US012415807B2

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Olmstead et al.

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(45) **Date of Patent: *Sep. 16, 2025**

(54) **PKC INHIBITOR SOLID STATE FORMS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1052 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/382,901**

(22) Filed: **Jul. 22, 2021**

(65) **Prior Publication Data**

US 2022/0048918 A1 Feb. 17, 2022

Related U.S. Application Data

(63) Continuation of application No. 16/615,784, filed as application No. PCT/US2018/034740 on May 25, 2018, now Pat. No. 11,104,679.

(60) Provisional application No. 62/511,210, filed on May 25, 2017.

(51) **Int. Cl.**
C07D 487/04 (2006.01)
C07D 519/00 (2006.01)

(52) **U.S. Cl.**
CPC ***C07D 487/04*** (2013.01); ***C07D 519/00*** (2013.01); *C07B 2200/13* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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No Name. Bulk Drug Form Screening and Selection in Noriyuki Takada and Innovative Drug Development Stage. Pharm Stage 6(10):20-25 (2017) (w/Machine Translation).

Primary Examiner — Po-Chih Chen
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(57) **ABSTRACT**

The present disclosure relates to various solid state forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and methods of making the same. Such forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine are useful in preparation of pharmaceutical compositions and dosage forms for the treatment of cancer, immune disorders and inflammation.

15 Claims, 50 Drawing Sheets

Figure 1.

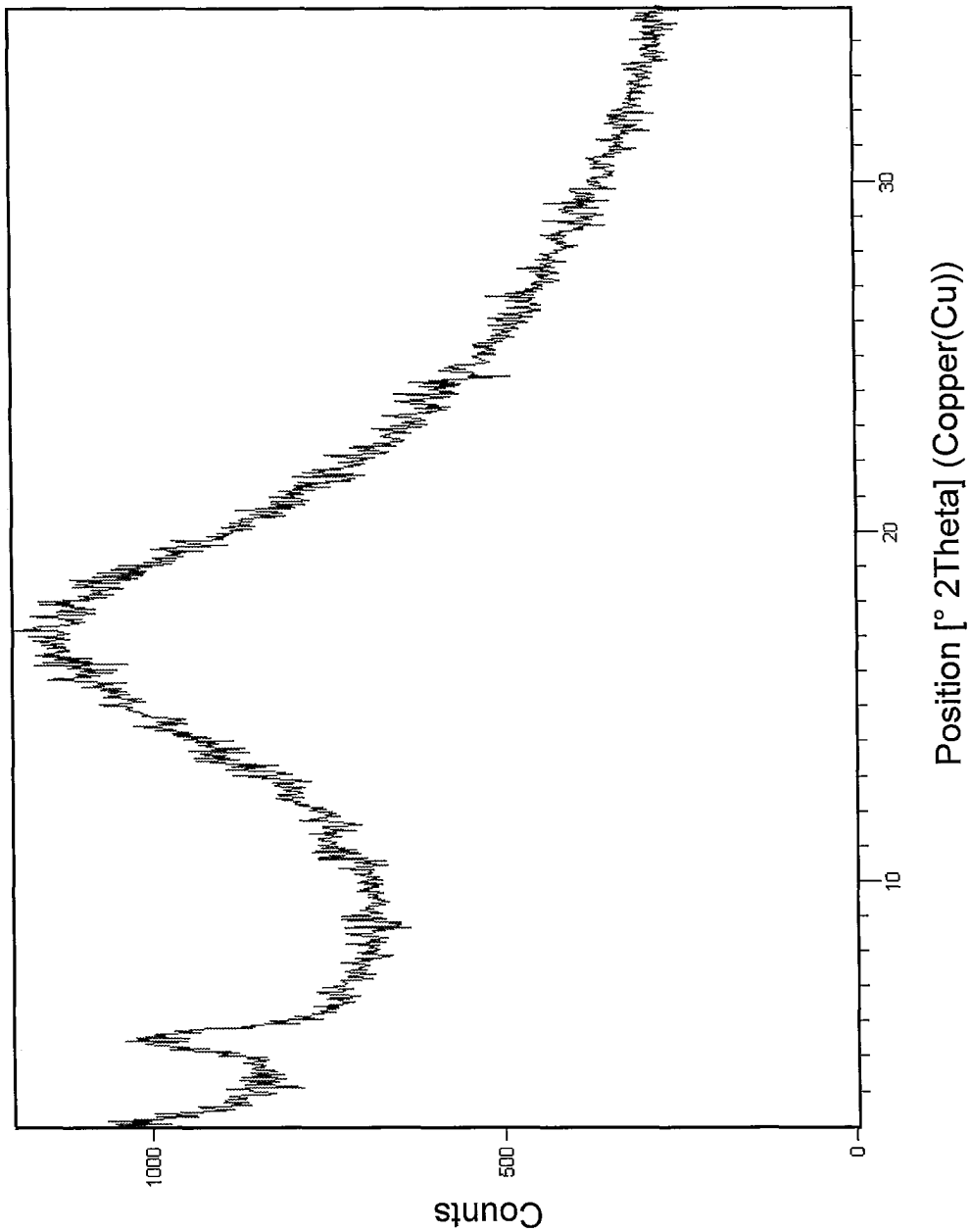


Figure 2a.

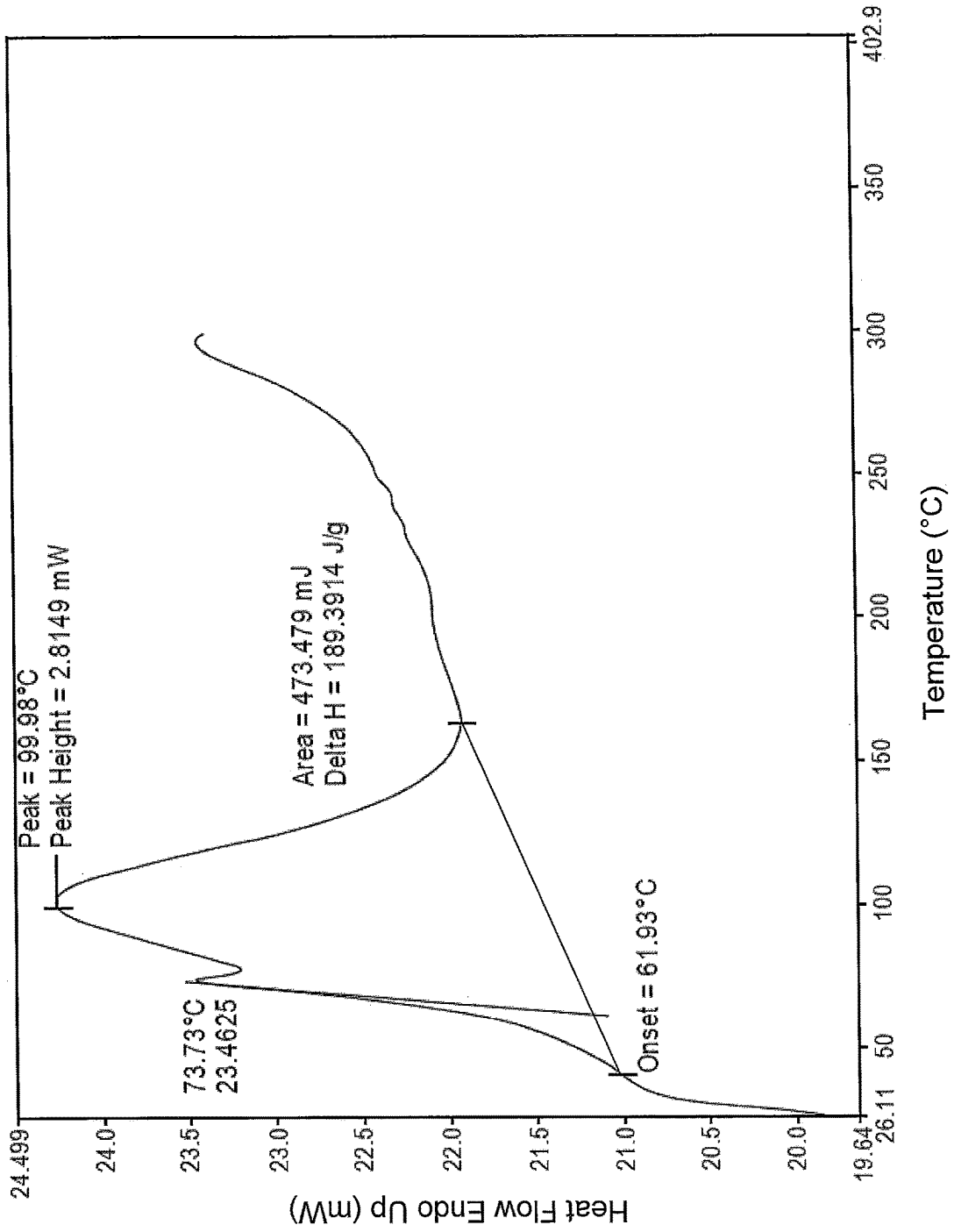

Peak = 99.98°C
Peak Height = 2.8149 mW
Area = 473.479 mJ
Delta H = 189.3914 J/g
73.73°C
23.4625
Onset = 61.93°C
Heat Flow Endo Up (mW)
24.499
24.0
23.5
23.0
22.5
22.0
21.5
21.0
20.5
20.0
19.64
26.11
50
100
150
200
250
300
350
402.9
Temperature (°C)

Figure 2b.

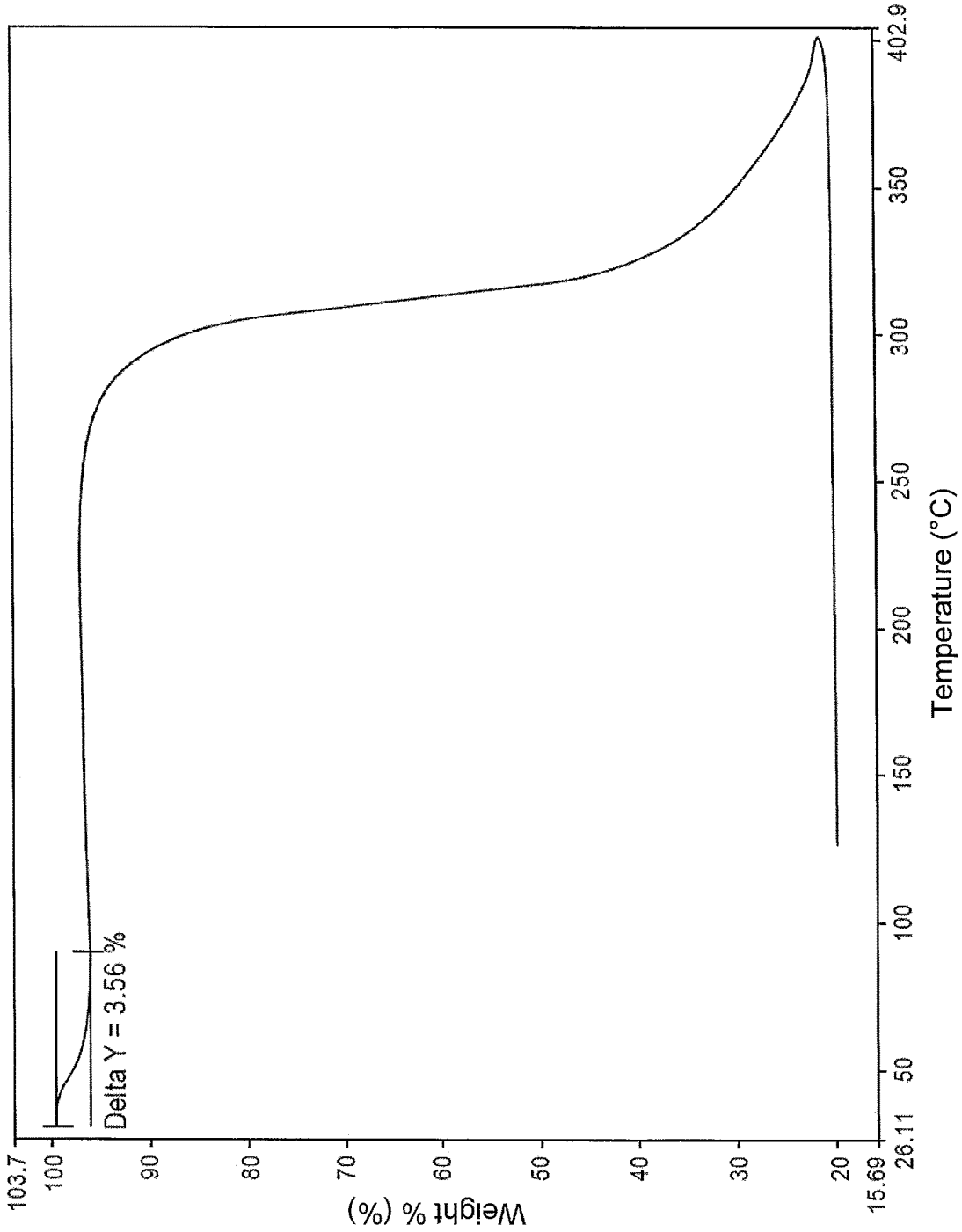

Delta Y = 3.56 %
Weight % (%)
103.7
100
90
80
70
60
50
40
30
20
15.69
26.11
50
100
150
200
250
300
350
402.9
Temperature (°C)

Figure 3.

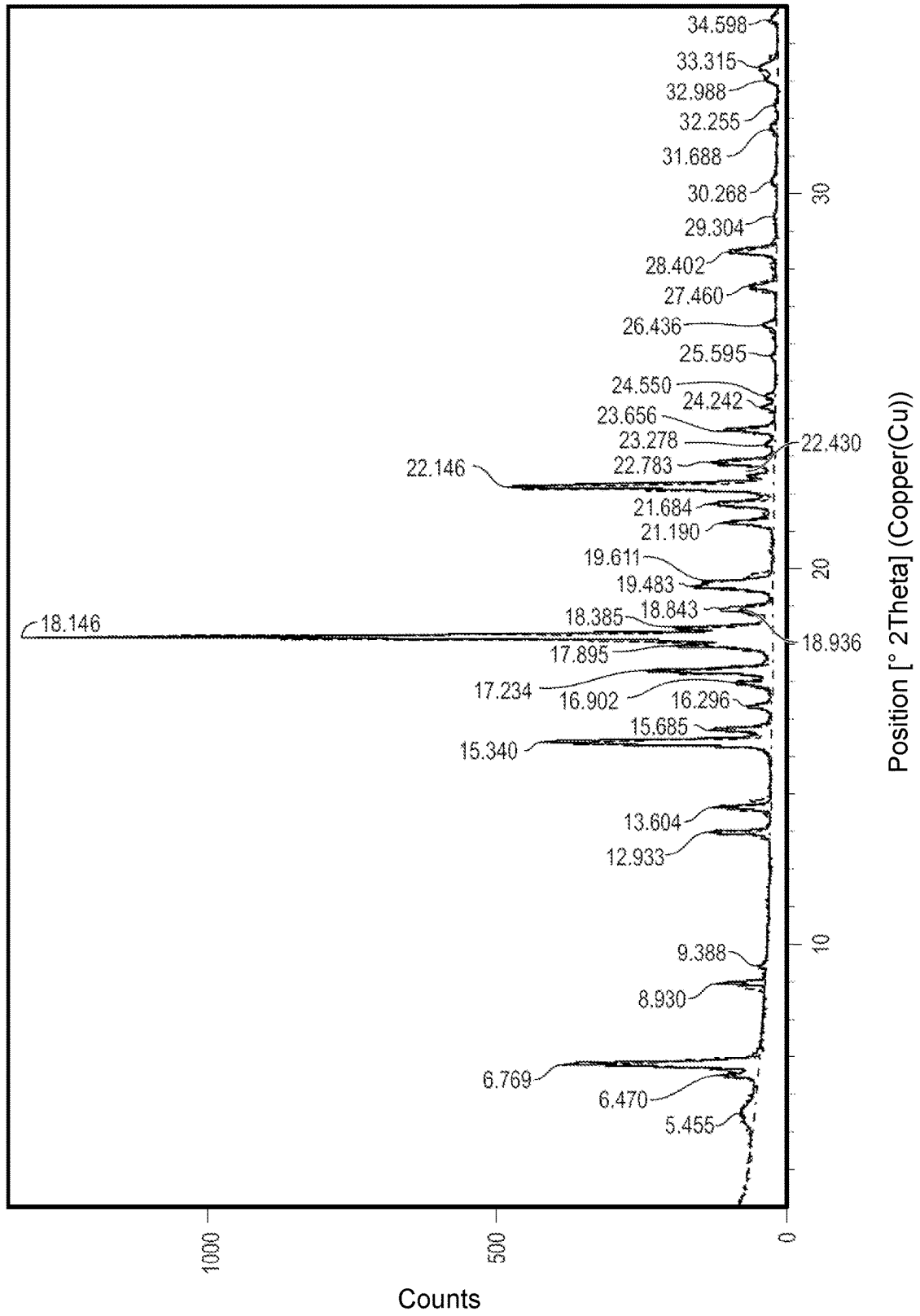

34.598
33.315
32.988
32.255
31.688
30.268
29.304
28.402
27.460
26.436
25.595
24.550
24.242
23.656
23.278
22.783
22.146
22.430
21.684
21.190
19.611
19.483
18.843
18.385
18.146
18.936
17.895
17.234
16.902
16.296
15.685
15.340
13.604
12.933
9.388
8.930
6.769
6.470
5.455
30
20
10
0
500
1000
Counts
Position [° 2Theta] (Copper(Cu))

Figure 4.

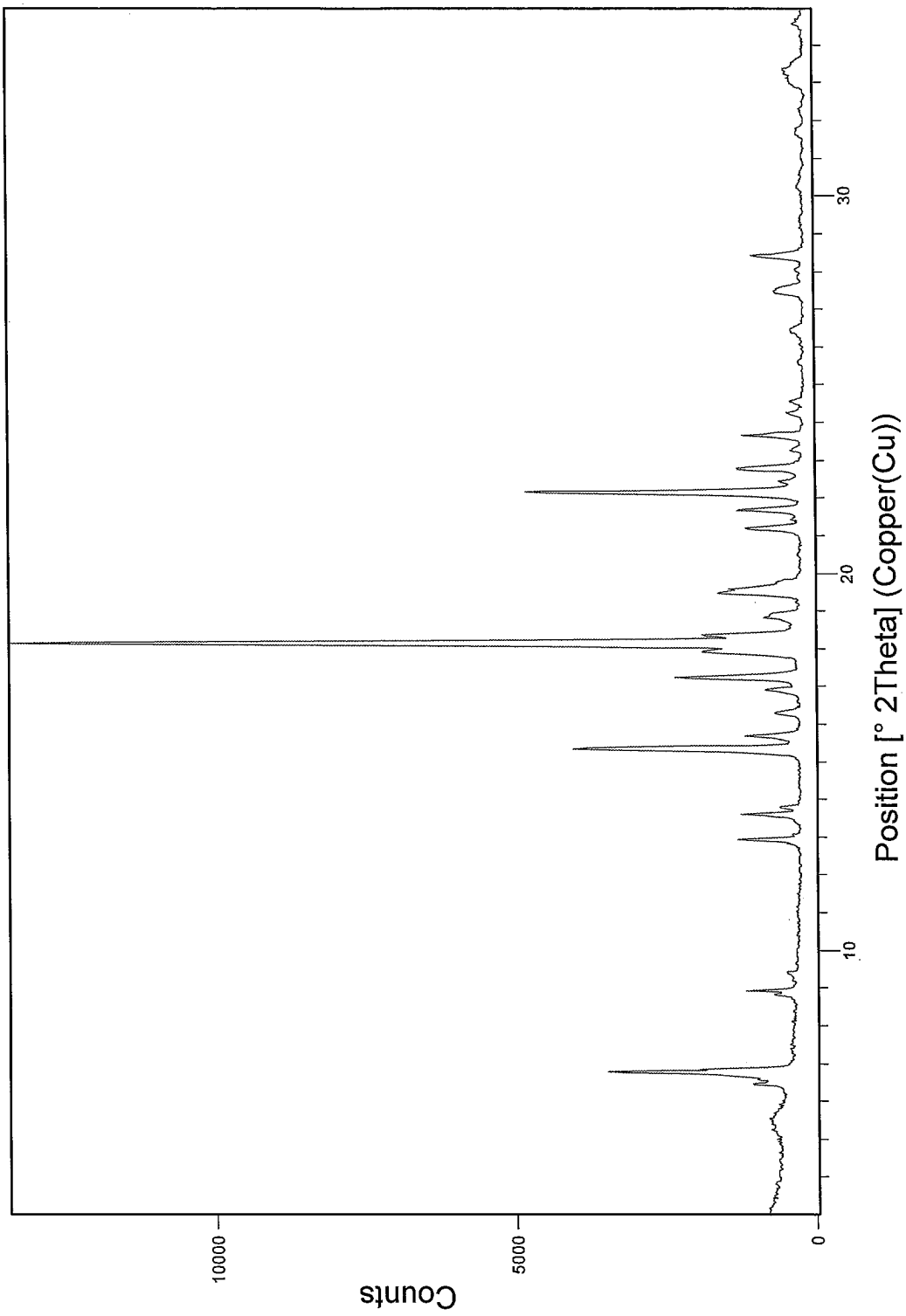


Figure 5.

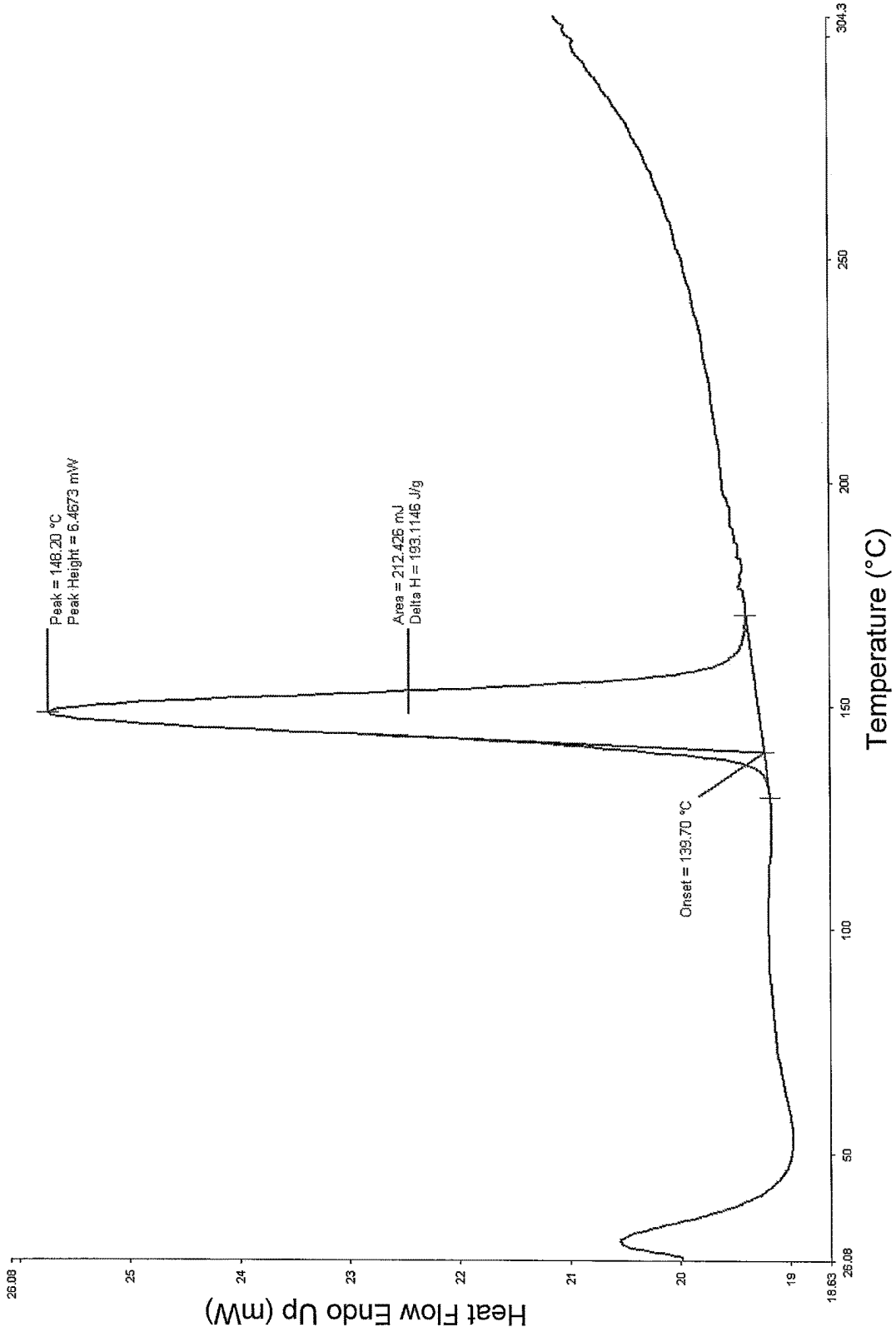

Peak = 148.20 °C
Peak Height = 6.4673 mW
Area = 212.426 mJ
Delta H = 193.1146 J/g
Onset = 139.70 °C
Heat Flow Endo Up (mW)
26.08
25
24
23
22
21
20
19
18.63
26.08
50
100
150
200
250
304.3
Temperature (°C)

Figure 6.

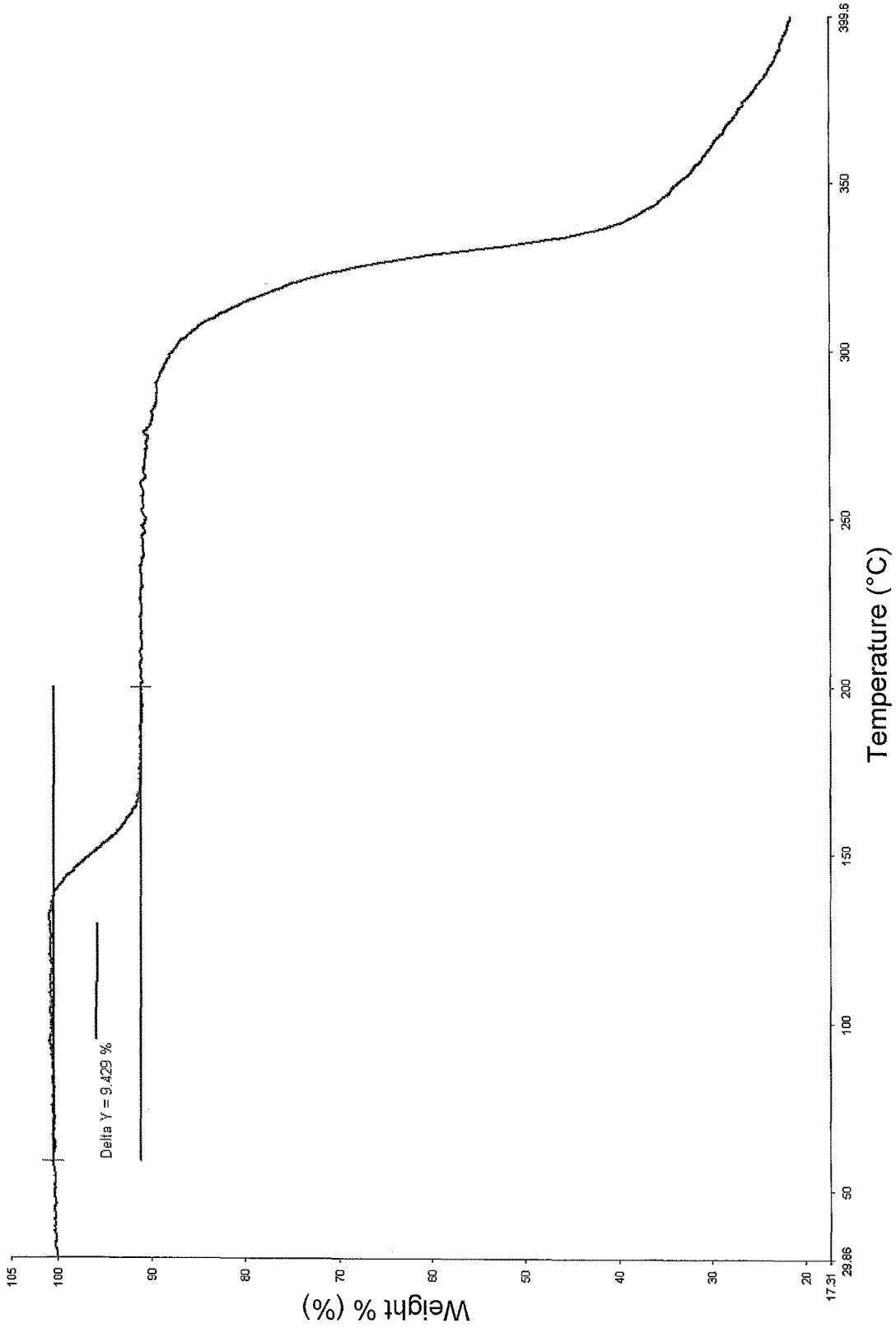

Delta Y = 9.429 %
Weight % (%)
105
100
90
80
70
60
50
40
30
20
17.31
29.86
50
100
150
200
250
300
350
399.6
Temperature (°C)

Figure 7.

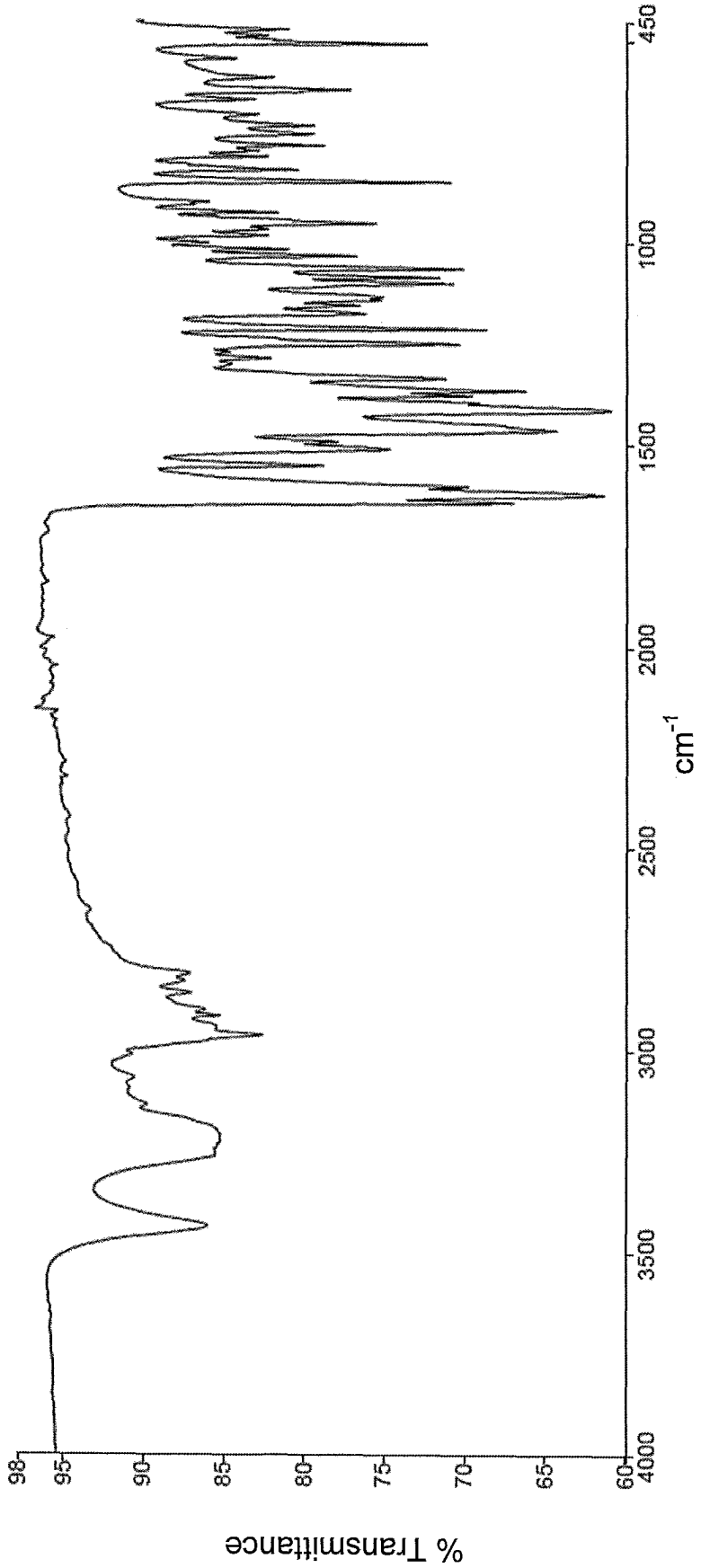

% Transmittance
98
95
90
85
80
75
70
65
60
4000
3500
3000
2500
2000
1500
1000
450
cm-1

Figure 8.

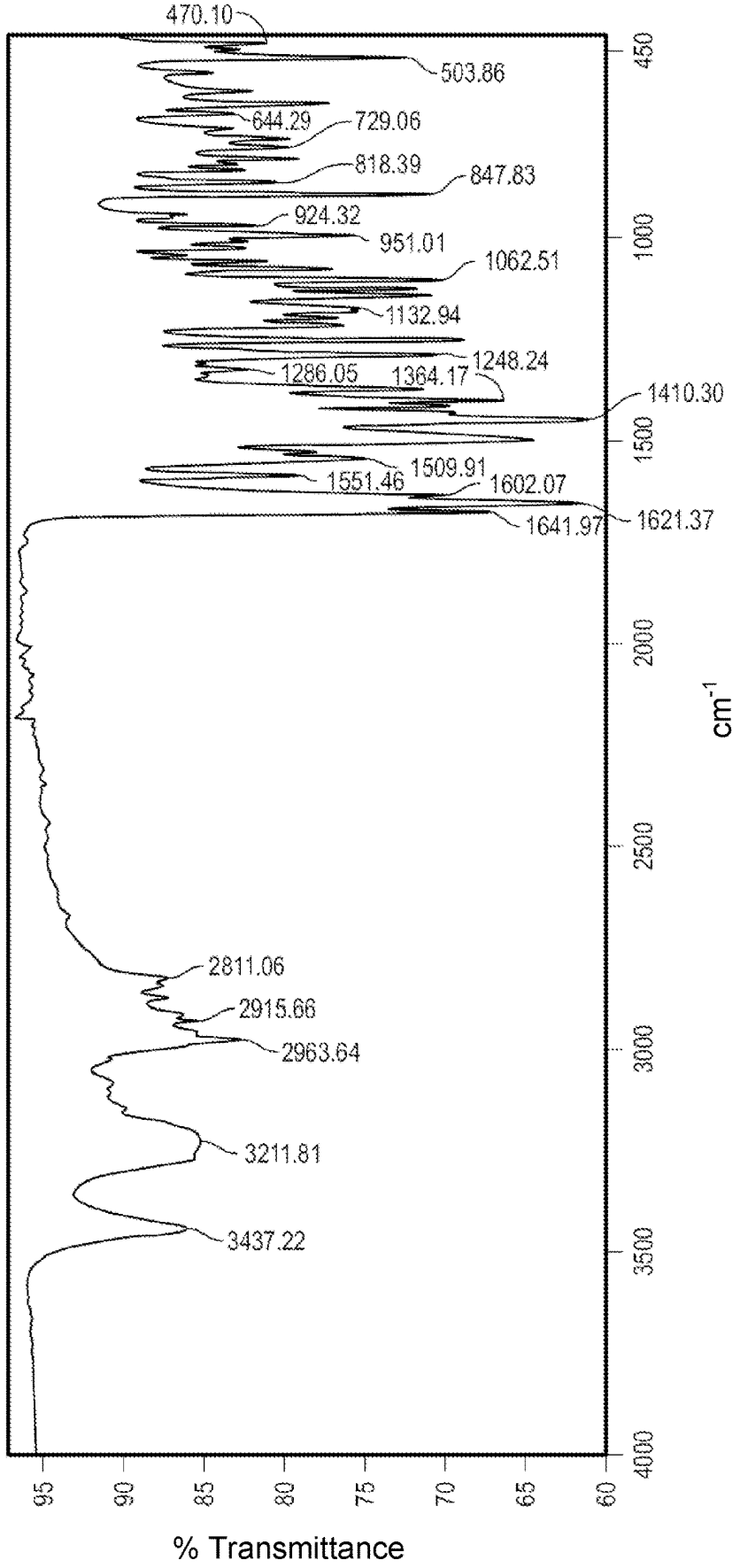

470.10
503.86
644.29
729.06
818.39
847.83
924.32
951.01
1062.51
1132.94
1248.24
1286.05
1364.17
1410.30
1509.91
1551.46
1602.07
1621.37
1641.97
2811.06
2915.66
2963.64
3211.81
3437.22
450
1000
1500
2000
2500
3000
3500
4000
cm-1
95
90
85
80
75
70
65
60
% Transmittance

Figure 9.

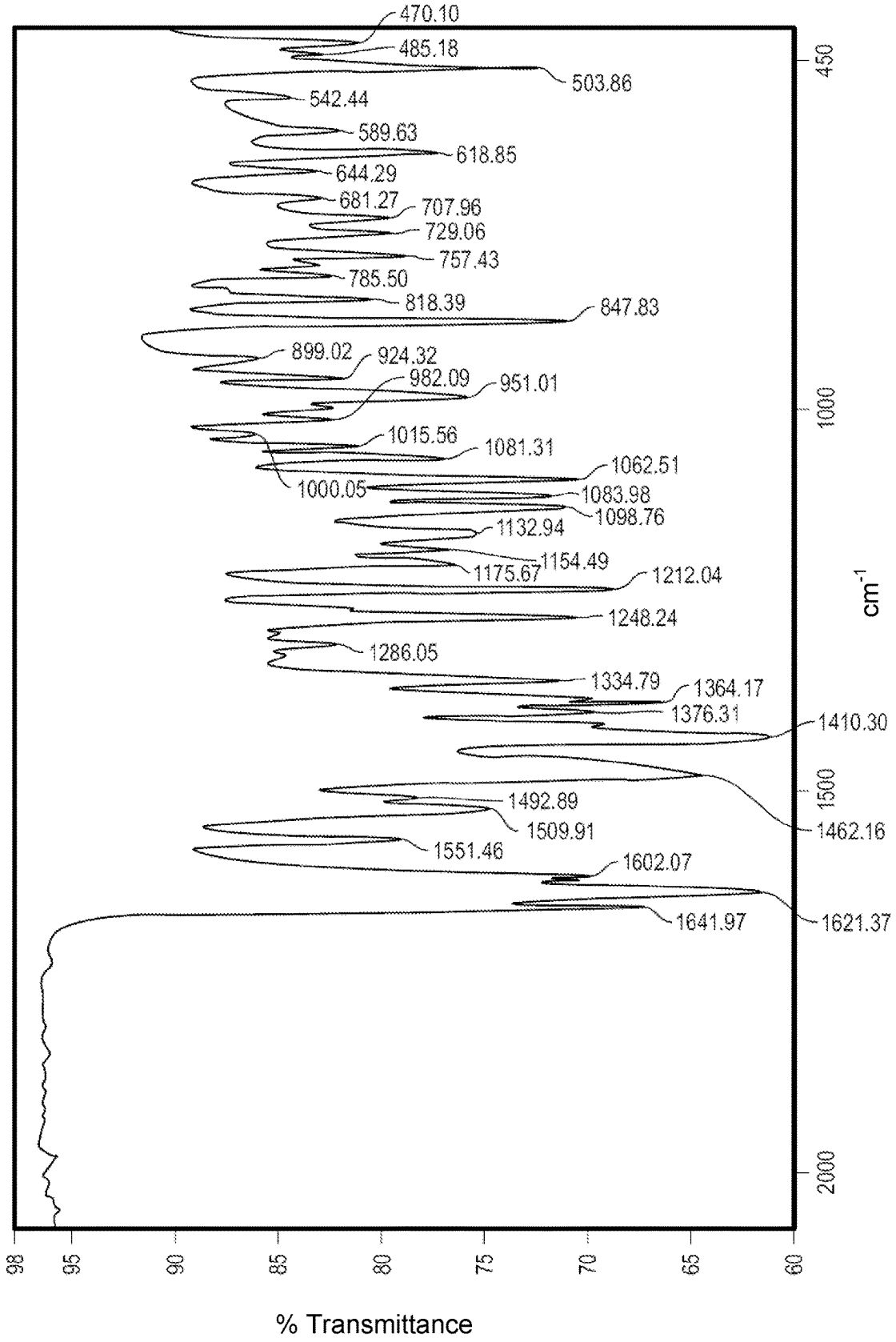

470.10
485.18
503.86
542.44
589.63
618.85
644.29
681.27
707.96
729.06
757.43
785.50
818.39
847.83
899.02
924.32
982.09
951.01
1015.56
1081.31
1062.51
1000.05
1083.98
1098.76
1132.94
1154.49
1175.67
1212.04
1248.24
1286.05
1334.79
1364.17
1376.31
1410.30
1492.89
1509.91
1462.16
1551.46
1602.07
1641.97
1621.37
450
1000
1500
2000
cm-1
98
95
90
85
80
75
70
65
60
% Transmittance

Figure 10.

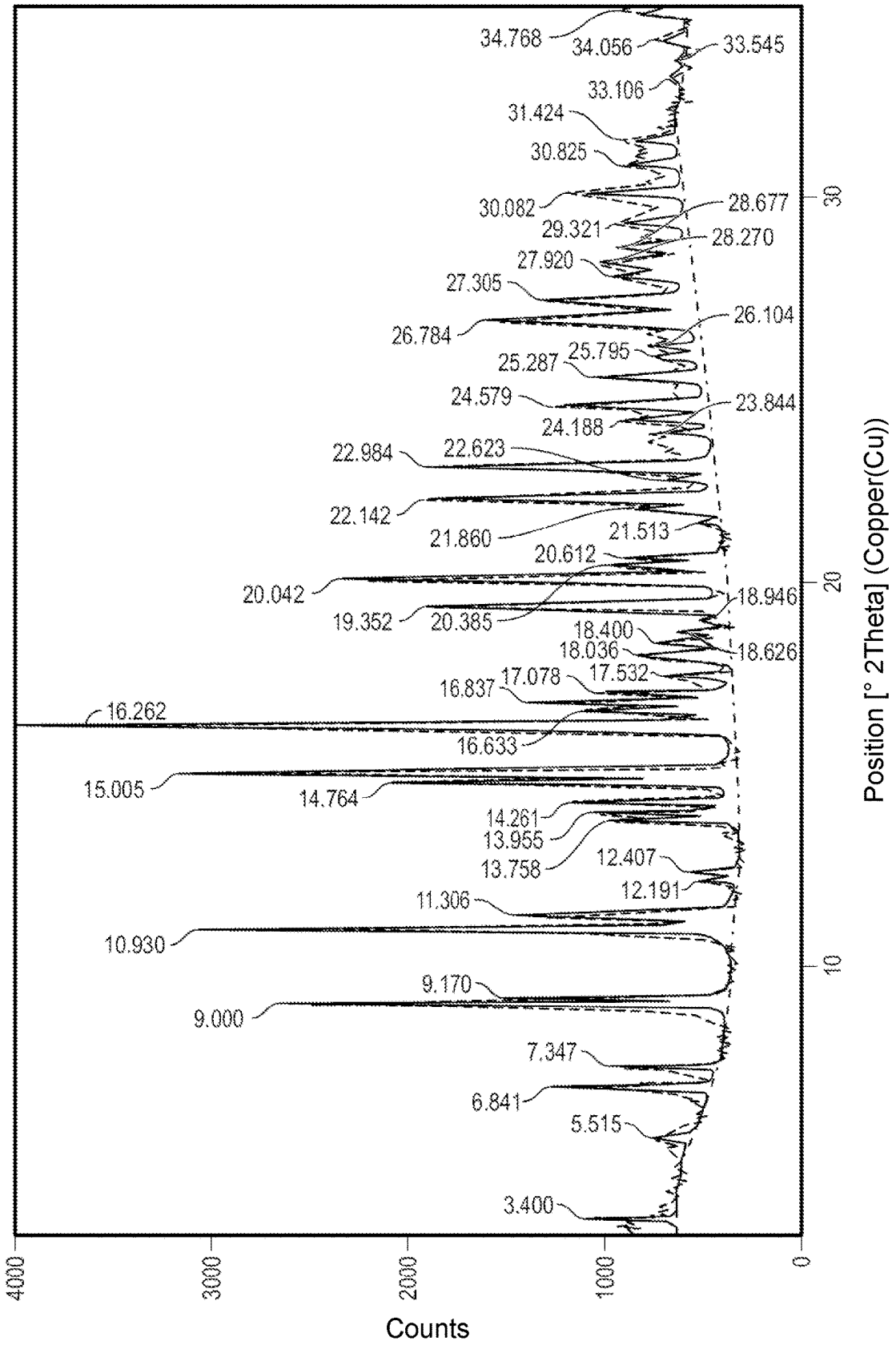

34.768
34.056
33.545
33.106
31.424
30.825
30.082
28.677
29.321
28.270
27.920
27.305
26.104
26.784
25.795
25.287
24.579
23.844
24.188
22.984
22.623
22.142
21.860
21.513
20.612
20.042
18.946
19.352
20.385
18.400
18.036
18.626
17.078
17.532
16.837
16.262
16.633
15.005
14.764
14.261
13.955
13.758
12.407
12.191
11.306
10.930
9.170
9.000
7.347
6.841
5.515
3.400
4000
3000
2000
1000
0
Counts
30
20
10
Position [° 2Theta] (Copper(Cu))

Figure 11.

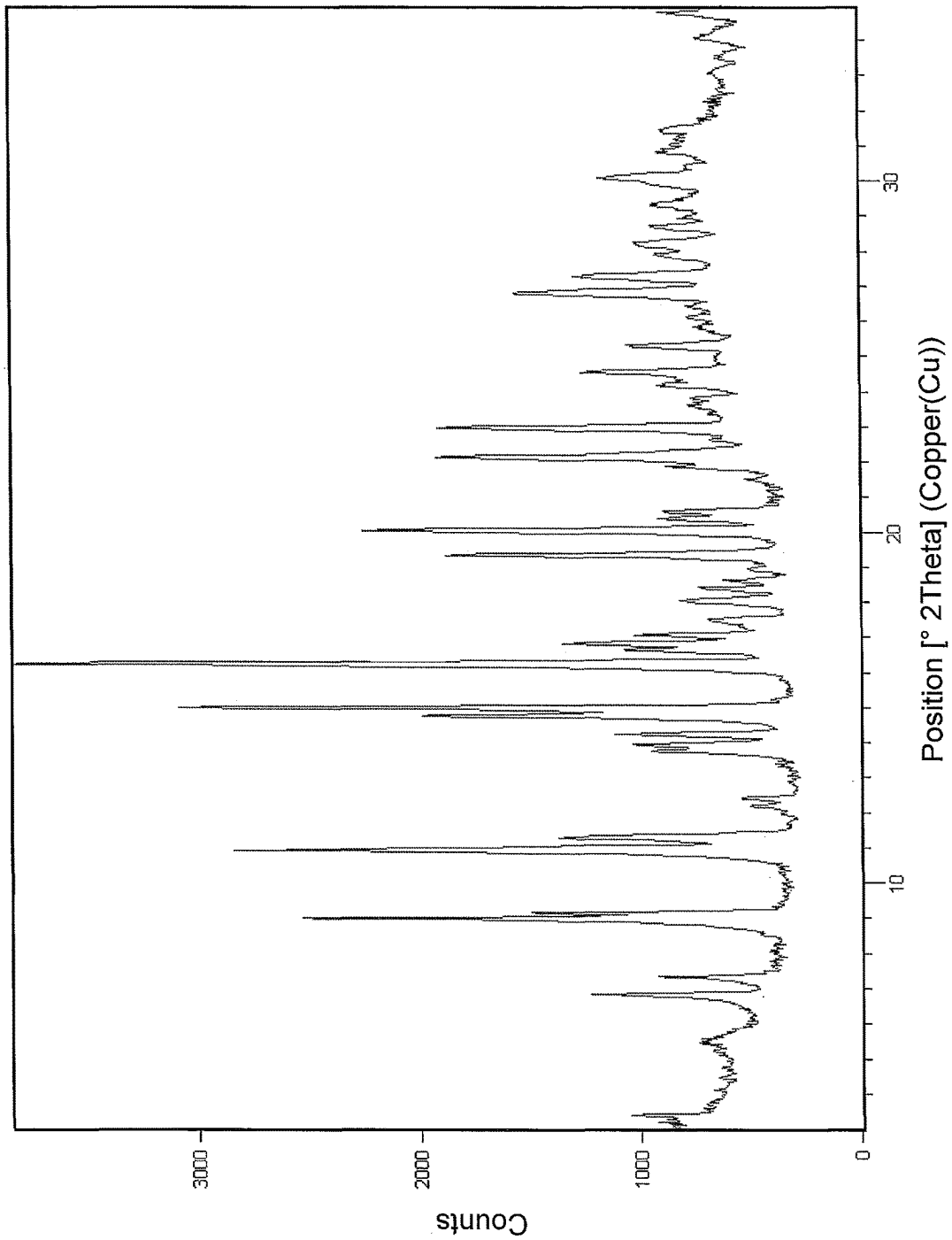


Figure 12.

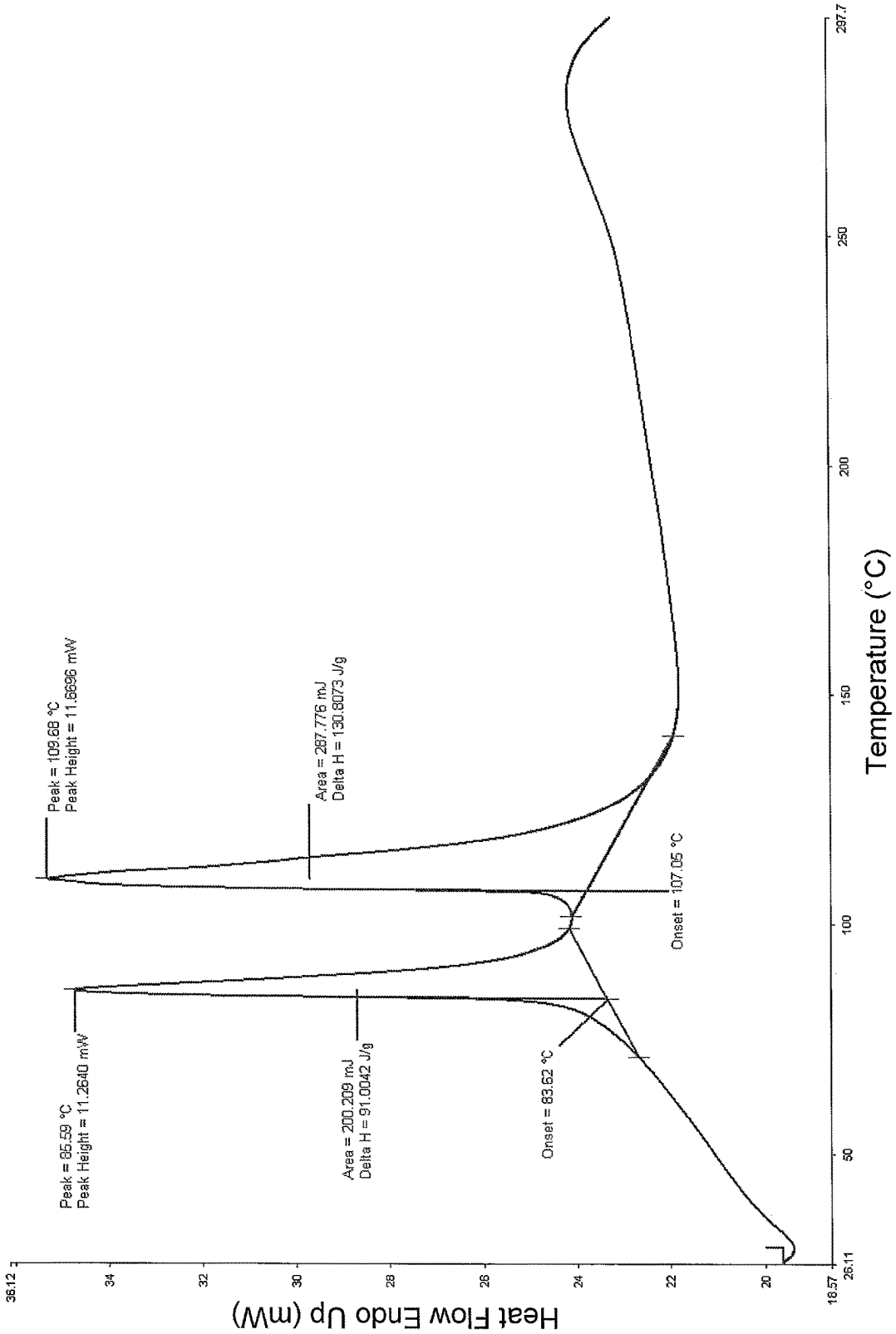

Peak = 109.68 °C
Peak Height = 11.8696 mW
Area = 297.776 mJ
Delta H = 130.8073 J/g
Onset = 107.05 °C
Peak = 85.59 °C
Peak Height = 11.2640 mW
Area = 200.209 mJ
Delta H = 91.0042 J/g
Onset = 83.62 °C
Heat Flow Endo Up (mW)
Temperature (°C)
36.12
34
32
30
28
26
24
22
20
18.57
26.11
50
100
150
200
250
297.7

Figure 13.

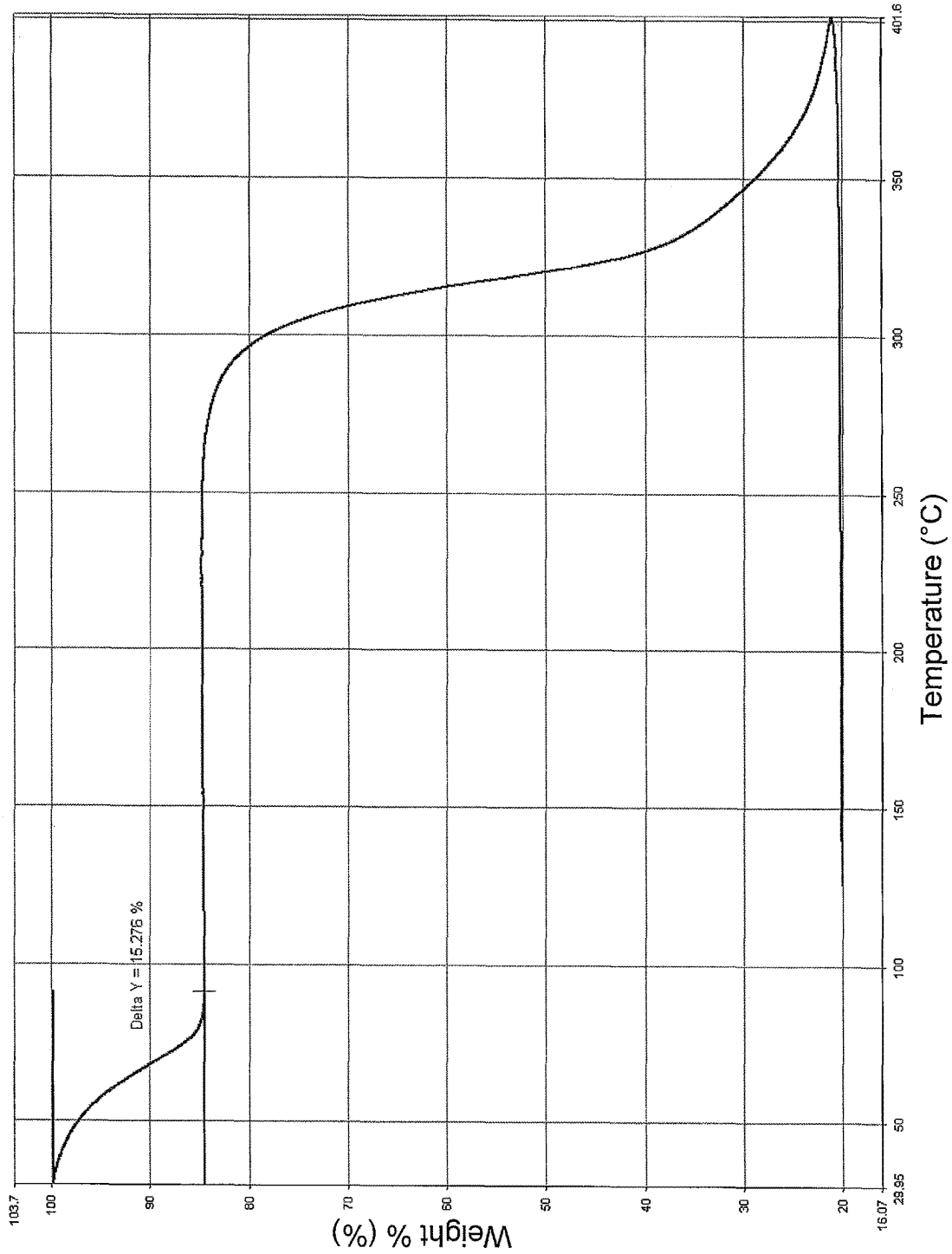

Delta Y = 15.276 %
103.7
100
90
80
70
60
50
40
30
20
16.07
29.95
50
100
150
200
250
300
350
401.6
Weight % (%)
Temperature (°C)

Figure 14.

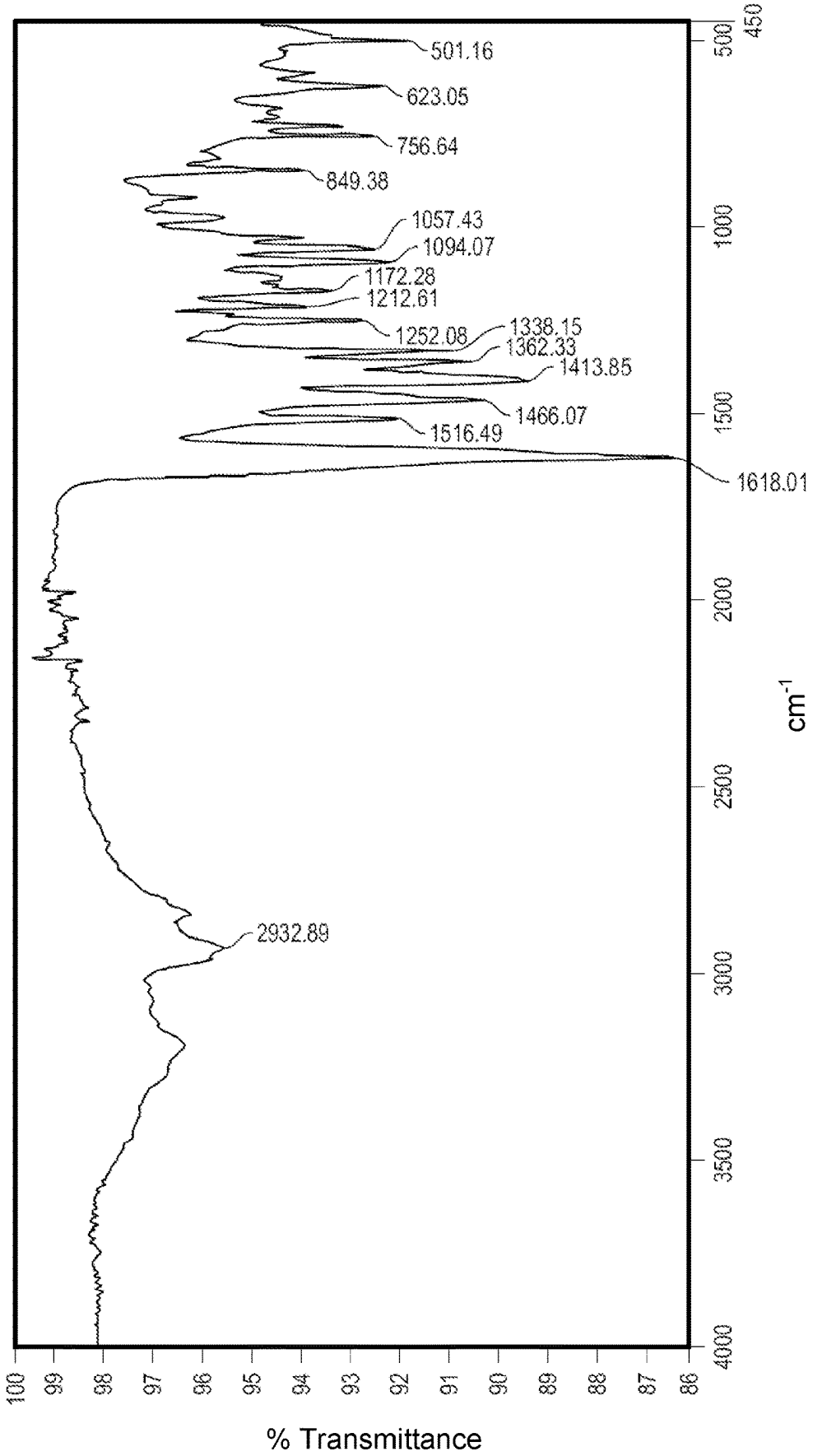

501.16
623.05
756.64
849.38
1057.43
1094.07
1172.28
1212.61
1252.08
1338.15
1362.33
1413.85
1466.07
1516.49
1618.01
2932.89
450
500
1000
1500
2000
2500
3000
3500
4000
cm-1
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
% Transmittance

Figure 15.

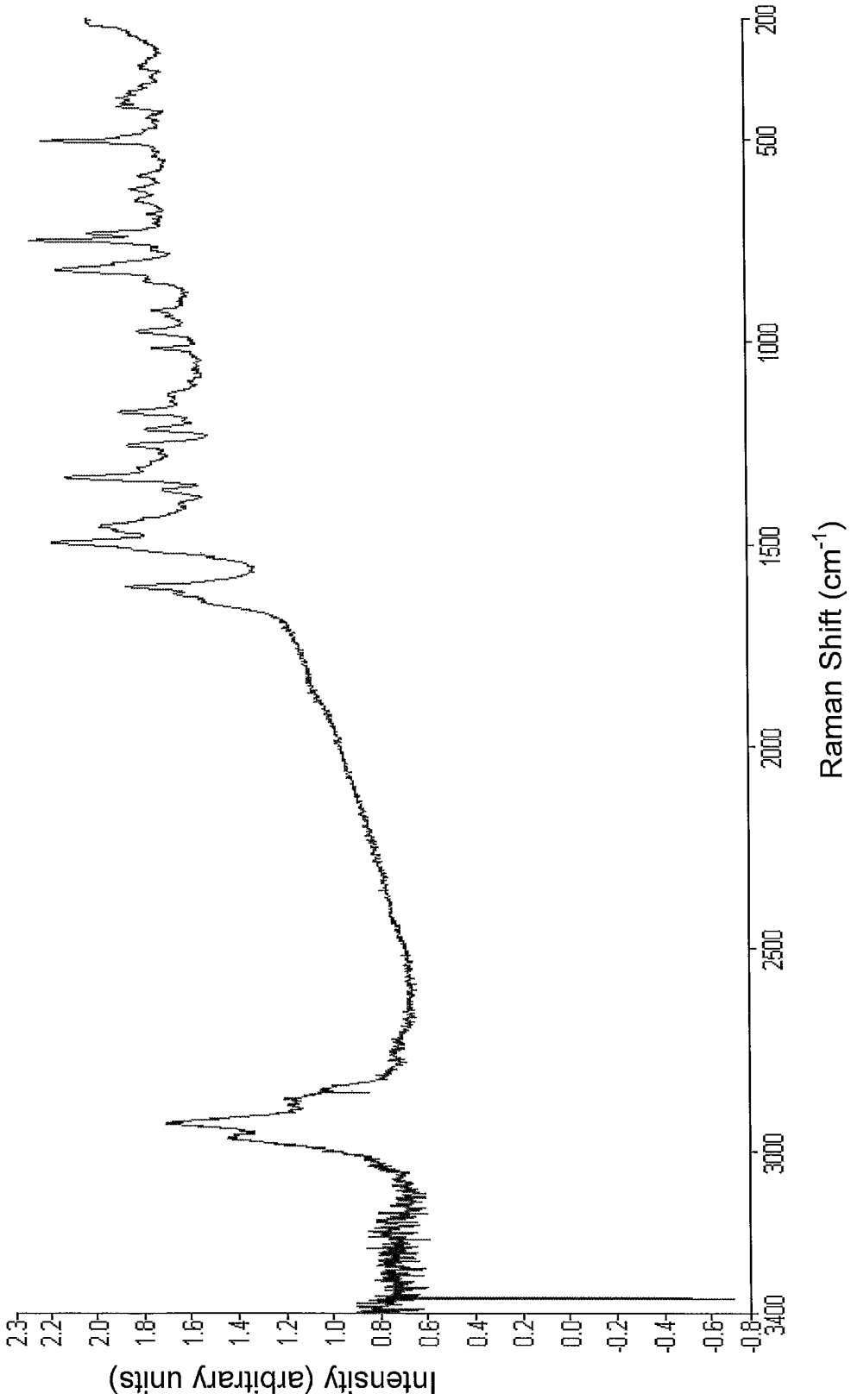

Intensity (arbitrary units)
2.3
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
3400
3000
2500
2000
1500
1000
500
200
Raman Shift (cm-1)

Figure 16.

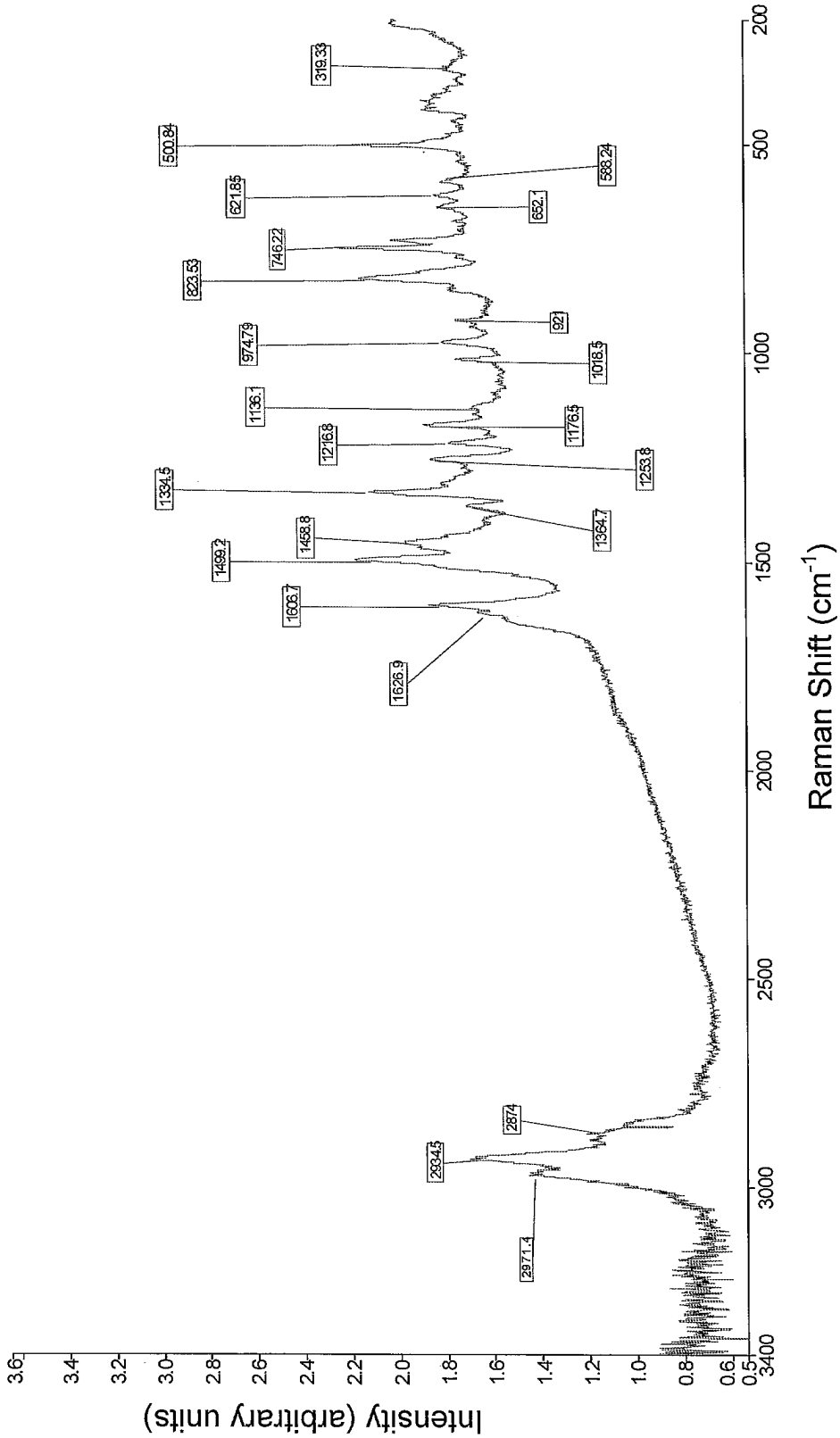

319.33
500.84
588.24
621.85
652.1
746.22
823.53
921
974.79
1018.5
1136.1
1176.5
1216.8
1253.8
1334.5
1364.7
1458.8
1499.2
1606.7
1626.9
2874
2934.5
2971.4
Intensity (arbitrary units)
Raman Shift (cm^{-1})
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.5
3400
3000
2500
2000
1500
1000
500
200

Figure 17.

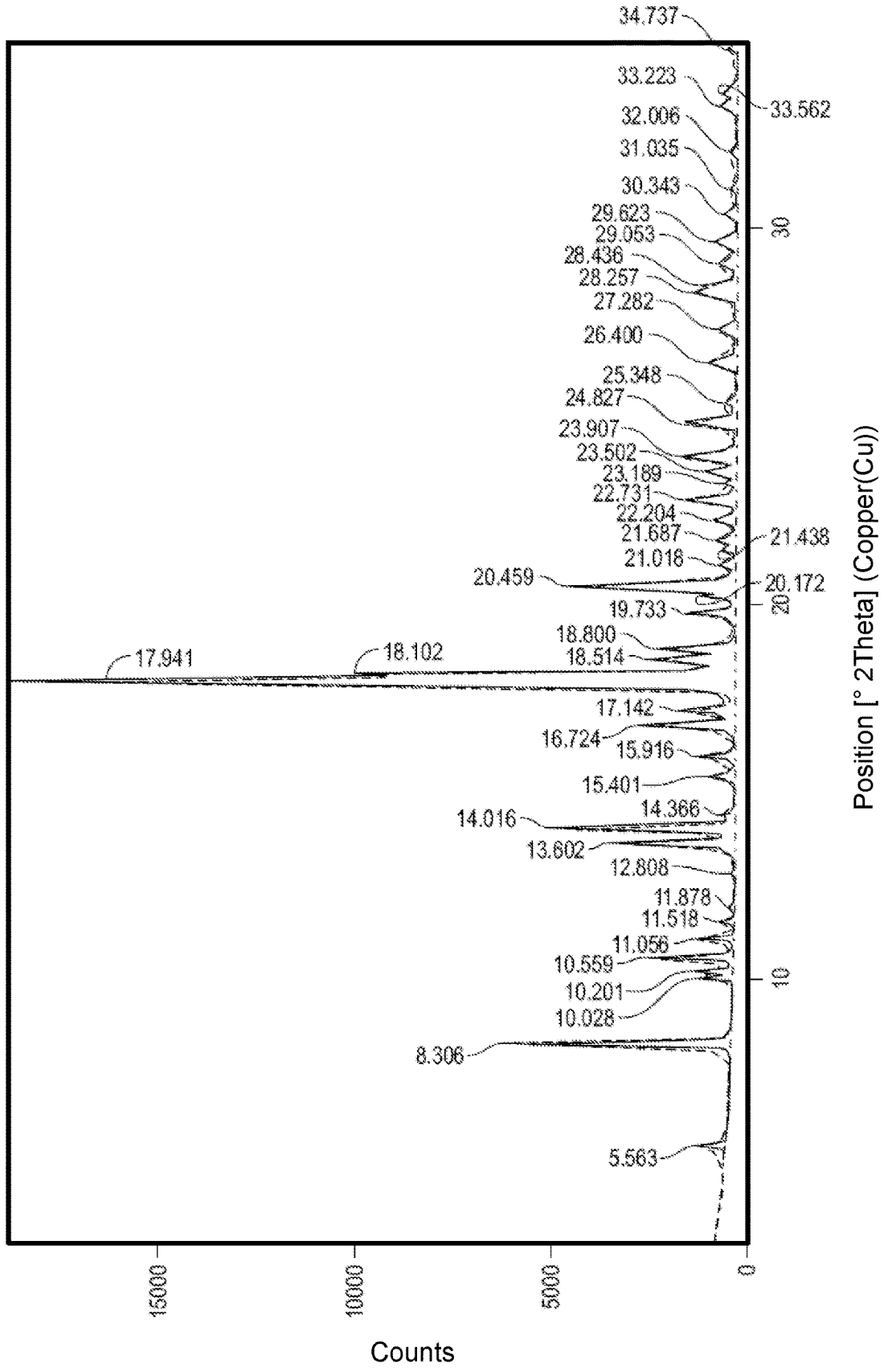

34.737
33.223
33.562
32.006
31.035
30.343
29.623
29.053
28.436
28.257
27.282
26.400
25.348
24.827
23.907
23.502
23.189
22.731
22.204
21.687
21.438
21.018
20.459
20.172
19.733
18.800
18.514
18.102
17.941
17.142
16.724
15.916
15.401
14.366
14.016
13.602
12.808
11.878
11.518
11.056
10.559
10.201
10.028
8.306
5.563
30
20
10
15000
10000
5000
0
Counts
Position [° 2Theta] (Copper(Cu))

Figure 18.

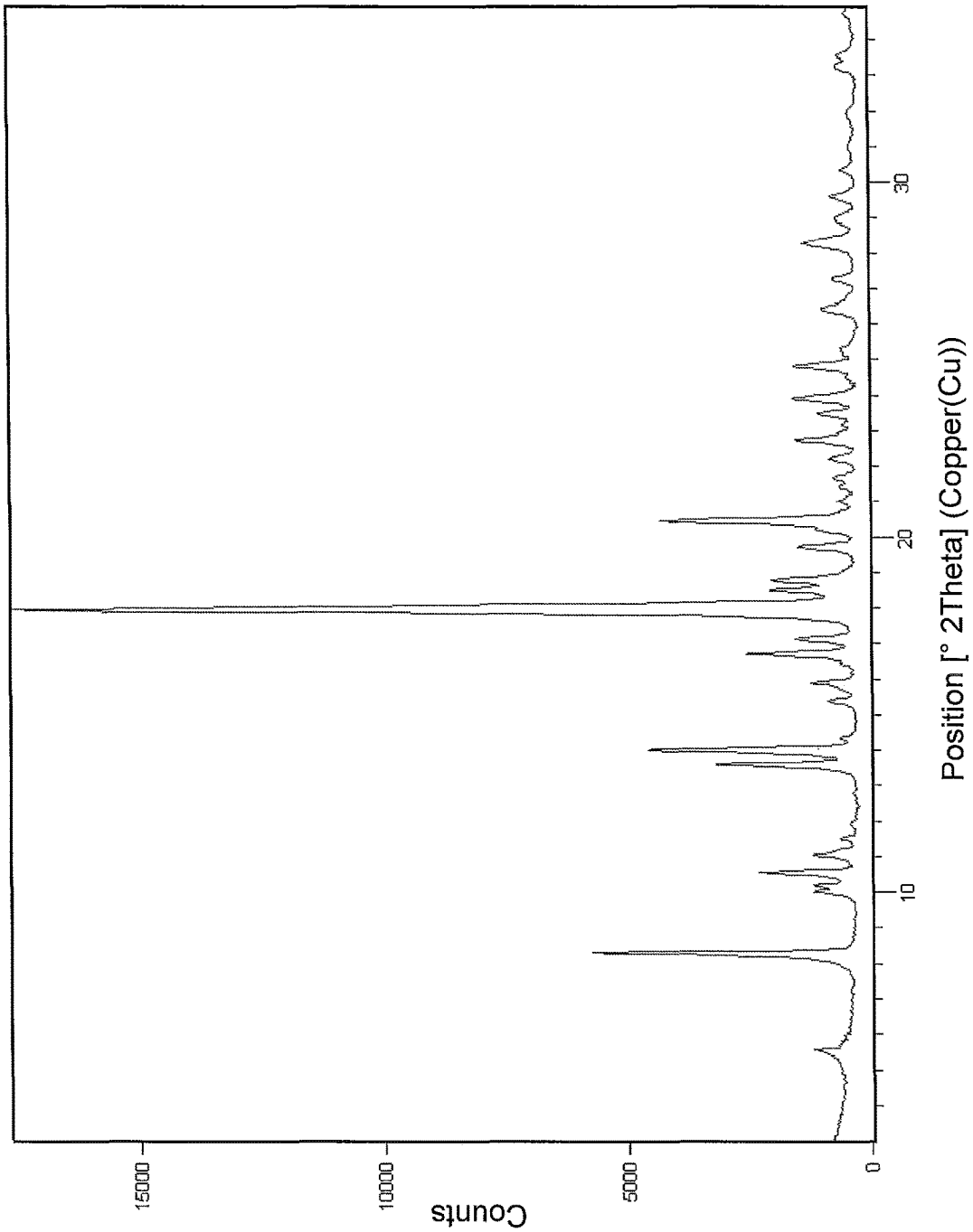


Figure 19.

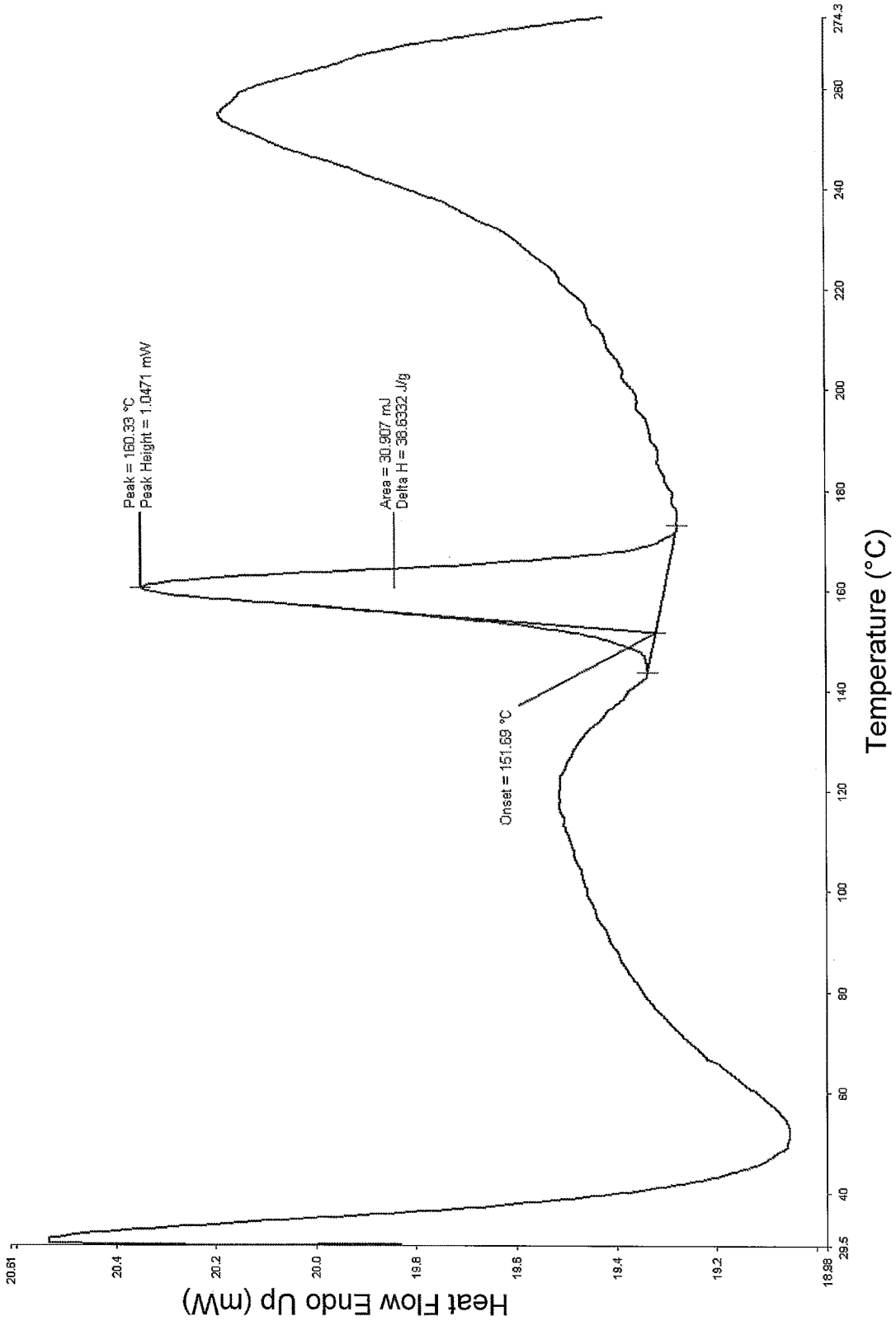
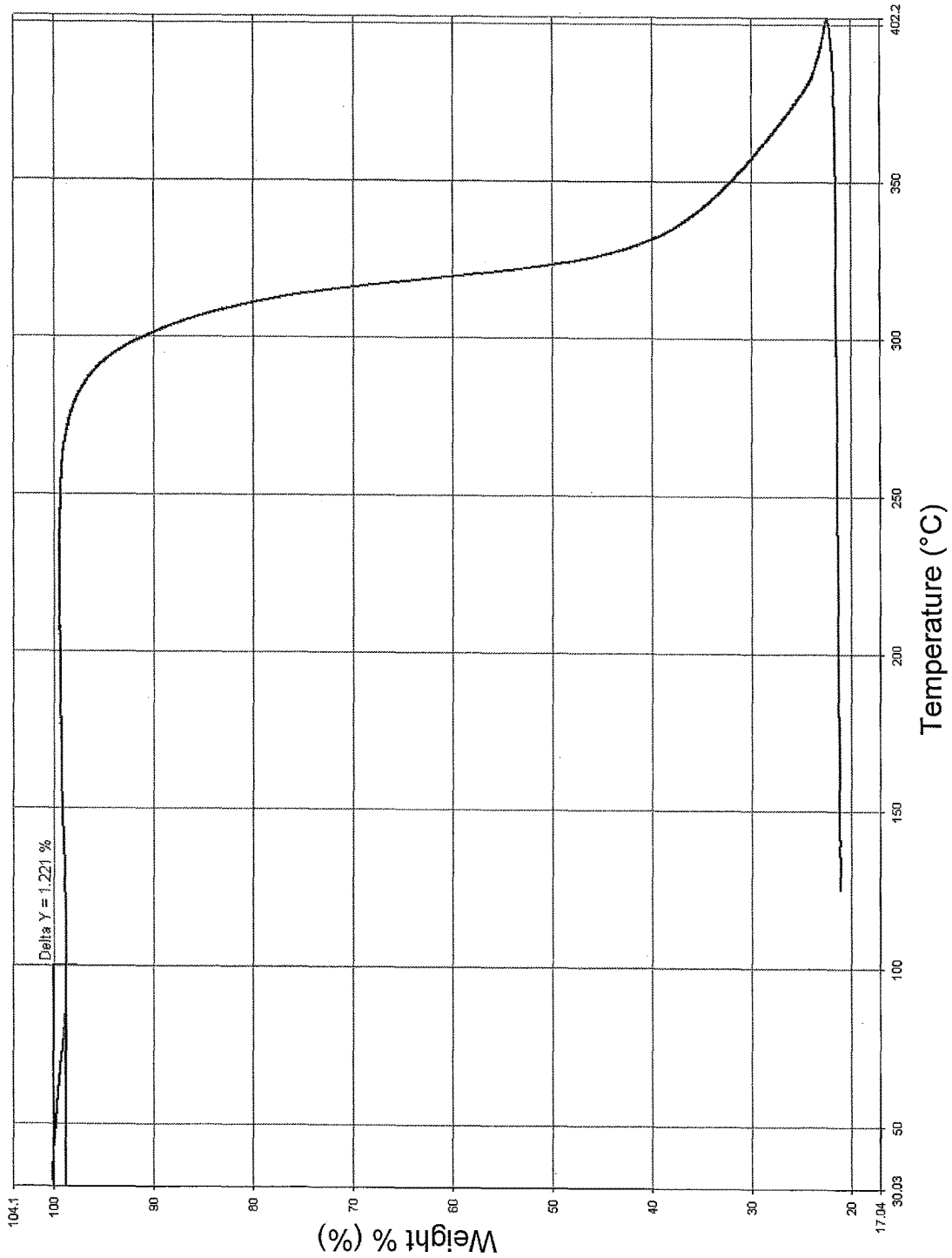

Peak = 160.33 °C
Peak Height = 1.0471 mW
Area = 30.907 mJ
Delta H = 38.6332 J/g
Onset = 151.69 °C
Heat Flow Endo Up (mW)
20.61
20.4
20.2
20.0
19.8
19.6
19.4
19.2
18.98
29.5
40
60
80
100
120
140
160
180
200
220
240
260
274.3
Temperature (°C)

Figure 20.


Delta Y = 1.221 %
104.1
100
90
80
70
60
50
40
30
20
17.04
Weight % (%)
30.03
50
100
150
200
250
300
350
402.2
Temperature (°C)

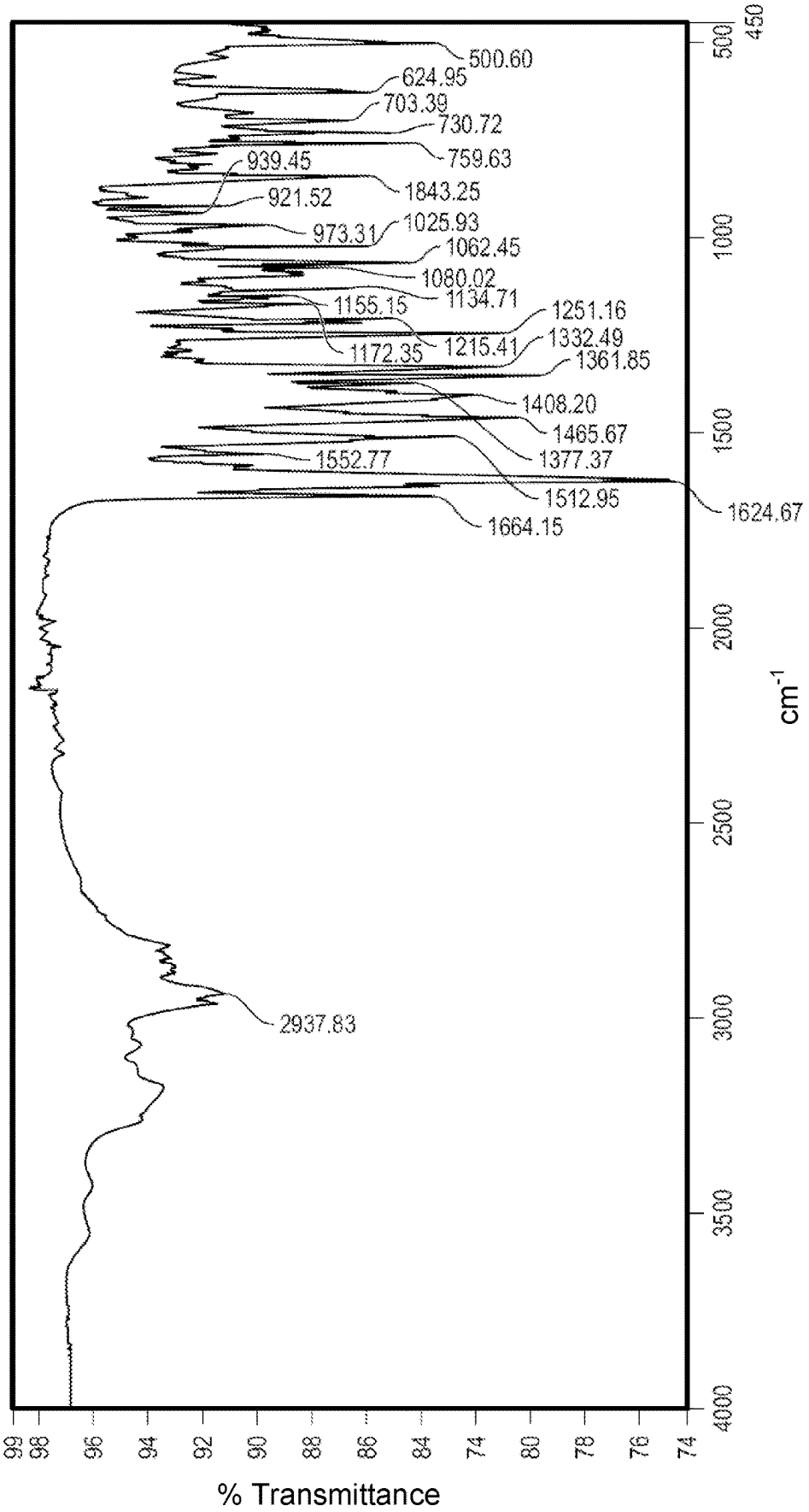

500.60
624.95
703.39
730.72
759.63
939.45
1843.25
921.52
973.31
1025.93
1062.45
1080.02
1134.71
1155.15
1251.16
1172.35
1215.41
1332.49
1361.85
1408.20
1465.67
1377.37
1552.77
1512.95
1624.67
1664.15
2937.83
450
500
1000
1500
2000
2500
3000
3500
4000
cm-1
99
98
96
94
92
90
88
86
84
74
80
78
76
74
% Transmittance

Figure 21.

Figure 22.

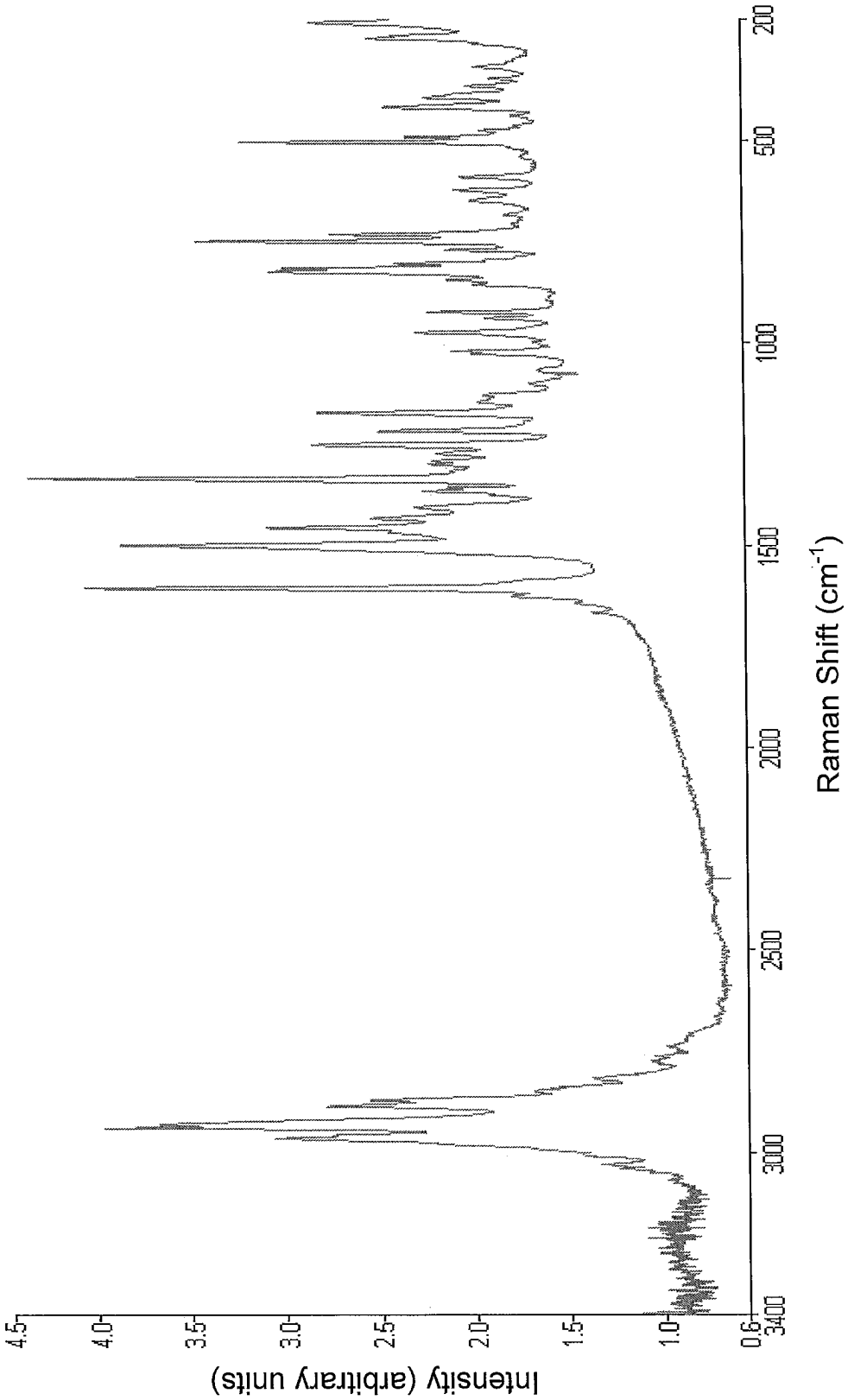

Intensity (arbitrary units)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.6
3400
3000
2500
2000
1500
1000
500
200
Raman Shift (cm-1)

Figure 23.

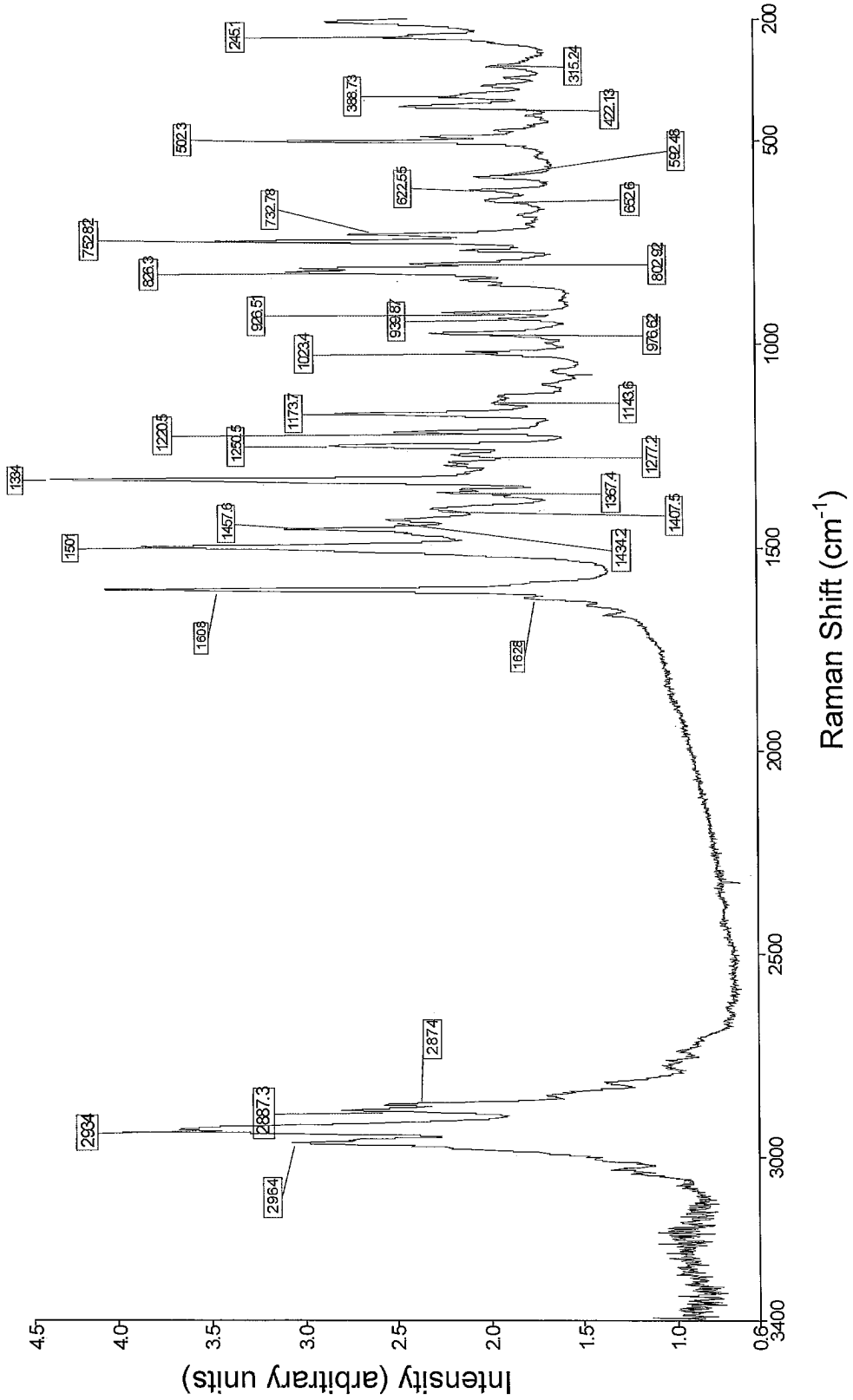

Intensity (arbitrary units)
Raman Shift (cm^{-1})
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.6
200
500
1000
1500
2000
2500
3000
3400
245.1
315.24
368.73
422.13
502.3
592.48
622.55
652.6
732.79
752.82
826.3
802.92
926.51
938.87
976.62
1023.4
1143.6
1173.7
1220.5
1250.5
1277.2
1334
1367.4
1407.5
1457.9
1434.2
150
1608
1628
2874
2887.3
2934
2964

Figure 24.

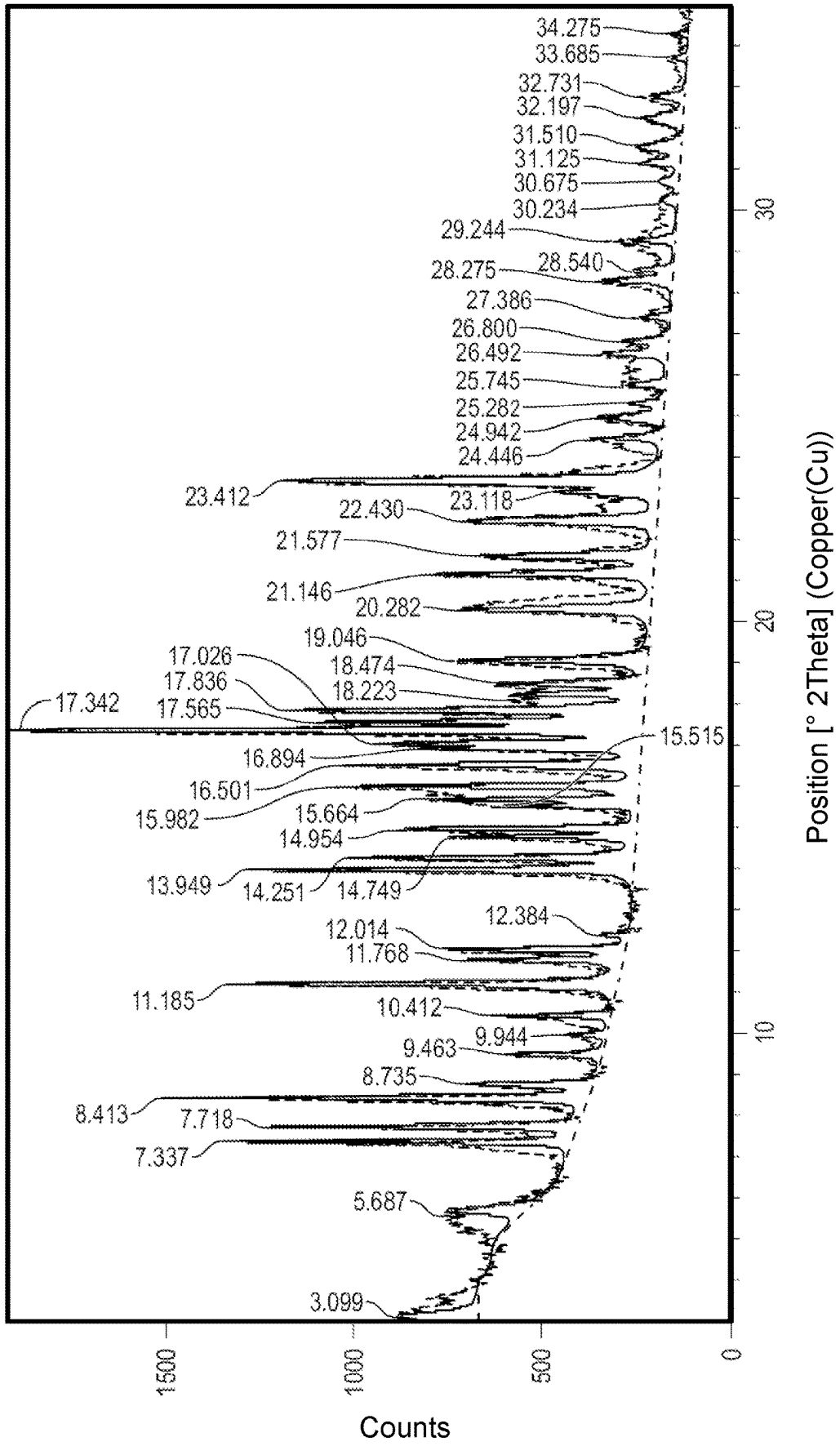

34.275
33.685
32.731
32.197
31.510
31.125
30.675
30.234
29.244
28.275
28.540
27.386
26.800
26.492
25.745
25.282
24.942
24.446
23.412
23.118
22.430
21.577
21.146
20.282
19.046
18.474
18.223
17.026
17.836
17.565
17.342
15.515
16.894
16.501
15.982
15.664
14.954
13.949
14.251
14.749
12.384
12.014
11.768
11.185
10.412
9.944
9.463
8.735
8.413
7.718
7.337
5.687
3.099
1500
1000
500
0
Counts
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 25.

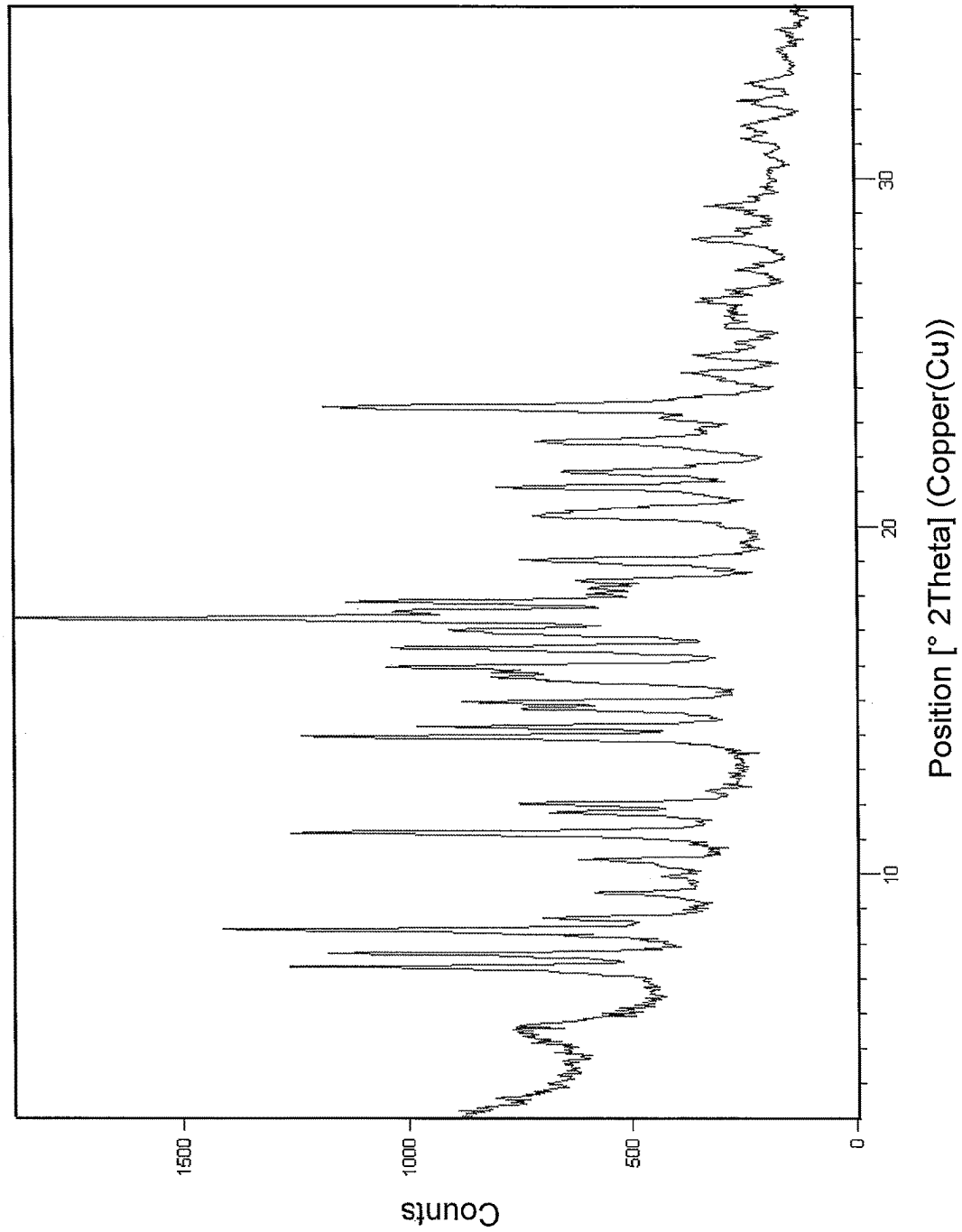


Figure 26.

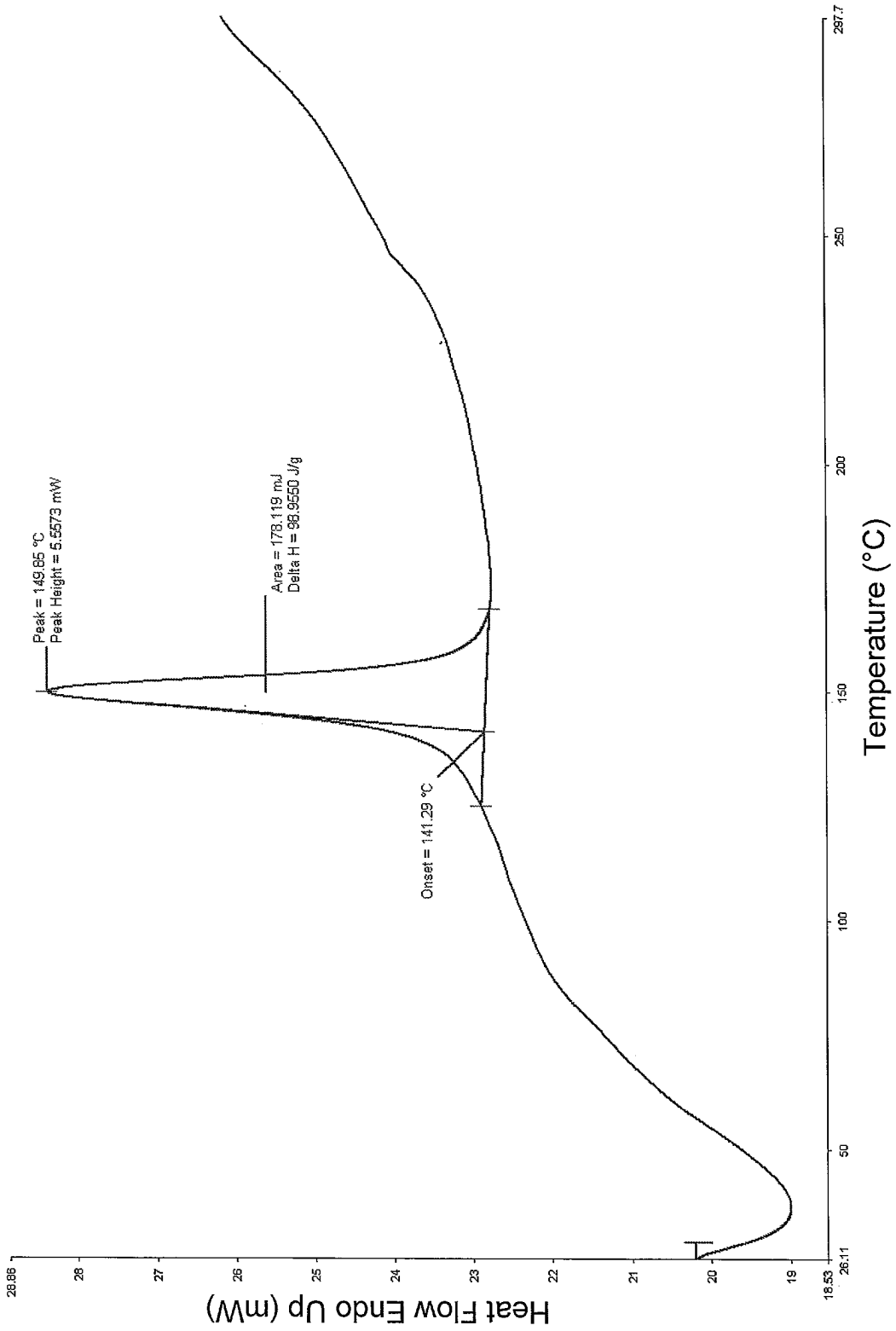

Peak = 149.85 °C
Peak Height = 5.5573 mW
Area = 178.119 mJ
Delta H = 98.9550 J/g
Onset = 141.29 °C
Heat Flow Endo Up (mW)
28.86
28
27
26
25
24
23
22
21
20
19
18.53
26.11
50
100
150
200
250
297.7
Temperature (°C)

Figure 27.

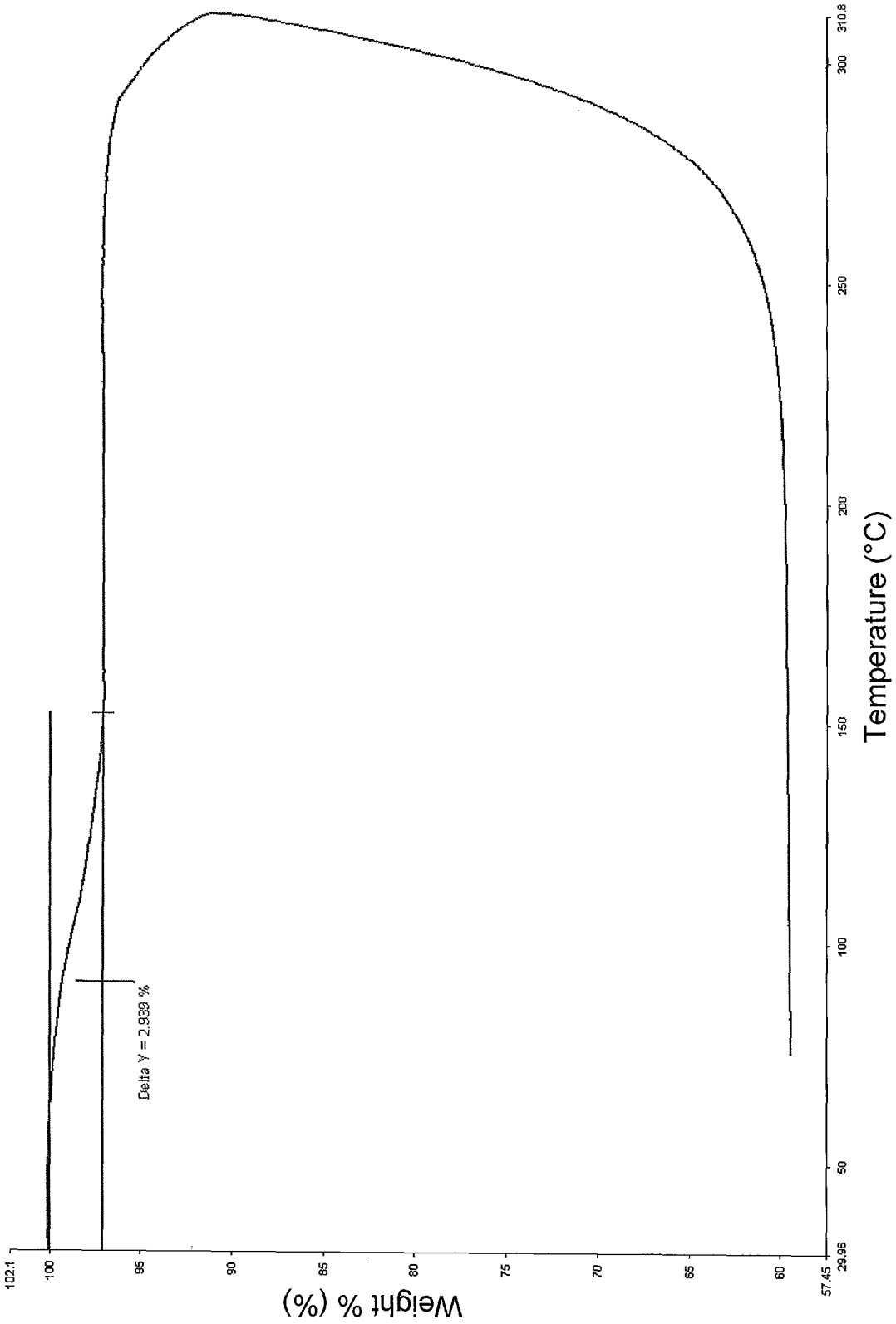

Weight % (%)
102.1
100
95
90
85
80
75
70
65
60
57.45
Delta Y = 2.939 %
29.96
50
100
150
200
250
300
310.8
Temperature (°C)

Figure 28.

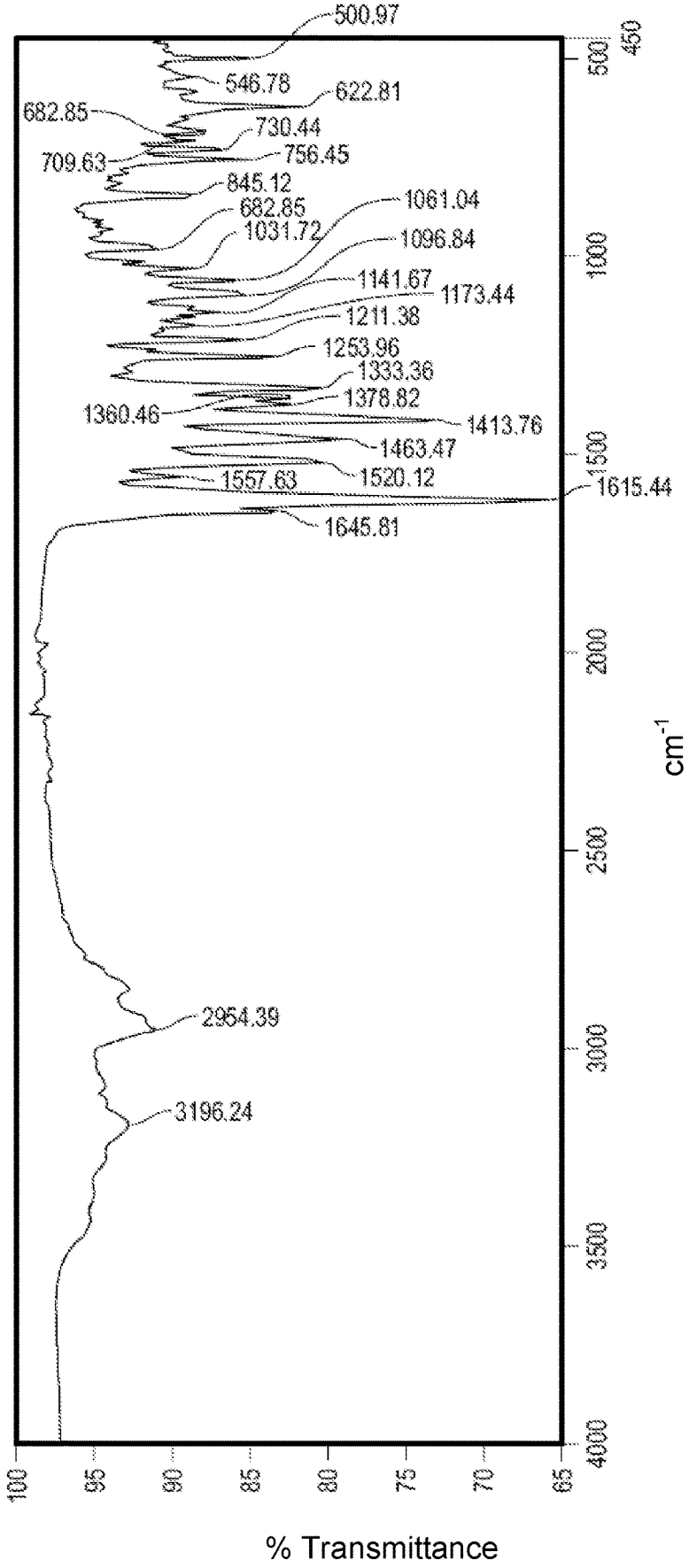

500.97
546.78
622.81
682.85
730.44
709.63
756.45
845.12
682.85
1061.04
1031.72
1096.84
1141.67
1173.44
1211.38
1253.96
1333.36
1378.82
1360.46
1413.76
1463.47
1557.63
1520.12
1615.44
1645.81
2954.39
3196.24
450
500
1000
1500
2000
2500
3000
3500
4000
cm-1
100
95
90
85
80
75
70
65
% Transmittance

Figure 29.

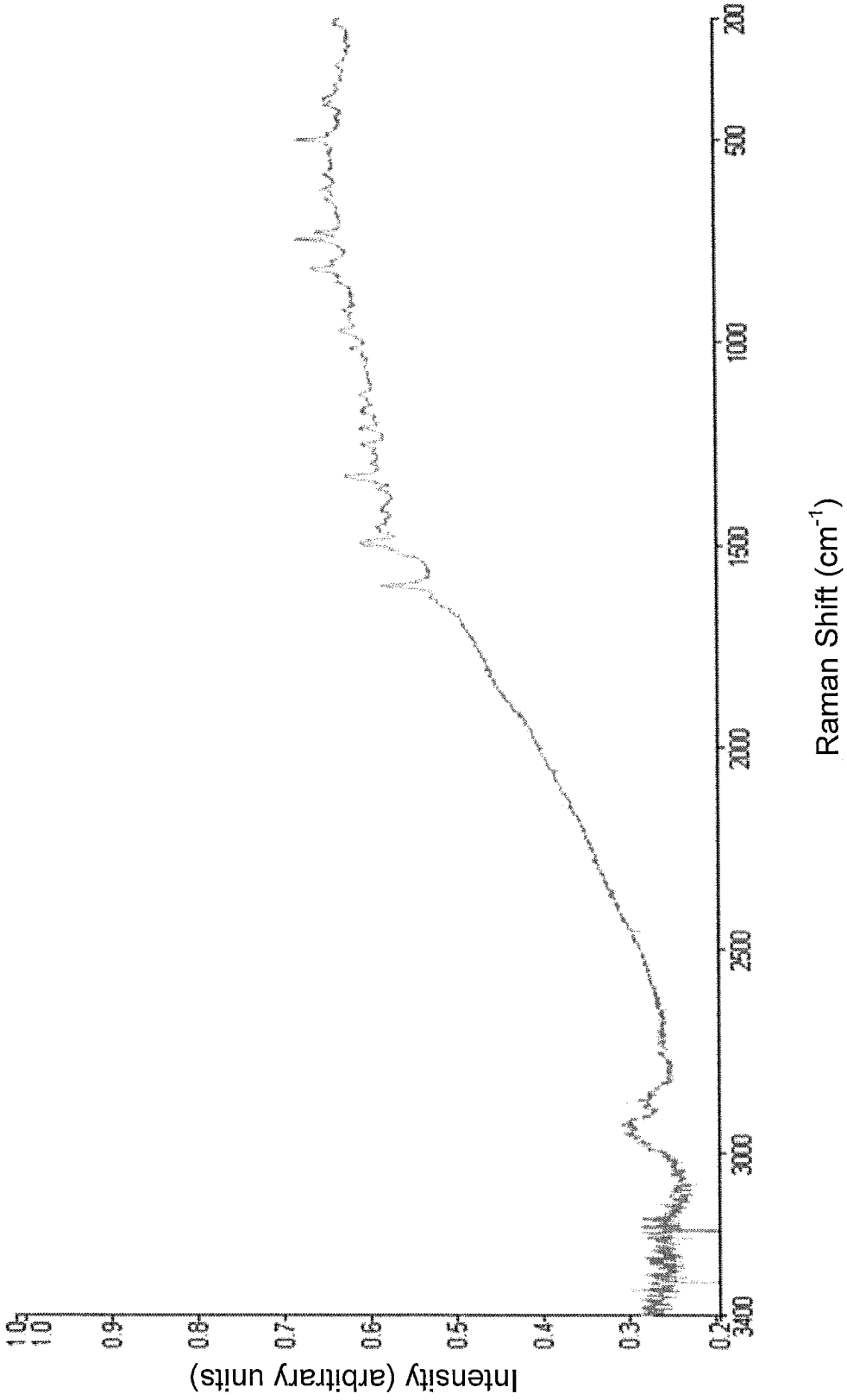

Intensity (arbitrary units)
1.0
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
3500
3000
2500
2000
1500
1000
500
200
Raman Shift (cm-1)

Figure 30.

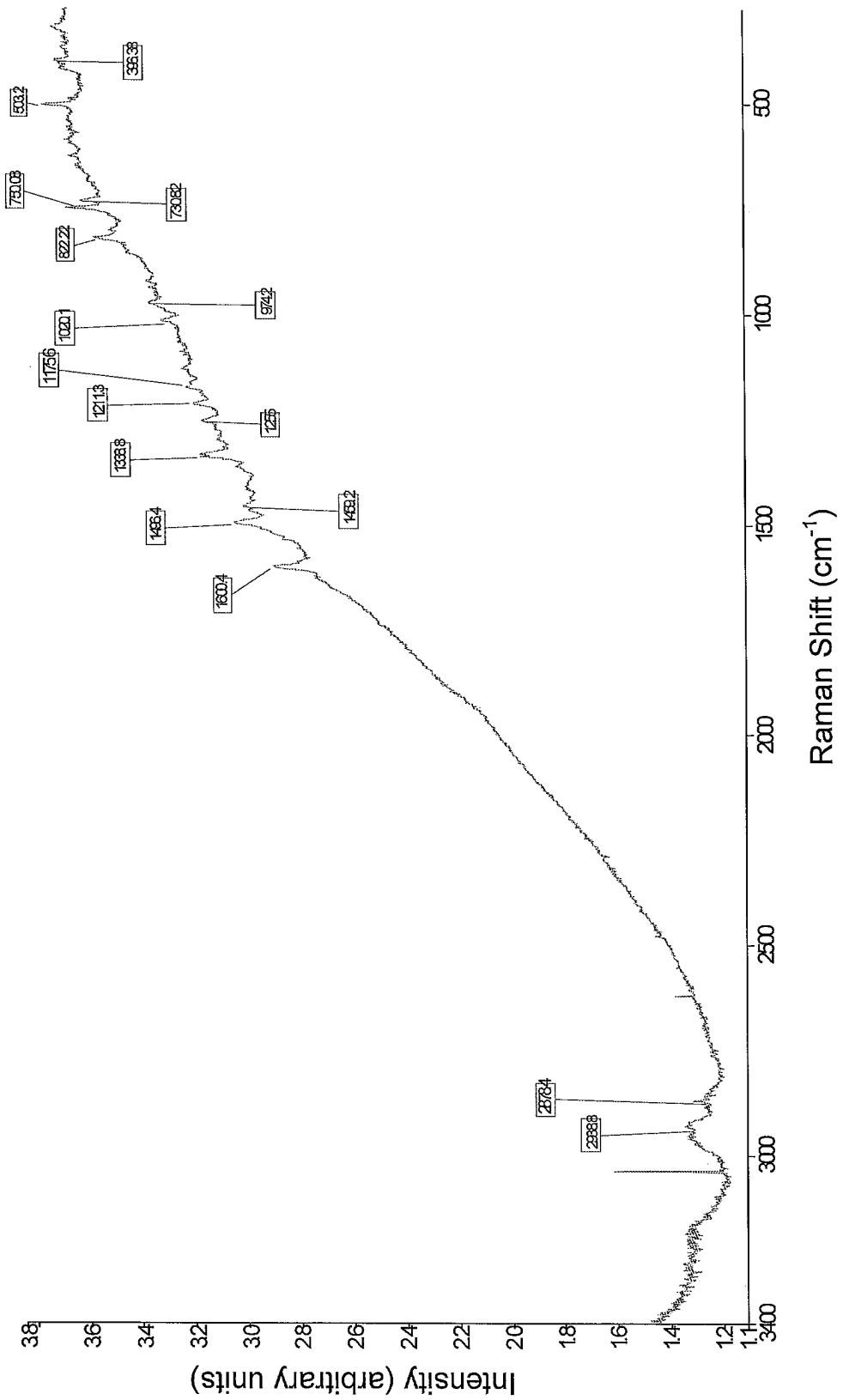

Intensity (arbitrary units)
Raman Shift (cm-1)
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.1
3400
3000
2500
2000
1500
1000
500
2878.4
2938.8
1630.4
1469.4
1459.2
1338.8
1211.3
1175.6
1126
1020.1
974.2
822.22
730.08
730.82
503.2
396.38

Figure 31.

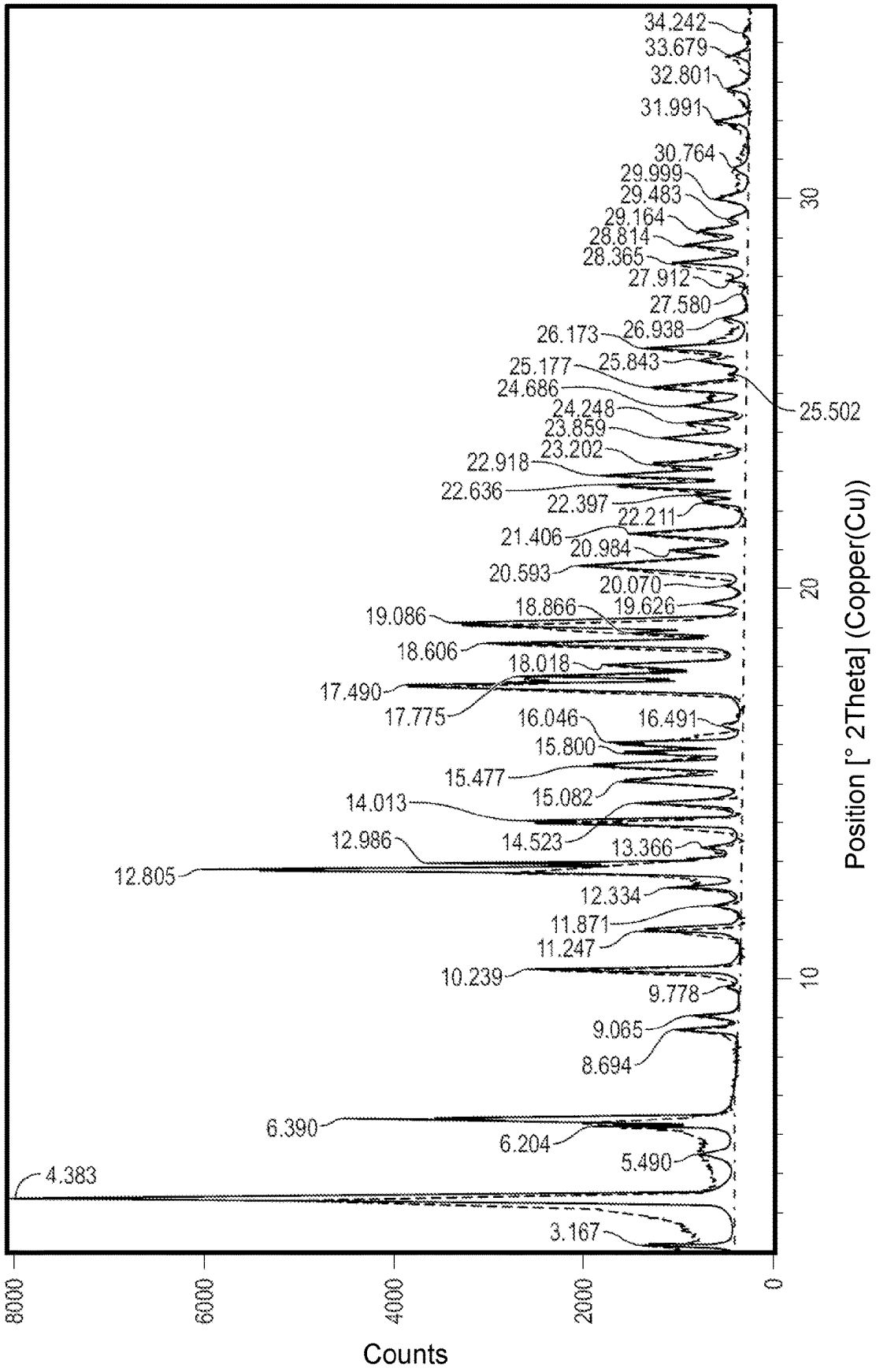

34.242
33.679
32.801
31.991
30.764
29.999
29.483
29.164
28.814
28.365
27.912
27.580
26.938
26.173
25.843
25.177
24.686
24.248
23.859
23.202
22.918
22.636
22.397
22.211
21.406
20.984
20.593
20.070
19.626
18.866
19.086
18.606
18.018
17.490
17.775
16.046
16.491
15.800
15.477
15.082
14.013
14.523
13.366
12.986
12.805
12.334
11.871
11.247
10.239
9.778
9.065
8.694
6.390
6.204
5.490
4.383
3.167
25.502
30
20
10
0
2000
4000
6000
8000
Counts
Position [° 2Theta] (Copper(Cu))

Figure 32.

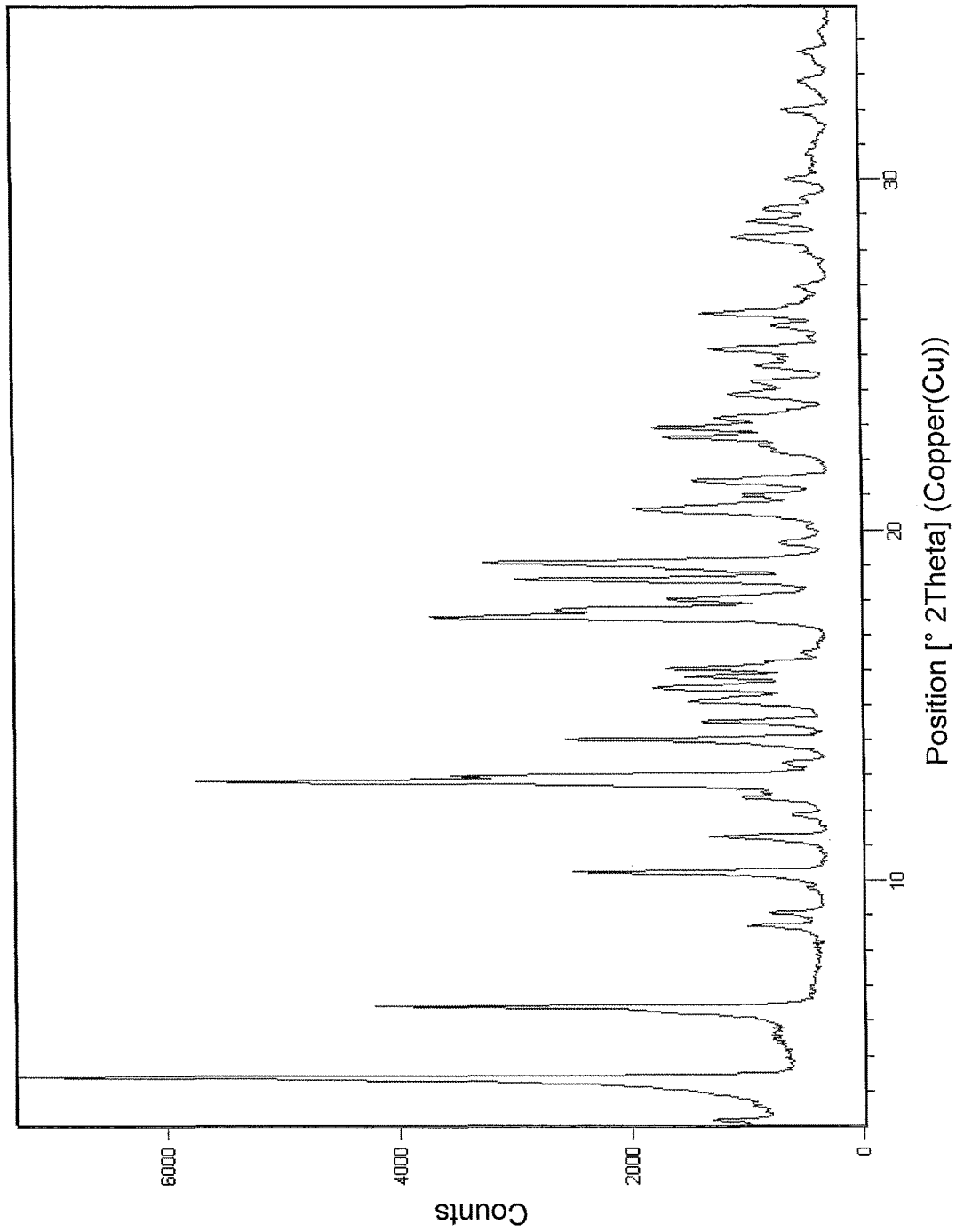


Figure 33.

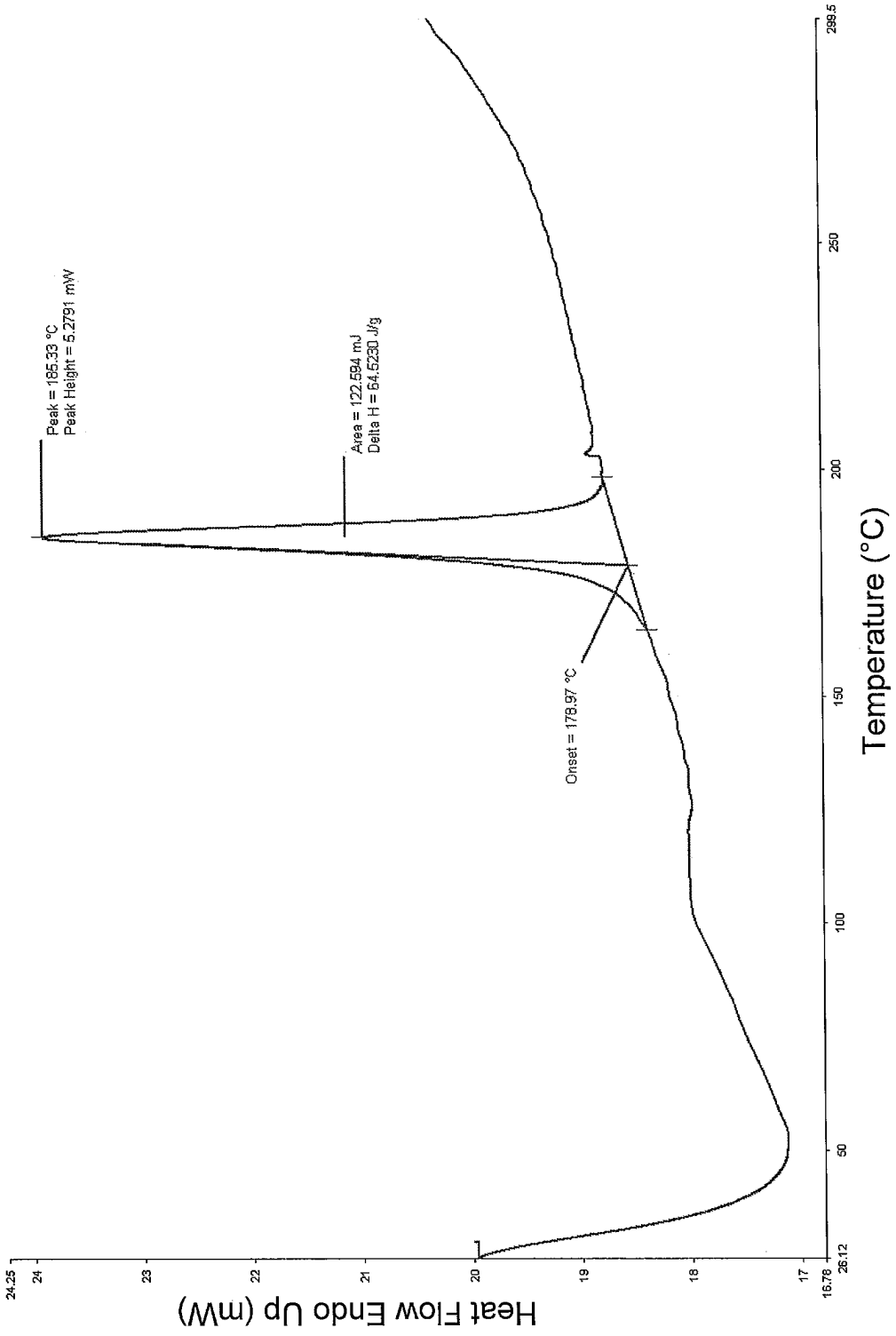

Peak = 185.33 °C
Peak Height = 5.2791 mW
Area = 122.594 mJ
Delta H = 64.5230 J/g
Onset = 178.97 °C
Heat Flow Endo Up (mW)
24.25
24
23
22
21
20
19
18
17
16.78
26.12
50
100
150
200
250
299.5
Temperature (°C)

Figure 34.

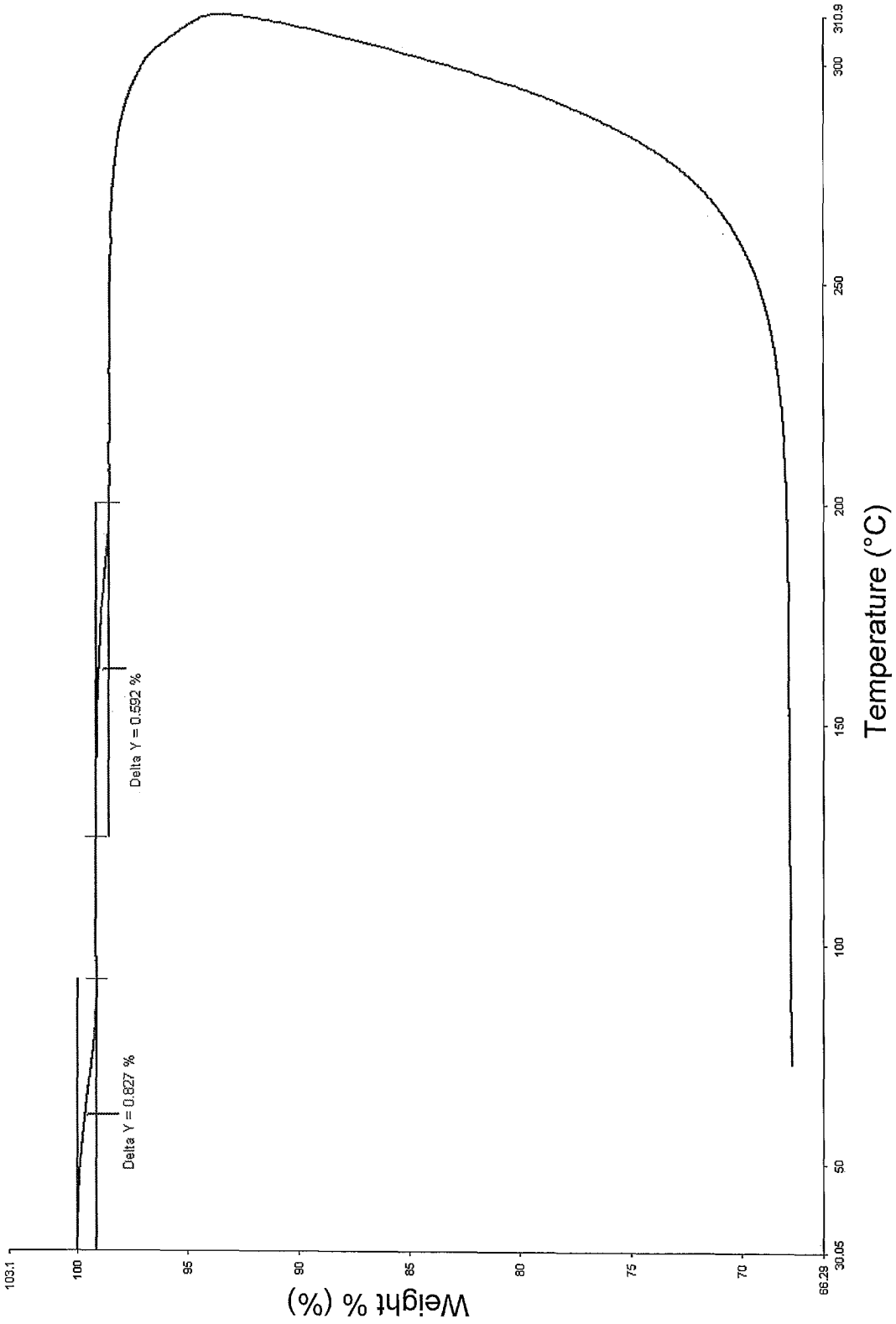

Delta Y = 0.827 %
Delta Y = 0.592 %
103.1
100
95
90
85
80
75
70
66.29
Weight % (%)
30.05
50
100
150
200
250
300
310.9
Temperature (°C)

Figure 35.

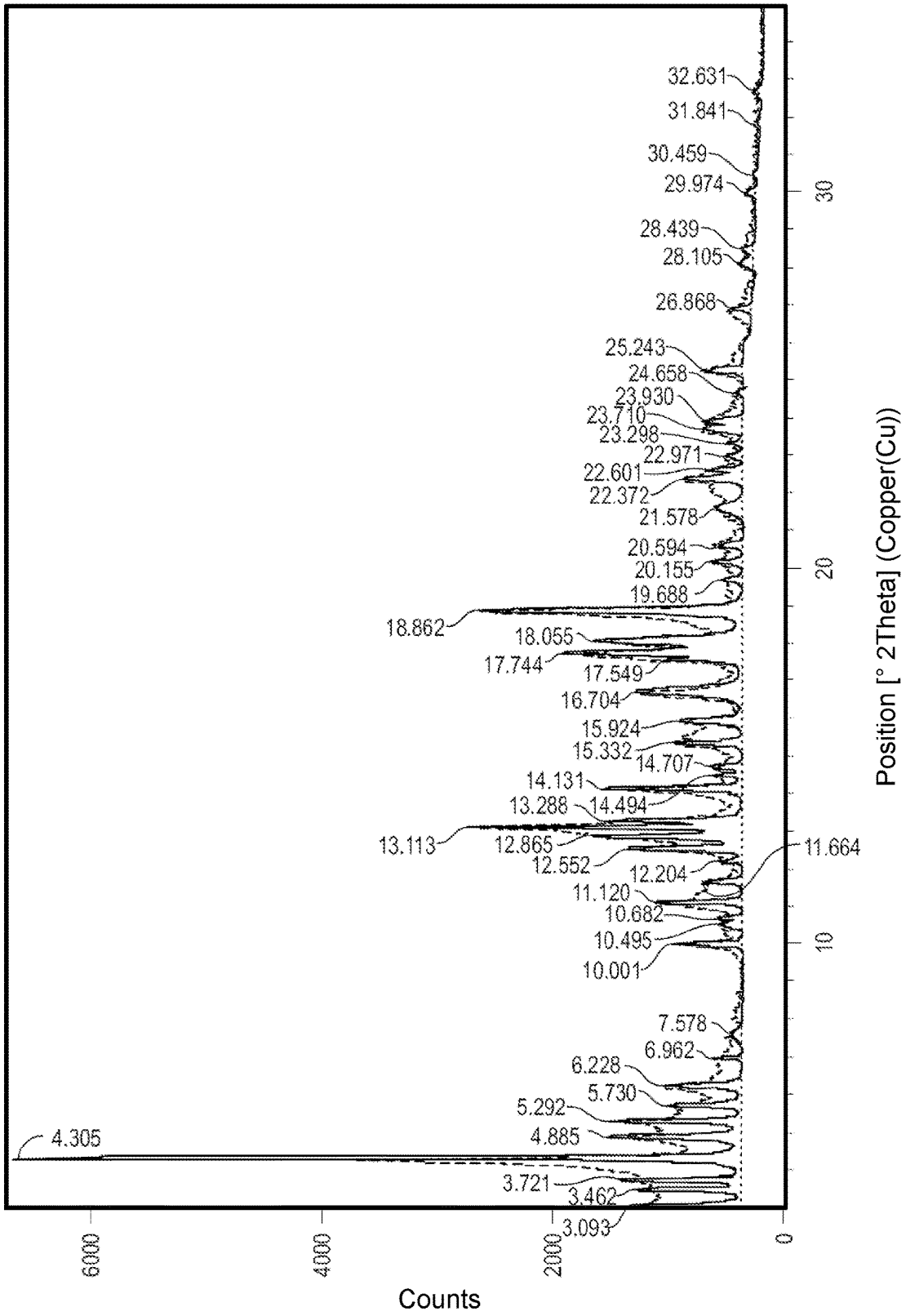

32.631
31.841
30.459
29.974
28.439
28.105
26.868
25.243
24.658
23.930
23.710
23.298
22.971
22.601
22.372
21.578
20.594
20.155
19.688
18.862
18.055
17.744
17.549
16.704
15.924
15.332
14.707
14.131
13.288
14.494
13.113
12.865
12.552
12.204
11.664
11.120
10.682
10.495
10.001
7.578
6.962
6.228
5.730
5.292
4.885
4.305
3.721
3.462
3.093
6000
4000
2000
0
Counts
30
20
10
Position [° 2Theta] (Copper(Cu))

Figure 36.

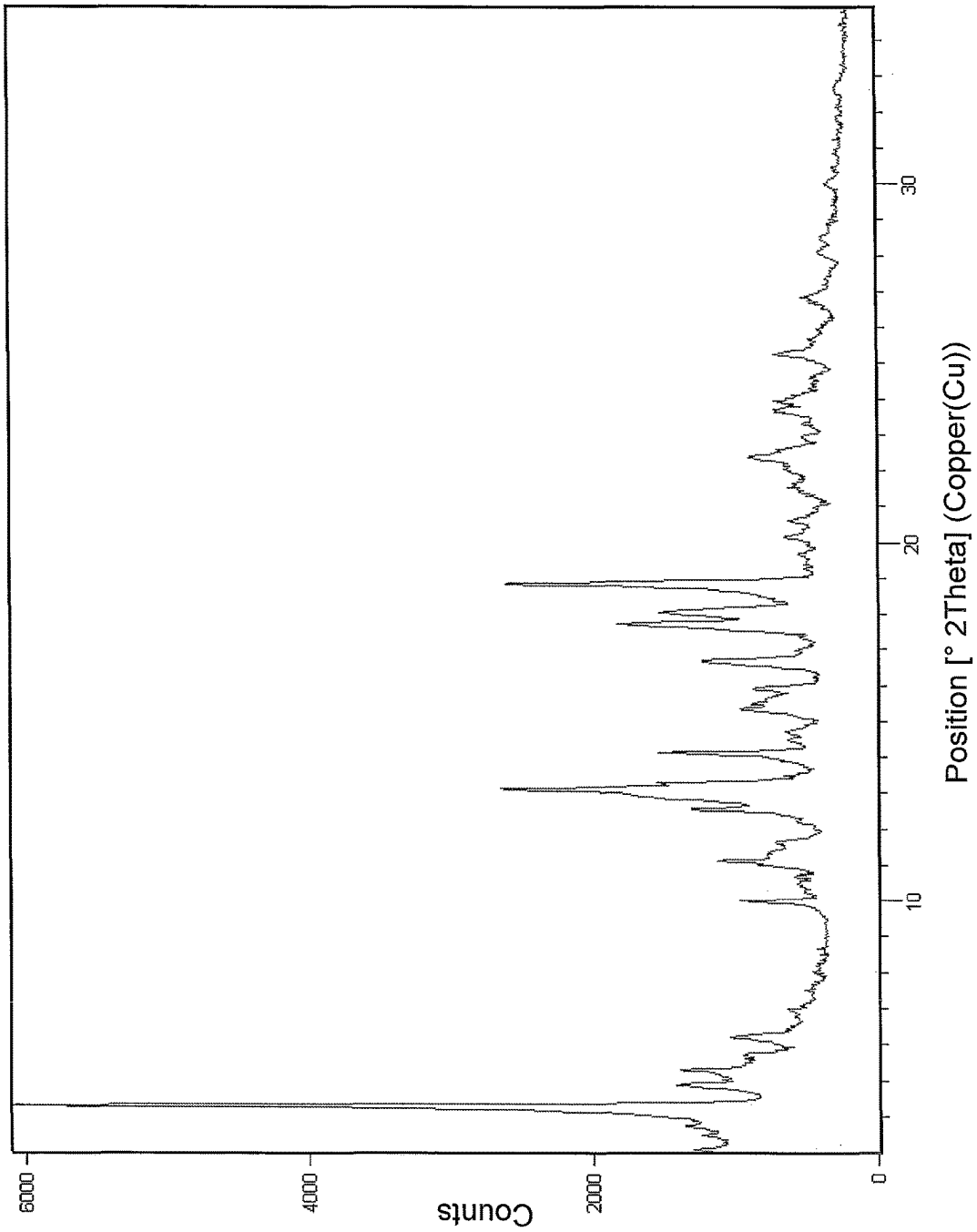


Figure 37.

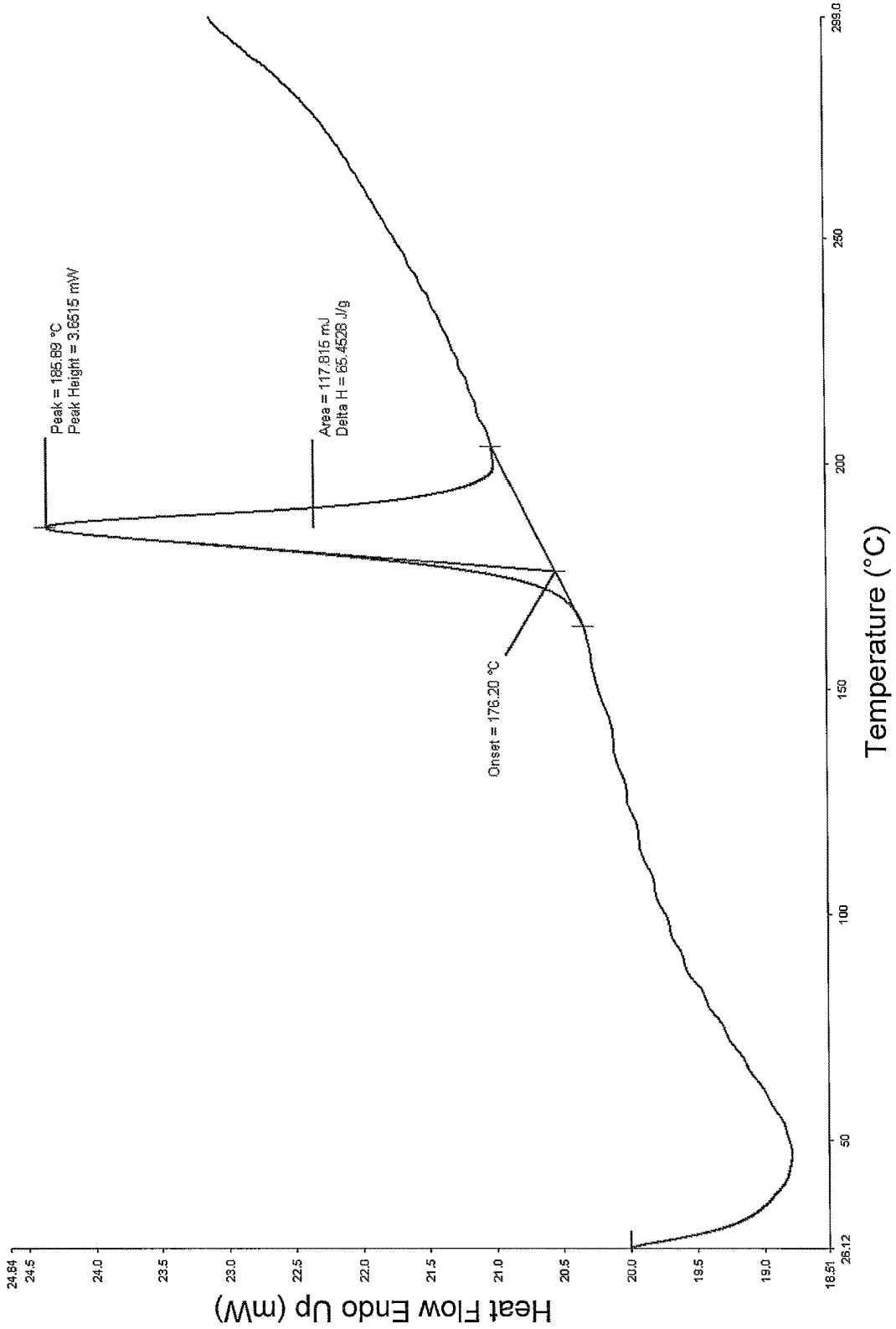

Peak = 185.89 °C
Peak Height = 3.6515 mW
Area = 117.815 mJ
Delta H = 65.4528 J/g
Onset = 176.20 °C
Heat Flow Endo Up (mW)
24.64
24.5
24.0
23.5
23.0
22.5
22.0
21.5
21.0
20.5
20.0
19.5
19.0
18.51
26.12
50
100
150
200
250
299.0
Temperature (°C)

Figure 38.

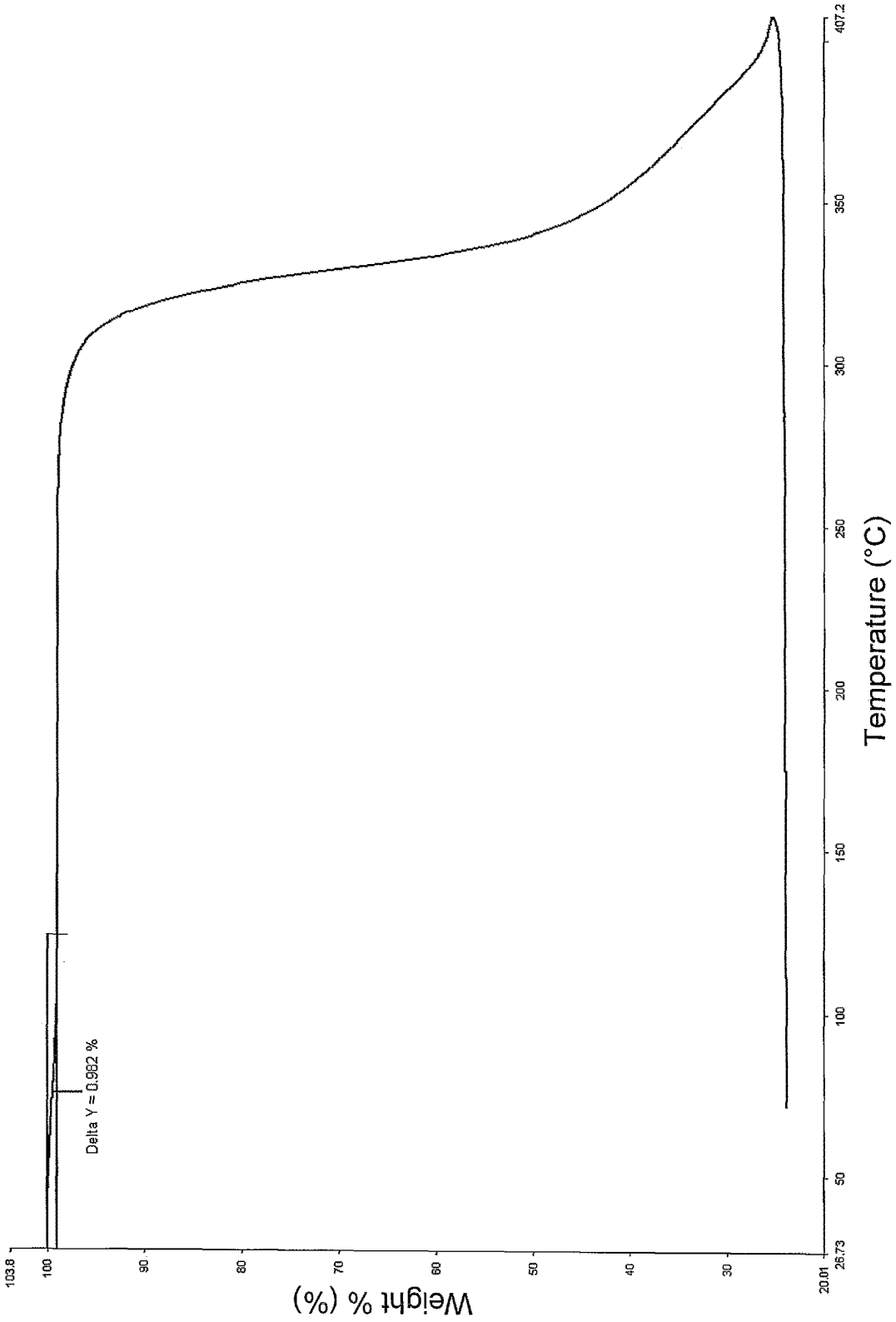

Delta Y = 0.982 %
103.8
100
90
80
70
60
50
40
30
20.01
Weight % (%)
26.73
50
100
150
200
250
300
350
407.2
Temperature (°C)

Figure 39.

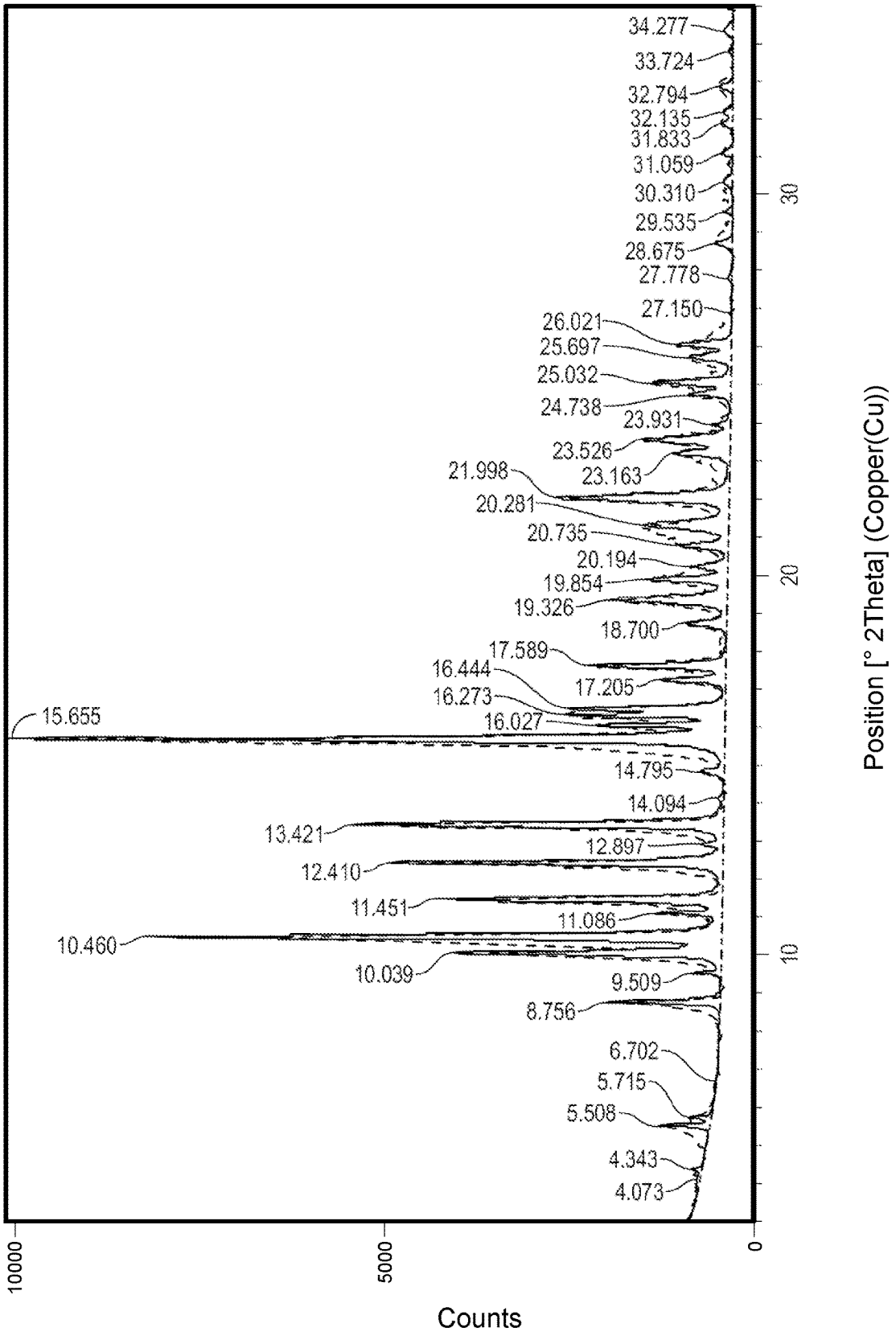

34.277
33.724
32.794
32.135
31.833
31.059
30.310
29.535
28.675
27.778
27.150
26.021
25.697
25.032
24.738
23.931
23.526
23.163
21.998
20.281
20.735
20.194
19.854
19.326
18.700
17.589
16.444
17.205
16.273
16.027
15.655
14.795
14.094
13.421
12.897
12.410
11.451
11.086
10.460
10.039
9.509
8.756
6.702
5.715
5.508
4.343
4.073
10000
5000
0
Counts
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 40.

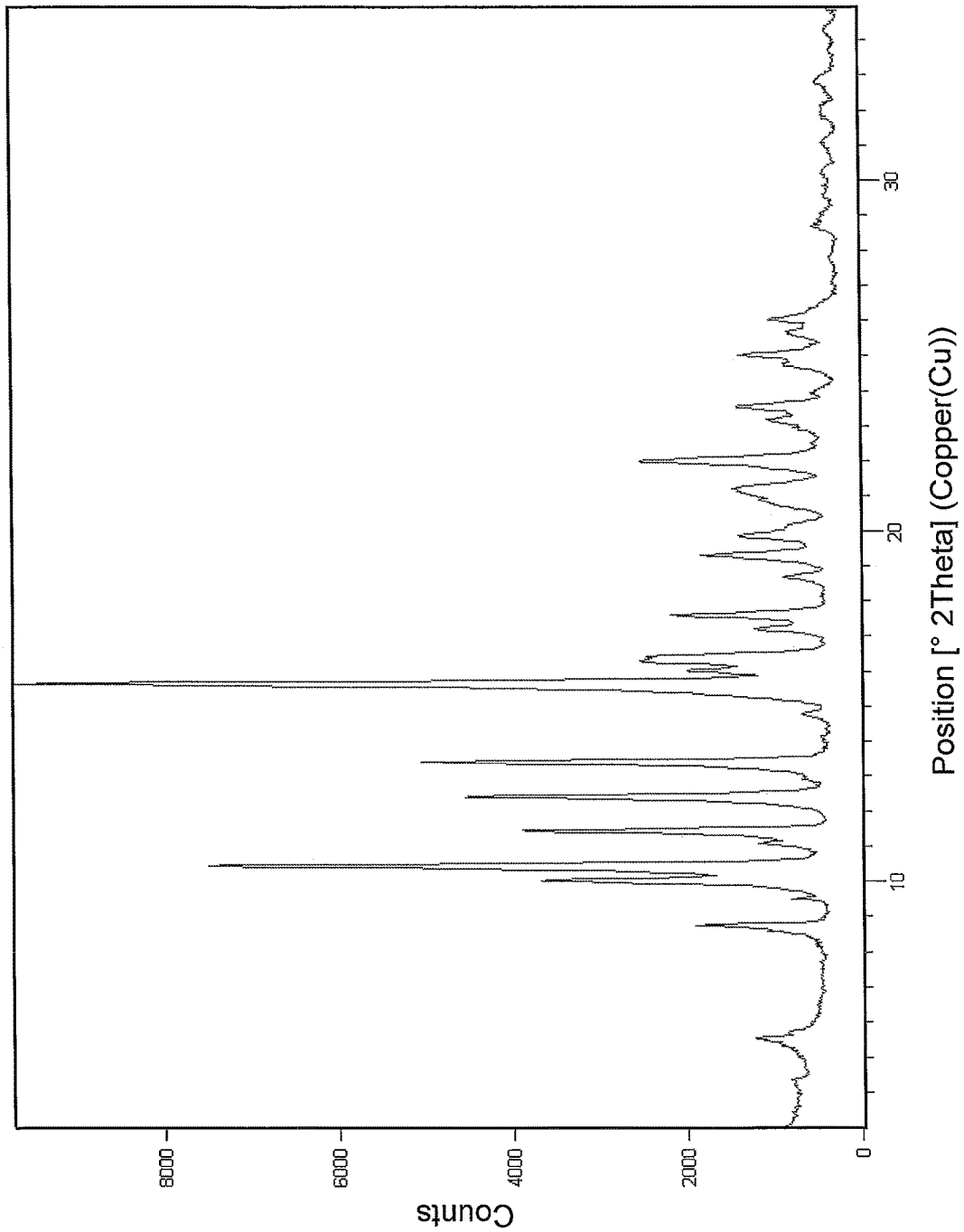

Counts
8000
6000
4000
2000
0
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 41.

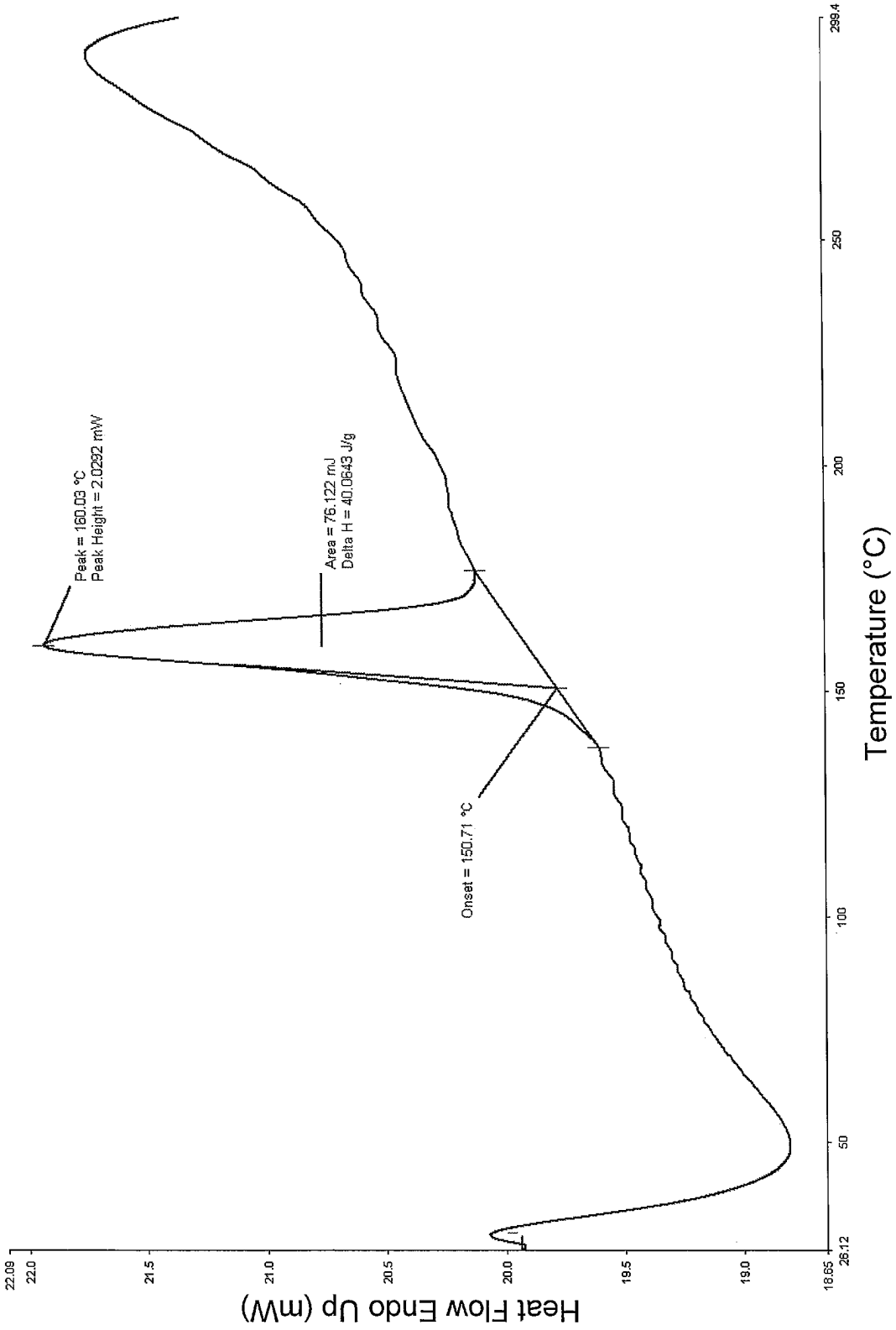

Peak = 160.03 °C
Peak Height = 2.0292 mW
Area = 76.122 mJ
Delta H = 40.0643 J/g
Onset = 150.71 °C
Heat Flow Endo Up (mW)
22.09
22.0
21.5
21.0
20.5
20.0
19.5
19.0
18.65
Temperature (°C)
26.12
50
100
150
200
250
299.4

Figure 42.

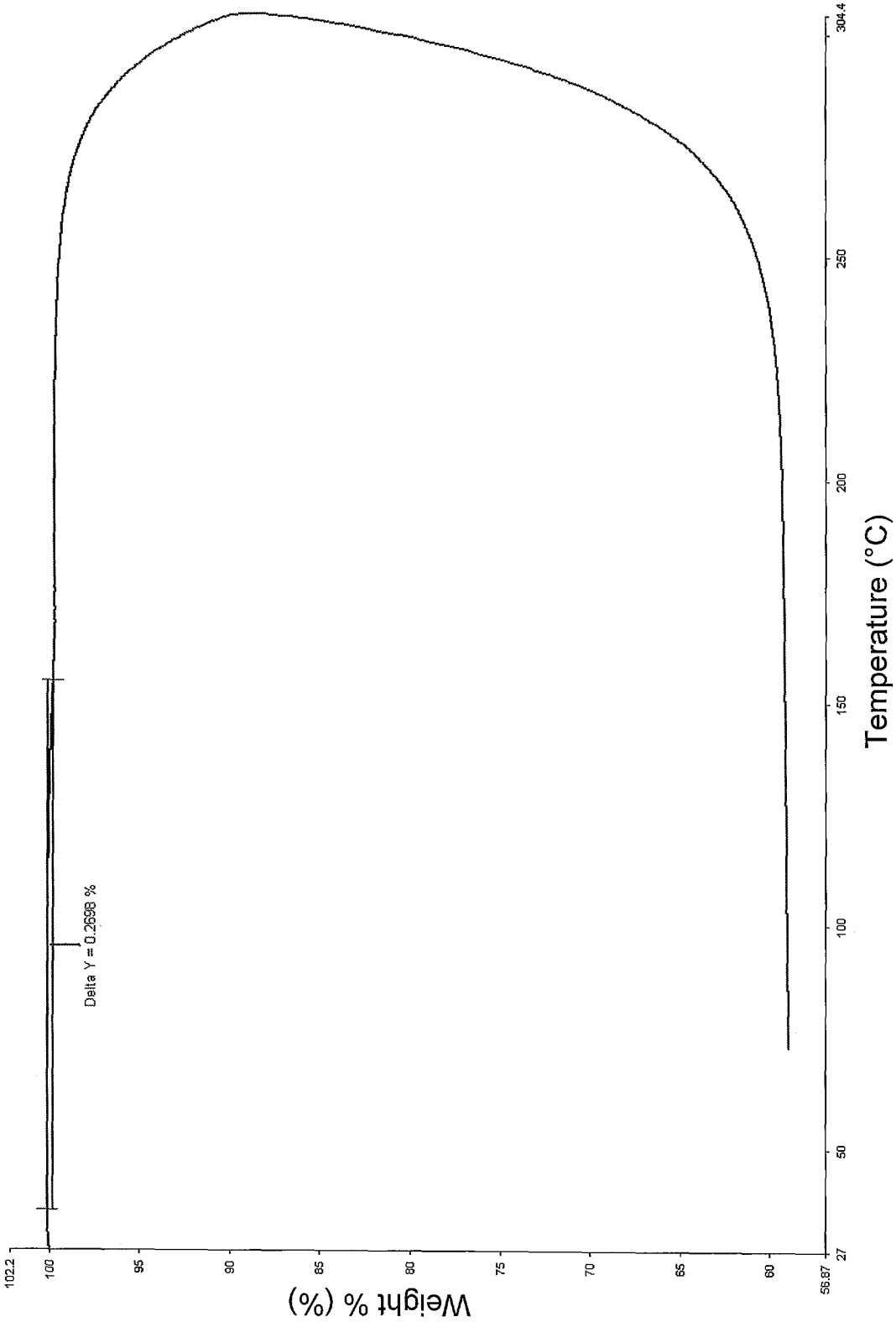

Delta Y = 0.2698 %
102.2
100
95
90
85
80
75
70
65
60
56.87
Weight % (%)
27
50
100
150
200
250
304.4
Temperature (°C)

Figure 43.

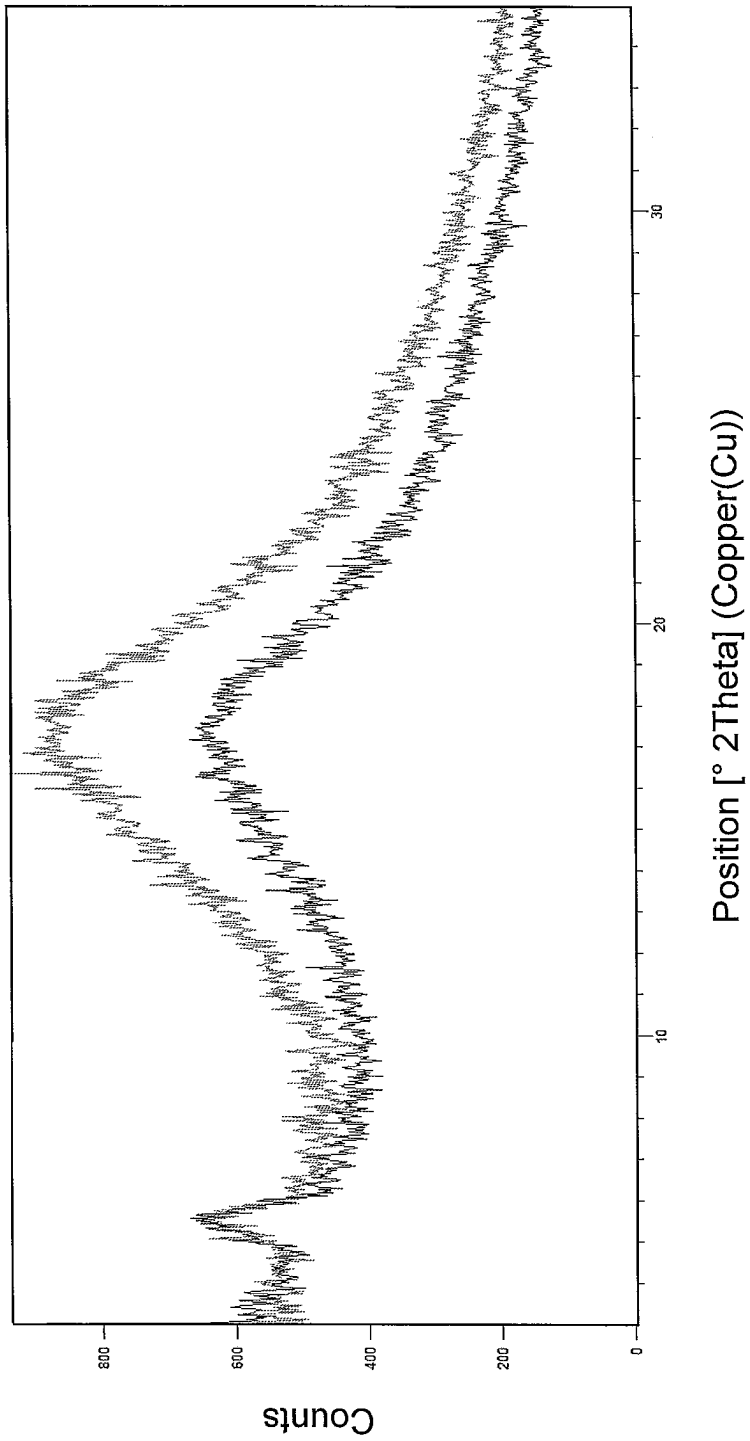


Figure 44.

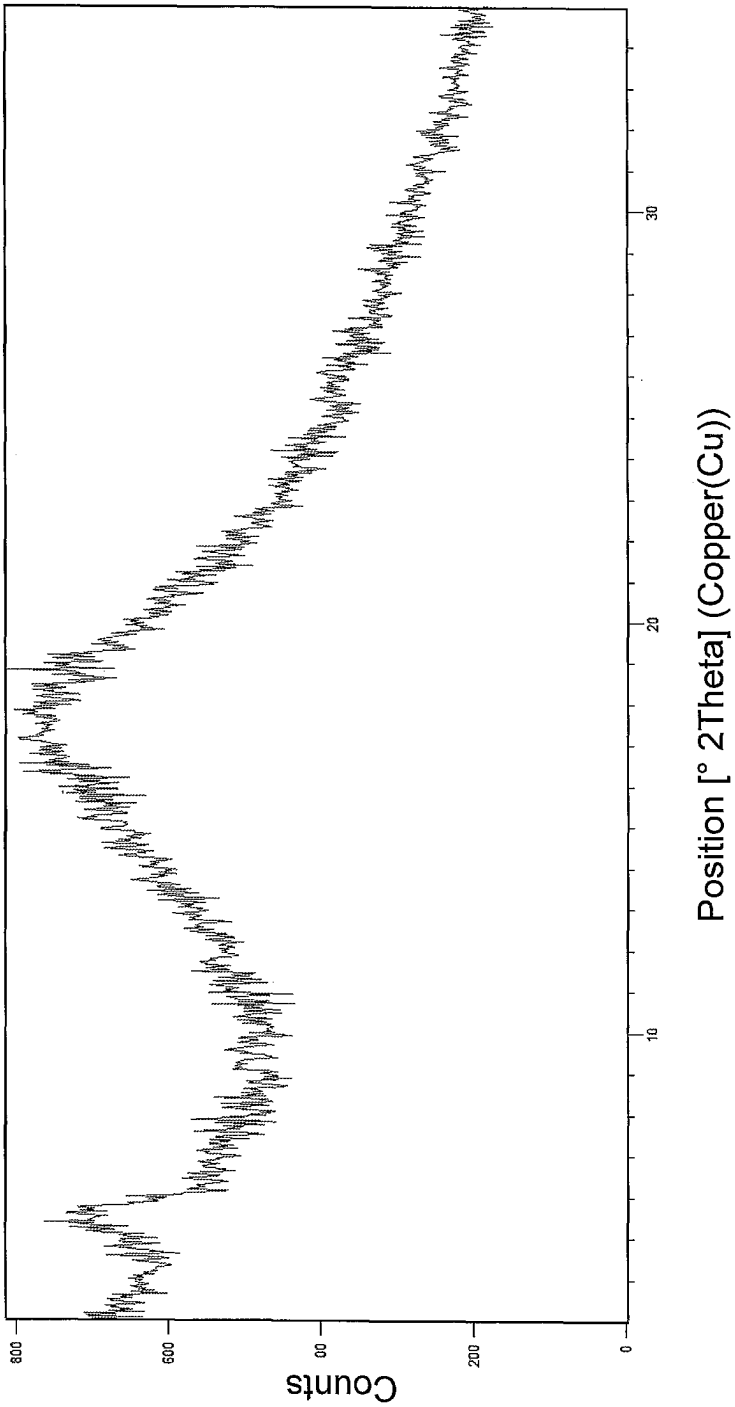


Figure 45.

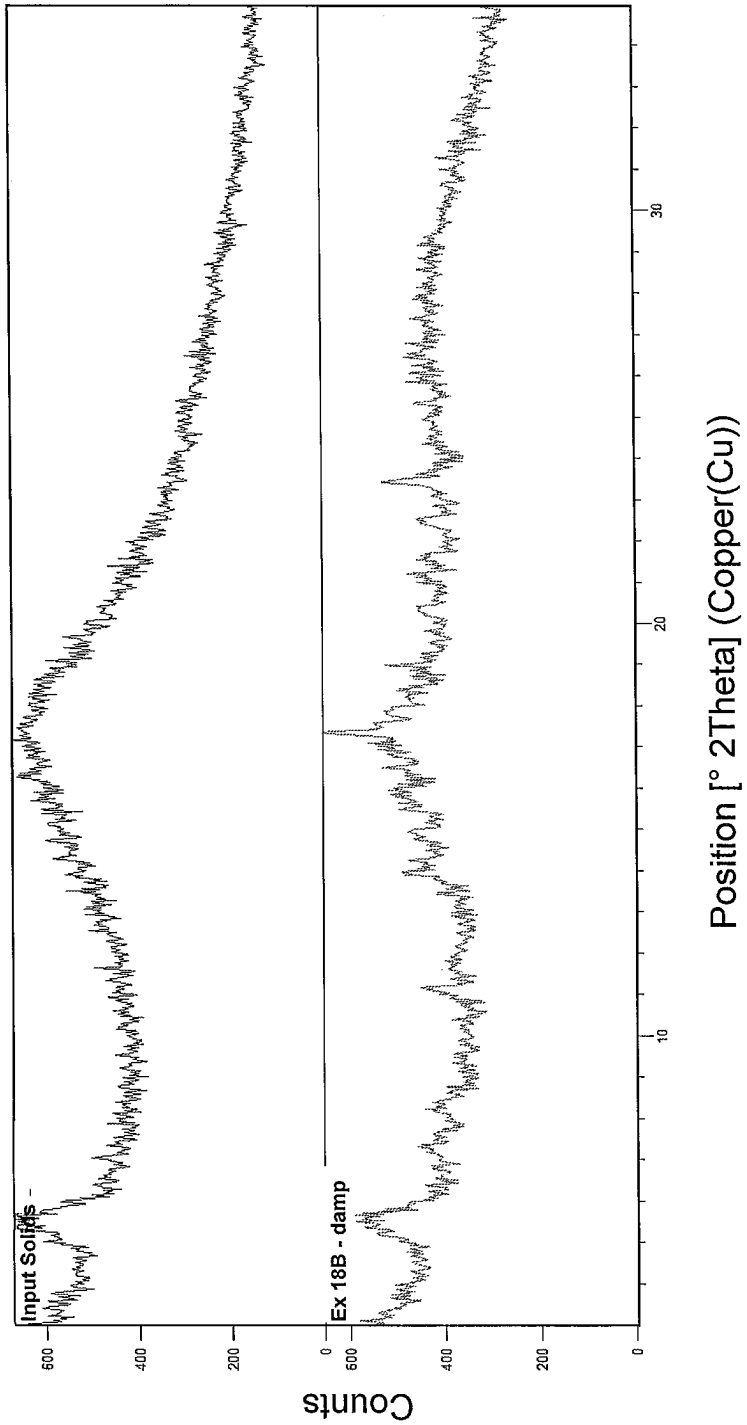

Input Solids -
Ex 18B - damp
Counts
600
400
200
0
600
400
200
0
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 46.

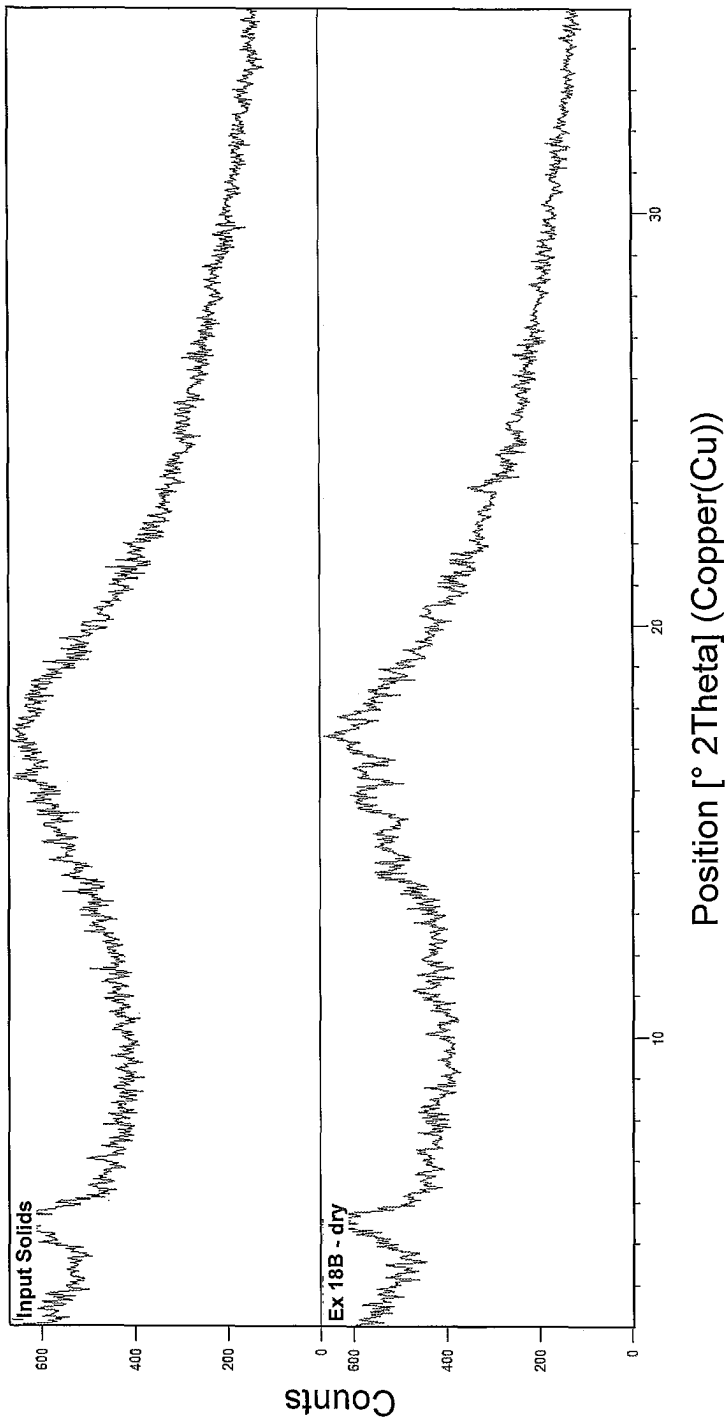

Input Solids
Ex 18B - dry
Counts
600
400
200
0
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 47.

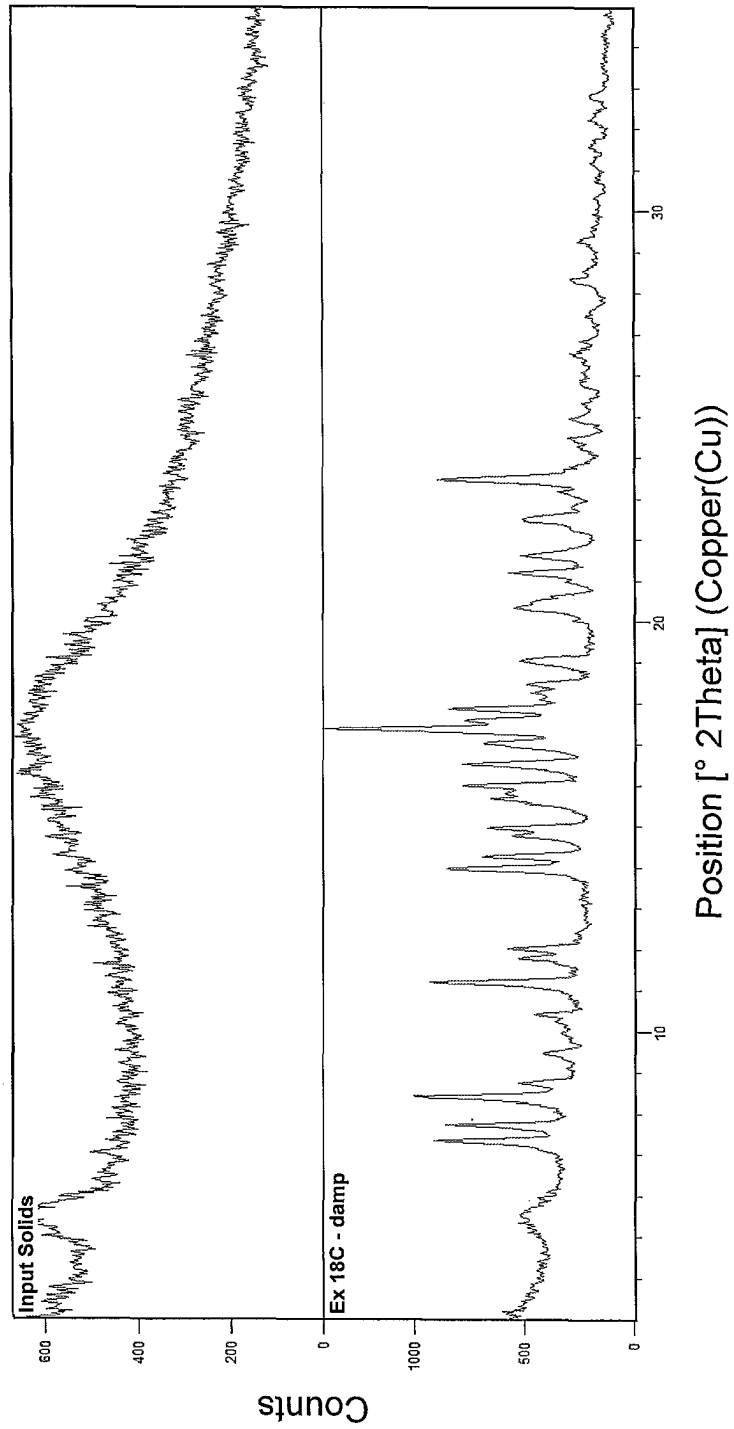

Input Solids
Ex 18C - damp
Counts
600
400
200
0
1000
500
0
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 48.

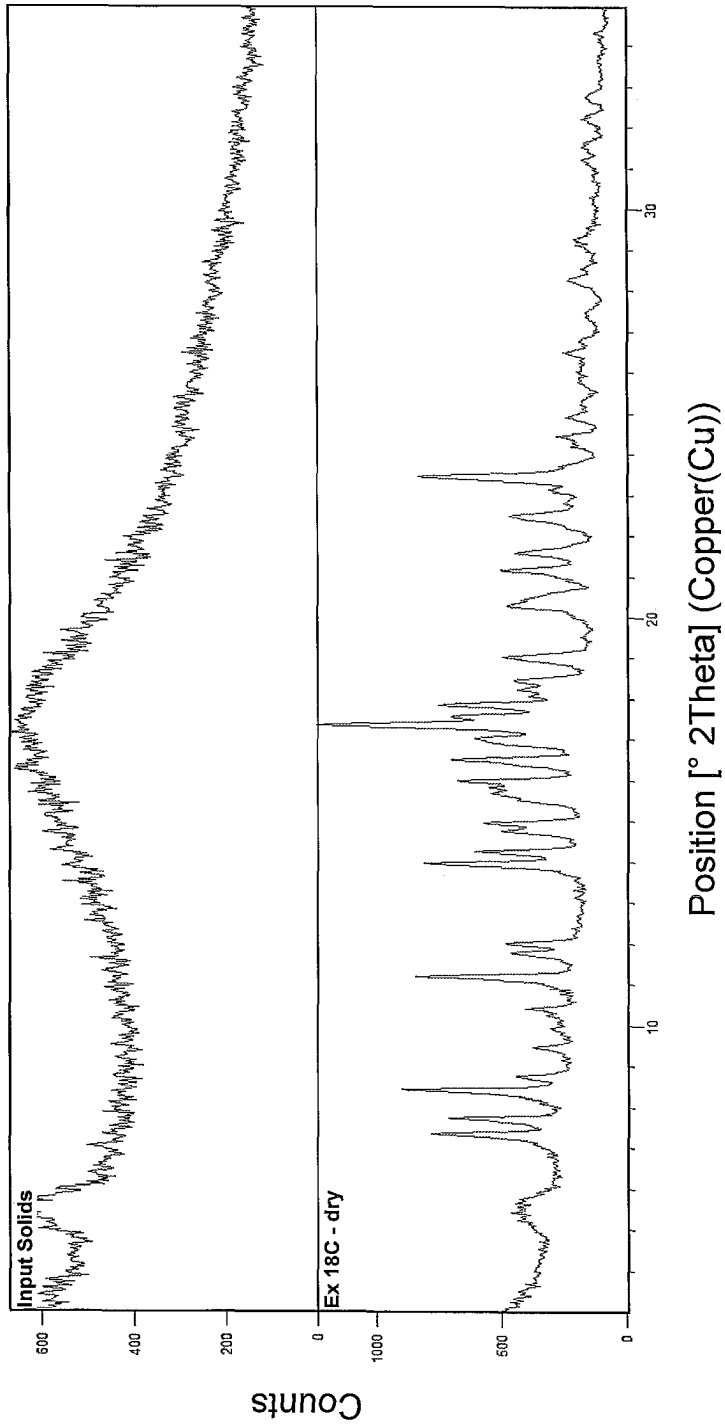
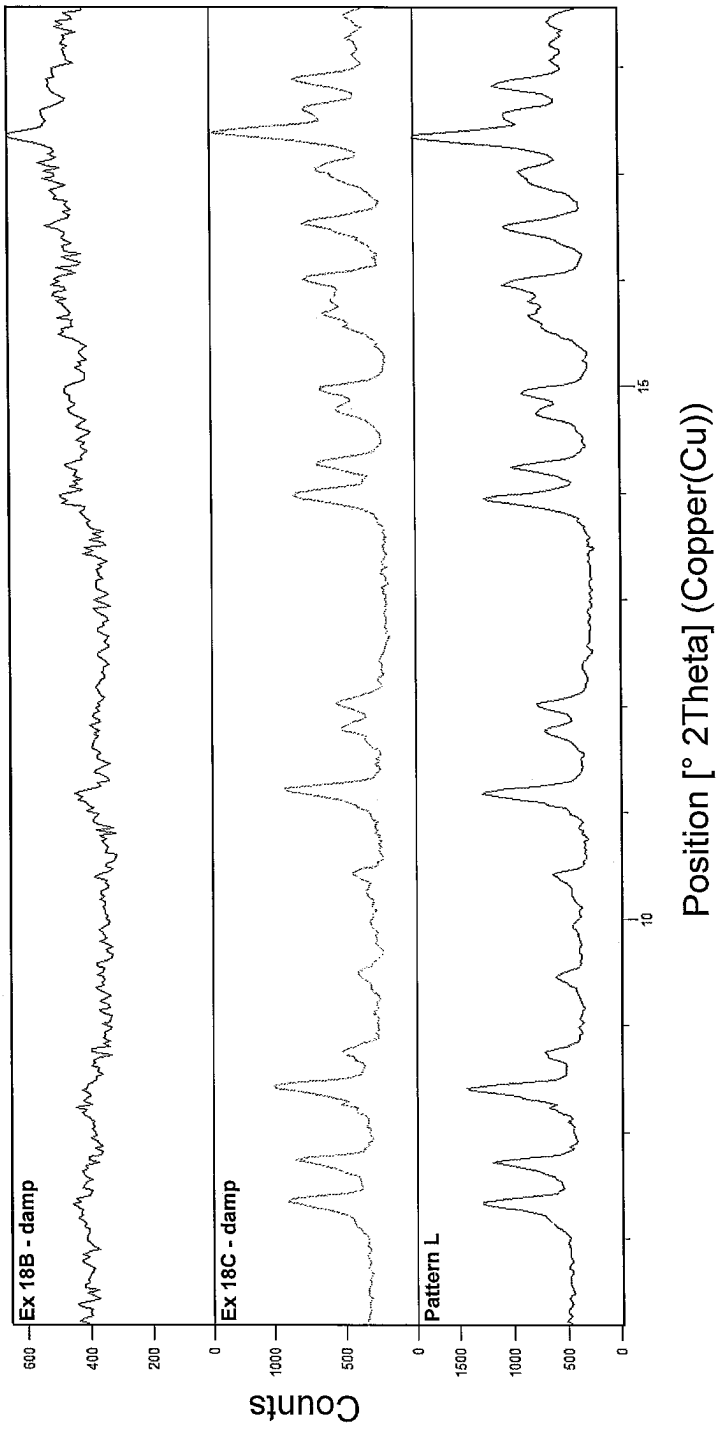

Input Solids
Ex 18C - dry
Counts
600
400
200
0
1000
500
0
10
20
30
Position [° 2Theta] (Copper(Cu))

Figure 49.


Ex 18B - damp
Ex 18C - damp
Pattern L
Counts
600
400
200
0
1000
500
0
1500
1000
500
0
10
15
Position [° 2Theta] (Copper(Cu))

PKC INHIBITOR SOLID STATE FORMS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. patent application Ser. No. 16/615,784, filed Nov. 21, 2019, which is the National Phase application under 35 U.S.C. § 371 of International Application No. PCT/US2018/034740, filed May 25, 2018, which claims the benefit of U.S. Provisional Application No. 62/511,210, filed on May 25, 2017, each of which is hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

The present disclosure relates to a protein kinase inhibitor compound and pharmaceutical compositions of said compound as well as the use of said compound in pharmaceutical compositions and medicine.

SUMMARY OF THE INVENTION

The present disclosure relates to various solid state forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and methods of making the same. Such forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine are useful in the treatment of cancer, immune disorders and inflammation.

Provided herein is a composition comprising amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 18.1.

Provided herein is a composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 16.3.

Provided herein is a composition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.9.

Provided herein is a composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.3.

Provided herein is a composition comprising crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 4.4.

Provided herein is a composition comprising crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 4.4.

Provided herein is a composition comprising crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition comprising crystalline hydrate Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 15.7.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dim-

ethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt, solution or hydrate thereof, substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a pharmaceutical composition comprising amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

Provided herein is a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and at least one pharmaceutically acceptable excipient.

INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The features of the invention are set forth with particularity in the appended claims. A better understanding of the features of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1** shows the X-ray powder diffractogram of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **2***a* shows the differential scanning calorimetry pattern of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **2***b* shows the thermal gravimetric analysis pattern of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **3** shows the X-ray powder diffractogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **4** shows the X-ray powder diffractogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **5** shows the differential scanning calorimetry thermogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **6** shows the thermal gravimetric analysis thermogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **7** shows the infrared spectrum of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **8** shows the infrared spectrum of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine] with peaks numerically identified at all wavenumbers;

FIG. **9** shows the infrared spectrum of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified at low wavenumbers;

FIG. **10** shows the X-ray powder diffractogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **11** shows the X-ray powder diffractogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **12** shows the differential scanning calorimetry thermogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **13** shows the thermal gravimetric analysis thermogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **14** shows the infrared spectrum of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **15** shows the Raman spectrum of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **16** shows the Raman spectrum of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **17** shows the X-ray powder diffractogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **18** shows the X-ray powder diffractogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **19** shows the differential scanning calorimetry thermogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **20** shows the thermal gravimetric analysis thermogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **21** shows the infrared spectrum of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **22** shows the Raman spectrum of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **23** shows the Raman spectrum of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **24** shows the X-ray powder diffractogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **25** shows the X-ray powder diffractogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **26** shows the differential scanning calorimetry thermogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **27** shows the thermal gravimetric analysis thermogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **28** shows the infrared spectrum of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **29** shows the Raman spectrum of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **30** shows the Raman spectrum of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **31** shows the X-ray powder diffractogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **32** shows the X-ray powder diffractogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-

2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **33** shows the differential scanning calorimetry thermogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **34** shows the thermal gravimetric analysis thermogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **35** shows the X-ray powder diffractogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **36** shows the X-ray powder diffractogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **37** shows the differential scanning calorimetry thermogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **38** shows the thermal gravimetric analysis thermogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **39** shows the X-ray powder diffractogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine with peaks numerically identified;

FIG. **40** shows the X-ray powder diffractogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine without annotation;

FIG. **41** shows the differential scanning calorimetry thermogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **42** shows the thermal gravimetric analysis thermogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **43** shows the X-ray powder diffractogram of the "input solid" for the isolation experiments in Example 18, which is the amorphous solid of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine;

FIG. **44** shows the X-ray powder diffractogram of the solid isolated from CH_3CN post chromatography in Example 18A;

FIG. **45** shows the X-ray powder diffractogram comparison of the input solid (top) and of the damp solid (bottom) of the solid isolated from 9:1 CH_3CN/water post chromatography and evaporation at 18° C. overnight in Example 18B, demonstrating a partially crystalline pattern of the isolated solid;

FIG. **46** shows the X-ray powder diffractogram comparison of the input solid (top) and of the dry solid (bottom) of the solid isolated from 9:1 CH_3CN/water post chromatography and evaporation at 18° C. overnight, and then further evaporation at 35° C. in Example 18B, demonstrating a partially crystalline pattern of the isolated solid;

FIG. **47** shows the X-ray powder diffractogram comparison of the input solid (top) and of the damp solid (bottom) of the solid isolated from 1:9 CH_3CN/water post chromatography and evaporation at 18° C. overnight in Example 18C, demonstrating a highly crystalline pattern of the isolated solid;

FIG. **48** shows the X-ray powder diffractogram comparison of the input solid (top) and of the dry solid (bottom) of the solid isolated from 1:9 CH_3CN/water post chromatography and evaporation at 18° C. overnight, and then further evaporation at 35° C. in Example 18C, demonstrating a highly crystalline pattern of the isolated solid; and

FIG. **49** shows an expansion of the X-ray powder diffractogram comparison of the damp solid isolated from Example 18B (top), of the damp solid isolated from Example 18C (middle), and of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine (bottom), demonstrating that the solid forms isolated in Examples 18B and 18C correspond to crystalline hydrate Form L.

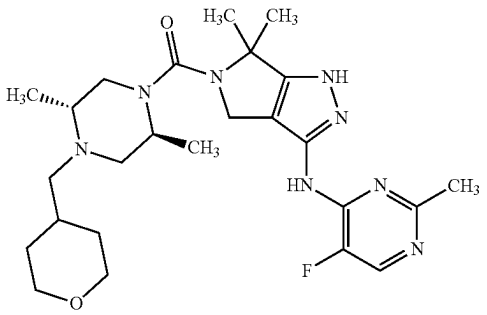
DETAILED DESCRIPTION OF THE INVENTION

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compounds that are kinase inhibitors have the potential to provide therapeutically effective pharmaceutical compositions that would be expected to have beneficial and improved pharmaceutical properties for the treatment of kinase related conditions or disorders such as cancer and other proliferative disorders.

Discussed herein is 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and referred to herein as Compound 1. Compound 1 has been previously described in WO 2008/096260 and related patents and patent applications, e.g. U.S. Pat. Nos. 8,183,255, 8,877,761, 9,518,060 and U.S. patent application Ser. No. 15/376,279, each of which is incorporated by reference in their entirety.

Compound 1



5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A summary of the Protein Kinase C (PKC) inhibition by Compound 1 is provided in Table 1. The methods for these determinations have been described (Grant, et al. 2010, Eur. J. Pharmacol. 627:16-25). Compound 1 is a potent, ATP-competitive and reversible inhibitor of conventional PKC enzymes with a Ki=5.3 nM for recombinant PKC beta and a Ki=10.4 nM for recombinant PKC alpha. It also is a potent inhibitor of the novel isoform PKC theta with an IC_{50}=25.6 nM. Furthermore, it demonstrated some potency for conventional isoform PKC gamma with an IC_{50}=57.5 nM. Otherwise, it demonstrated a high degree of selectivity for the other members of the conventional, novel and atypical isoforms of PKC as shown by lower potency against these isoforms (Table 1). Compound 1 does not significantly inhibit PKC delta.

TABLE 1

In Vitro Assays	IC_{50} (nM)	Ki (nM)
Human PKC alpha		10.4
Human PKC betaII		5.3
Human PKC alpha	2.3	
Human PKC betaI	8.1	
Human PKC betaII	7.6	
Human PKC theta	25.6	
Human PKC gamma	57.5	
Human PKC mu	314	
Human PKC epsilon	808	
Human PKC delta	>1000	
Human PKC eta	>1000	
Human PKC iota	>1000	
Human PKC zeta	>1000	
Human PRKCN (PKD3)	131	
pSHP2 (PKCβ cell assay)	9.8	
Interleukin-8 release	39	

As a selective inhibitor of PKC, Compound 1 is useful in the treatment of conditions in which PKC has demonstrated a role in the pathology, such as cancer, immune disorders and inflammation. Two critical aspects in the development of Compound 1 as a useful therapy for such diseases and disorders are the discovery of practical methods for the preparation of Compound 1, and the discovery of pharmaceutically acceptable forms of Compound 1 and pharmaceutical compositions comprising said forms.

As used herein, the term "amorphous" or "amorphous solid form" refers to a solid form which is substantially free of any crystalline solid state form. One embodiment provides a composition wherein substantially free means less than about 10% (w/w), less than about 9% (w/w), less than about 8% (w/w), less than about 7% (w/w), less than about 6% (w/w), less than about 5% (w/w), less than about 4.75% (w/w), less than about 4.5% (w/w), less than about 4.25% (w/w), less than about 4% (w/w), less than about 3.75% (w/w), less than about 3.5% (w/w), less than about 3.25% (w/w), less than about 3% (w/w), less than about 2.75% (w/w), less than about 2.5% (w/w), less than about 2.25% (w/w), less than about 2% (w/w), less than about 1.75% (w/w), less than about 1.5% (w/w), less than about 1.25% (w/w), less than about 1% (w/w), less than about 0.9% (w/w), less than about 0.8% (w/w), less than about 0.7% (w/w), less than about 0.6% (w/w), less than about 0.5% (w/w), less than about 0.4% (w/w), less than about 0.3% (w/w), less than about 0.25% (w/w), less than about 0.20% (w/w), less than about 0.15% (w/w), less than about 0.1% (w/w), less than about 0.08% (w/w), or less than about 0.05% (w/w). One embodiment provides a composition wherein substantially free means an undetectable amount. One embodiment provides a composition wherein substantially free means less than about 5% (w/w), less than about 3% (w/w), less than about 1% (w/w), less than about 0.5% (w/w), or less than about 0.2% (w/w).

As used herein, the term "crystalline," "highly crystalline," "crystalline solid form," or "highly crystalline solid form" refers to a solid form which is substantially free of any amorphous solid state form. In some embodiments, the crystalline solid form is a single solid state form, e.g. crystalline Form A. One embodiment provides a composition wherein substantially free means less than about 10% (w/w), less than about 9% (w/w), less than about 8% (w/w), less than about 7% (w/w), less than about 6% (w/w), less than about 5% (w/w), less than about 4.75% (w/w), less than about 4.5% (w/w), less than about 4.25% (w/w), less than about 4% (w/w), less than about 3.75% (w/w), less than about 3.5% (w/w), less than about 3.25% (w/w), less than about 3% (w/w), less than about 2.75% (w/w), less than about 2.5% (w/w), less than about 2.25% (w/w), less than about 2% (w/w), less than about 1.75% (w/w), less than about 1.5% (w/w), less than about 1.25% (w/w), less than about 1% (w/w), less than about 0.9% (w/w), less than about 0.8% (w/w), less than about 0.7% (w/w), less than about 0.6% (w/w), less than about 0.5% (w/w), less than about 0.4% (w/w), less than about 0.3% (w/w), less than about 0.25% (w/w), less than about 0.20% (w/w), less than about 0.15% (w/w), less than about 0.1% (w/w), less than about 0.08% (w/w), or less than about 0.05% (w/w). One embodiment provides a composition wherein substantially free means an undetectable amount. One embodiment provides a composition wherein substantially free means less than about 5% (w/w), less than about 3% (w/w), less than about 1% (w/w), less than about 0.5% (w/w), or less than about 0.2% (w/w).

As used herein, the term "partially crystalline" or "partially crystalline material" refers to an ad-mixture of two or more solid state forms. In some embodiments, partially crystalline refers to an ad-mixture of an amorphous solid form and at least one crystalline solid form. Partially crystalline material is not amorphous.

In some embodiments, crystallinity of a solid form is determined by X-Ray Powder Diffraction (XRPD). In some embodiments, crystallinity of a solid form is determined by solid state NMR.

Provided herein is the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)pip-

erazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **1**.

One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits a differential scanning calorimetry pattern shown in FIG. **2***a*.

One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits a thermogravimetric analysis pattern shown in FIG. **2***b*.

One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is stable over 36 months at ambient temperature. One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is stable over 60 months at ambient temperature.

One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine remains amorphous over 36 months at ambient temperature. One embodiment provides a composition wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine remains amorphous over 60 months at ambient temperature.

One embodiment provides a composition wherein the stability of amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is determined by the X-ray powder diffraction pattern.

Provided herein is the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **3**.

Provided herein is a composition comprising crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 18.1.

One embodiment provides a composition wherein the crystalline Form A is further characterized by X-ray diffraction pattern reflections at 2 theta values of 6.8, 15.3 and 22.1.

One embodiment provides a composition wherein the crystalline Form A is further characterized by X-ray diffraction pattern reflections at 2 theta values of 12.9, 13.6, 15.7, 17.2, 21.2, 21.7, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline Form A is further characterized by at least six X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 12.9, 13.6, 15.3, 15.7, 17.2, 18.1, 21.2, 21.7, 22.1, 22.8 and 28.4.

One embodiment provides a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **5**.

One embodiment provides a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **6**.

One embodiment provides a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the infrared spectrum as shown in FIG. **7**, **8**, or **9**.

Provided herein is the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-

(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **10**.

Provided herein is a composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 16.3.

One embodiment provides a composition wherein the crystalline Form B is further characterized by X-ray diffraction pattern reflections at 2 theta values of 9.0, 10.9 and 15.0.

One embodiment provides a composition wherein the crystalline Form B is further characterized by X-ray diffraction pattern reflections at 2 theta values of 6.8, 9.2, 11.3, 14.8, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline Form B is further characterized by at least six X-ray diffraction pattern reflections selected from a 2 theta value of 6.8, 9.0, 9.2, 10.9, 11.3, 14.8, 15.0, 16.3, 19.4, 20.0, 22.1, 23.0 and 26.8.

One embodiment provides a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **12**.

One embodiment provides a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **13**.

One embodiment provides a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the infrared spectrum as shown in FIG. **14**.

Provided herein is the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **17**.

Provided herein is a composition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.9.

One embodiment provides a composition wherein the crystalline Form D is further characterized by X-ray diffraction pattern reflections at 2 theta values of 8.3, 14.0 and 20.4.

One embodiment provides a composition wherein the crystalline Form D is further characterized by X-ray diffraction pattern reflections at 2 theta values of 5.5, 8.3, 10.5, 13.6, 16.7, 18.1, 18.7, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline Form D is further characterized by at least six X-ray diffraction pattern reflections selected from a 2 theta value of 5.5, 8.3, 10.5, 13.6, 14.0, 16.7, 17.9, 18.1, 18.7, 20.4, 23.9, 24.8 and 28.2.

One embodiment provides a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **19**.

One embodiment provides a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **20**.

One embodiment provides a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the infrared spectrum as shown in FIG. **21**.

Provided herein is the crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **24**.

Provided herein is a composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.3.

One embodiment provides a composition wherein the crystalline Form L is further characterized by X-ray diffraction pattern reflections at 2 theta values of 7.3, 7.7, 8.4, 11.2, 13.9, 17.8 and 23.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by X-ray diffraction pattern reflections at 2 theta values of 5.7, 8.7, 12.0, 14.3, 16.0, 16.5, 17.6, 17.8, 19.0, 20.3, 21.1 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline Form L is further characterized by at least six X-ray diffraction pattern reflections selected from a 2 theta value of 5.7, 7.3, 7.7, 8.4, 8.7, 11.2, 12.0, 13.9, 14.3, 16.0, 16.5, 17.3, 17.6, 17.8, 19.0, 20.3, 21.1, 23.4 and 22.4.

One embodiment provides a composition wherein the crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **26**.

One embodiment provides a composition wherein the crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **27**.

One embodiment provides a composition wherein the crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the infrared spectrum as shown in FIG. **28**.

Provided herein is the crystalline solid Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **31**.

Provided herein is a composition comprising crystalline hydrate Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 4.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by X-ray diffraction pattern reflections at 2 theta values of 6.4, 10.2, 12.8, 13.0, 14.0, 17.5, 17.8, 18.6, and 19.1.

One embodiment provides a composition wherein the crystalline Form G is further characterized by X-ray diffraction pattern reflections at 2 theta values of 6.2, 11.2, 14.5, 15.5, 16.0, 18.0, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least two X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least three X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least four X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least five X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G is further characterized by at least six

X-ray diffraction pattern reflection selected from a 2 theta value of 4.4, 6.2, 6.4, 10.2, 11.2, 12.8, 13.0, 14.0, 14.5, 15.5, 16.0, 17.5, 17.8, 18.0, 18.6, 19.1, 20.6, 22.6, 22.9, and 28.4.

One embodiment provides a composition wherein the crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **33**.

One embodiment provides a composition wherein the crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **34**.

Provided herein is the crystalline solid Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **35**.

Provided herein is a composition comprising crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 4.4.

One embodiment provides a composition wherein the crystalline Form H is further characterized by X-ray diffraction pattern reflections at 2 theta values of 12.6, 12.9, 13.1, 14.1, 16.7, 17.7, 18.1, and 18.9.

One embodiment provides a composition wherein the crystalline Form H is further characterized by X-ray diffraction pattern reflections at 2 theta values of 3.1, 3.7, 4.9, 5.3, 10.0, 11.1, 13.3, 15.3, 17.5, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least two X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least three X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least four X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least five X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H is further characterized by at least six X-ray diffraction pattern reflection selected from a 2 theta value of 3.1, 3.7, 4.4, 4.9, 5.3, 10.0, 11.1, 12.6, 12.9, 13.1, 13.3, 14.1, 15.3, 16.7, 17.5, 17.7, 18.1, 18.9, 22.3, and 25.2.

One embodiment provides a composition wherein the crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **37**.

One embodiment provides a composition wherein the crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **38**.

Provided herein is the crystalline solid Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

One embodiment provides a composition wherein the crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the X-ray powder diffraction pattern as shown in FIG. **39**.

Provided herein is a composition comprising crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine characterized by an X-ray diffraction pattern reflection at a 2 theta value of 15.7.

One embodiment provides a composition wherein the crystalline Form I is further characterized by X-ray diffraction pattern reflections at 2 theta values of 8.8, 10.0, 10.5, 11.5, 12.4, 13.4, 16.3, 16.4, 17.6, and 22.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by X-ray diffraction pattern reflections at 2 theta values of 5.5, 11.0, 17.2, 19.3, 19.9, 21.3, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least two X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least three X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least four X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least five X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I is further characterized by at least six X-ray diffraction pattern reflection selected from a 2 theta value of 5.5, 8.8, 10.0, 10.5, 11.0, 11.5, 12.4, 13.4, 15.7, 16.3, 16.4, 17.2, 17.6, 19.3, 19.9, 21.3, 22.0, 23.1, 23.5, and 25.0.

One embodiment provides a composition wherein the crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the differential scanning calorimetry pattern as shown in FIG. **41**.

One embodiment provides a composition wherein the crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits the thermogravimetric analysis pattern as shown in FIG. **42**.

Provided herein is the maleate salt of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is the fumarate salt of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.05% (w/w).

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-di-

hydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-

1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are not detectable.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, free of impurities. In some embodiments, the compound is free of structurally related impurities. Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, essentially free of impurities. In some embodiments, the compound is essentially free of structurally related impurities.

Provided herein is the compound 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine or a pharmaceutically acceptable salt, solution or hydrate thereof, substantially free of impurities. In some embodiments, the compound is substantially free of structurally related impurities. One embodiment provides a composition wherein the amount of impurities is less than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is not more

than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not detectable.

One embodiment provides a composition wherein substantially free means less than about 10% (w/w), less than about 9% (w/w), less than about 8% (w/w), less than about 7% (w/w), less than about 6% (w/w), less than about 5% (w/w), less than about 4.75% (w/w), less than about 4.5% (w/w), less than about 4.25% (w/w), less than about 4% (w/w), less than about 3.75% (w/w), less than about 3.5% (w/w), less than about 3.25% (w/w), less than about 3% (w/w), less than about 2.75% (w/w), less than about 2.5% (w/w), less than about 2.25% (w/w), less than about 2% (w/w), less than about 1.75% (w/w), less than about 1.5% (w/w), less than about 1.25% (w/w), less than about 1% (w/w), less than about 0.9% (w/w), less than about 0.8% (w/w), less than about 0.7% (w/w), less than about 0.6% (w/w), less than about 0.5% (w/w), less than about 0.4% (w/w), less than about 0.3% (w/w), less than about 0.25% (w/w), less than about 0.20% (w/w), less than about 0.15% (w/w), less than about 0.1% (w/w), less than about 0.08% (w/w), or less than about 0.05% (w/w). One embodiment provides a composition wherein substantially free means an undetectable amount. One embodiment provides a composition wherein substantially free means less than about 5% (w/w), less than about 3% (w/w), less than about 1% (w/w), less than about 0.5% (w/w), or less than about 0.2% (w/w).

Amorphous Solid Form

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not detectable.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyr-

rolo[3,4-c]pyrazol-3-amine is free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpy-

rimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are not detectable.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition

wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-

2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable. One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable in its X-ray diffraction pattern.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-

dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable. One embodiment provides a composition wherein the amount of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable in its X-ray diffraction pattern.

Provided herein is a composition of the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine wherein the X-ray diffraction pattern has no detectable reflections. One embodiment provides a composition whose X-ray diffraction pattern does not have a reflection at a 2 theta value of 16.3. One embodiment provides a composition whose X-ray diffraction pattern does not have a reflection at a 2 theta value of 17.3. One embodiment provides a composition whose X-ray diffraction pattern does not have a reflection at a 2 theta value of 17.9. One embodiment provides a composition whose X-ray diffraction pattern does not have a reflection at a 2 theta value of 18.1.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of impurities. In some embodiments, the composition is free of structurally related impurities. Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetra-

hydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of impurities. In some embodiments, the composition is essentially free of structurally related impurities.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of impurities. In some embodiments, the composition is substantially free of structurally related impurities. One embodiment provides a composition wherein the amount of impurities is less than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not detectable.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of solvent. One embodiment provides a composition wherein the amount of solvent is less than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of solvent is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.0 equivalent.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of water. One embodiment provides a composition wherein the amount of water is less than 20% (w/w). One embodiment provides a composition wherein the amount of water is less than 15% (w/w). One embodiment provides a composition wherein the amount of water is less than 10% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 20% (w/w). One embodiment provides a composition wherein the amount of water is not more than 15% (w/w). One embodiment provides a composition wherein the amount of water is not more than 10% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of water is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of water is not more than 1.0 equivalent.

Provided herein is a composition wherein the amorphous solid form of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine comprises a small amount of water. One embodiment provides a composition wherein the amount of water is from 1.5% (w/w) to 7.0% (w/w) of water. One embodiment provides a composition wherein the amount of water is from 2.0% (w/w) to 6.0% (w/w One

embodiment provides a composition wherein the amount of water is from 2.2% (w/w) to 5.9% (w/w). One embodiment provides a composition wherein the amount of water is from 2.4% (w/w) to 5.8% (w/w). One embodiment provides a composition wherein the amount of water is from 2.5% (w/w) to 5.7% (w/w). One embodiment provides a composition wherein the amount of water is from 2.7% (w/w) to 5.5% (w/w). One embodiment provides a composition wherein the amount of water is from 0.25 equivalents to 3.0 equivalents. One embodiment provides a composition wherein the amount of water is from 0.5 equivalents to 2.5 equivalents. One embodiment provides a composition wherein the amount of water is from 0.75 equivalents to 2.25 equivalents. One embodiment provides a composition wherein the amount of water is from 1.0 equivalent to 2.0 equivalents.

Crystalline Hydrate Form B

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-

dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)

methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are not detectable.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetra-

hydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-

fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of impurities. In some embodiments, the composition is free of structurally related impurities. Provided herein is a composition wherein crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of impurities. In some embodiments, the composition is essentially free of structurally related impurities.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of impurities. In some embodiments, the composition is substantially free of structurally related impurities. One embodiment provides a composition wherein the amount of impurities is less than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is not more

than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of solvent. One embodiment provides a composition wherein the amount of solvent is less than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of solvent is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.0 equivalent.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of water. One embodiment provides a composition wherein the amount of water is less than 20% (w/w). One embodiment provides a composition wherein the amount of water is less than 15% (w/w). One embodiment provides a composition wherein the amount of water is less than 10% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 20% (w/w). One embodiment provides a composition wherein the amount of water is not more than 15% (w/w). One embodiment provides a composition wherein the amount of water is not more than 10% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of water is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of water is not more than 1.0 equivalent.

Crystalline Hydrate Form D

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)

amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)

methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are not detectable.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-

(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of impurities. In some embodiments, the composition is free of structurally related impurities. Provided herein is a composition wherein crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of impurities. In some embodiments, the composition is essentially free of structurally related impurities.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of impurities. In some embodiments, the composition is substantially free of structurally related impurities. One embodiment provides a composition wherein the amount of impurities is less than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not detectable.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of solvent. One embodiment provides a composition wherein the amount of solvent is less than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of solvent is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.0 equivalent.

Provided herein is a composition wherein the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of water. One embodiment provides a composition wherein the amount of water is less than 20% (w/w). One embodiment provides a composition wherein the amount of water is less than 15% (w/w). One embodiment provides a composition wherein the amount of water is less than 10% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is less than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 20% (w/w). One embodiment provides a composition wherein the amount of water is not more than 15% (w/w). One embodiment provides a composition wherein the amount of water is not more than 10% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 7.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 6.0% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.5% (w/w). One embodiment provides a composition wherein the amount of water is not more than 5.0% (w/w). One embodiment provides a composition wherein the amount of water is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of water is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of water is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of water is not more than 1.5 equiva-

lents. One embodiment provides a composition wherein the amount of water is not more than 1.0 equivalent.

Crystalline 2-Propanol Solvate Form A

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl) methanone. One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl) amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is less than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c] pyrazol-5(1H)-yl)methanone is less than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl) amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is less than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl) amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is less than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is less than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl) amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is less than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 1% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl) amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is not more than 0.5% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.4% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is not more than 0.3% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.25% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is not more than 0.20% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.15% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5 (1H)-yl)methanone is not more than 0.10% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.08% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not more than 0.05% (w/w). One embodiment provides a composition wherein the bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone is not detectable.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl) methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl) methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)

piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each less than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 1% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.5% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.4% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.3% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,

6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.25% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.20% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.15% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.10% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.08% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are each not more than 0.05% (w/w). One embodiment provides a composition wherein the ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate are not detectable.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 1% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of other solid forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is not detectable.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of impurities. In some embodiments, the composition is free of structurally related impurities. Provided herein is a composition wherein crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of impurities. In some embodiments, the composition is essentially free of structurally related impurities.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of impurities. In some embodiments, the composition is substantially free of structurally related impurities. One embodiment provides a composition wherein the amount of impurities is less than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is less than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 1% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.5% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.4% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.3% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.25% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.20% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.15% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.10% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.08% (w/w). One embodiment provides a composition wherein the amount of impurities is not more than 0.05% (w/w). One embodiment provides a composition wherein the amount of impurities is not detectable.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of solvent. One embodiment provides a composition wherein the amount of solvent is less than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 10% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 20% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 15% (w/w). One embodiment provides a composition wherein the amount of solvent is not more than 10%

(w/w). One embodiment provides a composition wherein the amount of solvent is not more than 5% (w/w). One embodiment provides a composition wherein the amount of solvent is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of solvent is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of solvent is not more than 1.0 equivalent.

Provided herein is a composition wherein the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of 2-propanol. One embodiment provides a composition wherein the amount of 2-propanol is less than 20% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is less than 15% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is less than 10% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is less than 5% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is not more than 20% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is not more than 15% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is not more than 10% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is not more than 5% (w/w). One embodiment provides a composition wherein the amount of 2-propanol is less than 2.0 equivalents. One embodiment provides a composition wherein the amount of 2-propanol is less than 1.5 equivalents. One embodiment provides a composition wherein the amount of 2-propanol is less than 1.0 equivalent. One embodiment provides a composition wherein the amount of 2-propanol is not more than 2.0 equivalents. One embodiment provides a composition wherein the amount of 2-propanol is not more than 1.5 equivalents. One embodiment provides a composition wherein the amount of 2-propanol is not more than 1.0 equivalent.

Pharmaceutical Compositions

Provided herein is a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising an amorphous solid of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising an amorphous solid of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising the maleate salt of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising the fumarate salt of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical compo-

sition comprising crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline solid Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline solid Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline solid Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline solid Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein is a pharmaceutical composition comprising crystalline solid Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. Also provided herein is a pharmaceutical composition comprising crystalline solid Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of impurities. In some embodiments, the composition is free of structurally related impurities. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of impurities. In some embodiments, the composition is essentially free of structurally related impurities. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of impurities. In some embodiments, the composition is substantially free of structurally related impurities.

One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is essentially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-

c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate. One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is substantially free of ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate, and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate.

One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 20% of solvent (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 15% of solvent (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 10% of solvent (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 5% of solvent (w/w). 100216 One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 20% of water (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 15% of water (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 10% of water (w/w). One embodiment provides a pharmaceutical composition, wherein the 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 5% of water (w/w).

Provided herein is a pharmaceutical compositions comprising any pharmaceutically acceptable salt of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and one or more pharmaceutically acceptable excipients or carriers. In various embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Provided herein are pharmaceutical compositions in film-coated dosage forms, which comprise a combination of an active ingredient, and one or more tableting excipients to form a tablet core using conventional tableting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating.

The pharmaceutical compositions provided herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the combinations may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition. In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the combinations may be given continuously or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In some embodiments, once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro studies initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment in accordance with the present disclosure. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

The pharmaceutical compositions provided herein are formulated in various dosage forms for oral administration. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see, *Remington: The Science and Practice of Pharmacy*, Loyd V., Jr, Allen, Ed., Pharmaceutical Press.: New York, NY, 2002; Vol. 22).

As used herein, oral administration also include buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, and effervescent or

non-effervescent powders or granules. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents. In some embodiments, the oral dosage form is a tablet, capsule, or pill.

In further embodiments, the pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach.

The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

The pharmaceutical compositions provided herein may be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule, consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides.

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

The examples and preparations provided below further illustrate and exemplify the polymorphs of the present disclosure and methods of preparing such polymorphs. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations.

The present disclosure relates to various solid state forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and methods of making the same. Such forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine are useful in the treatment of cancer, immune disorders and inflammation. In one embodiment the various solid state forms of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine disclosed herein are useful for the treatment of inflammatory disorders such as uveitis.

EXAMPLES

The present disclosure is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. The disclosure has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

General Experimental Details—Instrument and Methodology Details

X-Ray Powder Diffraction (XRPD)

X-Ray Powder Diffraction patterns were collected on a PANalytical diffractometer using Cu Kα radiation (45 kV, 40 mA), 0-0 goniometer, focusing mirror, divergence slit (½"), soller slits at both incident and divergent beam (4 mm) and a PIXcel detector. The software used for data collection was X'Pert Data Collector, version 2.2f and the data was presented using X'Pert Data Viewer, version 1.2d.

XRPD patterns were acquired under ambient conditions via a transmission foil sample stage (polyimide—Kapton, 12.7 μm thickness film) under ambient conditions using a PANalytical X'Pert PRO. The data collection range was 2.994-35°2θ with a continuous scan speed of 0.202004°s^{-1}.

Nuclear Magnetic Resonance (NMR)

^{1}H NMR spectra were collected using a JEOL EX 270 MHz spectrometer equipped with an auto-sampler. The samples were dissolved in a suitable deuterated solvent for analysis. The data was acquired using Delta NMR Processing and Control Software version 4.3.

Differential Scanning Calorimetry (DSC)

DSC data was collected on a PerkinElmer Pyris 4000 DSC equipped with a 45 position sample holder. The instrument was verified for energy and temperature calibration using certified indium. A predefined amount of the sample, 0.5-3.0 mg, was placed in a pin holed aluminum pan and heated at 20° C.·min^{-1} from 30 to 350° C., or varied as experimentation dictated. A purge of dry nitrogen at 60 mL·min^{-1} was maintained over the sample. The instrument control, data acquisition and analysis was performed with Pyris Software v9.0.1.0203.

Thermo-Gravimetric Analysis (TGA)

TGA data were collected on a PerkinElmer Pyris 1 TGA equipped with a 20 position auto-sampler. The instrument was calibrated using a certified weight and certified Alumel and Perkalloy for temperature. A predefined amount of the sample, 1-5 mg, was loaded onto a pre-tared aluminium crucible and was heated at 20° C.·min^{-1} from ambient temperature to 400° C. A nitrogen purge at 20 mL·min^{-1} was maintained over the sample. The instrument control, data acquisition and analysis was performed with Pyris Software v9.0.1.0203.

Infrared Spectroscopy

Data was collected on a Perkin Elmer Spectrum Two instrument with pATR Two accessory. The software used for data collection and presentation was Spectrum, version 10.03.08. A few grains <1 mg of sample was compressed under a diamond tip for data collection.

Raman Spectroscopy

Raman spectra were collected on a PerkinElmer Raman Station 400. The software used for data collection and presentation was Spectrum, version 10.03.06. Raman spectra were acquired under ambient conditions with the sample presented on a glass microscope slide with Raman autofocus. The laser power was optimized as governed by the nature of the sample. The data collection range was 3400 to 200 cm-1 with an exposure time of 5-10 seconds at a data interval of 1 cm-1 over 10-30 accumulations as required for each sample.

Optical Microscopy

Optical microscopy examination was undertaken using a Leica DME polarized light microscope and an Infinity 1 digital video camera for image capture. A small amount of each sample was placed onto a glass slide and dispersed as best as possible. The samples were viewed with appropriate magnification and various images recorded. The image scale bar was calibrated against an external graticule, 0.1 mm/0.002 mm DIV.

Gravimetric Vapor Sorption (GVS)

Sorption isotherms were obtained using a Hiden Isochema moisture sorption analyzer (model IGAsorp), controlled by IGAsorp Systems Software V6.50.48. The sample was maintained at a constant temperature (25° C.) by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen, with a total flow of 250 $mL \cdot min^{-1}$. The instrument was verified for relative humidity content by measuring three calibrated Rotronic salt solutions (10-50-88%). The weight change of the sample was monitored as a function of humidity by a microbalance (accuracy+/−0.005 mg). A defined amount of sample was placed in a tared mesh stainless steel basket under ambient conditions. A full experimental cycle typically consisted of three scans (sorption, desorption and sorption) at a constant temperature (25° C.) and 10% RH intervals over a 0-90% range (60 minutes for each humidity level). This type of experiment should demonstrate the ability of samples studied to absorb moisture (or not) over a set of well-determined humidity ranges.

Chemical Purity Determination by HPLC

Purity analysis was performed on an Agilent 1100 series liquid chromatograph.

TABLE 2

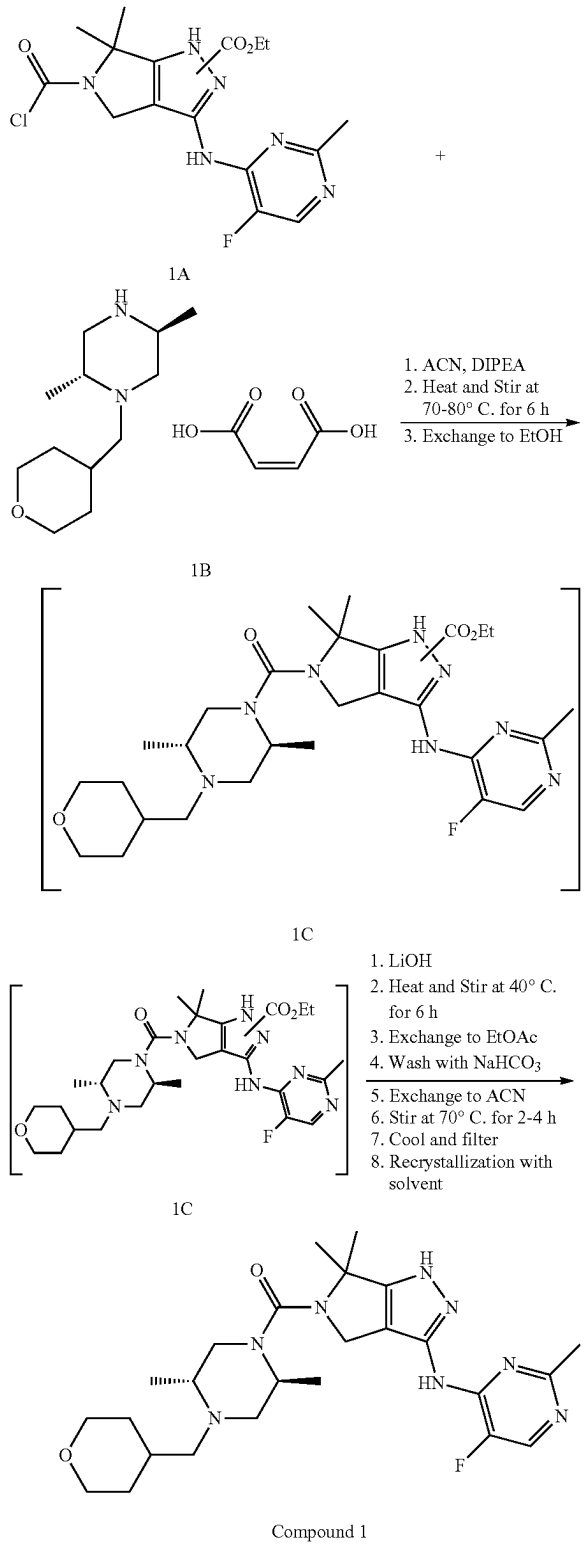
HPLC Method Parameters for Chemical Purity Determinations

Sample Preparation:	0.5 mg · ml^{-1} in Acetonitrile: Water (1:1)		
Column:	Sunfire C18 4.6 × 250 mm; 5 μm		
Column Temperature:	40 ° C.		
Injection:	5 μl & Needle wash vial with diluent		
Detection:	254 nm		
Wavelength, Bandwidth:			
Flow Rate:	1.0 mL · min^{-1}		
Phase A:	10 mM Ammonium acetate pH 4.0 (100)		
Phase B:	Acetonitrile (100)		
Timetable:	Time (min)	% Phase A	% Phase
	0	95	5
	5	95	5
	20	65	35
	30	5	95
	32.1	95	5
	40	95	5

Example 1: Processes for the Synthesis of 5-{[(2S, 5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine (Compound 1)

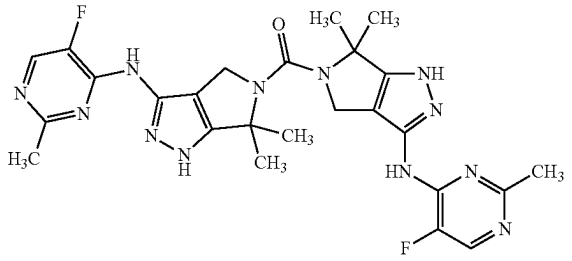
A synthesis of Compound 1 was previously reported in WO 2008/096260. Optimized synthetic routes to Compound 1 are presented below.

Scheme 1- Synthesis of Compound 1



A reaction vessel was charged with compound 1A, compound 1B, N,N-diisopropylethylamine and acetonitrile. The reaction was heated to 70-80° C. for approximately 6 hours. Following the cooling of the reaction mixture to room temperature, the acetonitrile solvent was removed and

replaced with ethanol to afford a solution of 1 C. The solution of 1 C was subsequently charged with lithium hydroxide and heated to 40° C. for approximately 6 hours. The reaction solvent was then exchanged for ethyl acetate and washed with a solution of sodium bicarbonate. Ethyl acetate was removed as the solvent, and exchanged for acetonitrile. The solution was subsequently stirred at 70° C. for 2-4 hours. The solution was then allowed to cool, and was filtered to afford solid Compound 1. Recrystallization of Compound 1 using acetonitrile or 2-propanol followed by water slurry and drying served to purify Compound 1 and eliminate the presence of impurity bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone (structure shown below), unreacted 1 C (two carbamate isomers: ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-2(4H)-carboxylate and ethyl 5-((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazine-1-carbonyl)-3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-5,6-dihydropyrrolo[3,4-c]pyrazole-1(4H)-carboxylate), and other unidentified impurities. Following this purification process, Compound 1 exhibited a purity of greater than 99.8% as determined by the analytical HPLC method described in Table 2.



bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone

Example 2: Process for the Synthesis of Amorphous Solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

The crystalline hydrate of Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine was dried in a vacuum oven at 50-70° C. for 6-12 hours. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIG. **1**, and the DSC and TGA displayed in FIGS. **2***a*-**2***b*.

Example 3: Process for the Synthesis of a Crystalline 2-propanol Solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Following the final step of the procedure outlined in Scheme 1, recrystallization of Compound 1 from 2-propanol provided crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. Recrystallization was accomplished by dissolving 30 g of Compound 1 in 200 mL 2-propanol at 70-85° C. Cooling the solution to 0-10° C. afforded crystalline material collected via filtration. Drying at 45° C. temperature for 5-10 hours yielded crystalline Form A in 64% yield. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIGS. **3**-**4**, and Table 3, the DSC and TGA displayed in FIGS. **5**-**6**, and the infrared spectrum displayed in FIGS. **7**-**9**.

TABLE 3

Peak listing for the X-ray powder diffractogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.4553	218.33	0.5117	16.20011	1.64
6.4698	570.19	0.0768	13.66181	4.27
6.7690	3089.14	0.1279	13.05877	23.14
8.9299	843.34	0.0512	9.90296	6.32
9.3883	158.50	0.0768	9.42042	1.19
12.9330	1058.45	0.0768	6.84533	7.93
13.6041	1007.70	0.0768	6.50910	7.55
15.3404	3812.12	0.1279	5.77607	28.55
15.6855	962.24	0.1023	5.64977	7.21
16.2965	433.60	0.1023	5.43930	3.25
16.9017	612.88	0.1023	5.24585	4.59
17.2342	2115.39	0.1279	5.14539	15.84
17.8950	1592.15	0.0768	4.95686	11.93
18.1461	13350.91	0.1023	4.88884	100.00
18.3845	1526.00	0.0768	4.82596	11.43
18.8431	637.53	0.0936	4.70563	4.78
18.9361	523.54	0.0768	4.68662	3.92
19.4872	1355.32	0.1279	4.55531	10.15
19.6110	1030.01	0.0768	4.52683	7.71
21.1904	915.90	0.1279	4.19286	6.86
21.6838	1108.16	0.1279	4.09856	8.30
22.1456	4612.68	0.1279	4.01412	34.55

TABLE 3-continued

Peak listing for the X-ray powder diffractogram of crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
22.4303	387.74	0.0768	3.96381	2.90
22.7827	1112.80	0.1279	3.90329	8.33
23.2781	167.09	0.1023	3.82133	1.25
23.6557	995.86	0.1023	3.76118	7.46
24.2423	260.14	0.1023	3.67148	1.95
24.5501	212.39	0.1023	3.62615	1.59
25.5948	77.56	0.1535	3.48046	0.58
26.4362	213.47	0.1535	3.37156	1.60
27.4602	472.93	0.1279	3.24812	3.54
28.4022	852.95	0.1535	3.14250	6.39
29.3038	35.14	0.3070	3.04784	0.26
30.2677	88.49	0.2047	2.95293	0.66
31.6879	110.80	0.2047	2.82375	0.83
32.2548	43.58	0.2558	2.77541	0.33
32.9883	208.05	0.1535	2.71535	1.56
33.3155	313.83	0.2047	2.68943	2.35
34.5977	122.72	0.1535	2.59264	0.92

Example 4: Process for the Synthesis of Crystalline Hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine (10 g) was suspended in 120 mL of water and stirred for 24 hours. The solid was isolated via filtration and dried under ambient conditions on the filter for 2 hours to afford the crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine which exhibited the powder X-ray diffraction pattern displayed in FIGS. **10-11**, and Table 4, the DSC and TGA displayed in FIGS. **12-13**, the infrared spectrum displayed in FIG. **14** and the Raman spectra displayed in FIGS. **15-16**.

TABLE 4

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.3999	421.69	0.0768	25.98791	11.93
5.5146	174.51	0.1535	16.02591	4.94
6.8414	784.32	0.0768	12.92058	22.19
7.3467	514.29	0.0768	12.03315	14.55
8.9999	2193.96	0.0768	9.82611	62.06
9.1700	1135.28	0.0512	9.64424	32.12
10.9295	2491.74	0.1279	8.09524	70.49
11.3063	994.88	0.1535	7.82631	28.14
12.1911	189.73	0.1023	7.26021	5.37
12.4074	234.16	0.1023	7.13411	6.62
13.7582	623.68	0.0768	6.43655	17.64
13.9555	723.13	0.1023	6.34602	20.46
14.2607	791.06	0.1023	6.21088	22.38
14.7640	1684.45	0.1023	6.00024	47.65
15.0050	2755.94	0.1023	5.90442	77.96
16.2619	3534.98	0.1279	5.45080	100.00
16.6330	730.39	0.0768	5.32999	20.66
16.8369	1014.46	0.1023	5.26590	28.70
17.0783	683.10	0.0768	5.19202	19.32
17.5325	316.45	0.1279	5.05853	8.95
18.0365	435.62	0.1791	4.91830	12.32
18.4002	348.00	0.1279	4.82189	9.84
18.6360	253.81	0.1023	4.76139	7.18
18.9462	130.97	0.1023	4.68414	3.71
19.3520	1499.85	0.1279	4.58683	42.43
20.0424	1882.77	0.1535	4.43036	53.26
20.3853	545.35	0.1023	4.35660	15.43
20.6123	513.60	0.1023	4.30913	14.53
21.5128	129.59	0.0768	4.13074	3.67
21.8602	417.75	0.1023	4.06588	11.82
22.1424	1512.60	0.1279	4.01469	42.79

TABLE 4-continued

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
22.6232	243.57	0.0768	3.93044	6.89
22.9842	1482.27	0.1279	3.86952	41.93
23.8435	306.35	0.0768	3.73198	8.67
24.1876	434.97	0.1023	3.67967	12.30
24.5795	759.68	0.1279	3.62188	21.49
25.2870	543.04	0.1535	3.52213	15.36
25.7950	230.10	0.1535	3.45390	6.51
26.1041	272.44	0.0768	3.41371	7.71
26.7841	1050.92	0.1791	3.32856	29.73
27.3055	733.34	0.2047	3.26618	20.75
27.9204	368.68	0.2047	3.19563	10.43
28.2701	424.91	0.2047	3.15689	12.02
28.6771	355.41	0.1791	3.11300	10.05
29.3211	337.18	0.1535	3.04607	9.54
30.0823	590.94	0.1023	2.97071	16.72
30.8254	302.08	0.1279	2.90077	8.55
31.4243	255.93	0.1023	2.84684	7.24
33.1065	64.16	0.2047	2.70593	1.81
33.5449	42.56	0.1535	2.67156	1.20
34.0559	152.09	0.1279	2.63264	4.30
34.7678	307.22	0.1023	2.58035	8.69

Example 5: Process for the Synthesis of Crystalline Hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A reaction vessel was charged with 10 g of the crystalline 2-propanol solvate Form A of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 200 mL water. The slurry was stirred for 2-4 hours. The solid was isolated via filtration and dried on the filter for 1-2 hours to afford the crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIGS. **17-18**, and Table 5, the DSC and TGA displayed in FIGS. **19-20**, the infrared spectrum displayed in FIG. **21** and the Raman spectra displayed in FIGS. **22-23**.

TABLE 5

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°Th.]	d-spacing [Å]	Rel. Int. [%]
5.5630	690.13	0.0768	15.88671	4.00
8.3060	5435.10	0.0768	10.64530	31.51
10.0280	879.24	0.0768	8.82087	5.10
10.2012	893.49	0.0768	8.67151	5.18
10.5593	1995.84	0.1023	8.37818	11.57
11.0555	883.63	0.0768	8.00324	5.12
11.5183	320.77	0.1023	7.68270	1.86
11.8781	129.95	0.1279	7.45081	0.75
12.8085	69.41	0.1023	6.91160	0.40
13.6019	2957.43	0.1279	6.51016	17.14
14.0165	4349.92	0.1279	6.31852	25.22
14.3661	369.35	0.0768	6.16556	2.14
15.4007	633.14	0.1279	5.75361	3.67
15.9161	966.01	0.1023	5.56843	5.60
16.7238	2308.41	0.1279	5.30125	13.38
17.1424	1291.23	0.1279	5.17275	7.49
17.9407	17250.59	0.1791	4.94434	100.00
18.1017	7667.64	0.0512	4.90072	44.45
18.5141	1832.80	0.1279	4.79249	10.62
18.8004	1799.56	0.1279	4.72013	10.43
19.7326	1228.73	0.1535	4.49920	7.12
20.1720	765.07	0.1023	4.40217	4.44
20.4586	4099.20	0.1535	4.34116	23.76
21.0178	391.95	0.1023	4.22690	2.27
21.4381	355.28	0.1023	4.14498	2.06
21.6873	505.08	0.1535	4.09791	2.93
22.2036	553.03	0.1791	4.00377	3.21

TABLE 5-continued

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°Th.]	d-spacing [Å]	Rel. Int. [%]
22.7313	1258.93	0.1535	3.91200	7.30
23.1886	293.46	0.0768	3.83589	1.70
23.5022	802.91	0.1535	3.78540	4.65
23.9072	1323.54	0.1791	3.72219	7.67
24.8266	1308.18	0.1535	3.58638	7.58
25.3477	294.63	0.1279	3.51382	1.71
26.4001	712.70	0.1791	3.37610	4.13
27.2824	473.91	0.1791	3.26889	2.75
28.2575	1083.07	0.2047	3.15826	6.28
28.4360	661.36	0.1023	3.13884	3.83
29.0530	408.09	0.2303	3.07357	2.37
29.6230	525.69	0.2303	3.01572	3.05
30.3425	340.97	0.1535	2.94582	1.98
31.0351	150.13	0.1791	2.88164	0.87
32.0059	168.87	0.2047	2.79642	0.98
32.5007	33.40	0.2047	2.75497	0.19
33.2227	429.46	0.2047	2.69673	2.49
33.5621	380.49	0.1791	2.67024	2.21
34.7368	234.98	0.1535	2.58258	1.36

Example 6: Process for the Synthesis of Crystalline Hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A reaction vessel was charged with 2 g of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 100 mL of water. The slurry was stirred and heated to 60° C. for 2 hours. The solid was isolated via hot filtration, yielding 1.12 g of material. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIGS. **24-25**, and Table 6, the DSC and TGA displayed in FIGS. **26-27**, the infrared spectrum displayed in FIG. **28** and the Raman spectra displayed in FIG. **29-30**.

TABLE 6

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.0992	198.60	0.2558	28.50850	11.88
5.6875	189.52	0.2047	15.53922	11.34
7.3367	875.84	0.0768	12.04940	52.39
7.7184	778.87	0.1023	11.45434	46.59
8.4128	1045.52	0.1023	10.51042	62.54
8.7352	312.43	0.1023	10.12329	18.69
9.4626	248.39	0.1023	9.34658	14.86
9.9438	107.95	0.0768	8.89539	6.46
10.4116	304.46	0.0768	8.49675	18.21
11.1849	956.96	0.1279	7.91093	57.24
11.7679	400.75	0.1023	7.52034	23.97
12.0141	476.70	0.0768	7.36678	28.51
12.3836	67.54	0.1023	7.14778	4.04
13.9488	988.27	0.1023	6.34902	59.11
14.2513	725.29	0.1023	6.21496	43.38
14.7487	496.69	0.0768	6.00643	29.71
14.9540	629.52	0.0768	5.92443	37.65
15.5148	364.82	0.0768	5.71154	21.82
15.6636	573.78	0.0768	5.65761	34.32
15.9816	749.15	0.1023	5.54573	44.81
16.5007	800.16	0.1023	5.37242	47.86
16.8936	504.28	0.0768	5.24835	30.16
17.0260	665.98	0.1023	5.20784	39.83
17.3416	1671.90	0.1023	5.11377	100.00
17.5649	802.14	0.1023	5.04927	47.98
17.8362	906.95	0.1279	4.97307	54.25
18.2227	372.06	0.0768	4.86846	22.25
18.4737	375.78	0.1279	4.80288	22.48
19.0459	485.98	0.1535	4.65984	29.07
20.2820	493.50	0.1535	4.37855	29.52
21.1457	568.45	0.1279	4.20162	34.00

TABLE 6-continued

Peak listing for the X-ray powder diffractogram of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
21.5774	457.90	0.1279	4.11853	27.39
22.4297	499.99	0.1535	3.96393	29.91
23.1183	241.96	0.1279	3.84739	14.47
23.4118	989.13	0.1535	3.79982	59.16
24.4459	153.39	0.1279	3.64138	9.17
24.9424	166.56	0.1791	3.57000	9.96
25.2820	92.01	0.1279	3.52281	5.50
25.7449	114.48	0.1023	3.46051	6.85
26.4916	169.99	0.1535	3.36464	10.17
26.7999	120.42	0.1535	3.32663	7.20
27.3858	101.08	0.0768	3.25677	6.05
28.2746	203.68	0.1279	3.15639	12.18
28.5404	104.74	0.1023	3.12760	6.27
29.2441	136.15	0.1023	3.05392	8.14
30.2344	48.05	0.2047	2.95611	2.87
30.6752	54.83	0.1791	2.91463	3.28
31.1253	108.48	0.1279	2.87350	6.49
31.5101	114.77	0.2047	2.83928	6.86
32.1968	98.33	0.2558	2.78027	5.88
32.7310	99.94	0.1023	2.73611	5.98
33.6855	47.23	0.1023	2.66074	2.83
34.2749	57.08	0.0768	2.61632	3.41

Example 7: Process for the Synthesis of Crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A reaction vessel was charged with 1 g of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 20 mL of EtOH. The solution was stirred and heated to 60° C. for about 1 hour. The solution was held at 60° C. while nitrogen gas was passed over the solution, evaporating the solvent and concentrating the reaction mixture until crystallization began. The solution was then allowed to slowly cool overnight to afford crystalline material. The crystalline solid was isolated by filtration and dried at 55° C. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIGS. **31-32**, and Table 7, and the DSC and TGA displayed in FIGS. **33-34**.

TABLE 7

Peak listing for the X-ray powder diffractogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.1672	891.23	0.0768	27.89703	12.86
4.3834	6931.96	0.1023	20.15889	100.00
5.4897	330.94	0.2047	16.09860	4.77
6.2044	1288.01	0.0512	14.24578	18.58
6.3899	3790.66	0.1023	13.83258	54.68
8.6938	607.37	0.1023	10.17139	8.76
9.0652	444.30	0.1023	9.75546	6.41
9.7777	119.45	0.0768	9.04615	1.72
10.2389	2157.07	0.1023	8.63965	31.12
11.2467	983.77	0.1279	7.86760	14.19
11.8707	278.59	0.1279	7.45540	4.02
12.3338	692.41	0.1023	7.17652	9.99
12.8049	5399.63	0.1023	6.91351	77.89
12.9862	3094.86	0.0768	6.81741	44.65
13.3662	354.08	0.1535	6.62445	5.11
14.0133	2211.62	0.1023	6.31995	31.90
14.5229	1052.58	0.1279	6.09933	15.18
15.0822	1158.80	0.1791	5.87436	16.72
15.4766	1477.85	0.1535	5.72554	21.32
15.7997	1205.59	0.1023	5.60917	17.39
16.0464	1349.02	0.1023	5.52348	19.46
16.4905	188.08	0.1279	5.37572	2.71
17.4901	3355.74	0.1535	5.07068	48.41
17.7745	2248.51	0.1023	4.99018	32.44
18.0179	1355.40	0.1279	4.92333	19.55
18.6063	2679.28	0.1279	4.76894	38.65

TABLE 7-continued

Peak listing for the X-ray powder diffractogram of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
18.8665	1133.73	0.0512	4.70376	16.36
19.0860	2899.34	0.1535	4.65015	41.83
19.6262	404.17	0.1279	4.52335	5.83
20.0698	166.76	0.1023	4.42436	2.41
20.5929	1626.38	0.2047	4.31314	23.46
20.9838	697.62	0.1279	4.23367	10.06
21.4061	1154.31	0.1791	4.15110	16.65
22.2105	447.69	0.1023	4.00254	6.46
22.3974	577.13	0.0512	3.96956	8.33
22.6356	1403.27	0.1023	3.92833	20.24
22.9179	1502.49	0.1279	3.88057	21.67
23.2023	963.24	0.1279	3.83365	13.90
23.8591	843.13	0.2047	3.72959	12.16
24.2484	611.50	0.1279	3.67058	8.82
24.6862	603.74	0.1535	3.60647	8.71
25.1765	973.86	0.1791	3.53733	14.05
25.5023	143.35	0.0768	3.49288	2.07
25.8431	470.21	0.1791	3.44758	6.78
26.1733	1089.43	0.1535	3.40483	15.72
26.9377	271.79	0.1023	3.30992	3.92
27.5800	57.80	0.1535	3.23428	0.83
27.9121	231.35	0.0768	3.19656	3.34
28.3654	786.82	0.1535	3.14649	11.35
28.8139	643.08	0.1535	3.09853	9.28
29.1637	527.47	0.1535	3.06216	7.61
29.4832	211.62	0.1023	3.02969	3.05
29.9991	354.99	0.1535	2.97876	5.12
30.7636	157.51	0.1535	2.90645	2.27
31.9908	376.81	0.1279	2.79771	5.44
32.8014	249.45	0.1279	2.73040	3.60
33.6788	195.64	0.1279	2.66125	2.82
34.2423	74.36	0.1535	2.61873	1.07

Example 8: Process for the Synthesis of Crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A reaction vessel was charged with 1 g of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 14 mL of CH_3CN. The suspension was stirred and heated to 80° C. for 5 hours. The solid was isolated via hot filtration and dried at 55° C. The resulting solid exhibited the powder X-ray diffraction pattern displayed in FIGS. **35-36**, and Table 8, and the DSC and TGA displayed in FIGS. **37-38**.

TABLE 8

Peak listing for the X-ray powder diffractogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5 -fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.0930	922.45	0.0768	28.56528	16.01
3.4623	858.41	0.0768	25.51979	14.90
3.7214	1002.49	0.0768	23.74331	17.40
4.3050	5761.00	0.0768	20.52571	100.00
4.8848	1042.74	0.1279	18.09080	18.10
5.2922	1027.76	0.0768	16.69897	17.84
5.7296	574.24	0.1023	15.42521	9.97
6.2279	612.97	0.1279	14.19205	10.64
6.9617	246.22	0.0512	12.69760	4.27
7.5776	83.70	0.3070	11.66691	1.45
10.0012	598.63	0.0768	8.84447	10.39
10.4954	192.91	0.1279	8.42909	3.35
10.6820	215.23	0.0768	8.28224	3.74
11.1198	766.71	0.0768	7.95716	13.31
11.6640	336.86	0.1023	7.58707	5.85
12.2039	196.89	0.0768	7.25259	3.42
12.5522	951.49	0.1023	7.05214	16.52
12.8646	1197.30	0.1279	6.88159	20.78
13.1130	2313.45	0.0768	6.75176	40.16
13.2878	1134.51	0.0768	6.66336	19.69

TABLE 8-continued

Peak listing for the X-ray powder diffractogram of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5 -fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
14.1311	1182.73	0.1023	6.26753	20.53
14.4939	257.96	0.0768	6.11148	4.48
14.7071	278.75	0.1023	6.02336	4.84
15.3319	587.84	0.1023	5.77925	10.20
15.9237	506.90	0.1535	5.56579	8.80
16.7038	853.13	0.2303	5.30756	14.81
17.5492	645.84	0.0768	5.05375	11.21
17.7443	1462.08	0.1279	4.99862	25.38
18.0546	1168.83	0.2047	4.91340	20.29
18.8622	2263.23	0.1279	4.70480	39.29
19.6876	180.88	0.1279	4.50938	3.14
20.1549	279.92	0.1279	4.40589	4.86
20.5942	234.25	0.1023	4.31288	4.07
21.5782	216.48	0.3070	4.11838	3.76
22.3720	529.04	0.1279	3.97401	9.18
22.6009	318.28	0.0768	3.93428	5.52
22.9708	146.62	0.1279	3.87175	2.55
23.2981	128.68	0.1023	3.81809	2.23
23.7100	347.34	0.1791	3.75269	6.03
23.9304	351.85	0.0768	3.71862	6.11
24.6578	70.05	0.1535	3.61055	1.22
25.2428	359.68	0.1023	3.52819	6.24
26.8677	185.62	0.1023	3.31839	3.22
28.1046	131.15	0.2047	3.17510	2.28
28.4386	112.67	0.1279	3.13857	1.96
29.9739	88.40	0.1535	2.98121	1.53
30.4594	49.98	0.1279	2.93478	0.87
31.8405	22.73	0.1791	2.81057	0.39
32.6315	56.01	0.3070	2.74423	0.97

Example 9: Process for the Synthesis of Crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

A reaction vessel was charged with 1 g of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 50 mL of Et_2O. The suspension was stirred and heated to 30° C. for 5 hours. The solid was isolated via hot filtration and dried at 55° C.

An alternative preparation of the crystalline solid of Form I was achieved by charging a reaction vessel with 1 g of amorphous solid 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine and 50 mL of methyl ethyl ketone. The solution was stirred and heated to 60° C. for about 1 hour. The solution was held at 60° C. while nitrogen gas was passed over the solution, evaporating the solvent and concentrating the reaction mixture until crystallization began. The solution was then allowed to slowly cool overnight to afford crystalline material. The solid was isolated by filtration and dried at 55° C. The resulting solids from both preparations exhibited the powder X-ray diffraction pattern displayed in FIGS. **39-40**, and Table 9, and the DSC and TGA displayed in FIGS. **41-42**.

TABLE 9

Peak listing for the X-ray powder diffractogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-4-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.0731	43.01	0.4093	21.69391	0.46
4.3427	115.06	0.0768	20.34782	1.23
5.5083	656.95	0.0768	16.04437	7.04
5.7151	275.84	0.0768	15.46416	2.96
6.7017	12.46	0.3070	13.18967	0.13
8.7564	1484.80	0.1023	10.09883	15.92
9.5087	388.35	0.0512	9.30142	4.16
10.0391	3286.18	0.1279	8.81113	35.23
10.4596	7112.00	0.1279	8.45783	76.24
11.0863	795.84	0.0768	7.98112	8.53
11.4510	3567.88	0.1279	7.72771	38.25
12.4105	4192.64	0.1279	7.13235	44.94
12.8969	249.53	0.0768	6.86441	2.67
13.4212	4726.90	0.1279	6.59742	50.67

TABLE 9-continued

Peak listing for the X-ray powder diffractogram of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-4-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
14.0940	63.40	0.1535	6.28394	0.68
14.7950	312.95	0.1279	5.98775	3.35
15.6550	9328.88	0.1279	5.66069	100.00
16.0269	1638.18	0.0768	5.53019	17.56
16.2734	2146.72	0.0768	5.44696	23.01
16.4440	1924.64	0.1279	5.39085	20.63
17.2048	861.47	0.1279	5.15412	9.23
17.5888	1822.40	0.1279	5.04246	19.54
18.7002	514.07	0.1535	4.74519	5.51
19.3264	1490.04	0.2047	4.59284	15.97
19.8539	1061.34	0.1279	4.47199	11.38
20.1935	464.22	0.1535	4.39754	4.98
20.7352	609.58	0.1535	4.28388	6.53
21.2813	1028.46	0.2303	4.17516	11.02
21.9984	2223.41	0.1791	4.04065	23.83
23.1627	715.41	0.1535	3.84011	7.67
23.5262	1103.15	0.2047	3.78160	11.83
23.9307	211.75	0.0768	3.71858	2.27
24.7383	571.53	0.1279	3.59899	6.13
25.0316	1089.44	0.1279	3.55749	11.68
25.6969	540.10	0.1791	3.46687	5.79
26.0210	751.12	0.1279	3.42441	8.05
27.1503	20.59	0.1535	3.28449	0.22
27.7785	64.82	0.1535	3.21162	0.69
28.6746	214.56	0.1535	3.11327	2.30

Pharmaceutical Dosage Forms

Example 10: A tablet is prepared by mixing 48% by weight of amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 45% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 11: A tablet is prepared by mixing 48% by weight of crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 40% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, 5% by weight of croscarmellose sodium, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 12: A tablet is prepared by mixing 48% by weight of crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 45% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 13: A tablet is prepared by mixing 48% by weight of crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 40% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, 5% by weight of croscarmellose sodium, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 14: A tablet is prepared by mixing 48% by weight of crystalline Form G of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 40% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, 5% by weight of croscarmellose sodium, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 15: A tablet is prepared by mixing 48% by weight of crystalline Form H of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,

4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 40% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, 5% by weight of croscarmellose sodium, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Example 16: A tablet is prepared by mixing 48% by weight of crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, 40% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, 5% by weight of croscarmellose sodium, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250-500 mg.

Treatment of Uveitis

Example 17: Evaluate the Efficacy and Safety of Amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine in subjects with Uveitis

Study design: Allocation: randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Primary Outcome Measures:
- Control of intraocular inflammation [Time Frame: at 6-month visit] [Designated as safety issue: No]
- Absence of intraocular inflammation (e.g. less than trace AC cells; no vitreous haze; inactive chorioretinal lesions).
- Evaluation of Adverse Events [Time Frame: Baseline to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: Yes]
- Significant laboratory value changes [Time Frame: Baseline to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: Yes]
- Significant vital sign changes [Time Frame: Baseline to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: Yes]

Secondary Outcome Measures:
- Control of intraocular inflammation [Time Frame: 12-month clinical visit] [Designated as safety issue: No]
- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Week 8 for subjects who had active uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point with a Grade <=0.5+ in AC cells in both eyes on Slit Lamp Exam according to SUN criteria. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point with a Grade <=0.5+ in vitreous haze in both eyes on indirect ophthalmoscopy according to NEI/SUN criteria. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point without a worsening of BCVA by >=15 letters on the ETDRS in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point without a worsening of BCVA by >=15 letters on the ETDRS in both eyes relative to Week 8 for subjects who had active uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study. [Time Frame: Baseline to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Week 8 for subjects who had active uveitis when they entered the study.
  [Time Frame: Week 8 to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Change in NEI Visual Functioning Questionnaire (VFQ-25) score at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study. [Time Frame: Baseline to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Change in NEI Visual Functioning Questionnaire (VFQ-25) score at each study time point relative to week 8 for subjects who had active uveitis when they entered the study. [Time Frame: Week 8 to Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point achieving a >=50% reduction in immunosuppression load relative to Baseline for subjects who had inactive uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]
- Proportion of subjects at each study time point achieving a >=50% reduction in immunosuppression load relative to Week 8 for subjects who had active uveitis when they entered the study. [Time Frame: Final Visit (Final Visit could occur at any point up to 52 weeks)] [Designated as safety issue: No]

Other Outcome Measures:
- Elevation of IOP [Time Frame: At 3-month, 6-month, and 12-month visit] [Designated as safety issue: Yes]
- Ocular hypertension and IOP>30 and 10 mm Hg increase or greater in IOP will be assessed.

Progression of cataract or need for cataract surgery [Time Frame: At 3-month, 6-month, and 12-month visit] [Designated as safety issue: Yes]

Arms	Assigned Interventions
Experimental: amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4 -ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine Low-dose Group. Amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyppiperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3 -amine will be given at the predetermined dosing intervals as specified in the protocol	Low dose of amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyppiperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine administered at the predetermined intervals
Experimental: amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine High-dose Group. Amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine will be given at the predetermined dosing intervals as specified in the protocol	High dose of amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine administered at predetermined intervals
Placebo Comparator: Matching Placebo Group Placebo matching experimental dose will be given at the predetermined dosing intervals as specified in the protocol	Other: Placebo Matching placebo to experimental dose administered at predetermined intervals

DETAILED DESCRIPTION

Background: Intermediate and posterior uveitis are known to induce severe intraocular inflammation that may lead to permanent visual loss. It is estimated that these forms of uveitis comprise the fifth or sixth leading cause of blindness and tend to affect working class age patients, thus causing loss of work hours and diminished productivity and quality of life. Because disease in the posterior segment of the eye is not adequately treated by corticosteroid drops often systemic drug therapy is used including oral corticosteroids or prednisone. Prednisone can have a myriad of side effects. In approximately one-quarter to one-third of cases treated in tertiary care centers, additional medications such as immunosuppressive drugs are required to control the disease and/or to allow for appropriate tapering of oral prednisone to subsequent levels that have a low side effect profile when delivered over a long period of time. Typically, chronic prednisone therapy in doses of 7.5 mg daily or less are thought to have a low enough side effect profile to be amenable to long-term therapy. However frequently additional immunosuppressive drugs are required to get the dosing to this level. There are occasions when patients are intolerant of any dose of oral corticosteroids or are intolerant of the higher doses of oral corticosteroids (30-60 mg daily) and therefore this treatment modality is avoided due to prednisone's attendant side effects. Although periocular and intravitreal corticosteroids injections may be performed, with these modalities the standard of care is to wait until the disease reactivates before instituting such therapy and therefore a chronic suppressive dose is not obtained. The fluocinolone acetonide implant (Retisert®, Bausch and Lomb, Tampa, FL) is FDA-approved for the treatment of intermediate and posterior uveitis and it is equally effective in controlling uveitis as high-dose oral corticosteroids but avoids the systemic side effects associated with the use of high doses of oral corticosteroids. However, this form of local therapy has high rates of ocular side effects, including ocular hypertension causing glaucoma and/or requiring glaucoma surgery and cataracts. Furthermore, every two and half to three years the implant is exhausted of corticosteroid and therefore repeat surgical insertion of another implant may be required.

Eligibility
- Ages Eligible for Study: 18 Years and older
- Gender Eligible for Study: Both
- Accepts Healthy Volunteers: No

Inclusion Criteria:
- Active sight-threatening intermediate or posterior uveitis.
- Patients must be age 18 years or older and sign an informed consent.
- The ocular media must be clear enough to obtain OCT and fundus photographs.
- No elective intraocular surgery should be planned for the first 3 months after enrollment.

Exclusion Criteria:
- Infectious uveitis
- History of scleritis
- Active or suspected viral infection of the cornea or conjunctiva
- History of mycobacterial or fungal disease
- HIV positivity
- Age <18 years old
- Uncontrolled IOP
- Advanced glaucoma
- Aphakia with rupture of the posterior lens capsule
- ACIOL with rupture of the posterior lens capsule
- Media opacity that would preclude evaluation of the posterior pole via fundus photography or OCT assessment
- Planned elective ocular surgery within 3 months of enrollment

Additional Experiments

Example 18: HPLC Isolation of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine

Aims and Objectives

To assess the propensity of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-

N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine to form amorphous or crystalline phases following isolation from a CH_3CN/water eluent system, post transit/purification via a C18 reverse phase column.

Summary

Isolation of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine using acetonitrile (CH_3CN) and water systems provided varied results.

Three trials were completed:

18A CH_3CN

18B CH_3CN/water (9:1)

18C CH_3CN/water (1:9)

The trial using CH_3CN provided an amorphous solid. The two wet systems provided either partially crystalline or highly crystalline solids in the form of Pattern L. The crystalline phases did not dry back to amorphous solids.

Characterization of Input Solid

5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine was analyzed as received with the appearance of a beige to off-white glassy solid. Chemical purity by HPLC (generic low-pH method) was 92.98%. 1H NMR spectroscopy revealed a spectrum that conformed to structure (D_6DMSO). XRPD examination (FIG. **43**) revealed that the solid was completely amorphous for both samples tested.

General Procedure for Isolation Following Elution via a C18 Reverse Phase Column

5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine (150 mg) was dissolved in eluent at 45-50 mL and eluted via a C18 reverse phase column at 2 mL/minute. This was followed by flushing the column and testing for product content using 50-100 mL of eluent. The eluent was reduced in vacuo using a rotary evaporator at 35° C. to produce solids for analysis. The resulting samples were then dried overnight at 18-35° C. in vacuo ahead of analysis. In some instances, analysis of the damp solids was collected.

Column details: C18 Phenomenex 5 micron, Luna; 100 Å; 150×4.6 mm Example 18A: 100% CH_3CN

The column was loaded with 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine in 50 mL of CH_3CN. Note that precipitation of a voluminous solid takes place over 10 minutes in 10 mL CH_3CN used to initially mobilize solids. At 50 mL volume with warming at <40° C., dissolution takes place. Clarification via a 0.45 micron frit was employed prior to chromatography.

Elution was completed using 40 mL CH_3CN.

Evaporation at 35° C. was complete within 2 hours and dried at 18° C. overnight (18 h) in vacuo.

The resulting solid was a yellow glass in appearance.

Result: XRPD of the solid post reduction in vacuo was amorphous (FIG. **44**).

Example 18B: 9:1 CH_3CN:Water

The column loaded with 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine in 50 mL CH_3CN/water (9:1). Solids dissolved at 50 mL volume with warming at <40° C., dissolution readily takes place. Clarification via a 0.45 micron frit was employed prior to chromatography.

Elution was complete using 50 mL CH_3CN/water (9:1).

Evaporation at 35° C. was complete within 2.9 hours and dried at 18° C. overnight (18 h) in vacuo. Solids remain damp.

The resulting mass was a yellow glass in appearance with white granular solids present.

Result: XRPD of the solid post drying in vacuo was predominantly amorphous, or equally relevant, partially crystalline, XRPD pattern (FIG. **45**).

The solids post drying in vacuo at 35° C. to remove further water demonstrated a predominantly amorphous, or equally relevant, partially crystalline, XRPD pattern (FIG. **46**).

Example 18C: 1:9 CH_3CN:Water

The column was loaded with 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine in 45 mL CH_3CN/water (1:9) and 5 mL CH_3CN used to mobilize the solid (50 mL total). Solids dissolved at 50 mL volume with warming at <40° C., dissolution takes place following mild agitation. Clarification via a 0.45 micron frit was employed prior to chromatography.

Elution was complete using 50 mL CH_3CN/water (1:9).

Evaporation of half of the batch at 35° C. was complete within 3 hours to leave an aqueous emulsion/solid state that was held overnight due to time constraints. The remainder was reduced in vacuo the next day and 6 h were required to remove water without product loss due to bumping at <35° C.

The resulting mass was a white powder in appearance in the damp state.

Result: XRPD of the solid post reduction in vacuo was highly crystalline (FIG. **47**).

The solids post drying in vacuo at 35° C. to remove further water demonstrated a highly crystalline and equivalent profile (FIG. **48**).

CONCLUSIONS

The crystalline phase represented within Example 18B and 18C was identified as Pattern L. This phase requires drying at temperatures in excess of 70° C. to remove water and provide an amorphous phase.

Isolation of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine from acetonitrile/water provides crystalline or partially crystalline solids with results varying dependent upon the starting eluent composition being removed and the conditions employed within the laboratory. Standard drying conditions of <40° C. in vacuo do not return an amorphous solid.

Use of acetonitrile alone provides amorphous solids, but this does require speed or a solid phase that is likely to be a solvate will form.

What is claimed is:

1. A composition comprising amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-

dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits an X-ray powder diffraction pattern as shown in FIG. **1**.

2. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits a analysis differential scanning calorimetry pattern as shown in FIG. **2***a*.

3. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits a thermogravimetric analysis pattern as shown in FIG. **2***b*.

4. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine remains amorphous over 36 months at ambient temperature, as determined by X-ray powder diffraction.

5. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine remains amorphous over 60 months at ambient temperature, as determined by X-ray powder diffraction.

6. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-7 tetrahydropyrrolo[3,4-c]pyrazol-3-amine contains less than 5.5% of water (w/w).

7. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine comprises less than 0.25% (w/w) of impurities.

8. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine comprises less than 0.10% (w/w) of bis(3-((5-fluoro-2-methylpyrimidin-4-yl)amino)-6,6-dimethyl-4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methanone.

9. The composition of claim **1**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free of any crystalline solid state form as determined by X-ray powder diffraction.

10. The composition of claim **9**, wherein the amount of any crystalline solid state form is not detectable by X-ray powder diffraction.

11. The composition of claim **9**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free from crystalline hydrate Form B of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, which is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 16.3 as determined by X-ray powder diffraction.

12. The composition of claim **9**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free from crystalline hydrate Form D of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, which is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.9 as determined by X-ray powder diffraction.

13. The composition of claim **9**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free from crystalline hydrate Form L of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, which is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 17.3 as determined by X-ray powder diffraction.

14. The composition of claim **9**, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine is free from crystalline Form I of 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, which is characterized by an X-ray diffraction pattern reflection at a 2 theta value of 15.7 as determined by X-ray powder diffraction.

15. A pharmaceutical composition comprising amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, wherein the amorphous 5-{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine exhibits an X-ray powder diffraction pattern as shown in FIG. **1**, and at least one pharmaceutically acceptable excipient.

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