.75 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 2.99 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.96, 153.53, 131.35, 117.42, 111.22, 40.10. Mass Spectral data was obtained under API-ES positive ionization mode and the ^{13}C isotope incorporation was determined to be 28.8%.

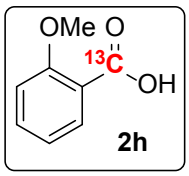


[^{13}C]2,4,6-Trimethylbenzoic acid: 2,4,6-Trimethylbenzoyl chloride was purchase from Sigma Aldrich. All reagents and COware were transferred into a glove box. To COware Chamber B was added 2,4,6-trimethylbenzoyl chloride (0.2 g, 1.095 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.078g, 0.110 mmol) dissolved in toluene (3.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.400 g, 1.64 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.084 g, 0.164 mmol), NMP (2.0 mL) and then N,N-dicyclohexylmethylamine (0.642 g, 3.29 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chambers A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with 0.1N NaOH (2 mL) and aged 15min. The aqueous layer was acidified with 0.1N HCl (3 mL) and the product was extracted with EtOAc. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 168mg (84%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 2H), 2.46 (s, 6H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.67, 140.07, 136.17, 129.52, 129.25, 128.95, 128.79, 21.14, 20.33. Mass Spectral data was obtained under

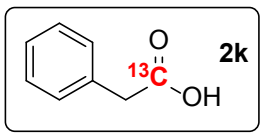
API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 13.8 %.



[^{13}C]2-Methylbenzoic acid (2g): 2-Methylbenzoyl chloride was purchase from Sigma Aldrich. All reagents and COware were transferred into the glove box. To COware Chamber B was added 2-methylbenzoyl chloride (0.200 g, 1.294mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.093g, 0.129 mmol) dissolved in toluene (3.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.473 g, 1.941 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.099 g, 0.194 mmol), NMP (2.0 mL) and then N,N-dicyclohexylmethylamine (0.758 g, 3.88 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with 0.1N NaOH (2 mL) and aged 15min. The aqueous layer was acidified with 0.1N HCl (3 mL) and the product was extracted with EtOAc. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 170 mg (85%) of a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 – 7.99 (m, 1H), 7.61 – 7.42 (m, 1H), 7.31 (m, 2H), 2.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.25, 141.36, 132.94, 131.93, 131.91, 131.90, 131.58, 128.58, 128.31, 128.01, 125.85, 22.10. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 28.3 %.

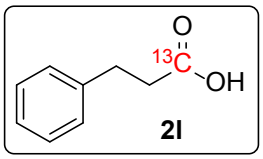


[^{13}C]2-Methoxybenzoic acid (2h): 2-Methoxybenzoyl chloride was purchase from Sigma Aldrich. All reagents and COware were transferred into the glove box. To COware Chamber B was added 2-methoxybenzoyl chloride (0.200 g, 1.172mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.084g, 0.117 mmol) dissolved in toluene (3.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.429 g, 1.76 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.090 g, 0.176 mmol), NMP (2.0 mL) and then N,N-dicyclohexylmethylamine (0.687 g, 3.52 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with 0.1N NaOH (2 mL) and aged 15min. The aqueous layer was acidified with 0.1N HCl (3 mL) and the product was extracted with EtOAc. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 164 mg (82%) of a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.80 (br s, 1H), 8.21 (dq, J = 7.7, 2.2 Hz, 1H), 7.60 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.31, 158.01, 135.05, 133.81, 122.22, 117.86, 117.60, 117.32, 111.62, 56.66. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 42.4 %.

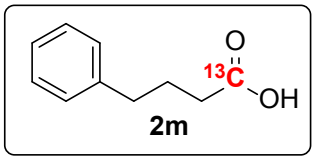


[^{13}C]2-Phenylacetic acid (2k): The acid chloride substrate was obtained from Sigma Aldrich and used as received. CO exchange was performed in a similar fashion as described in the experimental section. The product

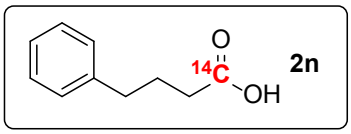
was purified by column chromatography eluting with 0-10 % MeOH/DCM, 83 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 3.68 (t, J = 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.03, 133.26, 129.38, 128.65, 127.35, 41.09. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 46.9 %.



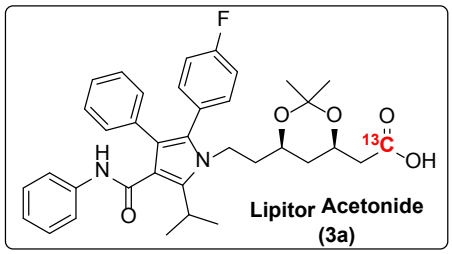
[^{13}C]3-Phenylpropanoic acid (2l): The acid chloride substrate was obtained from Sigma Aldrich and used as received. CO exchange was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 78 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.28 – 7.20 (m, 3H), 3.04 – 2.96 (m, 2H), 2.77 – 2.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.41, 140.36, 128.77, 128.46, 126.58, 35.82, 30.79. Mass Spectral data was obtained under API-ES negative ionization mode and the C-13 isotope incorporation was determined to be 51.4 %.



[^{13}C]4-Phenylbutanoic acid (2m): The acid chloride substrate was obtained from Sigma Aldrich and used as received. CO exchange was performed in a similar fashion as described in the experimental section. The product The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 89 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.23 – 7.14 (m, 3H), 2.68 (t, 2H), 2.43 – 2.33 (m, 2H), 2.04 – 1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.04, 141.19, 128.48, 128.43, 126.06, 35.01, 33.36, 26.21. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 47.5 %.

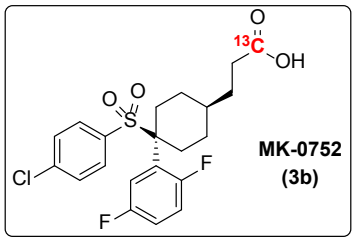


[^{14}C]4-Phenylbutanoic acid (2n): The acid chloride substrate was obtained from Sigma Aldrich and used as received. CO exchange was performed in a similar fashion as described in the experimental section (Note that ^{14}COgen (11.64 mCi) was used for the CO exchange reaction). The product was purified by column chromatography eluting with 0-10 % MeOH/DCM to give the C-14 labeled product in 99.5 % radiochemical purity; 16 % yield based on the ^{14}COgen starting material used. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{14}C isotope incorporation was determined to be 27 % or 16.8 mCi/mmol Specific Activity.

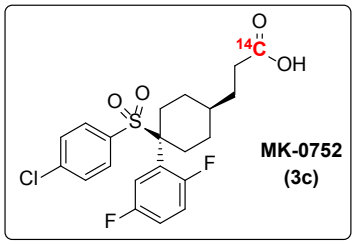


[^{13}C]Lipitor Acetonide (3a): The acid chloride substrate was prepared from commercially available atorvastatin acetonide in a similar fashion as described in the experimental section using 1-chloro-N,N,2-trimethylprop-1-en-1-amine as chlorinating reagent (Acid chloride formation Method B). The CO exchange reaction was performed in a similar fashion as described in the experimental section (Note: JohnPhos was used as a ligand instead of tri-o-tolylphospine for the CO exchange reaction). The product was purified by column chromatography eluting with 20 % - 100 % EtOAc/ hexanes, 20 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 9H), 7.09

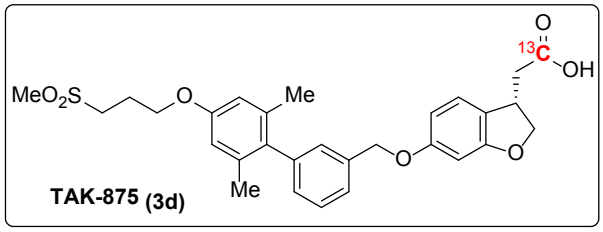
(d, J = 7.8 Hz, 2H), 7.06 – 6.95 (m, 3H), 6.89 (s, 1H), 4.26 – 4.18 (m, 1H), 4.15 – 4.05 (m, 1H), 3.92 – 3.81 (m, 1H), 3.76 – 3.68 (m, 1H), 3.59 (p, J = 7.1 Hz, 1H), 2.64 – 2.49 (m, 1H), 2.48 – 2.36 (m, 1H), 1.79 – 1.62 (m, 2H), 1.55 (d, J = 7.1 Hz, 6H), 1.45 – 1.25 (m, 8H), 1.09 (dd, J = 11.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.80, 164.93, 162.26 (d, J = 247.8 Hz), 141.42, 138.28, 134.53, 133.15 (d, J = 8.1 Hz), 130.47, 128.77, 128.68, 128.35, 128.24 (d, J = 3.4 Hz), 126.58, 123.61, 121.85, 119.65, 115.40 (d, J = 21.4 Hz), 115.37, 99.04, 66.36, 65.46, 40.84, 40.80, 37.84, 35.70, 29.85, 26.11, 21.79, 21.62, 19.66. Mass Spectral data was obtained under API-ES positive ionization mode and the ^{13}C isotope incorporation was determined to be 37.8 %.



[^{13}C]MK-0752 (3b): The acid chloride substrate was prepared from 3-(4-((4-chlorophenyl)sulfonyl)-4-(2,5-difluorophenyl)cyclohexyl)-propanoic acid as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 67 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 4H), 7.12 – 7.00 (m, 2H), 6.88 – 6.79 (m, 1H), 2.55 – 2.33 (m, 6H), 1.90 – 1.79 (m, 2H), 1.73 (dd, J = 14.0, 3.3 Hz, 2H), 1.65 – 1.57 (m, 1H), 1.56 – 1.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.54, 159.87 (dd, J = 41.5, 2.1 Hz), 157.42 (dd, J = 35.3, 2.1 Hz), 140.70, 133.58, 131.53, 128.71, 122.76 – 122.06 (m), 118.81 (dd, J = 25.5, 4.4 Hz), 118.11 (dd, J = 29.2, 8.5 Hz), 117.69 (dd, J = 23.8, 10.0 Hz), 70.78 (d, J = 4.0 Hz), 32.21, 31.50, 26.86, 25.99, 25.45 (d, J = 6.6 Hz). Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 52.5%.

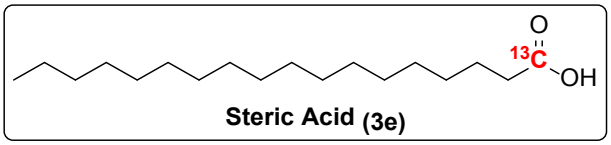


[^{14}C]MK-0752 (3c): The acid chloride substrate was prepared from the corresponding acid derivative as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{14}C isotope incorporation was determined to be 37.4%, specific activity 23.3 mCi/mmol in 20.0% radiochemical yield.



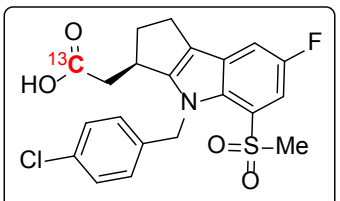
[^{13}C]TAK-875 (3d): TAK-875 was procured from BOC Sciences and used as received. To a solution of TAK-875 (100 mg, 0.191 mmol) in DCM (1 mL) was added DMF (1 µL) and oxalyl chloride (18.4 µL, 0.210 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The solution was concentrated to an oil. All reagents and COware were transferred into the glove box. To COware Chamber B was added TAK-875 acid chloride (0.191 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.014g, 0.019 mmol) in toluene (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-

9-carbonyl chloride (0.070 g, 0.287 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.015 g, 0.029 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.112 g, 0.573 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with H_2O (0.1 mL) and aged 2h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 45 mg (45%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.18 (s, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.67 (s, 2H), 6.52 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.15 (t, *J* = 5.8 Hz, 2H), 3.83 (ddd, *J* = 14.6, 9.0, 5.7 Hz, 1H), 3.35 – 3.24 (m, 2H), 2.99 (s, 3H), 2.83 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.37 (ddd, *J* = 13.1, 6.6, 3.9 Hz, 2H), 2.01 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.10, 159.96, 157.08, 140.92, 137.64, 137.14, 134.84, 129.13, 128.66, 128.55, 125.63, 125.60, 124.29, 121.31, 121.29, 121.27, 113.19, 107.39, 97.51, 77.52, 77.28, 77.03, 76.77, 70.30, 65.34, 51.90, 40.89, 39.52, 39.31, 39.08, 37.57, 22.74, 21.12. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 57.3 %.



Steric Acid (3e)

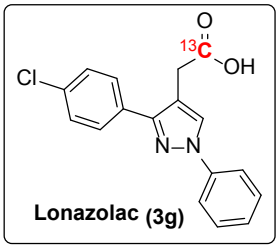
[^{13}C]Steric Acid (3e): The acid chloride substrate was obtained from commercial source. CO exchange was performed in a similar fashion as described in the experimental section. The crude product was crystallized from acetonitrile, then taken up in dioxane and 5N NaOH and heated to 60 °C. The hydrolyzed crude material was then concentrated down, diluted with toluene (3 mL) and acetic acid (100 µL) and the organic layer was washed with water (3x1.5 mL), The organic layer was dried over $MgSO_4$, filtered and concentrated down to give the desired product in 69 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 – 2.09 (m, 2H), 1.80 – 1.52 (m, 2H), 1.45 – 1.04 (m, 32H), 0.90 (t, *J* = 6.8 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.41, 34.11, 31.94, 29.70, 29.68, 29.65, 29.60, 29.44, 29.37, 29.25, 29.07, 24.67, 22.70, 14.11. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 45.1 %.



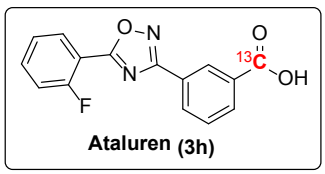
MK-0524 (3f)

[^{13}C]MK-0524 (3f): The acid chloride substrate was prepared from (*R*)-2-(4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid in a similar fashion as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.42 (dd, *J* = 7.9, 2.6 Hz, 1H), 7.27 – 7.20 (m, 2H), 6.76 – 6.63 (m, 2H), 6.15 (d, *J* = 17.9 Hz, 1H), 5.67 (d, *J* = 17.9 Hz, 1H), 3.54 – 3.42 (m, 1H), 3.02 – 2.90 (m, 1H), 2.89 – 2.77 (m, 2H), 2.72 (s, 3H), 2.68 – 2.57 (m, 1H), 2.53 – 2.40 (m, 1H), 2.31 (ddd, *J* = 12.6, 9.1, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.37, 155.89 (d, *J* = 240.1 Hz), 151.93, 137.41, 133.49, 132.61, 129.24, 129.05 (d, *J* = 8.7 Hz), 126.73, 125.97 (d, *J* = 7.5 Hz), 121.46 (d, *J* = 4.4 Hz), 112.75 (d, *J* = 28.9 Hz), 110.94 (d, *J* = 22.4 Hz),

50.19, 44.53, 38.60, 35.86, 35.55, 22.87. Mass Spectral data was obtained under API-ES positive ionization mode and the ^{13}C isotope incorporation was determined to be 32.0 %.

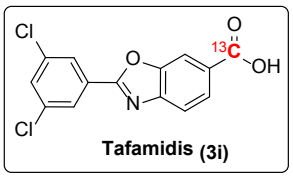


[^{13}C]2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)acetic acid (3g): Lonazolac (100 mg, 0.320 mmol, procured from Enamine) in DCM (1 mL) was added DMF (1 µL) and oxalyl chloride (31 µL, 0.352 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The solution was concentrated to an oil. All reagents and COware were transferred into the glove box. To COware Chamber B was added Lonazolac acid chloride (0.320 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.023g, 0.032 mmol) in toluene (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.117 g, 0.480 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.025 g, 0.048 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.188 g, 0.960 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with H_2O (0.1 mL) and aged 2h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 68 mg (68%) of a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 11.5 – 8.70 (br s, 1H), 8.04 (s, 1H), 7.77 – 7.71 (m, 2H), 7.67 – 7.59 (m, 2H), 7.51 – 7.40 (m, 4H), 7.34 – 7.27 (m, 1H), 4.05 – 3.19 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.40, 150.98, 139.78, 134.16, 131.29, 129.43, 128.85, 128.17, 126.67, 119.08, 112.34, 30.28, 30.06, 29.83. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 30.1 %.

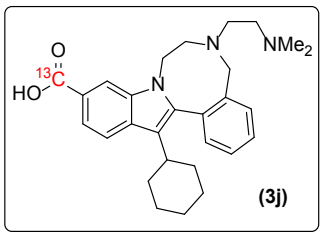


[^{13}C]3-(5-(2-Fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid (3h): Ataluran (100 mg, 0.352 mmol, eMolecules, Inc.) in 1,4-dioxane (1 mL) was added DMF (1 µL) and oxalyl chloride (34 µL, 0.387 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to an oil. All reagents and COware were transferred into a glove box. To COware Chamber B was added ataluren acid chloride (0.352 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.025g, 0.035 mmol) in 1,4-dioxane (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.129 g, 0.528 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.027 g, 0.053 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.206 g, 1.055 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with H_2O (0.1 mL) and aged 2h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 71 mg (71%) of a white solid. ^1H NMR (500

MHz, DMSO-d_6) δ 13.34 (br s, 1H), 8.65 – 8.58 (m, 1H), 8.30 (dd, J = 7.8, 1.3 Hz, 1H), 8.24 (td, J = 7.6, 1.6 Hz, 1H), 8.18 – 8.13 (m, 1H), 7.79 (tdd, J = 7.2, 5.2, 1.7 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.54 (dd, J = 10.7, 8.6 Hz, 1H), 7.51 – 7.45 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.18, 173.15, 167.86, 166.97, 161.47, 159.42, 136.27, 136.20, 132.56, 132.29, 131.99, 131.56, 131.39, 130.29, 128.25, 126.83, 125.96, 125.94, 117.85, 117.68, 112.19, 112.10. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 32.7 %.

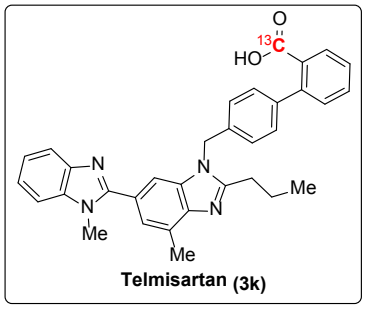


[^{13}C]2-(3,5-Dichlorophenyl)benzo[d]oxazole-6-carboxylic acid (3i): Tafamidis (100 mg, 0.324 mmol, eMolecules, Inc) in 1,4-dioxane (1 mL) was added DMF (1 µL) and oxalyl chloride (31 µL, 0.356 mmol). The white suspension was aged at 40 °C. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to a white solid. All reagents and COware were transferred into a glove box. To COware Chamber B was added tafamidis acid chloride (0.324 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.023g, 0.032 mmol) in NMP(1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.118 g, 0.485 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.025 g, 0.049 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.190 g, 0.971 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with H_2O (0.1 mL) and aged 2h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 61 mg (61%) of a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.24 (s, 1H), 8.14 – 8.06 (m, 2H), 8.01 (d, J = 6.9 Hz, 1H), 7.95 – 7.74 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.09, 162.45, 150.52, 145.12, 135.62, 132.12, 129.58, 129.47, 129.19, 128.90, 126.94, 126.32, 120.43, 112.63. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 17.2 %.



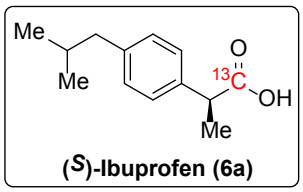
[^{13}C]14-cyclohexyl-6-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[1,8-a]indole-11-carboxylic acid (3j): The acid chloride substrate was prepared from 14-cyclohexyl-6-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydrobenzo[6,7][1,4]diazocino[1,8-a]indole-11-carboxylic acid in a similar fashion as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section (NMP was used instead of toluene as solvent for the CO exchange reaction). The product was purified by reverse phase column chromatography eluting with 20-40 % ACN/ Water (0.06 % TFA), 80 % yield. ^{1}H NMR (400 MHz, Acetic Acid-d_4) δ 8.29 (s, 1H), 8.01 – 7.88 (m, 2H), 7.85 (d, J = 7.7 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.57 – 7.52 (m, 1H), 4.71 (dd,

J = 16.7, 4.5 Hz, 1H), 4.51 (d, J = 13.8 Hz, 1H), 4.18 – 3.95 (m, 2H), 3.97 – 3.73 (m, 5H), 3.56 – 3.39 (m, 1H), 3.00 (s, 6H), 2.87 – 2.73 (m, 1H), 2.17 – 1.97 (m, 4H), 1.91 (s, 1H), 1.80 (d, J = 14.2 Hz, 2H), 1.69 (d, J = 11.9 Hz, 1H), 1.40 (q, J = 12.6, 11.0 Hz, 2H), 1.34 – 1.15 (m, 1H). ^{13}C NMR (101 MHz, Acetic Acid-d_4) δ 175.12, 140.46, 138.40, 135.96, 134.83, 134.44, 133.86, 133.82, 132.61, 132.58, 125.18, 123.66, 123.30, 122.62, 115.20, 59.31, 58.16, 54.44, 54.37, 45.80, 42.53, 39.48, 36.06, 35.94, 29.60, 28.66. Mass Spectral data was obtained under API-ES positive ionization mode and the ^{13}C isotope incorporation was determined to be 22.0 %.



Telmisartan (3k)

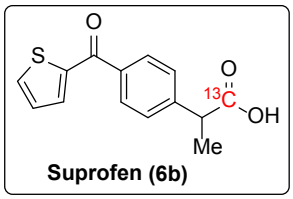
[^{13}C] 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid (3k): To Telmisartan (100 mg, 0.194 mmol, Sigma Aldrich) in DCM (1 mL) was added DMF (1 µL) and oxalyl chloride (19 µL, 0.214 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to an oil. All reagents and COware were transferred into a glove box. To COware Chamber B was added Telmisartan acid chloride (0.194 mmol) and bis(tri-o-tolylphosphine)palladium(0) (0.014g, 0.019 mmol) in NMP (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.071 g, 0.291 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.015 g, 0.029 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.114 g, 0.583 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both chamber A and B were submerged in a 75 °C oil bath and aged at 75 °C for 18h. The reaction mixture was quenched with H_2O (0.1 mL) and aged 2h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 67 mg (67%) of a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 – 7.70 (m, 2H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.54 (td, J = 7.6, 1.2 Hz, 1H), 7.49 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.32 – 7.22 (m, 4H), 7.19 (d, J = 8.2 Hz, 2H), 5.63 (s, 2H), 3.83 (s, 3H), 2.94 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 1.83 (h, J = 7.4 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.98, 156.72, 154.43, 143.13, 142.63, 140.96, 140.64, 136.99, 136.38, 135.15, 132.99, 132.72, 132.42, 131.32, 130.81, 129.58, 129.16, 128.71, 127.79, 126.87, 123.70, 123.52, 122.62, 122.37, 119.06, 110.91, 109.81, 46.62, 32.24, 29.21, 21.22, 16.92, 14.32. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 24.2 %.



(*S*)-Ibuprofen (6a)

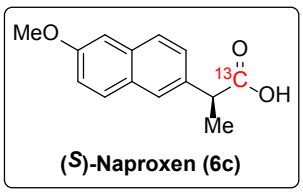
[^{13}C](S)-2-(4-isobutylphenyl)propanoic acid (6a): All reagents and COware were transferred into a glove box. To COware Chamber B was added (*S*)-ibuprofen chloride (100 mg, 0.402 mmol, Sigma Aldrich, 98% ee), bis(tri-*tert*-butylphosphine)palladium(0) (0.021g, 0.040 mmol) and toluene (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.147 g, 0.603 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.031 g, 0.060 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.258 mL, 1.206 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Chamber A was warmed to 75 °C and aged 15min, while chamber B was kept cool in an ice

bath. Both chambers were then allowed to age at ambient temperature for 18h. The reaction mixture was quenched with H_2O (0.2 mL) and aged 24h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 86 mg (86%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 3.82 – 3.61 (m, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.92 – 1.78 (m, 1H), 1.52 (dt, *J* = 7.2, 2.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.53, 140.84, 136.96, 129.37, 127.26, 45.11, 45.04, 44.91, 44.68, 30.15, 22.38, 22.38, 18.10. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 31.8 %. Enantiomeric excess (ee) was determined to be 98 % using a chiral SFC method (Column; AD-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: MeOH, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).



Suprofen (6b)

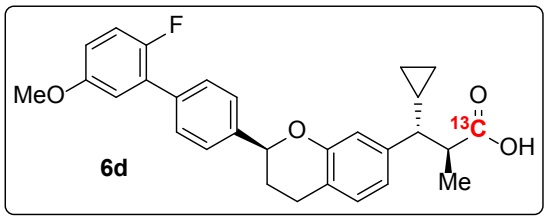
[^{13}C] 2-(4-(thiophene-2-carbonyl)phenyl)propanoic acid (6b): To Suprofen (200 mg, 0.768 mmol, eMolecules, Inc) in DCM (2 mL) was added DMF (2 µL) and oxalyl chloride (74 µL, 0.845 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to an oil. All reagents and COware were transferred into a glove box. To COware Chamber B was added Suprofen chloride (0.768 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.039g, 0.077 mmol) and toluene (2.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.281 g, 1.152 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.059 g, 0.115 mmol), NMP (2.0 mL) and then N,N-dicyclohexylmethylamine (0.450 mL, 2.305 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Chamber A was warmed to 75 °C and aged 15min, while chamber B was kept cool in an ice bath. Both chambers were then allowed to age at ambient temperature for 18h. The reaction mixture was quenched with H_2O (0.2 mL) and aged 24h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 162 mg (81%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.00 – 9.00 (br s, 1H), 7.91 – 7.82 (m, 2H), 7.74 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.67 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.18 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.87 (tq, *J* = 7.2, 4.0 Hz, 1H), 1.71 – 1.45 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.69, 179.69, 144.12, 143.46, 137.21, 134.83, 134.26, 129.61, 127.95, 127.76, 45.53, 45.32, 45.09, 18.04. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 58.9 %.



(*S*)-Naproxen (6c)

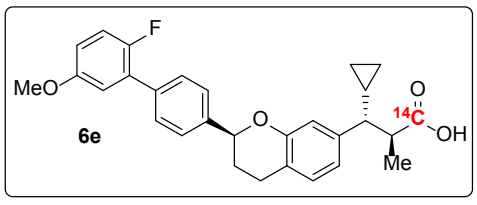
[^{13}C](*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid (6c): All reagents and COware were transferred into a glove box. To COware Chamber B was added (*S*)-Naproxen chloride (100 mg, 0.402 mmol, Sigma Aldrich, 98% ee), bis(tri-*tert*-butylphosphine)palladium(0) (0.021g, 0.040 mmol) and toluene (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.147 g, 0.603 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.031 g, 0.060 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.258 mL, 1.206 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Chamber A was warmed to 75 °C and aged 15min, while chamber B was kept cool in an

ice bath. Both chambers were then allowed to age at ambient temperature for 18h. The reaction mixture was quenched with H_2O (0.2 mL) and aged 24h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 86 mg (92%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 3H), 7.42 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 3.91 (s, 3H), 3.90 – 3.83 (m, 1H), 1.85 – 1.34 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.48, 157.70, 134.85, 133.81, 129.28, 128.88, 127.22, 126.17, 126.13, 119.02, 105.59, 55.29, 45.42, 45.22, 44.99, 18.12. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 37.2 %. Enantiomeric excess (ee) was determined to be 98 % using a chiral SFC method (Column; AD-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: MeOH, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).



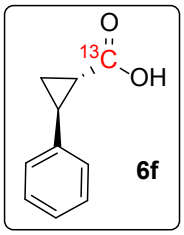
6d

[^{13}C] (2S,3R)-3-cyclopropyl-3-((S)-2-(2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)chroman-7-yl)-2-methylpropanoic acid (6d): The acid chloride substrate was prepared from (2S,3R)-3-cyclopropyl-3-((S)-2-(2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)chroman-7-yl)-2-methylpropanoic acid as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 0-40 % Ethyl acetate/Hexane, 39.0 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.02 (m, 2H), 6.98 (dd, *J* = 6.3, 3.2 Hz, 1H), 6.86 (dt, *J* = 8.9, 3.5 Hz, 1H), 6.79 (d, *J* = 1.5 Hz, 1H), 6.73 (dd, *J* = 7.8, 1.6 Hz, 1H), 5.12 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.04 (ddd, *J* = 17.0, 11.5, 6.0 Hz, 1H), 2.95 – 2.76 (m, 2H), 2.28 (ddd, *J* = 10.8, 5.8, 2.9 Hz, 1H), 2.17 (dtd, *J* = 13.6, 11.4, 5.3 Hz, 1H), 1.97 (t, *J* = 9.9 Hz, 1H), 1.14 (dtt, *J* = 10.2, 7.7, 5.4 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.73 – 0.60 (m, 1H), 0.40 (tt, *J* = 6.9, 4.0 Hz, 2H), 0.18 – 0.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.10, 171.62, 169.52, 155.78, 155.76, 155.05, 153.26, 141.70, 141.16, 135.43, 129.47, 129.29, 129.16, 129.13, 129.11, 126.17, 120.17, 120.14, 116.71, 116.52, 116.19, 115.50, 115.47, 113.90, 113.83, 55.83, 53.68, 47.48-47.02 (m), 29.90, 24.94, 15.92, 15.63, 7.05, 3.74. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 43.1%.

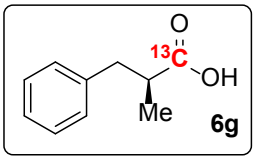


6e

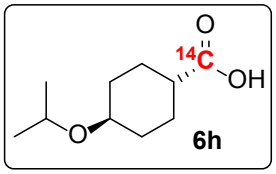
[^{14}C] (2S,3R)-3-cyclopropyl-3-((S)-2-(2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)chroman-7-yl)-2-methyl propanoic acid (6e): The acid chloride substrate was prepared from the corresponding acid derivative as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography (twice) eluting with 0-40 % Ethyl acetate/Hexane, 24.0 % yield. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{14}C isotope incorporation was determined to be 40.3%, specific activity 25.2 mCi/mmol.



[^{13}C](1S,2S)-2-Phenylcyclopropane-1-carboxylic acid (6f): To (1S,2S)-2-Phenylcyclopropane-1-carboxylic (200 mg, 1.23 mmol, Sigma Aldrich) in DCM (2 mL) was added DMF (2 µL) and oxalyl chloride (118 mL, 1.353 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to an oil. All reagents and COware were transferred into a glove box. To COware Chamber B was added the acid chloride (1.23 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.063g, 0.123 mmol) and toluene (2.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.450 g, 1.845 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.047 g, 0.092 mmol), NMP (2.0 mL) and then N,N-dicyclohexylmethylamine (0.791 mL, 3.69 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both Chamber A and B was warmed to 75 °C and aged 18h. After 18h, the COware was cooled to ambient temperature. The reaction mixture was quenched with H_2O (0.2 mL) and aged 24h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 154 mg (77%) of a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.5 – 8.0 (br S, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 2.62 (s, 1H), 1.92 (dt, *J* = 8.6, 4.6 Hz, 1H), 1.75 – 1.60 (m, 1H), 1.51 – 1.34 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.65, 139.48, 128.52, 126.69, 126.27, 27.09, 24.20, 23.92, 23.61, 17.49. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 46.8 %.

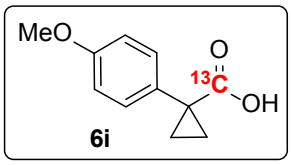


[^{13}C](S)-2-Methyl-3-phenylpropanoic acid (6g): The acid chloride substrate was prepared from commercially available (*S*)-2-methyl-3-phenylpropanoic acid as described in the experimental section using 1-chloro-N,N-2-trimethylprop-1-en-1-amine as chlorinating reagent (Acid chloride formation Method B). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 5-20% EtOAc/Hexanes, 54 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 – 7.18 (m, 3H), 3.11 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.74 – 2.66 (m, 1H), 1.28 – 1.08 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.23, 139.02, 128.99, 128.41, 126.42, 41.19, 39.30, 16.48. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 17.6 %. Enantiomeric excess (ee) was determined to be 98.8 % using a chiral SFC method (Column; OJ-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: EtOH with 25mM isobutylamine, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).



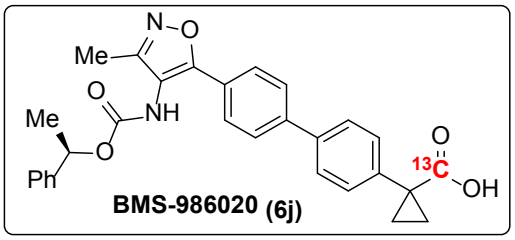
[^{14}C](1r,4r)-4-isopropoxycyclohexane-1-carboxylic acid (6h): The acid chloride substrate was prepared from (1r,4r)-4-isopropoxycyclohexane-1-carboxylic acid in a similar fashion as described in the experimental section using 1-chloro-N,N,2-trimethylprop-1-en-1-amine as chlorinating reagent (Acid chloride formation Method B). CO exchange was performed in a similar fashion as described in the experimental section (Note that ^{14}COgen (22.8 mCi) was used for the CO exchange reaction).

The ^{14}C labeled product was obtained in 96 % radiochemical purity; 23 % yield based on the $^{14}COgen$ starting material used. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{14}C isotope incorporation was determined to be 33 % or 20.7 mCi/mmol Specific Activity.



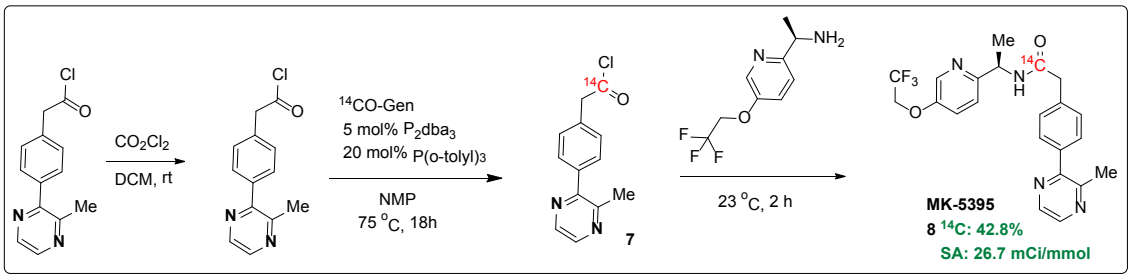
6i

[^{13}C] 1-(4-Methoxyphenyl)cyclopropane-1-carboxylic acid (6i): The acid chloride substrate was prepared from commercially available 1-(4-methoxyphenyl)cyclopropane-1-carboxylic acid as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 47 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.03 (m, 2H), 7.09 – 6.51 (m, 2H), 3.81 (s, 3H), 1.66 (m, 2H), 1.24 (m,2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.81, 158.81, 131.55, 130.90, 113.64, 55.25, 28.56 – 27.35 (m), 17.46. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 50.3%.

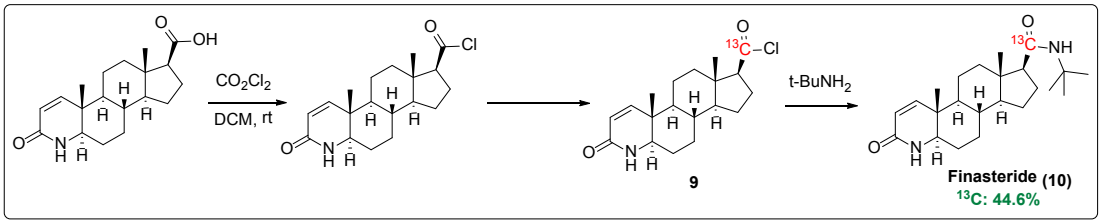


BMS-986020 (6j)

[^{13}C](R)-1-(4'-(3-methyl-4-(((1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid (6j): To BMS-986020 (100 mg, 0.207 mmol, eMolecules, Inc) in DCM (1 mL) was added DMF (2 µL) and oxalyl chloride (0.020 mL, 1.34 mmol). The solution was aged at ambient temperature. The reaction was monitored by quenching 5 µL of the reaction solution into 100:1 MeOH/Et_3N (1 mL) and assaying by HPLC. After 1h, assay shows complete conversion to Me-ester. The acid chloride solution was concentrated to an oil. All reagents and COware were transferred into a glove box. To COware Chamber B was added the acid chloride (0.207 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.0106g, 0.021 mmol) and toluene (1.0 mL) and the chamber was sealed. To chamber A was added [^{13}C]-9-methylfluorene-9-carbonyl chloride (0.076 g, 0.311 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (0.008 g, 0.016 mmol), NMP (1.0 mL) and then N,N-dicyclohexylmethylamine (0.133 mL, 0.621 mmol) was added last and the chamber was quickly sealed. The COware apparatus was then taken out of the glove box. Both Chamber A and B was warmed to 75 °C and aged. After 18h, the COware was cooled to ambient temperature. The reaction mixture was quenched with H_2O (0.2 mL) and aged 24h. Column chromatography (1-10% MeOH in DCM) was used to purify. Isolated 30 mg (30%) of a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 12.39 (br s, 1H), 9.32 (s, 0.8H), 8.89 (s, 0.2H), 7.80 (br d, J = 7.5 Hz, 4H), 7.66 (d, J = 8.1 Hz, 2H), 7.52 – 6.98 (m, 5H), 5.98 – 5.51 (m, 1H), 2.14 (s, 3H), 1.56 (d, J = 5.1 Hz, 3H), 1.49 (s, 3H), 1.40 – 1.23 (m, 1H), 1.20 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.65, 161.27, 160.11, 154.84, 142.68, 141.92, 140.48, 137.91, 131.42, 128.91, 128.13, 127.56, 126.79, 126.67, 126.07, 125.82, 114.25, 73.29, 28.99, 28.72, 28.42, 22.90, 16.27, 9.64. Mass Spectral data was obtained under API-ES negative ionization mode and the ^{13}C isotope incorporation was determined to be 44.5 %.

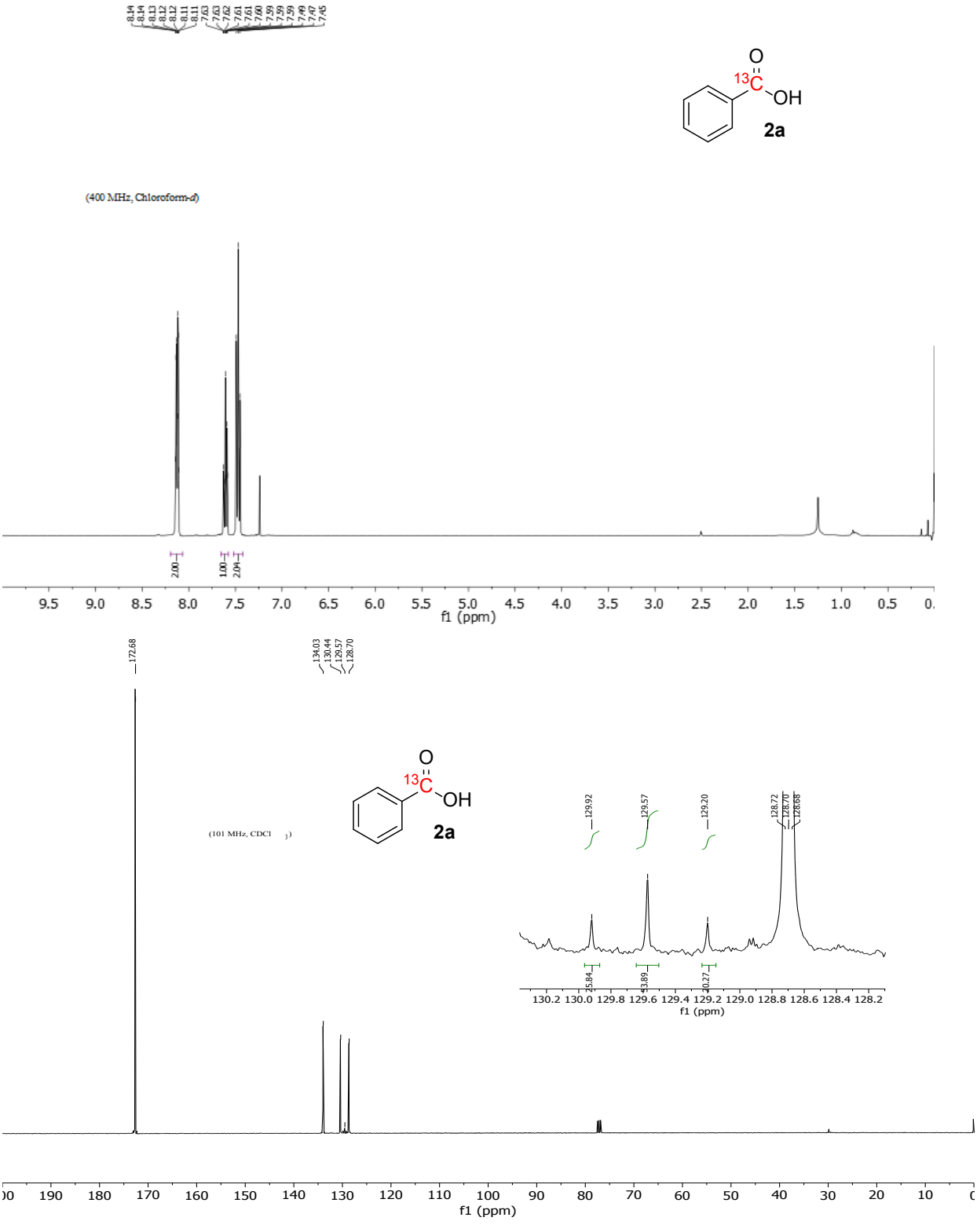


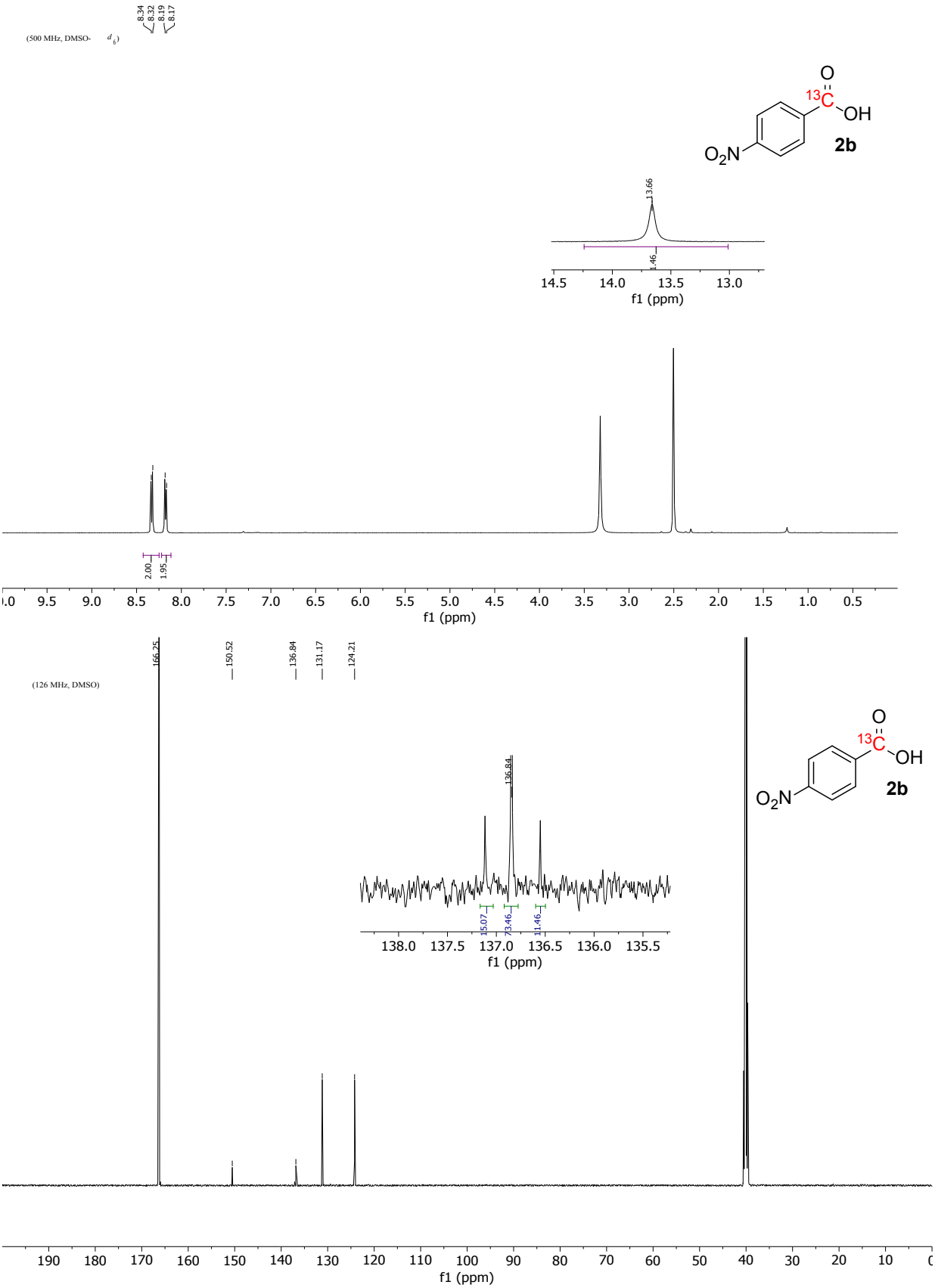
[^{14}C]MK-5395: The acid chloride substrate was prepared from 2-(4-(3-methylpyrazin-2-yl)phenyl)acetic acid as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section. Upon completion of the CO exchange reaction, a stoichiometric amount of (R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethan-1-amine was then added to the reaction mixture, leading to the formation of amide product MK-5395. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 41 % yield. Mass Spectral data was obtained under API-ES positive ionization mode and the ^{14}C isotope incorporation was determined to be 42.8%, specific activity 26.7 mCi/mmol.



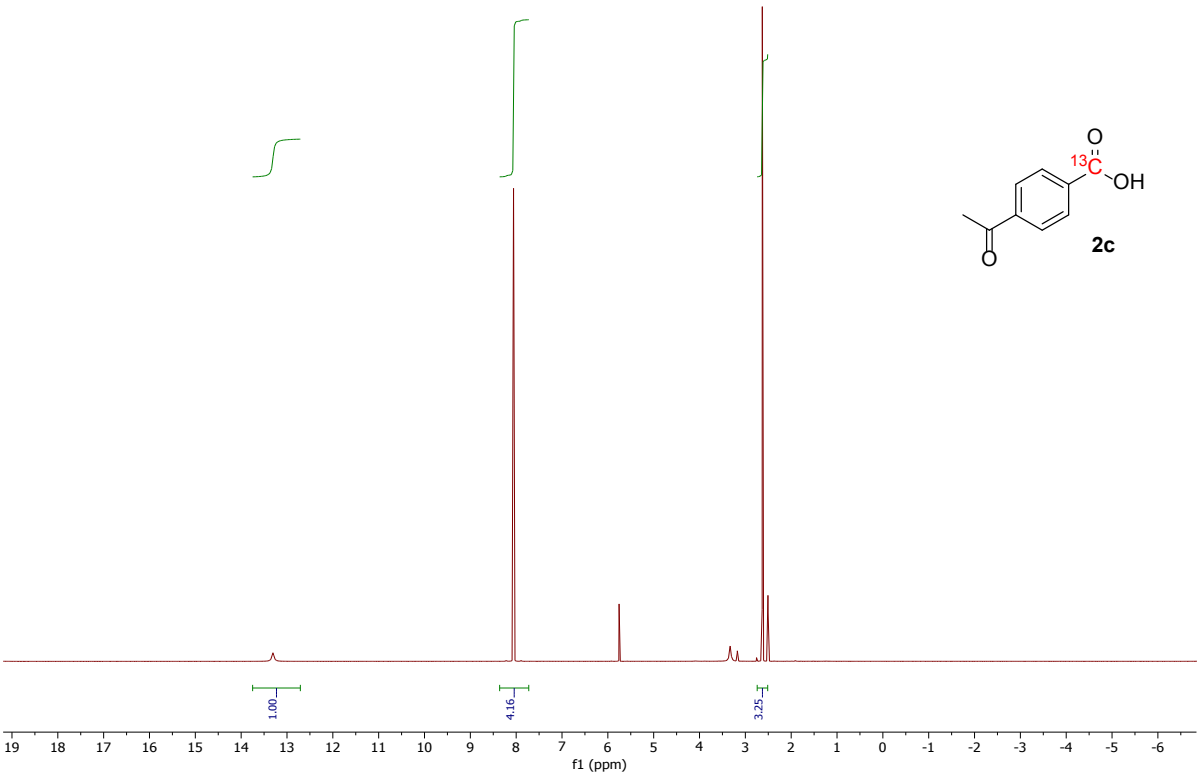
[^{13}C]Finasteride (10): The acid chloride substrate was prepared from (4aR,4bS,6aS,7S,9aS,9bS,11aR)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-indeno[5,4-f]quinoline-7-carboxylic acid as described in the experimental section using oxalyl chloride as chlorinating reagent (Acid chloride formation Method A). The CO exchange reaction was performed in a similar fashion as described in the experimental section except the acid chloride was first dissolved in NMP and diluted with an equal volume of toluene. Upon completion of the CO exchange reaction, a stoichiometric amount of tert-butylamine was then added to the reaction mixture, leading to the formation of amide product finasteride. The product was purified by column chromatography eluting with 0-10 % MeOH/DCM, 41 % yield. The product was further purified by C18 column chromatography eluting with 0-70% acetonitrile containing 0.1% formic acid/water containing 0.1% formic acid. 32.0 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) 6.80 (d, J = 10.0 Hz, 1H), 5.83 (dd, J = 9.9, 2.3 Hz, 1H), 5.43 (s, 1H), 5.09 (s, 1H), 3.42 – 3.25 (m, 1H), 2.28 – 2.11 (m, 1H), 2.09 – 1.96 (m, 2H), 1.83 – 1.68 (m, 4H), 1.64 –1.59 (m, 2H), 1.54 – 1.42 (m, 2H), 1.37 (s, 9H, ^{t}Bu), 1.33 – 1.23 (m, 2H), 1.20 – 1.02 (m, 3H), 1.00 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.58, 166.38, 150.81, 123.05, 59.70, 57.50, 55.67, 51.12, 47.62, 43.94, 39.51, 38.47, 35.35, 29.45, 29.06, 26.06, 24.29, 23.28, 21.28, 13.29, 12.02. Mass Spectral data was obtained under API-ES negative ionization mode and the C-13 isotope incorporation was determined to be 44.6%.

3. NMR Spectra:

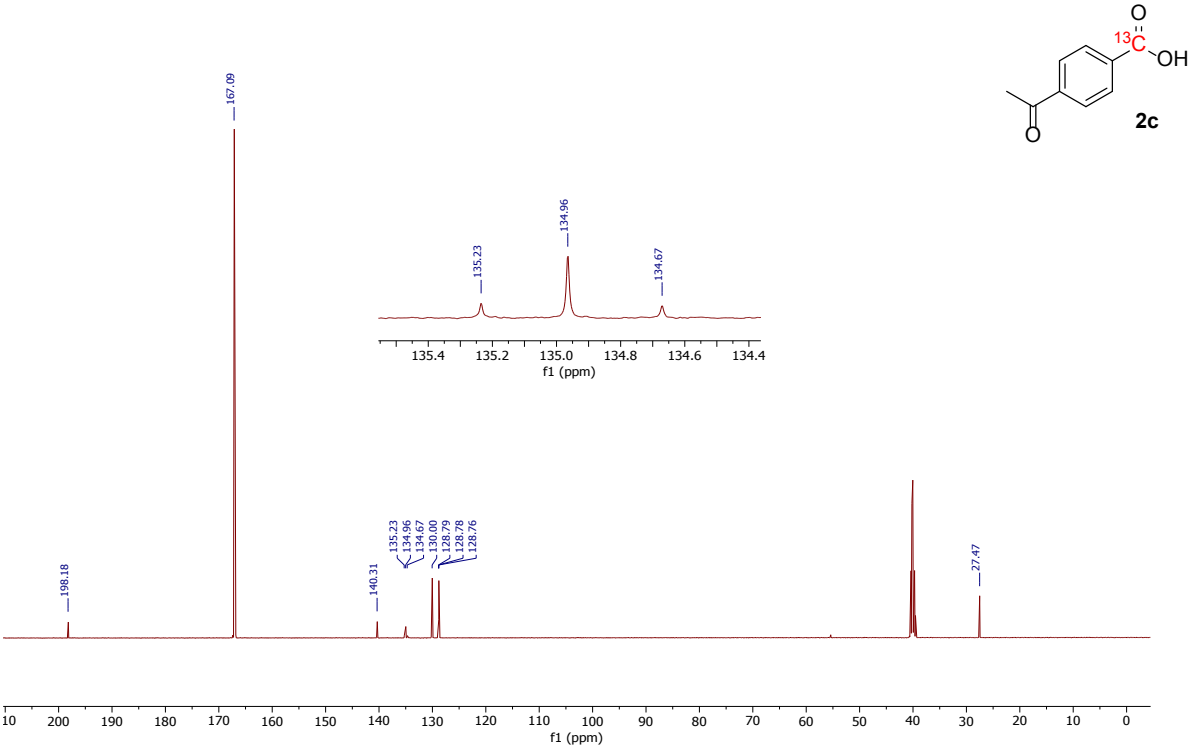


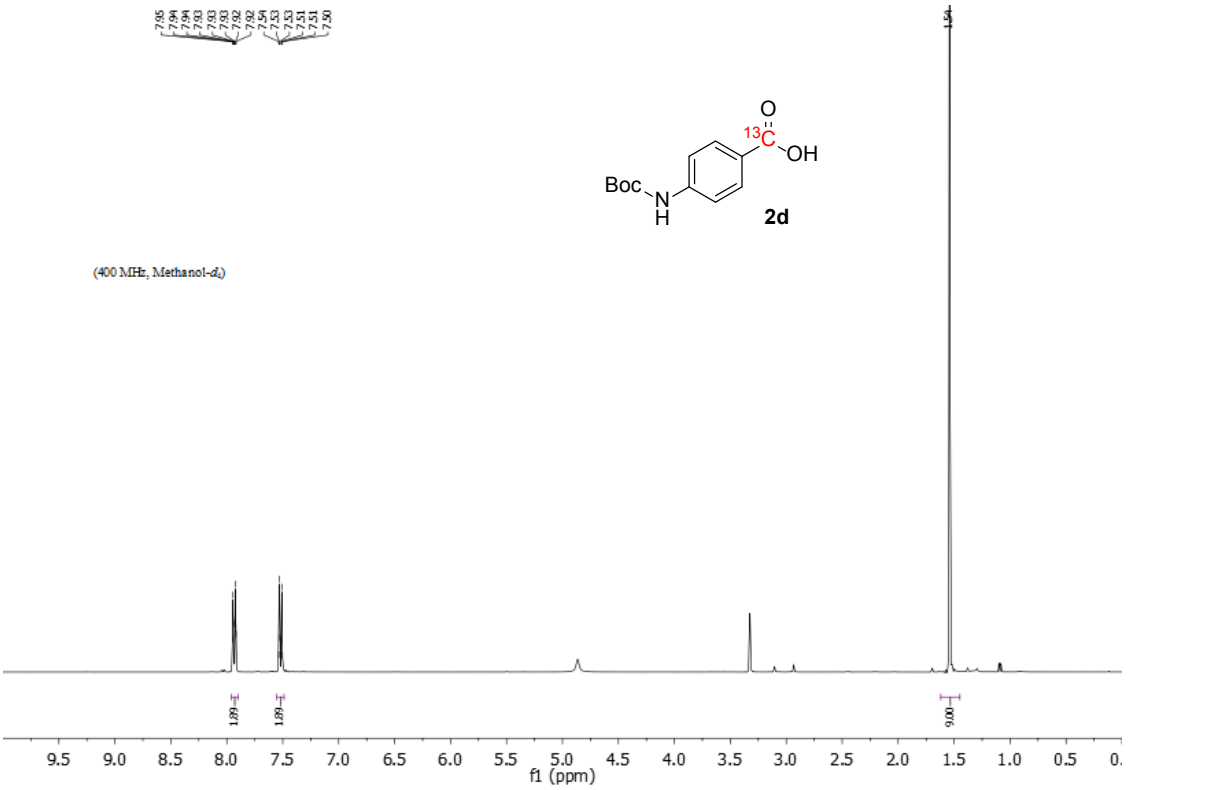

(500 MHz, DMSO- d_6)
8.34
8.32
8.19
8.17
O
13C
OH
O2N
2b
13.66
1.46
14.5
14.0
13.5
13.0
f1 (ppm)
2.00
1.95
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
(126 MHz, DMSO)
166.25
150.52
136.84
131.17
124.21
136.84
15.07
73.46
11.46
138.0
137.5
137.0
136.5
136.0
135.5
f1 (ppm)
O
13C
OH
O2N
2b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

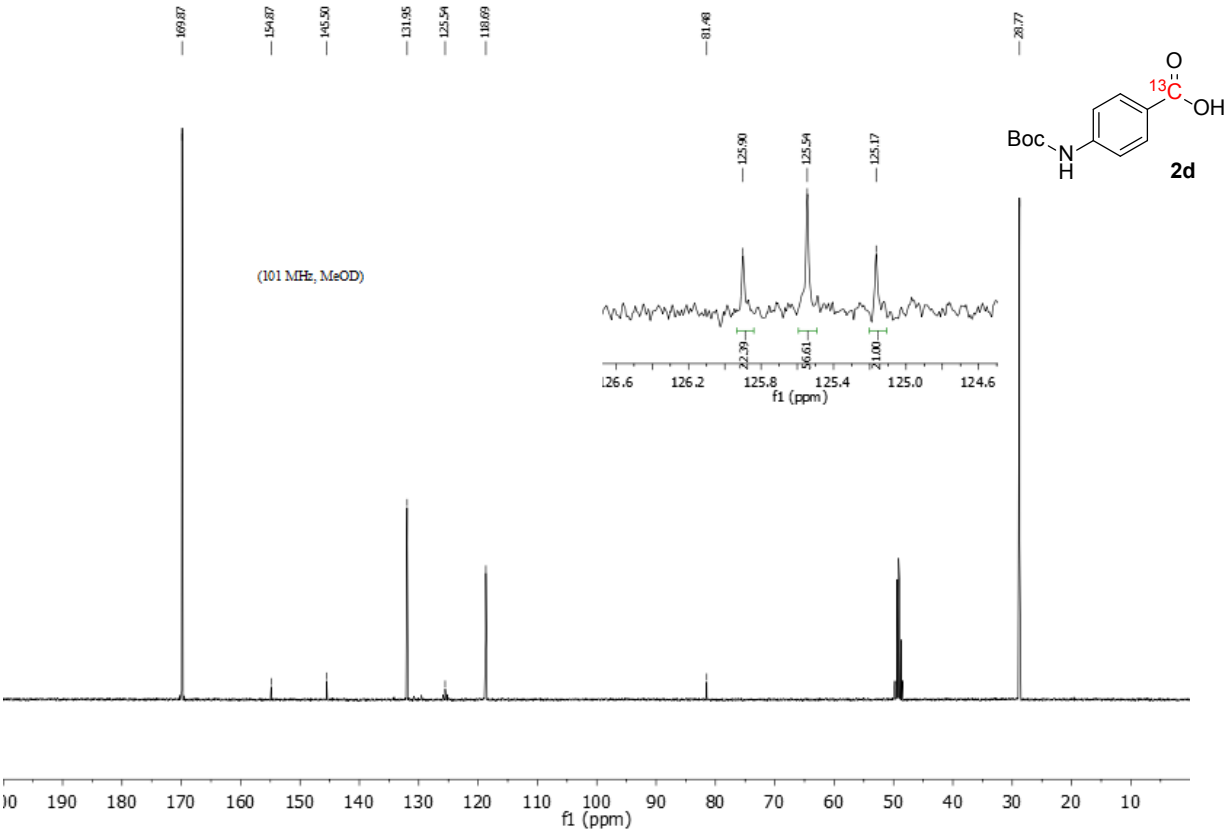
(500 mHz, DMSO-d6)

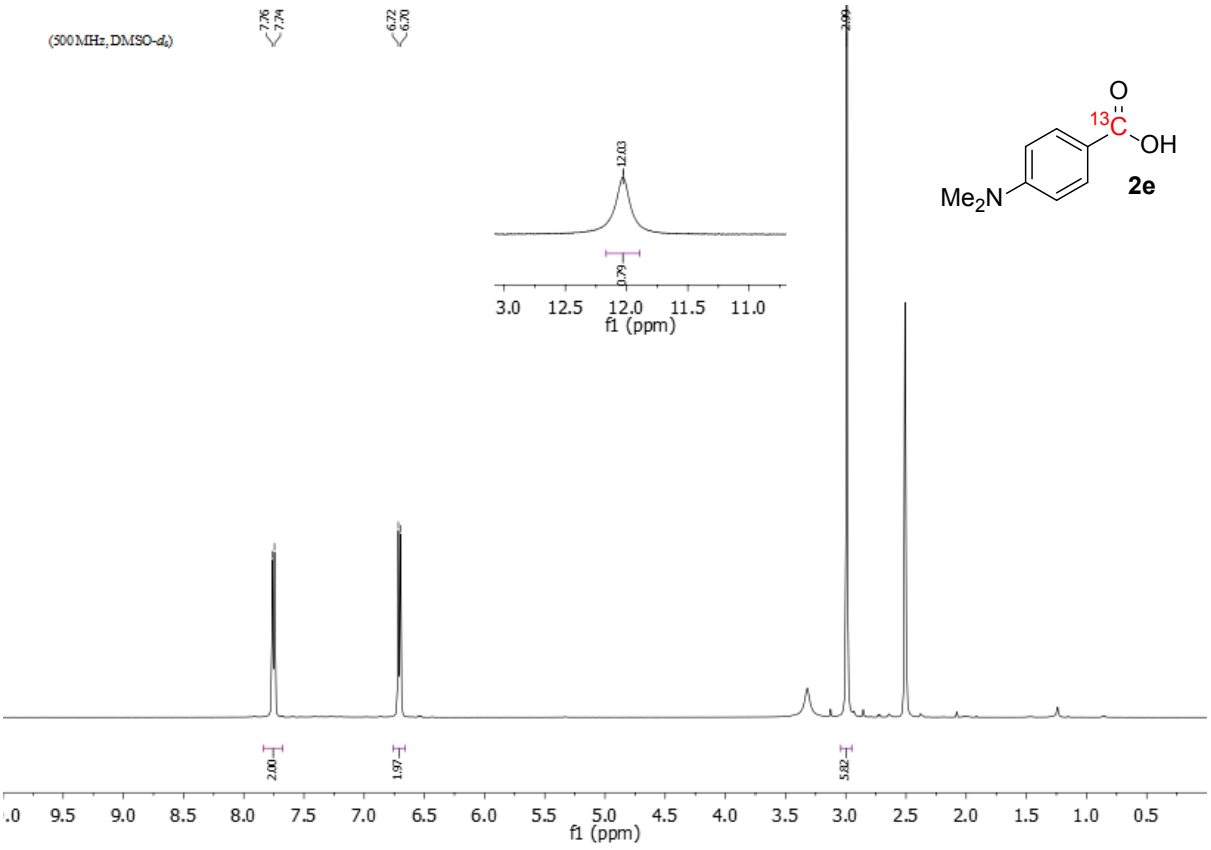


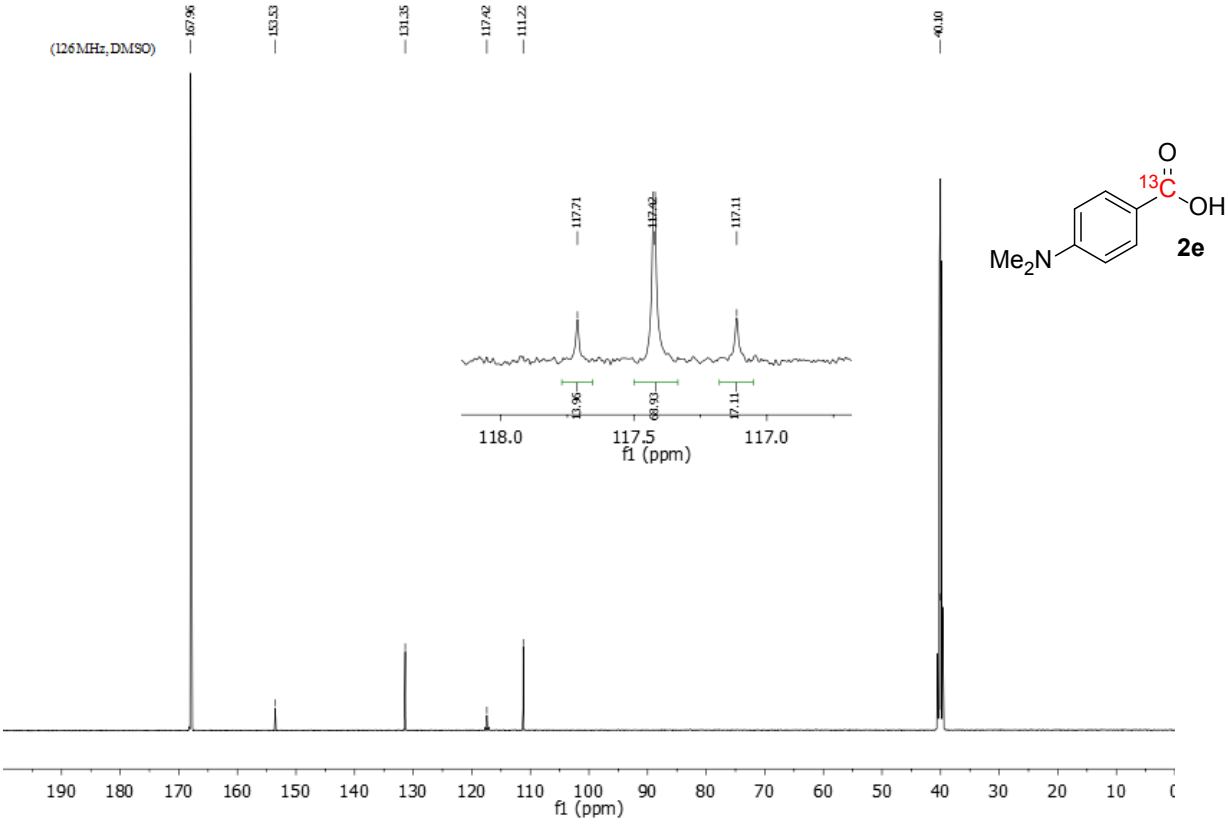
(125mHz, DMSO-d6)



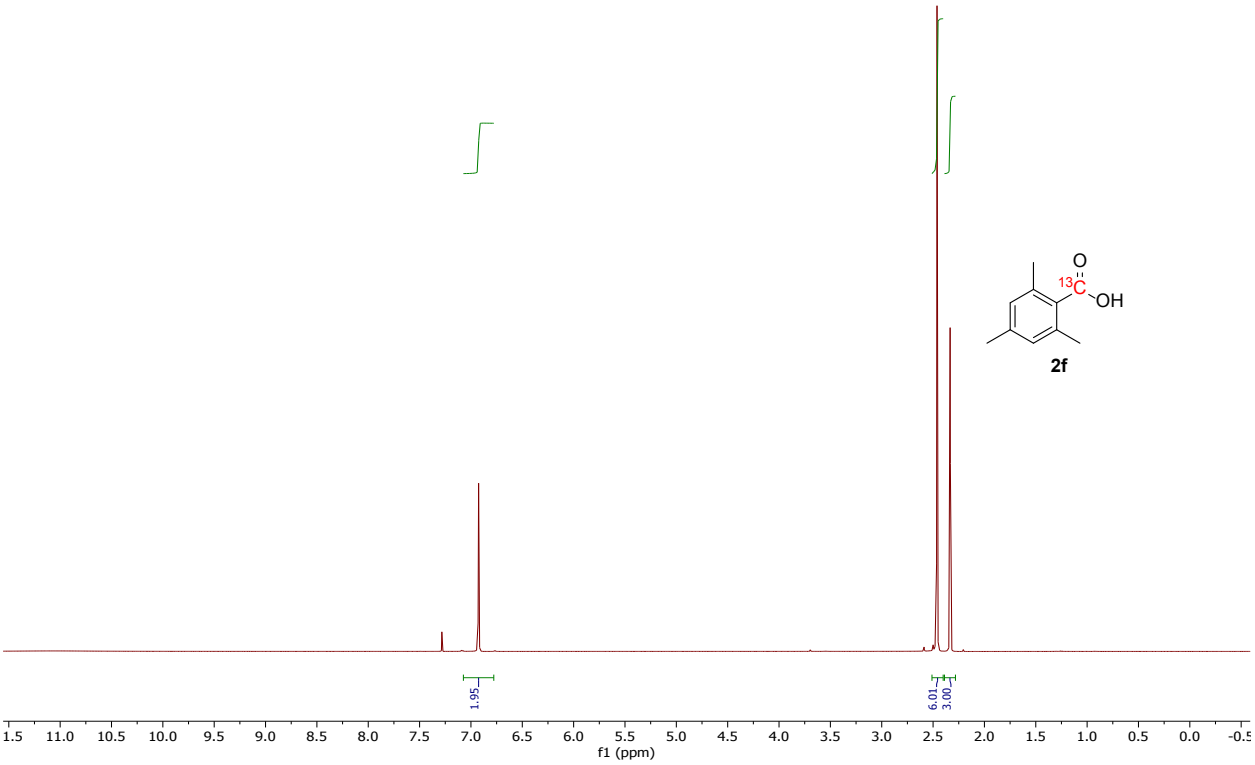

(400 MHz, Methanol-d4)
Boc
N
H
O
13C
OH
2d
f1 (ppm)


(101 MHz, MeOD)
Boc
N
H
O
13C
OH
2d
f1 (ppm)

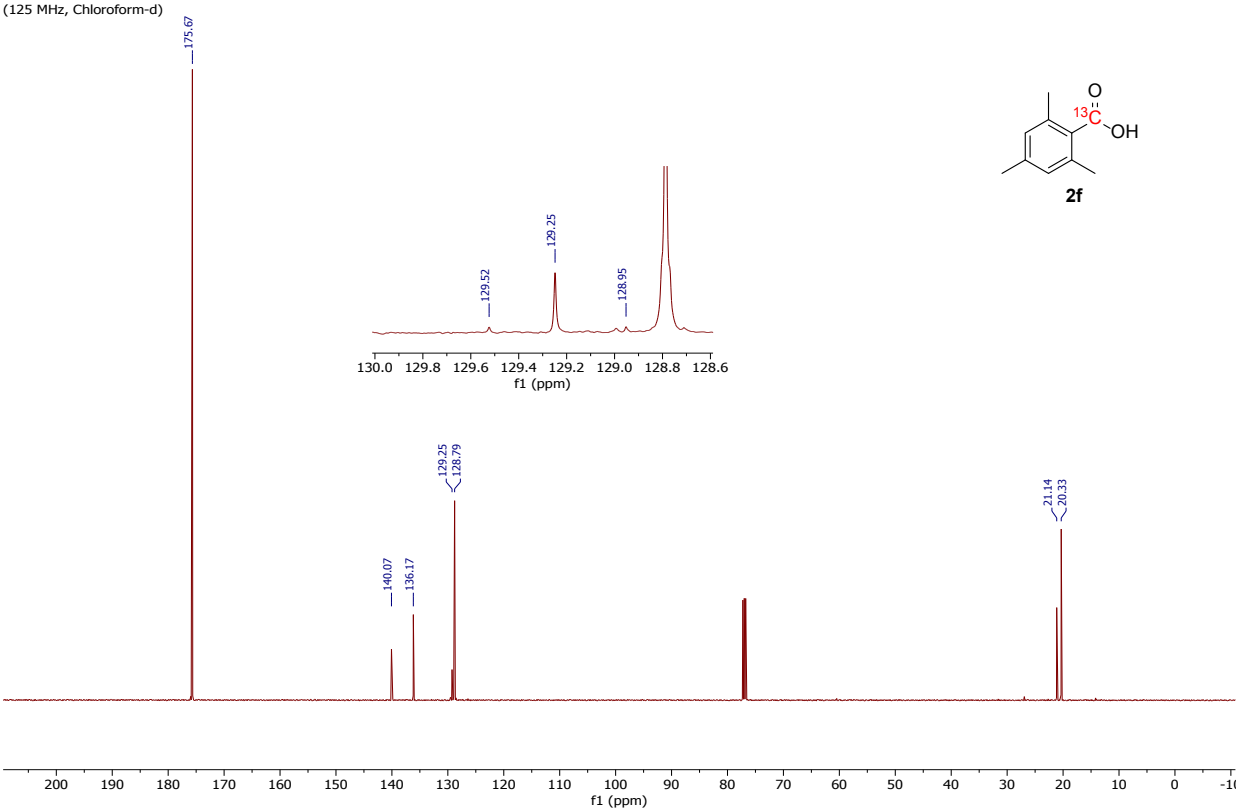

(500 MHz, DMSO-d_6)
7.76
7.74
6.72
6.70
2.99
12.03
0.79
2.00
1.97
5.82
f1 (ppm)
O
^{13}C
OH
Me_2N
2e


(126 MHz, DMSO)
167.96
153.53
131.35
117.42
111.22
40.10
117.71
117.42
117.11
13.96
69.93
17.11
f1 (ppm)
O
^{13}C
OH
Me_2N
2e

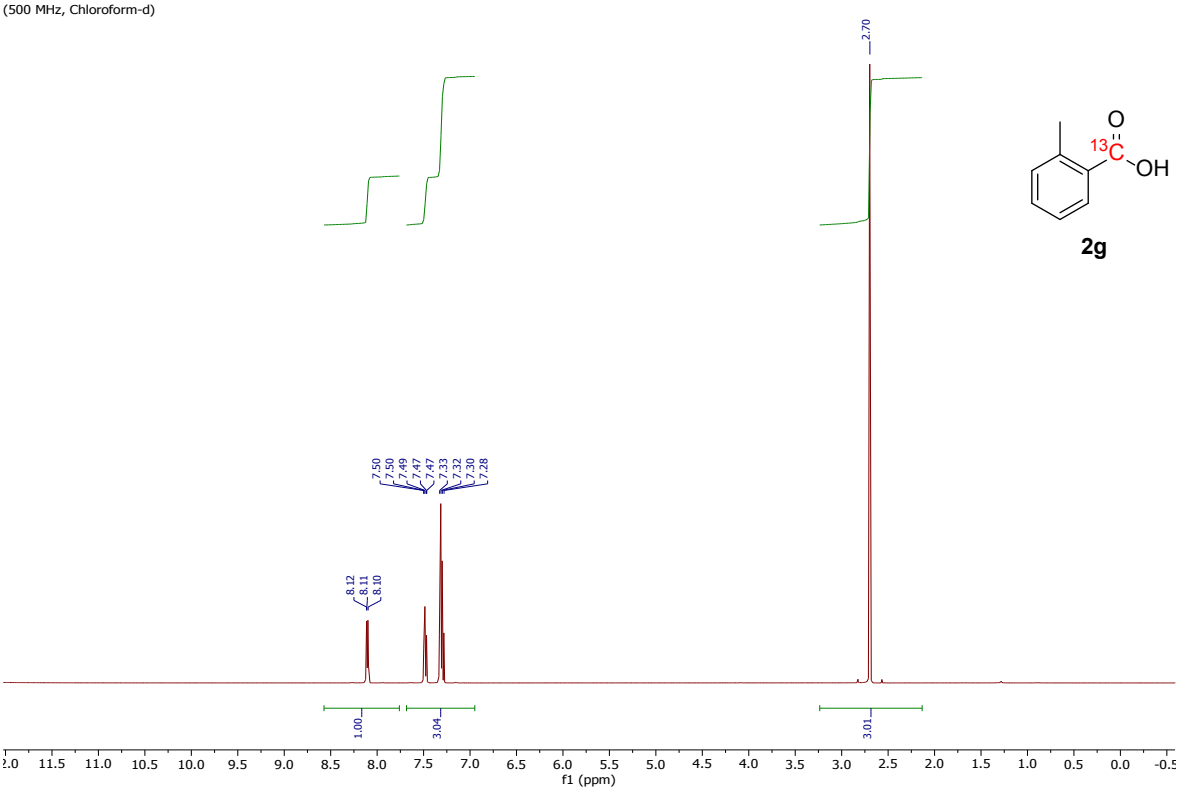
(500 MHz, Chloroform-d)



(125 MHz, Chloroform-d)

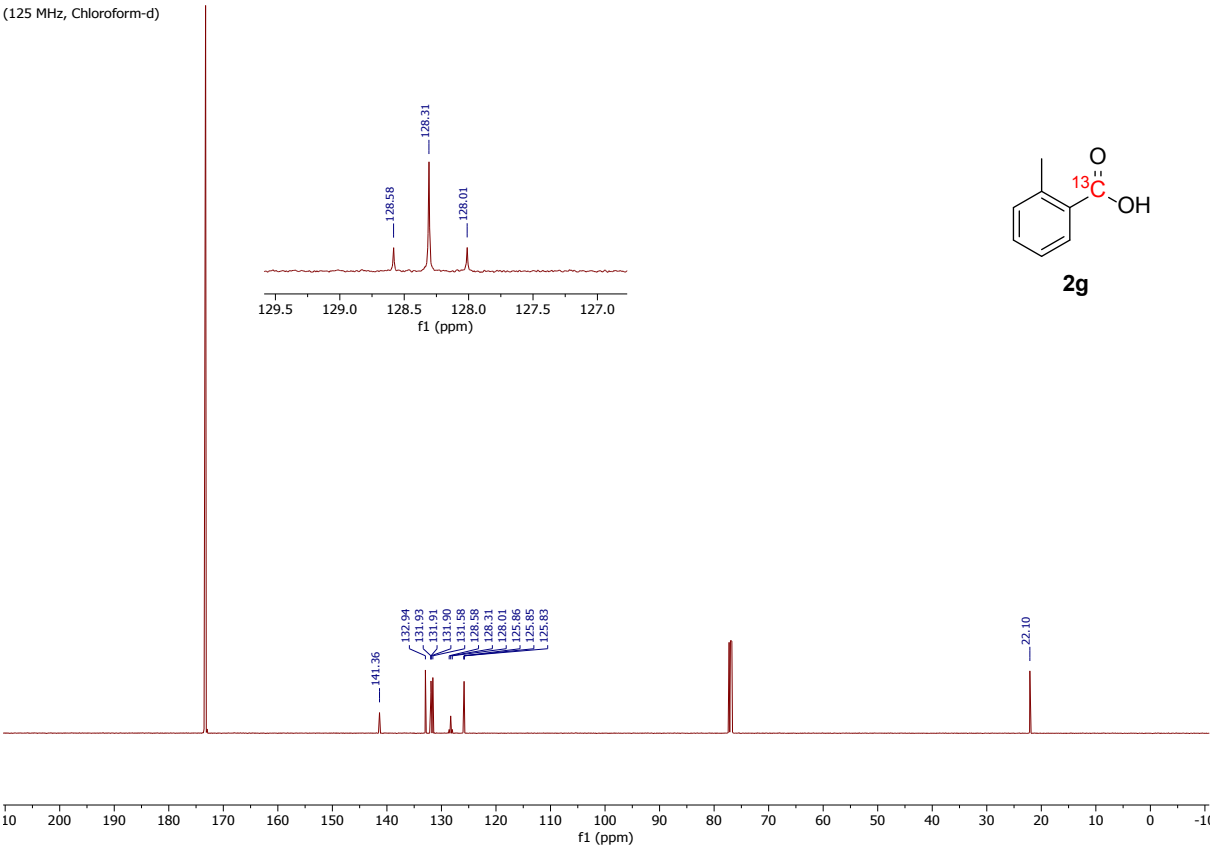


(500 MHz, Chloroform-d)

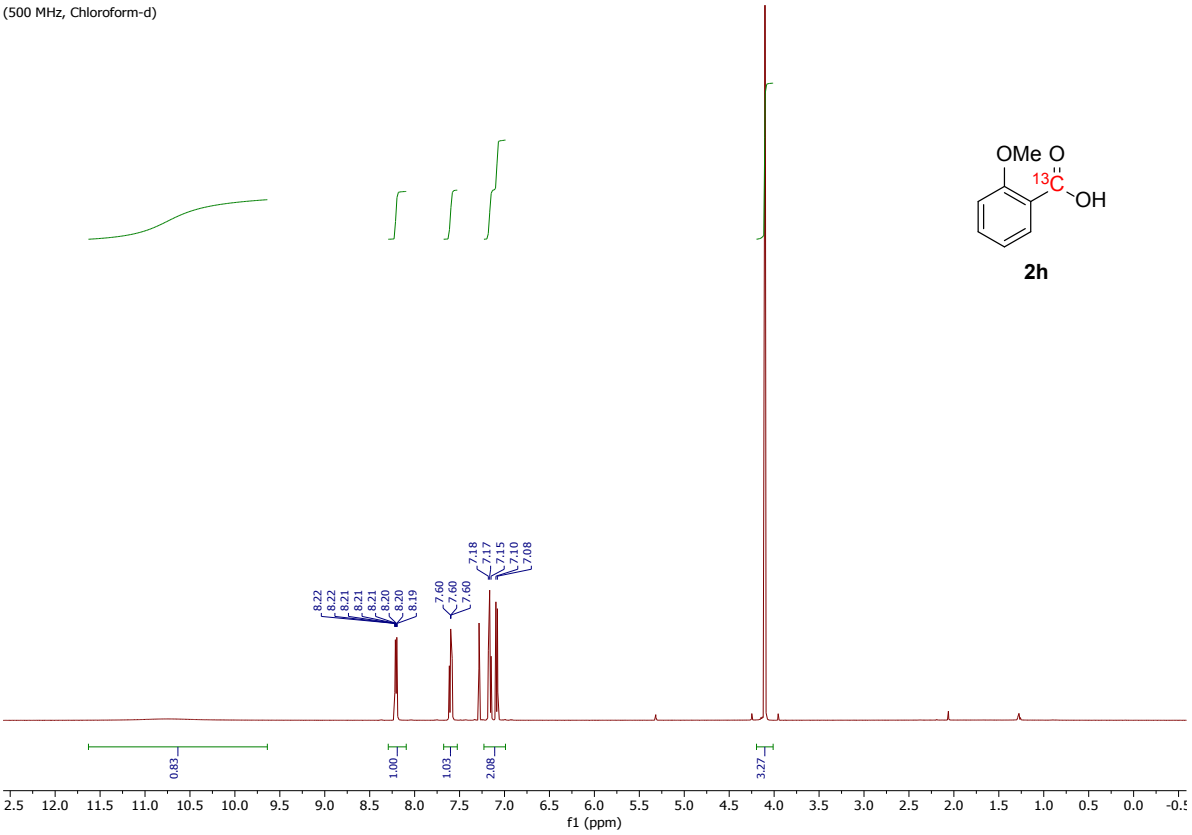


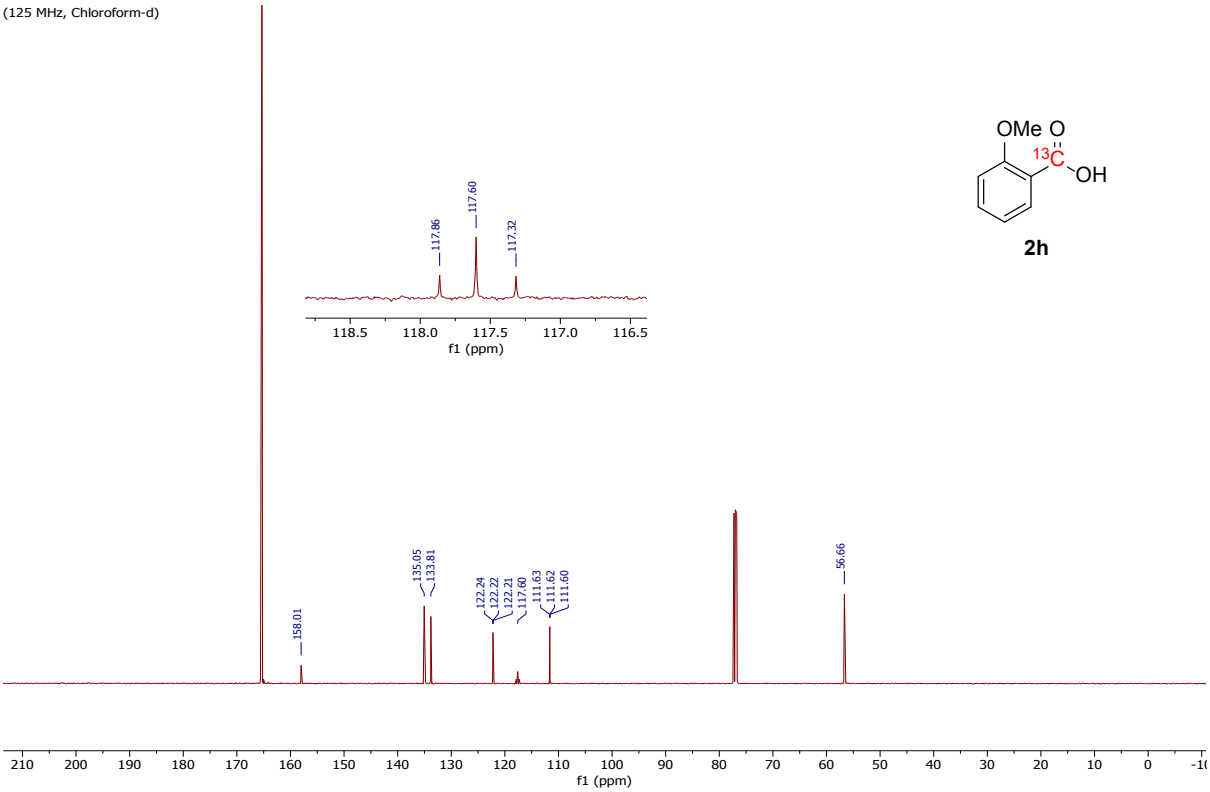
2g

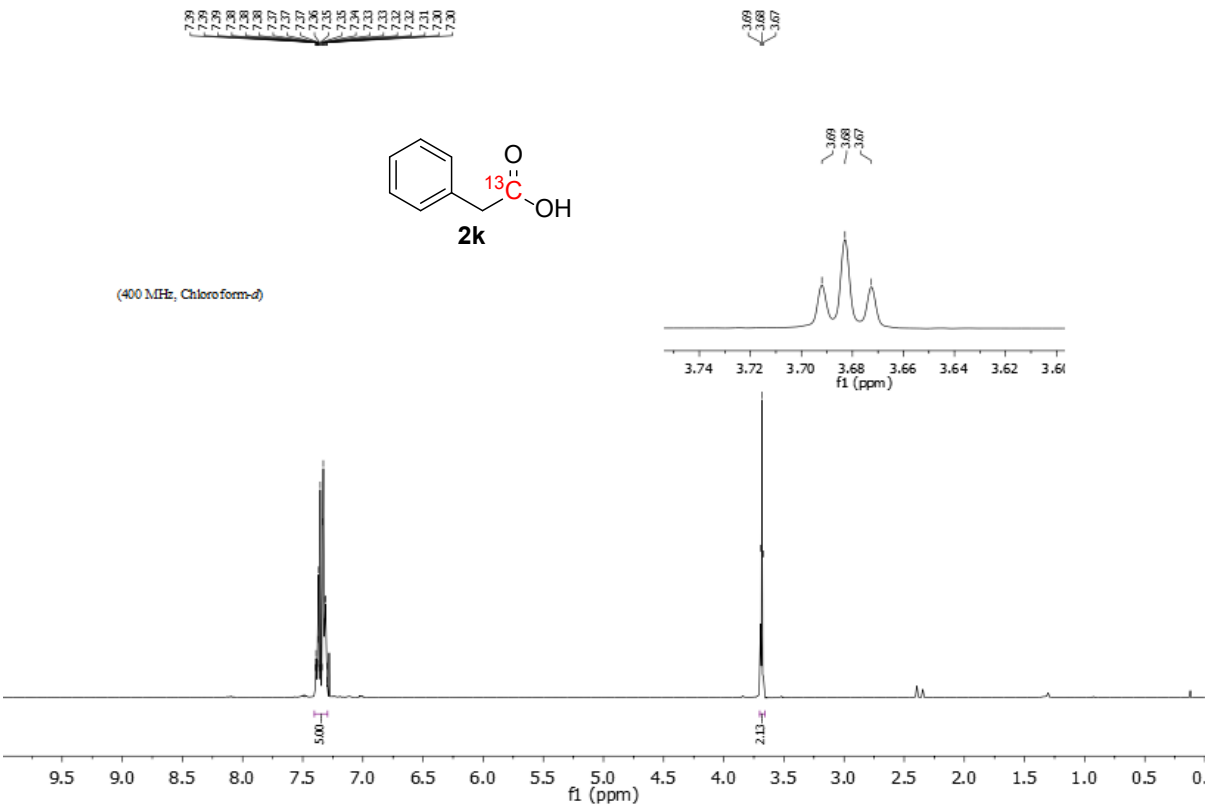
(125 MHz, Chloroform-d)

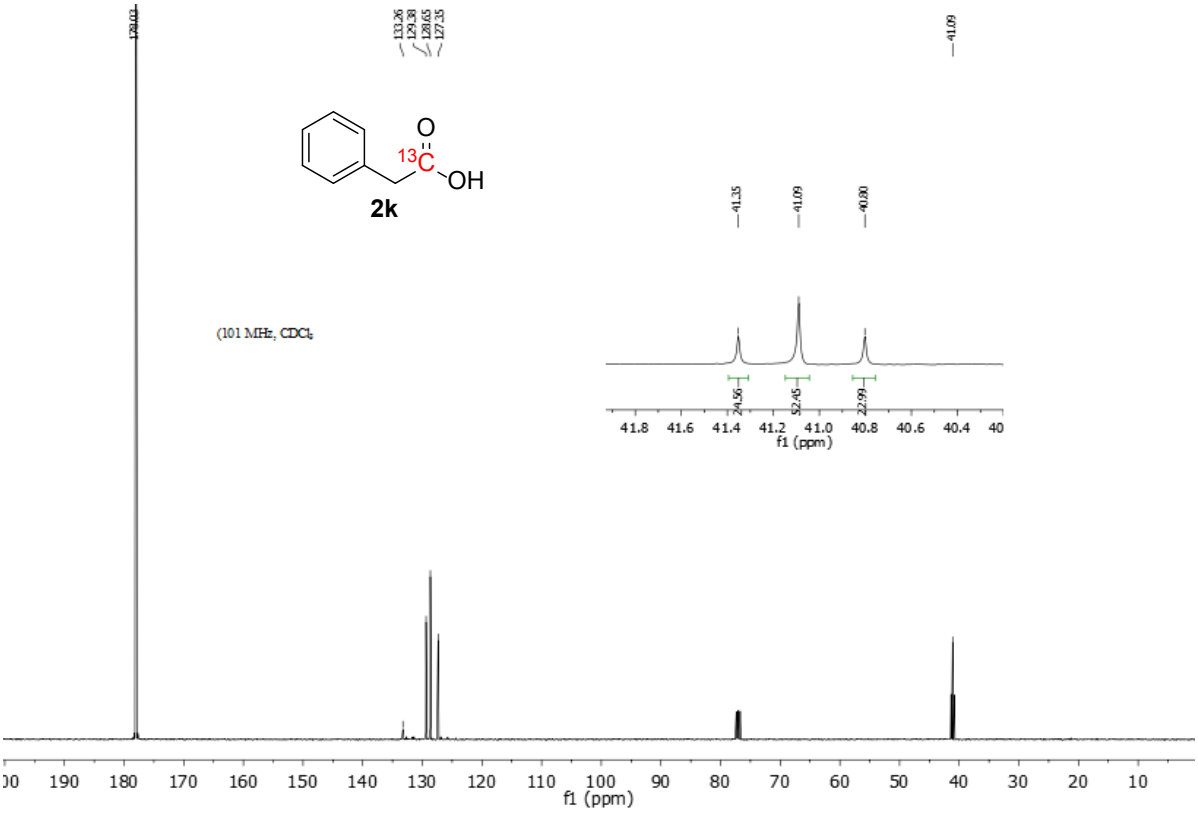


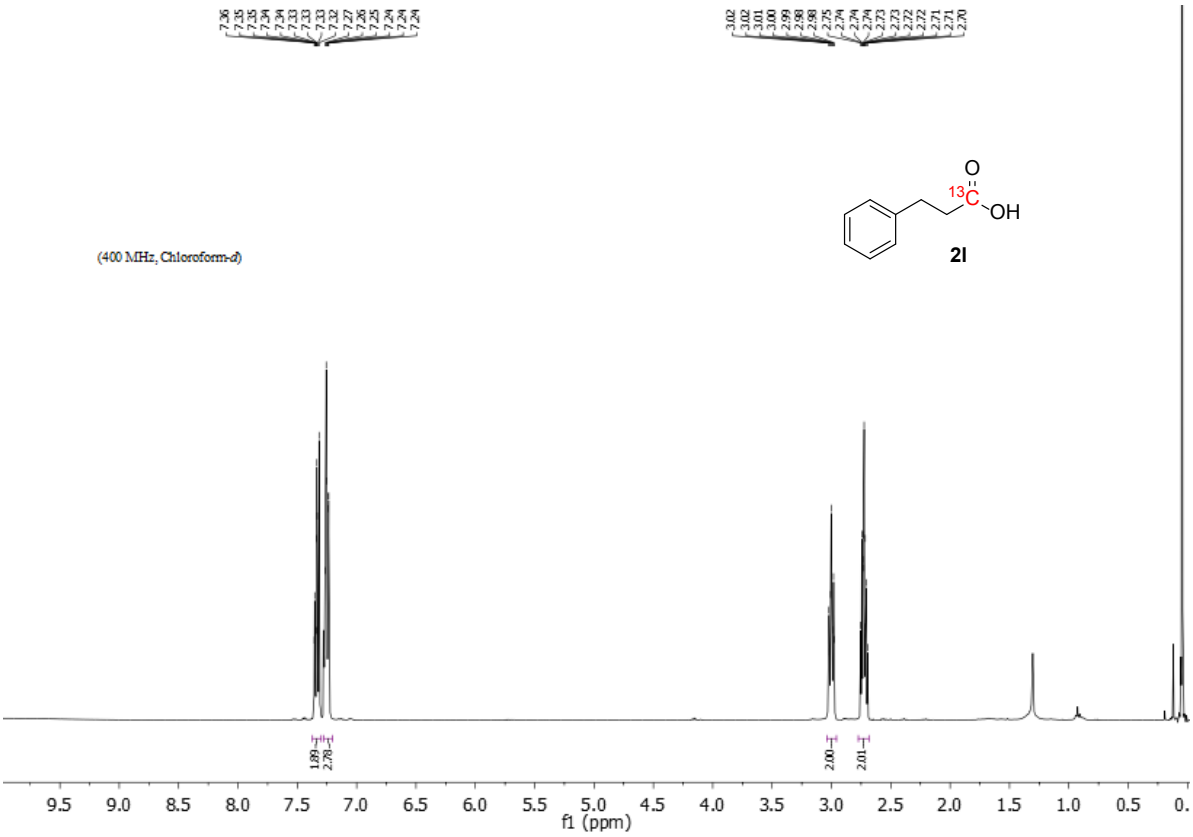
2g

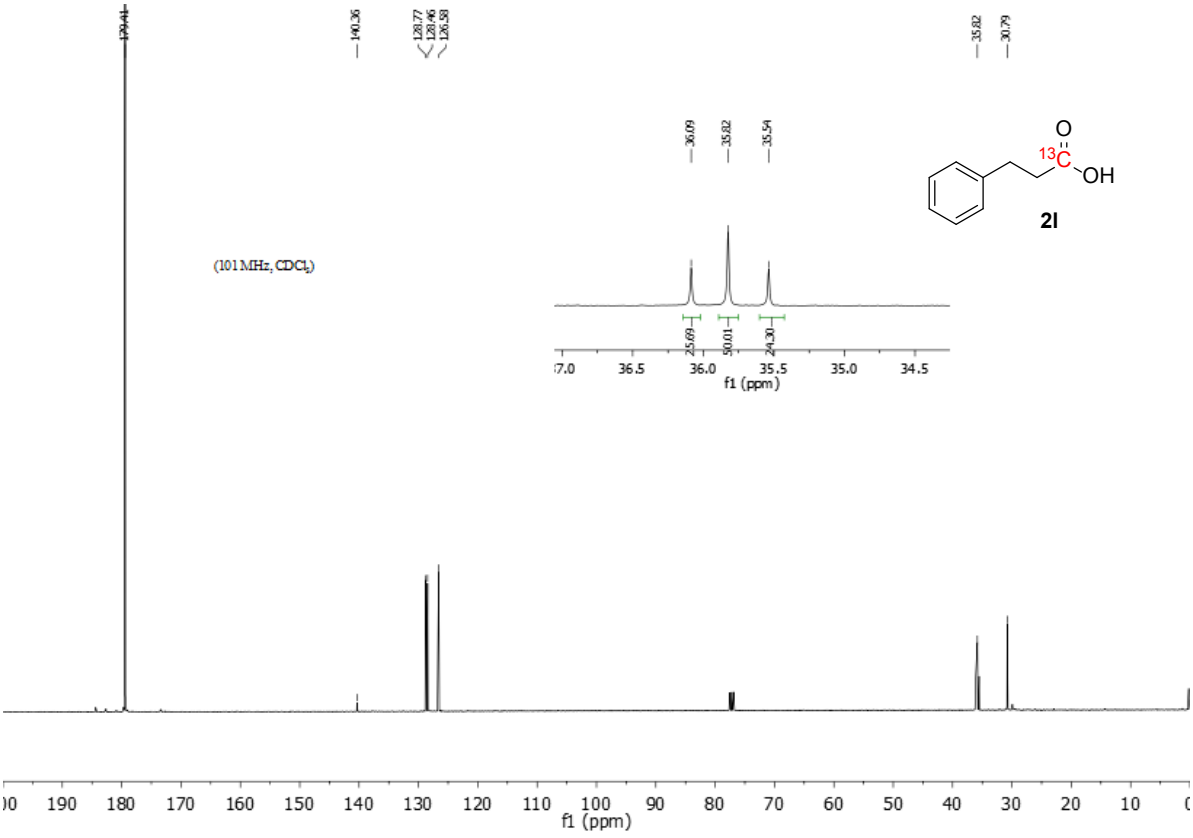

(500 MHz, Chloroform-d)
OMe O
13C
OH
2h
8.22
8.22
8.21
8.21
8.21
8.20
8.20
8.19
7.60
7.60
7.60
7.18
7.17
7.15
7.10
7.08
0.83
1.00
1.03
2.08
3.27
f1 (ppm)

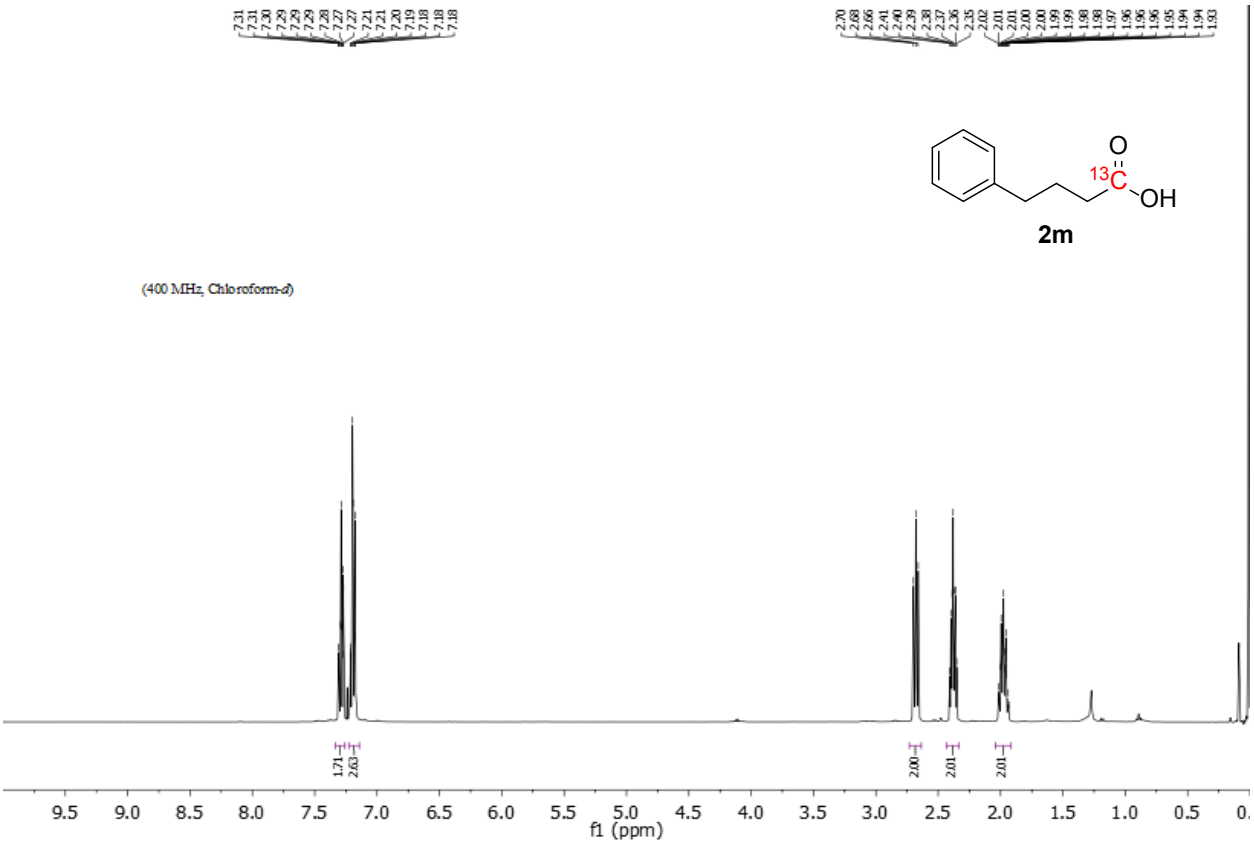

(125 MHz, Chloroform-d)
OMe O
13C
OH
2h
117.86
117.60
117.32
f1 (ppm)
158.01
135.05
133.81
122.24
122.22
122.21
117.60
111.63
111.62
111.60
56.66
f1 (ppm)

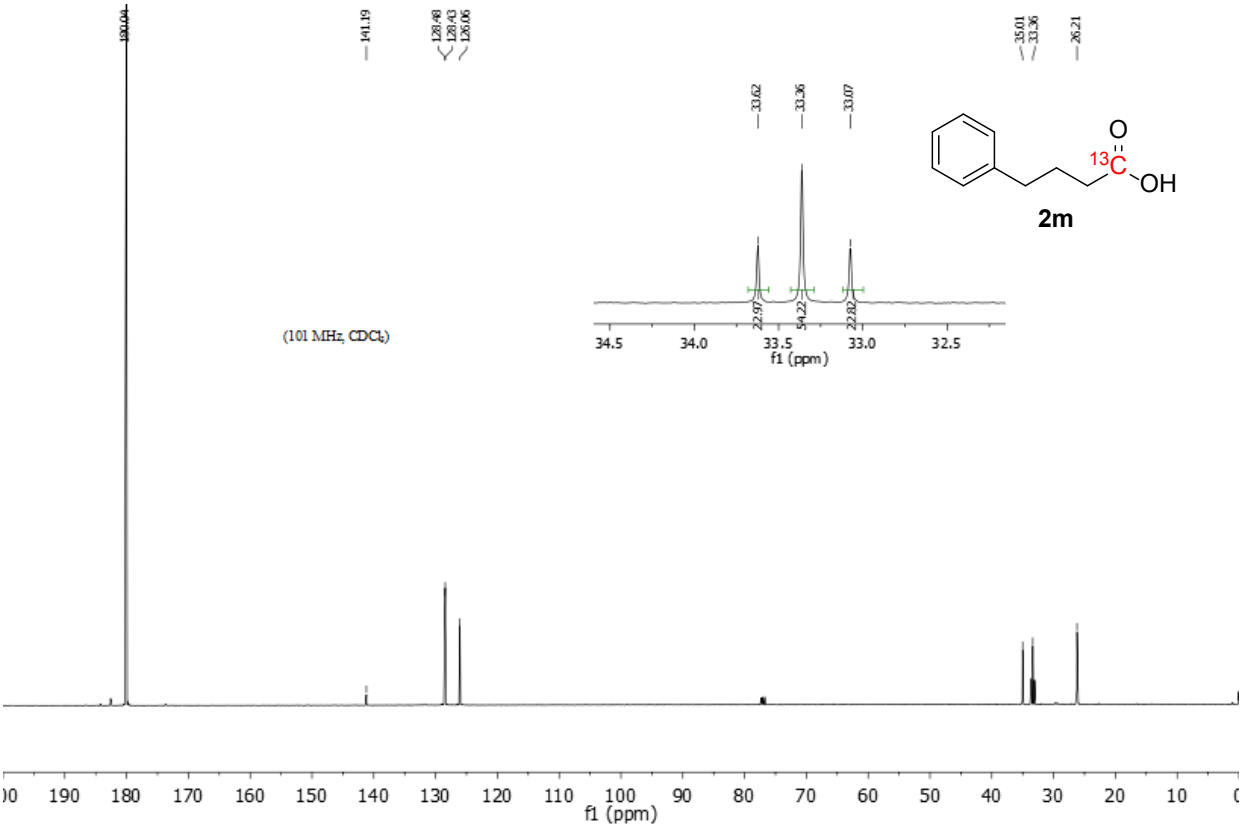

7.39
7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.30
7.30
3.69
3.68
3.67
O
13C
OH
2k
(400 MHz, Chloroform-d)
3.74
3.72
3.70
3.68
3.66
3.64
3.62
f1 (ppm)
5.00
2.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

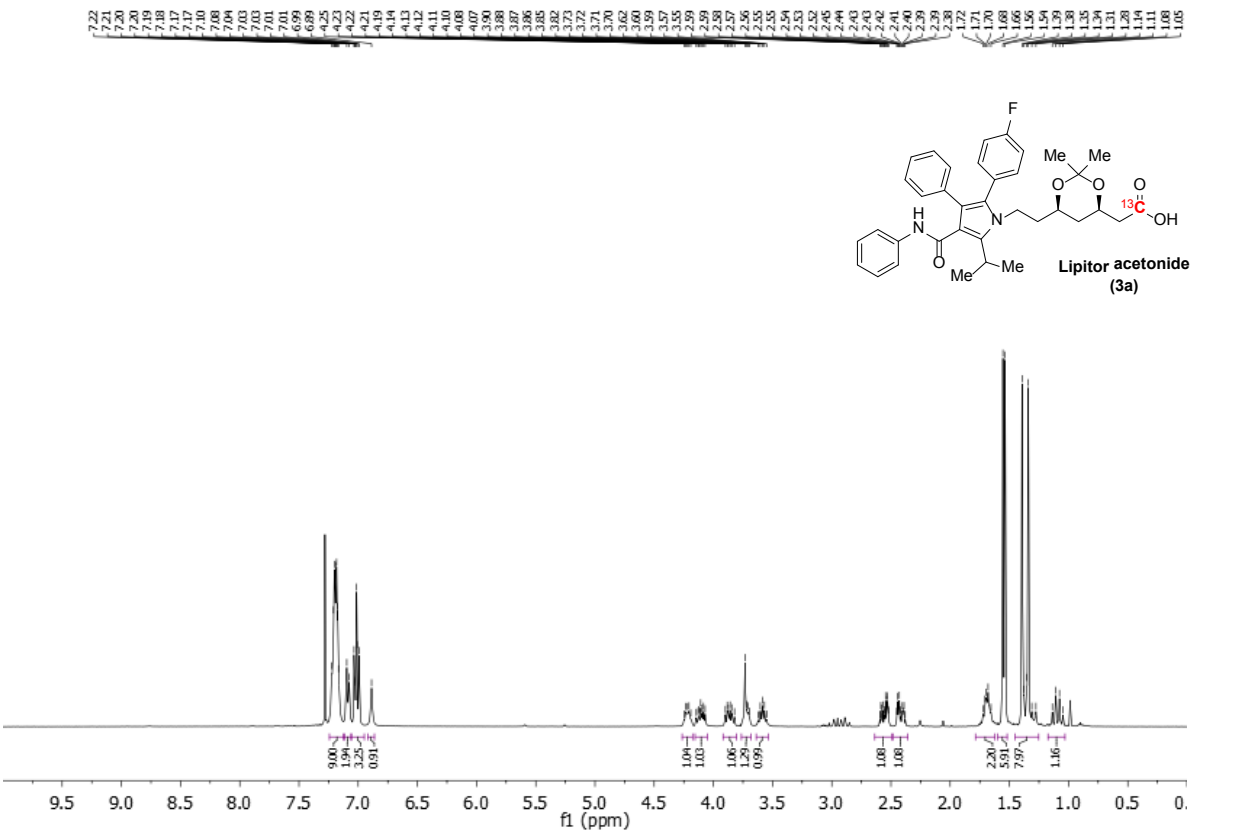

179.03
133.26
129.38
128.65
127.35
41.09
O
13C
OH
2k
(101 MHz, CDCl3)
41.35
41.09
40.80
24.56
52.45
22.99
41.8
41.6
41.4
41.2
41.0
40.8
40.6
40.4
40
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

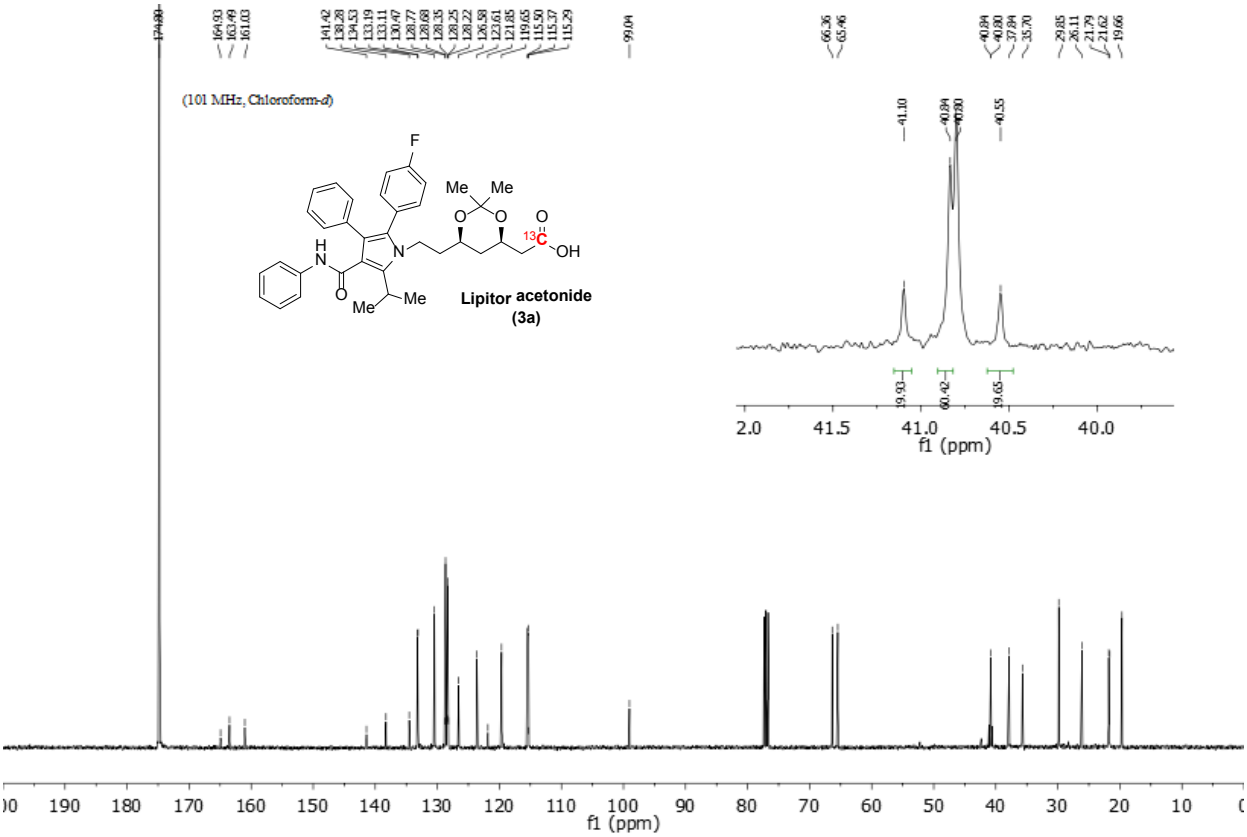

(400 MHz, Chloroform-d)
2l
f1 (ppm)

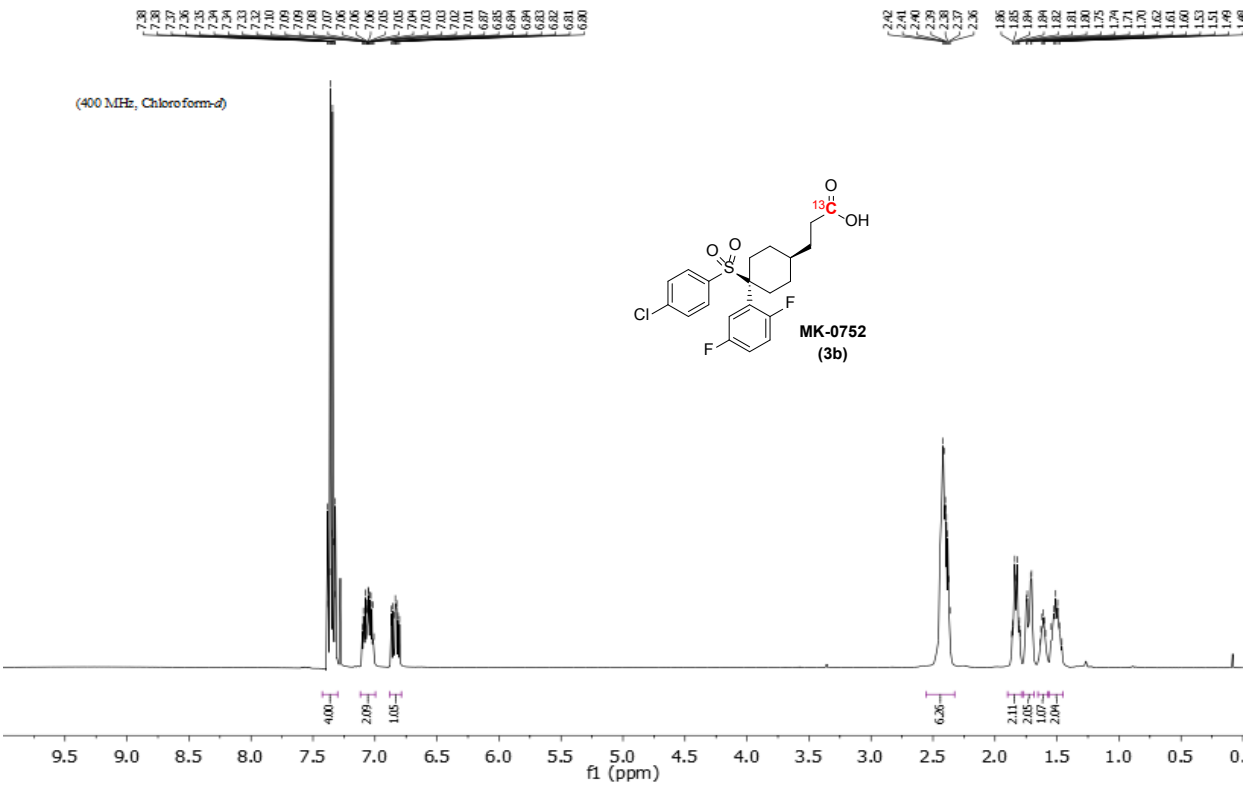

(101 MHz, CDCl3)
2l
f1 (ppm)

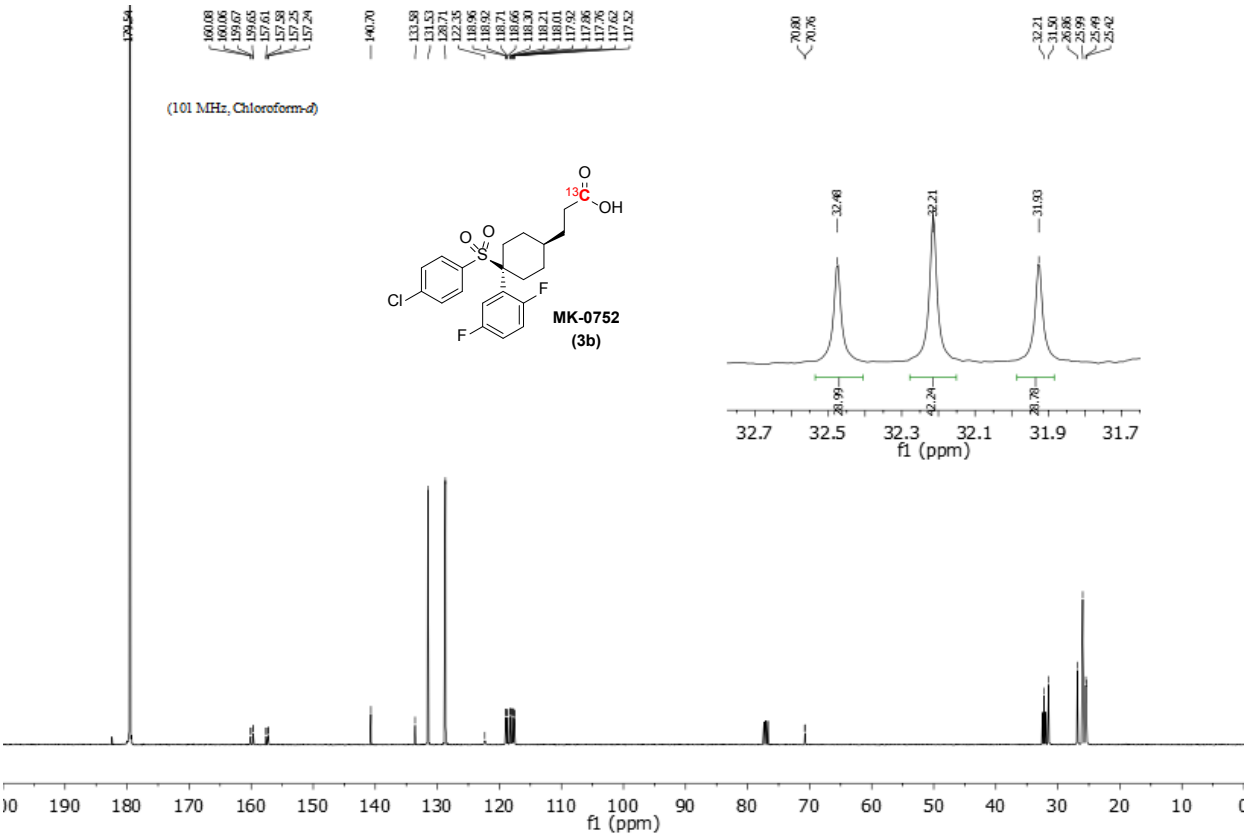

(400 MHz, Chloroform-d)
2m
f1 (ppm)


(101 MHz, CDCl3)
2m
f1 (ppm)

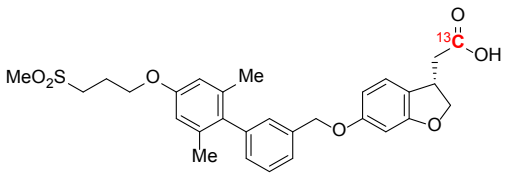

F
Me
Me
O
O
O
H
N
O
13C
OH
Me
Me
Lipitor acetonide
(3a)
f1 (ppm)


(101 MHz, Chloroform-d)
F
Me
Me
O
O
O
H
N
O
13C
OH
Me
Me
Lipitor acetonide
(3a)
f1 (ppm)
f1 (ppm)


(400 MHz, Chloroform-d)
MK-0752
(3b)
f1 (ppm)

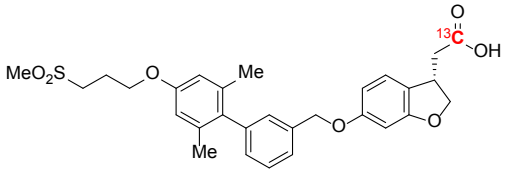

(101 MHz, Chloroform-d)
MK-0752
(3b)
f1 (ppm)

(500 MHz, Chloroform-d)



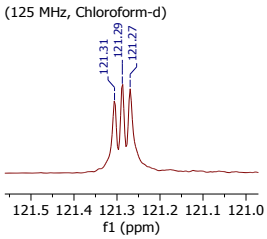
TAK-875 (3d)

(125 MHz, Chloroform-d)

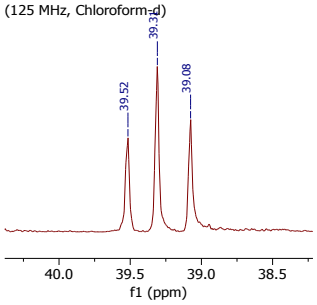


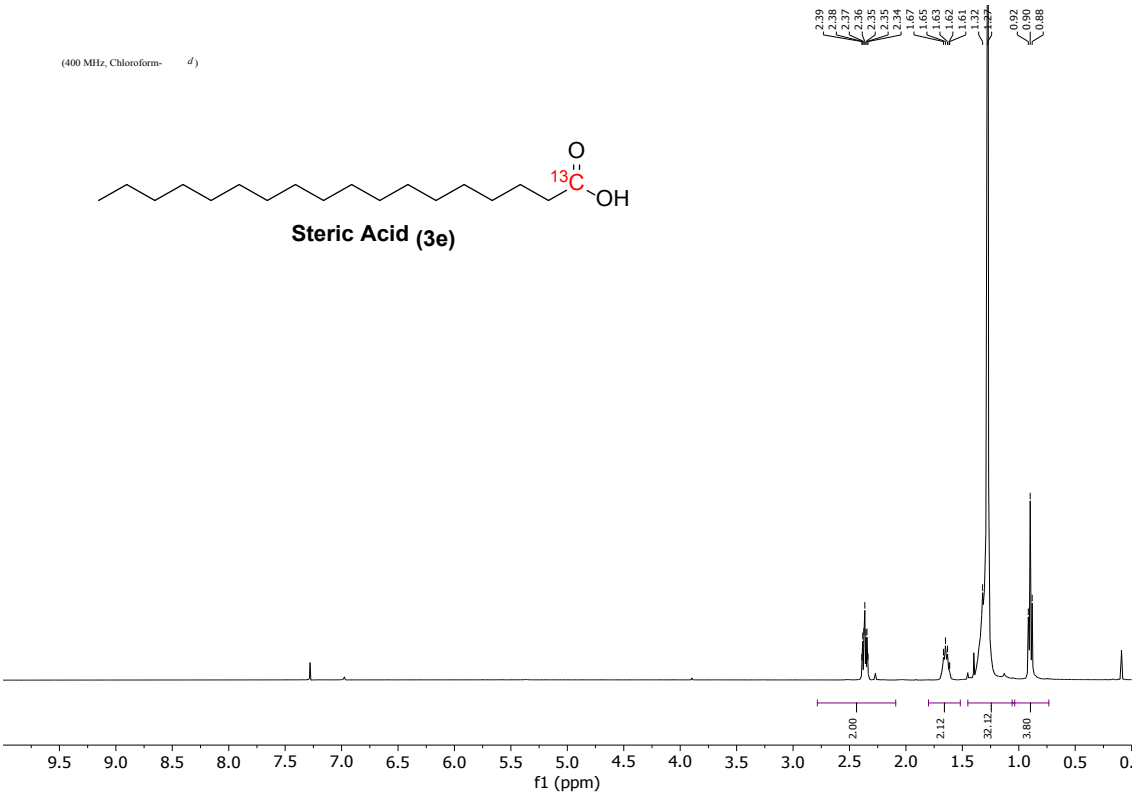
TAK-875 (3d)

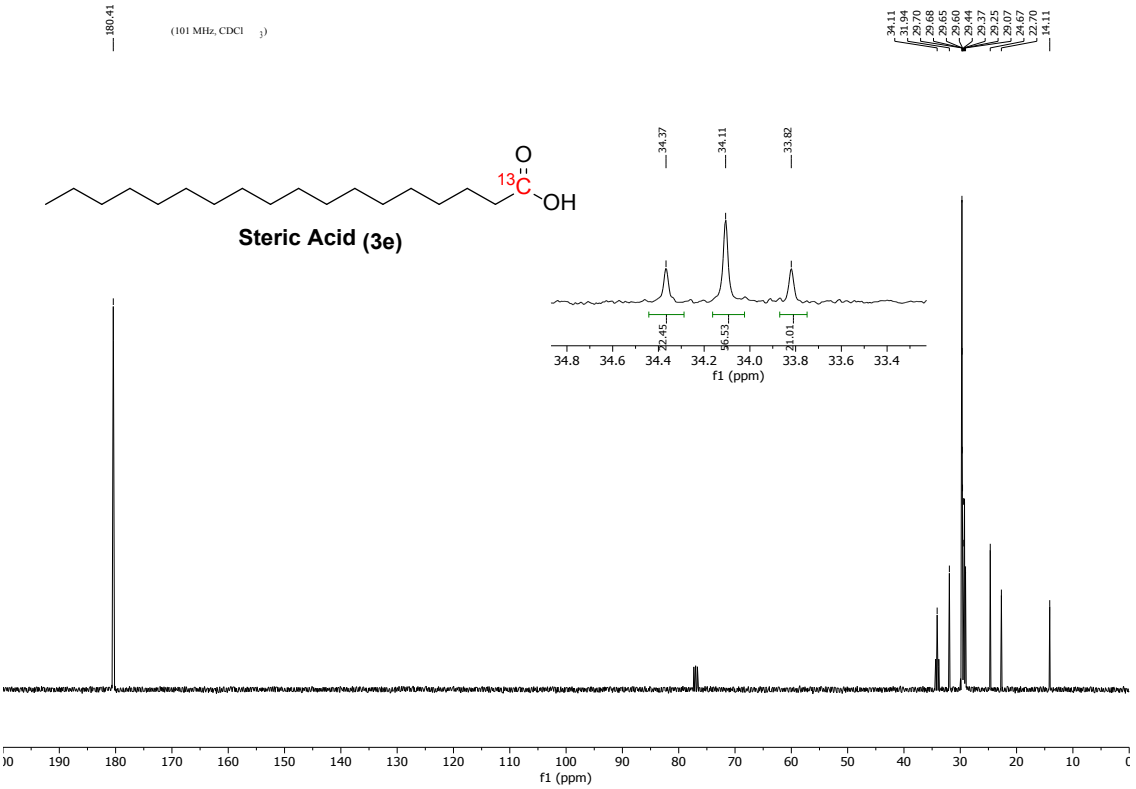
(125 MHz, Chloroform-d)

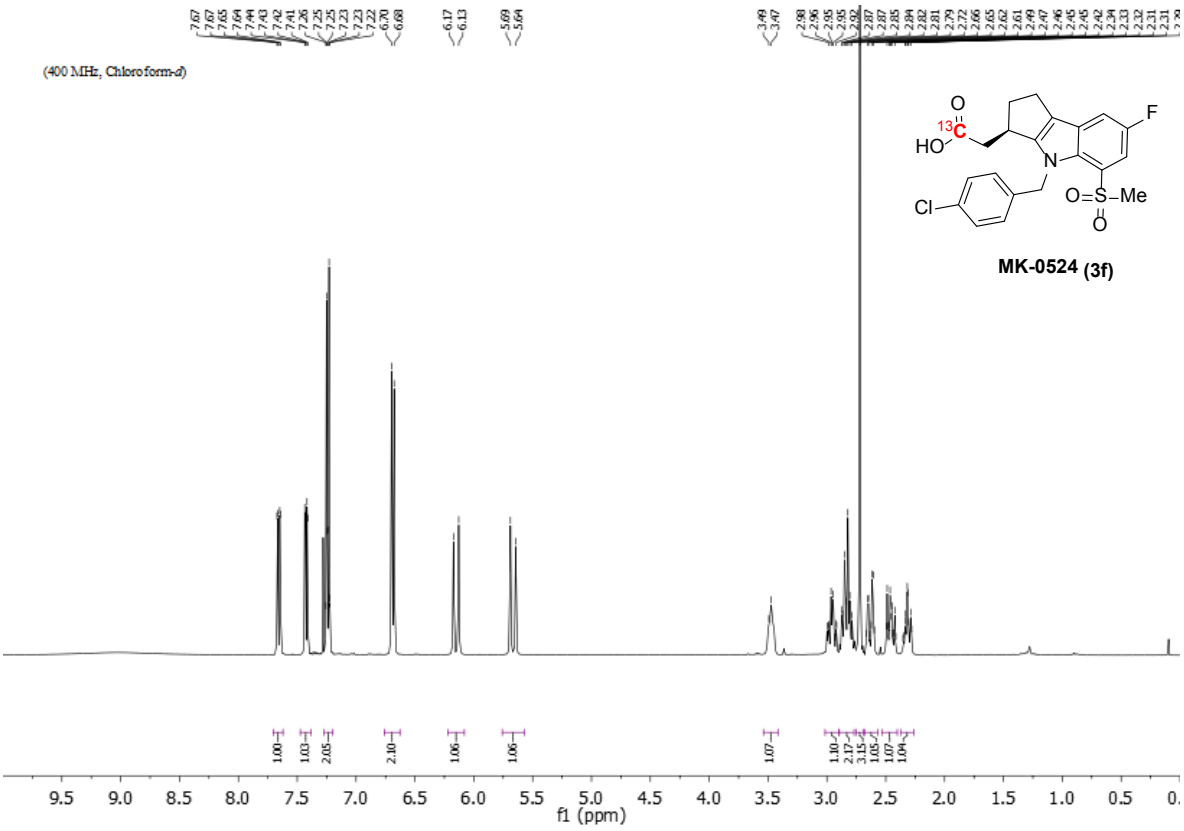


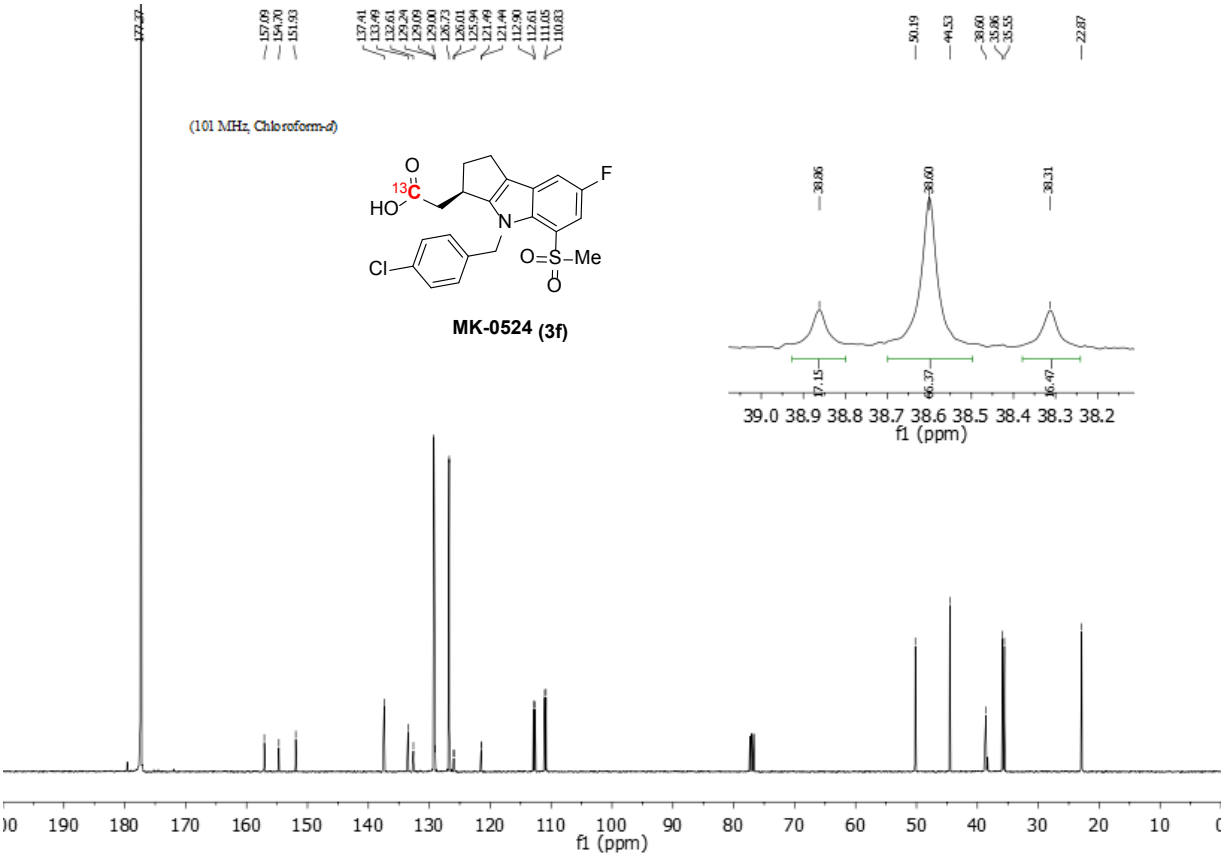
(125 MHz, Chloroform-d)



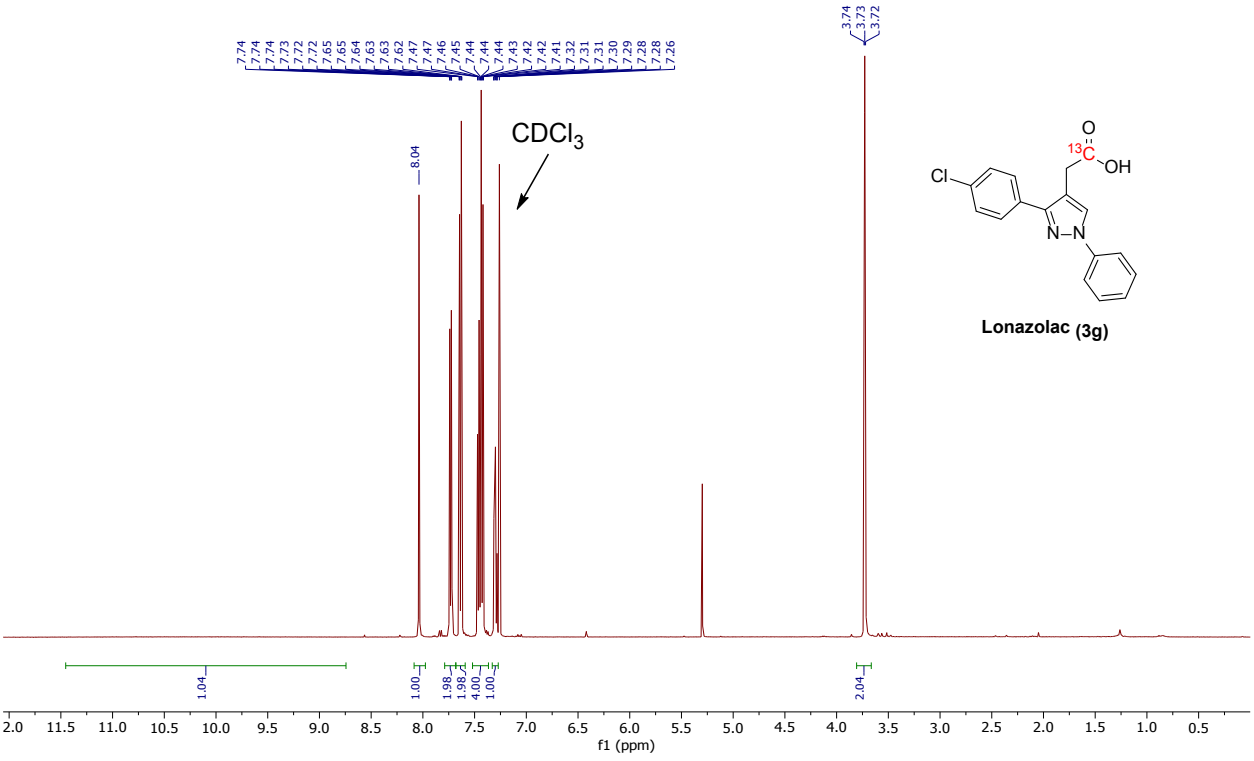

(400 MHz, Chloroform-d)
Steric Acid (3e)
f1 (ppm)


(101 MHz, CDCl3)
Steric Acid (3e)
f1 (ppm)
f1 (ppm)

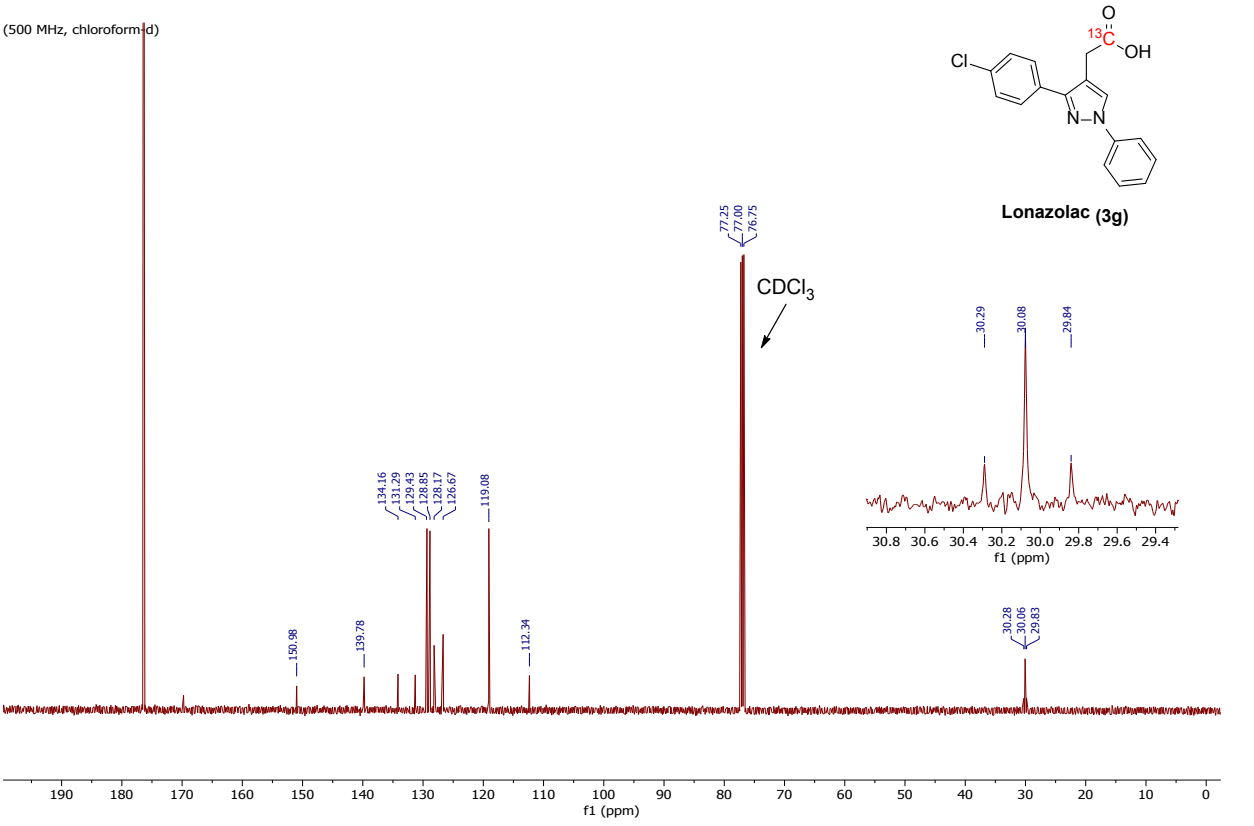

(400 MHz, Chloroform-d)
MK-0524 (3f)
f1 (ppm)


(101 MHz, Chloroform-d)
MK-0524 (3f)
f1 (ppm)

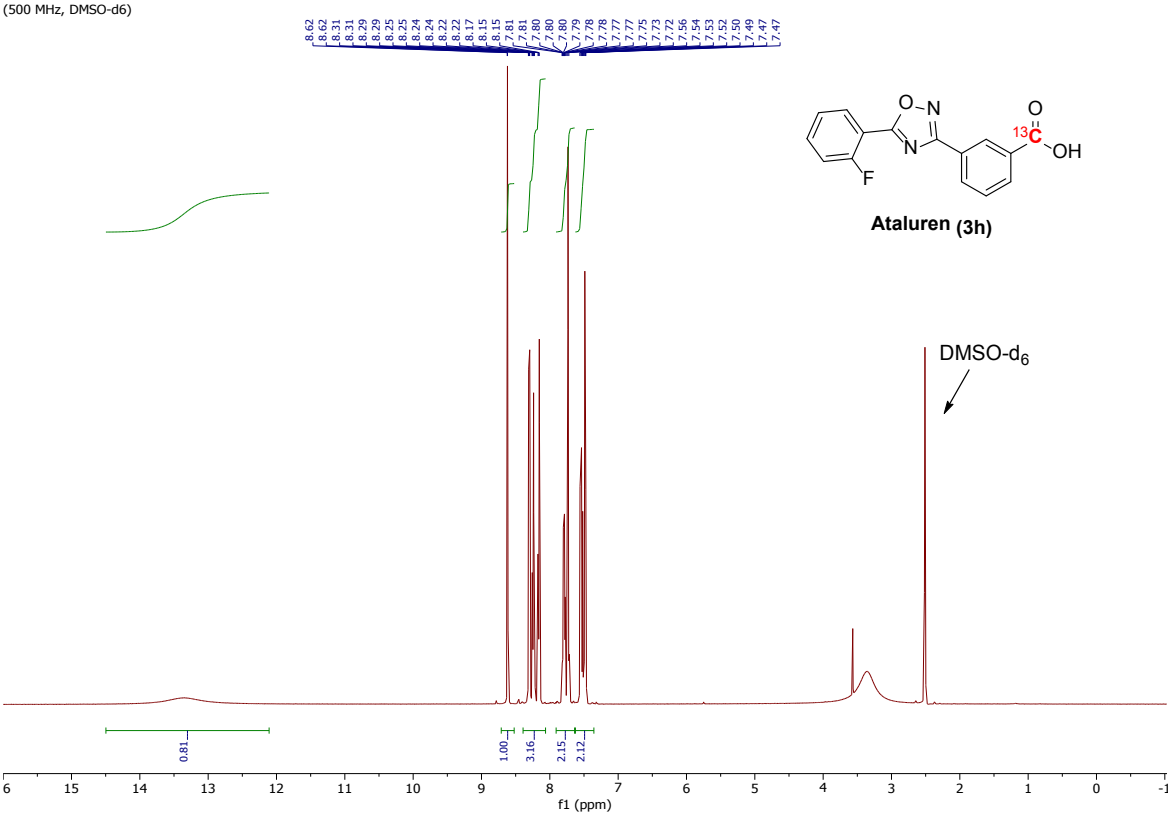
(500 MHz, chloroform-d)



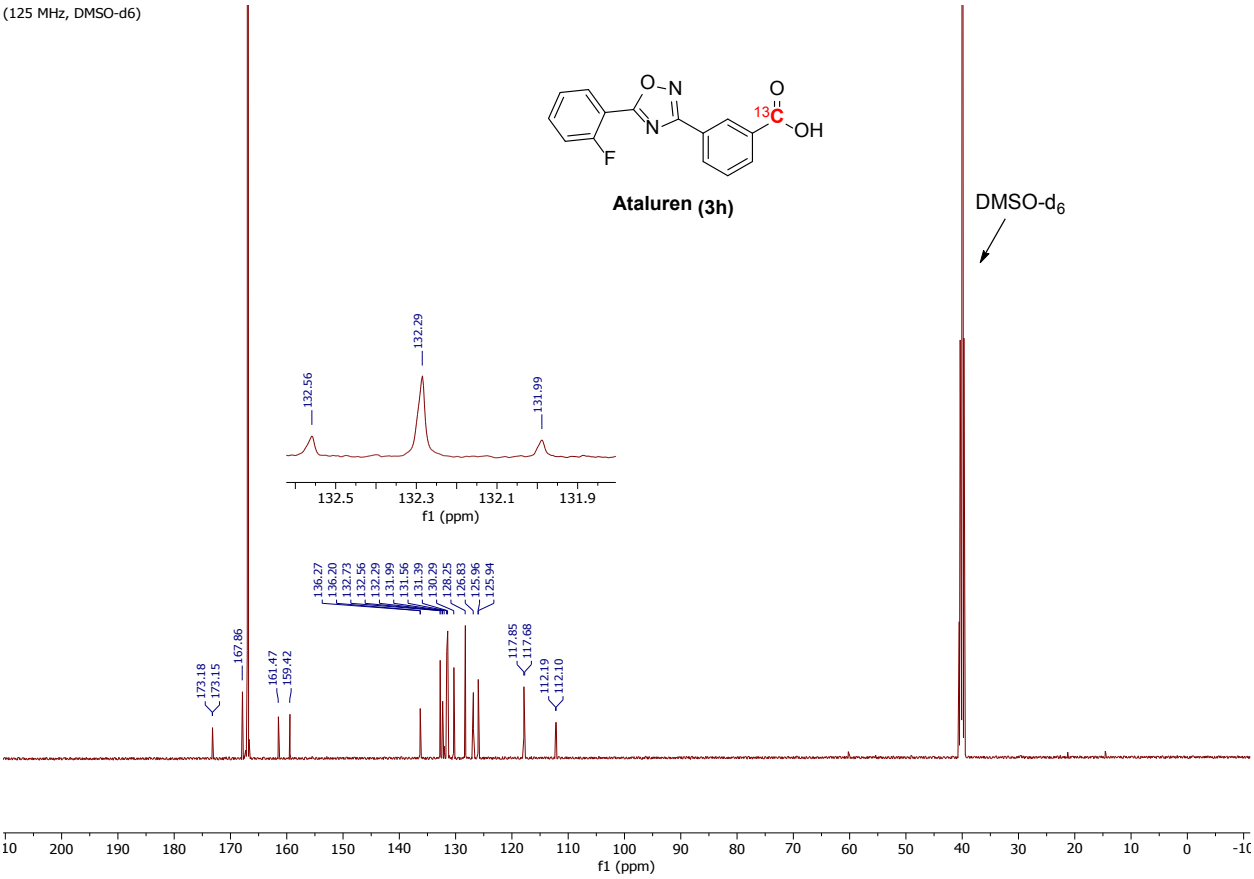
(500 MHz, chloroform-d)



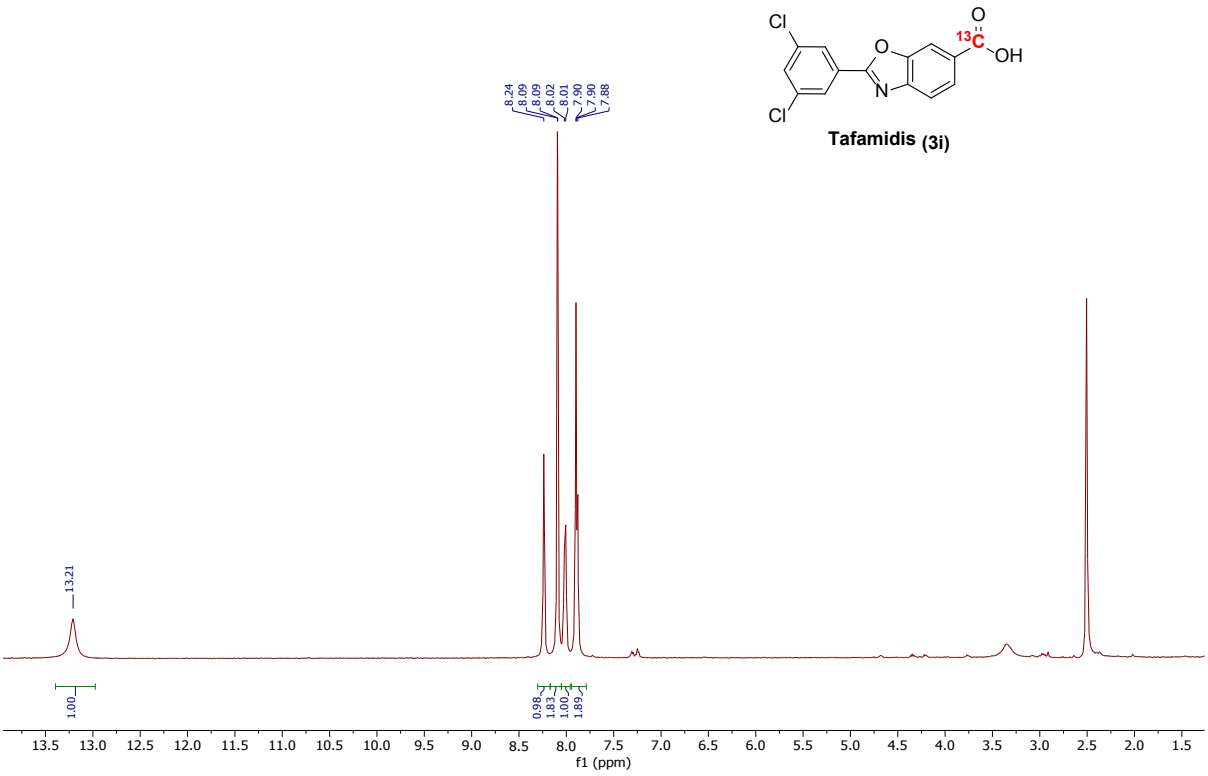
(500 MHz, DMSO-d6)



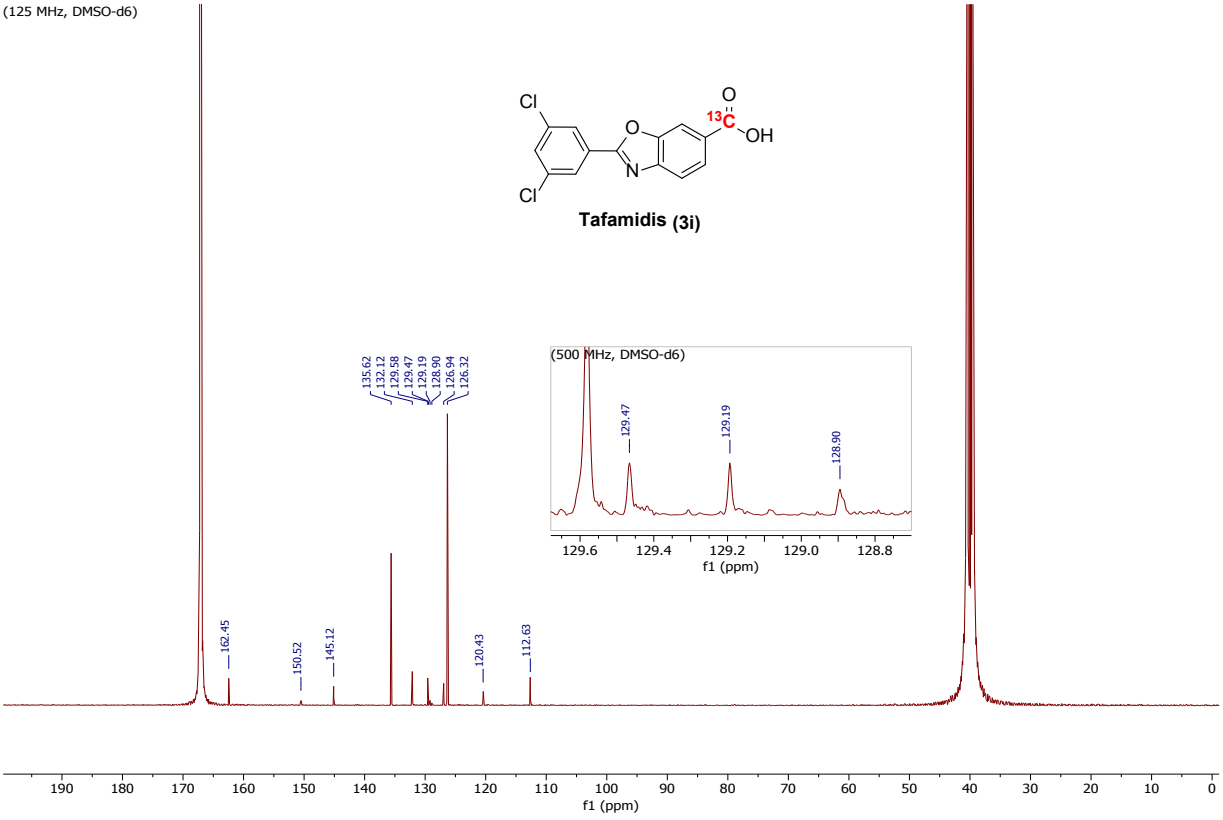
(125 MHz, DMSO-d6)

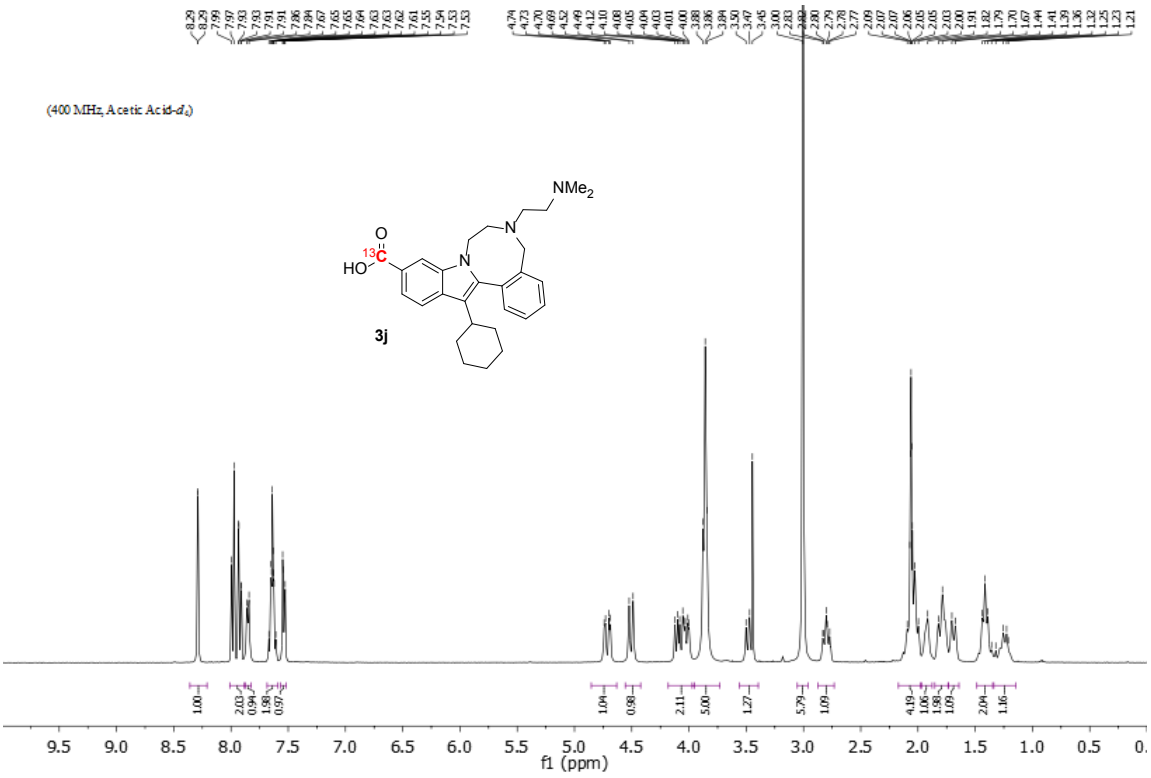


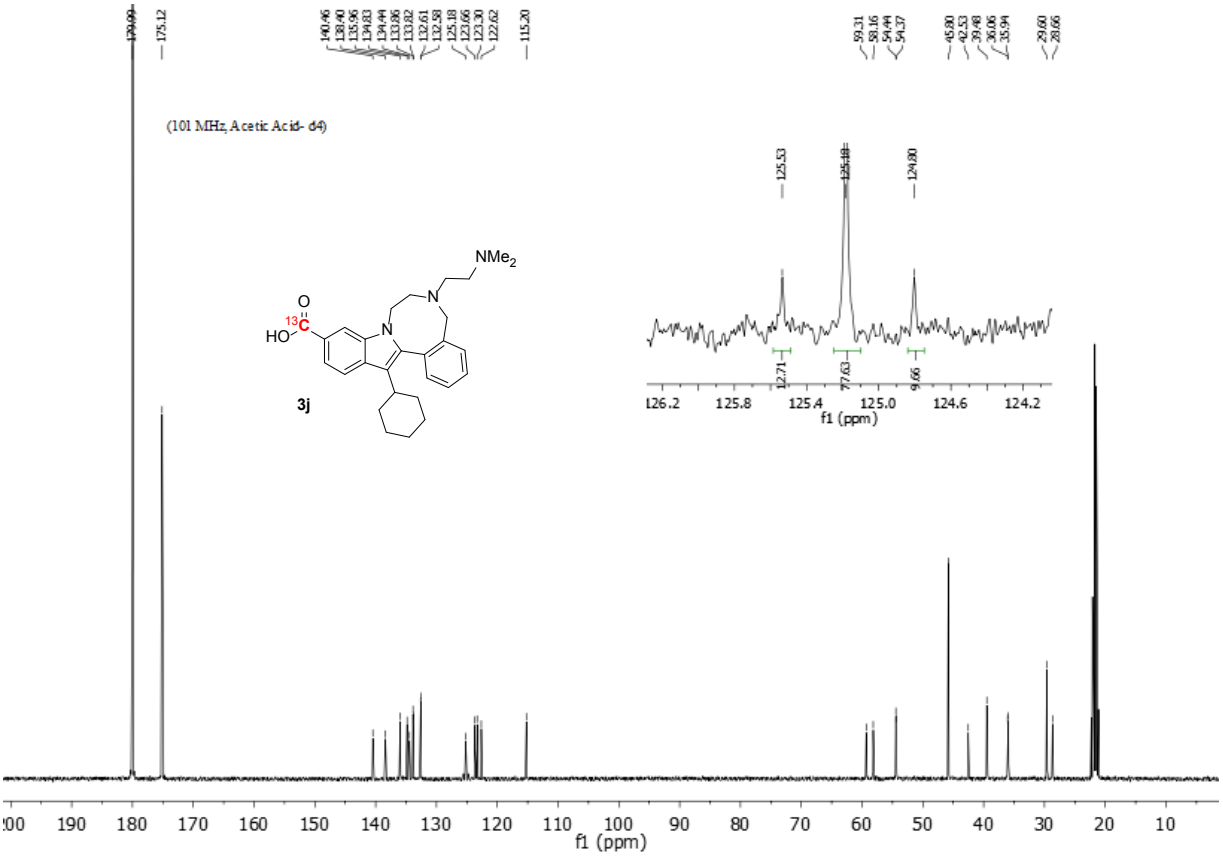
(500 MHz, DMSO-d6)



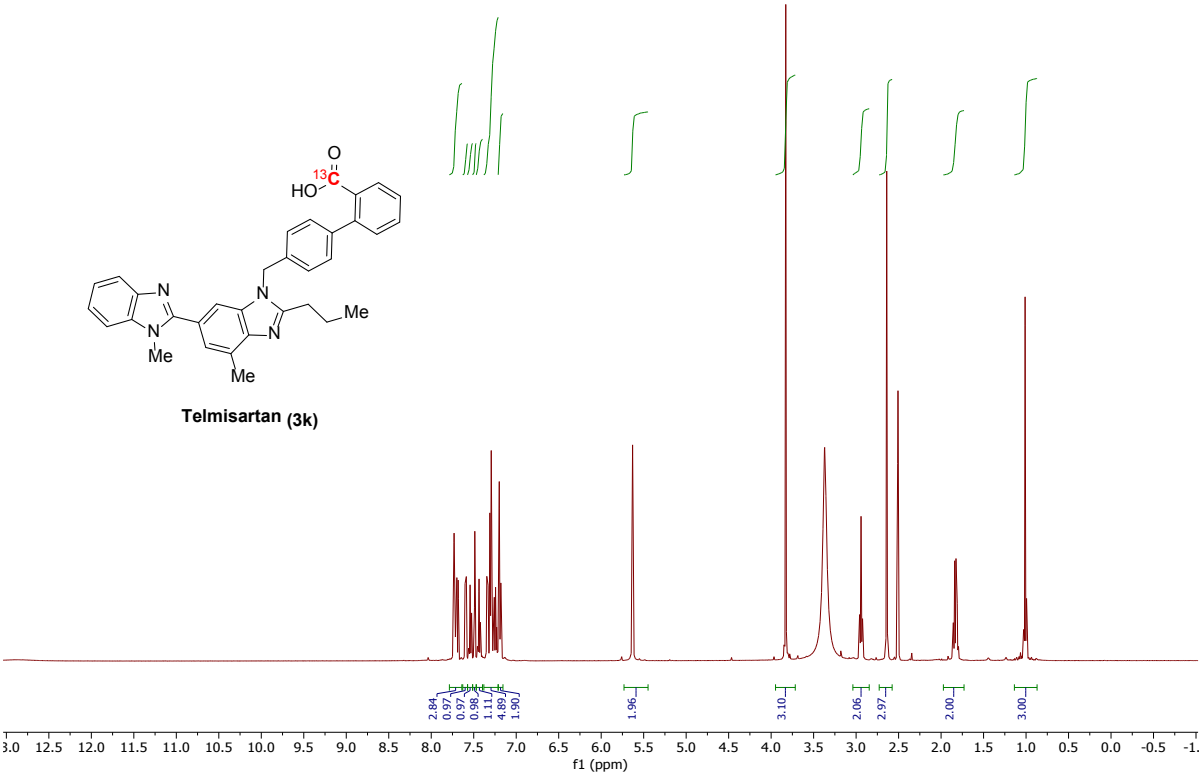
(125 MHz, DMSO-d6)



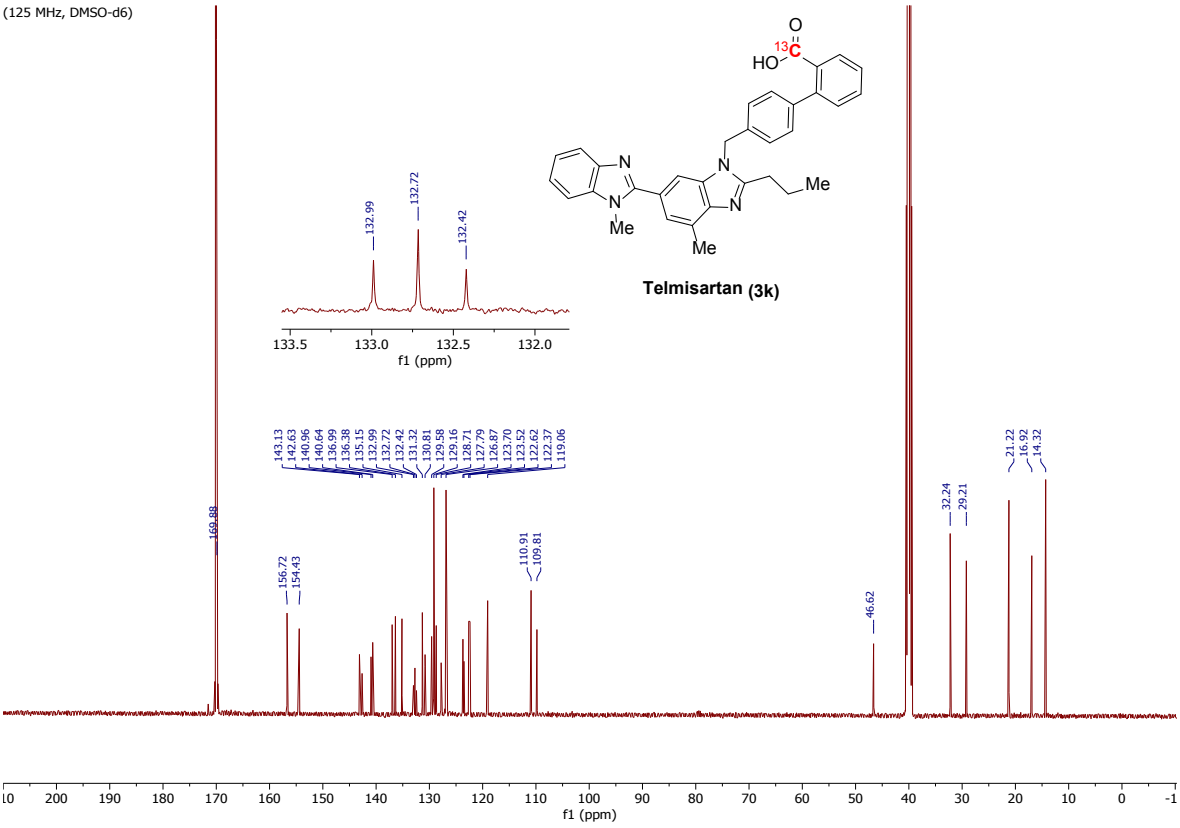

(400 MHz, Acetic Acid-d_4)
NMe2
O
HO
13C
N
N
3j
f1 (ppm)


(101 MHz, Acetic Acid- d4)
NMe2
O
HO
13C
N
N
3j
f1 (ppm)

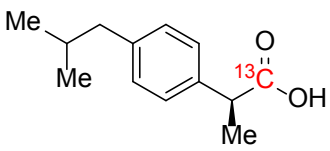
(500 MHz, DMSO-d6)



(125 MHz, DMSO-d6)

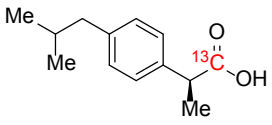


(500 MHz, Chloroform-d)

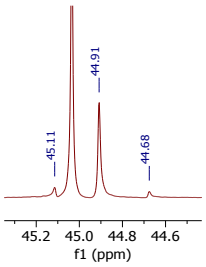


(*S*)-Ibuprofen (6a)

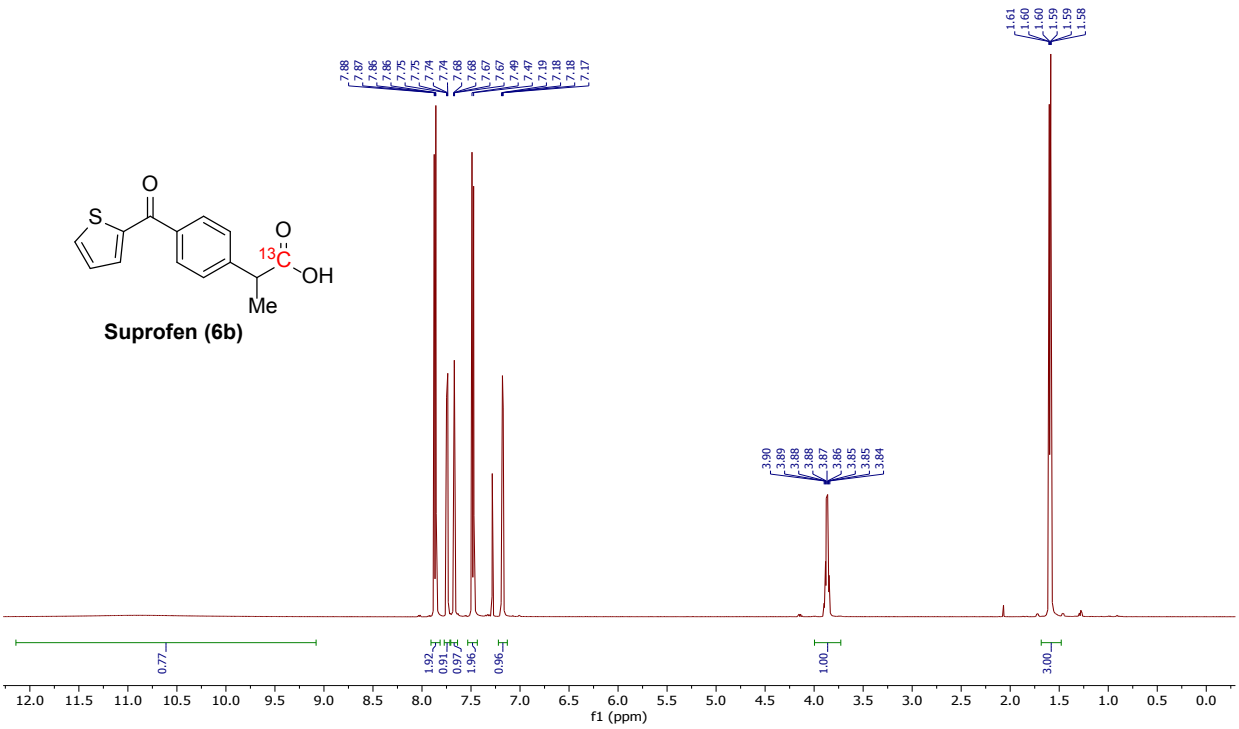
126 MHz, Chloroform-d)



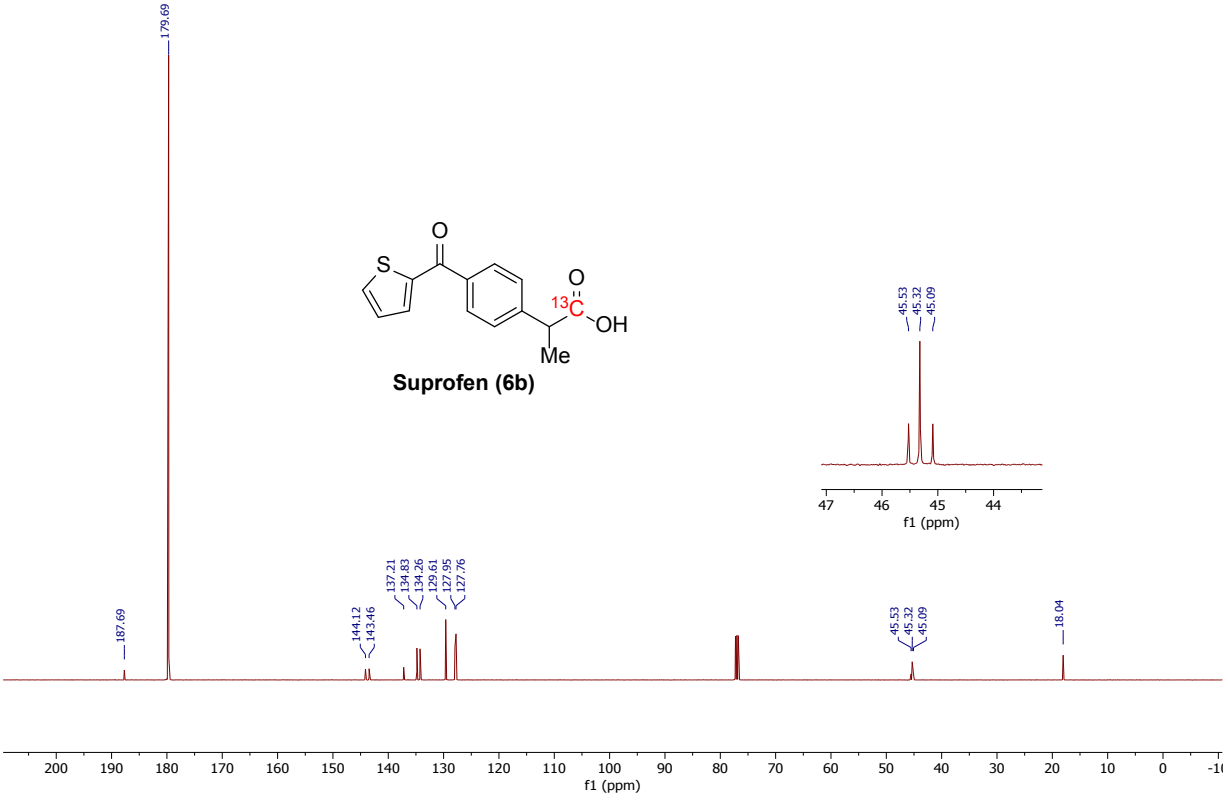
(*S*)-Ibuprofen (6a)



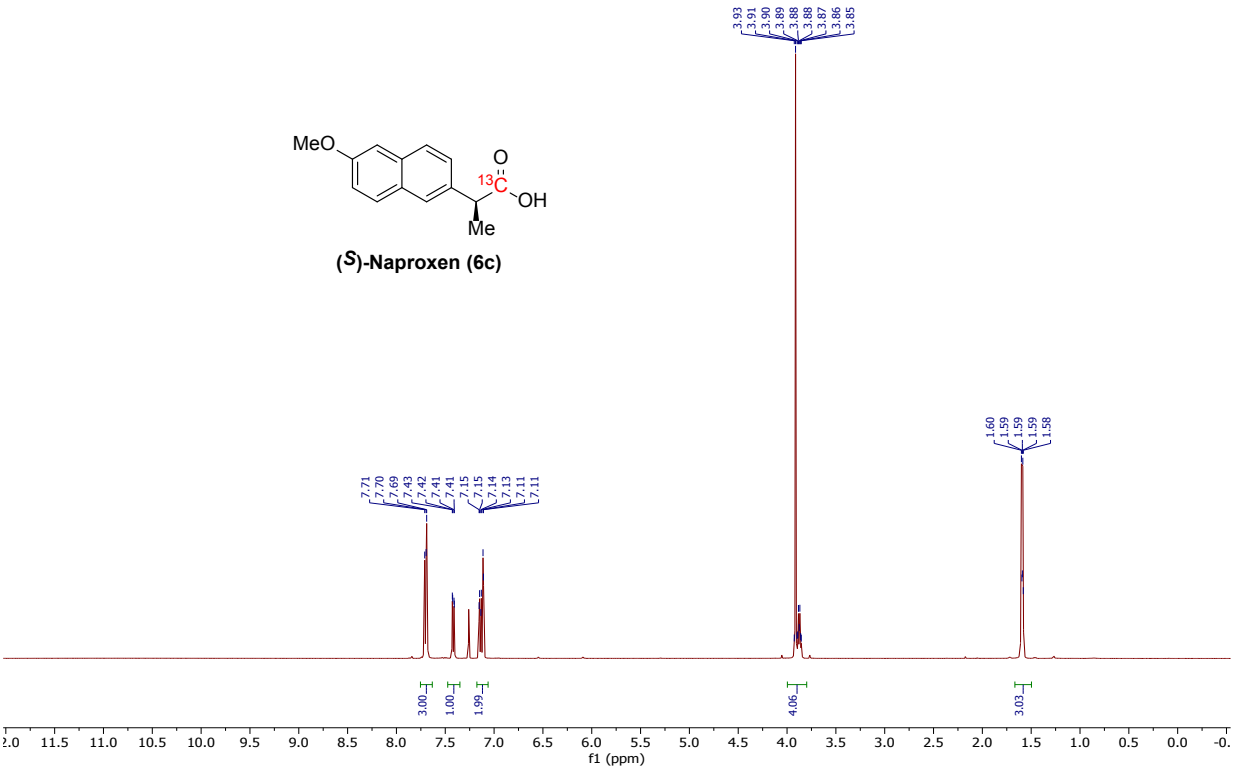
(500 MHz, Chloroform-d)



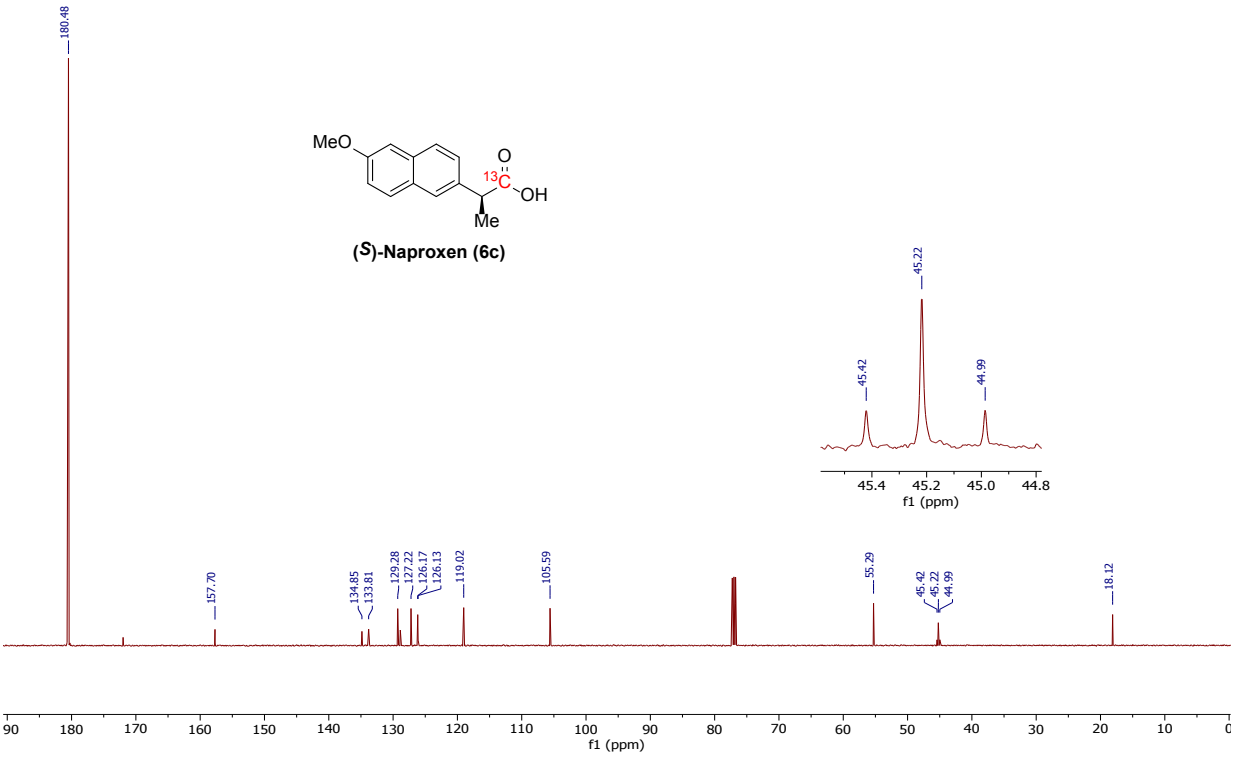
(126 MHz, Chloroform-d)

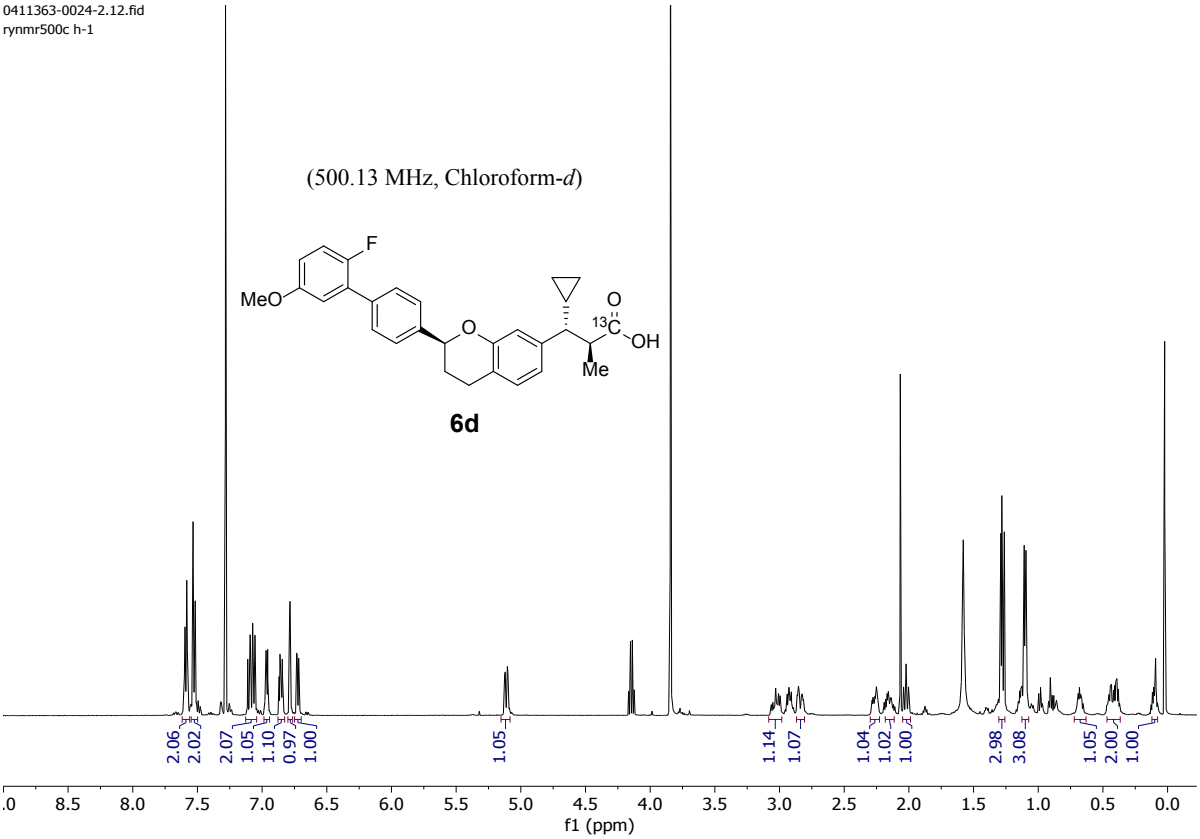


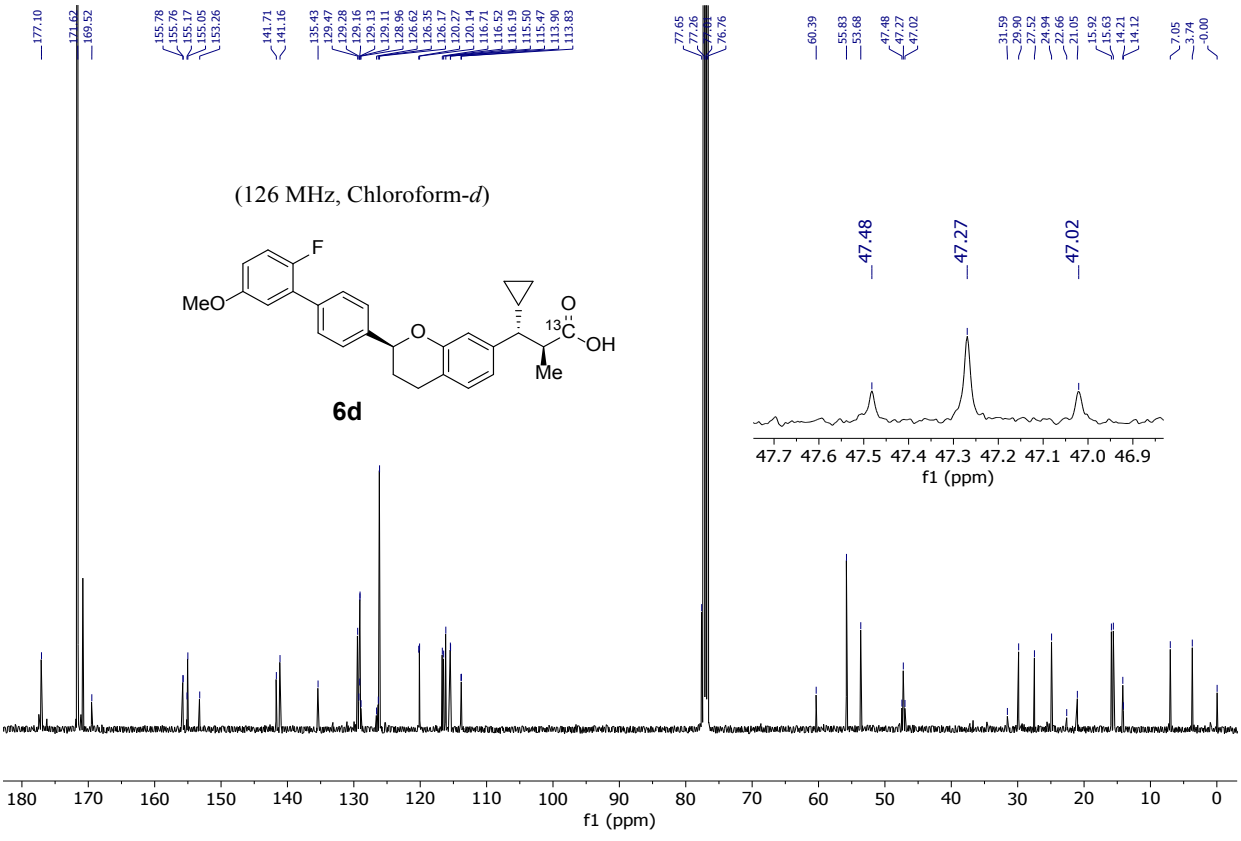
(500 MHz, Chloroform-d)



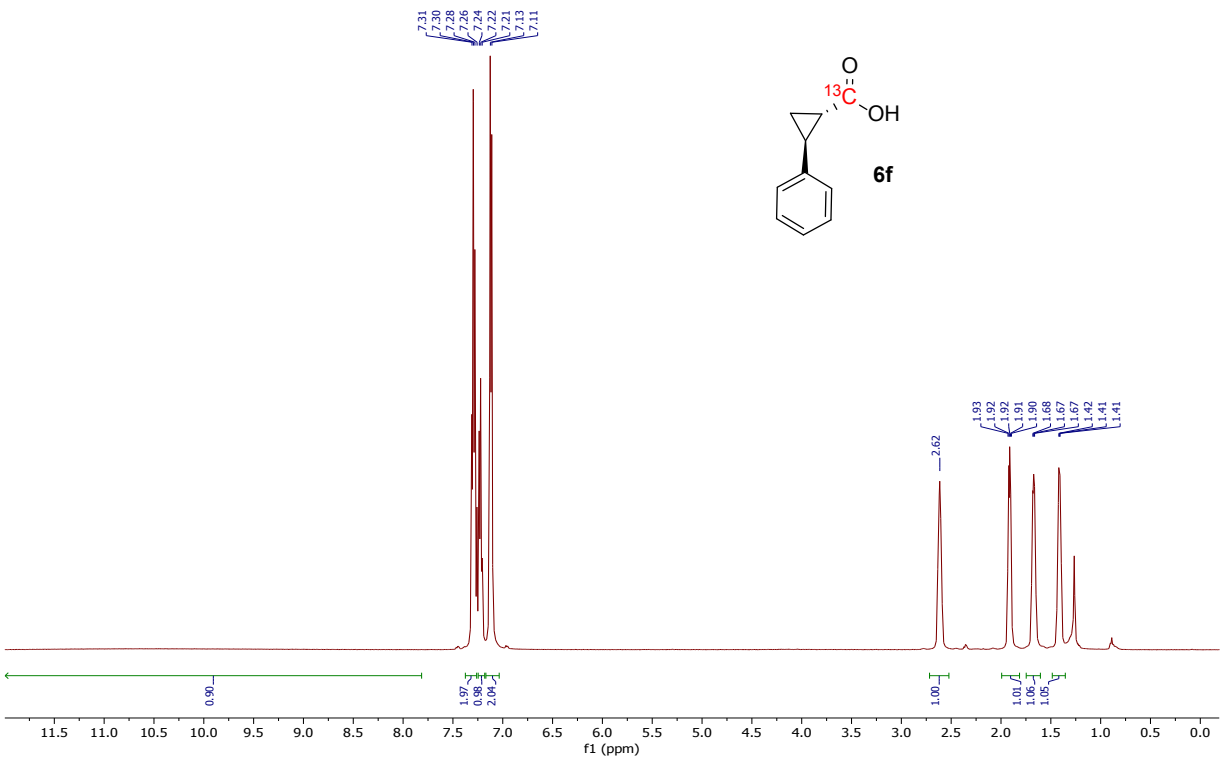
(126 MHz, Chloroform-d)




0411363-0024-2.12.fid
rynmr500c h-1
(500.13 MHz, Chloroform-d)
F
MeO
O
O
13C
OH
Me
6d
2.06
2.02
2.07
1.05
1.10
0.97
1.00
1.05
1.14
1.07
1.04
1.02
1.00
2.98
3.08
1.05
2.00
1.00
f1 (ppm)

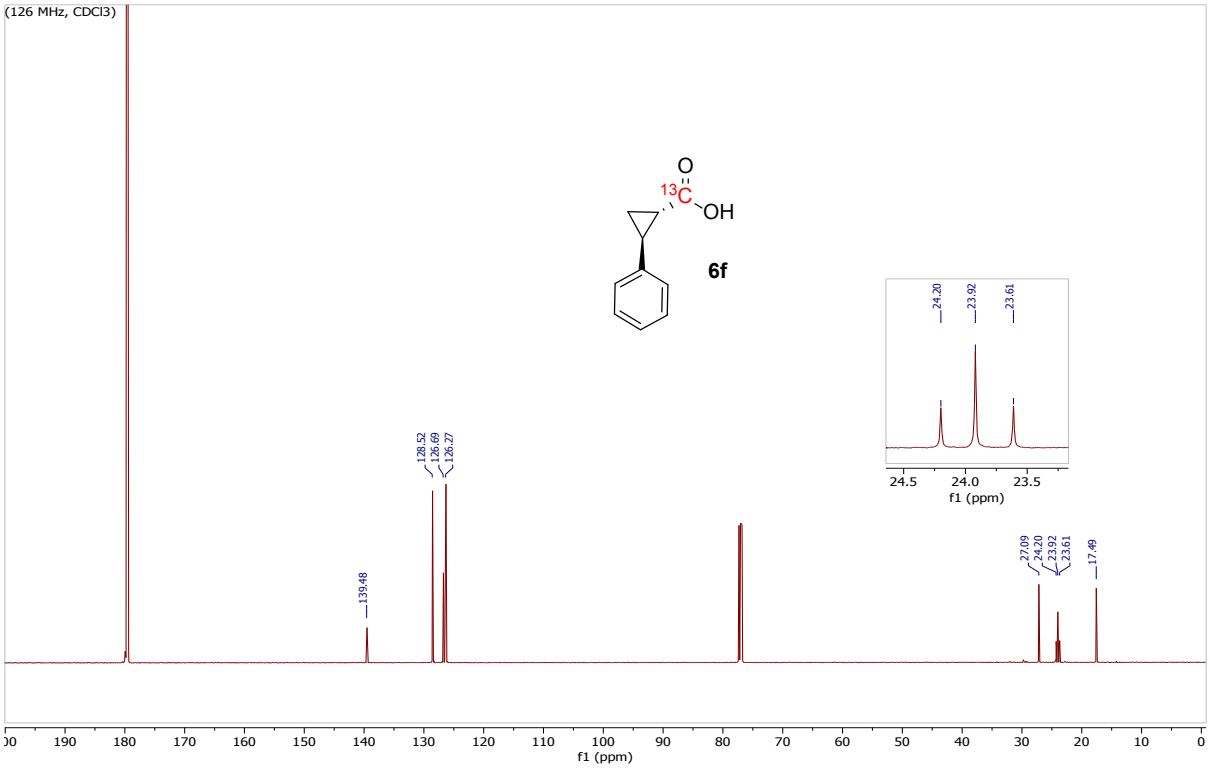

177.10
171.62
169.52
155.78
155.76
155.17
155.05
153.26
141.71
141.16
135.43
129.47
129.28
129.16
129.13
129.11
128.86
126.62
126.35
126.17
120.27
120.14
116.71
116.52
116.19
115.50
115.47
113.90
113.83
77.65
77.26
76.87
76.76
60.39
55.83
53.68
47.48
47.27
47.02
31.59
29.90
27.52
24.94
22.66
21.05
15.92
15.63
14.21
14.12
7.05
3.74
-0.00
(126 MHz, Chloroform-d)
F
MeO
O
O
13C
OH
Me
6d
47.48
47.27
47.02
47.7 47.6 47.5 47.4 47.3 47.2 47.1 47.0 46.9
f1 (ppm)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(500 MHz, CDCl3)

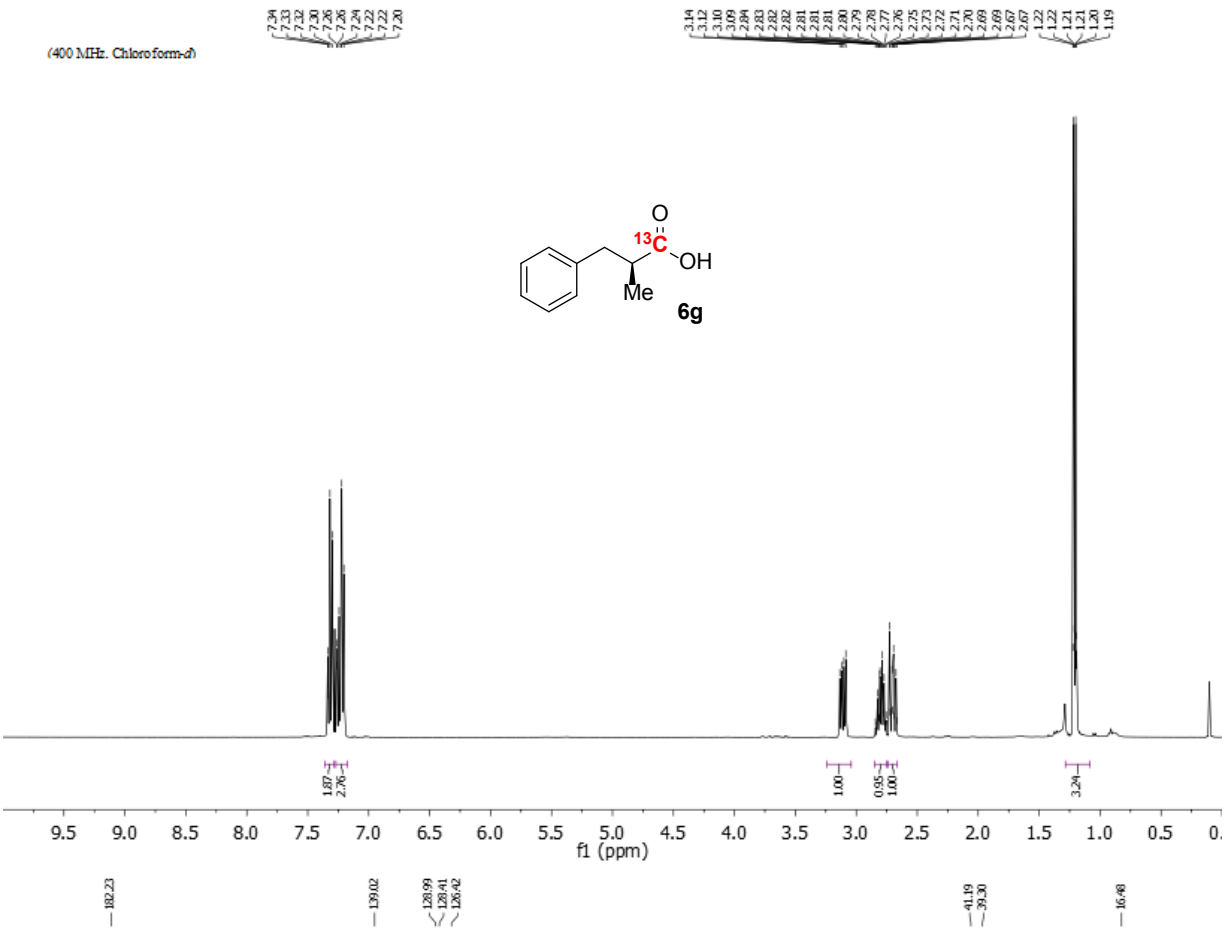


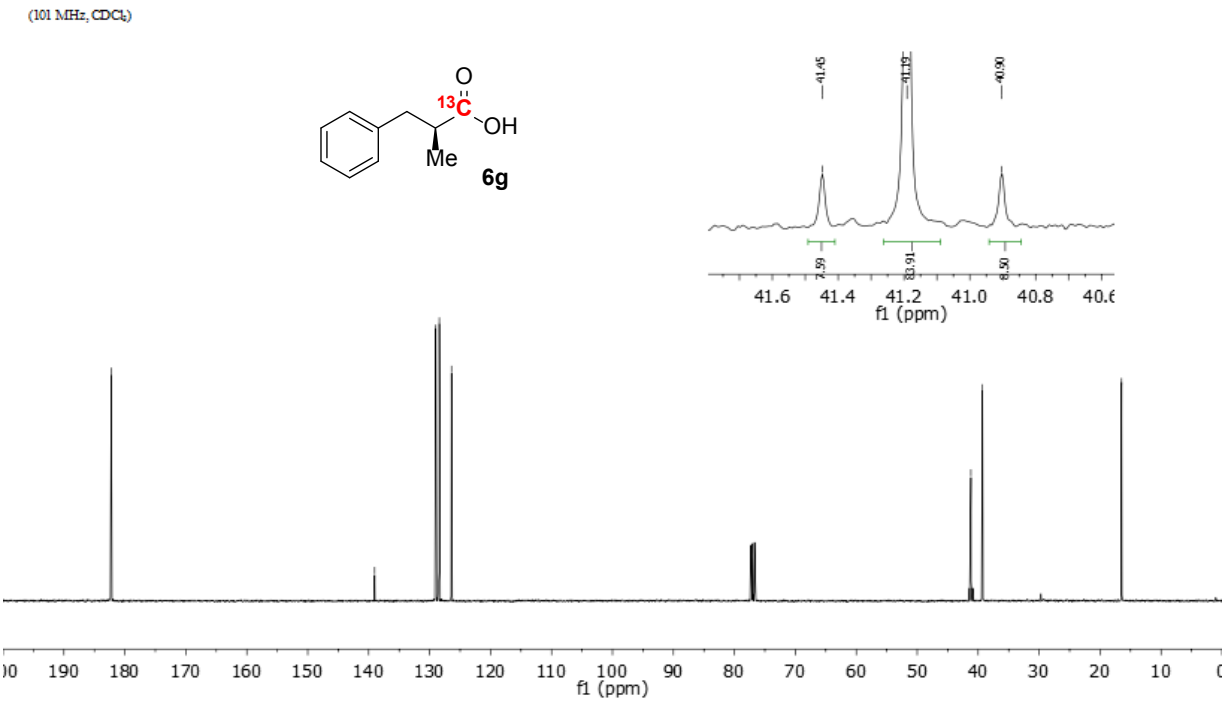
6f

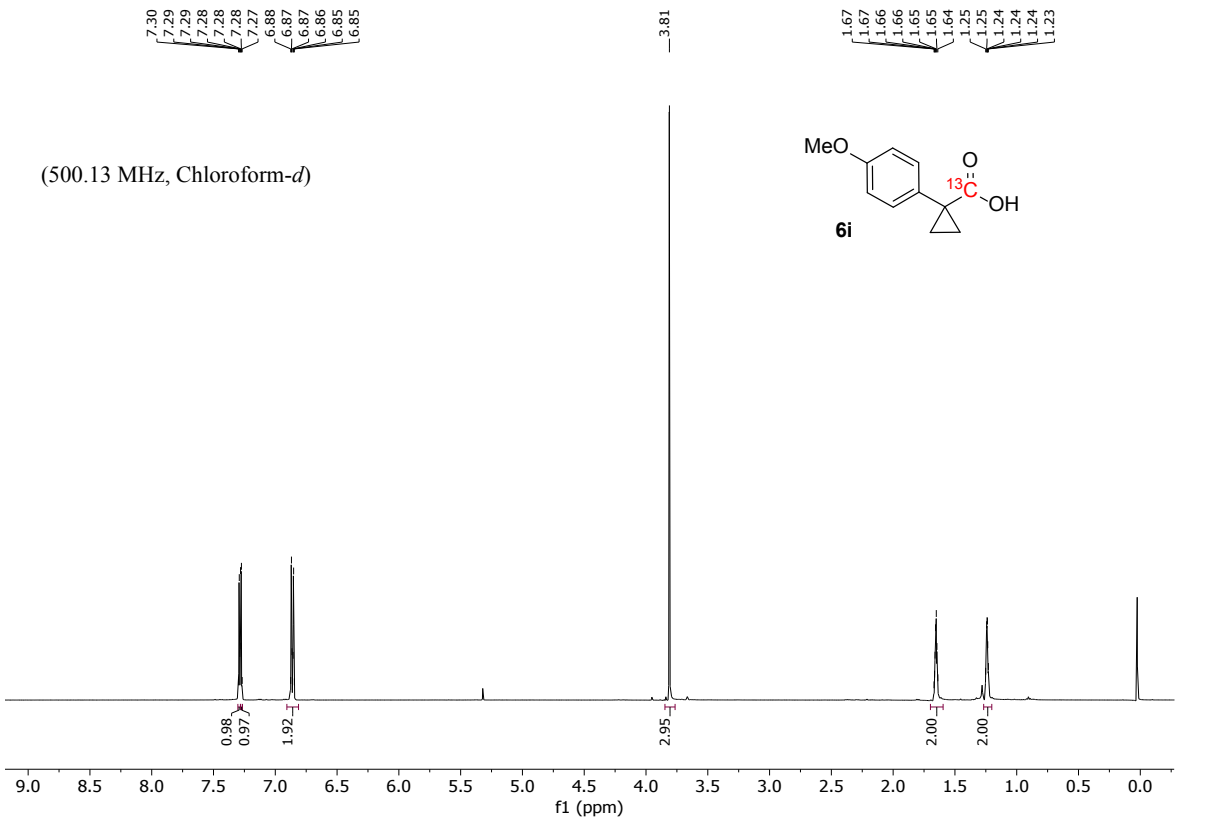
(126 MHz, CDCl3)

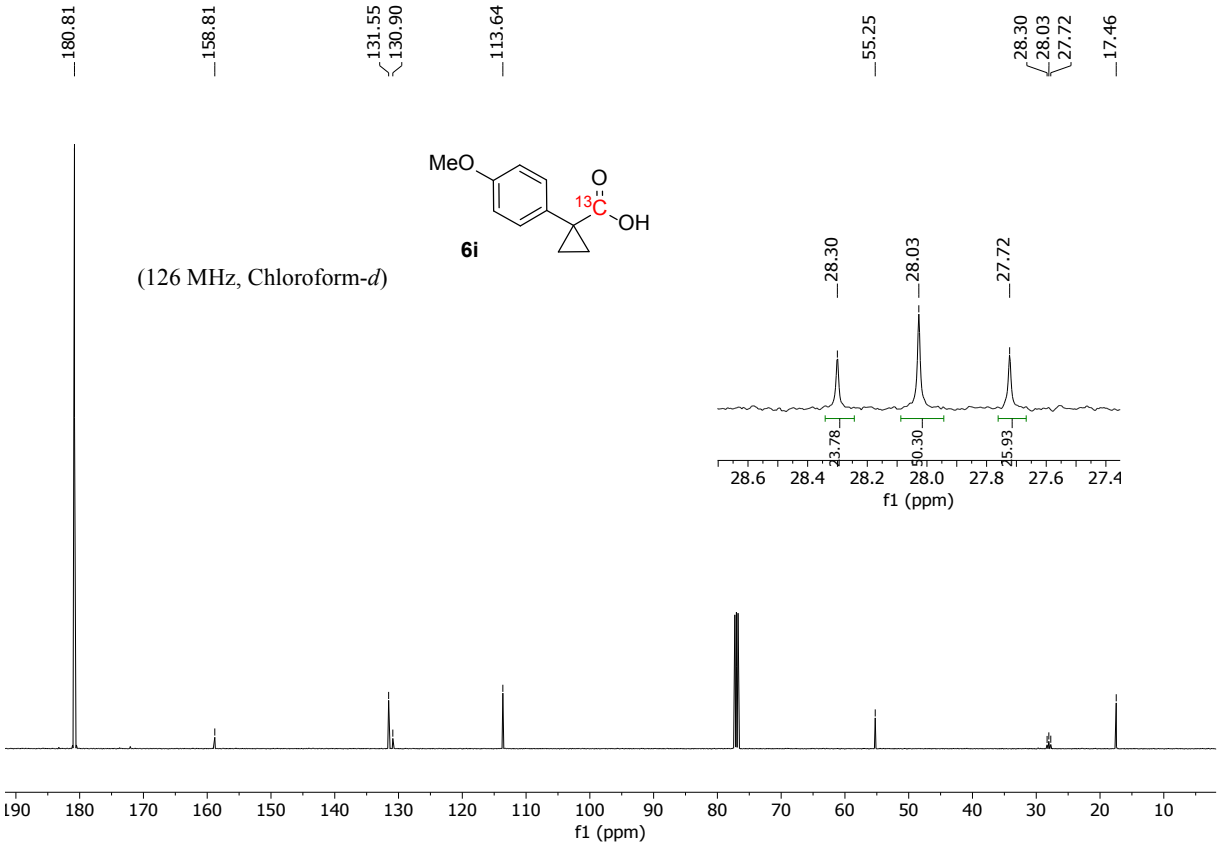


6f

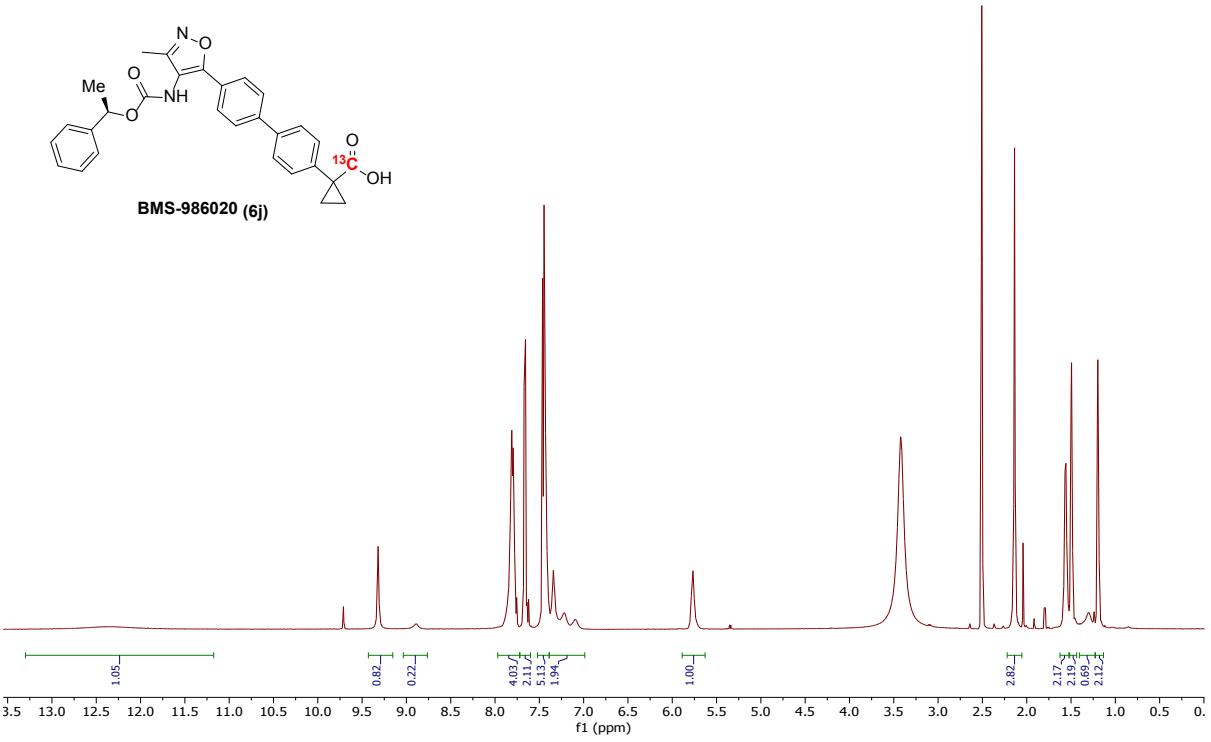

(400 MHz, Chloroform-d)
O
13C
OH
Me
6g
f1 (ppm)


(101 MHz, CDCl3)
O
13C
OH
Me
6g
f1 (ppm)

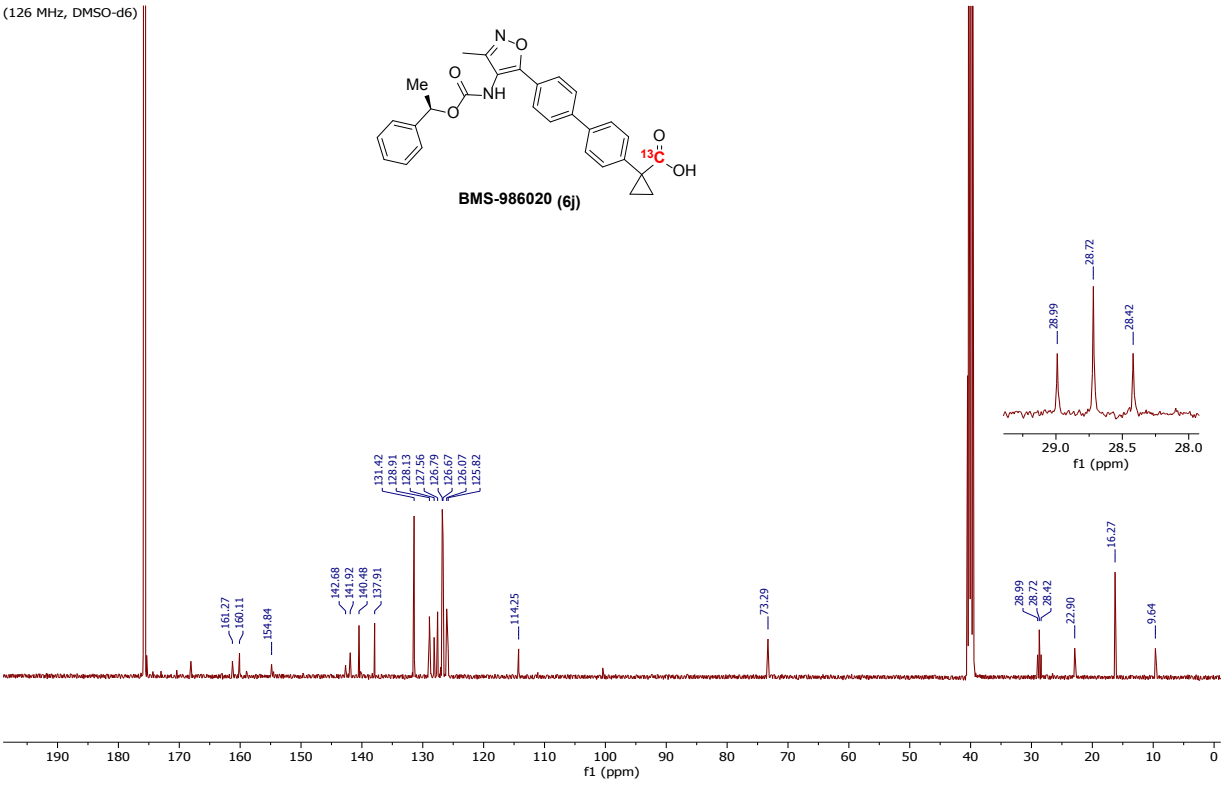

7.30
7.29
7.29
7.28
7.28
7.28
7.28
7.27
6.88
6.87
6.87
6.86
6.85
6.85
3.81
1.67
1.67
1.66
1.66
1.65
1.65
1.64
1.25
1.25
1.24
1.24
1.24
1.23
(500.13 MHz, Chloroform-d)
MeO
O
13C
OH
6i
0.98
0.97
1.92
2.95
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

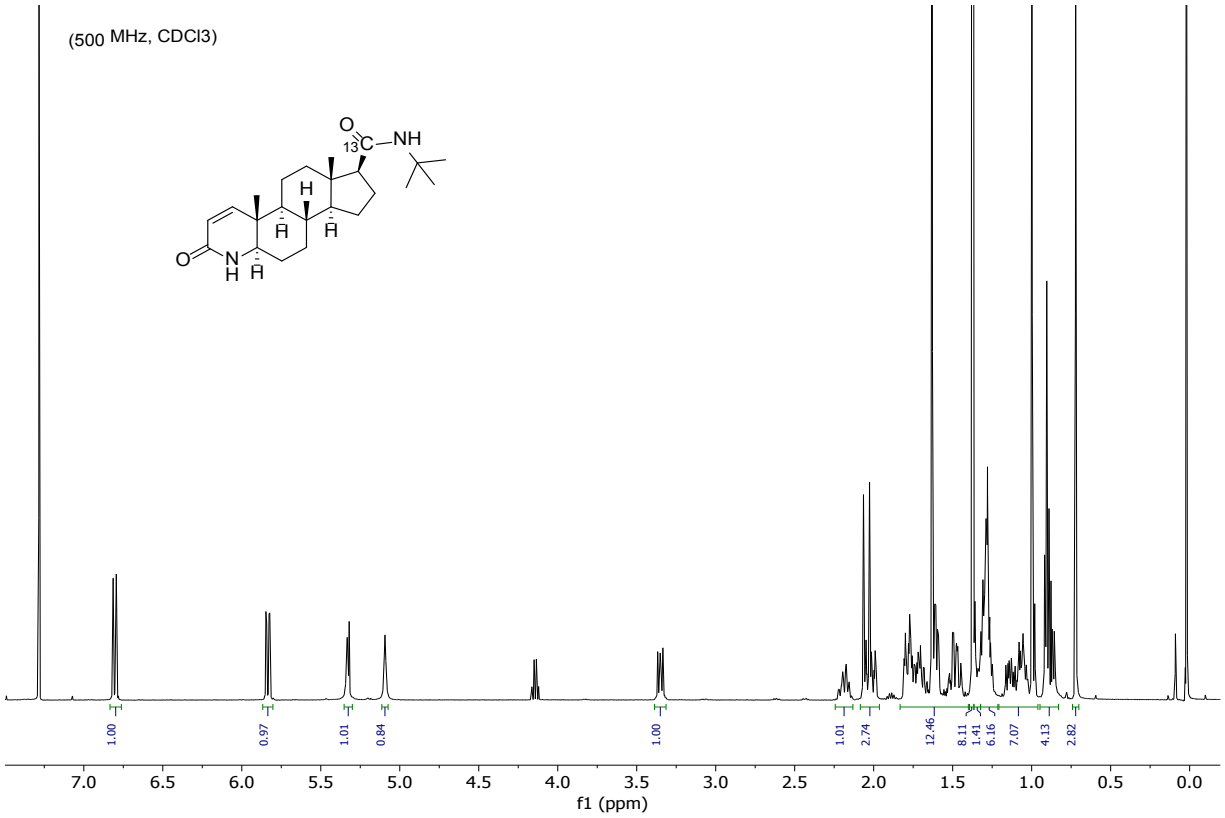

180.81
158.81
131.55
130.90
113.64
55.25
28.30
28.03
27.72
17.46
MeO
O
13C
OH
6i
(126 MHz, Chloroform-d)
28.30
28.03
27.72
23.78
50.30
25.93
28.6
28.4
28.2
28.0
27.8
27.6
27.4
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

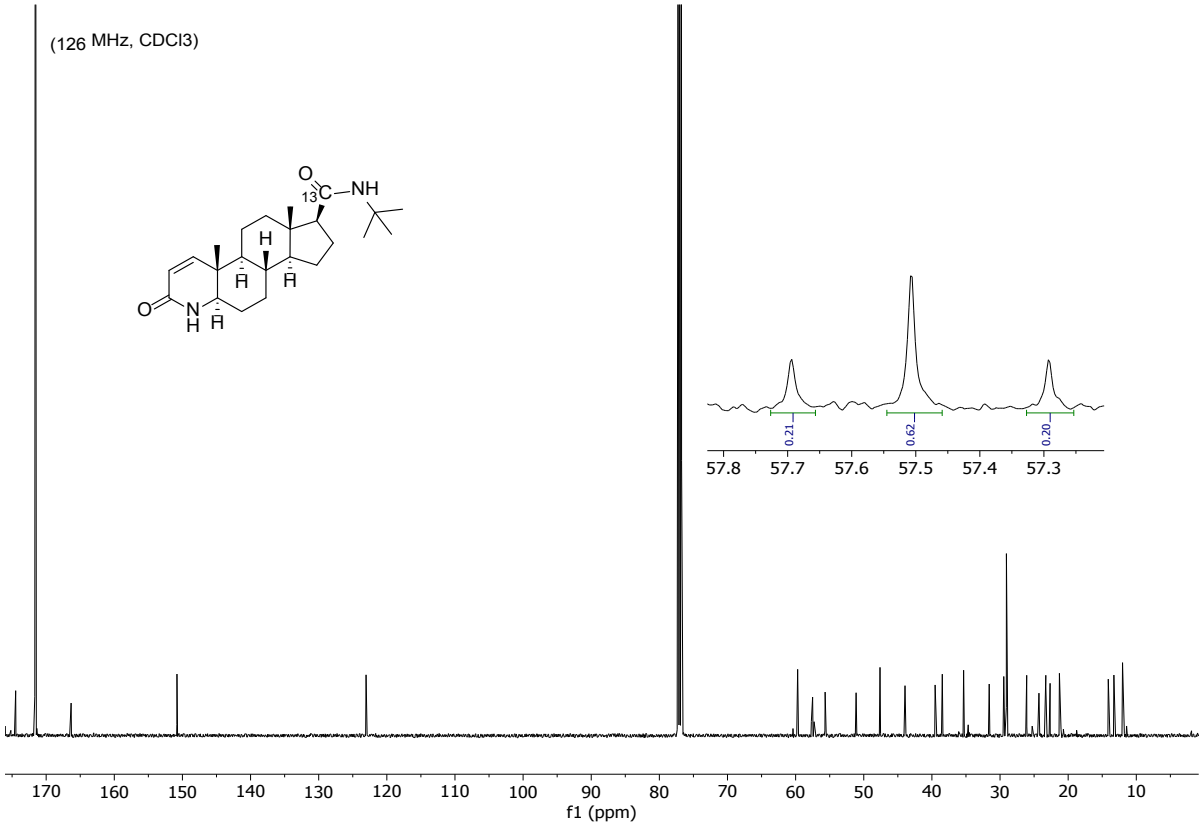
(500 MHz, DMSO-d6)



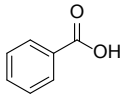
(126 MHz, DMSO-d6)



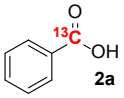

(500 MHz, CDCl3)
O
13C
NH
H
O
N
H
1.00
0.97
1.01
0.84
1.00
1.01
2.74
12.46
8.11
1.41
6.16
7.07
4.13
2.82
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


(126 MHz, CDCl3)
O
13C
NH
H
O
N
H
0.21
0.62
0.20
57.8
57.7
57.6
57.5
57.4
57.3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

4. Mass Spectral Data and IsoPat analysis: Percent isotope incorporation was determined by comparison of the mass spectral patterns of carbon-13 or carbon-14 labeled product versus authentic starting material using the IsoPat2 spreadsheet.[2] The mass spectra were tabulated for abundance vs. m/z, and these data were inputted to the Isopat2 spreadsheet, which uses its programmed algorithm to determine the relative percentage of each labeled species differentiated in the number of incorporated isotopes. Sum of these percentages give rise to the overall isotope enrichment. For carbon-14 labeled compounds, specific activity (SA) is the radioactivity per quantity of a radionuclide, expressed as Ci/mmol in this work. Carbon-14 has a maximum theoretical specific activity of 62.4 mCi per mmol, which refers to 100% of the molecules contain one carbon-14 label. Therefore, specific activity is calculated proportionally to the value of maximum theoretical specific activity – that is, multiplying overall enrichment of carbon-14 (%) by the maximum theoretical specific activity of 62.4 mCi per mmol.



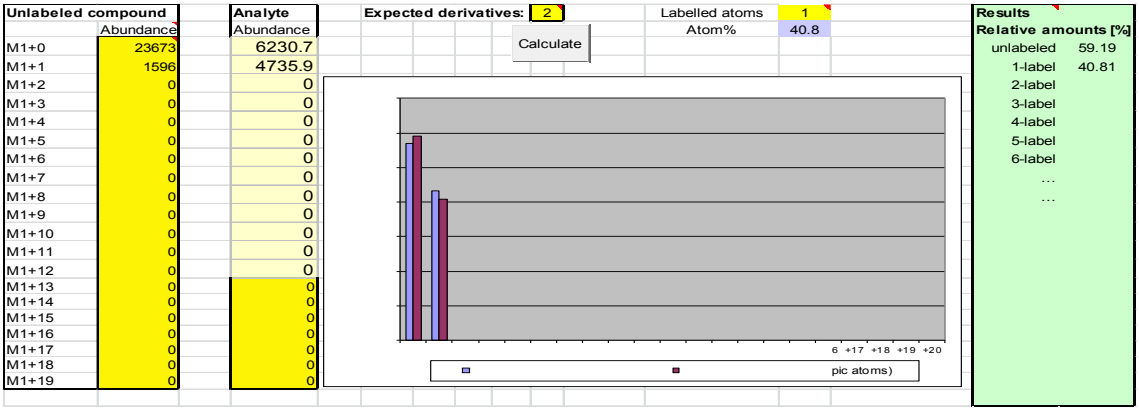
Exact Mass: 122.0368

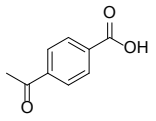


2a

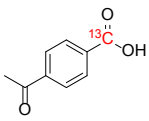
Exact Mass: 123.0401

Isopat Calculation



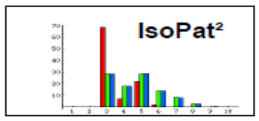


Exact Mass: 164.0473



2c

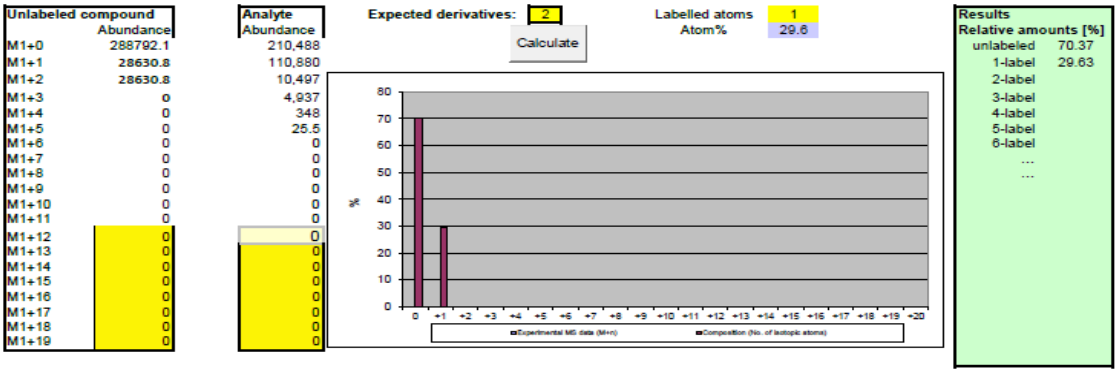
Exact Mass: 165.0507



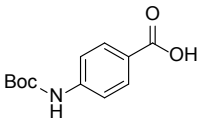
Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

© Christian C. Gruber, Wolfgang Kroutil 2006.

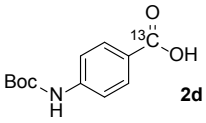
Changes and additions to the original and excellent IsoPat² have been made by W J S Lockley (Mod21) to facilitate its use by isotopic chemists. For details of the original spreadsheet see: C. C. Gruber, G. Oberdorfer, C. V. Voss, J. M. Kremsner, C. O Kappe, W. Kroutil, J. Org. Chem. 2007, 72, 5778-5783. The original IsoPat² Excel spreadsheet can be downloaded from ftp://biocatalysis.uni-graz/pub/IsoPat2/. Further supporting data is available at http://pubs.acs.org



Analyte =5002729_003-2c



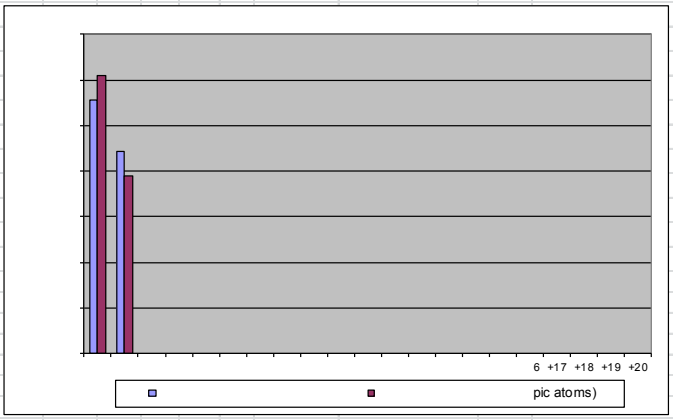
Exact Mass: 237.1001

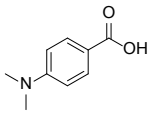


2d

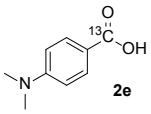
Exact Mass: 238.1035

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1	Results
	Abundance	Abundance		Atom% 39.0	Relative amounts [%]
M1+0	281493	162749	Calculate		unlabeled 60.99
M1+1	40893	130195			1-label 39.01
M1+2	0	0			2-label
M1+3	0	0			3-label
M1+4	0	0			4-label
M1+5	0	0			5-label
M1+6	0	0			6-label
M1+7	0	0			…
M1+8	0	0			…
M1+9	0	0			
M1+10	0	0			
M1+11	0	0			
M1+12	0	0			
M1+13	0	0			
M1+14	0	0			
M1+15	0	0			
M1+16	0	0			
M1+17	0	0			
M1+18	0	0			
M1+19	0	0			





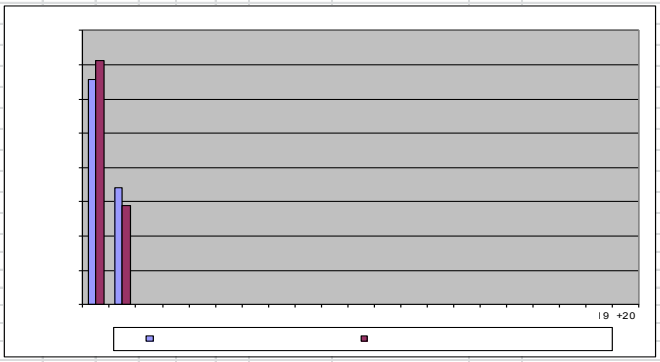
Exact Mass: 165.08

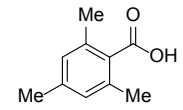


2e

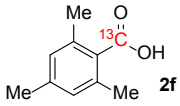
Exact Mass: 166.0823

	Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1	Results
		Abundance	Abundance		Atom% 28.8	Relative amounts [%]
166	M1+0	1177493	1067693	Calculate		unlabeled 71.20
167	M1+1	129496	554799			1-label 28.80
	M1+2	0	0			2-label
	M1+3	0	0			3-label
	M1+4	0	0			4-label
	M1+5	0	0			5-label
	M1+6	0	0			6-label
	M1+7	0	0			…
	M1+8	0	0			…
	M1+9	0	0			
	M1+10	0	0			
	M1+11	0	0			
	M1+12	0	0			
	M1+13	0	0			
	M1+14	0	0			
	M1+15	0	0			
	M1+16	0	0			
	M1+17	0	0			
	M1+18	0	0			
	M1+19	0	0			



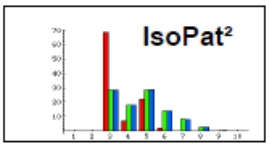


Exact Mass: 164.0837



2f

Exact Mass: 165.0871



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

© Christian C. Gruber, Wolfgang Kroutil 2006.

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Unlabeled compound	Abundance
M1+0	239090.1
M1+1	27656.4
M1+2	2175.1
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

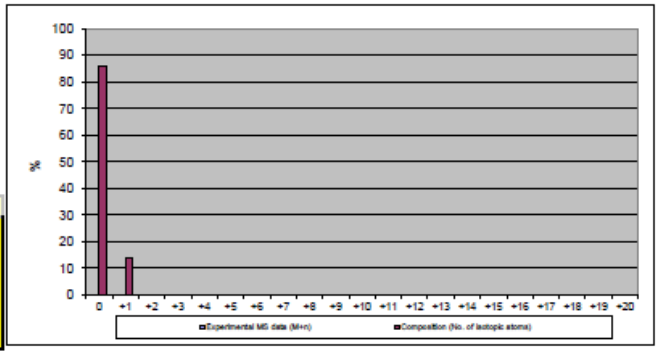
Analyte	Abundance
	176,796
	48,735
	4,701
	1,334
	67
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

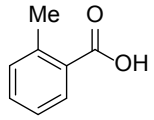
Calculate

Labelled atoms 1

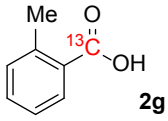
Atom% 13.8



Results	
Relative amounts [%]	
unlabeled	86.21
1-label	13.79
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	

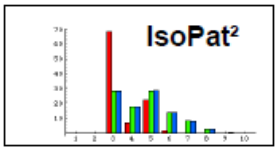


Exact Mass: 136.0524



2g

Exact Mass: 137.0558



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

© Christian C. Gruber, Wolfgang Kroutil 2006.

Changes and additions to the original and excellent IsoPat² have been made by W J S Lockley (Mod21) to facilitate its use by isotopic chemists. For details of the original spreadsheet see: C. C. Gruber, G. Oberdorfer, C. V. Voss, J. M. Kremsner, C. O Kappe, W. Kroutil, J. Org. Chem. 2007, 72, 5778-5783. The original IsoPat² Excel spreadsheet can be downloaded from ftp://biocatalysis.uni-graz/pub/IsoPat2/. Further supporting data is available at http://pubs.acs.org

Unlabeled compound	Abundance
M1+0	63291.2
M1+1	5424.3
M1+2	0
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

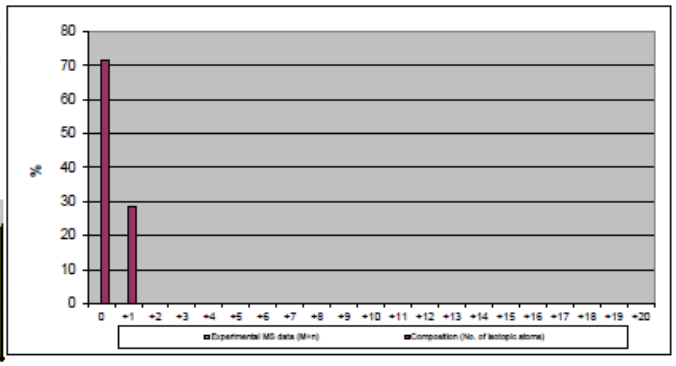
Analyte	Abundance
	15,352
	7,346
	894
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

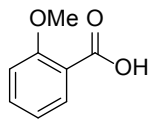
Calculate

Labelled atoms 1

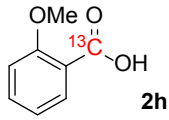
Atom% 28.3



Results	
Relative amounts [%]	
unlabeled	71.68
1-label	28.32
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	

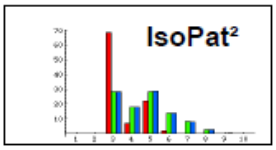


Exact Mass: 152.0473



2h

Exact Mass: 153.0507



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

© Christian C. Gruber, Wolfgang Kroutil 2006.

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Unlabeled compound	Abundance
M1+0	114919.1
M1+1	9875
M1+2	3727.4
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

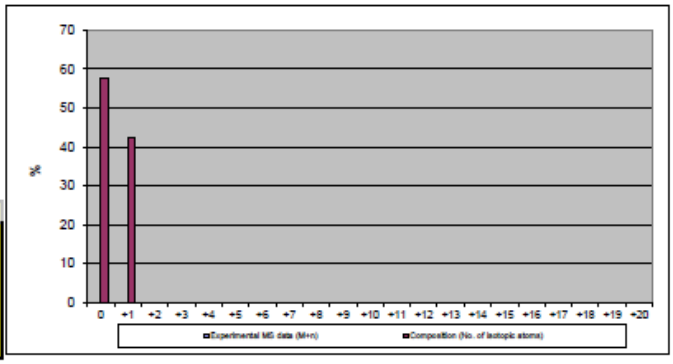
Analyte	Abundance
	31,002
	25,592
	2,208
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

Calculate

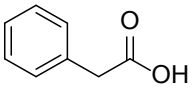
Labelled atoms 1

Atom% 42.4

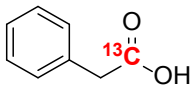


Results	
Relative amounts [%]	
unlabeled	57.57
1-label	42.43
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	

Analyte =5002729_003-2g



Exact Mass: 136.0524



2k

Exact Mass: 137.0558

Unlabeled compound	Abundance
M1+0	36123
M1+1	3637
M1+2	0
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

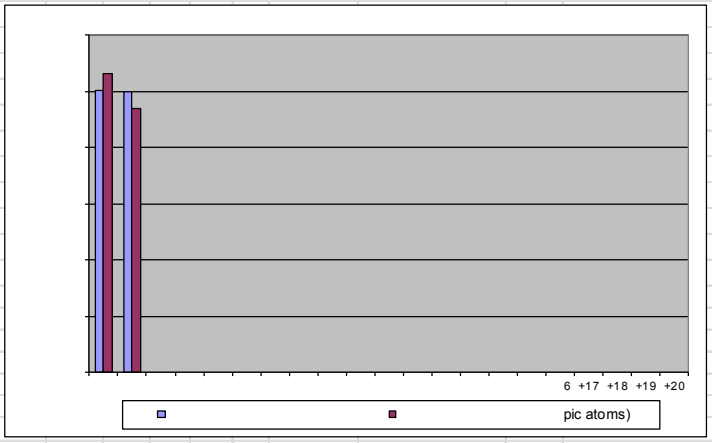
Analyte	Abundance
	8997.7
	8947.7
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

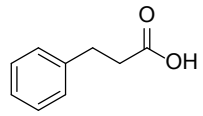
Calculate

Labelled atoms 1

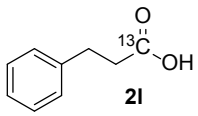
Atom% 46.9



Results	
Relative amounts [%]	
unlabeled	53.08
1-label	46.92
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



Exact Mass: 150.0681

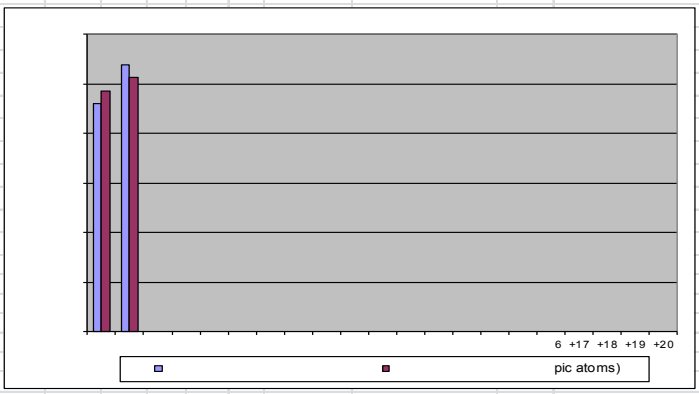


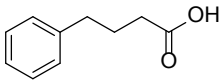
2l

Exact Mass: 151.0714

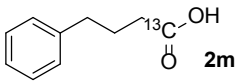
Isopat Calculation

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1	Results
	Abundance	Abundance	Calculate	Atom% 51.4	Relative amounts [%]
M1+0	102821	26174			unlabeled 48.60
M1+1	10210	30582			1-label 51.40
M1+2	0	0			2-label
M1+3	0	0			3-label
M1+4	0	0			4-label
M1+5	0	0			5-label
M1+6	0	0			6-label
M1+7	0	0			…
M1+8	0	0			…
M1+9	0	0			
M1+10	0	0			
M1+11	0	0			
M1+12	0	0			
M1+13	0	0			
M1+14	0	0			
M1+15	0	0			
M1+16	0	0			
M1+17	0	0			
M1+18	0	0			
M1+19	0	0			





Exact Mass: 164.0837

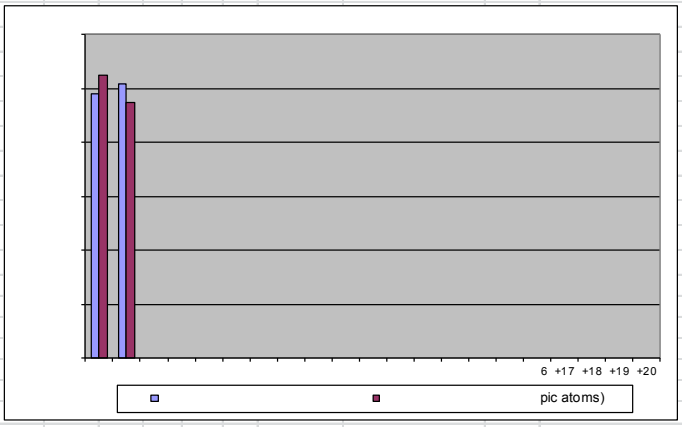


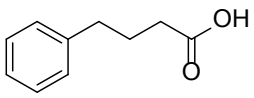
2m

Exact Mass: 165.0871

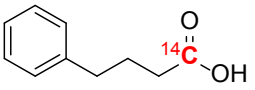
Isopat Calculation

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1	Results
	Abundance	Abundance	Calculate	Atom% 47.5	Relative amounts [%]
M1+0	148632	21524.4			unlabeled 52.52
M1+1	17456	22286.7			1-label 47.48
M1+2	0	0			2-label
M1+3	0	0			3-label
M1+4	0	0			4-label
M1+5	0	0			5-label
M1+6	0	0			6-label
M1+7	0	0			…
M1+8	0	0			…
M1+9	0	0			
M1+10	0	0			
M1+11	0	0			
M1+12	0	0			
M1+13	0	0			
M1+14	0	0			
M1+15	0	0			
M1+16	0	0			
M1+17	0	0			
M1+18	0	0			
M1+19	0	0			





Exact Mass: 164.0837

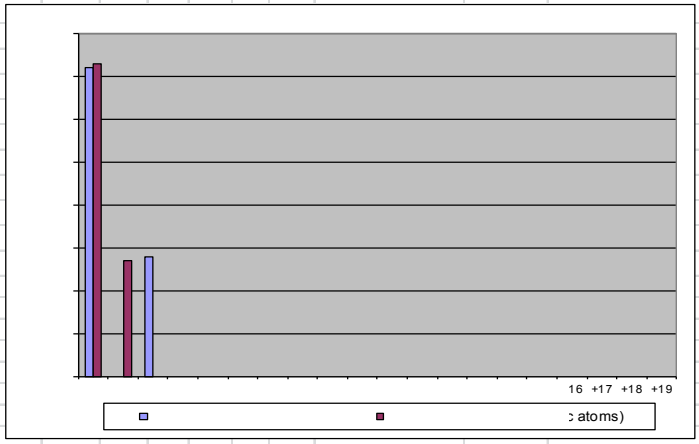


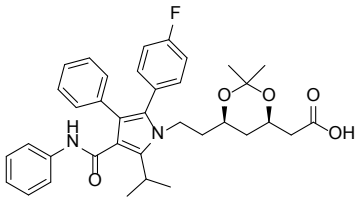
2n

Exact Mass: 166.0870

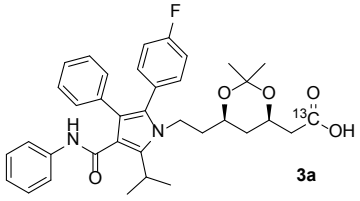
MW tracer mg/mmol	290.834		14C
SA mCi/mmol if 14C	16.848		14C
SA uCi/mg if 14C	57.9298		14C

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms	1	Results
	Abundance	Abundance		Atom%	27.0	Relative amounts [%]
M1+0	58330	14025	Calculate	Mole Weight AVE:	290.294 g/mol	unlabeled 73.0
M1+1	0	0		Solution Count:	0 mCi/mL	1-label 27.0
M1+2	1079	5448.4				2-label
M1+3	0	0				3-label
M1+4	0	0				4-label
M1+5	0	0				5-label
M1+6	0	0				6-label
M1+7	0	0				
M1+8	0	0				
M1+9	0	0				
M1+10	0	0				
M1+11	0	0				
M1+12	0	0				
M1+13	0	0				
M1+14	0	0				
M1+15	0	0				
M1+16	0	0				
M1+17	0	0				
M1+18	0	0				
M1+19	0	0				





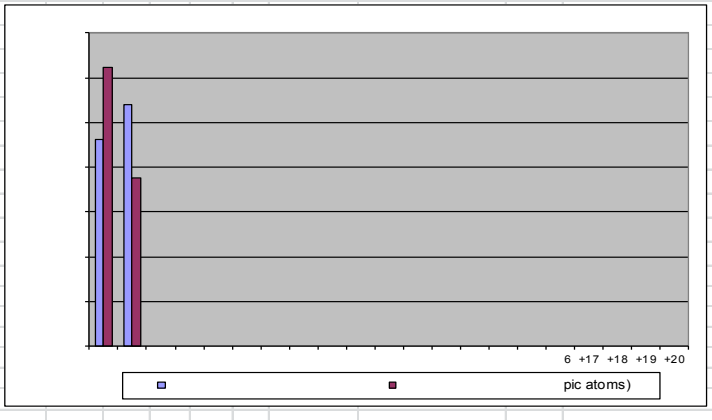
Exact Mass: 598.2843

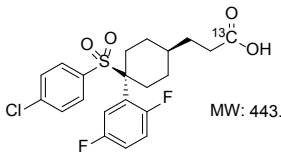


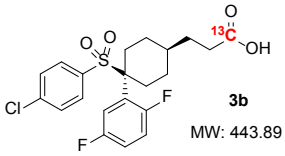
3a

Exact Mass: 599.2877

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms	1	Results
	Abundance	Abundance		Atom%	37.8	Relative amounts [%]
M1+0	994560	1305537	Calculate			unlabeled 62.23
M1+1	407639	1524145				1-label 37.77
M1+2	0	0				2-label
M1+3	0	0				3-label
M1+4	0	0				4-label
M1+5	0	0				5-label
M1+6	0	0				6-label
M1+7	0	0				…
M1+8	0	0				…
M1+9	0	0				
M1+10	0	0				
M1+11	0	0				
M1+12	0	0				
M1+13	0	0				
M1+14	0	0				
M1+15	0	0				
M1+16	0	0				
M1+17	0	0				
M1+18	0	0				
M1+19	0	0				







Unlabeled compound	Abundance
M1+0	222528
M1+1	57061
M1+2	0
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

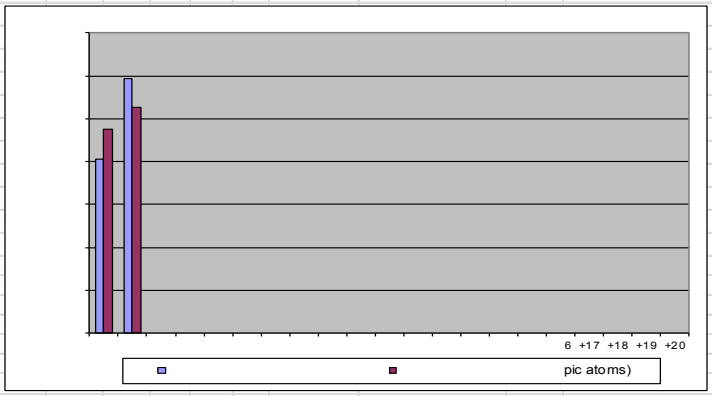
Analyte	Abundance
M1+0	47078.4
M1+1	68852.4
M1+2	0
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

Expected derivatives: 2

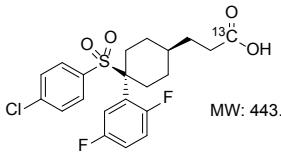
Calculate

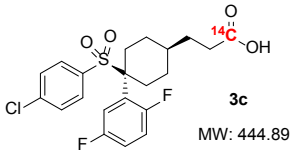
Labelled atoms 1

Atom% 52.5



Results	
Relative amounts [%]	
unlabeled	47.48
1-label	52.52
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	





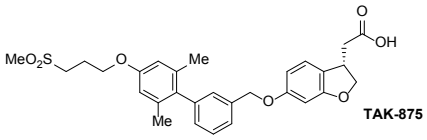
Carbon-14 Specific Activity From Mass Spectrometry

SPACTCAL ver2.10

[M-H] [M+H]	Reference	Percent of Parent	Percent of Total	Carbon-14 Labeled	Percent of Parent	Percent of Total
497	265,724	100.00%	55.558%	87,370	100.00%	35.141%
498	69,964	26.33%	14.628%	22,548	25.81%	9.069%
499	105,049	39.53%	21.964%	86,761	99.30%	34.896%
500	28,017	10.54%	5.858%	23,726	27.16%	9.543%
501	8,573	3.23%	1.792%	22,613	25.88%	9.095%
502	951	0.36%	0.199%	4,984	5.70%	2.004%
503	0	0.00%	0.000%	623	0.71%	0.251%
504	0	0.00%	0.000%	0	0.00%	0.000%
505	0	0.00%	0.000%	0	0.00%	0.000%
506	0	0.00%	0.000%	0	0.00%	0.000%
507	0	0.00%	0.000%	0	0.00%	0.000%
508	0	0.00%	0.000%	0	0.00%	0.000%
509	0	0.00%	0.000%	0	0.00%	0.000%
510	0	0.00%	0.000%	0	0.00%	0.000%
511	0	0.00%	0.000%	0	0.00%	0.000%
512	0	0.00%	0.000%	0	0.00%	0.000%
513	0	0.00%	0.000%	0	0.00%	0.000%
Total	478,279			248,625		

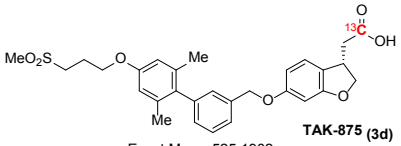
Molecular Weight	[M-H] [M+H]	# 14C Atoms	Tracer Intensity	Reference Ion Intensity	Net Tracer Intensity	Theoretical mCi/mmol	Measured mCi/mmol	Mol. Wt. Calculation	Tracer % of Total (corr)
497.800	497	0	87,370	100.00%	87,370	0.0	0.0000	311.57	62.59%
499.789	499	1	86,761	39.53%	52,221	62.4	23.3438	186.97	37.41%
501.778	501	2	22,613	3.23%	0	124.8	0.0000	0.00	0.00%
503.767	503	3	623	0.00%	0	187.2	0.0000	0.00	0.00%
505.756	505	4	0	0.00%	0	249.6	0.0000	0.00	0.00%
507.745	507	5	0	0.00%	0	312.0	0.0000	0.00	0.00%
509.734	509	6	0	0.00%	0	374.4	0.0000	0.00	0.00%
511.723	511	7	0	0.00%	0	436.8	0.0000	0.00	0.00%
513.712	513	8	0	0.00%	0	499.2	0.0000	0.00	0.00%
Total	Total		197,368		139,591		23.3438	498.544	

mCi/mmol	23.344
Mol. Wt.	498.544
uCi/mg:	46.8239
mCi/mL:	1
mg/mL:	21.35663461



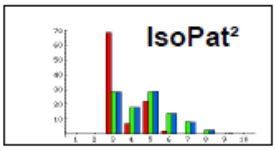
TAK-875

Exact Mass: 524.1869



TAK-875 (3d)

Exact Mass: 525.1902



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

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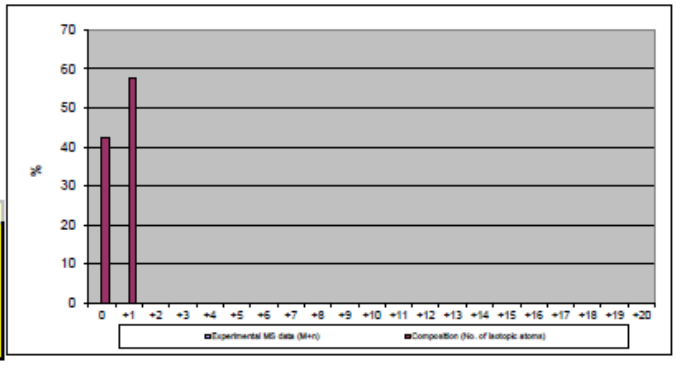
Unlabeled compound	Abundance	Analyte Abundance
M1+0	224613	86,340
M1+1	72800.8	143,756
M1+2	25485.7	49,611
M1+3	5273.2	18,740
M1+4	0	4,478
M1+5	0	0
M1+6	0	0
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

Expected derivatives: 2

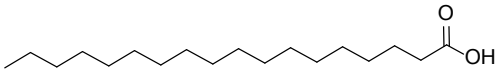
Calculate

Labelled atoms 1

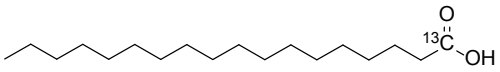
Atom% 57.5



Results	
Relative amounts [%]	
unlabeled	42.48
1-label	57.52
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



Exact Mass: 284.2715



Exact Mass: 285.2749

3e

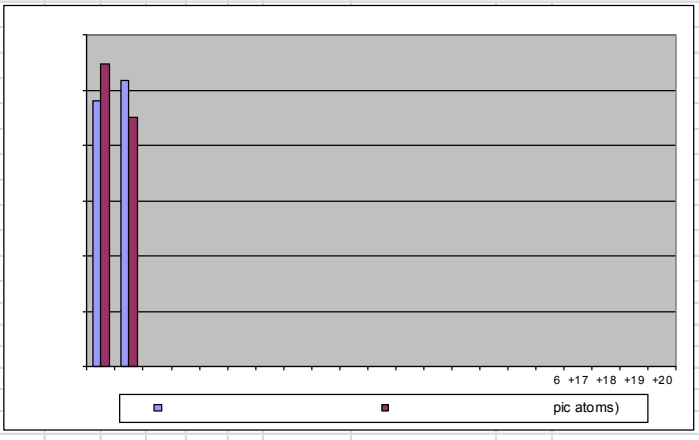
Unlabeled compound	Abundance	Analyte Abundance
M1+0	26876	5965.1
M1+1	5685	6435.5
M1+2	0	0
M1+3	0	0
M1+4	0	0
M1+5	0	0
M1+6	0	0
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

Expected derivatives: 2

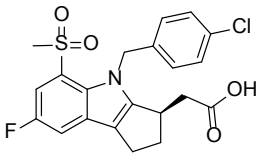
Calculate

Labelled atoms 1

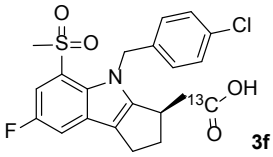
Atom% 45.1



Results	
Relative amounts [%]	
unlabeled	54.88
1-label	45.12
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



Exact Mass: 435.0707



3f

Exact Mass: 436.0741

Unlabeled compound	Abundance
M1+0	20580
M1+1	5355
M1+2	0
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

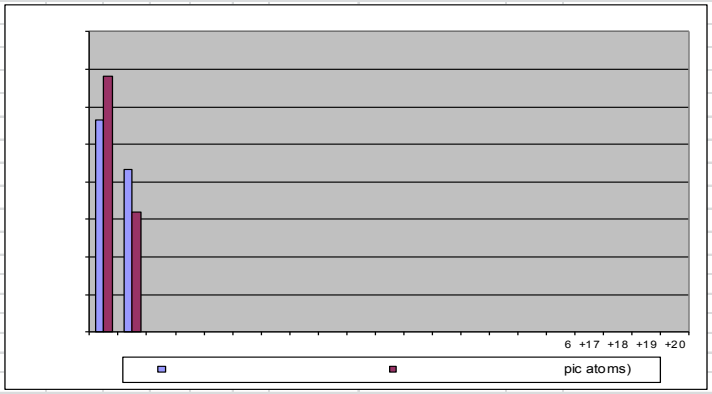
Analyte	Abundance
	32852.1
	25234
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

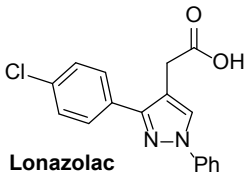
Calculate

Labelled atoms 1

Atom% 32.0

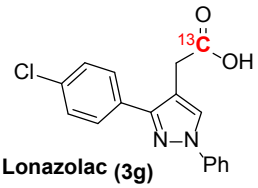


Results	
Relative amounts [%]	
unlabeled	68.04
1-label	31.96
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



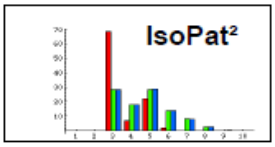
Lonazolac

Exact Mass: 312.0666



Lonazolac (3g)

Exact Mass: 313.0699



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

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Unlabeled compound	Abundance
M1+0	80705.6
M1+1	16025.7
M1+2	26670.1
M1+3	5327.2
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

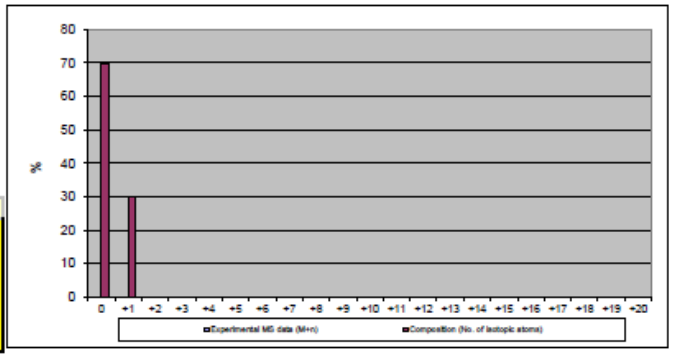
Analyte	Abundance
	37,154
	23,127
	15,062
	8,431
	1,417
	281.2
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

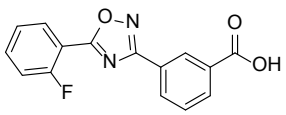
Calculate

Labelled atoms 1

Atom% 30.1

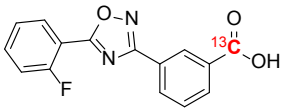


Results	
Relative amounts [%]	
unlabeled	69.89
1-label	30.11
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



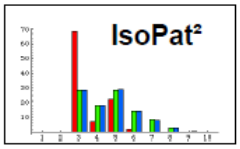
Ataluren

Exact Mass: 284.0597



Ataluren (3h)

Exact Mass: 285.0631



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

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Unlabeled compound	Abundance
M1+0	223108
M1+1	39026
M1+2	4726
M1+3	0
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

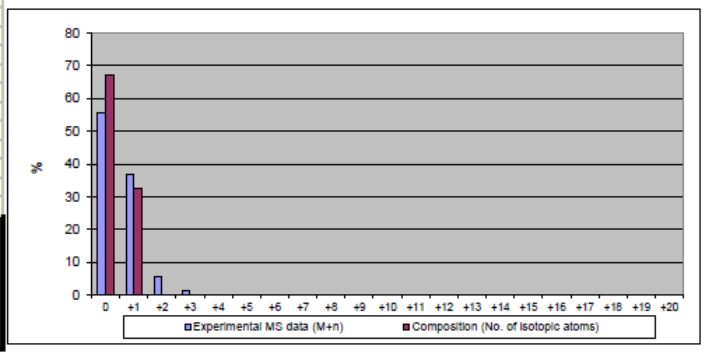
Analyte	Abundance
	247613.3
	163530.3
	26111.1
	6216.1
	1046.3
	44.1
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

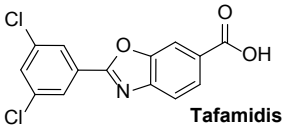
Calculate

Labelled atoms 1

Atom% 32.7

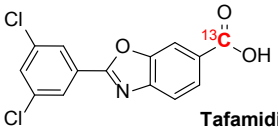


Results	
Relative amounts [%]	
unlabeled	67.3
1-label	32.7
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	



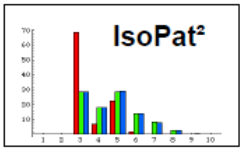
Tafamidis

Exact Mass: 306.9803



Tafamidis (3i)

Exact Mass: 307.9837



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Unlabeled compound	Abundance
M1+0	144320.5
M1+1	24723.6
M1+2	96481
M1+3	15556
M1+4	17825
M1+5	3097
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

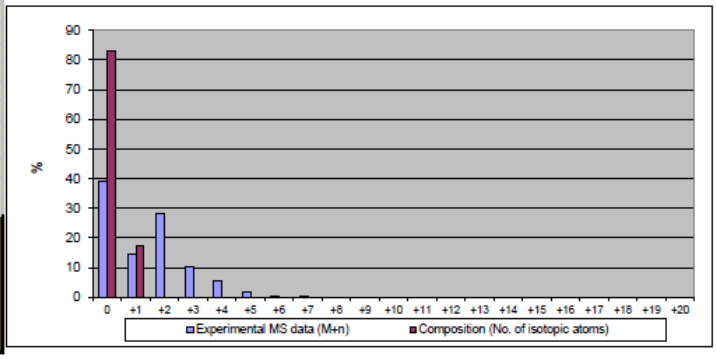
Analyte	Abundance
	114057.1
	42704.3
	82639.9
	29230.3
	16020.6
	5587.5
	1057.4
	346.1
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

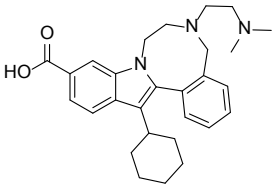
Calculate

Labelled atoms 1

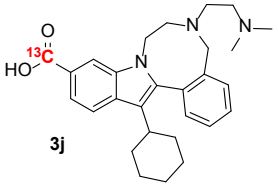
Atom% 17.2



Results	
Relative amounts [%]	
unlabeled	82.8
1-label	17.2
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	



Exact Mass: 445.2729



3j

Exact Mass: 446.2763

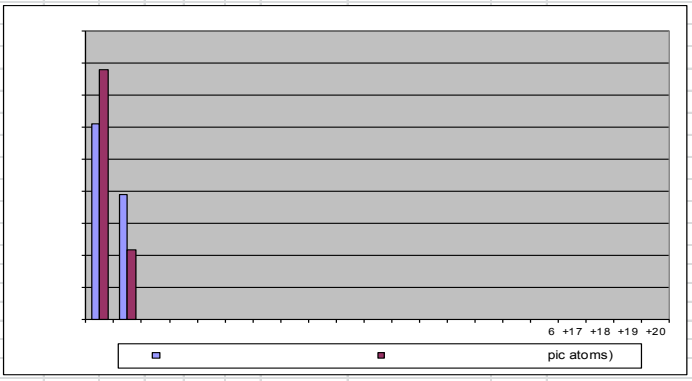
Unlabeled compound	Abundance	Analyte Abundance
M1+0	1365870	1500127
M1+1	439890	958692
M1+2	0	0
M1+3	0	0
M1+4	0	0
M1+5	0	0
M1+6	0	0
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

Expected derivatives: 2

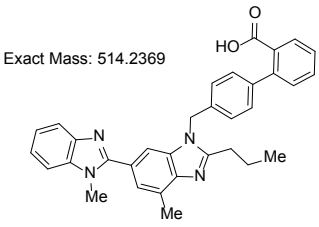
Calculate

Labelled atoms 1

Atom% 22.0

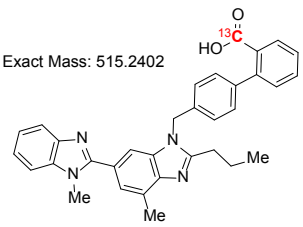


Results	
Relative amounts [%]	
unlabeled	78.02
1-label	21.98
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



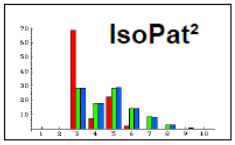
Exact Mass: 514.2369

Telmisartan



Exact Mass: 515.2402

Telmisartan (3k)



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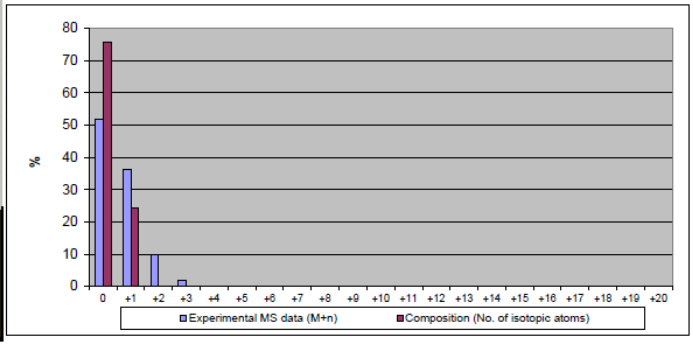
Unlabeled compound	Abundance	Analyte Abundance
M1+0	116145.6	47659
M1+1	43421.5	33219.3
M1+2	8775	8891.5
M1+3	1483	1810.2
M1+4	52	260.1
M1+5	0	46.5
M1+6	0	0
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

Expected derivatives: 2

Calculate

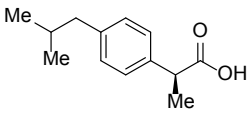
Labelled atoms 1

Atom% 24.2

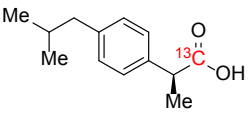


Results	
Relative amounts [%]	
unlabeled	75.8
1-label	24.2
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	

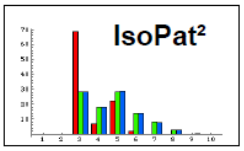
5002729-Telmisartan



(*S*)-Ibuprofen
Exact Mass: 206.1307



(*S*)-Ibuprofen (6a)
Exact Mass: 207.1340



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

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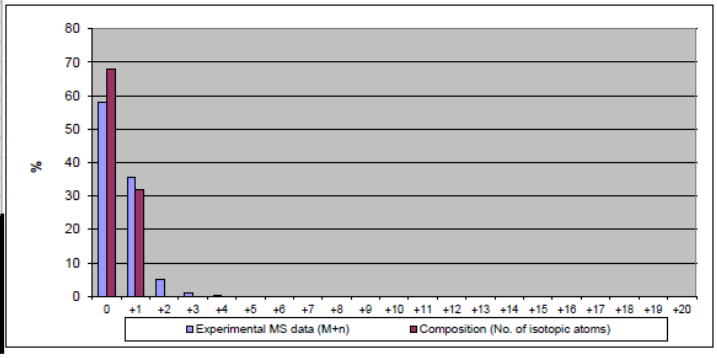
Unlabeled compound	Abundance
M1+0	328541.3
M1+1	48680.5
M1+2	4440
M1+3	406
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

Analyte	Abundance
	125252.5
	76953.1
	11092.6
	1971.1
	217.3
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

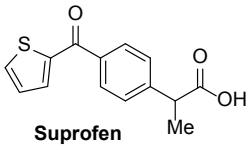
Expected derivatives: 2
Calculate

Labelled atoms 1
Atom% 31.8

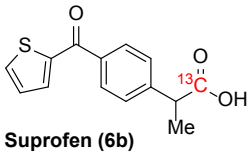


Results	
Relative amounts [%]	
unlabeled	68.2
1-label	31.8
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	

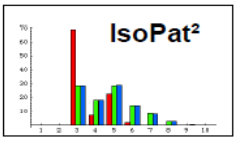
5002729-003-6a



Suprofen
Exact Mass: 260.0507



Suprofen (6b)
Exact Mass: 261.0541



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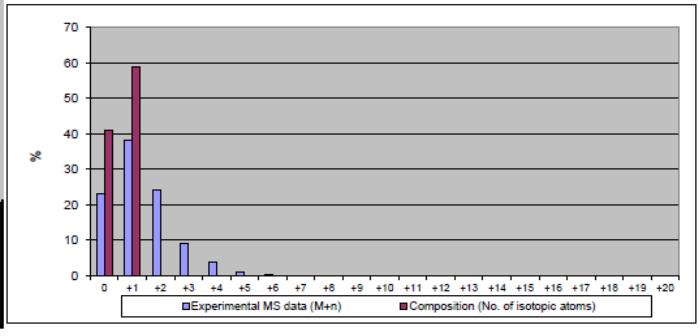
Unlabeled compound	Abundance
M1+0	268219.3
M1+1	89187.6
M1+2	44059
M1+3	11043
M1+4	2471
M1+5	522
M1+6	211
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

Analyte	Abundance
	135052.4
	222869.9
	139605.3
	53649.6
	21841.1
	5813.4
	1568.1
	639.9
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2
Calculate

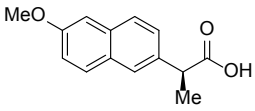
Labelled atoms 1
Atom% 58.9



Results	
Relative amounts [%]	
unlabeled	41.1
1-label	58.9
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	

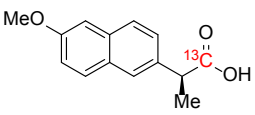
Suprofen -6b

Exact Mass: 230.0943

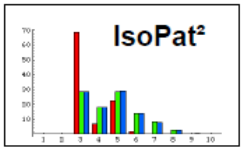


(*S*)-Naproxen

Exact Mass: 231.0976



[^{13}C](*S*)-Naproxen (6c)



Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

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Unlabeled compound	Abundance
M1+0	170655.1
M1+1	26268.7
M1+2	2781
M1+3	181
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

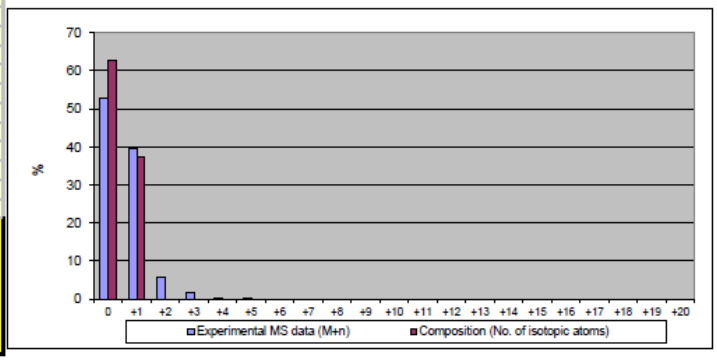
Analyte	Abundance
	95561.8
	71245
	10306.5
	2830.6
	217.3
	509.9
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

Calculate

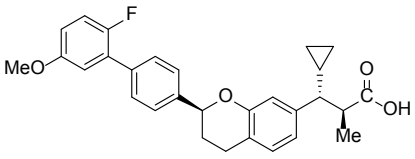
Labelled atoms 1

Atom% 37.2

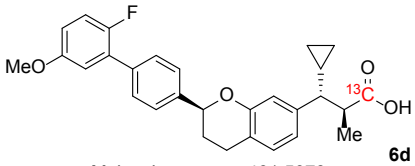


Results	
Relative amounts [%]	
unlabeled	62.8
1-label	37.2
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	

5002729-003-6c



Molecular Weight: 460.55



6d

Molecular Weight: 461.5378

Unlabeled compound	Abundance
M1+0	87920
M1+1	27360.2
M1+2	4865
M1+3	730
M1+4	0
M1+5	0
M1+6	0
M1+7	0
M1+8	0
M1+9	0
M1+10	0
M1+11	0
M1+12	0
M1+13	0
M1+14	0
M1+15	0
M1+16	0
M1+17	0
M1+18	0
M1+19	0

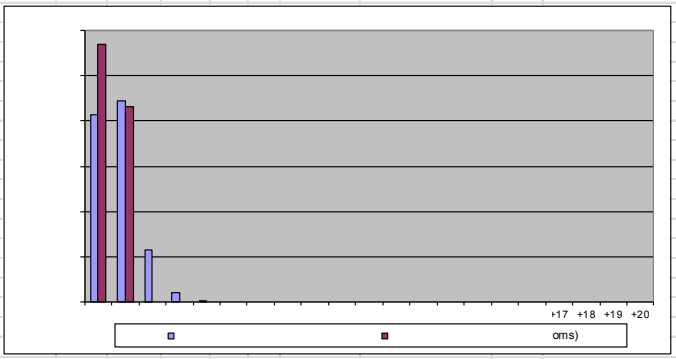
Analyte	Abundance
	135537
	145519.5
	38079
	6498.6
	1037.1
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0

Expected derivatives: 2

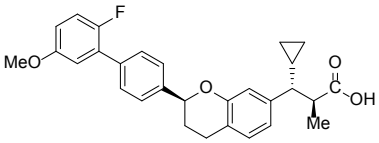
Calculate

Labelled atoms 1

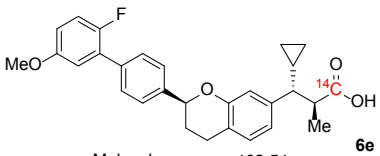
Atom% 43.1



Results	
Relative amounts [%]	
unlabeled	56.9
1-label	43.1
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



Molecular Weight: 460.55



Molecular Weight: 462.54

6e

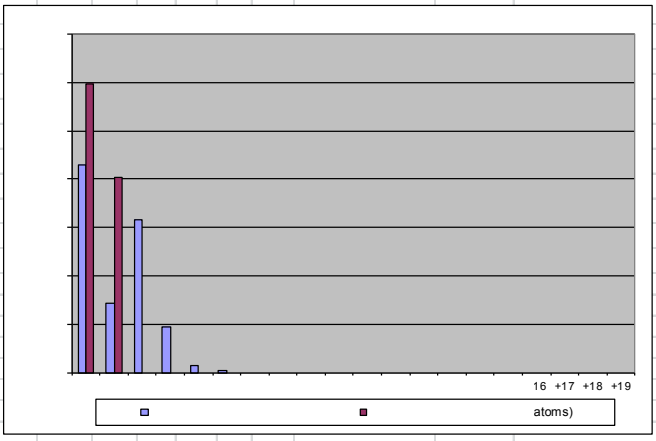
MW tracer mg/mmol	291.101
SA mCi/mmol if 14C	25.1723
SA uCi/mg if 14C	86.4729
Concentration 3H	0

Unlabeled compound	Abundance	Analyte	Abundance
M1+0	87920		65188
M1+1	27360		21816
M1+2	4865		48006
M1+3	730		14384
M1+4	0		2196
M1+5	0		520.7
M1+6	0		0
M1+7	0		0
M1+8	0		0
M1+9	0		0
M1+10	0		0
M1+11	0		0
M1+12	0		0
M1+13	0		0
M1+14	0		0
M1+15	0		0
M1+16	0		0
M1+17	0		0
M1+18	0		0
M1+19	0		0

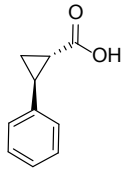
Expected derivatives: 2

Calculate

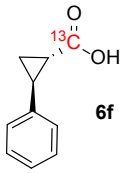
Labelled atoms	1	
Atom%	40.3	
Mole Weight AVE:	290.294	g/mol
Solution Count:	0	mCi/mL



Results	
Relative amounts [%]	
unlabeled	59.7
1-label	40.3
2-label	
3-label	
4-label	
5-label	
6-label	
calculations	
stop here	

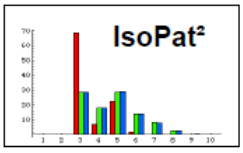


Exact Mass: 162.0681



6f

Exact Mass: 163.0714



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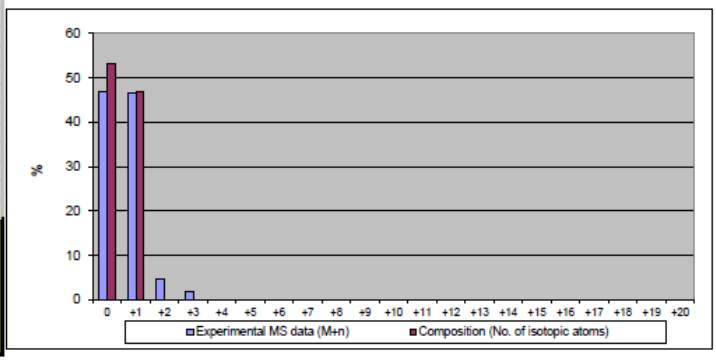
Unlabeled compound	Abundance	Analyte	Abundance
M1+0	159530		45935.8
M1+1	17930.5		45575.6
M1+2	1017		4451.1
M1+3	137		1720.7
M1+4	0		65.1
M1+5	0		0
M1+6	0		0
M1+7	0		0
M1+8	0		0
M1+9	0		0
M1+10	0		0
M1+11	0		0
M1+12	0		0
M1+13	0		0
M1+14	0		0
M1+15	0		0
M1+16	0		0
M1+17	0		0
M1+18	0		0
M1+19	0		0

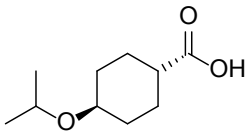
Expected derivatives: 2

Calculate

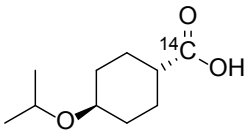
Labelled atoms	1	
Atom%	46.8	



Results	
Relative amounts [%]	
unlabeled	53.2
1-label	46.8
2-label	
3-label	
4-label	
5-label	
6-label	
...	
...	



Exact Mass: 186.13

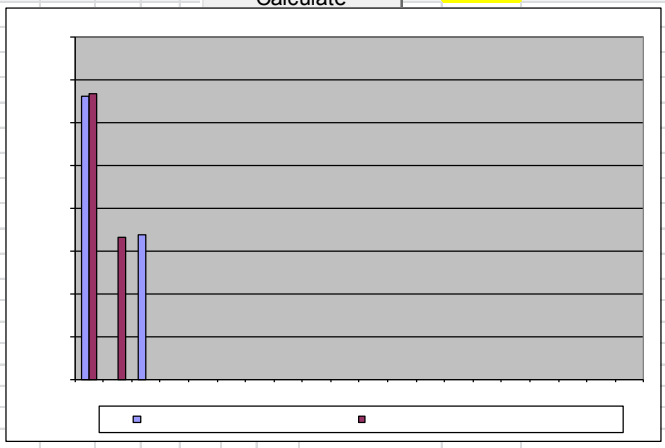


6h

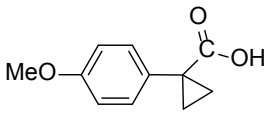
Exact Mass: 188.1288

MW tracer mg/mmol	290.959
SA mCi/mmol if 14C	20.7558
SA uCi/mg if 14C	71.3357

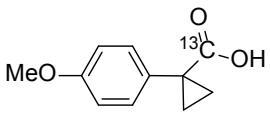
Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1
	Abundance	Abundance		33.3
M1+0	96142	11958		AVE: 290.294 g/mol
M1+1	0	0	Calculate	t: 0 mCi/mL
M1+2	1284	6120.9		
M1+3	0	0		
M1+4	0	0		
M1+5	0	0		
M1+6	0	0		
M1+7	0	0		
M1+8	0	0		
M1+9	0	0		
M1+10	0	0		
M1+11	0	0		
M1+12	0	0		
M1+13	0	0		
M1+14	0	0		
M1+15	0	0		
M1+16	0	0		
M1+17	0	0		
M1+18	0	0		
M1+19	0	0		



Results	
Relative amounts [%]	
unlabeled	66.7
1-label	33.3
2-label	
3-label	
4-label	
5-label	
6-label	



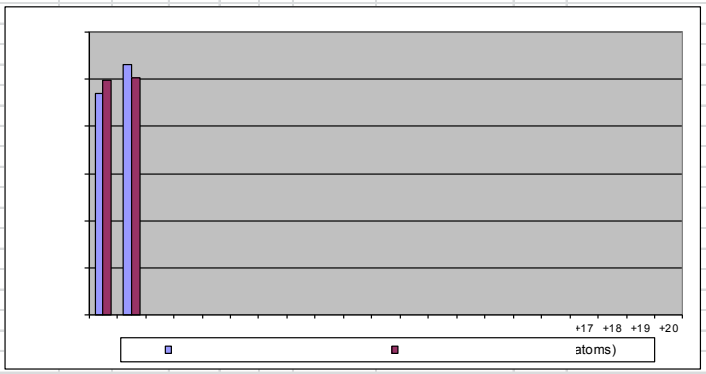
Exact Mass: 192.08



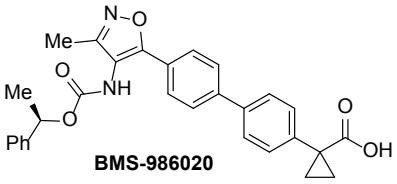
6i

Exact Mass: 193.0820

Unlabeled compound		Analyte	Expected derivatives: 2	Labelled atoms 1
	Abundance	Abundance		Atom% 50.3
M1+0	18925.8	4633.6	Calculate	
M1+1	2064.8	5248.4		
M1+2	0	0		
M1+3	0	0		
M1+4	0	0		
M1+5	0	0		
M1+6	0	0		
M1+7	0	0		
M1+8	0	0		
M1+9	0	0		
M1+10	0	0		
M1+11	0	0		
M1+12	0	0		
M1+13	0	0		
M1+14	0	0		
M1+15	0	0		
M1+16	0	0		
M1+17	0	0		
M1+18	0	0		
M1+19	0	0		

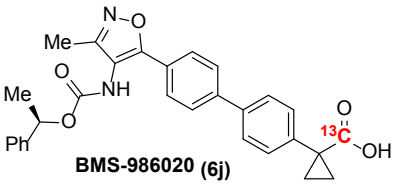


Results	
Relative amounts [%]	
unlabeled	49.7
1-label	50.3
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	



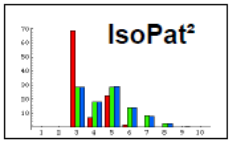
BMS-986020

Exact Mass: 482.1842



BMS-986020 (6j)

Exact Mass: 483.1875



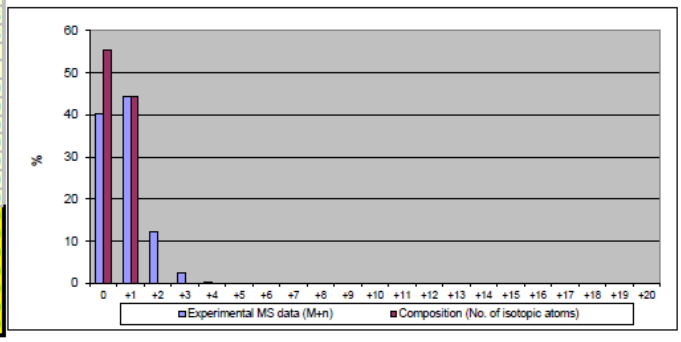
Excel-Worksheet for deconvolution of MS-patterns (D,17O,13C,15N)

Changes and additions to the original and excellent IsoPat² have been made by W J S Lockley (Mod21) to facilitate its use by isotopic chemists. For details of the original spreadsheet see: C. C. Gruber, G. Oberdorfer, C. V. Voss, J. M. Kremsner, C. O Kappe, W. Kroutil, J. Org. Chem. 2007, 72, 5778-5783. The original IsoPat² Excel spreadsheet can be downloaded from ftp://biocatalysis.uni-graz/pub/IsoPat2/. Further supporting data is available at http://pubs.acs.org

Unlabeled compound	Abundance	Analyte Abundance
M1+0	103689.1	78632.2
M1+1	31162.4	86700.5
M1+2	6587	23947.6
M1+3	1918	4862.8
M1+4	449	690.1
M1+5	0	91
M1+6	0	0
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

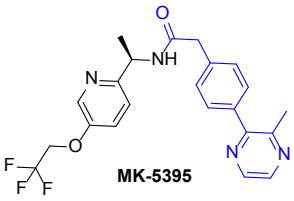
Expected derivatives: 2 — Calculate

Labelled atoms 1 — Atom% 44.5



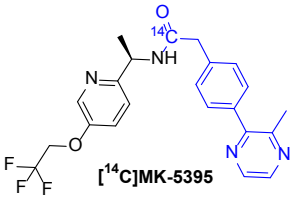
Results	
Relative amounts [%]	
unlabeled	55.5
1-label	44.5
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	

BMS-986020-6f



MK-5395

Molecular Weight: 430.43



[^{14}C]MK-5395

Molecular Weight: 432.42

MW tracer mg/mmol	291.15
SA mCi/mmol if 14C	26.7224
SA uCi/mg if 14C	91.7822

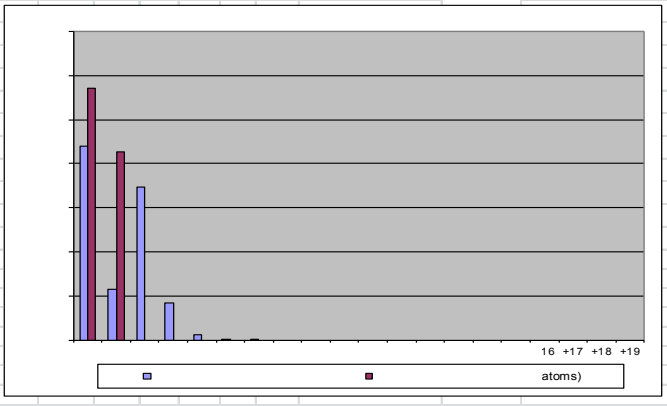
Unlabeled compound	Abundance	Analyte Abundance
M1+0	2022651.7	763962
M1+1	618568.7	202170
M1+2	81680	605537
M1+3	6738	145794
M1+4	333	19741
M1+5	0	2227.5
M1+6	0	170.2
M1+7	0	0
M1+8	0	0
M1+9	0	0
M1+10	0	0
M1+11	0	0
M1+12	0	0
M1+13	0	0
M1+14	0	0
M1+15	0	0
M1+16	0	0
M1+17	0	0
M1+18	0	0
M1+19	0	0

Expected derivatives: 2 — Calculate

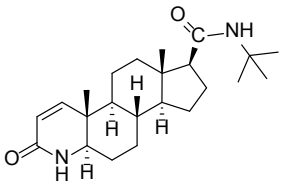
Labelled atoms 1 — Atom% 42.8

Mole Weight AVE: 290.294 g/mol

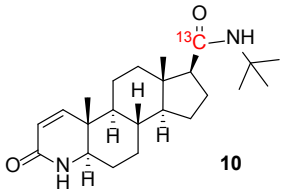
Solution Count: 0 mCi/mL



Results	
Relative amounts [%]	
unlabeled	57.2
1-label	42.8
2-label	
3-label	
4-label	
5-label	
6-label	
calculations	
stop here	



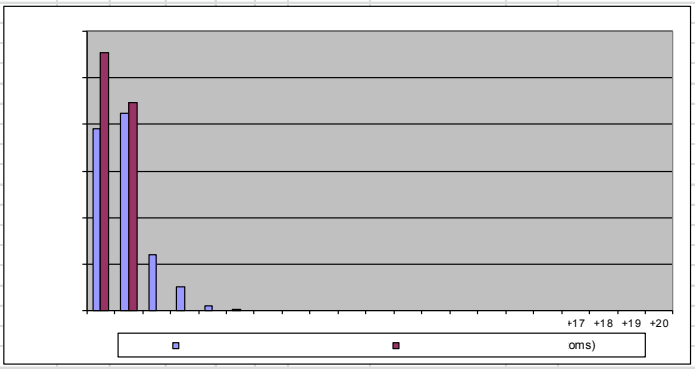
Molecular Weight: 372.5530



10

Molecular Weight: 373.55

Unlabeled compound		Analyte	Expected derivatives:	2	Labelled atoms	1
	Abundance	Abundance			Atom%	44.6
M1+0	1189413.6	306303		Calculate		
M1+1	347268.1	333070.7				
M1+2	69277	94095.8				
M1+3	10494	41545.6				
M1+4	1333	8791.4				
M1+5	95	1082.5				
M1+6	0	0				
M1+7	0	0				
M1+8	0	0				
M1+9	0	0				
M1+10	0	0				
M1+11	0	0				
M1+12	0	0				
M1+13	0	0				
M1+14	0	0				
M1+15	0	0				
M1+16	0	0				
M1+17	0	0				
M1+18	0	0				
M1+19	0	0				



Results	
Relative amounts [%]	
unlabeled	55.4
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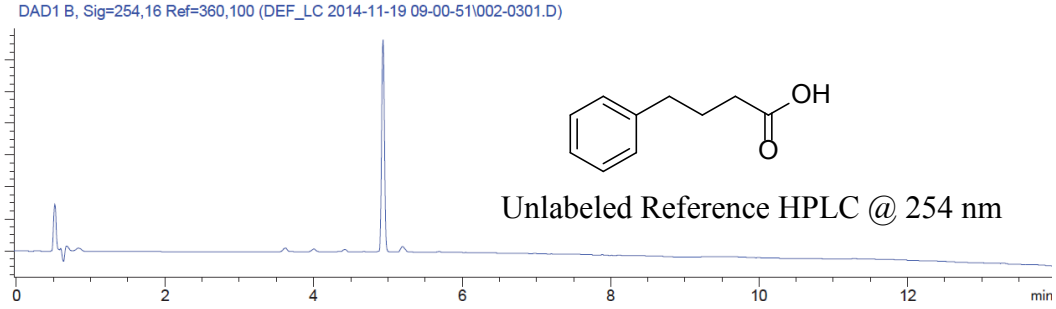
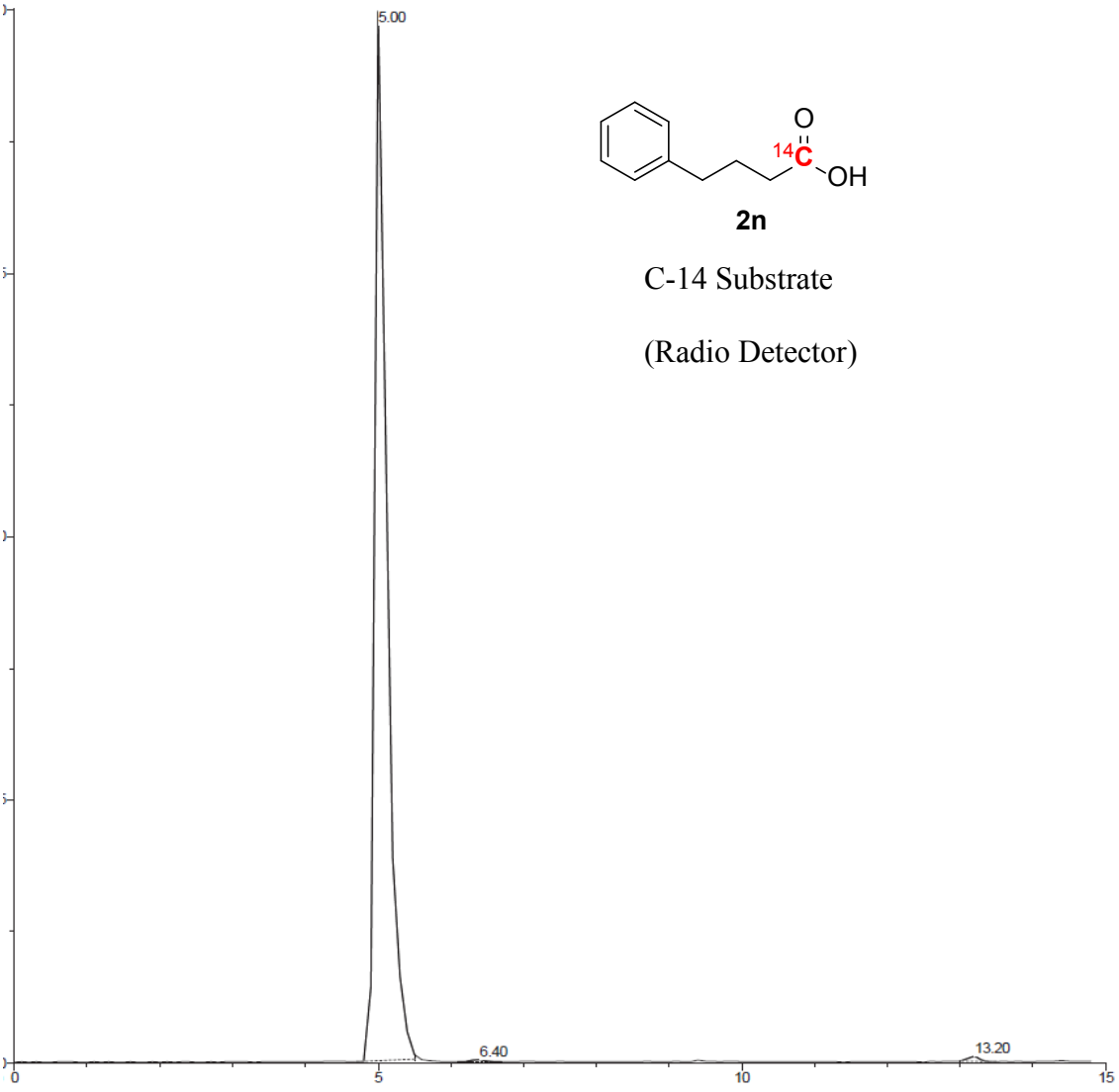
2-label	
3-label	
4-label	
5-label	
6-label	
…	
…	

5. HPLC Chromatograms



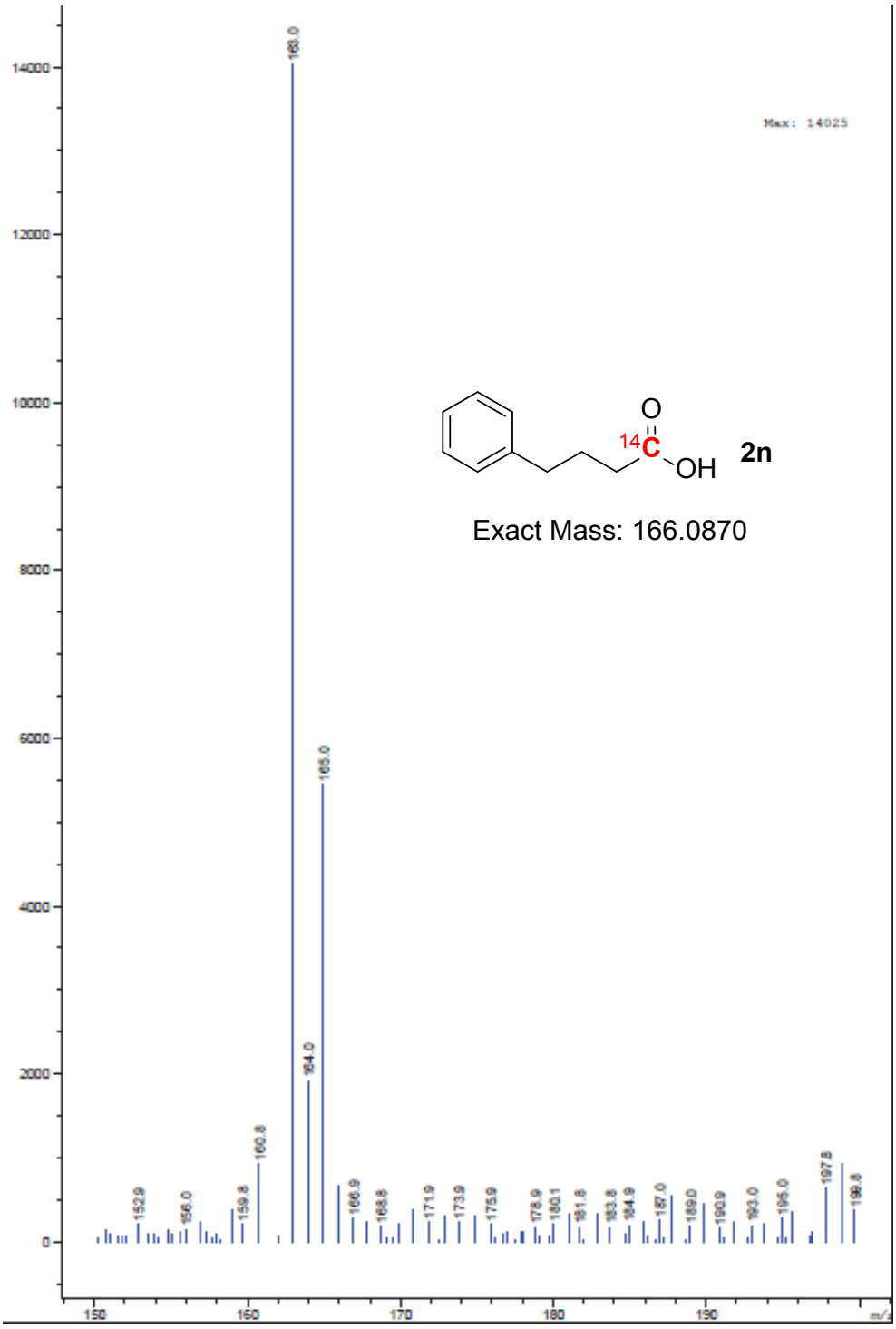
Unlabeled Reference HPLC @ 254 nm



2n

C-14 Substrate

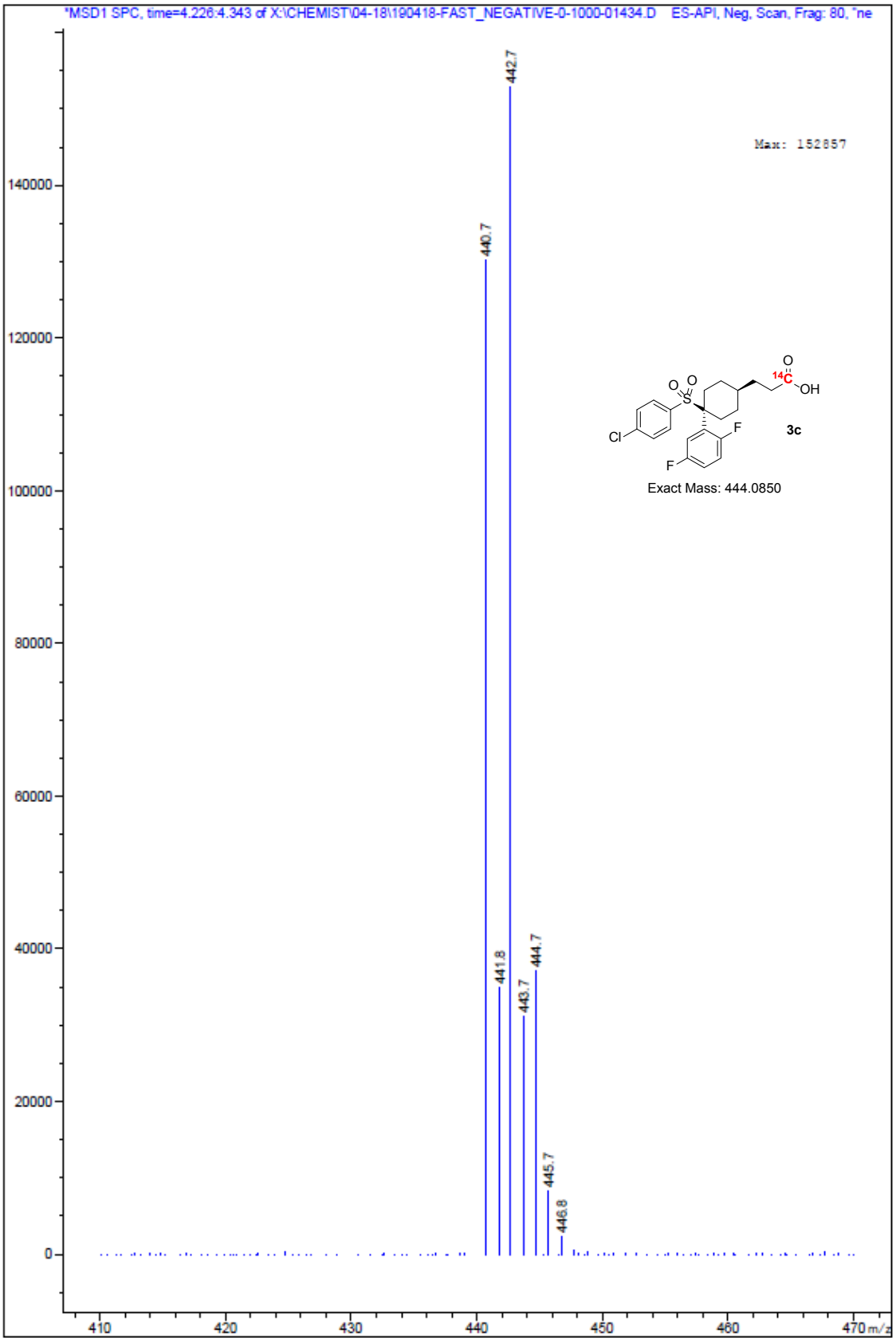
(Radio Detector)



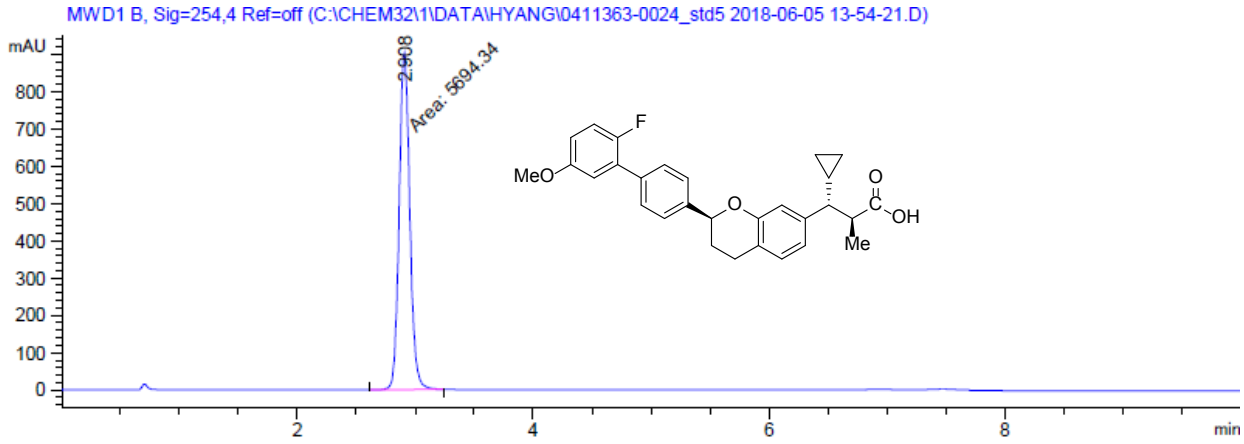
2n

Exact Mass: 166.0870

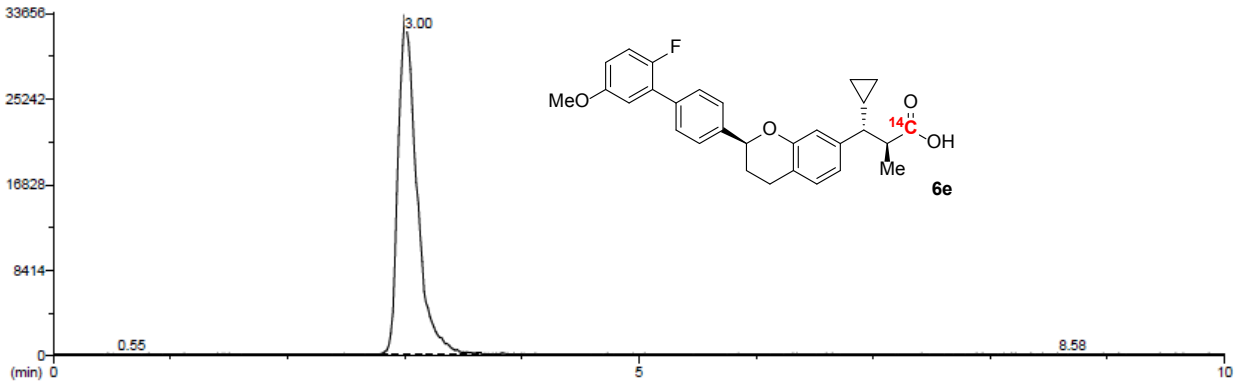
MS Spectrum


*MSD1 SPC, time=4.226:4.343 of X:\CHEMIST\04-18\190418-FAST_NEGATIVE-0-1000-01434.D ES-API, Neg, Scan, Frag: 80, "ne
Max: 152857
442.7
440.7
441.8
443.7
444.7
445.7
446.8
140000
120000
100000
80000
60000
40000
20000
0
410
420
430
440
450
460
470 m/z
O
14C
OH
O
O
S
Cl
F
F
3c
Exact Mass: 444.0850

HPLC/ UV trace for authentic unlabeled standard of **6e**

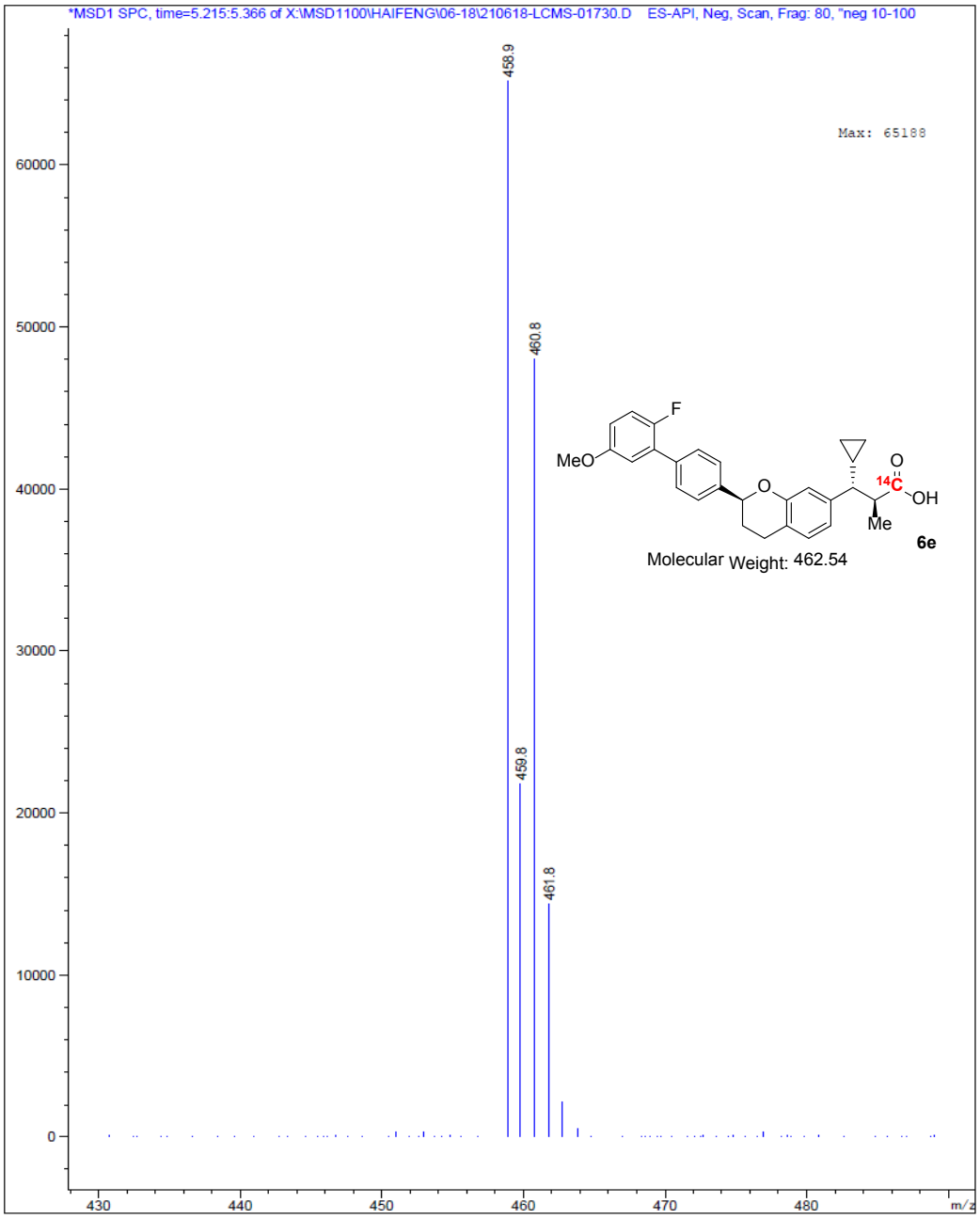


Radio-HPLC/ Radioactivity trace **[^{14}C] 6e**

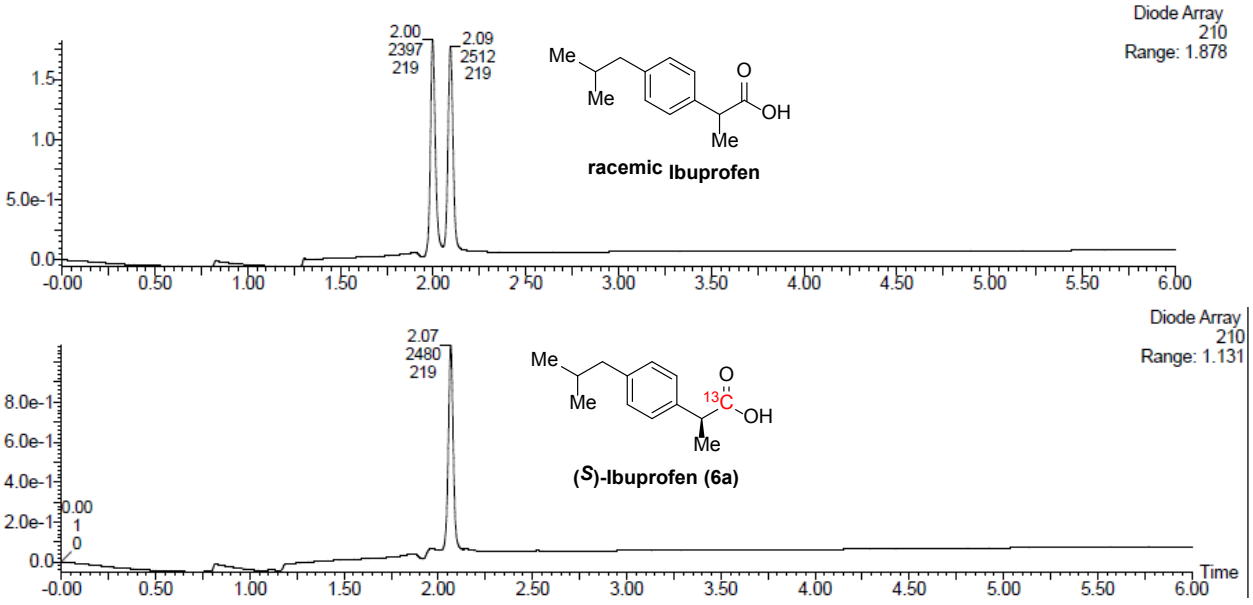


Peak Area Report (%Pks) Channel 1

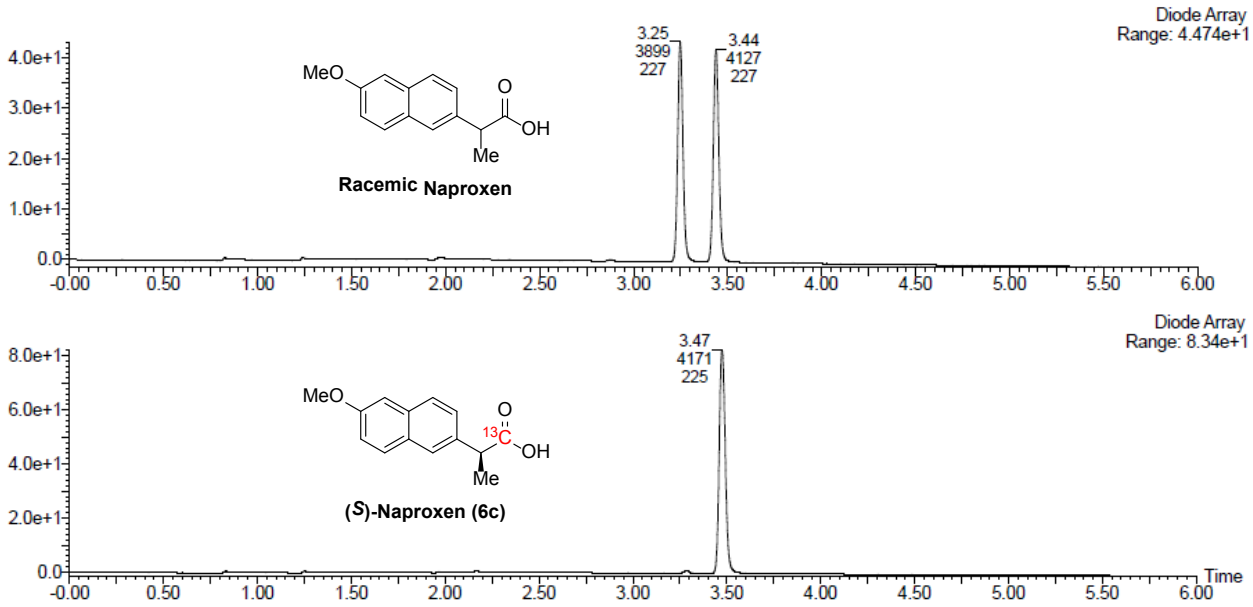
Name	Ret. Time (min.)	Pk#	Area	% Pks	Conc.	Units
	0.55	1	4328	1.10	0.00	
	3.00	2	378240	96.54	0.00	
	8.58	3	9208	2.35	0.00	


*MSD1 SPC, time=5.215:5.366 of X:\MSD1100\HAIFENG\06-18\210618-LCMS-01730.D ES-API, Neg, Scan, Frag: 80, "neg 10-100
Max: 65188
458.9
460.8
459.8
461.8
60000
50000
40000
30000
20000
10000
0
430
440
450
460
470
480
m/z
F
MeO
O
O
14C
OH
Me
6e
Molecular Weight: 462.54

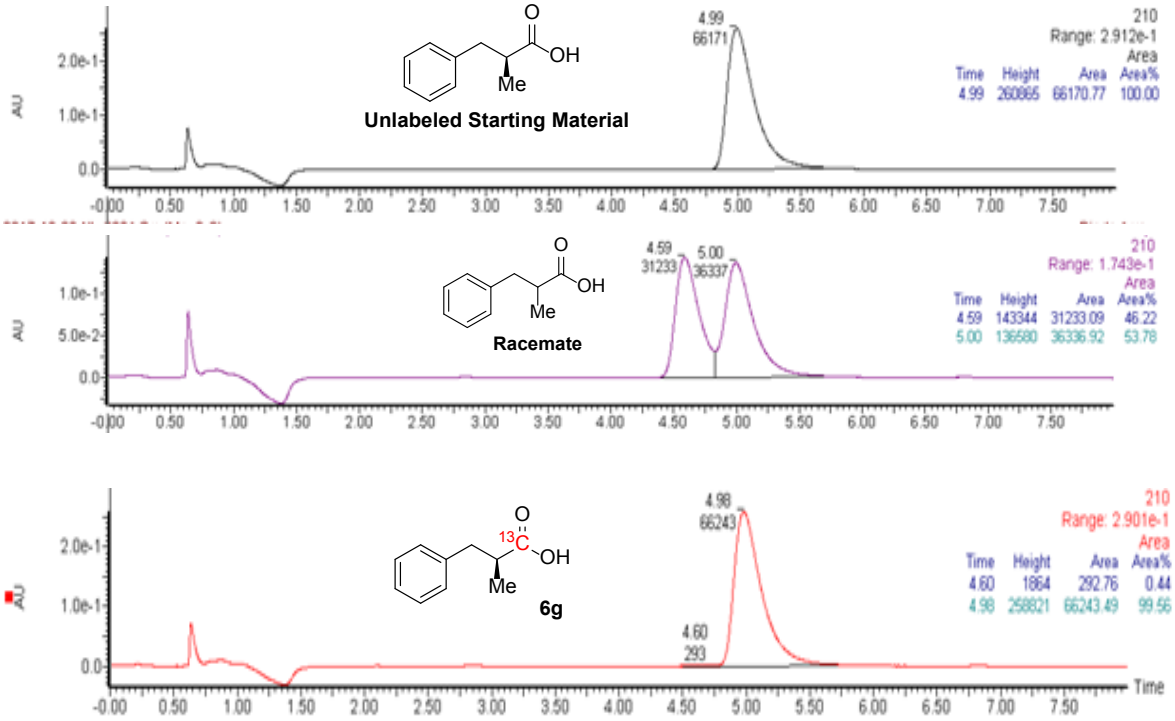
Chiral Assay Chromatograms of **6a:** Enantiomeric excess (ee) was determined to be 98 % using a chiral SFC method (Column; AD-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: MeOH, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).

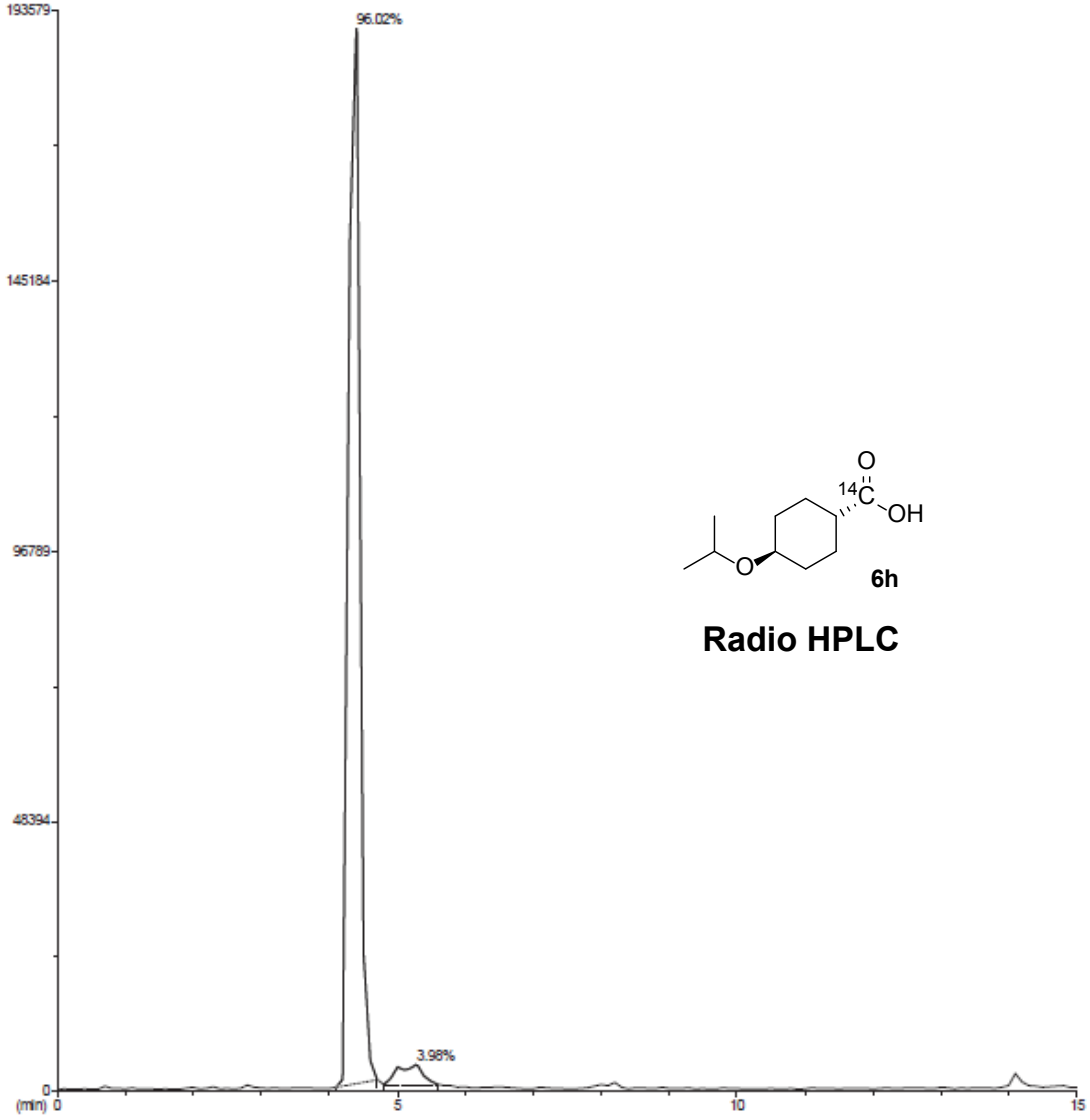


Chiral Assay Chromatograms of **6c**: Enantiomeric excess (ee) was determined to be 98 % using a chiral SFC method (Column; AD-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: MeOH, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).



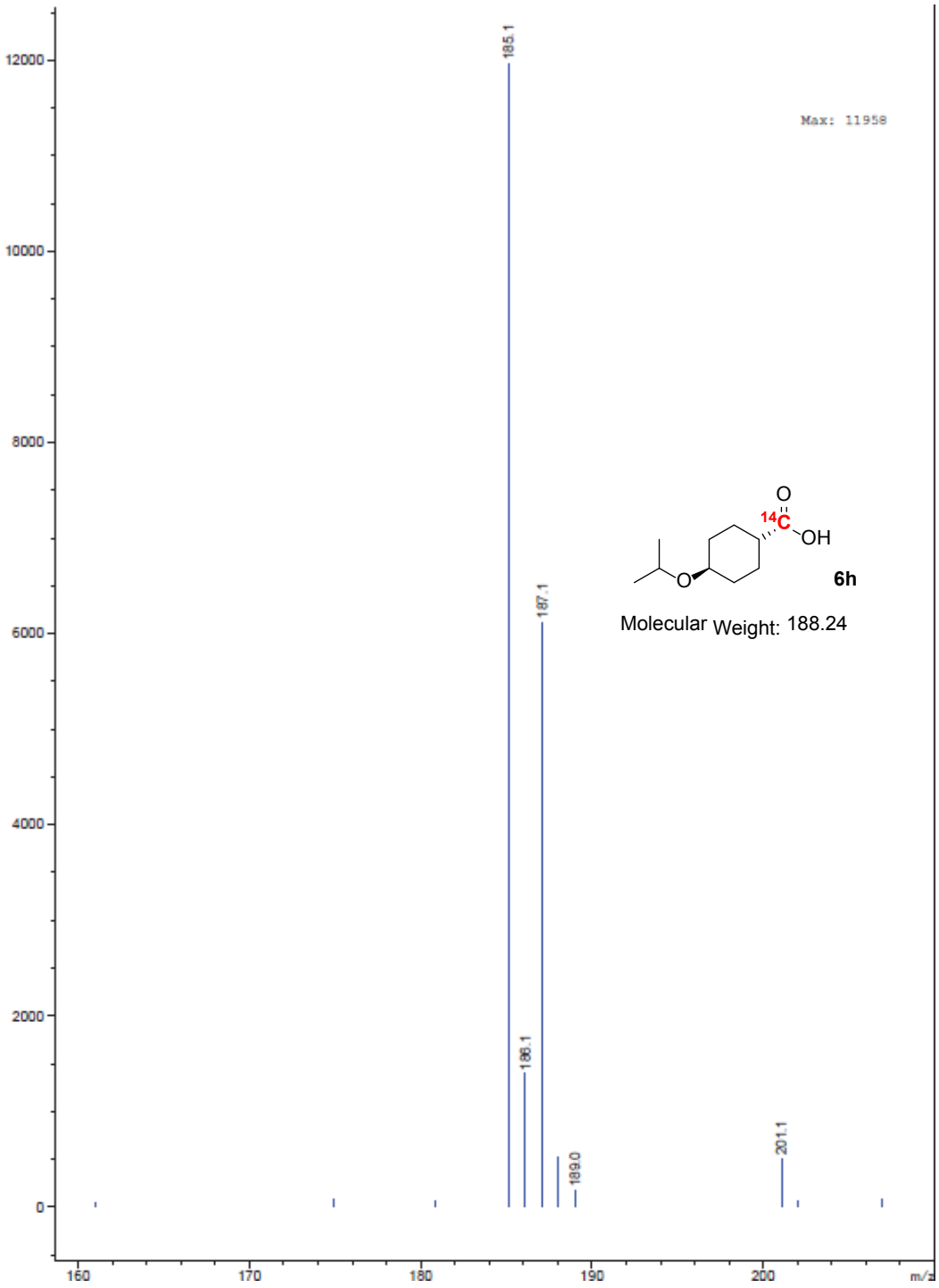
Chiral Assay Chromatograms of **6g**: Enantiomeric excess (ee) was determined to be 98.8 % using a chiral SFC method (Column; OJ-3 150x4.6mm at 40 °C, mobile phase A: CO_2 mobile phase B: EtOH with 25mM isobutylamine, 2% mobile phase B isocratic for 6 minutes, Flow = 3.0 mL/min; pressure=150 bar).



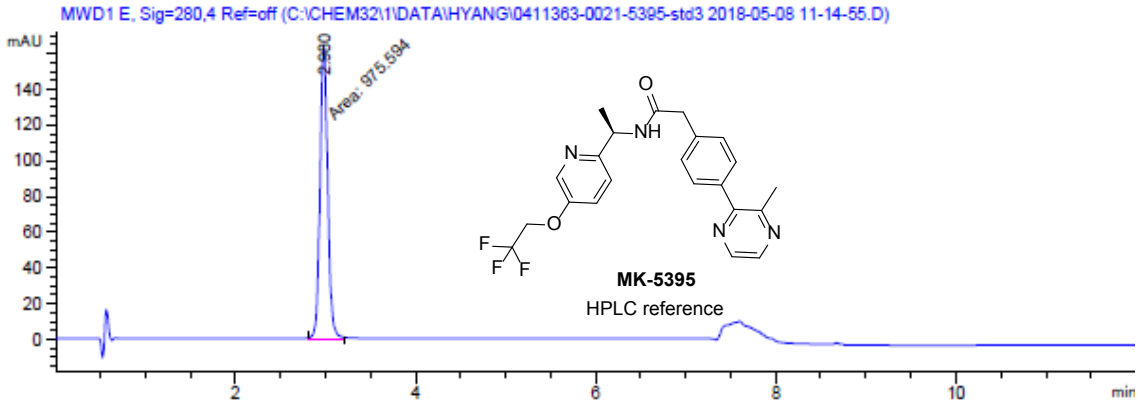


6h

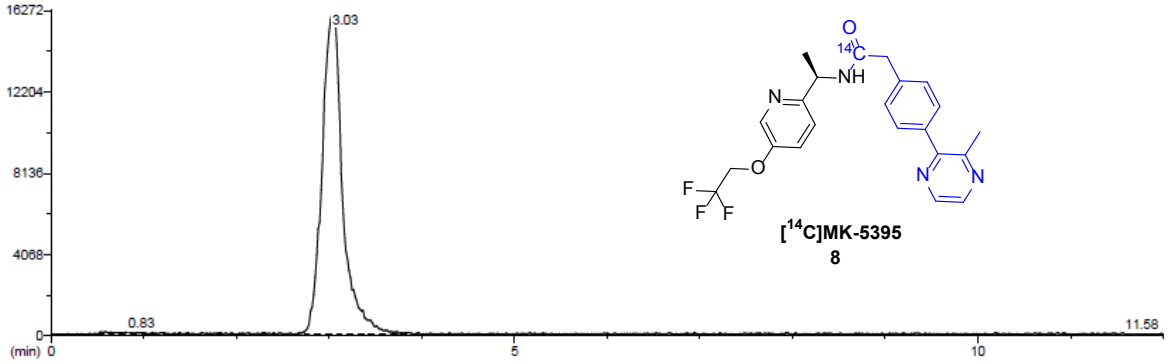
Radio HPLC


185.1
Max: 11958
187.1
186.1
189.0
201.1
12000
10000
8000
6000
4000
2000
0
160
170
180
190
200
m/z
O
14C
OH
O
6h
Molecular Weight: 188.24

HPLC/ UV trace for authentic standard, **MK-5395 (8)**



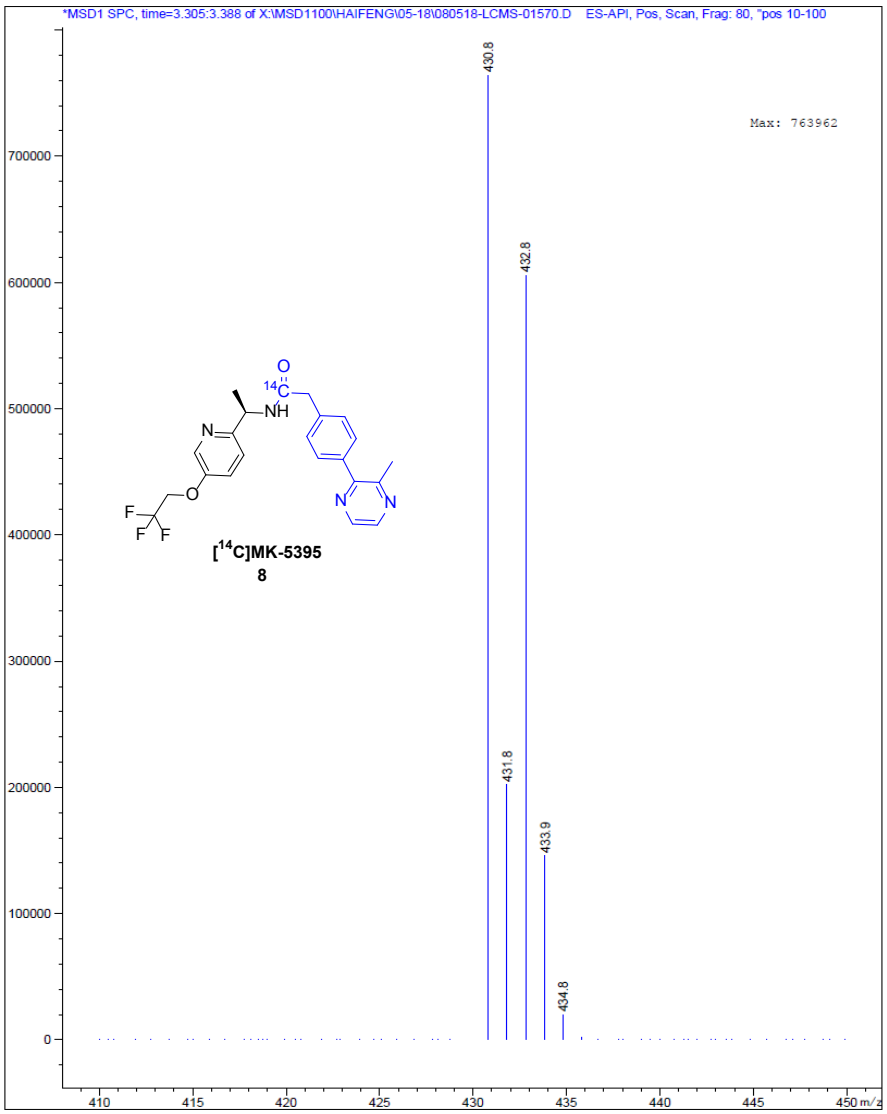
Radio-HPLC/ Radioactivity trace [^{14}C] MK-5395



Peak Area Report (%Pks) Channel 1

Ret. Time C-14 CPM

Name	(min.)	Pk#	Area	% Pks	Conc.	Units
	0.83	1	3256	1.19	0.00	
	3.03	2	263152	96.48	0.00	
	11.58	3	6336	2.32	0.00	



[1] Moravek, Brea, California 92821 USA.

[2] Isotope distribution was calculated based on mass spectrometry data using IsoPat2. Excel-Worksheet for deconvolution of MS-patterns (D,^{17}O,^{13}C,^{15}N) © Christian C. Gruber, Wolfgang Kroutil **2006**. Changes and additions to the original and excellent IsoPat2 have been made by W J S Lockley (Mod21) to facilitate its use by isotopic chemists. For details of the original spreadsheet see: Gruber, C.; Oberdorfer, G.; Voss, C.; Kremsner, J.; Kappe, C.; Kroutil, W. An Algorithm for the Deconvolution of Mass Spectroscopic Patterns in Isotope Labeling Studies. Evaluation for the Hydrogen−Deuterium Exchange Reaction in Ketones. *J. Org. Chem.* **2007**, *72*, 5778. The original IsoPat2 Excel spreadsheet can be downloaded from ftp://biocatalysis.uni-graz/pub/IsoPat2/.

[3] Lindhardt, A. T.; Simonssen, R.; Taaning, R. H.; Gogsig, T. M.; Nilsson, G. N.; Stenhagen, G.; Elmore, C. S.; Skrydstrup, T. 14Carbon monoxide made simple – novel approach to the generation, utilization, and scrubbing of ^{14}carbon monoxide. *J. Label. Compd. Radiopharm.* **2012**, *55*, 411.

[4] Ghosez, L.; George-Koch, I.; Patiny, L.; Houtekie, M.; Bovy, P.; Nshimyumukiza, P.; Phan, T. A general and practical method of synthesis of 2-disubstituted-l-chloro- and 1-bromoenamines. *Tetrahedron* **1998**, *54*, 9207.