FIG. 1A

Salt Formers (pKa)	Solubility and Solid Formation Behavior as Function of Salt Former, Stoichiometric Ratio, Solvent, and Temperature																
	MEK	MIBK	EtOAc	iPrOAc	Water	Hep-tane	MTBE	Cyclo-hex	Tol-uene	MeOH	EtOH	nPrOH	iPrOH	nBuOH	2-BuOH	iAmOH	THF	ACN
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H_2SO_4 1:1 <1, (-10)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)
H_2SO_4 2:1 <1, (-10)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)
HCl 1:1 <1 (-7)	I (rt.) PS (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	S (rt.)	I (rt.) S (ref.)	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) PS (ref.) X	I (rt.) S (ref.) X
HCl 2:1 <1 (-7)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X (rt.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X	PS (rt.) S (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) PS (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)
MsOH 1:1 (-1.9)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	S (rt.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X	PS (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) PS (ref.) X	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) S (ref.) X
MsOH 2:1 (-1.9)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	S (rt.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	I (rt.) I (ref.)	PS (rt.) S (ref.) X	PS (rt.) S (ref.) X	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) S (ref.) X	I (rt.) I (ref.)	I (rt.) I (ref.)
TsOH 1:1 (-1.34)	S (rt.)	S (rt.)	S (rt.)	PS (rt.) S (ref.) X	PS (rt.) melt (ref.) X	I (rt.) I (ref.)	PS (rt.) S (ref.) X	I (rt.) melt (ref.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)	S (rt.)

(rt.) = room temperature (ref) = reflux S = soluble PS = partially soluble I = insoluble X = solids observed

FIG. 1B

Salt Formers (pKa)	Solubility and Solid Formation Behavior as Function of Salt Former, Stoichiometric Ratio, Solvent, and Temperature																	
	MEK	MIBK	EtOAc	iPrOAc	Water	Hep-tane	MTBE	Cyclo hex.	Tol-uene	MeOH	EtOH	nPrOH	iPrOH	nBuOH	2-BuOH	iAm OH	THF	ACN
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Saccharin	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	PS (rt.)	I (rt.)
1:1	S (ref.)	S (ref.)	S (ref.)	S (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)
(1.6)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Malonic	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)
1:1	S (ref.)	S (ref.)	S (ref.)	PS (ref.)	S (ref.)	I (ref.)	I (ref.)	I (ref.)	PS (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)
(2.9, 5.7)	X	X	X	X	X	X	X	X	X	X(+1[b])	X	X	X	X	X	X	X	X
Maleic	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	S (rt.)	PS (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	S (rt.)	PS (rt.)
1:1	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S-oil	I (ref.)	I (ref.)	I (ref.)	S (ref.)		S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)		S (ref.)
(1.9, 6.07)	X	X	X	X	(ref.)				X		X	X	X	X	X	X		X
L-	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)
Tartaric	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	S (ref.)	S (ref.)	I (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)
1:1											X	X		X	X	X	X	X
(2.89, 4.4)																		
Fumaric	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)
1:1	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	I (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	PS (ref.)	S (ref.)	I (ref.)	I (ref.)
(3.0, 4.4)										X	X	X	X	X	X	X	X	
D,L-	S (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	I (rt.)	PS (rt.)	I (rt.)	I (rt.)	I (rt.)	PS (rt.)	I (rt.)	I (rt.)	S (rt.)	I (rt.)
Mandelic	X (+1[b])	S (ref.)	S (ref.)	S (ref.)	I (ref.)	I (ref.)	S (ref.)	PS (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)	S (ref.)		S (ref.)
1:1		X	X	X			X		X		X (+1[b])		X		X	X		X
(3.4)																		

(rt.) = room temperature (ref) = reflux S = soluble PS = partially soluble I = insoluble X = solids observed

FIG. 2

A	B	C	D	E	F	G	H
Salt	**Free base (g)**	**Solvent**	**Yield (g)**	**Major Endotherm Peaks (^{0}C)**	**Theoretical**	**Found**	**^{1}H NMR solvent**
HCl **(31a)**	1.0	1:20 EtOH/Et_2O (31 mL/g)	1.0	213.47	C: 48.58 H: 7.34 N: 30.21	C: 48.38 H: 7.34 N: 30.12	CD_3OD
Bis HCl **(31b)**	14.0	1:13 EtOH/Et_2O (14 mL/g)	16.4	213.23, 241.38)	C: 44.23 H: 6.93 N: 27.51	C: 44.24 H: 6.81 N :27.42	CD_3OD
Hydrogen Malonate **(31c)**	0.9	20:1 EtOAc/EtOH (35 mL/g)	1.1	148.82, 159.16	C: 49.31 H: 6.90 N: 25.55	C: 49.26 H: 6.88 N: 25.65	CD_3OD
Hydrogen Maleinate **(31d-1)** (form Mal-A)	1.5	1:16 EtOH/Et_2O (28 mL/g)	1.8	105.20 118.86 (exoth) 153.14 158.28	C: 50.66 H: 6.71 N: 24.87	C: 50.57 H: 6.66 N: 24.69	CD_3OD
Hydrogen Maleinate **(31d-2)** (form Mal-B)		From exposure of of Mal-A to humidity		159.04			
Hydrogen Fumarate **(31e)**	1.5	EtOH (23 mL/g)	1.8	232.36	C: 50.66 H: 6.71 N: 24.87	C: 50.56 H: 6.67 N: 24.95	CD_3OD
Hydrogen *L(+)*-Tartrate **(31f)**	1.5	1:16 EtOH/Et_2O (28 mL/g)	1.8	215.71	C: 49.05 H: 7.00 N: 26.12	C: 48.95 H: 7.16 N: 26.12	DMSO
D,L-Mandelate **(31g)**	1.5	1:16 EtOH/Et_2O (28 mL/g)	2.0	163.04	C: 56.78 H: 7.04 N: 23.03	C: 56.86 H: 7.04 N: 23.12	CD_3OD
Tosylate **(31h-1)** (Tos-A)	1.2	MTBE (15 mL/g)	1.6	110.34	C: 52.16 H: 6.76 N: 22.12 S: 6.33	C: 52.23 H: 6.82 N: 22.32 S: 6.34	CD_3OD
Tosylate **(31h-2)** (Tos-B)	1.2	From exposure of of Tos-A to humidity		51.18			
Mesylate **(31i)**	1.5	MeCN (15 mL/g)	1.2	183.52	C: 44.64 H: 7.02 N: 26.03 S: 7.45	C: 44.67 H: 7.09 N: 26.13 S: 7.27	CD_3OD
Saccharinate **(31j)**	1.2	1:16 EtOH/Et_2O (30 mL/g)	1.7	204.96	C: 51.05 H: 6.04 N: 24.35	C: 51.09 H: 6.06 N: 24.36	DMSO

FIG. 3A

XRPD of **31a**, Hydrochloride Salt Form

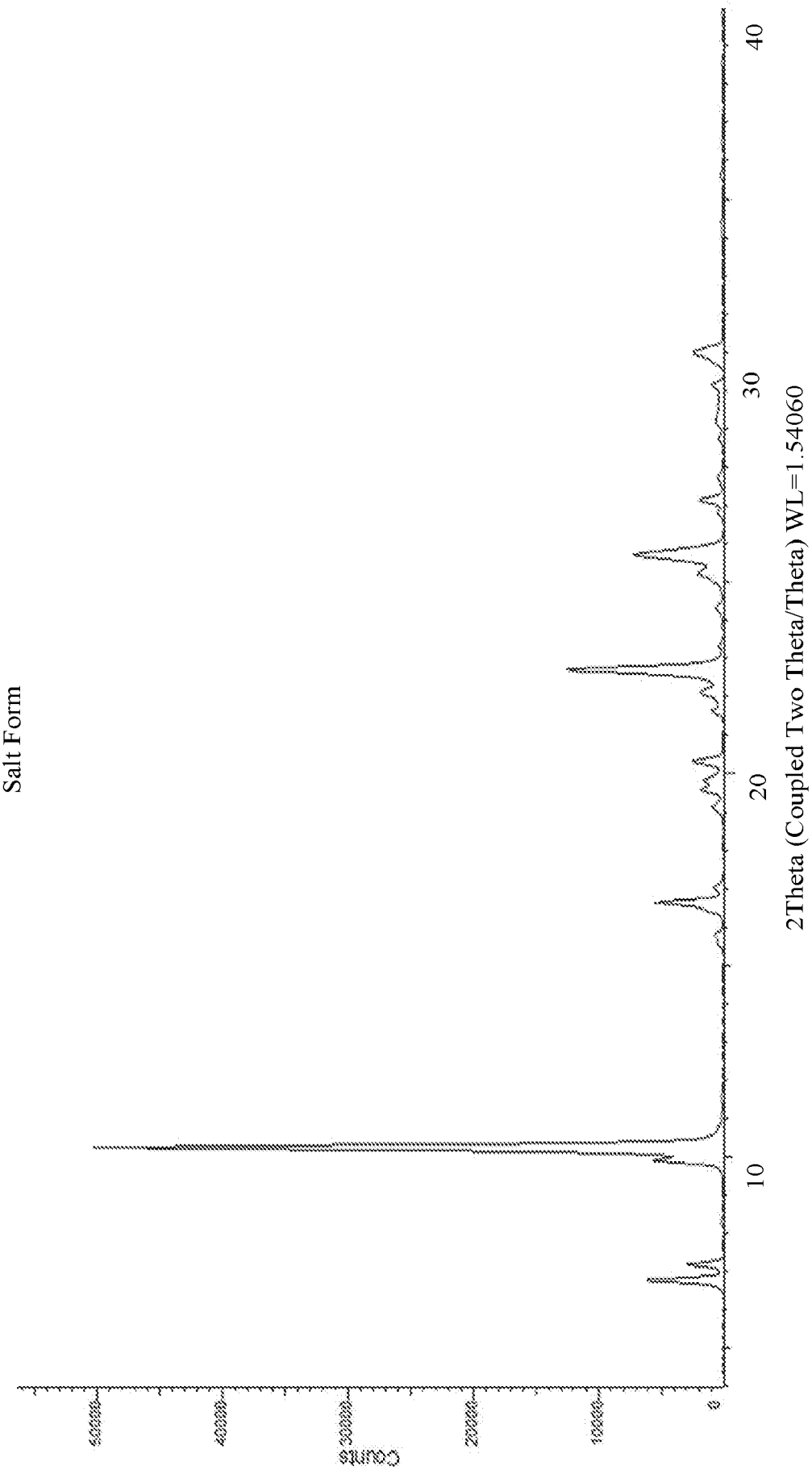


FIG. 3B

Selected XRPD Peak List for **31a**, Hydrochloride Salt Form

Angle, 2θ	d spacing, °A	Relative intensity, %
6.78	13.02681	12.2
7.19	12.28934	5.8
9.92	8.91107	10.9
10.24	8.63187	100
16.63	5.32583	10.9
19.59	4.52644	3.7
19.82	4.47601	3.2
20.32	4.36694	4.9
22.13	4.01431	3.7
22.71	3.91184	24.8
25.24	3.52565	4.2
25.72	3.46098	14.4
27.14	3.28345	3.9
30.99	2.88319	4.9

FIG. 3C

DSC of **31a**, Hydrochloride Salt Form

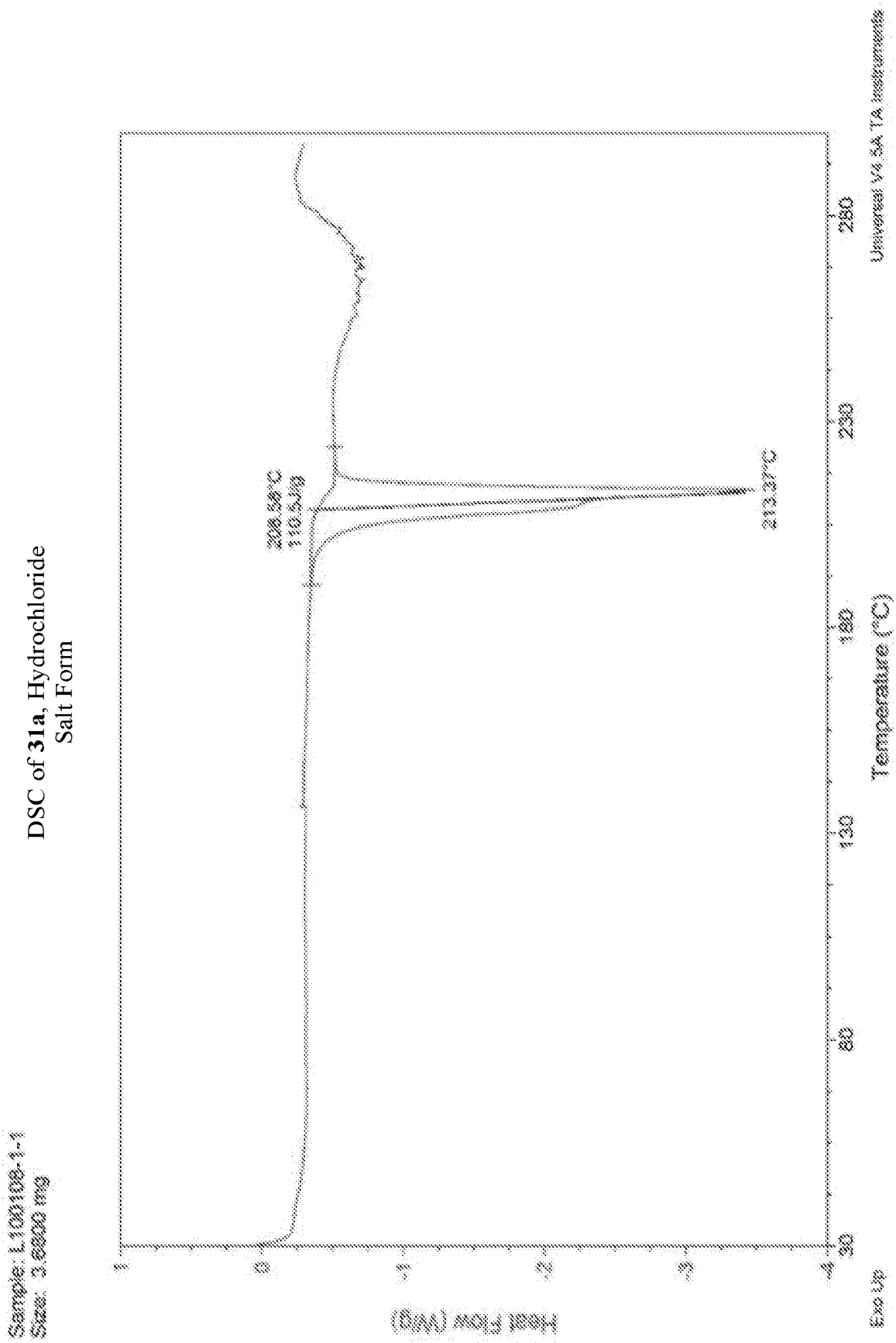


FIG. 4A

XRPD of **31b**, bis-Hydrochloride Salt Form

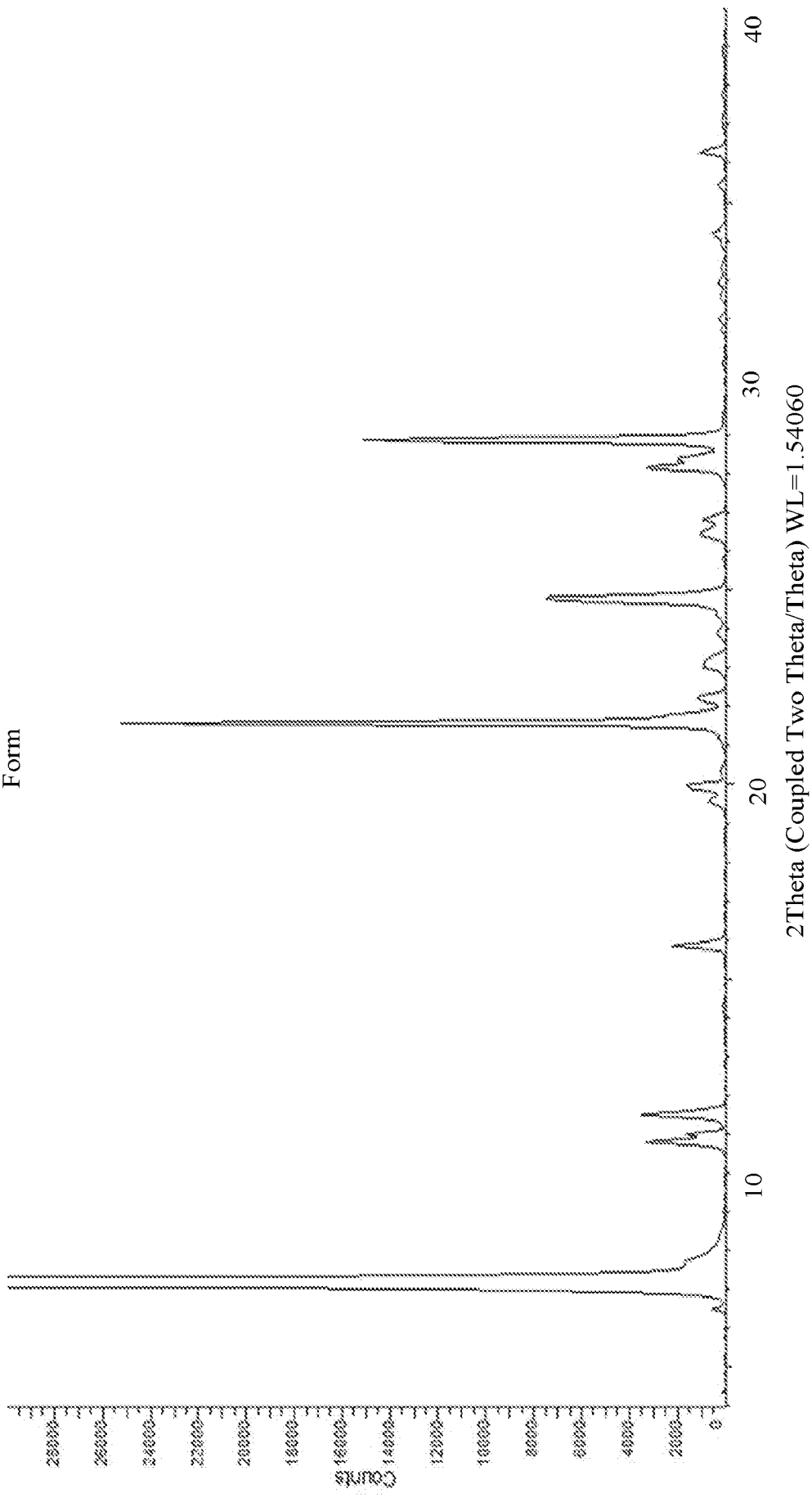


FIG. 4B

Selected XRPD Peak List for **31b**, bis-Hydrochloride Salt Form

Angle, 2θ	d spacing, °A	Relative intensity, %
7.20	12.27252	100
10.80	8.18326	1
10.97	8.06214	0.4
11.50	7.68791	1
15.85	5.58721	0.6
19.94	4.44923	0.4
21.58	4.11506	7.5
24.78	3.59028	2.3
26.83	3.32073	0.3
28.18	3.16451	1
28.88	3.0895	4.5

FIG. 4C

DSC for **31b**, bis-Hydrochloride Salt Form

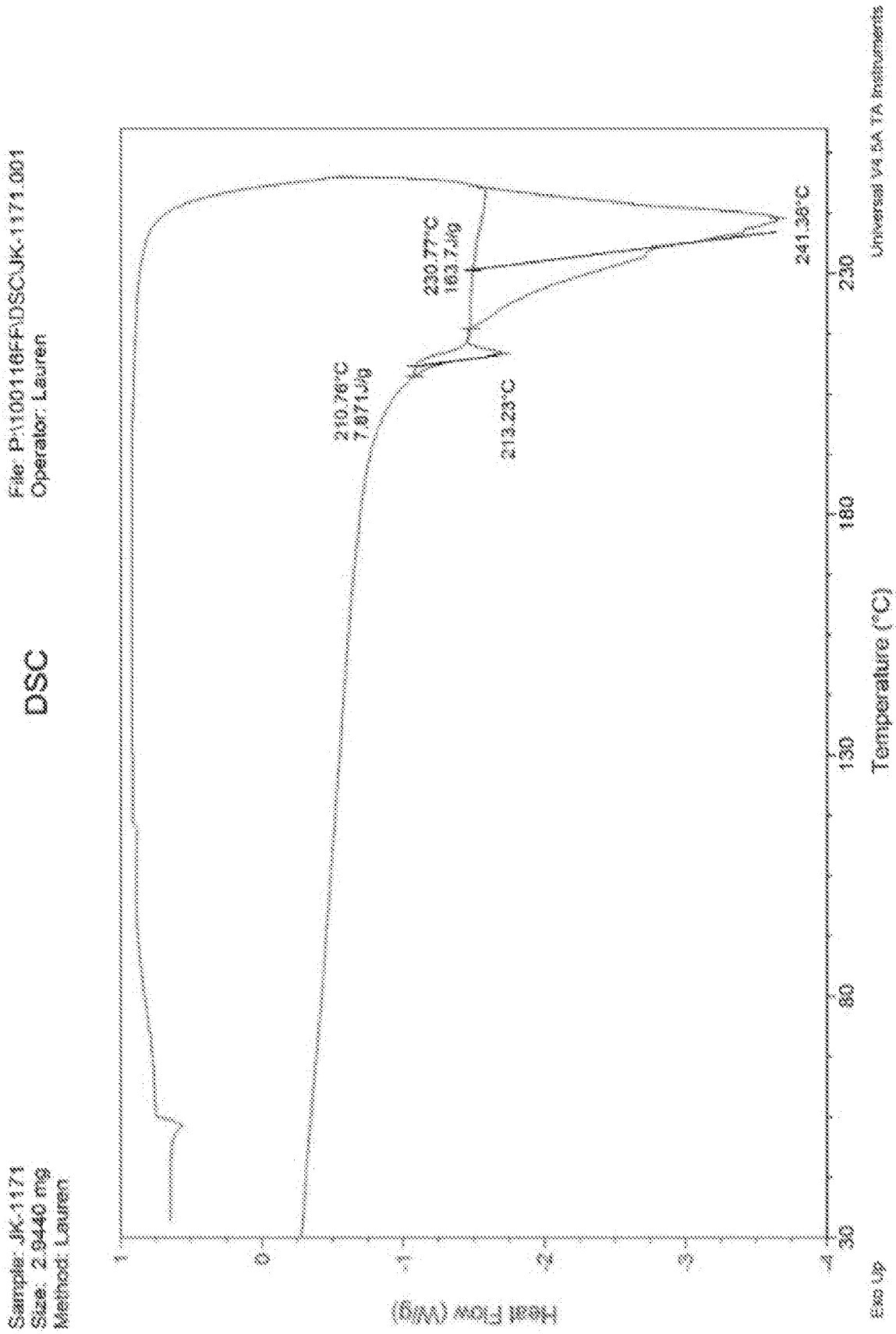


FIG. 5A

XRPD of **31c**, Hydrogen Malonate Salt Form

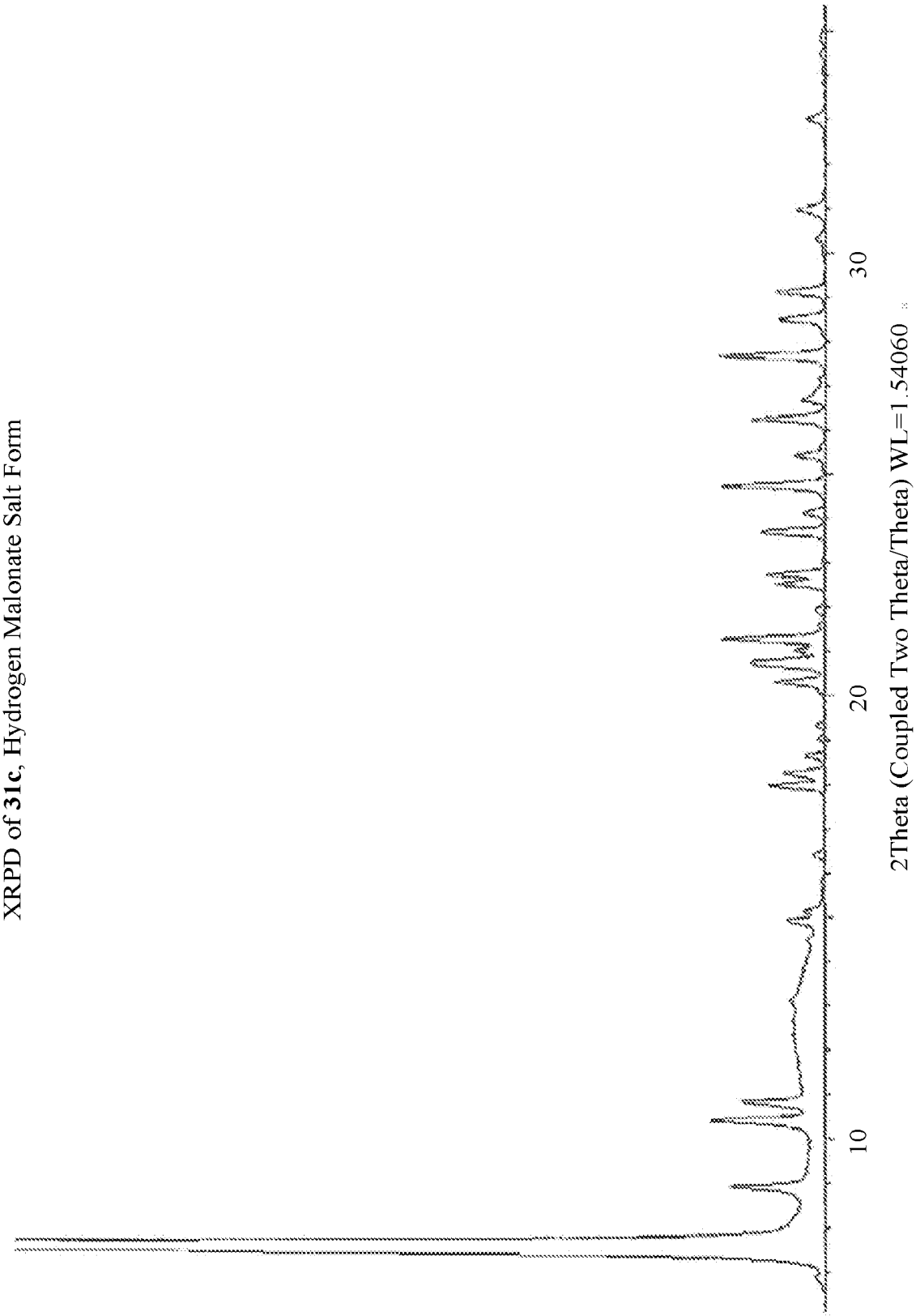


FIG. 5B

Selected XRPD Peak List for **31c**, Hydrogen Malonate Salt Form

Angle, 2 θ	d spacing, °A	Relative intensity, %
7.59	11.63447	100
8.92	9.90534	2
10.40	8.49625	2.4
10.80	8.18579	1.8
17.98	4.92979	1.2
20.30	4.37071	1
20.74	4.27862	1.6
21.28	4.17159	2.2
22.73	3.90913	1.3
23.67	3.7552	1.3
24.73	3.59764	2.3
26.23	3.3949	1.6
27.67	3.22152	2.4
28.48	3.13163	1
29.12	3.06452	1.1

FIG. 5C

DSC of **31c**, Hydrogen Malonate Salt Form

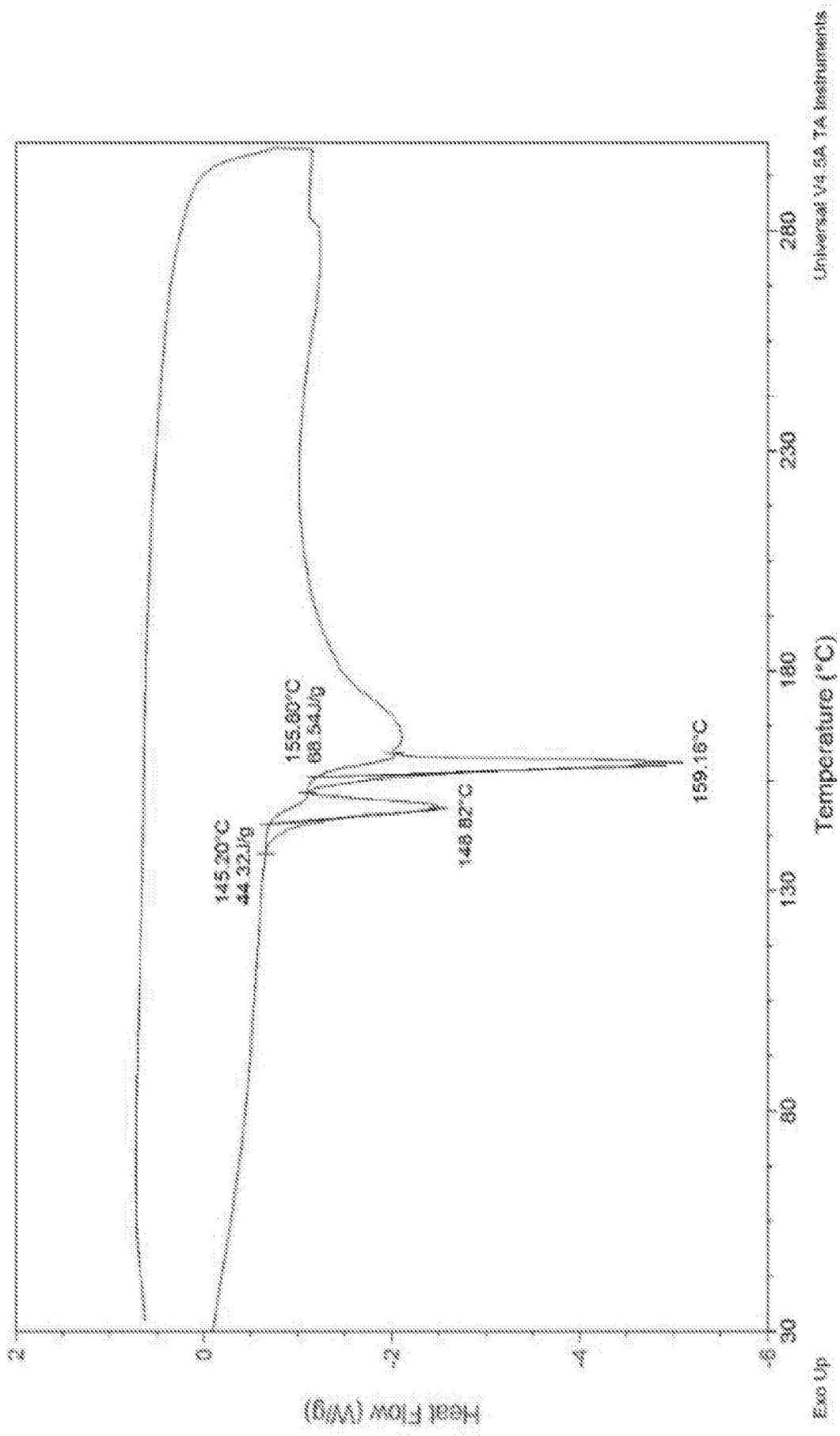


FIG. 6A

XRPD of **31d-1**, Hydrogen Maleinate Salt, Form Mal-A

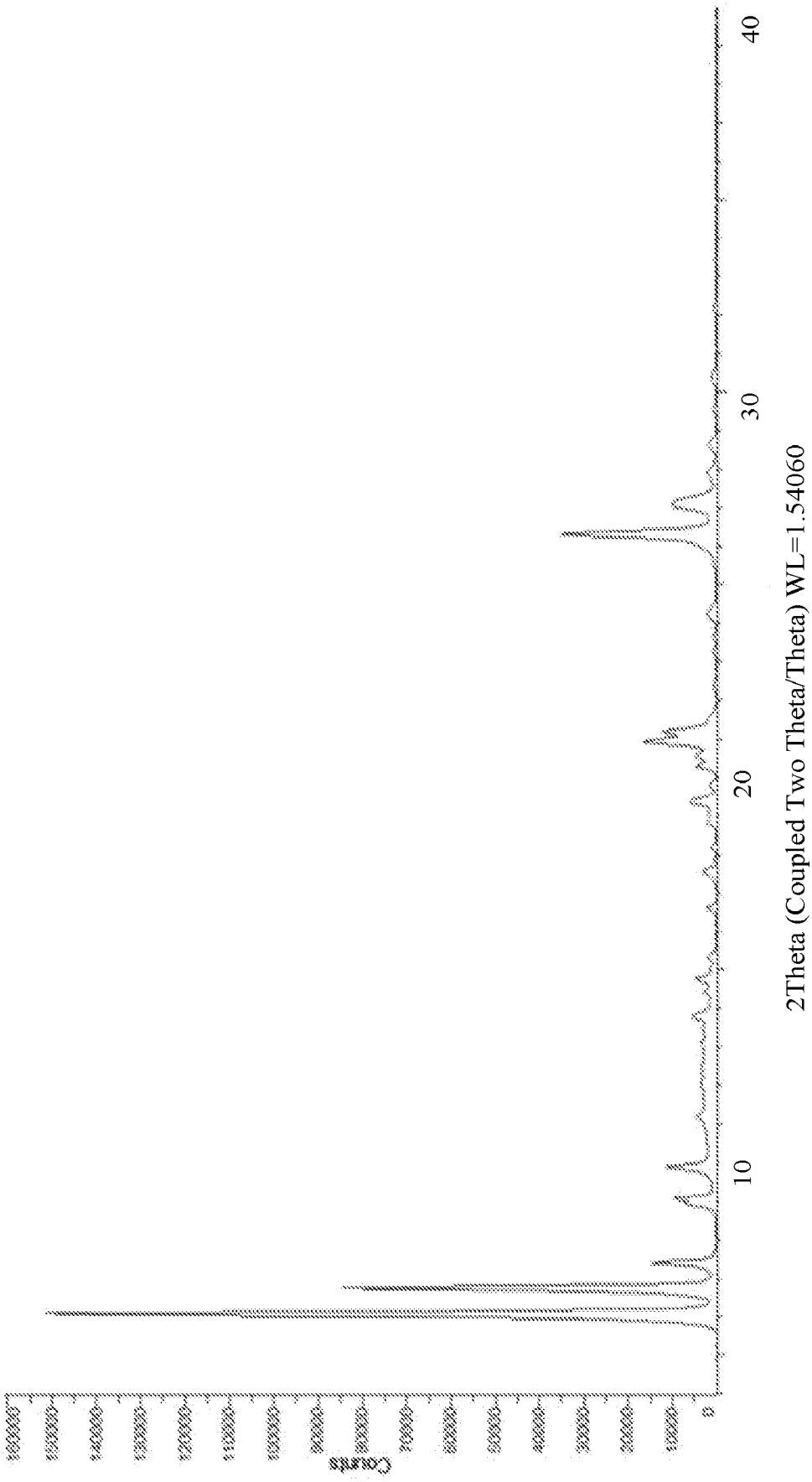


FIG. 6B

Selected XRPD Peak List for **31d-1** Hydrogen Maleinate Form Mal-A

Angle, 2 θ	d spacing, °A	Relative intensity, %
6.08	14.52263	100
6.74	13.10492	56.4
7.40	11.94069	8.9
8.94	9.87886	4.3
9.08	9.73529	5.5
9.89	8.9369	8.1
19.39	4.57431	4
20.93	4.24119	9.85
21.18	4.19183	7.3
26.31	3.38423	24.1
27.12	3.28575	7.1

FIG. 6C

DSC of **31d-1**, Hydrogen Maleinate Salt, Form Mal-A

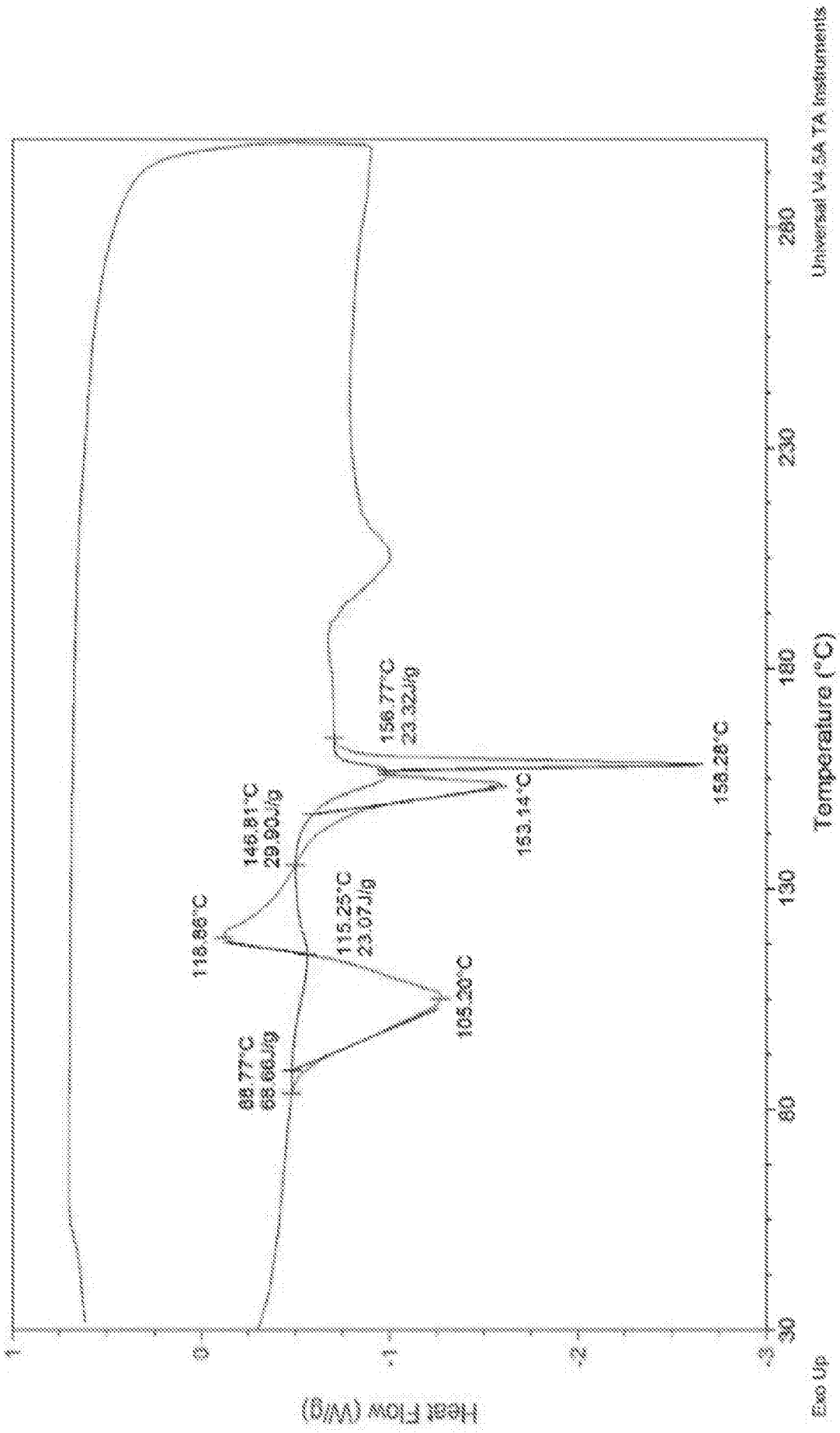


FIG. 7A

XRPD of **31d-2**, Hydrogen Maleinate Salt, Form Mal-B

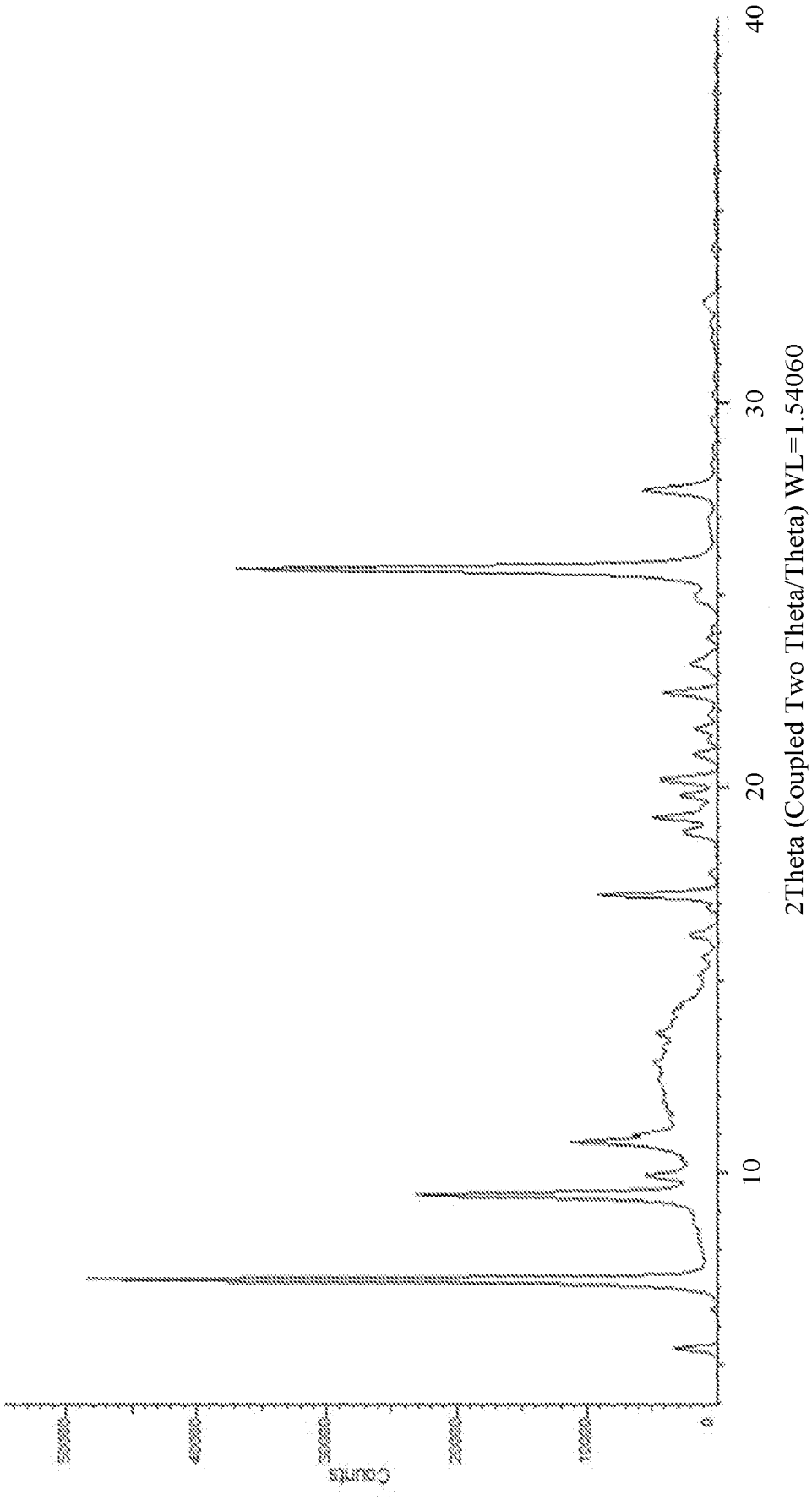


FIG. 7B

Selected XRPD Peak List for **31d-2**, Hydrogen Maleinate Salt, Form Mal-B

Angle, 2θ	d spacing, °A	Relative intensity, %
5.45	16.21189	5
7.24	12.19919	100
9.43	9.37101	45
10.79	8.19325	6.7
16.20	5.46745	3.6
17.21	5.14751	16
18.84	4.70602	4.5
19.23	4.61256	9
19.80	4.48068	5
20.21	4.38948	7.5
22.48	3.95265	8.9
23.23	3.82667	5.2
25.67	3.4673	89.9
27.73	3.21485	14

FIG. 7C

DSC of **31d-2**, Hydrogen Maleinate Salt, Form Mal-B

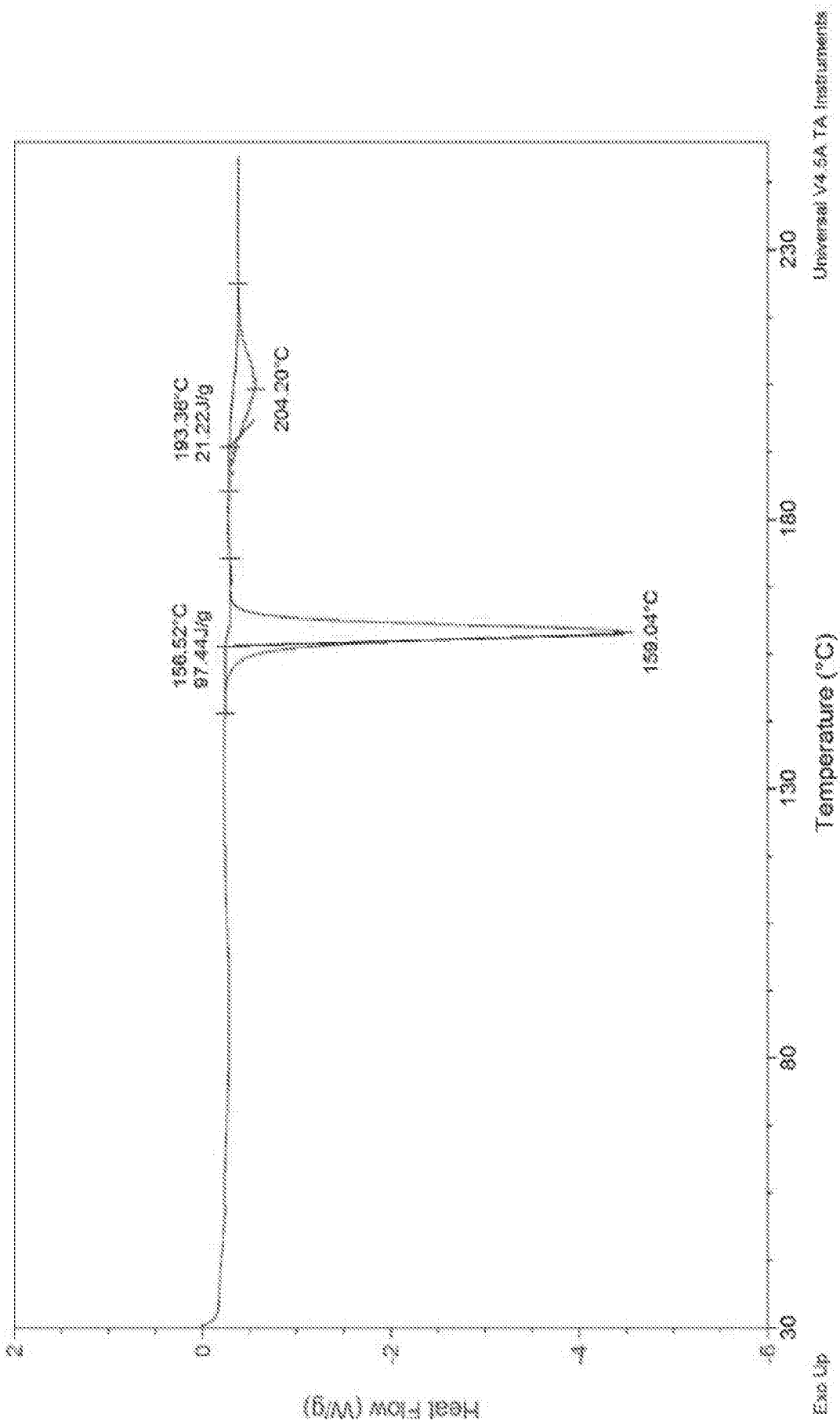


FIG. 8A

XRPD of **31e**, Hydrogen Fumarate Salt Form

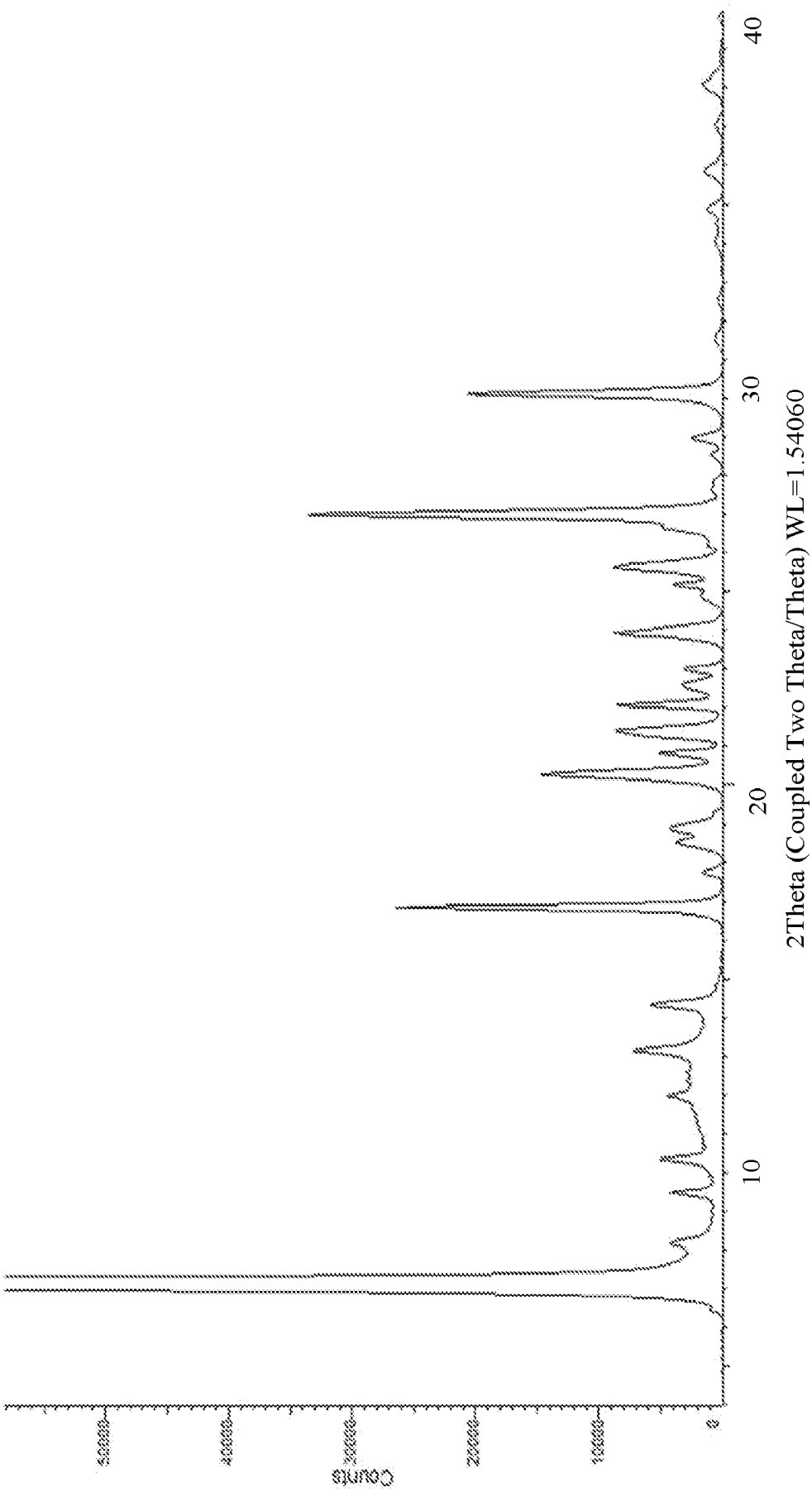


FIG. 8B

Selected XRPD Peak List for **31e**, Hydrogen Fumarate Salt Form

Angle, 2θ	d spacing, °A	Relative intensity, %
7.18	12.31057	100
10.34	8.54465	1.1
13.19	6.74397	1.6
14.28	6.1978	1.1
16.84	5.26205	6.1
20.28	4.37553	3.4
20.81	4.26428	1.2
21.39	4.15	2
22.08	4.02316	1.8
23.94	3.71411	1.9
25.63	3.47318	2
26.97	3.30309	7.7
30.11	2.96552	4.7

FIG. 8C

DSC of **31e**, Hydrogen Fumarate Salt Form

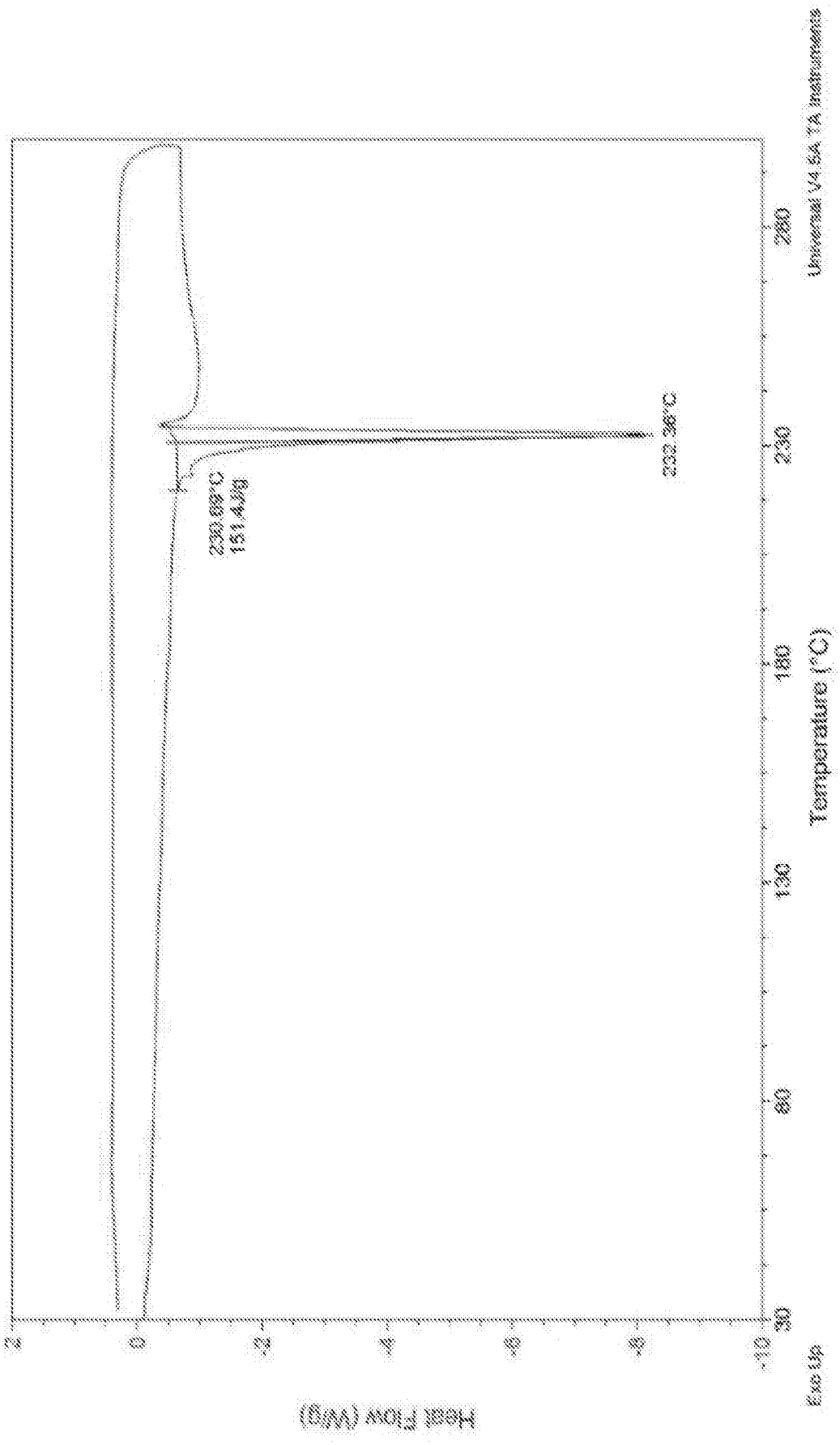


FIG. 9A

XRPD for **31f**, Hydrogen-*L*(+)Tartrate Salt Form

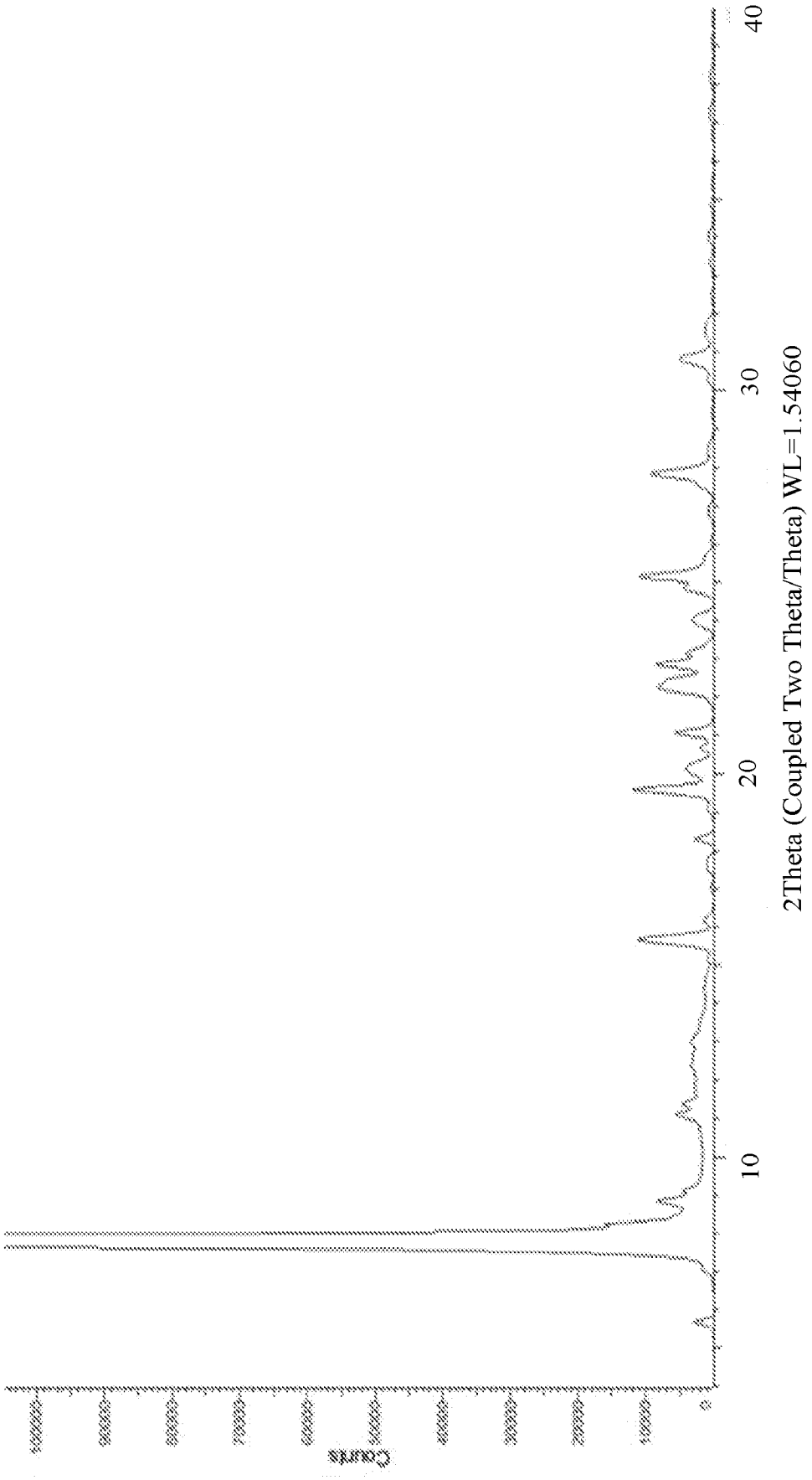


FIG. 9B

Selected XRPD Peak List for **31f**, Hydrogen-*L*(+)Tartrate Salt Form

Angle, 2θ	d spacing, °A	Relative intensity, %
7.80	11.32371	100
8.83	10.00916	1.28
9.09	9.7195	0.7
11.09	7.9704	0.9
15.67	5.6515	1.7
19.59	4.52881	1.9
20.11	4.41252	0.7
21.08	4.21114	0.9
22.34	3.97692	1.2
22.87	3.88501	1.4
25.11	3.54371	1.6
27.82	3.20476	1.5
30.82	2.89875	0.8

FIG. 9C

DSC for **31f**, Hydrogen-*L*(+)Tartrate Salt Form

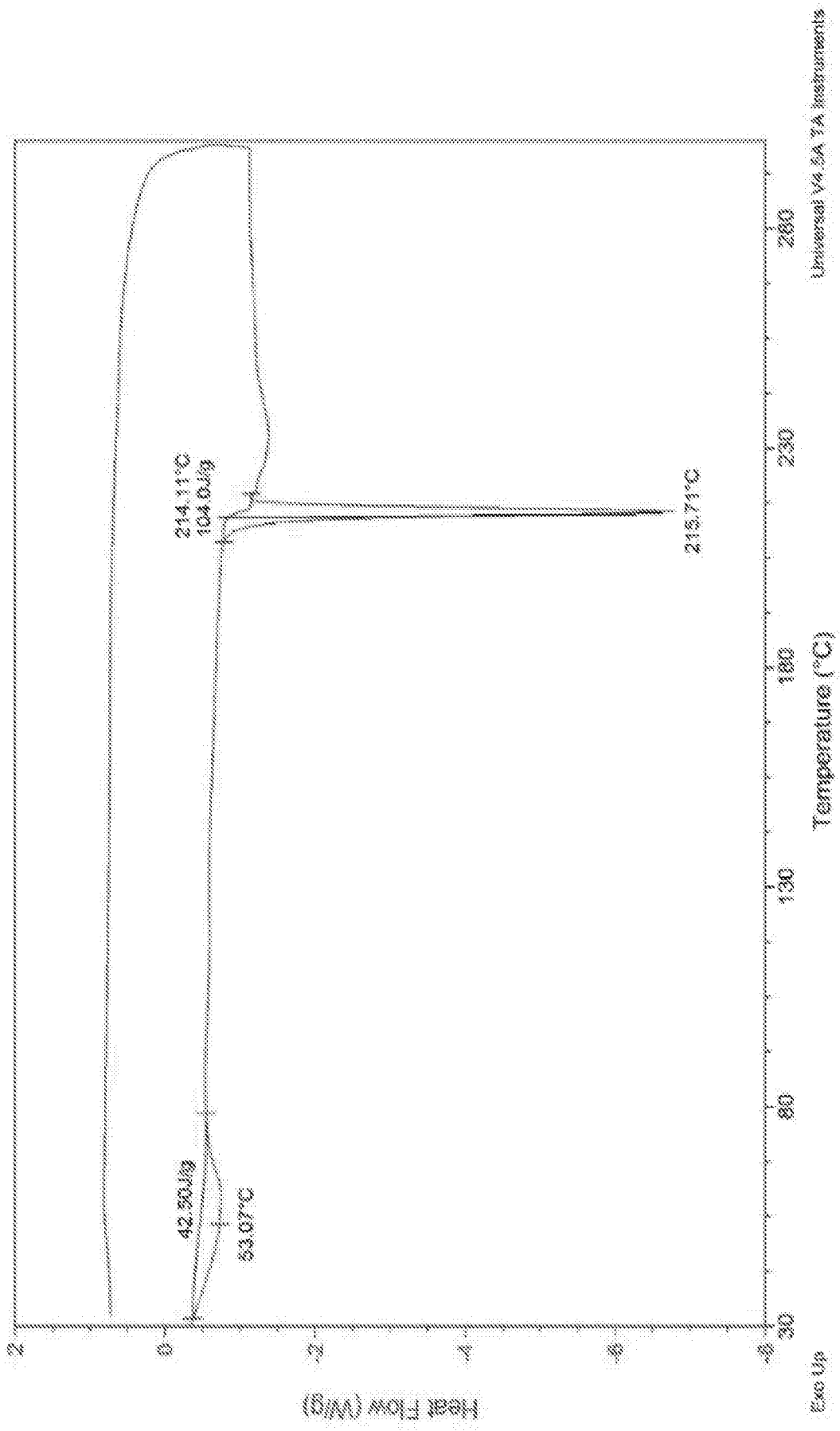


FIG. 10A

XRPD of **31g**, D,L-Mandelate Salt Form

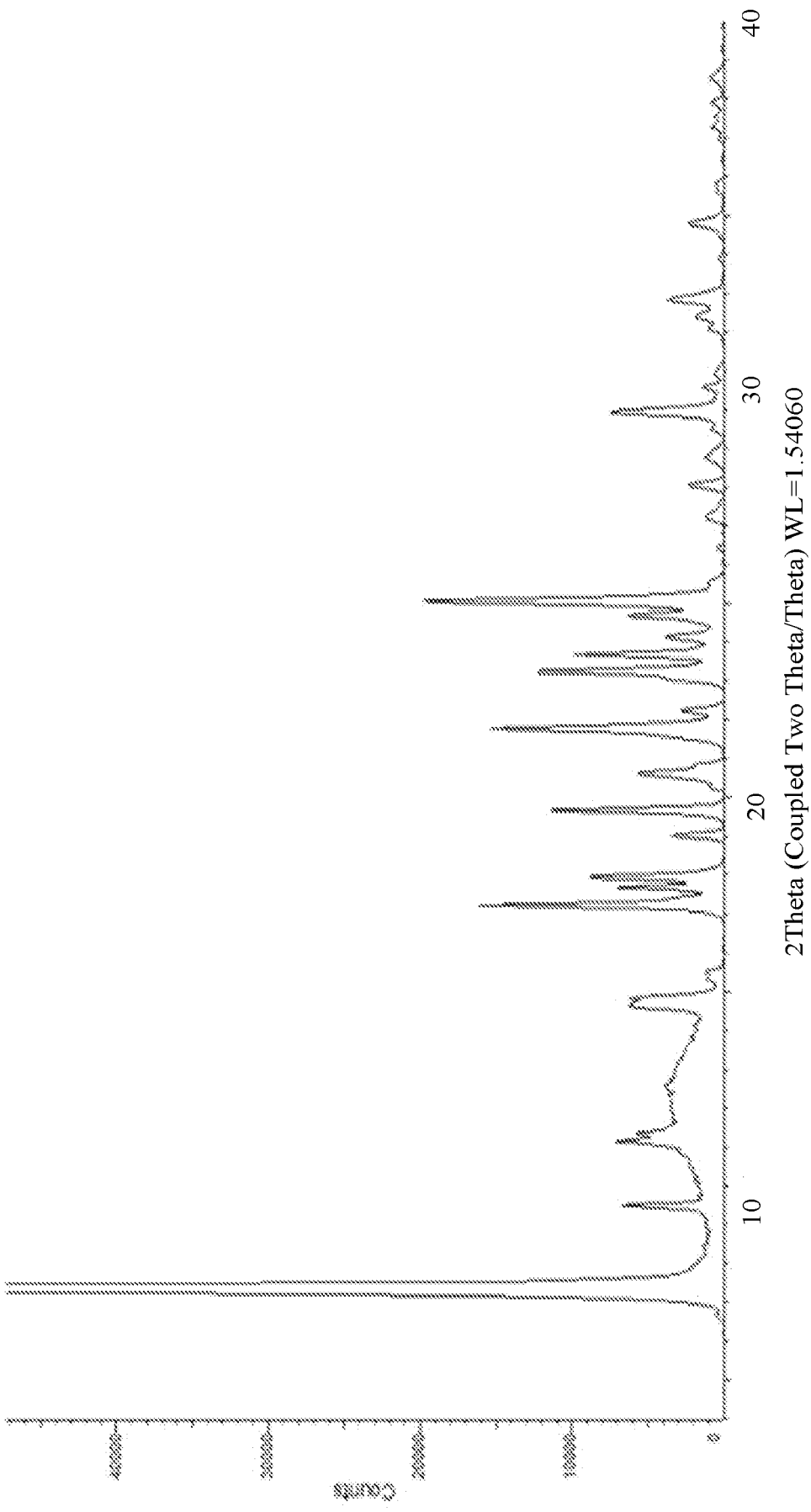


FIG. 10B

Selected XRPD Peak List for **31g**, D,L-Mandelate Salt Form

Angle, 2 θ	d spacing, °A	Relative intensity, %
7.39	11.9574	100
9.50	9.30745	2.8
11.14	7.93382	2.7
17.23	5.14296	6
17.68	5.01169	2.6
17.95	4.93691	3.3
19.68	4.50847	4.6
20.63	4.30283	2.4
21.77	4.07913	6.3
23.25	3.82359	4.6
23.68	3.74551	3.7
24.68	3.60391	2.4
25.06	3.55048	7.2
29.93	2.98311	3.1

FIG. 10C

DSC of **31g**, D,L-Mandelate Salt Form

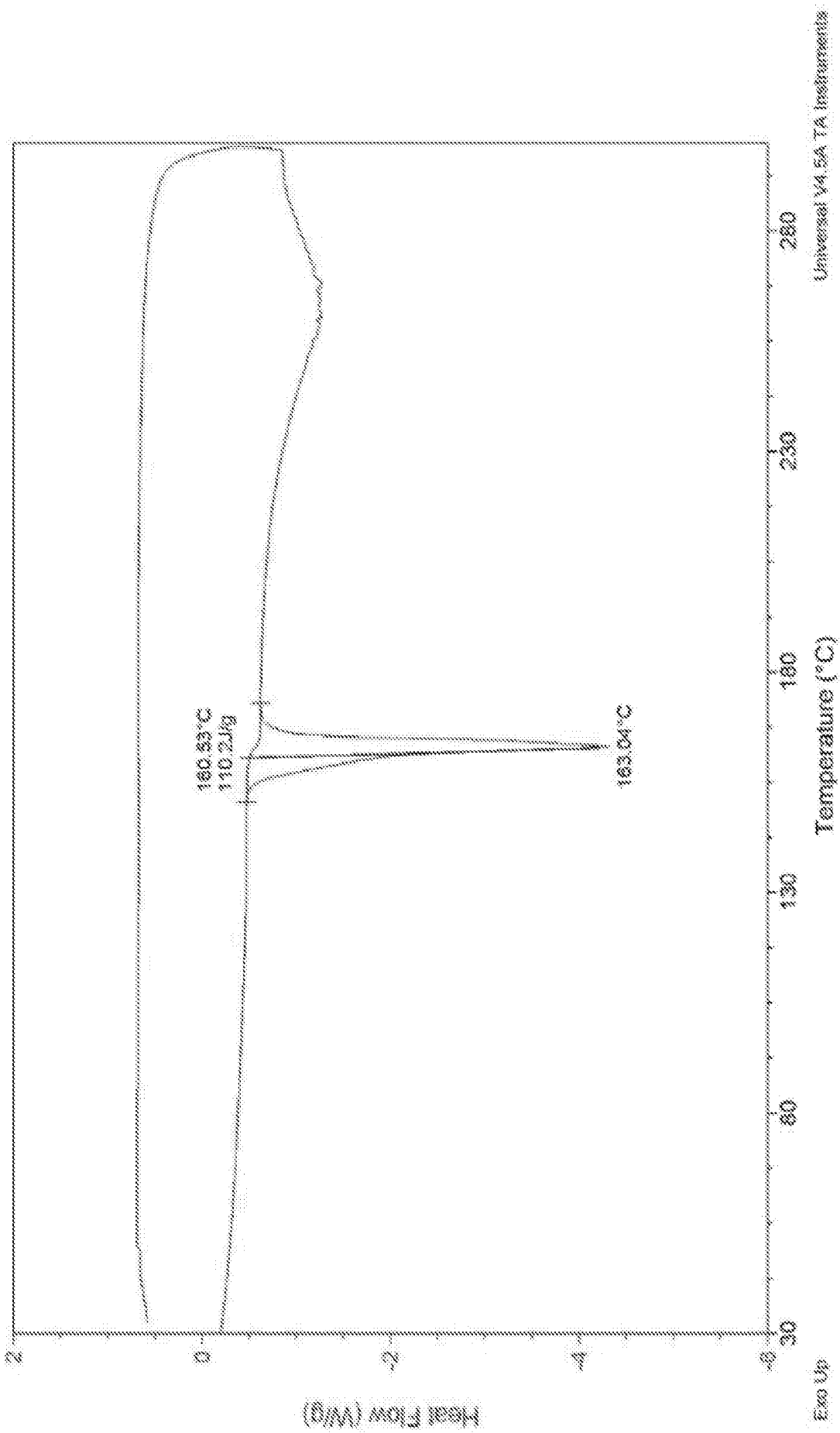


FIG. 11A

XRPD for **31h-1**, Tosylate Salt Form Tos-A

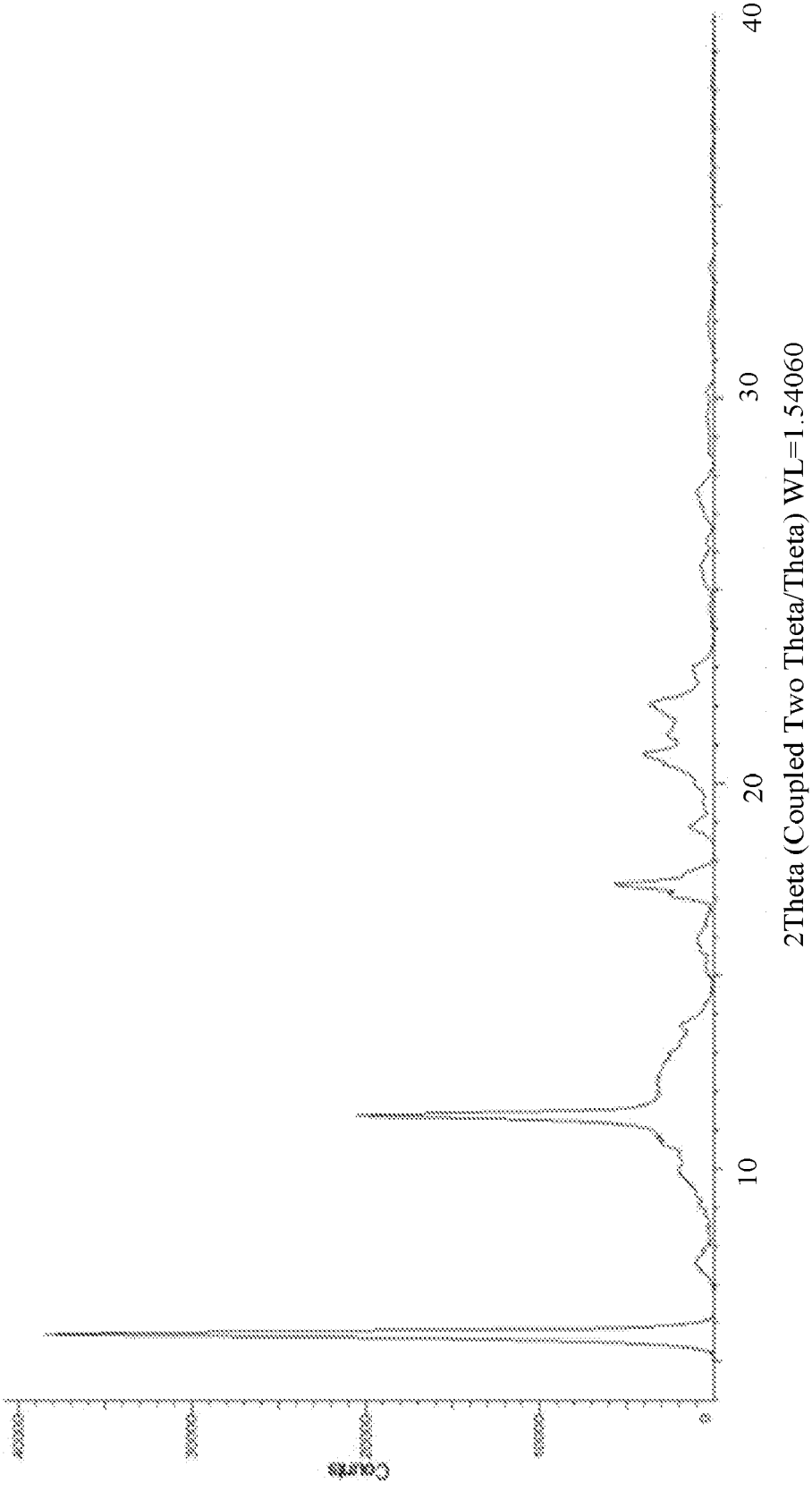


FIG. 11B

Selected XRPD Peak List for **31h-1**, Tosylate Salt Form Tos-A

Angle, 2 θ	d spacing, °A	Relative intensity, %
5.70	15.4874	100
11.35	7.78855	62.9
17.12	5.17511	4.5
17.38	5.09975	14.8
18.86	4.70049	4
20.72	4.28416	12.9
21.32	4.16358	8.3
21.97	4.04287	10.9

FIG. 11C

DSC for **31h-1**, Tosylate Salt Form Tos-A

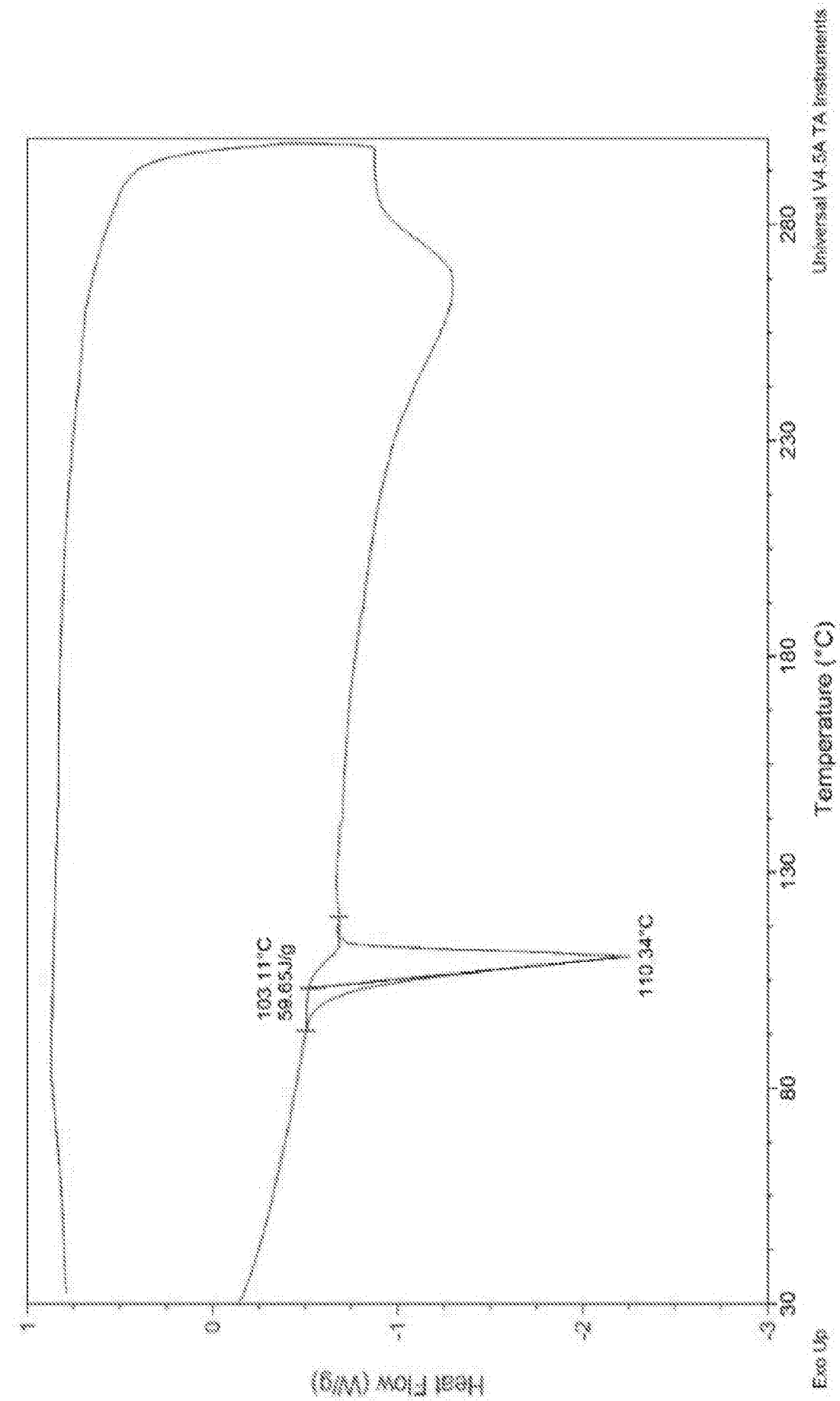


FIG. 12A

XRPD for **31h-2**, Tosylate Salt Form Tos-B

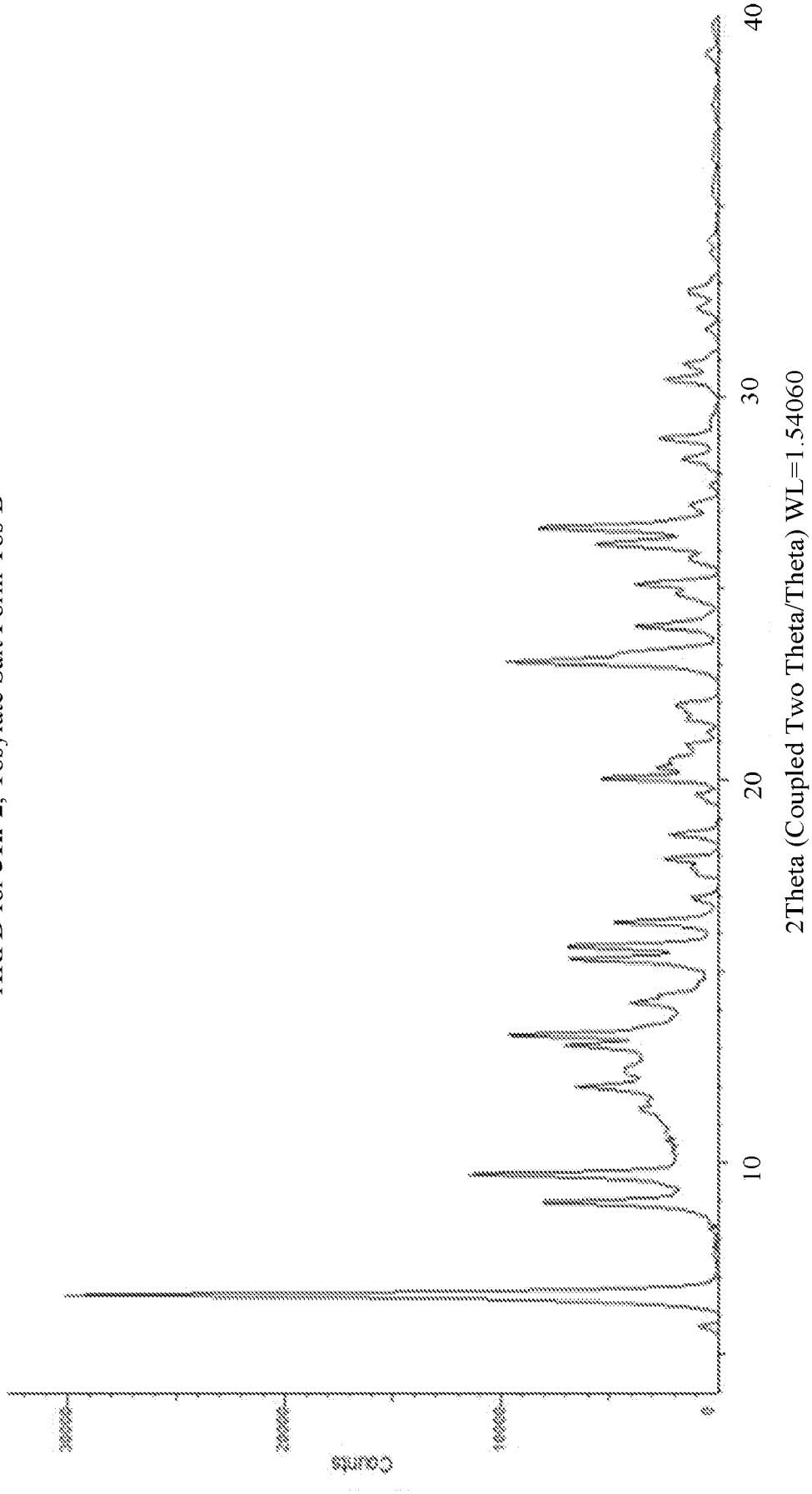


FIG. 12B

Selected XRPD Peak List for **31h-2**, Tosylate Salt Form Tos-B

Angle, 2 θ	d spacing, °A	Relative intensity, %
6.54	13.50497	100
8.97	9.85096	27.7
9.69	9.12314	38.6
11.99	7.3729	22.6
13.08	6.76363	24.6
13.34	6.63223	33.6
15.33	5.77497	23.9
15.66	5.65551	24
16.29	5.4381	16.6
20.04	4.42826	18.4
23.08	3.85138	33.5
26.15	3.40443	19.2
26.59	3.34967	28.2

FIG. 12C

DSC for **31h-2**, Tosylate Salt Form Tos-B

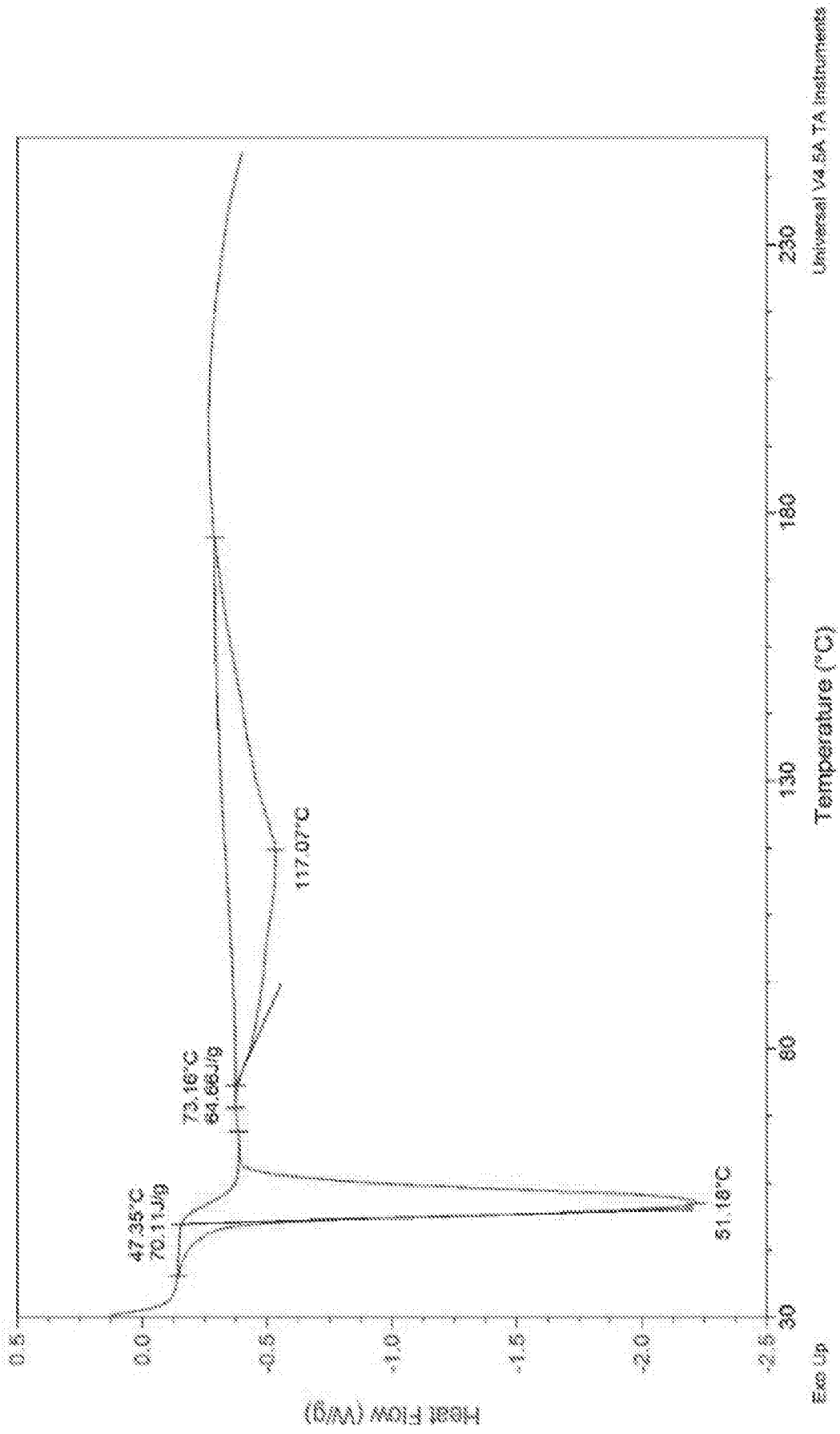


FIG. 13A

XRPD of **31i**, Mesylate Salt Form

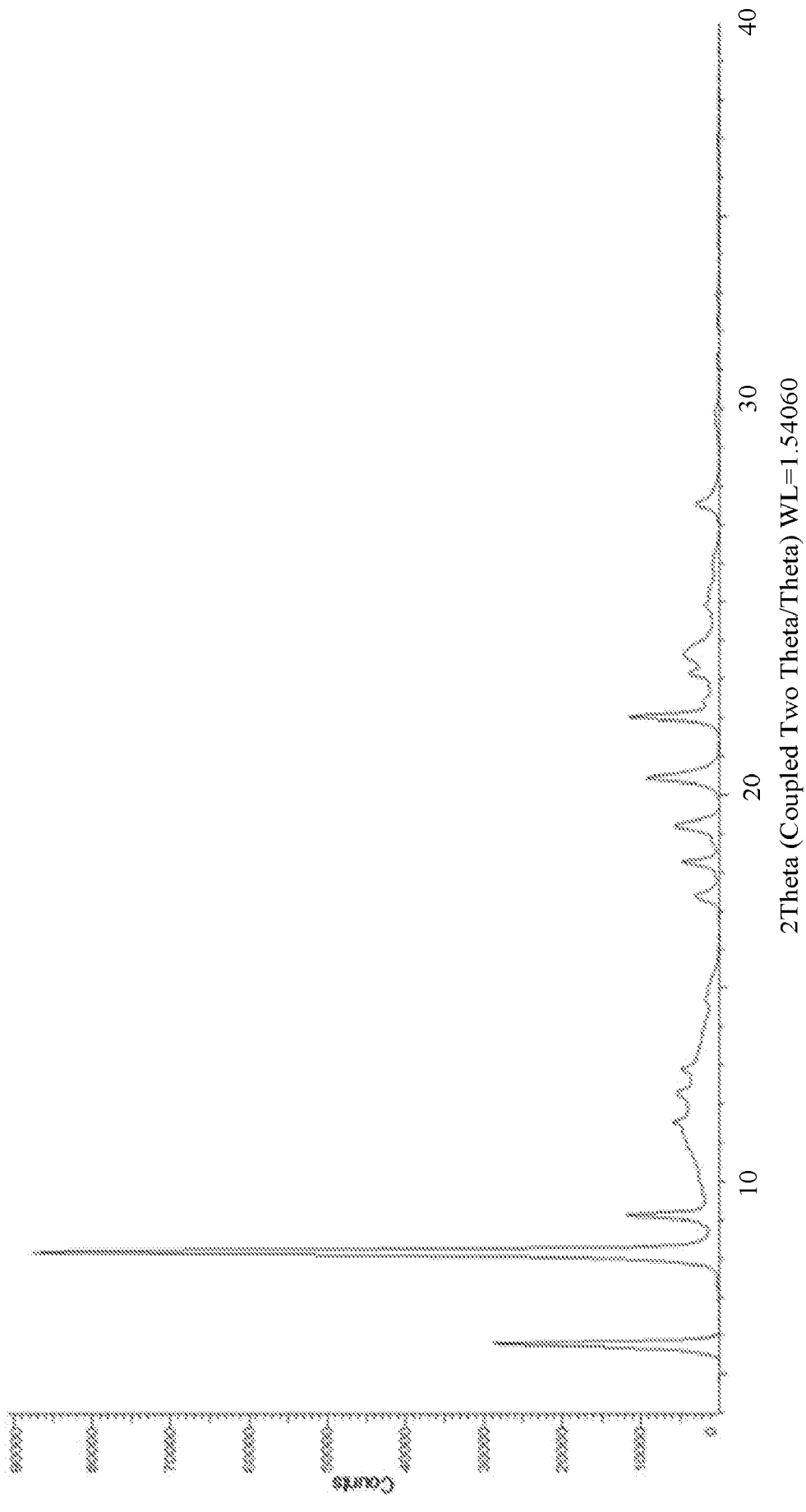


FIG. 13B

Selected XRPD Peak List **31i**, Mesylate Salt Form

Angle, 2 θ	d spacing, °A	Relative intensity, %
5.79	15.26275	25.7
8.15	10.84326	100
9.11	9.70536	12.5
12.90	6.8576	2.8
17.39	5.09461	3.5
18.27	4.85104	2.8
19.19	4.62145	6.5
20.48	4.33397	10.2
22.02	4.03292	11.4
23.65	3.75967	5.1
27.53	3.23687	3.2

FIG. 13C

DSC of **31i**, Mesylate Salt Form

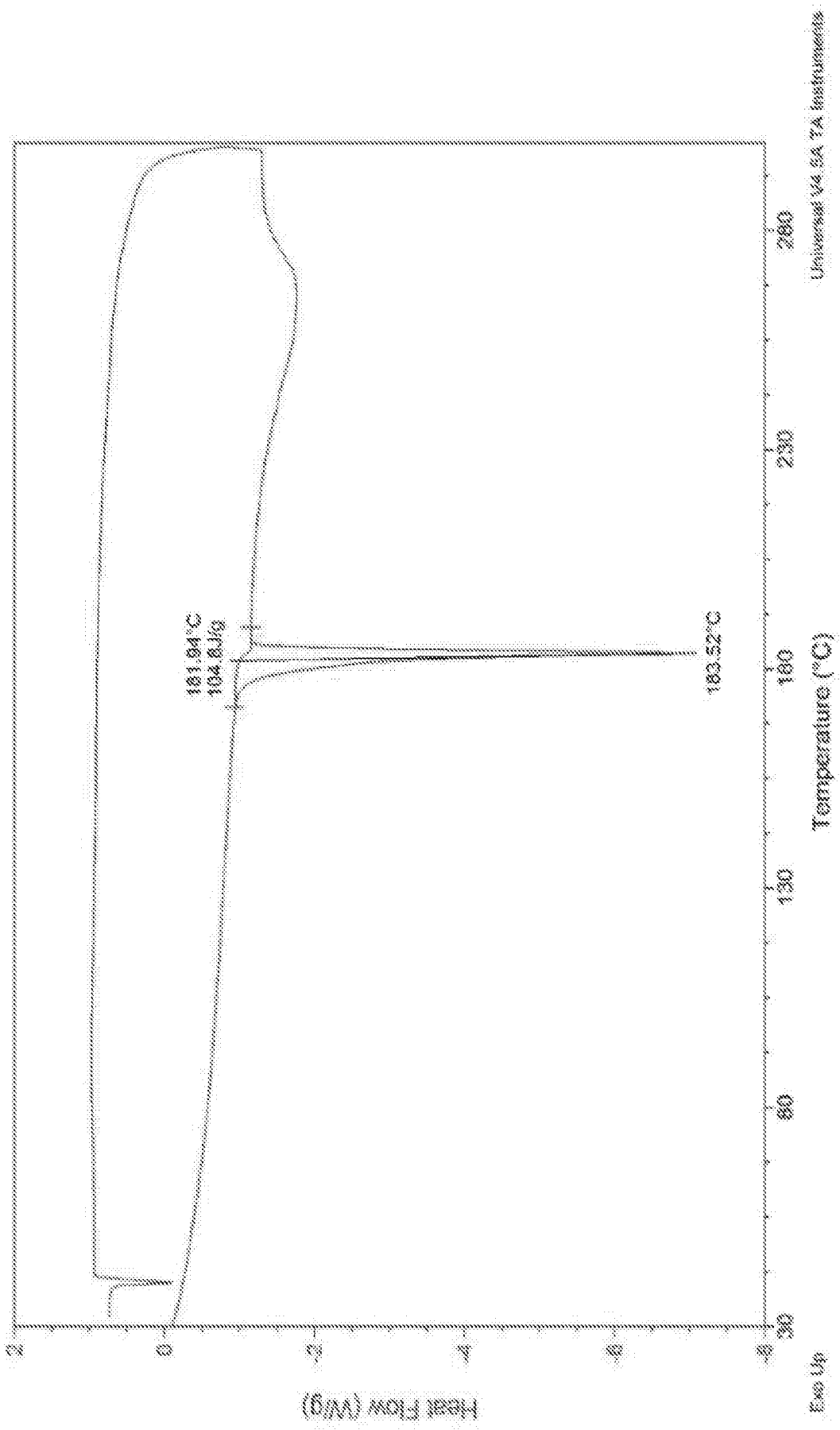


FIG. 14A

XRPD for **31j**, Saccharinate Salt Form

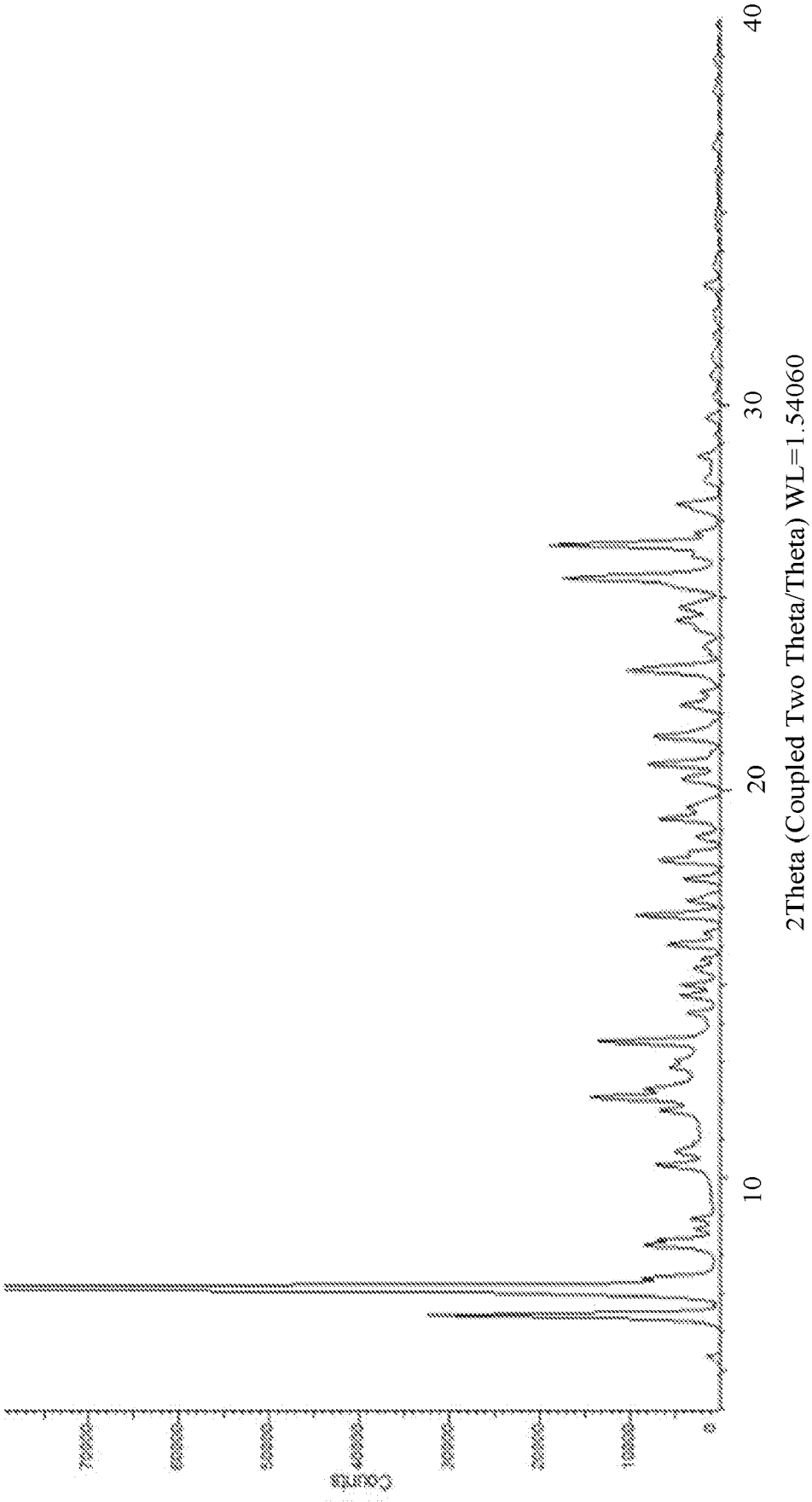


FIG. 14B

Selected XRPD Peak List for **31j**, Saccharinate Salt Form

Angle, 2 θ	d spacing, °A	Relative intensity, %
6.44	13.71068	14.2
7.15	12.3583	100
8.26	10.69115	3.6
10.34	8.54959	3
11.73	7.53643	2.9
12.10	7.30768	6.2
12.29	7.19734	3.6
13.54	6.53621	6
16.79	5.27542	4
18.22	4.86621	2.9
19.28	4.59954	2.8
20.71	4.2864	3.4
21.40	4.14888	3.1
23.14	3.84128	4.6
25.52	3.48725	7.4
26.37	3.37697	8.4

FIG. 14C

DSC for **31j**, Saccharinate Salt Form

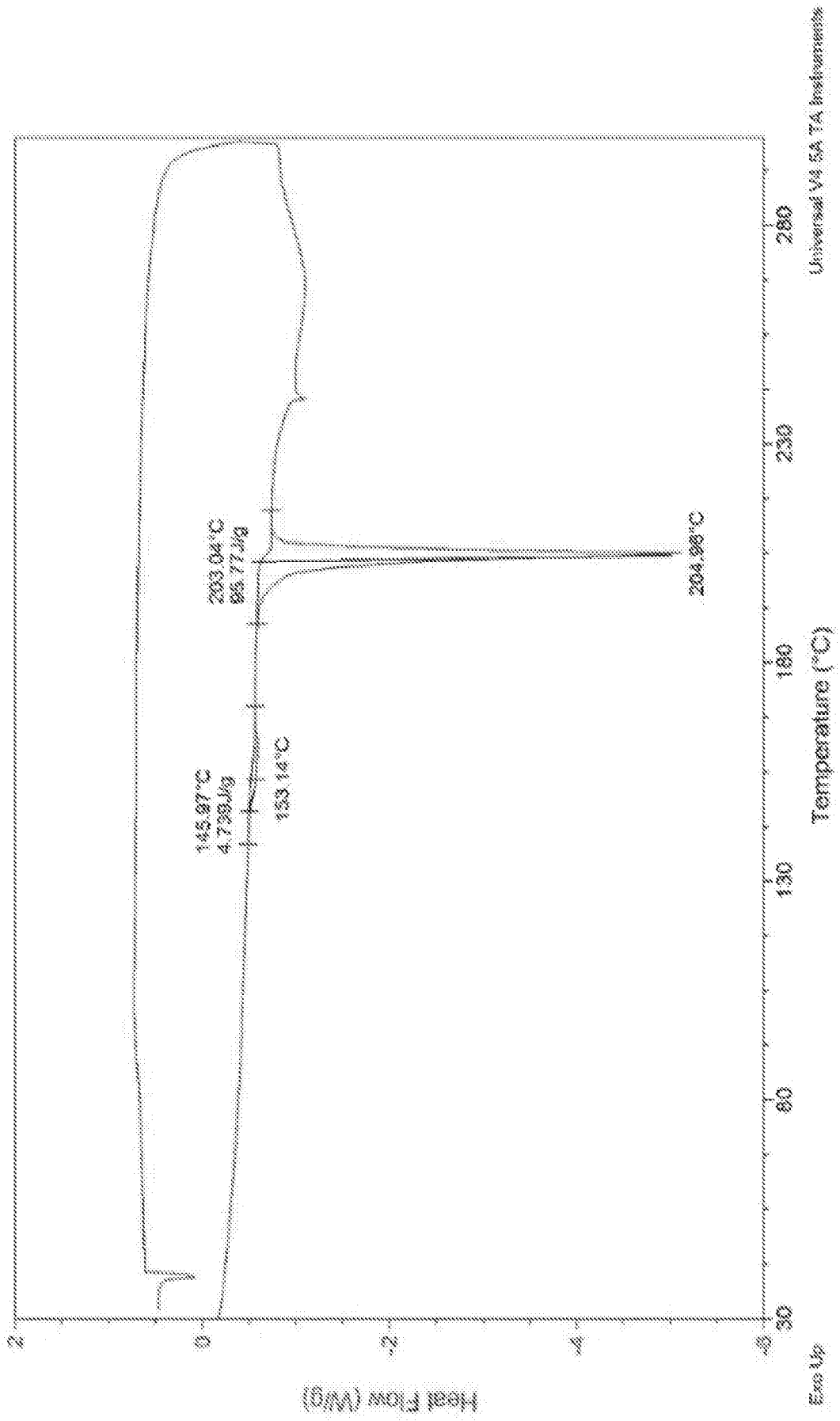


FIG. 15

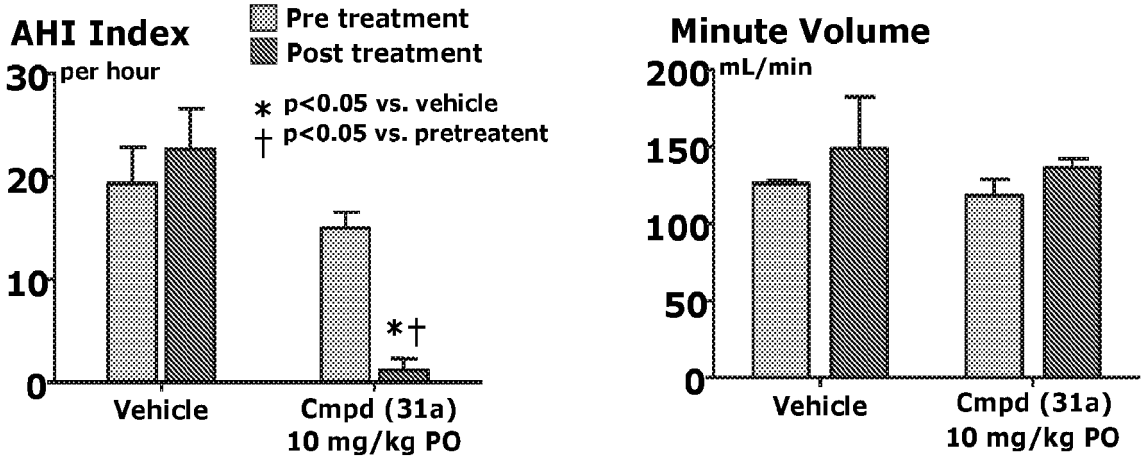


FIG. 16A

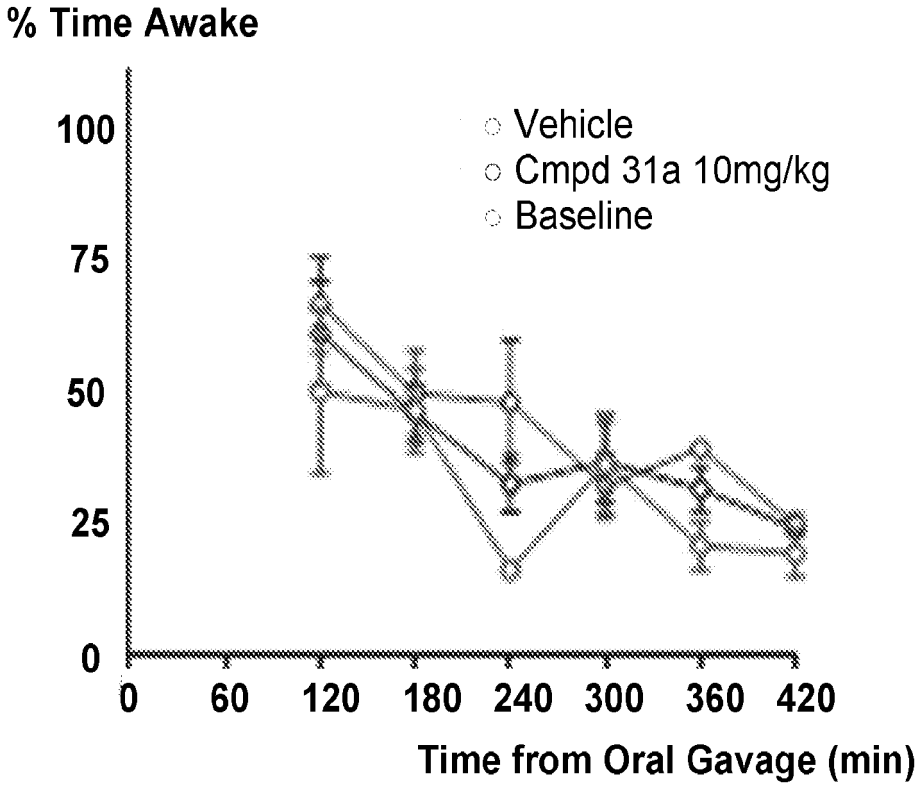


FIG. 16B

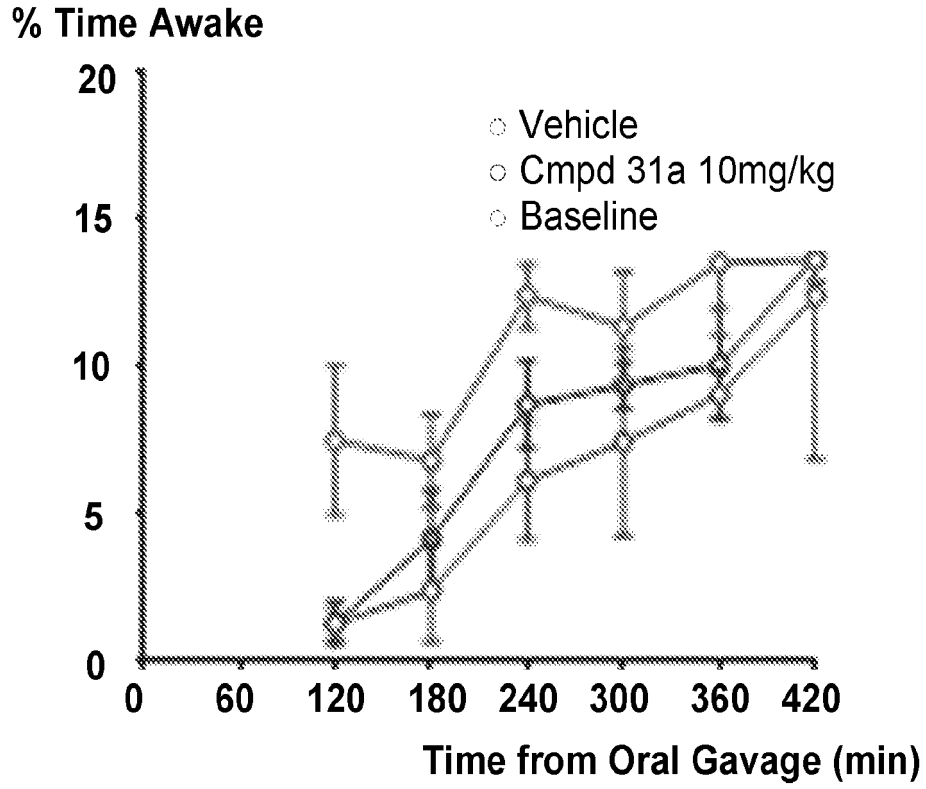


FIG. 16C

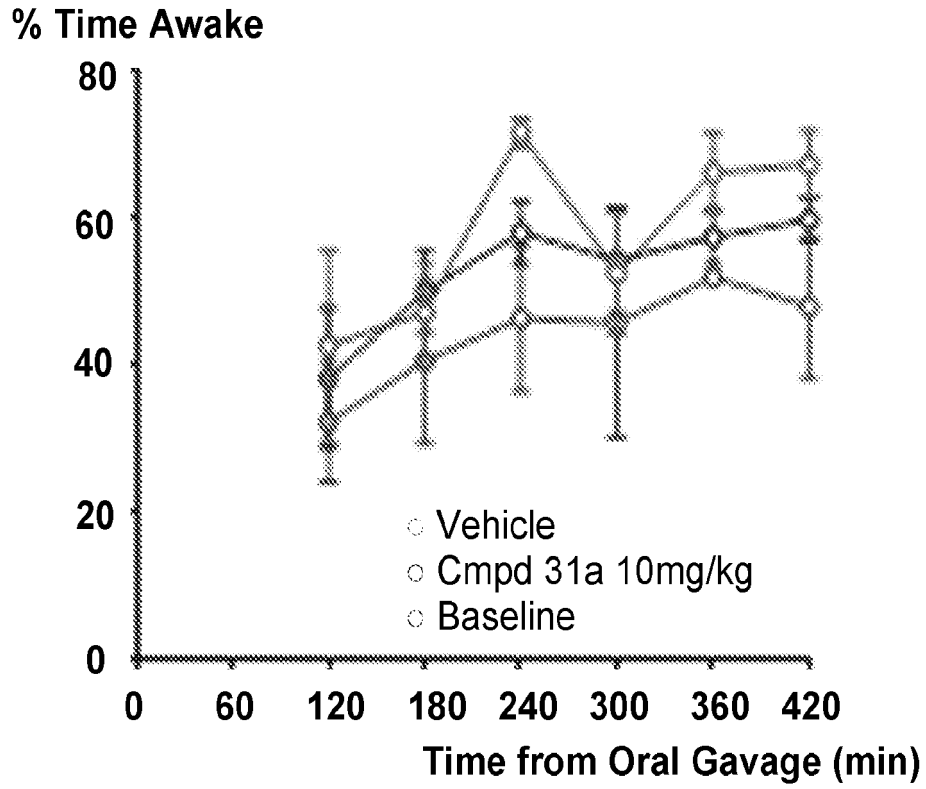
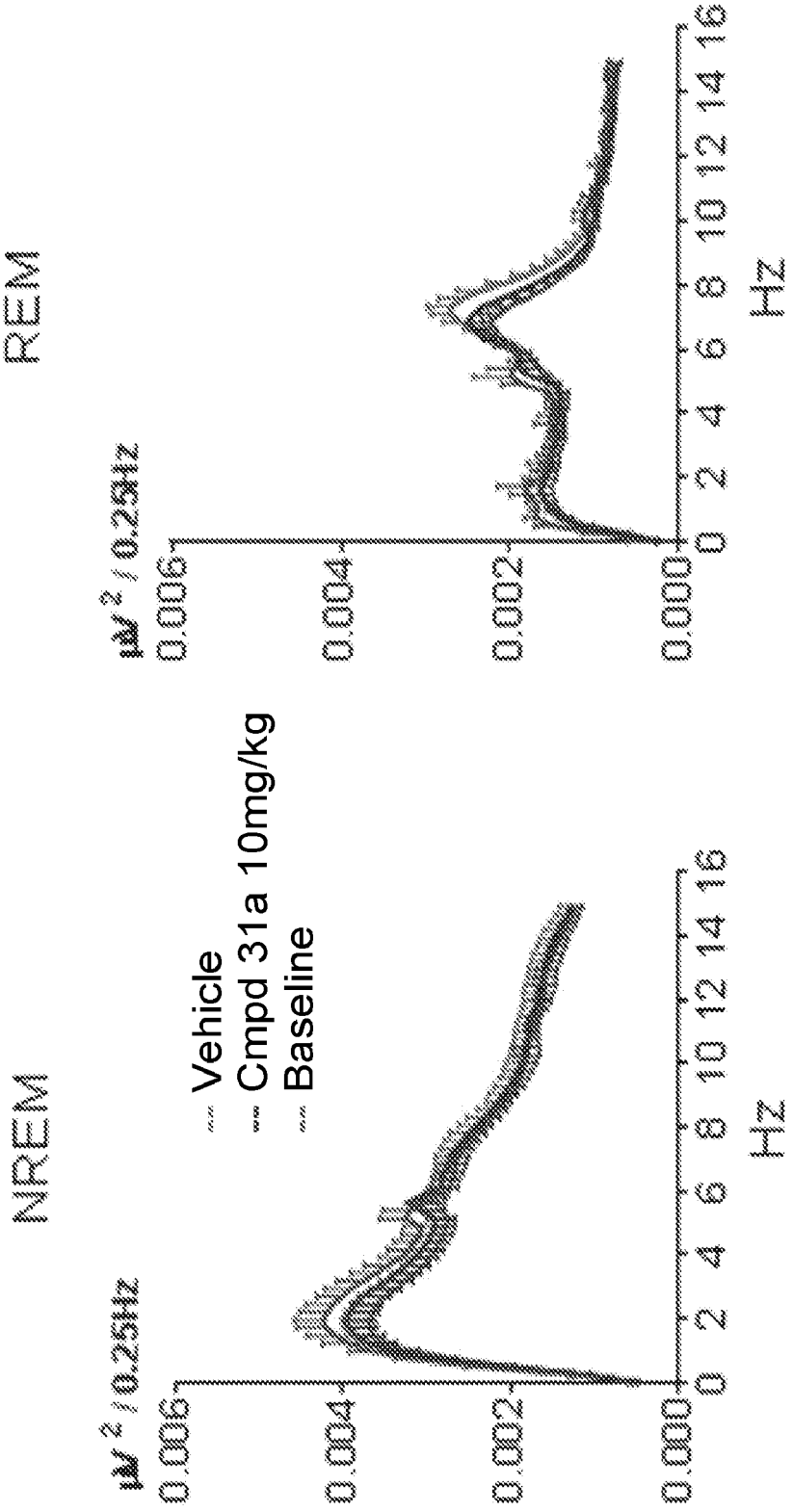


FIG. 17A


NREM
REM
μV² / 0.25Hz
0.006
0.004
0.002
0.000
0 2 4 6 8 10 12 14 16
Hz
Vehicle
Cmpd 31a 10mg/kg
Baseline

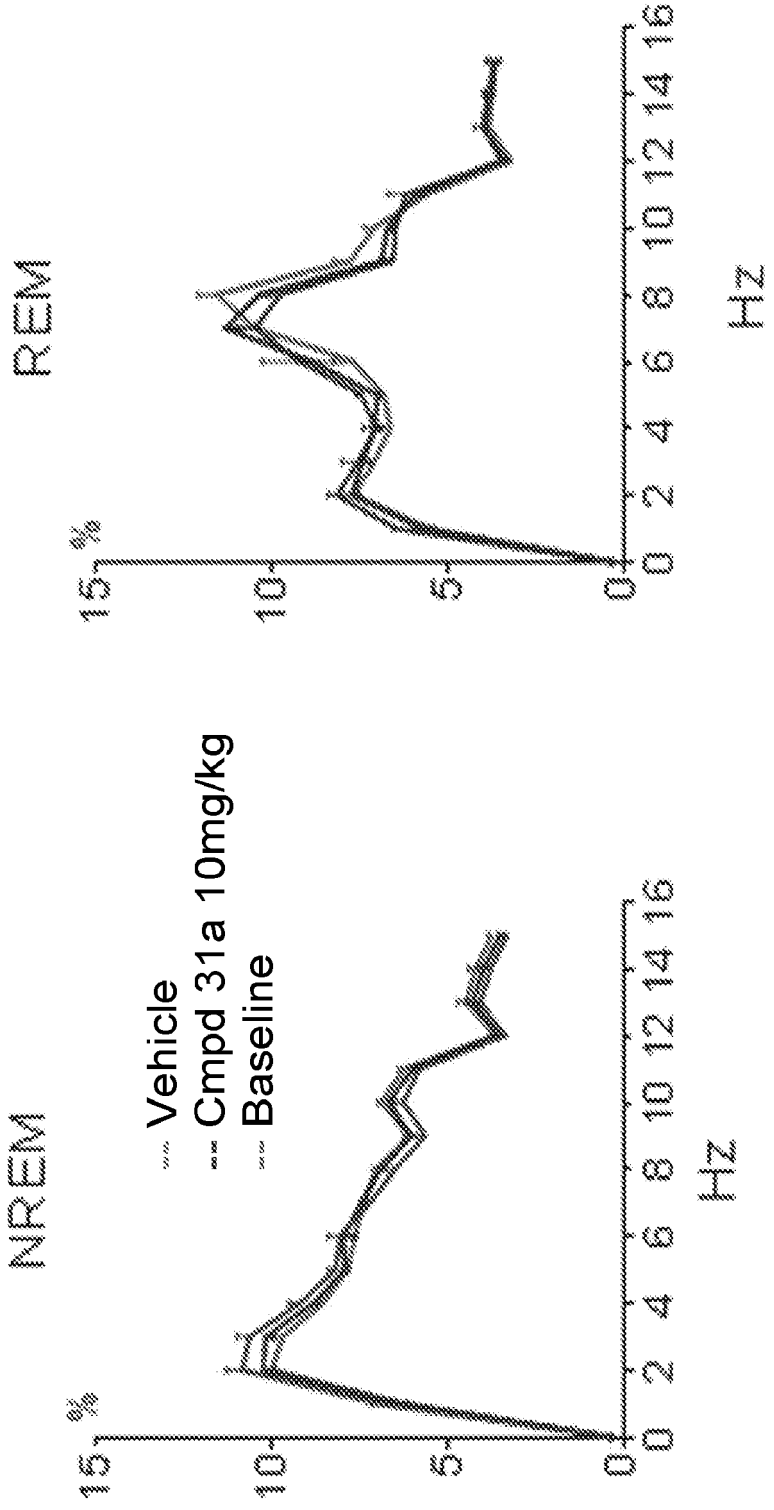

REM
NREM
%
15
10
5
0
0 2 4 6 8 10 12 14 16
Hz
Vehicle
Cmpd 31a 10mg/kg
Baseline

FIG. 17B

FIG. 18

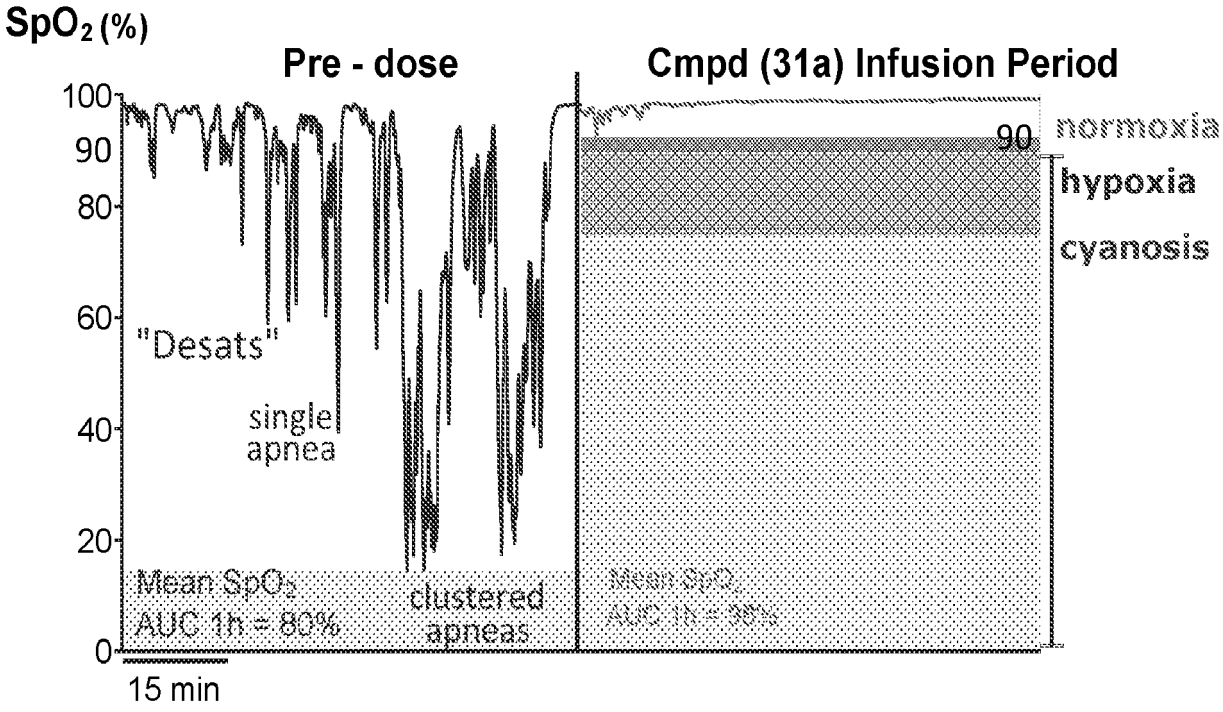

SpO2 (%)
Pre - dose
Cmpd (31a) Infusion Period
100
90
80
60
40
20
0
"Desats"
single apnea
clustered apneas
Mean SpO2
AUC 1h = 80%
90
normoxia
hypoxia
cyanosis
15 min

FIG. 19

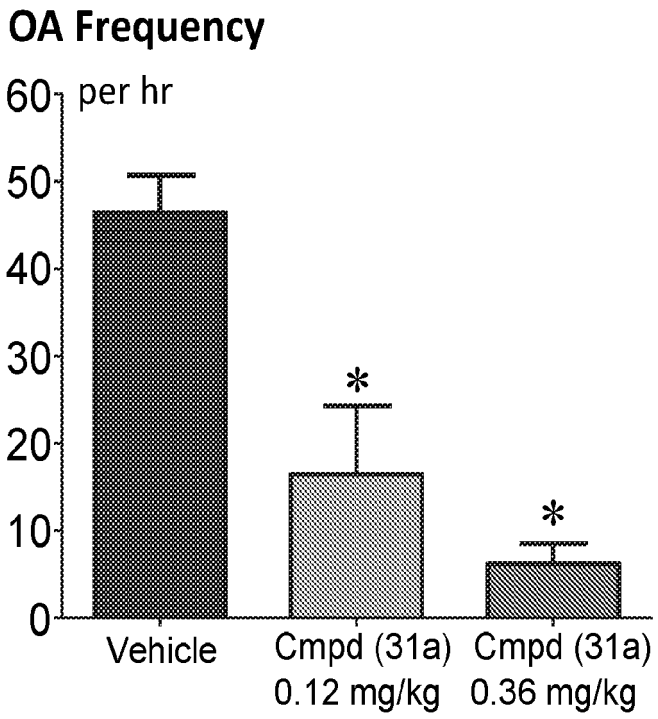

OA Frequency
per hr
60
50
40
30
20
10
0
*
*
Vehicle
Cmpd (31a) 0.12 mg/kg
Cmpd (31a) 0.36 mg/kg

FIG. 20

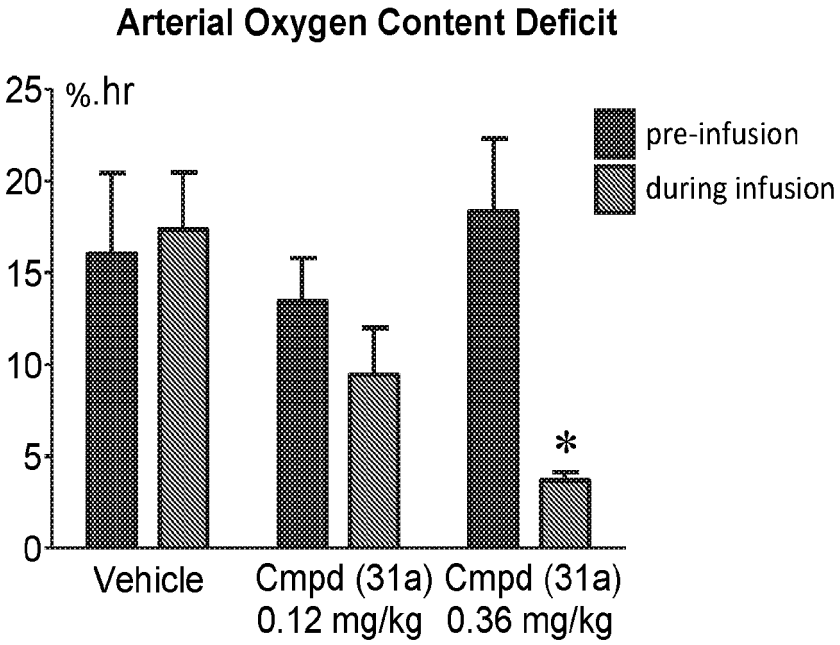


FIG. 21A

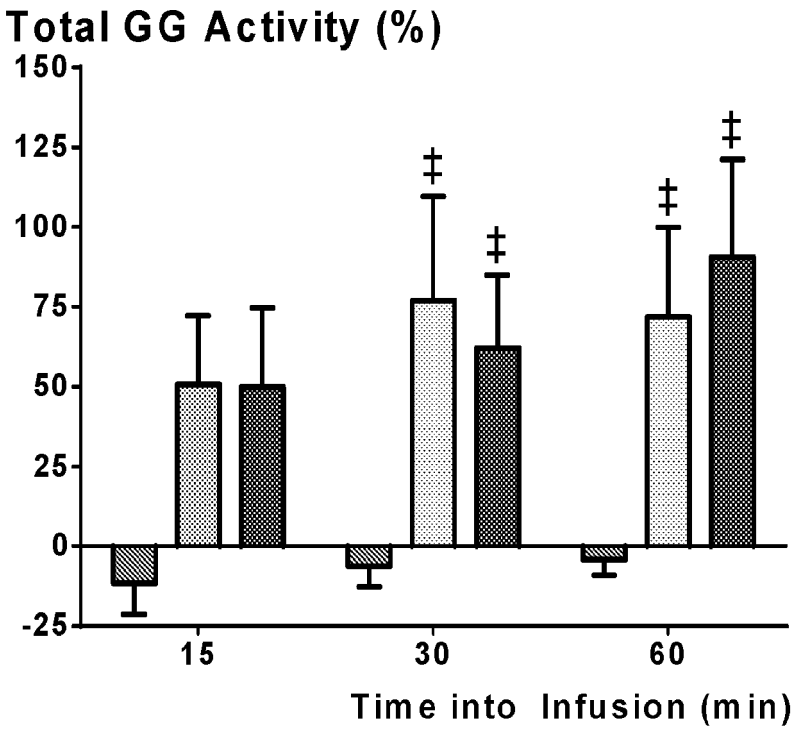


FIG. 21B

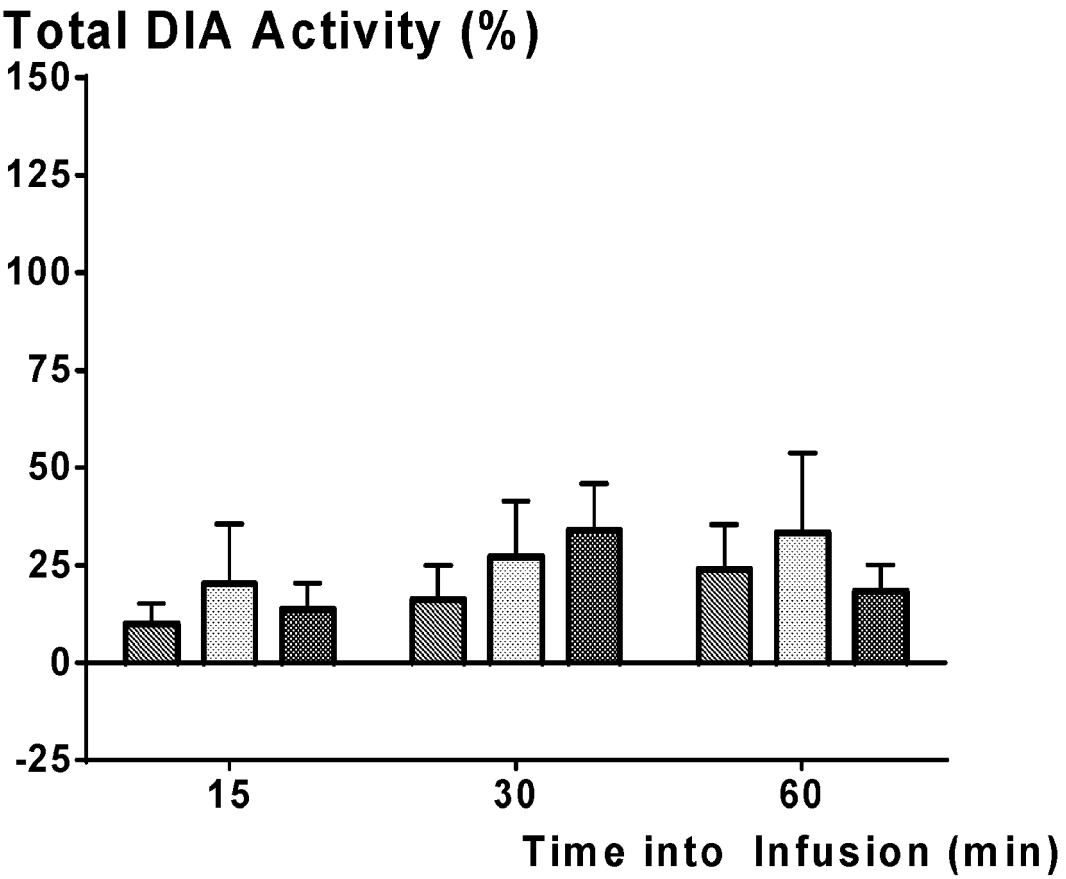

Total DIA Activity (%)
150
125
100
75
50
25
0
-25
15
30
60
Time into Infusion (min)

FIG. 22

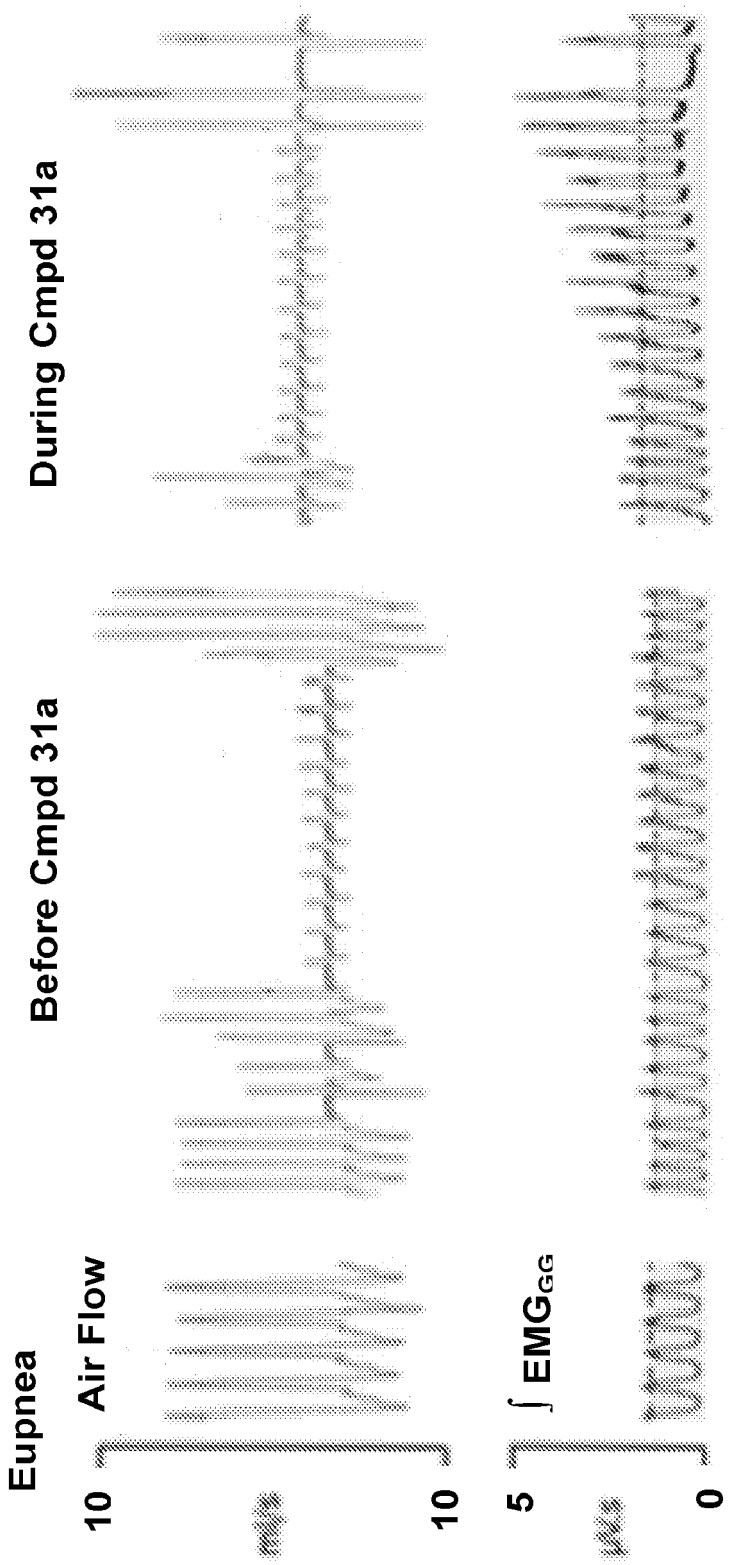

10s Spontaneous Obstructions
Before Cmpd 31a
During Cmpd 31a
Eupnea
Air Flow
10
10
∫ EMGGG
5
0

FIG. 23

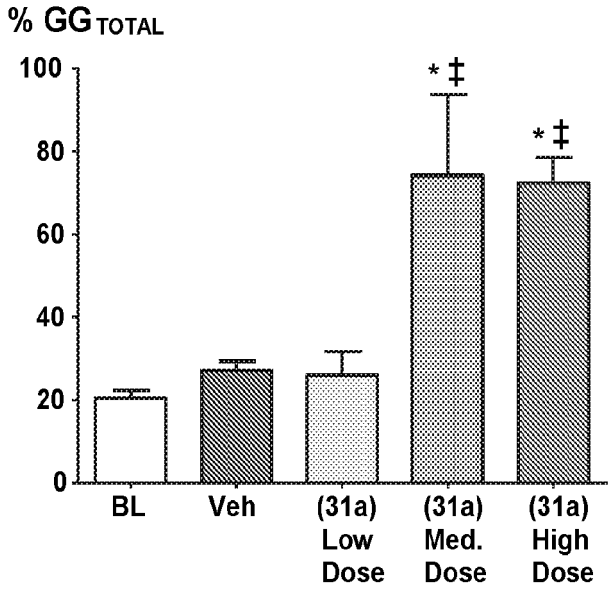


FIG. 24

Parameter	Baseline (mean ± SEM)	Vehicle (mean ± SEM)	Cmpd (31a) (mean ± SEM)
% Time Spent In NREM	59 ± 2	50 ± 4	56 ± 4
% Time Spent In REM	11 ± 1	8 ± 2	10 ± 1
% Time Spent In WAKE	30 ± 1	42 ± 5†	34 ± 3
# NREM Bouts / Hr	20 ± 1	20 ± 3	20 ± 2
# REM Bouts / Hr	8 ± 1	3 ± 1†	6 ± 1
# NREM Epochs / Hr	24 ± 2	25 ± 3	24 ± 2
# REM Epochs / Hr	11 ± 1	5 ± 1†	9 ± 1
NREM Bout Length (s)	133 ± 8	109 ± 18	130 ± 16
REM Bout Length (s)	67 ± 3	96 ± 6†	75 ± 6*
# WAKE Bouts / Hr	15 ± 1	24 ± 5	16 ± 3
# Arousals / Hr	7 ±1	9 ± 2	8 ± 1
Arousal Index	22 ± 1	33 ± 6	24 ± 3