

SUPPORTING INFORMATION

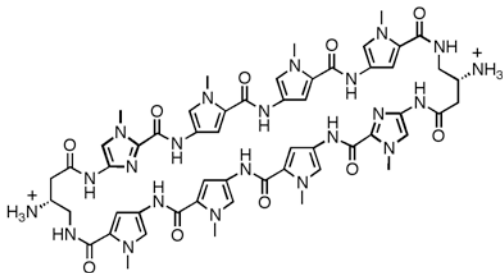
Cyclic Pyrrole-Imidazole Polyamides Targeted to the Androgen Response Element

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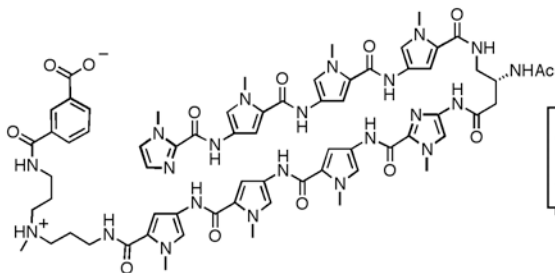
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Polyamides submitted for ADMET evaluation by Apredica, LLC (Watertown, MA):



Cyclic polyamide 1 (as shown in accompanying manuscript)
 Denoted as **DMC2-239** on ADMET Report



Hairpin polyamide 5 (as shown in accompanying manuscript)
 Denoted as **DH-V-88** on ADMET Report

Summary of results from ADMET study:

Polyamides **1** and **5** were subjected to preclinical ADMET testing by contract service at Apredica (Watertown, MA). Shown below (I-VII) are summaries of the ADMET results taken directly from the final report provided by Apredica. The full ADMET report, which includes experimental conditions, can be accessed via the Dervan laboratory homepage at <http://dervan.caltech.edu>.

(I) Caco-2 permeability:

4.2.1 Caco-2 permeability summary

Client ID	test conc (μM)	Assay duration (hr)	mean A->B P_{app}^a ($10^{-6} \text{ cm s}^{-1}$)	mean A->B P_{app}^a ($10^{-6} \text{ cm s}^{-1}$)	Asymmetry ratio ^b	comment
Warfarin	50	2	35.4	7.9	0.2	high permeability control
Ranitidine	50	2	1.4	2.4	1.7	low permeability control
DH-V-88	10	2	ND	0.11	UD	
DMC2-239	10	2	ND	ND	ND	

^aApparent permeability

^b $P_{app}(B \rightarrow A) / P_{app}(A \rightarrow B)$

ND = no compound detected in receiver solution

(II) Cytotoxicity in HepG2 cells:

4.2.2 Cytotoxicity summary

Client ID	Cell line	IC ₅₀ (μM)	comment
Chlorpromazine	HepG2	13	Higly cytotoxic control
Propranolol	HepG2	80	Low cytotoxic control
DH-V-88	HepG2	>100	
DMC2-239	HepG2	>100	

(III) Cyp inhibition:

4.2.3 Fluorescent Cyp IC₅₀ summary

Client ID	IC ₅₀ (μM)						
	Cyp1A2 / CEC	Cyp2C8/D BF	Cyp2C9 / DBF	Cyp2C19 / DBF	Cyp2D6 / AMMC	Cyp3A4 / BFC	Cyp3A4 / DBF
Controls	0.2 <i>α</i> -naphtho-flavone	2.3 ketoconazol e	1.1 sulpha-phenazole	5.6 tranyl-cypramine	0.05 quinindine	1.26 ketoconazol e	1.26 ketoconazol e
DH-V-88	>50	>50	>50	>50	>50	47.6	>50
DMC2-239	>50	>50	>50	>50	>50	37.7	>50

(IV) hERG inhibition:

4.2.4 hERG FastPatch summary

Client ID	IC ₅₀ (μM)	comment
	99% at 0.5 μM	
E-4031		positive control
DH-V-88	>100	*
DMC2-239	>100	*

*The solubility limit for this experiment, as determined by vehicle controls, was 17.3 x 10³ LSU (horizontal black line). Based on the data obtained, there may be solubility issues for both test articles at 30 and 100 μM in our physiological saline solution (HB-PS, 0.3%DMSO). Precipitation of DH-V-88 at 100 μM was visible to the naked eye.

(V) Liver microsome stability:

4.2.5 Microsomal intrinsic clearance summary

Client ID	test conc (µM)	test species	NADPH-dependent CL _{int} ^a (µl min ⁻¹ mg ⁻¹)	NADPH-dependent T _{1/2} ^b (min)	NADPH-free CL _{int} ^a (µl min ⁻¹ mg ⁻¹)	NADPH-free T _{1/2} ^b (min)	comment
Verapamil	1	Human	411.3	5.6	0.6	>180	metabolized control
Verapamil	1	Rat	2276	1	0.0	>180	metabolized control
Warfarin	1	Human	0.0	>180	0.0	>180	non-metabolized control
Warfarin	1	Rat	0.0	>180	0.0	>180	non-metabolized control
DH-V-88	5	Human	0.0	>180	0.0	>180	
DH-V-88	5	Rat	0.0	>180	0.0	>180	
DMC2-239	5	Human	0.0	>180	0.0	>180	
DMC2-239	5	Rat	0.0	>180	0.0	>180	

^aMicrosomal Intrinsic Clearance

^bHalf-life

(VI) Plasma half-life:

4.2.6 Plasma half-life summary

Compound	test conc (µM)	medium	T1/2 (min)	Fraction remaining, max time (%)	comment
Proprantheline	10.0	Human Plasma	35.5	5.8%	control
Proprantheline	10.0	Rat Plasma	149.0	51.6%	control
DH-V-88	10.0	Human Plasma	>120	95.6%	
DH-V-88	10.0	Rat Plasma	>120	94.0%	
DMC2-239	10.0	Human Plasma	>120	124.5%	
DMC2-239	10.0	Rat Plasma	>120	120.3%	

^aHalf-life

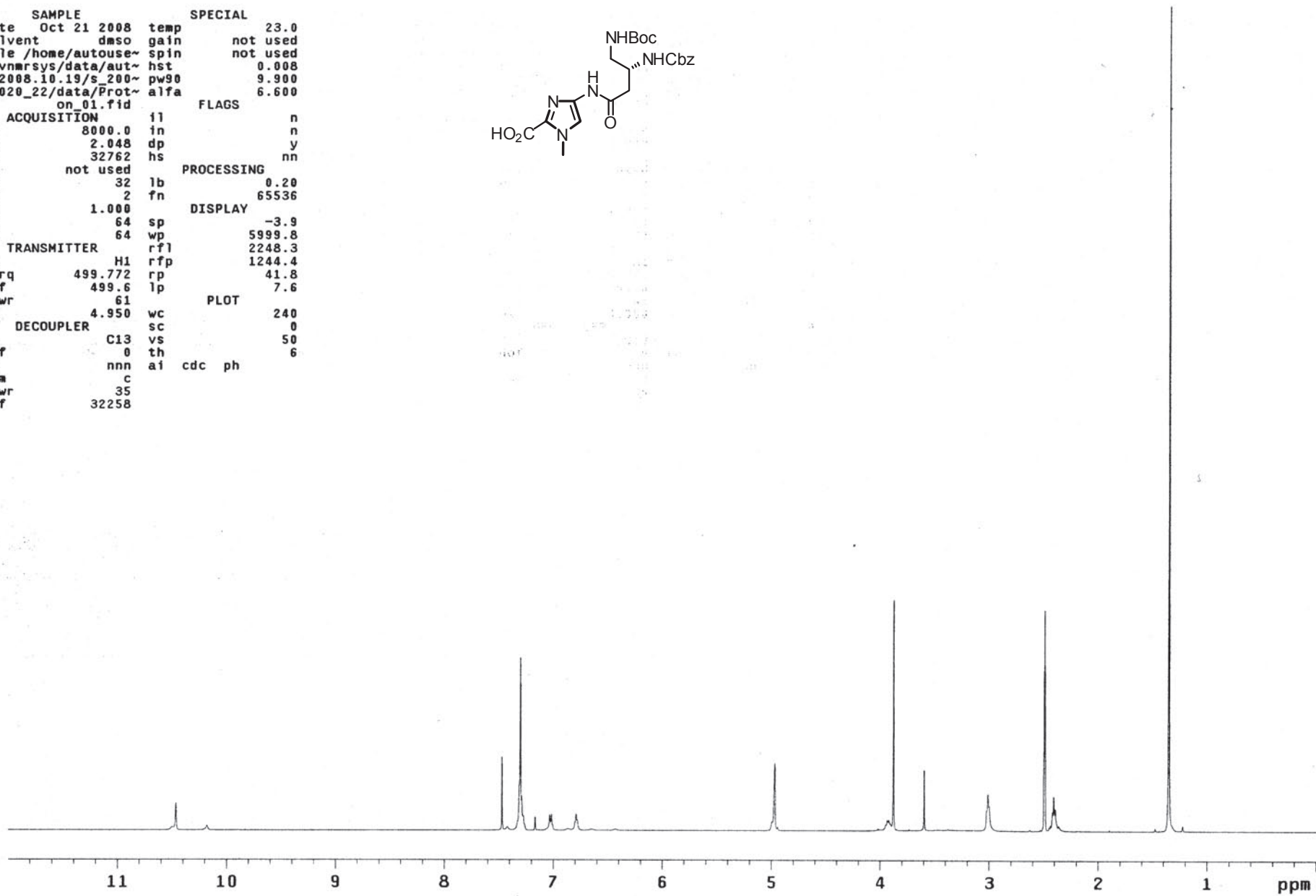
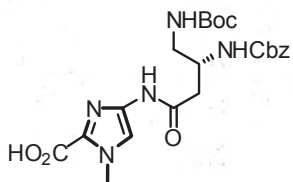
(VII) Plasma protein binding:

4.2.7 Plasma protein binding summary

Client ID	test conc (µM)	Assay duration	Species	Mean free fraction (%)	comment
Warfarin	10	4 hr	Human	0.73%	high binding control
Warfarin	10	4 hr	Rat	5.47%	high binding control
Atenolol	10	4 hr	Human	76.2%	low binding control
Atenolol	10	4 hr	Rat	84.7%	low binding control
DH-V-88	10	4 hr	Human	0.0015%	
DH-V-88	10	4 hr	Rat	0.0016%	
DMC2-239	10	4 hr	Human	0.0000%	
DMC2-239	10	4 hr	Rat	0.0040%	

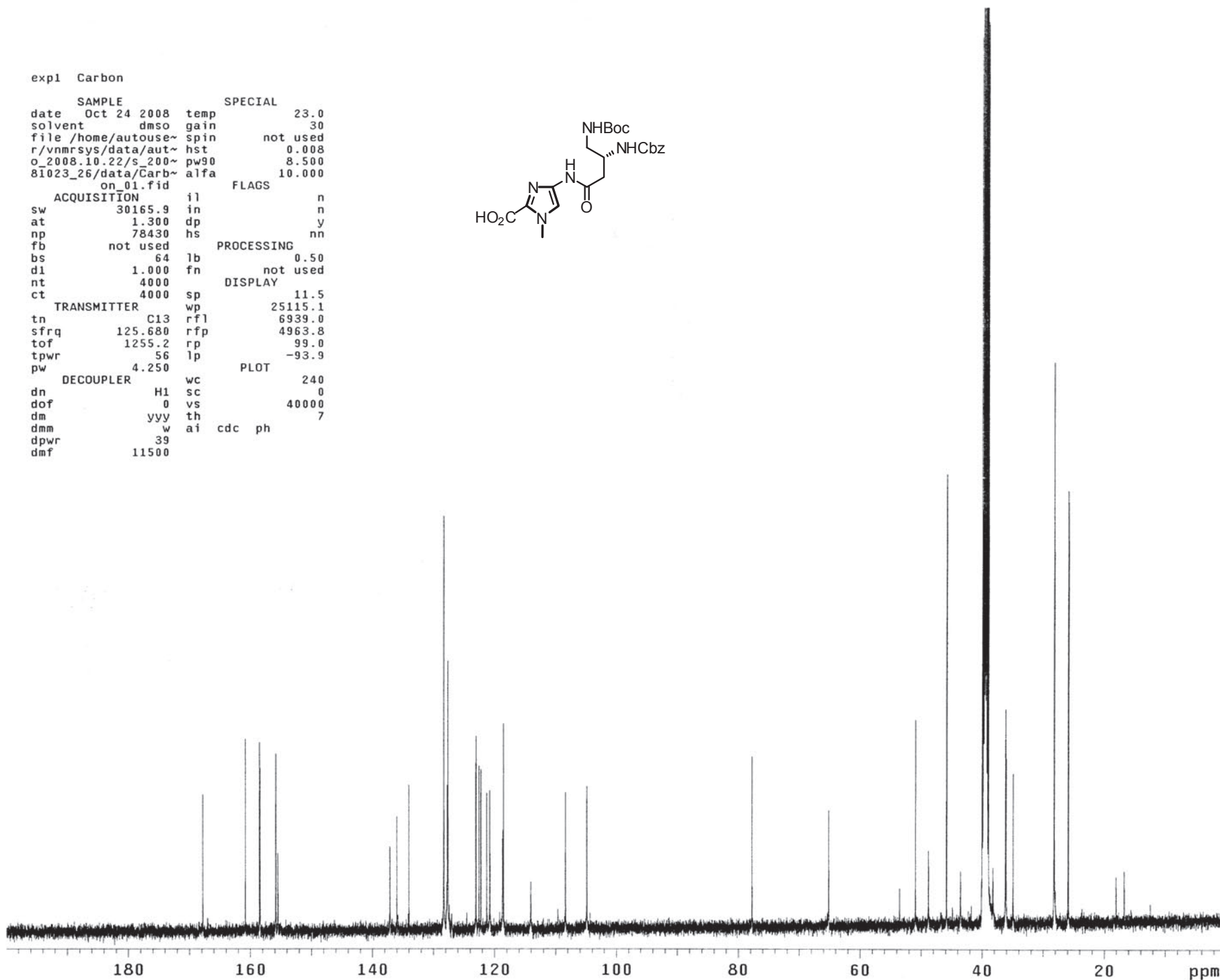
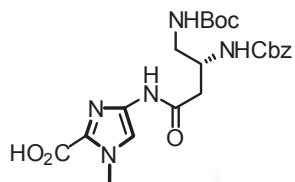
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81020_22	/data/Prot~	alfa	6.600
on_01.fid		FLAGS	
sw	8000.0	il	n
at	2.048	in	n
np	32762	dp	y
fb	not used	hs	nn
bs	32	lb	0.20
ss	2	fn	65536
d1	1.000	PROCESSING	
nt	64	sp	-3.9
ct	64	wp	5999.8
tn	H1	rfl	2248.3
sfrq	499.772	rfl	2248.3
tof	499.6	rfp	1244.4
tpwr	61	rp	41.8
pw	4.950	lp	7.6
dn	C13	PLOT	
dof	0	wc	240
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dpwr	35	th	6
dmf	32258	ai	cdc ph



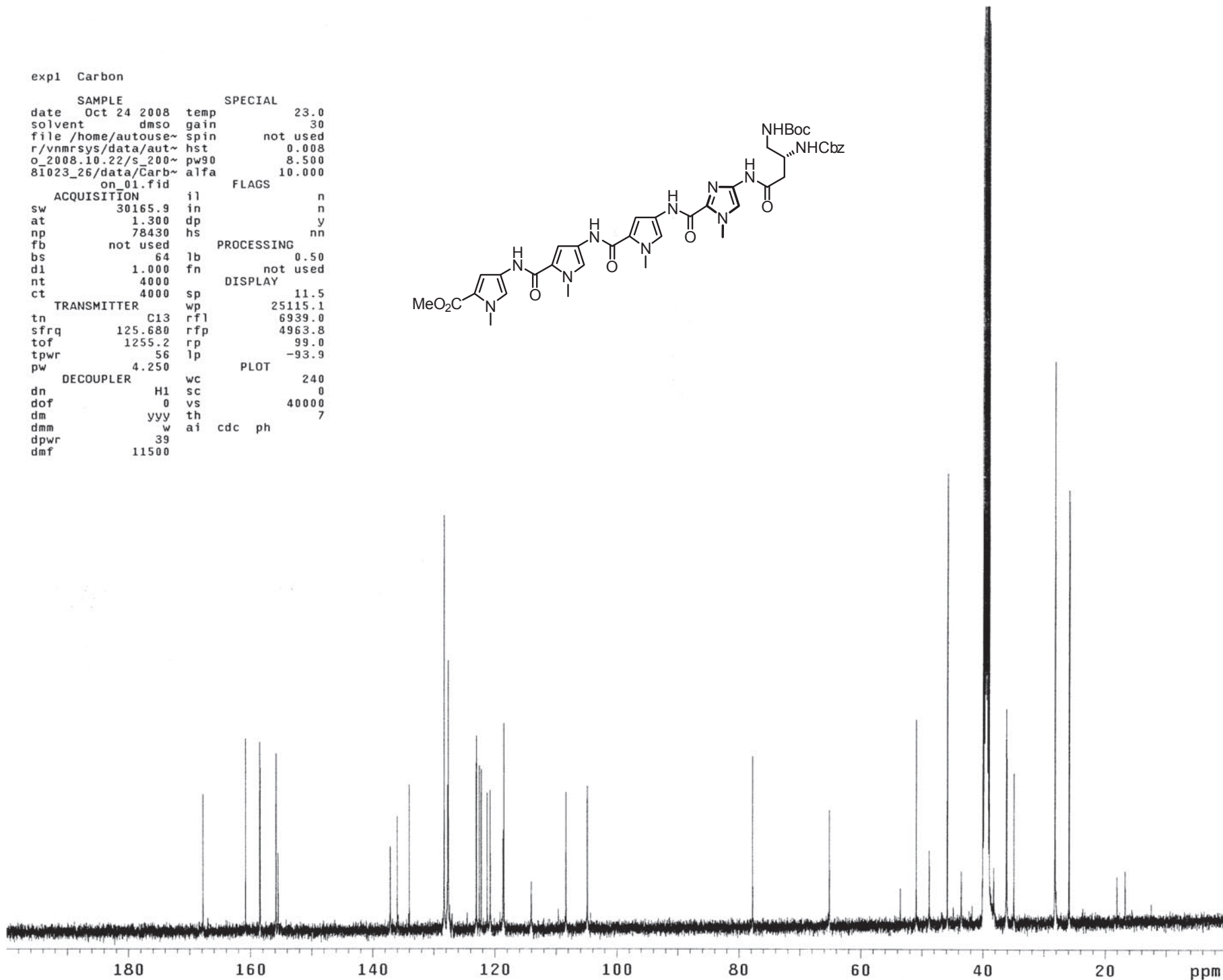
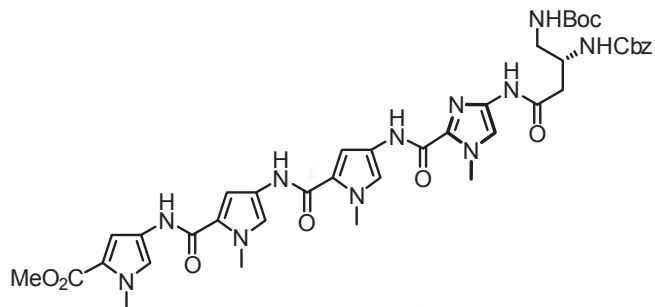
exp1 Carbon

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81023_26	/data/Carb~	alfa	10.000
on_01.fid			
ACQUISITION		FLAGS	
sw	30165.9	il	n
at	1.300	in	n
np	78430	dp	y
fb	not used	hs	nn
bs	64	lb	0.50
d1	1.000	fn	not used
nt	4000		
ct	4000	sp	11.5
TRANSMITTER		DISPLAY	
tn	C13	wp	25115.1
sfrq	125.680	rfl	6939.0
tof	1255.2	rfp	4963.8
tpwr	56	rp	99.0
pw	4.250	lp	-93.9
DECOUPLER		PLOT	
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dmm	w	th	7
dpwr	39	ai	cdc ph
dmf	11500		



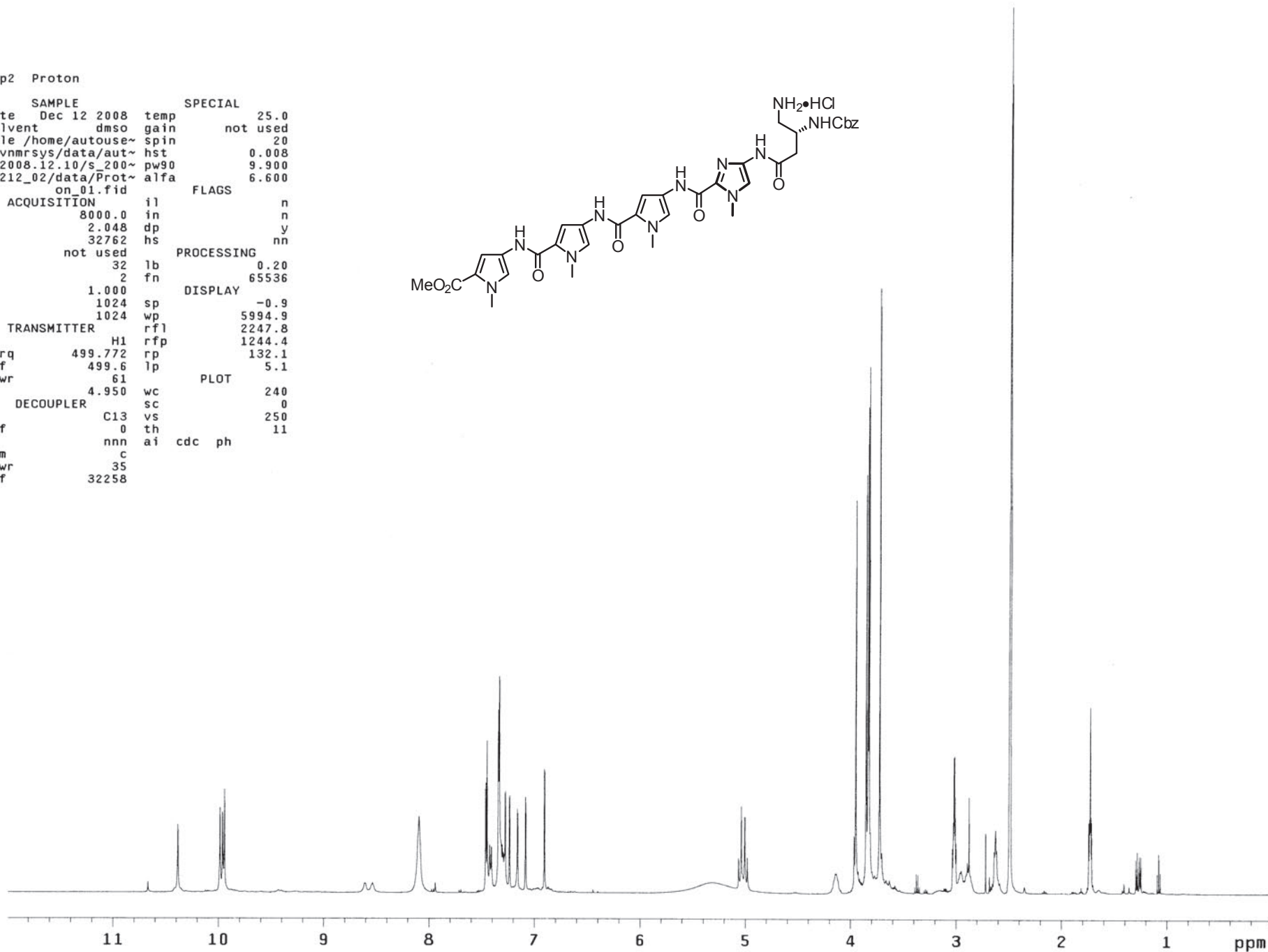
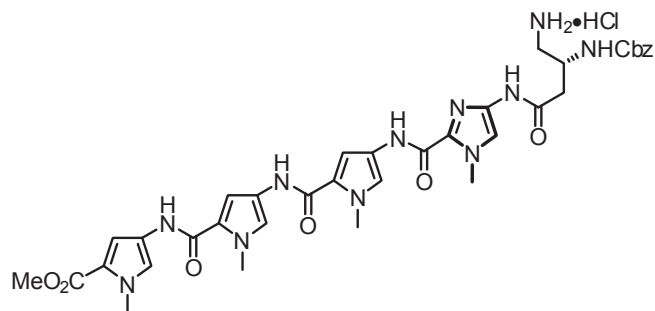
exp1 Carbon

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solvent	dmsd	gain	30
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o_2008	.10.22/s_200~	pw90	8.500
81023_26	/data/Carb~	alfa	10.000
on_01.fid		FLAGS	
ACQUISITION		il	n
sw	30165.9	in	n
at	1.300	dp	y
np	78430	hs	nn
fb	not used	PROCESSING	
bs	64	lb	0.50
d1	1.000	fn	not used
nt	4000	DISPLAY	
ct	4000	sp	11.5
TRANSMITTER		wp	25115.1
tn	C13	rfl	6939.0
sfrq	125.680	rfp	4963.8
tof	1255.2	rp	99.0
tpwr	56	lp	-93.9
pw	4.250	PLOT	
DECOUPLER		wc	240
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dof	0	vs	40000
dm	yyy	th	7
dmm	w	ai	cdc ph
dpwr	39		
dmf	11500		



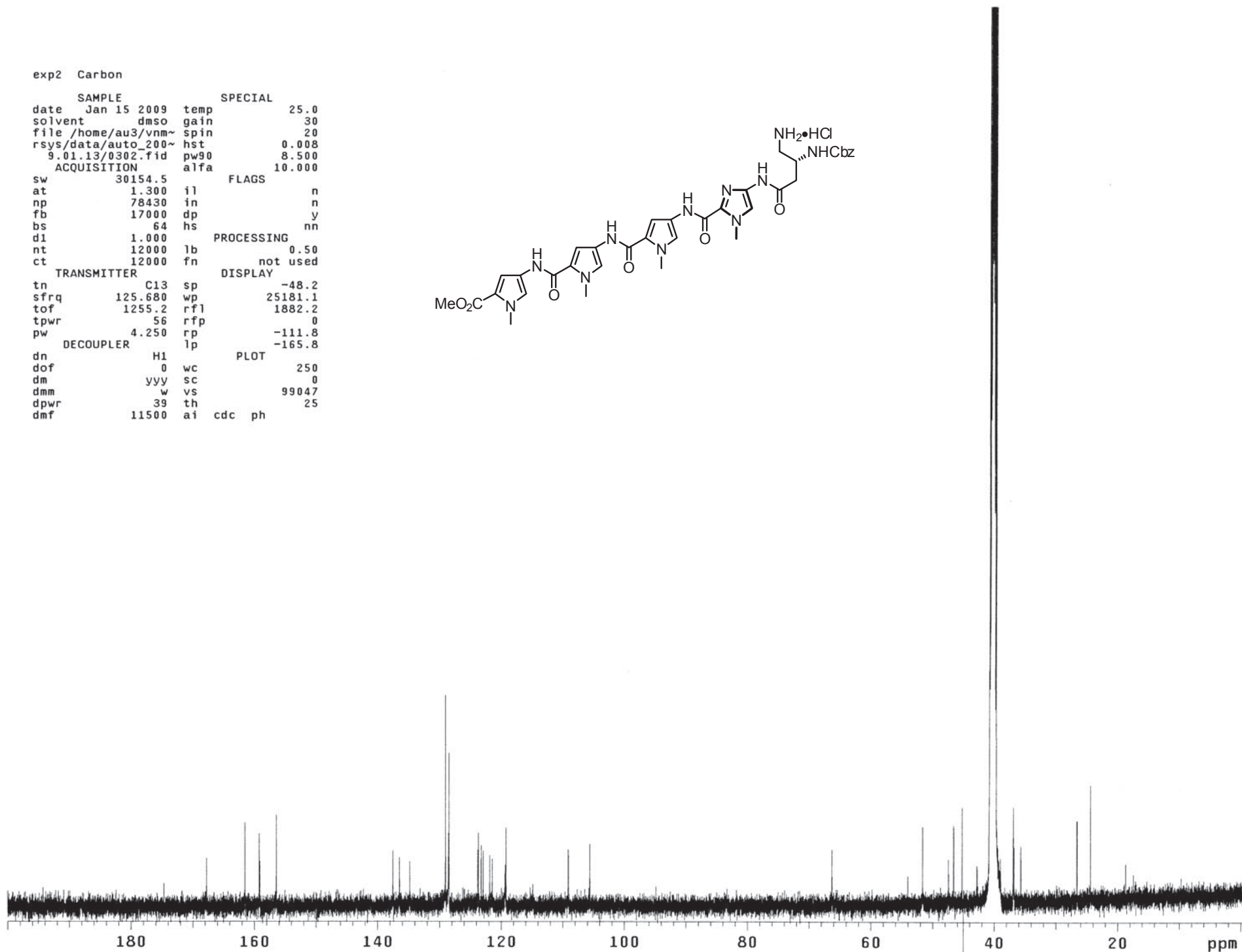
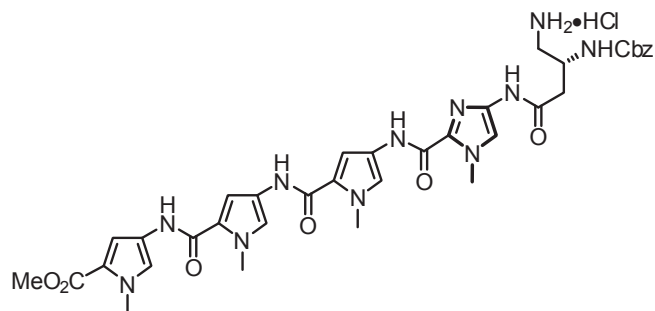
exp2 Proton

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r/vnmr	sys/data/aut~	hst	0.008
o_2008.12.10/s_200~		pw90	9.900
8I212_02/data/Prot~		alfa	6.600
on_01.fid		FLAGS	
ACQUISITION		il	n
sw	8000.0	in	n
at	2.048	dp	y
np	32762	hs	nn
fb	not used	PROCESSING	
bs	32	lb	0.20
ss	2	fn	65536
d1	1.000	DISPLAY	
nt	1024	sp	-0.9
ct	1024	wp	5994.9
TRANSMITTER		rfl	2247.8
tn	H1	rfp	1244.4
sfrq	499.772	rp	132.1
tof	499.6	lp	5.1
tpwr	61	PLOT	
pw	4.950	wc	240
DECOUPLER		sc	0
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dmm	c		
dpwr	35		
dmf	32258		



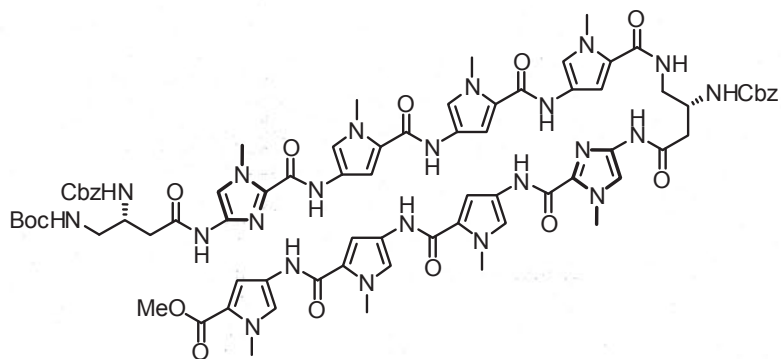
exp2 Carbon

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sw	30154.5	FLAGS	
at	1.300	il	n
np	78430	in	n
fb	17000	dp	y
bs	64	hs	nn
d1	1.000	PROCESSING	
nt	12000	lb	0.50
ct	12000	fn	not used
TRANSMITTER		DISPLAY	
tn	C13	sp	-48.2
sfrq	125.680	wp	25181.1
tof	1255.2	rfl	1882.2
tpwr	56	rpf	0
pw	4.250	rp	-111.8
		lp	-165.8
DECOUPLER		PLOT	
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dm	yyy	vs	99047
dmm	w	th	25
dpwr	39		
dmf	11500	ai	cdc ph



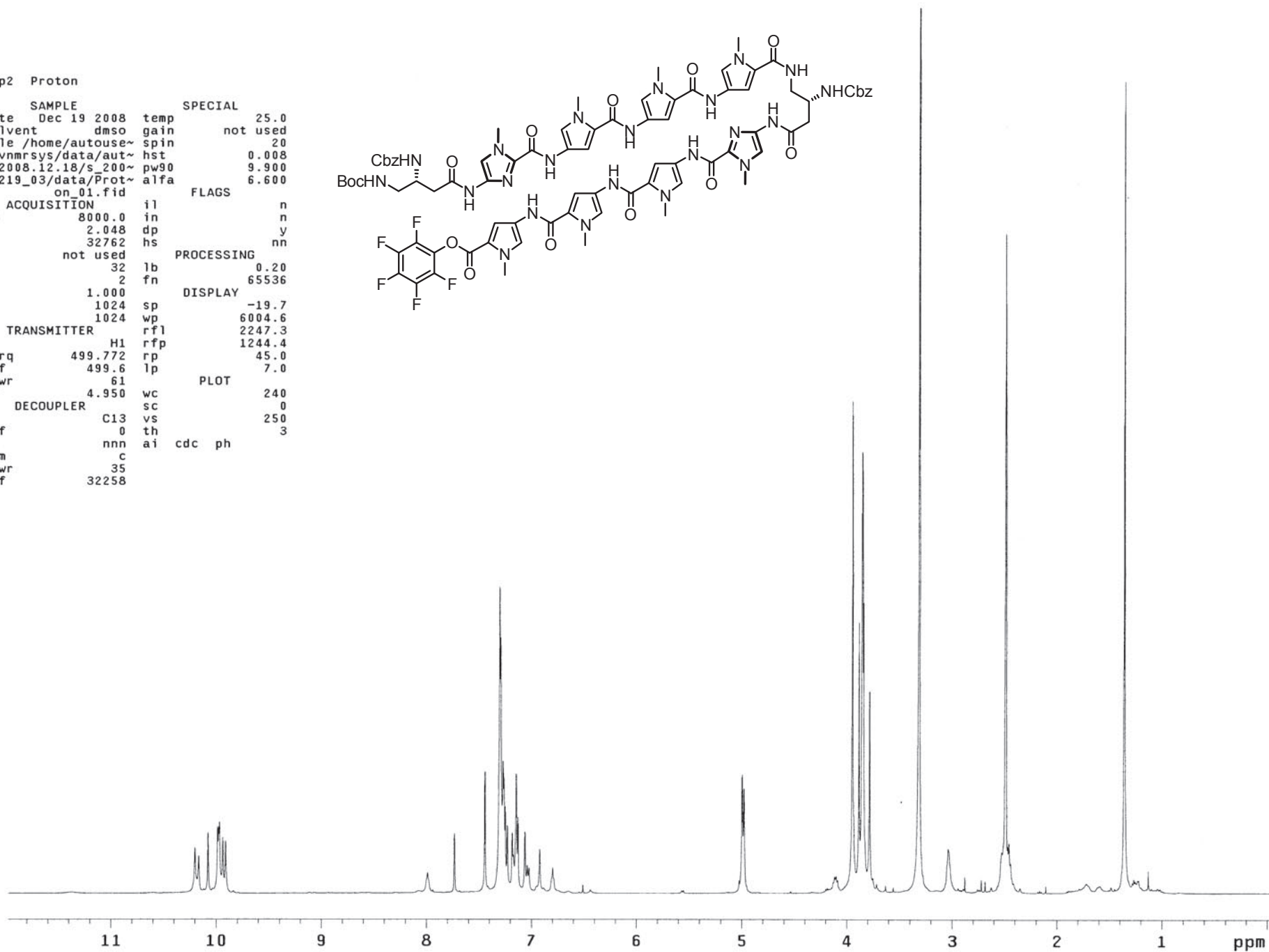
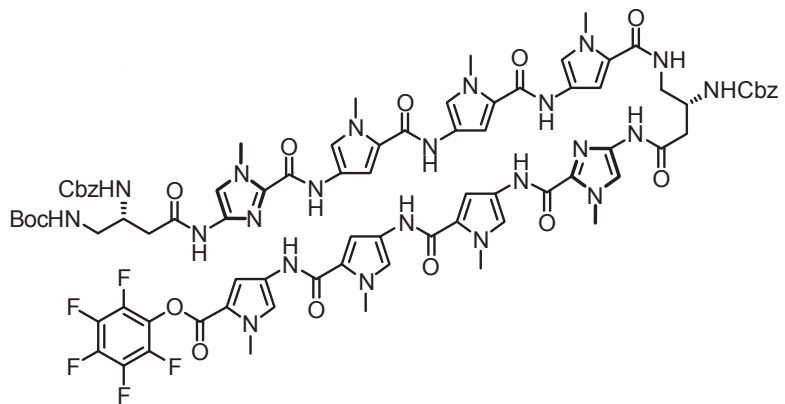
expl Proton

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o_2008	.12.14/s_200~	pw90	9.900
81217_06	/data/Prot~	alfa	6.600
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sw	8000.0	in	n
at	2.048	dp	y
np	32762	hs	nn
fb	not used	PROCESSING	
bs	32	lb	0.20
ss	2	fn	65536
d1	1.000	DISPLAY	
nt	1024	sp	-2.6
ct	1024	wp	5999.8
TRANSMITTER		rfl	2247.1
tn	H1	rfp	1244.4
sfrq	499.772	rp	136.2
tof	499.6	lp	2.7
tpwr	61	PLOT	
pw	4.950	wc	240
DECOUPLER		sc	0
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dmm	c		
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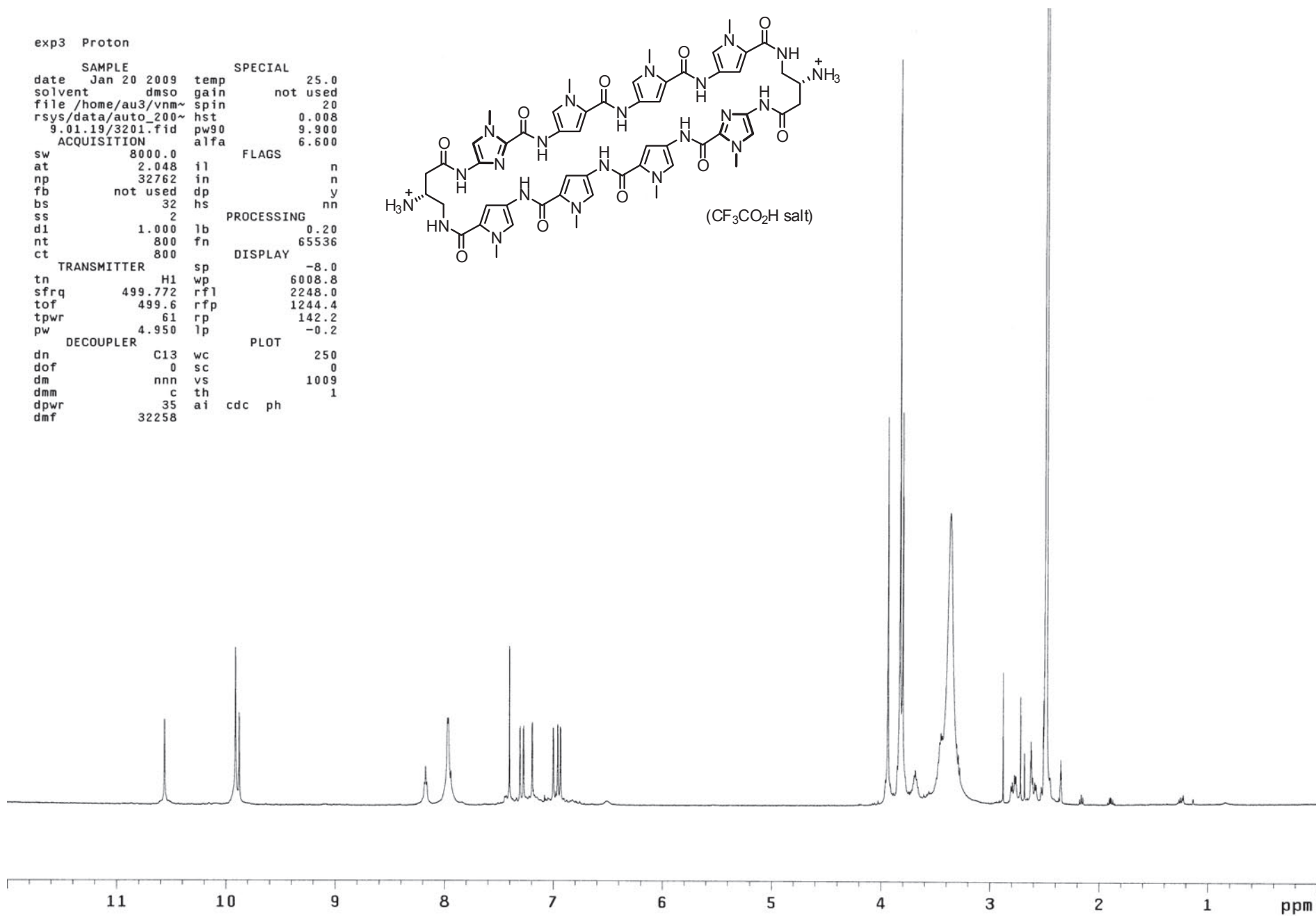
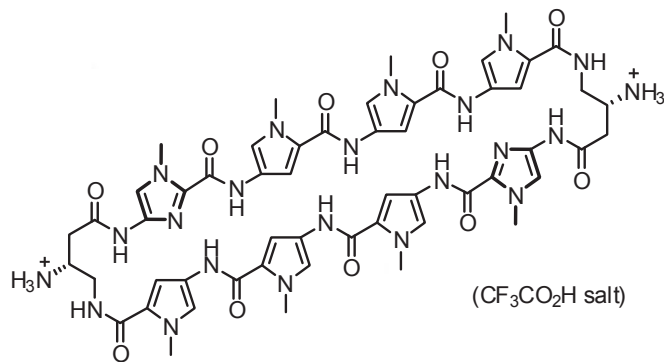
exp2 Proton

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solvent	dms	gain	not used
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o_2008	.12.18/s_200~	pw90	9.900
81219_03	/data/Prot~	alfa	6.600
on_01.fid		FLAGS	
ACQUISITION		il	n
sw	8000.0	in	n
at	2.048	dp	y
np	32762	hs	nn
fb	not used	PROCESSING	
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d1	1.000	DISPLAY	
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tpwr	61	PLOT	
pw	4.950	wc	240
DECOUPLER		sc	0
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dm	nnn	ai	cdc ph
dmm	c		
dpwr	35		
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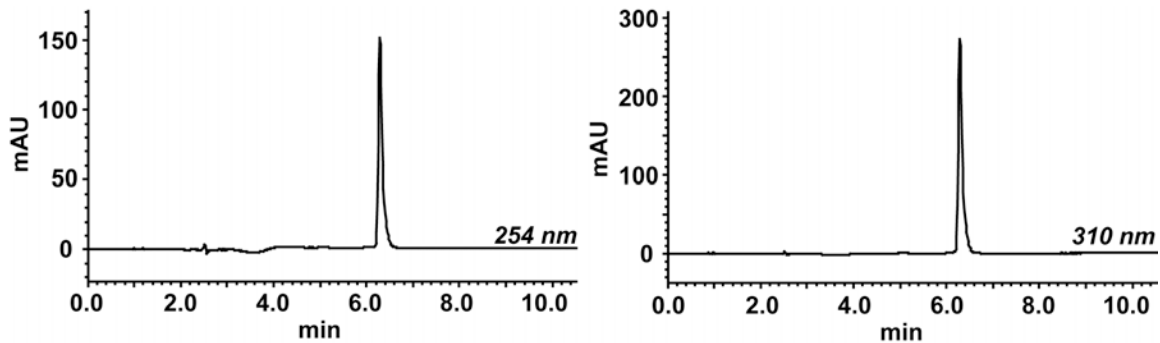


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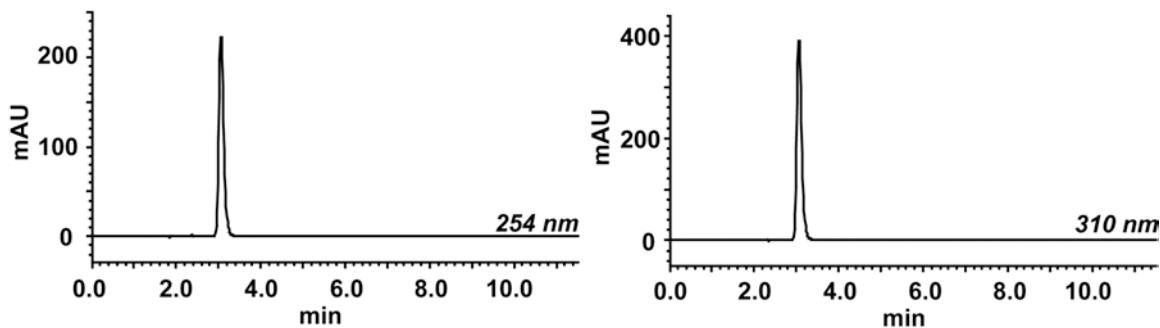
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		alfa	6.600
ACQUISITION		FLAGS	
sw	8000.0		
at	2.048	il	n
np	32762	in	n
fb	not used	dp	y
bs	32	hs	nn
ss	2		
TRANSMITTER		PROCESSING	
tn	H1	wp	-8.0
sfrq	499.772	rfl	6008.8
tof	499.6	rfp	2248.0
tpwr	61	rp	1244.4
pw	4.950	lp	142.2
			-0.2
DECOUPLER		PLOT	
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dmm	c	th	1
dpwr	35	ai	cdc
dmf	32258	ph	



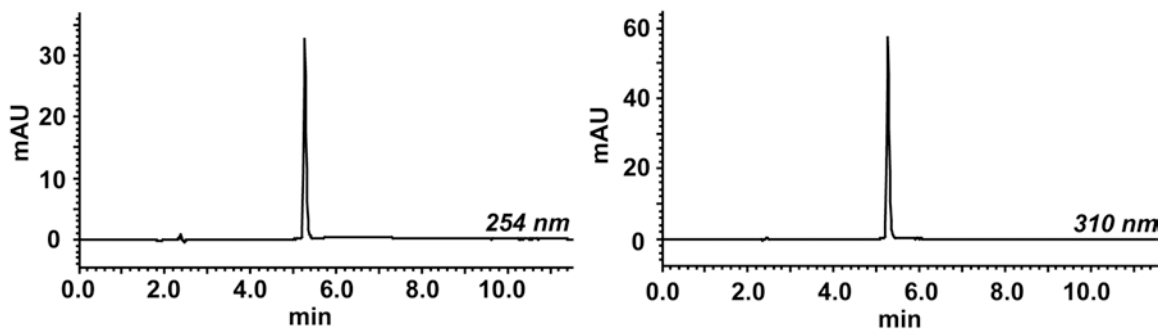
Analytical HPLC characterization of cyclic polyamide 15:



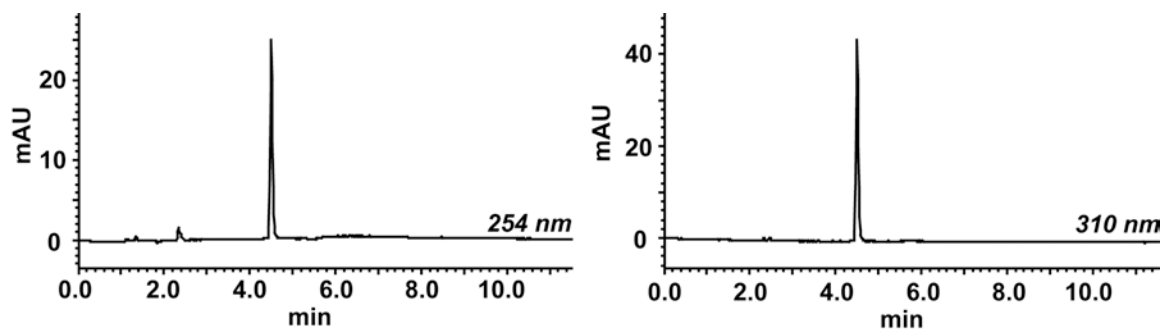
Analytical HPLC characterization of cyclic polyamide 1:



Analytical HPLC characterization of cyclic polyamide 2:



Analytical HPLC characterization of cyclic polyamide 3:



Analytical HPLC characterization of hairpin polyamide 5:

