Electronic Supplementary Information

Dehydration of primary amides to nitriles in water. Late-stage functionalization and 1-pot multistep chemoenzymatic processes under micellar catalysis conditions

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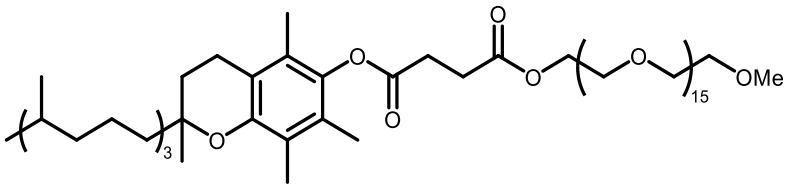
1. General Information

All commercial reagents were used without further purification unless otherwise noted. Organic solvents specified as dry and/or degassed such as THF or toluene were either taken from a solvent purification system (Pure-Solv 400, Innovative Technology, Inc. (now Inert, Inc.)), or degassed using a stream of bubbling argon for a minimum of 1 h and involved less than 25 mL of volume. All other solvents were used as received, such as MeOH, EtOAc, hexanes, and Et_2O, unless otherwise noted, and purchased from Fisher Scientific. Palladium acetate was purchased from Johnson Matthey and kept in its solid state within a glove box. Starting materials, such as carboxylic acids or primary amides, were purchased either from Millipore-Sigma or Combi-Blocks. The surfactant, TPGS-750-M, was prepared via a standard literature procedure,[1] or can be purchased from Millipore-Sigma (catalog #733857 for a 2 wt % solution of the wax dissolved in water). A standard 2 wt % aqueous solution of TPGS-750-M was typically prepared on a 100 g scale by dissolving 2 g of the wax into 98 g of thoroughly degassed (steady stream of argon, minimum of 1 h bubbling time with stirring) HPLC grade water in a 250 mL round bottomed flask equipped with a stir bar and allowed to dissolve overnight with vigorous stirring under argon pressure (**NOTE**: Do not attempt to degas the aqueous phase with surfactant wax submerged; vigorous foaming to the point of overflowing may occur). The 2 wt % TPGS-750-M/H_2O solution, once prepared, was kept under argon pressure at all times. Thin-layer chromatography (TLC) was performed using Silica Gel 60 F_{254} plates (Merck, 0.25 mm thick). Flash chromatography is either performed in glass columns or an automated Biotage system using Silica Gel 60 (Silicycle, 40-63 nm). ^1H and ^{13}C NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz, or on a Varian Unity Inova 600 MHz spectrometer in $CDCl_3$ with residual $CHCl_3$ (^1H = 7.26 ppm, ^{13}C = 77.16 ppm) or in DMSO-d_6 with residual $(CH_3)_2SO$ (^1H = 2.50 ppm, ^{13}C = 39.52 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). NMR Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets,

ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable), and integration. High-resolution mass analyses (HRMS) were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization.

[1] B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais and A. Krasovskiy, *J. Org. Chem.*, 2011, **76**, 4379–4391.



TPGS-750-M

2. General Procedures

General procedure A: Amide dehydration in water at 0.5 mmol scale with 0.8 mol % $Pd(OAc)_2$

A stock catalyst solution of was prepared by dissolving 4.5 mg of $Pd(OAc)_2$ into 500 µL of THF with gentle heating until an orange homogeneous solution had formed.

To a 1-dram vial containing a PTFE-coated magnetic stir bar was added oxone (30 mg, 0.1 mmol, 0.2 equiv) and the primary amide (0.5 mmol, 1.0 equiv). 2 wt % TPGS-750-M in H_2O (0.9 mL, 0.56 M) was then added, followed by either methoxyacetonitrile (300 µL, 8 equiv) or fluoroacetonitrile (250 µL, 8 equiv). A sample of the catalyst stock solution (100 µL) in THF was then added and the vial was sealed using a threaded cap and PTFE tape. The reaction was then allowed to stir vigorously (~1500 RPM) at 45 °C internal temperature (aluminum block reactor set to heat to 50 °C) until deemed complete by TLC. The aqueous phase was then extracted using EtOAc (3 x 1 mL) and dried directly onto SiO_2 to be purified via column chromatography.

Note: If DMSO is used as a co-solvent for the reaction, 10-20 v/v% of DMSO (compared to the total volume of water and THF) is added directly to the primary amide followed by heating with a heat gun until a change of the solid is noted, in many cases being liquefication. The TPGS-750-M solution, nitrile, and

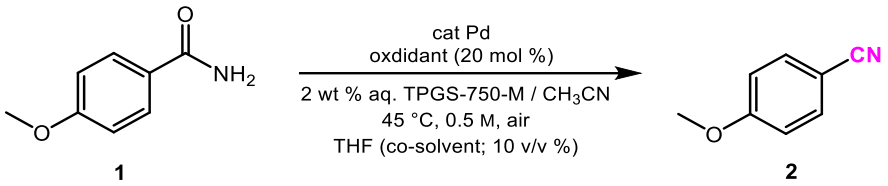
catalyst stock solution followed by oxone are then added quickly. The vial is then sealed and allowed to stir as described above.

General procedure B: Amide dehydration in water at 0.5 mmol scale with 1.0 mol % $Pd(OAc)_2$

A stock catalyst solution of was prepared by dissolving 5.6 mg of $Pd(OAc)_2$ into 500 µL of THF with gentle heating until an orange homogeneous solution had formed. The remainder of the experimental then follows General Procedure A.

3. Trials and Reaction Optimization

3.1 Initial trials using acetonitrile (or isobutyronitrile)/water



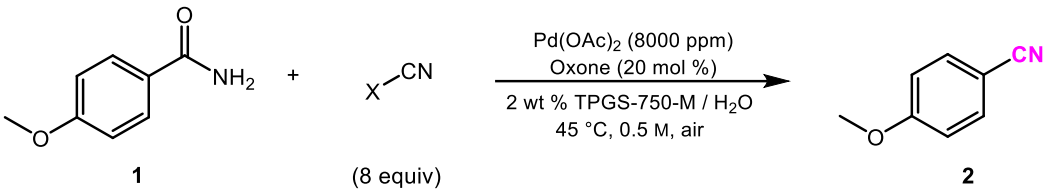
1 **2**

entry	Pd source	Pd loading (mol %)	aq. : org volume ratio[a]	nitrile (eq.)	[oxidant]	**2** (%)[b]
1	$Pd(OAc)_2$	10%	1:1 (no THF)	ACN (19)	Selectfluor	40
2	$Pd(OAc)_2$	1%	1:1 (no THF)	ACN (19)	Selectfluor	53
3	$Pd(OAc)_2$	10%	9:1 (no THF)	ACN (4)	Selectfluor	39
4	5% Pd/C	10%	1:1 (no THF)	ACN (19)	Selectfluor	47
5	$Pd(OAc)_2$	1%	9:1 (no THF)	ACN (4)	Selectfluor	49
6	5% Pd/C	0.2%	9:1	ACN (4)	Selectfluor	trace
7	$Pd(OAc)_2$	0.2%	9:1	ACN (4)	Selectfluor	77
8	$Pd(OAc)_2$	0.2%	9 (3 M NaCl):1	ACN (4)	Selectfluor	trace
9	$Pd(OAc)_2$	0.2%	4:1 (1.0 M)	ACN (4)	Selectfluor	77
10	$Pd(OAc)_2$	0.1%	9:1	ACN (4)	Selectfluor	75
11	$Pd(OAc)_2$	0.2%	9:1	ACN (4)	Air (none)	36
12	$Pd(OAc)_2$	0.2%	9:1	ACN (4)	Benzoquinone	trace
13	$Pd(OAc)_2$	0.4%	9:1	ACN (4)	Selectfluor	72
14	$Pd(OAc)_2$	0.2%	9:1	ACN (4)	O_2 (1 atm)	trace
15	$Pd(OAc)_2$	0.2%	9:1	ACN (4)	oxone	82
16	$Pd(OAc)_2$	0.2%	9:2	ACN (8)	Selectfluor	90
17	$Pd(OAc)_2$	0.2%	9:2	ACN (8)	oxone	85
18	$Pd[dtbpf]Cl_2$	0.2%	9:2	ACN (8)	oxone	85
19	$[Xantphos]PdCl_2$	0.2%	9:2	ACN (8)	oxone	93
20	$Pd(OAc)_2$	0.2%	9:1.75	Isobutyronitrile (4)	oxone	68
21	$Pd(OAc)_2$	0.2%	9:3.5	Isobutyronitrile (8)	oxone	85
22	$Pd(OAc)_2$	0.1%	9:3.5	Isobutyronitrile (8)	oxone	78
23[c]	$Pd(OAc)_2$	0.1%	9:3.5	Isobutyronitrile (8)	oxone	43
24[d]	$Pd(OAc)_2$	0.2%	9:3.5	Isobutyronitrile (8)	oxone	82
25[d]	$Pd(OAc)_2$	0.1%	9:3.5	Isobutyronitrile (8)	oxone	76
26	$Pd(OAc)_2$	0.2%	1:1	ACN (19)	oxone	97

[a] Run using 10 v/v% THF unless otherwise indicated. [b] Isolated yields. [c] Room temperature. [d] 70 °C.

The authors would like to note that, for this section, it was difficult to reproduce yields at 0.2 mol % and below for this specific model reaction. The reason, including the purity of the palladium source, was ultimately not resolved; thus more reproduceable and higher yielding trials were run using 0.8-1.0 mol % $Pd(OAc)_2$ in most of these studies reported (*vide infra*).

3.2 Nitrile additive screening

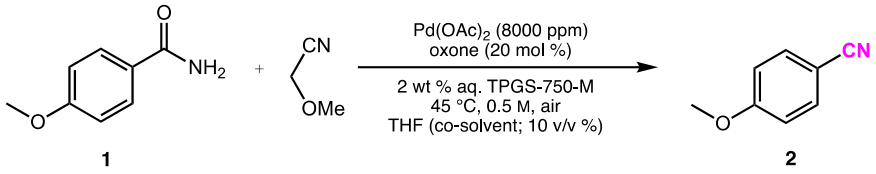


1 (8 equiv) **2**

entry	X	**2** (%)[a]
1	CH_2SMe	0
2	$CH_2N(Me)_2$	0
3	NH_2	<50[a]
4	CH_2CN	0
5	**CH_2OMe**	**97**
6	CH_2F	75
7	CH_2CF_3	90
8	$CHCl_2$	94
9	CH_2SO_2Me	40

Conditions: 0.5 mmol 4-methoxybenzamide, 4.0 mmol (8 equiv.) nitrile additive, 0.8 mol % $Pd(OAc)_2$, 20 mol % Oxone, 2 wt % TPGS-750-M/H_2O (0.5 M), THF (10 v/v %), 45 °C, 16 h, under air atmosphere. [a] Isolated yields

3.3 Effect of equivalences of nitrile additive

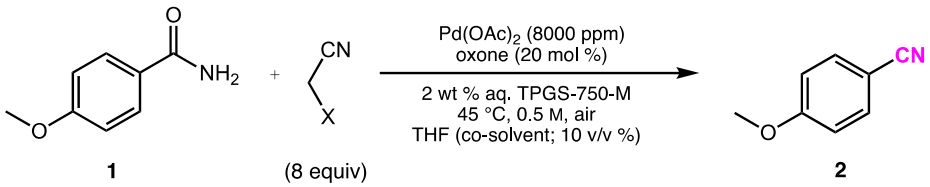


1 **2**

entry	$MeOCH_2CN$ (equiv)	**2** (%)[a]
1	6	72
2	7	86
3	**8**	**93**

Conditions: 0.5 mmol 4-methoxybenzamide, 0.8 mol % $Pd(OAc)_2$, 20 mol % oxone, 2 wt % TPGS-750-M/H_2O (0.5 M), 10 v/v% THF, 45 °C, 16 h, under air atmosphere. [a] Isolated yields.

3.4 Effect of Pd catalyst loading

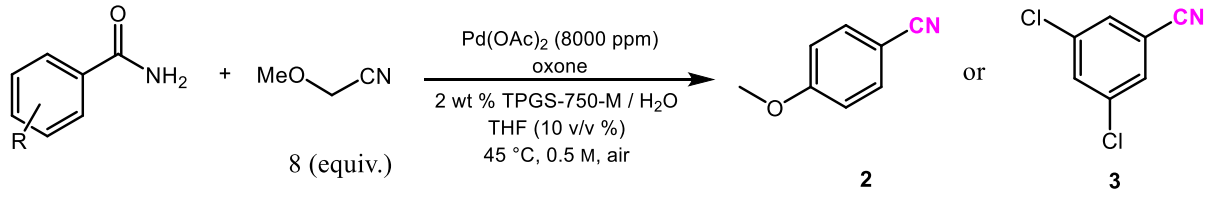


1 (8 equiv) **2**

entry	Pd loading (mol %)	X = OMe, **2** (%)[a]	X = Cl, **2** (%)[a]
1	**0.8**	**97**	**94**
2	0.6	89	-
3	0.4	95	85
4	0.2	trace	trace

Conditions: 0.5 mmol 4-methoxybenzamide, 4.0 (8 equiv.) nitrile additive, 20 mol % Oxone, 2 wt % TPGS-750-M/H_2O (0.5 M), THF (10 v/v %), 45 °C, 16 h, under air atmosphere. [a] Isolated yields.

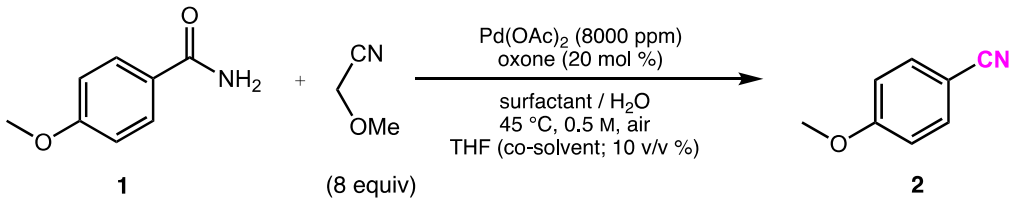
3.5 Effect of Oxone loading



entry	oxone (mol %)	**2** (%)[a]	**3** (%)[a]
1	1	78	86
2	5	-	90
3	10	94	87
4	**20**	**97**	**93**

Conditions: 0.5 mmol 4-methoxybenzamide, 4.0 mmol (8 equiv) methoxyacetonitrile, 0.8 mol % $Pd(OAc)_2$, 2 wt % TPGS-750-M/H_2O (0.5 M), THF (10 v/v %), 45 °C, 16 h, under air atmosphere. [a] Isolated yields

3.6 Effect of surfactant



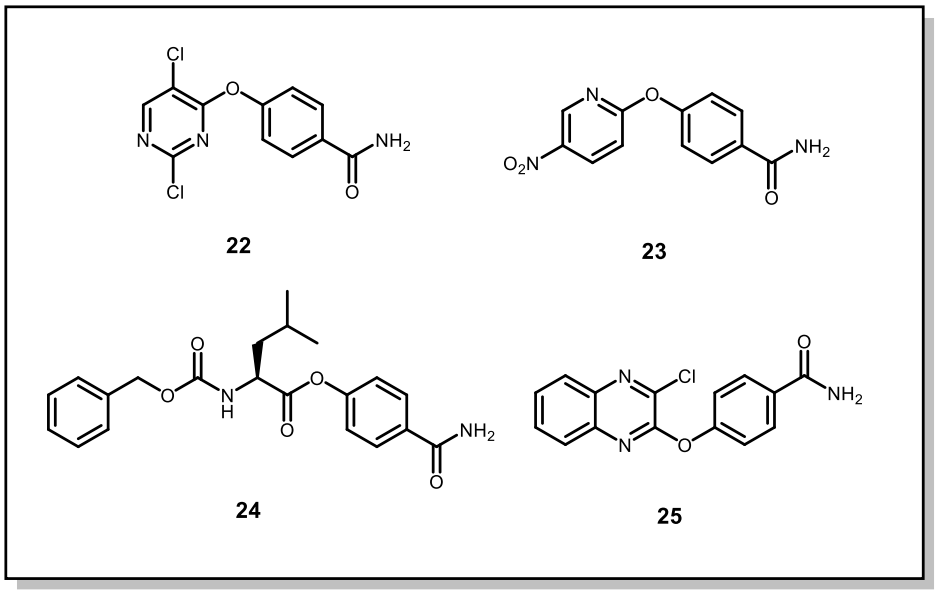
1 (8 equiv) 2

entry	amphiphile	**2** (%)[a]
1	**TPGS-750-M, 2 wt %**	**97**
2	PTS-1000, 5 wt %	90
3	Triton X-100, 2 wt %	89
4	Coolade, 2 wt %	80
5	Brij-30, 2 wt %	83
6	none (“on water”)	81

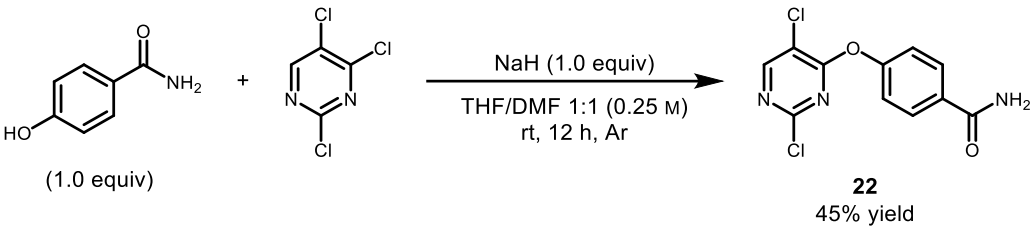
Conditions: 0.5 mmol 4-methoxybenzamide, 4.0 mmol (8 equiv) methoxyacetonitrile, 0.8 mol % $Pd(OAc)_2$, 20 mol % oxone, surfactant/H_2O (0.5 M), THF (10 v/v %), 45 °C, 16 h, under air. [a] Isolated yields

4. Results and Discussion

4.1 Synthesis of unreported starting materials

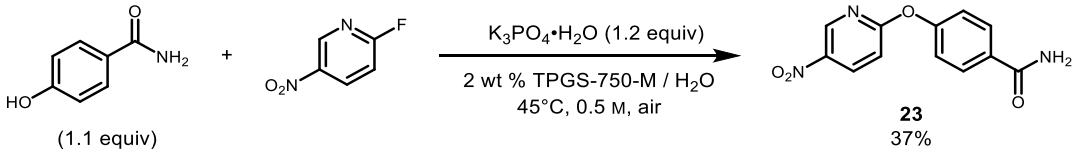


Synthesis of 4-((2,5-dichloropyrimidin-4-yl)oxy)benzonitrile (22)



To an oven-dried 100 mL round-bottom flask equipped with a PTFE-coated magnetic stir bar was added NaH (60% in mineral oil, 200 mg, 5.0 mmol, 1 equiv) in an argon-filled glovebox. The flask was sealed with a rubber septum, removed from the glove box, and adapted to a stir plate. In a separate 50 mL oven-dried pear-shaped flask, 4-hydroxybenzamide (685.7 mg, 5.0 mmol, 1 equiv) was dissolved in a 50:50 mixture of anhydrous THF and DMF (20 mL), then this solution was transferred via syringe to the flask containing NaH, with stirring, under a positive flow of argon. The solution was allowed to stir until bubbling ceased, then 2,4,5-trichloropyrimidine (0.573 mL, 5.0 mmol, 1 equiv) was added via syringe and the reaction was allowed to stir at rt overnight. Upon completion, the resulting solids were filtered off and 150 mL of DI water was added to the filtrate to precipitate the product **22**, which was collected via filtration, washed twice with 50 mL of water, then dried on vacuum overnight resulting in a white solid (599 mg, 45% yield). R_f = 0.38 (7:3 EtOAc/hexanes).

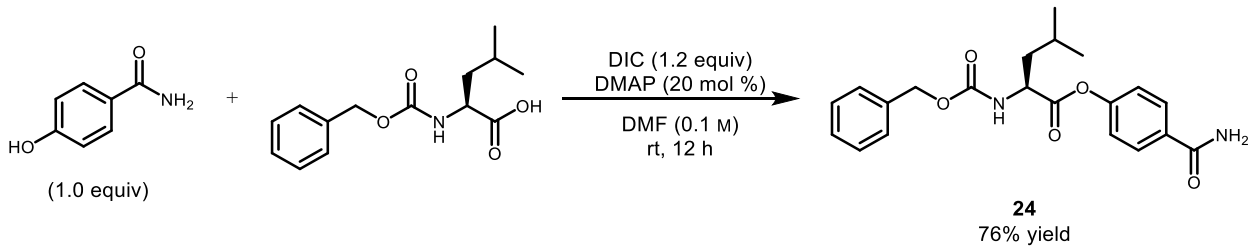
Synthesis of 4-((5-nitropyridin-2-yl)oxy)benzamide (23)



To a 25 mL round bottom flask equipped with a football-shaped stir bar was added 4-hydroxybenzamide (755 mg, 5.5 mmol, 1.1 equiv), 2-fluoro-5-nitropyridine (710 mg, 5.0 mmol, 1.0 equiv), and $K_3PO_4 \cdot H_2O$ (1400 mg, 6.0 mmol, 1.2 equiv). 2 wt % TPGS-750-M / H_2O (10 mL, 0.5 M) was

then added, and the flask was sealed using a rubber septum. The reaction mixture was then allowed to stir vigorously for 12 h in a 50 °C oil bath (45 °C internal temperature). The reaction mixture was then diluted in water (50 mL) and extracted with EtOAc (3 x 50 mL). The crude product mixture was then purified by column chromatography (eluent: 75% EtOAc/25% hexanes) and was ultimately recrystallized in hot EtOH to result in product as white crystals (480 mg, 37% yield). R_f = 0.35 (3:1 EtOAc/hexanes).

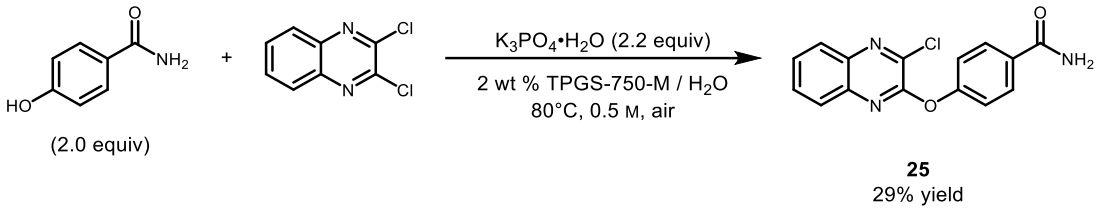
Synthesis of 4-carbamoylphenyl ((benzyloxy)carbonyl)-L-leucinate (24)



24
76% yield

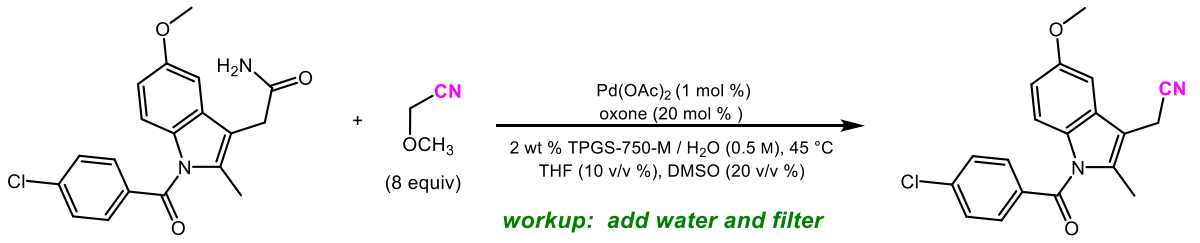
To a 1-dram vial equipped with a PTFE-coated magnetic stir bar was added Z-leu-OH (132.7 mg, 0.5 mmol, 1 equiv) and 4-hydroxybenzamide (68.6 mg, 0.5 mmol, 1 equiv) which were then dissolved in DMF (3 mL). Once dissolved, diisopropylcarbodiimide (94 µL, 0.6 mmol, 1.2 equiv) and DMAP (12.2 mg, 0.1 mmol, 0.2 equiv) were added and the reaction was allowed to stir at rt overnight. Upon completion, as determined by TLC, the reaction mixture was filtered through cotton and the product was precipitated with water (15 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with water (2 x 3 mL), brine (2 mL), and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (eluent: 0-100% EtOAc/hexanes gradient) resulting in a white solid (146.1 mg, 76% yield). R_f = 0.34 (7:3 EtOAc/hexanes, CAM stain).

Synthesis of 4-((3-chloroquinoxalin-2-yl)oxy)benzamide (25)



To a 25 mL round bottomed flask equipped with a football-shaped stir bar was added 4-hydroxybenzamide (1000 mg, 7.3 mmol, 2.0 equiv), 2,3-dichloroquinoxaline (730 mg, 3.67 mmol, 1.0 equiv), and $K_3PO_4 \cdot H_2O$ (1850 mg, 7.94 mmol, 2.2 equiv). 2 wt % TPGS-750-M / H_2O (7.5 mL, 0.5 M) was then added and the flask was sealed using a rubber septum. The reaction mixture was then allowed to stir vigorously for 48 h in a 90 °C oil bath (80 °C internal temperature). The crude product was then slurried with 2 M NaOH (50 mL), filtered, and washed with 1 M HCl. The filtrate was then slurried in EtOH, heated to reflux, and filtered hot to result in product as a white solid (314.5 mg, 29% yield). R_f = 0.31 (3:1 EtOAc/hexanes).

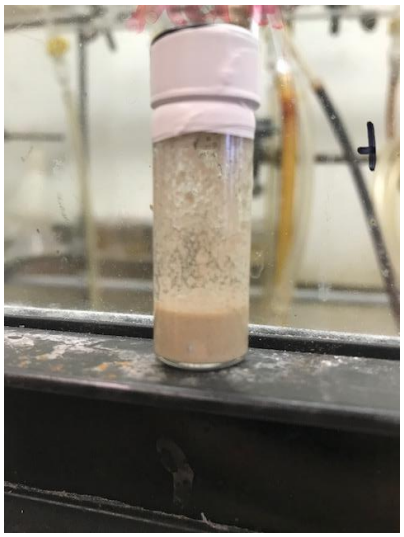
4.2 E Factor evaluation



To a 1-dram vial was added 5.6 mg of $Pd(OAc)_2$ and THF (500 µL). The mixture was then gently heated using a heat gun until a homogeneous mixture had formed resulting in the catalyst stock solution.

To a separate 1-dram vial equipped with a Teflon coated stir bar was added the amide (89.0 mg, 0.25 mmol, 1 equiv) followed by DMSO (100 µL, 20 v/v %). The resulting slurry was then heated with a heat gun until a homogeneous liquid formed. Very quickly after liquefication, methoxyacetonitrile (143.4 mg, 150 µL, 2.0 mmol, 8 equiv), 50 µL of the catalyst stock solution (1 mol % Pd), and 2 wt % TPGS-750-M / H_2O (450 µL) was added followed by oxone (16 mg, 0.05 mmol, 20 mol %). This mixture was then stirred with a metal spatula until a mixture that could be stirred was achieved, and the vial was sealed using a screw cap followed by Teflon tape under air. The resulting slurry was then allowed to stir vigorously (~1500 RPM) in an aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C).

TLC of reaction for E Factor evaluation



E Factor reaction prior to dilution and filtration

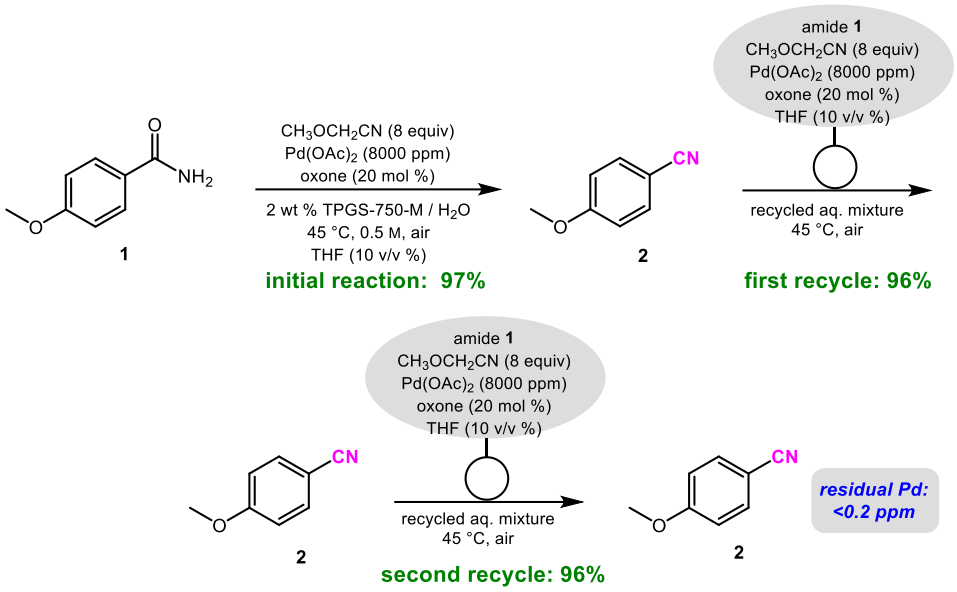
The resulting grey reaction mixture was then cooled to rt and water (4 mL) was then added and the product mixture stirred for 5 min. The suspension was then filtered, washed with water (10 mL), and allowed to dry under suction overnight resulting in product as a grey solid (70.1 mg, 83% yield).

E Factor = (mass waste organics) / (mass product)

= ($mass_{MeOACN}$ + $mass_{2\text{-}MeOAcetamide}$ + $mass_{DMSO}$ + $mass_{THF}$) / ($mass_{product}$)

= (138.4+22.3+90.9+44.4) / 70.1 = 4.22

4.3 Aqueous recycling study



To a 1-dram vial was added 4.5 mg of $Pd(OAc)_2$ and THF (500 µL). The mixture was then gently heated using a heat gun until a homogeneous solution had formed resulting in the catalyst stock solution.

Initial reaction: To a 1-dram vial equipped with a Teflon coated stir bar was added benzamide **1** (75 mg, 0.5 mmol) and oxone (30 mg, 0.1 mmol, 20 mol %). 2 wt % TPGS-750-M (900 µL), methoxyacetonitrile (300 µL, 4 mmol, 8 equiv), and 100 µL of the catalyst stock solution (0.8 mol % Pd) was then added and the vial was sealed under air using a threaded cap followed by Teflon tape. The resulting slurry was then allowed to stir vigorously (~1500 RPM) in an aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) overnight. The contents of the vial were then extracted using methyl *t*-butyl ether (MTBE; 3 x 1.0 mL). The combined organics were then dried onto SiO_2 and purified via column chromatography (20% EtOAc/hexanes) and the product was dried under high vacuum to result in a white solid (64.3 mg, 97% yield).

First recycle: To the 1-dram vial containing the 2 wt % TPGS-750-M aqueous phase used for the previous reaction (and extracted with MTBE) was added fresh benzamide **1** (75 mg, 0.5 mmol) and oxone (30 mg, 0.1 mmol, 20 mol %). Fresh methoxyacetonitrile (300 µL, 4 mmol, 8 equiv) and 100 µL of the catalyst stock solution (0.8 mol % Pd) was then added and the vial was sealed under air using a threaded cap followed by Teflon tape. The resulting slurry was then allowed to stir vigorously (~1500 RPM) in an aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) overnight. The contents of the vial were then extracted using methyl *t*-butyl ether (MTBE; 1.0 mL x 3). The combined organics were then dried onto SiO_2 and purified via column chromatography (20% EtOAc/hexanes) and the product was dried under high vacuum to result in a white solid (63.4 mg, 96% yield).

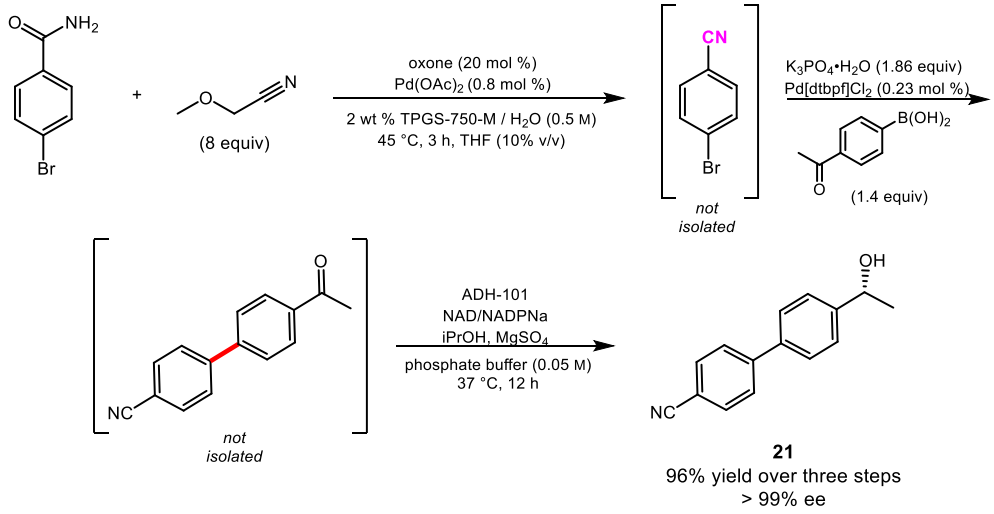
Second recycle: To the 1-dram vial containing the 2 wt % TPGS-750-M aqueous phase used for the previous two reactions (and extracted with MTBE twice) was added fresh benzamide **1** (75 mg, 0.5 mmol) and oxone (30 mg, 0.1 mmol, 20 mol %). Fresh methoxyacetonitrile (300 µL, 4 mmol, 8 equiv), and 100 µL of the catalyst stock solution (0.8 mol % Pd) was then added and the vial was sealed under air using a threaded cap followed by Teflon tape. The resulting slurry was then allowed to stir vigorously (~1500 RPM) in an aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) overnight. The contents of the vial were then extracted using methyl *t*-butyl ether (MTBE; 1.0 mL x 3). The combined organics were then dried onto SiO_2 and purified via column chromatography (20% EtOAc/hexanes) and the product was dried under high vacuum to result in a white solid (63.5 mg, 96% yield).

At this point, the aqueous phase had become too saturated with salts (see picture) and much of the water had been lost due to small scale extraction.

Aqueous phase after two recycling steps

4.4 Multi-step, 1-pot chemoenzymatic sequence

4.4 A: Procedure for multi-step, 1-pot chemoenzymatic sequence in water: synthesis of 21



To a 1-dram vial was added 4.5 mg of $Pd(OAc)_2$ and THF (500 µL). The mixture was then gently heated using a heat gun until a homogeneous solution had formed resulting in the catalyst stock solution.

To a 1-dram vial equipped with a Teflon coated stir bar was added 4-bromobenzamide (107 mg, 0.535 mmol, 1 equiv) and oxone (33 mg, 0.11 mmol, 20 mol %). 2 wt % TPGS-750-M / H_2O (900 µL), methoxyacetonitrile (300 µL, 4.5 mmol, 8 equiv), and 100 µL of the catalyst stock solution was then added and the vial was sealed under air using a threaded cap followed by Teflon tape. The resulting slurry was allowed to react for 3 h at 45 °C internal temperature where the reaction was deemed complete by TLC and the mixture had become homogeneous. This mixture was then carried through to the next step without isolation or workup.

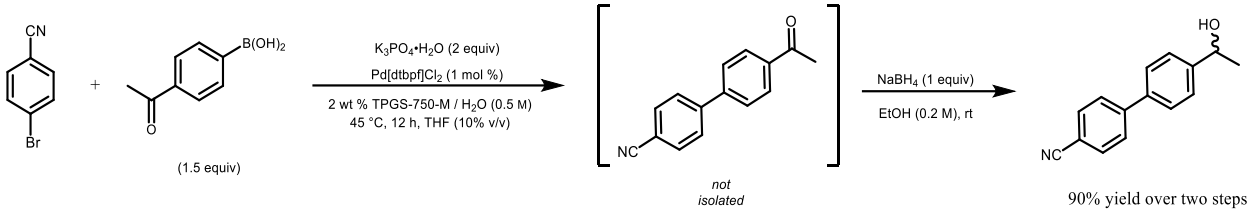
To the vial containing the dehydration product mixture was added 4-acetylphenylboronic acid (123 mg, 0.75 mmol, 1.4 equiv) and $K_3PO_4 \cdot H_2O$ (233 mg, 1.0 mmol, 1.87 equiv). The vial was sealed using a rubber septum and the headspace of the vial was then purged with argon for 10 min with constant stirring. In a separate vial was added 1.6 mg of Pd[dtbpf]Cl_2 which was taken up in 200 µL of dry, degassed toluene. To the argon purged reaction vial was then added 100 µL of this catalyst stock solution (0.8 mg Pd[dtbpf]Cl_2, 1.25 x 10^{-3} mmol, 2300 ppm Pd). The contents of the vial were allowed to stir vigorously (~1500 RPM) overnight at 45 °C internal temperature until deemed complete by TLC. This mixture was then carried through to the next step without isolation or workup.

To a 20 mL scintillation vial equipped with a Teflon coated stir bar was added NAD^+ (6.5 mg), $NADP^+$ (6.0 mg), $MgSO_4$ (2 mg), and ADH-101 (50 mg). The solids were then taken up in 2 wt % TPGS-750-M in 0.23 M phosphate buffer in H_2O (5.0 mL)[2] and allowed to stir for 5 min. The contents of the previous reaction vial containing the Suzuki-Miyaura product were then transferred to the 20 mL scintillation vial and the previous vial washed with 4.0 mL of the 2 wt % TPGS-750-M phosphate buffer solution in H_2O. The vial was then heated in a 20 mL scintillation vial aluminum block heater set to 37.5 °C, and the contents were stirred at ~750 RPM. This reaction was allowed to run overnight until deemed complete by TLC analysis. The contents of the vial were then extracted using EtOAc (3 x 5 mL), dried onto SiO_2, and purified via

column chromatography (45% EtOAc/55% hexanes) resulting in product as a white solid (114.5 mg, 96% yield, >99% ee).

[2] N. Akporji, V. Singhania, J. Dussart-Gautheret, F. Gallou and B. H. Lipshutz, *Chem. Commun.*, **2021**, *57*, 11847–11850.

4.4 B: Procedure: racemic 21

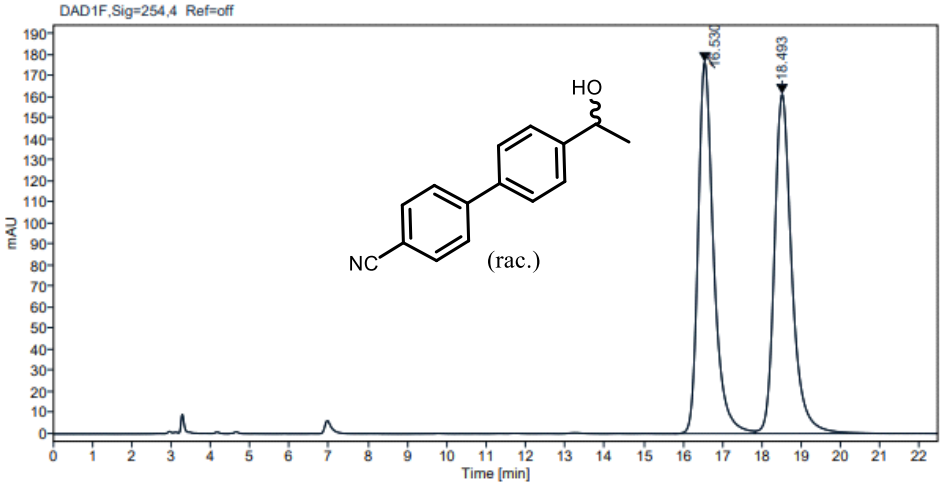


To a 1-dram vial equipped with a Teflon coated stir bar was added Pd[dtbpf]Cl_2 (3.2 mg, 0.005 mmol, 1 mol %), 4-bromobenzonitrile (91 mg, 0.5 mmol, 1.0 equiv), 4-acetylphenylboronic acid (123 mg, 0.75 mmol, 1.5 equiv), and $K_3PO_4 \cdot H_2O$ (233 mg, 1.0 mmol, 2.0 equiv). The headspace of the vial was then evacuated and backfilled with argon three times. 2 wt % TPGS-750-M / H_2O (900 µL) and degassed toluene (100 µL) were then added. The contents of the vial were then allowed to stir vigorously (~1500 RPM) in an aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) overnight under argon pressure.

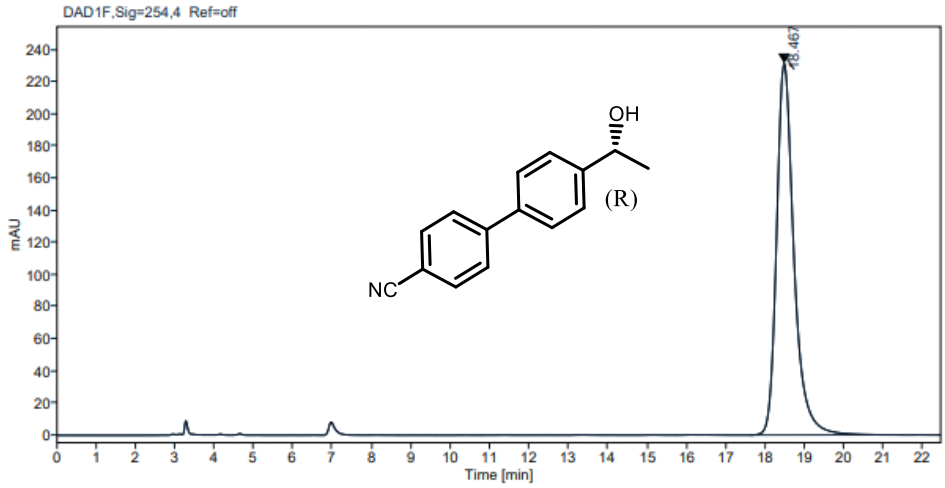
The aqueous phase was then extracted with EtOAc (3 x 1 mL). The combined organics were placed in a 10 mL round bottomed flask and evaporated. EtOH (2.5 mL) was then added followed by $NaBH_4$ (19 mg, 0.5 mmol, 1.0 equiv). This mixture was allowed to react at rt for 2 h until deemed complete by TLC analysis. The solvent was removed under vacuum and the crude organics were dried onto SiO_2 and purified via column chromatography (45% EtOAc/55% hexanes) to result in the racemic product as a white solid (99.7 mg, 90% yield).

4.4 C: HPLC chromatographs for ee(%) determination of (*R*)-4'-(1-hydroxyethyl)-[1,1'-biphenyl]-4-carbonitrile (21)

HPLC: Chiracel AD-H, detected at 254 nm, eluent *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, 25 °C.[3]



Signal:	DAD1F,Sig=254,4	Ref=off
RT [min]	**Area**	**Area%**
16.530	4849.3089	49.6503
18.493	4917.6284	50.3497
Sum	9766.9374	



Signal:	DAD1F,Sig=254,4	Ref=off
RT [min]	**Area**	**Area%**
18.467	7047.6374	100.0000
Sum	7047.6374	

[3] X. Shu, R. Jin, Z. Zhao, T. Cheng and G. Liu, *Chem. Commun.* **2018,** *54*, 13244–13247.

4.5: ICP-MS data for residual palladium

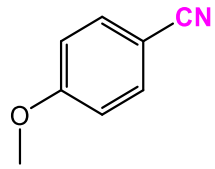
ICP-MS data for residual Pd was obtained from University of California, Los Angeles ICP-MS Core Facility.

		Palladium		**Source**
		[µg/g]		
Sample #	Sample weight in analysis [mg]	Average*	stdev	
ABW.04.259	18.10	0.177	0.004	Second recycle product
ABW.04.263	14.50	3.592	0.030	Multi-step, final product

**Each sample was done in triplicated measurements with background correction.*
n/a represents below detection limit.

5. Analytical Data

Synthesis of 4-methoxybenzonitrile (2)



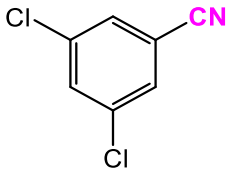
Compound **2** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (64.5 mg, 97% yield). R_f = 0.31 (1:4 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8, 134.0, 119.2, 114.7, 103.9, 55.5.

Spectral data matched those previously reported.[4]

Synthesis of 3,5-dichlorobenzonitrile (3)



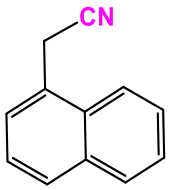
Compound **3** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 10% EtOAc/90% hexanes) to provide the desired compound as a white solid (80.1 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, J = 1.8 Hz, 1H), 7.53 (d, J = 1.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.3, 133.5, 130.4, 116.3, 115.1.

Spectral data matched those previously reported.[5]

Synthesis of 2-(naphthalen-1-yl)acetonitrile (4)



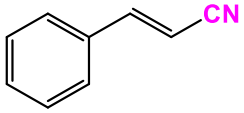
Compound **4** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a yellow oil (76.0 mg, 94% yield). R_f = 0.29 (1:4 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.65 – 7.53 (m, 3H), 7.51 – 7.44 (m, 1H), 4.11 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 133.8, 130.8, 129.2, 129.1, 127.2, 126.5, 126.5, 125.8, 125.6, 122.5, 117.8, 21.8.

Spectral data matched those previously reported.[6]

Synthesis of cinnamonitrile (5)



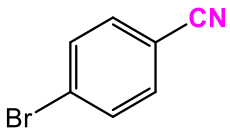
Compound **5** was obtained using the General Procedure A using fluoroacetonitrile on a 0.5 mmol scale, in this case only requiring 0.2 mol % (2000 ppm) $Pd(OAc)_2$. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a yellow oil (62.7 mg, 98% yield). R_f = 0.86 (2:3 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.34 (m, 6H), 5.88 (d, *J* = 16.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.6, 133.5, 131.2, 129.1, 127.4, 118.2, 96.3.

Spectral data matched those previously reported.[7]

Synthesis of 4-bromobenzonitrile (6)



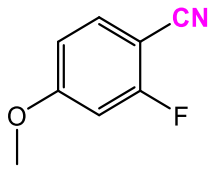
Compound **6** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (85.1 mg, 94% yield). R_f = 0.59 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 133.5, 132.7, 128.1, 118.1, 111.4.

Spectral data matched those previously reported.[4]

Synthesis of 2-fluoro-4-methoxybenzonitrile (7)



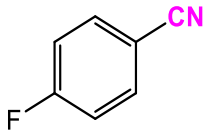
Compound **7** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 50% EtOAc/50% hexanes) to provide the desired compound as a yellow solid (72.7 mg, 96% yield). R_f = 0.52 (1:1 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 8.7, 7.4 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.70 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 164.8, 164.7, 163.3, 134.2 (d, *J* = 2.3 Hz), 114.4, 111.3 (d, *J* = 2.7 Hz), 102.3 (d, *J* = 22.9 Hz), 93.0 (d, *J* = 15.6 Hz), 56.0.

Spectral data matched those previously reported.[8]

Synthesis of 4-fluorobenzonitrile (8)



Compound **8** was obtained using the General Procedure A using methoxyacetonitrile on a 2.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 15% Et_2O/85% hexanes) to provide the desired compound as white crystals (198 mg, 66% yield) which sublimate on high vacuum. R_f = 0.34 (1:9 EtOAc/hexanes).

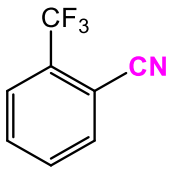
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 – 7.62 (m, 2H), 7.21 – 7.12 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1 (d, *J* = 256.7 Hz), 134.7 (d, *J* = 9.5 Hz), 118.1, 116.9 (d, *J* = 22.5 Hz), 108.6 (d, *J* = 3.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -102.5.

Spectral data matched those previously reported.[9]

Synthesis of 2-(trifluoromethyl)benzonitrile (9)



Compound **9** was obtained using the General Procedure A using methoxyacetonitrile on a 2.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 25 Et_2O/75 hexanes) to provide the desired compound as a yellow oil (301.2 mg, 71% yield). R_f = 0.34 (1:4 EtOAc/hexanes).

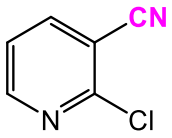
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.4 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.70 (td, *J* = 7.4, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.7, 133.0, 132.6 (q, *J* = 32.8 Hz), 132.4, 126.7 (q, *J* = 4.8 Hz), 126.5 – 118.1 (m), 115.5, 110.0 (q, *J* = 2.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.1.

Spectral data matched those previously reported.[10]

Synthesis of 2-chloronicotinonitrile (10)



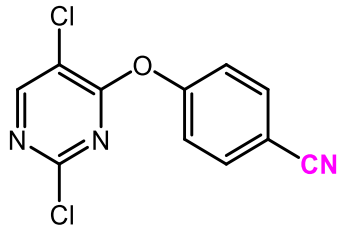
Compound **10** was obtained using the General Procedure B using fluoroacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 50% Et_2O/50% pentanes) to provide the desired compound as a white solid (53.5 mg, 77% yield). R_f = 0.52 (1:1 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (dd, *J* = 4.9, 1.9 Hz, 1H), 8.01 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.40 (dd, *J* = 7.7, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.9, 152.8, 142.6, 122.2, 114.6, 110.9.

Spectral data matched those previously reported.[11]

Synthesis of 4-((2,5-dichloropyrimidin-4-yl)oxy)benzonitrile (11)



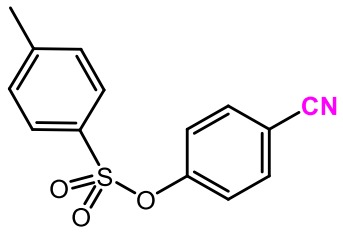
Compound **11** was obtained using the General Procedure B using fluoroacetonitrile on a 0.5 mmol scale with 10 v/v% DMSO. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (70.3 mg, 53% yield). R_f = 0.35 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.3, 158.9, 157.4, 154.6, 134.1, 122.6, 118.0, 117.1, 110.5.

HRMS (CI): *m/z* calcd for $C_{11}H_5Cl_2N_3O^+$: 264.9810 $[M]^+$; found 264.9801.

Synthesis of 4-cyanophenyl 4-methylbenzenesulfonate (12)



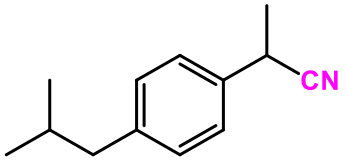
Compound **12** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (132.9 mg, 97% yield). R_f = 0.27 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.67 (m, 2H), 7.64 – 7.55 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.08 (m, 2H), 2.44 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.6, 146.2, 133.9, 131.8, 130.1, 128.4, 123.4, 117.8, 111.2, 21.8.

Spectral data matched those previously reported.[12]

Synthesis of 2-(4-isobutylphenyl)propanenitrile (13)



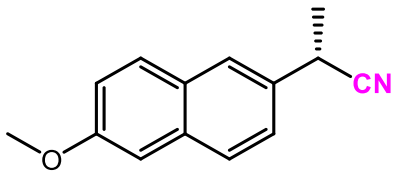
Compound **13** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 5% EtOAc/95% hexanes) to provide the desired compound as a light-yellow oil (72.2 mg, 77% yield). R_f = 0.36 (5:95 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 3.87 (q, J = 7.3 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.86 (m, 1H), 1.63 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.8, 134.5, 130.0, 126.6, 122.0, 45.2, 31.1, 30.4, 22.5, 21.6.

Spectral data matched those previously reported.[13]

Synthesis of (S)-2-(6-methoxynaphthalen-2-yl)propanenitrile (14)



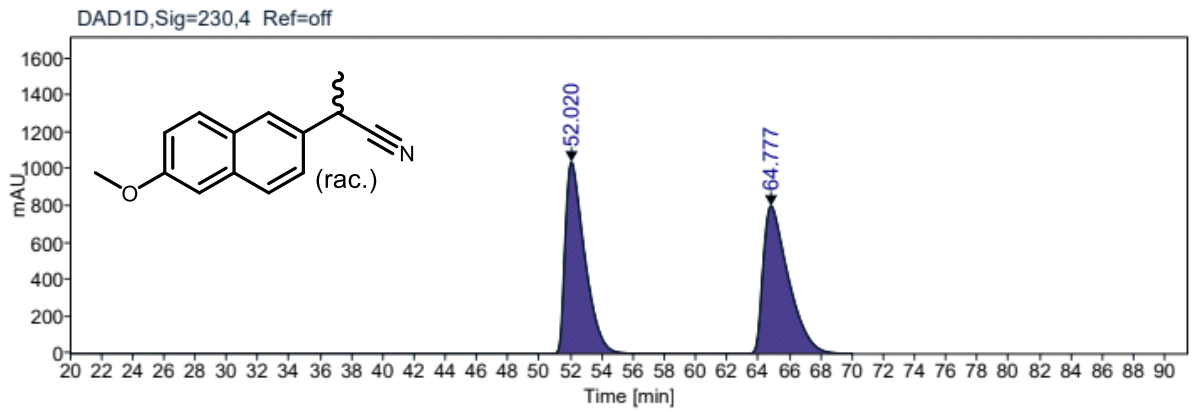
Compound **14** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (104.3 mg, 99% yield) with >99% ee. R_f = 0.66 (1:1 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.67 (m, 3H), 7.39 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.19 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 1.71 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 134.0, 132.0, 129.3, 128.8, 127.9, 125.4, 124.9, 121.8, 119.6, 105.6, 55.3, 31.2, 21.4.

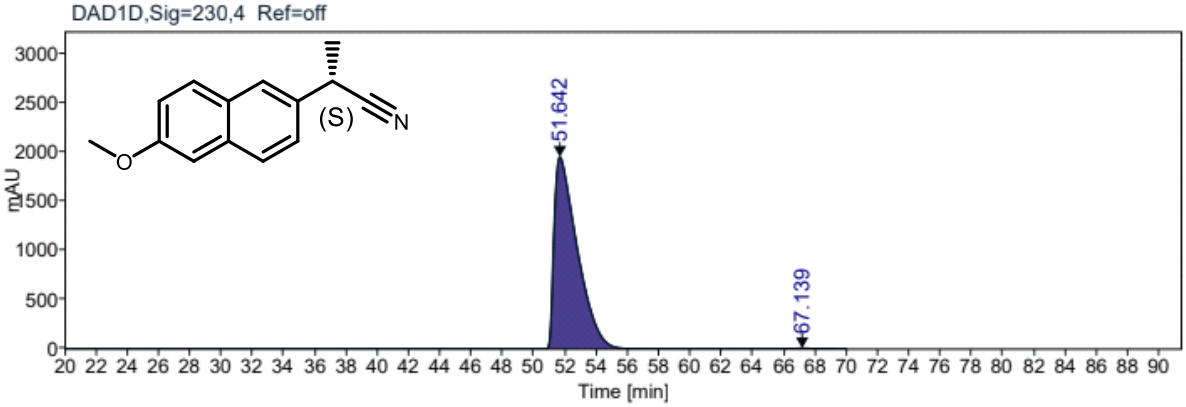
Spectral data matched those previously reported.[14]

Enantiopure (>99% ee) starting material was used, and the enantiomeric excess of the product was obtained with respect to a racemic standard (Chiralcel OJ-H column, 4.6 x 250 mm, 5-micron, hexane/isopropanol 95:5, 1.0 mL/min flow rate, 230 nm detection).



Signal: DAD1D,Sig=230,4 Ref=off

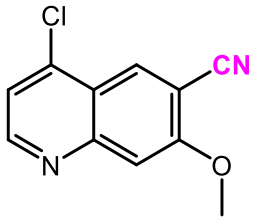
RT [min]	Area	Area%
3.174	57.6642	0.0
3.982	22.1529	0.0
7.624	245.2120	0.1
52.020	89651.9304	49.9
64.777	89785.6813	49.9
Sum	179762.6408	



Signal: DAD1D,Sig=230,4 Ref=off

RT [min]	Area	Area%
3.172	82.8626	0.0
3.983	17.9895	0.0
7.638	233.5197	0.1
51.642	200958.9668	99.3
67.139	1076.1807	0.5
Sum	202369.5194	

Synthesis of 4-chloro-7-methoxyquinoline-6-carbonitrile (15)



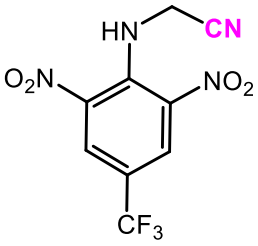
Compound **15** was obtained using the General Procedure B using fluoroacetonitrile on a 0.25 mmol scale with 20 v/v % DMSO. The crude product was purified by silica gel column chromatography (eluent: 70% EtOAc/30% hexanes) to provide the desired compound as a light-yellow solid (47.6 mg, 87% yield). R_f = 0.47 (7:3 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 4.8 Hz, 1H), 8.53 (s, 1H), 7.51 (s, 1H), 7.44 (d, *J* = 4.8 Hz, 1H), 4.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1, 153.3, 151.9, 143.3, 132.5, 121.1, 120.8, 115.6, 108.9, 105.7, 56.8.

HRMS (CI): *m/z* calcd for $C_{11}H_7ClN_2O+H^+$: 219.0320 $[M+H]^+$: found 219.0325.

Synthesis of 2-((2,6-dinitro-4-(trifluoromethyl)phenyl)amino)acetonitrile (16)



Compound **16** was obtained using the General Procedure B using fluoroacetonitrile on a 0.25 mmol scale with 20 v/v % DMSO. The crude product was purified by silica gel column chromatography (eluent: 15% EtOAc/85% hexanes) to provide the desired compound as a yellow solid (30.6 mg, 42% yield). R_f = 0.28 (15:85 EtOAc/hexanes).

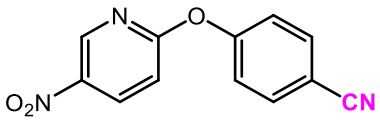
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (t, *J* = 5.9 Hz, 1H), 8.58 (s, 2H), 4.23 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.8, 138.7, 129.8 (q, *J* = 3.4 Hz), 122.2 (q, *J* = 272.7 Hz), 120.4 (q, *J* = 36.4 Hz), 113.8, 34.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4.

HRMS (EI): *m/z* calcd for $C_9H_5F_3N_4O_4^+$: 290.0263 $[M]^+$; found 290.0251.

Synthesis of 4-((5-nitropyridin-2-yl)oxy)benzonitrile (17)



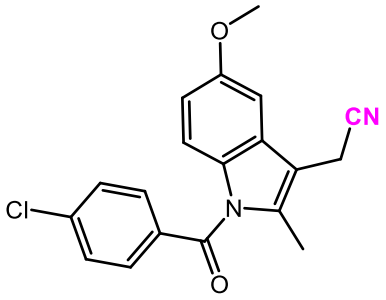
Compound **17** was obtained using the General Procedure A using methoxyacetonitrile on a 0.5 mmol scale with 10 v/v % DMSO. The crude product was purified by silica gel column chromatography (eluent: 20-70% EtOAc/hexanes gradient) to provide the desired compound as an off-white solid (120.0 mg, quant.). R_f = 0.29 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (d, *J* = 2.9 Hz, 1H), 8.54 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.34 – 7.27 (m, 2H), 7.15 (dd, *J* = 9.0, 0.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 156.0, 144.7, 141.0, 135.4, 134.0, 122.6, 118.2, 112.1, 109.7.

HRMS (CI): *m/z* calcd for $C_{12}H_7N_3O_3^+$: 241.0487 $[M]^+$: found 241.0497.

Synthesis of 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetonitrile (18)



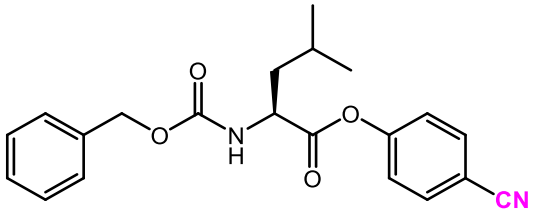
Compound **18** was obtained using the General Procedure A using methoxyacetonitrile on a 0.25 mmol scale with 20 v/v % DMSO. The crude product was purified by silica gel column chromatography (eluent: 40% EtOAc/60% hexanes with 0.5 % AcOH) to provide the desired compound as a white solid (72.8 mg, 86% yield). R_f = 0.59 (1:1 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 6.98 (s, 1H), 6.83 (d, *J* = 9.1 Hz, 1H), 6.71 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 2H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 156.3, 139.8, 136.0, 133.4, 131.4, 130.7, 129.3, 129.1, 117.1, 115.2, 112.5, 108.1, 100.5, 55.8, 13.2, 13.1.

Spectral data matched those previously reported.[14]

Synthesis of 4-cyanophenyl ((benzyloxy)carbonyl)-*L*-leucinate (19)



Compound **19** was obtained using the General Procedure A using methoxyacetonitrile on a 0.25 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 25% EtOAc/75%

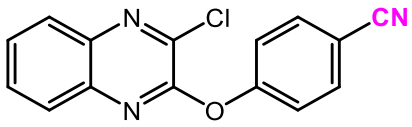
hexanes) to provide the desired compound as a white solid (91.4 mg, 99% yield). R_f = 0.21 (15:85 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.44 – 7.29 (m, 5H), 7.23 (d, *J* = 8.6 Hz, 2H), 5.15 (m, 3H), 4.60 (td, *J* = 8.9, 4.3 Hz, 1H), 1.81 (m, 2H), 1.70 (m, 1H), 1.01 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 156.2, 153.9, 136.2, 133.9, 128.8, 128.5, 128.4, 122.8, 118.3, 110.3, 67.5, 53.0, 41.4, 25.1, 23.1, 22.0.

HRMS (ESI): *m/z* calcd for $C_{21}H_{22}N_2O_4$+Na^+: 389.1472 [*M*+Na]$^+$; found 389.1477.

Synthesis of 4-((3-chloroquinoxalin-2-yl)oxy)benzonitrile (20)



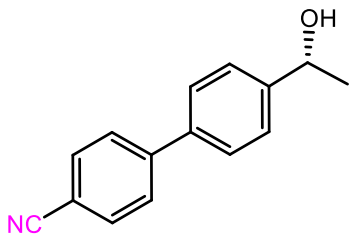
Compound **20** was obtained using General Procedure B using fluoroacetonitrile on a 0.25 mmol scale with 20 v/v % DMSO. The crude product was purified by silica gel column chromatography (eluent: 20% EtOAc/80% hexanes) to provide the desired compound as a white solid (20.7 mg, 29% yield). R_f = 0.45 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 – 7.98 (m, 1H), 7.82 – 7.77 (m, 2H), 7.77 – 7.73 (m, 1H), 7.73 – 7.66 (m, 2H), 7.48 – 7.42 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9, 151.8, 139.6, 138.9, 138.7, 133.9, 130.9, 129.0, 128.1, 127.3, 122.6, 118.3, 109.6.

HRMS (CI): *m/z* calcd for $C_{15}H_8ClN_3O^+$: 281.0356 [*M*]$^+$; found 281.0356.

Synthesis of (*R*)-4'-(1-hydroxyethyl)-[1,1'-biphenyl]-4-carbonitrile (21)



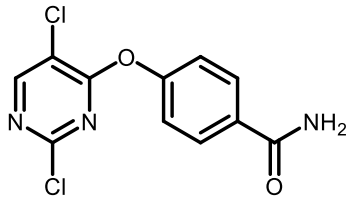
Compound **21** was prepared as outlined in the multi-step, 1-pot procedure outlined in **Section 4.4A.**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 4.97 (q, *J* = 6.5 Hz, 1H), 2.00 (s, 1H), 1.54 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 145.3, 138.3, 132.6, 127.6, 127.4, 126.2, 118.9, 110.9, 70.0, 25.3.

Spectral data matched those previously reported.[15]

4-((2,5-dichloropyrimidin-4-yl)oxy)benzamide (22)



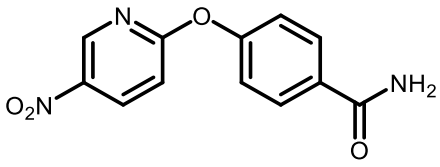
Compound **22** was prepared as in **Section 4.1**.

^{1}H NMR (600 MHz, DMSO-*d*6): δ 8.83 (d, *J* = 3.3 Hz, 1H), 8.06 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.44 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-*d*6): δ 167.0, 164.7, 159.3, 156.2, 153.6, 132.5, 129.4, 121.4, 116.8.

HRMS (ESI): *m/z* calcd for $C_{11}H_7Cl_2N_3O_2$+H^+: 283.9988 [*M*+H]$^+$: found 283.9994.

Synthesis of 4-((5-nitropyridin-2-yl)oxy)benzamide (23)



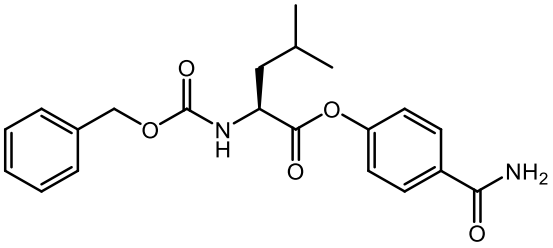
Compound **23** was prepared as in **Section 4.1**.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.02 (d, *J* = 2.9 Hz, 1H), 8.63 (dd, *J* = 9.1, 3.0 Hz, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.39 (s, 1H), 7.33 – 7.26 (m, 3H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ 167.6, 166.4, 155.4, 145.1, 141.2, 136.4, 132.2, 129.9, 121.8, 112.5.

HRMS (ESI): *m/z* calcd for $C_{12}H_9N_3O_4$+H^+: 260.0671 [*M*+H]$^+$: found 260.0676.

Synthesis of 4-carbamoylphenyl ((benzyloxy)carbonyl)-*L*-leucinate (24)



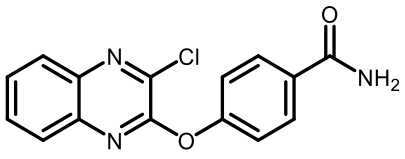
Compound **24** was prepared as in **Section 4.1**.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.43 – 7.29 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.02 (s, 1H), 5.88 (s, 1H), 5.22 (d, *J* = 8.7 Hz, 1H), 5.14 (s, 2H), 4.62 (td, *J* = 8.8, 4.6 Hz, 1H), 1.92 – 1.76 (m, 2H), 1.69 (m, 1H), 1.02 (m, 6H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 171.8, 169.0, 156.3, 153.4, 136.3, 131.4, 129.2, 128.8, 128.5, 128.3, 121.8, 67.4, 53.0, 41.5, 25.1, 23.1, 22.0.

HRMS (ESI): *m/z* calcd for $C_{21}H_{24}N_2O_5$+Na^+: 407.1577 [*M*+Na]$^+$; found 407.1583.

Synthesis of 4-((3-chloroquinoxalin-2-yl)oxy)benzamide (25)



Compound **25** was prepared as in **Section 4.1**.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09 – 7.97 (m, 4H), 7.83 – 7.67 (m, 3H), 7.49 – 7.39 (m, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 167.6, 155.2, 152.9, 139.3, 139.2, 139.0, 132.4, 131.5, 129.84, 129.2, 128.1, 127.4, 121.8.

HRMS (ESI): *m/z* calcd for $C_{15}H_{10}ClN_3O_2$+H^+: 300.0534 [*M*+H]$^+$; found 300.0540.

6. References

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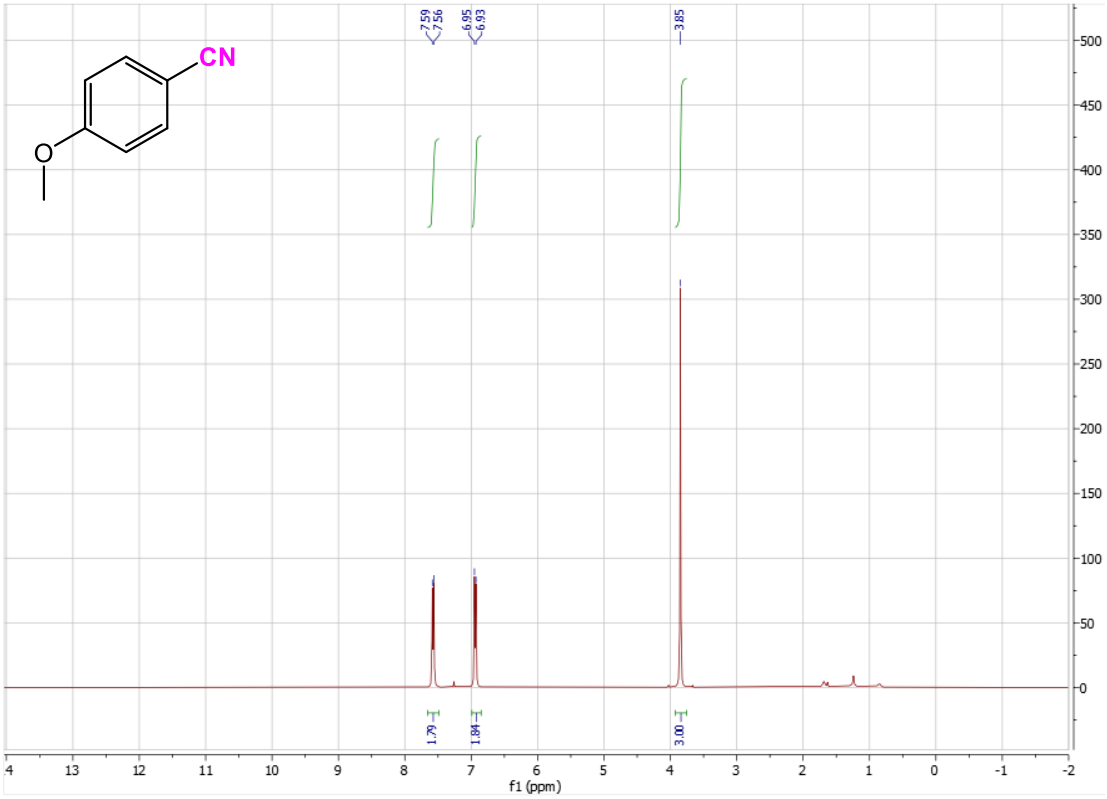
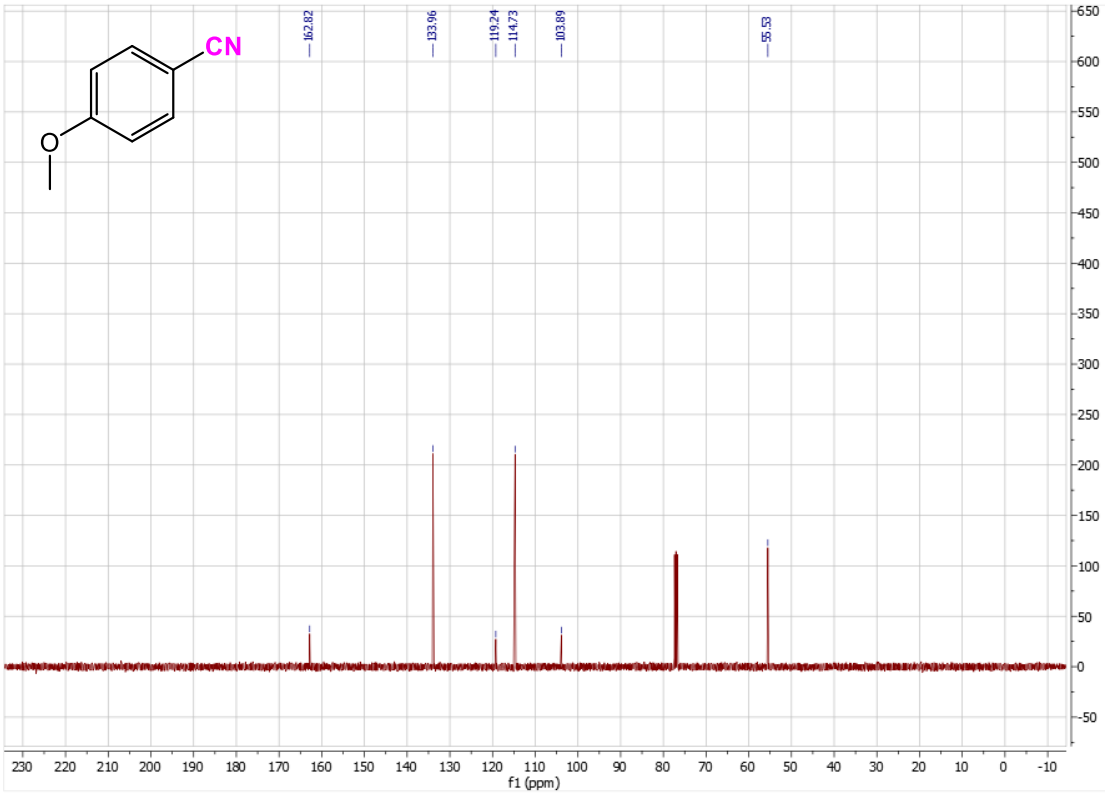
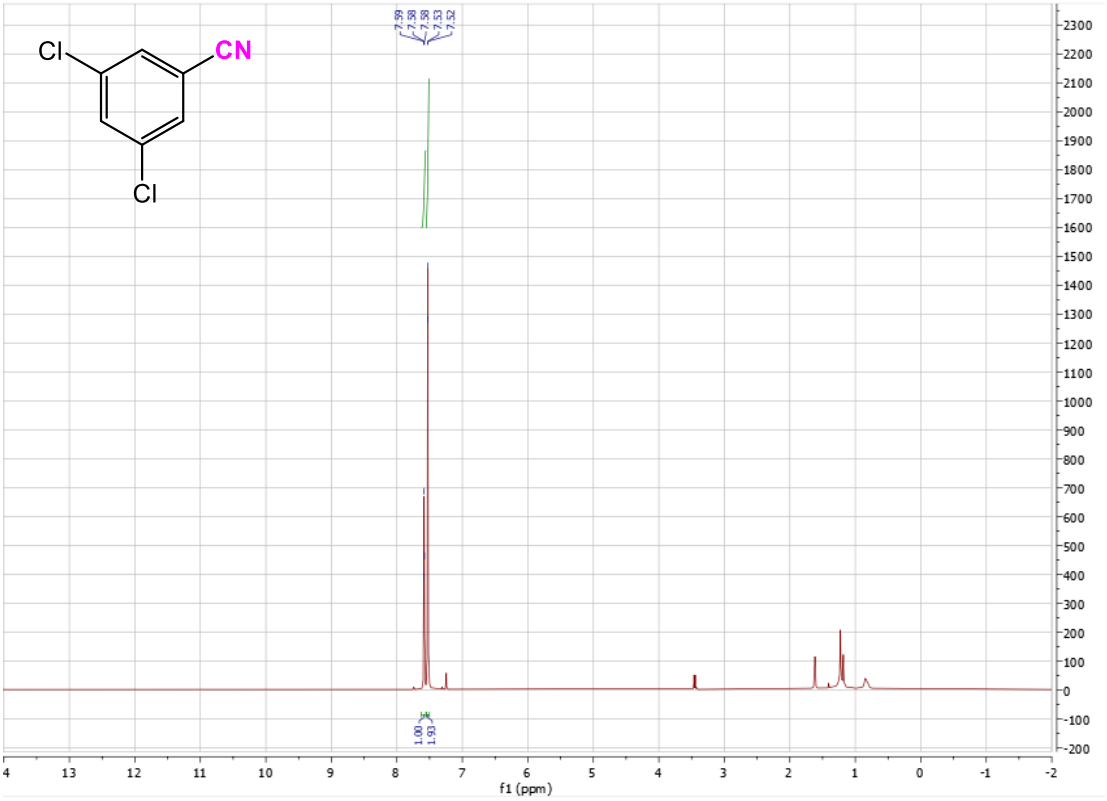
7. NMR Spectral Data



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CN
Cl
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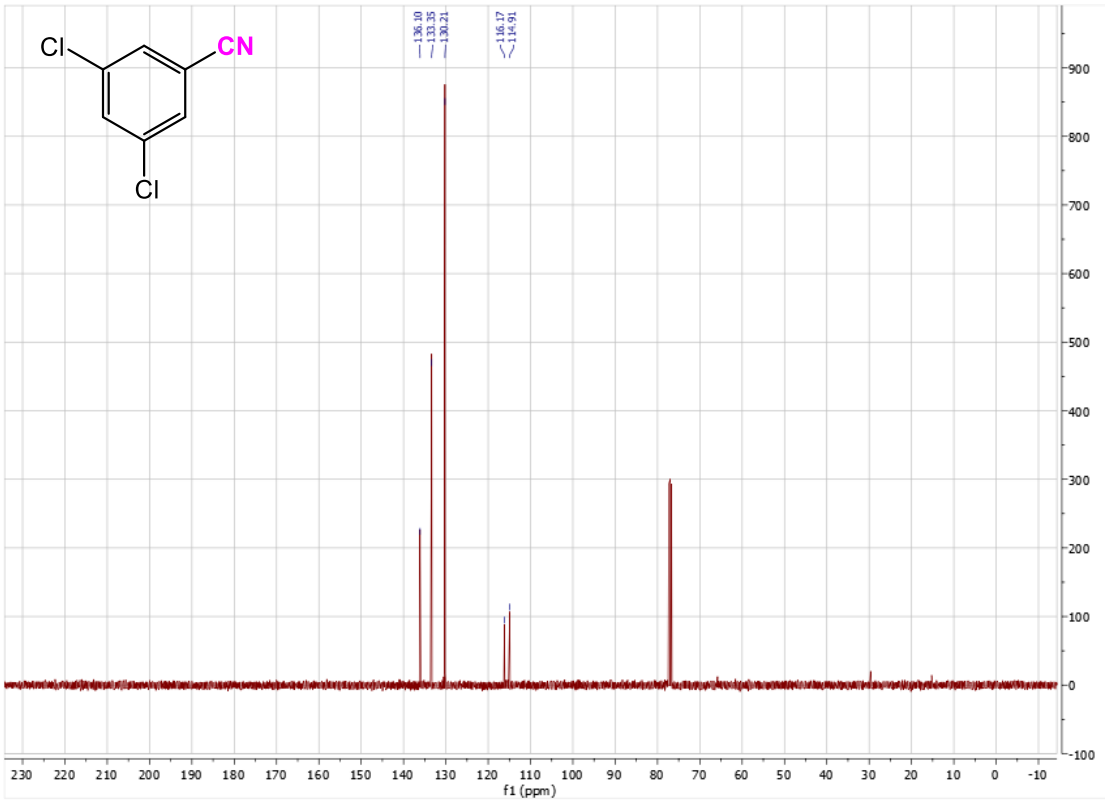
7.58
7.58
7.53
7.52
1.00
1.93
f1 (ppm)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CN
Cl
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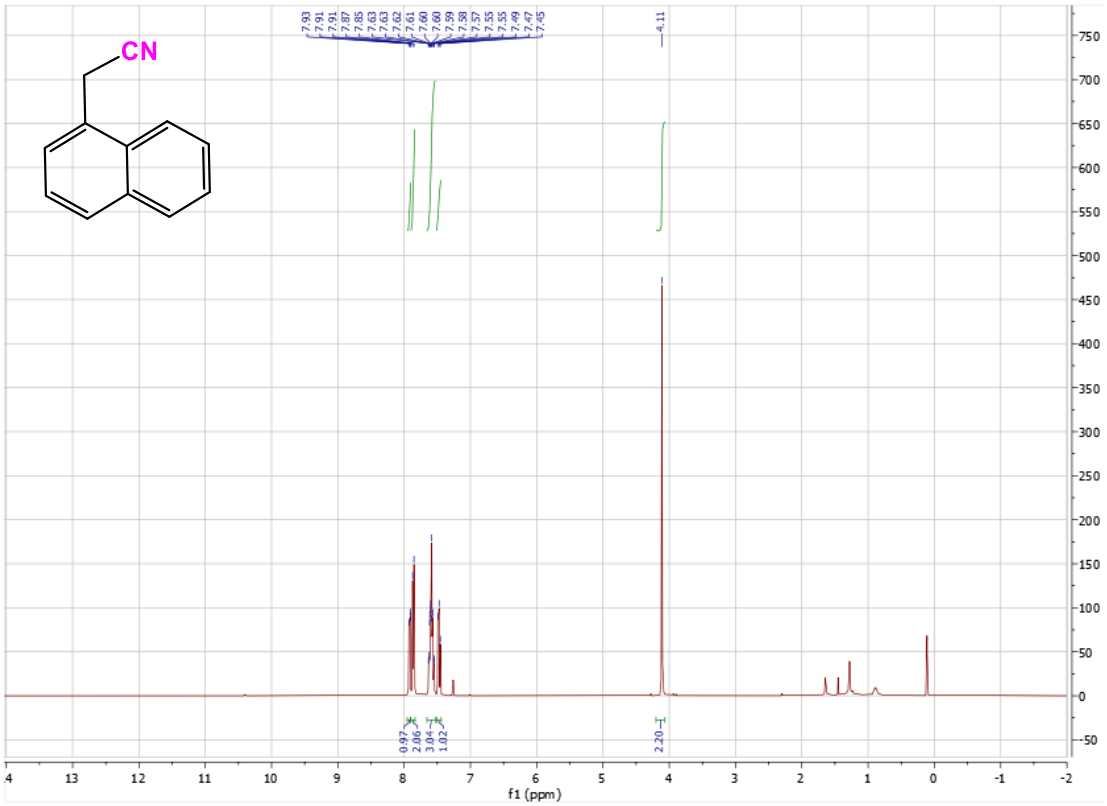
114.91
f1 (ppm)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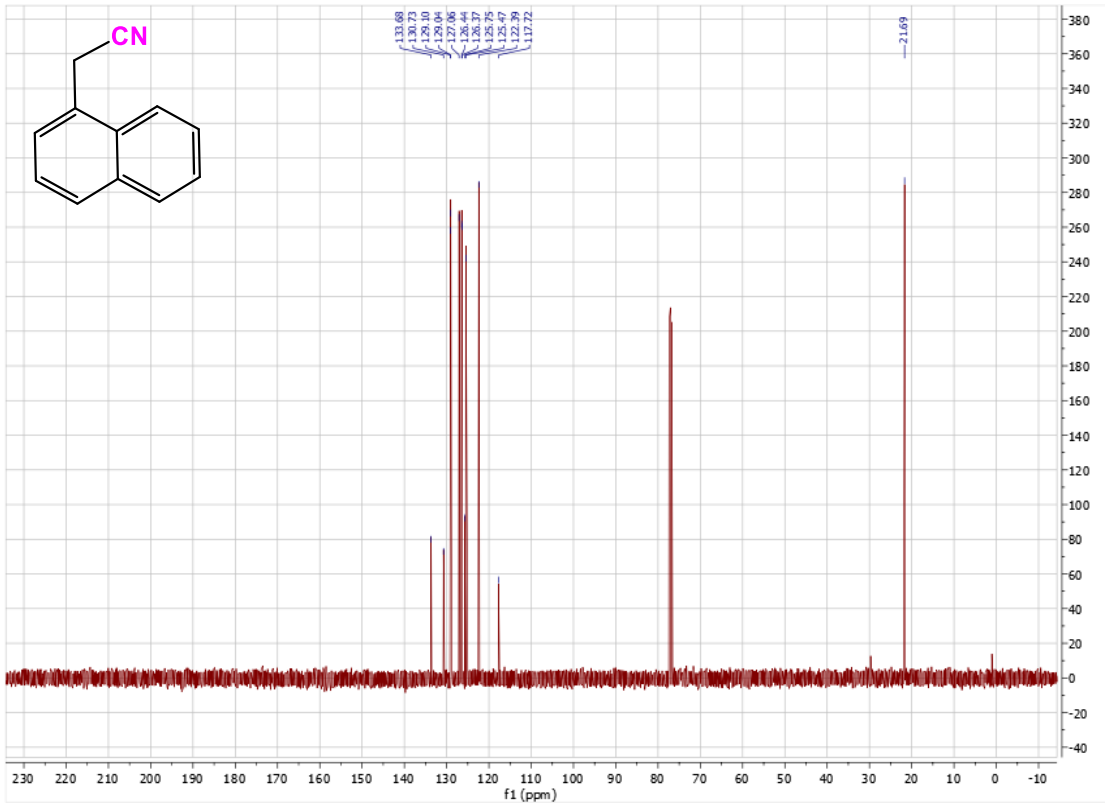
7.93
7.91
7.91
7.87
7.85
7.63
7.63
7.62
7.61
7.60
7.60
7.59
7.58
7.57
7.55
7.55
7.49
7.47
7.45
4.11
0.97
2.06
3.04
1.02
2.20
f1 (ppm)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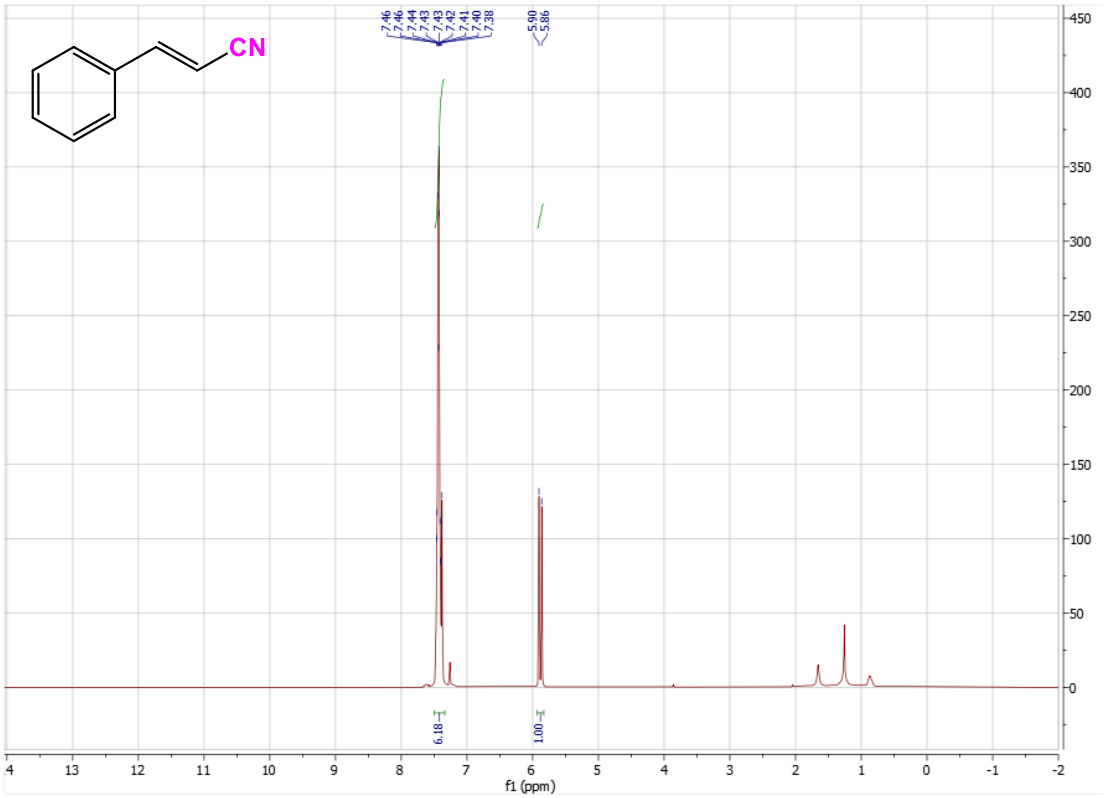
125.47
122.39
117.72
21.69
f1 (ppm)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7.40
7.38
5.90
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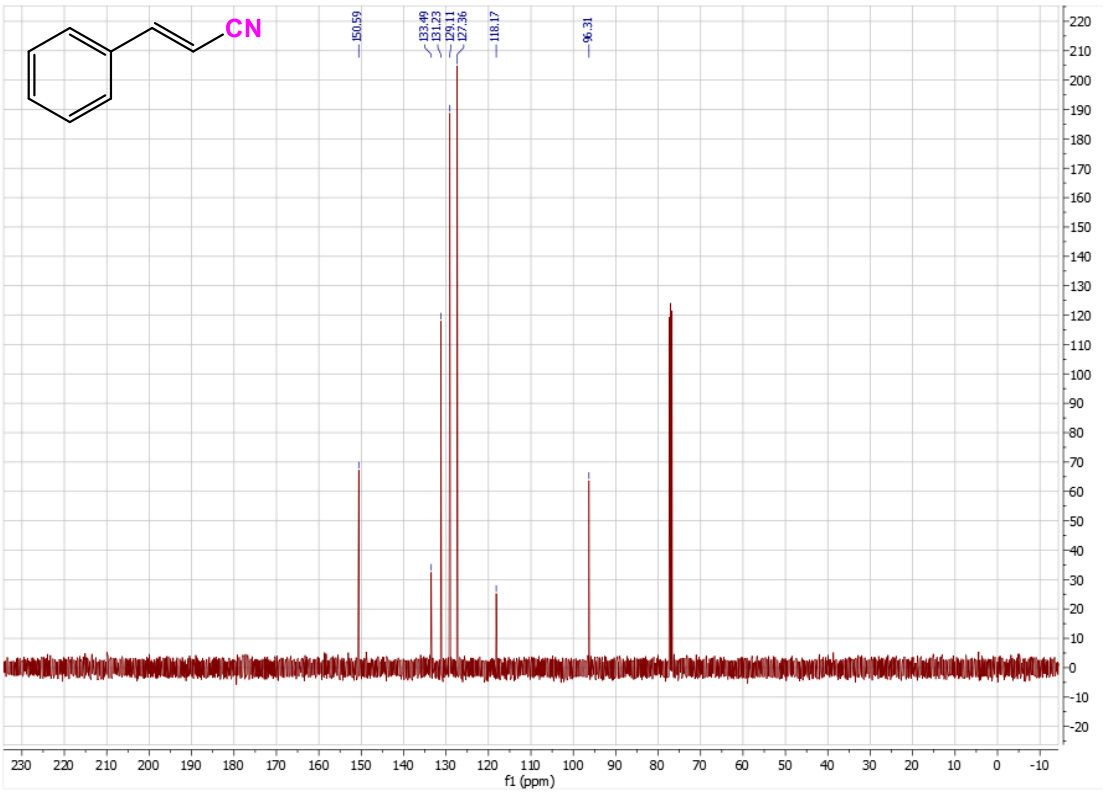
1.00
f1 (ppm)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129.11
127.36
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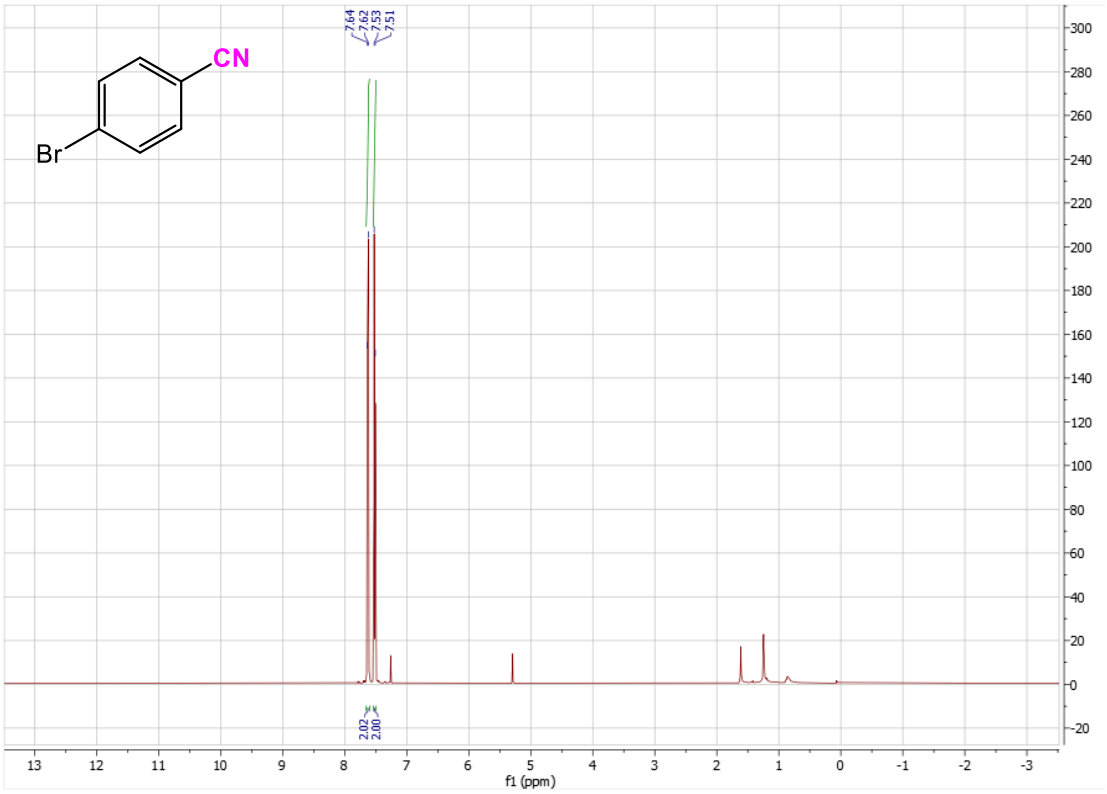
96.31
f1 (ppm)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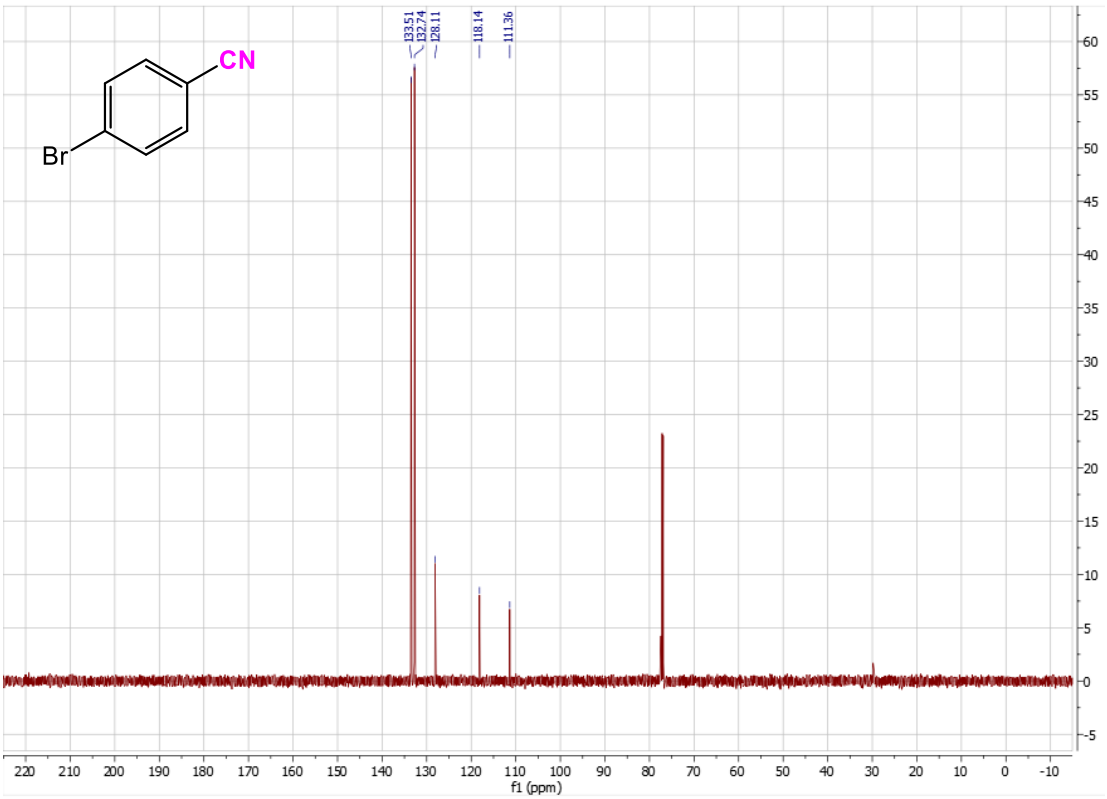
2.00
f1 (ppm)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Br
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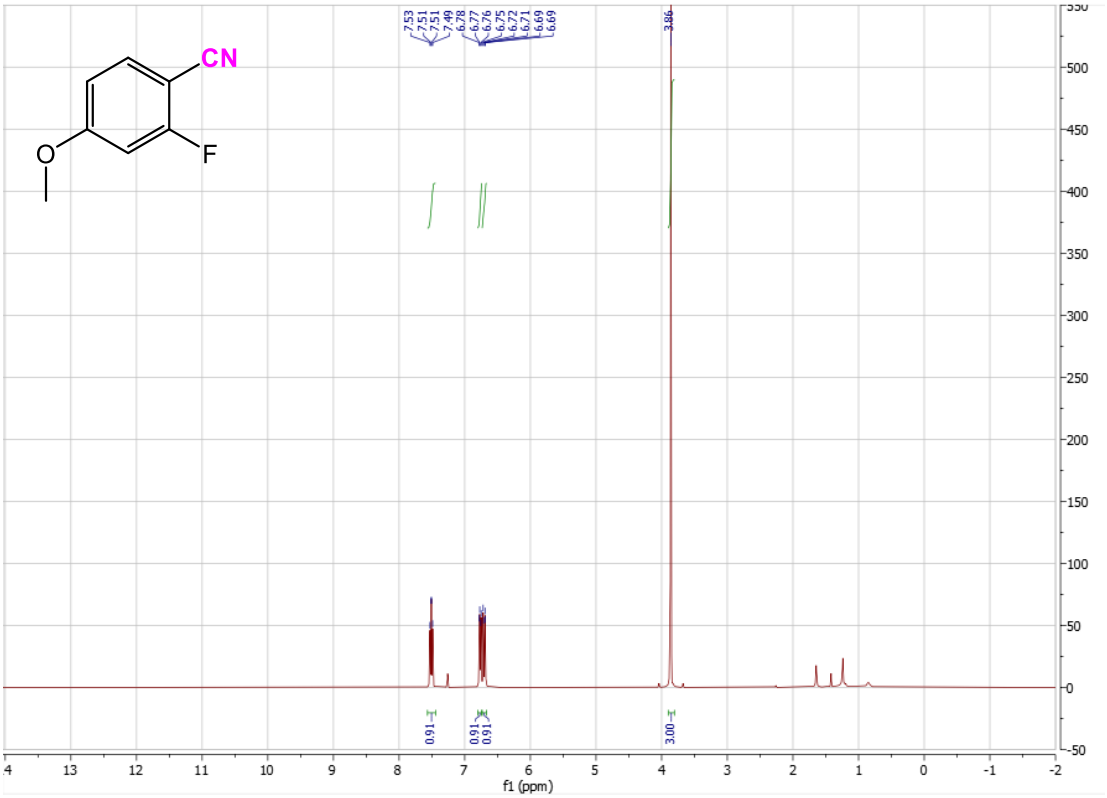
118.14
111.36
f1 (ppm)


CN
O
F
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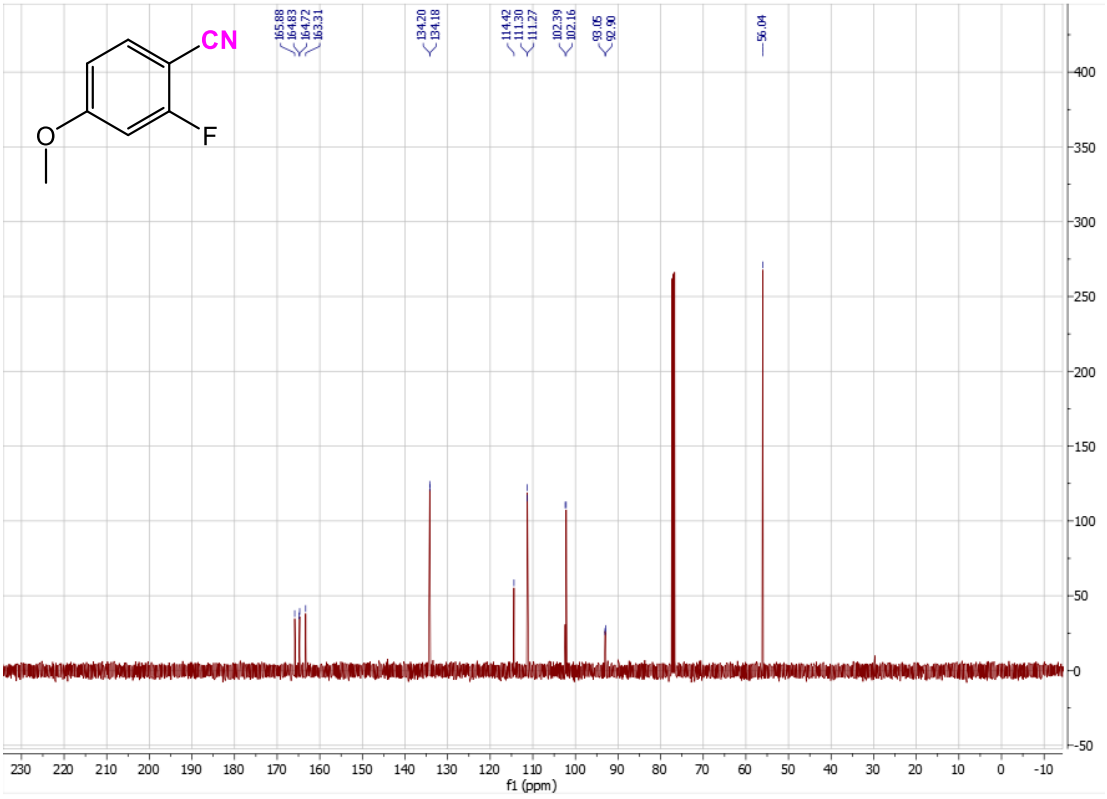
7.51
7.51
7.49
6.78
6.77
6.76
6.75
6.72
6.71
6.69
6.69
3.86
0.91
0.91
0.91
3.00
f1 (ppm)


CN
O
F
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163.31
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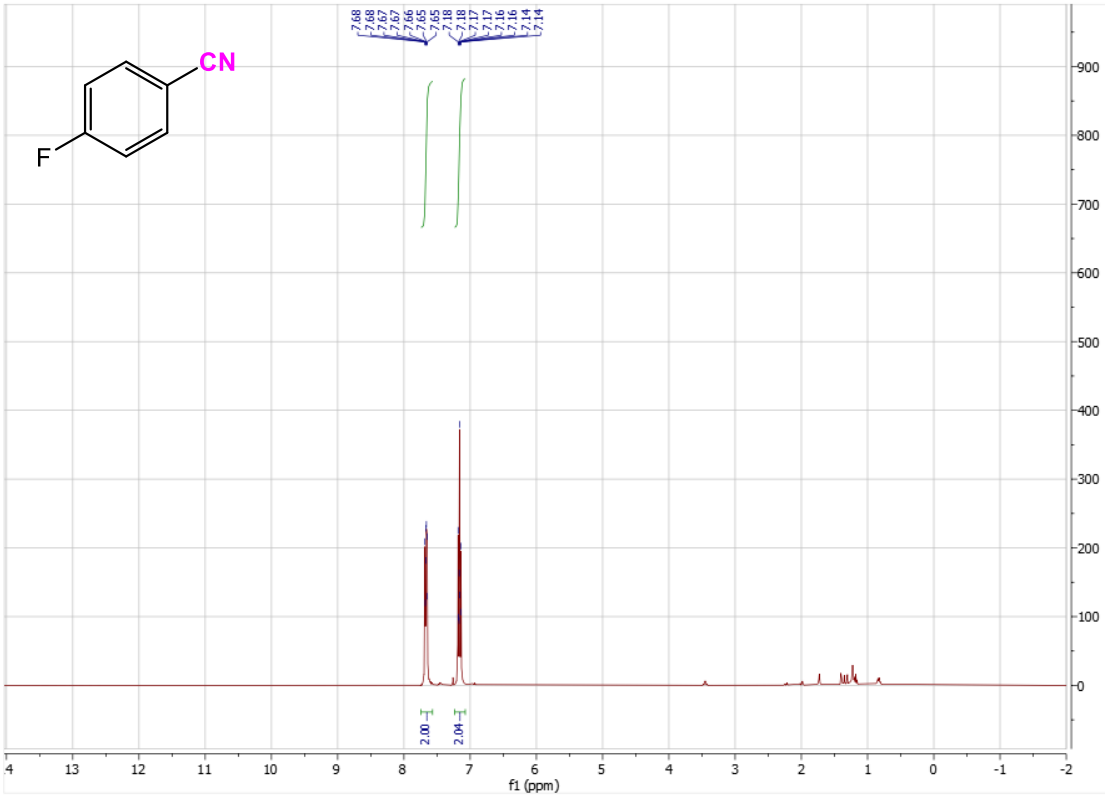
111.30
111.27
102.39
102.16
93.05
92.90
56.04
f1 (ppm)


CN
F
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7.67
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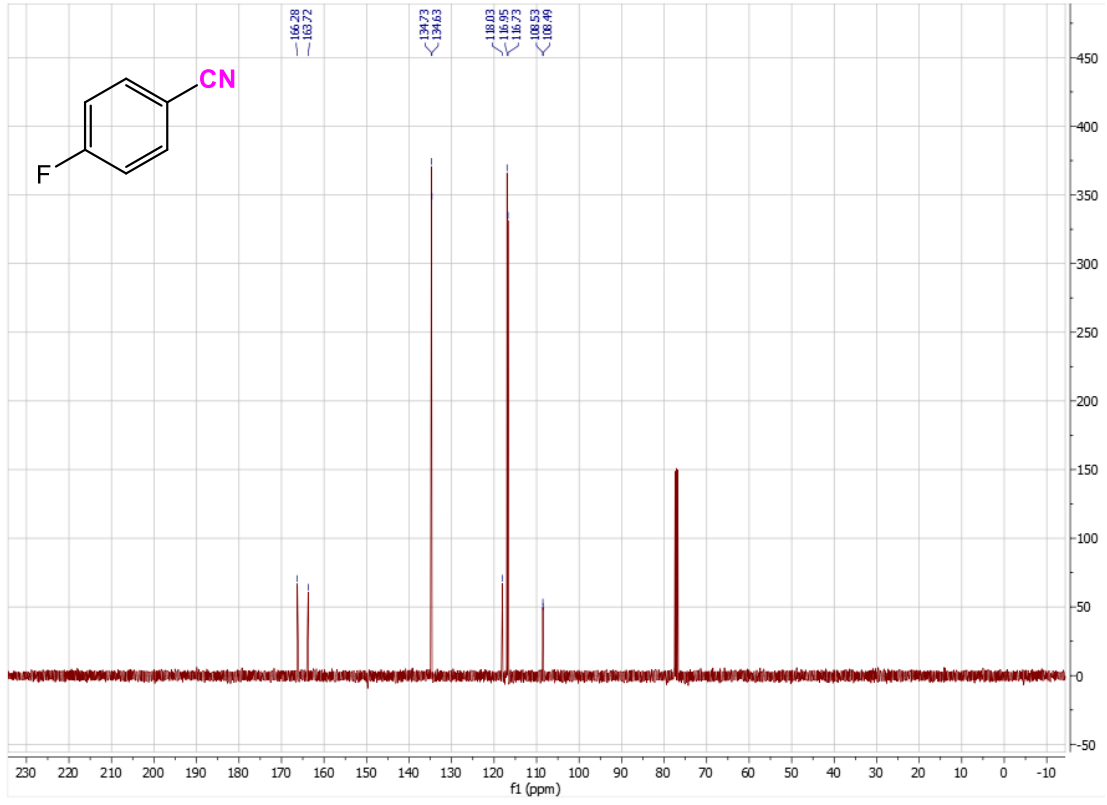
7.14
7.14
2.00
2.04
f1 (ppm)


CN
F
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134.73
134.63
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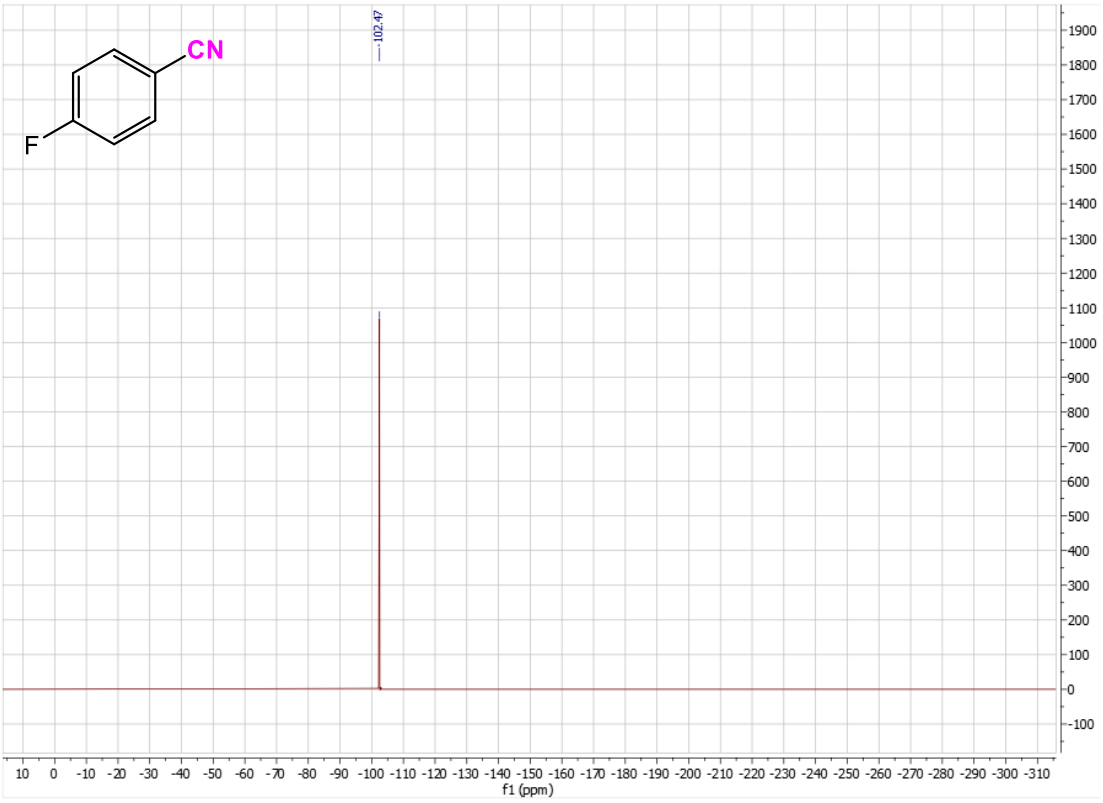
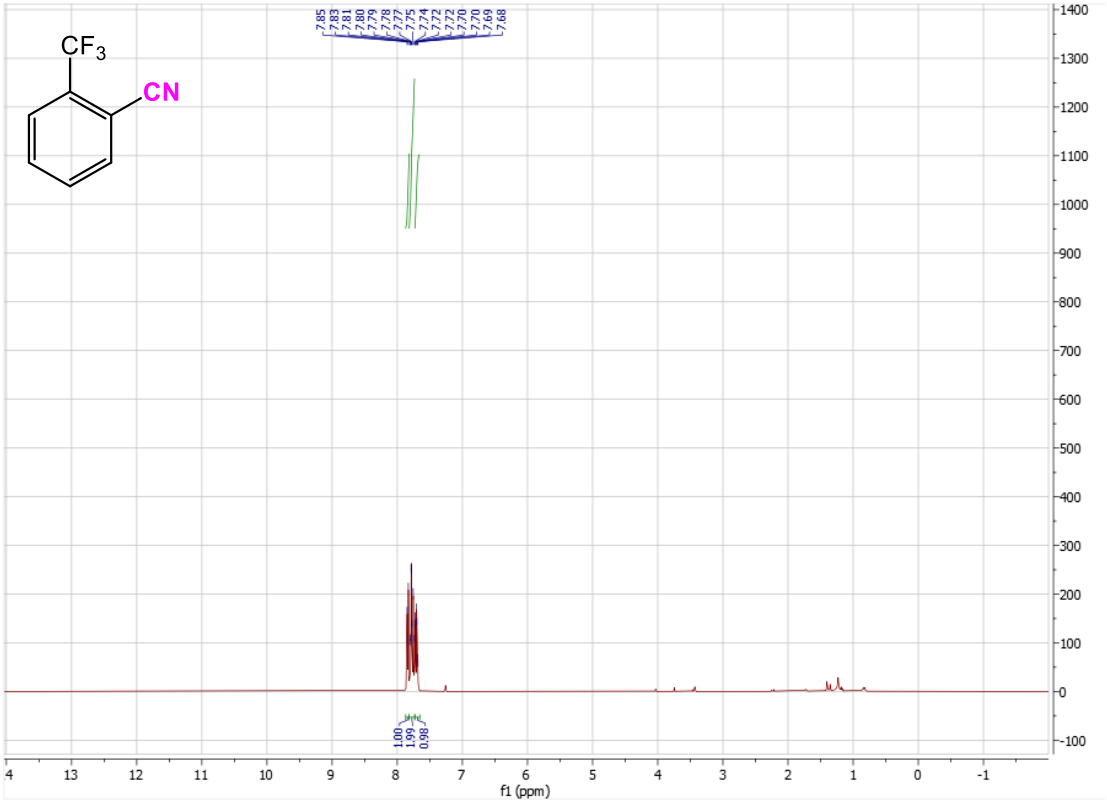
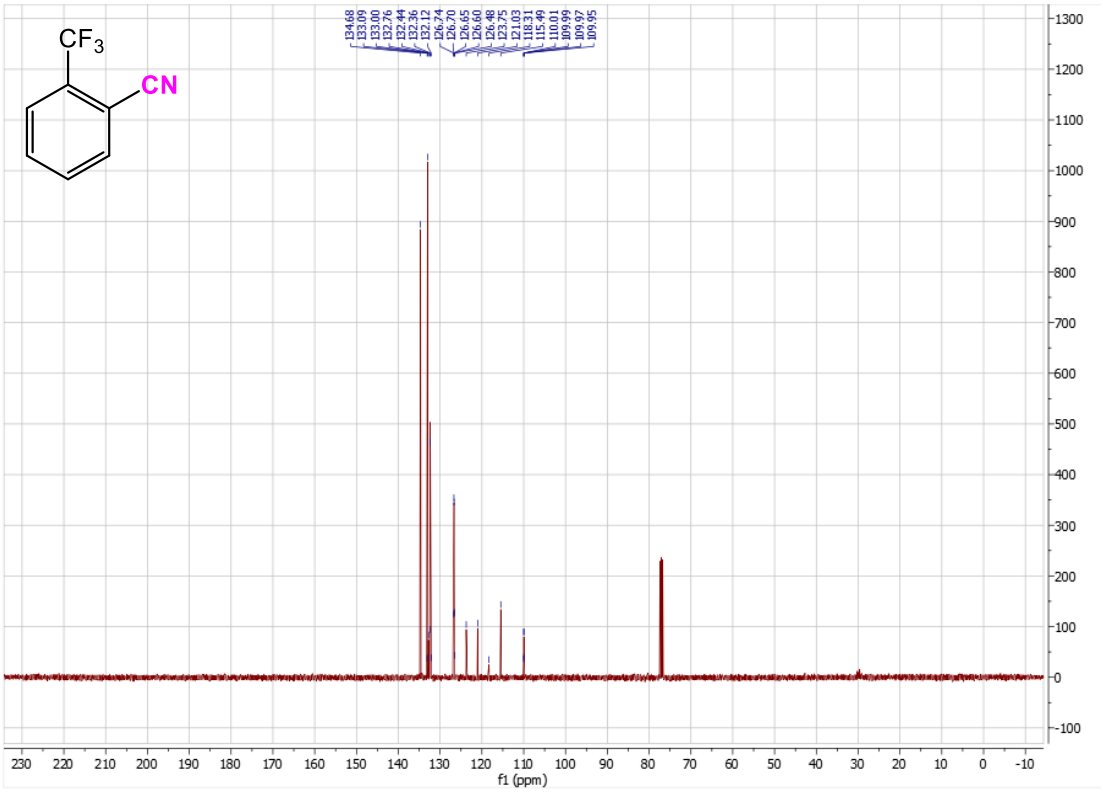
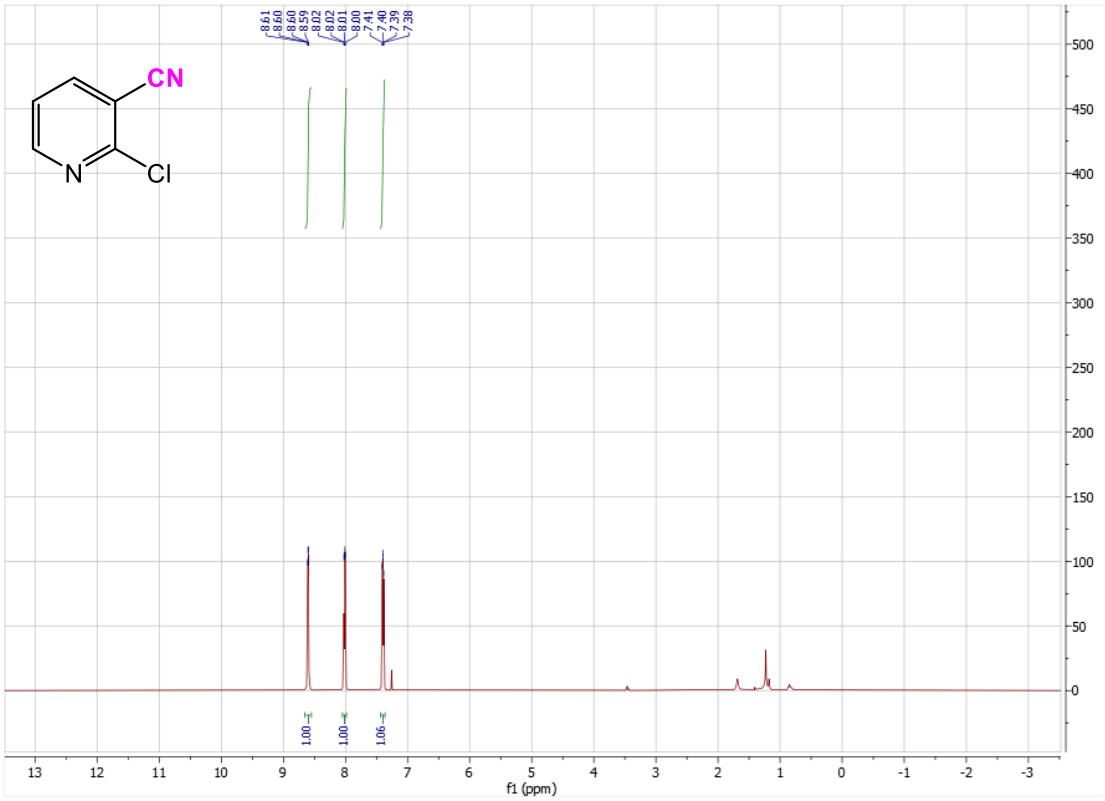
116.95
116.73
108.53
108.49
f1 (ppm)

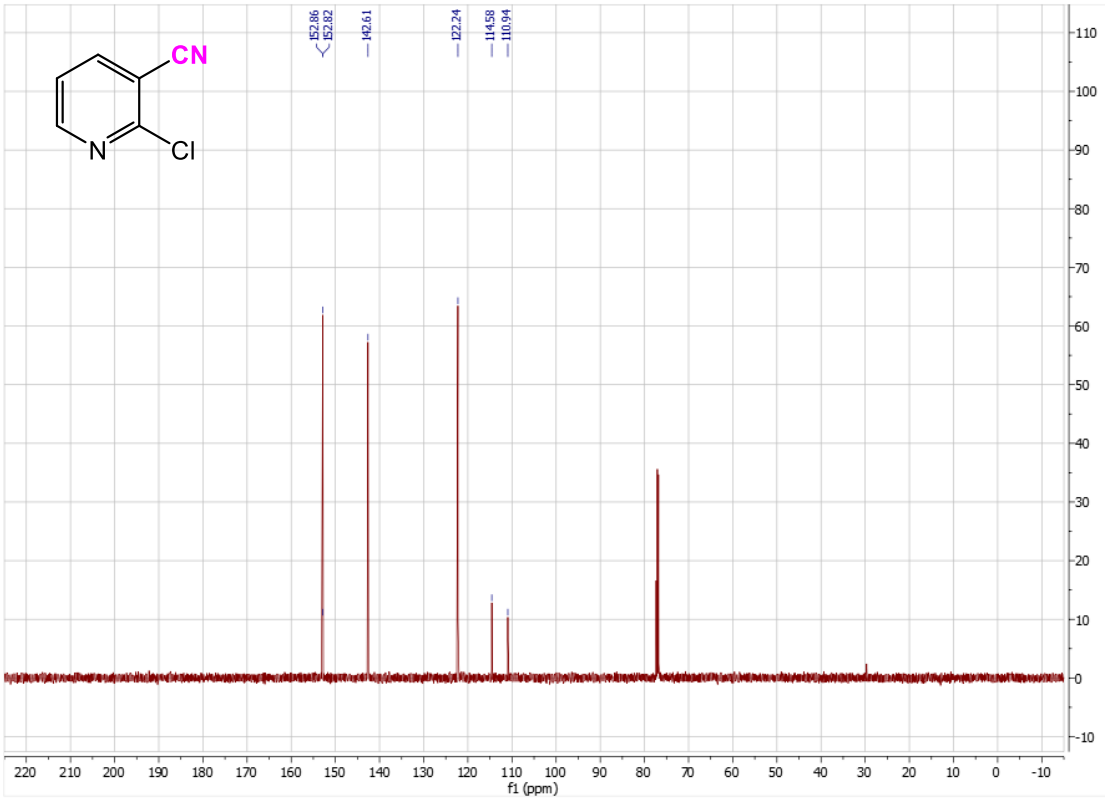

CN
F
-102.47
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)

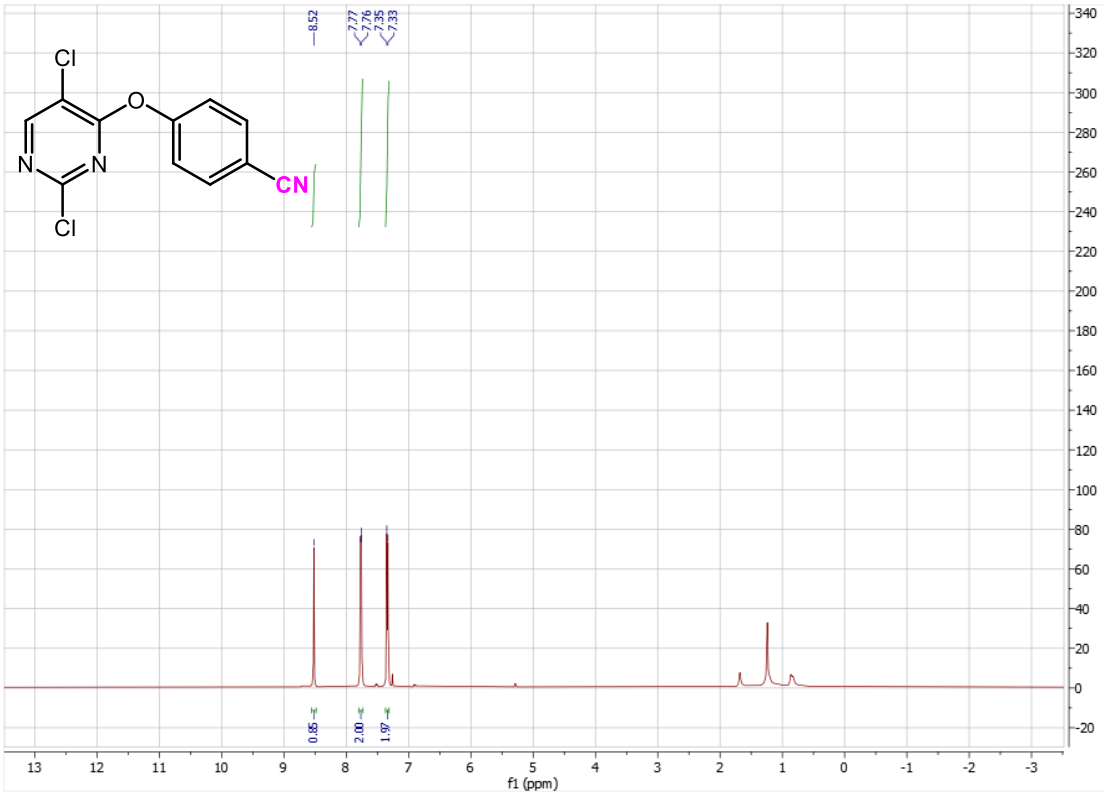

CF3
CN
7.85
7.83
7.81
7.80
7.79
7.78
7.77
7.75
7.74
7.72
7.72
7.70
7.70
7.69
7.68
1.00
1.99
0.98
f1 (ppm)

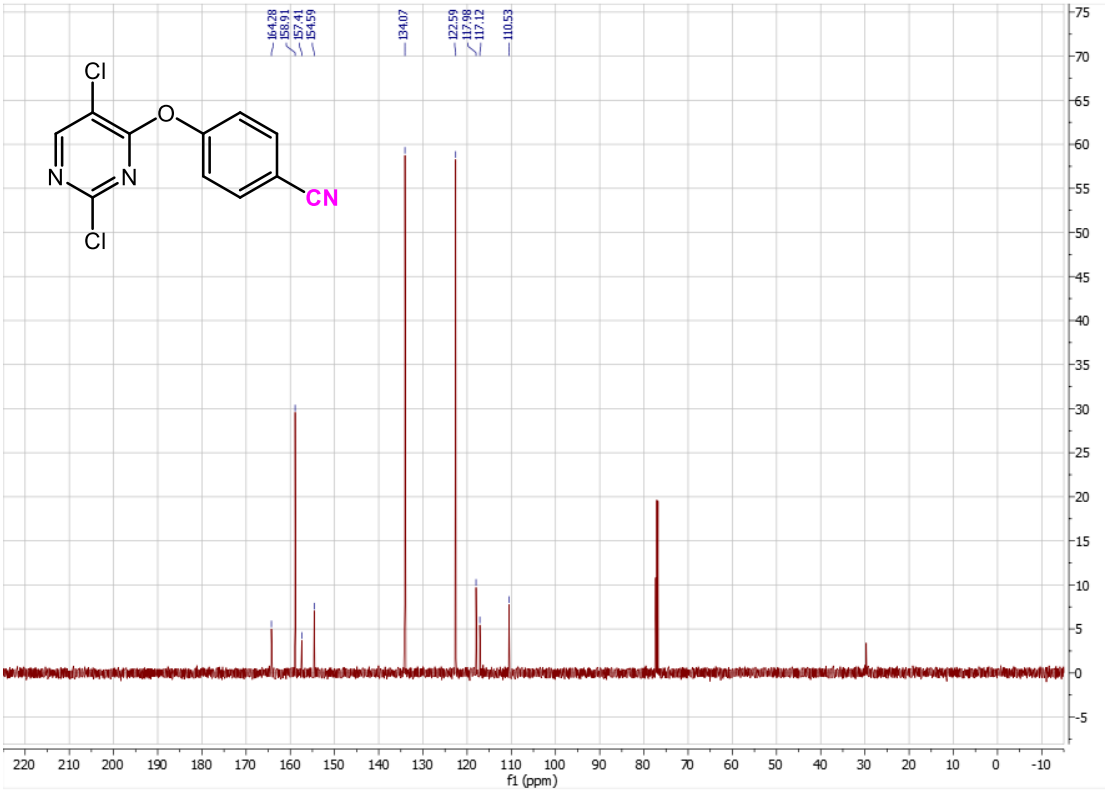

CF3
CN
134.68
133.99
133.00
132.76
132.44
132.36
132.12
126.74
126.70
126.65
126.60
125.48
125.25
121.03
118.31
115.49
110.01
109.99
109.97
109.95
f1 (ppm)

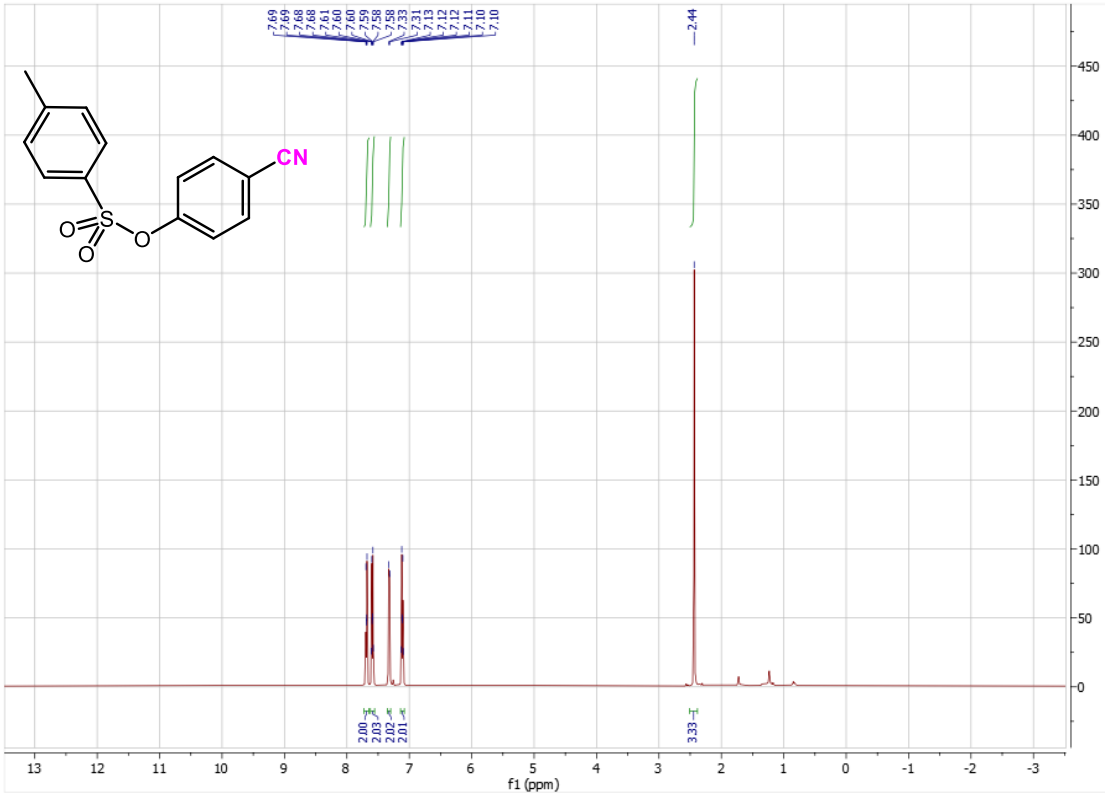

62.08
CF3
CN
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300 -310
f1 (ppm)

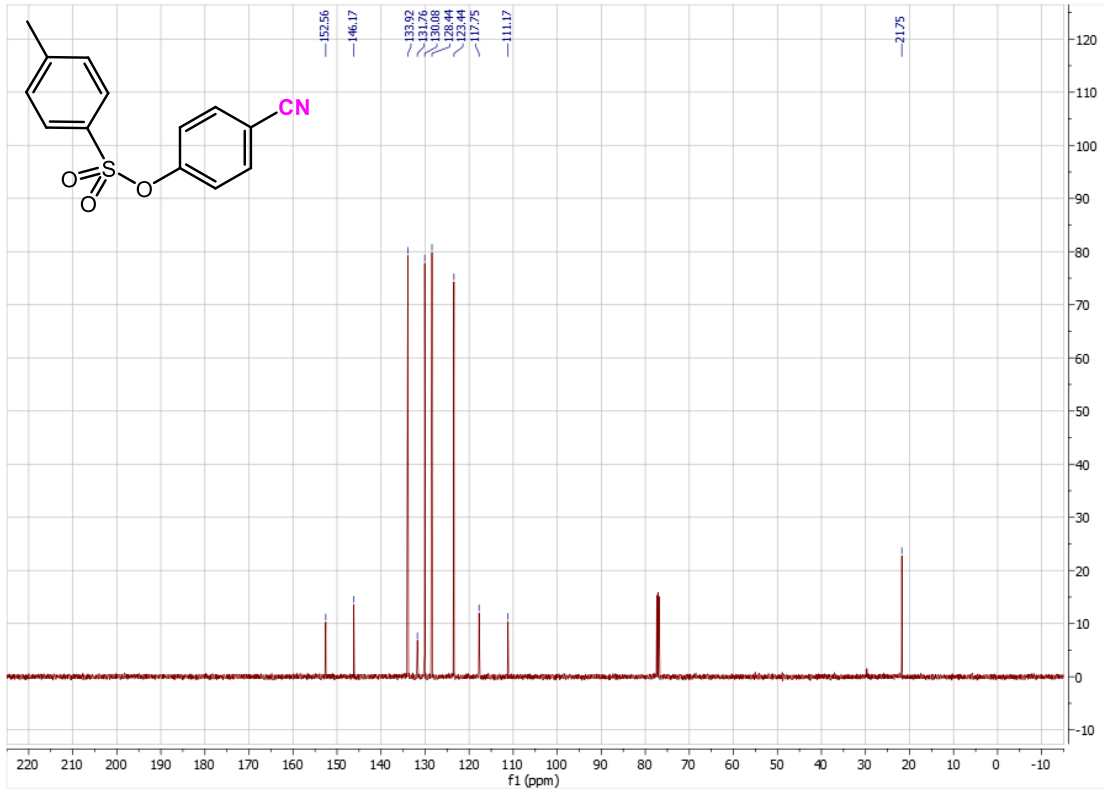

CN
N
Cl
8.61
8.60
8.60
8.59
8.02
8.02
8.01
8.00
7.41
7.40
7.39
7.38
1.00
1.00
1.06
f1 (ppm)

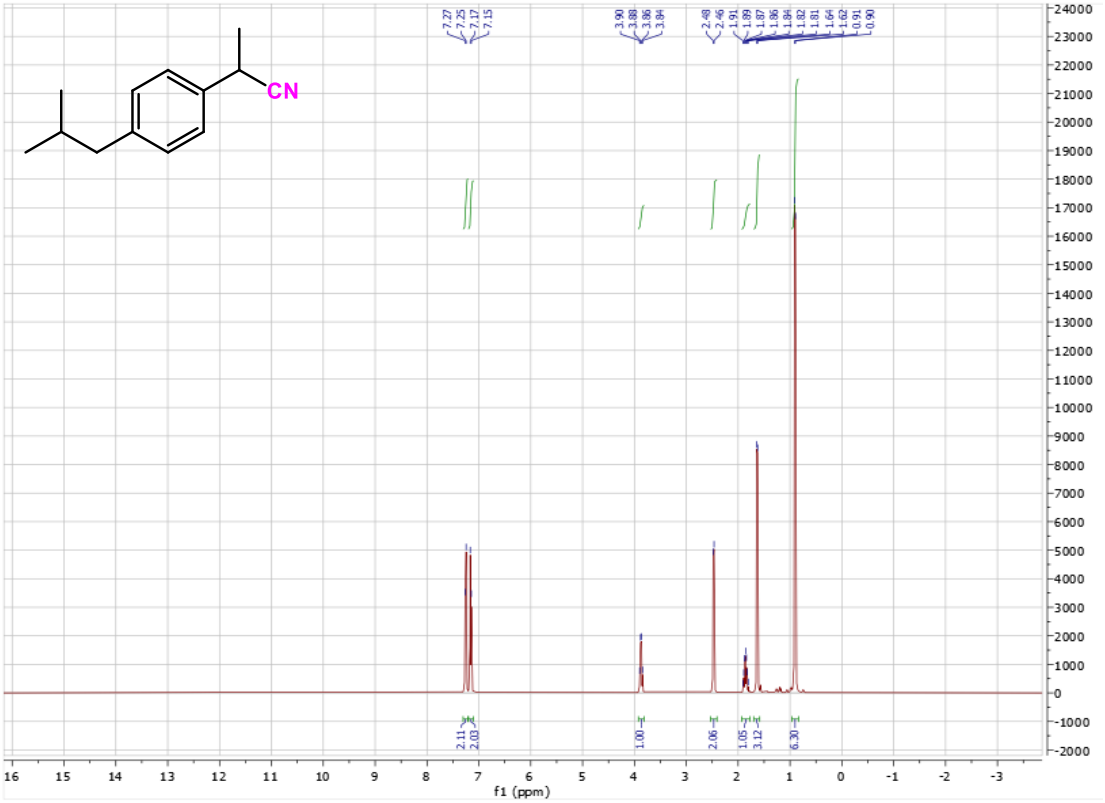

CN
N
Cl
152.86
152.82
142.61
122.24
114.58
110.94
f1 (ppm)

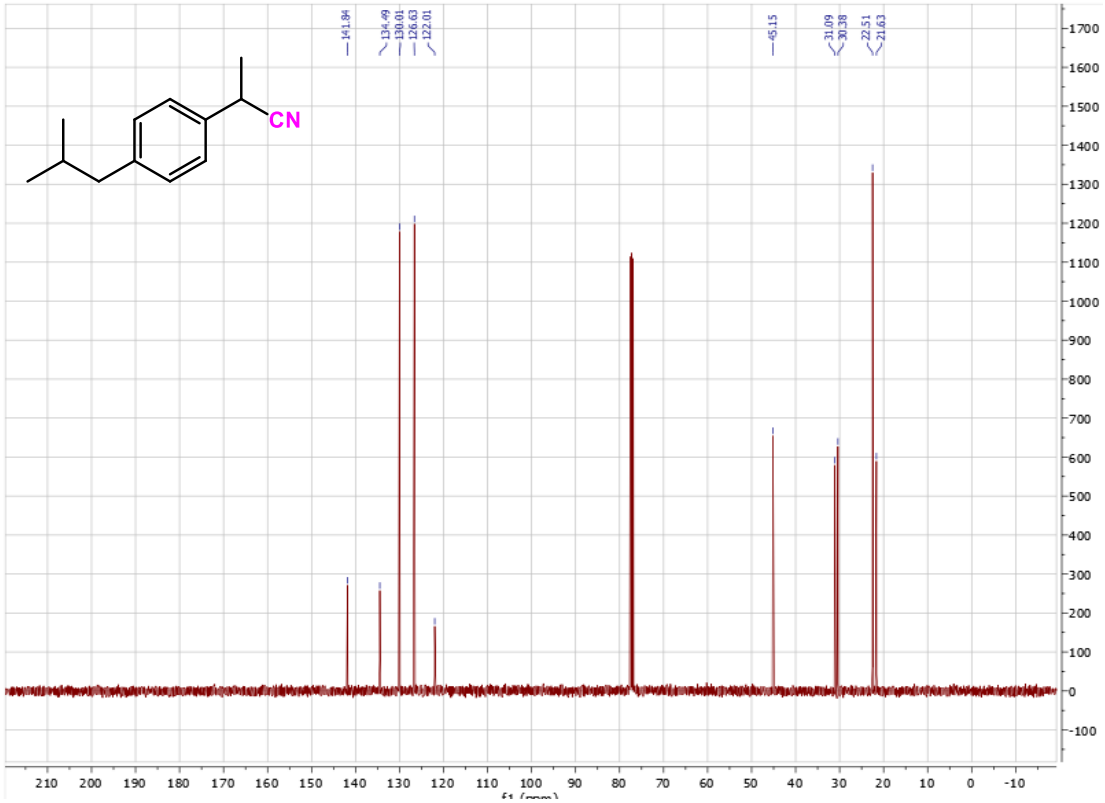

Cl
O
N
N
Cl
CN
8.52
7.77
7.76
7.35
7.33
0.85
2.00
1.97
f1 (ppm)

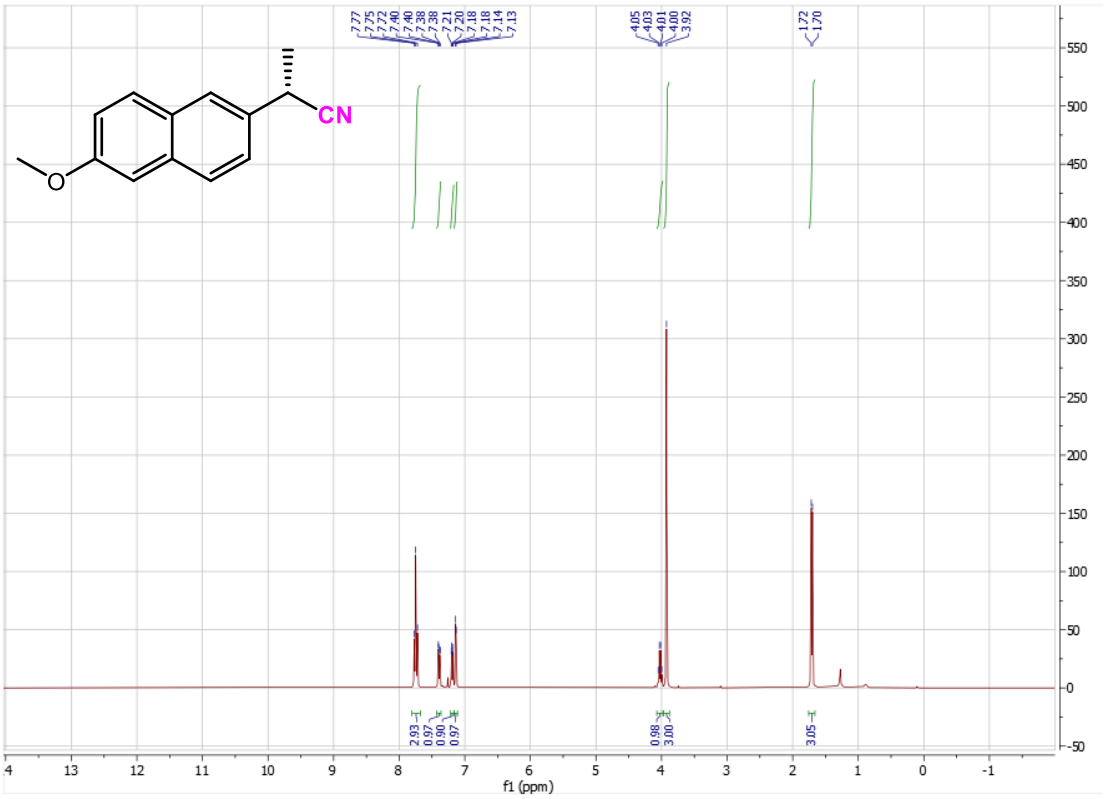

Cl
O
N
N
Cl
CN
164.28
158.91
157.41
154.59
134.07
122.59
117.98
117.12
110.53
f1 (ppm)

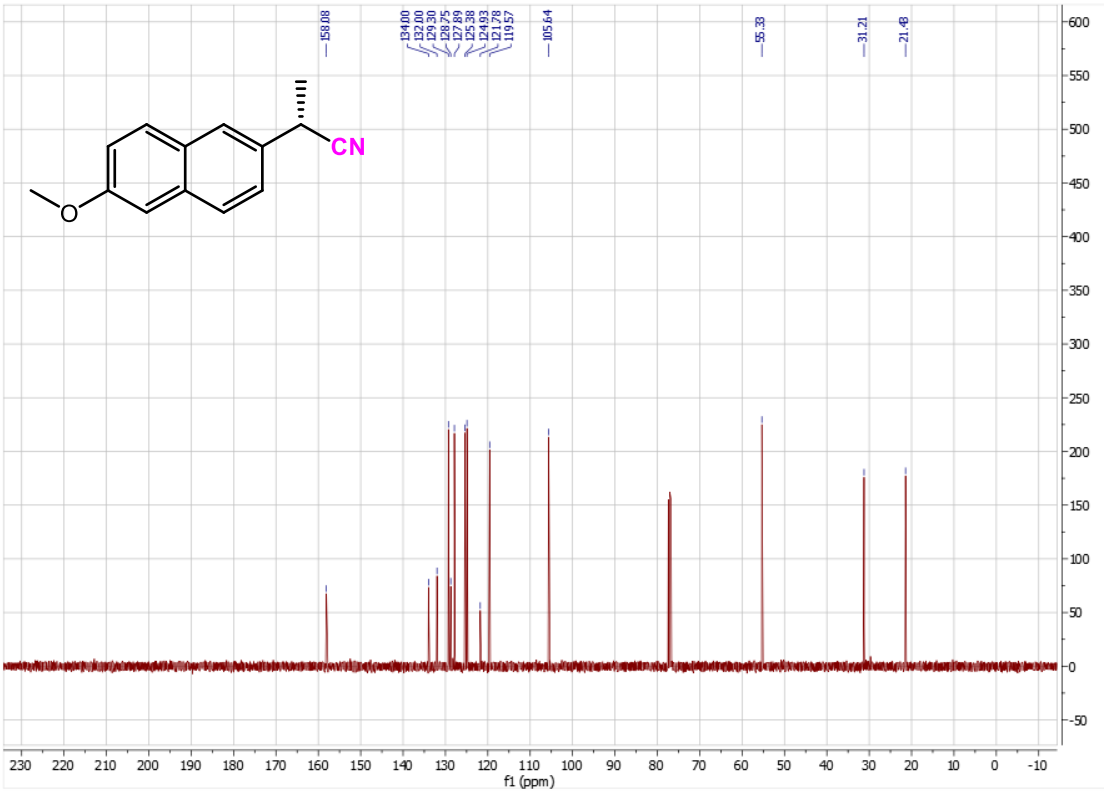

7.69
7.69
7.68
7.68
7.61
7.60
7.60
7.59
7.58
7.58
7.33
7.31
7.13
7.12
7.12
7.11
7.10
7.10
2.44
CN
O
S
O
O
2.00
2.03
2.02
2.01
3.33
f1 (ppm)

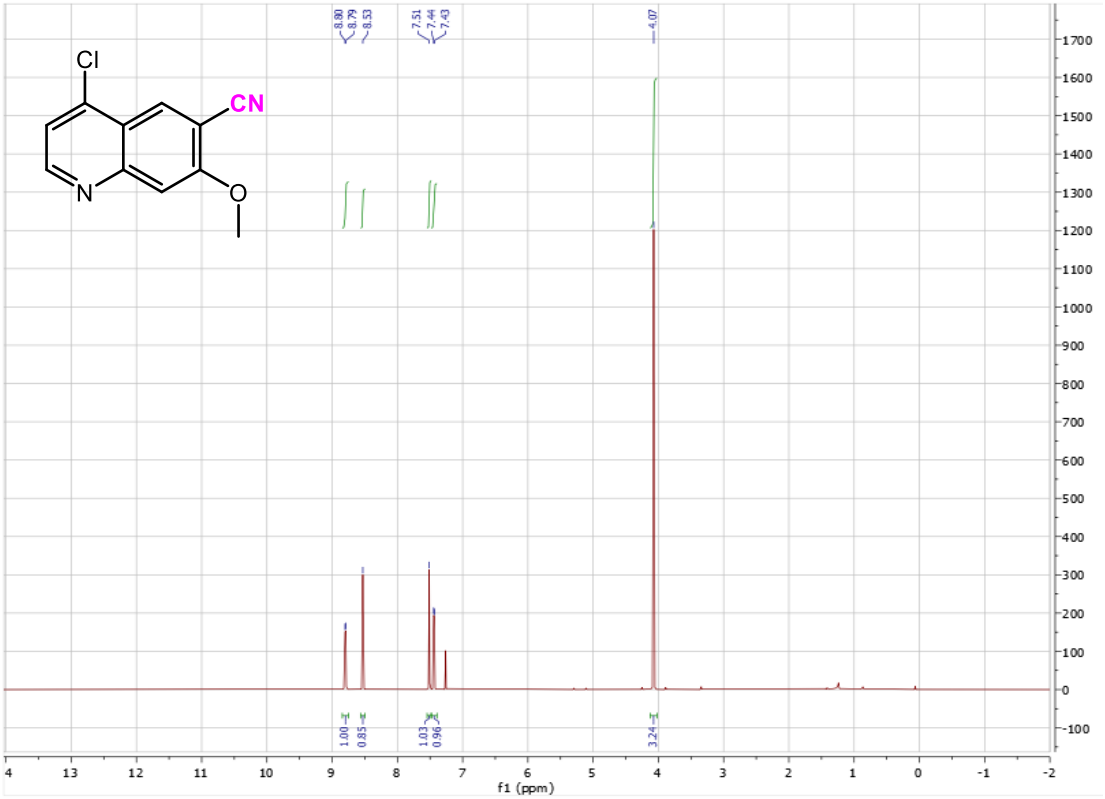

152.56
146.17
133.92
131.76
130.08
128.44
123.44
117.75
111.17
21.75
CN
O
S
O
O
f1 (ppm)

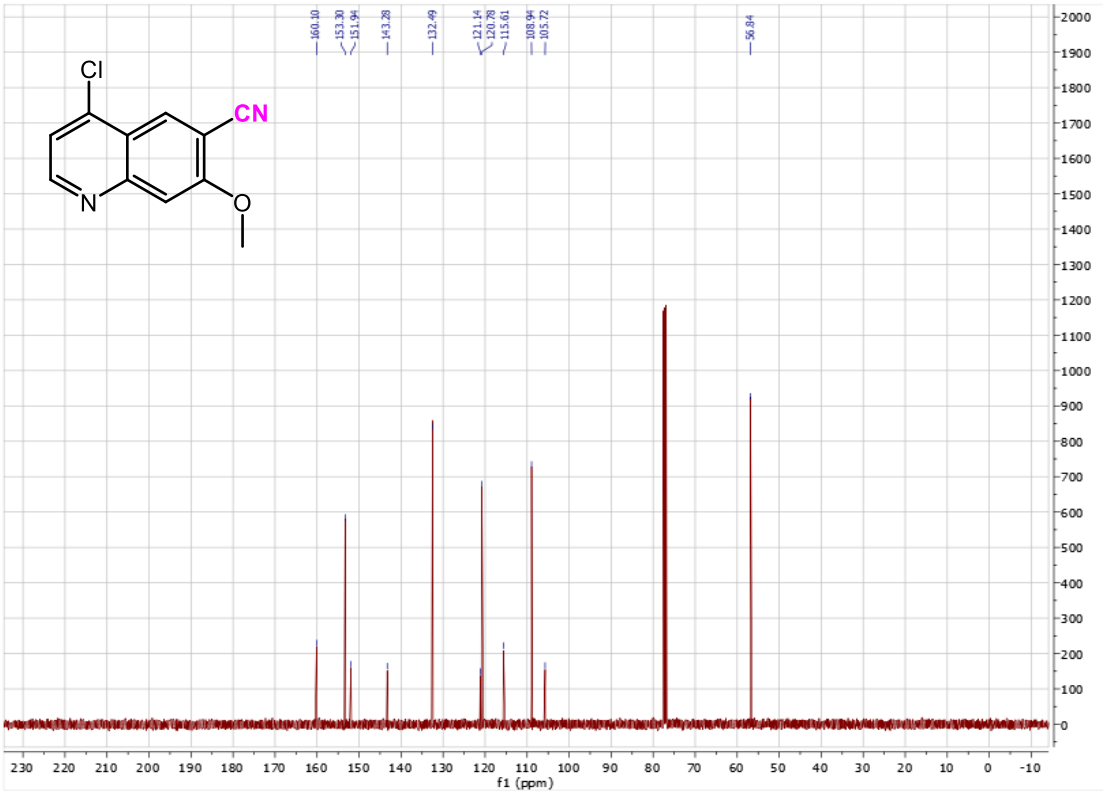

CN
7.27
7.25
7.17
7.15
3.90
3.88
3.86
3.84
2.48
2.46
1.91
1.89
1.87
1.86
1.84
1.82
1.81
1.64
1.62
0.91
0.90
2.11
2.03
1.00
2.06
1.05
3.12
6.30
f1 (ppm)

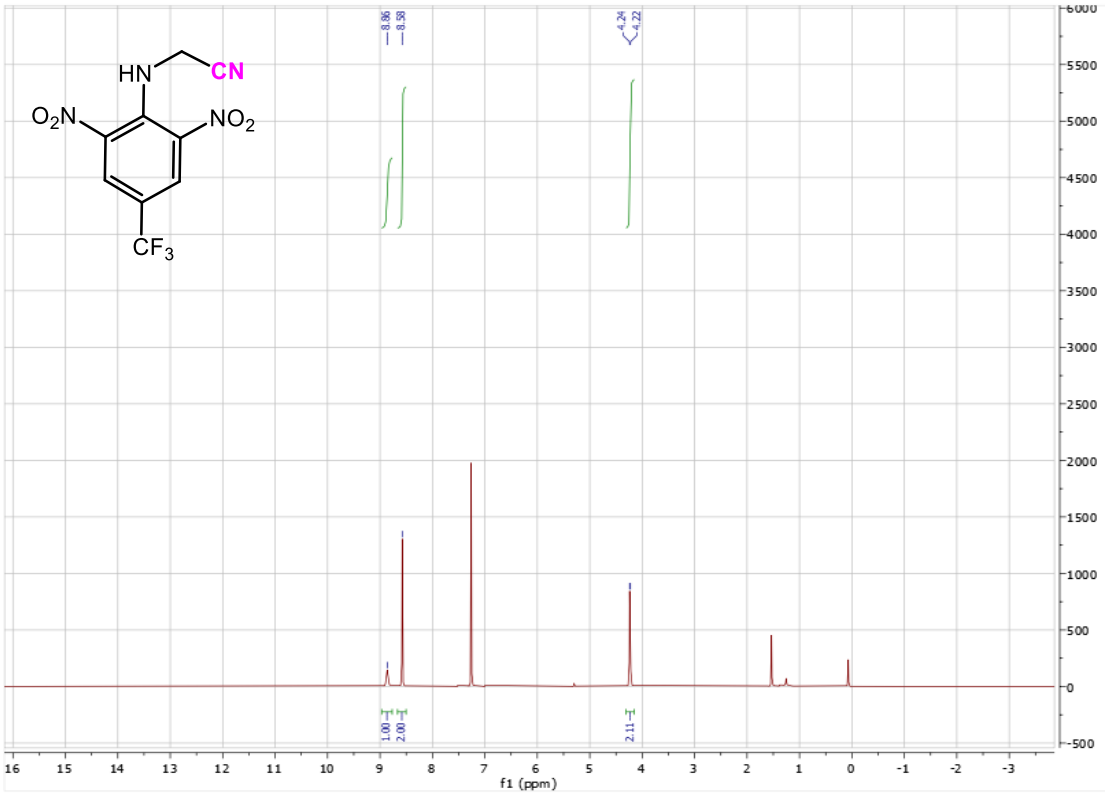

CN
141.84
134.49
130.01
126.63
122.01
45.15
31.09
30.38
22.51
21.63

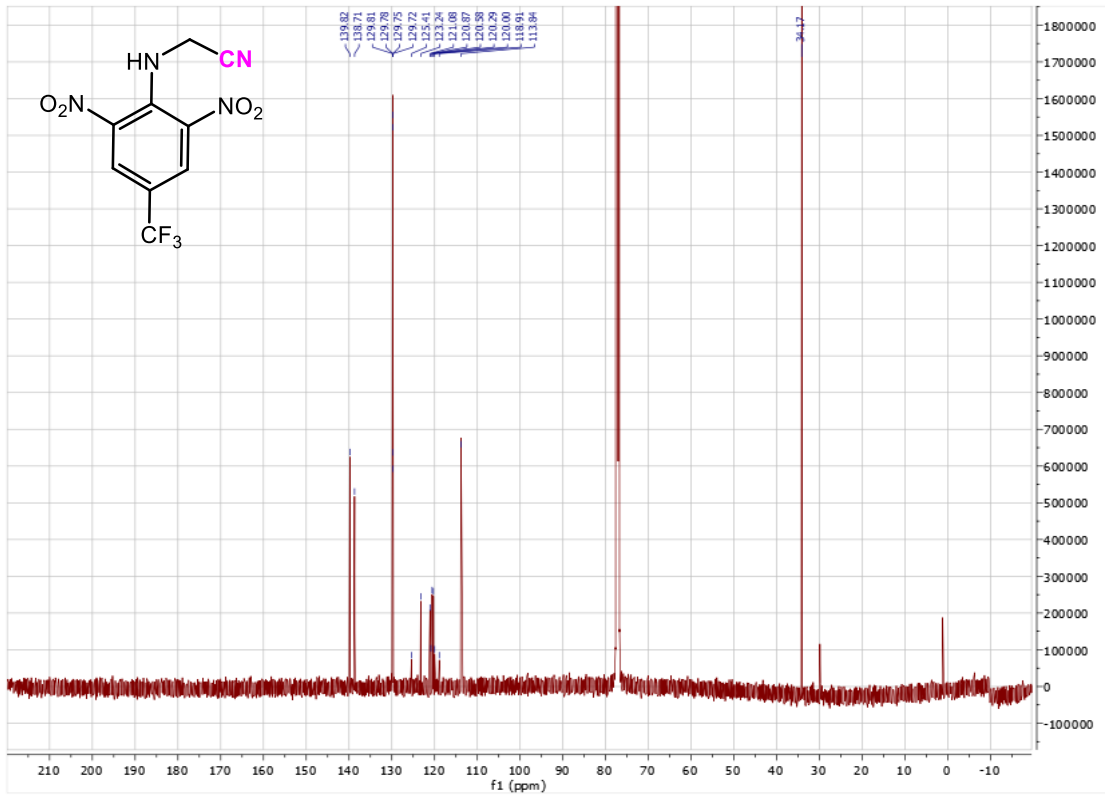

CN
O
7.77
7.75
7.72
7.40
7.40
7.38
7.38
7.21
7.20
7.18
7.18
7.14
7.13
4.05
4.03
4.01
4.00
3.92
1.72
1.70
2.93
0.97
0.90
0.97
0.98
3.00
3.05
f1 (ppm)

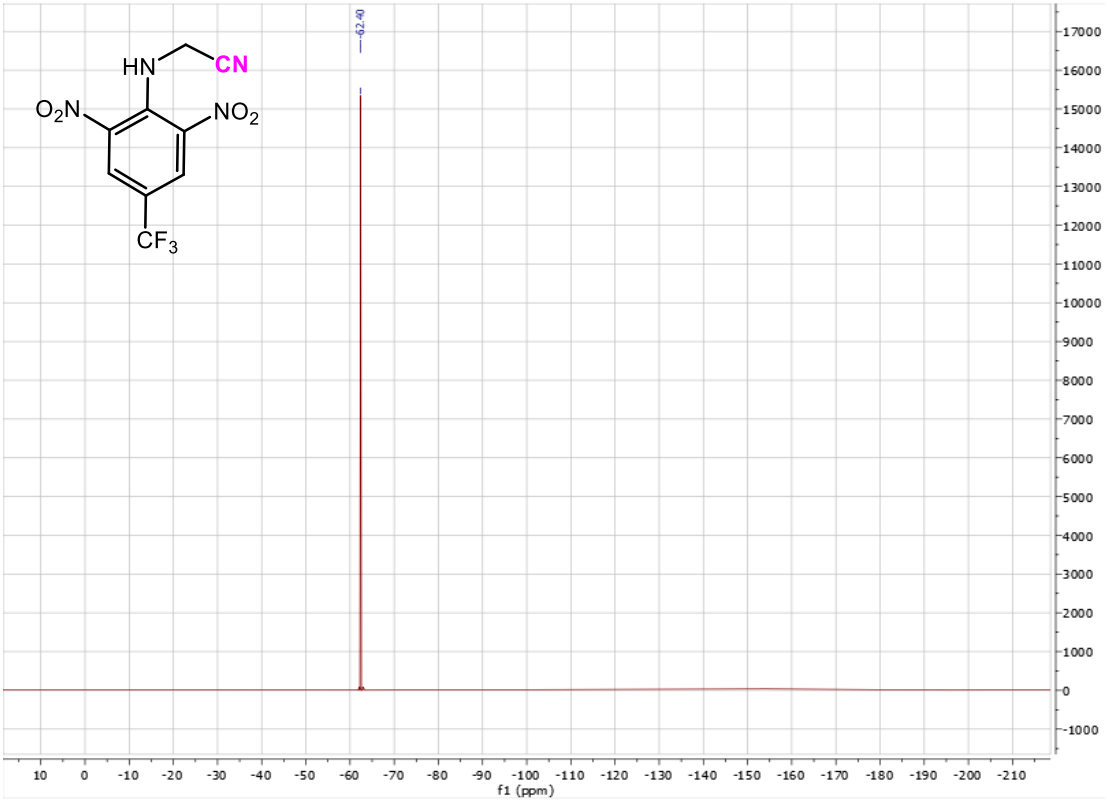

CN
O
158.08
134.00
132.00
129.30
128.75
127.89
125.38
124.93
121.78
119.57
105.64
55.33
31.21
21.48
f1 (ppm)

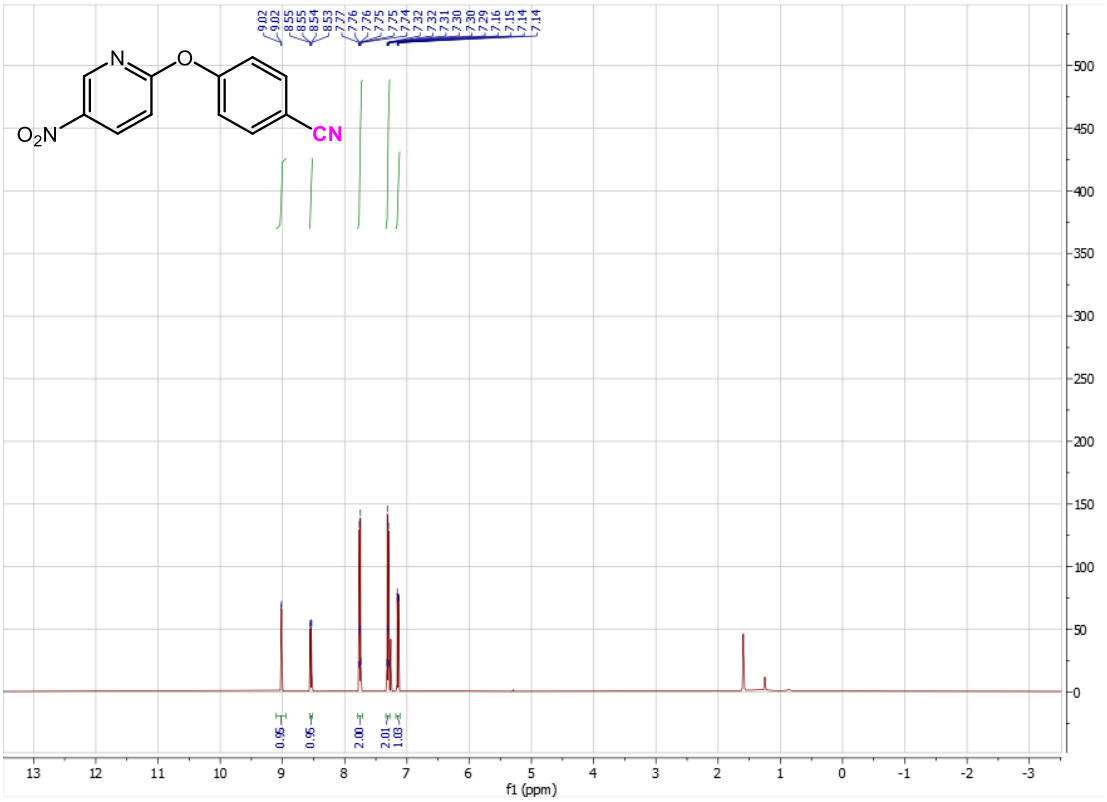

Cl
CN
N
O
8.80
8.79
8.53
7.51
7.44
7.43
4.07
1.00
0.85
1.03
0.96
3.24
f1 (ppm)

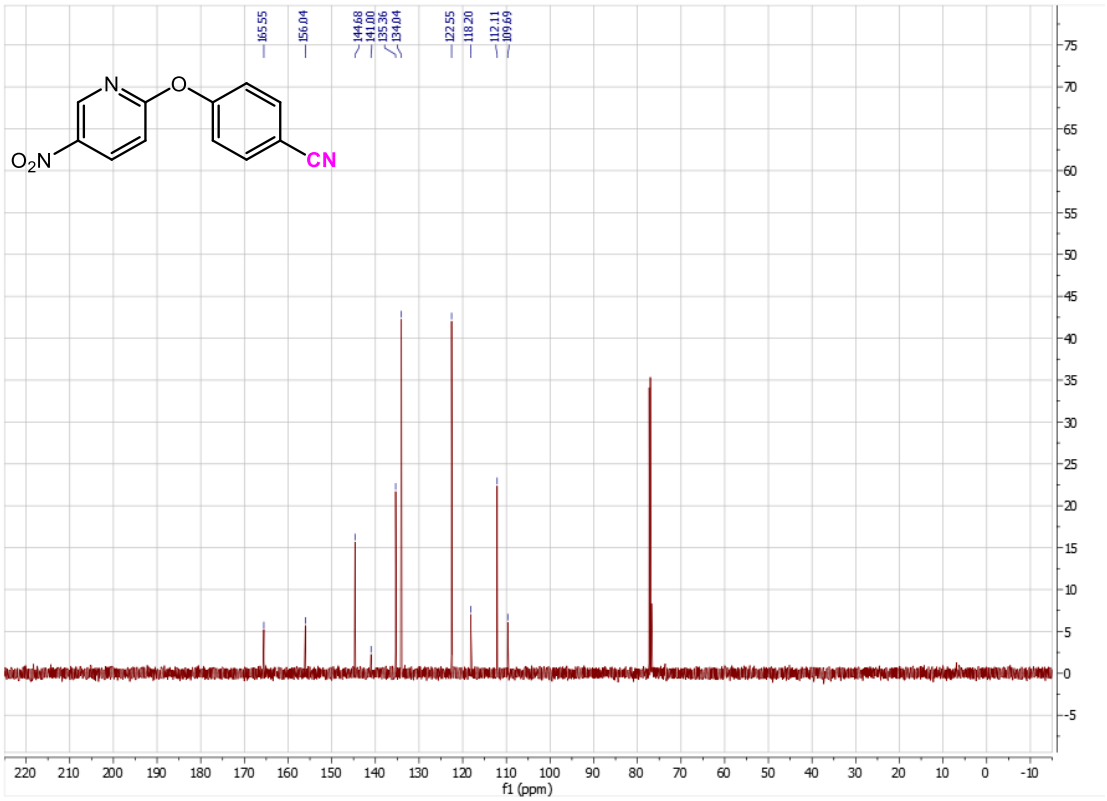

Cl
CN
N
O
160.10
153.30
151.94
143.28
132.49
121.14
120.78
115.61
108.94
105.72
56.84
f1 (ppm)

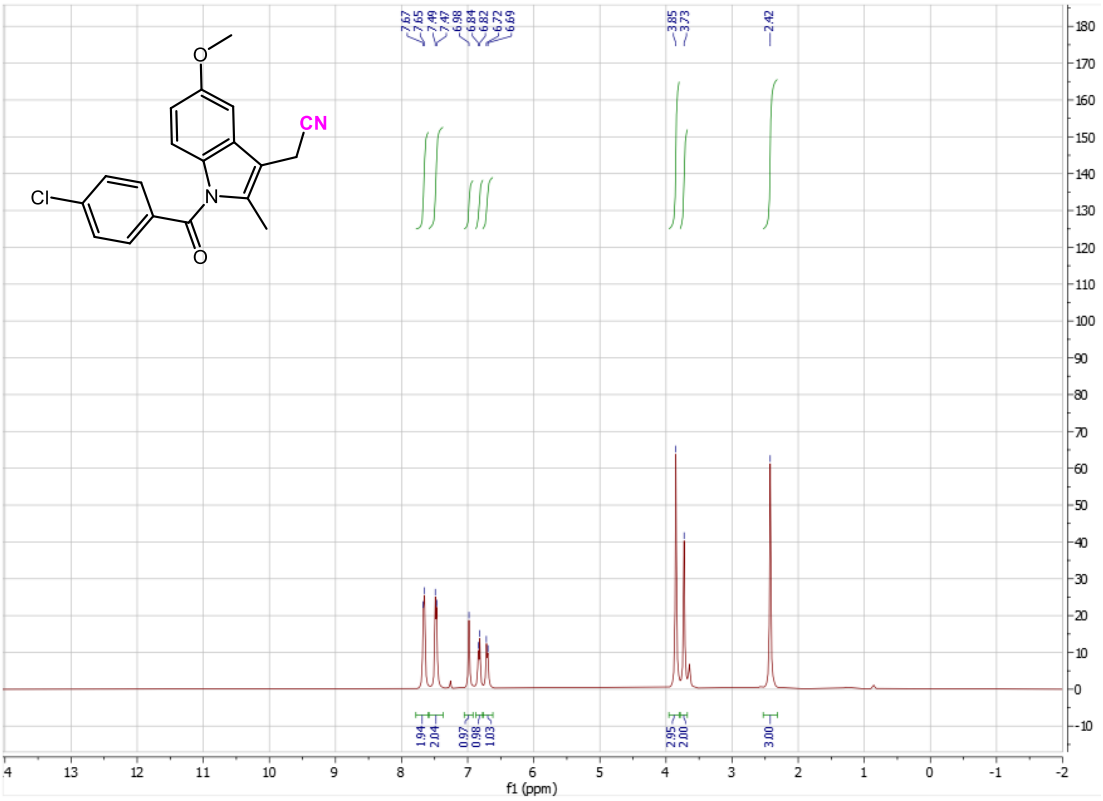

HN
CN
O2N
NO2
CF3
8.86
8.58
4.24
4.22
1.00
2.00
2.11
f1 (ppm)

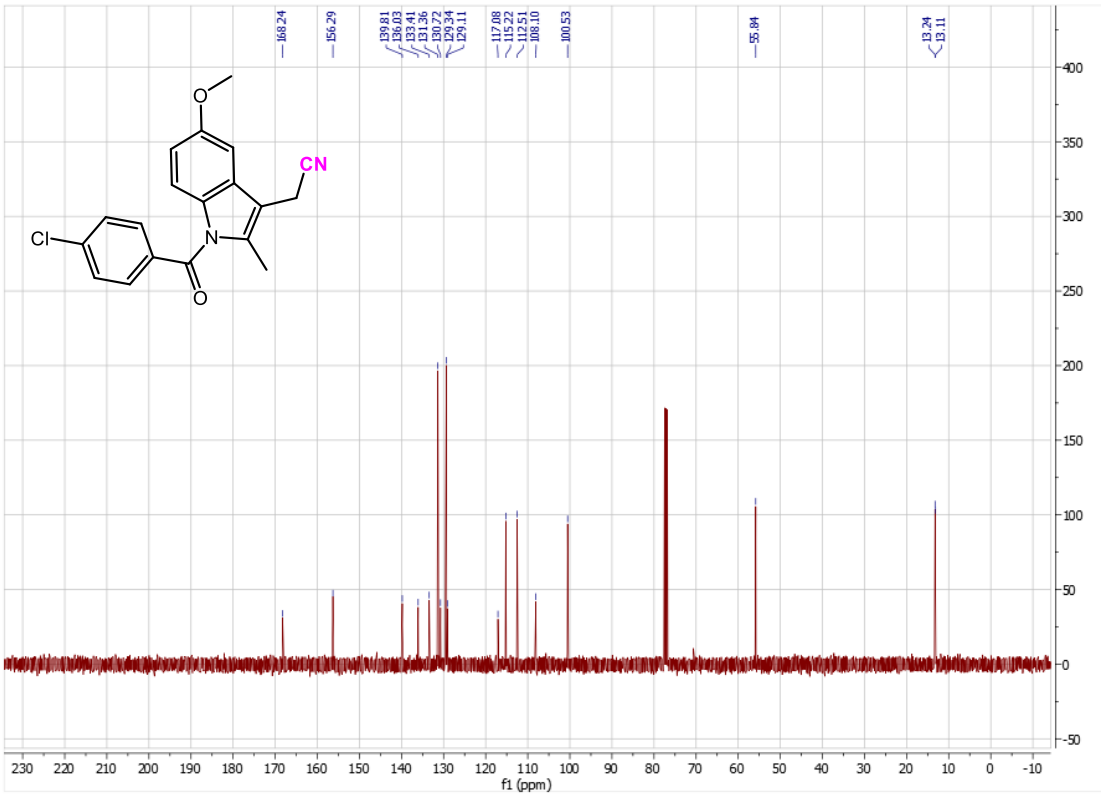

HN
CN
O2N
NO2
CF3
139.82
138.71
129.81
129.78
129.75
129.72
125.41
123.24
121.08
120.97
120.58
120.29
120.00
118.91
113.84
34.17
f1 (ppm)

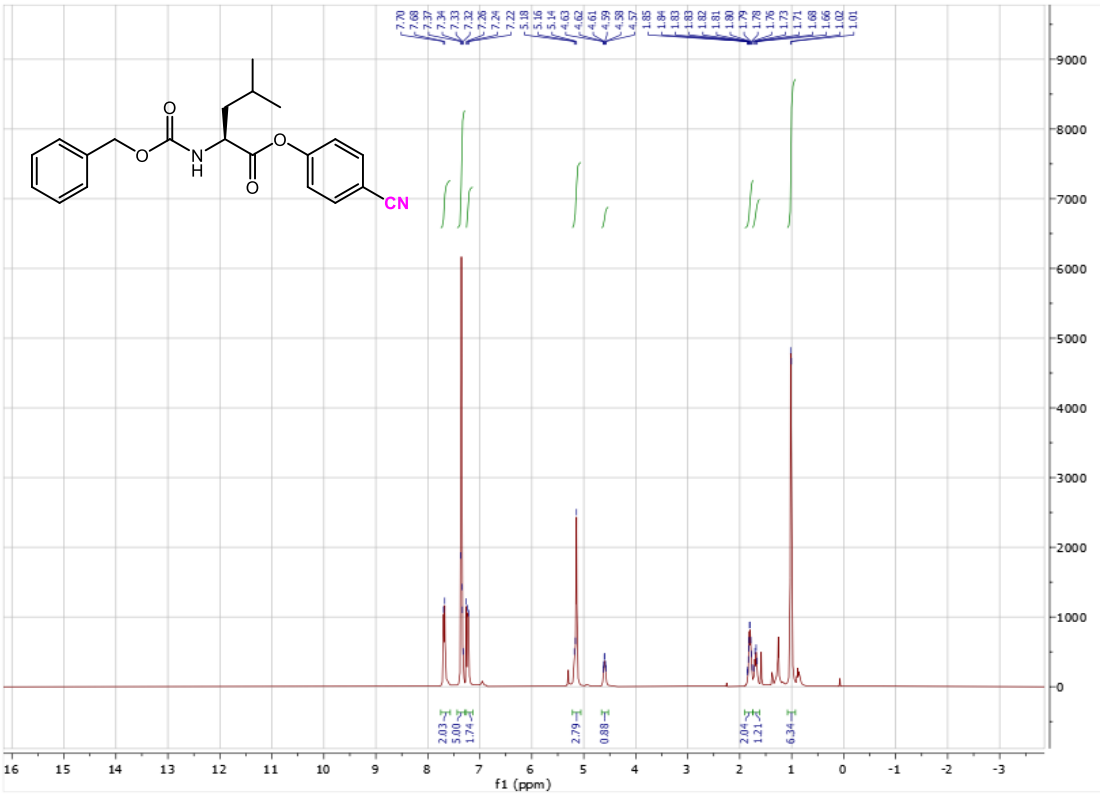

HN
CN
O2N
NO2
CF3
-62.40
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


9.02
9.02
8.55
8.55
8.54
8.54
8.53
8.53
7.77
7.76
7.76
7.75
7.75
7.74
7.32
7.32
7.31
7.30
7.30
7.29
7.16
7.15
7.14
7.14
N
O
O_2N
CN
0.96
0.95
2.00
2.01
1.03
f1 (ppm)


165.55
156.04
144.68
141.00
135.36
134.04
122.55
118.20
112.11
109.69
N
O
O_2N
CN
f1 (ppm)


7.67
7.65
7.49
7.47
6.98
6.84
6.82
6.72
6.69
3.85
3.73
2.42
1.94
2.04
0.97
0.98
1.03
2.95
2.00
3.00
f1 (ppm)


168.24
156.29
139.81
136.03
133.41
131.36
130.22
129.34
129.11
117.08
115.22
112.51
108.10
100.53
55.84
13.24
13.11
f1 (ppm)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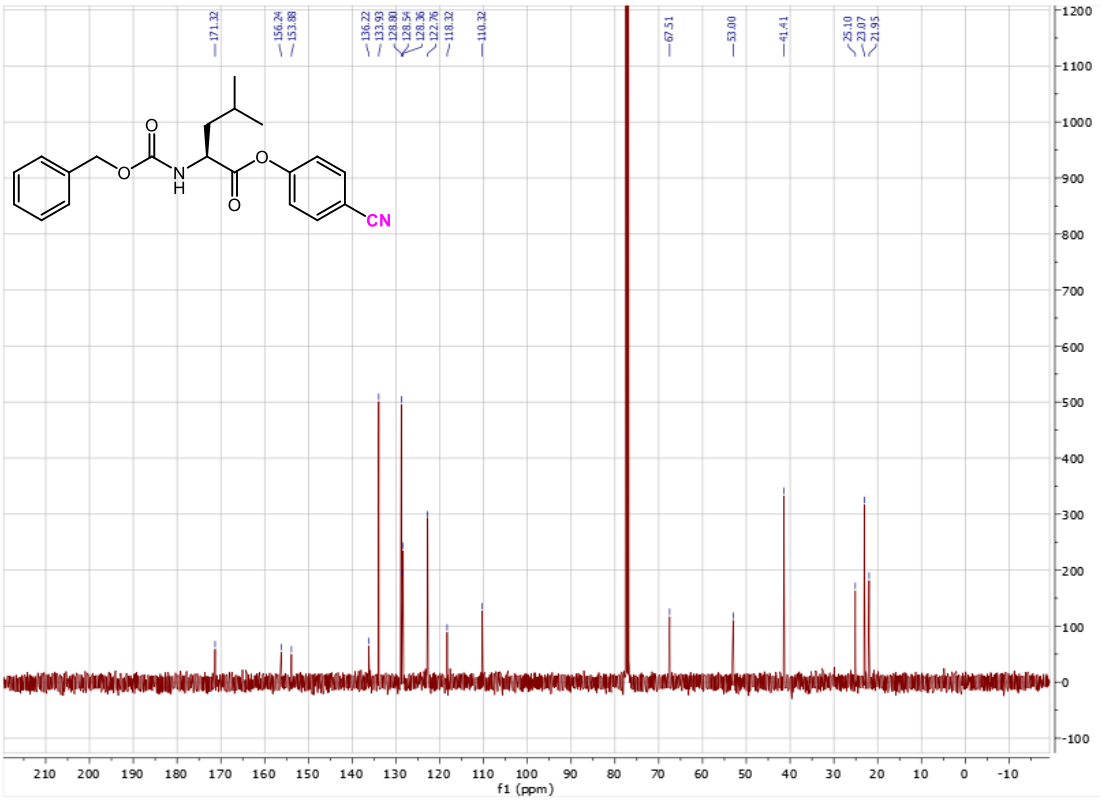
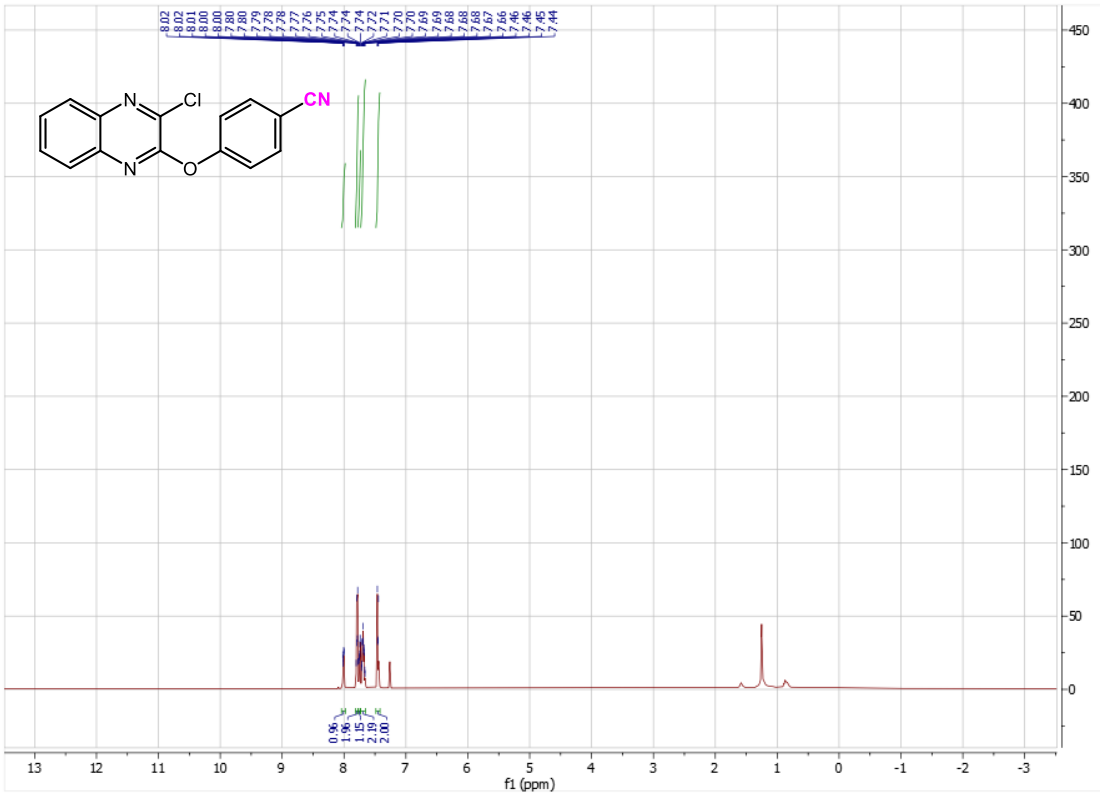
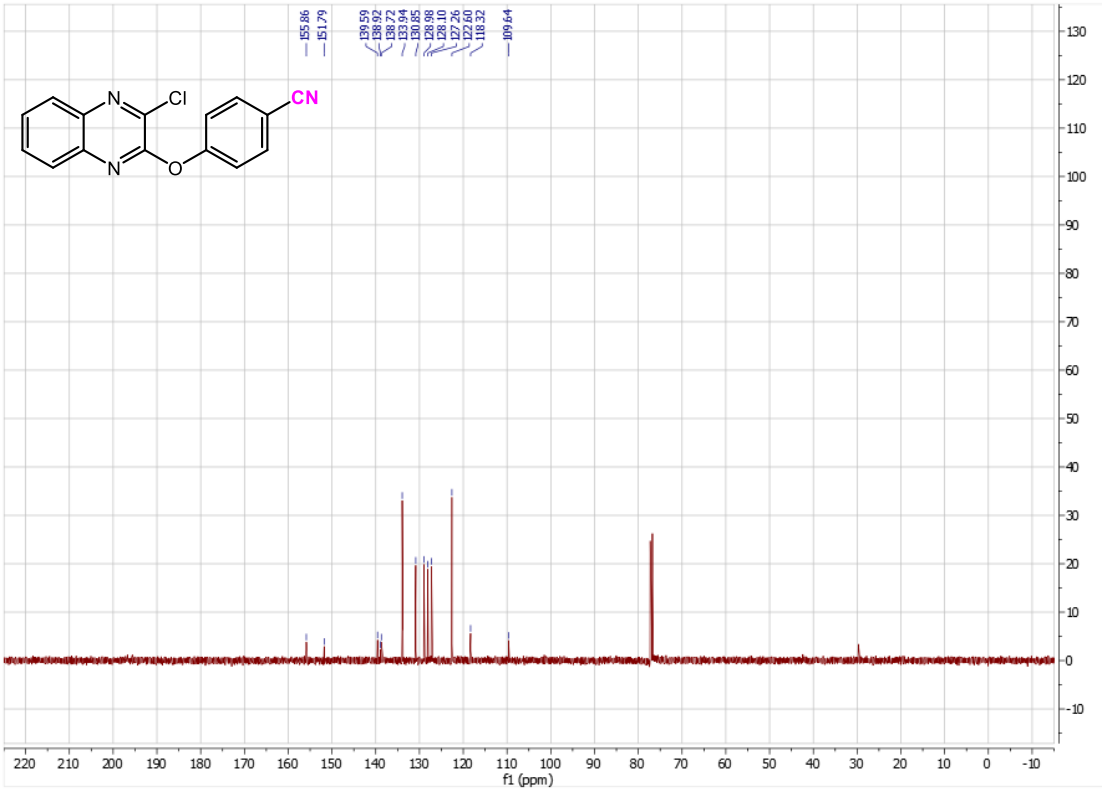
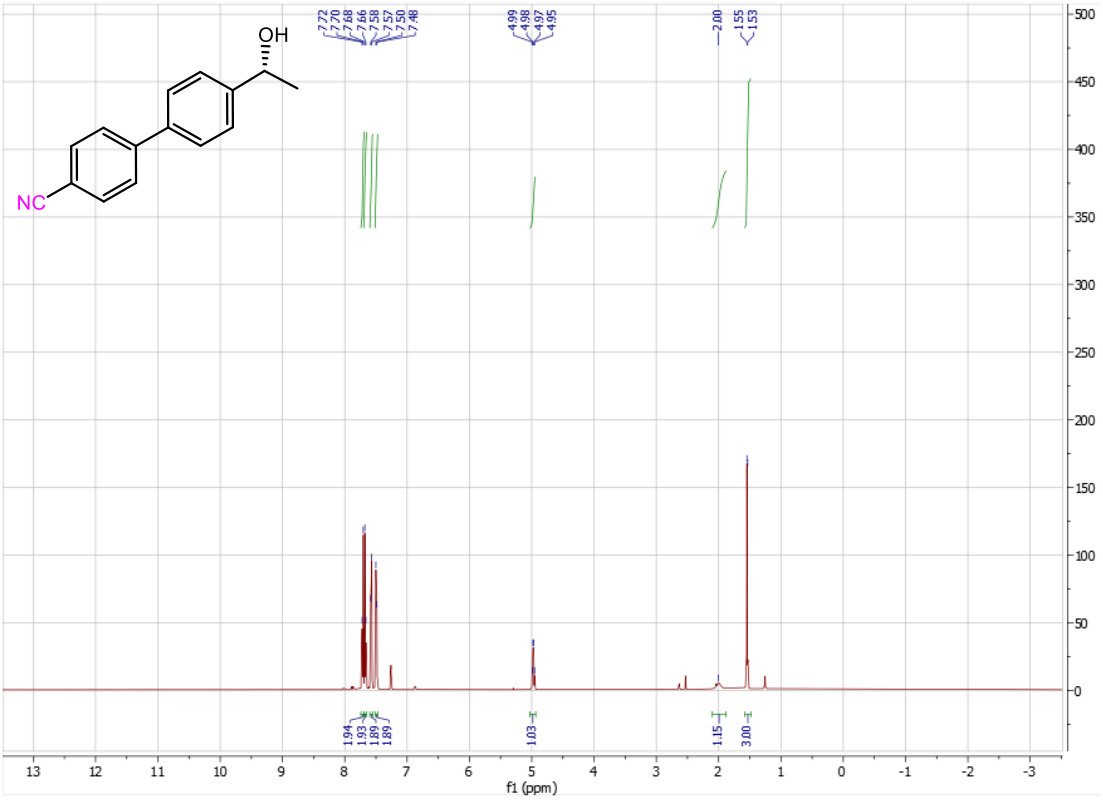
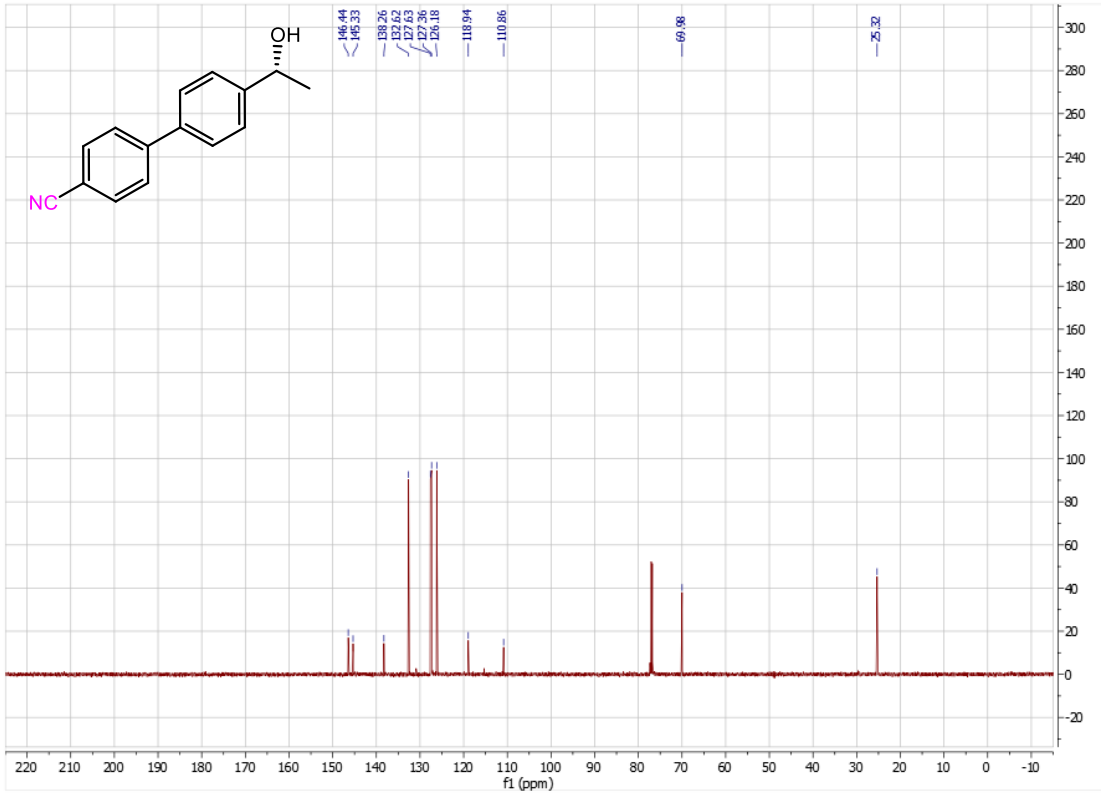
7.68
7.37
7.34
7.33
7.32
7.26
7.24
7.22
5.18
5.16
5.14
4.63
4.62
4.61
4.59
4.58
4.57
1.85
1.84
1.83
1.83
1.82
1.81
1.80
1.79
1.78
1.76
1.73
1.71
1.68
1.66
1.02
1.01
O
O
N
H
O
O
CN
2.03
5.00
1.74
2.79
0.88
2.04
1.21
6.34
f1 (ppm)

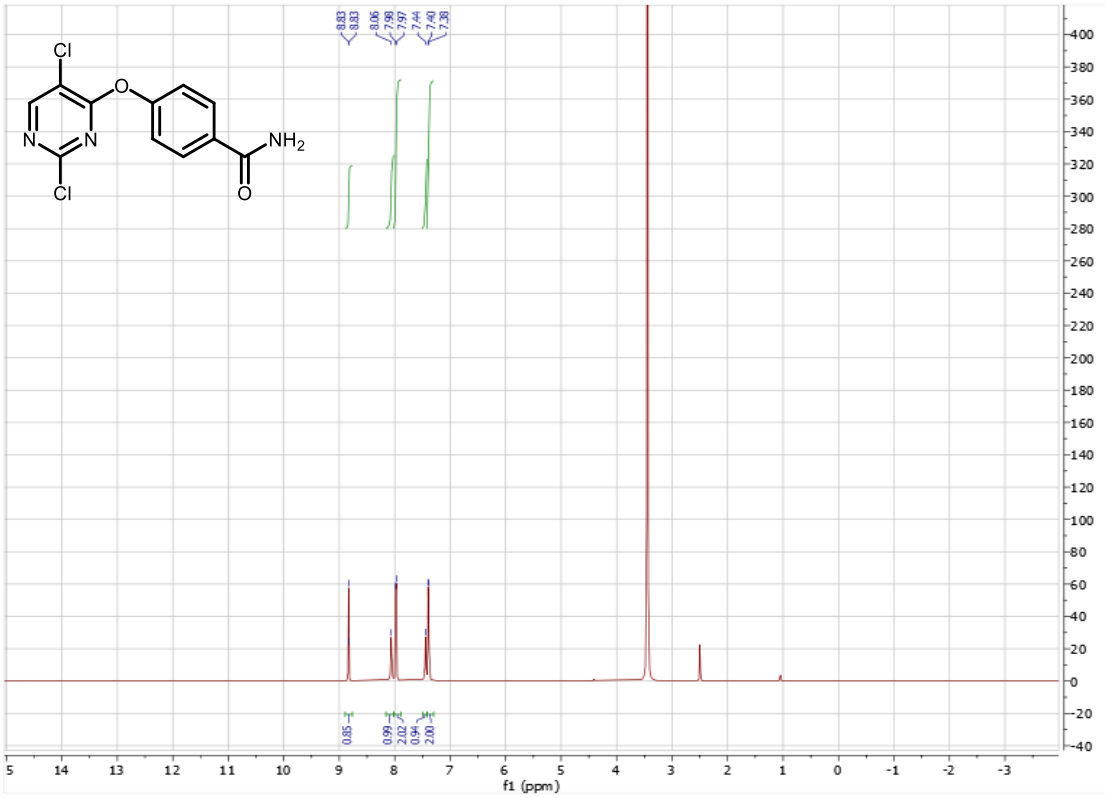

171.32
156.24
153.88
136.22
133.93
128.80
128.54
128.36
122.76
118.32
110.32
67.51
53.00
41.41
25.10
23.07
21.95
O
O
N
H
O
O
CN
f1 (ppm)

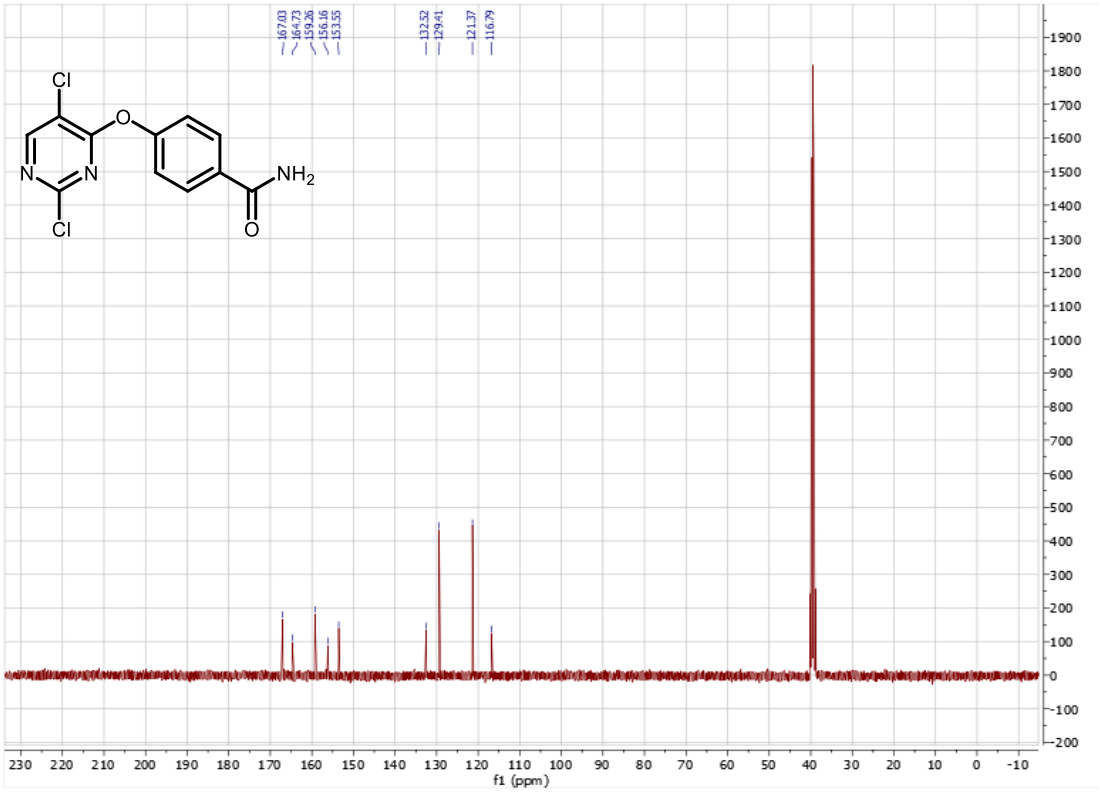

8.02
8.02
8.01
8.00
8.00
7.80
7.80
7.79
7.78
7.78
7.77
7.76
7.75
7.74
7.74
7.74
7.72
7.71
7.70
7.70
7.69
7.69
7.68
7.68
7.68
7.67
7.66
7.46
7.46
7.45
7.44
N
Cl
CN
N
O
0.96
1.96
1.15
2.19
2.00
f1 (ppm)

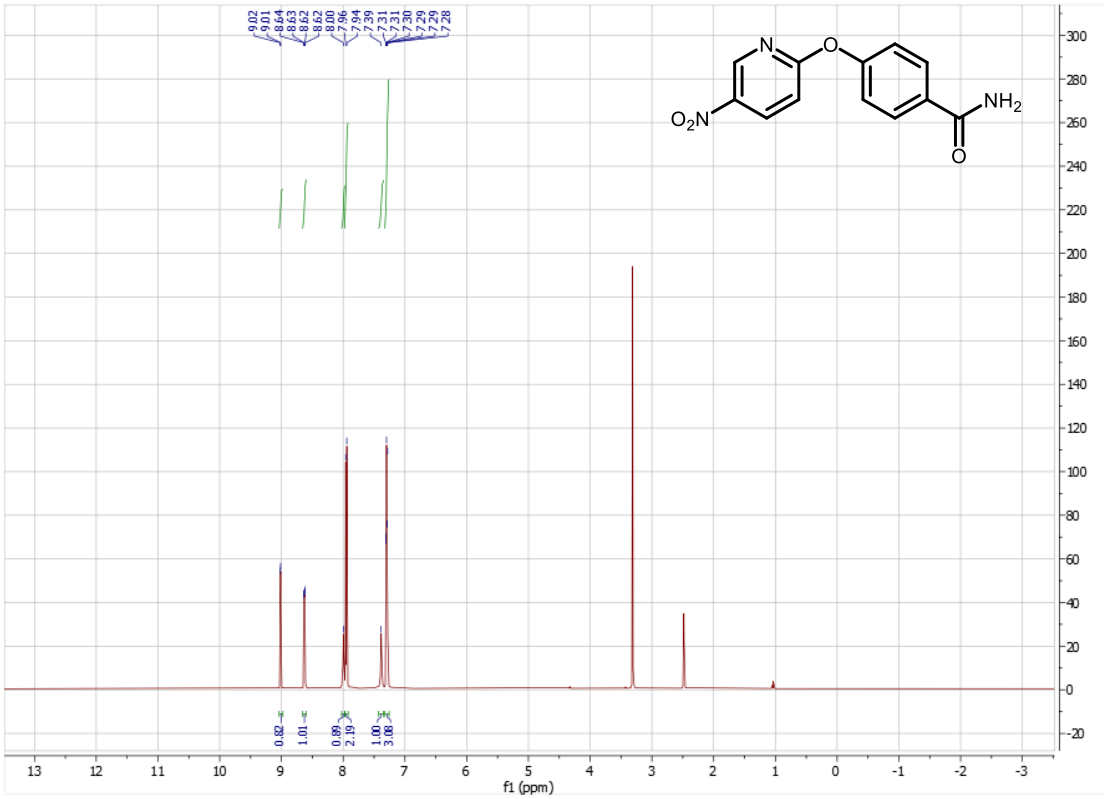

155.86
151.79
139.59
138.92
138.72
133.94
130.85
128.98
128.10
127.26
122.60
118.32
109.64
N
Cl
CN
N
O
f1 (ppm)

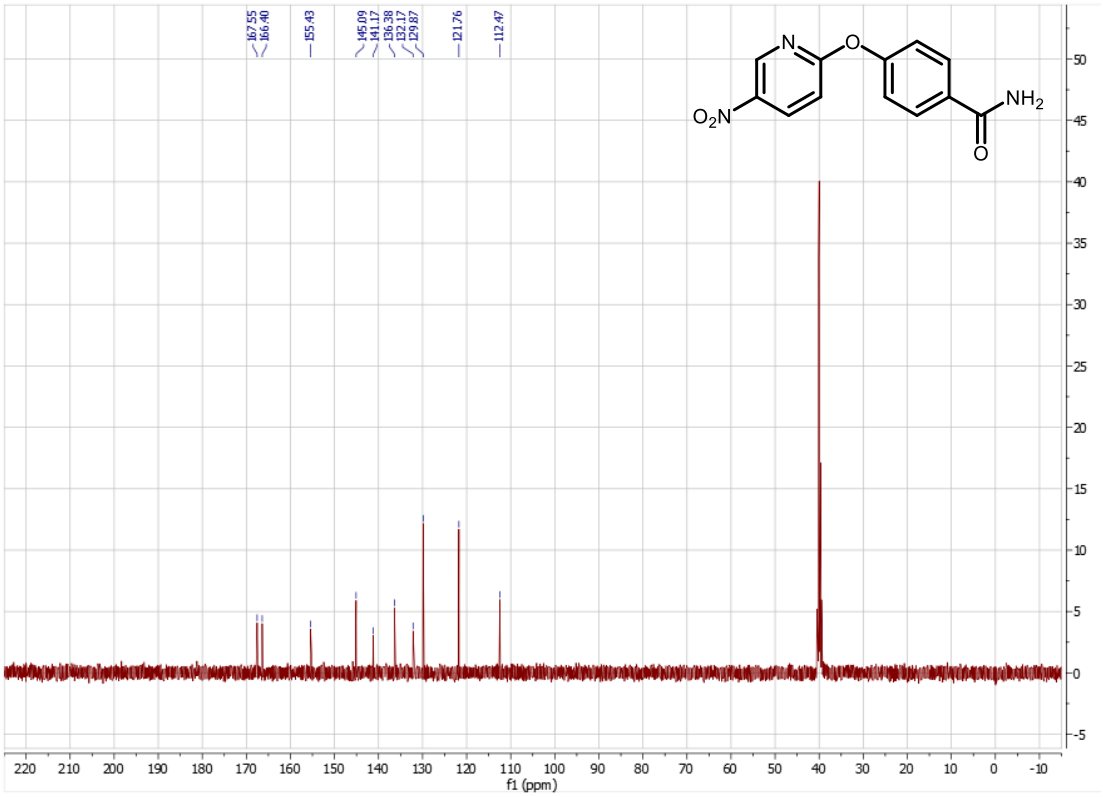

OH
NC
7.72
7.70
7.68
7.66
7.58
7.57
7.50
7.48
4.99
4.98
4.97
4.95
2.00
1.55
1.53
1.94
1.93
1.89
1.89
1.03
1.15
3.00
f1 (ppm)

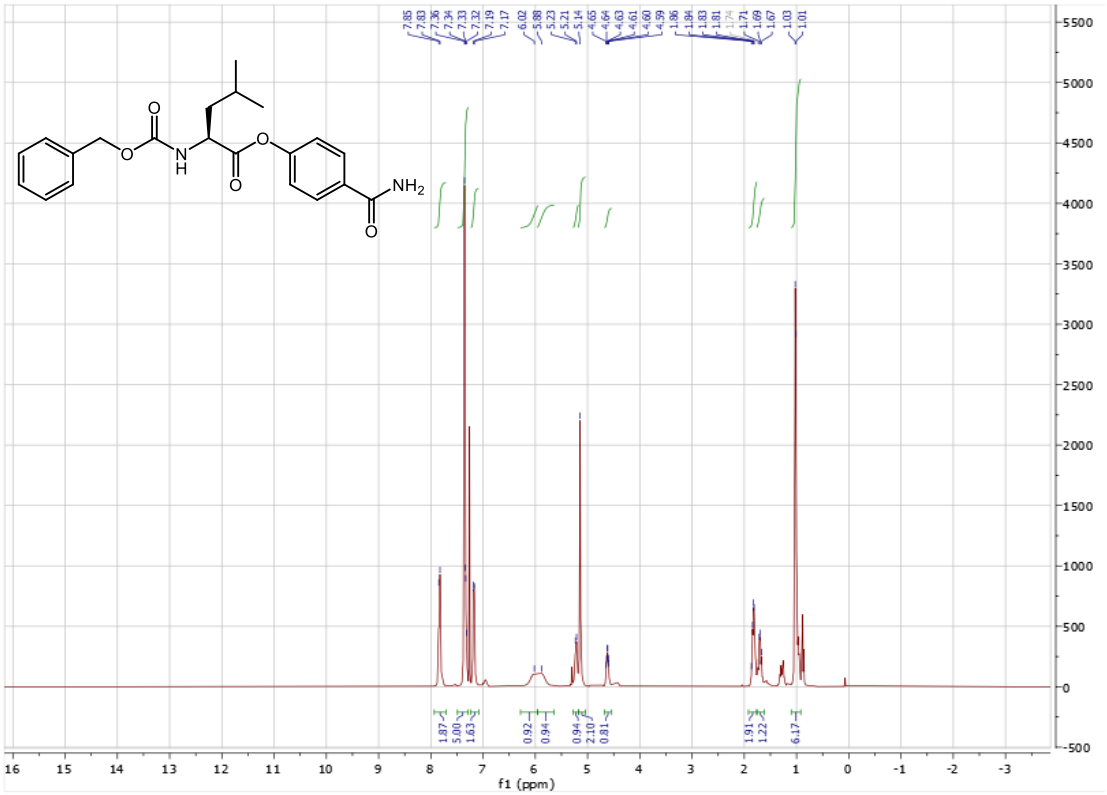

OH
NC
146.44
145.33
138.26
132.62
127.63
127.36
126.18
118.94
110.86
69.98
25.32
f1 (ppm)

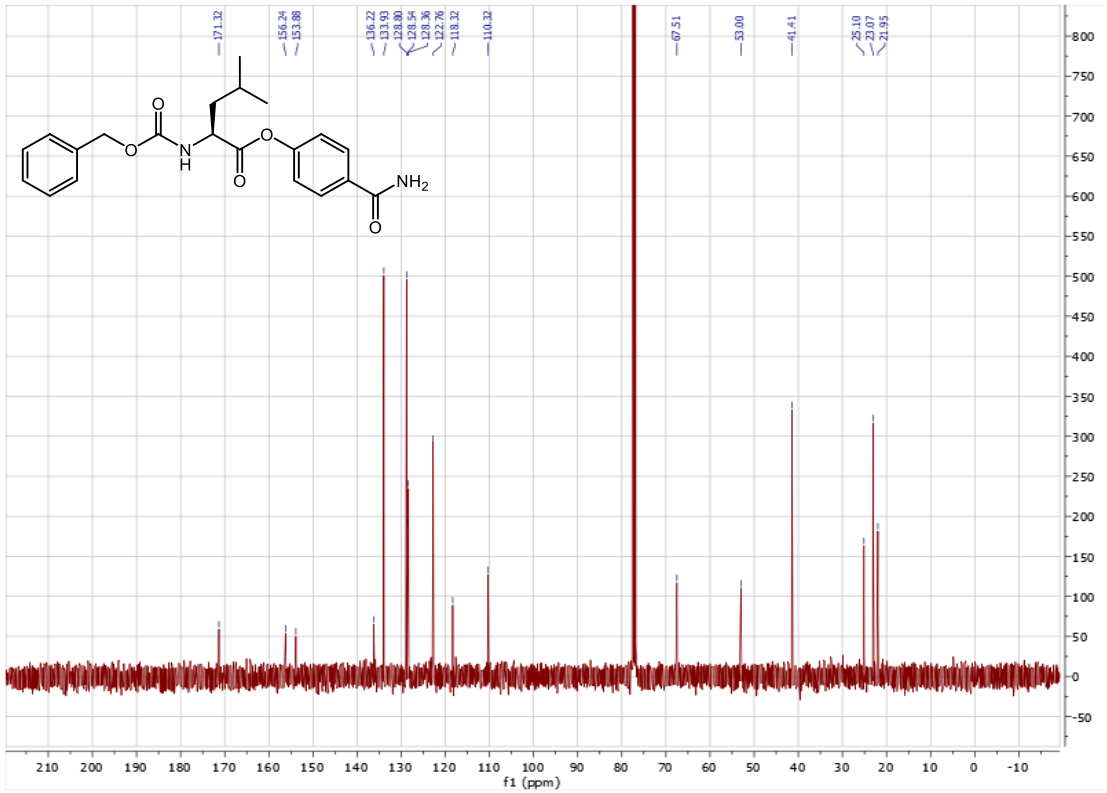

Cl
O
N
N
Cl
NH2
O
8.83
8.83
8.06
7.98
7.97
7.44
7.40
7.38
0.85
0.99
2.02
0.94
2.00
f1 (ppm)

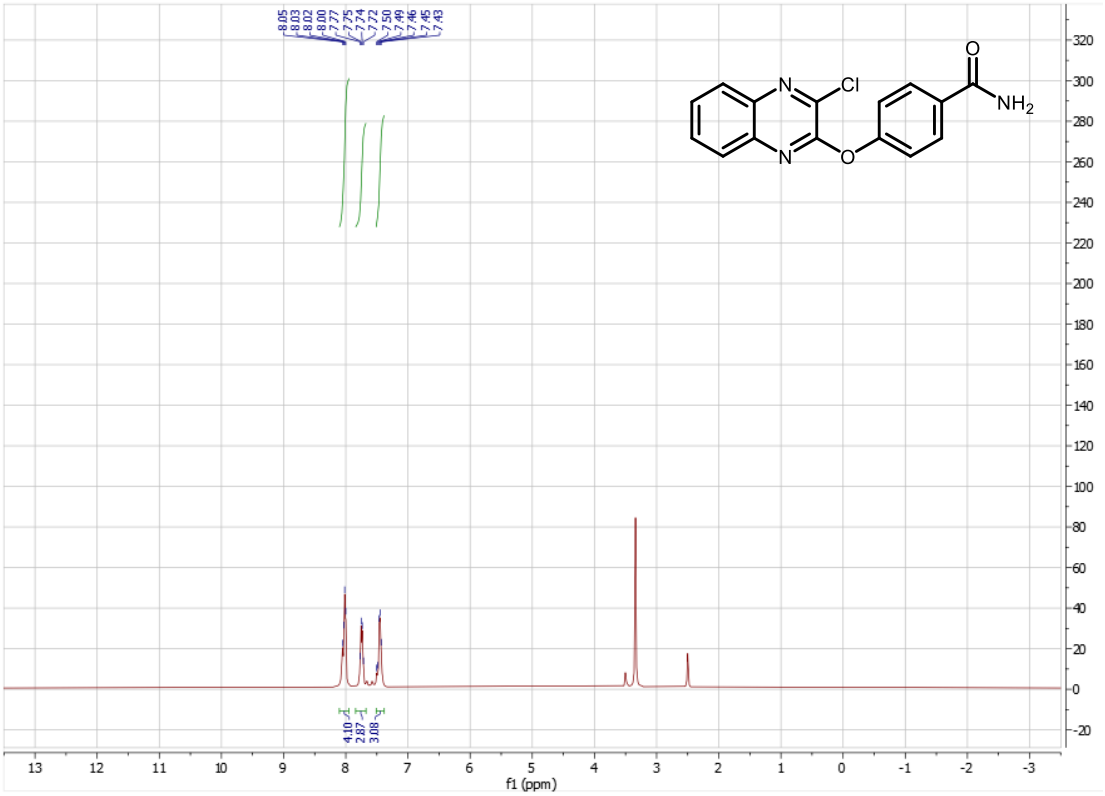

Cl
O
N
N
Cl
NH2
O
167.03
164.73
159.26
156.16
153.55
132.52
129.41
121.37
116.79
f1 (ppm)

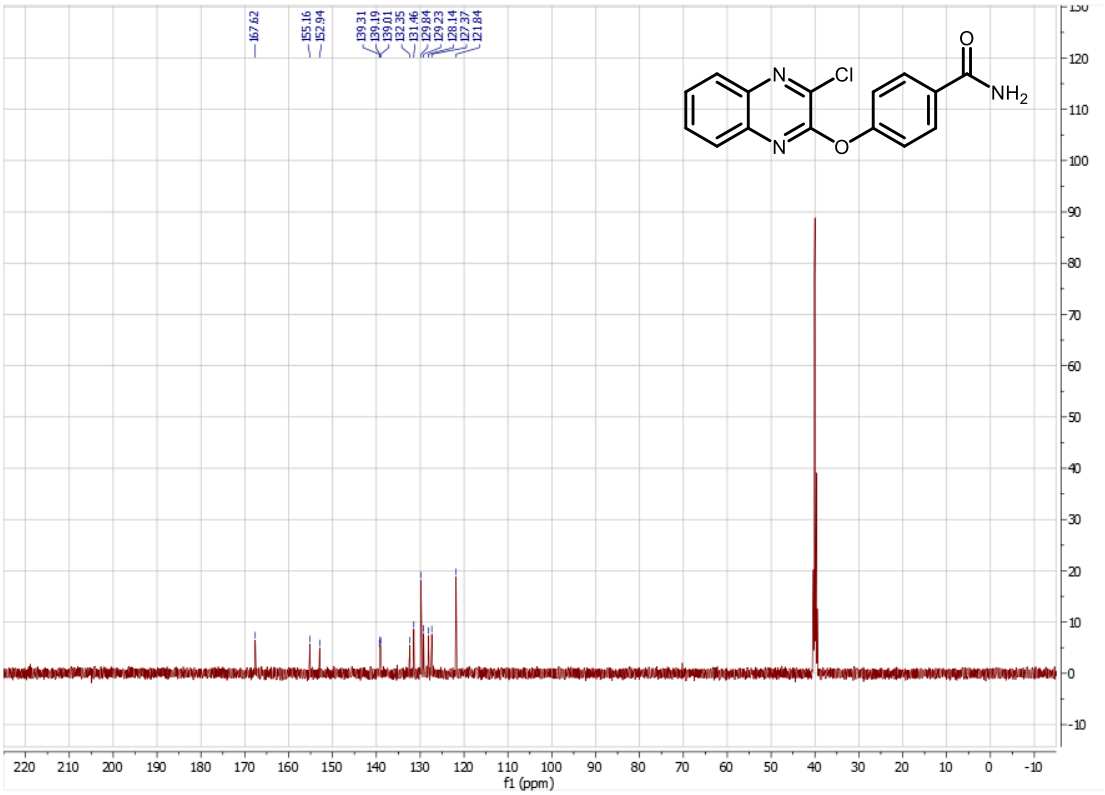

9.02
9.01
8.64
8.63
8.62
8.62
8.00
7.96
7.94
7.39
7.31
7.31
7.30
7.29
7.29
7.28
0.82
1.01
0.89
2.19
1.00
3.08
f1 (ppm)


167.55
166.40
155.43
145.09
141.17
136.38
132.17
129.87
121.76
112.47
f1 (ppm)


7.85
7.83
7.36
7.34
7.33
7.32
7.19
7.17
6.02
5.88
5.23
5.21
5.14
4.65
4.64
4.63
4.61
4.60
4.59
1.86
1.84
1.83
1.81
1.71
1.69
1.67
1.03
1.01
NH2
1.87
5.00
1.63
0.92
0.94
0.94
2.10
0.81
1.91
1.22
6.17
f1 (ppm)


171.32
156.24
153.88
136.22
133.93
128.80
128.54
128.36
122.76
118.32
110.32
67.51
53.00
41.41
25.10
23.07
21.95
NH2
f1 (ppm)


8.05
8.03
8.02
8.00
7.77
7.75
7.74
7.72
7.50
7.49
7.46
7.45
7.43
4.10
2.87
3.08
Cl
N
O
NH2
f1 (ppm)


167.62
155.16
152.94
139.31
139.19
139.01
132.35
131.46
129.84
129.23
128.14
127.37
121.84
Cl
N
O
NH2
f1 (ppm)