

DATA-DRIVEN STRATEGIES FOR THE DEVELOPMENT OF
STEREOCONVERGENT NICKEL-CATALYZED CROSS-COUPPLINGS

Thesis by

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The logo for the California Institute of Technology (Caltech), featuring the word "Caltech" in a bold, orange, sans-serif font.

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To my family and friends, thank you for everything

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The opportunities and guidance that I have been afforded is what ultimately led me here to my time at Caltech. My growth as a scientist is (hopefully) documented within this thesis, but the life and world outside of the lab are truly what made the work possible. There are countless friends and family who have shaped these past five years, and I have certainly missed every individual that has contributed. Know that

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ABSTRACT

Stereoconvergent cross-coupling reactions have emerged in recent decades as powerful methods for the construction of carbon–carbon bonds. Nickel catalysis in particular has been particularly enabling for the formation of C(sp²)–C(sp³) bonds. Stereoconvergent reductive and redox-neutral Ni-catalyzed cross-coupling reactions has been useful for the synthesis of pharmaceutically-relevant stereodefined small molecules.

Herein we describe our recent efforts in the development of new nickel-catalyzed stereoconvergent cross-coupling reactions. First, the redox-neutral nickel/photoredox dual catalytic coupling of *N*-heterocyclic trifluoroborates and aryl bromides is described. In collaboration with researchers at Merck, the enantioselective synthesis of *N*-benzylic heterocycles provides rapid access to pharmaceutically relevant motifs. We next discuss the development of a diastereoselective reductive cross coupling of *meso*-1,3-cyclobutyl NHP esters with aryl iodides. When chiral bis(oxazoline) ligands are employed, this reaction biases the formation of the *cis* isomer, prompting the exploration of the scope of the transformation using data science tools. The desire to further increase the yield and diastereoselectivity of this transformation motivated the application of a Bayesian optimizer to efficiently explore the reaction condition space. This optimization campaign led to the identification of new reductive conditions. Finally, the asymmetric coupling of 2-piperidine NHP esters and aryl iodides is described.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following communications:

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E.P.C. conducted experiments and participated in preparation of the supporting data and writing of the manuscript.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
alk	alkyl
^t Am	<i>tert</i> -amyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere(s)
bathophen	bathophenanthroline
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol (“ <u>b</u> utylated <u>h</u> ydroxy <u>t</u> oluene”)
BiIM	bi(imidazoline)
BiOX	bi(oxazoline)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
BO	Bayesian optimziation
Boc	<i>tert</i> -butoxycarbonyl
BOX	bis(oxazoline)

bp	boiling point
br	broad
Bu	butyl
ⁱ Bu	<i>iso</i> -butyl
ⁿ Bu	butyl or <i>norm</i> -butyl
^s Bu	<i>sec</i> -butyl
^t Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	concentration of sample for measurement of optical rotation
¹³ C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAM	cerium ammonium molybdate
cat.	catalyst
Cbz	benzyloxycarbonyl
cf.	consult or compare to (Latin: <i>confer</i>)
<i>cis</i>	on the same side
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl

^c Pr	cyclopropyl
Cy	cyclohexyl
Δ	heat or difference
δ	chemical shift in ppm
d	doublet
<i>d</i>	deutero or dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DIBAL	diisobutylaluminum hydride
DFT	density functional theory
DKR	dynamic kinetic resolution
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMBA	2,6-dimethylbenzoic acid
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane

dppbz	1,2-bis(diphenylphosphino)benzene
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
dtbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
DYKAT	dynamic kinetic asymmetric transformation
E	methyl carboxylate (CO ₂ CH ₃)
E ⁺	electrophile
<i>E</i>	trans (entgegen) olefin geometry
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
ee	enantiomeric excess
e.g.	for example (Latin: <i>exempli gratia</i>)
EI	electron impact
<i>epi</i>	epimeric
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	and others (Latin: <i>et alii</i>)
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
¹ H	proton

[H]	reduction
HC	homocoupling
hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC ₅₀	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: <i>id est</i>)
<i>in situ</i>	in the reaction mixture
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LC/MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide

LED	light-emitting diode
m	multiplet or meter(s)
M	molar or molecular ion
<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
ML	machine learning
MLR	multivariate linear regression
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves or mass spectrometry
<i>m/z</i>	mass-to-charge ratio
naph	naphthyl
nbd	norbornadiene
NBS	<i>N</i> -bromosuccinimide

n.d.	not determined
NHC	<i>N</i> -heterocyclic carbene
NHP	<i>N</i> -hydroxyphthalimide
nm	nanometer(s)
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
<i>o</i>	ortho
[O]	oxidation
<i>p</i>	para
Pc	phthalocyanine
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
phen	1,10-phenanthroline
PHOX	phosphinooxazoline
pin	pinacol
Piv	pivaloyl
pK_a	acid dissociation constant
Pr	propyl
^{<i>i</i>} Pr	isopropyl
^{<i>n</i>} Pr	propyl or <i>norm</i> -propyl
py	pyridine
PyBOX	pyridine-bis(oxazoline)
PyOx	pyridine-oxazoline

pyphos	(2-diphenylphosphino)ethylpyridine
q	quartet
quant.	quantitative
QuinOx	quinoline-oxazoline
R	alkyl group
R _L	large group
<i>R</i>	rectus
RCM	ring-closing metathesis
recry.	recrystallization
ref	reference
<i>R_f</i>	retention factor
rt	room temperature
s	singlet or seconds
<i>S</i>	sinister
sat.	saturated
SET	single-electron transfer
SFC	supercritical fluid chromatography
SM	starting material
t	triplet
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate

TBS	<i>tert</i> -butyldimethylsilyl
TDAE	tetrakis(dimethylamino)ethylene
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
temp	temperature
terpy	2,2':6',2''-terpyridine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	toluene
<i>trans</i>	on the opposite side
Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
<i>vide infra</i>	see below
v/v	volume per volume
w/v	weight per volume
X	anionic ligand or halide
xs	excess
Y	anionic ligand or halide
Z	cis (zusammen) olefin geometry

Chapter 1

Enantioselective Synthesis of N-Benzylic Heterocycles using Ni/Photoredox

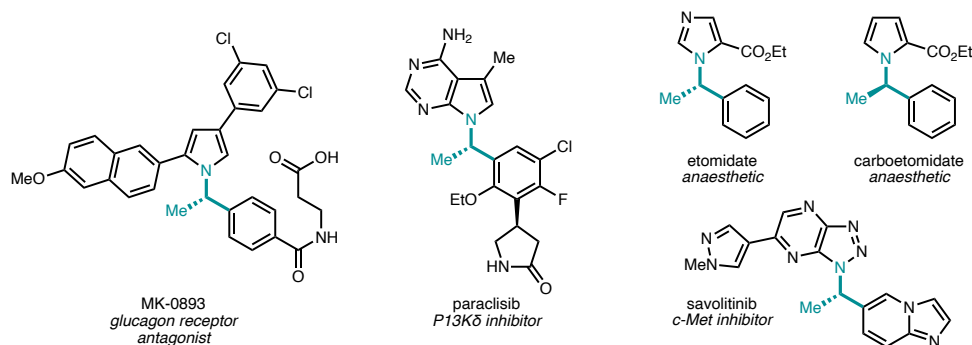
*Dual Catalysis*¹

1.1 INTRODUCTION

1.1.1 Chiral *N*-benzylic heterocycles

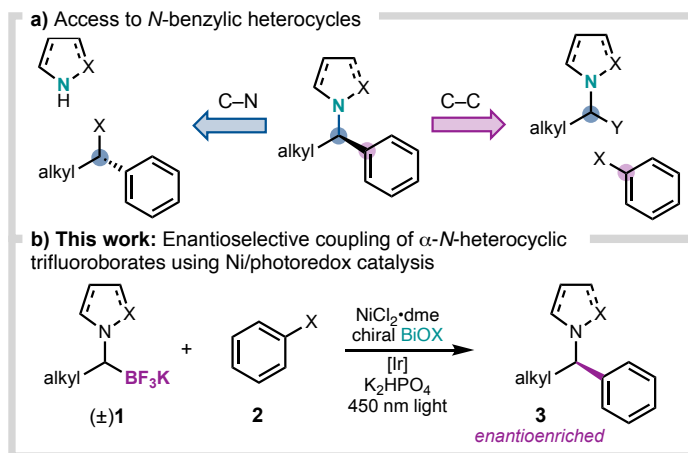
Chiral nitrogen heterocycles are among the most common structural elements in small-molecule pharmaceutical targets.¹ While such compounds can be synthesized as racemates and separated by chiral chromatography or resolution strategies, the development of asymmetric methods to directly access one stereoisomer is desirable.² Chiral α,α -disubstituted *N*-benzylic heterocycles are common substructures in bioactive compounds, and a number of marketed drugs and clinical candidates possess this conserved structural motif (Figure 1.1).^{3–7}

¹ Portions of this chapter have been reproduced from a published manuscript.¹ This research was conducted in collaboration with 1) Drs. Caitlin R Lacker and Travis J. Delano, graduate students in the Reisman group, and 2) Drs. Kevin Belyk, Jongrock Kong, and Tiffany Piou, researchers employed by Merck & Co., Inc. Fellowship support was provided by the NSF (T.J.D, C.R.L. DGE-1144469). Financial support was provided by the NIH (S.E.R. R35GM118191) and in kind support from Merck Sharp and Dohme, a subsidiary of Merck & Co., Inc.

Figure 1.1 Bioactive chiral *N*-benzylic heterocycles

Common disconnections to access enantioenriched *N*-benzylic heterocycles can be categorized by 1) C–N bond formation or 2) C–C cross-coupling methodologies (Figure 1.2).^{8–16} C–N bond formation by S_N2 displacement is well-precedented but requires the synthesis of enantioenriched electrophiles, is sensitive to the nucleophilicity of the heterocycle, and can suffer from erosion of enantiopurity depending on the identity of the coupling partners. Alkene hydrofunctionalization reactions are a promising alternative to S_N2 reactions; however, the scope of enantioselective reactions to access *N*-benzylic heterocycles is extremely limited.¹⁷ In addition, regioselectivity issues arise for heterocycles with multiple nitrogen atoms for azoles bearing multiple nitrogen atoms (e.g., pyrazoles, imidazoles, and triazoles). As an alternate approach, *N*-benzylic heterocycles can be constructed through C(sp²)–C(sp³) cross-coupling methodologies utilizing readily available aryl halides or pseudohalides.^{18–21} In drug discovery, this approach can enable systematic structure–activity relationship studies by permutation of the aryl halide coupling partners.²²

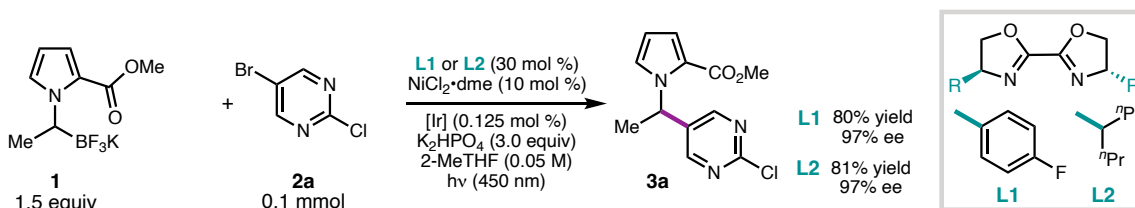
In this context, cross-coupling reactions using Ni/photoredox dual catalysis have gained considerable traction in medicinal chemistry due to their ability to form challenging C(sp²)–C(sp³) linkages.²³ Despite the versatility of this mode of catalysis, most reactions developed to date employ achiral ligands and give racemic or achiral products.^{1,2} This can pose a challenge, as lead

Figure 1.2 Strategies to access *N*-benzylic heterocycles

compounds prepared using these methods progress through development and require enantioselective synthesis. Notable examples of asymmetric reactions involving Ni/photoredox dual catalysis include the direct α -arylation of benzamide-protected saturated amines by Huo,²⁴ arylation of *N*-Boc-protected amino acids developed by Fu and MacMillan,²⁵ and the arylation of α -*N*-heterocyclic carboxylic acids reported by Pezzetta, Bonifazi, and Davidson.²⁶ The Bonifazi/Davidson method provides access to *N*-benzylic heterocycles; however, the products were typically formed in 40–80% ee, with the most selective reactions proceeding with yields under 50%.

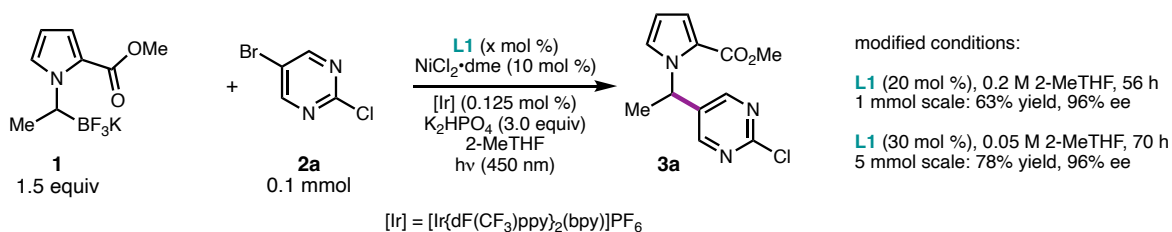
1.1.2 Motivation

In collaboration with Merck, enantioselective arylation of *N*-heteroaryl trifluoroborate salts **1** via Ni/photoredox dual catalysis was developed (Scheme 1.1). Reaction development and extensive optimization can be found in great detail in the theses of Drs. Caitlin Lackner and Travis DeLano and a published manuscript.^{27–29} The use of high-throughput experimentation and traditional screening methods rapidly enabled the exploration of different ligands, bases, and solvents.

Scheme 1.1 Optimal conditions

Ultimately, optimal reaction conditions for efficient cross-coupling between aryl bromides and alkyl BF_3K salts were identified: $\text{NiCl}_2 \cdot \text{dme}$ as the nickel source, $\text{Ir}[\text{df}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ as the photocatalyst, K_2HPO_4 as the base, and 2-MeTHF as the solvent. Chiral bioxazoline (BiOX) ligands 4-heptyl-BiOX (**L1**) and 4-fluoro-phenyl (4-F-PhBiOX, **L2**) groups exhibited promising reactivity and selectivity (Scheme 1.1). Both ligands were used in subsequent studies.

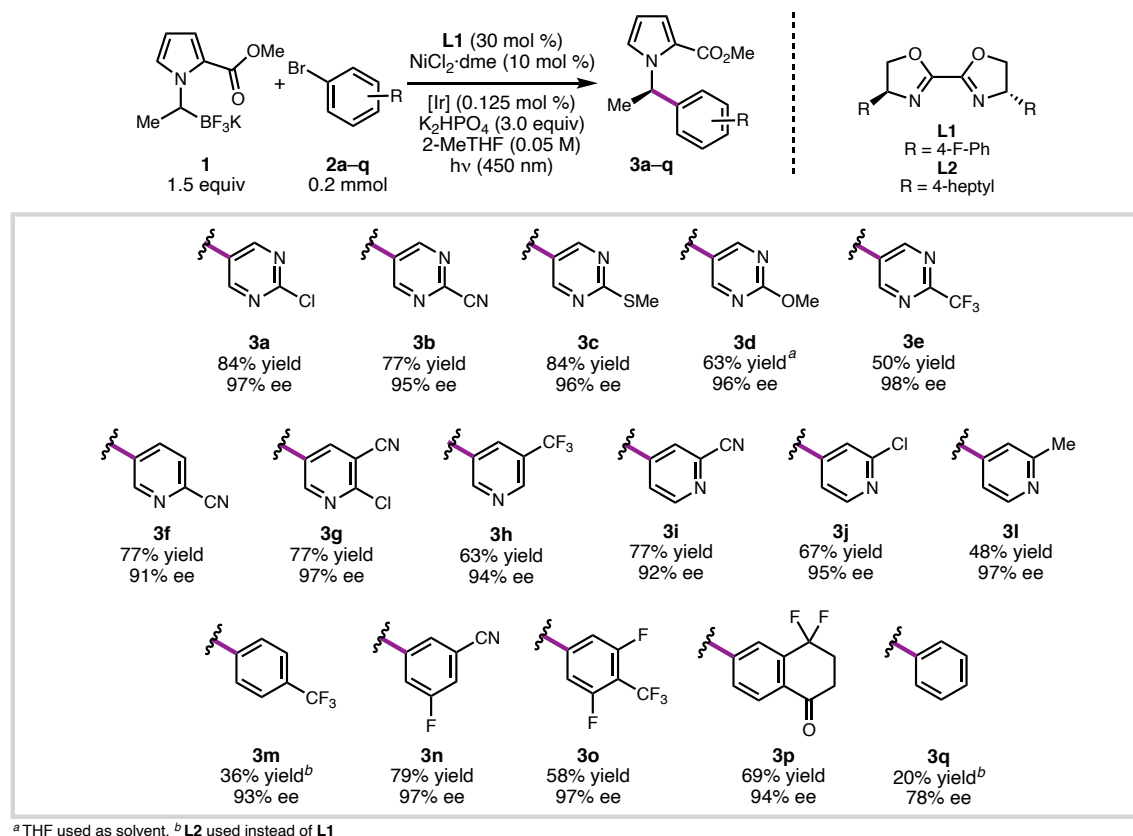
Notably, the reaction could be scaled in batch from 0.1 mmol to larger scales (e.g., 1 and 5 mmol scale) using 440 nm Kessil lamps, modified procedures, and longer reaction times to afford product in good yields and high enantioselectivities (Scheme 1.2). The reaction works at 1 mmol scale in higher concentration (0.2 M) and with 2:1 ligand/Ni ratios without loss of enantioselectivity. At 5 mmol scale without changes to the reaction conditions (with the exception of reaction time), the yield and enantioselectivity were comparable to that of the reaction at 0.1 mmol scale.

Scheme 1.2 Optimal conditions

1.2 REACTION SCOPE

A variety of aryl coupling partners were explored in this transformation with a particular emphasis on heteroaromatic bromides (Scheme 1.3). Electron-deficient aryl bromides performed well with good yields and excellent enantioselectivities. Pyrimidinyl bromides with both electron-withdrawing and -donating substitution at the 2-position were tolerated, affording products **3a–3e** with uniformly high enantioselectivities. In addition, 3-pyridyl bromides (**2f–2h**) and 4-pyridyl bromides (**2i–2l**) coupled efficiently. Notably, pyridyl bromide **2h** coupled even without an electron-deficient functional group *ortho* to the Lewis-basic pyridine nitrogen.

While the reaction conditions were optimized for heteroaryl bromides, several electron-deficient benzene derivatives afforded coupled products (**3m–3p**) with comparable enantioselectivities, albeit in decreased yields in some cases. In particular, simple arenes such as bromobenzene coupled in considerably lower yield and ee (**3q**, 20% yield and 78% ee). Use of **L2** was found to give higher yields when coupling some less electron-deficient aryl bromides (e.g., to form **3l** and **3p**).

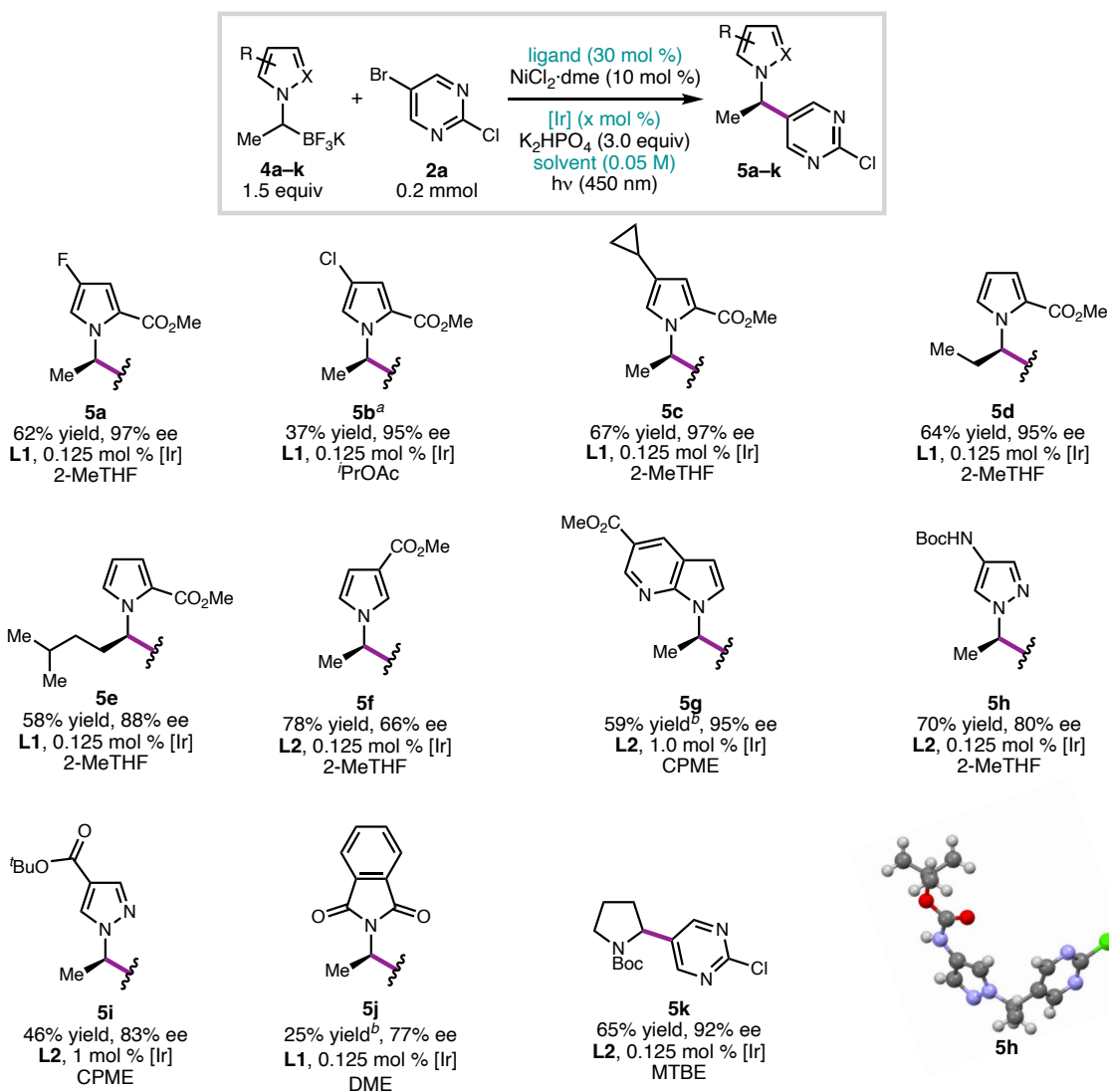
Scheme 1.3 Scope of aryl bromides

While the conditions in Scheme 1.3 were suitable for the coupling of pyrrole-2-carboxylate **1a**, and 2-MeTHF was the most general solvent across a range of alkyl BF_3K salts, further optimization of the solvent provided improved yields for specific substrate combinations (Scheme 1.4). A key observation was that products were generally formed in higher yields when the trifluoroborate salt was sparingly soluble in the reaction solvent. We hypothesized that controlled release of the alkyl radical in solution — which is influenced by the solubility of the alkyl BF_3 salt — favors coupling and mitigates the formation of protodeborylation and dimerization products.

For example, whereas *N*-Boc-aminopyrazole **4h**, which is sparingly soluble in 2-MeTHF, coupled with **2a** to give **5h** in 70% yield and 80% ee (Figure 4), the structurally similar pyrazole **4i** (precursor to **5i**) is highly soluble in 2-MeTHF and under standard conditions, protodeborylation dominated. Improved reactivity was observed in cyclopentyl methyl ether (CPME), in which **4i** is

less soluble, with **5i** being formed in 46% yield and 83% ee. Due to the limited solubility of both the [Ni]·**L1** complex and [Ir] photocatalyst in CPME, for this substrate the more soluble **L2** was used instead of **L1** and the [Ir] loading was increased to 1 mol %. Given these initial findings, a HTE screen of various alkyl trifluoroborates against **L1** and **L2** in different solvents was performed to rapidly identify which solvent and ligand combinations performed best for a given trifluoroborate.

Scheme 1.4 Scope of alkyl trifluoroborates salts



Using the conditions identified in the HTE screen, the coupling of pyrrole- and other five membered heterocycle-containing trifluoroborate salts were performed (Figure 4). 4-Substituted pyrrole 2-carboxylate esters were generally tolerated (**4a–d**), though chlorinated product **5b** was formed in moderate yield.ⁱ When the ester substituent was shifted from the 2- to the 3-position, the product **5e** was formed in only 66% ee; the decrease in ee from **3a** to **5e** might suggest that this dative functionality can coordinate the nickel center in the selectivity-determining step. Consistent with this hypothesis, 7-azaindole-containing substrate **4g** also performed well, giving **5g** in 59% yield and 95% ee. The pyrazoles **5h** and **5i** and phthalimide **5j** can also be prepared in more moderate enantioselectivity. Finally, it was demonstrated that commercially available trifluoroborate salt derived from *N*-Boc-pyrrolidine couples to give the corresponding product **5k** in 65% yield and 92% ee. It is notable that under the decarboxylative conditions reported by Fu and MacMillan, *N*-Boc-proline was not a competent coupling partner.

1.3 EXPLORATION OF NON-HETEROARYL BROMIDE SCOPE

Based on the (hetero)aryl bromide substrates explored (Scheme 1.3), electron-deficient heteroaromatics tended to perform with higher yields and enantioselectivities. While in some cases, use of **L2** instead of **L1** with less electron-deficient aryl bromides could provide coupled product, we wanted to explore the scope and limitations of this transformation in a systematic fashion.

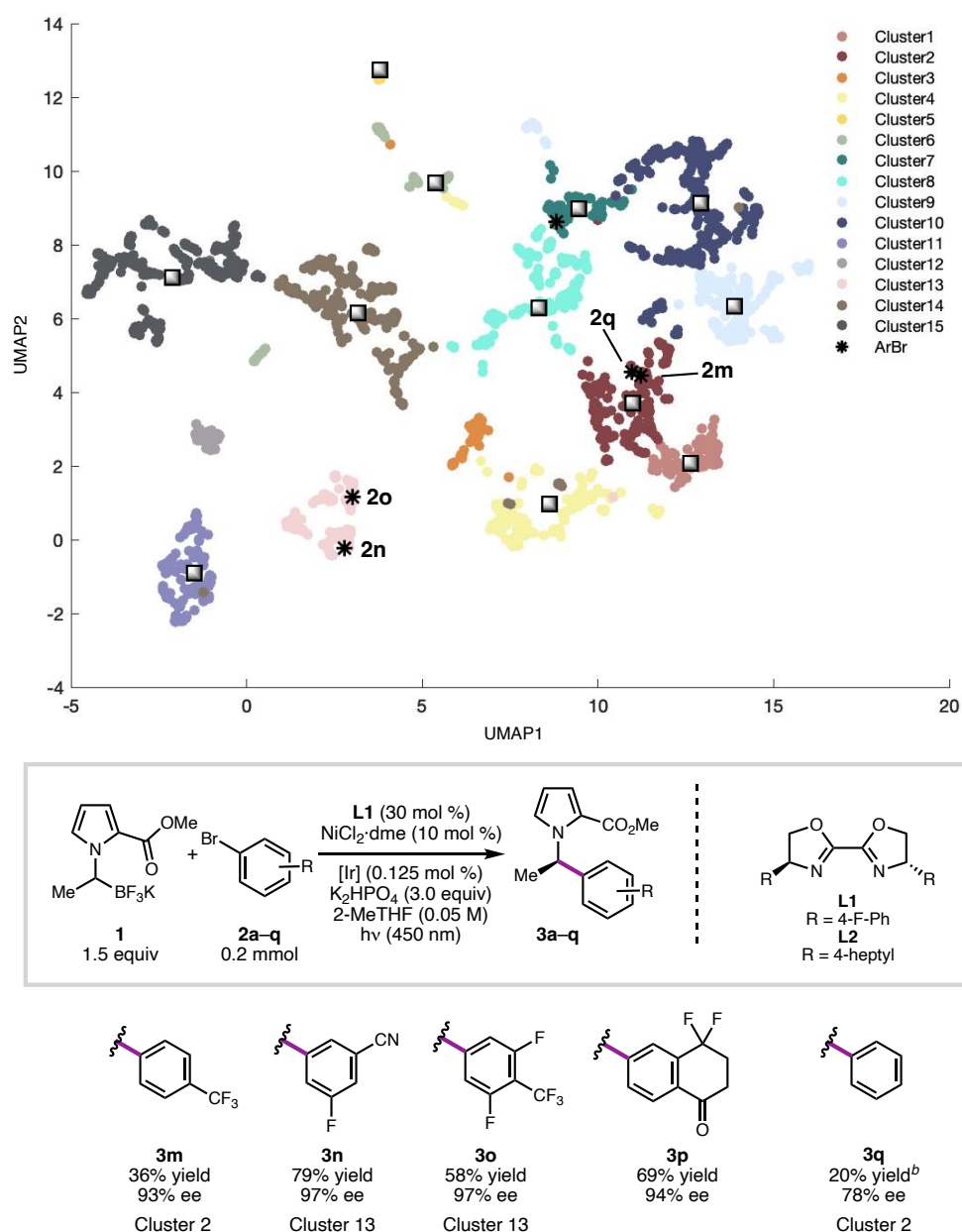
1.3.1 Motivation

There is a lack of general consensus among synthetic chemists on what constitutes a good substrate table that evaluates the performance of new reactions and the functional groups they tolerate.^{30–32} New strategies have been proposed to systematically approach scope selection. For instance, multi-substrate screening approaches have been demonstrated in high-throughput

settings to assess generality, although, these are often employed in a retrospective sense to evaluate substrate generality across various synthetic methods.³³ Alternatively, screening of additives has been proposed where functional group tolerance is assessed by their addition as exogenous additives to standard reaction conditions.^{34,35} While the reaction yield and recovery of the additive provide functional group tolerance, they do not capture the steric or electronic influences on the reaction center. Informer libraries have been designed as a diagnostic set such as Merck's drug-like coupling partners to assess cross-coupling methodologies.³⁶ More recently, data-driven scope selections have been reported using a clustering analysis to evaluate broader chemical space.³⁷⁻⁴⁰ These techniques leverage statistical tools to arrange multivariate data into natural groupings referred as clusters.

1.3.2 Clustering Analysis Workflow

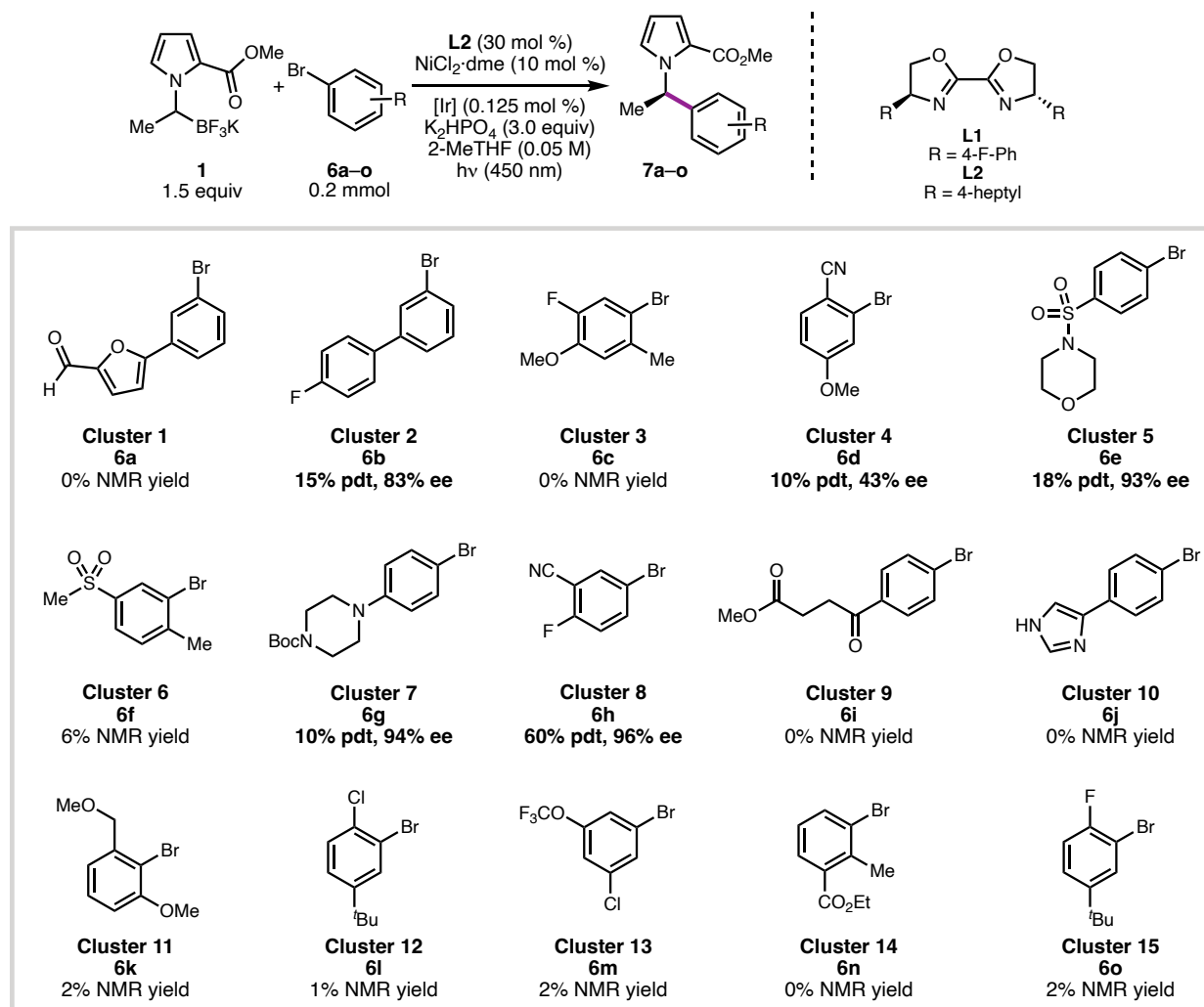
A non-heteroaryl bromide dataset (2683 molecules) and heteroaryl bromide dataset (2613 molecules) with DFT featurization were released by Doyle and coworkers on auto-qchem and used without modification.^{41,42} Similar to Doyle and coworkers, UMAP dimensionality reduction and clustering, as described below, were performed to group molecules with similar features into clusters.⁴⁰ DFT featurization of the molecules provided 96 unique descriptors that detailed electronic (e.g., HOMO-LUMO gap energy) and steric (e.g., minimum percent volume buried) properties. Uniform Manifold Approximation and Projection (UMAP) was selected as the algorithm for dimensionality reduction to identify molecules of similar properties and to generate fifteen clusters (Figure 1.3). A similar clustering procedure was performed for the heteroaryl bromide substrates (see Experimental Section for more details); however, many substrates used in our study were not included in the reported dataset by Doyle and coworkers.

Figure 1.3 Non-heteroaryl bromide clustering analysis

Of the non-heteroaryl bromide compounds in Scheme 1.2, four non-heteroaryl bromides (**2m**, **2n**, **2o**, **2q**) were identified in two of the fifteen clusters (Figure 1.3). Unfortunately, aryl bromide **2p** was not found in the literature dataset. Clustering demonstrated that the collection of aryl bromides did not cover a broad range of chemical space. Thus, the centermost molecule of a

cluster was selected from each of the fifteen clusters as a collection of non-heteroaryl bromide molecules to further evaluate broader chemical space in the reaction (Scheme 1.4).

Scheme 1.4 Non-heteroaryl bromide clustering analysis



NMR yields determined by ^1H NMR vs. ethylene carbonate as an internal standard.

Non-heteroaryl bromides from each cluster (**6a–6o**) were subjected to optimized reaction conditions (Scheme 1.4). In this case, results using 4-heptylBiOX **L2** were reported as reactivity with 4-F-PhBiOX **L1** was generally lower. Of the products that were generated in greater than 10% NMR yield, four new clusters of reactivity were discovered (cluster 4, 5, 7, and 8). Consistent with cluster 2 substrates (4- CF_3 -iodobenzene **2m** and iodobenzene **2q**), the centermost aryl

bromide of cluster 2 (**6b**) coupled in modest yield and moderate ee (15% yield and 83% ee). To our surprise, the aryl bromide for cluster 13 did not give tractable yields of the product. While we did not expect each representative cluster compound to be a perfect surrogate for reactivity within its corresponding cluster, sampling two or three examples from each cluster would be recommended in future studies to help to mitigate outliers.

Subjecting this collection of non-heteroaryl bromides to reaction conditions revealed limitations of the methodology: overall poor reactivity and generality for less electron-deficient non-heteroaryl bromides. Gratifyingly, we observed uniformly excellent enantioselectivity for substrates that did afford good yields of cross-coupled products (with the exception of cluster 4). With cluster 4 aryl bromide **6d**, we observed lower enantioselectivity (43% ee) perhaps due to coordination with the *ortho*-nitrile group. Functional groups such as sulfonamide **6e** and protected piperazine **6g** were tolerated in excellent enantioselectivities (93% ee and 94% ee, respectively) albeit with low yields. Electron-deficient aryl bromide **6h** of cluster 8 coupled in 60% yield and 96% ee.

Sterically hindered substrates such as *ortho*-substituted bromides **6c**, **6f**, **6k**, **6l**, **6n**, and **6o** were challenging in this reaction; oftentimes, poor conversion and near quantitative recovery of the aryl bromide was observed. Based on these experiments, the reaction performed as predicted: electron-deficient non-heteroaryl bromides are good substrates for this transformation but the reaction conditions are not generalizable to a diverse scope of non-heteroaryl bromides. Contrary to observed trends, however, one electron-rich substrate (**6g**) was identified, coupling in low yield but high enantioselectivity. Though the coverage of non-heteroaryl bromide space was not complete, this initial cluster scope could provide a good starting point for further condition optimization due to its chemical diversity.

1.4 CONCLUDING REMARKS

In conclusion, we have developed an enantioselective cross-coupling of α -*N*-heterocyclic trifluoroborates with aryl bromides using Ni/photoredox dual catalysis. The use of an Ir photocatalyst with chiral bioxazoline-ligated Ni catalysts formed α,α -disubstituted *N*-benzylic heterocycles in excellent enantioselectivities (up to >99% ee). Electron-deficient heteroaryl bromides and trifluoroborate salts with coordinating groups perform particularly well in this transformation. A data science-guided non-heteroaryl bromide scope was evaluated to explore the scope and limitations of this transformation. This approach served as a useful tool to probe reaction generality.

1.5 EXPERIMENTAL SECTION

1.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using dried solvents. Anhydrous 2-Methyltetrahydrofuran (2-MeTHF), anhydrous tert-butyl methyl ether (TBME), anhydrous cyclopentyl methyl ether (CPME), anhydrous tetrahydrofuran (THF), and anhydrous potassium phosphate monobasic (K_2HPO_4) were purchased from Millipore Sigma and stored in the glovebox. Nickel(II) chloride dimethoxyethane adduct ($NiCl_2 \cdot dme$) was purchased from Strem or Aldrich. Potassium (1-(tert-butoxycarbonyl)pyrrolidin-2-yl)trifluoroborate was purchased from Combi-Blocks. Unless otherwise stated, chemicals were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by ultraviolet (UV) light or with p-anisaldehyde or potassium permanganate staining. Flash column chromatography was performed as described by Still et al.¹ using silica gel (230-400 mesh) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589

nm or on a Rudolph Automatic Polarimeter (part # A22502; model APV-Plus 6W) using a 100 mm path-length cell at 589 nm (compound 5l). Melting points were measured on a Buchi melting point B-545 apparatus (compound 5h). ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively). ¹H and ¹⁹F NMR spectra were also recorded on a Varian Inova 300 (at 300 MHz and 282 MHz, respectively). Proton nuclear magnetic resonance for compound 5h (¹H NMR) spectra, proton decoupled carbon nuclear magnetic resonance (¹³C{¹H} NMR) spectra were recorded at 25 °C on a Bruker DRX-500 spectrometer using CDCl₃. NMR chemical shifts are reported relative to internal CHCl₃ (¹H, δ = 7.26), CDCl₃ (¹³C, δ = 77.16), C₆F₆ (¹⁹F, δ = -164.9). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer or a Thermo Fischer Scientific Nicolet 6700 FT-IR (compound 5h) and are reported in frequency of absorption (cm⁻¹). Analytical chiral SFC was performed with a Mettler SFC supercritical CO₂ chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm) or a Waters Acquity UPC2 with Chiralpak IC-3 (4.6 mm x 15 cm). LRMS were obtained using an Agilent 1290 Infinity/6140 Quadrupole system (LC-MS) or an Agilent 7890A GC/5975C VL MSD system (GC-MS). HRMS were acquired from the Caltech Mass Spectral Facility using fast-atom bombardment (FAB), electrospray ionization (ESI-TOF), electron impact (EI), or field ionization (FI). X-ray diffraction was performed at the Caltech X-ray Crystal Facility.

Commonly Used Abbreviations:

CPME – cyclopentyl methyl ether; **1,2-DME** – 1,2-dimethoxyethane; **EA** – elemental analysis; **ee** – enantiomeric excess; **Et₂O** – diethyl ether; **EtOAc** – ethyl acetate; **FTIR** – Fourier transform infrared; **HRMS** – high-resolution mass spectrometry; **IPA** – isopropanol; ***i*PrOAc** – isopropyl acetate; **LRMS** – low-resolution mass spectrometry; **MeCN** – acetonitrile; **MeOH** – methanol; **2-MeTHF** – 2-methyl tetrahydrofuran; **m.p.** – melting point; **NHP** – N-hydroxyphthalimide; **NMR** – nuclear magnetic resonance; **PhCF₃** – 1,1,1-trifluorotoluene, **R_f** – retention factor; **SFC** – supercritical fluid chromatography; **TBME** – *tert*-butyl methyl ether; **THF** – tetrahydrofuran.

1.5.2 Ligand Preparation

4-Heptyl BiOX (**L2**) was prepared as previously described. 4-F-Ph BiOX (**L1**) was prepared as described by Hu and coworkers.⁴³ Additional ligands for high-throughput experimentation were purchased or prepared according to known procedures.

1.5.3 Optimization of Reaction Parameters

High-Throughput Experimentation (HTE) Methods

All reactions were performed inside a positive-pressure glovebox under a nitrogen atmosphere using standard high-throughput experimentation techniques unless stated otherwise.⁴⁴ All reactions were carried out in 8x30 shell vials (Analytical Sales & Services, Inc.; Part No. 884001) using parylene coated stir dowels (V&P Scientific, Inc.; Part No. VP711D-1) as stir bars. The 8x30 shell vials were sealed in a Para-dox 96-well photoredox block assembly (Analytical Sales & Services, Inc.; Part No. 96973). Irradiation of all parallel reactions were carried out in 96-well plate format using a Lumidox™ Gen 1 Blue LED array (Analytical Sales & Services; catalog number LUM96B; λ = 470 nm, 30 mW intensity). The stirring mechanism used for all parallel experimentation was a heated/cooled tumble stirring module obtained from Symyx Technologies

(Unchained Labs). All *in vacuo* solvent removal from 96-well reaction blocks were performed inside a glovebox under a nitrogen atmosphere using a Genevac™ centrifugal evaporator. Analytical chiral RPLC-MS analysis was performed on a Waters Acquity UPLC interfaced with a Waters Xevo G2 QToF ESI. Chiral UPLC Column: Regis (*S,S*)-Whelk-O1 (4.6 mm x 10 cm; Part 1-780161-300), Binary eluent system: eluent A = aqueous mobile phase (3960 mL H₂O, 40 mL pH 3.5 buffer, details below), eluent B = (3600 mL MeCN, 360 mL H₂O, 40 mL pH 3.5 buffer. The pH 3.5 buffer is prepared by dissolving ammonium formate (12.6 g, 0.200 mol) and formic acid (7.9 mL, 9.6 g, 0.21 mol) in 1000 mL water. Isocratic conditions: 20% A until *t* = 3.0 min. Flow rate: 0.8 mL/min; Column temperature: 40 °C; UV detection: 210 nm (primary); 254 nm (secondary).

Chiral Ligand Evaluation Procedure and Results:

A solution of NiCl₂·dme (0.20 equiv, 1.0 μmol, 0.22 mg) in a 27:1 (v:v) mixture of THF:MeOH (58.3 μL) was added to each ligand (0.21 equiv, 1.05 μmol) in a 8x30 shell vial containing a dowel, the vial sealed, and the mixture agitated at 45 °C for 1 h. The solvent was removed *in vacuo* and K₂HPO₄ (6 equiv, 30 μmol, 5.2 mg) was added. Next, a well-stirred suspension of **1a** (1.5 equiv, 7.5 μmol, 1.94 mg), 5-bromo-2-chloropyrimidine (**2a**, 1.0 equiv, 5 μmol, 0.97 mg), and Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.01 equiv, 0.05 μmol, 50.5 μg) in 2-MeTHF (100 μL; 0.05 M in **2a**) was added. The sealed reaction was agitated at 350 RPM while being irradiated for 20 h, maintaining a measured external reaction block temperature of about 35 °C. Following reaction completion, a solution of biphenyl (0.20 equiv, 1.0 μmole, 0.15 mg) in MeCN (400 μL) was added and the resulting mixture analyzed by chiral stationary RPLC for the yield determination (vs. biphenyl as a standard) and enantiomeric excess of **3**. Chiral RPLC: *t*_R (**2**) = 2.0 min, *t*_R (**3**, major) = 2.2 min, *t*_R (**3**, minor) = 2.3 min, *t*_R (biphenyl) = 2.8 min.

Table S1: Chiral Ligand Evaluation

Ligand	Yield ^b (%) / ee ^c (%)	Ligand	Yield ^b (%) / ee ^c (%)	Ligand	Yield ^b (%) / ee ^c (%)
L1	64 / 95	L17	28 / 0	L33	6 / 5
L2	64 / 91	L18	33 / 1	L34	2 / -
L3	65 / 73	L19	34 / 0	L35	2 / -
L4	53 / 87	L20	42 / -36	L36	35 / 41
L5	55 / 75	L21	46 / 38	L37	29 / 3
L6	63 / 73	L22	43 / 56	L38	31 / -2
L7	51 / 93	L23	43 / 56	L39	29 / -7
L8	55 / 57	L24	8 / 6	L40	31 / -27
L9	57 / 40	L25	1 / -	L41	27 / 11
L10	55 / 59	L26	1 / -	L42	29 / 1
L11	46 / 52	L27	9 / -15	L43	31 / 0
L12	31 / 49	L28	6 / -2	L44	29 / 0
L13	46 / 58	L29	4 / -17	L45	35 / 10
L14	58 / 75	L30	6 / -8	L46	54 / -32
L15	19 / 66	L31	2 / -	L47	2 / -
L16	26 / 71	L32	2 / -	L48	2 / -

^aReaction conditions: **1a** (7.5 μ mol, 150 mol %), **2a** (5 μ mol), NiCl₂·dme (1 μ mol, 20 mol %), **L1–L48** (1.05 μ mol, 21 mol %), K₂HPO₄ (30 μ mol, 600 mol %), [Ir] = Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.05 μ mol, 1.0 mol %), 2-MeTHF (100 μ L, 0.05 M in **2a**), irradiation at 470 nm, 35 °C (20 h).

^bDetermined by stationary RPLC vs. biphenyl as an internal standard. ^cEnantiomeric excess determined by chiral stationary RPLC.

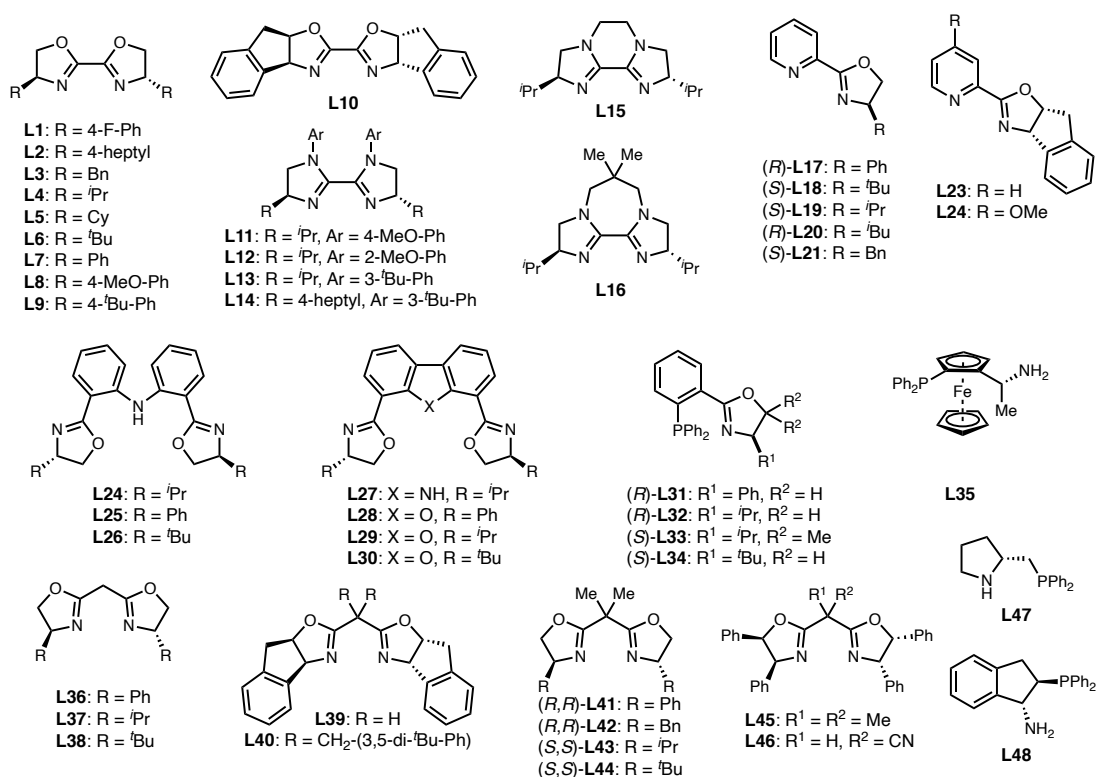
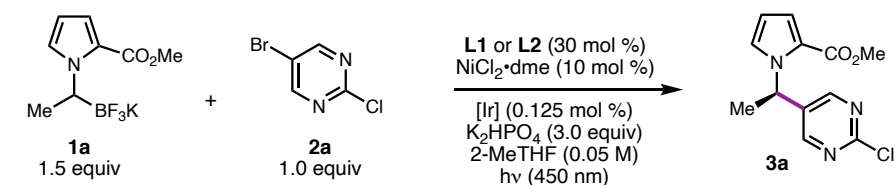


Figure S1. Chiral Ligands L1-L48

Standard Procedure for Optimization of Reaction Conditions using L1:

Standard Conditions using L1 as Ligand: 2-MeTHF (1.0 mL) was added to NiCl₂•dme (0.10 equiv, 0.01 mmol, 2.2 mg) and ligand **L1** (0.30 equiv, 0.03 mmol, 9.8 mg) in a sealed vial containing a Teflon-coated stirbar and the mixture agitated at approximately 55 °C for 1 h then cooled to ambient temperature. Separately, K₂HPO₄ (3 equiv, 0.30 mmol, 52.3 mg), methyl 1-(1-(trifluoroborate)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 1.5 equiv, 0.15 mmol, 38.9 mg), and 5-bromo-2-chloropyrimidine (**2a**, 1.0 equiv, 0.10 mol, 19.3 mg) were added to a 1 dram vial containing a Teflon-coated stir bar. Next, the NiCl₂•dme/**L1** mixture in 2-MeTHF was added to the 1 dram vial containing the substrates and base. A solution of Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.00125 equiv, 125 μmol, 0.126 mg) in 2-MeTHF (1.0 mL) was added to the 1 dram reaction vial, the vial sealed with Teflon-lined cap and parafilm, then removed from the glovebox. The vial was mounted in a PennOC 8 mL cone reflector (Part No. PR-R08001-2) inside a PennOC M1 Photoreactor Base Unit (Model No. PR001) with the bottom of the vial 2.1 cm from the LED. The vial was irradiated with a PennOC 450 nm Light source (part no. PR1M-102AD-01) for 18 h at 100% LED intensity with an agitation setpoint of 500 RPM and a fan speed of 5200 RPM, maintaining a measured external reaction block temperature of about 35 °C. After 18 hours, the reaction was diluted with EtOAc (1.5 mL) and washed with saturated aqueous NH₄Cl (0.5 mL). The aqueous layer was extracted 3 times with EtOAc (3 mL), and the combined organic layers were dried over Na₂SO₄. The dried organic layer was concentrated *in vacuo* and the resulting residue dissolved in a solution of ethylene carbonate (1.0 equiv, 0.10 mmol, 8.8 mg) in CDCl₃ (1.0 mL). The resulting mixture analyzed by quantitative ¹H NMR (CDCl₃) for yield determination of **3a** vs. ethylene carbonate as internal standard. The enantiomeric excess of **3a** was determined by chiral stationary RPLC.

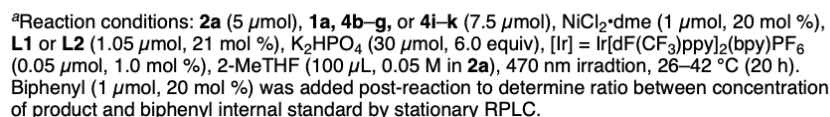
Table S2: Optimization of Reaction Parameters for Ligands **L1** and **L2**

Entry	Deviation from Standard Conditions ^a	L1	L2
		Yield ^b (%) / ee ^c (%)	Yield ^b (%) / ee ^c (%)
1	None	80 / 97	81 / 97
2	10 mol % [Ni], 10 mol % L	48 / 97	53 / 94
3	10 mol % [Ni], 15 mol % L	62 / 97	81 / 96
4	10 mol % [Ni], 20 mol % L	78 / 97	81 / 97
5	5 mol % [Ni], 15 mol % L	74 / 96	73 / 97
6	1.0 mol % [Ir]	73 / 96	74 / 93
7	0.5 mol % [Ir]	73 / 96	71 / 95
8	0.25 mol % [Ir]	72 / 96	81 / 97
9	1.0 mol % 4-CzIPN	76 / 97	69 / 94
10	No L	19 / 0	19 / 0
11	No K_2HPO_4	33 / 97	32 / 97
12	No light	<1 / –	N.D. / –
13	No [Ir]	N.D. / –	N.D. / –
14	No [Ni] or L	N.D. / –	N.D. / –

^aReaction conditions: **1a** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol), $\text{NiCl}_2 \cdot \text{dme}$ (10 μmol , 10 mol %), **L1** or **L2** (30 μmol , 30 mol %), K_2HPO_4 (300 μmol , 3.0 equiv), $[\text{Ir}] = \text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ (0.125 μmol , 0.125 mol %), 2-MeTHF (2 mL, 0.05 M in **2a**), 450 nm irradiation, 500 RPM stir rate, 5200 RPM fan speed (18 h). ^bDetermined by ^1H NMR vs. ethylene carbonate as an internal standard. ^cEnantiomeric excess determined by chiral stationary RPLC.; N.D. = not detected.

BF_3K -salt Solvent Screening Procedure and Results:

Procedure: A solution of $\text{NiCl}_2 \cdot \text{dme}$ (0.20 equiv, 1.0 μmol , 0.22 mg) in a 27:1 (v:v) mixture of THF:MeOH (58.3 μL) was added to each ligand (0.21 equiv, 1.05 μmol) in a 8x30 shell vial containing a dowel, the vial sealed, and the mixture agitated at 45 °C for 1 h. The solvent was removed *in vacuo* and a well-stirred suspension of the aryl bromide (**2a**, 1.0 equiv, 5 μmol) and K_2HPO_4 (6 equiv, 30 μmol , 5.2 mg) in TBME (100 μL) was added. The solvent was removed *in vacuo* and a well-stirred suspension of the BF_3K salt (**1a** or **4a-4k**, 1.5 equiv, 7.5 μmol) in TBME (100 μL) was added. The solvent was removed *in vacuo* and a solution (or well-stirred suspension) of $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ (0.01 equiv, 5 μL , 0.05 μmol , 50.5 μg) in the desired reaction solvent (100 μL ; 0.5 mM in $[\text{Ir}]$) was added. The sealed reaction was agitated at 350 RPM while being irradiated for 20 h, maintaining a measured external reaction block temperature of about 36–42 °C.

Table S3: BF₃-K-salts Solvent Screening Results

ND: not determined due to solvent interference

^aReaction conditions: **2a** (5 μ mol), **1a** (7.5 μ mol), NiCl₂·dme (1 μ mol, 20 mol %), **L1** or **L2** (1.05 μ mol, 21 mol %), K₂HPO₄ (30 μ mol, 6.0 equiv), [Ir] = Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.05 μ mol, 1.0 mol %), solvent (100 μ L, 0.05 M in **2a**), 470 nm irradiation, 26–42 °C (20 h).

BF ₃ -K Salt	ArBr	Ligand	THF	2-MeTHF	CPME	1,2-DME	MTBE	95:5 MTBE: 2-MeTHF	80:20 MTBE: 2-MeTHF	acetone	IPrAc	toluene	Ph-CF ₃	90:10 2-MeTHF: MeOH
1a	2a	L1	90.6	93.5	91.9	94.9	92.4	91.7	90.3	90.3	95.9	88.1	94.5	91.7
1a	2a	L2	85.8	85.1	84.2	85.8	83.6	81.8	82.1	84.8	86.6	86.5	88.2	86.7

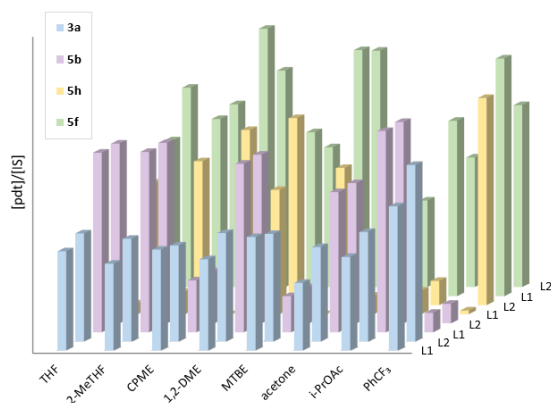
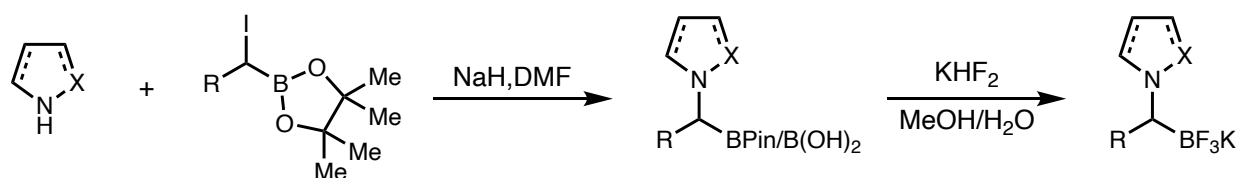


Figure S2. HTE screen of conditions for alkyl BF₃K salts. HTE conditions: **1a** (7.5 μ mol, 1.5 equiv), **2a** (5.0 μ mol, 1.0 equiv), NiCl₂·dme (1.0 μ mol, 10 mol %), **L1** or **L2** (3.0 μ mol, 30 mol %), [Ir] = Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.05 μ mol, 0.1 mol %), K₂HPO₄ (30 μ mol, 6 equiv), solvent (100 μ L, 0.05 M in **2a**), hv (450 nm). Ratio between concentration of product and biphenyl internal standard were measured by HPLC.

1.5.4 Substrate Preparation



General procedure A:

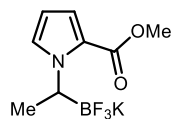
A round bottom flask was charged with the corresponding *N*-heterocycle (1.0 equiv, 6.98 mmol) and dry DMF (0.3 M) was added under N₂ atmosphere. The resulting solution was cooled at 0 °C then NaH (1.2 equiv, 60 wt. %, 8.38 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 30-60 min. The iodoalkyl borane (2.0 equiv, 13.97 mmol) was added dropwise

at 0 °C over 2 h. The reaction was aged overnight at rt. Around 30% of the DMF was removed *in vacuo* and the resulting crude material was directly charged in a ISCO C18 column and purified by reverse phase chromatography (water/MeCN). The corresponding product **SI-1** was obtained in the form of a mixture of boronic acid and pinacol borane. The material was used in the next step without further purification.

The residue was charged in a round bottom flask and dissolved in a mixture of MeOH/H₂O (2/1, 0.2 M). Potassium bifluoride (4.0 equiv, 14.54 mmol) was introduced in one portion in the reaction mixture. The reaction was aged overnight at rt. The mixture was then concentrated *in vacuo* and the resulting residue was redissolved in dry acetone (10 ml/g) then filtered. The filtrate was concentrated *in vacuo* and recrystallized in a mixture of acetone/MTBE (1/10, 100 mL/g). The solid was filtrated, washed with a mixture of acetone/MTBE (1/10), and dried under vacuum to give the desired BF₃K starting material.

Note: Despite purification of compounds **4a**, **4c**, **4e**, and **4g** by recrystallization, impurities are observed in ¹¹B NMR. Nevertheless, cross-coupling reactions allowed isolation of desired products in good yields and good enantioselectivities.

Potassium trifluoro(1-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)ethyl)borate (1a) : prepared



from commercially available methyl 1H-pyrrole-2-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.⁴⁵ following General

Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield

1a (2.6 g, 65% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.28 – 7.10 (m, 1H), 6.79 – 6.61 (m, 1H), 6.01 – 5.85 (m, 1H), 4.08 (m, 1H), 3.66 (s, 3H), 1.17 – 0.86 (m, 3H).

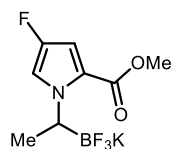
¹³C NMR (101 MHz, DMSO-*d*₆): δ 160.8, 128.5, 120.7, 116.4, 106.0, 50.3, 25.0, 20.1.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -139.69.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 3.58.

HRMS (FAB, *m/z*): calc'd for C₈H₉BF₃NO₂ [M-H]⁻: 219.0684; found: 219.0798.

Potassium trifluoro(1-(4-fluoro-2-(methoxycarbonyl)-1H-pyrrol-1-yl)ethyl)borate (4a):



Prepared from commercially available methyl 4-fluoro-1H-pyrrole-2-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General

Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield

4a (654 mg, 56% yield over two steps).

¹H NMR (500 MHz, DMSO-*d*₆): δ 6.99 (s, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 4.12 (s, 1H), 3.68 (s, 3H), 1.06 (d, *J* = 7.2 Hz, 3H).

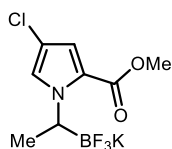
¹³C NMR (126 MHz, DMSO-*d*₆): δ 160.9, 149.0 (d, *J* = 243.3 Hz), 117.3 (d, *J* = 7.5 Hz), 113.2 (dd, *J* = 27.2, 2.2 Hz), 101.8 (d, *J* = 14.4 Hz), 51.1, 31.7, 20.1.

¹⁹F NMR (376 MHz, DMSO): δ -145.08, -167.29.

¹¹B NMR (128 MHz, DMSO-*d*₆): δ 3.33.

HRMS (FAB, *m/z*): calc'd for [C₈H₈BF₄NO₂] [M-H]⁻: 237.0590 ; found: 237.0704.

Potassium (1-(4-chloro-2-(methoxycarbonyl)-1H-pyrrol-1-yl)ethyl)trifluoroborate (4b):



prepared from commercially available methyl 4-chloro-1H-pyrrole-2-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General

Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield **4b** (390 mg, 74% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.12 (d, *J* = 2.1 Hz, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 4.17 – 4.00 (m, 1H), 3.68 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H).

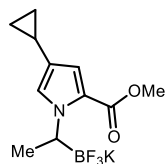
¹³C NMR (101 MHz, DMSO-*d*₆): δ 160.1, 125.4, 120.8, 114.5, 107.9, 50.8, 19.7.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -145.01.

¹¹B NMR (128 MHz, DMSO-*d*₆): δ 2.93.

HRMS (FAB, *m/z*): calc'd for C₈H₈BClF₃NO₂ [M-H]⁻: 253.0294 ; found: 253.0409

Potassium (1-(4-cyclopropyl-2-(methoxycarbonyl)-1H-pyrrol-1-yl)ethyl)trifluoroborate



(4c): Prepared from commercially available methyl 4-cyclopropyl-1H-pyrrole-2-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A. The crude residue was purified by recrystallization in

acetone/MTBE (1/10) to yield **4c** (780 mg, 68% yield over two steps).

¹H NMR (500 MHz, DMSO-*d*₆): δ 7.01 (d, *J* = 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 4.13 – 3.91 (m, 1H), 3.64 (s, 3H), 1.70 – 1.43 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.72 (dd, *J* = 8.3, 2.2 Hz, 2H), 0.37 (td, *J* = 4.9, 1.9 Hz, 2H).

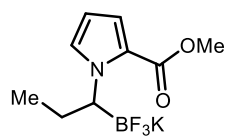
¹³C NMR (126 MHz, DMSO-*d*₆): δ 161.1, 126.5, 123.8, 120.6, 113.7, 50.6, 20.5, 8.4, 8.2, 8.2.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -144.37.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 3.35.

HRMS (FAB, *m/z*): calc'd for C₁₁H₁₃BF₃NO₂ [M-H]⁻: 259.0997; found: 259.1114.

Potassium trifluoro(1-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)propyl)borate (4d): prepared



from commercially available methyl 1H-pyrrole-2-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.⁴⁶ The crude residue was

purified by recrystallization in acetone/MTBE (1/10) to yield **4d** (480 mg, 84% yield over two steps).

¹H NMR (500 MHz, DMSO-*d*₆): δ 7.72 (s, 1H), 7.40 – 7.25 (m, 1H), 6.58 (s, 1H), 4.83 (s, 1H), 4.29 (s, 3H), 2.30 (dp, *J* = 13.7, 7.2 Hz, 1H), 2.17 (dp, *J* = 14.9, 7.5 Hz, 1H), 1.24 (t, *J* = 7.4 Hz, 3H).

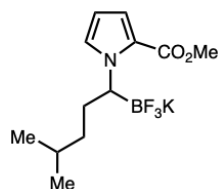
¹³C NMR (126 MHz, DMSO-*d*₆): δ 162.6, 128.6, 123.0, 117.9, 116.6, 106.9, 50.6, 27.0, 11.8, 0.9 (dp, *J* = 41.5, 20.8 Hz).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -142.89.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 5.60 – 2.44 (m).

HRMS (FAB, *m/z*): calc'd for C₉H₁₁BF₃NO₂ [M-H]⁻: 233.0840 ; found: 233.0955.

Potassium trifluoro((1-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)-4-methylpentyl)borate (4e):



prepared from commercially available 1H-pyrrole-2-carboxylate and 2-(1-iodo-4-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following

General Procedure A. The crude residue was purified by recrystallization in

MTBE/hexane (1/1) to yield **4f** (286 mg, 45% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (s, 1H), 6.67 (d, *J* = 3.4 Hz, 1H), 5.91 (t, *J* = 3.2 Hz, 1H), 4.20 (dt, *J* = 9.7, 4.5 Hz, 1H), 3.65 (s, 3H), 1.58 (tt, *J* = 11.0, 5.2 Hz, 1H), 1.50 – 1.27 (m, 2H), 0.96 (tt, *J* = 11.8, 5.9 Hz, 1H), 0.74 (t, *J* = 5.8 Hz, 6H).

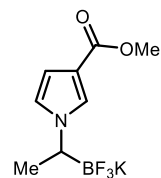
^{13}C NMR (101 MHz, DMSO- d_6): δ 161.15, 128.08, 121.70, 115.76, 106.11, 50.19, 35.89, 31.78, 27.62, 22.80, 22.60.

^{19}F NMR (376 MHz, DMSO- d_6): δ -143.51.

^{11}B NMR (128 MHz, DMSO- d_6): δ 3.33.

HRMS (ESI-TOF, m/z): calc'd for $\text{C}_{12}\text{H}_{20}\text{BF}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 278.1534; found: 278.1533.

Potassium trifluoro(1-(3-(methoxycarbonyl)-1H-pyrrol-1-yl)ethyl)borate (4f): Prepared from



commercially available methyl 1H-pyrrole-3-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield **4f** (270

mg, 45% yield over two steps).

^1H NMR (400 MHz, DMSO- d_6): δ 7.30 (t, J = 2.0 Hz, 1H), 6.65 (t, J = 2.4 Hz, 1H), 6.29 – 6.09 (m, 1H), 3.64 (s, 3H), 3.06 – 2.82 (m, 1H), 1.13 (d, J = 7.3 Hz, 3H).

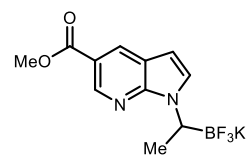
^{13}C NMR (101 MHz, DMSO- d_6): δ 164.7, 126.1, 122.4, 112.2, 107.4, 50.2, 19.2.

^{19}F NMR (376 MHz, DMSO- d_6): δ -145.84.

^{11}B NMR (161 MHz, DMSO- d_6): δ 3.25.

HRMS (FAB, m/z): calc'd for $\text{C}_{10}\text{H}_{14}\text{BF}_3\text{N}_2\text{O}_2$ $[\text{M}-\text{H}]^-$: 262.1106 ; found: 262.1220.

Potassium trifluoro(1-(5-(methoxycarbonyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)ethyl)borate



(4g): prepared from commercially available methyl 1H-pyrrolo[2,3-b]pyridine-5-carboxylate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane following General Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield **4g** (841 mg, 68% yield over two steps).

¹H NMR (500 MHz, DMSO-*d*₆): δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 3.4 Hz, 1H), 6.46 (d, *J* = 3.5 Hz, 1H), 3.95 (dd, *J* = 7.1, 3.7 Hz, 1H), 3.87 (s, 4H), 1.16 (d, *J* = 7.3 Hz, 3H).

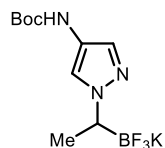
¹³C NMR (126 MHz, DMSO-*d*₆): δ 167.2, 149.7, 143.2, 131.8, 129.6, 119.6, 116.7, 99.0, 52.2, 18.7.

¹⁹F NMR (376 MHz, DMSO-*d*₆): -144.86.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 2.70.

HRMS (FAB, *m/z*): calc'd for C₁₁H₁₀BF₃N₂O₂ [M-H]⁻: 270.0793 ; found: 270.0913.

Potassium (1-(4-((tert-butoxycarbonyl)amino)-1H-pyrazol-1-yl)ethyl)trifluoroborate (4h**):**



prepared from commercially available tert-butyl (1H-pyrazol-4-yl)carbamate and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General

Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield **4h** (4.5 g, 76% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.82 (s, 1H), 7.54 (s, 1H), 7.07 (s, 1H), 3.18 – 3.02 (m, 1H), 1.43 (s, 9H), 1.08 (d, *J* = 7.3 Hz, 3H).

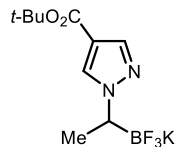
¹³C NMR (101 MHz, DMSO-*d*₆): δ 152.7, 126.8, 120.3, 118.6, 78.0, 28.2, 18.9.

¹⁹F NMR (376 MHz, DMSO- *d*₆) δ -145.84.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 3.26.

HRMS (FAB, *m/z*): calc'd for C₁₀H₁₅BF₃N₃O₂ [M-H]⁻: 277.1215 ; found: 277.1316.

Potassium (1-(4-(tert-butoxycarbonyl)-1H-pyrazol-1-yl)ethyl)trifluoroborate (4i): prepared



from commercially available *tert*-butyl 1H-pyrazole-4-carboxylate compound with carbon dioxide and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A. The crude residue was purified by recrystallization

in acetone/MTBE (1/10) to yield **4i** (2.8 g, 82% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.88 (s, 1H), 7.58 (s, 1H), 3.28 – 3.15 (m, 1H), 1.47 (s, 9H), 1.14 (d, *J* = 7.3 Hz, 3H).

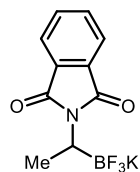
¹³C NMR (101 MHz, DMSO-*d*₆): δ 162.4, 138.4, 131.4, 113.7, 79.0, 28.1, 18.5.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -145.34.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 3.26.

HRMS (FAB, *m/z*): calc'd for C₁₀H₁₄BF₃N₂O₂ [M-H]⁻: 262.1106 ; found: 262.1220.

Potassium (1-(1,3-dioxoisindolin-2-yl)ethyl)trifluoroborate (4j): prepared from commercially



available isoindoline-1,3-dione and 2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following General Procedure A. The crude residue was purified by recrystallization in acetone/MTBE (1/10) to yield **4j** (1.1 g, 35% yield over two steps).

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.80 – 7.68 (m, 4H), 3.29 – 3.21 (m, 1H), 1.18 (d, *J* = 7.7 Hz, 3H).

¹³C NMR (101 MHz, DMSO-*d*₆): δ 168.6, 133.5, 132.2, 121.9, 14.5.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -143.33.

¹¹B NMR (161 MHz, DMSO-*d*₆): δ 2.82.

HRMS (FAB, *m/z*): calc'd for C₁₀H₇BF₃NO₂ [M-H]⁻: 241.0527 ; found: 241.0636.

1.5.5 Enantioselective Cross-Coupling

General Procedure B: Cross-coupling on 0.2 mmol scale

On the benchtop, to a 2 dram vial containing an 12 mm Teflon-coated stir bar were added aryl bromide (if solid) (1.0 equiv, 0.2 mmol) and BF_3K salt (1.5 equiv, 0.3 mmol). The reaction vial was then brought into a N_2 -filled glovebox and K_2HPO_4 (3 equiv, 0.6 mmol, 105 mg) was added. $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ (0.125 mol%, 0.25 μmol , 0.25 mg) was added as a stock solution in 2.0 mL solvent followed by aryl bromide (if liquid) (1.0 equiv, 0.2 mmol). Meanwhile, $\text{NiCl}_2\cdot\text{dme}$ (0.1 equiv, 0.02 mmol, 4.4 mg), ligand (0.30 equiv, 0.06 mmol) and the remaining solvent (2.0 mL) (4.0 mL total in final reaction, 0.05 M) were added to a 1 dram vial with a stir bar, sealed with a cap, heated to 55–60 °C in a heating block, and stirred until complexation was complete, everything was dissolved, and a color change occurred (4-heptyl BiOX: clear peachy orange solution; 4-F-Ph BiOX: clear yellow solution). Once complexation was complete, the complexed catalyst solution was cooled to ambient then added to the reaction vial. The vial was sealed with a Teflon cap and electrical tape, then removed from the glovebox. The reaction vial was then placed in a vial holder in a 7 cm tall cone in a Penn PhD m2 photoreactor with a 450 nm light module. Stirring was set to 500 rpm, the fan speed was set to 5200 rpm, the LED intensity was set to 100%, and the reaction time was set to 18 hours. After 18 hours, the reaction was diluted with EtOAc and sat. aq. NH_4Cl . The aqueous layer was extracted 3 times with EtOAc, and the combined organic layers were pushed through a ~8 mm by 6 cm plug of MgSO_4 with a layer of celite on top. The solution was concentrated *in vacuo*, and the crude material was purified by flash column chromatography over silica gel to afford the desired product.

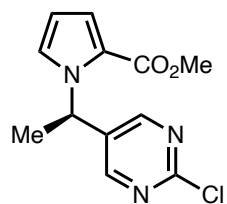
General Procedure C: Cross-coupling on 1.0 mmol scale

On the benchtop, to a 40 mL vial (Chemglass; catalog CG-4912-06) containing a Teflon-coated cross-type stir bar (Fisherbrand Starburst; catalog 14-513-76; 19.1 x 9.5 mm) were added aryl bromide (if solid) (1.0 equiv, 1.0 mmol) and BF_3K salt (1.5 equiv, 1.5 mmol). The reaction vial was then brought into a N_2 -filled glovebox and K_2HPO_4 (3 equiv, 3.0 mmol, 523 mg) was added. $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ (0.125 mol%, 1.25 μmol , 1.26 mg) was added as a stock solution in 5.0 mL solvent followed by aryl bromide (if liquid) (1.0 equiv, 1.0 mmol). Meanwhile, $\text{NiCl}_2\cdot\text{dme}$ (0.1 equiv, 0.1 mmol, 22.0 mg), ligand (0.20 equiv, 0.20 mmol) and the remaining solvent (5.0 mL) (10 mL total in final reaction, 0.10 M) were added to a 2 dram vial with a stir bar, sealed with a cap, heated to 55–60 °C in a heating block, and stirred until complexation was complete, everything was dissolved, and a color change occurred (4-heptyl BiOX: clear peachy orange solution; 4-F-Ph BiOX: clear yellow solution). Once complexation was complete, the complexed catalyst solution was cooled to ambient then added to the reaction vial. The vial was sealed with a Teflon cap and electrical tape, then removed from the glovebox. The vial was mounted in a PennOC 8 mL cone reflector (Part No. PR-R08001-2) inside a PennOC M1 Photoreactor Base Unit (Model No. PR001) with the bottom of the vial 2 cm from the LED. The vial was irradiated with a PennOC 450 nm Light source (part no. PR1M-102AD-01) for 56 h at 100% LED intensity with an agitation setpoint of 500 RPM and a fan speed of 5200 RPM. After 56 hours, the reaction was diluted with EtOAc and sat. aq. NH_4Cl . The aqueous layer was extracted 3 times with EtOAc, and the combined organic layers were pushed through a plug of MgSO_4 with a layer of celite on top. The solution was concentrated *in vacuo*, and the crude material was purified by flash column chromatography over silica gel to afford the desired product.

General Procedure D: Cross-coupling on 5.0 mmol scale

On the benchtop, to a 150 mL round-bottom pressure flask with PTFE plug seal top containing a Teflon-coated egg-shaped stir bar (Fisherbrand Egg-Shaped Bar; catalog 14-512-123; 38 x 16 mm) were added aryl bromide (if solid) (1.0 equiv, 5.0 mmol) and BF_3K salt (1.5 equiv, 7.5 mmol). The reaction vessel was then brought into a N_2 -filled glovebox, and K_2HPO_4 (3 equiv, 15 mmol, 1.94 g), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{bpy})\text{PF}_6$ (0.125 mol%, 6.25 μmol , 6.3 mg), aryl bromide (if liquid), and 90 mL 2-MeTHF were added. Meanwhile, $\text{NiCl}_2\cdot\text{dme}$ (0.1 equiv, 0.5 mmol, 110 mg), ligand (0.30 equiv, 0.30 mmol) and 2-MeTHF (10 mL) (100 mL total in final reaction, 0.10 M) were added to a 20 mL scintillation vial with a stir bar, sealed with a cap, heated to 55–60 °C in a heating block, and stirred until complexation was complete, everything was dissolved, and a color change occurred (4-heptyl BiOX: clear peachy orange solution; 4-F-Ph BiOX: clear yellow solution). Once complexation was complete, the complexed catalyst solution was cooled to ambient then added to the reaction vessel. The vessel was sealed with threaded PTFE plug seal and FETFE o-ring, then removed from the glovebox. The vessel was irradiated with a 440 nm Kessil LED light source (part no. PR160-440 nm) for 60 h at 100% LED intensity positioned 5 cm from the flask and an agitation setpoint of 500 RPM. A cooling fan was positioned at a 45° angle overhead, positioned 30 cm from the reaction vessel. Measured steady-state temperature was 28 °C. After 60 hours, the reaction was diluted with EtOAc and sat. aq. NH_4Cl . The aqueous layer was extracted 3 times with EtOAc, and the combined organic layers were pushed through a plug of MgSO_4 with a layer of celite on top. The solution was concentrated *in vacuo*, and the crude material was purified by flash column chromatography over silica gel to afford the desired product.

methyl (R)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3a): Prepared



according to General Procedure B from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica

gel, 8.5–9% EtOAc/hexane) to yield **3a** (44.5 mg, 84% yield) in 97% ee as a colorless oil.

Prepared according to General Procedure C (1.0 mmol **2a**) in 2-MeTHF with 4-F-Ph BiOX (**L1**) and purified by column chromatography to yield **3a** (158 mg, 60% yield) in 96% ee. Prepared according to General Procedure D (5.0 mmol **2a**) in 2-MeTHF with 4-F-Ph BiOX (**L1**) and purified by column chromatography to yield **3a** (1.04 g, 78% yield) in 95% ee.

R_f = 0.36 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{21} = 79^\circ$ ($c = 1.1$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 8.33 (d, $J = 0.6$ Hz, 2H), 7.10 (dd, $J = 2.8, 1.7$ Hz, 1H), 7.03 (dd, $J = 4.0, 1.7$ Hz, 1H), 6.59 (q, $J = 7.3$ Hz, 1H), 6.28 (dd, $J = 4.0, 2.8$ Hz, 1H), 3.75 (s, 3H), 1.86 (d, $J = 7.3$ Hz, 3H).

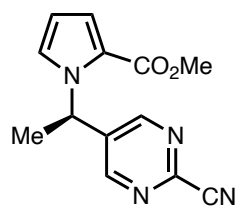
^{13}C NMR (101 MHz, CDCl_3): δ 161.6, 160.5, 157.7, 135.5, 124.6, 122.2, 119.5, 109.8, 51.4, 51.3, 21.7.

FTIR (NaCl, thin film, cm^{-1}): 3126, 2984, 2949, 1698, 1549, 1439, 1398, 1338, 1226, 1113, 1059, 940, 829, 740.

HRMS (ESI-TOF, m/z): calc'd for $\text{C}_{12}\text{H}_{13}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 266.0691; found: 266.0702.

Chiral SFC: (IC, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): t_R (minor) = 3.3 min, t_R (major) = 3.9 min.

methyl (*R*)-1-(1-(2-cyanopyrimidin-5-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3b): Prepared from



5-bromopyrimidine-2-carbonitrile (**2b**, 36.8 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-

Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 10 to 40% EtOAc/hexanes) to yield **3b** (39 mg, 77% yield) in 95% ee as a colorless oil.

R_f = 0.43 (silica gel, 30% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 60° (c = 1.1, CHCl₃).

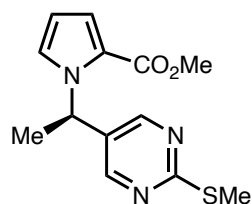
¹H NMR (400 MHz, CDCl₃): δ 8.48 (d, J = 0.6 Hz, 2H), 7.15 (dd, J = 2.8, 1.7 Hz, 1H), 7.06 (dd, J = 4.0, 1.7 Hz, 1H), 6.61 (q, J = 7.3 Hz, 1H), 6.32 (dd, J = 4.0, 2.8 Hz, 1H), 3.74 (s, 3H), 1.90 (d, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.5, 155.8, 144.0, 139.7, 124.6, 122.3, 119.8, 115.7, 110.1, 52.0, 51.5, 21.60.

FTIR (NaCl, thin film, cm⁻¹): 2950, 1699, 1555, 1438, 1416, 1339, 1242, 1214, 1114, 942, 793, 761, 743.

HRMS (ESI-TOF, m/z): calc'd for C₁₃H₁₃N₄O₂ [M+H]⁺ : 257.1033; found: 257.1023.

Chiral SFC: (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 280 nm): t_R (minor) = 4.5 min, t_R (major) = 4.2 min.



methyl (*R*)-1-(1-(2-(methylthio)pyrimidin-5-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3c): Prepared from 5-bromo-2-(methylthio)pyrimidine (**2c**, 41.0 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-

pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B

in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 15% EtOAc/hexanes) to yield **3c** (46.5 mg, 84% yield) in 96% ee as a colorless oil.

R_f = 0.39 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 127° (c = 1.0, CHCl₃).

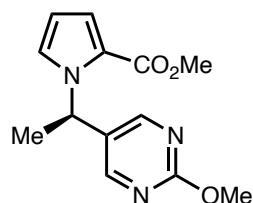
¹H NMR (400 MHz, CDCl₃): δ 8.27 (s, 2H), 7.06 (dd, J = 2.8, 1.7 Hz, 1H), 7.01 (dd, J = 3.9, 1.7 Hz, 1H), 6.55 (q, J = 7.2 Hz, 1H), 6.23 (dd, J = 3.9, 2.7 Hz, 1H), 3.76 (s, 3H), 2.53 (s, 3H), 1.83 (d, J = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 171.9, 161.6, 155.4, 131.3, 124.7, 122.2, 119.3, 109.5, 51.5, 51.3, 21.7, 14.3.

FTIR (NaCl, thin film, cm⁻¹): 2948, 1699, 1584, 1537, 1438, 1400, 1338, 1227, 1111, 942, 738.

HRMS (ESI-TOF, m/z): calc'd for C₁₃H₁₆N₃O₂S [M+H]⁺ : 278.0958 ; found: 278.0970.

Chiral SFC: (IC, 2.5 mL/min, 25% IPA in CO₂, λ = 280 nm): t_R (minor) = 3.7 min, t_R (major) = 4.3 min.



methyl (R)-1-(1-(2-methoxypyrimidin-5-yl)ethyl)-1H-pyrrole-2-carboxylate (3d): Prepared from 5-bromo-2-methoxypyrimidine (**2d**, 37.8

mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1H-pyrrole-2-

carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 30 to 40% EtOAc/hexanes) to yield **3d** (33 mg, 63% yield) in 96% ee as a colorless oil.

R_f = 0.30 (silica gel, 30% EtOAc/hexanes, UV).

$[\alpha]_D^{21}$ = 99° (c = 1.51, CHCl₃).

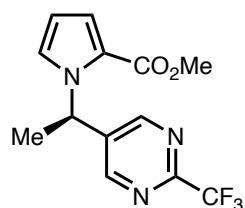
¹H NMR (400 MHz, CDCl₃): δ 8.28 (d, *J* = 0.6 Hz, 2H), 7.04 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.99 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.57 (q, *J* = 7.2 Hz, 1H), 6.22 (dd, *J* = 4.0, 2.8 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 3H), 1.82 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 165.1, 161.6, 157.5, 129.7, 124.6, 122.0, 119.1, 109.4, 55.1, 51.3, 51.1, 21.7.

FTIR (NaCl, thin film, cm⁻¹): 2952, 1702, 1598, 1560, 1474, 1411, 1338, 1228, 1112, 1039, 943, 805, 738.

HRMS (ESI-TOF, m/z): calc'd for C₁₃H₁₆N₃O₃ [M+H]⁺ : 262.1186 ; found: 262.1183.

Chiral SFC: (IC, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R (minor) = 4.1 min, *t*_R (major) = 4.4 min.



methyl (*R*)-1-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-1*H*-pyrrole-2-

carboxylate (3e**):** Prepared from 5-bromo-2-(trifluoromethyl)pyrimidine (**3e**, 45.4 mg, 0.3 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-

pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.2 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 2.5% EtOAc/PhMe) to yield **3e** (30 mg, 50% yield) in 98% ee as a colorless oil.

R_f = 0.54 (silica gel, 30% EtOAc/hexanes, UV).

[α]_D²¹ = 46° (c = 1.5, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.55 (s, 2H), 7.15 (dd, *J* = 2.8, 1.7 Hz, 1H), 7.05 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.67 (q, *J* = 7.3 Hz, 1H), 6.31 (dd, *J* = 4.0, 2.7 Hz, 1H), 3.74 (s, 3H), 1.91 (d, *J* = 7.2 Hz, 3H).

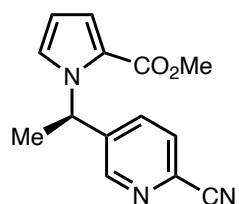
¹³C NMR (101 MHz, CDCl₃): δ 161.6, 155.8 (q, *J* = 36.9 Hz), 155.8, 139.1, 124.6, 122.3, 119.6 (q, *J* = 275.3 Hz), 119.7, 110.0, 51.8, 51.4, 21.7.

¹⁹F NMR (282 MHz, CDCl₃) δ -73.42.

FTIR (NaCl, thin film, cm⁻¹): 3124, 2991, 1956, 1704, 1698, 1714, 1568, 1441, 1353, 1118, 941.

HRMS (ESI-TOF, *m/z*): calc'd for C₁₃H₁₃F₃O₂N₃ [M+H]⁺ : 300.0954 ; found: 300.0973.

Chiral SFC: (IC, 2.5 mL/min, 5% IPA in CO₂, λ = 254 nm): *t*_R (minor) = 3.0 min, *t*_R (major) = 3.7 min.



methyl (R)-1-(1-(6-cyanopyridin-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate

(3f): Prepared from 5-bromo-2-pyridinecarbonitrile (**2f**, 36.6 mg, 0.2 mmol)

and methyl 1-(1-(trifluoro-λ⁴-boranethyl)ethyl)-1*H*-pyrrole-2-carboxylate,

potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 10-30% EtOAc/hex) to yield **3f** (39 mg, 77% yield) in 91% ee as a colorless oil.

R_f = 0.39 (silica gel, 30% EtOAc/hex, UV).

[α]_D²⁵ = 71° (c = 0.7784, CHCl₃).

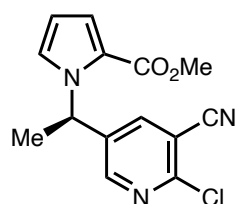
¹H NMR (400 MHz, CDCl₃): δ 8.46 (d, *J* = 2.3 Hz, 1H), 7.61 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.39 (ddd, *J* = 8.1, 2.3, 0.7 Hz, 1H), 7.12 (dd, *J* = 2.8, 1.7 Hz, 1H), 7.04 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.63 (q, *J* = 7.2 Hz, 1H), 6.29 (dd, *J* = 4.0, 2.7 Hz, 1H), 3.73 (d, *J* = 0.5 Hz, 3H), 1.86 (d, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.5, 149.3, 143.2, 134.3, 132.7, 128.5, 124.8, 122.3, 119.5, 117.2, 109.6, 53.6, 51.4, 21.9.

FTIR (NaCl, thin film, cm⁻¹): 2987, 2950, 2236, 1702, 1438, 1414, 1339, 1240, 1213, 1112, 1054, 1022, 946, 848, 760, 741.

HRMS (ESI-TOF, m/z): calc'd for C₁₄H₁₄N₃O₂ [M+H]⁺ : 256.1081 ; found: 256.1074.

Chiral SFC: (AD-H, 2.5 mL/min, 15% IPA in CO₂, λ = 254 nm): *t*_R (minor) = 3.3 min, *t*_R (major) = 3.1 min.



methyl (R)-1-(1-(6-chloro-5-cyanopyridin-3-yl)ethyl)-1H-pyrrole-2-

carboxylate (3g): Prepared from 5-bromo-2-chloronicotinonitrile (**2g**, 43.5 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boranethyl)-1H-pyrrole-2-

carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 15% EtOAc/hexanes) to yield **3g** (44.6 mg, 77% yield) in 97% ee as a colorless oil.

R_f = 0.39 (silica gel, 20% EtOAc/hexanes, UV).

[α]_D²² = 87° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.35 (dd, J = 2.5, 0.6 Hz, 1H), 7.55 (dd, J = 2.5, 0.7 Hz, 1H), 7.12 (dd, J = 2.8, 1.7 Hz, 1H), 7.04 (dd, J = 4.0, 1.7 Hz, 1H), 6.58 (q, J = 7.2 Hz, 1H), 6.30 (dd, J = 4.0, 2.8 Hz, 1H), 3.75 (s, 3H), 1.85 (d, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.5, 151.5, 150.9, 140.0, 138.9, 124.5, 122.2, 119.7, 114.7, 110.8, 109.9, 52.7, 51.4, 21.9.

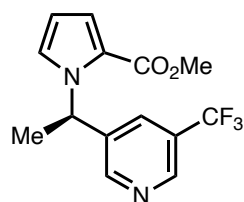
FTIR (NaCl, thin film, cm⁻¹): 2949, 1698, 1558, 1532, 1414, 1341, 1238, 1115, 913, 739.

HMRS (ESI-TOF, m/z): C₁₄H₁₃N₃O₂Cl; cal'd for [M+H]⁺: 290.0696, found: 290.0682.

Chiral SFC: (IC, 2.5 mL/min, 15% MeOH in CO₂, λ = 254 nm): *t*_R (minor) = 3.8 min, *t*_R (major) = 4.0 min.

methyl (R)-1-(1-(5-(trifluoromethyl)pyridin-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3h):

Prepared from 3-bromo-5-(trifluoromethyl)pyridine (**2h**, 45.2 mg, 0.2 mmol) and methyl 1-(1-



(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**,

77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-

F-Ph BiOX (**L1**). The crude residue was purified by column chromatography

(silica gel, 12.5% EtOAc/hexanes). The resulting colorless oil was purified again by column chromatography (silica gel, 0–1.5% Et₂O/DCM) to yield **3h** (37.6 mg, 63% yield) in 94% ee as a colorless oil.

R_f = 0.42 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 40° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.76 (s, 1H), 8.56 (s, 1H), 7.63 – 7.51 (m, 1H), 7.10 (dd, J = 2.8, 1.8 Hz, 1H), 7.03 (dd, J = 3.9, 1.8 Hz, 1H), 6.69 (q, J = 7.2 Hz, 1H), 6.27 (dd, J = 3.9, 2.8 Hz, 1H), 3.75 (s, 3H), 1.87 (d, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.9, 151.2, 145.6 (q, J = 4.6 Hz), 139.4, 130.6 (q, J = 3.8 Hz), 126.8 (q, J = 32.9), 124.8, 123.5 (q, J = 272.8 Hz), 122.2, 119.3, 109.6, 53.2, 51.3, 22.0.

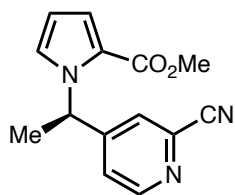
¹⁹F NMR (282 MHz, CDCl₃): δ -65.6.

FTIR (NaCl, thin film, cm⁻¹): 2952, 1703, 1531, 1440, 1339, 11240, 1132, 1026, 735.

HRMS (FI, m/z): calc'd for C₁₄H₁₃N₂O₂F₃ [M+•]⁺ : 298.0924 ; found: 298.0936.

Chiral SFC: (AD-H, 2.5 mL/min, 3% IPA in CO₂, (λ = 280 nm): t_R (major) = 3.8 min, t_R (minor) = 4.3 min.

methyl (*R*)-1-(1-(2-cyanopyridin-4-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3i**):** Prepared from 4-



bromopicolinonitrile (**2i**, 36.6 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX

(**L1**). The crude residue was purified by column chromatography (silica gel, 20% EtOAc/hexanes) to yield **3i** (39.2 mg, 77% yield) in 92% ee as a colorless oil.

R_f = 0.25 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 38° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.60 (d, *J* = 5.1 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.15 – 7.08 (m, 2H), 7.08 – 7.03 (m, 1H), 6.55 (q, *J* = 7.3 Hz, 1H), 6.34 – 6.27 (m, 1H), 3.73 (s, 3H), 1.83 (d, *J* = 7.3 Hz, 3H).

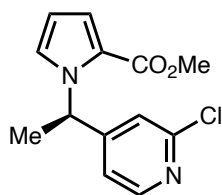
¹³C NMR (101 MHz, CDCl₃): δ 161.5, 154.7, 151.5, 134.5, 125.7, 124.9, 124.0, 122.3, 119.5, 117.3, 109.7, 54.6, 51.4, 21.6.

FTIR (NaCl, thin film, cm⁻¹): 2949, 2237, 1703, 1596, 1438, 1342, 1240, 1213, 1114, 948, 743.

HRMS (FI, *m/z*): calc'd for C₁₄H₁₃N₃O₂ [*M*+•]⁺ : 255.1002; found: 255.1006.

Chiral SFC: (OJ-H, 2.5 mL/min, 10% IPA in CO₂, (λ = 254 nm): *t_R* (minor) = 3.9 min, *t_R* (major) = 4.6 min.

methyl (*R*)-1-(1-(2-chloropyridin-4-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3j**):** Prepared from 4-



bromo-2-chloropyridine (**2j**, 38.5 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**).

The crude residue was purified by column chromatography (silica gel, 15% EtOAc/hexanes). The resulting sticky white solid was dissolved in CDCl₃, then pentane was added to precipitate a white solid. The solid was filtered off, then the filtrate was concentrated to yield **3j** (35.6 mg, 67% yield) in 95% ee as a colorless oil.

R_f = 0.40 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 47° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.28 (d, J = 5.2 Hz, 1H), 7.09 – 7.06 (m, 1H), 7.06 – 7.02 (m, 1H), 6.94 – 6.90 (m, 1H), 6.87 – 6.82 (m, 1H), 6.53 (q, J = 7.2 Hz, 1H), 6.30 – 6.24 (m, 1H), 3.74 (s, 3H), 1.80 (d, J = 7.2 Hz, 3H).

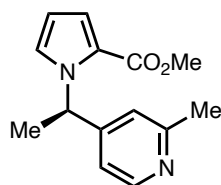
¹³C NMR (101 MHz, CDCl₃): δ 161.5, 156.1, 152.2, 150., 125.0, 122.3, 121.3, 119.8, 119.2, 109.4, 54.5, 51.3, 21.6.

FTIR (NaCl, thin film, cm⁻¹): 3124, 2986, 1949, 1698, 1593, 1549, 1415, 1342, 1240, 1110, 948, 839.

HRMS (FI, m/z): calc'd for C₁₃H₁₃N₂O₂Cl [M+•]⁺ : 264.0660; found: 264.0665.

Chiral SFC: (AD-H, 2.5 mL/min, 10% IPA in CO₂, (λ = 254 nm): t_R (minor) = 4.0 min, t_R (major) = 4.4 min.

methyl (*R*)-1-(1-(2-methylpyridin-4-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3k**):** Prepared from



4-bromo-2-methylpyridine (**2k**, 34.4 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-

heptyl BiOX (**L2**). The crude residue was purified by column chromatography (silica gel, 70% EtOAc/hexanes). to yield **3k** (23.4 mg, 48% yield) in 97% ee as a colorless oil.

R_f = 0.44 (silica gel, 80% EtOAc/hexanes, UV).

$[\alpha]_D^{21}$ = 27° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.39 (d, J = 5.2 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.82 – 6.77 (m, 1H), 6.73 (ddd, J = 5.2, 1.5, 0.8 Hz, 1H), 6.52 (q, J = 7.2 Hz, 1H), 6.24 (dd, J = 3.9, 2.7 Hz, 1H), 3.74 (s, 3H), 2.50 (s, 3H), 1.78 (d, J = 7.2 Hz, 3H).

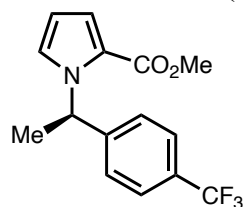
¹³C NMR (101 MHz, CDCl₃): δ 161.6, 158.9, 152.8, 149.6, 125.3, 122.3, 120.4, 118.9, 118.1, 109.0, 54.8, 51.2, 24.7, 21.8.

FTIR (NaCl, thin film, cm⁻¹): 2930, 1702, 1602, 1438, 1414, 1340, 1236, 1210, 1110.

HRMS (FD+, m/z): calc'd for C₁₄H₁₆N₂O₂ [M+•]⁺ : 244.1206; found: 244.1215.

Chiral SFC: (OB-H, 2.5 mL/min, 15% IPA in CO₂, (λ = 254 nm): t_R (major) = 2.1 min, t_R (minor) = 3.7 min.

methyl (*R*)-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1*H*-pyrrole-2-carboxylate (3I): Prepared from 1-bromo-4-(trifluoromethyl)benzene (**2I**, 45.0 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-



boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-heptyl BiOX (**L2**). The crude residue was purified by column chromatography (silica gel,

3% EtOAc/hexanes) to yield **3I** (21.4 mg, 36% yield) in 93% ee as a colorless oil.

R_f = 0.32 (silica gel, 3.5% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 44° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.59 – 7.49 (m, 2H), 7.23 – 7.14 (m, 2H), 7.07 (dd, J = 2.8, 1.7 Hz, 1H), 7.02 (dd, J = 3.9, 1.8 Hz, 1H), 6.62 (q, J = 7.2 Hz, 1H), 6.24 (dd, J = 3.9, 2.7 Hz, 1H), 3.75 (s, 3H), 1.82 (d, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.6, 147.5 (q, J = 1.4 Hz), 129.6 (q, J = 23.3 Hz), 126.4, 125.7 (q, J = 3.8 Hz), 125.3, 124.9 (q, J = 272.3 Hz), 122.3, 118.9, 108.9, 55.3, 51.2, 22.2.

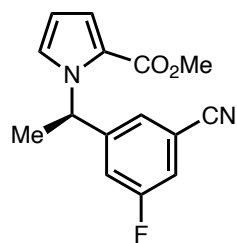
^{19}F NMR (282 MHz, CDCl_3): δ -65.7.

FTIR (NaCl, thin film, cm^{-1}): 2988, 2951, 1704, 1621, 1530, 1440, 1324, 1240, 1108, 1017, 948, 739.

HRMS (FI, m/z): calc'd for $\text{C}_{15}\text{H}_{14}\text{NO}_2\text{F}_3$ $[\text{M}+\bullet]^+$: 297.0971; found: 297.0976.

Chiral SFC: (OD-H, 2.5 mL/min, 5% IPA in CO_2 , (λ = 254 nm): t_R (major) = 2.5 min, t_R (minor) = 3.5 min.

methyl (*R*)-1-(1-(3-cyano-5-fluorophenyl)ethyl)-1*H*-pyrrole-2-carboxylate (3m**):** Prepared



from 3-bromo-5-fluorobenzonitrile (**2m**, 40.0 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column

chromatography (silica gel, 8.5% EtOAc/hexanes) to yield **3m** (43 mg, 79% yield) in 97% ee as a colorless oil.

R_f = 0.55 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{21}$ = 56° (c = 1.0, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 7.24 – 7.17 (m, 1H), 7.15 – 6.94 (m, 4H), 6.58 (q, J = 7.2 Hz, 1H), 6.33 – 6.22 (m, 1H), 3.75 (d, J = 1.6 Hz, 3H), 1.87 – 1.76 (m, 3H).

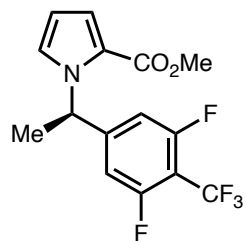
^{13}C NMR (101 MHz, CDCl_3): δ 162.5 (d, J = 250.9 Hz), 161.6, 148.4 (d, J = 7.3 Hz), 125.6 (d, J = 3.3 Hz), 124.9, 122.2, 119.3, 118.3 (d, J = 20.2 Hz), 118.2 (d, J = 22.9 Hz), 114.1 (d, J = 9.6 Hz), 109.5, 54.7, 51.3, 2.0.

^{19}F NMR (282 MHz, CDCl_3) δ -112.41 (dd, J = 9.3, 7.9 Hz).

FTIR (NaCl, thin film, cm^{-1}): 2950, 2233, 1699, 1596, 1531, 1437, 1343, 1236, 1115, 964, 874, 743.

HRMS (ESI-TOF, m/z): $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2\text{F}$; cal'd for $[\text{M}+\text{H}]^+$: 273.1034, found: 273.1036.

Chiral SFC: (OD-H, 2.5 mL/min, 10% MeOH in CO_2 , (λ = 254 nm): t_R (major) = 2.5 min, t_R (minor) = 2.8 min.

methyl (R)-1-(1-(3,5-difluoro-4-(trifluoromethyl)phenyl)ethyl)-1*H*-pyrrole-2-carboxylate

(3mn): Prepared from 5-bromo-1,3-difluoro-2-(trifluoromethyl)benzene (**2n**, 52.2 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue

was purified by column chromatography (silica gel, 2–20% EtOAc/hexanes) to yield **3n** (38.7 mg, 58% yield) in 97% ee as a colorless oil.

R_f = 0.68 (silica gel, 30% EtOAc/hexanes, UV).

$[\alpha]_D^{25}$ = 38° (c = 0.97, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.09 (dd, J = 2.8, 1.8 Hz, 1H), 7.05 (dd, J = 3.9, 1.7 Hz, 1H), 6.70 – 6.61 (m, 2H), 6.55 (q, J = 7.2 Hz, 1H), 6.28 (dd, J = 4.0, 2.7 Hz, 1H), 3.76 (s, 3H), 1.81 (d, J = 7.2 Hz, 3H).

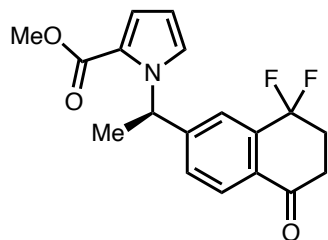
¹³C NMR (101 MHz, CDCl₃): δ 161.7 – 158.8 (m) 161.6, 151.6 (t, J = 9.3 Hz), 124.9, 122.3, 122.1 (qt, J = 274.8, 1.5 Hz), 119.3, 110.3 – 110.0 (m), 109.5, 107.0 – 106.1 (m), 54.9, 51.3, 21.8.

¹⁹F NMR (282 MHz, CDCl₃) δ -59.59 (t, J = 21.6 Hz), -111.09 – -114.78 (m).

FTIR (NaCl, thin film, cm⁻¹): 2952, 1704, 1644, 1584, 1532, 1440, 1340, 1240, 1214, 1139, 1115, 1046, 859, 762, 737, 573.

HRMS (ESI-TOF, m/z): calc'd for C₁₅H₁₃NO₂F₅ [M+H]⁺ : 334.0861 ; found: 334.0862.

Chiral SFC: (OJ-H, 2.5 mL/min, 7% IPA in CO₂, λ = 254 nm): t_R (minor) = 2.9 min, t_R (major) = 2.3 min.

methyl (*R*)-1-(1-(8,8-difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)-1*H*-pyrrole-2-

carboxylate (3o): Prepared from 6-bromo-4,4-difluoro-3,4-dihydronaphthalen-1(2*H*)-one (**2o**, 52.2 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-

MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 15% EtOAc/hexanes) to yield **3o** (45.9 mg, 69% yield) in 94% ee as a colorless oil.

R_f = 0.43 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 73° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.97 (dt, *J* = 8.2, 1.3 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.29 – 7.23 (m, 1H), 7.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 7.03 (dd, *J* = 3.9, 1.7 Hz, 1H), 6.66 (q, *J* = 7.2 Hz, 1H), 6.26 (dd, *J* = 3.9, 2.7 Hz, 1H), 3.75 (s, 3H), 2.94 – 2.82 (m, 2H), 2.70 – 2.55 (m, 2H), 1.85 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 194.4 (t, *J* = 1.4 Hz), 161.6, 150.6 (t, *J* = 1.1 Hz), 137.3 (t, *J* = 25.9 Hz), 130.5 (t, *J* = 5.5 Hz), 128.9 (t, *J* = 1.4 Hz), 127.8, 125.2, 122.3, 122.0 (t, *J* = 4.1 Hz), 119.1, 119.09 (t, *J* = 238.7 Hz), 109.2, 55.4, 51.2, 34.6 (t, *J* = 5.3 Hz), 32.4 (t, *J* = 25.7 Hz), 22.0.

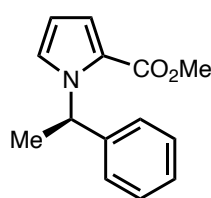
¹⁹F NMR (282 MHz, CDCl₃) δ -95.60 (t, *J* = 13.0 Hz).

FTIR (NaCl, thin film, cm⁻¹): 3378, 2950, 1694, 1611, 1530, 1448, 1238, 975, 849, 746.

HRMS (ESI-TOF, *m/z*): C₁₈H₁₈NO₃F₂; cal'd for [M+H]⁺: 334.1249, found: 334.1259.

Chiral SFC: (OD-H, 2.5 mL/min, 20% IPA in CO₂, (λ = 254 nm): *t_R* (minor) = 2.6 min, *t_R* (major) = 3.2 min.

methyl (*R*)-1-(1-phenylethyl)-1*H*-pyrrole-2-carboxylate (3p): Prepared from bromobenzene



(**3p**, 31.4 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to

General Procedure B in 2-MeTHF with 4-heptyl BiOX (**L2**). The crude residue was purified by column chromatography (silica gel, 2.5% EtOAc/hexanes) to yield **3p** (9.1 mg, 20% yield) in 78% ee as a colorless oil.

R_f = 0.33 (silica gel, 3% EtOAc/hexanes, UV).

$[\alpha]_D^{21}$ = 62° (c = 0.51, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.17 – 7.10 (m, 2H), 7.03 – 6.98 (m, 2H), 6.59 (q, J = 7.1 Hz, 1H), 6.18 (dd, J = 3.9, 2.7 Hz, 1H), 3.77 (s, 3H), 1.80 (d, J = 7.1 Hz, 3H).

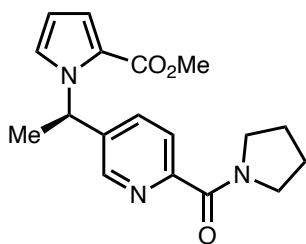
¹³C NMR (101 MHz, CDCl₃): δ 161.7, 143.1, 128.7, 127.4, 126.3, 125.6, 122.2, 118.6, 108.5, 55.5, 51.2, 22.3.

FTIR (NaCl, thin film, cm⁻¹): 2947, 2478, 1699, 1462, 1436, 1340, 1231, 1110, 1024, 946.

HRMS (FI, m/z): calc'd for C₁₄H₁₅NO₂ [$M+\bullet$]⁺ : 229.1097; found: 229.1105.

Chiral SFC: (OD-H, 2.5 mL/min, 5% IPA in CO₂, (λ = 254 nm): t_R (major) = 5.1 min, t_R (minor) = 5.8 min.

methyl 1-(1-(6-(pyrrolidine-1-carbonyl)pyridin-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate (3q):



Prepared from (5-bromopyridin-2-yl)(pyrrolidin-1-yl)methanone (**2q**, 51 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with heptyl BiOX (**L2**).

The crude residue was purified by column chromatography (silica gel, 60–100% EtOAc/hexanes)

to yield **3q** (35.8 mg, 55% yield) in 0% ee as a colorless oil.

$R_f = 0.3$ (silica gel, 80% EtOAc/DCM, UV).

$[\alpha]_D^{25} = -1.5^\circ$ ($c = 1.89$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 8.35 (d, $J = 2.3$ Hz, 1H), 7.77 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.43 (ddd, $J = 8.2, 2.3, 0.7$ Hz, 1H), 7.07 (dd, $J = 2.8, 1.7$ Hz, 1H), 7.02 (dd, $J = 3.9, 1.7$ Hz, 1H), 6.65 (q, $J = 7.2$ Hz, 1H), 6.24 (dd, $J = 3.9, 2.7$ Hz, 1H), 3.78 – 3.70 (m, 5H), 3.70 – 3.62 (m, 2H), 1.95 – 1.87 (m, 4H), 1.84 (d, $J = 7.2$ Hz, 3H).

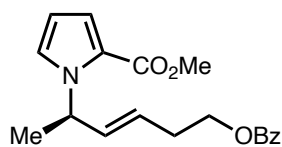
^{13}C NMR (101 MHz, CDCl_3): δ 166.2, 161.6, 153.5, 146.1, 140.0, 134.4, 125.1, 124.0, 122.2, 119.1, 109.2, 53.5, 51.2, 49.3, 47.0, 26.8, 24.1, 22.0.

FTIR (NaCl, thin film, cm^{-1}): 2967, 2876, 1702, 1625, 1436, 1339, 1237, 1212, 1111, 1022, 736.

HRMS (FAB, m/z): calc'd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 328.1656 ; found: 328.1657.

Chiral SFC: (OD-H, 2.5 mL/min, 30% IPA in CO_2 , ($\lambda = 254$ nm): t_R (major) = 3.3 min, t_R (major) = 3.7 min.

methyl (*R,E*)-1-(6-(benzoyloxy)hex-3-en-2-yl)-1*H*-pyrrole-2-carboxylate (3r**):** Prepared from



(*E*)-4-bromobut-3-en-1-yl benzoate (**2r**, 51.0 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure 2 in 2-MeTHF with 4-heptyl BiOX (**L2**). The crude residue was purified by column chromatography (silica gel, 10% EtOAc/hexanes) to yield **3r** (18.2 mg, 28% yield) in 83% ee as a colorless oil.

$R_f = 0.29$ (silica gel, 10% EtOAc/DCM, UV).

$[\alpha]_D^{21} = 21^\circ$ ($c = 1.0$, CHCl_3).

¹H NMR (500 MHz, CDCl₃): δ 8.06 – 7.96 (m, 2H), 7.60 – 7.52 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 6.98 – 6.92 (m, 2H), 6.14 – 6.07 (m, 1H), 6.01 – 5.93 (m, 1H), 5.80 (ddt, *J* = 15.5, 5.6, 1.4 Hz, 1H), 5.58 (dtd, *J* = 15.3, 6.9, 1.5 Hz, 1H), 4.35 (td, *J* = 6.6, 1.2 Hz, 2H), 3.79 (s, 3H), 2.51 (q, *J* = 6.7 Hz, 2H), 1.51 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 166.6, 161.8, 134.4, 133.1, 130.4, 129.7, 128.5, 127.0, 125.1, 121.5, 118.3, 108.4, 64.0, 53.3, 51.1, 31.9, 21.3.

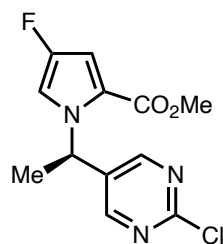
FTIR (NaCl, thin film, cm⁻¹): 2953, 1715, 1437, 1411, 1378, 1338, 1274, 1227, 1107, 1026, 970, 713.

HRMS (FD⁺, *m/z*): calc'd for C₁₉H₂₁NO₄ [*M*+•]⁺ : 327.1465; found: 327.1479.

Chiral SFC: (OJ-H, 2.5 mL/min, 15% IPA in CO₂, (λ = 254 nm): *t_R* (minor) = 2.8 min, *t_R* (major) = 3.2 min.

Characterization of Reaction Products – Nucleophile Scope

methyl (R)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-4-fluoro-1*H*-pyrrole-2-carboxylate (5a):



Prepared from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 4-fluoro-1-(1-(trifluoro-λ⁴-boranethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**4a**, 83.1 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 5–30% EtOAc/hexanes) to yield **5a** (35.4 mg, 62% yield) in 97% ee as a colorless oil.

R_f = 0.47 (silica gel, 30% EtOAc/hexanes, UV).

[α]_D²¹ = 84° (*c* = 1.8, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.36 (d, *J* = 0.6 Hz, 2H), 6.87 (dd, *J* = 3.3, 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.64 – 6.52 (m, 1H), 3.75 (s, 3H), 1.82 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.1 (d, *J* = 2.9 Hz), 160.7, 157.6, 151.0 (d, *J* = 243.5 Hz), 134.9, 118.7 (d, *J* = 5.8 Hz), 109.2 (d, *J* = 28.0 Hz), 105.7 (d, *J* = 15.3 Hz), 51.7, 51.3, 21.4.

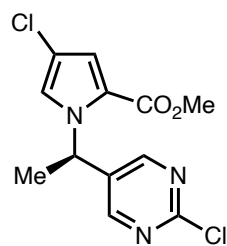
¹⁹F NMR (282 MHz, CDCl₃): δ -165.22 (dd, *J* = 3.3, 1.6 Hz).

FTIR (NaCl, thin film, cm⁻¹): 3139, 2954, 1708, 1574, 1549, 1474, 1440, 1399, 1295, 1242, 1174, 1160, 1095, 1008, 773.

HRMS (FAB, *m/z*): calc'd for C₁₂H₁₂ClN₃O₂F [M+H]⁺ : 284.0597 ; found: 284.0601.

Chiral SFC: (IC, 2.5 mL/min, 15% IPA in CO₂, λ = 254 nm): *t_R* (minor) = 7.8 min, *t_R* (major) = 8.6 min.

methyl (R)-4-chloro-1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrrole-2-carboxylate (5b):



Prepared from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.1 mmol) and methyl 4-chloro-1-(1-(trifluoro-λ⁴-boranethyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**4b**, 44 mg, 0.15 mmol) according to General Procedure B in *i*-PrOAc with 4-F-Ph BiOX (**L1**). The crude residue was purified by column

chromatography (silica gel, 5–30% EtOAc/hexanes) to yield **5b** (11.1 mg, 37% yield) in 95% ee as white solid.

R_f = 0.52 (silica gel, 30% EtOAc/hexanes, UV).

[α]_D²¹ = 2.3° (c = 0.54, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.38 (d, *J* = 0.6 Hz, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.57 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 1.84 (d, *J* = 7.3 Hz, 3H).

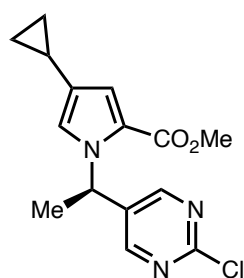
¹³C NMR (101 MHz, CDCl₃): δ 160.82, 160.79, 157.67, 134.64, 121.86, 121.75, 118.41, 113.69, 51.73, 51.67, 21.56.

FTIR (NaCl, thin film, cm⁻¹): 2924, 2357, 1706, 1550, 1456, 1436, 1399, 1347, 1233, 1181, 1085, 944, 775.

HRMS (ESI-TOF, m/z): calc'd for C₁₂H₁₂Cl₂N₃O₂ [M+H]⁺ : 300.0301 ; found: 300.0293.

Chiral SFC: (AD-H, 2.5 mL/min, 15% IPA in CO₂, (λ = 210 nm): *t*_R (minor) = 3.0 min, *t*_R (major) = 3.3 min.

methyl (R)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-4-cyclopropyl-1*H*-pyrrole-2-carboxylate



(5c): Prepared from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 4-cyclopropyl-1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**5c**, 89.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-Ph BiOX (**L1**). The crude residue was

purified by column chromatography (silica gel, 10% EtOAc/PhMe) to yield **5c** (41.2 mg, 67% yield) in 97% ee as a colorless oil.

R_f = 0.49 (silica gel, 20% EtOAc/hexanes, UV).

[α]_D²² = 24° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.53 (q, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 1.83 (d, *J* = 7.3 Hz, 3H), 1.76 – 1.62 (m, 1H), 0.91 – 0.76 (m, 2H), 0.56 – 0.44 (m, 2H).

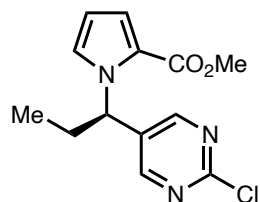
¹³C NMR (101 MHz, CDCl₃): 161.5, 160.4, 157.7, 135.5, 128.2, 121.7, 121.7, 116.7, 51.3, 51.0, 21.5, 8.2, 8.1, 7.8.

FTIR (NaCl, thin film, cm⁻¹): 2950, 1699, 1549, 1439, 1401, 1340, 1238, 1105, 980, 830, 677.

HRMS (ESI-TOF, m/z): C₁₅H₁₇N₃O₂Cl; cal'd for [M+H]⁺: 306.1004, found: 306.0992.

Chiral SFC: (IC, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): t_R (minor) = 3.3 min, t_R (major) = 5.8 min.

methyl (*R*)-1-(1-(2-chloropyrimidin-5-yl)propyl)-1*H*-pyrrole-2-carboxylate (5d**):** Prepared



from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boraneryl)propyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**4d**, 81.9 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF

with 4-F-Ph BiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 9% EtOAc/hexanes) to yield **5d** (35.6 mg, 64% yield) in 95% ee as a colorless oil.

R_f = 0.56 (silica gel, 20% EtOAc/hexanes, UV).

$[\alpha]_D^{22}$ = 71° (c = 1.0, CHCl₃).

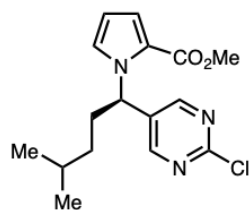
¹H NMR (400 MHz, CDCl₃): δ 8.41 (s, 2H), 7.10 (dd, J = 2.8, 1.7 Hz, 1H), 7.00 (dd, J = 4.0, 1.7 Hz, 1H), 6.36 (dd, J = 9.0, 6.9 Hz, 1H), 6.27 (dd, J = 4.0, 2.8 Hz, 1H), 3.76 (s, 3H), 2.37 – 2.08 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.7, 160.6, 158.2, 134.2, 124.4, 122.5, 119.2, 110.0, 57.1, 51.4, 28.5, 11.0.

FTIR (NaCl, thin film, cm⁻¹): 2972, 1698, 1579, 1549, 1439, 1400, 1338, 1227, 1155, 1109, 1070, 851, 744.

HRMS (ESI-TOF, m/z): C₁₃H₁₅N₃O₂Cl; cal'd for [M+H]⁺: 280.0847, found: 280.0842.

Chiral SFC: (IC, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): t_R (minor) = 4.0 min, t_R (major) = 4.4 min.

Methyl (R)-1-(1-(2-chloropyrimidin-5-yl)-4-methylpentyl)-1*H*-pyrrole-2-carboxylate (5e):

Prepared according to General Procedure B from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 1-(3-methyl-1-(trifluoro- λ 4-boraneyl)butyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**4e**,

77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-PhBiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 2% to 10% EtOAc/hexanes) to yield **5e** (36.0 mg, 58% yield) in 88% ee as a colorless oil.

R_f = 0.26 (silica gel, 20% EtOAc/hexanes, UV and p-anisaldehyde (yellow)).

= -131.5° (c = 0.1, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.45 – 8.38 (m, 2H), 7.11 (dd, J = 2.8, 1.7 Hz, 1H), 7.00 (dd, J = 3.9, 1.7 Hz, 1H), 6.42 (dd, J = 9.0, 6.9 Hz, 1H), 6.27 (dd, J = 4.0, 2.7 Hz, 1H), 3.76 (s, 3H), 2.30 – 2.16 (m, 1H), 2.16 – 2.01 (m, 1H), 1.67 – 1.52 (m, J = 6.7 Hz, 1H), 1.24 – 1.15 (m, 2H), 0.88 (dd, J = 6.6, 4.3 Hz, 6H).

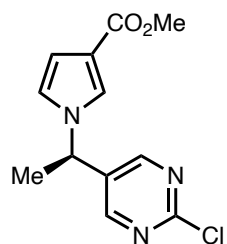
¹³C NMR (101 MHz, CDCl₃): δ 161.71, 160.52, 158.18, 134.43, 124.37, 122.41, 119.23, 109.98, 55.78, 51.36, 35.31, 33.23, 27.87, 22.61, 22.41.

FTIR (NaCl, thin film, cm⁻¹): 2955, 1699, 1546, 1456, 1437, 1398, 1364, 1336, 1225, 1153, 1107, 1079, 865, 828, 810.

HMRS (ESI-TOF, m/z): calc'd for C₁₆H₂₁ClN₃O₂: [M+H]⁺: 322.1317; found 322.1332

Chiral SFC: (OJ-H, 5 mL/min, 7% IPA in CO₂, λ = 210 nm): t_R (minor) = 4.0 min, t_R (major) = 3.5 min.

methyl (*R*)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrrole-3-carboxylate (5f**):** Prepared from



5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrole-3-carboxylate, potassium salt (**4f**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-heptyl BiOX (**L2**). The crude residue was purified by column chromatography

(silica gel, 30% EtOAc/hexanes) to yield **5f** (41.2 mg, 78% yield) in 66% ee as a colorless oil.

R_f = 0.50 (silica gel, 50% EtOAc/hexanes, UV).

$[\alpha]_D^{22} = -13^\circ$ ($c = 1.0$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 8.34 (d, $J = 0.6$ Hz, 2H), 7.39 (t, $J = 1.9$ Hz, 1H), 6.70 – 6.63 (m, 2H), 5.33 (q, $J = 7.1$ Hz, 1H), 3.81 (s, 3H), 1.91 (d, $J = 7.1$ Hz, 3H).

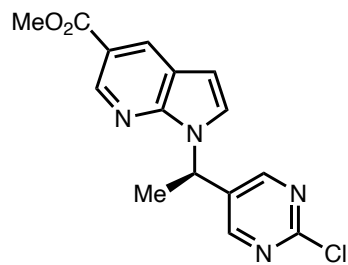
^{13}C NMR (101 MHz, CDCl_3): δ 164.9, 161.3, 157.5, 134.2, 124.2, 120.4, 117.3, 111.5, 54.3, 51.4, 21.4.

FTIR (NaCl, thin film, cm^{-1}): 2950, 1698, 1538, 1398, 1158, 994, 826, 762.

HRMS (ESI-TOF, m/z): $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2\text{Cl}$; cal'd for $[\text{M}+\text{H}]^+$: 266.0691, found: 266.0703.

Chiral SFC: (AD-H, 2.5 mL/min, 25% IPA in CO_2 , ($\lambda = 280$ nm): t_R (minor) = 3.0 min, t_R (major) = 3.2 min.

methyl (*R*)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate



(5g**):** Prepared from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate, potassium salt (**4g**, 93.0 mg, 0.3 mmol) according to General Procedure B in CPME with 4-heptyl

BiOX (**L2**) and 1.0 mol % [Ir]. Internal NMR standard 1,1,2,2-tetrachloroethane (21.0 mg) was

added, and the yield was calculated by ^1H NMR (59% yield **5g**). The crude material was purified by column chromatography (silica, 1.1% MeOH/DCM). The resulting colorless oil was purified by prep TLC (1.5% MeOH/DCM). The middle of the band containing product was collected, and purified again by prep TLC (40% Et₂O/PhMe) to afford 0.9 mg **5g** (95% ee).

R_f = 0.28 (silica gel, 1.5% MeOH/DCM, UV).

$[\alpha]_D^{21}$ = 190° (c = 0.3, CHCl₃).

^1H NMR (500 MHz, CDCl₃): δ 8.96 (s, 1H), 8.60 (s, 1H), 8.53 (s, 2H), 7.35 (d, *J* = 3.5 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 6.38 – 6.26 (m, 1H), 3.97 (s, 3H), 2.09 – 1.96 (m, 3H).

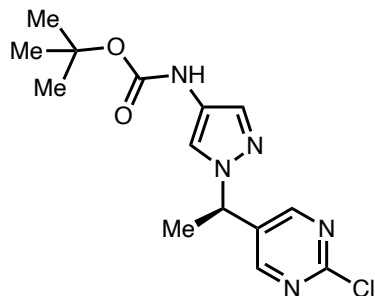
^{13}C NMR (101 MHz, CDCl₃): δ 167.0, 160.9, 158.1, 149.0, 145.5, 134.0, 131.6, 125.6, 120.1, 119.6, 103.1, 52.3, 48.6, 20.0.

FTIR (NaCl, thin film, cm⁻¹): 2922, 1716, 1602, 1576, 1549, 1404, 1315, 1210, 1162, 937, 730.

HRMS (ESI-TOF, *m/z*): C₁₅H₁₄N₄O₂Cl; cal'd for [M+H]⁺: 317.0800, found: 317.0805.

Chiral SFC: (OJ-H, 2.5 mL/min, 30% IPA in CO₂, λ = 280 nm): *t_R* (major) = 3.6 min, *t_R* (minor) = 4.0 min.

***tert*-butyl (*R*)-(1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrazol-4-yl)carbamate (**5h**):** Prepared



from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and *tert*-butyl (1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrrol-3-yl)carbamate, potassium salt (**4h**, 95.1 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-heptyl BiOX (**L2**). The crude residue was purified by column chromatography (silica gel,

30/20/50 EtOAc/DCM/hexanes) to yield **5h** (45.6 mg, 70% yield) in 80% ee as a white solid. The

white solid was dissolved in minimal CHCl₃ and filtered through a cotton-plugged pipette into a 1-dram vial. The vial was equipped with a septum cap that was punctured with a 21G needle. This vial was then placed in a sealed jar with pentane and allowed to crystallize over 4 days. A single crystal was analyzed by X-ray diffraction to confirm the structure and assign absolute stereochemistry.

R_f = 0.4.6 (silica gel, 50% EtOAc/hexanes, UV).

Melting point = 149–150 °C.

[α]_D²² = −7° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.46 (s, 2H), 7.82 (s, 1H), 7.35 (s, 1H), 6.29 (s, 1H), 5.44 (q, J = 7.1 Hz, 1H), 1.92 (d, J = 7.1 Hz, 3H), 1.49 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): δ 161.0, 157.9, 153.0, 134.0, 130.8, 122.5, 118.7, 80.9, 56.7, 28.4, 20.8.

FTIR (NaCl, thin film, cm⁻¹): 2954, 1700, 1598, 1550, 1399, 1249, 1164, 772, 676.

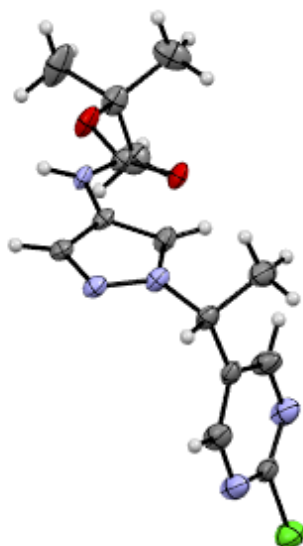
HRMS (ESI-TOF, m/z): C₁₄H₁₉N₅O₂Cl; cal'd for [M+H]⁺: 324.1222, found: 324.1240.

Chiral SFC: (AD-H, 2.5 mL/min, 35% IPA in CO₂, λ = 254 nm): *t_R* (major) = 1.9 min, *t_R* (minor) = 2.3 min.

Low-temperature diffraction data (ϕ - and ω -scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu *K_α* radiation (λ = 1.54178 Å) from an I μ S micro-source for the structure of compound **5h**. The structure was solved by direct methods using SHELXS⁴⁷ and refined against *F*² on all data by full-matrix least squares with SHELXL-2017⁴⁸ using established refinement techniques.⁴⁹ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of

all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

Compound **5g** crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. The coordinates for the hydrogen atoms bound to N5 and N25 were located in the difference Fourier synthesis and refined semi-freely with the help of a restraint on the N-H distance (0.88(4) Å).

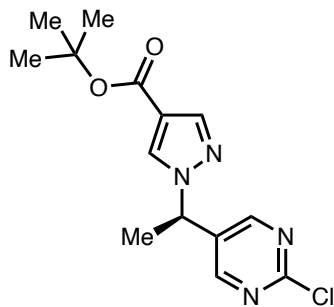


Crystal data and structure refinement for 5h.

Identification code	V21273
CCDC deposition number	2121889
Empirical formula	C ₂₈ H ₃₆ N ₁₀ O ₄ Cl ₂
Formula weight	647.57
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
<i>a</i> /Å	9.4715(9)
<i>b</i> /Å	13.2722(10)

$c/\text{\AA}$	13.5160(13)
$\alpha/^\circ$	90
$\beta/^\circ$	105.965(6)
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	1633.5(3)
Z	2
$\rho_{\text{calc}}/\text{cm}^3$	1.317
μ/mm^{-1}	2.200
$F(000)$	680.0
Crystal size/ mm^3	$0.15 \times 0.1 \times 0.05$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54178$)
2Θ range for data collection/ $^\circ$	6.802 to 148.614
Index ranges	$-11 \leq h \leq 11, -16 \leq k \leq 16, -16 \leq l \leq 16$
Reflections collected	41899
Independent reflections	6561 [$R_{\text{int}} = 0.0397, R_{\text{sigma}} = 0.0243$]
Data/restraints/parameters	6561/3/411
Goodness-of-fit on F^2	1.040
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0380, wR_2 = 0.1007$
Final R indexes [all data]	$R_1 = 0.0395, wR_2 = 0.1025$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.80/-0.41
Flack parameter	-0.007(4)

***tert*-butyl (*R*)-1-(1-(2-chloropyrimidin-5-yl)ethyl)-1*H*-pyrazole-4-carboxylate (**5i**):** Prepared



from 5-bromo-2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and *tert*-butyl 1-(1-(trifluoro- λ^4 -boraneyl)ethyl)-1*H*-pyrazole-4-carboxylate, potassium salt (**4i**, 90.6 mg, 0.3 mmol) according to General Procedure B in CPME with 4-heptyl BiOX (**L2**) and 1.0 mol % [Ir]. The crude residue was purified by column chromatography (silica gel,

5–25% EtOAc/DCM) to yield **5i** (28.3 mg, 46% yield) in 83% ee as a yellow oil.

R_f = 0.43 (silica gel, 20% EtOAc/DCM, UV).

$[\alpha]_D^{21} = -2^\circ$ ($c = 1.0$, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.52 (s, 2H), 7.93 (d, $J = 0.6$ Hz, 1H), 7.91 – 7.86 (m, 1H), 5.52 (q, $J = 7.1$ Hz, 1H), 1.96 (d, $J = 7.1$ Hz, 3H), 1.54 (s, 9H).

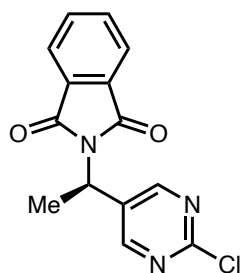
¹³C NMR (101 MHz, CDCl₃): δ 162.11, 161.35, 157.99, 141.98, 133.15, 131.19, 117.65, 81.15, 56.99, 29.85, 28.42, 21.04.

FTIR (NaCl, thin film, cm⁻¹): 2979, 2927, 1710, 1552, 1401, 1253, 1164, 1001, 832, 770.

HRMS (ESI-TOF, *m/z*): calc'd for C₁₄H₁₈ClN₄O₂ [M+H]⁺ : 309.1113 ; found: 309.1122.

Chiral SFC: (IC, 2.5 mL/min, 30% IPA in CO₂, $\lambda = 210$ nm): t_R (minor) = 3.0 min, t_R (major) = 4.0 min.

(*R*)-2-(1-(2-chloropyrimidin-5-yl)ethyl)isoindoline-1,3-dione (5j**):** Prepared from 5-bromo-2-



chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and 2-(1-(trifluoro- λ^4 -boraneyl)ethyl)isoindoline-1,3-dione, potassium salt (**4j**, 84.3 mg, 0.3 mmol) according to General Procedure B in 1,2-DME with 4-F-Ph BiOX (**L1**). 2.0 mg ethylene carbonate added, and the ^1H NMR was calculated (25% yield

5j). The crude residue was purified by column chromatography (silica gel, 20–40% EtOAc/hexanes). The material was then repurified by prep TLC (5% EtOAc/DCM) to afford **5j** as a white solid (77% ee).

R_f = 0.4 (silica gel, 30% EtOAc/hexanes, UV).

$[\alpha]_D^{21}$ = 65° (c = 0.37, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, J = 0.5 Hz, 2H), 7.91 – 7.79 (m, 2H), 7.79 – 7.69 (m, 2H), 5.67 – 5.49 (m, 1H), 1.94 (d, J = 7.4 Hz, 3H).

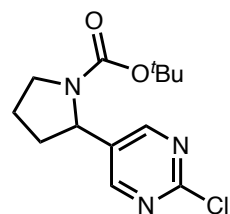
^{13}C NMR (101 MHz, CDCl_3): δ 167.71, 160.96, 159.27, 134.60, 132.16, 131.67, 123.74, 44.90, 17.13.

FTIR (NaCl, thin film, cm^{-1}): 2924, 1774, 1712, 1550, 1400, 1382, 1160, 1030, 878, 771, 723.

HRMS (ESI-TOF, m/z): calc'd for $\text{C}_{14}\text{H}_{11}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 288.0534 ; found: 288.0543.

Chiral SFC: IC, 2.5 mL/min, 35% MeCN in CO_2 , λ = 254 nm): t_R (minor) = 3.3 min, t_R (major) = 4.0 min.

***tert*-butyl 2-(2-chloropyrimidin-5-yl)pyrrolidine-1-carboxylate (**5k**):** Prepared from 5-bromo-



2-chloropyrimidine (**2a**, 38.7 mg, 0.2 mmol) and potassium (1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)trifluoroborate (**4k**, 83 mg, 0.3 mmol) according to General Procedure B in *tert*-butyl methyl ether with heptyl BiOX

(**L2**) with modifications to the work-up. A 50% (v:v) aqueous solution of trifluoroacetic acid (6 equiv, 92 μ L, 137 mg, 1.2 mmol) was added to the reaction with vigorous agitation upon reaction completion. The resulting biphasic mixture was diluted with water (1 mL) after 0.5 h following hydrolysis of the ligand (as determined by SFC analysis). The layers were separated, the organic phase washed with brine (1 mL), the layers separated, the organic phase dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (silica gel, 0 to 30% EtOAc/hexanes) to yield **5k** (37 mg, 65% yield, mixture of rotamers 1.1:1 A:B) in 92% *ee* as a white solid.

R_f = 0.21 (silica gel, 30% EtOAc/hexanes, UV).

$[\alpha]_{589}^{25} = 90^\circ$ ($c = 1.0$, CHCl_3).

m.p.: 101-102 $^\circ\text{C}$.

^1H NMR (500 MHz, CDCl_3): δ 8.47 (br. s, 4H, A+B), 4.91 (br. m, 1H, B), 4.77 (br. m, 1H, A), 3.75-3.45 (br. m, 4H, A+B), 2.41 (br. m, 2H, A+B), 2.02-1.88 (br. m, 4H, A+B), 1.84 (br. m, 2H, A+B), 1.44 (br. s, 9H, B), 1.26 (br. s, 9H, A).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 160.04 (A+B), 157.58 (A+B), 154.59 (B), 154.00 (A), 136.62 (A), 135.74 (B), 80.63 (A), 80.55 (B), 56.85 (A), 56.52 (B), 47.38 (B), 47.25 (A), 35.71 (A), 34.37 (B), 28.50 (B), 28.41 (A), 24.03 (B), 23.54 (A).

FT-IR (KBr, thin film, cm^{-1}): 2970, 1688, 1681, 1580, 1551, 1390, 1365, 1149, 1114, 899, 873, 773.

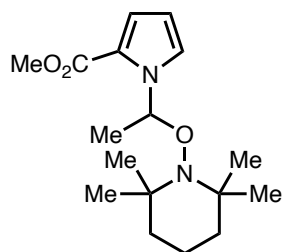
HRMS (ESI-TOF, m/z): calc'd for $\text{C}_{13}\text{H}_{19}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 284.1160; found: 284.1169.

Chiral SFC: (Chiralpak IC-3, 3.0 mL/min, 1 to 40% IPA over 5 min. in CO_2 (2900 psi; 45 $^\circ\text{C}$ column temp.; $\lambda = 210$ nm): t_R (ligand **L2**) = 3.2 min; t_R (minor) = 3.6 min, t_R (major) = 3.8 min.

Radical Trapping with TEMPO

The reactions were conducted according to General Procedure B on 0.5 mmol scale using 5-bromo-2-chloropyrimidine (**2a**, 9.7 mg, 0.05 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 19.4 mg, 0.075 mmol) in 2-MeTHF with 4-F-Ph BiOX (**L1**). TEMPO (11.7 mg, 0.075 mmol, 1.5 equiv) was added to the vial before stock solutions of [Ir] and [Ni]. After workup as described in General Procedure B, 0.025 mmol 1,1,2,2-tetrachloroethane was added to the reaction as an internal standard. ¹H-NMR yields of **3a** was determined relative to this internal standard. An aliquot of the reaction was purified by preparative TLC (10% EtOAc/PhMe) and analyzed by SFC to determine ee, using the method described above for **3a**. An additional aliquot of the reaction was purified by preparative TLC (10% EtOAc/hexanes) to isolate TEMPO adduct **S1**.

methyl 1-(1-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethyl)-1*H*-pyrrole-2-carboxylate (**S1**)



R_f = 0.46 (silica gel, 10% EtOAc/hexanes, UV).

¹H NMR (500 MHz, CDCl₃): δ 7.18 (t, J = 2.3 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.18 (dd, J = 3.8, 2.7 Hz, 1H), 3.82 (s, 3H), 1.64 (d, J = 6.2 Hz, 3H), 1.56 – 1.21 (m, 9H), 1.15 (s, 3H), 0.98 (s, 3H), 0.35 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 161.9, 124.7, 122.1, 117.5, 109.1, 88.0, 60.7, 59.2, 51.2, 40.6, 40.2, 33.6, 31.1, 29.9, 22.6, 20.2, 17.2.

FTIR (NaCl, thin film, cm⁻¹): 2934, 1698, 1435, 1410, 1346, 1278, 1231, 1210, 1134, 1108, 1067, 930.

HRMS (FD+, m/z): calc'd for C₁₇H₂₈N₂O₃ [M+•]⁺ : 308.2094 ; found: 308.2109.

1.5.6 Non-Heteroaryl Bromide Clustering Analysis

1.5.6.1 Clustering Workflow

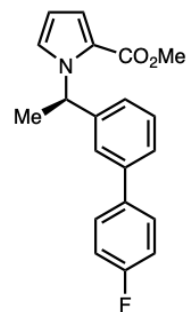
To analyze the non-heteroaryl bromide substrate scope, we followed the workflow developed by Doyle and coworkers.⁹ We performed dimensionality reduction and clustering analysis using the dataset, molecular similarity construction, clustering workflow as presented in the Doyle Supporting Information. The centermost non-heteroaryl bromides were selected for scope evaluation from each of the fifteen clusters, shown below (**Figure S3**). We note that aryl bromides **3l**, **3m**, **3n**, and **3p** from the initial scope studies were found in the Doyle dataset and identified in 2 of 15 clusters.

The code used for this analysis can be found at:

<https://colab.research.google.com/drive/1YE2OAA1KDg1uBYR3rc5BPhyCXjuov5Nk>

1.5.6.2 Characterization of Products

methyl (R)-1-(1-(4'-fluoro-[1,1'-biphenyl]-3-yl)ethyl)-1H-pyrrole-2-carboxylate (7b):



Prepared according to General Procedure B from 3-bromo-4'-fluoro-1,1'-biphenyl (**6b**, 50.2 mg, 0.2 mmol) and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1H-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-PhBiOX (**L1**). The crude residue was

purified by column chromatography (silica gel, 2% to 10% EtOAc/hexanes) to yield **7b** (9.7 mg, 15% yield) in 83% ee as a colorless oil.

R_f = 0.75 (silica gel, 30% EtOAc/hexanes, UV and p-anisaldehyde (yellow)).

$[\alpha]_D^{24}$ = 63° (c=0.55, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.55 – 7.41 (m, 2H), 7.38 (dt, *J* = 15.2, 7.7 Hz, 2H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.15 – 7.03 (m, 4H), 7.01 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.66 (q, *J* = 7.1 Hz, 1H), 6.20 (dd, *J* = 3.9, 2.7 Hz, 1H), 3.77 (d, *J* = 0.7 Hz, 3H), 1.84 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 162.6 (d, *J* = 246.4 Hz), 161.7, 143.8, 140.7, 137.2 (d, *J* = 3.2 Hz), 129.2, 128.9 (d, *J* = 8.0 Hz), 126.2, 125.6, 125.2, 125.1, 122.3, 118.7, 115.8 (d, *J* = 21.5 Hz), 108.7, 55.5, 51.2, 22.4.

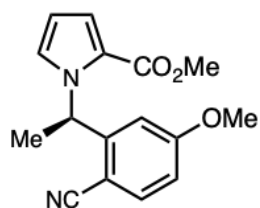
¹⁹F NMR (376 MHz, CDCl₃) δ -115.7.

FTIR (NaCl, thin film, cm⁻¹): 2977, 1697, 1513, 1483, 1410, 1341, 1233, 1207, 1158, 1113, 796.

HMRS (ESI-TOF, m/z): calc'd for C₂₀H₁₉FNO₂: [M+H]⁺: 324.1394; found 324.1408.

Chiral SFC: (AD-H, 8 mL/min, 20% IPA in CO₂, λ = 254 nm): *t*_R (minor) = 2.8 min, *t*_R (major) = 2.6 min.

methyl (*R*)-1-(1-(2-cyano-5-methoxyphenyl)ethyl)-1*H*-pyrrole-2-carboxylate (7d): Prepared



according to General Procedure B from 2-bromo-4-methoxybenzonitrile (**6d**, 42.4 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-PhBiOX (**L1**). The crude

residue was purified by column chromatography (silica gel, 5% to 10% EtOAc/hexanes) to yield **7d** (10.2 mg, 18% yield) in 43% ee as a colorless oil.

*R*_f = 0.45 (silica gel, 30% EtOAc/hexanes, UV and p-anisaldehyde (yellow)).

[α]_D²⁴ = 121° (c = 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 8.6 Hz, 1H), 7.18 (t, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.78 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.66 (q, *J* = 7.1 Hz, 1H), 6.27 (dd, *J* = 3.9, 2.8 Hz, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 3.72 (s, 6H), 1.86 (d, *J* = 7.1 Hz, 3H).

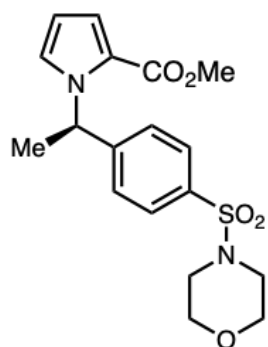
¹³C NMR (101 MHz, CDCl₃) δ 163.4, 160.9, 150.3, 134.9, 124.9, 122.7, 119.3, 117.7, 112.3, 111.3, 108.6, 102.5, 55.4, 55.1, 51.2, 21.6.

FTIR (NaCl, thin film, cm⁻¹): 2987, 2080, 1640, 1460, 1423, 1183, 1106, 818, 755.

HMRS (ESI-TOF, m/z): calc'd for C₁₆H₁₇N₂O₃: [M+H]⁺: 285.1234; found: 285.1237.

Chiral SFC: (AD-H, 5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t_R* (minor) = 4.2 min, *t_R* (major) = 4.6 min.

methyl (R)-1-(1-(4-(morpholinosulfonyl)phenyl)ethyl)-1*H*-pyrrole-2-carboxylate (7e):



Prepared from 4-((4-bromophenyl)sulfonyl)morpholine (**6e**, 61.2 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-PhBiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 0% to 20%

EtOAc/hexanes) to yield **7e** (13.6 mg, 18% yield) in 93% ee as a colorless oil.

R_f = 0.41 (silica gel, 30% EtOAc/hexanes, UV and p-anisaldehyde (yellow)).

[α]_D²³ = -17° (c = 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.64 (q, *J* = 7.2 Hz, 1H), 6.26 (dd, *J* = 3.9, 2.8 Hz, 1H), 3.77 – 3.70 (m, 7H), 2.98 (t, *J* = 4.7 Hz, 4H), 1.84 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 161.6, 149.2, 134.0, 128.4, 126.7, 125.2, 122.3, 119.0, 109.1, 66.2, 55.3, 51.3, 46.1, 22.3.

FTIR (NaCl, thin film, cm⁻¹): 2921, 2853, 2361, 1700, 1654, 1598, 1526, 1453, 1437, 1413, 1377, 1344, 1297, 1261, 1237, 1212, 1191, 1166, 1112, 1070, 1016, 984, 944, 835, 793, 748, 738, 615.

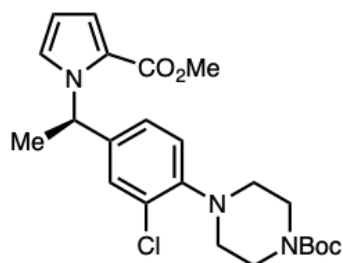
HMRS (ESI-TOF, m/z): calc'd for C₁₈H₂₃N₂O₅S: [M+H]⁺: 379.1322; found 379.1323.

Chiral SFC: (IC, 5 mL/min, 40% IPA in CO₂, λ = 254 nm): *t_R* (minor) = 4.2 min, *t_R* (major) = 4.6 min.

tert-butyl

(*R*)-4-(2-chloro-4-(1-(2-(methoxycarbonyl)-1*H*-pyrrol-1-

yl)ethyl)phenyl)piperazine-1-carboxylate (**7g**): Prepared from *tert*-butyl 4-(4-bromo-2-



chlorophenyl)piperazine-1-carboxylate (**6g**, 75.1 mg, 0.2 mmol) and methyl 1-(1-(trifluoro-λ⁴-boraneyl)ethyl)-1*H*-pyrrole-2-carboxylate, potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in 2-MeTHF with 4-F-PhBiOX (**L1**). The crude residue

was purified by column chromatography (silica gel, 0% to 20% EtOAc/hexanes) to yield **7g** (9.0 mg, 10% yield) in 94% ee as a colorless oil.

R_f = 0.32 (silica gel, 30% EtOAc/hexanes, UV).

[α]_D²³ = -24° (c = 0.5, CHCl₃).

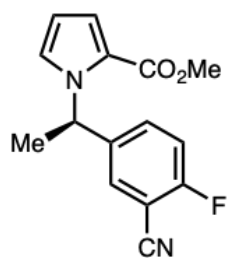
¹H NMR (500 MHz, CDCl₃): δ 7.15, 7.14, 7.00, 6.99, 6.98, 6.98, 6.94, 6.92, 6.55, 6.53, 6.52, 6.51, 6.20, 6.19, 6.18, 3.79, 3.78, 3.63, 3.59, 3.58, 3.57, 2.96, 1.78, 1.76, 1.75, 1.49, 1.47, 1.46, 1.27, 1.26, 1.25, 1.24, 1.22.

^{13}C NMR (101 MHz, CDCl_3): δ 162.8, 154.8, 147.1, 136.1, 129.6, 127.9, 127.2, 123.2, 123.1, 117.6, 117.6, 111.8, 79.3, 58.3, 51.1, 50.0, 45.6, 28.4, 22.2.

FTIR (NaCl, thin film, cm^{-1}): 3178, 3083, 3038, 2967, 2834, 1750, 1583, 1526, 1464, 1413, 1402, 1355, 1217, 1153, 1104, 1020, 833, 712.

HMRS (ESI-TOF, m/z): calc'd for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{ClO}_4$: $[\text{M}+\text{H}]^+$: 448.1998; found 448.1997

Chiral SFC: (IC, 5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): t_R (minor) = 3.3 min, t_R (major) = 4.0 min.



methyl (*R*)-1-(1-(3-cyano-4-fluorophenyl)ethyl)-1*H*-pyrrole-2-carboxylate

(7h): Prepared from 5-bromo-2-fluorobenzonitrile (**6h**, 40.0 mg, 0.2 mmol)

and methyl 1-(1-(trifluoro- λ^4 -boranethyl)-1*H*-pyrrole-2-carboxylate,

potassium salt (**1a**, 77.7 mg, 0.3 mmol) according to General Procedure B in

2-MeTHF with 4-F-PhBiOX (**L1**). The crude residue was purified by column chromatography (silica gel, 0 to 5% EtOAc/hexanes) to yield **7h** (32.7 mg, 60% yield) in 96% ee as a colorless oil.

$[\alpha]_D^{23} = 58^\circ$ ($c = 1.0$, CHCl_3)

$R_f = 0.48$ (silica gel, 30% EtOAc/hexanes, UV and p-anisaldehyde (yellow)).

^1H NMR (500 MHz, CDCl_3): δ 7.39 (ddd, $J = 8.5, 5.1, 2.4$ Hz, 1H), 7.36 – 7.30 (m, 1H), 7.13 (t, $J = 2.2$ Hz, 1H), 7.08 (dd, $J = 4.0, 1.8$ Hz, 1H), 6.61 (q, $J = 7.2$ Hz, 1H), 6.31 (t, $J = 3.3$ Hz, 1H), 3.81 (s, 3H), 1.86 (d, $J = 7.2$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 162.3 (d, $J = 259.0$ Hz), 161.6, 140.9 (d, $J = 3.8$ Hz), 132.9 (d, $J = 8.2$ Hz), 130.8, 124.8, 122.1, 119.2, 116.7 (d, $J = 19.8$ Hz), 114.0, 109.3, 101.7 (d, $J = 15.8$ Hz), 54.4, 51.3, 22.2.

^{19}F NMR (376 MHz, CDCl_3) δ -108.8.

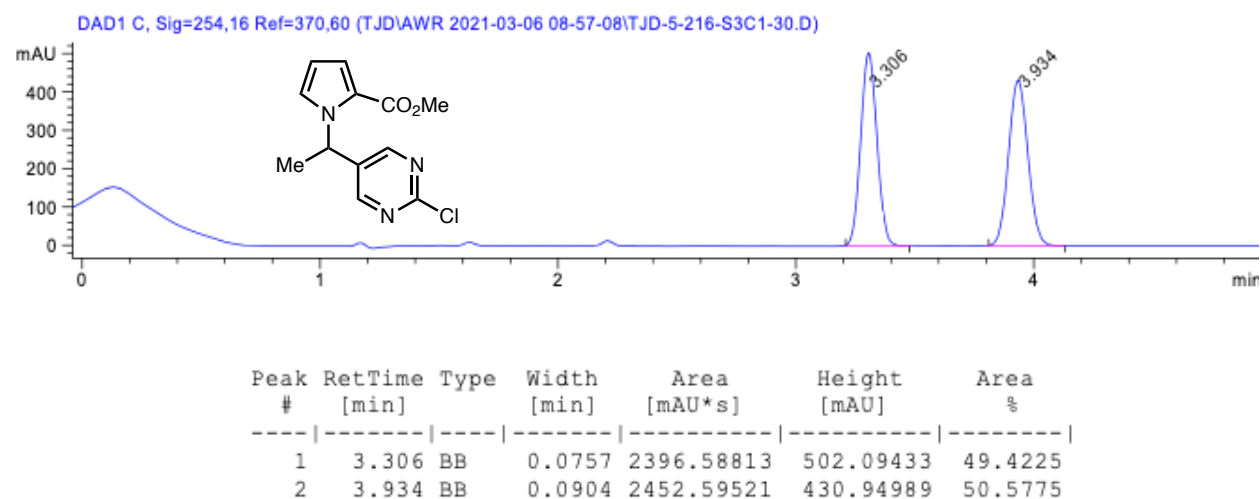
FTIR (NaCl, thin film, cm⁻¹): 3048, 1718, 1587, 1531, 1411, 1210, 1110, 970, 767, 712

HMRS (ESI-TOF, m/z): calc'd for C₁₅H₁₄FN₂O₂: [M+H]⁺: 273.1034; found 273.1032

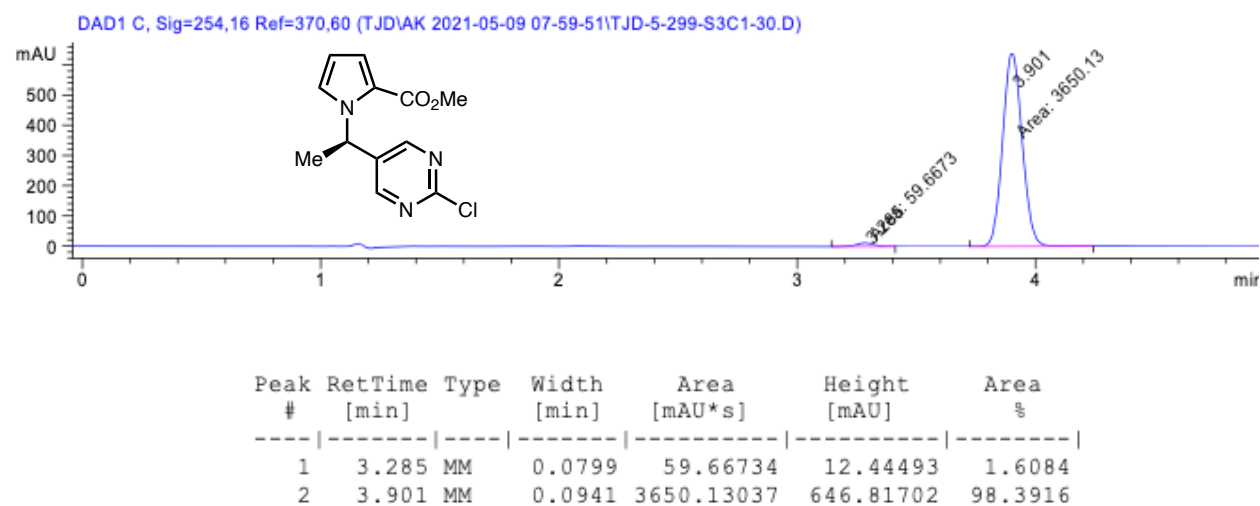
Chiral SFC: (IC, 5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t*_R (minor) = 4.2 min, *t*_R (major) = 3.6 min.

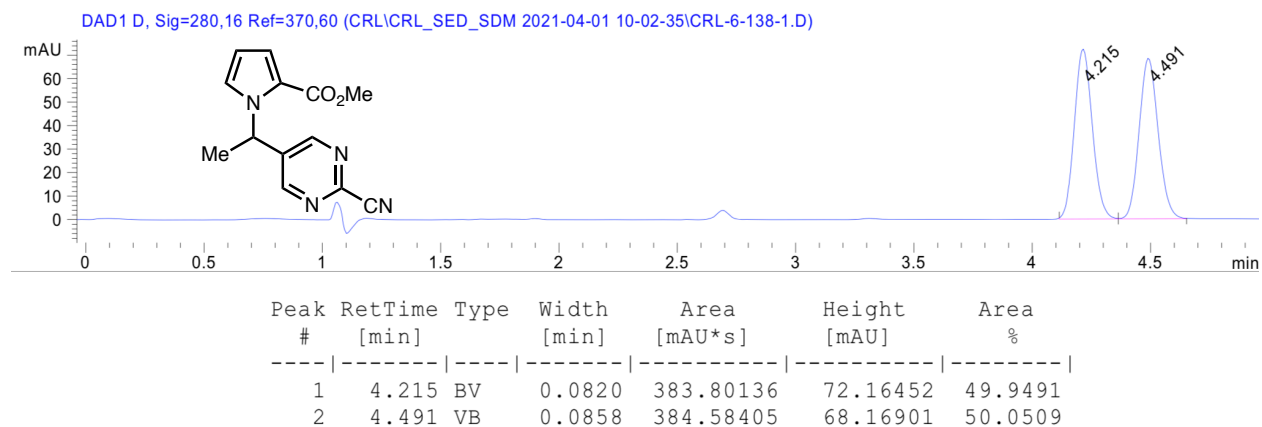
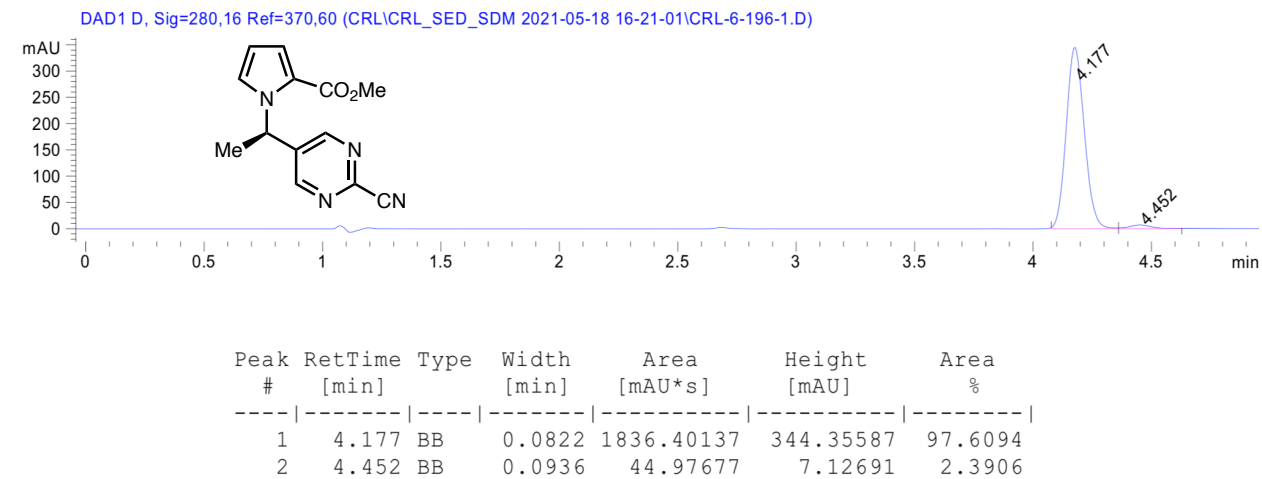
1.6 SFC Traces of Racemic and Enantioenriched Products

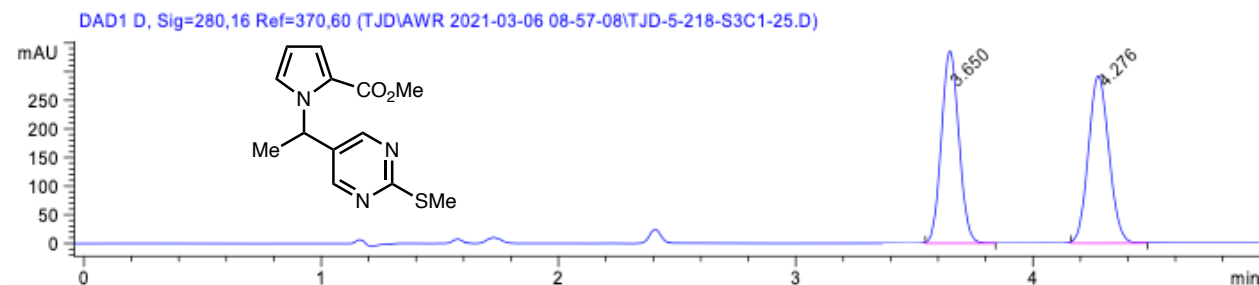
Racemic **3a**:



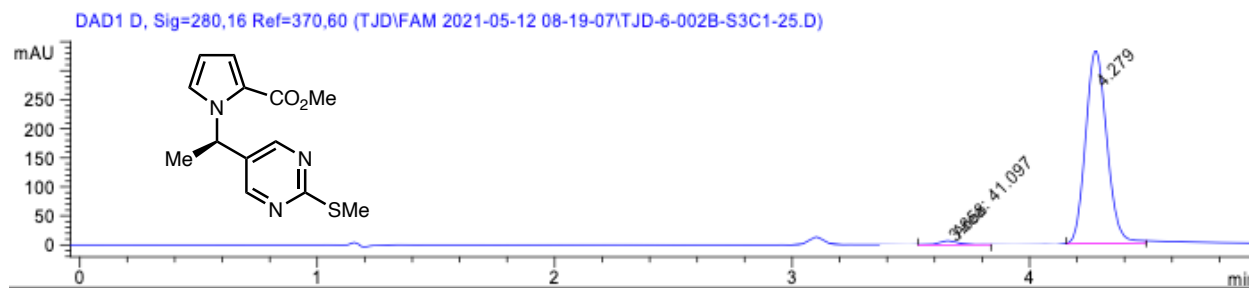
Enantioenriched **3a**:



Racemic **3b**:Enantioenriched **3b**:

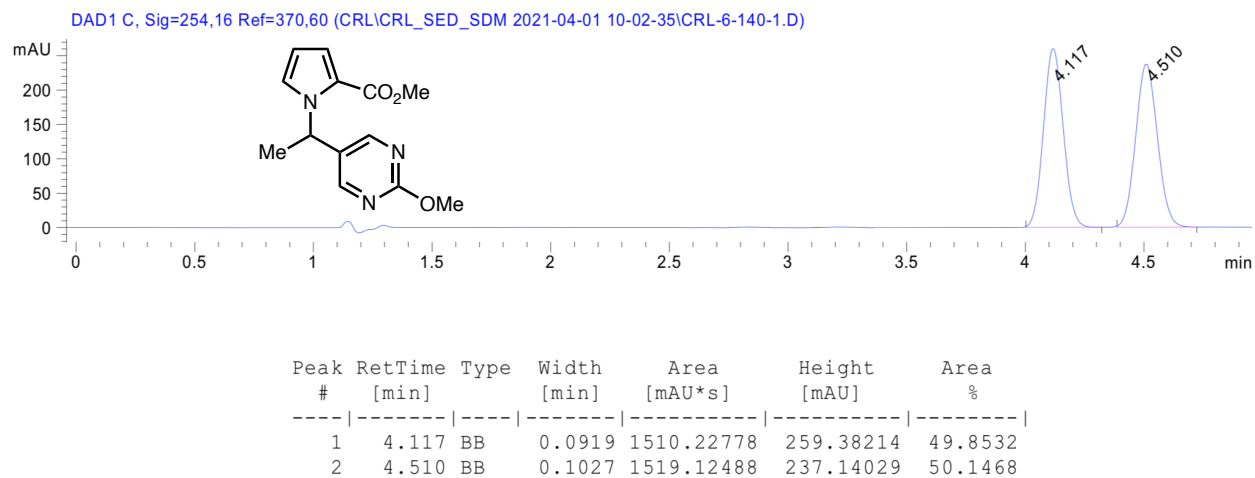
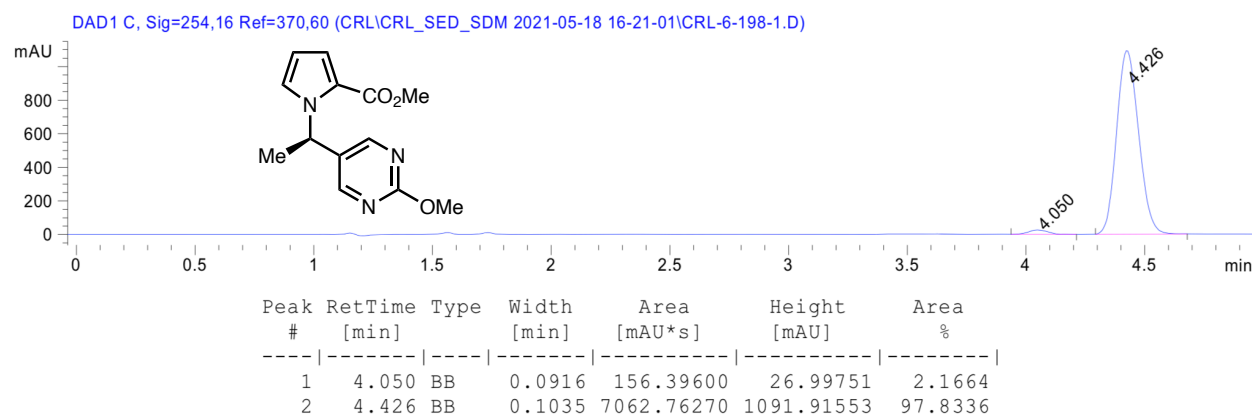
Racemic **3c**:

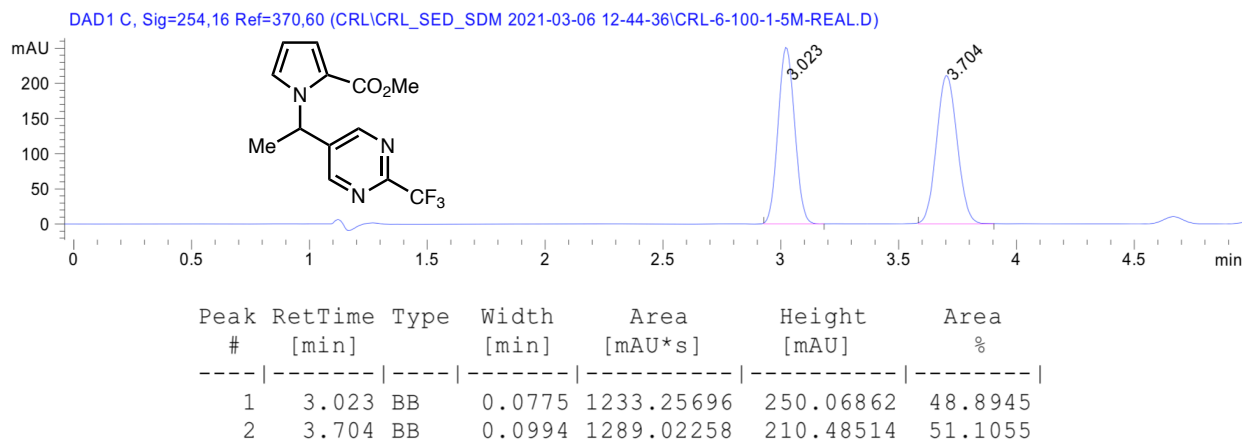
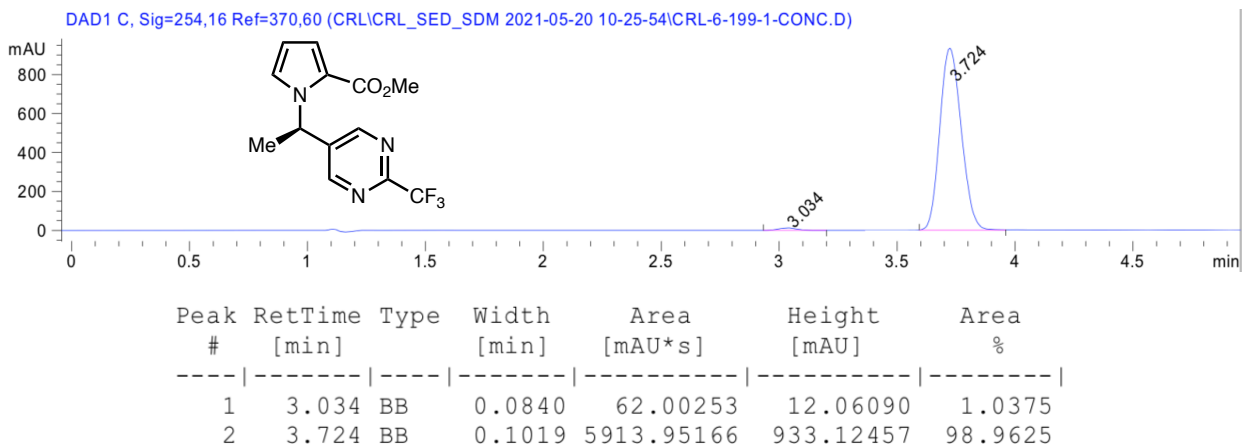
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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2	4.276	BB	0.0944	1758.11243	291.36157	50.5398

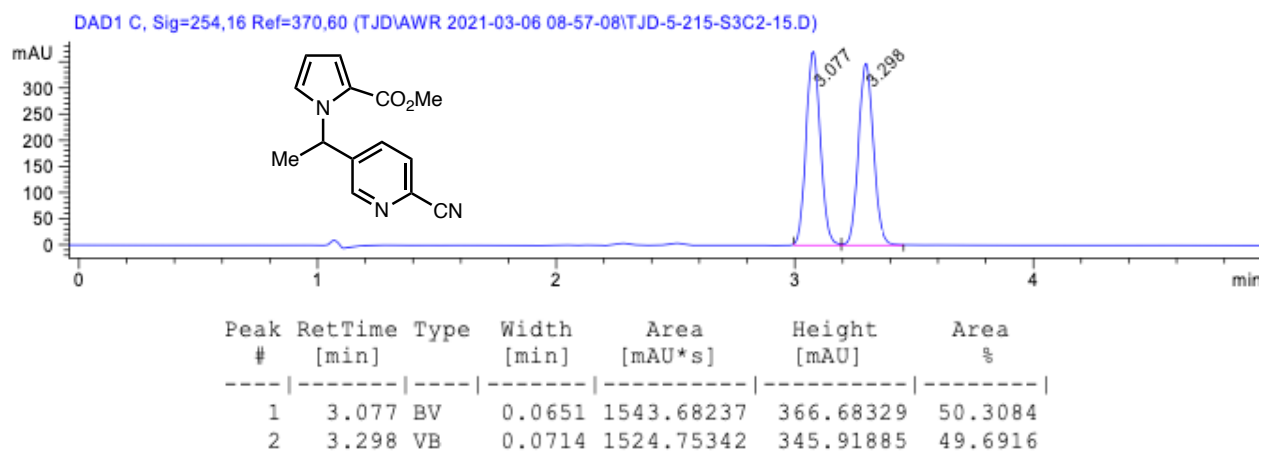
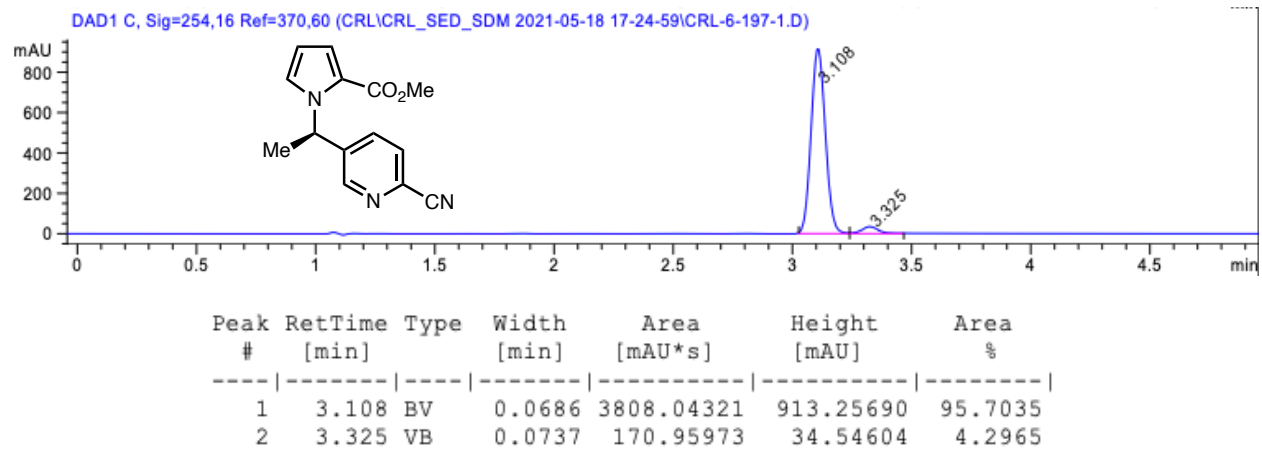
Enantioenriched **3c**:

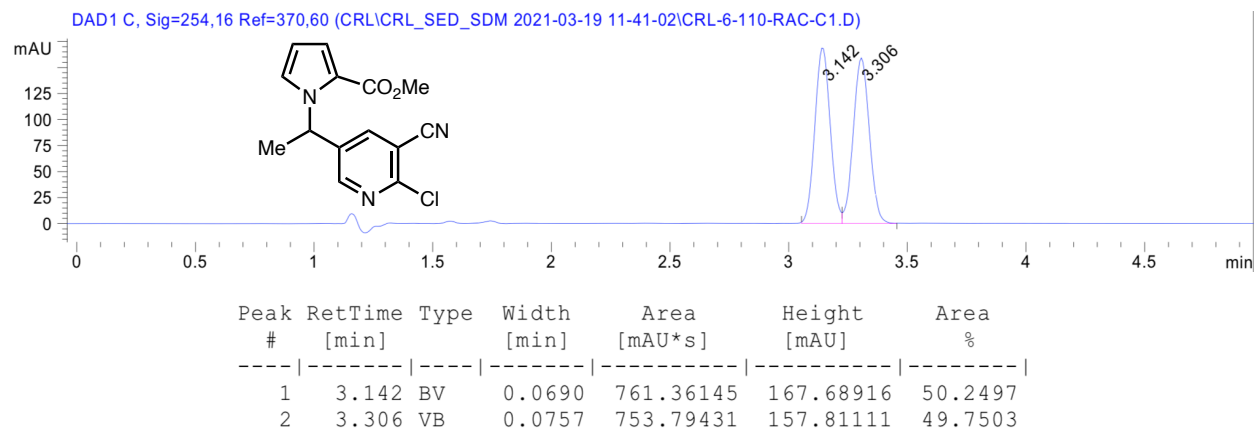
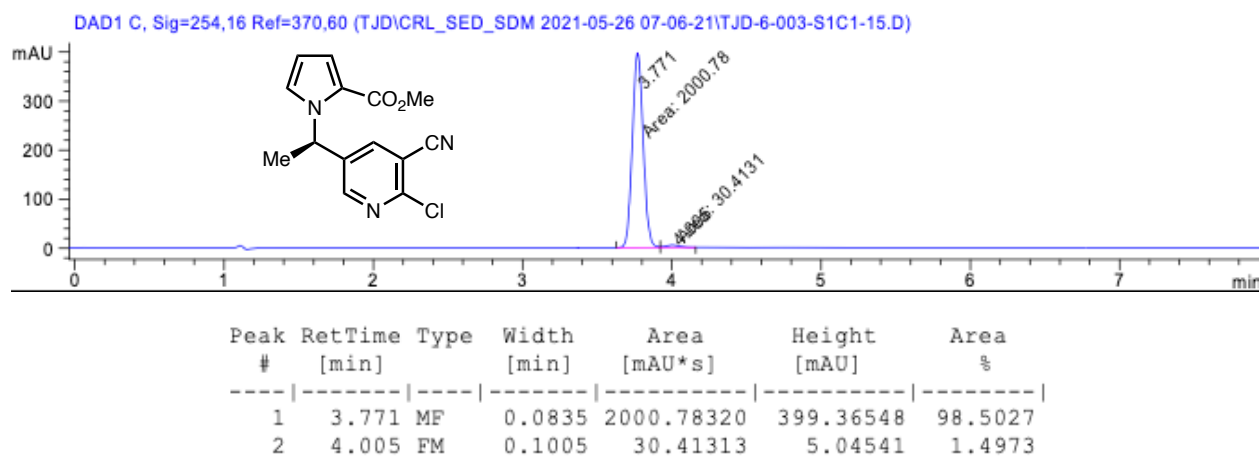
Signal 3: DAD1 D, Sig=280,16 Ref=370,60

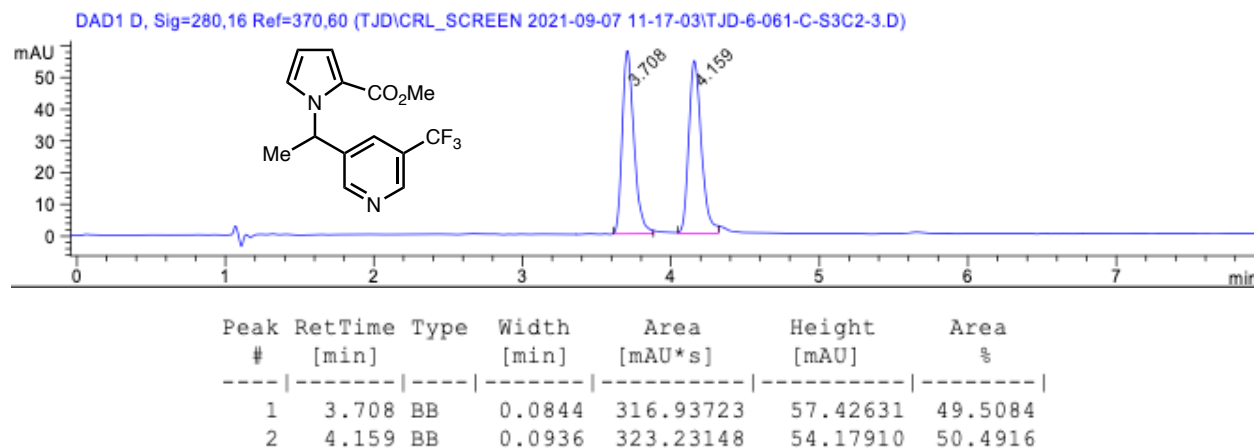
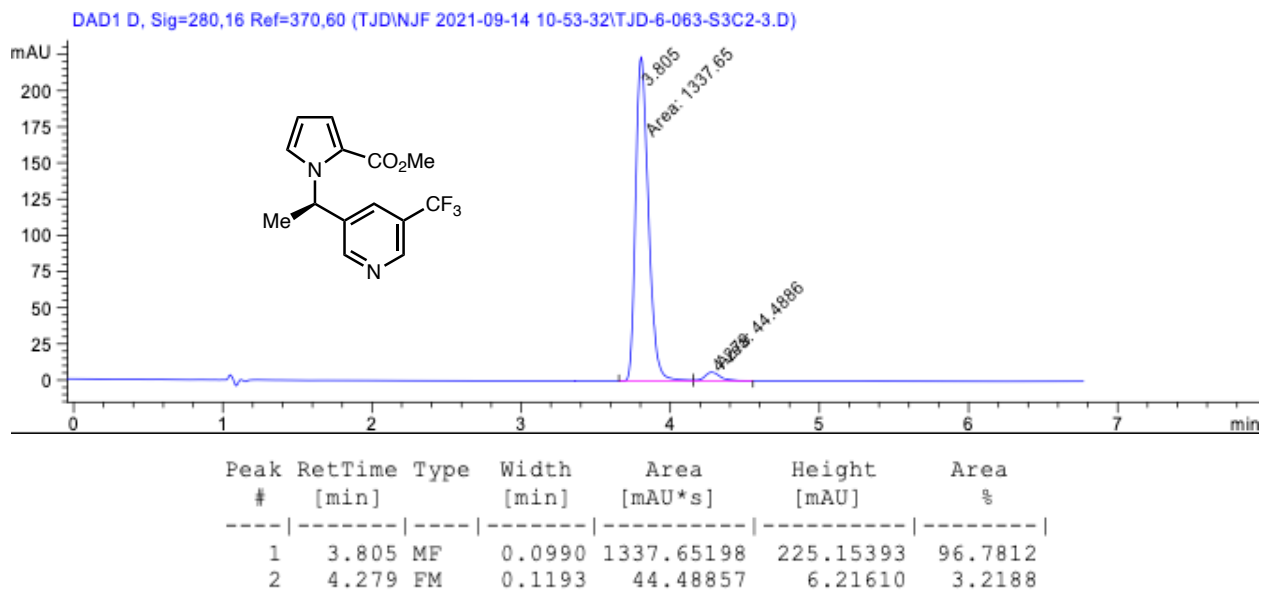
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.658	MM	0.0949	41.09700	7.22124	1.9534
2	4.279	BB	0.1006	2062.78174	331.37088	98.0466

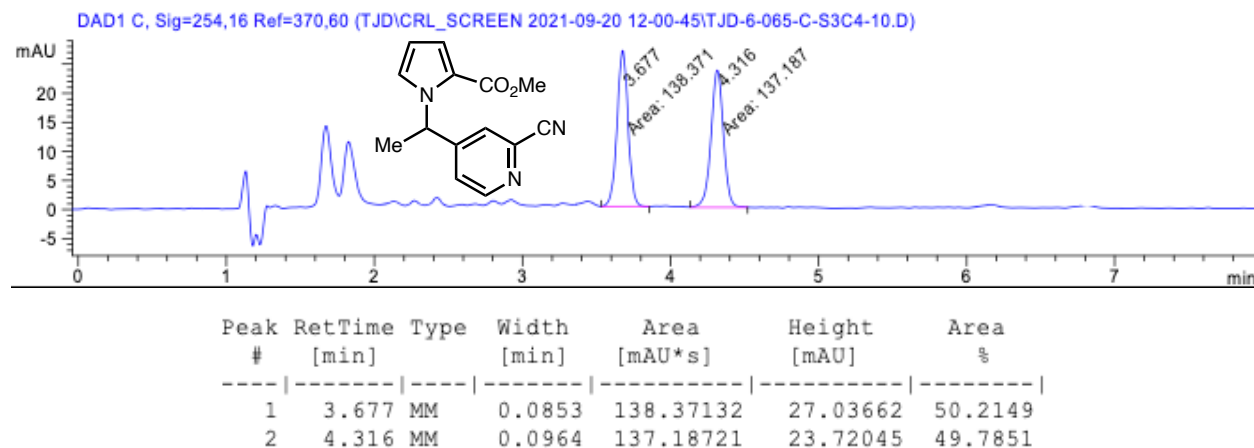
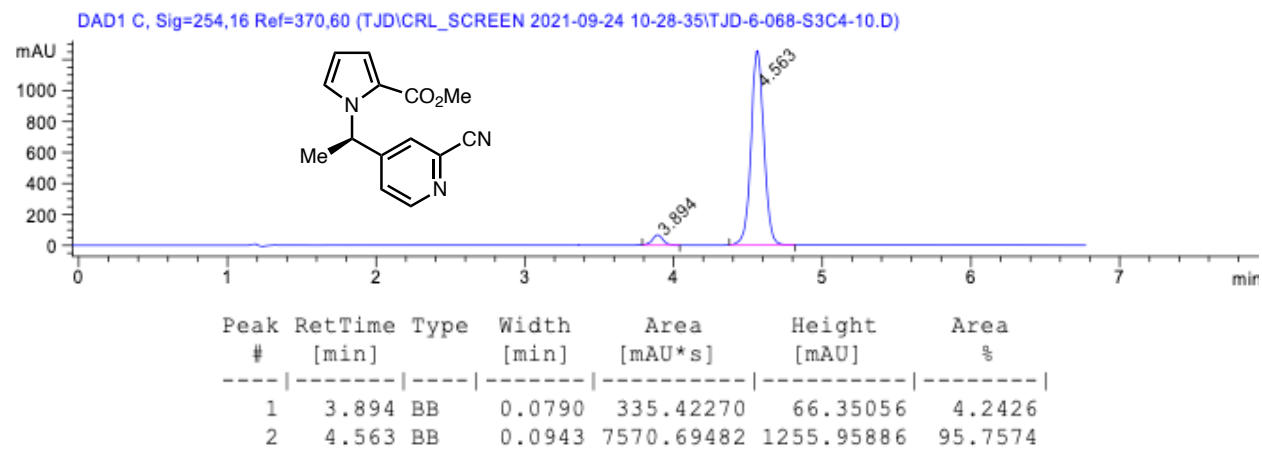
Racemic **3d**:Enantioenriched **3d**:

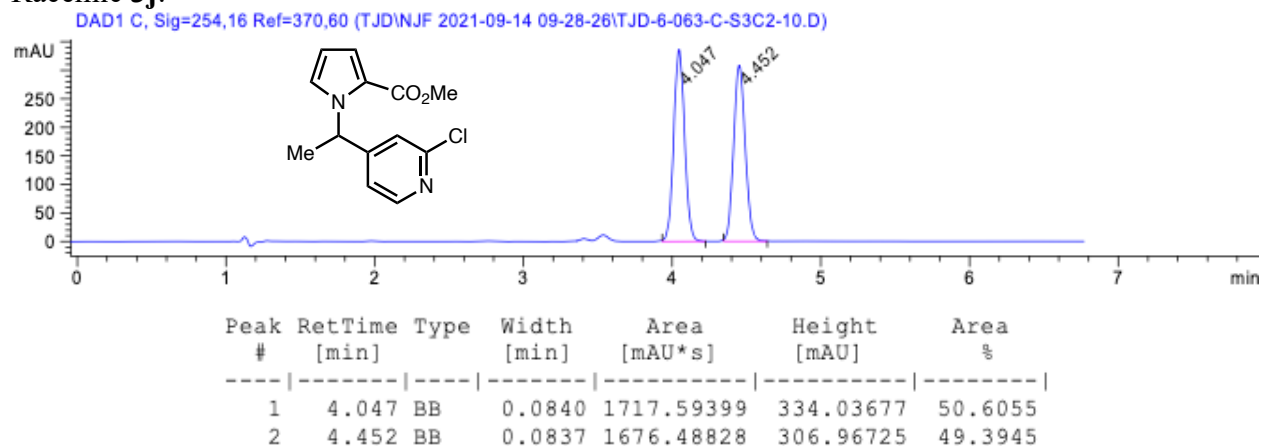
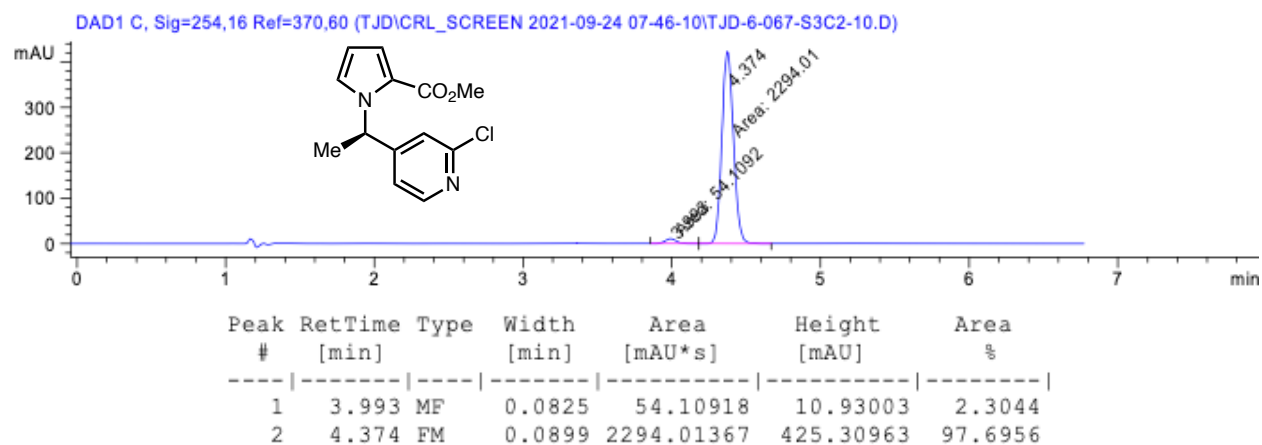
Racemic **3e**:Enantioenriched **3e**:

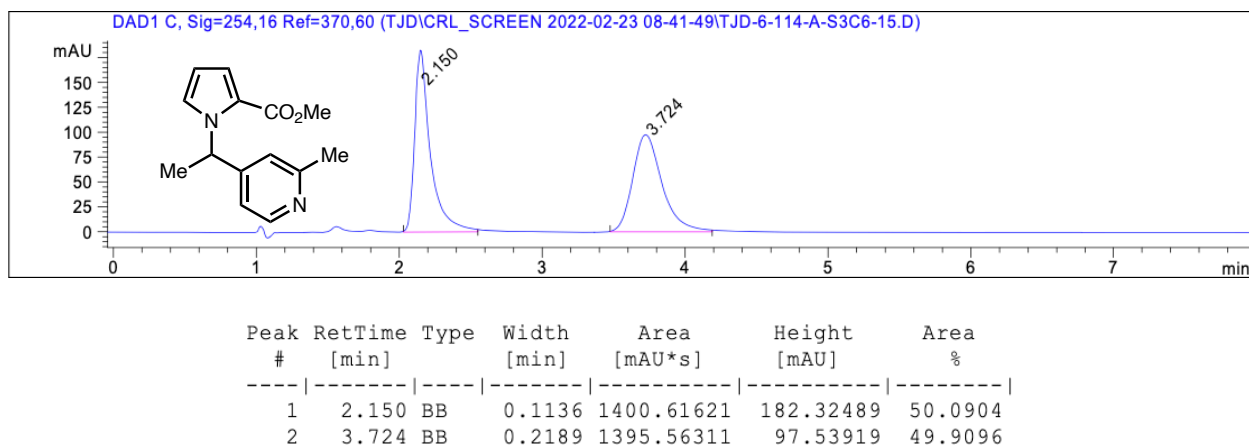
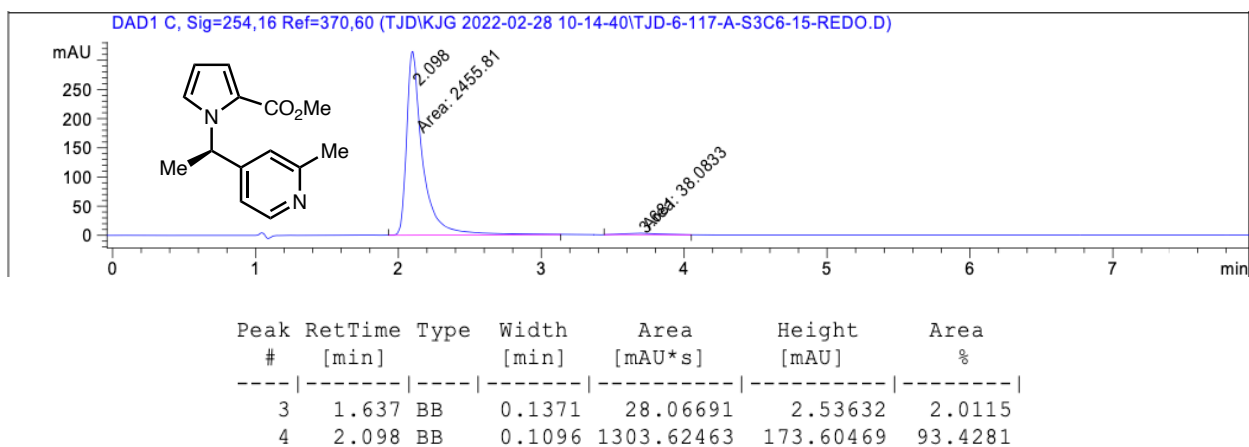
Racemic **3f**:Enantioenriched **3f**:

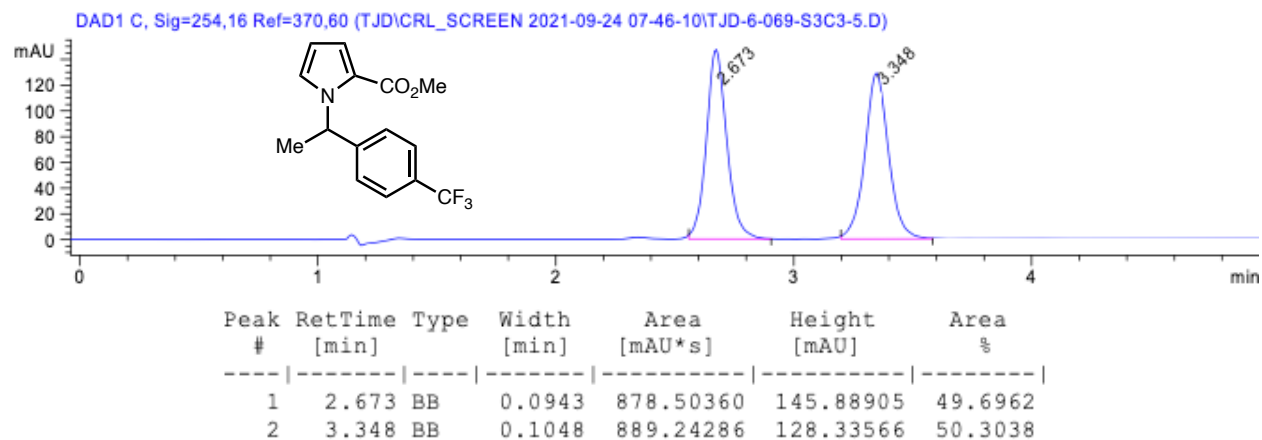
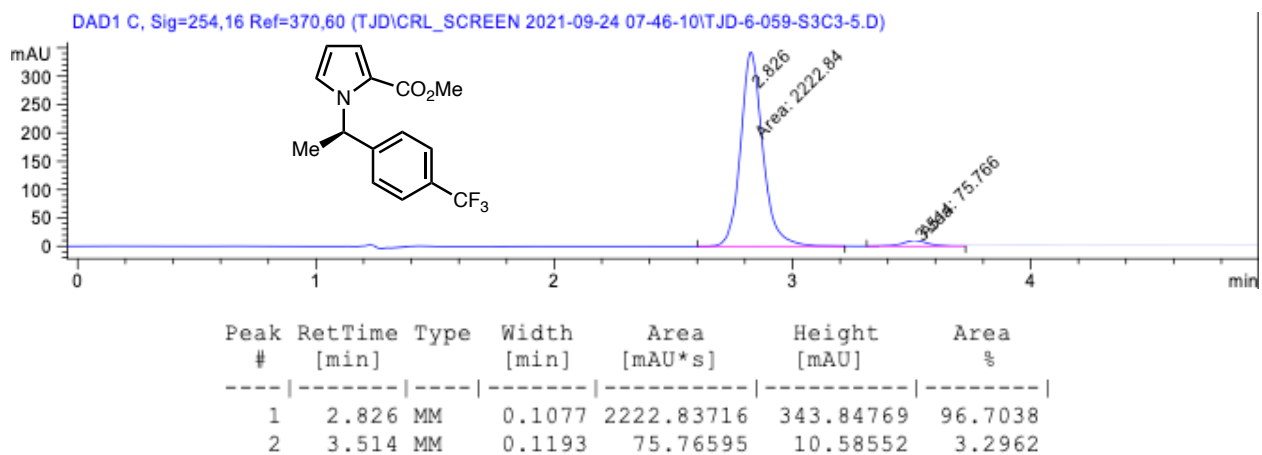
Racemic **3g**:Enantioenriched **3g**:

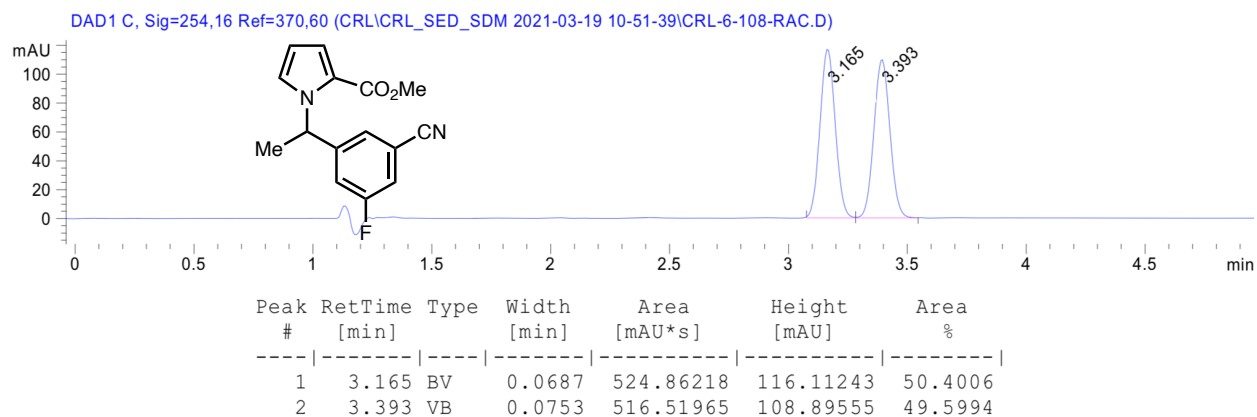
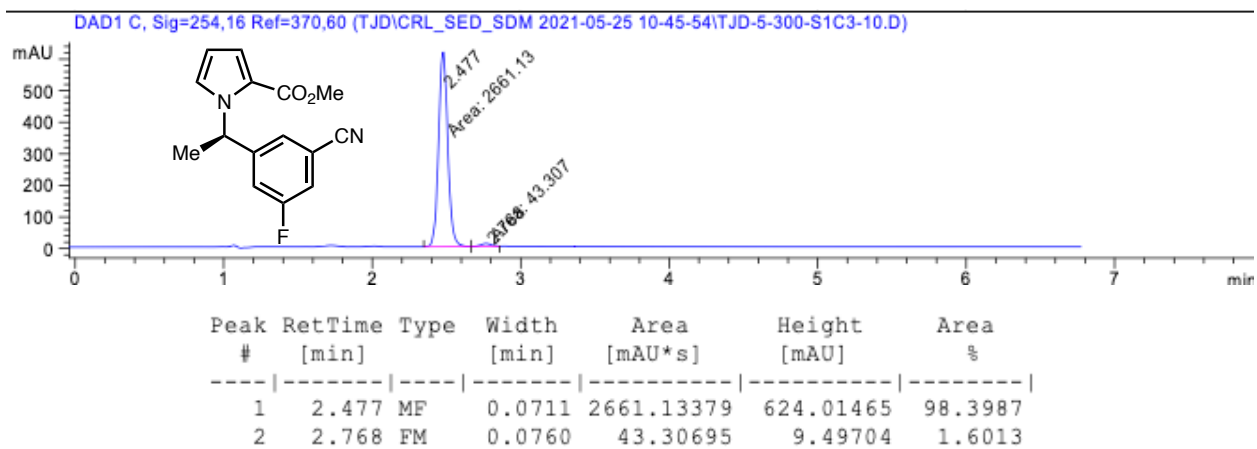
Racemic **3h**:Enantioenriched **3h**:

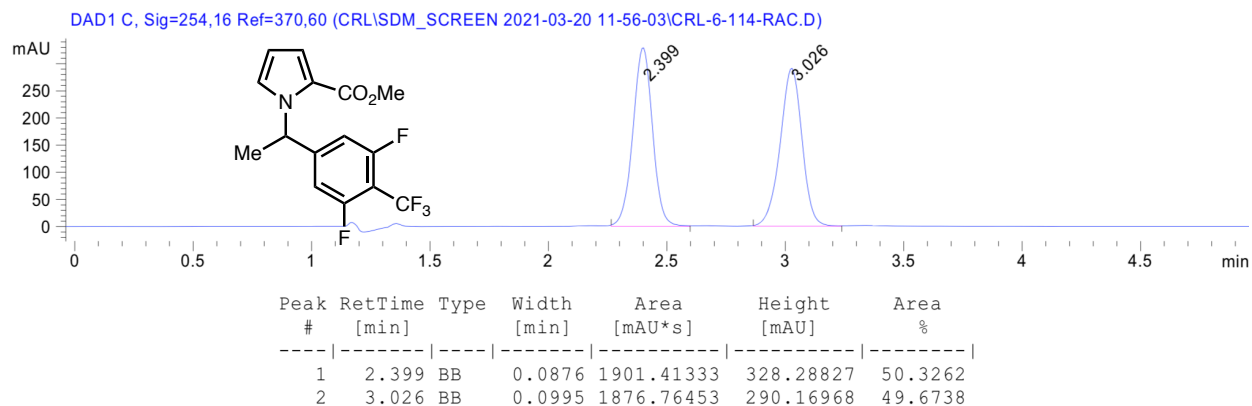
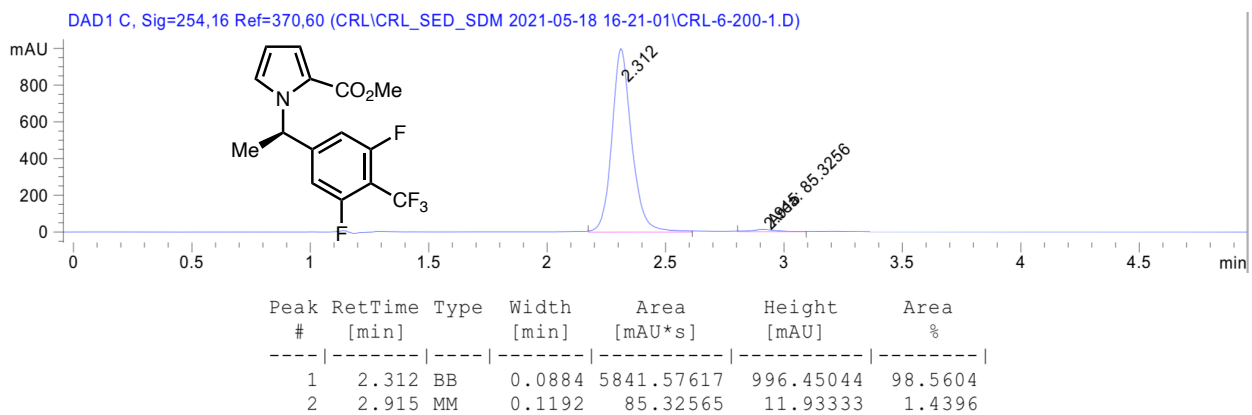
Racemic **3i**:Enantioenriched **3i**:

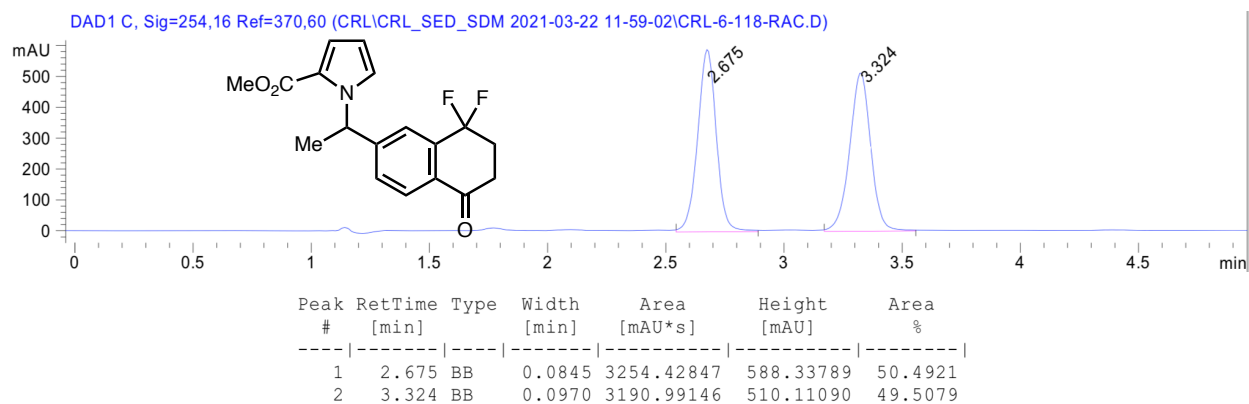
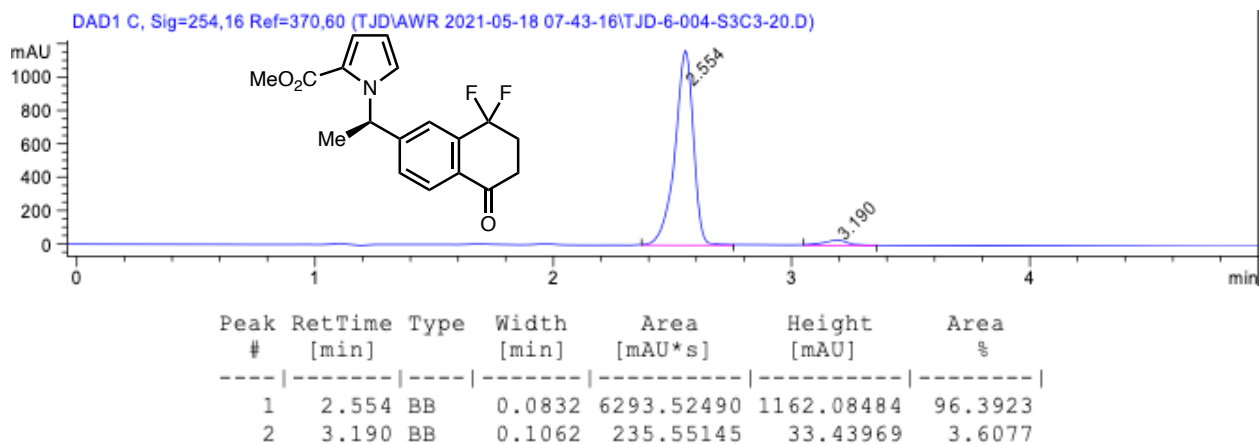
Racemic **3j**:Enantioenriched **3j**:

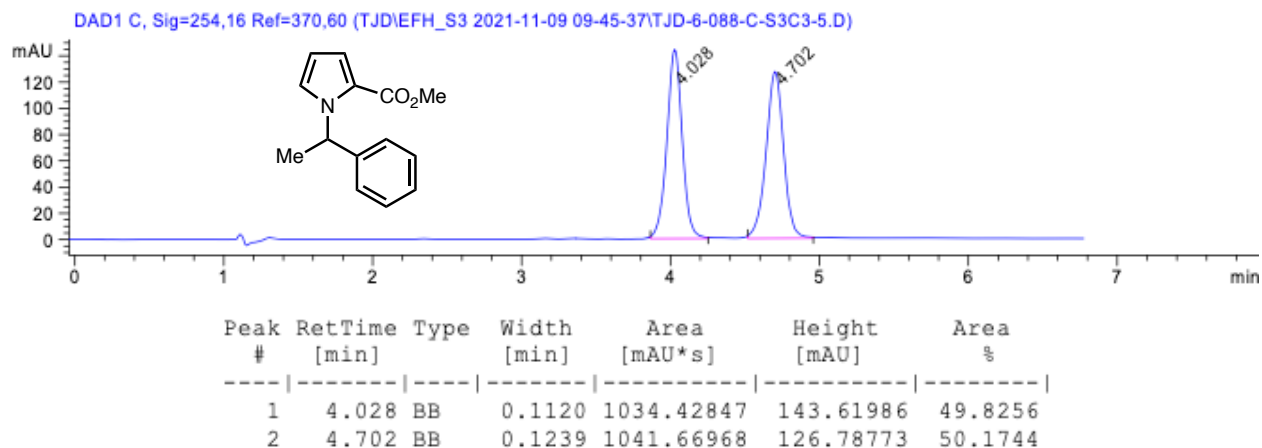
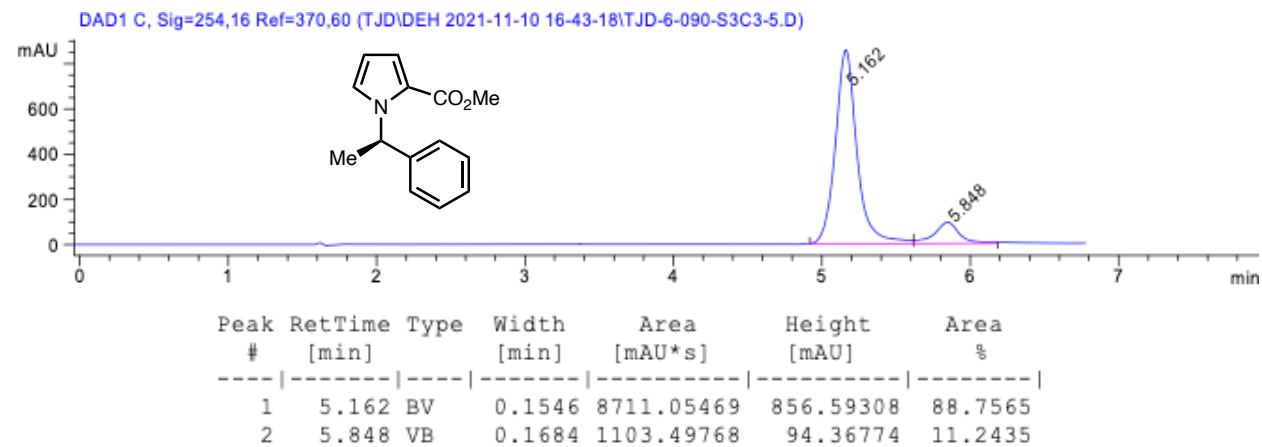
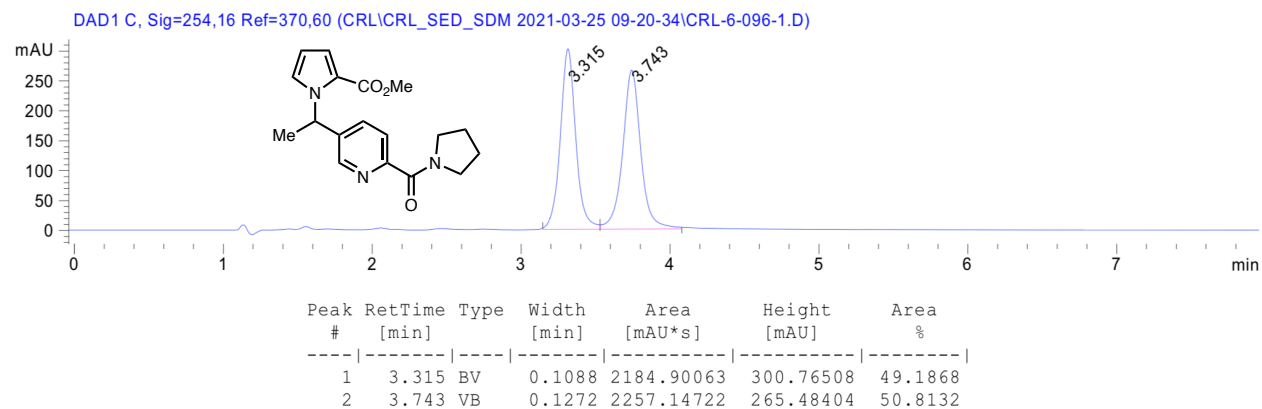
Racemic **3k**:Enantioenriched **3k**:

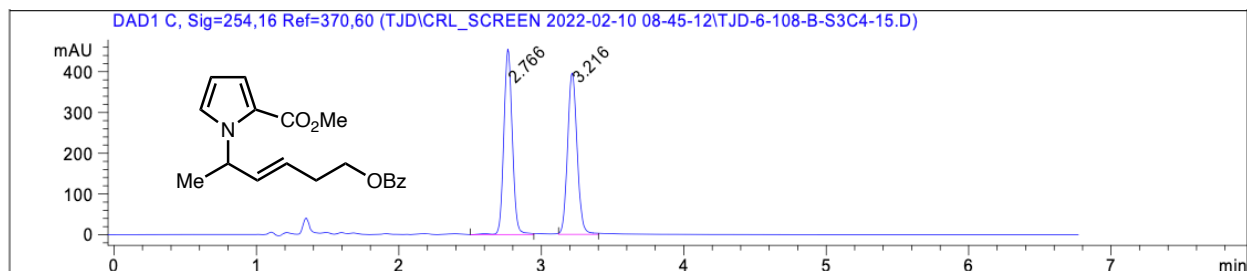
Racemic **3l**:Enantioenriched **3l**:

Racemic **3m**:Enantioenriched **3m**:

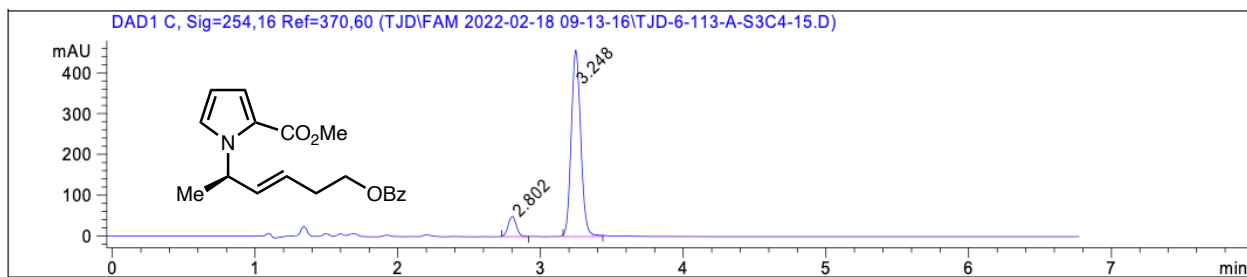
Racemic **3n**:Enantioenriched **3n**:

Racemic **3o**:Enantioenriched **3o**:

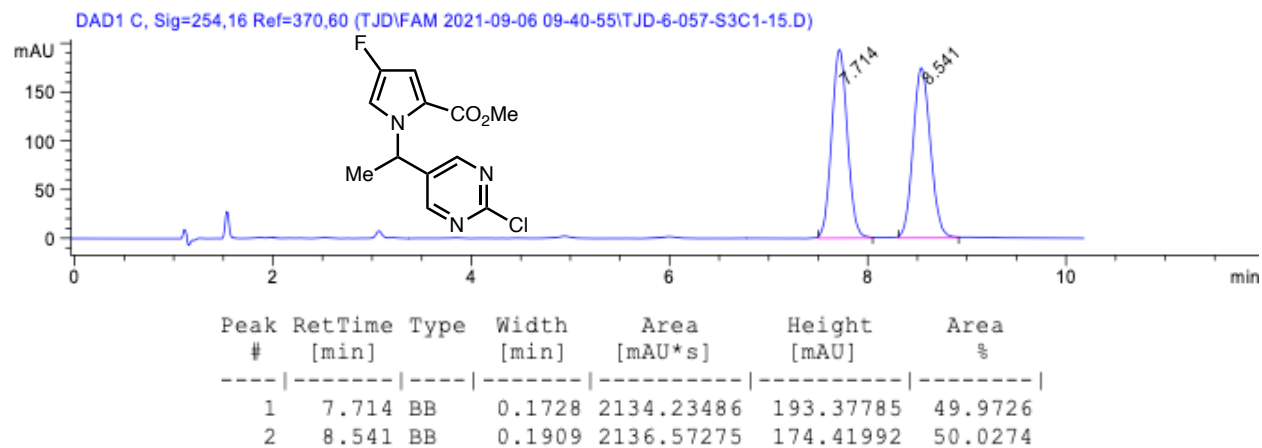
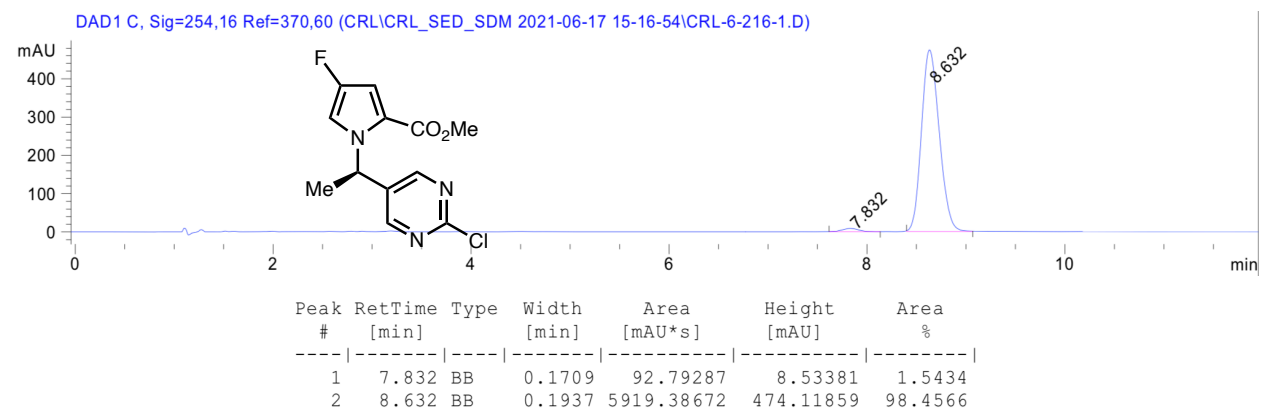
Racemic **3p**:Enantioenriched **3p**:Racemic **3q**:

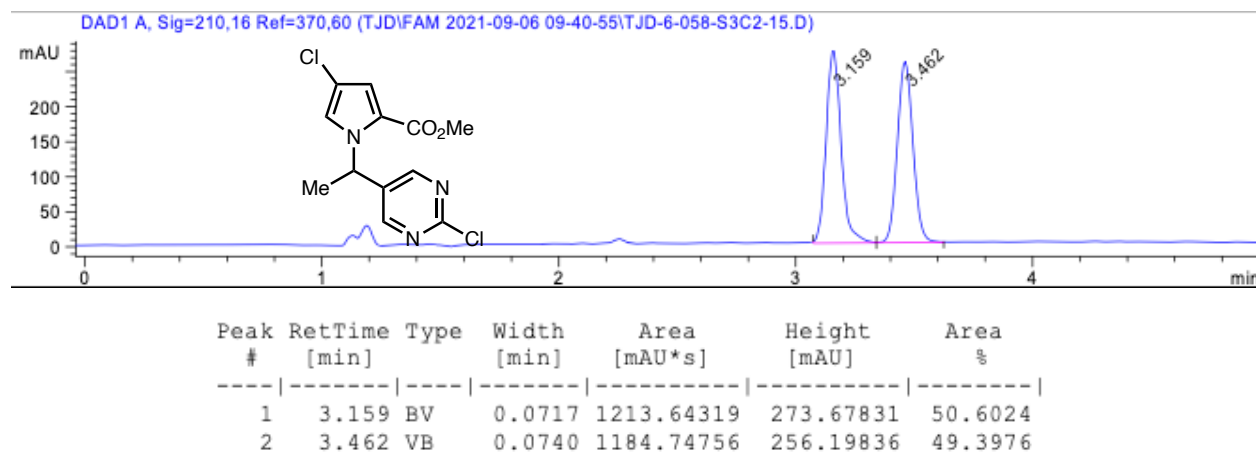
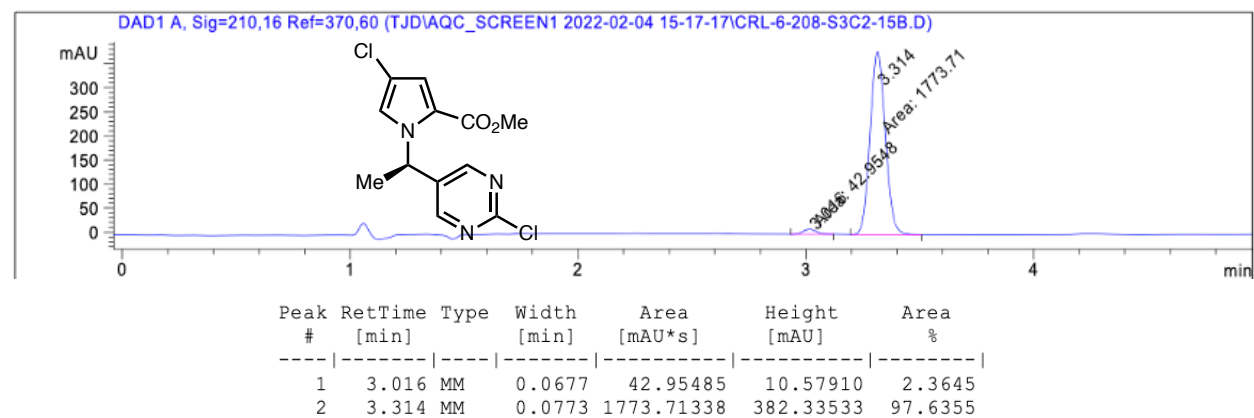
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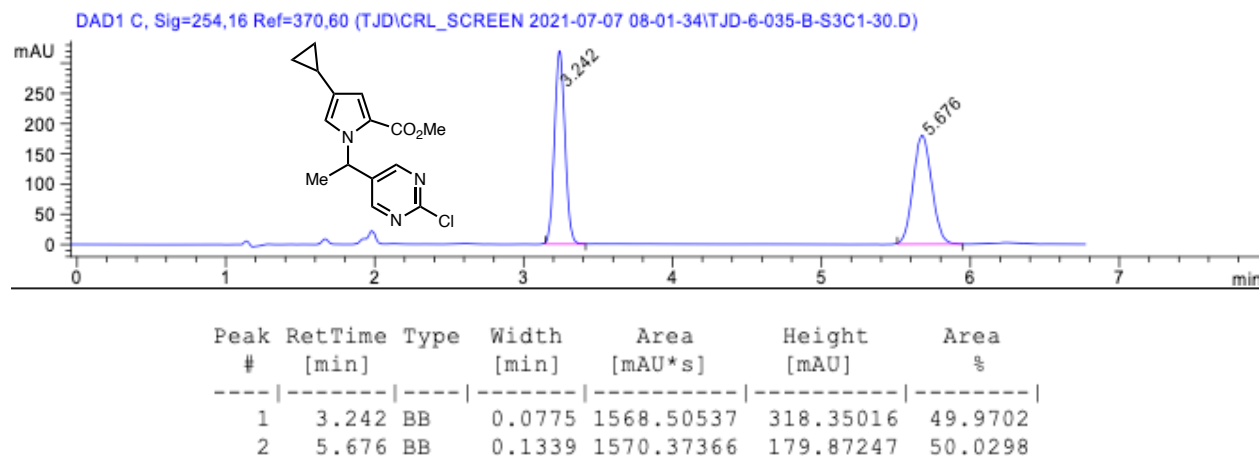
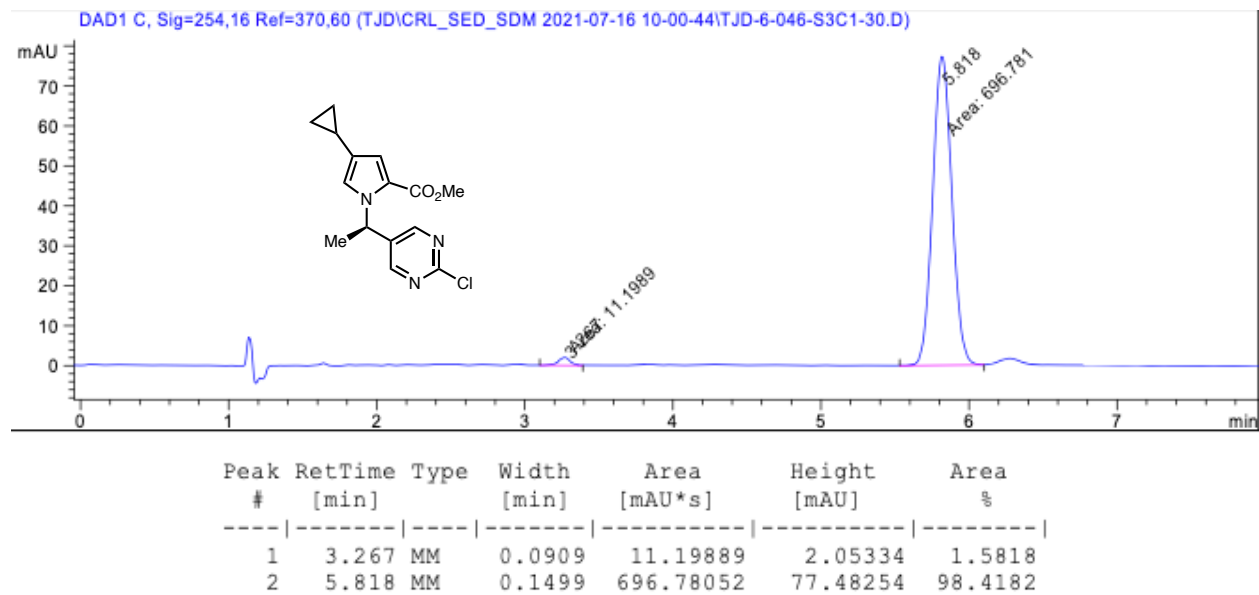
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.766	VB	0.0645	1871.41614	450.40173	50.3413
2	3.216	BB	0.0746	1846.04333	394.16595	49.6587

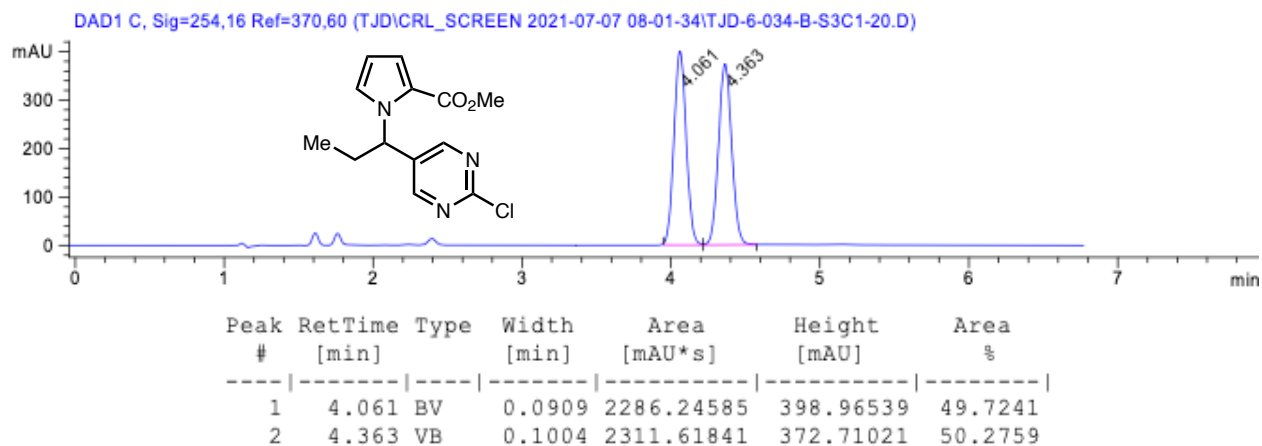
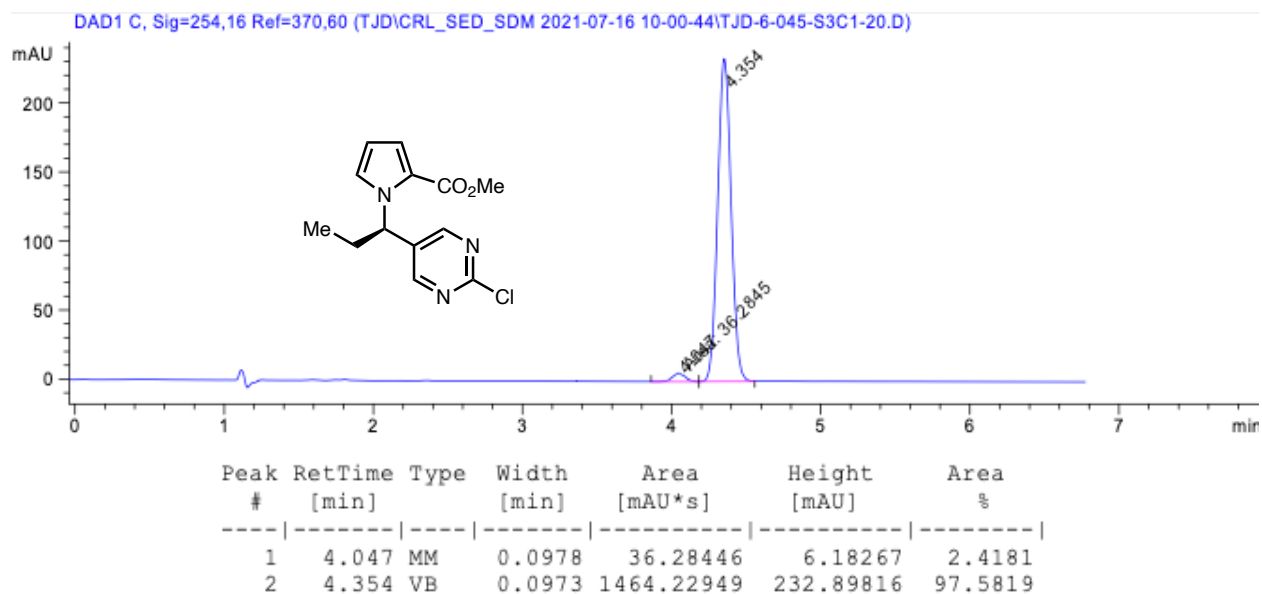
Enantioenriched **3r**:

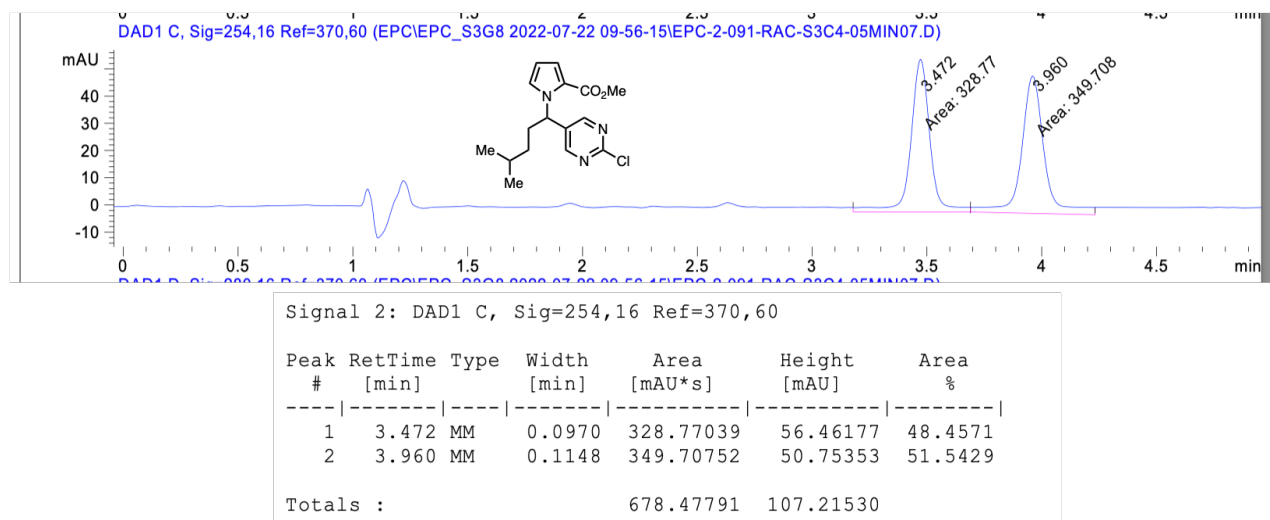
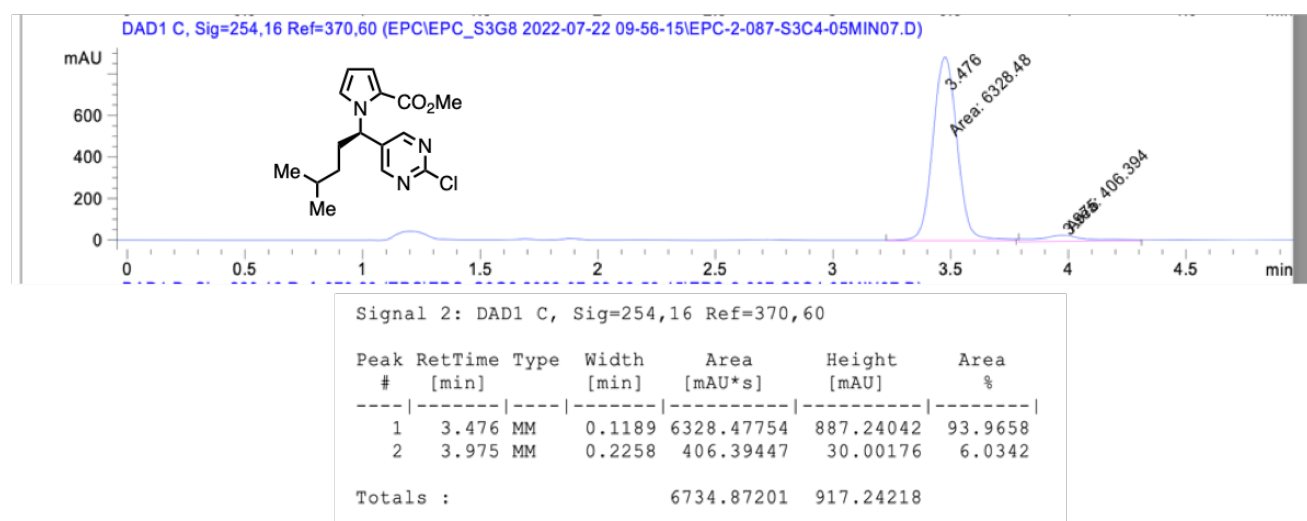
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.802	BB	0.0629	198.14445	49.28078	8.5774
2	3.248	BB	0.0744	2111.92212	452.89645	91.4226

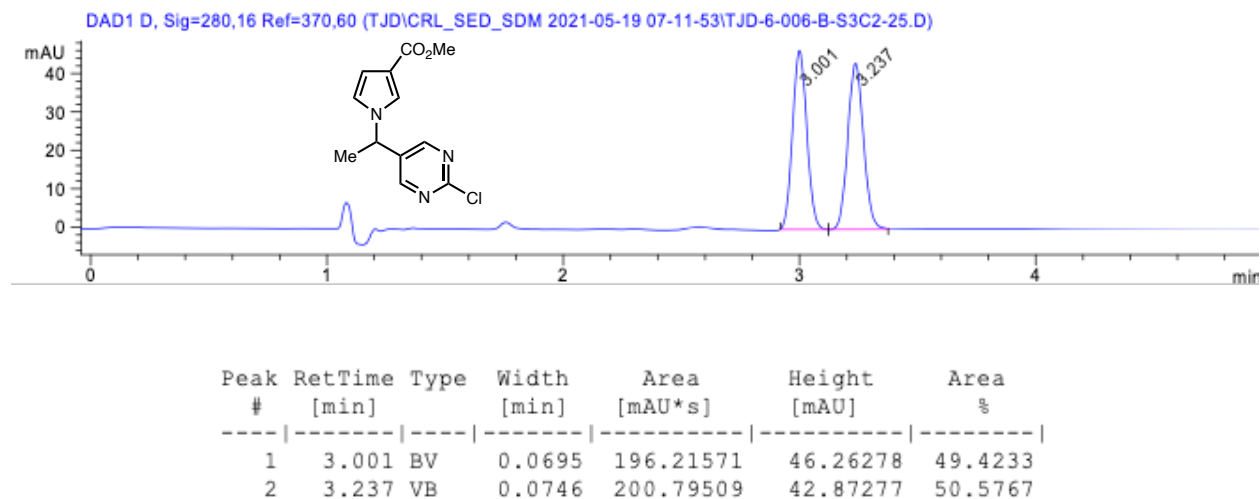
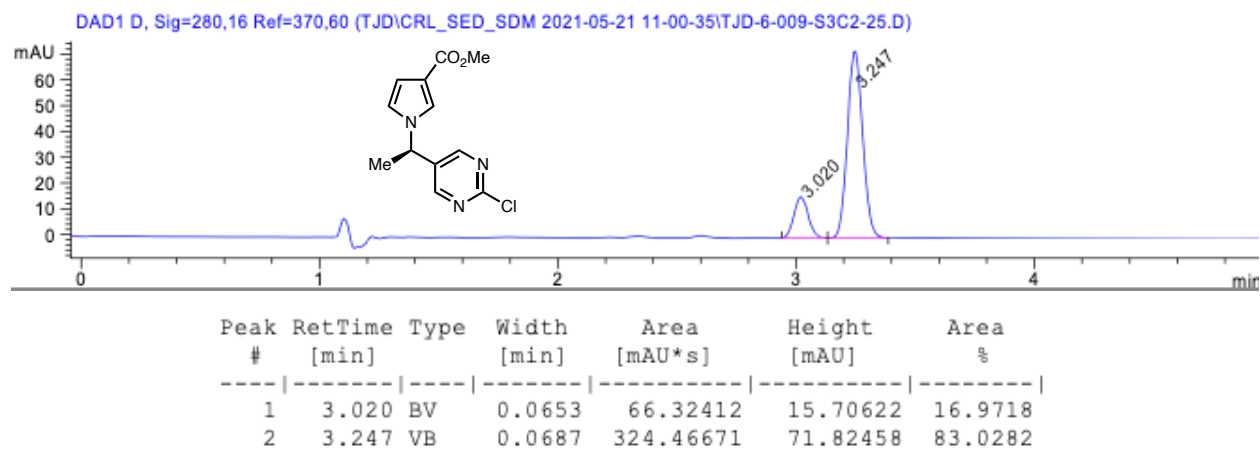
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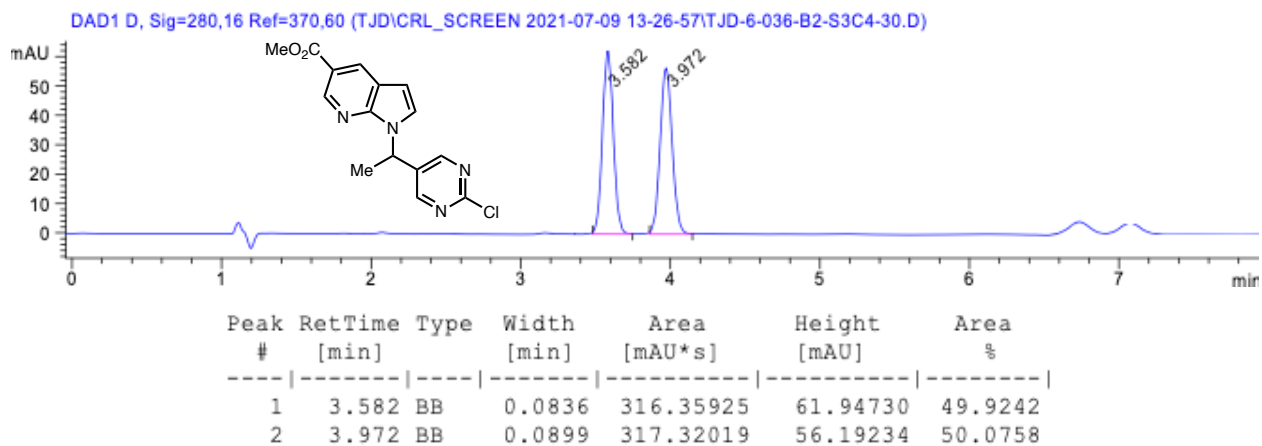
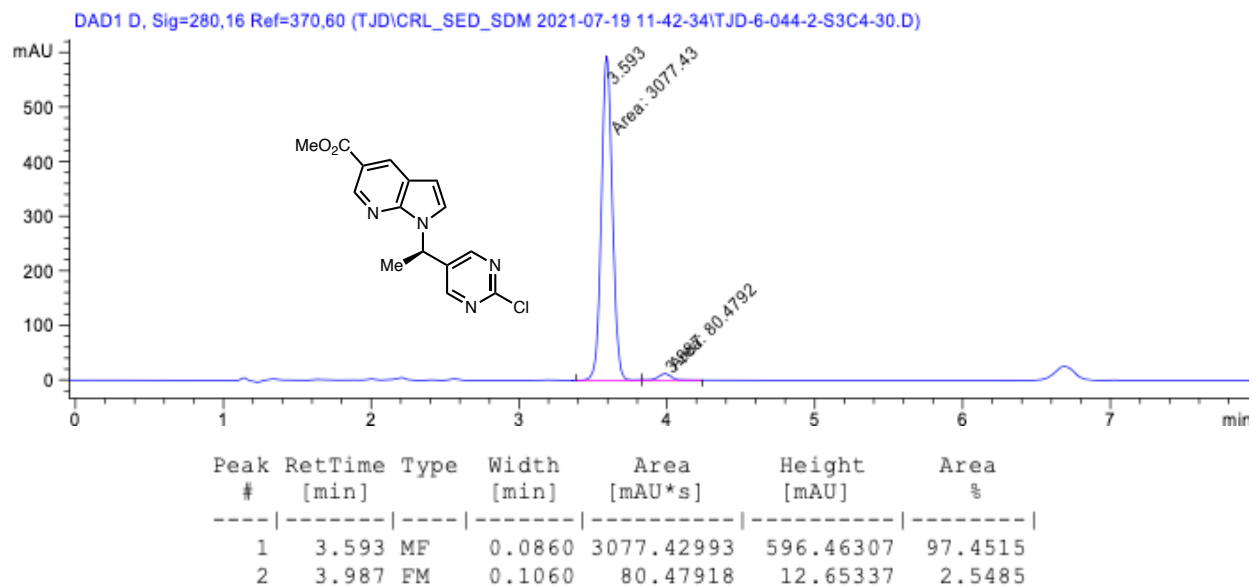
Racemic **5b**:Enantioenriched **5b**:

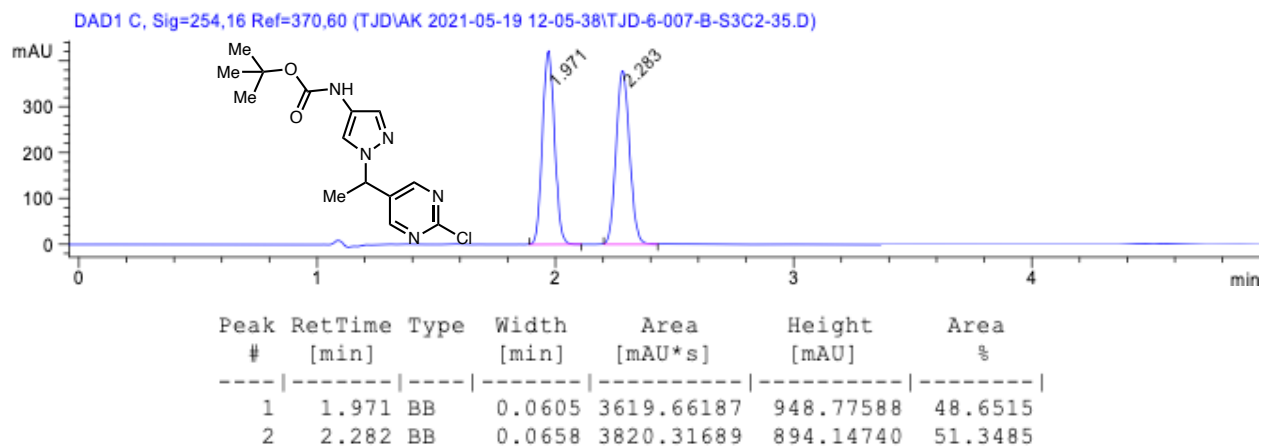
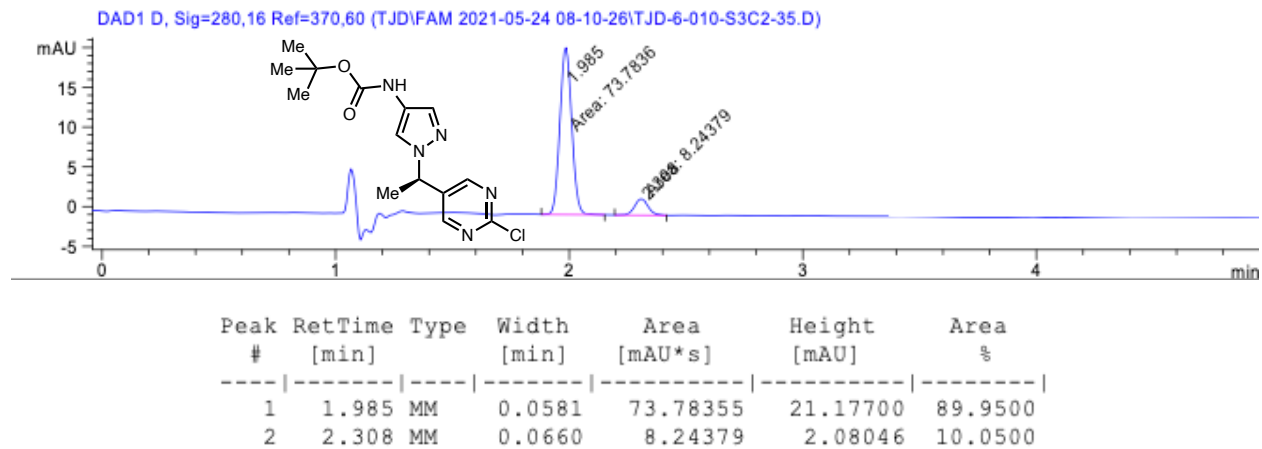
Racemic **5c**:Enantioenriched **5c**:

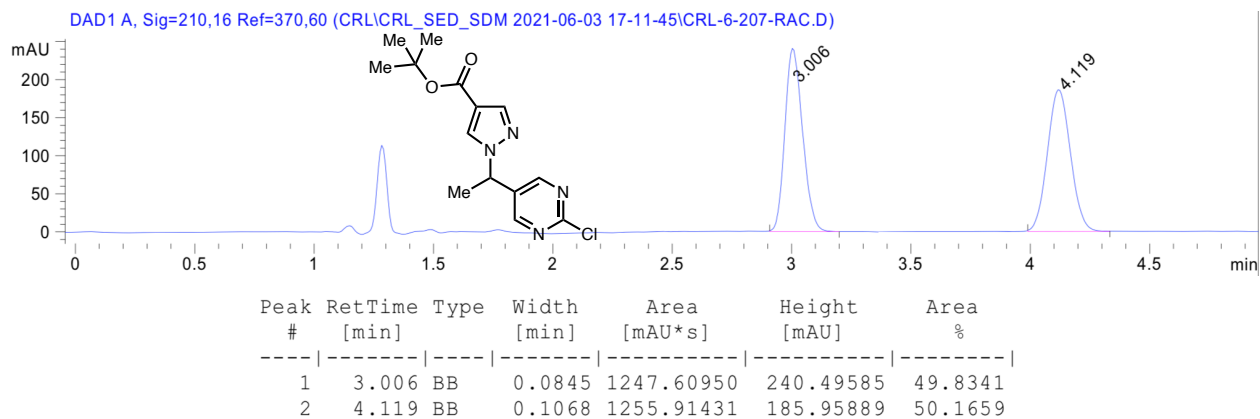
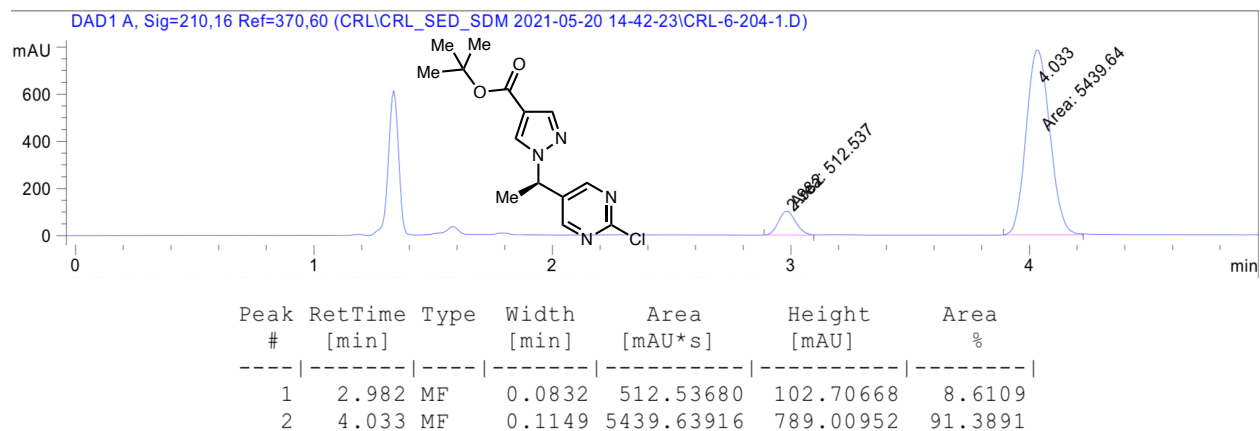
Racemic **5d**:Enantioenriched **5d**:

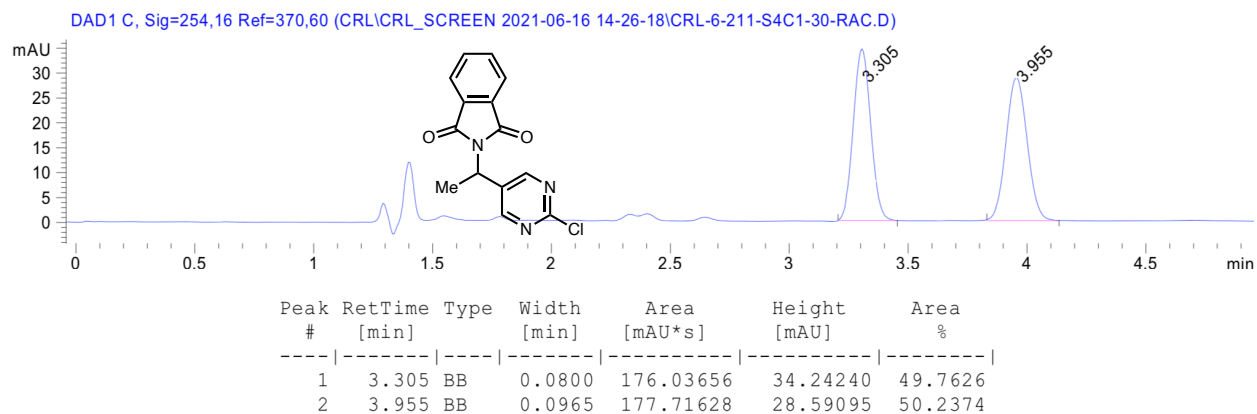
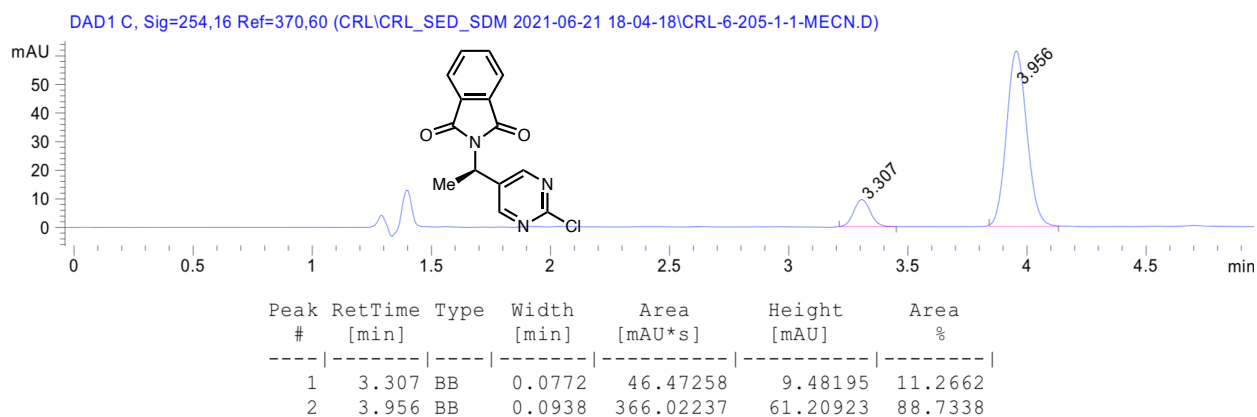
Racemic **5e**:Enantioenriched **5e**:

Racemic **5f**:Enantioenriched **5f**:

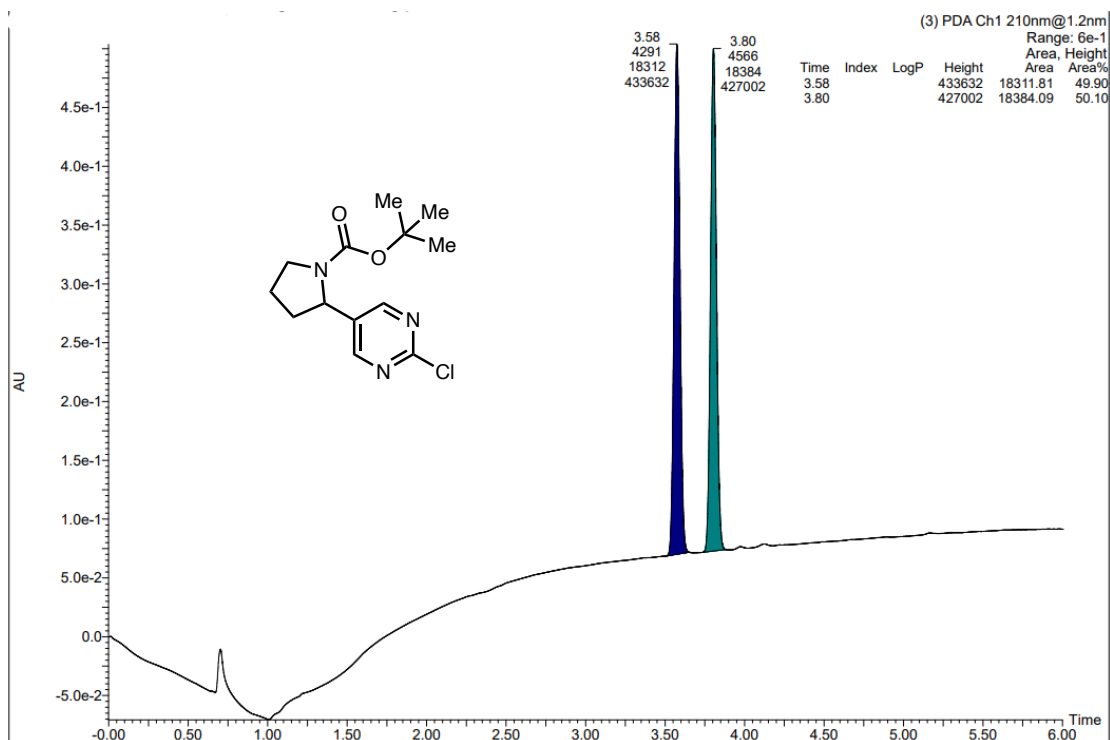
Racemic **5g**:Enantioenriched **5g**:

Racemic **5h**:Enantioenriched **5h**:

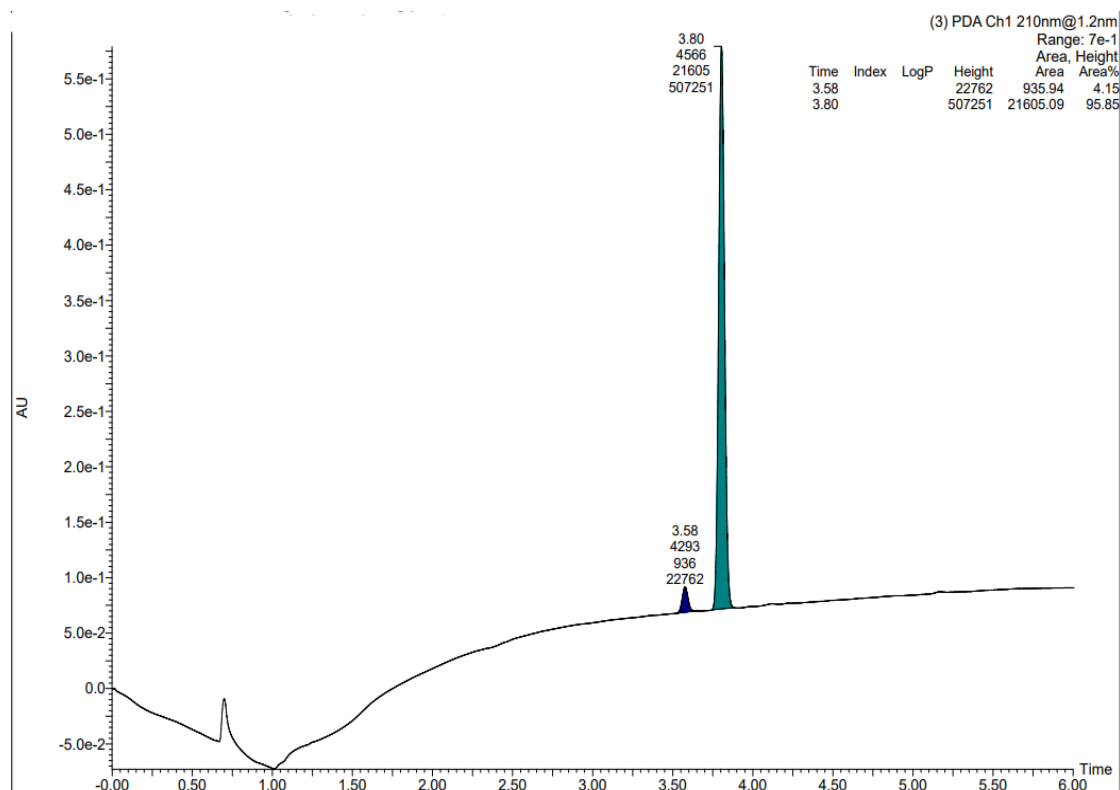
Racemic **5i**:Enantioenriched **5i**:

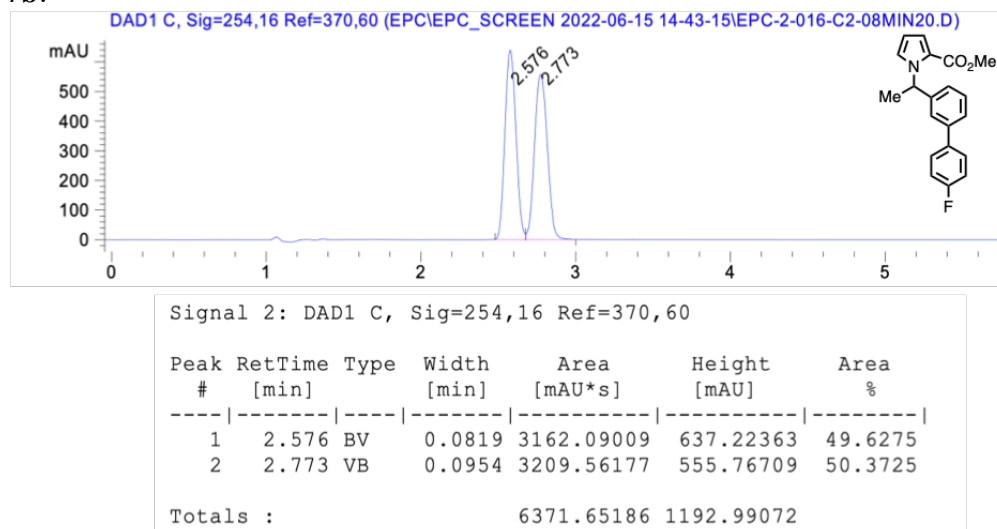
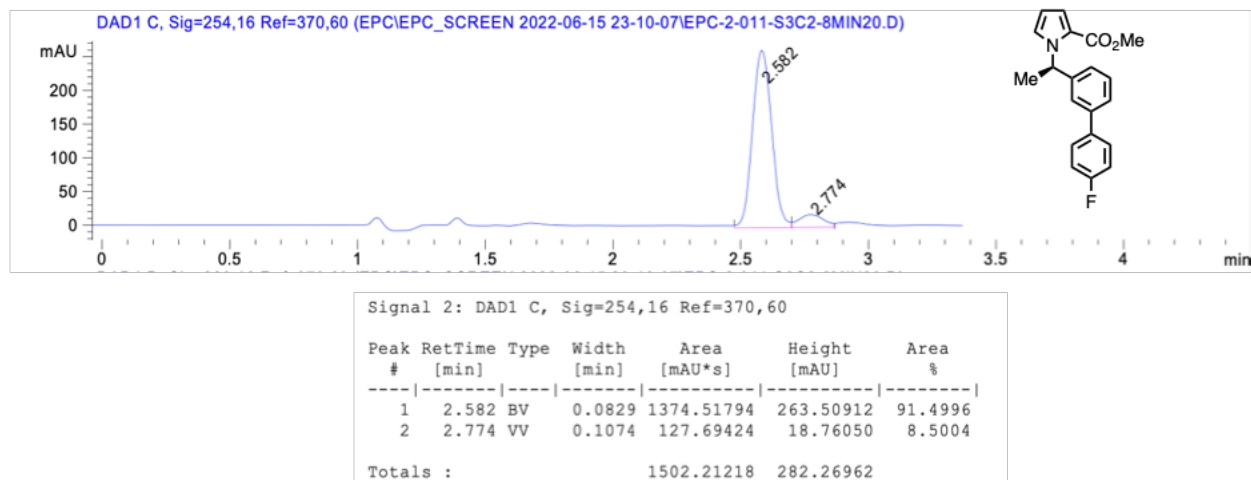
Racemic **5j**:Enantioenriched **5j**:

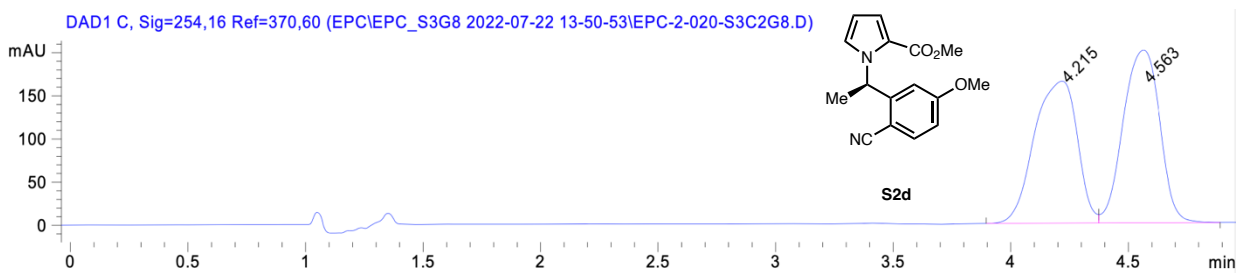
Racemic **5k**:



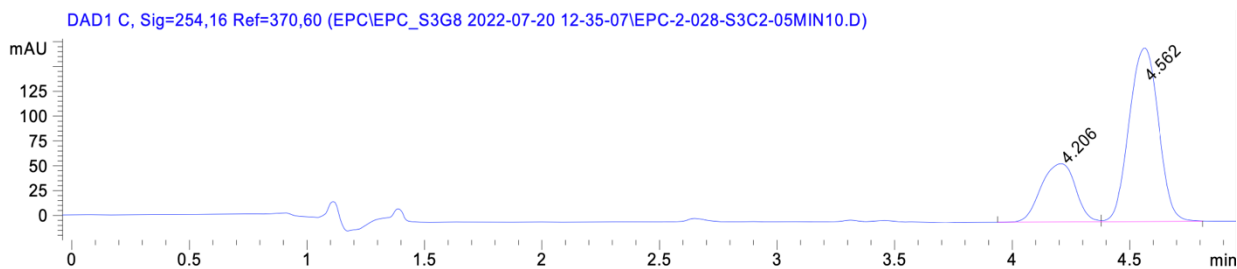
Enantioenriched **5k**:



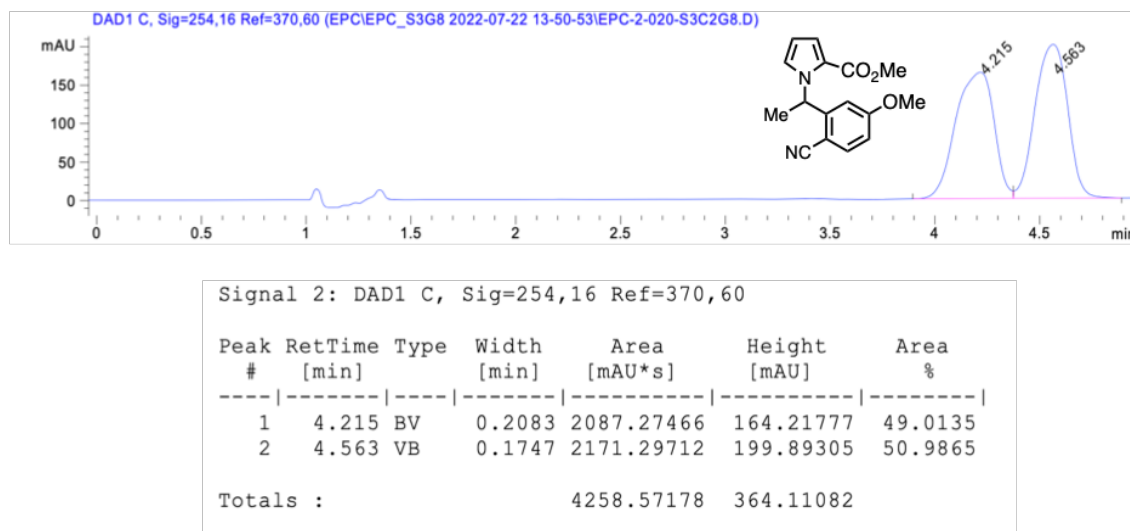
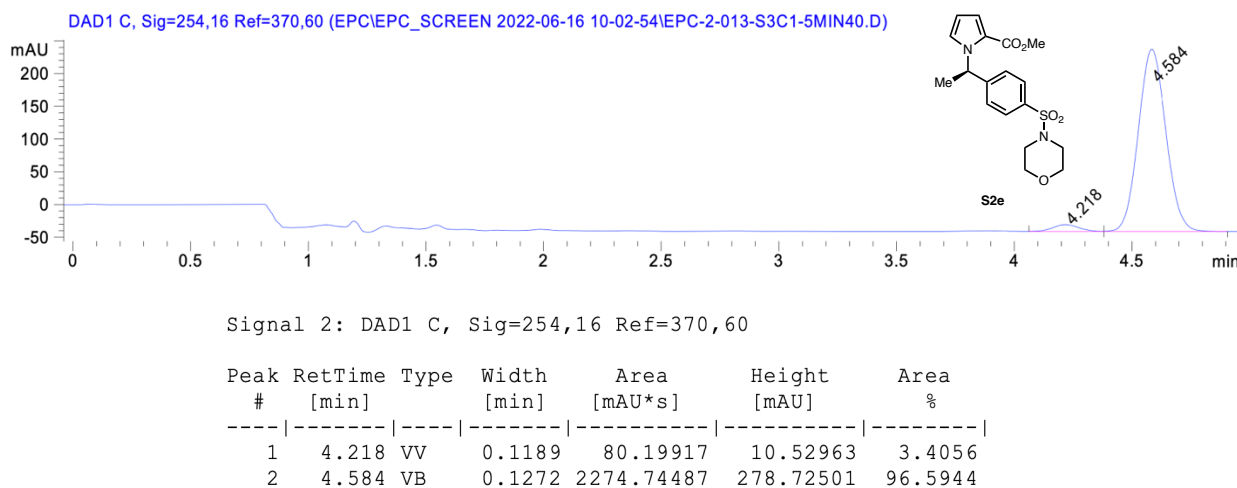
Racemic **7b**:Enantioenriched **7b**:

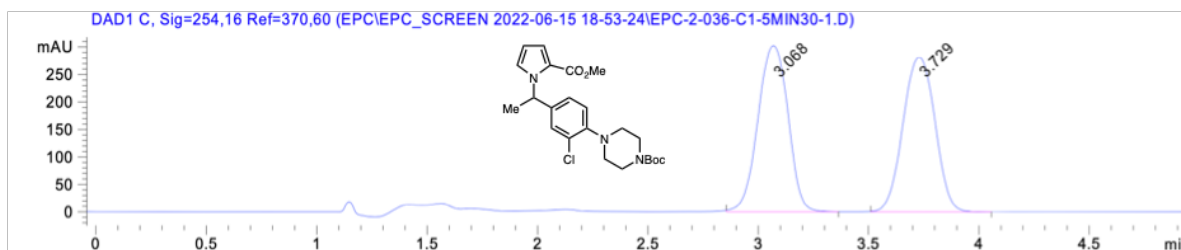
Racemic 7d:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.215	BV	0.2083	2087.27466	164.21777	49.0135
2	4.563	VB	0.1747	2171.29712	199.89305	50.9865

Enantioenriched 7d:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.206	BV	0.1664	595.55023	58.68734	28.1381
2	4.562	VB	0.1376	1520.97705	174.58441	71.8619

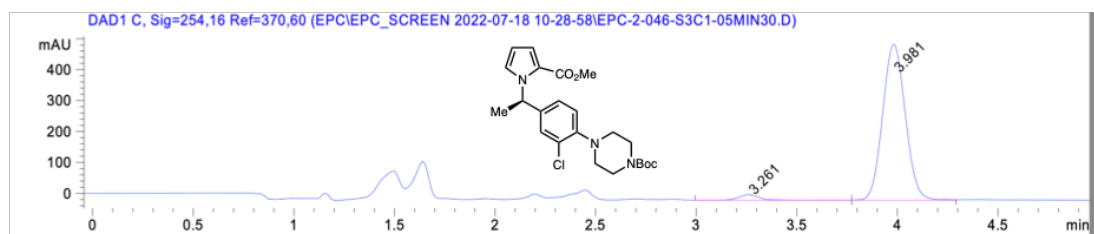
Racemic **7e**:Enantioenriched **7e**:

Racemic **7g**:

Signal 2: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.068	BB	0.1547	2864.52856	301.84140	50.1563
2	3.729	BB	0.1659	2846.67896	281.67029	49.8437

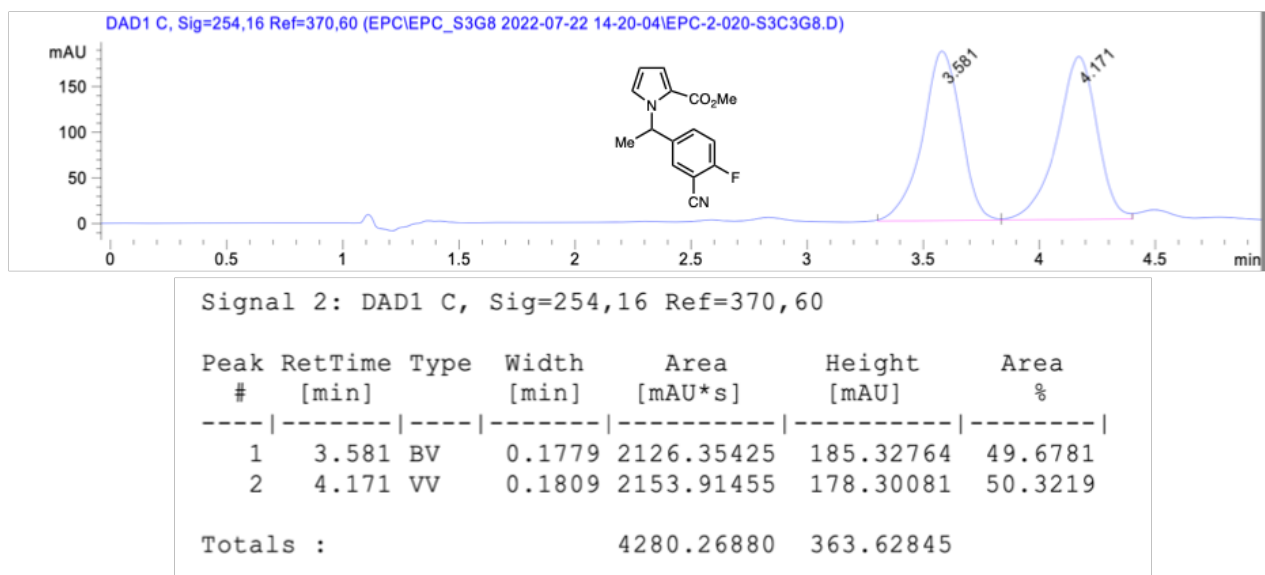
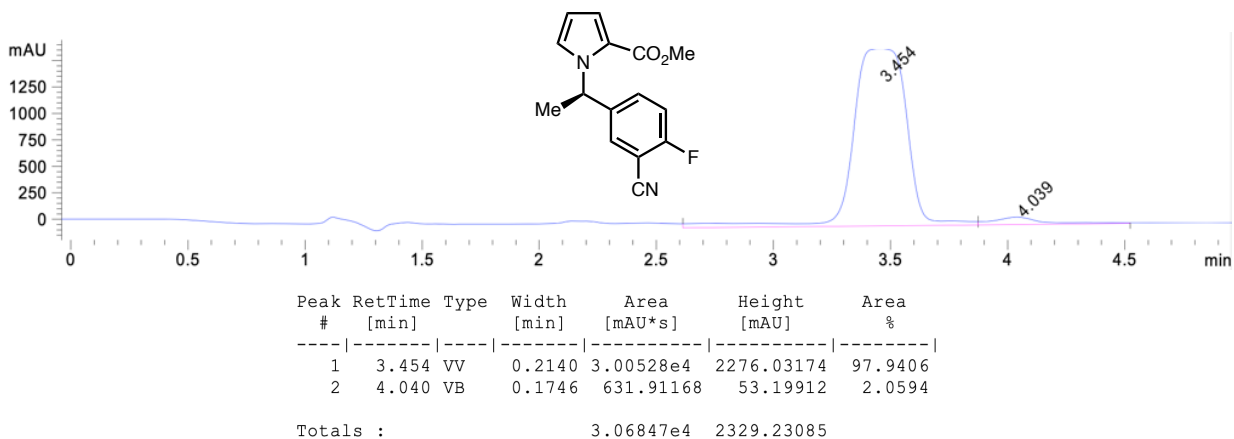
Totals : 5711.20752 583.51169

Enantioenriched **7g**:

Signal 2: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.261	VV	0.1130	128.29601	17.59957	3.1566
2	3.981	VV	0.1230	3936.14014	504.56064	96.8434

Totals : 4064.43614 522.16021

Racemic **7h**:Enantioenriched **7h**:

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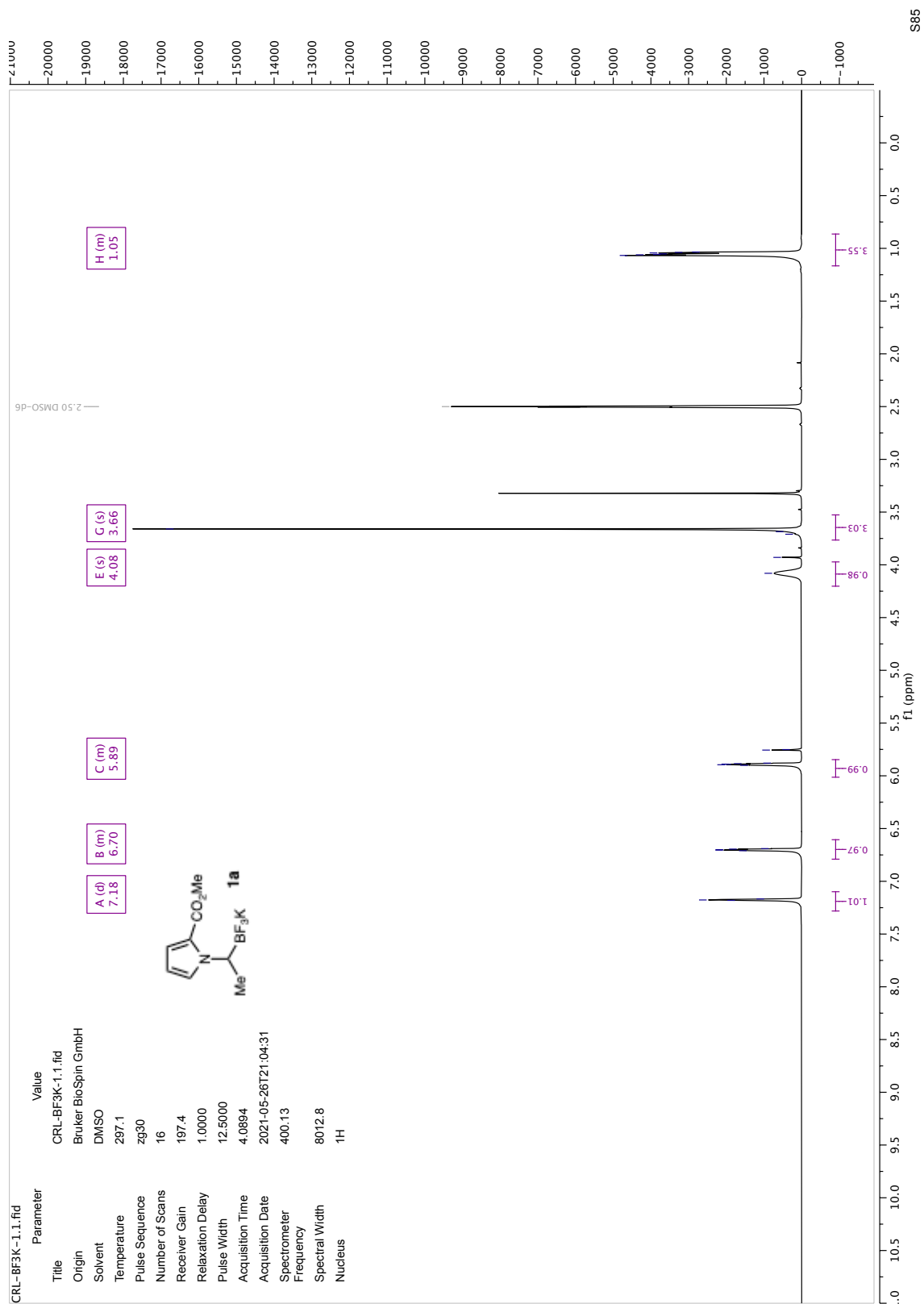
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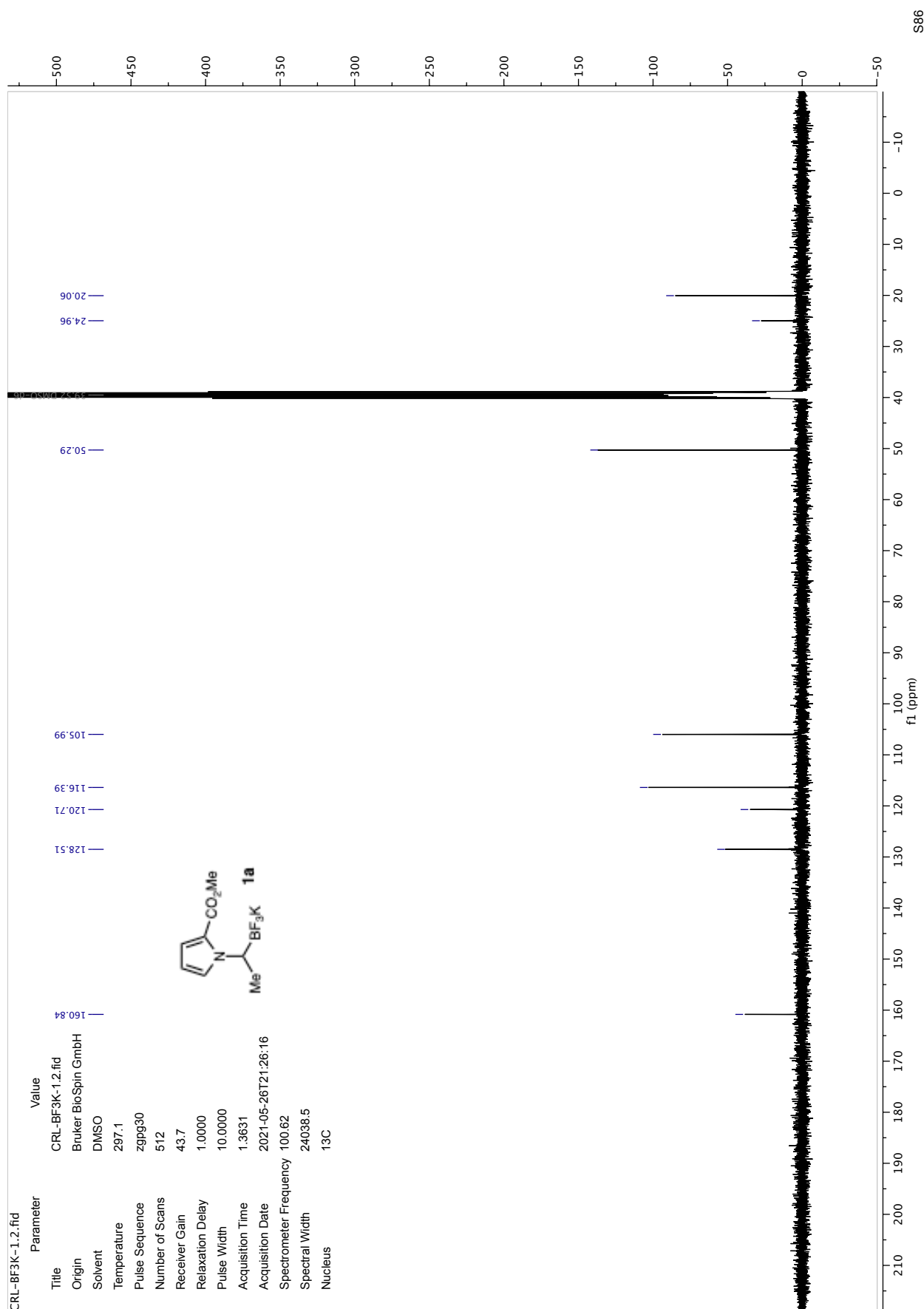
Appendix 1

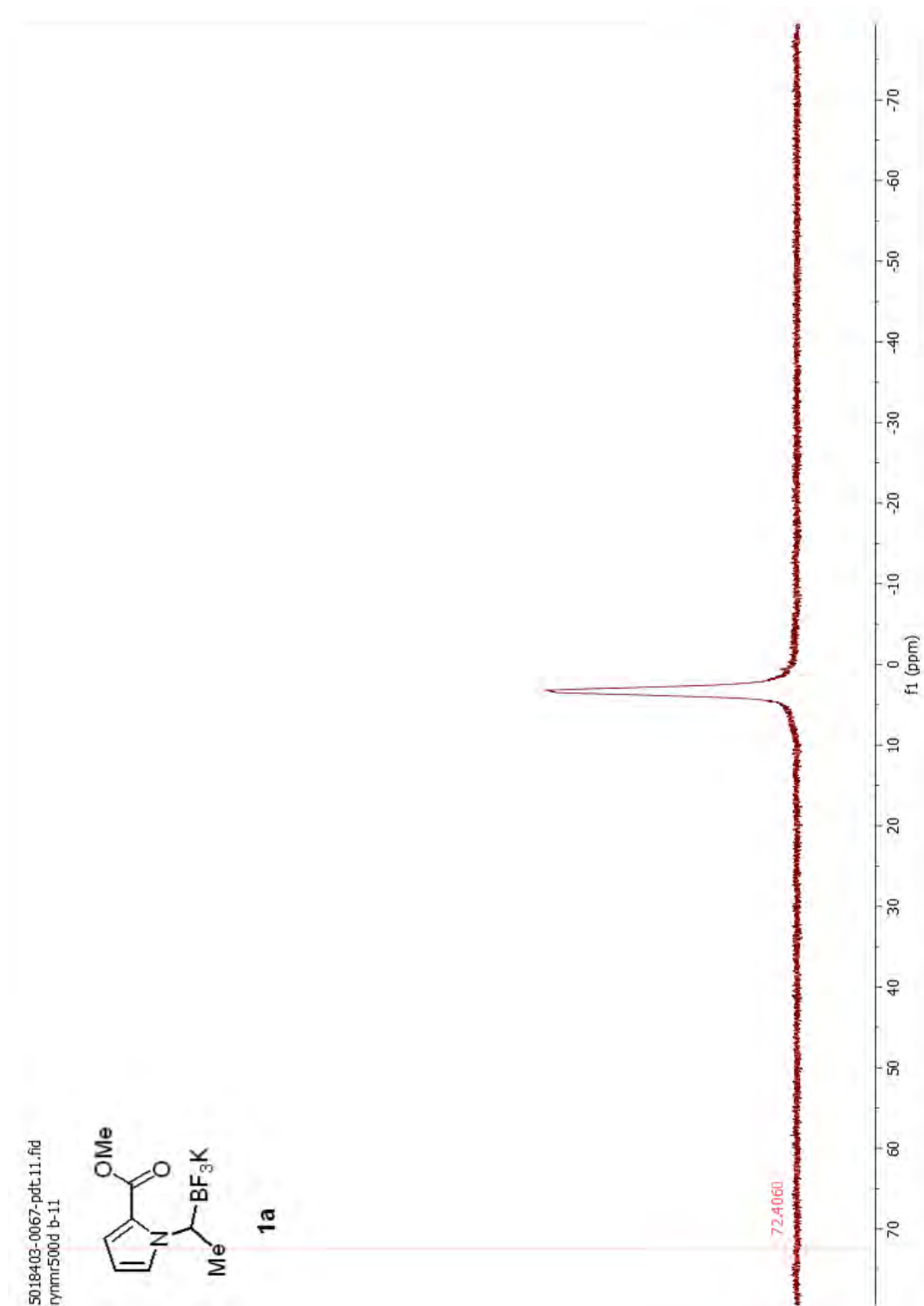
Spectra Relevant to Chapter 1:

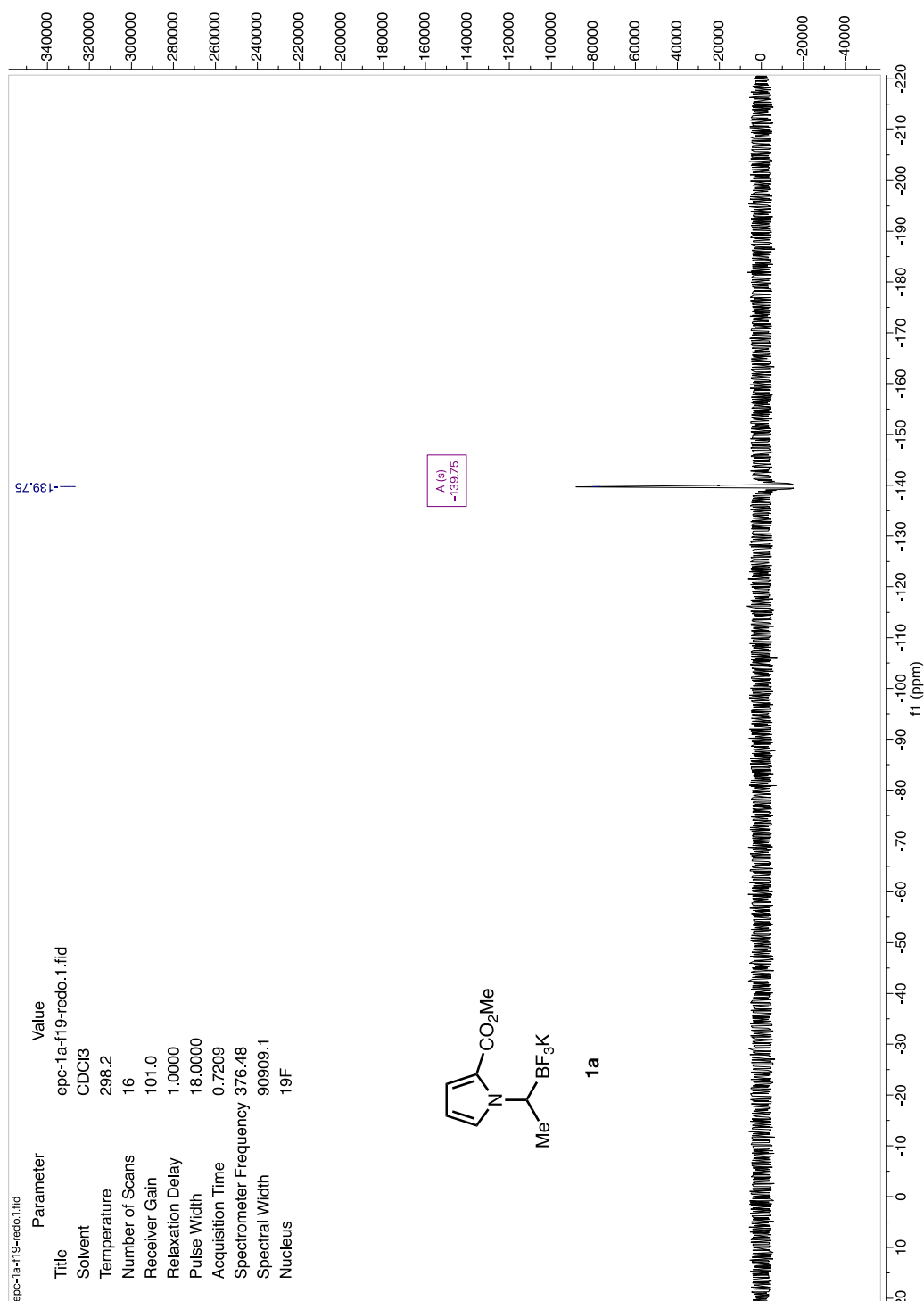
Enantioselective Synthesis of N-Benzylic Heterocycles using

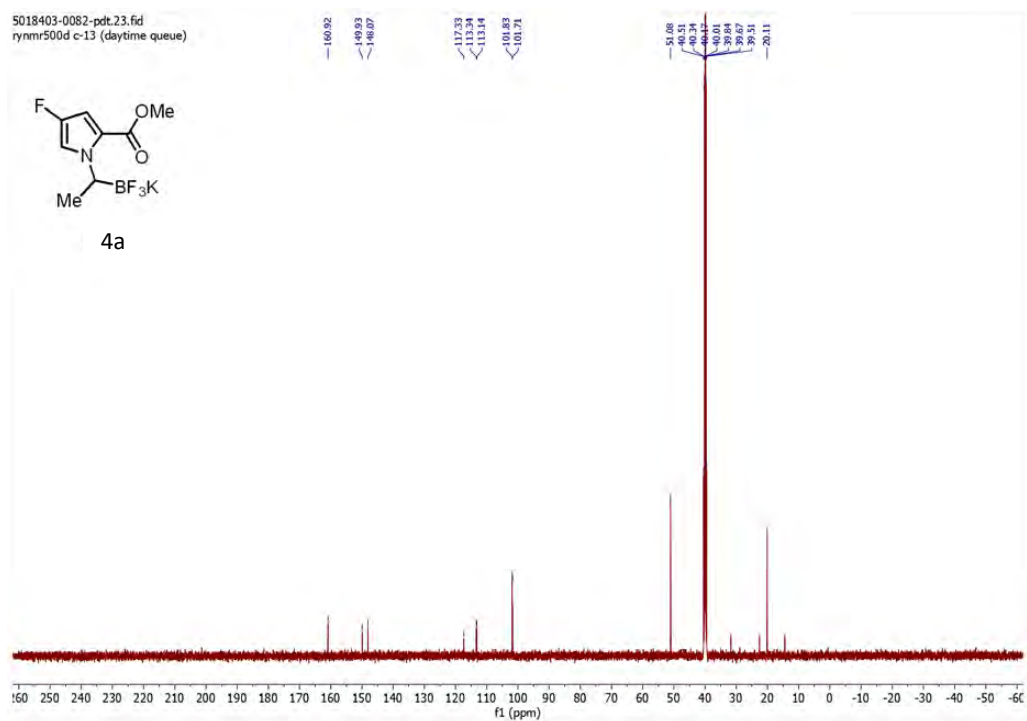
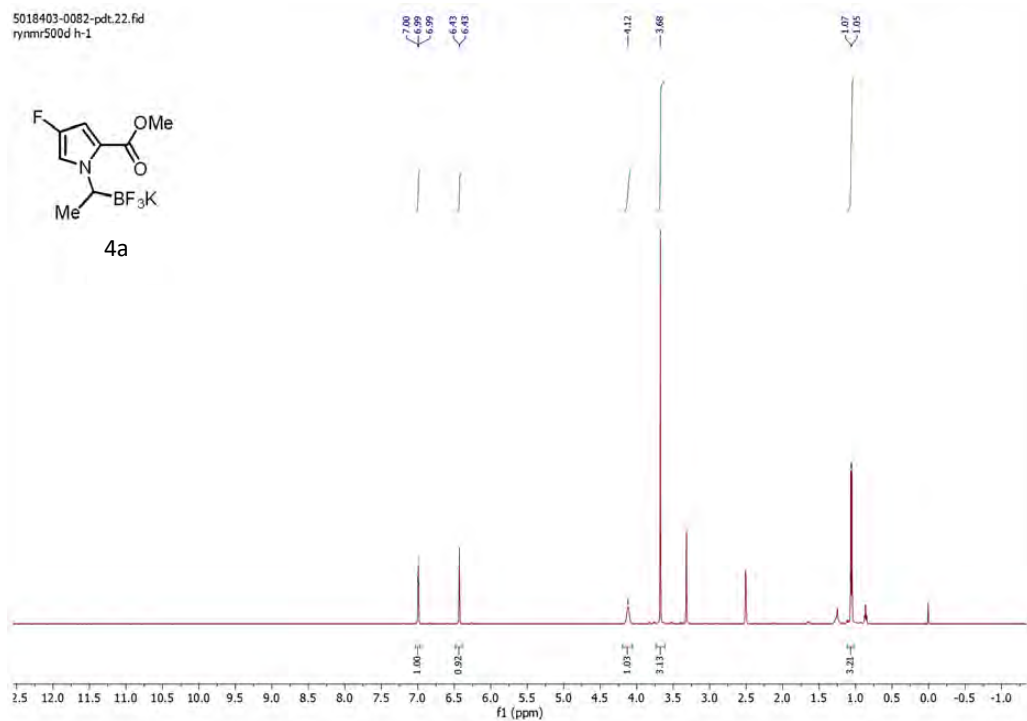
Ni/Photoredox Dual Catalysis

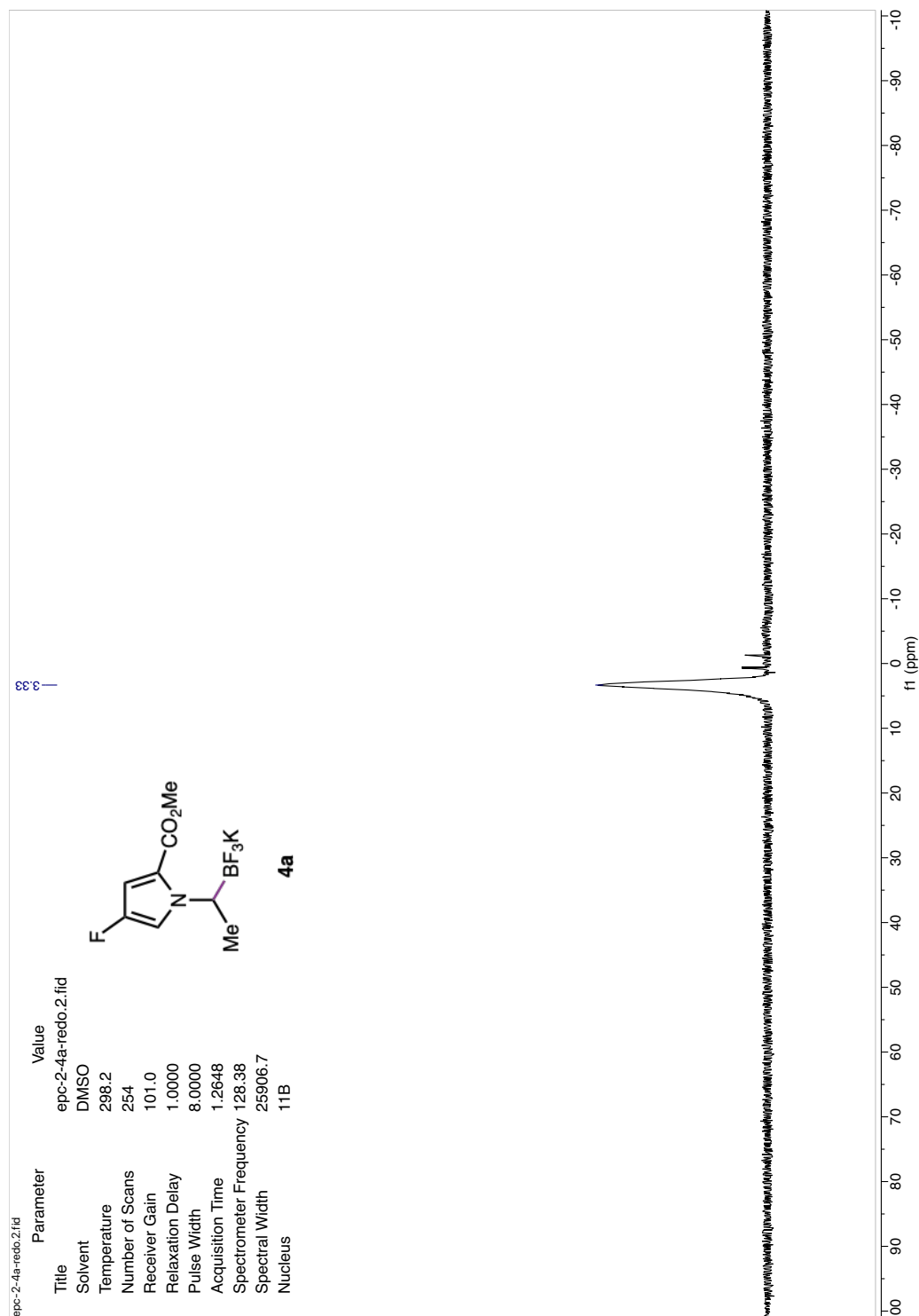


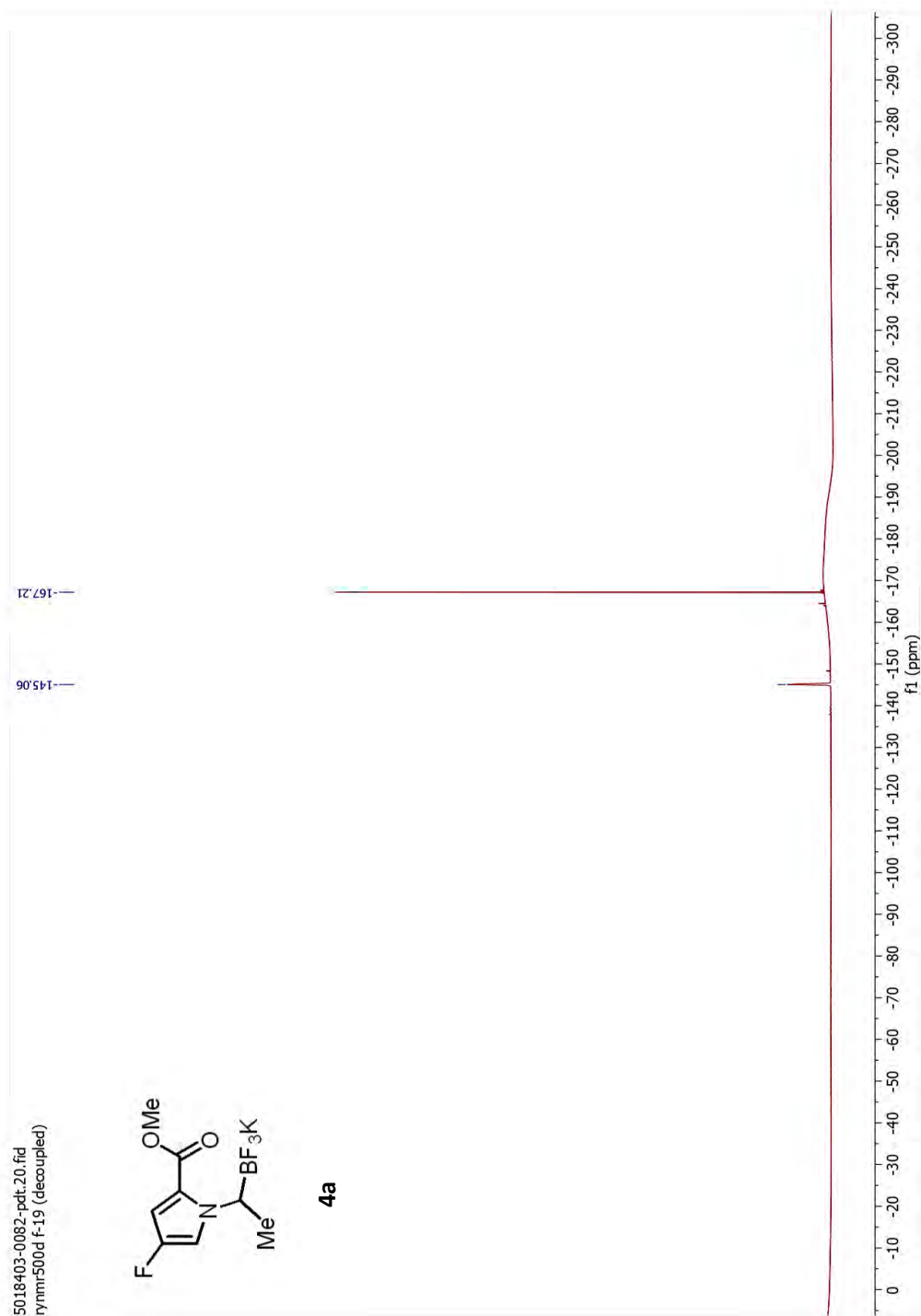


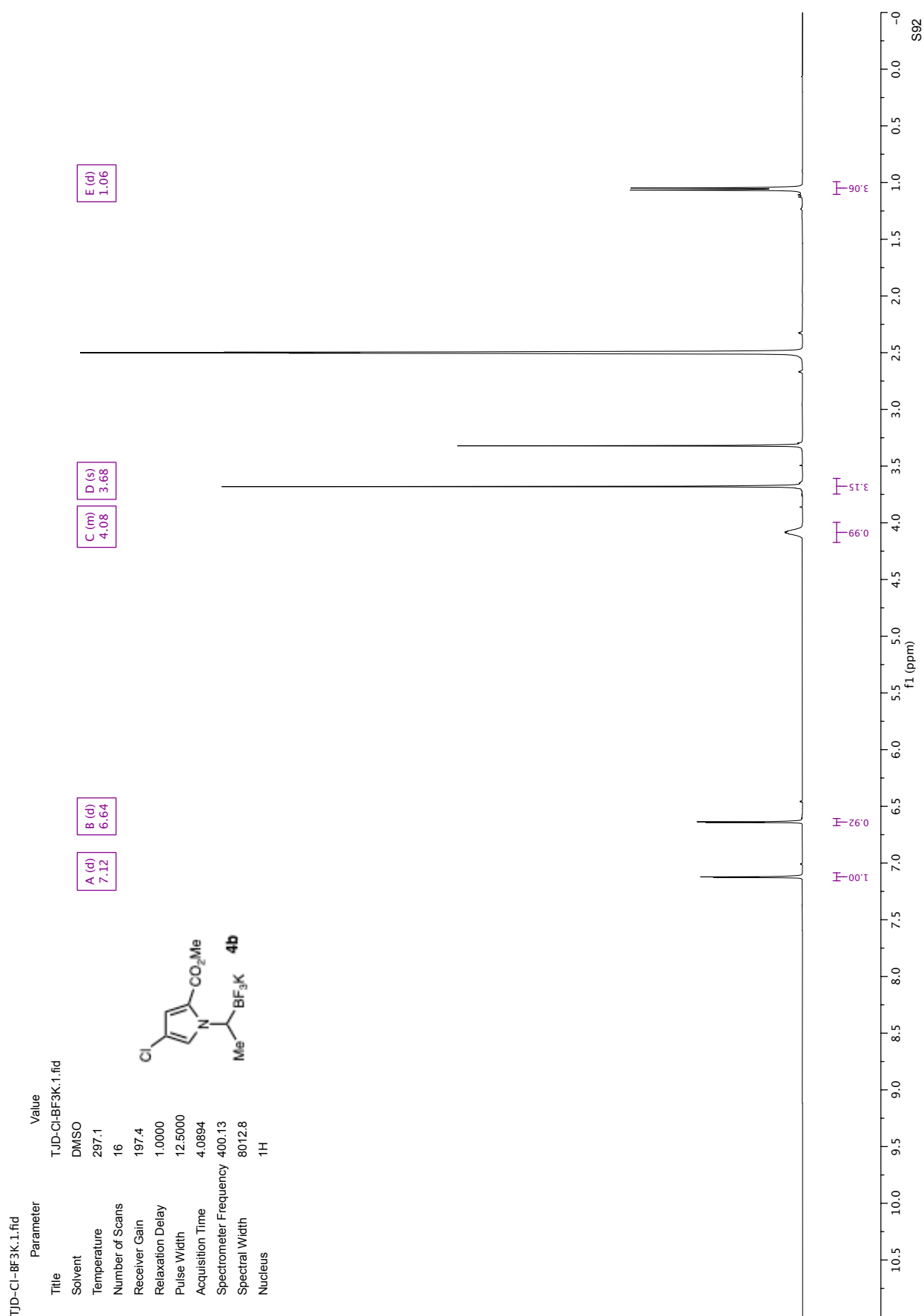


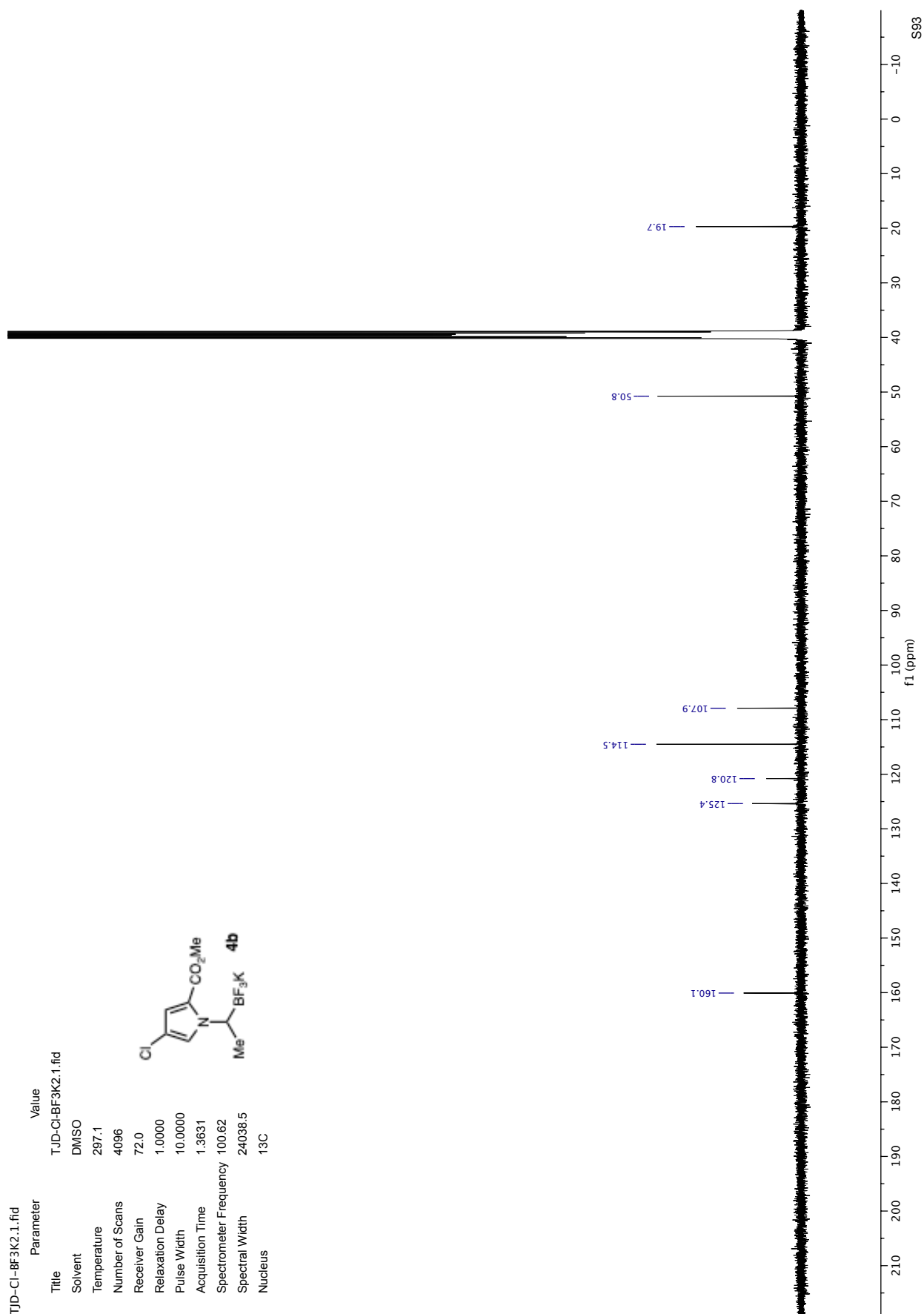


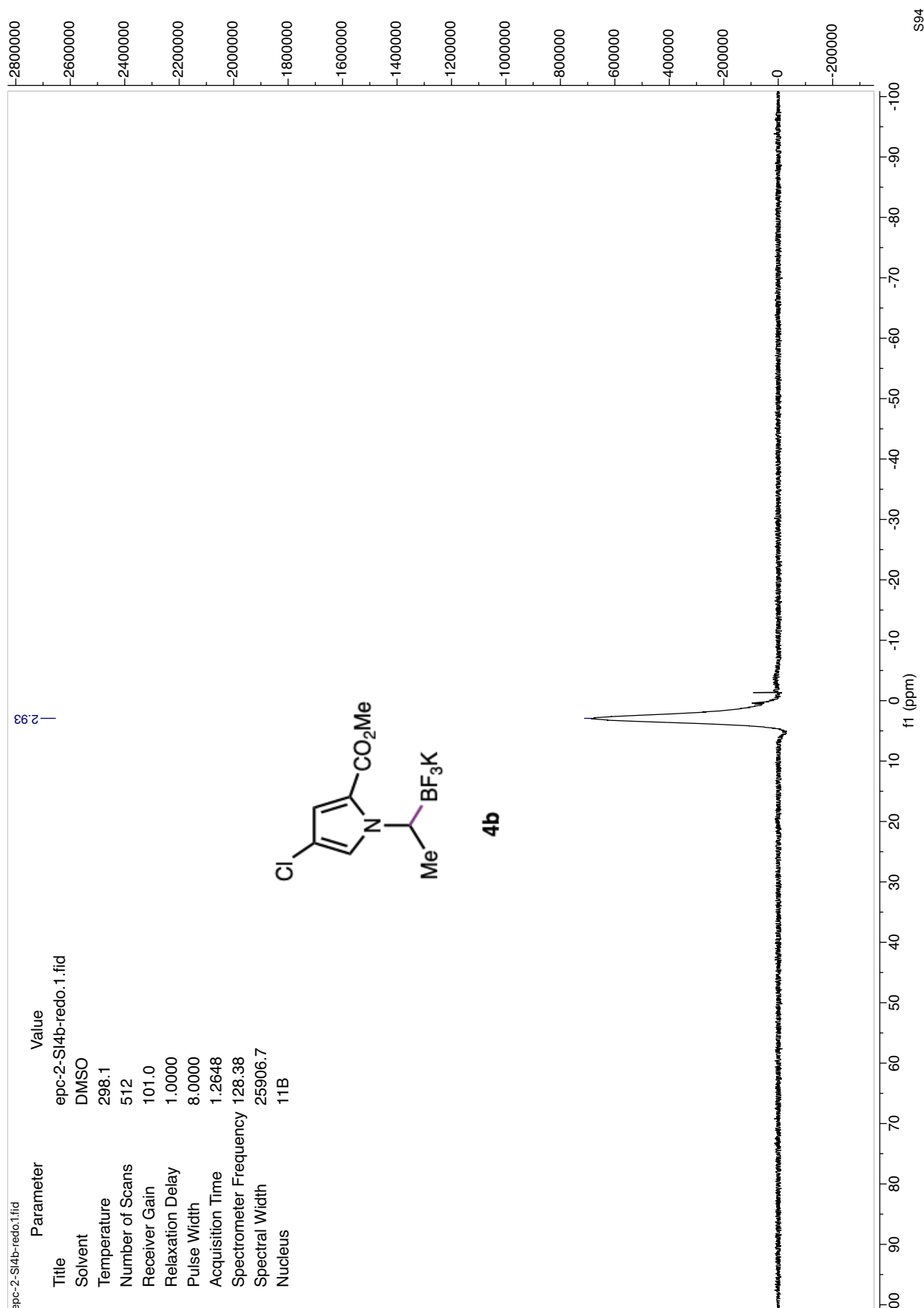


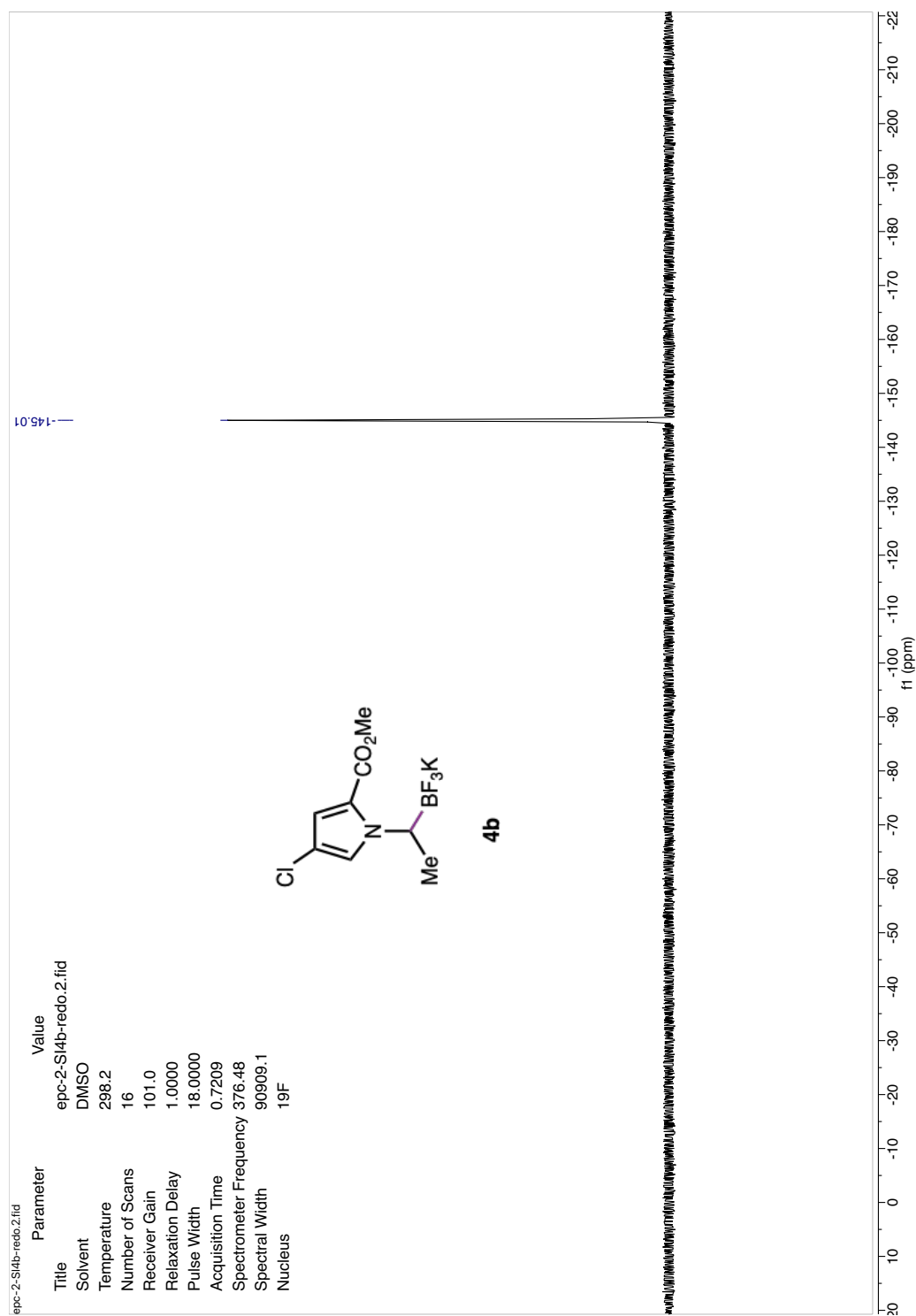


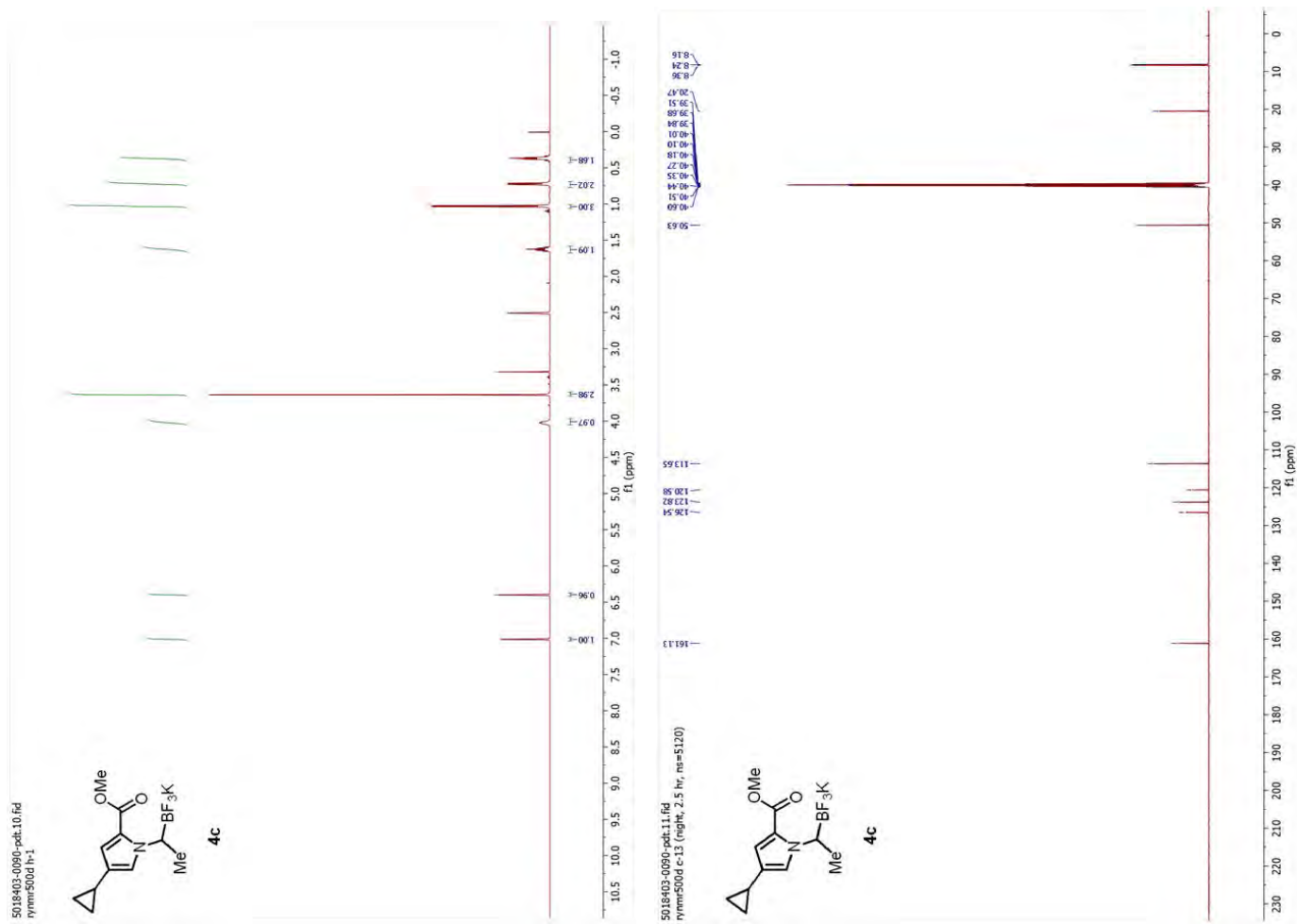




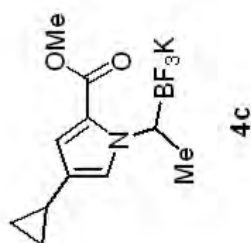




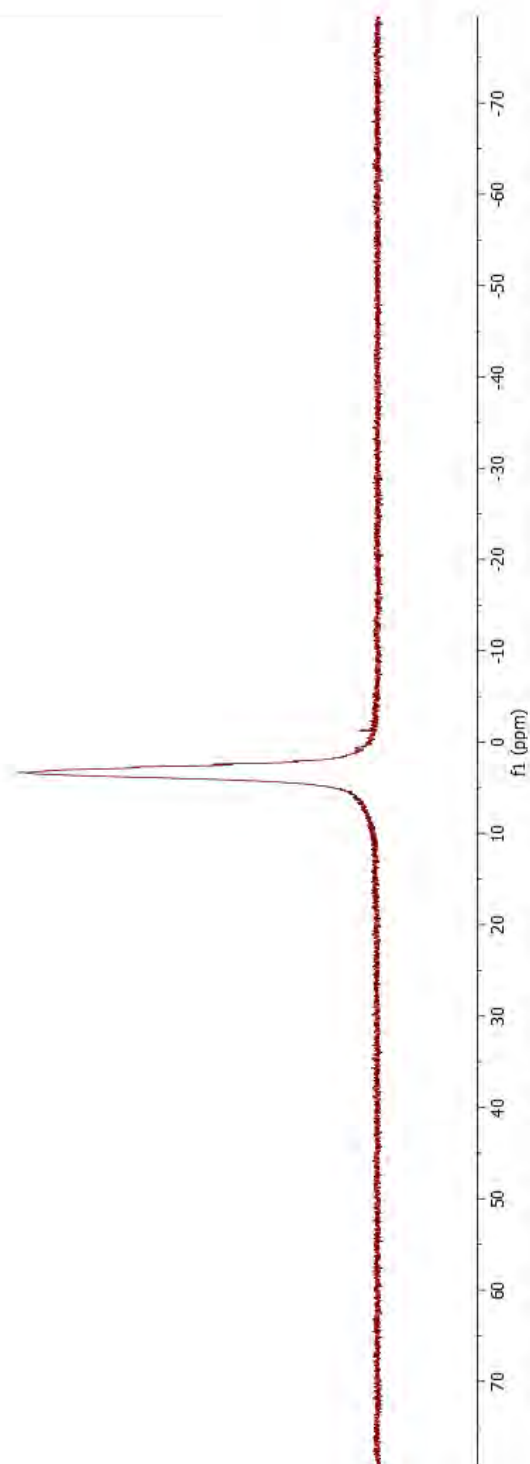




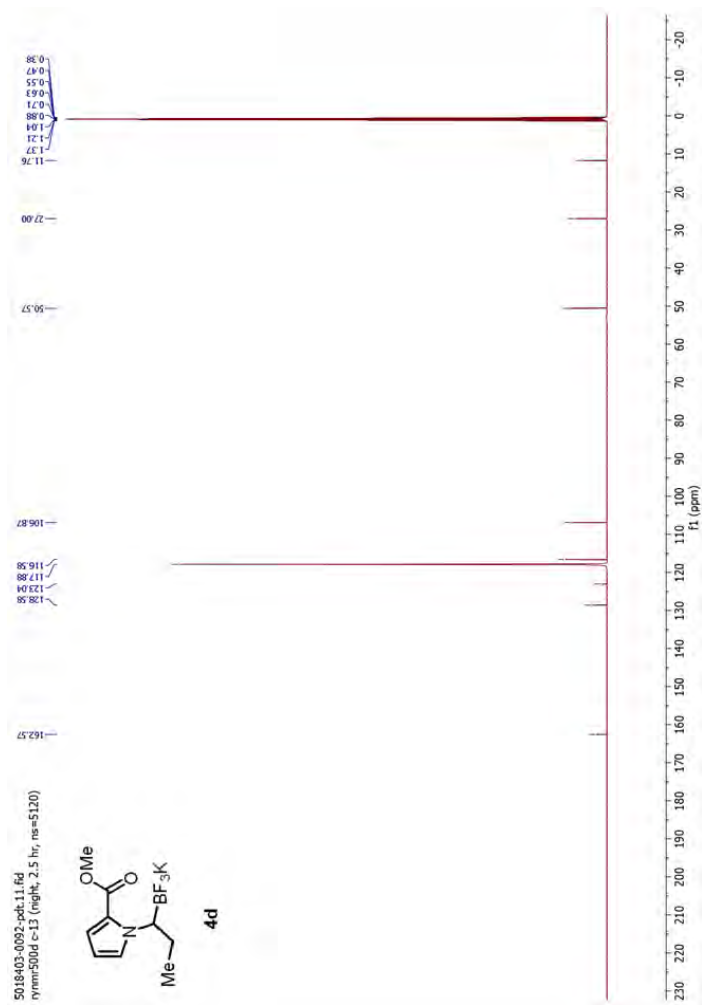
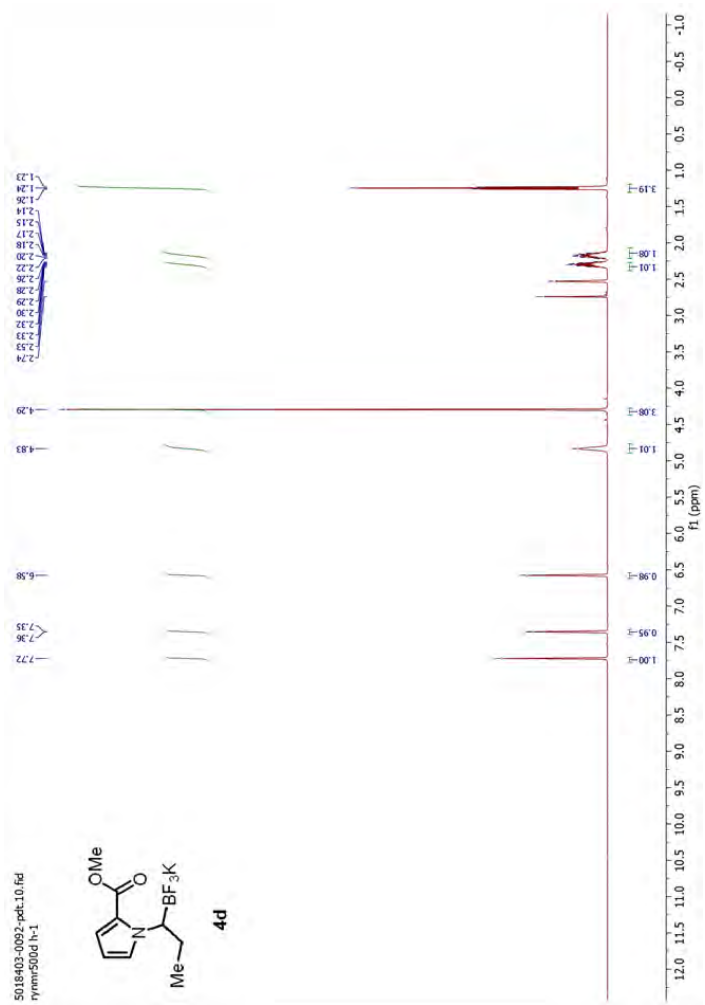
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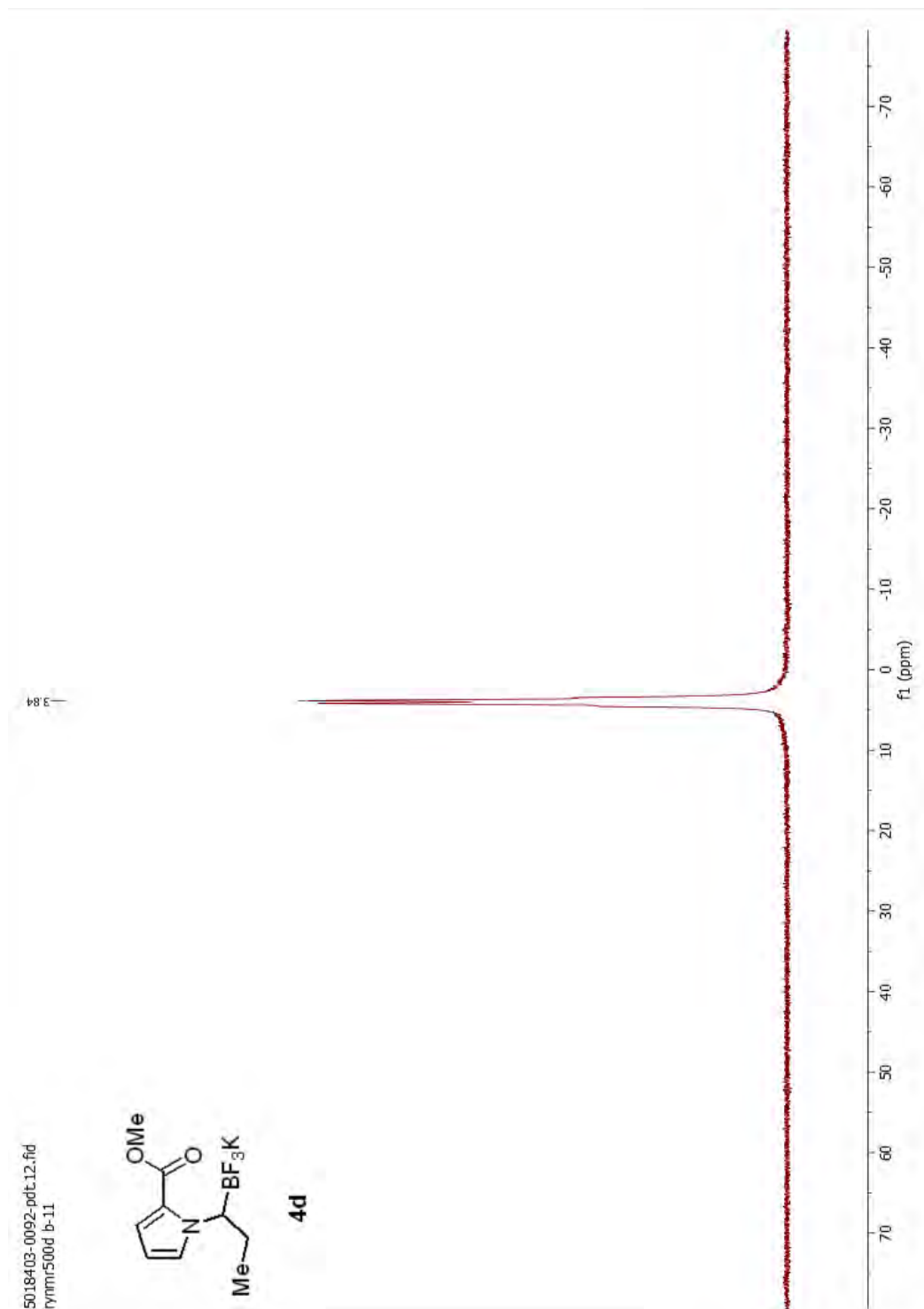


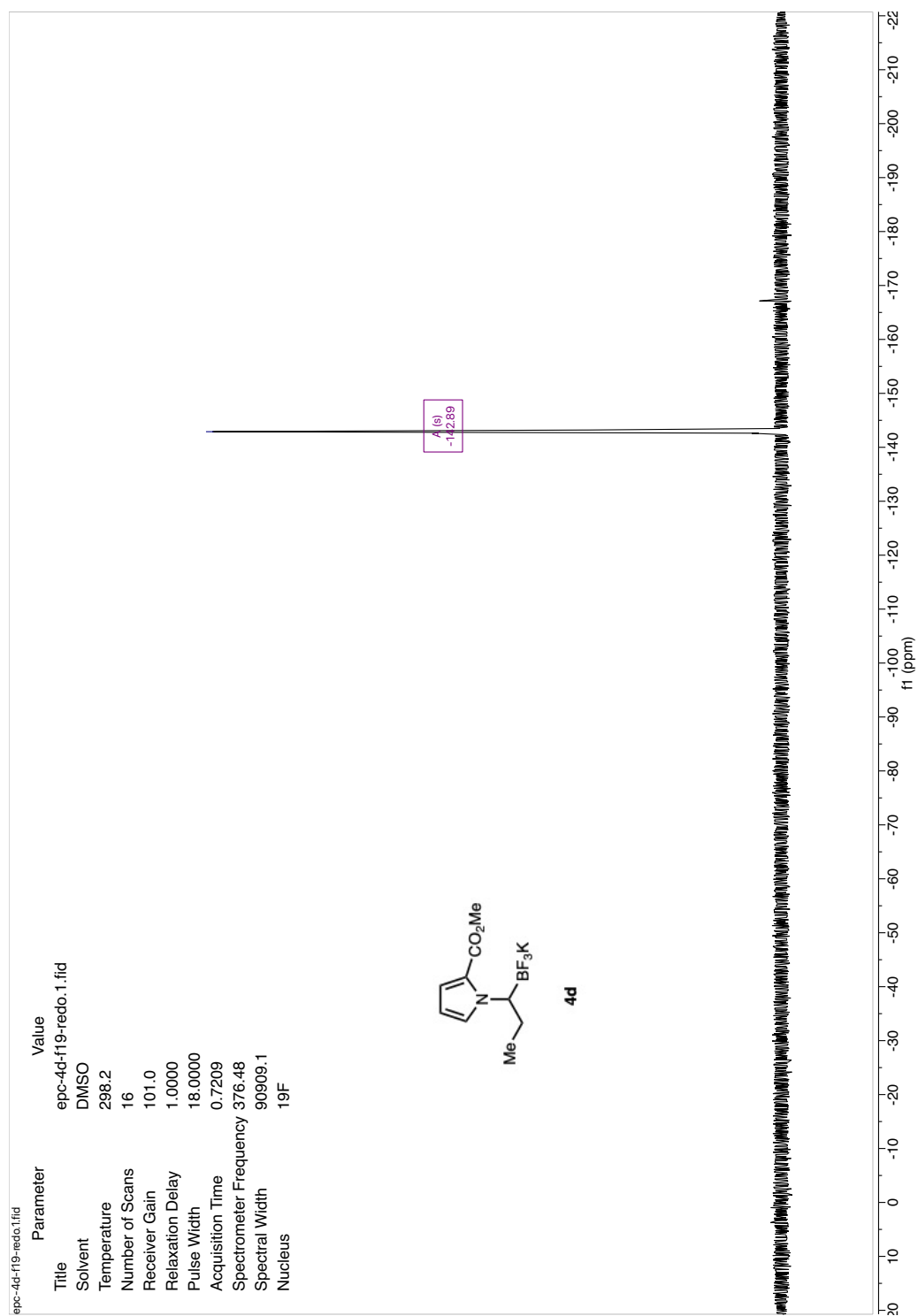
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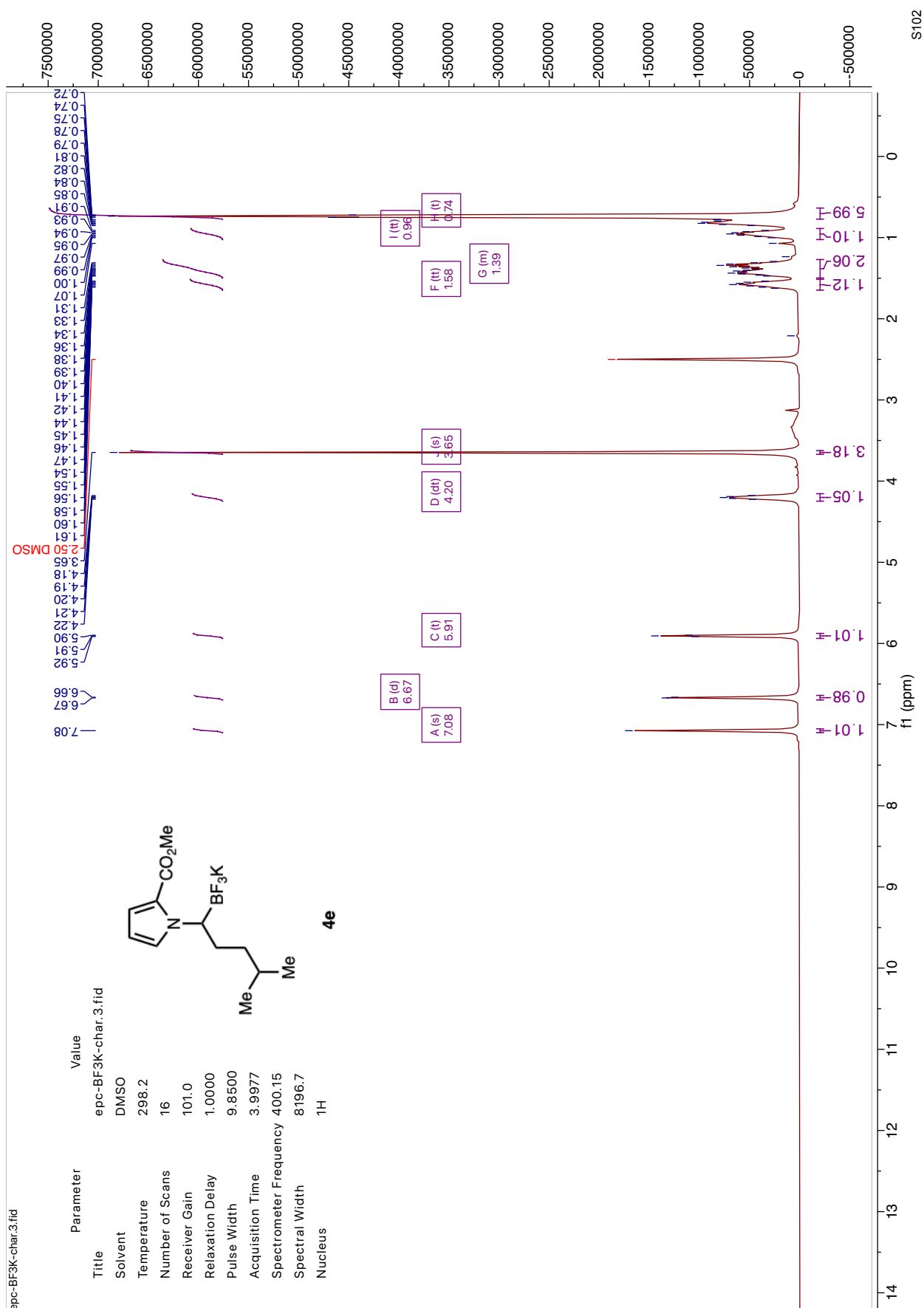


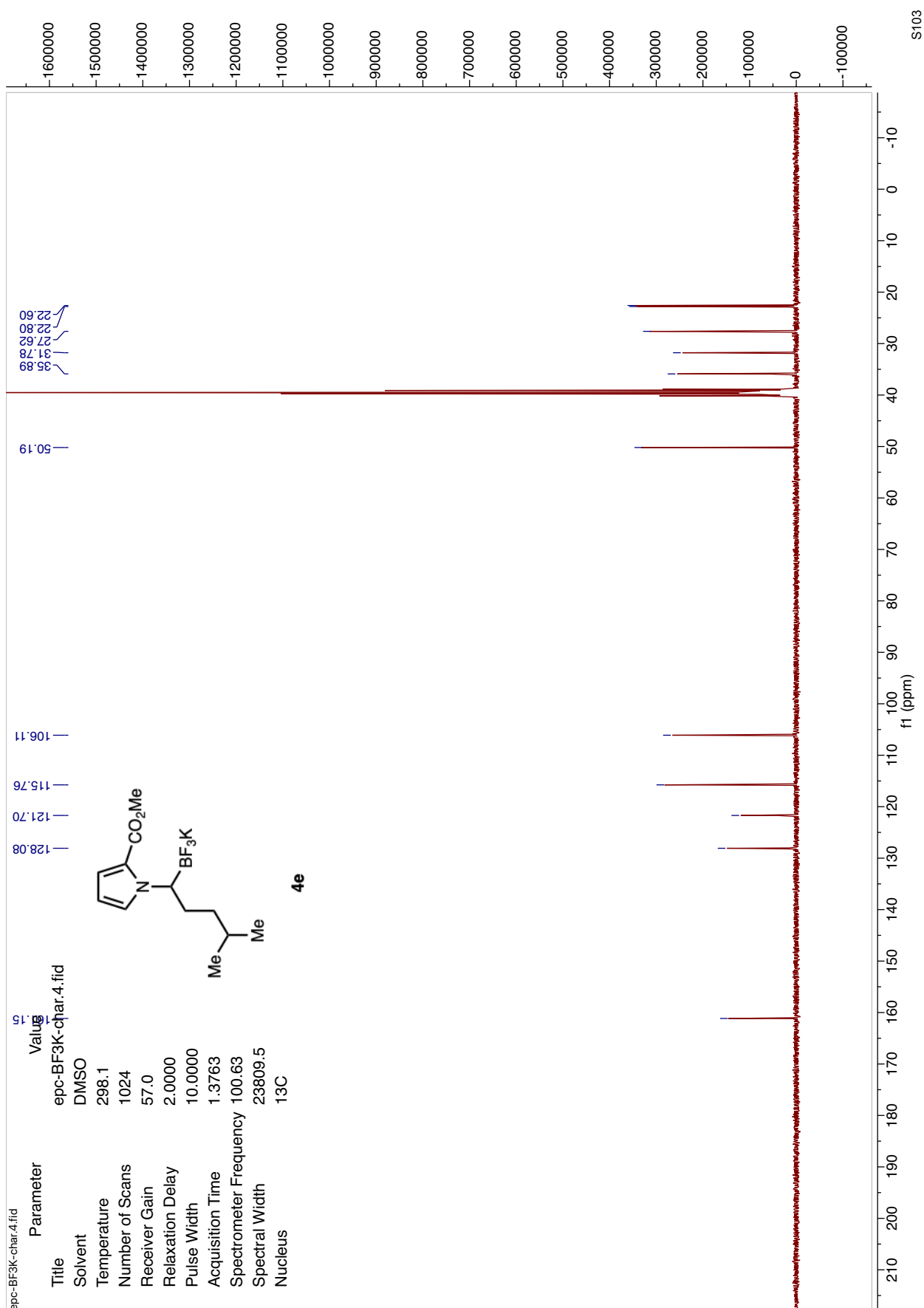


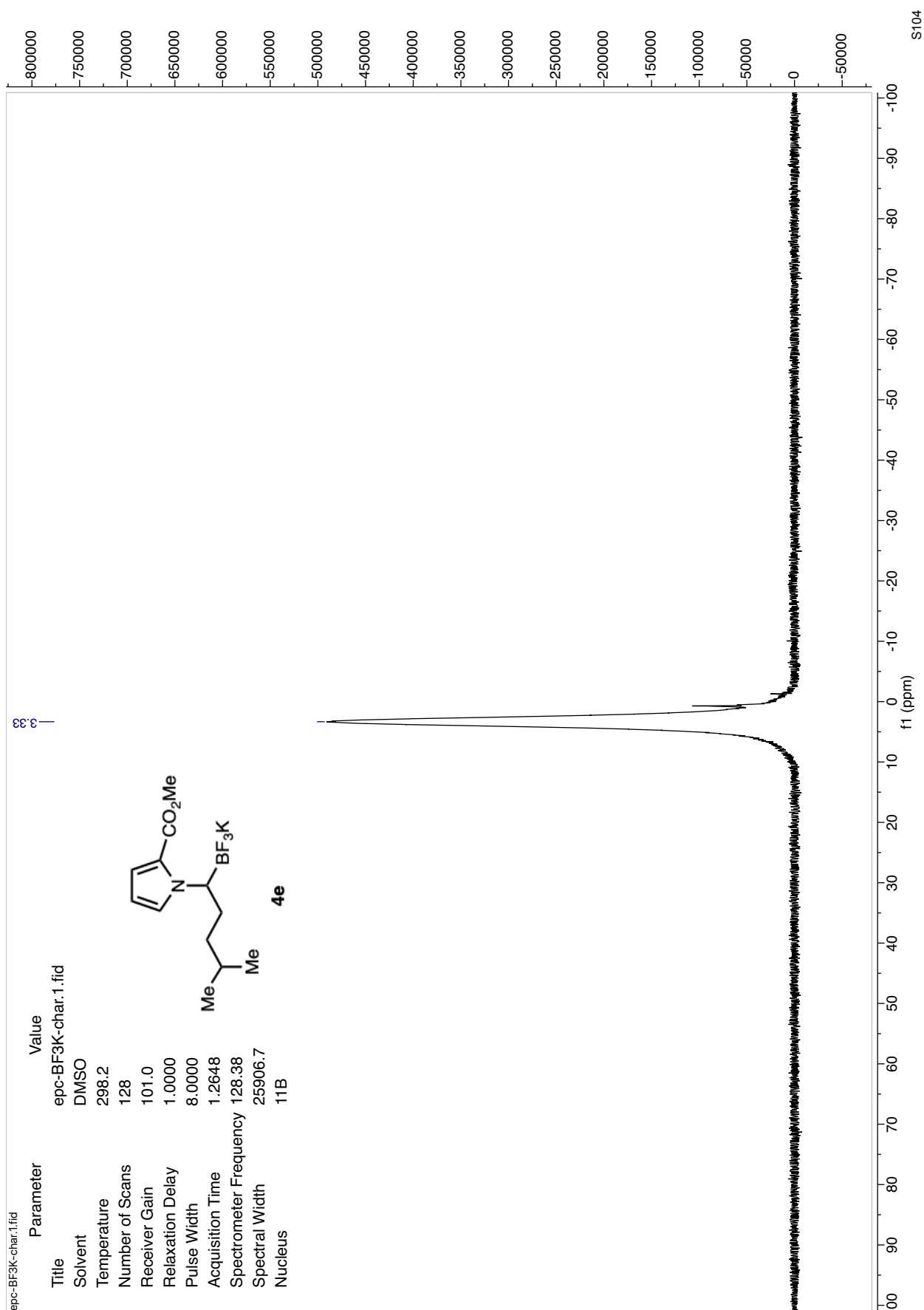


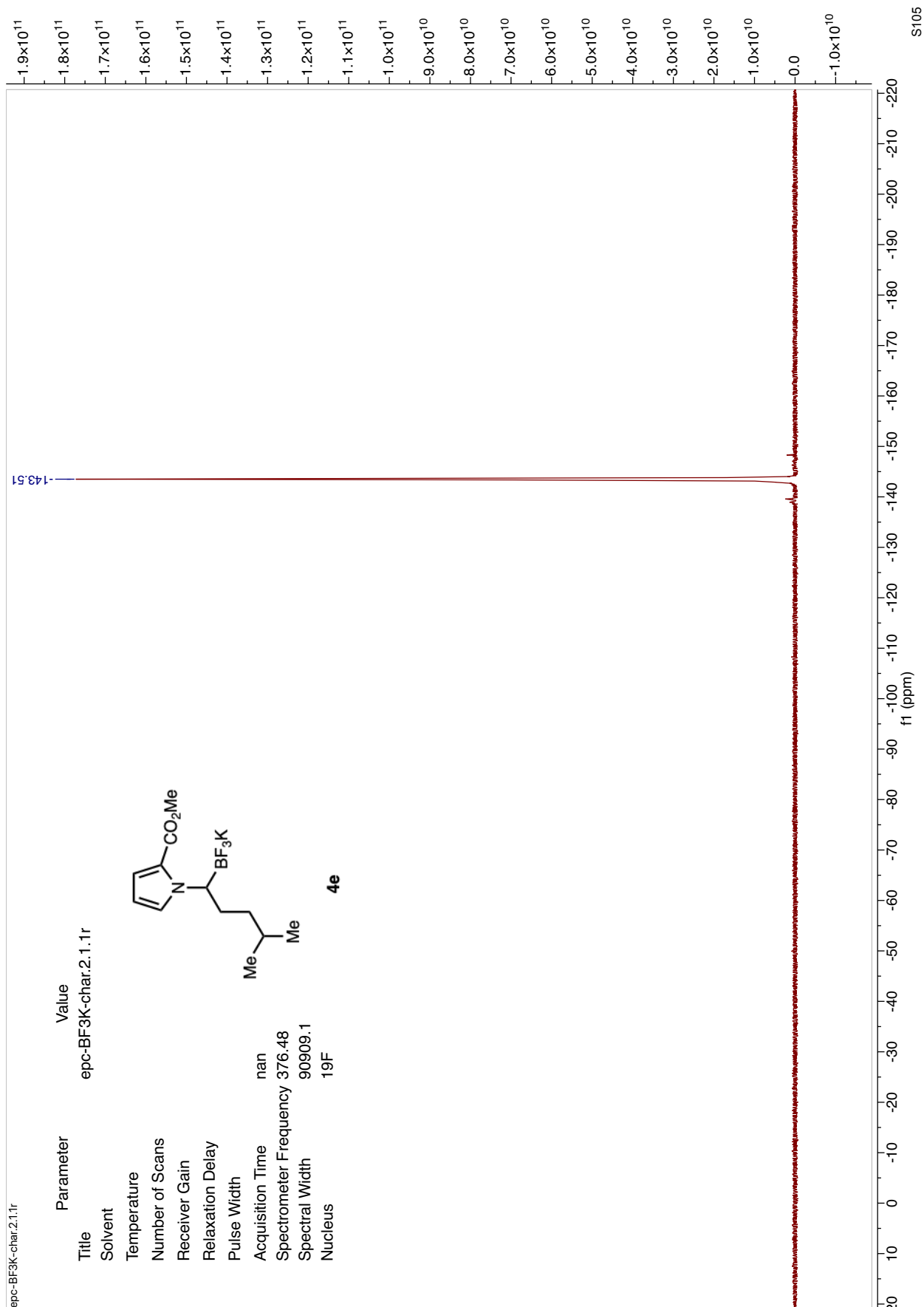


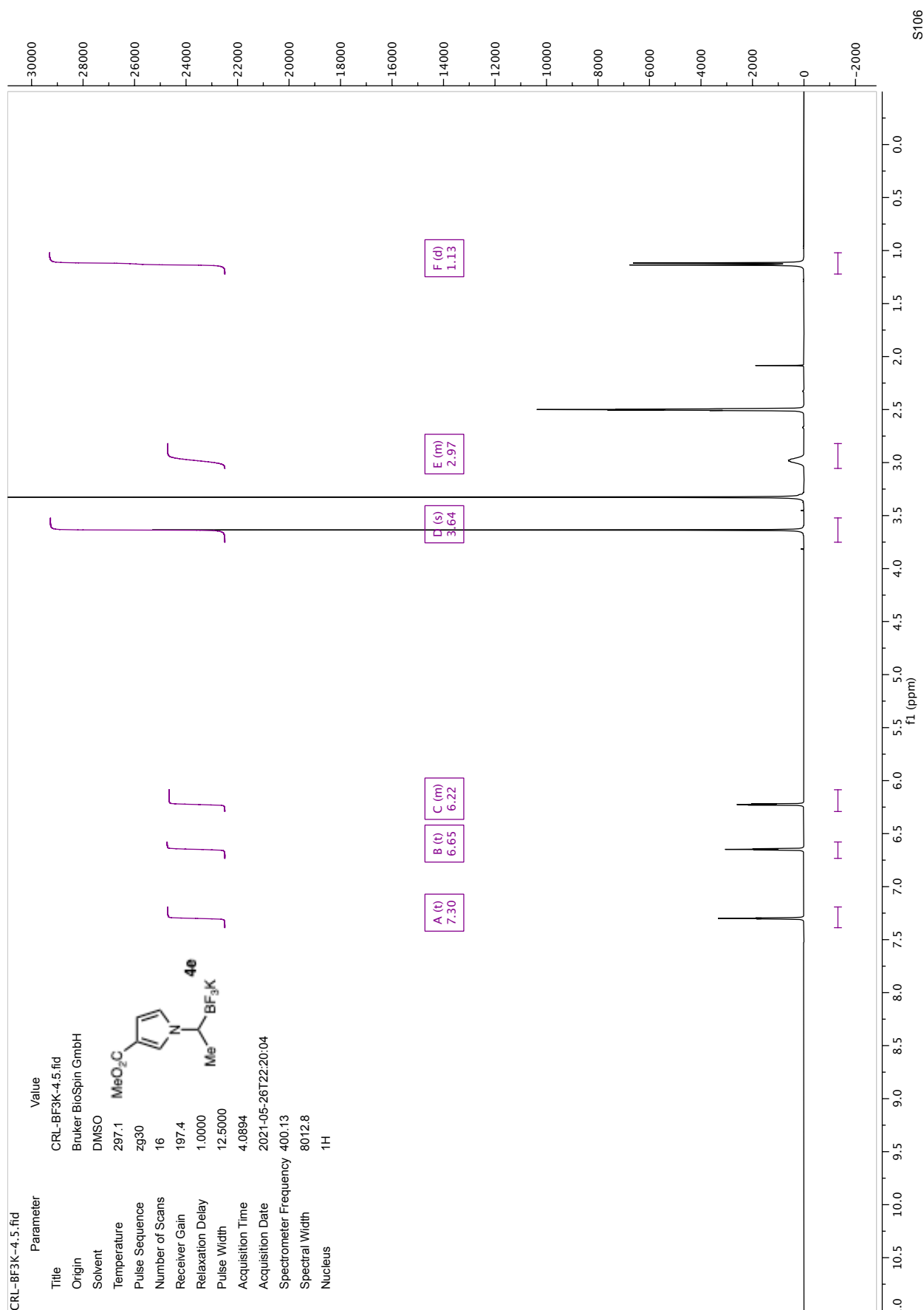


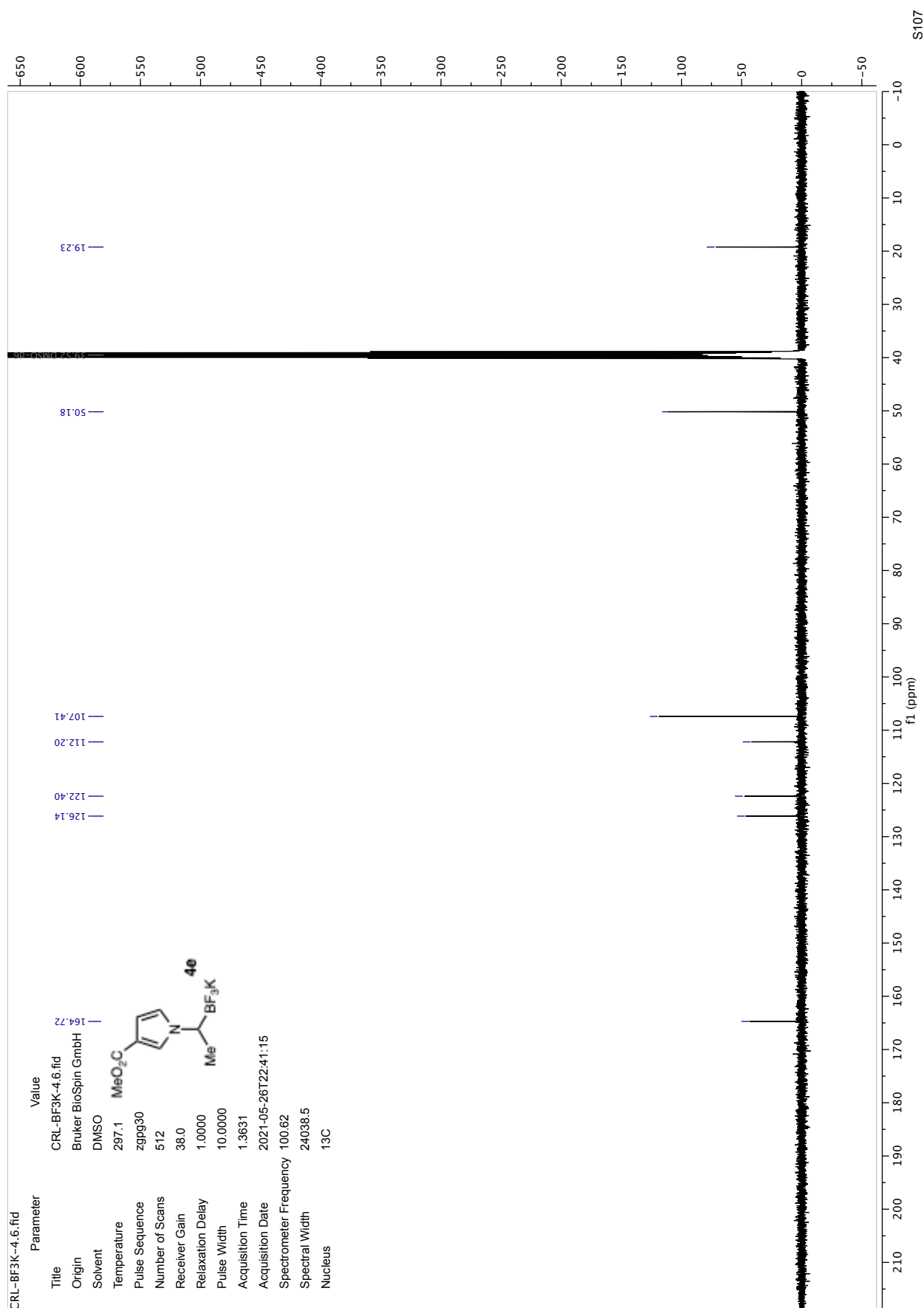


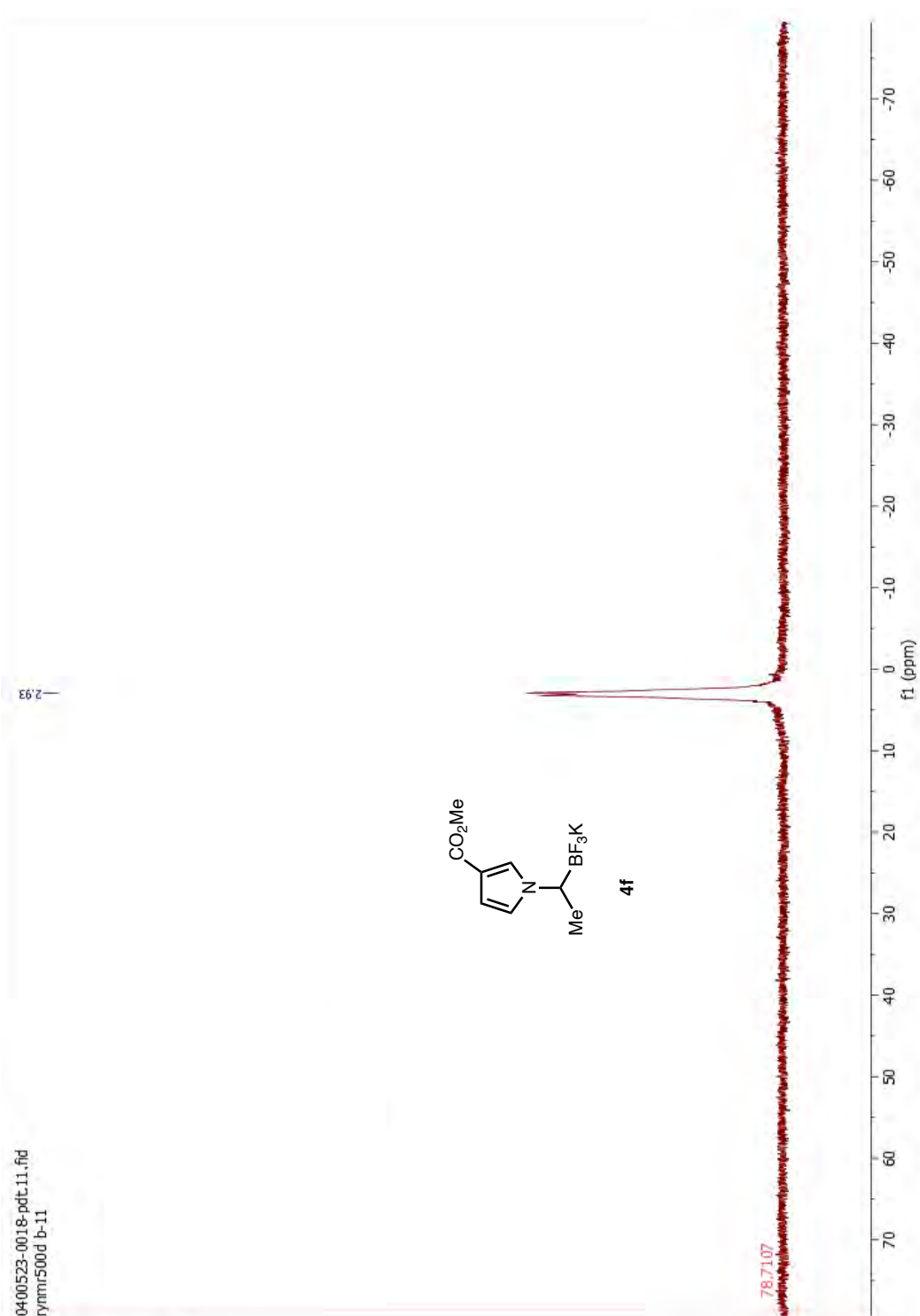


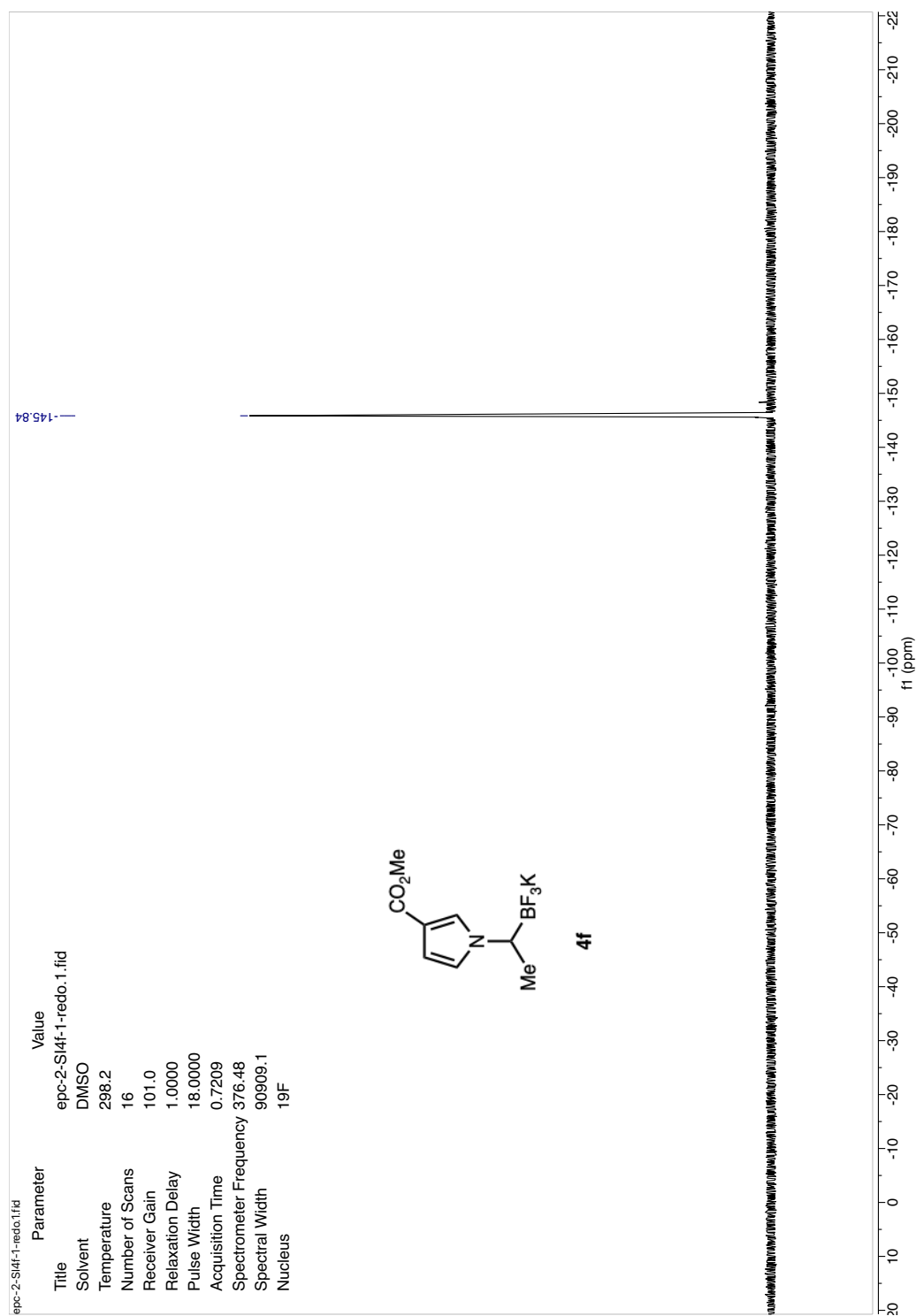


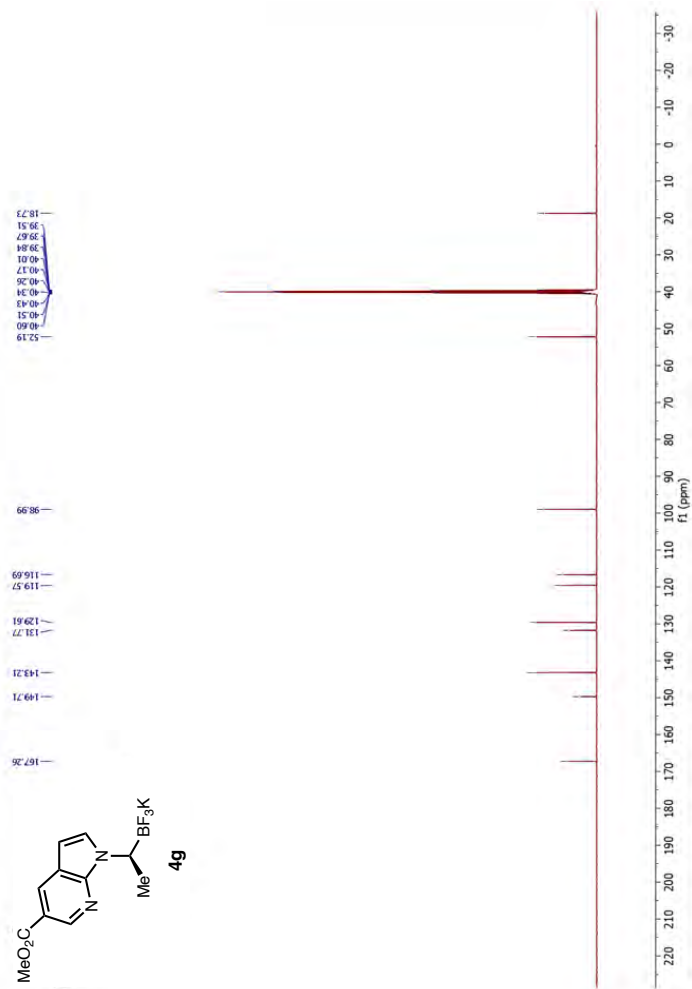
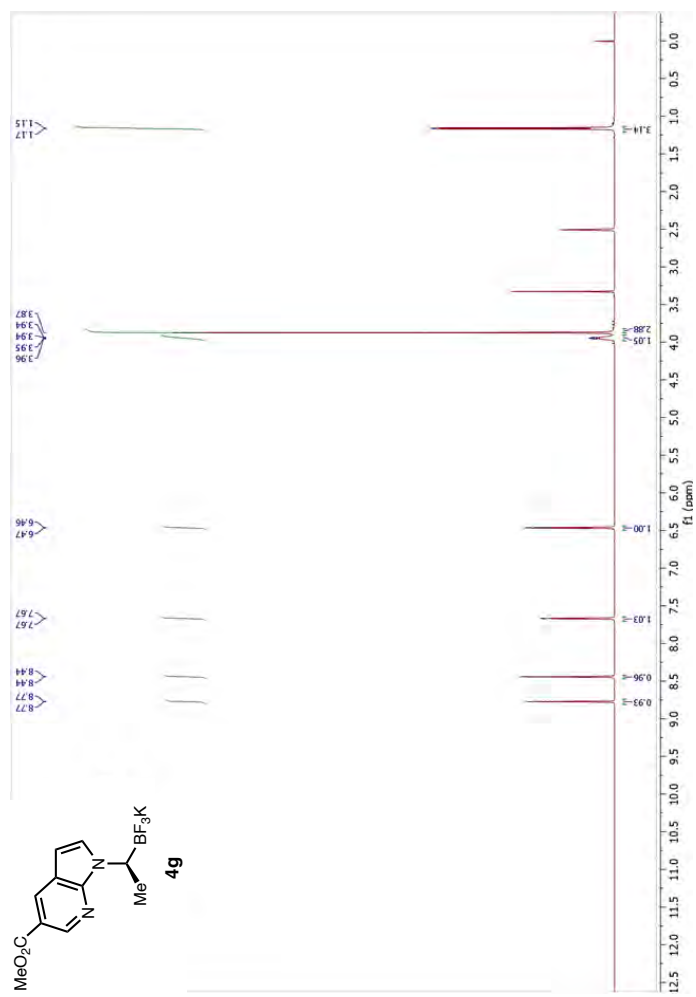




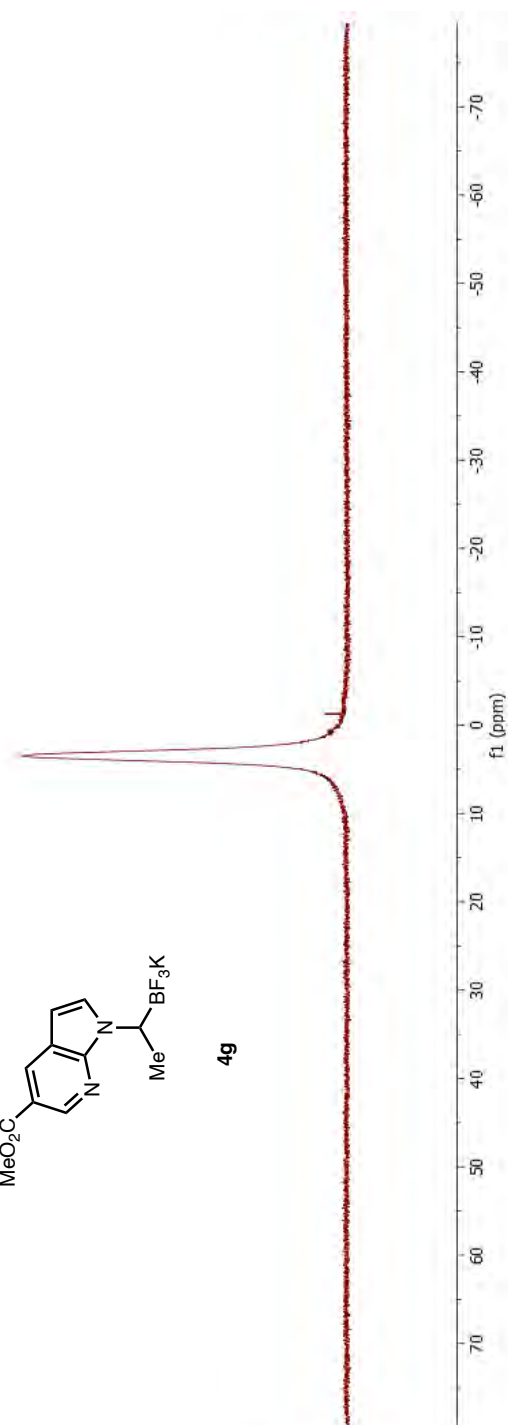
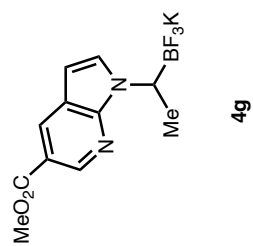


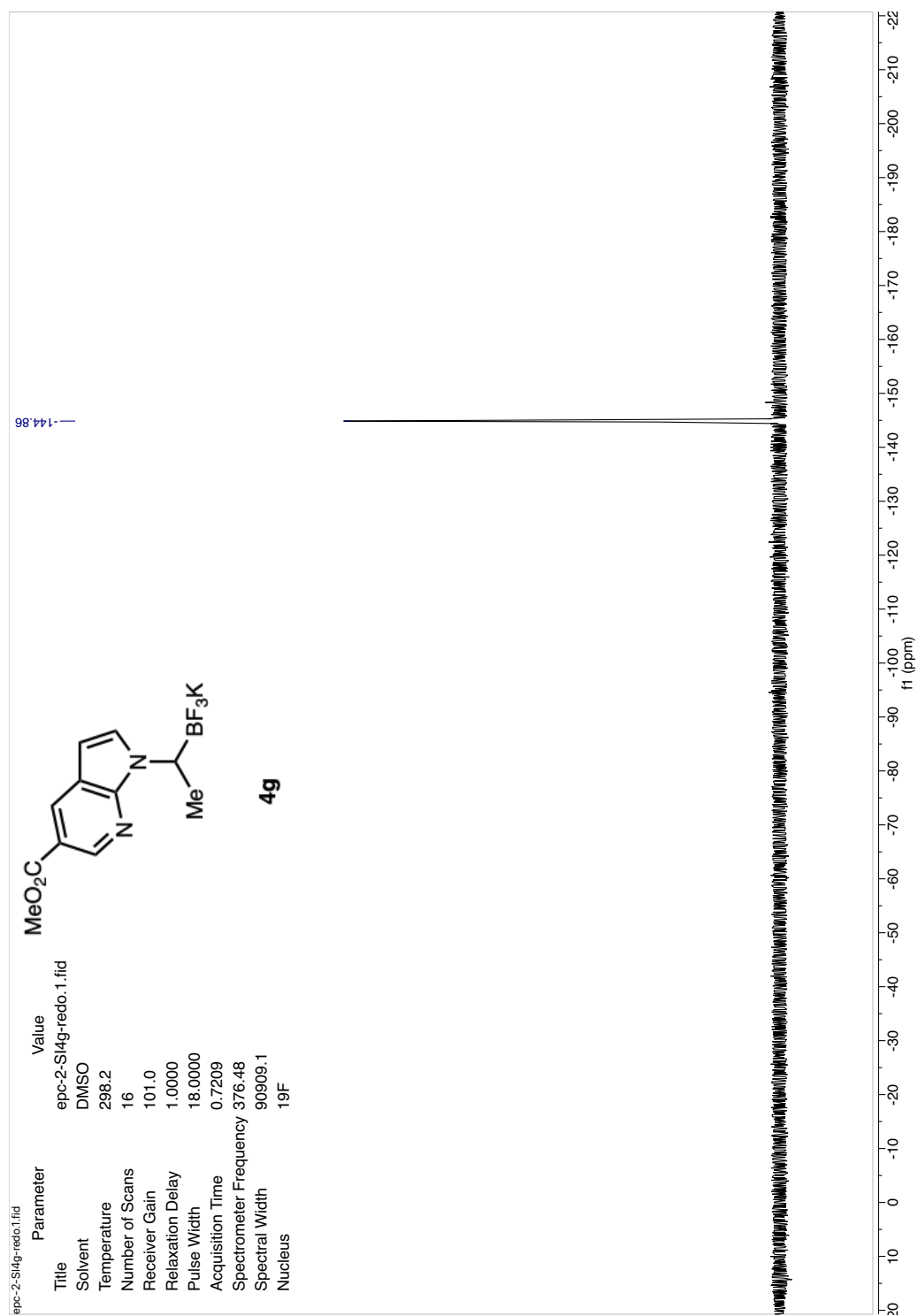


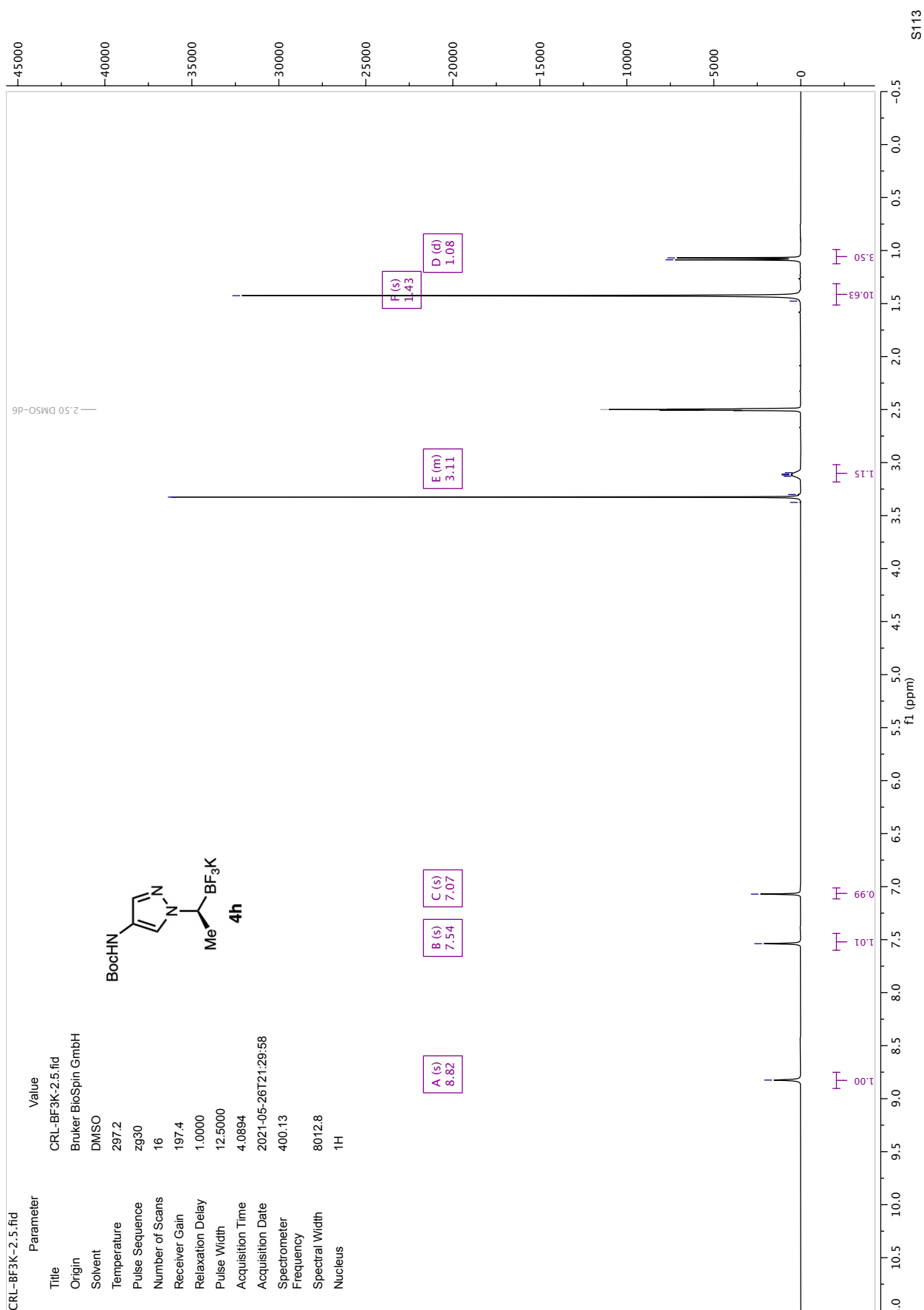


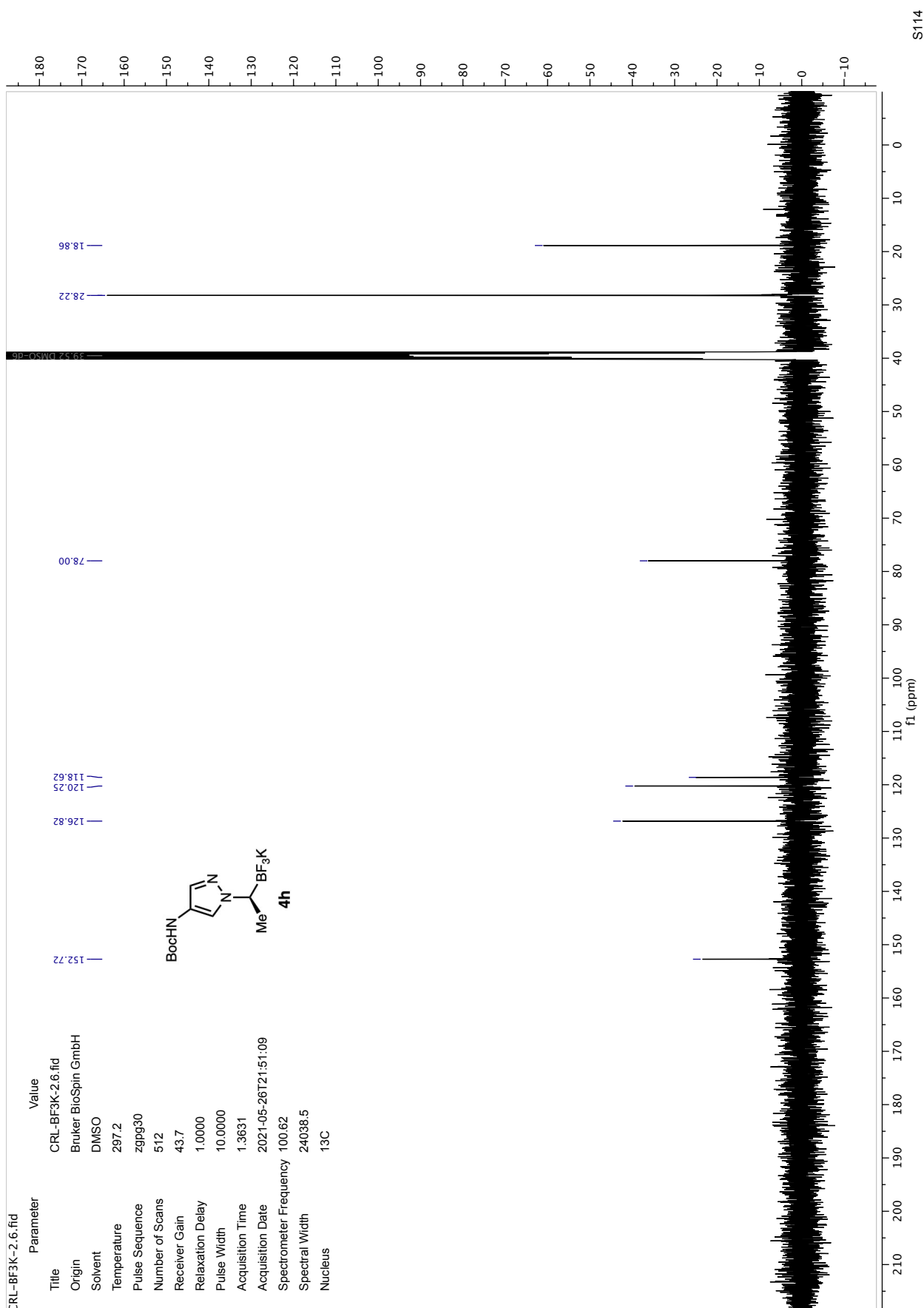


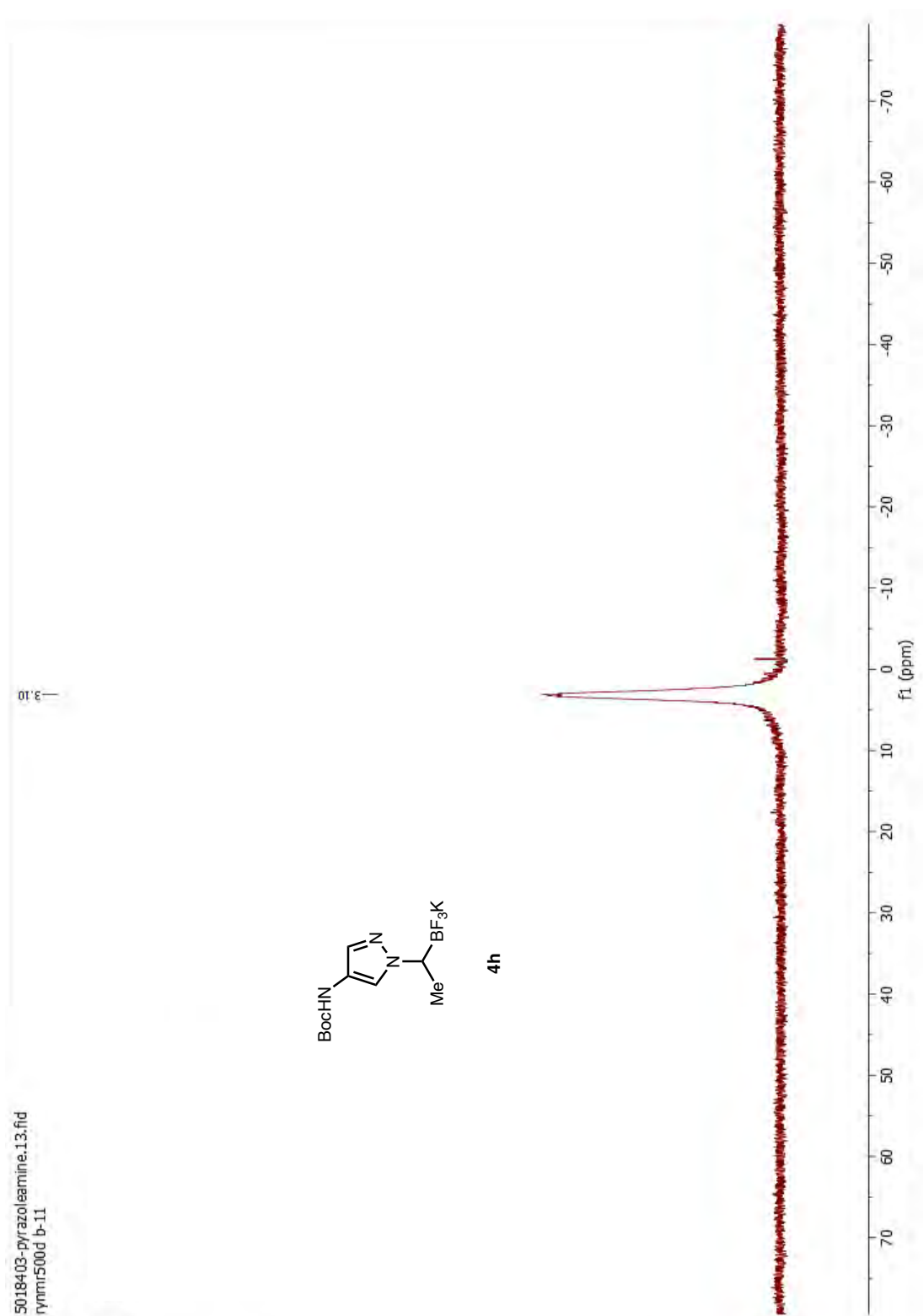
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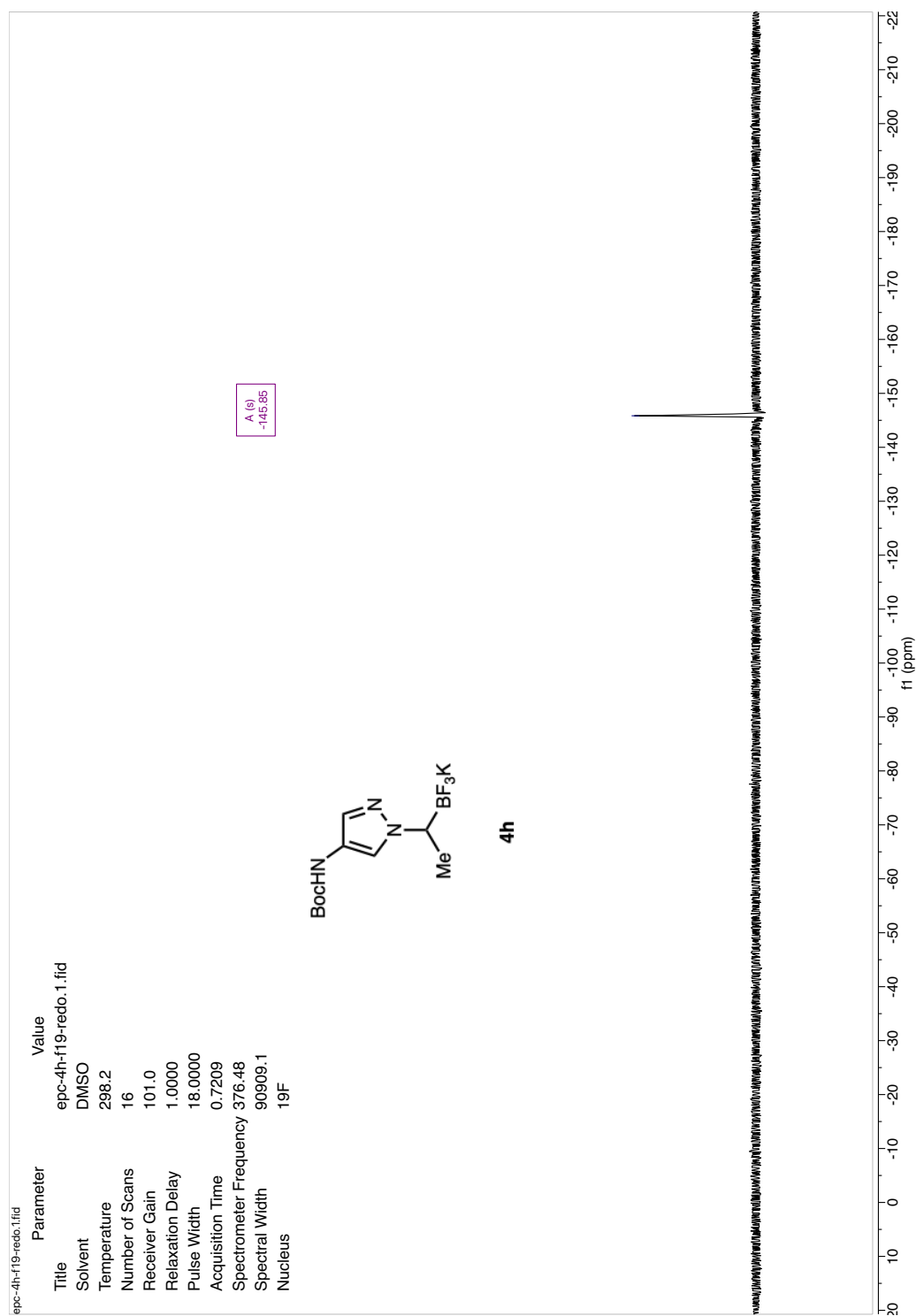


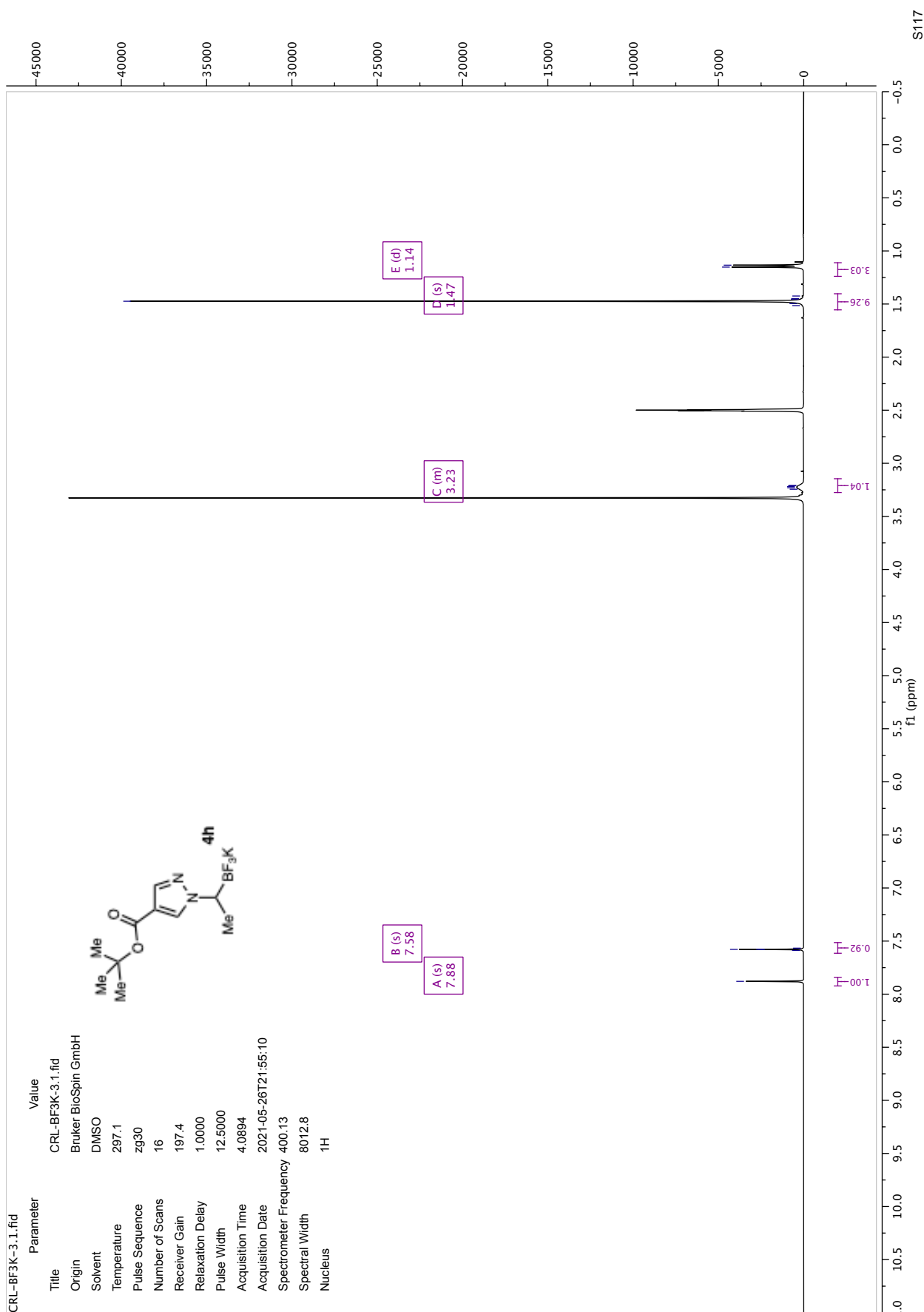


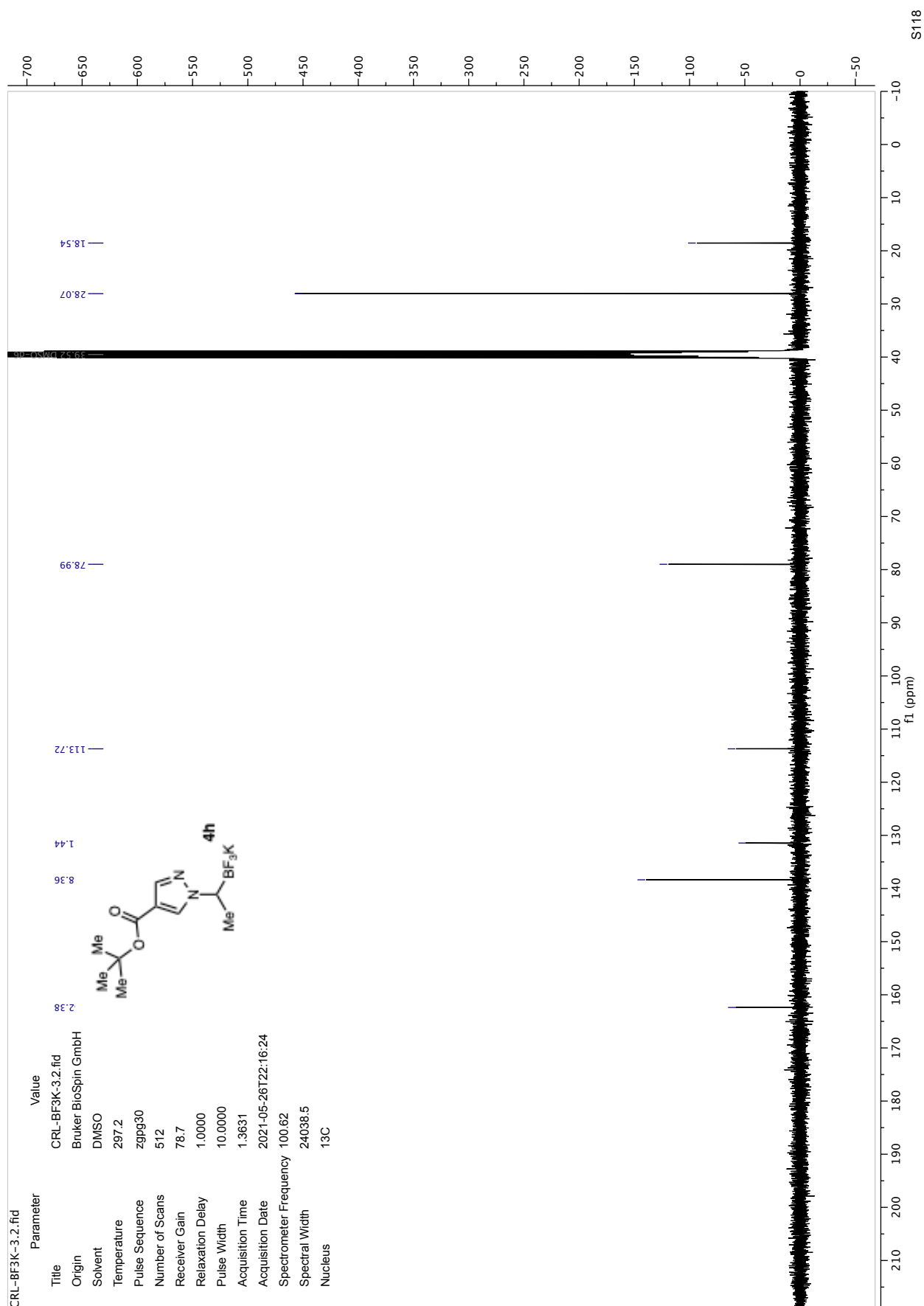




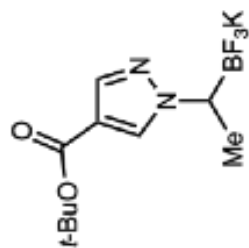




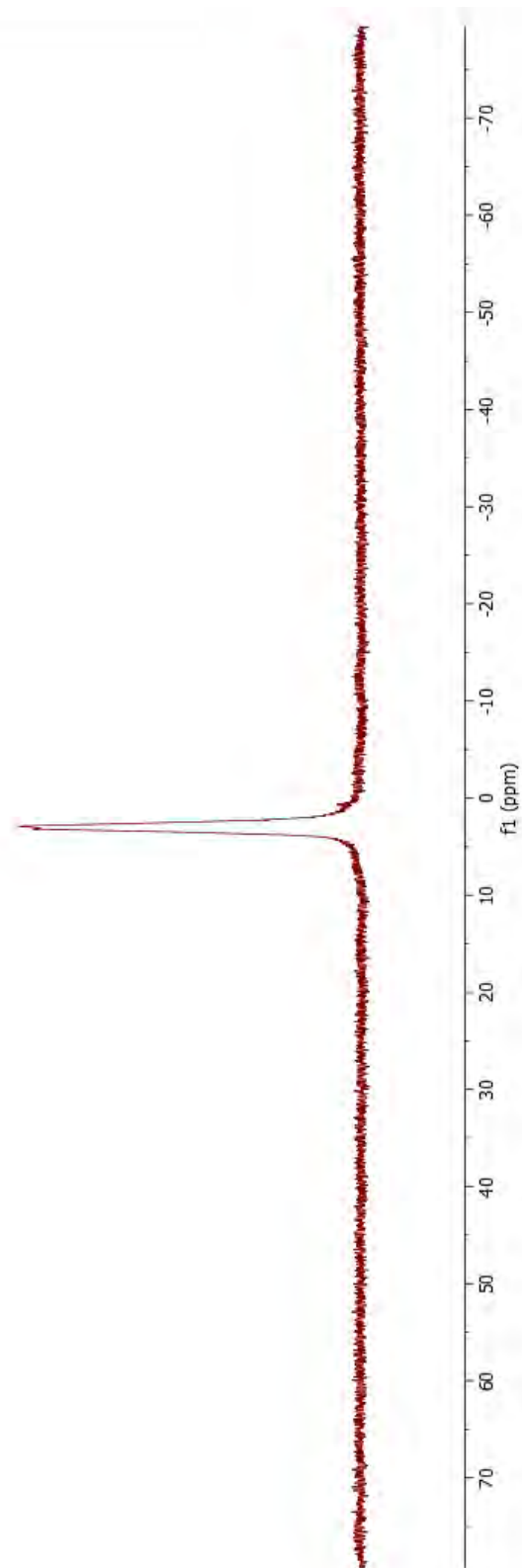


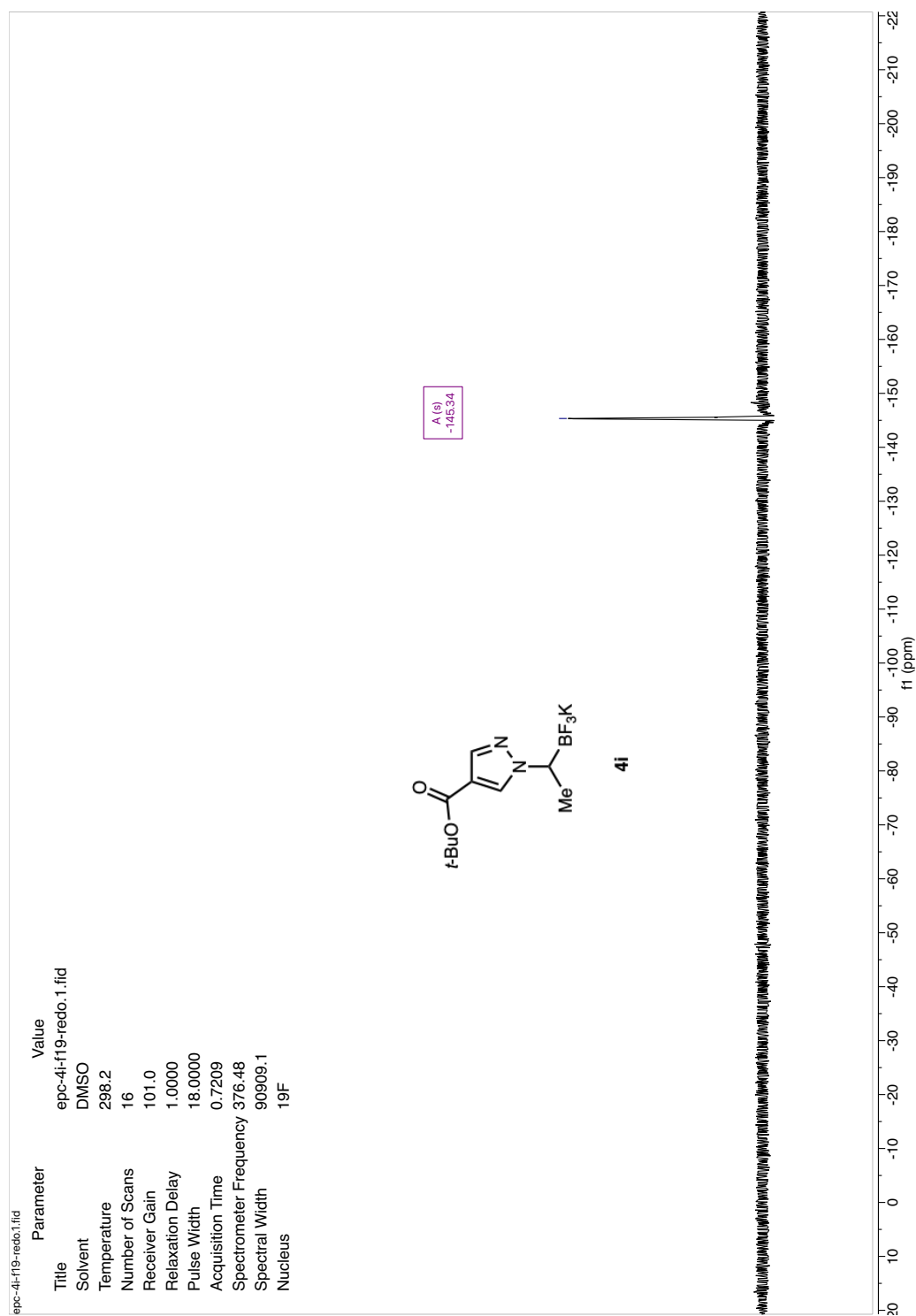


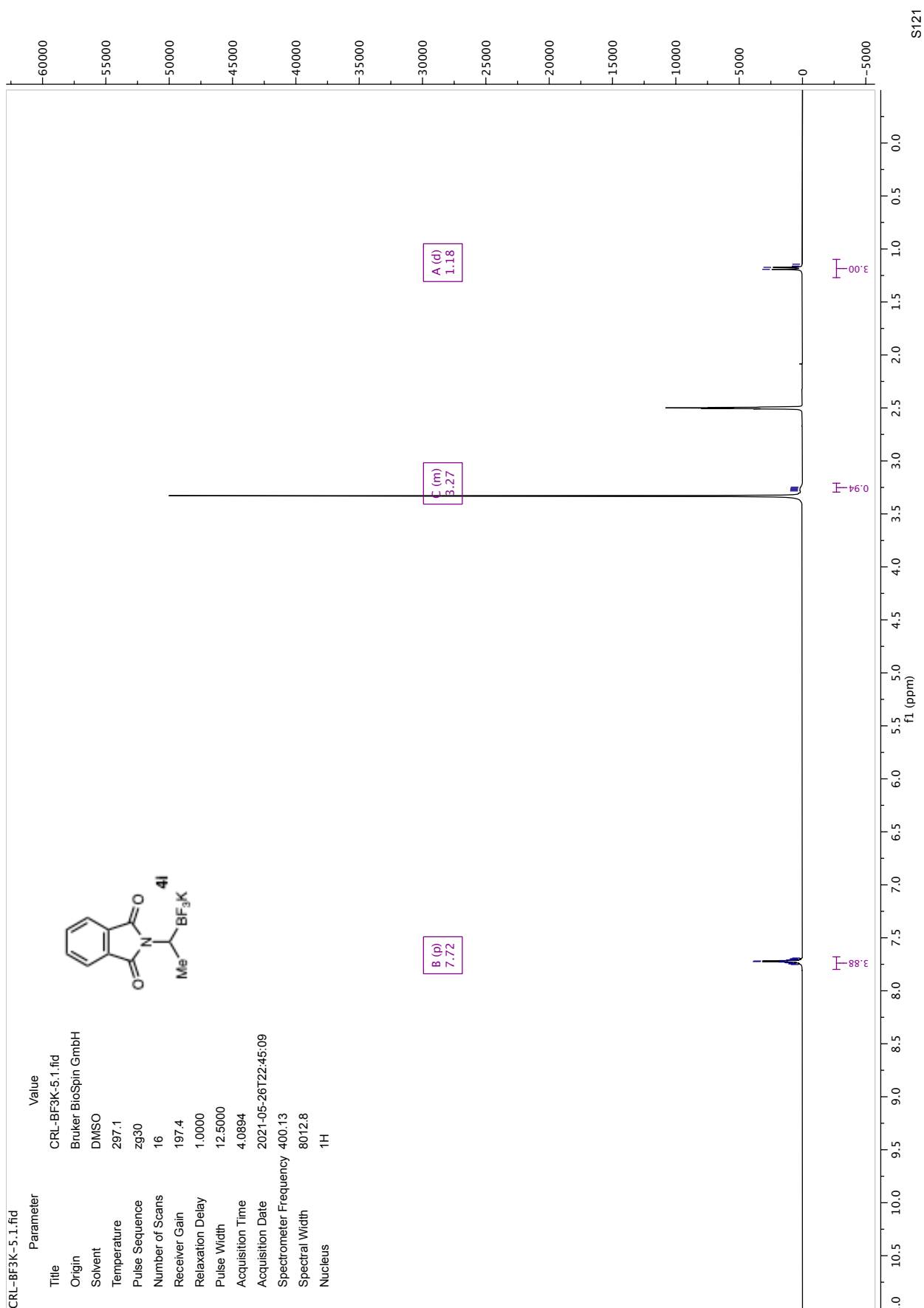
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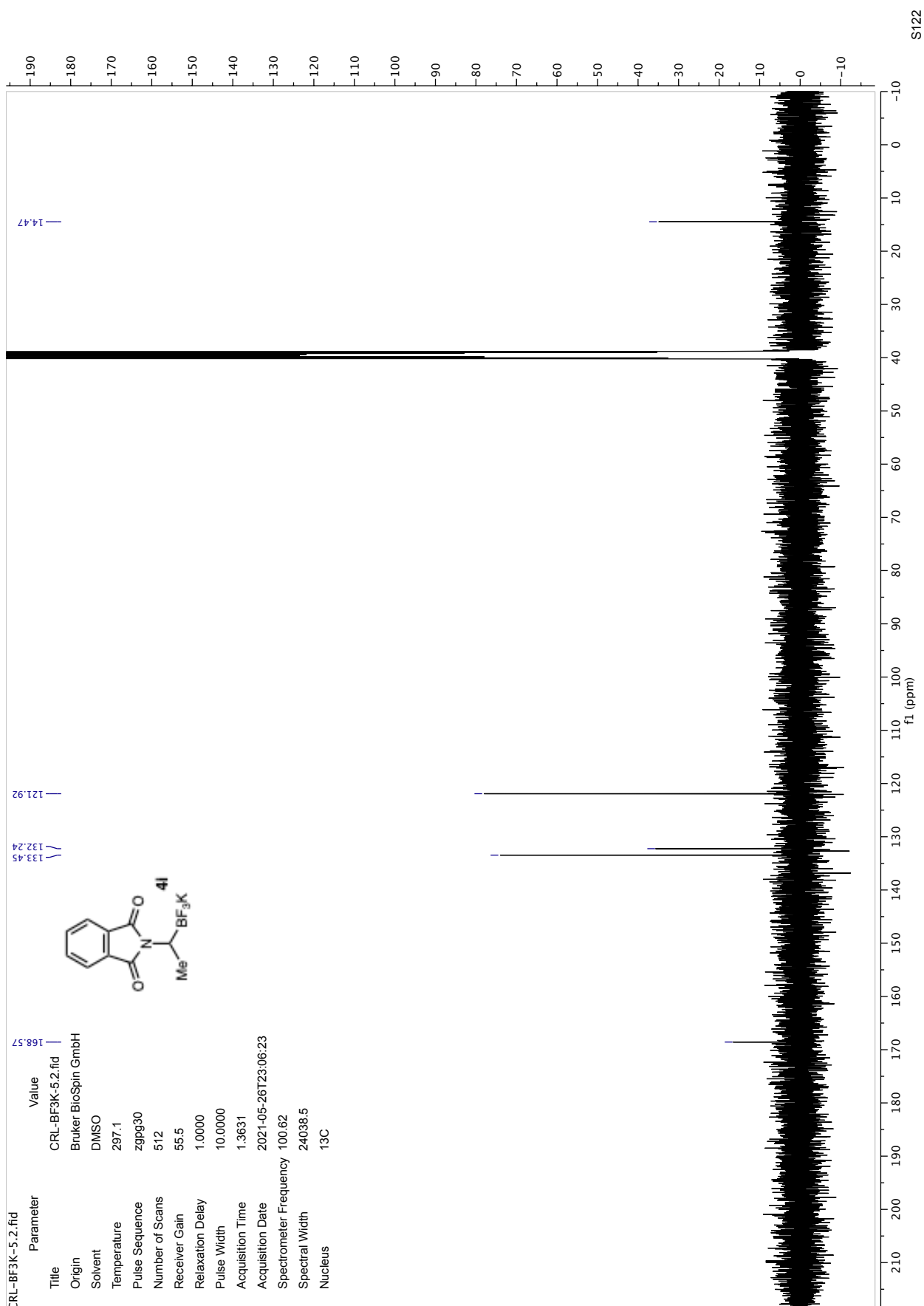


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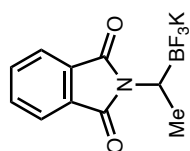




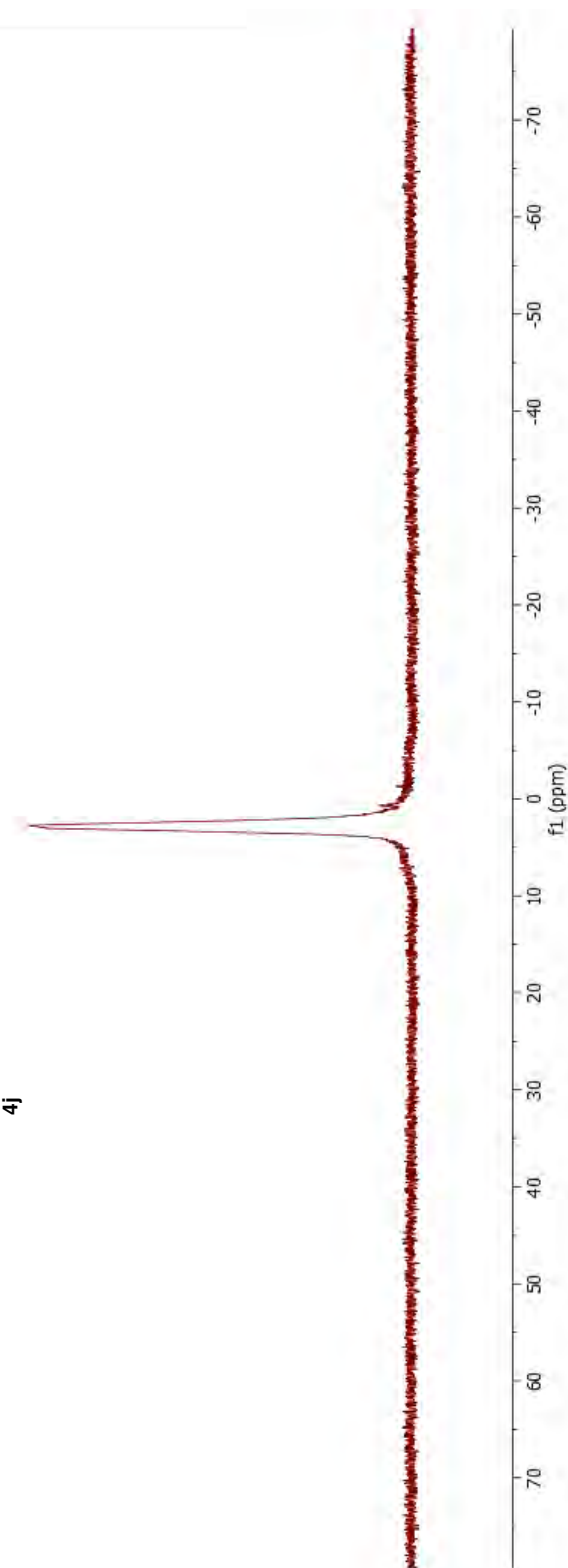




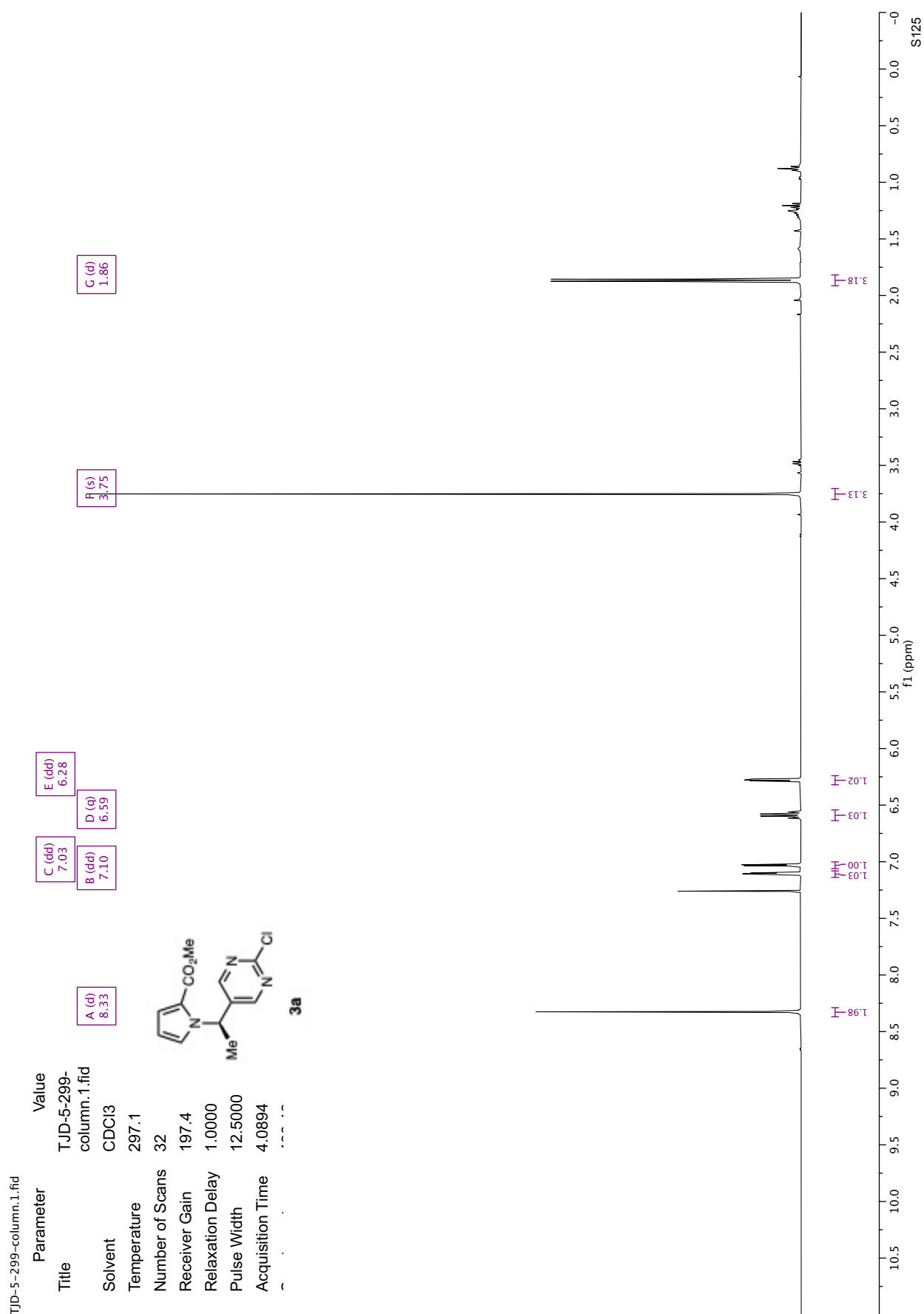
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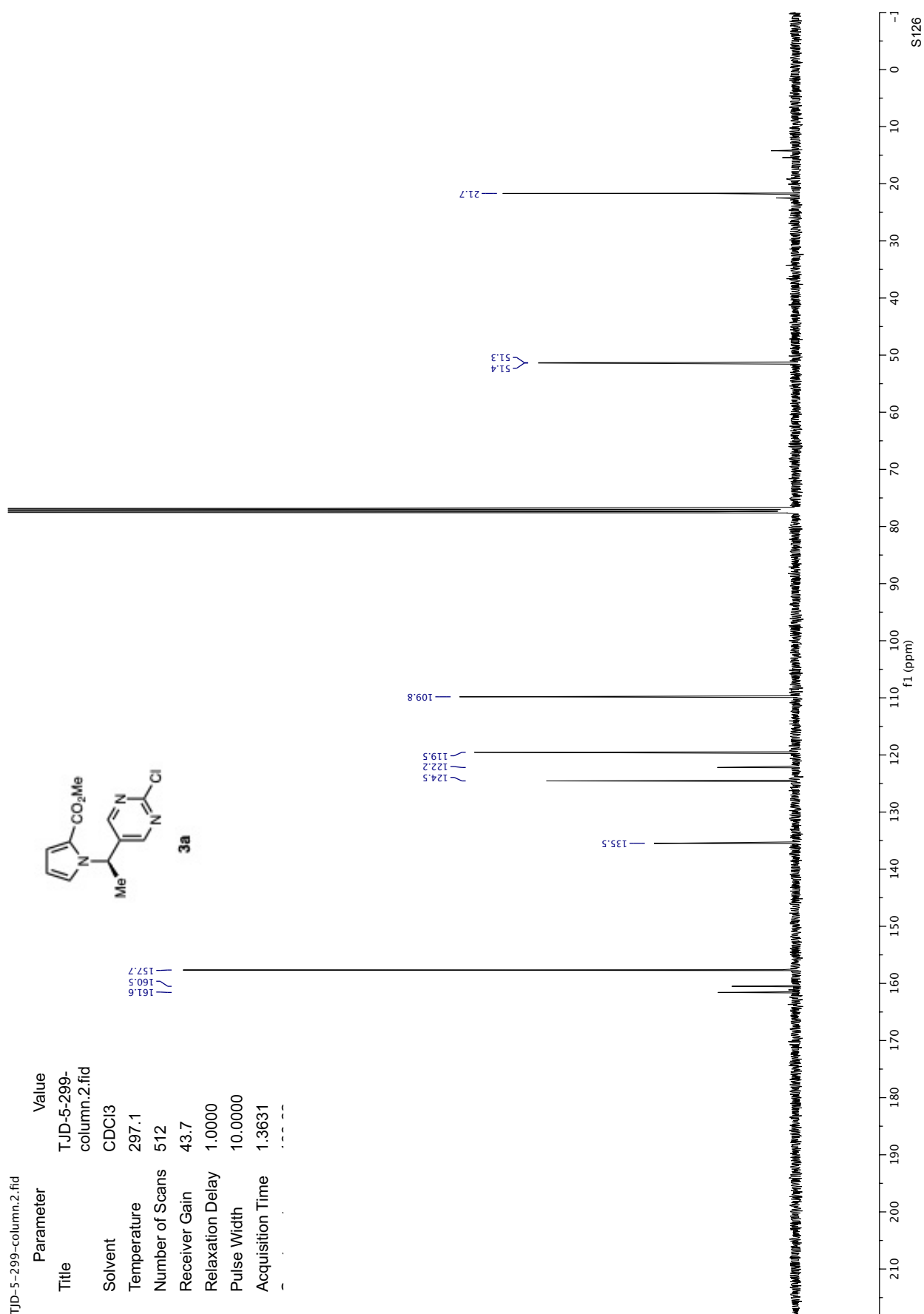


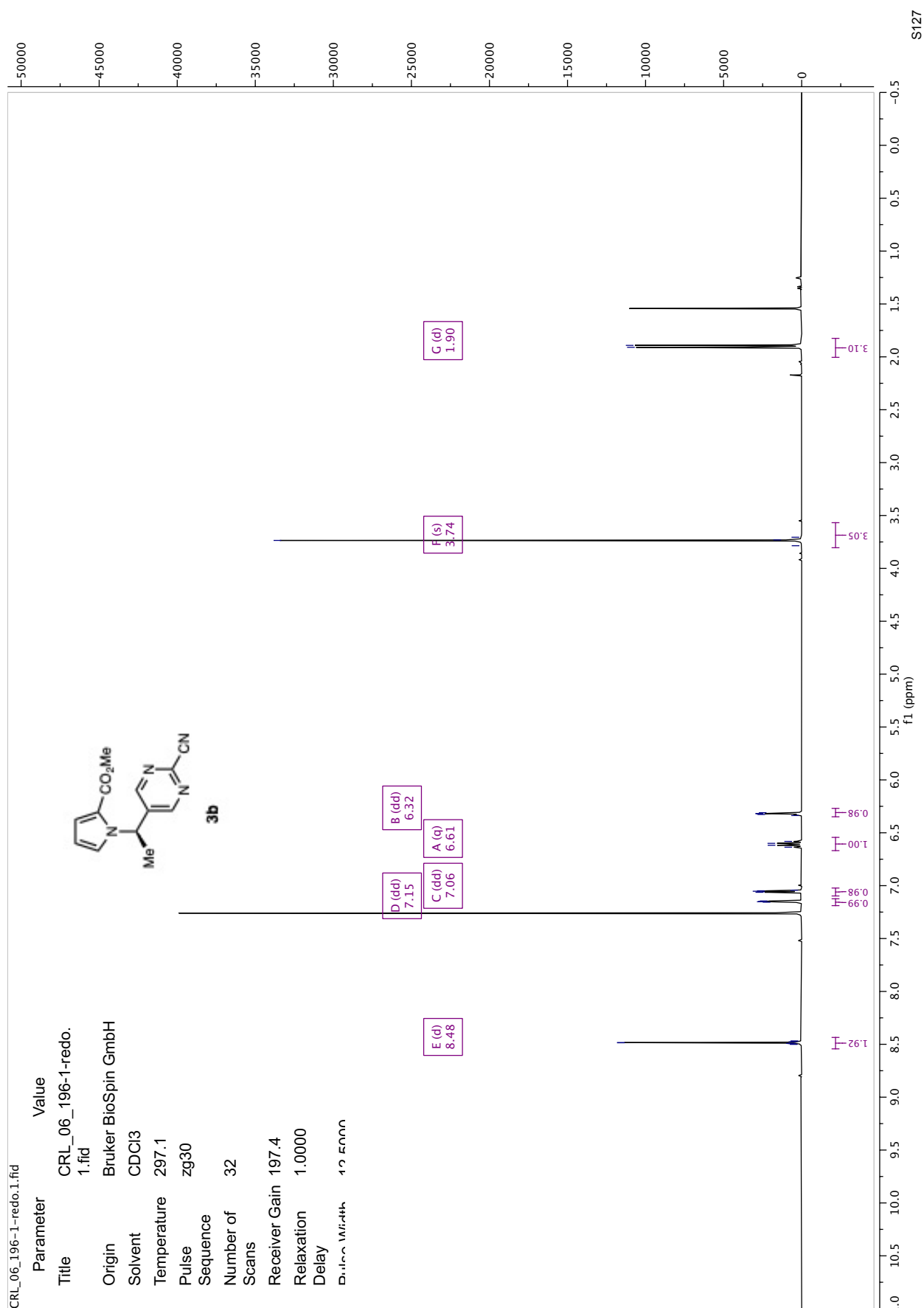
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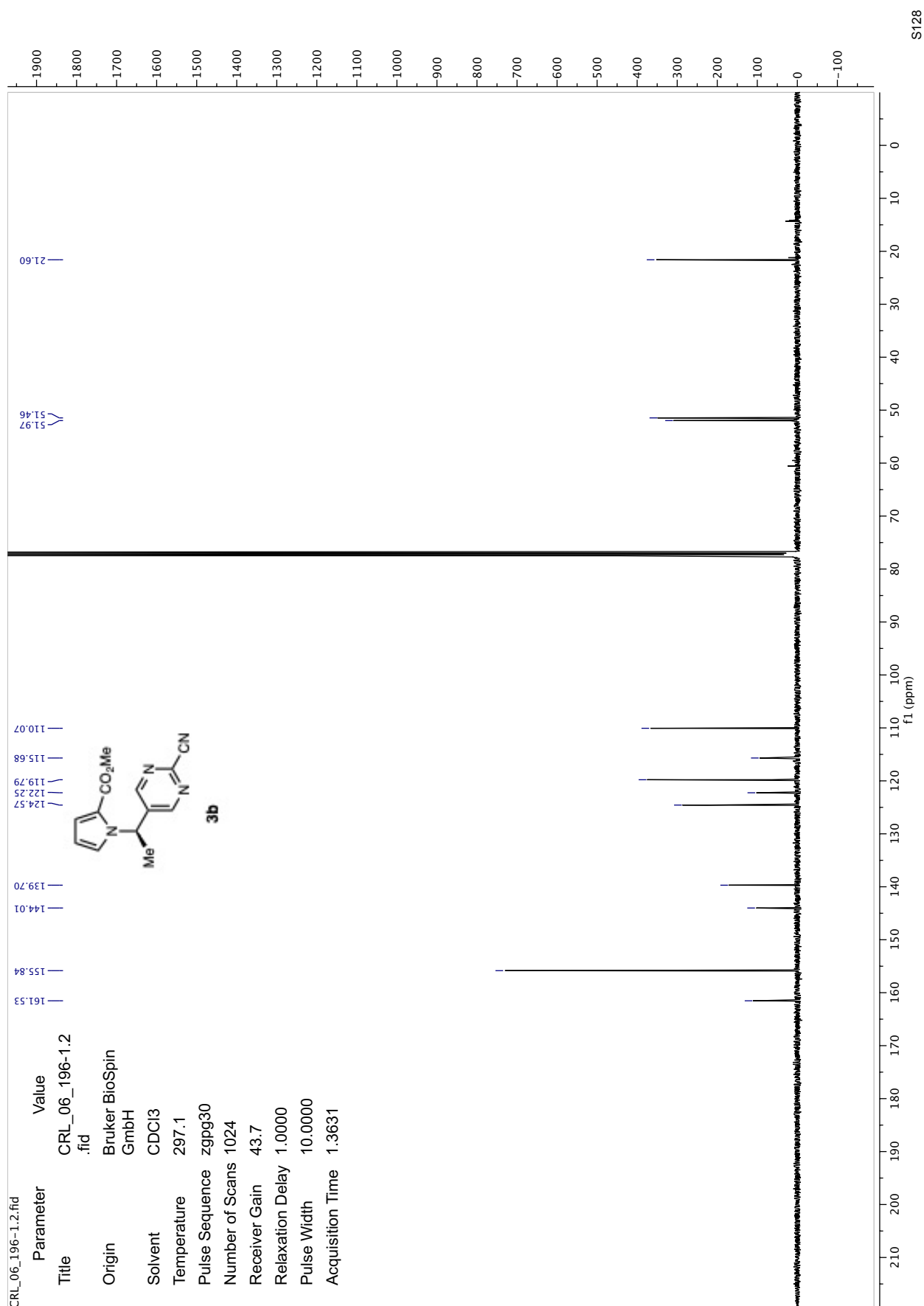


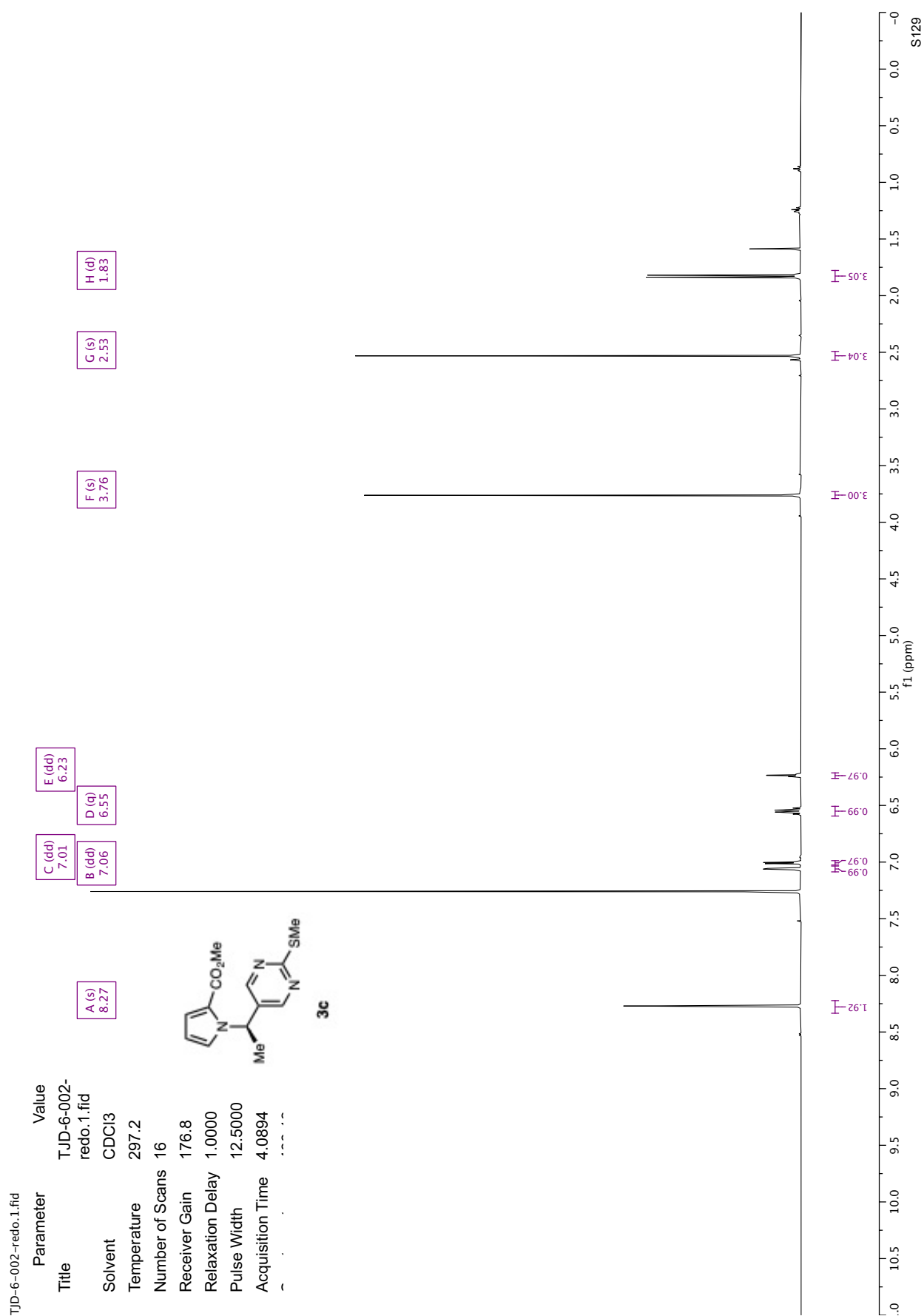


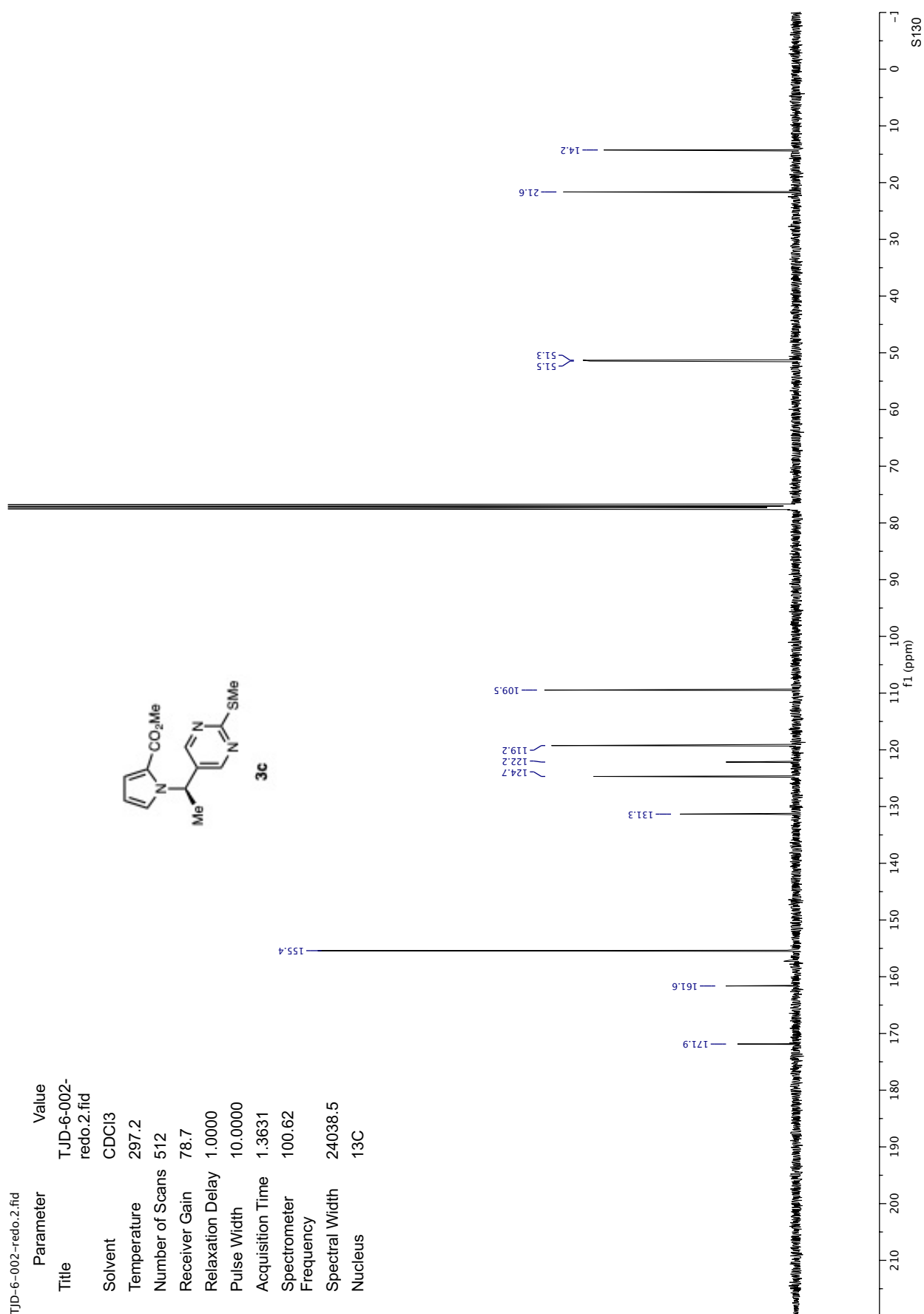


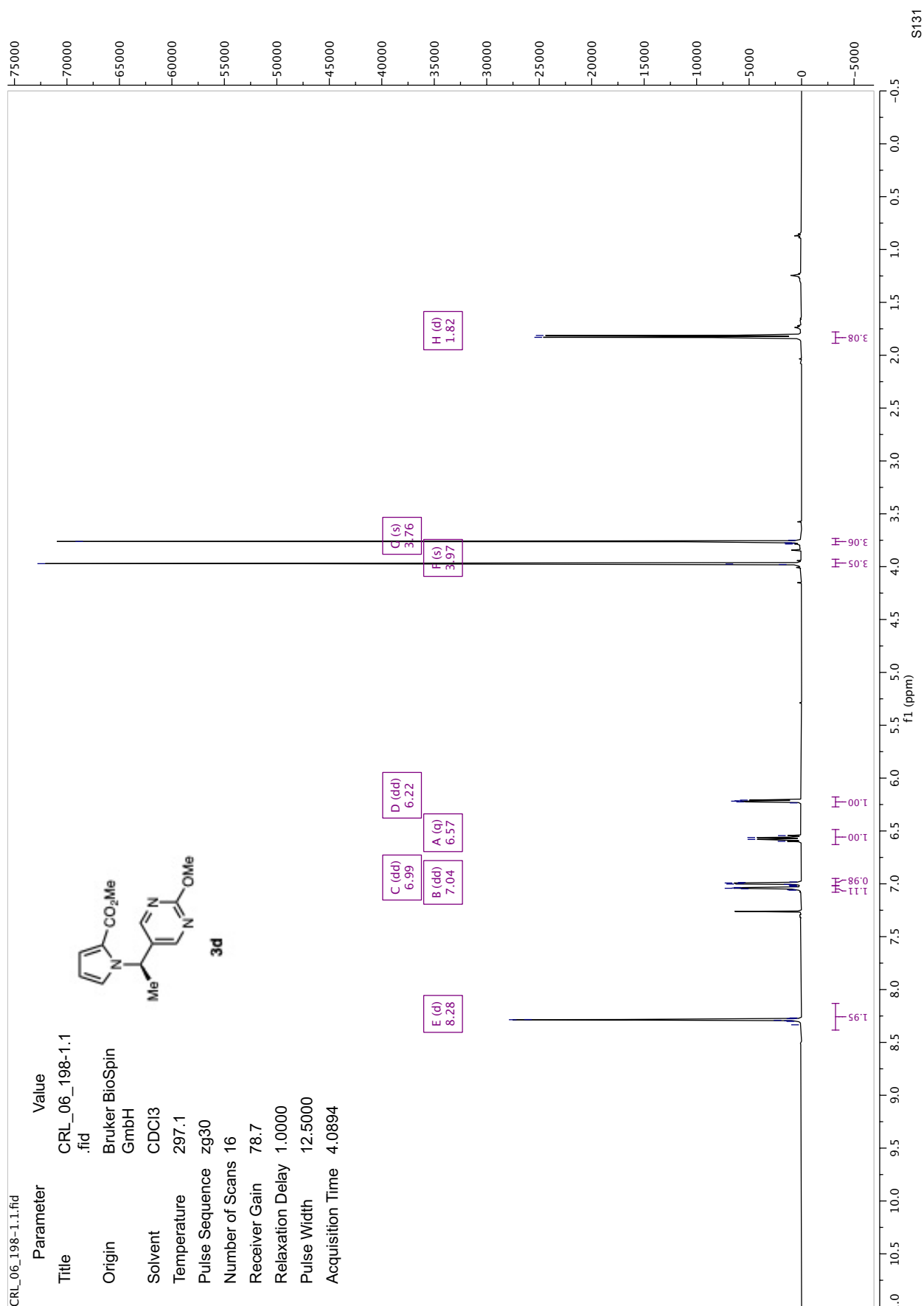


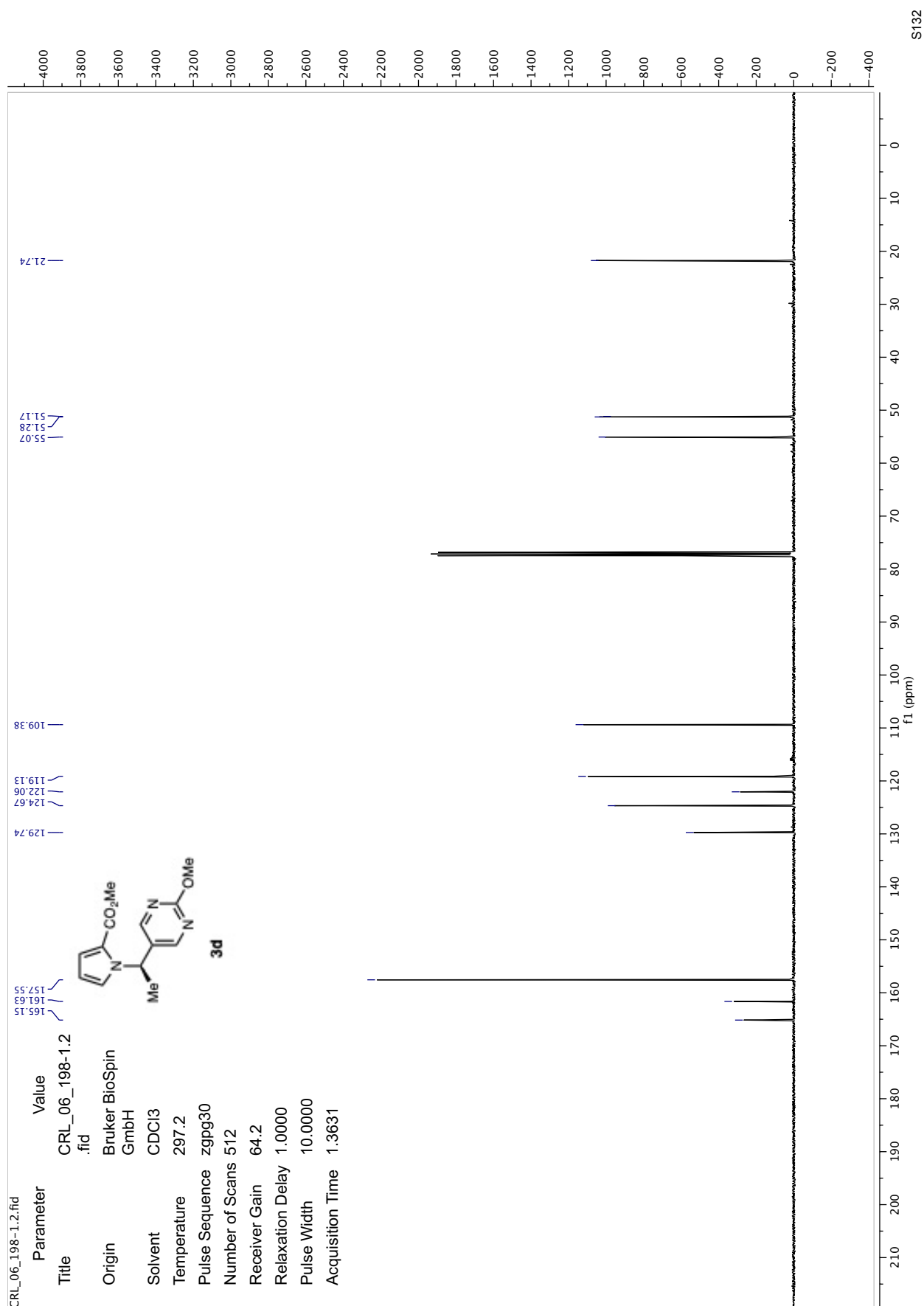


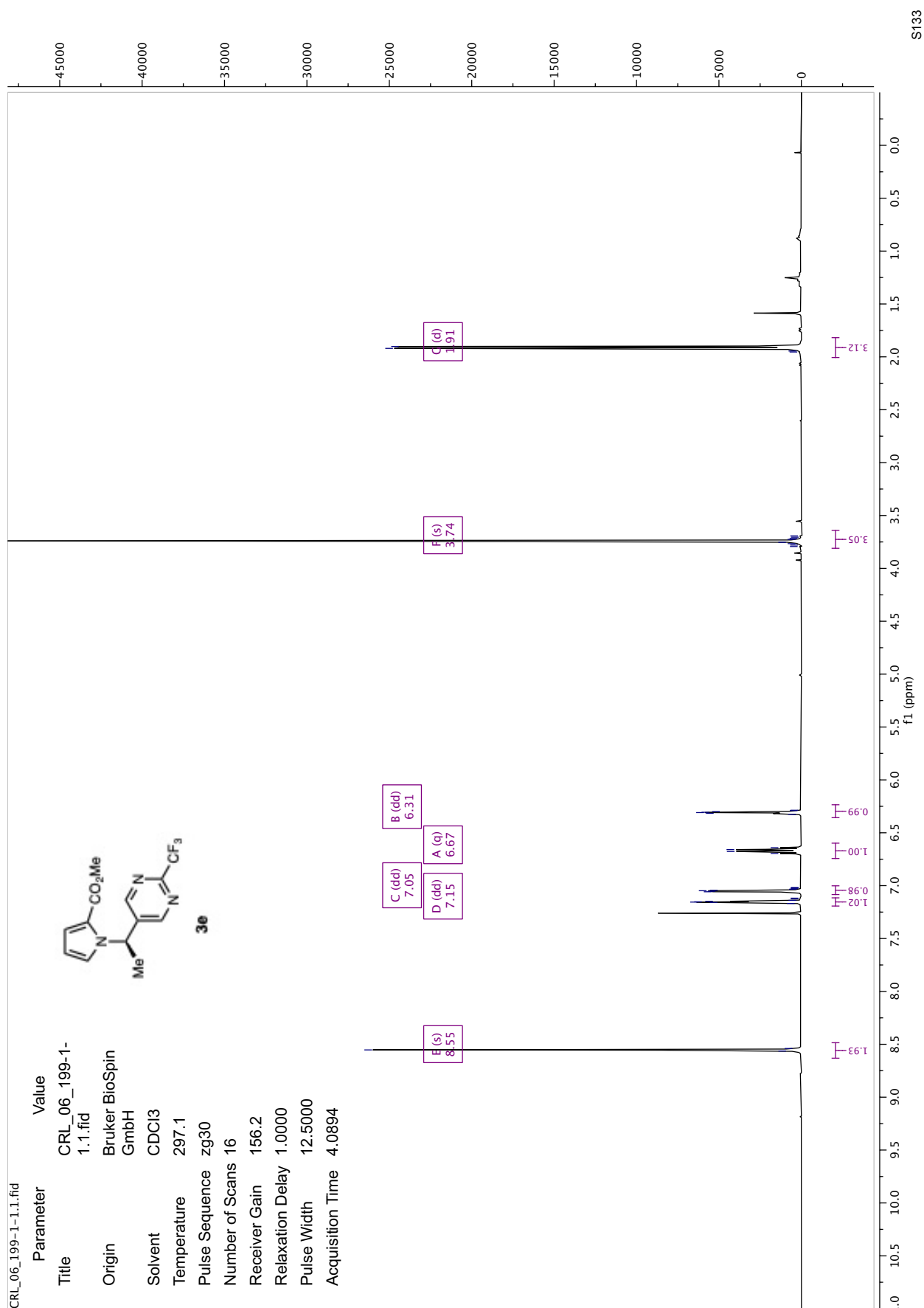


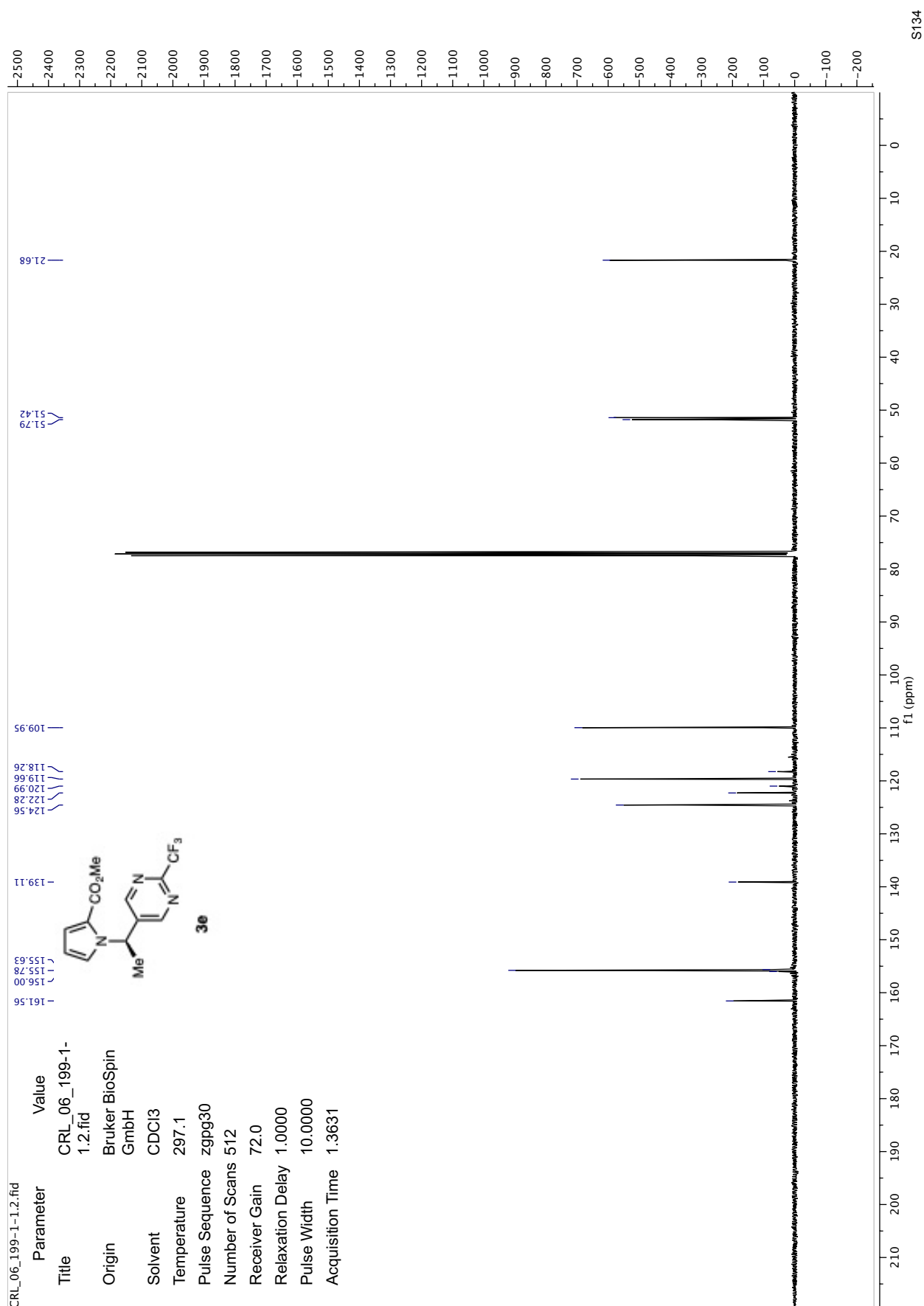


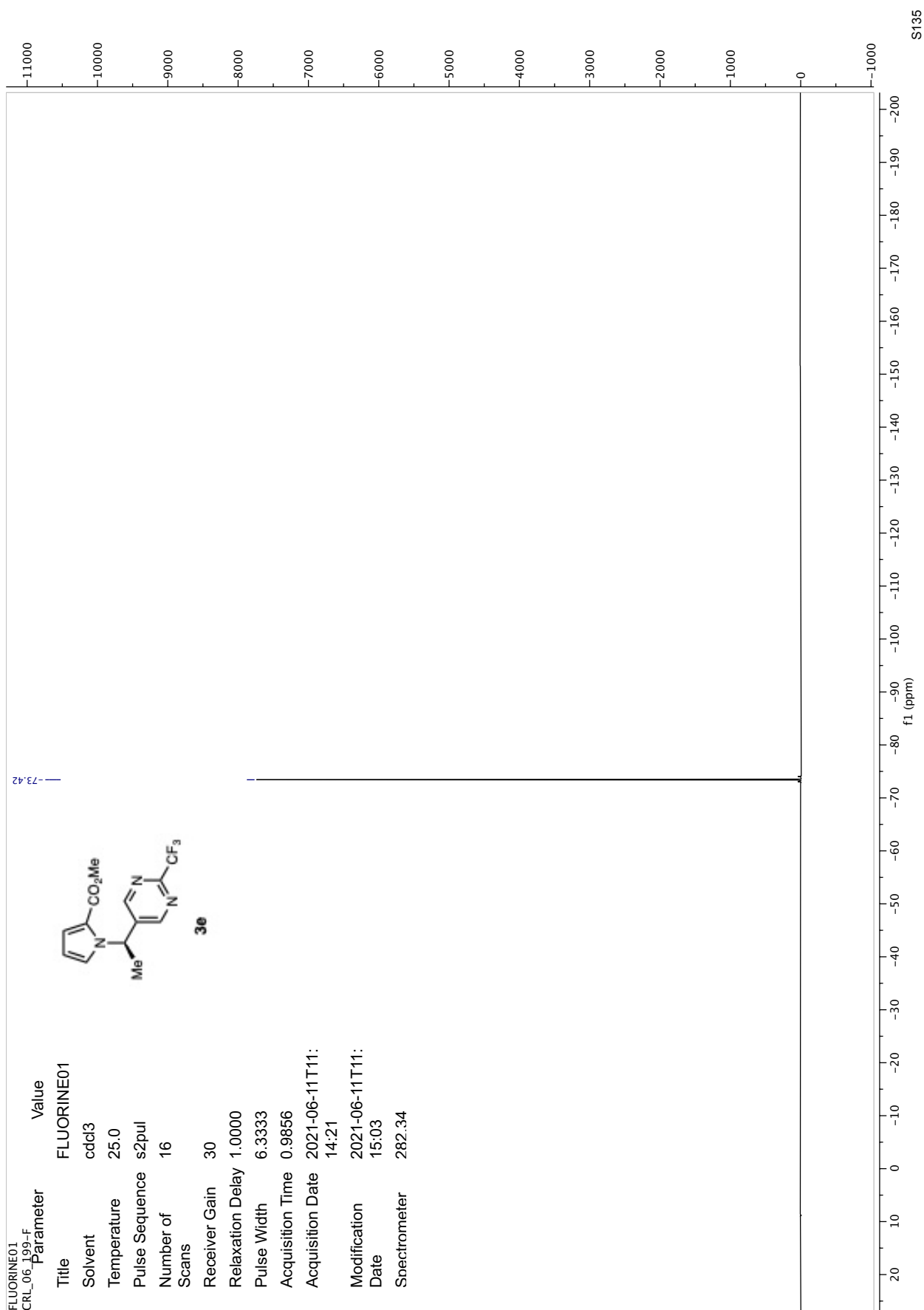


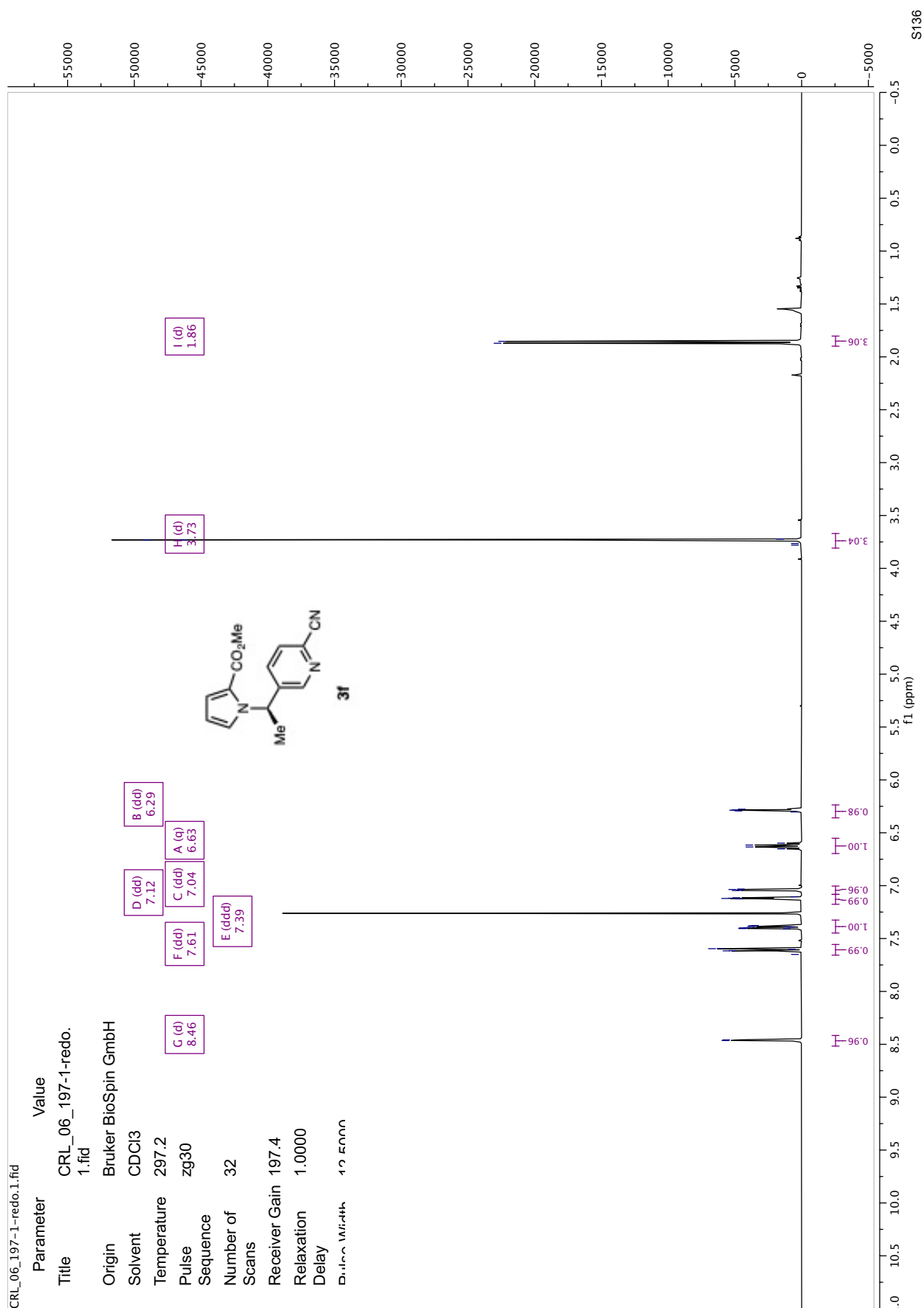


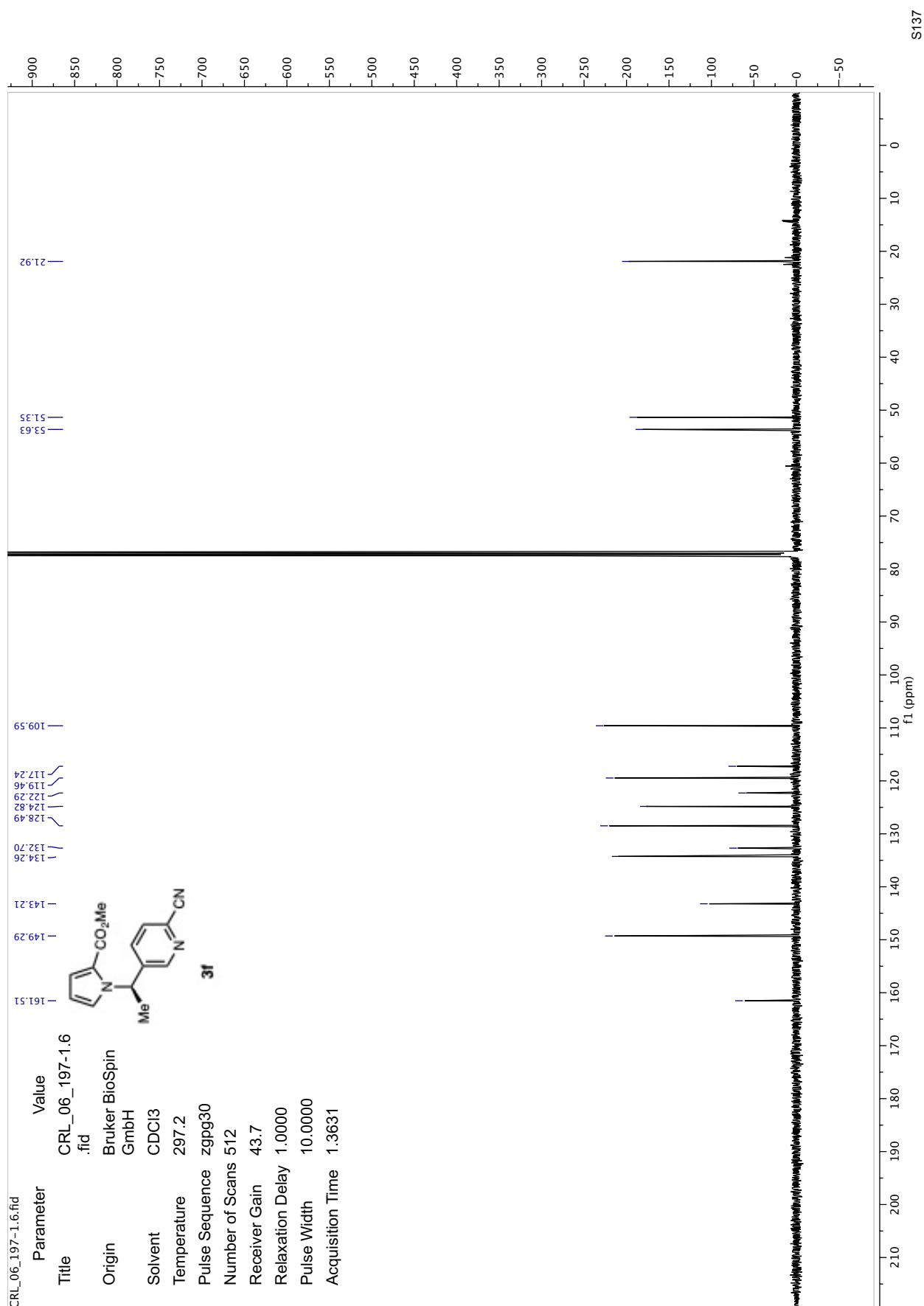


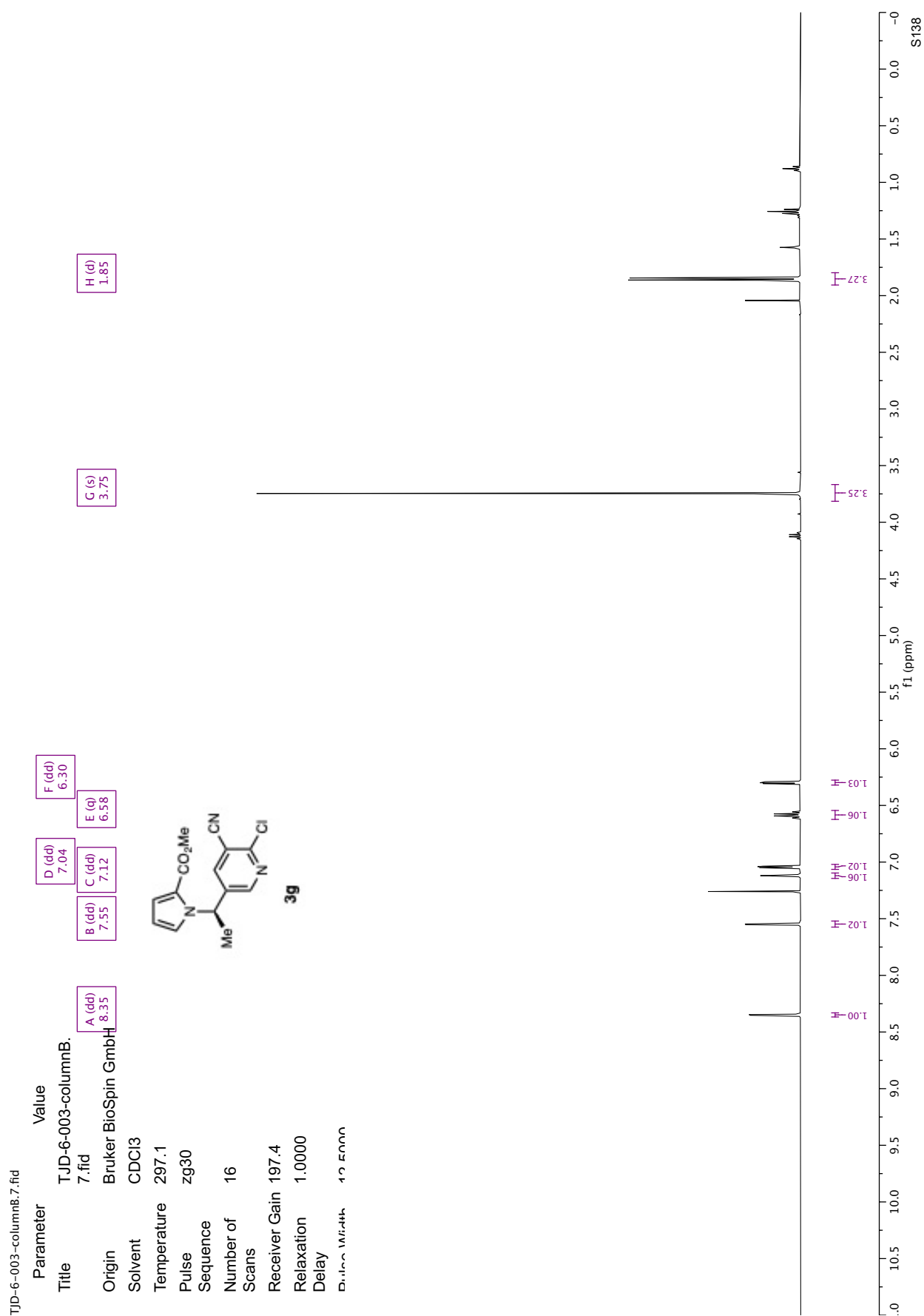


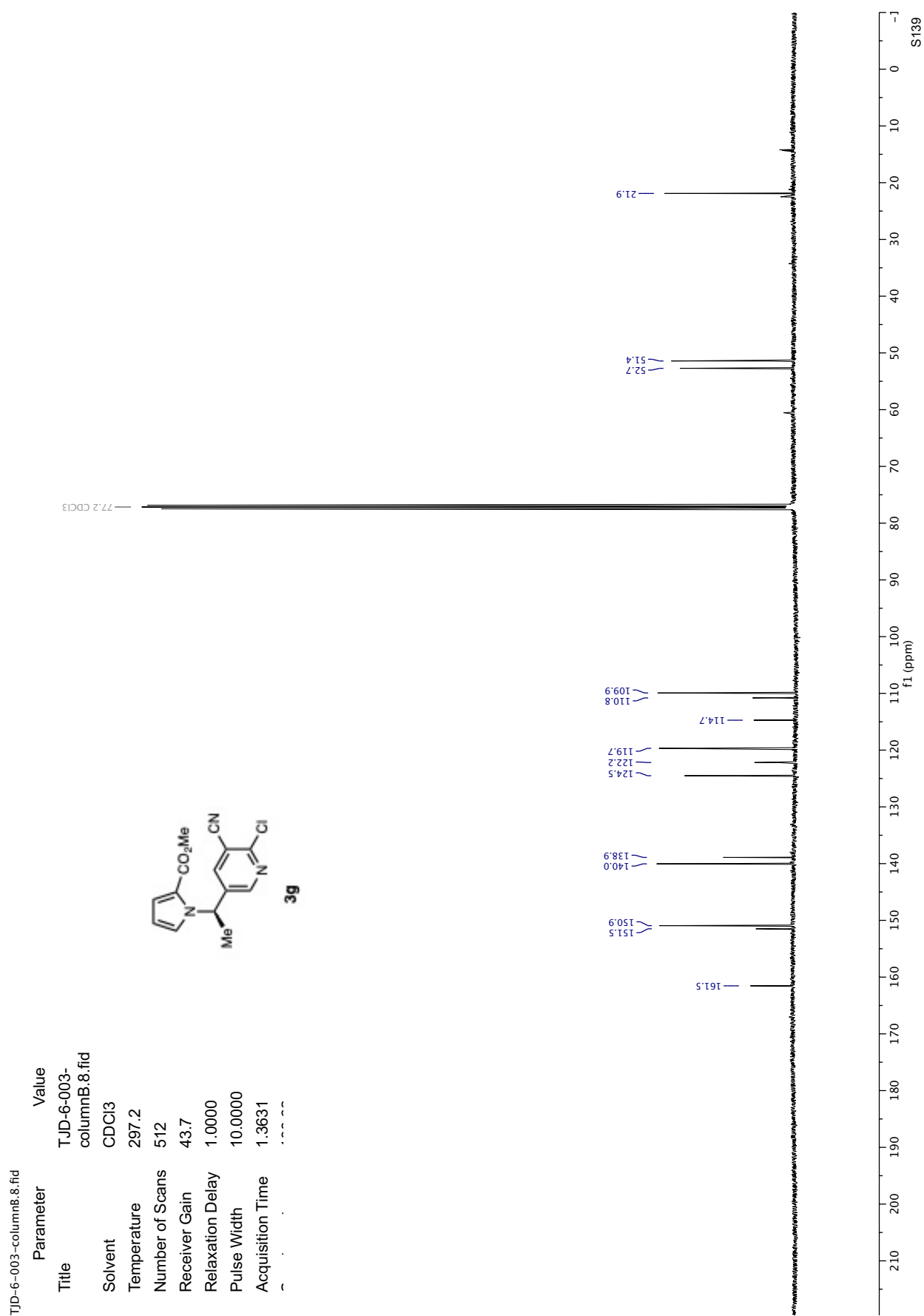


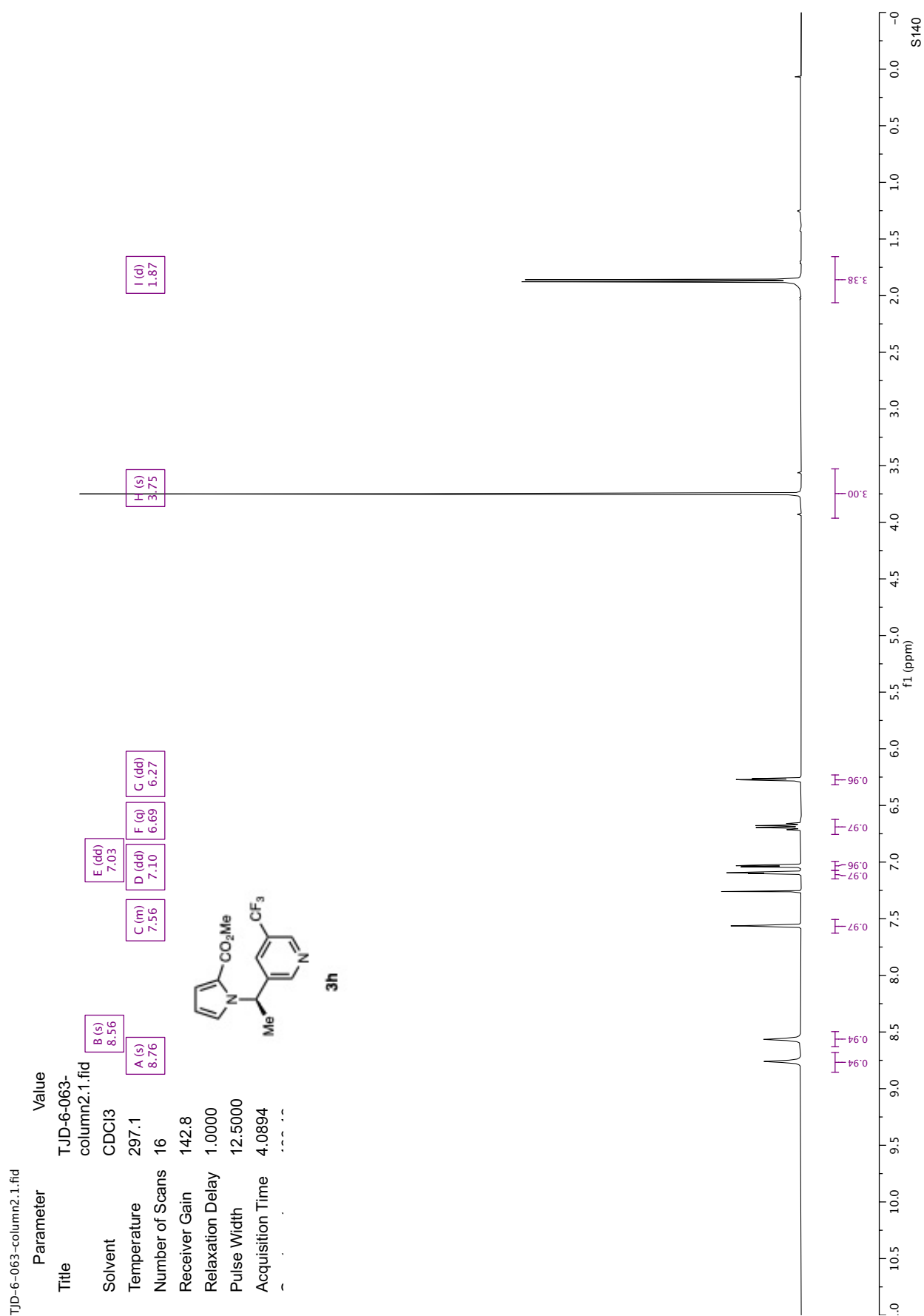


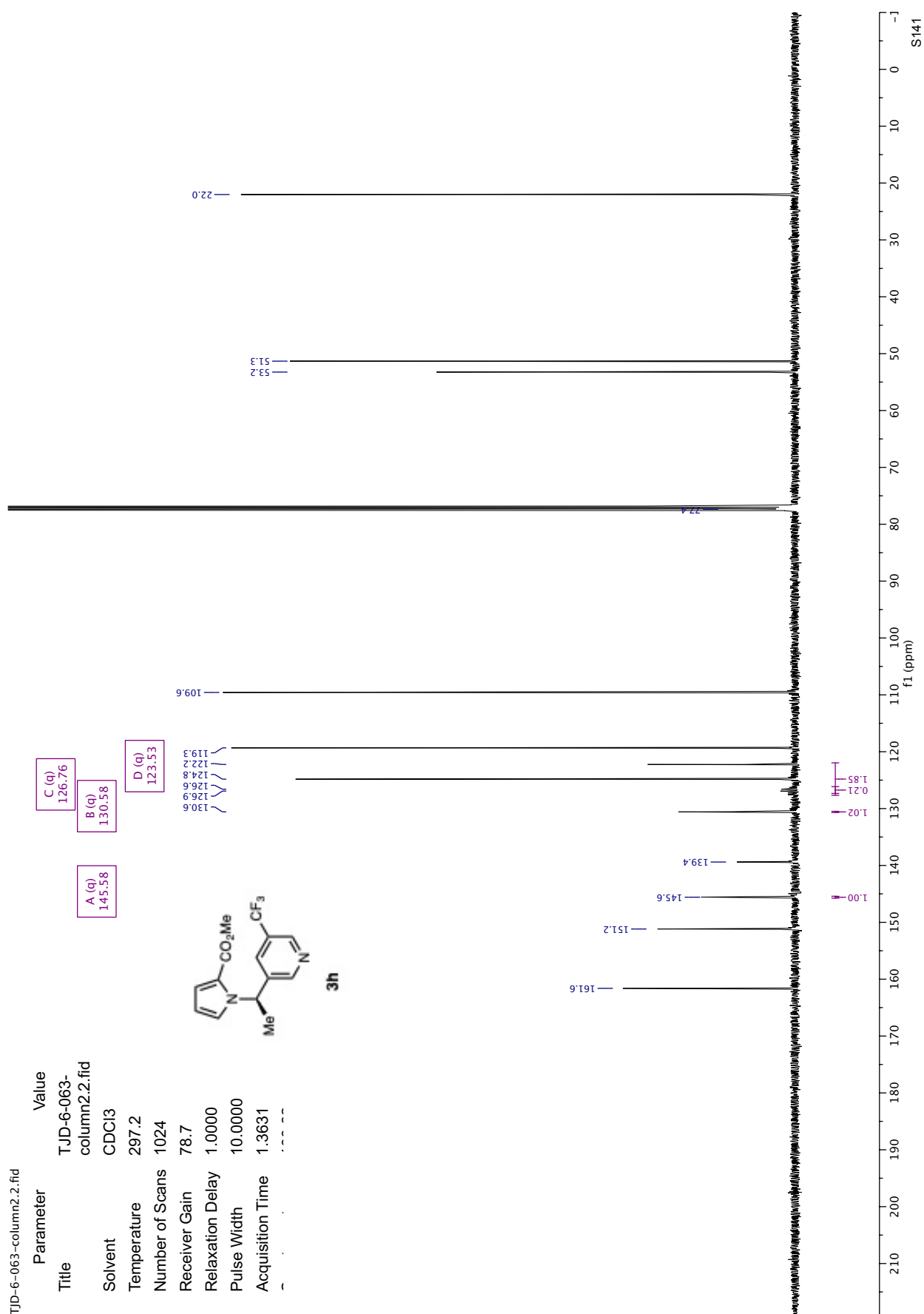


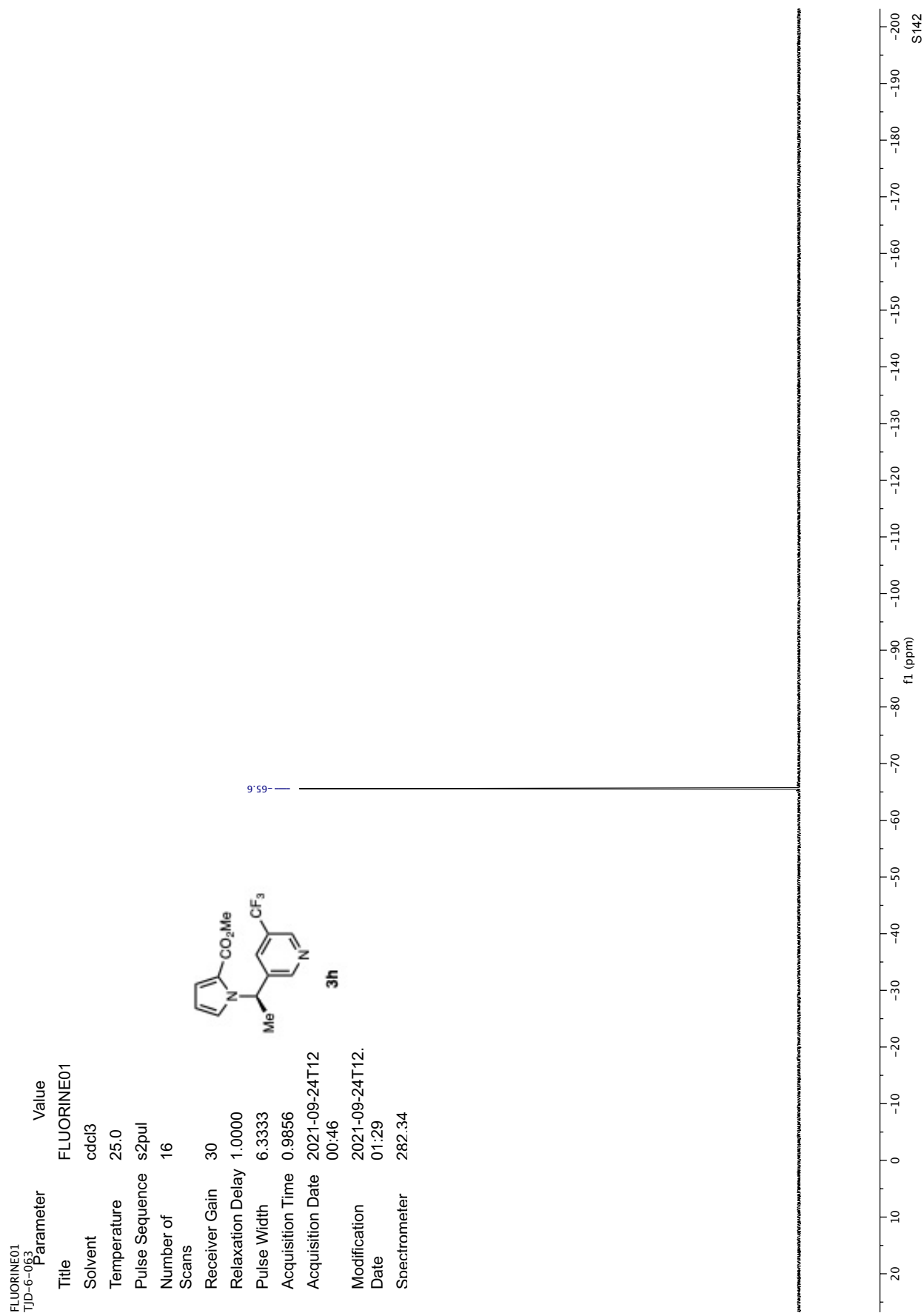


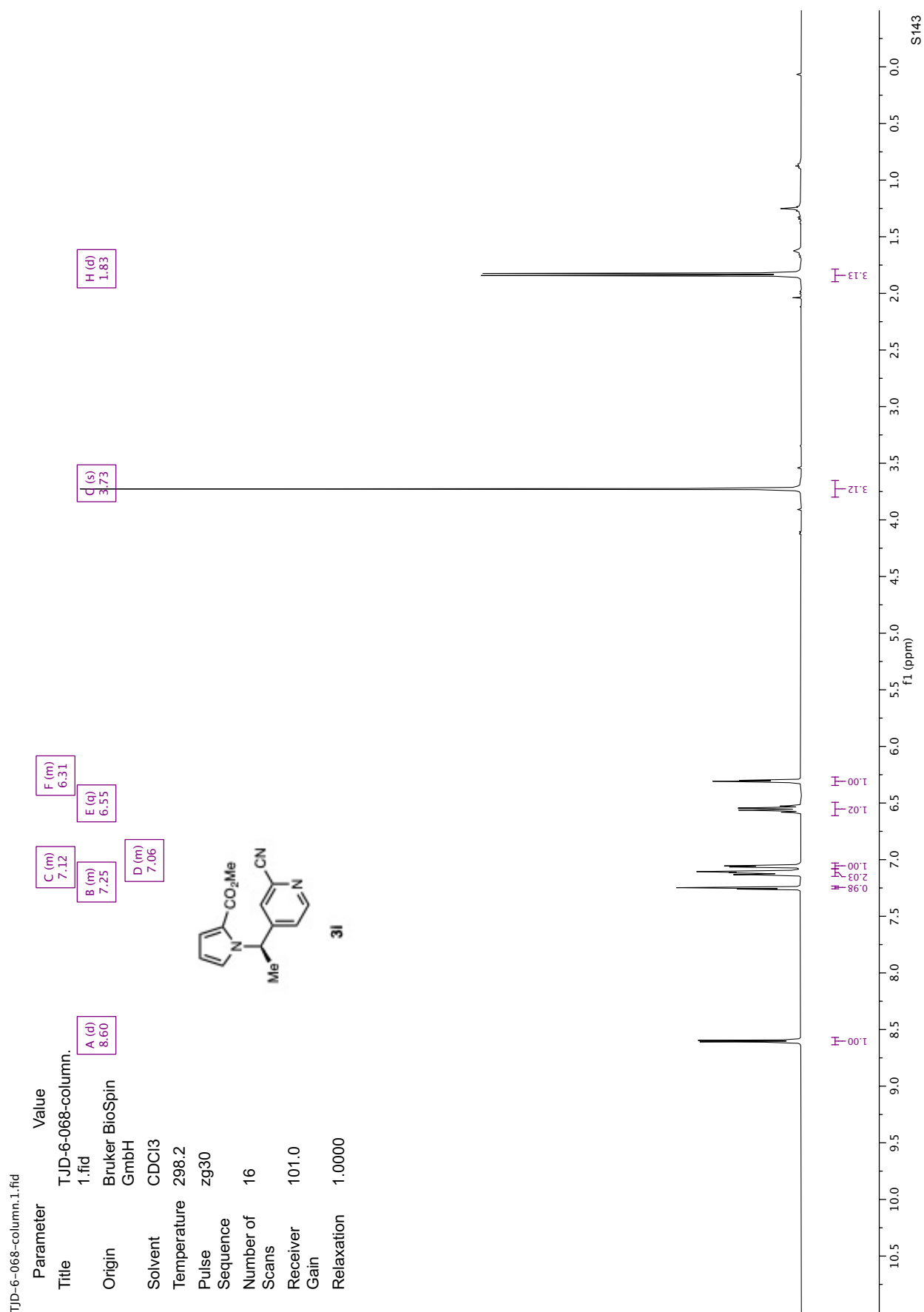


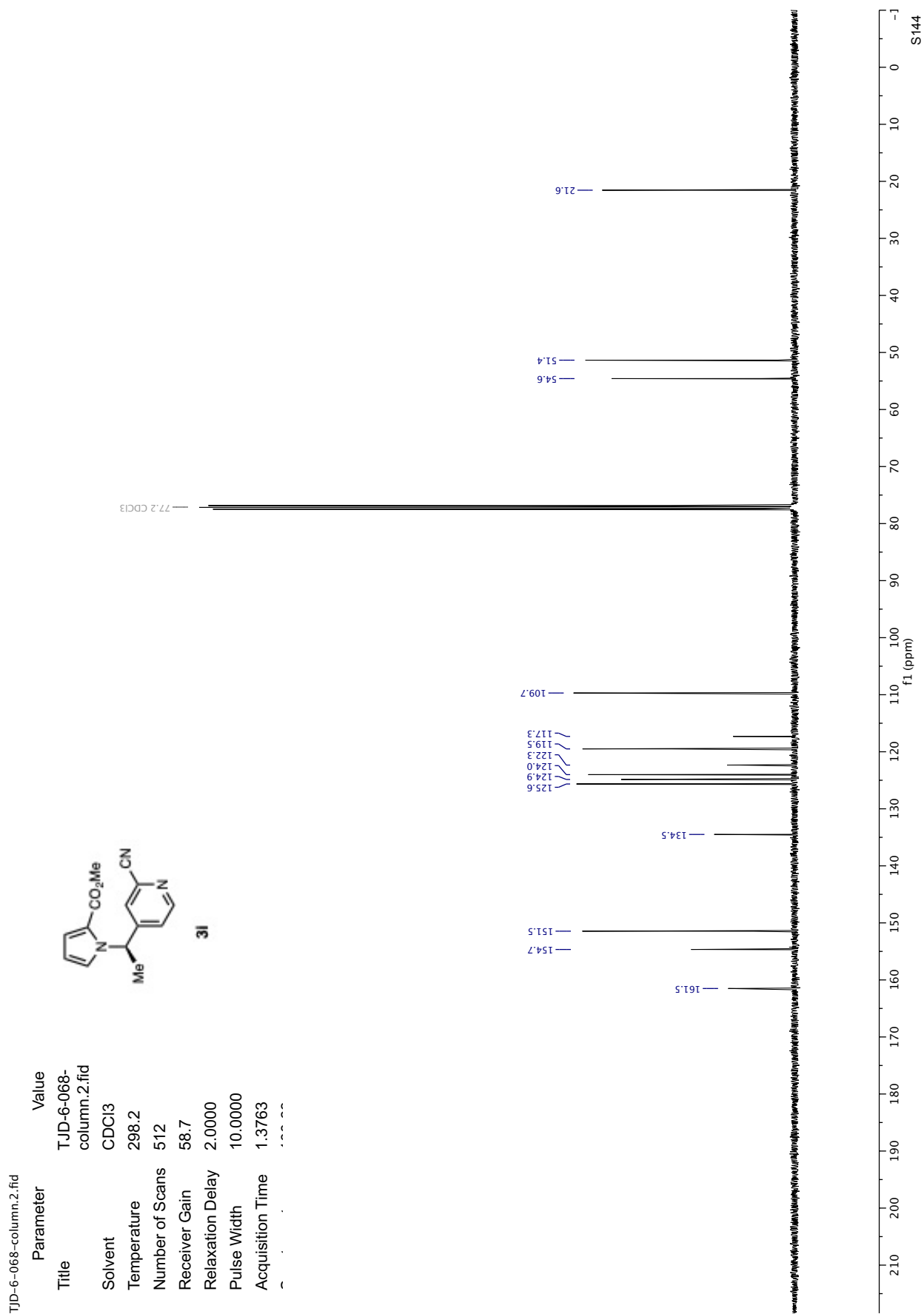


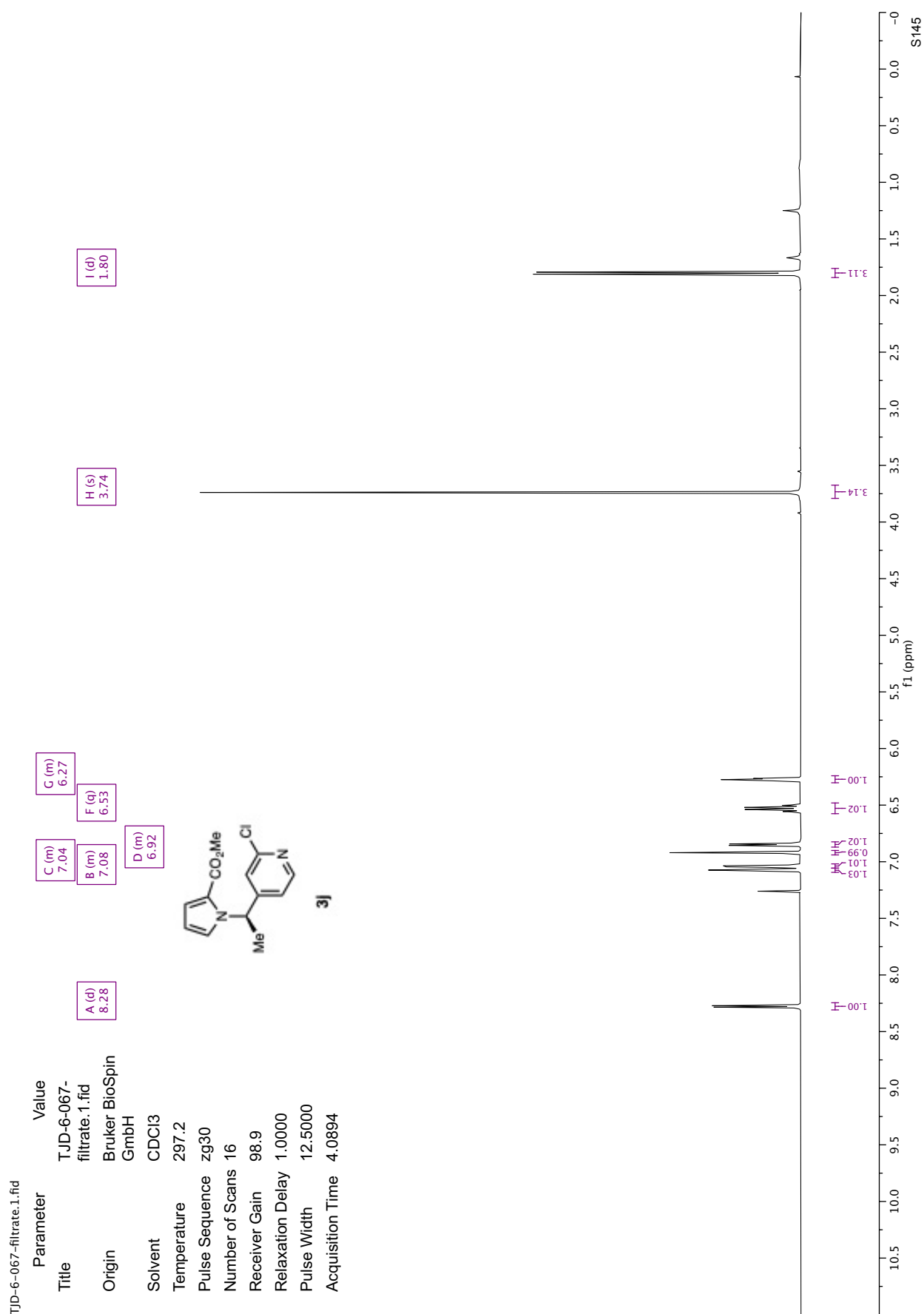




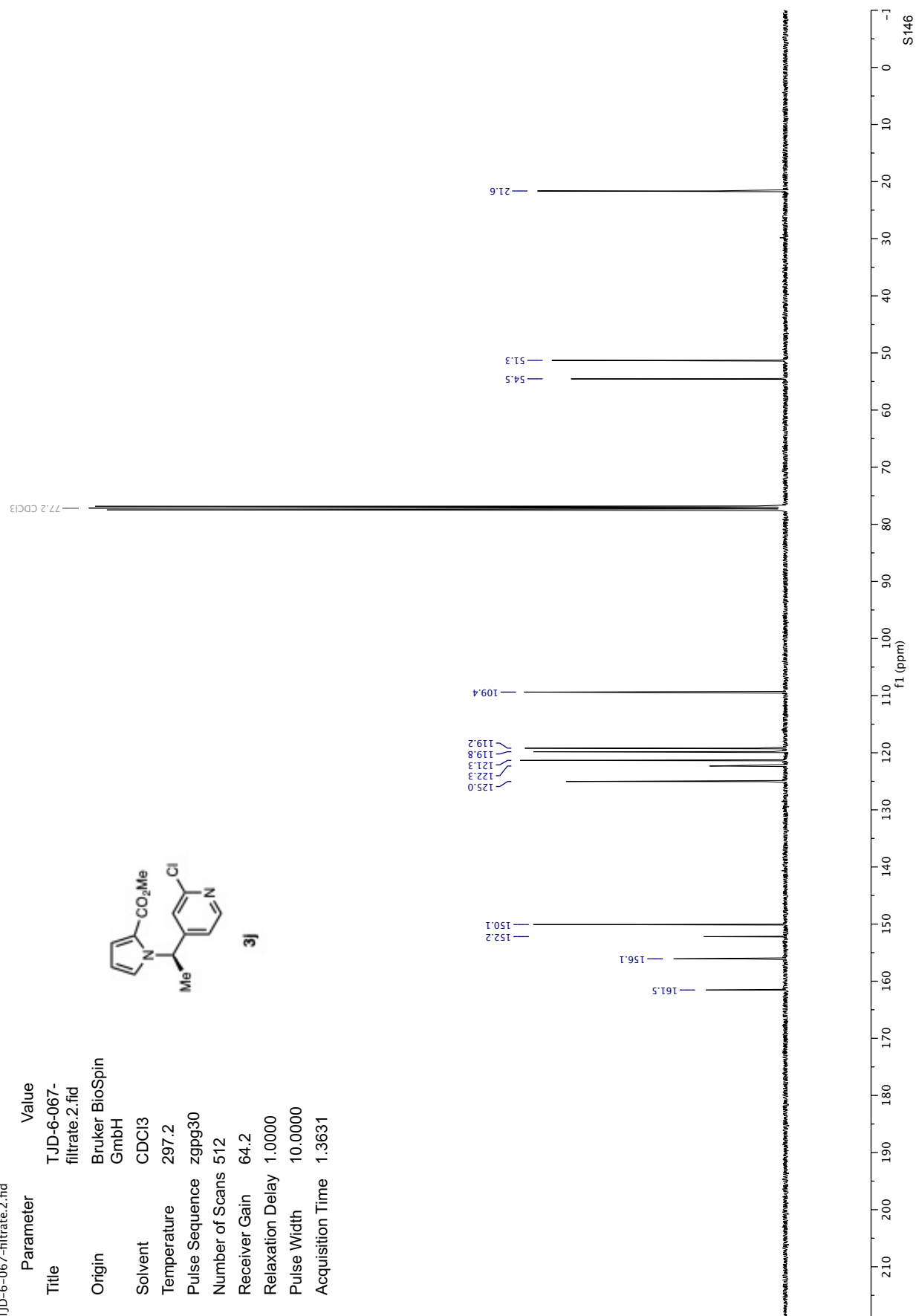
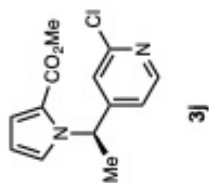


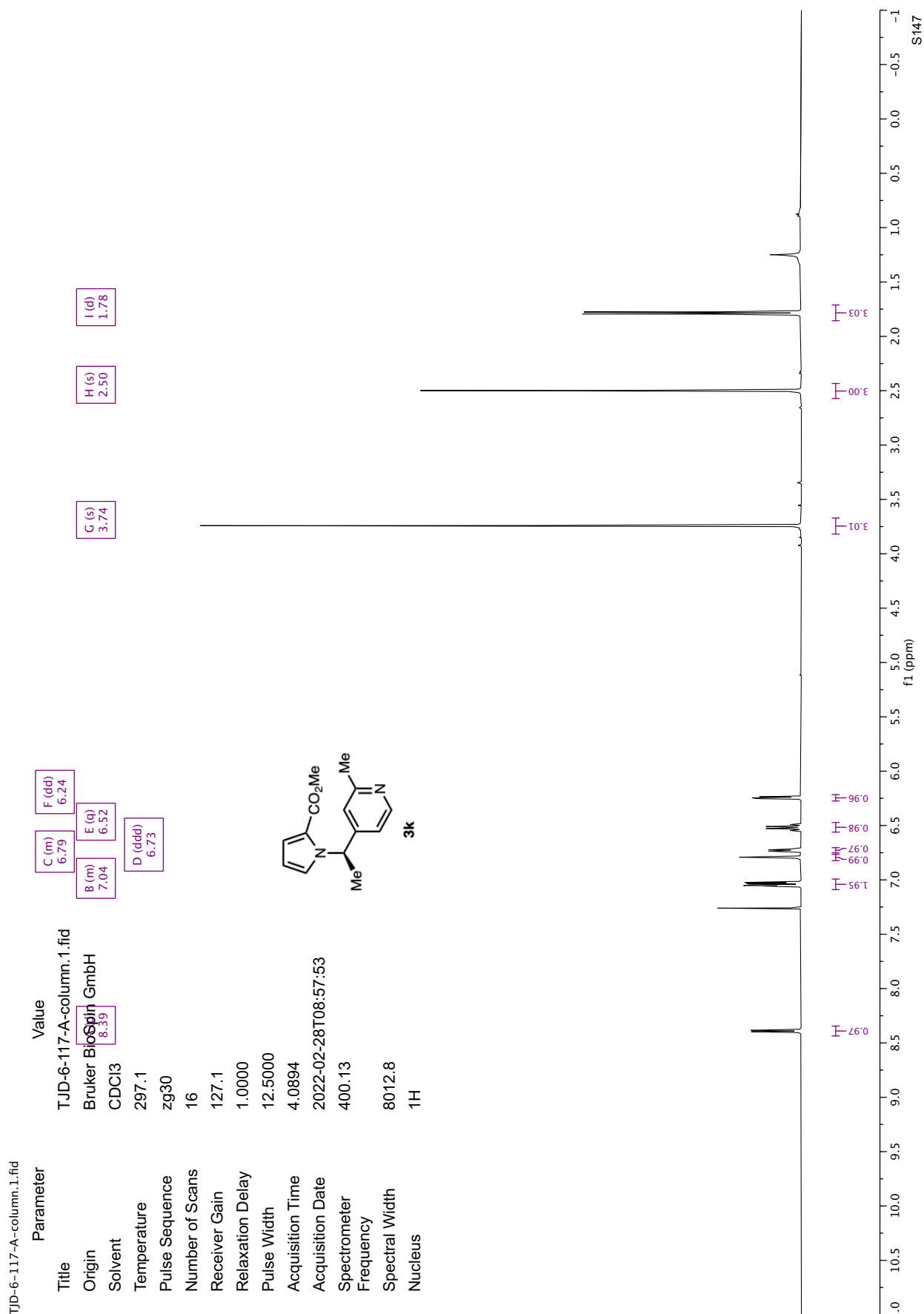


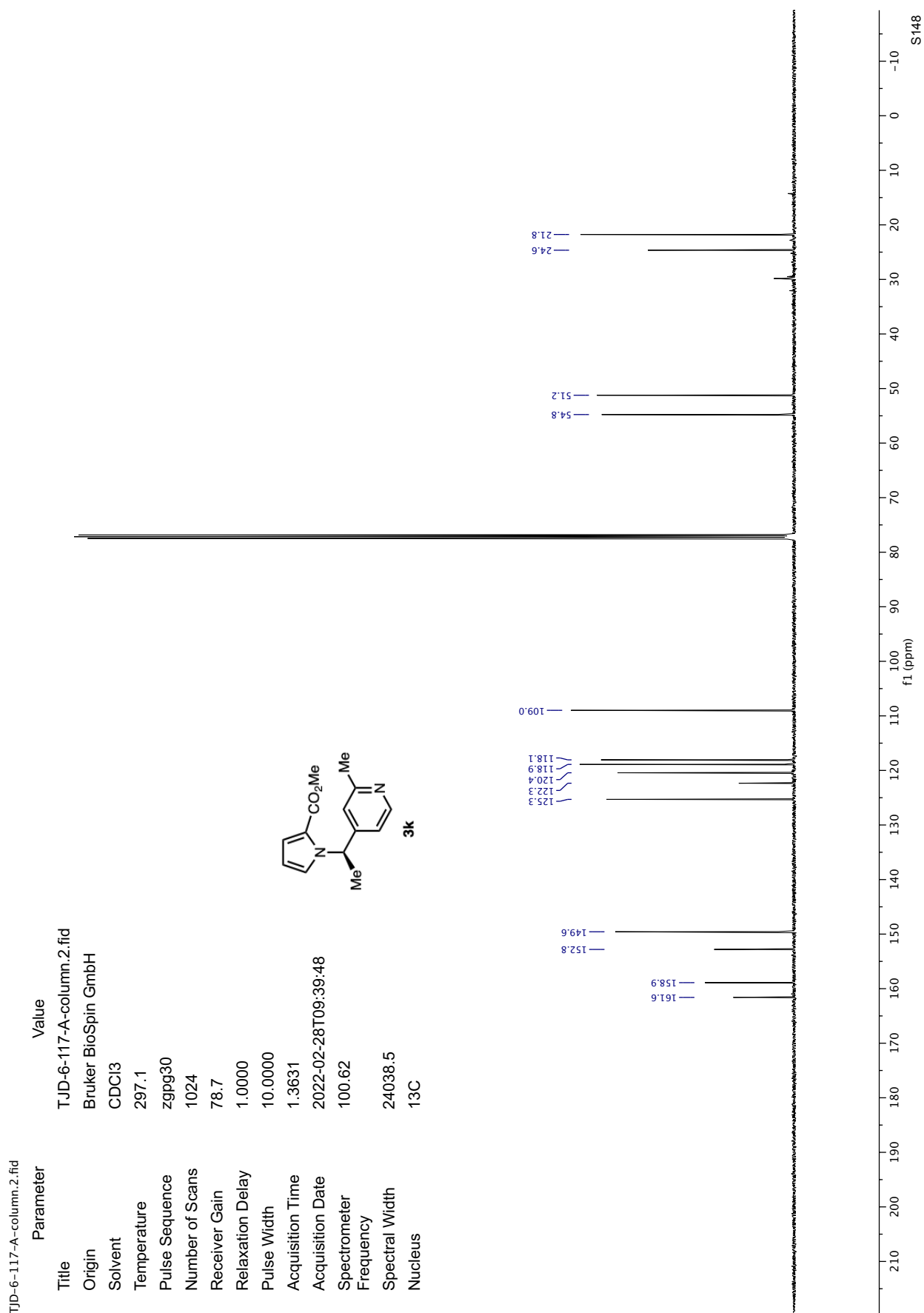


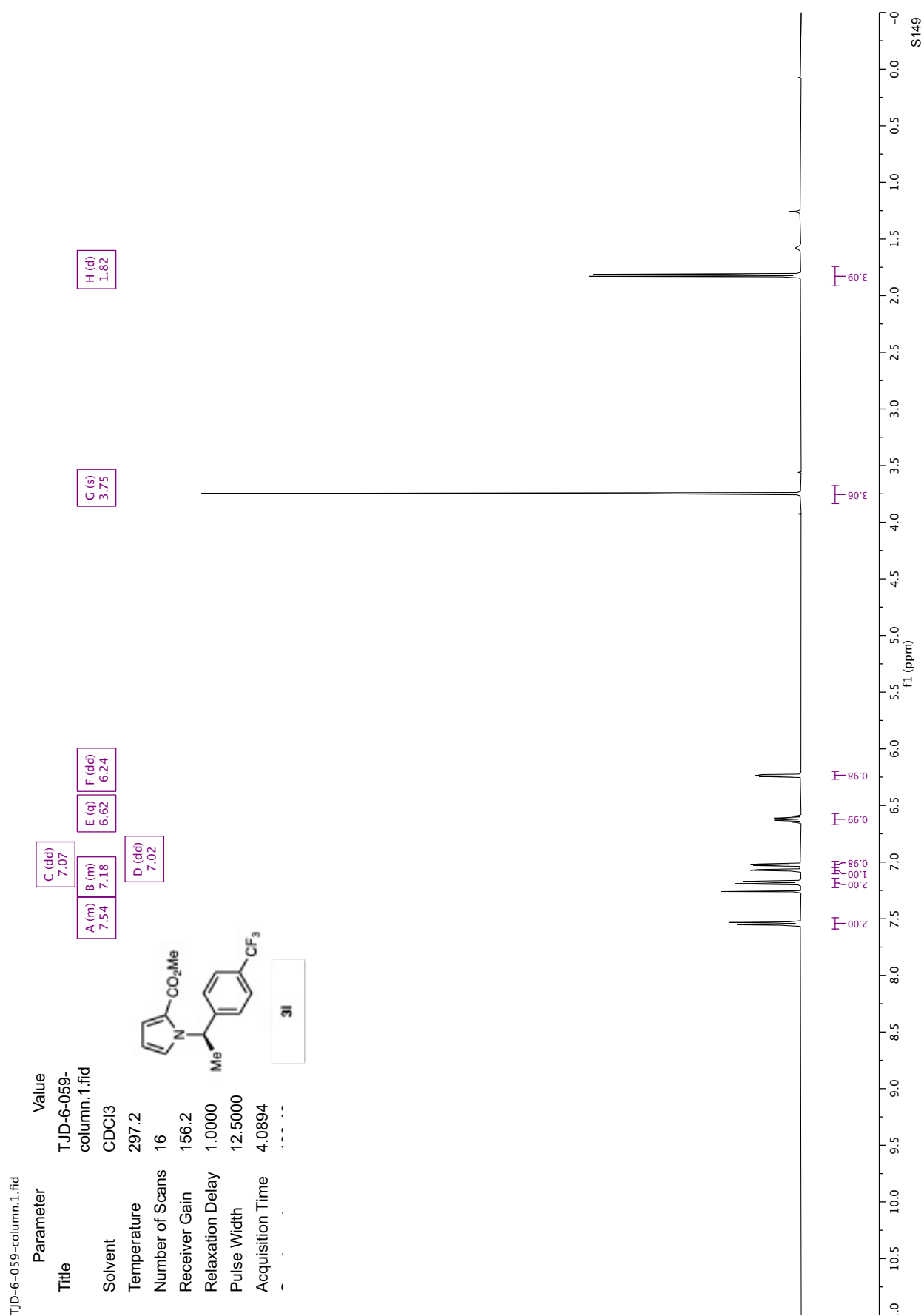


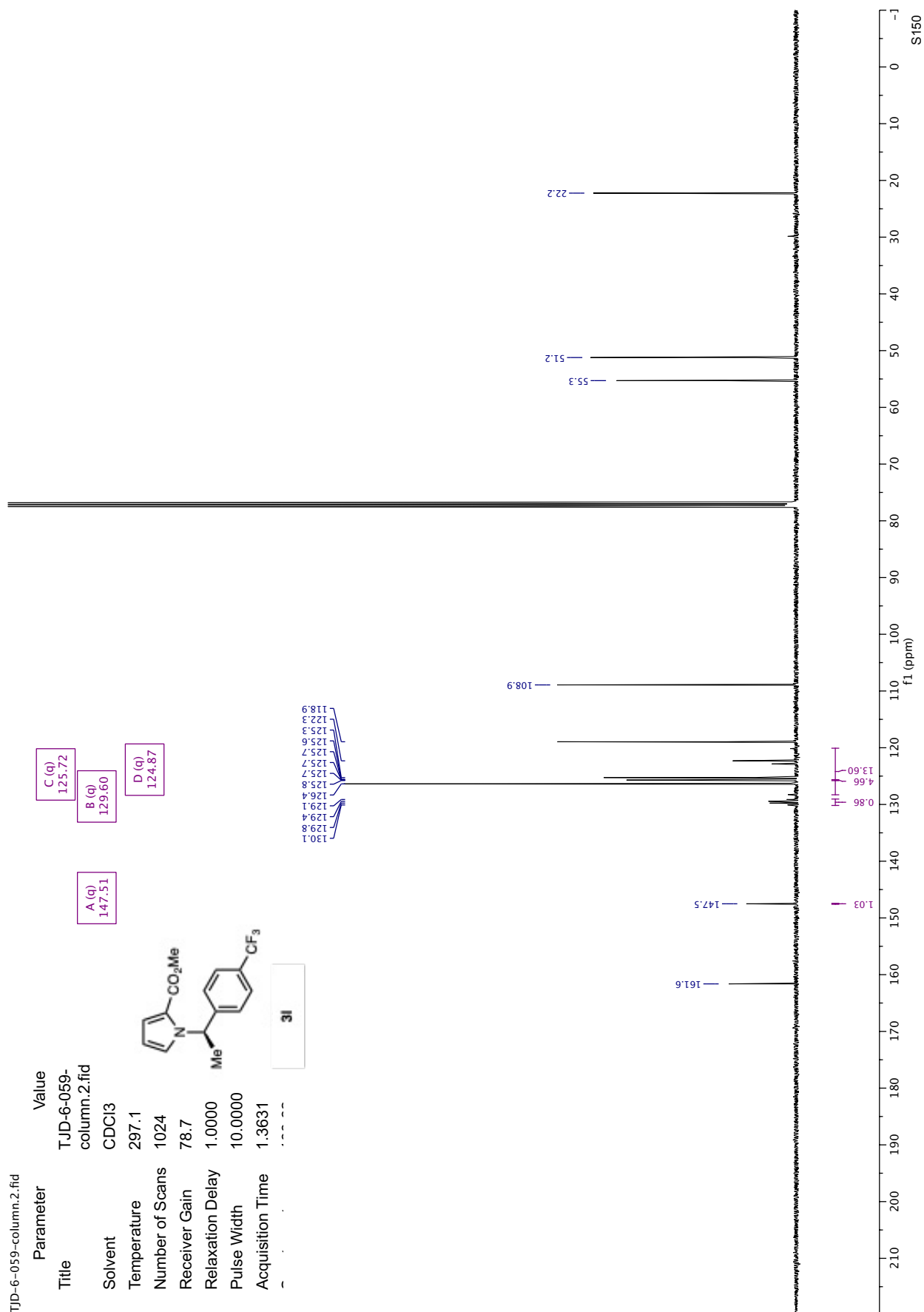
TJD-6-067-filtrate.2.fid		
Title	Parameter	Value
Origin	TJD-6-067-filtrate.2.fid	
	Brucker BioSpin GmbH	
Solvent	CDCI3	
Temperature	297.2	
Pulse Sequence	zgpg30	
Number of Scans	512	
Receiver Gain	64.2	
Relaxation Delay	1.0000	
Pulse Width	10.0000	
Acquisition Time	1.3631	

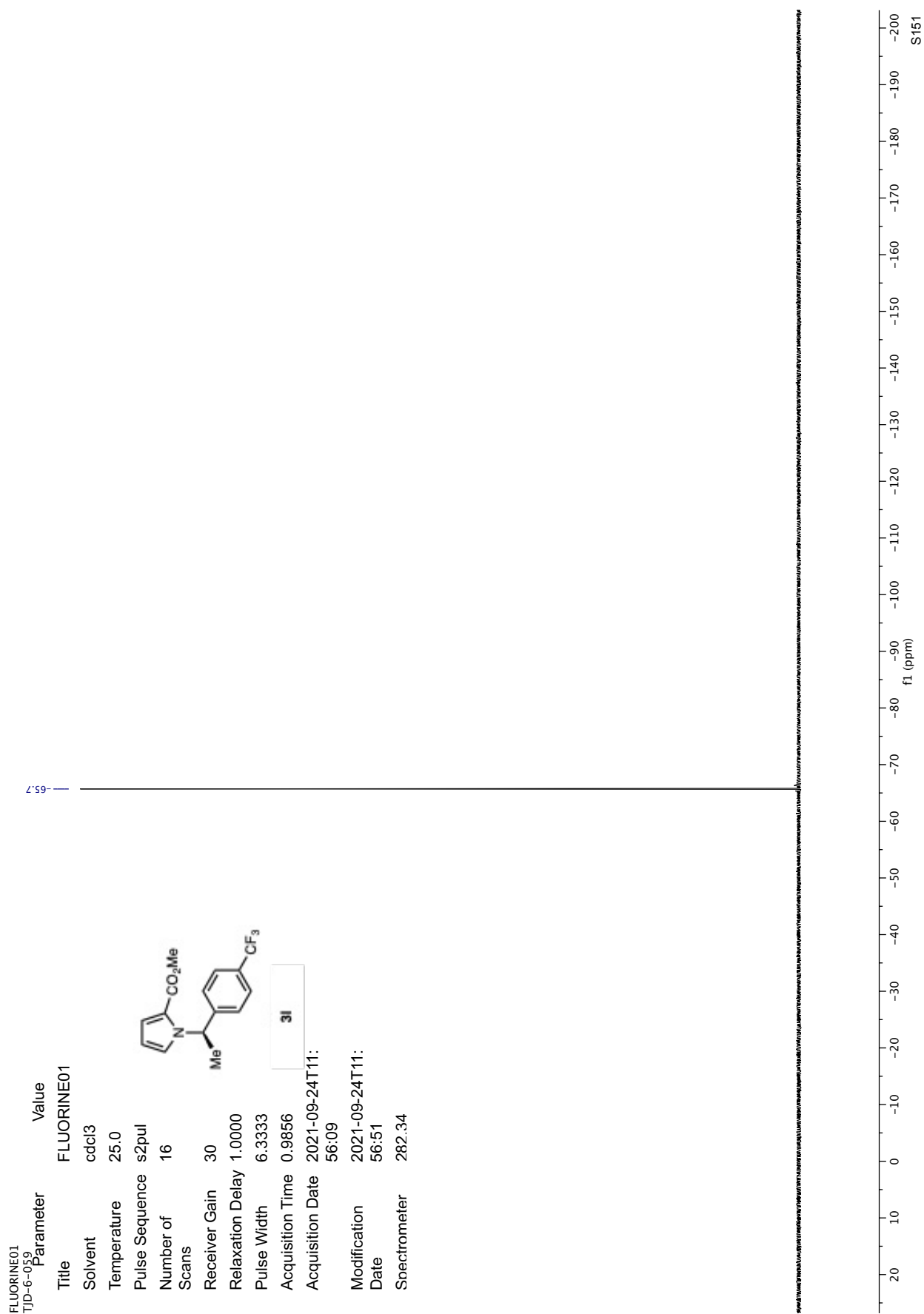






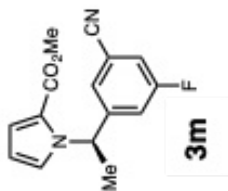




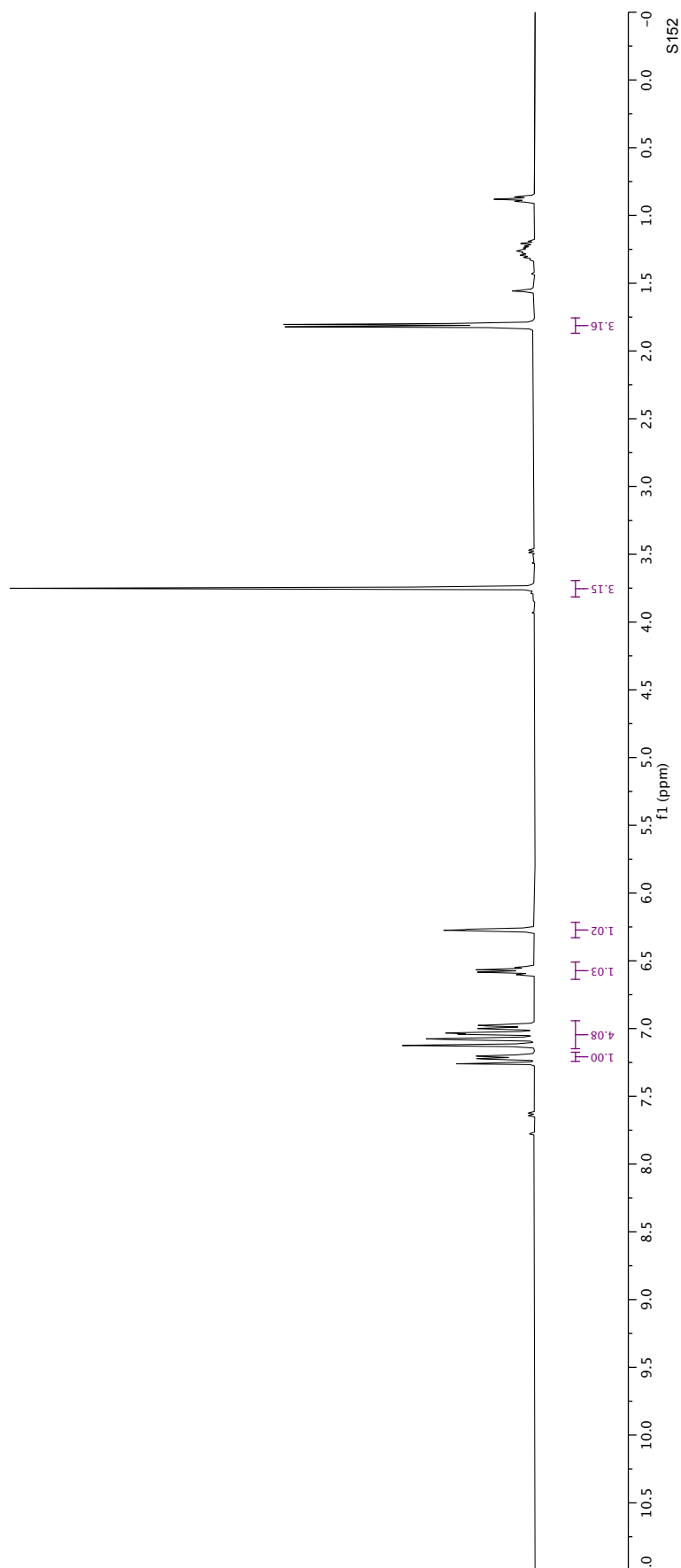


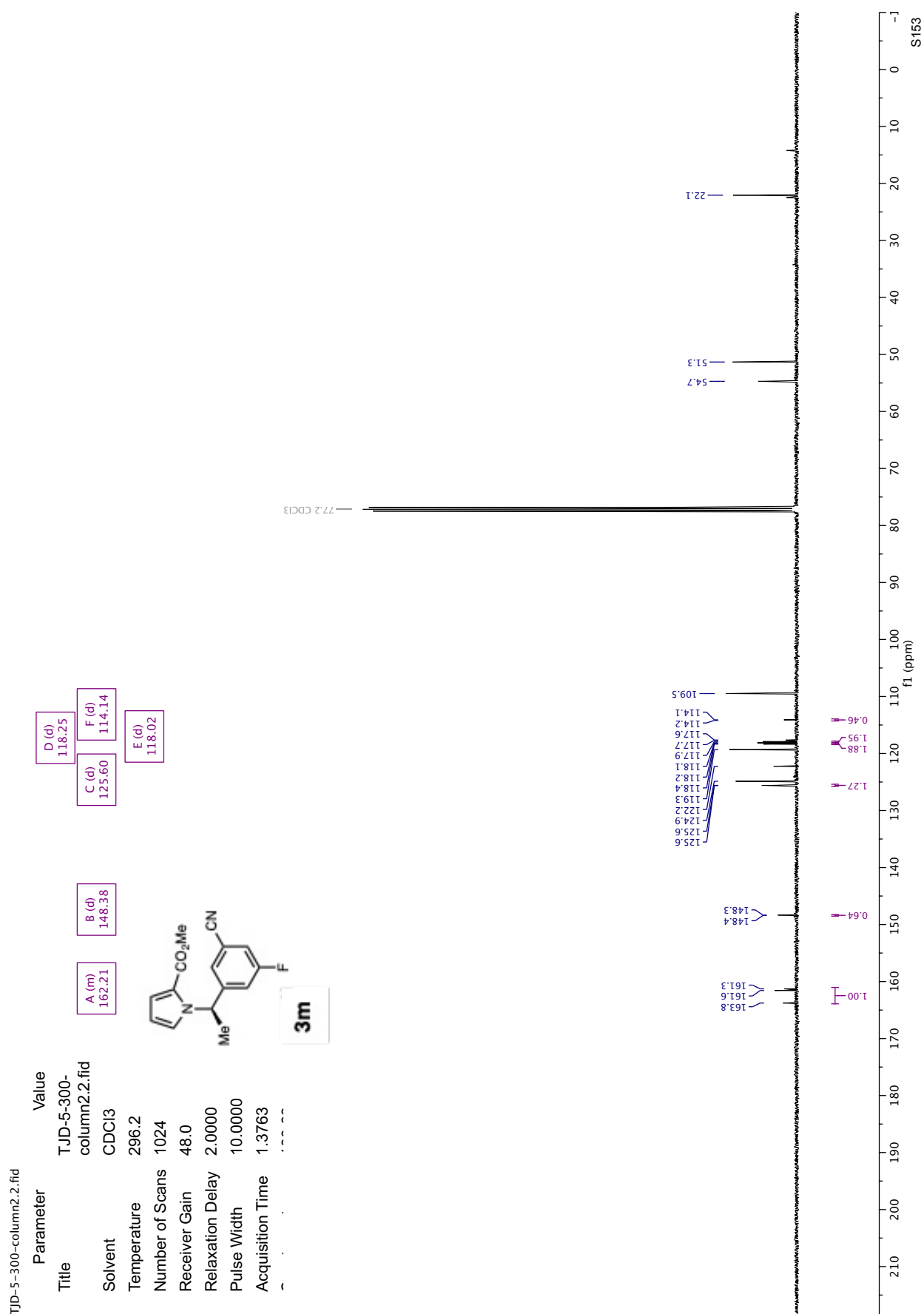
TJD-5-300-column2.1.fid

Parameter	Value
Title	TJD-5-300-column2.1.fid
Solvent	CDCl ₃
Temperature	296.1
Number of Scans	16
Receiver Gain	101.0
Relaxation Delay	1.0000
Pulse Width	9.8500
Acquisition Time	3.9977

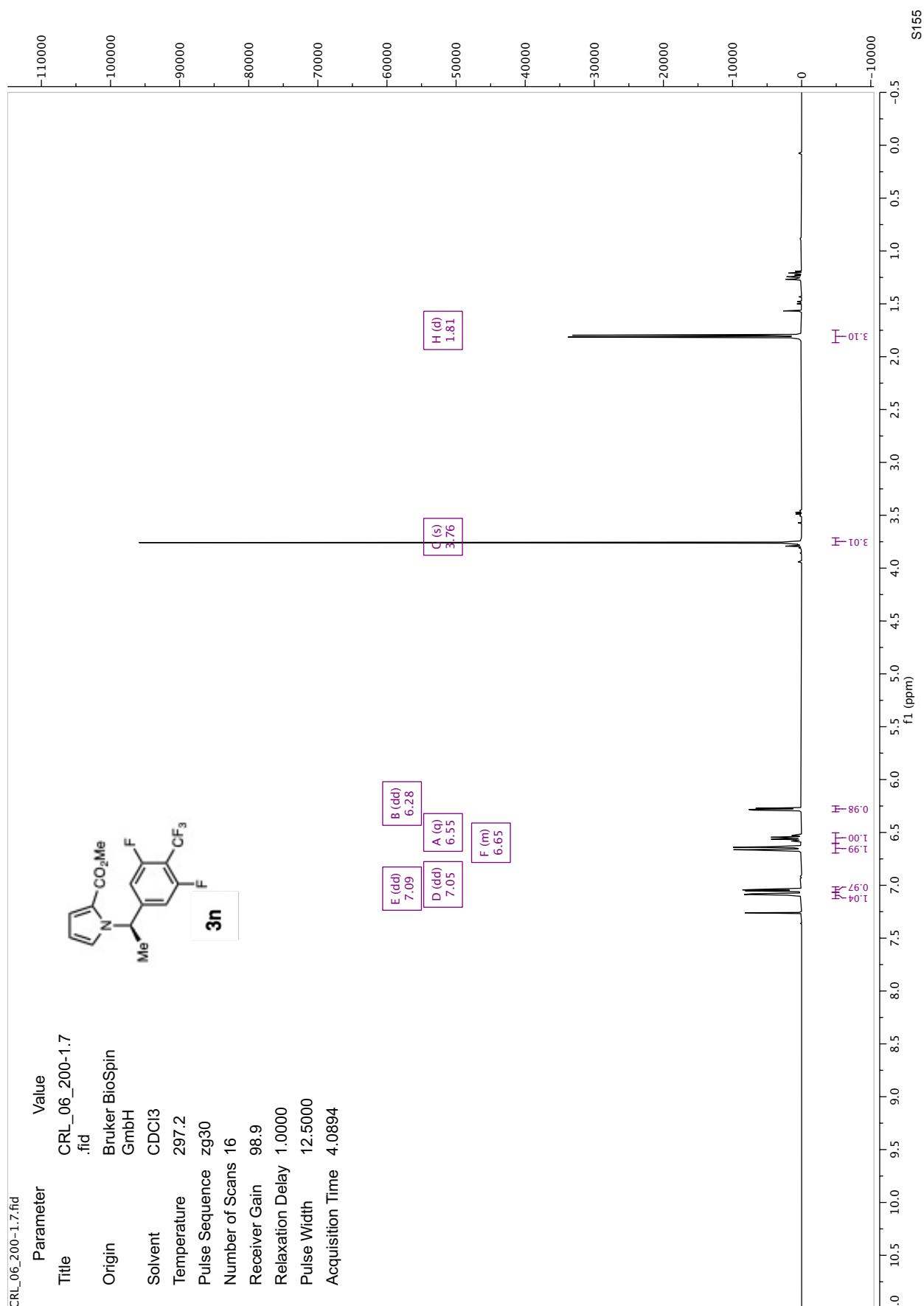


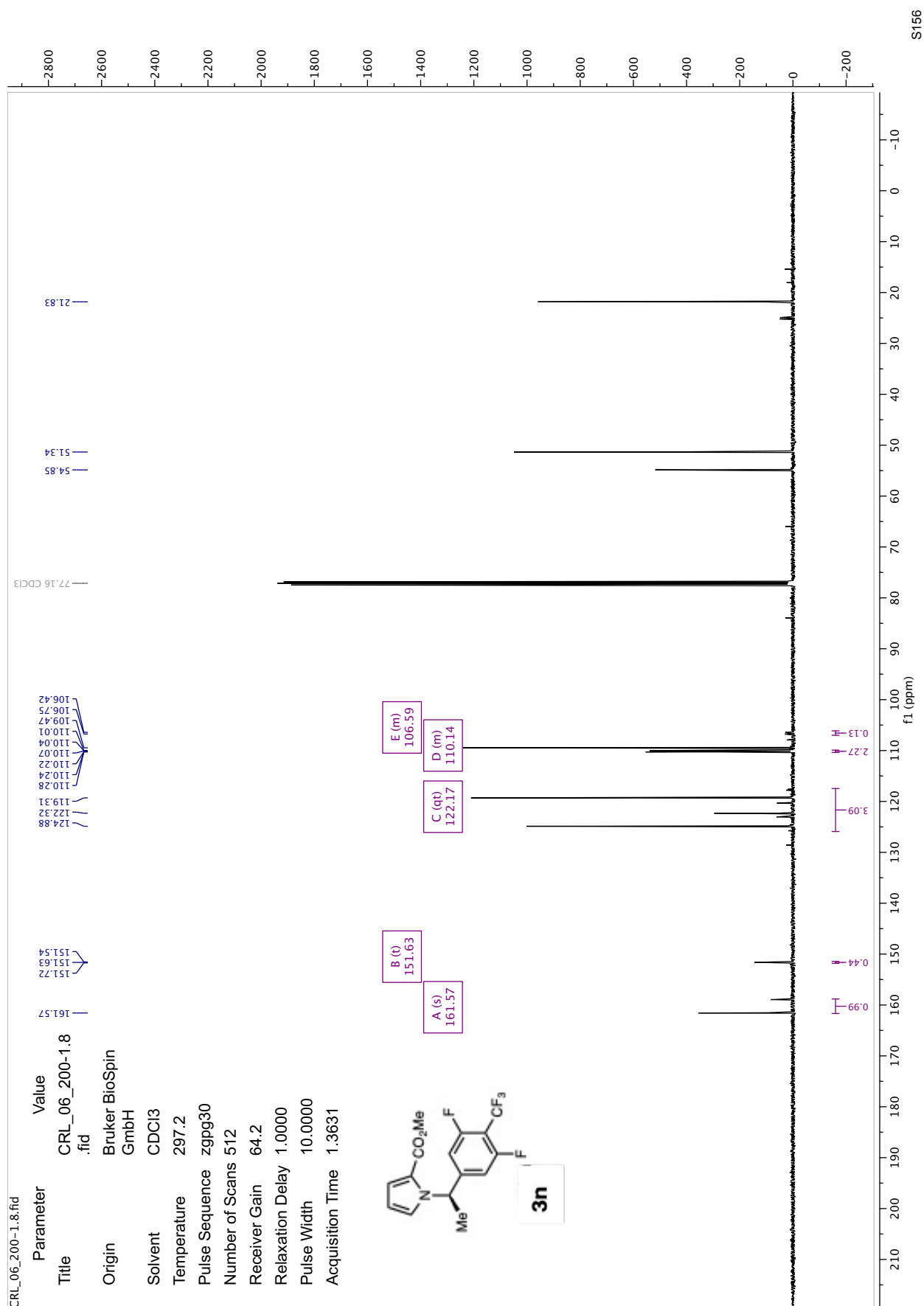
B (m)	7.05
A (m)	7.21
C (q)	6.58
D (m)	6.27
E (d)	3.75
F (m)	1.81

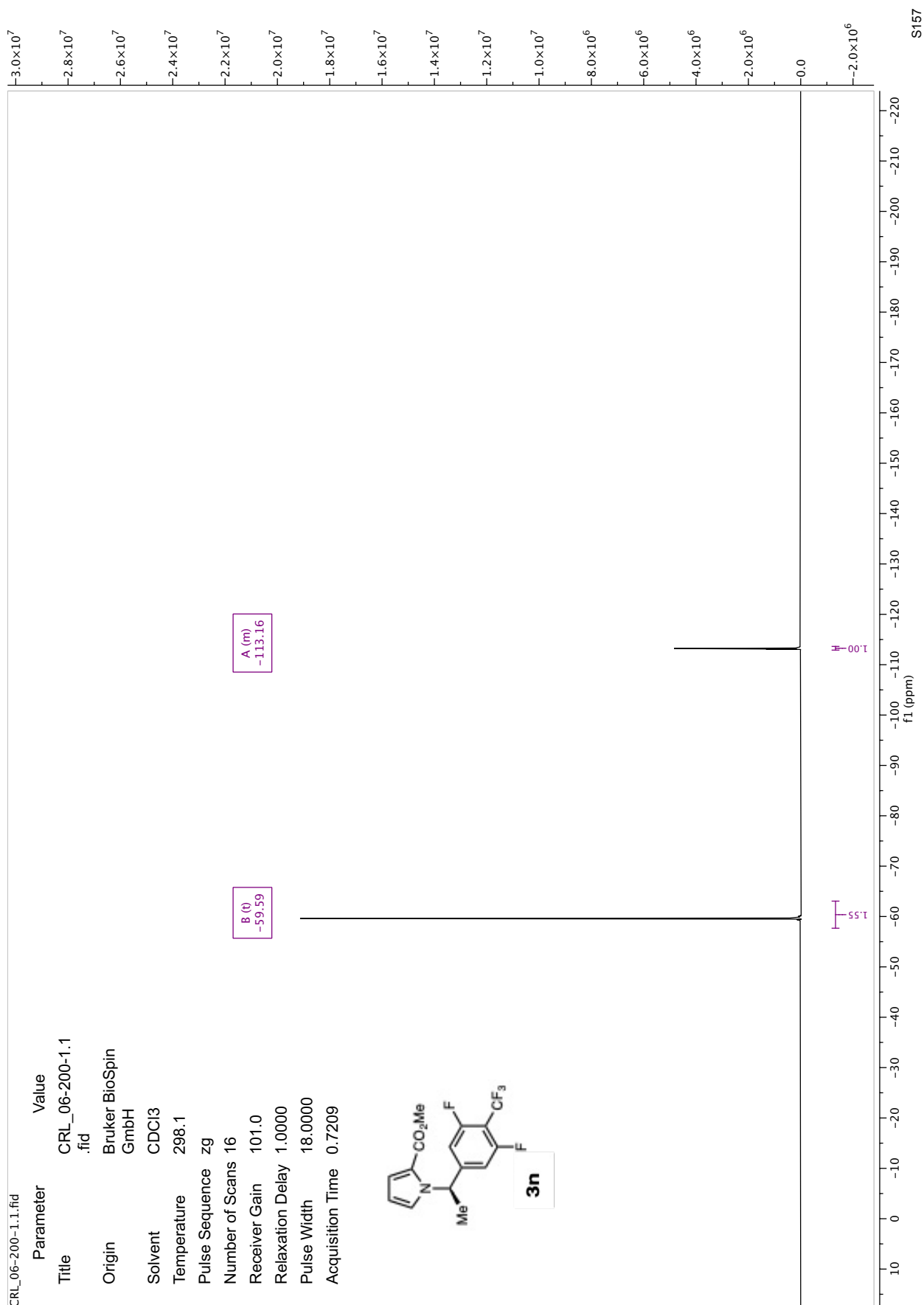


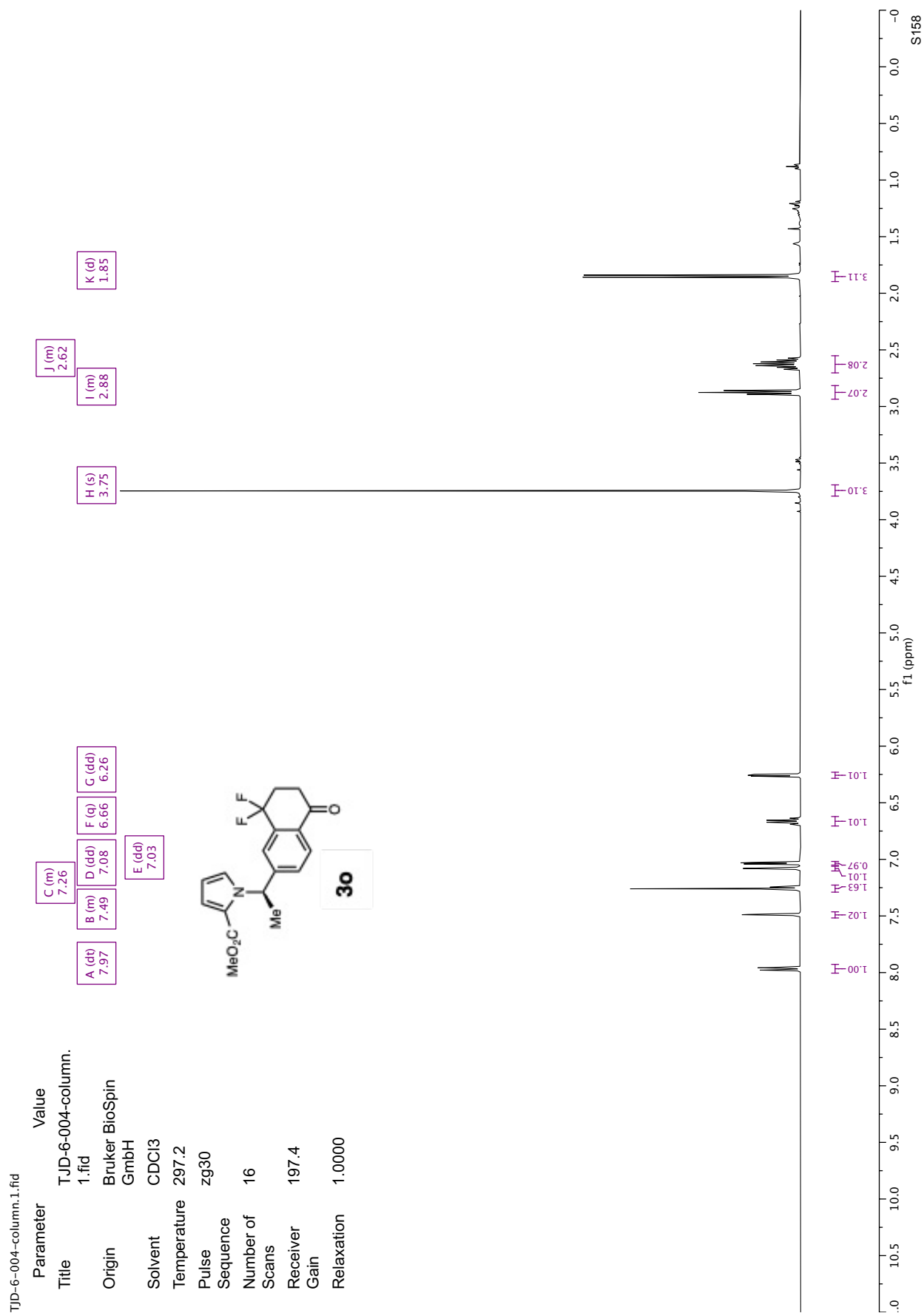


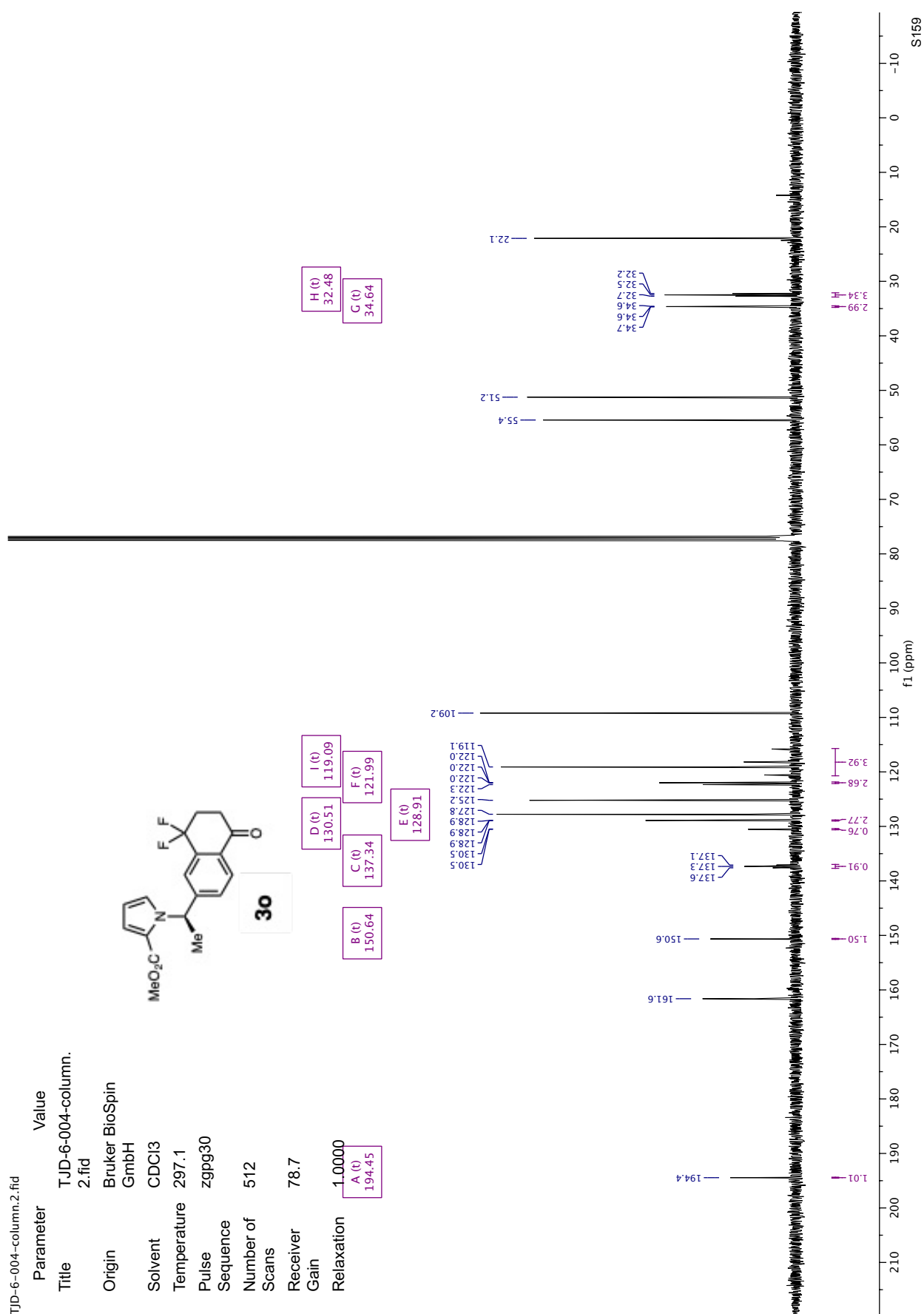


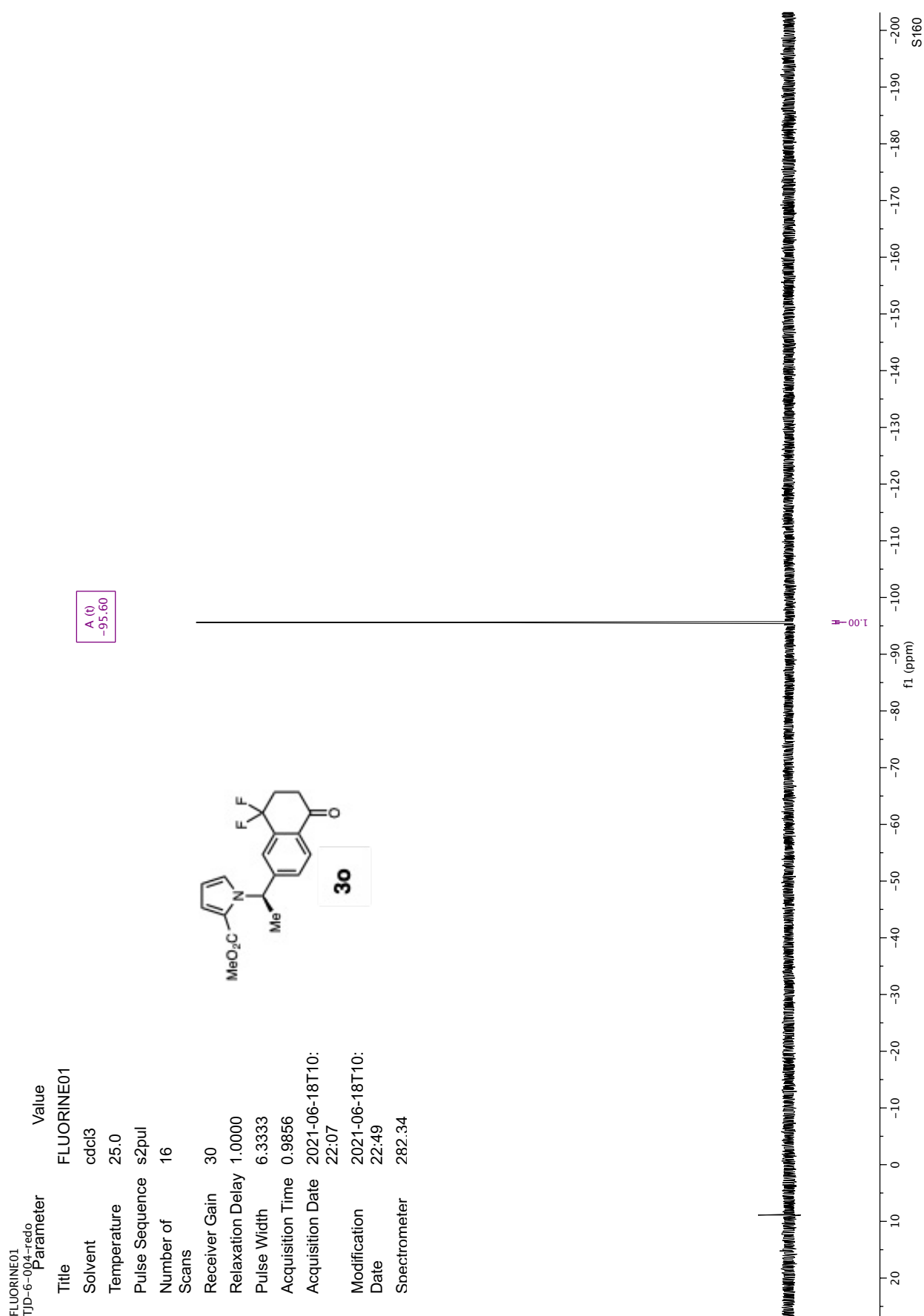


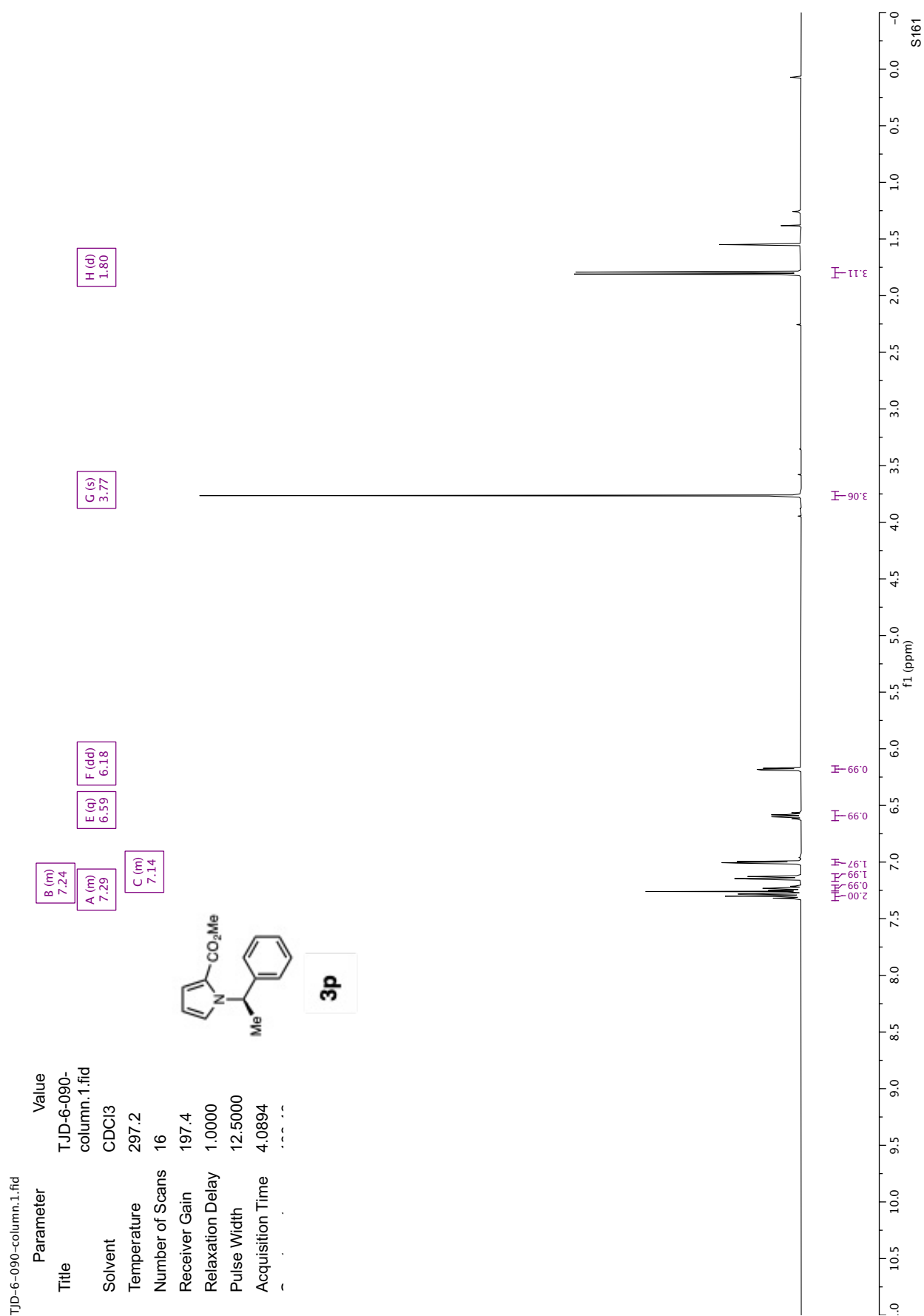


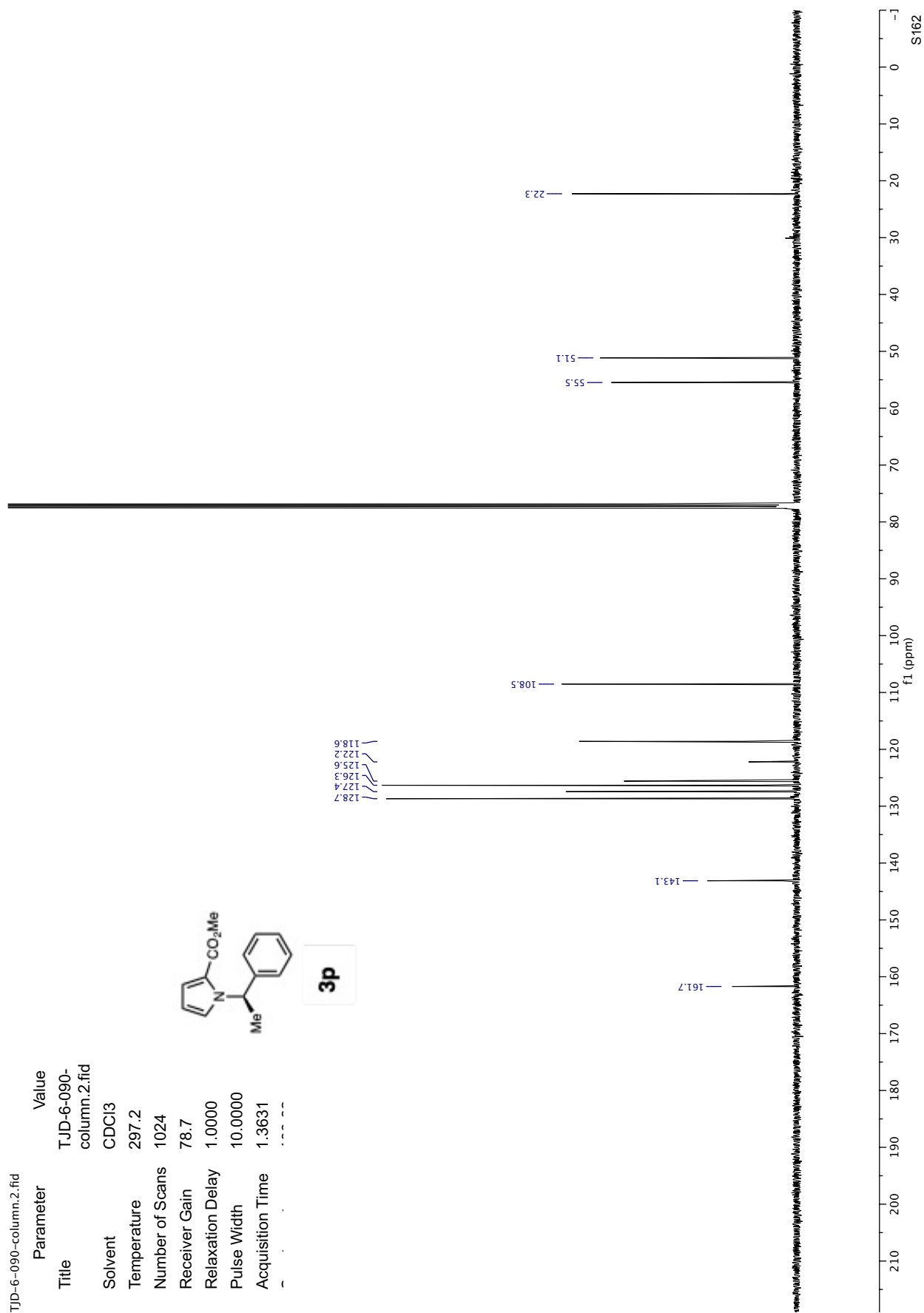












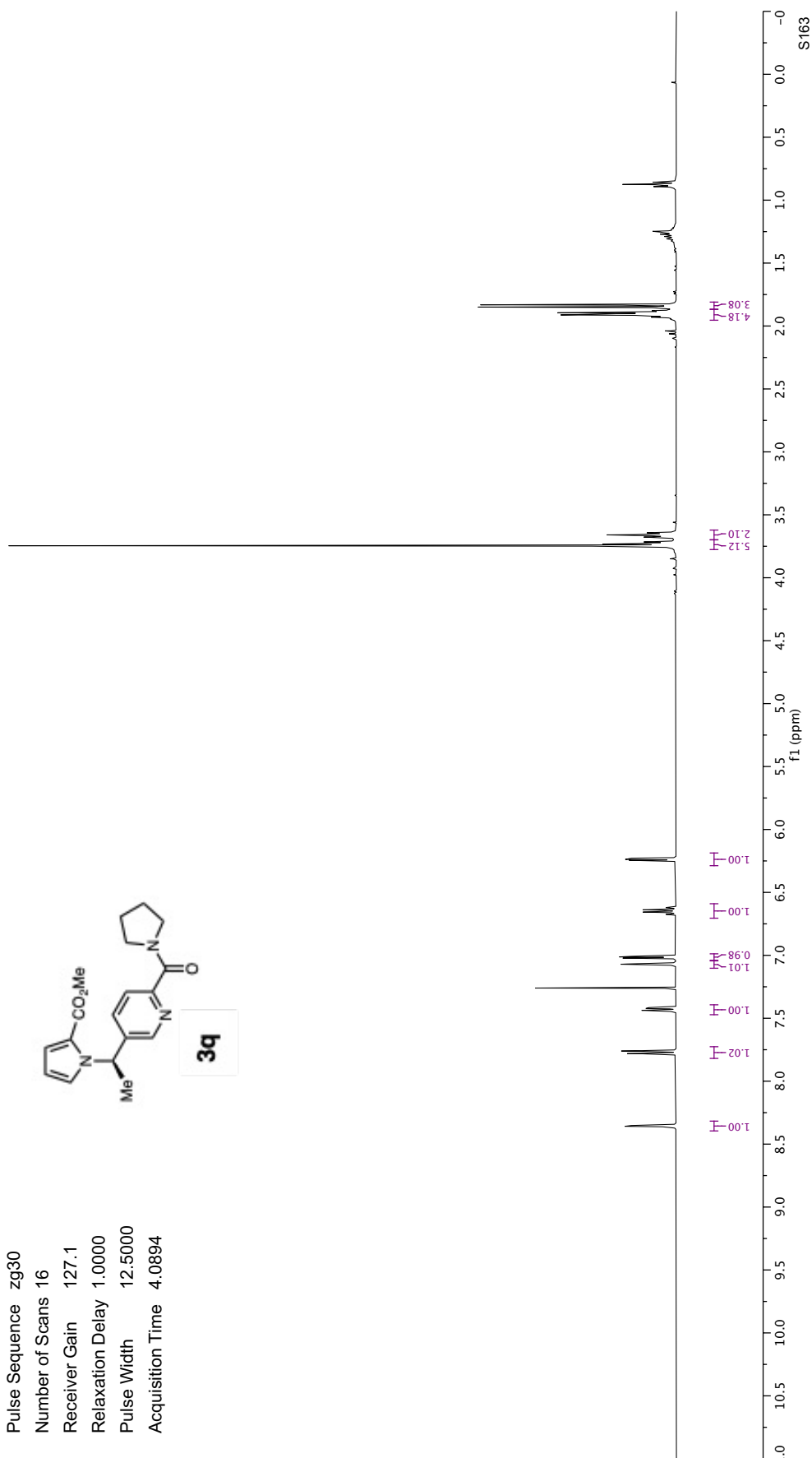
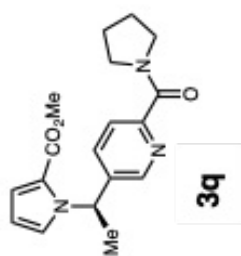
CRL_06_096-1.5.fid

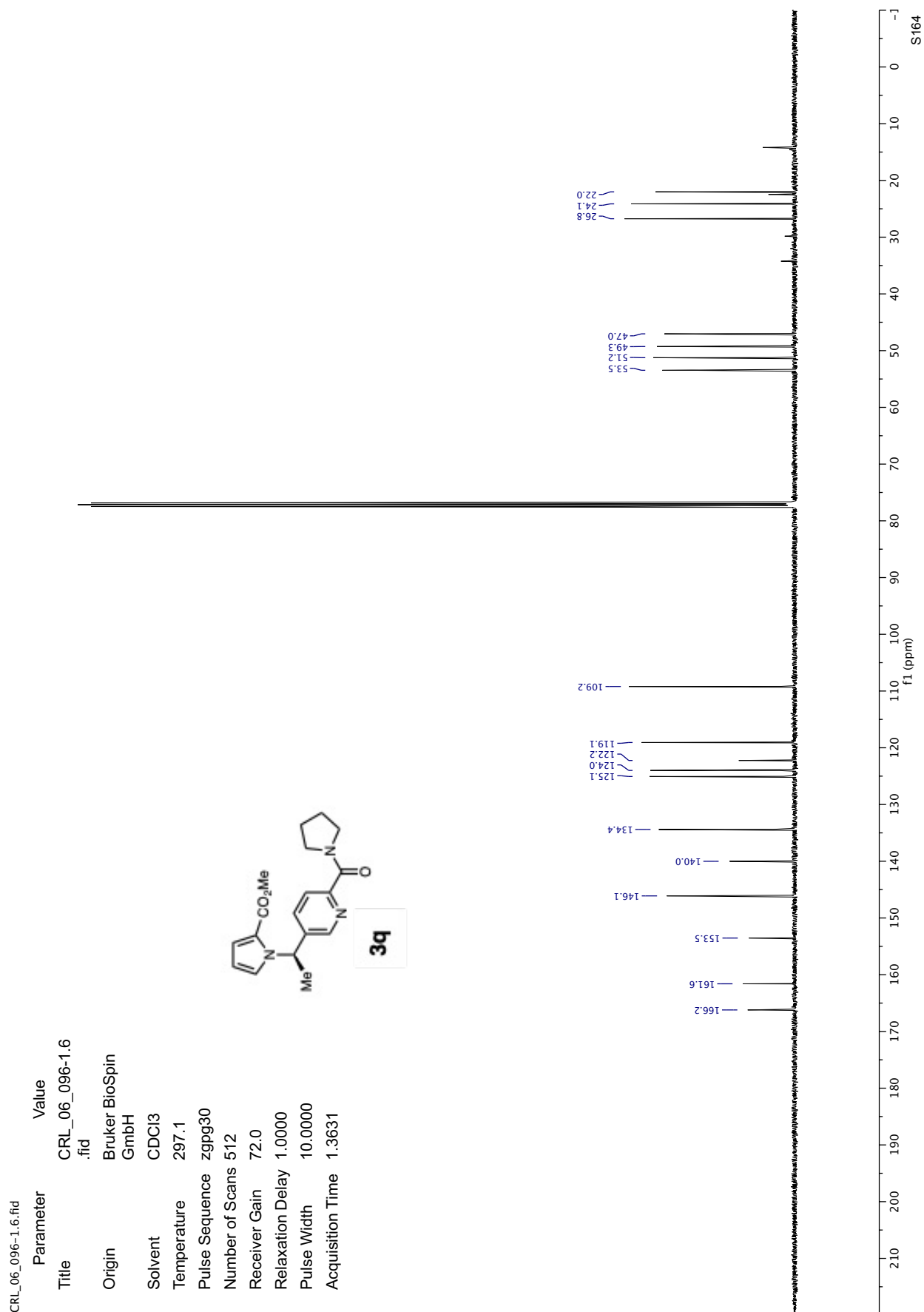
Parameter	Value
Title	CRL_06_096-1.5.fid
Origin	Brucker BioSpin GmbH
Solvent	CDCl ₃
Temperature	297.2
Pulse Sequence	zg30
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894

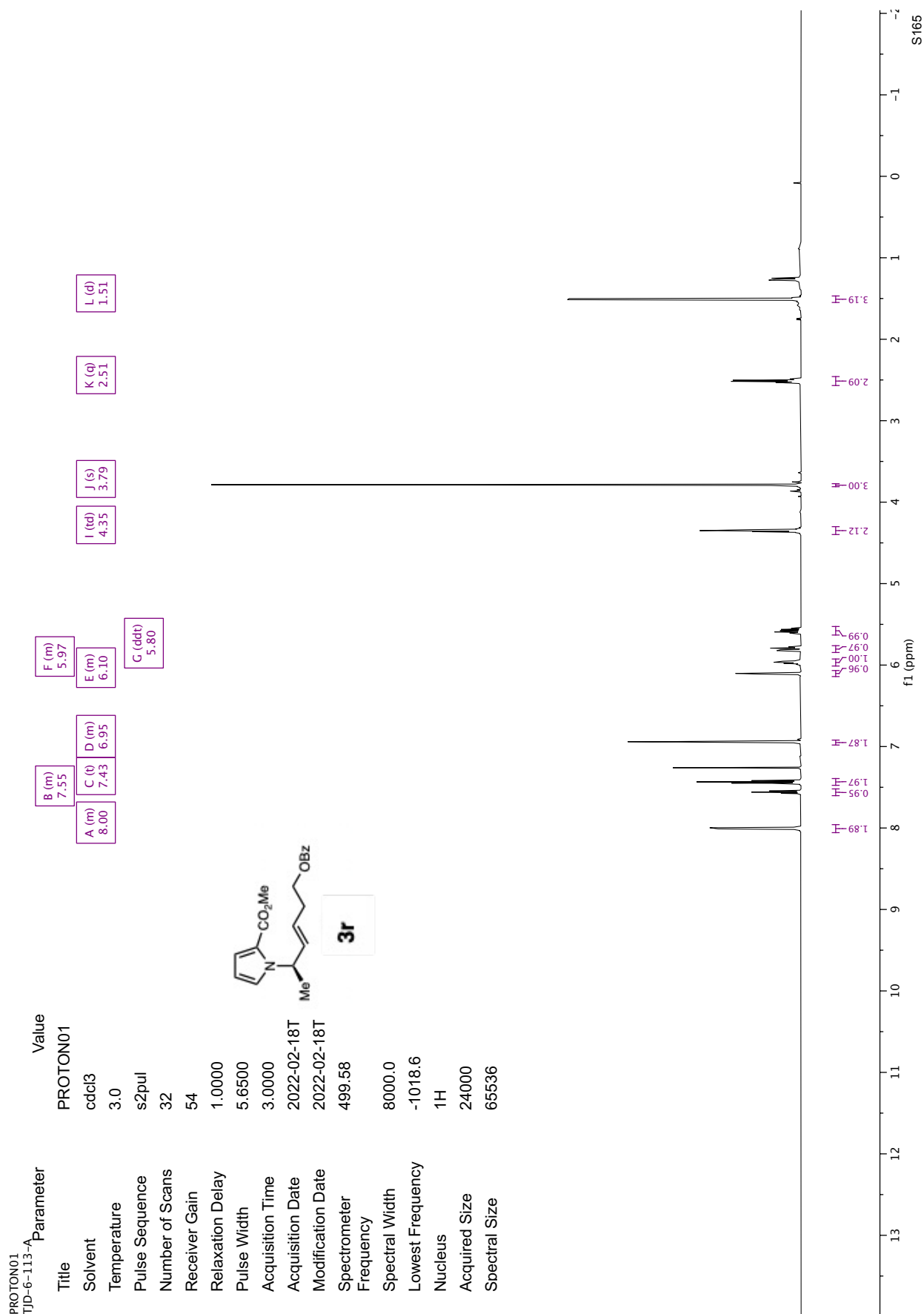
A (d)	8.35
B (dd)	7.77
C (ddd)	7.43
D (dd)	7.07
E (d)	6.65
F (dd)	6.24
K (dd)	7.02

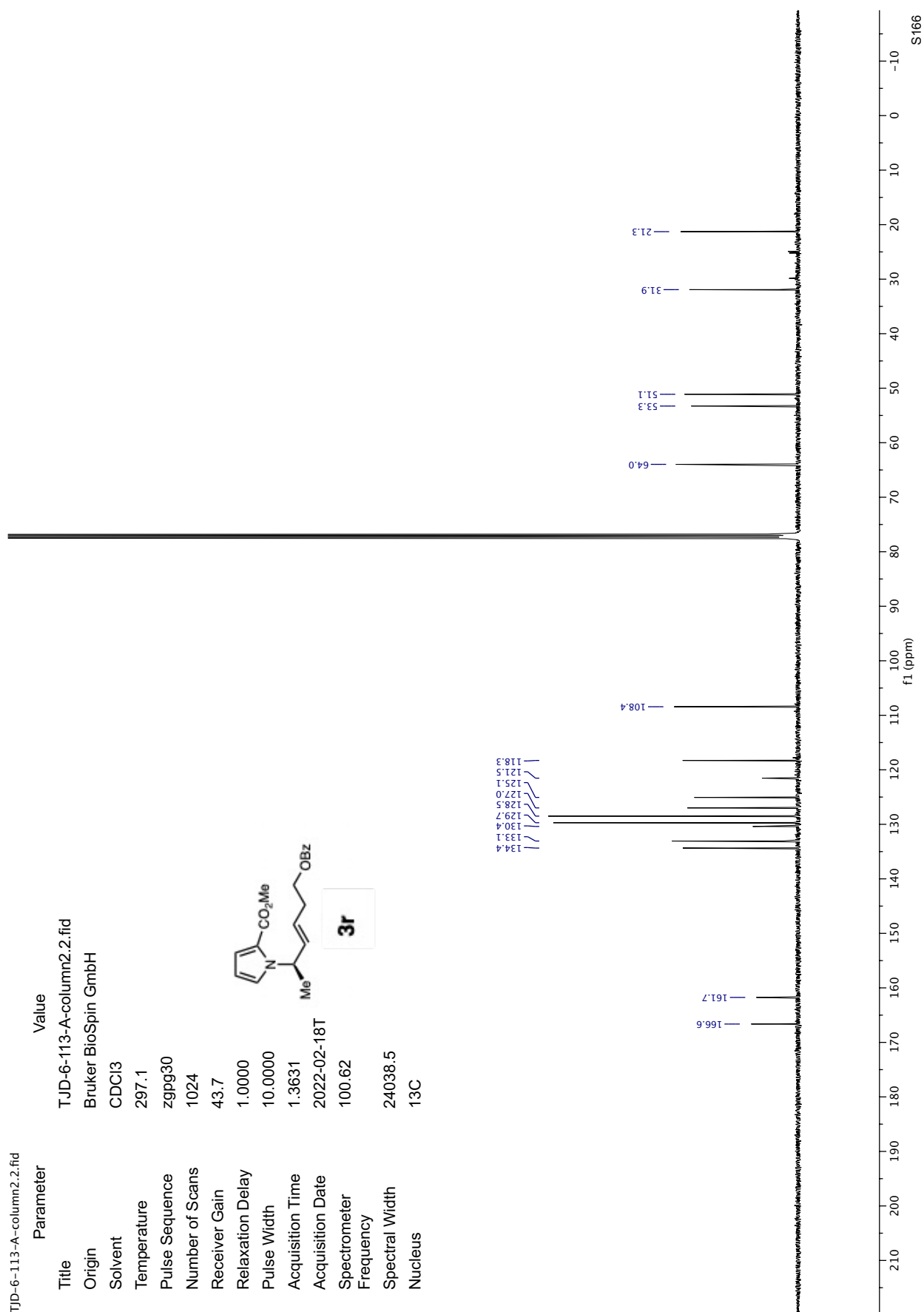
H (m)	3.66
G (m)	3.75

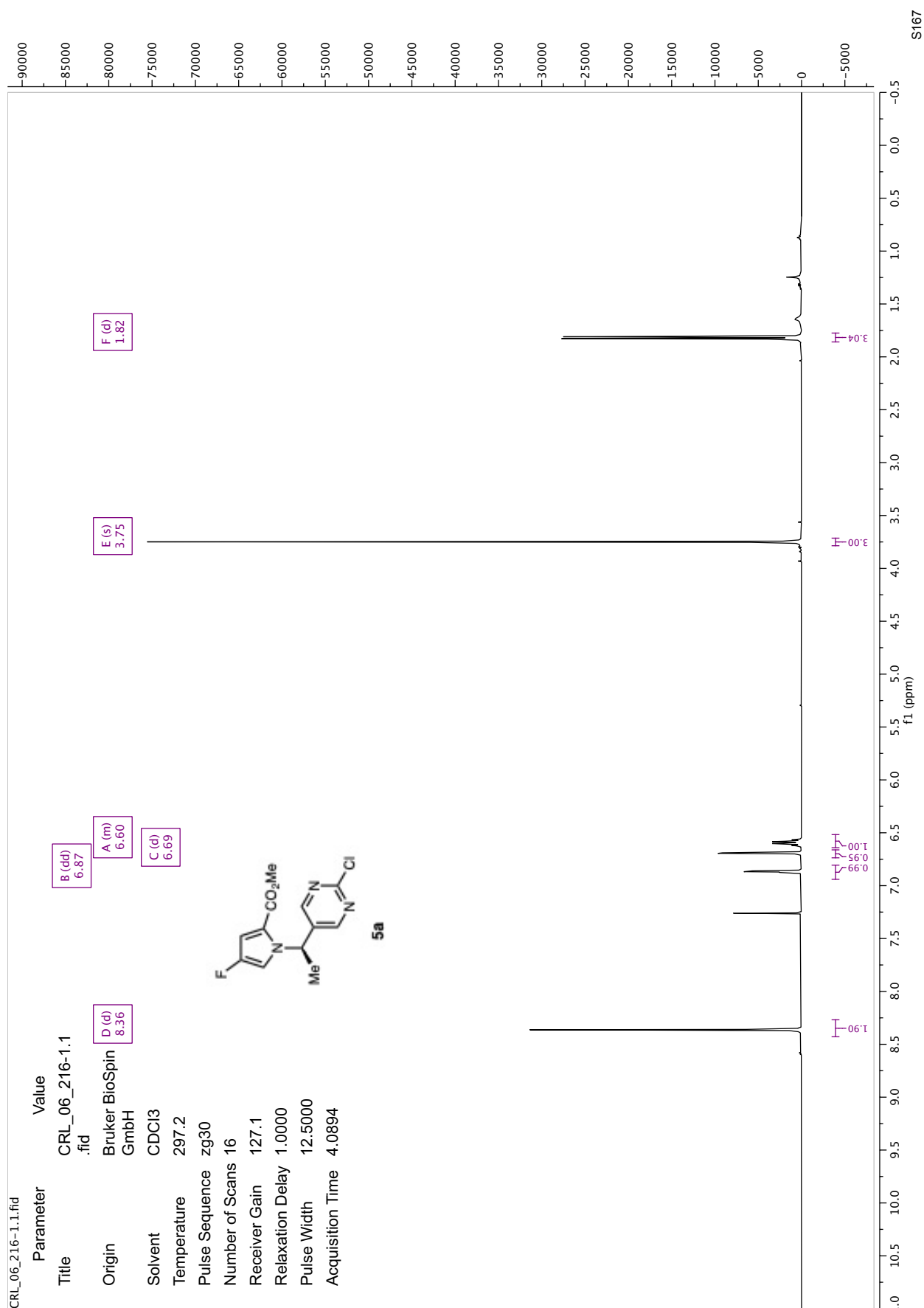
J (d)	1.84
I (m)	1.91

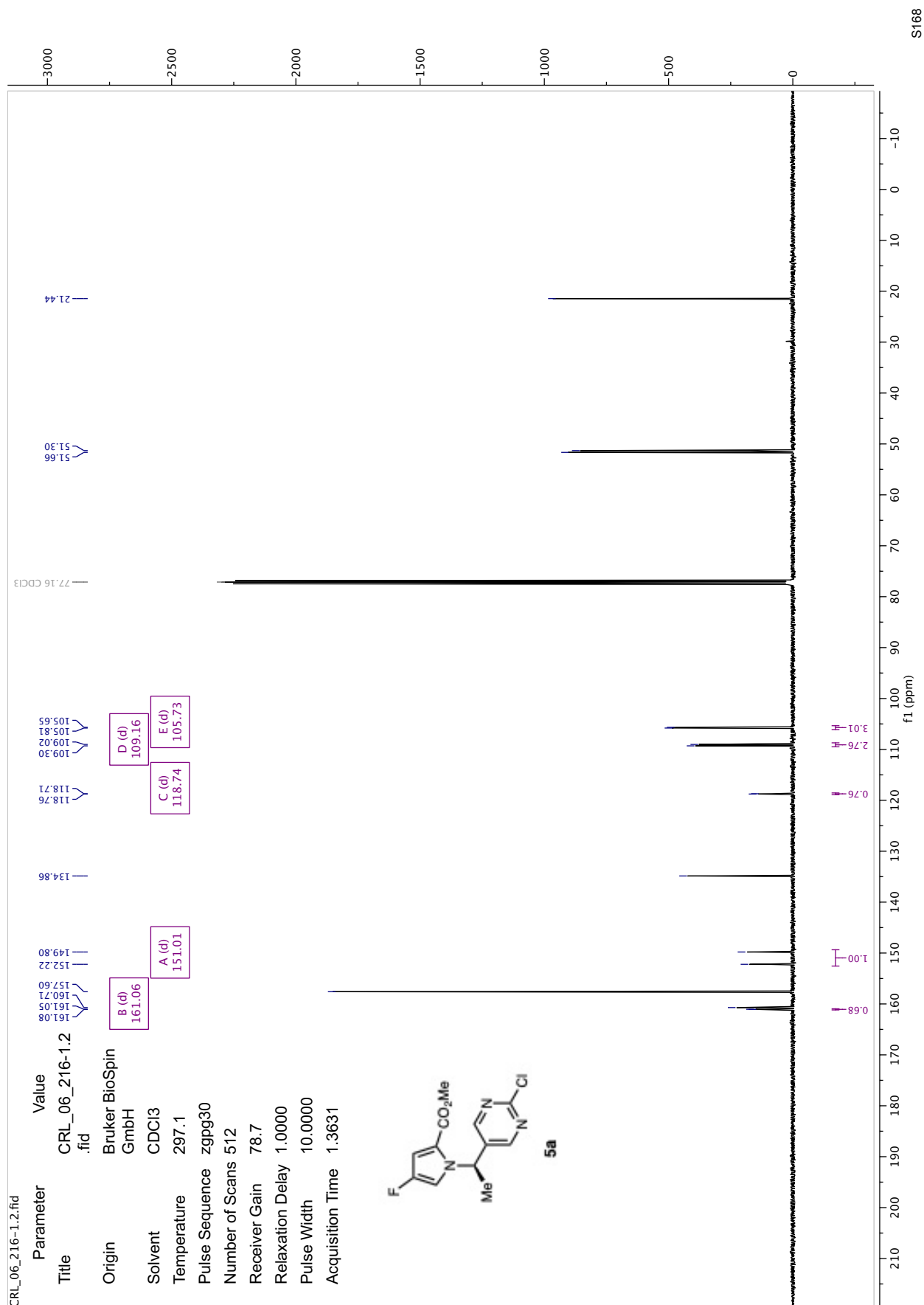


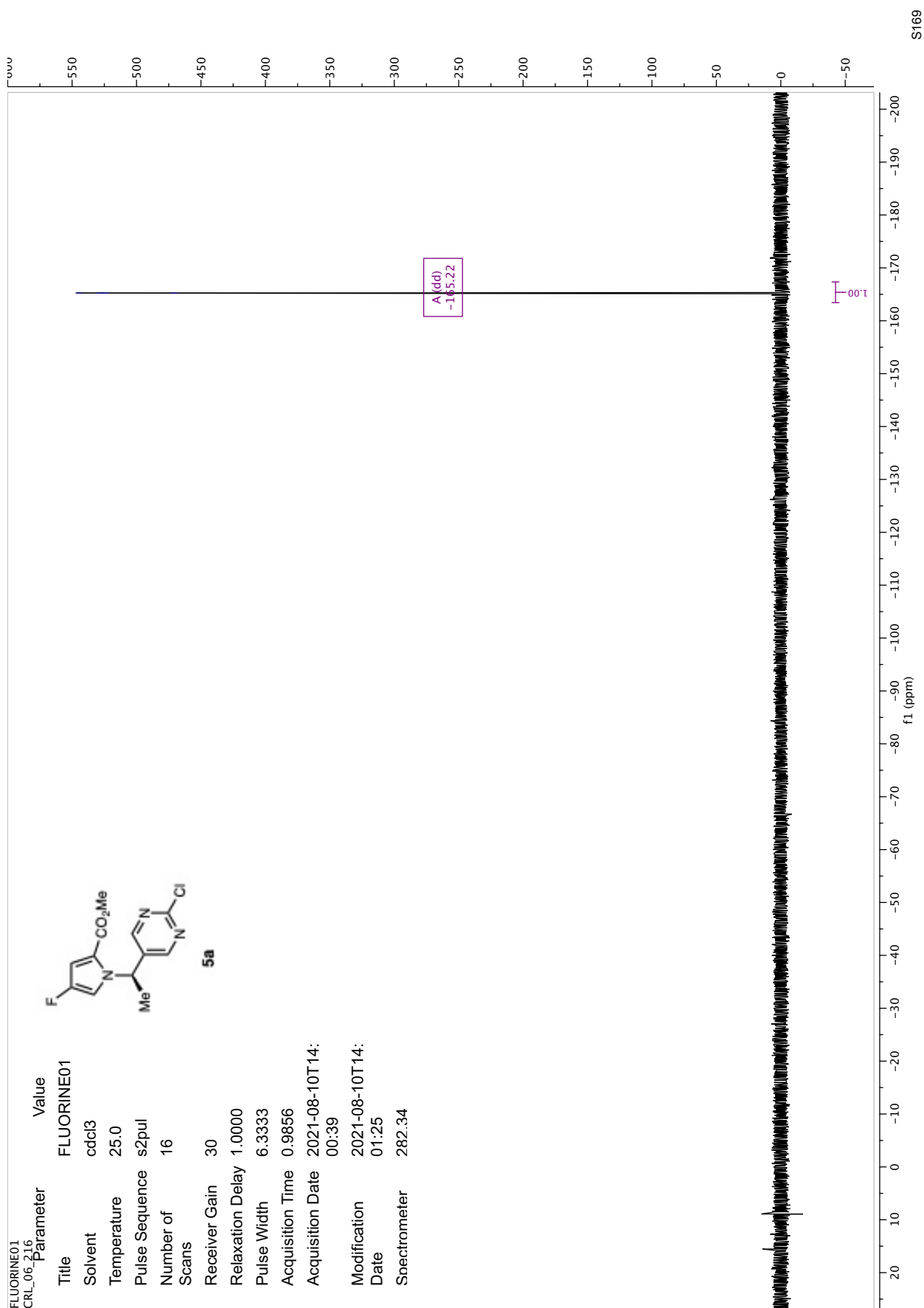


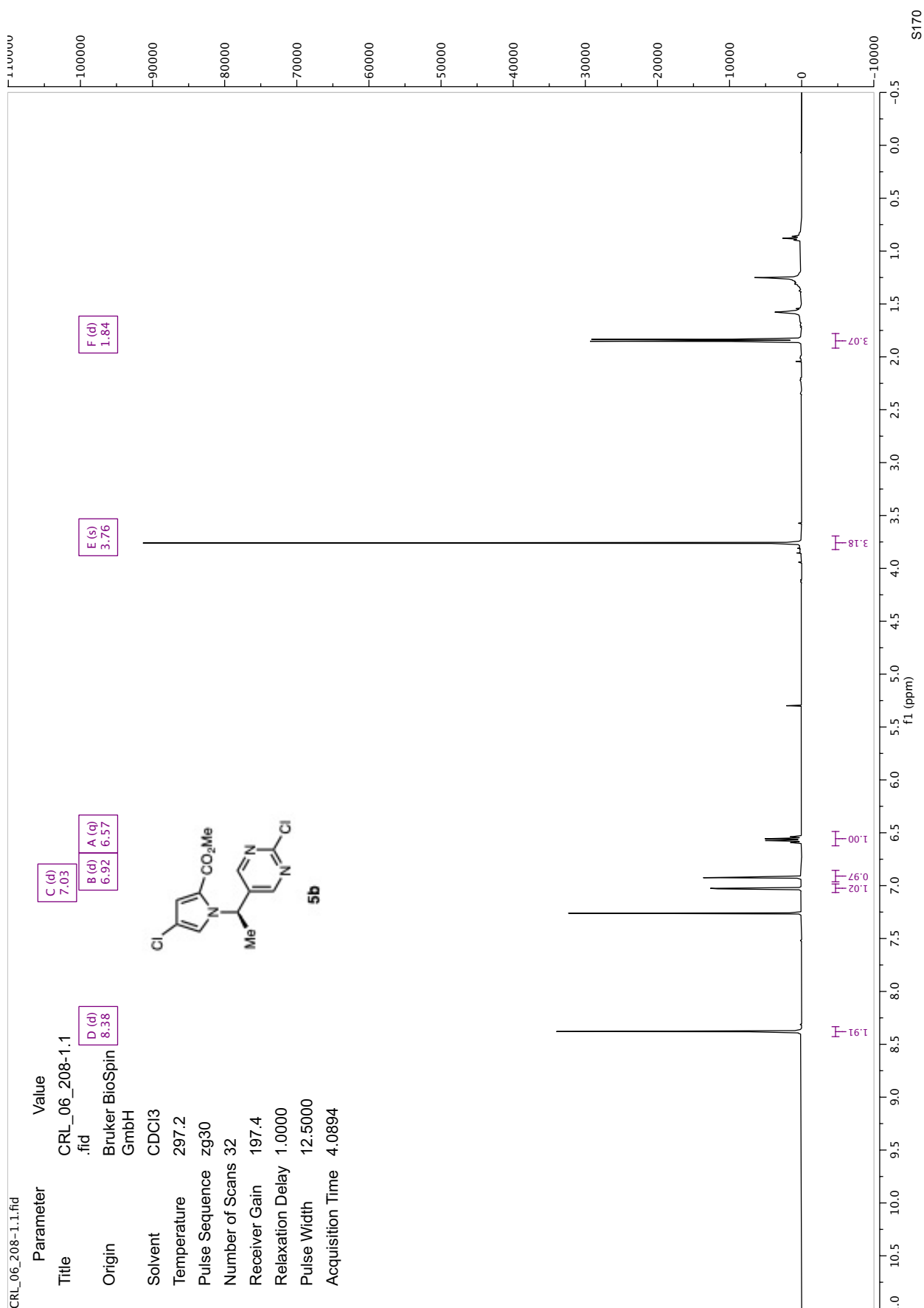


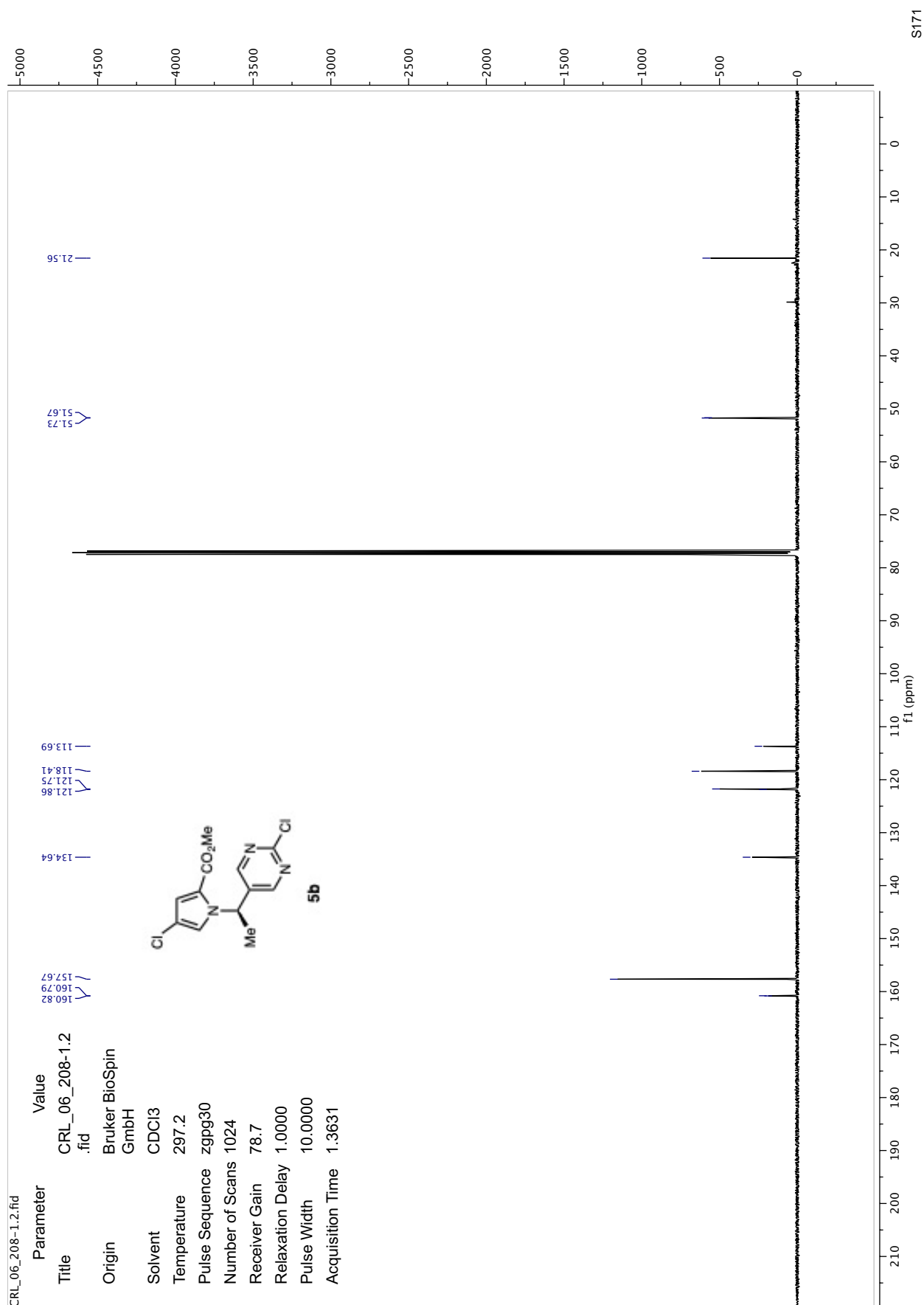


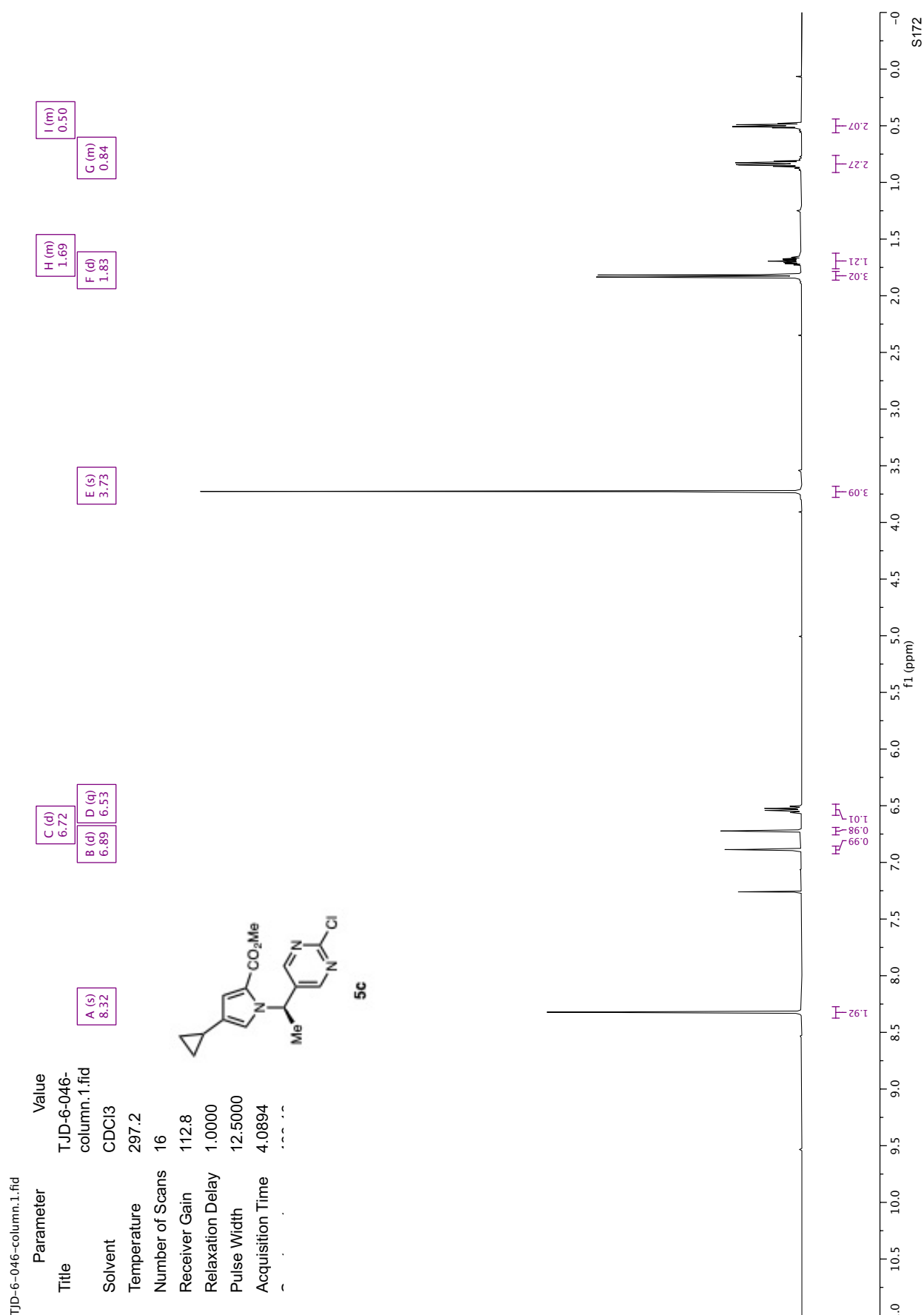


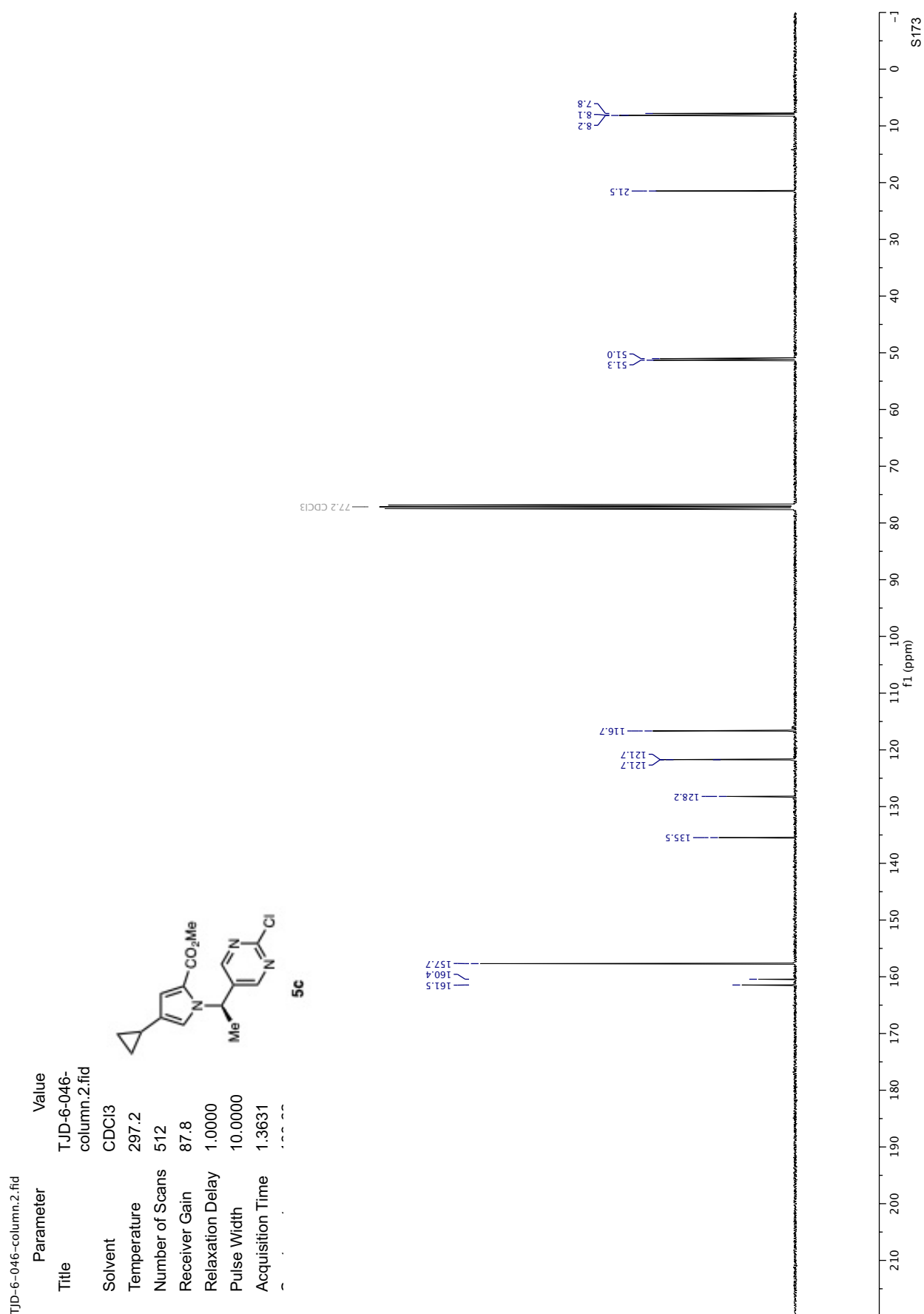


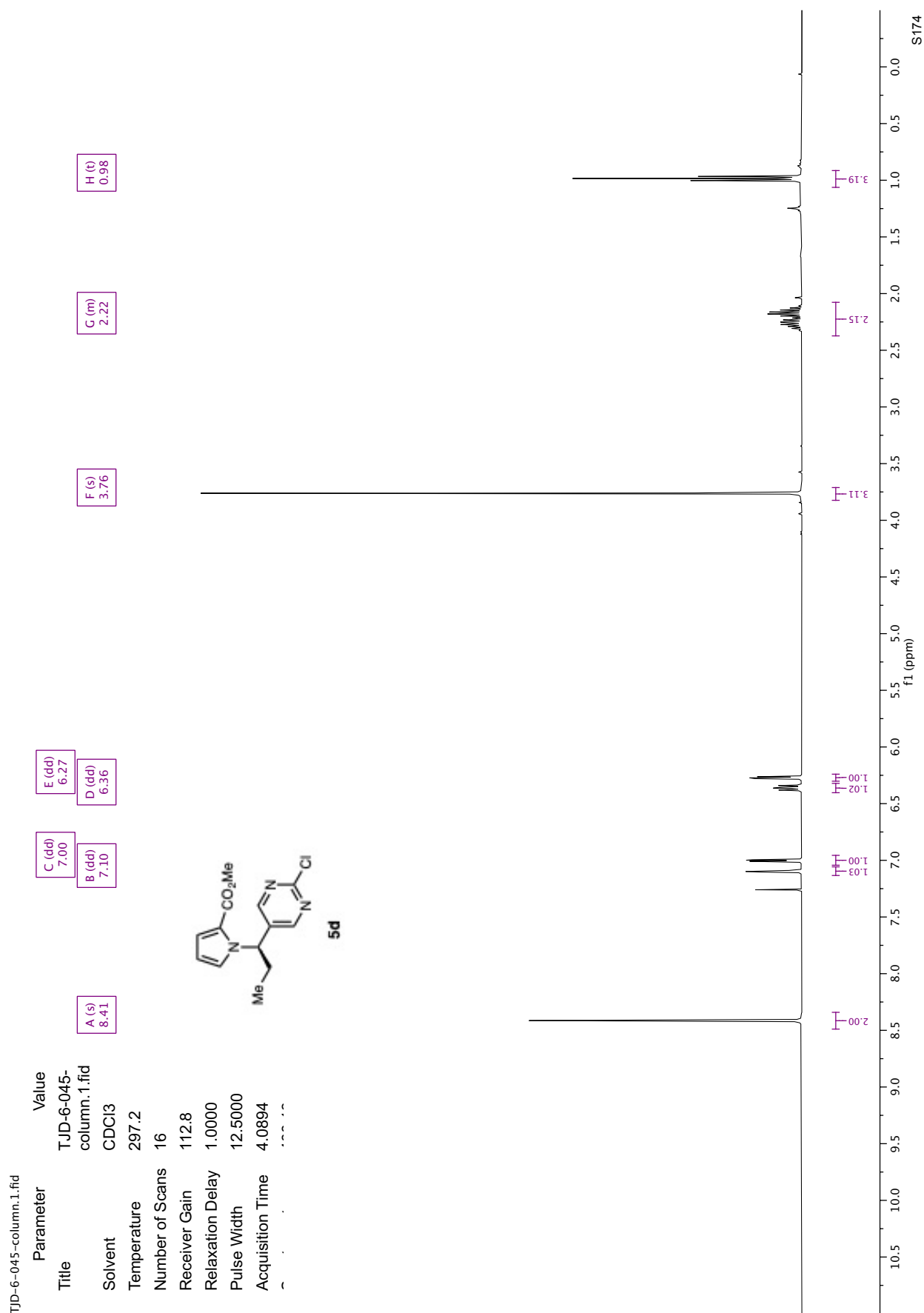


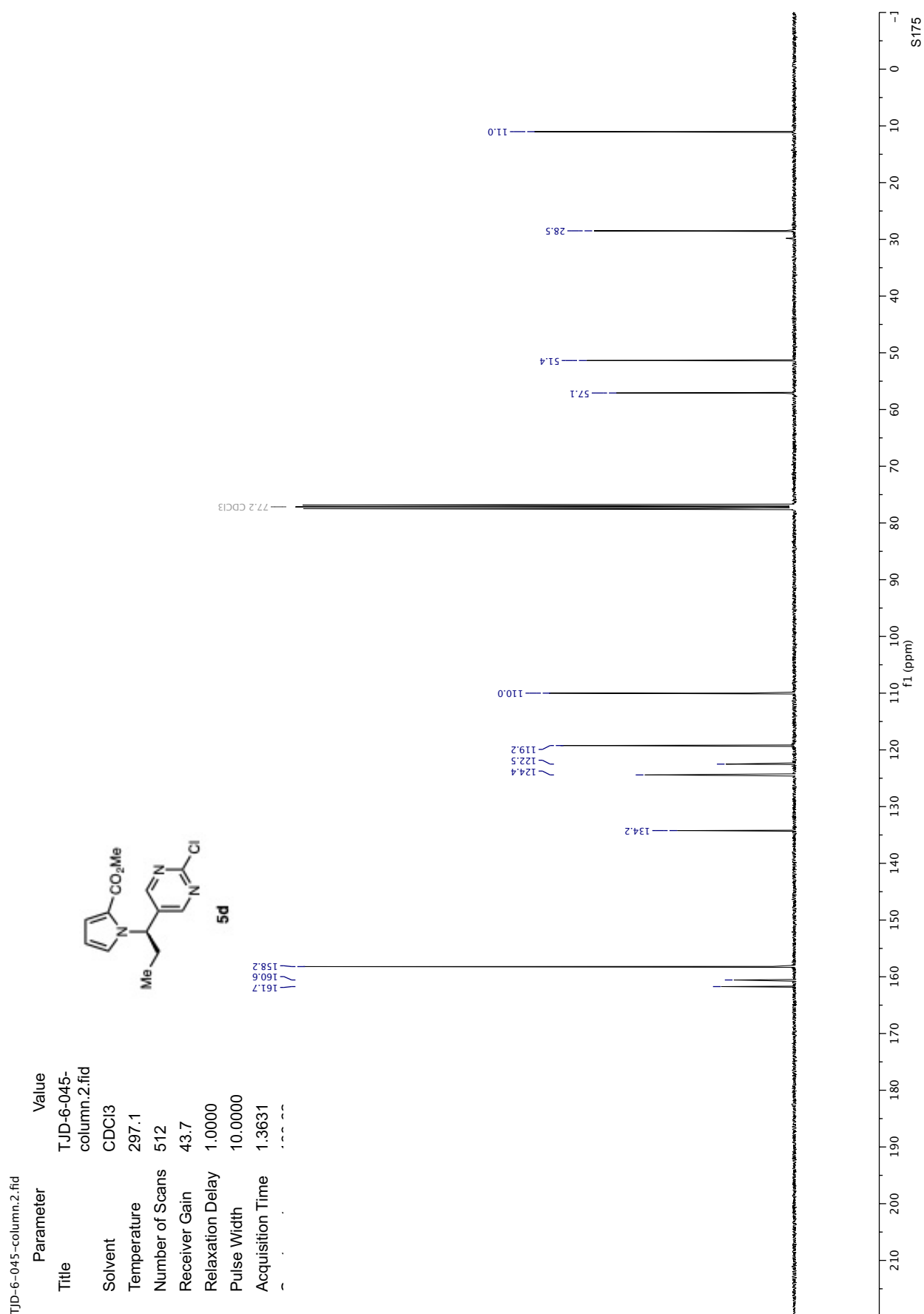


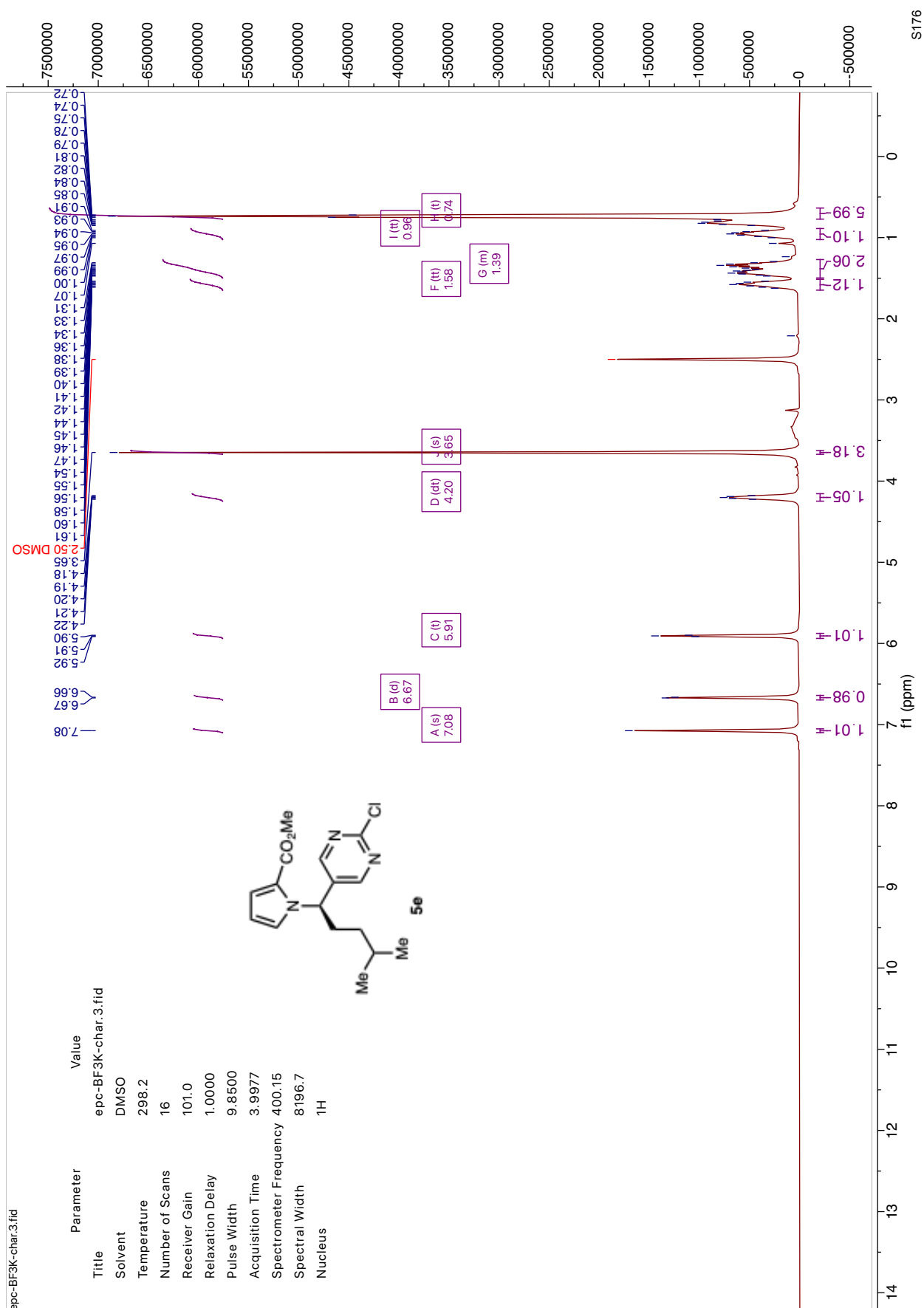


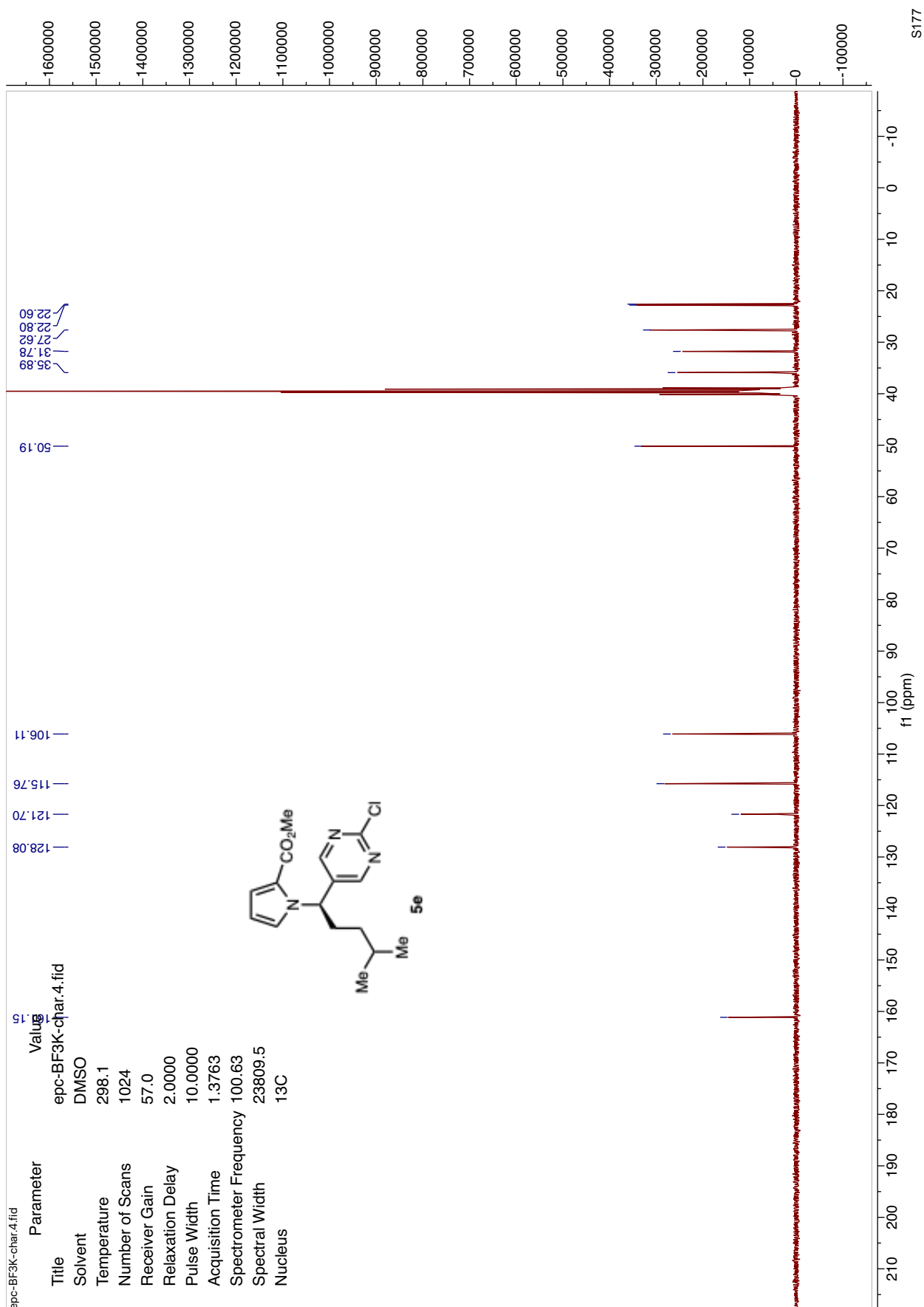


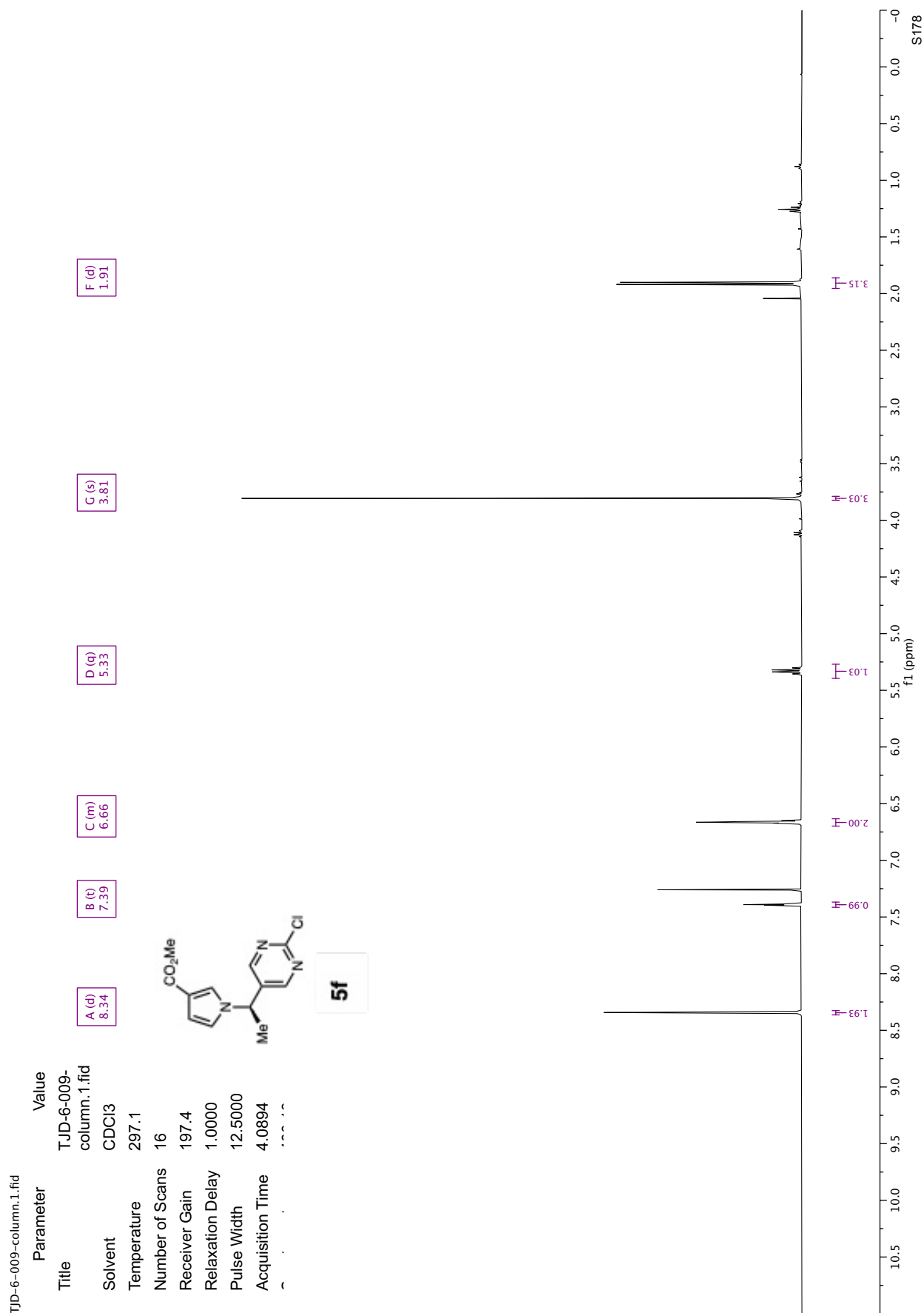


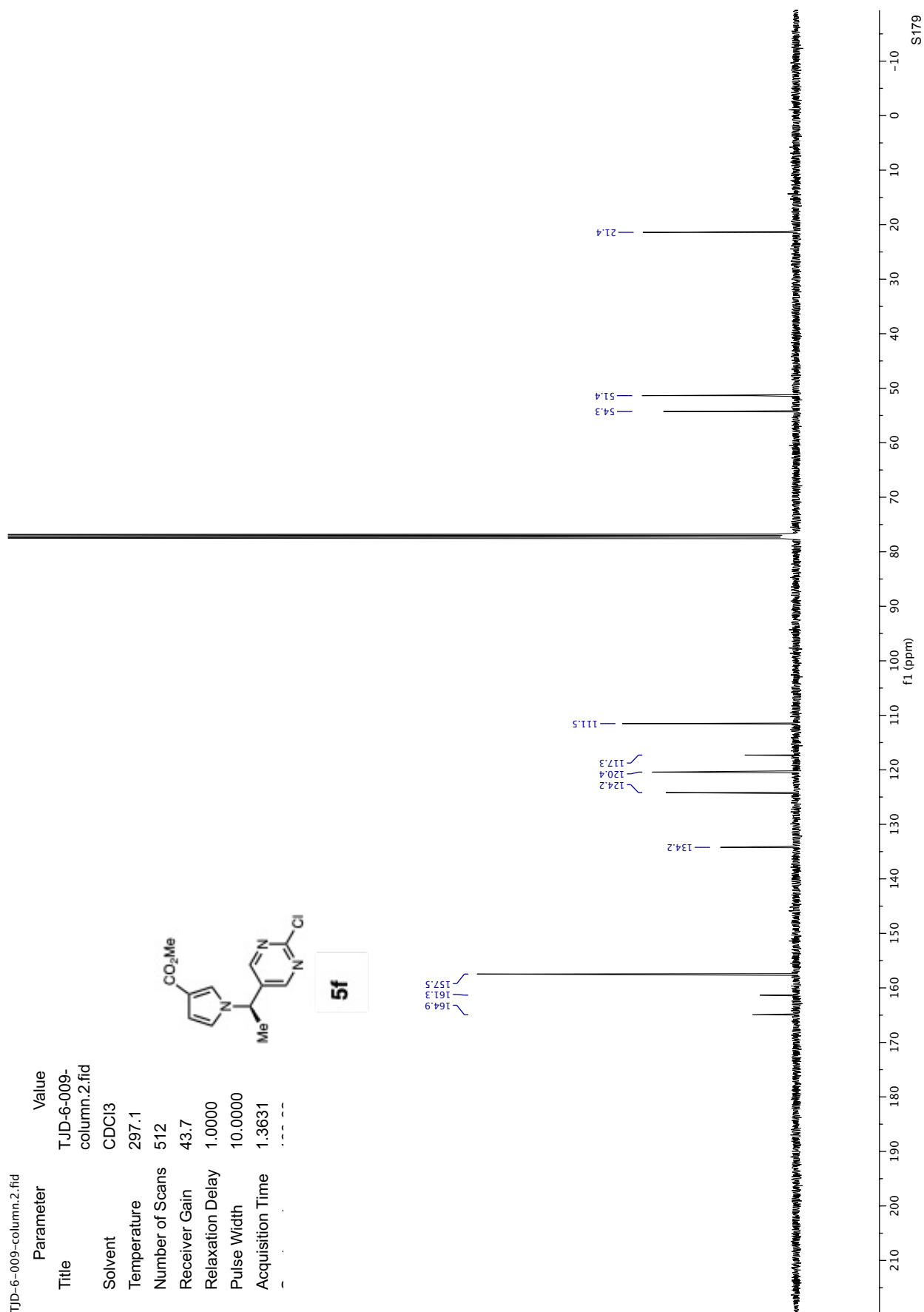


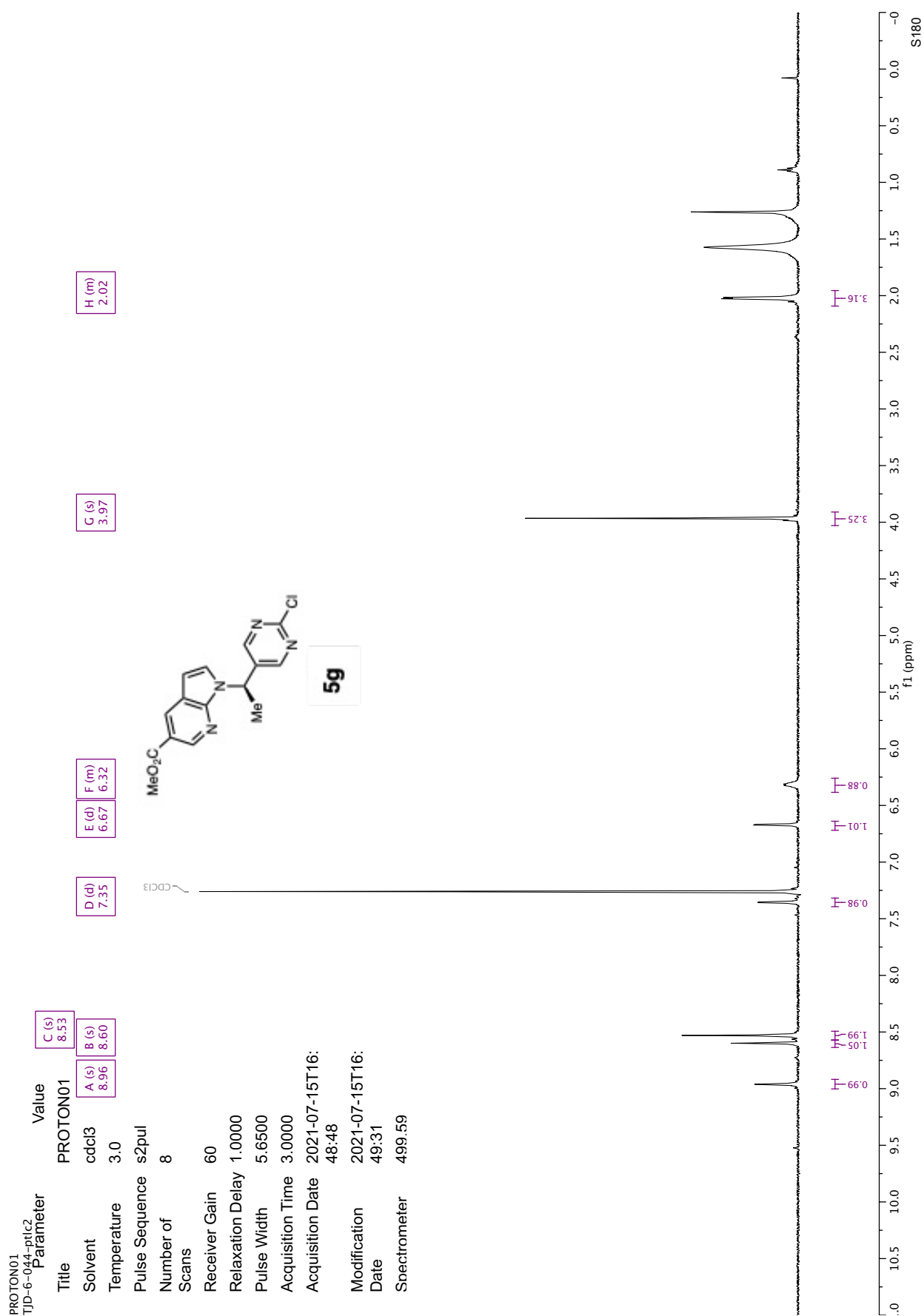


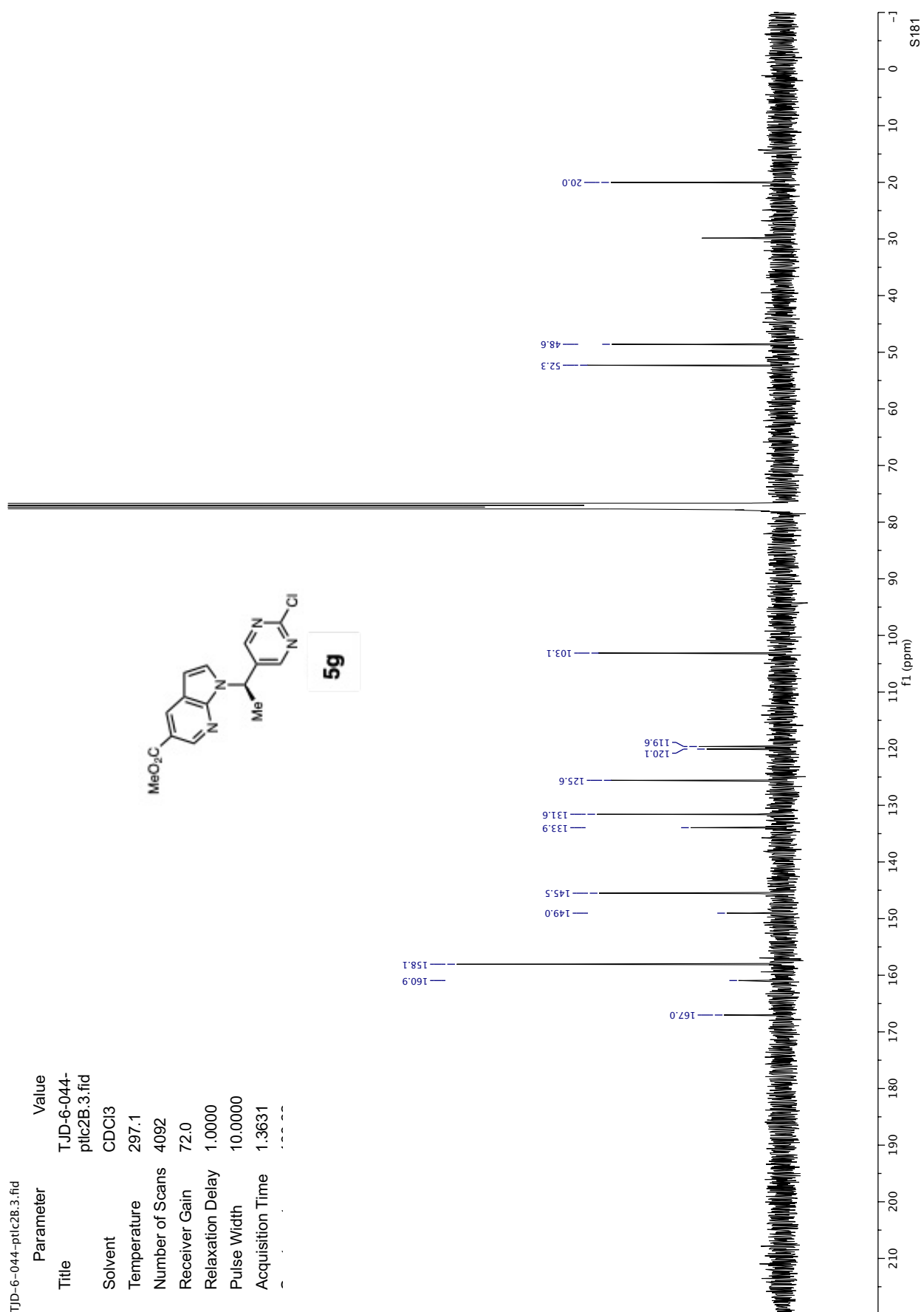


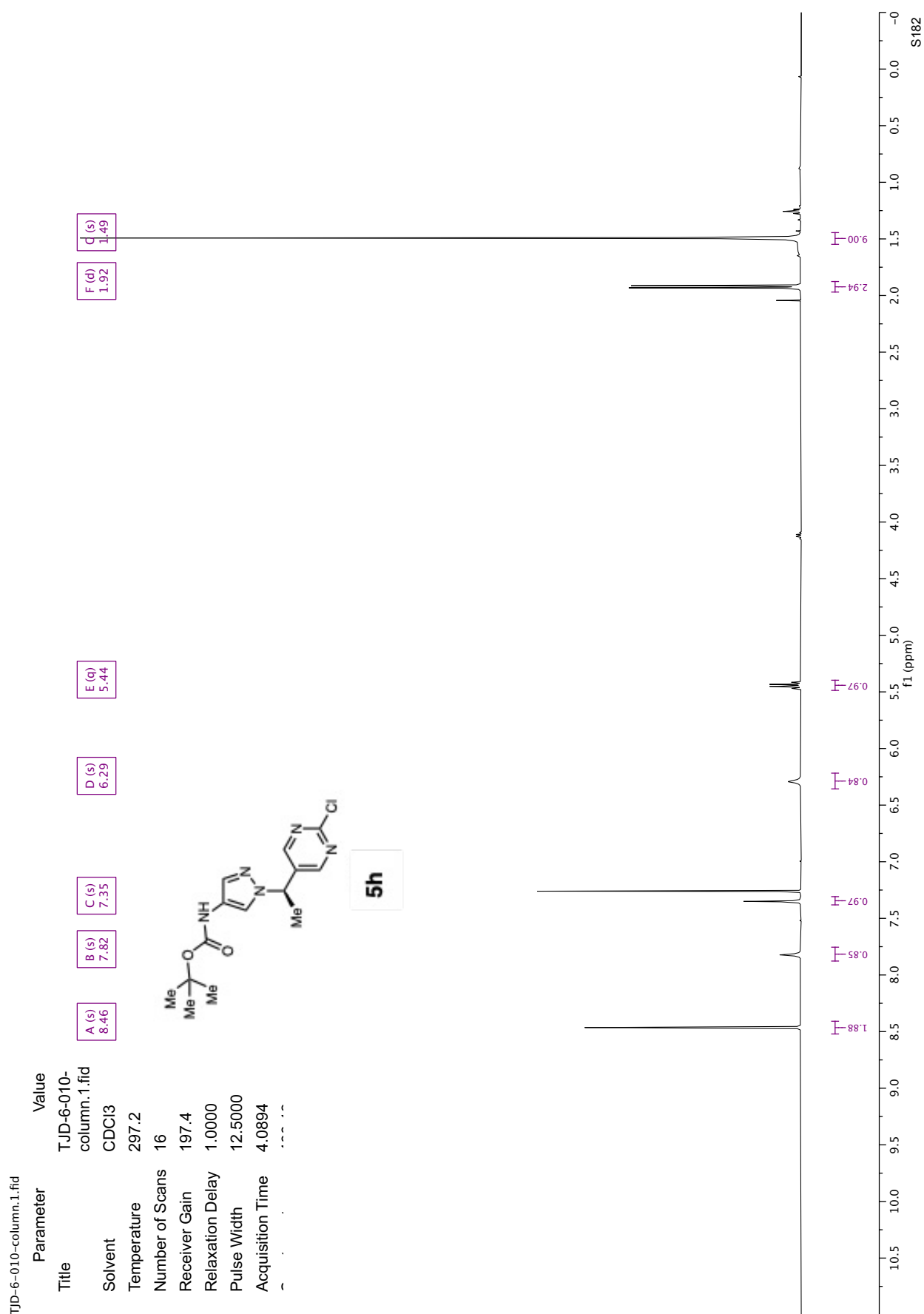


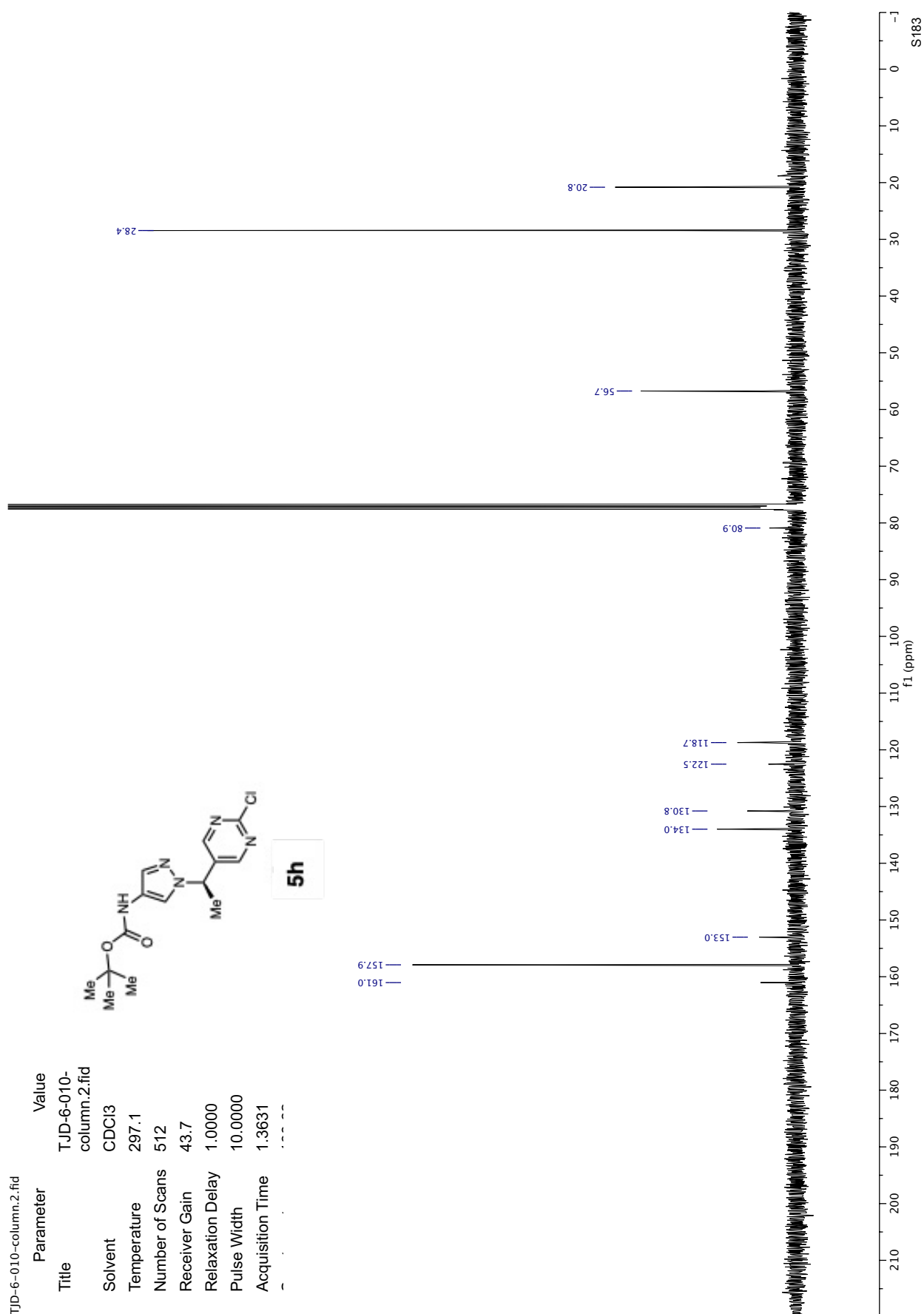


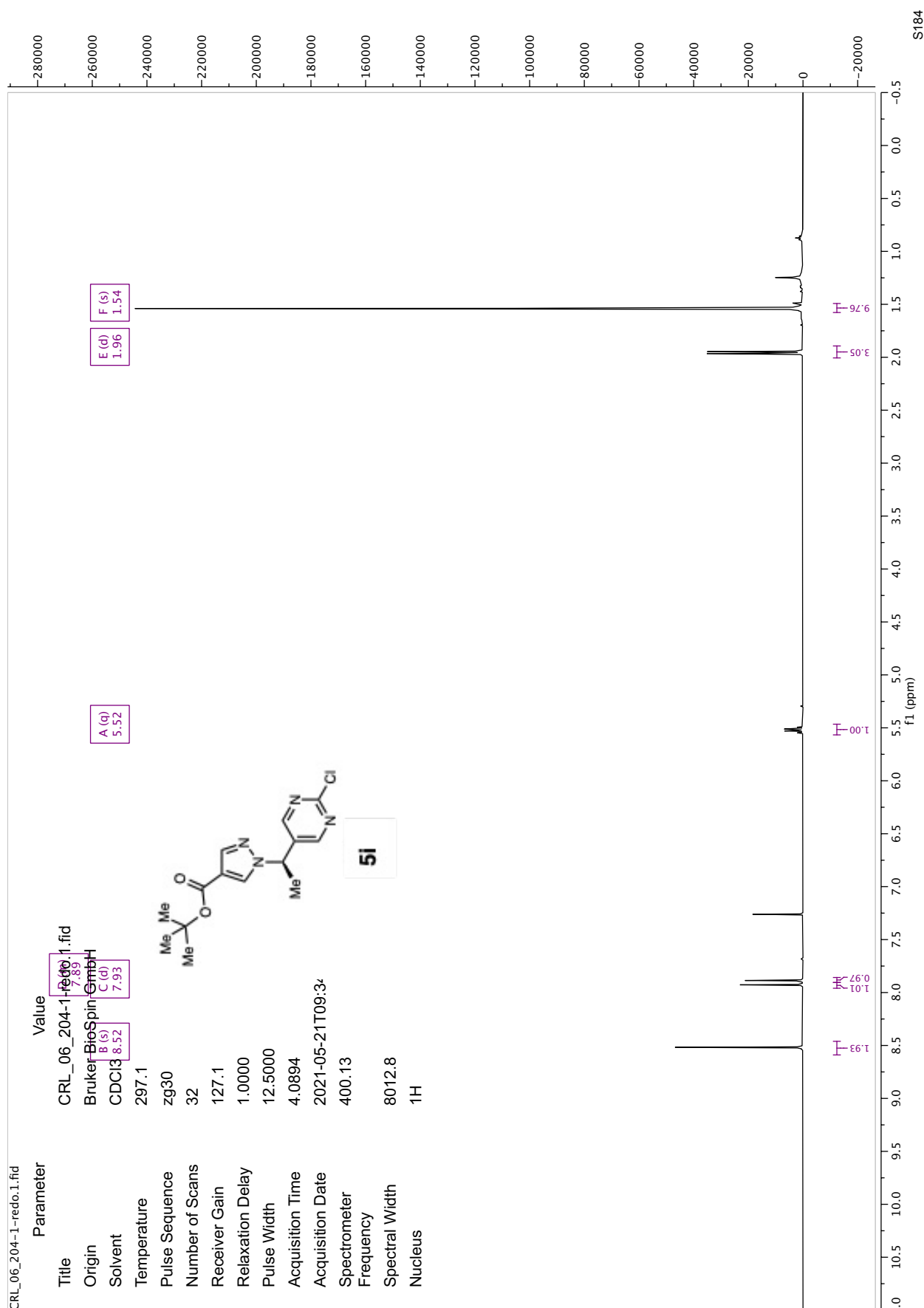


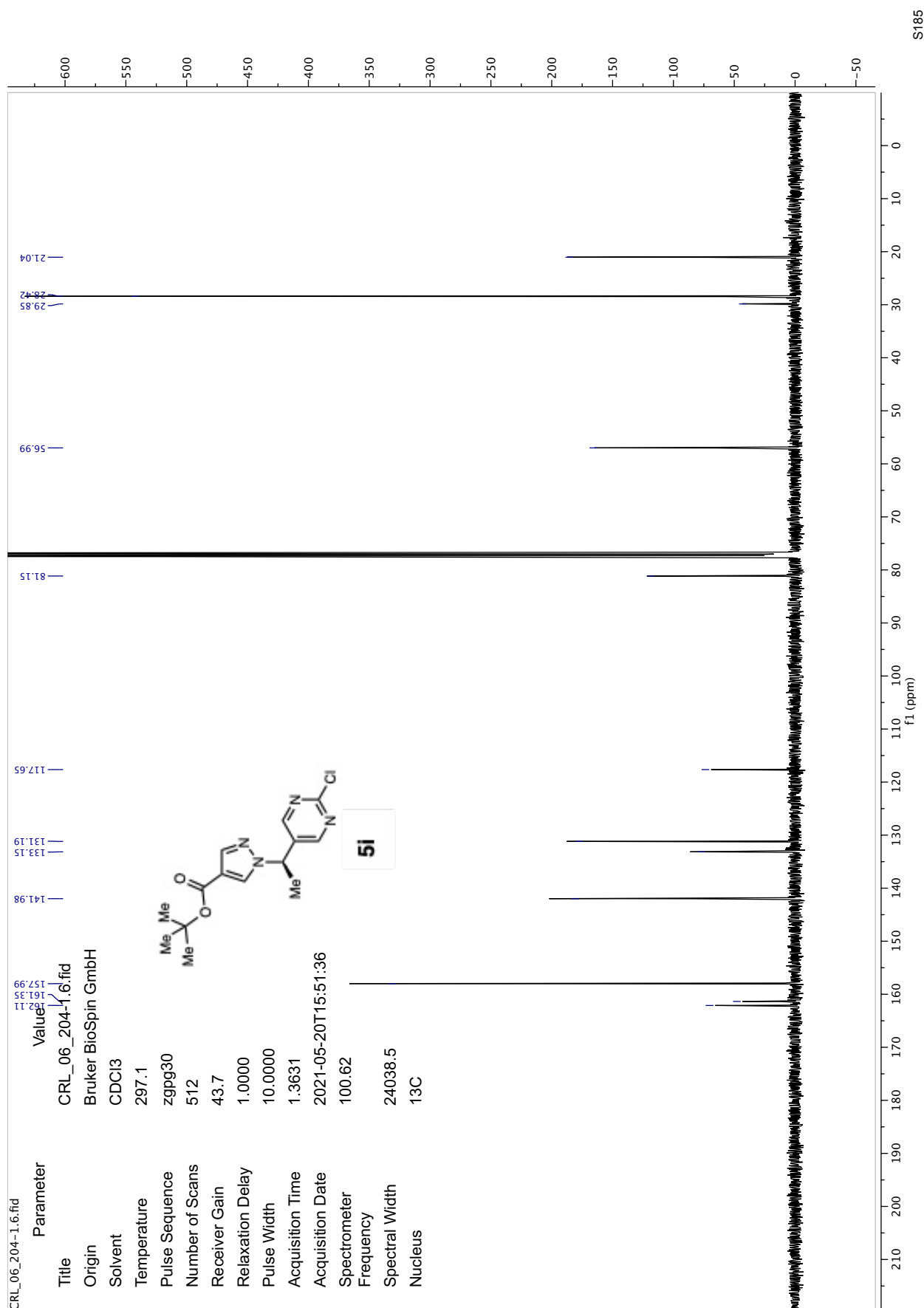


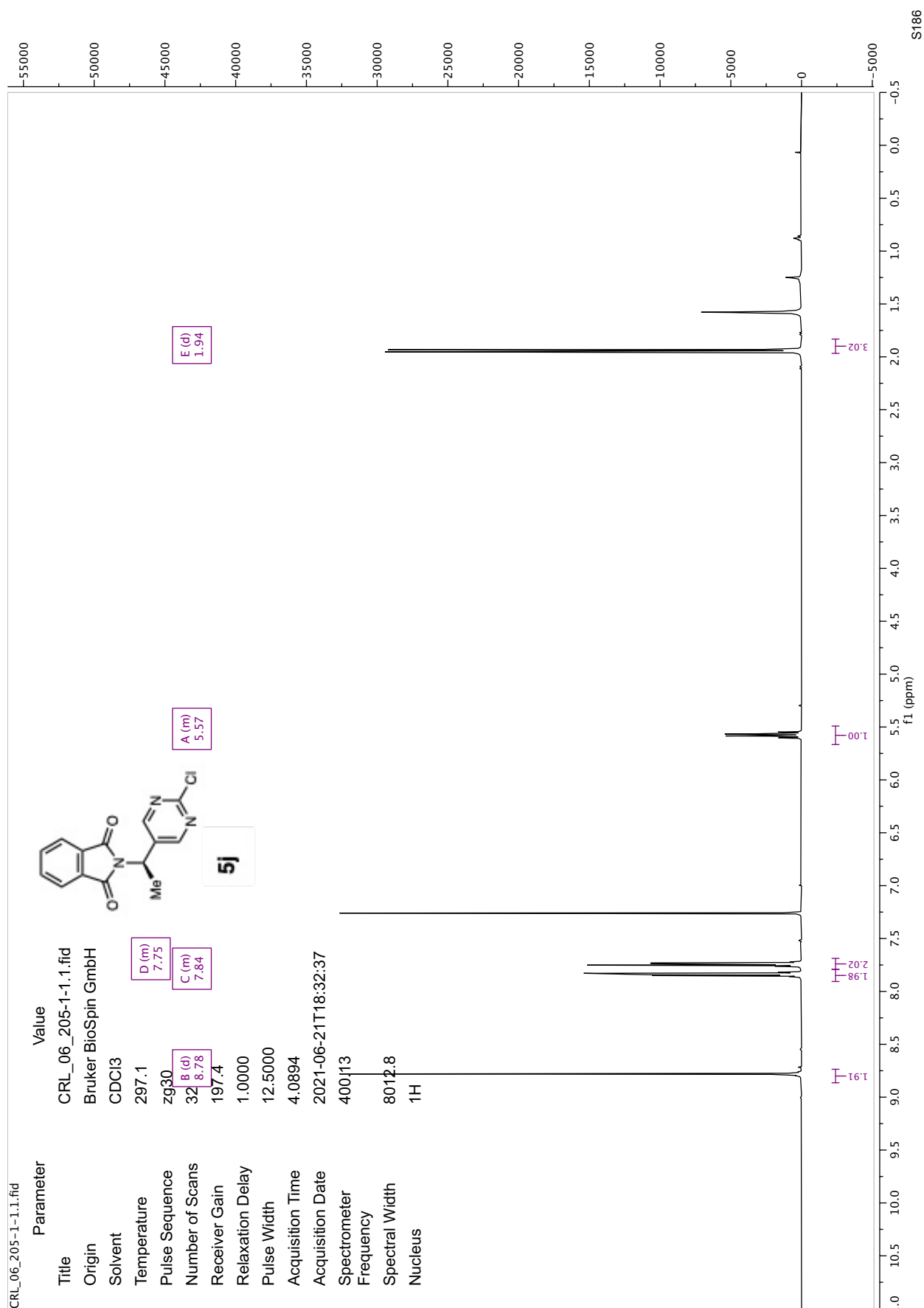


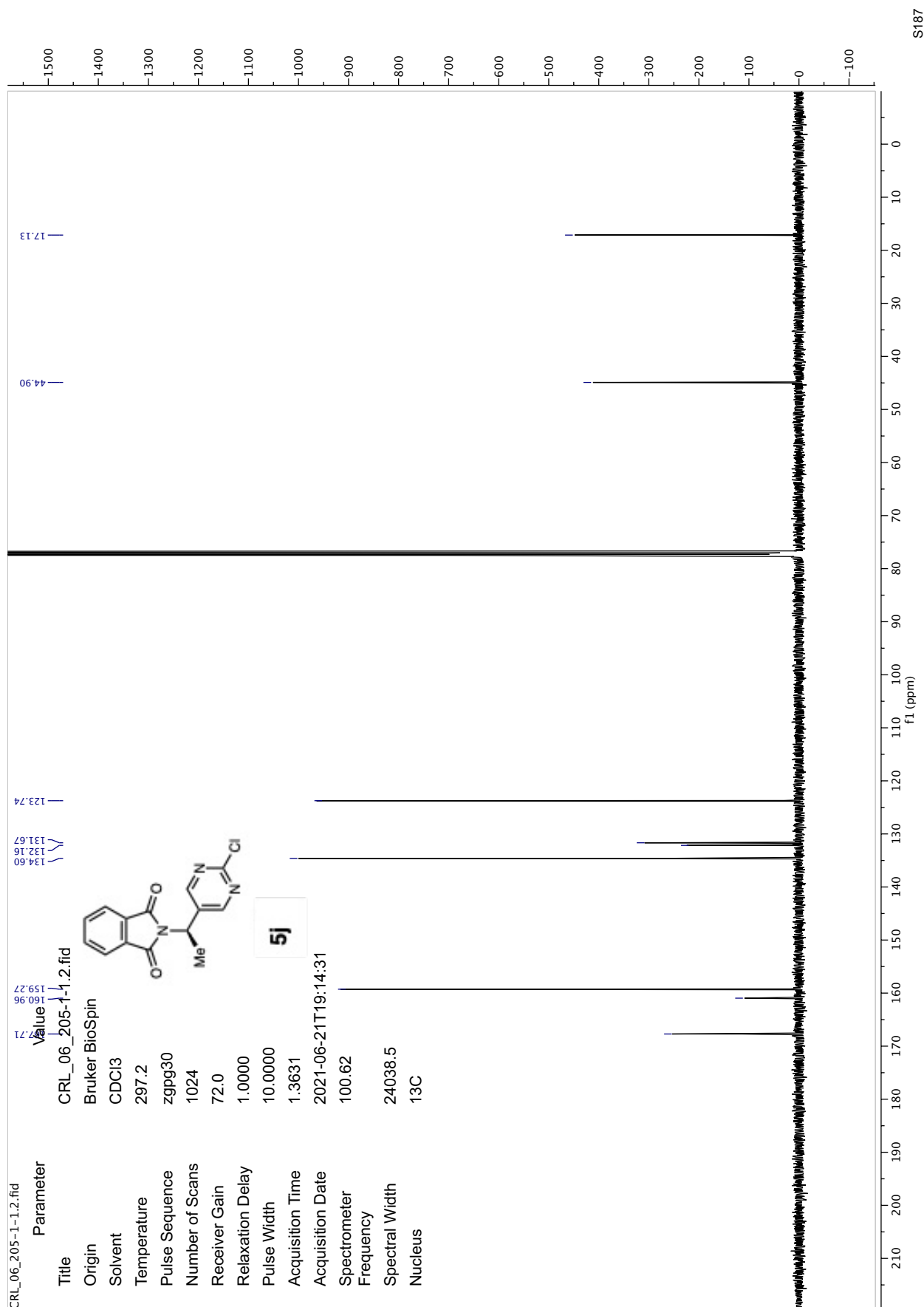


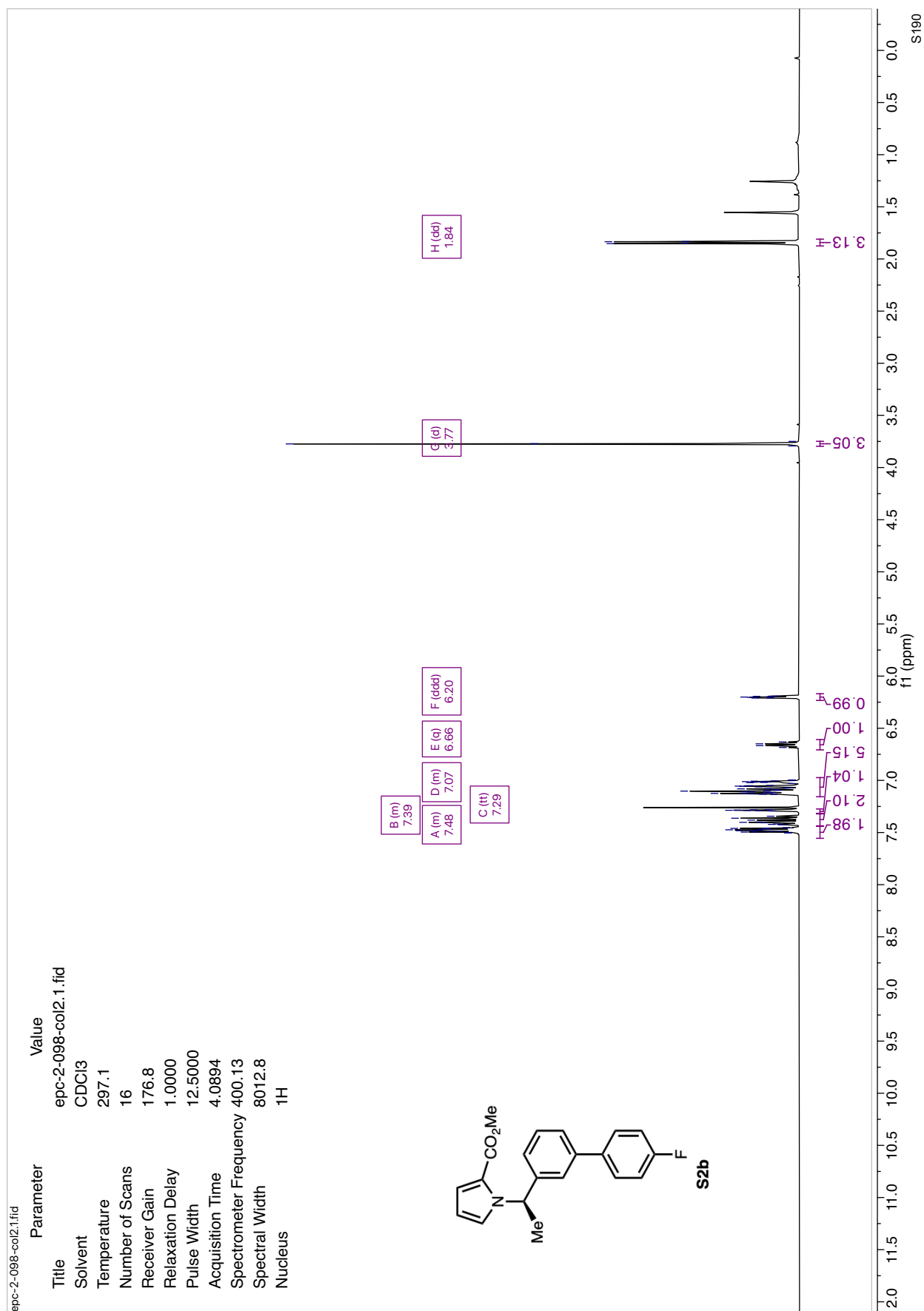


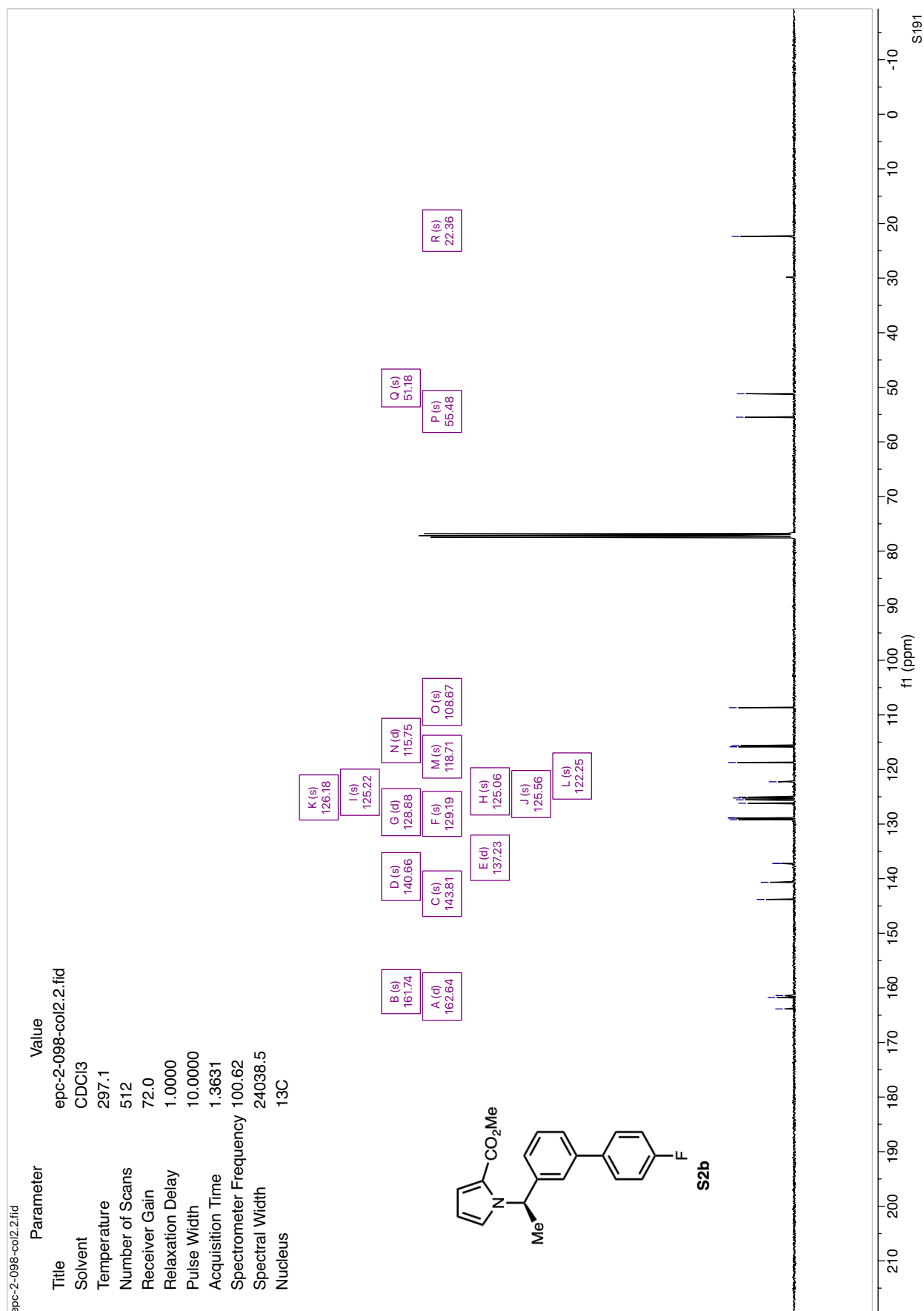


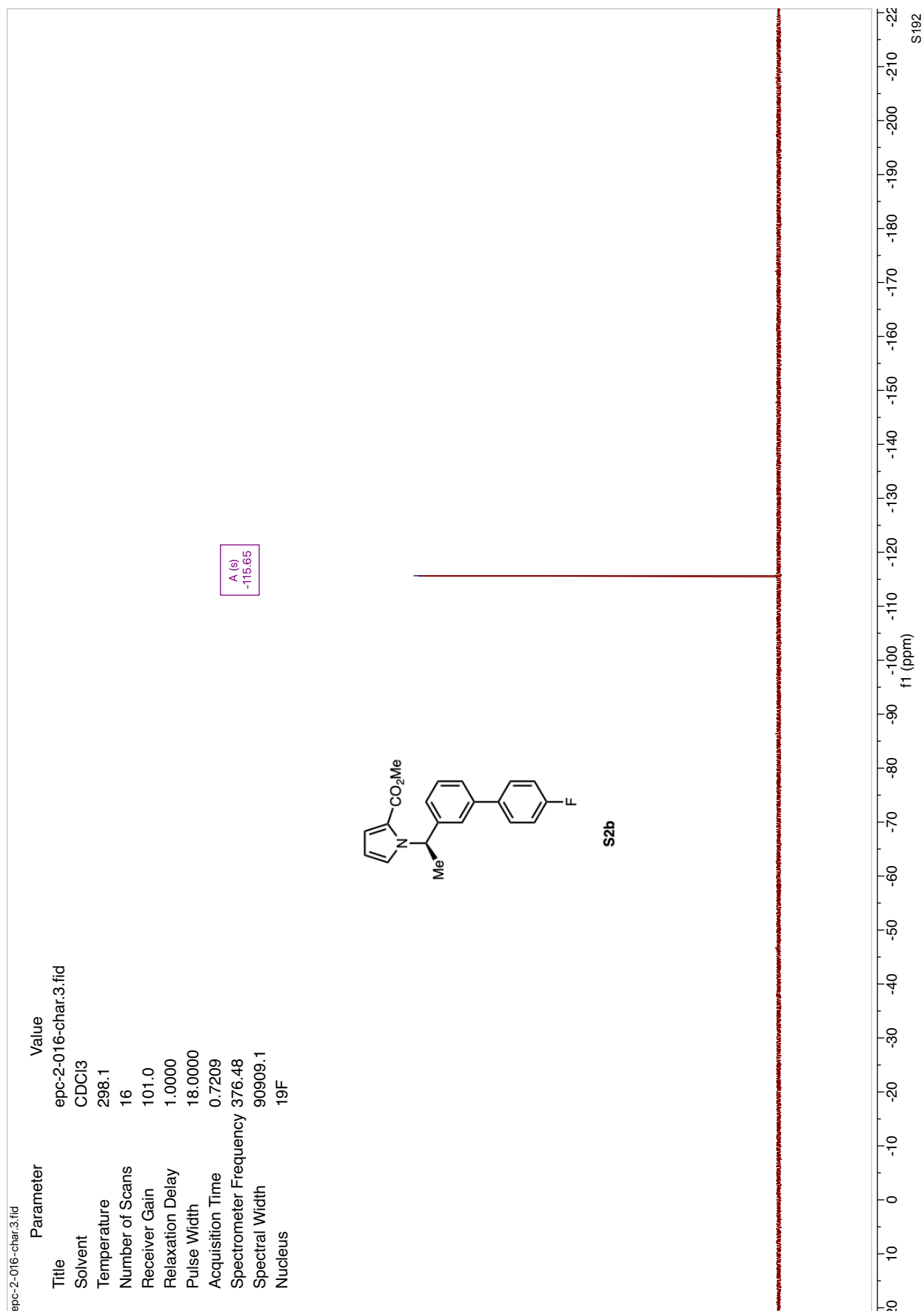


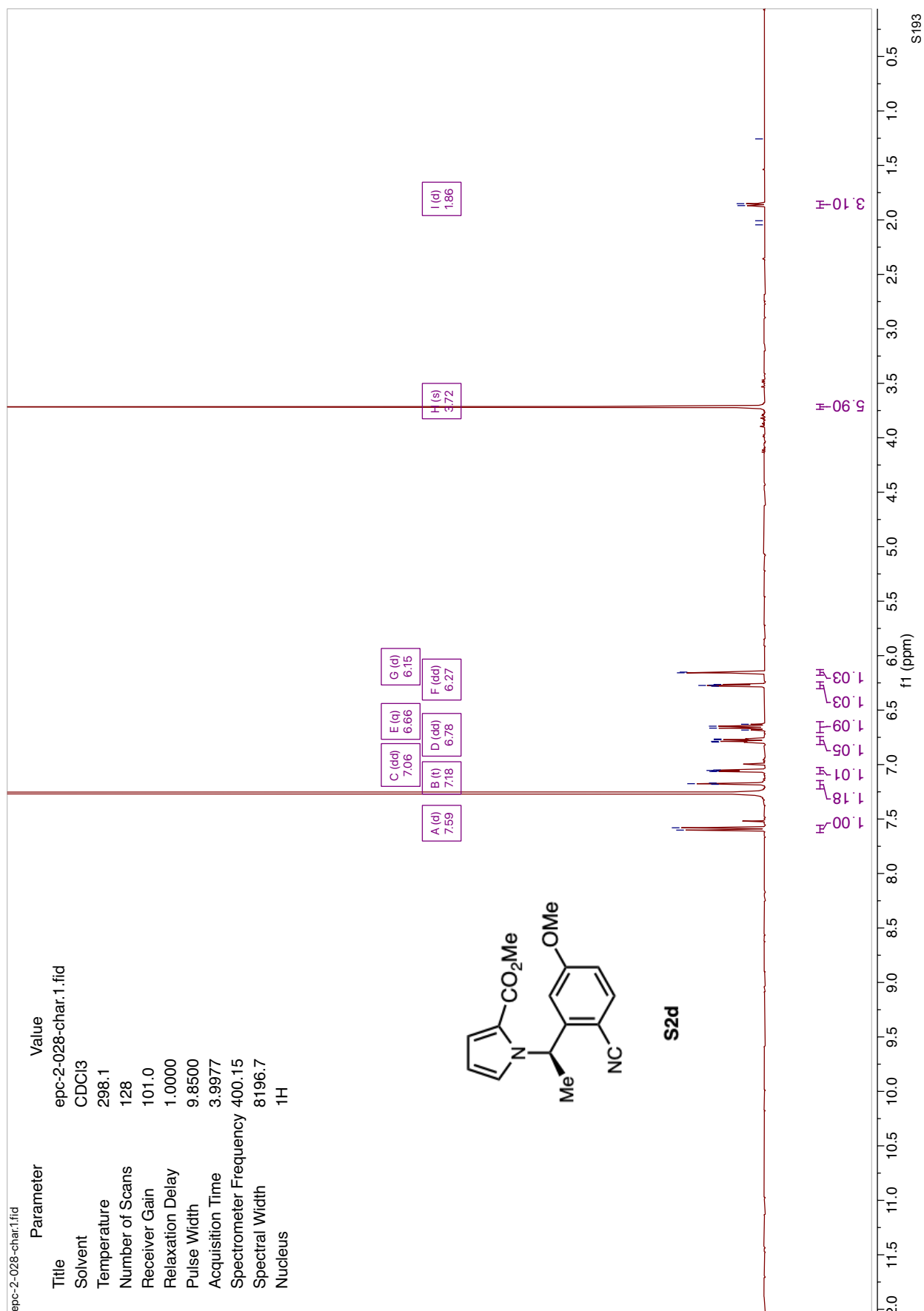


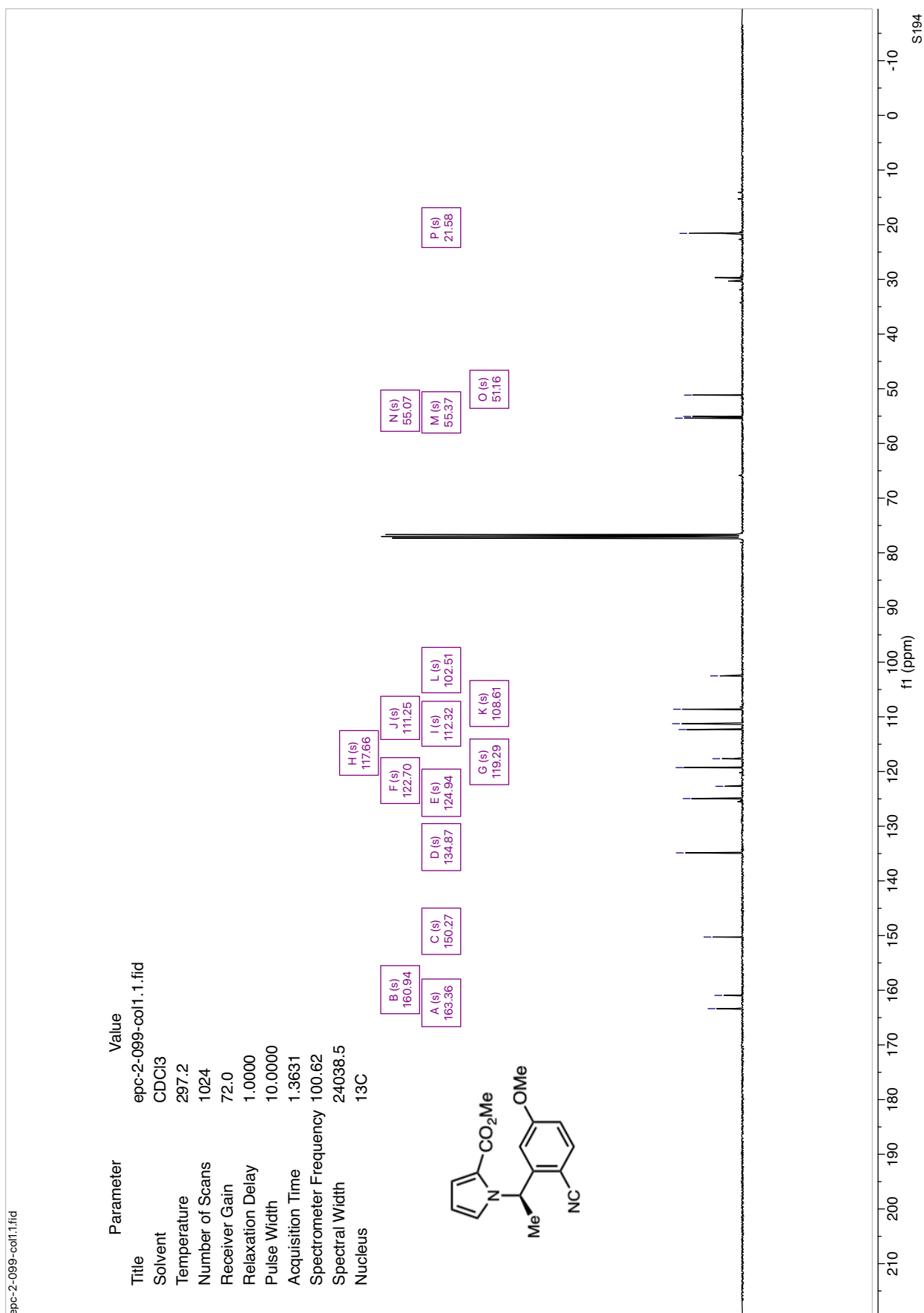


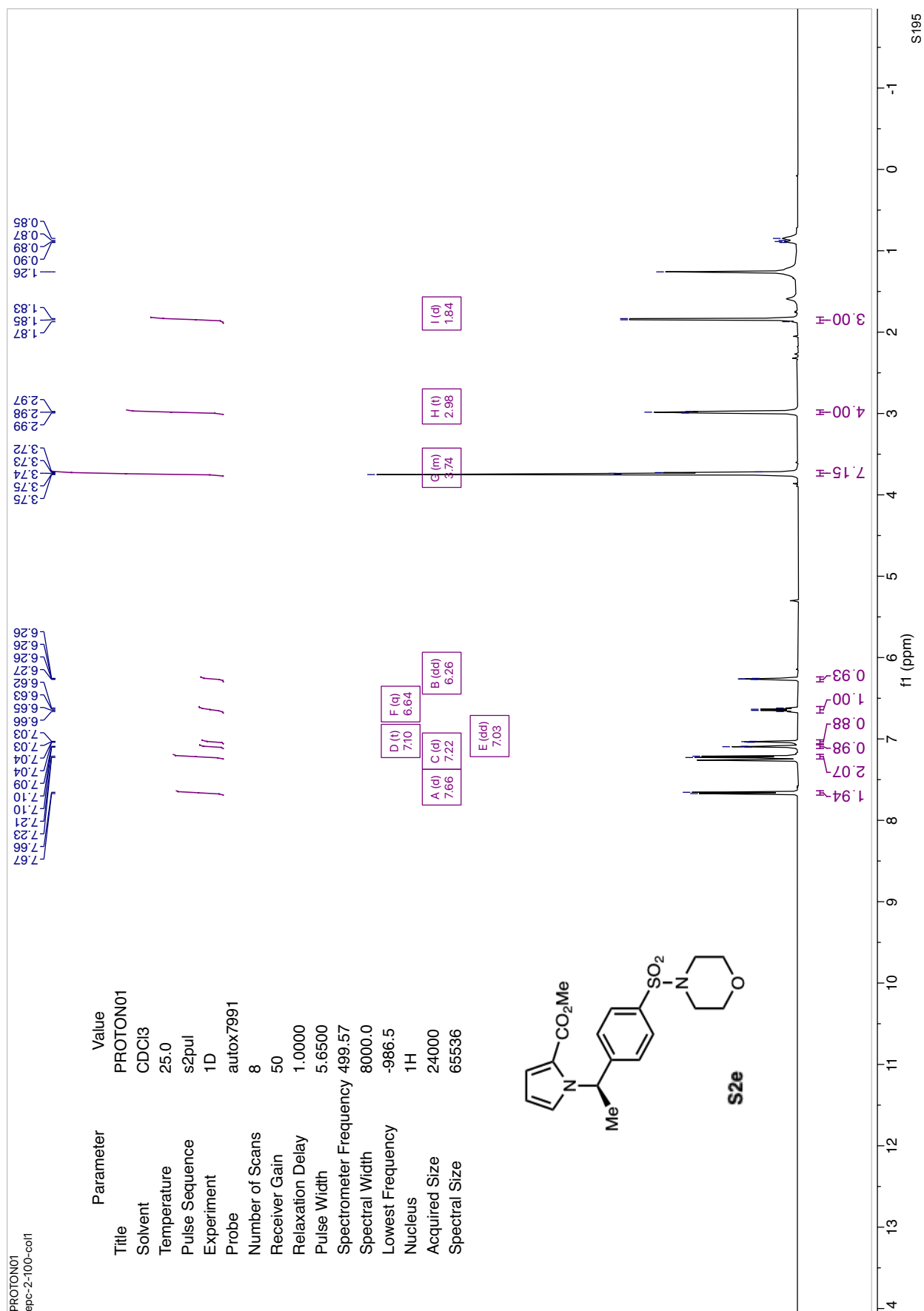


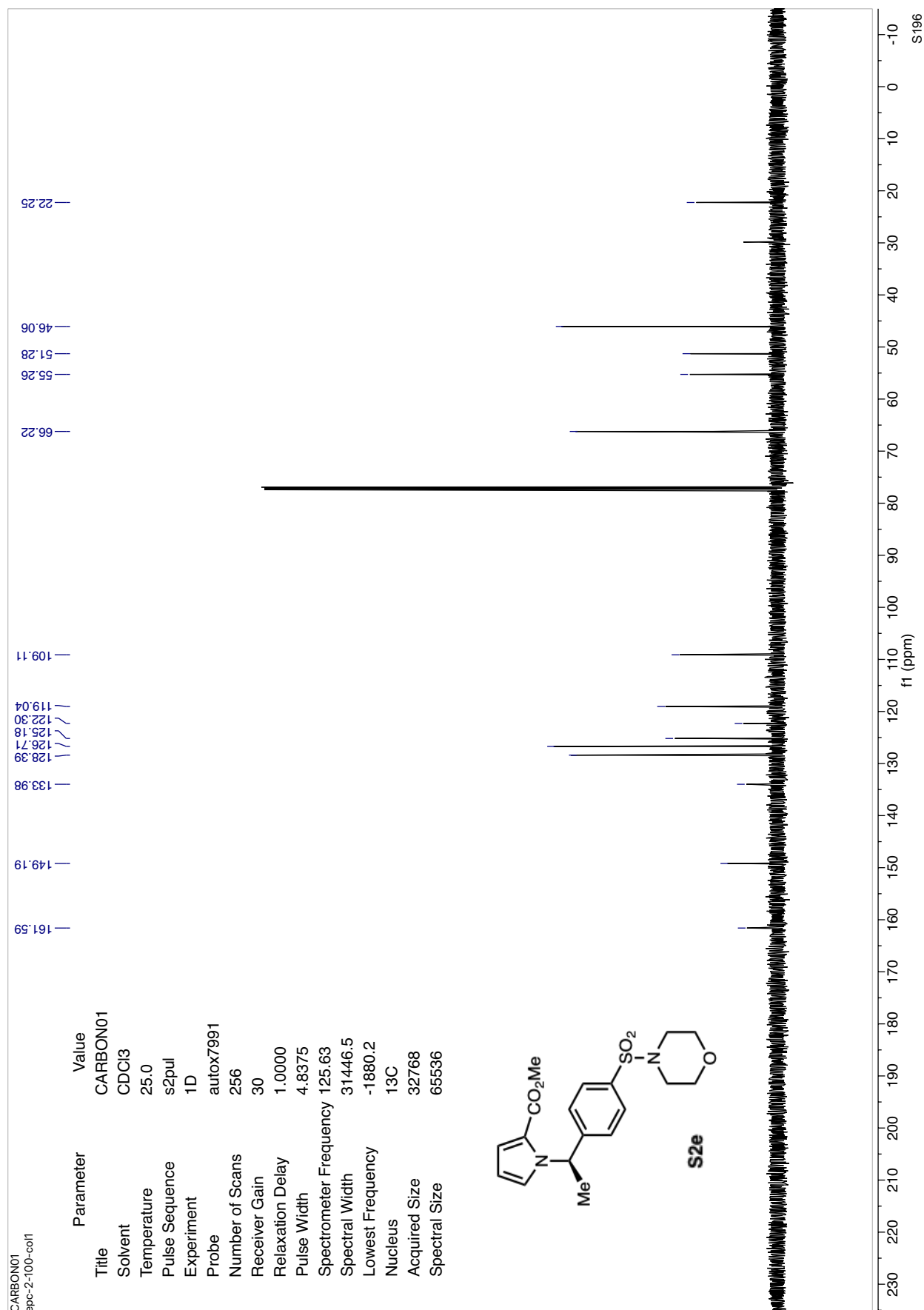


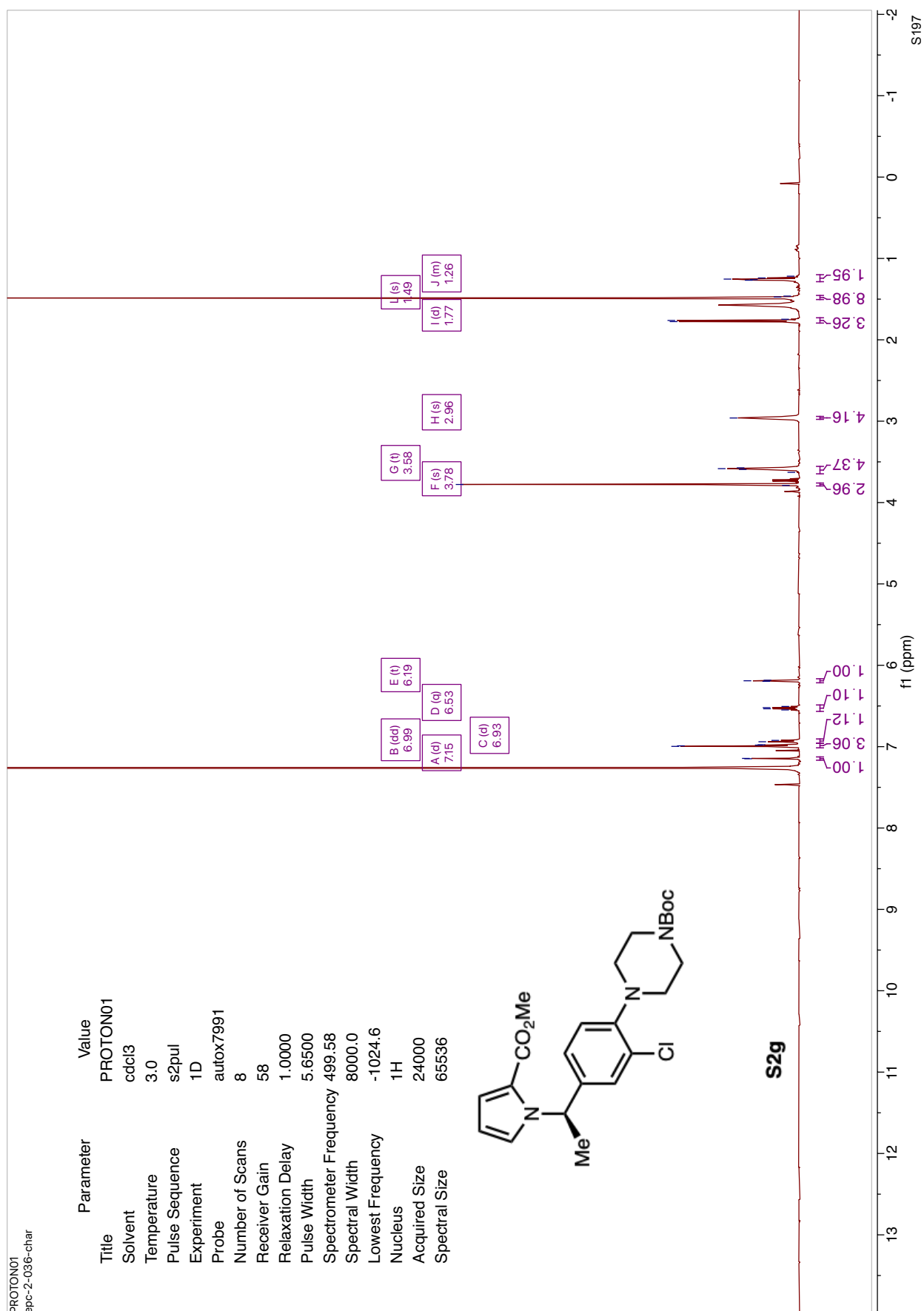


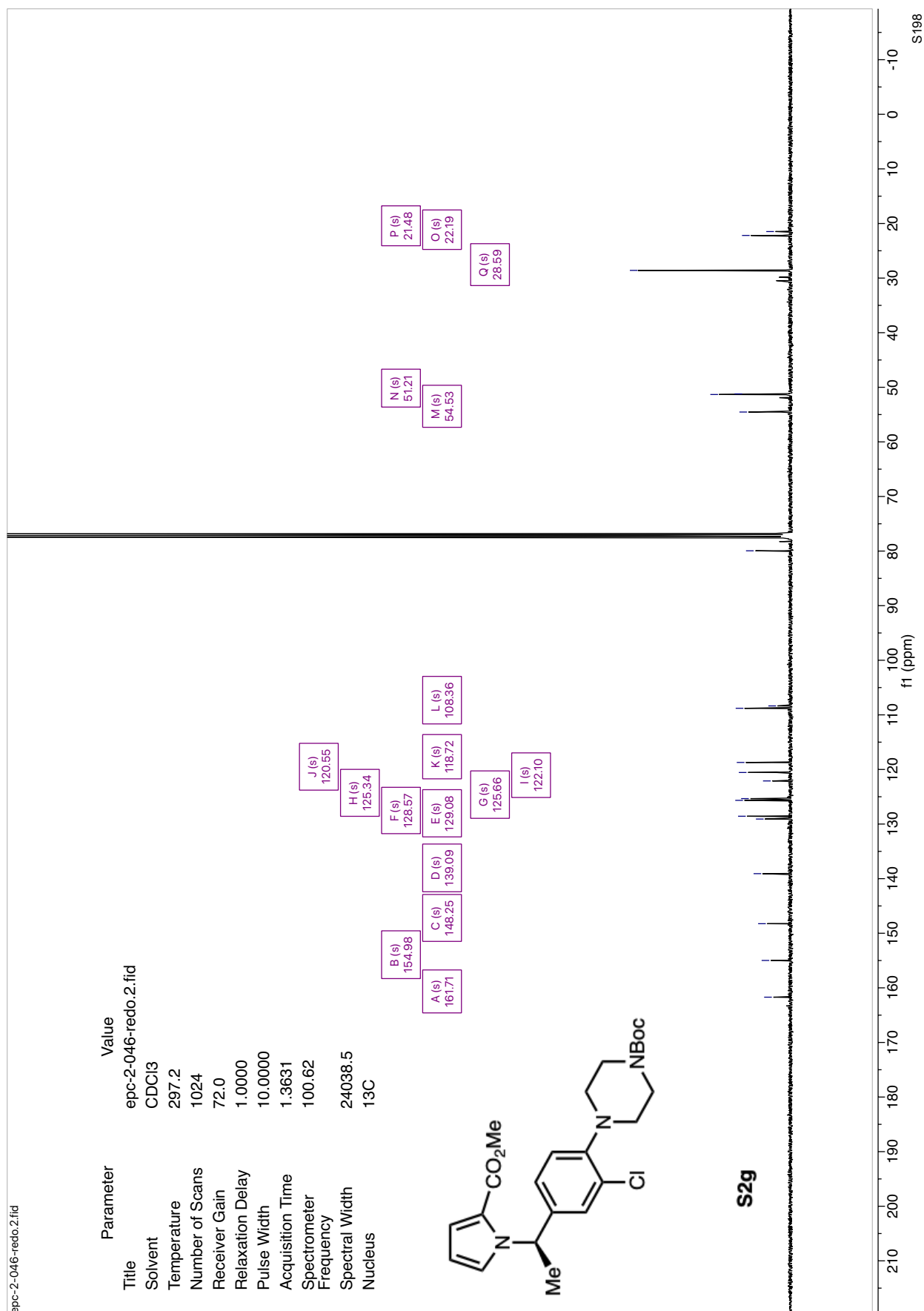


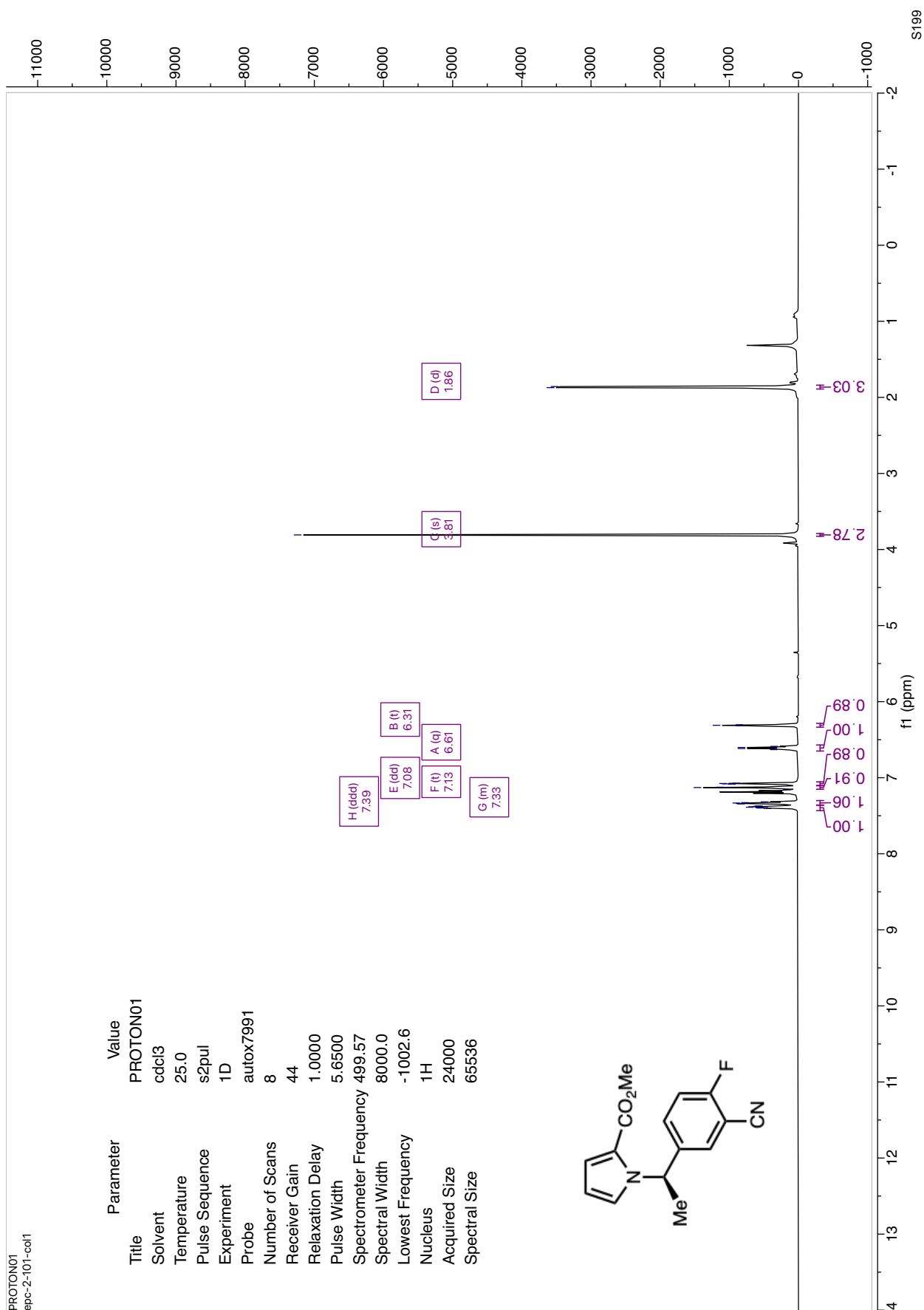


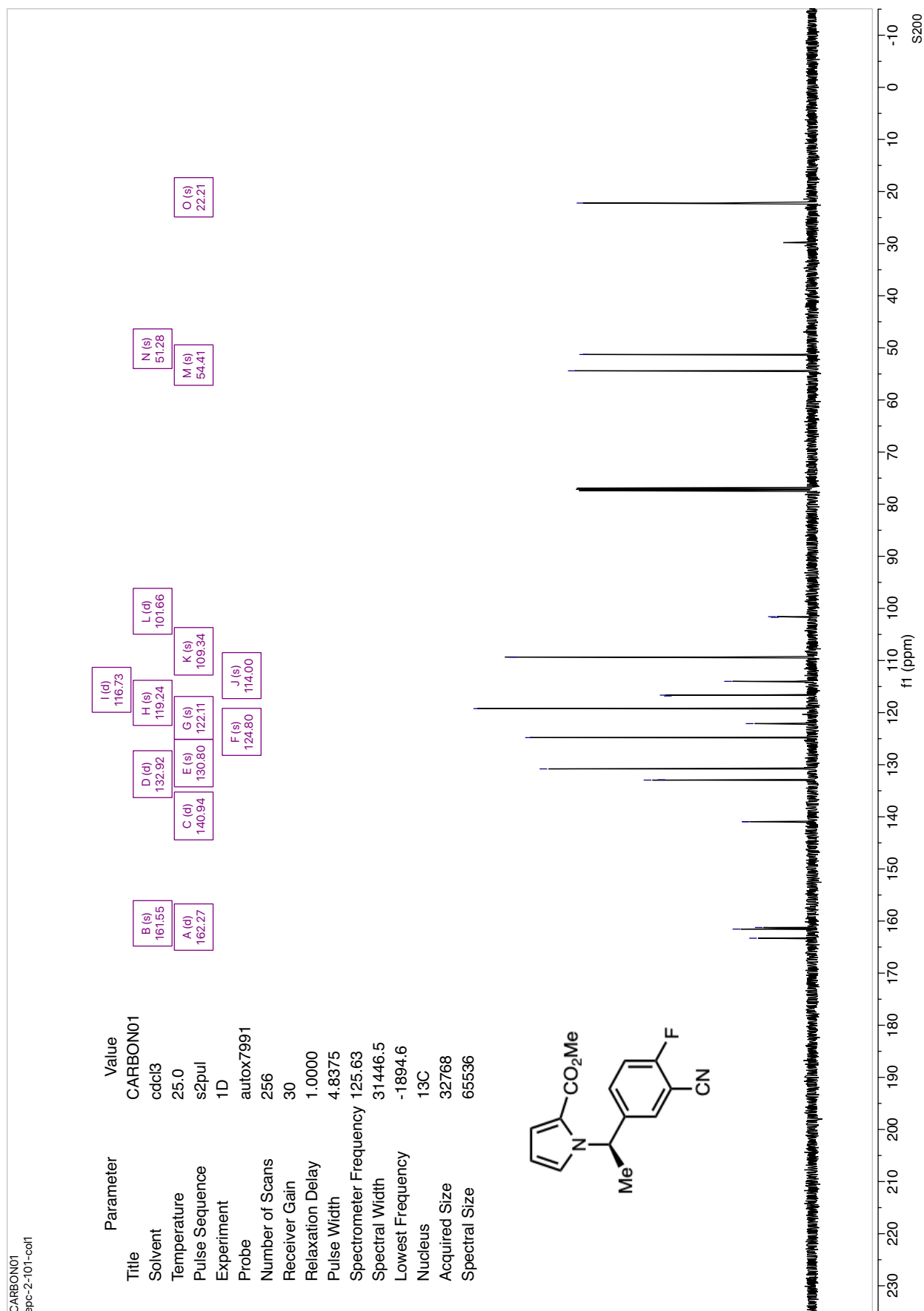


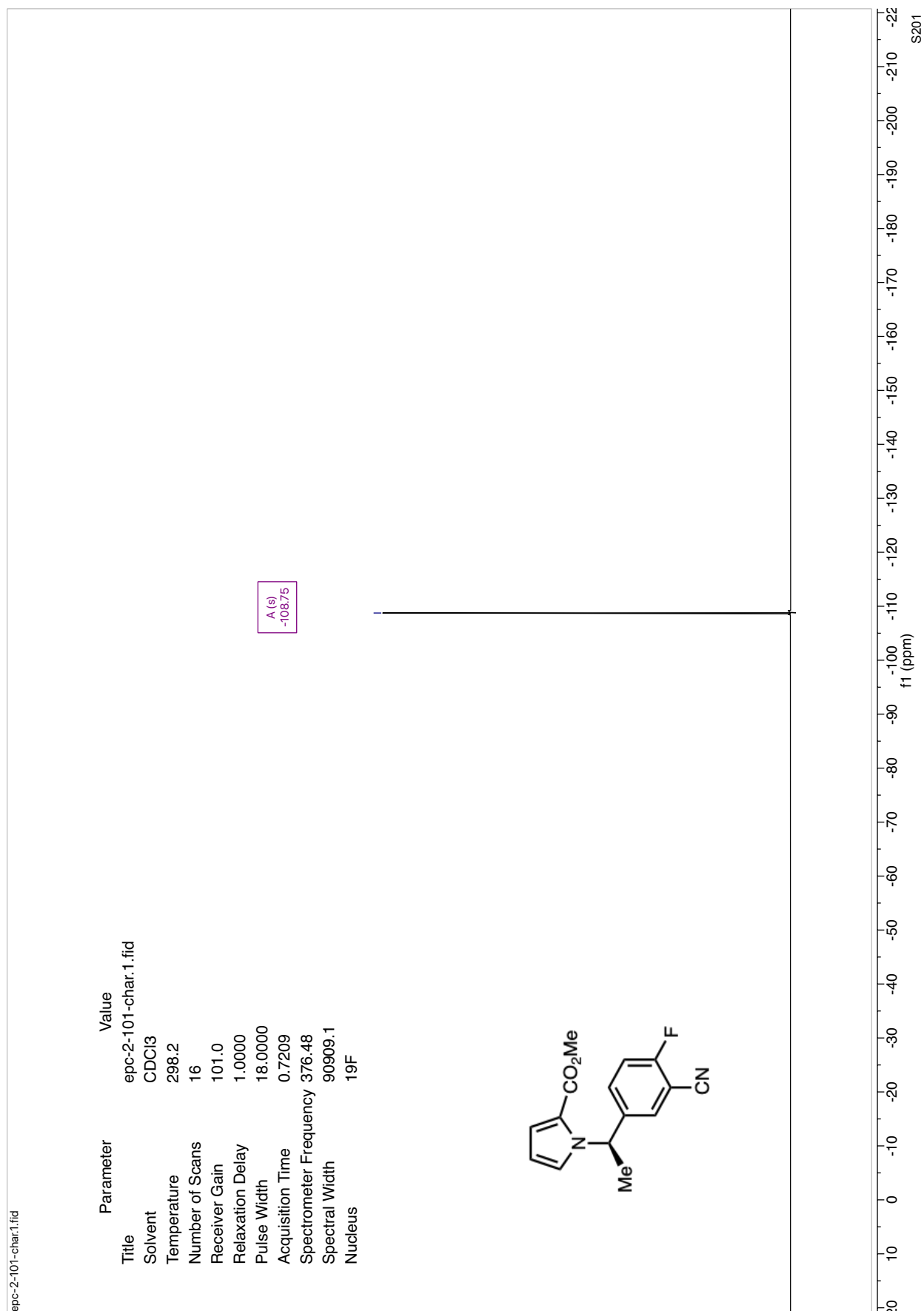












Chapter 2

Ni-Catalyzed Reductive Arylation of 1,3-Cyclobutyl NHP Esters[†]

[This chapter is temporarily embargoed.]

[†]This research was conducted in collaboration with Dr. Caitlin R Lacker and Anjali Gurajapu, graduate students in the Reisman group, and Brennan McManus from Professor Ana Bahamonde's group at the University of California Riverside. Financial support was provided by the National Institutes of Health (S.E.R. R35GM118191).

Appendix 2

Spectra Relevant to Chapter 2:

Ni-Catalyzed Reductive Arylation of 1,3-Cyclobutyl NHP Esters

[This appendix is temporarily embargoed.]

Chapter 3

Bayesian Optimization of Ni-Catalyzed Arylation of 1,3 Cyclobutanes[†]

[This chapter is temporarily embargoed.]

[†] This research was conducted in collaboration with 1) Anjali Gurajapu, graduate student in the Reisman group, and 2) Dr. José A. Garrido Torres, a postdoctoral fellow in the Doyle Lab at the University of California Los Angeles. Financial support was provided by the NSF C-CAS (SER.UNOTRED.204512).

Appendix 3

Spectra Relevant to Chapter 3:

Bayesian Optimization of Ni-Catalyzed Arylation of 1,3-Cyclobutanes

[This appendix is temporarily embargoed.]

Chapter 4

Enantioselective Ni-Catalyzed Arylation of 2-Piperidine N-Hydroxyphthalimide Esters[†]

[This chapter is temporarily embargoed.]

[†] This research was conducted in collaboration with Golsa Gheibi and Nathan Friede, graduate students in the Reisman group, and Drs. Andrew Parsons, Kyle Quasdorf, and Ryan Wurz, researchers employed by Amgen Inc.

Appendix 4

Spectra Relevant to Chapter 4:

Enantioselective Ni-Catalyzed Arylation of 2-Piperidine

N-Hydroxyphthalimide Esters

[This appendix is temporarily embargoed.]

ABOUT THE AUTHOR

Emily Peijia was born on August 1, 1998 to Yuejian and Dan Chen in Irvine, California. Early on, her family moved to upstate New York and she spent her childhood in the town of Clifton Park playing with her sister Peiwen, her brother Charles, and her best friend and neighbor, Sara. She spent much of her high school years playing in orchestras and competing on the track and field team.

In 2016, Emily began her undergraduate education at Stony Brook University, with the original intention of studying chemical engineering. However, she very quickly was enthralled by organic chemistry during her freshman year. She then had the opportunity to work in the laboratory of Professor Felix R. Fischer at the University of California, Berkeley as a summer undergraduate researcher sponsored by the Center for Energy Efficient Electronics Science. At Stony Brook, she researched host-guest polymerization processes with Professor Nancy Goroff and cationic polymerization reactions with Professor Melanie Chiu. While she earned her engineering degree with highest honors, the support from her mentors inspired her to pursue her doctorate in organic chemistry.

Following her graduation from Stony Brook, Emily moved across the country during the midst of a global pandemic to pursue her graduate studies under the direction of Professor Sarah E. Reisman at the California Institute of Technology. Her graduate work focused on the development of nickel-catalyzed stereoconvergent cross-coupling reactions, with forays into photoredox catalysis, electroorganic chemistry, and applications of machine learning. Following the completion of her Ph.D, Emily will move to Boston to join the medicinal chemistry team at Novartis Institutes for BioMedical Research.