

Supporting Information:

Structure-Activity Relationships of Hydrophobic Alkyl Acrylamides as Tissue Transglutaminase Inhibitors

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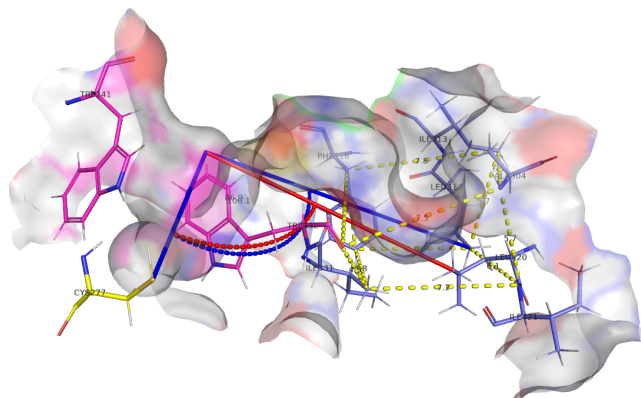
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Table S1: Comparison of k_{inact}/K_I ratios obtained from linear vs non-linear regression

Compd.	k_{inact}/K_I ($10^3 \text{ M}^{-1}\text{min}^{-1}$)	
	Non-linear hyperbolic (all [I])	Linear (low [I])
22a	412 ± 142	290 ± 30
23a	1508 ± 1608	1250 ± 40
24a	27.5 ± 18.6	20 ± 1
25a	108 ± 37	79 ± 7

Figure S1: Comparison of protein models

Structural differences between two crystallographic structures of TG2, namely 2Q3Z (left) and 3S3J (right).

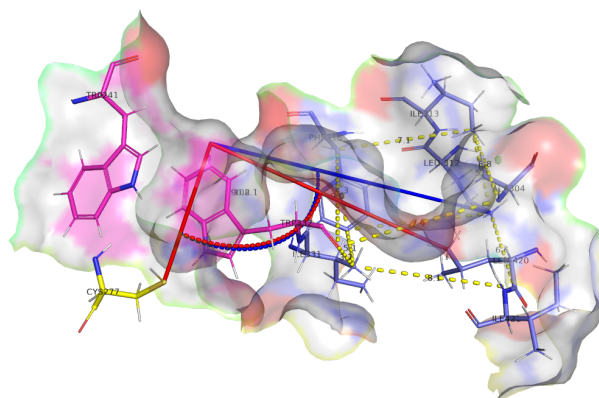


2Q3Z

Angle (SH_CYS277, H5_TRP332, CH3_LEU312) = 106°

Angle (SH_CYS277, H5_TRP332, CH3_LEU420) = 87°

Approximate V_{cavity} (Ca_PHE316, CO_LEU420, Ca_ALA304) = 250 Å³



3S3J

Angle (SH_CYS277, H5_TRP332, CH3_LEU312) = 108°

Angle (SH_CYS277, H5_TRP332, CH3_LEU420) = 90°

Approximate V_{cavity} (Ca_PHE316, CO_LEU420, Ca_ALA304) = 236 Å³

Table S2: Summary of docking results using crystallographic structure 3S3J.

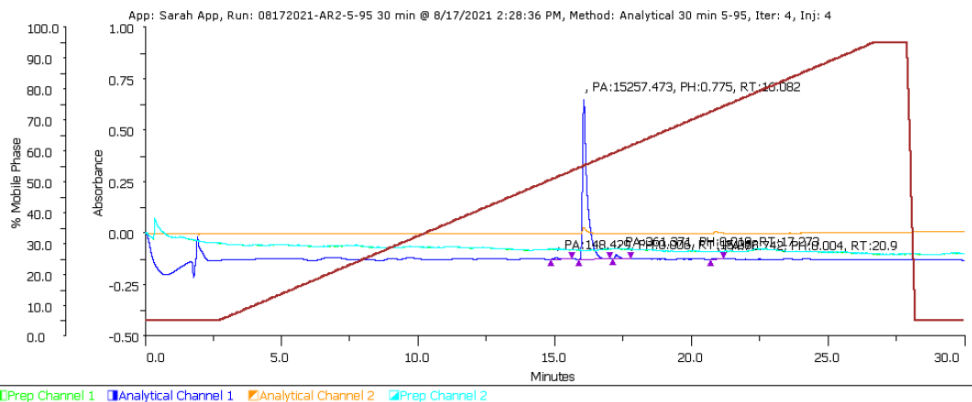
Compound	n	Non-covalent		Covalent	
		S score	d (Å)	S score	d (Å)
22a	1	-5.73	5.3	-5.61	5.3
22b	2	-4.97	9.2	-5.45	8.2
22c	3	-6.58	3.9	-5.79	4.6
22d	4	-6.58	3.7	-6.45	4.1
22e	5	-6.36	4.1	-6.14	4.5
23a	1	-6.19	5.1	-5.65	7.8
23b	2	-5.77	7.9	-5.46	7
23c	3	-6.20	4.6	-5.70	6.8
23d	4	-7.05	3.6	-5.21	7.2
23e	5	-7.32	6	-6.38	4.6
24a	1	-6.22	6.6	-5.80	5.1
24b	2	-6.51	4.4	-5.99	4.6
24c	3	-6.48	4.4	-6.05	4.4
24d	4	-6.61	4.8	-6.08	5.4
24e	5	-6.99	4.2	-6.20	5.2

HPLC Analyses

The purity of the final inhibitors was determined by Gilson-Mandel GXP271 high performance liquid chromatography (HPLC) with UV detection at 214 and 254 nm (Phenomenex Luna, 150 mm × 4.6 mm, 30 min, 1.5 mL/min flow rate, 5-95% 0.1% TFA in CH₃CN/0.1% TFA in H₂O).

Inhibitor	Retention Time (min)	Purity (%)
22a	16.082	96.298
22b	16.323	99.474
22c	16.498	97.823
22d	16.952	97.395
22e	17.643	90.742
23a	12.363	100
23b	12.679	98.442
23c	12.847	96.059
23d	13.354	96.171
23e	14.068	93.84
24a	13.578	97.965
24b	13.816	97.99
24c	14.052	97.772
24d	14.556	97.923
24e	15.335	98.592
25a	16.631	97.057

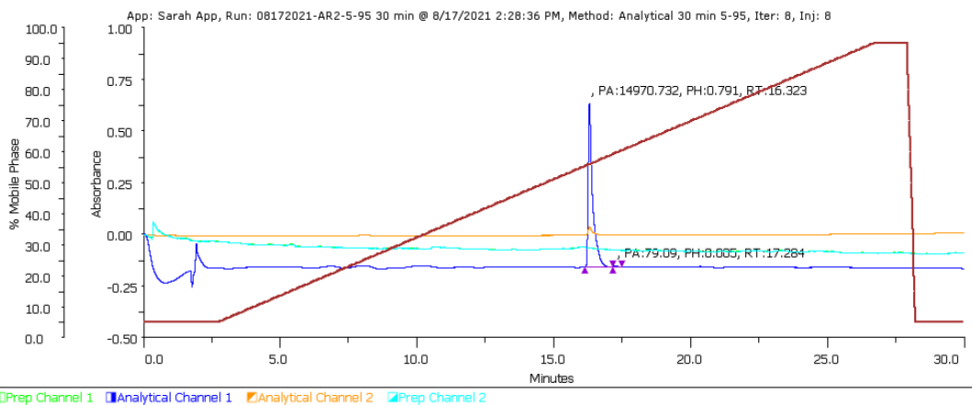
22a



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAU/min x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
4	1	16.082	15257.4729	0.775	AR2-82	Sample Zone->153		96.298
4	2	17.273	361.3712	0.019	AR2-82	Sample Zone->153		2.281
4	3	20.9	76.7417	0.004	AR2-82	Sample Zone->153		0.484
4	4	15.068	148.4287	0.006	AR2-82	Sample Zone->153		0.937

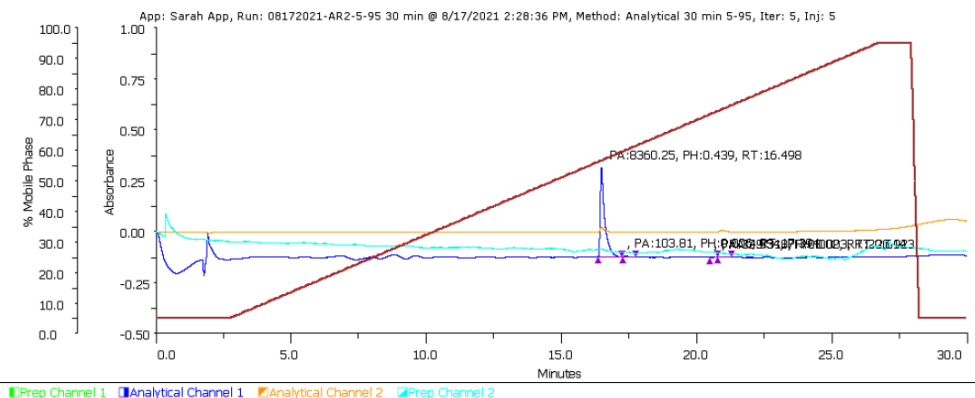
22b



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAU/min x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
8	1	16.323	14970.7325	0.791	AR2-74	Sample Zone->152		99.474
8	2	17.284	79.0903	0.005	AR2-74	Sample Zone->152		0.526

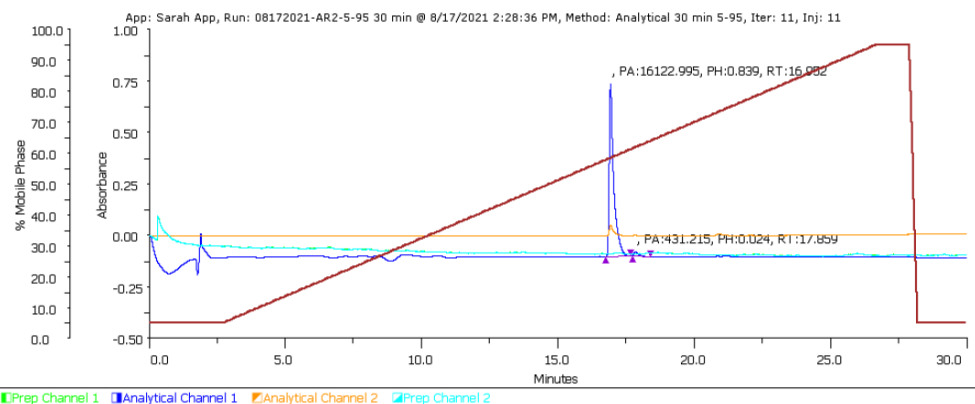
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Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
5	1	16.498	8360.2504	0.439	AR2-80	Sample Zone->154		97.823
5	2	17.394	103.81	0.006	AR2-80	Sample Zone->154		1.215
5	3	20.614	32.9538	0.002	AR2-80	Sample Zone->154		0.386
5	4	20.923	49.3179	0.003	AR2-80	Sample Zone->154		0.577

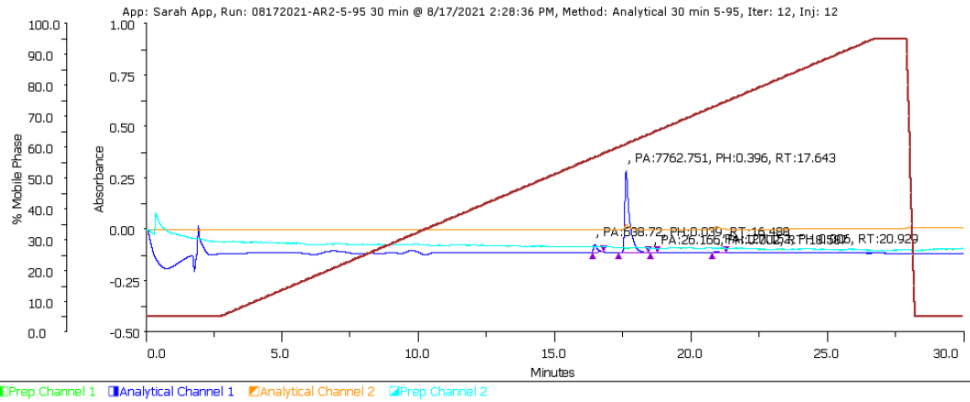
22d



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
11	1	16.952	16122.9947	0.839	AR2-89	Sample Zone->155		97.395
11	2	17.859	431.2154	0.024	AR2-89	Sample Zone->155		2.605

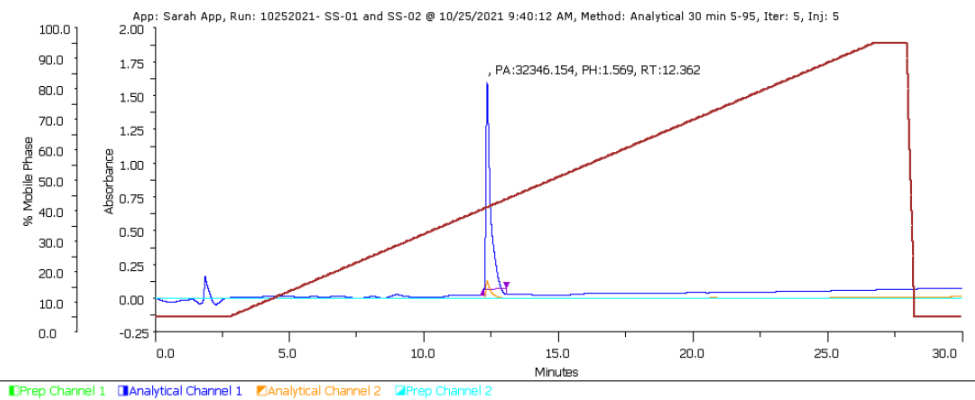
22e



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
12	1	16.488	638.7204	0.039	AR2-90	Sample Zone->148		7.466
12	2	17.643	7762.7512	0.396	AR2-90	Sample Zone->148		90.742
12	3	20.929	127.1522	0.006	AR2-90	Sample Zone->148		1.486
12	4	18.587	26.1666	0.002	AR2-90	Sample Zone->148		0.306

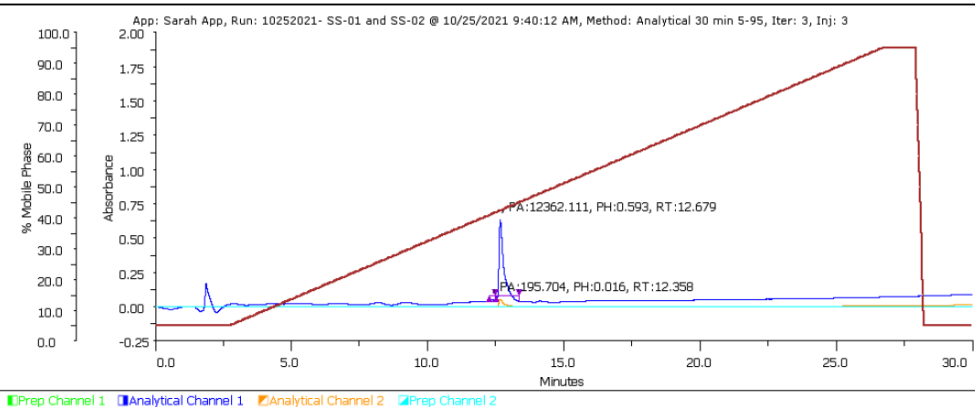
23a



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
5	1	12.362	32346.1535	1.569	SS-01	Sample Zone->148		100

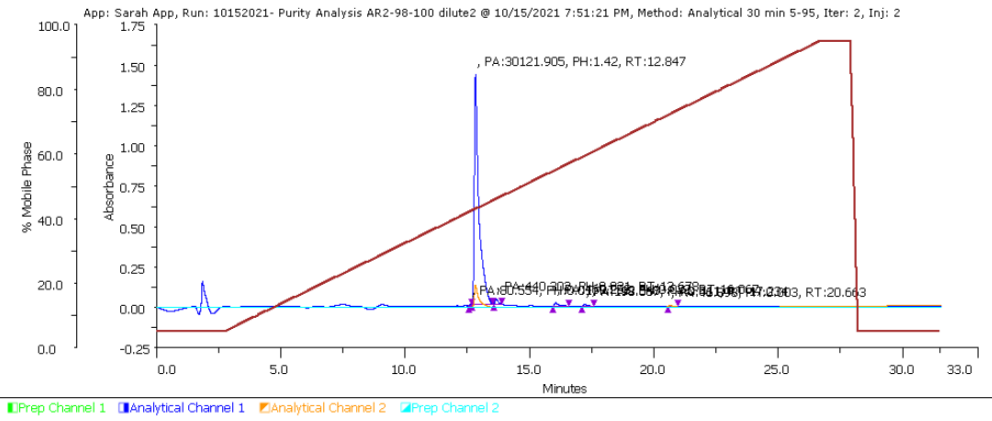
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Sample Table

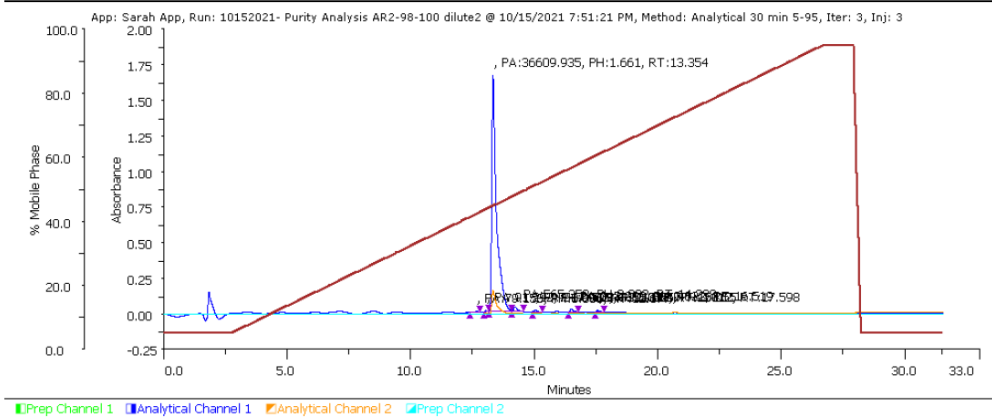
Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
3	1	12.358	195.7043	0.016	SS-02	Sample Zone->149		1.558
3	2	12.679	12362.1108	0.593	SS-02	Sample Zone->149		98.442

23c



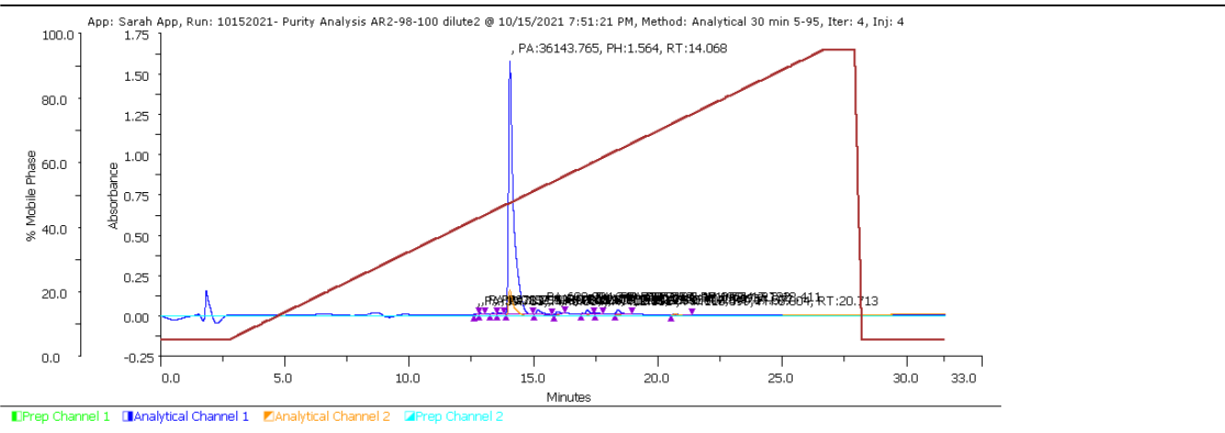
Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (mAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
2	1	12.847	30121.9049	1.42	AR2-98	Sample Zone->152		96.059
2	2	13.678	440.3021	0.031	AR2-98	Sample Zone->152		1.404
2	3	16.067	469.2582	0.022	AR2-98	Sample Zone->152		1.496
2	4	17.234	198.6667	0.011	AR2-98	Sample Zone->152		0.634
2	5	20.663	46.8985	0.003	AR2-98	Sample Zone->152		0.15
2	6	12.648	80.5541	0.01	AR2-98	Sample Zone->152		0.257



Sample Table

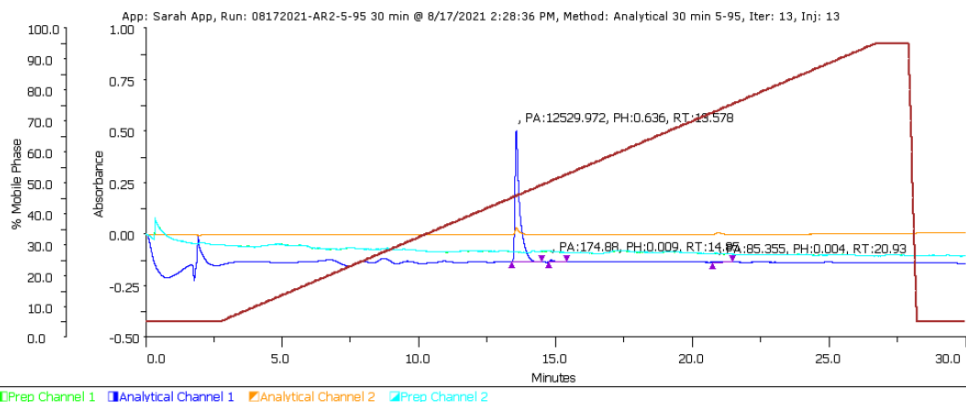
Injection Number	Peak Name	Retention Time (min)	Area (nA/min x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
3	1	12.677	79.1575	0.006	AR2-99	Sample Zone->153		0.208
3	2	13.057	91.2922	0.009	AR2-99	Sample Zone->153		0.24
3	3	13.354	36609.9346	1.661	AR2-99	Sample Zone->153		96.171
3	4	14.238	565.3516	0.032	AR2-99	Sample Zone->153		1.485
3	5	15.055	217.9062	0.012	AR2-99	Sample Zone->153		0.572
3	6	16.519	312.288	0.022	AR2-99	Sample Zone->153		0.82
3	7	17.598	191.6038	0.012	AR2-99	Sample Zone->153		0.503



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
4	1	12.681	39.7333	0.004	AR2-100	Sample Zone->154		0.103
4	2	12.874	69.182	0.006	AR2-100	Sample Zone->154		0.18
4	3	13.656	132.536	0.009	AR2-100	Sample Zone->154		0.344
4	4	14.068	36143.7648	1.564	AR2-100	Sample Zone->154		93.84
4	5	15.196	680.9043	0.027	AR2-100	Sample Zone->154		1.768
4	6	15.975	266.1555	0.016	AR2-100	Sample Zone->154		0.691
4	7	17.182	349.7175	0.021	AR2-100	Sample Zone->154		0.908
4	8	17.577	109.0098	0.007	AR2-100	Sample Zone->154		0.283
4	9	18.411	530.5577	0.024	AR2-100	Sample Zone->154		1.377
4	10	13.366	78.2836	0.006	AR2-100	Sample Zone->154		0.203
4	11	20.713	116.699	0.004	AR2-100	Sample Zone->154		0.303

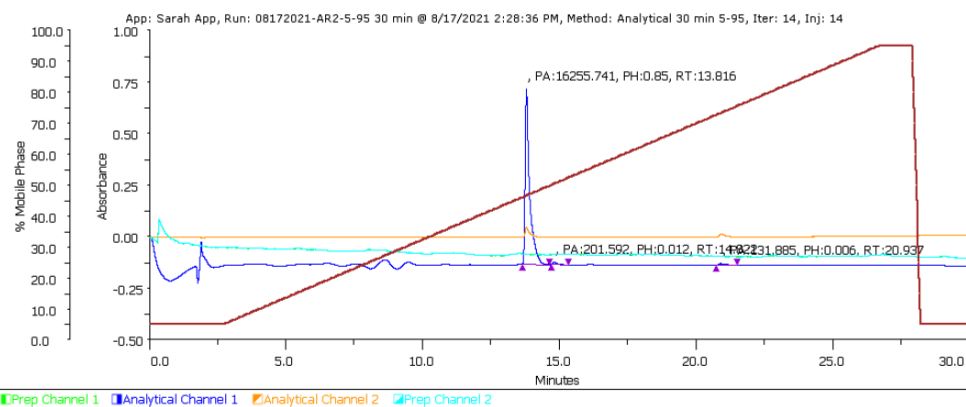
24a



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAU/min x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
13	1	13.578	12529.9715	0.636	AR2-43	Sample Zone->149		97.965
13	2	14.85	174.8805	0.009	AR2-43	Sample Zone->149		1.367
13	3	20.93	85.355	0.004	AR2-43	Sample Zone->149		0.667

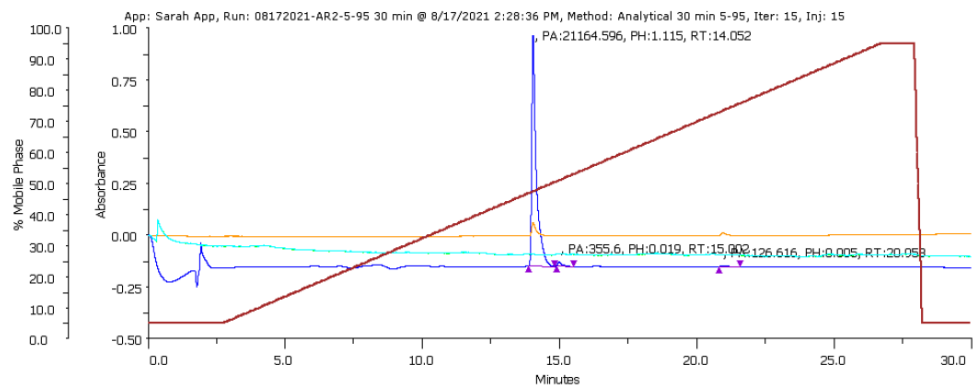
24b



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAU/min x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
14	1	13.816	16255.7412	0.85	AR2-44	Sample Zone->150		97.99
14	2	14.822	201.5925	0.012	AR2-44	Sample Zone->150		1.215
14	3	20.937	131.8853	0.006	AR2-44	Sample Zone->150		0.795

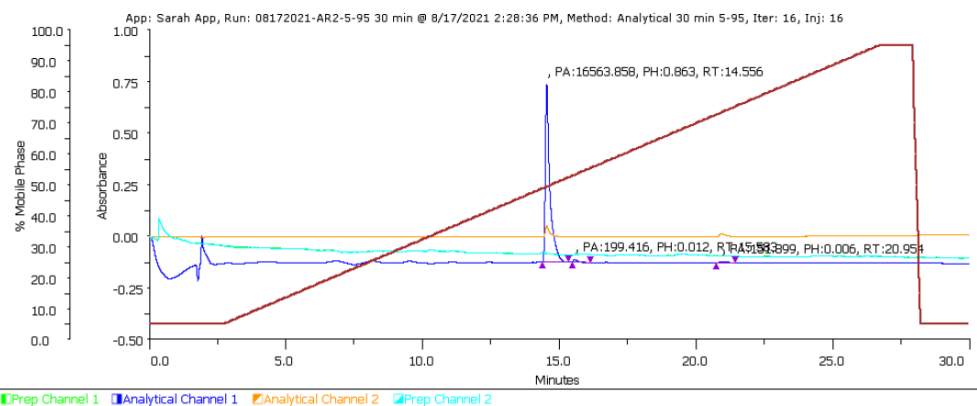
24c



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
15	1	14.052	21164.5964	1.115	AR2-45	Sample Zone->151		97.772
15	2	15.002	355.5997	0.019	AR2-45	Sample Zone->151		1.643
15	3	20.958	126.6156	0.005	AR2-45	Sample Zone->151		0.585

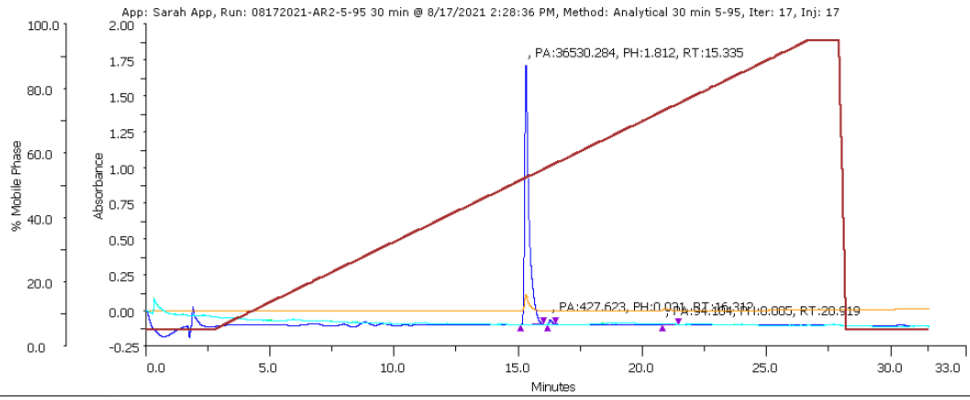
24d



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
16	1	14.556	16563.8581	0.863	AR2-46	Sample Zone->144		97.923
16	2	15.583	199.4161	0.012	AR2-46	Sample Zone->144		1.179
16	3	20.954	151.8965	0.006	AR2-46	Sample Zone->144		0.898

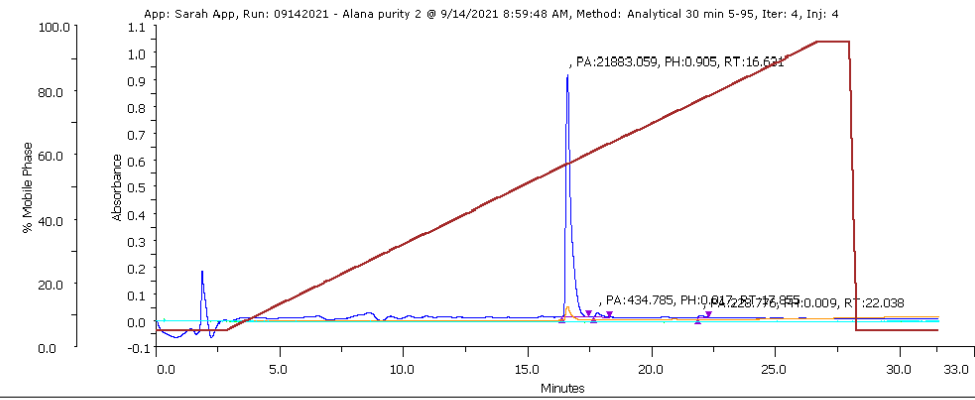
24e



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (nAUmin x100)	Height (AU)	Sample Name	Sample Location	Fraction Site(s)	Area %
17	1	15.335	36530.2839	1.812	AR2-47	Sample Zone->145		98.592
17	2	16.312	427.6225	0.031	AR2-47	Sample Zone->145		1.154
17	3	20.919	94.1039	0.005	AR2-47	Sample Zone->145		0.254

25a



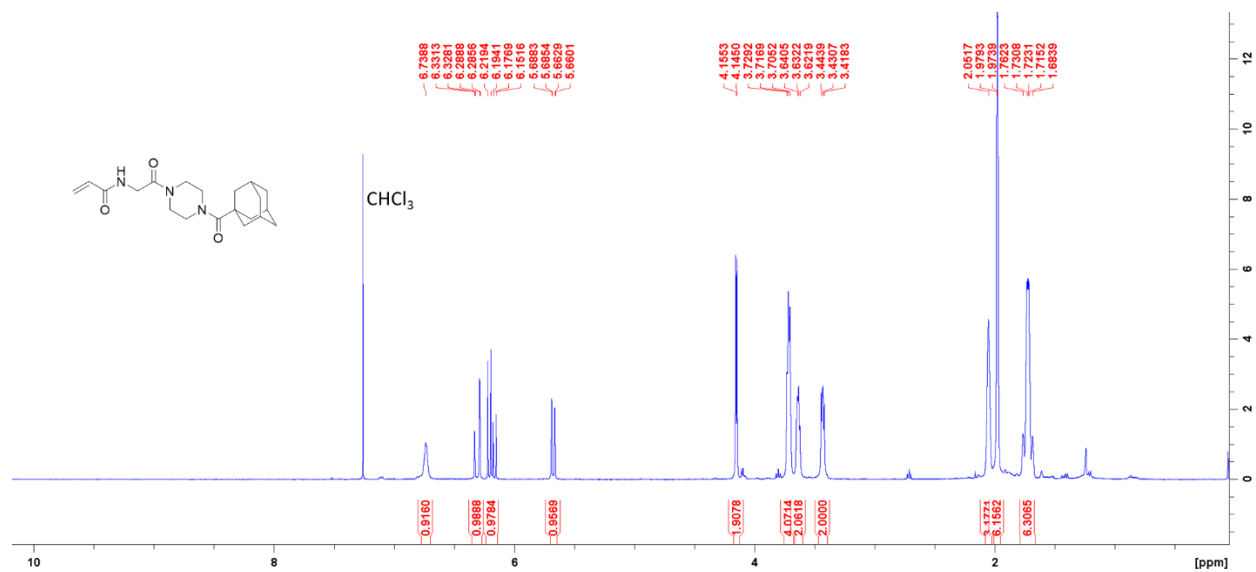
Sample Table

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4	1	16.631	21883.0587	0.905	AR2-77	Sample Zone->152		97.057
4	2	17.855	434.7949	0.017	AR2-77	Sample Zone->152		1.928
4	3	22.038	228.776	0.009	AR2-77	Sample Zone->152		1.015

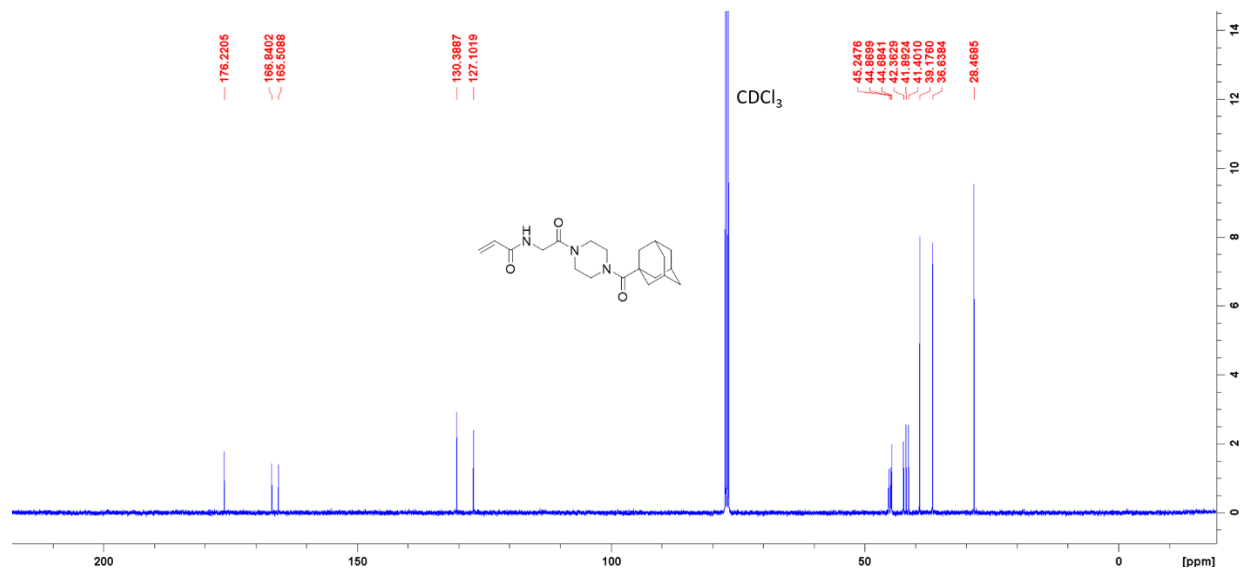
NMR Spectra

The ^1H - and ^{13}C -NMR spectra of all final compounds are shown here:

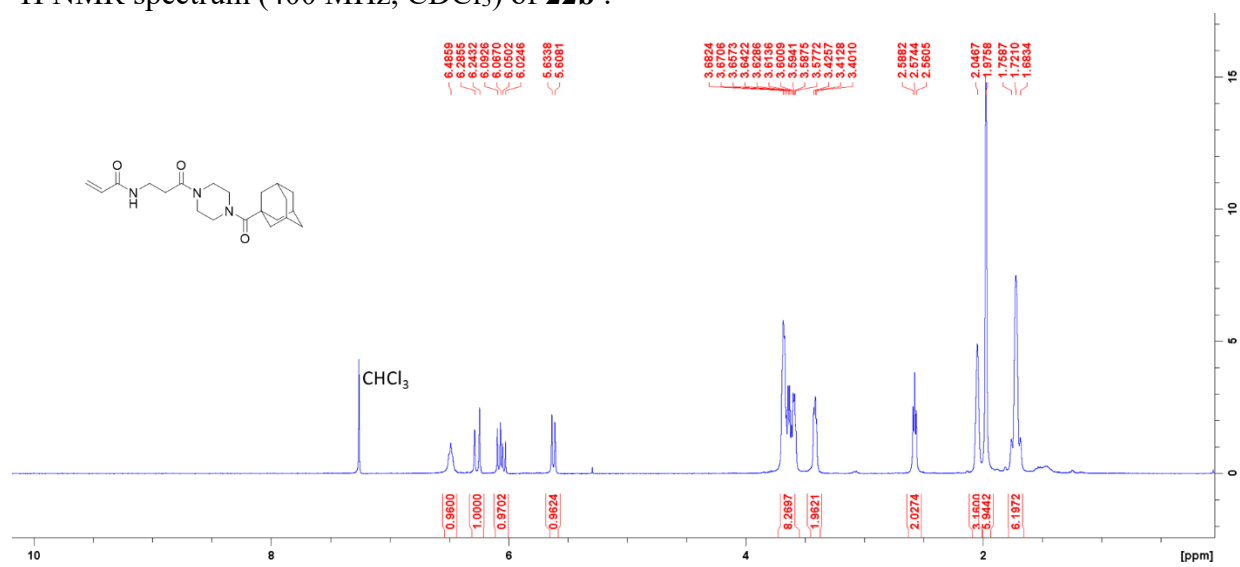
^1H NMR spectrum (400 MHz, CDCl_3) of **22a** :



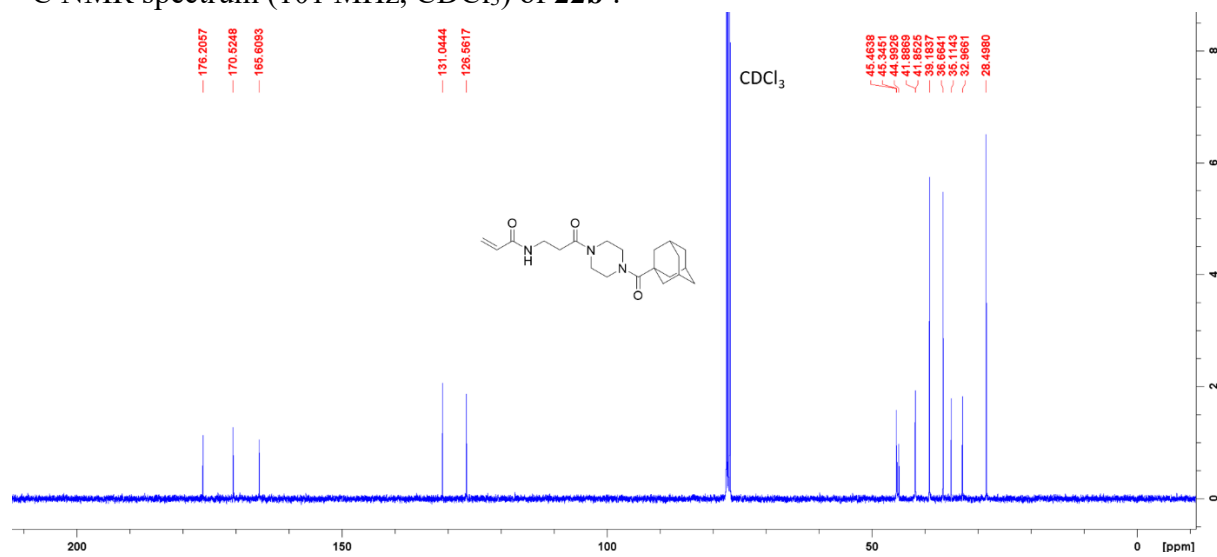
^{13}C NMR spectrum (101 MHz, CDCl_3) of **22a** :



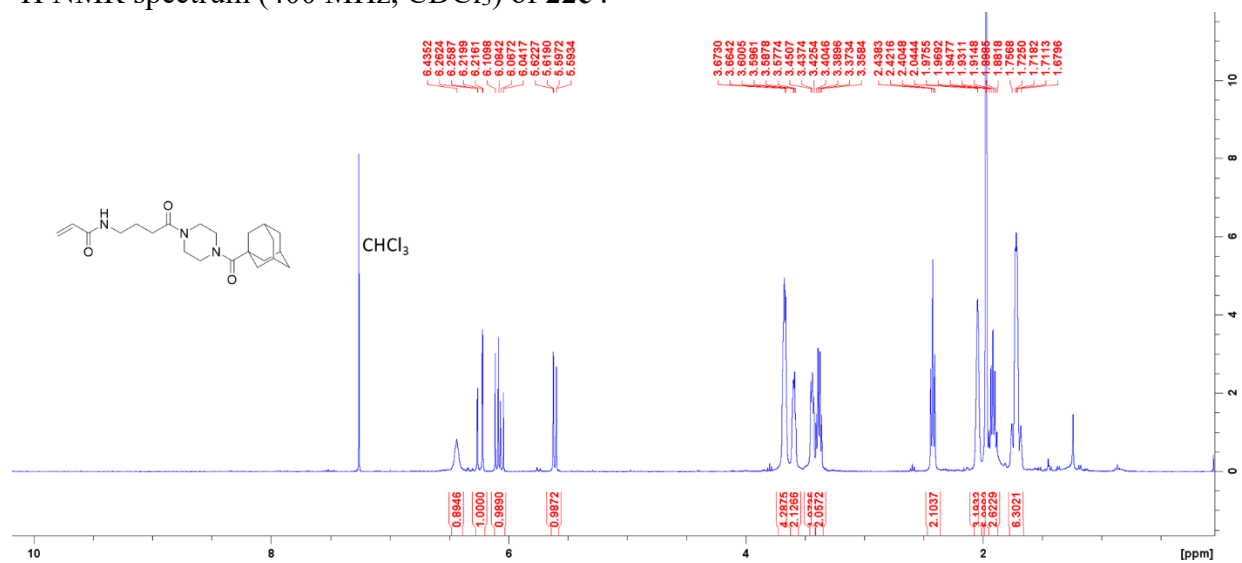
^1H NMR spectrum (400 MHz, CDCl_3) of **22b** :



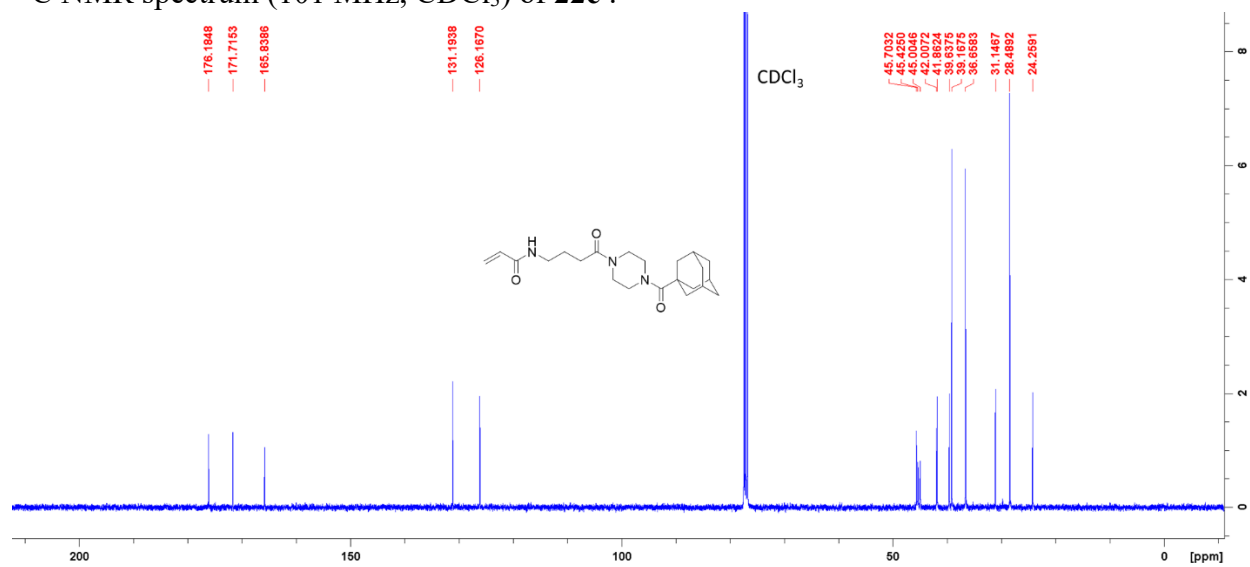
^{13}C NMR spectrum (101 MHz, CDCl_3) of **22b** :



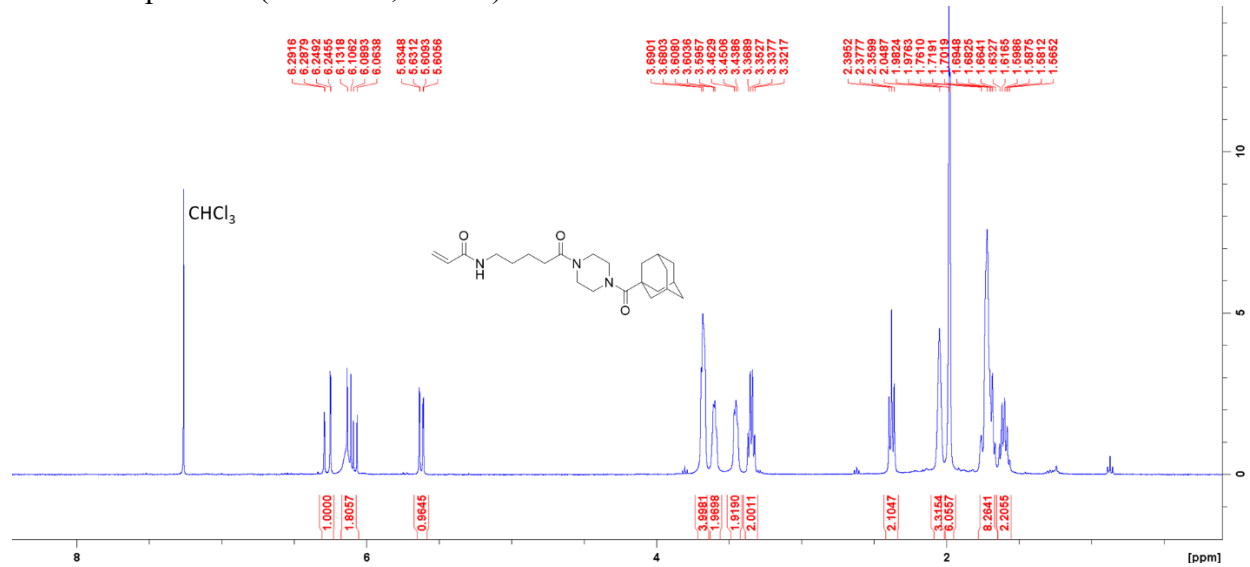
^1H NMR spectrum (400 MHz, CDCl_3) of **22c** :



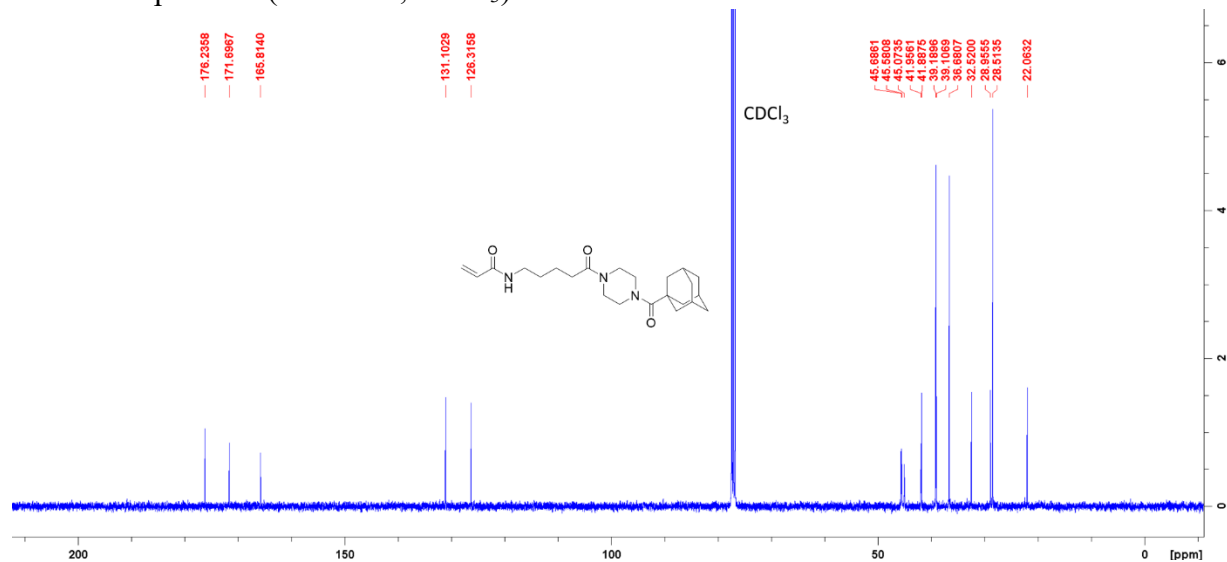
^{13}C NMR spectrum (101 MHz, CDCl_3) of **22c** :



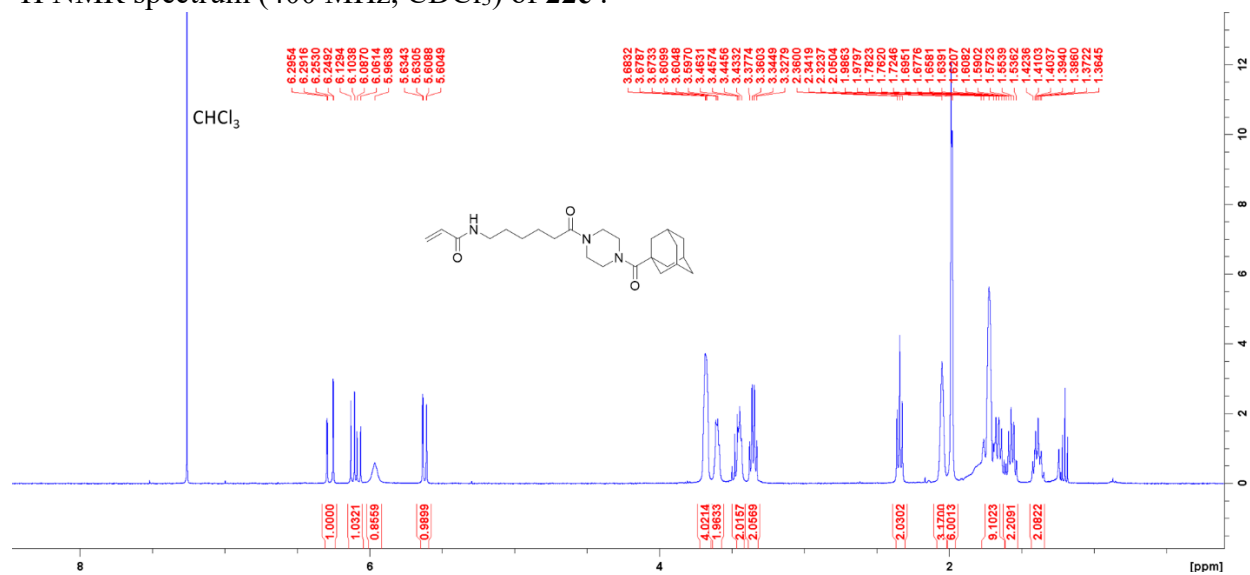
^1H NMR spectrum (400 MHz, CDCl_3) of **22d** :



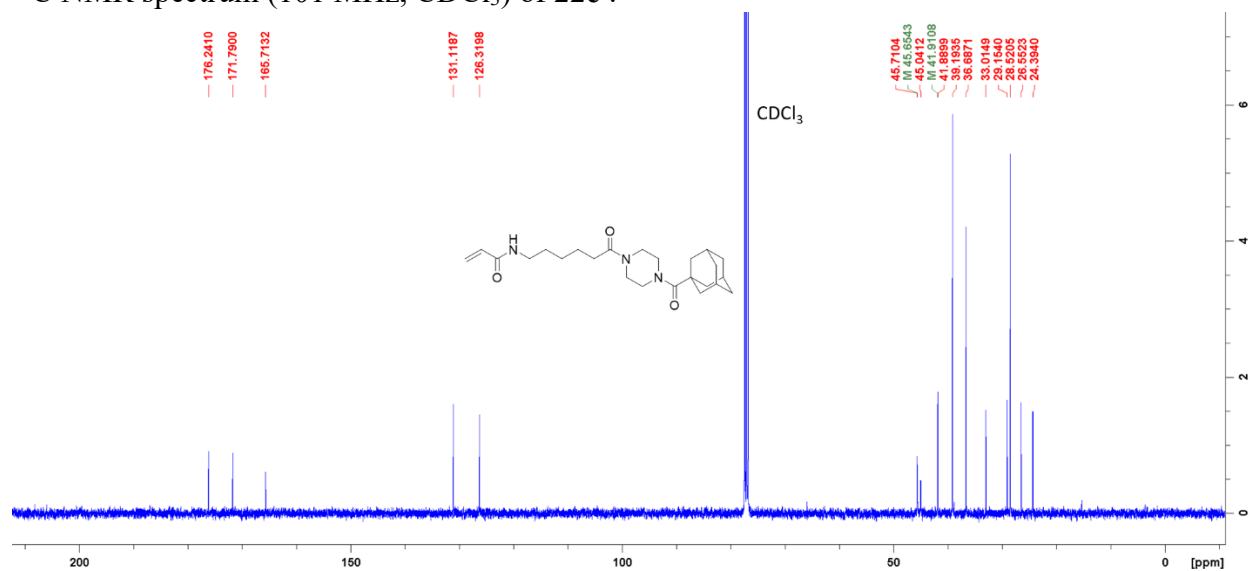
^{13}C NMR spectrum (101 MHz, CDCl_3) of **22d** :



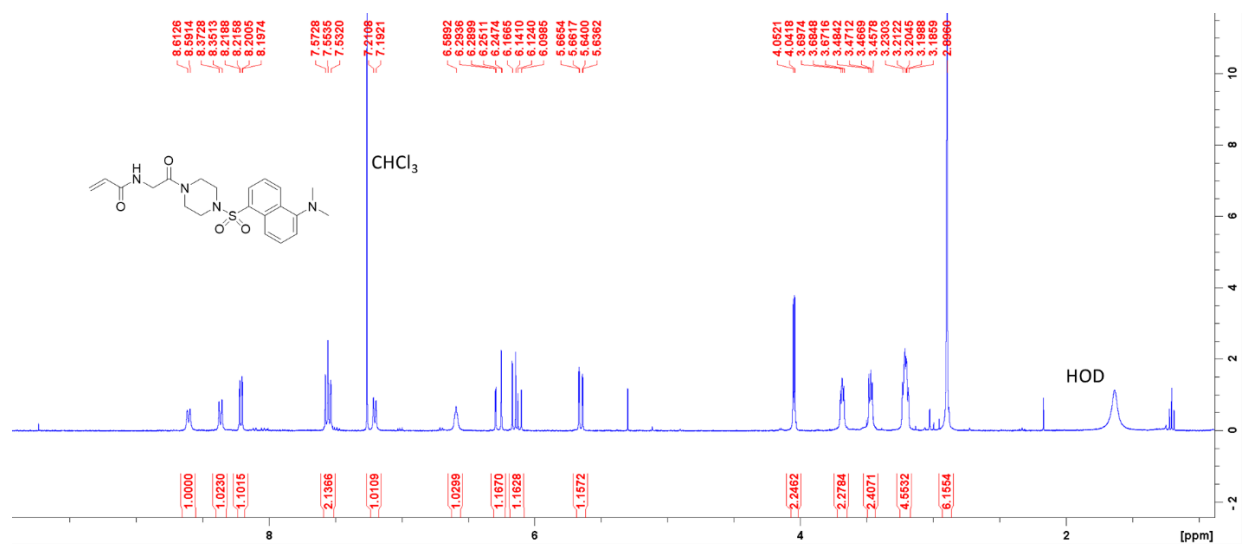
^1H NMR spectrum (400 MHz, CDCl_3) of **22e** :



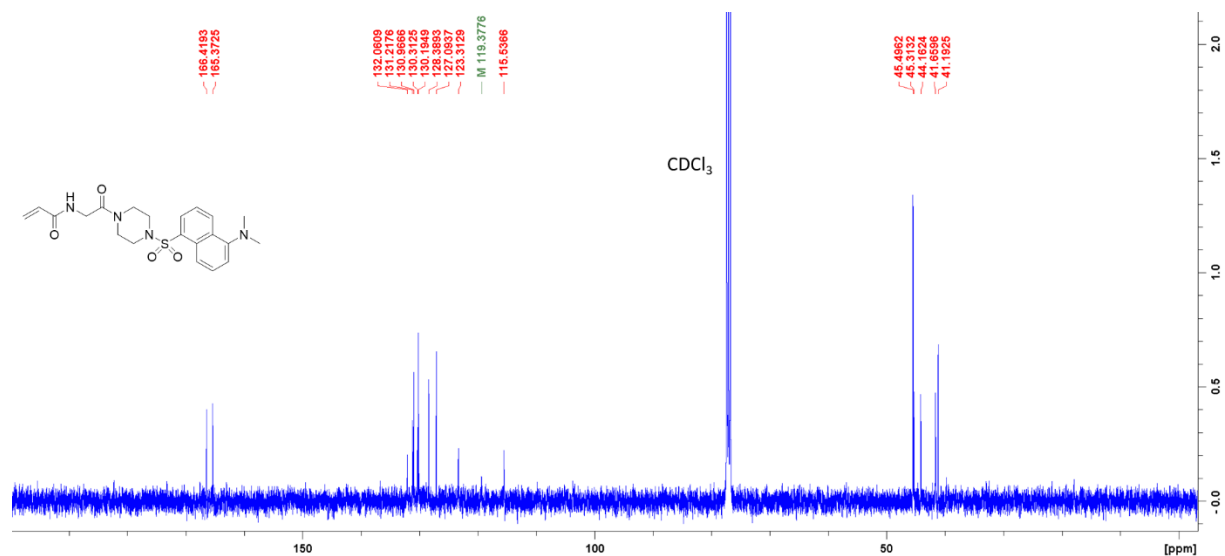
^{13}C NMR spectrum (101 MHz, CDCl_3) of **22e** :



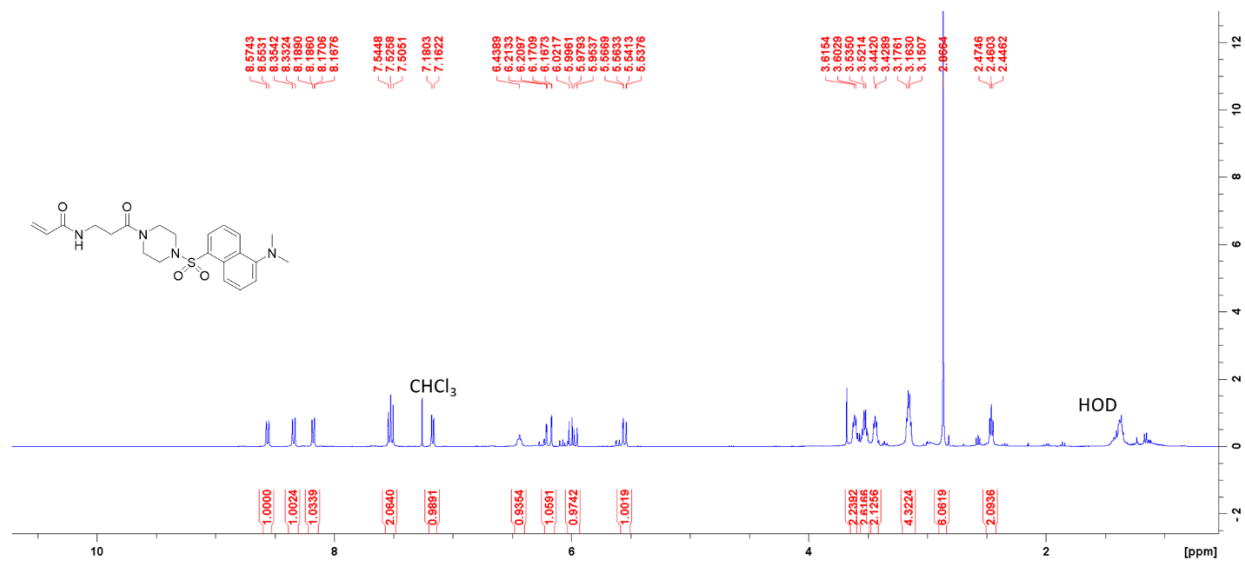
^1H NMR spectrum (400 MHz, CDCl_3) of **23a** :



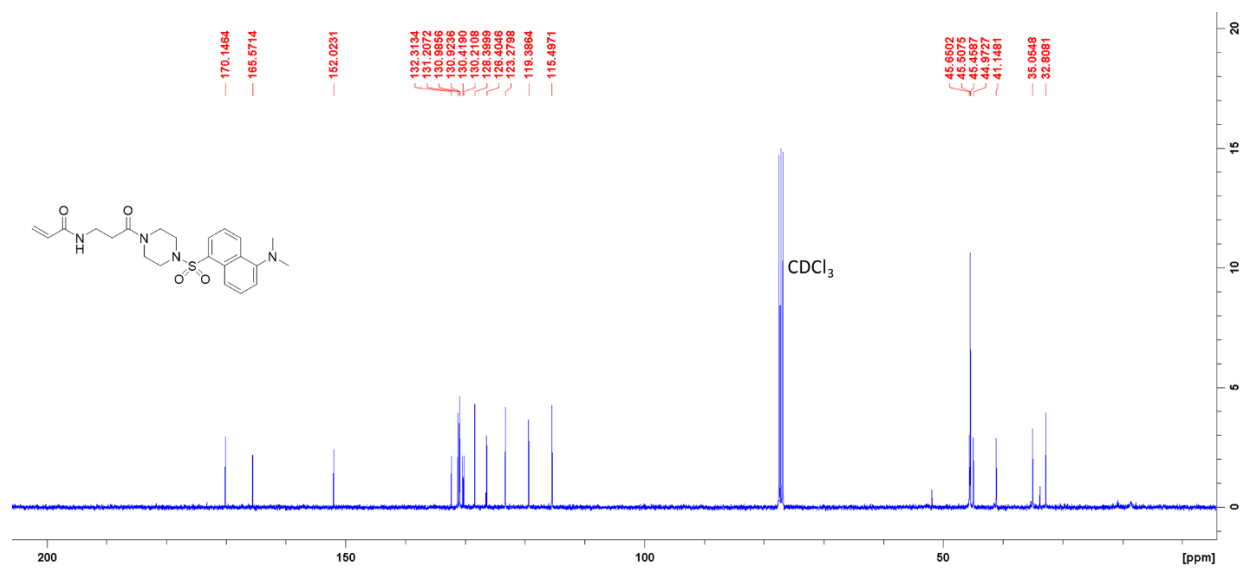
^{13}C NMR spectrum (101 MHz, CDCl_3) of **23a** :



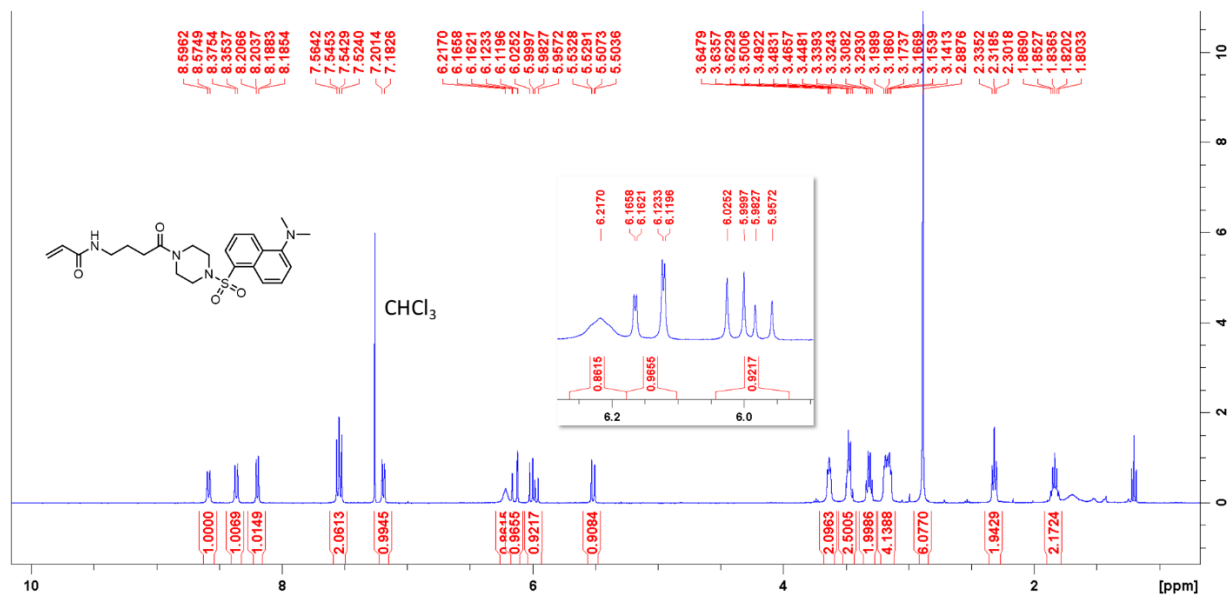
¹H NMR spectrum (400 MHz, CDCl₃) of **23b**:



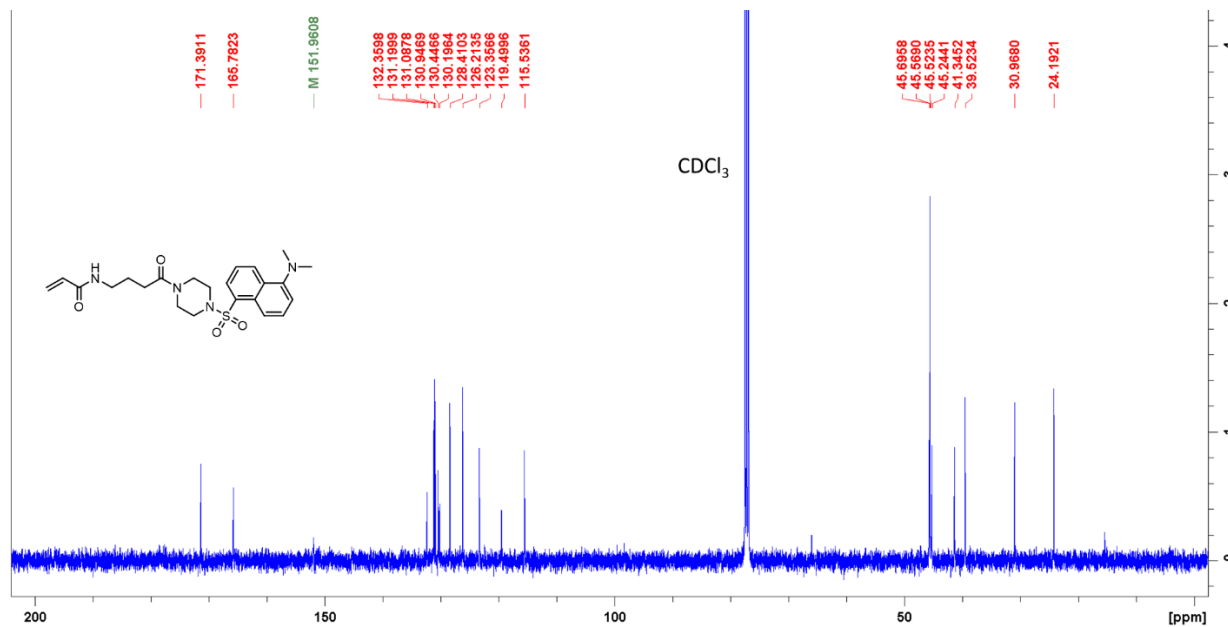
¹³C NMR spectrum (101 MHz, CDCl₃) of **23b**:



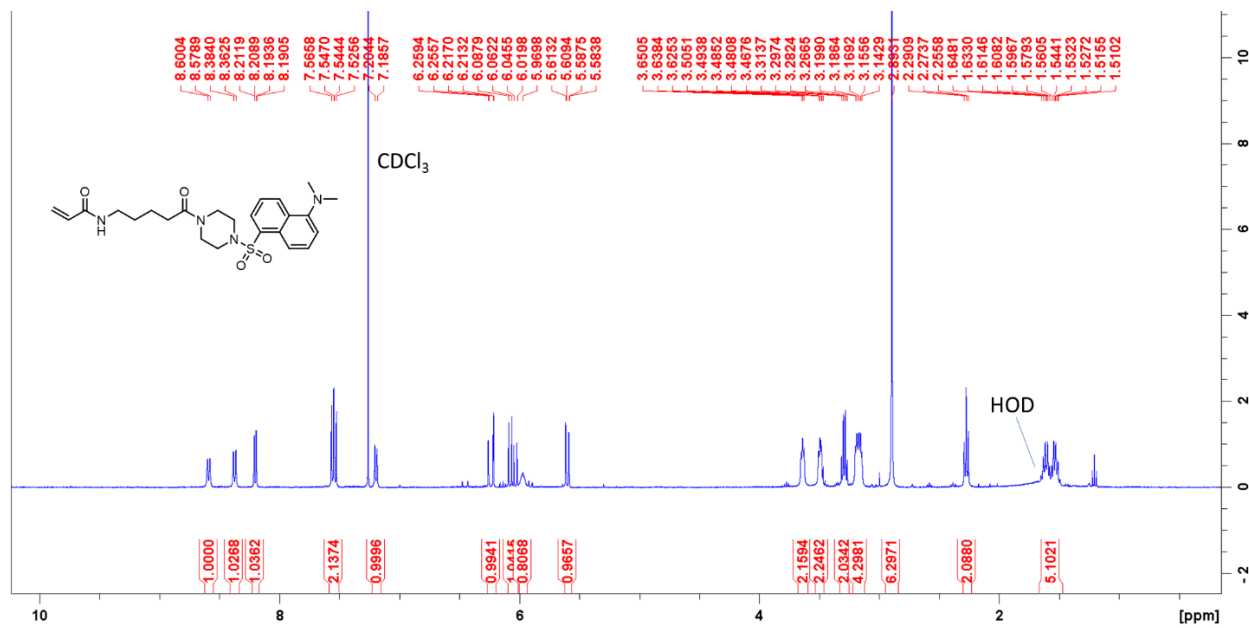
¹H NMR spectrum (400 MHz, CDCl₃) of **23c**:



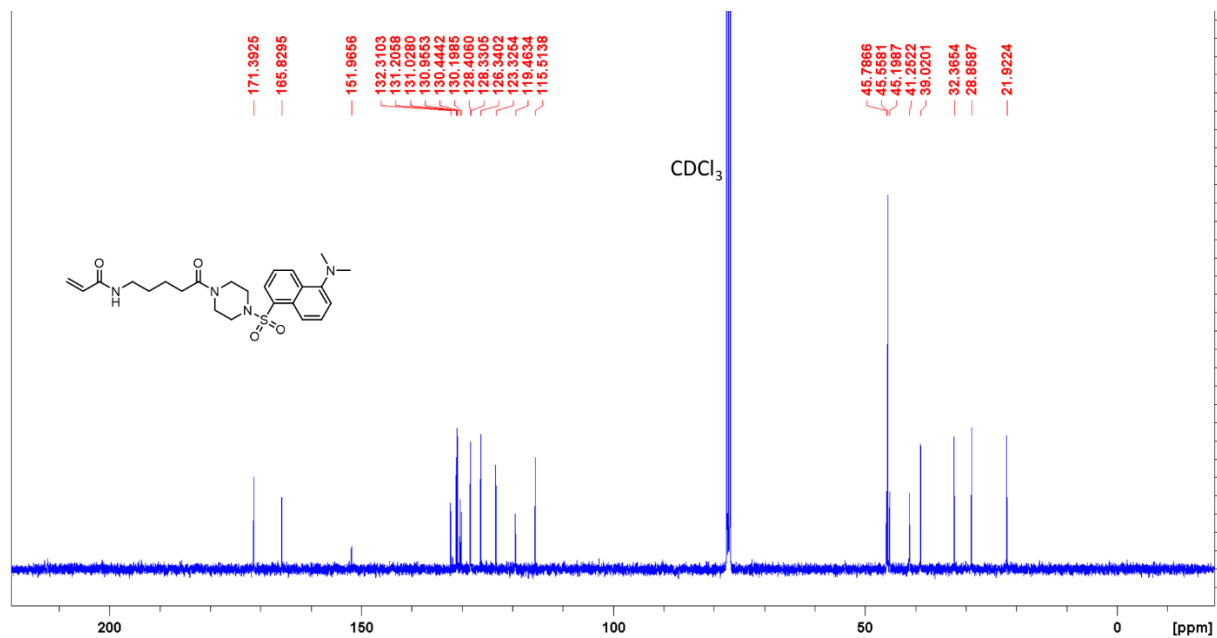
¹³C NMR spectrum (101 MHz, CDCl₃) of **23c**:



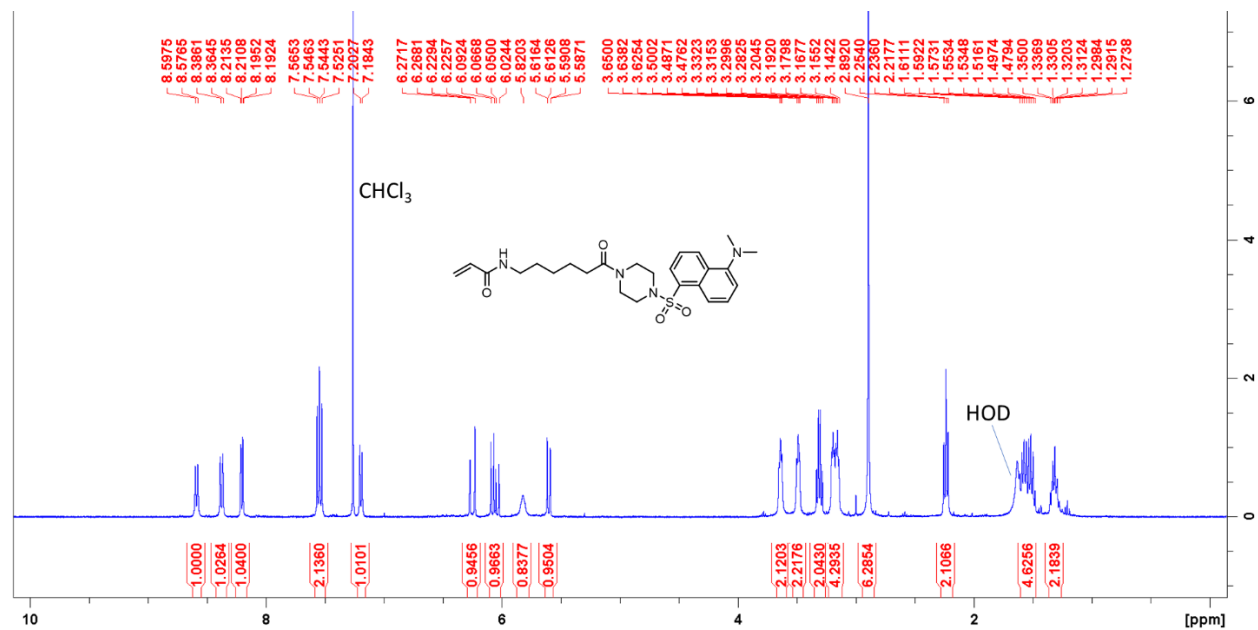
¹H NMR spectrum (400 MHz, CDCl₃) of **23d**:



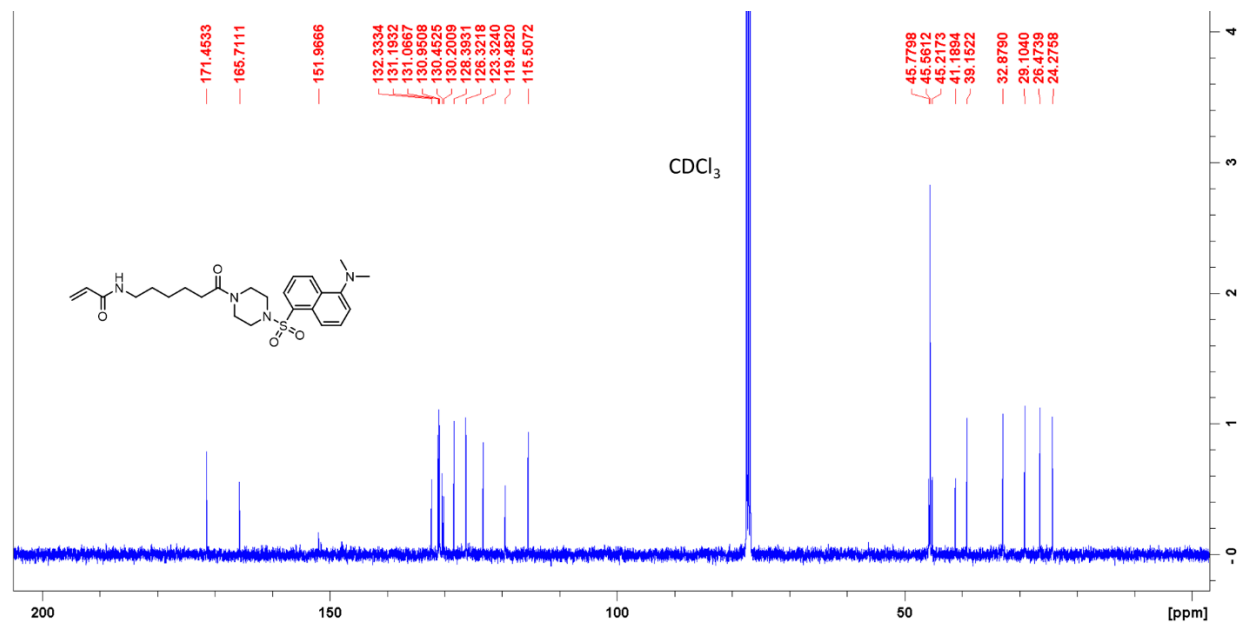
¹³C NMR spectrum (101 MHz, CDCl₃) of **23d**:



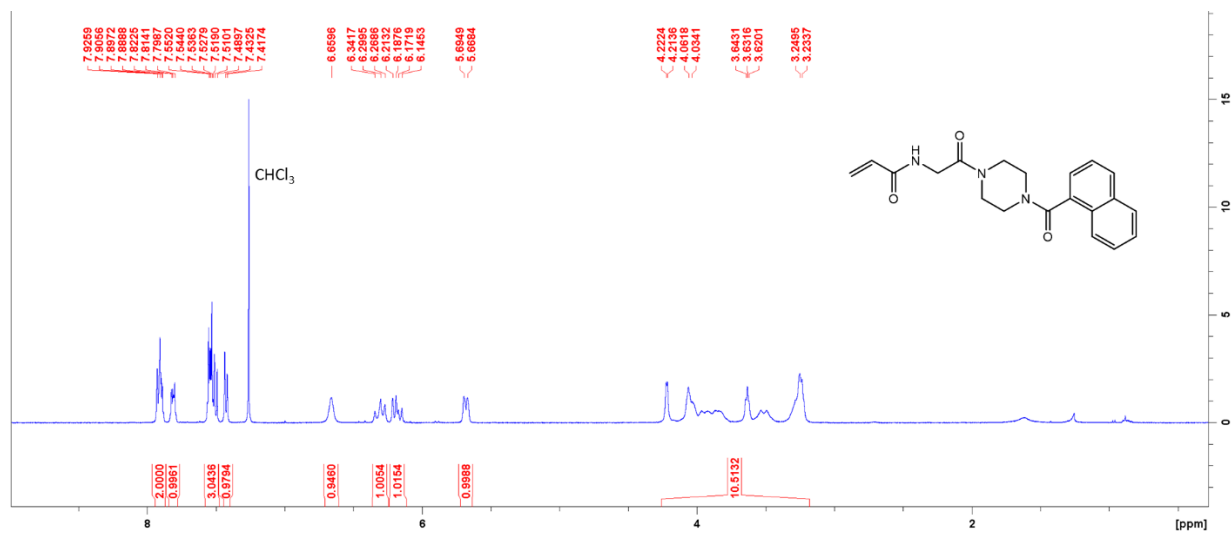
^1H NMR spectrum (400 MHz, CDCl_3) of **23e**:



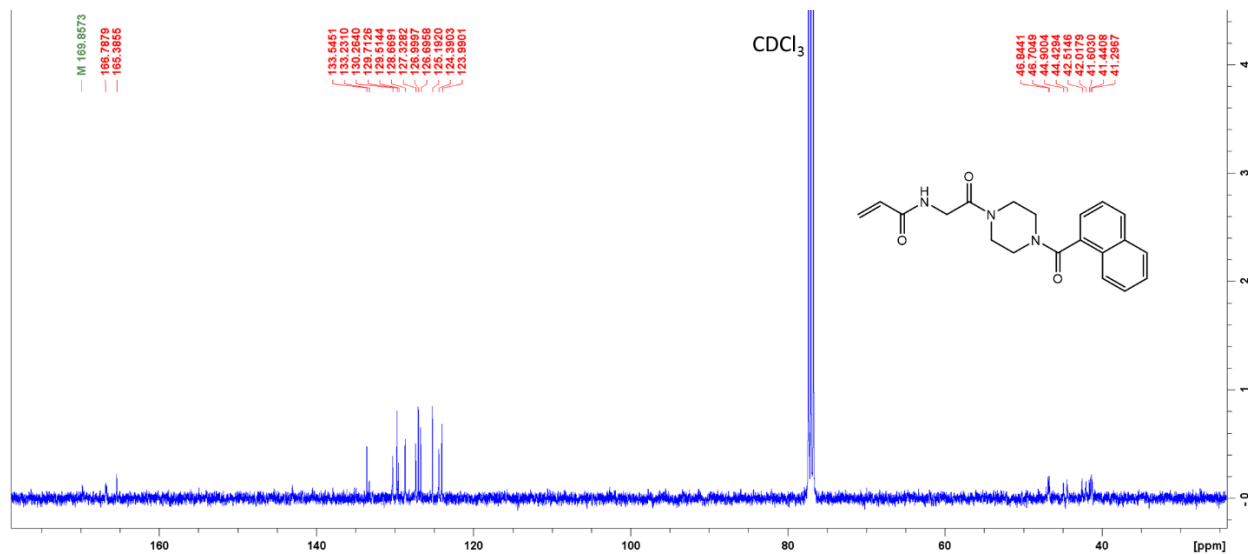
^{13}C NMR spectrum (101 MHz, CDCl_3) of **23e**:



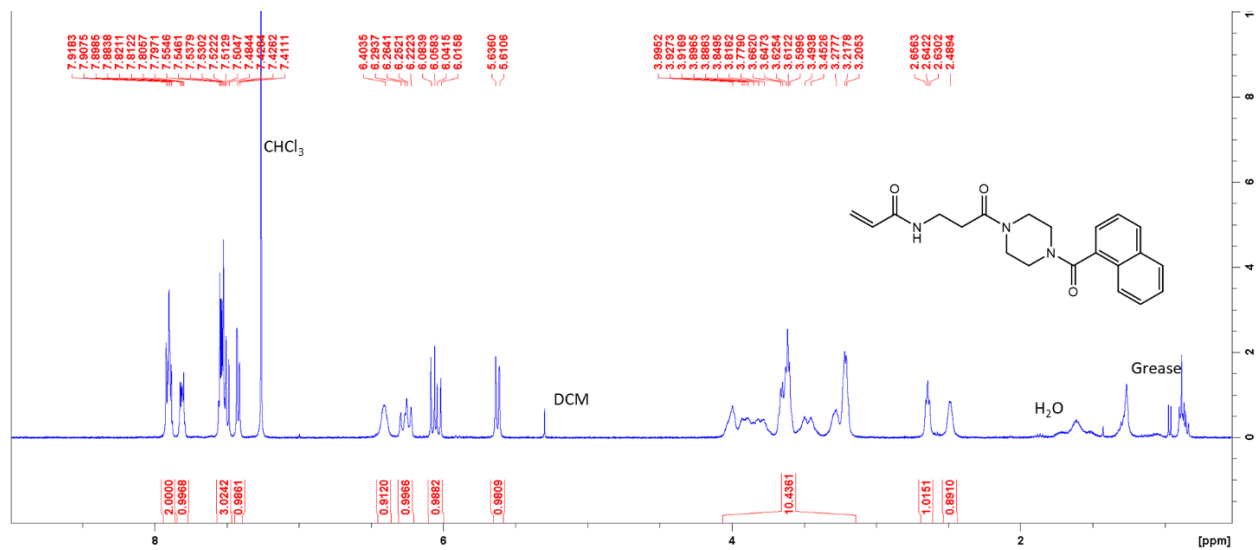
^1H NMR spectrum (400 MHz, CDCl_3) of **24a**:



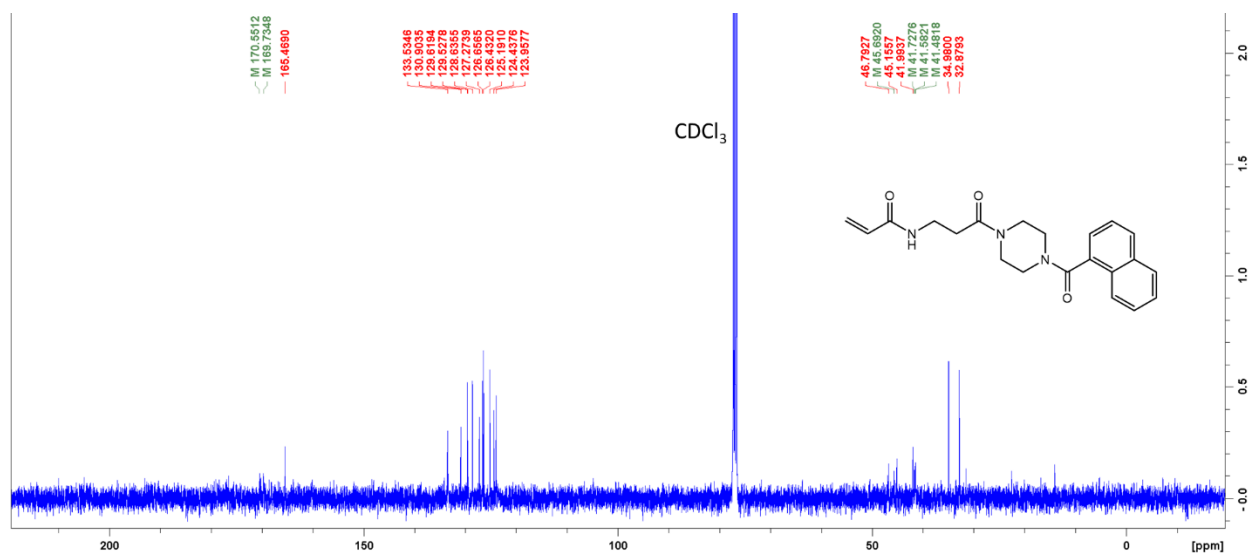
^{13}C NMR spectrum (101 MHz, CDCl_3) of **24a**:



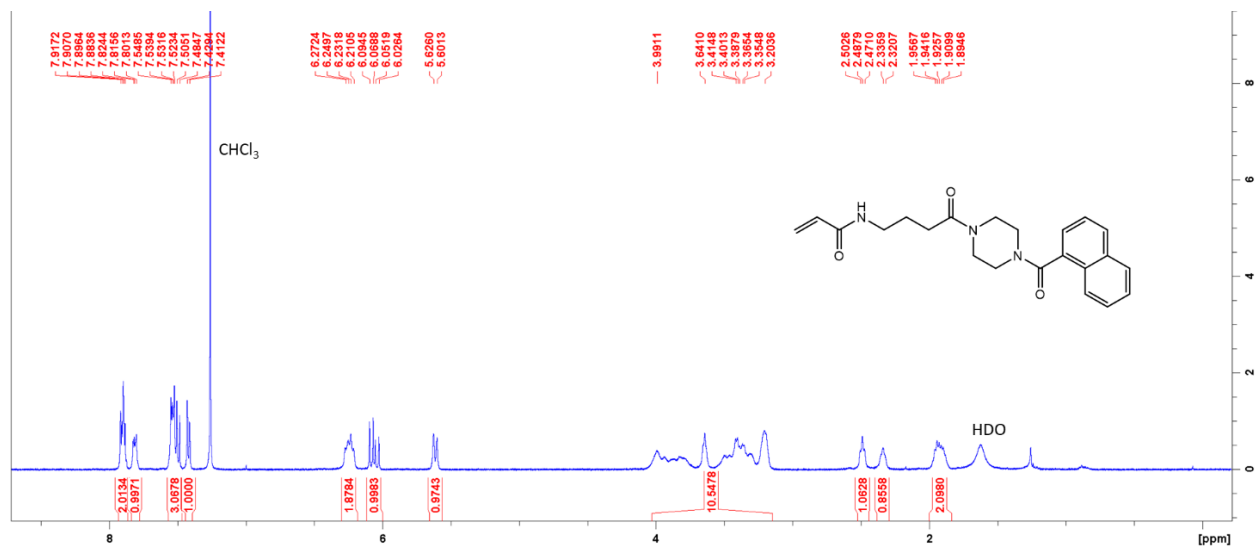
^1H NMR spectrum (400 MHz, CDCl_3) of **24b**:



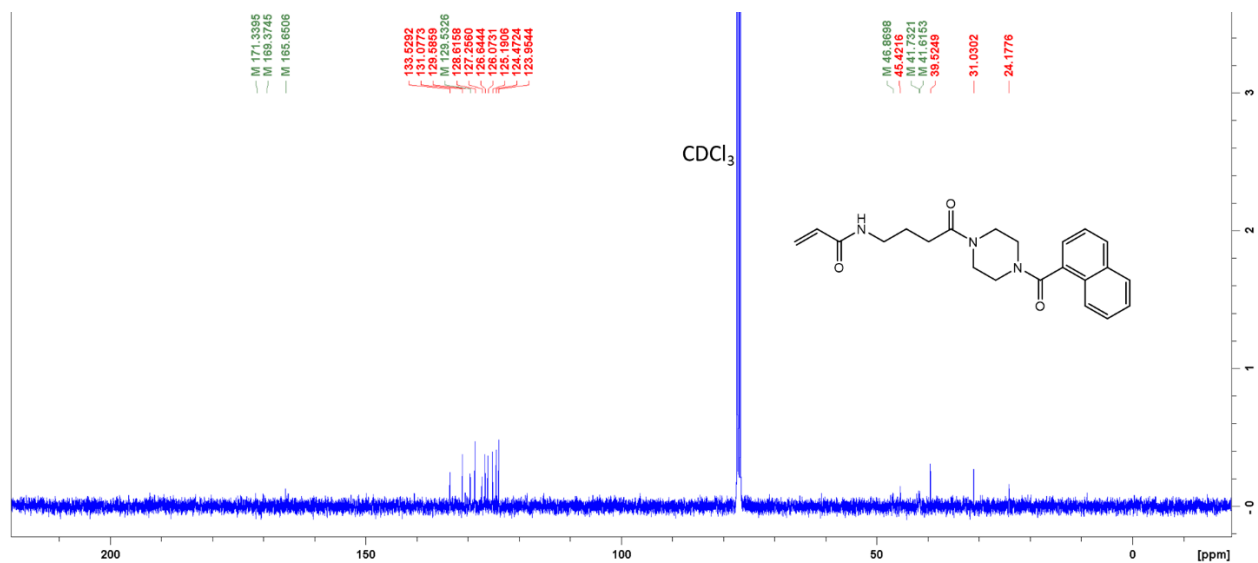
^{13}C NMR spectrum (101 MHz, CDCl_3) of **24b**:



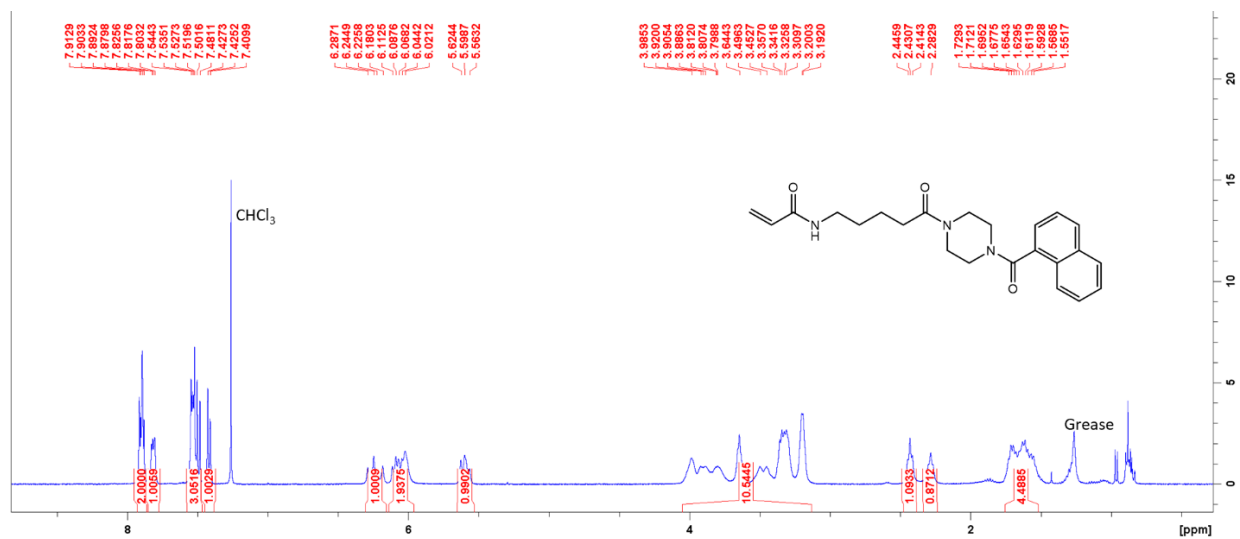
^1H NMR spectrum (400 MHz, CDCl_3) of **24c**:



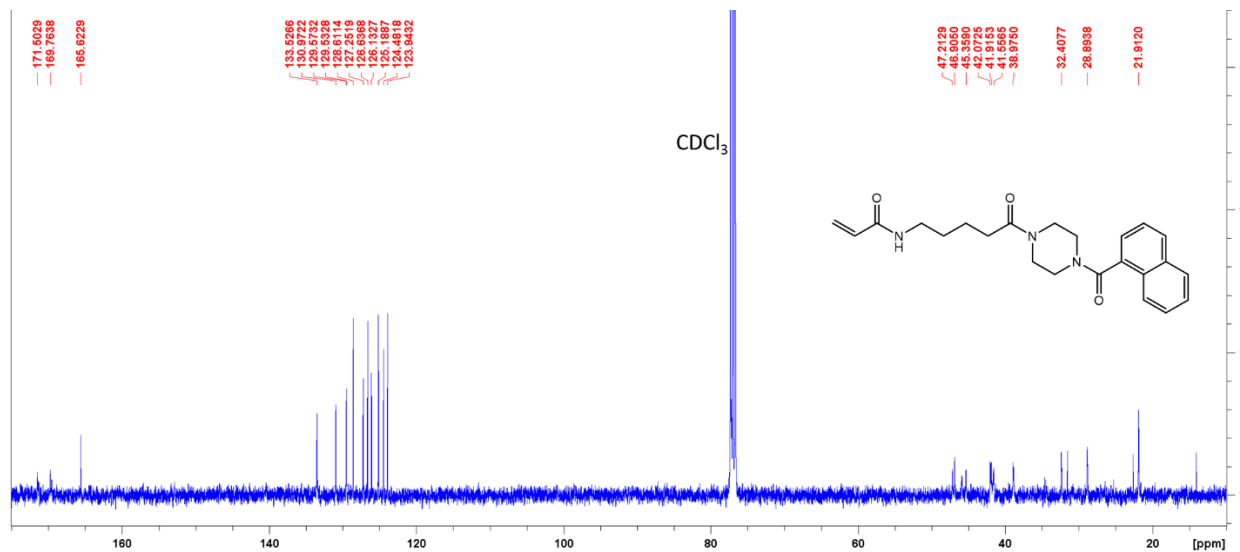
^{13}C NMR spectrum (101 MHz, CDCl_3) of **24c**:



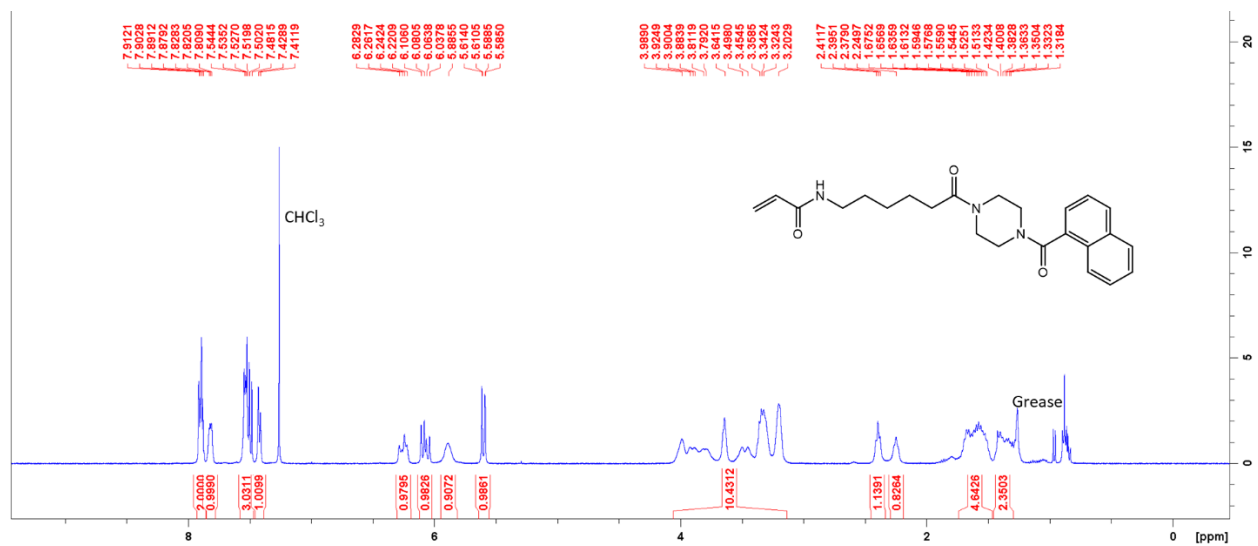
^1H NMR spectrum (400 MHz, CDCl_3) of **24d**:



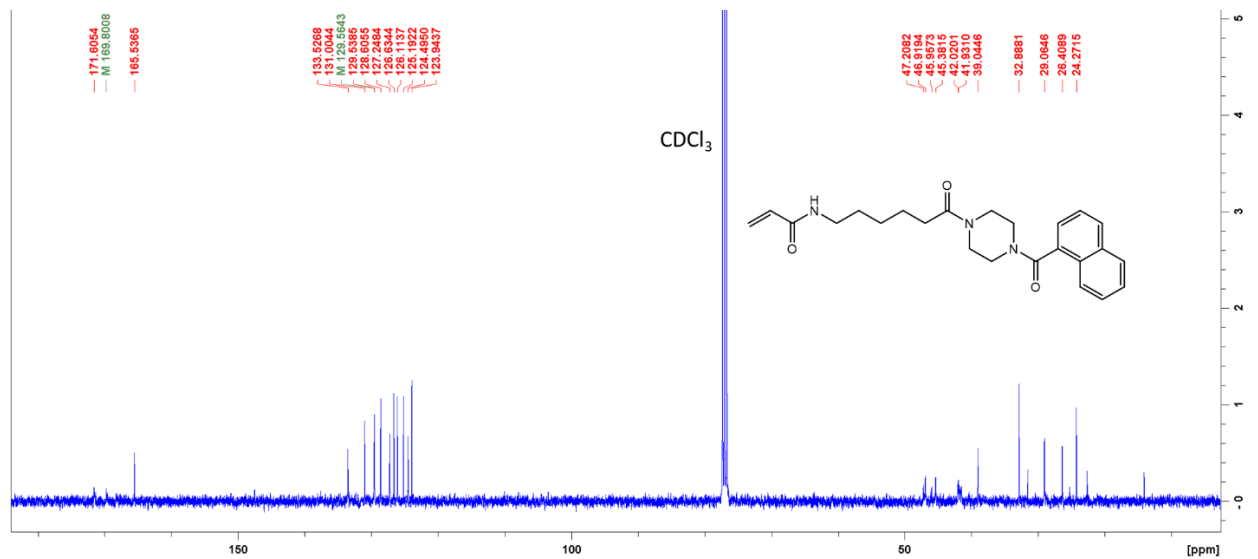
^{13}C NMR spectrum (101 MHz, CDCl_3) of **24d**:



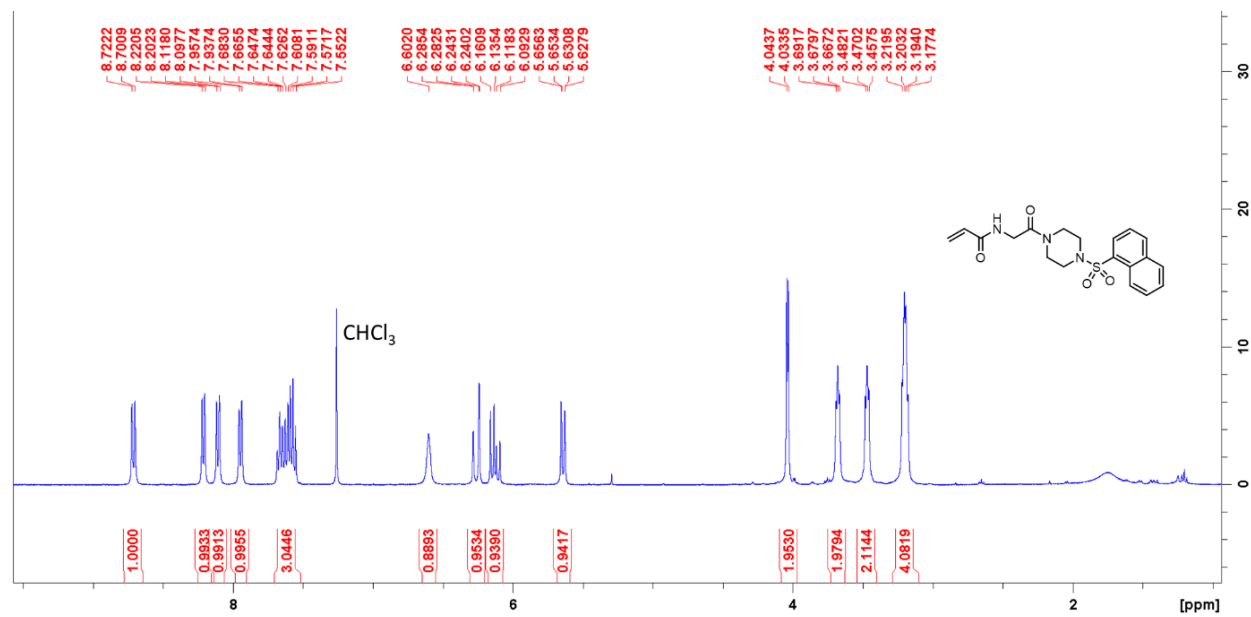
^1H NMR spectrum (400 MHz, CDCl_3) of **24e**:



^{13}C NMR spectrum (101 MHz, CDCl_3) of **24e**:



^1H NMR spectrum (400 MHz, CDCl_3) of **25a**:



^{13}C NMR spectrum (101 MHz, CDCl_3) of **25a**:

