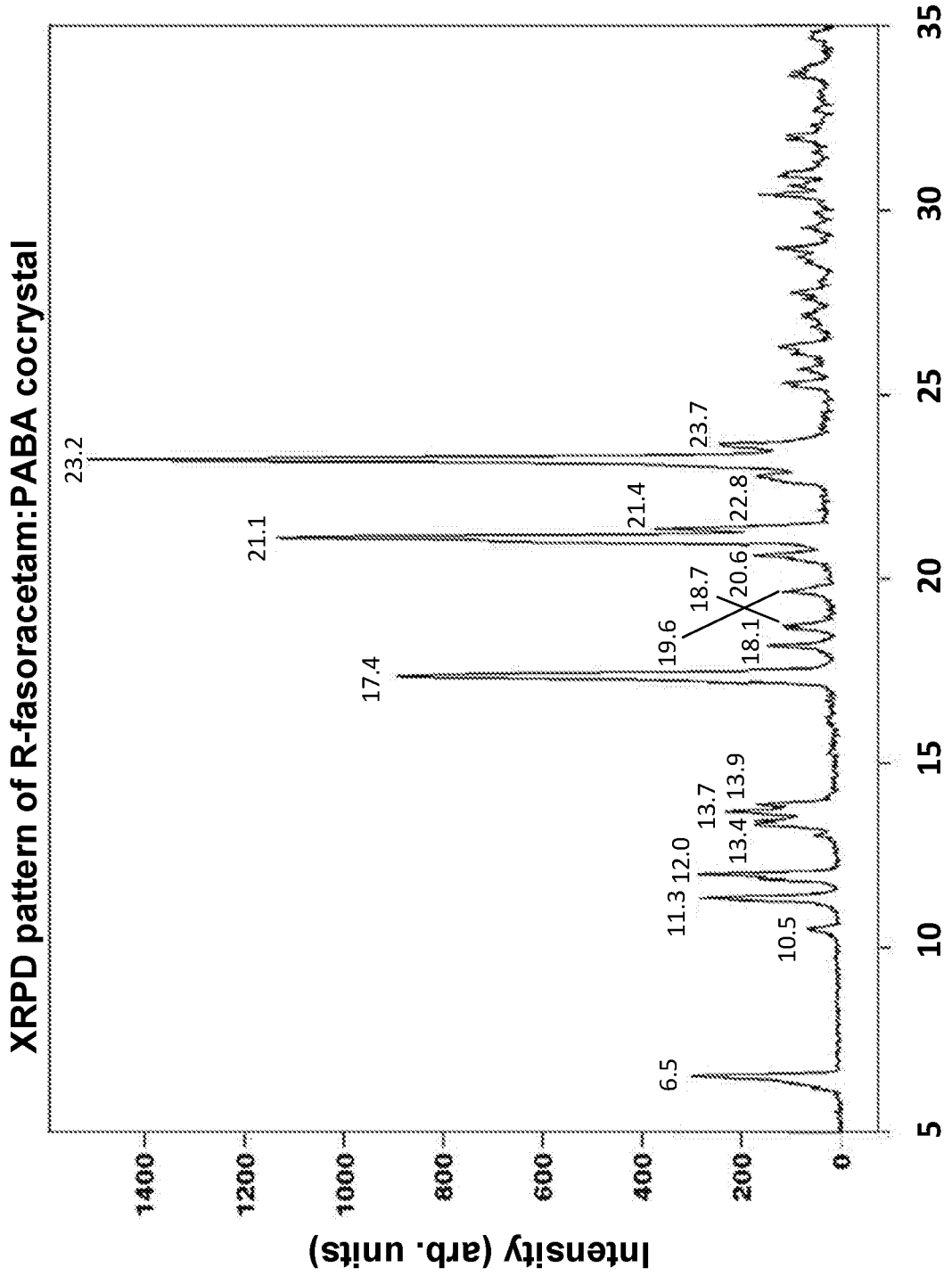

XRPD pattern of R-fasoracetam:PABA cocrystal
Intensity (arb. units)
2theta (deg)
0
200
400
600
800
1000
1200
1400
5
10
15
20
25
30
35
6.5
10.5
11.3
12.0
13.4
13.7
13.9
17.4
18.1
18.7
19.6
20.6
21.1
21.4
22.8
23.2
23.7

Figure 1

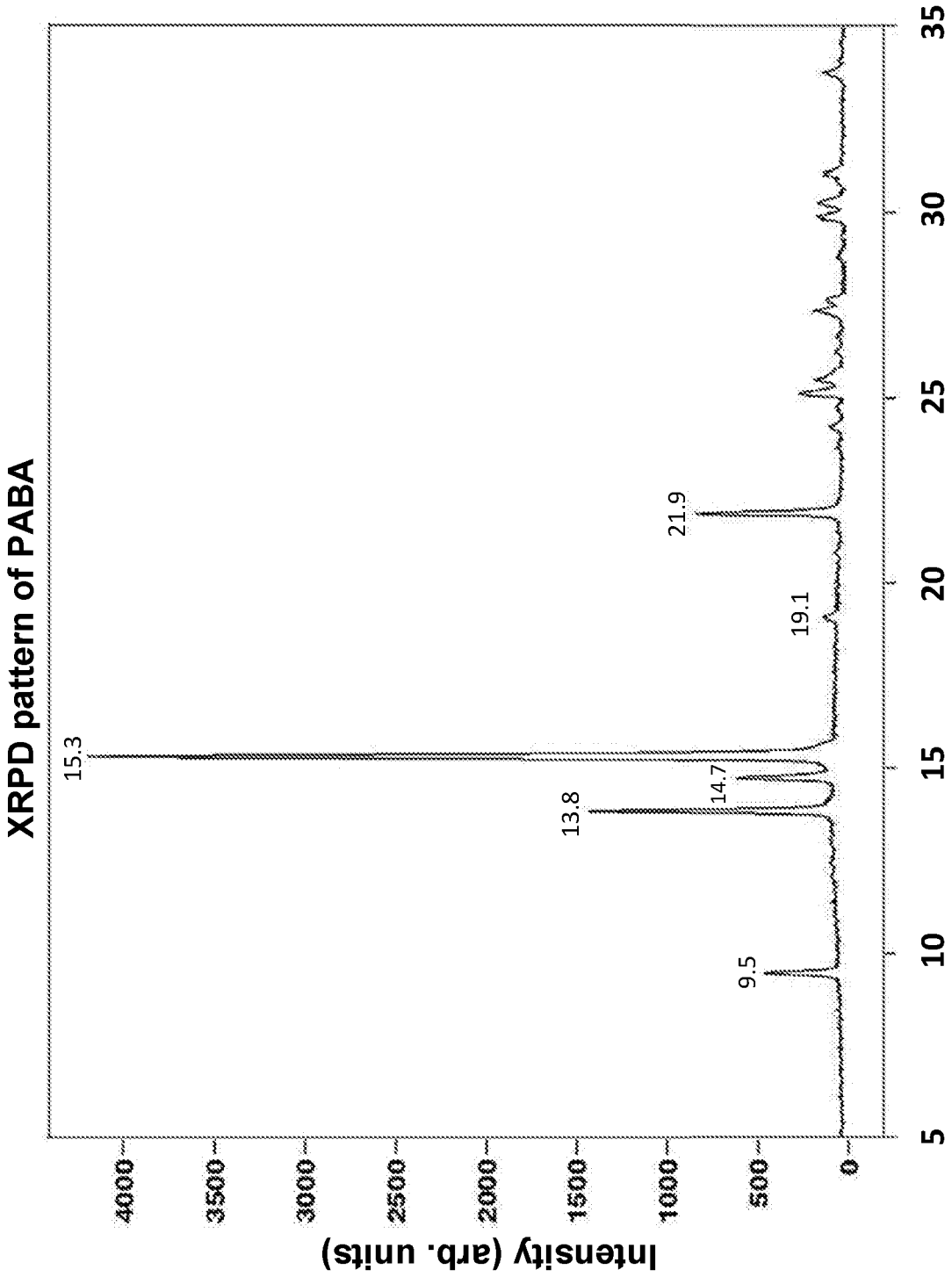

XRPD pattern of PABA
Intensity (arb. units)
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2theta (deg)
15.3
13.8
14.7
9.5
19.1
21.9

Figure 2

^{1}H-NMR spectrum of R-fasoracetam: PABA cocrystal

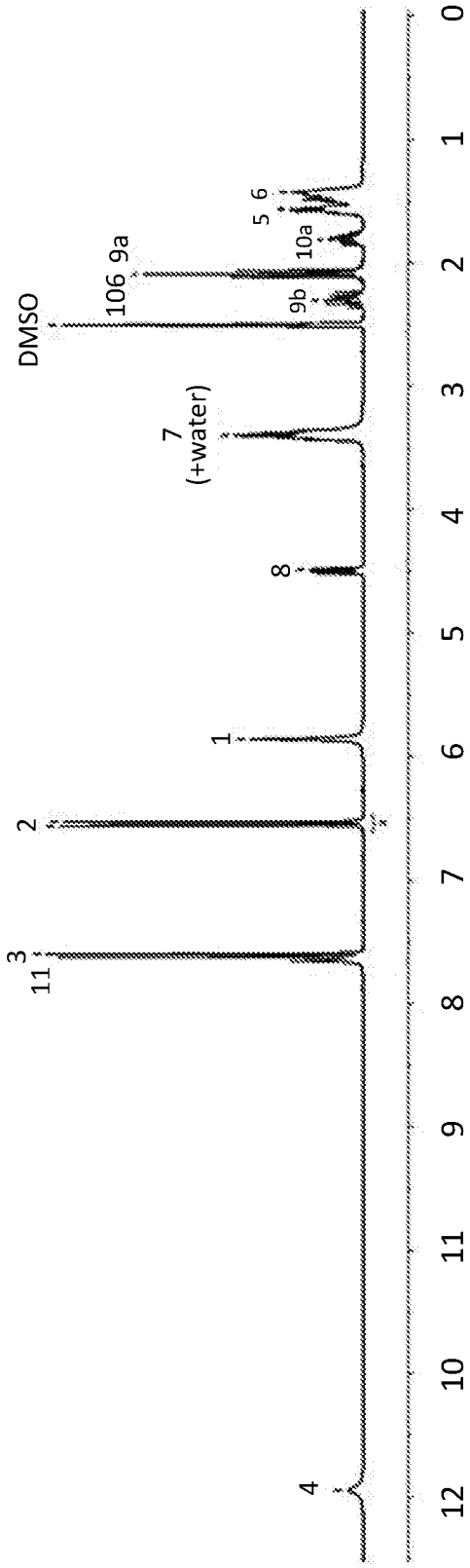


Figure 3

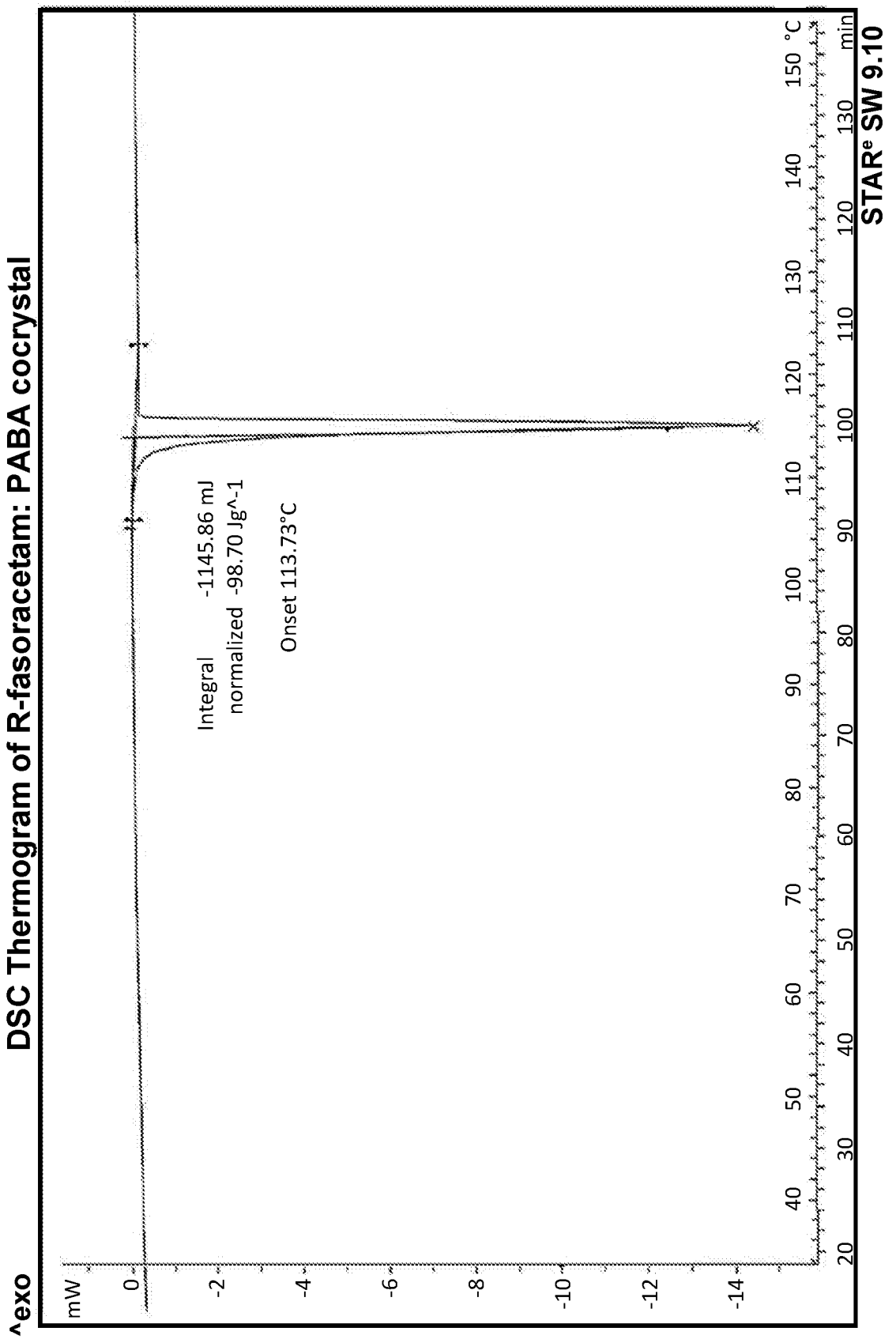

DSC Thermogram of R-fasoracetam: PABA cocrystal
^exo
mW
0
-2
-4
-6
-8
-10
-12
-14
Integral -1145.86 mJ
normalized -98.70 Jg^-1
Onset 113.73°C
20 30 40 50 60 70 80 90 100 110 120 130 140 150 °C
40 50 60 70 80 90 100 110 120 130 min
STARe SW 9.10

Figure 4

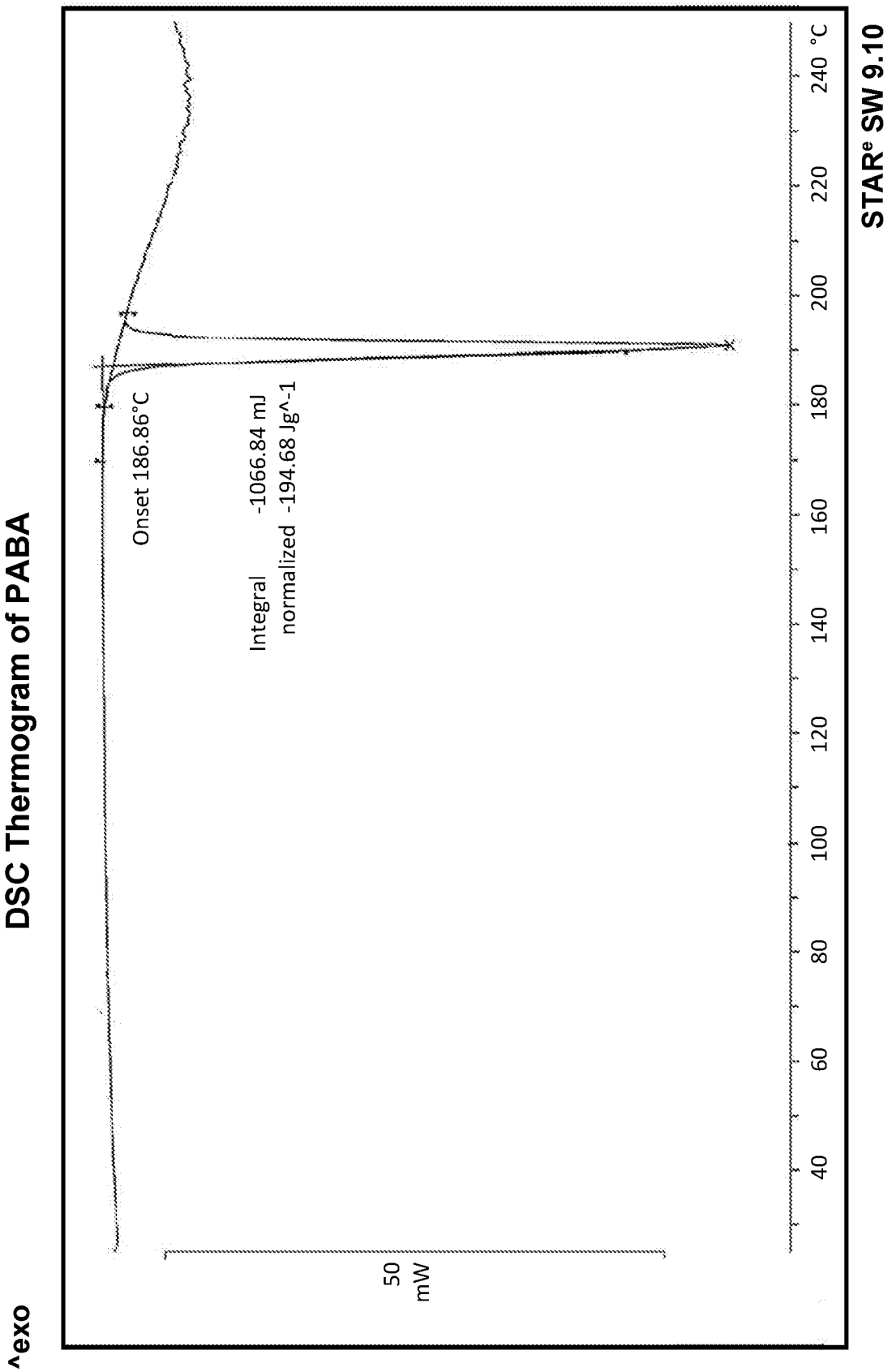

DSC Thermogram of PABA
^exo
50
mW
Onset 186.86°C
Integral -1066.84 mJ
normalized -194.68 Jg^-1
40
60
80
100
120
140
160
180
200
220
240 °C
STARe SW 9.10

Figure 5

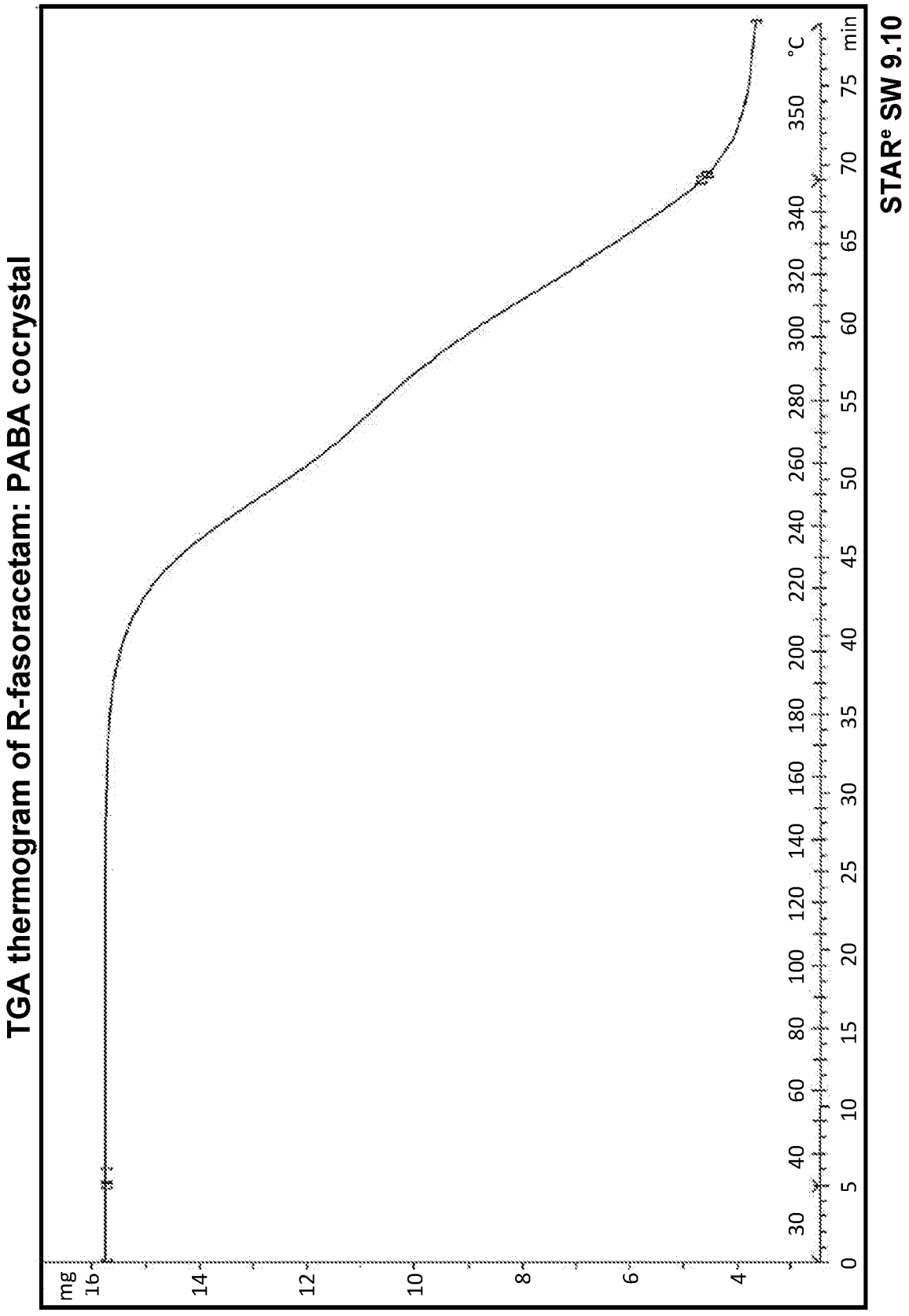

TGA thermogram of R-fasoracetam: PABA cocrystal
STARe SW 9.10
mg
16
14
12
10
8
6
4
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
min
30
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
350
°C

Figure 6

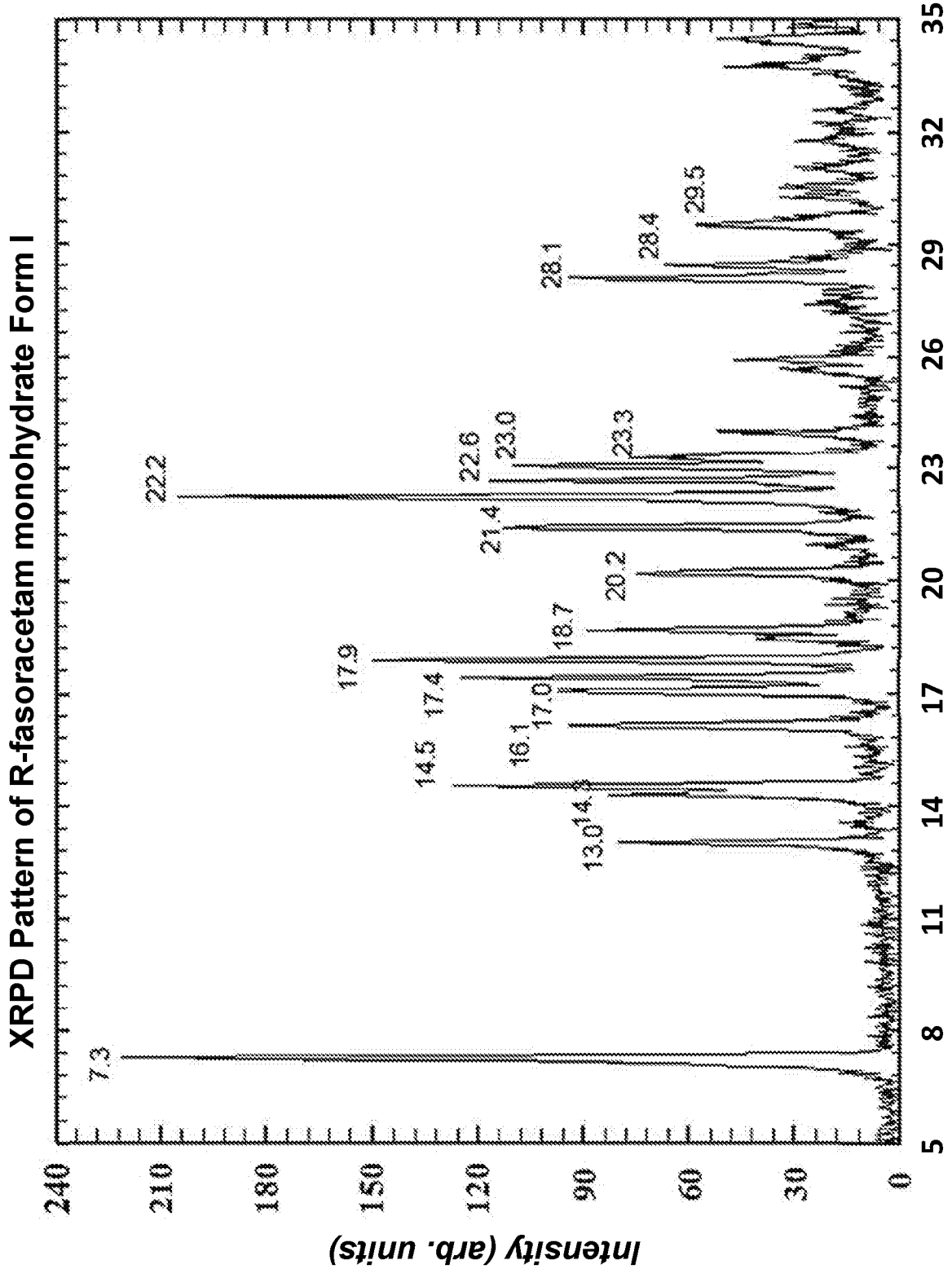

XRPD Pattern of R-fasoracetam monohydrate Form I
Intensity (arb. units)
240
210
180
150
120
90
60
30
0
5
8
11
14
17
20
23
26
29
32
35
7.3
13.0
14.3
14.5
16.1
17.0
17.4
17.9
18.7
20.2
21.4
22.2
22.6
23.0
23.3
28.1
28.4
29.5

Figure 7

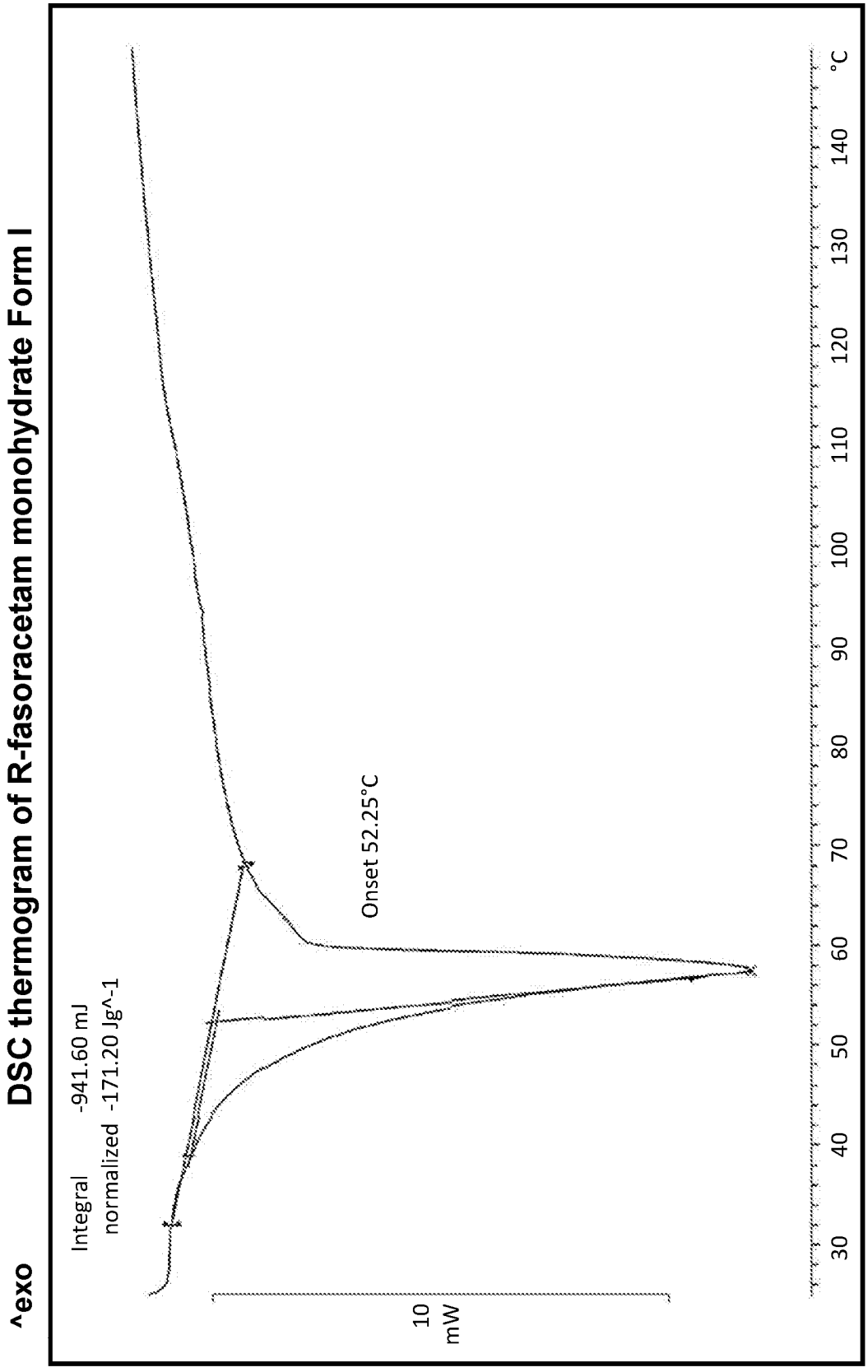

DSC thermogram of R-fasoracetam monohydrate Form I
^exo
Integral -941.60 mJ
normalized -171.20 Jg^-1
Onset 52.25°C
10 mW
30 40 50 60 70 80 90 100 110 120 130 140 °C
STARe SW 9.10

Figure 8

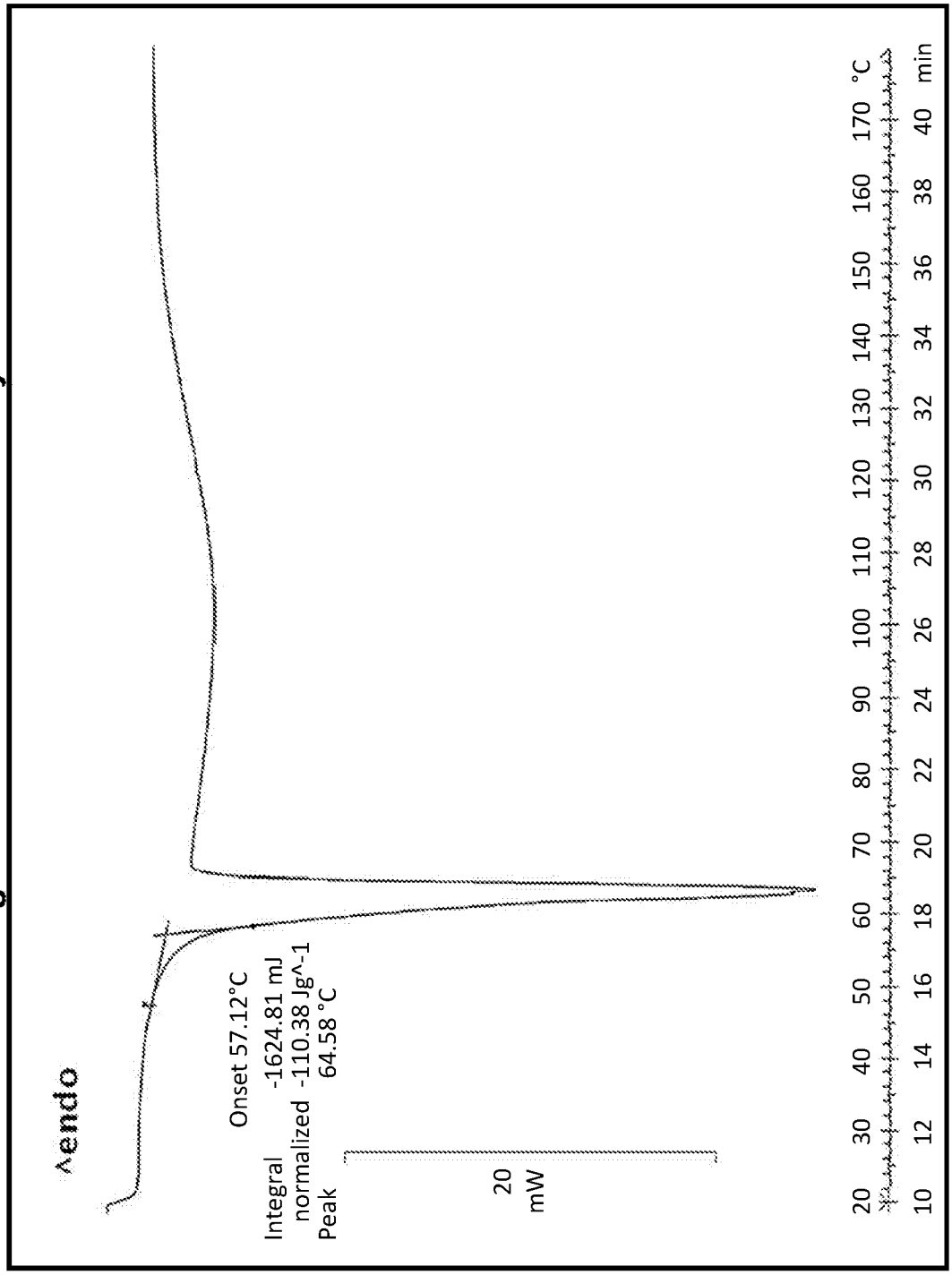

DSC thermogram of R-fasoracetam monohydrate Form I
Endo
Onset 57.12°C
Integral -1624.81 mJ
normalized -110.38 Jg^-1
Peak 64.58 °C
20
mW
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 °C
10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 min
STARe SW 9.10

Figure 9

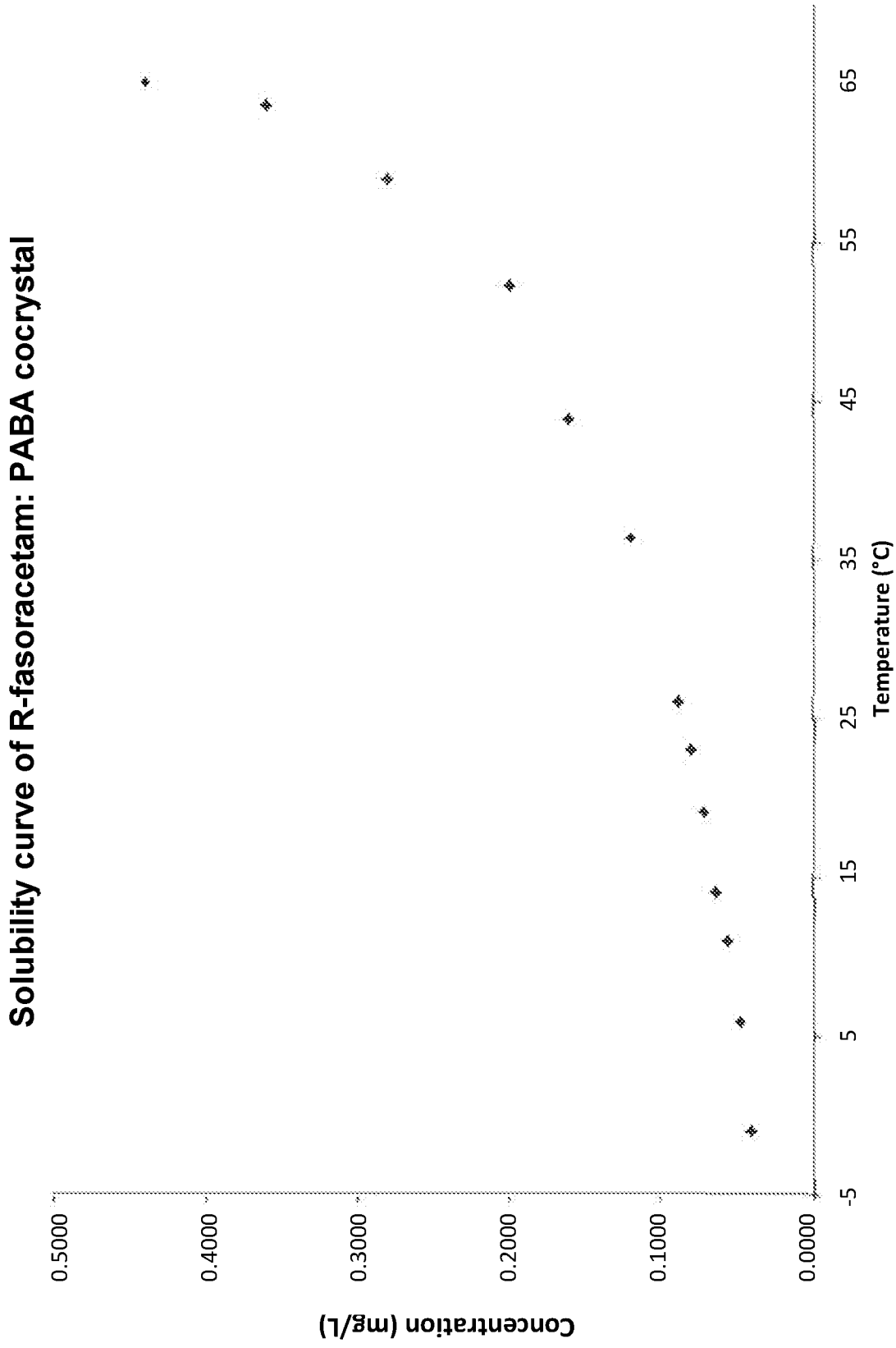

Solubility curve of R-fasoracetam: PABA cocrystal
Concentration (mg/L)
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
Temperature (°C)
-5
5
15
25
35
45
55
65

Figure 10

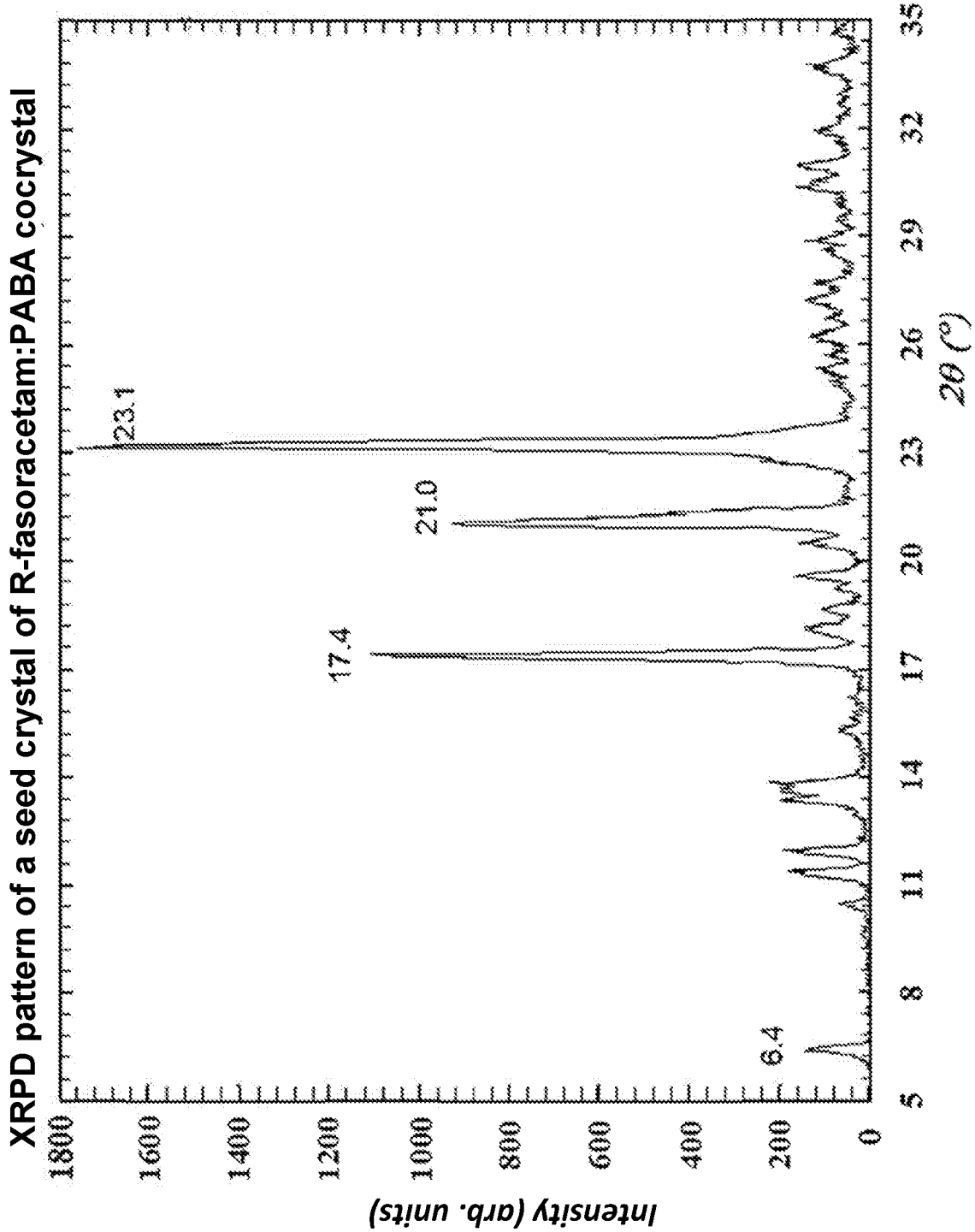

XRPD pattern of a seed crystal of R-fasoracetam:PABA cocrystal
Intensity (arb. units)
2θ (°)
6.4
17.4
21.0
23.1
0
200
400
600
800
1000
1200
1400
1600
1800
5
8
11
14
17
20
23
26
29
32
35

Figure 11

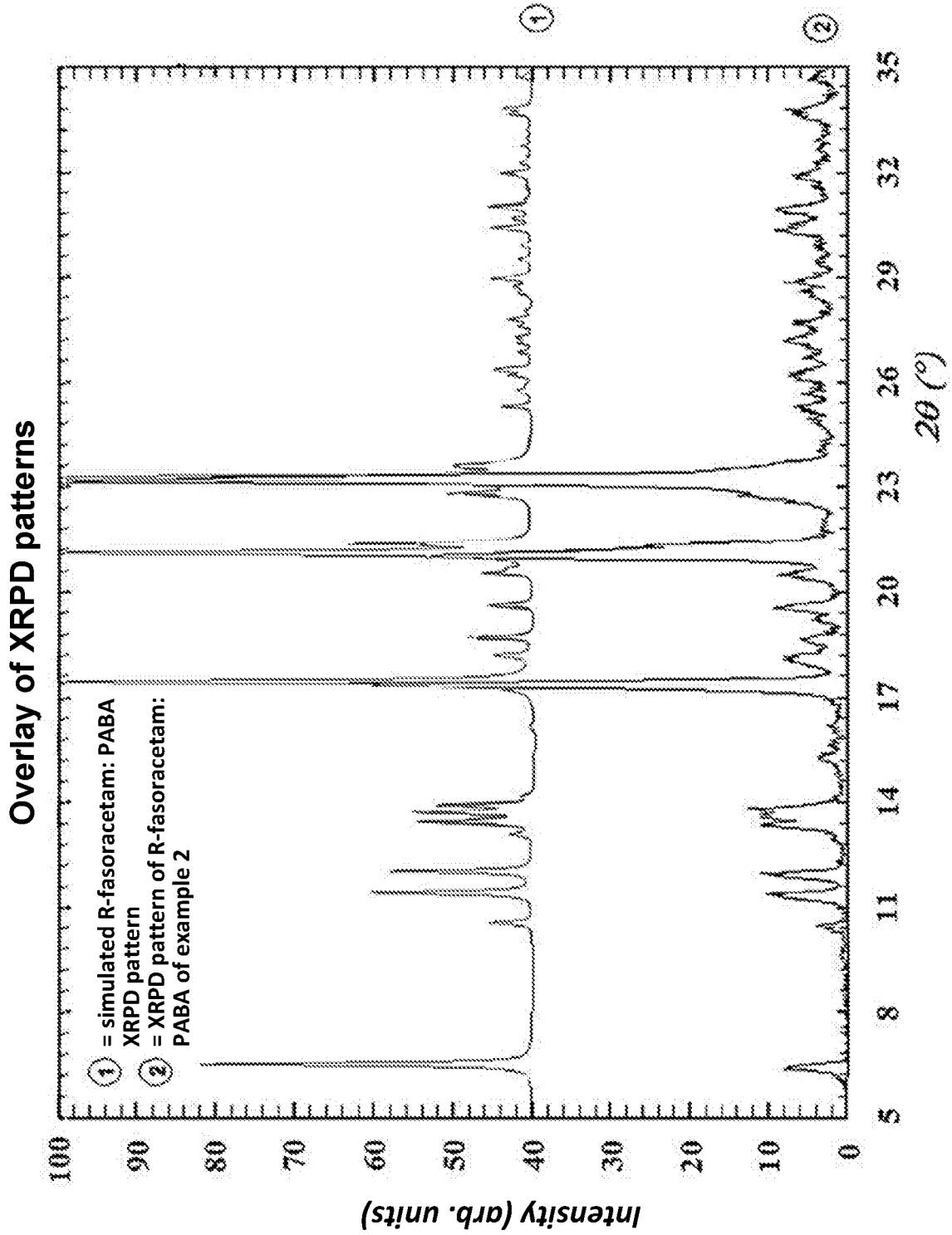

Overlay of XRPD patterns
① = simulated R-fasoracetam: PABA XRPD pattern
② = XRPD pattern of R-fasoracetam: PABA of example 2
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35

Figure 12

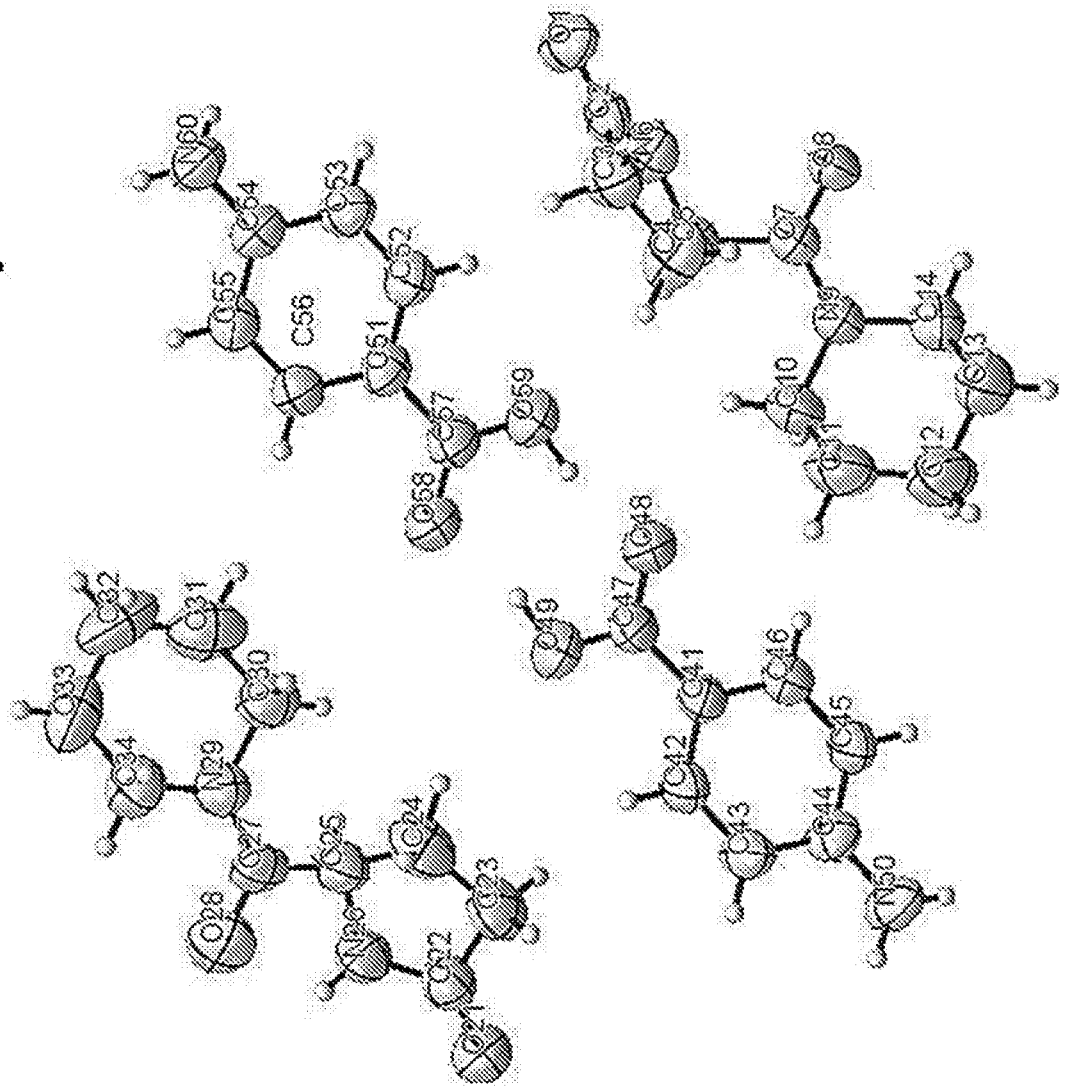


Figure 13

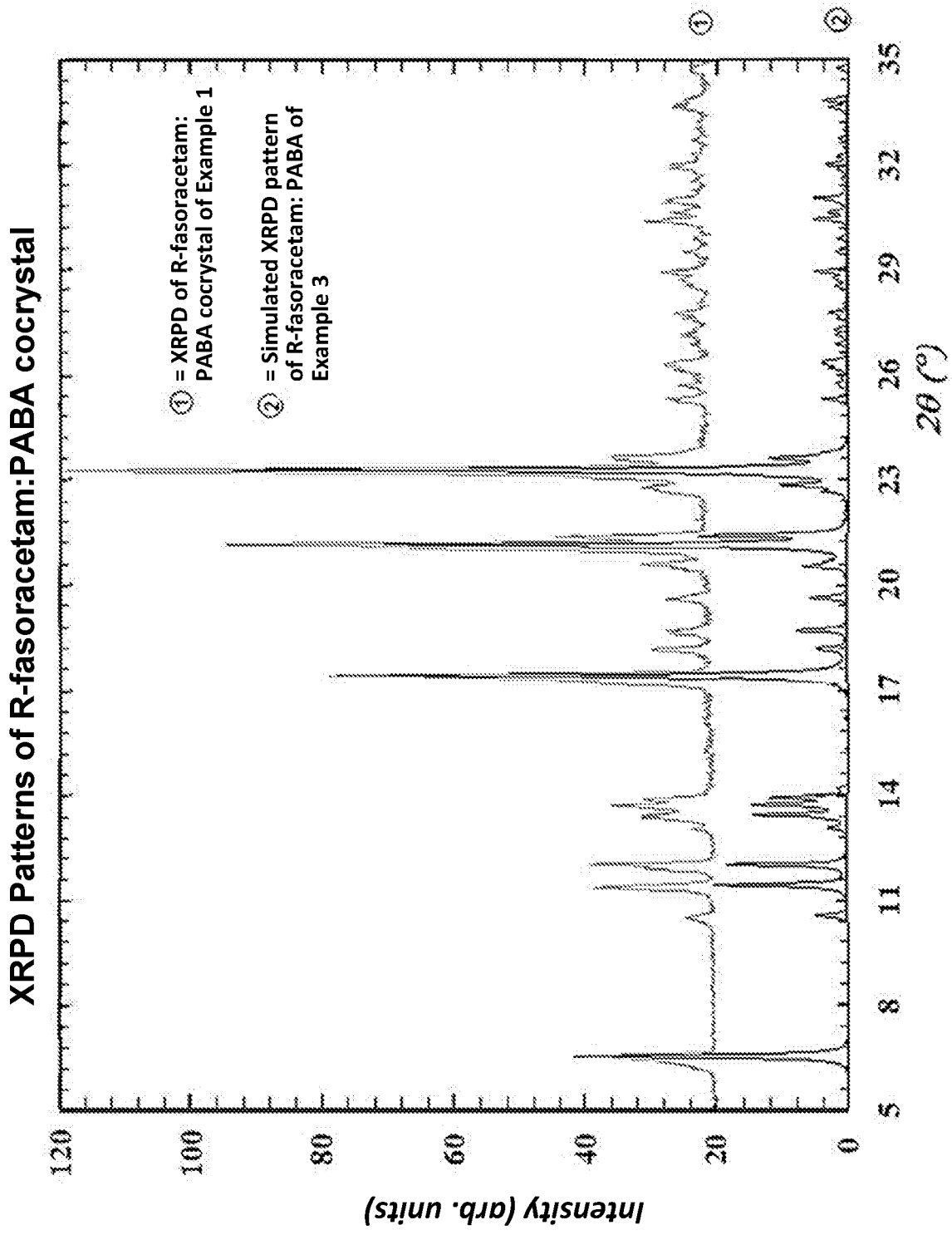

XRPD Patterns of R-fasoracetam:PABA cocrystal
① = XRPD of R-fasoracetam: PABA cocrystal of Example 1
② = Simulated XRPD pattern of R-fasoracetam: PABA of Example 3
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
5
8
11
14
17
20
23
26
29
32
35

Figure 14

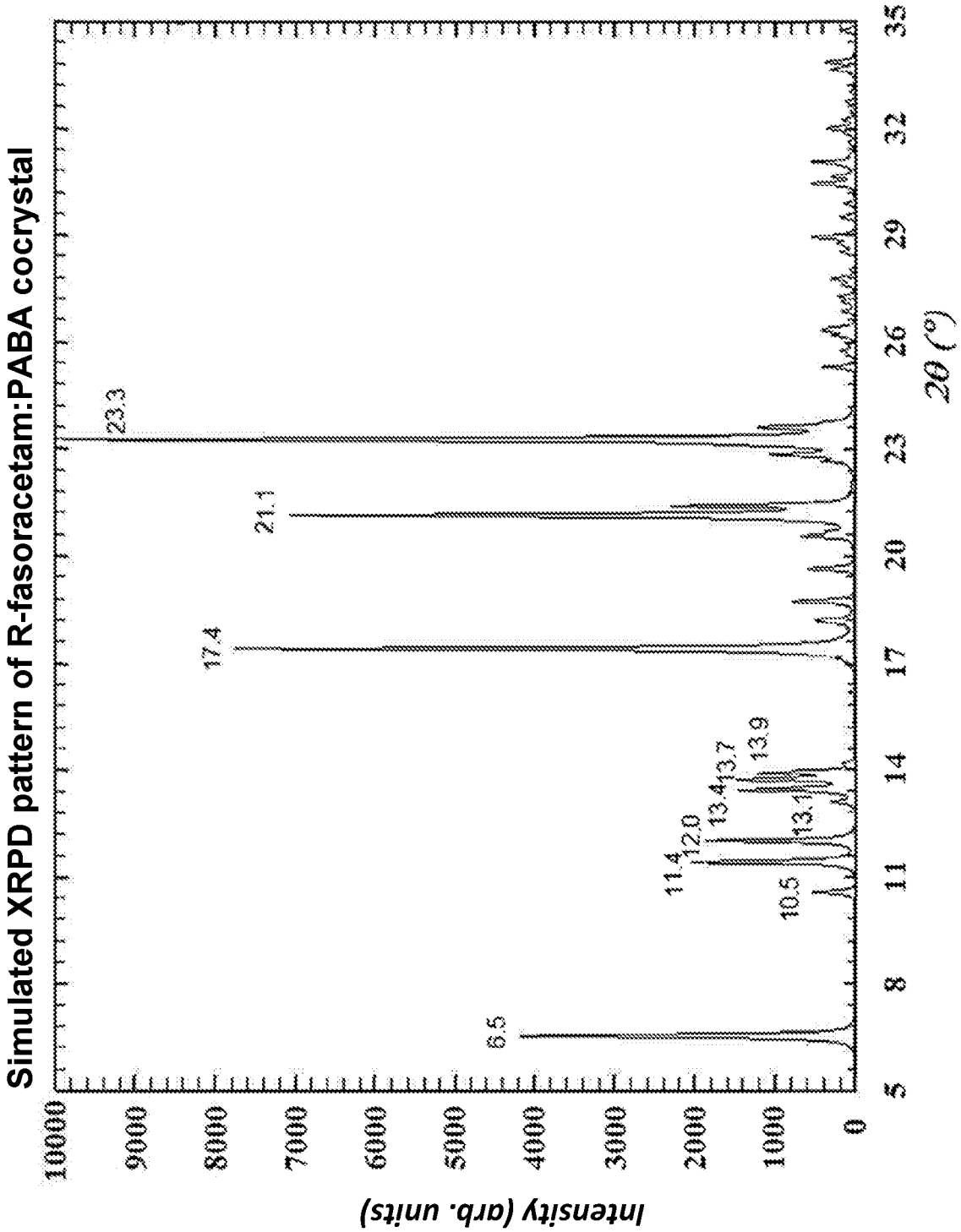

Simulated XRPD pattern of R-fasoracetam:PABA cocrystal
Intensity (arb. units)
2θ (°)
23.3
21.1
17.4
6.5
11.4
12.0
13.4
13.7
13.9
13.1
10.5
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35

Figure 15

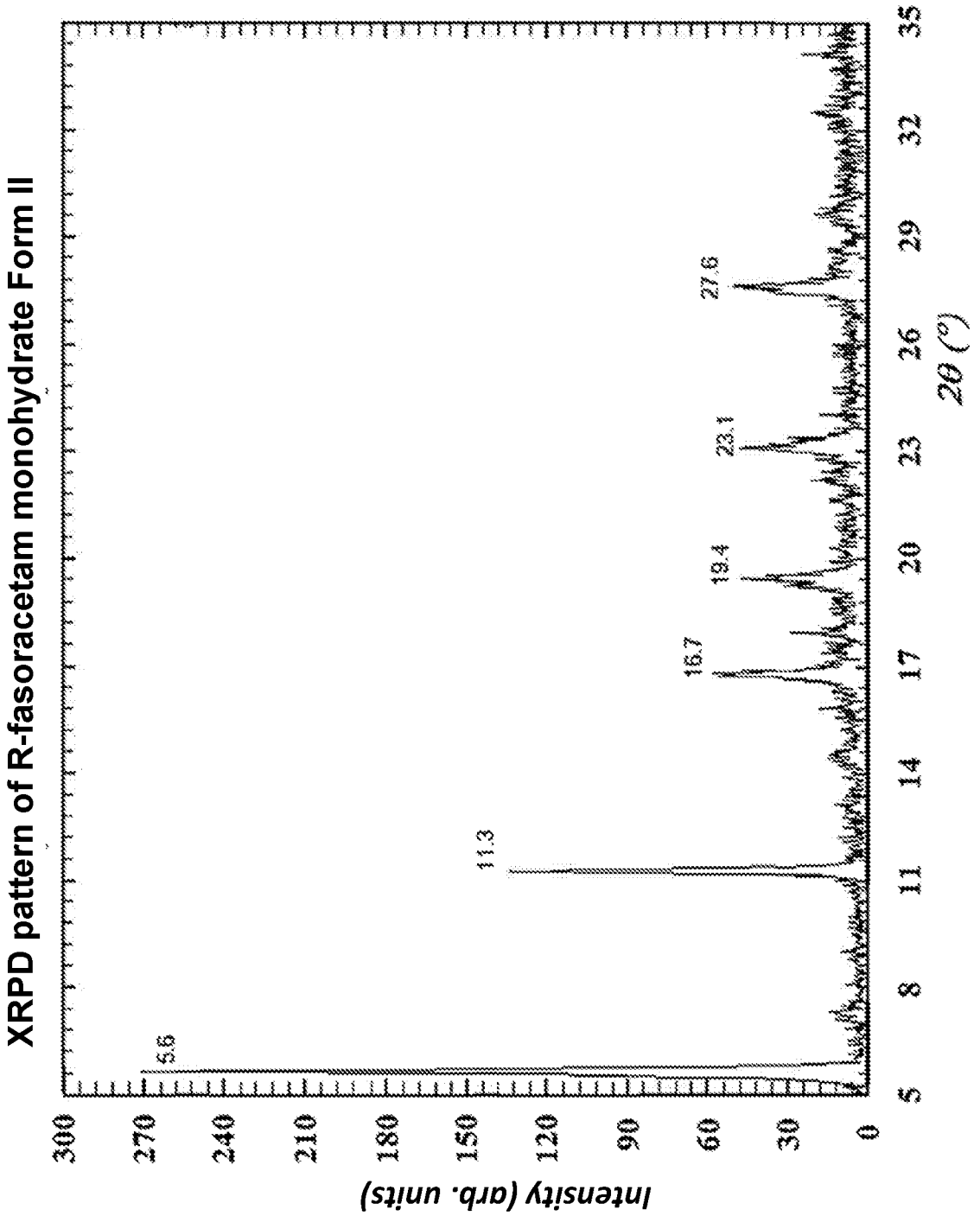

XRPD pattern of R-fasoracetam monohydrate Form II
Intensity (arb. units)
2θ (°)
5.6
11.3
16.7
19.4
23.1
27.6
0
30
60
90
120
150
180
210
240
270
300
5
8
11
14
17
20
23
26
29
32
35

Figure 16

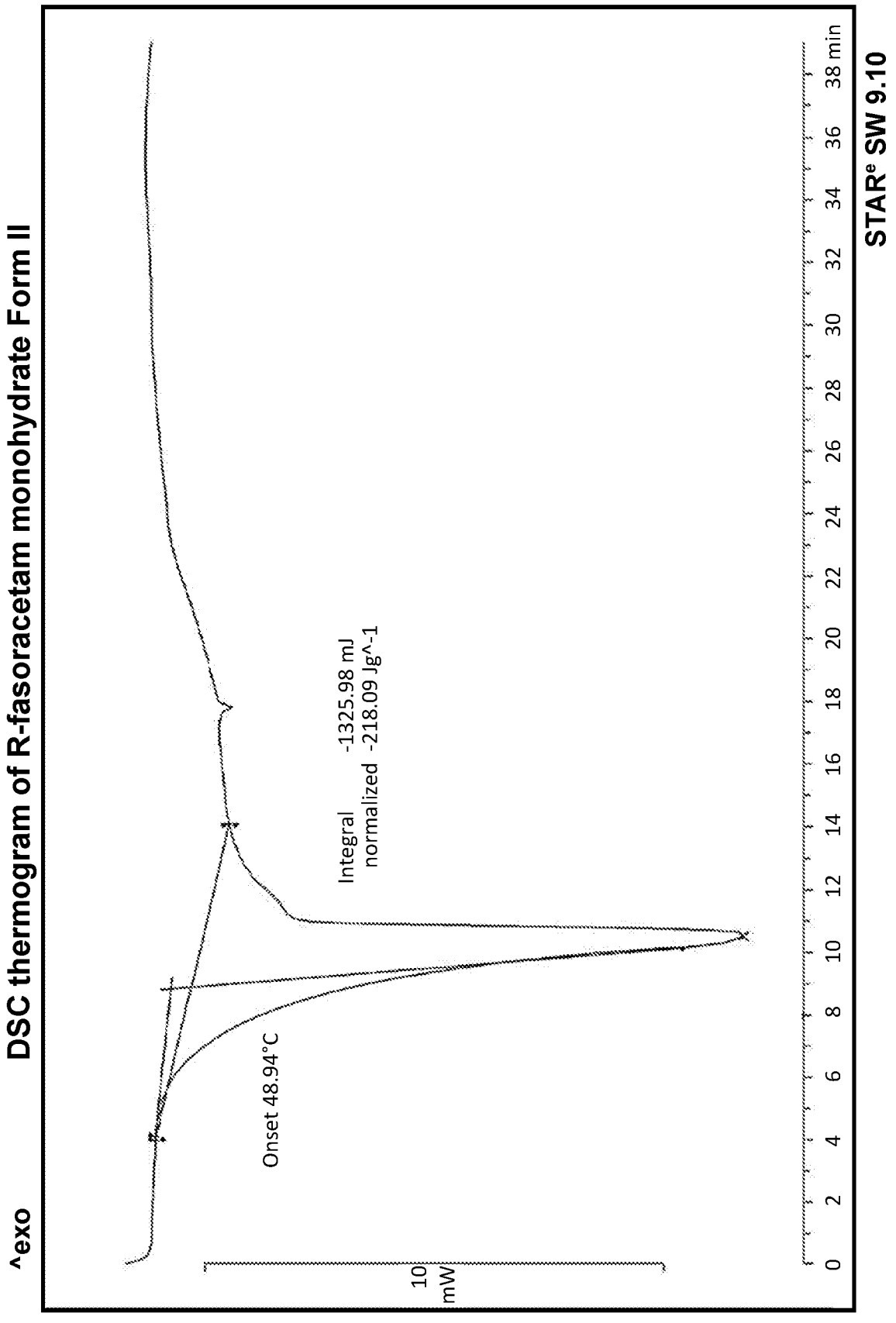

DSC thermogram of R-fasoracetam monohydrate Form II
^exo
Onset 48.94°C
Integral -1325.98 mJ
normalized -218.09 Jg^-1
10 mW
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 min
STARe SW 9.10

Figure 17

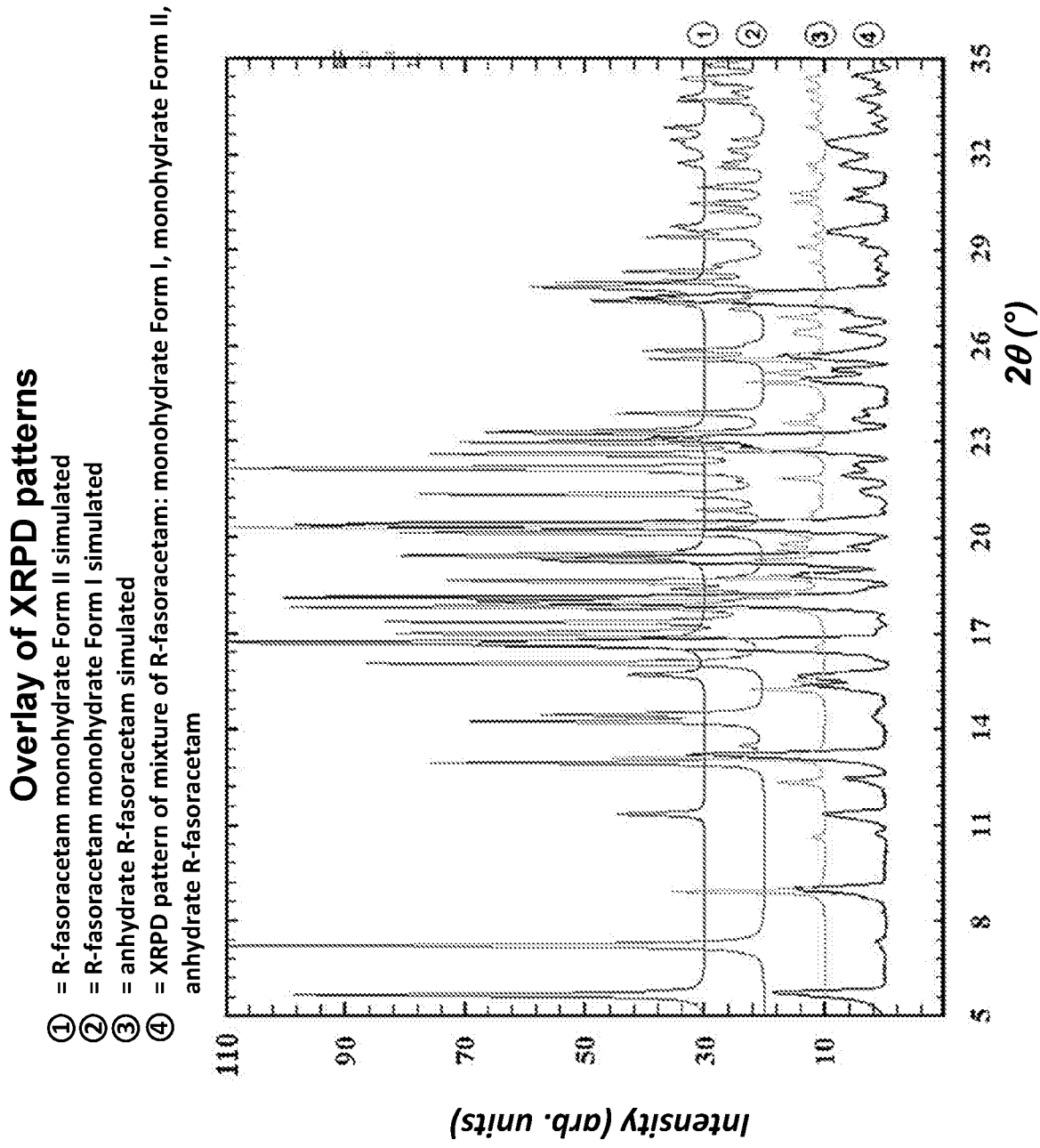

Overlay of XRPD patterns
① = R-fasoracetam monohydrate Form II simulated
② = R-fasoracetam monohydrate Form I simulated
③ = anhydrate R-fasoracetam simulated
④ = XRPD pattern of mixture of R-fasoracetam: monohydrate Form I, monohydrate Form II, anhydrate R-fasoracetam
Intensity (arb. units)
2θ (°)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35

Figure 18

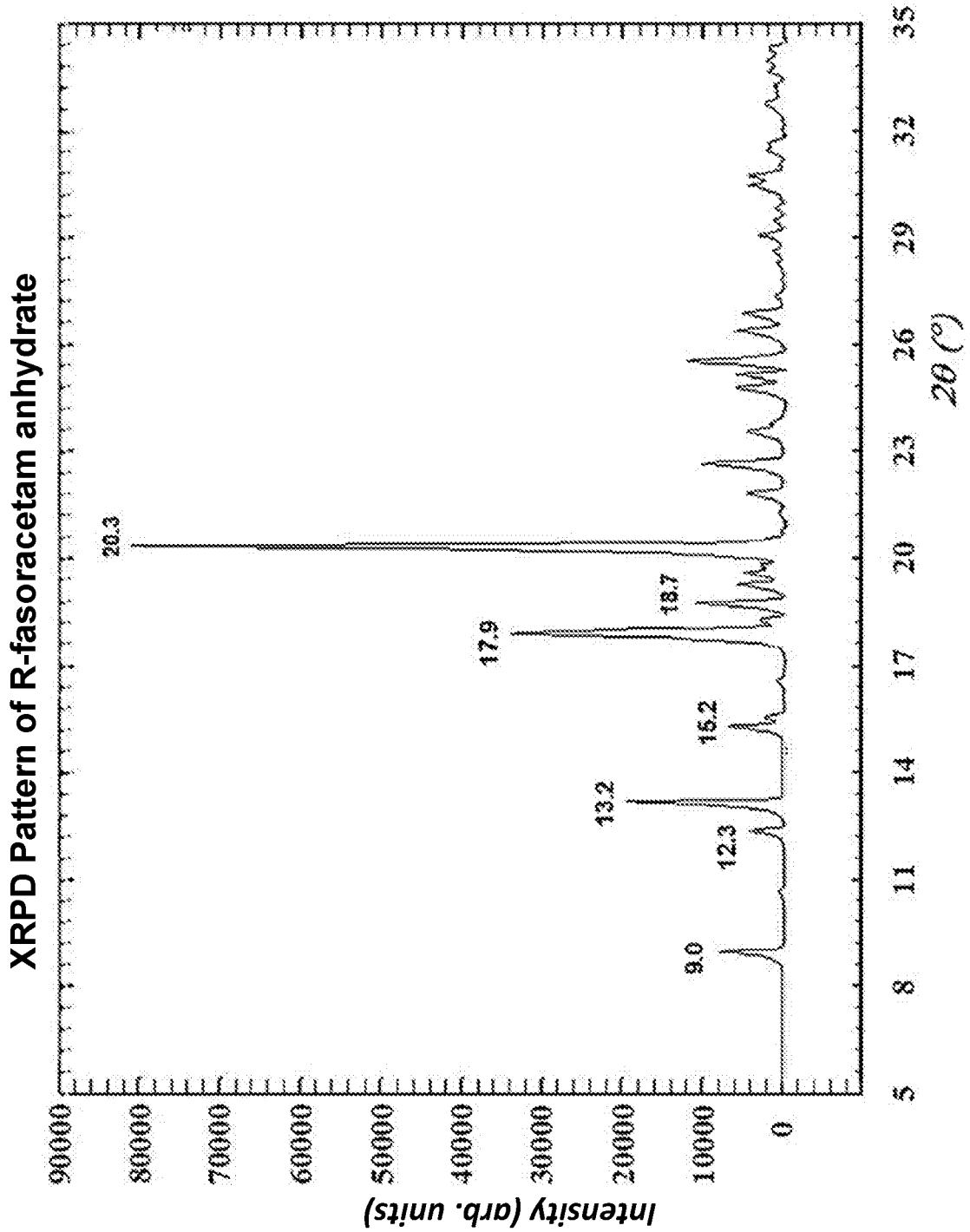

XRPD Pattern of R-fasoracetam anhydrate
Intensity (arb. units)
2θ (°)
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
5
8
11
14
17
20
23
26
29
32
35
20.3
17.9
18.7
16.2
13.2
12.3
9.0

Figure 19

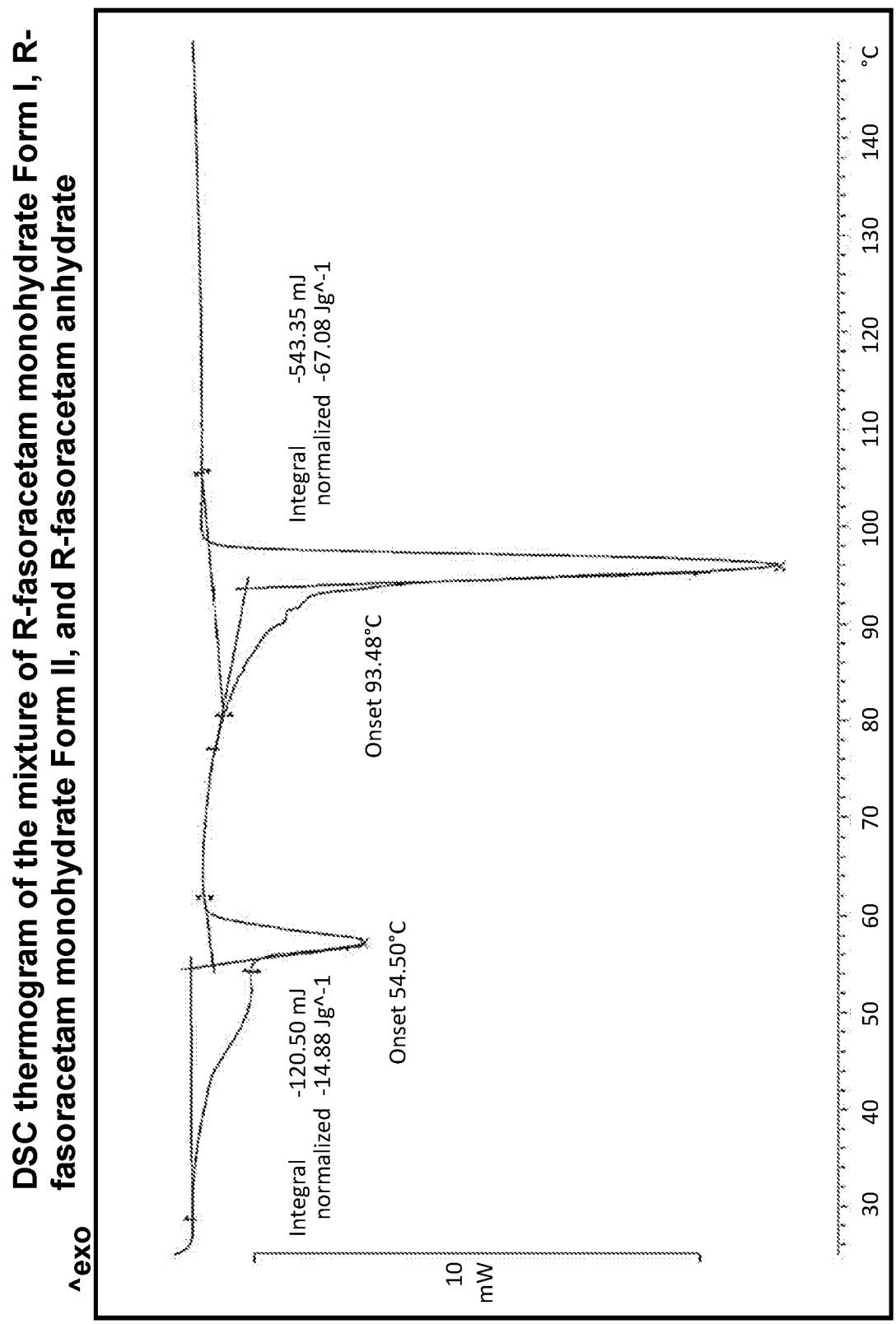

DSC thermogram of the mixture of R-fasoracetam monohydrate Form I, R-fasoracetam monohydrate Form II, and R-fasoracetam anhydrate
^exo
10 mW
Integral -120.50 mJ
normalized -14.88 Jg^-1
Onset 54.50°C
Onset 93.48°C
Integral -543.35 mJ
normalized -67.08 Jg^-1
30 40 50 60 70 80 90 100 110 120 130 140 °C
STARe SW 9.10

Figure 20

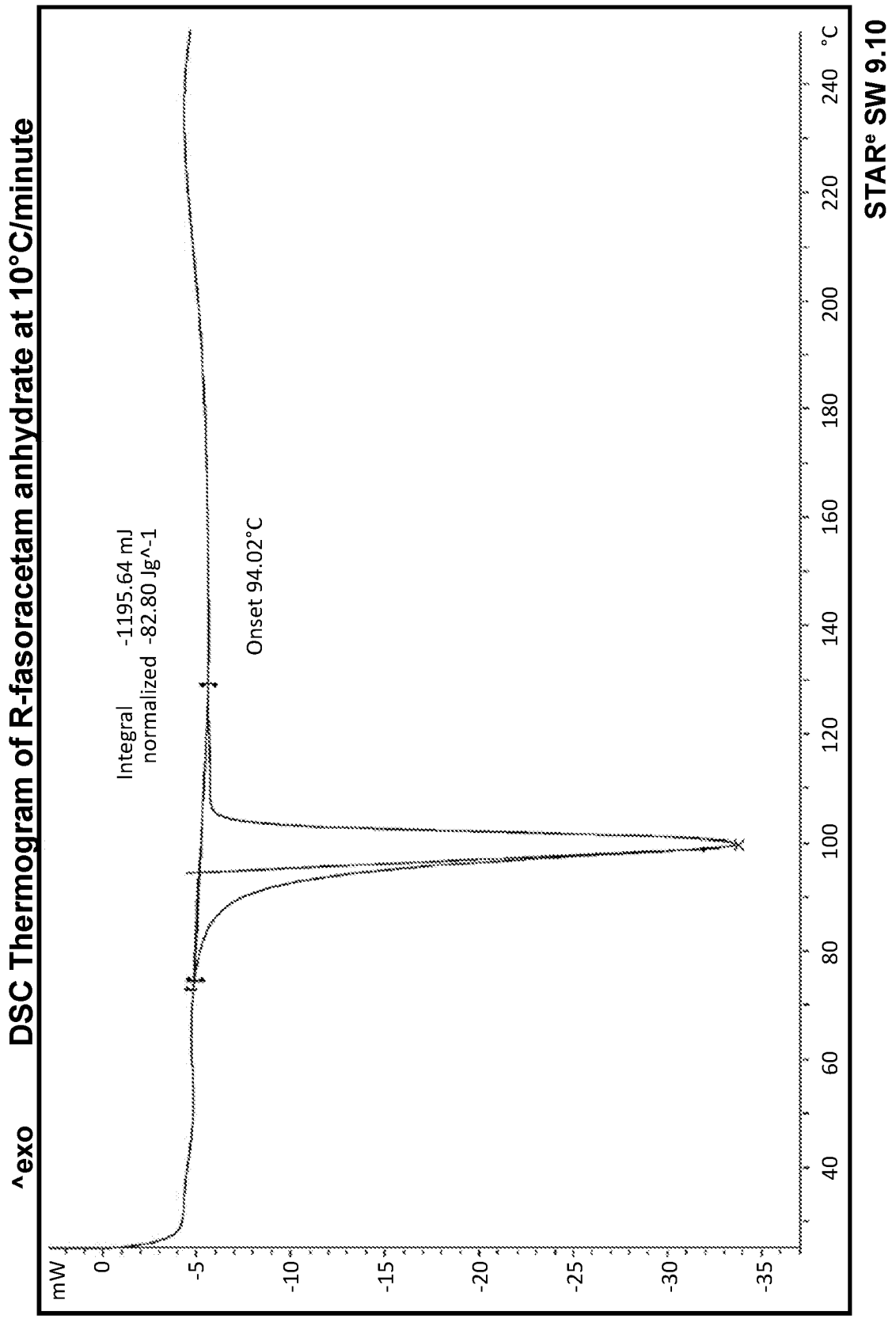

^exo DSC Thermogram of R-fasoracetam anhydrate at 10°C/minute
Integral -1195.64 mJ
normalized -82.80 Jg^-1
Onset 94.02°C
mW
0
-5
-10
-15
-20
-25
-30
-35
40
60
80
100
120
140
160
180
200
220
240
°C
STARe SW 9.10

Figure 21

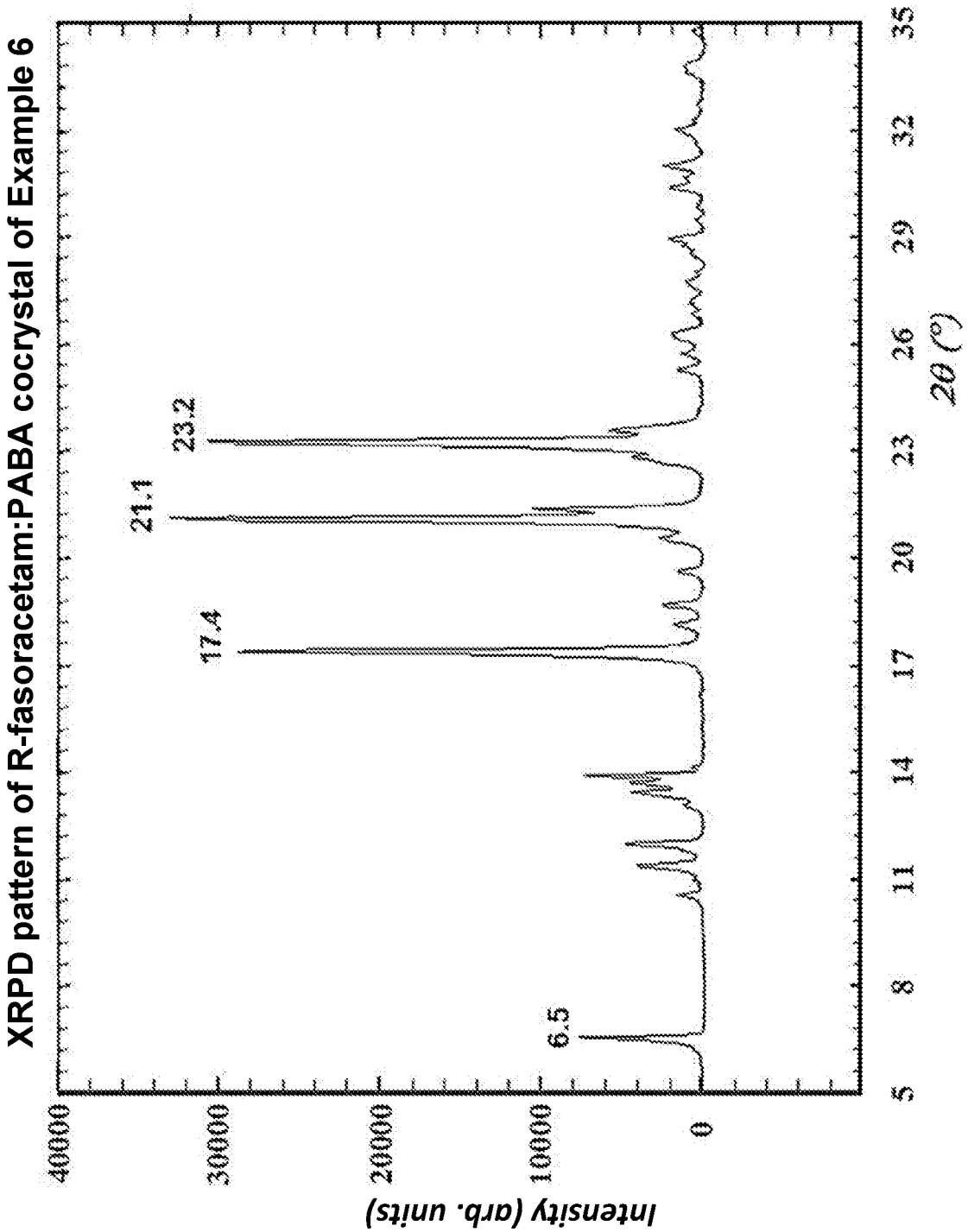

XRPD pattern of R-fasoracetam:PABA cocrystal of Example 6
Intensity (arb. units)
40000
30000
20000
10000
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
6.5
17.4
21.1
23.2

Figure 22

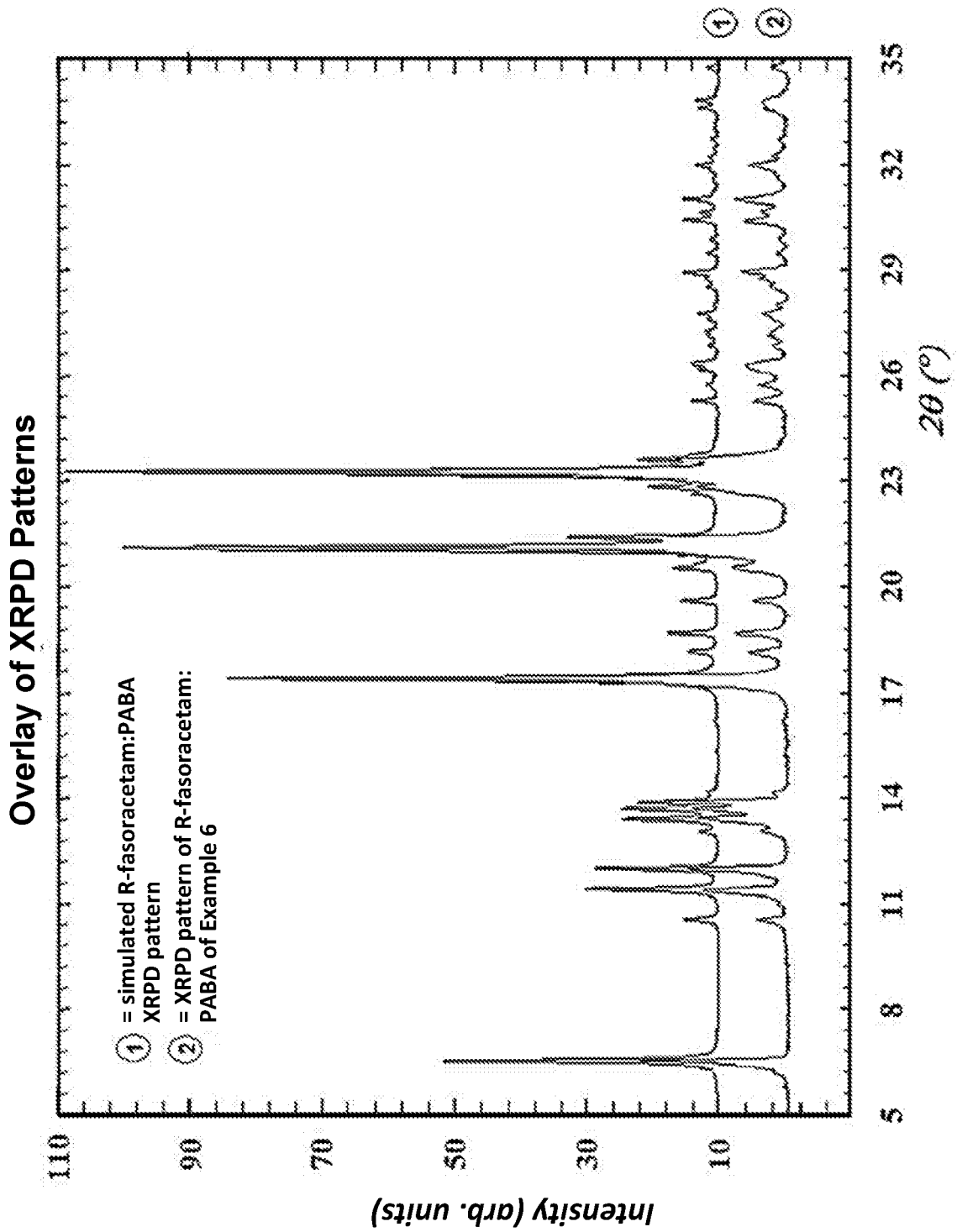

Overlay of XRPD Patterns
① = simulated R-fasoracetam:PABA XRPD pattern
② = XRPD pattern of R-fasoracetam: PABA of Example 6
Intensity (arb. units)
2θ (°)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35

Figure 23

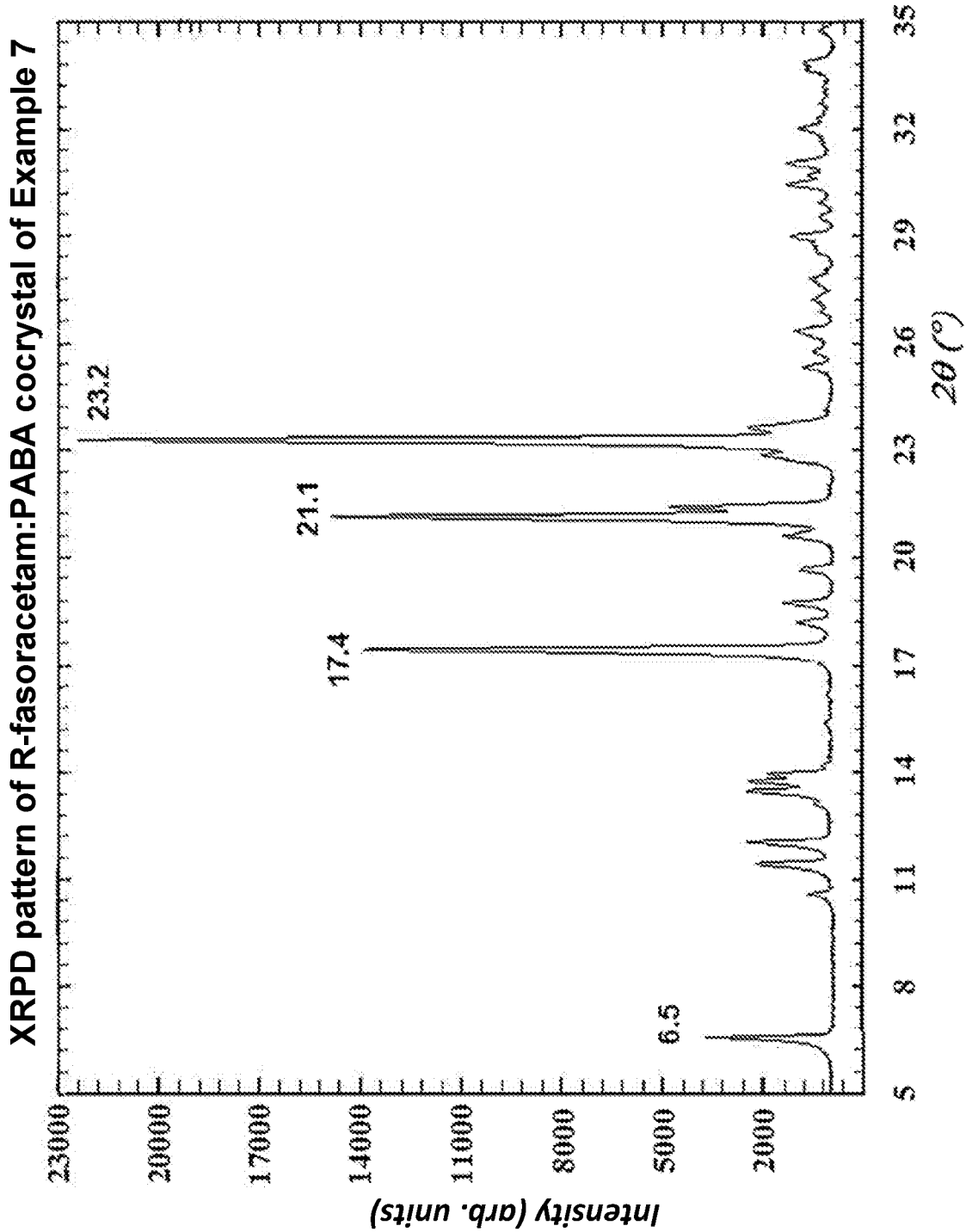

XRPD pattern of R-fasoracetam:PABA cocrystal of Example 7
Intensity (arb. units)
23000
20000
17000
14000
11000
8000
5000
2000
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
23.2
21.1
17.4
6.5

Figure 24

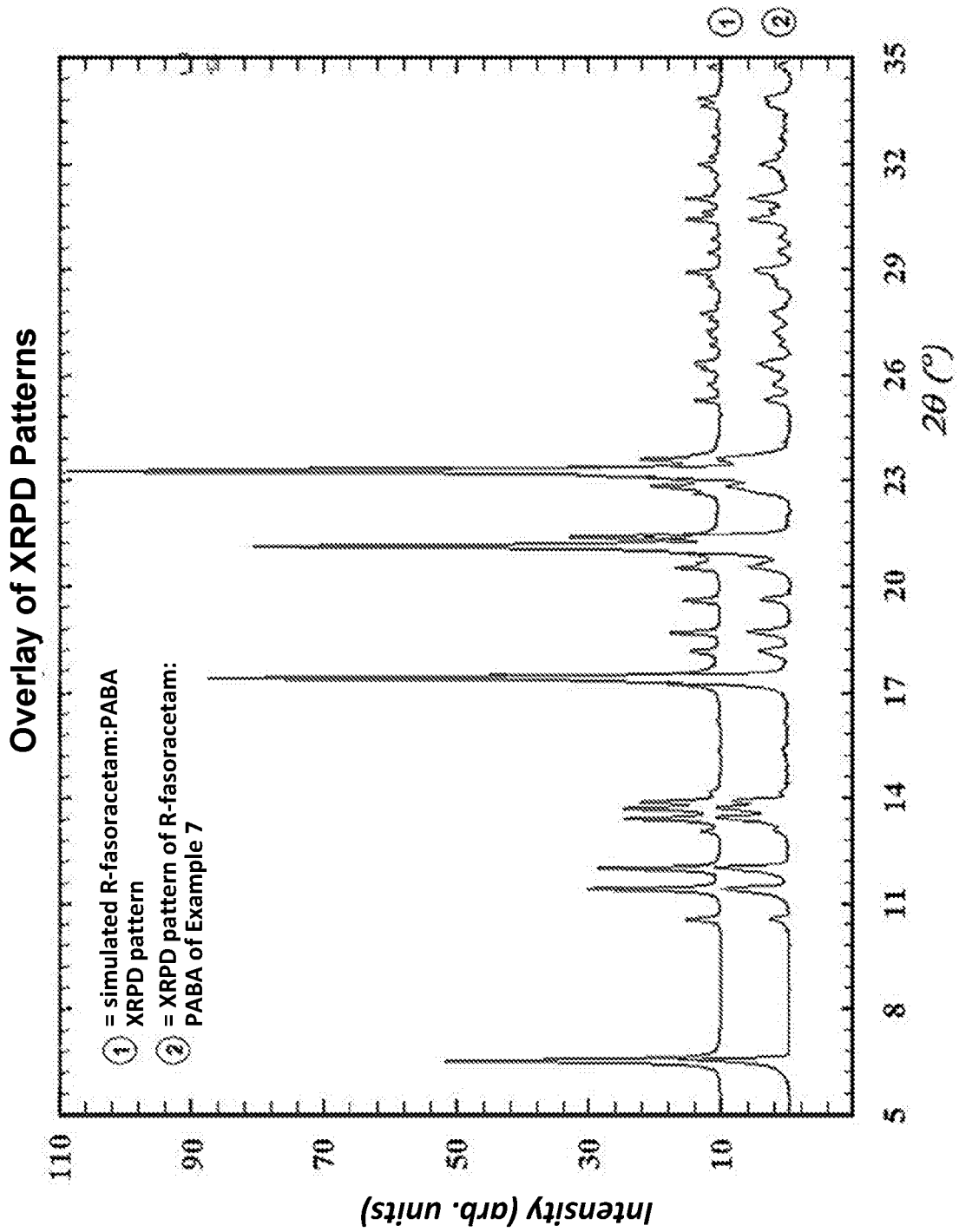

Overlay of XRPD Patterns
① = simulated R-fasoracetam:PABA XRPD pattern
② = XRPD pattern of R-fasoracetam: PABA of Example 7
Intensity (arb. units)
2θ (°)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35

Figure 25

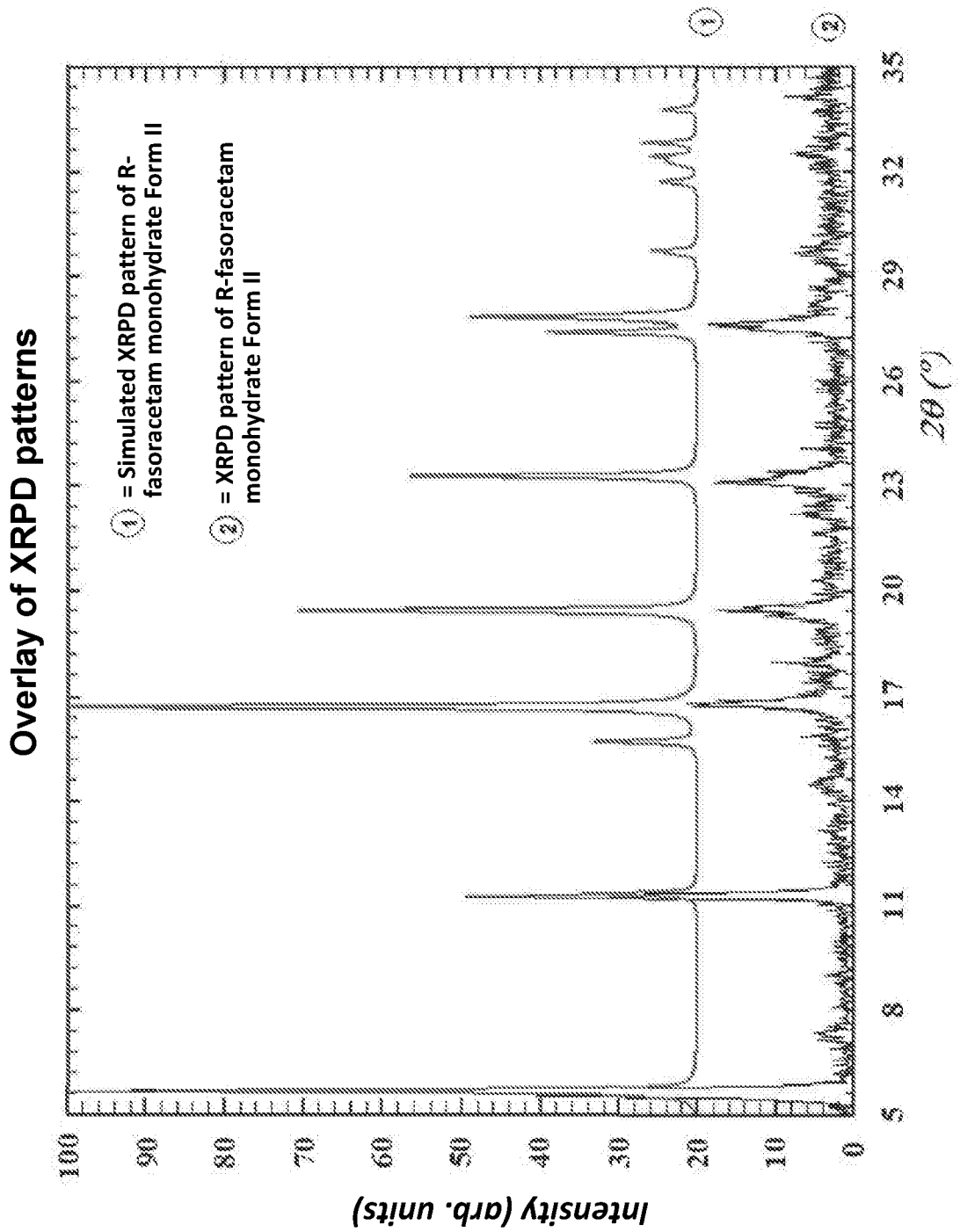

Overlay of XRPD patterns
① = Simulated XRPD pattern of R-fasoracetam monohydrate Form II
② = XRPD pattern of R-fasoracetam monohydrate Form II
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
80
90
100
5
8
11
14
17
20
23
26
29
32
35

Figure 26

ORTEP of R-fasoracetam monohydrate Form II

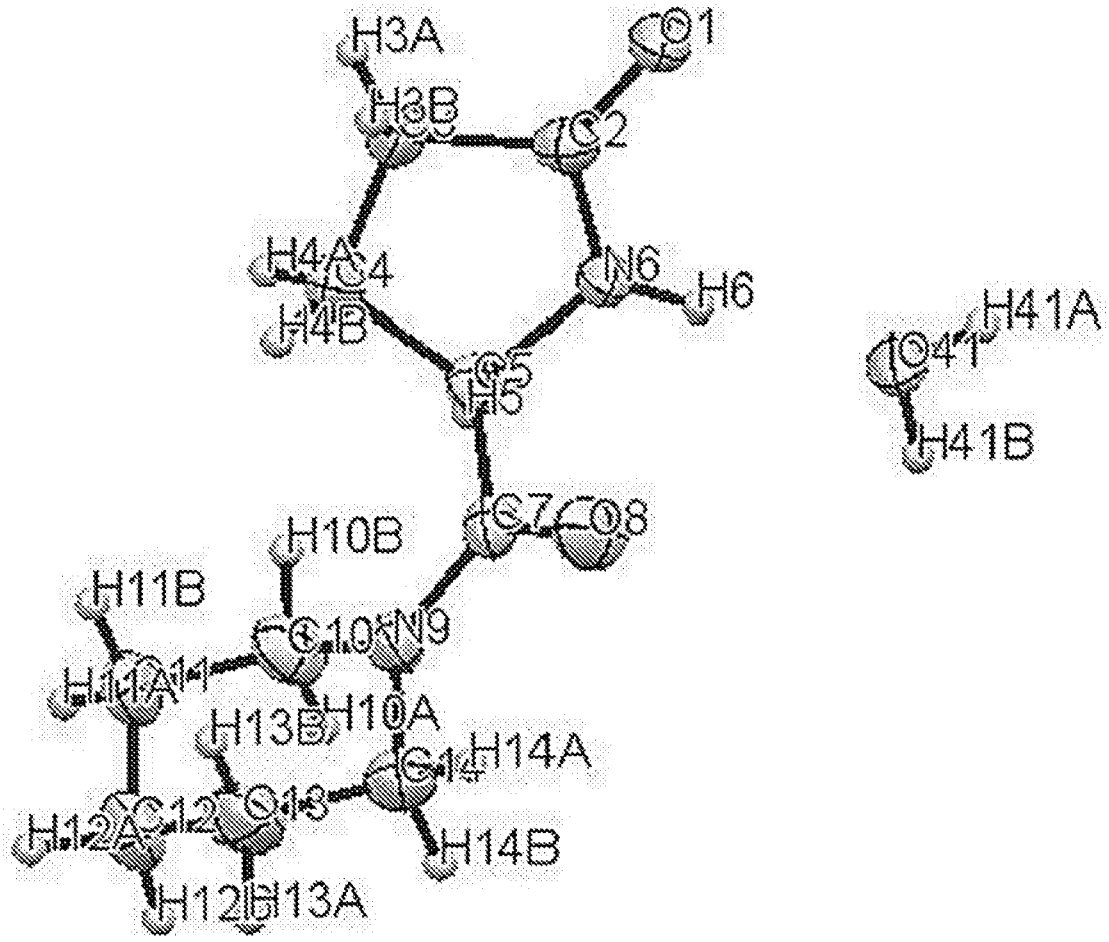


Figure 27

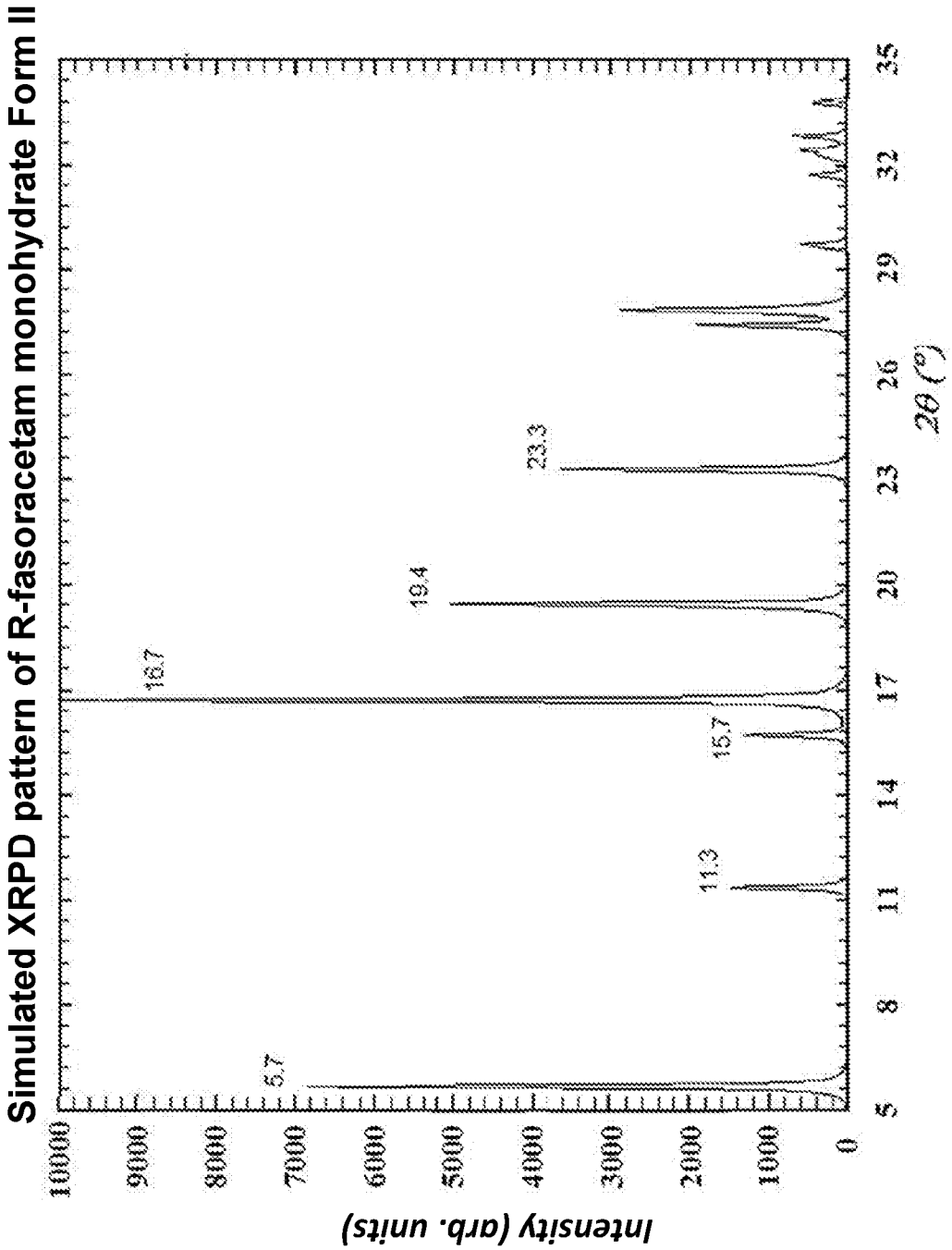

Simulated XRPD pattern of R-fasoracetam monohydrate Form II
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
5.7
16.7
19.4
23.3
11.3
15.7

Figure 28

ORTEP of R-fasoracetam anhydrate

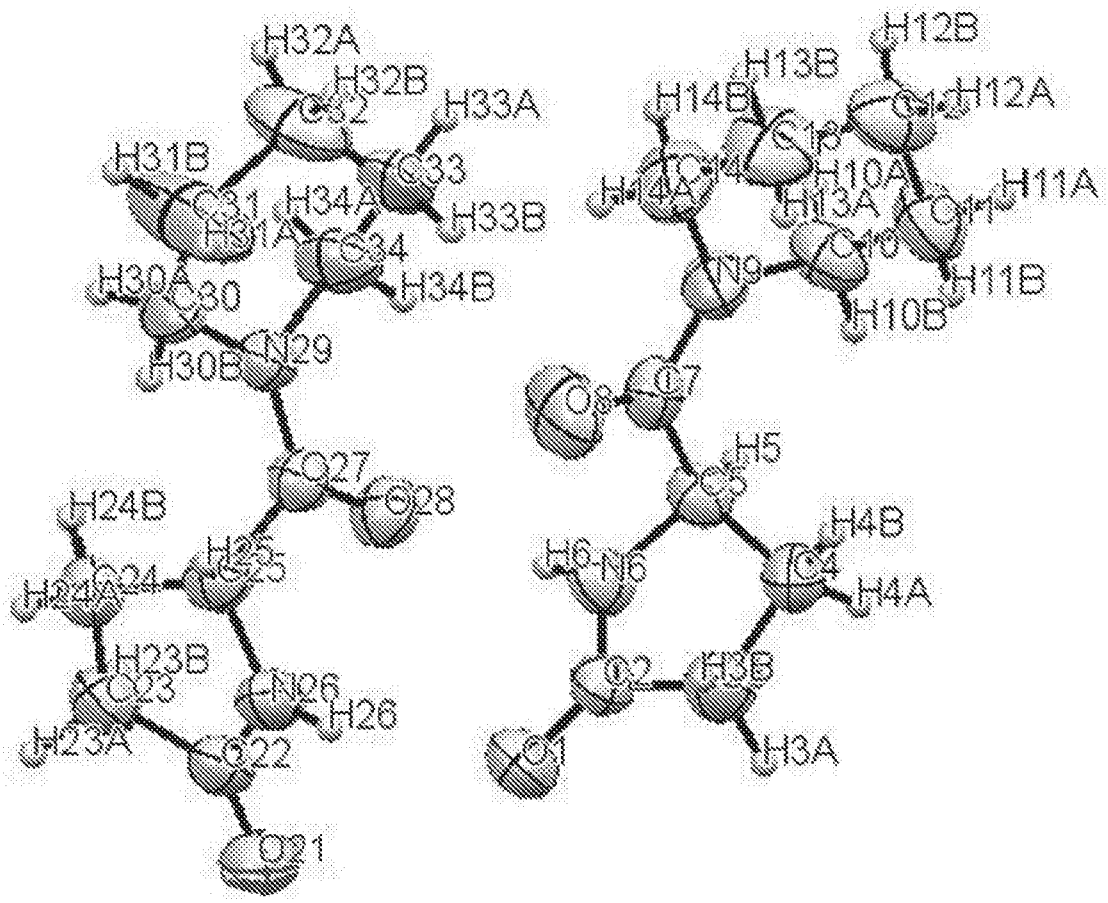


Figure 29

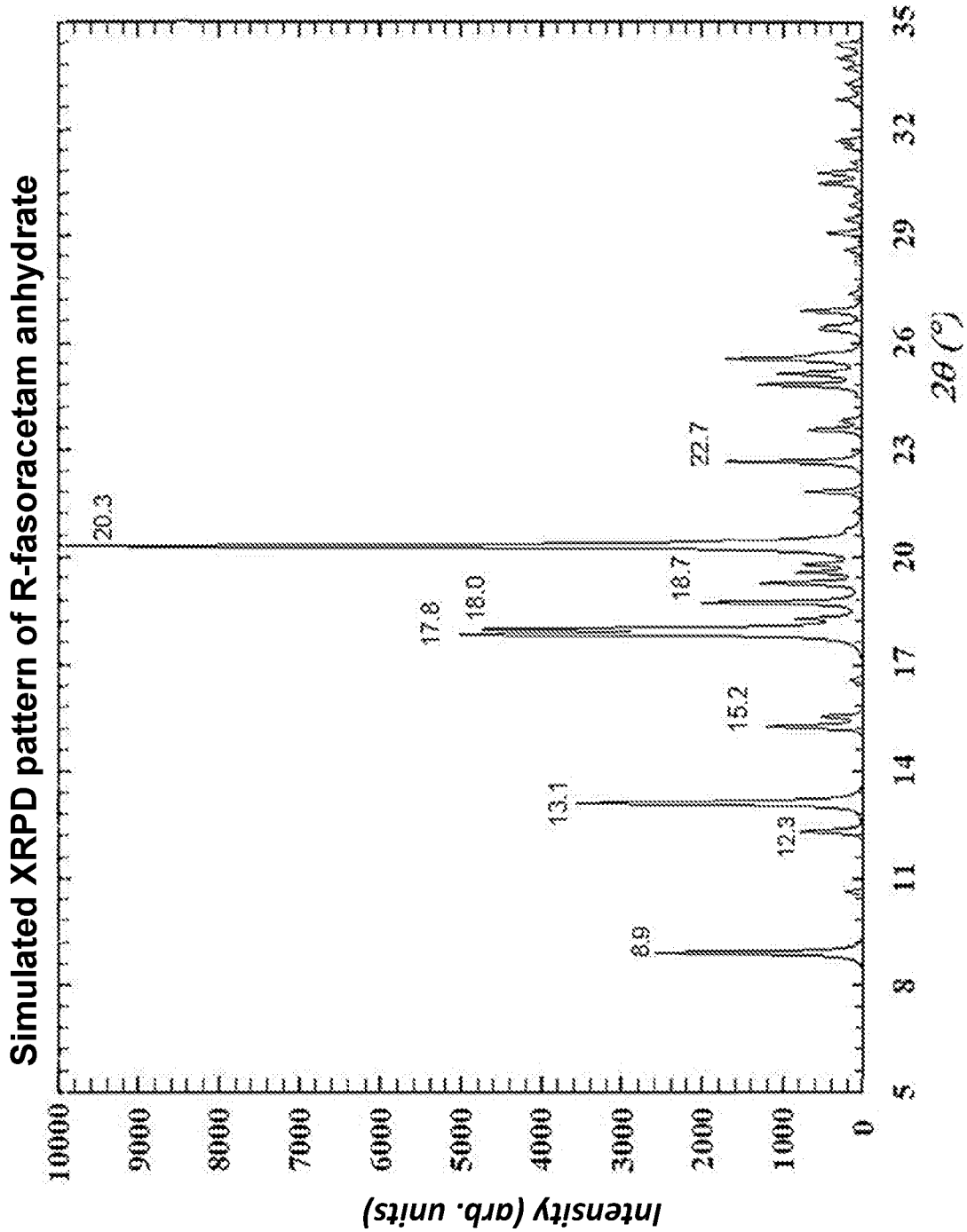

Simulated XRPD pattern of R-fasoracetam anhydrate
Intensity (arb. units)
2θ (°)
20.3
22.7
18.7
18.0
17.8
15.2
13.1
12.3
8.9

Figure 30

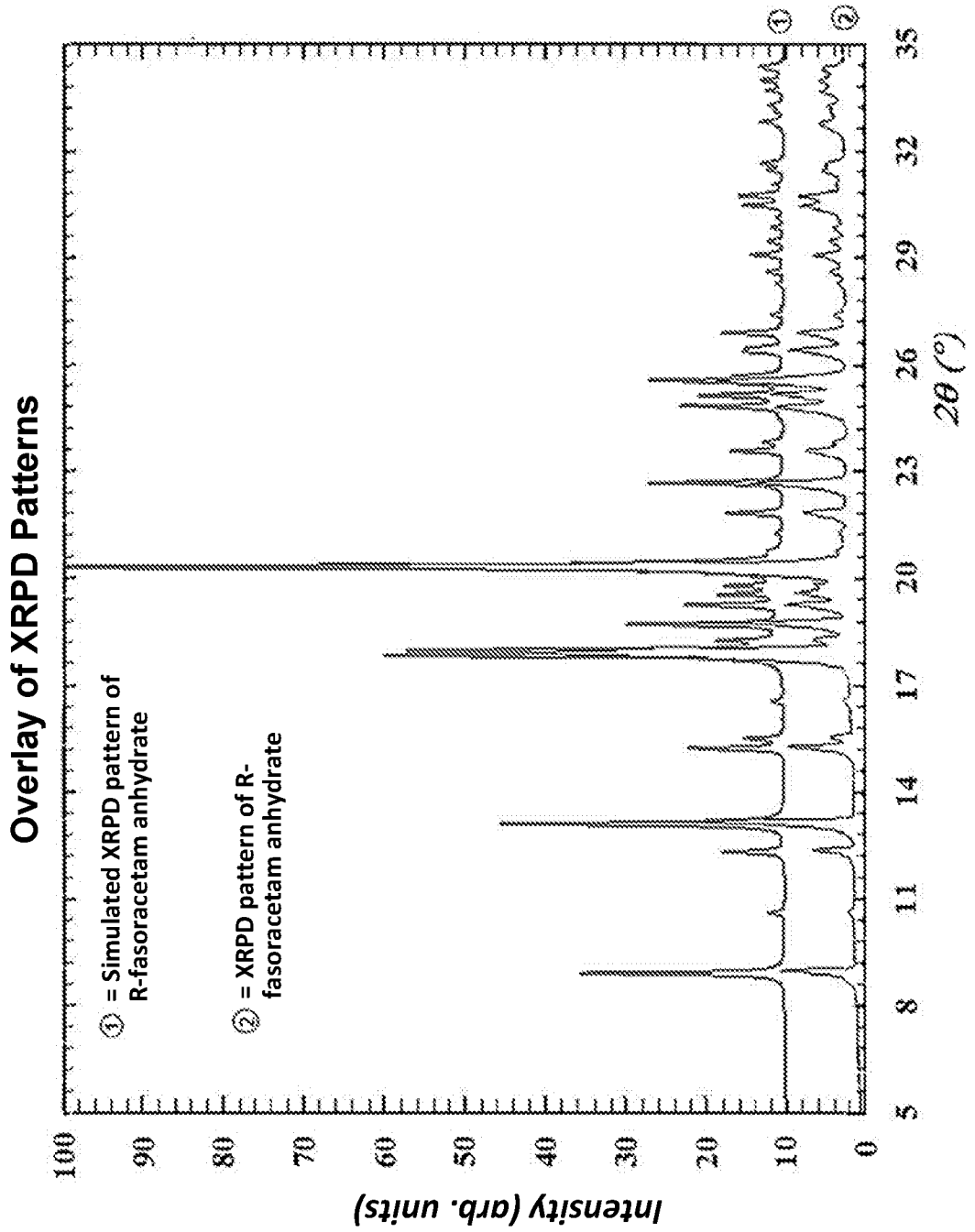

Overlay of XRPD Patterns
① = Simulated XRPD pattern of R-fasoracetam anhydrate
② = XRPD pattern of R-fasoracetam anhydrate
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35
①
②

Figure 31

ORTEP of R-fasoracetam monohydrate Form I

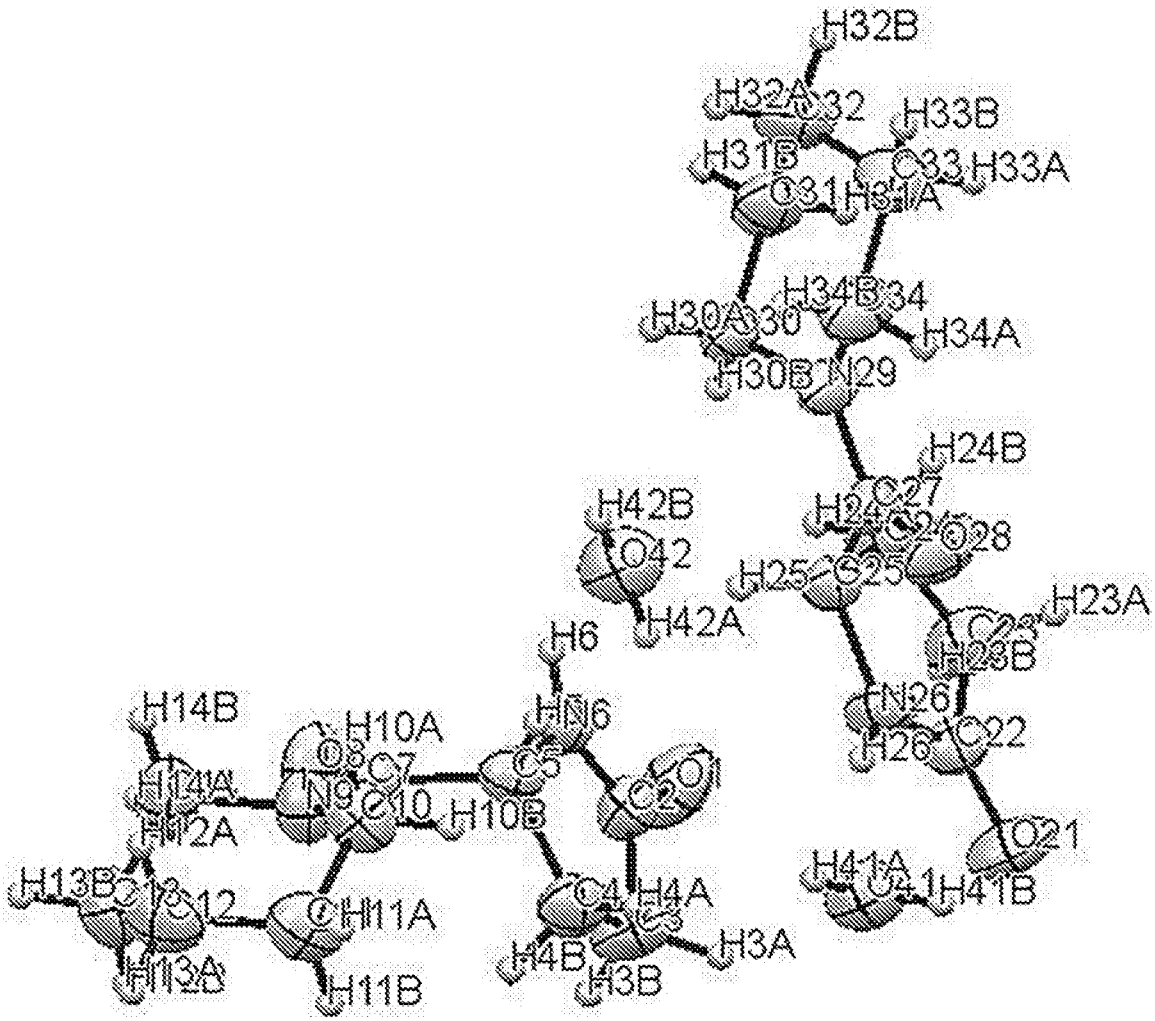


Figure 32

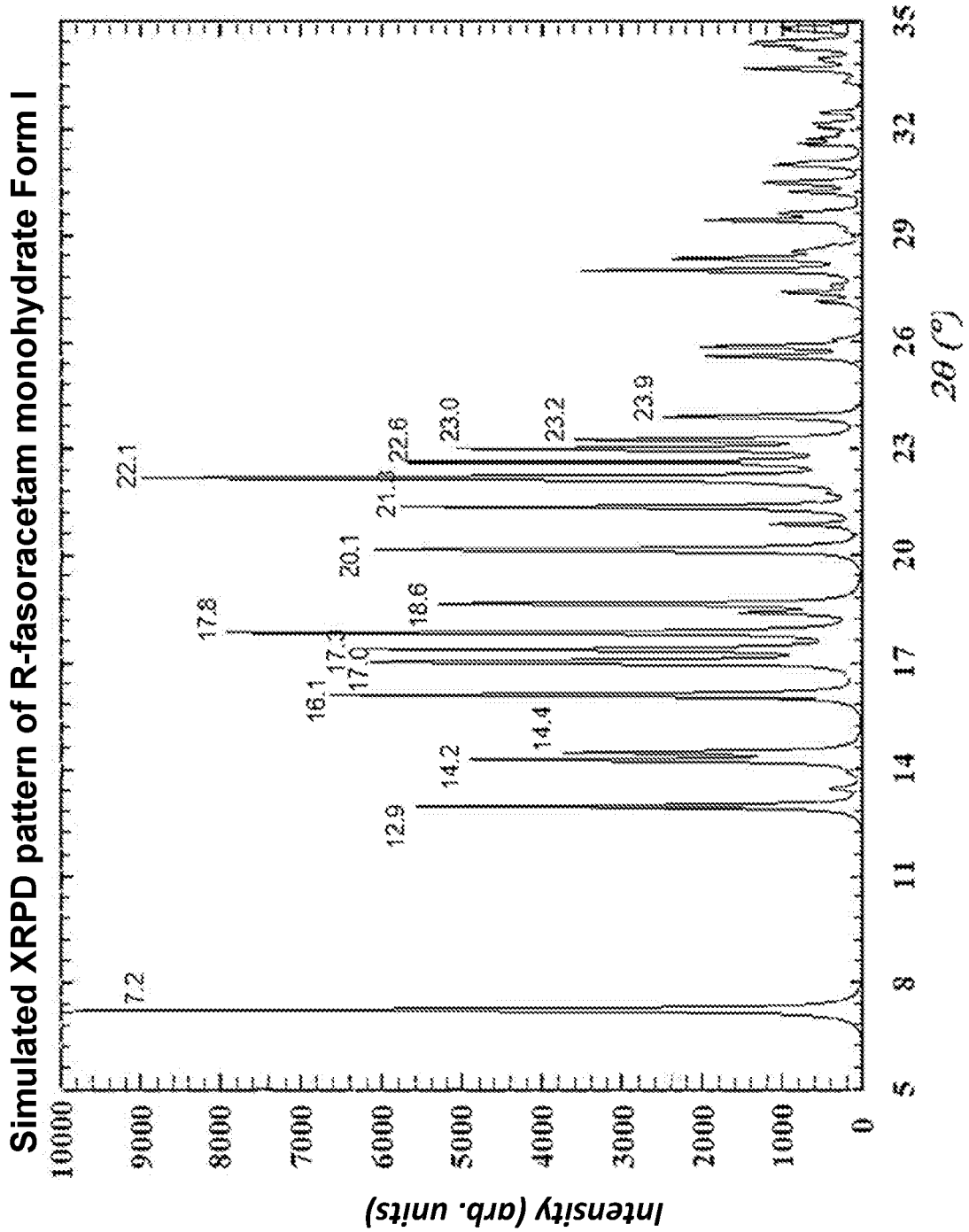

Simulated XRPD pattern of R-fasoracetam monohydrate Form I
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
7.2
12.9
14.2
14.4
16.1
17.0
17.3
17.8
18.6
20.1
21.8
22.1
22.6
23.0
23.2
23.9

Figure 33

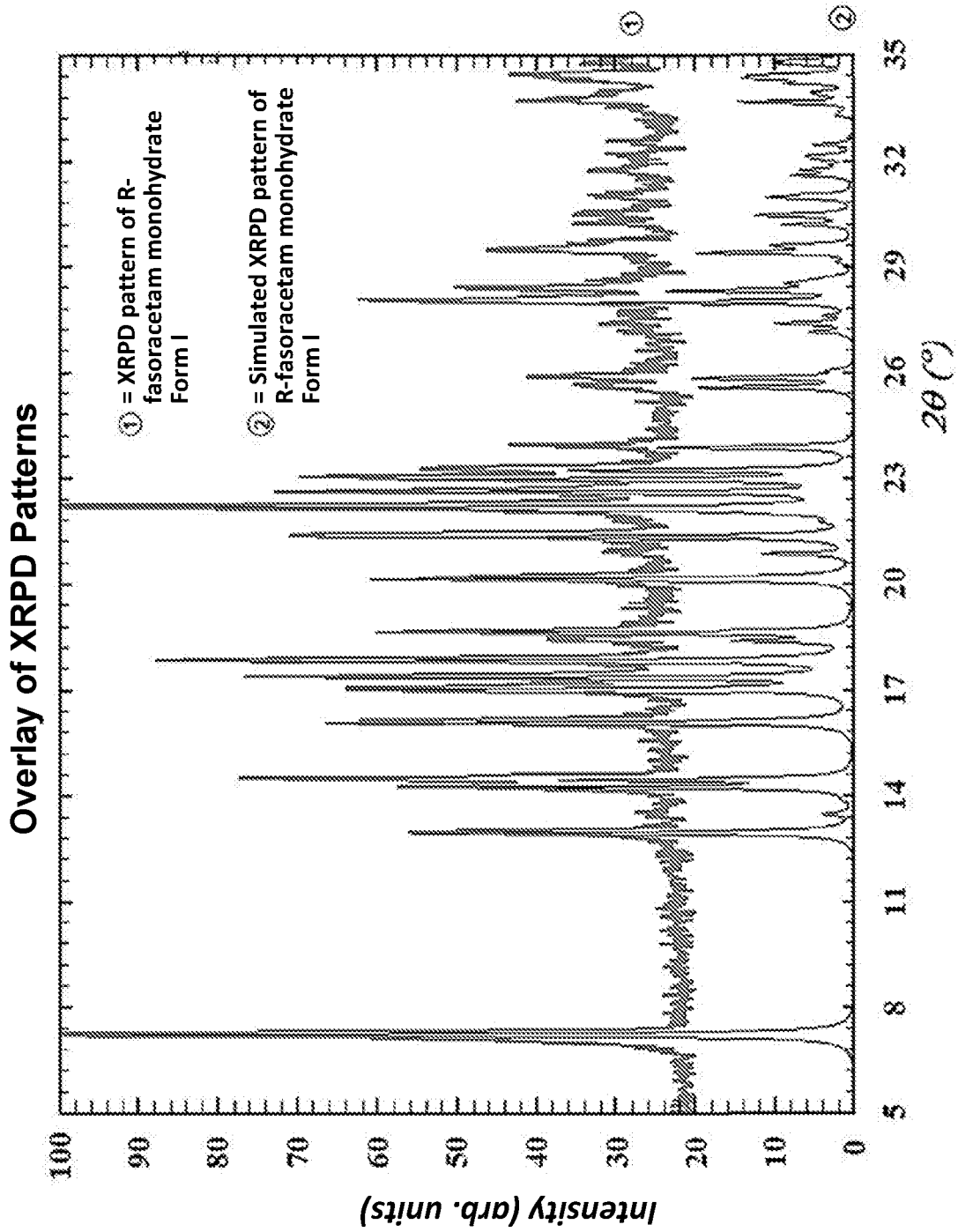

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam monohydrate Form I
② = Simulated XRPD pattern of R-fasoracetam monohydrate Form I
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35

Figure 34

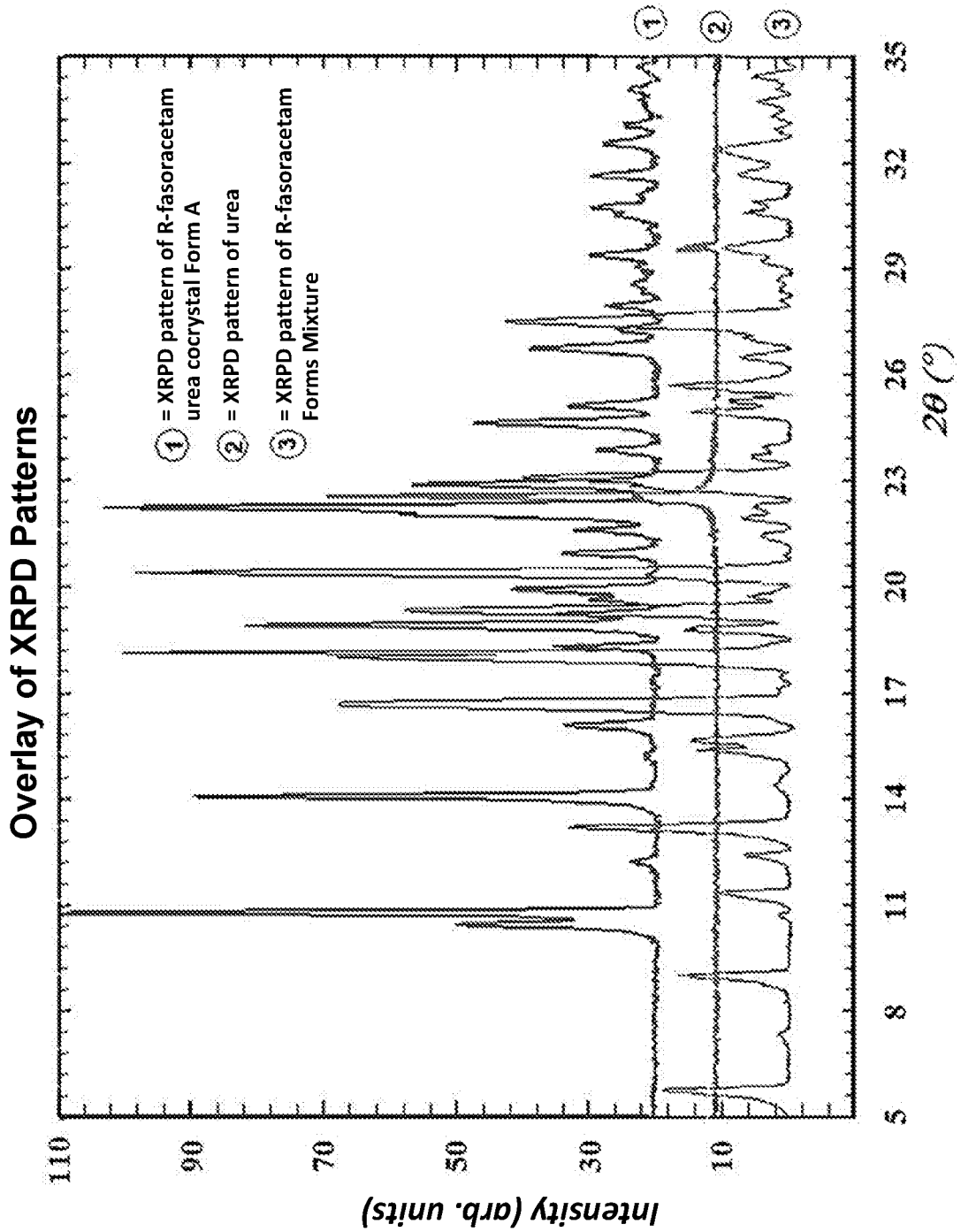

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam urea cocrystal Form A
② = XRPD pattern of urea
③ = XRPD pattern of R-fasoracetam Forms Mixture
Intensity (arb. units)
2θ (°)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35

Figure 35

ORTEP of R-fasoracetam urea cocrystal Form B

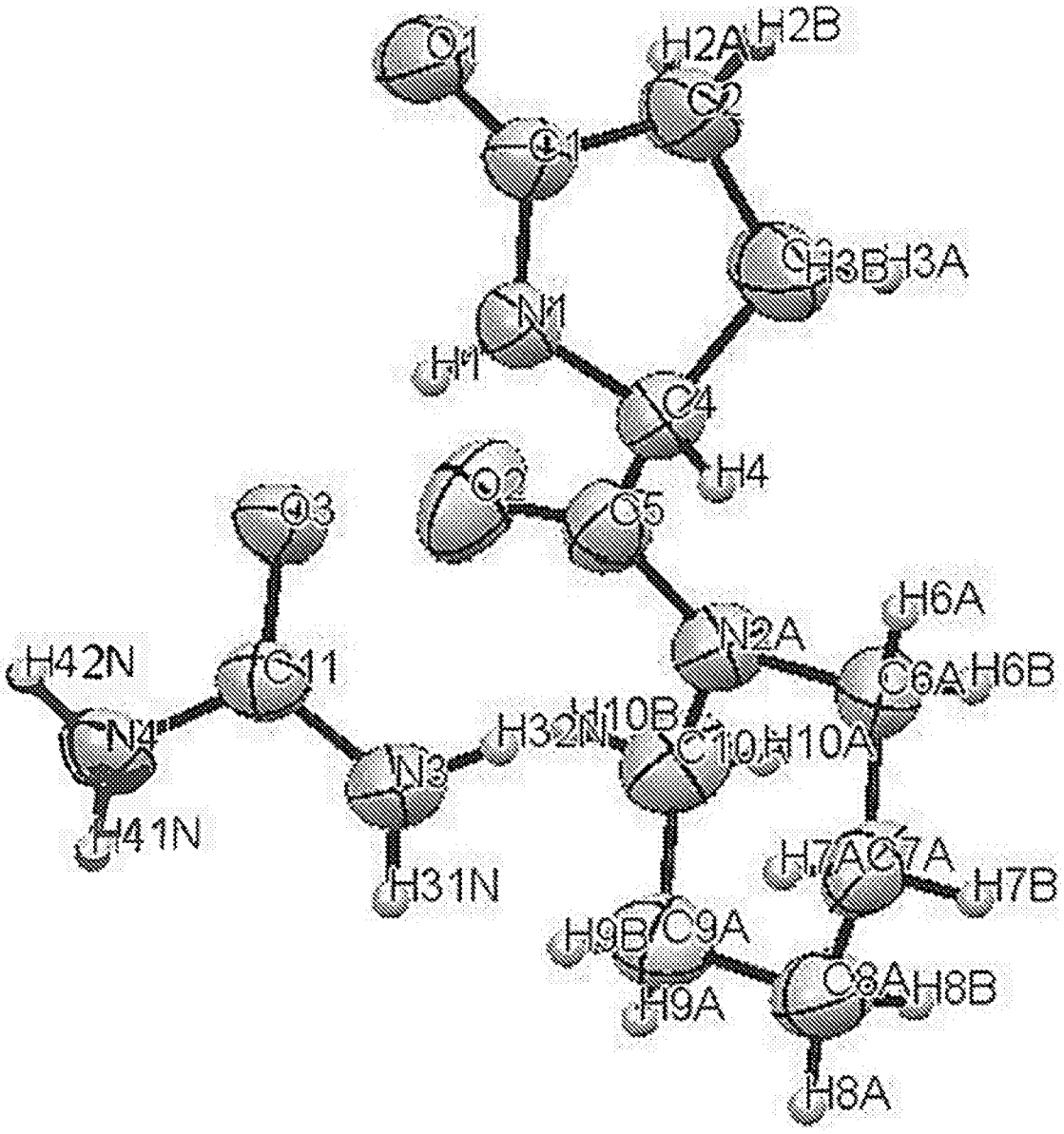


Figure 36

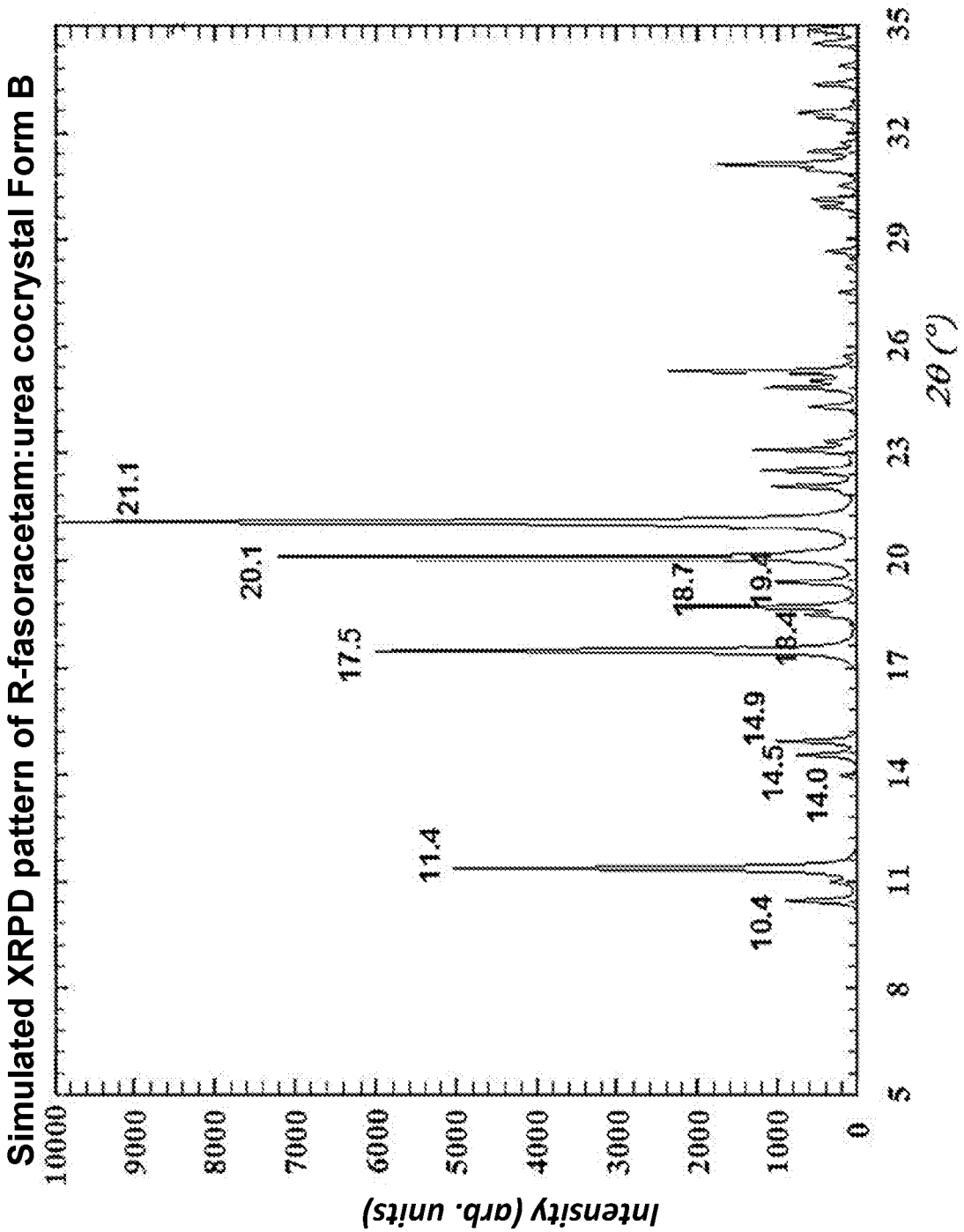

Simulated XRPD pattern of R-fasoracetam:urea cocrystal Form B
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
21.1
20.1
17.5
11.4
10.4
14.5
14.9
14.0
18.7
19.4
18.4

Figure 37

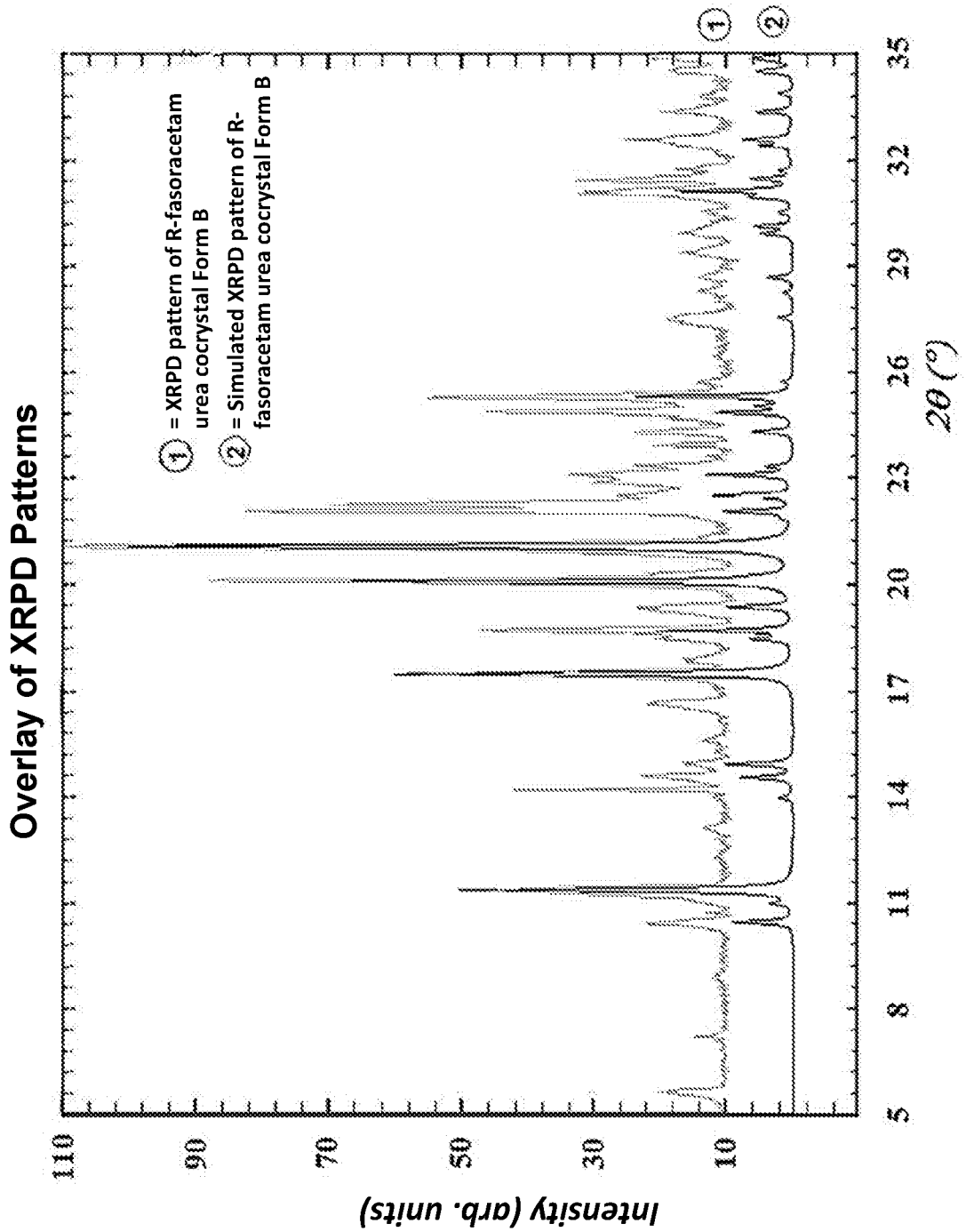

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam urea cocrystal Form B
② = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form B
Intensity (arb. units)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 38

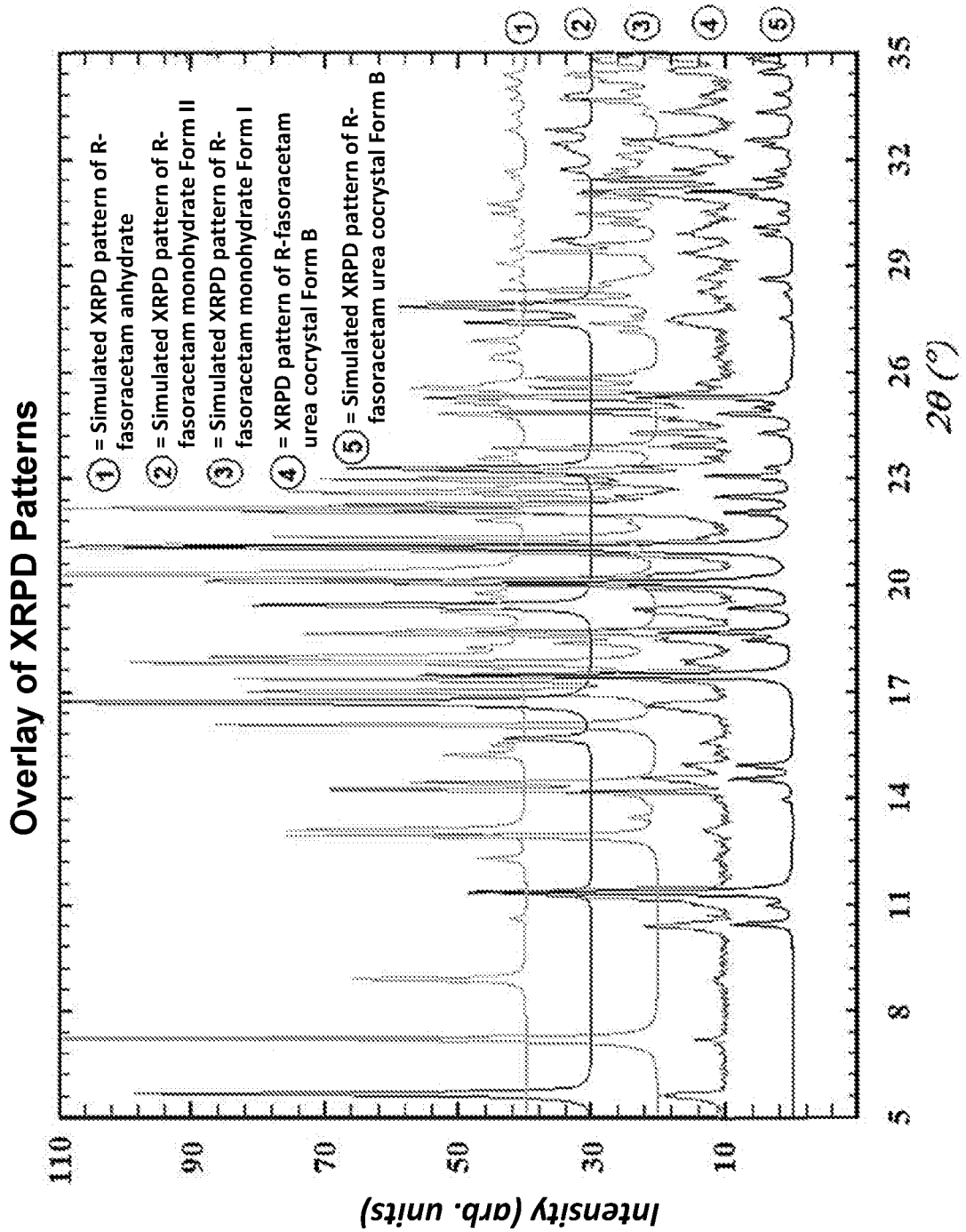

Overlay of XRPD Patterns
1 = Simulated XRPD pattern of R-fasoracetam anhydrate
2 = Simulated XRPD pattern of R-fasoracetam monohydrate Form II
3 = Simulated XRPD pattern of R-fasoracetam monohydrate Form I
4 = XRPD pattern of R-fasoracetam urea cocrystal Form B
5 = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form B
Intensity (arb. units)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 39

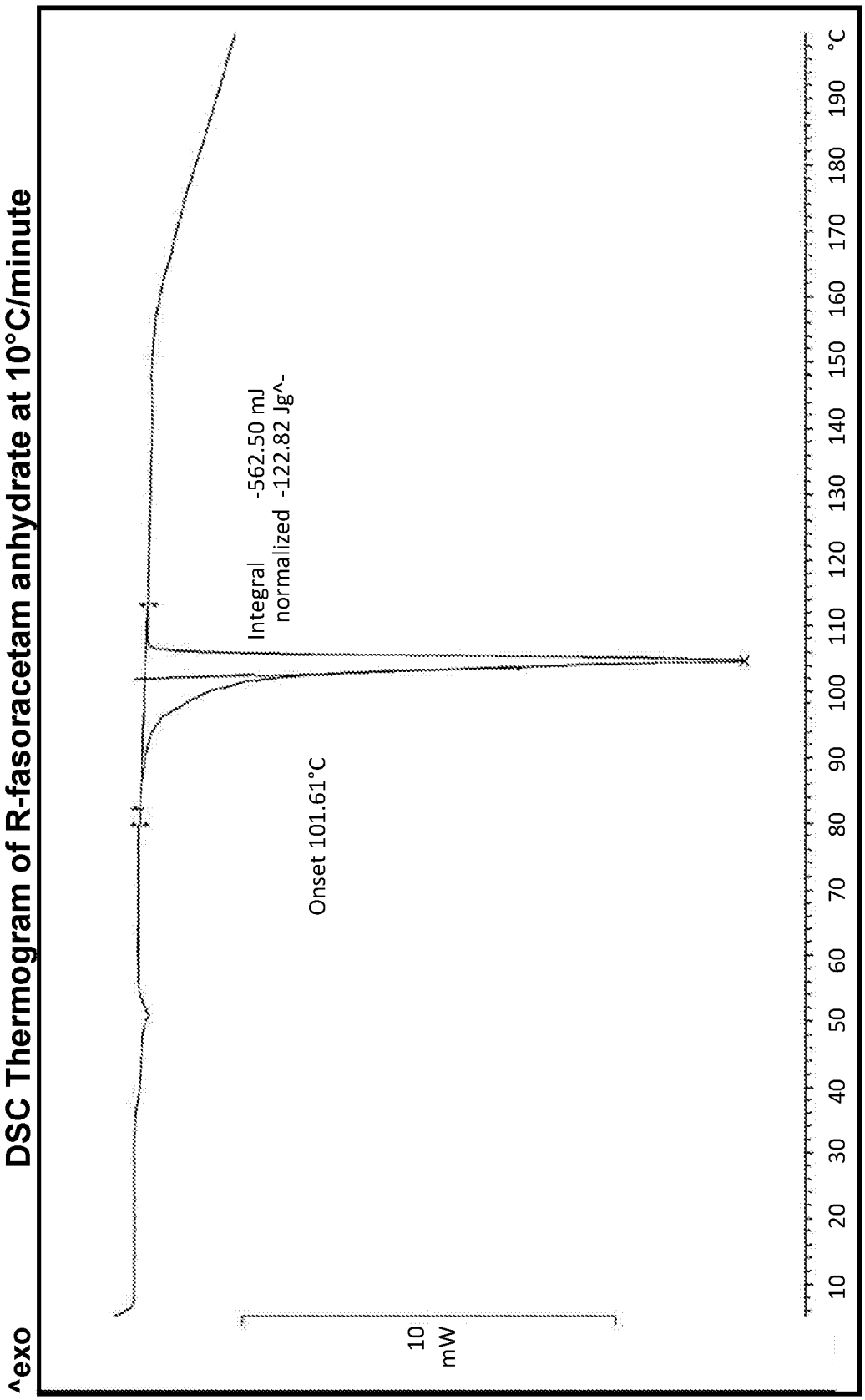

DSC Thermogram of R-fasoracetam anhydrate at 10°C/minute
^exo
Integral -562.50 mJ
normalized -122.82 Jg^-
Onset 101.61°C
10 mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 40

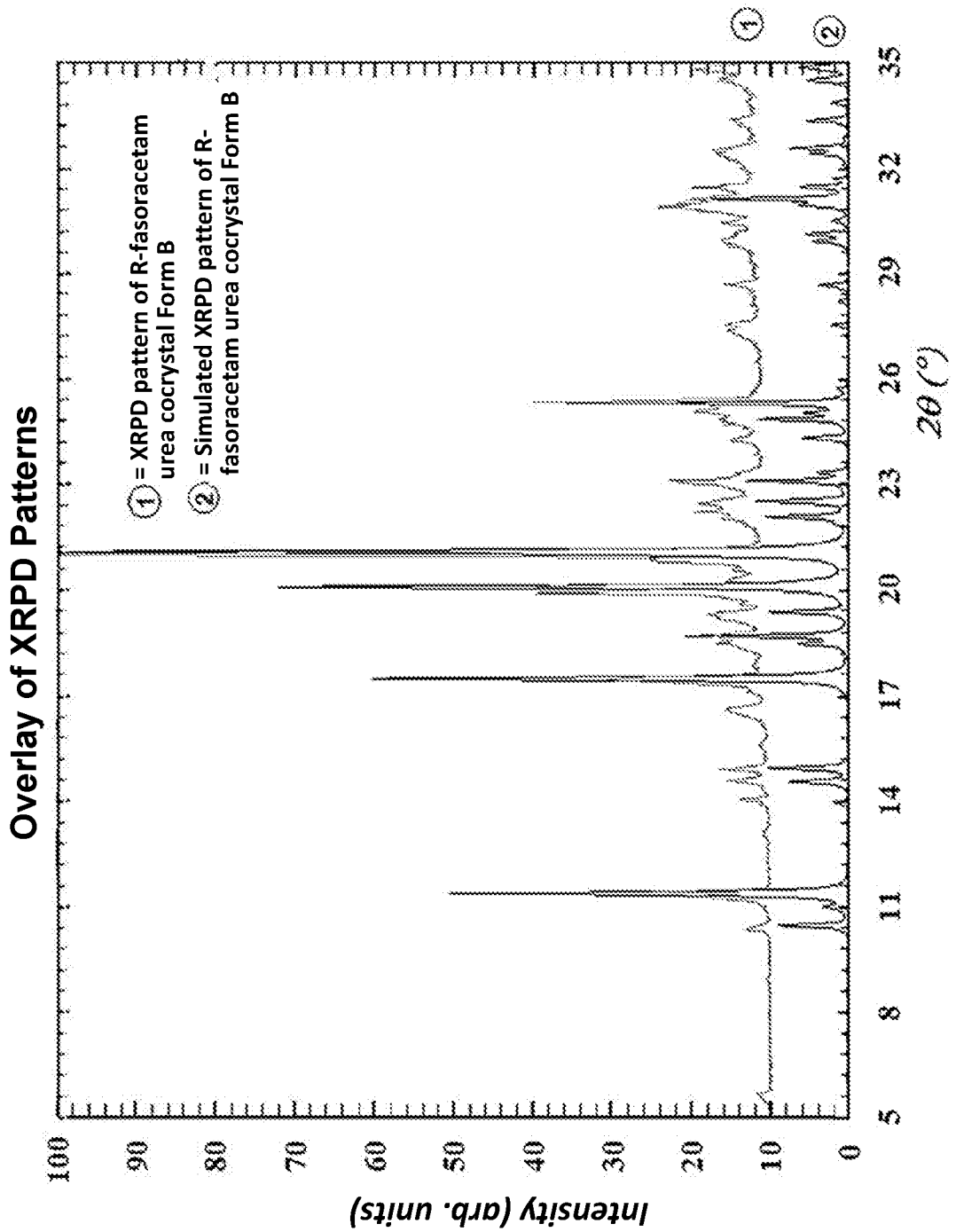

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam urea cocrystal Form B
② = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form B
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
80
90
100
5
8
11
14
17
20
23
26
29
32
35

Figure 41

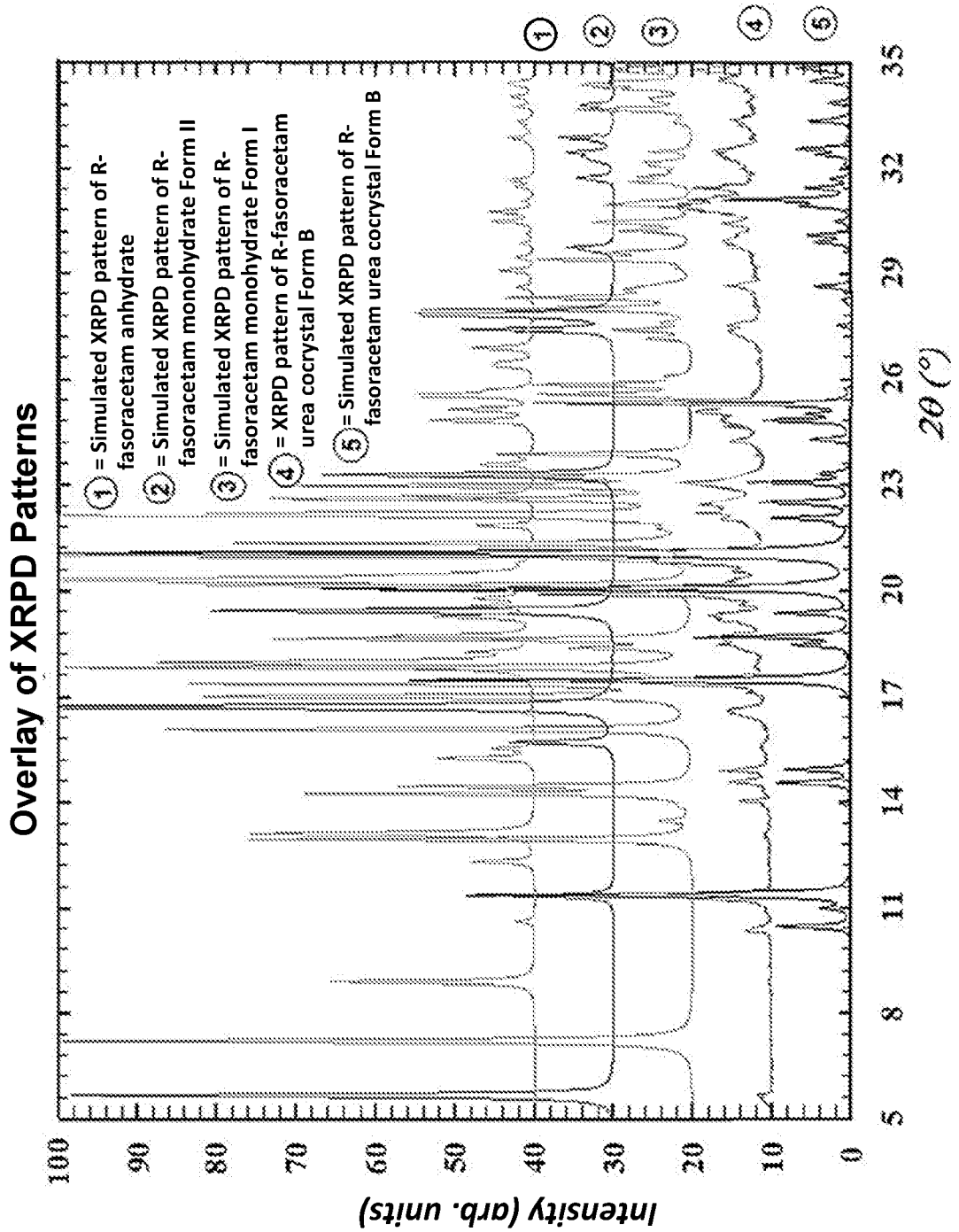

Overlay of XRPD Patterns
1 = Simulated XRPD pattern of R-fasoracetam anhydrate
2 = Simulated XRPD pattern of R-fasoracetam monohydrate Form II
3 = Simulated XRPD pattern of R-fasoracetam monohydrate Form I
4 = XRPD pattern of R-fasoracetam urea cocrystal Form B
5 = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form B
Intensity (arb. units)
2θ (°)

Figure 42

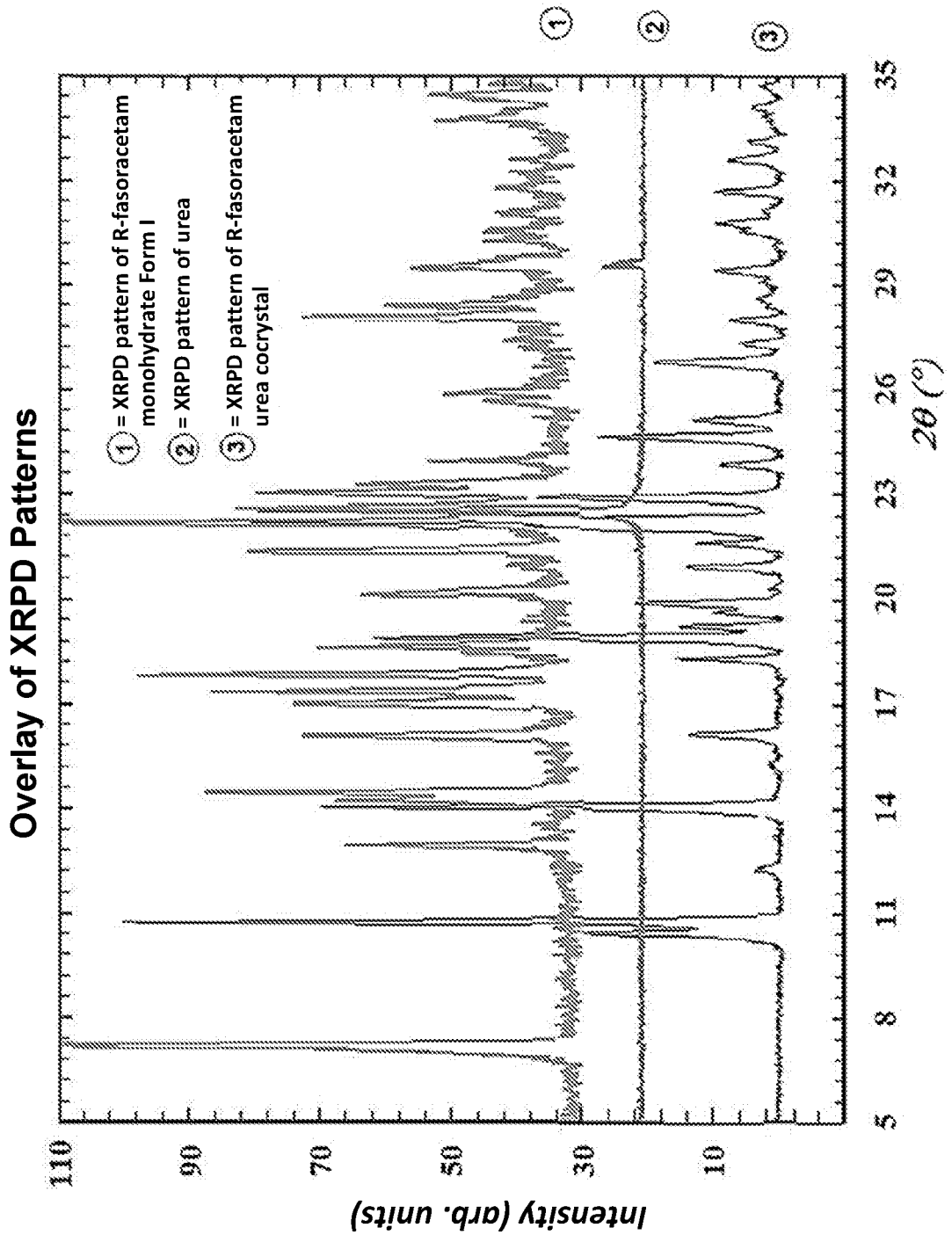

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam monohydrate Form I
② = XRPD pattern of urea
③ = XRPD pattern of R-fasoracetam urea cocrystal
Intensity (arb. units)
2θ (°)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35

Figure 43

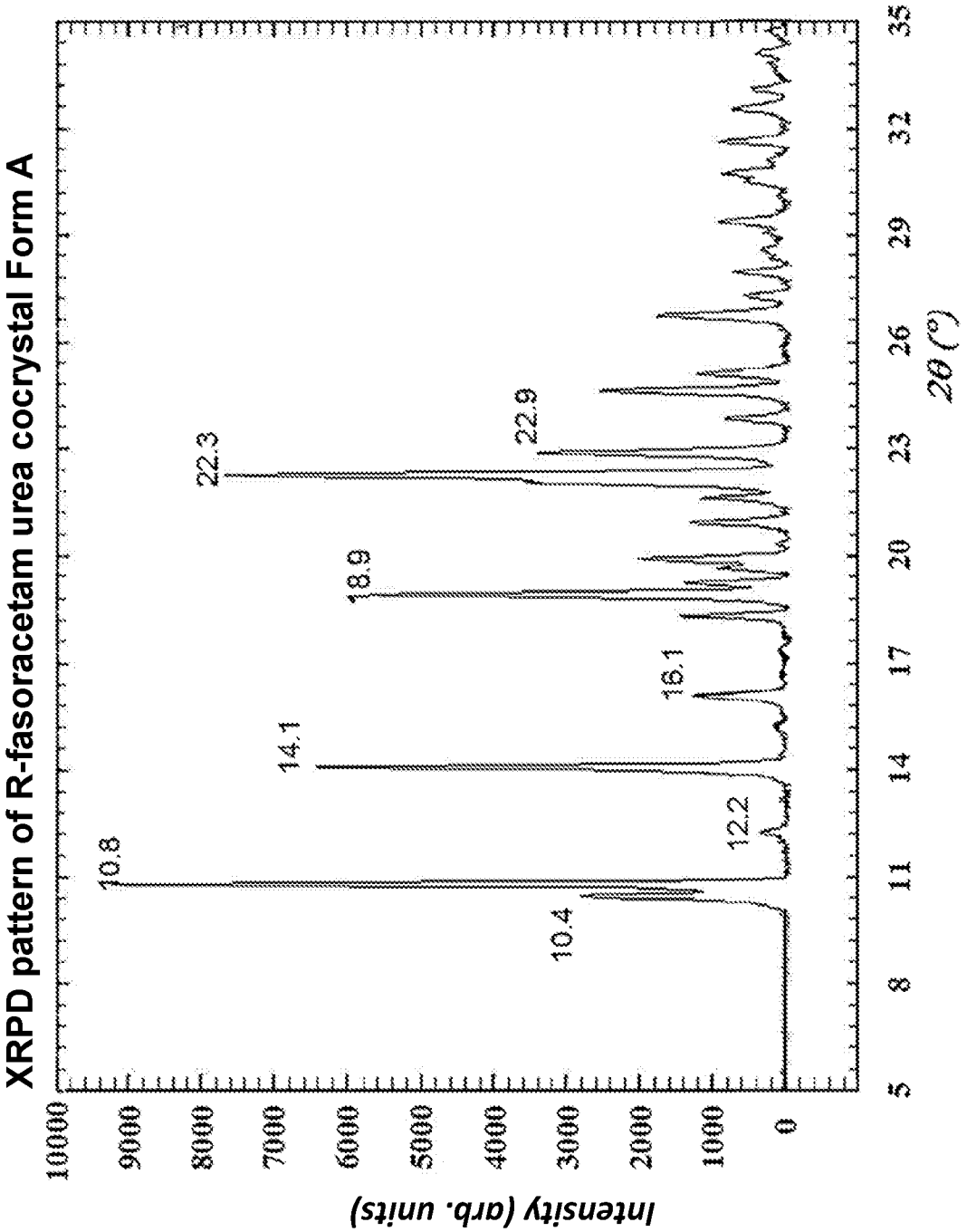

XRPD pattern of R-fasoracetam urea cocrystal Form A
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
10.8
10.4
12.2
14.1
16.1
18.9
22.3
22.9

Figure 44

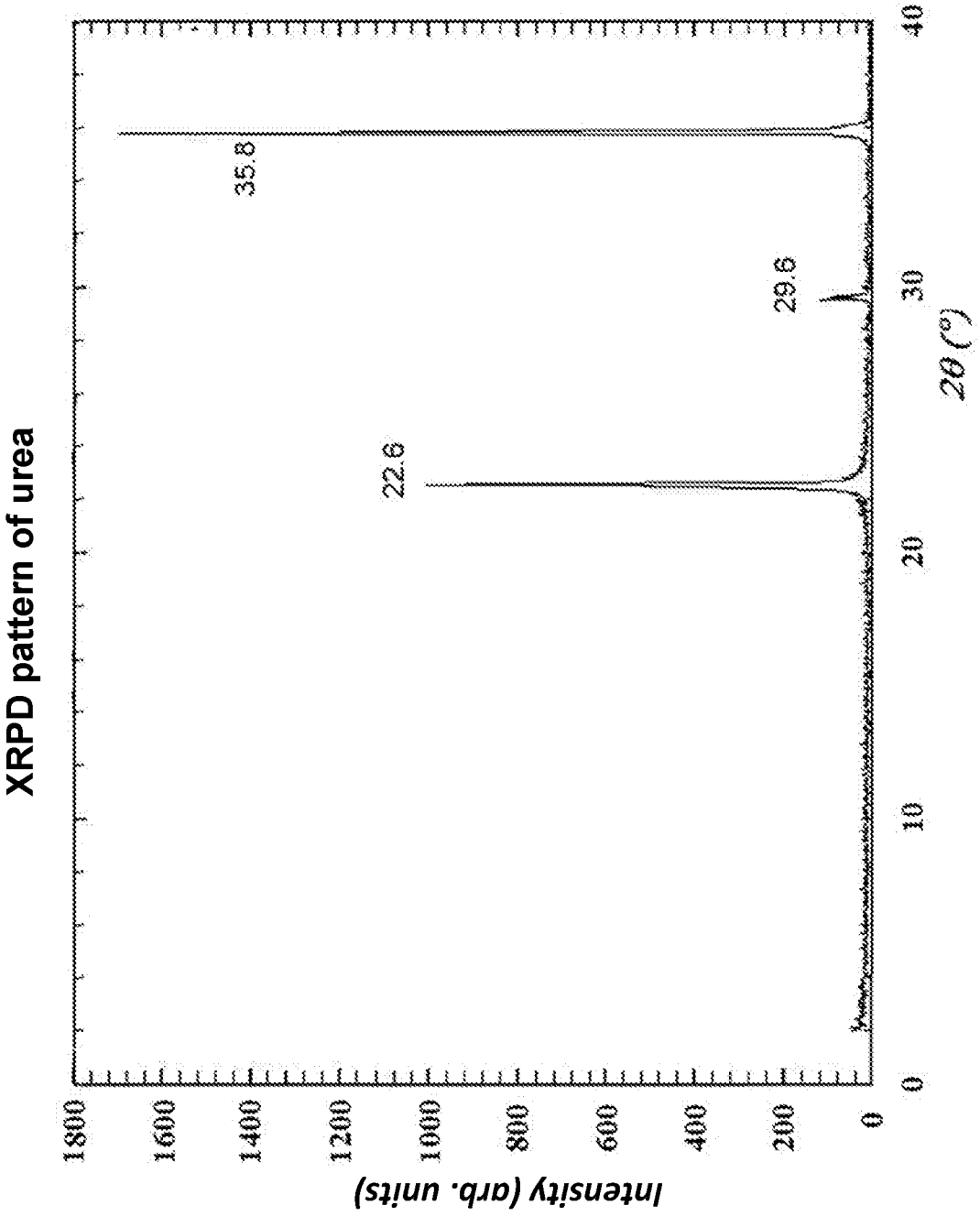

XRPD pattern of urea
35.8
29.6
22.6
2θ (°)
Intensity (arb. units)
0
200
400
600
800
1000
1200
1400
1600
1800
10
20
30
40

Figure 45

^{1}H-NMR spectrum of dissolved R-fasoracetam urea cocrystal

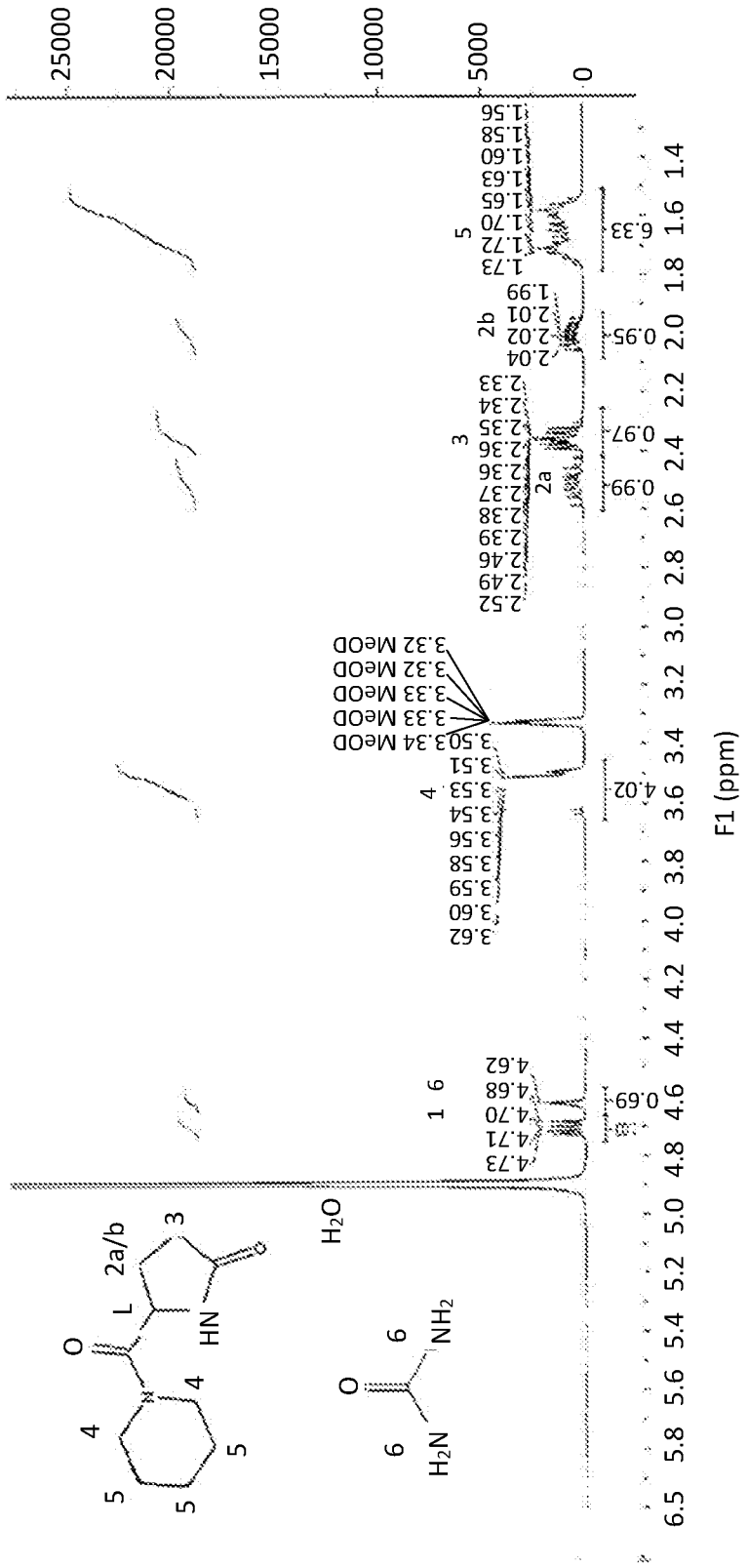


Figure 46

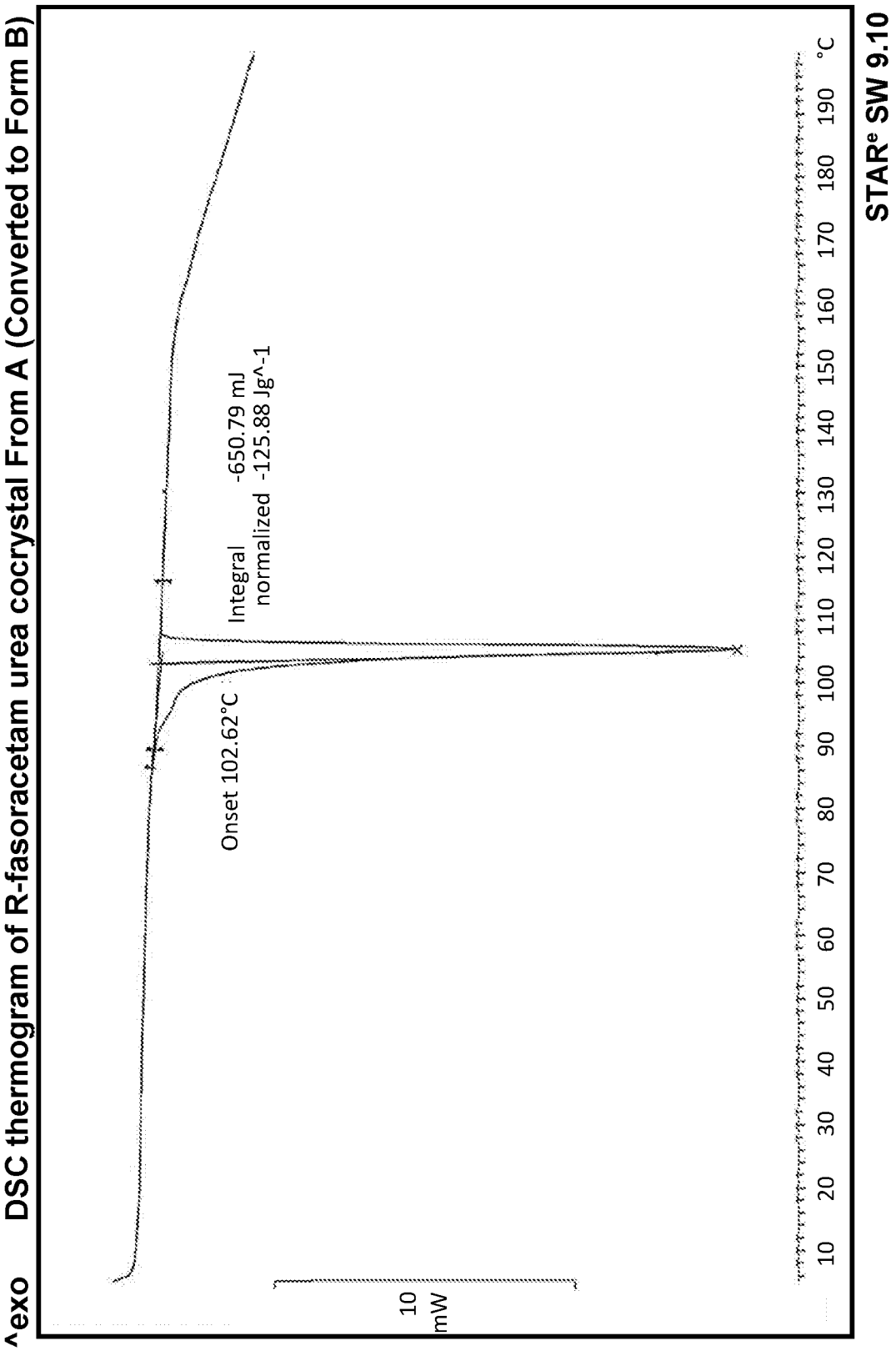

^exo DSC thermogram of R-fasoracetam urea cocrystal From A (Converted to Form B)
Integral -650.79 mJ
normalized -125.88 Jg^-1
Onset 102.62°C
10 mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 47

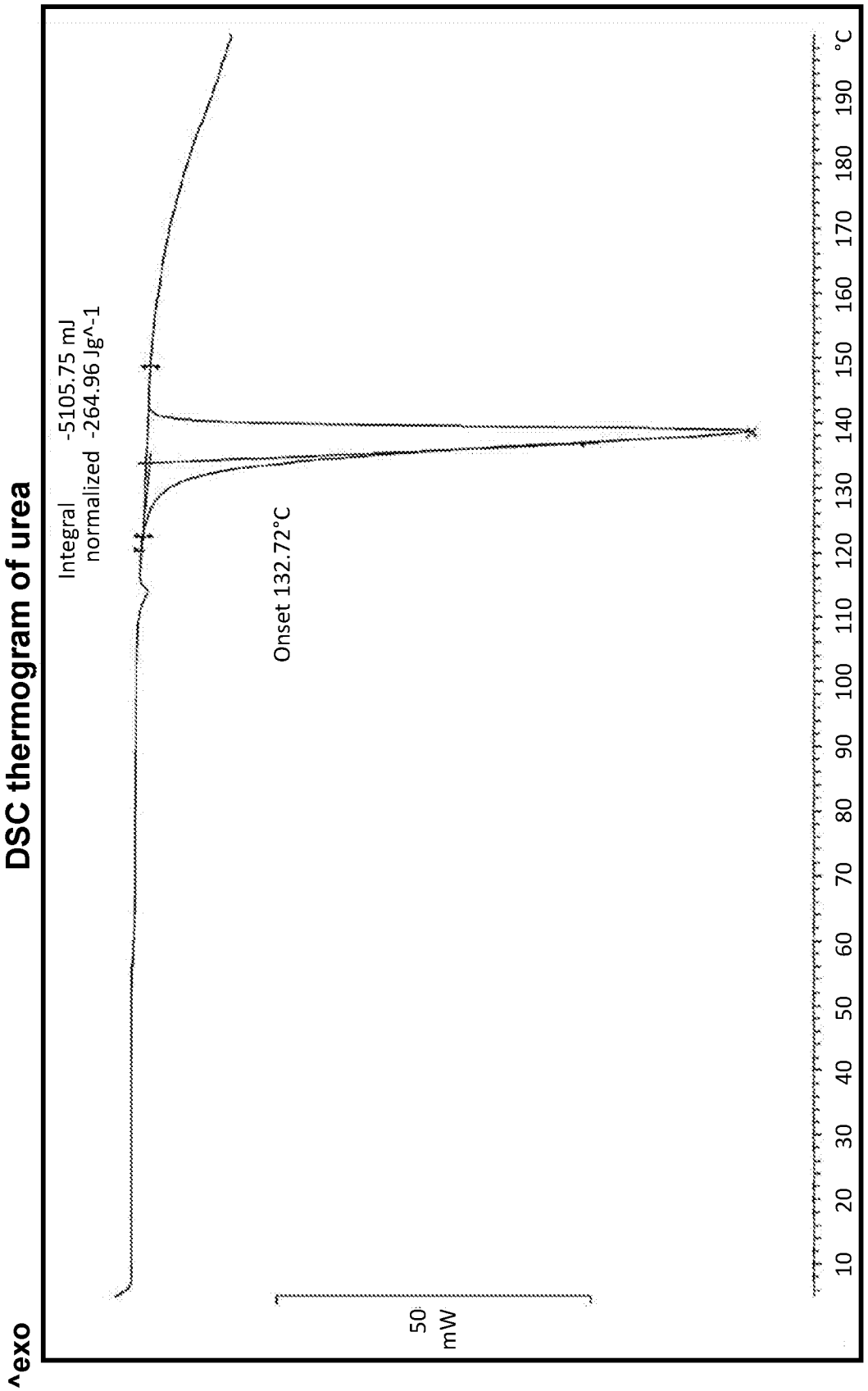

DSC thermogram of urea
^exo
Integral -5105.75 mJ
normalized -264.96 Jg^-1
Onset 132.72°C
50
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 48

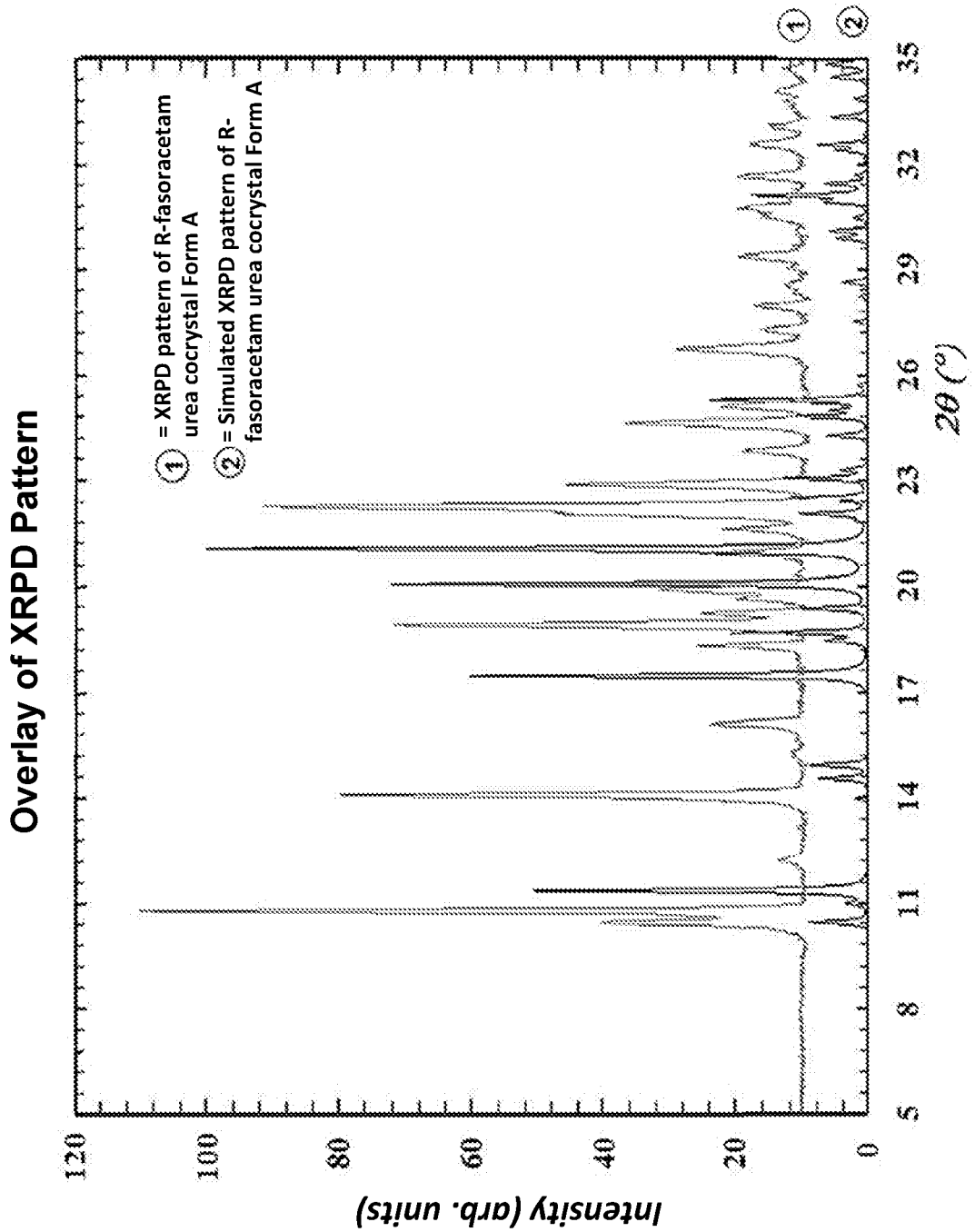

Overlay of XRPD Pattern
① = XRPD pattern of R-fasoracetam urea cocrystal Form A
② = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form A
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
5
8
11
14
17
20
23
26
29
32
35

Figure 49

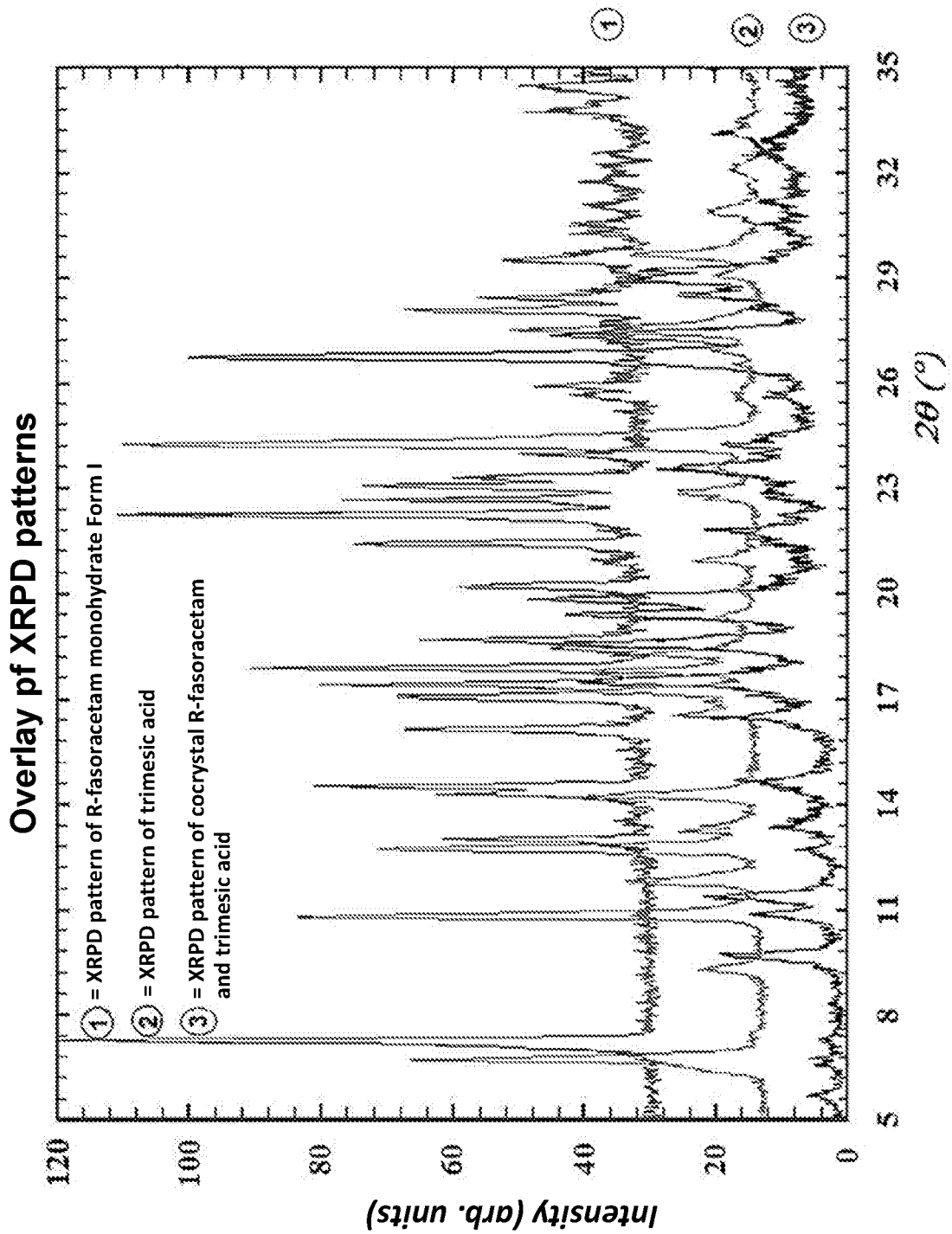

Overlay pf XRPD patterns
1 = XRPD pattern of R-fasoracetam monohydrate Form I
2 = XRPD pattern of trimesic acid
3 = XRPD pattern of cocrystal R-fasoracetam and trimesic acid
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
5
8
11
14
17
20
23
26
29
32
35

Figure 50

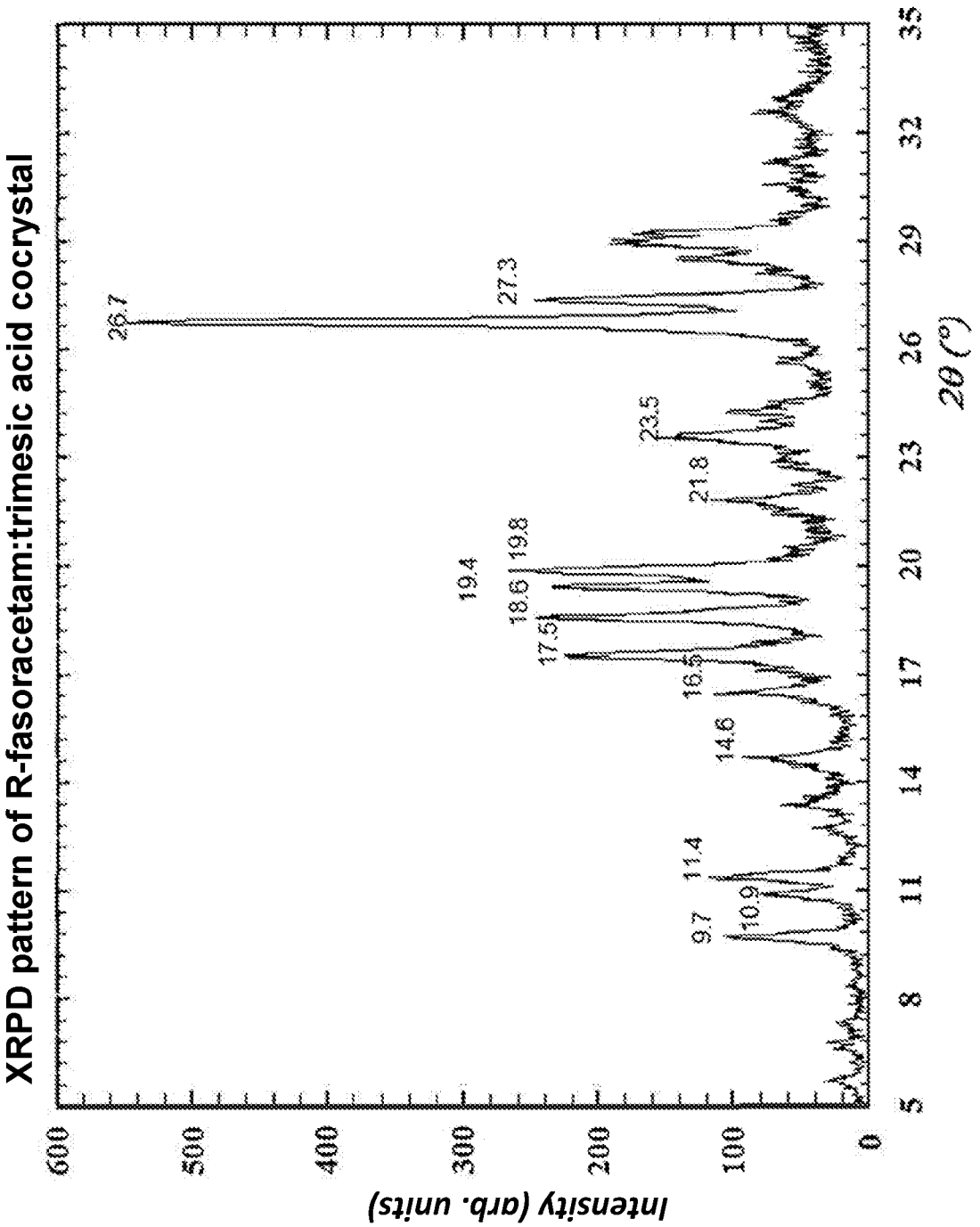

XRPD pattern of R-fasoracetam:trimesic acid cocrystal
Intensity (arb. units)
2θ (°)
0
100
200
300
400
500
600
5
8
11
14
17
20
23
26
29
32
35
26.7
27.3
23.5
21.8
19.8
19.4
18.6
17.5
16.5
14.6
11.4
10.9
9.7

Figure 51

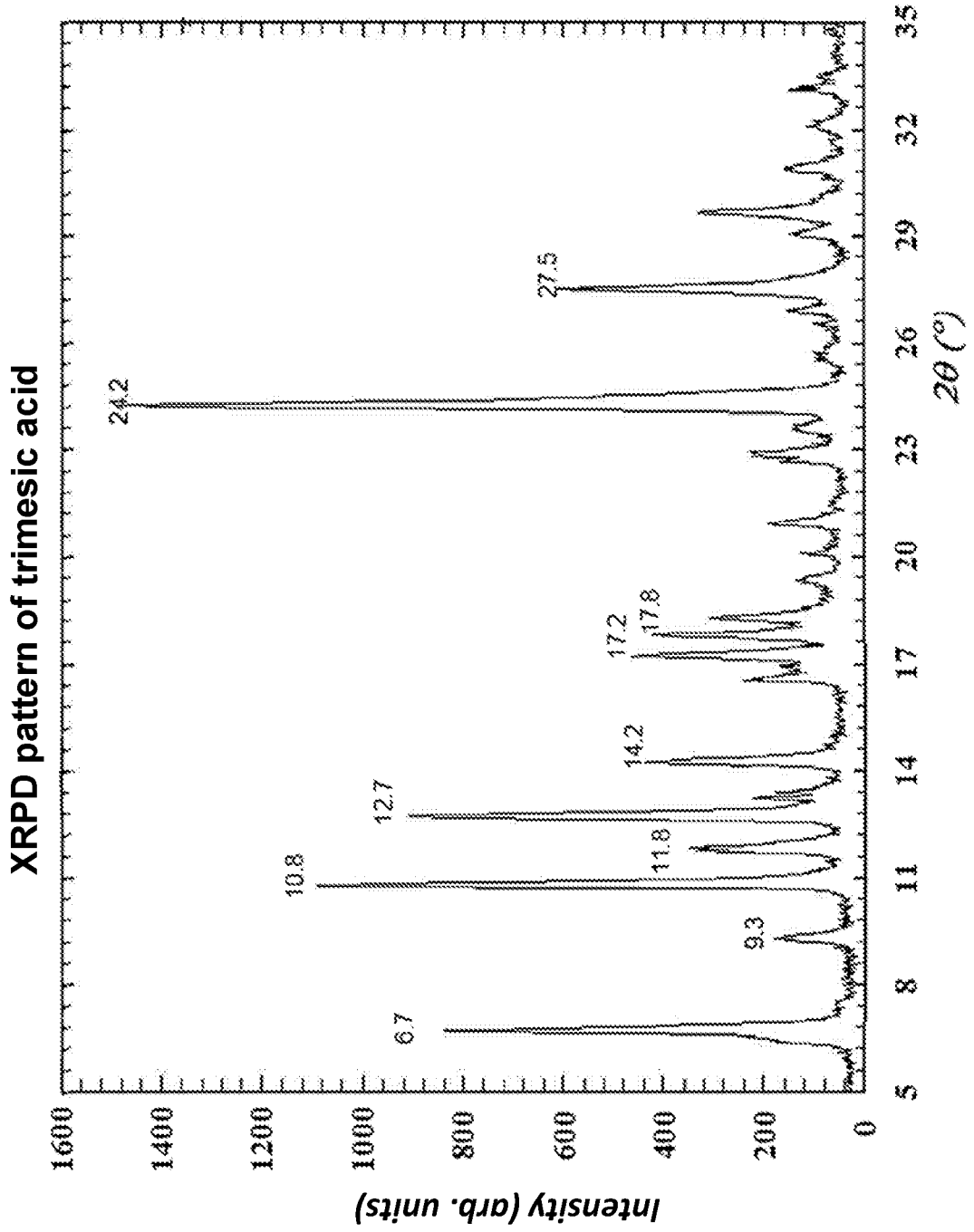

XRPD pattern of trimesic acid
Intensity (arb. units)
2θ (°)
6.7
9.3
10.8
11.8
12.7
14.2
17.2
17.8
24.2
27.5
0
200
400
600
800
1000
1200
1400
1600
5
8
11
14
17
20
23
26
29
32
35

Figure 52

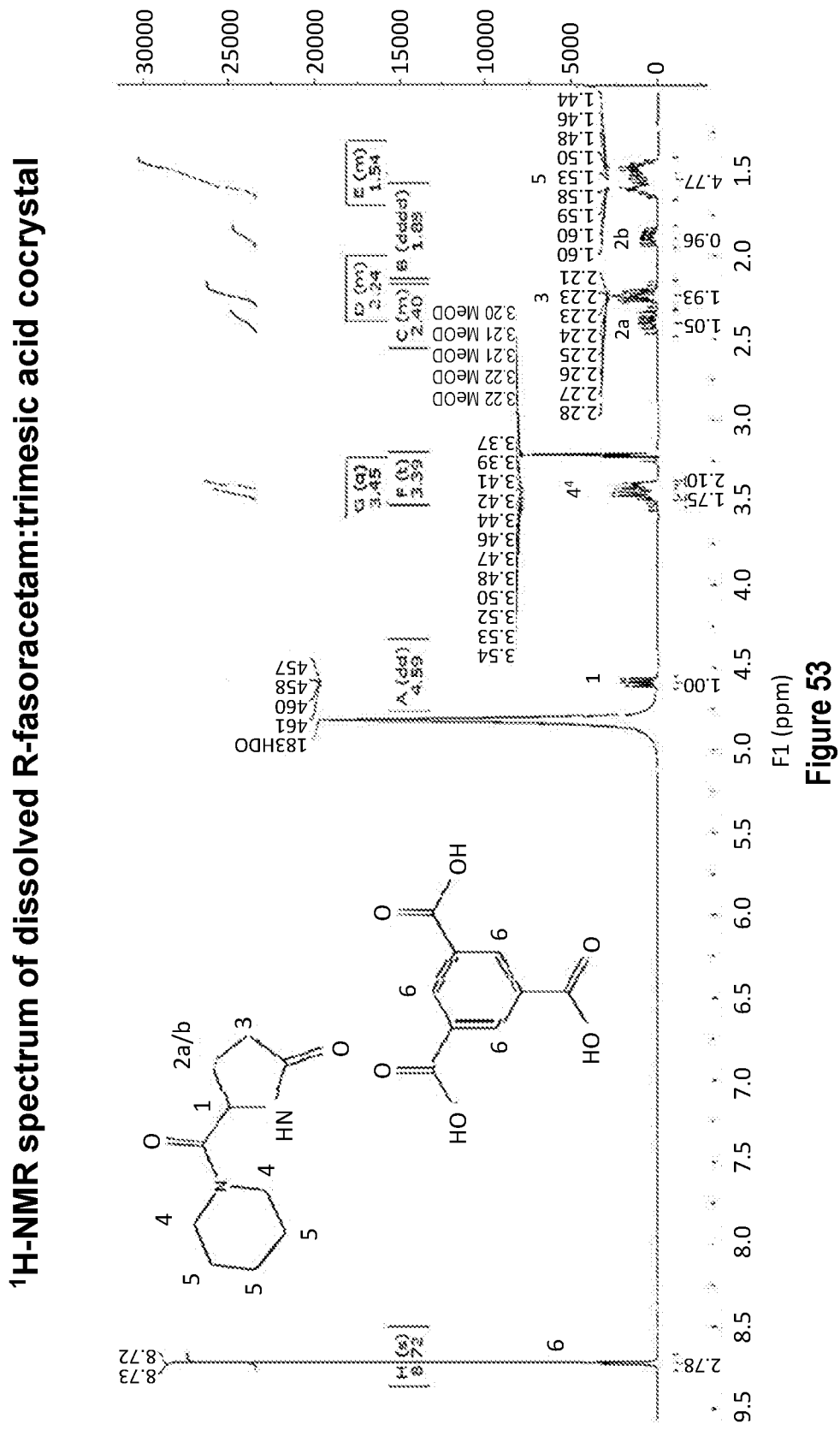

1H-NMR spectrum of dissolved R-fasoracetam:trimesic acid cocrystal
F1 (ppm)

Figure 53

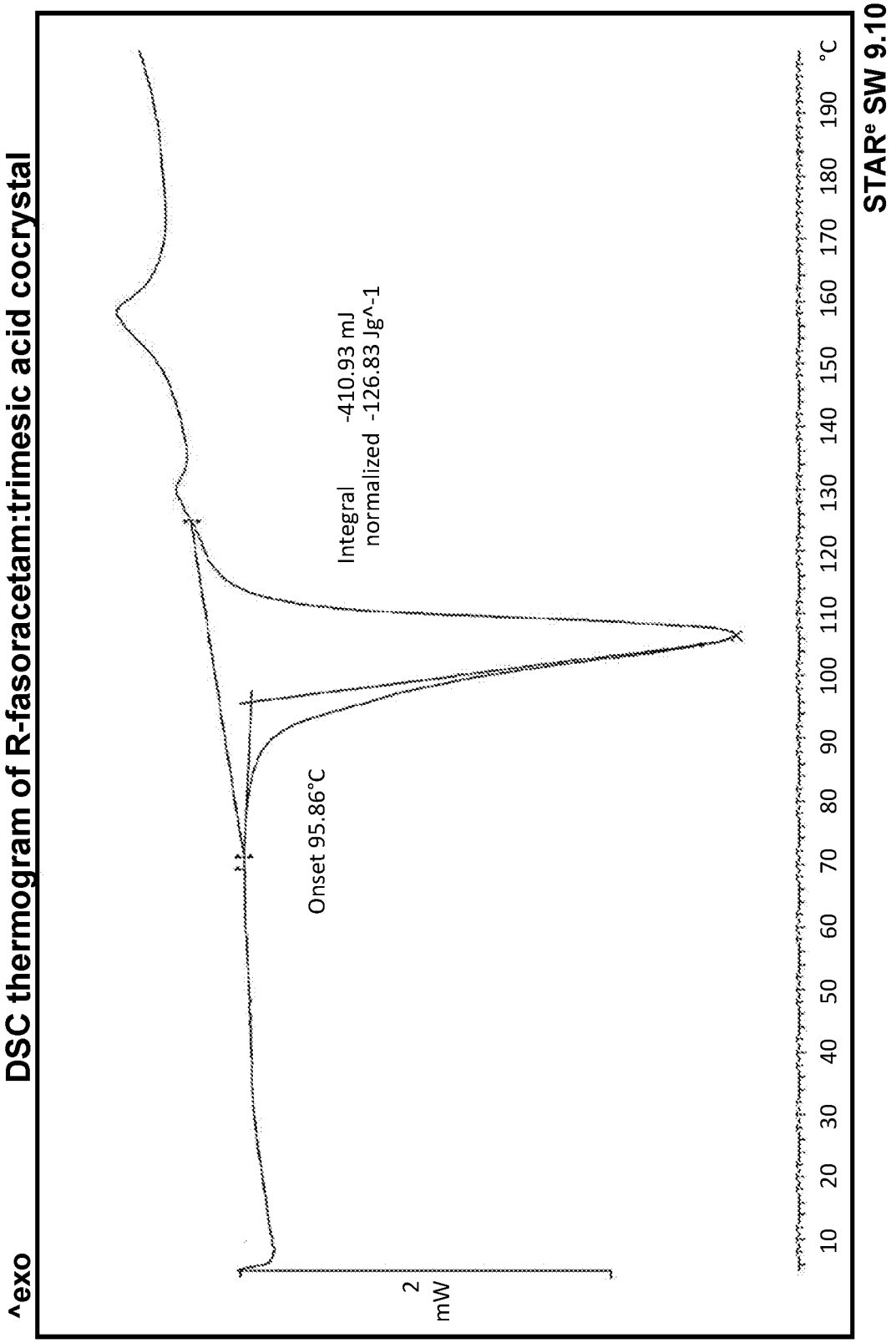

DSC thermogram of R-fasoracetam:trimesic acid cocrystal
^exo
2
mW
Onset 95.86°C
Integral -410.93 mJ
normalized -126.83 Jg^-1
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 54

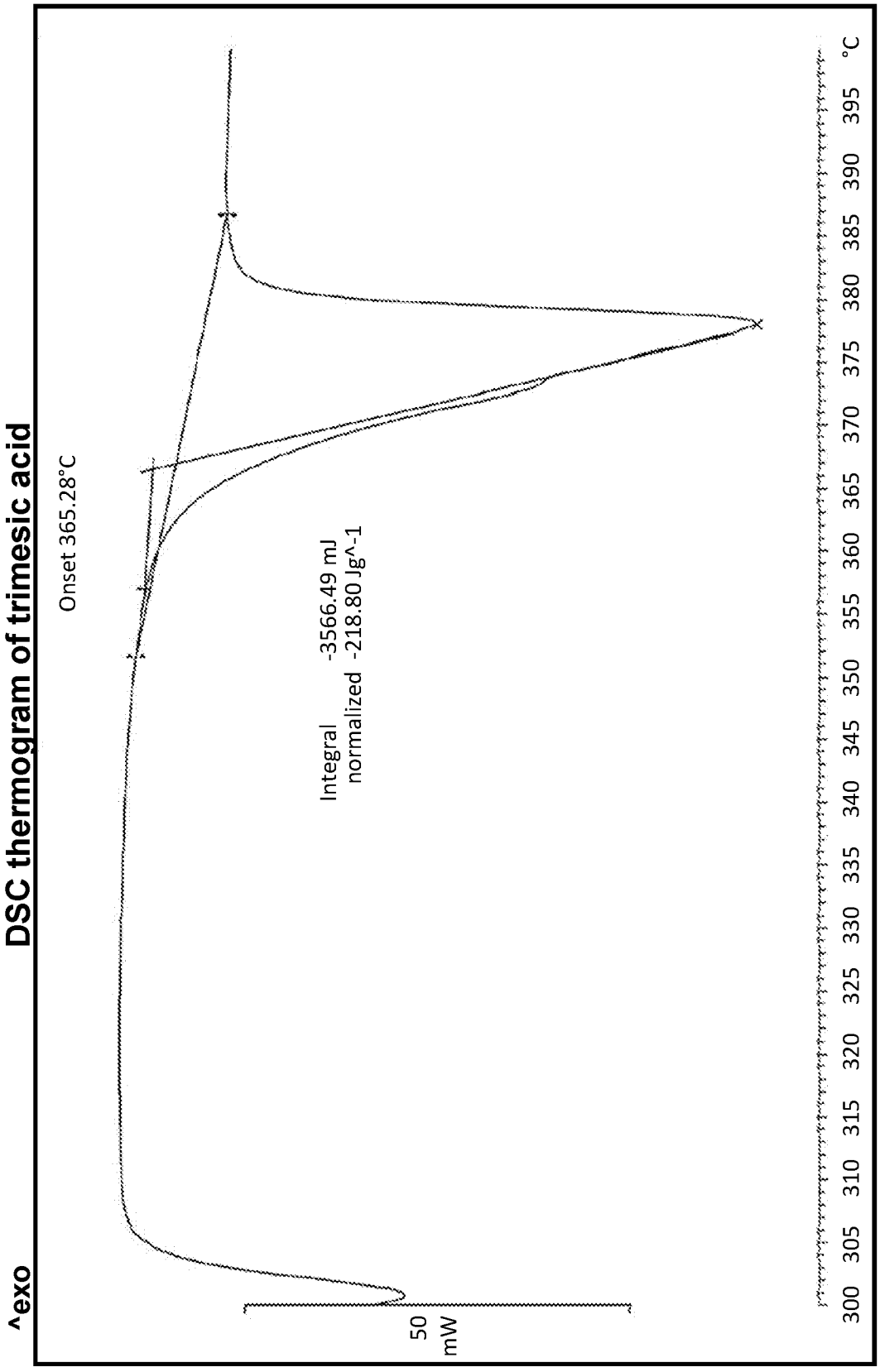

DSC thermogram of trimesic acid
^exo
Onset 365.28°C
Integral -3566.49 mJ
normalized -218.80 Jg^-1
50
mW
300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 °C
STARe SW 9.10

Figure 55

ORTEP of R-fasoracetam: R-ibuprofen cocrystal

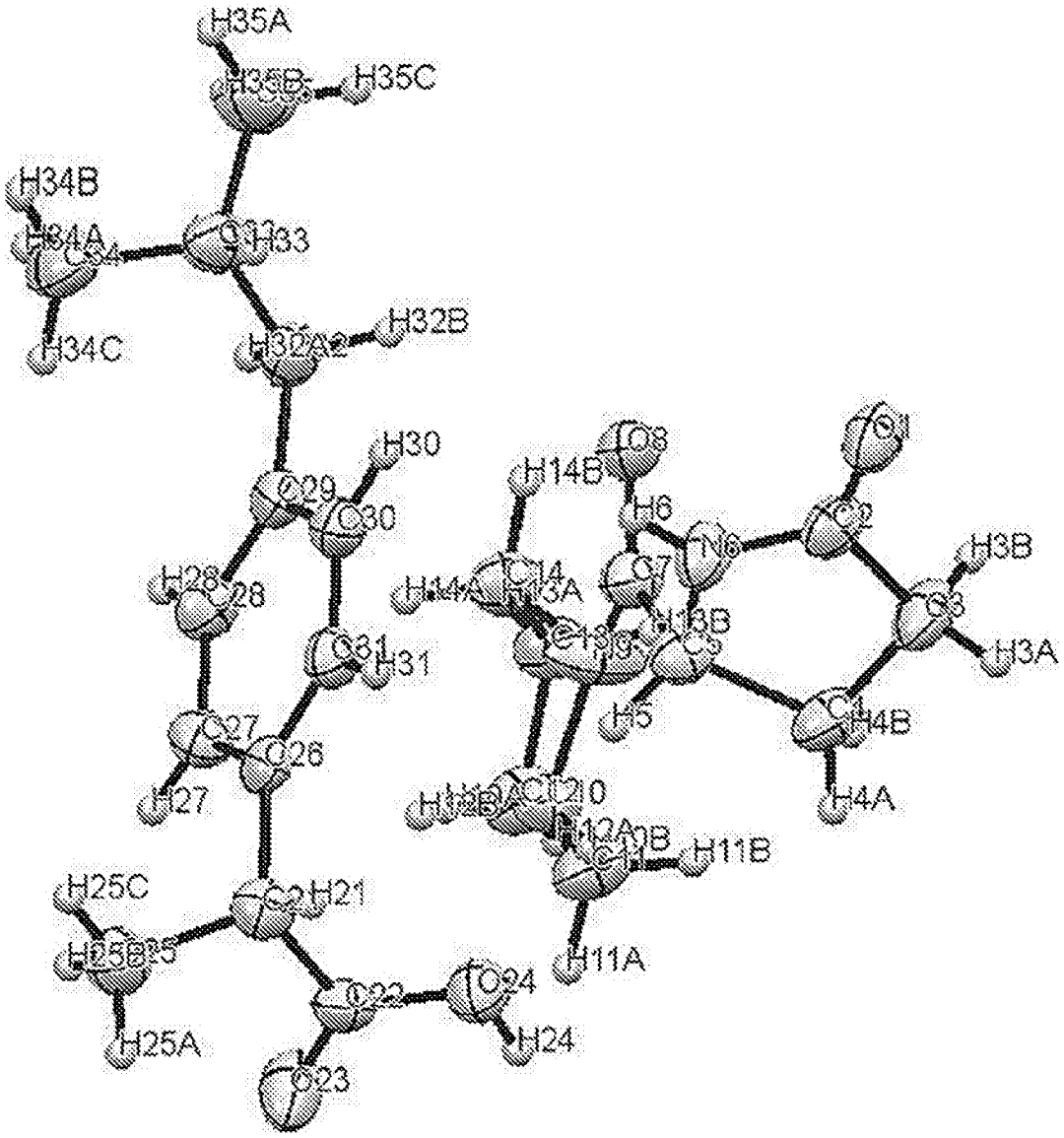


Figure 56

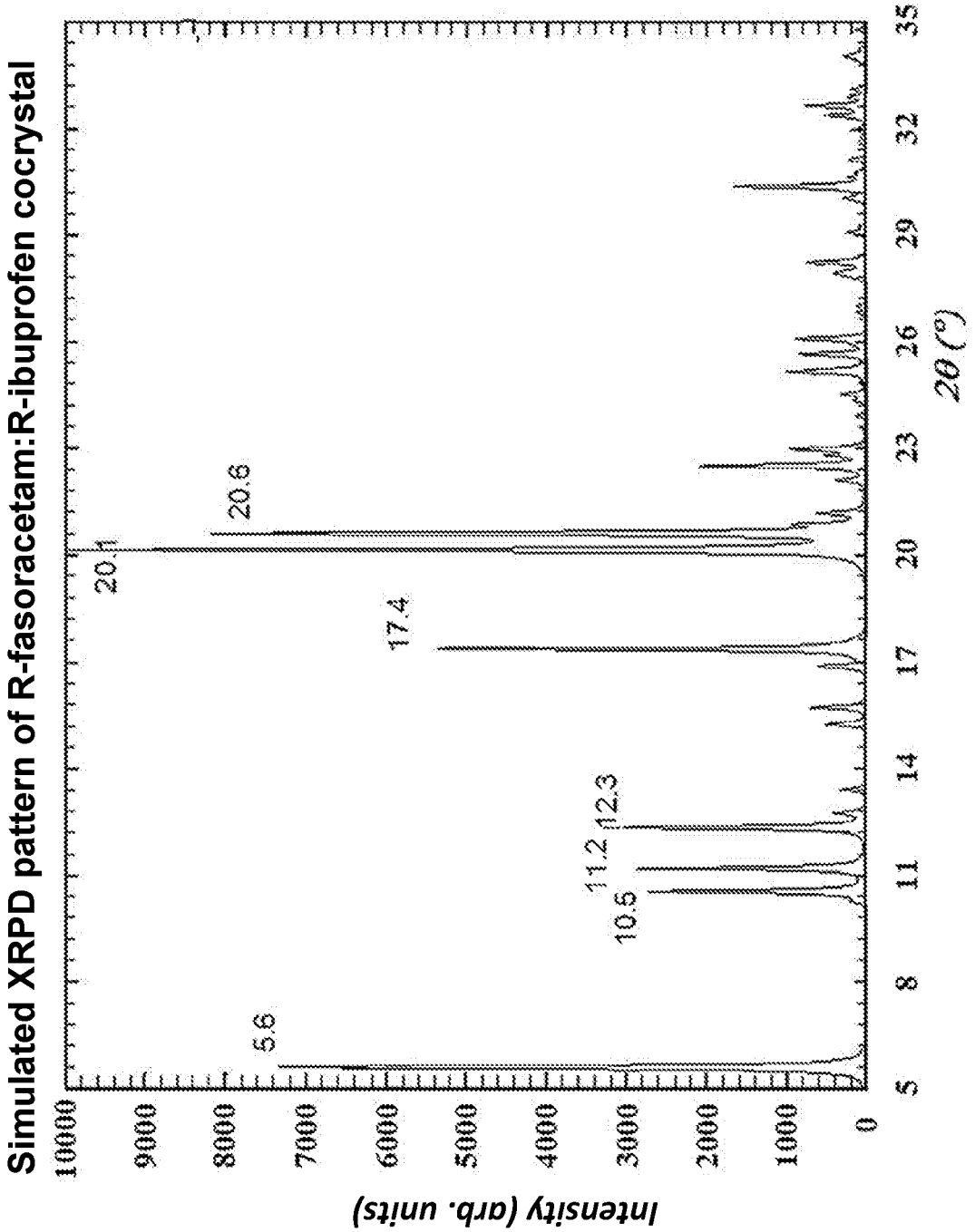

Simulated XRPD pattern of R-fasoracetam:R-ibuprofen cocrystal
Intensity (arb. units)
2θ (°)
5.6
10.5
11.2
12.3
17.4
20.1
20.6

Figure 57

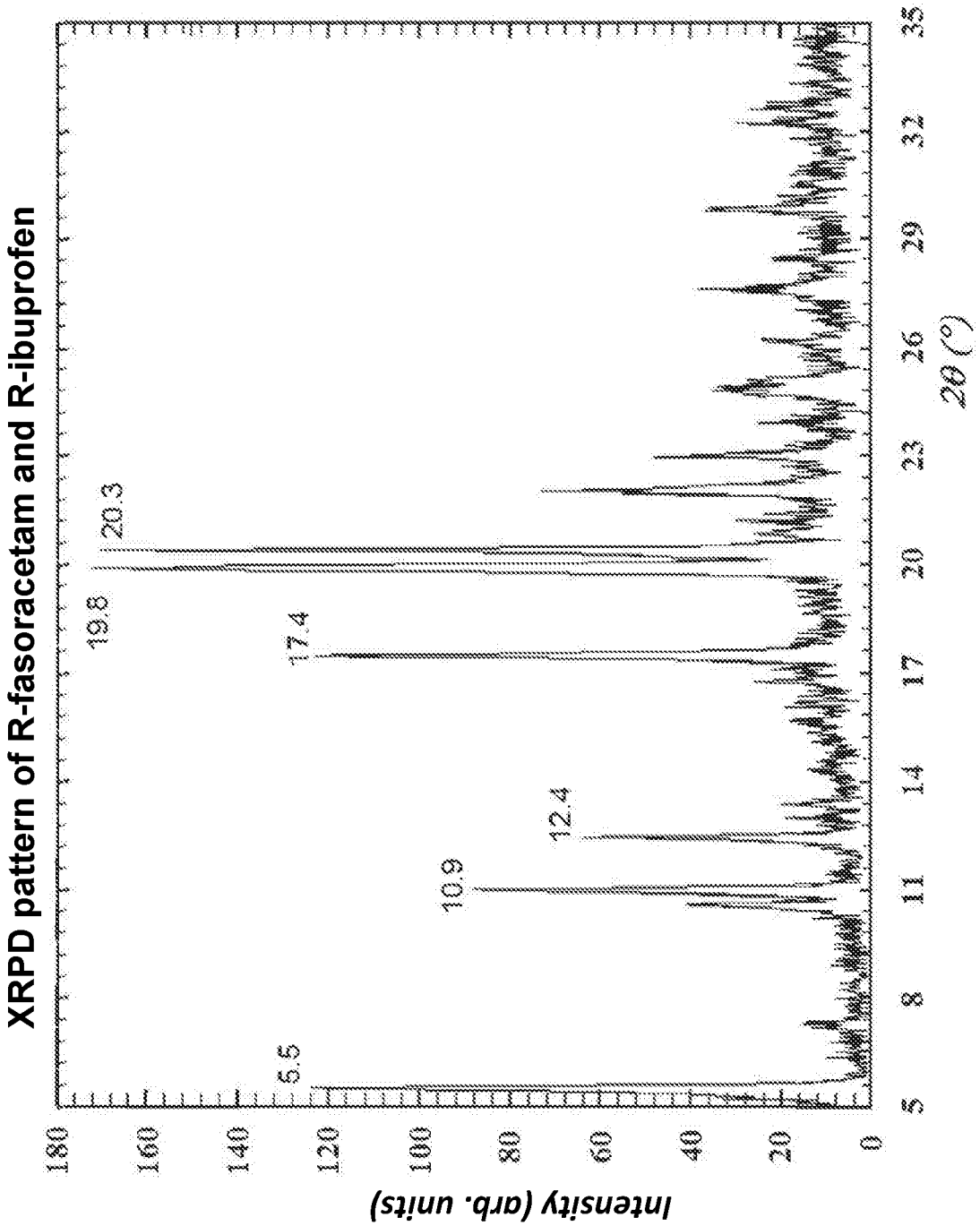

XRPD pattern of R-fasoracetam and R-ibuprofen
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
160
180
5
8
11
14
17
20
23
26
29
32
35
5.5
10.9
12.4
17.4
19.8
20.3

Figure 58

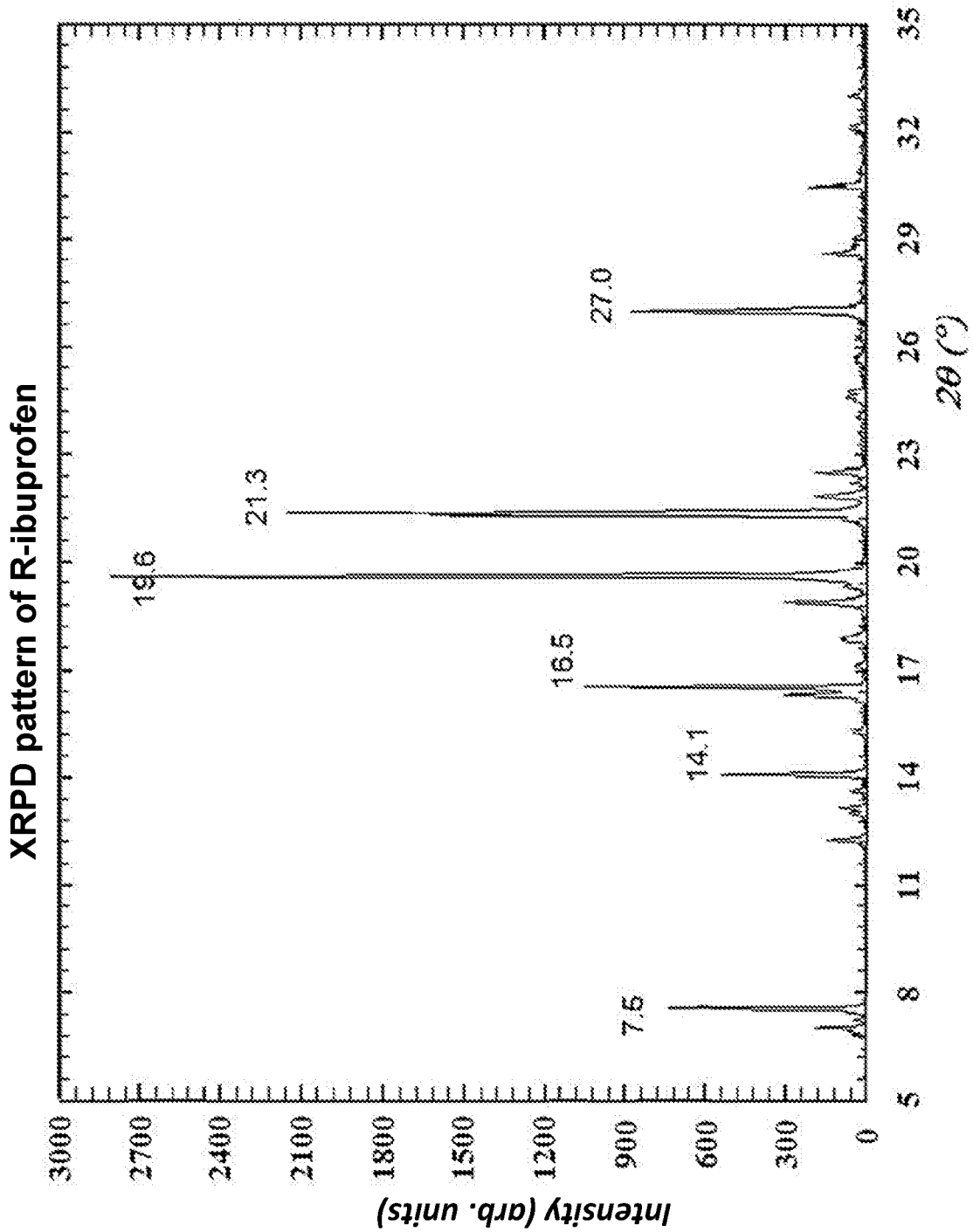

XRPD pattern of R-ibuprofen
Intensity (arb. units)
2θ (°)
7.5
14.1
16.5
19.6
21.3
27.0
0
300
600
900
1200
1500
1800
2100
2400
2700
3000
5
8
11
14
17
20
23
26
29
32
35

Figure 59

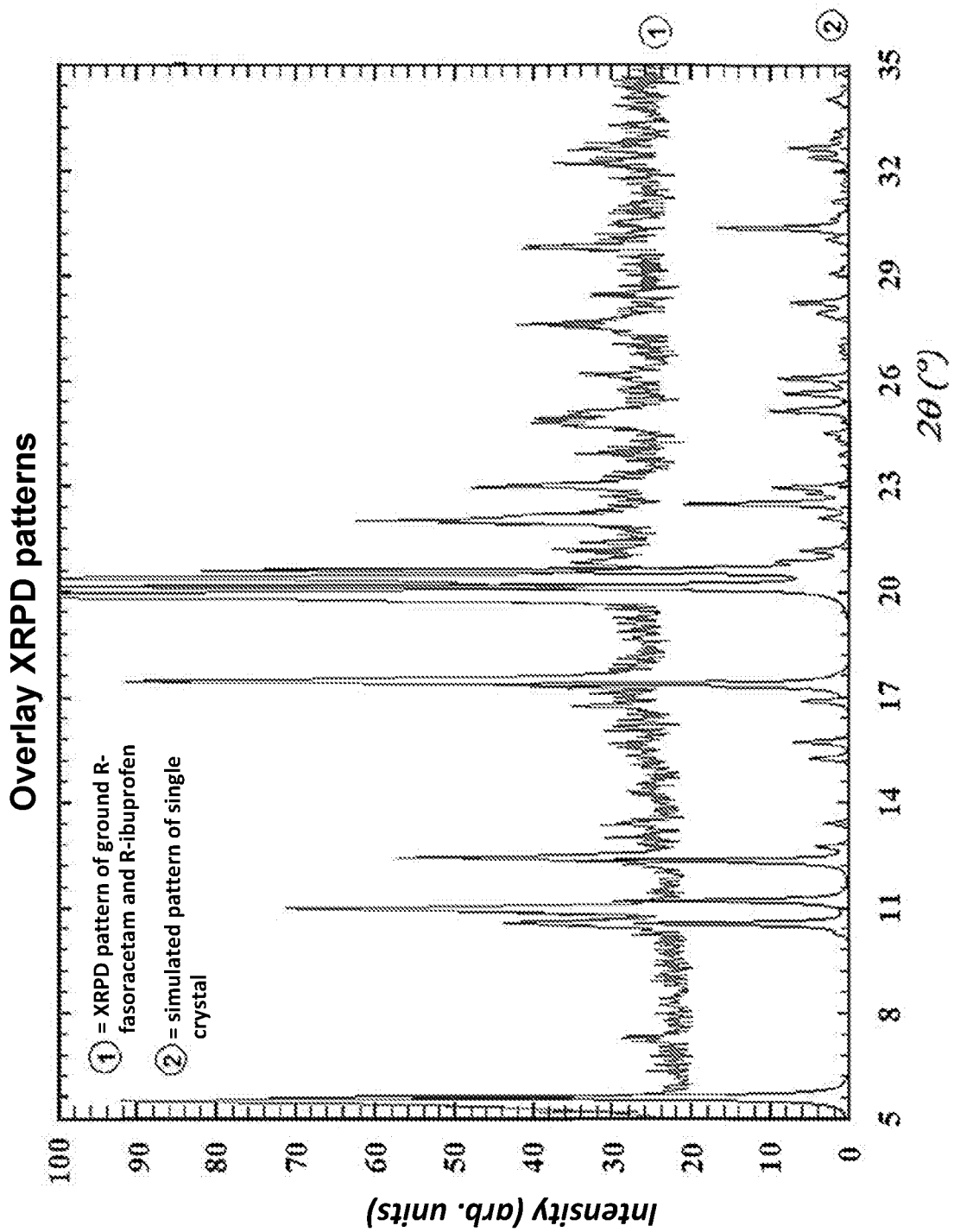

Overlay XRPD patterns
① = XRPD pattern of ground R-fasoracetam and R-ibuprofen
② = simulated pattern of single crystal
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
80
90
100
5
8
11
14
17
20
23
26
29
32
35

Figure 60

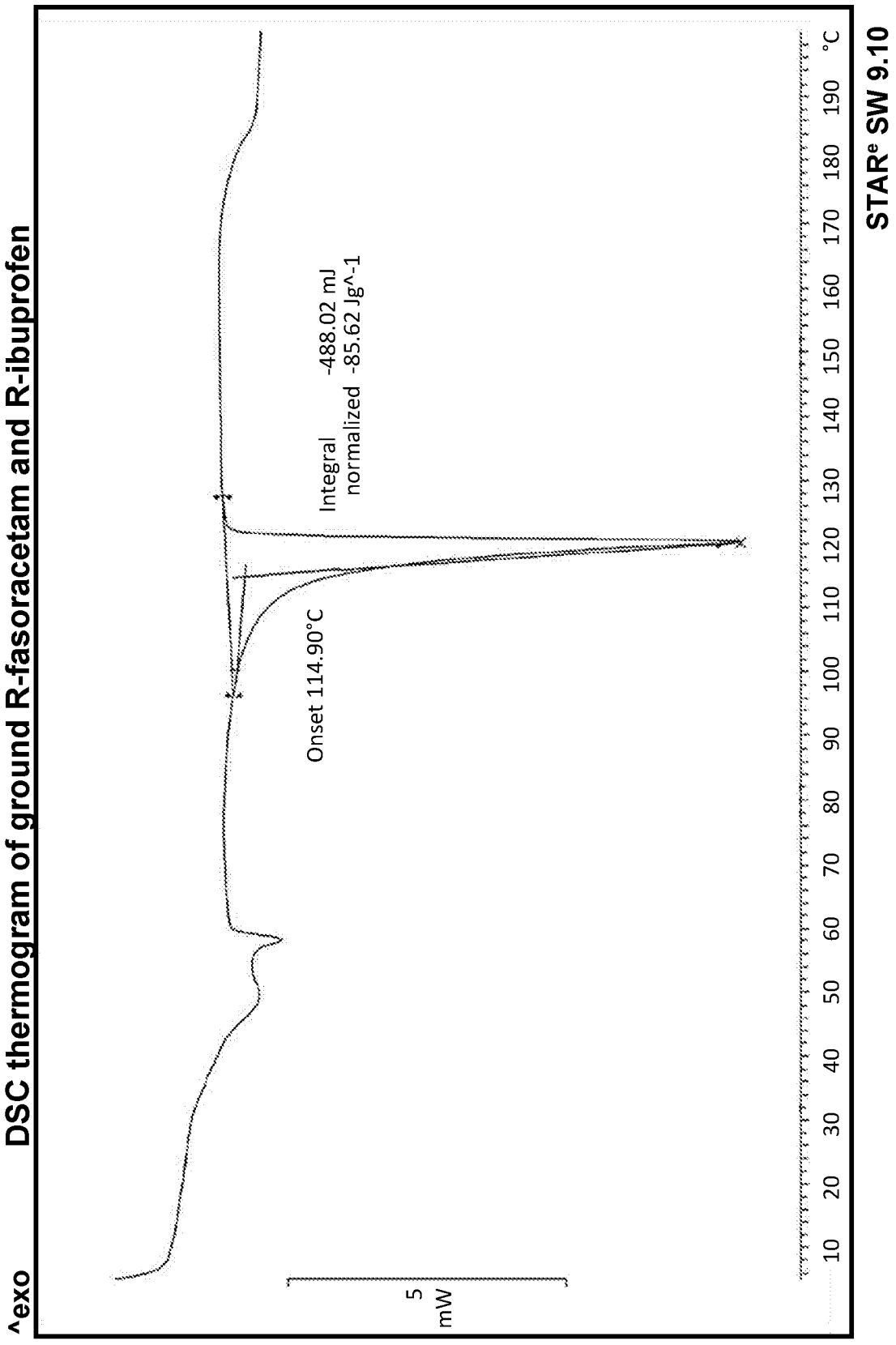

DSC thermogram of ground R-fasoracetam and R-ibuprofen
^exo
5
mW
Onset 114.90°C
Integral -488.02 mJ
normalized -85.62 Jg^-1
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 61

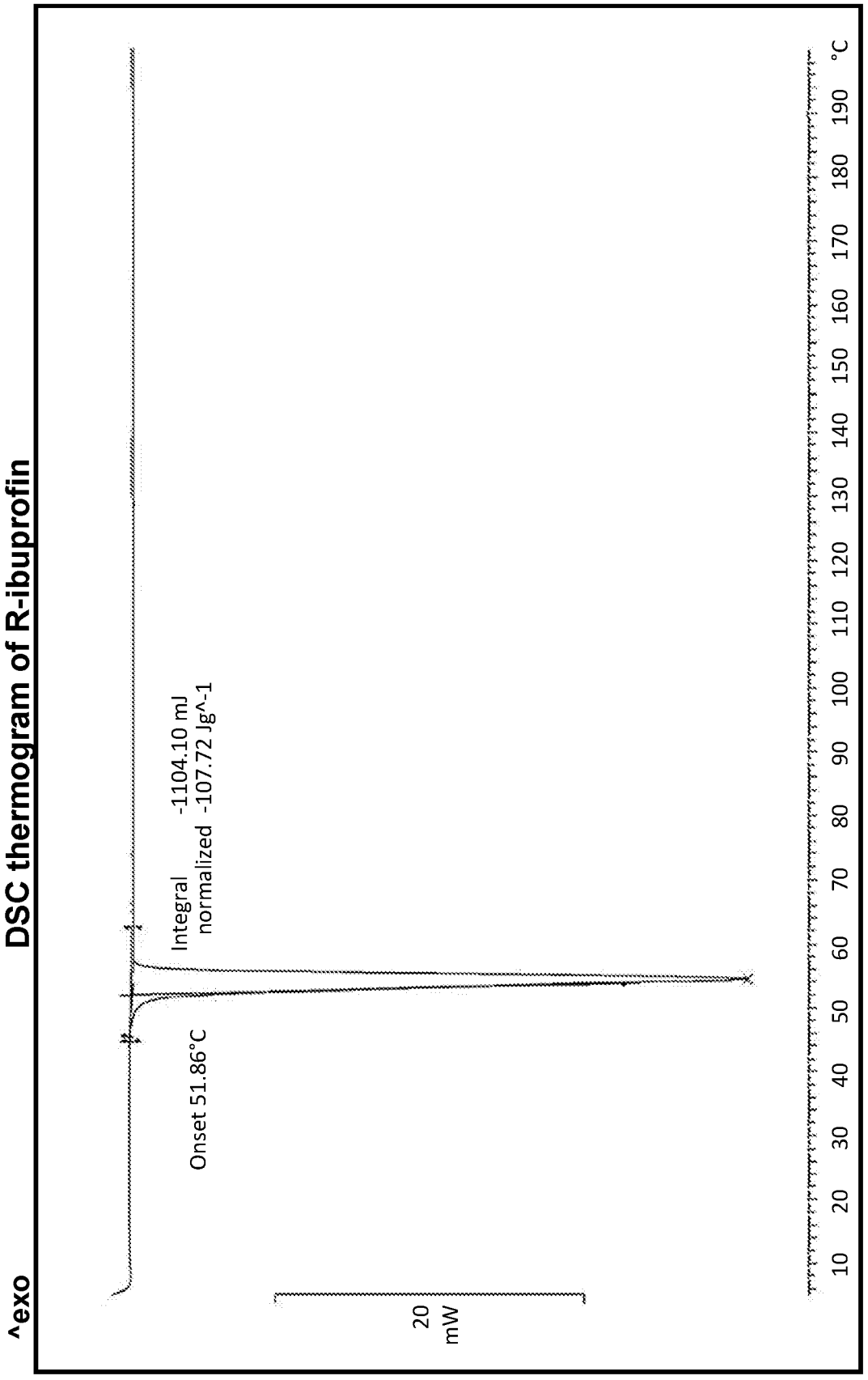

DSC thermogram of R-ibuprofin
^exo
Integral -1104.10 mJ
normalized -107.72 Jg^-1
Onset 51.86°C
20
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
UCL Poly: TL
STARe SW 9.10

Figure 62

ORTEP of R-fasoracetam phthalic acid cocrystal

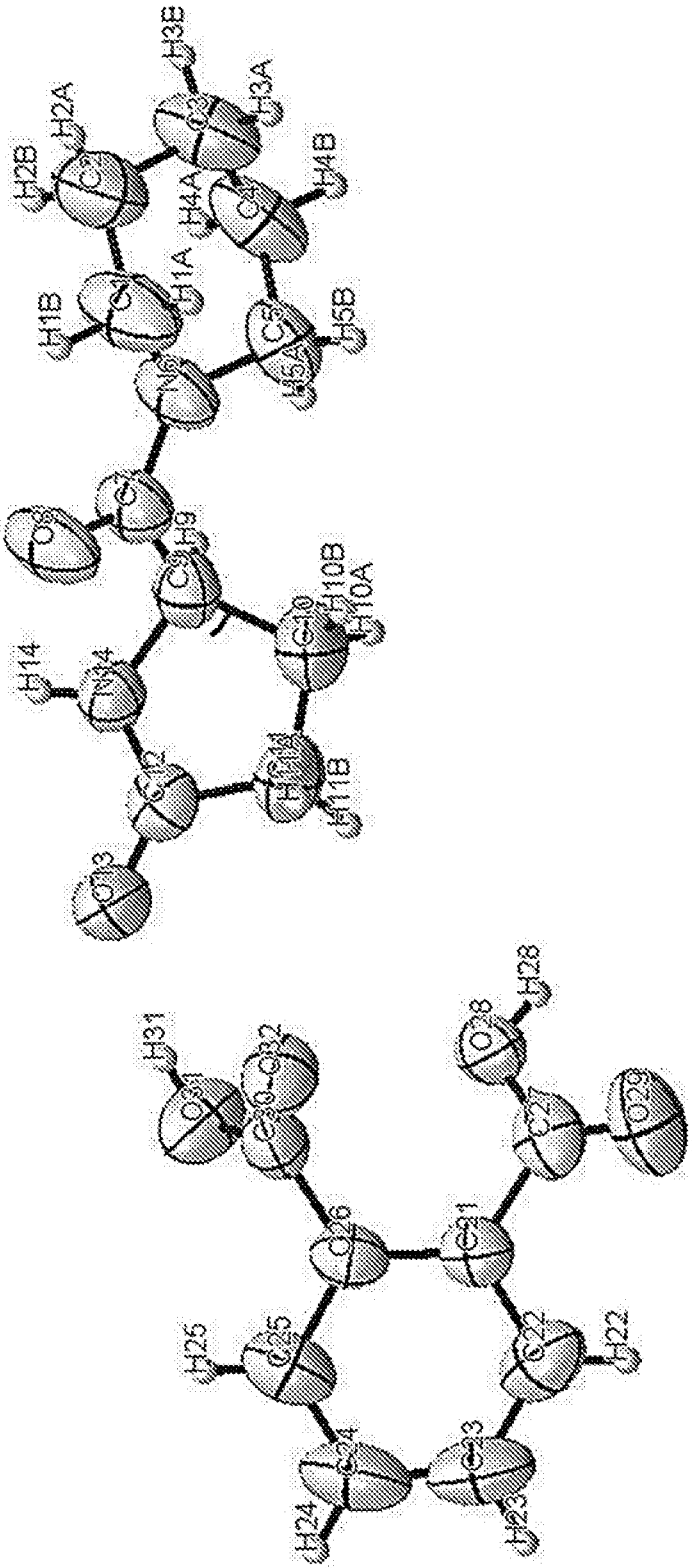


Figure 63

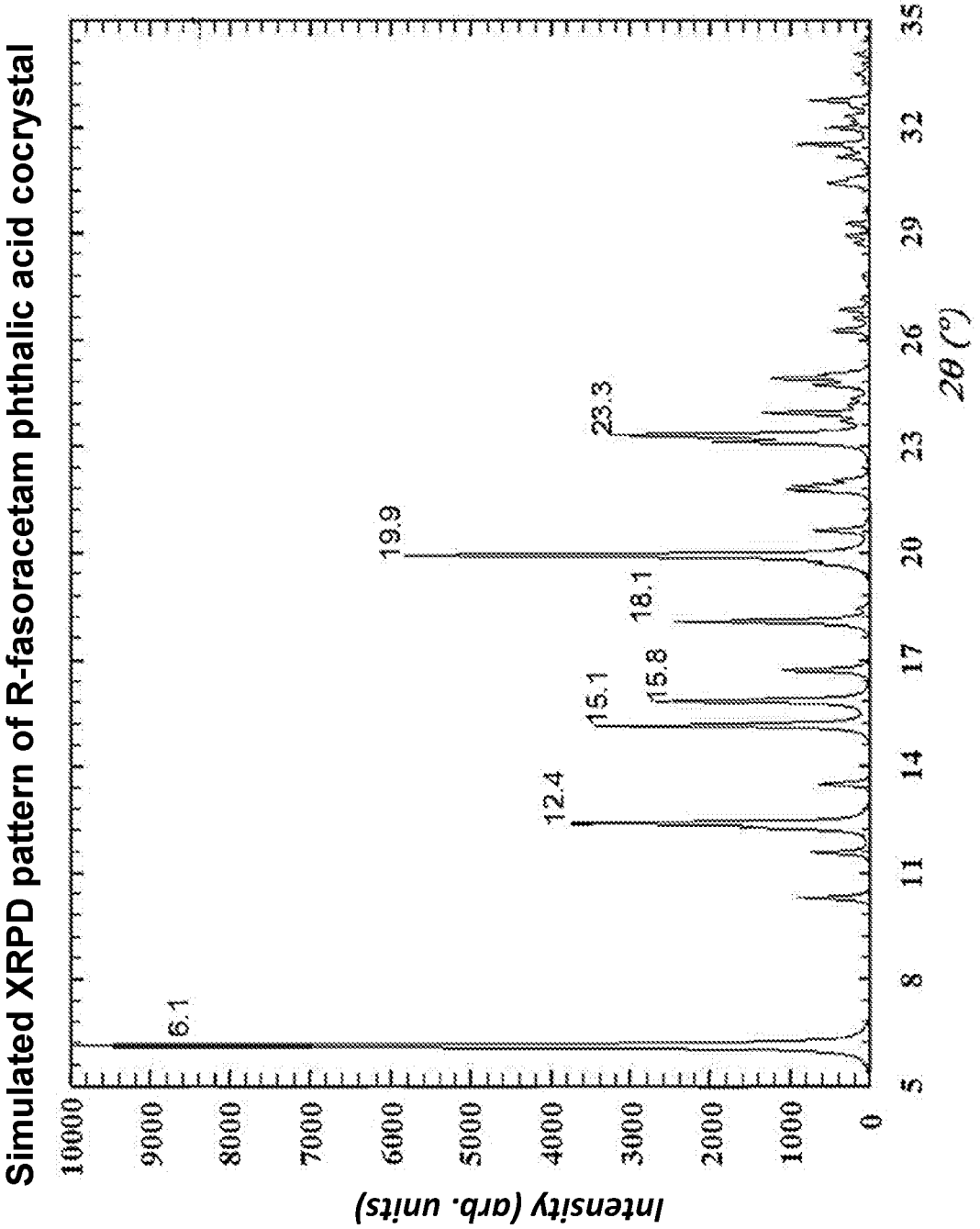

Simulated XRPD pattern of R-fasoracetam phthalic acid cocrystal
Intensity (arb. units)
2θ (°)
6.1
12.4
15.1
15.8
18.1
19.9
23.3
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35

Figure 64

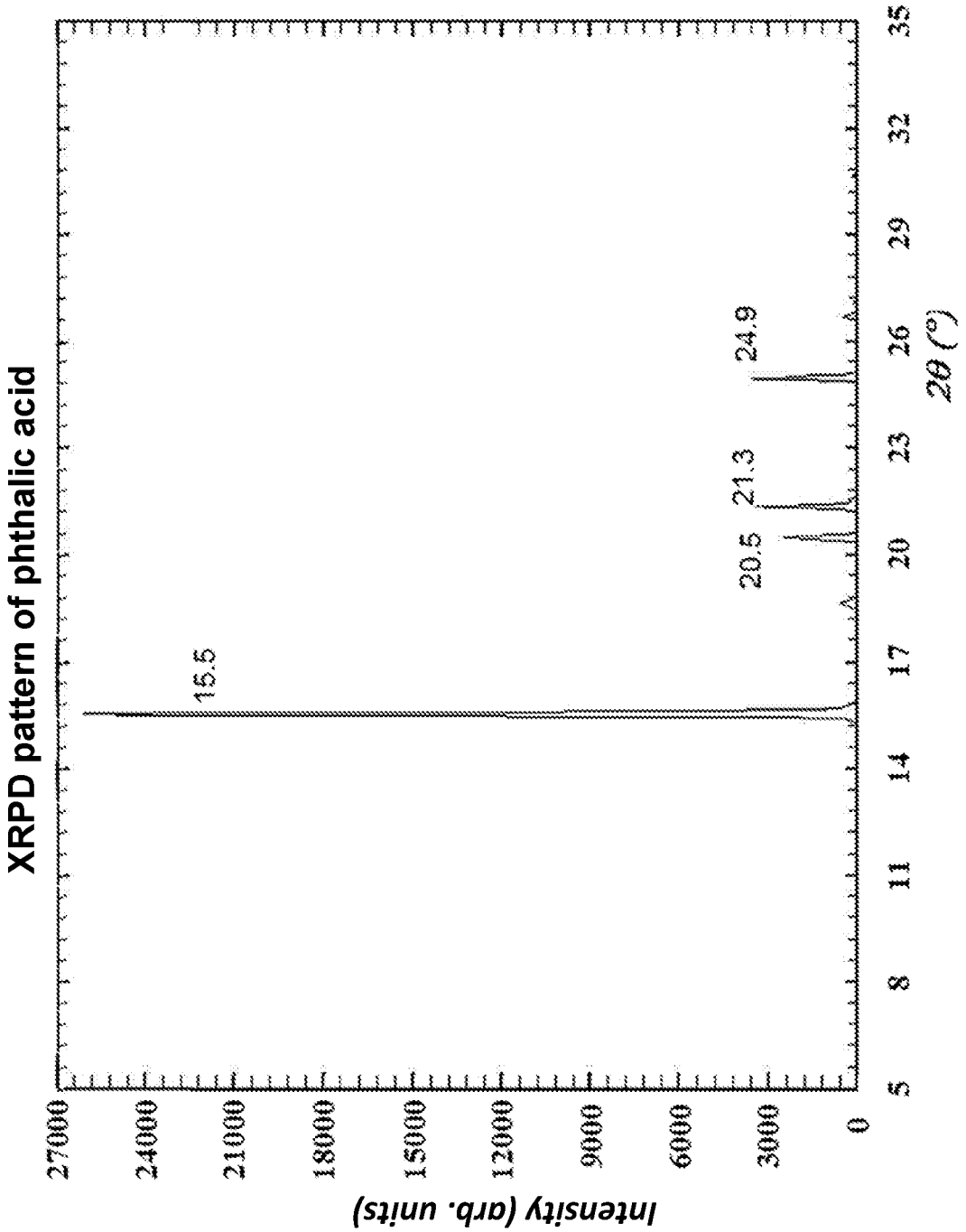

XRPD pattern of phthalic acid
Intensity (arb. units)
27000
24000
21000
18000
15000
12000
9000
6000
3000
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
15.5
20.5
21.3
24.9

Figure 65

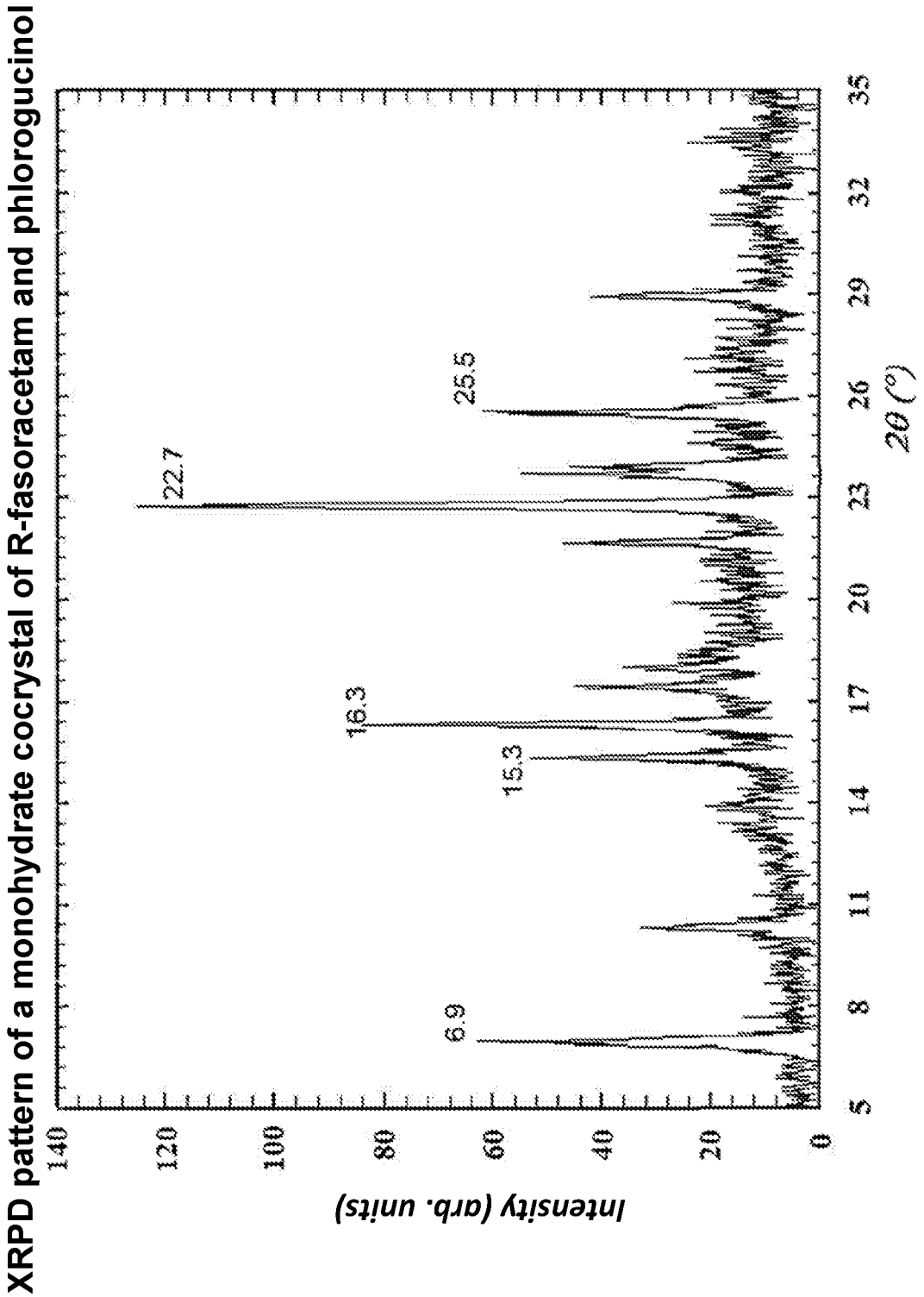

XRPD pattern of a monohydrate cocrystal of R-fasoracetam and phloroglucinol
Intensity (arb. units)
2θ (°)
6.9
15.3
16.3
22.7
25.5
0
20
40
60
80
100
120
140
5
8
11
14
17
20
23
26
29
32
35

Figure 66

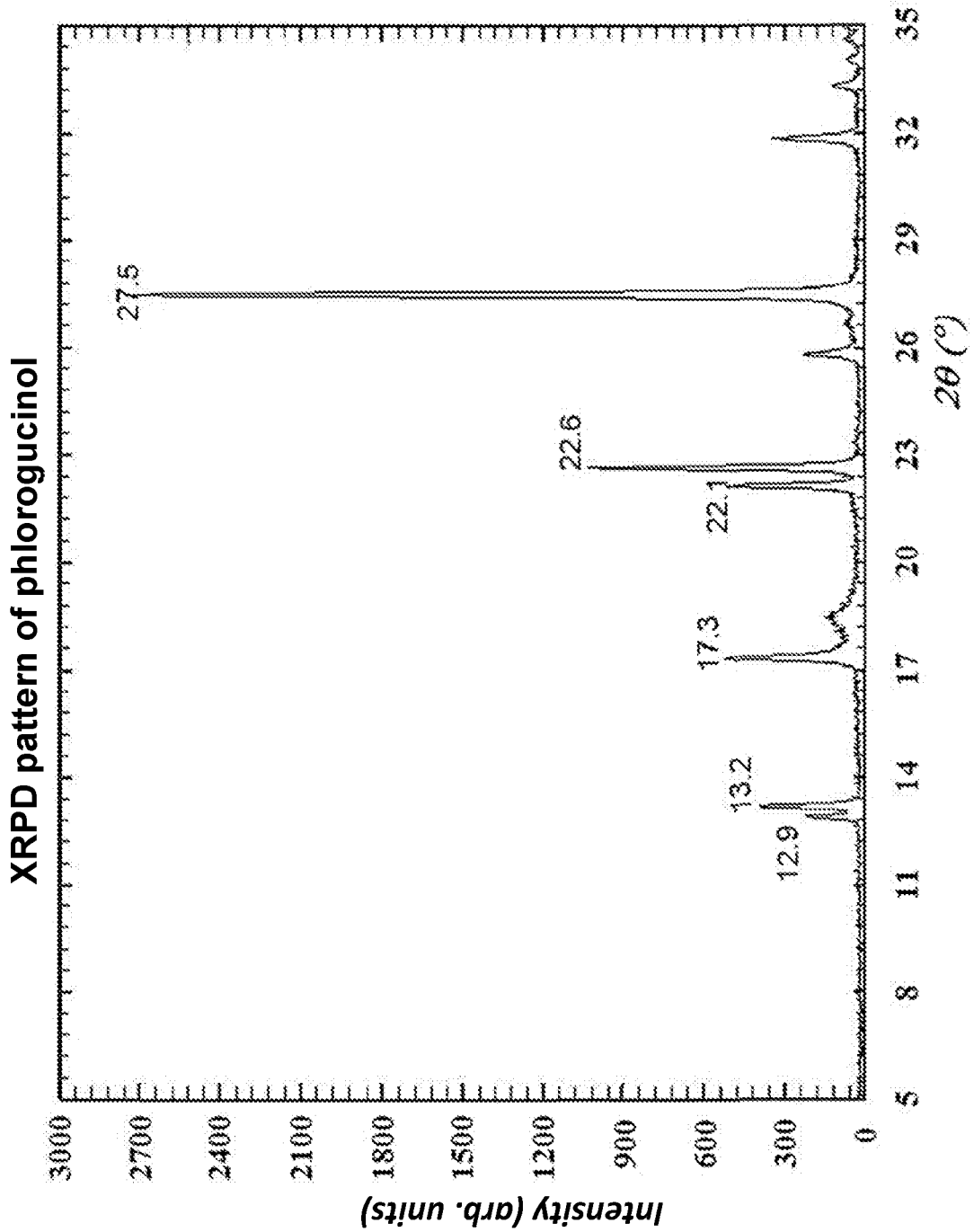

XRPD pattern of phloroglucinol
Intensity (arb. units)
2θ (°)
27.5
22.6
22.1
17.3
13.2
12.9
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
5
8
11
14
17
20
23
26
29
32
35

Figure 67

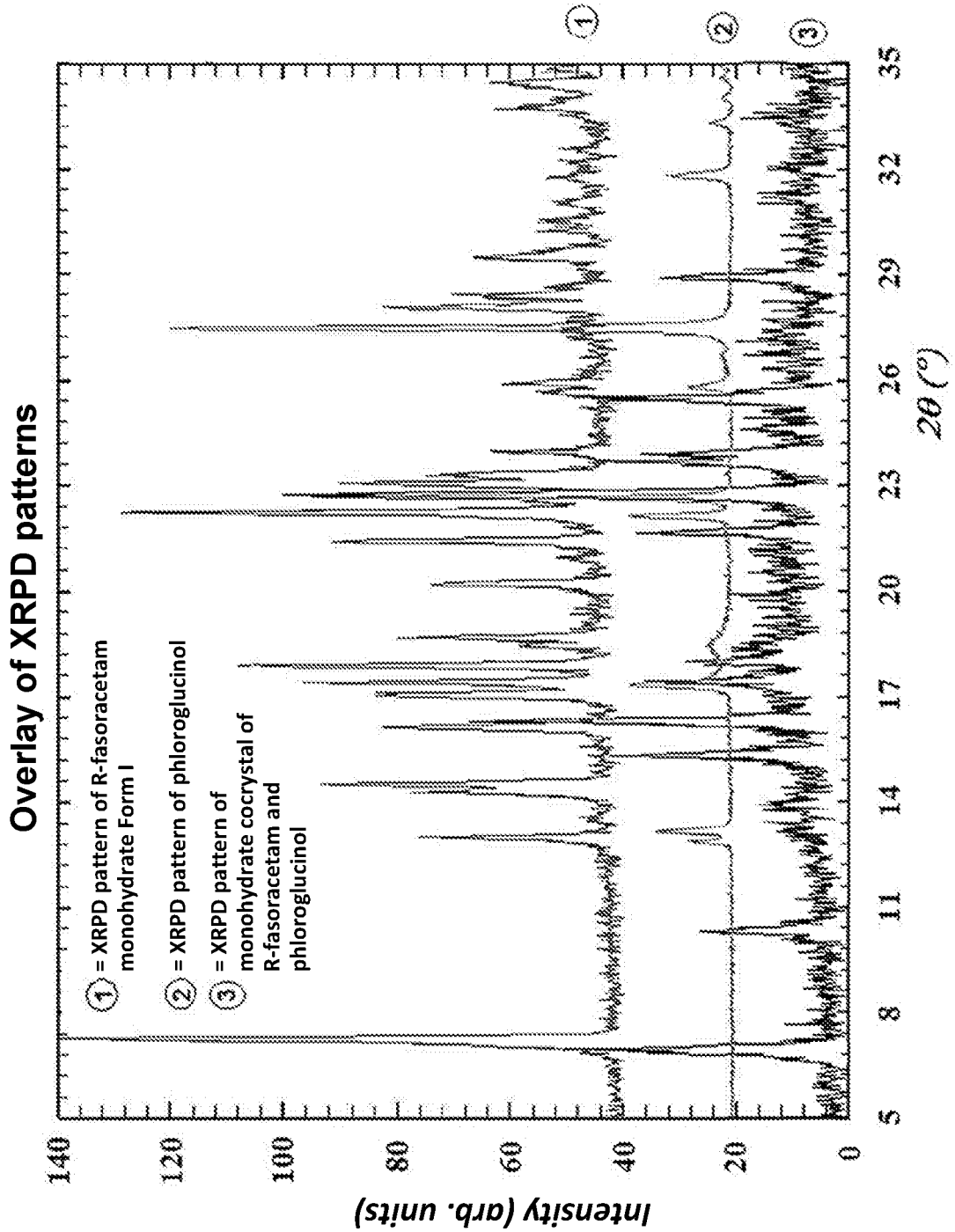

Overlay of XRPD patterns
① = XRPD pattern of R-fasoracetam monohydrate Form I
② = XRPD pattern of phloroglucinol
③ = XRPD pattern of monohydrate cocrystal of R-fasoracetam and phloroglucinol
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
5
8
11
14
17
20
23
26
29
32
35

Figure 68

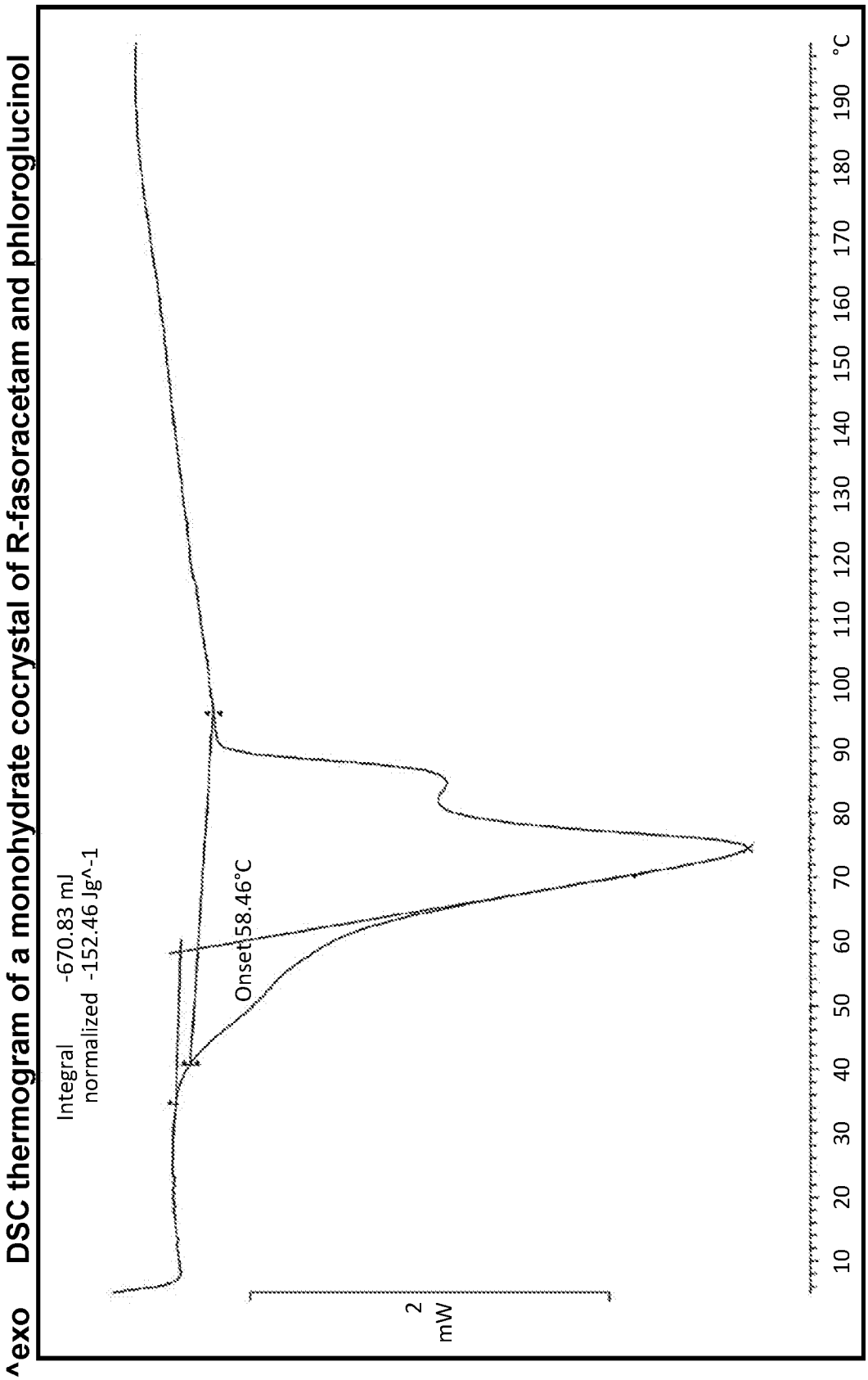

^exo DSC thermogram of a monohydrate cocrystal of R-fasoracetam and phloroglucinol
Integral -670.83 mJ
normalized -152.46 Jg^-1
Onset 58.46°C
2
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 69

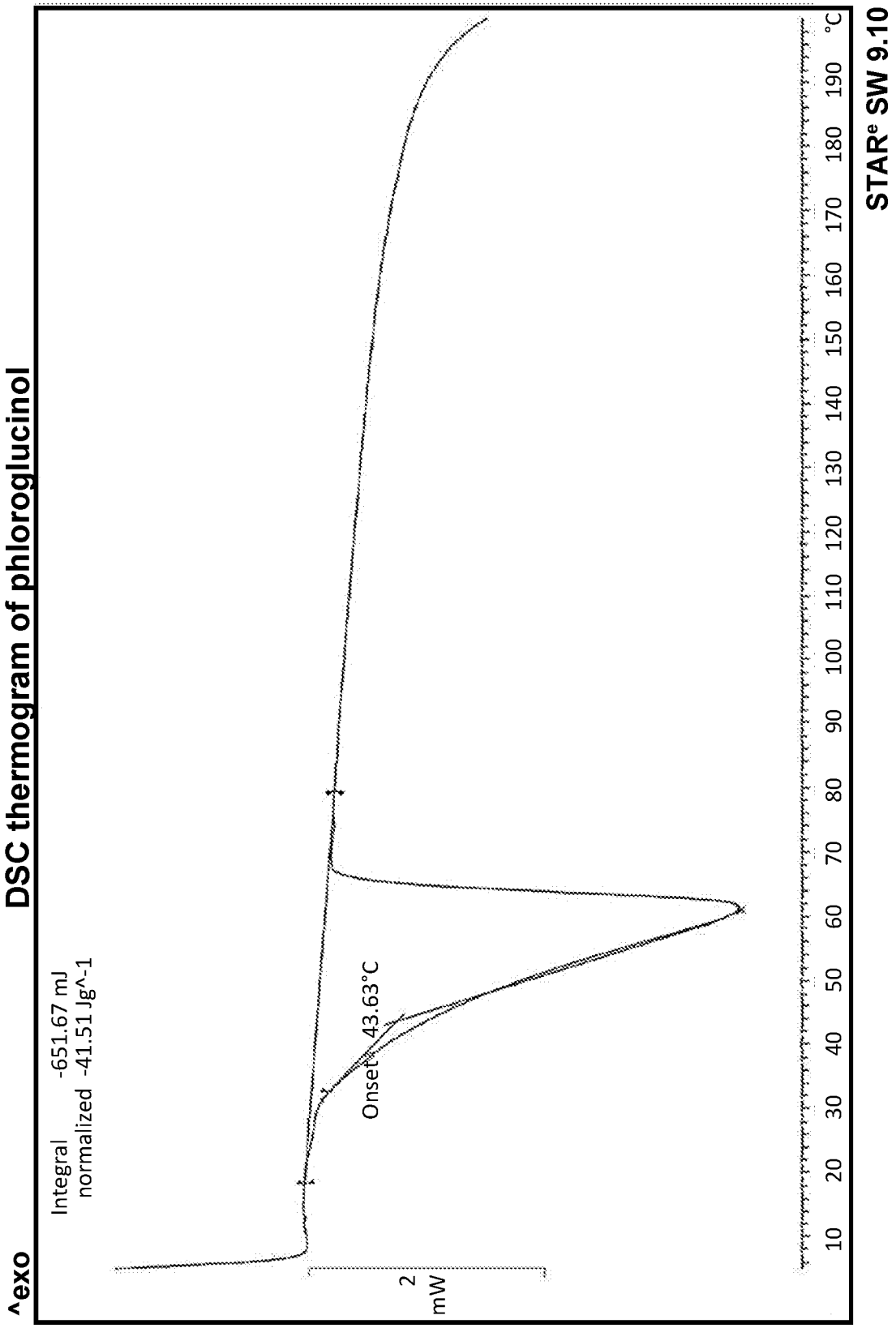

DSC thermogram of phloroglucinol
^exo
Integral -651.67 mJ
normalized -41.51 Jg^-1
Onset 43.63°C
2 mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 70

ORTEP of a monohydrate cocrystal of R-fasoracetam and phloroglucinol

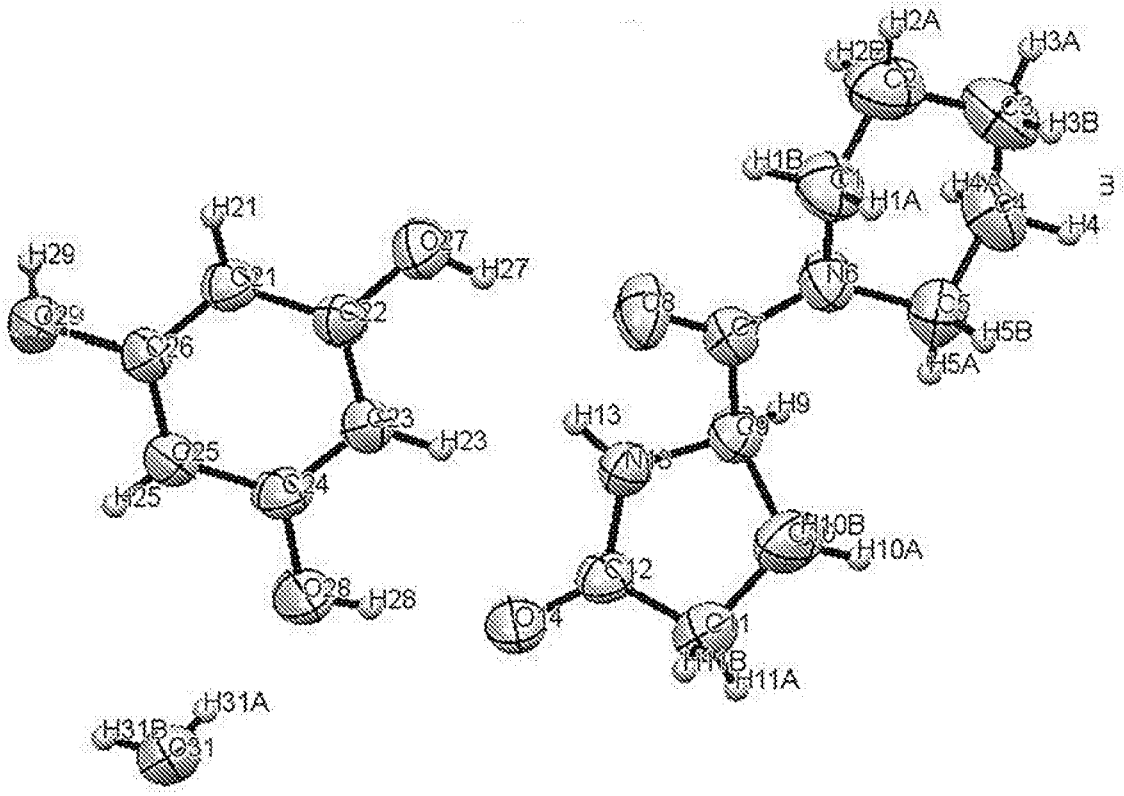


Figure 71

Simulated XRPD pattern of a monohydrate cocrystal of R-fasoracetam and phloroglucinol

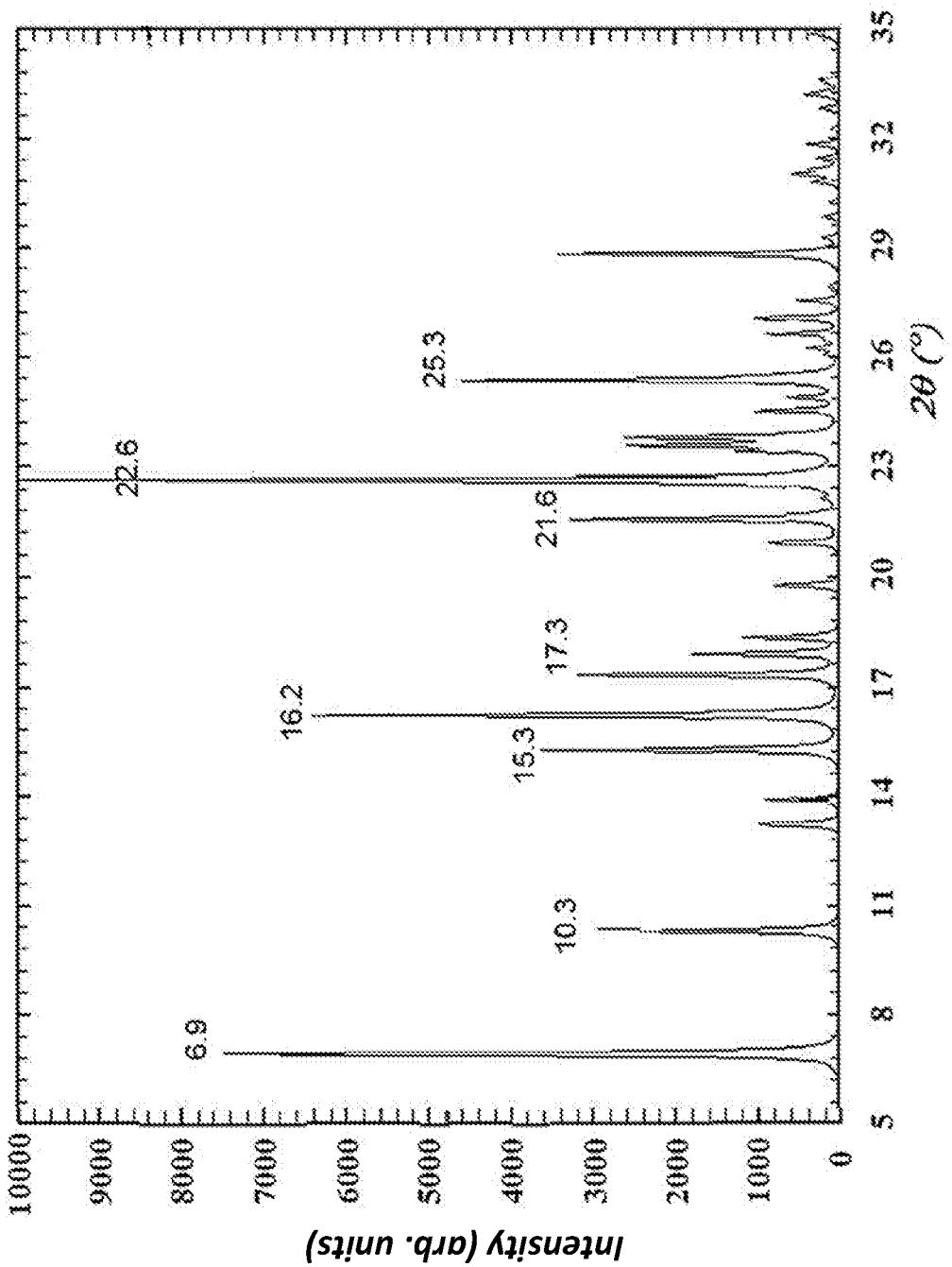


Figure 72

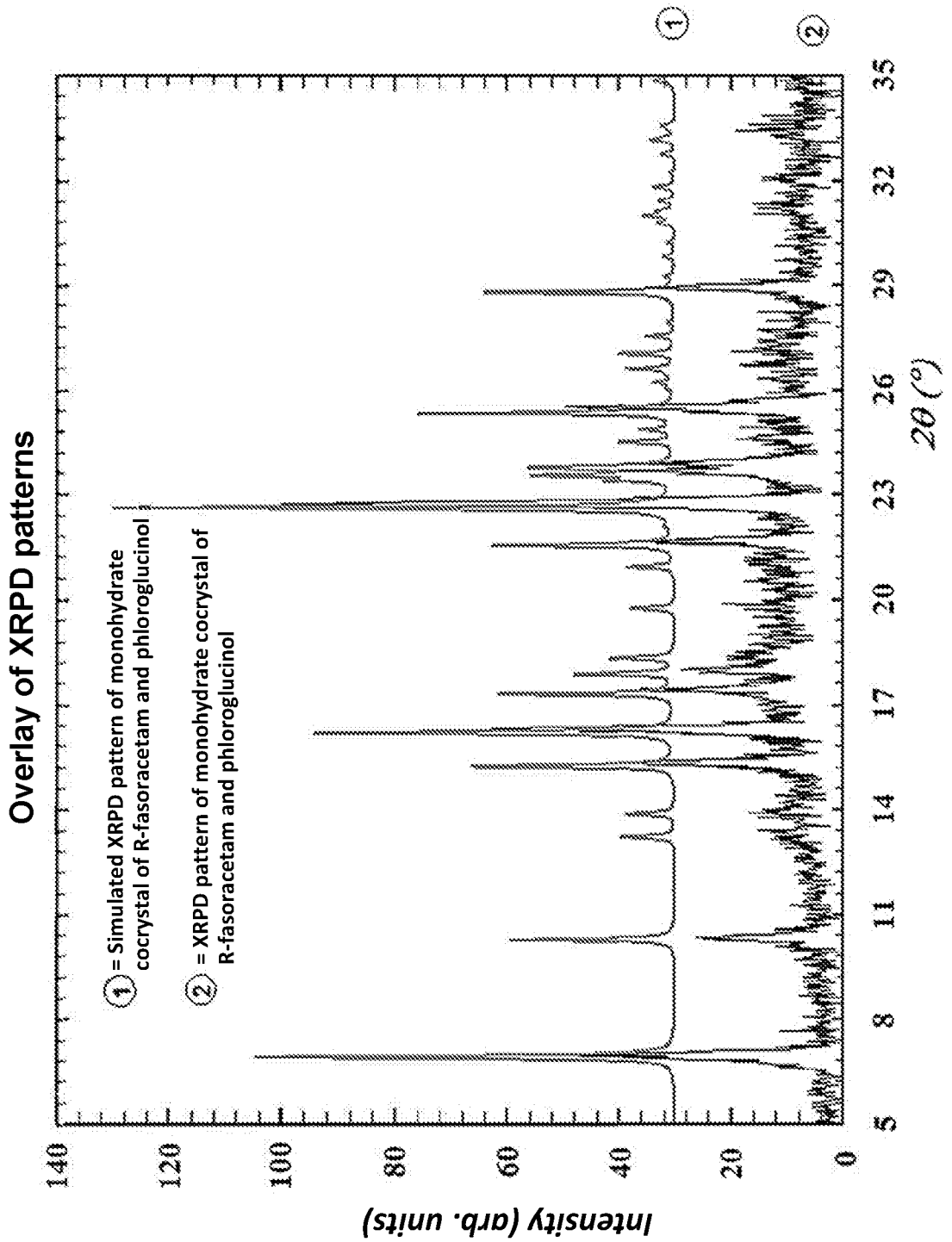

Overlay of XRPD patterns
① = Simulated XRPD pattern of monohydrate cocrystal of R-fasoracetam and phloroglucinol
② = XRPD pattern of monohydrate cocrystal of R-fasoracetam and phloroglucinol
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
5
8
11
14
17
20
23
26
29
32
35

Figure 73

ORTEP of a monohydrate of R-fasoracetam and methyl-3, 4, 5-trihydroxybenzoate cocrystal

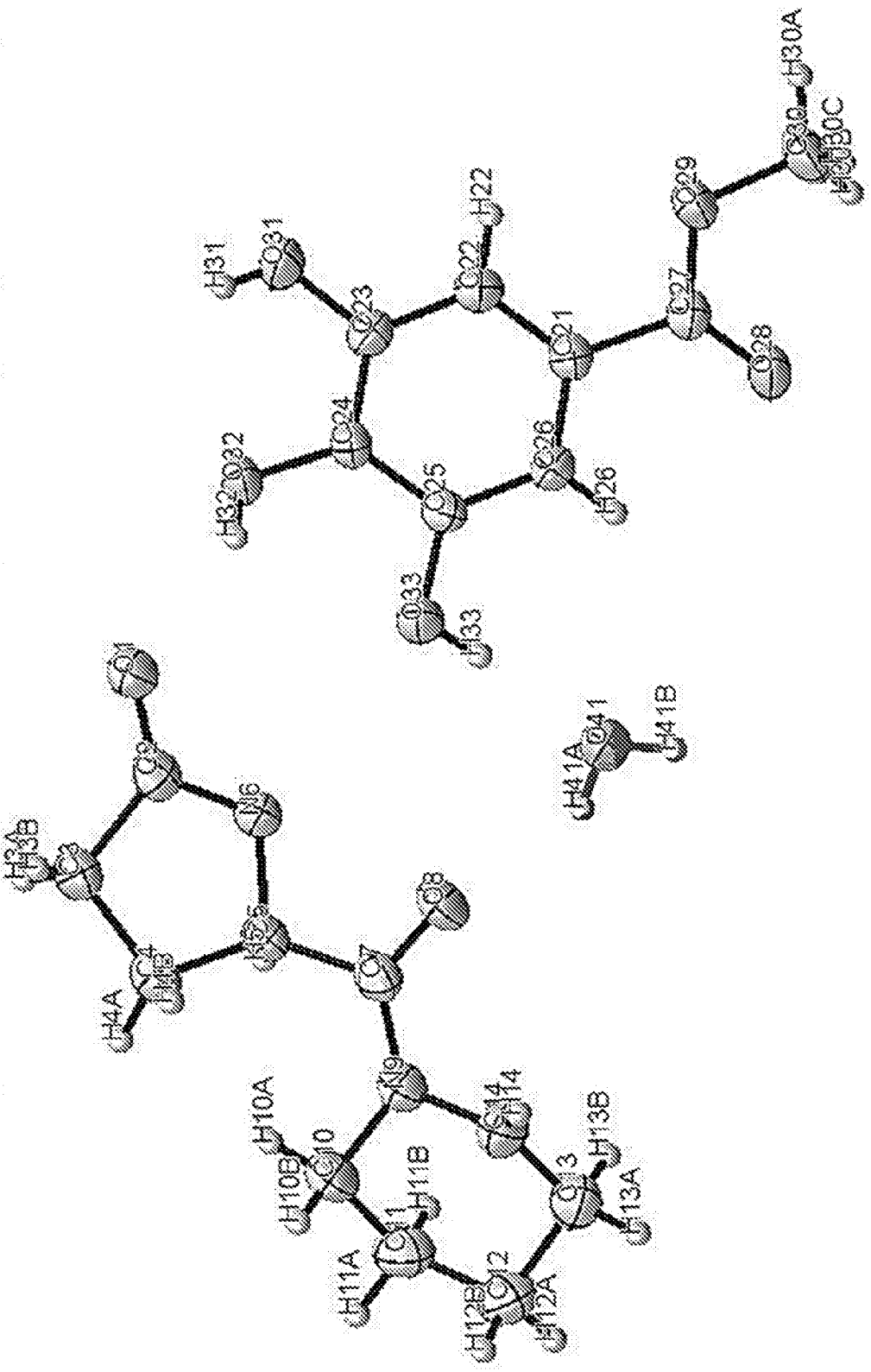


Figure 74

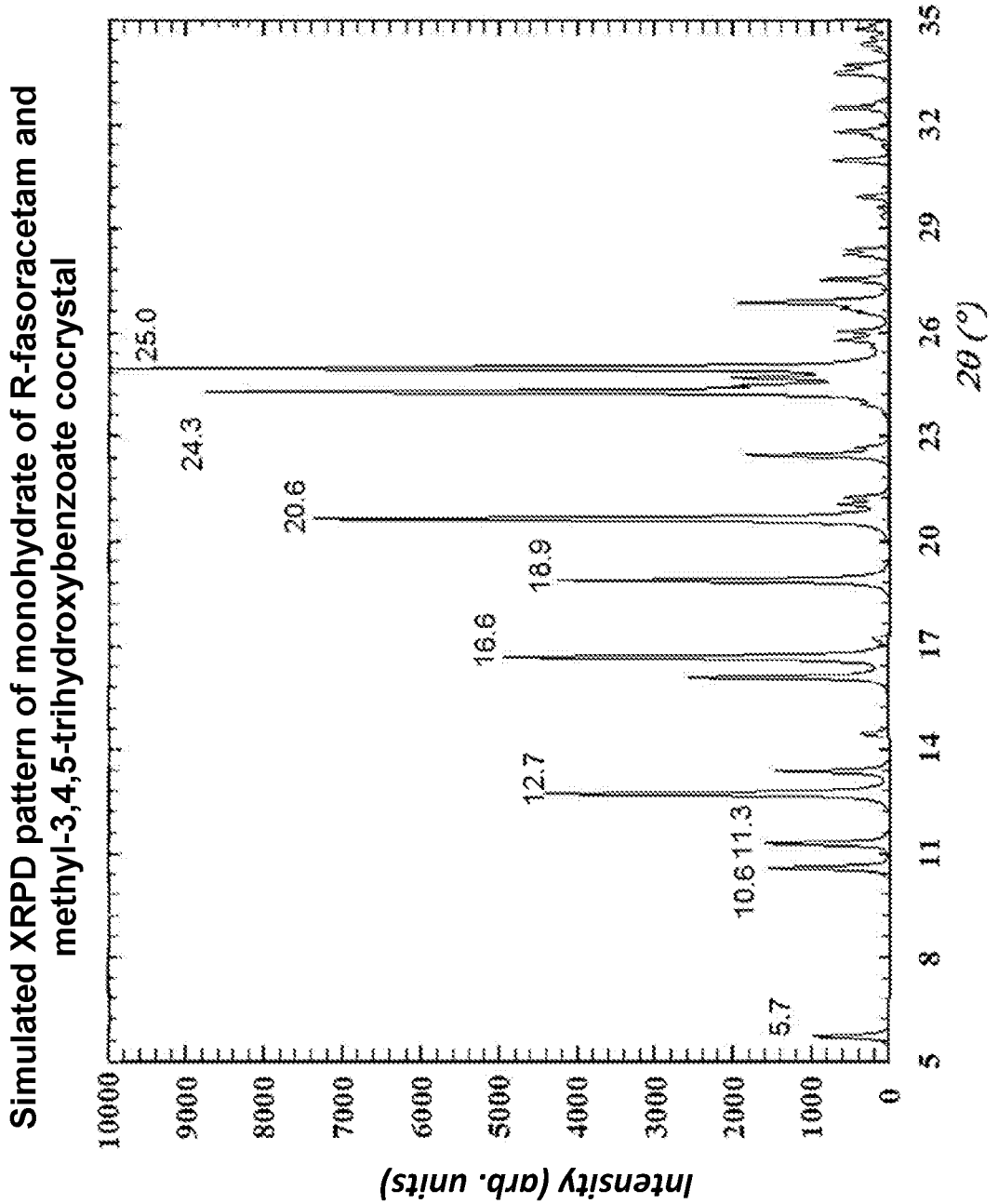

Simulated XRPD pattern of monohydrate of R-fasoracetam and methyl-3,4,5-trihydroxybenzoate cocrystal
Intensity (arb. units)
2θ (°)
25.0
24.3
20.6
18.9
16.6
12.7
11.3
10.6
5.7
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35

Figure 75

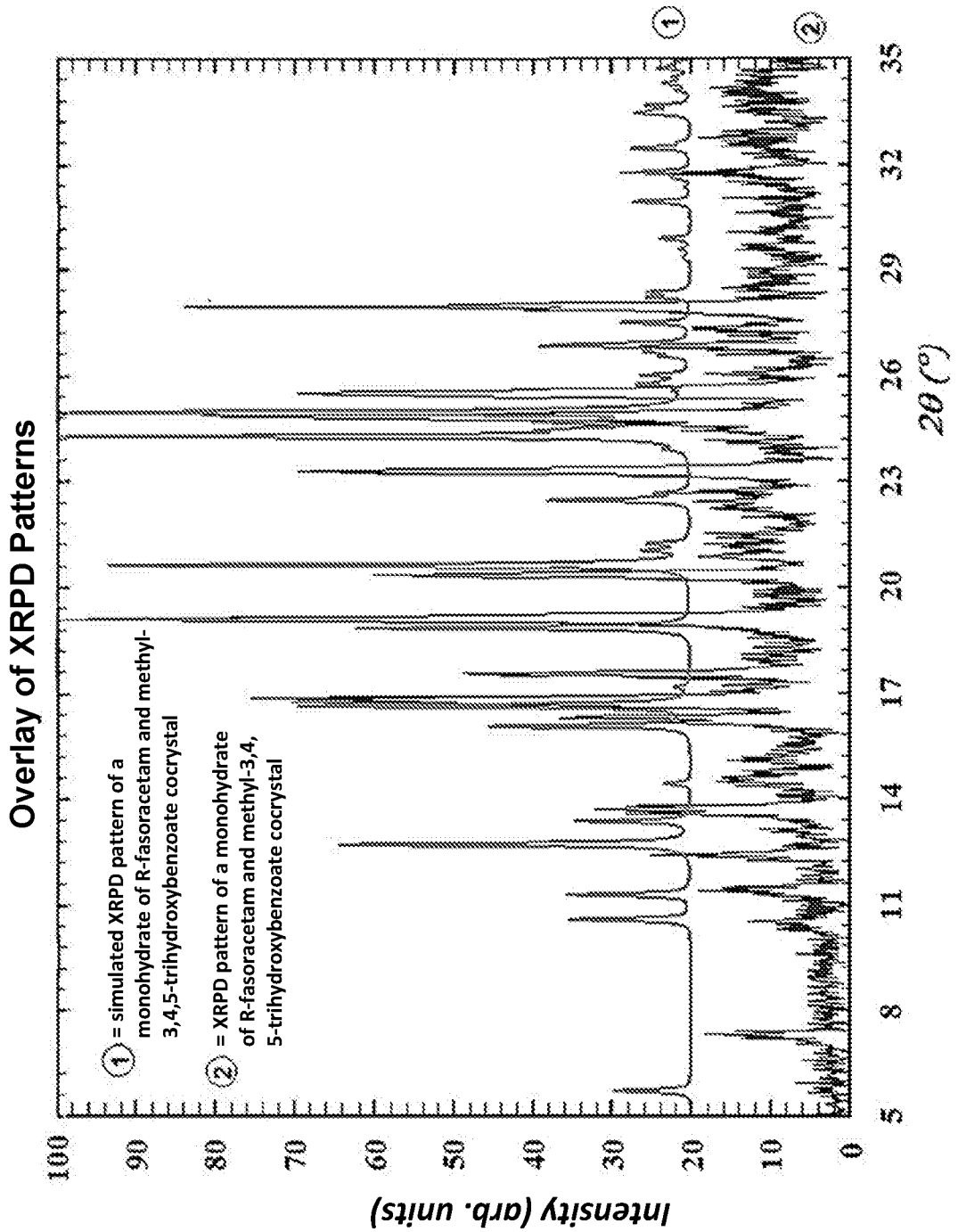

Overlay of XRPD Patterns
① = simulated XRPD pattern of a monohydrate of R-fasoracetam and methyl-3,4,5-trihydroxybenzoate cocrystal
② = XRPD pattern of a monohydrate of R-fasoracetam and methyl-3,4,5-trihydroxybenzoate cocrystal
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35

Figure 76

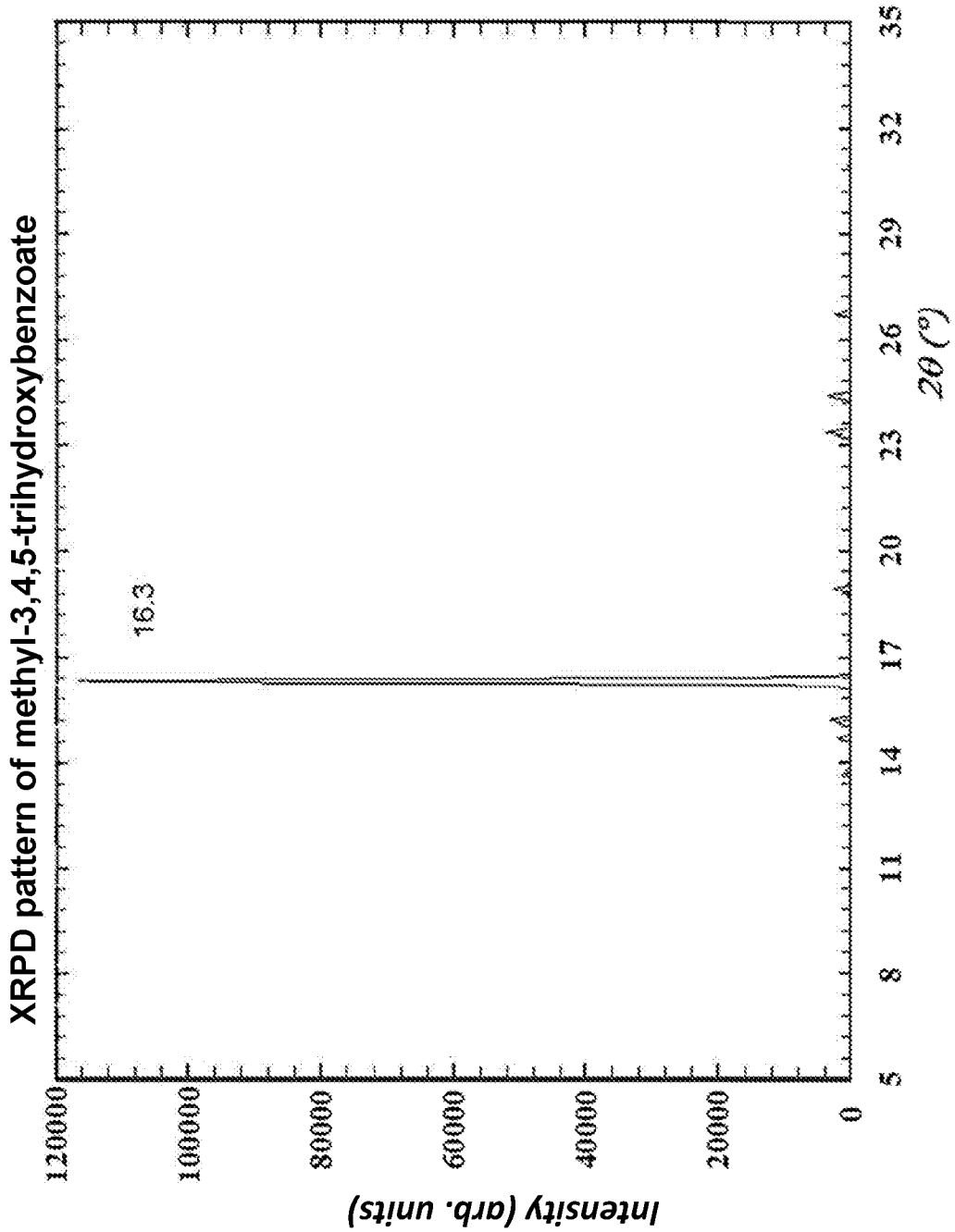

XRPD pattern of methyl-3,4,5-trihydroxybenzoate
16.3
Intensity (arb. units)
2θ (°)
120000
100000
80000
60000
40000
20000
0
5
8
11
14
17
20
23
26
29
32
35

Figure 77

ORTEP of a 1:1 cocrystal of R-fasoracetam to ethyl gallate

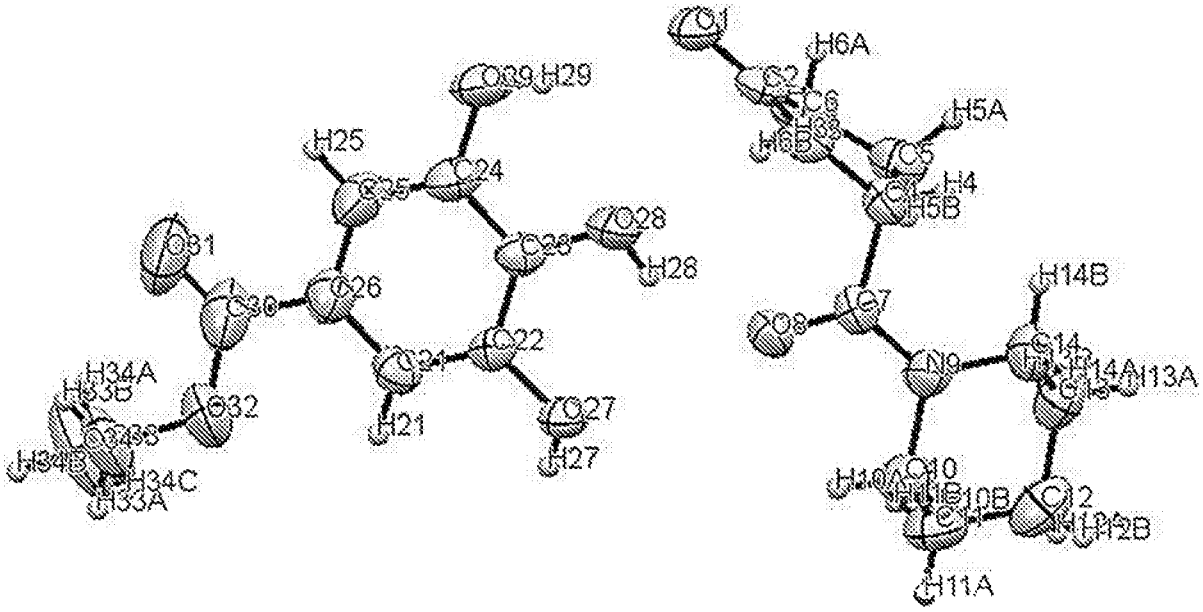


Figure 78

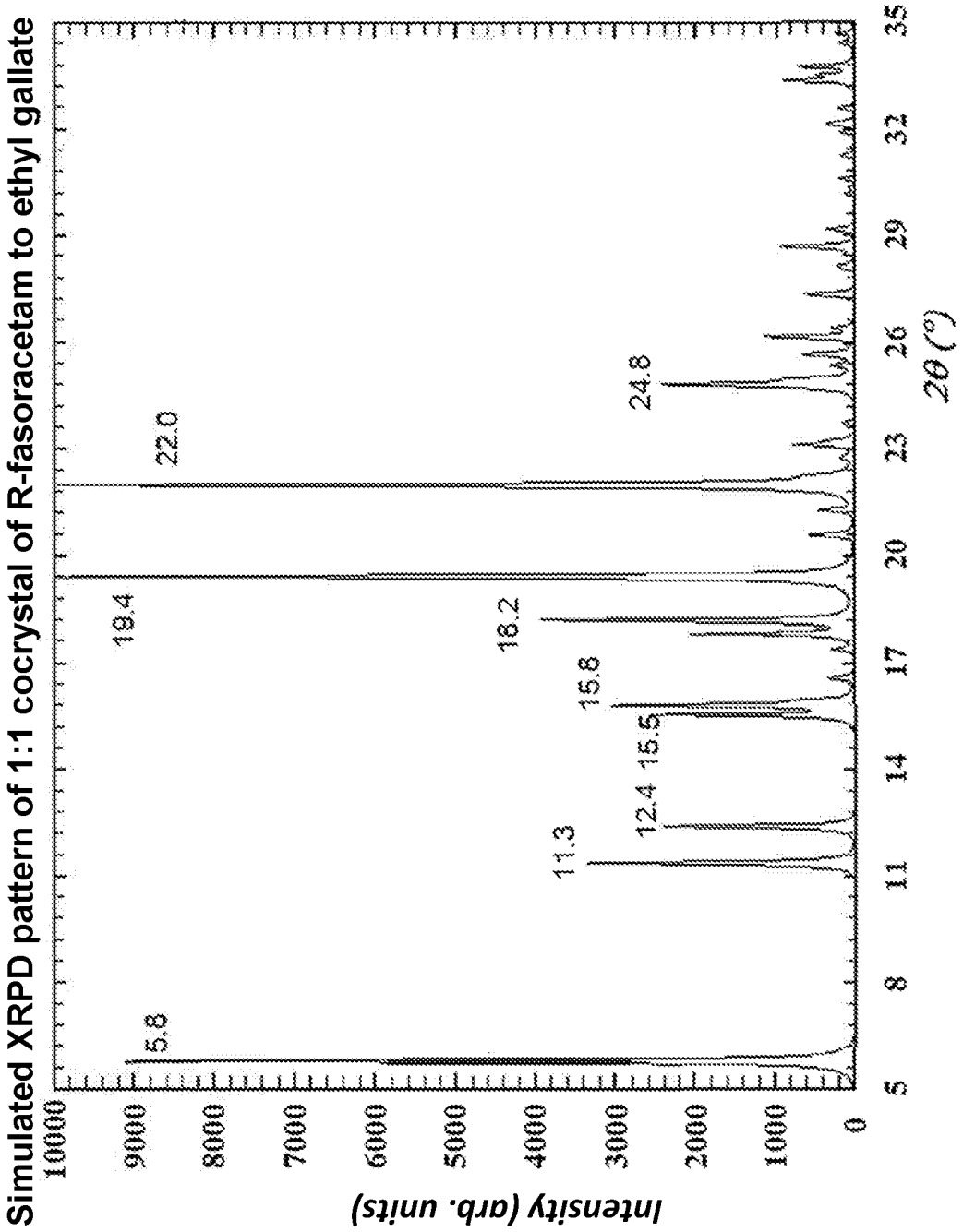

Simulated XRPD pattern of 1:1 cocrystal of R-fasoracetam to ethyl gallate
Intensity (arb. units)
2θ (°)
5.8
19.4
22.0
11.3
12.4
15.5
15.8
18.2
24.8
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35

Figure 79

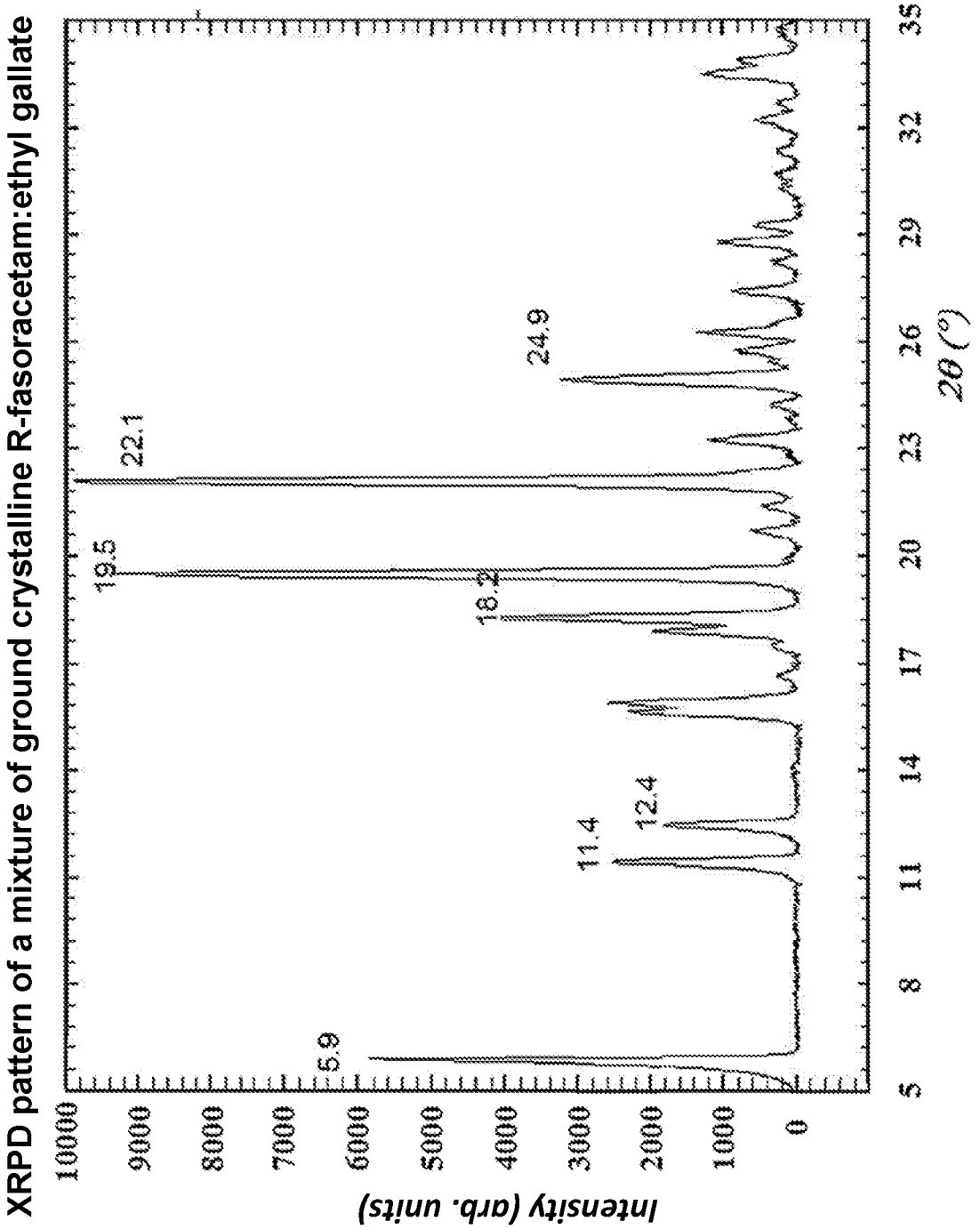

XRPD pattern of a mixture of ground crystalline R-fasoracetam:ethyl gallate
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
5.9
11.4
12.4
18.2
19.5
22.1
24.9

Figure 80

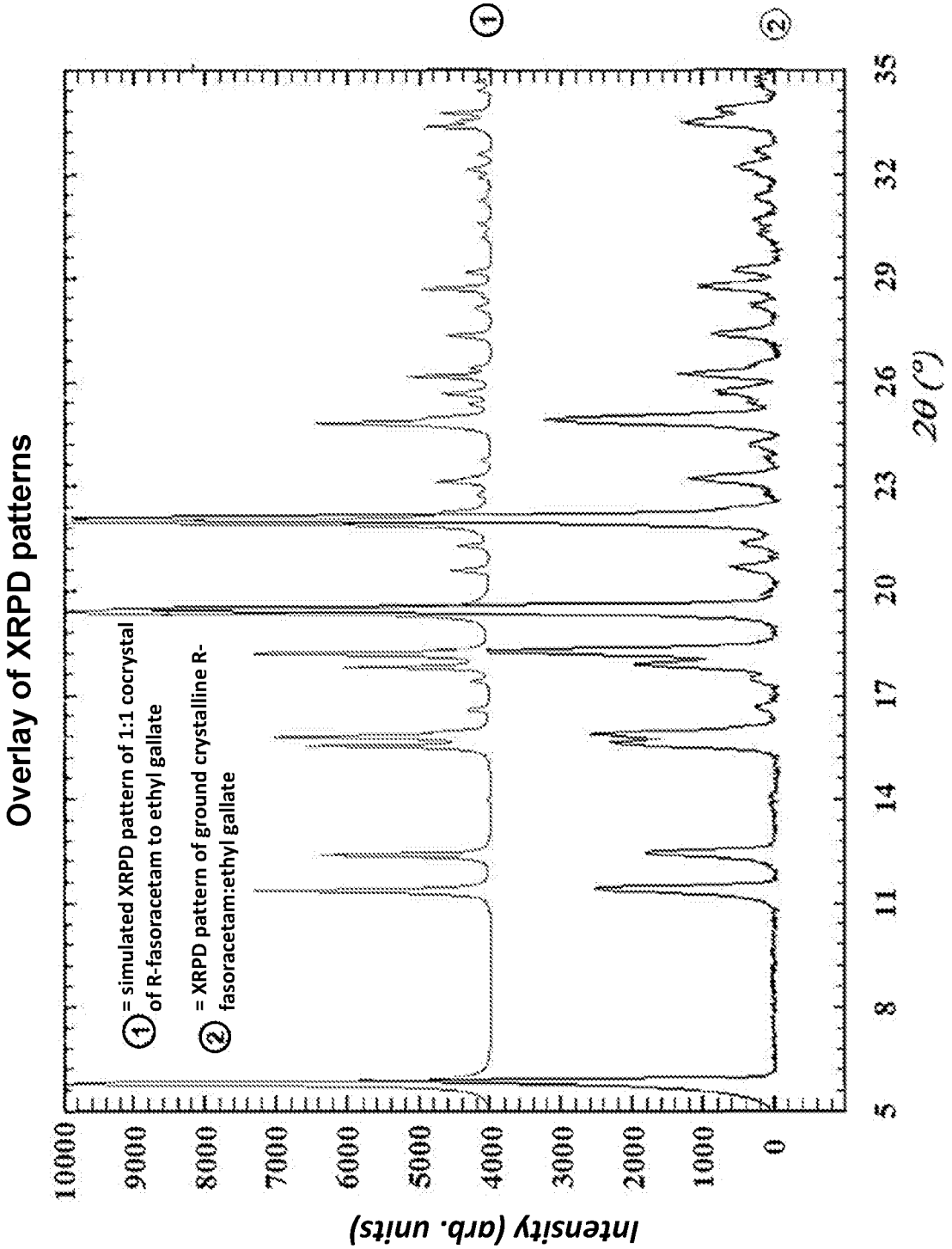

Overlay of XRPD patterns
① = simulated XRPD pattern of 1:1 cocrystal of R-fasoracetam to ethyl gallate
② = XRPD pattern of ground crystalline R-fasoracetam:ethyl gallate
Intensity (arb. units)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 81

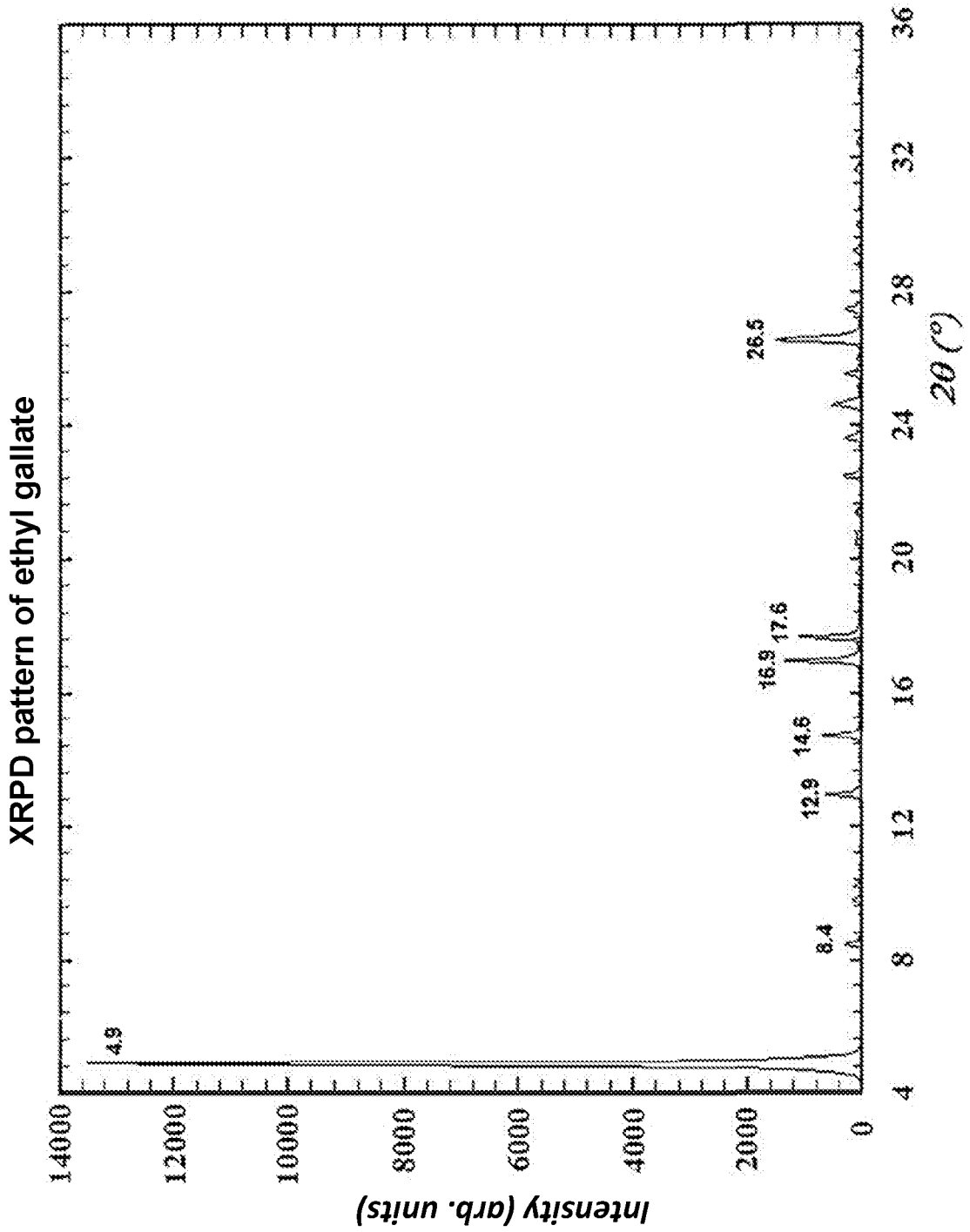

XRPD pattern of ethyl gallate
Intensity (arb. units)
2θ (°)
14000
12000
10000
8000
6000
4000
2000
0
4
8
12
16
20
24
28
32
36
4.9
8.4
12.9
14.6
16.9
17.6
26.5

Figure 82

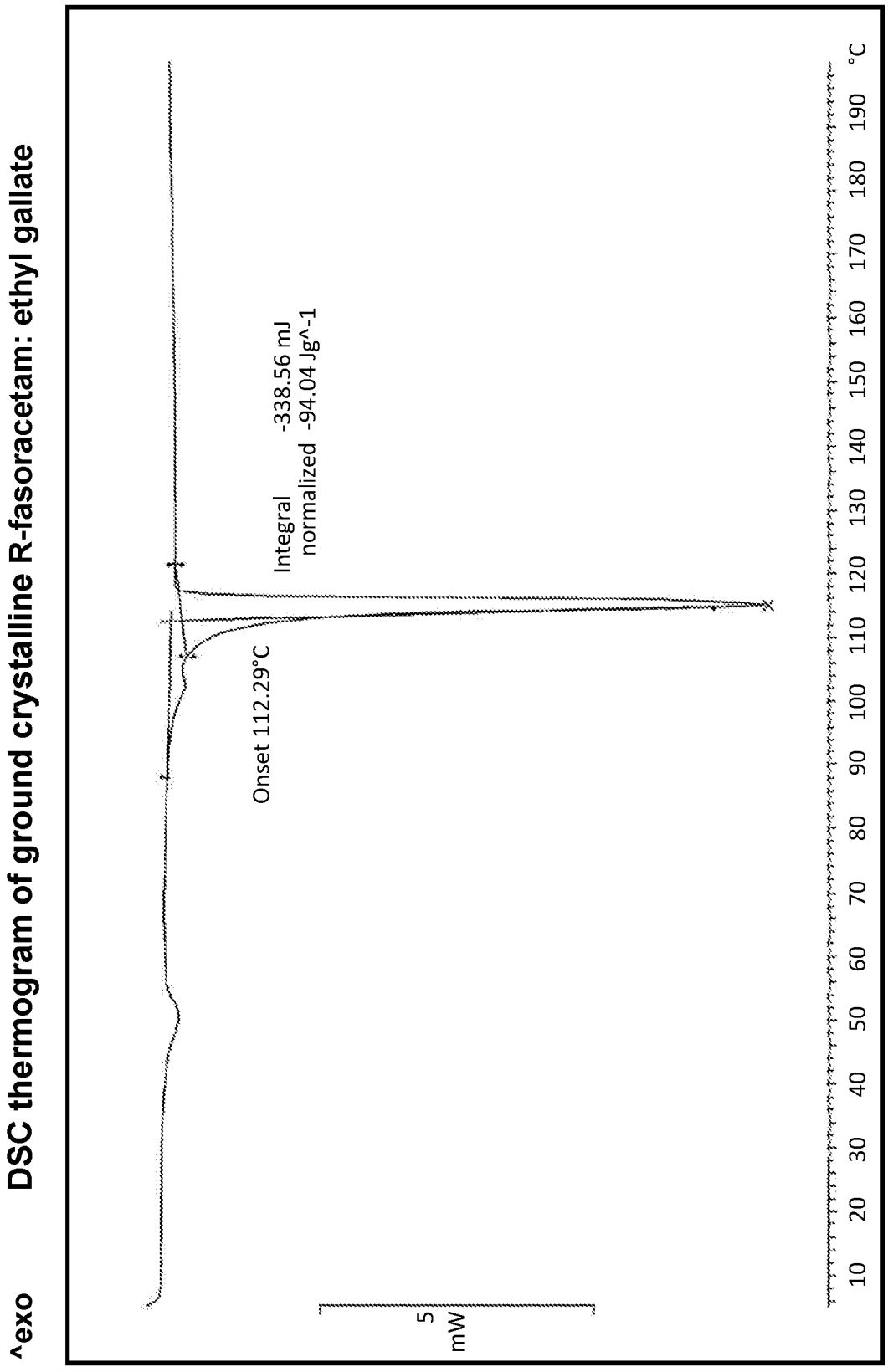

^exo
DSC thermogram of ground crystalline R-fasoracetam: ethyl gallate
Integral -338.56 mJ
normalized -94.04 Jg^-1
Onset 112.29°C
5
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 83

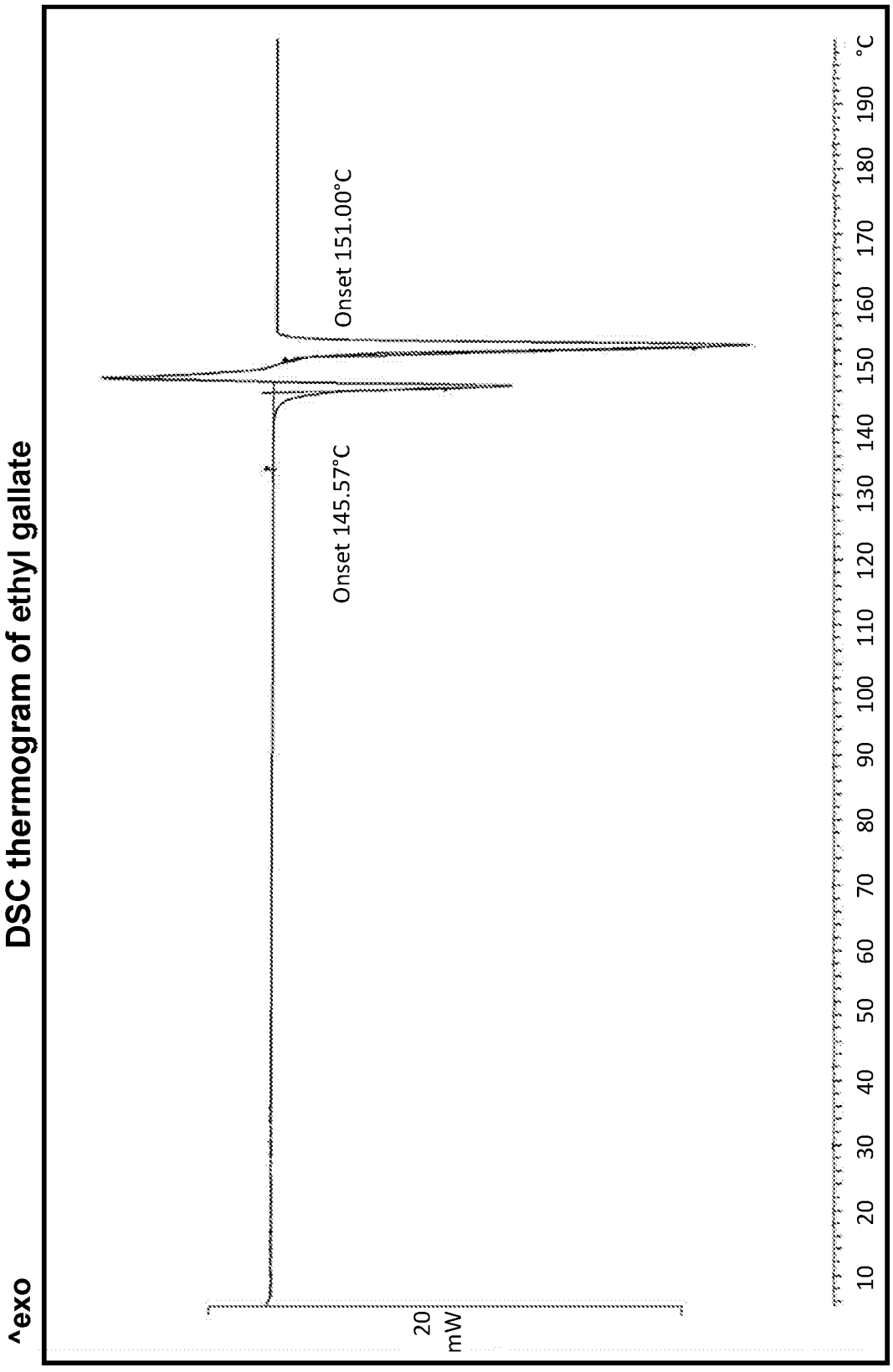

DSC thermogram of ethyl gallate
^exo
20
mW
Onset 151.00°C
Onset 145.57°C
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 84

ORTEP of 1:2 R-fasoracetam:ethyl gallate cocrystal

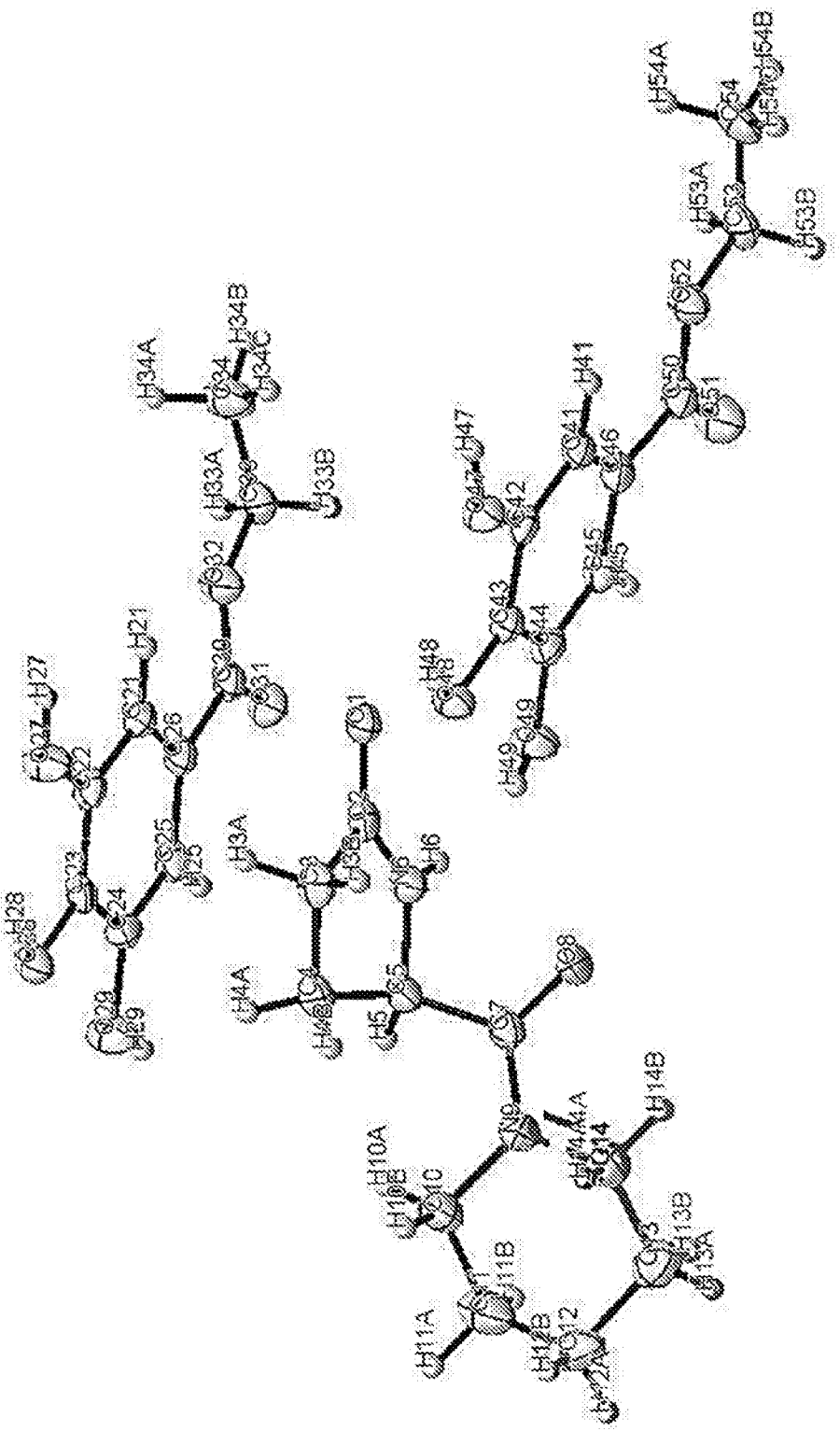


Figure 85

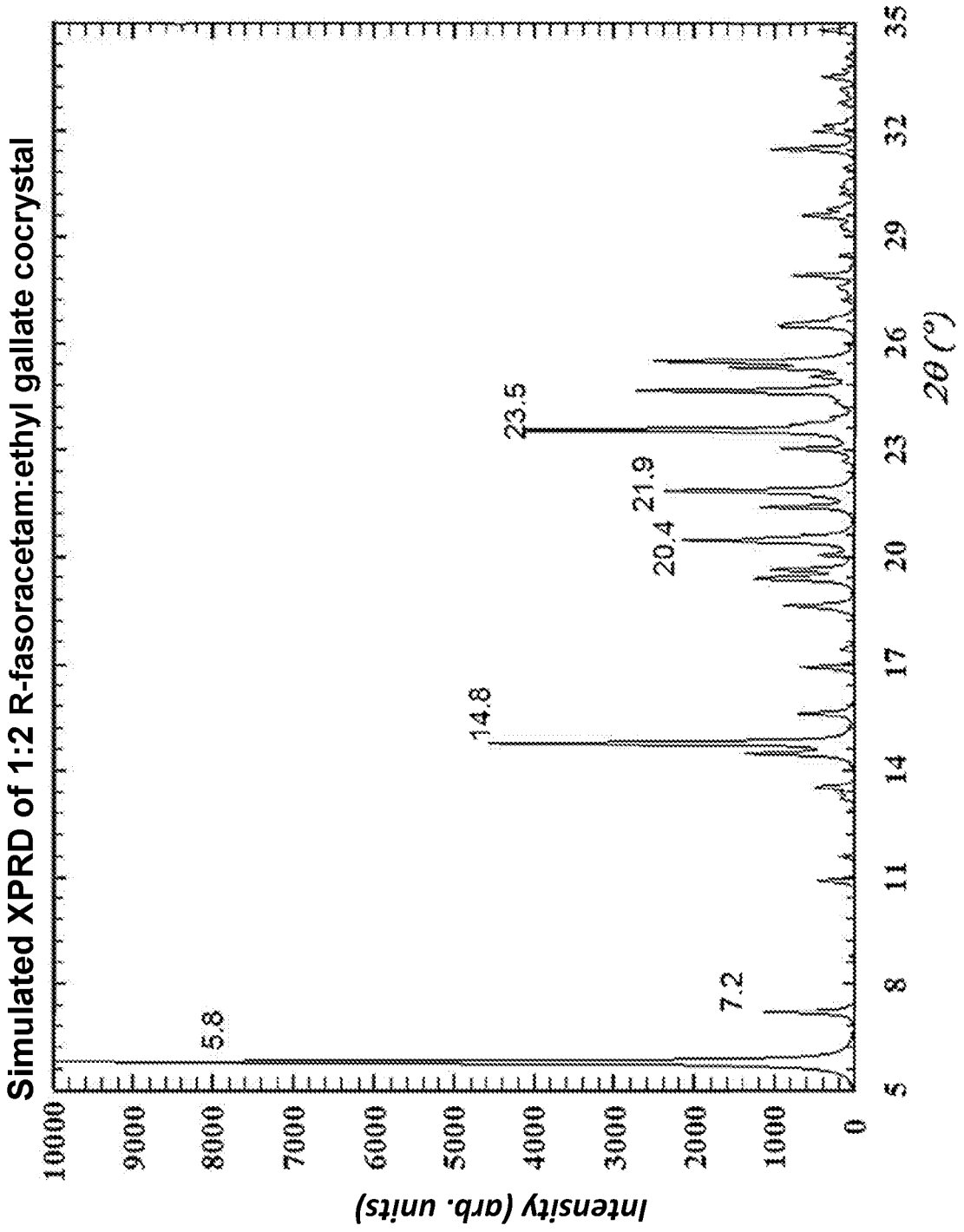

Simulated XPRD of 1:2 R-fasoracetam:ethyl gallate cocrystal
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
5.8
7.2
14.8
20.4
21.9
23.5

Figure 86

ORTEP of dihydrate 1:2 R-fasoracetam to ethyl gallate cocrystal

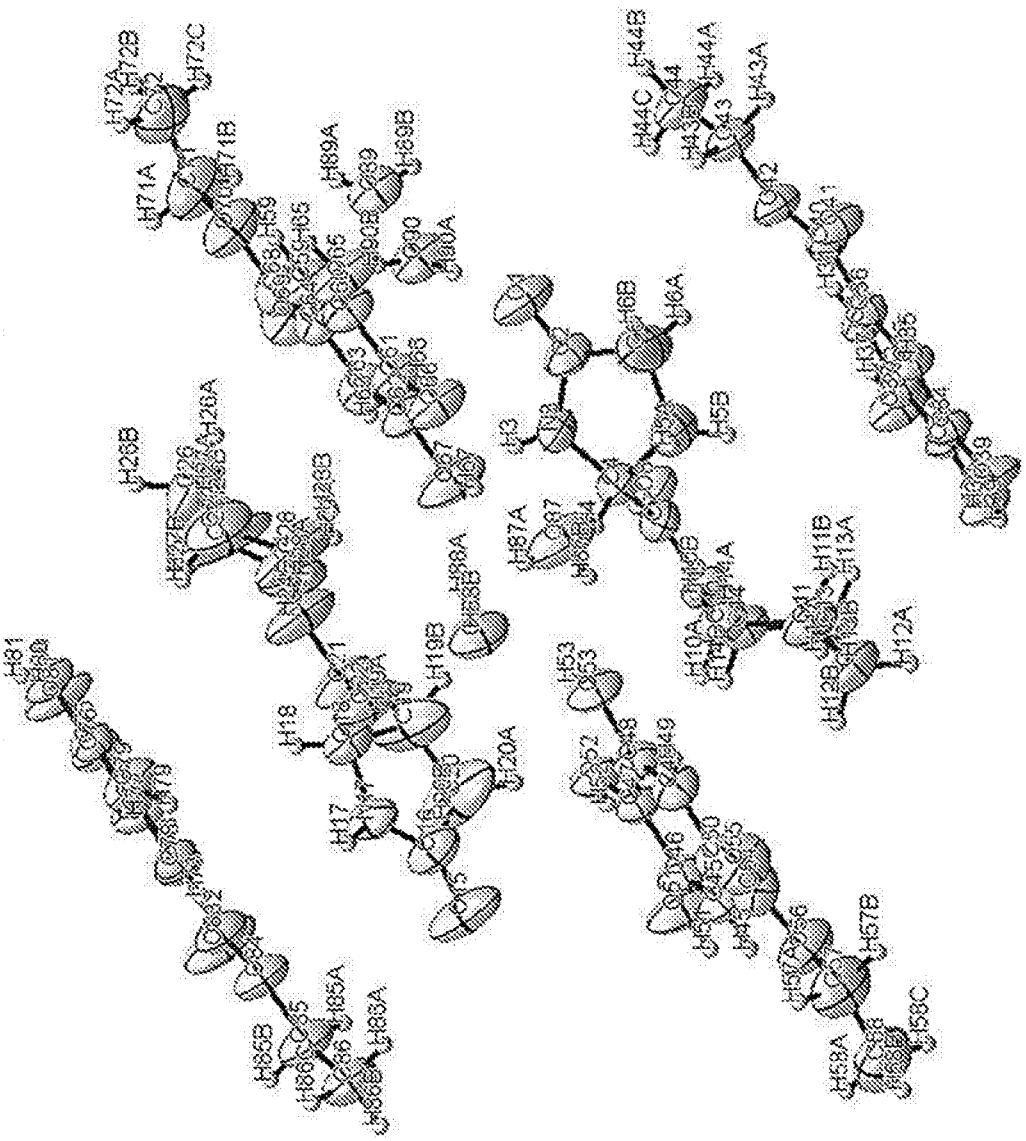


Figure 87

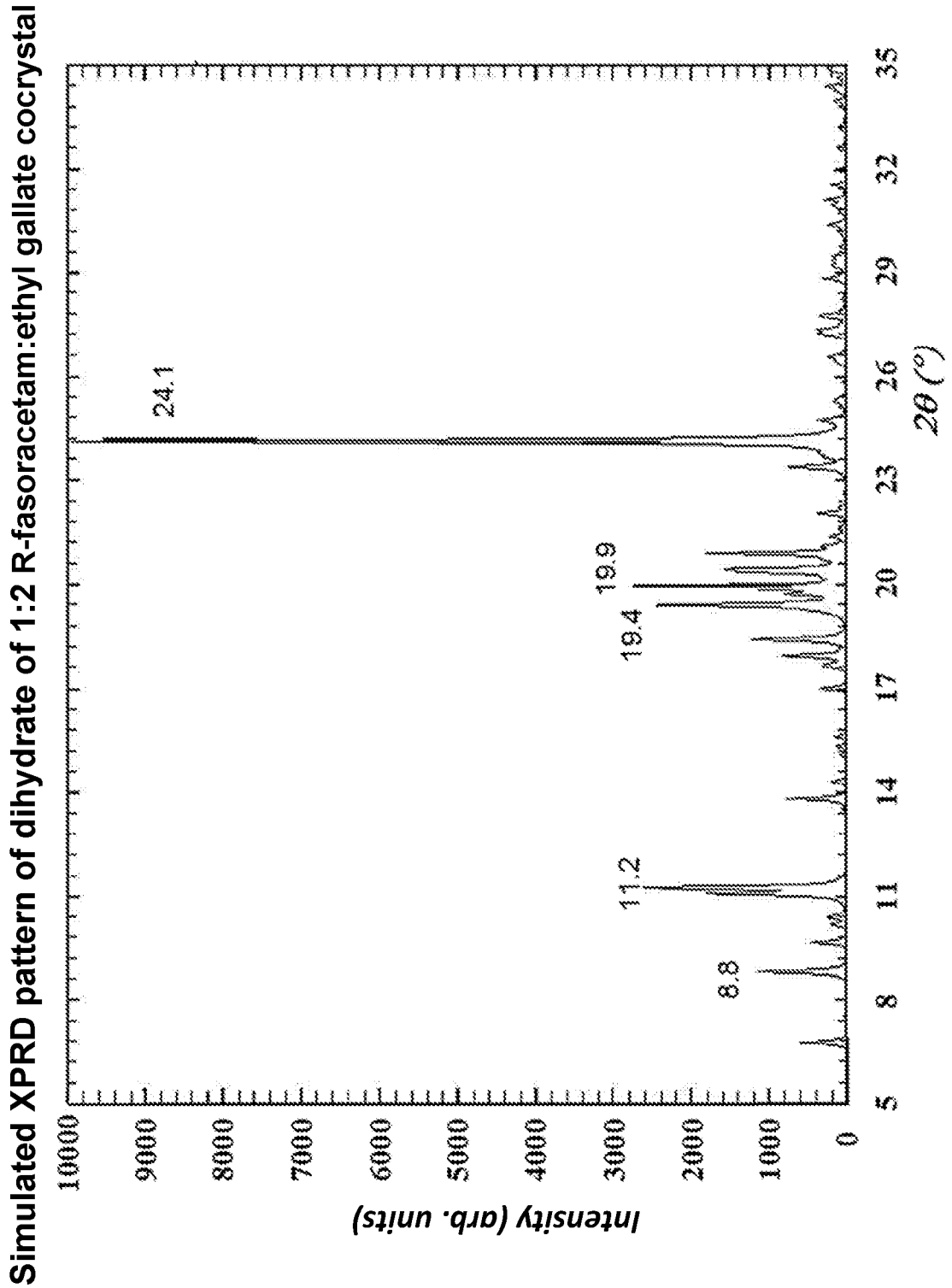

Simulated XPRD pattern of dihydrate of 1:2 R-fasoracetam:ethyl gallate cocrystal
Intensity (arb. units)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
24.1
19.9
19.4
11.2
8.8

Figure 88

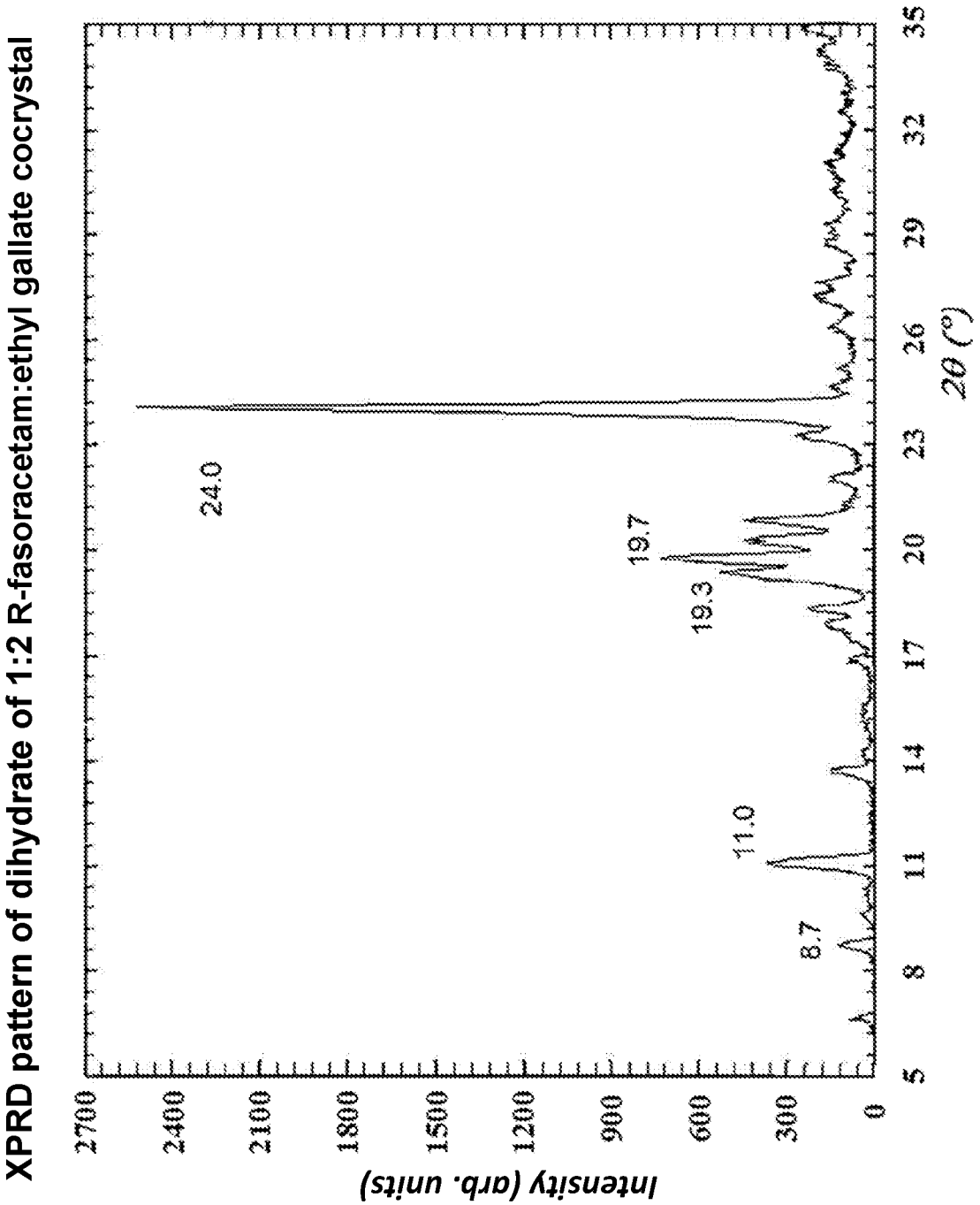

XPRD pattern of dihydrate of 1:2 R-fasoracetam:ethyl gallate cocrystal
Intensity (arb. units)
2700
2400
2100
1800
1500
1200
900
600
300
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
24.0
19.7
19.3
11.0
8.7

Figure 89

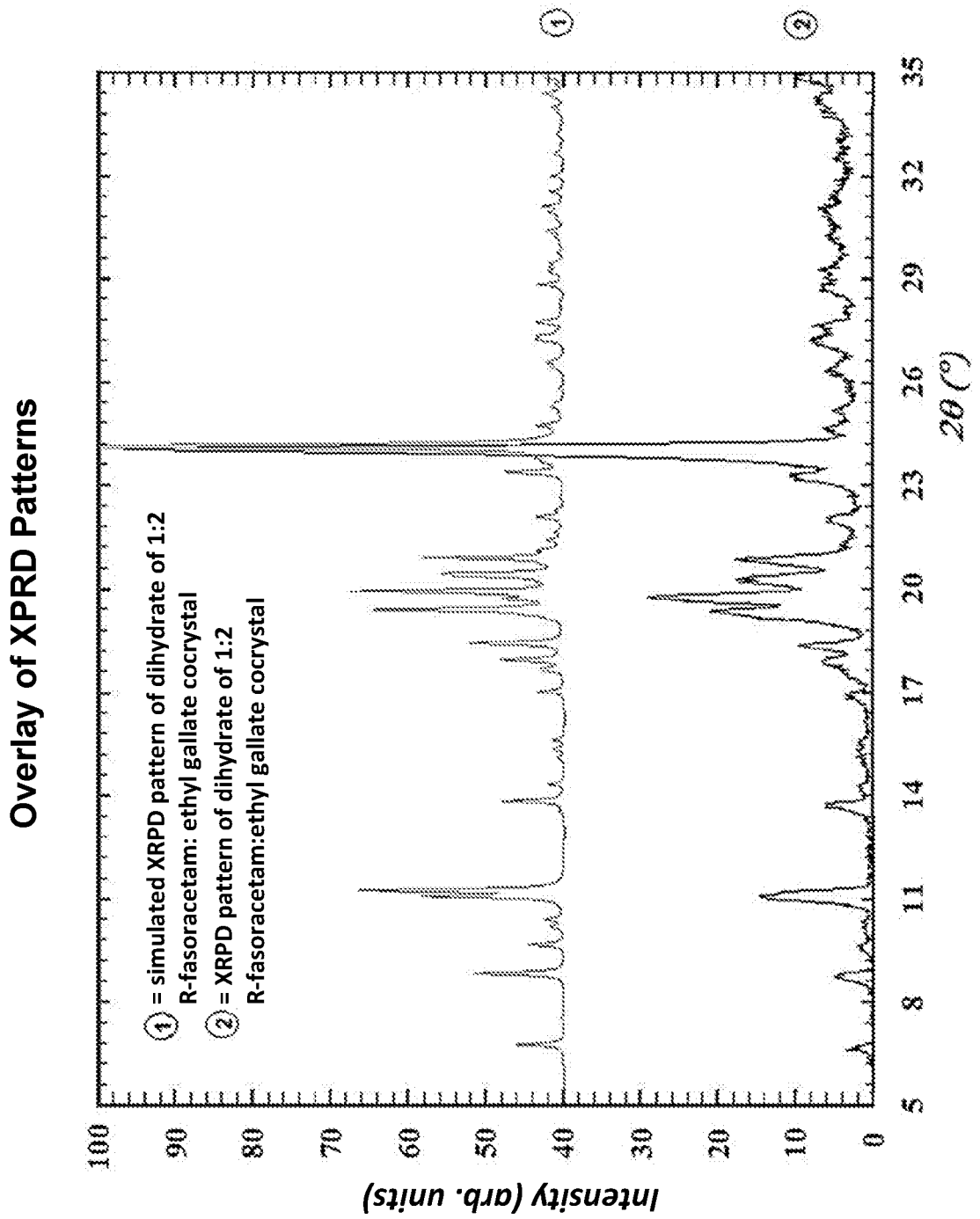

Overlay of XPRD Patterns
① = simulated XRPD pattern of dihydrate of 1:2
R-fasoracetam: ethyl gallate cocrystal
② = XRPD pattern of dihydrate of 1:2
R-fasoracetam:ethyl gallate cocrystal
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35

Figure 90

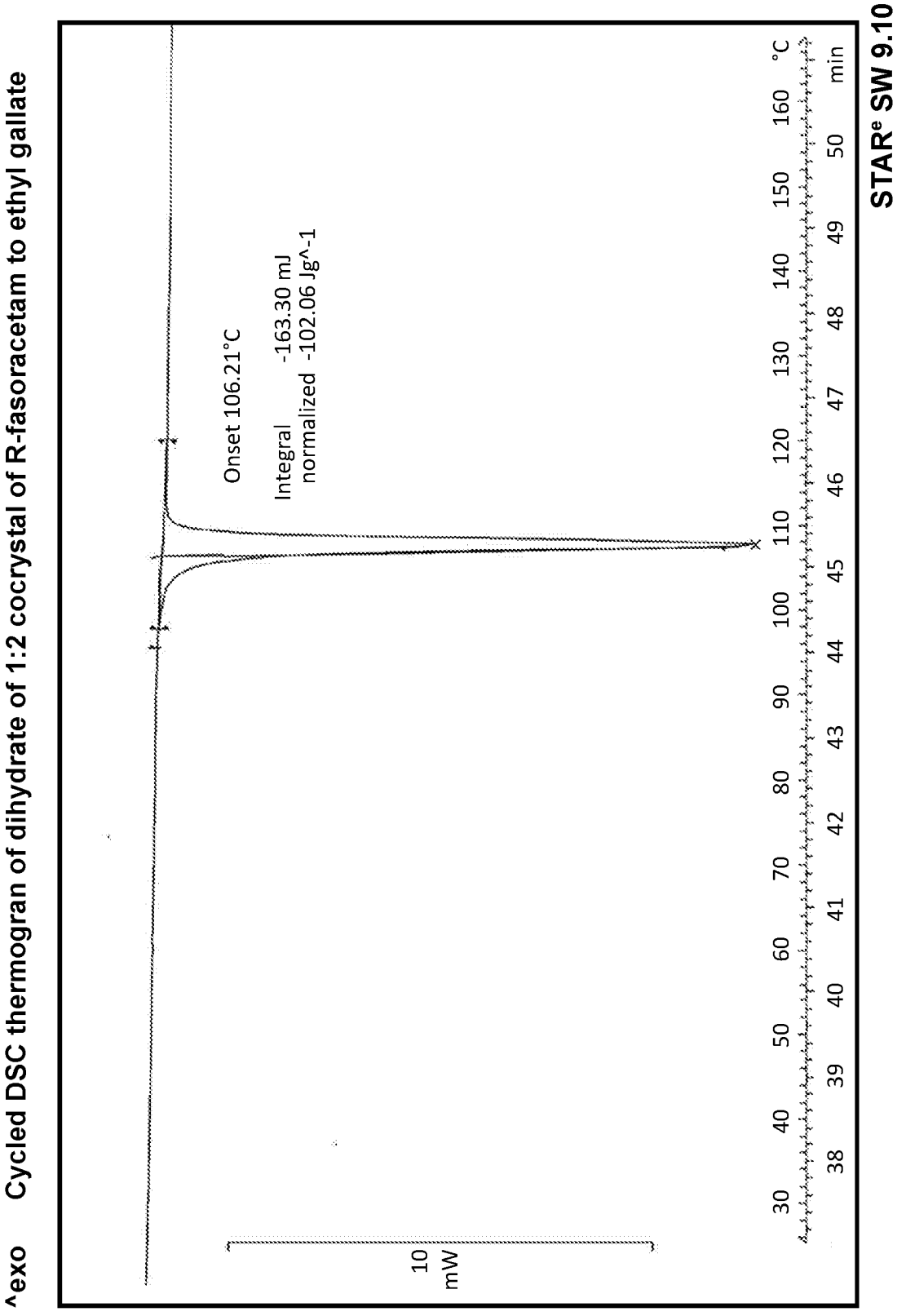

^exo Cycled DSC thermogran of dihydrate of 1:2 cocrystal of R-fasoracetam to ethyl gallate
Onset 106.21°C
Integral -163.30 mJ
normalized -102.06 Jg^-1
10 mW
30 40 50 60 70 80 90 100 110 120 130 140 150 160 °C
38 39 40 41 42 43 44 45 46 47 48 49 50 min
STARe SW 9.10

Figure 91

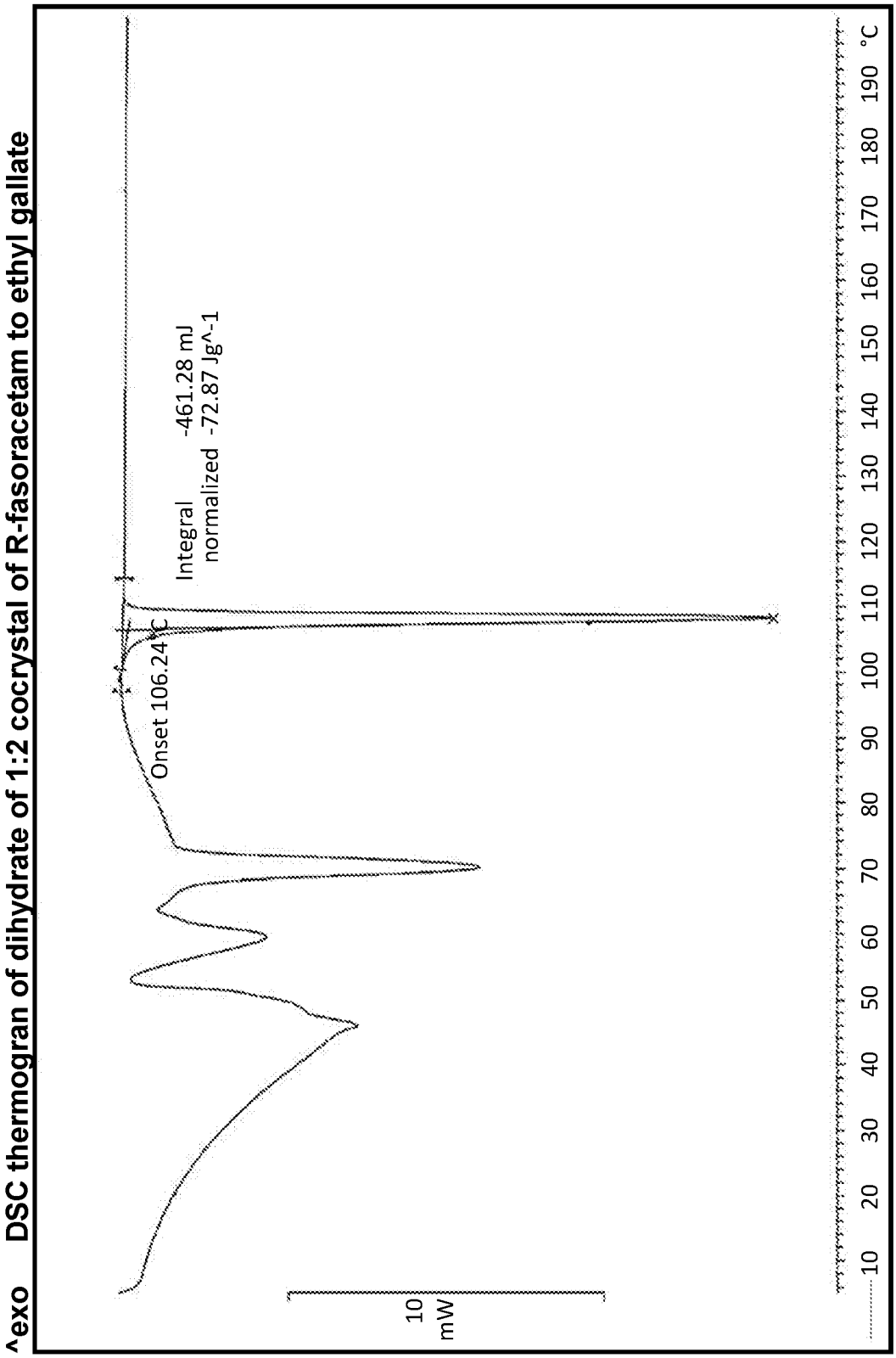

^exo DSC thermogran of dihydrate of 1:2 cocrystal of R-fasoracetam to ethyl gallate
Onset 106.24 °C
Integral -461.28 mJ
normalized -72.87 Jg^-1
10
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 92

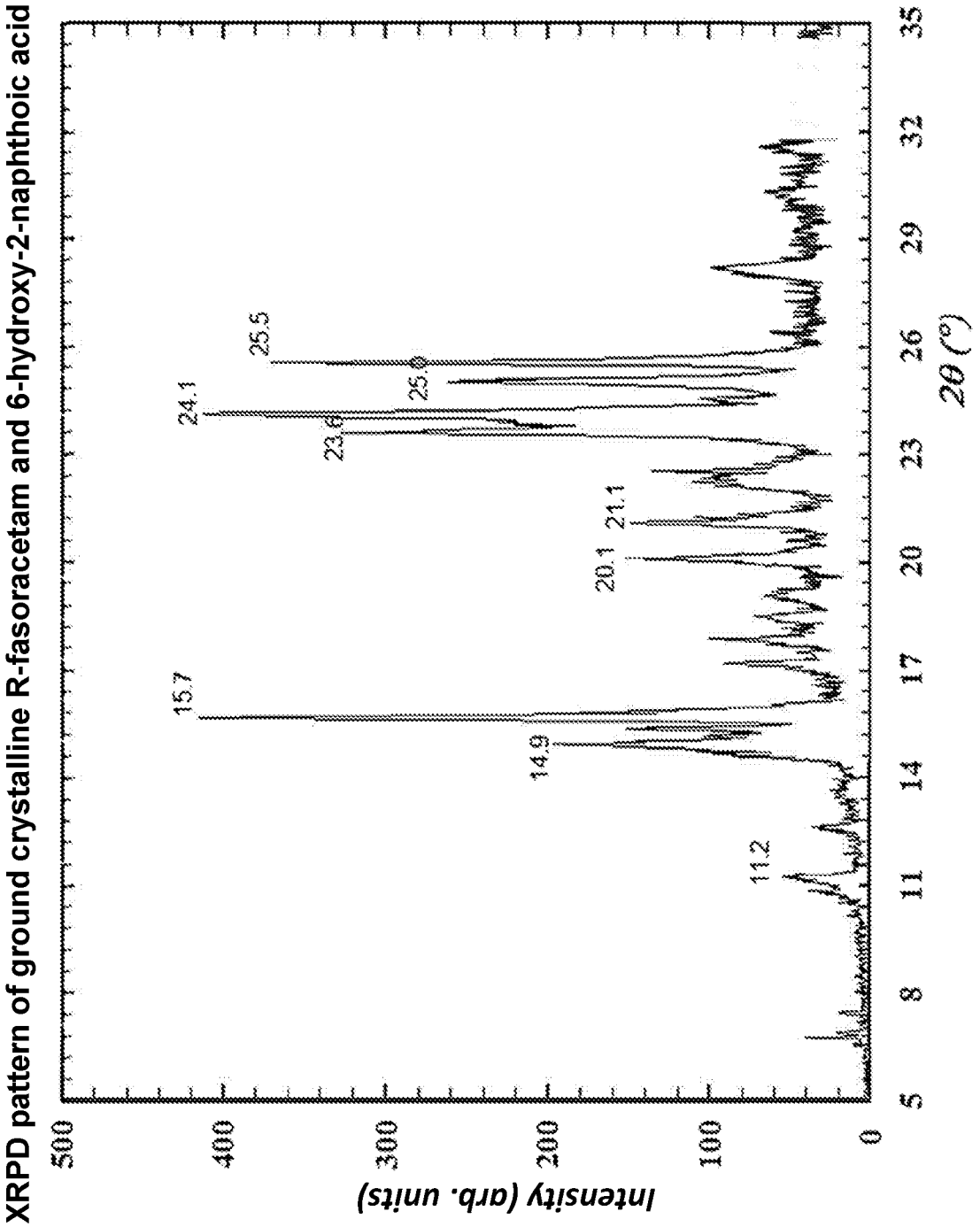

XRPD pattern of ground crystalline R-fasoracetam and 6-hydroxy-2-naphthoic acid
Intensity (arb. units)
2θ (°)
15.7
14.9
11.2
24.1
23.6
25.6
25.5
20.1
21.1
0
100
200
300
400
500
5
8
11
14
17
20
23
26
29
32
35

Figure 93

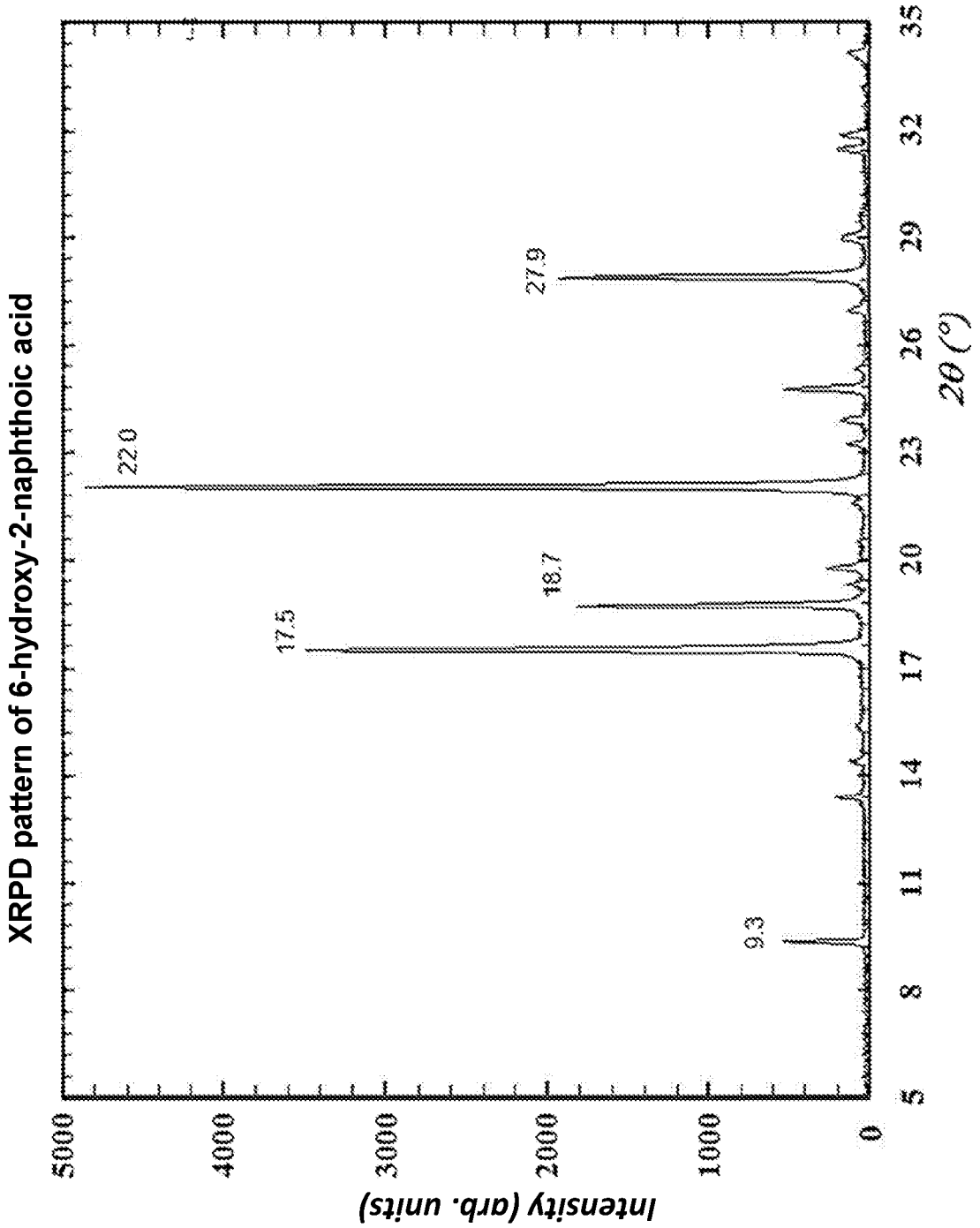

XRPD pattern of 6-hydroxy-2-naphthoic acid
Intensity (arb. units)
2θ (°)
0
1000
2000
3000
4000
5000
5
8
11
14
17
20
23
26
29
32
35
9.3
17.5
18.7
22.0
27.9

Figure 94

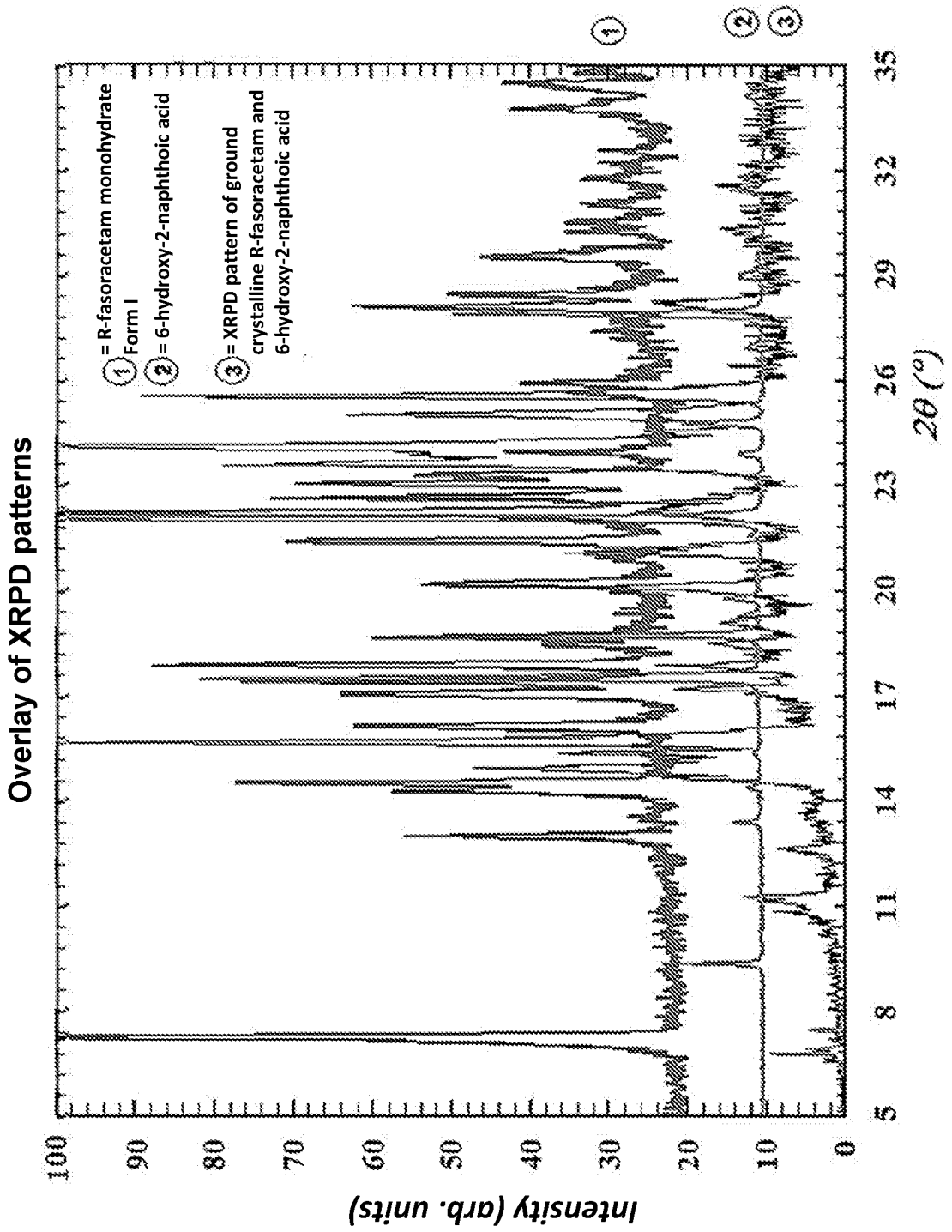

Overlay of XRPD patterns
1 = R-fasoracetam monohydrate Form I
2 = 6-hydroxy-2-naphthoic acid
3 = XRPD pattern of ground crystalline R-fasoracetam and 6-hydroxy-2-naphthoic acid
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
80
90
100
5
8
11
14
17
20
23
26
29
32
35

Figure 95

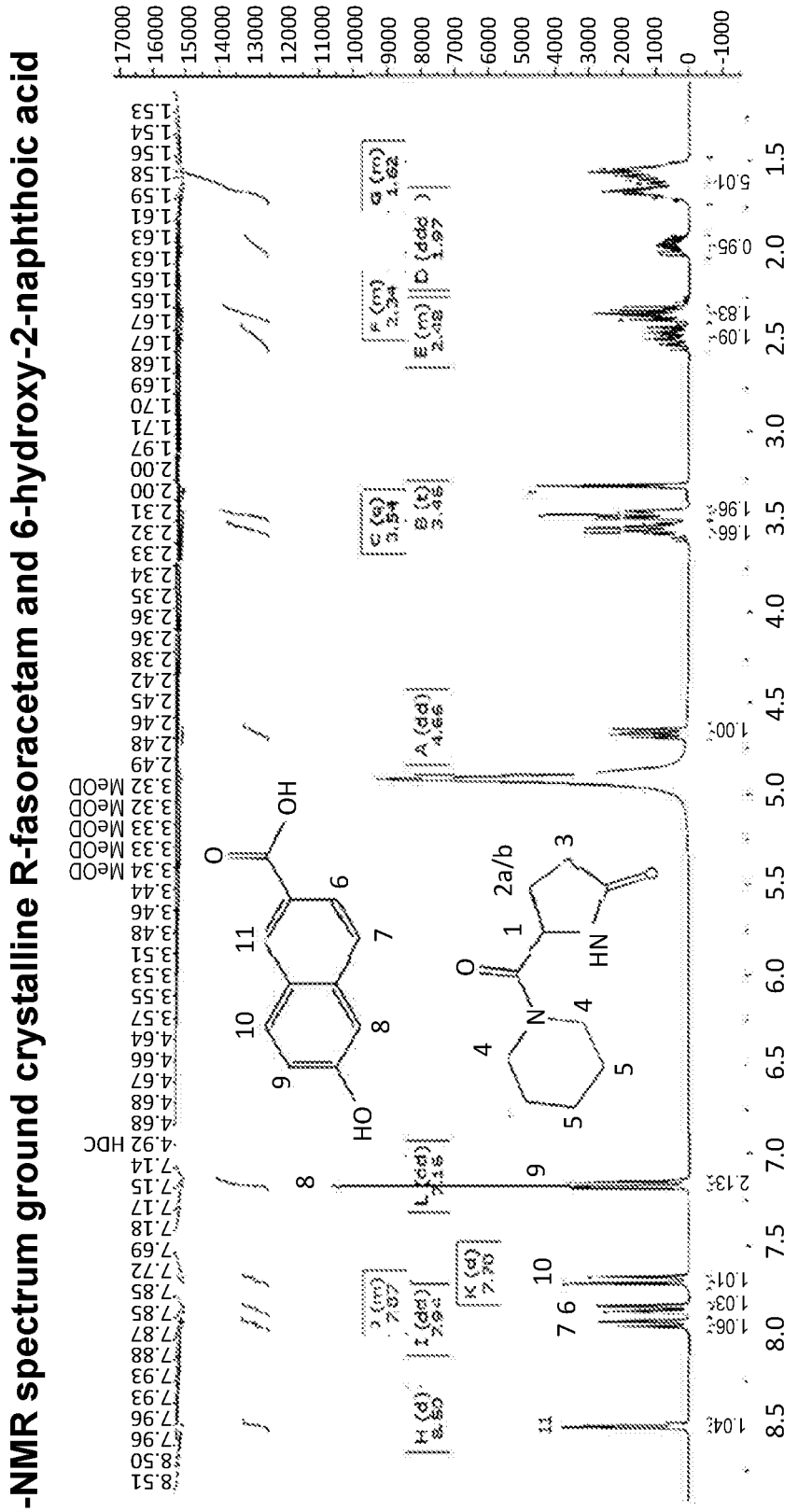

1H-NMR spectrum ground crystalline R-fasoracetam and 6-hydroxy-2-naphthoic acid
MeOD
HDO
OH
HO
HN
N
2a/b

Figure 96

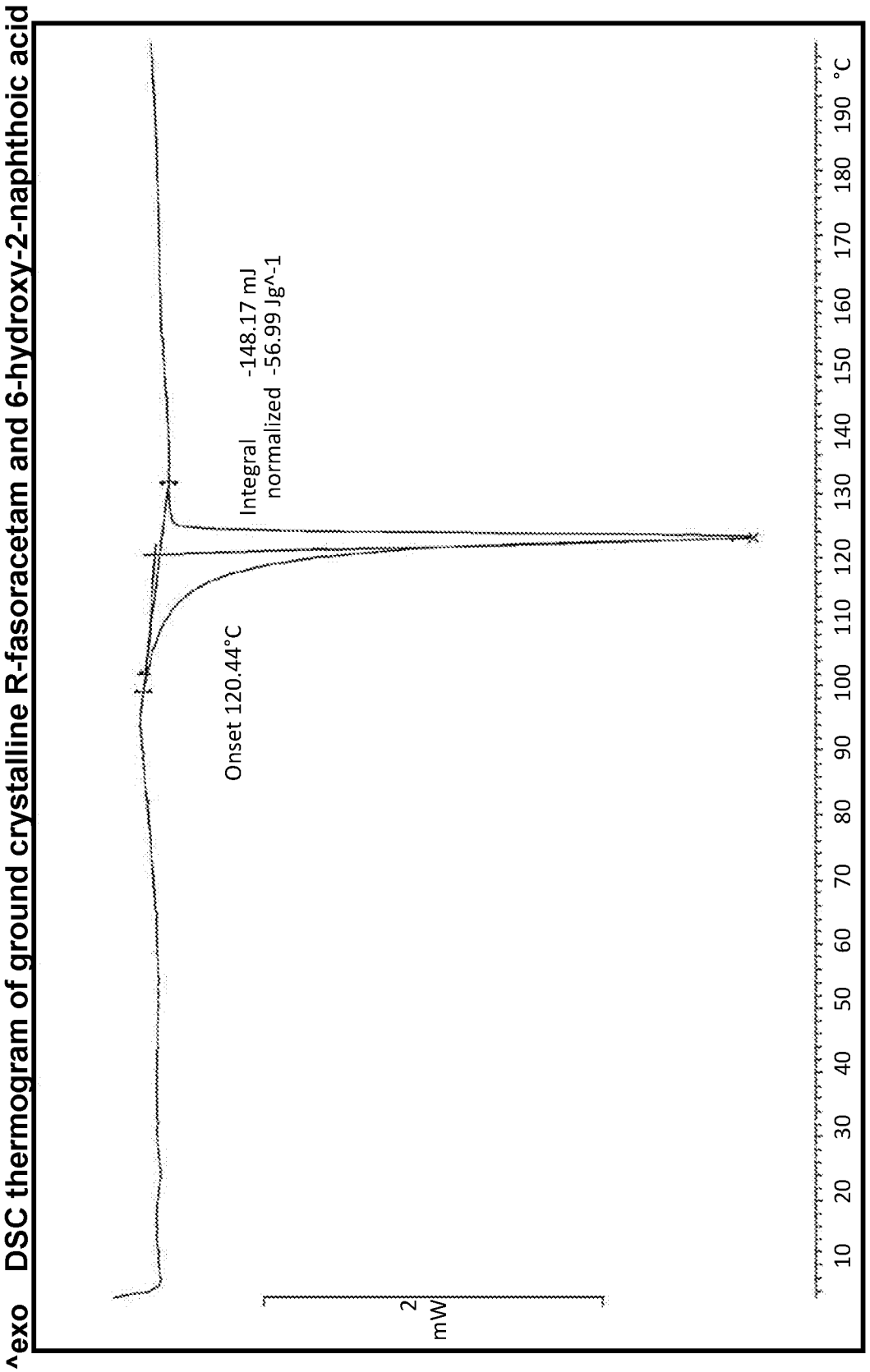

^exo DSC thermogram of ground crystalline R-fasoracetam and 6-hydroxy-2-naphthoic acid
Integral -148.17 mJ
normalized -56.99 Jg^-1
Onset 120.44°C
2
mW
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 97

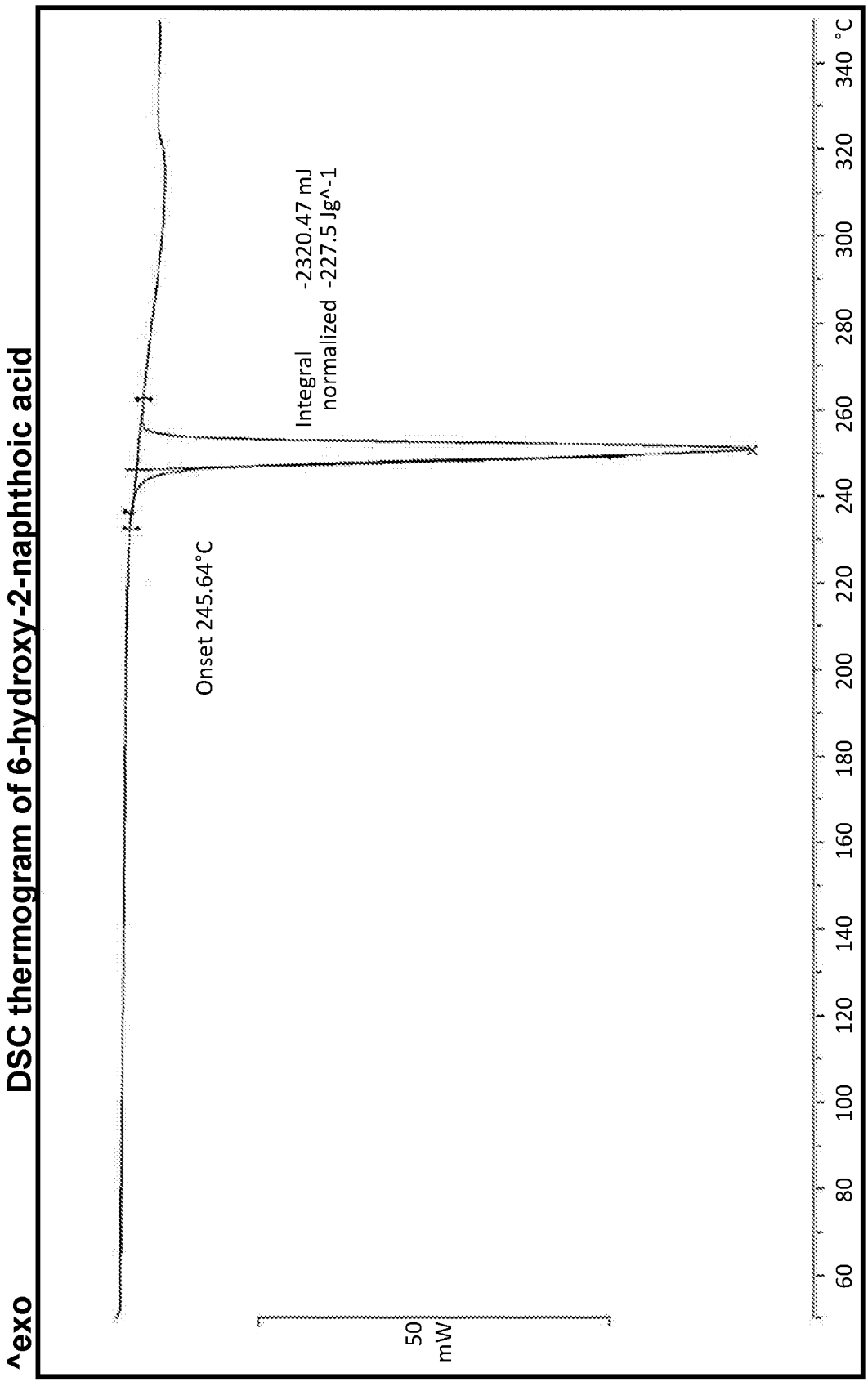

DSC thermogram of 6-hydroxy-2-naphthoic acid
^exo
50
mW
Onset 245.64°C
Integral -2320.47 mJ
normalized -227.5 Jg^-1
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
STARe SW 9.10

Figure 98

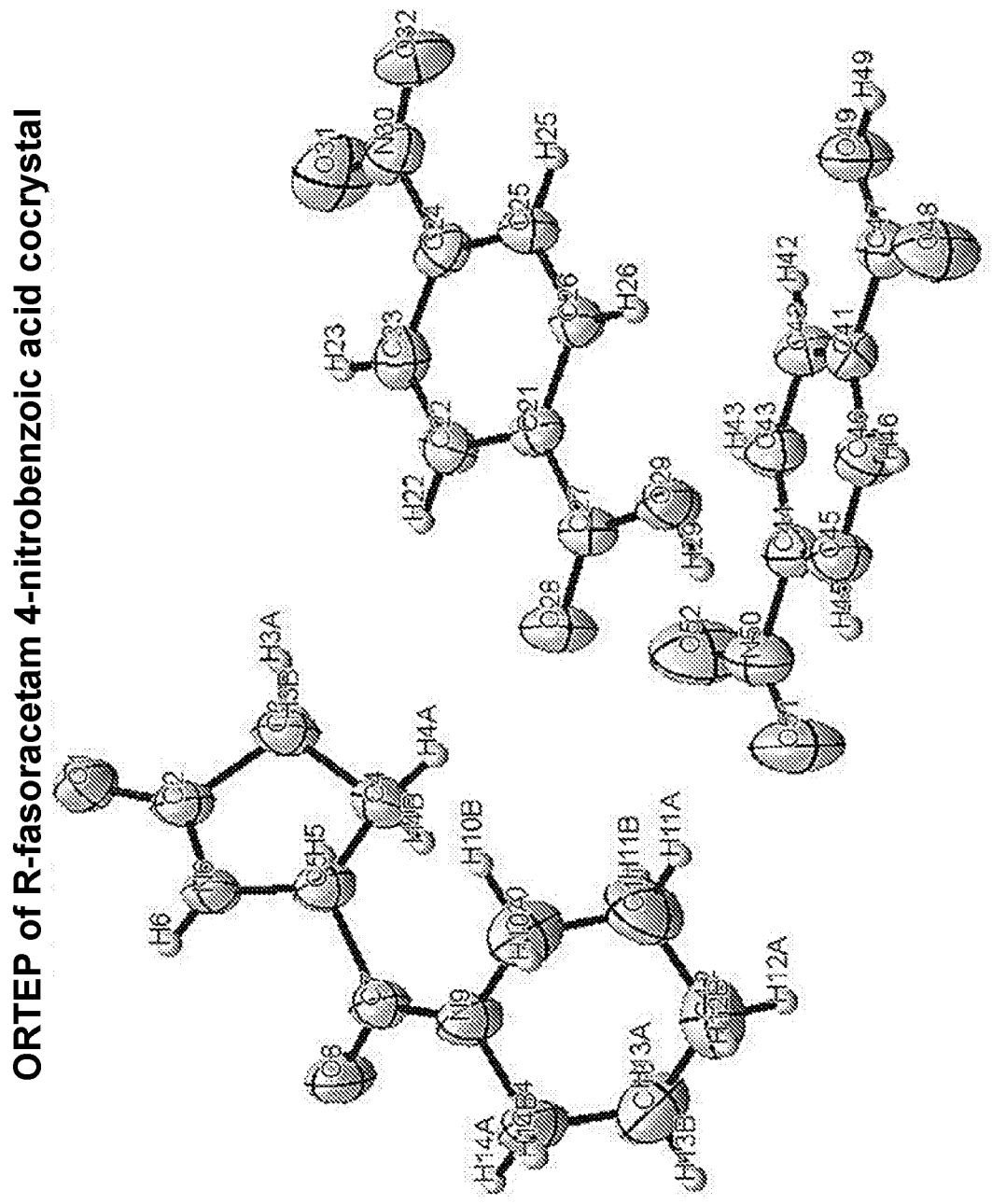


Figure 99

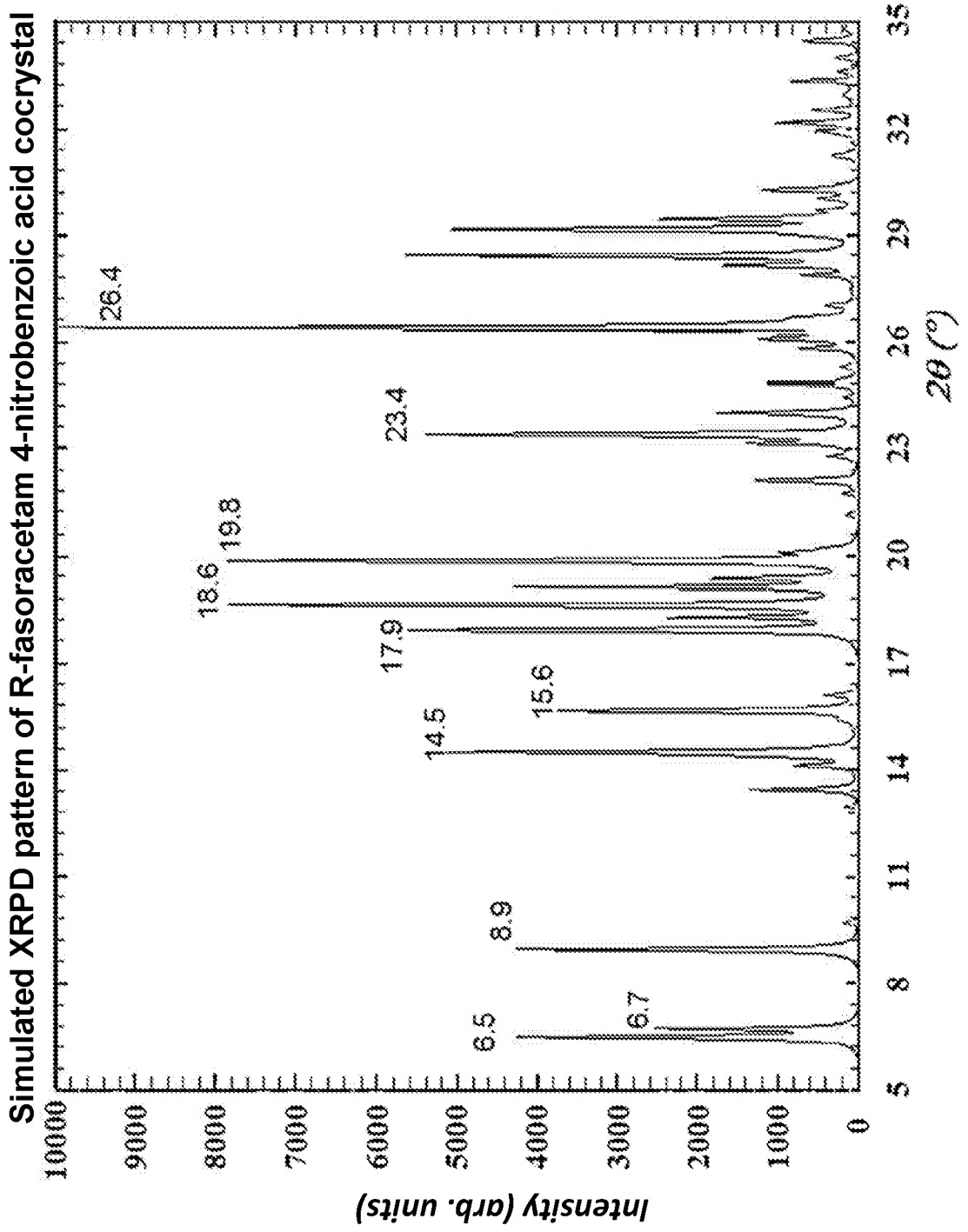

Simulated XRPD pattern of R-fasoracetam 4-nitrobenzoic acid cocrystal
Intensity (arb. units)
2θ (°)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
26.4
23.4
19.8
18.6
17.9
15.6
14.5
8.9
6.7
6.5

Figure 100

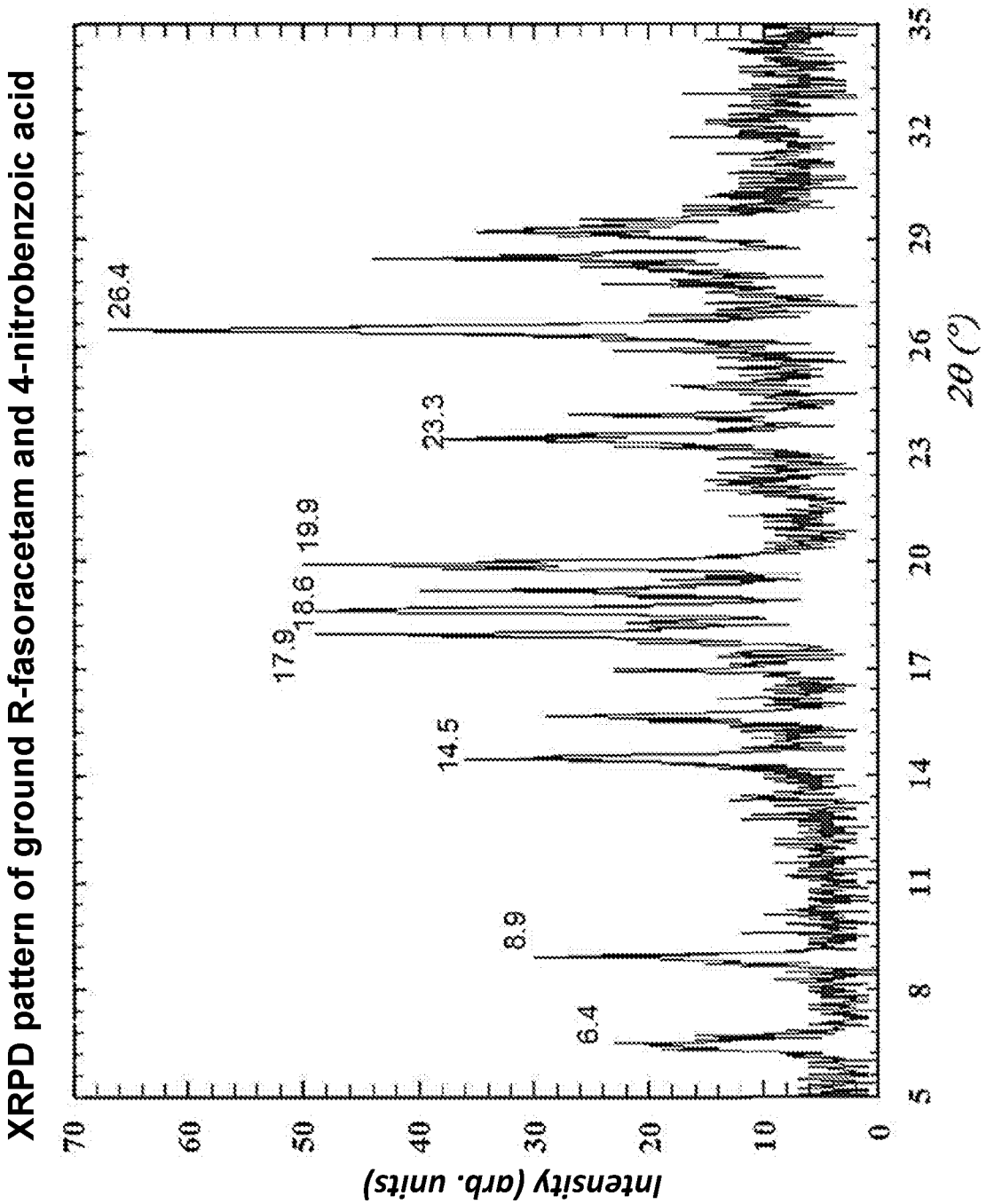

XRPD pattern of ground R-fasoracetam and 4-nitrobenzoic acid
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
5
8
11
14
17
20
23
26
29
32
35
6.4
8.9
14.5
17.9
18.6
19.9
23.3
26.4

Figure 101

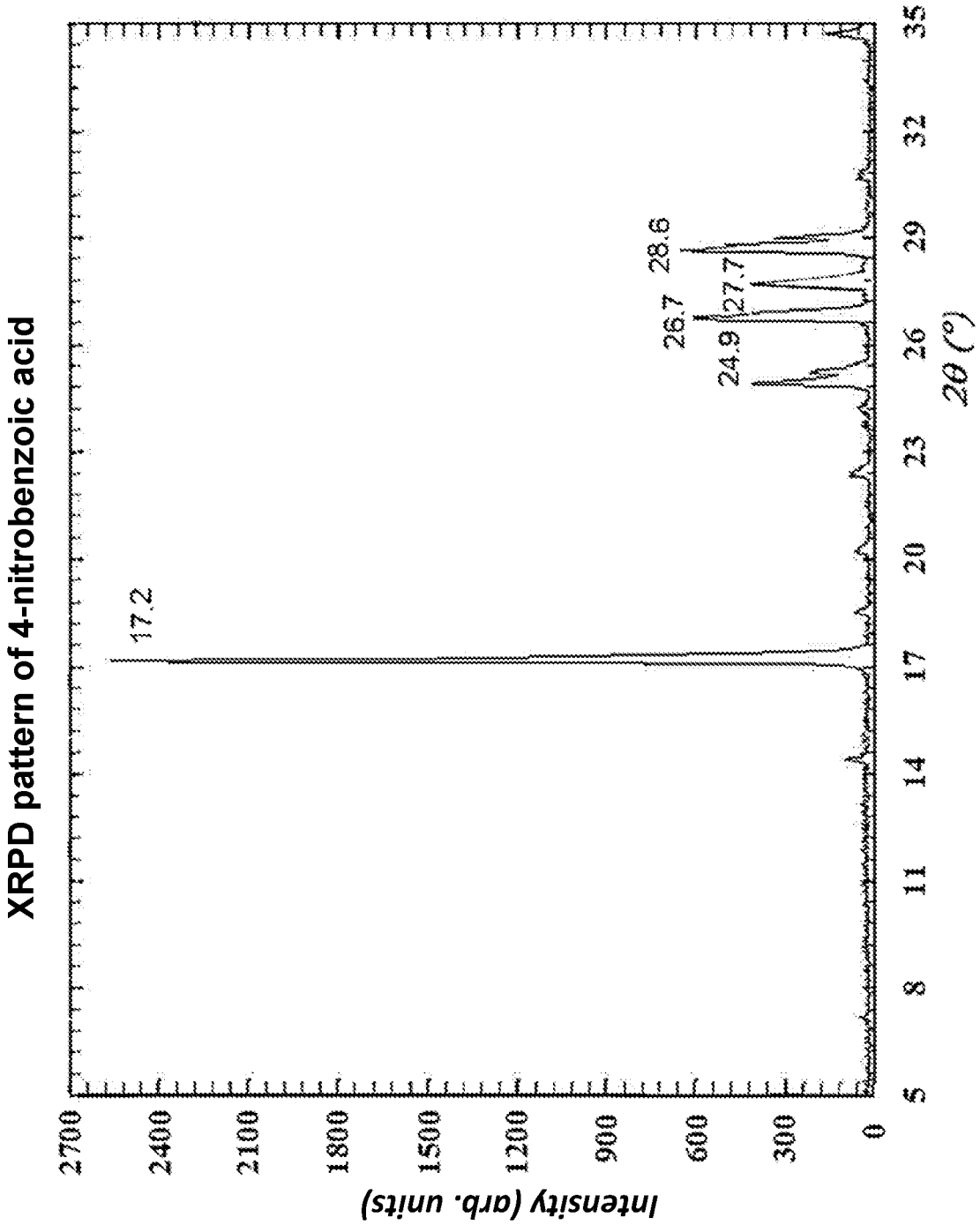

XRPD pattern of 4-nitrobenzoic acid
Intensity (arb. units)
2700
2400
2100
1800
1500
1200
900
600
300
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)
17.2
24.9
26.7
27.7
28.6

Figure 102

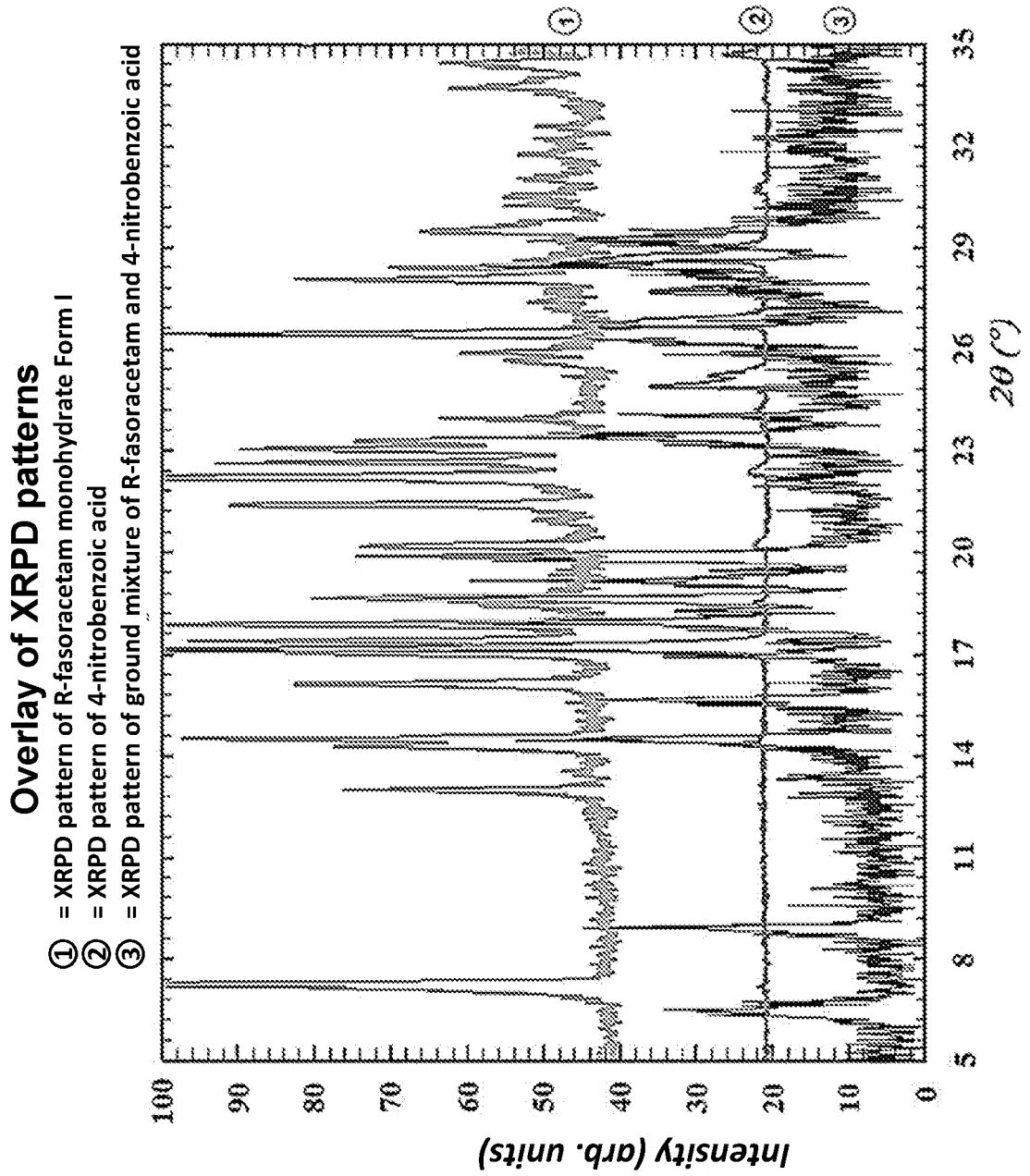

Overlay of XRPD patterns
① = XRPD pattern of R-fasoracetam monohydrate Form I
② = XRPD pattern of 4-nitrobenzoic acid
③ = XRPD pattern of ground mixture of R-fasoracetam and 4-nitrobenzoic acid
Intensity (arb. units)
2θ (°)

Figure 103

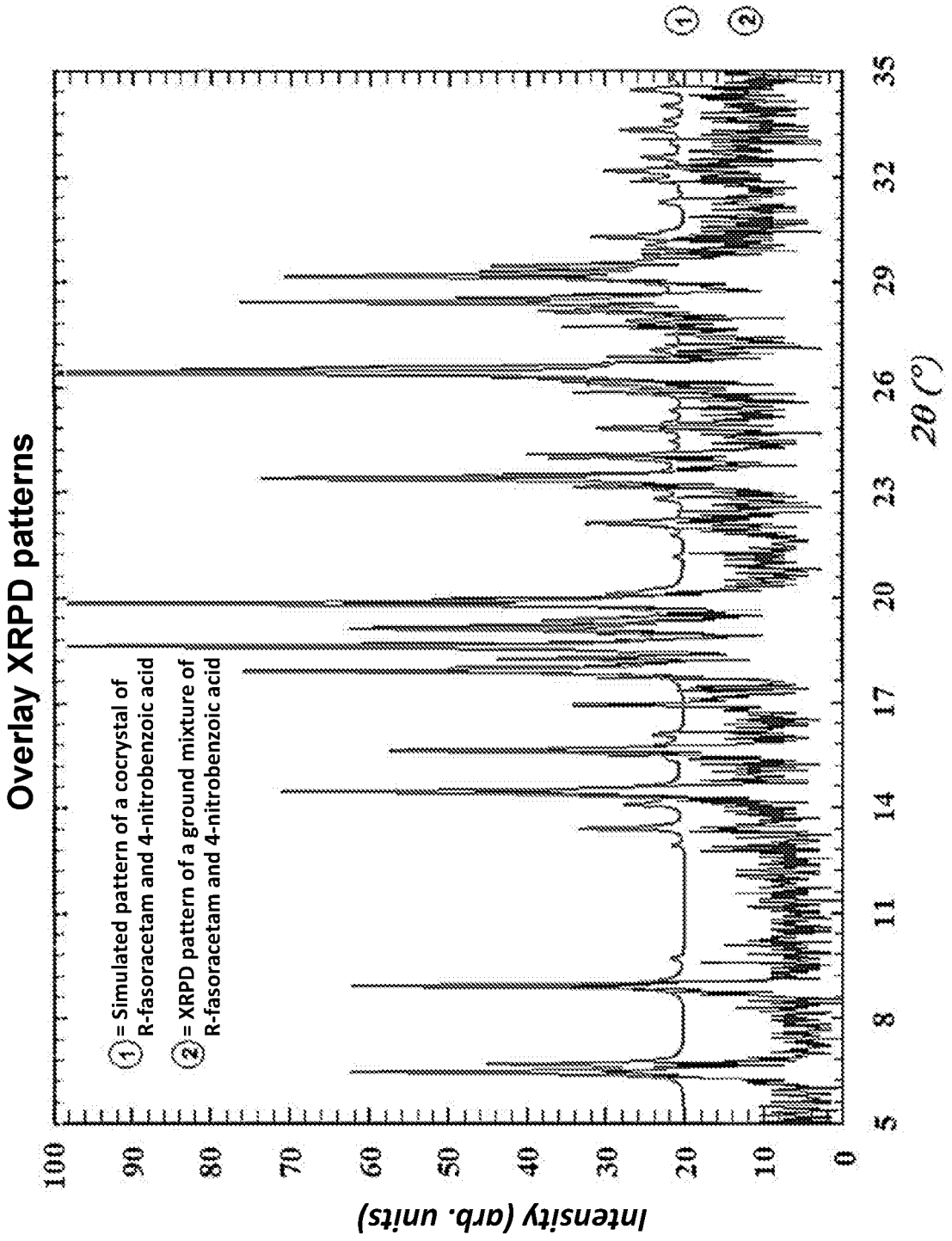

Overlay XRPD patterns
1 = Simulated pattern of a cocrystal of R-fasoracetam and 4-nitrobenzoic acid
2 = XRPD pattern of a ground mixture of R-fasoracetam and 4-nitrobenzoic acid
Intensity (arb. units)
2θ (°)
100
90
80
70
60
50
40
30
20
10
0
5
8
11
14
17
20
23
26
29
32
35

Figure 104

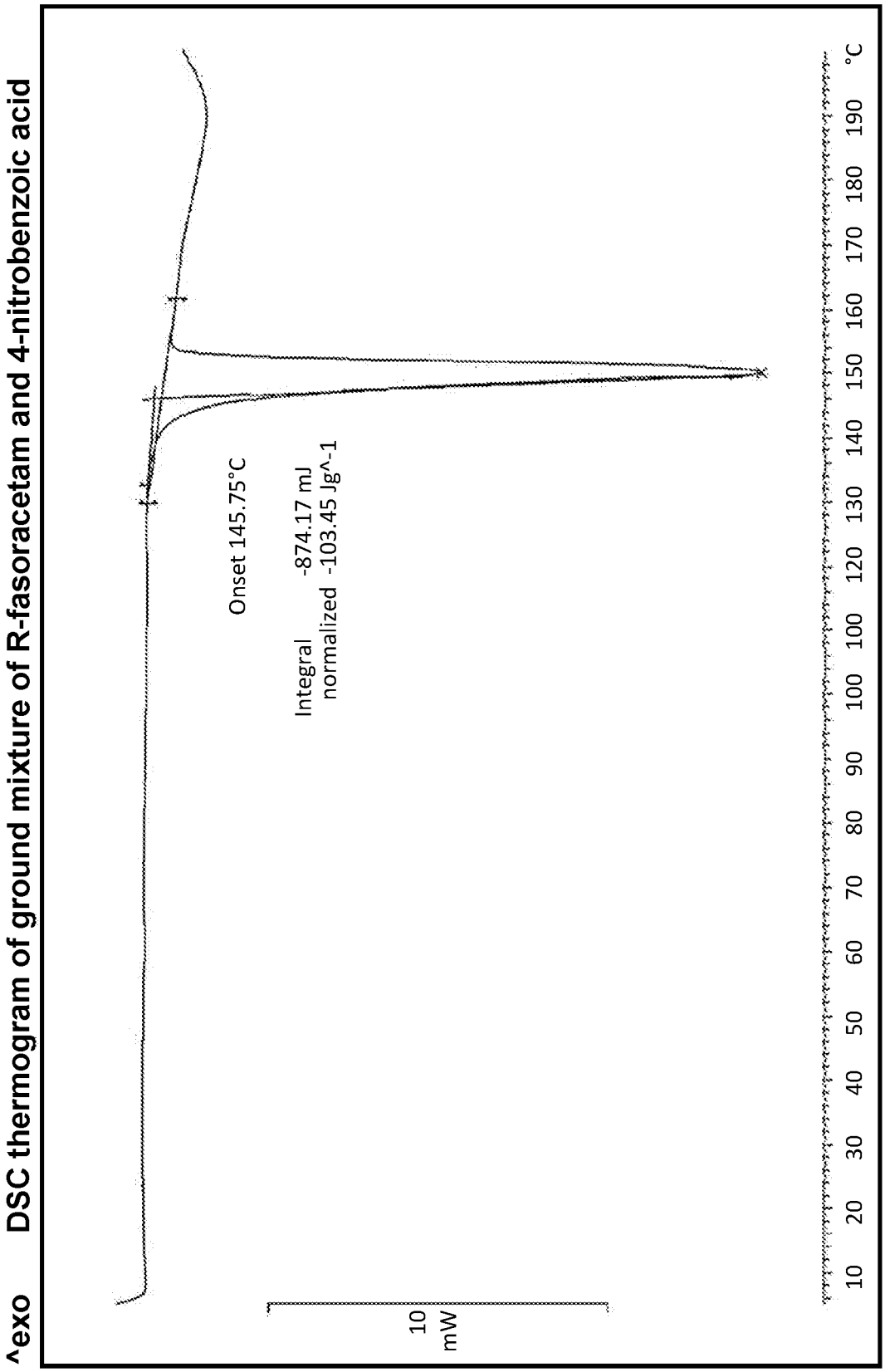

^exo DSC thermogram of ground mixture of R-fasoracetam and 4-nitrobenzoic acid
Onset 145.75°C
Integral -874.17 mJ
normalized -103.45 Jg^-1
10
mW
10 20 30 40 50 60 70 80 90 100 100 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 105

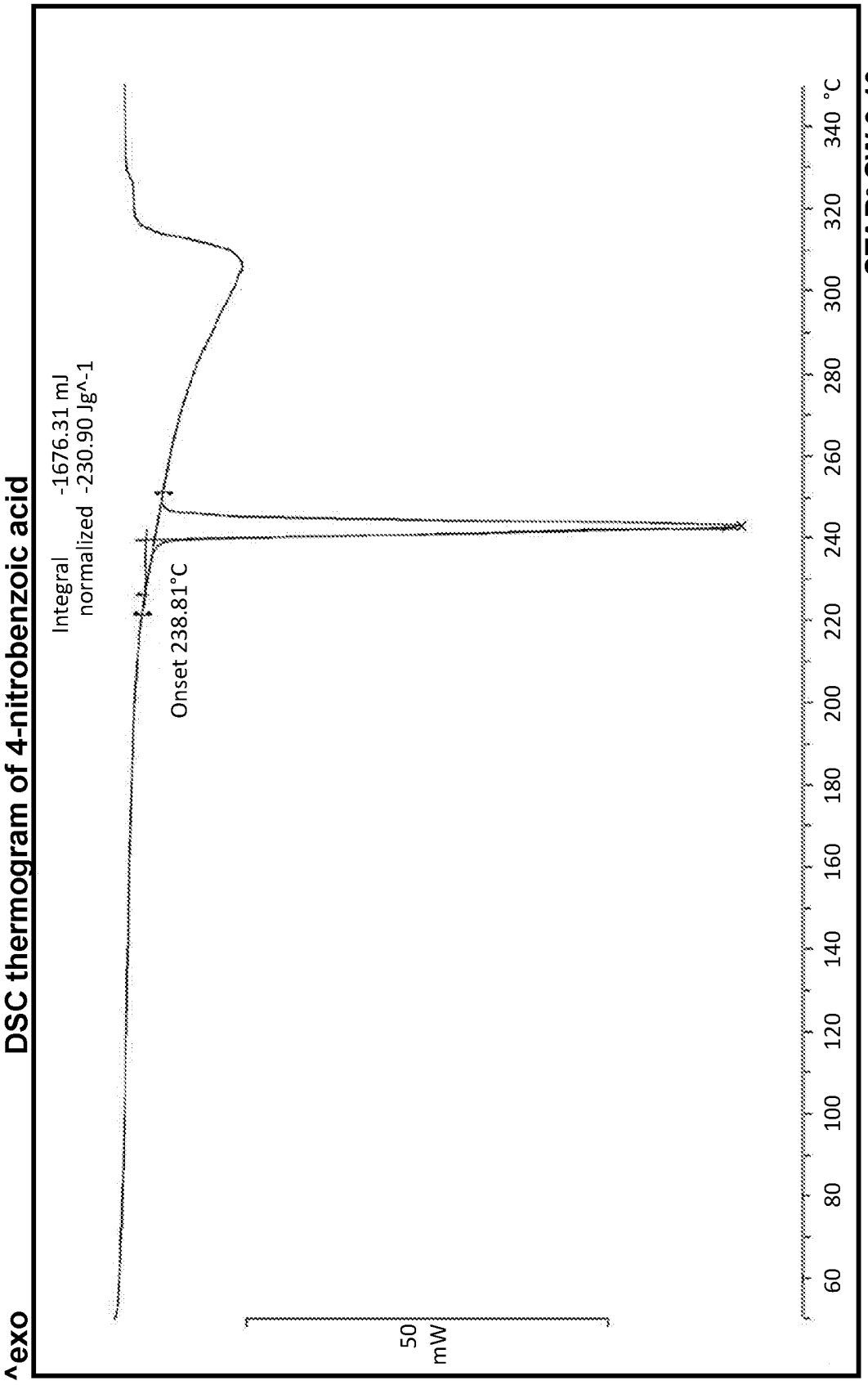

DSC thermogram of 4-nitrobenzoic acid
^exo
Integral -1676.31 mJ
normalized -230.90 Jg^-1
Onset 238.81°C
50
mW
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
STARe SW 9.10

Figure 106

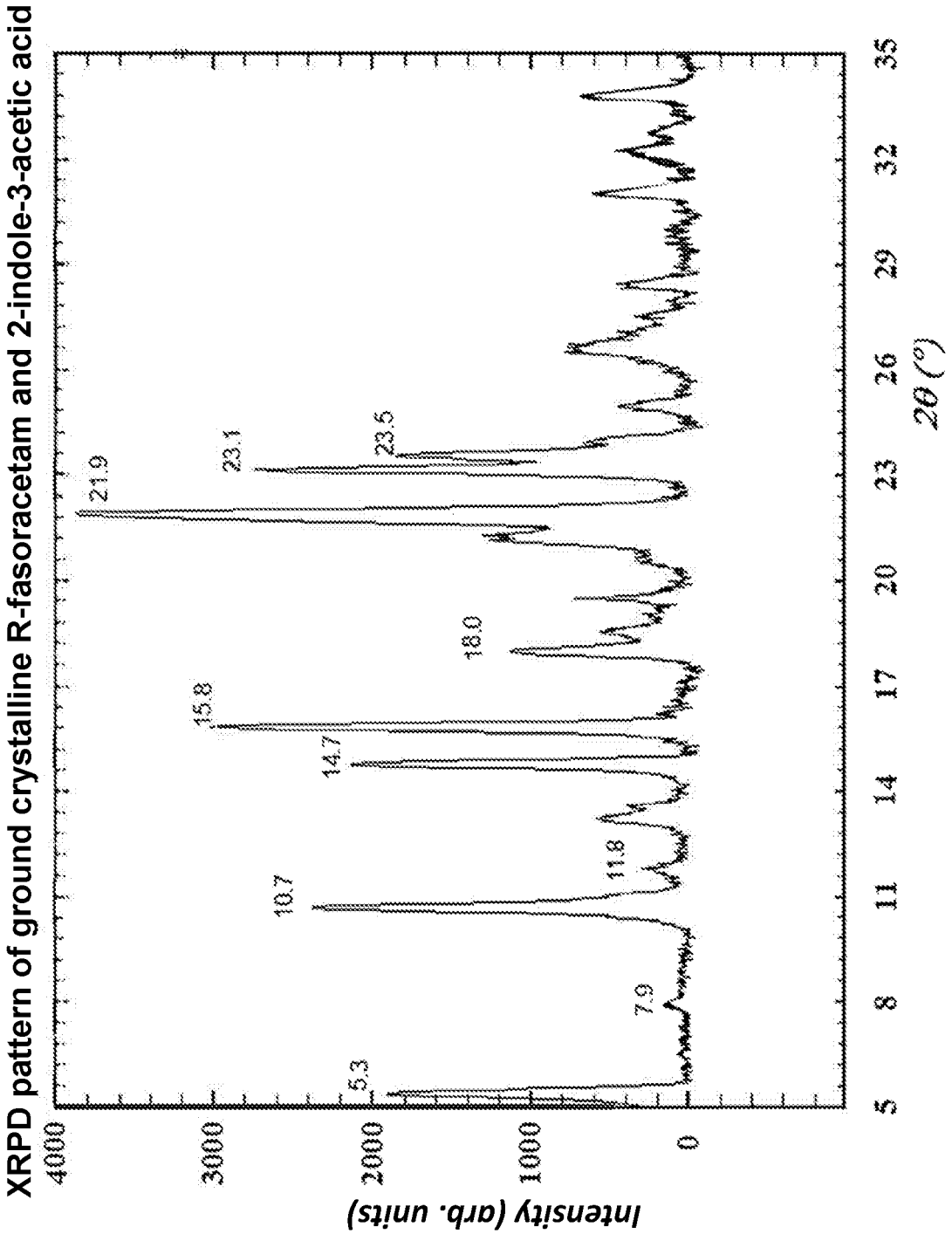

XRPD pattern of ground crystalline R-fasoracetam and 2-indole-3-acetic acid
Intensity (arb. units)
2θ (°)
4000
3000
2000
1000
0
5
8
11
14
17
20
23
26
29
32
35
21.9
23.1
23.5
18.0
15.8
14.7
10.7
11.8
7.9
5.3

Figure 107

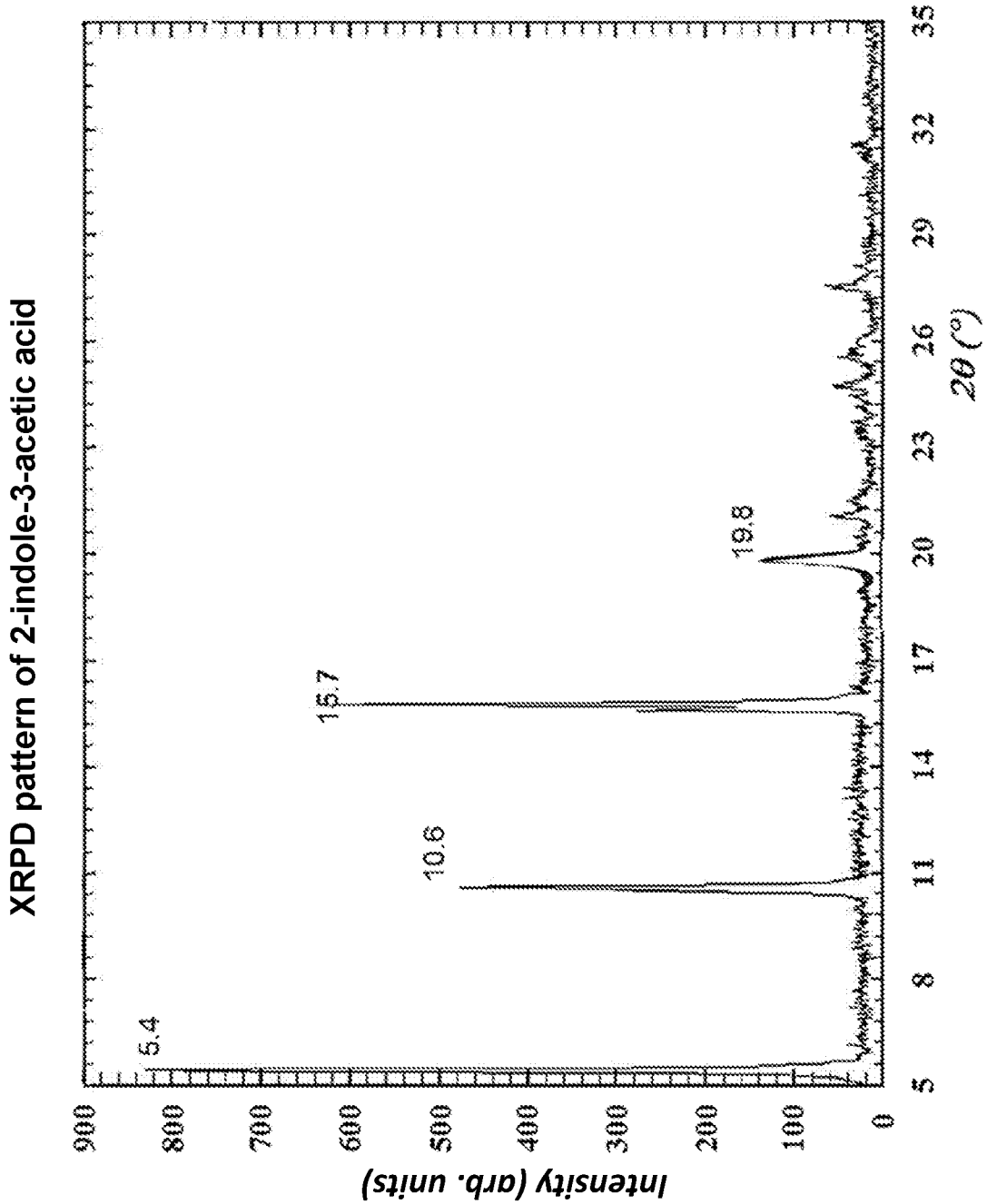

XRPD pattern of 2-indole-3-acetic acid
Intensity (arb. units)
2θ (°)
5.4
10.6
15.7
19.8
0
100
200
300
400
500
600
700
800
900
5
8
11
14
17
20
23
26
29
32
35

Figure 108

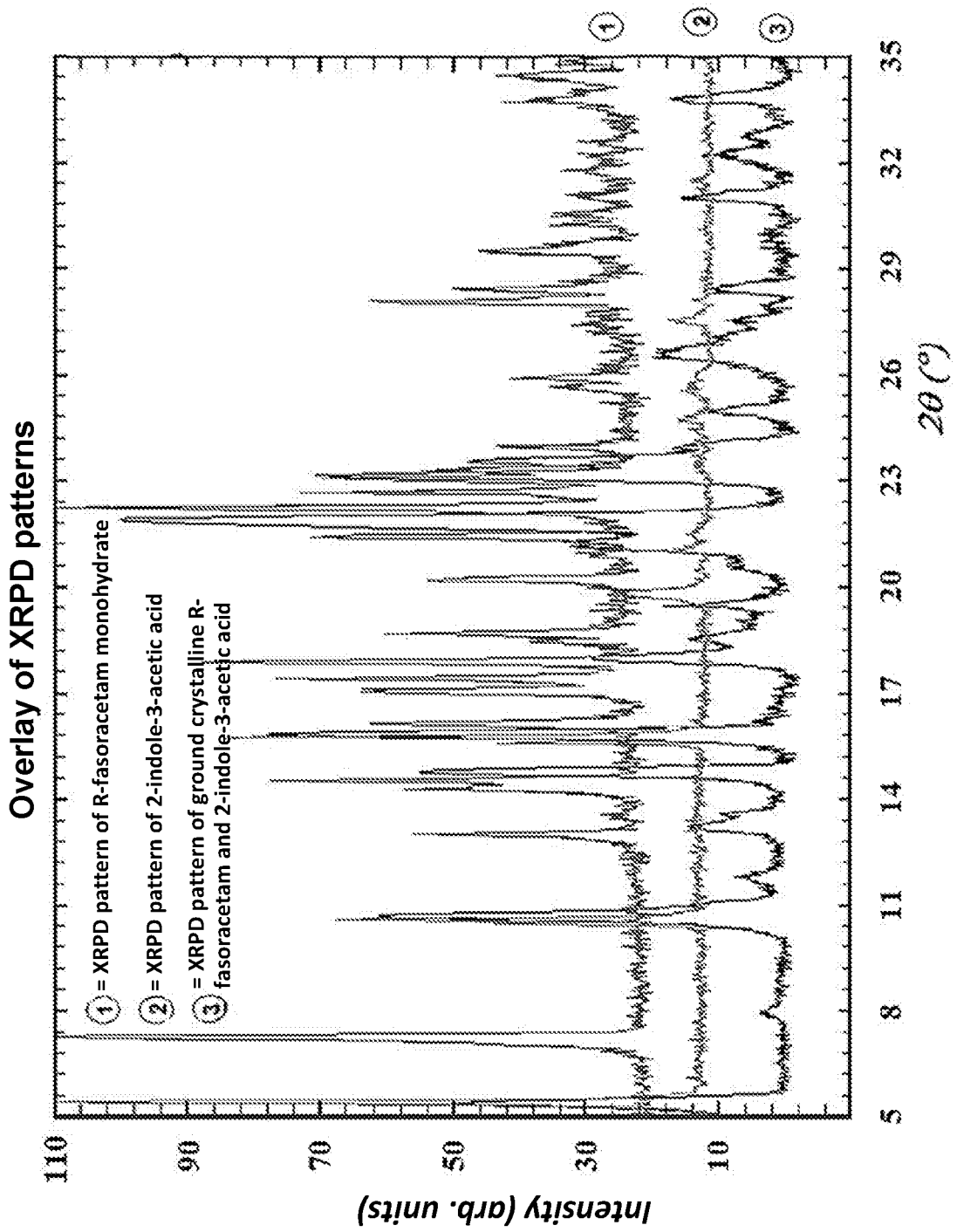
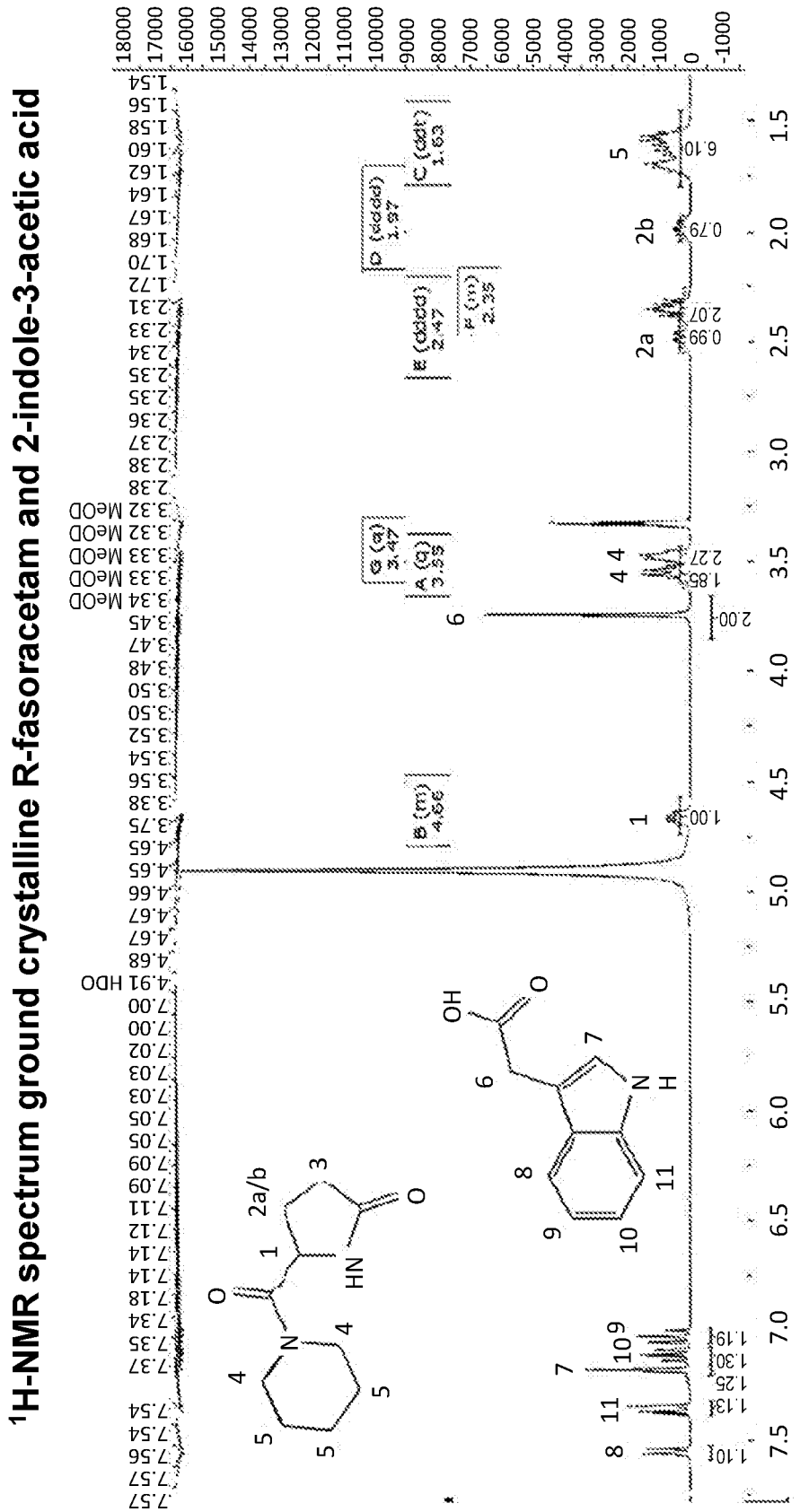

Overlay of XRPD patterns
① = XRPD pattern of R-fasoracetam monohydrate
② = XRPD pattern of 2-indole-3-acetic acid
③ = XRPD pattern of ground crystalline R-fasoracetam and 2-indole-3-acetic acid
Intensity (arb. units)
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 109



1H-NMR spectrum ground crystalline R-fasoracetam and 2-indole-3-acetic acid
F1 (ppm)

Figure 110

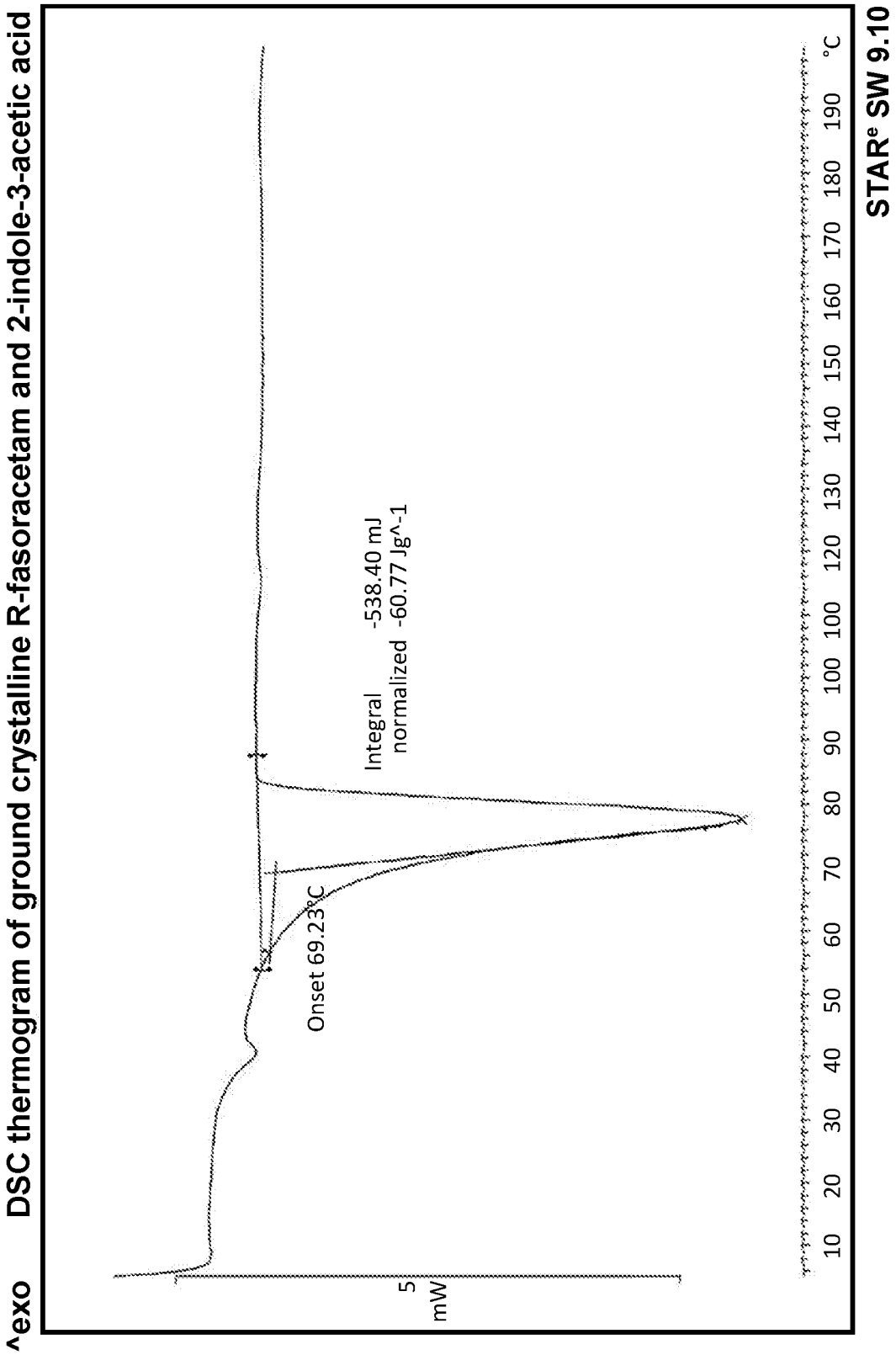

^exo
DSC thermogram of ground crystalline R-fasoracetam and 2-indole-3-acetic acid
5
mW
Onset 69.23°C
Integral -538.40 mJ
normalized -60.77 Jg^-1
10 20 30 40 50 60 70 80 90 100 100 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 111

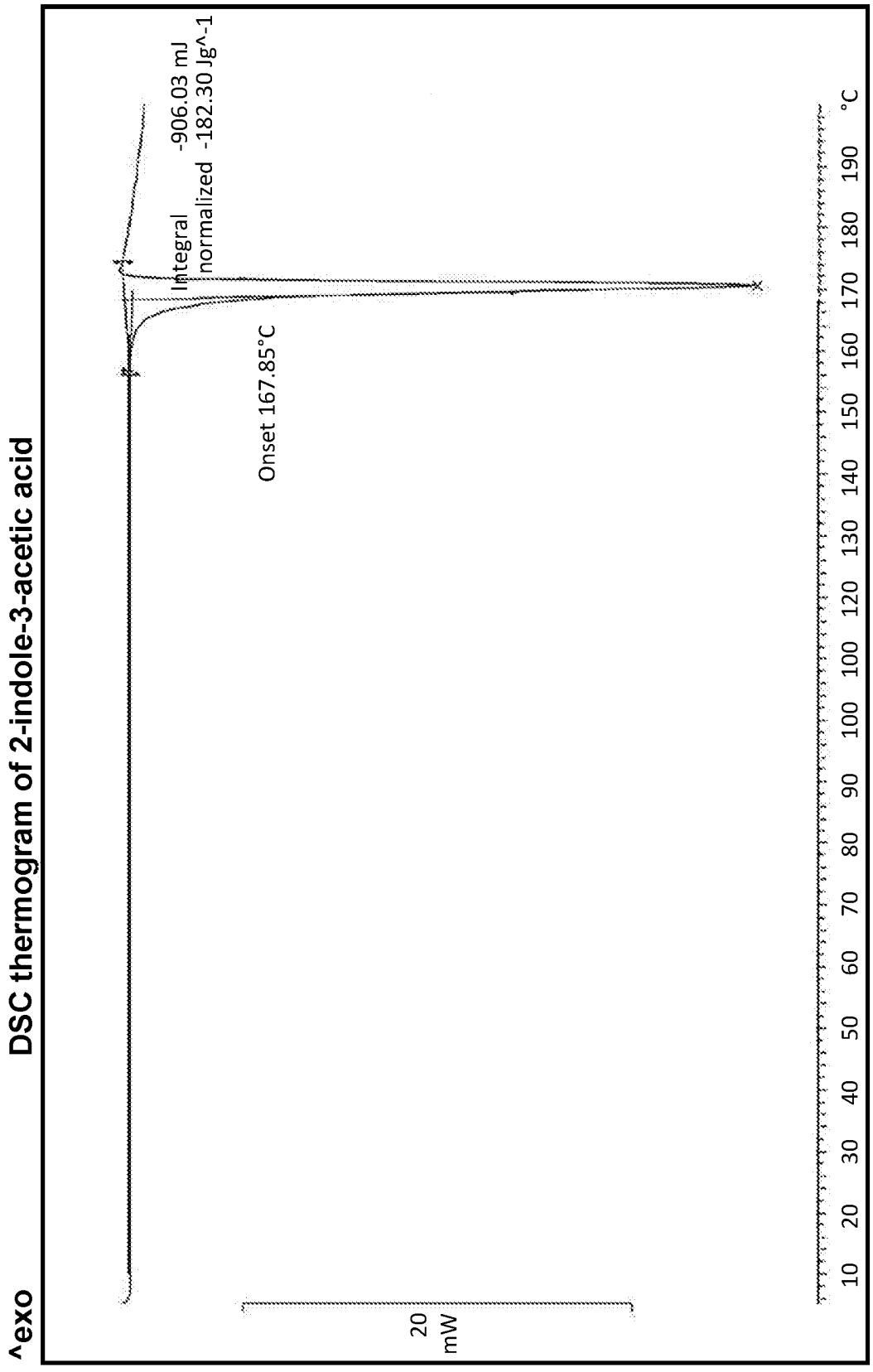

DSC thermogram of 2-indole-3-acetic acid
^exo
20
mW
Onset 167.85°C
Integral -906.03 mJ
normalized -182.30 Jg^-1
10 20 30 40 50 60 70 80 90 100 100 120 130 140 150 160 170 180 190 °C
STARe SW 9.10

Figure 112

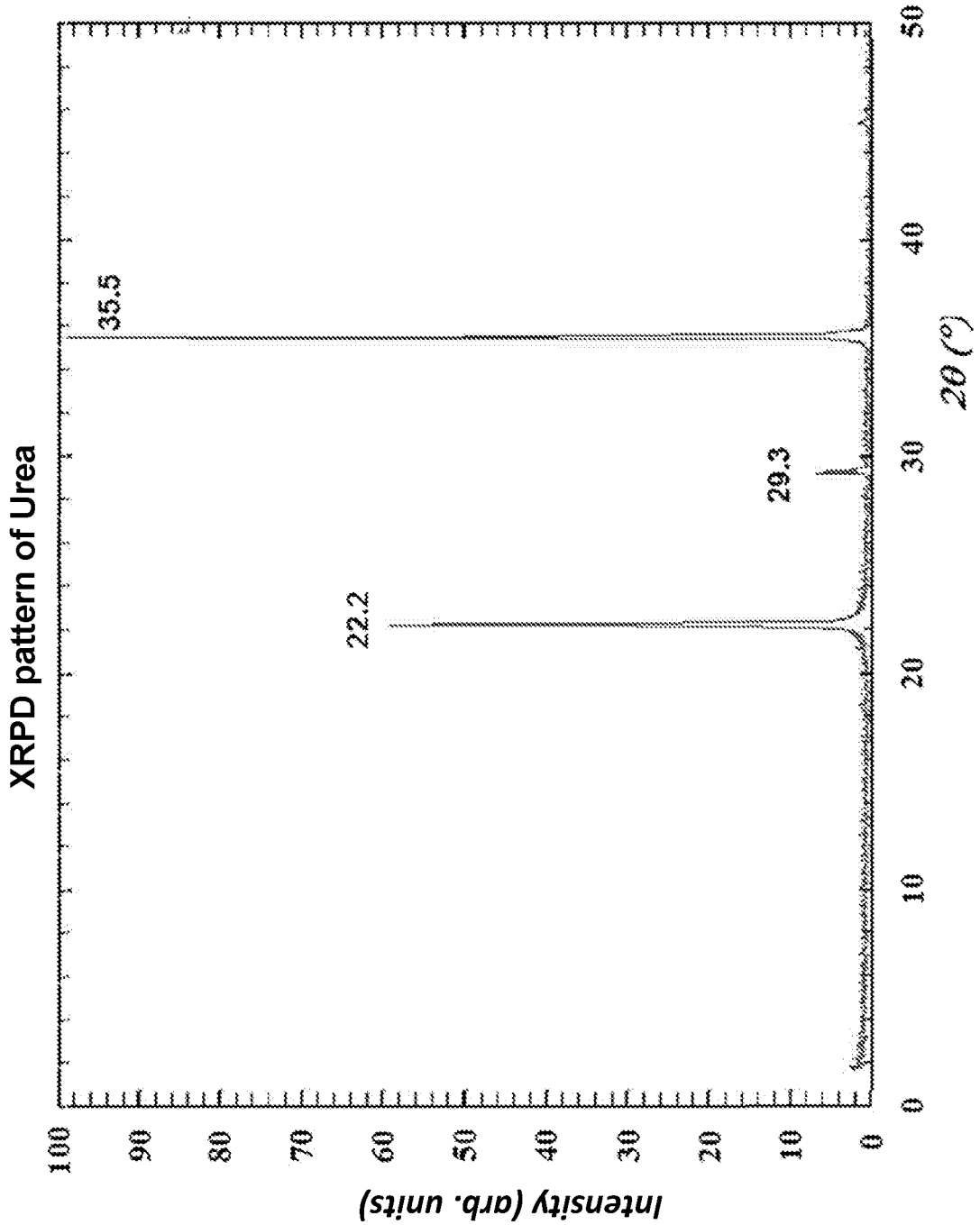

XRPD pattern of Urea
35.5
29.3
22.2
Intensity (arb. units)
2θ (°)
0
10
20
30
40
50
60
70
80
90
100

Figure 113

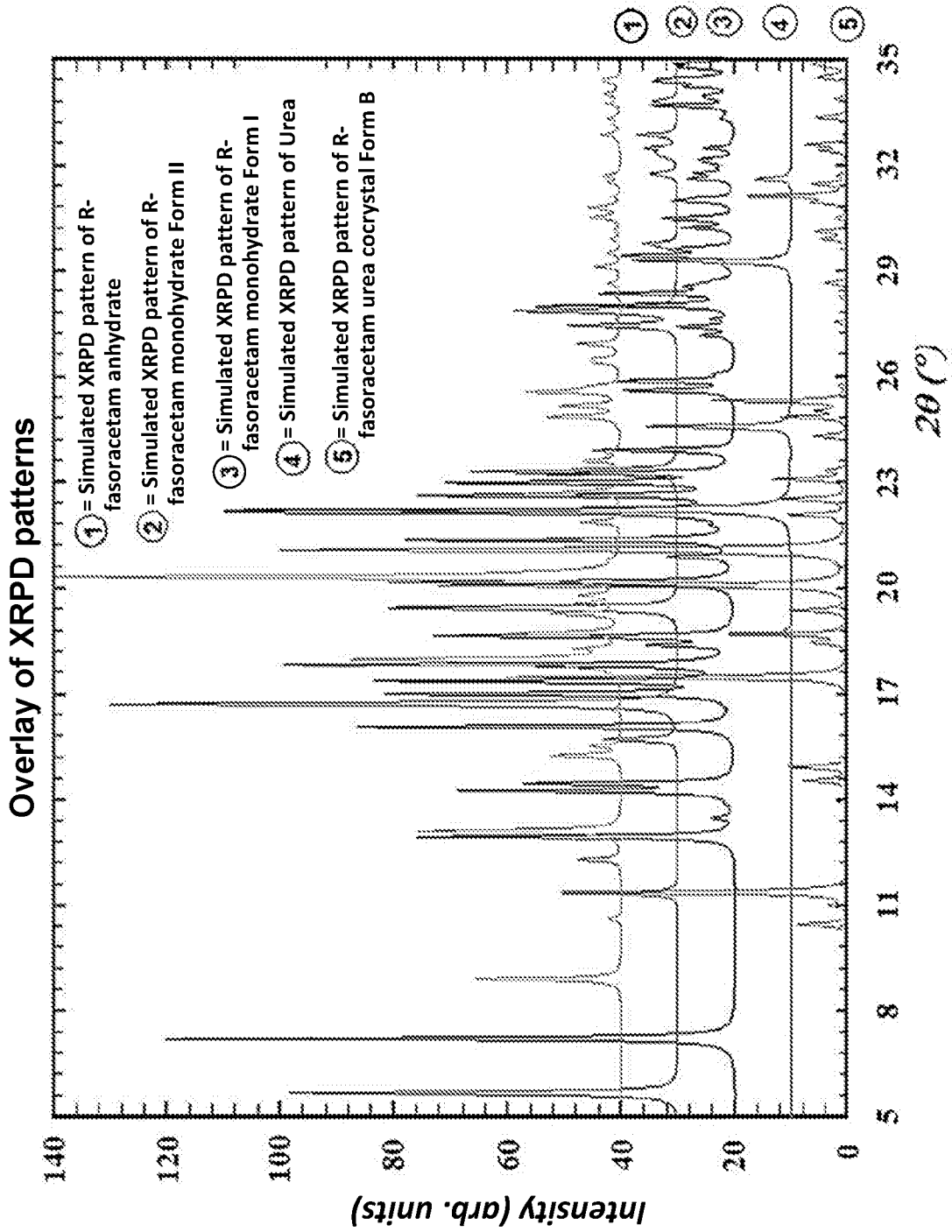

Overlay of XRPD patterns
1 = Simulated XRPD pattern of R-fasoracetam anhydrate
2 = Simulated XRPD pattern of R-fasoracetam monohydrate Form II
3 = Simulated XRPD pattern of R-fasoracetam monohydrate Form I
4 = Simulated XRPD pattern of Urea
5 = Simulated XRPD pattern of R-fasoracetam urea cocrystal Form B
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
5
8
11
14
17
20
23
26
29
32
35

Figure 114

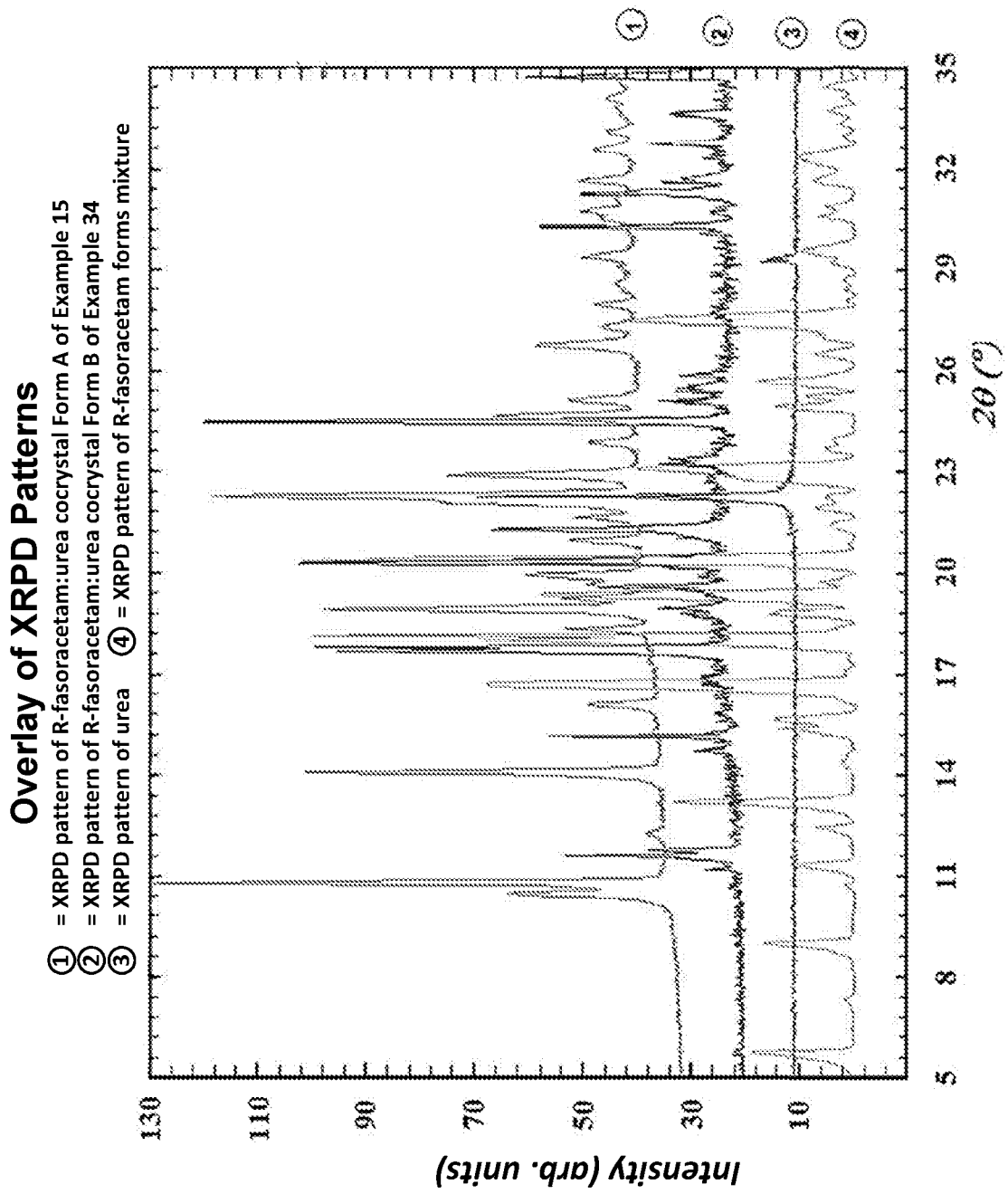

Overlay of XRPD Patterns
① = XRPD pattern of R-fasoracetam:urea cocrystal Form A of Example 15
② = XRPD pattern of R-fasoracetam:urea cocrystal Form B of Example 34
③ = XRPD pattern of urea
④ = XRPD pattern of R-fasoracetam forms mixture
Intensity (arb. units)
130
110
90
70
50
30
10
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 115

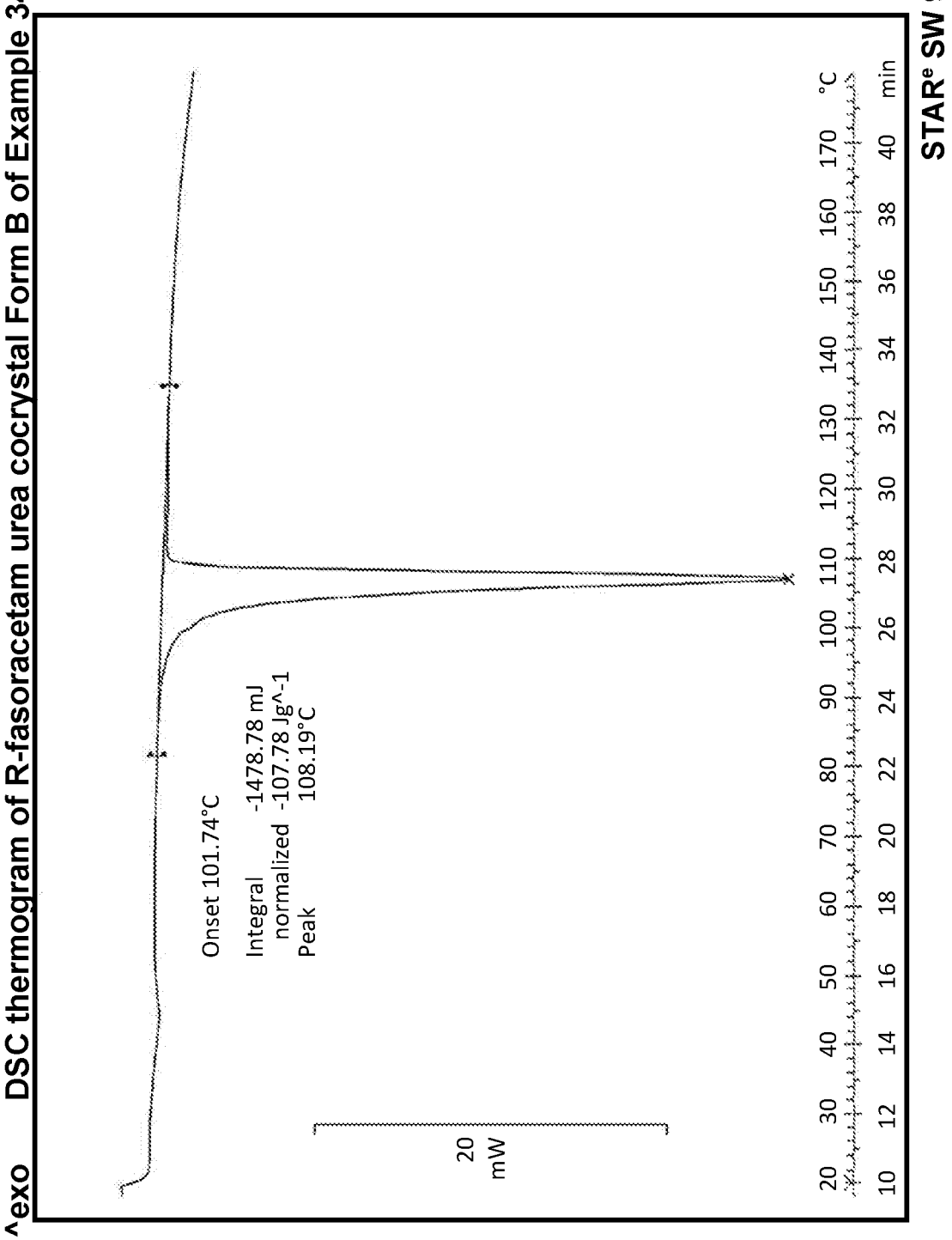

^exo DSC thermogram of R-fasoracetam urea cocrystal Form B of Example 34
Onset 101.74°C
Integral -1478.78 mJ
normalized -107.78 Jg^-1
Peak 108.19°C
20
mW
10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 min
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 °C
STARe SW 9.10

Figure 116

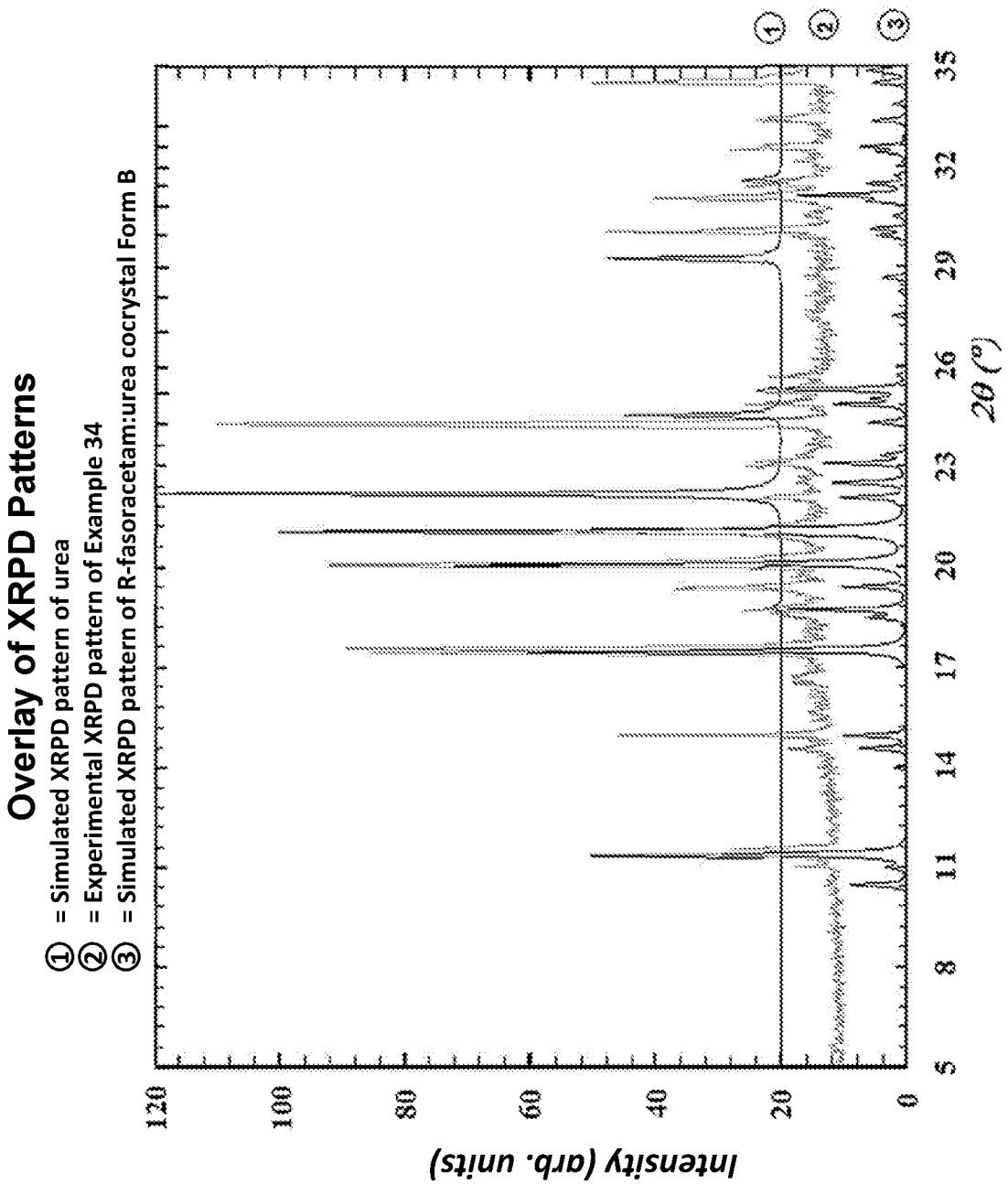

Overlay of XRPD Patterns
① = Simulated XRPD pattern of urea
② = Experimental XRPD pattern of Example 34
③ = Simulated XRPD pattern of R-fasoracetam:urea cocrystal Form B
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
5
8
11
14
17
20
23
26
29
32
35
①
②
③

Figure 117

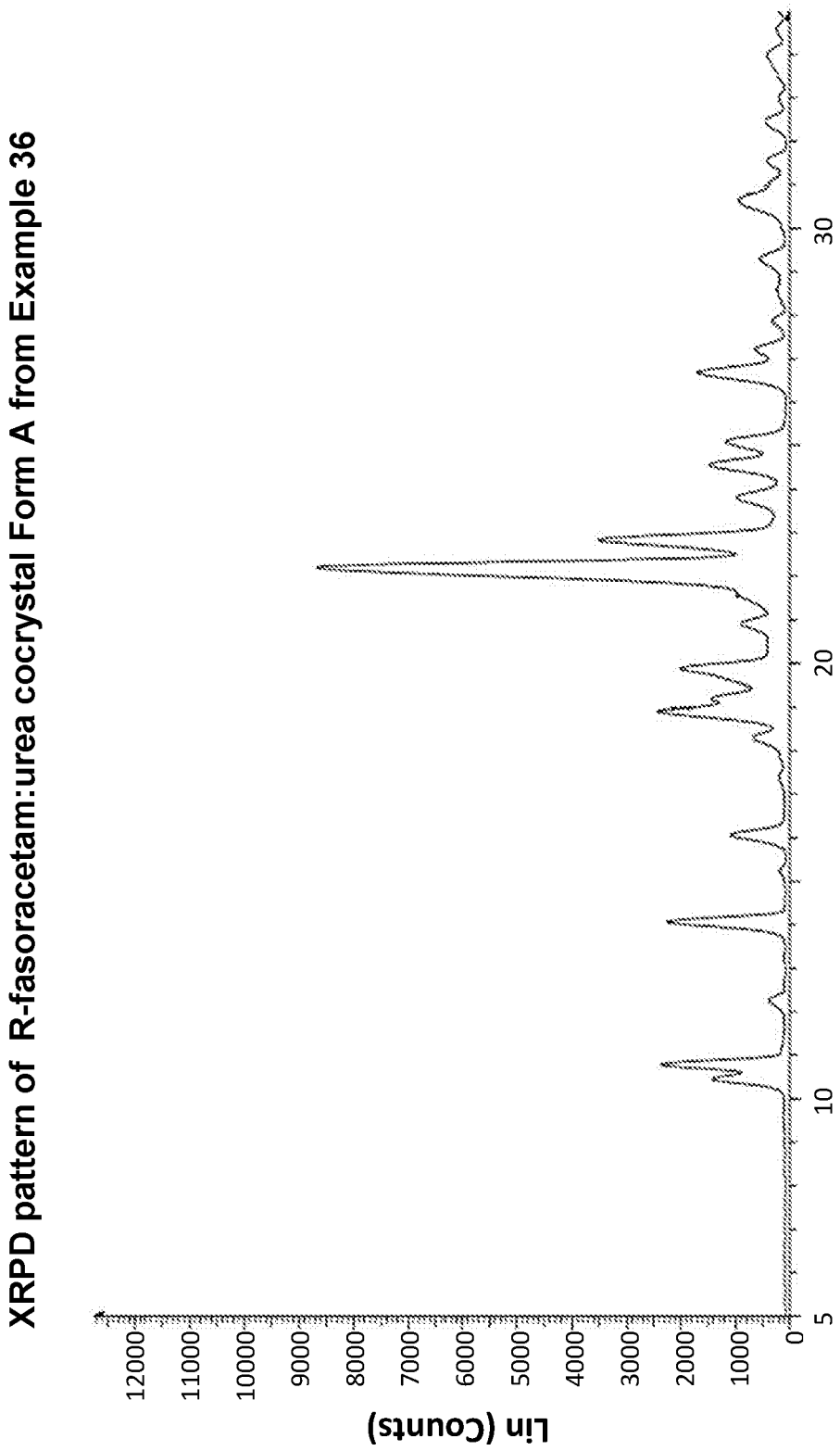

XRPD pattern of R-fasoracetam:urea cocrystal Form A from Example 36
Lin (Counts)
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
10
20
30
2-Theta - Scale

Figure 118

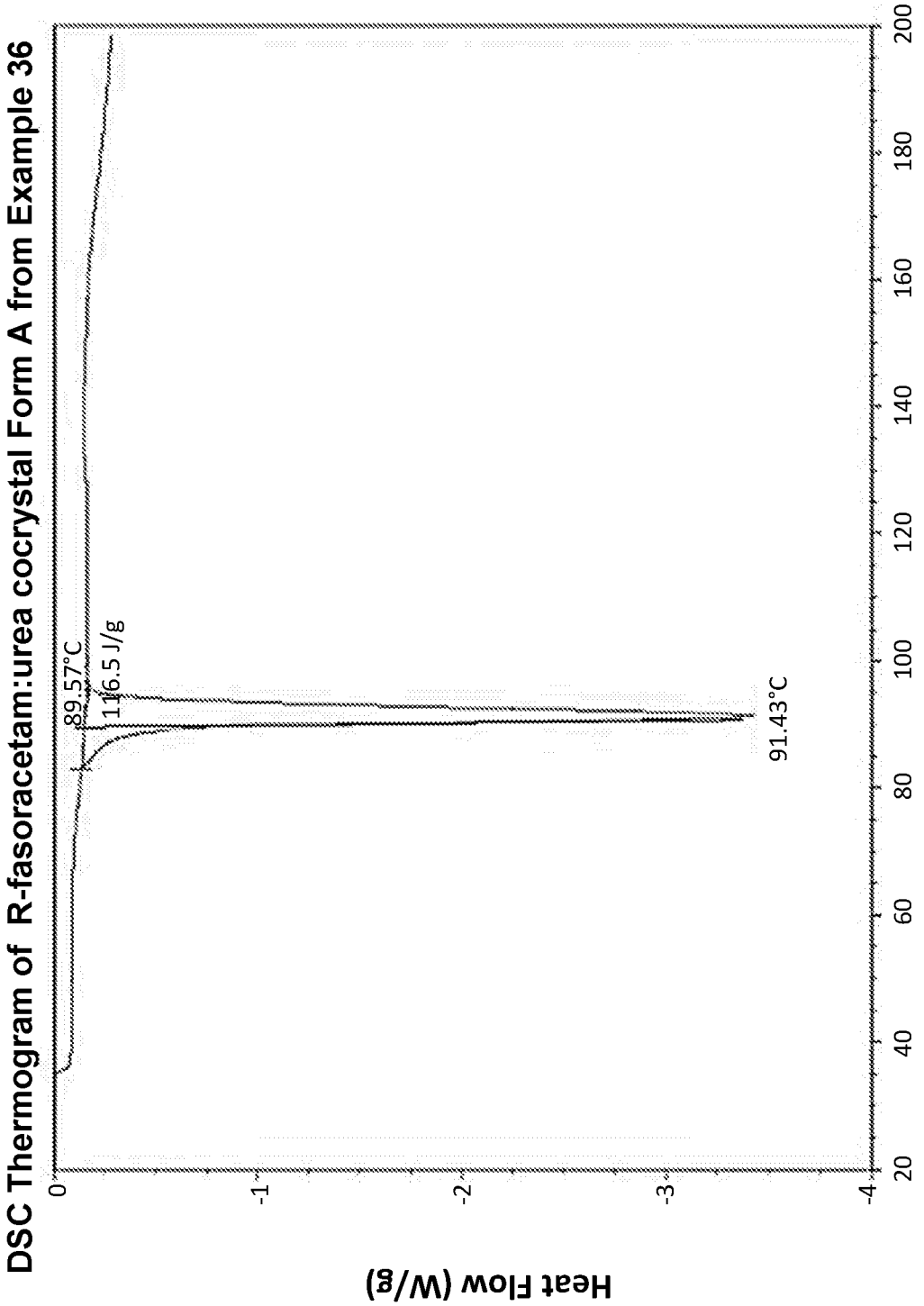

DSC Thermogram of R-fasoracetam:urea cocrystal Form A from Example 36
89.57°C
116.5 J/g
91.43°C
Heat Flow (W/g)
Temperature (°C)
0
-1
-2
-3
-4
20
40
60
80
100
120
140
160
180
200

Figure 119

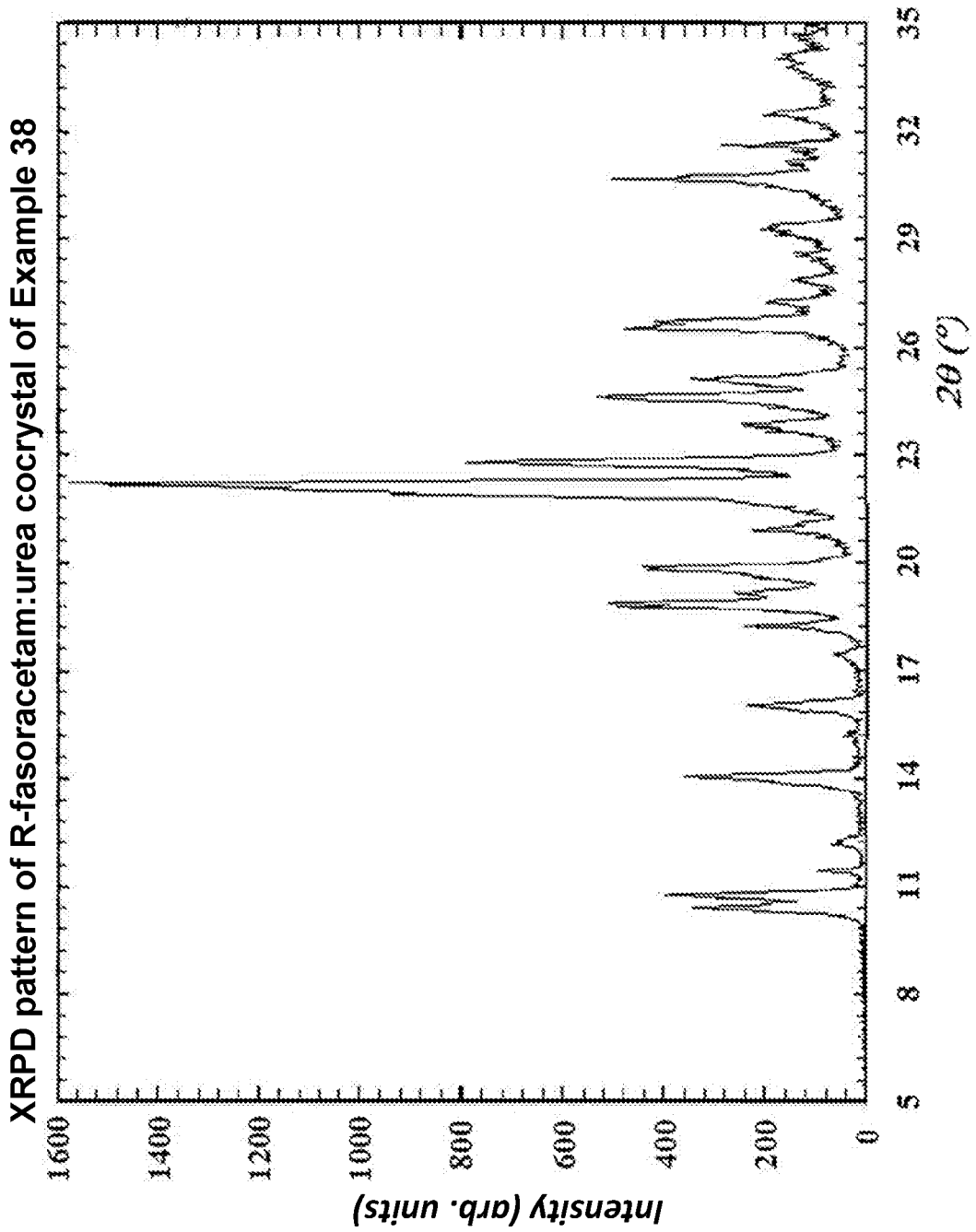

XRPD pattern of R-fasoracetam:urea cocrystal of Example 38
Intensity (arb. units)
1600
1400
1200
1000
800
600
400
200
0
5
8
11
14
17
20
23
26
29
32
35
2θ (°)

Figure 120

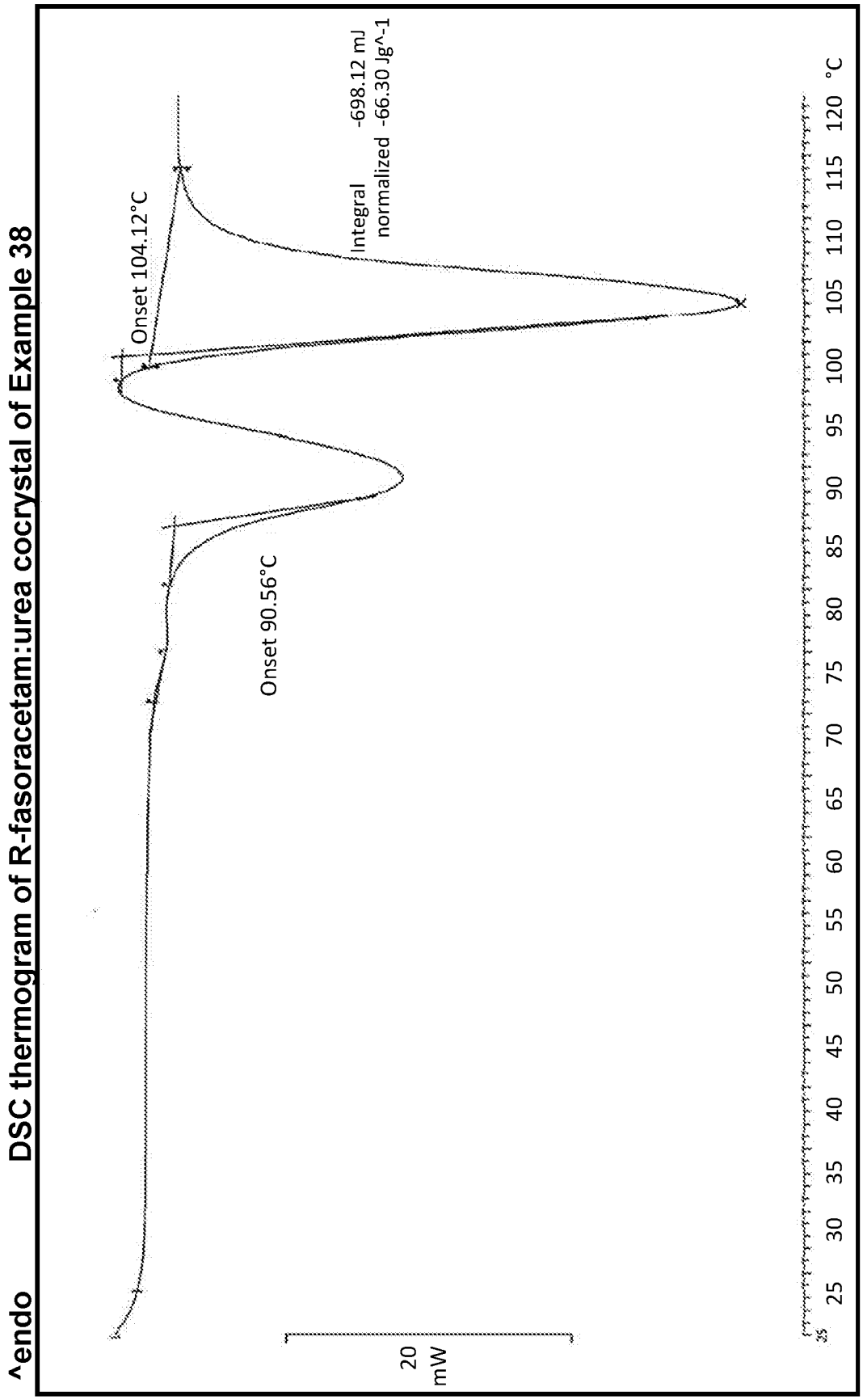

^endo
DSC thermogram of R-fasoracetam:urea cocrystal of Example 38
Onset 104.12°C
Integral -698.12 mJ
normalized -66.30 Jg^-1
Onset 90.56°C
20 mW
25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 °C
STARe SW 9.10

Figure 121

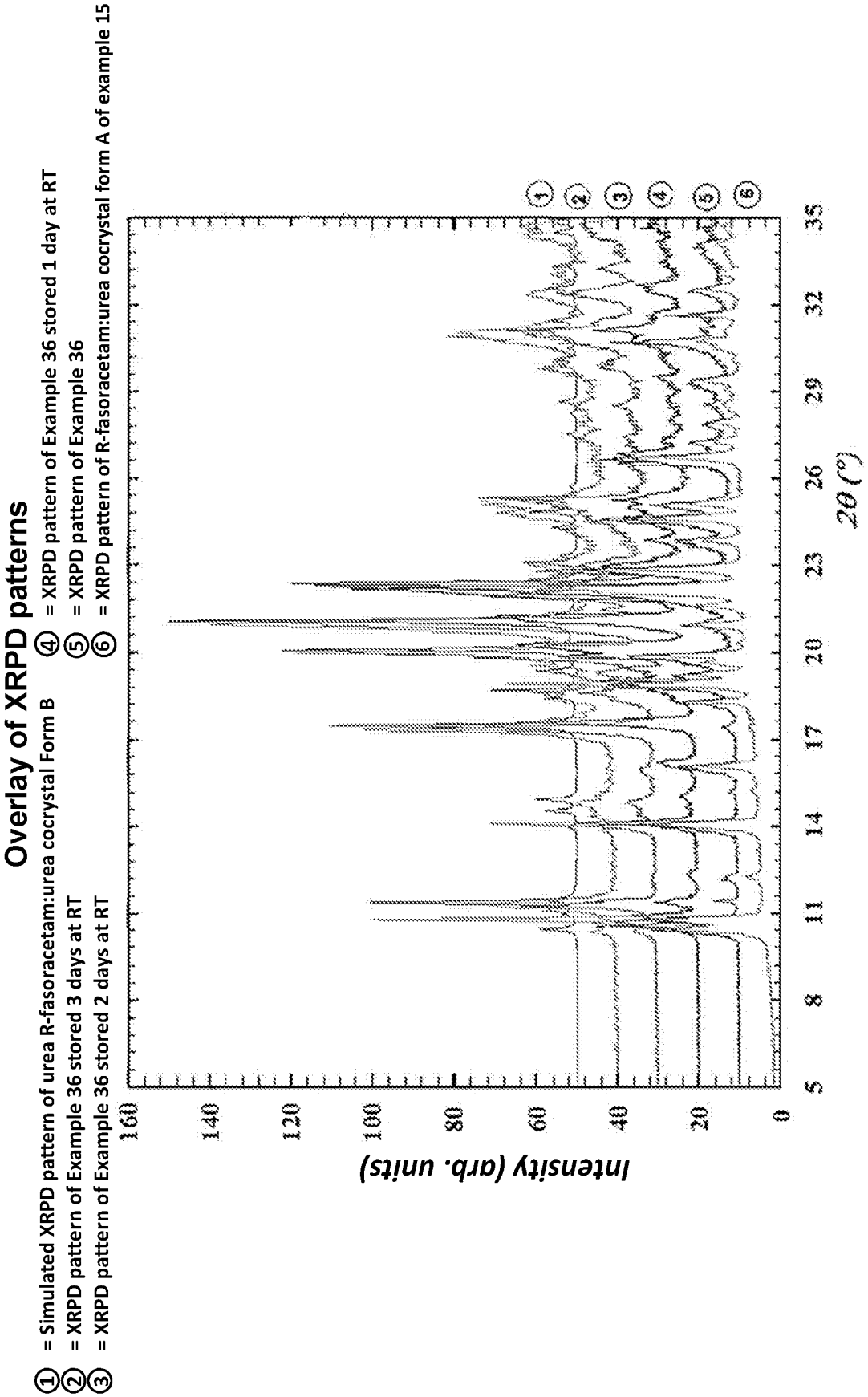

Overlay of XRPD patterns
① = Simulated XRPD pattern of urea R-fasoracetam:urea cocrystal Form B
② = XRPD pattern of Example 36 stored 3 days at RT
③ = XRPD pattern of Example 36 stored 2 days at RT
④ = XRPD pattern of Example 36 stored 1 day at RT
⑤ = XRPD pattern of Example 36
⑥ = XRPD pattern of R-fasoracetam:urea cocrystal form A of example 15
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
160
5
8
11
14
17
20
23
26
29
32
35

Figure 122

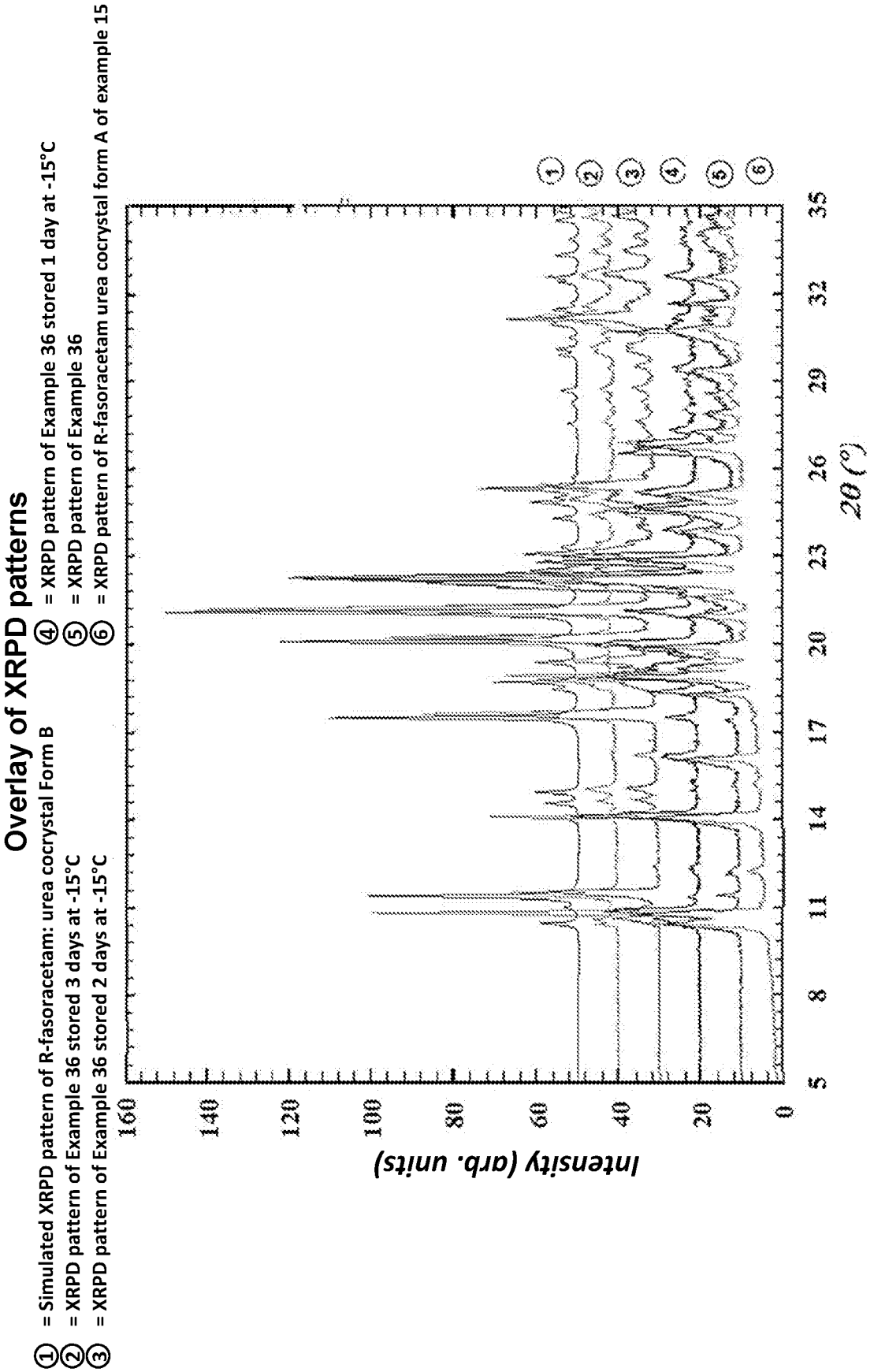

Overlay of XRPD patterns
① = Simulated XRPD pattern of R-fasoracetam: urea cocrystal Form B
② = XRPD pattern of Example 36 stored 3 days at -15°C
③ = XRPD pattern of Example 36 stored 2 days at -15°C
④ = XRPD pattern of Example 36 stored 1 day at -15°C
⑤ = XRPD pattern of Example 36
⑥ = XRPD pattern of R-fasoracetam urea cocrystal form A of example 15
Intensity (arb. units)
2θ (°)
0
20
40
60
80
100
120
140
160
5
8
11
14
17
20
23
26
29
32
35

Figure 123

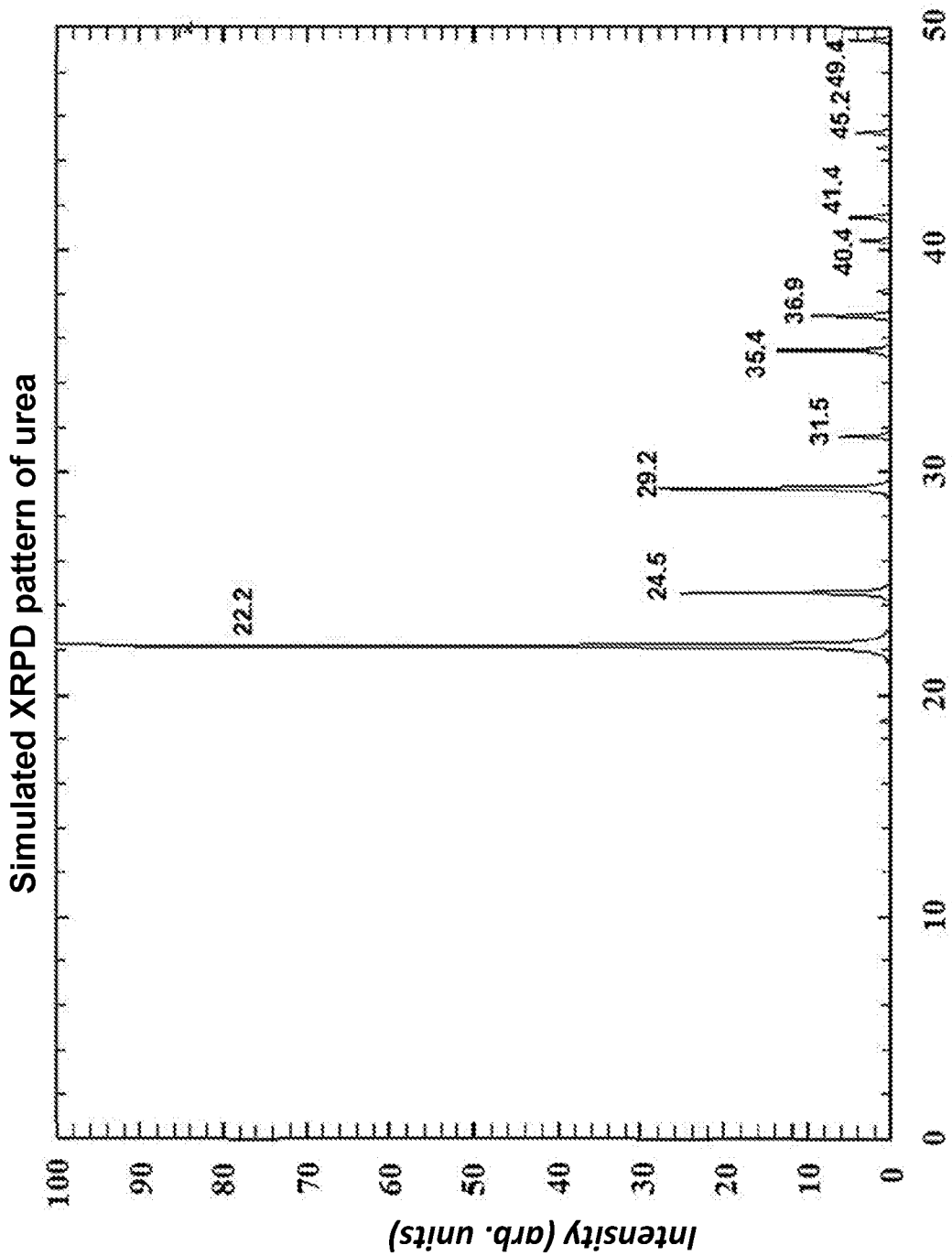

Simulated XRPD pattern of urea
Intensity (arb. units)
2θ (°)
22.2
24.5
29.2
31.5
35.4
36.9
40.4
41.4
45.2
49.4
0
10
20
30
40
50
0
10
20
30
40
50
60
70
80
90
100

Figure 124

Hydrogen bonding pattern of a R-fasoracetam:PABA cocrystal

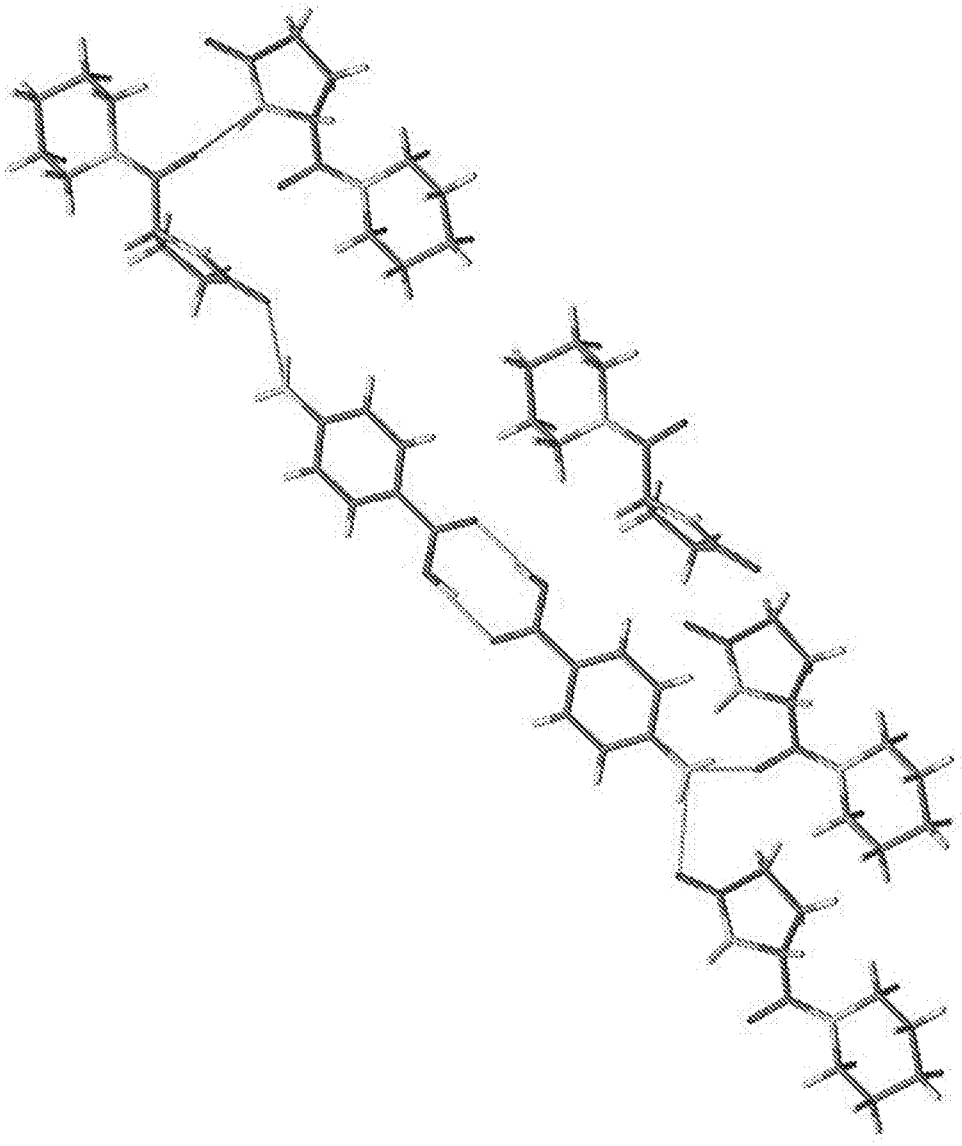


Figure 125

Hydrogen bonding pattern of a R-fasoracetam:4-nitrobenzoic acid cocrystal

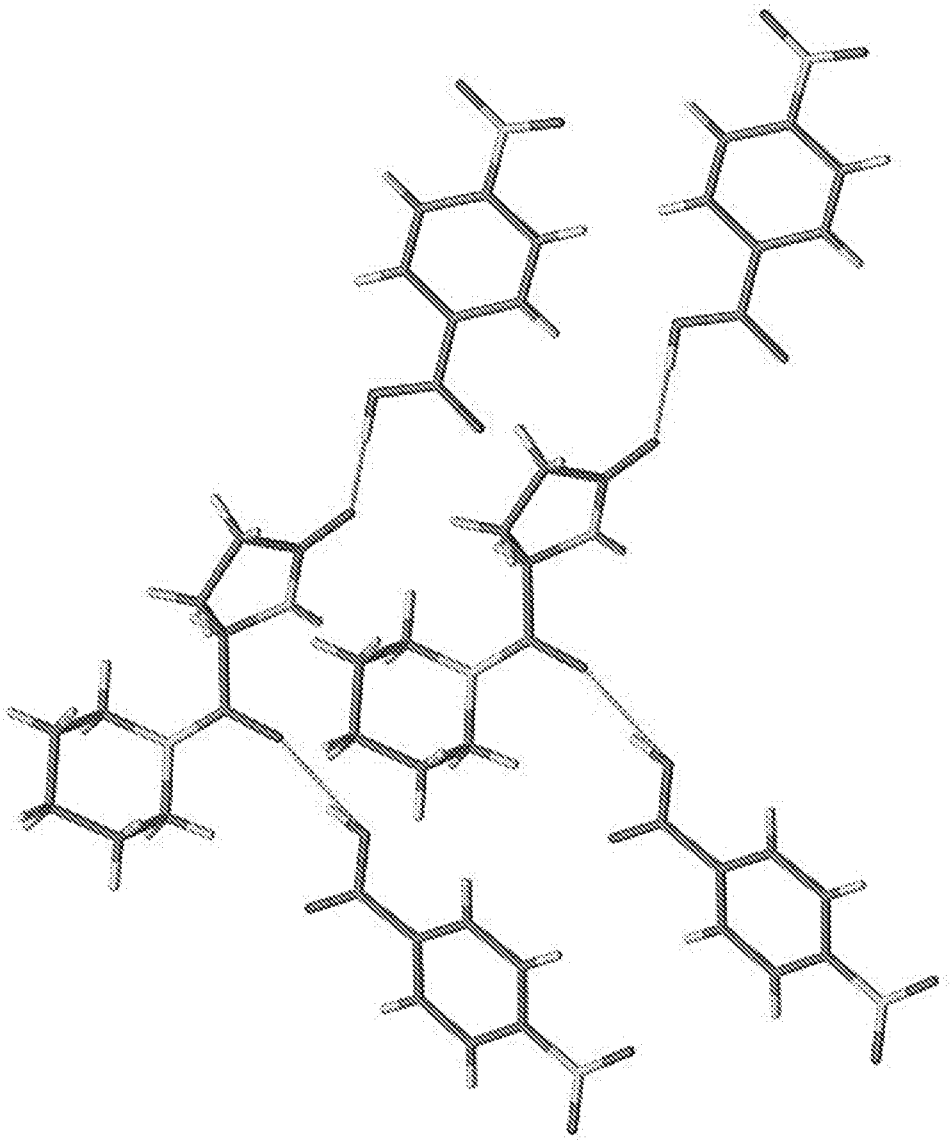


Figure 126

Hydrogen bonding pattern of a R-fasoracetam:Urea cocrystal Form B

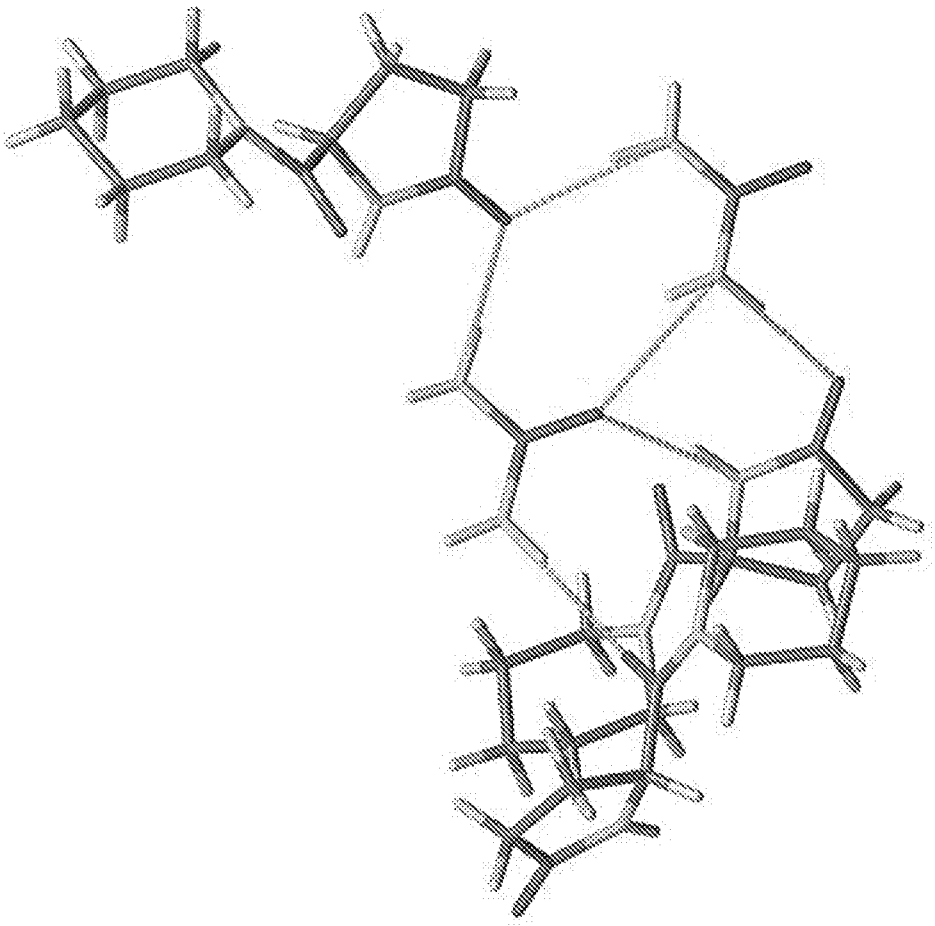


Figure 127

Hydrogen bonding pattern of a R-fasoracetam:phthalic acid cocrystal

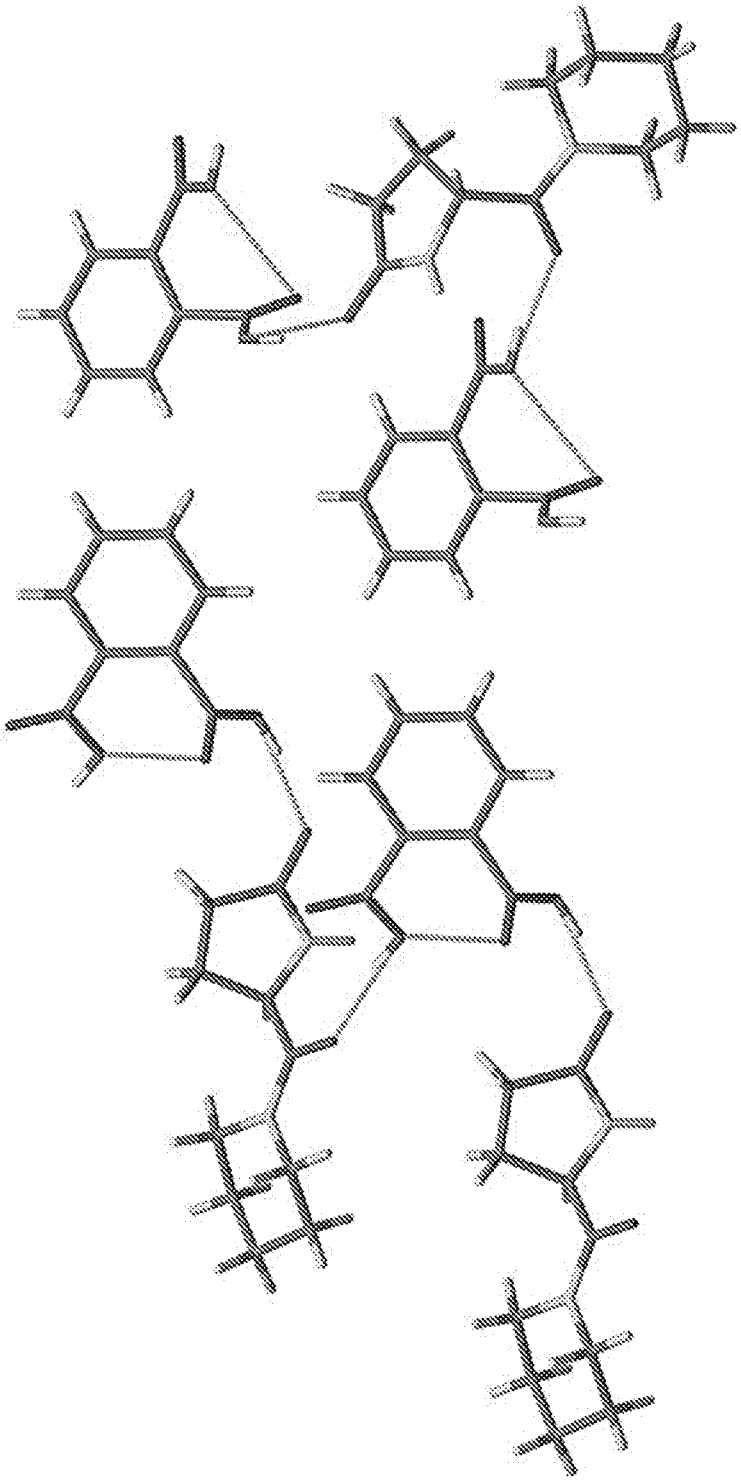


Figure 128

Hydrogen bonding pattern of a monohydrate of R-fasoracetam:phloroglucinol cocrystal

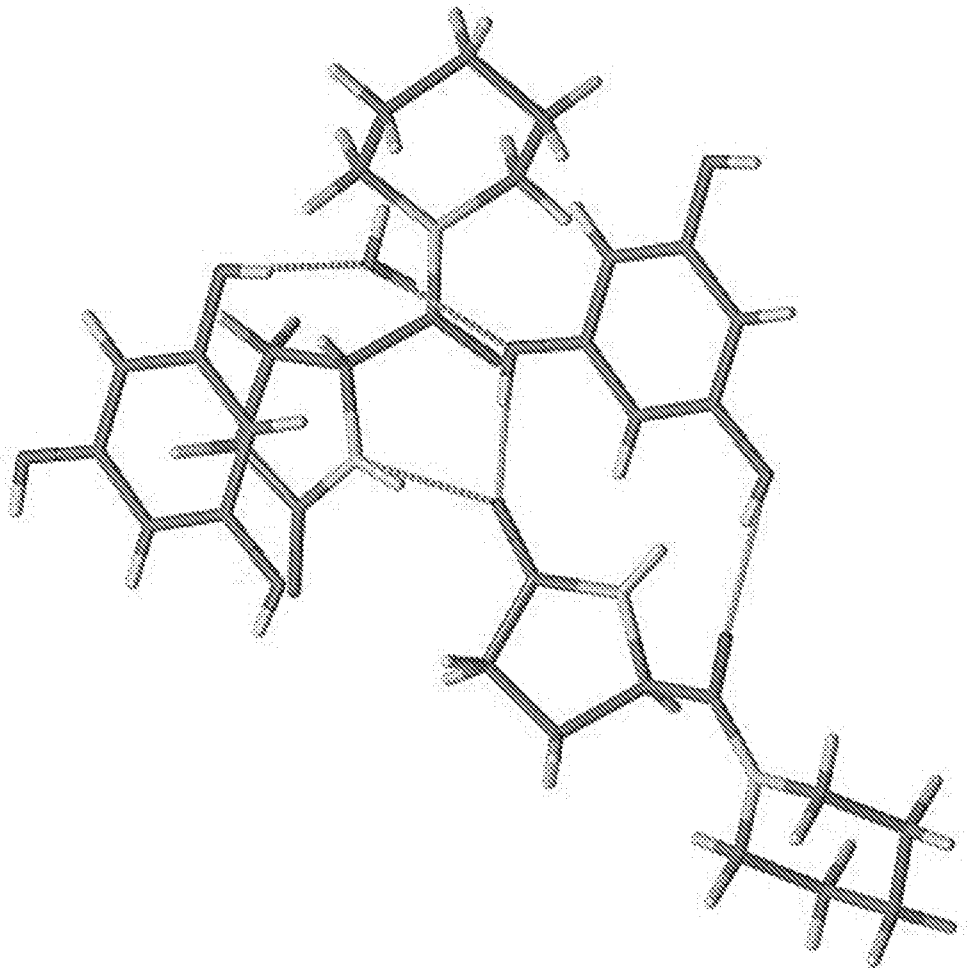


Figure 129

Hydrogen bonding pattern of a monohydrate of R-fasoracetam:methyl-3,4,5-trihydroxybenzoate cocrystal

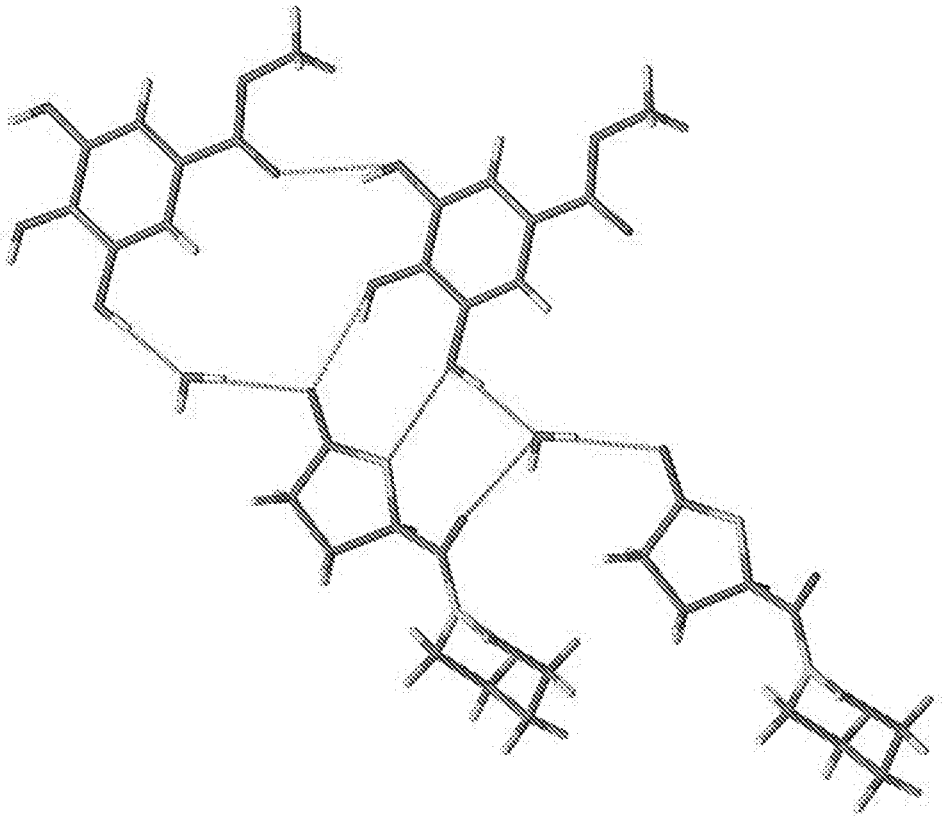


Figure 130

Hydrogen bonding pattern of a 1:1 cocrystal of R-fasoracetam:ethyl gallate

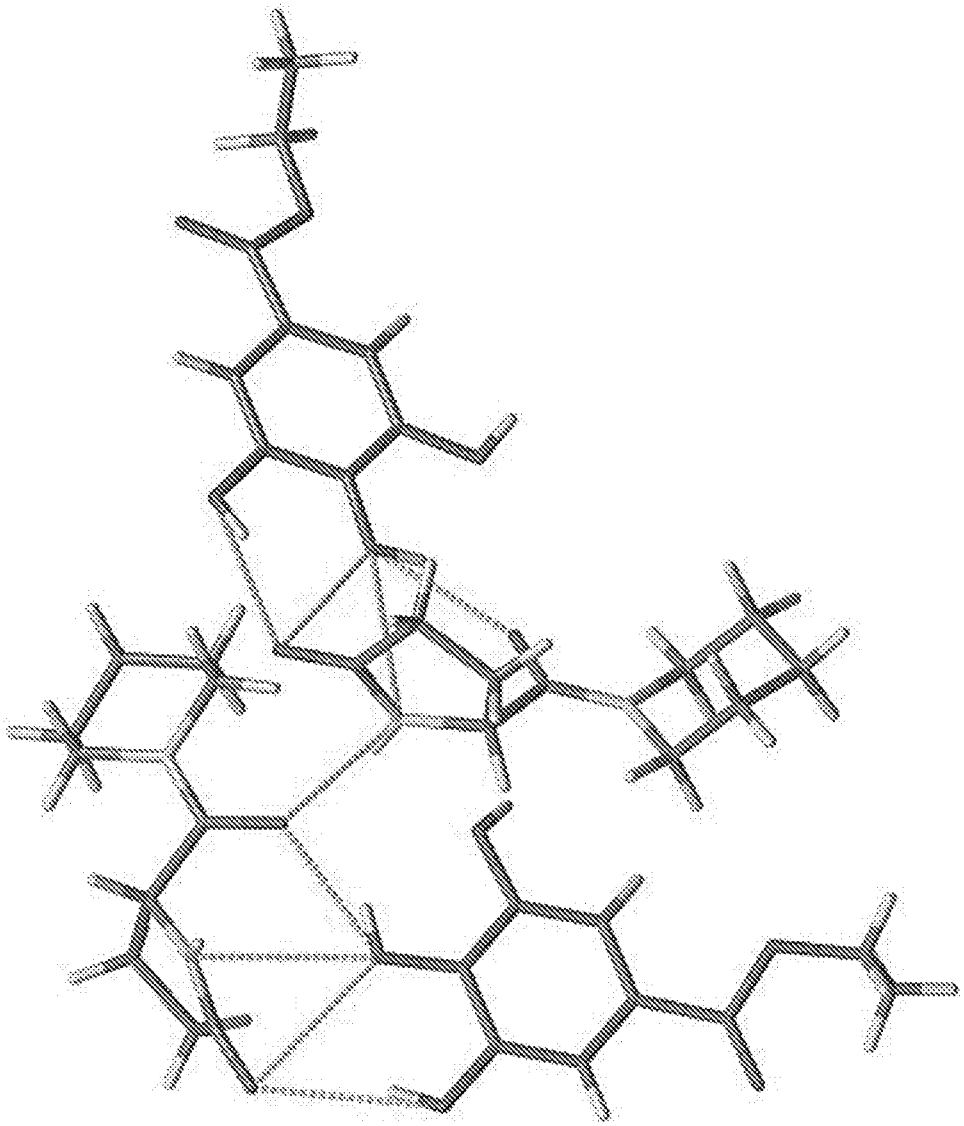


Figure 131

Hydrogen bonding pattern of a 1:2 cocrystal of R-fasoracetam:ethyl gallate

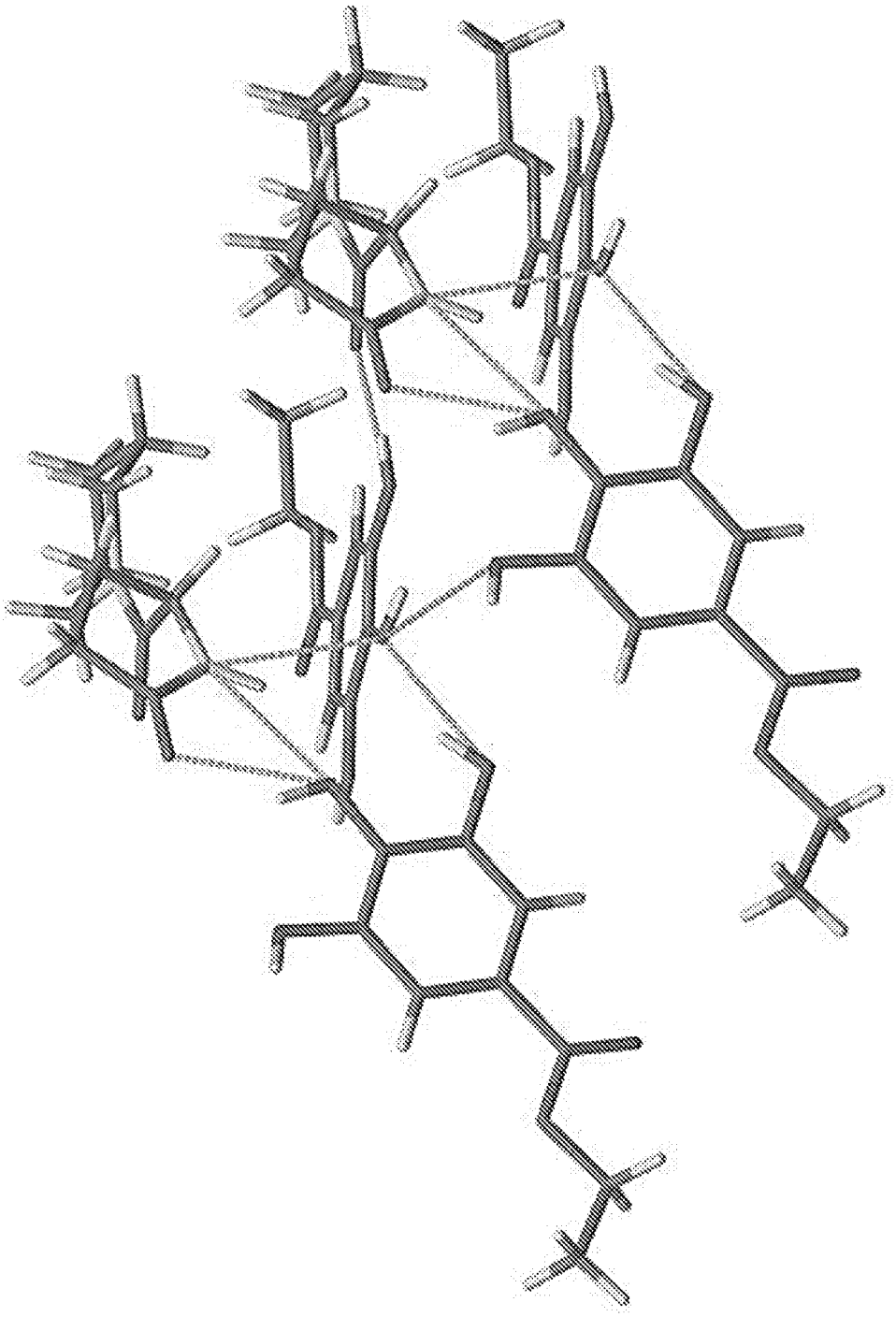


Figure 132

Hydrogen bonding pattern of a dihydrate of a 1:2 cocrystal of R-fasoracetam: ethyl gallate

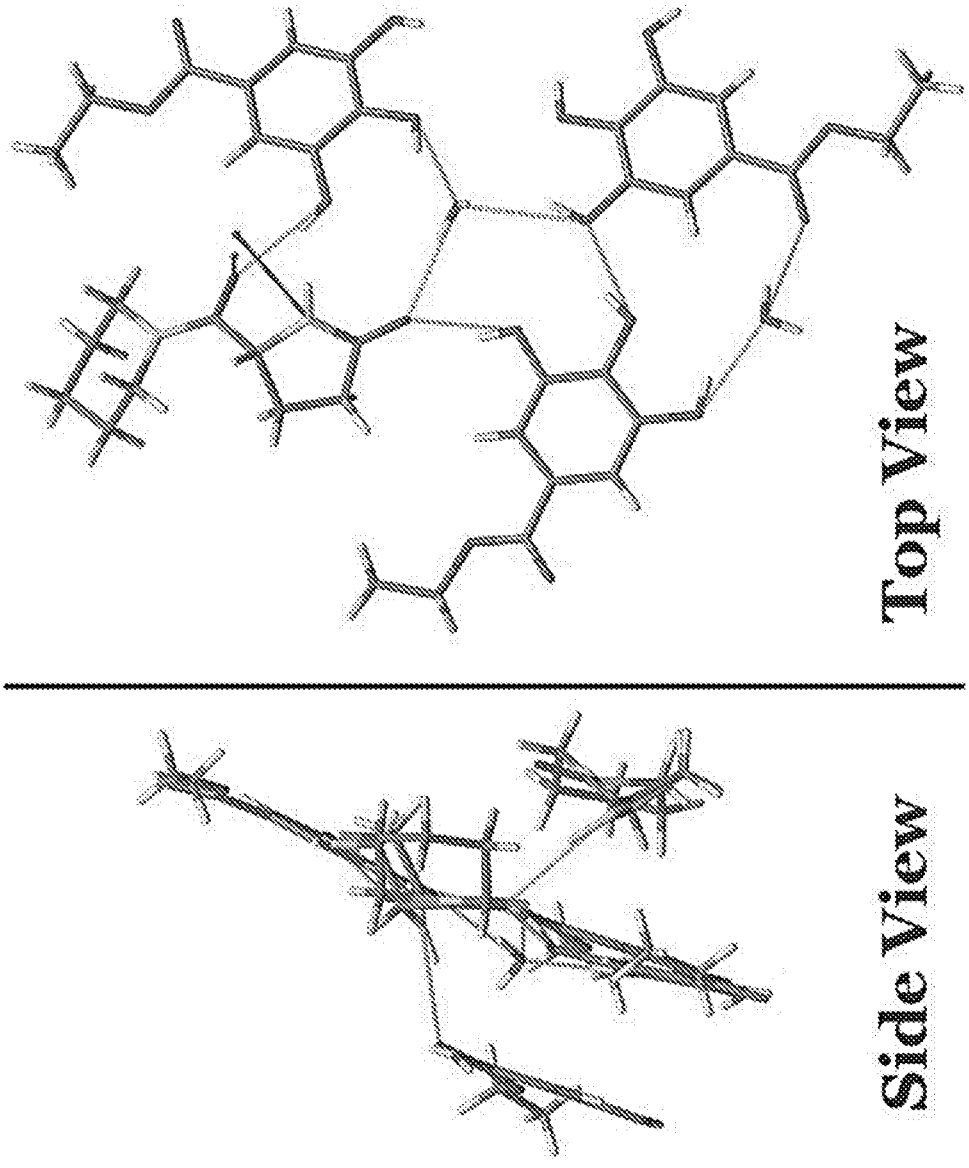


Figure 133

Hydrogen bonding pattern of a R-fasoracetam:R-ibuprofen cocrystal

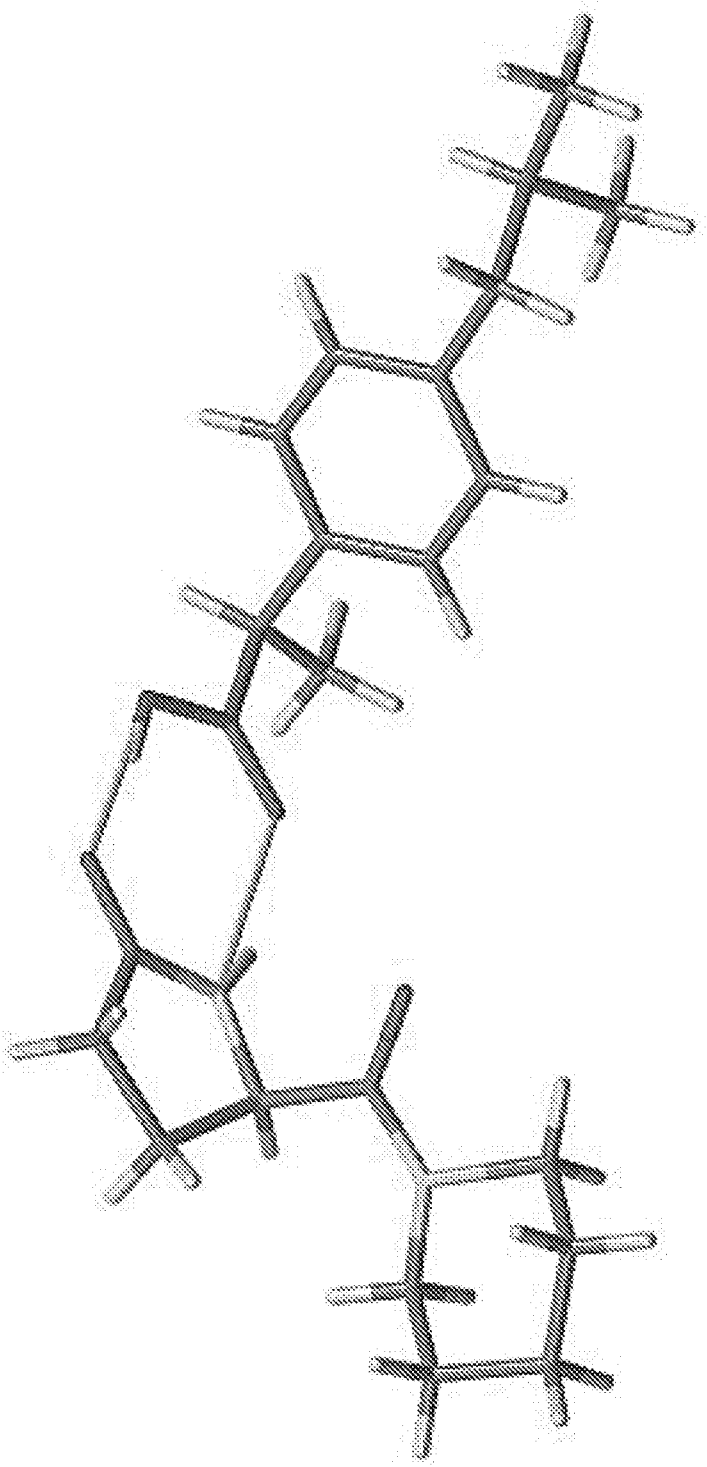


Figure 134

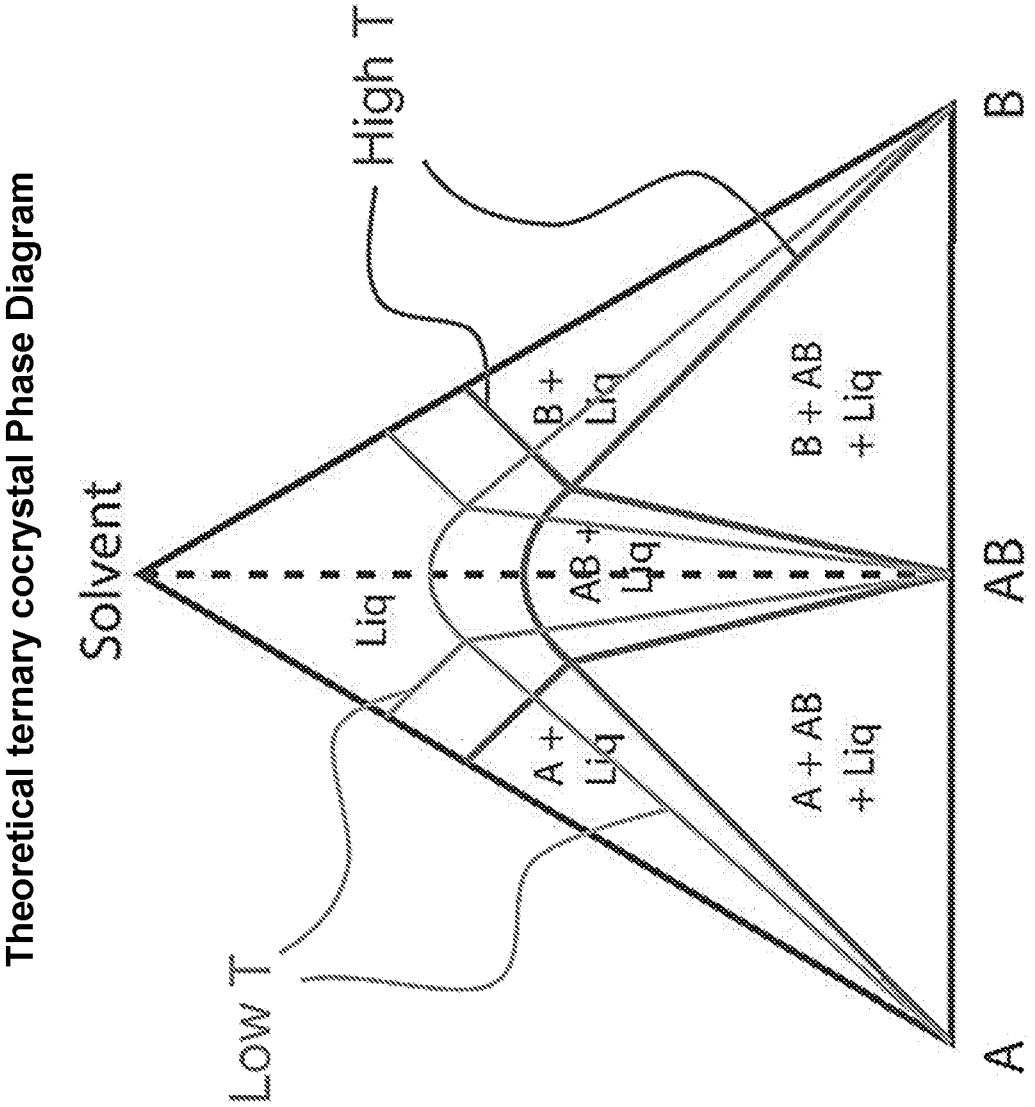

Theoretical ternary cocrystal Phase Diagram
Solvent
High T
Low T
A
B
AB
Liq
B + Liq
AB + Liq
B + AB + Liq
A + Liq
A + AB + Liq

Figure 135

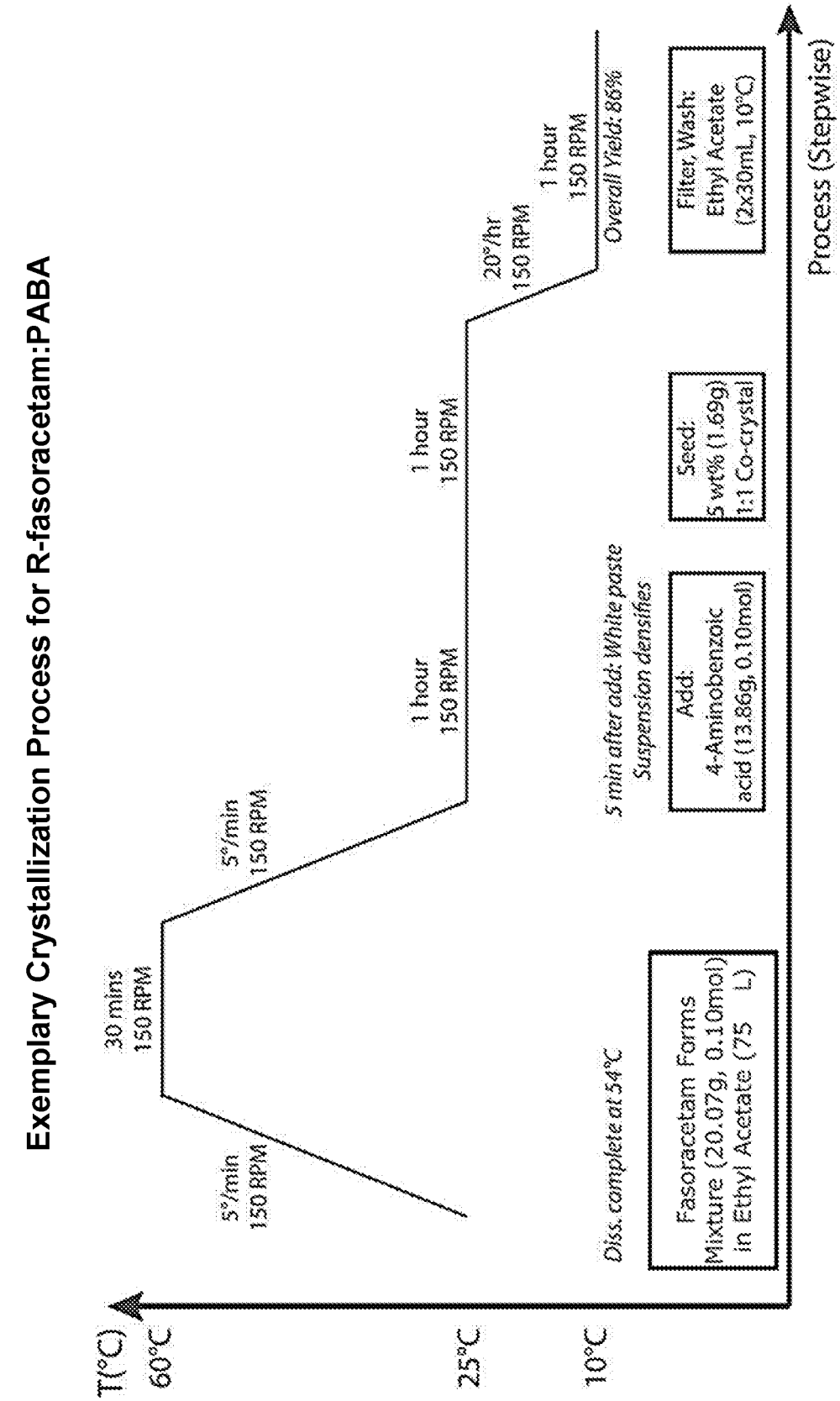

Exemplary Crystallization Process for R-fasoracetam:PABA
T(°C)
60°C
25°C
10°C
30 mins
150 RPM
5°/min
150 RPM
5°/min
150 RPM
1 hour
150 RPM
1 hour
150 RPM
20°/hr
150 RPM
1 hour
150 RPM
Overall Yield: 86%
Fasoracetam Forms Mixture (20.07g, 0.10mol) in Ethyl Acetate (75 L)
Diss. complete at 54°C
Add: 4-Aminobenzoic acid (13.86g, 0.10mol)
5 min after add: White paste Suspension densifies
Seed: 5 wt% (1.69g) 1:1 Co-crystal
Filter, Wash: Ethyl Acetate (2x30mL, 10°C)
Process (Stepwise)

Figure 136

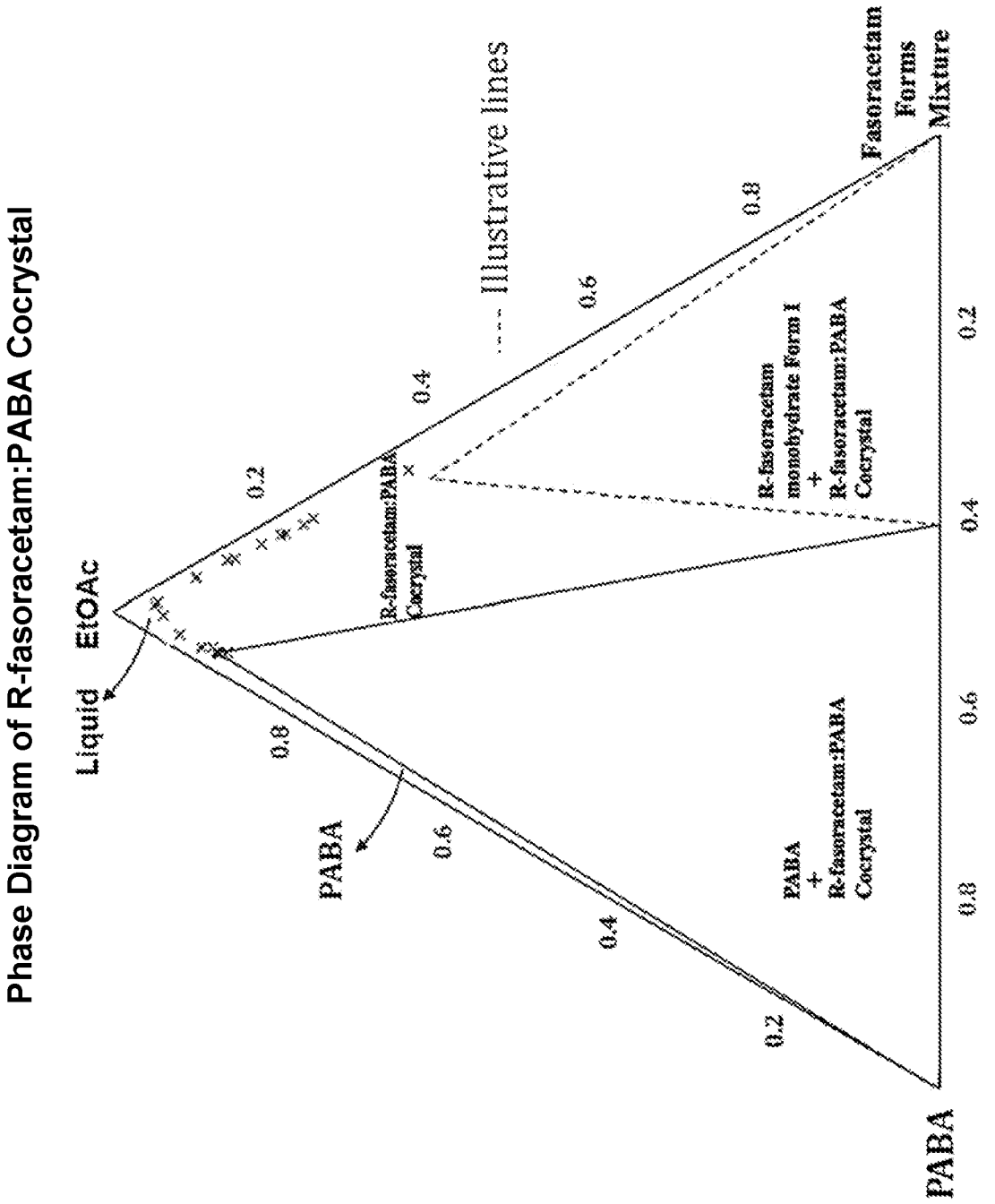

Phase Diagram of R-fasoracetam:PABA Cocrystal
Liquid
EtOAc
PABA
PABA
Illustrative lines
R-fasoracetam:PABA Cocrystal
R-fasoracetam monohydrate Form I
+
R-fasoracetam:PABA Cocrystal
PABA
+
R-fasoracetam:PABA Cocrystal
Fasoracetam Forms Mixture
0.2
0.4
0.6
0.8

Figure 137