Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2022

Electronic Supplemental information

A Direct Fixation of CO_2 for Isotopic Labelling of Hydantoins Using I_2-Trimethyl-λ^5-phosphine Charge Transfer Complexes

John-Paul J. Bow[a], Valentina Adami[b], Agostino Marasco[b], Gaute Grønnevik[a], Dean A. Rivers[c], Guiseppe Alvaro[c], Patrick J. Riss*[a,d]

1. Table of Contents

2. Experimental Procedures

2.1. General Considerations

All chemicals and consumables used in the experiment were obtained from Sigma-Aldrich (Sigma-Aldrich AS Oslo, Norway) and used without further purification unless otherwise stated. Nuclear magnetic resonance spectra were recorded on a Bruker AVII 400 NMR instrument (Bruker ASX Nordic AB) unless otherwise stated. Chemical shifts (δ) for ^{1}H (400 MHz) and ^{13}C (100 MHz) resonances are reported in parts per million (ppm), downfield from a theoretical tetramethyl silane signal (TMS, δ = 0 ppm). Spectra are normalized relative to the solvent residual signal ($CHCl_3$ in $CDCl_3$, δ = 7.223 ppm). Acetonitrile-d_3 was dried over 3Å molecular sieves prior to use to reduce the water content. Mass spectrometry was conducted on a Q-Tof-2 mass analyzer (Micromass, Q-Tof-2TM) using ESI ion source in positive mode. Radiosynthesis was conducted on a modified Synthra MeI plus research radiosynthesis platform (Synthra GmbH, Hamburg, Germany). Purification of reaction mixtures was achieved on a Macherey-Nagel Pyramid C_{18} HPLC column (250 x 10 mm) using MeCN-0.1%TFA. Analytical HPLCs were obtained with a 35% Acetonitrile 65% Water mobile phase on a Macherey-Nagel Pyramid C_{18} HPLC column (250 x 4.6 mm) analytical column. Quality control was conducted using a rapid gradient (MeCN-0.1%TFA). Chiral HPLC characterization was conducted to confirm enantiomeric purity of the products using a CHIRACEL OD-H HPLC column (250 x 4.6 mm), column temperature 40 °C, flow rate: 1.000 ml/min, solvent A: 0.05% TFA in water, solvent B: 0.05% TFA in acetonitrile, gradient: 0-3 50%B, 3-20 80%B, 20-25 95%B, 25-32 50%B.

2.2. Production of $[^{11}C]CO_2$

$[^{11}C]CO_2$ was produced via the $^{14}N(p,\alpha)^{11}C$ nuclear reaction on a GE PETtrace 880 cyclotron using 5 μA x 5 min irradiation with 16.5 MeV protons for analytical experiments. For imaging studies 20 μA x 5 min were employed. The $[^{11}C]CO_2$ was then trapped at -180 °C prior to being trapped in the reaction vessel at -40 °C.

2.3. Determination of Radiochemical Yield and Purity

Reaction mixtures were diluted with 0.1%TFA in H_2O mixture, degassed with He for 30s and injected into a radioHPLC where the product was separated by an isocratic mixture of MeCN/H_2O; 40:60 at a flow rate of 1 mL/min (analytical) or 5mL/min (production). Following separation, the radiochemical yield (RCY) was determined by dividing the decay-corrected ^{11}C-activity fixated in the product by the activity received in the reactor at -40 °C. All measured activity was decay corrected to the time of end of bombardment (EOB).

$$RCY\ (\%) = \frac{RCP\ x\ Activity\ following\ purge}{Total\ Activity}$$

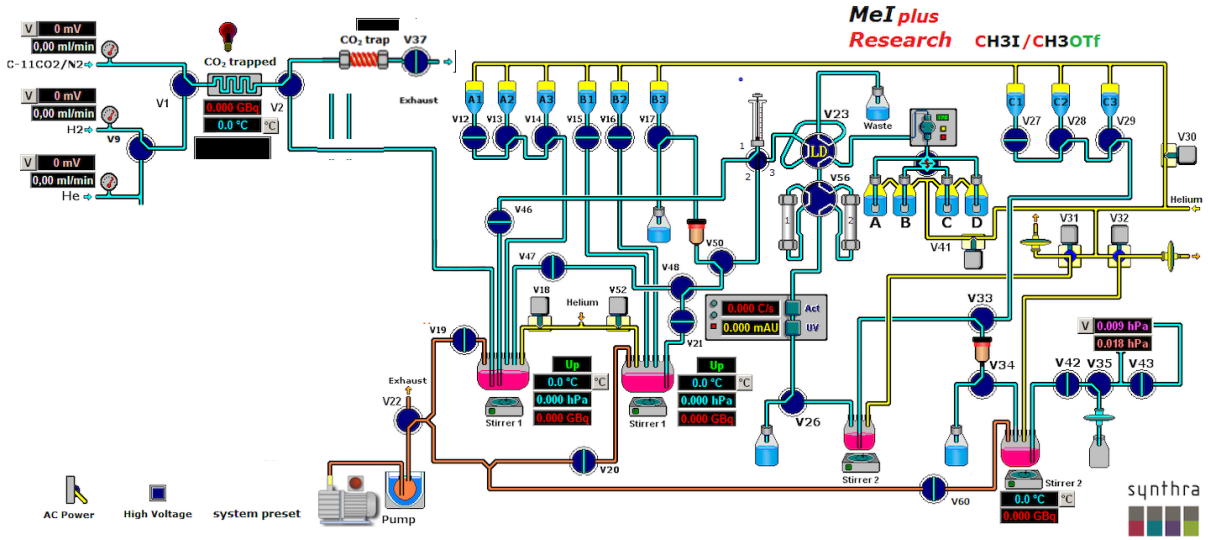
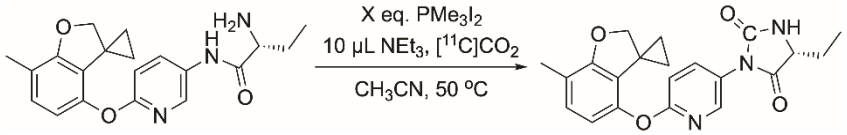


Figure S1. Layout and plumbing scheme of the Synthesis module

2.4. Stoichiometry Screen

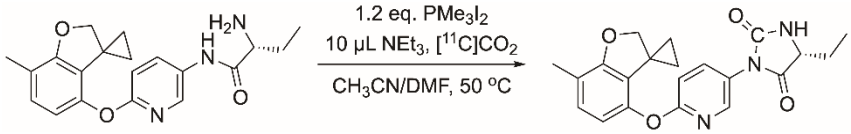
The appropriate amount of a 1 mg/100 µL stock solution of the starting material (1.0 mg, 0.0027 mmol) in acetonitrile and 10 µL of triethylamine (7.26 mg, 0.0718 mmol) was added to a vial. To the reactor vial iodine (1.0 mg, 0.0039 mmol) was dissolved in 200 µL of anhydrous acetonitrile, to this an excess of trimethylphosphine (~15 µL for each reaction, 11.0 mg, 0.15 mmol) was added to form the PMe_3I2 reagent. At the start of the irradiation the starting material and base were pipetted into the reactor vial, resulting in a 5-minute activation time and the total volume was diluted to 500 µL with acetonitrile if required. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 300 µL of 0.1% TFA/H_2O solution.



Scheme S1. Stoichiometry Effects on Hot Run

2.5. Phosphine Screen

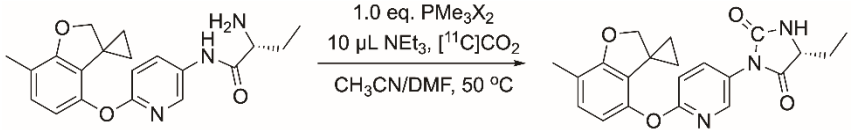
200 µL of a 1 mg/100 µL solution of the starting material (2 mg, 0.0054 mmol) in DMF was added to a reactor vial. To the reactor vial 10 µL of triethylamine (7.26 mg, 0.0718 mmol) was added. In a separate vial iodine (1.2 mg, 0.00473 mmol, 0.9 eq) was dissolved in 200 µL of anhydrous acetonitrile, to this an excess of phosphine (~15 µL for each reaction) was added slowly with agitation to form the PR_3I_2 reagent. This was then pipetted into the reactor vial at the start of the irradiation time, resulting in a 5-minute activation time. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 300 µL of 0.1% TFA/H_2O solution.



Scheme S2. Phosphine Screen for Hot Runs

2.6. Halide Screen

The appropriate halide complex (1 equiv.) was added to the reactor vial with 200 µL of Acetonitrile. 200 uL of a 1 mg/200 µL solution of the starting material AUT15 Precursor (1.0 mg, 0.0027 mmol) in DMF was added to a vial. To the vial 10 µL of triethylamine (7.26 mg, 0.0718 mmol) was added. The starting material and base stock solution was pipetted into the reactor vial at the start of the irradiation time, resulting in a 5-minute activation time. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 300 µL of 0.1% TFA/H_2O solution.



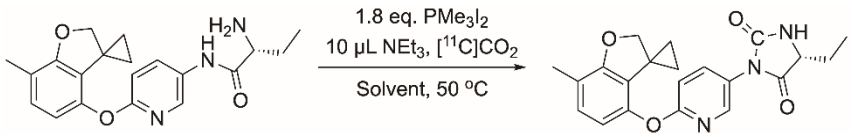
Scheme S3. Halide Screen for Hot Runs

Table S1. Halide screen for $[^{11}C]CO_2$ runs

Entry	Halides	RCY (%)
1	PMe_3Br_2 solid	0
2	PMe_3Br_2 fresh	0
3	PMe_3ICl solid	0

2.7. Solvent Screen

200 µL of a 1 mg/200 µL solution of the starting material (1.0 mg, 0.0027 mmol) in solvent was added to a reactor vial. To the reactor vial 10 µL of triethylamine (7.26 mg, 0.0718 mmol) was added. 1.8 mg of PMe_3I_2 (1 eq., 0.0054 mmol) was added to a vial to this vial 200 µL of solvent was added. This was then pipetted into the reactor vial at the start of the irradiation time, resulting in a 5-minute activation time. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 300 µL of 0.1% TFA/H_2O solution.



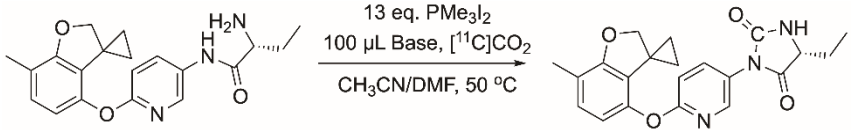
Scheme S4. Solvent Screen for Hot Runs

Table S2. Solvent screen for $[^{11}C]CO_2$ runs

Entry	Solvent	RCY (%)
1	DMF	0
2	DMF	0
3	MeCN (PMe_3I_2 *in situ*)	18.4
4	MeCN (Solid PMe_3I_2)	15.5

2.8. Base Screen

100 µL of a 1 mg/100 µL solution of the starting material (1 mg, 0.0027 mmol) in DMF and 100 µL of base stock solution (0.0718 mmol) in DMF was added to a reactor vial. To a separate vial containing iodine (13 mg, 0.051 mmol, 13 eq), 200 µL of anhydrous acetonitrile containing PMe_3 (40 mg/mL) was added slowly with agitation to form the PMe_3I_2 reagent. This was then pipetted into the reactor vial at the start of the irradiation time, resulting in a 5-minute activation time. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 200 µL of 0.1% TFA/H_2O solution.



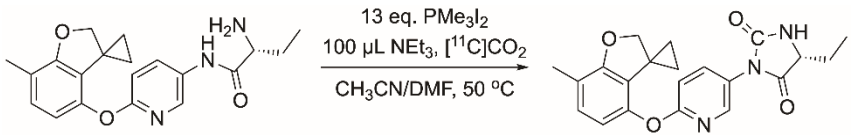
Scheme S5. Base Screen for Hot Runs

Table S3. Base screen of $[^{11}C]CO_2$ runs

Entry	Base	RCY
1	Et_3N	14.0% ± 1.1 (n=2)
2	TMEDA	8.8% (n=1)
3	DiPEA	5.5% ± 3.8 (n=3)
4	DBU	4.1%± 1.6 (n=2)
5	DMAP	4.5% ± 6.3 (n=2)
6	TBD	0%
7	Tribenzylamine	0%
8	Proton Sponge	0%

2.9. Incubation Time

100 µL of a 1 mg/100µL solution of the starting material (1 mg, 0.0027 mmol) in DMF and 100 µL of triethylamine stock solution (0.0718 mmol) in DMF was added to a reactor vial. To a separate vial containing iodine (13 mg, 0.051 mmol, 13 eq), 200 µL of anhydrous acetonitrile containing PMe_3 (40 mg/mL) was added slowly with agitation to form the PMe_3I_2 reagent. This was then pipetted into the reactor vial at the start of the irradiation time, resulting in a 5-minute incubation time. The reactor vial was then attached to the Synthra Module where the addition of the $^{11}CO_2$ was automated. Before injection into the HPLC the reaction was diluted with 200 µL of 0.1% TFA/H_2O solution.

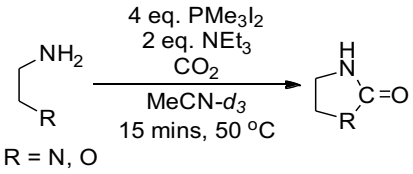


Scheme S6. Incubation Time for Hot Runs

Table S4. Incubation time screen with $[^{11}C]CO_2$

Entry	Incubation Time (min)	RCY (%)
1	0	0.6
2	0	1,6
3	5	12,4
4	5	26
5	10	17.7

2.10. Substrate Scope

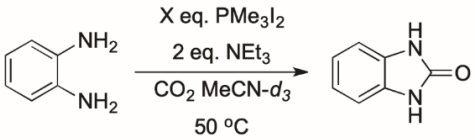


Scheme S7. Substrate Scope using NMR Spectroscopy

5 mg of substrate was added to a glass vial followed by triethylamine (2 equivalents) and 200 µL of dry Acetonitrile-d_3. In a separate vial the appropriate amount of I_2 (4 equivalents) was weighed in and 400 µL of dry acetonitrile-d_3 was added. To this mixture an excess of PMe_3 (~100 µL, 73.5 mg, 0.97 mmol) was slowly added dropwise until the solution had no yellow colour remaining and afforded a white suspension. The suspension was then transferred using a micro-pipette to the vial containing the substrate. The reaction mixture was then transferred to a 600 MHz Wilmad NMR tube fitted with a J-Young valve. Both vials were then washed with 200 µL of acetonitrile- d_3 and it was transferred to the NMR tube giving a final volume of 800 µL. A balloon fitted with a needle was used to sparge the NMR tube with CO_2 for 15 minutes. The NMR tube was then sealed using the J-Young valve and placed in an oil bath for 15 minutes at 50 °C. The NMR tube was removed from heat, cleaned, and a ^1H spectrum was acquired on a 300 MHz Bruker DPX NMR Spectrometer.

The NMR tube used was air-tight ensuring that CO_2 could not evade the reaction vessel. Ensuring an excess amount of CO_2 was available to react and allowed for the monitoring of consumption of other reagents.

2.11. General procedure for experiments with NMR Spectroscopy



Scheme S8. General Scheme of NMR Spectroscopy Runs

Phenylene diamine (15 mg, 0.14 mmol) was added to a glass vial, triethylamine (40 µL, 0.28 mmol) was micro-pipetted in and then 200 µL of Acetonitrile-d_3 was added. In a separate vial the appropriate amount of I_2 (1.2 equivalents, 43.9 mg, 0.17 mmol) was weighed in and 400 µL of anhydrous acetonitrile-d_3 was added. To this mixture an excess of PMe_3 (~100 µL, 73.5 mg, 0.97 mmol) was slowly added dropwise until the solution had no yellow colour remaining and afforded a white suspension. The suspension was then transferred using a micro-pipette to a 600 MHz Wilmad NMR tube fitted with a J-Young valve. The solution containing the starting material and base was then added to the vial containing the PMe_3I_2 compound ensuring all material was transferred to the NMR tube. Both vials were then washed with 200 µL of acetonitrile- d_3 and it was transferred to the NMR tube giving a final volume of 800 µL. Using a balloon fitted with a needle, the NMR tube was sparged with CO_2 for 10 minutes. The NMR tube was then sealed using the J-Young valve. The sealed tube was then placed in an oil bath at 50 °C and time points were taken at 15 minutes. The NMR tube was removed from heat, cleaned, and ^1H spectra were acquired on a 300 MHz Bruker DPX spectrometer.

2.12. General procedure for labelling with $^{13}CO_2$

10 mg of substrate was added to a glass vial followed by trimethylamine (2 equivalents) and 400 µL of dry Acetonitrile. In a separate vial the appropriate amount of I_2 (4 equivalents) was weighed in and 400 µL of dry Acetonitrile was added. To this mixture an excess of PMe_3 (~100 µL, 73.5 mg, 0.97 mmol) was slowly added dropwise until the solution had no yellow colour remaining and afforded a white suspension. The suspension was then transferred using a micro-pipette to the vial containing the substrate. This vial was sealed with a cap containing a septum and using a balloon fitted with a needle sparged with $^{13}CO_2$ (Sigma Aldrich <3 atom % ^{18}O, 99.0 atom % ^{13}C) for 10 minutes. The sealed vial was placed in a heating block on a hot plate and heated for 15 minutes at 50 °C. The mixture was removed from the heating block, cooled to room temperature, and opened. The reaction mixture was then transferred to a round bottom flask and evaporated to dryness and purified by silica gel column

chromatography (1% acetic acid/5% methanol/chloroform) to provide the desired product. ^{1}H and ^{13}C NMR spectra were then obtained on a 400 MHz Bruker AVII HD spectrometer.

2.13. Original procedure

A solution of trimethylphosphine (40mg/mL, 1 mL, 0.5 mmol) was added to iodine (0.5 equiv.) in a 1.5 ml HPLC sample vial. The contents were gently agitated until the iodine was completely dissolved and a fine colourless precipitate had formed. The contents of the vial were combined with an equal volume of a stock solution of amine (0.5 equiv.) in DMF containing triethylamine (100 µL/mL) to give a homogeneous solution. An aliquot of 0.5mL was transferred to the reactor of a Synthra MeI Plus synthesis module, the reactor was closed and the solution was purged with He (25mL/min) for 1 minute. Carbon-11 was added in the form of $[^{11}C]CO_2$ at -40 °C after which the reactor was pressurized to 2.3 bar and heated at 50 °C for 5 minutes. At the end of the reaction time, the reactor was cooled to 25 °C and the reaction was quenched with 0.1% TFA in water (1 mL). The mixture was degassed with He prior to injection into an HPLC system equipped for either analytical or preparative chromatography.

2.14. Synthesis of PMe_3I_2 for NMR studies

Iodine (1 eq.) was dissolved in acetonitrile-d_3 to this solution PMe_3 (1.1 eq.) was added dropwise with agitation until all yellow colour was gone and a fine colourless precipitate had formed. The solution was transferred to an NMR tube and spectra were obtained.

HRMS: m/z Calc: 329.8531 Found: decomposition

PMe_3 ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 0.98 (s, 9H).
^{31}P NMR (121 MHz, Acetonitrile-d_3) δ -60.79.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (d, *J* = 1.7 Hz, 9H).
^{31}P NMR (162 MHz, Chloroform-*d*) δ -61.10.

PMe_3I_2 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 2.20 (d, *J* = 14.4 Hz), 2.06 (d, *J* = 14.2 Hz).
^{31}P NMR (121 MHz, Chloroform-*d*) δ 52.20, 25.04.

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 1.91 (d, *J* = 14.9 Hz), 1.67 – 1.55 (d), 1.38 (d, *J* = 13.1 Hz).
^{31}P NMR (121 MHz, Acetonitrile-d_3) δ 53.46, 25.36, -1.15.

Table S5. Important NMR shifts in ppm of the Phosphine, Phosphine Oxide, and Phosphine Diiodide

	MeCN-d_3		$CDCl_3$	
Phosphine Species	^{1}H	^{31}P	^{1}H	^{31}P
PMe_3	0.98	-60.79	0.95	-60,08
$OPMe_3$	1.40	38.8	1.47	39.5
PMe_3I_2	1.91, 1.8, 1.72	53.46, 25.36, -1.15	2.20, 2.06	52.20, 25.04

We theorize that due to the different possible binding of the iodine to the phosphine multiple shifts can be seen in NMR spectroscopy. This is supported by Wolf Walther du Mont et al. [1]

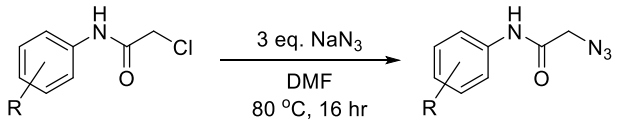
2.15. Analytical Quality Control for the synthesis of 19; synthesis of [19]

LC/MS-ES+ under acidic conditions was performed on a Zorbax SB C18 column (1.8 µm 3 x 50 mm). Mobile phase: A: (H2O + 0.05% TFA by vol.) / B: (CH3CN + 0.05% TFA by vol). Gradient: t = 0 min 0% (B), from 0 to 95% (B) in 2.5 min, 95% (B) for 0.2 min, from 95 to 100% (B) in 0.2 min, 100% (B) for 0.4 min, From 100% to 0% (B) in 0.1 min. Stop time 4 min. Column T = 60°C. Flow rate: 1.5 ml/min. Mass range ES+: (100-1000 amu, F=60). UV detection wavelengths: DAD 1A = 220.8, DAD 1B = 254.8. The use of this methodology is indicated by "LC/MS: QC_3_MIN" in the analytic characterization of the described compounds.

2.16. General Synthesis of Chlorides

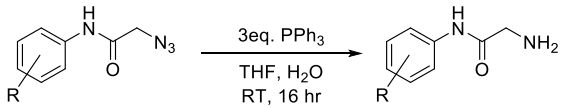
Synthesis of chlorides followed the literature procedure from Klein et al.[2]

2.17. General Synthesis of Azides



Synthesis of azides followed the literature procedure from Zhou et al.[3]

2.18. General Synthesis of Amines



Synthesis of amines followed the literature procedure from Zhou et al.[3]

2.19. 4-(4-nitrophenoxy)spiro[2H-benzofuran-3,1'-cyclopropane]; synthesis of [19]

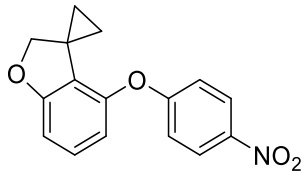


Figure S2. Precursor to [19], 4-(4-nitrophenoxy)spiro[2H-benzofuran-3,1'-cyclopropane]

To a solution of spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 85 WO2012076877, 200mg, 1.2331mmol), 1-fluoro-4-nitrobenzene (165.29mg, 1.1715mmol) in N,N-dimethylformamide (2mL), dipotassium carbonate (255.64mg, 1.8497mmol) was added at room temperature. The reaction mixture was stirred at 100°C for 3 h. The reaction mixture was diluted with EtOAc (50mL) and Brine (50mL) was added. The two phases were separated and the organic one was dried with Na_2SO_4, concentrated under vacuum affording 4-(4-nitrophenoxy)spiro[2H-benzofuran-3,1'-cyclopropane] (274mg) as orange oil. The crude was used in the next step without further purifications.[4]

LC/MS: QC_3_MIN: Rt = 2.520 min; m/z 284 $[M+H]^+$

2.20. 4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyaniline; synthesis of [19]

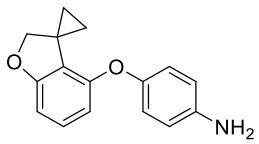


Figure S3. Precursor to [19], 4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyaniline

4-(4-nitrophenoxy)spiro[2H-benzofuran-3,1'-cyclopropane] (274mg, 0.9672mmol), iron (270.1mg, 4.8362mmol) and ammonium chloride (258.69mg, 4.8362mmol) were suspended on a mixture ethanol (8mL) water (2mL).The mixture was refluxed at 80°C for 5h. After cooling, the solids were filtered off and the filtrate was concentrated up to 5mL, diluted with EtOAc (30mL) and washed with brine (50mL). The residue was purified by flash chromatography (Biotage System) on silica gel using a SNAP 25g as column and Cyclohexane/Ethyl acetate from 80:20 to 40:60 as eluent, affording 4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyaniline (208mg) as a white solid.

LC/MS: QC_3_MIN: Rt = 1.965 min; m/z 254 $[M+H]^+$

2.21. tert-butyl N-[(1R)-1-[(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)carbamoyl]propyl]carbamate; synthesis of [19]

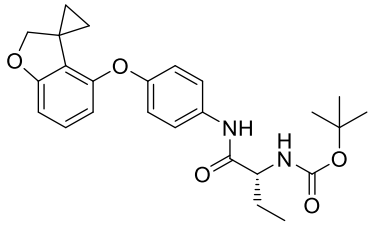


Figure S4. Precursor to [19], tert-butyl N-[(1R)-1-[(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)carbamoyl]propyl]carbamate

To a solution of 4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyaniline (208mg, 0.8212mmol), (R)-2-((tert-butoxycarbonyl)amino)butanoic acid (166.89mg, 0.8212mmol) and N,N-diethylethanamine (207.73mg, 2.0529mmol) in ethyl acetate (5mL), T3P 50%w/w in ethyl acetate (627.06mg, 0.9854mmol) was slowly added at 0°C. The reaction mixture was stirred at the same temperature for 2h. Ethyl acetate (50mL) was added, and the organic layer was washed with an aqueous solution of $NaHCO_3$ (20mL) and then with brine (50mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude material was purified on silica gel (Biotage system) using a SNAP 25g as column and cyclohexane/EtOAc from 100/0 to 60/40 as eluent to afford tert-butyl N-[(1R)-1-[(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)carbamoyl]propyl]carbamate (307mg).

LC/MS: QC_3_MIN: Rt = 2.686 min; mass ion not detected

2.22. (2*R*)-2-amino-*N*-(6-((3,7-dimethyl-2,3-dihydrobenzofuran-4-yl)oxy)pyridin-3-yl)butanamide; Precursor of [18]

Amine precursor to compound **18** was prepared following the method described within WO 2012076877, wherein the amine precursor to AUT15 [**18**] is Intermediate 160.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.26 – 8.15 (m, 2H), 6.84 (d, *J* = 14.5 Hz, 2H), 6.37 (d, *J* = 8.2 Hz, 1H), 4.45 (s, 2H), 3.45 (d, *J* = 3.8 Hz, 1H), 3.21 (s, 1H), 2.19 (d, *J* = 0.7 Hz, 3H), 1.98 (dd, *J* = 7.0, 2.8 Hz, 1H), 1.65 (d, *J* = 14.3 Hz, 2H), 1.58 (s, 4H), 1.37 (d, *J* = 2.2 Hz, 2H), 1.19 (s, 2H), 1.03 (s, 3H), 0.78 (d, *J* = 2.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53, 160.95, 160.48, 147.41, 138.93, 131.68, 130.28, 129.36, 121.62, 116.16, 113.82, 110.79, 78.78, 77.48, 77.16, 76.84, 56.70, 49.60, 27.92, 27.12, 24.78, 14.76, 13.77, 10.24.

$C_{20}H_{23}N_3O_3$ Calc. m/z+H: 354.1812 Found m/z+H: 354.1812

2.23. (R)-5-ethyl-3-(6-((7-methyl-2H-spiro[benzofuran-3,1'-cyclopropan]-4-yl)oxy)pyridin-3-yl)imidazolidine-2,4-dione; [18]

Compound **18** was prepared following the method described within WO 2012076877, wherein AUT15 [**18**] is example 62.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.7 Hz, 2H), 7.72 (s, 2H), 6.91 (s, 4H), 6.42 (d, *J* = 8.3 Hz, 4H), 4.46 (s, 4H), 4.19 (s, 2H), 2.20 (s, 6H), 1.90 (d, *J* = 7.1 Hz, 4H), 1.35 (d, *J* = 2.2 Hz, 4H), 1.05 (s, 6H), 0.80 (d, *J* = 2.2 Hz, 4H), 0.07 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.60, 163.10, 161.01, 156.30, 146.65, 145.36, 137.29, 129.43, 123.64, 121.82, 116.64, 114.11, 110.96, 78.76, 77.48, 77.16, 76.84, 58.31, 25.20, 24.77, 14.77, 13.87, 8.93, 1.15.

$C_{21}H_{21}N_3O_4$ Calc.: m/z+Na: 402.1424 Found m/z+Na: 402.1421

2.24. (2R)-2-amino-N-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)butanamide; Precursor of [19]

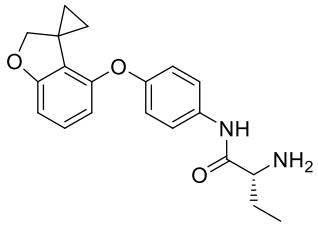


Figure S5. Amine precursor to [19], (2R)-2-amino-N-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)butanamide

To a solution of tert-butyl N-[(1R)-1-[(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)carbamoyl]propyl]carbamate (307mg, 0.7001mmol) in dichloromethane (5mL) was added 2,2,2-trifluoroacetic acid (1490mg, 12.937mmol) and stirred at 0°C for 5h. The mixture was diluted in DCM (50mL) and a saturated solution of sodium carbonate was added while the pH was allowed to reach 8. The organic layer was separated, washed with brine (50mL), dried with sodium sulphate, filtered and evaporated to dryness, producing (2R)-2-amino-N-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)butanamide (235mg). The crude was used for the next step without further purification.

LC/MS: QC_3_MIN: Rt = 1.967 min; m/z 339 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.60 – 7.50 (m, 2H), 7.04 – 6.90 (m, 2H), 6.91 (d, *J* = 2.2 Hz, 1H), 6.55 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.25 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.30 (s, 1H), 4.47 (s, 2H), 3.44 (dd, *J* = 8.0, 4.2 Hz, 1H), 2.17 (s, 3H), 2.06 – 1.89 (m, 1H), 1.73 – 1.58 (m, 1H), 1.57 – 1.45 (m, 2H), 1.25 (s, 0H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.95 – 0.78 (m, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.03, 163.04, 153.48, 152.74, 133.47, 128.18, 121.08, 120.82, 119.05, 110.89, 104.83, 78.98, 56.80, 31.08, 28.00, 24.50, 13.63, 10.25.
$C_{20}H_{22}N_2O_3$ Calc. m/z+H: 339.1704 Found m/z+H: 339.1703

2.25. (5R)-5-ethyl-3-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)imidazolidine-2,4-dione; [19]

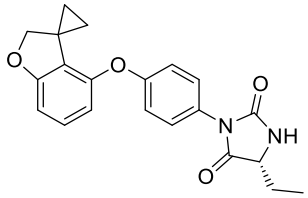


Figure S6. Compound [19], Aut18

To a mixture of triethylamine (26.912mg, 0.2660mmol) 0.04 mL and (2R)-2-amino-N-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)butanamide (30mg, 0.0887mmol) in dichloromethane (3mL), at 0°C a solution of bis(trichloromethyl) carbonate (9.2077mg, 0.0310mmol) in dichloromethane (3mL) was slowly added and the reaction mixture was stirred for 30 minutes at the same temperature. The reaction mixture was diluted in EtOAc (30mL), washed with an aqueous solution 0.2N of HCl (20mL) then brine (20mL), dried with sodium sulphate, filtered and evaporated to dryness. The residues were purified by flash chromatography on silica gel (Biotage system) using a SNAP 25g as column and cyclohexane and EtOAc from 80/20 to 30/70 as eluent. The appropriate fractions were combined and evaporated to dryness affording (5R)-5-ethyl-3-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)imidazolidine-2,4-dione (12mg) as a white solid.

LC/MS: QC_3_MIN: Rt = 2.260 min; m/z 365$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.06 – 6.96 (m, 3H), 6.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.36 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.45 (s, 1H), 4.47 (s, 2H), 4.19 (ddd, *J* = 6.2, 4.7, 1.3 Hz, 1H), 2.17 (s, 15H), 2.06 – 1.84 (m, 2H), 1.50 – 1.39 (m, 2H), 1.25 (s, 0H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.86 – 0.79 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.12, 172.79, 163.20, 157.47, 156.38, 151.45, 128.37, 127.77, 126.20, 118.34, 112.09, 105.55, 78.99, 77.48, 77.16, 76.84, 58.05, 31.09, 25.26, 24.45, 13.86, 8.87.

$C_{21}H_{20}N_2O_4$ Calc. m/z+Na: 387.1316 Found m/z+Na: 387.1315

2.26. (*R*)-2-amino-*N*-(6-(3-methoxy-4-methylphenoxy)pyridin-3-yl)butanamide; Precursor of [20]

Amine precursor to compound **20** was prepared following the method described within WO 2011069951, wherein the amine precursor to AUT19 [**20**] is Intermediate 65.[5]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.53 (s, 1H), 8.24 – 8.17 (m, 2H), 7.11 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.92 – 6.83 (m, 1H), 6.65 – 6.54 (m, 2H), 3.79 (s, 3H), 3.45 (dd, *J* = 8.1, 4.2 Hz, 1H), 2.19 (d, *J* = 0.7 Hz, 3H), 2.00 (ddd, *J* = 14.0, 7.6, 4.2 Hz, 1H), 1.75 – 1.59 (m, 1H), 1.03 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53, 160.46, 158.65, 153.62, 138.94, 131.64, 130.98, 130.28, 122.96, 112.28, 111.37, 103.79, 56.72, 55.51, 27.94, 15.92, 10.25.

$C_{17}H_{21}N_3O_3$ Calc. m/z+H: 316.1656 Found m/z+H: 316.1656

2.27. (*R*)-5-ethyl-3-(6-(3-methoxy-4-methylphenoxy)pyridin-3-yl)imidazolidine-2,4-dione; [20]

Compound **20** was prepared following the method described within WO 2011069951, wherein AUT19 [**20**] is example 19.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.71 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.97 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.64 (d, *J* = 6.9 Hz, 2H), 5.65 (s, 1H), 4.21 (m, 1H), 3.80 (s, 3H), 2.21 (d, 3H), 2.17 (s, 7H), 2.08 – 1.84 (m, 2H), 1.21 (d, *J* = 6.1 Hz, 1H), 1.06 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.13, 172.51, 163.35, 158.69, 155.91, 152.71, 145.47, 137.24, 131.06, 123.65, 123.42, 112.83, 111.40, 104.19, 77.48, 77.16, 76.84, 58.26, 55.56, 31.09, 25.22, 15.98, 8.90.

$C_{18}H_{19}N_3O_4$ Calc. m/z+Na: 364.1268 Found m/z+Na: 364.1268

Labelled Products

2.28. 1,3-dihydro-2*H*-benzo[*d*]imidazole-2-one; [1]

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 9.42 (s, 2H), 7.17 (dd, *J* = 5.9, 3.5 Hz, 2H), 6.94 (dd, *J* = 6.0, 3.5 Hz, 2H).
^{13}C NMR (101 MHz, Acetone-d_6) δ **155.88**, 121.54, 109.55.

HRMS: [m/z+Na] Calc: 157.0372 Found: 157.0372

2.29. Benzyl 2-oxoimidazolidine-1-carboxylate; [2]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.30 (m, 5H), 5.29 (s, 2H), 3.95 – 3.79 (m, 4H). (experimental)
^{13}C NMR (101 MHz, Chloroform-d) δ 151.39, 150.26, 148.98, 135.16, 128.78, 128.68, 128.51, 68.74, 40.75, 40.66.[6]

2.30. (4*R*, 5*S*)-4, 5-bis(4-nitrophenyl)imidazolidin-2-one; [3]

^{1}H NMR (400 MHz, Acetonitrile-d3) δ 8.22 (d, J = 8.8 Hz, 4H), 7.51 (d, J = 8.8 Hz, 4H), 5.59 (s, 2H), 4.67 (s, 2H). (experimental)
^{13}C NMR (101 MHz, Acetonitrile-d3) δ 162.71, **148.77**, 128.83, 124.85, 65.09.

HRMS: [m/z+Na] Calc: 352.0733 Found: 352.0733

2.31. Pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione; [4]

Product not observed.

2.32. Thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione; [5]

Product not observed.

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 9.70 (s, 1H), 7.66 – 7.39 (m, 1H), 7.30 (dd, *J* = 5.4, 0.9 Hz, 1H), 6.69 (d, *J* = 5.3 Hz, 1H). [7]

2.33. Benzofuro[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione; [6]

Product not observed.

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 9.56 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.33 (m, 2H), 7.26 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 6.24 (s, 1H). [7]

2.34. 5-((1*H*-indol-3-yl)methyl)imidazolidine-2,4-dione; [7]

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 10.02 (s, 1H), 9.89 (s, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.37 (m, 1H), 7.33 (dd, *J* = 5.4, 2.5 Hz, 1H), 7.18 – 7.08 (m, 1H), 7.08 – 6.98 (m, 1H), 5.12 (t, *J* = 10.0 Hz, 1H), 3.37 (dd, *J* = 12.3, 6.5 Hz, 2H).

^{1}H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 9.08 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.41 – 7.27 (m, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 5.7 Hz, 1H), 6.33 (d, J = 21.1 Hz, 1H), 4.21 (s, 1H), 3.32 (d, J = 14.6 Hz, 1H), 2.97 (ddd, J = 12.5, 9.1, 4.5 Hz, 1H). (experimental)
^{13}C NMR (101 MHz, Chloroform-d) δ 175.23, **158.09**, 136.43, 127.17, 123.65, 122.06, 119.53, 118.59, 111.52, 109.24, 64.87, 59.41, 27.83.

^{13}C HRMS: [m/z+Na] Calc: 253.0777 Found: 253.0777

2.35. 3-(4-nitrophenyl)imidazolidine-2,4-dione; [8]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.31 (d, *J* = 9.2 Hz, 2H), 7.71 (d, *J* = 9.1 Hz, 2H), 6.35 (s, 1H), 4.03 (dd, *J* = 3.1, 1.3 Hz, 2H).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 171.51, **156.83**, 147.48, 139.20, 127.53, 125.08, 47.13.

^{13}C HRMS: [m/z-H] Calc: 221.0397 Found: 221.0397

2.36. 3-benzylimidazolidine-2,4-dione; [9]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.37 (m, 2H), 7.36 – 7.27 (m, 3H), 5.91 (s, 1H), 4.72 – 4.61 (m, 2H), 4.01 – 3.94 (m, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.03, **158.15**, 135.99, 128.82, 128.80, 128.14, 46.60, 42.40.
^{13}C HRMS: [m/z+Na] Calc: 214.0668 Found: 214.0668

2.37. 3-(4-iodophenyl)imidazolidine-2,4-dione; [10]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.21 (s, 1H), 3.99 – 3.90 (m, 2H).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ **157.40**, 138.99, 132.63, 129.47, 27.61.
^{13}C HRMS: [m/z+Na] Calc: 325.9478 Found: 325.9478

2.38. 3-(pyridin-2-yl)imidazolidine-2,4-dione; [11]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 – 7.62 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 (ddd, *J* = 8.5, 6.7, 3.1 Hz, 2H), 3.12 (qd, *J* = 7.3, 4.7 Hz, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 183.44, 155.88, 132.22, 128.64, 45.89.
^{13}C NMR (151 MHz, Chloroform-*d*) δ **156.11**, 149.88, 138.59, 123.92, 46.31.

^{13}C HRMS: [m/z+Na] Calc: 201.0464 Found: 201.0464

2.39. 3-(4-phenoxyphenyl)imidazolidine-2,4-dione; [12]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 4H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 8.8 Hz, 4H), 5.82 (s, 1H), 4.15 (d, *J* = 3.0 Hz, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.11, **157.19**, 156.54, 130.05, 127.84, 126.06, 124.10, 119.70, 119.02, 46.50.

^{13}C HRMS: [m/z+Na] Calc: 292.0774 Found: 292.0773

2.40. 3-(4-isopropylphenyl)imidazolidine-2,4-dione; [13]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (q, *J* = 8.6 Hz, 4H), 6.29 – 6.15 (m, 1H), 4.12 (dd, *J* = 3.1, 1.1 Hz, 2H), 2.94 (p, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.27, **157.66**, 149.33, 134.06, 127.49, 126.23, 46.57, 34.07, 24.01.

^{13}C HRMS: [m/z+Na] Calc: 242.0981 Found: 242.0981

2.41. 4-(2,5-dioxoimidazolidin-1-yl)benzonitrile; [14]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.89 – 7.75 (m, 2H), 7.62 (dd, *J* = 8.4, 2.1 Hz, 2H), 6.33 (s, 1H), 4.06 – 3.95 (m, 2H).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ **156.93**, 133.85, 127.66, 47.12.

^{13}C HRMS: [m/z+Na] Calc: 225.0464 Found: 225.0464

2.42. 3-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione; [15]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.81 – 7.68 (m, 2H), 7.67 – 7.58 (m, 2H), 6.06 (s, 1H), 4.18 (dd, J = 3.1, 1.1 Hz, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.60, **156.51**, 134.67, 130.48, 126.43, 126.39, 126.18, 122.47, 46.46.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.73.

^{13}C HRMS: [m/z+Na] Calc: 268.0385 Found: 268.0385

2.43. 3-(4-benzoylphenyl)imidazolidine-2,4-dione; [16]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.91 – 7.85 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.62 – 7.50 (m, 4H), 6.31 (s, 1H), 4.03 (d, *J* = 3.1 Hz, 2H).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 196.42, 171.77, **157.34**, 138.39, 137.46, 133.61, 131.39, 130.78, 129.45, 127.03, 47.18.

^{13}C HRMS: [m/z+Na] Calc: 304.0774 Found: 304.0773

2.44. 3-(2-methoxybenzyl)imidazolidine-2,4-dione; [17]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.94 – 6.83 (m, 2H), 5.74 (s, 1H), 4.74 (s, 2H), 4.00 (d, *J* = 1.2 Hz, 2H), 3.84 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.09, 158.23, **157.20**, 129.03, 128.49, 123.68, 120.54, 110.60, 55.59, 46.56, 37.60.
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.95, 158.87, 156.76, 153.45, 152.16, 147.48, 129.51, 128.00, 121.24, 111.61, 56.20, 47.20, 37.54.

^{13}C HRMS: [m/z+Na] Calc: 244.0774 Found: 244.0773

2.45. (R)-5-ethyl-3-(6-((7-methyl-2H-spiro[benzofuran-3,1'-cyclopropan]-4-yl)oxy)pyridin-3-yl)imidazolidine-2,4-dione; [18]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.7 Hz, 2H), 7.72 (s, 2H), 6.91 (s, 4H), 6.42 (d, *J* = 8.3 Hz, 4H), 4.46 (s, 4H), 4.19 (s, 2H), 2.20 (s, 6H), 1.90 (d, *J* = 7.1 Hz, 4H), 1.35 (d, *J* = 2.2 Hz, 4H), 1.05 (s, 6H), 0.80 (d, *J* = 2.2 Hz, 4H), 0.07 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.60, 163.10, 161.01, **156.30**, 146.65, 145.36, 137.29, 129.43, 123.64, 121.82, 116.64, 114.11, 110.96, 78.76, 58.31, 25.20, 24.77, 14.77, 13.87, 8.93.
$C_{21}H_{21}N_3O_4$ Calc.: m/z+Na: 402.1424 Found m/z+Na: 402.1421

^{13}C HRMS: [m/z+Na] Calc: 403.1458 Found: 403.1458

2.46. (5R)-5-ethyl-3-(4-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxyphenyl)imidazolidine-2,4-dione; [19]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.06 – 6.96 (m, 3H), 6.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.36 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.45 (s, 1H), 4.47 (s, 2H), 4.19 (ddd, *J* = 6.2, 4.7, 1.3 Hz, 1H), 2.17 (s, 15H), 2.06 – 1.84 (m, 2H), 1.50 – 1.39 (m, 2H), 1.25 (s, 0H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.86 – 0.79 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.79, 163.20, 157.47, **156.38**, 151.45, 128.37, 127.77, 126.20, 118.34, 112.09, 105.55, 78.99, 58.05, 25.26, 24.45, 13.86, 8.87.

$C_{21}H_{20}N_2O_4$ Calc. m/z+Na: 387.1316 Found m/z+Na: 387.1315
^{13}C HRMS: [m/z+Na] Calc: 388.1349 Found: 388.134

2.47. (*R*)-5-ethyl-3-(6-(3-methoxy-4-methylphenoxy)pyridin-3-yl)imidazolidine-2,4-dione; [20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.71 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.97 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.64 (d, *J* = 6.9 Hz, 2H), 5.65 (s, 1H), 4.21 (m, 1H), 3.80 (s, 3H), 2.21 (d, 3H), 2.17 (s, 7H), 2.08 – 1.84 (m, 2H), 1.21 (d, *J* = 6.1 Hz, 1H), 1.06 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.51, 163.35, 158.69, **155.91**, 152.71, 145.47, 137.24, 131.06, 123.65, 123.42, 112.83, 111.40, 104.19, 58.26, 55.56, 25.22, 15.98, 8.90.

$C_{18}H_{19}N_3O_4$ Calc. m/z+Na: 364.1268 Found m/z+Na: 364.1268
^{13}C HRMS: [m/z+Na] Calc: 365.1301 Found: 365.1301

Azides

2.48. 2-azido-N-(4-nitrophenyl)acetamide; [8i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 8.24 (d, *J* = 9.2 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 4.22 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.04, 144.30, 142.55, 125.29, 119.58, 119.50, 53.05.

HRMS: [m/z+Na] Calc: 244.0441 Found: 244.0441

2.49. 2-azido-N-benzylacetamide; [9i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H), 6.64 (s, 1H), 4.47 (d, *J* = 5.8 Hz, 2H), 4.03 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.55, 137.55, 128.96, 127.99, 127.92, 52.83, 43.61.

HRMS: [m/z+Na] Calc: 213.0747 Found: 213.0747

2.50. 2-azido-N-(4-iodophenyl)acetamide; [10i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 4.15 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.60, 138.23, 136.66, 121.92, 88.57, 53.13.

HRMS: [m/z+Na] Calc: 324.9557 Found: 324.9556

2.51. 2-azido-N-(pyridin-2-yl)acetamide; [11i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.31 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.09 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 4.15 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.26, 150.49, 148.23, 138.64, 120.65, 114.18, 53.16.

HRMS: [m/z+Na] Calc: 200.0543 Found: 200.0542

2.52. 2-azido-N-(4-phenoxyphenyl)acetamide; [12i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.33 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.04 – 6.93 (m, 4H), 4.16 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.52, 157.43, 154.35, 132.23, 129.92, 123.43, 121.98, 119.69, 118.78, 53.12.

HRMS: [m/z+Na] Calc: 291.0852 Found: 291.0852

2.53. 2-azido-N-(4-isopropylphenyl)acetamide; [13i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.14 (s, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.50, 146.00, 134.51, 127.17, 120.38, 53.15, 33.77, 24.12.

HRMS: [m/z+Na] Calc: 241.1060 Found: 241.1059

2.54. 2-azido-N-(4-cyanophenyl)acetamide; [14i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 4.20 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.94, 140.81, 133.54, 119.96, 118.70, 108.29, 53.05.

HRMS: [m/z+Na] Calc: 224.0543 Found: 224.0542

2.55. 2-azido-N-(4-(trifluoromethyl)phenyl)acetamide; [15i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 4.19 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.87, 139.89, 127.16, 126.84, 126.56 (d, *J* = 3.7 Hz), 125.43, 119.77, 53.08.

HRMS: [m/z+Na] Calc: 267.0464 Found: 267.0464

2.56. 2-azido-N-(4-benzoylphenyl)acetamide; [16i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 6.9 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 4.20 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.66, 164.91, 140.67, 137.80, 133.94, 132.49, 131.75, 130.03, 128.46, 119.24, 53.12.

HRMS: [m/z+Na] Calc: 303.0852 Found: 303.0852

2.57. 2-azido-N-(2-methoxybenzyl)acetamide; [17i]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 2H), 6.97 – 6.87 (m, 2H), 6.80 (s, 1H), 4.47 (d, *J* = 5.9 Hz, 2H), 3.98 (s, 2H), 3.88 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.24, 157.77, 130.04, 129.35, 125.62, 120.88, 110.55, 55.51, 52.95, 39.60.

HRMS: [m/z+Na] Calc: 243.0852 Found: 243.0852

Amines

2.58. 2-azido-N-(2-methoxybenzyl)acetamide; [8ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.88 (s, 1H), 8.23 (d, *J* = 9.2 Hz, 2H), 7.79 (d, *J* = 9.2 Hz, 2H), 3.53 (s, 2H), 1.68 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.39, 143.50, 125.29, 118.93, 45.21.

HRMS: [m/z+H] Calc: 196.0717 Found: 196.0722

2.59. 2-amino-N-benzylacetamide; [9ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.38 – 7.25 (m, 7H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.41 (s, 2H), 1.39 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.71, 138.53, 128.83, 127.94, 127.59, 44.90, 43.17.

HRMS: [m/z+H] Calc: 165.1022 Found: 165.1022

2.60. 2-amino-N-(4-iodophenyl)acetamide; [10ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.43 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 3.47 (s, 2H), 1.56 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.90, 138.06, 137.58, 121.38, 87.31, 45.24.

HRMS: [m/z+H] Calc: 276.9832 Found: 276.9832

2.61. 2-amino-N-(pyridin-2-yl)acetamide; [11ii]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.75 (s, 1H), 8.28 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 8.17 (dt, *J* = 8.4, 1.1 Hz, 1H), 7.75 (ddd, *J* = 8.3, 7.3, 2.0 Hz, 1H), 7.07 (ddd, *J* = 7.3, 4.9, 1.1 Hz, 1H), 3.35 (s, 2H), 1.82 (s, 2H).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.81, 149.24, 139.19, 120.48, 113.76, 45.90.

HRMS: [m/z+H] Calc: 152.0818 Found: 152.0826

2.62. 2-amino-N-(4-phenoxyphenyl)acetamide; [12ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.36 (s, 1H), 7.62 – 7.53 (m, 2H), 7.32 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.04 – 6.95 (m, 4H), 3.49 (s, 2H), 1.55 (s, 4H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.69, 157.83, 153.38, 137.13, 133.46, 129.84, 123.11, 121.20, 119.90, 118.47, 45.20.

HRMS: [m/z+H] Calc: 243.1128 Found: 243.1140

2.63. 2-amino-N-(4-isopropylphenyl)acetamide; [13ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 3.47 (s, 2H), 2.88 (hept, *J* = 6.9 Hz, 1H), 1.59 (s, 2H), 1.23 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.70, 144.97, 135.47, 127.02, 119.74, 45.26, 33.75, 24.18.

HRMS: [m/z+H] Calc: 193.1335 Found: 193.1346

2.64. 2-amino-N-(4-cyanophenyl)acetamide; [14ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 3.50 (s, 2H), 1.65 (s, 2H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.32, 141.70, 133.47, 119.38, 119.07, 107.18, 45.20.

HRMS: [m/z+Na] Calc: 198.0638 Found: 198.0637

2.65. 2-amino-N-(4-(trifluoromethyl)phenyl)acetamide; [15ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 3.50 (s, 2H), 1.61 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.21, 156.83, 140.79, 126.44, 125.85, 119.13, 45.22.

HRMS: [m/z+H] Calc: 219.0740 Found: 219.0752

2.66. 2-amino-N-(4-benzoylphenyl)acetamide; [16ii]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.69 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.81 – 7.69 (m, 4H), 7.58 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 3.52 (s, 2H), 1.64 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.78, 171.23, 141.64, 138.07, 133.08, 132.30, 131.82, 130.02, 128.40, 118.65, 45.29.

HRMS: [m/z+H] Calc: 255.1128 Found: 255.1127

2.67. 2-amino-N-(2-methoxybenzyl)acetamide; [17ii]

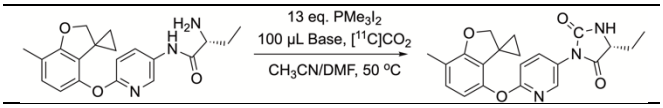
^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (s, 1H), 7.31 – 7.22 (m, 2H), 6.96 – 6.83 (m, 2H), 4.48 (d, J = 6.0 Hz, 2H), 3.87 (s, 3H), 3.36 (s, 2H), 1.59 (s, 1H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.46, 157.76, 129.75, 128.94, 126.55, 120.79, 110.47, 55.50, 45.05, 38.88.

HRMS: [m/z+H] Calc: 195.1128 Found: 195.1139

3. Results and Discussion

3.1. Base Screening

Table S6. Base screen with [**18**] and [^{11}C]CO_2



Entry	Base	RCY
1	Et_3N	14.0% ± 1.1 (n=2)
2	TMEDA	8.8% (n=1)
3	DiPEA	5.5% ± 3.8 (n=3)
4	DBU	4.1%± 1.6 (n=2)
5	DMAP	4.5% ± 6.3 (n=2)
6	TBD	0%
7	Tribenzylamine	0%
8	Proton Sponge	0%
9	P_2-^{t}Bu Base	0%

It was seen that triazabicyclodecene (TBD), tribenzylamine, 1,8-bis(dimethylamino)naphthalene (Proton Sponge), and 1-*tert*-Butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene) (P_2-^{t}Bu Base) (Table 1, Entries 6-9) all performed poorly and did not provide any product. 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and 4-Dimethylaminopyridine (DMAP) were low yielding around 4% (Table 1, Entries 4 and 5). N,N-diisopropylethylamine (DiPEA) performed only slightly better with 5.5% yield (Table 1, Entry 3). Tetramethylethylene diamine (TMEDA) provided a slightly higher yield at 8.8% (Table 1, Entry 2) and the highest yield obtained was with triethylamine at 14% (Table 1, Entry 1). It might be suggested that steric hindrance plays a larger role than basicity as proton sponge, a sterically hindered non-nucleophilic base, provided no yield. This can also be seen with TBD, a very strong base, which provided no yield. However, the weaker, less sterically hindered bases TMEDA and triethylamine outperformed the others.

3.2. NMR Studies

The ^{1}H NMR shift of pure PMe_3 in acetonitrile-d_3 was observed at δ = 0.98 ppm as a singlet. Whereas the PMe_3I_2 reagent ^{1}H NMR shift in acetonitrile-d_3 was observed at δ = 1.72 ppm as a doublet and at δ = 2.62 as a singlet. We observed the deactivation of the reagent in the presence of water and two new doublets observed at δ = 1.45 and 1.94 ppm which could be the deactivated species. When these new signals are observed in high concentrations in reactions with low yield this shows that there was water present in the reaction. However, these signals are observed in all of

the reactions indicating the consumption of the reagent. When extra caution taken to prevent excess water and sufficiently high equivalents of the reagent are used both high yields and lower concentrations of the deactivated species are observed. NMR yields were calculated by normalizing the number or protons in a signal and multiple runs were averaged to give final yields.

3.3. Radiotracer Production

*Production of [^{11}C]**18**:* The product peak of [^{11}C]**18** was collected after a purification time of 7.1±0.3 min, 24.4-25.1 min after EOB, directly into a 100mL glass vessel containing water for injection (60 mL) and a spinning magnetic stir bar. The obtained mixture was passed through an Oasis HLB SPE cartridge, the cartridge was washed with water (10 mL) and the product was eluted with EtOH (0.5 mL) followed by water (5 mL). 2.8 GBq to 9 GBq of [^{11}C]**18** were produced (n = 18), RCY = 48.7% with a molar activity of 290 MBq/nmol.
Quality control: The product [^{11}C]**18** eluted after 10.4±0.2 min in a radiochemical purity >97% and a molar activity of 288±63 MBq/nmol.

*Production of [^{11}C]**19***: The product peak of [^{11}C]**19** was collected after a purification time of 7.5±0.2 min, 24.0-25.0 min after EOB, directly into a 100mL glass vessel containing water for injection (60 mL) and a spinning magnetic stir bar. The obtained mixture was passed through an Oasis HLB SPE cartridge, the cartridge was washed with water (10 mL) and the product was eluted with EtOH (0.5 mL) followed by water (5 mL). 0.9 GBq to 4.8 GBq of [^{11}C]**19** were produced (n = 9), RCY = 34.9% with a molar activity of 332 MBq/nmol.
Quality control: The product [^{11}C]**19** eluted after 9.3±0.2 min in a radiochemical purity >97% and a molar activity of 332±79 MBq/nmol.

*Production of [^{11}C]**20**:* The product peak of [^{11}C]**20** was collected after a purification time of 7.5±0.2 min, 24.0-25.0 min after EOB, directly into a 100mL glass vessel containing water for injection (60 mL) and a spinning magnetic stir bar. The obtained mixture was passed through an Oasis HLB SPE cartridge, the cartridge was washed with water (10 mL) and the product was eluted with EtOH (0.5 mL) followed by water (5 mL).
2.7 GBq to 12 GBq of [^{11}C]**20** were produced (n = 9), RCY = 89.0% with a molar activity of 466 MBq/nmol was obtained.
Quality control: The product [^{11}C]**20** eluted after 10.5±0.2 min in a radiochemical purity >97% and a molar activity of 466±79 MBq/nmol.

4. HPLC Chromatograms for [^{11}C]CO_2 Runs

Note: The preparative traces for the screening reactions shown below have an X-axis that corresponds with synthesis time as opposed to true retention time.

4.1. Base screening

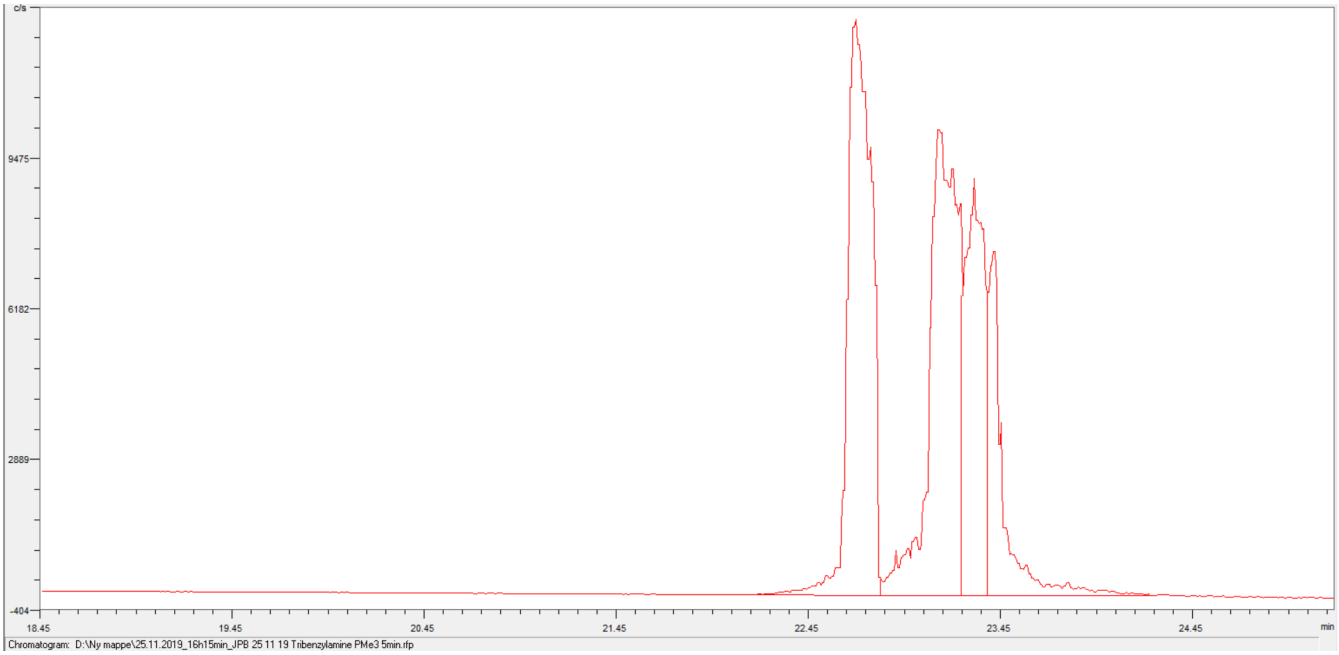


Figure S7. Preparative HPLC chromatogram from base screening using tribenzylamine, red = activity,

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
No products observed.				

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), Tribenzylamine PMe_3, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** is not observed.

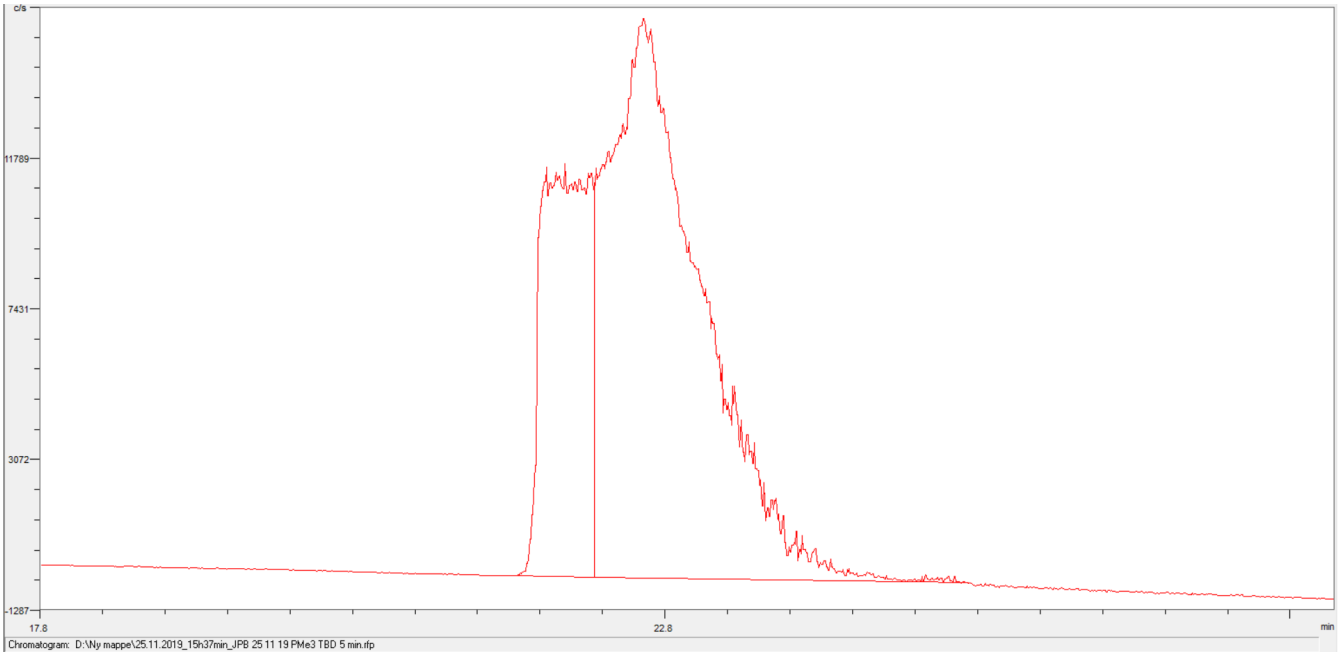


Figure S8. Preparative HPLC chromatogram from base screening using triazabicyclodecene (TBD), red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
No products observed.				

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), Triazabicyclodecene, PMe_3, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** is not observed.

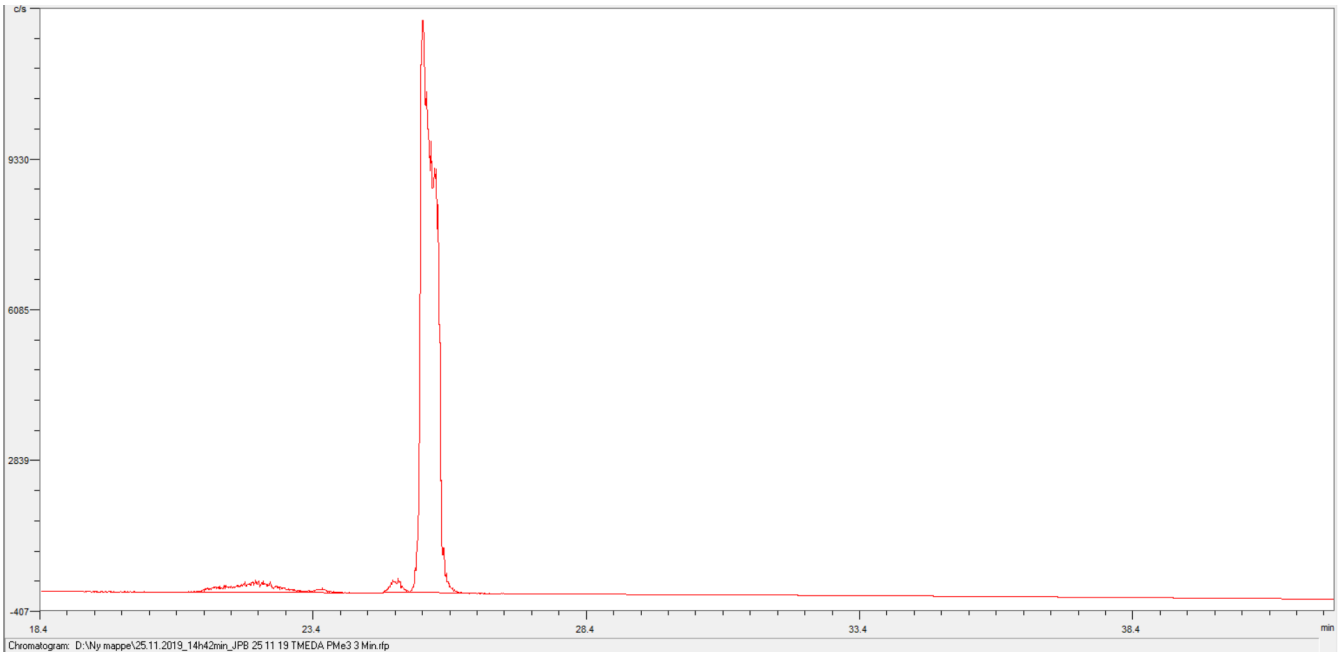


Figure S9. Preparative HPLC chromatogram from base screening using tetramethylethylenediamine, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
[^{11}C]CO_2	3.93	12537.38	5.05	0.5
[^{11}C]**18**	7.00	230637.30	92.94	8.8

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), Tetramethylethylenediamine, PMe_3, 50 °C, 3 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 7.00 minutes.

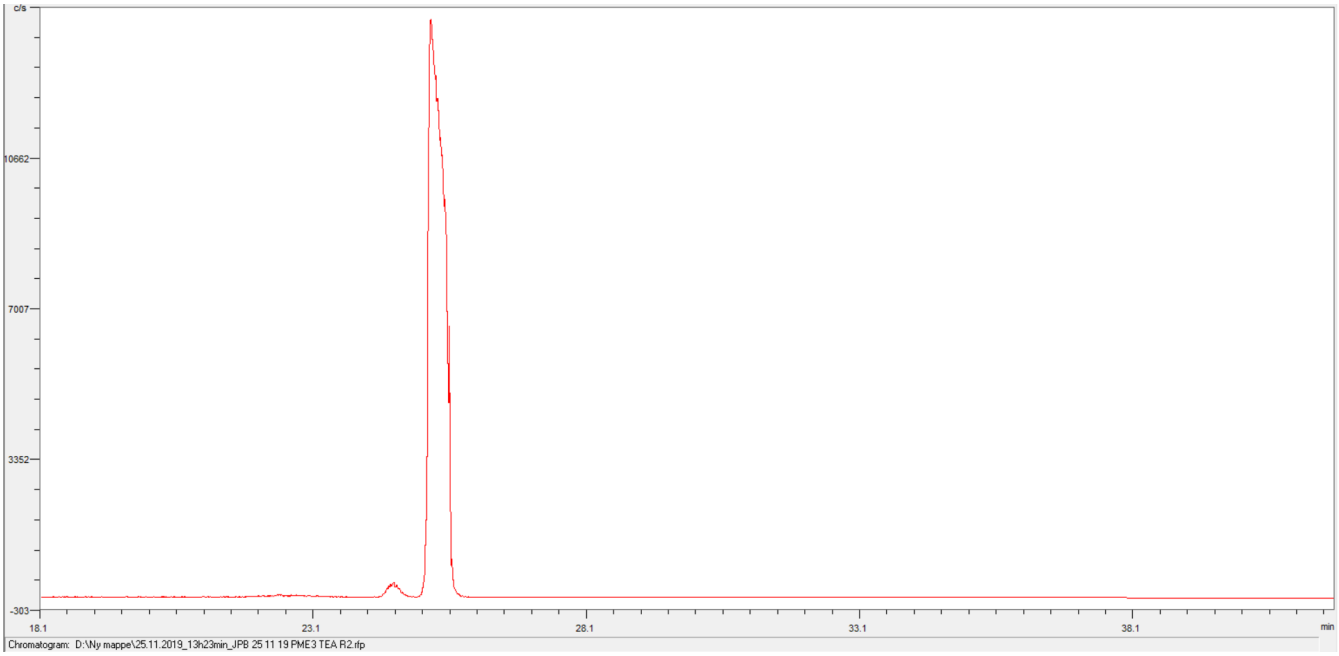


Figure S10. Preparative HPLC chromatogram from base screening using triethylamine (NEt_3), red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
[^{11}C]CO_2	4.36	2803.68	0.98	0.1
[^{11}C]**18**	7.15	277682.40	97.21	13.2

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), Triethylamine, PMe_3, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 7.2 minutes.

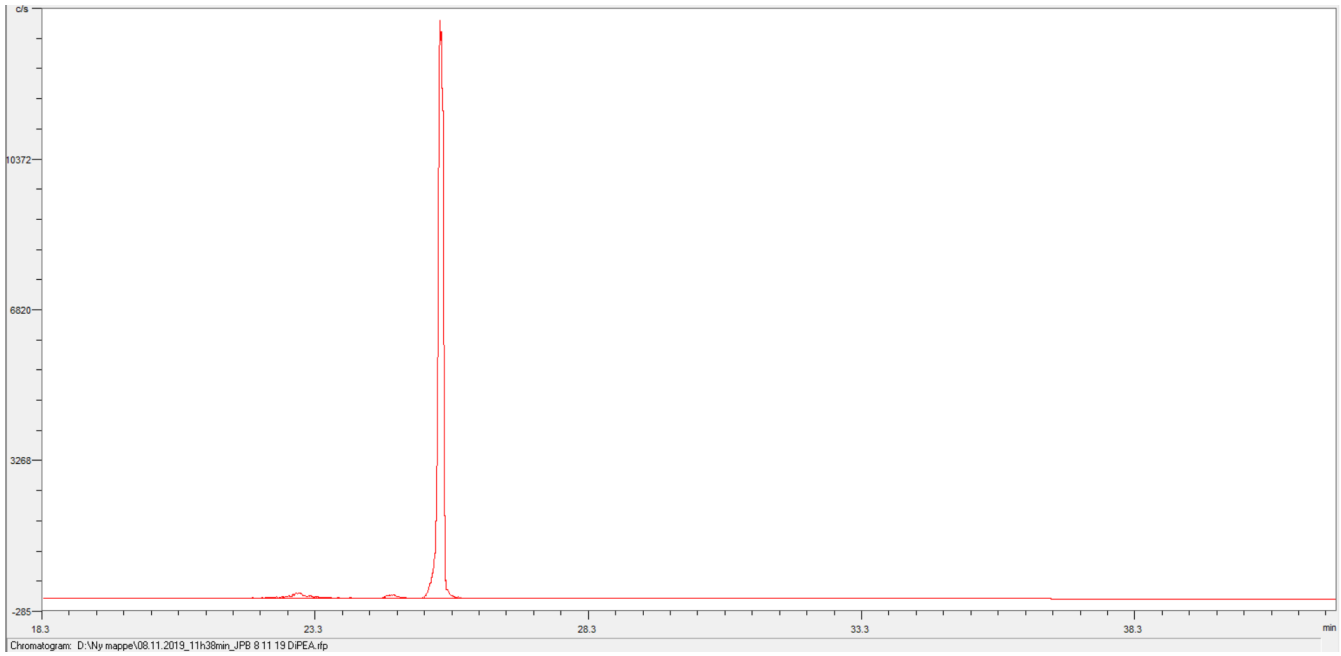


Figure S11. Preparative HPLC chromatogram from base screening using using N,N-Diisopropylethylamine (DiPEA), red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
[^{11}C]CO_2	4.71	3375.62	3.30	0.2
[^{11}C]**18**	7.27	97546.56	95.38	6.5

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), N,N-Diisopropylethylamine, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 7.3 minutes.

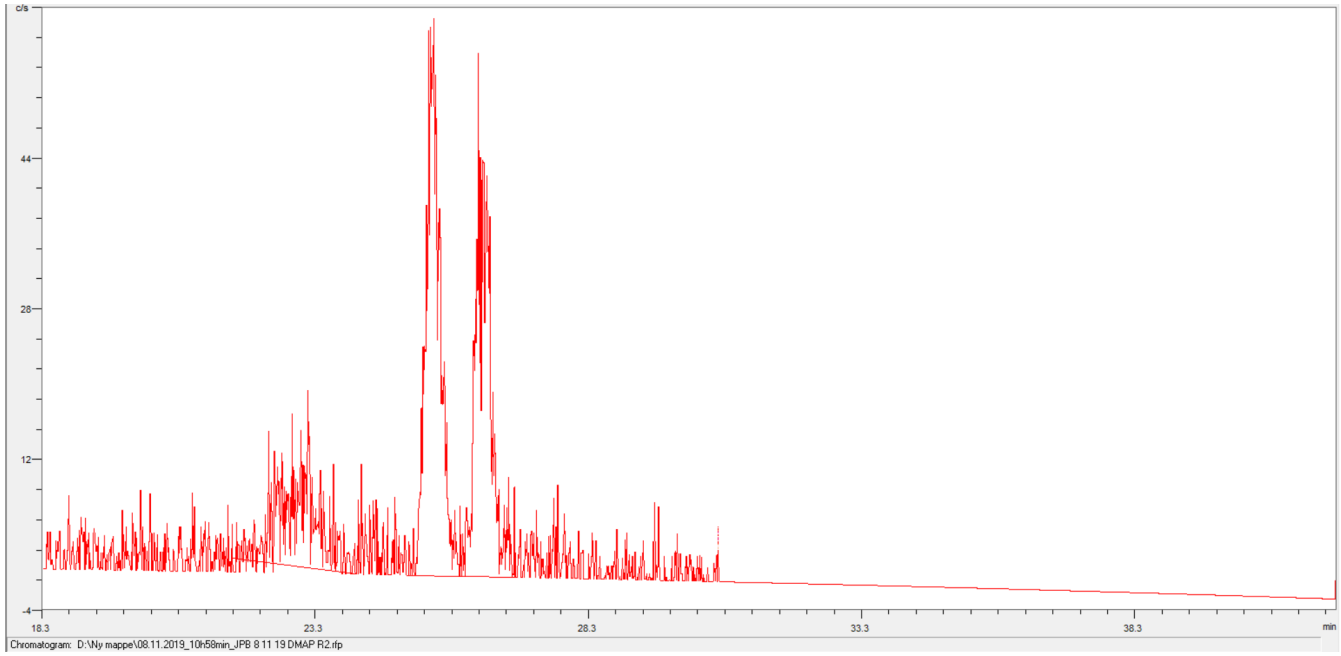


Figure S12. Preparative HPLC chromatogram from base screening using 4-Dimethylaminopyridine (DMAP) red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
[^{11}C]CO_2	4.84	544.47	21.81	4.5
[^{11}C]**18**	7.17	1067.88	42.77	8.9

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), 4-Dimethylaminopyridine, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 7.98 minutes.

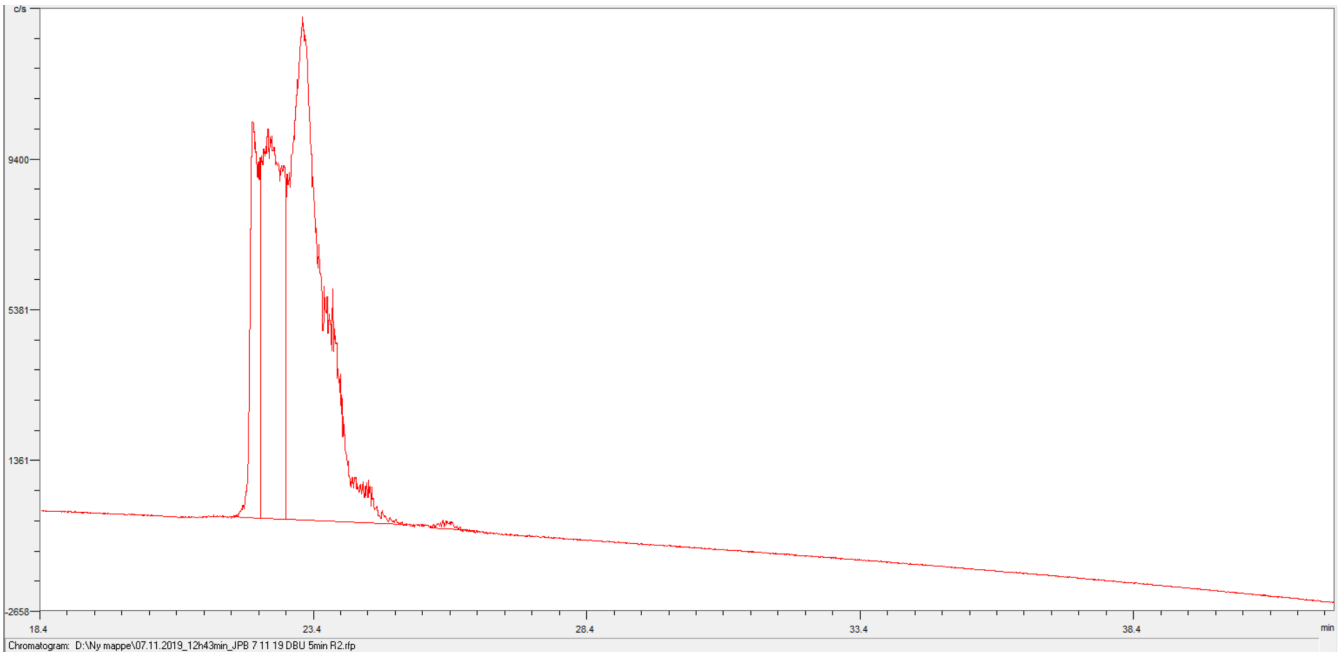


Figure S13. Preparative HPLC chromatogram from base screening using 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU), red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount RCY (%)
$[^{11}C]CO_2$	3.88	127526.40	13.50	7.3
$[^{11}C]$**18**	7.37	2901.07	0.31	0.2

Conditions: Precursor (2 mg, 0.0054 mmol), PMe_3I_2 (1.8 mg, 1 eq., 0.0054 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 7.37 minutes.

4.2. Solvent Screen

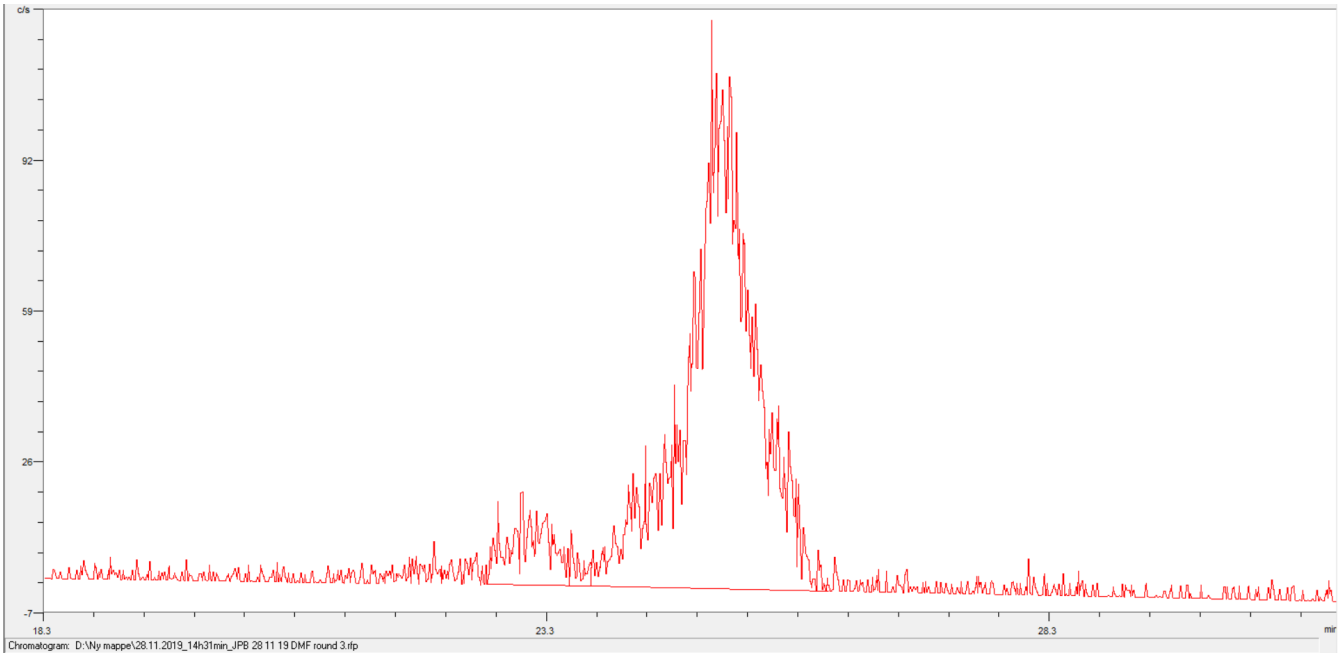


Figure S14. Preparative HPLC chromatogram from solvent screening using DMF, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	4.76	503.37	9.24	0.1

Conditions: Precursor (2 mg, 0.0054 mmol), Triethylamine, DMF, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** was not observed.

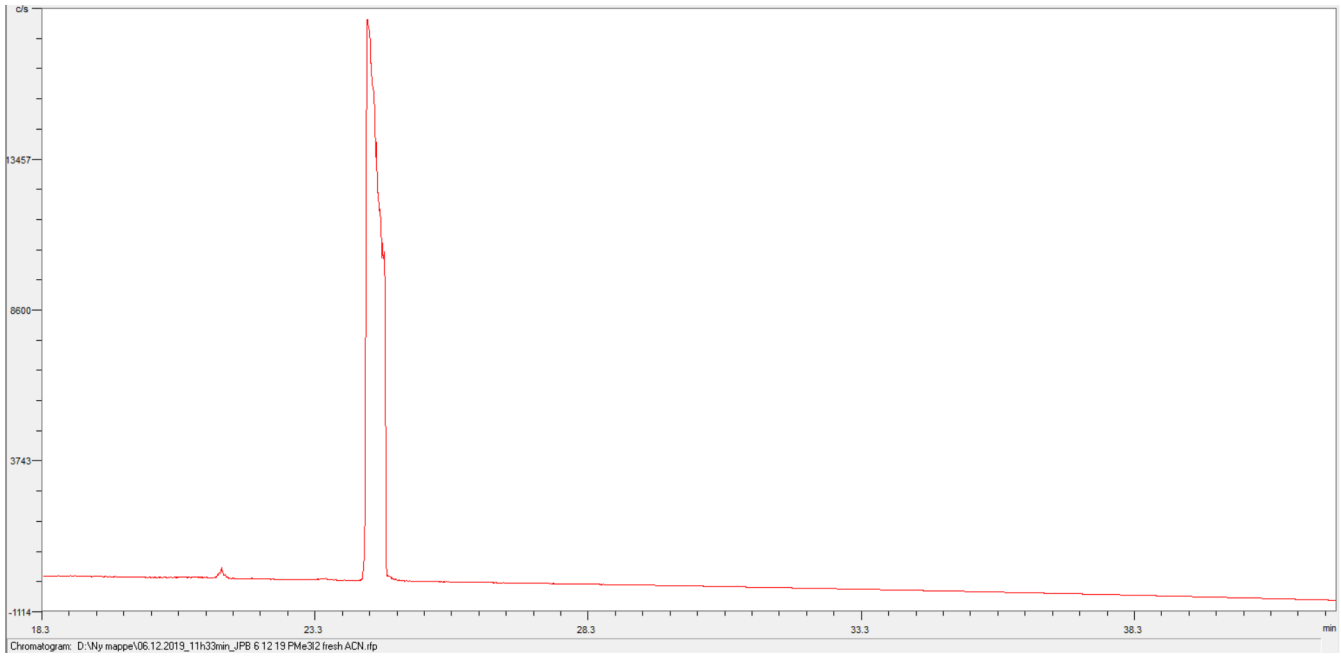


Figure S15. Preparative HPLC chromatogram from solvent screening using acetonitrile red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
[^{11}C]CO_2	3.27	1884.27	0.60	0.1
[^{11}C]**18**	5.95	311250.50	99.40	18.4

Conditions: Precursor (2 mg, 0.0054 mmol), MeCN, PMe_3I_2 Fresh, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 6.0 minutes.

4.3. Phosphine Screen

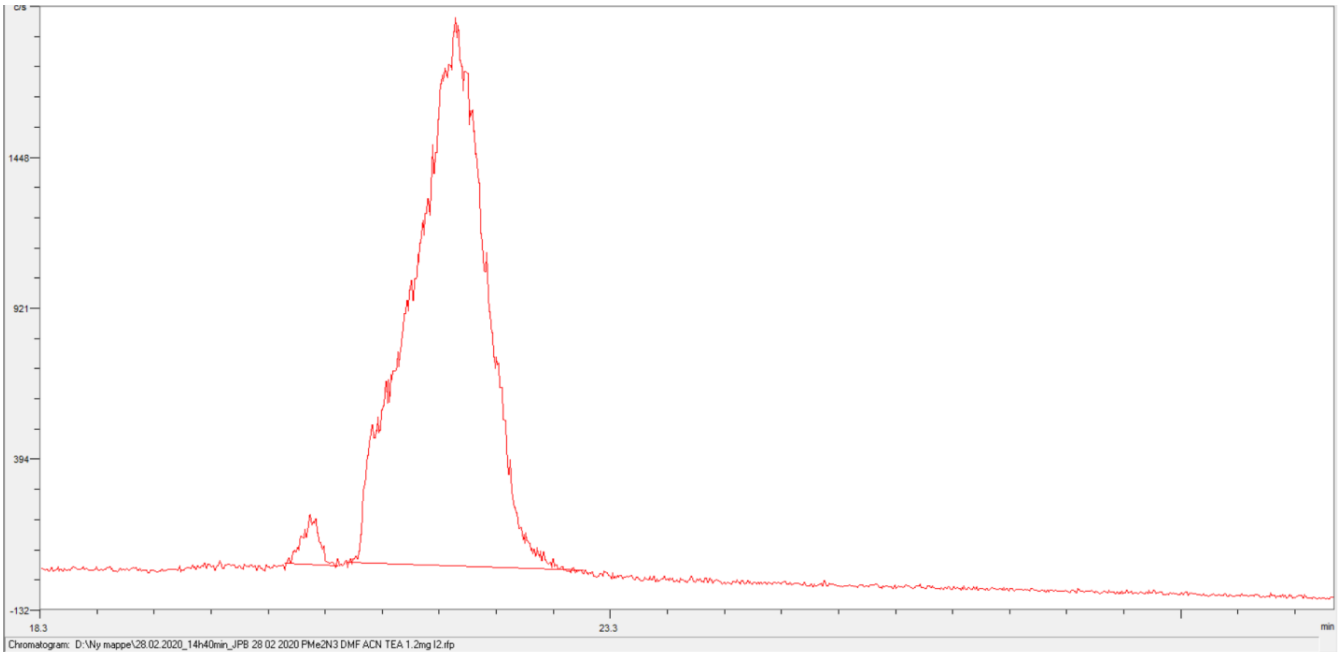


Figure S16. Preparative HPLC chromatogram from phosphine screening using $P(NMe_2)_3$, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	2.36	1756.55	2.04	1.2

Conditions: $P(NMe_2)_3$, 1.2 mg I_2 (0.0047 mmol), 2 mg Precursor (0.0054 mmol), Triethylamine, DMF/MeCN, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** was not observed.

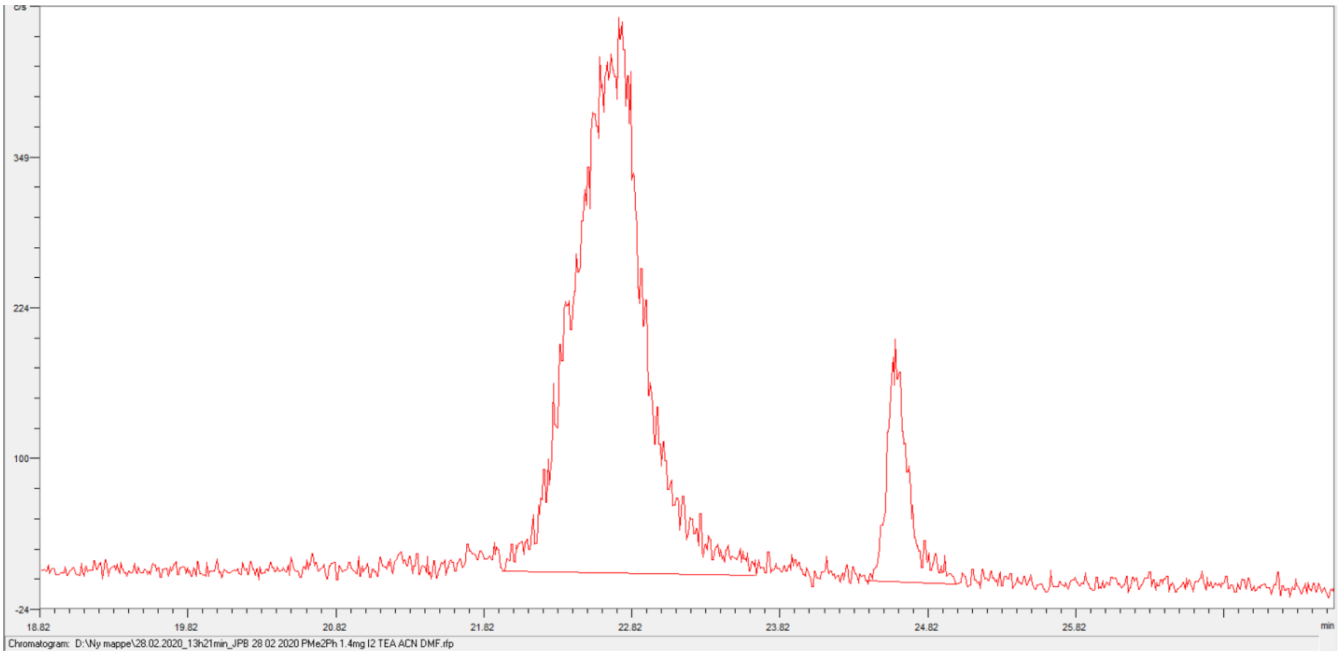


Figure S17. Preparative HPLC chromatogram from phosphine screening using PMe_2Ph, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.90	14669.81	88.45	19.5
$[^{11}C]$**18**	5.78	1915.60	11.55	2.5

Conditions: PMe_2Ph, 2 mg Precursor (0.0054 mmol), 1.4 mg I_2 (0.0055 mmol), Triethylamine, DMF/MeCN, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 5.8 minutes.

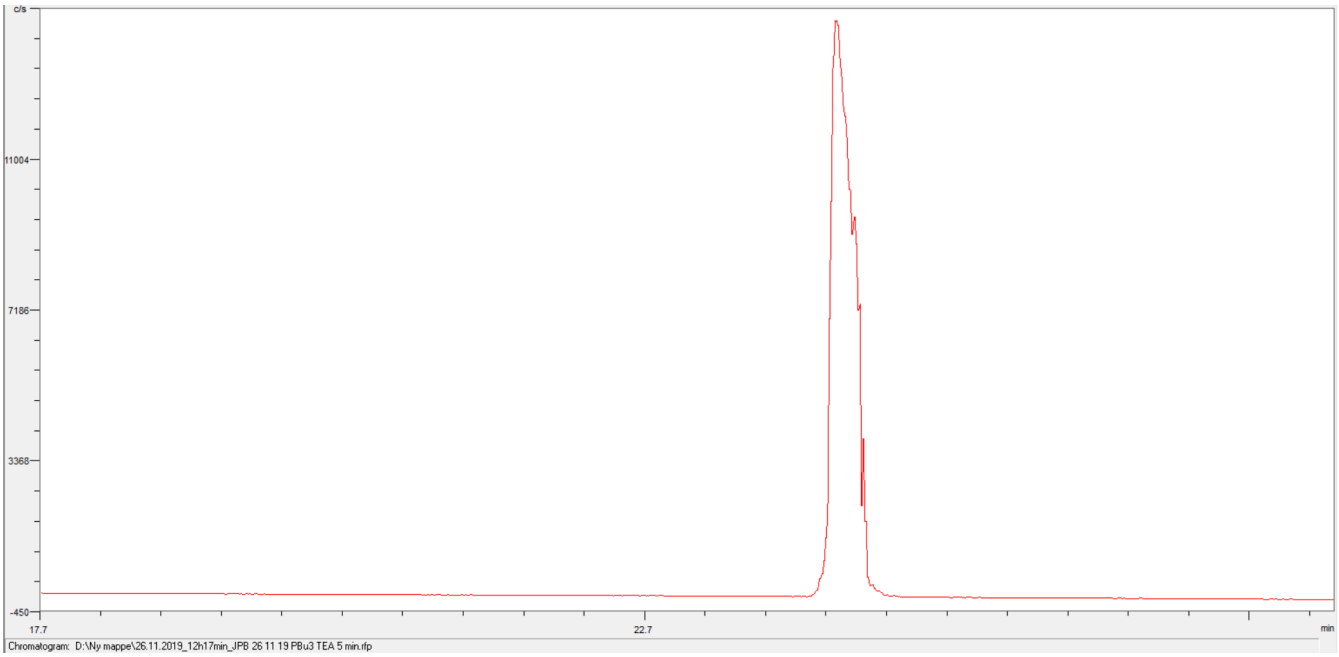


Figure S18. Preparative HPLC chromatogram from phosphine screening using PBu_3, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
[^{11}C]**18**	6.57	192094.00	100	8.2

Conditions: PBu_3, 2 mg Precursor (0.0054 mmol), 10 µL Triethylamine (72 µmol), PBu_3I_2, 5 min, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 6.6 minutes.

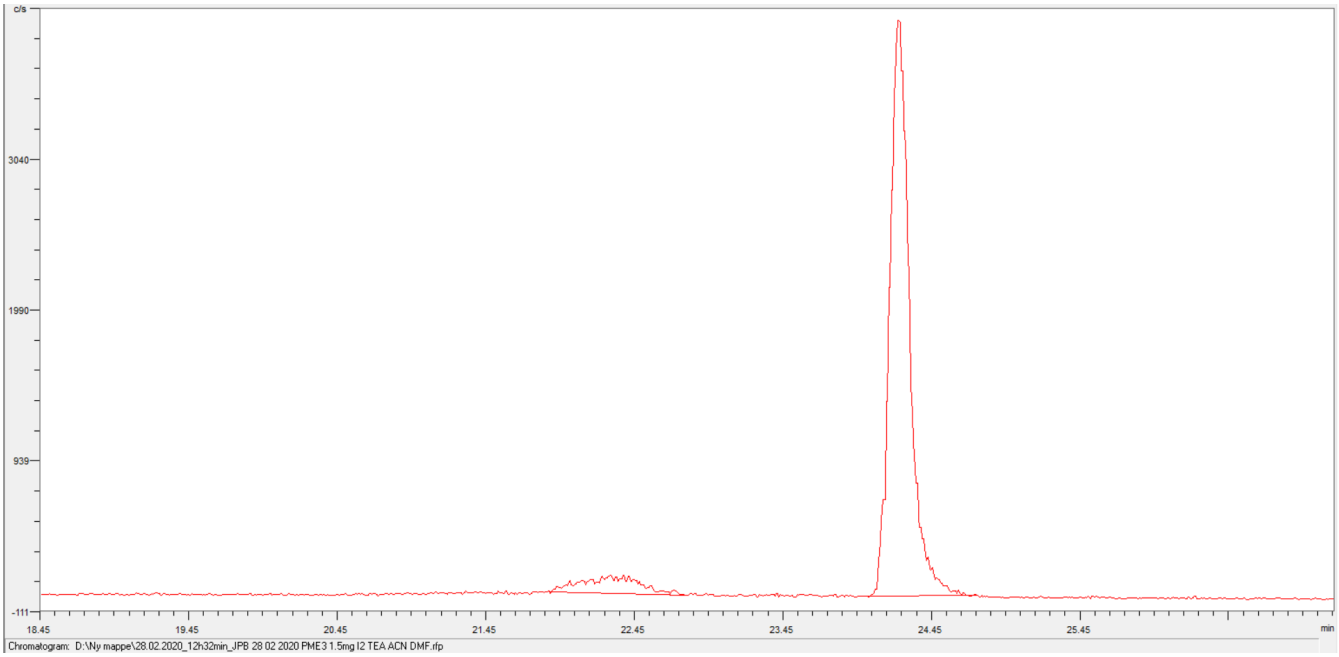


Figure S19. Preparative HPLC chromatogram from phosphine screening using PMe_3, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
[^{11}C]CO_2	3.83	3247.19	8.01	3.1
[^{11}C]**18**	5.78	37294.15	91.99	35.6

Conditions: 1.5 mg I_2 (0.0059 mmol), 2 mg Precursor (0.0054 mmol), PMe_3, ACN/DMF, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 5.8 minutes.

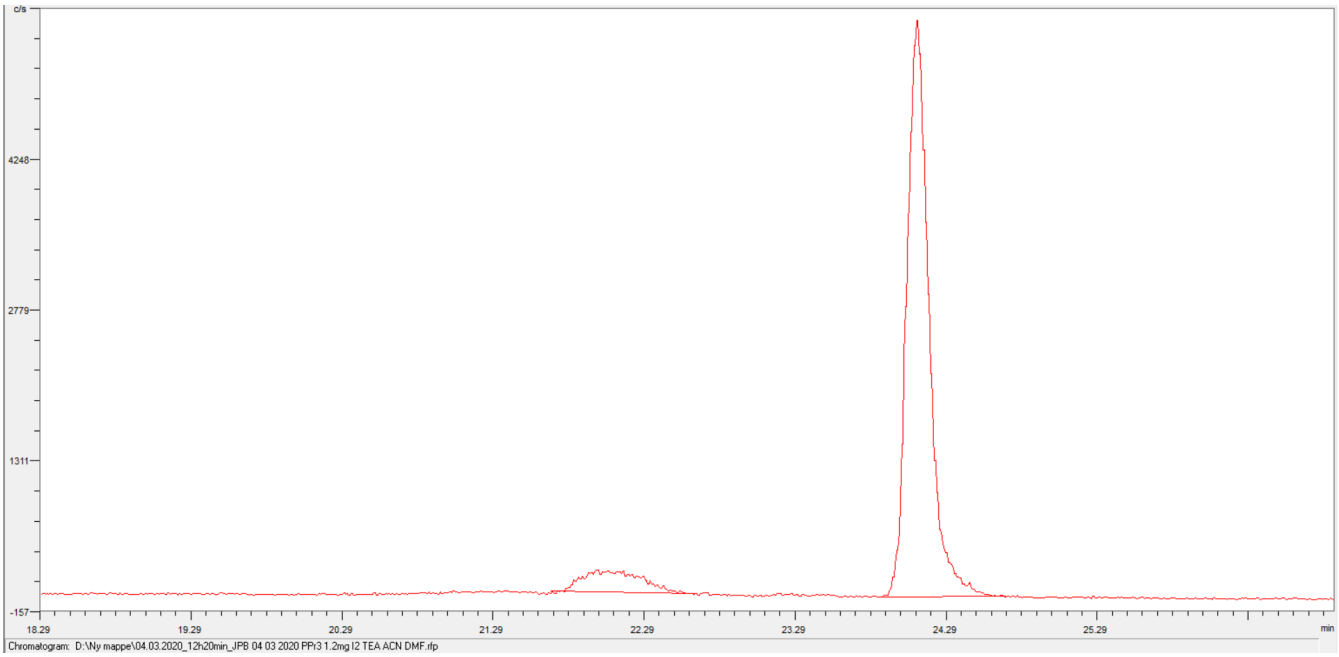


Figure S20. Preparative HPLC chromatogram from phosphine screening using PPr_3, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
[^{11}C]CO_2	3.69	5649.66	9.01	2.9
[^{11}C]**18**	5.81	57054.15	90.99	29.4

Conditions: 1.2 mg I_2 (0.0047 mmol), 2 mg Precursor (0.0054 mmol), PPr_3, MeCN/DMF, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** 5.8 minutes.

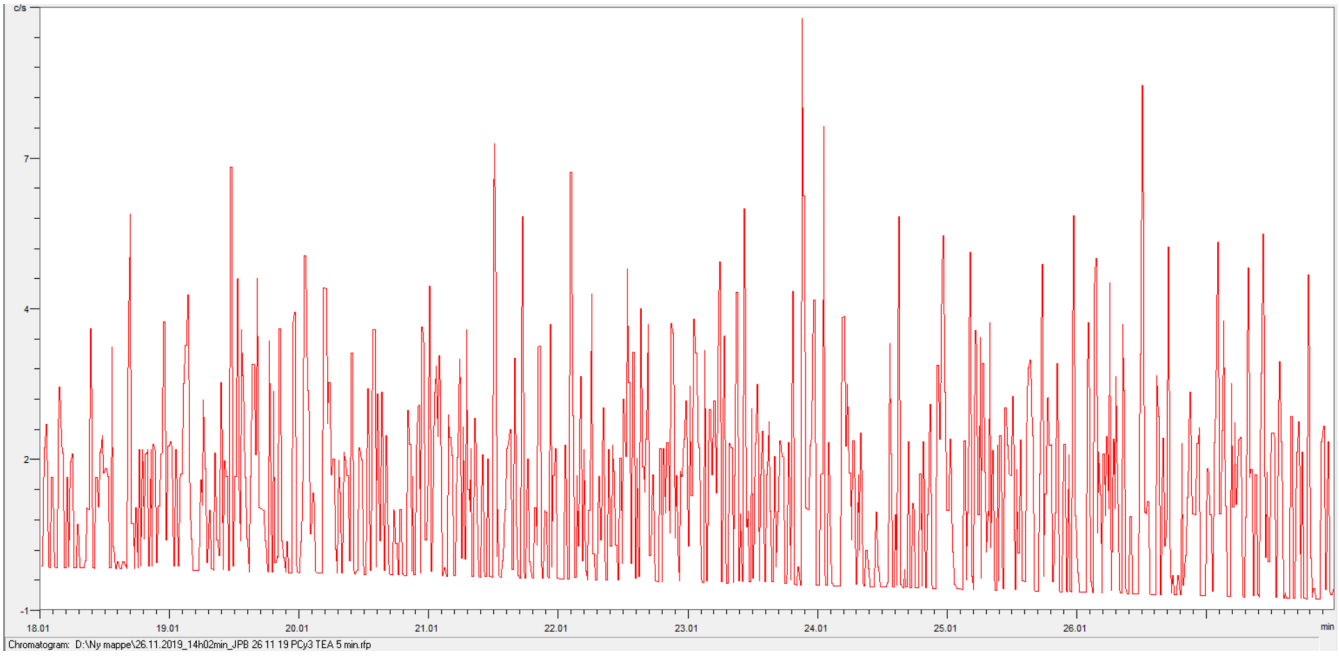


Figure S21. Preparative HPLC chromatogram from phosphine screening using PCy_3, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
No peaks observed				

Conditions: 1.2 mg I_2 (0.0047 mmol), 2 mg Precursor (0.0054 mmol), Triethylamine, DMF/MeCN, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product [^{11}C]**18** was not observed.

4.4. Stoichiometry Screen

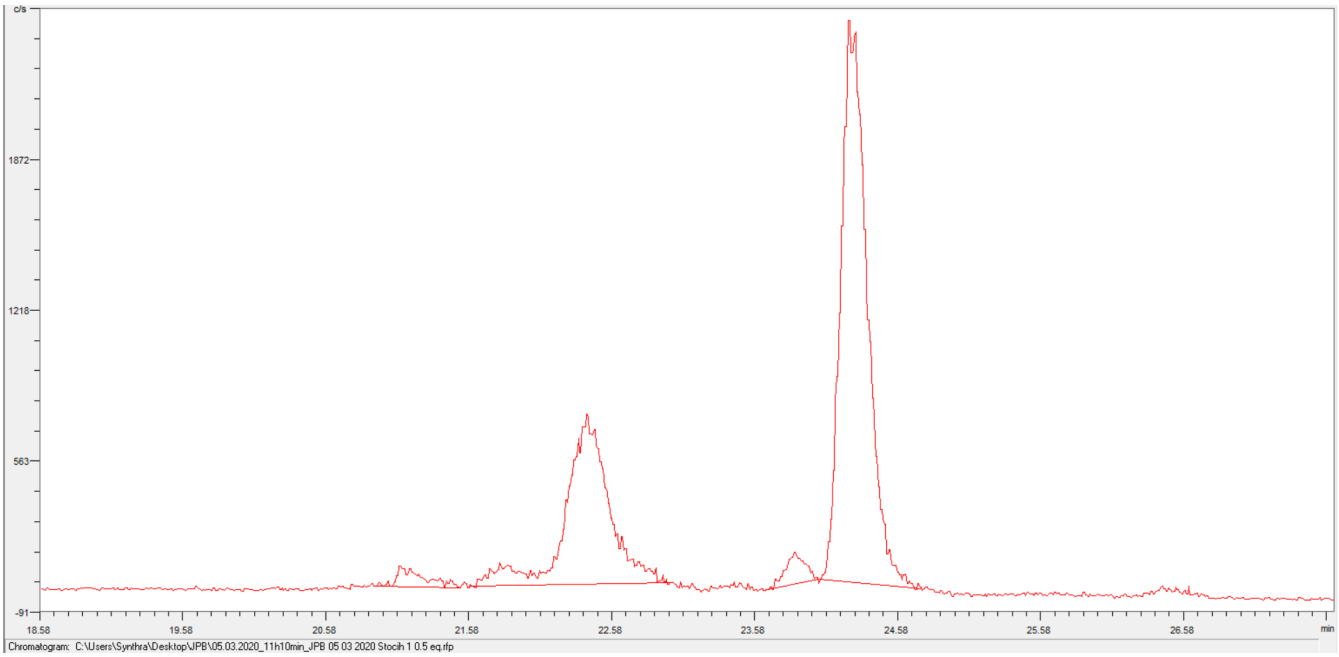


Figure S22. Preparative HPLC chromatogram from stoichiometry screening with 0.5 equivalents of PMe_3I_2 red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.82	14004.31	28.45	9.2
$[^{11}C]$**18**	5.66	31319.15	63.63	20.5

Conditions: 0.7 mg I_2 (0.003 mmol), 2 mg Precursor (0.0054 mmol), 0.5 Eq, PMe_3, MeCN, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 5.7 minutes.

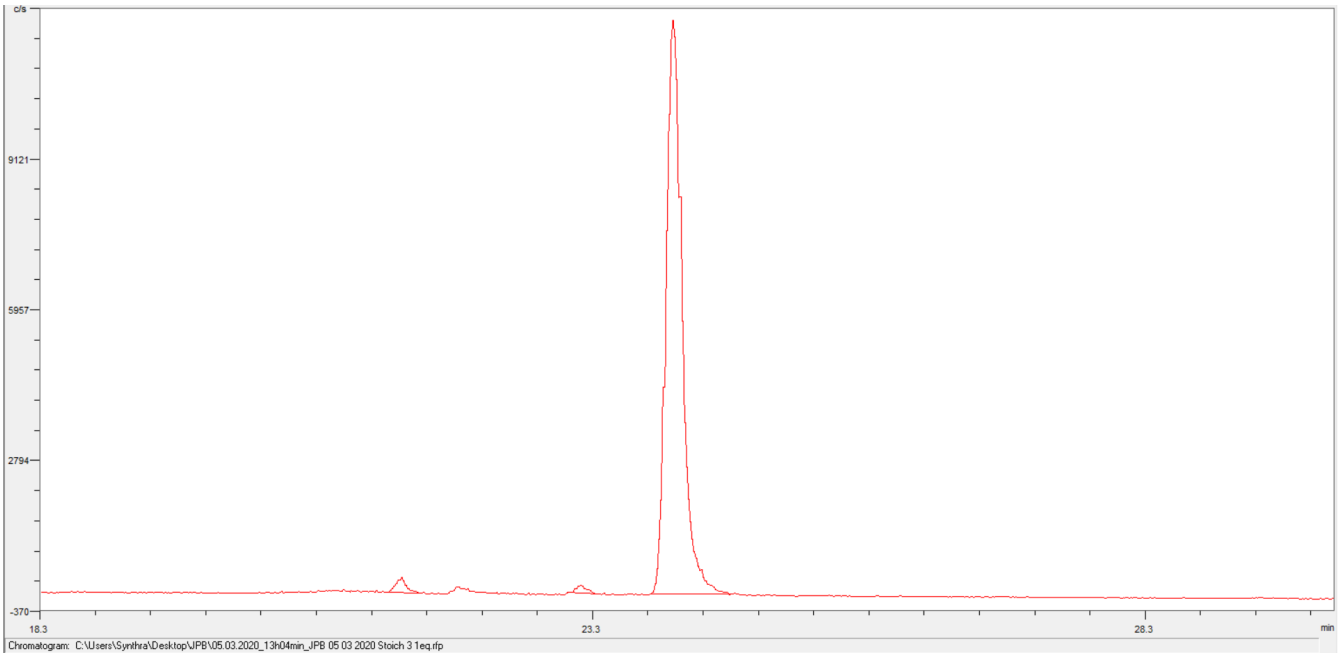


Figure S23. Preparative HPLC chromatogram from stoichiometry screening with 1.0 equivalents of PMe_3I_2, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.27	1950.09	1.55	0.6
$[^{11}C]$**18**	5.73	122549.30	97.54	53.7

Conditions: 1.4 mg I_2 (0.0055 mmol), 2 mg precursor (0.0054 mmol), 1 Eq, PMe_3, MeCN, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 5.7 minutes.

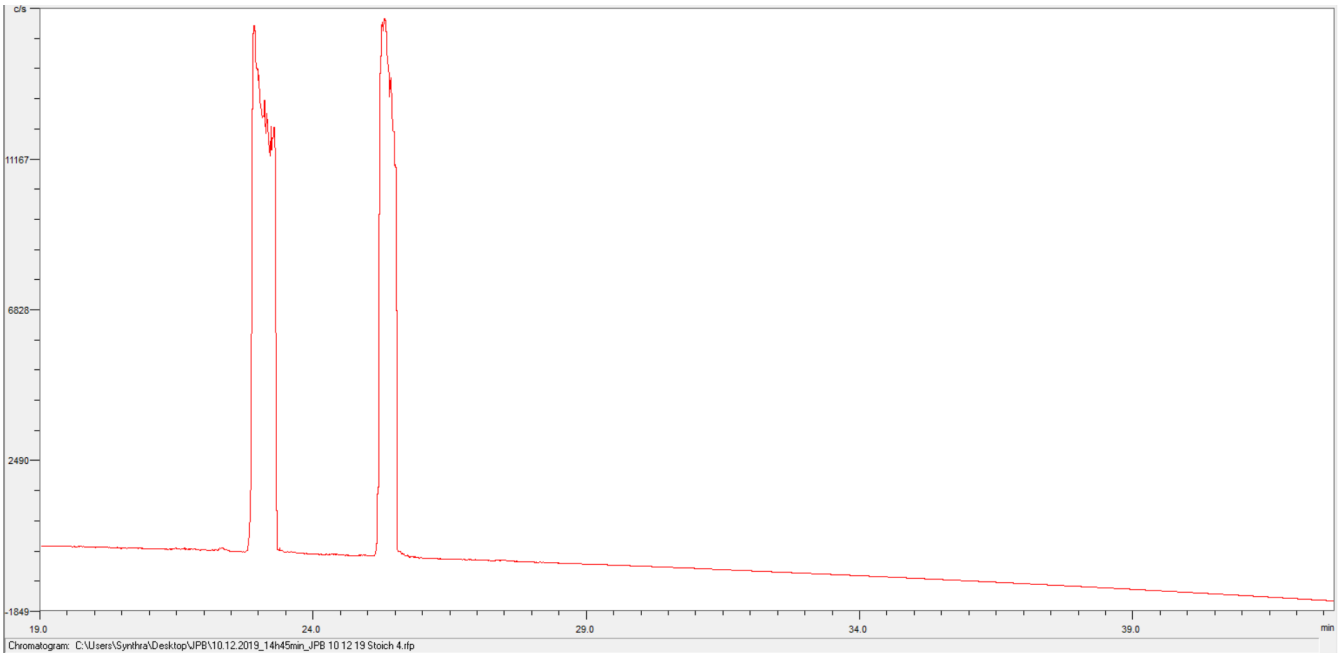


Figure S24. Preparative HPLC chromatogram from stoichiometry screening with 1.2 equivalents of PMe_3I_2, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.91	15178.54	350790.40	14.2
$[^{11}C]$**18**	6.29	15514.93	272044.50	11.0

Conditions: 3.0 mg I_2 (0.012 mmol), 3.5 mg Precursor (0.0095 mmol), 10 µL Triethylamine (72 µmol), PMe_3, 1.2 Eq, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 6.3 minutes.

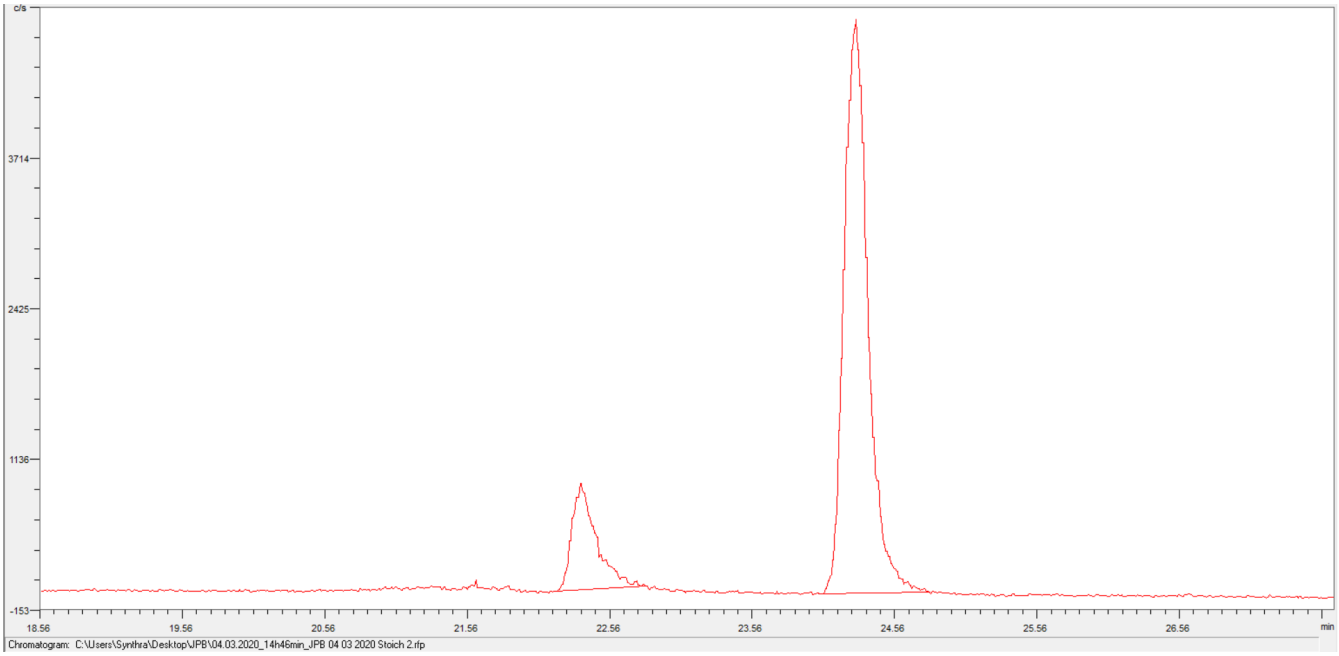


Figure S25. Preparative HPLC chromatogram from stoichiometry screening with 1.5 equivalents of PMe_3I_2 red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.79	10871.32	15.87	4.7
$[^{11}C]$**18**	5.73	57635.68	84.13	25.0

Conditions: 3.2 mg I_2 (0.013 mmol), 3 mg Precursor (0.008 mmol), 1.5 Eq, PMe_3, MeCN, 10 µL Triethylamine (72 µmol), 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 5.7 minutes.

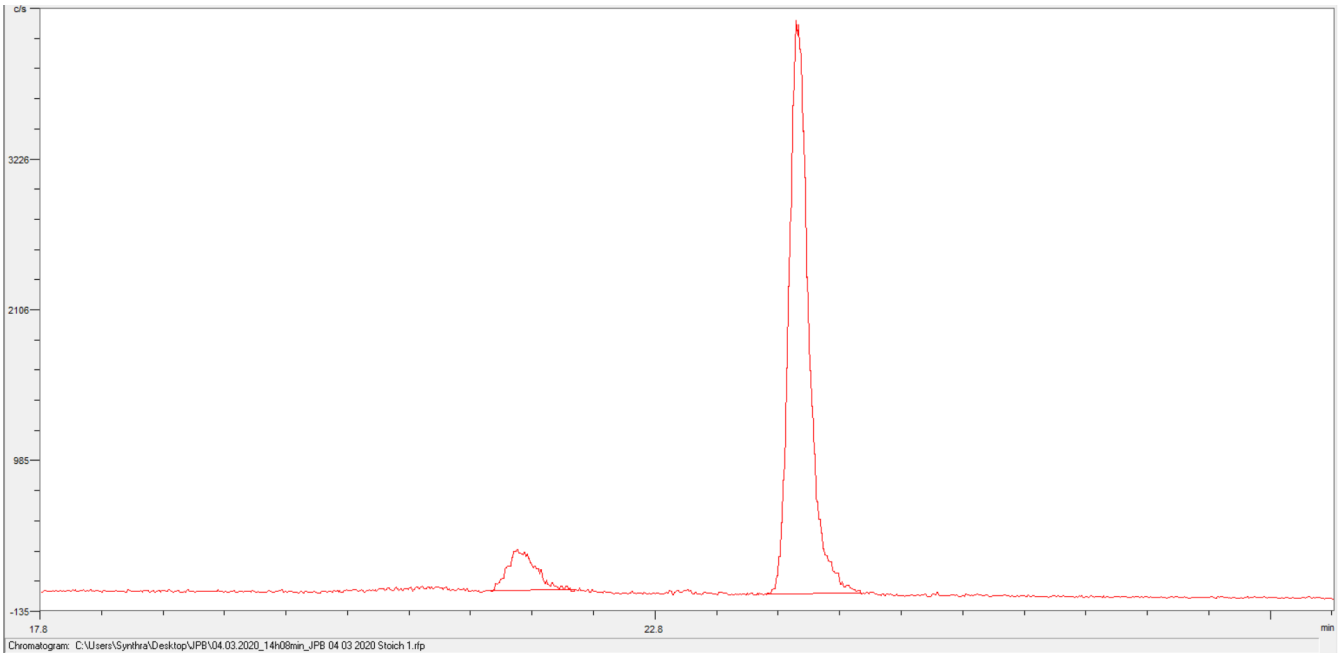


Figure S26. Preparative HPLC chromatogram from stoichiometry screening with 2.1 equivalents of PMe_3I_2 red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	3.88	4707.39	9.00	3.2
$[^{11}C]$**18**	6.14	47610.52	91.00	32.3

Conditions: 3 mg I_2 (0.012 mmol), 2mg Precursor (0.0054 mmol), 2.1 Eq, PMe_3, MeCN, 10 µL Triethylamine (72 µmol), 2 Eq, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 6.1 minutes.

4.5. Time Activation Screen

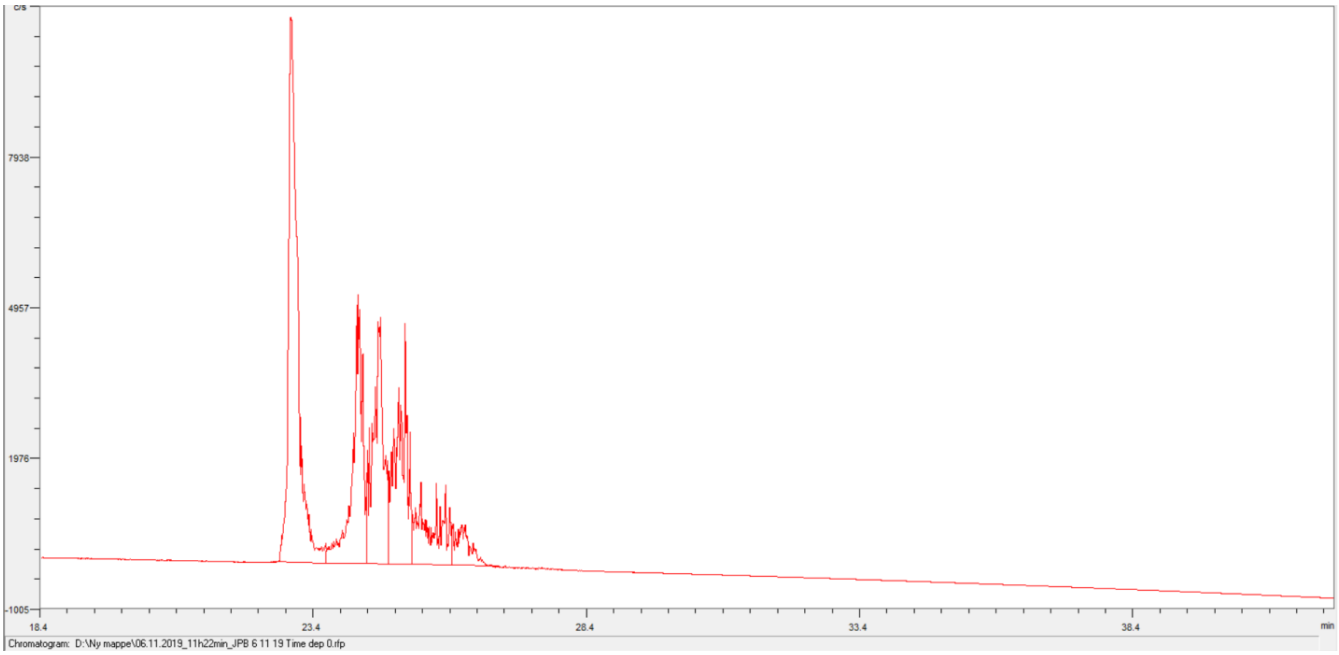


Figure S27. Preparative HPLC chromatogram from activation time screening of 0 minutes, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	4.58	129739.80	35.80	6.1
$[^{11}C]$**18**	6.67	55187.00	15.23	2.6

Conditions: PMe_3I_2, Precursor (1 mg, 0.0027 mmol), DMF/MeCN, 50 °C, 0 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 6.7 minutes.

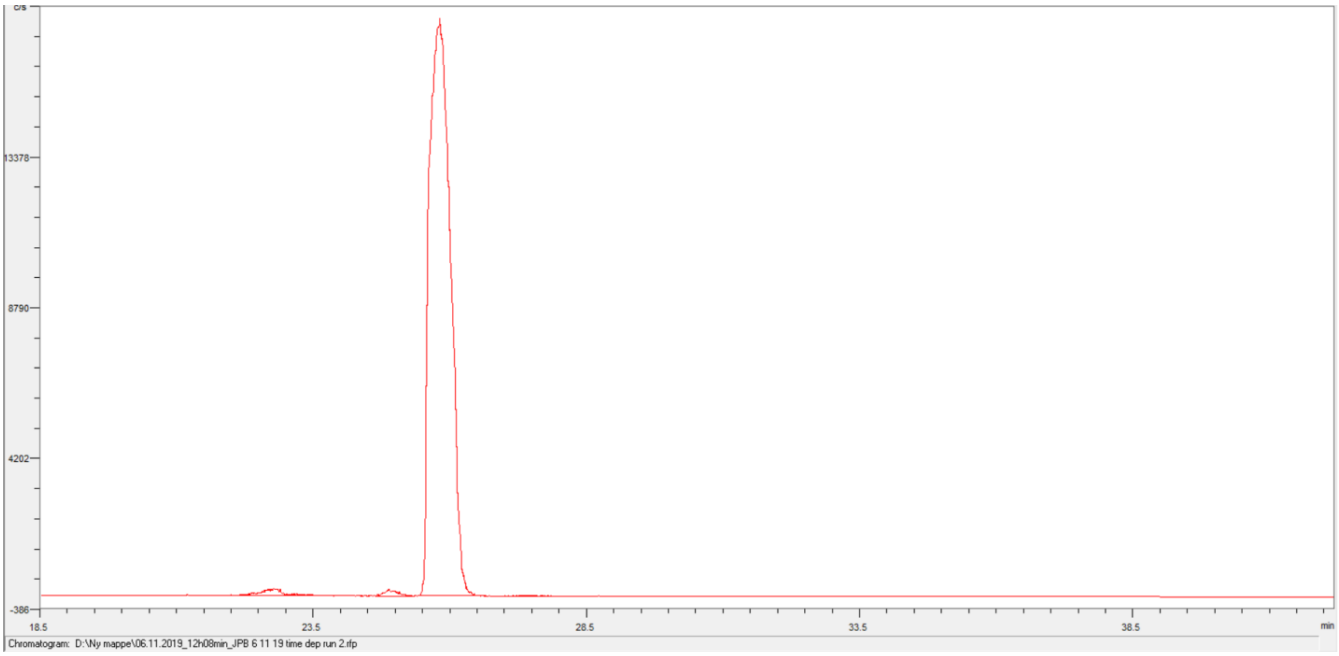


Figure S28. Preparative HPLC chromatogram from from activation time screening of 5 minutes, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	4.27	6128.89	1.28	0.3
$[^{11}C]$**18**	6.38	3031.07	0.63	0.2

Conditions: PMe_3I_2, Precursor (1 mg, 0.0027 mmol), DMF/MeCN, 50 °C, 5 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 6.4 minutes.

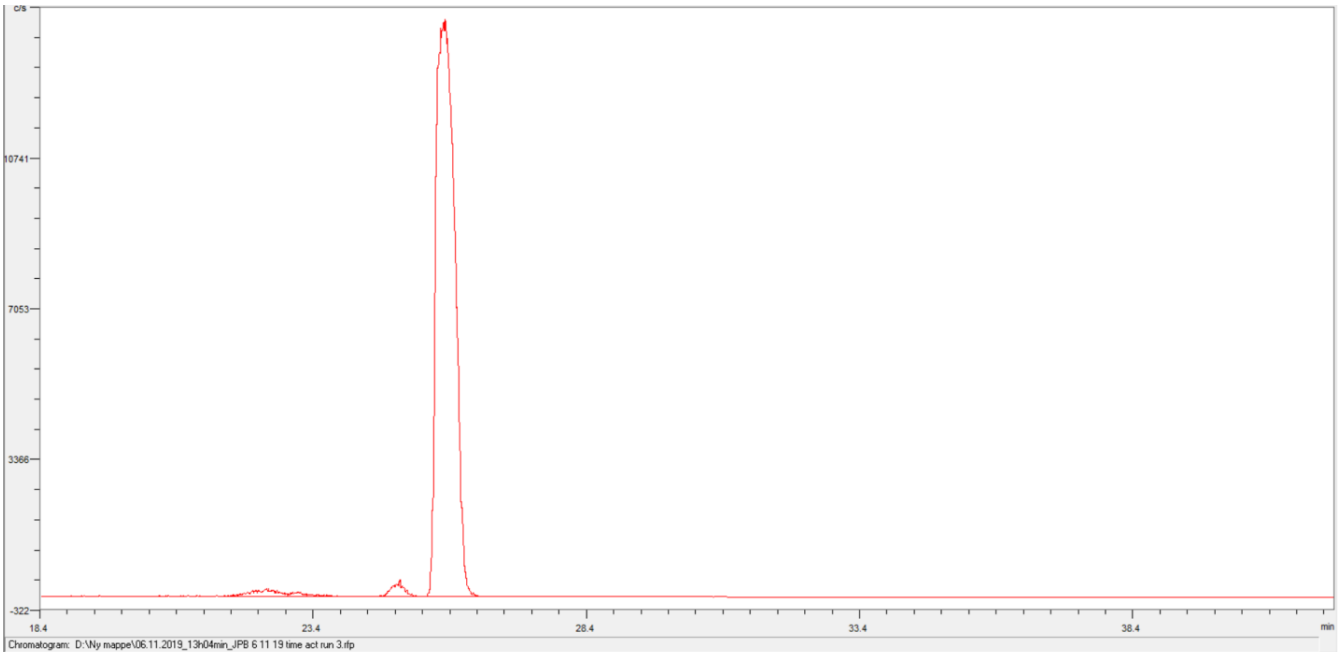


Figure S29.Preparative HPLC chromatogram from activation time screening of 10 minutes, red = activity.

Channel	t_R / min	Area(absolute) / mV^2	Area(relative) / %	Amount
$[^{11}C]CO_2$	4.13	5690.18	1.62	0.3
$[^{11}C]$**18**	6.58	5665.59	1.61	0.3

Conditions: PMe_3I_2, Precursor (1 mg, 0.0027 mmol), DMF/MeCN, 50 °C, 10 min. X-axis shows total process time from beginning of radionuclide production, corrected retention time for product $[^{11}C]$**18** 6.6 minutes.

4.6. QC

Examples of quality control chromatograms for confirmation of identity and determination of purity and molar activity of labelled products.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: AUT19_2010_2step		
Sample ID	: AUT19		
Data Filename	: test9.lcd		
Method Filename	: AB_gradient_short_qc.lcm		
Batch Filename	:		
Vial #	: 1-28	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 16.12.2019 11:38:59	Acquired by	: System Administrator
Date Processed	: 16.12.2019 11:51:01	Processed by	: System Administrator

<Chromatogram>

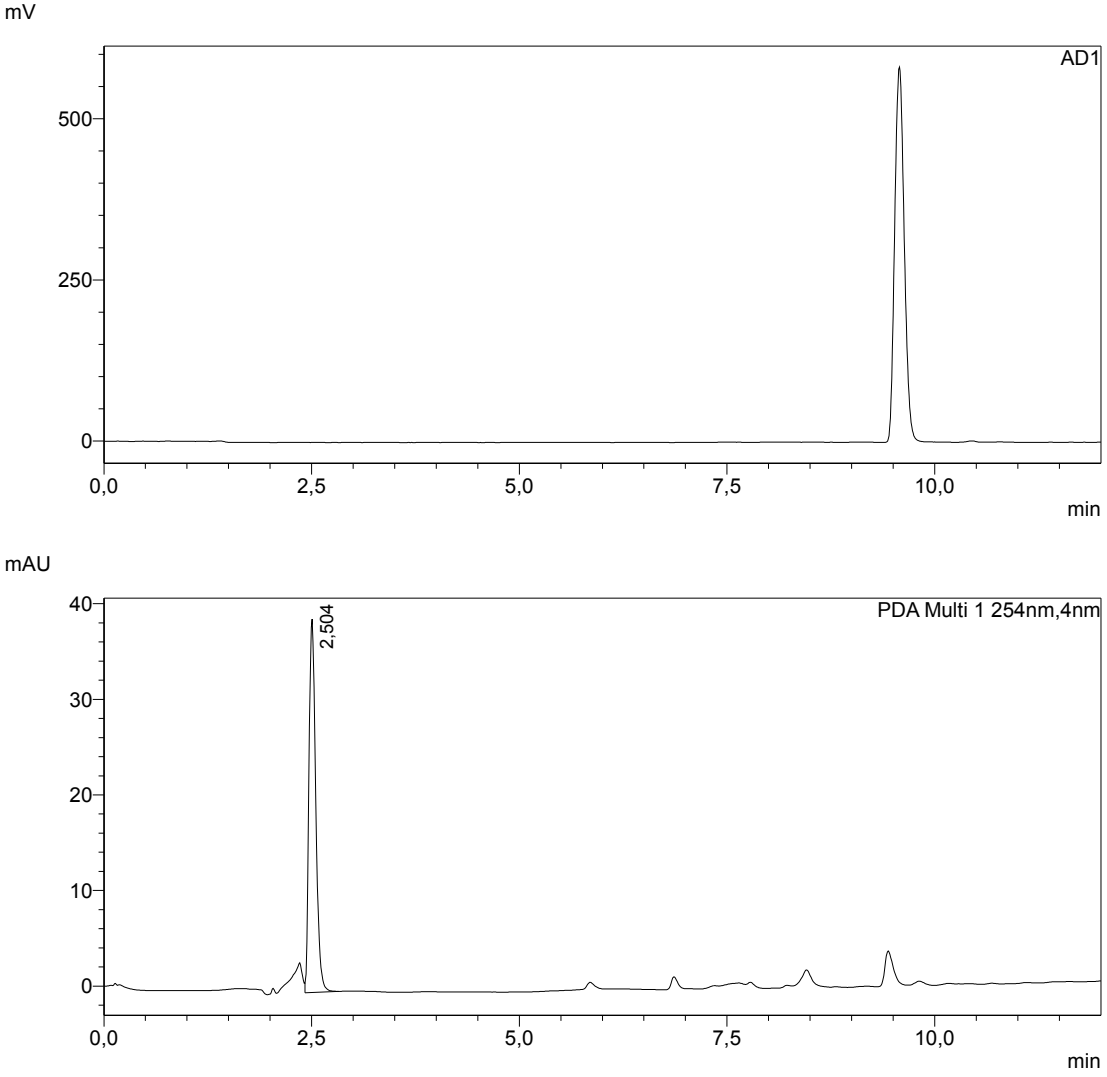


Figure S30. No-carrier-added [^{11}C]**20** QC chromatogram

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: AUT19_2010_2step		
Sample ID	: AUT194		
Data Filename	: test11.lcd		
Method Filename	: AB_gradient_short_qc.lcm		
Batch Filename	:		
Vial #	: 1-28	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 18.12.2019 13:40:10	Acquired by	: System Administrator
Date Processed	: 18.12.2019 13:52:11	Processed by	: System Administrator

<Chromatogram>

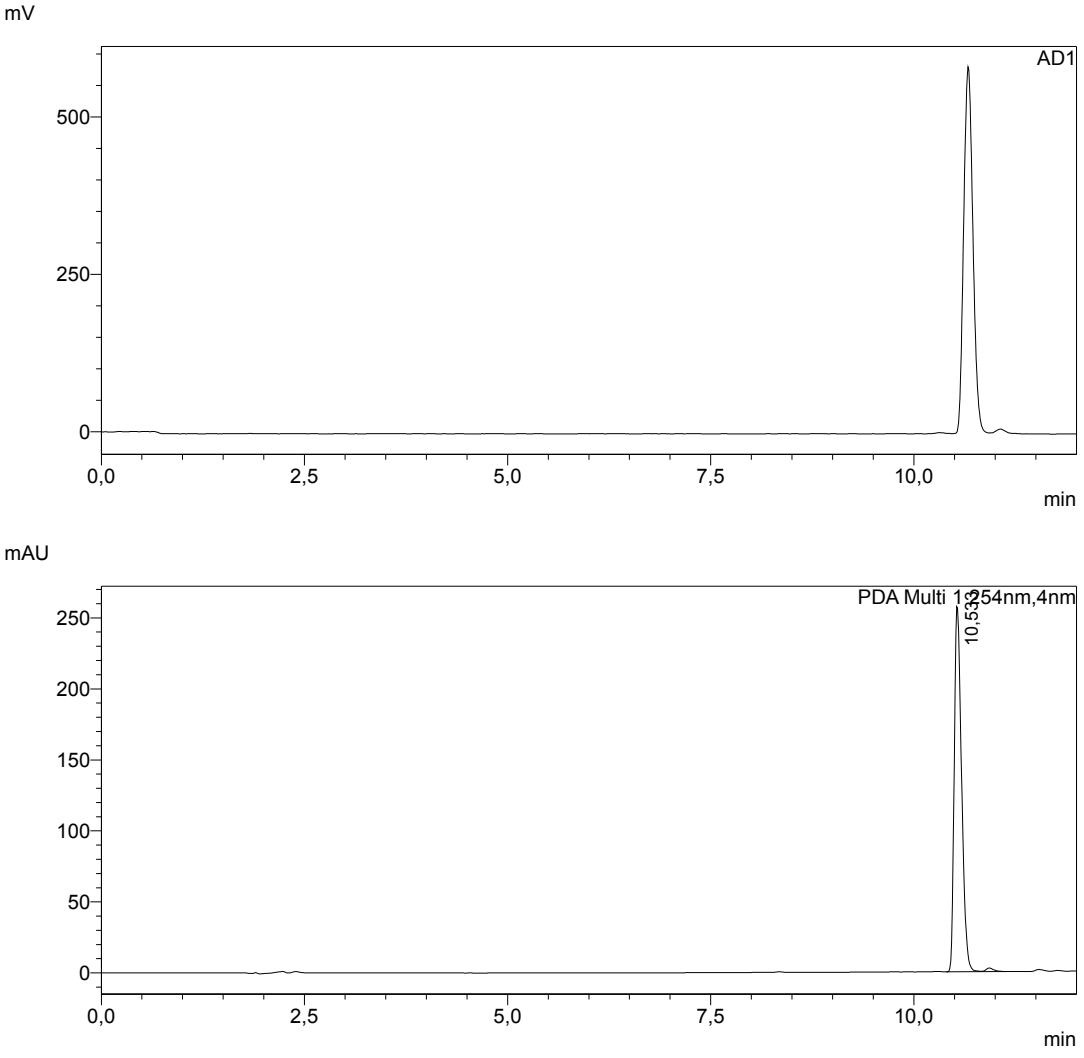


Figure S31. [^{11}C]**20** co-injected with non-radioactive reference **20** (0.1 mg/mL)

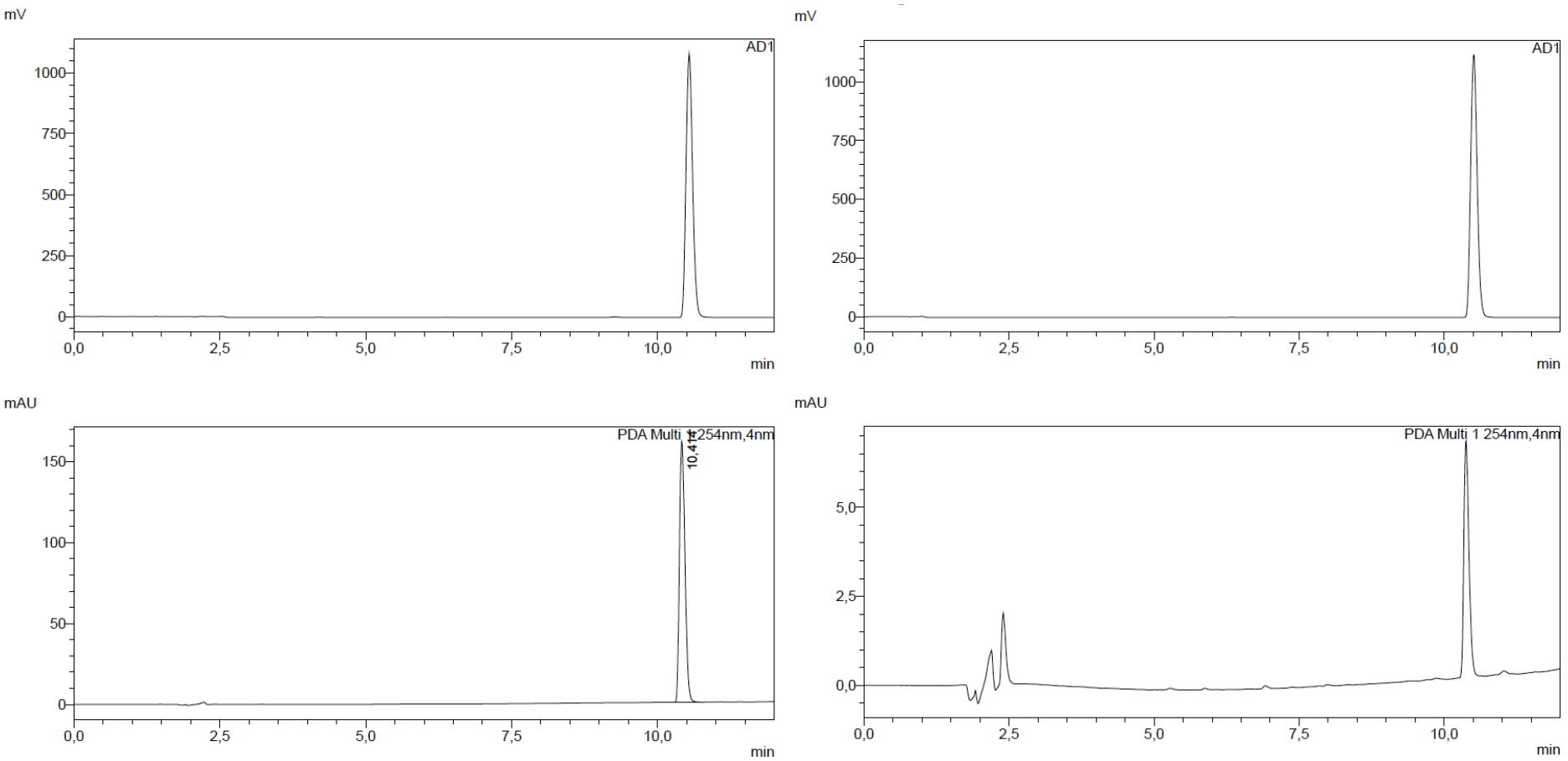


Figure S32. QC chromatograms for production of [^{11}C]**18** in two different molar activities. Left hand side: Carrier-added [^{11}C]**18** for low molar activity scans with high receptor occupancy obtained by addition of **18**; Right hand side.: No-carrier added [^{11}C]**18** for high molar activity scans with trace receptor occupancy

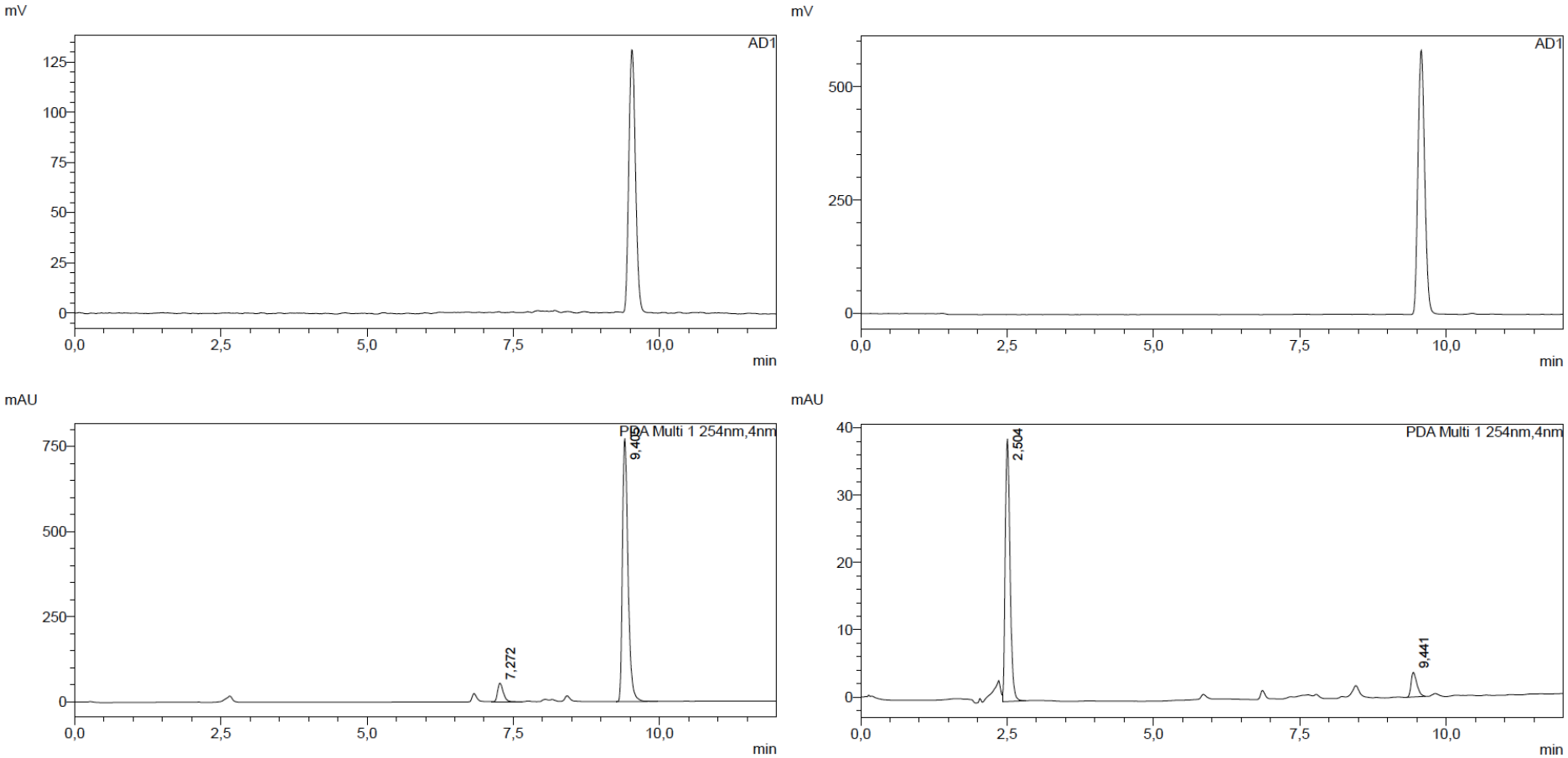


Figure S33. QC chromatograms for production of [^{11}C]**19** in two different molar activities. Left hand side: Carrier-added [^{11}C]**19** for low molar activity scans with high receptor occupancy obtained by addition of **19**; Right hand side: No-carrier added [^{11}C]**19** for high molar activity scans with trace receptor occupancy.

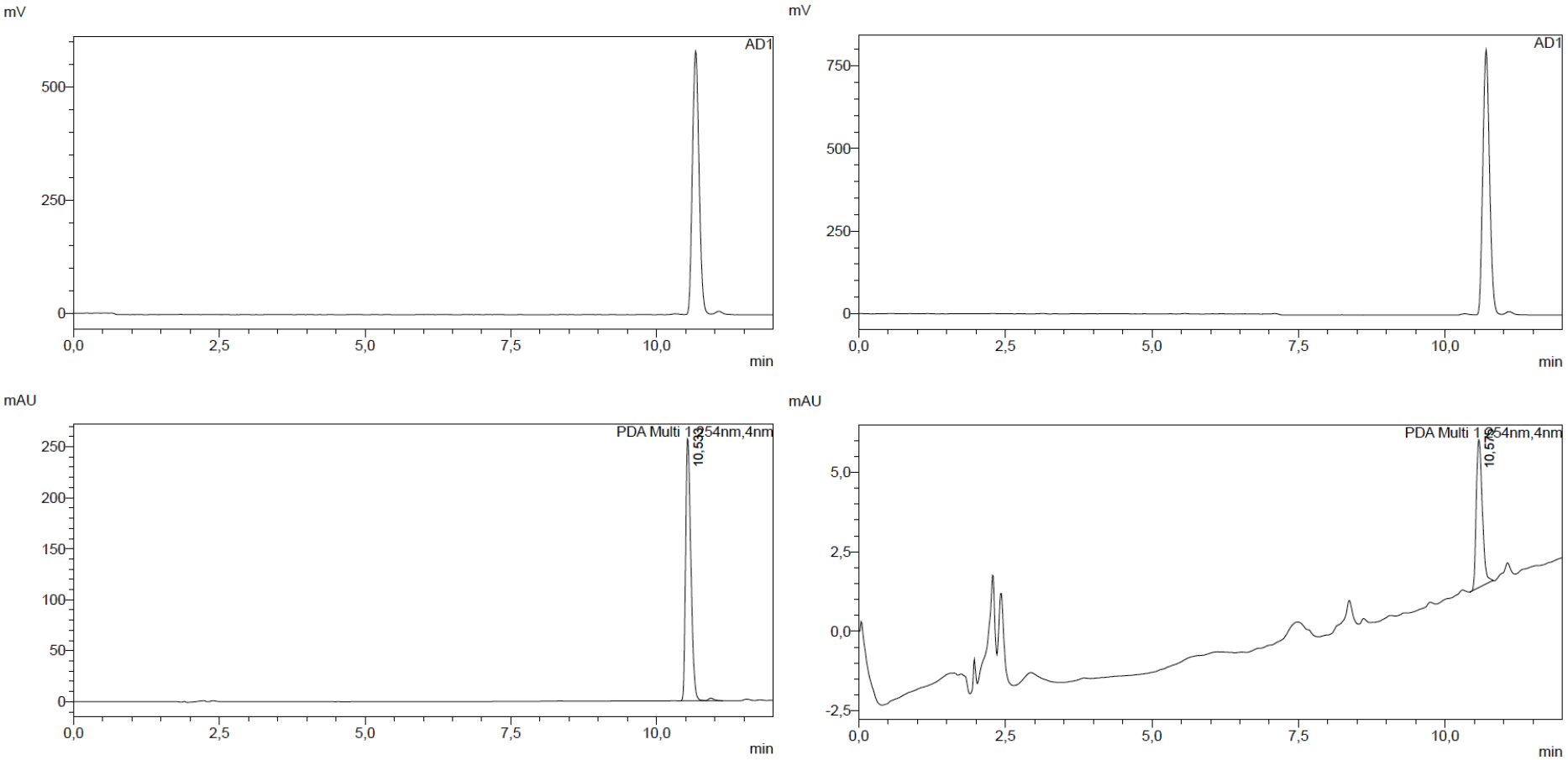


Figure S34. QC chromatograms for production of [^{11}C]**20** in two different molar activities. Left hand side: Carrier-added [^{11}C]**20** for low molar activity scans with high receptor occupancy obtained by addition of **20**; Right hand side: No-carrier added [^{11}C]**20** for high molar activity scans with trace receptor occupancy.

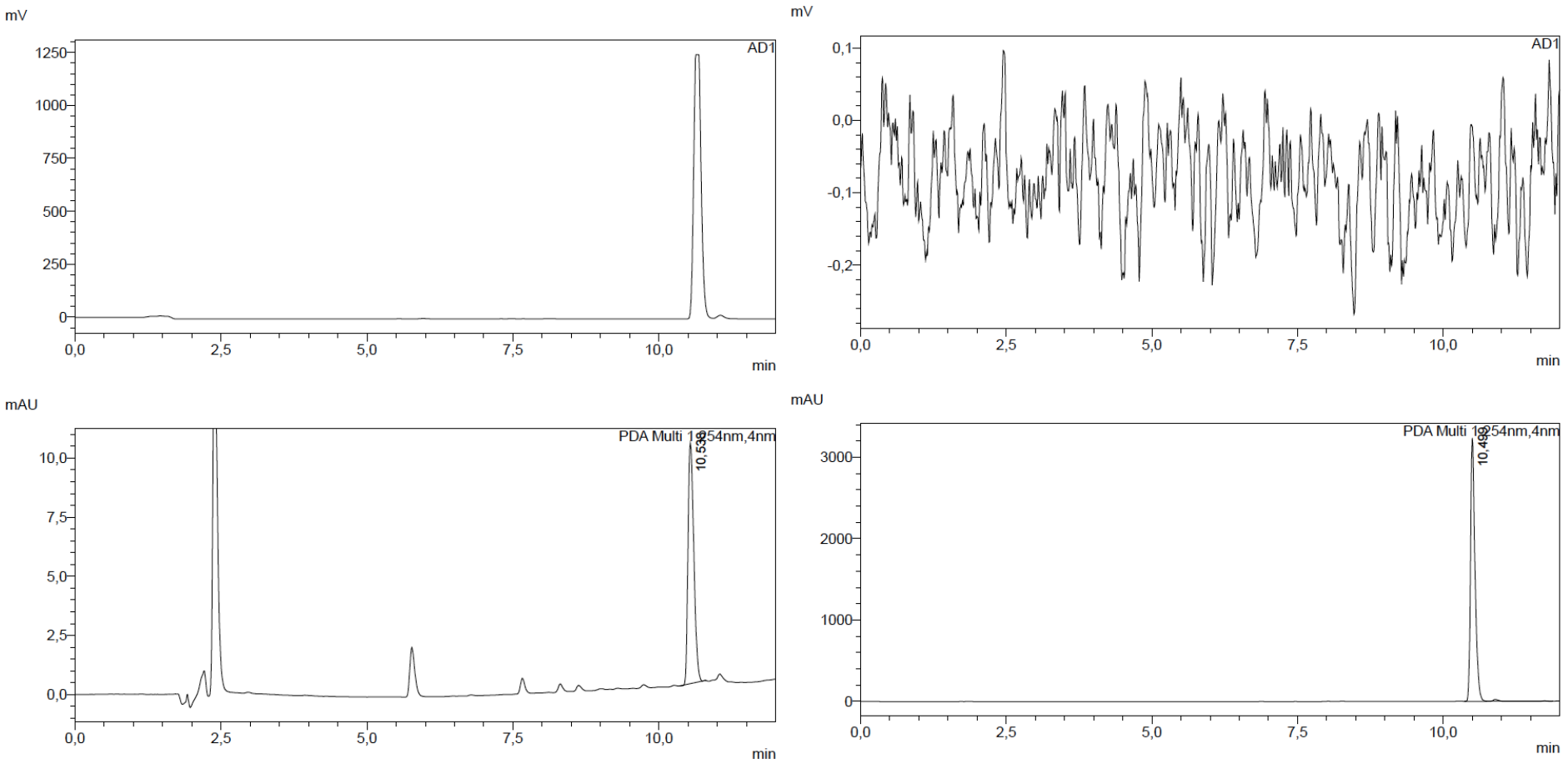
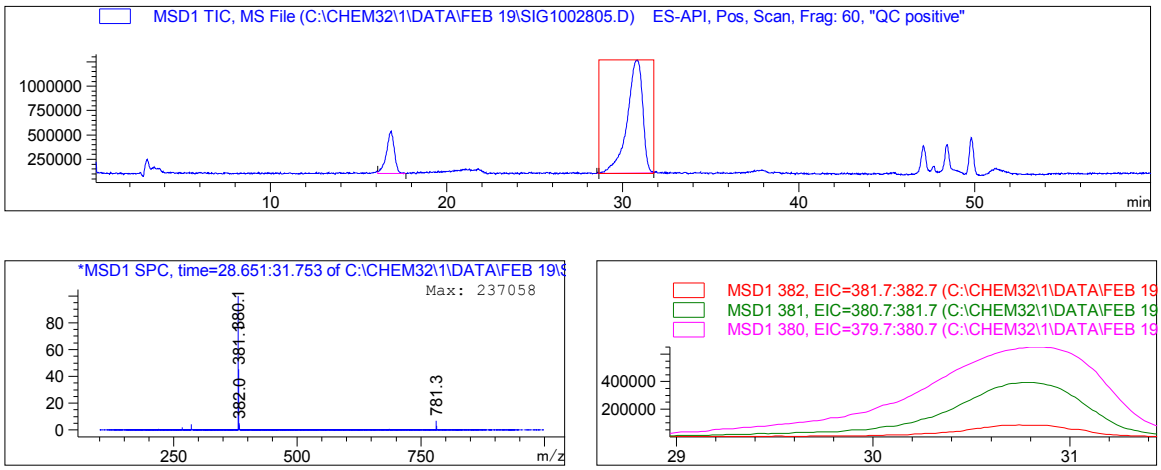
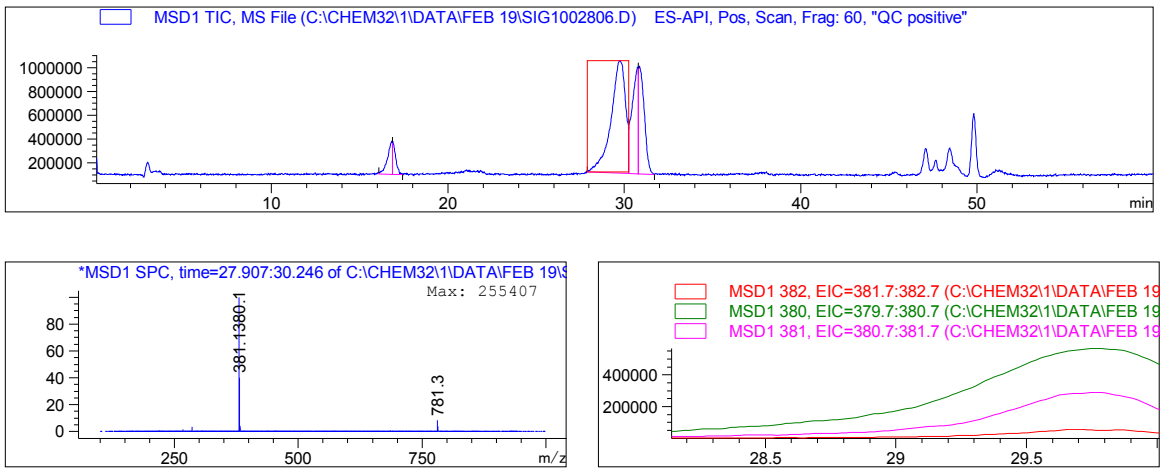


Figure S35. Comparison of a chromatogram for production of [^{11}C]**20** at low molar activity and a chromatogram for injection of the non-radioactive reference compound **20** alone, e.g. from method development and determination of retention times. Left hand side: A sample of no-carrier-added [^{11}C]**20** from a test production; Right hand side: A sample of **20** in high concentration from development and validation of the QC method.

4.7. Confirmation of enantiomeric purity



Peak #3 at 30.815 min (28.657 to 31.751 min)



Peak #3 at 29.747 min (27.907 to 30.243 min)

Figure S36. HPLC-MS analysis of the preparative sample (top) and the preparative sample spiked with the undesired enantiomer (bottom). The retention time of [^{11}C]**18** prepared under the labelling conditions is 30.7 min and its opposite enantiomer is at 29.7 min. As anticipated, the chiral purity (>>95%ee) appears to be very high for the preparative sample.

5. NMR Spectra

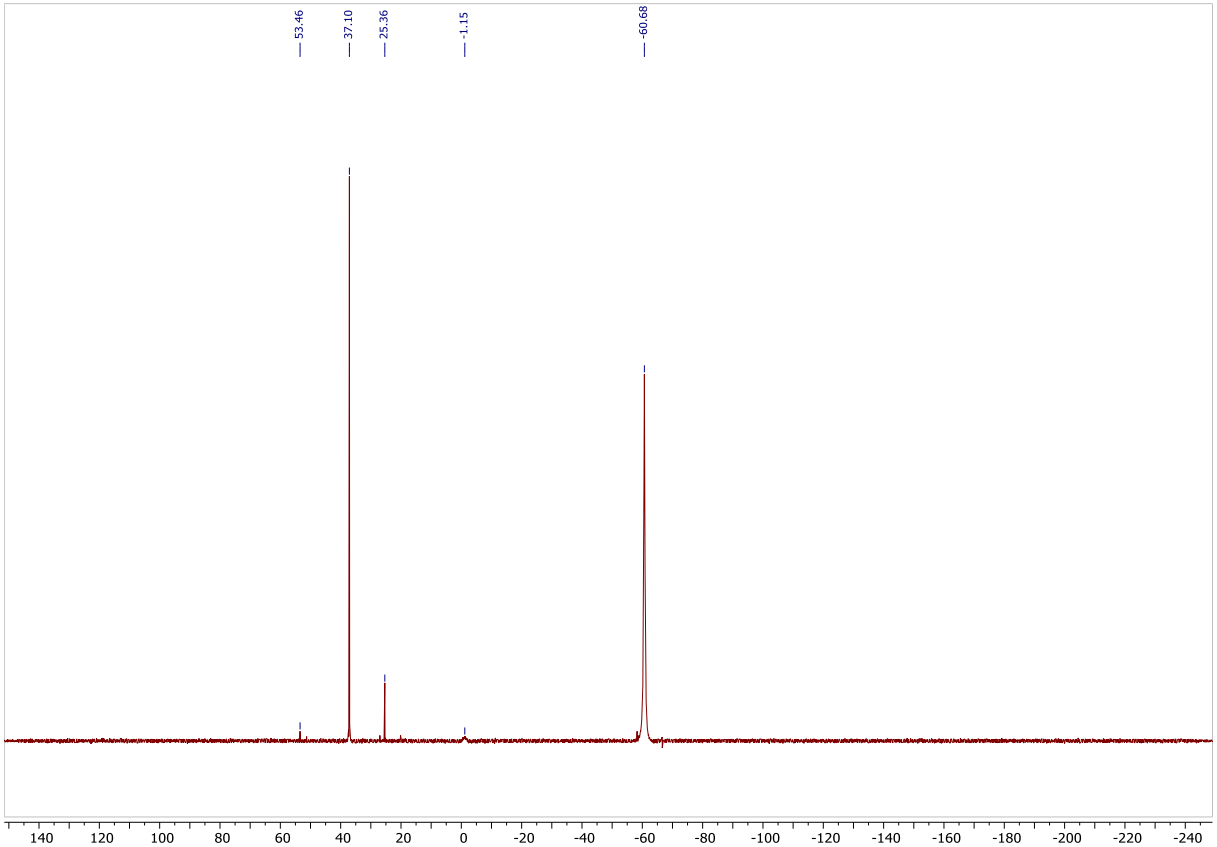


Figure S37. $^{31}P\{^{1}H\}$ NMR of PMe_3I_2 in Acetonitrile-d3, Free PMe_3: -60.08; $OPMe_3$: 37.10; PMe_3I_2: -1.15, 25.36, 53.46

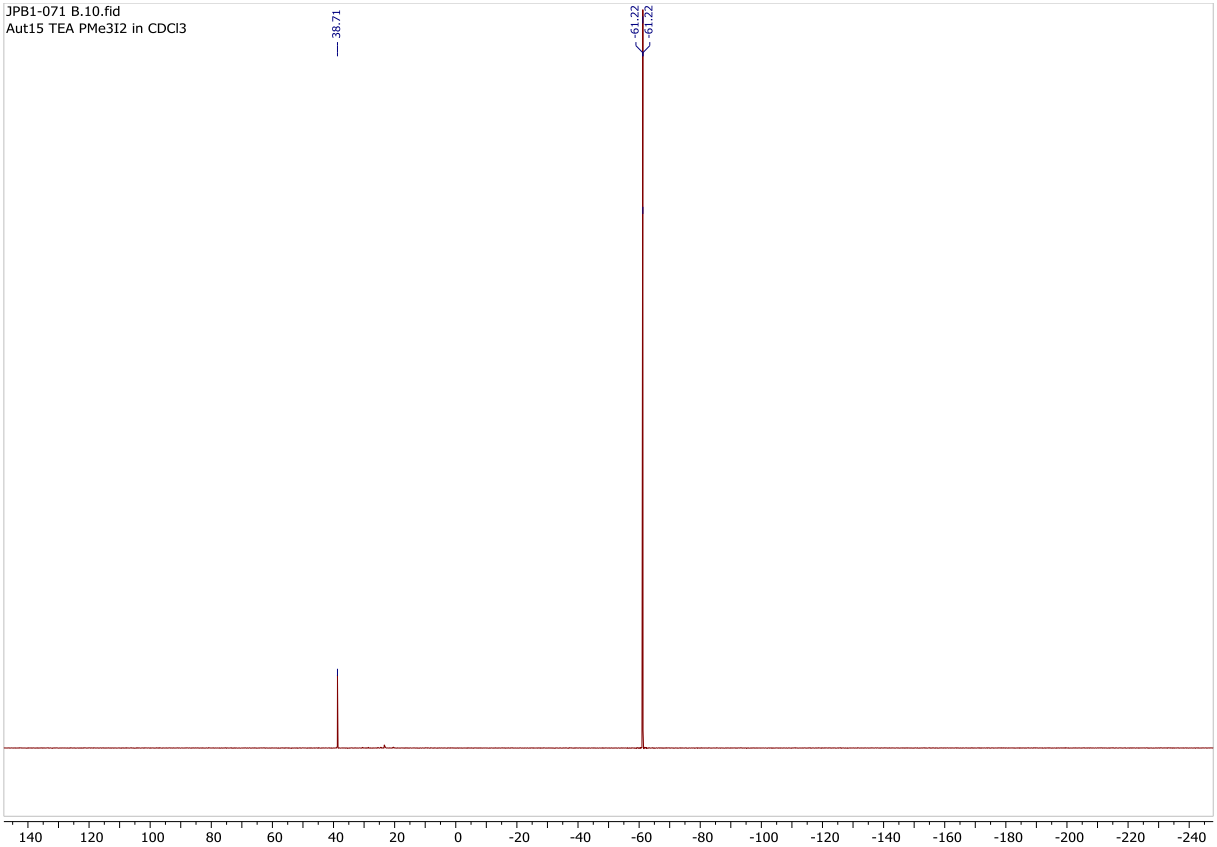


Figure S38. $^{31}P\{^{1}H\}$ NMR of PMe_3I_2 and **18** in $CDCl_3$, no new P=N signal is observed. Reaction conditions: 2.11 used for general NMR experiment however, no CO_2 was added.

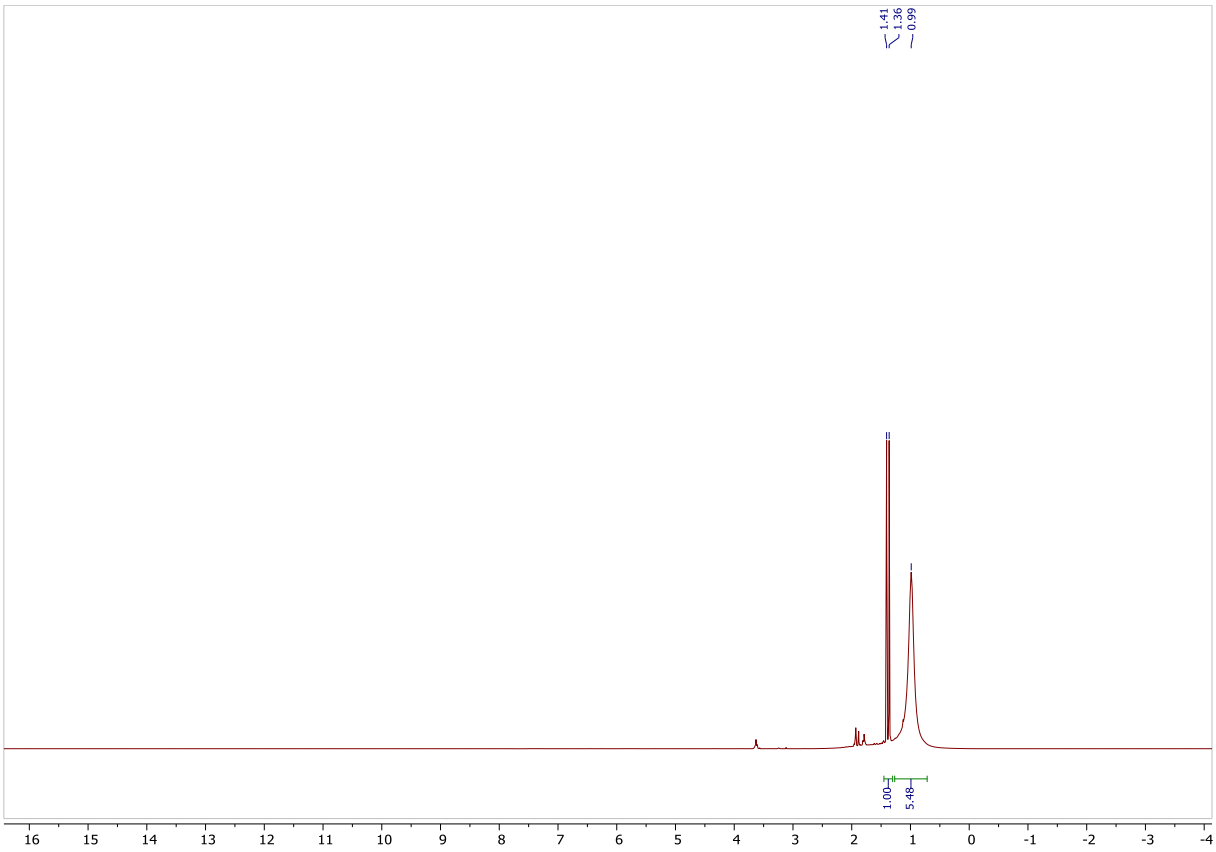


Figure S39. ^{1}H NMR PMe_3I_2 in ACN-d_3

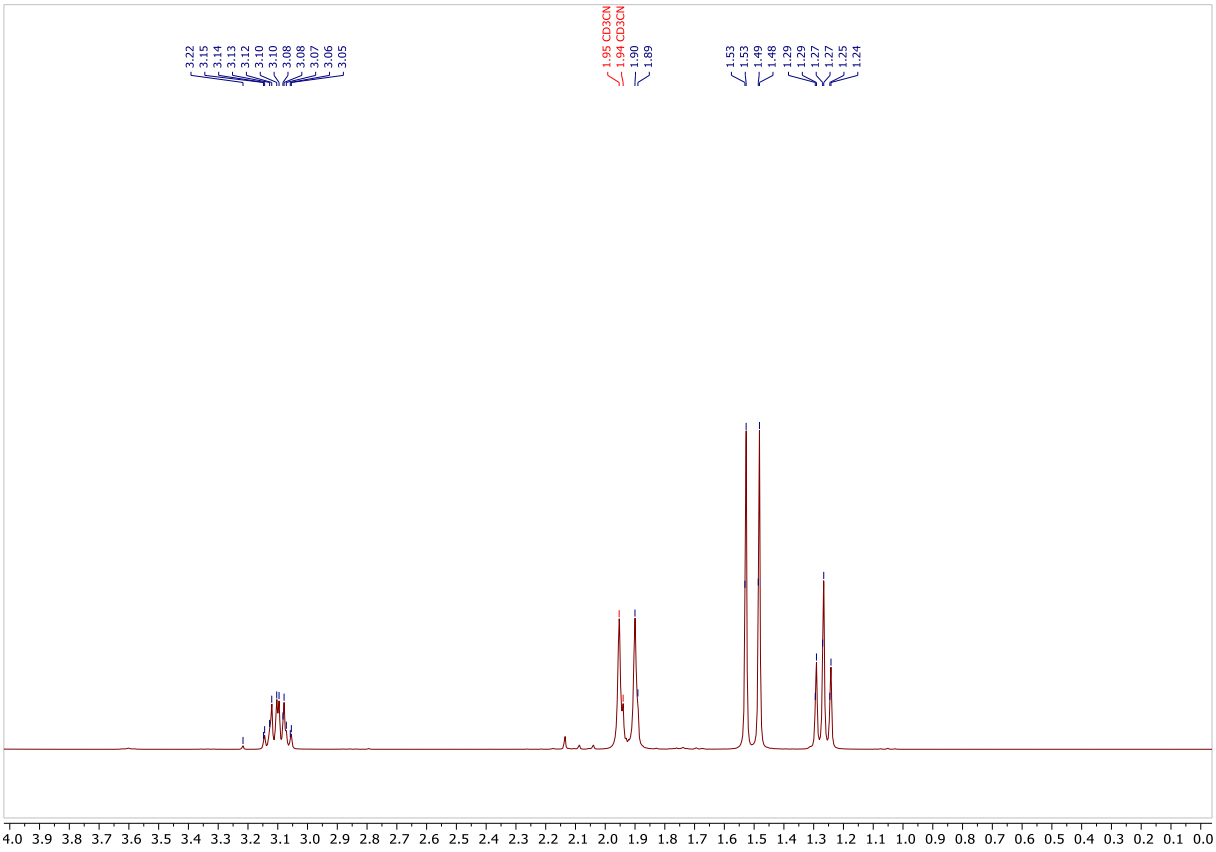


Figure S40. ^{1}H NMR PMe_3I_2 and NEt_3 in ACN-d_3 for identifying common signals in reaction mixtures. NEt3: 1.27 (t), 3.10 (q); PMe_3I_2: 1.51 (d), 1.91 (d), 2.06 (d): H_2O: 2.13 (s)

5.1. NMR Spectra of Azide precursors (8-17)

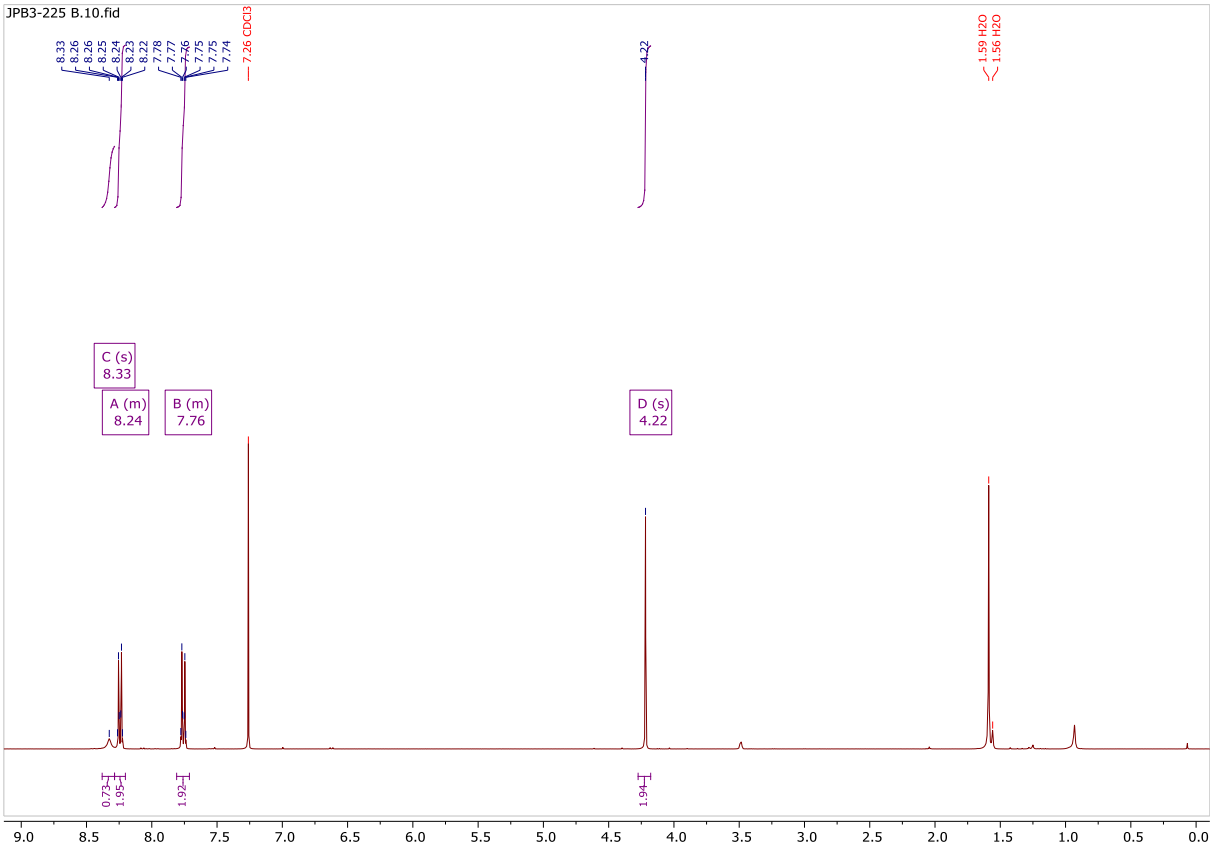


Figure S41. ^{1}H NMR Spectrum of 2-azido-N-(4-nitrophenyl)acetamide

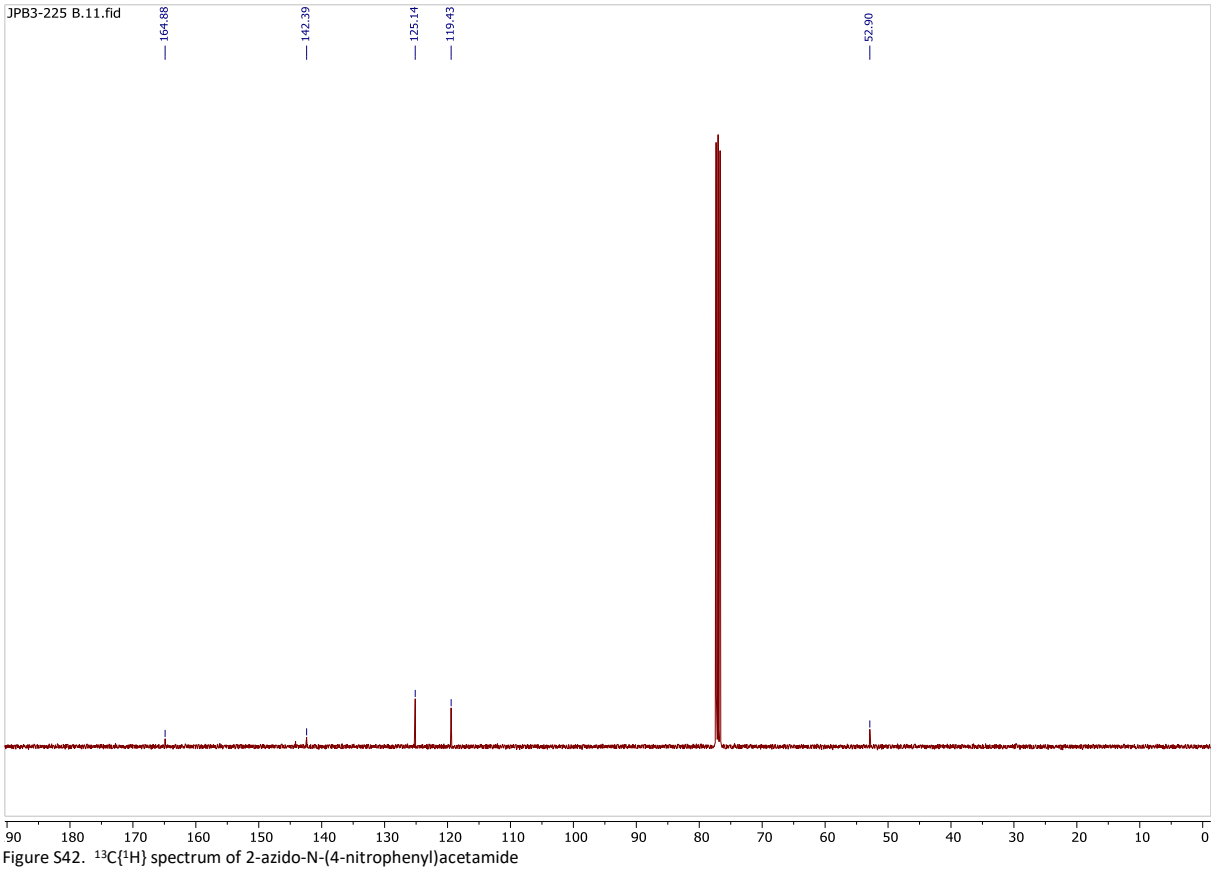


Figure S42. $^{13}C\{^{1}H\}$ spectrum of 2-azido-N-(4-nitrophenyl)acetamide

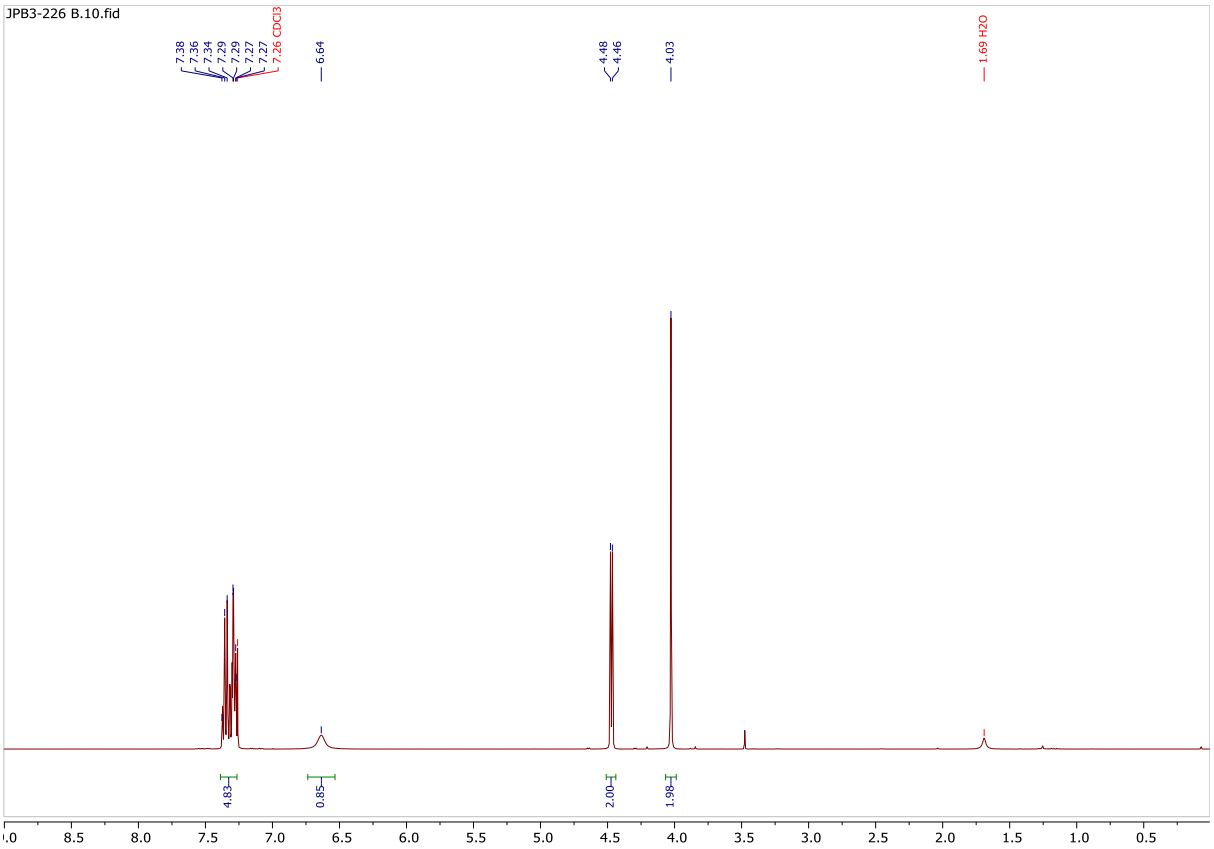


Figure S43. ^{1}H NMR Spectrum of 2-azido-N-benzylacetamide

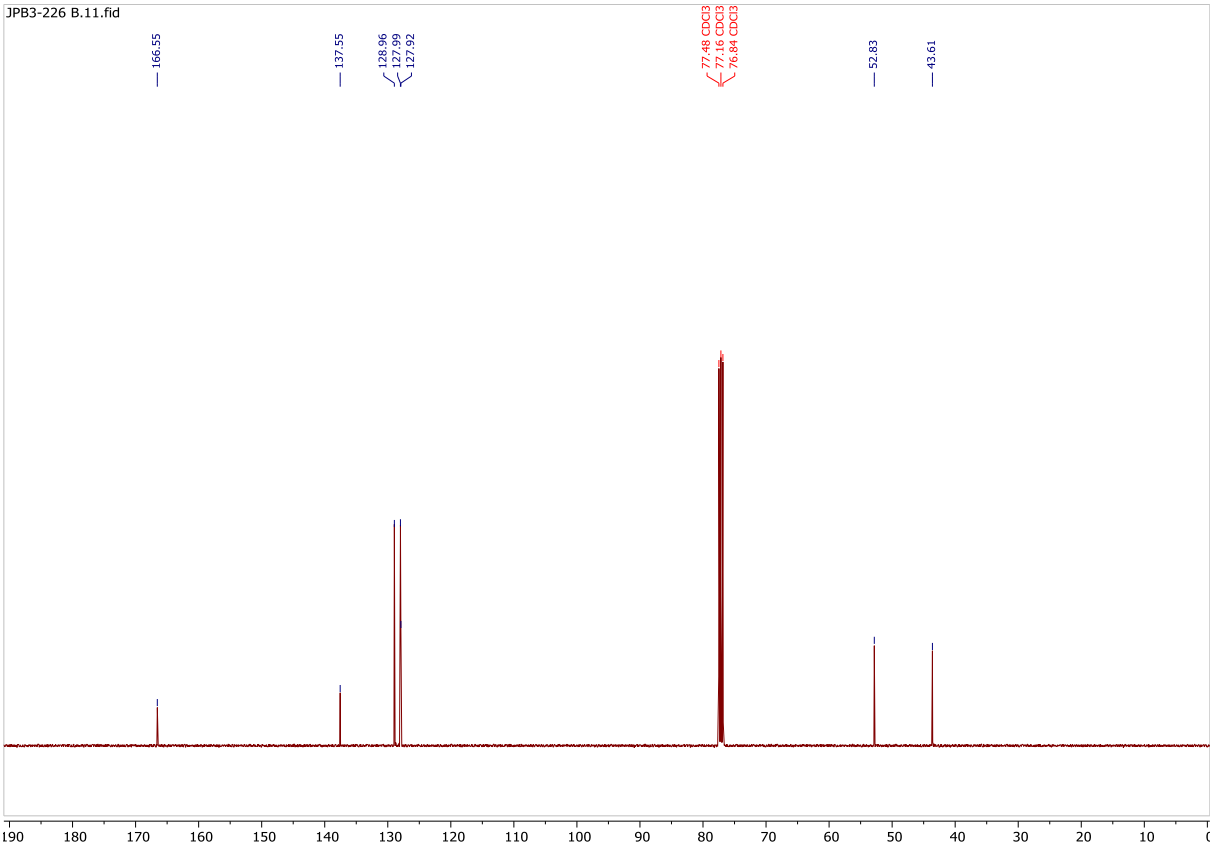


Figure S44. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-benzylacetamide

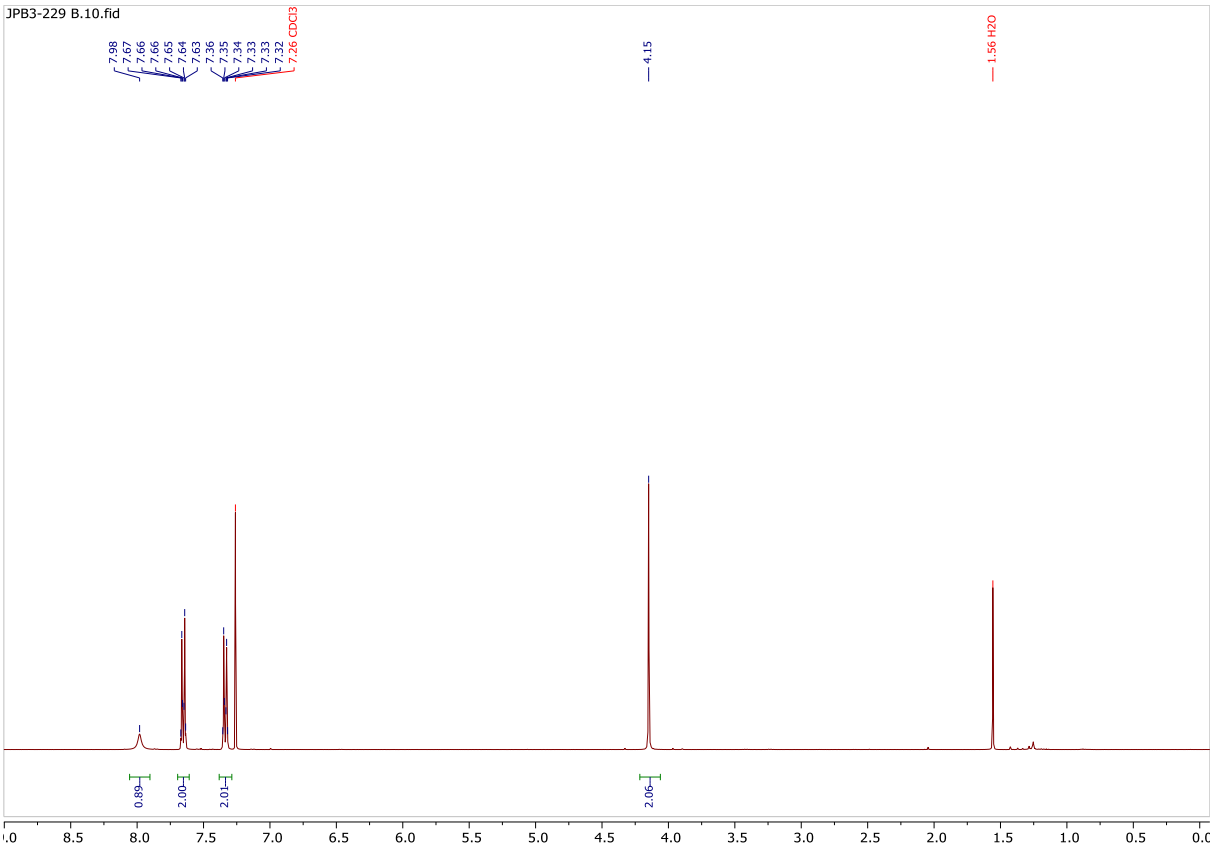


Figure S45. 1H NMR Spectrum of 2-azido-N-(4-iodophenyl)acetamide

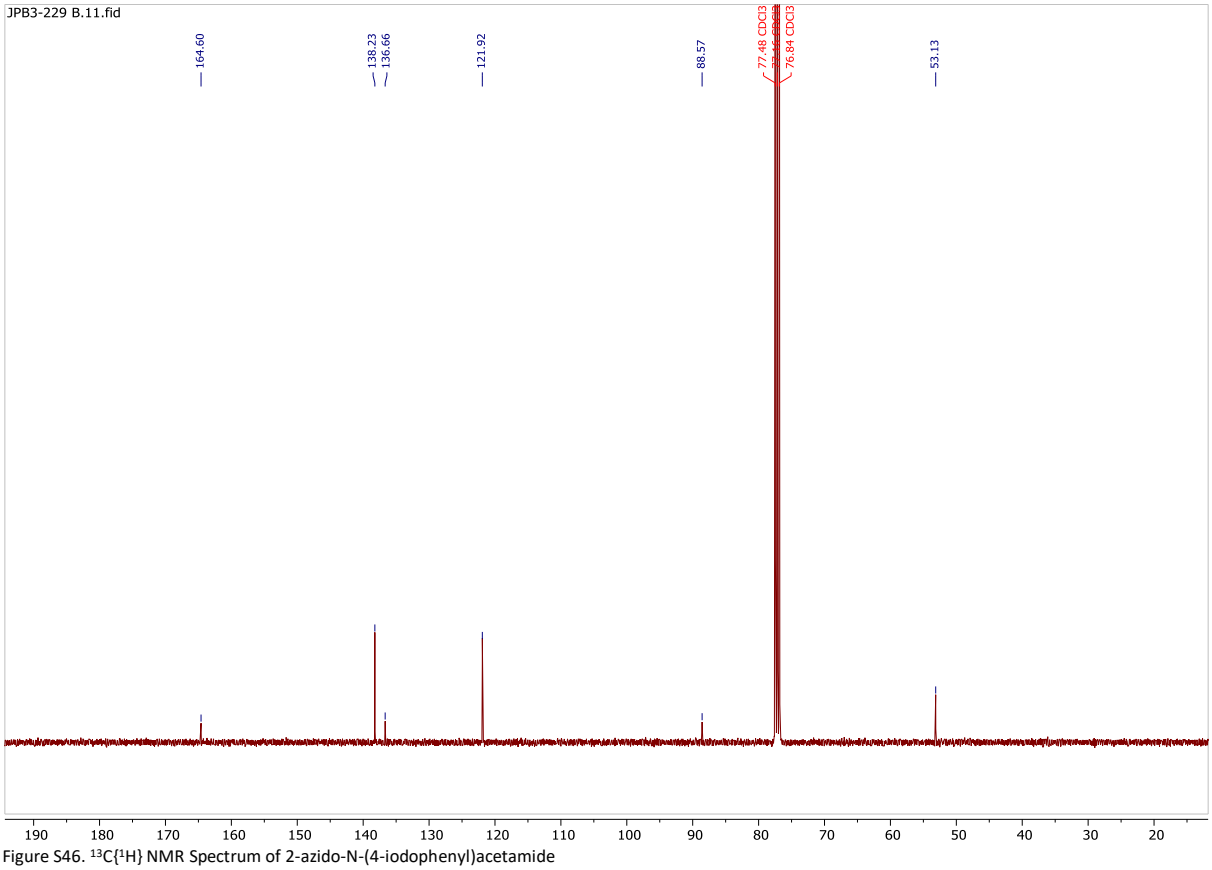


Figure S46. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-iodophenyl)acetamide

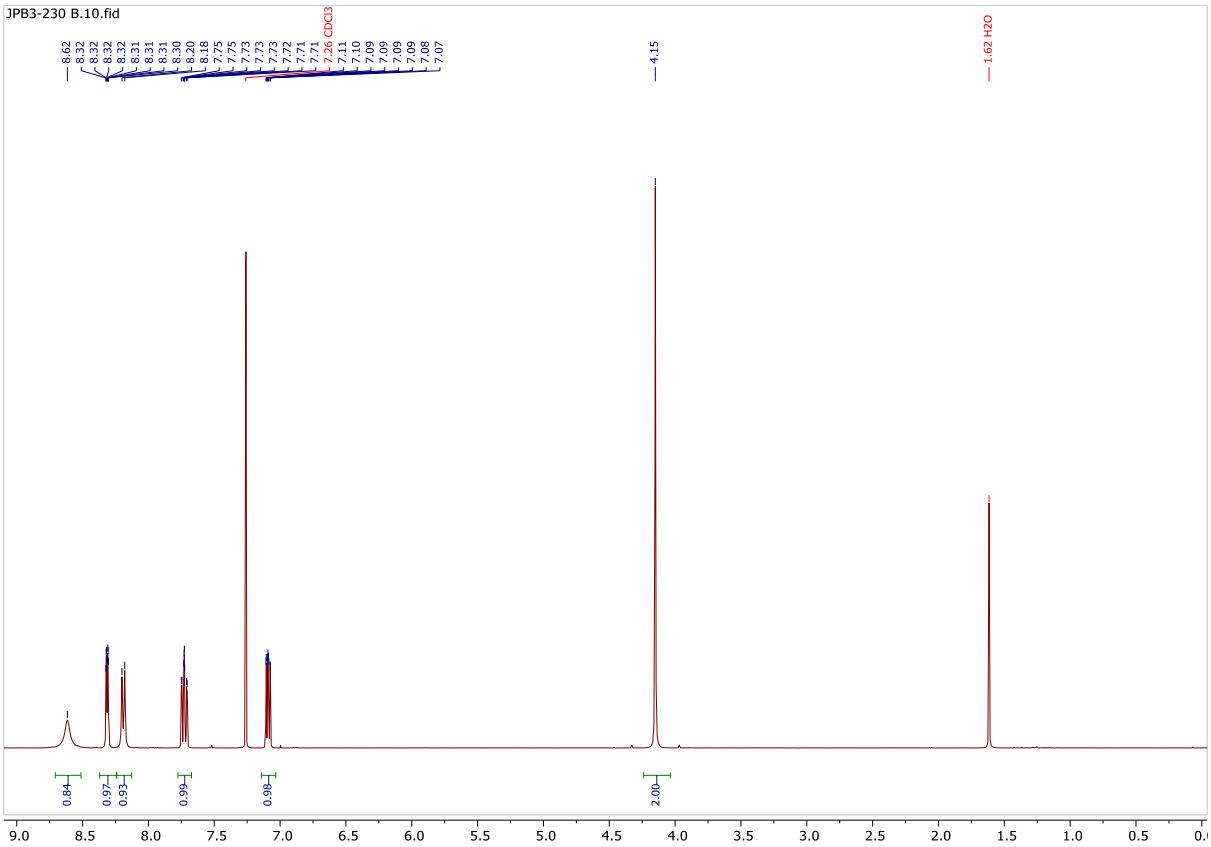


Figure S47.1H NMR Spectrum of 2-azido-N-(pyridin-2-yl)acetamide

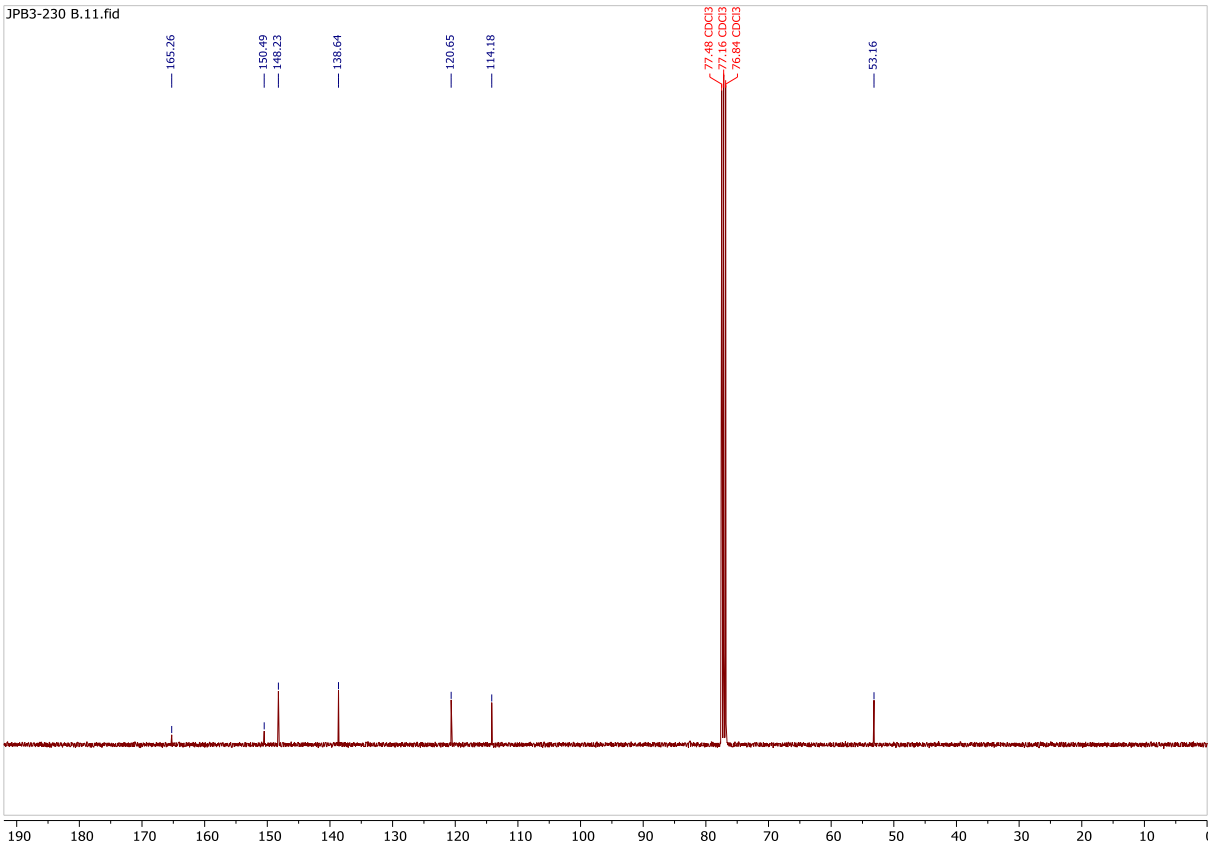


Figure S48. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(pyridin-2-yl)acetamide

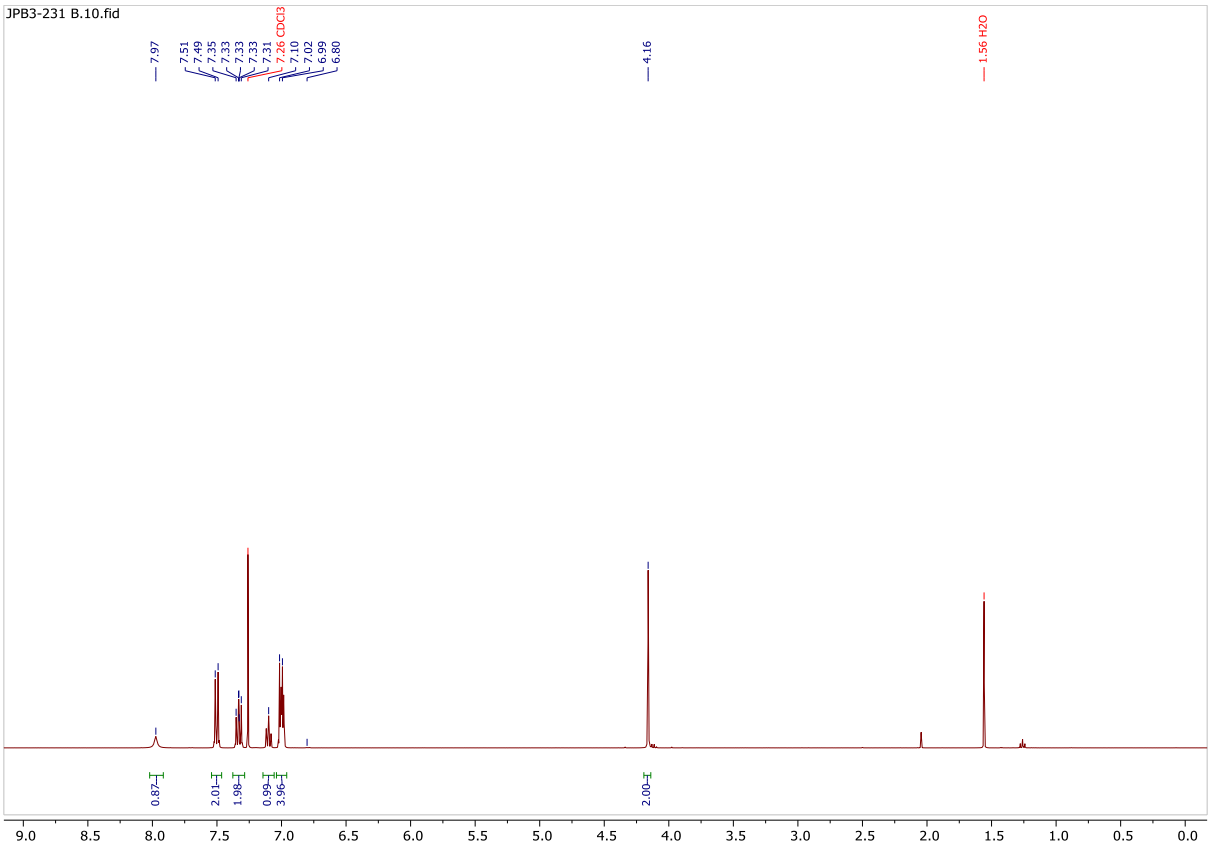


Figure S49.1H NMR Spectrum of 2-azido-N-(4-phenoxyphenyl)acetamide

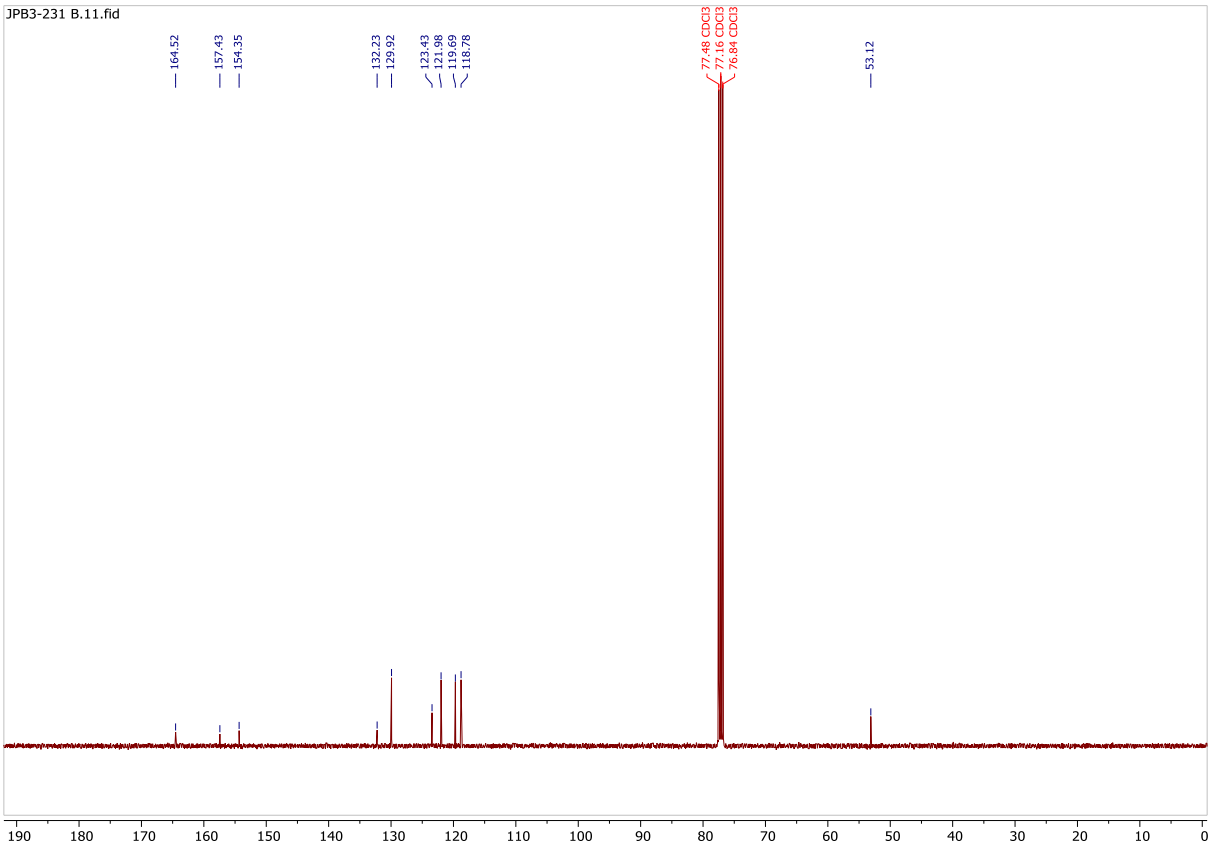


Figure S50. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-phenoxyphenyl)acetamide

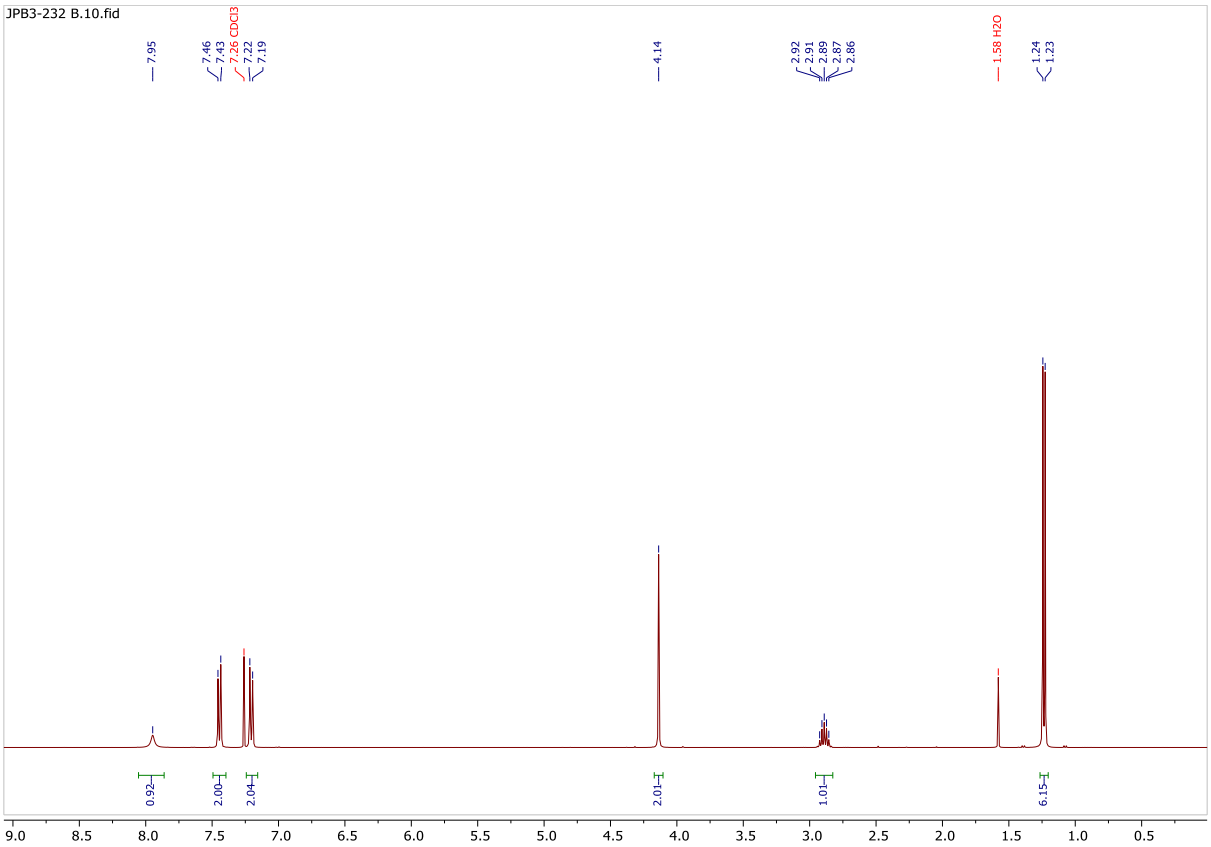


Figure S51. 1H NMR Spectrum of 2-azido-N-(4-isopropylphenyl)acetamide

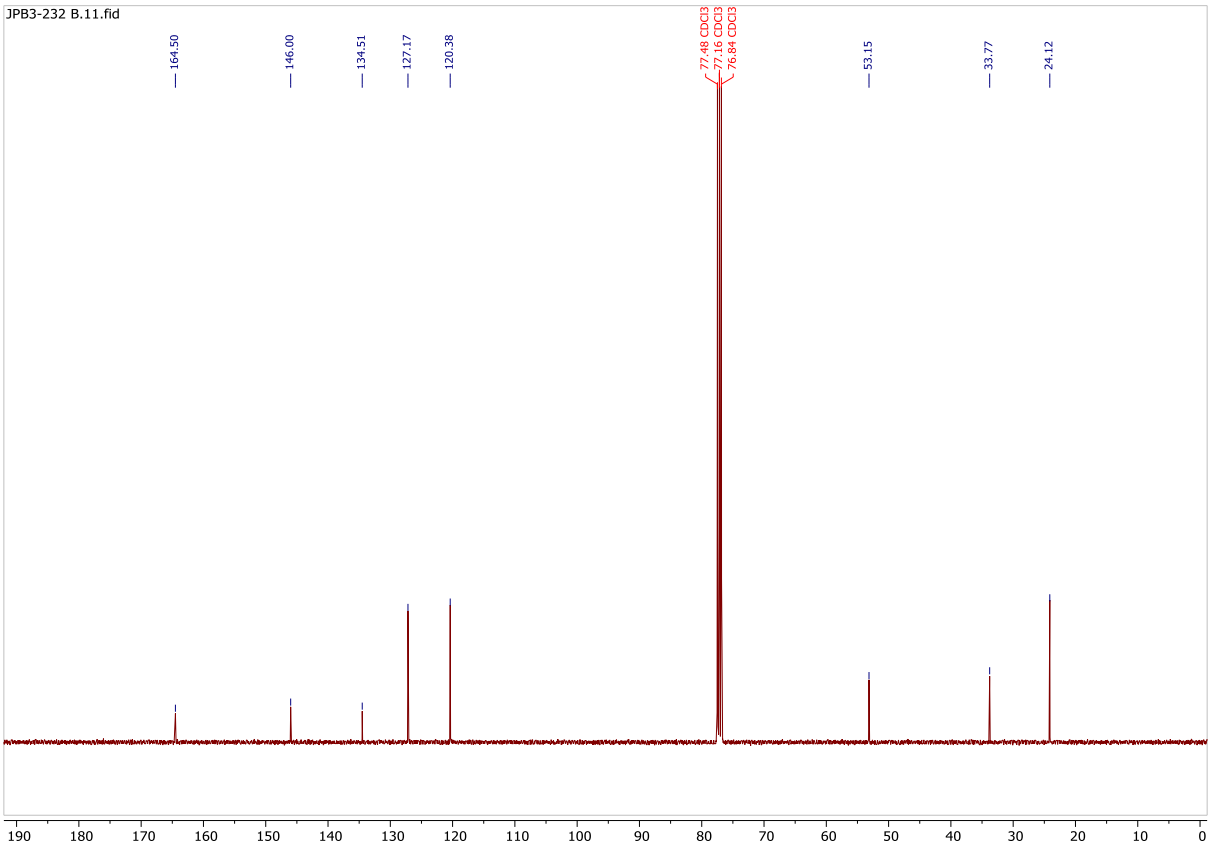


Figure S52. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-isopropylphenyl)acetamide

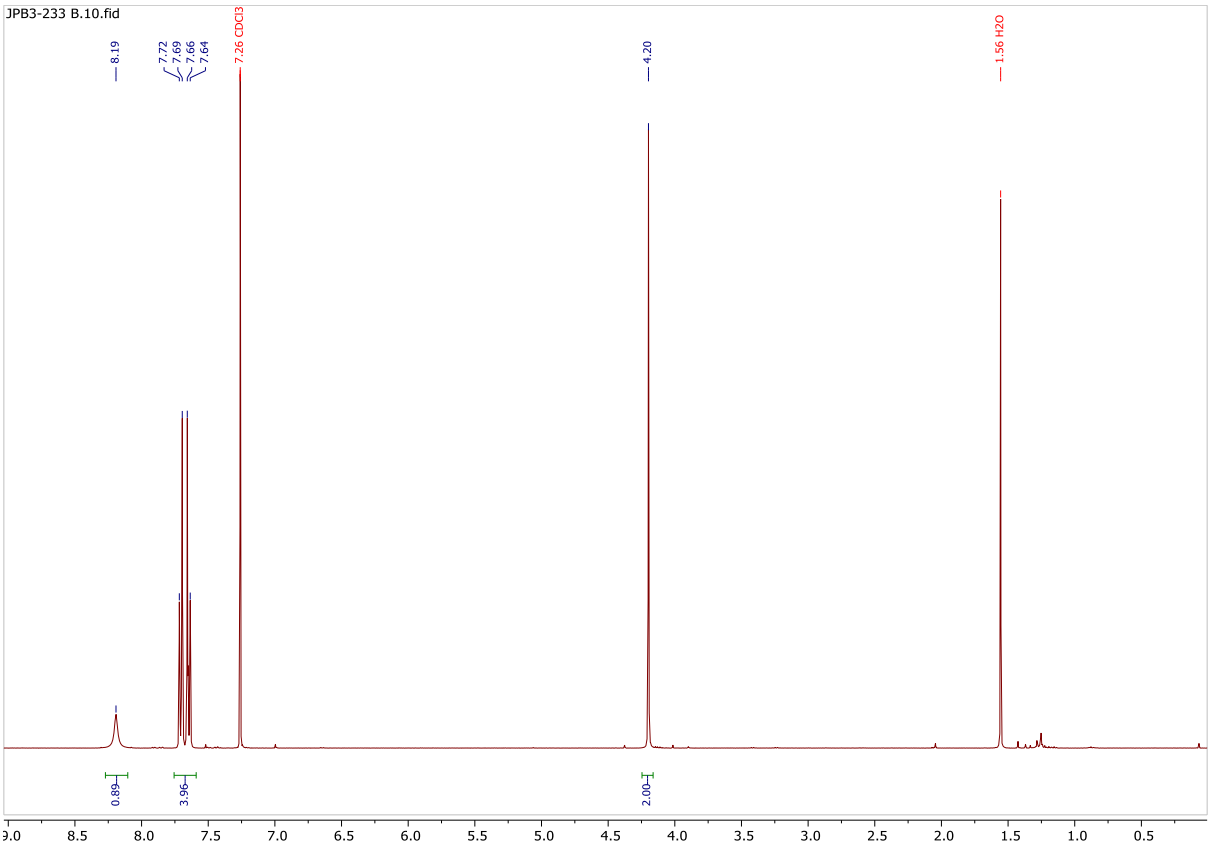


Figure S53.1H NMR Spectrum of 2-azido-N-(4-cyanophenyl)acetamide

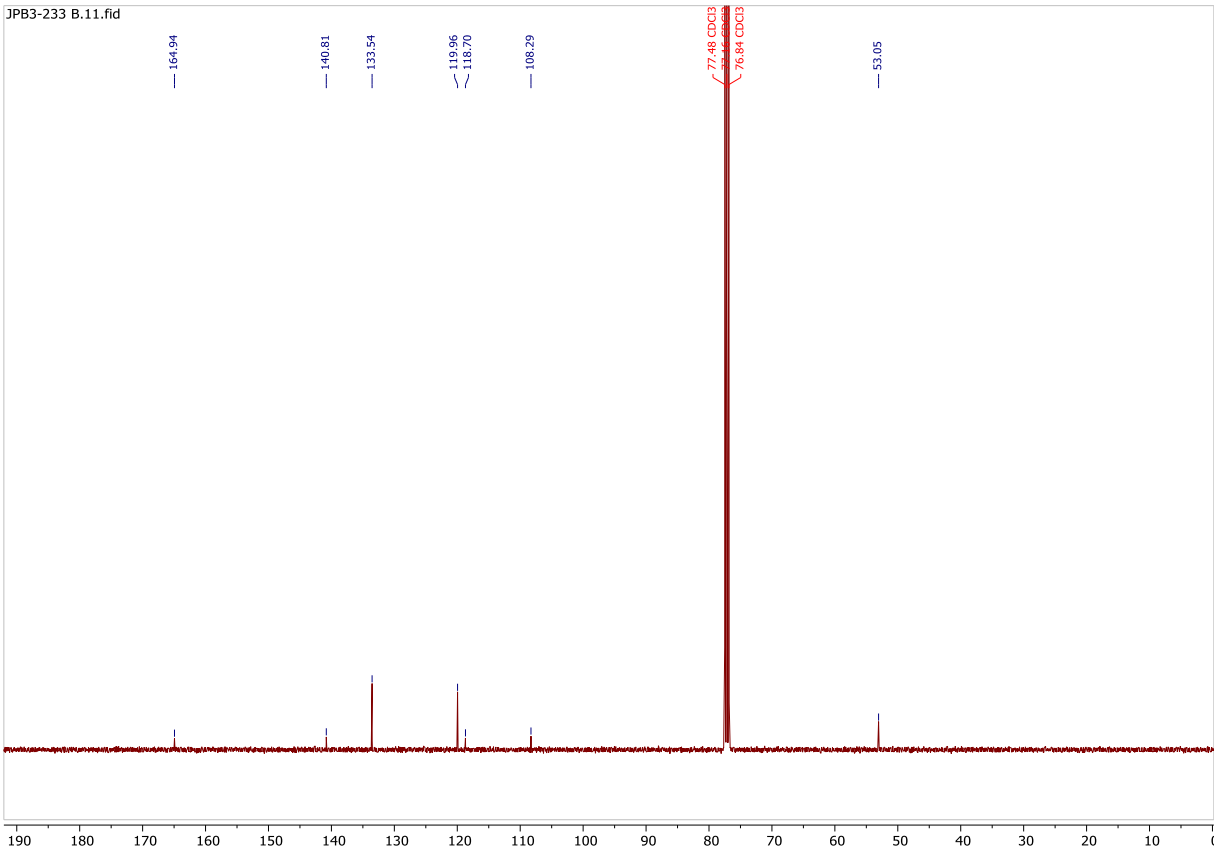


Figure S54. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-cyanophenyl)acetamide

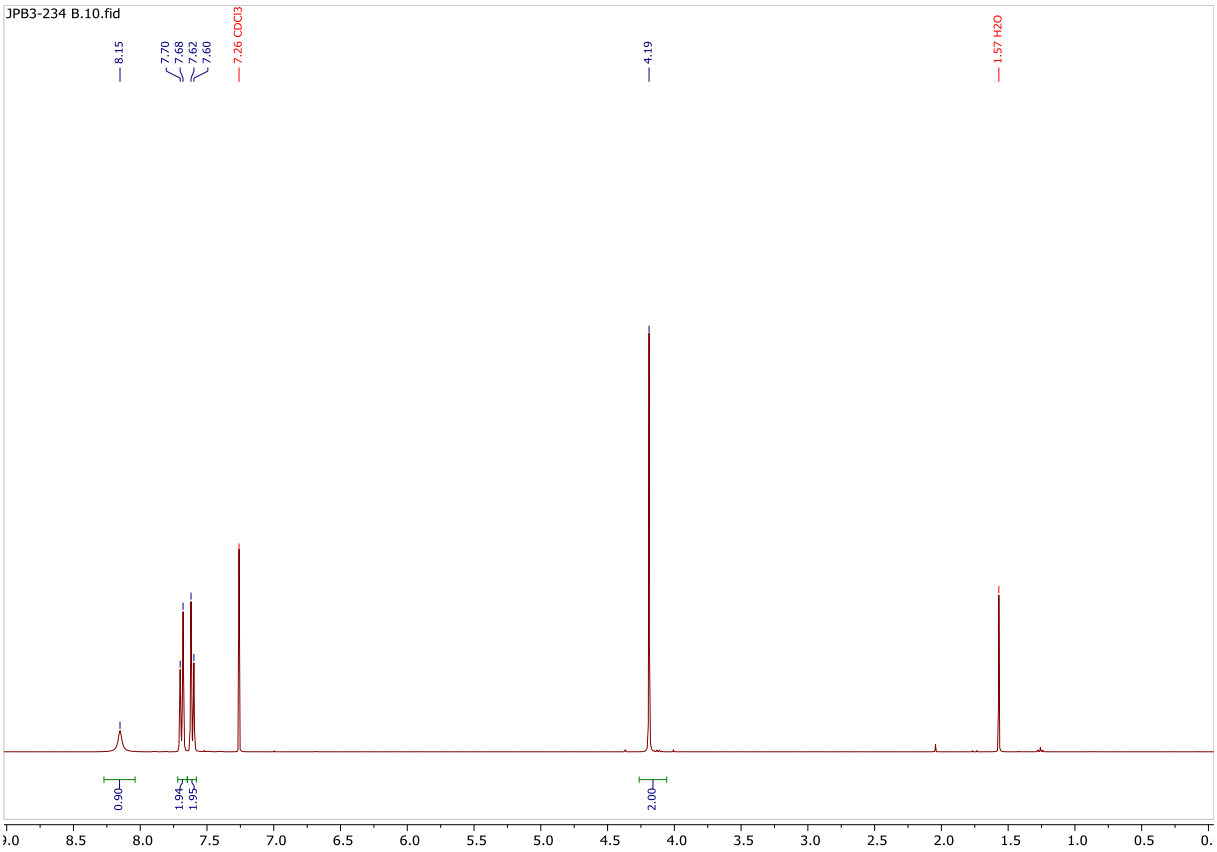


Figure S55. 1H NMR Spectrum of 2-azido-N-(4-(trifluoromethyl)phenyl)acetamide

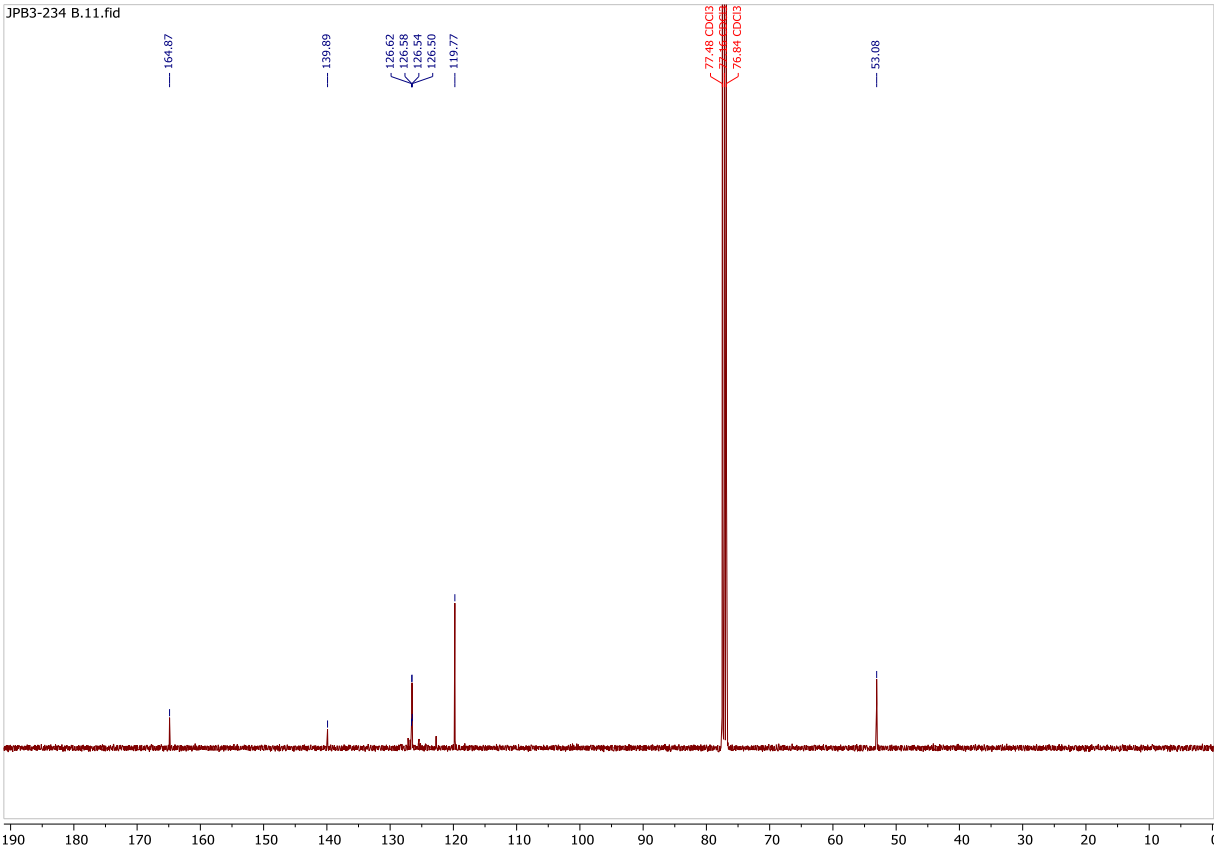


Figure S56. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-(trifluoromethyl)phenyl)acetamide

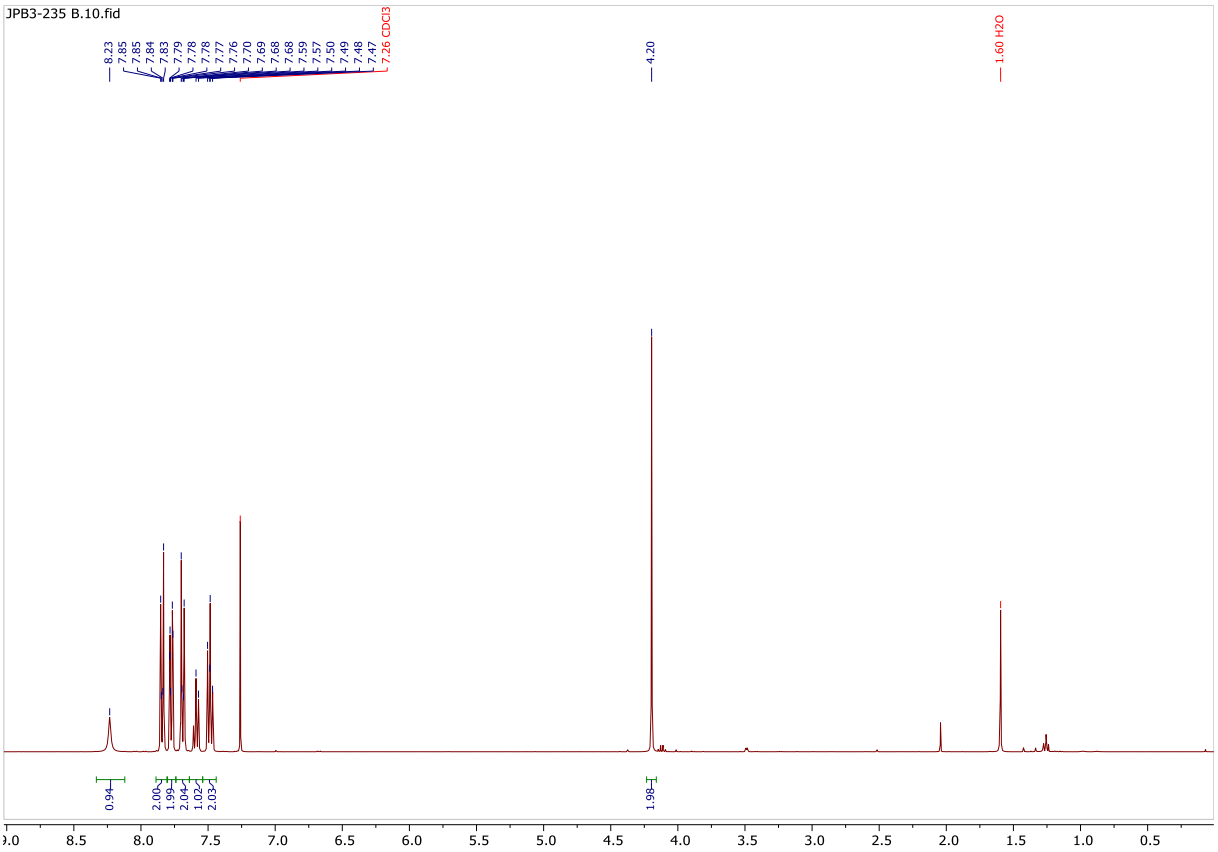


Figure S57. 1H NMR Spectrum of 2-azido-N-(4-benzoylphenyl)acetamide

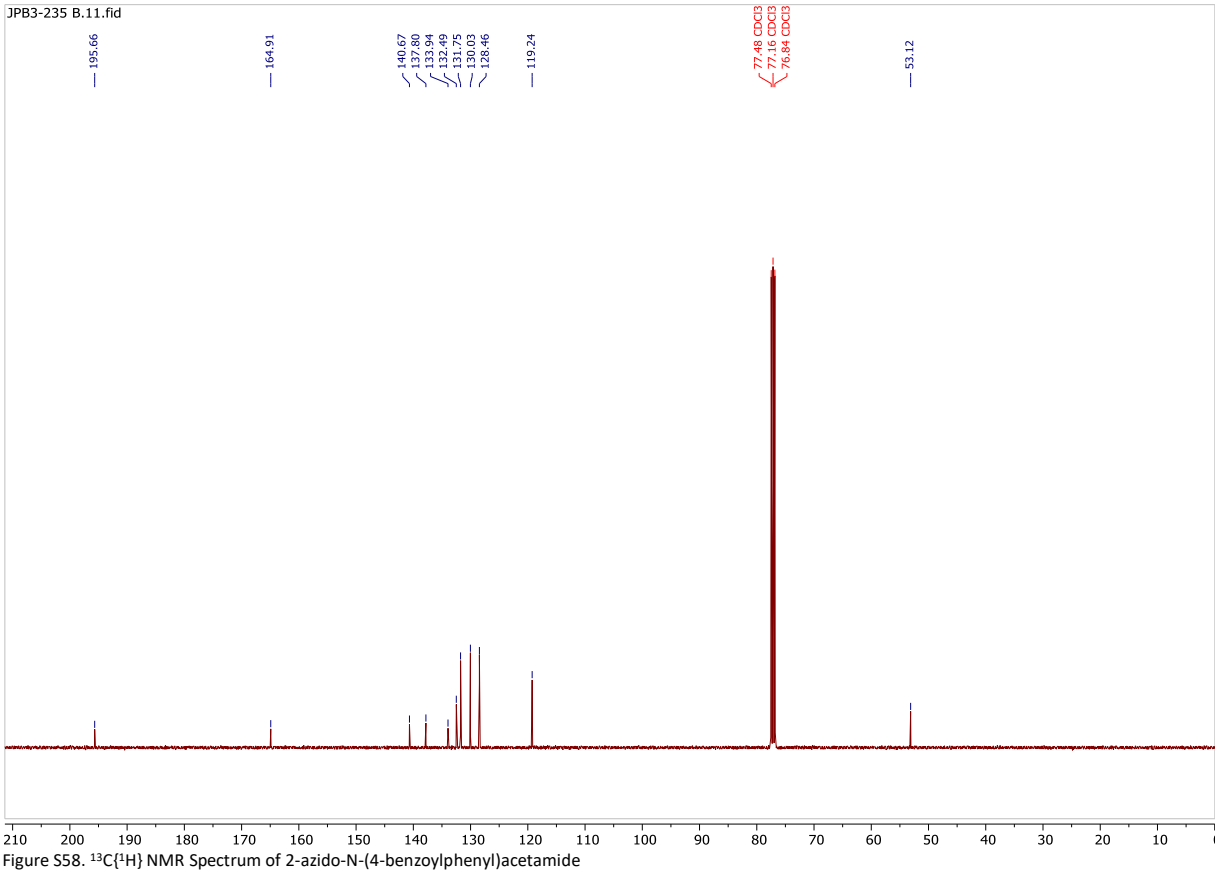


Figure S58. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(4-benzoylphenyl)acetamide

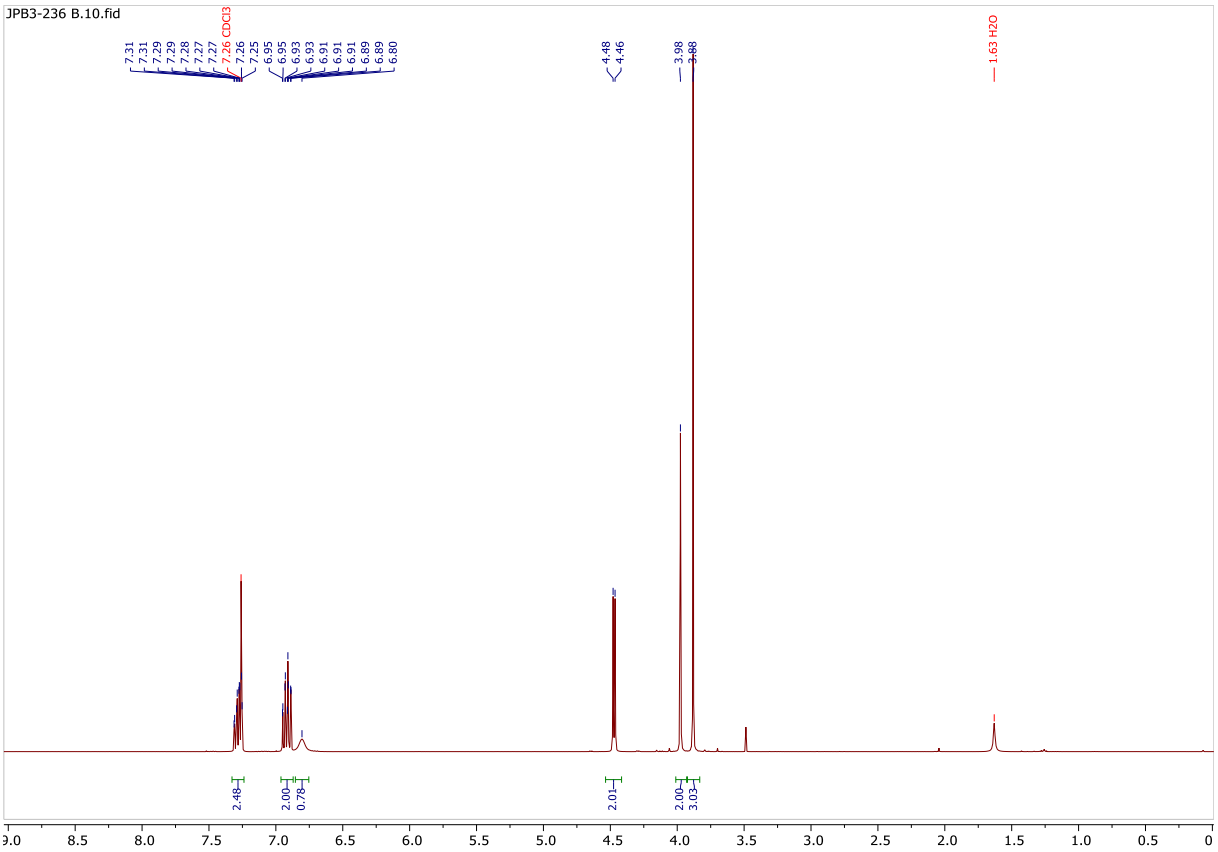


Figure S59. 1H NMR Spectrum of 2-azido-N-(2-methoxybenzyl)acetamide

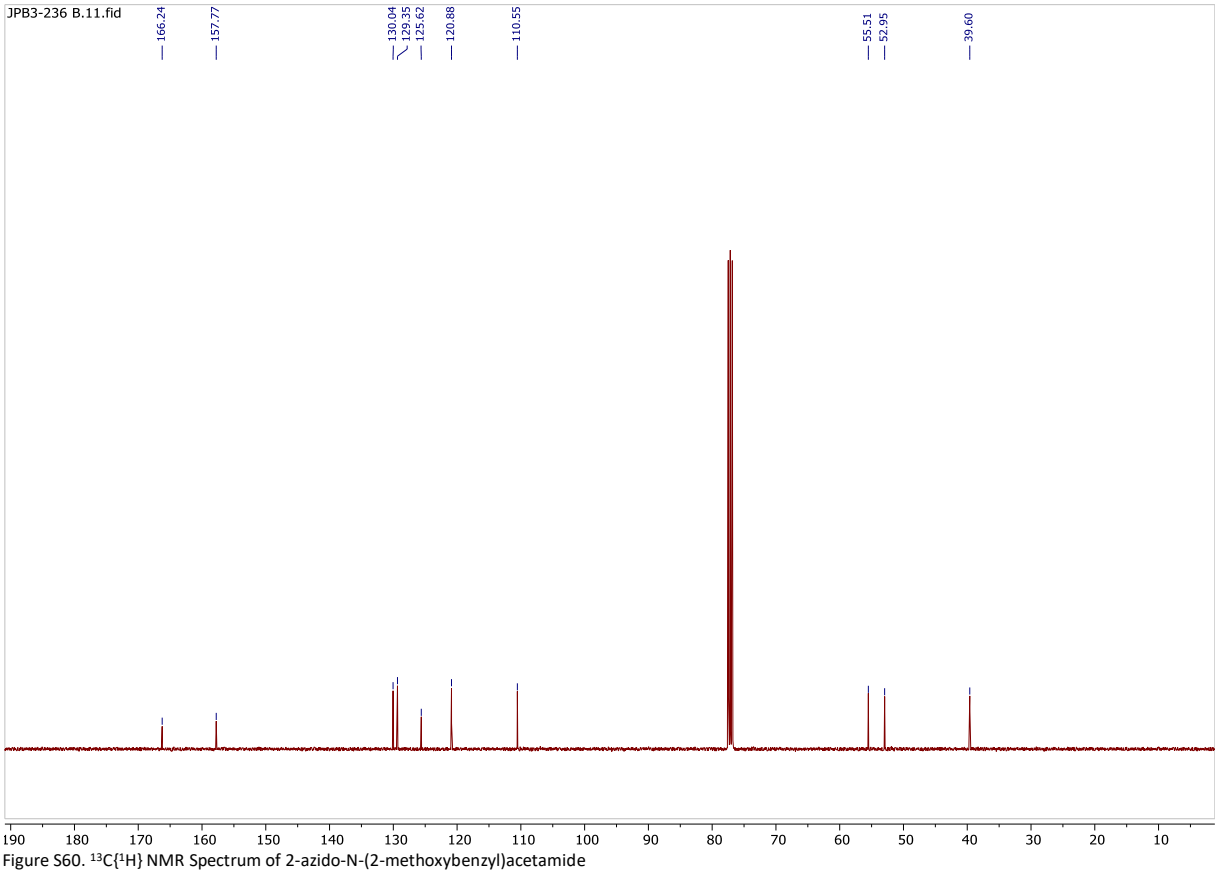


Figure S60. $^{13}C\{^{1}H\}$ NMR Spectrum of 2-azido-N-(2-methoxybenzyl)acetamide

5.2. NMR Spectra of Amine precursors (8-17)

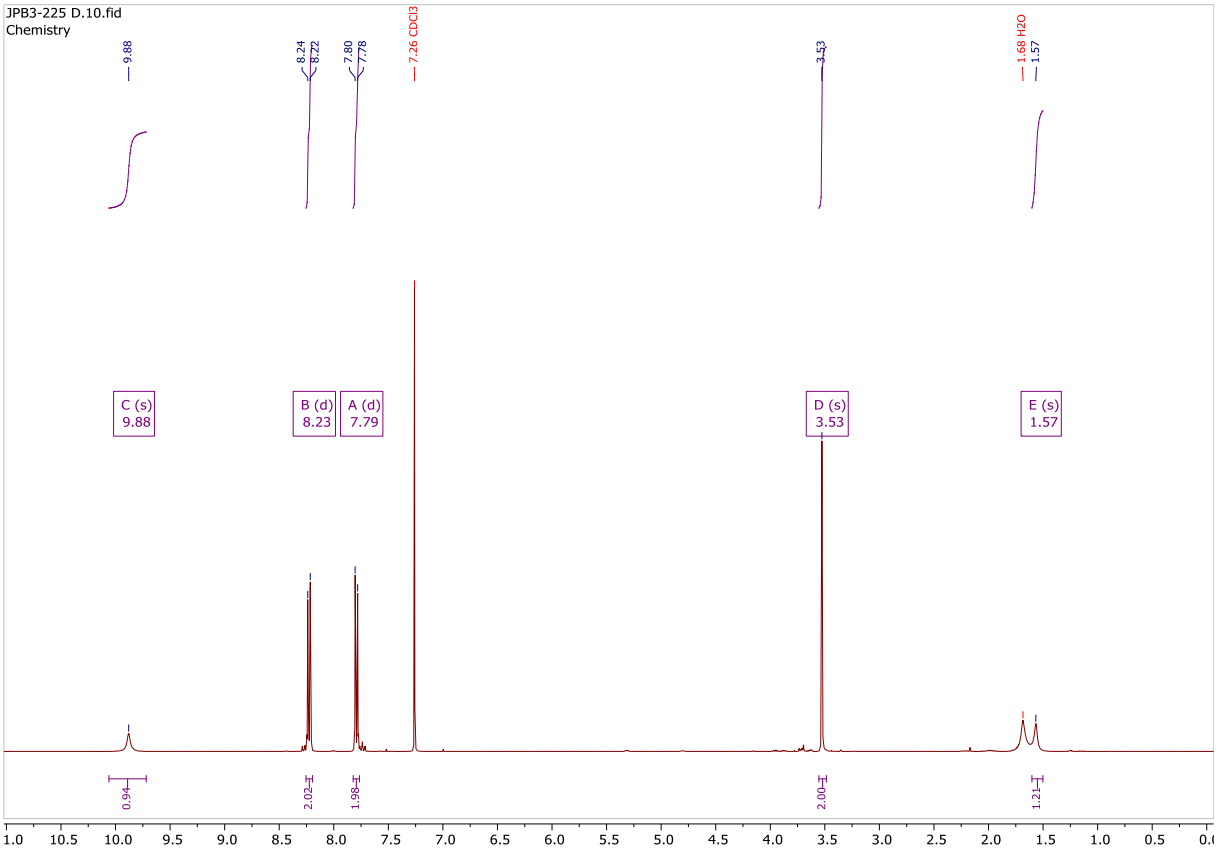


Figure S61. ^{1}H NMR of 2-amino-N-(4-nitrophenyl)acetamide

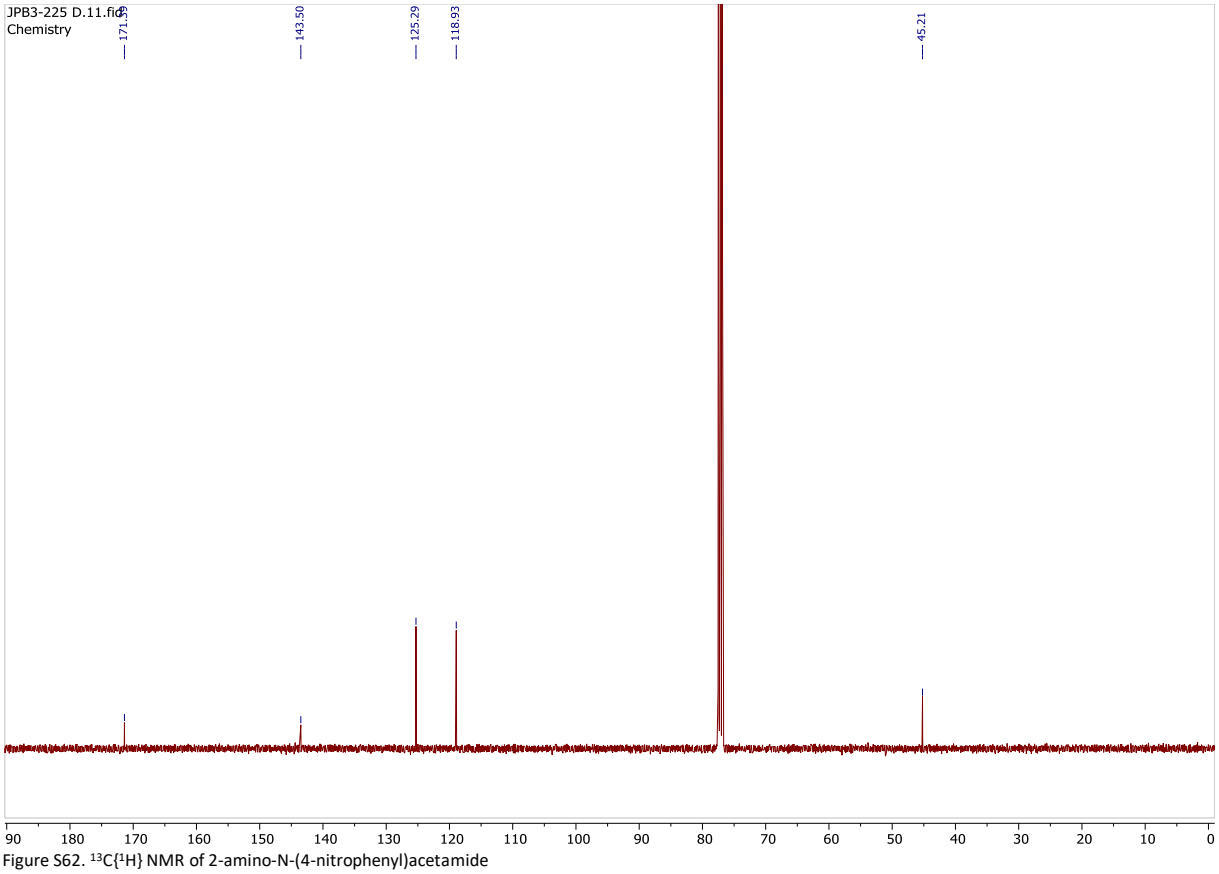


Figure S62. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-nitrophenyl)acetamide

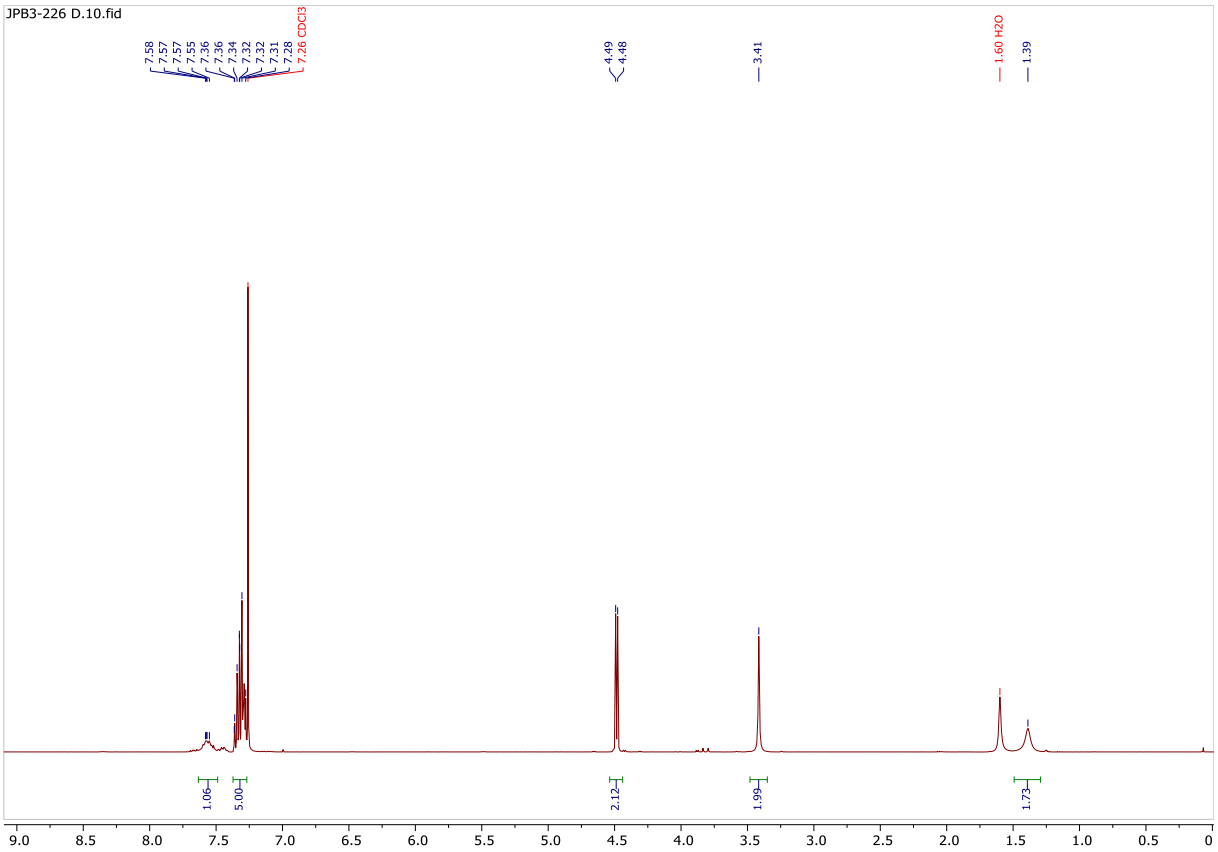


Figure S63. ^{1}H NMR of 2-amino-N-benzylacetamide

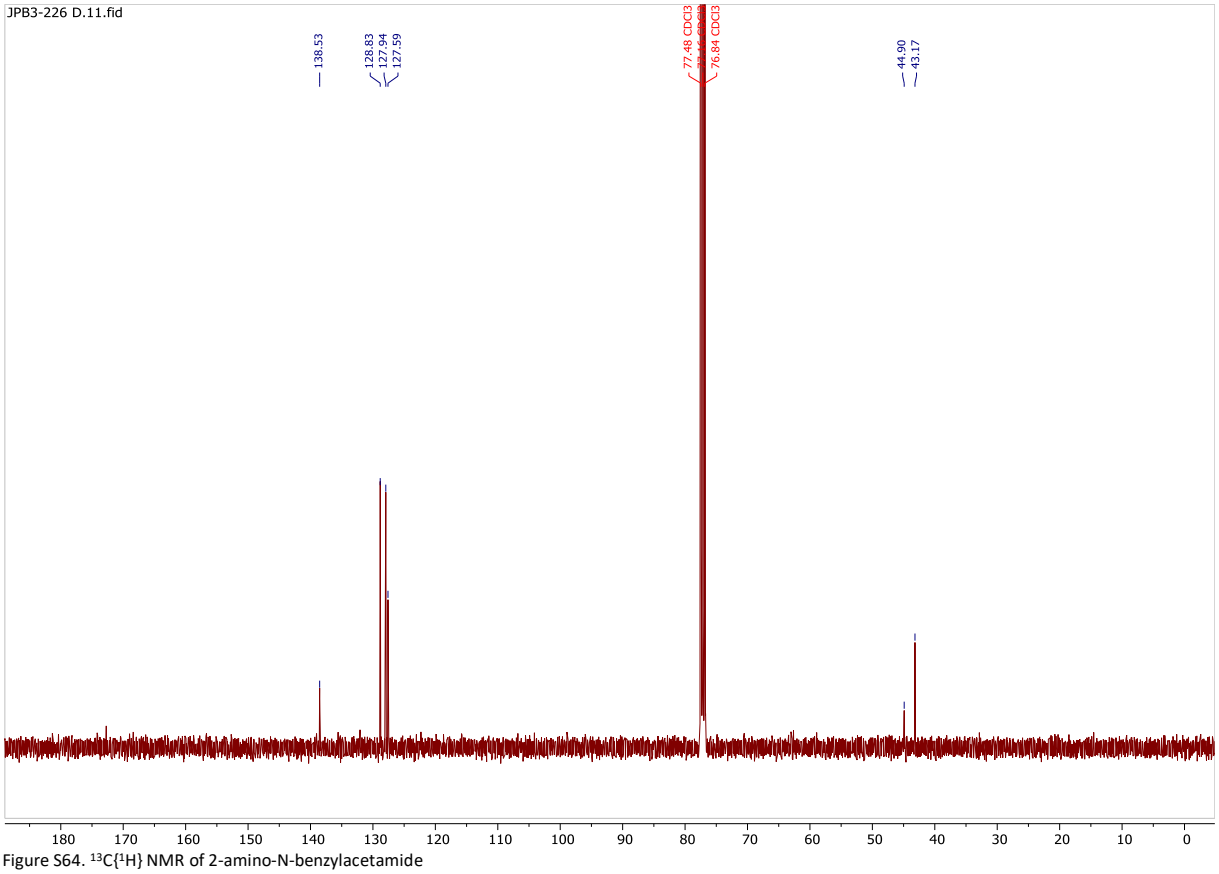


Figure S64. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-benzylacetamide

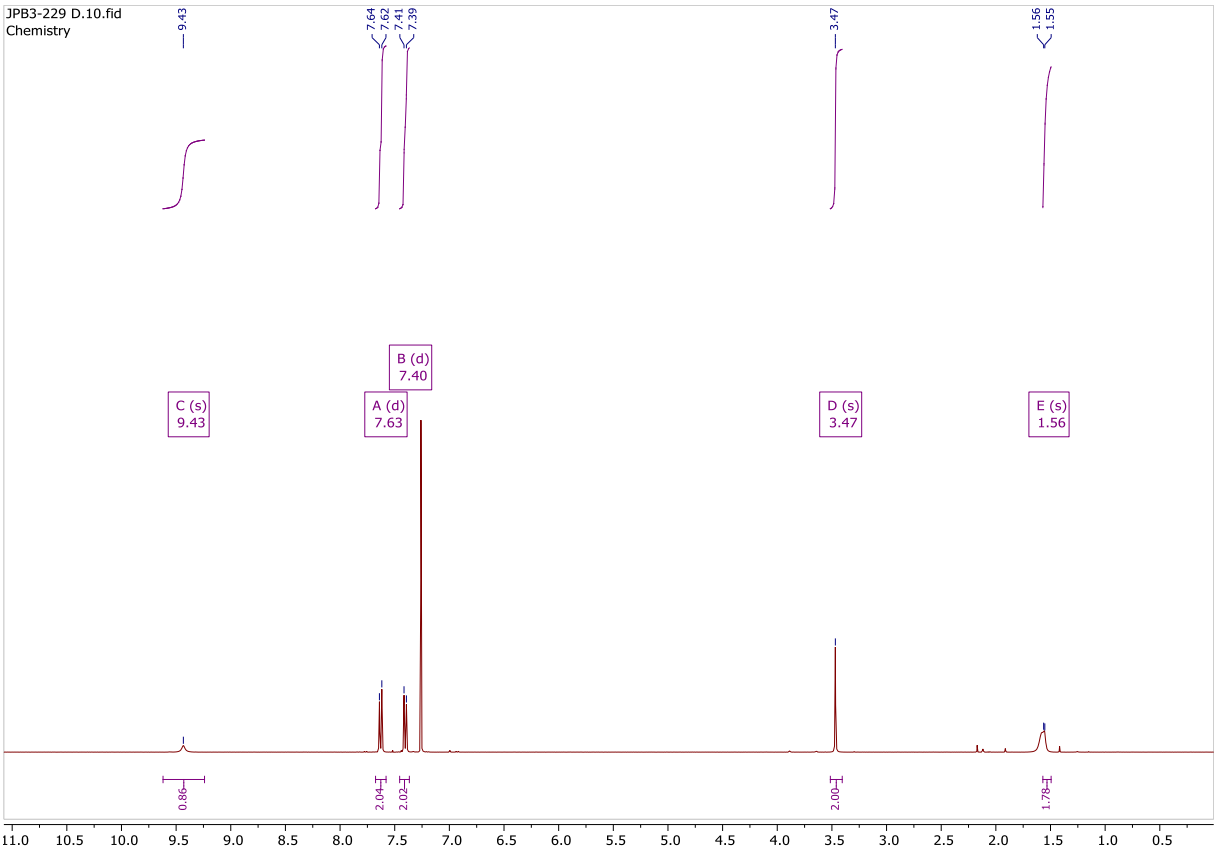


Figure S65. ^{1}H NMR of 2-amino-N-(4-iodophenyl)acetamide

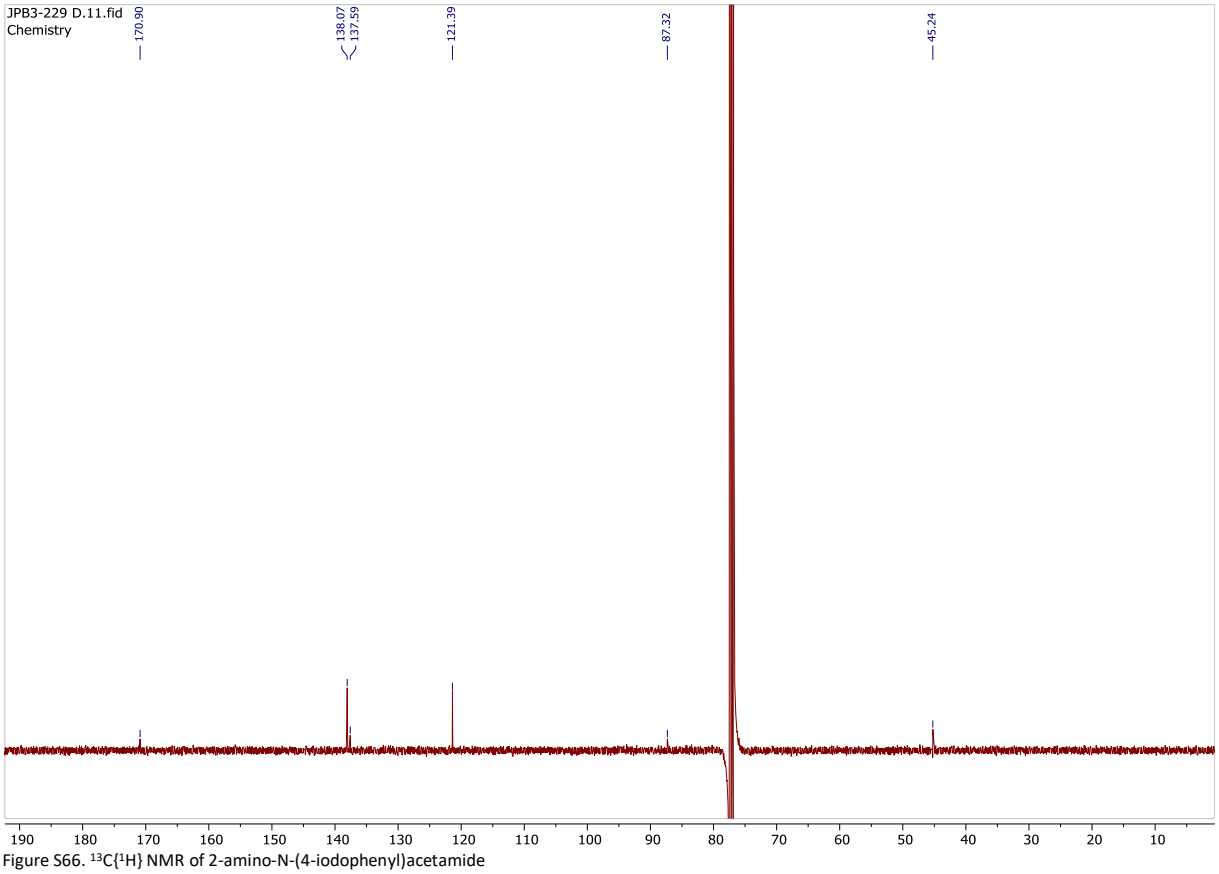


Figure S66. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-iodophenyl)acetamide

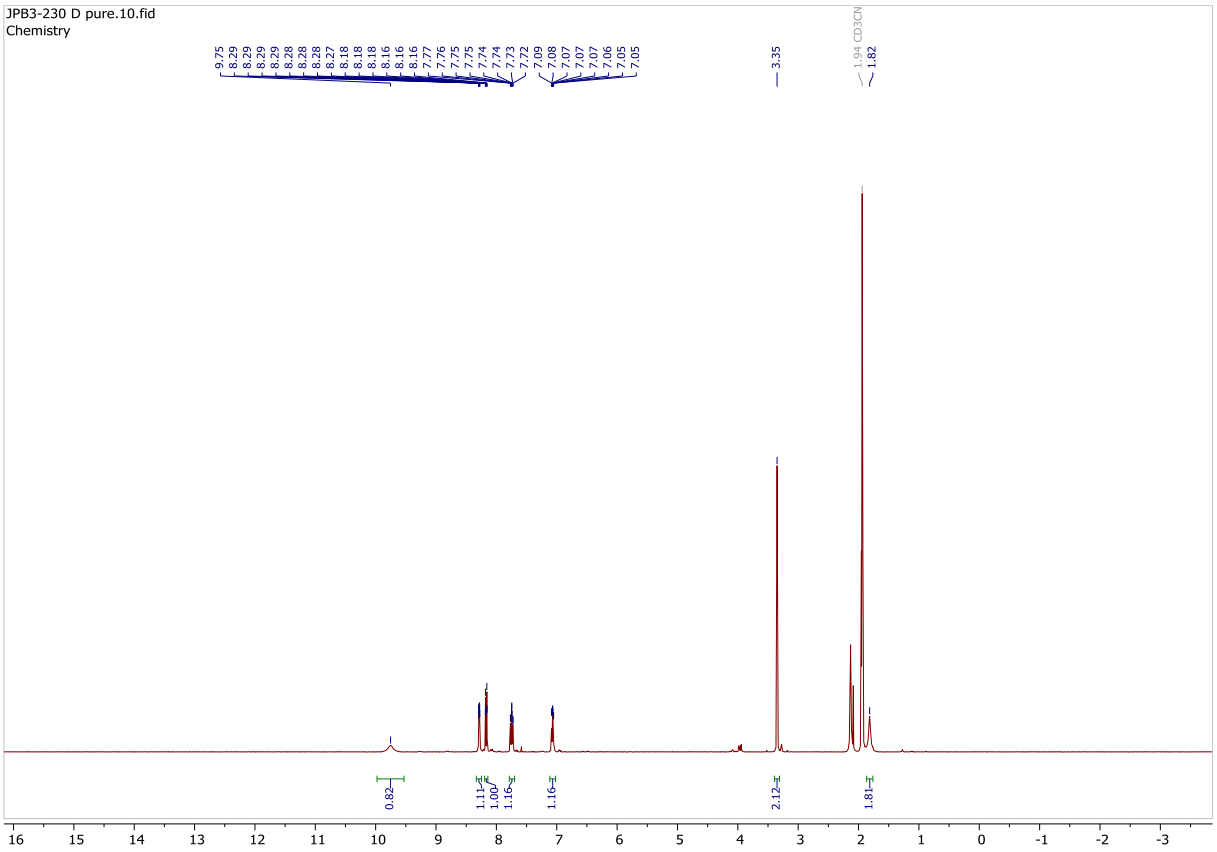


Figure S67. ^{1}H NMR of 2-amino-N-(pyridin-2-yl)acetamide

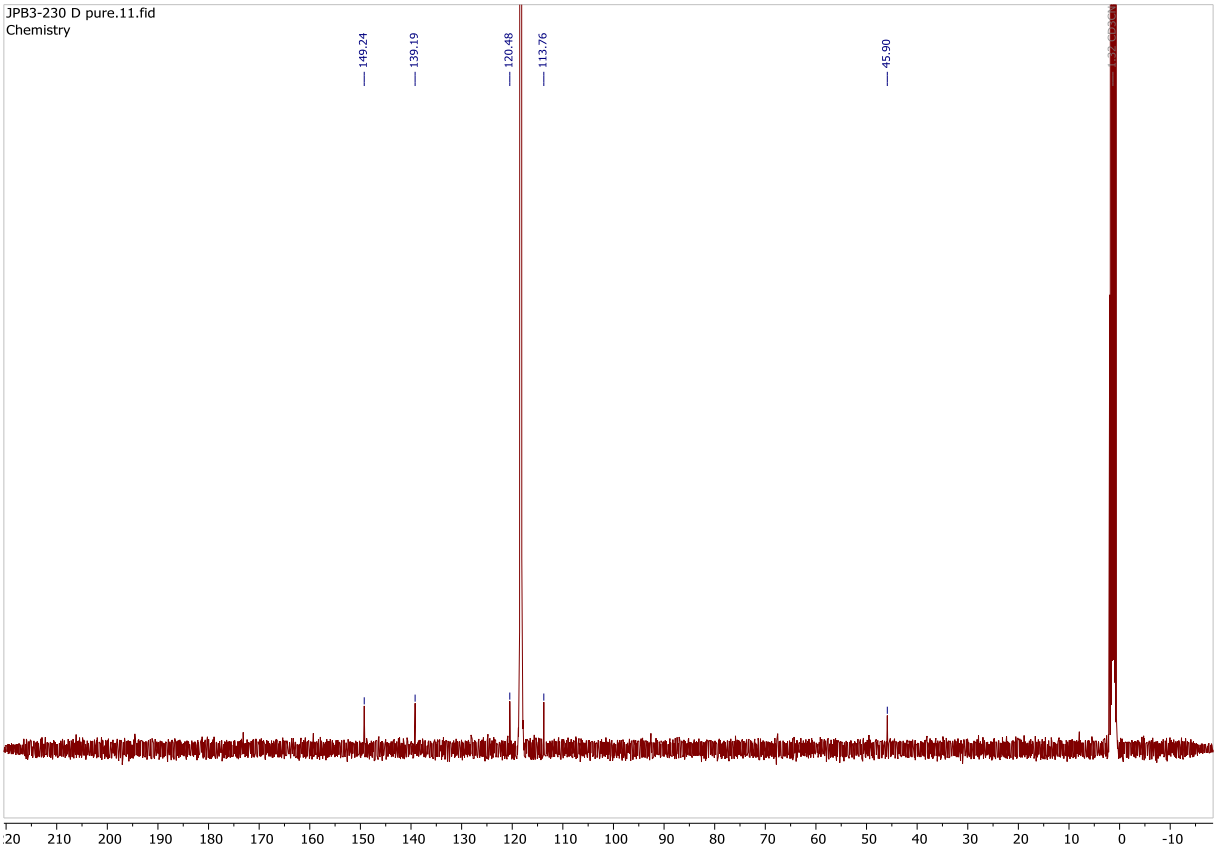


Figure S68. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(pyridin-2-yl)acetamide

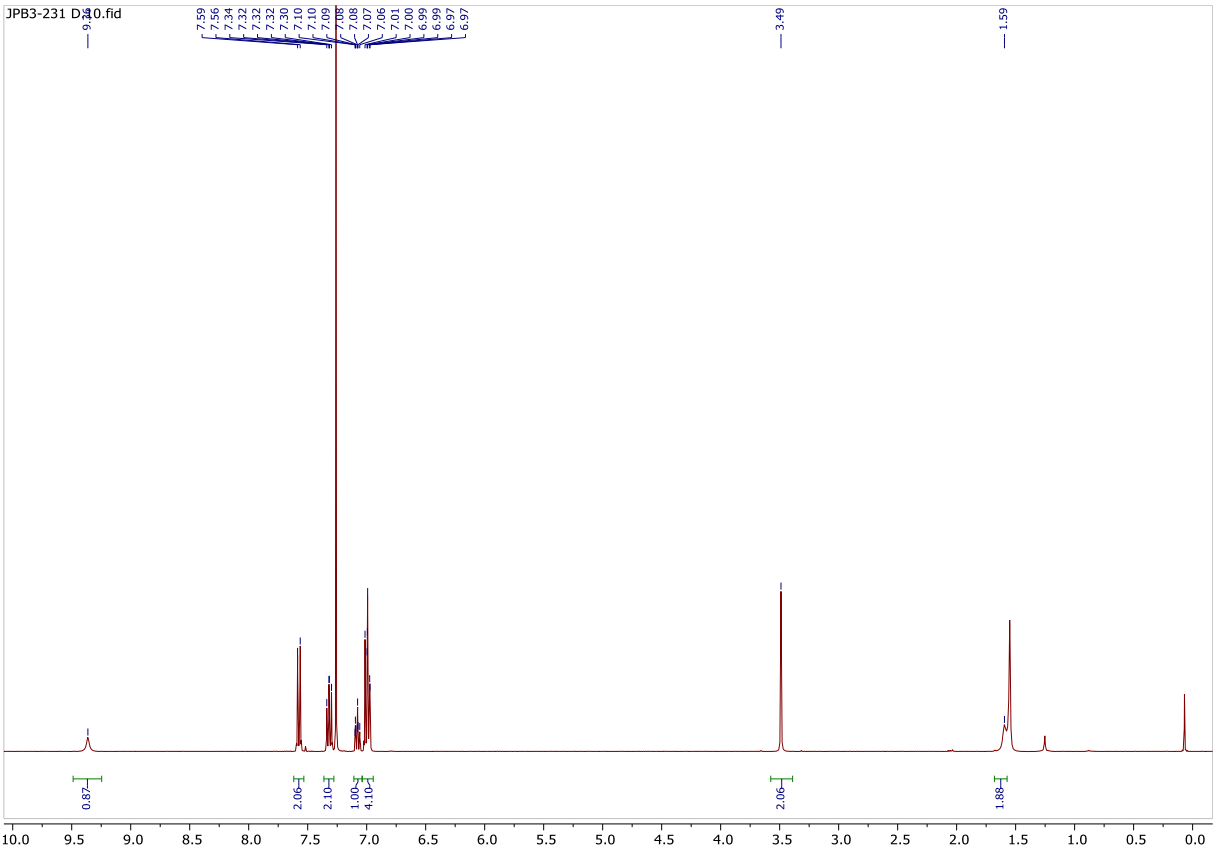


Figure S69. ^{1}H NMR of 2-amino-N-(4-phenoxyphenyl)acetamide

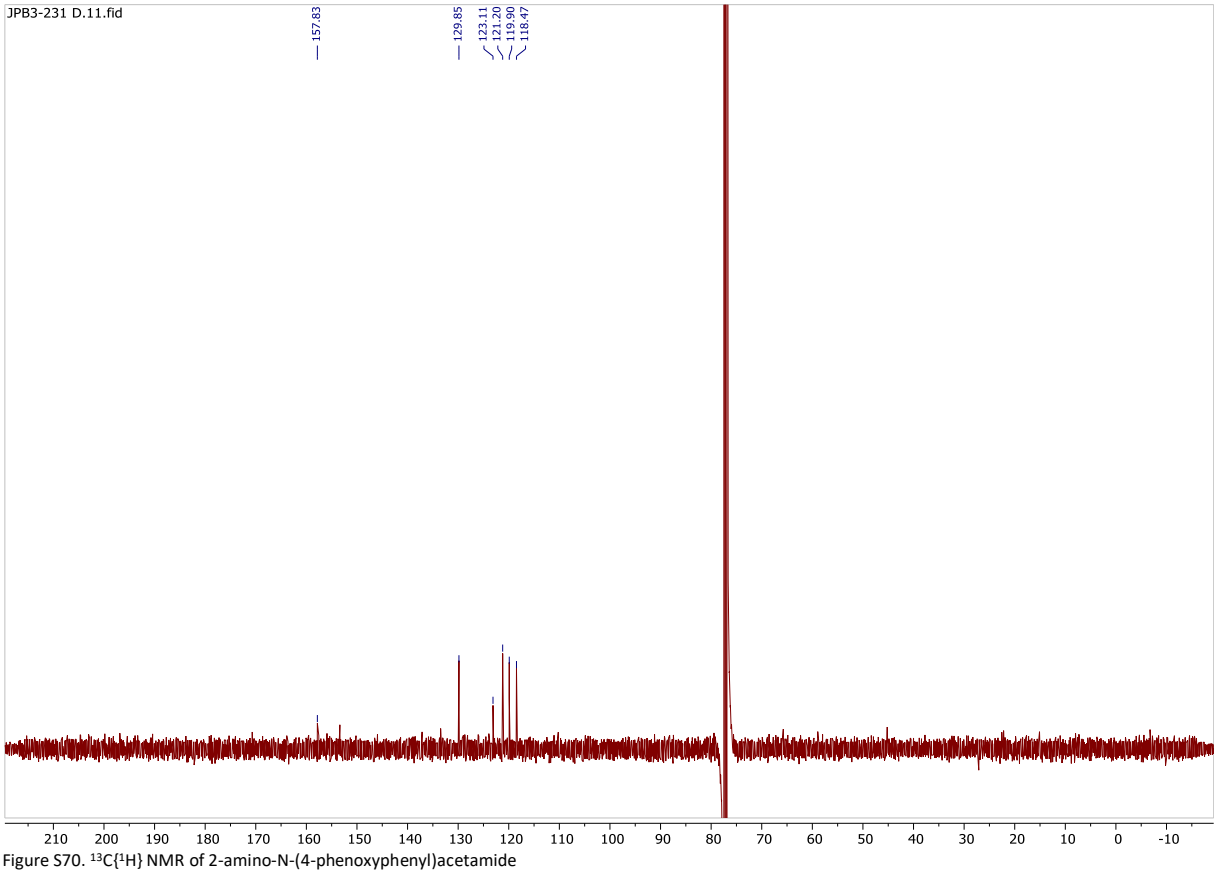


Figure S70. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-phenoxyphenyl)acetamide

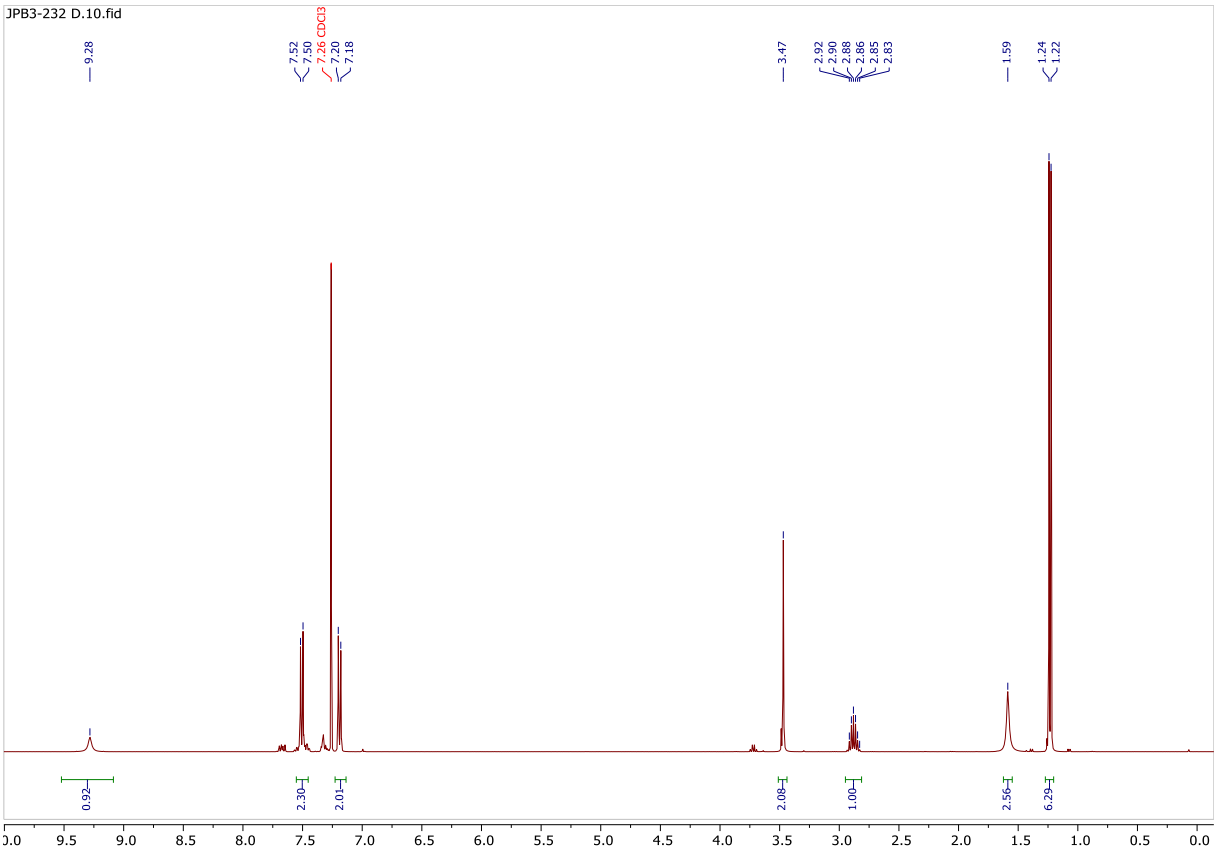


Figure S71. ^{1}H NMR of 2-amino-N-(4-isopropylphenyl)acetamide

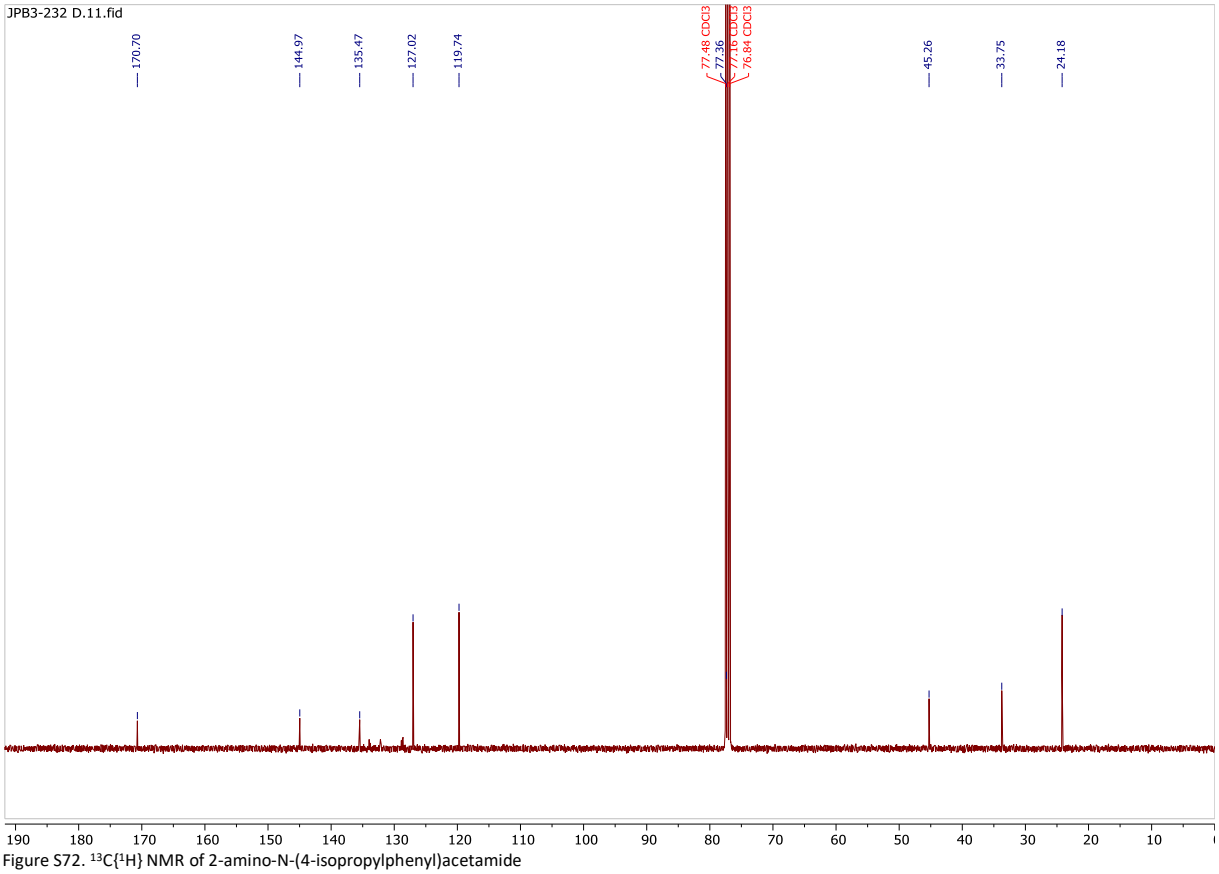


Figure S72. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-isopropylphenyl)acetamide

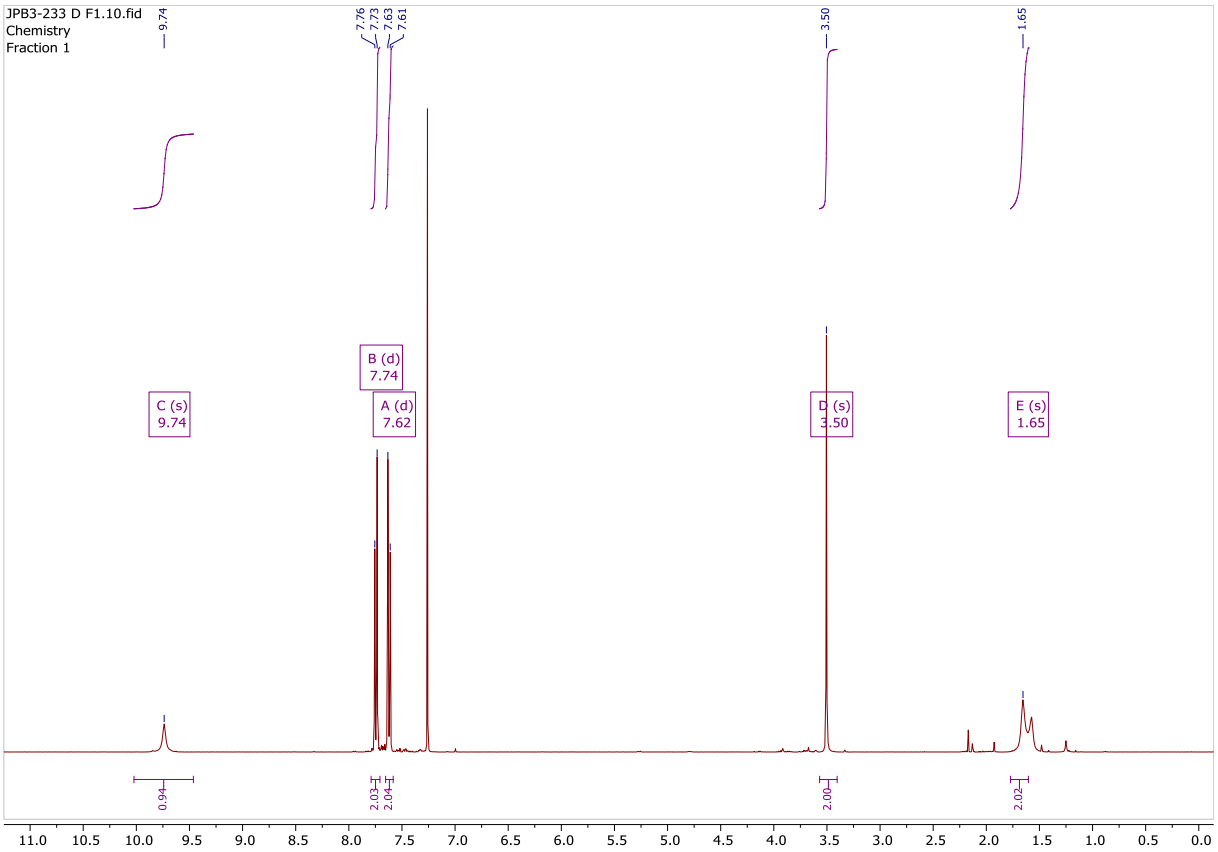


Figure S73. ^{1}H NMR of 2-amino-N-(4-cyanophenyl)acetamide

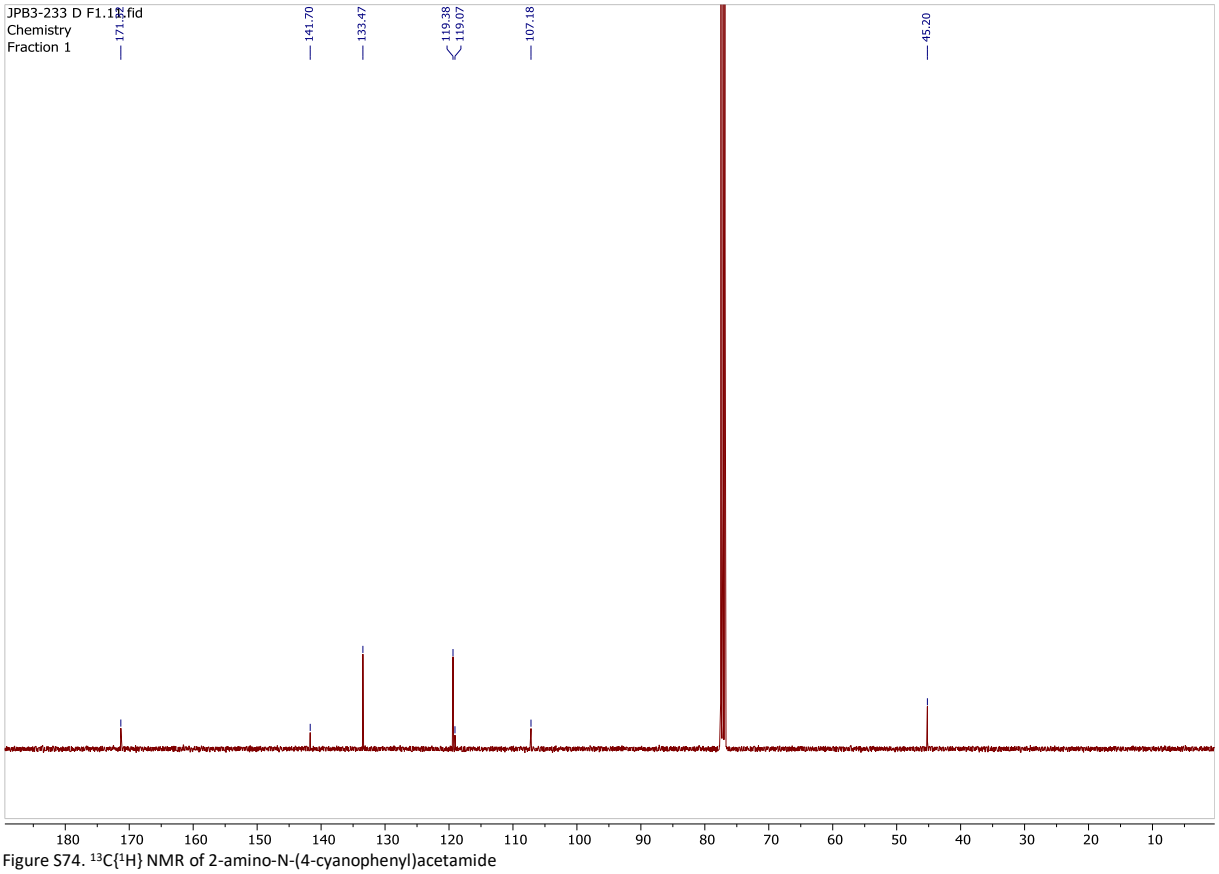


Figure S74. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-cyanophenyl)acetamide

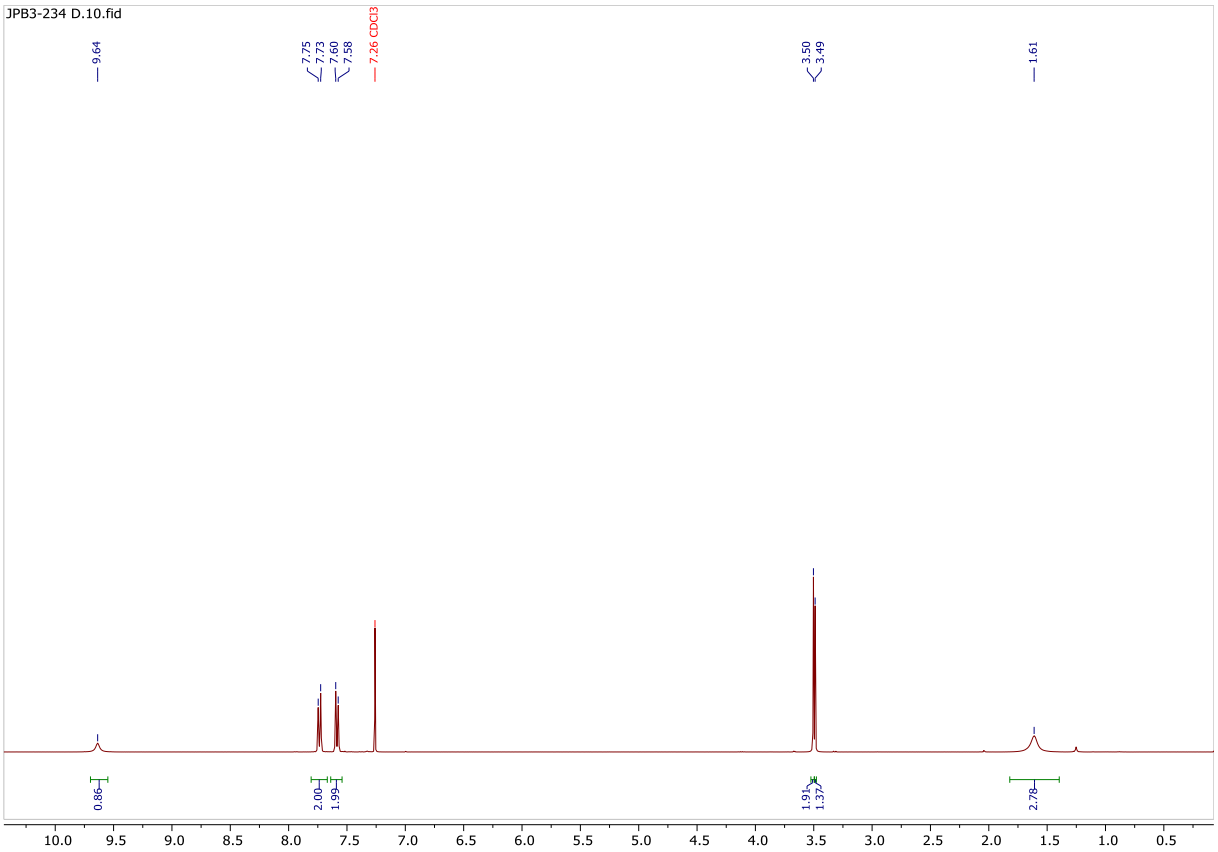


Figure S75. ^{1}H NMR of 2-amino-N-(4-(trifluoromethyl)phenyl)acetamide

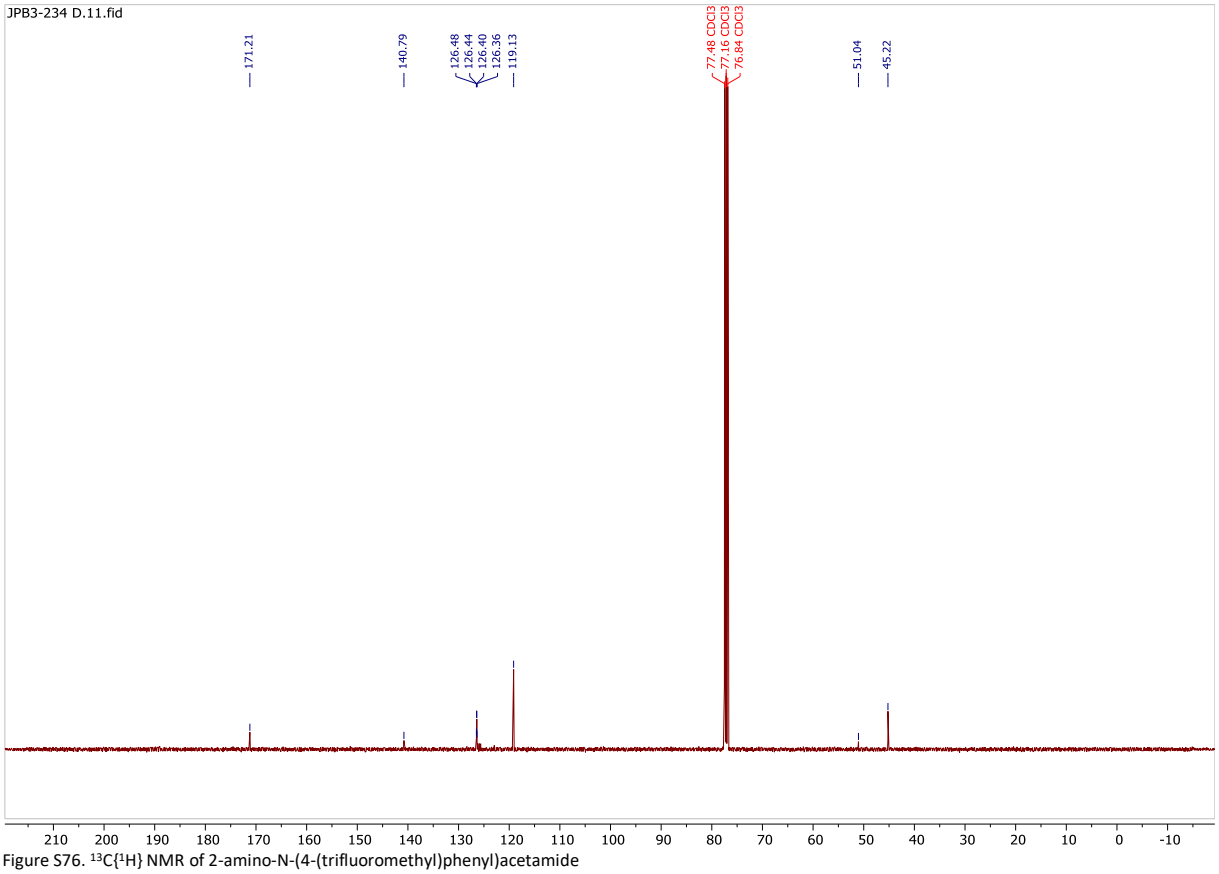


Figure S76. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-(trifluoromethyl)phenyl)acetamide

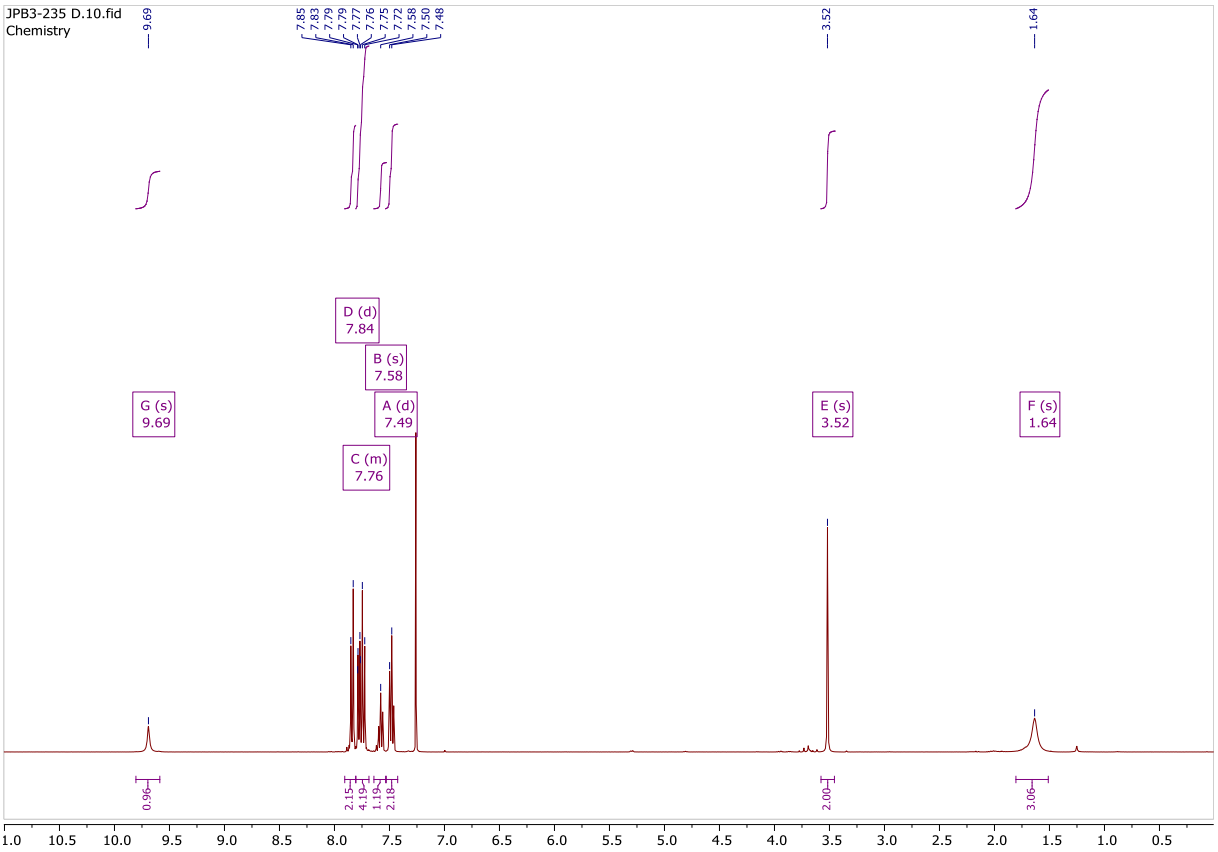


Figure S77. ^{1}H NMR of 2-amino-N-(4-benzoylphenyl)acetamide

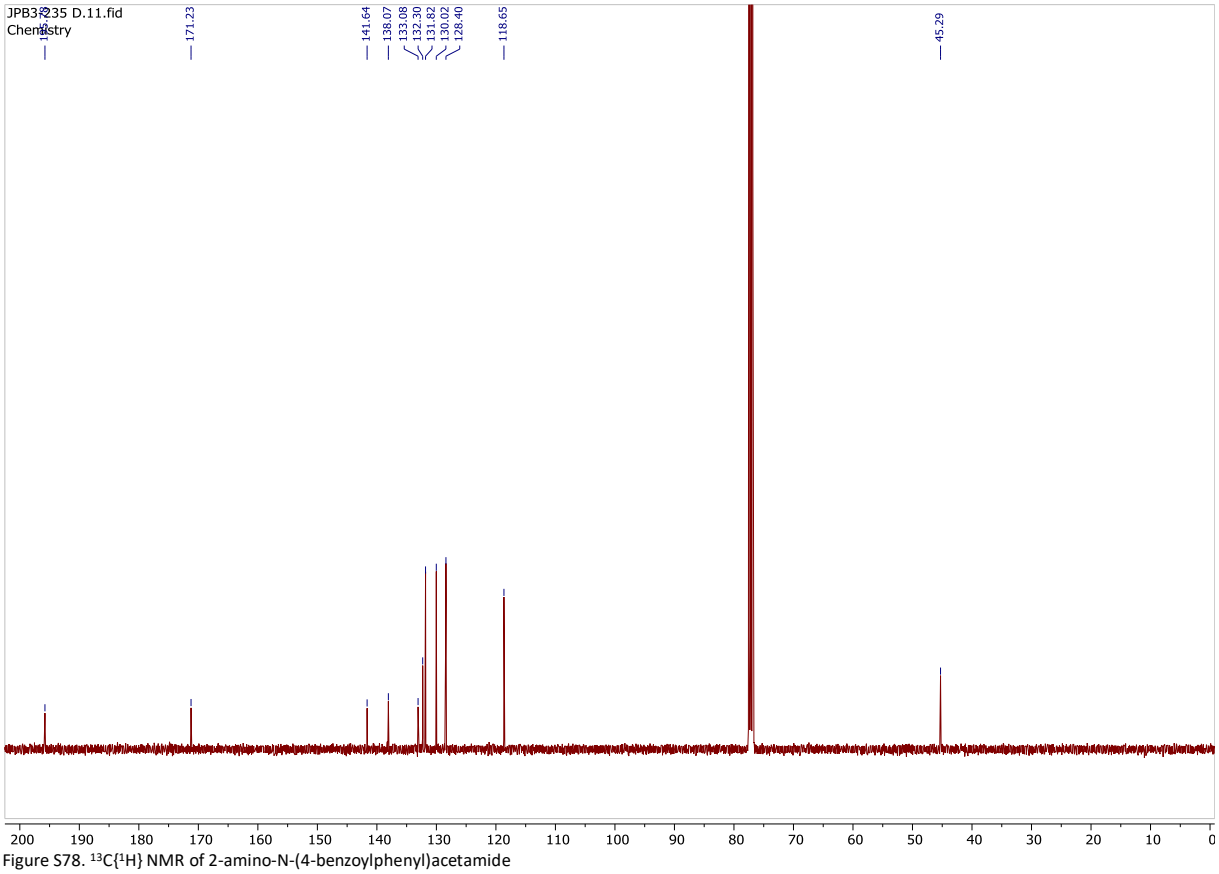


Figure S78. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(4-benzoylphenyl)acetamide

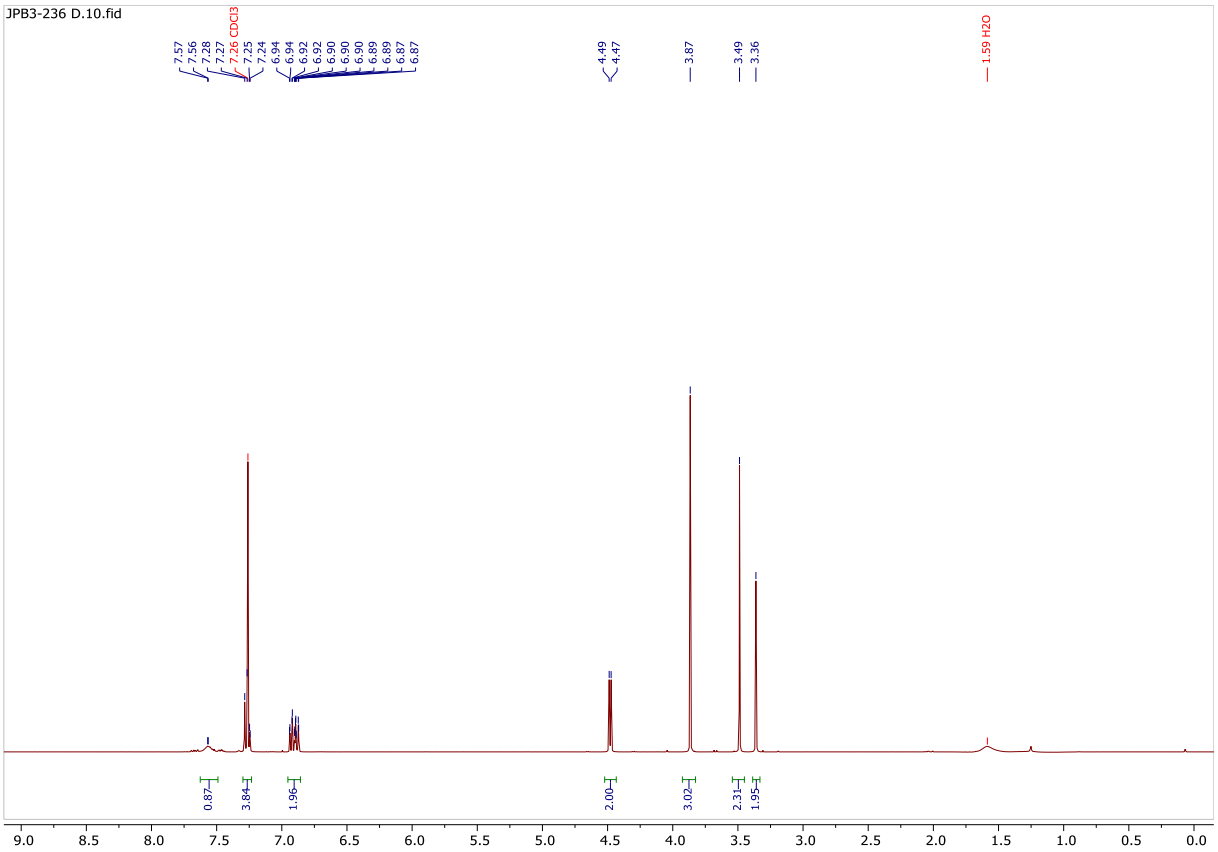


Figure S79. ^{1}H NMR of 2-amino-N-(2-methoxybenzyl)acetamide

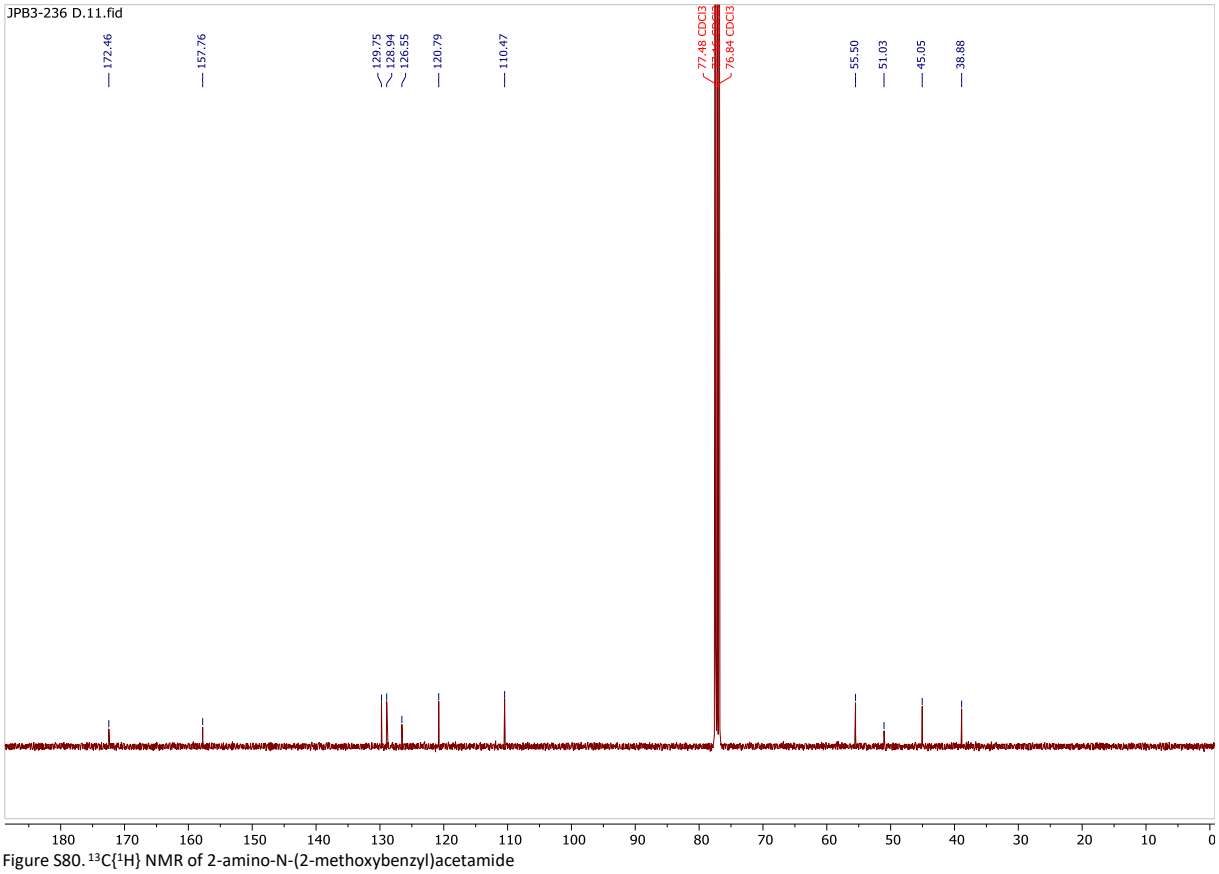


Figure S80. $^{13}C\{^{1}H\}$ NMR of 2-amino-N-(2-methoxybenzyl)acetamide

5.1. Labelling precursors and reference compounds

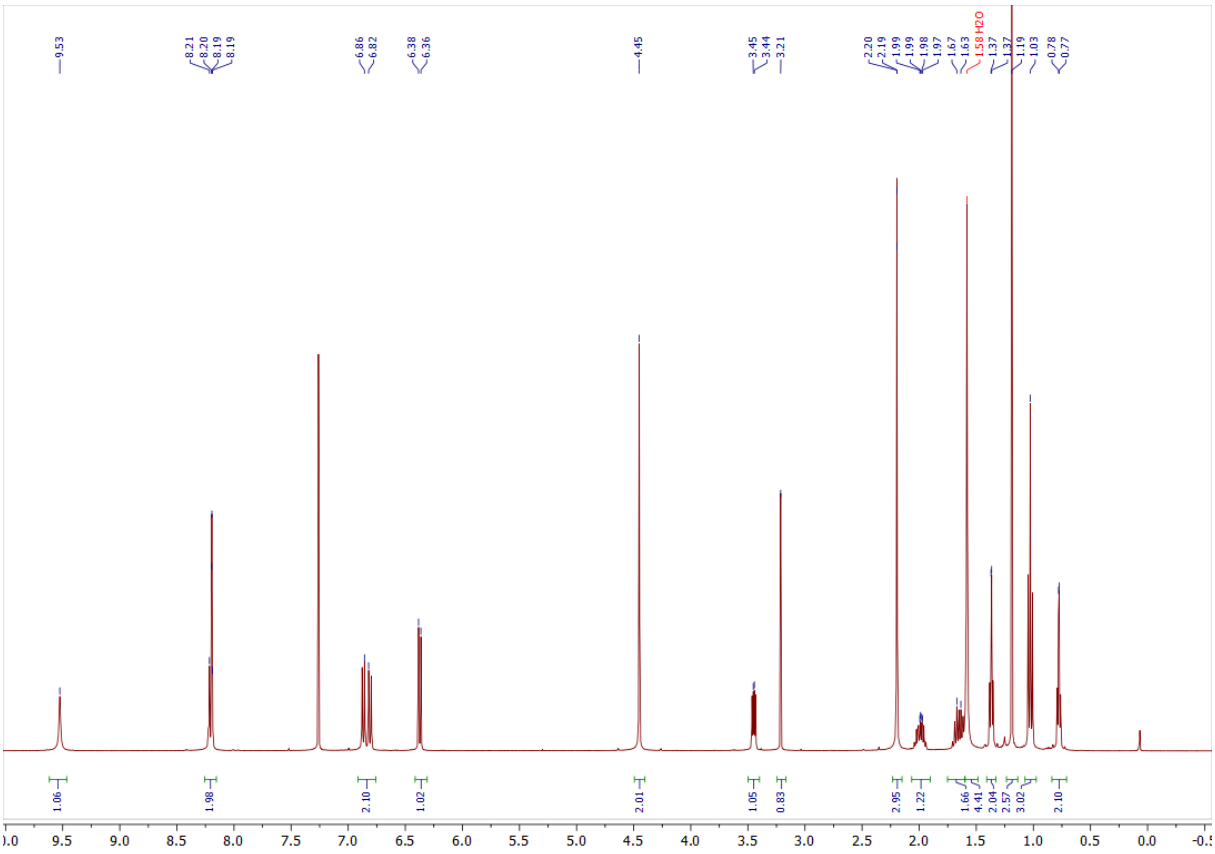


Figure S81. ^{1}H NMR of **18** Precursor

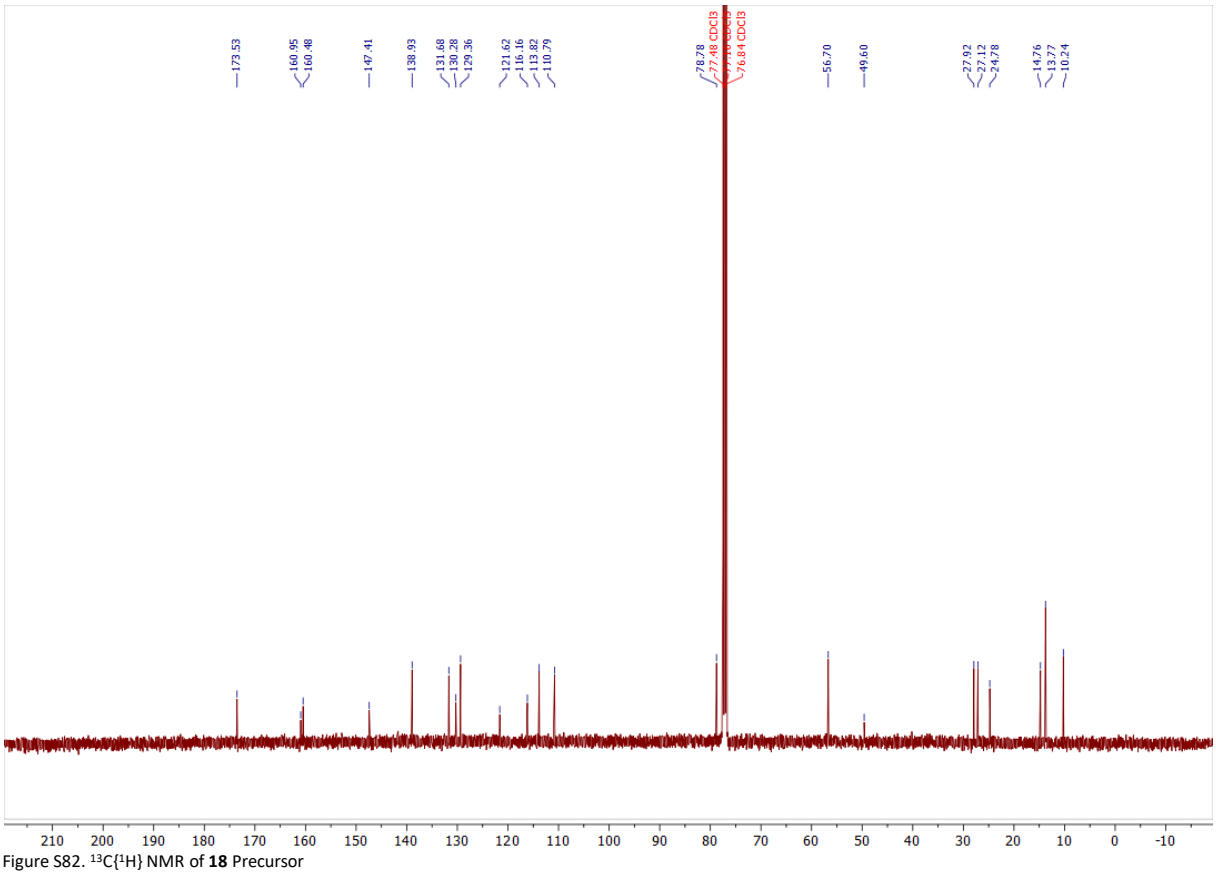


Figure S82. $^{13}C\{^{1}H\}$ NMR of **18** Precursor

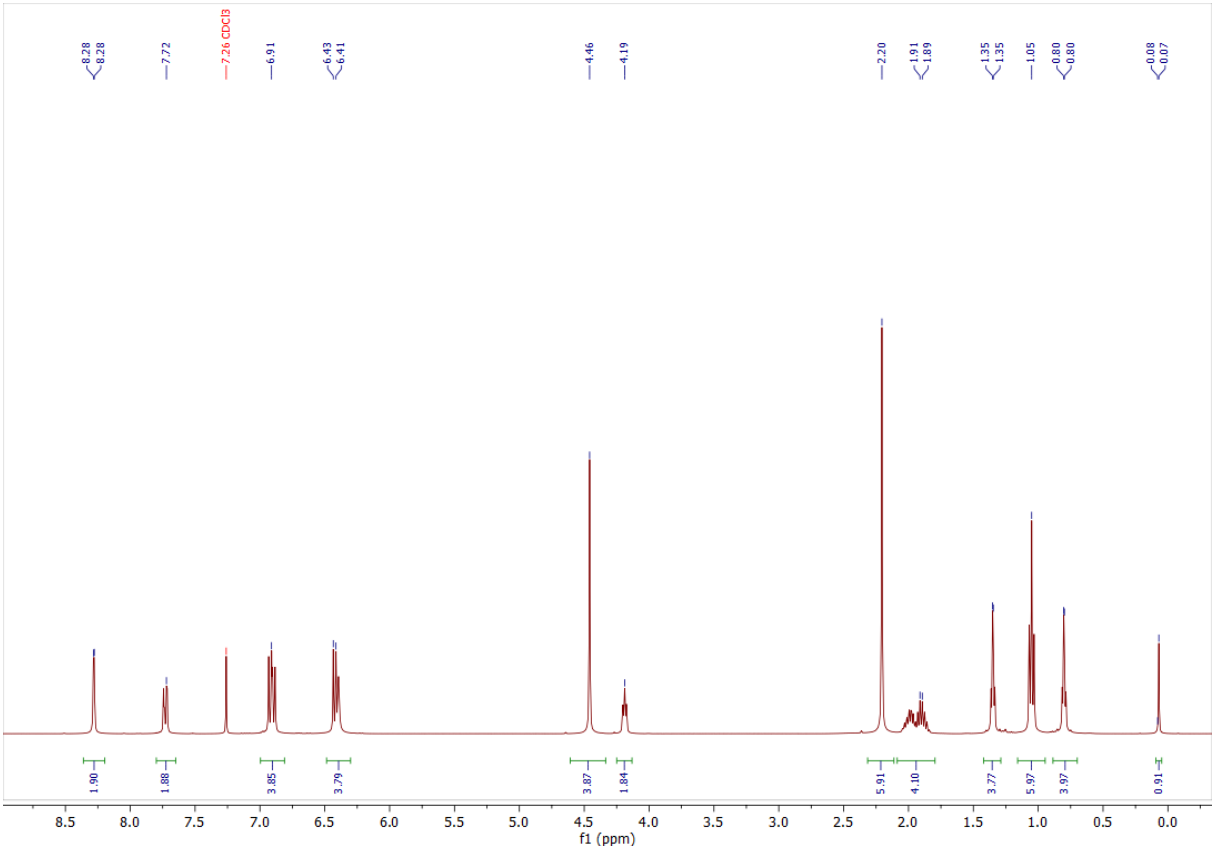


Figure S83. ^{1}H NMR of **18** Reference

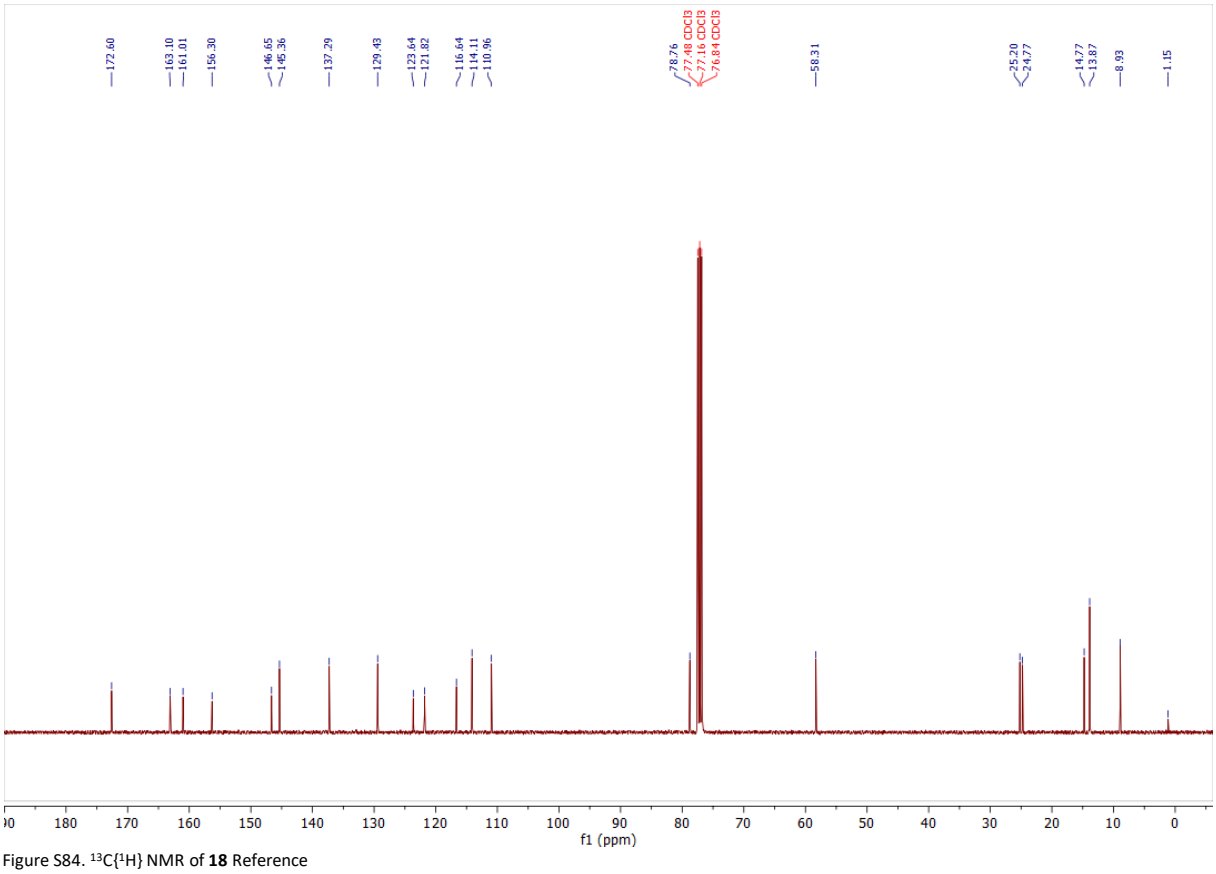


Figure S84. $^{13}C\{^{1}H\}$ NMR of **18** Reference

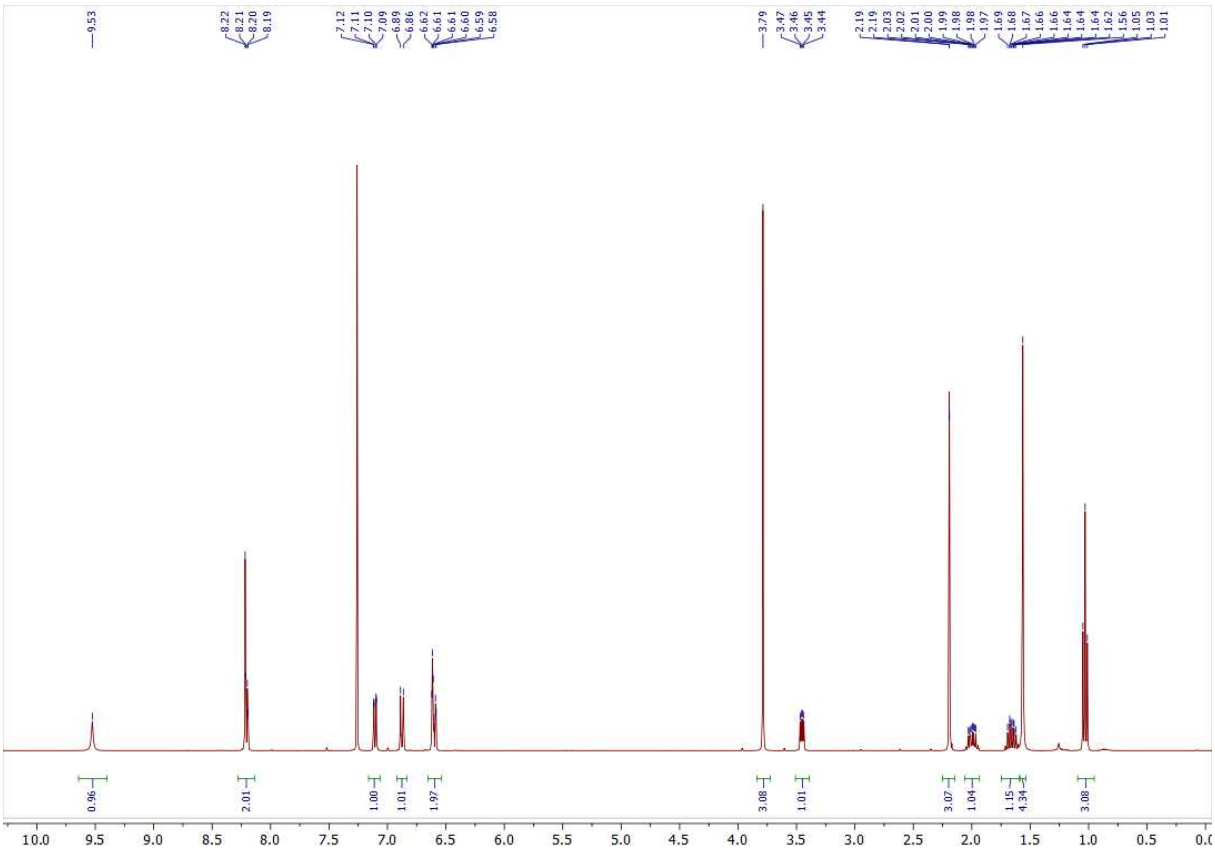


Figure S85 ^{1}H NMR of **20** Precursor

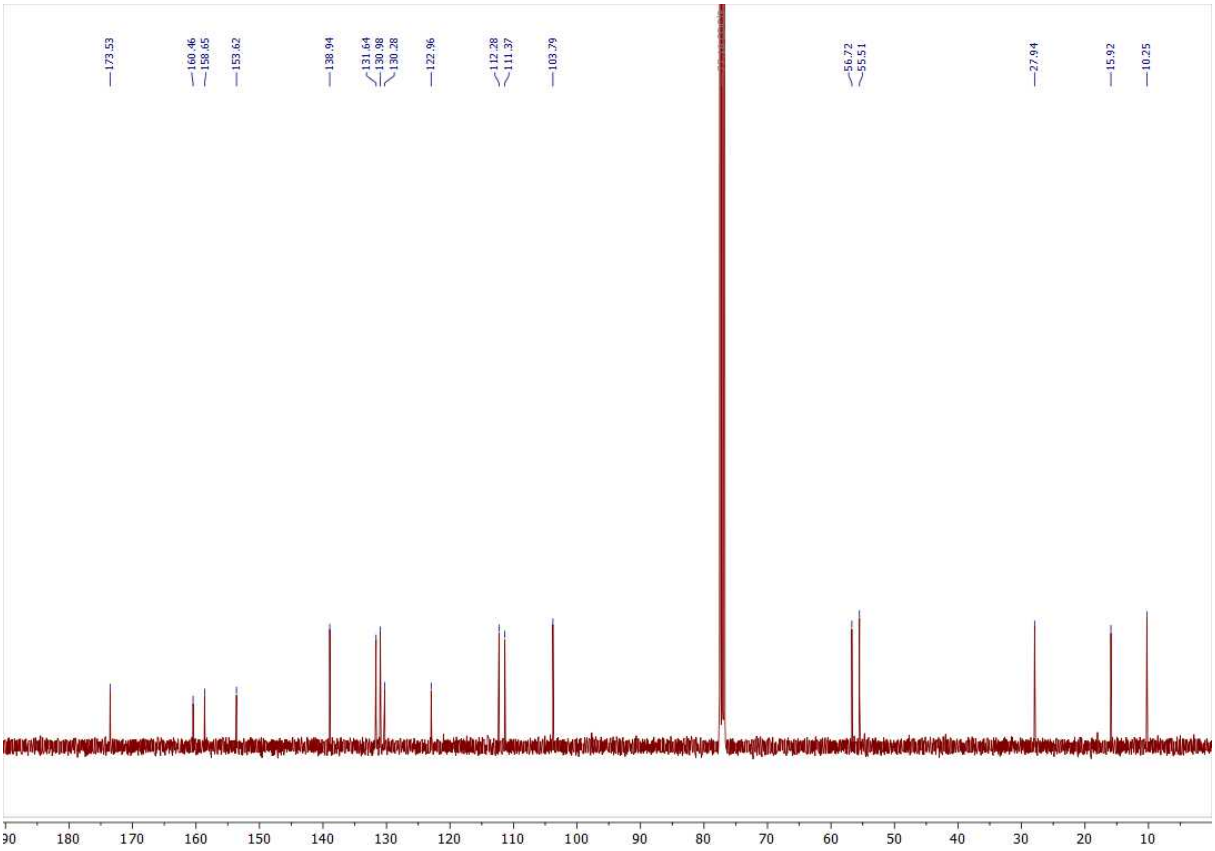


Figure S86 $^{13}C\{^{1}H\}$ NMR of **20** Precursor

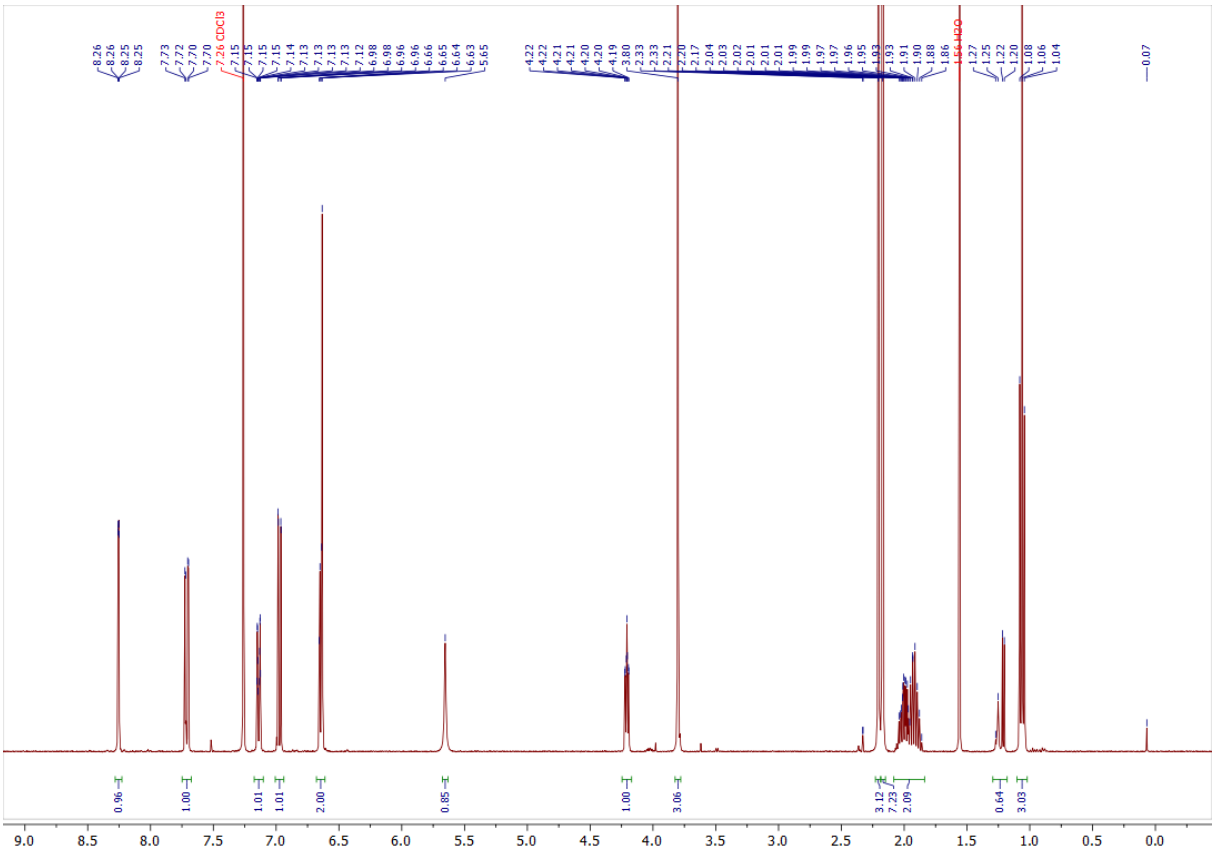


Figure S87 ^{1}H NMR of **20** Reference

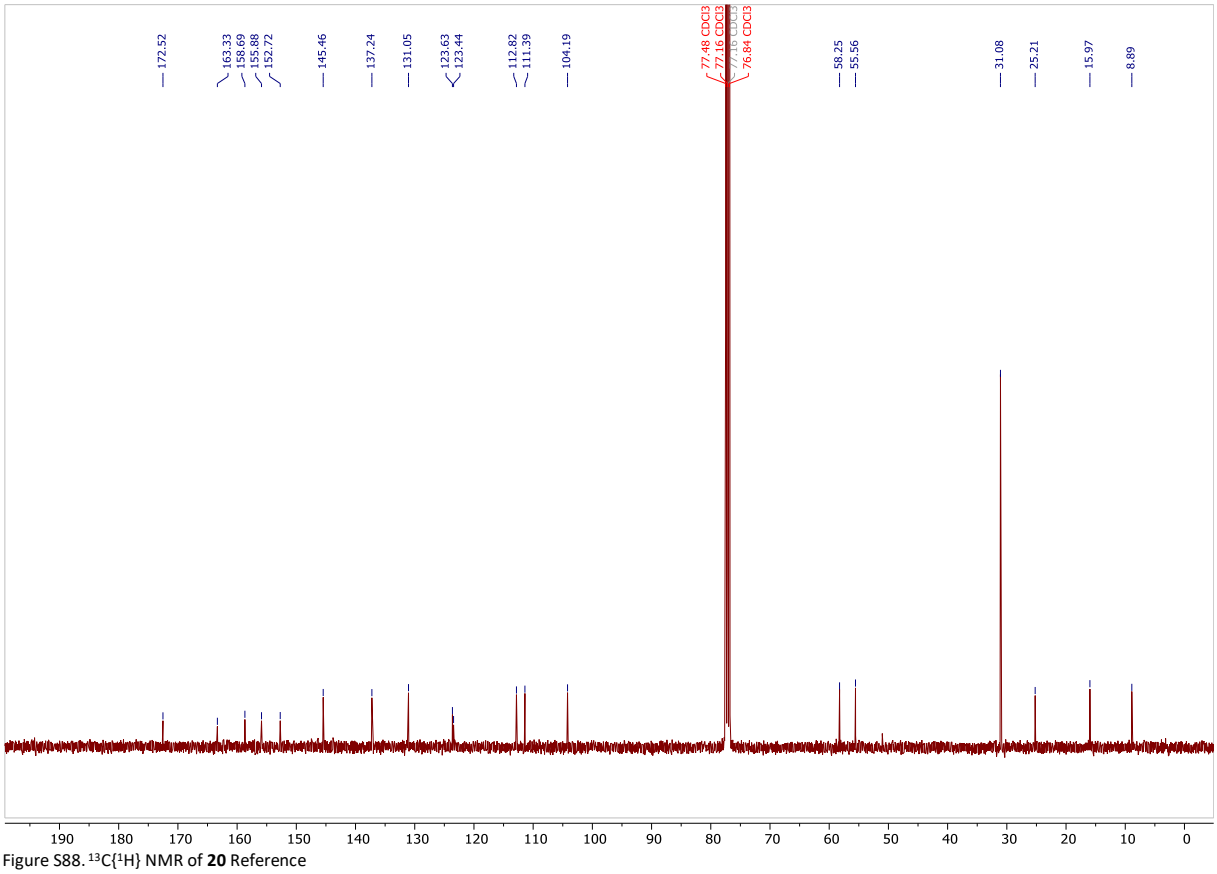


Figure S88. $^{13}C\{^{1}H\}$ NMR of **20** Reference

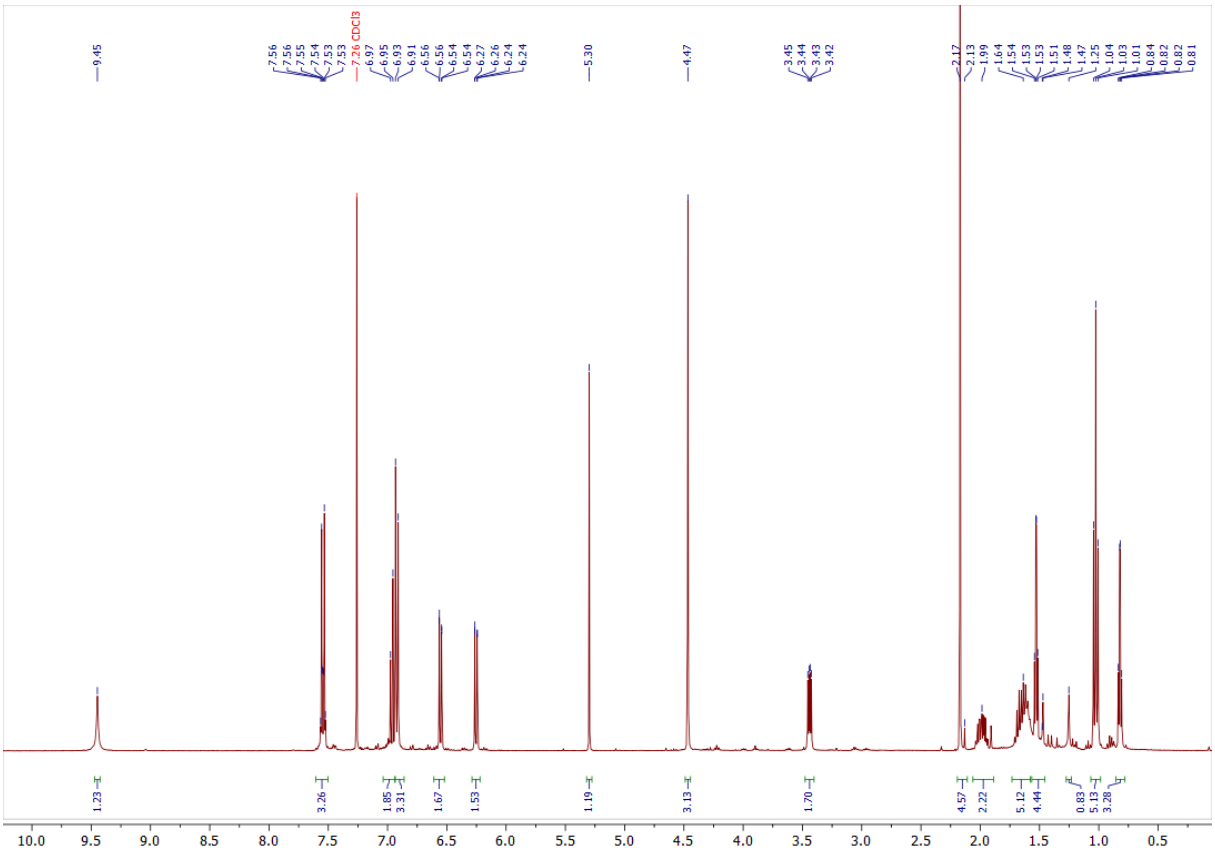


Figure S89 ^{1}H NMR of **19** Precursor

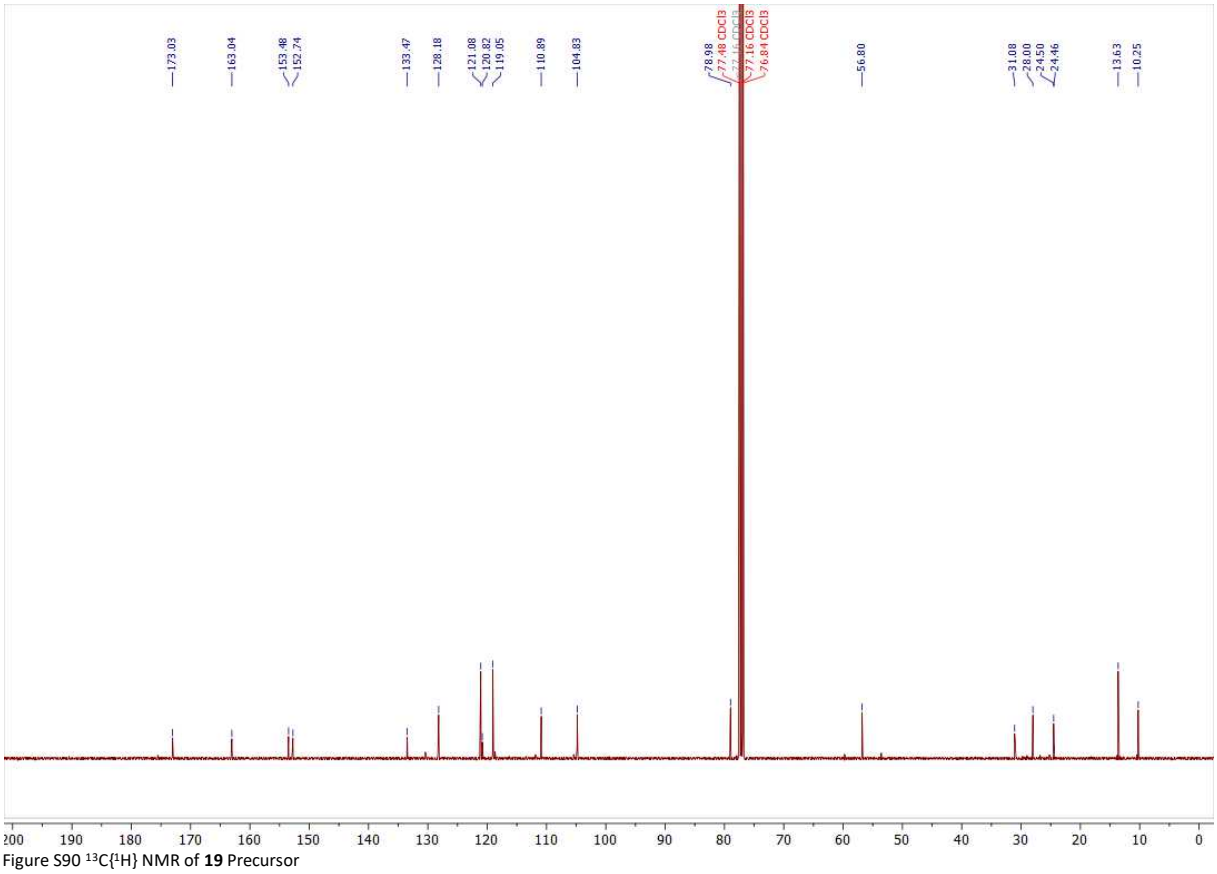


Figure S90 $^{13}C\{^{1}H\}$ NMR of **19** Precursor

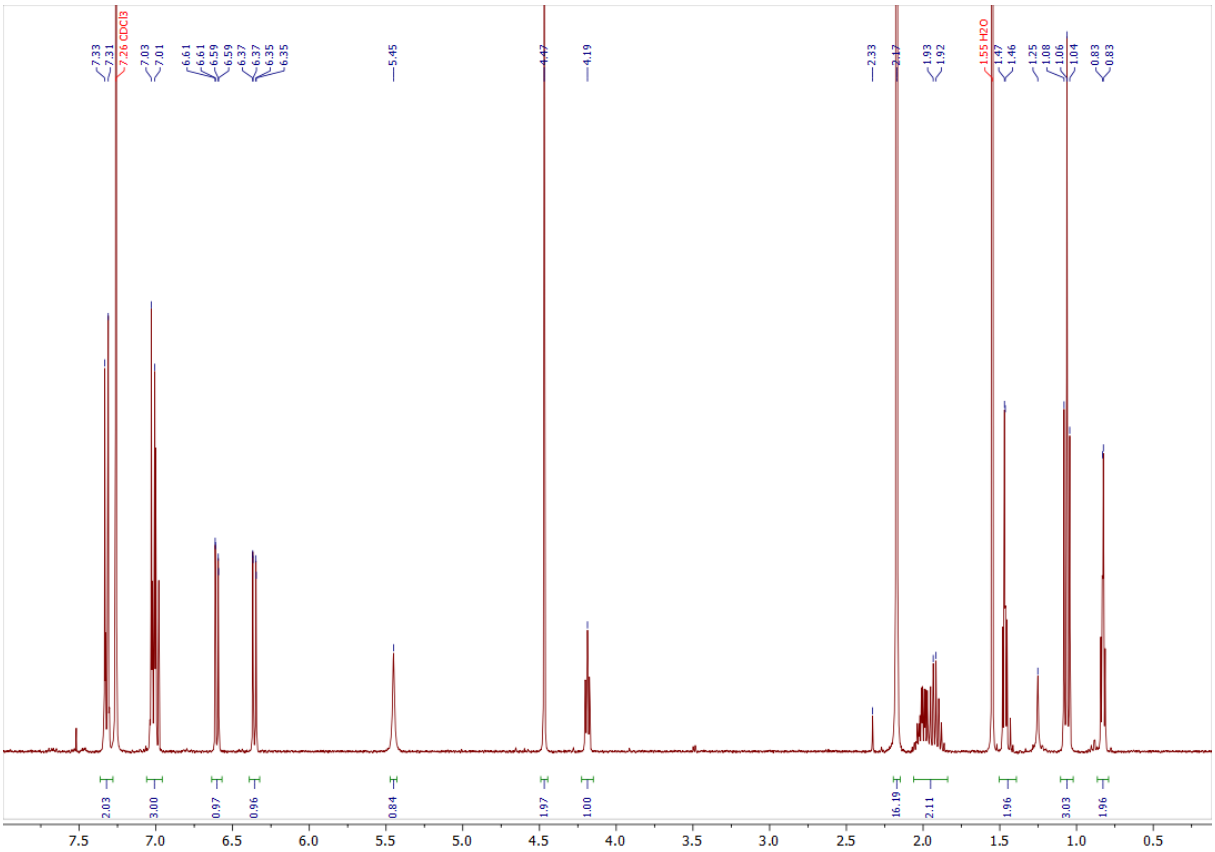


Figure S91 ^{1}H NMR of **19** Reference

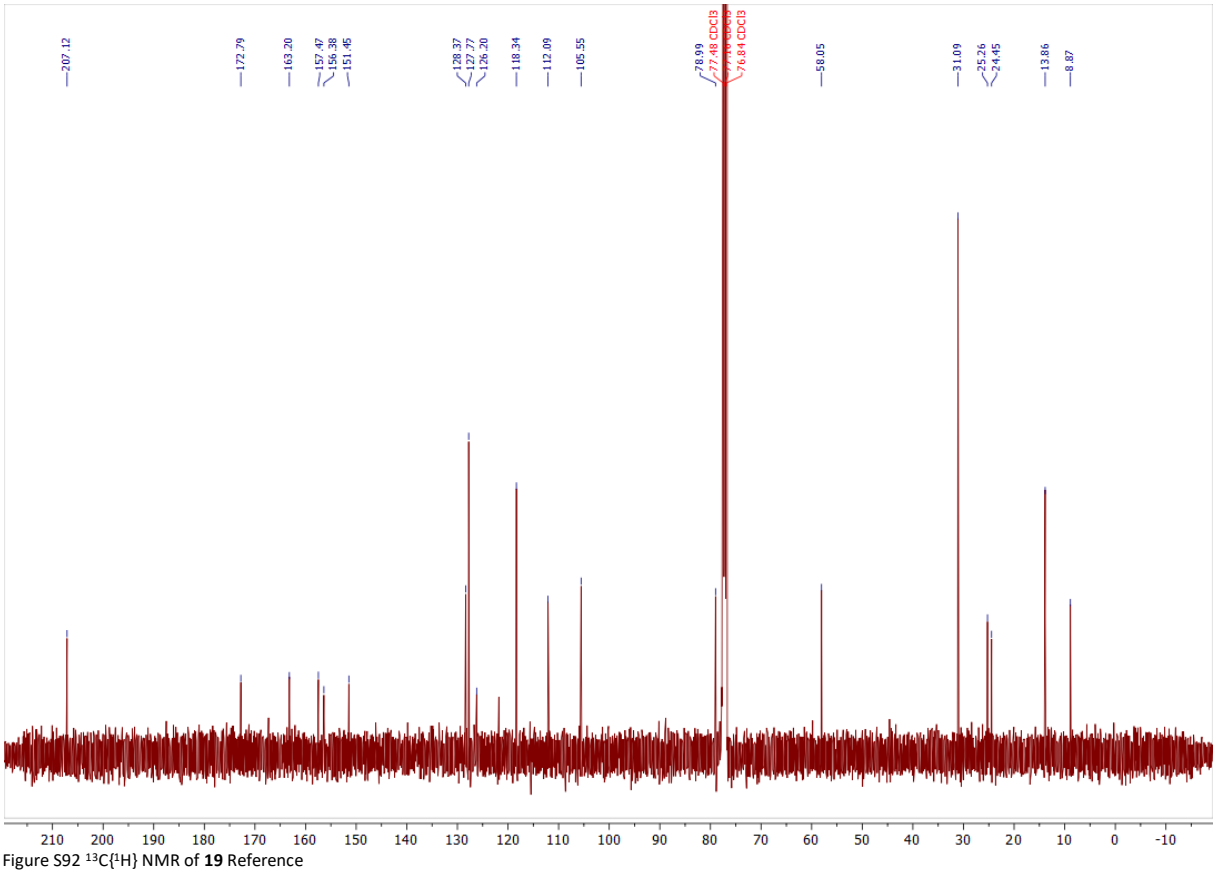


Figure S92 $^{13}C\{^{1}H\}$ NMR of **19** Reference

5.2. Isolated Substrates

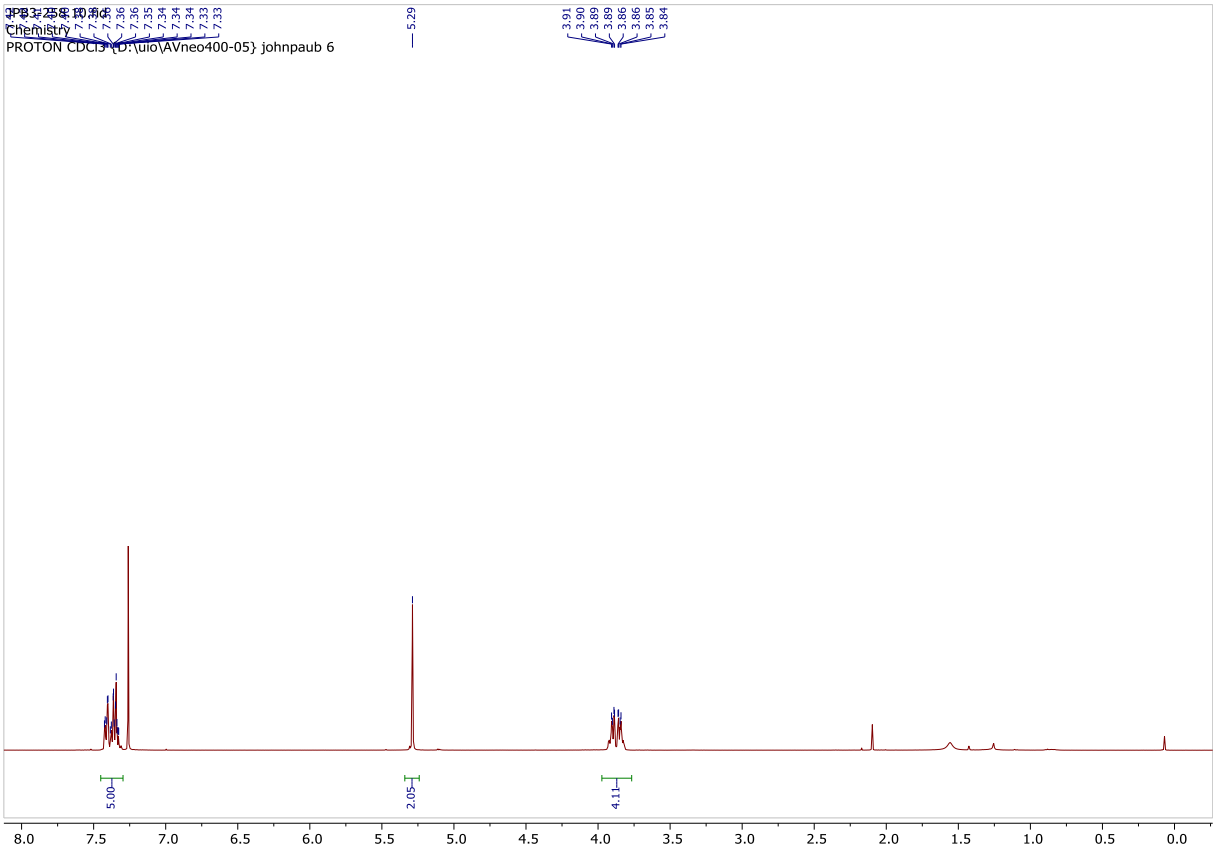


Figure S93. ^{1}H NMR of substrate **2**

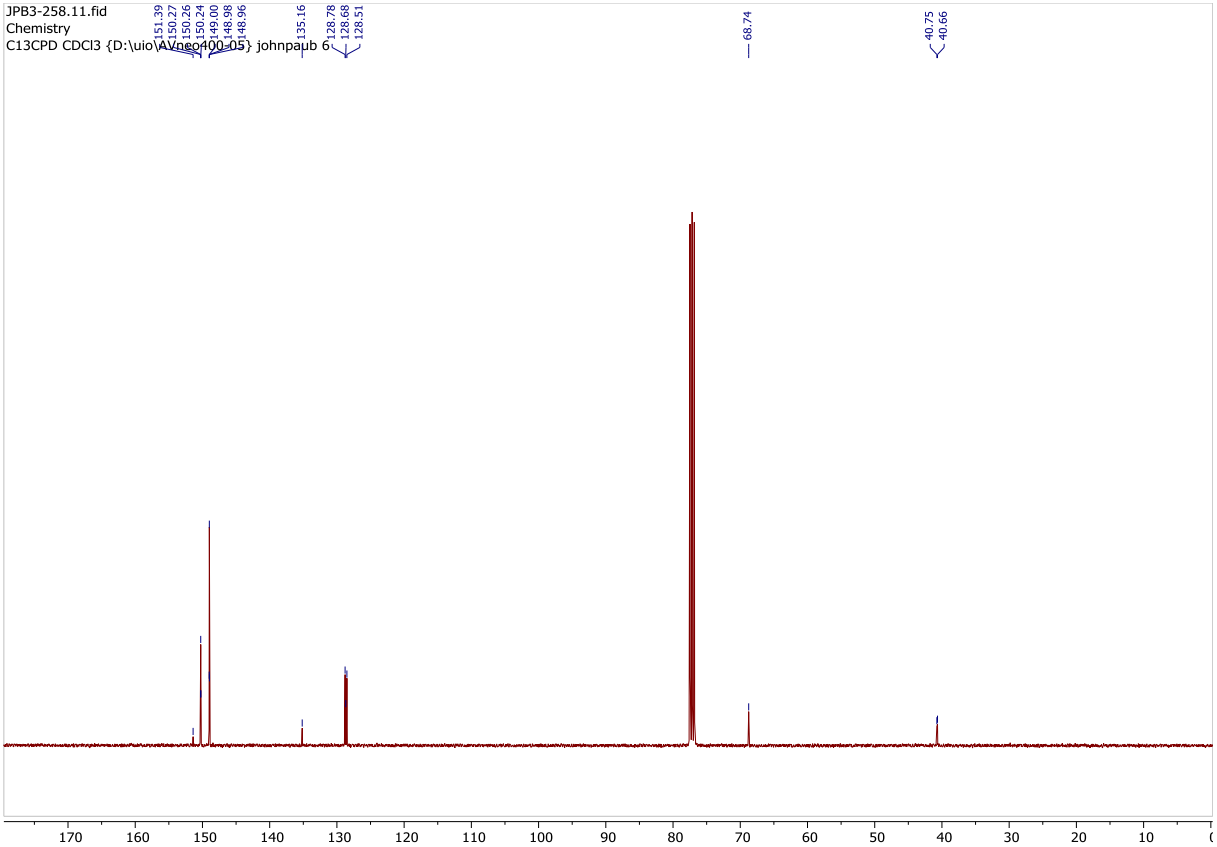


Figure S94. $^{13}C\{^{1}H\}$ NMR of substrate **2**

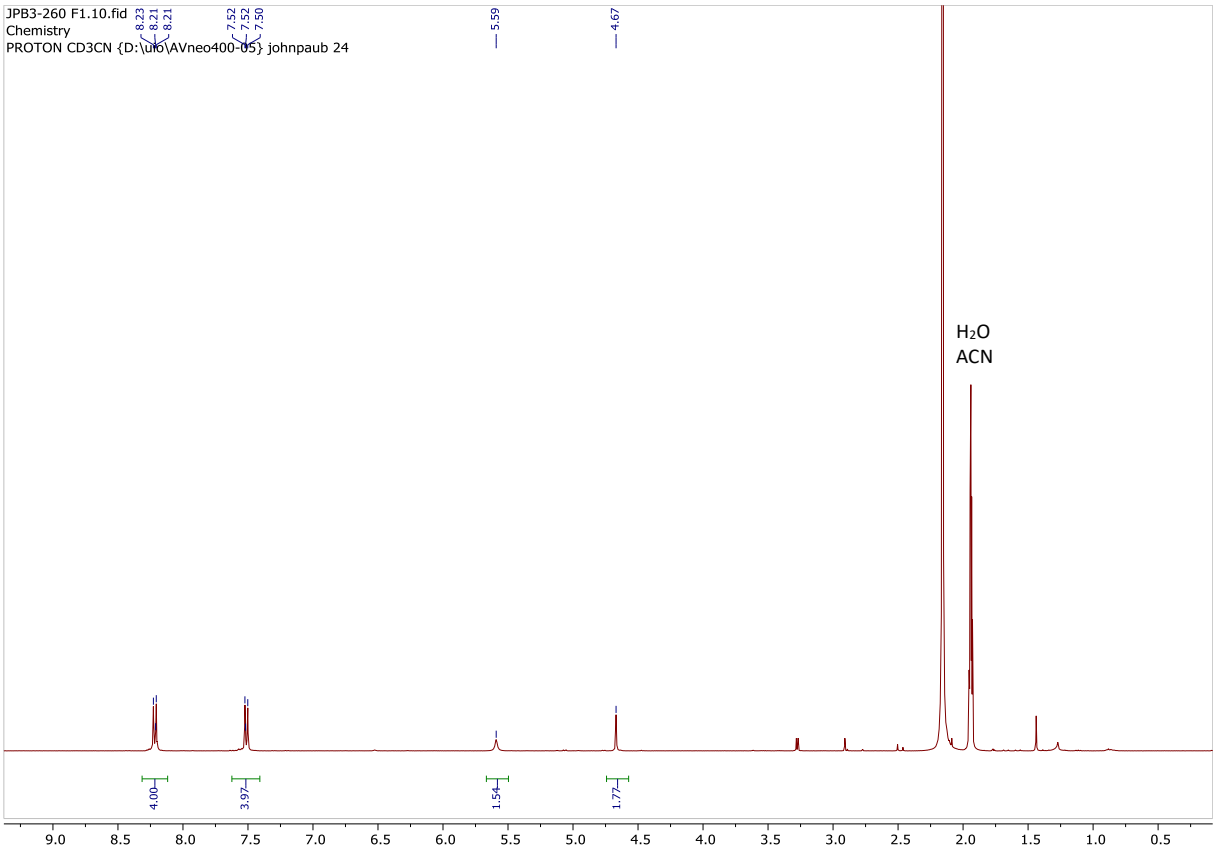


Figure S95 ^{1}H NMR of substrate **3**

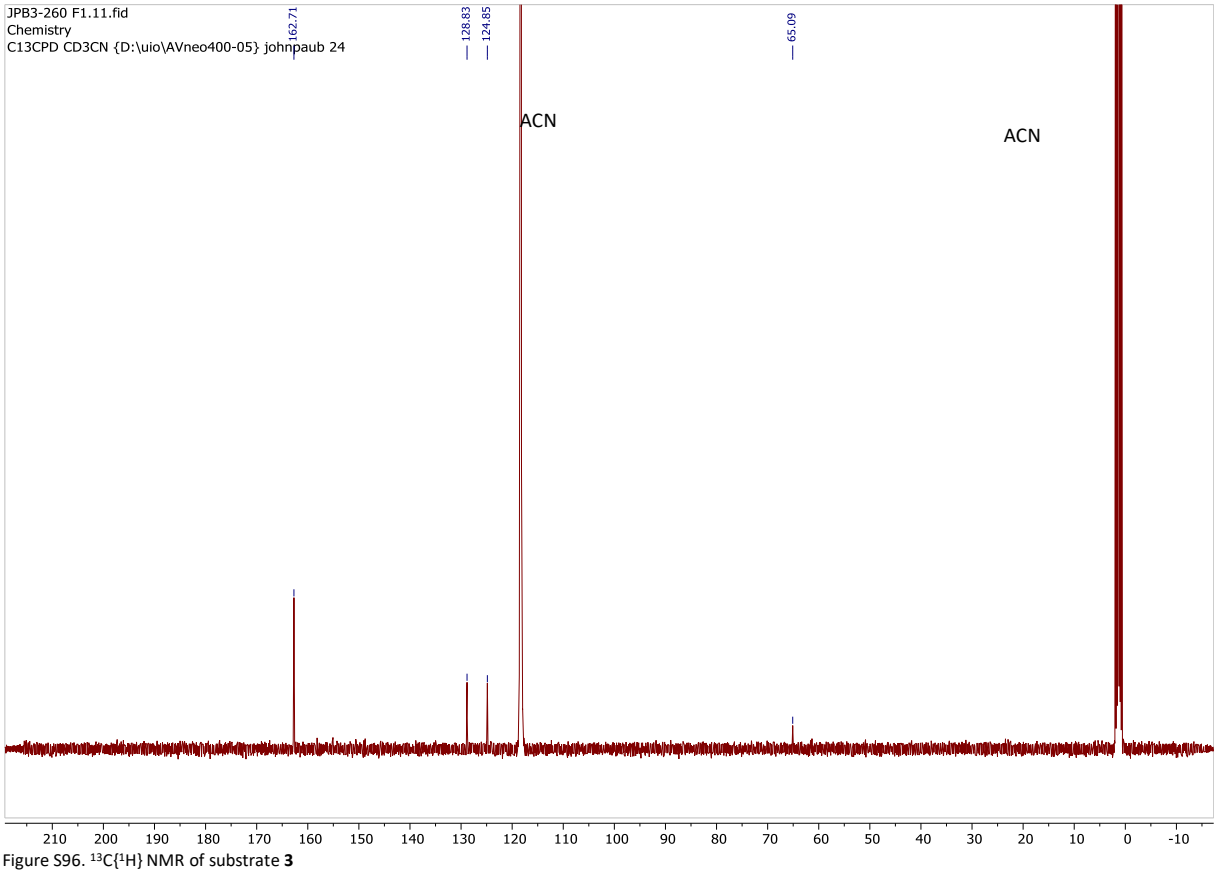


Figure S96. ^{13}C{^{1}H} NMR of substrate **3**

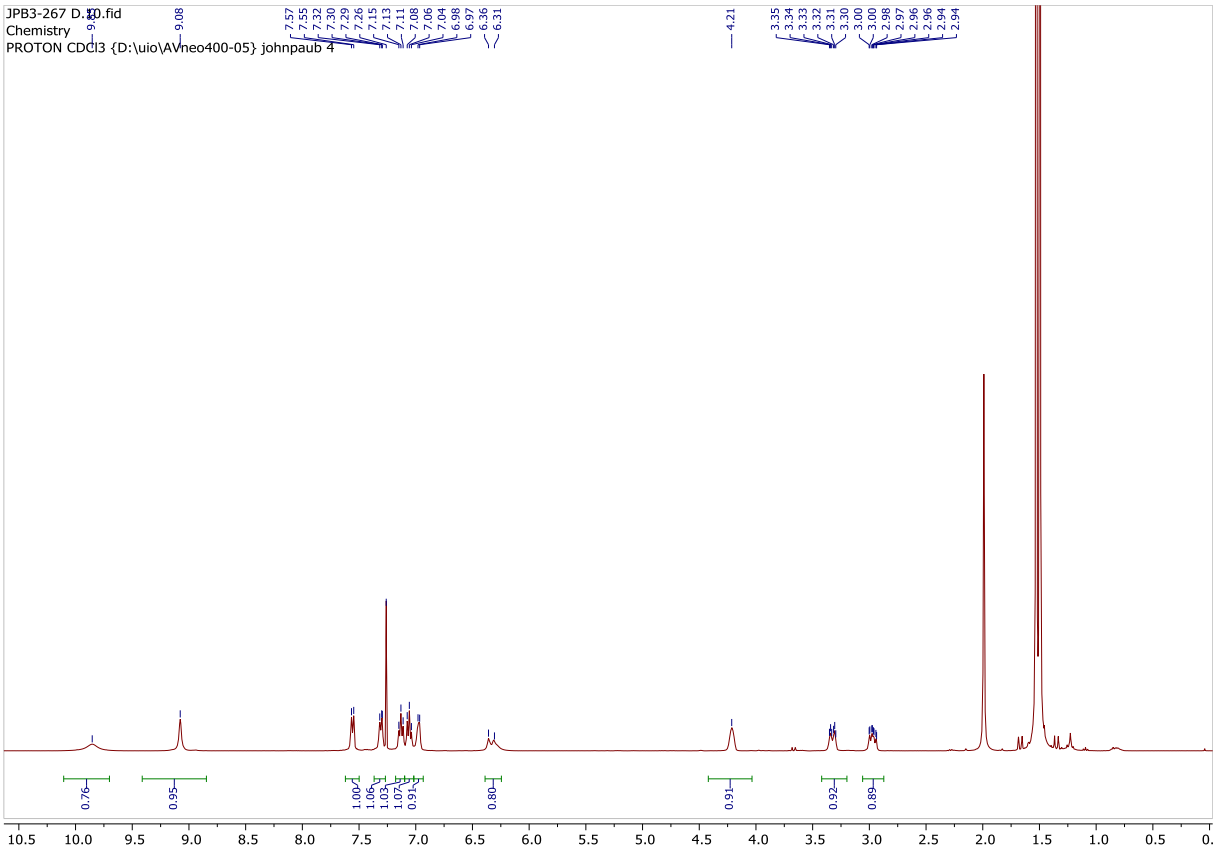


Figure S97. ^{1}H NMR of substrate **7**

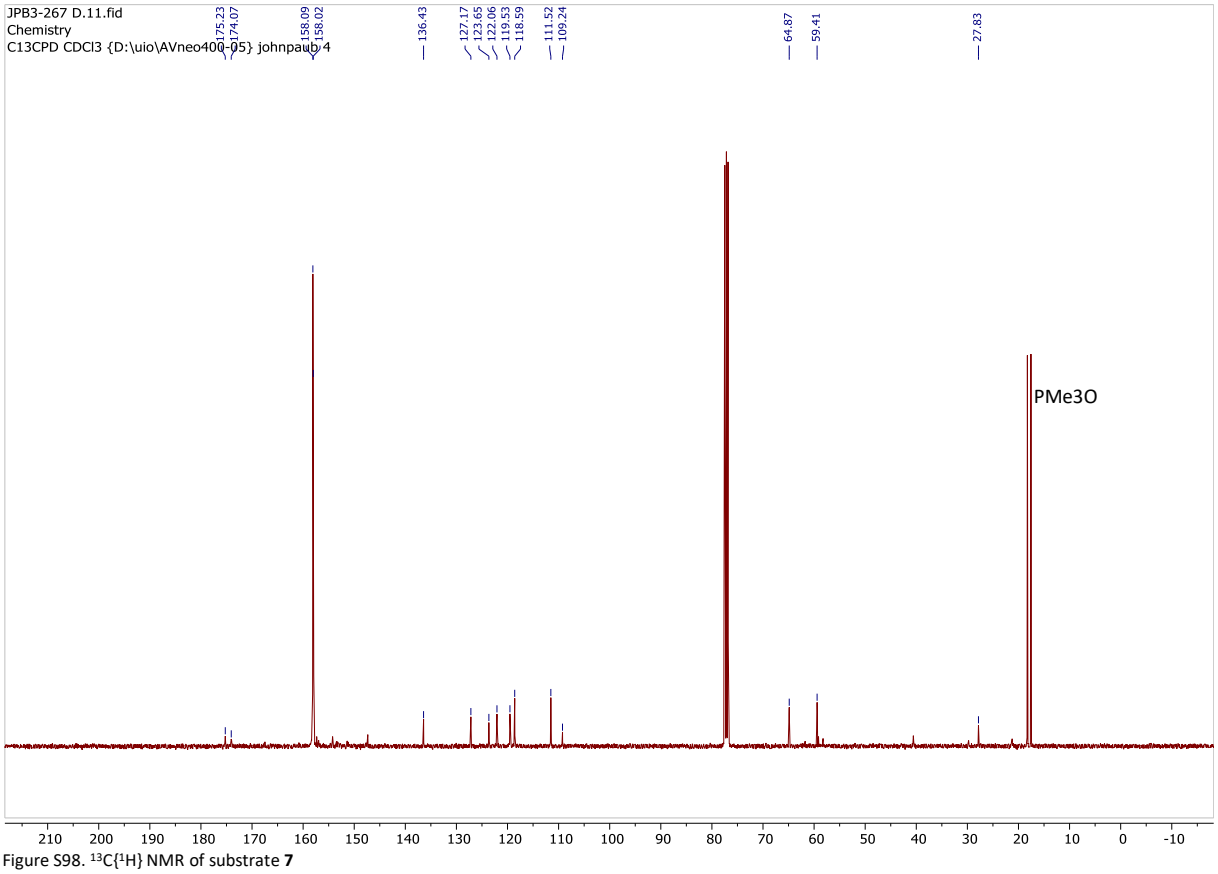


Figure S98. $^{13}C\{^{1}H\}$ NMR of substrate **7**

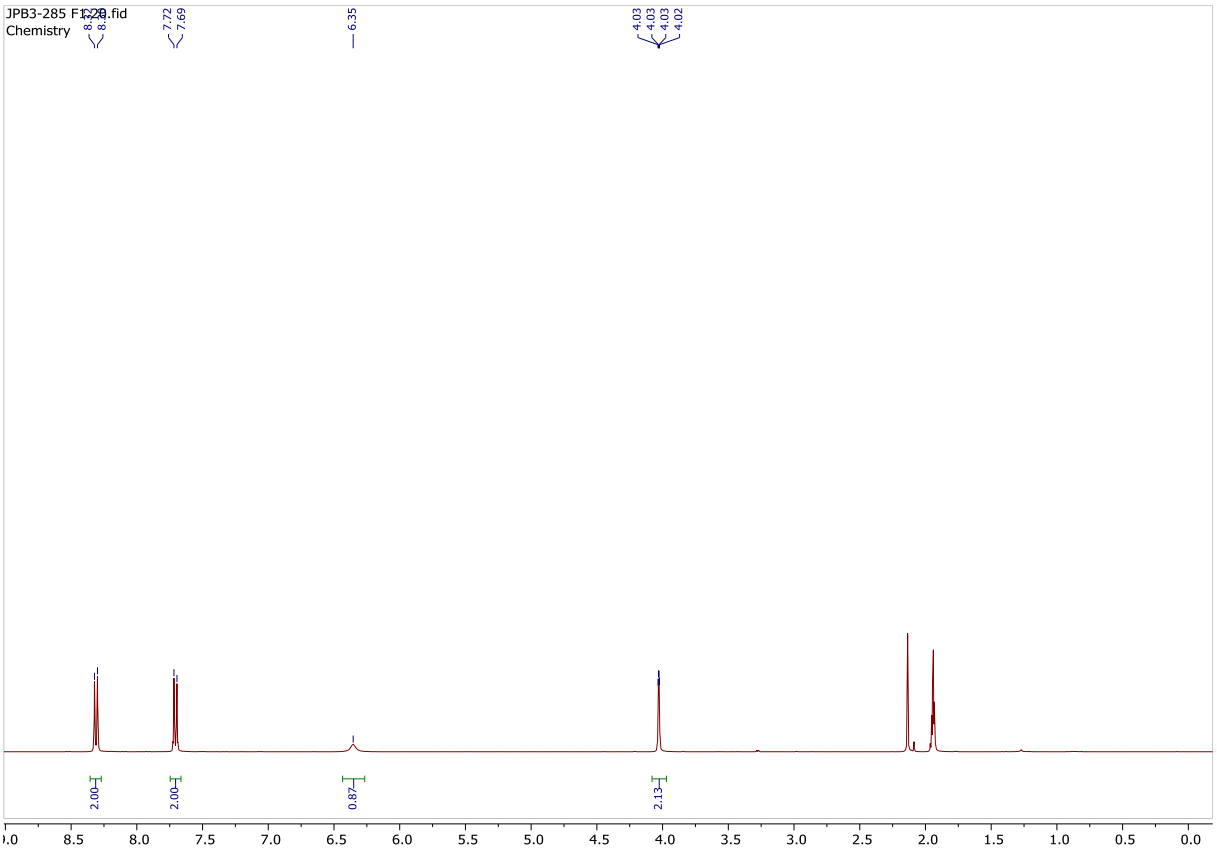


Figure S99 ^{1}H NMR of substrate **8**

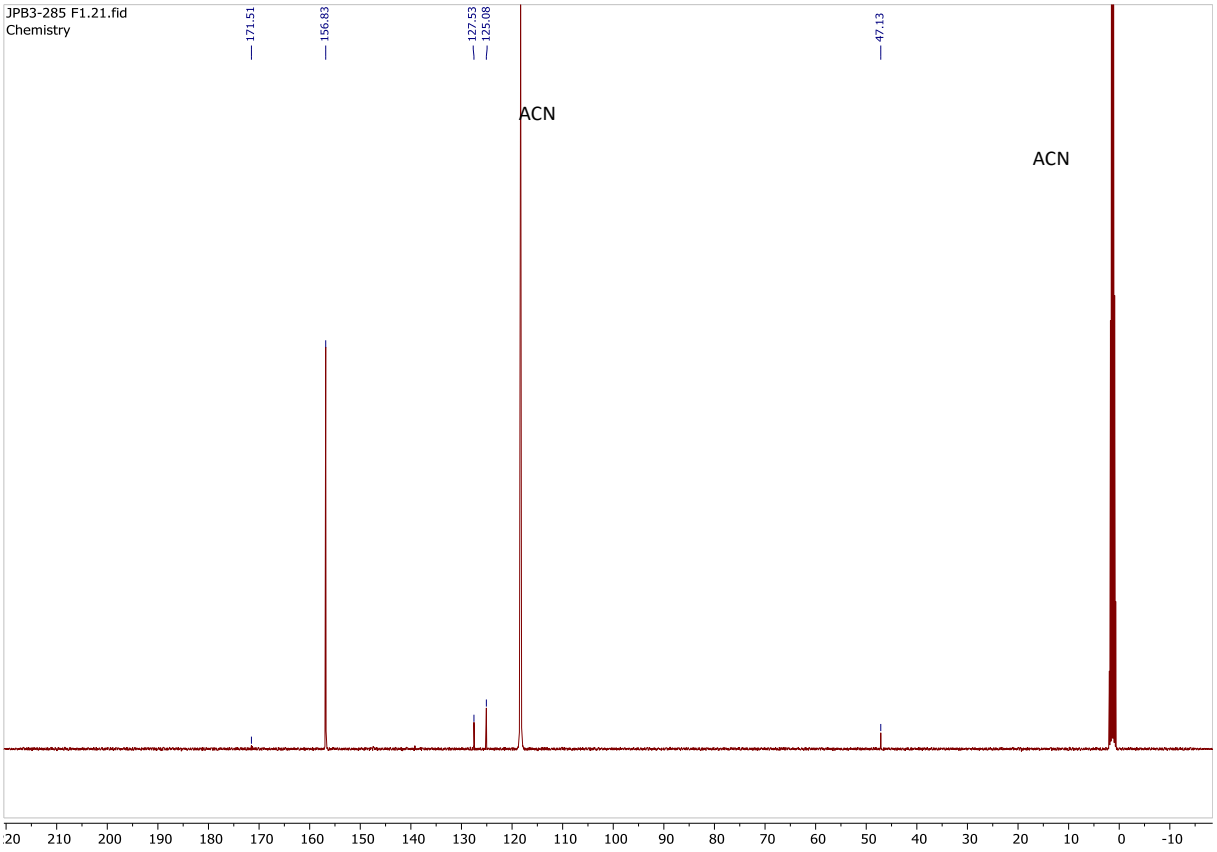


Figure S100. ^{13}C{^{1}H} NMR of substrate **8**

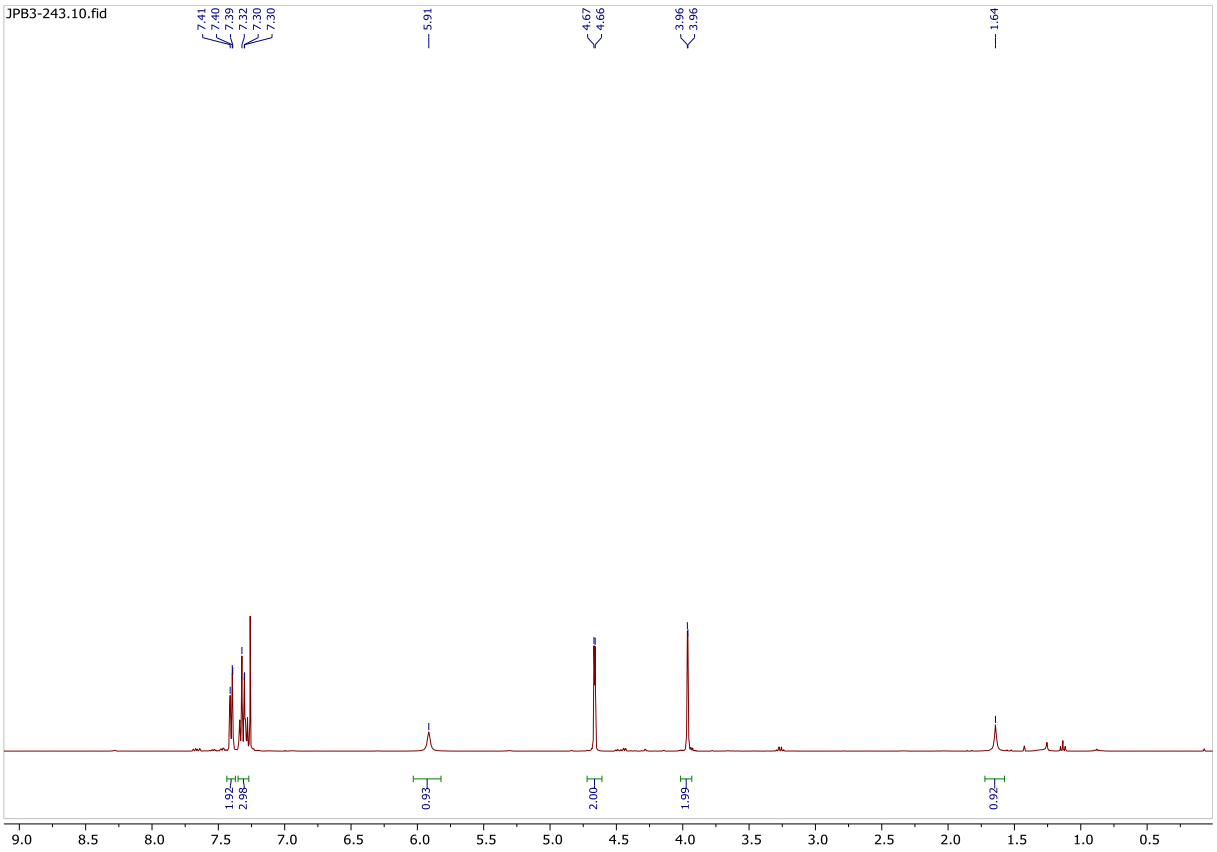


Figure S101. ^{1}H NMR of 3-benzylimidazolidine-2,4-dione [**9**]

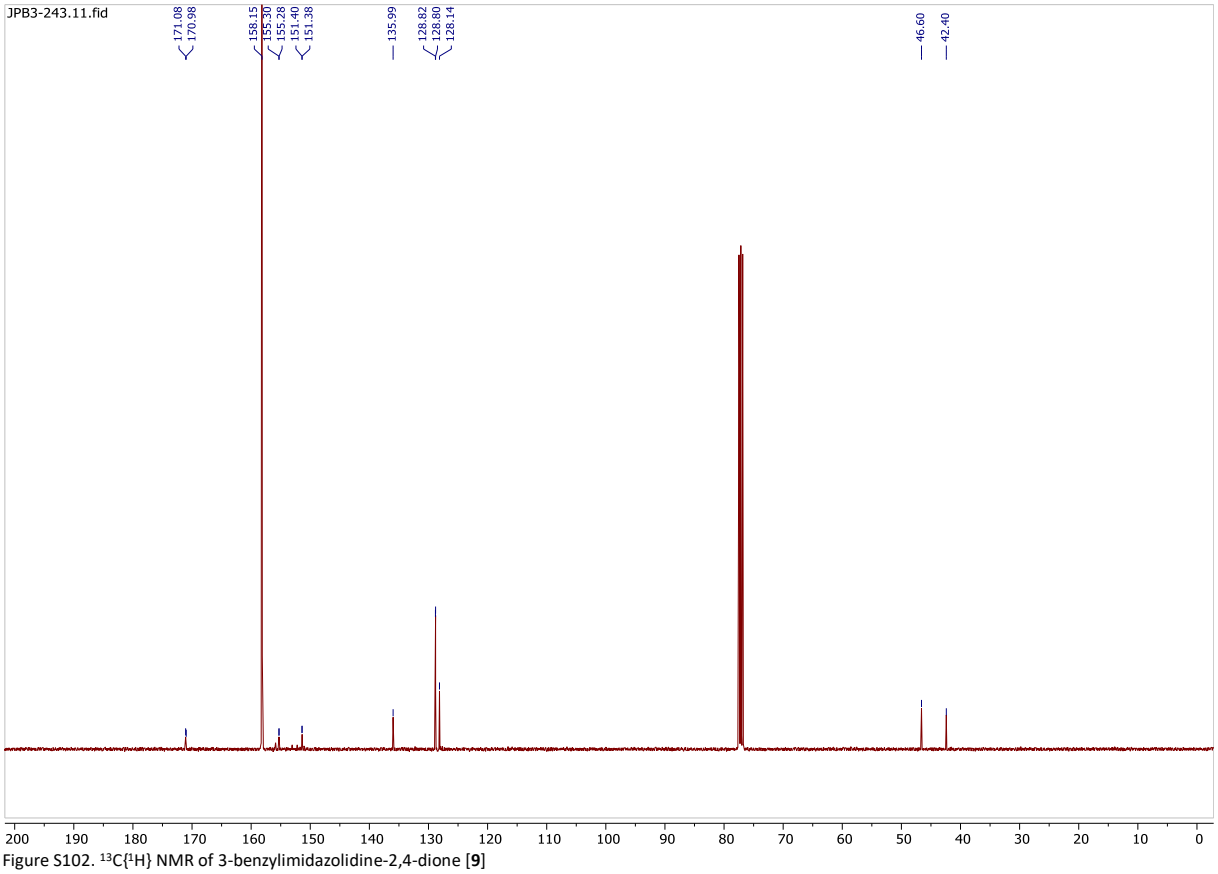


Figure S102. $^{13}C\{^{1}H\}$ NMR of 3-benzylimidazolidine-2,4-dione [**9**]

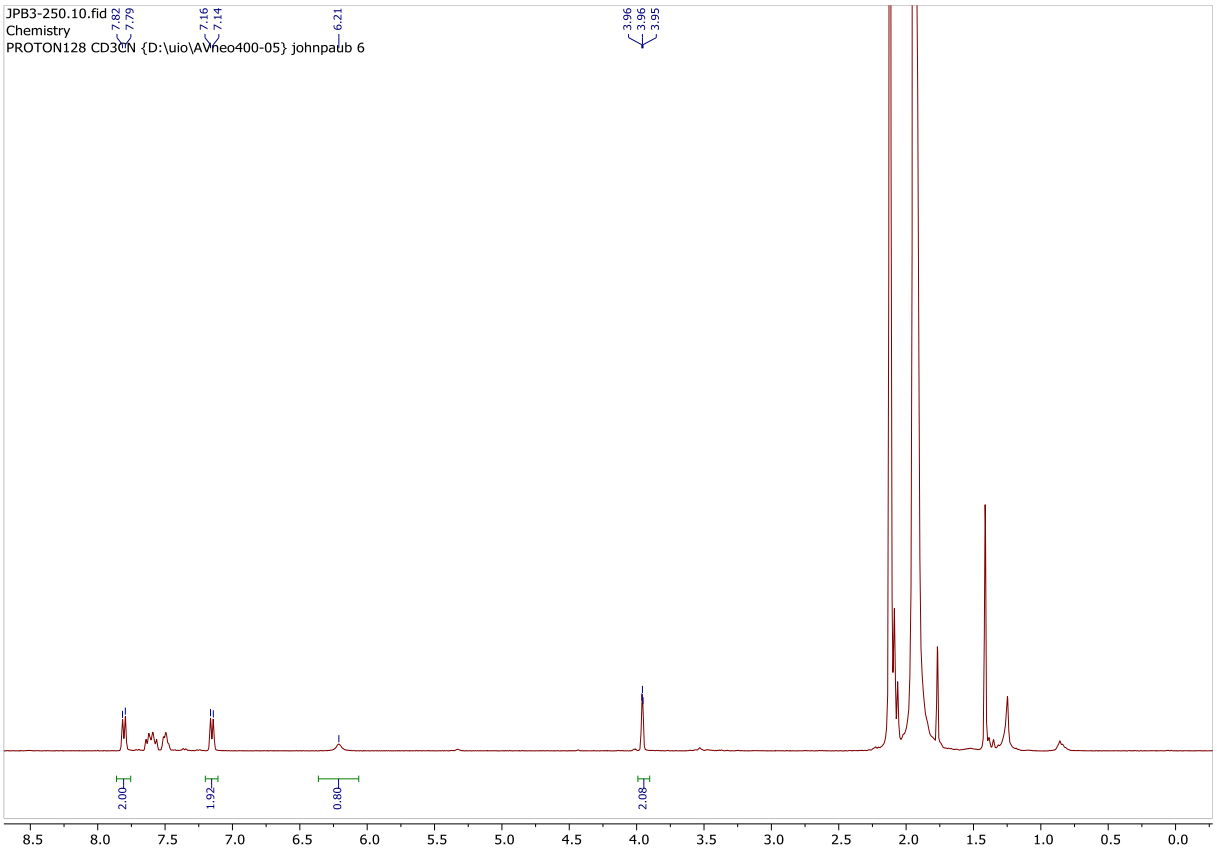


Figure S103. ^{1}H NMR of substrate [**10**]

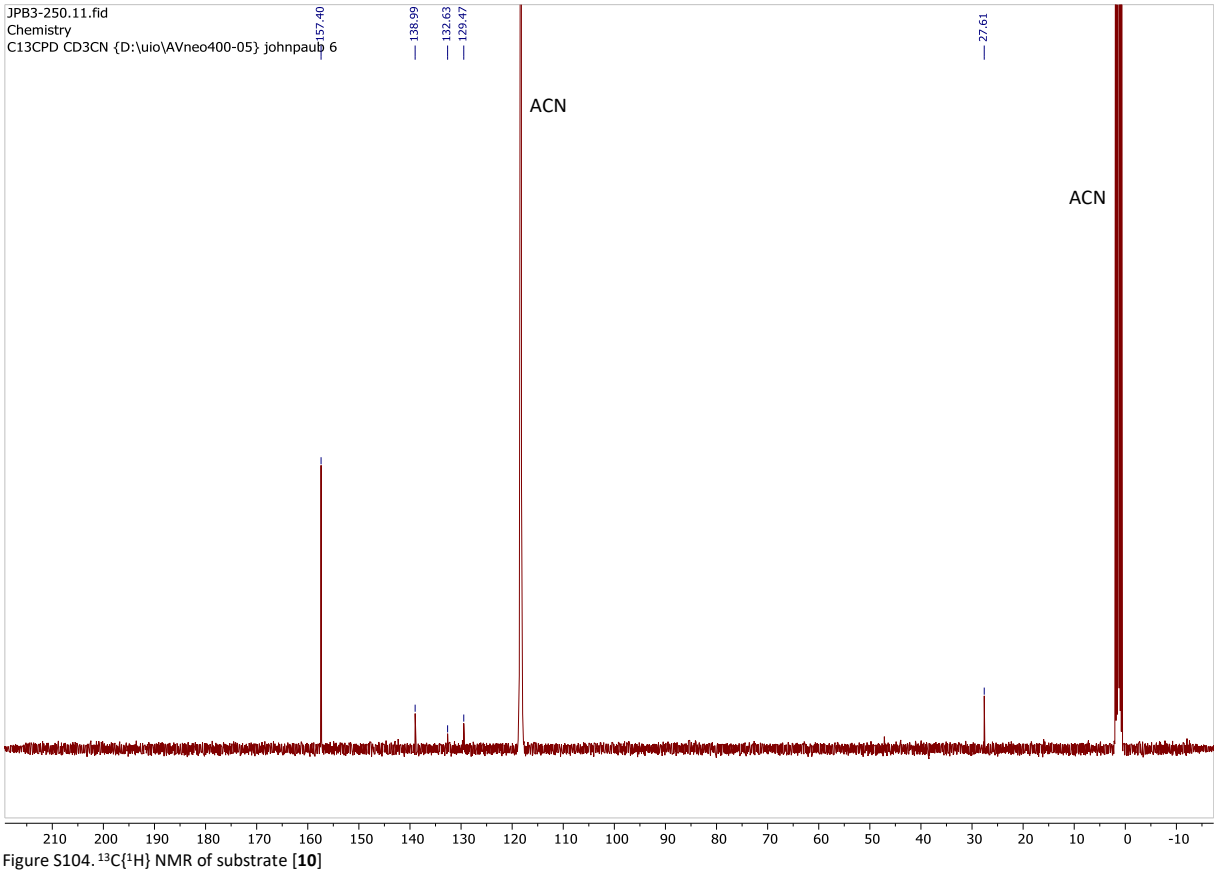


Figure S104. $^{13}C\{^{1}H\}$ NMR of substrate [**10**]

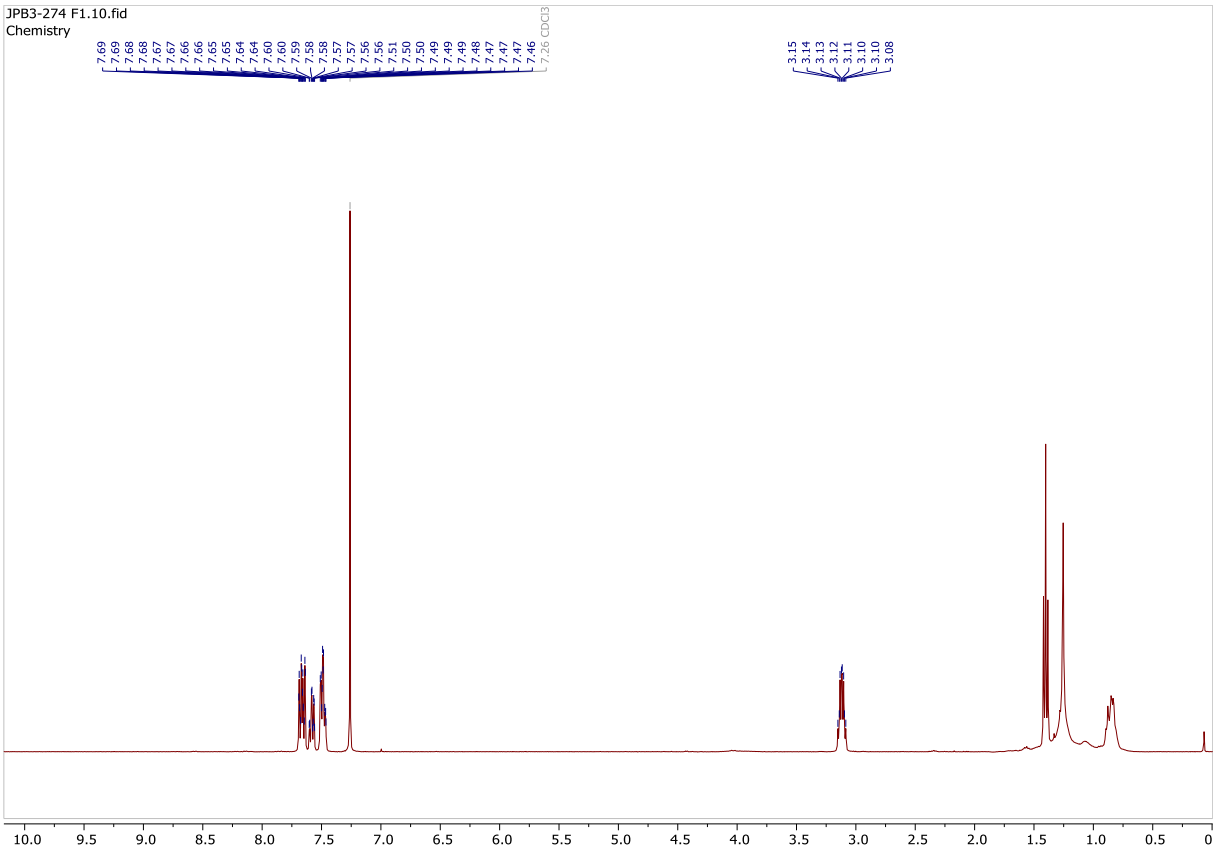


Figure S105. ^{1}H NMR of substrate **11**

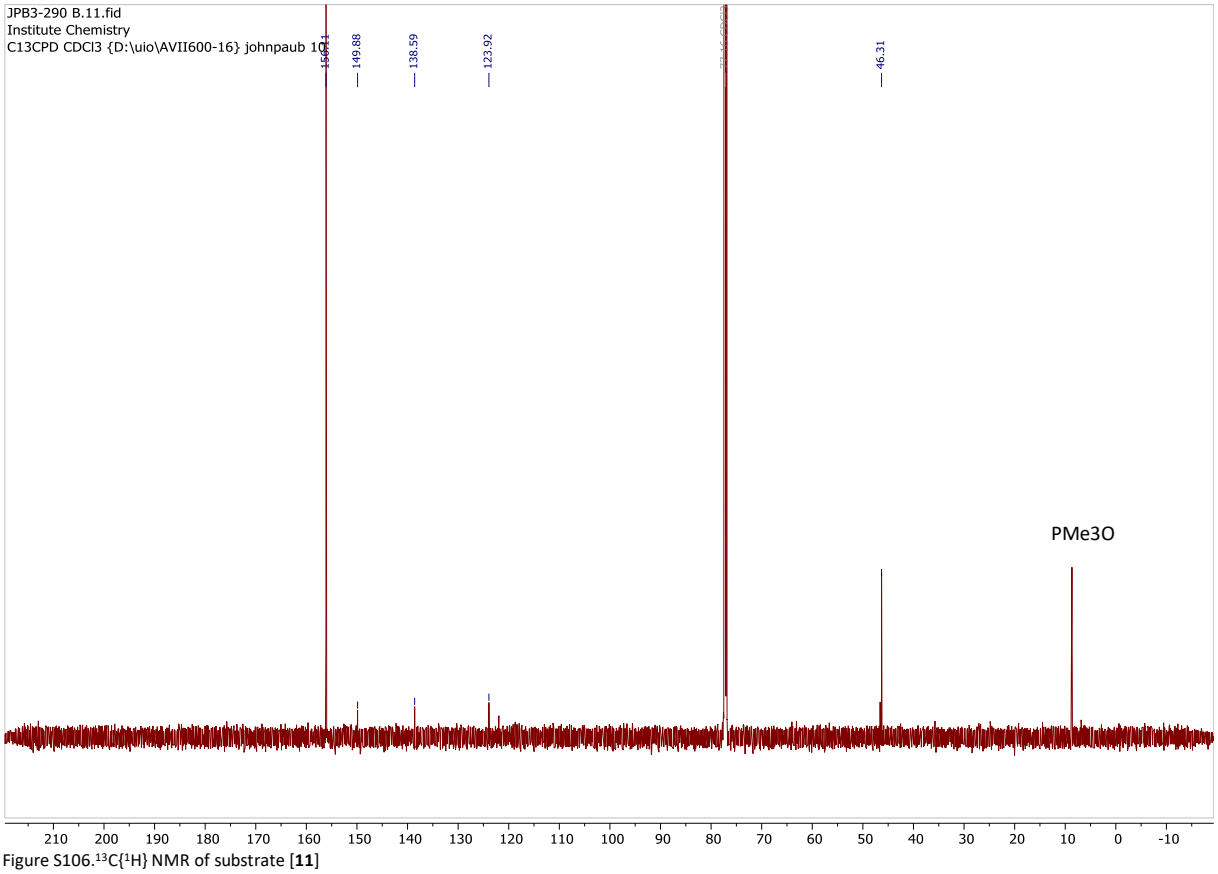


Figure S106.$^{13}C\{^{1}H\}$ NMR of substrate [**11**]

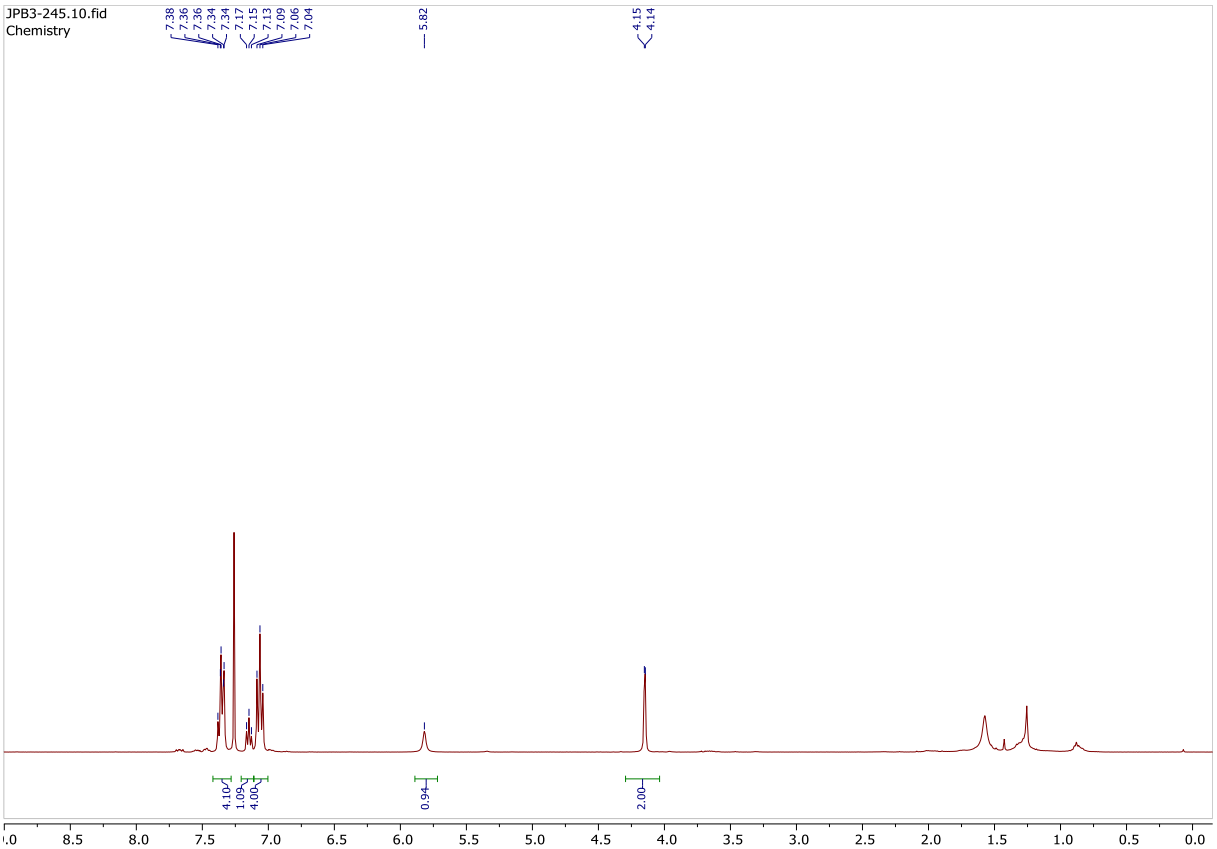


Figure S107. ^{1}H NMR of 3-(4-phenoxyphenyl)imidazolidine-2,4-dione [**12**]

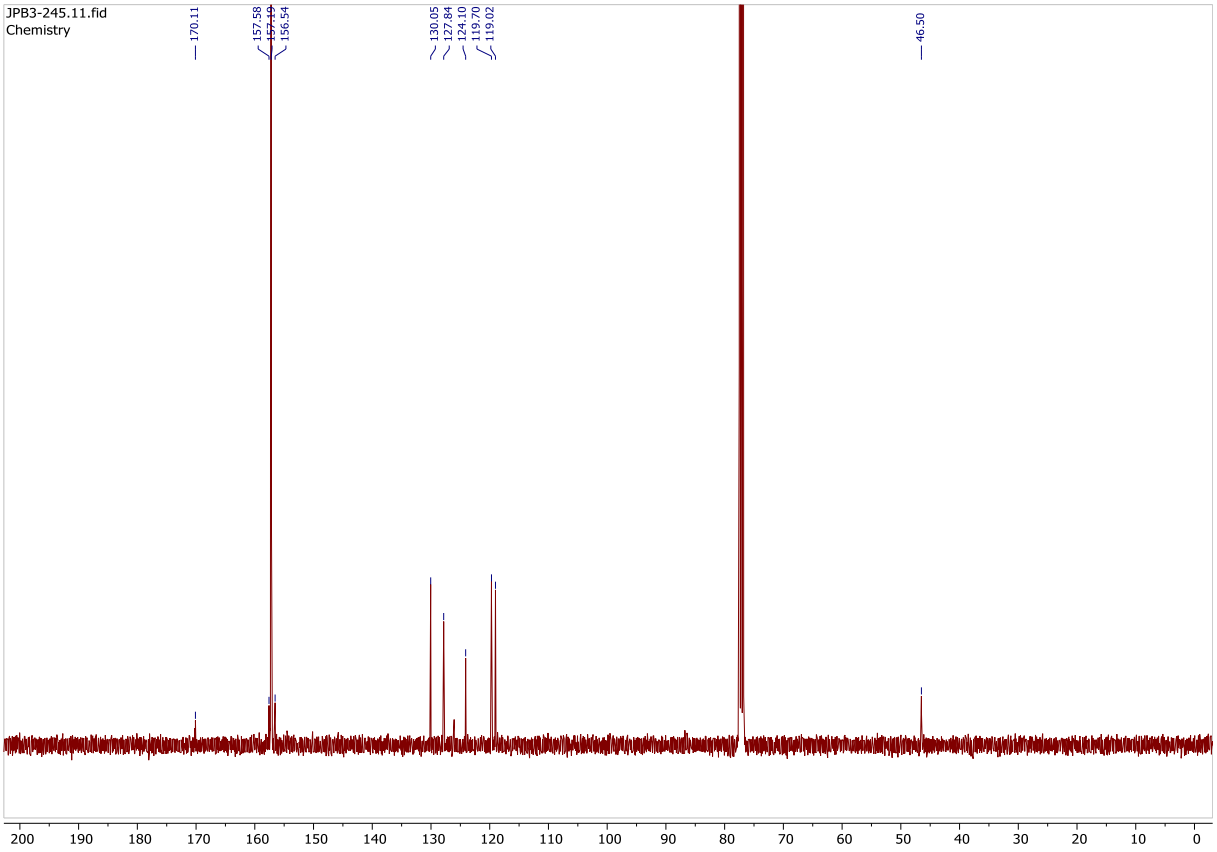


Figure S108. ^{13}C{^{1}H} NMR of 3-(4-phenoxyphenyl)imidazolidine-2,4-dione [**12**]

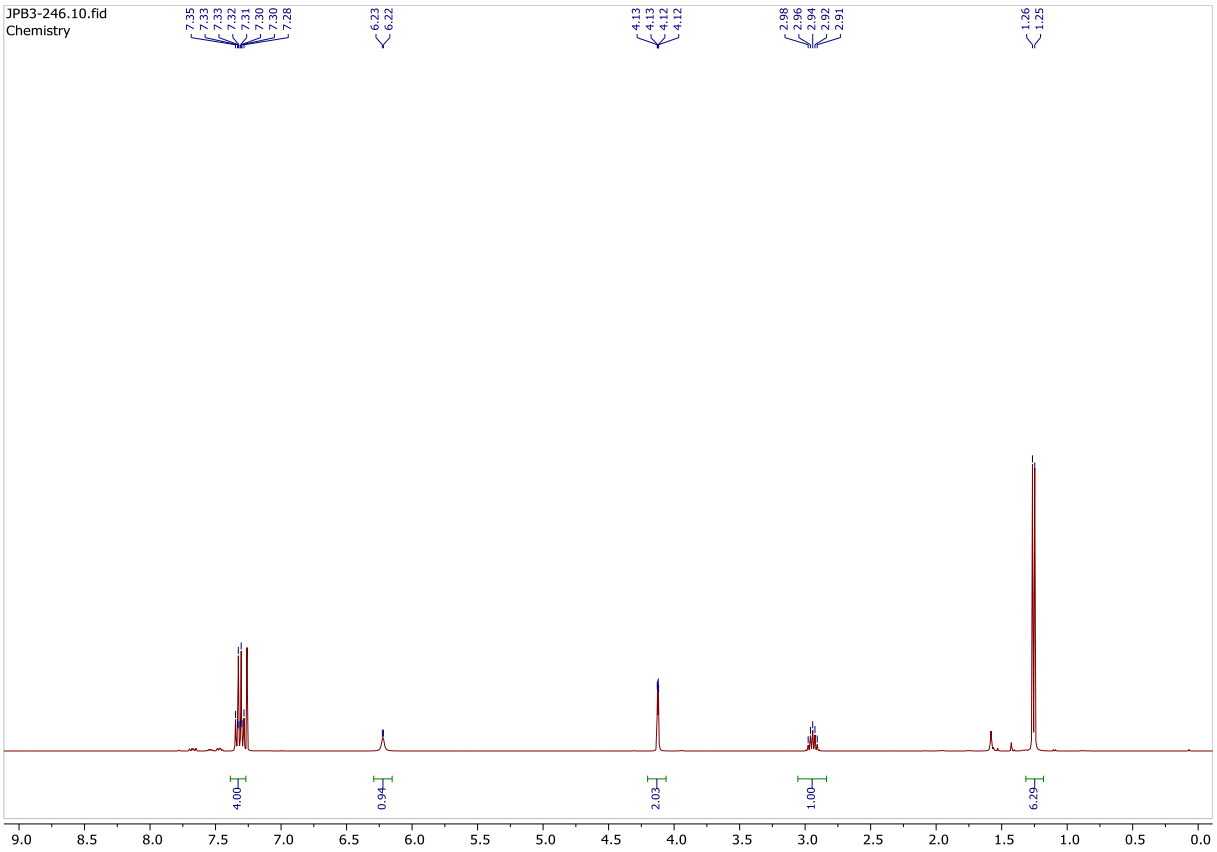


Figure S109. ^{1}H NMR of 3-(4-isopropylphenyl)imidazolidine-2,4-dione [**13**]

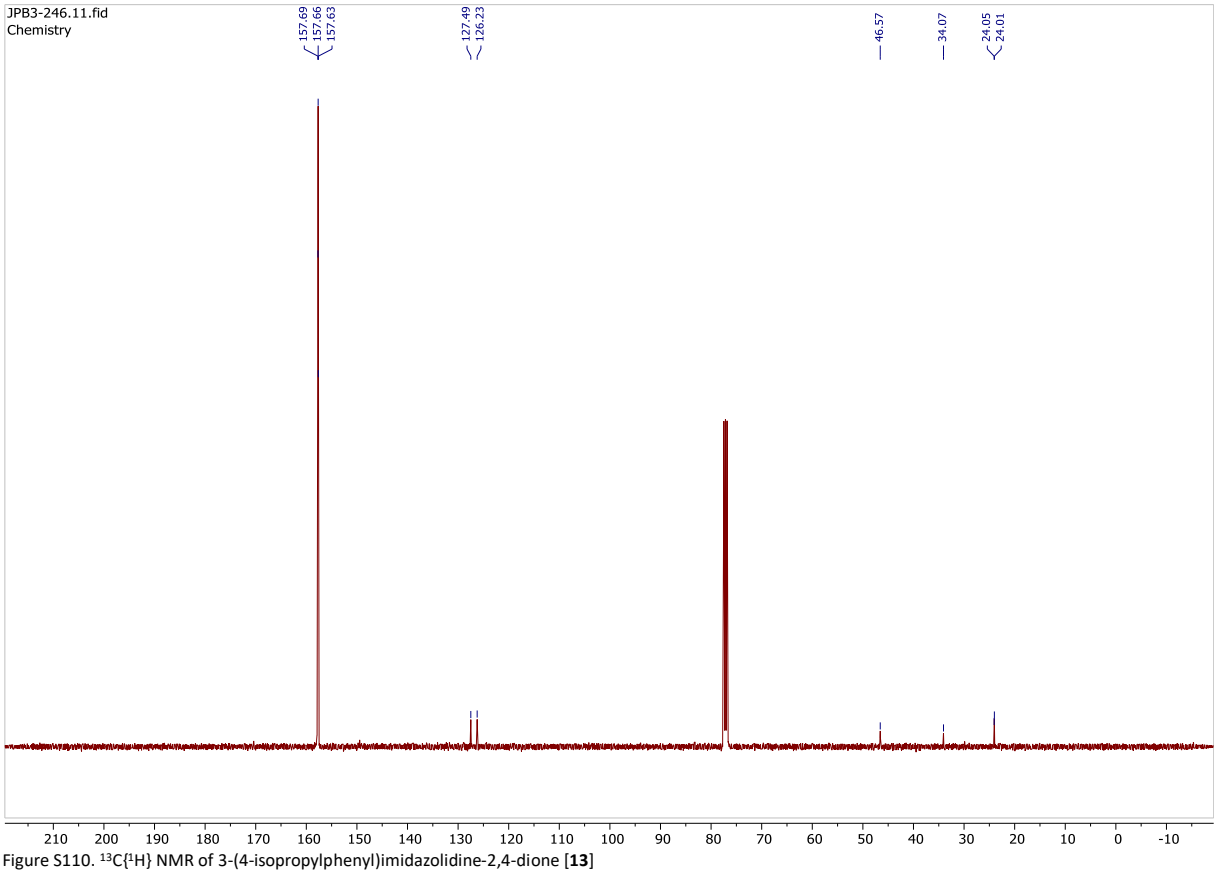


Figure S110. $^{13}C\{^{1}H\}$ NMR of 3-(4-isopropylphenyl)imidazolidine-2,4-dione [**13**]

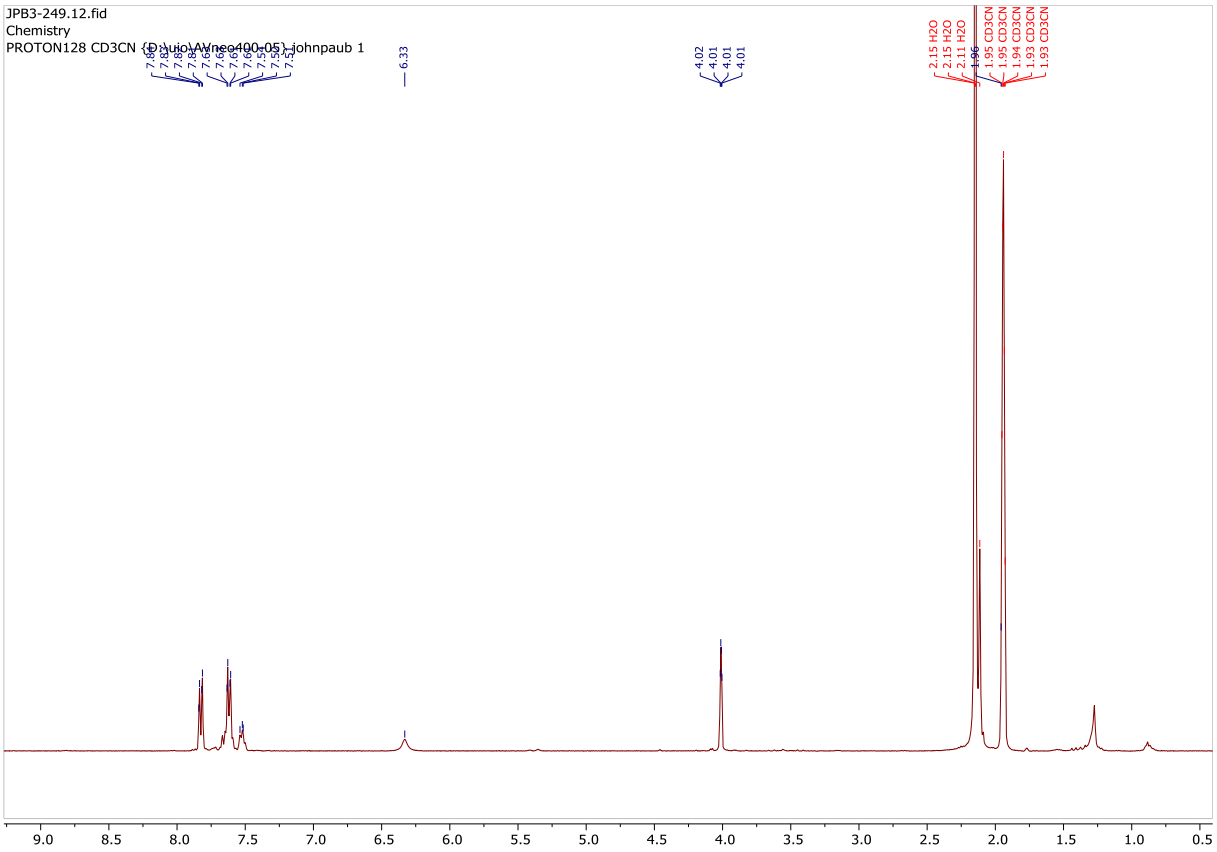


Figure S111. ^{1}H NMR of substrate [**14**]

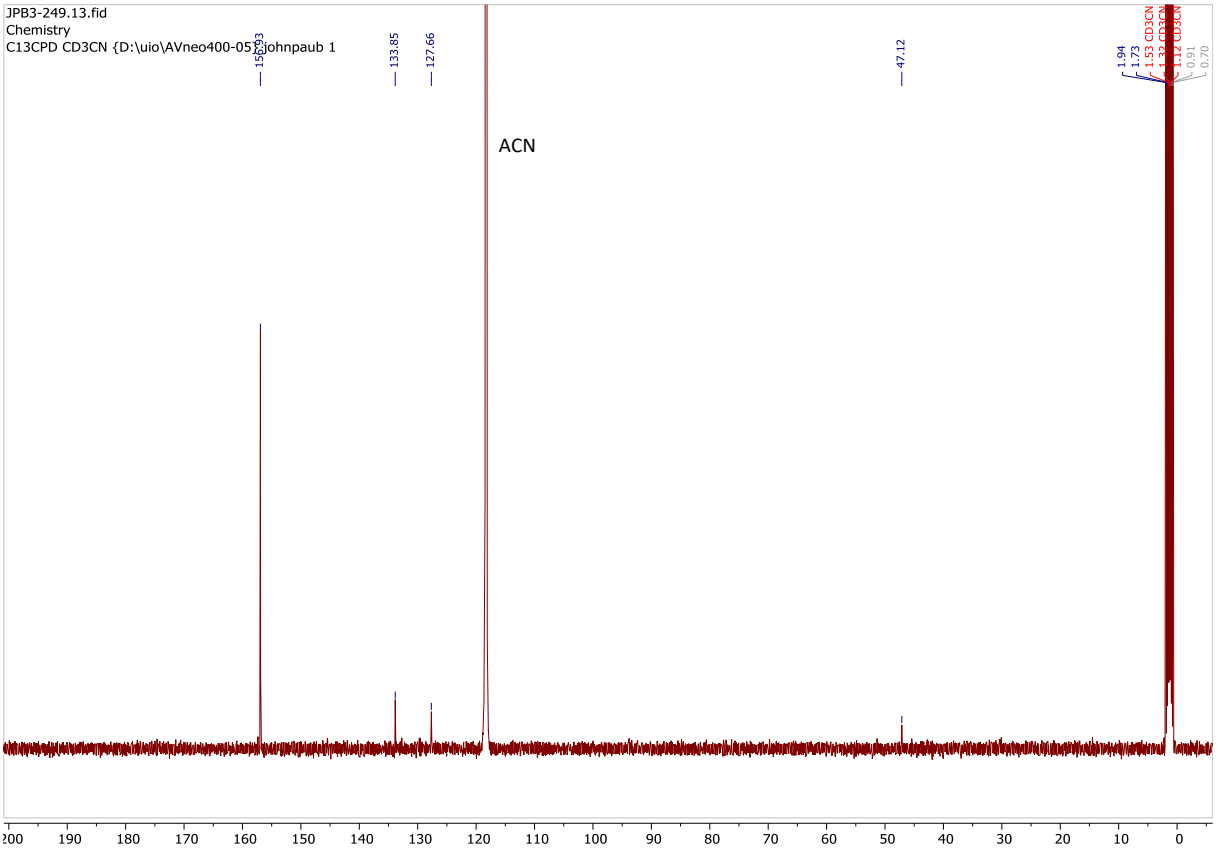


Figure S112. $^{13}C\{^{1}H\}$ NMR of substrate [**14**]

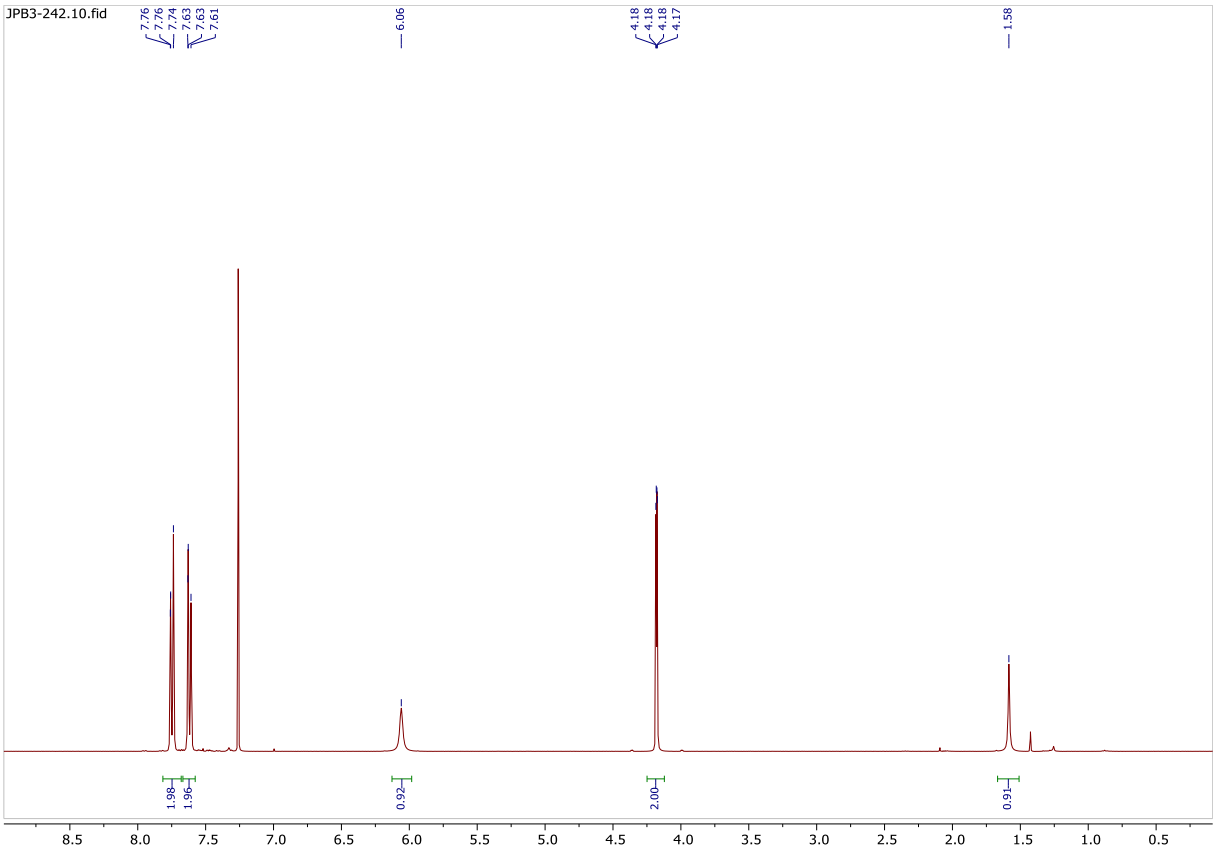


Figure S113. ^{1}H NMR of 3-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione [**15**]

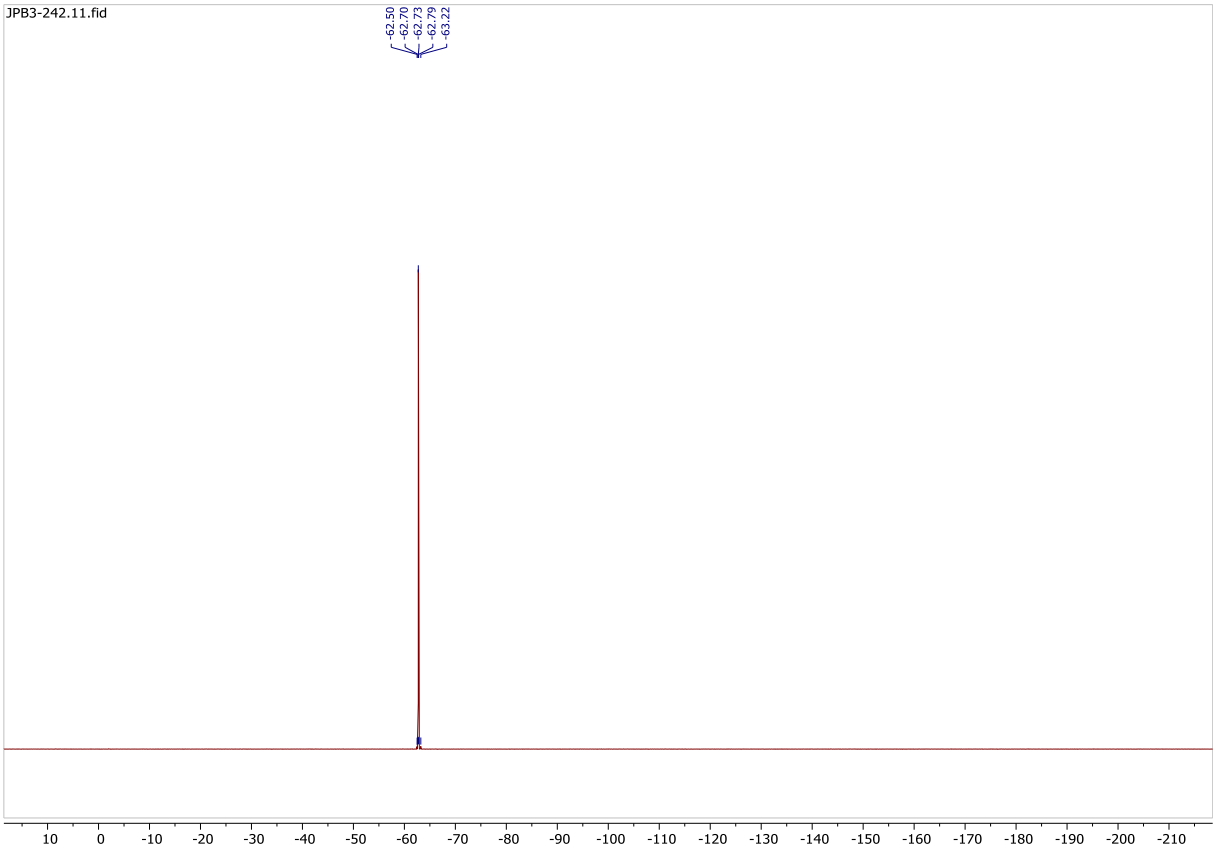


Figure S114. ^{19}F NMR of 3-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione [**15**]

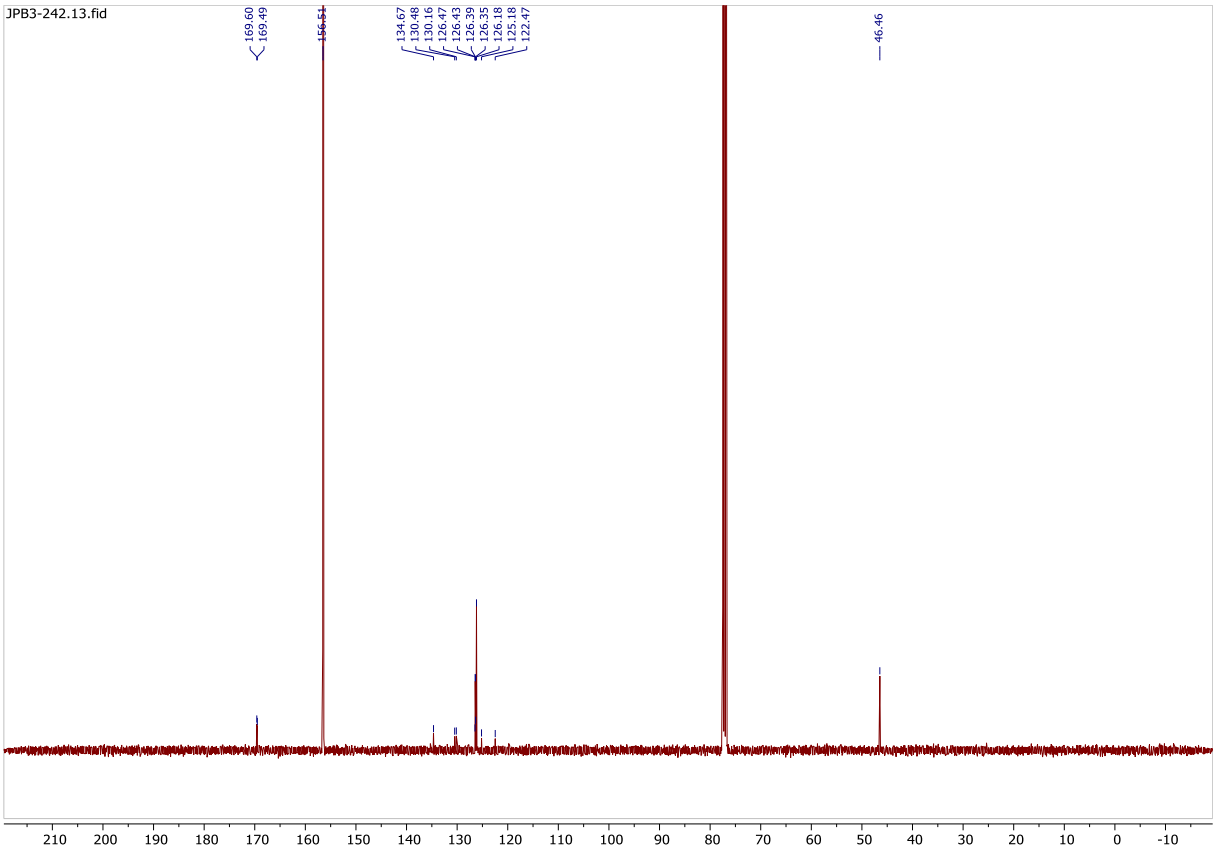


Figure S115. $^{13}C\{^{1}H\}$ NMR of 3-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione [**15**]

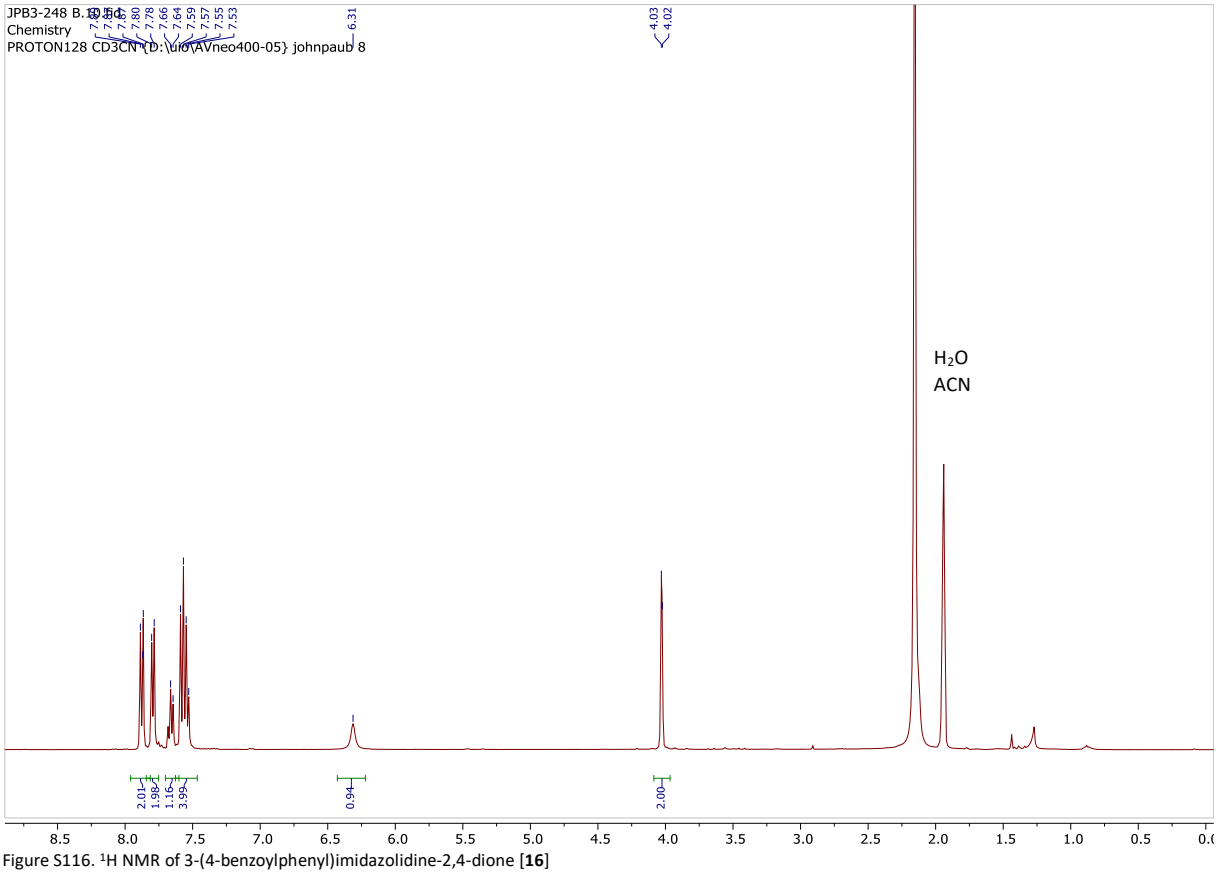


Figure S116. ^{1}H NMR of 3-(4-benzoylphenyl)imidazolidine-2,4-dione [**16**]

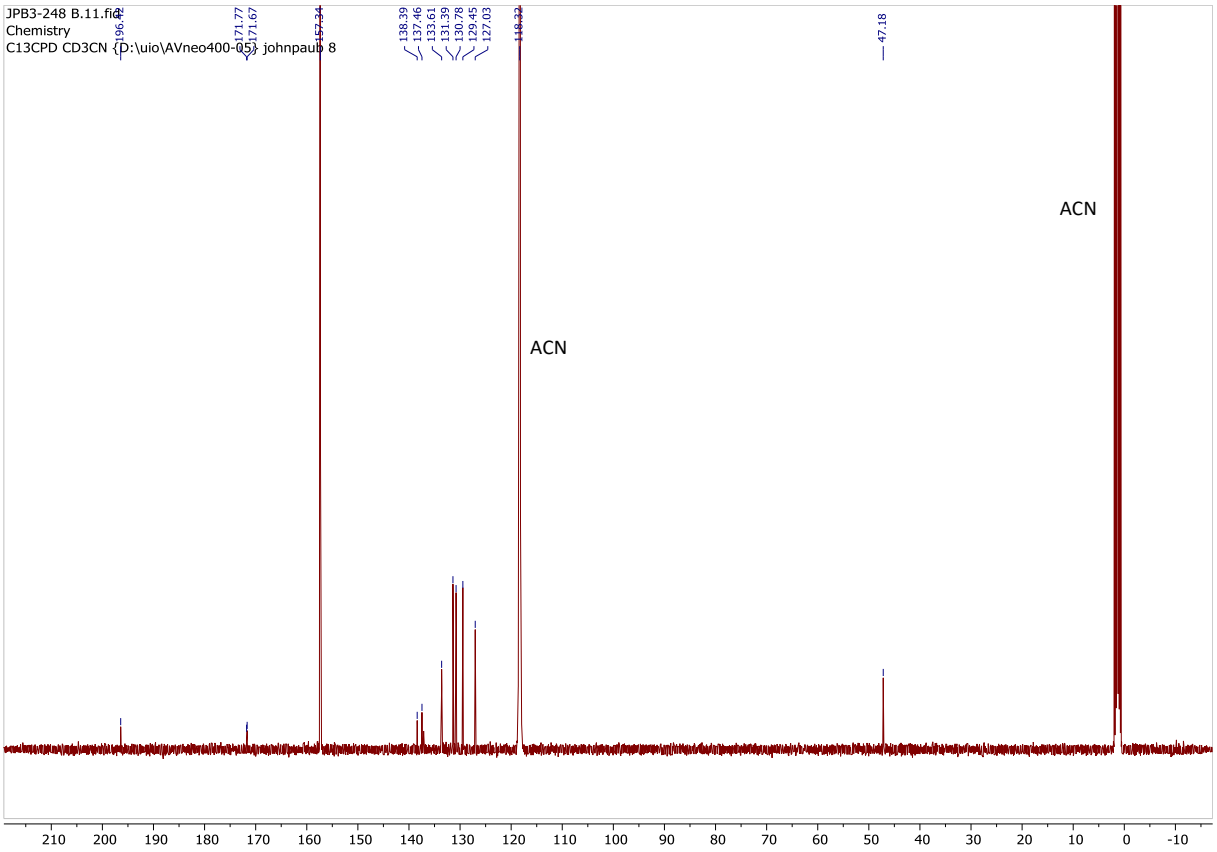


Figure S117. $^{13}C\{^{1}H\}$ NMR of 3-(4-benzoylphenyl)imidazolidine-2,4-dione [**16**]

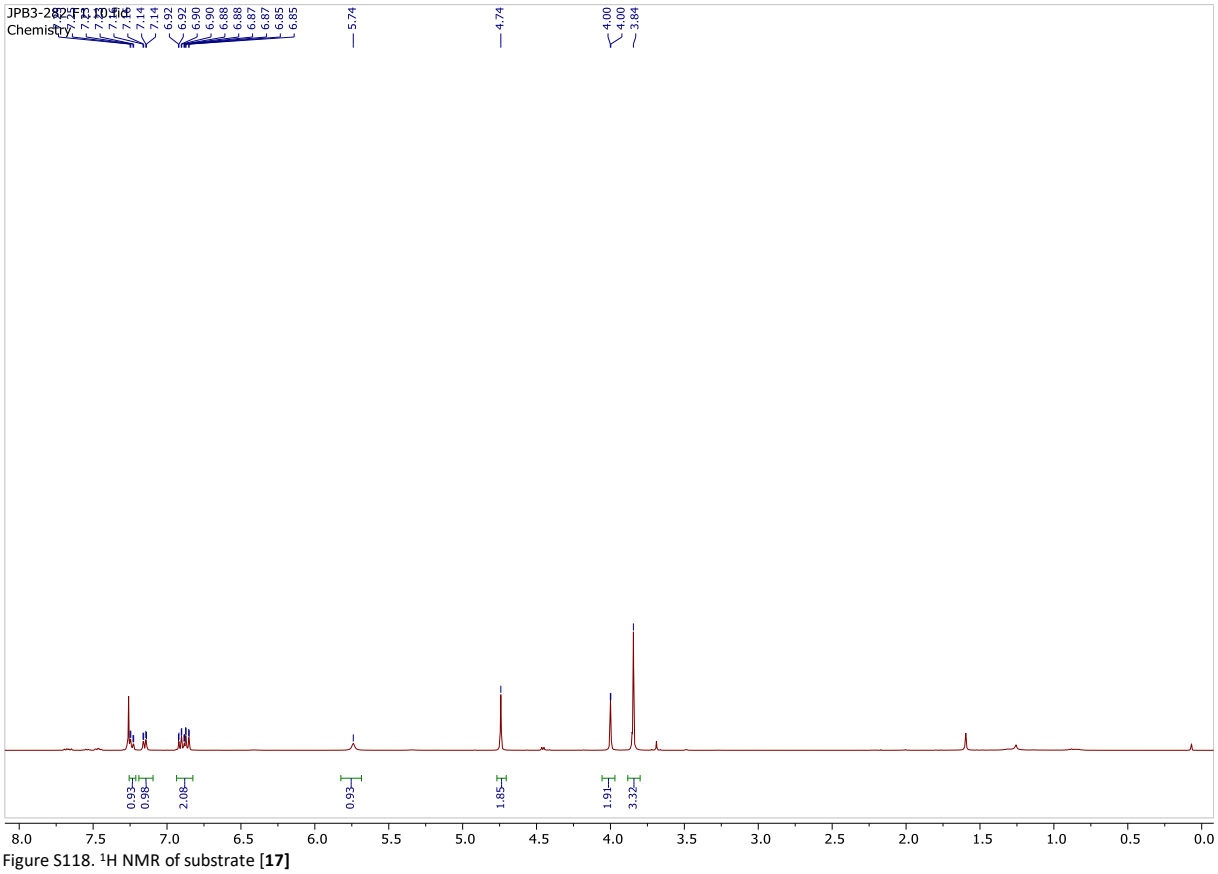


Figure S118. ^{1}H NMR of substrate [**17]**

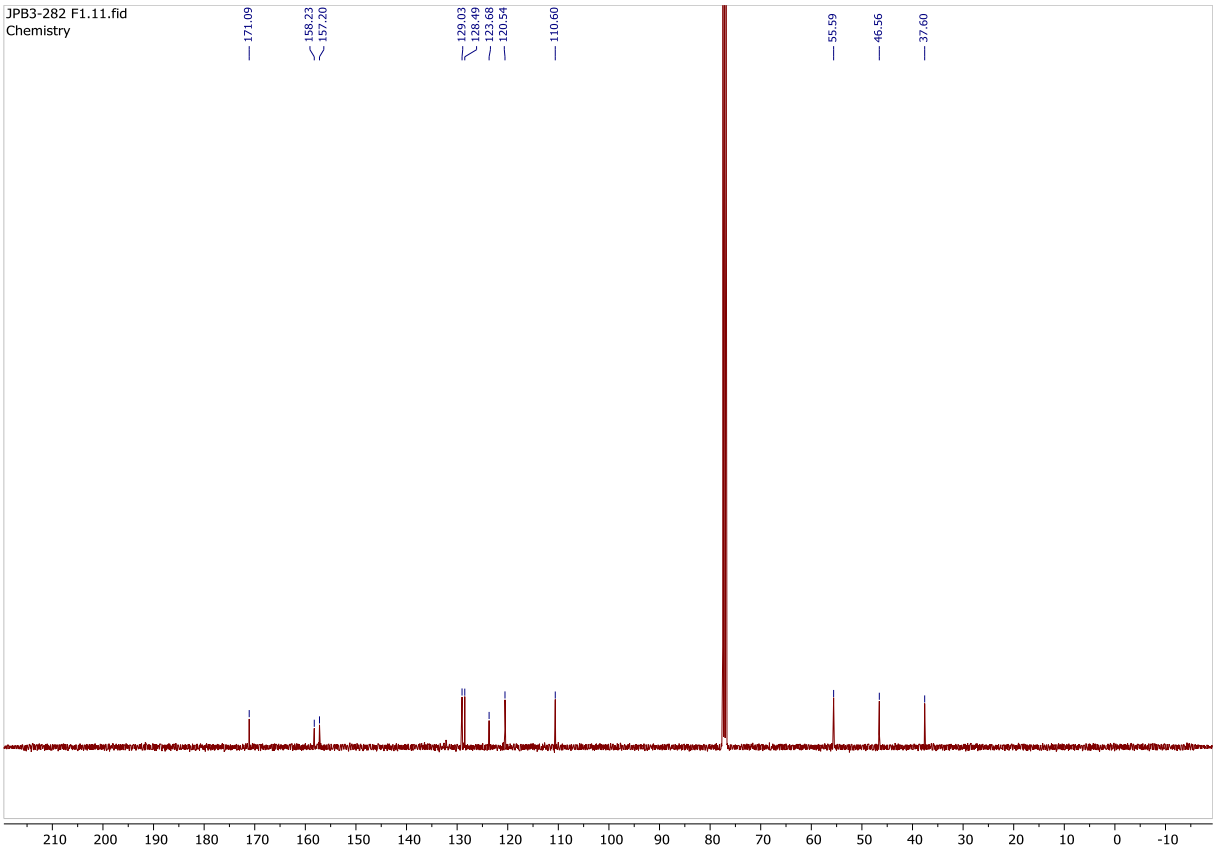


Figure S119. $^{13}C\{^{1}H\}$ NMR of substrate [**17**]

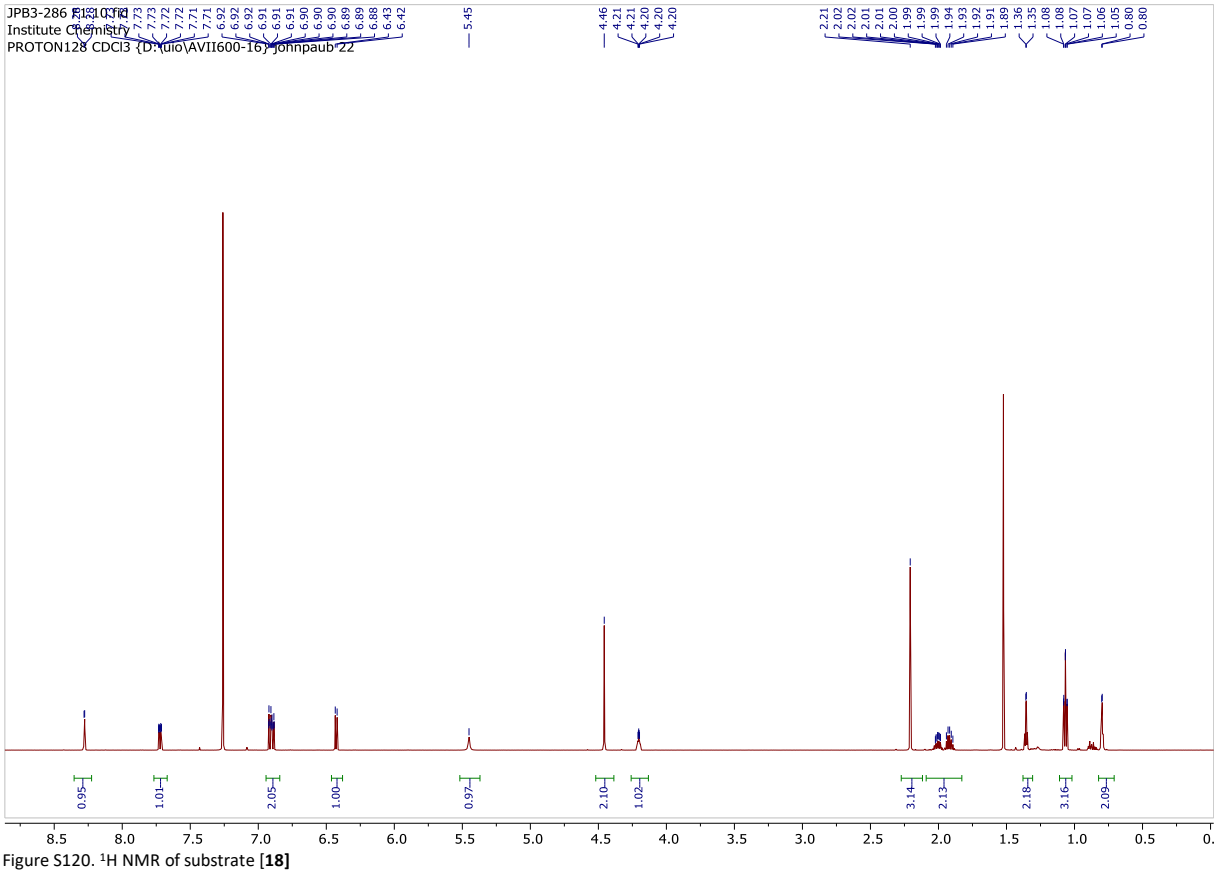


Figure S120. ^{1}H NMR of substrate [**18**]

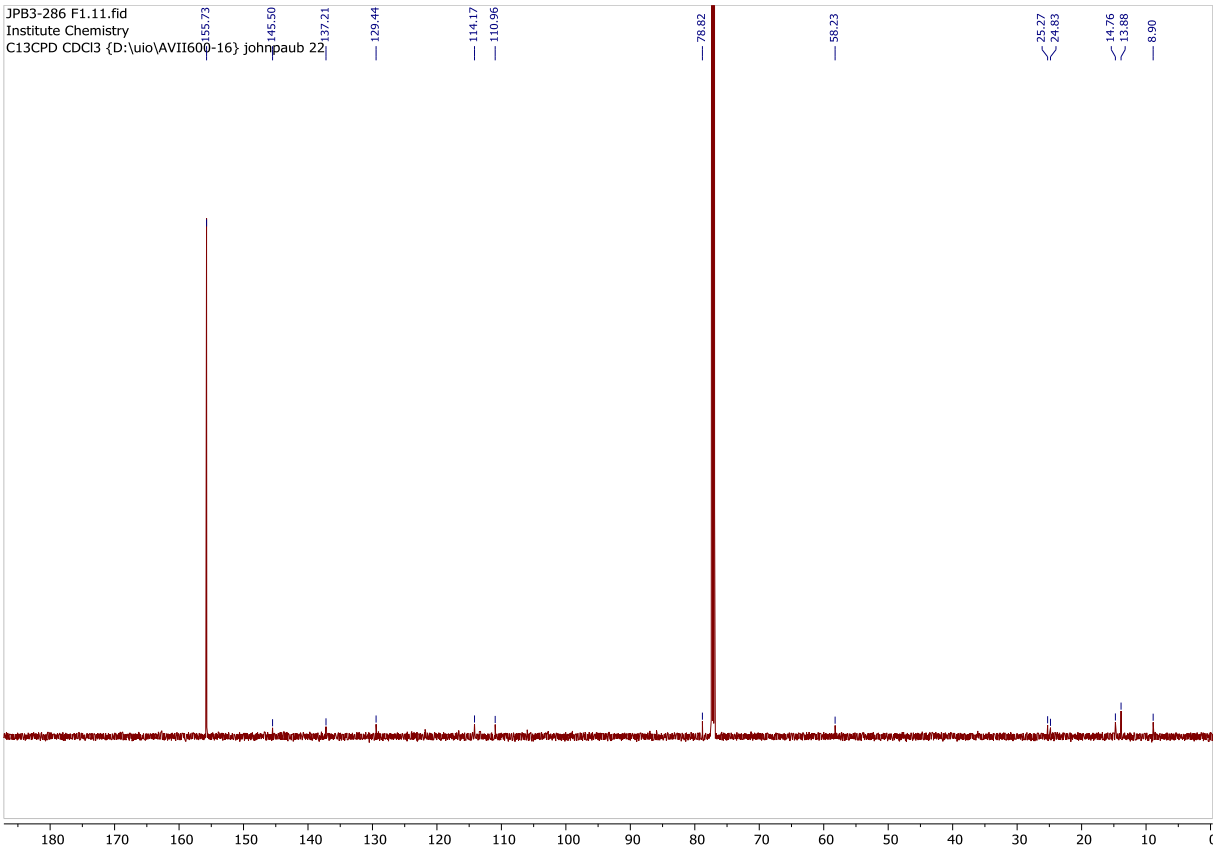


Figure S121. $^{13}C\{^{1}H\}$ NMR of substrate [**18**]

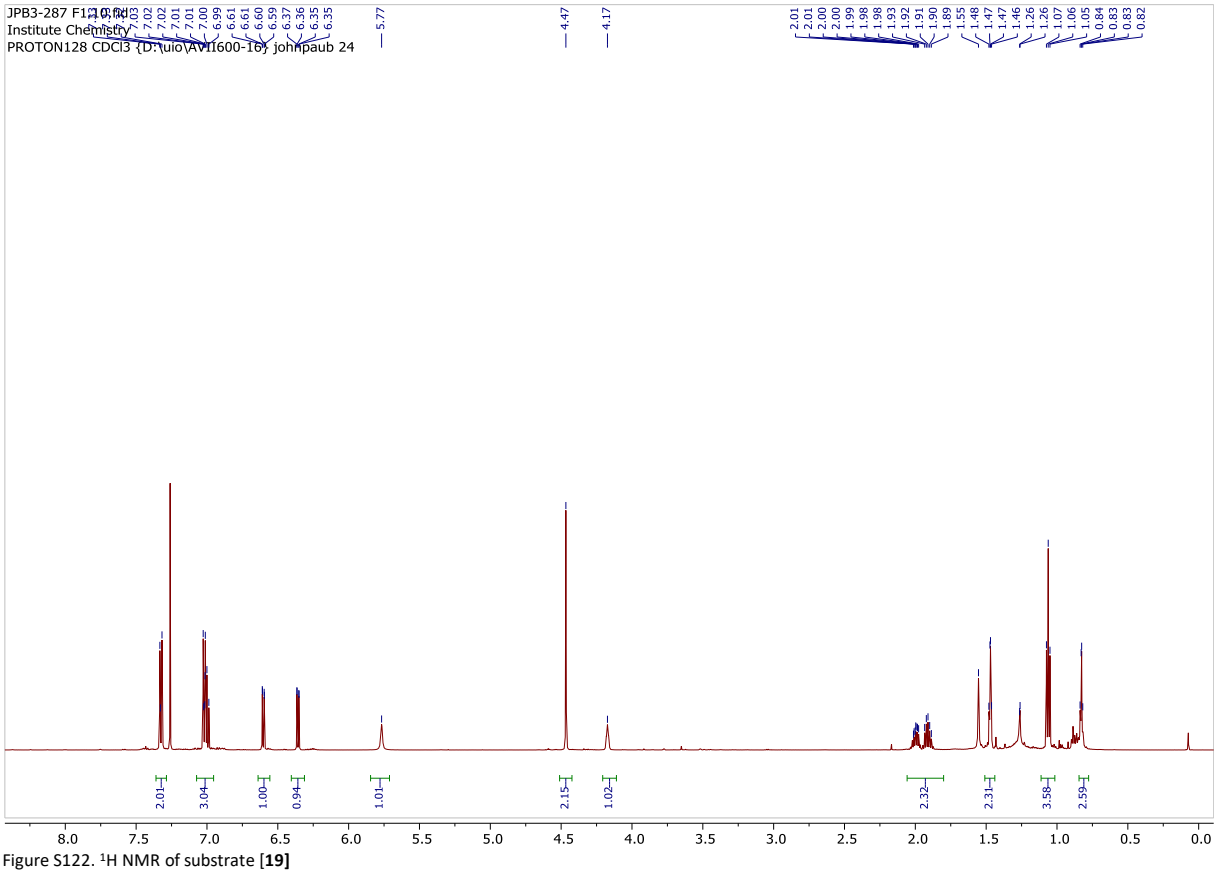


Figure S122. ^{1}H NMR of substrate [**19**]

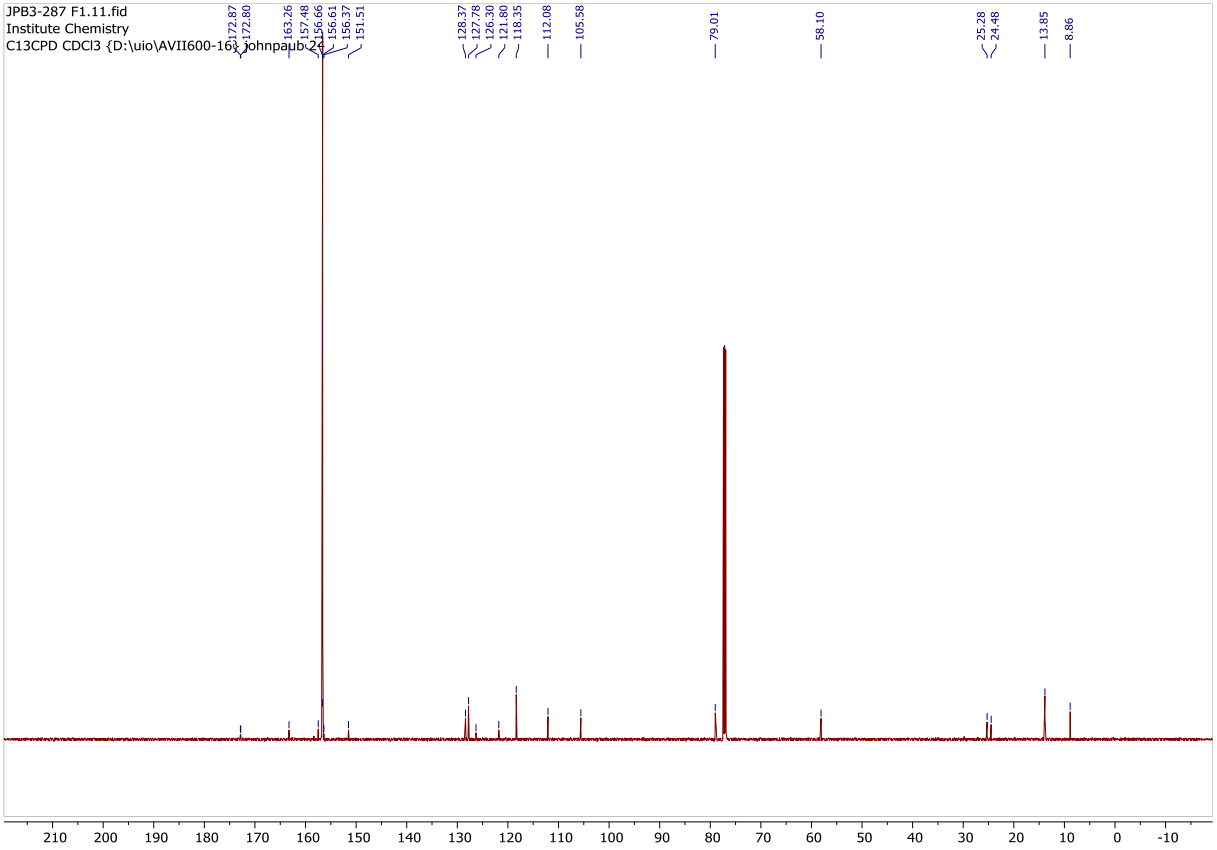


Figure S123. $^{13}C\{^{1}H\}$ NMR of substrate [**19**]

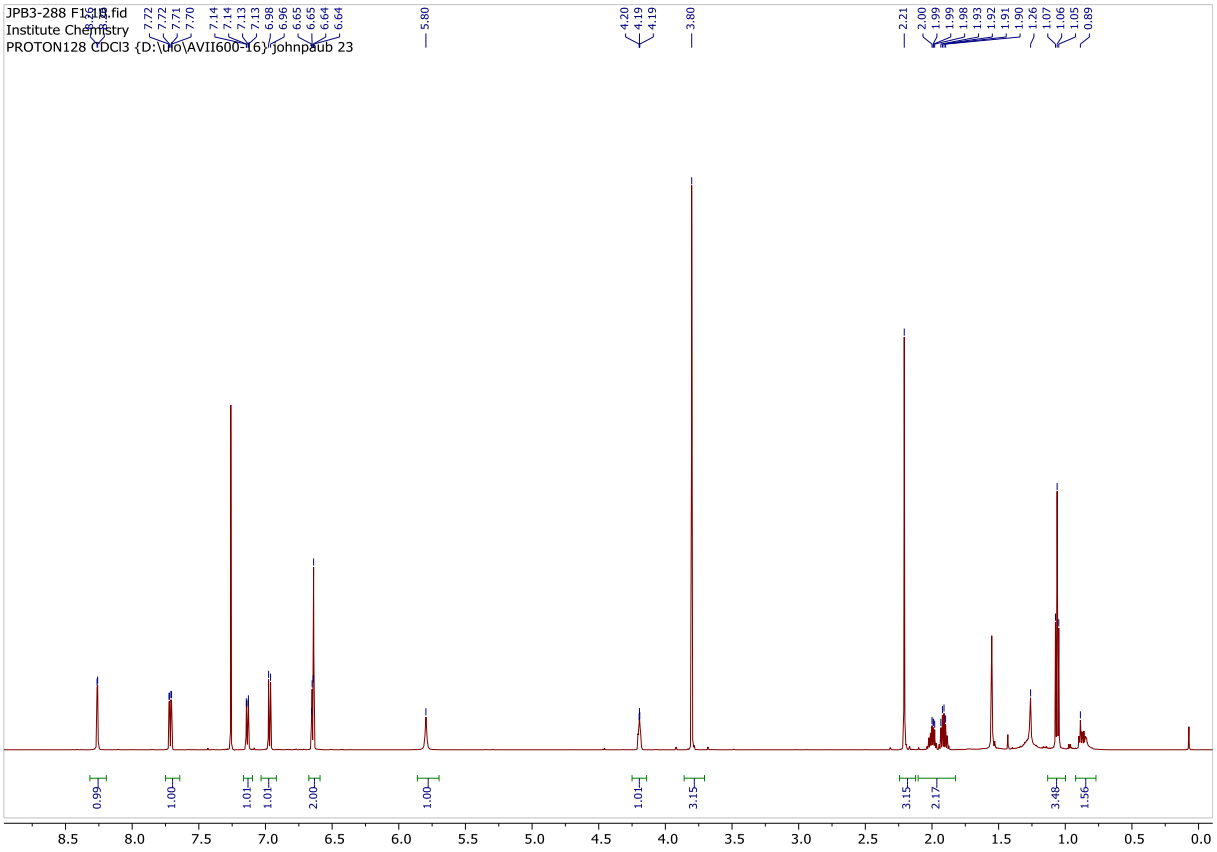


Figure S124. ^{1}H NMR of substrate [**20**]

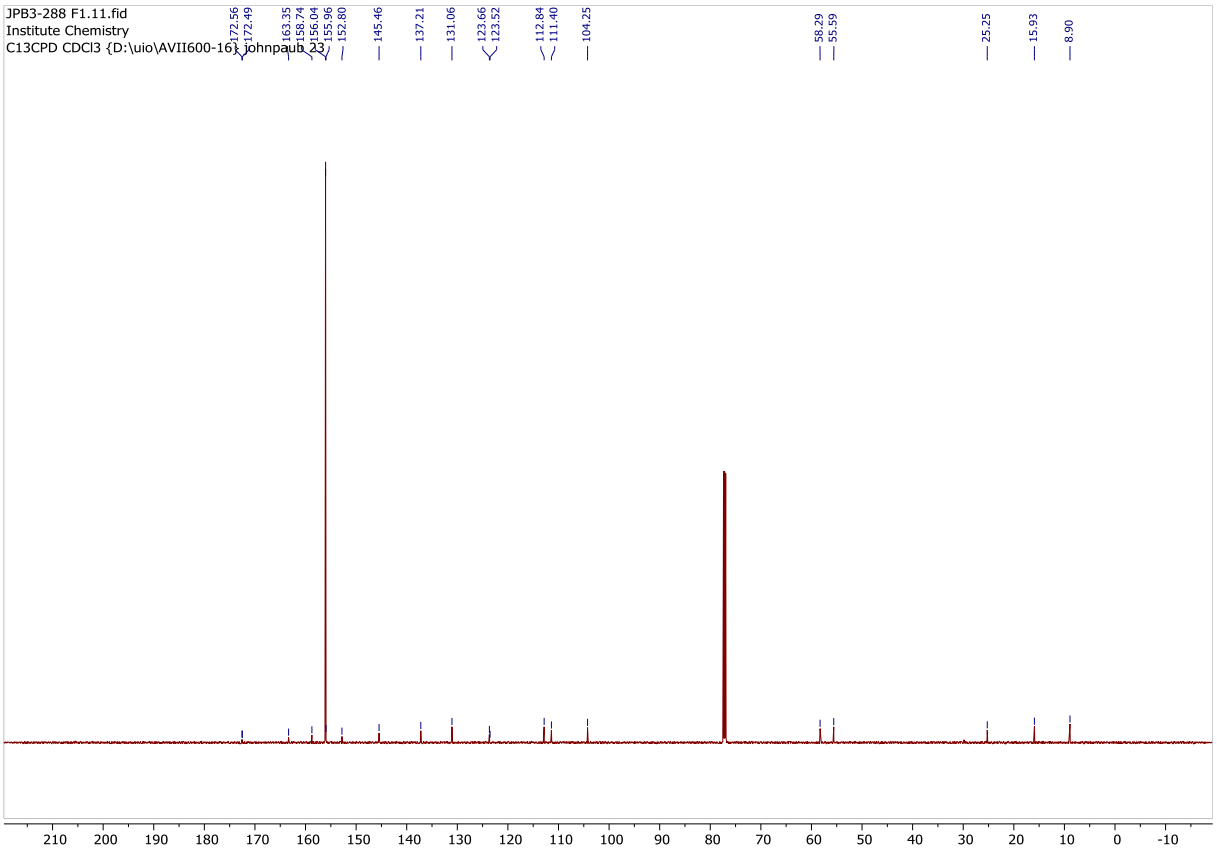


Figure S125. $^{13}C\{^{1}H\}$ NMR of substrate [**20]**

5.3. Substrate Scope NMR Spectra

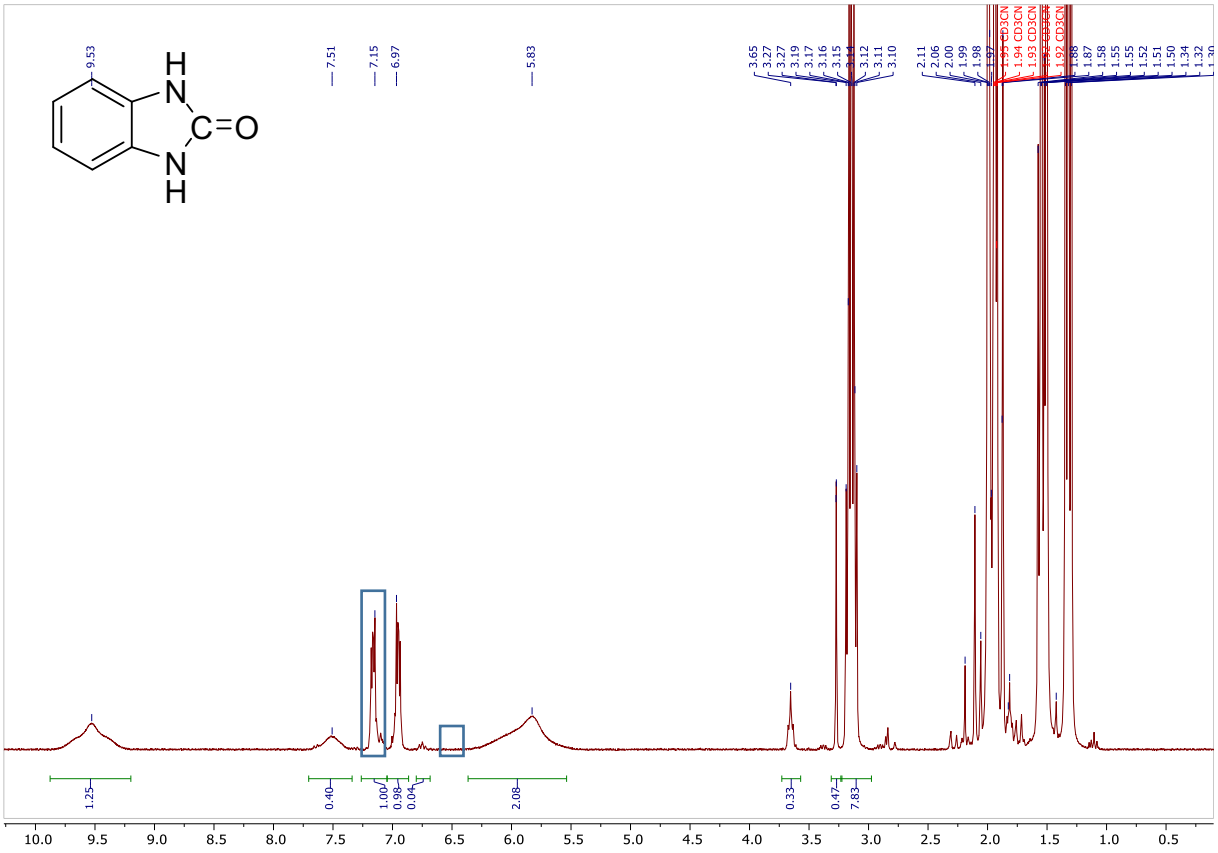


Figure S126. ^{1}H NMR of [**1**], product signal 7.17 ppm vs starting material 6.59 ppm (2:0)

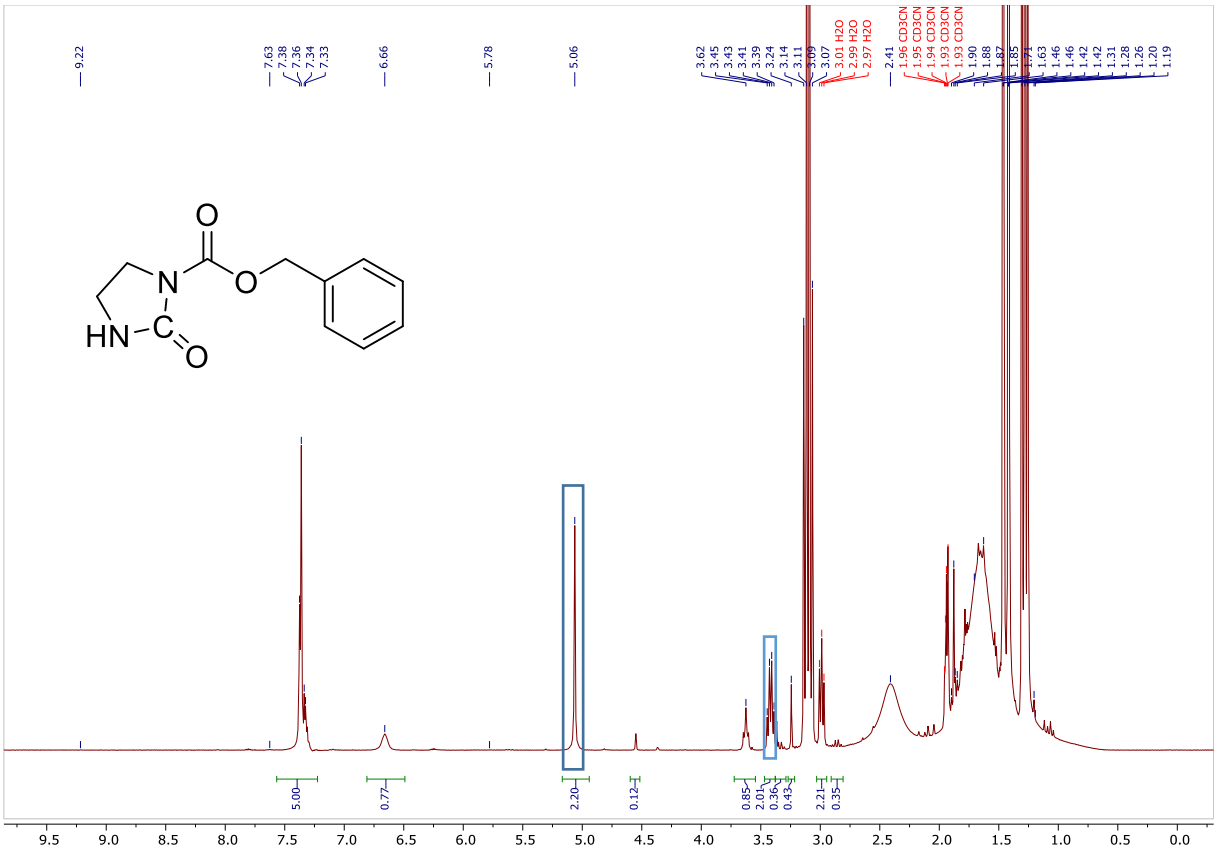


Figure S127. ^{1}H NMR of [**2**], product signal 5.06 ppm vs starting material 3.42 ppm (0.85:1.01)

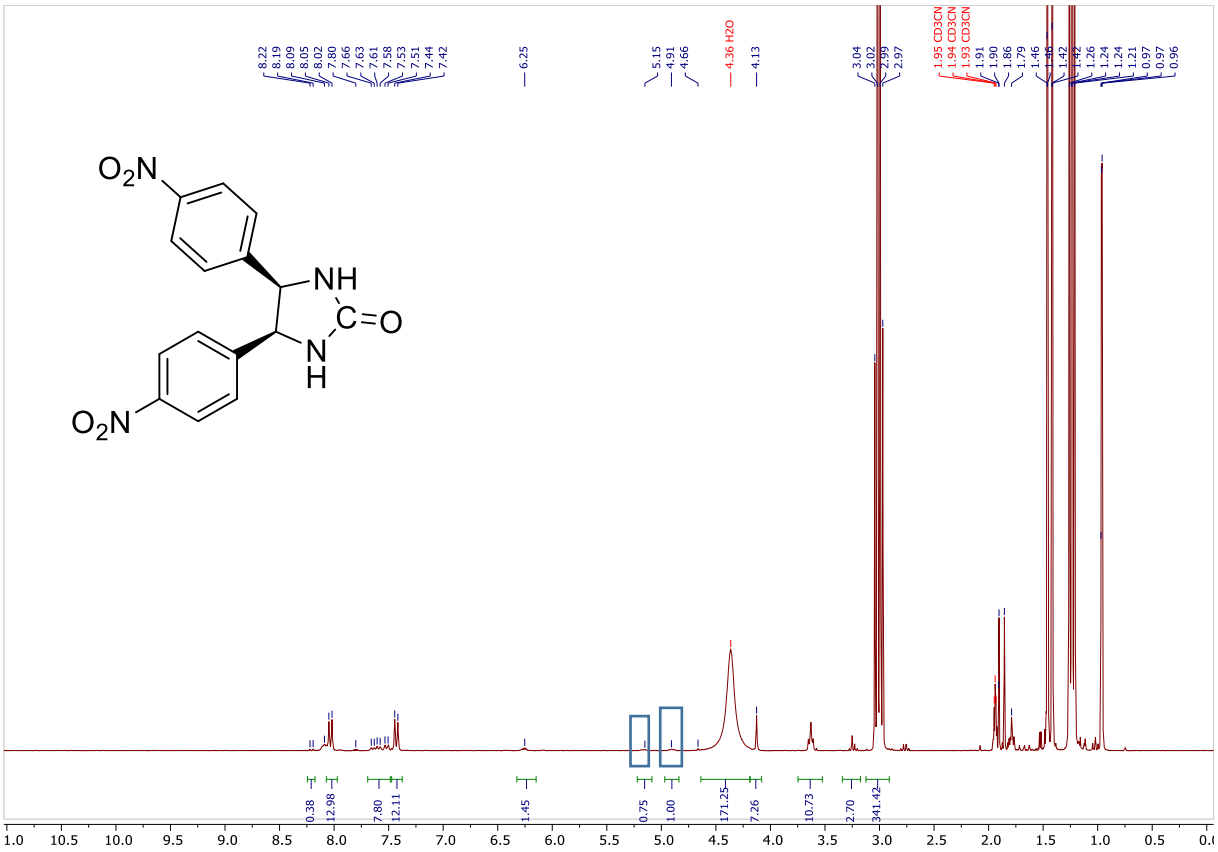


Figure S128. ^{1}H NMR of [**3**], product signal 5.15 ppm vs starting material 4.91 ppm (0.75:1.0)

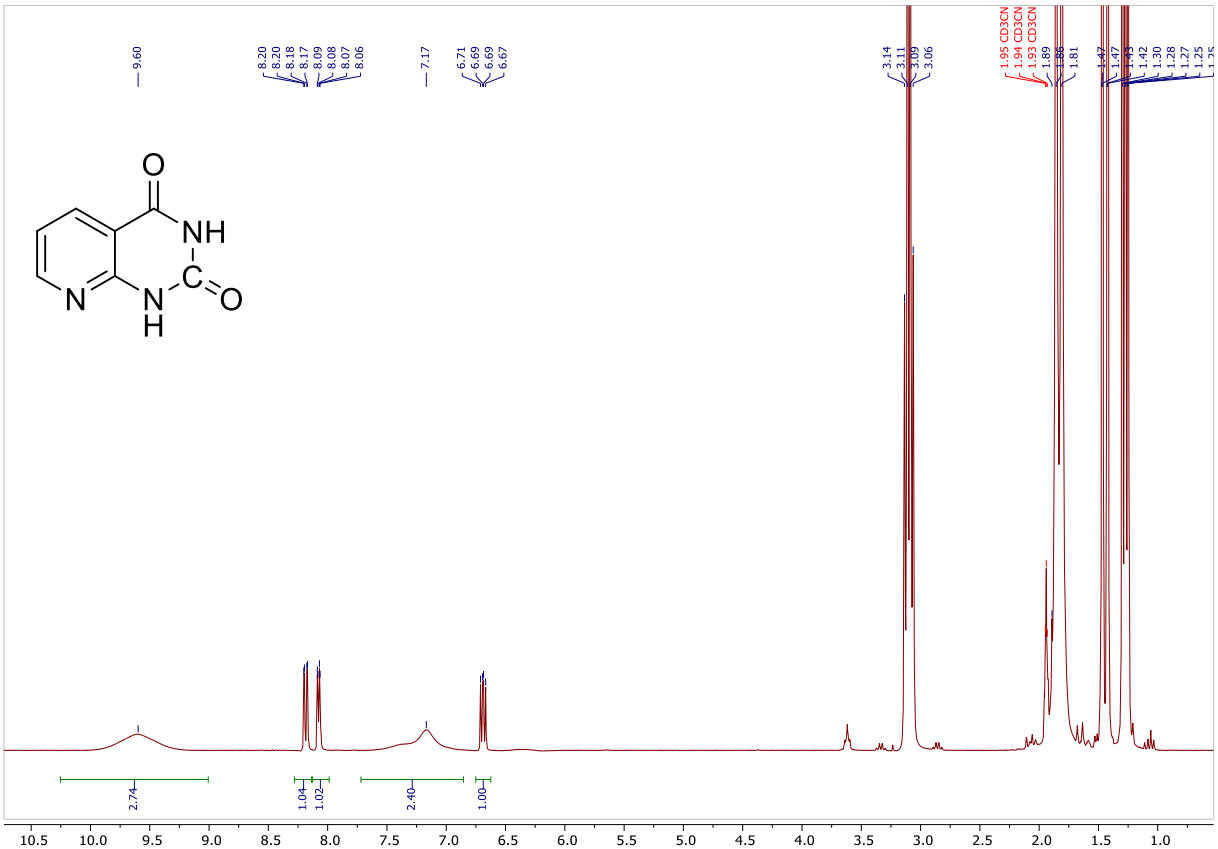


Figure S129 ^{1}H NMR of [**4**], no product signal observed.

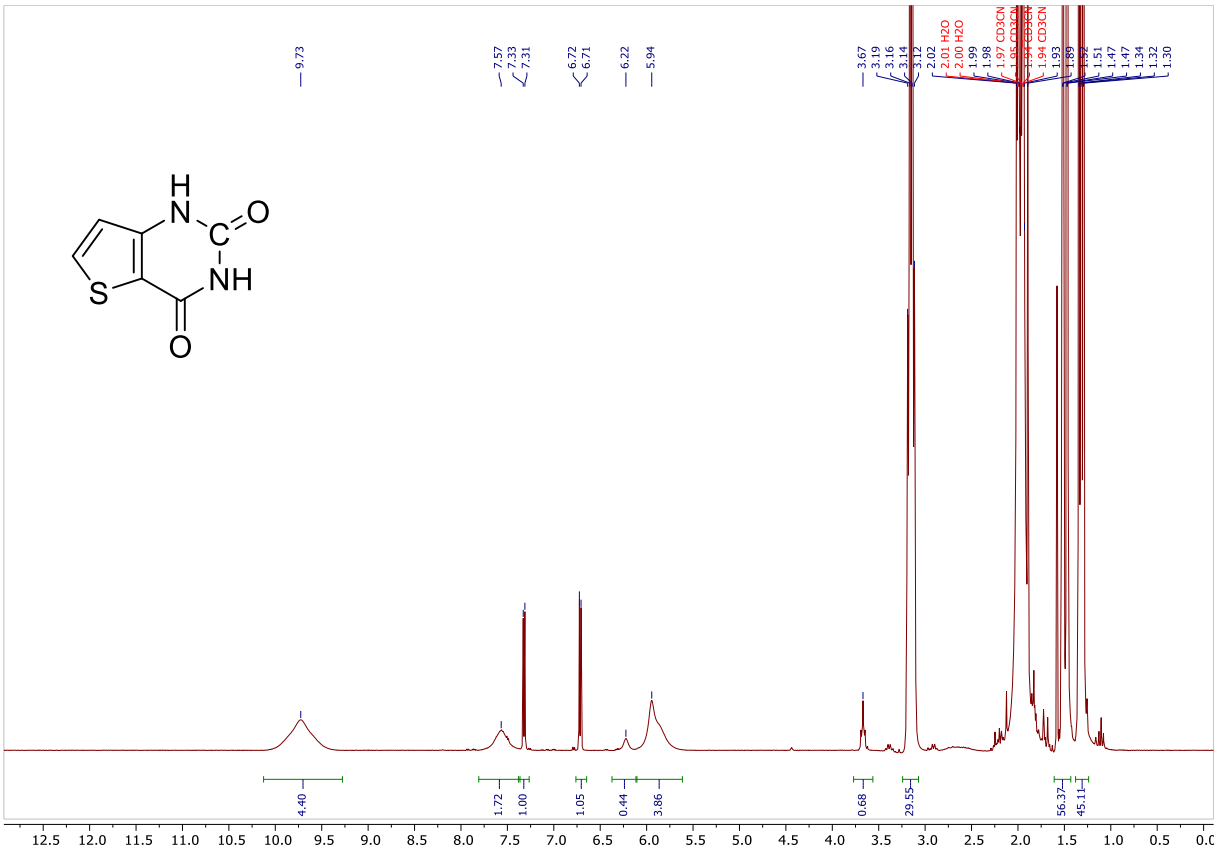


Figure S130. ^{1}H NMR of [**5**], no product signal observed

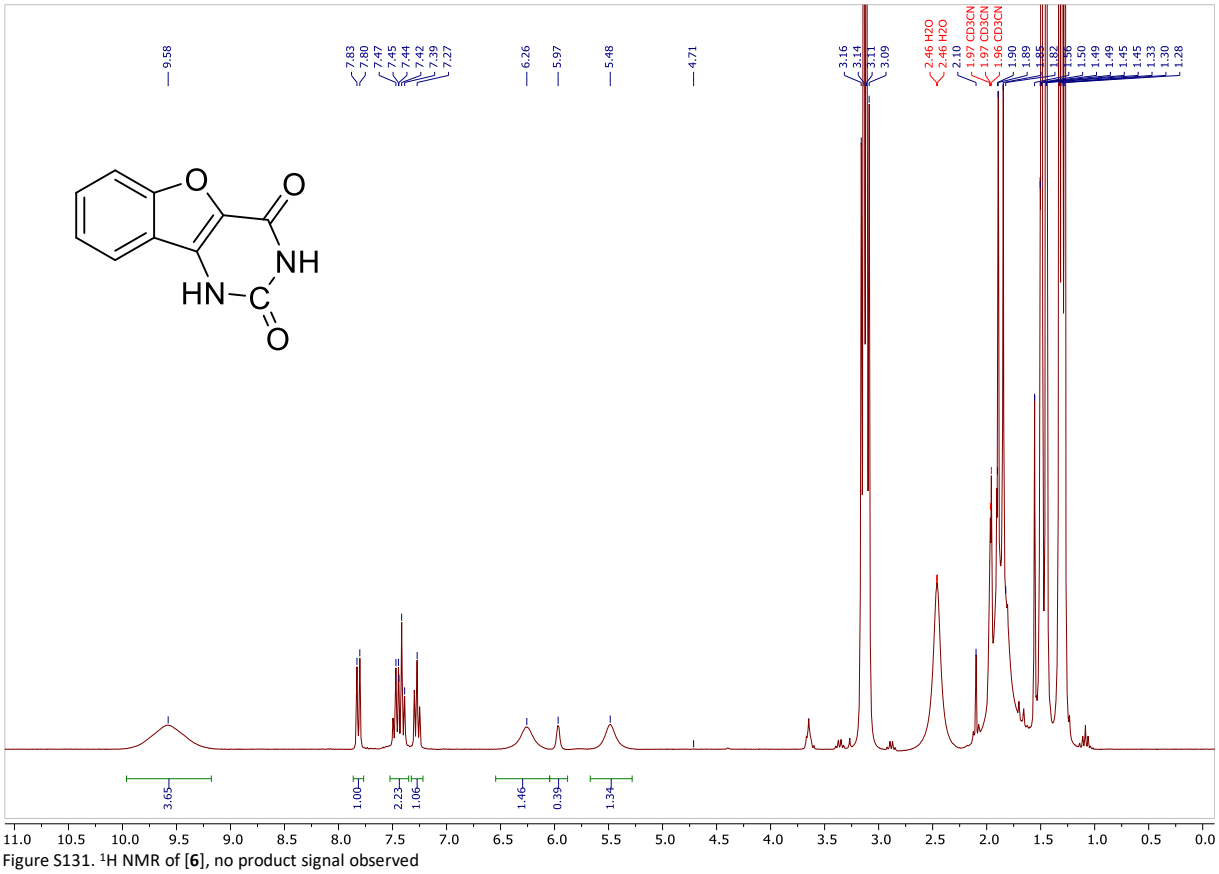


Figure S131. ^{1}H NMR of [**6**], no product signal observed

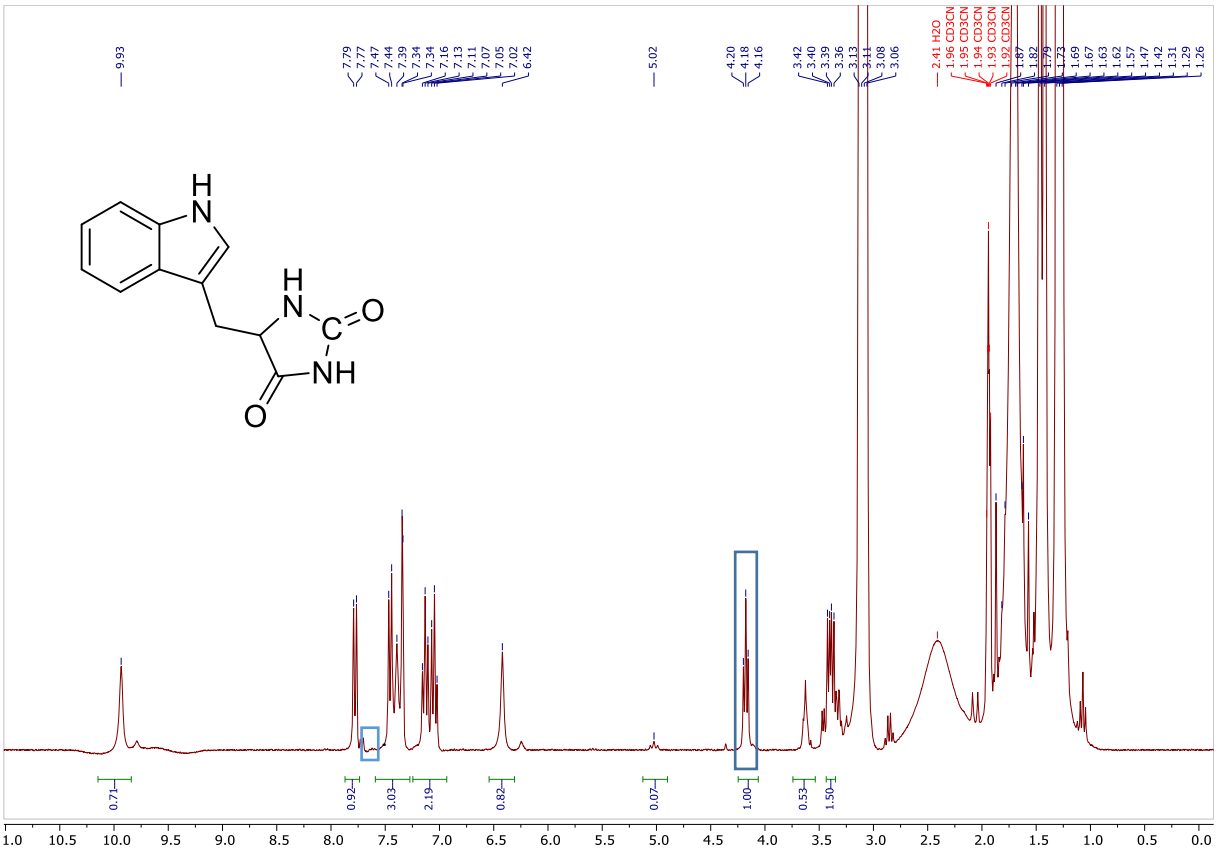


Figure S132 ^{1}H NMR of [**7**], product signal 4.18 ppm vs starting material 7.61 ppm (1:0.03)

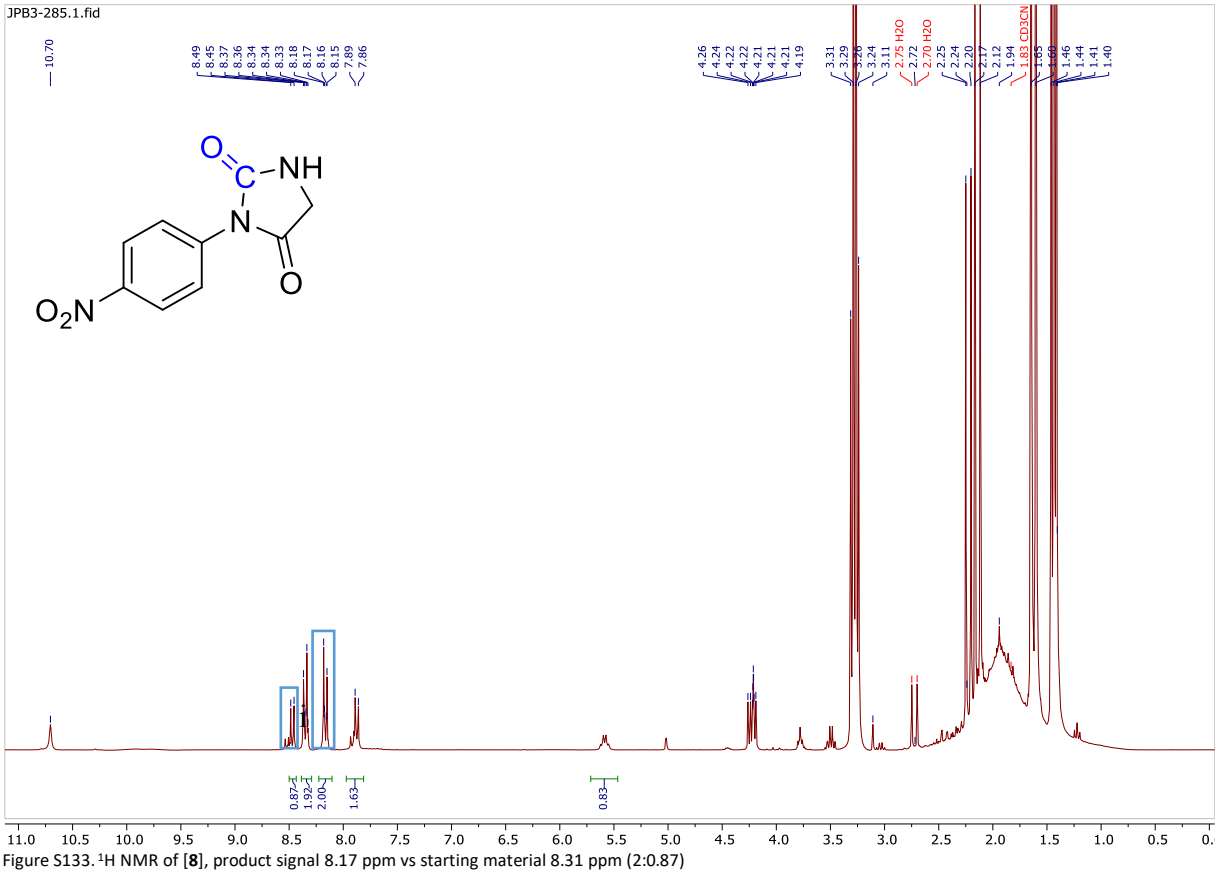


Figure S133. ^{1}H NMR of [**8**], product signal 8.17 ppm vs starting material 8.31 ppm (2:0.87)

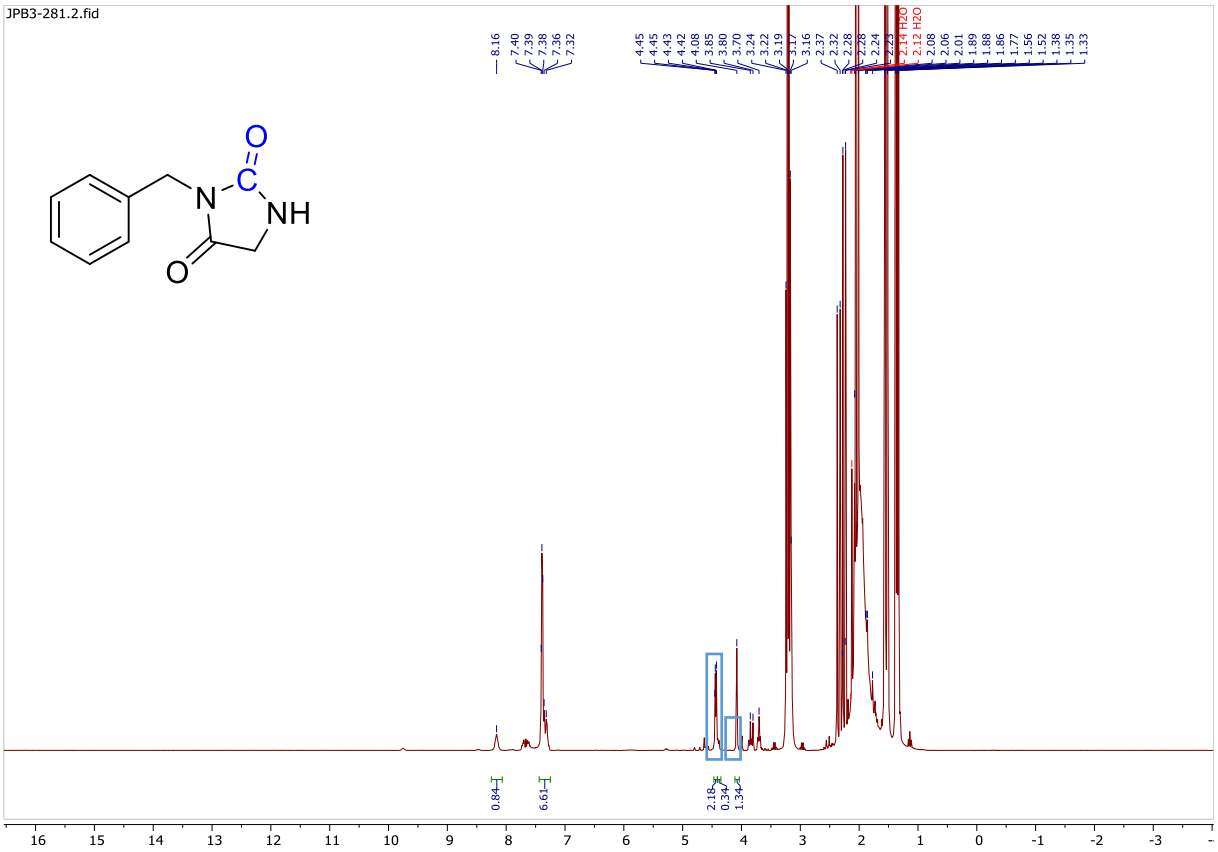


Figure S134. ^{1}H NMR of [**9**], product signal 4.37 ppm vs starting material 4.03 ppm (2.18:0.39)

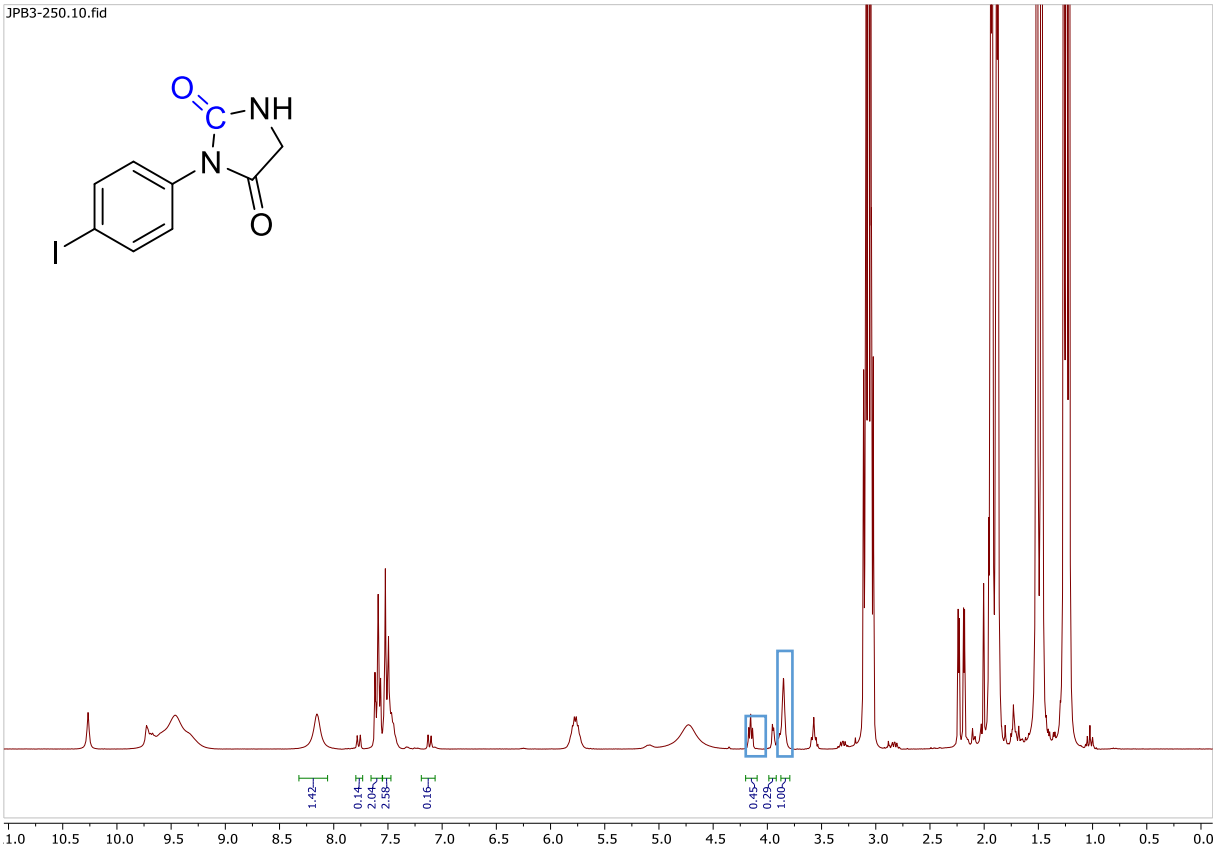


Figure S135. ^{1}H NMR of [**10**], product signal 3.87 ppm vs starting material 4.23 ppm (1.00:0.45)

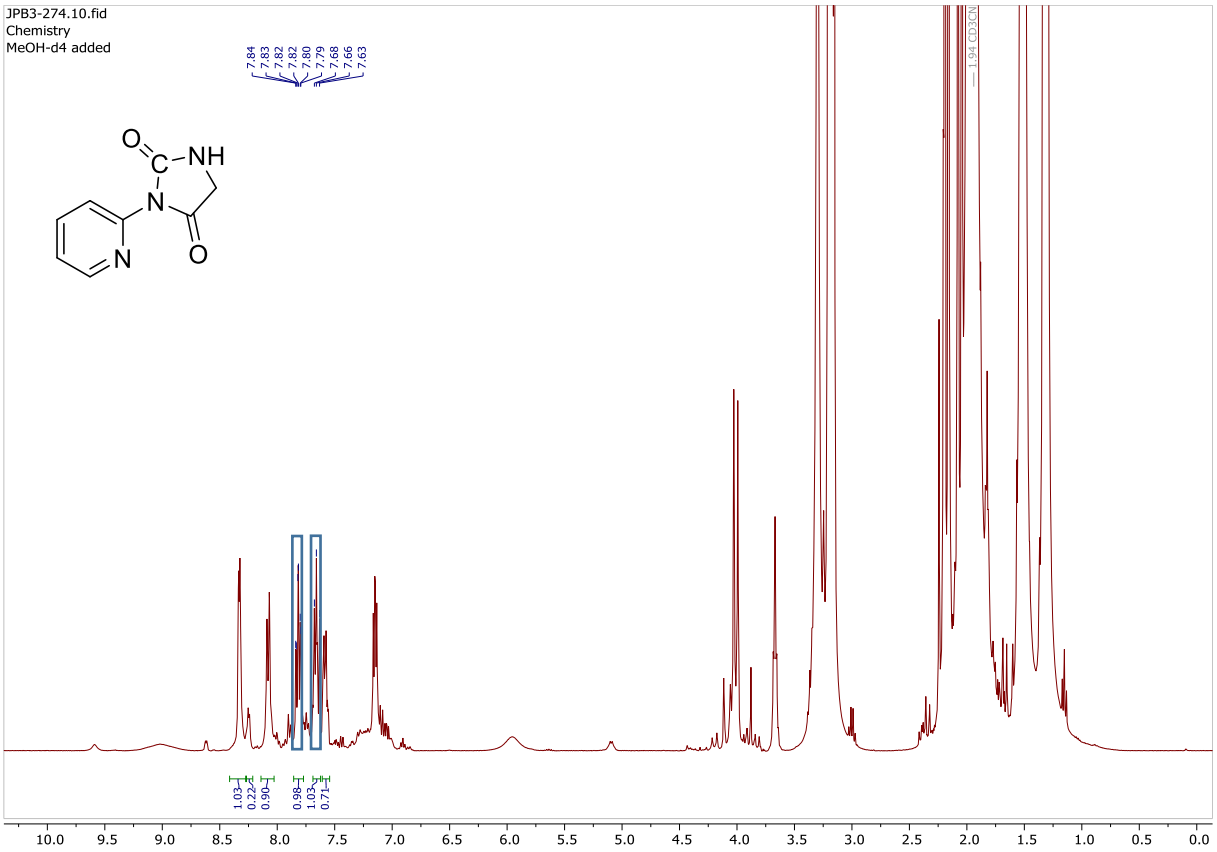


Figure S136. ^{1}H NMR of [**11**], product signal 7.66 ppm vs starting material 7.82 ppm (1.03:0.98)

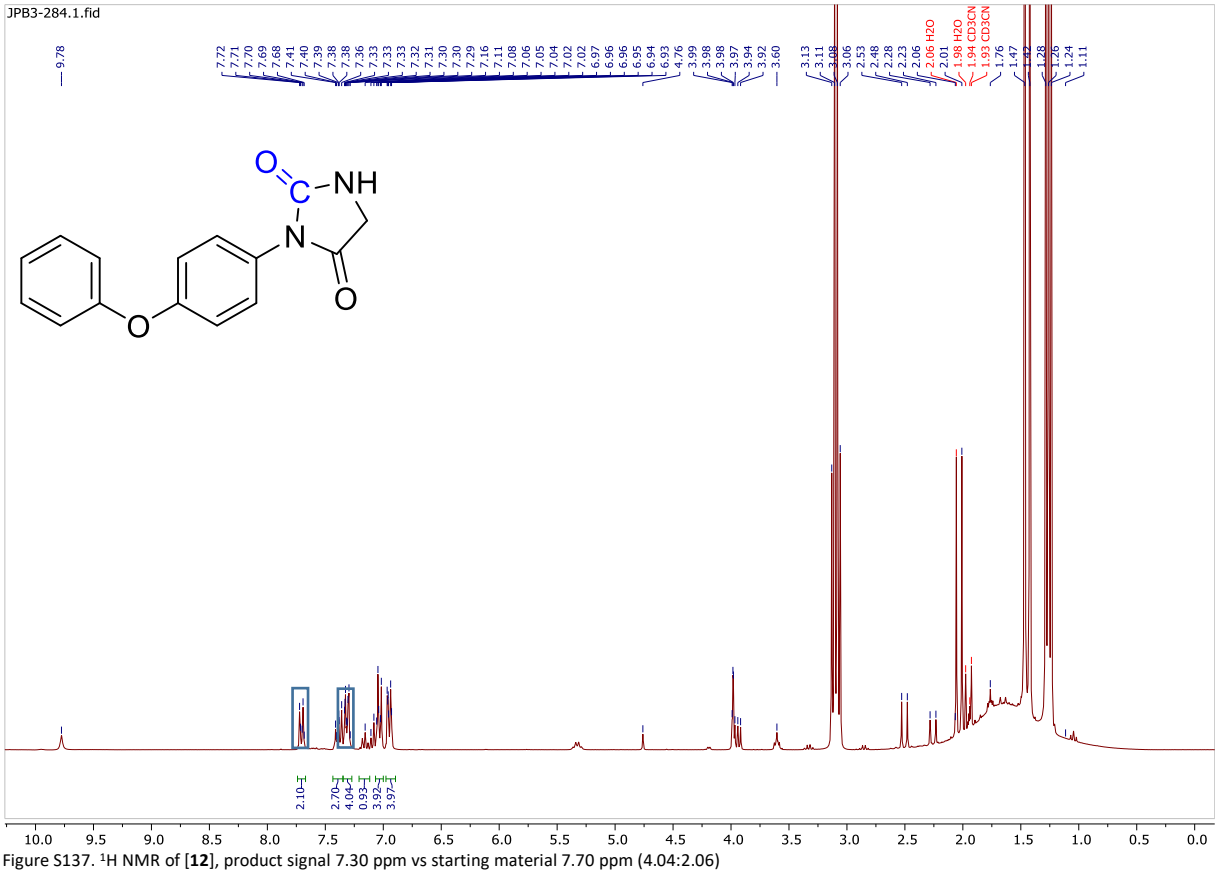


Figure S137. ^{1}H NMR of [**12**], product signal 7.30 ppm vs starting material 7.70 ppm (4.04:2.06)

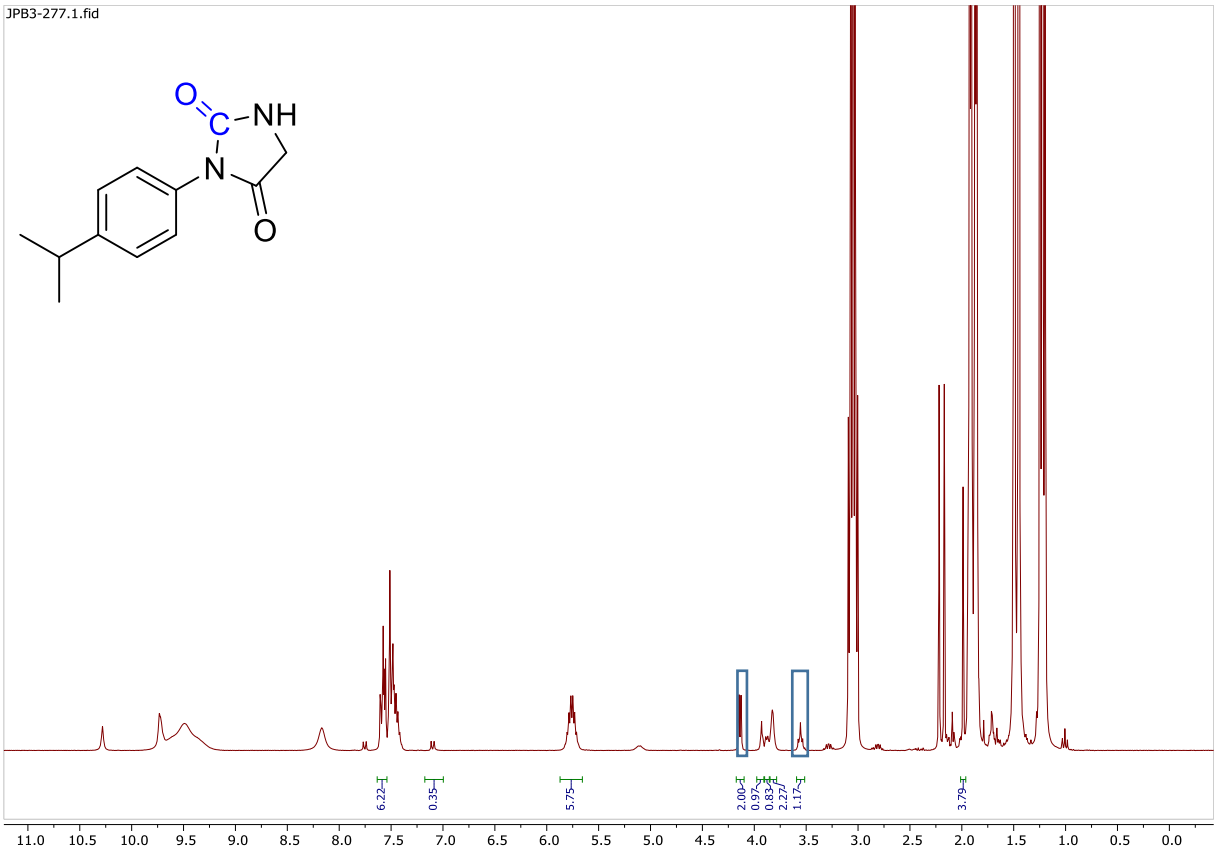


Figure S138. ^{1}H NMR of [**13**], product signal 4.23 ppm vs starting material 3.53 ppm (2.00:1.17)

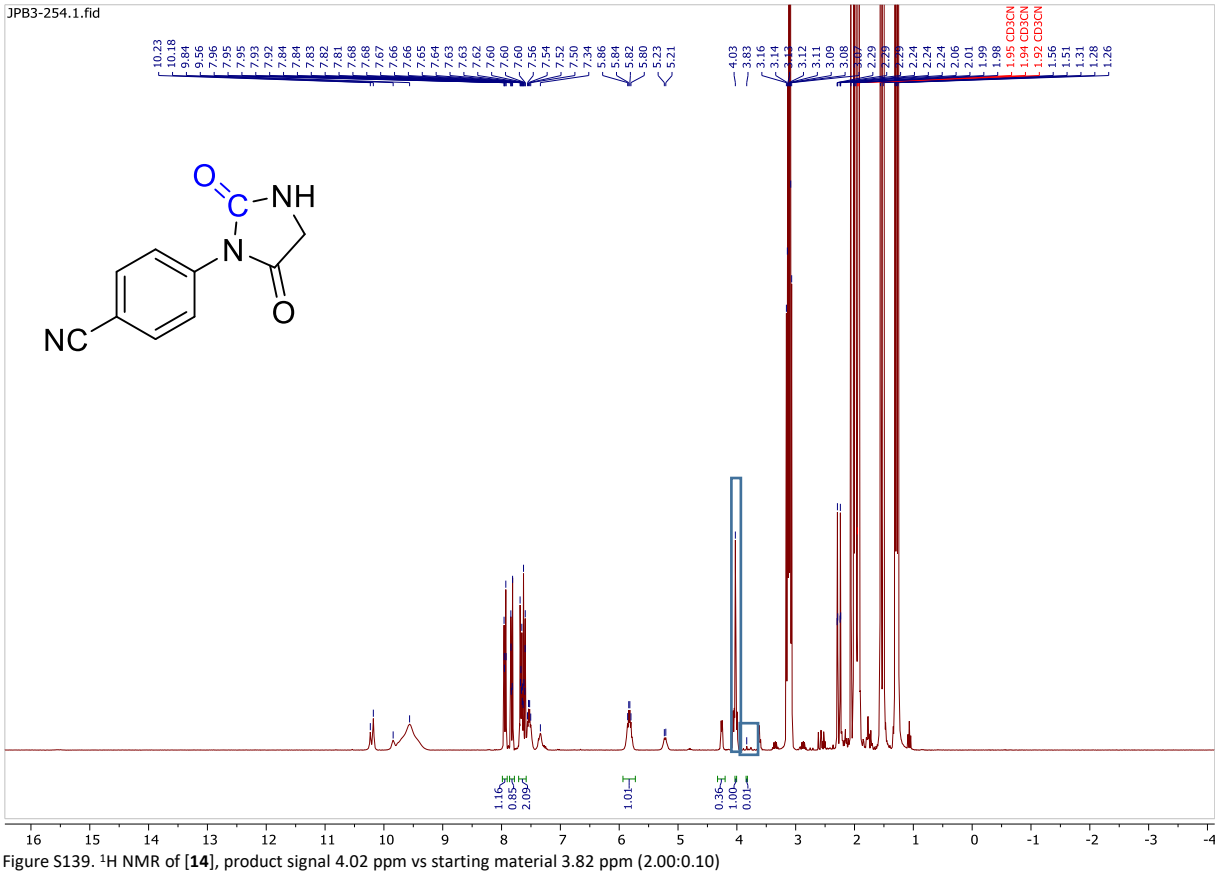


Figure S139. ^{1}H NMR of [**14**], product signal 4.02 ppm vs starting material 3.82 ppm (2.00:0.10)

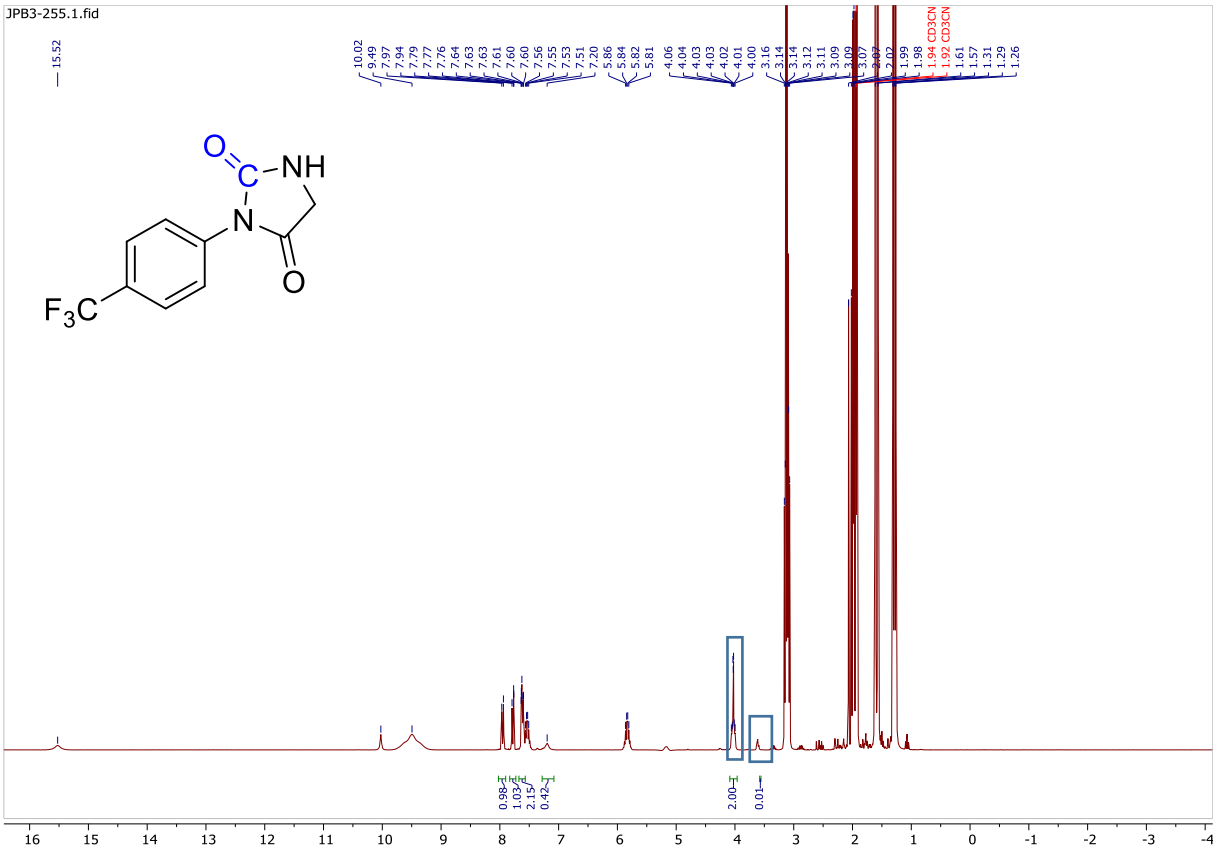


Figure S140.^{1}H NMR of [**15**], product signal 4.02 ppm vs starting material 3.54 ppm (2.00:0.10)

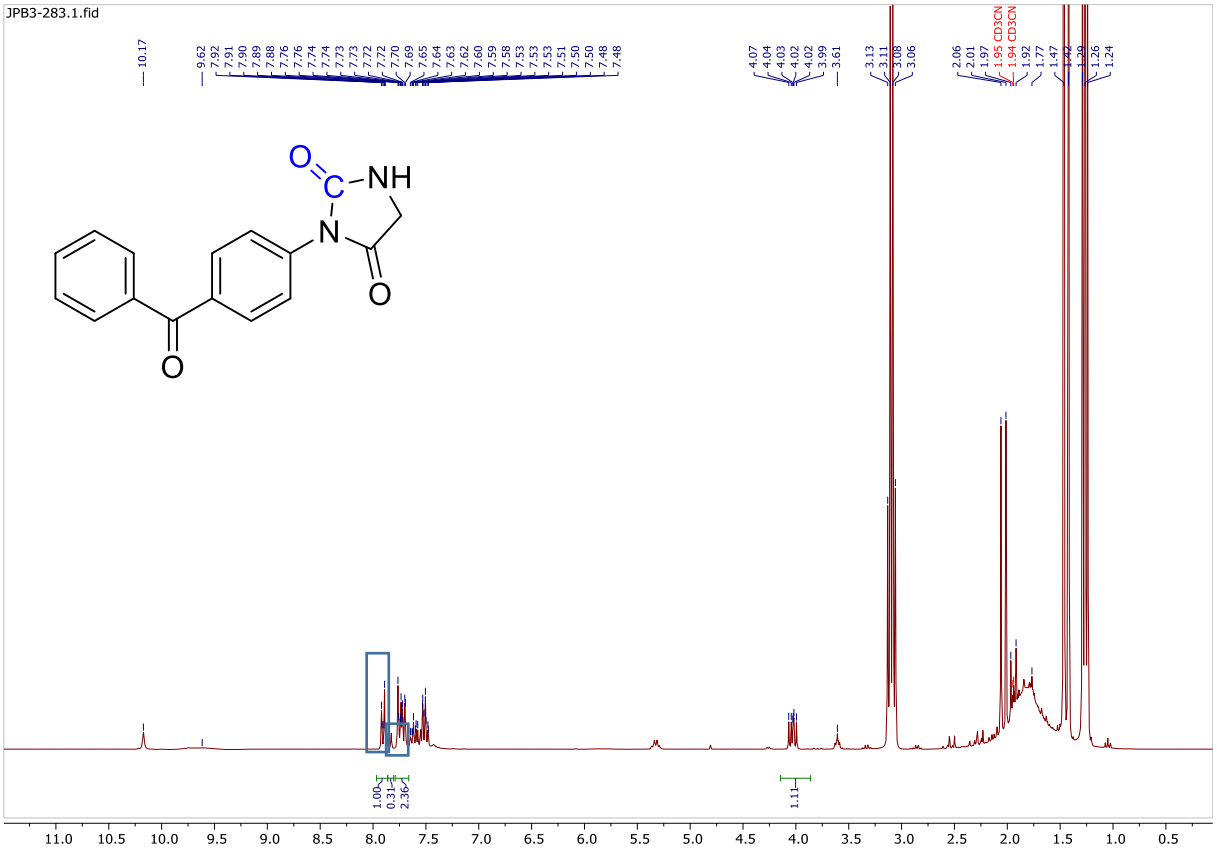


Figure S141.^{1}H NMR of [**16**], product signal 7.91 ppm vs starting material 7.84 ppm (1.00:0.37)

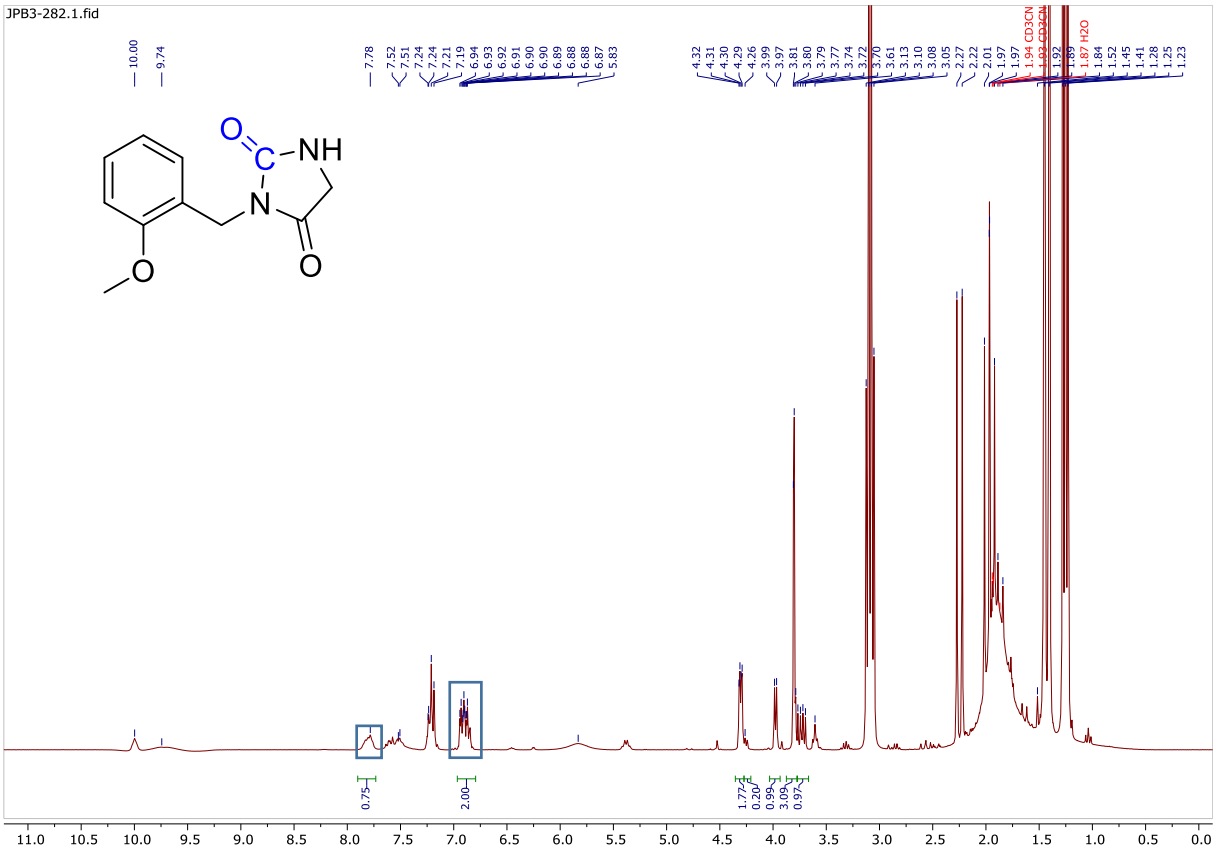


Figure S142. ^{1}H NMR of [**17**], product signal 6.90 ppm vs starting material 7.81 ppm (2.00:0.73)

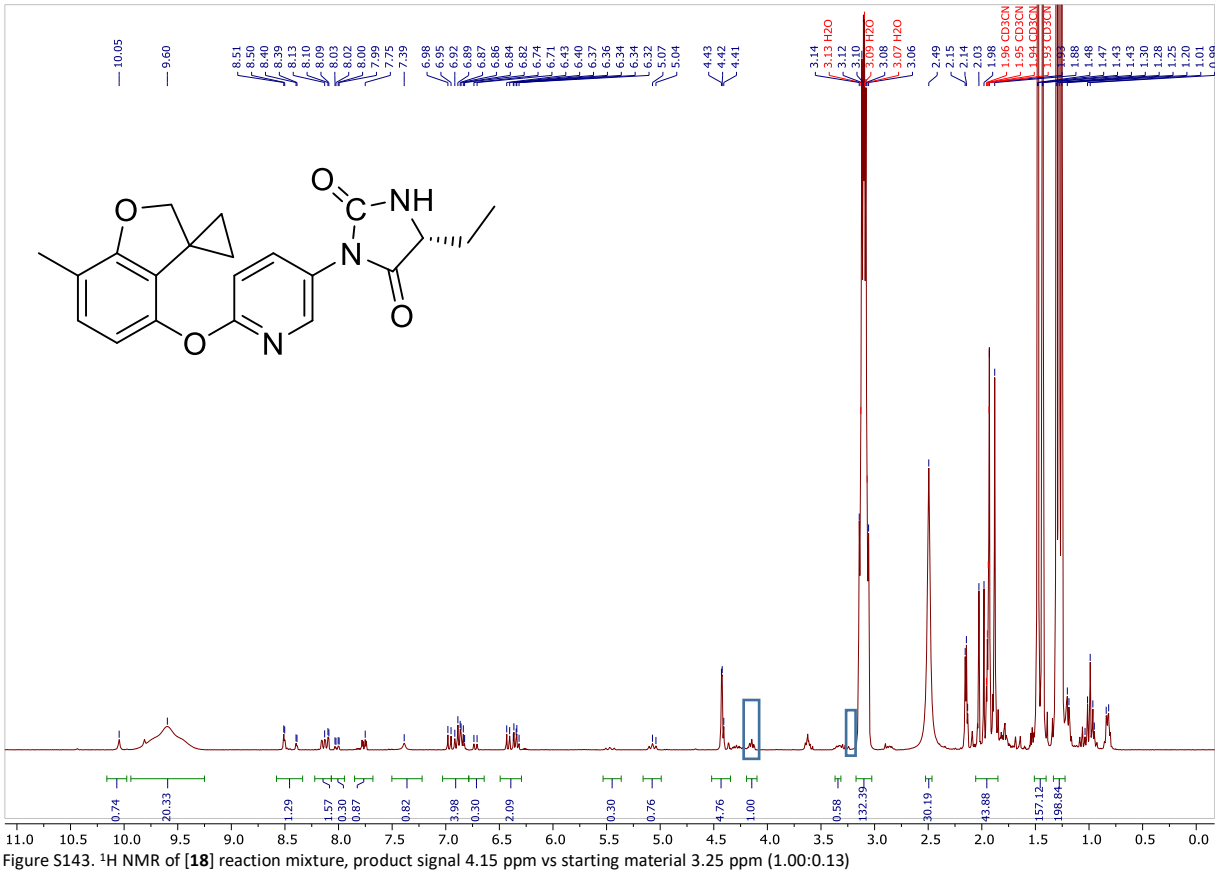


Figure S143. ^{1}H NMR of [**18**] reaction mixture, product signal 4.15 ppm vs starting material 3.25 ppm (1.00:0.13)

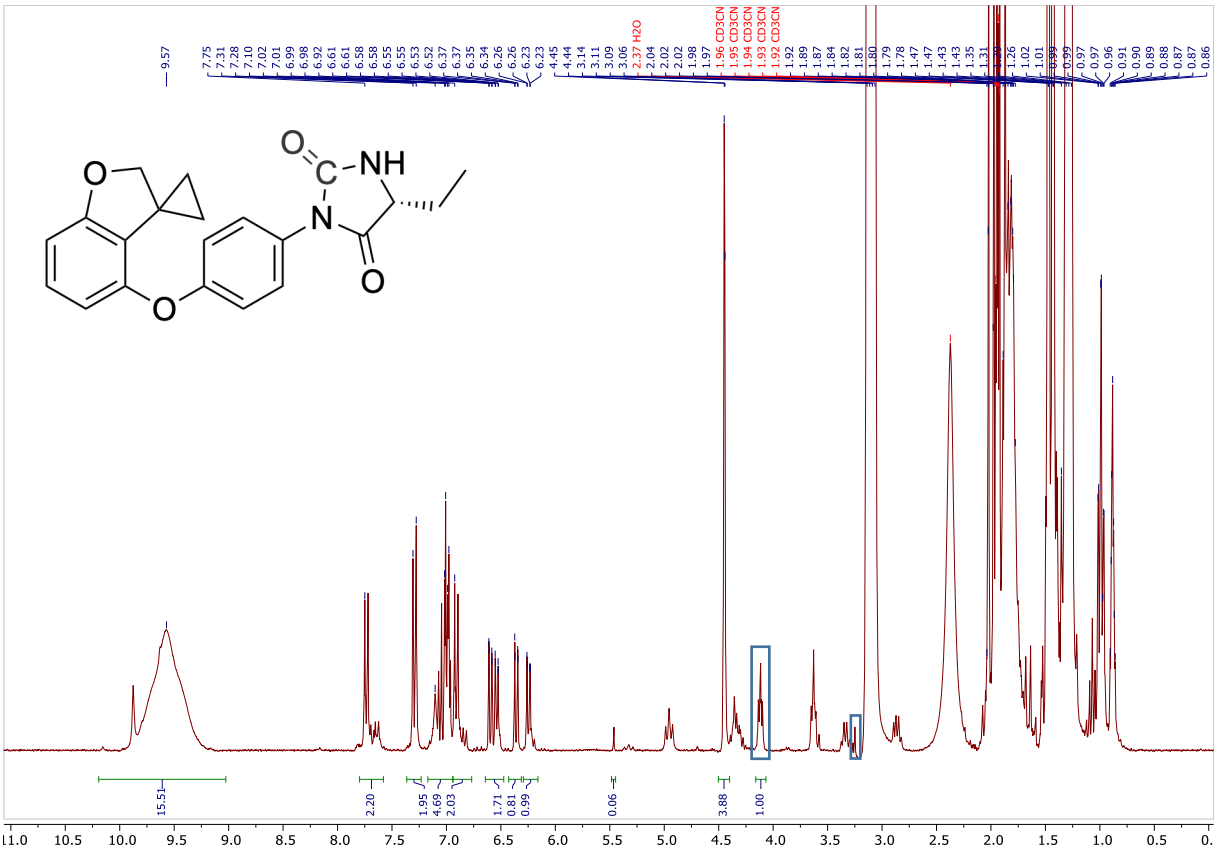


Figure S144 ^{1}H NMR of [**19**] reaction mixture, product signal 4.10 ppm vs starting material 3.25 ppm (1.00:0.05)

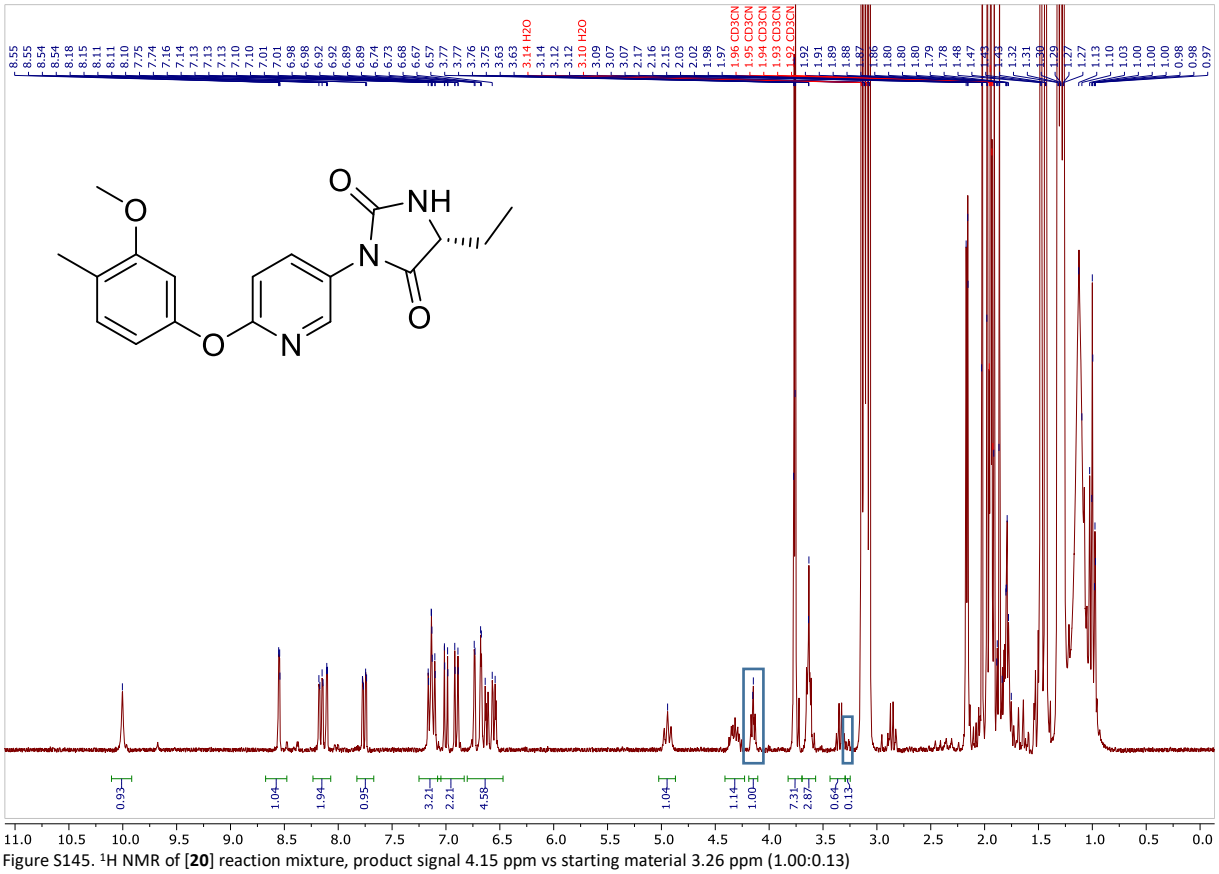


Figure S145. ^{1}H NMR of [**20**] reaction mixture, product signal 4.15 ppm vs starting material 3.26 ppm (1.00:0.13)

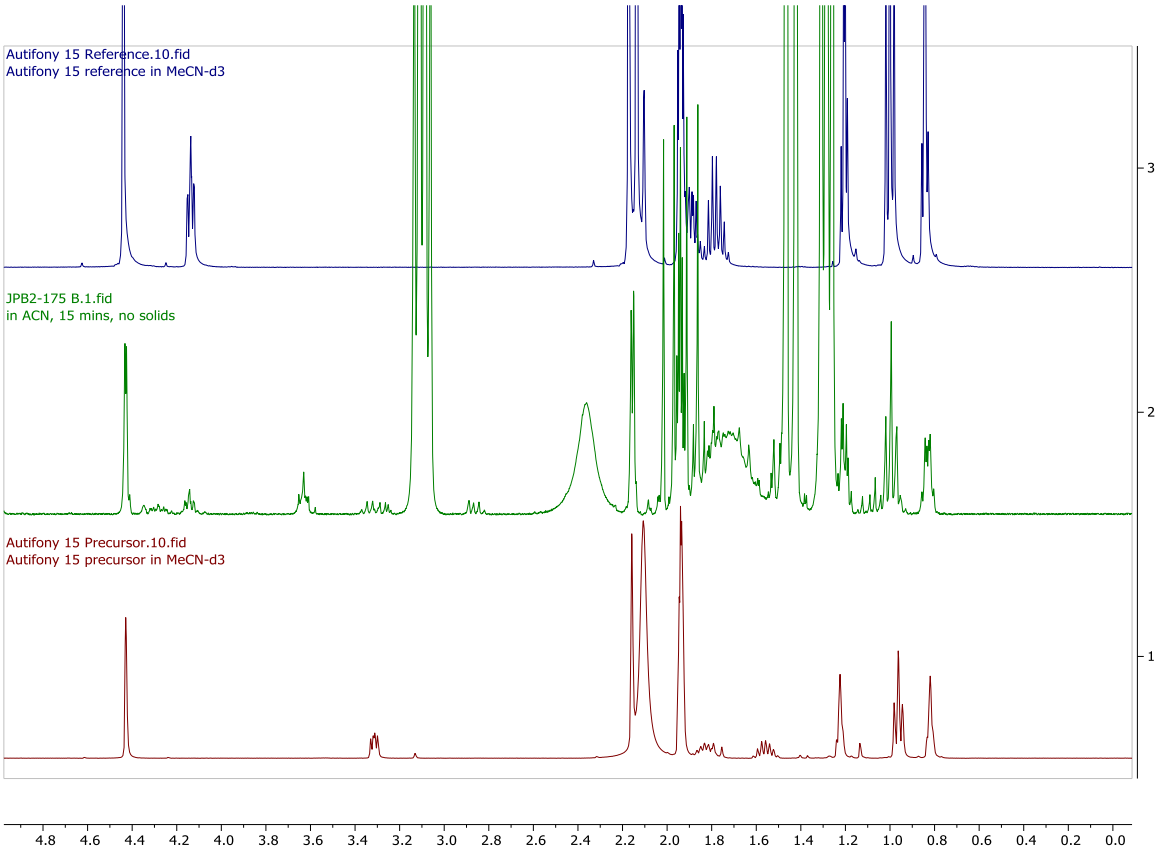


Figure S146. Comparison of Starting Material, Product, and Reaction Mixture for Compound **18** (Aut 15) in the aliphatic region. Spectrum 1: Starting Material Spectrum 2: Reaction Mixture Spectrum 3: Product

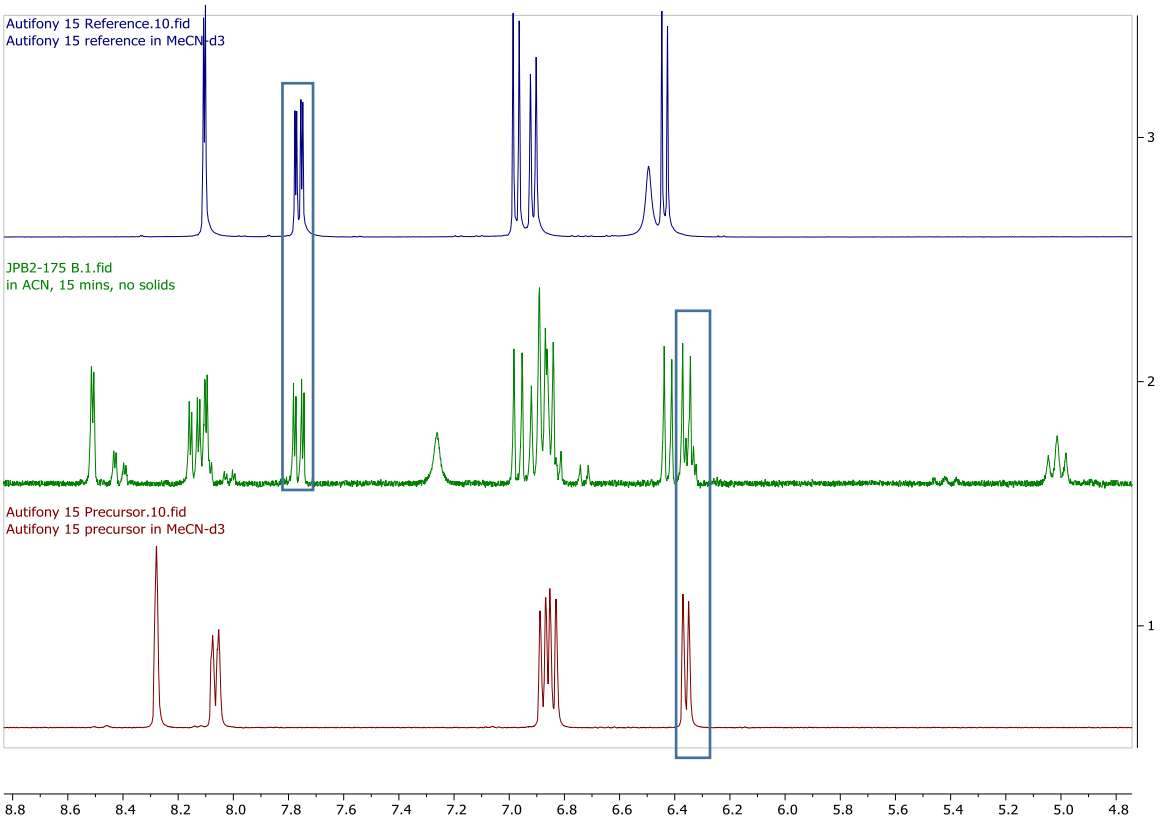


Figure S147. Comparison of Starting Material, Product, and Reaction Mixture for Compound **18** (Aut 15) in the aromatic region. Spectrum 1: Starting Material Spectrum 2: Reaction Mixture Spectrum 3: Product

6. References

[1] W.-W. du Mont, M. Bätcher, S. Pohl, W. Saak, *Angewandte Chemie International Edition in English* **1987**, *26*, 912-913.
[2] C. Jost, C. Nitsche, T. Scholz, L. Roux, C. D. Klein, *J Med Chem* **2014**, *57*, 7590-7599.
[3] W. Zhou, J. Xu, H. Zheng, H. Liu, Y. Li, D. Zhu, *The Journal of Organic Chemistry* **2008**, *73*, 7702-7709.
[4] WO2012076877, P. D. Giuseppe Alvaro, Anne Decor, Charles Large, Agostino Marasco, Simona Tommasi, **2011**.
[5] WO 2011069951, A. D. Giuseppe Alvaro, Stefano Fontana, Dieter Hamprecht, Charles Large, Agostino Marasco, **2010**.
[6] R. K. Olsen, W. J. Hennen, R. B. Wardle, *The Journal of Organic Chemistry* **1982**, *47*, 4605-4611.
[7] C. Li, X. Lu, Y. Yang, S. Yang, L. Zhang, *Tetrahedron Letters* **2018**, *59*, 2463-2466.