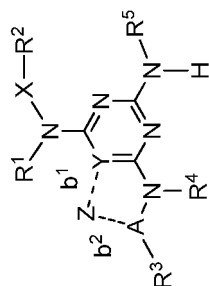


Fig. 1

Total # of Compounds = 4 (in both RLM & HLM)				Total # of Compounds = 8 (in both RLM & HLM)			
	Volume	Final Concentration	Unit		Volume	Final Concentration	Unit
potassium phosphate buffer	10 mL	100	mM		20 mL	100	mM
MgCl ₂	20 μ L of 1 M stock	1.5	mM		40 μ L of 1 M stock	1.5	mM
	Mix and aliquot 3.0 mL into Falcon tubes				Mix and aliquot 3.0 mL into Falcon tubes		
Compound	4 μ L of 5 mM stock	5	μ M		4 μ L of 5 mM stock	5	μ M
	Divide 300 μ L into cluster tubes				Divide 300 μ L into cluster tubes		
HLM (or RLM)	Dilute 20 mg/mL 5X (100 μ L 20 mg/mL stock + 400 μ L potassium phosphate buffer)				Dilute 20 mg/mL 5X (200 μ L 20 mg/mL stock + 800 μ L potassium phosphate buffer)		
	50 μ L of 4 mg/mL	0.5	mg/mL		50 μ L of 4 mg/mL	0.5	mg/mL
	50 μ L of 8 mM	1	mM		50 μ L of 8 mM	1	mM
8 mM NADPH	Prepare a minimum of 750 μ L solution				Prepare a minimum of 1,500 μ L solution		
Total volume (μ L)	400 μ L				400 μ L		

Fig. 2A

Cmpd #	R ¹	X	R ²	R ³ A=bond (except as noted)	R ⁴	R ⁵	Y Z=nil (except as noted)	V _E Peak (% Inc.)	MV Inc. AUC (2 min) vs. std**	RLM T ½ (min)	HLM T ½ (min)
5a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	143	1.45*	110	214
5b	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	nd	nd	74	180
7a	CH ₃	bond	H	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	85	0.78*	130	132
9a	CH ₂ C ₆ H ₄ pF	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	0	0.01	4	25
12a	CH ₂ C ₆ H ₄ pF	bond	H	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	110	0.47	4	20
14a	CH ₃	O	CH ₃	CH ₂ C ₆ H ₄ pF	H	CH ₂ C≡CH	N	3	0.03	12	63
16a	CH ₂ C ₆ H ₄ pF	O	CH ₃	CH ₂ C ₆ H ₄ pF	H	CH ₂ C≡CH	N	0	0.00	30	63
19a	CH ₂ C ₆ H ₄ pF	bond	H	CH ₂ C ₆ H ₄ pF	H	CH ₂ C≡CH	N	11	0.12	11	73
22a	CH ₂ C ₆ H ₄ pF	bond	H	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ CH ₃	N	116	2.80*	2	27
24a	CH ₂ C ₆ H ₄ pF	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ CH ₃	N	125	1.55*	6	29
27a	CH ₃	O	CH ₃	CH ₂ C≡CH	H	CH ₂ C≡CH	N	1	0.00*	302	374
29a	CH ₃	bond	H	CH ₂ C≡CH	H	CH ₂ C≡CH	N	1	0.03*	451	367
31a	CH ₂ C ₆ H ₄ pF	bond	H	CH ₂ C≡CH	H	CH ₂ C≡CH	N	10	0.04*	14	63
33a	CH ₂ C ₆ H ₄ pF	bond	H	CH ₂ CH ₂ CH ₃	H	CH ₂ C ₆ H ₄ pF	N	206	3.64*	6	34
37a	H	O	C ₆ H ₄ pF	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	4	0.04	7	55
40a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	C(CH ₃) ₂ C≡CH	N	14	0.03	40	97
43a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡C-CH ₃	N	51	0.15	36	153

Fig. 2B

Cmpd #	R ¹	X	R ²	R ³ A=bond (except as noted)	R ⁴	R ⁵	Y Z=nil (except as noted)	V _E Peak (% Inc.)	MV Inc. AUC (2 min) vs. std**	RLM T ½ (min)	HLM T ½ (min)
50a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	CH	125	0.59	11	90
51a	CH ₃	O	CH ₃	CH ₂ C≡CH	H	CH ₂ CH ₂ CH ₃	CH	149	0.49	15	105
55a	CH ₃	O	CH ₃	CH ₃	H	CH ₂ C≡CH	N	3	0.02	500+	346
58a	CH ₃	O	CH ₃	CH ₂ CH ₃	H	CH ₂ C≡CH	N	9	0.06	164	255
61a	CH ₃	O	CH ₃	CH(CH ₃) ₂	H	CH ₂ C≡CH	N	18	0.03	59	282
64a	CH ₃	O	CH ₃	cyclopropyl	H	CH ₂ C≡CH	N	6	0.04	500+	328
67a	CH ₃	O	CH ₃	(CH ₂) ₃ CH ₃	H	CH ₂ C≡CH	N	98	0.19	35	101
70a	CH ₃	O	CH ₃	cyclobutyl	H	CH ₂ C≡CH	N	28	0.11	70	237
73a	CH ₃	O	CH ₃	CH ₂ -cyclopropyl	H	CH ₂ C≡CH	N	3	0.01	39	106
76a	CH ₃	O	CH ₃	cyclohexyl	H	CH ₂ C≡CH	N	11	0.02	23	69
79a	CH ₃	O	CH ₃	CH ₂ -cyclohexyl	H	CH ₂ C≡CH	N	0	0.07	3	36
82a	CH ₃	O	CH ₃	CH ₂ Ph	H	CH ₂ C≡CH	N	-1	0.09	11	64
85a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH(CH ₃)C≡CH	N	25	0.08	44	104
88a	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ C≡CH	N	13	0.11	39	205
90a	CH ₃	bond	H	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ C≡CH	N	34	0.33	40	127
92a	H	O	C(CH ₃) ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	5	0.01	60	116
94a	CH ₃	O	CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	79	0.24	25	72
96a	H	O	CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	5	0.05	85	79
98a	H	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	19	0.18	468	500+
99	CH ₃	O	H	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	10	0.00	84	500+
100	H	O	H	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	5	0.05	478	348

Fig. 2C

Cmpd #	R ¹	X	R ²	R ³ A=bond (except as noted)	R ⁴	R ⁵	Y Z=nil (except as noted)	V _E Peak (% Inc.)	MV Inc. AUC (2 min) vs. std**	RLM T ½ (min)	HLM T ½ (min)
102a	CH ₃	O	(CH ₂) ₂ OCH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	51	0.15	37	202
104a	CH ₃	O	(CH ₂) ₃ CF ₂ CF ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	80	0.37	4	28
107a	H	bond	C ₆ H ₄ pF	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	1	0.01	16	38
109a	H	bond	CH ₂ C ₆ H ₃ (2-Me-3-Cl)	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	85	0.94	5	26
111a	H	bond	CH ₂ C ₆ H ₃ (3,4-diCl)	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	114	0.65	4	26
114a	CH ₃	O	CH ₃	H A=C, b ¹ =single bond, b ² =double bond	H	CH ₂ C≡CH	C Z=CH	114	0.42	130	500+
116a	CH ₂ C≡CH	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ CH ₃	N	11	0.05	58	211
118a	CH ₂ C≡CH	O	CH ₃	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	30	0.13	101	242
120a	CH ₃	O	CH ₂ C≡CH	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ CH ₃	N	58	0.12	24	105
122a	H	O	CH ₂ C≡CH	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₂ CH ₃	N	-1	0.00	53	154
124a	CH ₃	O	CH ₂ C≡CH	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	32	0.09	63	132
126a	H	O	CH ₂ C≡CH	CH ₂ CH ₂ CH ₃	H	CH ₂ C≡CH	N	11	0.09	124	500+
129a	CH ₃	O	CH ₃	CH ₂ CH=CH ₂	H	CH ₂ C≡CH	N	19	0.08	500+	500+
130	CH ₃	O	CH ₃	CH ₂ CH(OH)CH ₃	H	CH ₂ C≡CH	N	-2	0.02	500+	457
131	CH ₃	O	CH ₃	CH ₂ CH ₂ CH ₂ OH	H	CH ₂ C≡CH	N	2	0.03	500+	500+

* N-[4,6-di-(*n*-propylamino)-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine used as comparator compound; all other compounds were compared to N-[2,6-di-(*n*-propylamino)-[1,3]pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine.

Fig. 2D

CMPD #	GLN #	Test CMPD % V_E Inc 0.3 mg/kg IV	Ref cmpd #1 % VE Inc 0.3 mg/kg IV	Ref cmpd #2 % VE Inc 0.3 mg/kg IV	2-min VE AUC ratio vs Ref cmpd #1	2-min VE AUC ratio vs Ref cmpd #2
5a	21,160	143	102		1.45	
7a	21,161	85	138		0.775	
9a	21,169	-0.09		143		0.005
12a	21,168	110		146		0.469
14a	21,170	2.5		141		0.032
16a	21,172	-0.36		170		0.001
19a	21,167	11		135		0.122
22a	21,139	116	83		2.800	
24a	21,158	125	87		1.55	
27a	21,149	1	112		0.003	
29a	21,150	0.8	150		0.030	
31a	21,157	10	67		0.044	
33a	21,151	206	195		3.64	
37a	21,202	3.9		141		0.044
40a	21,199	14		147		0.028
43a	21,200	50.56		151		0.154
50a	21,198	125		140		0.587
51a	21,197	149		265		0.493
55a	21,226	2.5		145		0.022
58a	21,227	9.1		121		0.061
61a	21,224	17.65		158		0.025
64a	21,230	6.2		124		0.038
67a	21,228	97.7		135		0.186
70a	21,225	27.96		167		0.111
73a	21,231	3		157		0.005

Fig. 2E

CMPD #	GLN #	Test CMPD % V_E Inc 0.3 mg/kg IV	Ref cmpd #1 % VE Inc 0.3 mg/kg IV	Ref cmpd #2 % VE Inc 0.3 mg/kg IV	2-min VE AUC ratio vs Ref cmpd #1	2-min VE AUC ratio vs Ref cmpd #2
76a	21,239	11		156		0.015
79a	21,229	0.03		181		0.069
82a	21,232	-1.11		124		0.098
85a	21,208	24.57		134		0.084
88a	21,211	13		122		0.106
90a	21,212	34		132		0.332
92a	21,203	4.59		132		0.014
94a	21,207	78.99		130		0.237
96a	21,210	4.8		137		0.046
98a	21,251	19.12		160		0.175
99	21,248	10		125		0.003
100	21,249	4.66		122		0.050
102a	21,206	51.15		152		0.145
104a	21,215	80.2		128		0.373
107a	21,218	74.1		150		0.337
109a	21,216	85		115		0.938
111a	21,217	113.83		184		0.649
114a	21,242	114		181		0.422
116a	21,234	11.27		181		0.054
118a	21,235	30.43		205		0.125
120a	21,237	58		208		0.116
122a	21,238	-1		205		0.003
124a	21,240	32.48		131		0.086
126a	21,236	10.7		125		0.087
129a	21,244	19.3		132		0.075

Fig. 3

5.0 mg/kg Cmpd 5							
IV	Time (hr)	Conc (ng/mL)			Mean (ng/mL)	SD (ng/mL)	CV (%)
		R875	R876	R877			
	0.0833	3270	4040	3830	3713	398	10.7
	0.25	1870	1890	1680	1813	116	6.39
	0.50	927	732	815	825	97.9	11.9
	1.00	449	294	347	363	78.8	21.7
	2.00	158	102	112	124	29.9	24.1
	4.00	17.7	6.88	11.3	12.0	5.44	45.5
	6.00	3.94	1.29	9.80	5.01	4.35	86.9
	8.00	1.64	1.49	1.79	1.64	0.15	9.1
	24.0	0.00	0.00	0.00	0.00	0.00	NA
30 mg/kg Cmpd 5							
PO	Time (hr)	Conc (ng/mL)			Mean (ng/mL)	SD (ng/mL)	CV (%)
		R872	R873	R874			
	0.25	951	491	1160	867	342	39.5
	0.50	659	376	648	561	160	28.6
	1.00	424	372	368	388	31.2	8.05
	2.00	310	384	207	300	88.9	29.6
	4.00	215	301	94.4	203	104	51.0
	6.00	377	354	169	300	114	38.0
	8.00	246	261	83.9	197	98.2	49.9
	24.0	6.12	0.920	9.25	5.43	4.21	77.5

Fig. 4

IV Administration:			5.00	mg/kg									
Animal	# of Pts for $t_{1/2}$	$t_{1/2}$ (hr)	C_0 (ng/mL)	T_{last} (hr)	C_{last} (ng/mL)	AUC_{last} (hr*ng/mL)	AUC_{int} (hr*ng/mL)	AUC Extr (%)	MRT_{int} (hr)	AUC_{int}/D (hr*ng/mL)	V_z (L/kg)	V_{ss} (L/kg)	CL_p (mL/min/kg)
Rat #875	4.00	0.912	4320	8.00	1.64	1950	1950	0.080	0.685	389	3.38	1.76	42.8
Rat #876	4.00	0.966	5910	8.00	1.49	1810	1820	0.054	0.495	362	3.85	1.37	46.0
Rat #877	4.00	1.10	5780	8.00	1.79	1850	1860	0.160	0.609	370	4.31	1.65	45.0
N	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	4.00	0.993	5337	8.00	1.64	1870	1877	0.098	0.596	374	3.85	1.59	44.6
SD	0.00	0.097	883	0.00	0.150	72.1	66.6	0.055	0.096	13.9	0.465	0.201	1.64
CV%	0.00	9.75	16.5	0.00	9.15	3.86	3.55	56.4	16.0	3.71	12.1	12.6	3.67
Last time point for AUC_{last} : 8.0 hr													
PO Administration:			30.0	mg/kg									
Animal	# of Pts for $t_{1/2}$	$t_{1/2}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr*ng/mL)	AUC_{int} (hr*ng/mL)	AUC Extr (%)	MRT_{int} (hr)	AUC_{int}/D (hr*ng/mL)	F (%)			
Rat #872	3.00	3.02	951	0.25	4720	4740	0.563	5.76	158	42.1			
Rat #873	3.00	2.04	491	0.25	4790	4790	0.058	5.69	160	42.5			
Rat #874	3.00	4.55	1160	0.25	2480	2540	2.34	5.33	85.0	22.6			
N	3	3	3	3	3	3	3	3	3	3			
Mean	3.00	3.20	867	0.25	3997	4023	0.987	5.59	134	35.7			
SD	0.00	1.27	342	0.00	1314	1285	1.20	0.231	42.7	11.4			
CV%	0.00	39.5	39.5	0.00	32.9	31.9	121	4.12	31.8	31.9			
Last time point for AUC_{last} : 24 hr													

Fig. 5

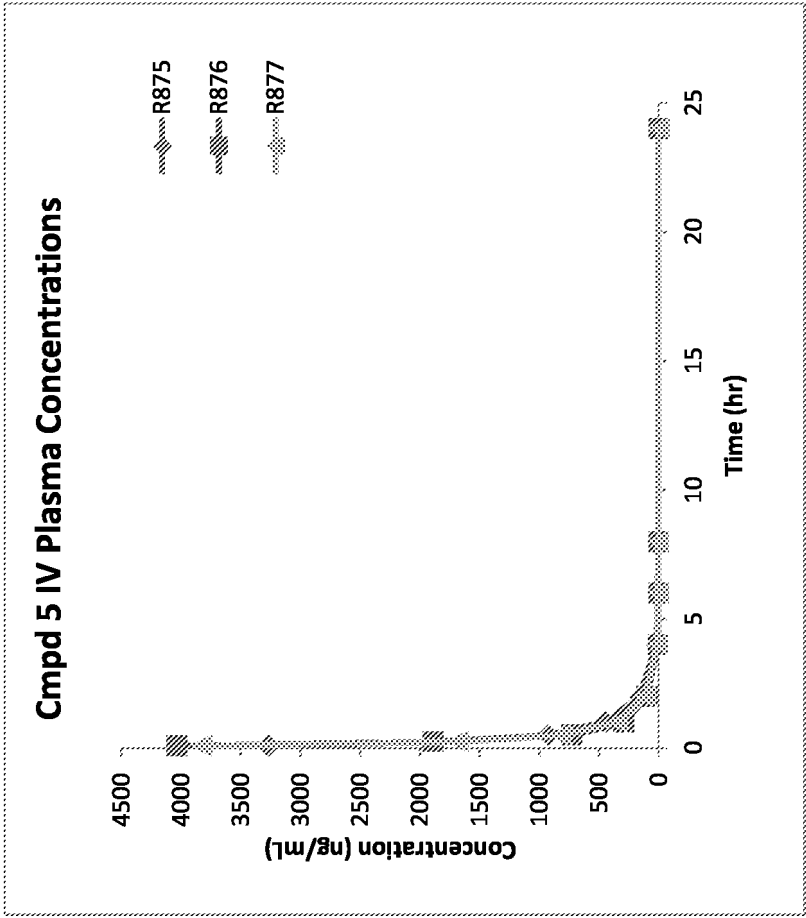


Fig. 6

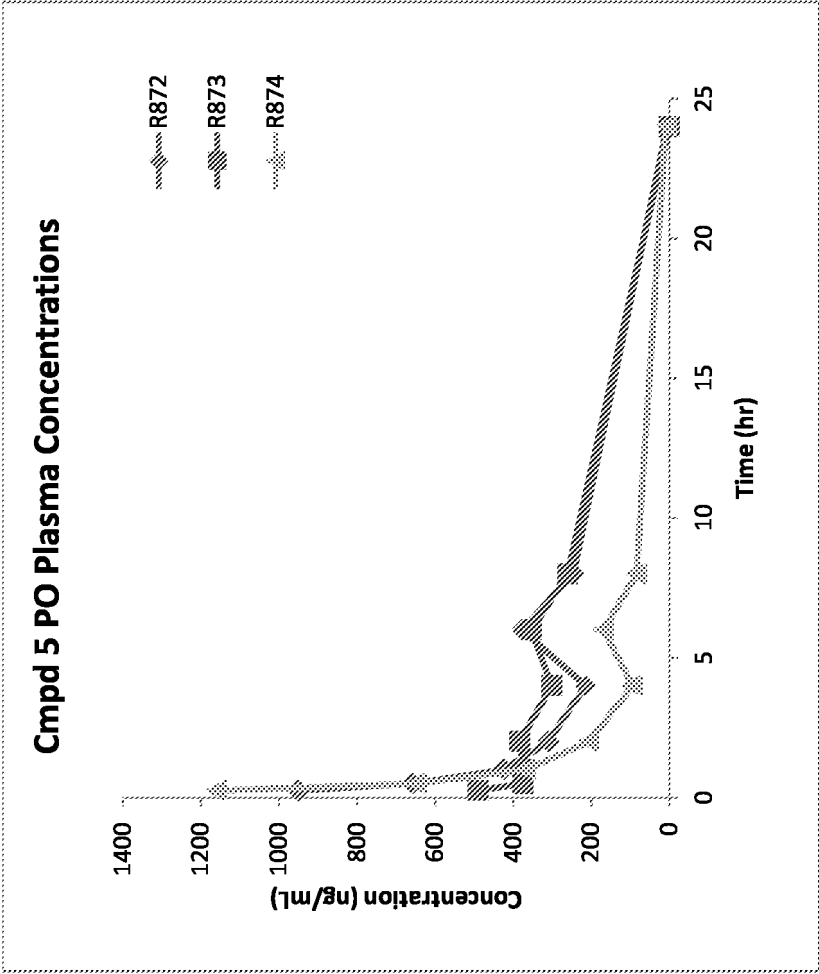


Fig. 7

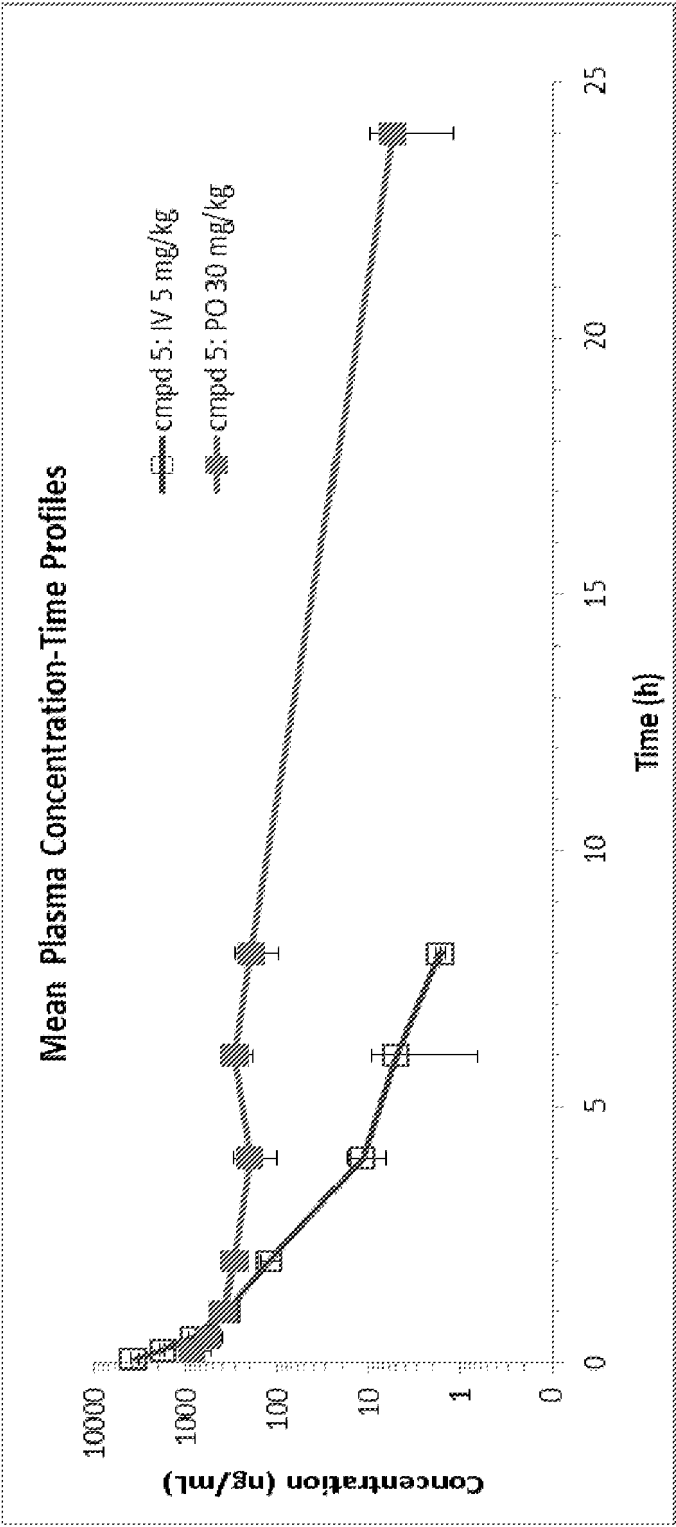


Fig. 8

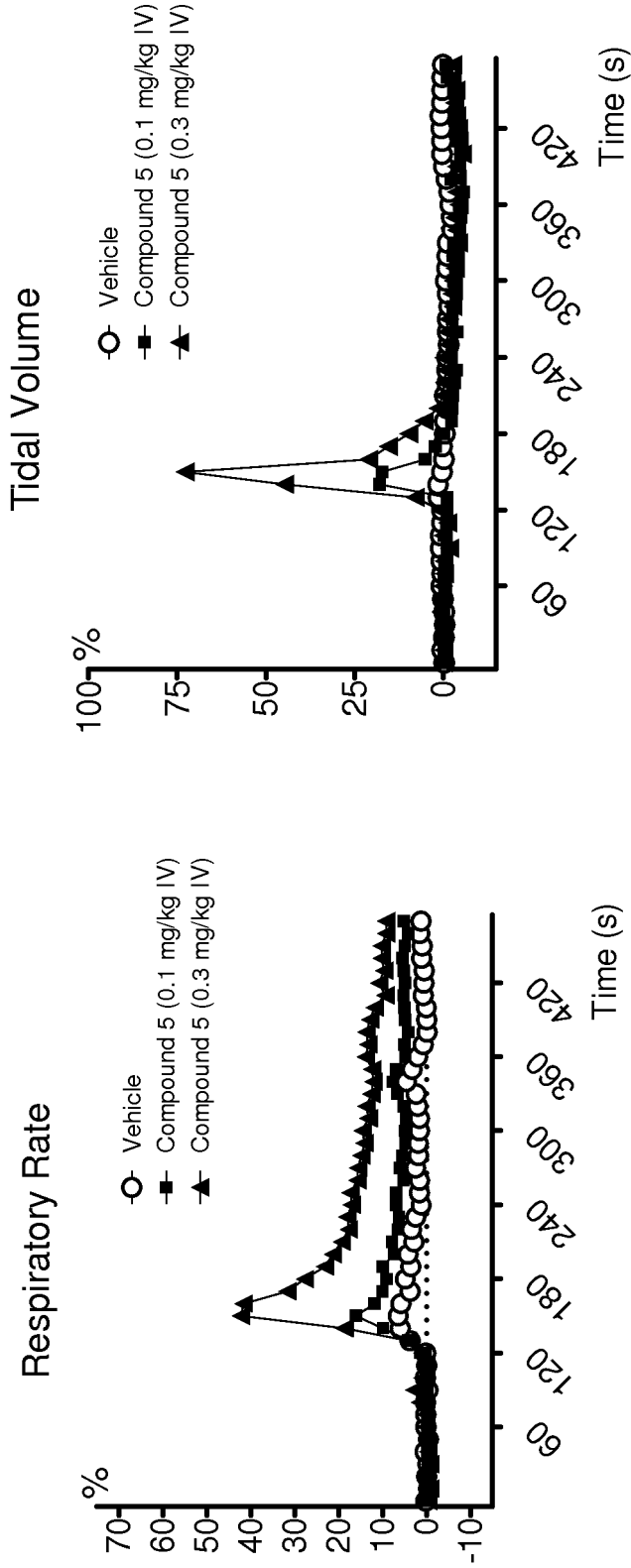


Fig. 9

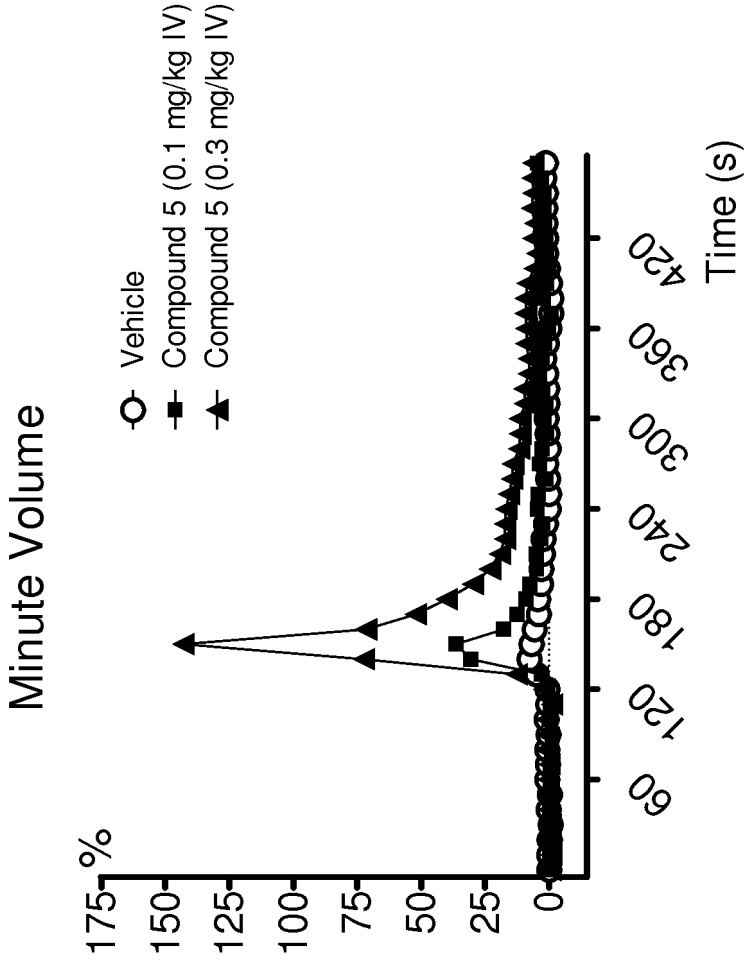


Fig. 10

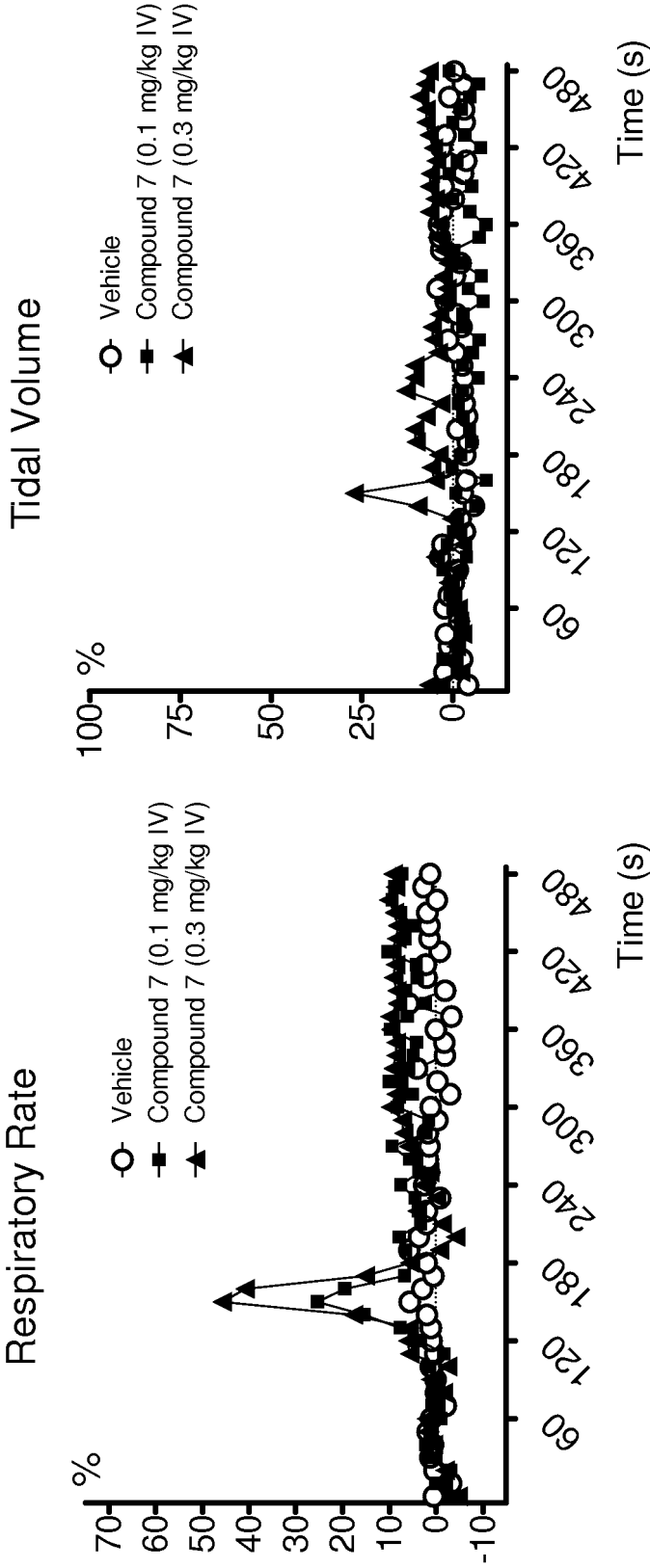


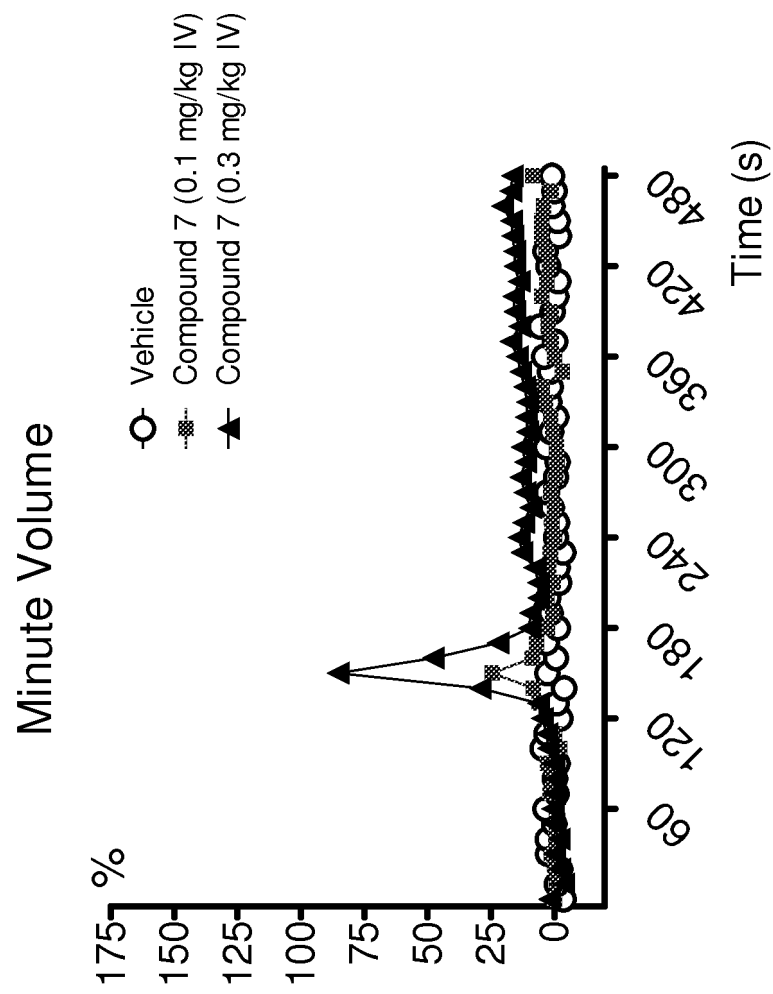
Fig. 11

Fig. 12

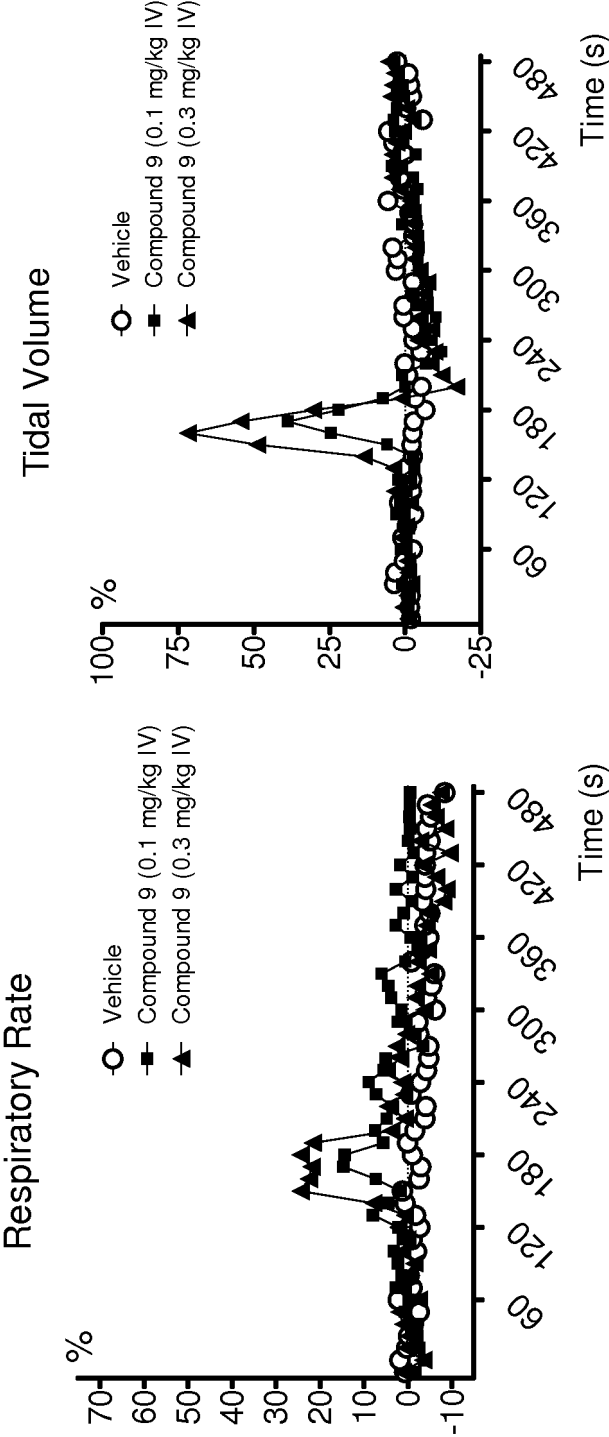


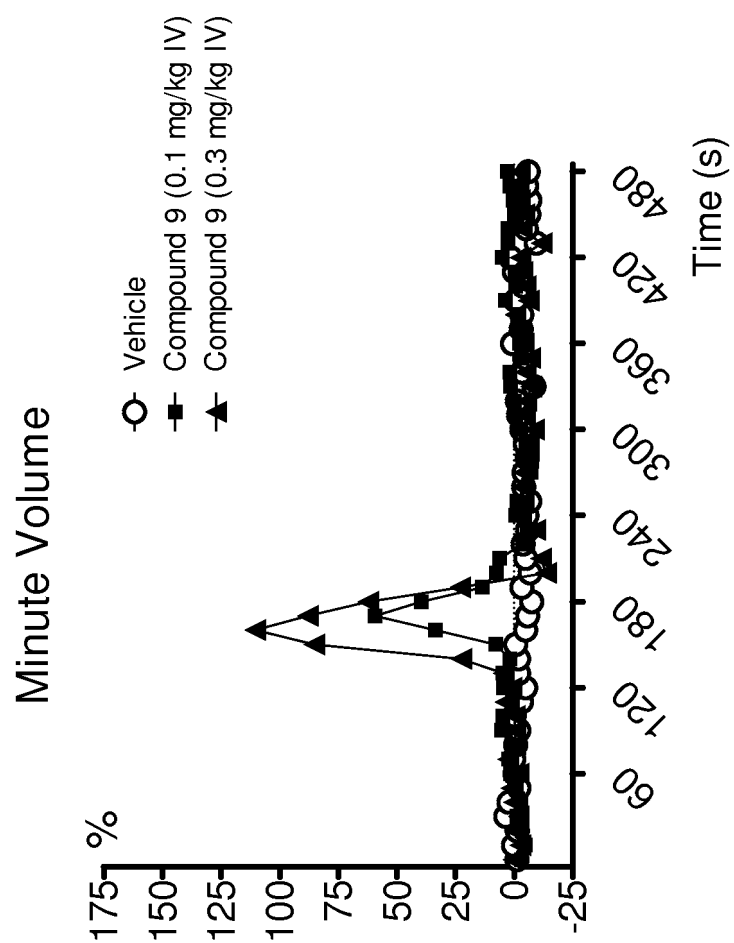
Fig. 13

Fig. 14

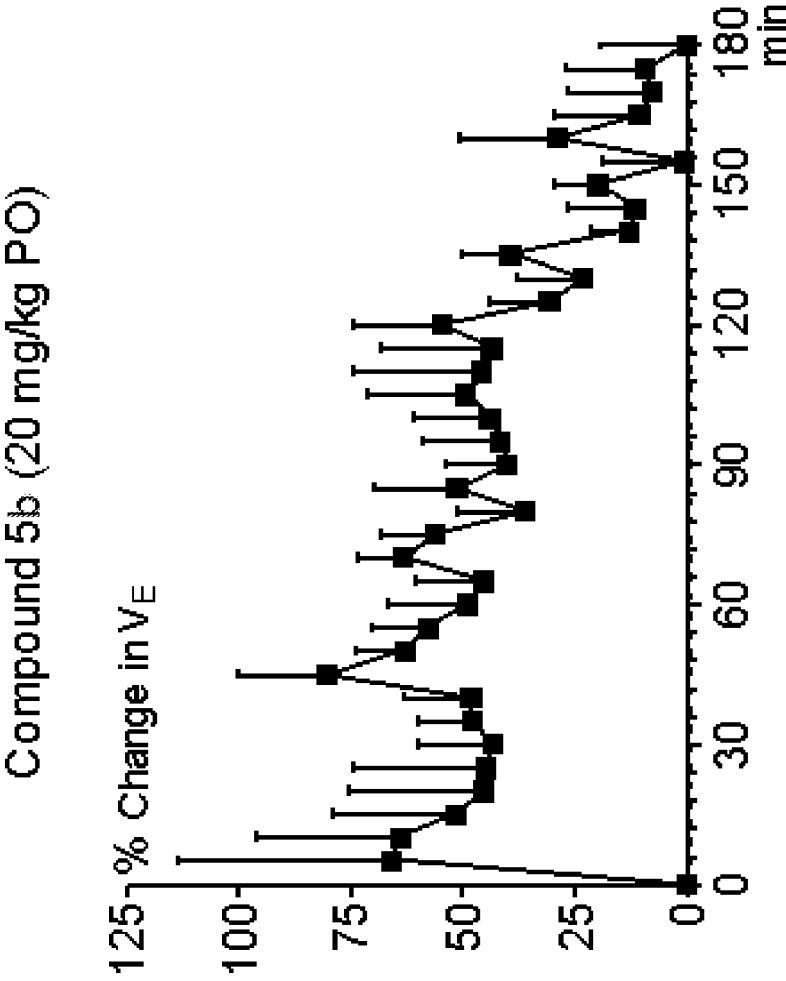
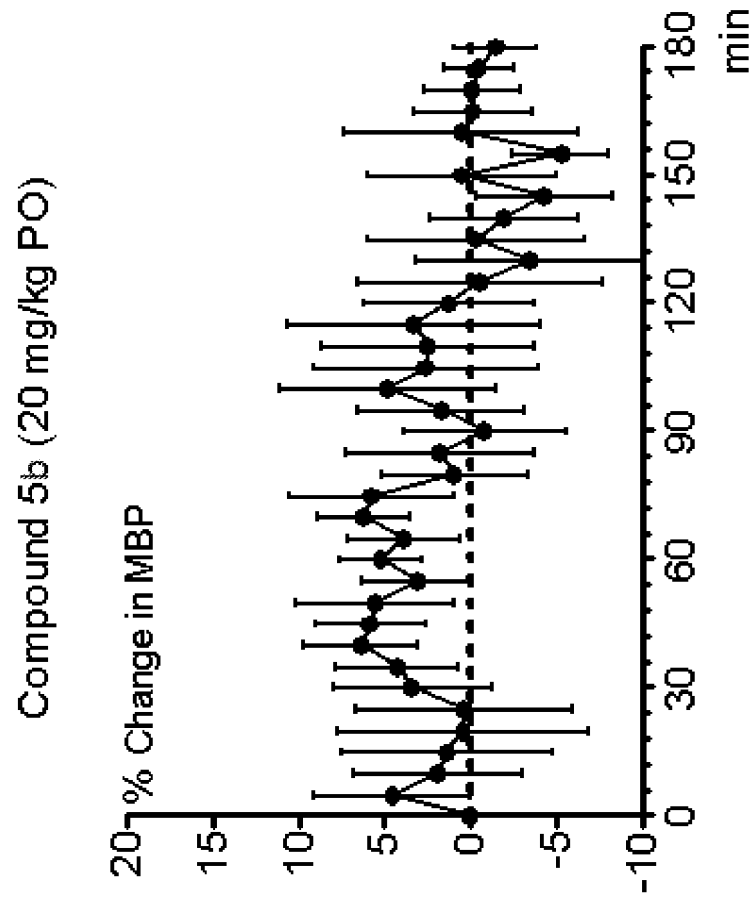


Fig. 15



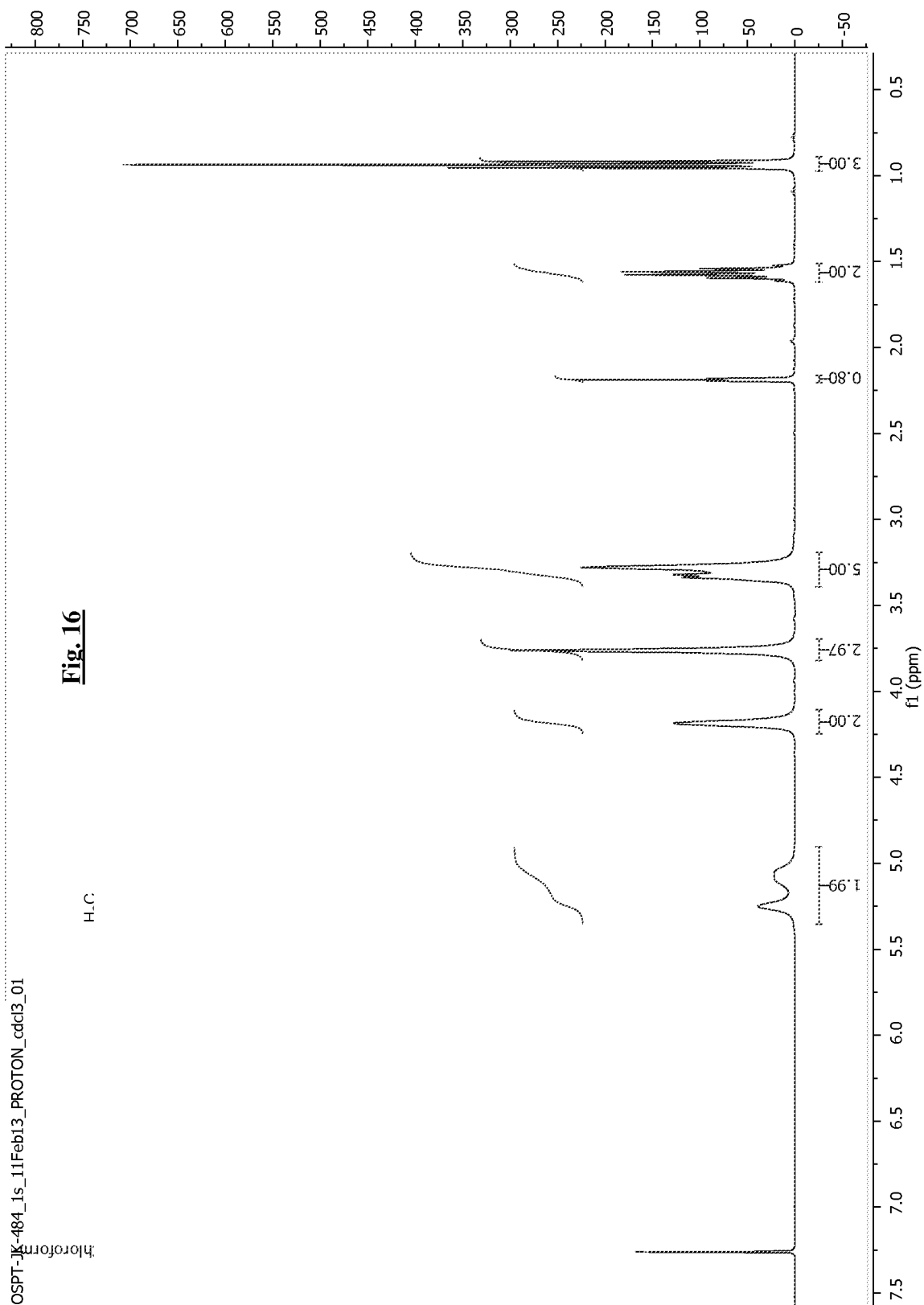


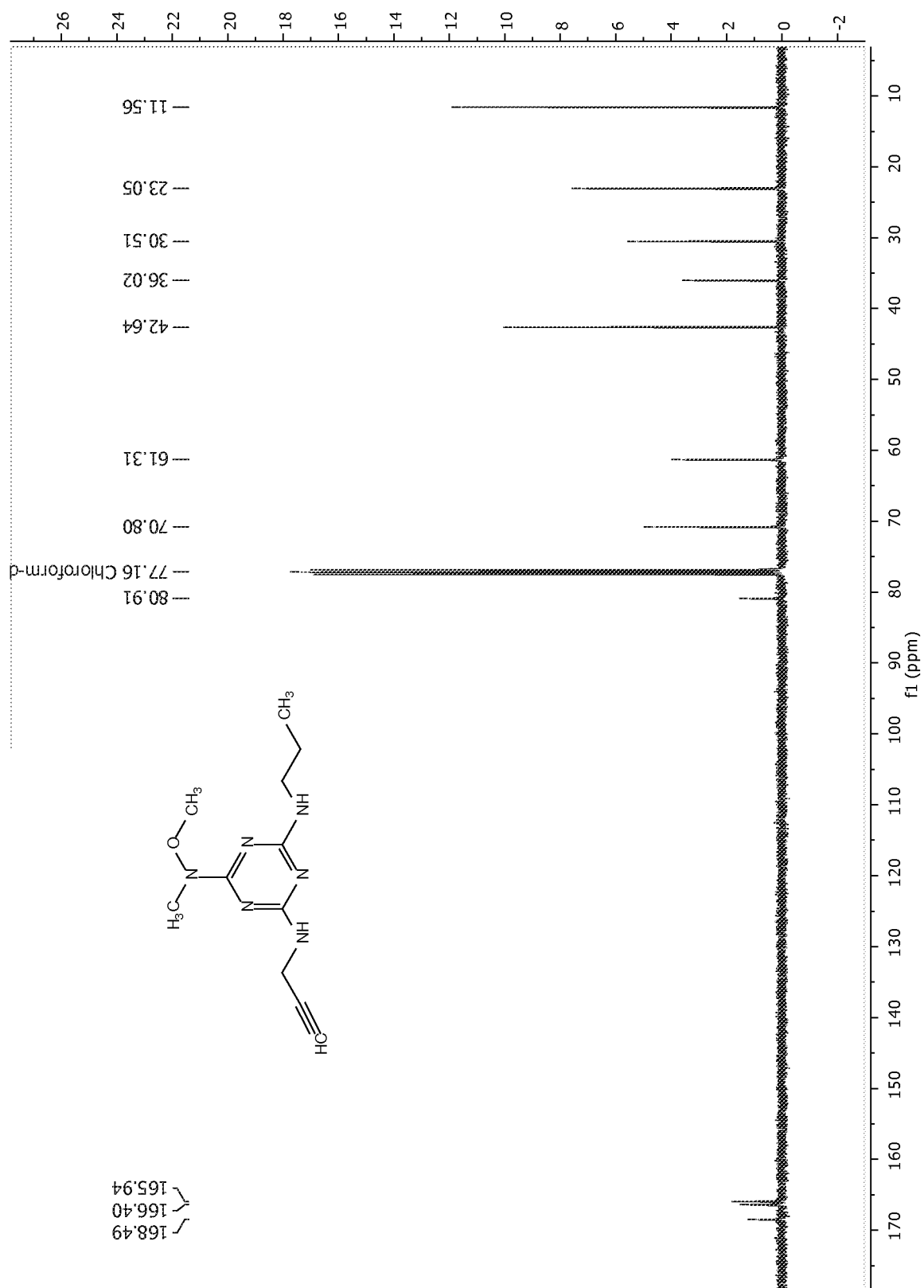
Fig. 17

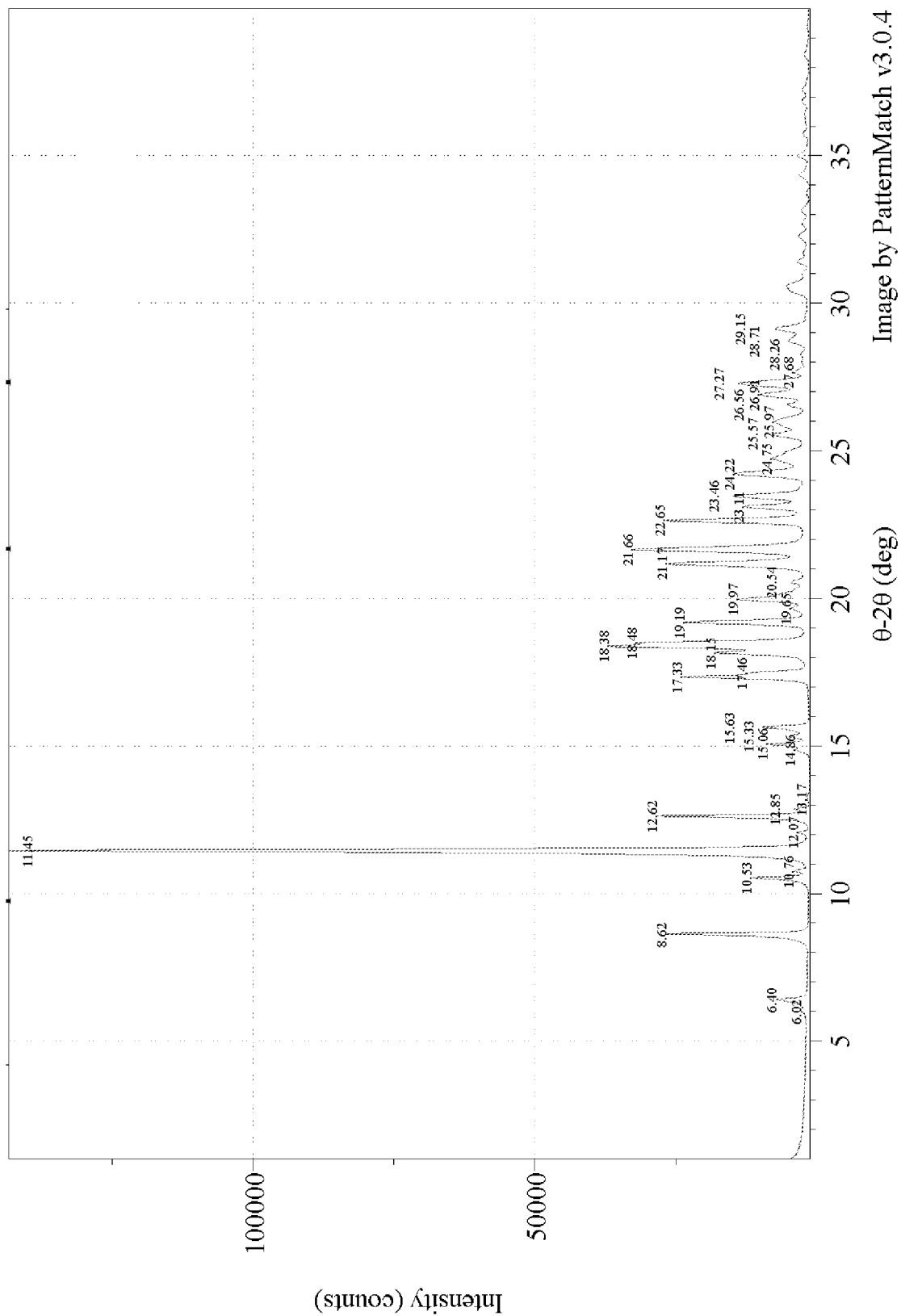
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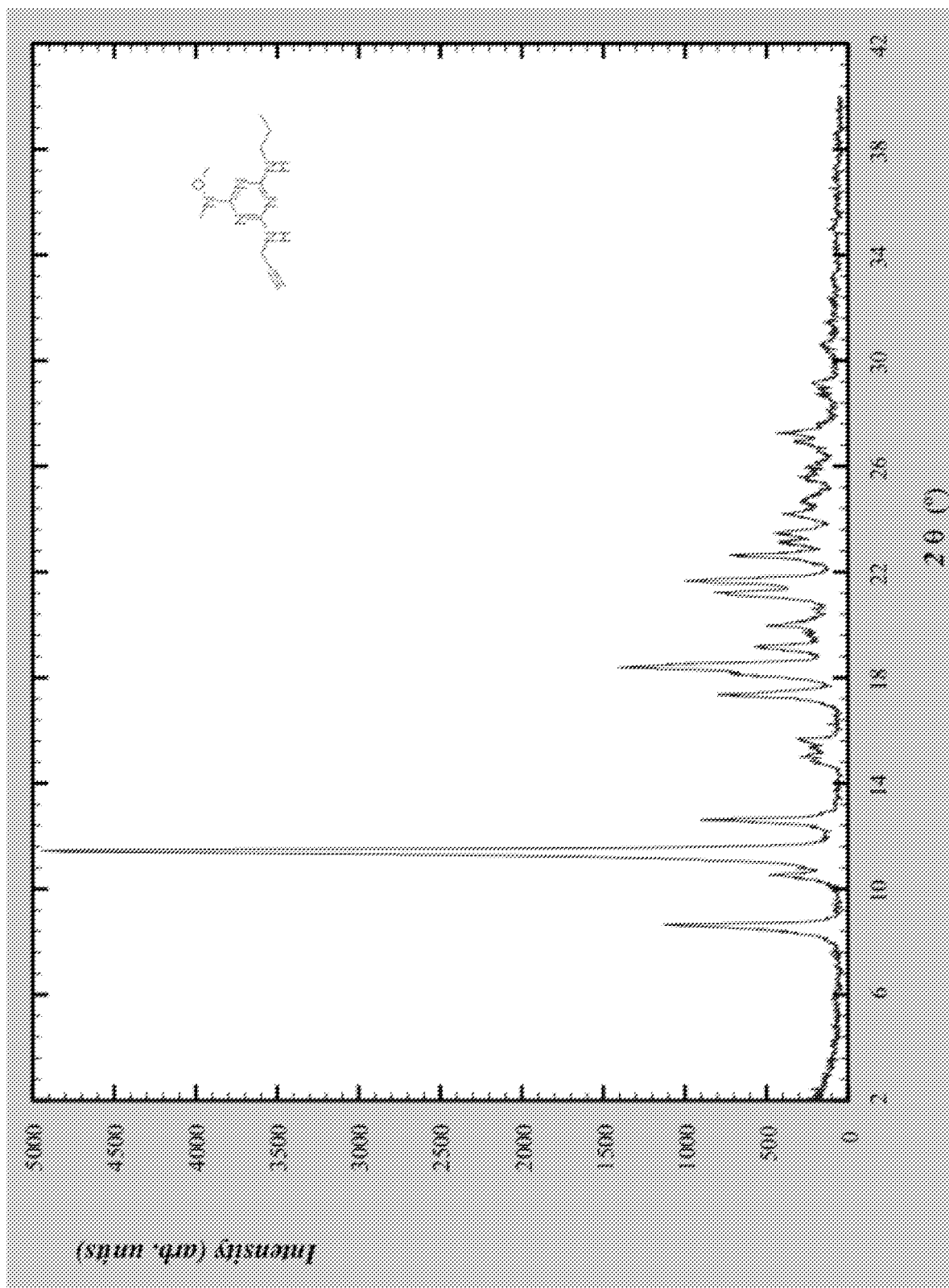
Fig. 19

Fig. 20

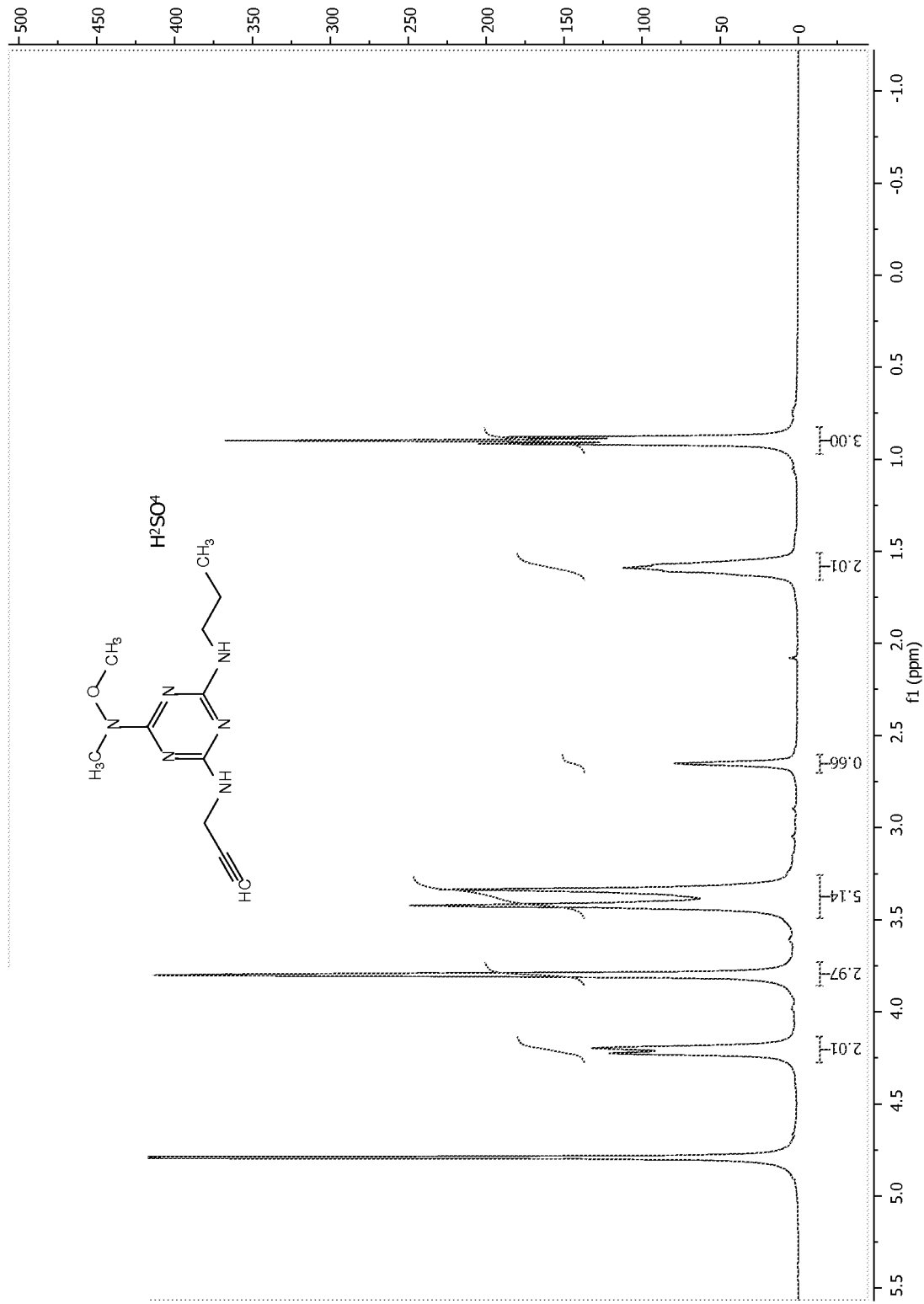


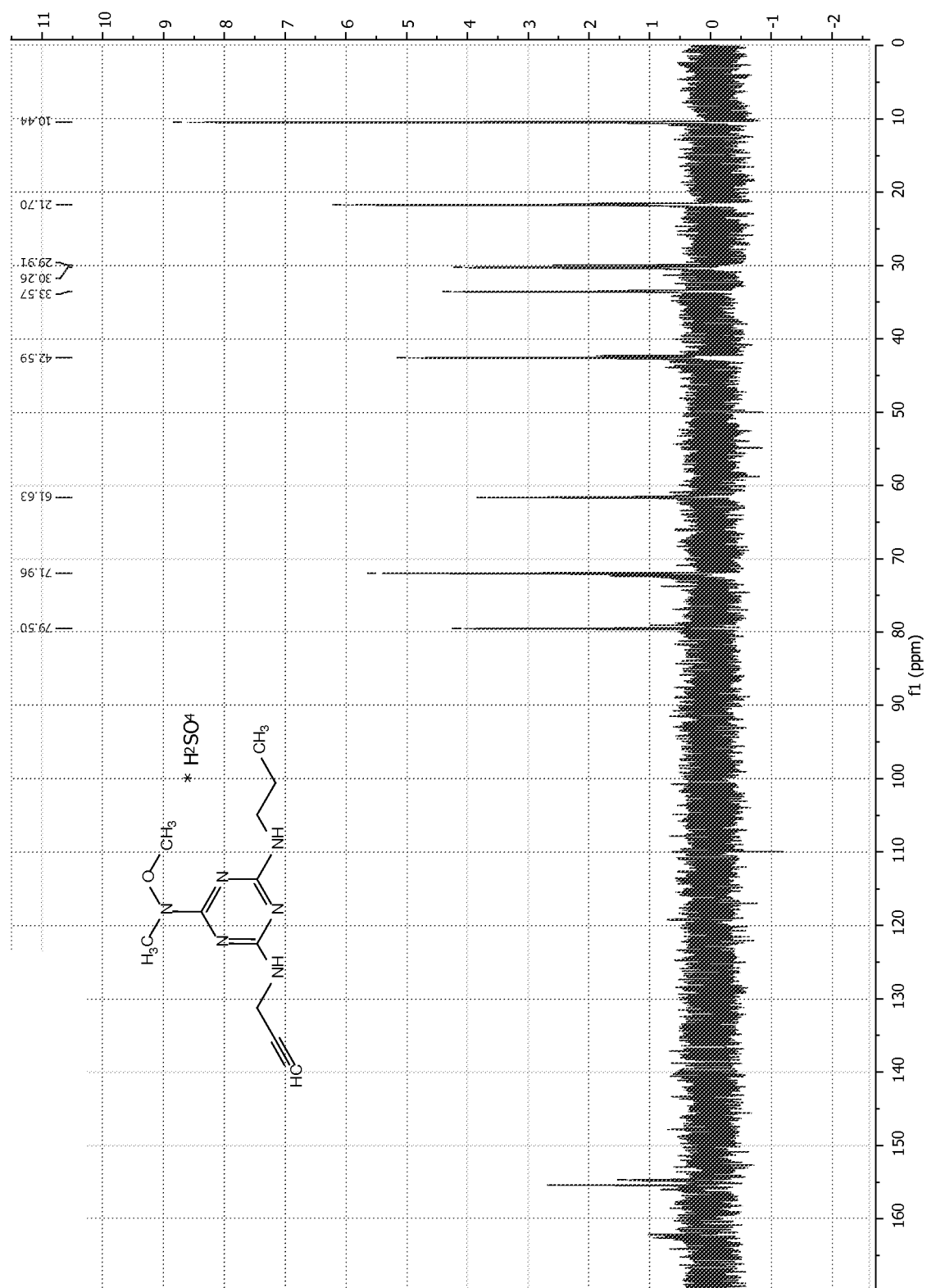
Fig. 21

Fig. 22

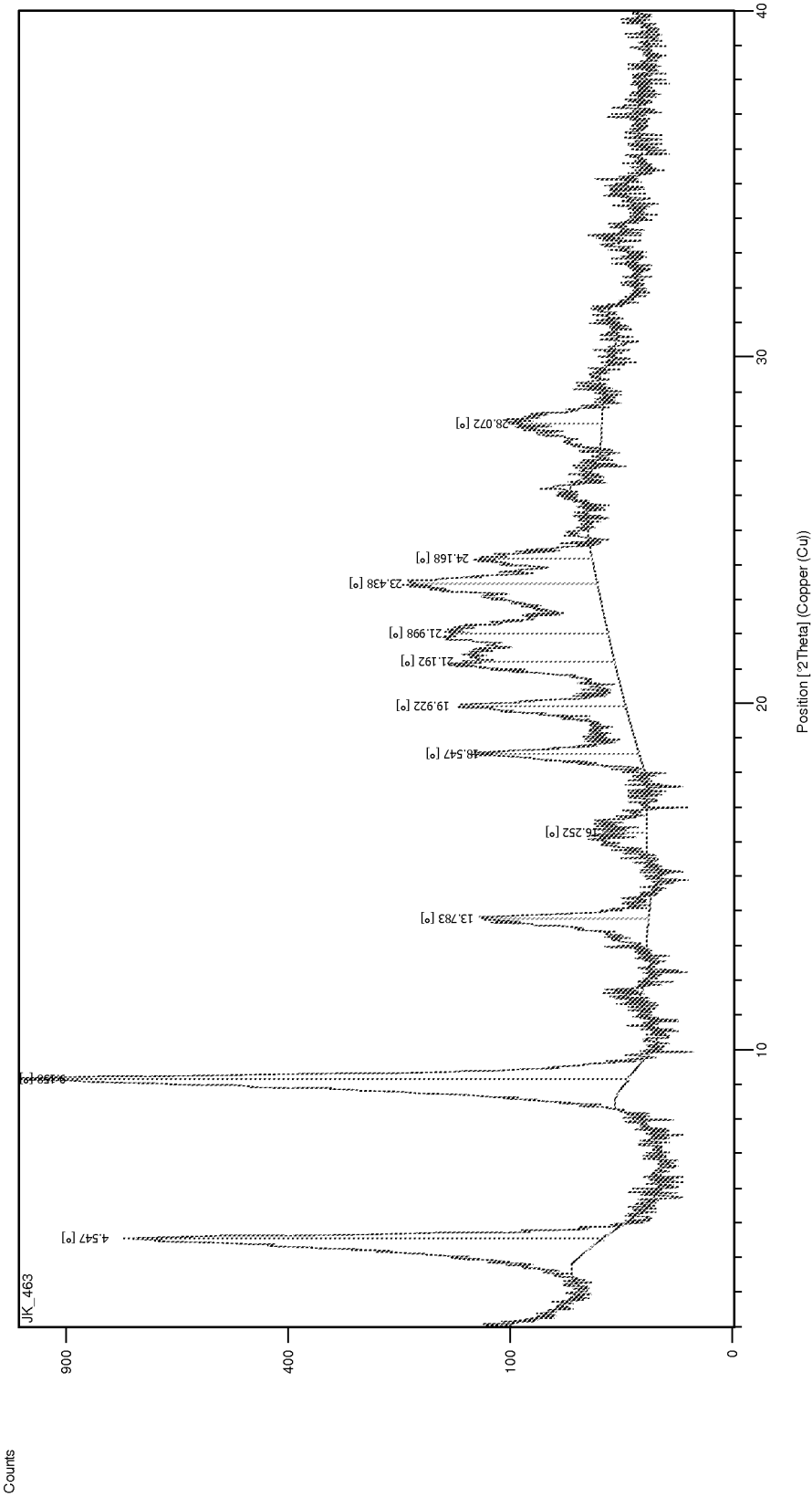


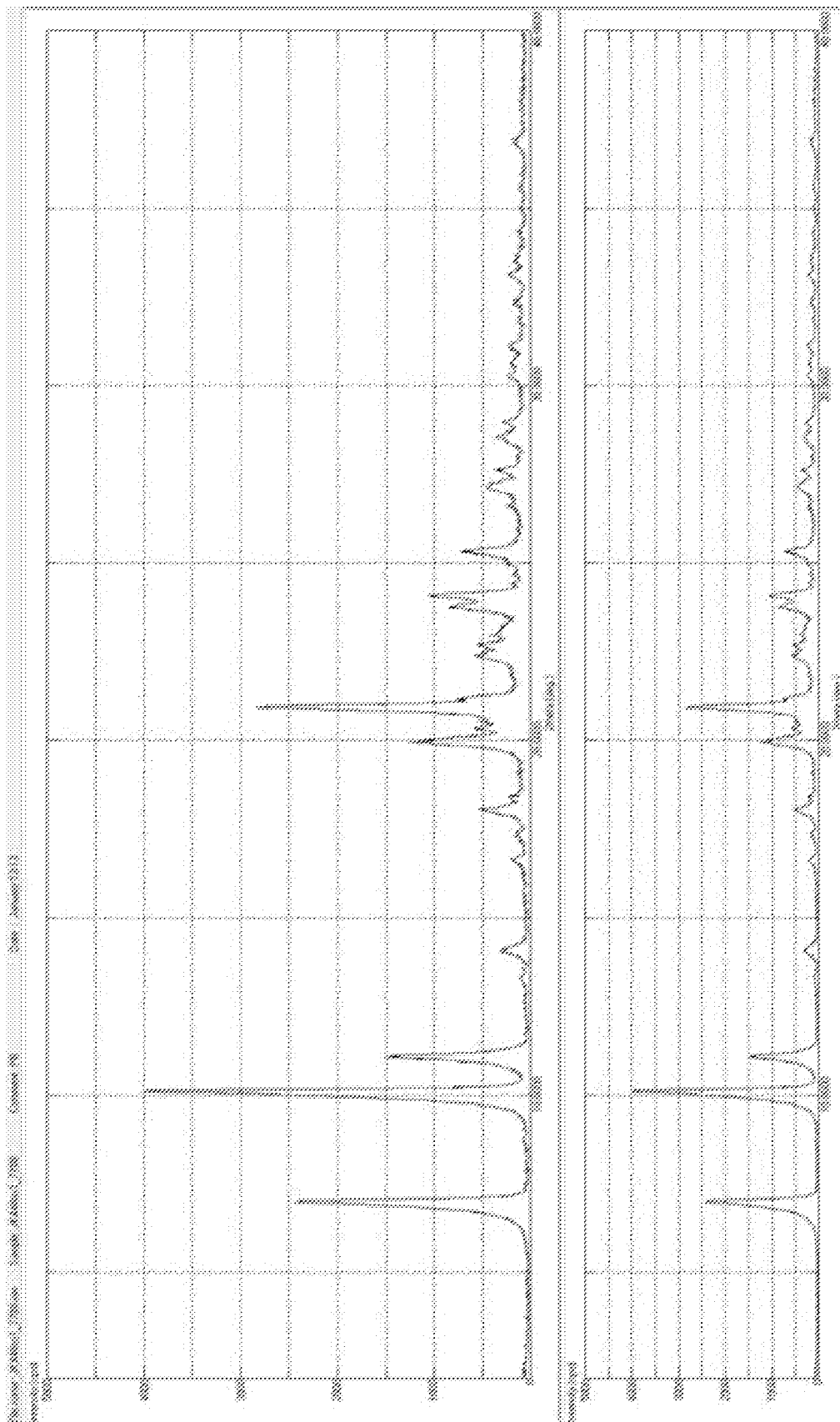
Fig. 23

Fig. 24

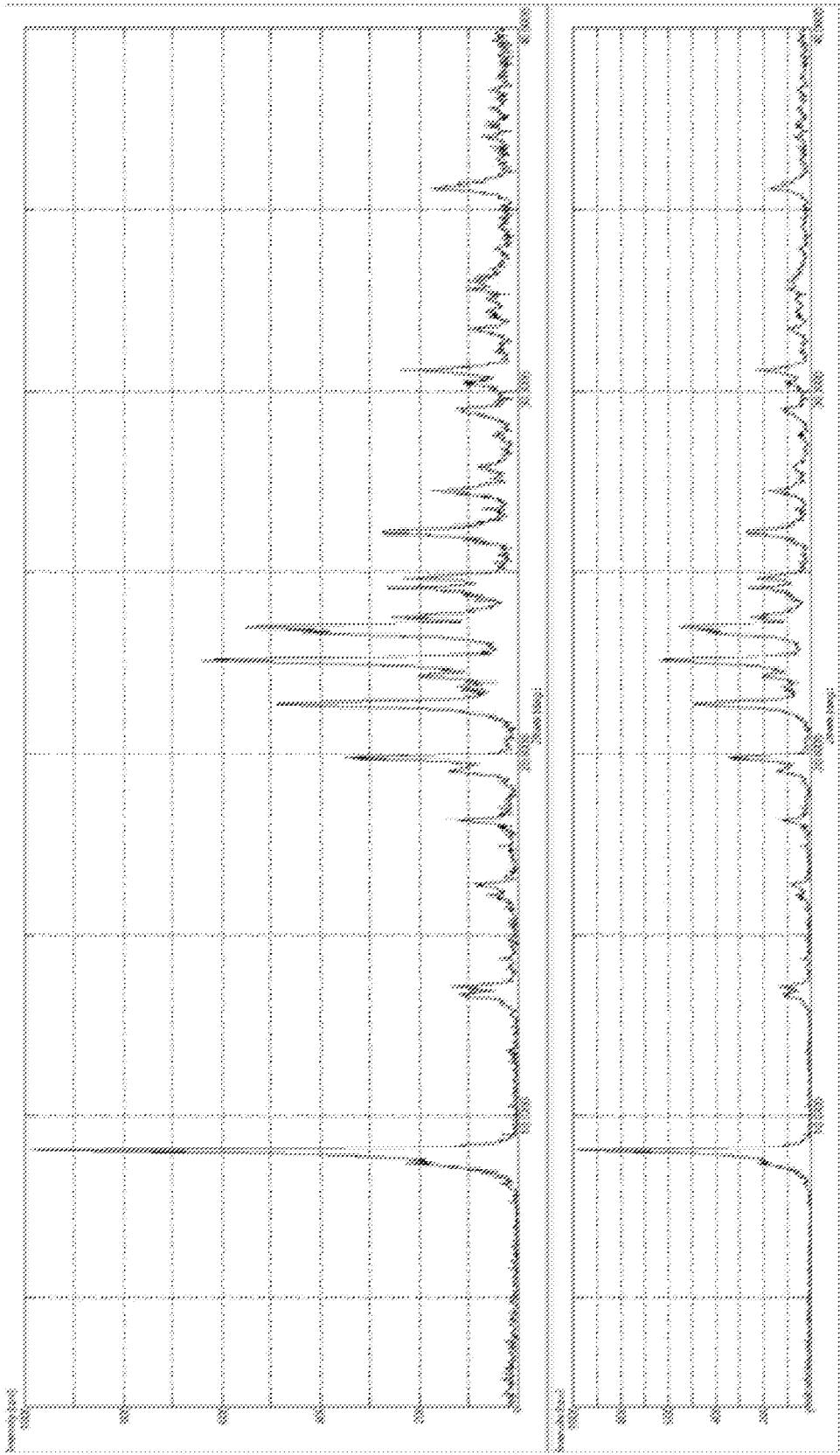


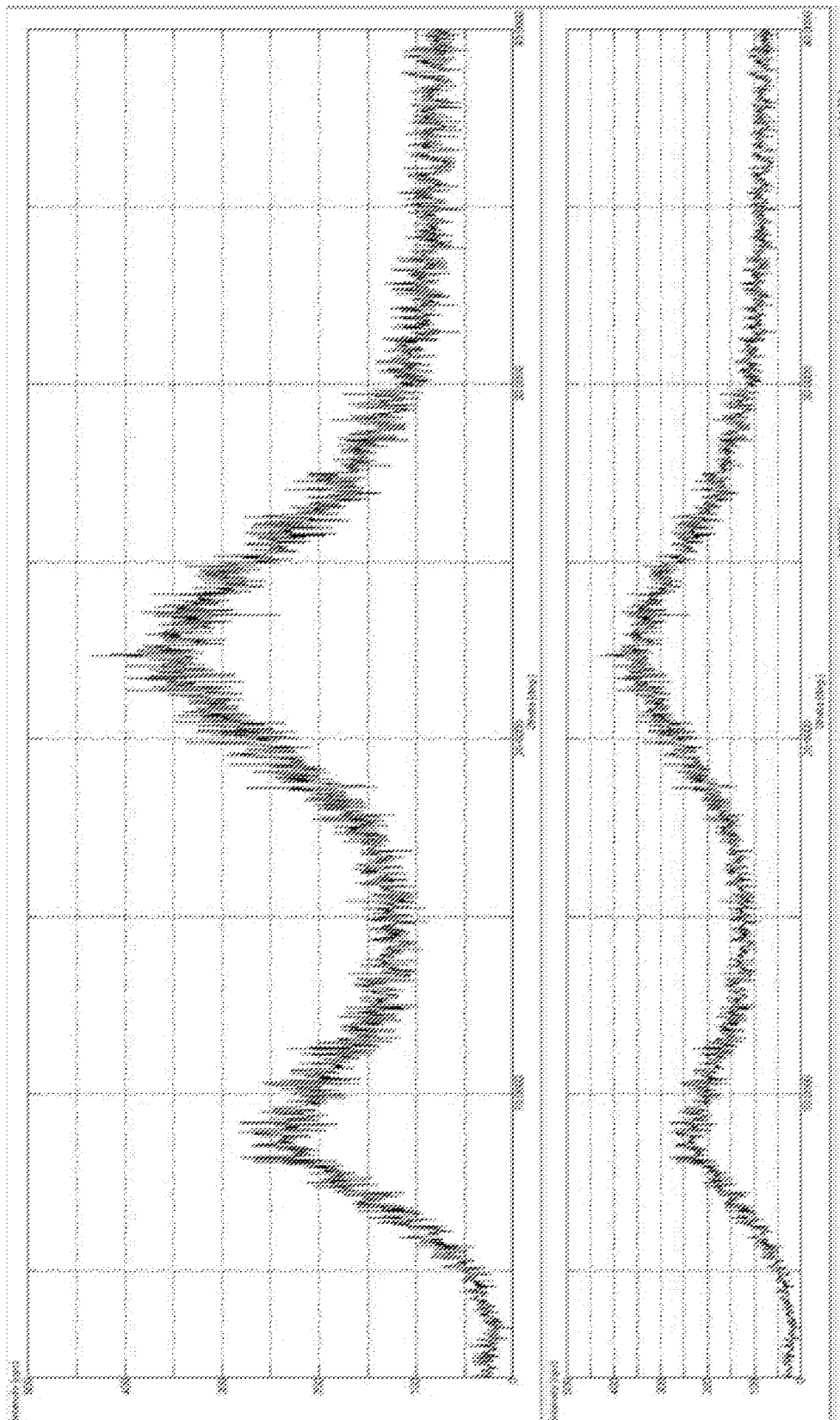
Fig. 25

Fig. 26

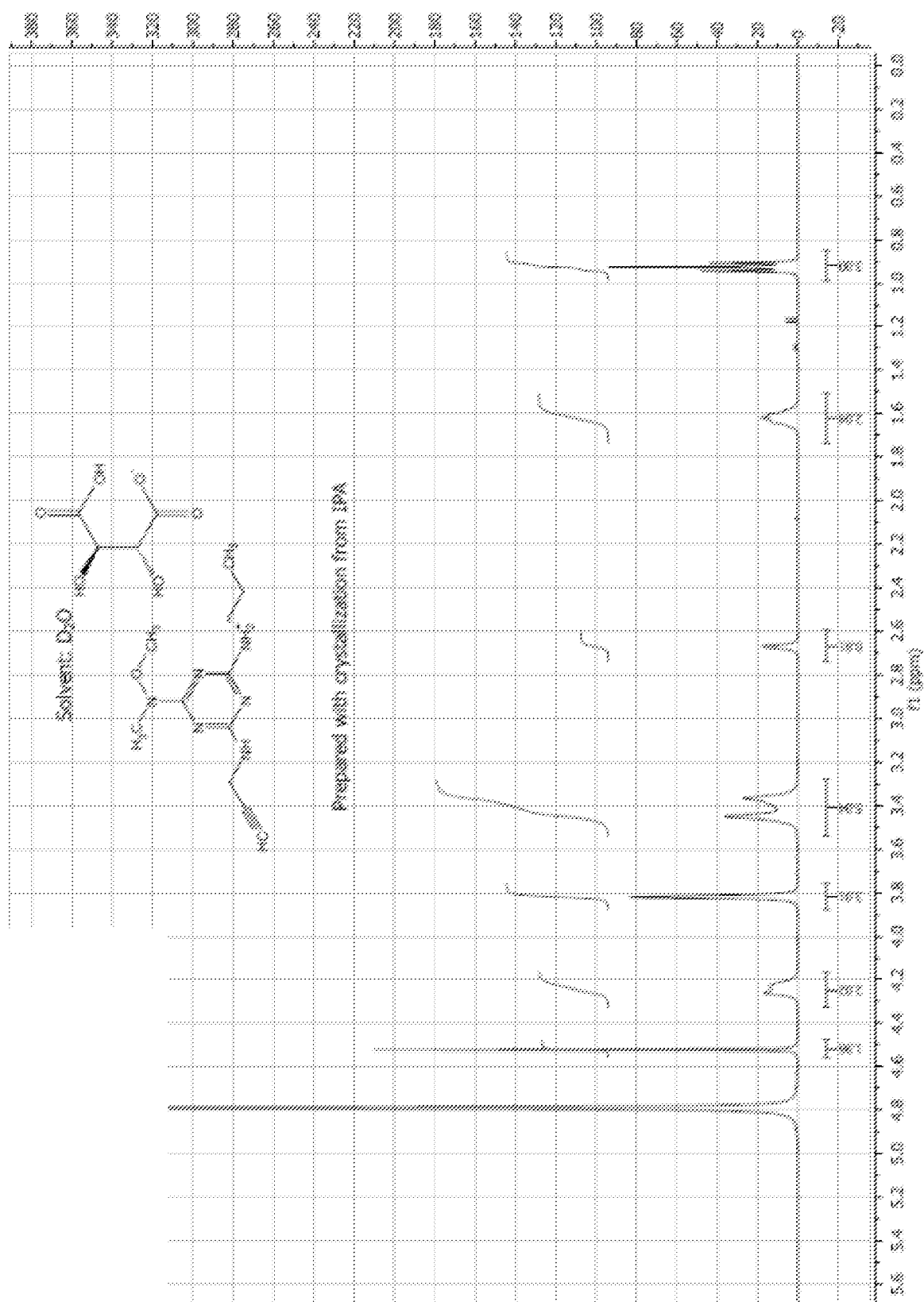


Fig. 27

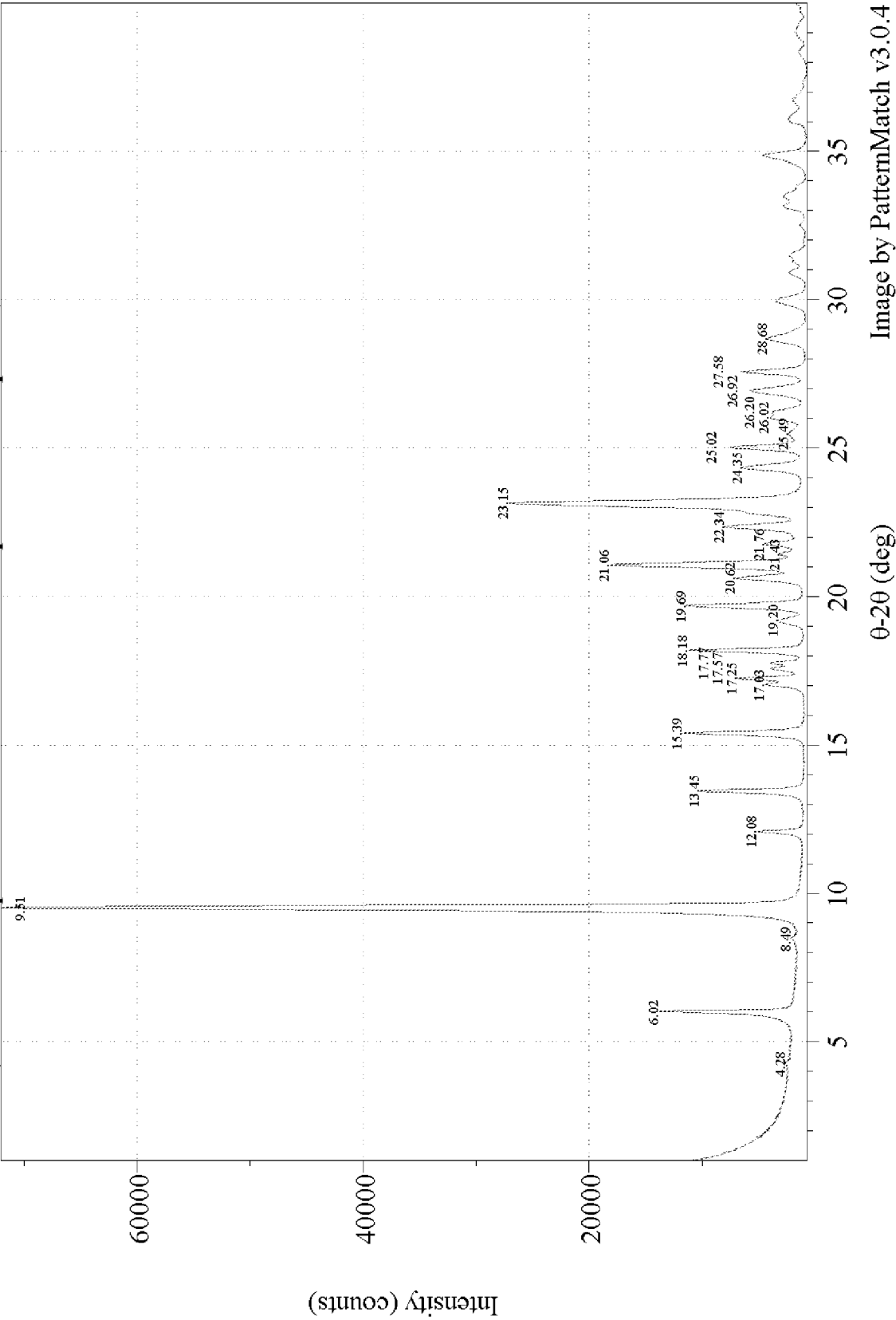


Fig. 28

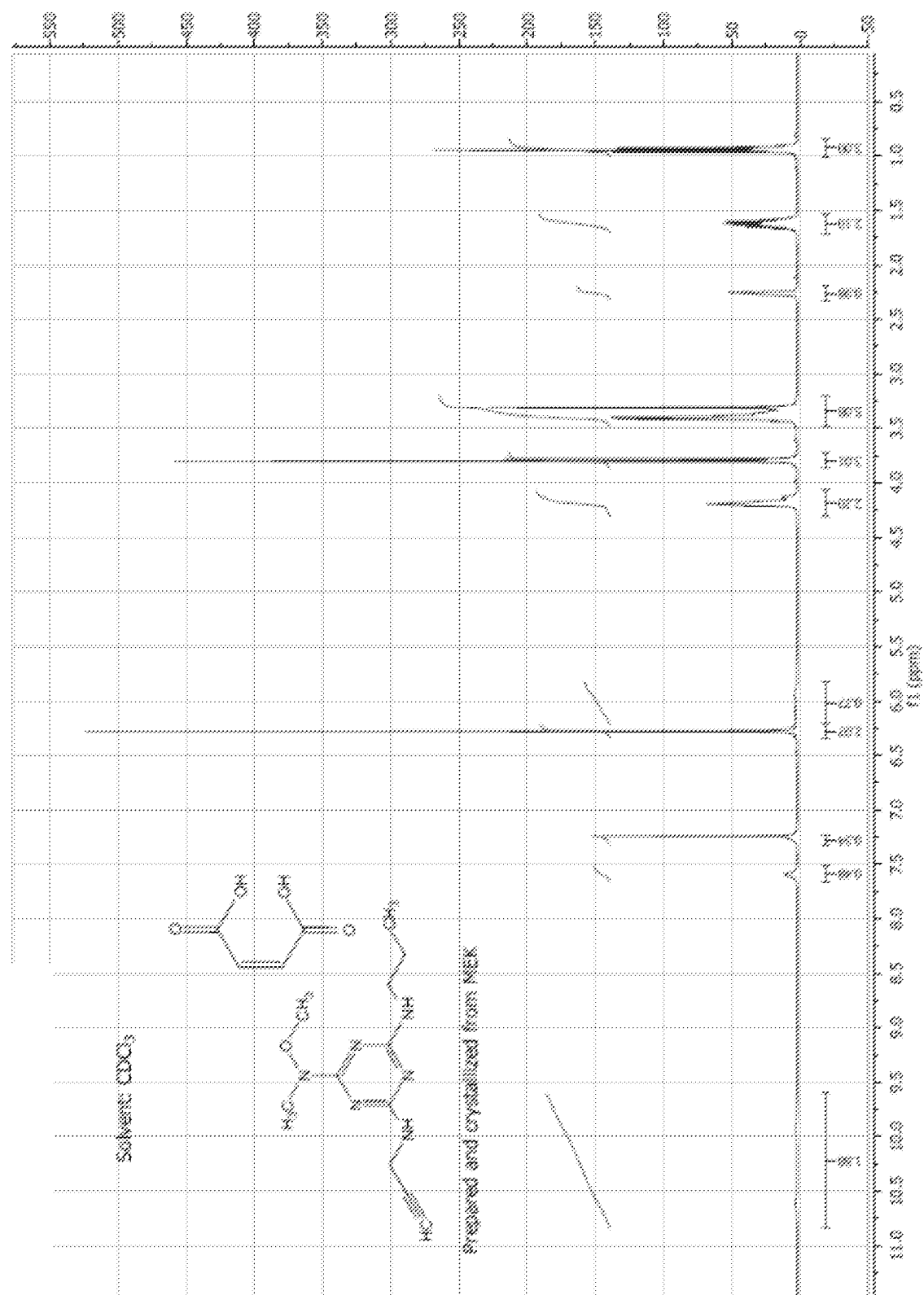


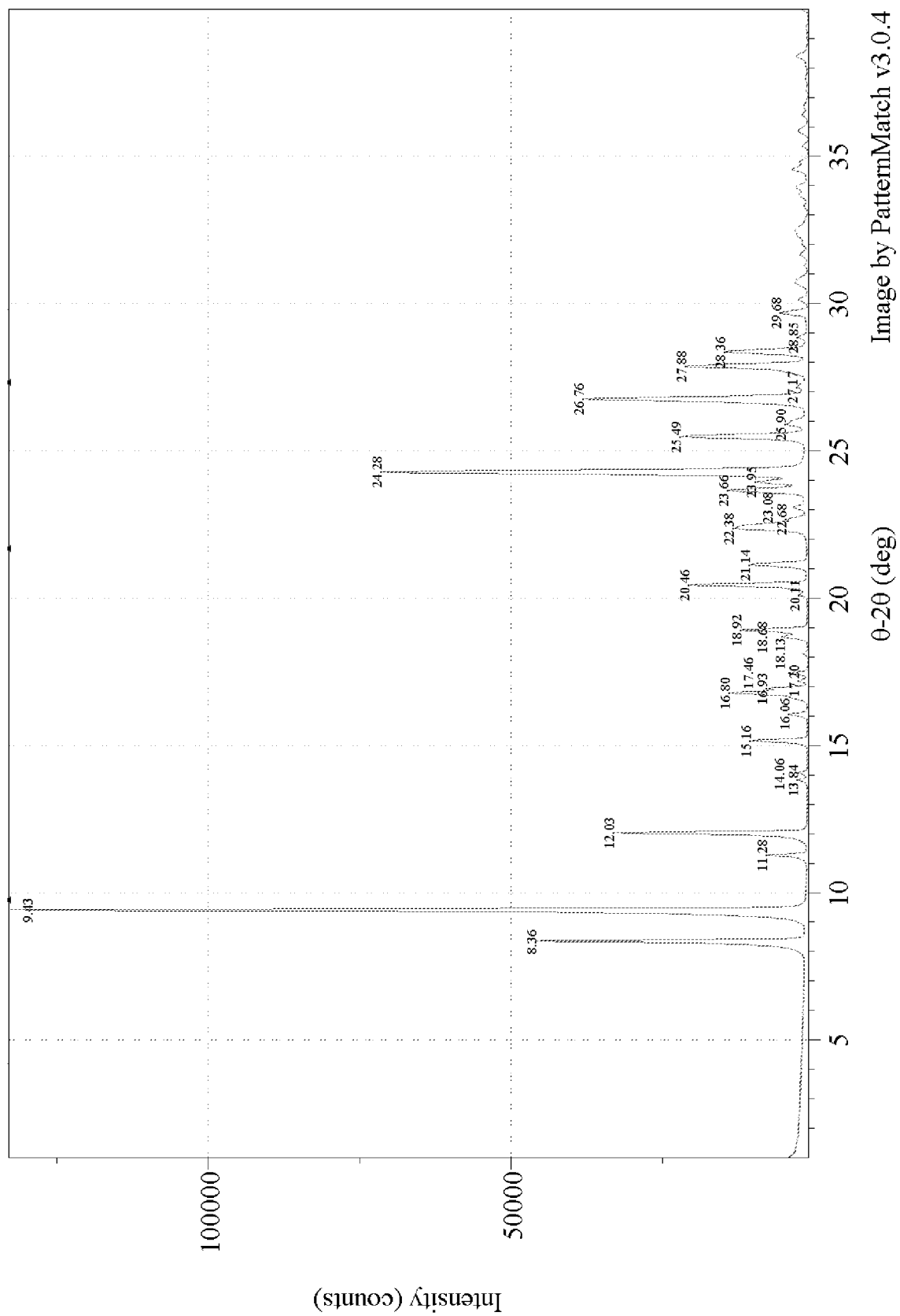
Fig. 29

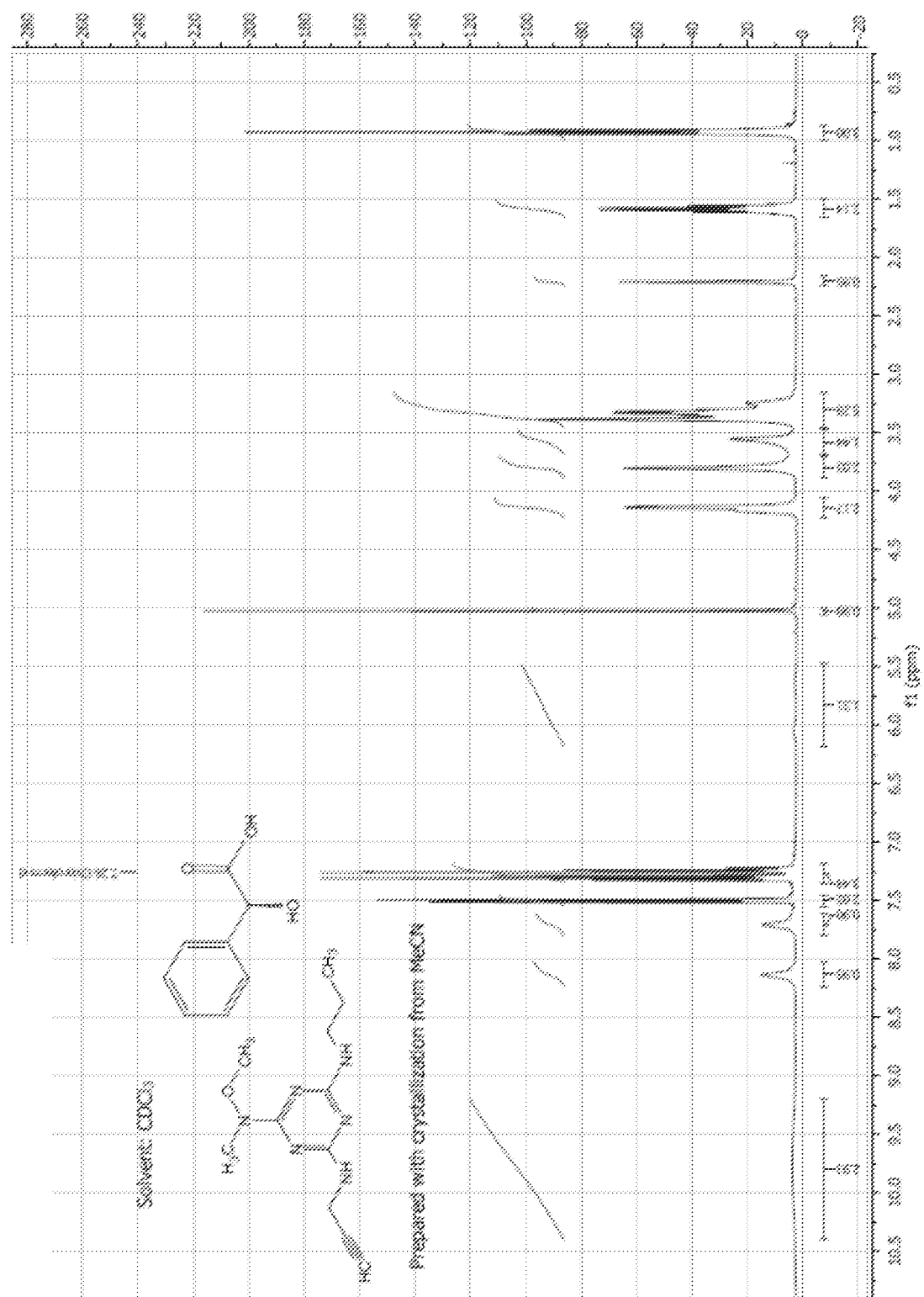
Fig. 30

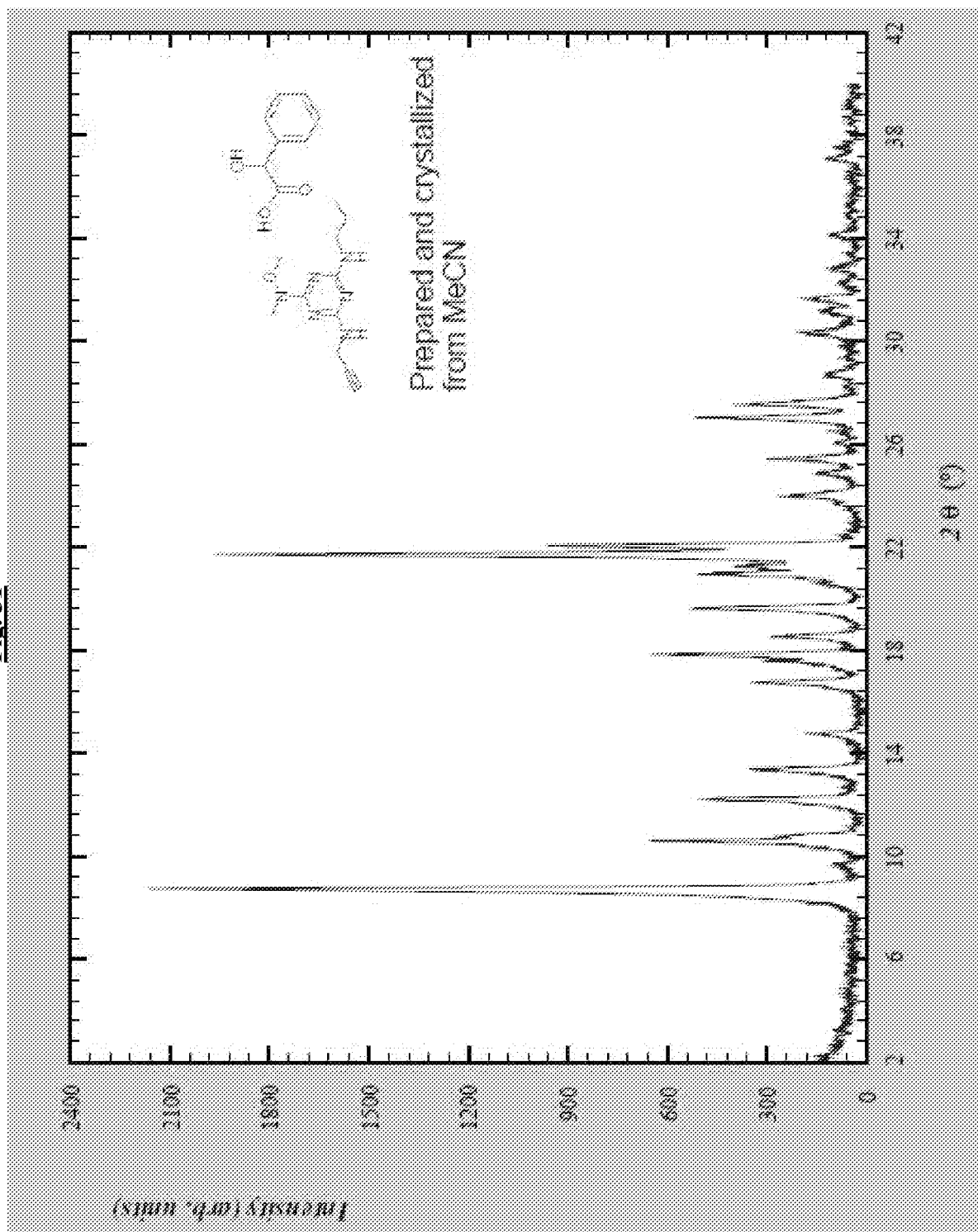
Fig. 31

Fig. 32

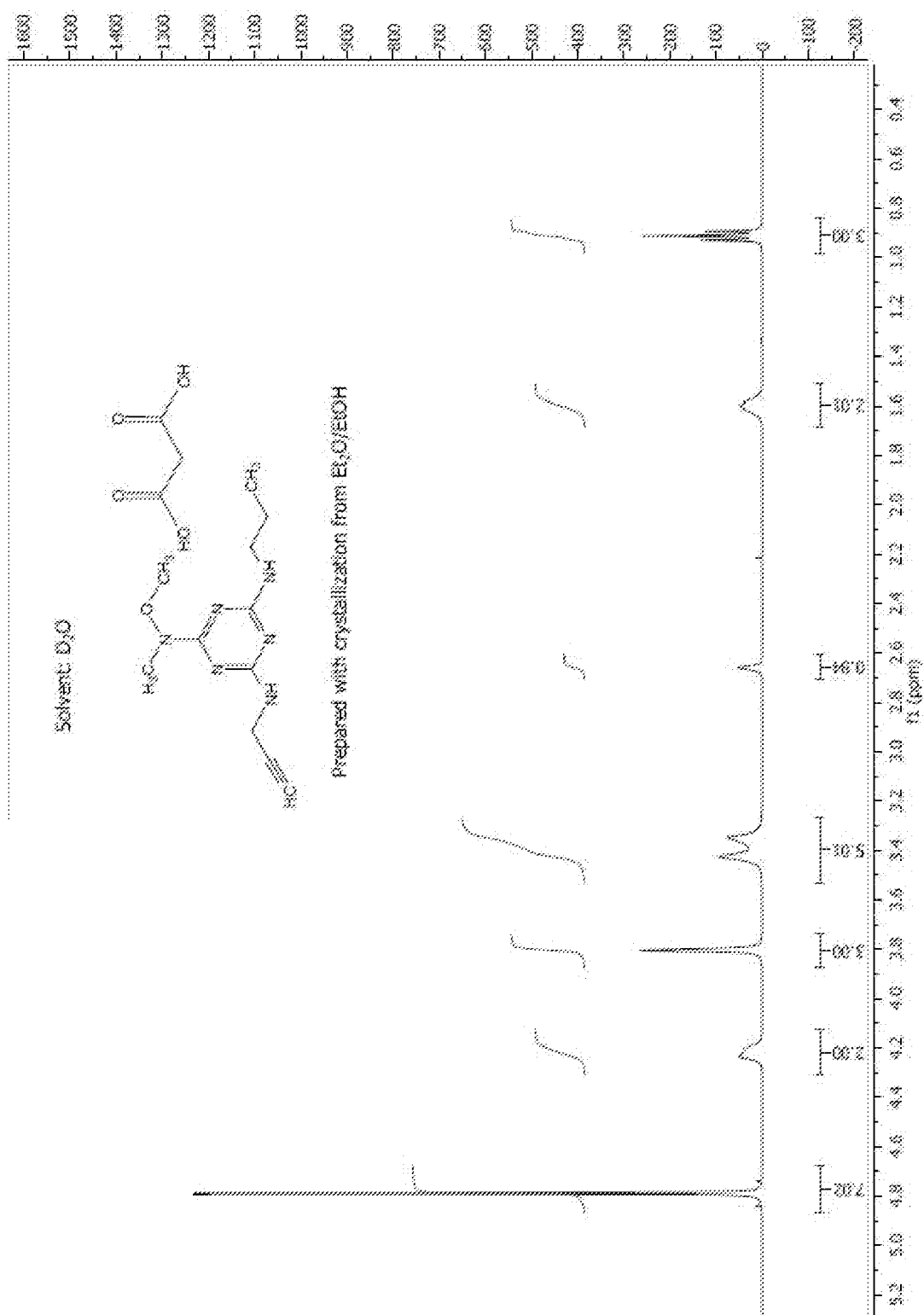


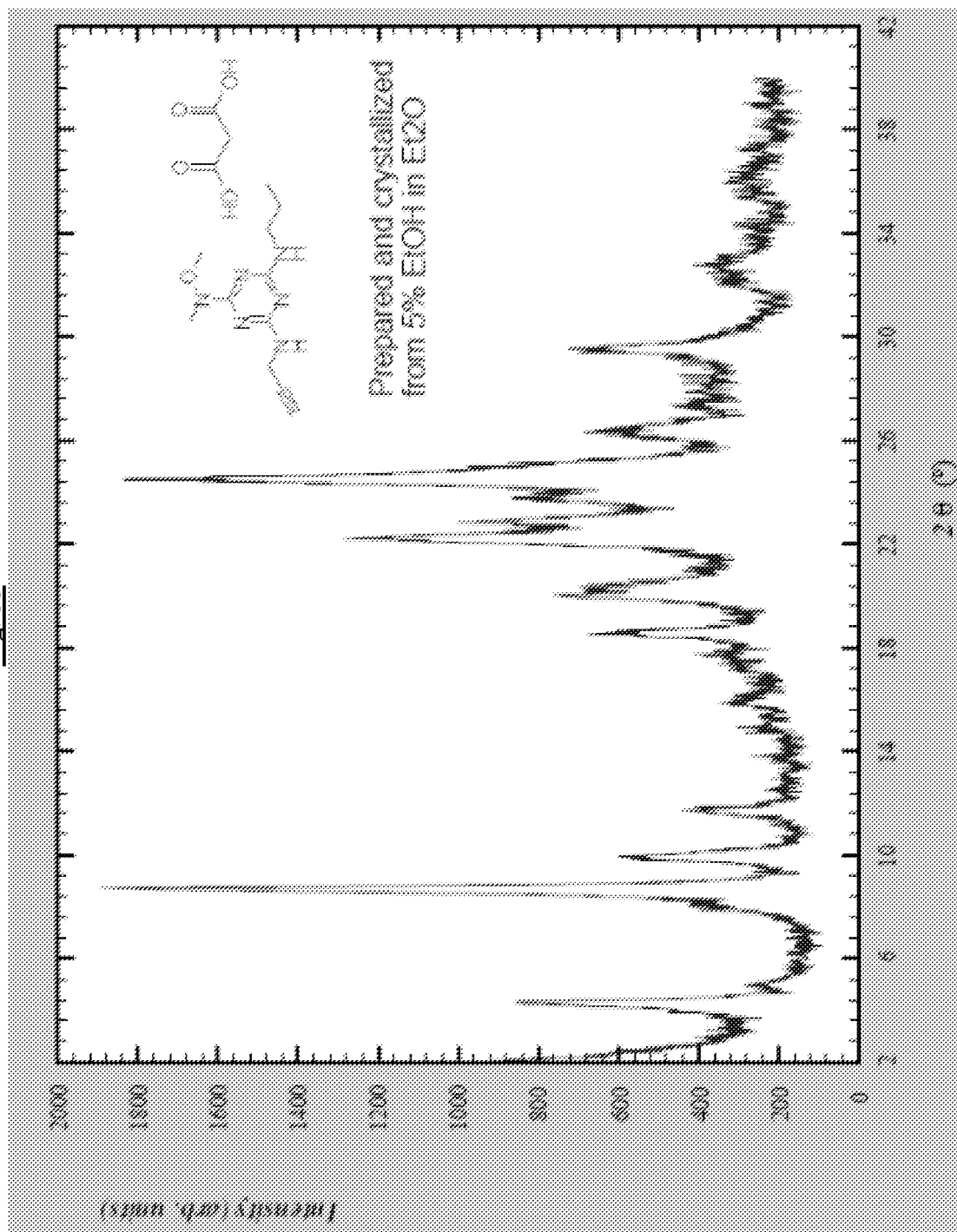
Fig. 33

Fig. 34

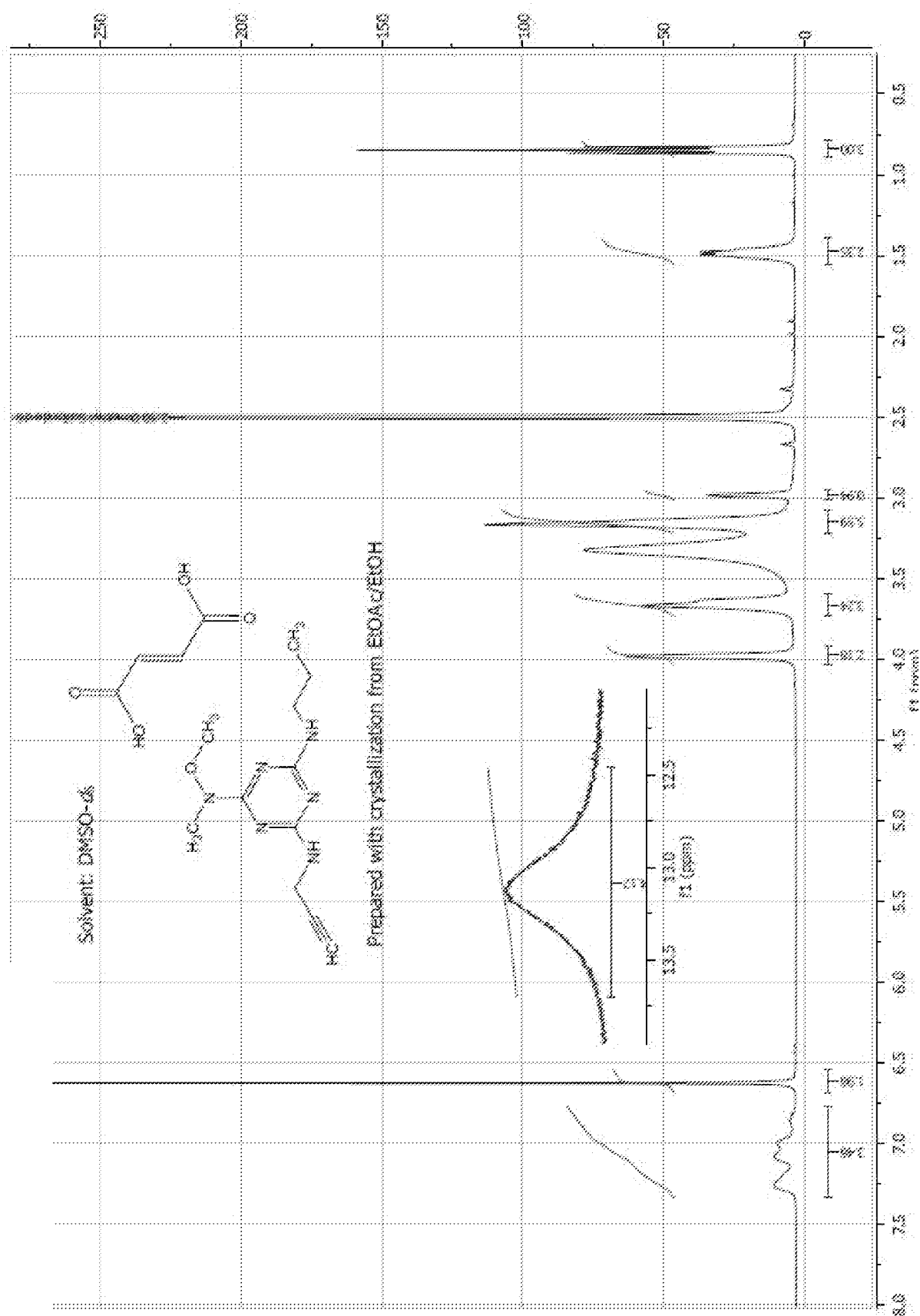


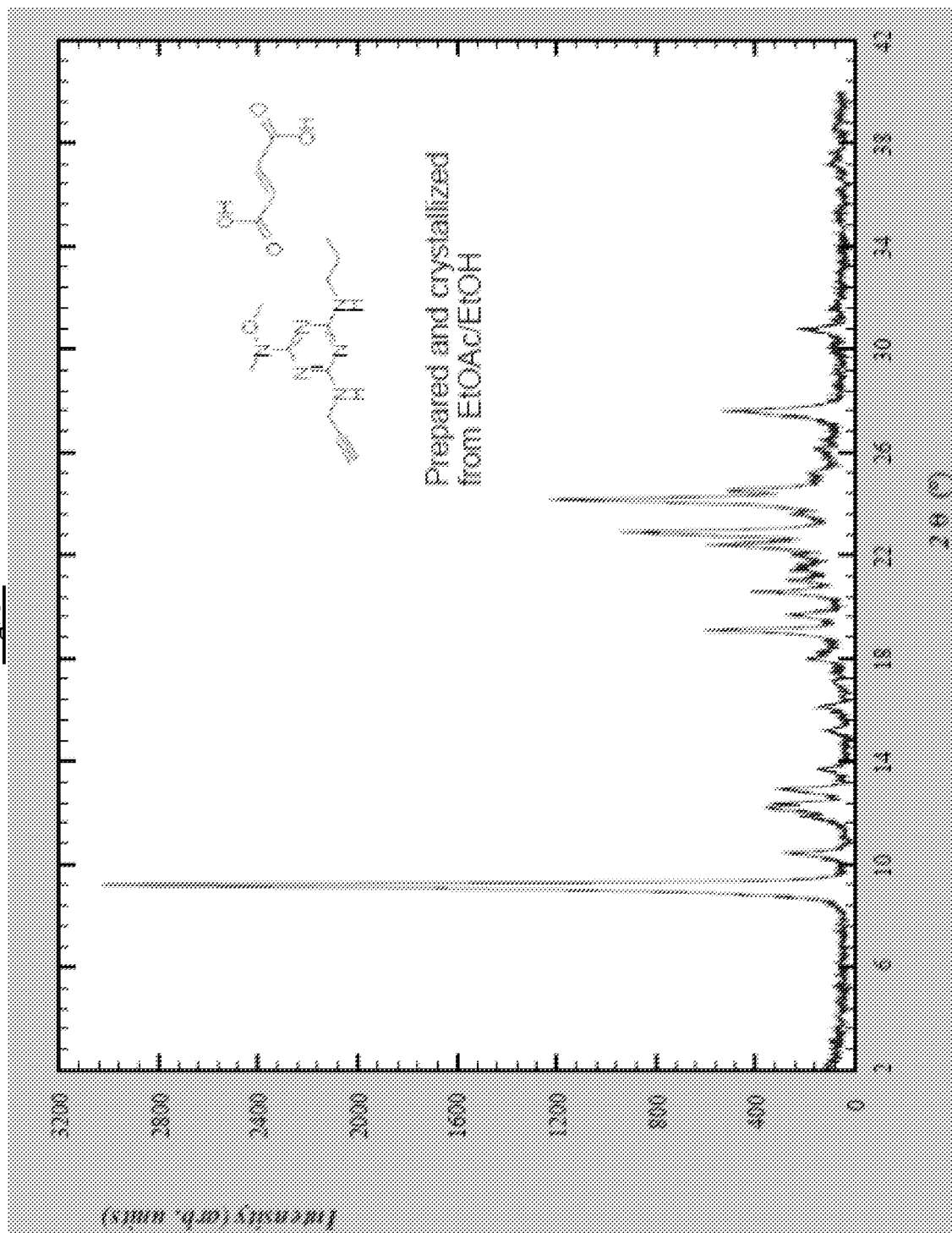
Fig. 35

Fig. 36

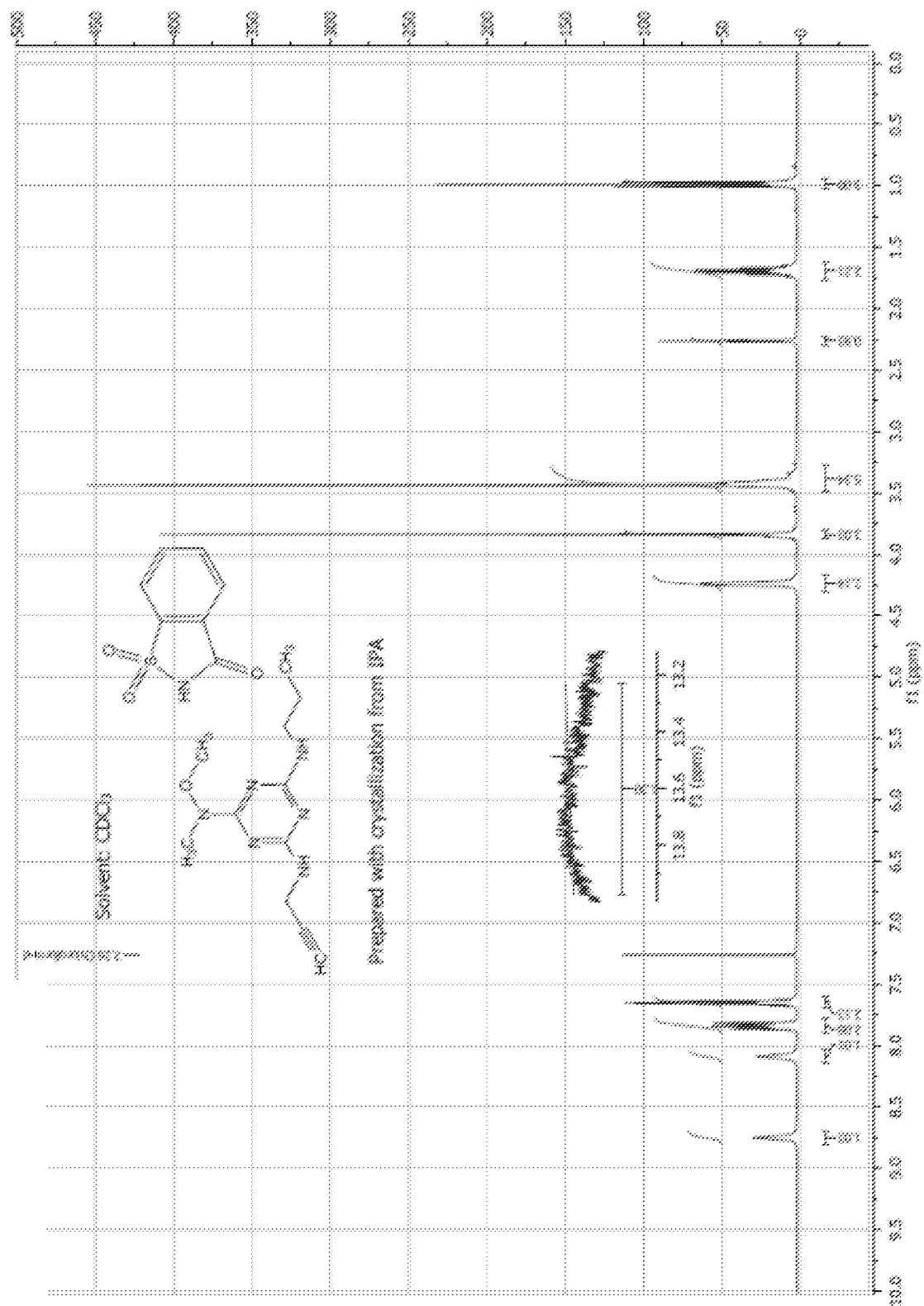




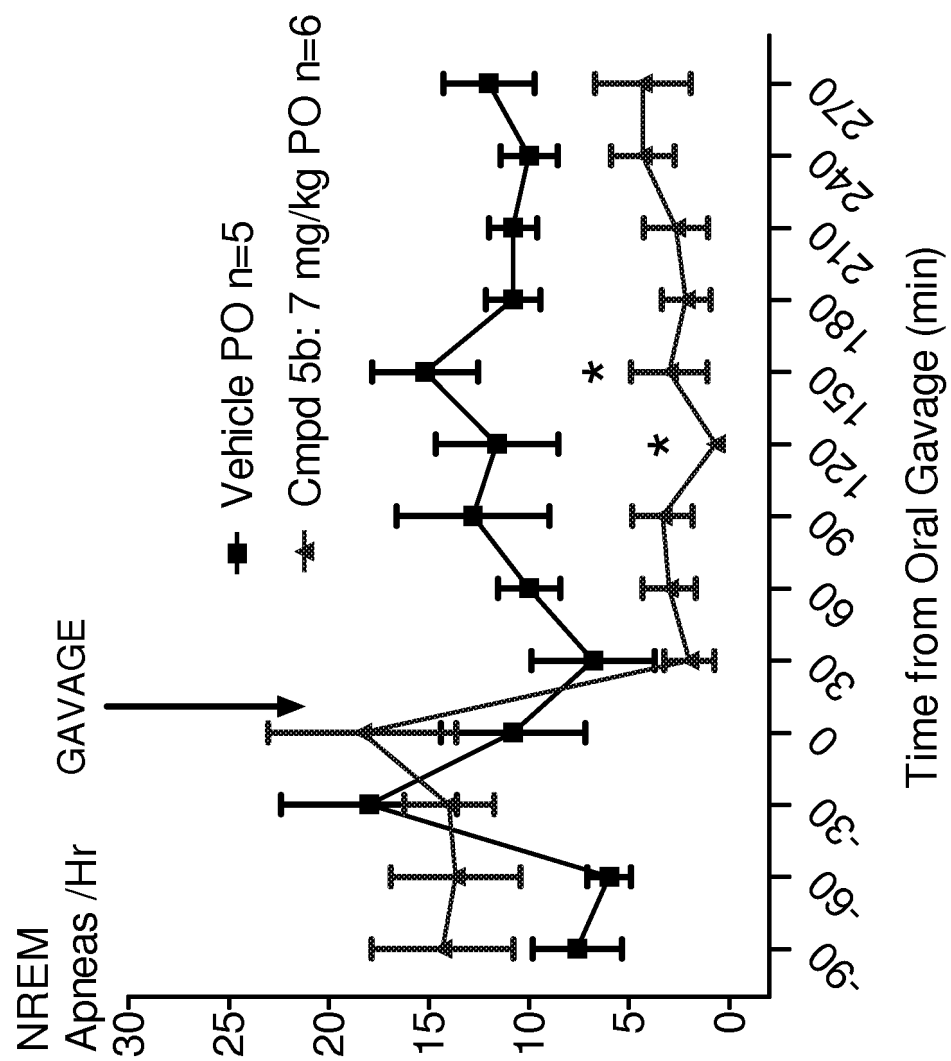
Fig. 38

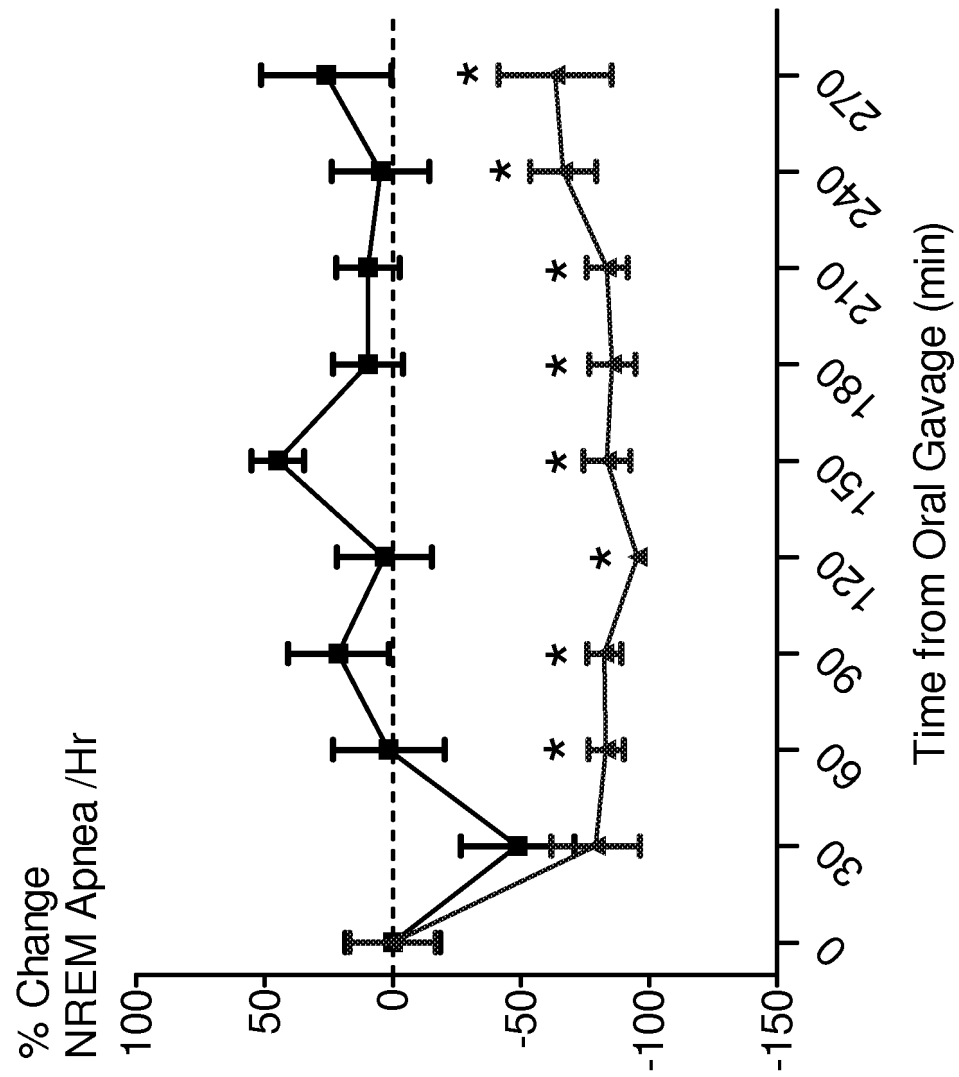
Fig. 39

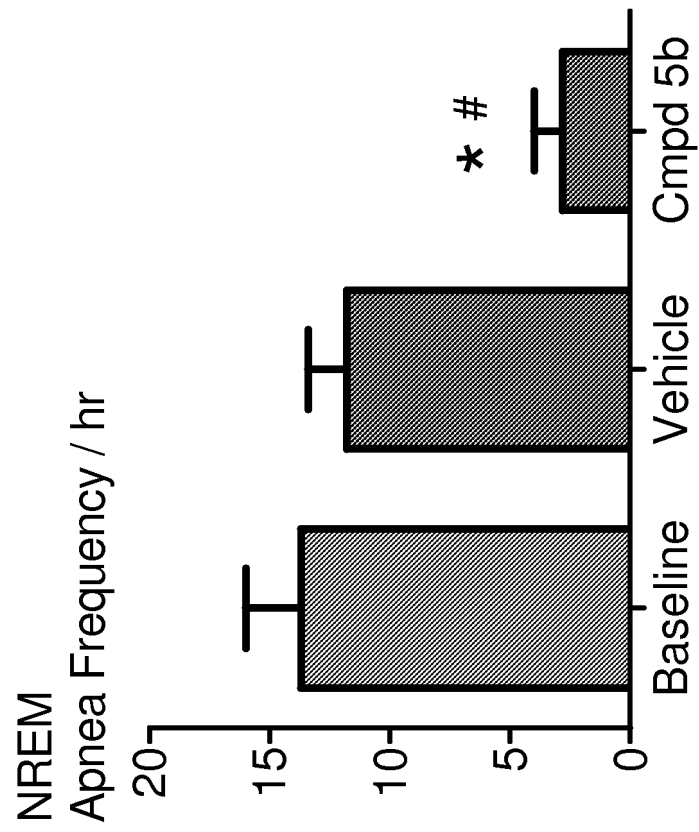
Fig. 40

Fig. 41

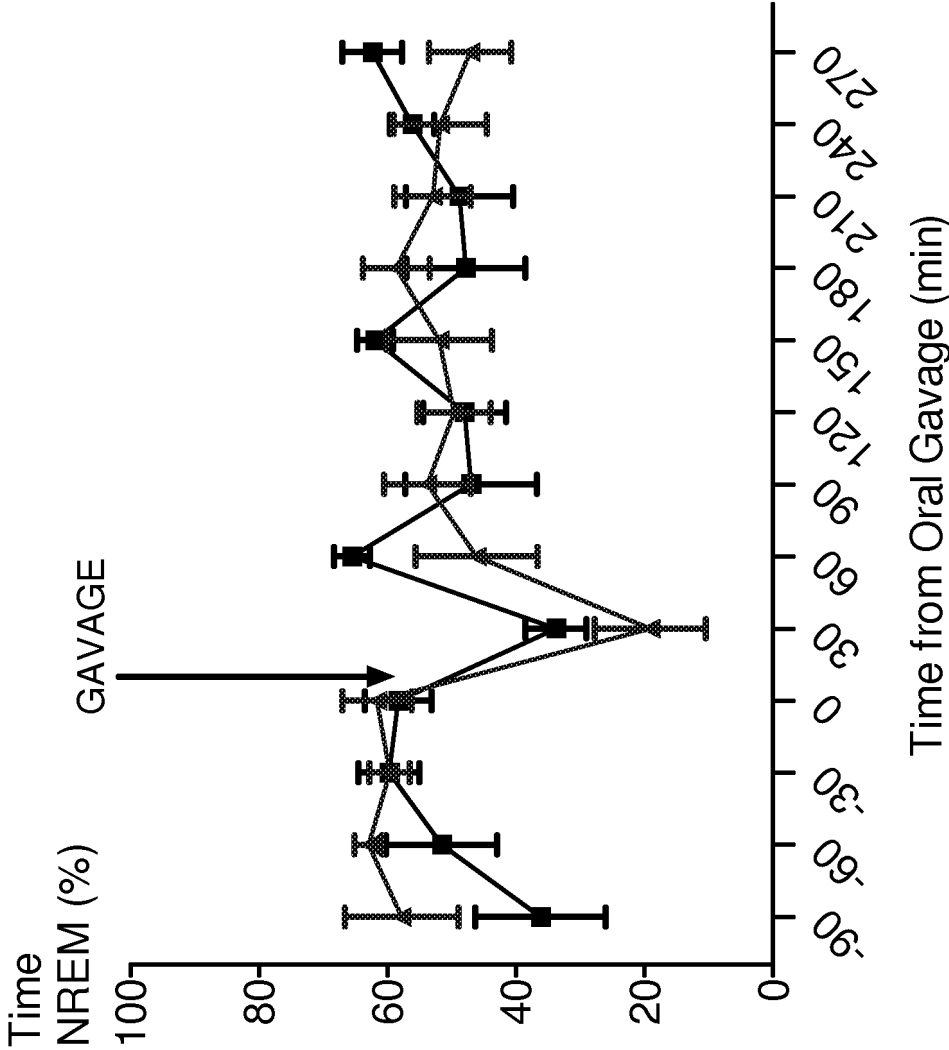


Fig. 42

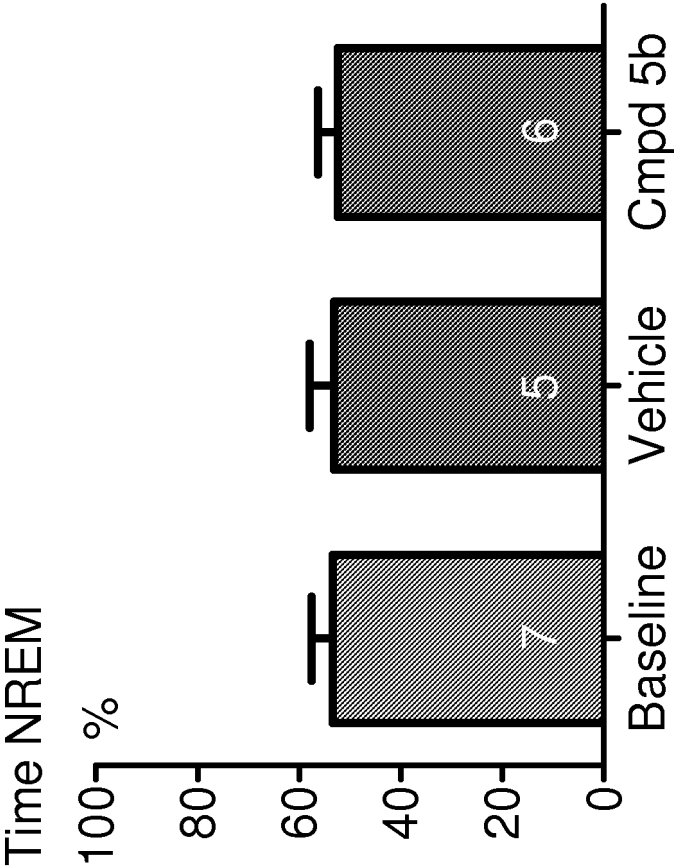


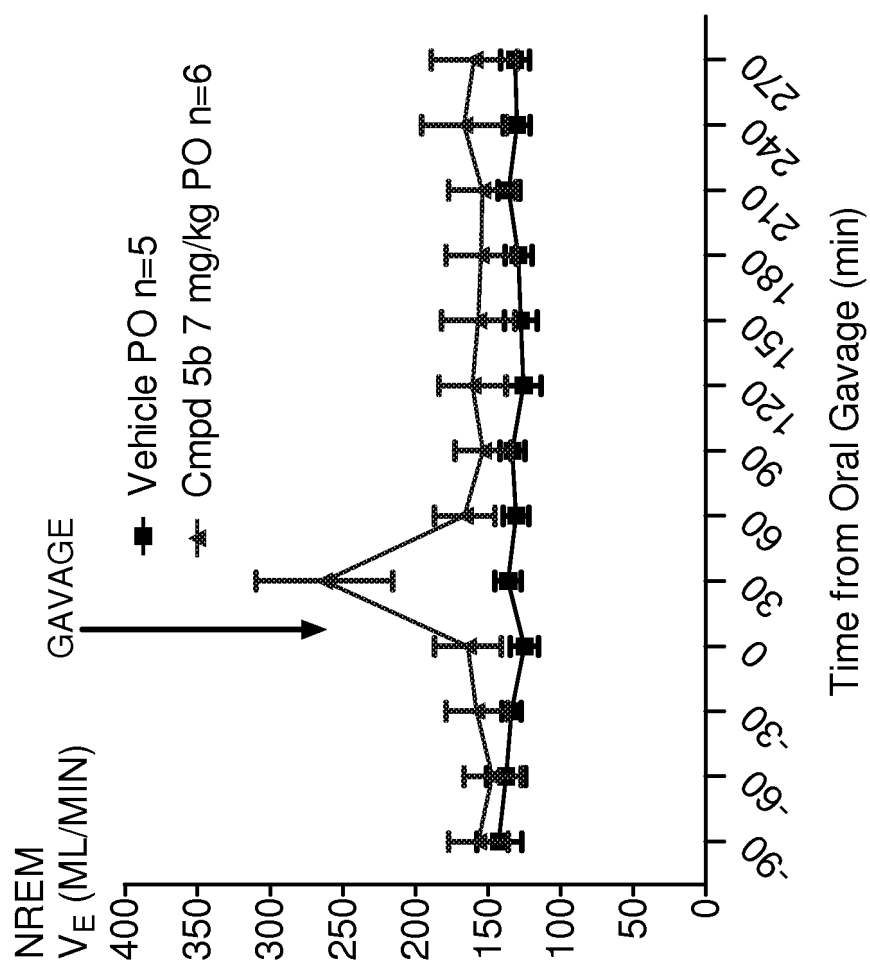
Fig. 43

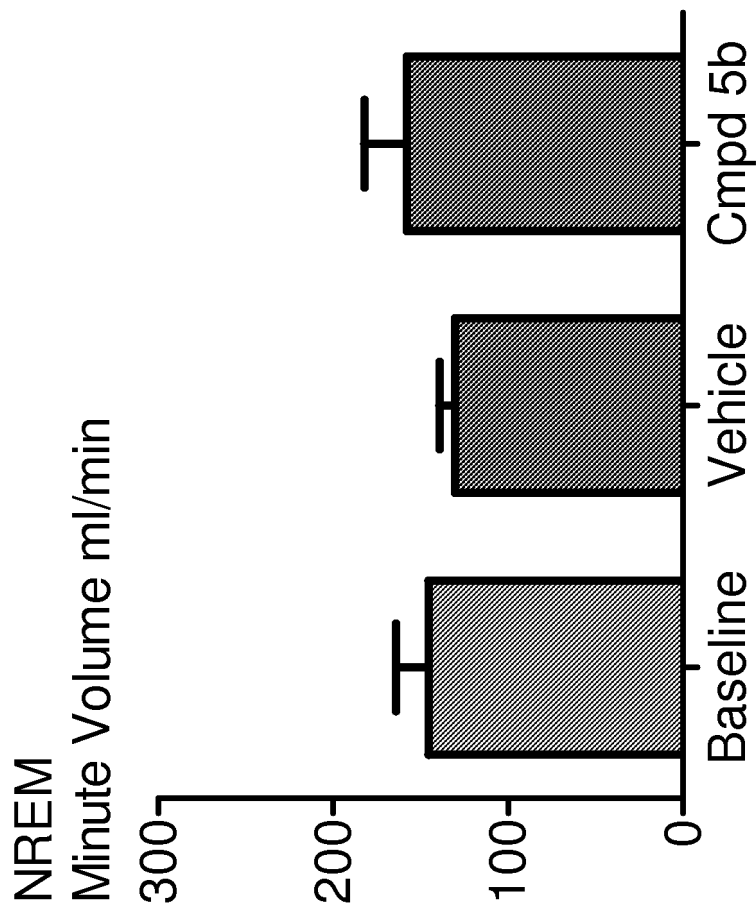
Fig. 44

Fig. 45

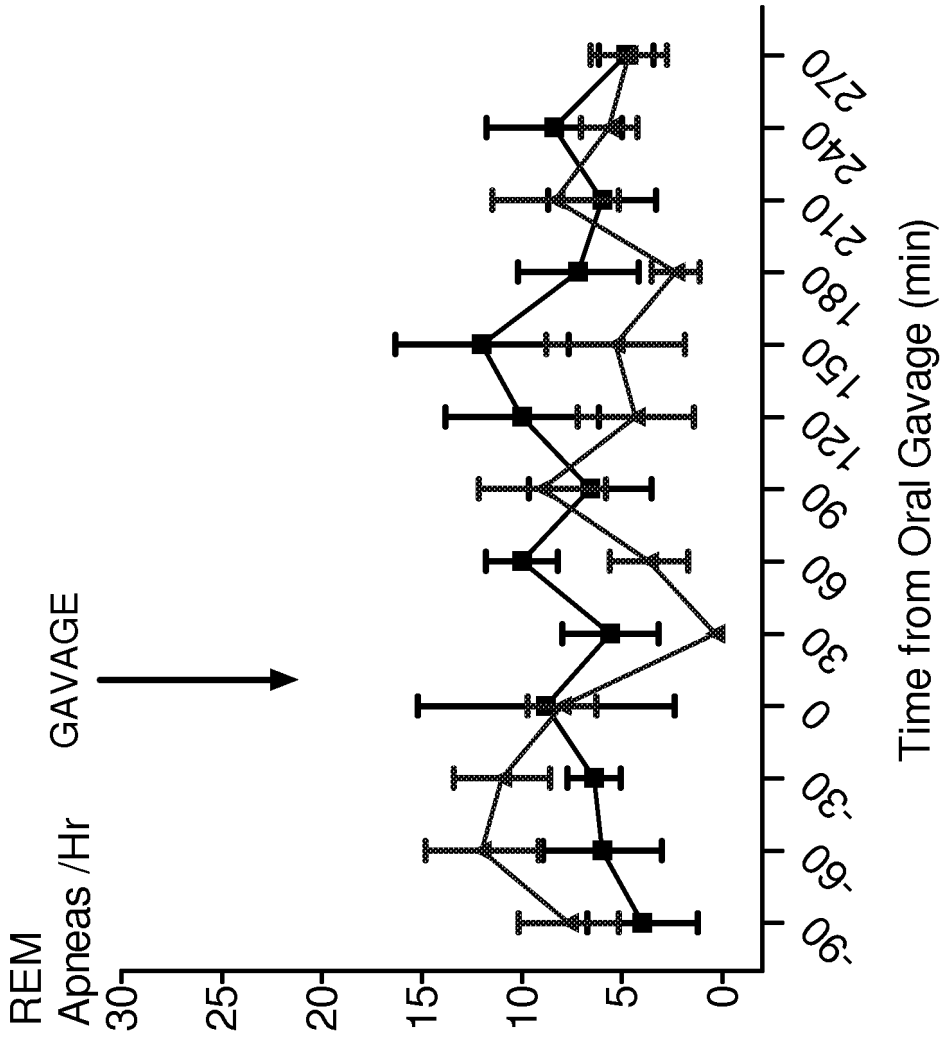


Fig. 46

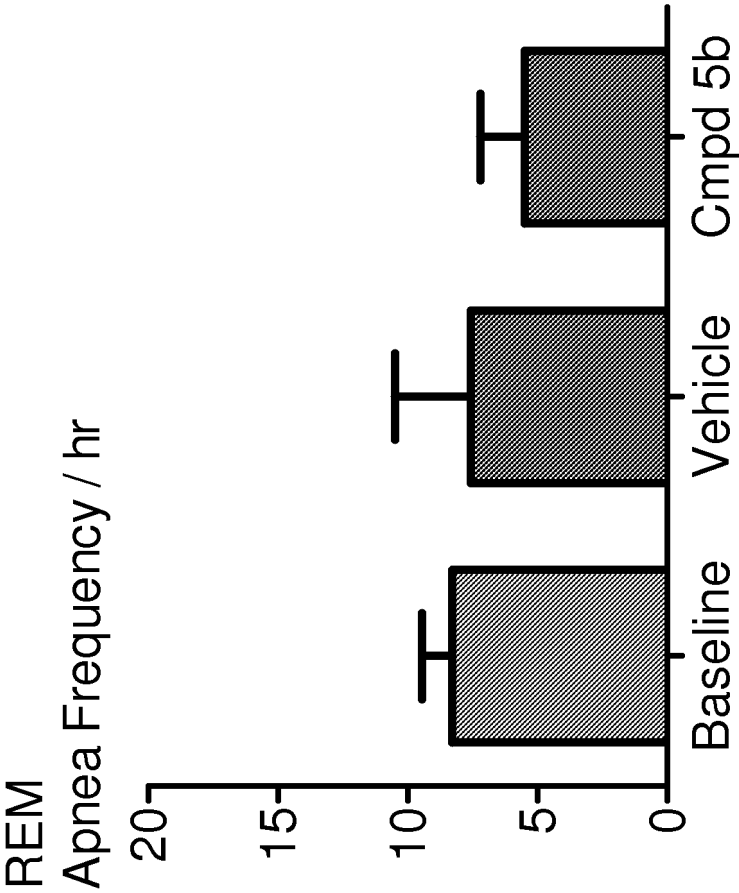


Fig. 47

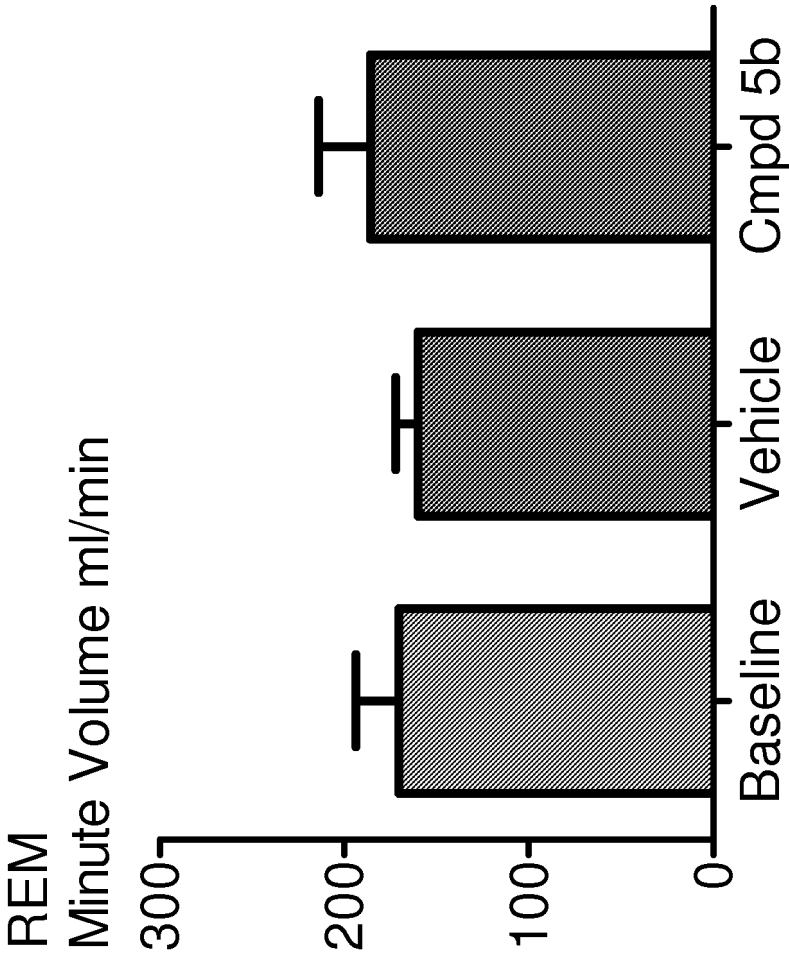


Fig. 48

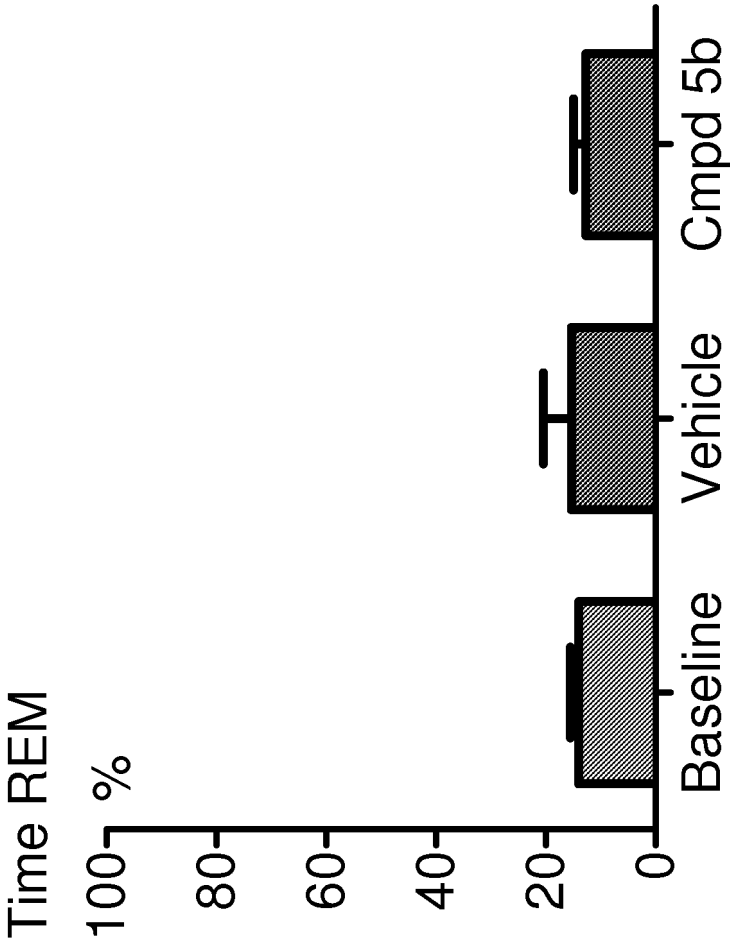


Fig. 49

