Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes

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Supporting Information

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I. Chemicals.

Palladium and Ligands:

$Pd(OAc)_2$, and ligands; 2,2'-bipyridine, 1,10-phenanthroline, 1,8-Diazafluoren-9-one, 8-hydroxyquinoline, 2,2'-bipyrimidine, 1,2-diaminobenzene, 1,1'-binaphthyl-2,2'-diamine, 1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethylphenyl)-imidazolium chloride, sparteine, 2,6-lutidine, pyridine, 2-phenylpyridine, acridine, quinuclidine, 3,5-dichloropyridine, benzoquinoline and tri-*tert*-butylphosphine were purchased from commercial sources (Strem, Aldrich, Acros, TCI America as available), stored in an Innovative Technologies nitrogen filled glove box, and used as received.

Oxidants:

Tert-butylperbenzoate, benzoquinone, potassium persulfate, copper (II) acetate, silver oxide, cerium sulfate, cerium ammonium nitrate, *p*-methoxy-iodosobenzene(diacetate), *o*-methoxy-iodosobenzene(diacetate), *o*-isopropyl-iodosobenzene(diacetate), iodosobenzene(trifluoroacetate), iodosobenzene(diacetate), *N*-fluoropyridiniumtriflate, selectfluor hexafluorophosphate, *N*-fluoro-2,4,6-trimethylpyridinium triflate, and *N*-fluorobenzenesulfonimide (NFSI) were purchased from commercial sources and used as received.

Arenes:

Benzene, toluene, isopropylbenzene, *tert*-butylbenzene, methoxybenzene, trifluoromethylbenzene, fluorobenzene, chlorobenzene, bromobenzene, iodobenzene, acetoxybenzene, 1,2,3-trimethylbenzne, 2,6-dimethylanisole, 2,6-dimethylfluorobenzene, 2,6-dimethylchlorobenzene, 2,6-dimethylbromobenzene, 2,6-dimethyliodobenzene, 1,2-dimethylbenzene, 1,2-dichlorobenzene, 2-fluorotoluene, 2-chlorotoluene, 2-bromotoluene, 2-iodotoluene, 2-iodoanisole, 2-fluoroiodobenzene, methyl-2-methylbenzoate, and methyl-3-methylbenzoate were purchased from commercial sources and used as received without further purification.

Nitrogen Sources:

Phthalimide, 4-methylphthalimide, 4-chlorophthalimide, 3,4,5,6-tetrachlorochlorophthalimide, saccharin, maleimide, succinimide, benzamide, thioacetamide, acetamide, *N*-methyltrifluoroacetamide, and trifluoromethanesulfonamide were purchased from commercial sources and used as received without further purification.

Solvents:

Anhydrous *N,N*-dimethylformamide (Acros), 1,2-dichloroethane (Aldrich), 1,4-dioxane (Aldrich), 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (Aldrich), acetonitrile (Acros), and cyclopentyl methyl ether (Aldrich) were purchased from commercial sources and used as received.

Other Reagents:

Dodecane (Aldrich), and glacial acetic acid (Mallinckrodt) were purchased commercially and used without further purification.

II. Methods.

NMR Spectroscopy: ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker model AM-400 (101 MHz, ^{13}C) spectrometer operating at 400.13 proton NMR frequency, and data analysis was performed using the iNMR software package (version 4.2.0, Nucleomatica, September 2011). NMR chemical shifts are reported in ppm and referenced to the residual solvent peak $CDCl_3$ (δ = 7.26 ppm, ^{1}H; δ = 77.16 ppm, ^{13}C) as an internal standard or 1% $CFCl_3$ in $CDCl_3$ as an external standard (δ = 0 ppm, ^{19}F) unless otherwise noted. Chemical shifts are reported in parts per million (ppm), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

Infrared Spectroscopy (IR): Infrared (IR) spectra were recorded on a Thermo Fisher Scientific Nicolet iS5 Fourier Transform Infrared (FT-IR) spectrophotometer and are reported in wavenumbers (cm^{-1}).

Gas Chromatography: GC analyses were performed on Hewlett Packard HP 6890 series GC system equipped with Agilent Technologies F693 autosampler, HP-5 columns (25 m x 200 µm x 0.33 µm), dual FID detectors, and helium as the carrier gas.

The analysis method for high-throughput experimentation (Procedure A, vide infra) was 1 µL injection of sample, injector temperature of 300 ºC, and 50:1 split ratio. The initial inlet pressure was 57.7 psi but varied as the column flow was held constant at 1.9 mL/min for the duration of the run. The initial oven temperature of 175 ºC was ramped to 300 ºC at 40 ºC/min, and the final temperature was held at 300 ºC for 1.88 min. The total run time was 5 min. The FID temperature was 325 ºC.

The analysis method used in all other cases (Procedures B-D, vide infra) was 1 µL injection of sample, injector temperature of 300 ºC, and 50:1 split ratio. The initial inlet pressure was 41.1 psi but varied as the column flow was held constant at 1.9 mL/min for the duration of the run. The initial oven temperature of 100 ºC was held for 3.0 min, followed by a temperature ramp to 300 ºC at 40 ºC/min. The final temperature was held at 300 ºC for 2.5 min. The total run time was 10.5 min. The FID temperature was 325 ºC.

Gas Chromatography/Mass Spectrometry: GC/MS analyses were performed on Agilent Technologies 5975C VLMSD equipped with an HP-5MS (5% Phenyl Methyl Siloxane) column Model 19091S-433 from Agilent (30 m x 0.25 mm x 0.25 µm) with a Triple Axis Detector and helium as the carrier gas. The analysis method used in all cases was 1 µL injection of sample, injector temp of 300 ºC, and 10:1 split ratio. The initial inlet pressure was 10.0 psi, but varied as the column flow was held constant at 100 mL/min for the duration of the run. The interface temperature was held at 300 ºC, and the electron impact (EI, 30 eV) ion source was held at 300 ºC. The initial oven temperature was held at 45 ºC for 2.25 min with the detector off, followed by a temperature ramp to 300 ºC at 40 ºC/min with the detector turned on at 3.75 min. The final temperature was held at 300 ºC for 3 min. The total run time was 12.00 min. Data are reported in the form of m/z (intensity relative to the base peak = 100, ion).

High Resolution Mass Spectrometry: High-resolution mass spectra (HRMS) under electron impact ionization (+ mode) were obtained on a LTQ-FT instrument at the University of California, Berkeley Mass Spectrometry Facility.

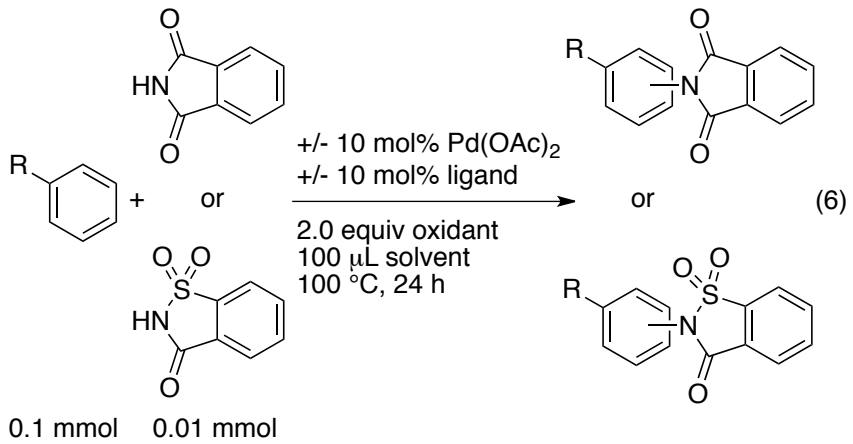
Thin Layer / Column Chromatography: Thin layer chromatography was performed on EMD Chemicals TLC Silica Gel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and *p*-anisaldehyde or potassium permanganate stain. Flash chromatography was performed with Fisher Scientific silica gel (230-400 mesh, grade 60) following standard methods.

High-Throughput Experiments: High-throughput experiments were performed on V&P Scientific Inc. 96-well plate heating block equipped with a Watlow SD temperature controller and a V & P Scientific Inc. Magnetic Tumble Stirrer.

III. Procedures.

(A) Procedure for reactions assembled in a glove box and run under nitrogen for high-throughput experimentation:

*This procedure was used for high-throughput experimentation (**Equation 6**)*

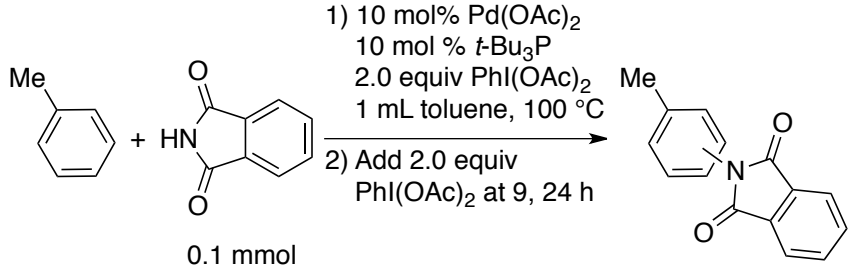


R = Me, *t*-Bu, OMe, CF_3

Reactions were assembled in a nitrogen-filled glove box in a 96-well anodized aluminum parallel synthesis reactor hardware kit. The aluminum plate was filled with 1 mL glass tubes (6 x 50 mm, d x l), and taken into the glove box. These ligands (1.0 mmol) were dosed into the 96-well reactor 1-mL vial as solutions (50 mL of a 0.02 M solution in THF). Plates of these ligands may be generated in advance of the experiment; the solvent is removed on a JKem-blow-down block, and the plates are stored in the glovebox. The reagent for amination (10 μmol, 50 mL of a 0.20 M solution in THF) was then added to the reaction vials, and the resulting mixture was evacuated under reduced pressure to dryness on a JKem-blow-down block. The oxidant (20 μmol, 50 mL of a 0.40 M solution in MeCN) was then added, and the mixture was again evacuated to dryness on a JKem-blow-down block. A parylene coated VP 711D, 1.98 mm x 4.80 mm stir bar was added to each reaction vial. $Pd(OAc)_2$ (1 μmol) and dodecane (1.00 μmol) were then dosed together in the reaction solvent (100 μL of a 0.0100 M solution each). The reaction vials were sealed with PFA sheet and bottom rubber mat. The top plate was fixed into place with screws tightened with a screwdriver. This sealed well plate was then removed from the glove box and heated in a V&P Scientific Inc. 96-well plate heating block on the benchtop at 300 rpm while the temperature was maintained at 100 °C. After 24 h, the reaction assembly was removed from the heating plate, cooled to room temperature and diluted with 1 mL ethyl acetate. The resulting solution was analyzed by gas chromatography, and the reported percent yield was calculated versus the dodecane internal standard.

(B) Procedure for reactions assembled in a glove box and run under nitrogen for optimization experiments and control reactions:

*This procedure was used for **Equation 5, Figure 1, and Table 1***



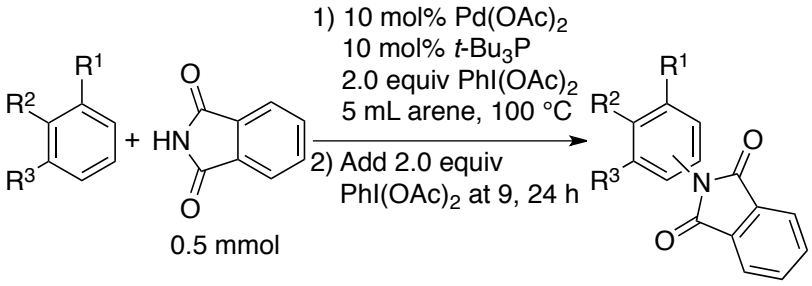
Reactions were conducted in a nitrogen-filled glovebox in an oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol, 0.10 equiv), phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64 mg, 0.20 mmol, 2.0 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Arene (1 mL), and dodecane (10.0 µL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C.

For reactions in **Equation 5** and **Figure 1**, at desired time points, the reactions were cooled to room temperature, taken back into a nitrogen-filled glovebox, and an aliquot (10 µL) of the reaction mixture was removed using an automatic pipet, and diluted with ethyl acetate (1 mL). The resulting solution was analyzed by gas chromatography. For reactions involving sequential addition of $PhI(OAc)_2$ (**Table 1**), at 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox, an aliquot (10 µL) of the reaction mixture was removed using an automatic pipet, diluted with ethyl acetate (1 mL) for GC analysis, and two portions of additional 2.00 equiv of $PhI(OAc)_2$ were added.

After 33 h total reaction time, the yield of amination product formed was determined by GC analysis vs dodecane internal standard. The ratios of constitutional isomers were determined by comparison to the authentic products synthesized from condensation of commercially available aniline isomers with phthalic anhydride in acetic acid at 120 °C. (See Procedure D below).

(C) Procedure for reactions assembled in a glovebox and run under nitrogen to isolate amination products.

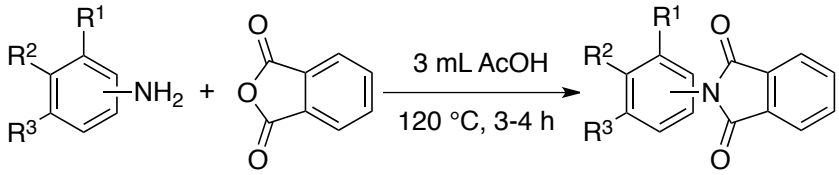
*This procedure was used **Schemes 1** and **2***



Reactions were conducted in a nitrogen-filled glovebox in oven-dried 20 mL scintillation vials. $Pd(OAc)_2$ (11.0 mg, 0.0500 mmol, 0.100 equiv), *t*-Bu_3P (10.0 mg, 0.0500 mmol, 0.100 equiv), phthalimide (73.6 mg, 0.500 mmol, 1.00 equiv) and $PhI(OAc)_2$ (322 mg, 1.00 mmol, 2.00 equiv) were weighed directly into a 20 mL scintillation vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Arene (5 mL), and dodecane (50.0 µL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. At 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox and two portions of additional 2.00 equiv of $PhI(OAc)_2$ were added. After 33 h total reaction time, the amount of amination product formed was determined by GC analysis. An aliquot (50 µL) of reaction mixture was removed using an automatic pipet and diluted with ethyl acetate (1 mL). The resulting solution was analyzed by gas chromatography. The reaction mixture was purified by silica gel column chromatography (5.5" l × 1.5" d column) and the selectivity of constitutional isomers of the *N*-aryl imide product was determined.

(D) Procedure for reactions assembled on the bench and run under air to synthesize authentic amination products[1]

This procedure was used for synthesis of authentic products to determine regioisomeric ratios of products formed in ***Schemes 1*** *and* ***2****.*



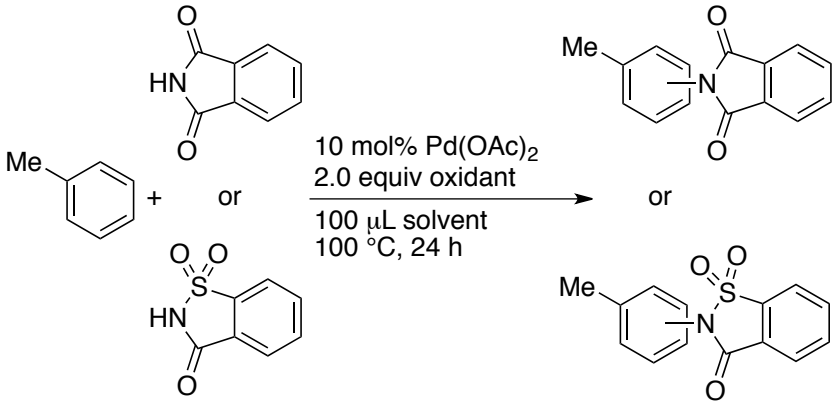
No precautions were taken to exclude air or moisture. On the benchtop, the arylamine (0.500 mmol, 1.00 equiv) and phthalic anhydride (74.0 mg, 0.500 mmol, 1.00 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Glacial acetic acid (3 mL) was added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum and stirred at 120 °C at 1200 rpm for 3-4 h. The reaction was then cooled to room temperature and added to cold water (10 mL), causing precipitation of the phthalimide protected aniline product. The resulting precipitate was filtered and washed with cold water (10 mL) and hexanes (10 mL), and then dried under high vacuum. The GC retention time of the resulting product was determined and compared to the crude reaction mixtures from Procedures A-C to determine the isomeric ratios of products formed from direct C-H amination reactions. ^{1}H and ^{13}C NMR were acquired.

1. Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 327.

IV. Supplementary Results

(A) High-Throughput Experiments (Selected data from reactions that provided the highest yield of products are shown in Table S1)

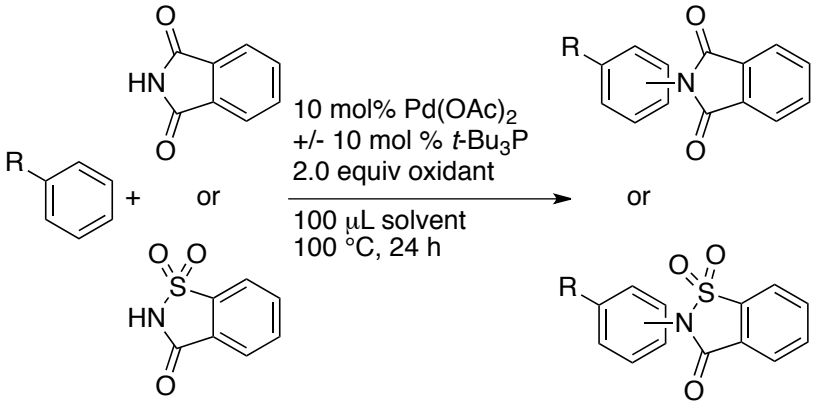
(i) High-throughput experiment (HTE) #1 consisted of two 96-well plates for amination of toluene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst under ligandless conditions. Sixteen oxidants in six different solvents were investigated.



Oxidants:
Tert-butylperbenzoate, benzoquinone, potassium persulfate, copper (II) acetate, silver oxide, cerium sulfate, cerium ammonium nitrate, *p*-methoxy-iodosobenzene(diacetate), *o*-methoxy-iodosobenzene(diacetate), *o*-isopropyl-iodosobenzene(diacetate), iodosobenzene(trifluoroacetate), iodosobenzene(diacetate), *N*-fluoropyridiniumtriflate, selectfluor hexafluorophosphate, *N*-fluoro-2,4,6-trimethylpyridinium triflate, *N*-fluorobenzenesulfonimide (NFSI).

Solvents:
N,N-dimethylformamide, 1,2-dichloroethane, 1,4-dioxane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU), acetonitrile, cyclopentyl methyl ether.

(***ii) High-throughput experiment (HTE) #2*** consisted of three 96-well plates for amination of anisole, *tert*-butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst in the presence and absence of *t*-Bu_3P ligand. Four oxidants and six different solvents were investigated.

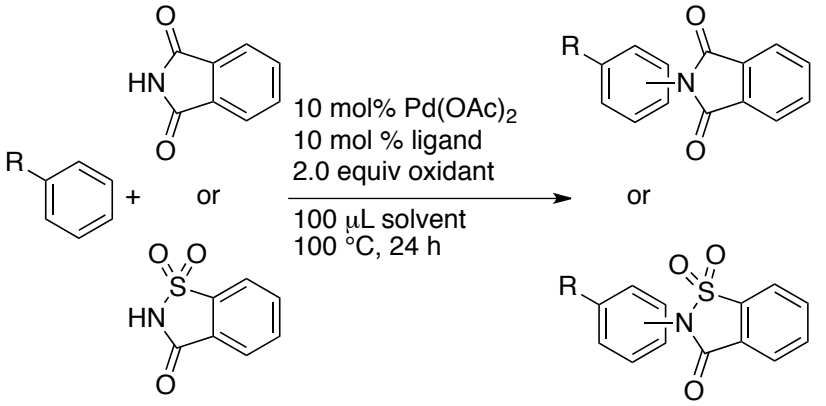


R = *t*-Bu, OMe, CF_3

Oxidants:
selectfluor hexafluorophosphate, iodosobenzene(diacetate), copper (II) acetate, benzoquinone

Solvents:
N,N-dimethylformamide, 1,2-dichloroethane, 1,4-dioxane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU), acetonitrile, cyclopentyl methyl ether.

(***iii) High-throughput experiment (HTE) #3*** consisted of six 96-well plates for amination of anisole, *tert*-butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst. Seven bidentate nitrogen ligands and one carbene ligand were investigated with three oxidants in four solvents.



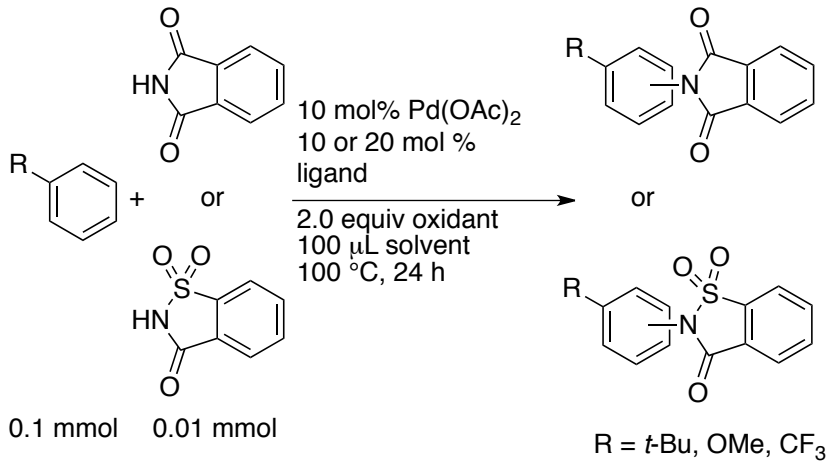
R = *t*-Bu, OMe, CF_3

Ligands:
2,2'-bipyridine, 1,10-phenanthroline, 1,8-Diazafluoren-9-one, 8-hydroxyquinoline, 2,2'-bipyrimidine, 1,2-diaminobenzene, 1,1'-binaphthyl-2,2'-diamine, 1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethylphenyl)-imidazolium chloride

Oxidants:
N-fluorobenzenesulfonimide (NFSI), iodosobenzene(diacetate), copper (II) acetate

Solvents:
1,2-dichloroethane, 1,4-dioxane, acetonitrile, neat arene.

(***iv) High-throughput experiment (HTE) #4*** consisted of three 96-well plates for amination of anisole, *tert*-butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as the pre-catalyst. Eight nitrogen ligands were investigated with three oxidants in two solvents.



Ligands:
Sparteine, 2,6-lutidine, pyridine, 2-phenylpyridine, acridine, quinuclidine, 3,5-dichloropyridine, benzoquinoline

Oxidants:
N-fluorobenzenesulfonimide (NFSI), iodosobenzene(diacetate), copper (II) acetate

Solvents:
1,2-dichloroethane, acetonitrile

Table S1. Selected data from reactions that gave product

Entry	Arene	Amine	Ligand	Oxidant	Solvent	Yield[a]	Selectivity[b] (*o*:*m*:*p*)
1	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	1,2-DCE	28%	1:4:3
2	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	MeCN	9%	1:4:3
3	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	Neat Arene	2%	1:5:3
4	*t*-BuPh	Phthalimide	Acridine	$PhI(OAc)_2$	1,2-DCE	29%	1:6:4
5	*t*-BuPh	Phthalimide	None	$PhI(OAc)_2$	1,2-DCE	10%	1:6:5
4	*t*-BuPh	Phthalimide	2,2'-bipyridine	$PhI(OAc)_2$	1,2-DCE	6%	1:6:5
7	*t*-BuPh	Phthalimide	2,2'-bipyridine	$PhI(OAc)_2$	MeCN	7%	1:4:3
8	*t*-BuPh	Phthalimide	1,8-diaza-fluoren-9-one	$PhI(OAc)_2$	1,2-DCE	28%	1:3:2
9	*t*-BuPh	Phthalimide	1,2-phenylene diamine	$PhI(OAc)_2$	1,2-DCE	30%	1:5:4
10	*t*-BuPh	Phthalimide	2,6-lutidine	$PhI(OAc)_2$	1,2-DCE	25%	1:3:2
11	*t*-BuPh	Phthalimide	Acridine	$PhI(OAc)_2$	1,2-DCE	32%	1:4:3
12	*t*-BuPh	Phthalimide	3,5-dichloropyridine	$PhI(OAc)_2$	1,2-DCE	26%	1:4:3
13	*t*-BuPh	Saccharin	1,10-phenanthroline	$PhI(OAc)_2$	1,2-DCE	28%	1:23:22
14	*t*-BuPh	Saccharin	2,2'-bipyridine	$PhI(OAc)_2$	1,2-DCE	28%	1:3:2
15	*t*-BuPh	Saccharin	pyridine	$PhI(OAc)_2$	MeCN	26%	1:26:24
16	*t*-BuPh	Saccharin	2,6-lutidine	$PhI(OAc)_2$	1,2-DCE	26%	1:12:13
17	*t*-BuPh	Saccharin	Acridine	$PhI(OAc)_2$	1,2-DCE	25%	0:12:13
18	*t*-BuPh	Saccharin	3,5-	$PhI(OAc)_2$	1,2-DCE	48%	0:21:27

			dichloropyridine				
19	*t*-BuPh	Saccharin	8-hydroxy quinoline	$PhI(OAc)_2$	1,2-DCE	48%	1:13:14
20	*t*-BuPh	Saccharin	pyridine	$PhI(OAc)_2$	MeCN	26%	1:26:24
21	*t*-BuPh	Saccharin	None	$PhI(OAc)_2$	1,2-DCE	39%	0:16:23
22	CF_3Ph	Phthalimide	*t*-Bu_3P	Any oxidant	Any solvent	<3%	Not determined

[a]Reactions were run in a nitrogen filled glove box using high-throughput experimentation assembled on 0.01 mmol scale. Yields reported are uncorrected GC yield vs dodecane internal standard. [b]Selectivity for amination with phthalimide determined based on GC analysis by comparison to authentic products. Selectivity for amination with saccharin determined analogously.

(B) Effect of Additives and Oxidants on Yield of Amination Product

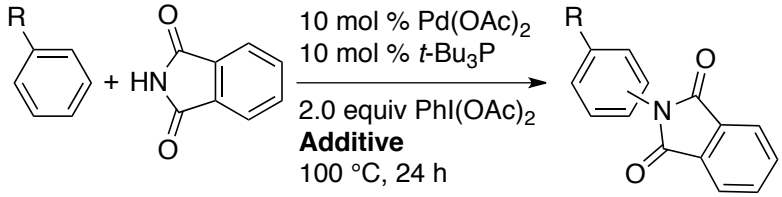


Table S2. Effect of Additives and Oxidants on Yield of Amination Product

Entry	Arene	Additive	% Yield[a]
1	MePh	None	30% (1:13:10)
2	MePh	None, $PhI(OC(O)^iPr)_2$ in place of $PhI(OAc)_2$	19% (1:11:8)
3	MePh	None, $PhI(OC(O)^tBu)_2$ in place of $PhI(OAc)_2$	14% (1:8:6)
4	MePh	None, $PhI(OC(O)CF_3)_2$ in place of $PhI(OAc)_2$	6% (1:2:2)
5	MePh	None, *t*-BuOOH in place of $PhI(OAc)_2$	0% (N.D.)
6	MePh	None, *t*-BuO_3CPh in place of $PhI(OAc)_2$	8% (1:4:4)
7	MePh	None, BzOOBz in place of $PhI(OAc)_2$	0% (N.D.)
8	MePh	None, Oxone in place of $PhI(OAc)_2$	0% (N.D.)
9	MePh	4.0 equiv 3-Å molecular sieves	30%
10	MePh	4.0 equiv 4-Å molecular sieves	33%
11	MePh	4.0 equiv 5-Å molecular sieves	21%
12	*t*-BuPh	None	43%
13	*t*-BuPh	0.25, 0.50 or 1.0 equiv Cs_2CO_3	<5%
14	*t*-BuPh	0.25, 0.50 or 1.0 equiv NaOAc	5-10%
15	PhH	None	35%
16	PhH	CsOH	NP
17	MePh	1eq AcOH	25% (1:17:14)
18	MePh	10eq AcOH	21% (1:16:14)
19	MePh	100eq AcOH	6% (1:4:5)
20	MePh	10 mol% $Pd(OAc)_2$ added at 2 or 5 h reaction time	37%
21	MePh	10 mol% *t*-Bu_3P added at 2 or 5 h reaction time	20%
22	PhH	10 mol% $Pd(OAc)_2$/*t*-Bu_3P added at 5 h reaction time	34%
23	PhH	1.0 equiv phthalimide added at 5 h reaction time	18%
24	PhH	2.0 equiv $PhI(OAc)_2$ added at 2 h reaction time	35%
25	PhH	2.0 equiv of $PhI(OAc)_2$ added at 5 h reaction time	53%
26	PhH	Three portions of 2.0 equiv of $PhI(OAc)_2$ added at 5 h intervals	83% (Figure S1)

[a] Reactions were assembled in a nitrogen-filled glove box in 1-dram vial on 0.1 mmol scale. Yields reported are uncorrected GC yield vs dodecane internal standard

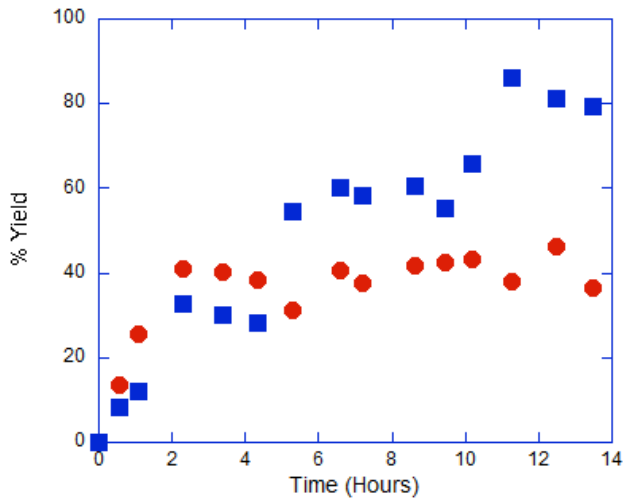
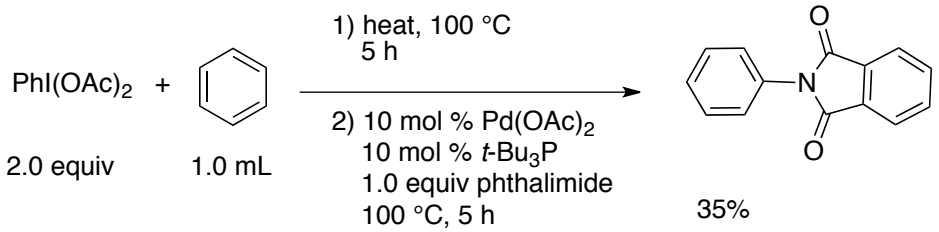


Figure S1. %Yield of benzene amination product with sequential addition of $PhI(OAc)_2$ at 5 h intervals (■) vs with only 2 equiv of $PhI(OAc)_2$ added at the beginning of the reaction (•).

(C) Probing the consumption of $PhI(OAc)_2$



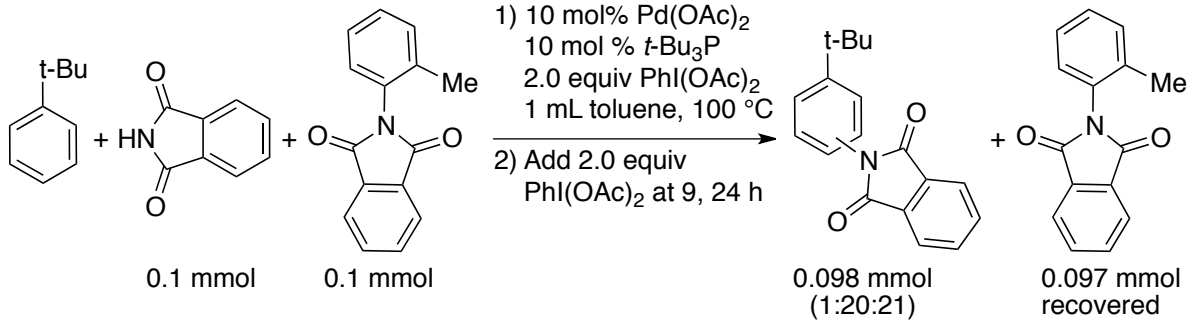
In a nitrogen-filled glove box, $PhI(OAc)_2$ (64.4 mg, 0.200 mmol, 2.00 equiv), benzene (950 μL) and a Teflon-coated stir bar (10 mm x 3 mm) were added to an oven-dried 1-dram vial. The vial was then capped with a PTFE-faced silicone septum cap 0.75", removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C for 5 h. After 5 h, the reaction was cooled to room temperature and taken back into the glove box. The vial was uncapped, and a 50 μL solution of $Pd(OAc)_2$ (11.0 mg, 0.0500 mmol, 0.100 equiv), *t*-Bu_3P (10.0 mg, 0.0500 mmol, 0.100 equiv) in 250 μL of benzene and phthalimide (14.7mg, 0.100 mmol, 1.00 equiv) and 10.0 μL of dodecane were added to the vial. The vial was recapped, removed from the glove box, and heated at 100 °C. After an additional 2 h of reaction time, the reaction was complete. The reaction vial was removed from heat, 50 μL of the reaction was removed from the vial (keeping the septum intact) and injected onto a 1 cm long plug of silica in a Pasteur pipet. The plug was then washed with 1 mL of ethyl acetate, and the filtrate was collected for GC analysis. The yield of the amination product was determined by GC analysis vs dodecane internal standard. The same procedure was repeated with *t*-butylbenzene in place of benzene. The yield of product from the amination of benzene was 35%.

The 35% yield for this experiment is comparable to that observed for the same reaction without heating the oxidant prior to addition of the catalyst. Thus, thermal decomposition of the oxidant $PhI(OAc)_2$

is not responsible for its consumption. Instead, competitive acetoxylation of the arene is observed.[2] The product from acetoxylation is observed when the reaction is run with *t*-butylbenzene in place of benzene.

Under the standard reaction conditions with 2 equiv of $PhI(OAc)_2$, the ratio of amination : acetoxylation product was observed to be 1:2 based on yield of amination product with respect to phthalimide versus acetoxylation product with respect to the oxidant. The regioselectivity of the acetoxylation product was 2.4:1:2.4 *o*:*m*:*p*. The selectivity was determined by comparison to the authentic products synthesized according to literature protocol. However, the relative amounts of product from amination vs acetoxylation vary with substrate and reaction time.

(D) Evaluation of the Stability of the *ortho*-Amination Product

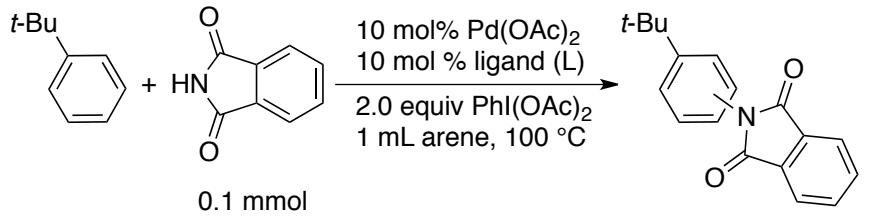


The reaction was conducted in a nitrogen-filled glovebox in an oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol, 0.10 equiv), phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv), $PhI(OAc)_2$ (64.4 mg, 0.200 mmol, 2.00 equiv) and *ortho*-phthalimido(toluene) (23.7 mg, 0.100 mmol, 1.00 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). *t*-Butylbenzene (1 mL), and dodecane (10.0 μL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C.

At 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox. An aliquot (10 μL) of the reaction mixture was removed using an automatic pipet, diluted with ethyl acetate (1 mL) for GC analysis, and two additional portions of 2.00 equiv of $PhI(OAc)_2$ were added.

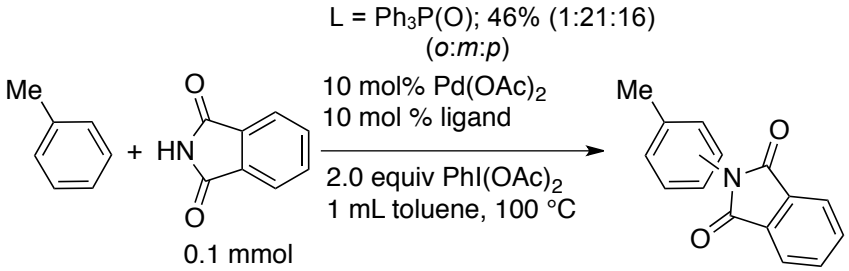
After 33 h total reaction time, the yield of the amination product, as well as the percentage of *ortho*-phthalimido(toluene) remaining after 33 h reaction time, was determined by GC analysis vs dodecane internal standard.

(E) Selectivity of Amination With a Phosphine vs a Phosphine Oxide Ligand



L = *t*-Bu_3P; 35% (1:24:22)
L = Ph_3P; 44% (1:25:19)

2. For Pd-catalyzed acetoxylation of arenes with $PhI(OAc)_2$ see: (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A.* **1996**, *108*, 35. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (c) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409.

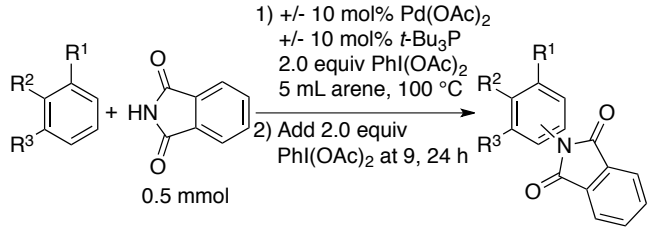


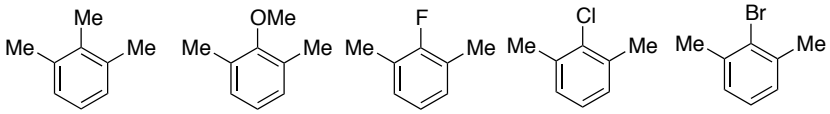
Entry	Ligand	% Yield[a]	Selectivity (*o*:*m*:*p*)[b]
1	None	23%	1:12:9
2	P^tBu_3	30%	1:13:10
3	P^iPr_3	29%	1:12:11
4	PCy_3	29%	1:13:11

Reactions were conducted in a nitrogen-filled glovebox in oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), ligand (0.010 mmol 0.10 equiv) phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64.4 mg 0.200 mmol, 2.00 equiv) were weighed directly into a 1-dram vial, and a Teflon-coated stir bar (10 mm x 3 mm) was added. *t*-Butylbenzene (1 mL) and dodecane (10.0 µL) were added using an automatic pipet. The vial was then capped with open PTFE-faced silicone septum caps 0.75", removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. At various reaction times, 50 µL of the reaction was removed from the vial (keeping the septa intact) and injected onto a 0.5 cm long plug of silica in a Pasteur pipet. The plug was then washed with 1 mL of ethyl acetate, and the filtrate was collected for GC analysis. After approximately 9 h, the reaction was removed from the heat and considered complete. The yields of the amination product were determined by GC analysis vs dodecane internal standard. The ratios of constitutional isomers were determined by comparison to the authentic products synthesized from condensation of commercially available aniline isomers with phthalic anhydride in acetic acid at 120 °C. (See Procedure D above)

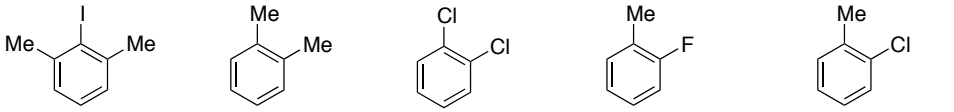
Similar selectivities were observed for reactions conducted with Ph_3P or $Ph_3P(O)$ as ligand, suggesting that the decrease in selectivity for reactions conducted on the benchtop cannot be attributed to ligand oxidation. Consistent with this conclusion, the selectivity of the reaction conducted without added ligand also decreases when air is introduced into the reaction vial.

(F) Comparison of Yield and Selectivity For Amination of Arenes Using $Pd(OAc)_2$/*t*-Bu_3P-Catalyst, $Pd(OAc)_2$-Catalyst and Without a Palladium Catalyst



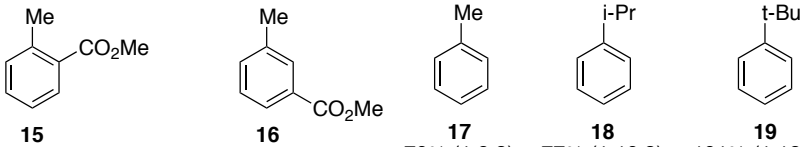


	1	**2**	**3**	**4**	**5**
$Pd(OAc)_2$/*t*-Bu_3P	57% (1:14)	46% (1:10)	45% (1:15)	57% (1:18)	52% (1:24)
$Pd(OAc)_2$	55% (1:14)	55% (1:10)	47% (1:7)	52% (1:6)	39% (1:10)
Uncatalyzed	21% (4:1)	12% (1:1)	7% (2:1)	71% (3:1)	8% (2:1)
	o:*m*	*o*:*m*	*o*:*m*	*o*:*m*	*o*:*m*

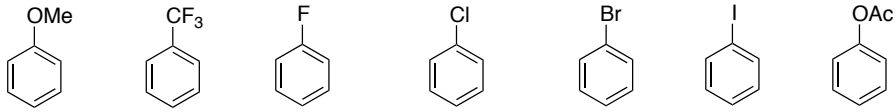


6	**7**	**8**	**9**	**10**
53% (1:9)	77% (1:28)	50% (1:7)	60 (2:1:26:15)	66% (0:0:1:1)
49% (1:7)	73% (1:22)	56% (1:4)	54% (2:1:25:14)	62% (0:0:1:1)
28% (3:1)	22% (1:1)	29% (1:2)	22% (2:1:3:2)	23% (2:1:4:4)
o:*m*	*o*:*m*	*o*:*m*	*o*-Me:*o*-X:*m*-Me:*m*-X	*o*-Me:*o*-X:*m*-Me:*m*-X

11	**12**	**13**	**14**
72% (0:1:7:9)	53% (0:0:1:14)	72% (0:0:1:5)	48% (1:7:3:1)
60% (0:0:1:1)	52% (0:0:1:14)	59% (1:3:15:1)	46% (2:13:6:1)
20% (1:1:1:1)	16% (0:0:1:2)	36% (5:1:2:10)	10% (1:2:2:0)
o-Me:*o*-X:*m*-Me:*m*-X	*o*-Me:*o*-X:*m*-Me:*m*-X	*o*-OMe:*o*-I:*m*-OMe:*m*-I	*o*-F:*o*-I:*m*-I:*m*-F



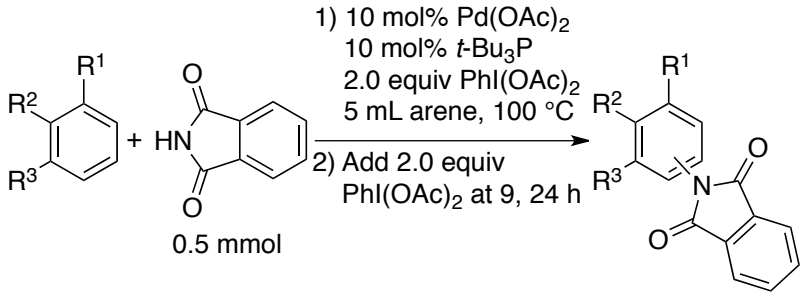
15	**16**	**17**	**18**	**19**
61% (0:1:4:1)	50% (1:1:2:8)	70% (1:9:8)	77% (1:10:8)	101% (1:18:14)
59% (0:1:4:1)	45% (1:1:2:9)	65% (1:6:6)	71% (1:12:10)	127% (1:16:14)
20% (0:2:2:1)	25% (1:1:2:2)	42% (1:1:1)	17% (1:2:2)	98% (1:3:2)
o-Me:*o*-X:*m*-X:*m*-Me	*o*-Me:*o'*-Me:*o*-X:*m*-Me	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*

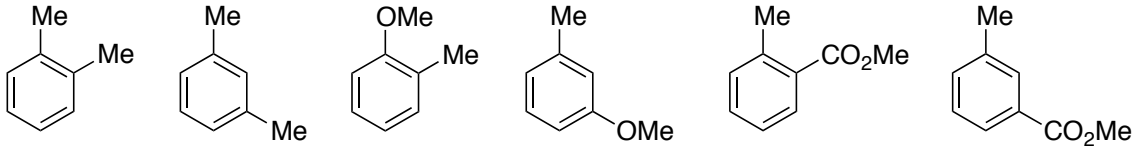


20	**21**	**22**	**23**	**24**	**25**	**26**
46% (1:1:4)	66% (1:16:5)	45% (15:3)	65% (2:18:1)	82% (1:5:5)	80% (1:4:3)	62% (1:8:9)
50% (1:1:3)	75% (1:10:4)	42% (1:5:2)	68% (2:20:1)	72% (1:4:4)	88% (1:3:2)	63% (1:6:7)
60% (1:0:1)	110% (1:4:1)	18% (1:2:1)	17% (1:3:1)	18% (1:1:2)	16% (1:1:1)	21% (1:1:2)
o:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*

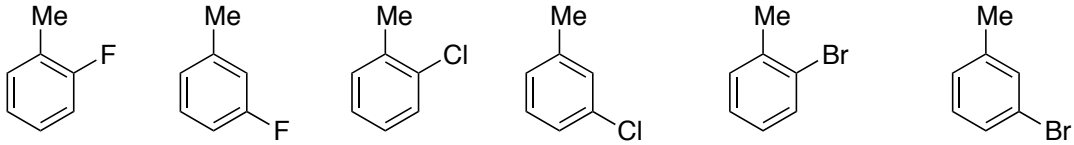
[a] Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents uncorrected GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis.

(G) Comparison of Yield and Selectivity For 1,2- vs 1,3-Disubstituted Arenes[a]

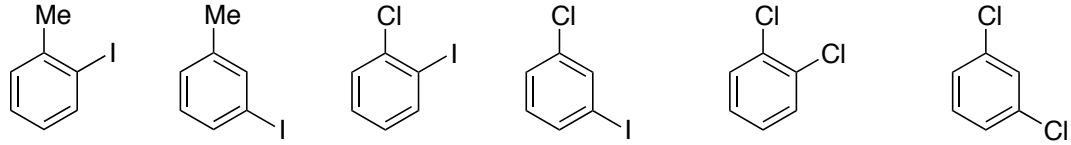




83% (1:40)	40% (0:0:1:6)	48% (0:0:1:2)	19% (0:1:2:4)	61% (0:1:4:1)	50% (1:1:2:8)



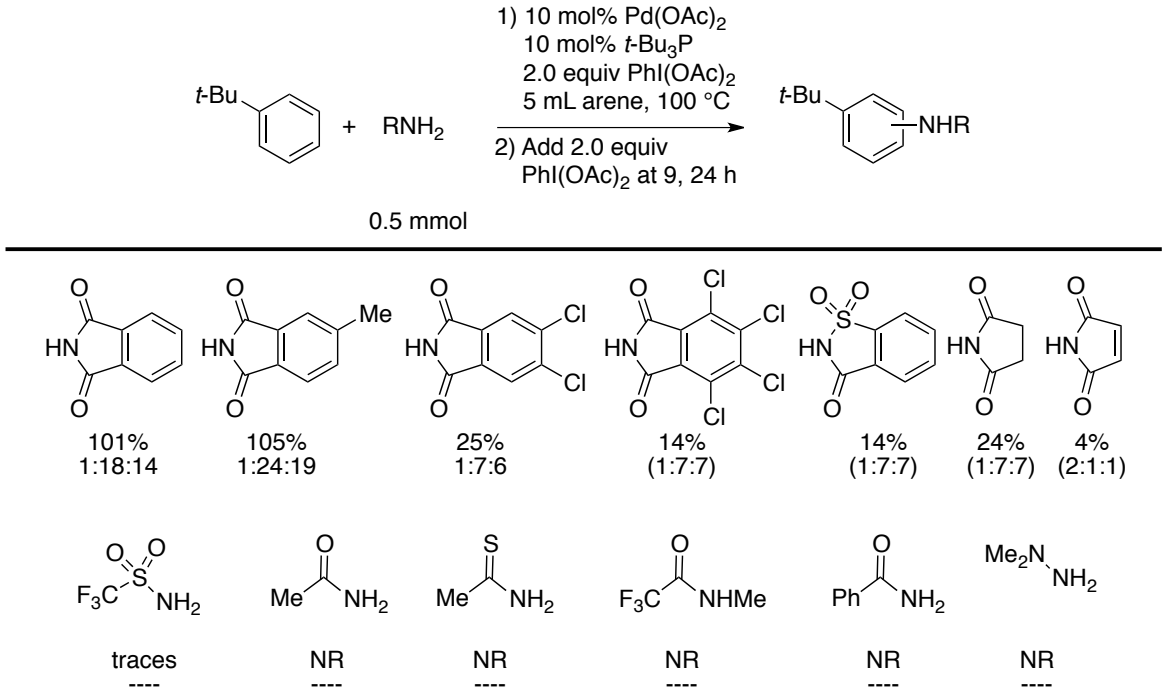
59% (1:1:37:20)	13% (0:0:1:2)	71% (1:1:16:16)	43% (2:6:1:34)	79% (0:0:1:1)	44% (0:1:3:18)



46% (0:0:1:11)	43% (1:1:2:9)	56% (1:1:7:5)	44% (1:2:2:4)	63% (1:7)	38% (0:0:1:1)

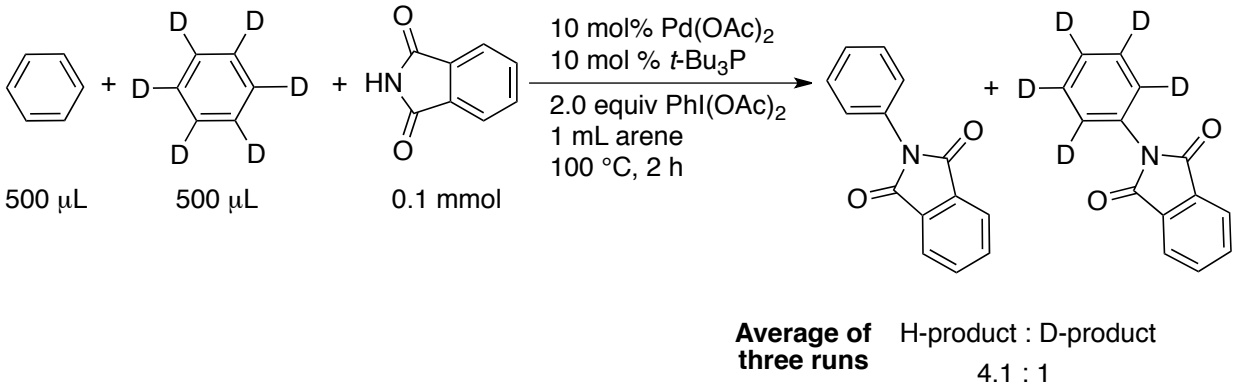
[a] Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis.

(H) Scope of Nitrogen Sources[a]



[a] Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis.

(I) Kinetic Isotope Effect



Average of three runs H-product : D-product 4.1 : 1

Reactions were conducted in a nitrogen-filled glovebox in oven-dried 1-dram vials in triplicates. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol 0.10 equiv) phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64.4 mg 0.200 mmol, 2.00 equiv) were weighed directly into a 1-dram vial, and a Teflon-coated stir bar (10 mm x 3 mm) was added. Benzene (500 μL), deuterated benzene (500 μL) and dodecane (10.0 μL) were added using an automatic pipet. The vial was then capped with PTFE-faced silicone septum cap, removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm, while the temperature was maintained at 100 °C. After 2 h reaction time,

the vial was cooled to room temperature, and 50 μL of the reaction mixture was removed using an automatic pipet and diluted with ethyl acetate (1 mL) for GC/MS analysis. The ratio of protonated product versus deuterated product was determined, based on the relative abundance of isotopomers observed (**Table S3**).

Table S3. Study on isotope effect for amination.[a]

Entry	Trial #	Ratio of H-product : D- product based on C-12 isotope	Ratio of H-product : D- product based on C-13 isotope
1	1	3.57	3.76
2	2	4.29	4.28
3	3	4.30	4.30
Average		4.05	4.11
Average of averages		4.10	
Standard deviation		0.06	

[a] Reactions were assembled in a nitrogen-filled glove box in 1-dram vials on 0.1 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 1 mL arene and 2.0 equiv of $PhI(OAc)_2$ and run for 2 h. H/D ratios are reported based on relative abundance of isotopomers observed by GC-MS.

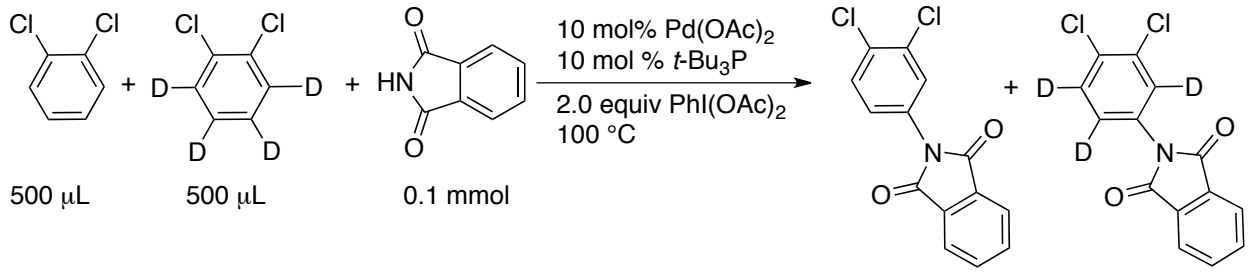
Isotope Effect for Acetoxylation Under Oxidative Amination Conditions

Table S4. Study on isotope effect for acetoxylation under oxidative amination conditions.[a]

Entry	Trial #	Ratio of H-product : D- product based on C-12 isotope	Ratio of H-product : D- product based on C-13 isotope
1	1	5.91	5.42
2	2	5.73	5.64
3	3	5.82	5.50
Average		5.82	5.52
Average of averages		5.67	
Standard deviation		0.21	

[a] Reactions were assembled in a nitrogen-filled glove box in 1-dram vials on 0.1 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 1 mL arene and 2.0 equiv of $PhI(OAc)_2$ and run for 2 h. H/D ratios are reported based on relative abundance of isotopomers observed by GC-MS.

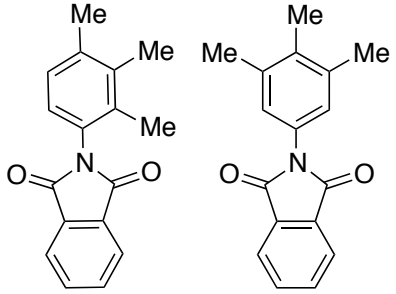
Isotope Effect of Disubstituted Arene



Average of two runs H-product : D-product 2.9 : 1

V. Compound Characterization.

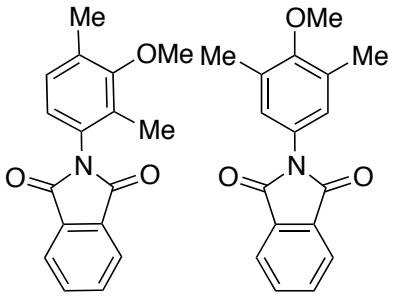
Amination of 1,2,3-trimethylbenzene (1)



1a **1b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,3-trimethylbenzene (**1**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **1b** was confirmed by the synthesis of authentic product.
Data for **1a**, **1b**
GC Yield (Selectivity; **1a**:**1b**): 50% (1:15)
Isolated Yield (Selectivity; **1a**:**1b**): 122 mg white solid, 46% (0:1)
TLC: R_f 0.41 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
1b: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.04 (s, 2H), 2.34 (s, 6H), 2.21 (s, 3H).
^{13}C NMR (101 MHz; $CDCl_3$)
1b: δ 167.7, 137.6, 135.9, 134.3, 132.0, 128.4, 125.9, 123.7, 20.8, 15.4
IR (υ, cm^{-1}):
2922, 2865, 1763, 1715, 1589, 1487, 1465, 1378, 1272, 1237, 1194, 1109, 1084, 1008, 959, 912, 886, 856, 817, 792 779, 764, 749, 714, 699, 662, 646.
HRMS (EI+):
Calc. for $C_1H_{15}NO_2$ $[M]^+$: 265.1103; Found: 265.1105

Amination of 2,6-dimethylanisole (2)

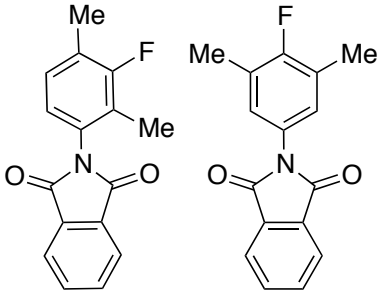


2a **2b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylanisole (**2**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **2b** was confirmed by the synthesis of authentic product.
Data for **2a**, **2b**
GC Yield (Selectivity; **2a**:**2b**): 56% (1:10)
Isolated Yield (Selectivity; **2a**:**2b**): 129 mg off-white solid, 46% (0:1)
TLC: R_f 0.35 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)
2b: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.04 (s, 2H), 3.75 (s, 3H), 2.33 (s, 6H).
^{13}C NMR (101 MHz; $CDCl_3$)
2b: δ 167.7, 156.9, 134.4, 132.09, 131.91, 127.3, 126.8, 123.8, 59.8, 16.4
IR (υ, cm^{-1}):
2948, 1720, 1604, 1486 1420, 1387, 1280, 1225, 1192, 1163, 1111, 1086, 1010, 953, 889, 866, 853, 791, 749, 716, 648, 605.
HRMS (EI+):
Calc. for $C_{17}H_{15}NO_3$ $[M]^+$: 281.1052; Found: 281.1059

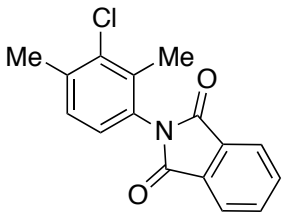
Amination of 2,6-dimethylfluorobenzene (3)



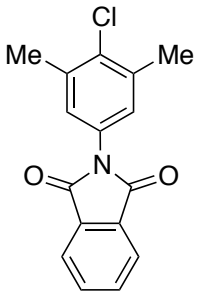
3a **3b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylfluorobenzene (**3**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.
Data for **3a**, **3b**
GC Yield (Selectivity; **3a**:**3b**): 50% (1:15)
Isolated Yield (Selectivity; **3a**:**3b**): 124 mg white solid, 46% (0:1)
TLC: R_f 0.42 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
3b: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.05 (d, *J* = 6.4 Hz, 2H), 2.31 (d, *J* = 2.2 Hz, 6H).
^{13}C NMR (101 MHz; $CDCl_3$)
3b: δ 167.6, 134.5, 131.9, 128.3, 127.44 (d, *J* = 5.6 Hz), 125.7 (d, *J* = 19.4 Hz), 123.9, 14.9 (d, *J* = 4.2 Hz).
^{19}F NMR (376 MHz; $CDCl_3$)
3b: δ -120.2
IR (υ, cm^{-1}):
2956, 1769, 1730, 1593, 1470, 1437, 1416, 1376, 1279, 1197, 1110, 1086, 1035, 956, 892, 856, 788, 749, 711, 669
HRMS (EI+):
Calc. for $C_{16}H_{12}FNO_2$ $[M]^+$: 269.0852 ; Found: 269.0850

Amination of 2,6-dimethylchlorobenzene (4)



4a



4b

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylchlorobenzene (**4**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.

Data for **4a**, **4b**

GC Yield (Selectivity; **4a**:**4b**): 66% (1:16)

Isolated Yield (Selectivity; **4a**:**4b**): 197 mg off-white solid, 69% (1:19)

TLC: R_f 0.49 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

4a: Not detected

4b: δ 7.94-7.92 (m, 2H), 7.79-7.77 (m, 2H), 7.15 (s, 2H), 2.42 (s, 6H).

^{13}C NMR (101 MHz; $CDCl_3$)

4a: Not detected

4b: δ 167.3, 137.4, 134.7, 134.5, 131.8, 129.3, 126.6, 123.8, 21.0

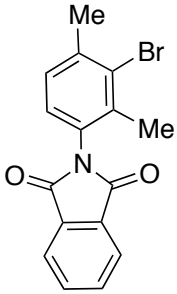
IR (υ, cm^{-1}):

2957, 1768, 1721, 1647, 1596, 1472, 1438, 1420, 1379, 1323, 1279, 1197, 1110, 1085, 1065, 1041, 956, 890, 856, 789, 764, 749, 711, 670, 648.

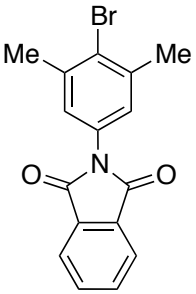
HRMS (EI+):

Calc. for $C_{16}H_{12}ClNO_2$ $[M]^+$: 285.0557; Found: 285.0559

Amination of 2,6-dimethylbromobenzene (5)



5a



5b

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylbromobenzene (**5**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.

Data for **5a**, **5b**

GC Yield (Selectivity; **5a**:**5b**): 46% (1:12)

Isolated Yield (Selectivity; **5a**:**5b**): 172 mg pale yellow solid, 52% (1:24)

TLC: R_f 0.44 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

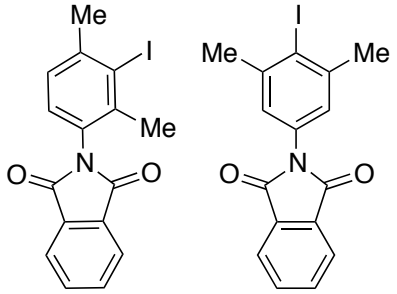
5a: Not detected

5b: δ 7.94 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.15 (s, 2H), 2.46 (s, 6H).

^{13}C NMR (101 MHz; $CDCl_3$)

5a: Not detected
5b: δ 167.3, 139.5, 134.6, 131.8, 130.0, 127.6, 126.3, 123.9, 24.2
IR (υ, cm^{-1}):
2955, 2361, 1770, 1751, 1717, 1590, 1468, 1436, 1414, 1374, 1278, 1197, 1169, 1110, 1099, 1086, 1030, 955, 893, 857, 787, 750, 711, 668.
HRMS (EI+):
Calc. for $C_{16}H_{12}BrNO_2$ $[M]^+$: 329.0051; Found: 329.0053

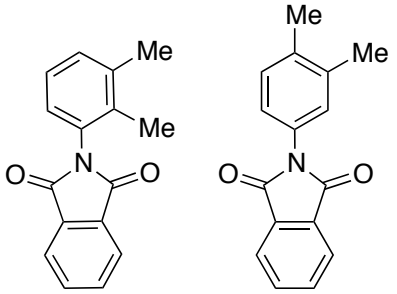
Amination of 2,6-dimethyliodobenzene (6)



6a **6b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethyliodobenzene (**6**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.
Data for **6a**, **6b**
GC Yield (Selectivity; **6a**:**6b**): 51% (1:12)
Isolated Yield (Selectivity; **6a**:**6b**): 245 mg pale yellow solid, 65% (1:19)
TLC: R_f 0.44 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
6a: Not detected
6b: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.14 (s, 2H), 2.53 (s, 6H).
^{13}C NMR (101 MHz; $CDCl_3$)
6a: Not detected
6b: δ 167.2, 143.2, 134.5, 131.7, 131.1, 124.9, 123.8, 108.1, 29.9
IR (υ, cm^{-1}):
3059, 2948, 1769, 1719, 1581, 1485, 1465, 1409, 1375, 1277, 1193, 1110, 1085, 1007, 950, 887, 857, 791, 735, 718, 663, 648.
HRMS (EI+):
Calc. for $C_{16}H_{12}INO_2$ $[M]^+$: 376.9913; Found: 376.9911

Amination of 1,2-dimethylbenzene (7)



7a **7b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,dimethylbenzene (**7**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **7b** was confirmed by the synthesis of authentic product.

Data for **7a**, **7b**

GC Yield (Selectivity; **7a**:**7b**): 83% (1:40)

Isolated Yield (Selectivity; **7a**:**7b**): 181 mg white solid, 72% (1:87)

TLC: R_f 0.40 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

7a: Not detected

7b: δ 7.94 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.28 (s,), 7.19-7.13 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (101 MHz; $CDCl_3$)

7a: Not detected

7b: δ 167.6, 137.7, 137.1, 134.4, 131.9, 130.4, 129.2, 127.8, 124.2, 123.7, 20.0, 19.7

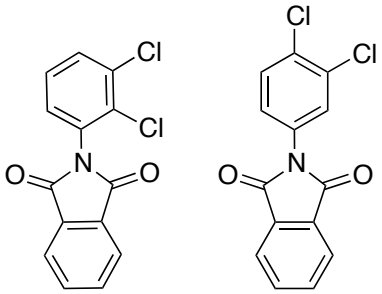
IR (υ, cm^{-1}):

3464, 3065, 2977, 1770, 1719, 1607, 1583, 1505, 1467, 1414, 1379, 1274, 1261, 1239, 1209, 1180, 1131, 1109, 1085, 1028, 1007, 940, 890, 873, 814, 791, 749, 715, 691.

HRMS (EI+):

Calc. for $C_{16}H_{13}NO_2$ $[M]^+$: 251.0946; Found: 251.0947

Amination of 1,2-dichlorobenzene (8)



8a **8b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,dichlorobenzene (**8**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **8b** was confirmed by the synthesis of authentic product.

Data for **8a**, **8b**

GC Yield (Selectivity; **8a**:**8b**): 46% (1:7)

Isolated Yield (Selectivity; **8a**:**8b**): 166 mg white solid, 57% (0:1)

TLC: R_f 0.34 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

8a: Not detected

8b: δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.4 Hz, 1H).

^{13}C NMR (101 MHz; $CDCl_3$)

8a: Not detected

8b: δ 166.8, 134.9, 133.2, 132.3, 131.6, 131.2, 130.8, 128.3, 125.7, 124.1

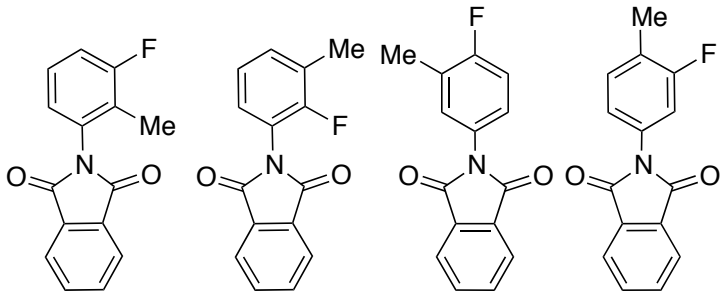
IR (υ, cm^{-1}):

1766, 1715, 1478, 1465, 1382, 1257, 1221, 1202, 1150, 1134, 1115, 1096, 1083, 1031, 886, 860, 821, 785, 710, 688, 680.

HRMS (EI+):

Calc. for $C_{14}H_7Cl_2NO_2$ $[M]^+$: 290.9854; Found: 290.9857

Amination of 2-fluorotoluene (9)



9a **9b** **9c** **9d**

General procedure **(III)(C)** was followed with 5 mL of 2-fluorotoluene (**9**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **9c** and **9d** were confirmed by the synthesis of authentic products.

Data for **9a-d**

GC Yield (Selectivity; **9a**:**9b**:**9c**:**9d**): 59% (1:1:37:20)

Isolated Yield (Selectivity; **9a**:**9b**:**9c**:**9d**): 191 mg white solid, 75% (1:1:50:29)

TLC: R_f 0.33 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

9c: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.29-7.22 (m, 2H), 7.15 (t, *J* = 8.9 Hz, 1H), 2.35 (d, *J* = 1.9 Hz, 3H).

9d: δ 7.95 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.26-7.20 (m, 2H), 7.17-7.11 (m, 1H), 2.33 (s, 3H)

^{13}C NMR (101 MHz; $CDCl_3$)

9c: δ 167.4, 160.7 (d, *J* = 242 Hz), 134.5, 131.7, 129.84 (d, *J* = 6 Hz), 127.21, 127.18, 126.07 (d, *J* = 19 Hz), 125.88 (d, *J* = 8 Hz), 123.8, 115.8 (d, *J* = 30 Hz), 14.72 (d, *J* = 4 Hz).

9d: δ 167.1, 161.0 (d, *J* = 242 Hz), 134.6, 131.63 (d, *J* = 6 Hz), 130.45 (d, *J* = 10 Hz), 125.08 (d, *J*= 17 Hz), 123.9, 121.97, 121.94, 113.6 (d, *J* = 30 Hz) 14.45 (d, *J* = 3 Hz).

^{19}F NMR (376 MHz; $CDCl_3$)

9c: δ -116.3

9d: δ -114.15, -114.17, -114.20

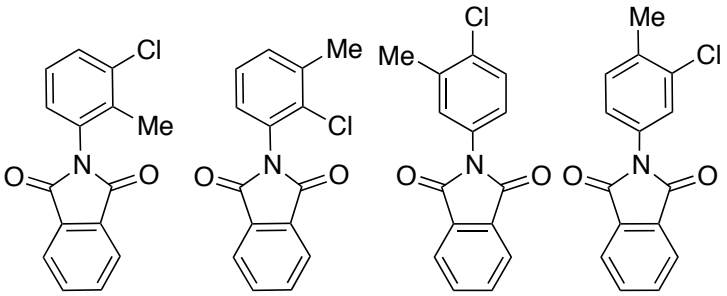
IR (υ, cm^{-1}):

1772, 1719, 1588, 1503, 1466, 1419, 1380, 1287, 1247, 1180, 1106, 1085, 943, 889, 872, 822, 792, 759, 714, 604, 579.

HRMS (EI+):

Calc. for $C_{15}H_{10}FNO_2$ $[M]^+$: 255.0696; Found: 255.0697

Amination of 2-chlorotoluene (10)



10a **10b** **10c** **10d**

General procedure **(III)(C)** was followed with 5 mL of 2-chlorotoluene (**10**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **10c** and **10d** were confirmed by the synthesis of authentic products.

Data for **10a-d**

GC Yield (Selectivity; **10a**:**10b**:**10c**:**10d**): 71% (1:1:16:16)

Isolated Yield (Selectivity; **10a**:**10b**:**10c**:**10d**): 182 mg white solid, 67% (1:1:19:19)

TLC: R_f 0.34 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

10c: δ 7.93 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.5 Hz, 1H), 2.42 (s, 3H).

10d: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.26 (dt, *J* = 5.6, 2.6 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (101 MHz; $CDCl_3$)

10c: δ 167.1, 137.2, 134.64, 134.58, 134.2, 131.69, 131.2, 130.3, 129.7, 128.9, 125.3, 123.86, 20.3

10d: δ 167.1, 136.3, 134.64, 134.58, 134.2, 131.7, 131.2, 130.3, 127.1, 124.8, 123.9, 123.86,19.9

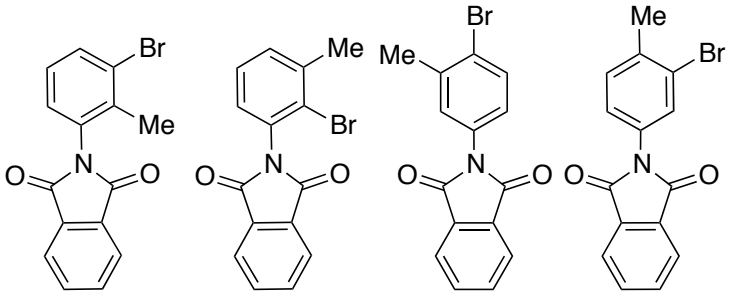
IR (υ, cm^{-1}):

3026, 1715, 1499, 1483, 1465, 1391, 1274, 1261, 1232, 1205, 1098, 1083, 1050, 887, 862, 806, 764, 750, 709, 703, 682.

HRMS (EI+):

Calc. for $C_{15}H_{10}ClNO_2$ $[M]^+$: 271.0407 ; Found: 271.0405

Amination of 2-bromotoluene (11)



11a **11b** **11c** **11d**

General procedure **(III)(C)** was followed with 5 mL of 2-bromotoluene (**11**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **11c** and **11d** were confirmed by the synthesis of authentic products.

Data for **11a-d**

GC Yield (Selectivity; **11a**:**11b**:**11c**:**11d**):79% (0:0:1:1)

Isolated Yield (Selectivity; **11a**:**11b**:**11c**:**11d**): 269 mg off-white solid, 85% (0:0:1:2)

TLC: R_f 0.32 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

11c: δ 7.92 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.1 Hz, 1H), 2.43 (s, 3H).

11d: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.36-7.34 (m, 1H), 7.29 (dd, *J* = 8.2, 2.0 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (101 MHz; $CDCl_3$)

11c: δ 167.1, 139.0, 134.6, 133.0, 131.6, 130.8, 128.7, 125.4, 124.7, 123.8, 23.2

11d: δ 167.0, 138.0, 134.6, 131.64, 131.0, 130.3, 125.4, 124.7, 124.0 22.8, 20.9

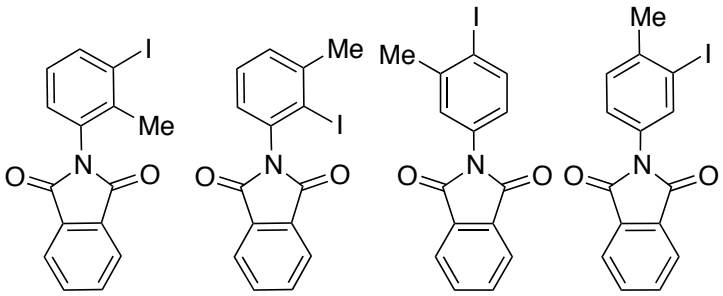
IR (υ, cm^{-1}):

2922, 1768, 1716, 1603, 1488, 1466, 1407, 1381, 1272, 1205, 1099, 1084, 1028, 888, 817, 749, 711.

HRMS (EI+):

Calc. for $C_{15}H_{10}BrNO_2$ $[M]^+$: 314.9895; Found: 314.9894, 316.9868

Amination of 2-iodotoluene (12)



12a **12b** **12c** **12d**

General procedure **(III)(C)** was followed with 5 mL of 2-iodotoluene (**12**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **12c** and **12d** were confirmed by the synthesis of authentic products.

Data for **12a-d**

GC Yield (Selectivity; **12a**:**12b**:**12c**:**12d**): 46% (0:0:1:1)

Isolated Yield (Selectivity; **12a**:**12b**:**12c**:**12d**): 185 mg pale yellow solid, 51% (0:0:1:1)

Single isomer could be recrystallized from MeOH/hexanes

TLC: R_f 0.34 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

12c: δ 7.91-7.88 (m, 3H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 (d, *J* = 2.3 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 2.45 (s, 3H)

12d: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.35 (t, *J* = 1.4 Hz, 2H), 2.48 (s, 3H)

^{13}C NMR (101 MHz; $CDCl_3$)

12c: δ 166.9, 142.5, 139.5, 134.5, 131.6, 127.5, 125.4, 123.77, 123.74, 100.4, 28.3

12d: δ 167.1, 141.7, 136.7, 134.6, 131.7, 130.1, 129.8, 126.4, 123.9, 100.5, 27.9

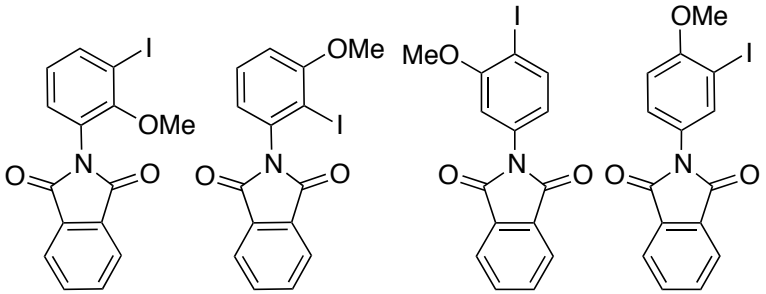
IR (υ, cm^{-1}):

1770, 1724, 1595, 1564, 1491, 1474, 1465, 1404, 1382, 1275, 1261, 1217, 1102, 1083, 889, 867, 818, 787, 764, 749, 716, 665, 645.

HRMS (EI+):

Calc. for $C_{15}H_{10}INO_2$ $[M]^+$: 362.9756; Found: 362.9763

Amination of 2-iodoanisole (13)



13a **13b** **13c** **13d**

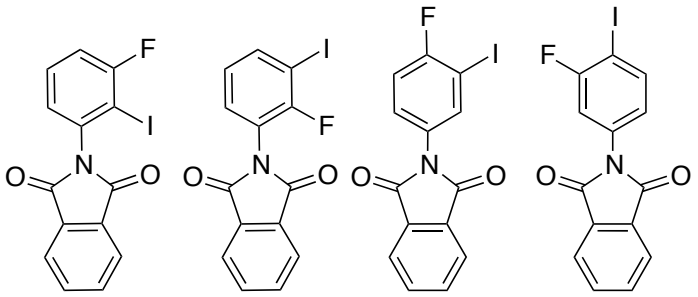
General procedure **(III)(C)** was followed with 5 mL of 2-iodoanisole (**13**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **13d** was confirmed by the synthesis of authentic product.

Data for **13a-d**

GC Yield (Selectivity; **13a**:**13b**:**13d**:**13c**): 72% (1:1:5:0)

Isolated Yield (Selectivity; **13a**:**13b**:**13d**:**13c**): 315 mg off-white solid, 83% (1:1:5:0)
Single isomer could be recrystallized from MeOH/hexanes
TLC: R_f 0.30 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
13d: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.81-7.78 (m, 2H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H).
^{13}C NMR (101 MHz; $CDCl_3$)
13d: δ 167.4, 158.1, 137.6, 134.6, 131.8, 128.0, 125.5, 123.9, 110.7, 85.8,56.8
IR (υ, cm^{-1}):
2956, 1770, 1600, 1491, 1460, 1407, 1275, 1261, 1219, 1111, 1083, 889, 867, 787, 749, 716, 645
HRMS (EI+):
Calc. for $C_{15}H_{10}INO_3$ $[M]^+$: 378.9705; Found: 378.9711

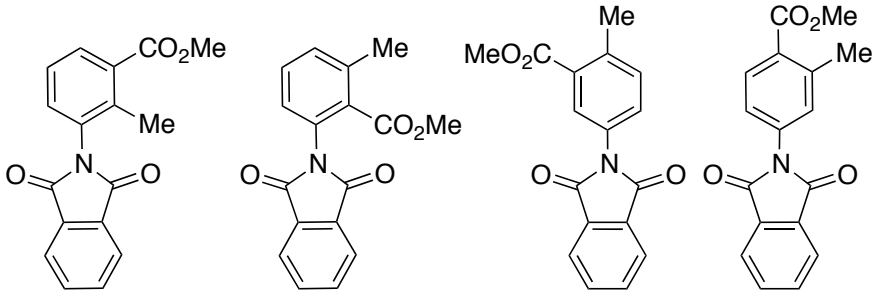
Amination of 2-fluoroiodobenzene (14)



14a **14b** **14c** **14d**

General procedure **(III)(C)** was followed with 5 mL of 2-fluoroiodobenzene (**14**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **14d** was determined by analogy to compound **13d**.
Data for **14a-d**
GC Yield (Selectivity; **14a**:**14b**:**14c**:**14d**): 45% (0:0:1:7)
Isolated Yield (Selectivity; **14a**:**14b**:**14c**:**14d**): 209 mg pale yellow solid, 57% (0:0:1:7)
TLC: R_f 0.35 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
14d: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.86 (dd, *J* = 5.4, 2.5 Hz, 1H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.43 (ddd, *J* = 8.8, 4.4, 2.5 Hz, 1H), 7.19 (dd, *J* = 8.8, 7.4 Hz, 1H)
^{13}C NMR (101 MHz; $CDCl_3$)
14d: δ 167.0, 137.39, 137.37, 134.8, 131.6, 128.41 (d, *J* = 8 Hz), 124.1, 115.9 (d, *J* = 20.2 Hz).
^{19}F NMR (376 MHz; $CDCl_3$)
IR (υ, cm^{-1}):
2925, 1771, 1717, 1590, 1489, 1466, 1423, 1408, 1377, 1276, 1260, 1236, 1192, 1099, 1085, 1007, 951, 886, 869, 906, 784, 764, 749, 713, 662, 647.
HRMS (EI+):
Calc. for $C_{14}H_7FINO_2[M]^+$: 366.9505; Found: 366.9511

Amination of methyl-2-methylbenzoate (15)



15a **15b** **15c** **15d**

General procedure **(III)(C)** was followed with 5 mL of methyl-2-methylbenzoate (**15**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **15c** and **15d** were confirmed by the synthesis of authentic products.

Data for **15a-d**

GC Yield (Selectivity; **15a**:**15b**:**15c**:**15d**): 61% (0:1:4:1)

Isolated Yield (Selectivity; **15a**:**15b**:**15c**:**15d**): 177 mg white solid, 60% (1:1:50:15)

Single isomer could be recrystallized from MeOH/hexanes

TLC: R_f 0.34 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

15c: δ 8.03 (d, *J* = 2.3 Hz, 1H), 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.49 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 2.66 (s, 3H).

15d: δ 8.06 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.39-7.37 (m, 2H), 3.92 (s, 3H), 2.67 (s, 3H)

^{13}C NMR (101 MHz; $CDCl_3$)

15c: δ 167.24, 167.04, 140.7, 134.6, 132.6, 131.8, 130.2, 130.0, 129.5, 128.9, 123.9, 52.1, 21.7

15d: δ 167.4, 167.0, 141.8, 134.88, 134.75, 131.77, 131.69, 129.5, 129.2, 129.0, 124.0, 123.6, 52.1, 22.1

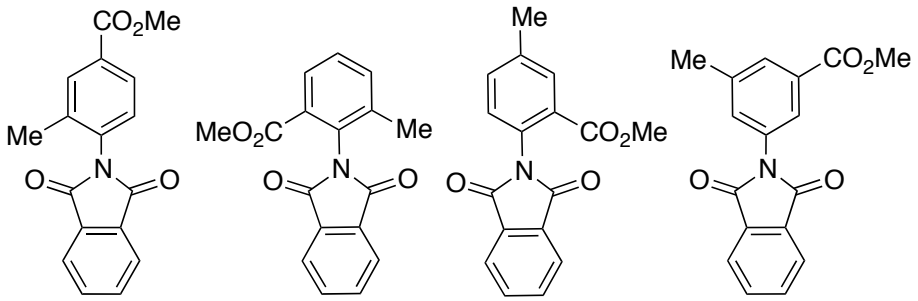
IR (υ, cm^{-1}):

2948, 1774, 1724, 1607, 1575, 1506, 1466, 1431, 1387, 1303, 1289, 1258, 1216, 1186, 1160, 1122, 1105, 1081, 980, 912, 880, 827, 778, 713, 677, 605.

HRMS (EI+):

Calc. for $C_{17}H_{13}NO_4$ $[M]^+$: 298.0845; Found: 298.0844

Amination of methyl-3-methylbenzoate (16)



16a **16b** **16c** **16d**

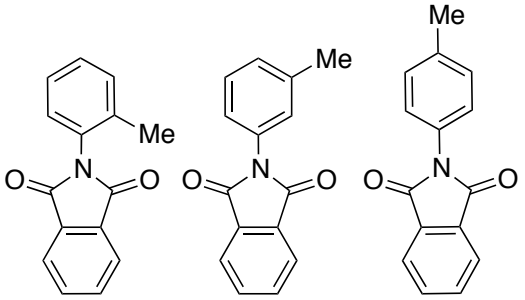
General procedure **(III)(C)** was followed with 5 mL of methyl-3-methylbenzoate (**16**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer **16d** was determined by splitting pattern on ^{1}H NMR.

Data for **16a-d**

GC Yield (Selectivity; **16a**:**16b**:**16c**:**16d**): 50% (1:1:2:8)

Isolated Yield (Selectivity; **16a**:**16b**:**16c**:**16d**): 153 mg white solid, 52% (1:1:4:17)
Single isomer could be recrystallized from MeOH/hexanes
TLC: R_f 0.28 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
16d: δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.92 (s, 2H), 7.81 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.45 (s, 1H), 3.92 (s, 3H), 2.47 (d, *J* = 0.5 Hz, 3H).
^{13}C NMR (101 MHz; $CDCl_3$)
16d: δ 167.2, 166.5, 139.6, 134.7, 131.88, 131.79, 131.77, 131.3, 130.1, 125.2, 124.0, 52.4, 21.5
IR (υ, cm^{-1}):
3206, 2952, 1773, 1719, 1604, 1466, 1435, 1377, 1294, 1224, 1107, 1084, 1053, 888, 867, 792, 769, 715, 676, 647
HRMS (EI+):
Calc. for $C_{17}H_{13}NO_4$ $[M]^+$: 298.0845; Found: 298.0851

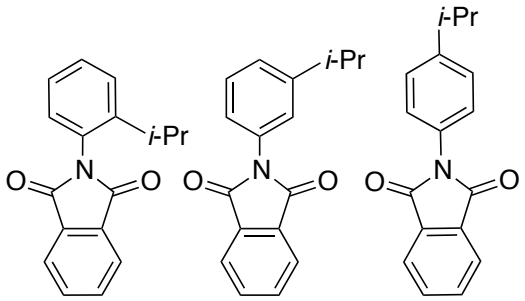
Amination of toluene (17)



17a **17b** **17c**

General procedure **(III)(C)** was followed with 5 mL of toluene (**17**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **17b** and **17c** were confirmed by the synthesis of authentic products.
Data for **17a-c**
GC Yield (Selectivity; **17a**:**17b**:**17c**): 80% (1:9:9)
Isolated Yield (Selectivity; **17a**:**17b**:**17c**): 185 mg white solid, 78% (1:10:9)
TLC: R_f 0.41 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
17b: δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.24 (t, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H).
17c: δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.26 (s, 4 H), 2.36 (s, 3 H).
^{13}C NMR (101 MHz; $CDCl_3$)
17b: δ 167.2, 138.9, 134.2, 131.8, 131.5, 128.9, 128.8, 127.1, 123.7, 123.6, 21.4.
17c: δ 167.3, 138.0, 134.2, 131.8, 129.6, 128.9, 126.3, 123.7, 21.2.
IR (υ, cm^{-1}):
2923, 1770, 1715, 1606, 1587, 1517, 1492, 1465, 1376, 1284, 1211, 1110, 1080, 904, 883, 817, 784, 750, 713, 697, 687, 630
HRMS (EI+):
Calc. for $C_{15}H_{11}NO_2$ $[M]^+$: 237.0790; Found: 237.0795

Amination of isopropylbenzene (18)



18a **18b** **18c**

General procedure **(III)(C)** was followed with 5 mL of isopropylbenzene (**18**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **18b** and **18c** were confirmed by the synthesis of authentic products.

Data for **18a-c**

GC Yield (Selectivity; **18a**:**18b**:**18c**): 77% (1:6:5)

Isolated Yield (Selectivity; **18a**:**18b**:**18c**): 207 mg white solid, 78% (1:13:13)

Single isomer could be recrystallized from MeOH/hexanes

TLC: R_f 0.44 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

18b: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.29-7.27 (m, 2H), 7.24 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H), 2.98 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H).

18c: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.36 (d, *J* = 3.2 Hz, 4H), 2.98 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz; $CDCl_3$)

18b: δ 167.4, 150.0, 134.3, 131.8, 131.5, 129.0, 126.4, 124.9, 124.0, 123.7, 71.8, 34.0, 23.9

18c: δ 167.6, 149.0, 134.5, 132.0, 129.3, 127.4, 126.6, 123.8, 34.1, 24.1

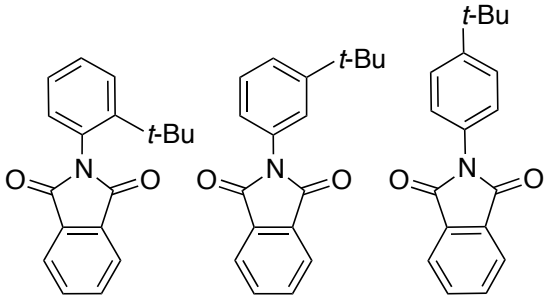
IR (υ, cm^{-1}):

3055, 2964, 2929, 2870, 1766, 1740, 1705, 1606, 1589, 1516, 1490, 1466, 1448, 1379, 1265, 1231, 1196, 1114, 1082, 884, 831, 790, 737, 716, 631.

HRMS (EI+):

Calc. for $C_{17}H_{15}NO_2$ $[M]^+$: 265.1103; Found: 265.1108

Amination of *tert*-butylbenzene (19)



19a **19b** **19c**

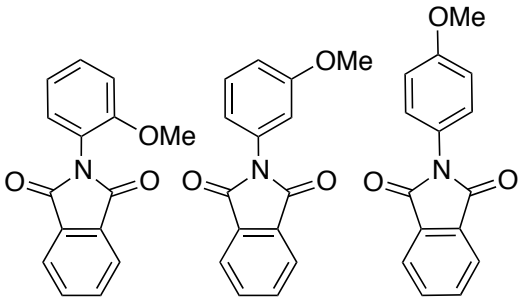
General procedure **(III)(C)** was followed with 5 mL of *tert*-butylbenzene (**19**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **19b** and **19c** were confirmed by the synthesis of authentic products.

Data for **19a-c**

GC Yield (Selectivity; **19a**:**19b**:**19c**): 118% (1:28:22)

Isolated Yield (Selectivity; **19a**:**19b**:**19c**): 251 mg white solid, 90% (1:40:30)
TLC: R_f 0.45 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
19b:
δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.24 (t, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H).
19c:
δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.26 (s, 4 H), 2.36 (s, 3 H).
^{13}C NMR (101 MHz; $CDCl_3$)
19b:
δ 167.2, 138.9, 134.2, 131.8, 131.5, 128.9, 128.8, 127.1, 123.7, 123.6, 21.4.
19c:
δ 167.3, 138.0, 134.2, 131.8, 129.6, 128.9, 126.3, 123.7, 21.2.
IR (υ, cm^{-1}):
3479, 3061, 2963, 2869, 1782, 1724, 1605, 1517, 1492, 1467, 1431, 1379, 1287, 1269, 1216, 1114, 1099, 1082, 1021, 885, 874, 830, 788, 716, 699, 631, 557, 530.
HRMS (EI+):
Calc. for $C_{18}H_{17}NO_2$ $[M]^+$: 279.1259; Found: 279.1260

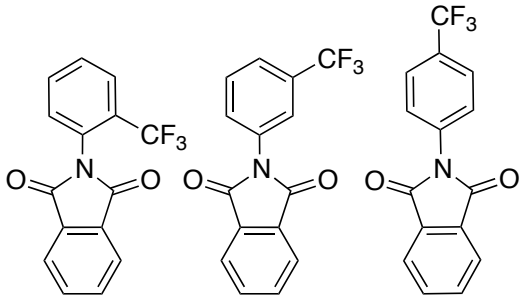
Amination of methoxybenzene (20)



20a **20b** **20c**

General procedure **(III)(C)** was followed with 5 mL of methoxybenzene (**20**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **20b** and **20c** were confirmed by the synthesis of authentic products.
Data for **20a-c**
GC Yield (Selectivity; **20a**:**20b**:**20c**): 53% (1:1:5)
Isolated Yield (Selectivity; **20a**:**20b**:**20c**): 154 mg off-white solid, 61% (1:1:5)
Single isomer could be recrystallized from MeOH/hexanes
TLC: R_f 0.25 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
20b: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.04-6.94 (m, 3H), 3.84 (s, 3H)
20c: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36-7.32 (m, 2H), 7.04-7.00 (m, 2H), 3.85 (s, 3H).
^{13}C NMR (101 MHz; $CDCl_3$)
20b: δ 167.3, 160.2, 134.5, 132.8, 131.9, 129.9, 123.9, 119.0, 114.2, 112.5
20c: δ 167.7, 159.4, 134.4, 132.0, 128.1, 124.4, 123.8, 114.6, 55.7
IR (υ, cm^{-1}):
3204, 3060, 2838, 1773, 1745, 1703, 1606, 1513, 1466, 1384, 1304, 1276, 1257, 1214, 1113, 1082, 1054, 1028, 883, 886, 827, 750, 715, 782, 715.
HRMS (EI+):
Calc. for $C_{15}H_{11}NO_3$ $[M]^+$: 253.0739; Found: 253.0745

Amination of trifluoromethylbenzene (21)



21a **21b** **21c**

General procedure **(III)(C)** was followed with 5 mL of trifluoromethylbenzene (**21**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **21b** and **21c** were confirmed by the synthesis of authentic products.

Data for **21a-c**

GC Yield (Selectivity; **21a**:**21b**:**201c**): 66% (1:16:5)

Isolated Yield (Selectivity; **21a**:**21b**:**21c**): 210 mg off-white solid, 72% (1:30:11)

Single isomer could be recrystallized from MeOH/hexanes

TLC: R_f 0.36 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

21b: δ 7.97 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.83-7.78 (m, 3H), 7.70-7.61 (m, 3H).

21c: δ 7.99 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.84-7.82 (m, 2H), 7.79-7.77 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (101 MHz; $CDCl_3$)

21b: δ 166.7, 134.7, 132.3, 131.4 (q, *J* = 24.2 Hz), 129.62, 129.57, 124.9 (q, *J* = 272.2 Hz), 124.6 (q, *J* = 4 Hz), 123.9, 122.3 (q, *J* = 4 Hz).

21c: δ 176.9, 134.9, 131.6, 126.6, 126.2 (q, *J* = 3 Hz), 124.2, 77.5, 77.2, 76.8, 20.8 (quartets for the CF_2 carbon could not be located).

^{19}F NMR (376 MHz; $CDCl_3$)

21b: δ -61.8

21c: δ -61.8

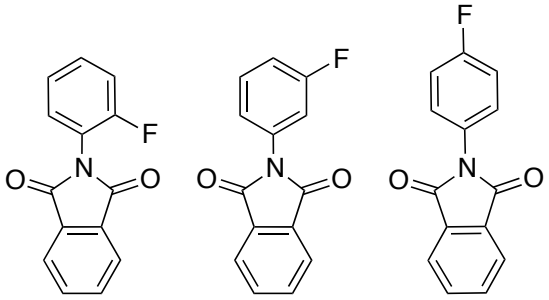
IR (υ, cm^{-1}):

3479, 3107, 1774, 1752, 1715, 1610, 1494, 1467, 1467, 1455, 1375, 1323, 1314, 1265, 1217, 1178, 1166, 1112, 1069, 1021, 954, 920, 891, 876, 836, 805, 785, 736, 710, 694, 658, 628.

HRMS (EI+):

Calc. for $C_{15}H_8F_3NO_2$ $[M]^+$: 291.0507; Found: 291.0508

Amination of fluorobenzene (22)



22a **22b** **22c**

General procedure **(III)(C)** was followed with 5 mL of fluorobenzene (**22**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **22b** and **22c** were confirmed by the synthesis of authentic products.

Data for **22a-c**

GC Yield (Selectivity; **22a**:**22b**:**22c**): 48% (1:7:4)

Isolated Yield (Selectivity; **22a**:**22b**:**22c**): 149 mg white solid, 62% (1:10:6)

TLC: R_f 0.40 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

22b: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.47 (td, *J* = 8.2, 6.2 Hz, 1H), 7.30-7.23 (m, 2H), 7.11 (td, *J* = 8.4, 2.5 Hz, 1H)

22c: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H).

^{13}C NMR (101 MHz; $CDCl_3$)

22b: δ 167.0, 162.7 (d, *J* = 252.5 Hz), 134.4 (d, *J* = 11 Hz), 133.14, 131.7, 130.33 (d, *J* = 9 Hz), 124.0, 122.14, 122.11, 115.1 (d, *J* = 20.2 Hz), 114.1 (d, *J* = 30.3 Hz).

22c: δ 167.3, 162.05 (d, *J* = 252.5 Hz), 134.6, 131.8, 128.50 (d, *J* = 9 Hz), 127.7, 123.9, 116.2 (d, *J* = 30.3 Hz).

^{19}F NMR (376 MHz; $CDCl_3$)

22b: δ -110.33, -110.36, -110.38, -110.40

22c: δ -112.21, -112.22, -112.23, -112.24, -112.26, -112.26, -112.28, -112.24

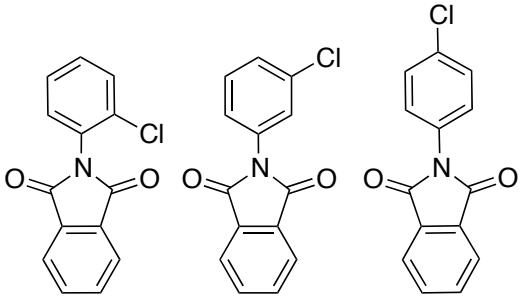
IR (υ, cm^{-1}):

3065, 2361, 1752, 1714, 1604, 1591, 1516, 1466, 1397, 1381, 1286, 1184, 1111, 1084, 885, 832, 785, 714, 680.

HRMS (EI+):

Calc. for $C_{14}H_8FNO_2$ $[M]^+$: 241.0539; Found: 241.0540

Amination of chlorobenzene (23)



23a **23b** **23c**

General procedure **(III)(C)** was followed with 5 mL of chlorobenzene (**23**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **23b** and **23c** were confirmed by the synthesis of authentic products.

Data for **23a-c**

GC Yield (Selectivity; **23a**:**23b**:**23c**): 65% (1:6:6)

Isolated Yield (Selectivity; **23a**:**23b**:**23c**): 196 mg white solid, 76% (1:6:6)

TLC: R_f 0.41 (20% EtOAc in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$)

23b: δ 7.95 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.46-7.42 (m, 1H), 7.38 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.36 (t, *J* = 2.1 Hz, 1H).

23c: δ 7.96-7.94 (m, 2H), 7.81-7.79 (m, 2H), 7.48-7.46 (m, 2H), 7.43-7.40 (m, 2H).

^{13}C NMR (101 MHz; $CDCl_3$)

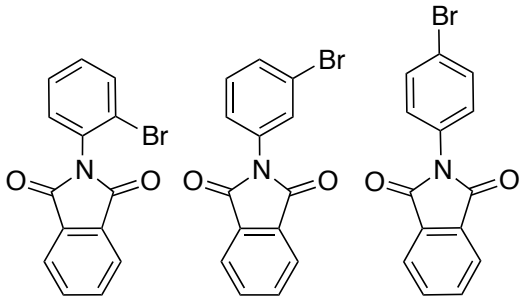
23b: δ 166.9, 134.72, 134.70, 132.9, 131.6, 130.1, 128.3, 126.8, 124.7, 124.0

23c: δ 167.1, 134.7, 133.9, 131.7, 130.3, 129.4, 127.8, 124.0

IR (υ, cm^{-1}):

3063, 2962, 1743, 1707, 1592, 1497, 1483, 1465, 1432, 1395, 1374, 1274, 1265, 1202, 1171, 1120, 1109, 1083, 1015, 942, 885, 869, 852, 823, 784, 763, 749, 714, 683, 627.
HRMS (EI+):
Calc. for $C_{14}H_8ClNO_2$ $[M]^+$: 257.0244; Found: 257.0249

Amination of bromobenzene (24)

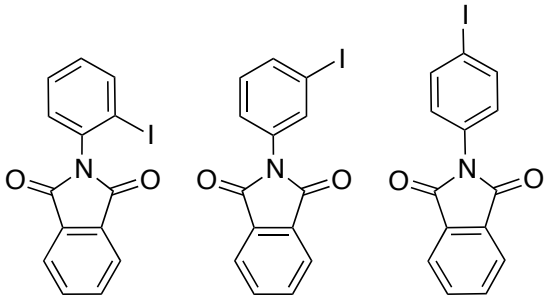


24a **24b** **24c**

General procedure **(III)(C)** was followed with 5 mL of bromobenzene (**24**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **24b** and **24c** were confirmed by the synthesis of authentic products.

Data for **24a-c**
GC Yield (Selectivity; **24a**:**24b**:**24c**): 84% (1:5:4)
Isolated Yield (Selectivity; **24a**:**24b**:**24c**): 247 mg off-white solid, 82% (1:5:5)
Single isomer could be recrystallized from MeOH/hexanes
TLC: R_f 0.38 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
24b: δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.65-7.61 (m, 2H), 7.37-7.34 (m, 2H).
24c: δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.65-7.61 (m, 2H), 7.37-7.34 (m, 2H).
^{13}C NMR (101 MHz; $CDCl_3$)
24b: δ 166.9, 134.7, 133.1, 131.6, 131.2, 130.4, 129.6, 125.2, 124.0, 122.5
24c: δ 167.0, 134.7, 132.4, 131.7, 130.9, 128.0, 124.0, 121.9
IR (υ, cm^{-1}):
3489, 3064, 2925, 1716, 1587, 1577, 1494, 1478, 1427, 1377, 1286, 1270, 1214, 1172, 1120, 1108, 1080, 1011, 942, 886, 868, 851, 819, 782, 715, 669, 677, 625.
HRMS (EI+):
Calc. for $C_{14}H_8BrNO_2$ $[M]^+$: 300.9738; Found: 300.9739, 302.9179

Amination of iodobenzene (25)

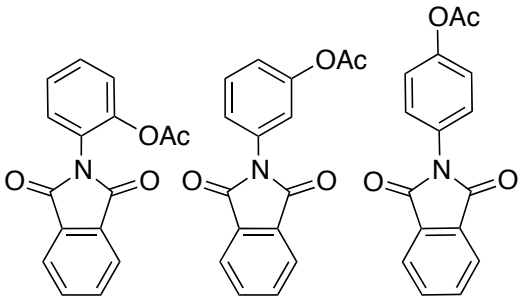


25a **25b** **25c**

General procedure **(III)(C)** was followed with 5 mL of iodobenzene (**25**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **25b** and **25c** were confirmed by the synthesis of authentic products.

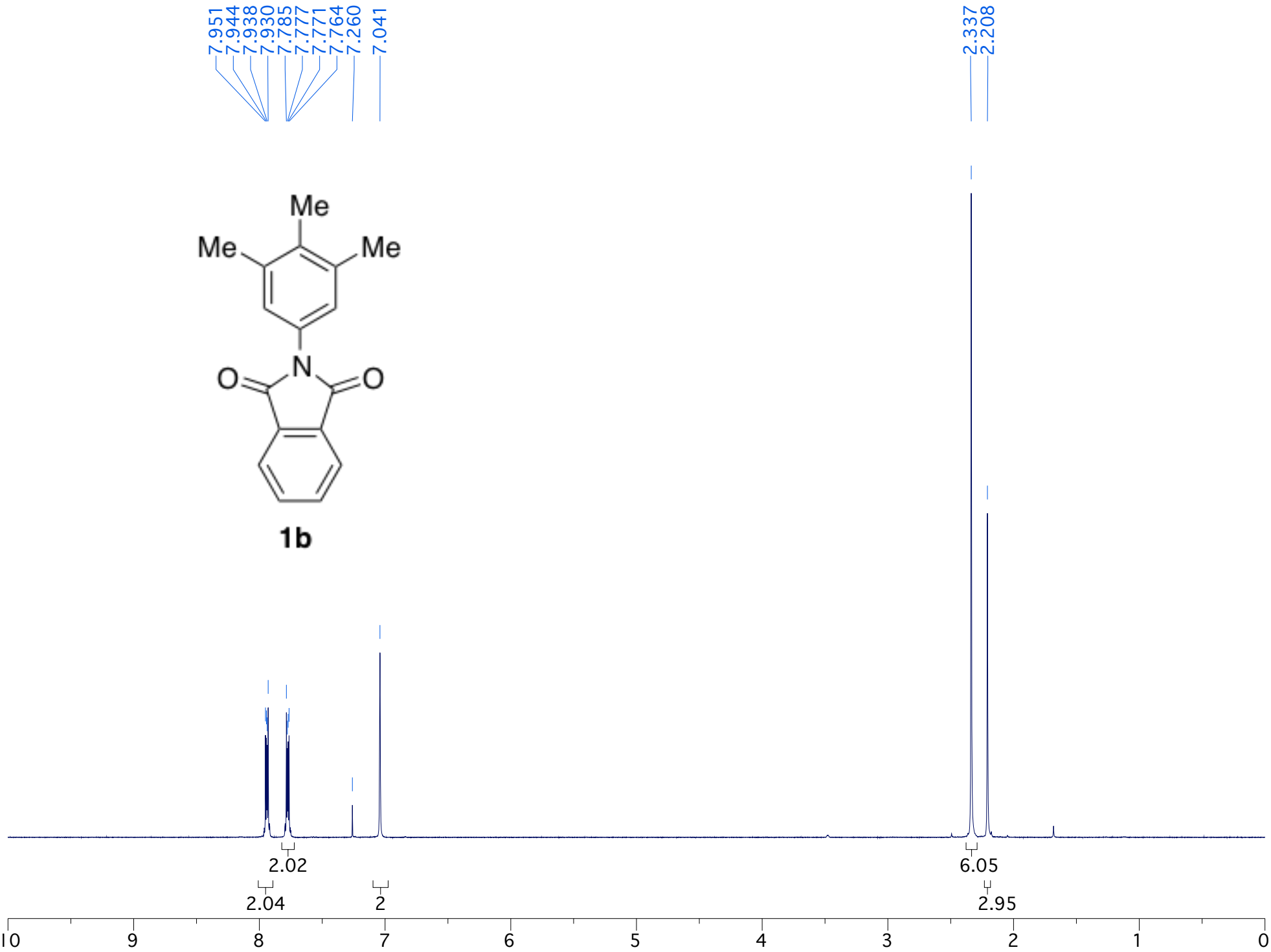
Data for **25a-c**
GC Yield (Selectivity; **25a**:**25b**:**25c**): 64% (1:4:3)
Isolated Yield (Selectivity; **25a**:**25b**:**25c**): 251 mg pale yellow solid, 72% (1:4:3)
TLC: R_f 0.35 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
25b: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.81 (td, *J* = 4.9, 2.8 Hz, 3H), 7.73 (ddd, *J* = 8.0, 1.6, 1.0 Hz, 1H), 7.44 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H).
25c: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.82 (tt, *J* = 8.8, 2.5 Hz, 4H), 7.24-7.21 (m, 2H).
^{13}C NMR (101 MHz; $CDCl_3$)
25b: δ 166.9, 137.2, 135.3, 134.7, 132.9, 131.6, 130.6, 125.9, 124.0, 93.8
25c: δ 167.0, 138.4, 134.7, 131.7, 128.2, 124.0, 93.4
IR (υ, cm^{-1}):
3061, 1742, 1712, 1585, 1475, 1423, 1395, 1371, 1262, 1204, 1120, 1081, 1061, 1007, 885, 849, 818, 783, 750, 713, 678, 657, 626.
HRMS (EI+):
Calc. for $C_{14}H_8INO_2$ $[M]^+$: 348.9600; Found: 348.9601

Amination of acetoxybenzene (26)



26a **26b** **26c**

General procedure **(III)(C)** was followed with 5 mL of acetoxybenzene (**26**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **26b** and **26c** were confirmed by the synthesis of authentic products.
Data for **26a-c**
GC Yield (Selectivity; **26a**:**26b**:**26c**): 62% (1:8:9)
Isolated Yield (Selectivity; **26a**:**26b**:**26c**): 163 mg white solid, 58% (1:8:9)
TLC: R_f 0.30 (20% EtOAc in hexanes)
^{1}H NMR (400 MHz, $CDCl_3$)
26b: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (td, *J* = 5.8, 2.6 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 2.1 Hz, 1H), 7.15 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 2.33 (s, 3H)
26c: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 2.31 (s, 3H).
^{13}C NMR (101 MHz; $CDCl_3$)
26b: δ 169.1, 167.0, 150.9, 148.7, 137.1, 134.7, 132.7, 131.6, 129.7, 124.2, 124.0, 123.6, 121.2, 119.7, 21.3
26c: δ 169.3, 167.2, 150.1, 134.6, 131.8, 129.3, 127.6, 124.0, 122.4, 21.3
IR (υ, cm^{-1}):
2973, 1767, 1724, 1605, 1466, 1387, 1292, 1237, 1101, 1089, 1061, 888, 867, 796, 766, 725, 686, 647
HRMS (EI+):
Calc. for $C_{16}H_{11}NO_4$ $[M]^+$: 281.0688; Found: 281.0694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7.938
7.930
7.785
7.777
7.771
7.764
7.260
7.041
2.337
2.208
Me
Me
Me
N
O
O
1b
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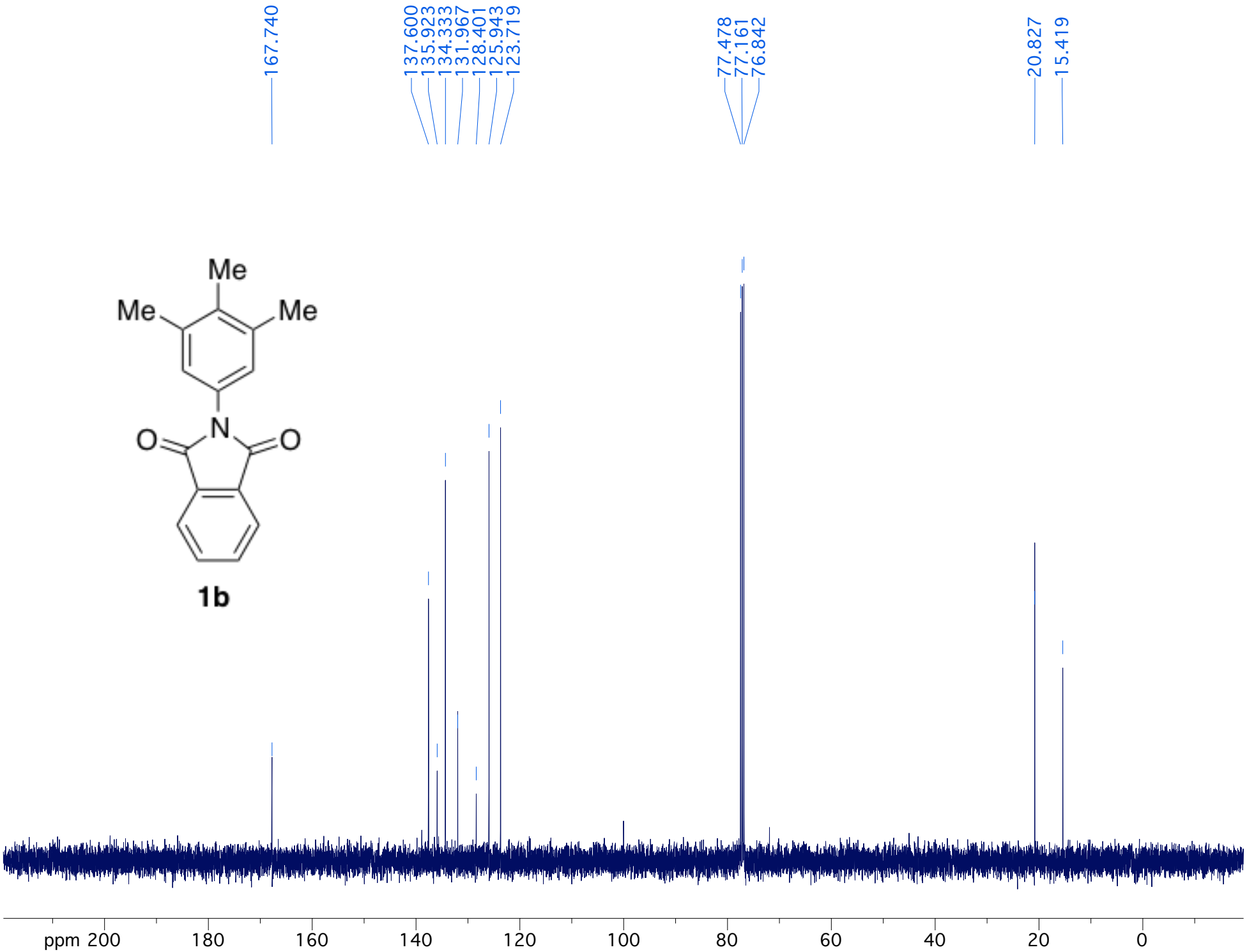
2.04
2
6.05
2.95
10
9
8
7
6
5
4
3
2
1
0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135.923
134.333
131.967
128.401
125.943
123.719
77.478
77.161
76.842
20.827
15.419
Me
Me
Me
N
O
O
1b
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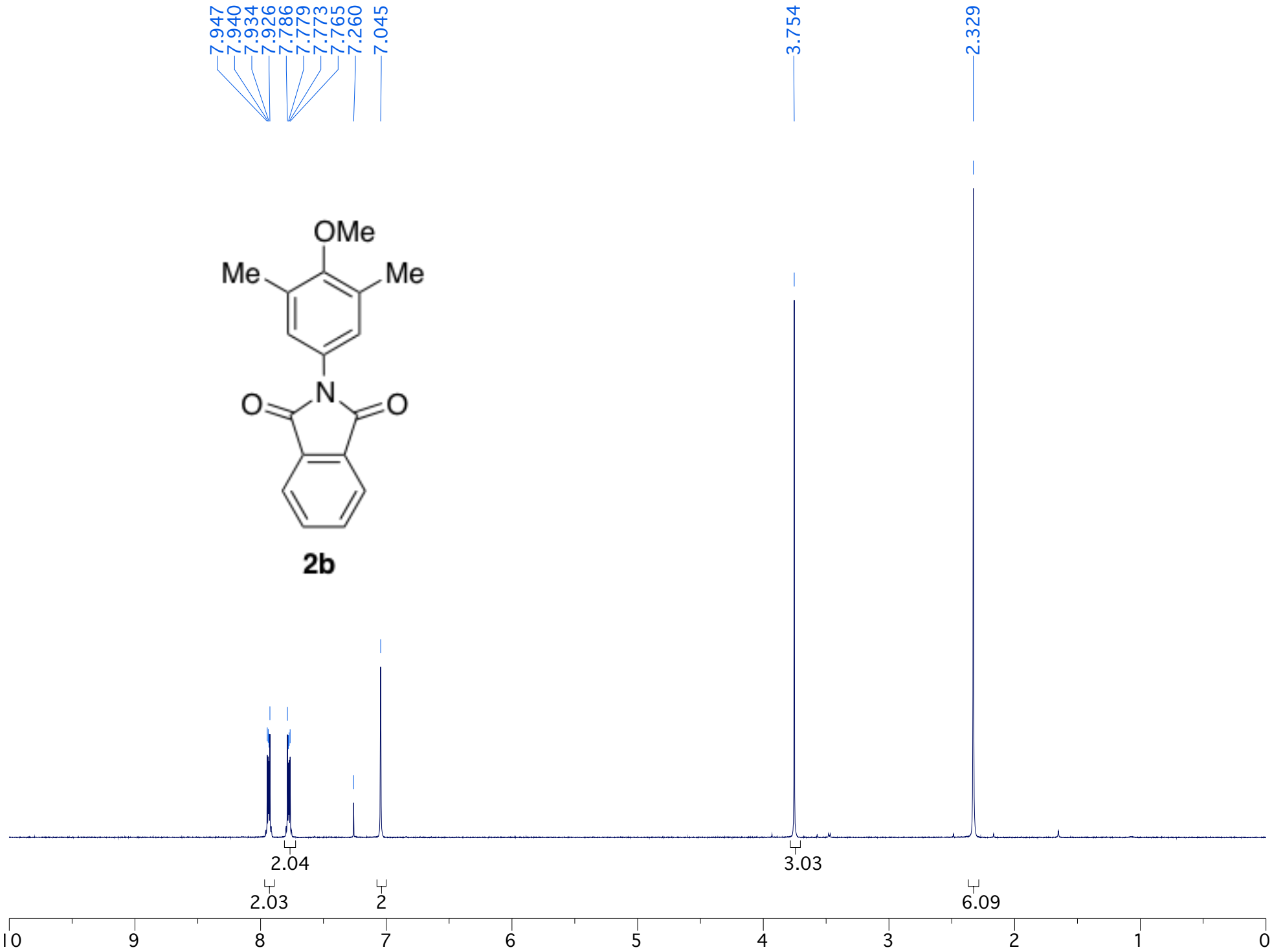
160
140
120
100
80
60
40
20
0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7.940
7.934
7.926
7.786
7.779
7.773
7.765
7.260
7.045
3.754
2.329
OMe
Me
Me
N
O
O
2b
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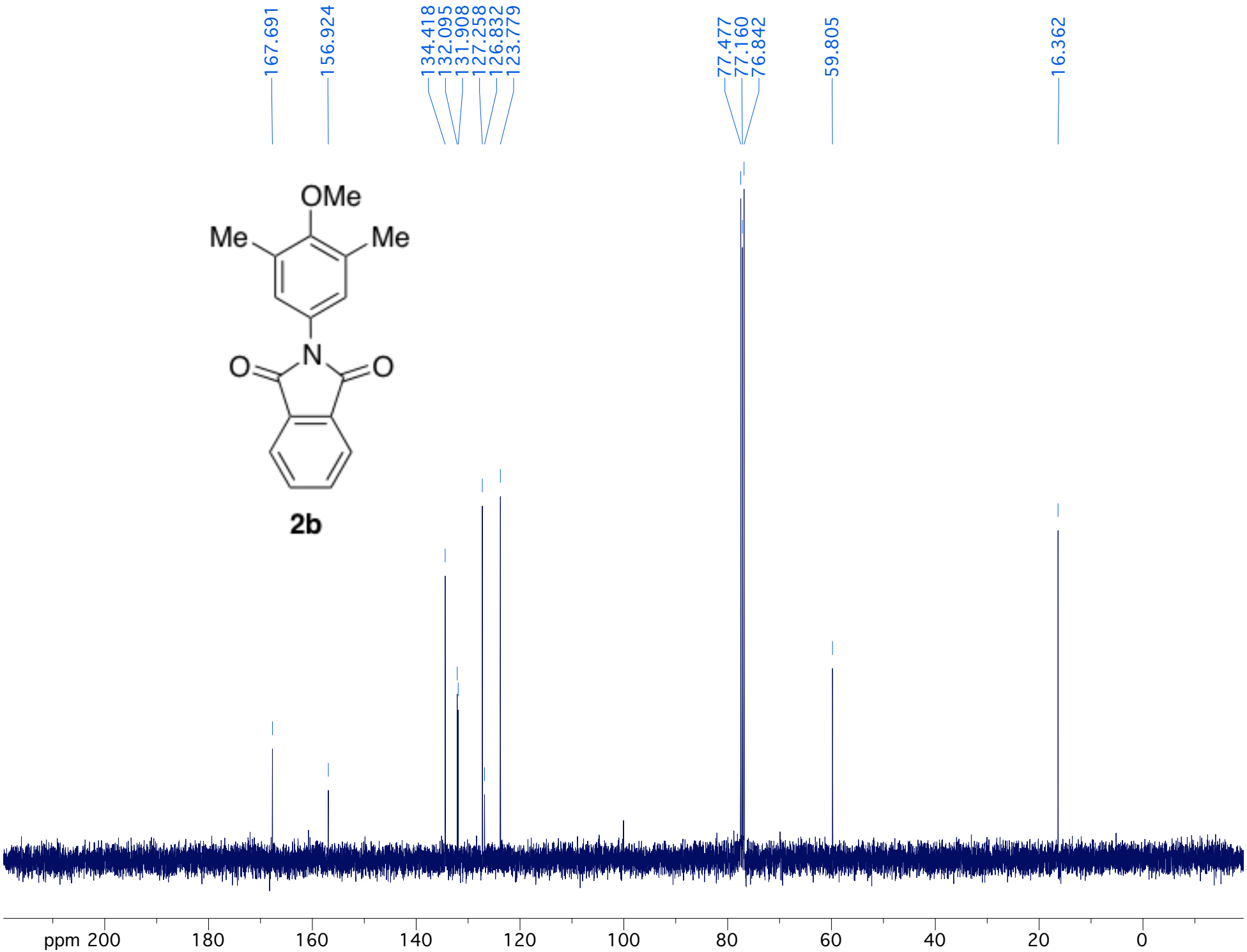
3.03
2.03
2
6.09
10
9
8
7
6
5
4
3
2
1
0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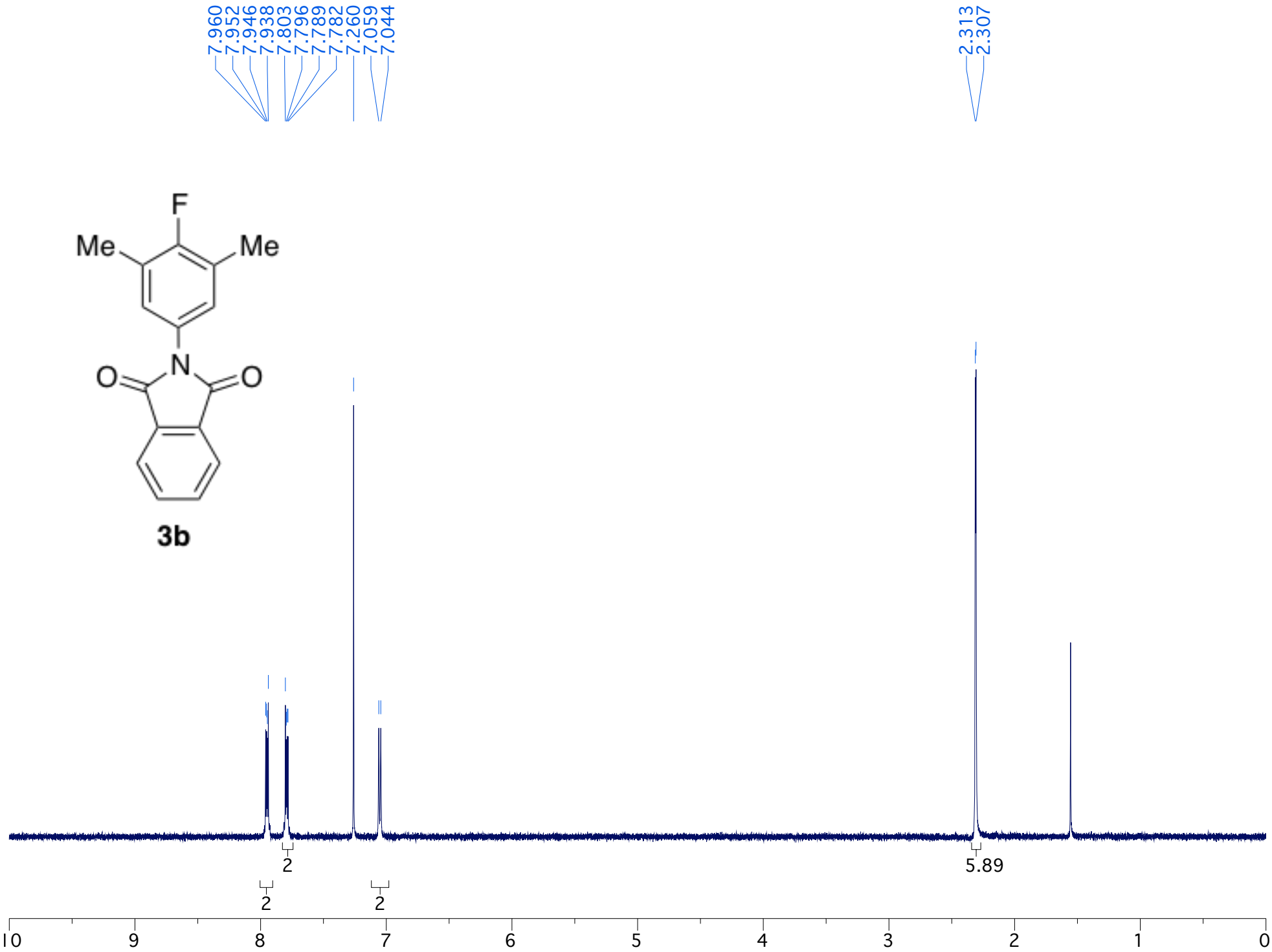
132.095
131.908
127.258
126.832
123.779
77.477
77.160
76.842
59.805
16.362
OMe
Me
Me
N
O
O
2b
ppm 200
180
160
140
120
100
80
60
40
20
0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7.946
7.938
7.803
7.796
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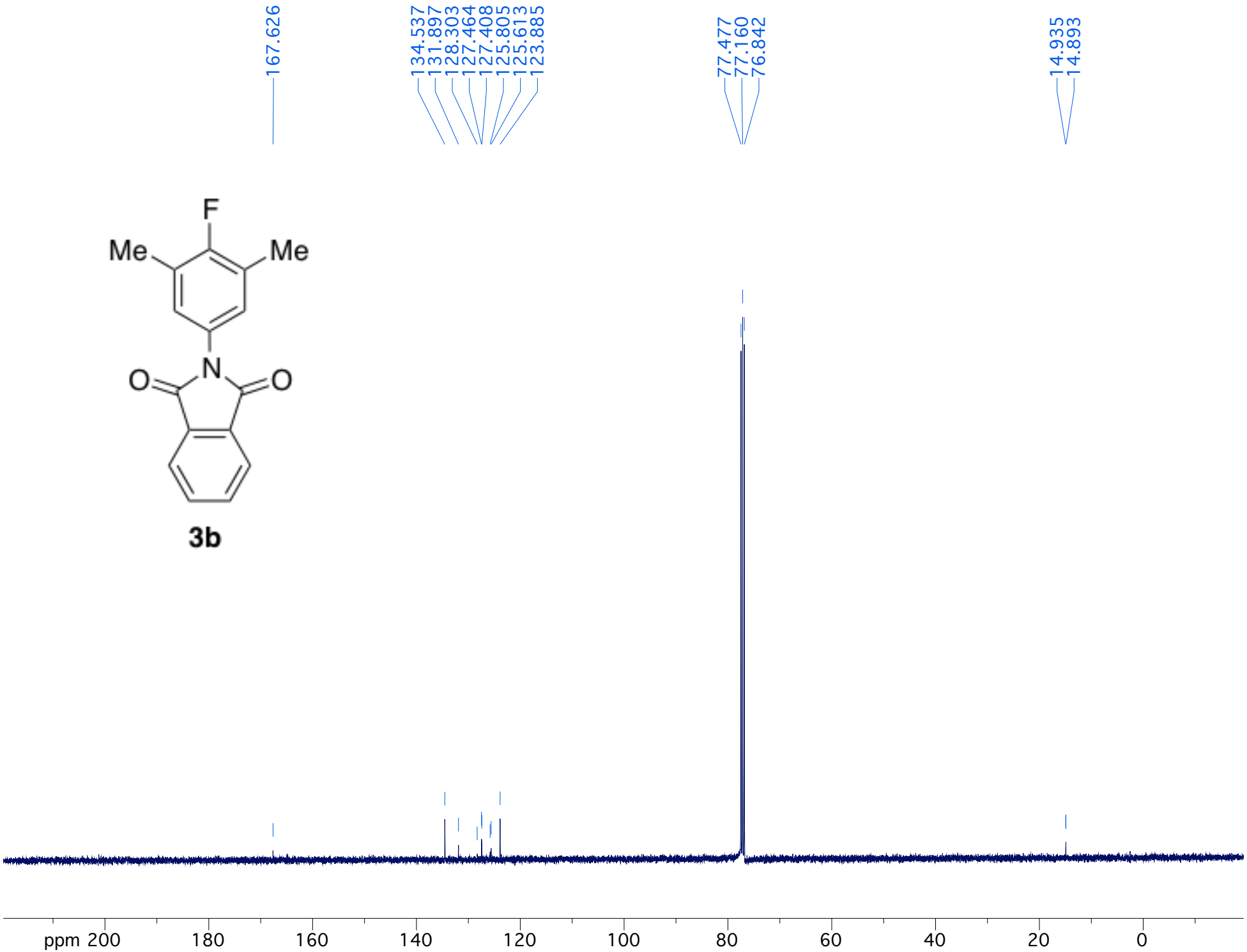
7.782
7.260
7.059
7.044
2.313
2.307
F
Me
Me
N
O
O
3b
2
2
2
5.89
10
9
8
7
6
5
4
3
2
1
0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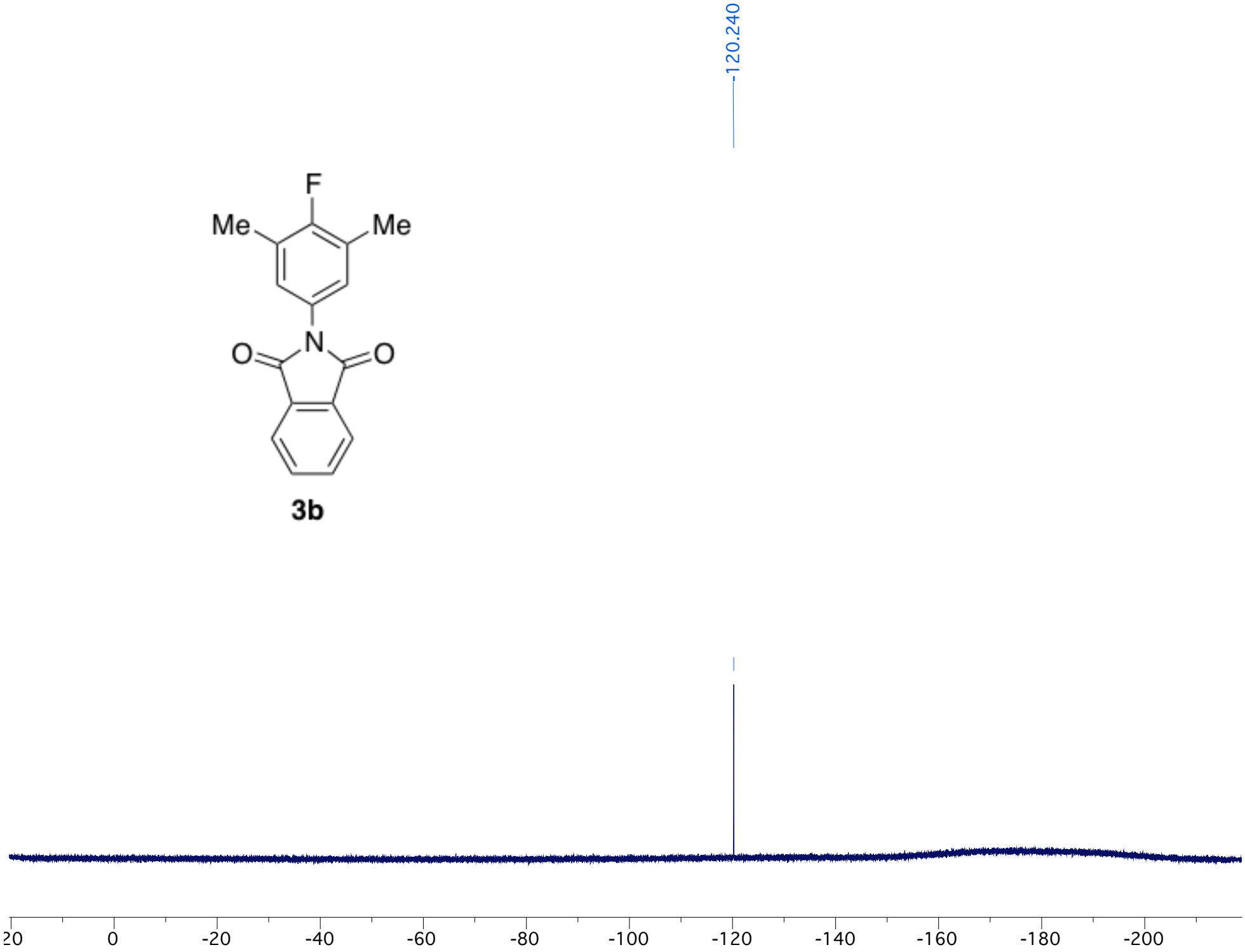
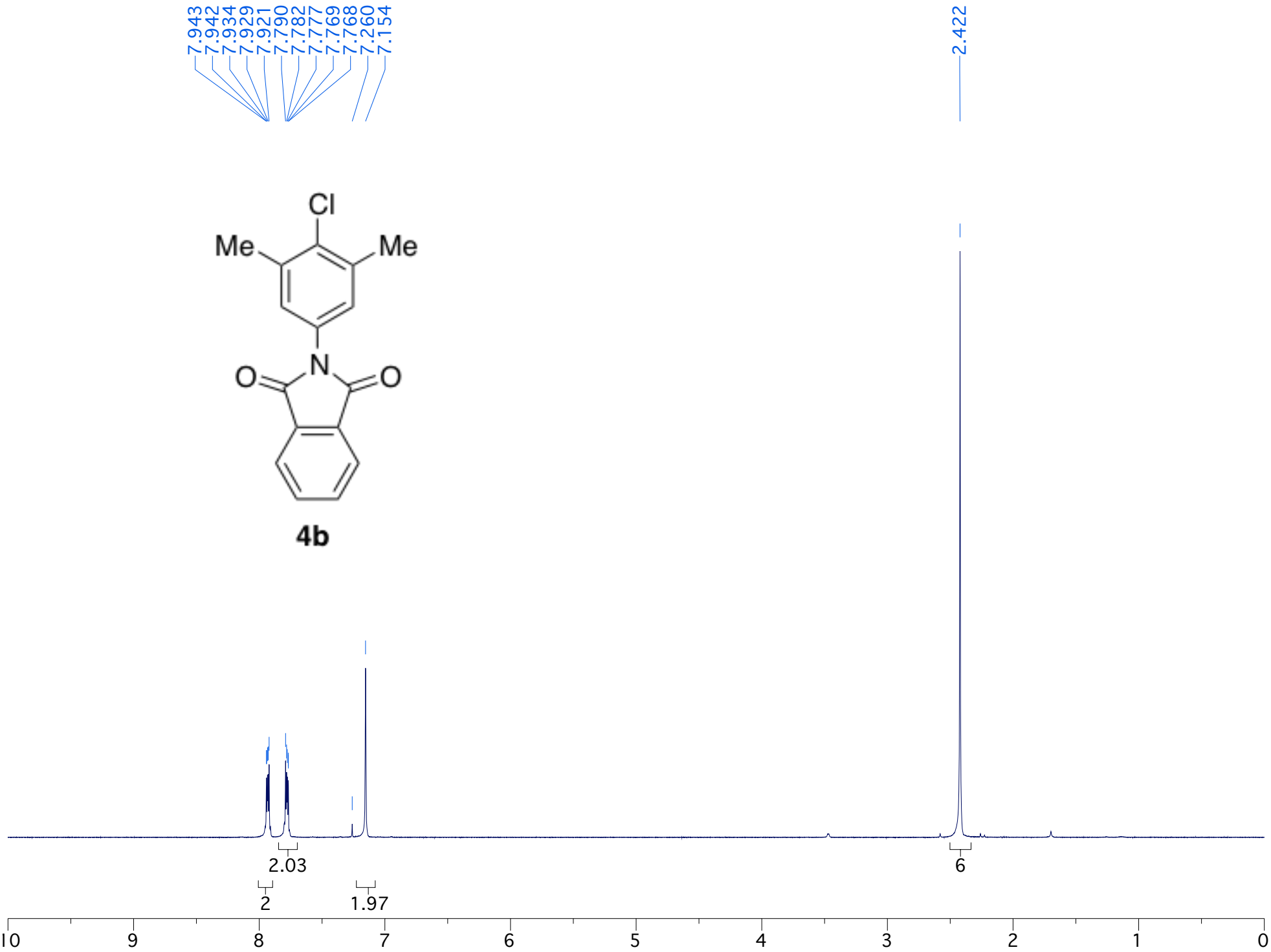
127.464
127.408
125.805
125.613
123.885
77.477
77.160
76.842
14.935
14.893
F
Me
Me
N
O
O
3b
ppm 200
180
160
140
120
100
80
60
40
20
0

3b

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7.929
7.921
7.790
7.782
7.777
7.769
7.768
7.260
7.154
2.422
Cl
Me
Me
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O
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9
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7
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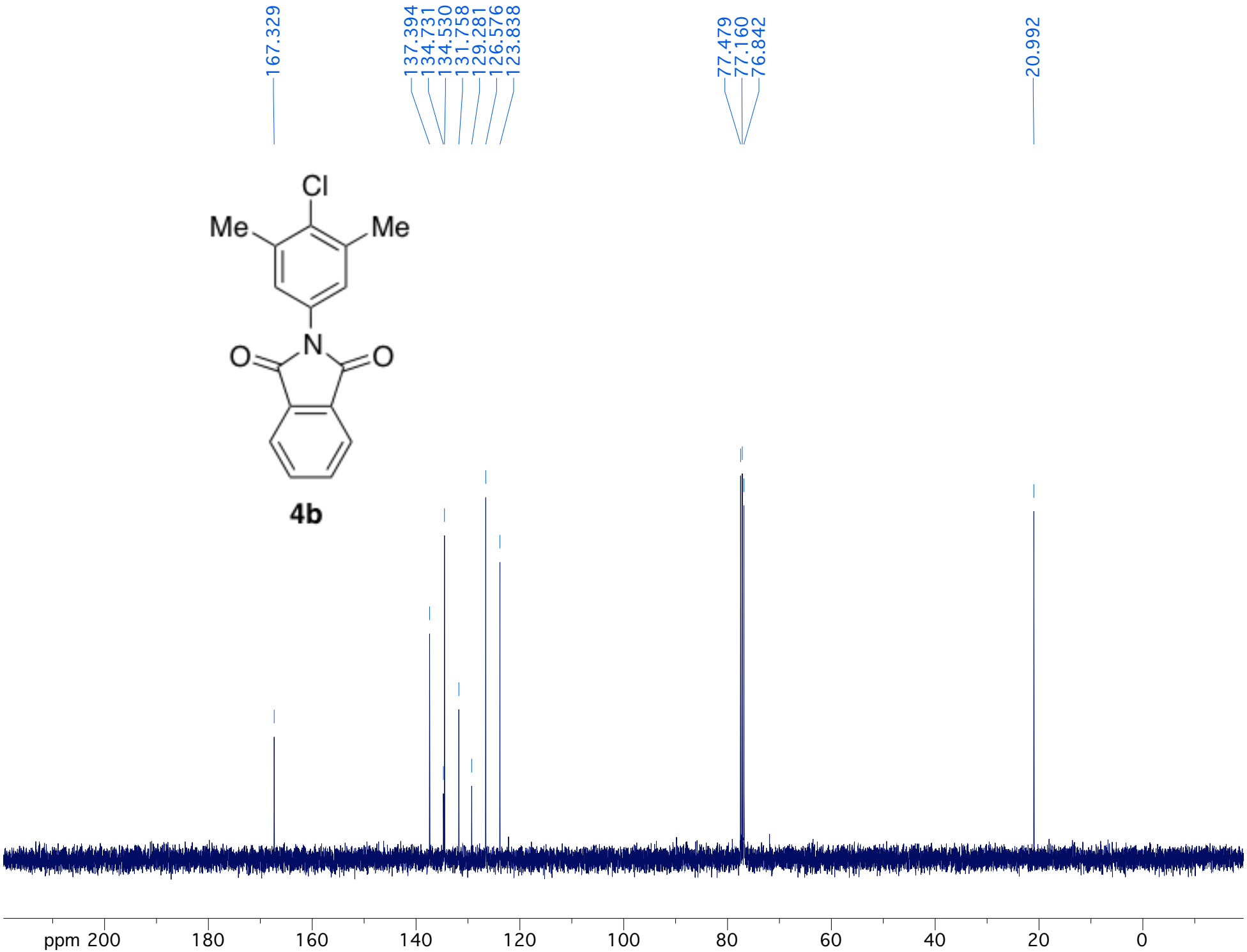
2
1
0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123.838
77.479
77.160
76.842
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Me
N
O
O
4b
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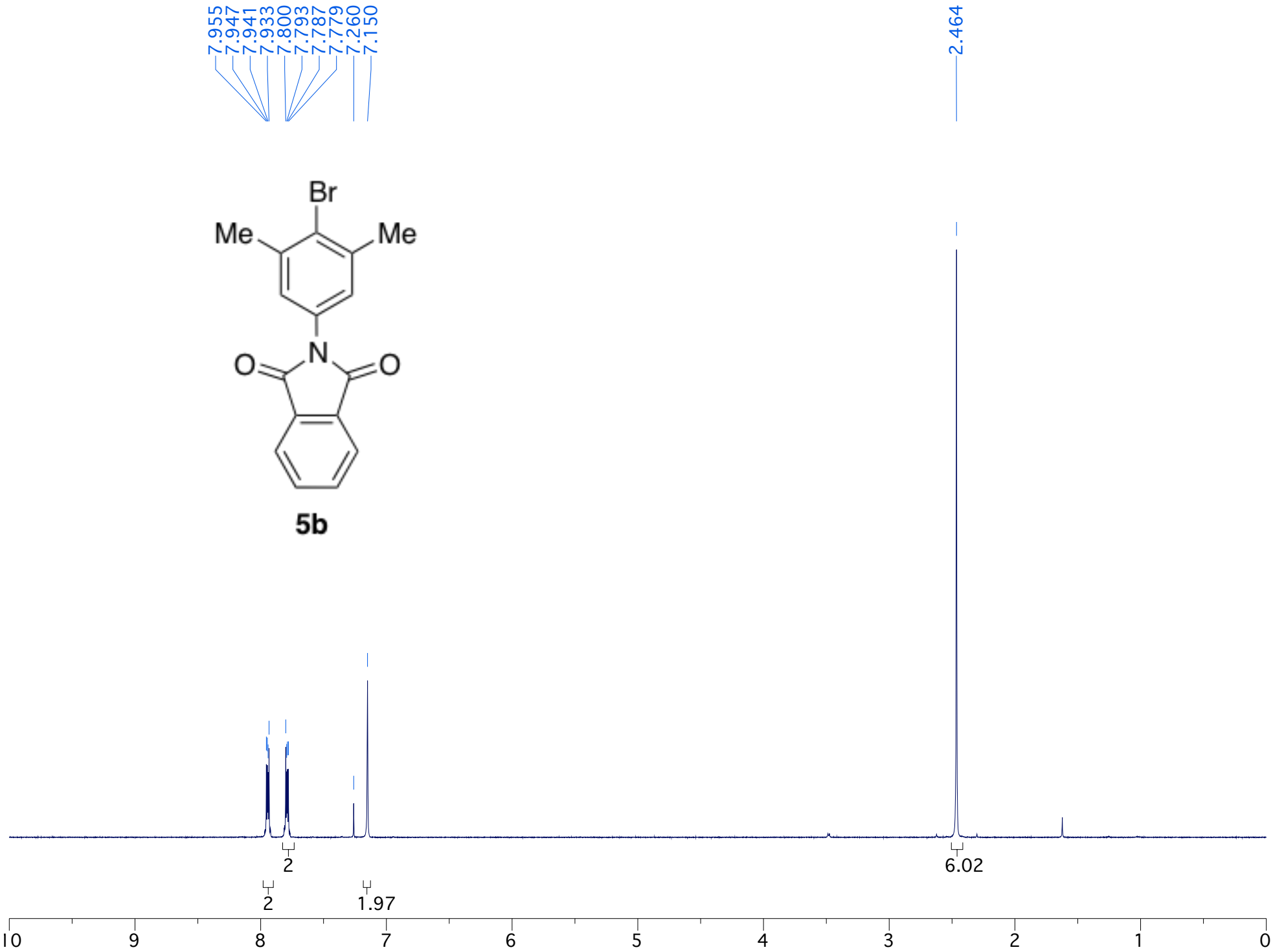
140
120
100
80
60
40
20
0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7.150
2.464
Br
Me
Me
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O
O
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1.97
6.02
10
9
8
7
6
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3
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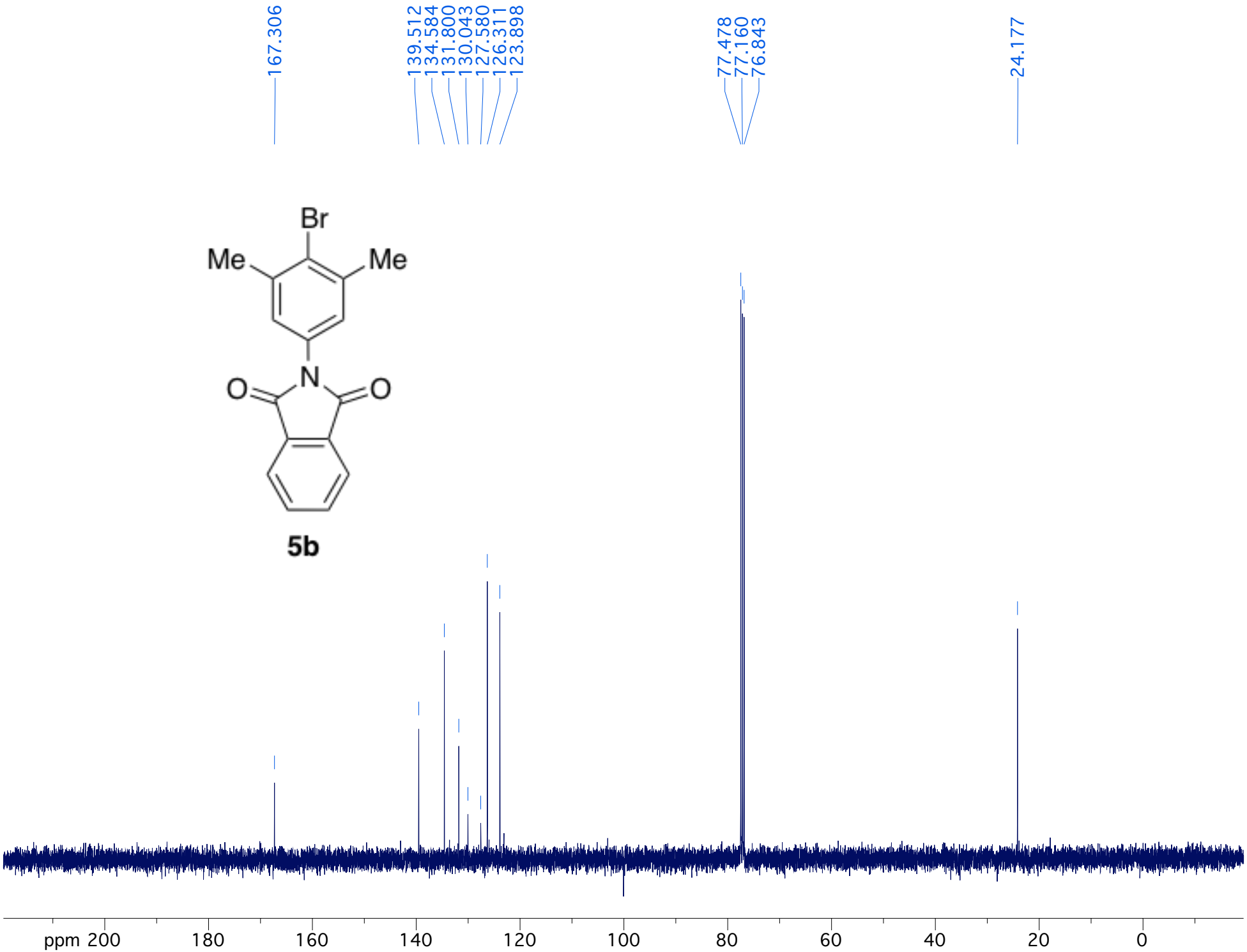
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77.160
76.843
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Br
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Me
N
O
O
5b
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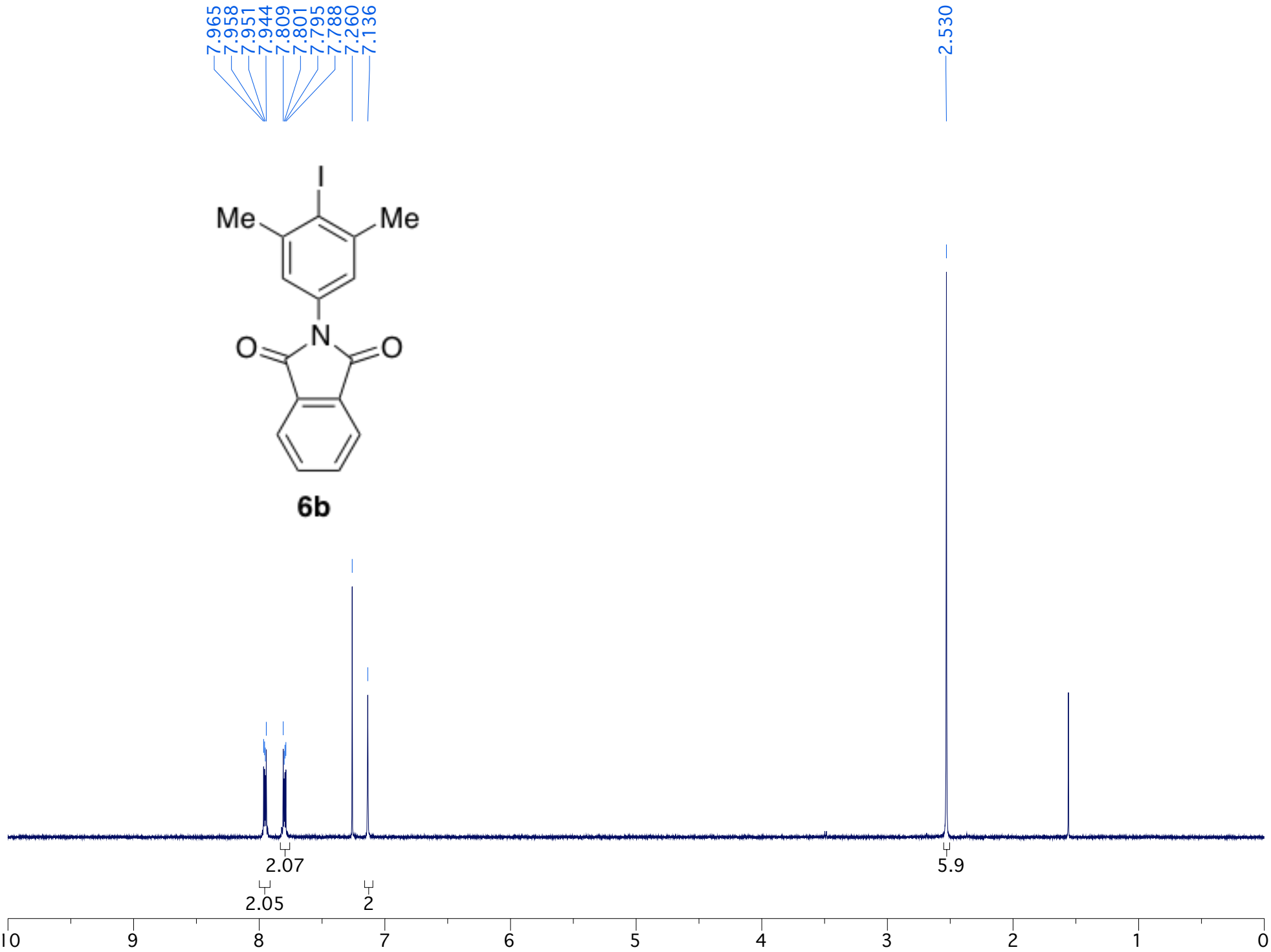
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7.788
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7.136
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I
Me
Me
N
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2
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7
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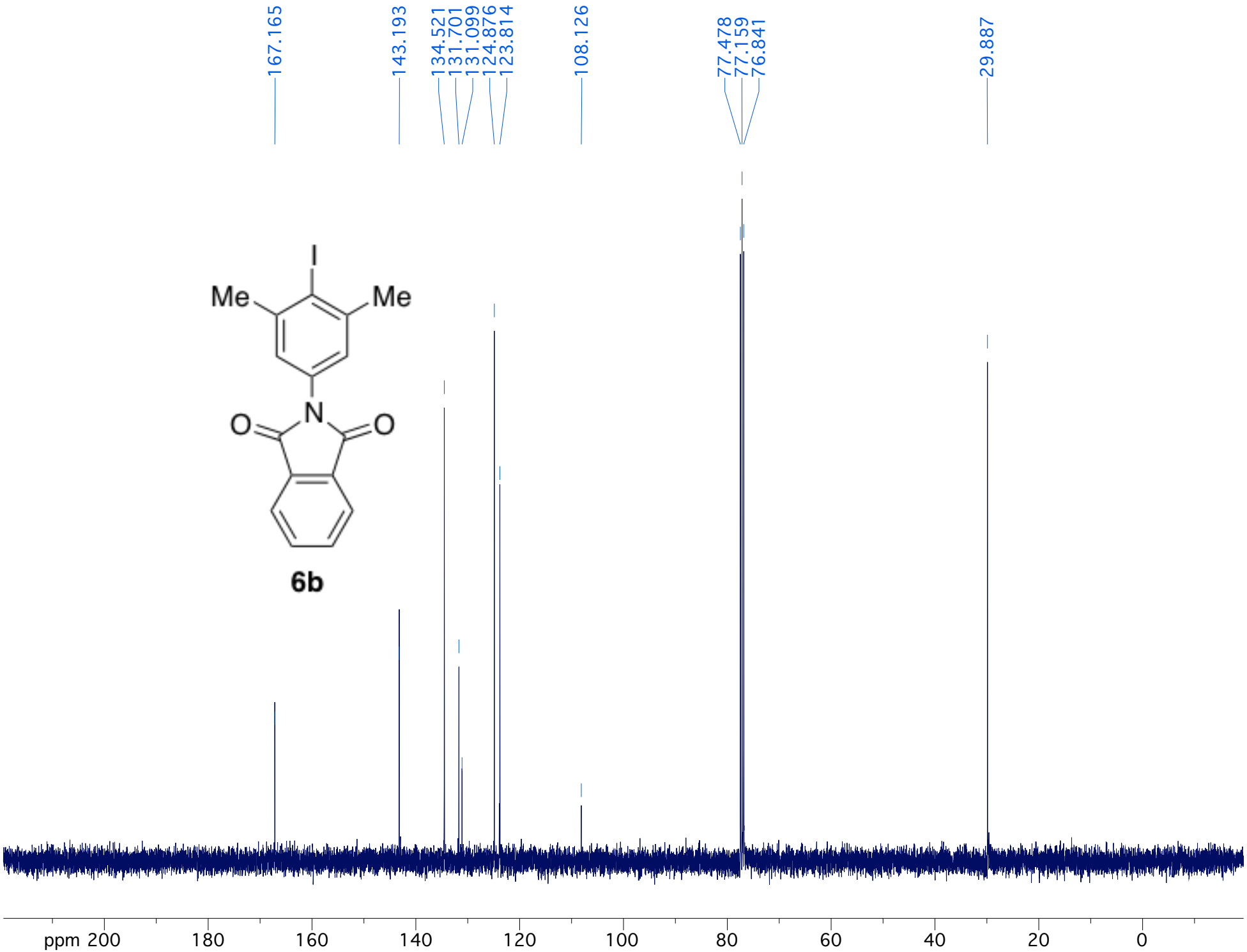
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108.126
77.478
77.159
76.841
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Me
N
O
O
6b
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140
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60
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20
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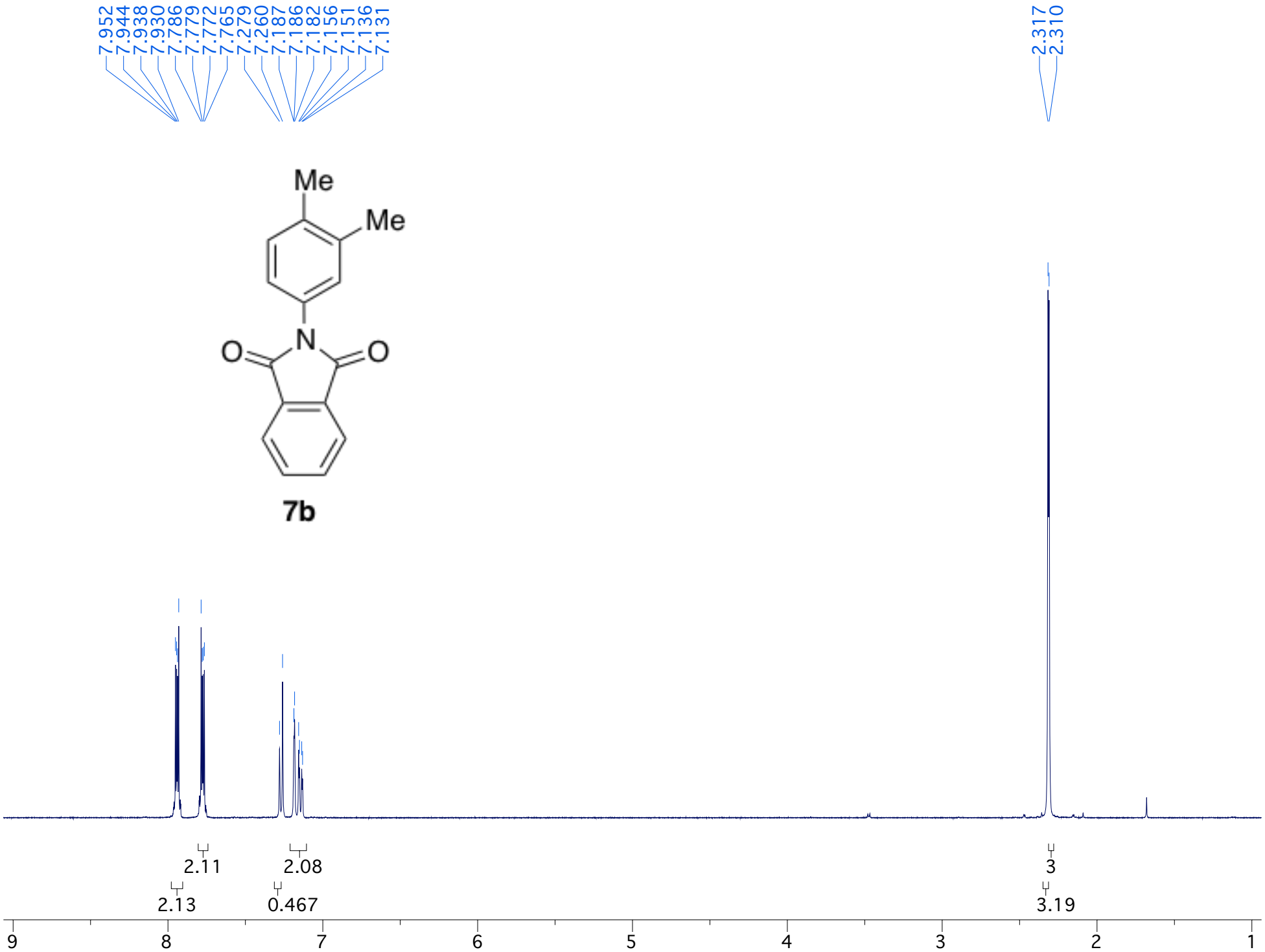
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Me
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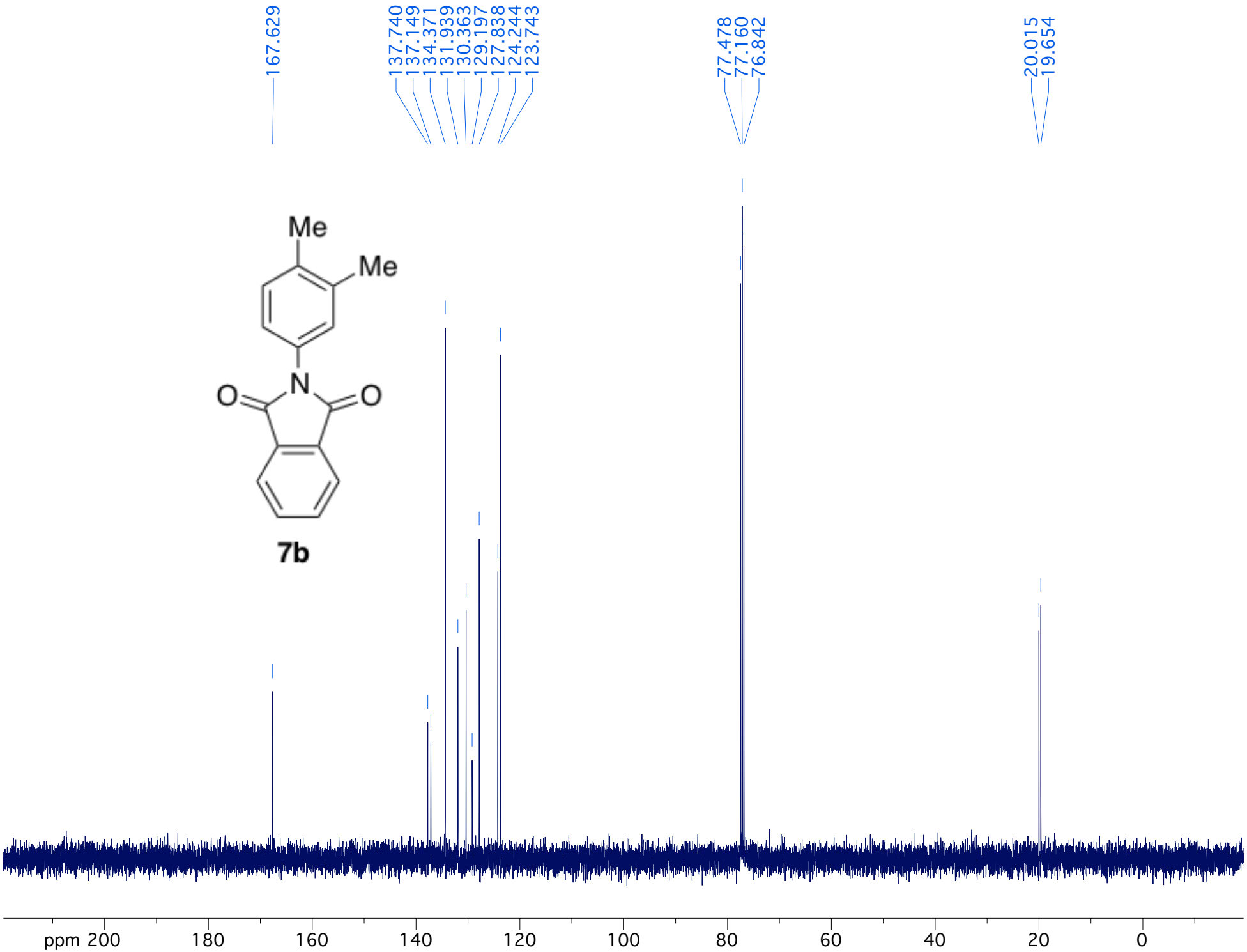
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76.842
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O
O
7b
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140
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40
20
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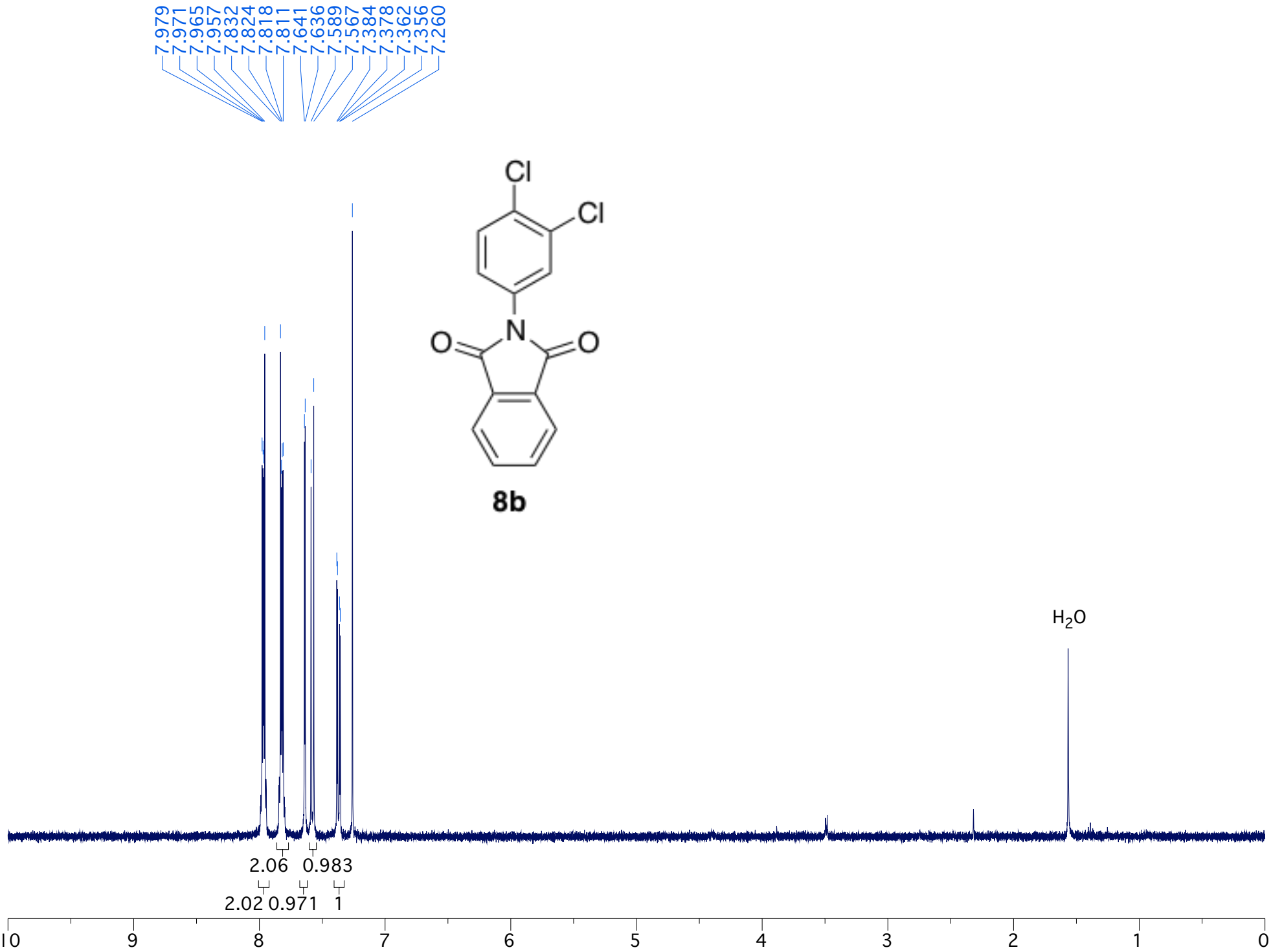
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7.567
7.384
7.378
7.362
7.356
7.260
Cl
Cl
N
O
O
8b
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7
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5
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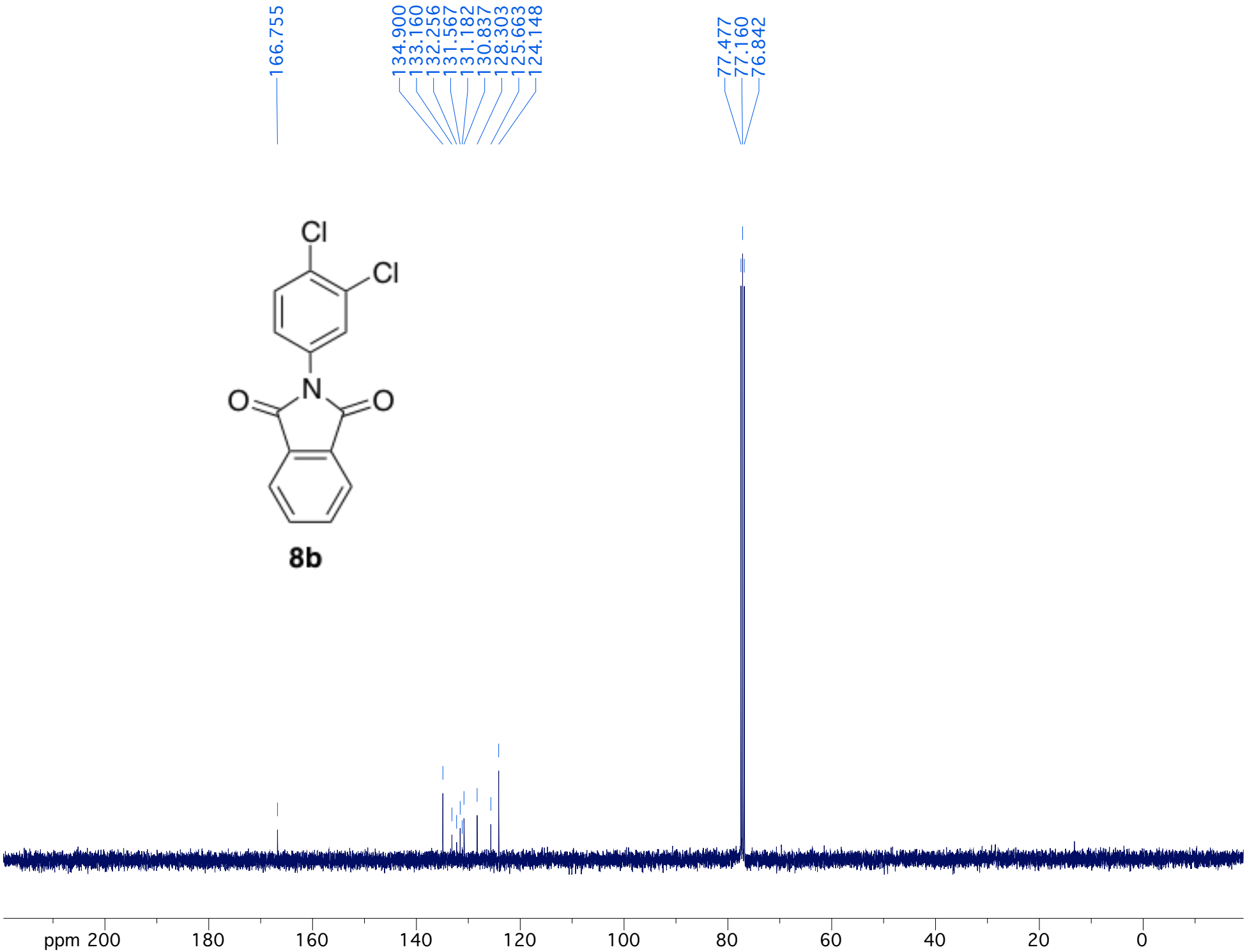
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131.182
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128.303
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77.477
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Cl
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N
O
O
8b
ppm 200
180
160
140
120
100
80
60
40
20
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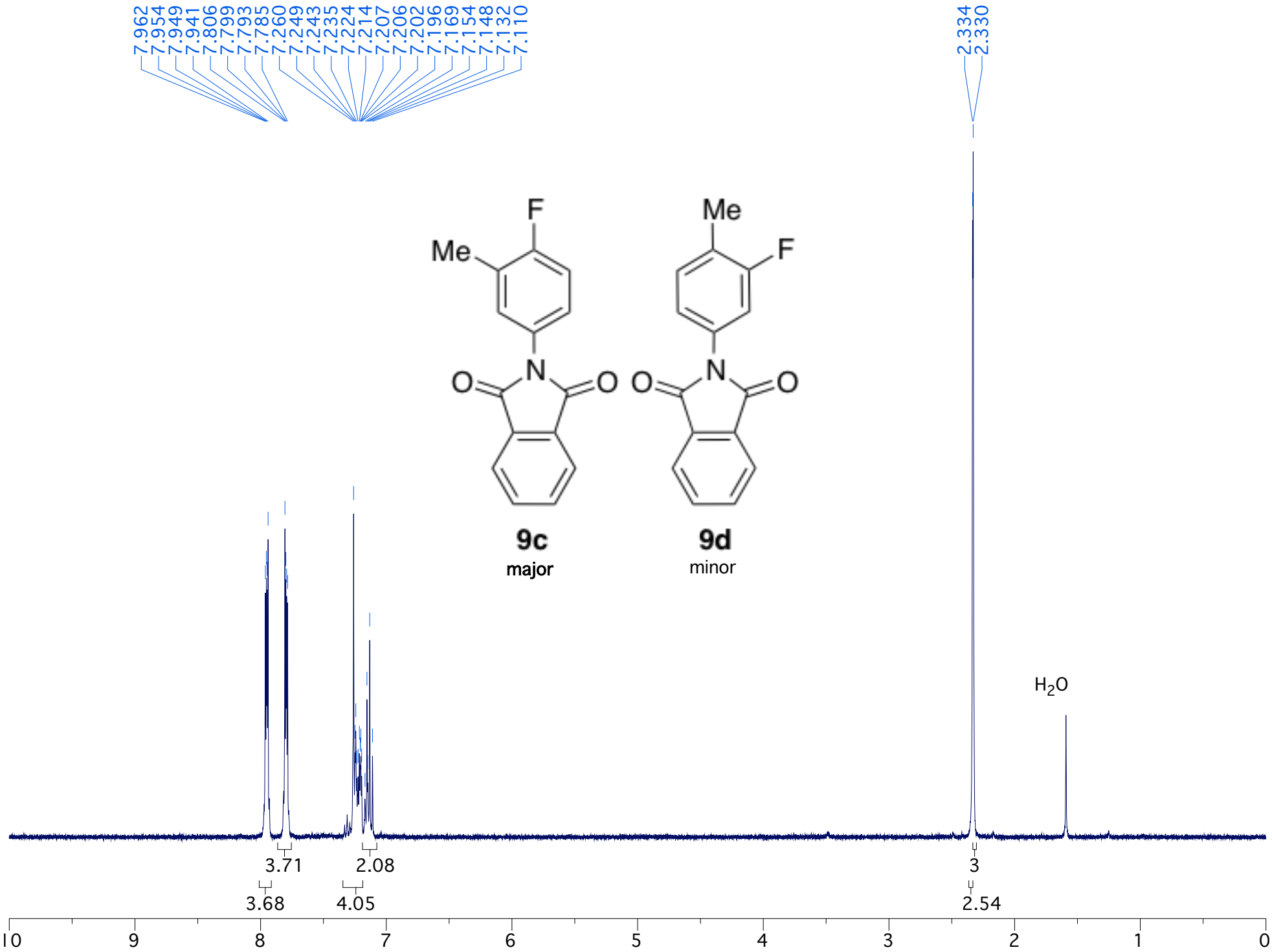
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7.243
7.235
7.224
7.214
7.207
7.206
7.202
7.196
7.169
7.154
7.148
7.132
7.110
2.334
2.330
F
Me
N
O
O
Me
F
N
O
O
9c
major
9d
minor
H2O
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7
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5
4
3
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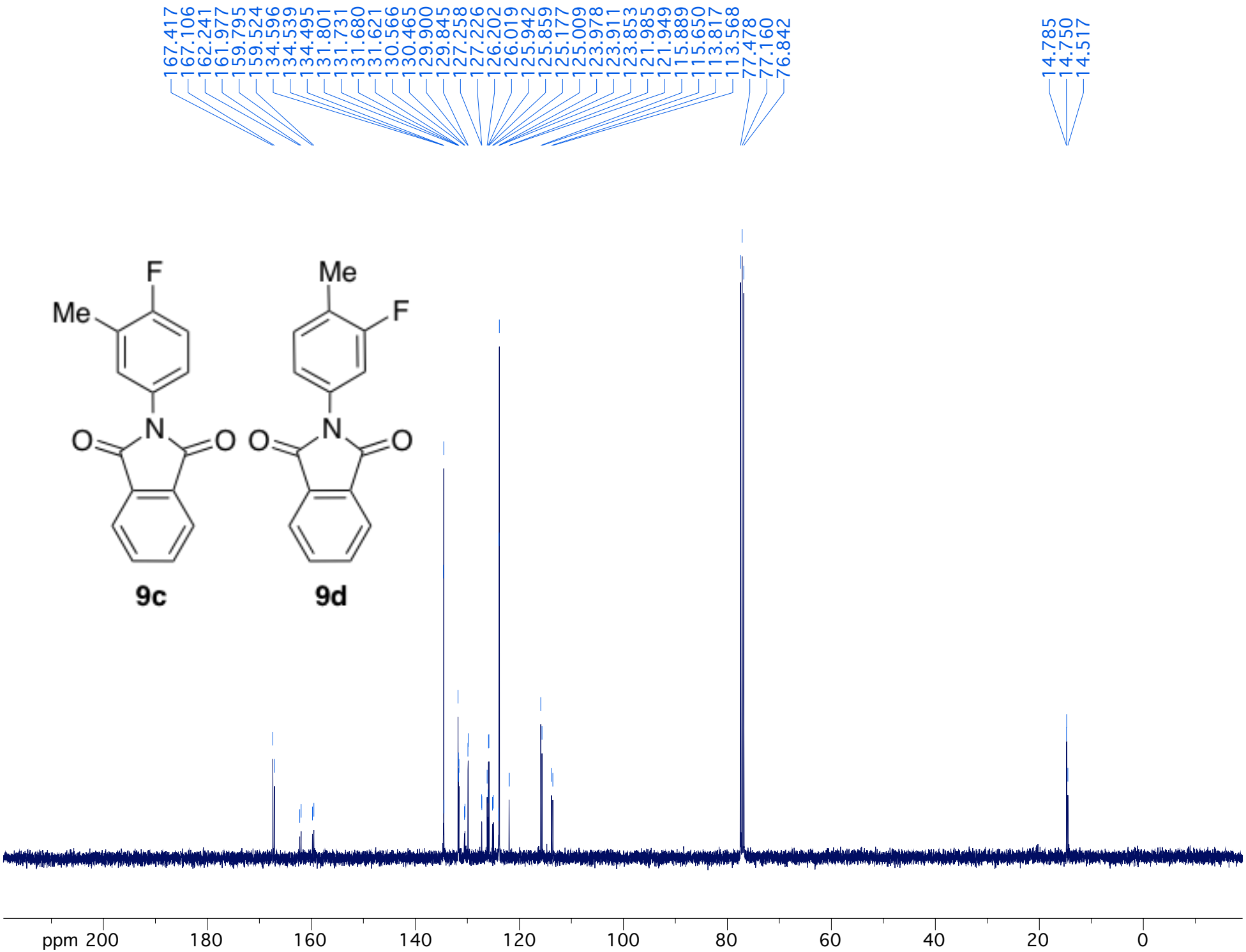
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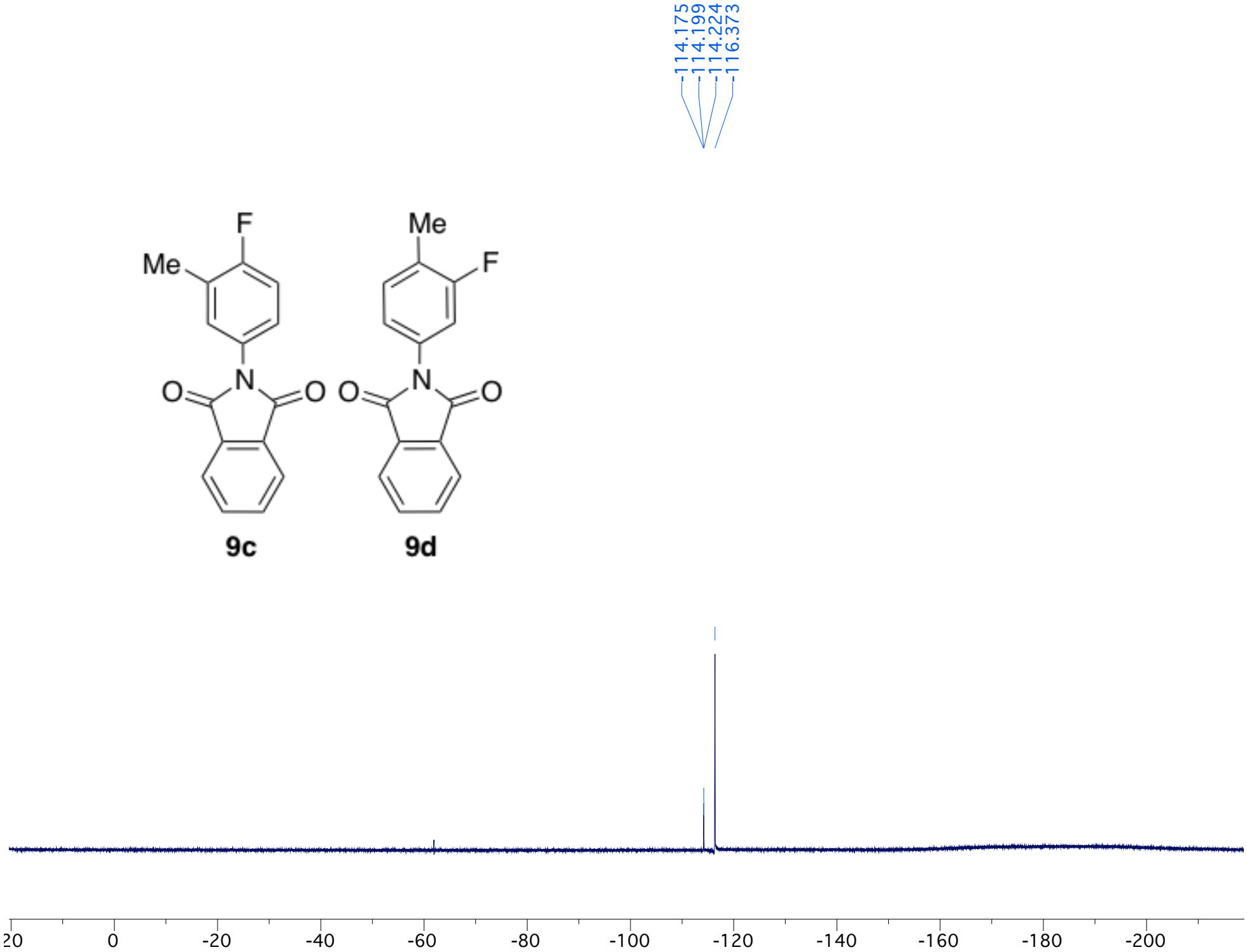
131.731
131.680
131.621
130.566
130.465
129.900
129.845
127.258
127.226
126.202
126.019
125.942
125.859
125.177
125.009
123.978
123.911
123.853
121.985
121.949
115.889
115.650
113.817
113.568
77.478
77.160
76.842
14.785
14.750
14.517
F
Me
N
O
O
9c
Me
F
N
O
O
9d
ppm 200
180
160
140
120
100
80
60
40
20
0

F
Me
N
O
O
Me
F
N
O
O

9c **9d**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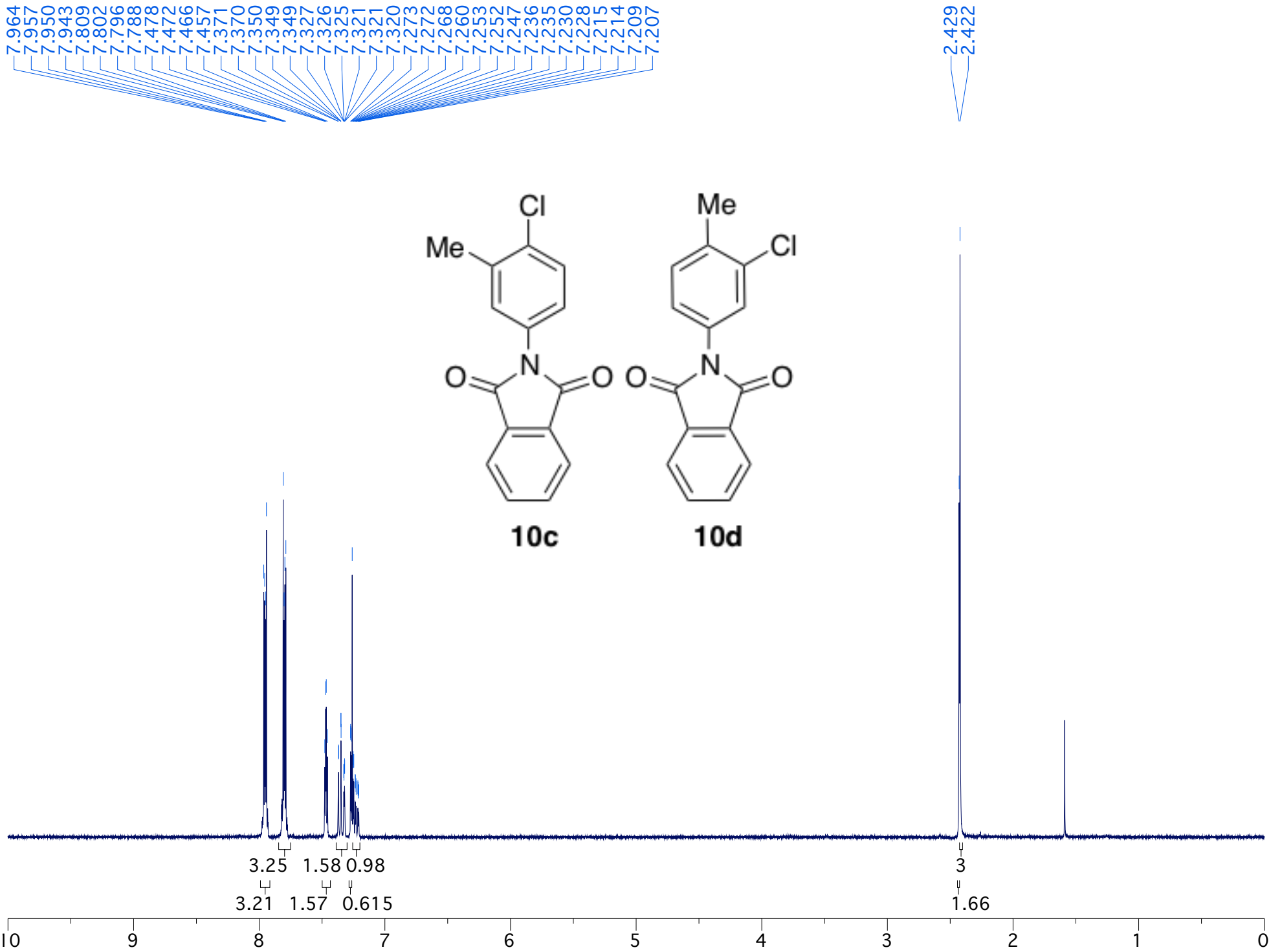
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7.370
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7.349
7.349
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7.326
7.325
7.321
7.321
7.320
7.273
7.272
7.268
7.260
7.253
7.252
7.247
7.236
7.235
7.230
7.228
7.215
7.214
7.209
7.207
2.429
2.422
Cl
Me
N
O
O
10c
Me
Cl
N
O
O
10d
3.25
1.58
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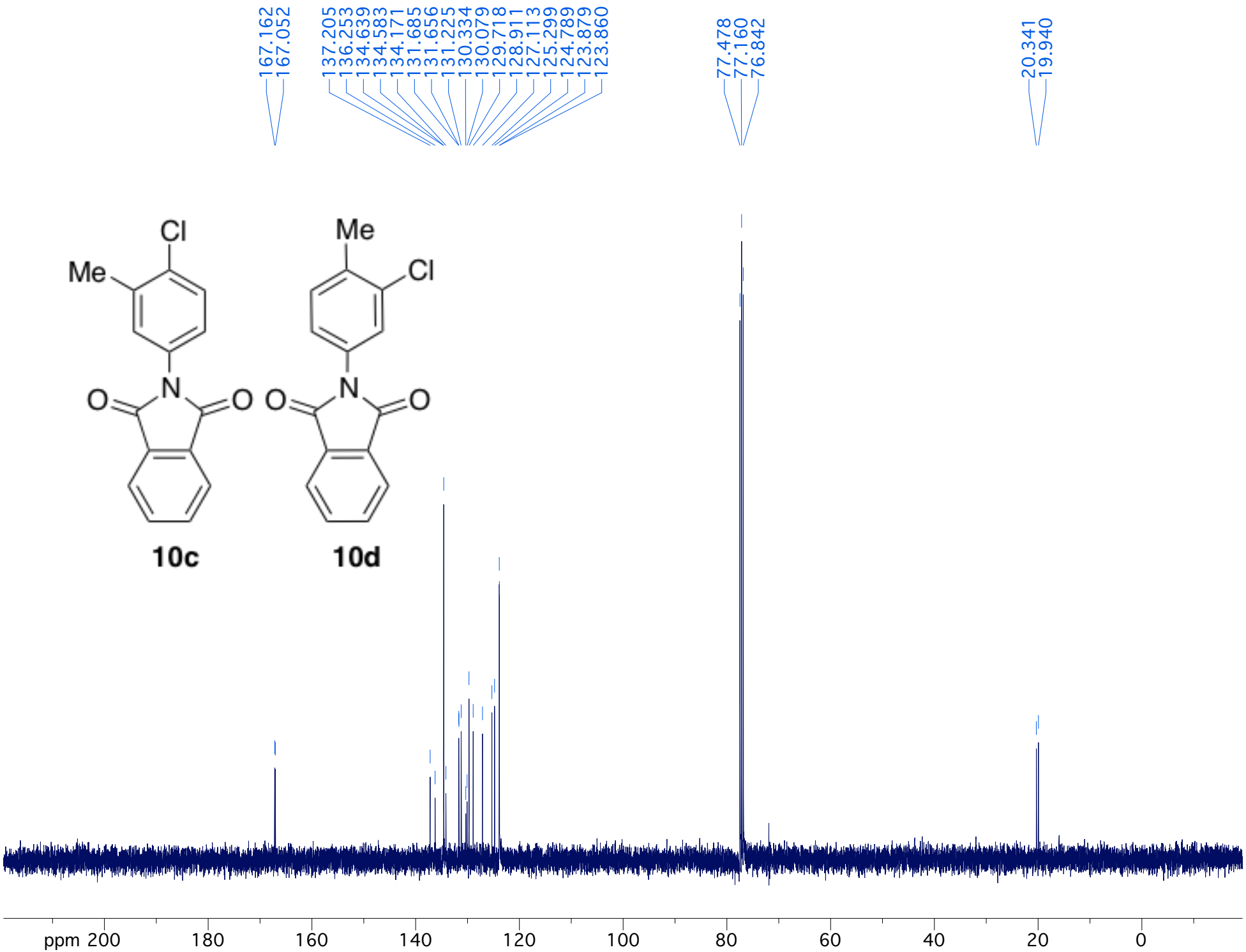
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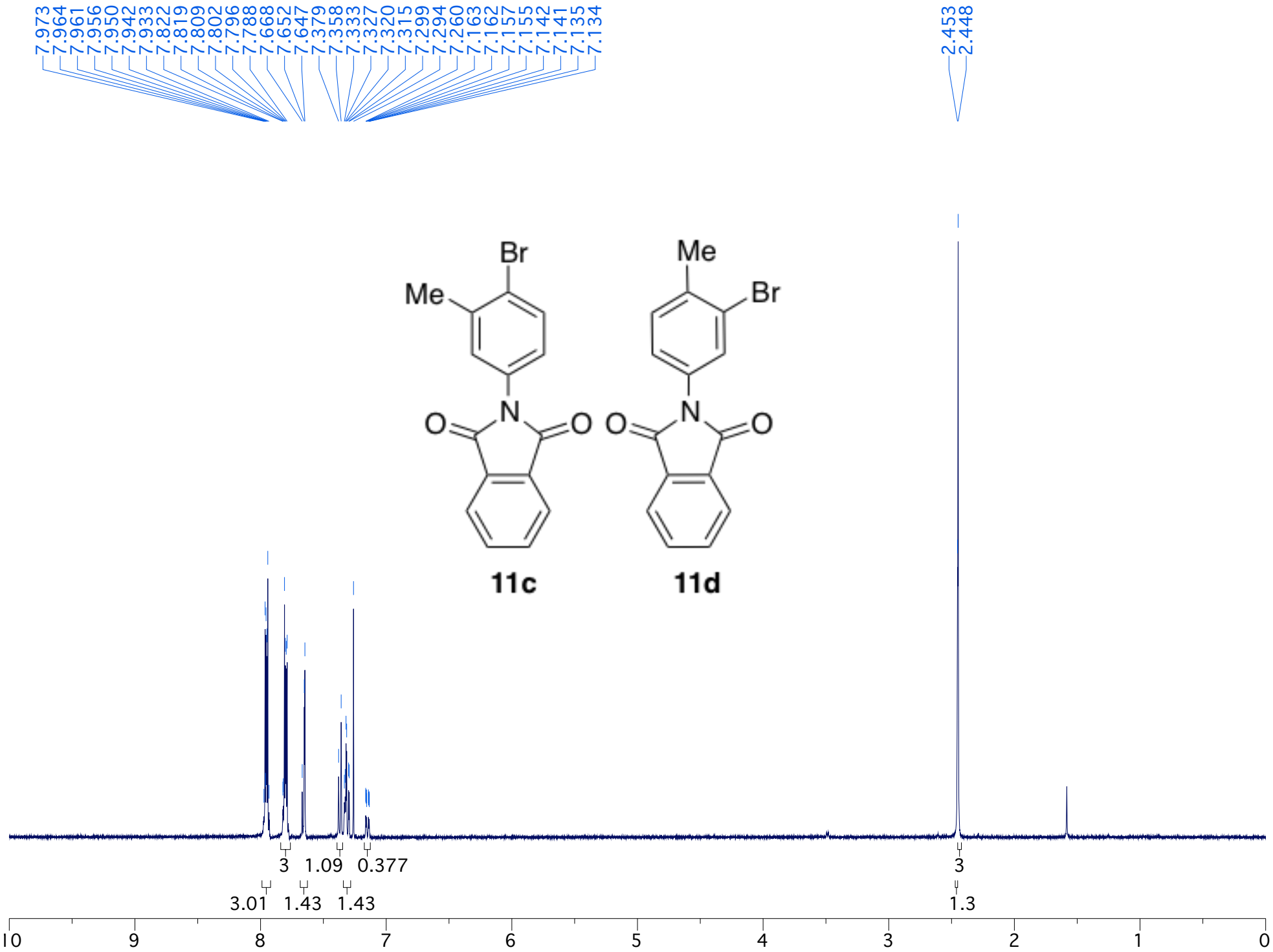
128.911
127.113
125.299
124.789
123.879
123.860
77.478
77.160
76.842
20.341
19.940
Cl
Me
N
O
O
10c
Me
Cl
N
O
O
10d
ppm 200
180
160
140
120
100
80
60
40
20
0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7.933
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7.809
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7.796
7.788
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7.652
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7.327
7.320
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7.299
7.294
7.260
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7.157
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7.141
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7.134
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2.448
Br
Me
N
O
O
11c
Me
Br
N
O
O
11d
3
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0.377
3.01
1.43
1.43
3
1.3
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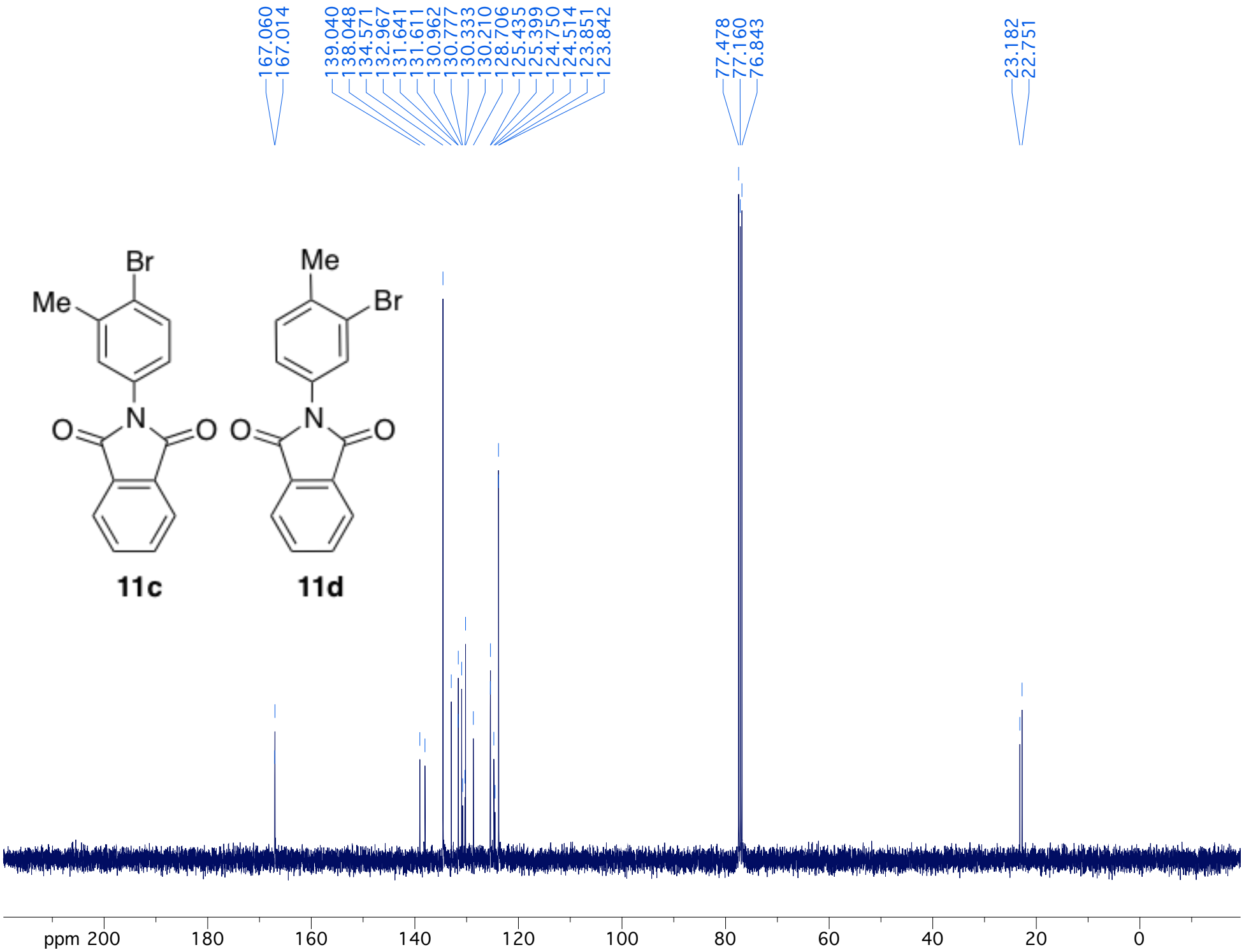
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Br
Me
N
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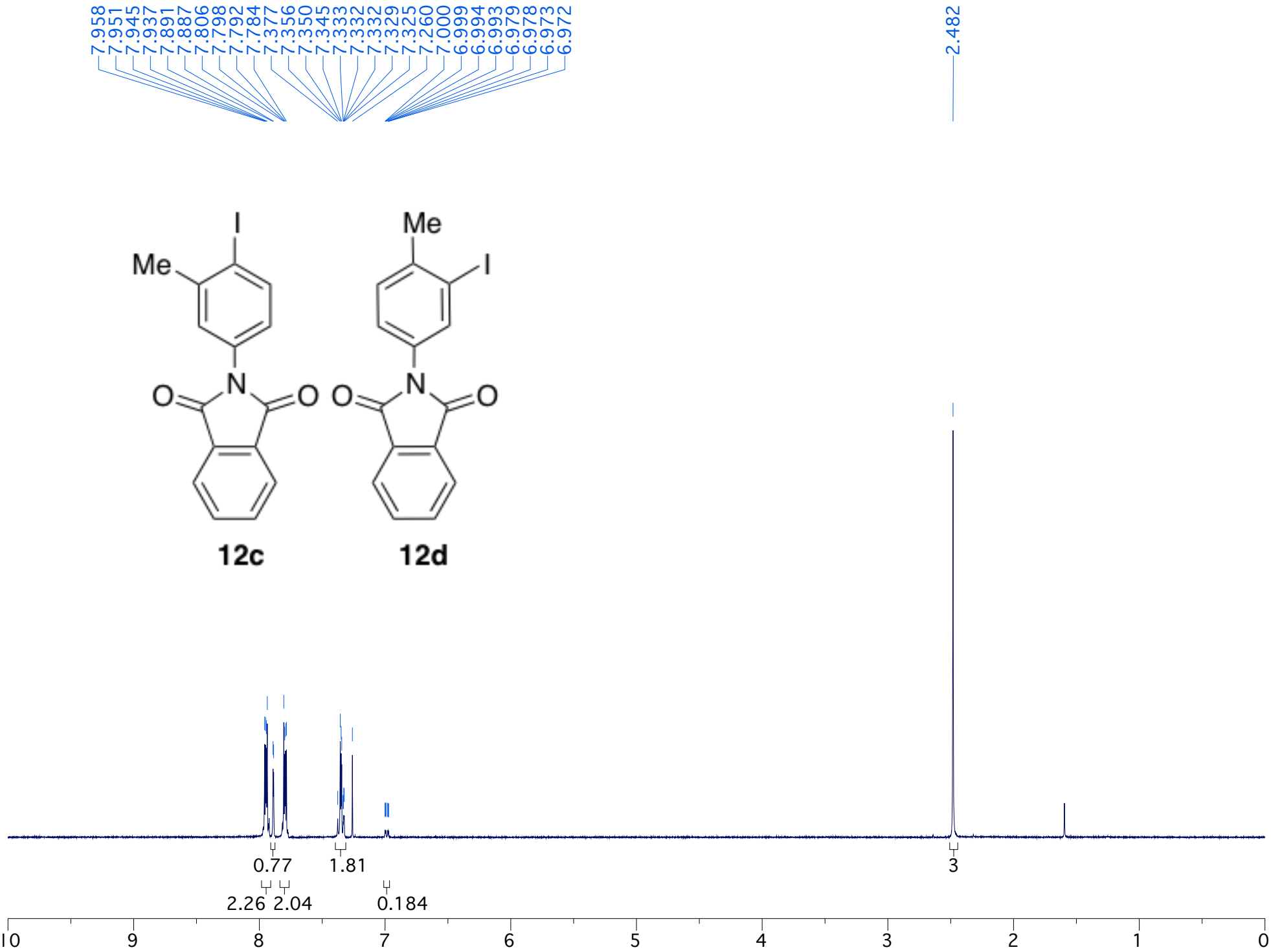
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6.973
6.972
2.482
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Me
N
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O
Me
I
N
O
O
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12d
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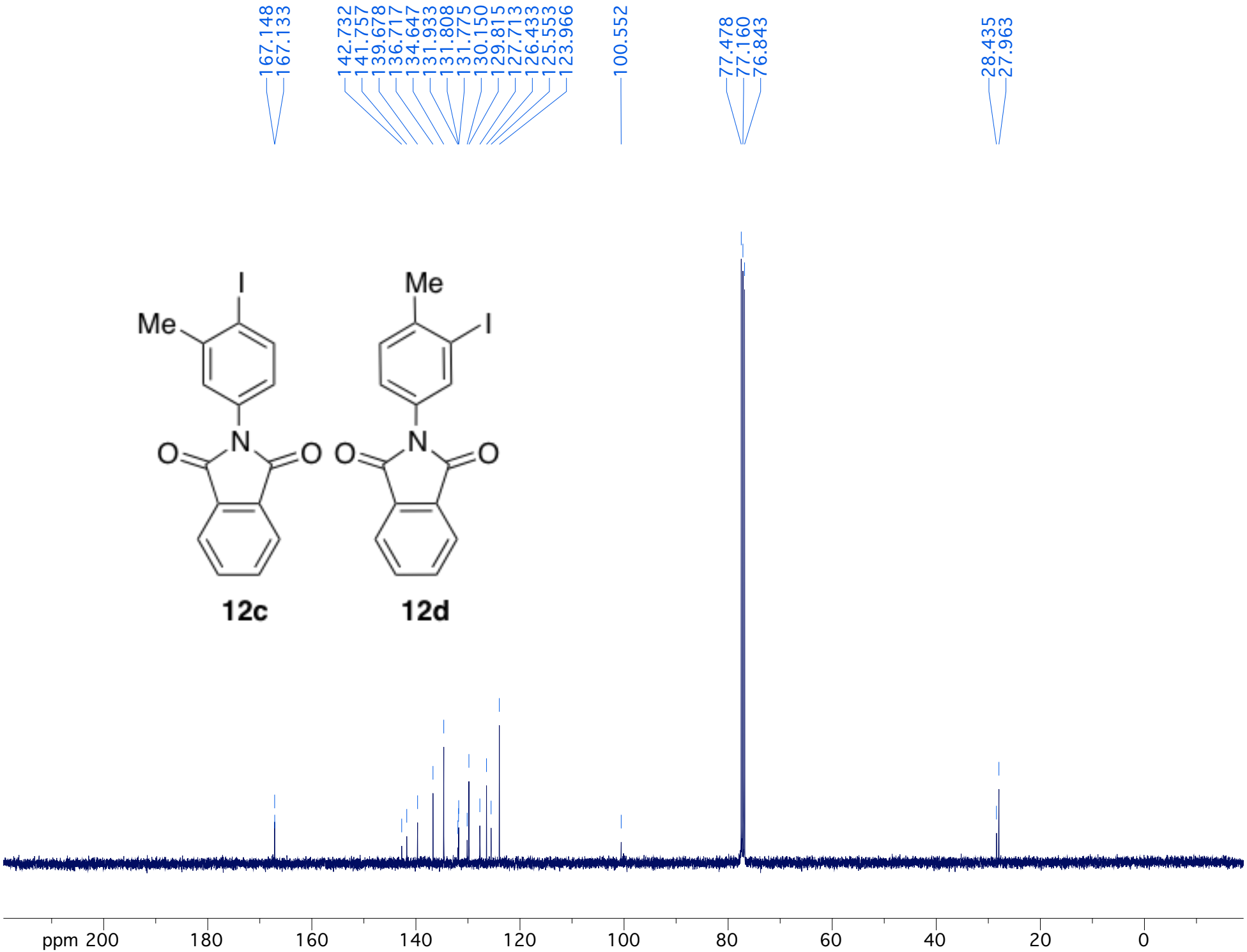
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N
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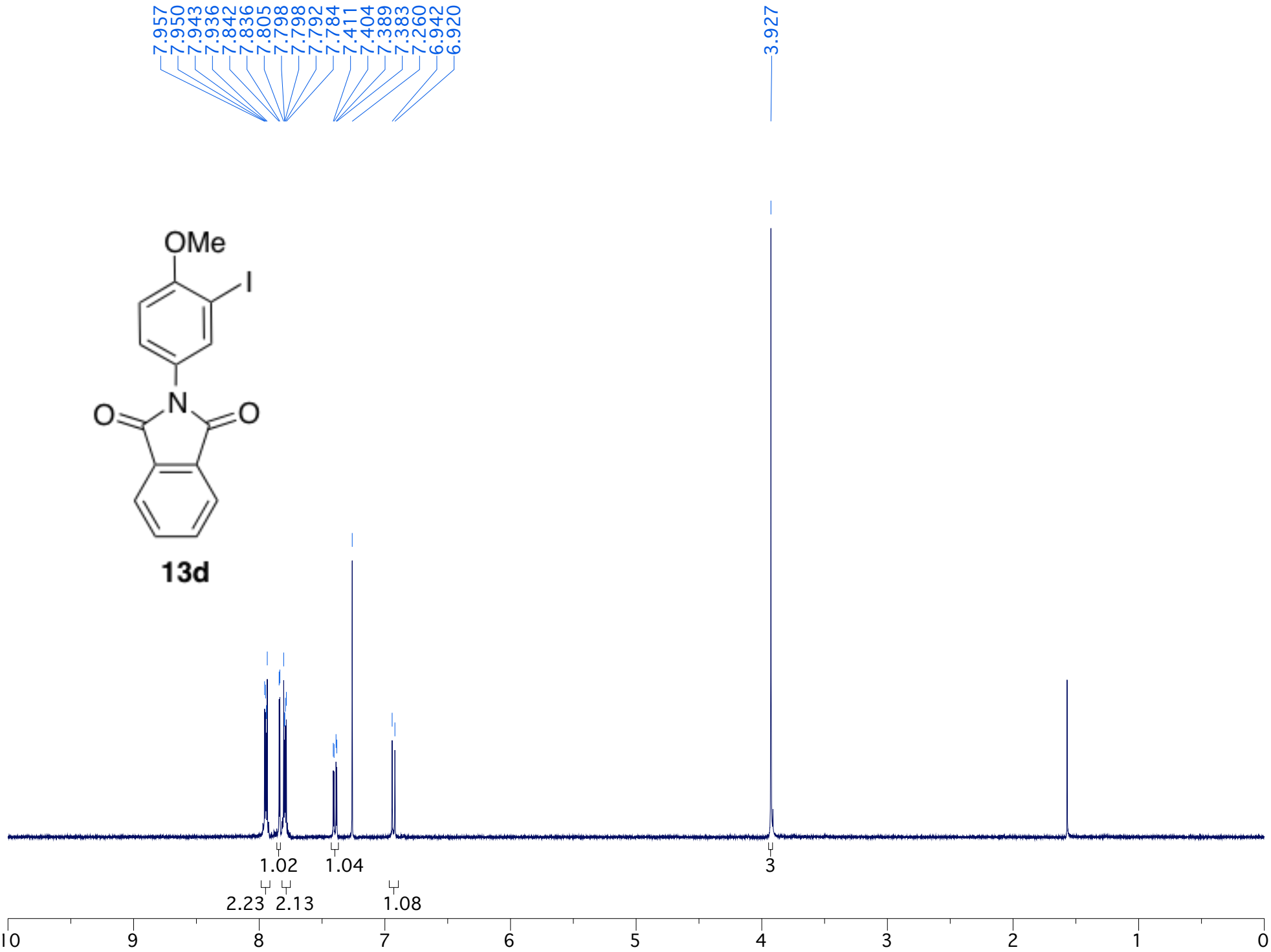
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O
13d
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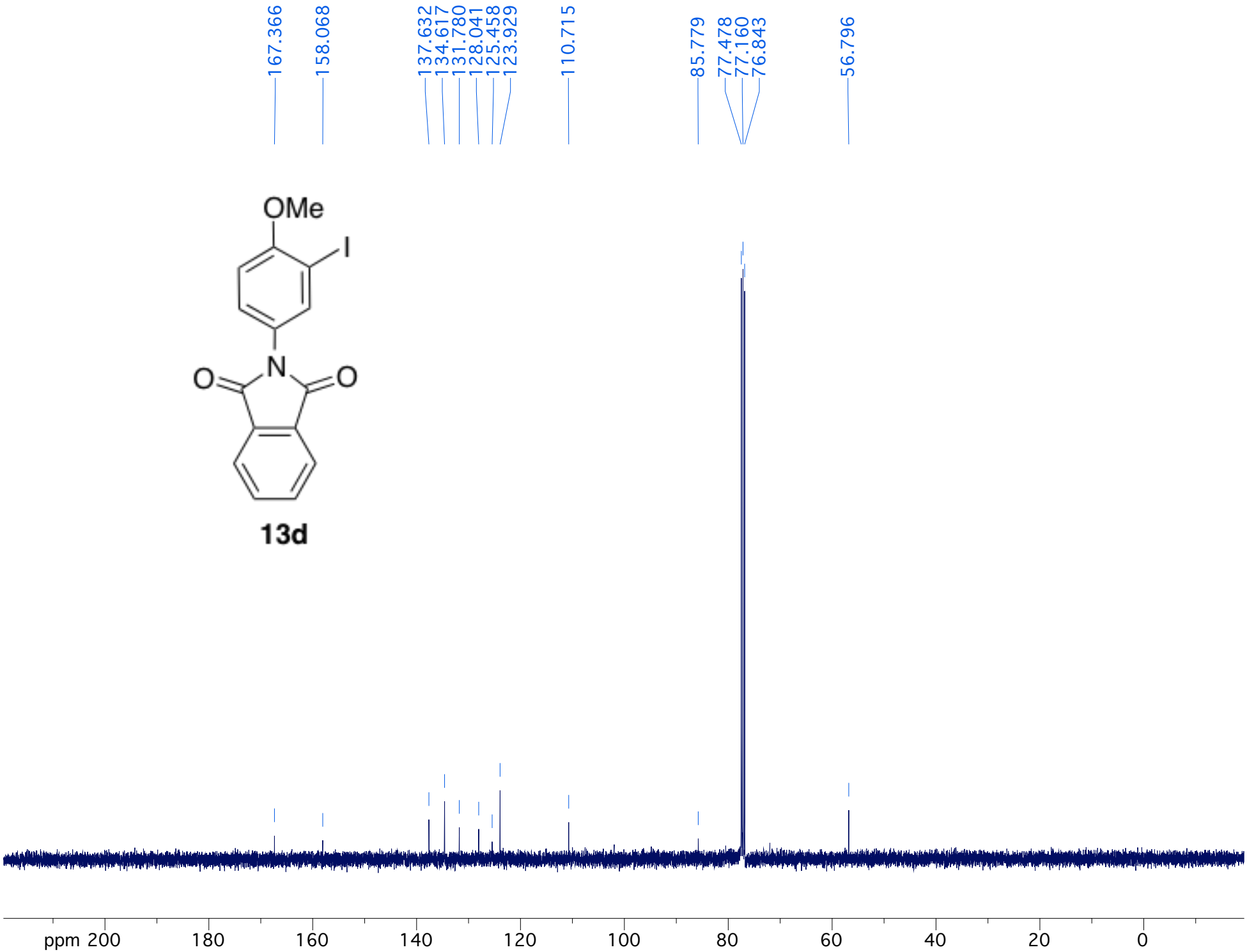
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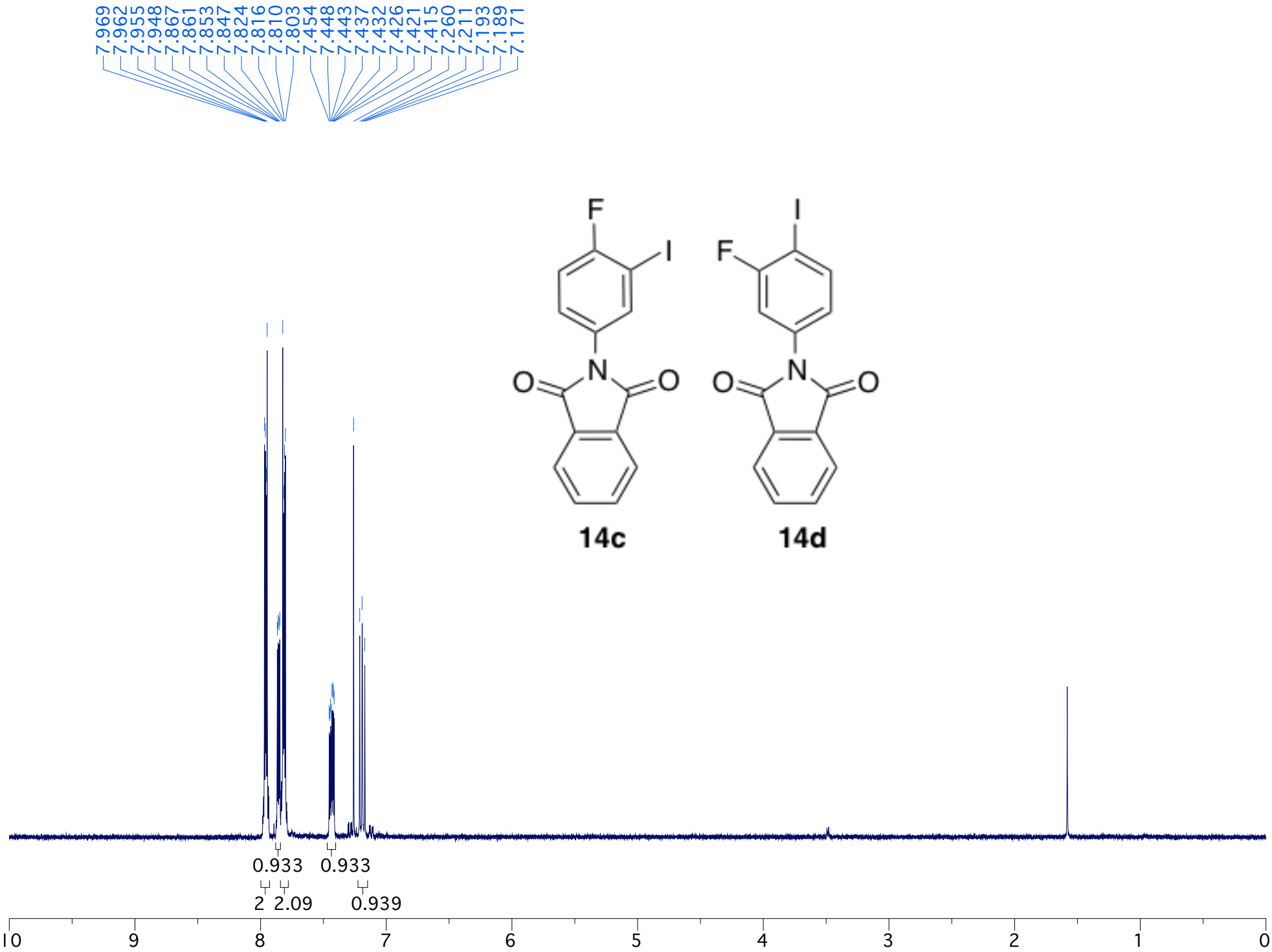
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7.426
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7.211
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7.189
7.171
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N
O
O
14c
I
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N
O
O
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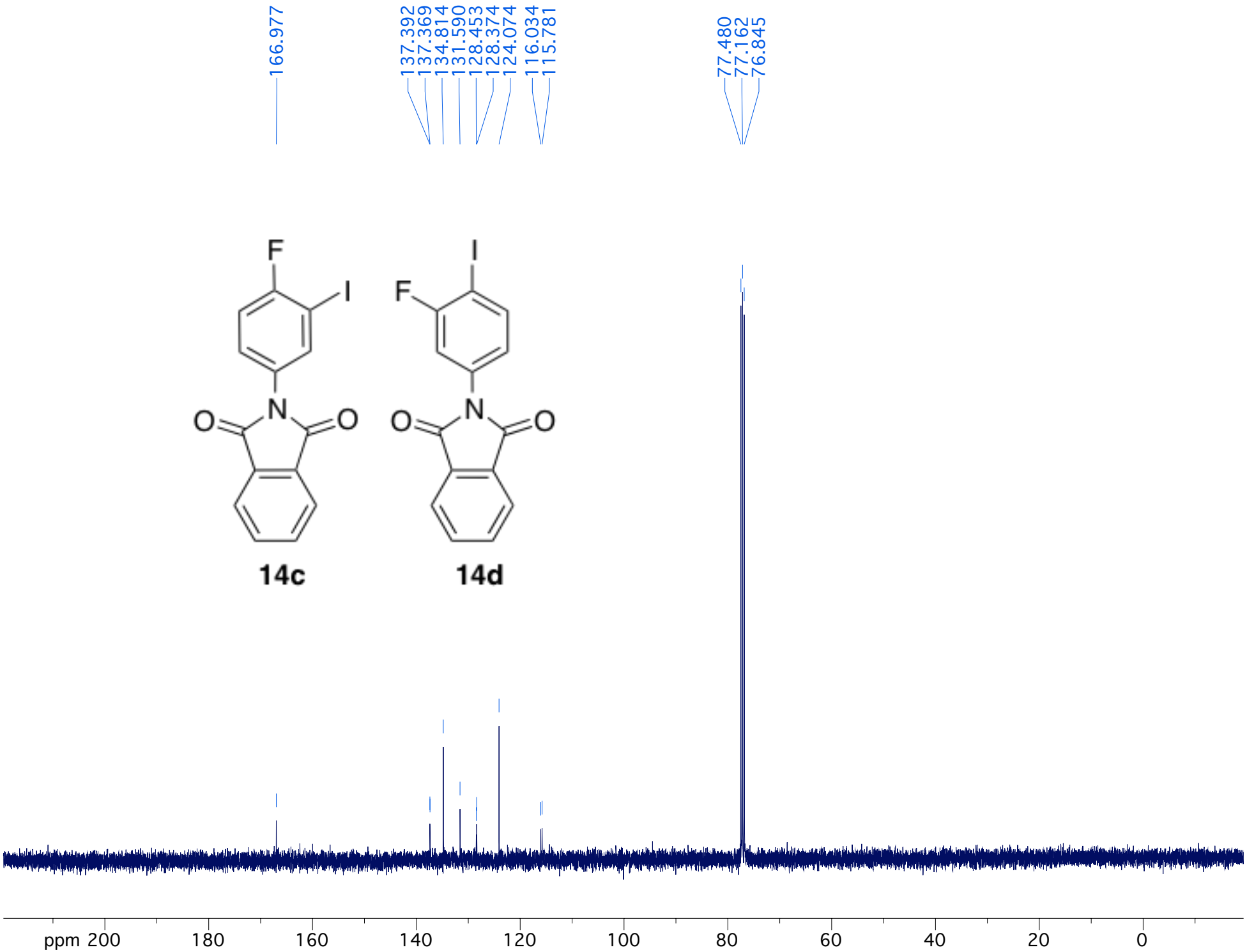
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I
N
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N
O
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14d
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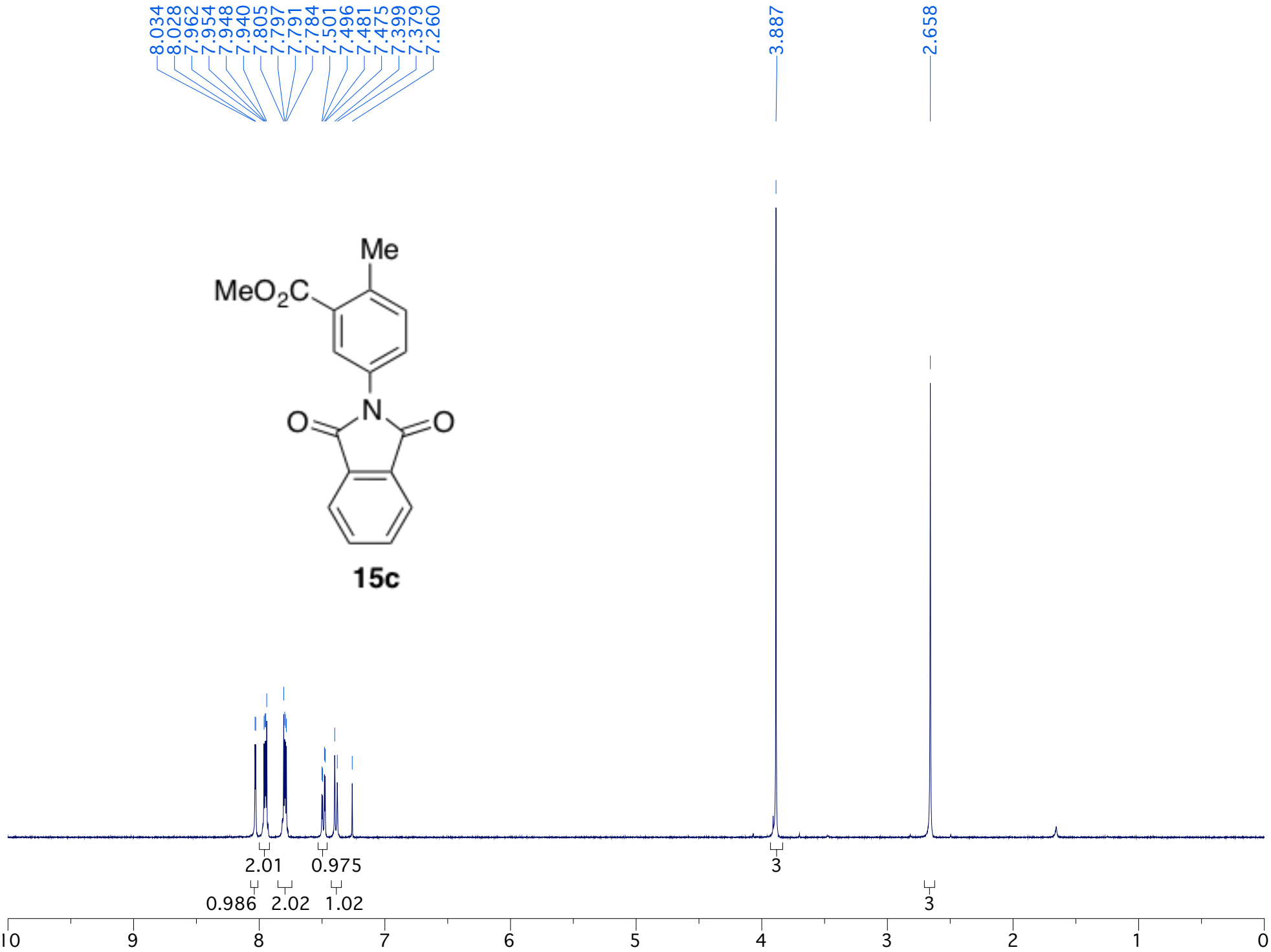
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7.475
7.399
7.379
7.260
3.887
2.658
Me
MeO2C
N
O
O
15c
2.01
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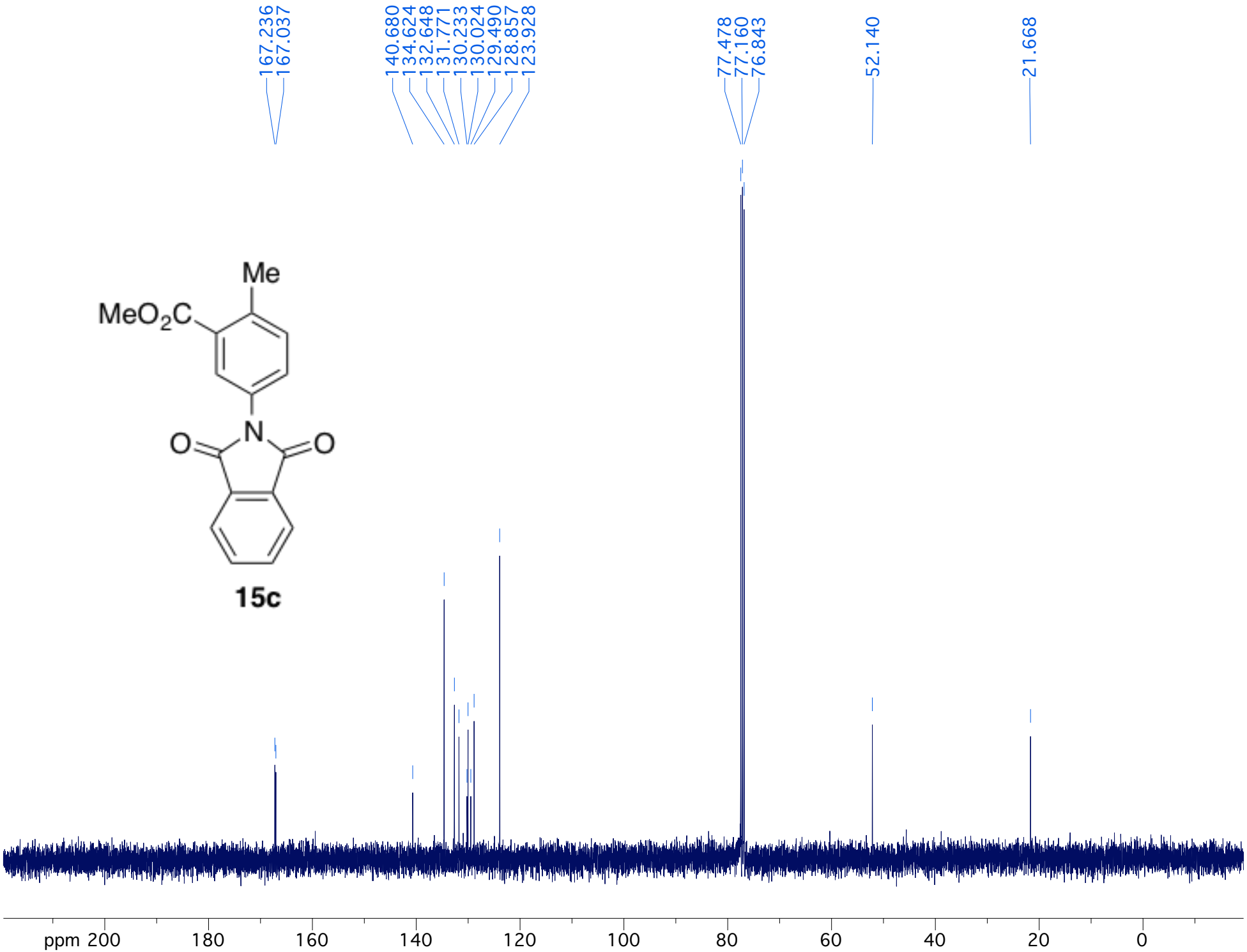
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52.140
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O
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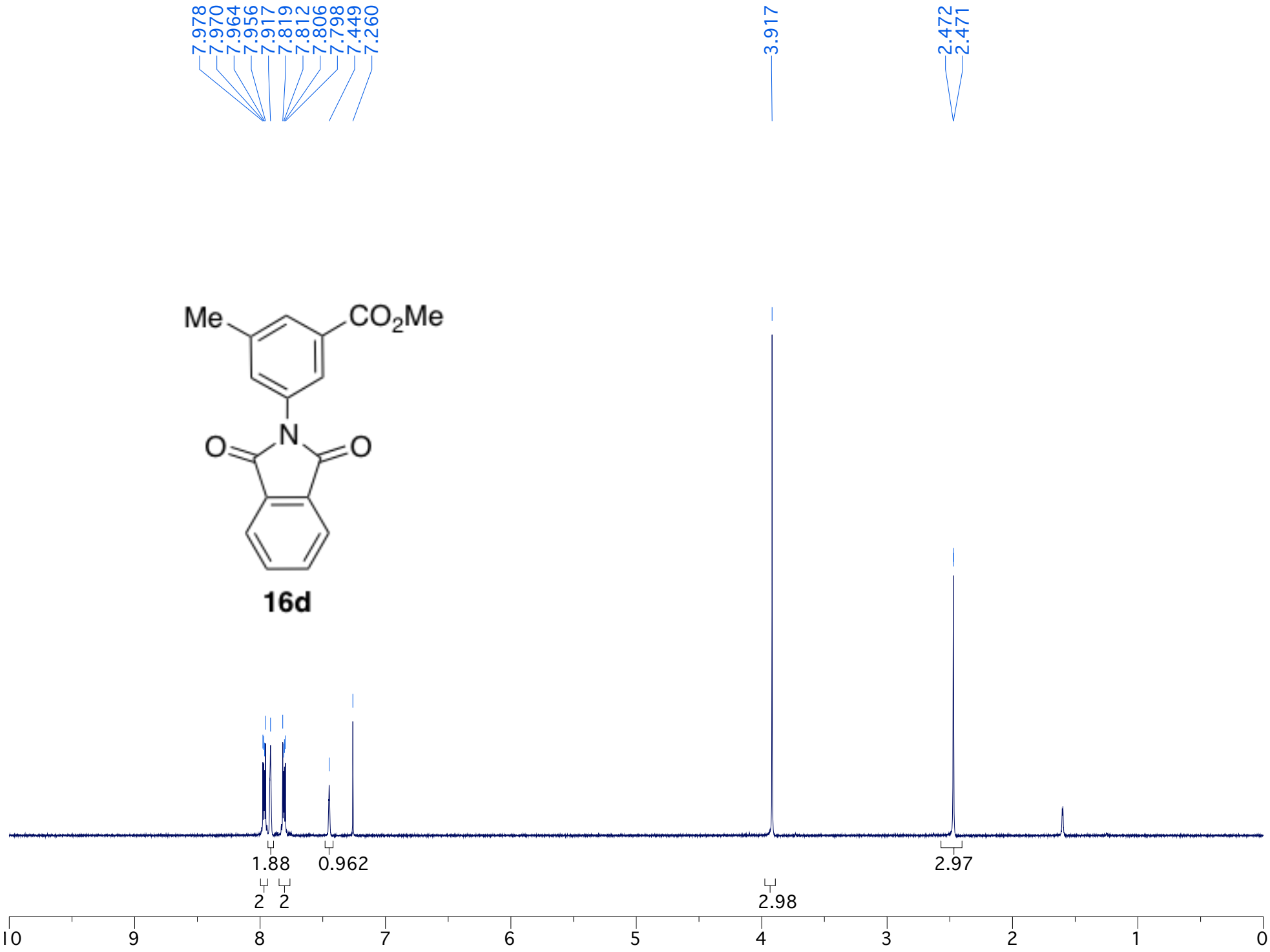
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2.471
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CO2Me
N
O
O
16d
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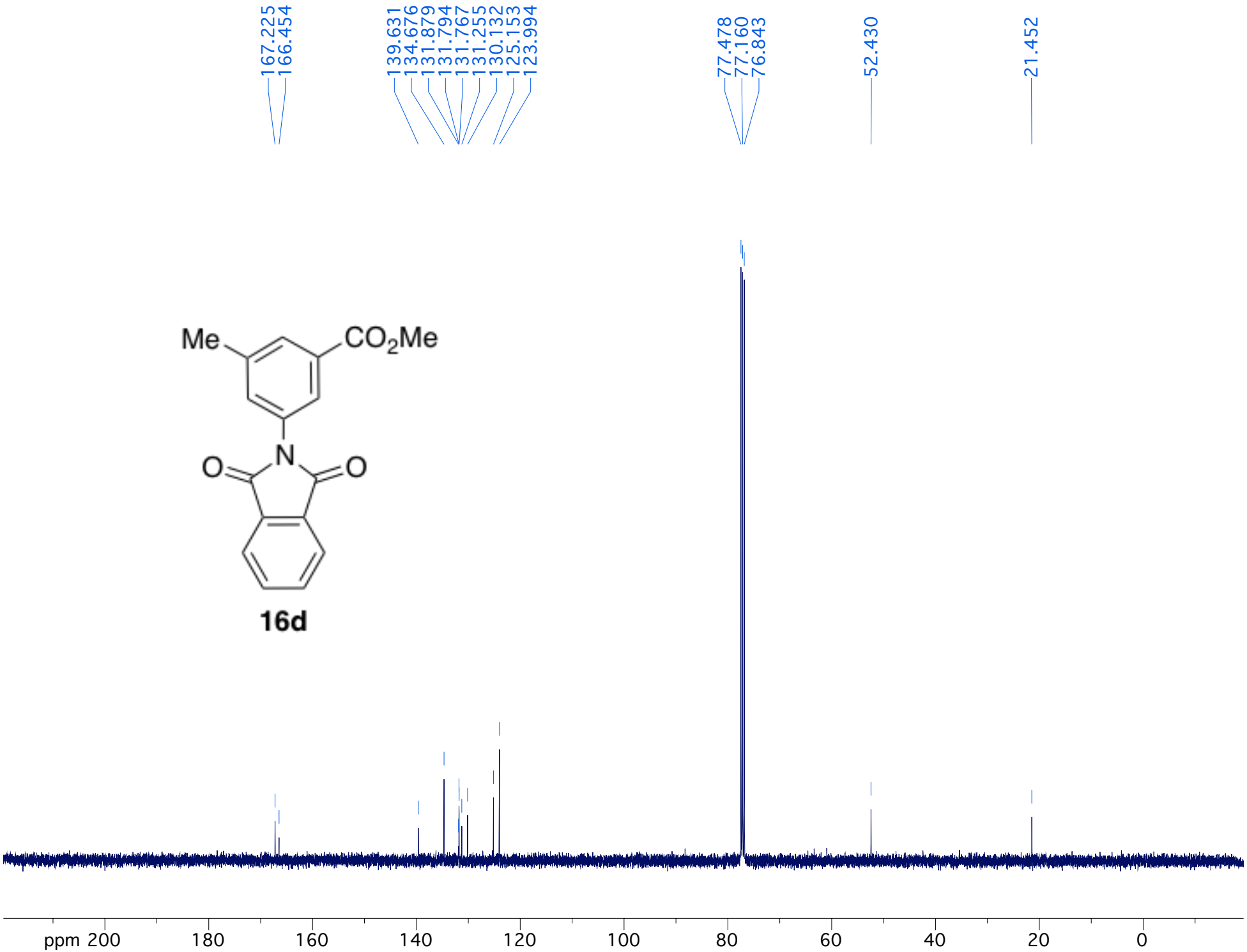
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O
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140
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60
40
20
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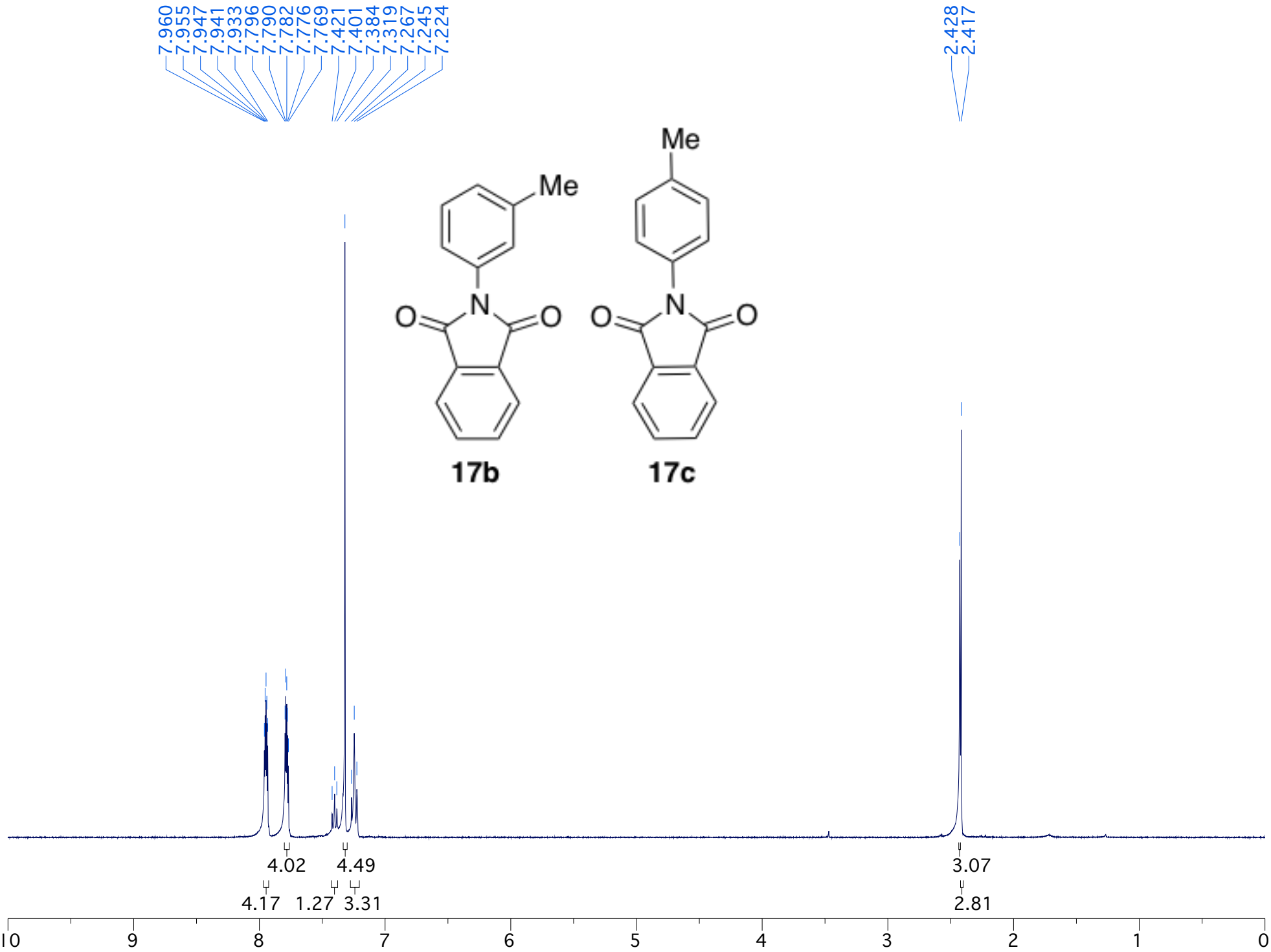
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7.245
7.224
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2.417
Me
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O
17b
Me
N
O
O
17c
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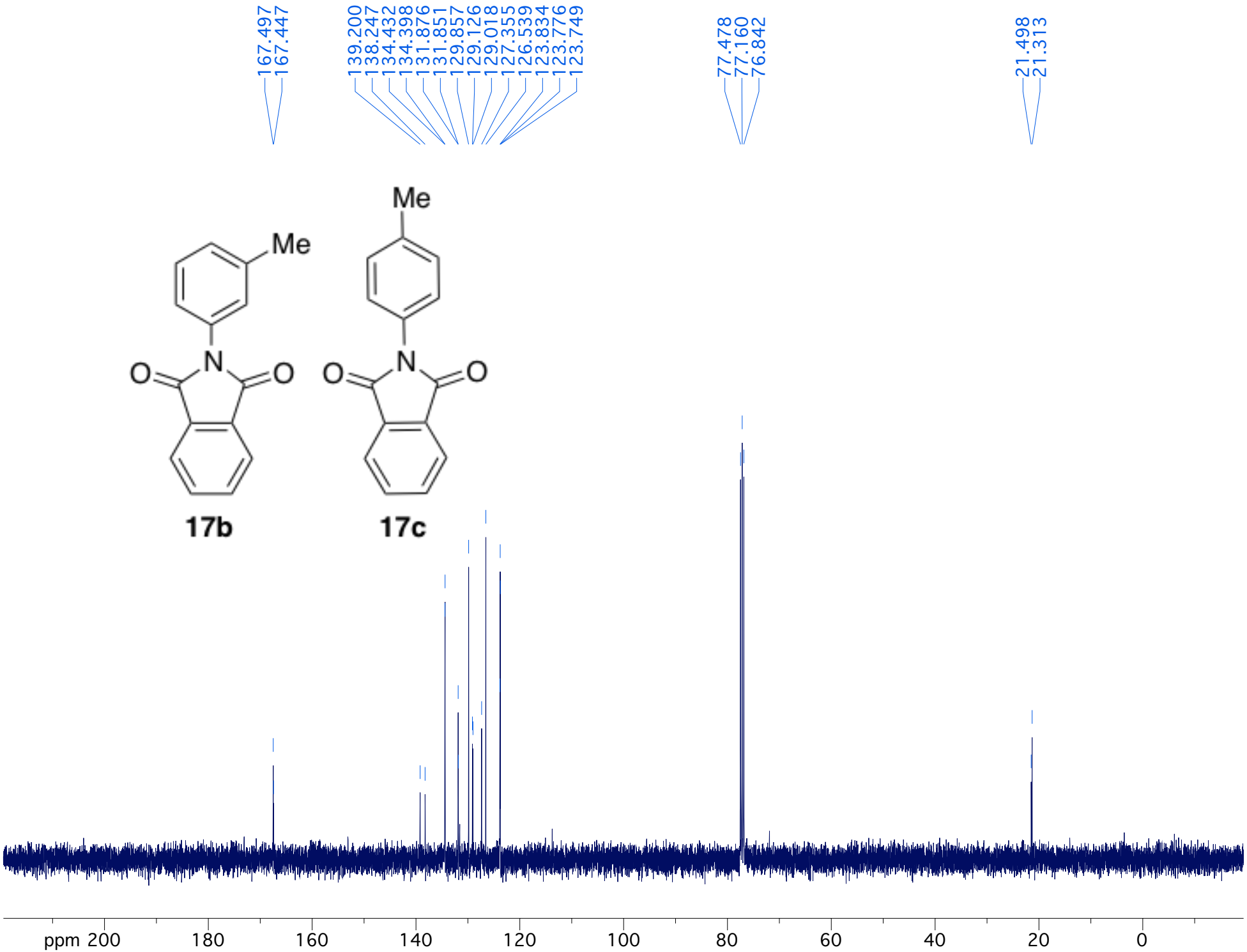
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123.834
123.776
123.749
77.478
77.160
76.842
21.498
21.313
Me
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O
O
17b
Me
N
O
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17c
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140
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20
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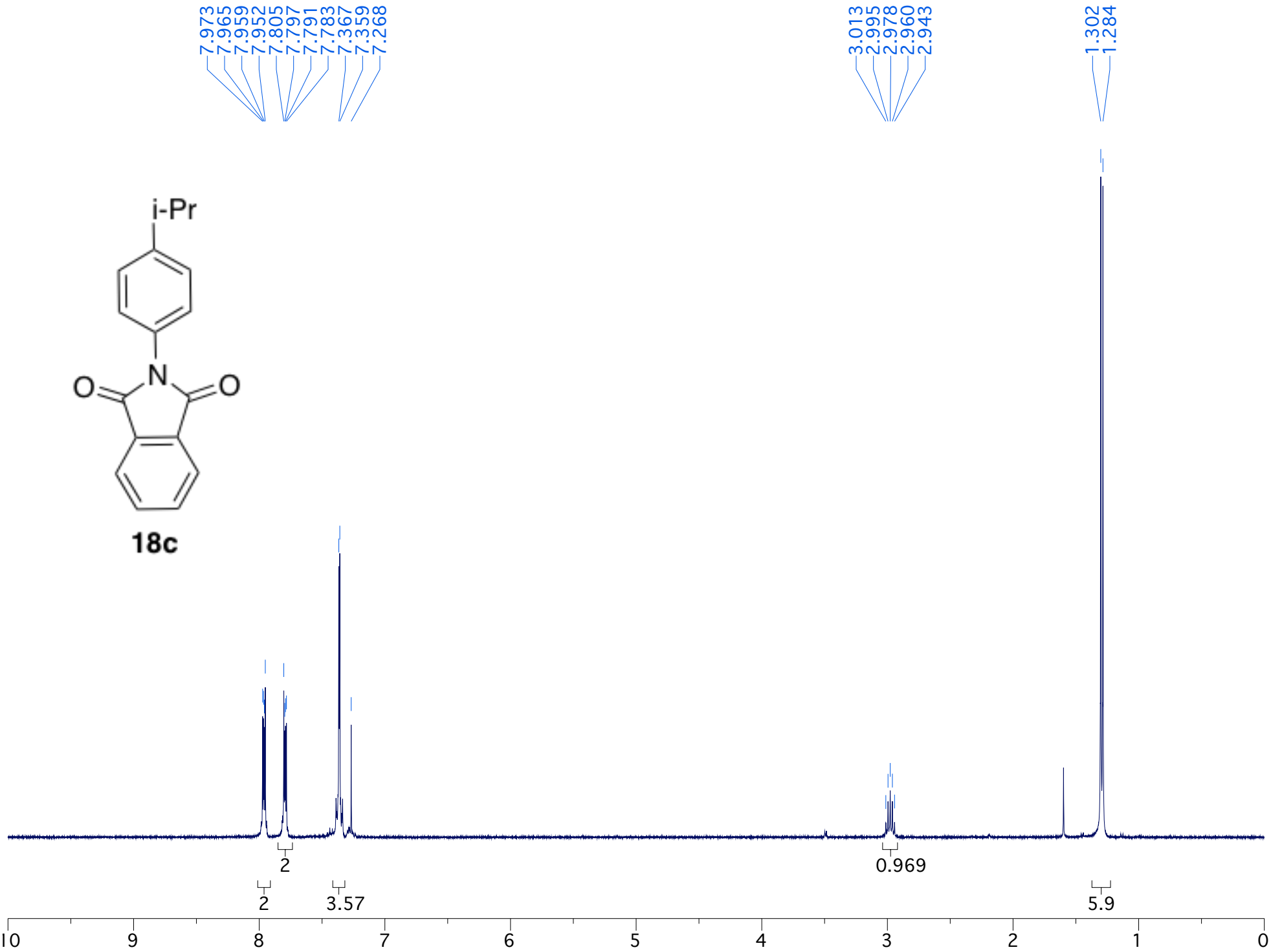
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1.284
i-Pr
N
O
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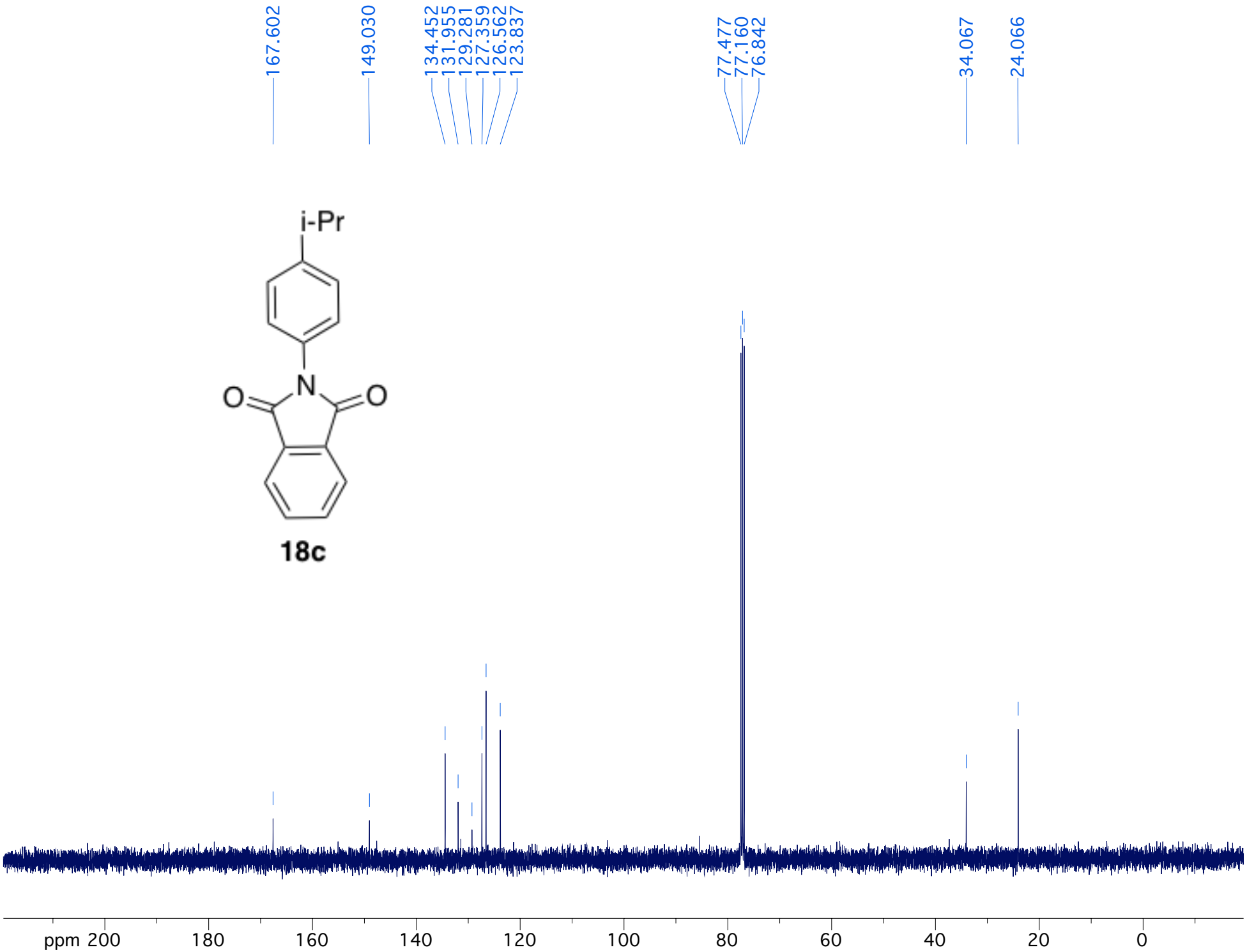
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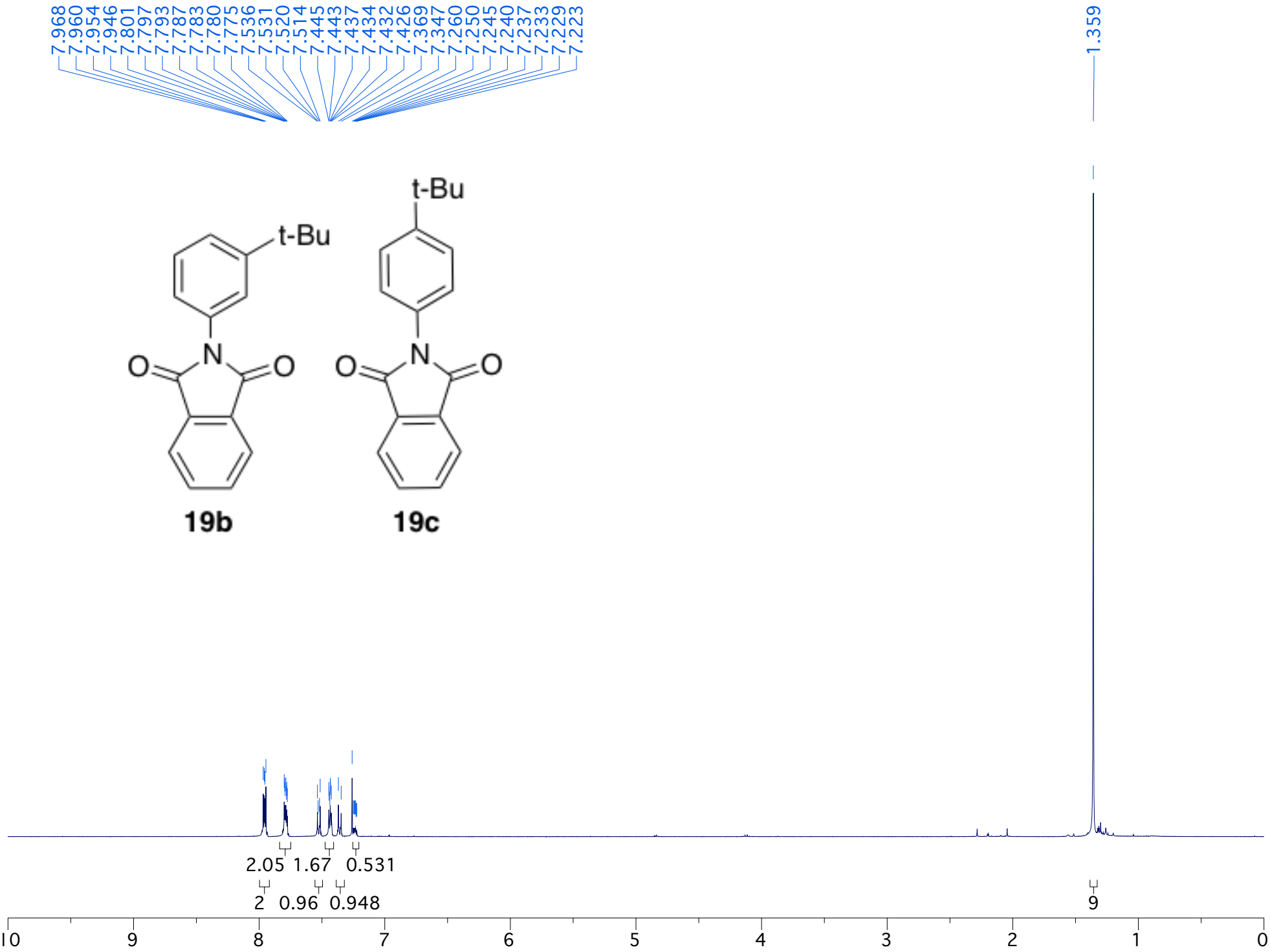
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7.229
7.223
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t-Bu
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O
O
19b
t-Bu
N
O
O
19c
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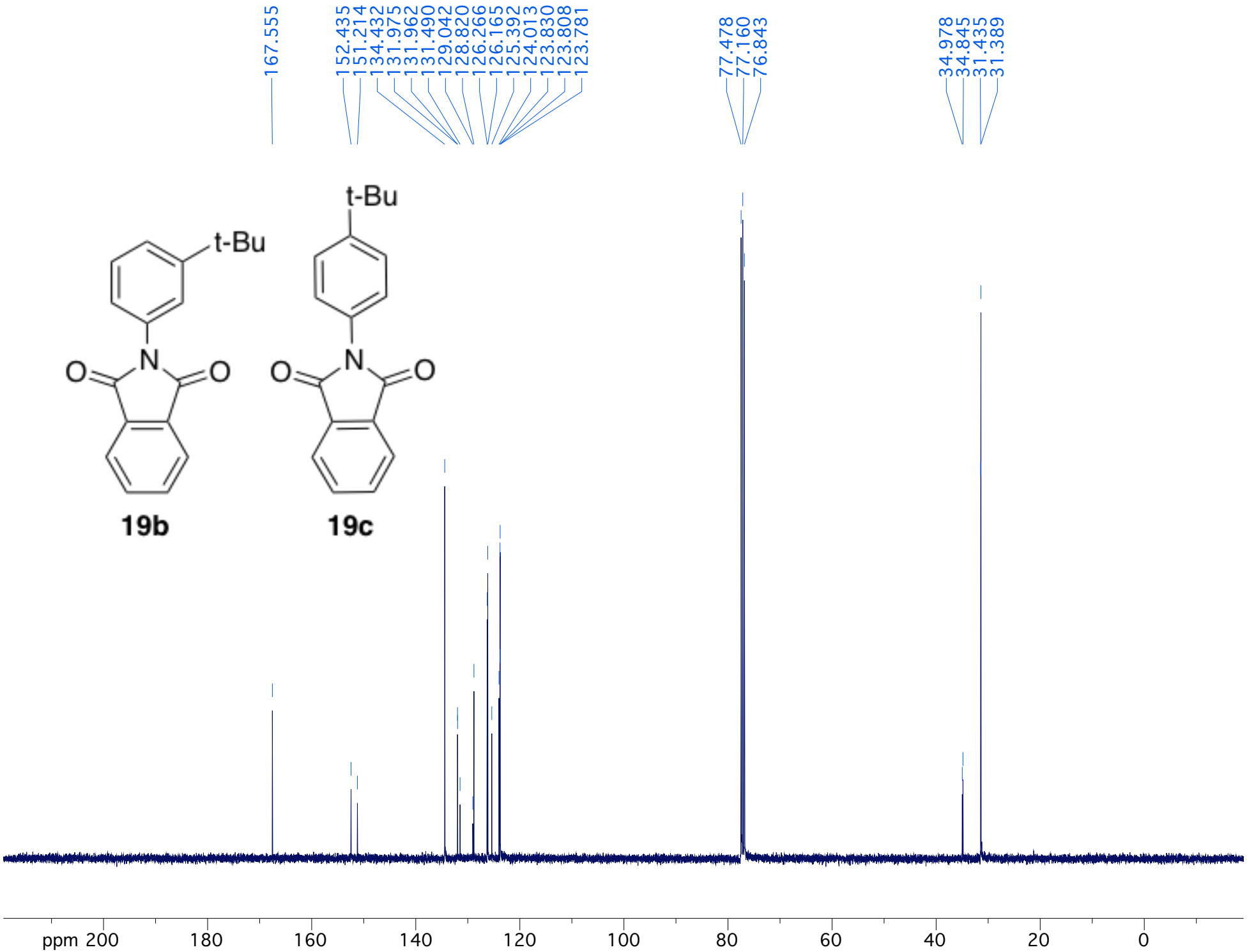
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123.781
77.478
77.160
76.843
34.978
34.845
31.435
31.389
t-Bu
N
O
O
19b
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O
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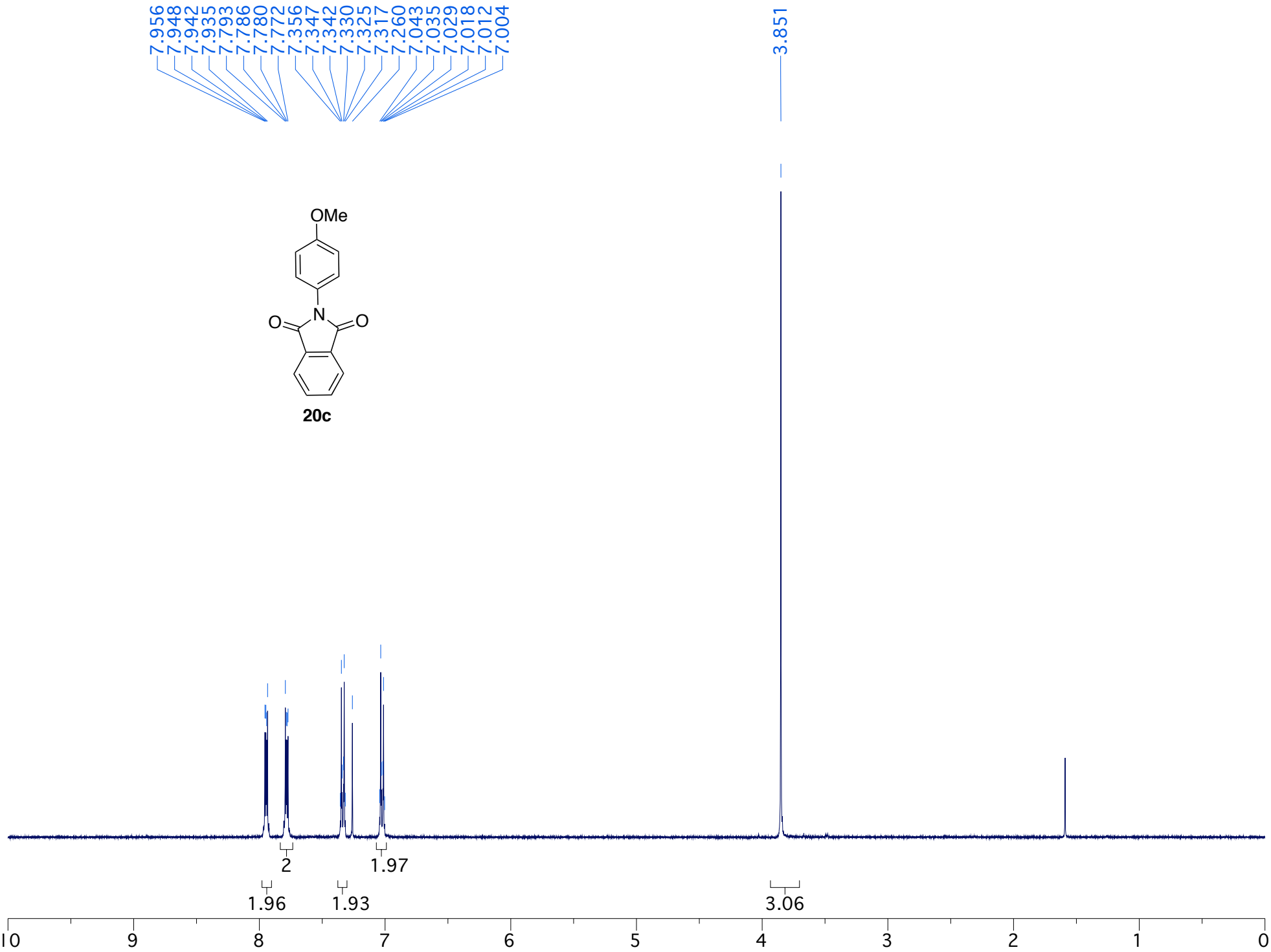
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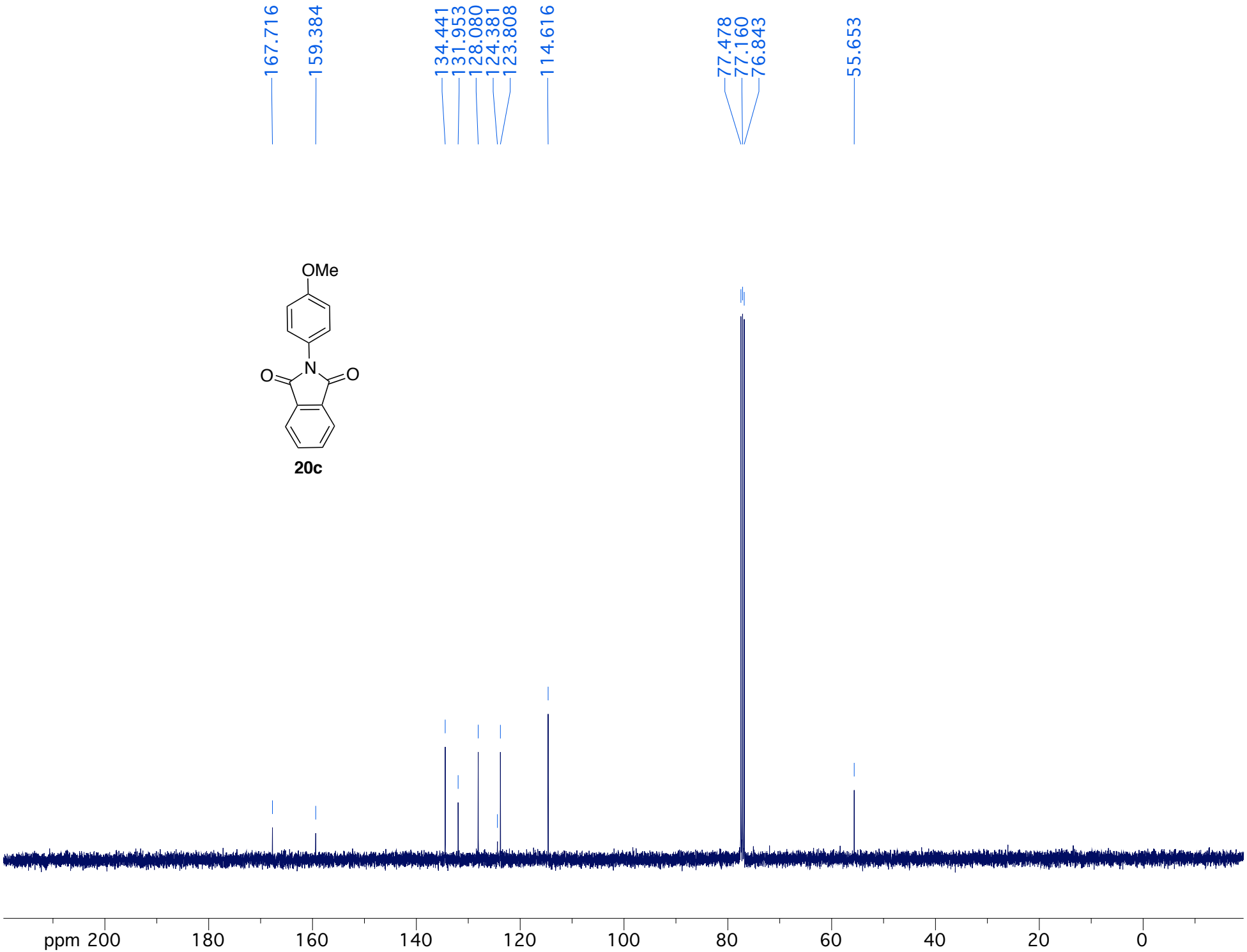
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77.160
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20c
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140
120
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80
60
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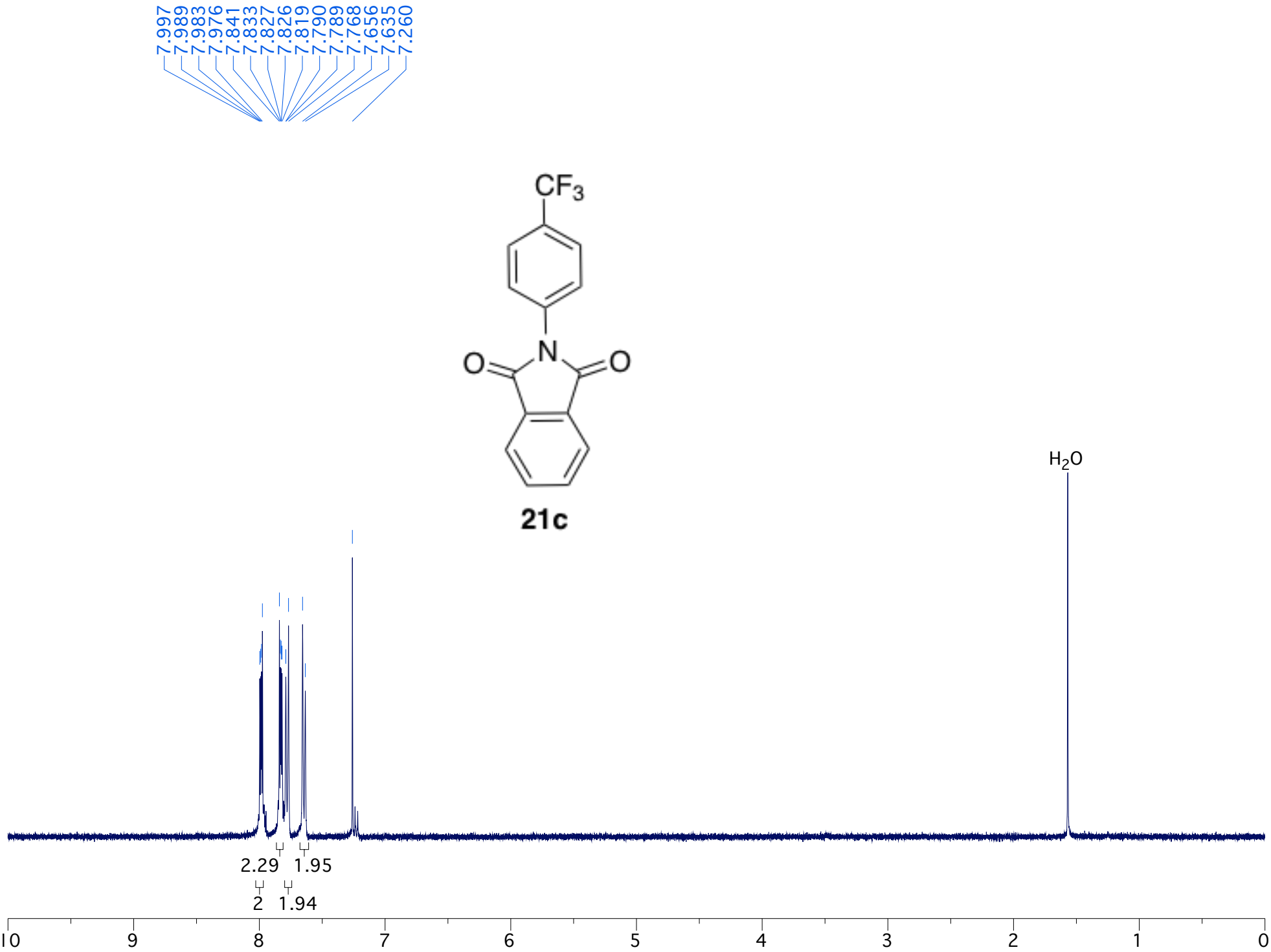
0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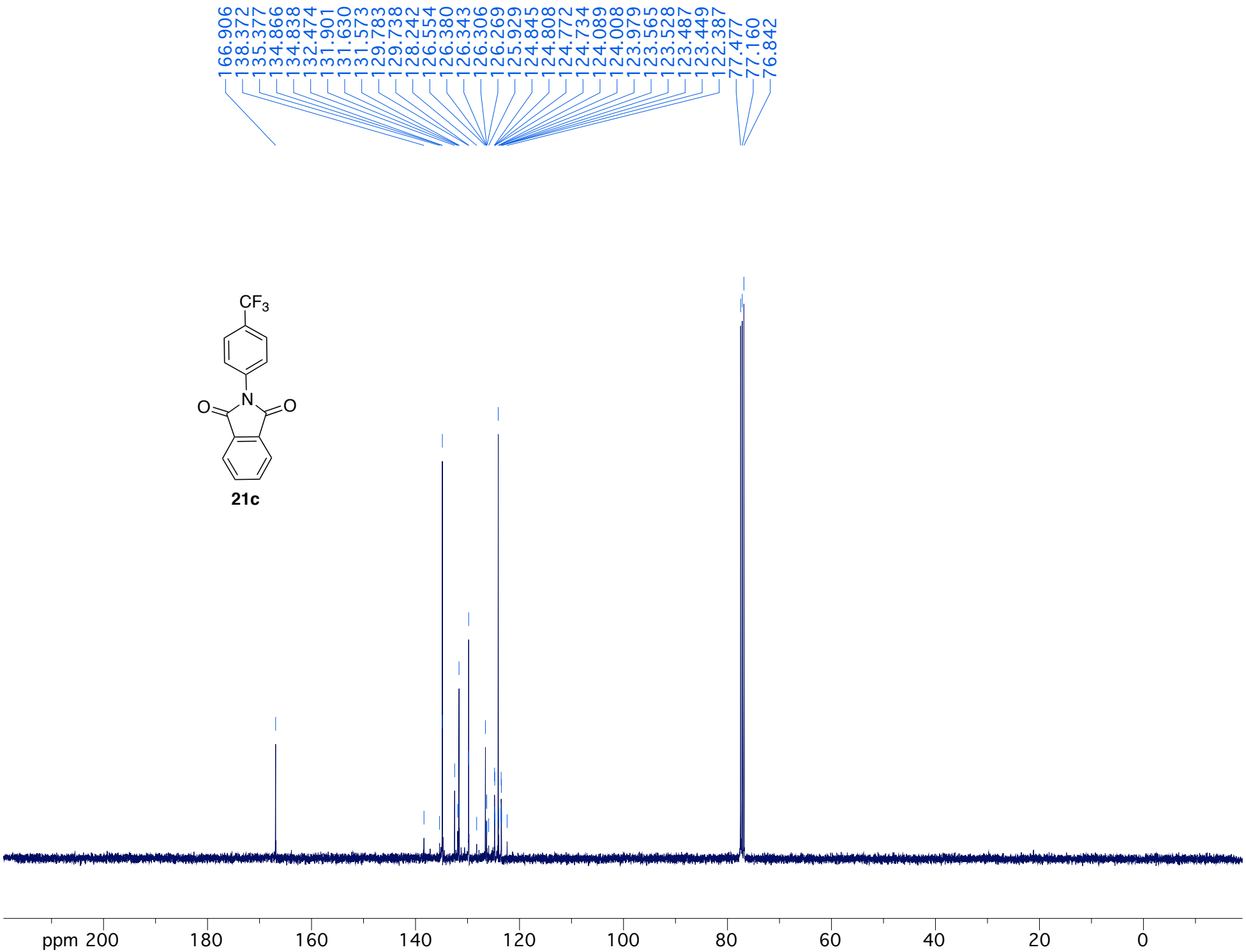
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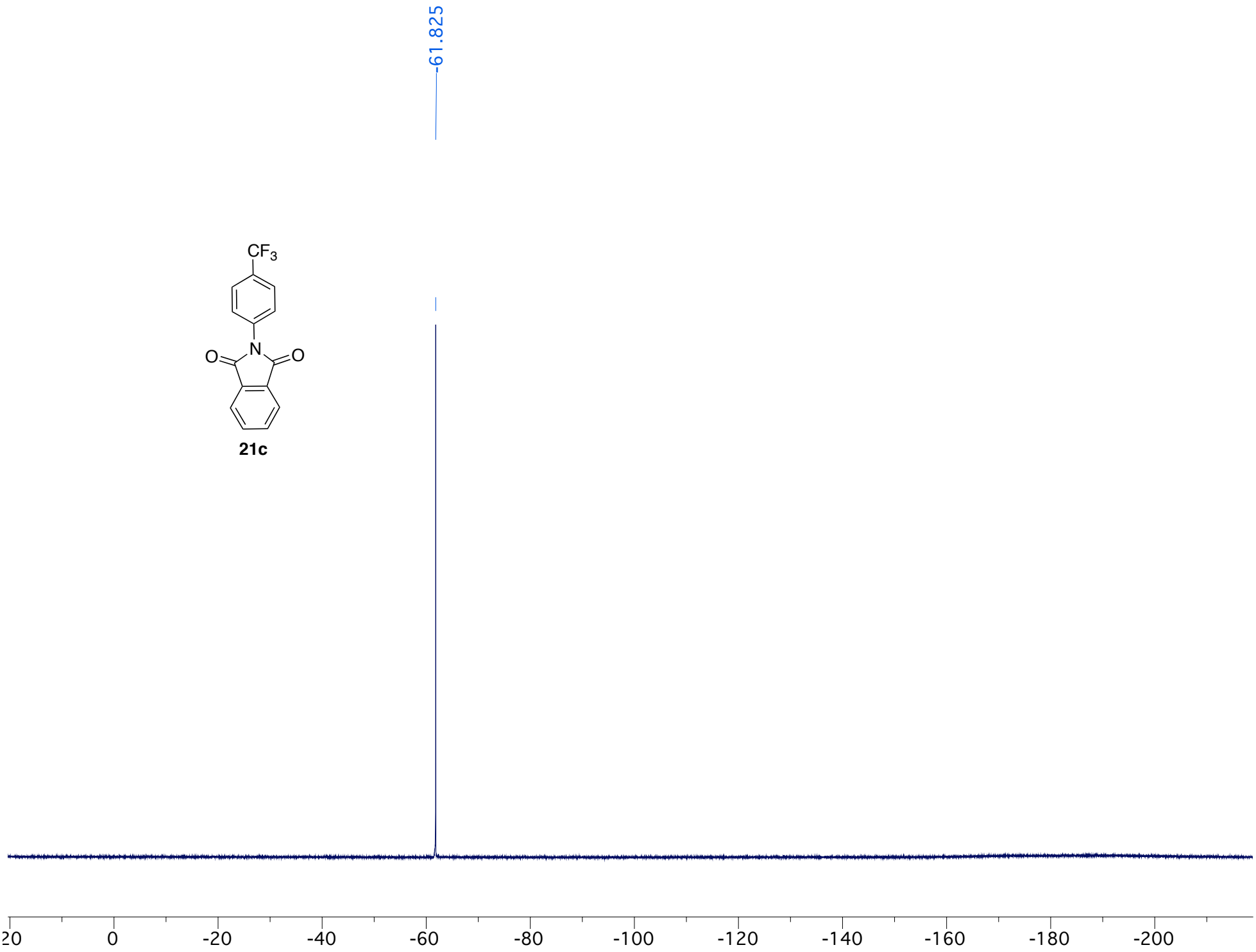
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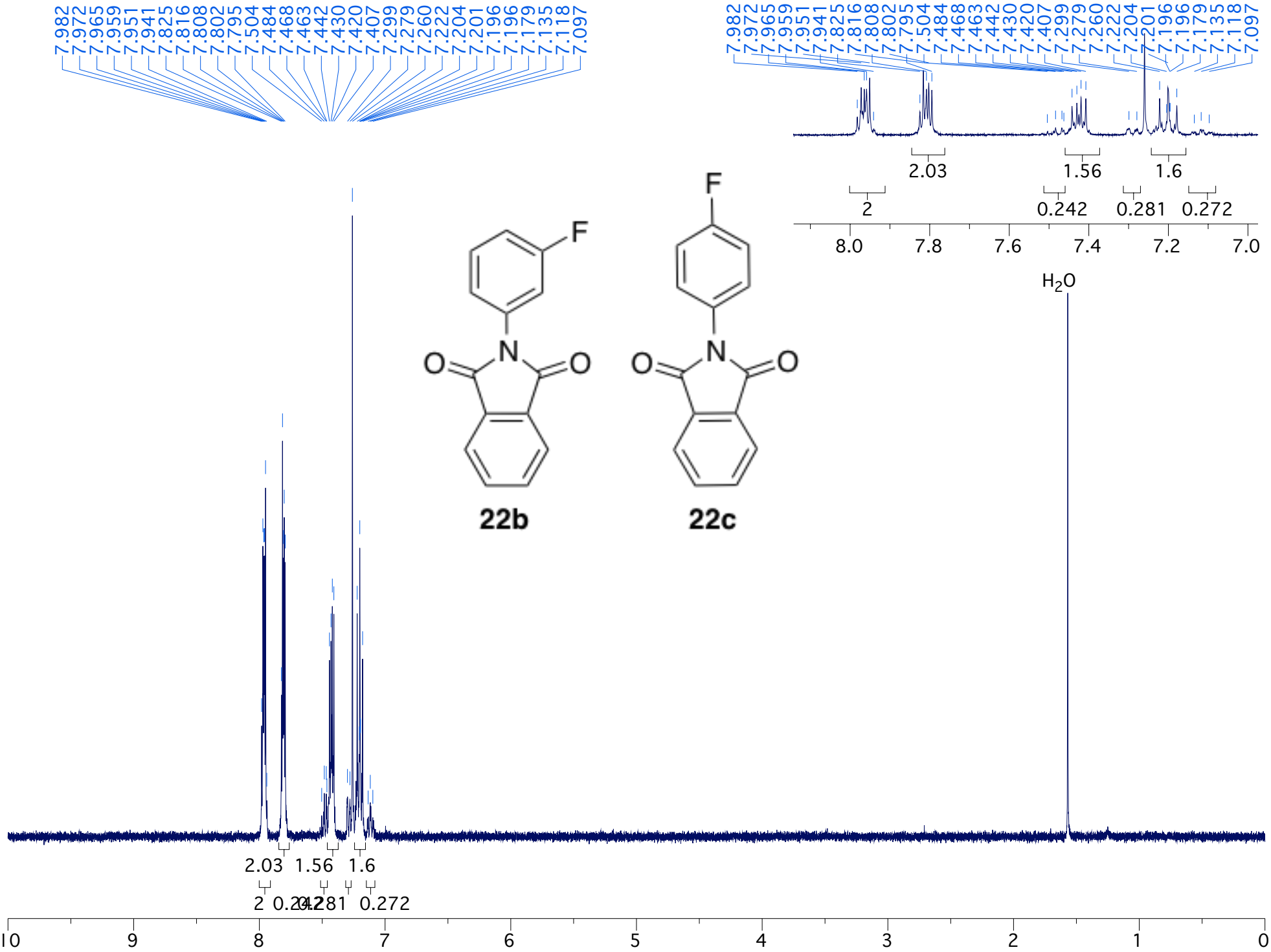
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7.4
7.2
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22c
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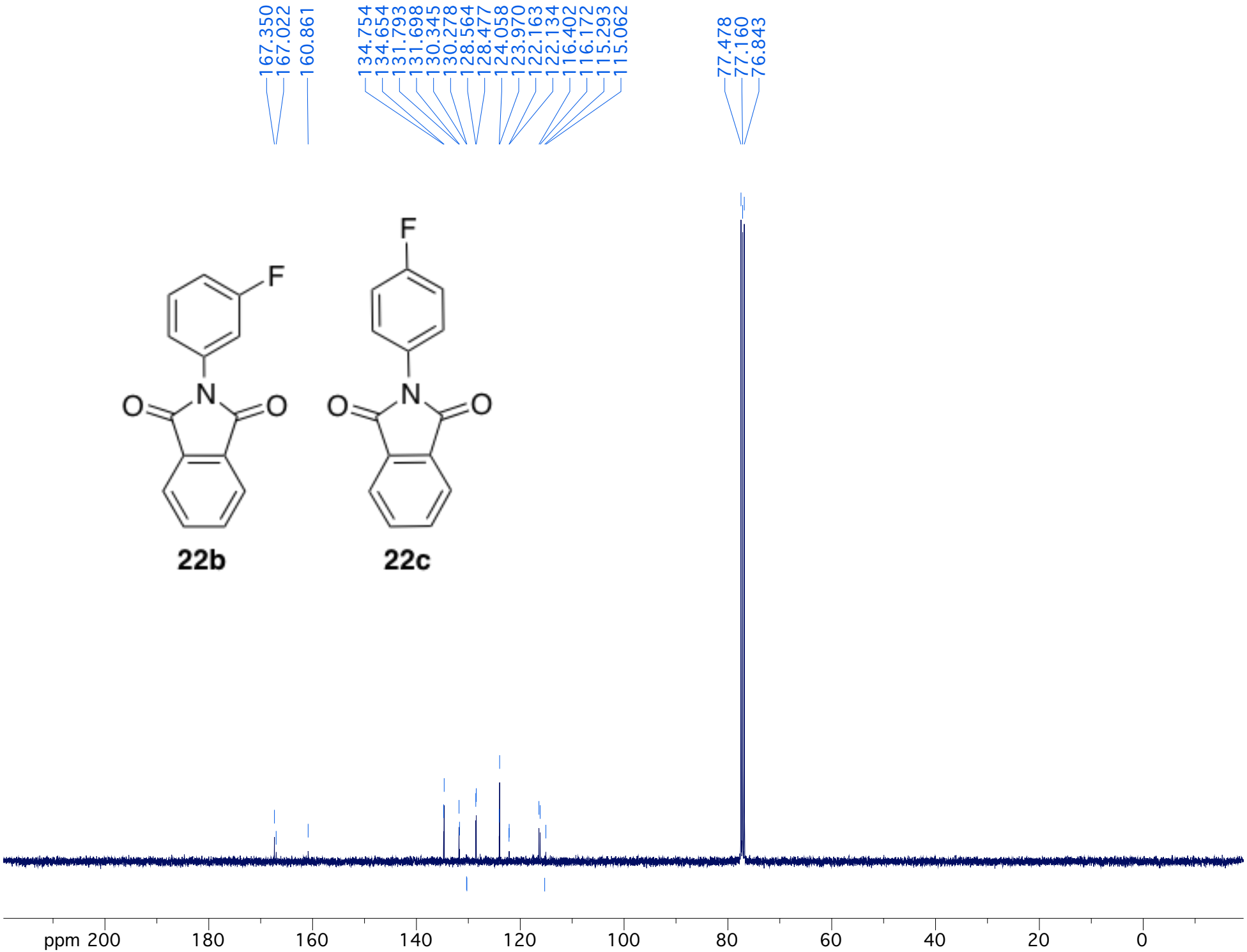
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122.134
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115.293
115.062
77.478
77.160
76.843
F
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O
22b
F
N
O
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22c
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140
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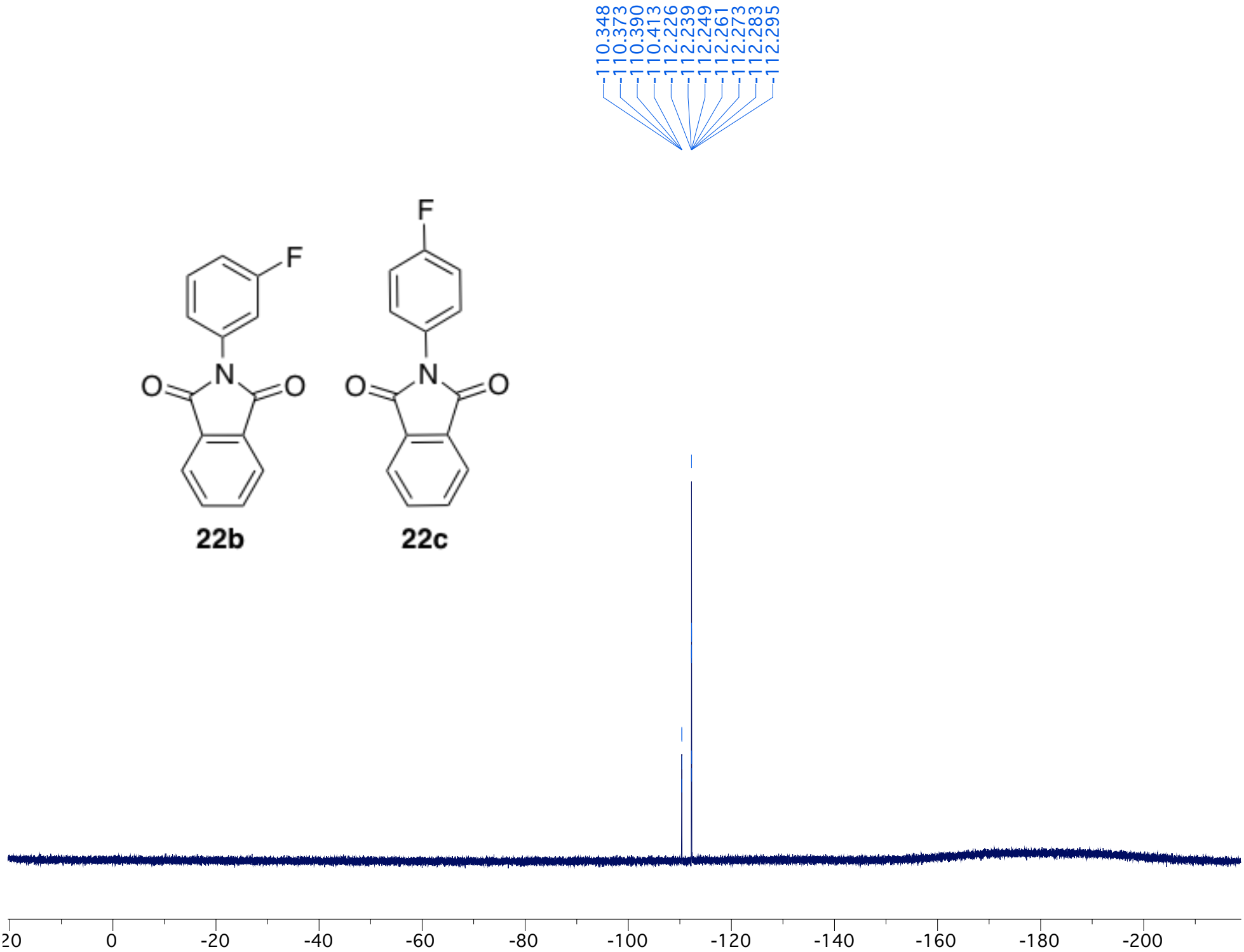
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O
O
22b
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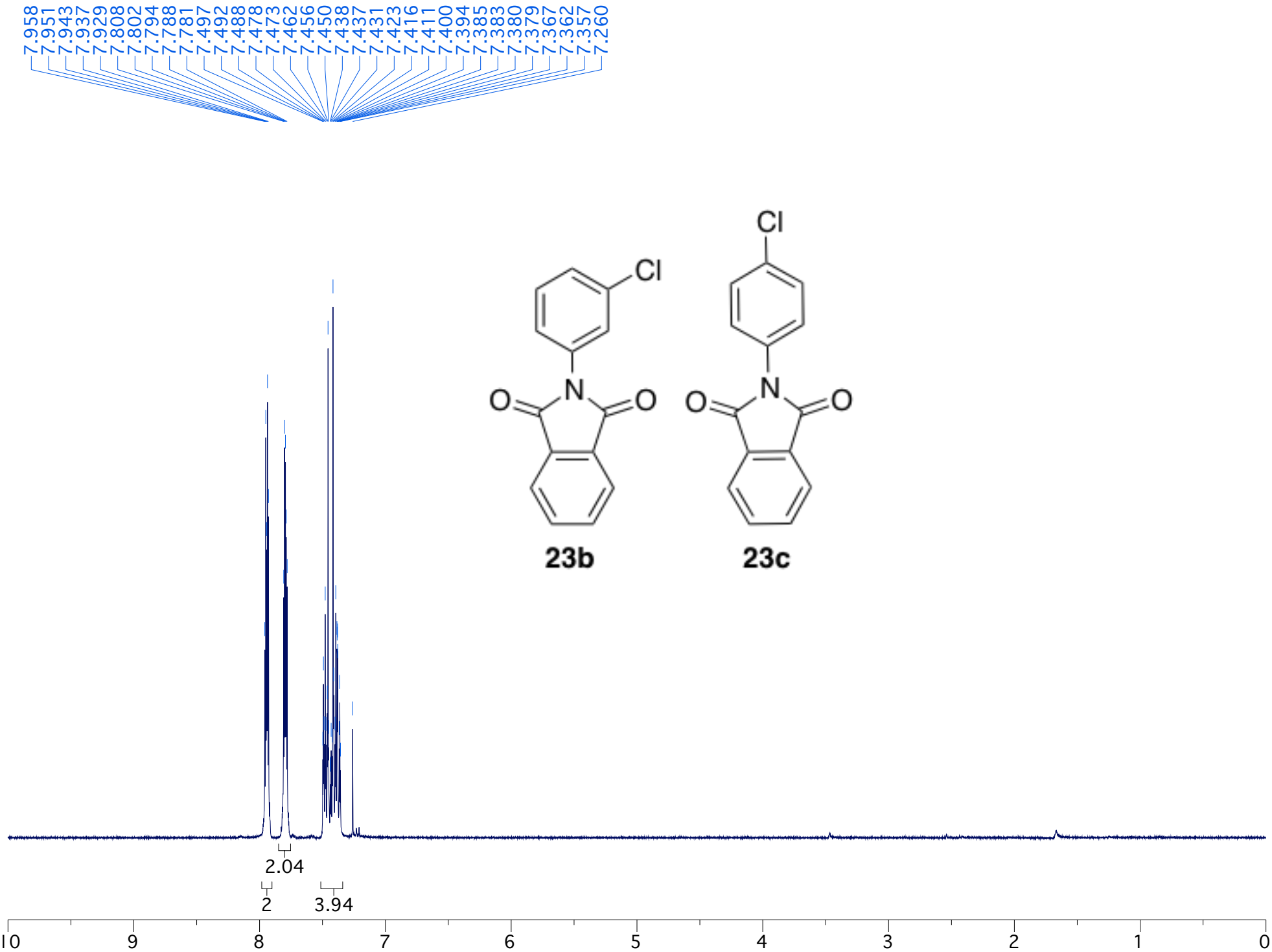
-200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Cl
N
O
O
23b
Cl
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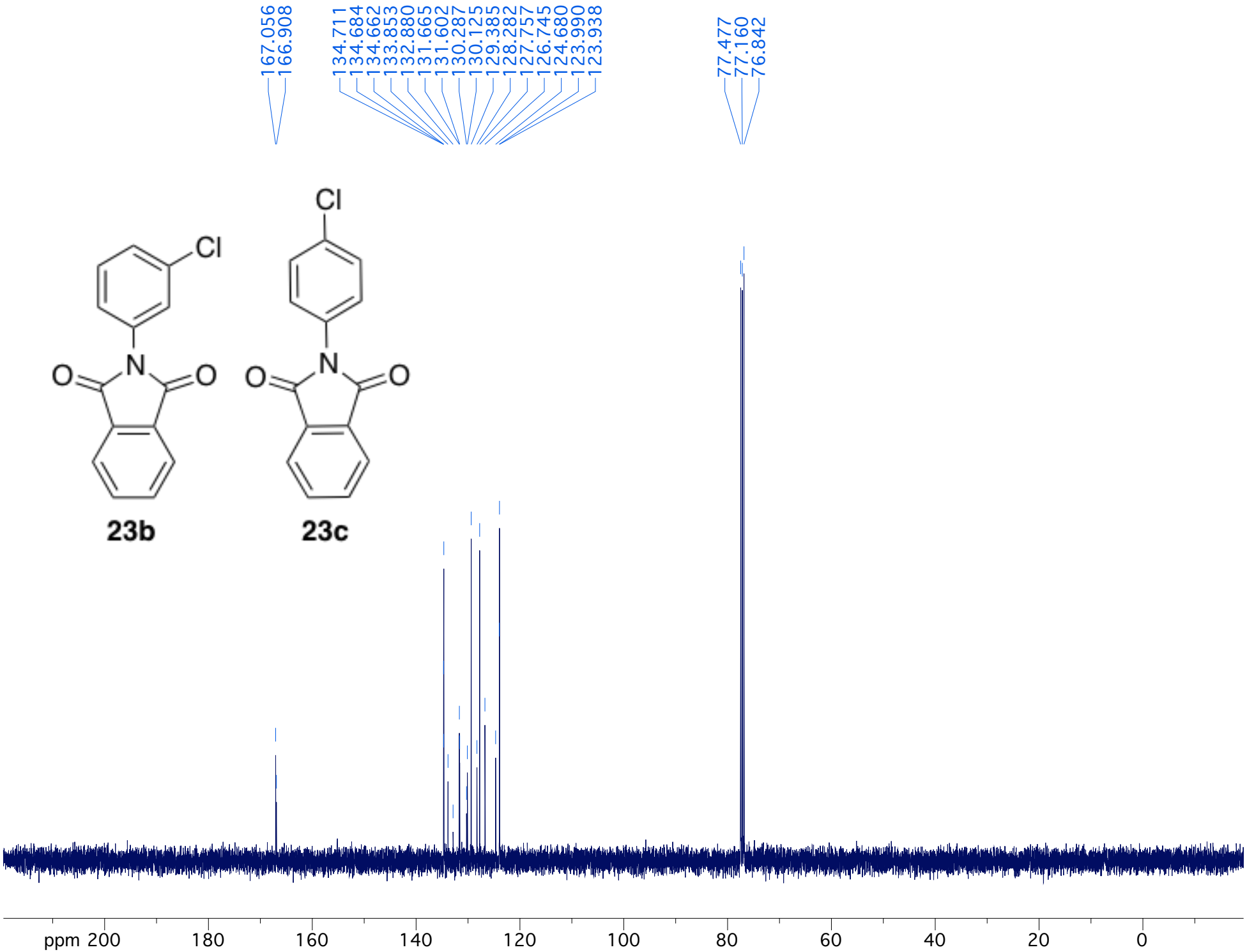
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123.938
77.477
77.160
76.842
Cl
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O
O
23b
Cl
N
O
O
23c
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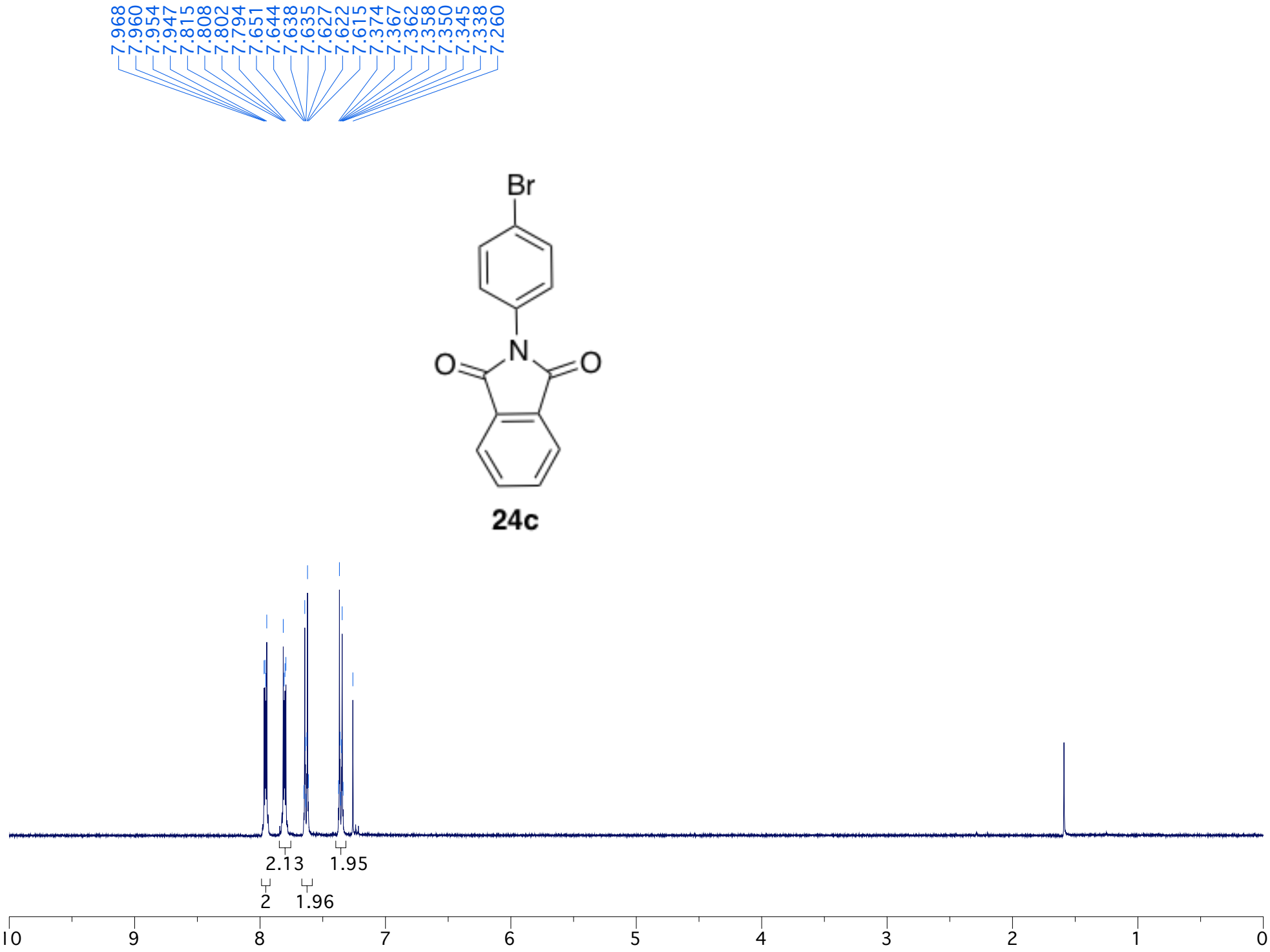
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7.815
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7.627
7.622
7.615
7.374
7.367
7.362
7.358
7.350
7.345
7.338
7.260
Br
N
O
O
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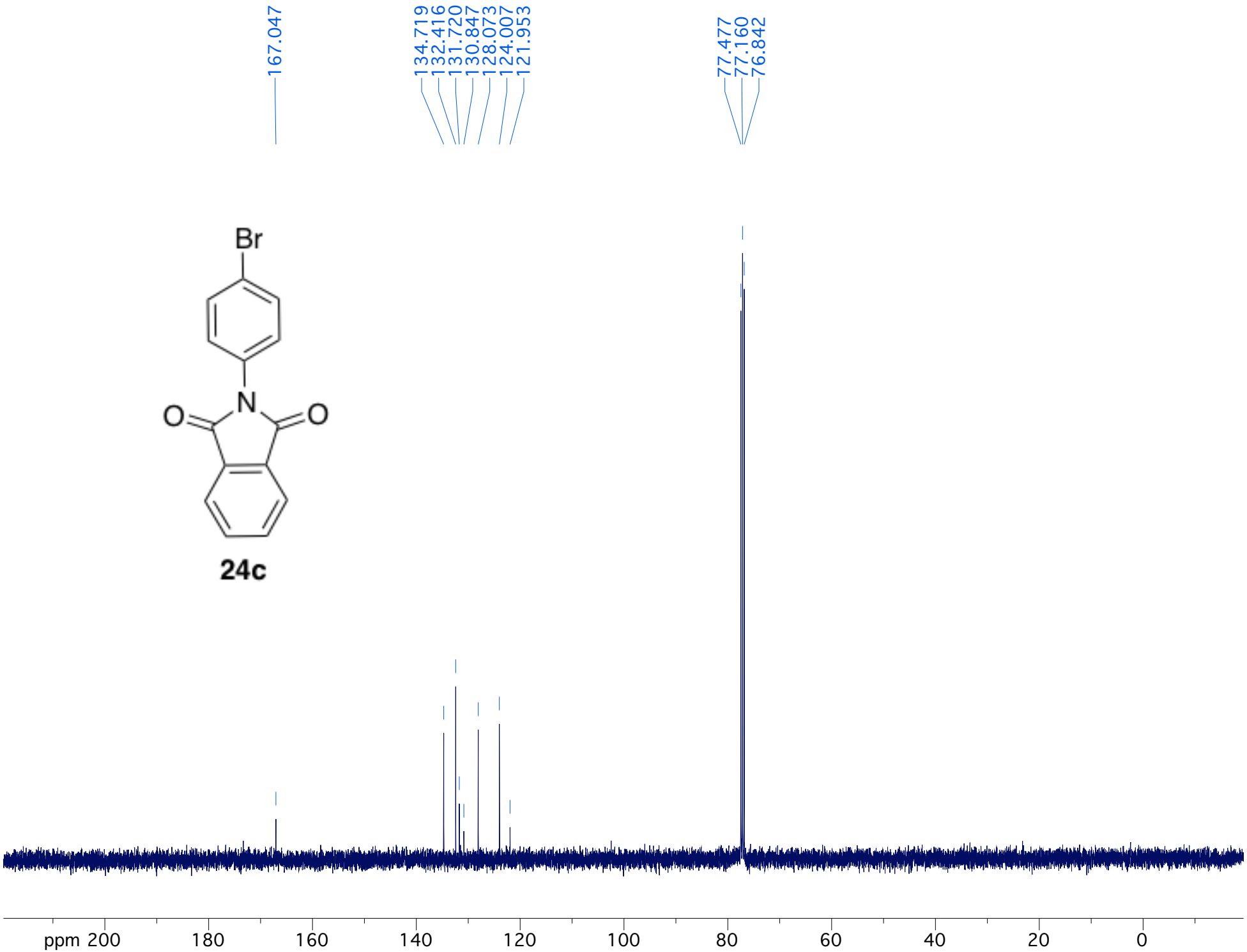
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132.416
131.720
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121.953
77.477
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Br
N
O
O
24c
ppm 200
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160
140
120
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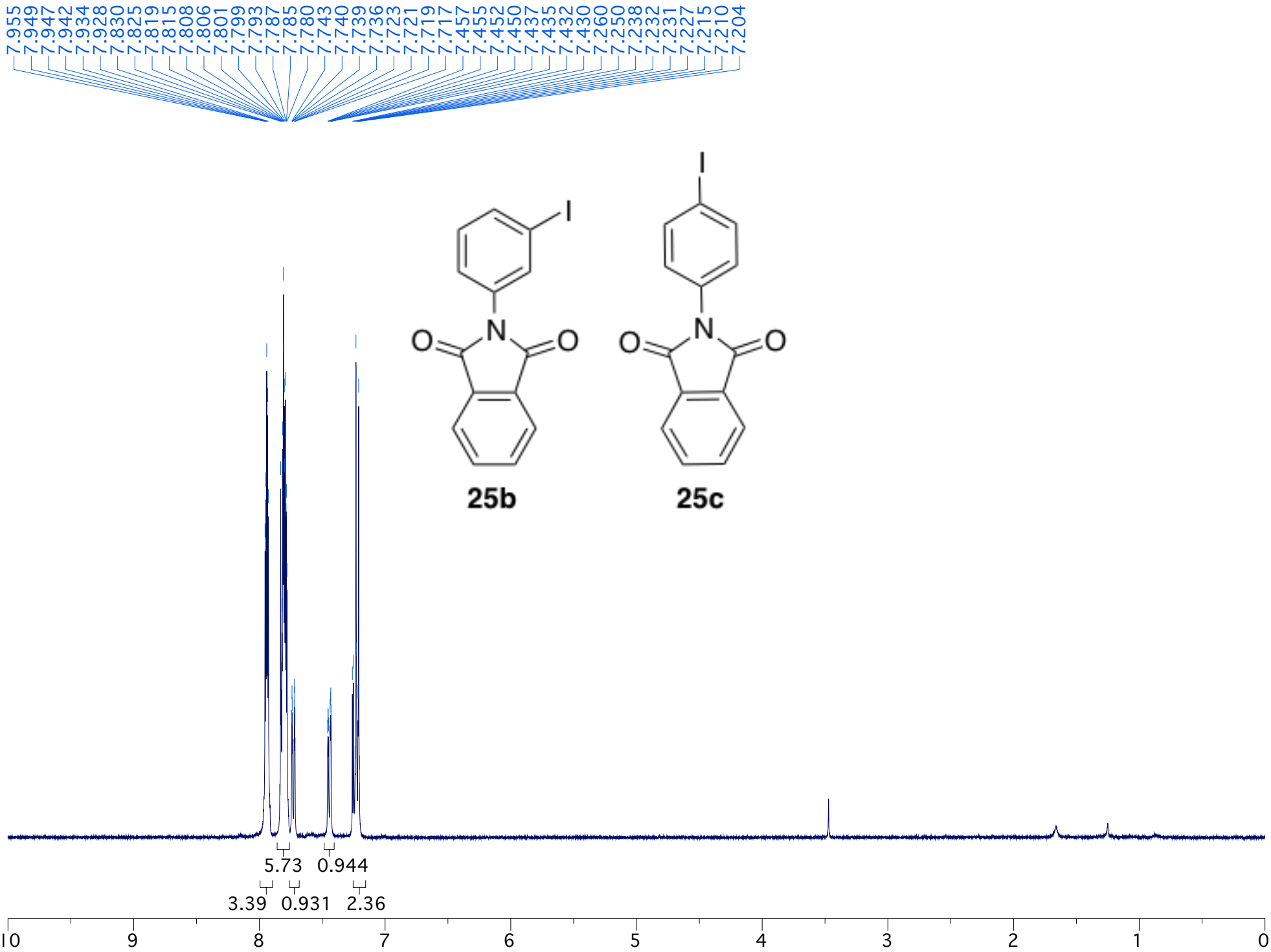
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7.825
7.819
7.815
7.808
7.806
7.801
7.799
7.793
7.787
7.785
7.780
7.743
7.740
7.739
7.736
7.723
7.721
7.719
7.717
7.457
7.455
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7.450
7.437
7.435
7.432
7.430
7.260
7.250
7.238
7.232
7.231
7.227
7.215
7.210
7.204
I
O
N
O
25b
I
O
N
O
25c
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0.931
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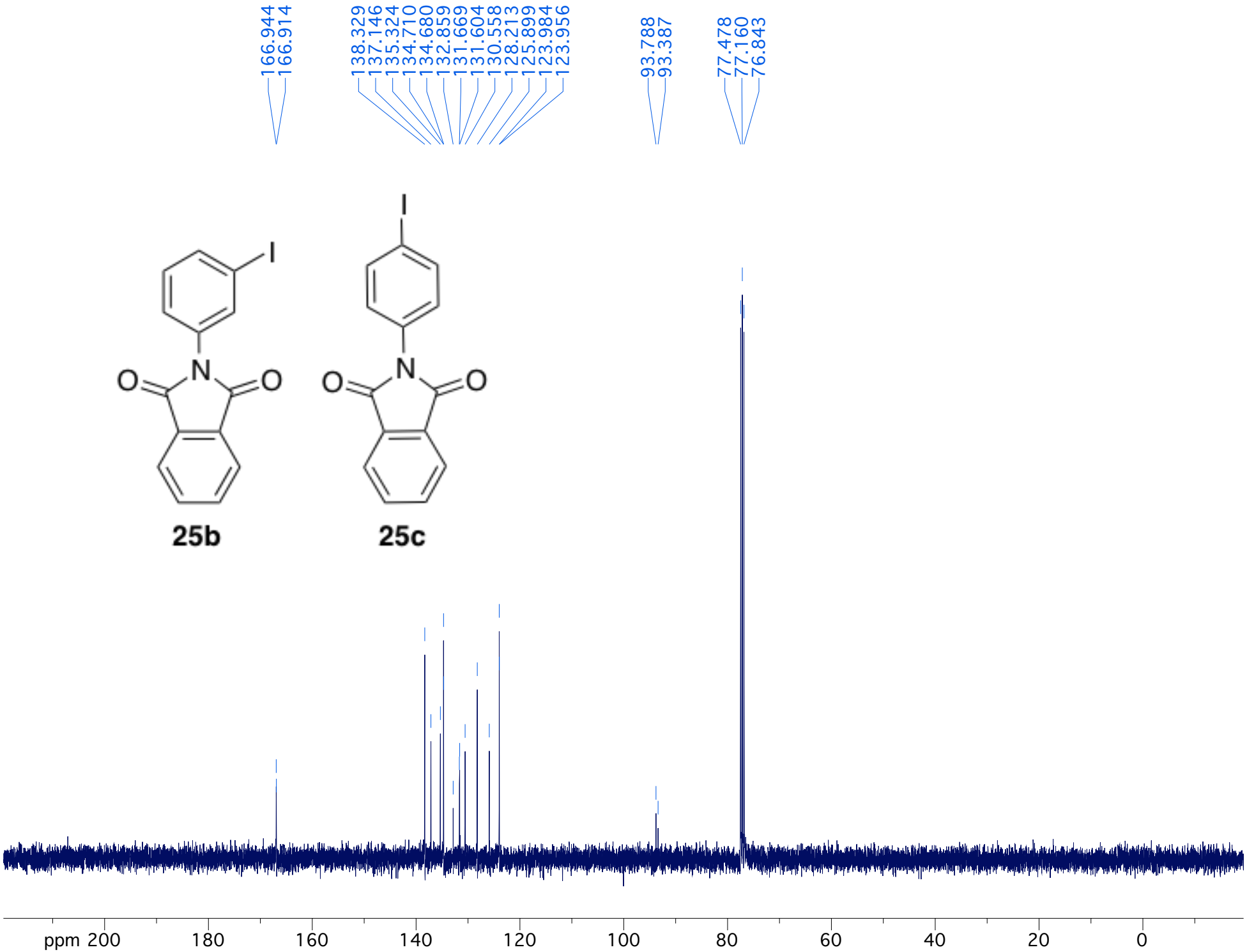
10
9
8
7
6
5
4
3
2
1
0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137.146
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128.213
125.899
123.984
123.956
93.788
93.387
77.478
77.160
76.843
I
N
O
O
25b
I
N
O
O
25c
ppm 200
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160
140
120
100
80
60
40
20
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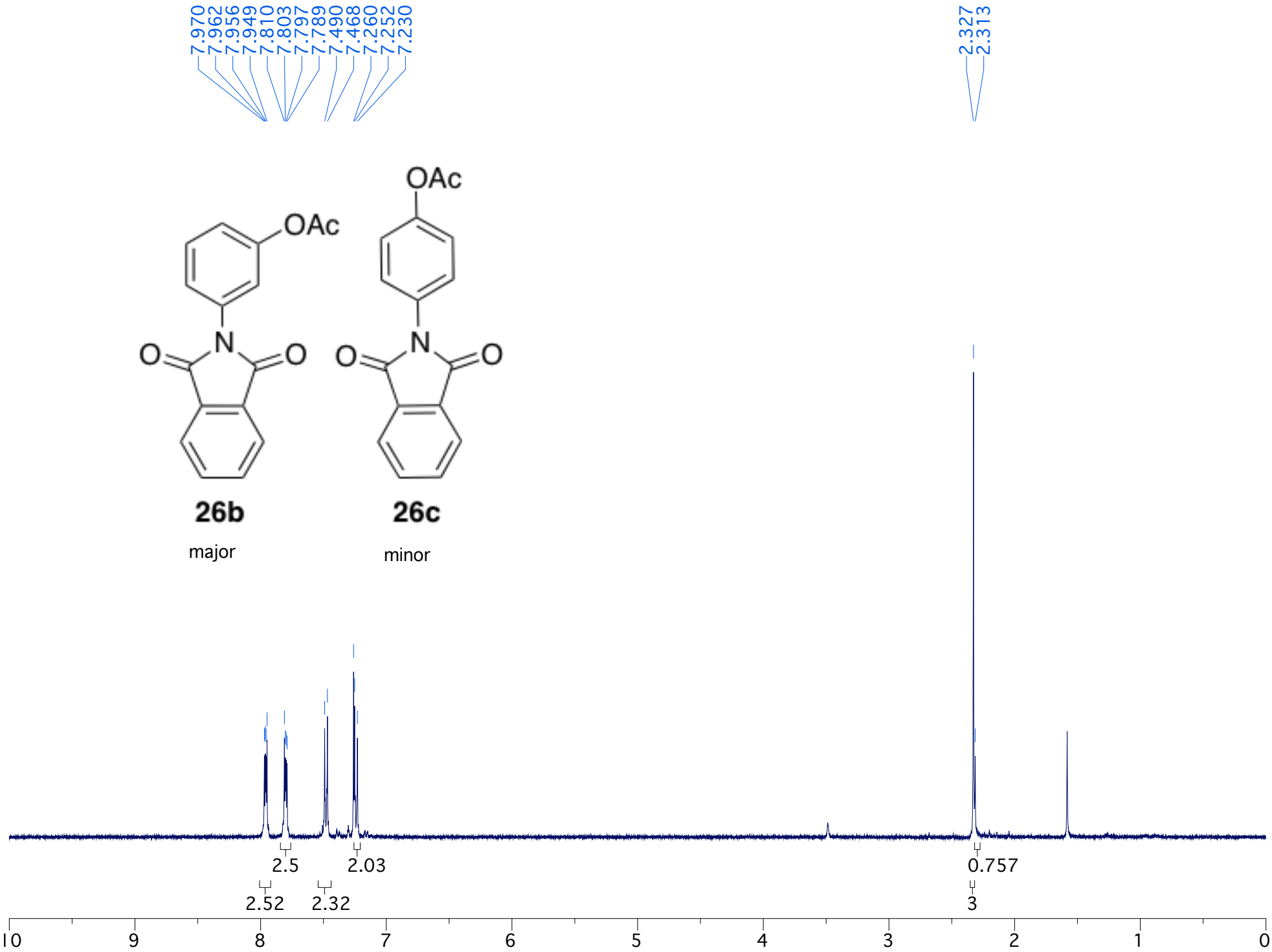
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7.468
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7.252
7.230
2.327
2.313
OAc
N
O
O
26b
major
OAc
N
O
O
26c
minor
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2.03
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2.32
3
10
9
8
7
6
5
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2
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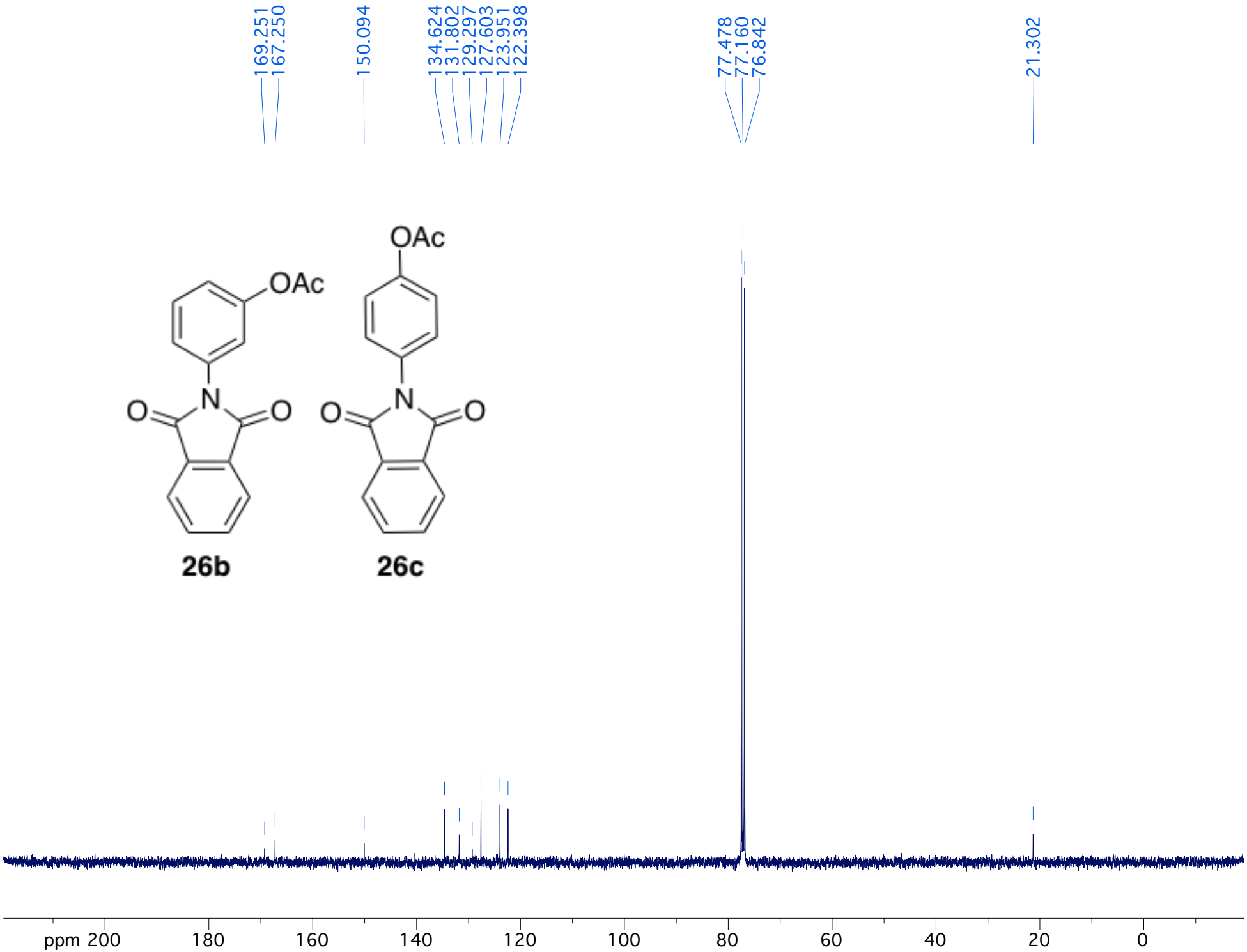
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127.603
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77.478
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76.842
21.302
OAc
N
O
O
26b
OAc
N
O
O
26c
ppm 200
180
160
140
120
100
80
60
40
20
0