



- (51) **International Patent Classification:**
C07D 498/04 (2006.01) *A61P 7/02* (2006.01)
A61K 31/5383 (2006.01)
- (21) **International Application Number:**
PCT/CN2015/079522
- (22) **International Filing Date:**
21 May 2015 (21.05.2015)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
201410220261.4 22 May 2014 (22.05.2014) CN
201410393531.1 11 August 2014 (11.08.2014) CN
- (71) **Applicant:** SUNSHINE LAKE PHARMA CO., LTD.
[CN/CN]; Northern Industrial Area, Songshan Lake, Dongguan, Guangdong 523000 (CN).
- (72) **Inventors:** CHEN, Liang; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). WANG, Xiaojun; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). ZUO, Yinglin; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). ZHANG, Yingjun; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). ZHANG, Jiancun; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN).
- (74) **Agent:** TSINGYIHUA INTELLECTUAL PROPERTY LLC; Room 301, Trade Building, Zhaolanyuan, Tsinghua University, Qinghuayuan, Haidian District, Beijing 100084 (CN).
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))

(54) **Title:** CRYSTALLINE FORMS AND AMORPHISM OF OXAZOLIDINONE COMPOUND

(57) **Abstract:** Provided herein are crystalline forms and amorphism of oxazolidinone compounds, and a pharmaceutical composition containing the crystalline form or amorphism or a combination thereof. The crystalline forms or amorphism, or the pharmaceutical composition disclosed herein can be used in the manufacture of a blood coagulation factor Xa inhibitor and/or in the treatment of thromboembolism diseases in a patient. Also provided herein is a process of preparing the crystal form I.



CRYSTALLINE FORMS AND AMORPHISM OF OXAZOLIDINONE COMPOUND**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to Chinese Patent Application Serial No. 201410220261.4, filed with the State Intellectual Property Office of China on May 22, 2014, and Chinese Patent Application Serial No. 201410393531.1, filed with the State Intellectual Property Office of China on August 11, 2014, both of which are hereby incorporated by reference in their entireties and for all purposes as if specifically and fully set forth herein.

FIELD

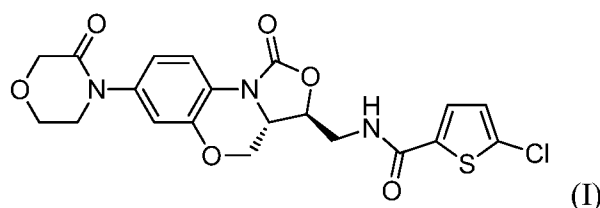
[0002] The present invention relates to the crystalline forms and amorphism of oxazolidinone compound, and a pharmaceutical composition containing the crystalline form or amorphism or a combination thereof. The crystalline forms, amorphism or the pharmaceutical composition disclosed herein can be used for the manufacture of a blood coagulation factor Xa inhibitor and/or in the treatment of thromboembolism diseases. The present invention also relates to a method of preparing form I.

BACKGROUND

[0003] Blood coagulation factor Xa is a serine protease, which can transform the prothrombin to thrombin. Blood coagulation factor Xa has a great clinical-value in anticoagulation as a target and plays an important role of controlling thrombin formation and coagulation cascade activation. Blood coagulation factor Xa mainly catalyzes the transformation of II factor to IIa factor in the interaction of intrinsic coagulation pathway and extrinsic coagulation pathway. One blood coagulation factor Xa inhibitor has the physiological effects of inhibiting 138 prothrombin molecules, because the biological signal amplification exists in the coagulation process. So, the production of thrombin and formation of thrombus can be inhibited effectively through inhibition of blood coagulation factor Xa. An effective and specific inhibitor of blood coagulation factor Xa could be a potential and valuable therapeutic agent to treat thromboembolism diseases in a patient.

[0004] Patent PCT WO 2014110971 (patent family: CN 103936763A) (incorporated herein by reference) published on July 24, 2014, disclosed an oxazolidinone compound of

5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide and its preparation method, and its structure represented by Formula (I) is as shown below. This compound has a good FXa inhibition activity, and can be used as anticoagulant drug for the treatment of thromboembolic-related disorders. However, the crystal form of compound of Formula (I) and preparation thereof were not disclosed in patent WO 2014110971.



[0005] Polymorphism of pharmaceuticals is a common phenomenon in drug research, which is a very important factor affecting the quality of drugs. Different crystalline forms of the same drug have significantly differences in appearance, solubility, melting point, dissolution rate, bio-availability, and so on, and which also have different influences on stability, bioavailability and curative effect of drugs. Hence, the person skilled in the art may consider the polymorphism of this compound in the drug research.

[0006] Amorphism is a form of polymorphism, and a non-crystalline form. The amorphous drug is different from the normal crystalline drug in physicochemical properties and clinical efficacy. Therefore, also it has important significance that exploring the amorphous substance in depth in the polymorphism research of solid drug.

SUMMARY

[0007] The present invention refers to crystalline forms and amorphism of the compound having 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (Formula (I)), specially refers to form I, form II, form III, form IV, form V and amorphism of the compound of Formula (I). The present invention also refers to a pharmaceutical composition containing the crystalline form or amorphism disclosed herein or a combination thereof, and uses of the crystalline forms, amorphism or the pharmaceutical composition disclosed herein for the manufacture of a blood coagulation factor Xa inhibitor and/or in the treatment of thromboembolism diseases in a patient.

[0008] Meanwhile, the present invention further refers to two preparation methods of crystalline form I of the compound of Formula (I). Wherein in method one, crystalline form I

was formed from the compound of Formula (I) through a reverse anti-solvent addition method; this method has low yields, and which is unsuitable for amplified production. In method two, crystalline form I was formed from amorphism of the compound of Formula (I) through a rotating crystal method by heating; this method has simple and practicable operations, good reproducibility, manageable process, stable technological process, and high yields, high purity of prepared crystalline form I, which is suitable for industrial production.

[0009] In one aspect, provided herein are crystalline forms of the compound (I) comprising form I, form II, form III, form IV or form V.

[0010] In some embodiments, the crystalline form disclosed herein is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$ and $34.27^\circ \pm 0.2^\circ$.

[0011] In some embodiments, the crystalline form disclosed herein is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $16.26^\circ \pm 0.2^\circ$, $16.95^\circ \pm 0.2^\circ$, $18.01^\circ \pm 0.2^\circ$, $18.69^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $20.75^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $22.96^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $27.08^\circ \pm 0.2^\circ$, $27.25^\circ \pm 0.2^\circ$, $28.96^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$, $31.61^\circ \pm 0.2^\circ$, $32.10^\circ \pm 0.2^\circ$, $32.86^\circ \pm 0.2^\circ$, $34.27^\circ \pm 0.2^\circ$ and $39.34^\circ \pm 0.2^\circ$.

[0012] In some embodiments, the crystalline form disclosed herein is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $12.64^\circ \pm 0.2^\circ$, $16.26^\circ \pm 0.2^\circ$, $16.66^\circ \pm 0.2^\circ$, $16.95^\circ \pm 0.2^\circ$, $18.01^\circ \pm 0.2^\circ$, $18.69^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $20.13^\circ \pm 0.2^\circ$, $20.75^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $22.23^\circ \pm 0.2^\circ$, $22.96^\circ \pm 0.2^\circ$, $23.39^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $24.96^\circ \pm 0.2^\circ$, $25.74^\circ \pm 0.2^\circ$, $26.36^\circ \pm 0.2^\circ$, $27.08^\circ \pm 0.2^\circ$, $27.25^\circ \pm 0.2^\circ$, $27.73^\circ \pm 0.2^\circ$, $28.53^\circ \pm 0.2^\circ$, $28.96^\circ \pm 0.2^\circ$, $29.36^\circ \pm 0.2^\circ$, $29.70^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$, $30.83^\circ \pm 0.2^\circ$, $31.61^\circ \pm 0.2^\circ$, $32.10^\circ \pm 0.2^\circ$, $32.86^\circ \pm 0.2^\circ$, $33.08^\circ \pm 0.2^\circ$, $33.76^\circ \pm 0.2^\circ$, $34.27^\circ \pm 0.2^\circ$, $35.34^\circ \pm 0.2^\circ$, $36.09^\circ \pm 0.2^\circ$, $37.20^\circ \pm 0.2^\circ$, $38.47^\circ \pm 0.2^\circ$ and $39.34^\circ \pm 0.2^\circ$.

[0013] In some embodiments, the crystalline form disclosed herein is form I having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 1.

[0014] In some embodiments, the crystalline form disclosed herein is form I having a differential scanning calorimetry thermogram comprising an endothermic peak at $204.81^\circ\text{C} \pm$

3 °C.

[0015] In some embodiments, the crystalline form disclosed herein is form I having a differential scanning calorimetry thermogram substantially the same as shown in Figure 2.

[0016] In some embodiments, the crystalline form disclosed herein is form I having a Raman spectrogram comprising absorption peaks at 163 cm^{-1} , 246 cm^{-1} , 280 cm^{-1} , 389 cm^{-1} , 516 cm^{-1} , 582 cm^{-1} , 672 cm^{-1} , 690 cm^{-1} , 715 cm^{-1} , 730 cm^{-1} , 796 cm^{-1} , 971 cm^{-1} , 1035 cm^{-1} , 1084 cm^{-1} , 1117 cm^{-1} , 1296 cm^{-1} , 1325 cm^{-1} , 1428 cm^{-1} , 1556 cm^{-1} , 1609 cm^{-1} , 1666 cm^{-1} , 2958 cm^{-1} and 2991 cm^{-1} , and the error margin is $\pm 2 \text{ cm}^{-1}$.

[0017] In some embodiments, the crystalline form disclosed herein is form I having a Raman spectrogram substantially the same as shown in Figure 3.

[0018] In some embodiments, the crystalline form disclosed herein is form I having a Fourier transform infrared spectrogram comprising absorption peaks at 418 cm^{-1} , 455 cm^{-1} , 480 cm^{-1} , 498 cm^{-1} , 516 cm^{-1} , 555 cm^{-1} , 568 cm^{-1} , 582 cm^{-1} , 605 cm^{-1} , 637 cm^{-1} , 687 cm^{-1} , 715 cm^{-1} , 739 cm^{-1} , 809 cm^{-1} , 883 cm^{-1} , 909 cm^{-1} , 937 cm^{-1} , 965 cm^{-1} , 996 cm^{-1} , 1025 cm^{-1} , 1048 cm^{-1} , 1087 cm^{-1} , 1115 cm^{-1} , 1153 cm^{-1} , 1188 cm^{-1} , 1217 cm^{-1} , 1237 cm^{-1} , 1290 cm^{-1} , 1324 cm^{-1} , 1344 cm^{-1} , 1385 cm^{-1} , 1427 cm^{-1} , 1474 cm^{-1} , 1510 cm^{-1} , 1560 cm^{-1} , 1625 cm^{-1} , 1642 cm^{-1} , 1673 cm^{-1} , 1766 cm^{-1} , 2870 cm^{-1} , 2927 cm^{-1} , 2970 cm^{-1} , 3065 cm^{-1} , 3101 cm^{-1} and 3292 cm^{-1} , and the error margin is $\pm 2 \text{ cm}^{-1}$.

[0019] In some embodiments, the crystalline form disclosed herein is form I having a Fourier transform infrared spectrogram substantially the same as shown in Figure 4.

[0020] In one aspect, provided herein is a pharmaceutical composition comprising form I disclosed herein; In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0021] In one aspect, provided herein is use of form I or the pharmaceutical composition containing form I disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[0022] In another aspect, provided herein is use of form I or the pharmaceutical composition containing I disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[0023] In one aspect, provided herein is a method of preventing, managing, treating or

lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of form I or the pharmaceutical composition containing form I disclosed herein.

[0024] In another aspect, provided herein is a method of inhibiting the activity of blood coagulation factor Xa comprising administering a therapeutically effective amount of form I or the pharmaceutical composition containing form I disclosed herein.

[0025] In one aspect, provided herein is form I or the pharmaceutical composition containing I disclosed herein for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[0026] In another aspect, provided herein is form I or the pharmaceutical composition containing form I disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[0027] In some embodiments, the crystalline form disclosed herein is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$, $27.56^\circ \pm 0.2^\circ$, $28.18^\circ \pm 0.2^\circ$ and $37.84^\circ \pm 0.2^\circ$.

[0028] In some embodiments, the crystalline form disclosed herein is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $14.65^\circ \pm 0.2^\circ$, $15.85^\circ \pm 0.2^\circ$, $16.90^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $20.99^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $23.07^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$, $27.56^\circ \pm 0.2^\circ$, $28.18^\circ \pm 0.2^\circ$, $30.36^\circ \pm 0.2^\circ$, $30.86^\circ \pm 0.2^\circ$, $33.43^\circ \pm 0.2^\circ$, $34.68^\circ \pm 0.2^\circ$, $35.22^\circ \pm 0.2^\circ$, $36.24^\circ \pm 0.2^\circ$ and $37.84^\circ \pm 0.2^\circ$.

[0029] In some embodiments, the crystalline form disclosed herein is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $12.70^\circ \pm 0.2^\circ$, $14.65^\circ \pm 0.2^\circ$, $15.41^\circ \pm 0.2^\circ$, $15.85^\circ \pm 0.2^\circ$, $16.90^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $20.99^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $22.45^\circ \pm 0.2^\circ$, $23.07^\circ \pm 0.2^\circ$, $23.32^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $25.42^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$, $27.56^\circ \pm 0.2^\circ$, $28.18^\circ \pm 0.2^\circ$, $29.94^\circ \pm 0.2^\circ$, $30.36^\circ \pm 0.2^\circ$, $30.86^\circ \pm 0.2^\circ$, $31.36^\circ \pm 0.2^\circ$, $33.43^\circ \pm 0.2^\circ$, $34.14^\circ \pm 0.2^\circ$, $34.37^\circ \pm 0.2^\circ$, $34.68^\circ \pm 0.2^\circ$, $35.22^\circ \pm 0.2^\circ$, $36.24^\circ \pm 0.2^\circ$, $36.85^\circ \pm 0.2^\circ$, $37.07^\circ \pm 0.2^\circ$, $37.84^\circ \pm 0.2^\circ$, $38.31^\circ \pm 0.2^\circ$ and $39.10^\circ \pm 0.2^\circ$.

[0030] In some embodiments, the crystalline form disclosed herein is form II having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 5.

[0031] In some embodiments, the crystalline form disclosed herein is form II having a

differential scanning calorimetry thermogram comprising an endothermic peak at $194.90\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

[0032] In some embodiments, the crystalline form disclosed herein is form II having a differential scanning calorimetry thermogram substantially the same as shown in Figure 6.

[0033] In some embodiments, the crystalline form disclosed herein is form II having a Raman spectrogram comprising absorption peaks at 174 cm^{-1} , 198 cm^{-1} , 270 cm^{-1} , 336 cm^{-1} , 401 cm^{-1} , 448 cm^{-1} , 524 cm^{-1} , 559 cm^{-1} , 669 cm^{-1} , 696 cm^{-1} , 729 cm^{-1} , 797 cm^{-1} , 880 cm^{-1} , 1078 cm^{-1} , 1092 cm^{-1} , 1234 cm^{-1} , 1294 cm^{-1} , 1328 cm^{-1} , 1390 cm^{-1} , 1428 cm^{-1} , 1478 cm^{-1} , 1562 cm^{-1} , 1605 cm^{-1} , 1642 cm^{-1} , 1770 cm^{-1} , 2877 cm^{-1} , 2926 cm^{-1} , 2955 cm^{-1} , 2987 cm^{-1} and 3089 cm^{-1} , and the error margin is $\pm 2\text{ cm}^{-1}$.

[0034] In some embodiments, the crystalline form disclosed herein is form II having a Raman spectrogram substantially the same as shown in Figure 7.

[0035] In some embodiments, the crystalline form disclosed herein is form II having a Fourier transform infrared spectrogram comprising absorption peaks at 421 cm^{-1} , 481 cm^{-1} , 497 cm^{-1} , 512 cm^{-1} , 558 cm^{-1} , 584 cm^{-1} , 607 cm^{-1} , 637 cm^{-1} , 682 cm^{-1} , 727 cm^{-1} , 749 cm^{-1} , 798 cm^{-1} , 829 cm^{-1} , 881 cm^{-1} , 938 cm^{-1} , 962 cm^{-1} , 985 cm^{-1} , 999 cm^{-1} , 1014 cm^{-1} , 1027 cm^{-1} , 1058 cm^{-1} , 1098 cm^{-1} , 1129 cm^{-1} , 1157 cm^{-1} , 1184 cm^{-1} , 1204 cm^{-1} , 1237 cm^{-1} , 1291 cm^{-1} , 1328 cm^{-1} , 1348 cm^{-1} , 1372 cm^{-1} , 1391 cm^{-1} , 1426 cm^{-1} , 1448 cm^{-1} , 1478 cm^{-1} , 1504 cm^{-1} , 1560 cm^{-1} , 1642 cm^{-1} , 1770 cm^{-1} , 1933 cm^{-1} , 2745 cm^{-1} , 2820 cm^{-1} , 2870 cm^{-1} , 2924 cm^{-1} , 2955 cm^{-1} , 2983 cm^{-1} , 3035 cm^{-1} , 3090 cm^{-1} and 3286 cm^{-1} , and the error margin is $\pm 2\text{ cm}^{-1}$.

[0036] In some embodiments, the crystalline form disclosed herein is form II having a Fourier transform infrared spectrogram substantially the same as shown in Figure 8.

[0037] In one aspect, provided herein is a pharmaceutical composition comprising form II disclosed herein; In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0038] In one aspect, provided herein is use of form II or the pharmaceutical composition containing form II disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[0039] In another aspect, provided herein is use of form II or the pharmaceutical composition containing II disclosed herein in the manufacture of a medicament for inhibiting the activity of

blood coagulation factor Xa.

[0040] In one aspect, provided herein is a method of preventing, managing, treating or lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of form II or the pharmaceutical composition containing form II disclosed herein.

[0041] In another aspect, provided herein is a method of inhibiting the activity of blood coagulation factor Xa comprising administering a therapeutically effective amount of form II or the pharmaceutical composition containing form II disclosed herein.

[0042] In one aspect, provided herein is form II or the pharmaceutical composition containing form II disclosed herein for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[0043] In another aspect, provided herein is form II or the pharmaceutical composition containing form II disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[0044] In some embodiments, the crystalline form disclosed herein is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $12.14^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$ and $34.49^\circ \pm 0.2^\circ$.

[0045] In some embodiments, the crystalline form disclosed herein is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.94^\circ \pm 0.2^\circ$, $12.14^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $16.13^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.49^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $22.40^\circ \pm 0.2^\circ$, $23.43^\circ \pm 0.2^\circ$, $23.83^\circ \pm 0.2^\circ$, $24.45^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $25.05^\circ \pm 0.2^\circ$, $25.77^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.52^\circ \pm 0.2^\circ$, $29.73^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$, $33.88^\circ \pm 0.2^\circ$, $34.05^\circ \pm 0.2^\circ$, $34.49^\circ \pm 0.2^\circ$ and $39.33^\circ \pm 0.2^\circ$.

[0046] In some embodiments, the crystalline form disclosed herein is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $4.73^\circ \pm 0.2^\circ$, $8.94^\circ \pm 0.2^\circ$, $9.46^\circ \pm 0.2^\circ$, $12.14^\circ \pm 0.2^\circ$, $14.23^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $16.13^\circ \pm 0.2^\circ$, $17.39^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.49^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $22.40^\circ \pm 0.2^\circ$, $23.43^\circ \pm 0.2^\circ$, $23.83^\circ \pm 0.2^\circ$, $24.45^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $25.05^\circ \pm 0.2^\circ$, $25.77^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $27.10^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.52^\circ \pm 0.2^\circ$, $29.73^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$, $30.76^\circ \pm 0.2^\circ$, $31.47^\circ \pm 0.2^\circ$, $32.66^\circ \pm 0.2^\circ$, $33.32^\circ \pm 0.2^\circ$, $33.88^\circ \pm 0.2^\circ$, $34.05^\circ \pm 0.2^\circ$, $34.49^\circ \pm$

0.2°, 35.21° ± 0.2°, 36.29° ± 0.2°, 37.08° ± 0.2°, 37.62° ± 0.2°, 38.19° ± 0.2°, 39.33° ± 0.2° and 39.43° ± 0.2°.

[0047] In some embodiments, the crystalline form disclosed herein is form III having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 9.

[0048] In some embodiments, the crystalline form disclosed herein is form III having a differential scanning calorimetry thermogram comprising an endothermic peak at 125.24 °C ± 3 °C.

[0049] In some embodiments, the crystalline form disclosed herein is form III having a differential scanning calorimetry thermogram substantially the same as shown in Figure 10.

[0050] In some embodiments, the crystalline form disclosed herein is form III having a Raman spectrogram comprising absorption peaks at 201 cm⁻¹, 245 cm⁻¹, 283 cm⁻¹, 367 cm⁻¹, 407 cm⁻¹, 450 cm⁻¹, 510 cm⁻¹, 525 cm⁻¹, 571 cm⁻¹, 639 cm⁻¹, 665 cm⁻¹, 693 cm⁻¹, 714 cm⁻¹, 742 cm⁻¹, 769 cm⁻¹, 802 cm⁻¹, 864 cm⁻¹, 903 cm⁻¹, 949 cm⁻¹, 974 cm⁻¹, 1005 cm⁻¹, 1034 cm⁻¹, 1080 cm⁻¹, 1099 cm⁻¹, 1231 cm⁻¹, 1272 cm⁻¹, 1291 cm⁻¹, 1309 cm⁻¹, 1328 cm⁻¹, 1388 cm⁻¹, 1426 cm⁻¹, 1507 cm⁻¹, 1554 cm⁻¹, 1608 cm⁻¹, 1640 cm⁻¹, 1662 cm⁻¹, 1762 cm⁻¹, 2834 cm⁻¹, 2874 cm⁻¹, 2939 cm⁻¹, 2981 cm⁻¹ and 3089 cm⁻¹, wherein the error margin is ± 2 cm⁻¹.

[0051] In some embodiments, the crystalline form disclosed herein is form III having a Raman spectrogram substantially the same as shown in Figure 11.

[0052] In some embodiments, the crystalline form disclosed herein is form III having a Fourier transform infrared spectrogram comprising absorption peaks at 416 cm⁻¹, 430 cm⁻¹, 451 cm⁻¹, 469 cm⁻¹, 484 cm⁻¹, 498 cm⁻¹, 510 cm⁻¹, 525 cm⁻¹, 554 cm⁻¹, 570 cm⁻¹, 584 cm⁻¹, 616 cm⁻¹, 639 cm⁻¹, 665 cm⁻¹, 688 cm⁻¹, 713 cm⁻¹, 727 cm⁻¹, 755 cm⁻¹, 769 cm⁻¹, 801 cm⁻¹, 816 cm⁻¹, 833 cm⁻¹, 880 cm⁻¹, 904 cm⁻¹, 939 cm⁻¹, 953 cm⁻¹, 974 cm⁻¹, 996 cm⁻¹, 1022 cm⁻¹, 1034 cm⁻¹, 1064 cm⁻¹, 1079 cm⁻¹, 1098 cm⁻¹, 1119 cm⁻¹, 1142 cm⁻¹, 1159 cm⁻¹, 1185 cm⁻¹, 1203 cm⁻¹, 1237 cm⁻¹, 1285 cm⁻¹, 1310 cm⁻¹, 1324 cm⁻¹, 1347 cm⁻¹, 1374 cm⁻¹, 1428 cm⁻¹, 1504 cm⁻¹, 1556 cm⁻¹, 1580 cm⁻¹, 1606 cm⁻¹, 1640 cm⁻¹, 1661 cm⁻¹, 1764 cm⁻¹, 2809 cm⁻¹, 2865 cm⁻¹, 2928 cm⁻¹, 2965 cm⁻¹, 2979 cm⁻¹, 3032 cm⁻¹, 3081 cm⁻¹, 3306 cm⁻¹ and 3340 cm⁻¹, the error margin is ± 2 cm⁻¹.

[0053] In some embodiments, the crystalline form disclosed herein is form III having a Fourier transform infrared spectrogram substantially the same as shown in Figure 12.

[0054] In one aspect, provided herein is a pharmaceutical composition comprising form III disclosed herein; In some embodiments, the pharmaceutical composition further comprises a

pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0055] In one aspect, provided herein is use of form III or the pharmaceutical composition containing form III disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[0056] In another aspect, provided herein is use of form III or the pharmaceutical composition containing form III disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[0057] In one aspect, provided herein is a method of preventing, managing, treating or lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of form III or the pharmaceutical composition containing form III disclosed herein.

[0058] In another aspect, provided herein is a method of inhibiting the activity of blood coagulation factor Xa comprising administering a therapeutically effective amount of form III or the pharmaceutical composition containing form III disclosed herein.

[0059] In one aspect, provided herein is form III or the pharmaceutical composition containing form III disclosed herein for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[0060] In another aspect, provided herein is form III or the pharmaceutical composition containing form III disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[0061] In some embodiments, the crystalline form disclosed herein is form IV having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $14.98^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm 0.2^\circ$, $26.56^\circ \pm 0.2^\circ$ and $29.67^\circ \pm 0.2^\circ$.

[0062] In some embodiments, the crystalline form disclosed herein is form IV having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.84^\circ \pm 0.2^\circ$, $14.98^\circ \pm 0.2^\circ$, $17.76^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $18.97^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $22.64^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm 0.2^\circ$, $24.56^\circ \pm 0.2^\circ$, $26.56^\circ \pm 0.2^\circ$, $29.39^\circ \pm 0.2^\circ$, $29.67^\circ \pm 0.2^\circ$, $33.64^\circ \pm 0.2^\circ$, $34.30^\circ \pm 0.2^\circ$, $34.59^\circ \pm 0.2^\circ$ and $37.00^\circ \pm 0.2^\circ$.

[0063] In some embodiments, the crystalline form disclosed herein is form IV having an X-ray

powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.84^\circ \pm 0.2^\circ$, $9.48^\circ \pm 0.2^\circ$, $14.26^\circ \pm 0.2^\circ$, $14.98^\circ \pm 0.2^\circ$, $16.12^\circ \pm 0.2^\circ$, $16.63^\circ \pm 0.2^\circ$, $17.76^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $18.97^\circ \pm 0.2^\circ$, $19.93^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $22.07^\circ \pm 0.2^\circ$, $22.64^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm 0.2^\circ$, $24.56^\circ \pm 0.2^\circ$, $25.08^\circ \pm 0.2^\circ$, $25.43^\circ \pm 0.2^\circ$, $26.56^\circ \pm 0.2^\circ$, $28.68^\circ \pm 0.2^\circ$, $29.39^\circ \pm 0.2^\circ$, $29.67^\circ \pm 0.2^\circ$, $30.35^\circ \pm 0.2^\circ$, $31.21^\circ \pm 0.2^\circ$, $32.39^\circ \pm 0.2^\circ$, $32.72^\circ \pm 0.2^\circ$, $33.64^\circ \pm 0.2^\circ$, $34.30^\circ \pm 0.2^\circ$, $34.59^\circ \pm 0.2^\circ$, $36.07^\circ \pm 0.2^\circ$, $37.00^\circ \pm 0.2^\circ$, $37.92^\circ \pm 0.2^\circ$ and $39.44^\circ \pm 0.2^\circ$.

[0064] In some embodiments, the crystalline form disclosed herein is form IV having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 13.

[0065] In some embodiments, the crystalline form disclosed herein is form IV having a differential scanning calorimetry thermogram comprising an endothermic peak at $116.97^\circ\text{C} \pm 3^\circ\text{C}$.

[0066] In some embodiments, the crystalline form disclosed herein is form IV, which transforms to form I at a temperature from about 150°C to about 215°C , and form IV has a differential scanning calorimetry thermogram comprising an endothermic peak at $203.20^\circ\text{C} \pm 3^\circ\text{C}$.

[0067] In some embodiments, the crystalline form disclosed herein is form IV having a differential scanning calorimetry thermogram comprising endothermic peaks at $116.97^\circ\text{C} \pm 3^\circ\text{C}$ and $203.20^\circ\text{C} \pm 3^\circ\text{C}$.

[0068] In some embodiments, the crystalline form disclosed herein is form IV having a differential scanning calorimetry thermogram substantially the same as shown in Figure 14.

[0069] In some embodiments, the crystalline form disclosed herein is form IV having a Raman spectrogram comprising absorption peaks at 202 cm^{-1} , 241 cm^{-1} , 283 cm^{-1} , 381 cm^{-1} , 510 cm^{-1} , 668 cm^{-1} , 692 cm^{-1} , 714 cm^{-1} , 742 cm^{-1} , 800 cm^{-1} , 1035 cm^{-1} , 1081 cm^{-1} , 1228 cm^{-1} , 1273 cm^{-1} , 1305 cm^{-1} , 1327 cm^{-1} , 1428 cm^{-1} , 1554 cm^{-1} , 1608 cm^{-1} , 1643 cm^{-1} , 1703 cm^{-1} , 1765 cm^{-1} , 2924 cm^{-1} , 2987 cm^{-1} and 3085 cm^{-1} , and the error margin is $\pm 2\text{ cm}^{-1}$.

[0070] In some embodiments, the crystalline form disclosed herein is form IV having a Raman spectrogram substantially the same as shown in Figure 15.

[0071] In some embodiments, the crystalline form disclosed herein is form IV having a Fourier transform infrared spectrogram comprising absorption peaks at 421 cm^{-1} , 481 cm^{-1} , 496 cm^{-1} , 511 cm^{-1} , 558 cm^{-1} , 584 cm^{-1} , 606 cm^{-1} , 637 cm^{-1} , 681 cm^{-1} , 727 cm^{-1} , 749 cm^{-1} , 798 cm^{-1} , 829

cm⁻¹, 840 cm⁻¹, 880 cm⁻¹, 894 cm⁻¹, 938 cm⁻¹, 961 cm⁻¹, 985 cm⁻¹, 999 cm⁻¹, 1014 cm⁻¹, 1027 cm⁻¹, 1058 cm⁻¹, 1098 cm⁻¹, 1114 cm⁻¹, 1128 cm⁻¹, 1157 cm⁻¹, 1184 cm⁻¹, 1204 cm⁻¹, 1237 cm⁻¹, 1291 cm⁻¹, 1328 cm⁻¹, 1348 cm⁻¹, 1372 cm⁻¹, 1390 cm⁻¹, 1426 cm⁻¹, 1449 cm⁻¹, 1478 cm⁻¹, 1504 cm⁻¹, 1561 cm⁻¹, 1606 cm⁻¹, 1642 cm⁻¹, 1771 cm⁻¹, 1933 cm⁻¹, 2745 cm⁻¹, 2820 cm⁻¹, 2869 cm⁻¹, 2923 cm⁻¹, 2955 cm⁻¹, 2983 cm⁻¹, 3035 cm⁻¹, 3090 cm⁻¹, 3285 cm⁻¹ and 3383 cm⁻¹, wherein the error margin is ± 2 cm⁻¹.

[0072] In some embodiments, the crystalline form disclosed herein is form IV having a Fourier transform infrared spectrogram substantially the same as shown in Figure 16.

[0073] In one aspect, provided herein is a pharmaceutical composition comprising form IV disclosed herein; In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0074] In one aspect, provided herein is use of form IV or the pharmaceutical composition containing form IV disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[0075] In another aspect, provided herein is use of form IV or the pharmaceutical composition containing form IV disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[0076] In one aspect, provided herein is a method of preventing, managing, treating or lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of form IV or the pharmaceutical composition containing form IV disclosed herein.

[0077] In another aspect, provided herein is a method of inhibiting the activity of blood coagulation factor Xa comprising administering a therapeutically effective amount of form IV or the pharmaceutical composition containing form IV disclosed herein.

[0078] In one aspect, provided herein is form IV or the pharmaceutical composition containing form IV disclosed herein for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[0079] In another aspect, provided herein is form IV or the pharmaceutical composition containing form IV disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[0080] In some embodiments, the crystalline form disclosed herein is form V having single-crystal structural parameters as shown in table 1:

Table 1: Single-crystal structural parameters of form V disclosed herein

Test Temperature:	150(2) K
Test Wavelength:	1.54178 Å
Crystal System:	triclinic system
Space Group:	P1
Unit Cell Dimensions:	$a = 6.8155(2) \text{ Å}$, $\alpha = 90.550(2)^\circ$, $b = 9.1213(2) \text{ Å}$, $\beta = 96.294(2)^\circ$, $c = 19.5897(5) \text{ Å}$, $\gamma = 91.719(2)^\circ$
Cell Volume:	$1209.83(5) \text{ Å}^3$
Molecules per unit cell (Z):	2.

[0081] Throughout the present application crystal parameters such as unit cell dimensions are given in standard crystallographic notation, such that the standard uncertainty for a specific value is stated in bracket. For example, the value of axis a in Table 1, “ $a = 6.8155(2)$ ” means that the value of a is $6.8155 \pm 0.0002 \text{ Å}$, *i.e.* lies between 6.8153 Å and 6.8157 Å .

[0082] In some embodiments, the crystalline form disclosed herein is form V having a single-crystal structure substantially the same as shown in Figure 21. It can be known from Figure 21 that, the form V is a crystalline form of the chloroform solvate of the compound of Formula (I), and each unit cell contains two molecules of the compound of Formula (I) and two molecules of chloroform, *i.e.* in unit cell structure, the ratio of the compound of Formula (I) to chloroform is 1:1.

[0083] In some embodiments, the crystalline form disclosed herein is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.97^\circ \pm 0.2^\circ$, $14.16^\circ \pm 0.2^\circ$, $19.18^\circ \pm 0.2^\circ$, $19.92^\circ \pm 0.2^\circ$, $20.20^\circ \pm 0.2^\circ$, $22.53^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $27.13^\circ \pm 0.2^\circ$ and $31.75^\circ \pm 0.2^\circ$.

[0084] In some embodiments, the crystalline form disclosed herein is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.97^\circ \pm 0.2^\circ$, $14.16^\circ \pm 0.2^\circ$, $17.58^\circ \pm 0.2^\circ$, $17.98^\circ \pm 0.2^\circ$, $19.18^\circ \pm 0.2^\circ$, $19.92^\circ \pm 0.2^\circ$, $20.20^\circ \pm 0.2^\circ$, $20.40^\circ \pm 0.2^\circ$, $22.53^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $26.39^\circ \pm 0.2^\circ$, $27.13^\circ \pm 0.2^\circ$, $28.77^\circ \pm 0.2^\circ$, $31.75^\circ \pm 0.2^\circ$ and $33.21^\circ \pm 0.2^\circ$.

[0085] In some embodiments, the crystalline form disclosed herein is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $4.50^\circ \pm 0.2^\circ$, $8.97^\circ \pm 0.2^\circ$, $10.55^\circ \pm 0.2^\circ$, $13.14^\circ \pm 0.2^\circ$, $14.16^\circ \pm 0.2^\circ$, $16.10^\circ \pm 0.2^\circ$, $16.50^\circ \pm 0.2^\circ$, $17.58^\circ \pm 0.2^\circ$, $17.98^\circ \pm 0.2^\circ$, $19.18^\circ \pm 0.2^\circ$, $19.92^\circ \pm 0.2^\circ$, $20.20^\circ \pm 0.2^\circ$, $20.40^\circ \pm 0.2^\circ$, $20.96^\circ \pm 0.2^\circ$, $21.23^\circ \pm 0.2^\circ$, $22.53^\circ \pm 0.2^\circ$, $23.07^\circ \pm 0.2^\circ$, $23.47^\circ \pm 0.2^\circ$, $24.11^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $25.94^\circ \pm 0.2^\circ$, $26.39^\circ \pm 0.2^\circ$, $26.70^\circ \pm 0.2^\circ$, $27.13^\circ \pm 0.2^\circ$, $28.42^\circ \pm 0.2^\circ$, $28.77^\circ \pm 0.2^\circ$, $29.41^\circ \pm 0.2^\circ$, $29.77^\circ \pm 0.2^\circ$, $30.01^\circ \pm 0.2^\circ$, $30.38^\circ \pm 0.2^\circ$, $31.41^\circ \pm 0.2^\circ$, $31.75^\circ \pm 0.2^\circ$, $32.13^\circ \pm 0.2^\circ$, $33.21^\circ \pm 0.2^\circ$, $34.59^\circ \pm 0.2^\circ$, $37.24^\circ \pm 0.2^\circ$ and $39.04^\circ \pm 0.2^\circ$.

[0086] In some embodiments, the crystalline form disclosed herein is form V having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 22.

[0087] In some embodiments, the crystalline form disclosed herein is form V having a differential scanning calorimetry thermogram comprising an endothermic peak at $106.98^\circ\text{C} \pm 3^\circ\text{C}$.

[0088] In some embodiments, the crystalline form disclosed herein is form V, which transforms to form I and form II at a temperature from about 175°C to about 210°C , and the form V has a differential scanning calorimetry thermogram comprising endothermic peaks at $193.82^\circ\text{C} \pm 3^\circ\text{C}$ and $203.62^\circ\text{C} \pm 3^\circ\text{C}$.

[0089] In some embodiments, the crystalline form disclosed herein is form V having a differential scanning calorimetry thermogram comprising endothermic peaks at $106.98^\circ\text{C} \pm 3^\circ\text{C}$, $193.82^\circ\text{C} \pm 3^\circ\text{C}$ and $203.62^\circ\text{C} \pm 3^\circ\text{C}$.

[0090] In some embodiments, the crystalline form disclosed herein is form V having a differential scanning calorimetry thermogram substantially the same as shown in Figure 23.

[0091] In some embodiments, the crystalline form disclosed herein is form V, which has a weight loss of 16.59% measured by thermogravimetric analysis in a temperature range from about 50°C to about 150°C ; the error margin is $\pm 0.1\%$.

[0092] In some embodiments, the crystalline form disclosed herein is form V having a thermogravimetric analysis pattern substantially the same as shown in Figure 24.

[0093] In one aspect, provided herein is a pharmaceutical composition comprising form V disclosed herein; In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0094] In one aspect, provided herein is use of form V or the pharmaceutical composition containing form V disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[0095] In another aspect, provided herein is use of form V or the pharmaceutical composition containing form V disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[0096] In one aspect, provided herein is a method of preventing, managing, treating or lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of form V or the pharmaceutical composition containing form V disclosed herein.

[0097] In another aspect, provided herein is a method of inhibiting the activity of blood coagulation factor Xa comprising administering a therapeutically effective amount of the crystalline form V or the pharmaceutical composition containing form V disclosed herein.

[0098] In one aspect, provided herein is form V or the pharmaceutical composition containing form V disclosed herein for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[0099] In another aspect, provided herein is form V or the pharmaceutical composition containing form V disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[00100] In one aspect, provided herein is an amorphism of a compound having Formula (I), wherein the amorphism has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 17.

[00101] In some embodiments, the amorphism disclosed herein has a glass transition temperature of $107.44\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

[00102] In some embodiments, the amorphism disclosed herein transforms to form I at a temperature from about $140\text{ }^{\circ}\text{C}$ to about $215\text{ }^{\circ}\text{C}$, and the amorphism has a differential scanning calorimetry thermogram comprising an endothermic peak at $203.43\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

[00103] In some embodiments, the amorphism disclosed herein has a differential scanning calorimetry thermogram substantially the same as shown in Figure 18.

[00104] In some embodiments, the amorphism disclosed herein has a Raman spectrogram comprising absorption peaks at 181 cm^{-1} , 276 cm^{-1} , 392 cm^{-1} , 425 cm^{-1} , 512 cm^{-1} , 672 cm^{-1} , 694

cm^{-1} , 739 cm^{-1} , 795 cm^{-1} , 1080 cm^{-1} , 1120 cm^{-1} , 1298 cm^{-1} , 1328 cm^{-1} , 1427 cm^{-1} , 1549 cm^{-1} , 1612 cm^{-1} , 2981 cm^{-1} and 3088 cm^{-1} , and wherein the error margin is $\pm 2 \text{ cm}^{-1}$.

[00105] In some embodiments, the amorphism disclosed herein has a Raman spectrogram substantially the same as shown in Figure 19.

[00106] In some embodiments, the amorphism disclosed herein has a Fourier transform infrared spectrogram comprising absorption peaks at 419 cm^{-1} , 487 cm^{-1} , 516 cm^{-1} , 548 cm^{-1} , 581 cm^{-1} , 605 cm^{-1} , 636 cm^{-1} , 689 cm^{-1} , 720 cm^{-1} , 747 cm^{-1} , 816 cm^{-1} , 883 cm^{-1} , 939 cm^{-1} , 968 cm^{-1} , 998 cm^{-1} , 1023 cm^{-1} , 1060 cm^{-1} , 1099 cm^{-1} , 1121 cm^{-1} , 1156 cm^{-1} , 1191 cm^{-1} , 1216 cm^{-1} , 1245 cm^{-1} , 1291 cm^{-1} , 1327 cm^{-1} , 1347 cm^{-1} , 1390 cm^{-1} , 1427 cm^{-1} , 1478 cm^{-1} , 1514 cm^{-1} , 1551 cm^{-1} , 1585 cm^{-1} , 1648 cm^{-1} , 1759 cm^{-1} , 2873 cm^{-1} , 2932 cm^{-1} , 2970 cm^{-1} , 3091 cm^{-1} , 3308 cm^{-1} and 3469 cm^{-1} , and wherein the error margin is $\pm 2 \text{ cm}^{-1}$.

[00107] In some embodiments, the amorphism disclosed herein has a Fourier transform infrared spectrogram substantially the same as shown in Figure 20.

[00108] In some embodiments, the amorphism disclosed herein has a weight loss ratio of about 1.75% to about 4.10% measured by thermogravimetric analysis at a high temperature from about 50°C to about 150°C .

[00109] In one aspect, provided herein is a pharmaceutical composition comprising the amorphism; In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[00110] In one aspect, provided herein is use of the amorphism or the pharmaceutical composition containing the amorphism disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[00111] In another aspect, provided herein is use of the amorphism or the pharmaceutical composition containing the amorphism disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[00112] In one aspect, provided herein is a method of preventing, managing, treating or lessening thromboembolism diseases in a patient comprising administering to the patient a therapeutically effective amount of the amorphism or the pharmaceutical composition containing the amorphism disclosed herein.

[00113] In another aspect, provided herein is a method of inhibiting the activity of blood

coagulation factor Xa comprising administering a therapeutically effective amount of the amorphism or the pharmaceutical composition containing the amorphism disclosed herein.

[00114] In one aspect, provided herein is the amorphism or the pharmaceutical composition disclosed herein containing the amorphism for use in preventing, managing, treating or lessening thromboembolism diseases in a patient.

[00115] In another aspect, provided herein is the amorphism or the pharmaceutical composition containing the amorphism disclosed herein for use in inhibiting the activity of blood coagulation factor Xa.

[00116] In one aspect, provided herein is a pharmaceutical composition comprising any one of the crystalline forms or the amorphism disclosed herein or a combination thereof; the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[00117] In one aspect, provided herein is use of the crystalline forms or the amorphism or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases.

[00118] In some embodiments, the thromboembolism diseases comprise myocardial infarction, stenocardia, reocclusion and restenosis after angioplasty or aortocoronary artery bypass surgery, stroke, transitory ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

[00119] In other aspect, provided herein is use of the crystalline forms or the amorphism or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.

[00120] In other aspect, provided herein is use of the crystalline forms or the amorphism or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening thromboembolism diseases in a patient; the use comprises administering to the patient a therapeutically effective amount of the crystalline form or the amorphism or the pharmaceutical composition disclosed herein.

[00121] In one aspect, provided herein is a method for preparing the crystalline form I of a compound having formula (I) disclosed herein comprising transforming an amorphism of the compound of formula (I) to form I by heating.

[00122] In some embodiments, the transforming an amorphism of the compound of formula (I)

to the form I by heating is carried out at a temperature from about 170 °C to about 200 °C; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out at a temperature from about 180 °C to about 190 °C; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out at a temperature of about 185 °C; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out at a temperature of about 180 °C; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out at a temperature of about 190 °C.

[00123] In some embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 2 to 24 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 5 to 24 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 5 to 12 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 5 to 7.5 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 5 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 5.5 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 6 hours; In other embodiments, wherein the transforming an amorphism of the compound of formula (I) to the form I by heating is carried out for 7.5 hours.

[00124] In some embodiments, the heating is carried out under aerobic or anaerobic condition, and the anaerobic condition is vacuum or inert gas protection.

[00125] In some embodiments, the heating is carried out by vacuum drying or blast drying.

[00126] In some embodiments, the method of preparing the crystalline form I further comprises preparation of the amorphism of the compound of Formula (I) which comprising: step (a) dissolving completely the compound of Formula (I) in a solvent by heating; and step (b) preparing the amorphous form of compound of Formula (I) by spray drying of the solution obtained from step (a). The aims of the heating are to make the raw materials dissolve completely, save cost and improve yield; the heating temperature is related to the boiling point of

the solvent that used and the amount of the solvent that used.

[00127] In some embodiments, the method of preparing the amorphism disclosed herein, wherein the solvent is methanol, ethanol, acetone, isopropanol, toluene, chloroform, dichloromethane, tetrahydrofuran, ethyl acetate, hexane or a combination thereof.

[00128] In other embodiments, the method of preparing the amorphism disclosed herein, wherein the solvent is ethanol, dichloromethane or a combination thereof. In some embodiments, wherein the solvent is a mixture of ethanol and dichloromethane; in other embodiments, wherein the solvent is a mixture of ethanol and dichloromethane in a volume ratio of 1/4; in other embodiments, wherein the solvent is a mixture of ethanol and dichloromethane in a volume ratio of 1/2.4.

[00129] In some embodiments, the method of preparing the amorphism disclosed herein, wherein the amount of the solvent is according to the ratio of the total volume of the solvent to the quality of the compound of Formula (I), which is ranged from 10 mL/1 g to 12 mL/1 g. In other embodiments, wherein the amount of the solvent is according to the ratio of the total volume of the solvent to the quality of the compound of Formula (I), which is 10 mL/1 g.

[00130] The yield of the amorphism prepared through spray drying disclosed herein is affected by air inlet temperature and air outlet temperature of apparatus, system pressure in spray drying process, and other factors. However, the air inlet temperature, the air outlet temperature and the system pressure in spray drying process, *etc*, are associated with the type of the apparatus, the solvent, and other factors. In some embodiments, wherein the air inlet temperature in spray drying process at the beginning is 90 °C, and which is then gradually transferred to 100 °C when the apparatus operates smoothly, and the air outlet temperature is controlled between 45 °C and 55 °C; in other embodiments, wherein the air inlet temperature in spray drying process at the beginning is 80 °C, and which is then gradually transferred to 100 °C when the apparatus operates smoothly, and the air outlet temperature is controlled between 45 °C and 55 °C; in other embodiments, wherein the air inlet temperature in spray drying process is 100 °C, and the air outlet temperature is 54 °C; in other embodiments, wherein the air inlet temperature in spray drying process is 80 °C, and the air outlet temperature is 48 °C; in other embodiments, wherein the air inlet temperature in spray drying process is 90 °C, and the air outlet temperature is 51 °C; in other embodiments, wherein the air inlet temperature in spray drying process is 80 °C, and the air outlet temperature is 48 °C.

[00131] There is no limitation on the solvent used in preparation of the amorphism disclosed herein, any solvent, so long as it can dissolve the raw materials to some extent and does not affect the quality thereof, all are within the scope of the invention. In addition, many similar changes, equivalent replacements in the art, or the equivalents of the solvent, solvent compositions and solvent compositions in different ratios described in the invention, are all deemed to be within the scope of the invention. The present invention provides the preferred solvents used in each reaction step.

[00132] Details and experimental results of the preparation of the amorphism of the invention are described in example 1. The preparation method of the amorphism of the invention has simple and practicable operations, high yields, and which is suitable for industrial production known from example 1.

[00133] Details and experimental results of the preparation of form I of the invention are described in example 2. Two preparation methods of form I of the invention have simple operations, and the method two has good reproducibility, manageable process, stable technological process, and high yields, high purity of prepared form I, which is suitable for industrial production.

[00134] The preparation method of the oxazolidinone compound having 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (represented by Formula (I)) disclosed herein can be illustrated by reference to patent PCT WO 2014110971.

[00135] The present invention provides solubility test, stability test, hygroscopicity test and pharmacokinetics test of the crystalline form and amorphism described herein, and the results are as shown in tables 5 to 9, and figures 25 to 27.

[00136] The solubility test results of form I, form II or amorphism are as shown in table 5. As can be seen in table 5, the solubility of form I, form II or amorphism is better than that of the compound of Formula (I) prepared according to the reference, *i.e.* the solubility of form I, form II or amorphism is evidently improved, which is benefit for improving drug effect and reducing drug loading capacity.

[00137] The stability test results of form I, form II or amorphism are as shown in table 7 and table 8. As can be seen in table 7 and table 8, the appearances and purities of form I, form II or amorphism have no obvious variation under high temperature (60 °C) and/or high humidity

(25°C, RH 90% ± 5%), and the quality of which is stable. *i.e.* the crystalline form I, form II or amorphism of the present invention has a good stability, and which can better avoid changes in the bioavailability and drug effect in the process of drug storage or drug development.

[00138] The hygroscopicity test results of form I, form II or amorphism are as shown in table 9 and figures 25 to 27. The hygroscopic features and definition of hygroscopic weight gain are summarized in table 2 (deriving from Chinese Pharmacopoeia 2010, appendix XIX J: Guideline on pharmaceutical hygroscopicity test, test conditions: 25°C±1°C, Relative Humidity 80%).

Table 2. The hygroscopic features and definition of hygroscopic weight gain

Hygroscopic features	Hygroscopic weight gain
Deliquescence	absorbing enough water to form liquid
High hygroscopicity	the weight increase of the hygroscopicity is no less than 15%
Having hygroscopicity	the weight increase of the hygroscopicity is between 15% and 2%
Slight hygroscopicity	the weight increase of the hygroscopicity is between 2% and 0.2%
No or almost no hygroscopicity	the weight increase of the hygroscopicity is less than 0.2%

[00139] As can be seen in table 9 and figures 25 to 27 of hygroscopicity test results, the crystalline form I has slight hygroscopicity; form II has almost no hygroscopicity; the amorphism has hygroscopicity, but there is no obvious increase in the weight on the hygroscopicity; *i.e.* form I, form II or amorphism is not easy to deliquesce under high humidity conditions, which is benefit for a long-term storage of drug.

[00140] The pharmacokinetics test results of the crystalline forms and amorphism of the invention are as shown in table 6. As can be seen in table 6, the crystalline forms and amorphism of the invention are all have good biological activities.

[00141] In conclusion, the crystalline forms and amorphism of the invention are all have good biological activities, and also have good solubilities, high stabilities, which are suitable for pharmaceutical use.

DEFINITIONS AND GENERAL TERMINOLOGY

[00142] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The disclosures of all patent and scientific literatures cited within are hereby expressly incorporated in their entirety by reference. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described.

[00143] The term "crystalline form" refers to a solid having a highly regular chemical structure, including, but not limited to, a single-component or multiple-component crystal, and/or a polymorph, a solvate, a hydrate, a clathrate, a co-crystal, a salt of a compound, solvates of salts, hydrates of salts. Crystalline forms of a substance can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt crystallization, melt cooling, solvent crystallization, crystallization in confined spaces such as, *e.g.*, in nanopores or capillaries, crystallization on surfaces or templates such as, *e.g.*, on polymers, crystallization in the presence of additives, such as, *e.g.*, co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, reaction crystallization, anti-solvent addition, grinding and solvent-drop grinding.

[00144] "Amorphism" or "amorphous form" refers to substance forming by particle (such as molecule, atom, ion) arranged in no periodic in three-dimensional space, which is characterized by a diffused X-ray powder diffraction pattern with no sharp peaks. Amorphism is a special physical form of solid substance, the ordered structural characteristics in a part of amorphous substance imply there are innumerable links between amorphous substance and crystal substance. Amorphous substance can be obtained through many methods as known in the art. These methods include, but are not limited to, rapid freezing method, anti-solvent flocculence, ball-milling method, spray drying method, freeze-drying method, wet granulating method and solid dispersion technique, and the like.

[00145] The term "solvent", as used herein, means a substance, typically a liquid, that is capable of completely or partially dissolving another substance, typically a solid. Solvents for the practice of this invention include, but are not limited to, water, acetic acid, acetone, acetonitrile, benzene, chloroform, tetrachloromethane, dichloromethane, dimethyl sulfoxide, 1,4-dioxane, ethanol, ethyl acetate, butanol, *tert*-butanol, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, formamide, formic acid, heptane, hexane, isopropanol, methanol, methyl ethyl ketone,

1-methyl-2-pyrrolidone, mesitylene, nitromethane, polyethylene glycol, propanol, 2-acetone, pyridine, tetrahydrofuran, toluene, xylene, mixtures thereof *etc.*

[00146] The term “anti-solvent” means a fluid which promotes precipitation from the solvent of the product (or of a precursor for the product). The anti-solvent may comprise a cold gas, or a fluid which promotes the precipitation via a chemical reaction, or which decreases the solubility of the product in the solvent; it may be the same liquid as the solvent but at a different temperature or it may be a different liquid from the solvent.

[00147] The term “solvate,” as used herein, means having on a surface, in a lattice or on a surface and in a lattice, a solvent such as water, acetic acid, acetone, acetonitrile, benzene, chloroform, tetrachloromethane, dichloromethane, dimethyl sulfoxide, 1,4-dioxane, ethanol, ethyl acetate, butanol, *tert*-butanol, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, formamide, formic acid, heptane, hexane, isopropanol, methanol, methylethylketone, methylpyrrolidone, mesitylene, nitromethane, polyethylene glycol, propanol, 2-acetone, pyridine, tetrahydrofuran, toluene, xylene, mixtures thereof *etc.* A specific example of a solvate is a hydrate, wherein the solvent on the surface, in the lattice or on the surface and in the lattice, is water. Hydrates may or may not have solvents other than water on the surface, in the lattice or on the surface and in the lattice of a substance.

[00148] Crystalline form or amorphism can be identified through multiple technological means, such as X-ray powder diffraction (XRPD), infrared spectroscopy (IR), melting point, differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), nuclear magnetic resonance, raman spectroscopy, single-crystal X-ray diffraction, solution calorimetry, scanning electron microscope (SEM), quantitative analysis, solubility, dissolution velocity, *etc.*

[00149] Some informations such as change in crystalline form, crystallinity, crystal structure state and so on can be obtained through detection of X-ray powder diffraction (XRPD) which is a common method used for identifying crystalline form. The peak position of XRPD spectra mainly depends on the crystal structure, which is relatively insensitive to experimental details, and the relative peak height depends on many factors related to sample preparation and the geometry of the instrument. Thus, in some embodiments, the crystalline form disclosed herein is characterized by an X-ray powder diffraction pattern having some peaks in certain positions, which is substantially the same as the XRPD pattern provided in appended figures of the present invention. Meanwhile, the measurement of 2θ in XRPD pattern could have some experimental

error, for example the measurements of 2θ in XRPD pattern could be different because of different instruments and different samples. Therefore, the value of 2θ is not absolute. According to the state of the instrument for the experiment disclosed herein, the error margin in 2θ of the characteristic peaks is $\pm 0.2^\circ$.

[00150] Differential scanning calorimetry (DSC) is a technology used for measuring the energy difference between sample and inert reference compound (usually $\alpha\text{-Al}_2\text{O}_3$) as a function of temperature, which is performed through constant heating or cooling under program control. The relative peak height of DSC thermogram depends on many factors related to sample preparation and geometry of the instrument, while the peak position is relatively insensitive to experiment details. Thus, in some embodiments, the crystalline form disclosed herein is characterized by a DSC thermogram having some peaks in certain positions, which is substantially the same as DSC thermogram provided in appended figures of the present invention. Meanwhile, the DSC thermogram could have some experimental error, for example the peak position and the peak value in DSC thermogram could exist a little difference because of different instruments and different samples. Therefore, the peak position and the peak value in DSC thermogram are not absolute. According to the state of the instrument for the experiment disclosed herein. The error margin in the melting peaks is $\pm 3^\circ\text{C}$.

[00151] Glass transition is a transition of non-crystalline substance between elastomeric state and glassy state, which is an intrinsic quality of the substance; the temperature corresponding to glass transition is glass transition temperature (T_g), which is an important physical property of non-crystalline substance. Glass transition is a phenomenon related with the molecular motion. Therefore, glass transition temperature (T_g) mainly depends on the substance structure, which is relatively insensitive to experimental details. In some embodiments, the glass transition temperature (T_g) of the amorphism disclosed herein is measured through differential scanning calorimetry (DSC), which is characterized by having a glass transition temperature of 107.44°C . According to the state of the instrument for the experiment disclosed herein, the error margin in the melting peaks is $\pm 3^\circ\text{C}$.

[00152] Differential scanning calorimetry (DSC) also is used for analysis of determining whether there is a phenomenon of crystal transformation or mixed crystal exist in crystalline form.

[00153] The solid having same chemical composition usually form different crystal structural

polymorph (or called modification) under different thermodynamic conditions, this phenomenon is called polymorphism. The transformations among the modifications will occur when the temperature and pressure change, this phenomenon is called crystal transition. The properties of crystalline form are largely changed such as mechanics, electronics, magnetic because of crystal transition. The crystal transition process could be described in differential scanning calorimetry (DSC) thermogram when the transition temperature is in the measuring ranges, which is characterized by having exothermic peaks reflected this transformation and two or more endothermic peaks which respectively are characteristic endothermic peaks of different crystalline forms before and after the transformation in DSC thermogram.

[00154] Crystal transition could occur in the crystalline form or amorphism of the compound disclosed herein under appropriate conditions. In some embodiments, the crystalline form IV disclosed herein can transfer to the crystalline form I under high temperature (150 °C to 215 °C), and there are endothermic peaks at 117.04 °C and 203.30 °C and exothermic peaks at temperatures from about 160 °C to about 200 °C in its DSC thermogram, wherein the endothermic peak at 203.30 °C is a characteristic endothermic peak of crystalline form I. In some embodiments, the crystalline form V disclosed herein can transfer to the crystalline form II and form I under high temperature (175 °C to 210 °C), there are endothermic peaks at 106.98 °C, 193.82 °C and 203.62 °C and exothermic peaks at temperatures from about 196 °C to about 201 °C in its DSC thermogram, wherein the endothermic peaks at 193.82 °C and 203.62 °C are respectively a characteristic endothermic peak of crystalline form II and form I. In other embodiments, crystal transition occurs in the amorphism disclosed herein under high temperature (140 °C to 215 °C), that is, amorphism transfers to crystalline form I, the endothermic peak at 203.30 °C and the exothermic peaks at temperatures from about 140 °C to about 180 °C are present in the DSC thermogram. According to the state of the instrument for the experiment disclosed herein, the error margin of each melting peak is $\pm 3^{\circ}$.

[00155] Thermogravimetric analysis (TGA) is a technology used for measuring the quality change of a substance which varies with temperature under program control, which can apply to detecting the process of the solvent loss in the crystal, sublimation and dissociation of the sample, and the crystal water and the crystal solvent contained in crystal may be speculated through analysis of the detection results. The measurement of quality change described in TGA curve depends on many factors related to sample preparation and instrument, which could be different

because of different instruments and different samples. In some embodiments, the crystalline form V disclosed herein loses 16.59% of weight by heating at temperatures from 50 °C to 150 °C. In some embodiments, the amorphism disclosed herein is characterized by the weight loss percentage ranged from 1.75% to 4.10% detected through TGA under high temperature (50 °C to 150 °C). According to the state of the instrument for the experiment disclosed herein, the error margin of the quality change is $\pm 0.1\%$.

[00156] Raman spectroscopy is a spectrophotometry used for studying vibration mode and rotation mode of molecule and other low frequency mode in one system. Different spatial structures of the same molecule have different Raman actives. Therefore, Raman spectroscopy could be used for measuring and identifying crystalline form or amorphism. The peak position of Raman spectroscopy mainly depends on the substance structure, which is relatively insensitive to experimental details, and the peak intensity depends on factors such as sample preparation and instrument. Thus, in some embodiments, the crystalline form or amorphism disclosed herein is characterized by a Raman spectrogram in which the peak positions are substantially in accordance with those shown in Raman spectrograms provided in appended figures of the present invention. Meanwhile, the Raman spectrogram could have some experimental error, for example the peak position and the peak value in Raman spectrogram could be different because of different instruments and different samples. Therefore, the peak position and the peak value in Raman spectrogram are not absolute. According to the state of the instrument for the experiment disclosed herein, the error margin in the absorption peaks is $\pm 2 \text{ cm}^{-1}$.

[00157] Bond length and bond angle of some chemical bonds in different spatial structures of the same molecule are different, which lead to different energy levels of vibration-rotational transition of the molecule and differences in the main characteristics of the relevant infrared spectroscopy such as frequency of absorption band, peak shape, peak position, peak intensity, and so on. Therefore, infrared spectroscopy could be used for studying drug polymorphism. In some embodiments, the crystalline form or amorphism disclosed herein is characterized by a Fourier infrared spectrogram in which the peak positions are substantially in accordance with those shown in a Fourier infrared spectrogram provided in appended figures of the present invention. Meanwhile, the Fourier infrared spectrogram could have some experimental error, for example the peak position and the peak value in Fourier infrared spectrogram could be different because of different instruments and different samples. Therefore, the peak position and the peak

value in Fourier infrared spectrogram are not absolute. According to the state of the instrument for the experiment disclosed herein, the error margin in the absorption peaks is $\pm 2 \text{ cm}^{-1}$.

[00158] As used herein, the value of 2θ described in an X-ray powder diffraction pattern is recorded in degree ($^{\circ}$).

[00159] As used herein, term “substantially the same as shown in a figure” refers to an X-ray powder diffraction (XRPD) pattern, or a differential scanning calorimetry (DSC) thermogram, or a Raman spectrogram, or a Fourier transform infrared spectrogram having at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% of the peaks shown in the figure.

[00160] As used herein, when referring to a spectrum and/or to data presented in a graph, the term “peak” refers to a feature that one skilled in the art would recognize as not attributable to background noise.

[00161] “The compound represented by Formula (I)” or “The compound of Formula (I)” disclosed herein is a solid compound 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide prepared by the method described in WO 2014110971.

[00162] The novel crystalline form of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (Formula (I)) disclosed herein is substantially pure, wherein the novel crystalline form is form I, form II, form III, form IV or form V.

[00163] The amorphism of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (Formula (I)) disclosed herein is substantially pure, and the X-ray powder diffraction pattern is basically as shown in Figure 17, and wherein the amorphism of the compound can be prepared through spray drying.

[00164] As used herein, a crystalline form that is “substantially pure” refers to a crystalline form that is substantially free of one or more other crystalline forms, *i.e.*, the crystalline form has a purity of at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 98%, at least about 99%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8%, or at least about 99.9%; or the crystalline form has less than 20%, less than 10%, less than 5%, less than 3%, less than 1%, less than 0.5%, less than

0.1%, or less than 0.01% of the one or more other crystalline forms, based on the total volume or weight of the crystalline form and the one or more other crystalline forms.

[00165] As used herein, a crystalline form that is “substantially free” of one or more other crystalline forms refers to a crystalline form containing less than 20%, less than 10%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, or less than 0.01% of the one or more other crystalline forms, based on the total volume or weight of the crystalline form and the one or more other crystalline forms.

[00166] As used herein, the term “relative intensity” refers to the intensity of a peak with respect to the intensity of the strongest peak in the X-ray powder diffraction (XRPD) pattern which is regarded as 100%.

[00167] As used herein, all numbers disclosed herein are approximate values, regardless whether the word “about” is used in connection therewith, which means within 10%, suitably within 5% and particularly within 1 % of a given value or range. Alternatively, the term “about” means within an acceptable standard error of the mean, when considered by one of the ordinary skill in the art. Therefore, whenever a number having a value N is disclosed, any number having the value $N \pm 1\%$, $N \pm 2\%$, $N \pm 3\%$, $N \pm 5\%$, $N \pm 7\%$, $N \pm 8\%$ or $N \pm 10\%$ is specifically disclosed, wherein “+/-” refers to plus or minus.

[00168] The term “comprise”, “comprising”, “include”, “including”, “contain” or “containing” refers to an open expression, *i.e.* comprising/ including/ containing the contents disclosed herein, but not excluding other contents.

[00169] The crystalline form or amorphism or pharmaceutical composition disclosed herein could be used for inhibiting the activity of blood coagulation factor Xa and/or treating thromboembolism diseases in a patient. Wherein the “thromboembolism diseases” are diseases caused by thrombosis and thromboembolism, which also are called thrombotic diseases. Thrombosis is a pathological process that the visible components form emboluses in blood vessels or local endocardium, and then causes a part or complete blockage in a blood vessel and a disturbance of the corresponding circulation. Thromboembolism is a pathological process that thrombus falls off from the region of thrombosis which blocks partly or completely blood vessel along with the flow of blood, and then causes blood vessel or system ischemia, anoxia, necrosis, extravasated blood and edema. Some non-limiting examples of the thromboembolism diseases include arterial thromboembolic disease, intravenous thromboembolic disease and

thromboembolic disease in cardiac chambers. Some non-limiting examples of the specific diseases include myocardial infarction, angina pectoris (including unstable angina), acute coronary syndrome, reocclusion and restenosis after angioplasty or aortocoronary artery bypass surgery, stroke, transient ischemic attack, peripheral arterial occlusive disease, arterial thrombosis, coronary thrombosis, cerebral arterial thrombosis, cerebral embolism, renal artery embolism, pulmonary embolism, thrombophlebitis, venous thrombosis and deep venous thrombosis, *etc.*

[00170] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, or geometric (or conformational) mixtures of the present compounds are within the scope disclosed herein.

[00171] Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms.

[00172] Stereochemical definitions and conventions used herein generally follow Parker, et al., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York and Eliel, et al., “*Stereochemistry of Organic Compounds*”, John Wiley & Sons, Inc., New York, 1994. The compounds disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds disclosed herein, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes *D* and *L*, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes *d* and *l* or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or *l* meaning that the compound is levorotatory. A compound prefixed with (+) or *d* is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific

stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” or “racemate” refers to an equimolar mixture of two enantiomeric species, devoid of optical activity.

PHARMACEUTICAL COMPOSITIONS, FORMULATION, ADMINISTRATION AND USE OF THE CRYSTALLINE FORMS OR AMORPHISM

[00173] As described above, the pharmaceutically acceptable compositions disclosed herein additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants *etc.*, as suited to the particular dosage form desired. Troy et al., *Remington: The Science and Practice of Pharmacy*, 21st ed., 2005, Lippincott Williams & Wilkins, Philadelphia, and Swarbrick et al., *Encyclopedia of Pharmaceutical Technology*, eds. 1988-1999, Marcel Dekker, New York, all of which are herein incorporated by reference in their entireties, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the crystalline forms or amorphism of the compound of Formula (I) disclosed herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[00174] Some non-limiting examples of materials which can serve as pharmaceutically acceptable carriers include ion exchangers, aluminum, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and

cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants.

[00175] The crystalline forms or amorphism of the compound of Formula (I) disclosed herein may be administered orally, such as tablets, capsules (each one all comprises formula released continuously or regularly), pills, powders, granules, elixirs, tinctures, suspending agents, syrups and emulsifiers. They also may be administered intravenously (bolus or infusion), intraperitoneally, subcutaneously or intramuscularly, all dosage forms used are well known to ordinary technical personnel in pharmaceutical field. They could be administered alone, but usually combined with a pharmaceutical carrier selected base on the selected method of administration and standard pharmacy practice.

[00176] The dosing schedule of crystalline form or amorphism of the compounds of Formula (I) disclosed herein may changes with the known various factors, such as pharmacokinetic characteristics of a specific reagent, and pattern and administrative way thereof; the race, age, sex, health conditions, medical conditions and weight of the receiver; the symptom property and degree; the types of treatment in parallel; the frequency of administration; the way of administration; kidney and liver function of the patient; and the desired effect. A physician or veterinarian can make a decision and prescribe effective amount of drugs to prevent, offset or stop the development of a thromboembolic disease.

[00177] The oral daily dosage of each one active ingredient can range from about 0.001 to 1000 mg/kg of body weight according to the common guidelines to achieve the specified effects. Preferably, the dosage is about from 0.01 to 100 mg/kg of body weight. And the most preferably, the dosage is about from 1.0 to 20 mg/kg of body weight per day. The most optimal dose range is from about 1 to about 10 mg/kg of body weight per minute in the transfusion process at a conventional rate for intravenous administration. The crystalline forms or amorphism of the compounds of Formula (I) disclosed herein can be administered in a single dose a day, or in two,

three or four divided doses a day.

[00178] The crystalline forms or amorphism of the compound of Formula (I) disclosed herein could be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches. To be administered in the form of a transdermal delivery system, the dosage administration will be continuous rather than intermittent throughout the dosage regimen.

[00179] The crystalline forms or amorphism of the compound of Formula (I) disclosed herein are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups *etc*, and consistent with conventional pharmaceutical practices.

[00180] For instance, for oral administration in the form of a tablet or capsule, the active pharmaceutical ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol *etc*; for oral administration in liquid form, the active pharmaceutical ingredient can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water *etc*. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes *etc*. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride *etc*. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, *etc*.

[00181] The crystalline forms or amorphism of the compound of Formula (I) disclosed herein can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[00182] The crystalline forms or amorphism of the compound of Formula (I) disclosed herein may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol,

polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the crystalline forms or amorphism of the compounds of Formula (I) disclosed herein may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymer of polylactic acid with polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyeric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

[00183] Each of these dosage units suited for administering dosage form could be contain from about 1 mg to about 100 mg active ingredient. In these pharmaceutical compositions, the activity ingredient accounts for about from 0.5 to 95% of the total weight.

[00184] Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, *etc.* Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00185] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00186] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

[00187] Where the crystalline forms or amorphism of the compound of Formula (I) disclosed herein are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the crystalline forms or amorphism of the compounds of Formula (I) disclosed herein and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the crystalline forms or amorphism of the

compounds of Formula (I) disclosed herein generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit. Wherein the other anticoagulants include, without limitation, apixaban, rivaroxaban, edoxaban, betrixaban, dabigatran etexilate, bemiparin sodium, enoxaparin sodium, tinzaparin sodium, danaparoid sodium, fondaparinux sodium, nadroparin calcium, ardeparin sodium and parnaparin sodium, *etc.*

[00188] Where the crystalline forms or amorphism of the compound of Formula (I) disclosed herein are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[00189] Where the crystalline forms or amorphism of the compound of Formula (I) disclosed herein are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the crystalline forms or amorphism of the compound of Formula (I) disclosed herein, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with the crystalline forms or amorphism of the compounds of Formula (I) disclosed herein.

[00190] Where two or more of the foregoing second therapeutic agents are administered with the crystalline forms or amorphism of the compound of Formula (I) disclosed herein, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination

[00191] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the crystalline forms or amorphism of the compound of Formula (I) disclosed herein and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced), although active ingredients are combined in one single dose unit. For example, one active ingredient may be enteric coated. By enteric coating

one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00192] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

DESCRIPTION OF THE FIGURES

[00193] Figure 1 provides an X-ray powder diffraction (XRPD) pattern of Form I of the compound of Formula (I).

[00194] Figure 2 provides a differential scanning calorimetry (DSC) curve of Form I of the compound of Formula (I).

[00195] Figure 3 provides a Raman spectrogram of Form I of the compound of Formula (I).

[00196] Figure 4 provides a Fourier transform infrared spectrogram of Form I of the compound of Formula (I).

[00197] Figure 5 provides an X-ray powder diffraction (XRPD) pattern of Form II of the compound of Formula (I).

[00198] Figure 6 provides a differential scanning calorimetry (DSC) curve of Form II of the compound of Formula (I).

[00199] Figure 7 provides a Raman spectrogram of Form II of the compound of Formula (I).

[00200] Figure 8 provides a Fourier transform infrared spectrogram of Form II of the compound of Formula (I).

[00201] Figure 9 provides an X-ray powder diffraction (XRPD) pattern of Form III of the compound of Formula (I).

[00202] Figure 10 provides a differential scanning calorimetry (DSC) curve of Form III of the compound of Formula (I).

[00203] Figure 11 provides a Raman spectrogram of Form III of the compound of Formula (I).

[00204] Figure 12 provides a Fourier transform infrared spectrogram of Form III of the compound of Formula (I).

[00205] Figure 13 provides an X-ray powder diffraction (XRPD) pattern of Form IV of the compound of Formula (I).

[00206] Figure 14 provides a differential scanning calorimetry (DSC) curve of Form IV of the compound of Formula (I).

[00207] Figure 15 provides a Raman spectrogram of Form IV of the compound of Formula (I).

[00208] Figure 16 provides a Fourier transform infrared spectrogram of Form IV of the compound of Formula (I).

[00209] Figure 17 provides an X-ray powder diffraction (XRPD) pattern of amorphism of the compound of Formula (I).

[00210] Figure 18 provides a differential scanning calorimetry (DSC) curve of amorphism of the compound of Formula (I).

[00211] Figure 19 provides a Raman spectrogram of amorphism of the compound of Formula (I).

[00212] Figure 20 provides a Fourier transform infrared spectrogram of amorphism of the compound of Formula (I).

[00213] Figure 21 provides a single-crystal structure of Form V of the compound of Formula (I).

[00214] Figure 22 provides an X-ray powder diffraction (XRPD) pattern of Form V of the compound of Formula (I).

[00215] Figure 23 provides a differential scanning calorimetry (DSC) curve of Form V of the compound of Formula (I).

[00216] Figure 24 provides a thermogravimetric analysis diagram of Form V of the compound of Formula (I).

[00217] Figure 25 provides a dynamic vapor sorption (DVS) profile of Form I of the compound of Formula (I).

[00218] Figure 26 provides a dynamic vapor sorption (DVS) profile of Form II of the compound of Formula (I).

[00219] Figure 27 provides a dynamic vapor sorption (DVS) profile of amorphism of the compound of Formula (I).

EXAMPLE

[00220] The invention is further illustrated by the following examples, which are not be construed as limiting the invention in scope.

[00221] The X-Ray powder Diffraction (XRPD) analysis method of the present invention comprises recording an X-ray powder diffraction diagram on a PANalytical Empyrean X-ray diffractometer using Cu-K α radiation (45 KV, 40 mA). A thin layer is prepared from powder sample on the single-crystal silicon wafer, and a sample spinner is used. The angular range extends from 3 ° to 40 ° in 2 θ with a 0.0168 ° step size in 2 θ . Data are collected by Data Collector software, and processed by HighScore Plus software, read by Data Viewer software.

[00222] X-Ray Single-crystal diffractometer of the present invention: X-ray powder diffraction diagram is recorded on an Agilent Technologies Gemini A Ultra X-ray diffractometer using Cu-K α radiation (40 KV, 40 mA) and ω -scan, the total number of diffraction counts is 29017, the number of observable counts (> 2 sigma (I)) is 7286, analyzing the single-crystal structure by SHELXS-97 software.

[00223] Differential Scanning Calorimetry (DSC): Differential scanning calorimetry thermogram is recorded on a TA Q2000 instrument with a thermoanalysis controller. The data are collected and analyzed by TA Instruments Thermal Solutions software. About 1-5 mg sample is weighed accurately in special aluminium pans with a cover lid, and heated under dry nitrogen purge. The scan rate is 10 °C /minute and the sample is heated from ambient temperature to 250 °C.

[00224] Thermogravimetric Analysis (TGA): Thermogravimetric curve is recorded on a TA Q500 instrument with a thermoanalysis controller. The data are collected and analyzed by TA Instruments Thermal Solutions software. About 10 mg sample is weighed accurately in platinum sample pans, and heated under dry nitrogen purge. The scan rate is 10 °C /minute and the sample

is heated from ambient temperature to 300 °C.

[00225] Raman spectrum: Raman spectrogram is recorded on a Thermo DXR confocal laser Raman spectrometer. The data are collected and analyzed by MONIC software. The laser wavelength is 780 nm, the laser energy is 24 Mw, the detection range is from 3500 cm^{-1} to 50 cm^{-1} , the scan times is 20 times, the resolution ratio is from 4.7 cm^{-1} to 8.7 cm^{-1} .

[00226] Fourier transform infrared spectrum: Fourier transform infrared spectrogram is recorded on TENSOR27 Germanic Bruker infrared spectrometer. The data are collected and analyzed by OPUS software. Using KBr disc method, the scan times is 16 times, the wave number range is from 4000 cm^{-1} to 400 cm^{-1} , the resolution ratio is 2 cm^{-1} .

[00227] The spay-drying instrument used herein is SHANGHAI OHKAWARA SCL-12 spay dryer and Swiss BUCHI B-290 spay dryer.

[00228] The solubility of the compound disclosed herein is measured by Aglient 1200 high performance liquid chromatography with VWD detector. The chromatographic column model is Waters Xbridge-C18 (4.6×150 mm, 5 μm), the detection wavelength is 250 nm, the flow rate is 1.0 mL/min, the column temperature is 35 °C, the mobile phase is acetonitrile-water (V/V = 40/60).

[00229] The hygroscopicity disclosed herein is detected on a DVS INT-Std dynamic vapor and gas absorption analyzer (England Surface Measurement Systems Company) under the humidity ranged from 0% to 95%, the airflow rate is 200 mL/min, the temperature is 25 °C, and one test point is provided per rising 5% humidity.

SPECIFIC IMPLEMENTATION METHODS

[00230] The invention discloses crystalline forms and amorphism of oxazolidinone compound named 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (represented by Formula (I)) and methods of preparation thereof. The person skilled in the art can learn from this article to properly improve the process parameters to implement the preparation method. It particularly needs to note that all the similar replacements and changes are obvious for the skilled persons and are deemed to be within the scope of the present invention. The methods disclosed herein are described in the preferred examples. Related person can clearly realize and apply the techniques disclosed herein by making some changes, appropriate

alterations or combinations to the methods without departing from spirit, principles and scope of the present disclosure.

[00231] In order to further understand the invention, it is detailed below through examples.

SPECIAL EXAMPLE

Example 1

1. Preparation of amorphism

[00232] To a solvent was added 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (the compound of Formula (I), the synthetic method was detailed in patent WO 2014110971). The mixture was refluxed until dissolved completely and filtered by suction. The filtrate was dried by spray-drying to give a white solid. The experiment conditions and results are shown in table 3:

Table 3: Preparation of amorphism

No.	Mass of material/g	Solvent	Dosage of solvent/L	Air inlet temperature/°C	Air outlet temperature/°C	Yield /%
1	1265	Dichloromethane/ Anhydrous ethanol	11.2 /2.8	The primary temperature was 90°C, after apparatus working stable, the temperature was adjusted gradually to 100°C.	45-55	94.23
2	2150	Dichloromethane/ Anhydrous ethanol	20.0 /5.0	The primary temperature was 80 °C, after apparatus worked stable, the temperature was adjusted gradually to 100 °C.	45-55	99.53
3	42	Dichloromethane/ Anhydrous ethanol	0.4/0.1	100	54	85.7
4	100	Dichloromethane/ Anhydrous ethanol	0.8/0.2	80	48	77

5	178	Dichloromethane/ Anhydrous ethanol	1.52/0.63	90	51	84.27
6	10.0	Dichloromethane/ Anhydrous ethanol	0.08/0.02	80	48	72.0
7	5.0	Dichloromethane	0.04	40	32	52

2. Identification of amorphism

[00233] (1) The XRPD pattern of amorphism was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD), which shows in figure 17.

[00234] (2) The DSC thermogram of amorphism was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of 10 °C/minute, glass transition temperature is 107.44 °C; the DSC thermogram comprises an endothermic peak at 203.43 °C, and the error margin is ± 3 °C.

[00235] (3) The Raman spectrogram of amorphism was analyzed and identified by using Thermo DXR confocal laser Raman spectrometer, having the following absorption peaks at 181, 276, 392, 425, 512, 672, 694, 739, 795, 1080, 1120, 1298, 1328, 1427, 1549, 1612, 2981 and 3088 cm^{-1} , the error margin is ± 2 cm^{-1} .

[00236] (4) The infrared spectrogram of amorphism was analyzed and identified by using TENSOR 27 infrared spectrometer, having the following absorption peaks at 419, 487, 516, 548, 581, 605, 636, 689, 720, 747, 816, 883, 939, 968, 998, 1023, 1060, 1099, 1121, 1156, 1191, 1216, 1245, 1291, 1327, 1347, 1390, 1427, 1478, 1514, 1551, 1585, 1648, 1759, 2873, 2932, 2970, 3091, 3308 and 3469 cm^{-1} , the error margin is ± 2 cm^{-1} .

[00237] (5) The TGA curve of amorphism was analyzed and identified by using TA Q500 thermal gravity analysis (TGA) with a scan rate of 10 °C/minute, the weight loss ratio is from 1.75% to 4.10%. The error margin in the weight loss ratio is $\pm 0.1\%$.

Example 2

1. Preparation of crystalline form I

[00238] Method one:

[00239] To a tetrahydrofuran (90 mL) solution was added 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*] [1,4] oxazin-3-yl)methyl)thiophene-2-carboxamide (2.0 g). The mixture was refluxed until the

most solid was dissolved and then filtered. The filtrate was kept at 50 °C, and *n*-heptane (180 mL) was added dropwise slowly. After addition, the mixture was further stirred for 30 min and crystals precipitated out. The resulting mixture was filtered by suction. The filter cake was washed with *n*-heptane and dried *in vacuo* at 60 °C to a constant weight to give the title compound as a white solid (880 mg, 44.0%).

[00240] Method two:

[00241] The amorphism of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide was placed in a vacuum drying oven or forced air drying oven, heated to crystal phase transformation to give a white solid. The experiment conditions and results are shown in table 4:

Table 4: Preparation of crystalline form I

No.	Mass of material/g	Drying method	Drying temperature/°C	Drying time/hours	Yield / %
1	1192	Vacuum drying	185	6	99.78
2	2140	Forced air drying	185	5	99.86
3	36	Vacuum drying	180	7.5	99.73
4	77	Vacuum drying	190	6	99.79
5	150	Forced air drying	185	5.5	99.73

2. Identification of crystalline form I

[00242] (1) The XRPD pattern of crystalline form I was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD) with Cu-K α radiation, having the following characteristic peaks expressed in degrees 2 θ at 5.41°, 11.06°, 12.64°, 16.26°, 16.66°, 16.95°, 18.01°, 18.69°, 18.93°, 19.39°, 19.57°, 20.13°, 20.75°, 21.05°, 21.72°, 22.23°, 22.96°, 23.39°, 23.85°, 24.68°, 24.96°, 25.74°, 26.36°, 27.08°, 27.25°, 27.73°, 28.53°, 28.96°, 29.36°, 29.70°, 30.21°, 30.83°, 31.61°, 32.10°, 32.86°, 33.08°, 33.76°, 34.27°, 35.34°, 36.09°, 37.20°, 38.47° and 39.34°. The error margin in 2 θ of the characteristic peaks is $\pm 0.2^\circ$.

[00243] (2) The DSC thermogram of crystalline form I was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of 10 °C/minute, comprising an endothermic peak at 204.81 °C. The error margin in the melting peaks is $\pm 3^\circ\text{C}$.

[00244] (3) The Raman spectrogram of crystalline form I was analyzed and identified by using Thermo DXR confocal laser Raman spectrometer, having the following absorption peaks at 163,

246, 280, 389, 516, 582, 672, 690, 715, 730, 796, 971, 1035, 1084, 1117, 1296, 1325, 1428, 1556, 1609, 1666, 2958 and 2991 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

[00245] (4) The infrared spectrogram of crystalline form I was analyzed and identified by using TENSOR 27 infrared spectrometer, having the following absorption peaks at 418, 455, 480, 498, 516, 555, 568, 582, 605, 637, 687, 715, 739, 809, 883, 909, 937, 965, 996, 1025, 1048, 1087, 1115, 1153, 1188, 1217, 1237, 1290, 1324, 1344, 1385, 1427, 1474, 1510, 1560, 1625, 1642, 1673, 1766, 2870, 2927, 2970, 3065, 3101 and 3292 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

Example 3

1. Preparation of crystalline form II

[00246] To acetic acid (50 mL) was added 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl) thiophene-2-carboxamide (28.0 g). The mixture was refluxed until dissolved, and further stirred for 1 hour. To the mixture was added water (45 mL) dropwise. After addition, the mixture was cooled to 20 °C, and then stirred for 5.0 hours and crystals precipitated out. The resulting mixture was filtered by suction. The filter cake was washed with acetic acid/water (m/m = 1/3) and water in turn, and then dried *in vacuo* at 60 °C to a constant weight to give the title compound as a white solid (25.66 g, 91.6%).

2. Identification of crystalline form II

[00247] (1) The XRPD pattern of crystalline form II was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD) with Cu-K α radiation, having the following characteristic peaks expressed in degrees 2 θ at 9.39°, 12.70°, 14.65°, 15.41°, 15.85°, 16.90°, 19.00°, 19.96°, 20.99°, 21.98°, 22.45°, 23.07°, 23.32°, 24.73°, 25.42°, 27.23°, 27.56°, 28.18°, 29.94°, 30.36°, 30.86°, 31.36°, 33.43°, 34.14°, 34.37°, 34.68°, 35.22°, 36.24°, 36.85°, 37.07°, 37.84°, 38.31° and 39.10°. The error margin in 2 θ of the characteristic peaks is $\pm 0.2^\circ$.

[00248] (2) The DSC thermogram of crystalline form II was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of 10 °C/minute, comprising an endothermic peak at 194.90 °C. The error margin in the melting peaks is $\pm 3^\circ\text{C}$.

[00249] (3) The Raman spectrogram of crystalline form II was analyzed and identified by using Thermo DXR confocal laser Raman spectrometer, having the following absorption peaks at 174, 198, 270, 336, 401, 448, 524, 559, 669, 696, 729, 797, 880, 1078, 1092, 1234, 1294, 1328, 1390, 1428, 1478, 1562, 1605, 1642, 1770, 2877, 2926, 2955, 2987 and 3089 cm^{-1} , the error margin is

$\pm 2 \text{ cm}^{-1}$.

[00250] (4) The infrared spectrogram of crystalline form II was analyzed and identified by using TENSOR 27 infrared spectrometer, having the following absorption peaks at 421, 481, 497, 512, 558, 584, 607, 637, 682, 727, 749, 798, 829, 881, 938, 962, 985, 999, 1014, 1027, 1058, 1098, 1129, 1157, 1184, 1204, 1237, 1291, 1328, 1348, 1372, 1391, 1426, 1448, 1478, 1504, 1560, 1642, 1770, 1933, 2745, 2820, 2870, 2924, 2955, 2983, 3035, 3090 and 3286 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

Example 4

1. Preparation of crystalline form III

[00251] To a *N,N*-dimethylformamide (8.0 mL) solution was added 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*] [1,4] oxazin-3-yl)methyl)thiophene-2-carboxamide (2.0 g). The mixture was refluxed until all the material was dissolved, and further stirred for 1 hour. The mixture was cooled gradually to 20 °C, and then stirred for 15.0 hours and crystals precipitated out. The resulting mixture was filtered by suction. The filter cake was dried *in vacuo* at 50 °C to a constant weight to give the title compound as a white solid (1.62 g, 81.0%).

2. Identification of crystalline form III

[00252] (1) The XRPD pattern of crystalline form III was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD) with Cu-K α radiation, having the following characteristic peaks expressed in degrees 2 θ at 4.73°, 8.94°, 9.46°, 12.14°, 14.23°, 15.22°, 16.13°, 17.39°, 17.97°, 19.00°, 19.75°, 20.49°, 20.89°, 22.40°, 23.43°, 23.83°, 24.45°, 24.87°, 25.05°, 25.77°, 26.12°, 27.10°, 28.67°, 29.06°, 29.52°, 29.73°, 29.97°, 30.76°, 31.47°, 32.66°, 33.32°, 33.88°, 34.05°, 34.49°, 35.21°, 36.29°, 37.08°, 37.62°, 38.19°, 39.33° and 39.43°. The error margin in 2 θ of the characteristic peaks is $\pm 0.2^\circ$.

[00253] (2) The DSC thermogram of crystalline form III was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of 10 °C/minute, comprising an endothermic peak at 125.24 °C. The error margin in the melting peaks is $\pm 3^\circ \text{C}$.

[00254] (3) The Raman spectrogram of crystalline form III was analyzed and identified by using Thermo DXR confocal laser Raman spectrometer, having the following absorption peaks at 201, 245, 283, 367, 407, 450, 510, 525, 571, 639, 665, 693, 714, 742, 769, 802, 864, 903, 949, 974, 1005, 1034, 1080, 1099, 1231, 1272, 1291, 1309, 1328, 1388, 1426, 1507, 1554, 1608, 1640,

1662, 1762, 2834, 2874, 2939, 2981 and 3089 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

[00255] (4) The infrared spectrogram of crystalline form III was analyzed and identified by using TENSOR 27 infrared spectrometer, having the following absorption peaks at 416, 430, 451, 469, 484, 498, 510, 525, 554, 570, 584, 616, 639, 665, 688, 713, 727, 755, 769, 801, 816, 833, 880, 904, 939, 953, 974, 996, 1022, 1034, 1064, 1079, 1098, 1119, 1142, 1159, 1185, 1203, 1237, 1285, 1310, 1324, 1347, 1374, 1428, 1504, 1556, 1580, 1606, 1640, 1661, 1764, 2809, 2865, 2928, 2965, 2979, 3032, 3081, 3306 and 3340 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

Example 5

1. Preparation of crystalline form IV

[00256] To a acetone (12.0 mL) solution was added 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4] oxazin-3-yl)methyl) thiophene-2-carboxamide (250 mg). The mixture was refluxed until all the material was dissolved, and further stirred for 2.5 hour and filtered. The filtrate was cooled rapidly to -20°C and crystals precipitated out. The resulting mixture was filtered by suction. The filter cake was dried *in vacuo* to a constant weight to give the title compound as a white solid (155 mg, 62.0%).

2. Identification of crystalline form IV

[00257] The XRPD pattern of crystalline form IV was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD) with Cu-K α radiation, having the following characteristic peaks expressed in degrees 2θ at 8.84° , 9.48° , 14.26° , 14.98° , 16.12° , 16.63° , 17.76° , 18.26° , 18.97° , 19.93° , 20.41° , 20.76° , 22.07° , 22.64° , 23.13° , 24.28° , 24.56° , 25.08° , 25.43° , 26.56° , 28.68° , 29.39° , 29.67° , 30.35° , 31.21° , 32.39° , 32.72° , 33.64° , 34.30° , 34.59° , 36.07° , 37.00° , 37.92° and 39.44° . The error margin in 2θ of the characteristic peaks is $\pm 0.2^{\circ}$.

[00258] (2) The DSC thermogram of crystalline form IV was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of $10^{\circ}\text{C}/\text{minute}$, comprising endothermic peaks at 116.97°C and 203.20°C . The error margin in the melting peaks is $\pm 3^{\circ}\text{C}$.

[00259] (3) The Raman spectrogram of crystalline form IV was analyzed and identified by using Thermo DXR confocal laser Raman spectrometer, having the following absorption peaks at 202, 241, 283, 381, 510, 668, 692, 714, 742, 800, 1035, 1081, 1228, 1273, 1305, 1327, 1428, 1554, 1608, 1643, 1703, 1765, 2924, 2987 and 3085 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

[00260] (4) The infrared spectrogram of crystalline form III was analyzed and identified by using TENSOR 27 infrared spectrometer, having the following absorption peaks at 421, 481, 496,

511, 558, 584, 606, 637, 681, 727, 749, 798, 829, 840, 880, 894, 938, 961, 985, 999, 1014, 1027, 1058, 1098, 1114, 1128, 1157, 1184, 1204, 1237, 1291, 1328, 1348, 1372, 1390, 1426, 1449, 1478, 1504, 1561, 1606, 1642, 1771, 1933, 2745, 2820, 2869, 2923, 2955, 2983, 3035, 3090, 3285 and 3383 cm^{-1} , the error margin is $\pm 2 \text{ cm}^{-1}$.

Example 6

1. Preparation of crystalline form V

[00261] A solution of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (200 mg) in chloroform (10 mL) was heated to 40 °C. The solution was kept at this temperature for 1.5 hours and filtered. The filtrate was cooled to rt slowly, kept standing for 14 days and crystals precipitated out to get a colorless crystal.

2. Identification of crystalline form V

[00262] (1) After detection and analysis of a single crystal, it can be known that, the crystalline form V is a chloroform solvate of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide, each unit cell of the single crystal structure contains two molecules of 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide and two molecules of chloroform, the characteristics parameters of the single crystalline are as shown in table 1, the single crystal structure of which is as shown in figure 21.

[00263] (2) The XRPD pattern of crystalline form V was analyzed and identified by using Empyrean X-ray powder diffraction (XRPD) with Cu-K α radiation, having the following characteristic peaks expressed in degrees 2 θ at 4.50°, 8.97°, 10.55°, 13.14°, 14.16°, 16.10°, 16.50°, 17.58°, 17.98°, 19.18°, 19.92°, 20.20°, 20.40°, 20.96°, 21.23°, 22.53°, 23.07°, 23.47°, 24.11°, 24.73°, 25.94°, 26.39°, 26.70°, 27.13°, 28.42°, 28.77°, 29.41°, 29.77°, 30.01°, 30.38°, 31.41°, 31.75°, 32.13°, 33.21°, 34.59°, 37.24° and 39.04°. The error margin in 2 θ of the characteristic peaks is $\pm 0.2^\circ$.

[00264] (3) The DSC thermogram of crystalline form V was analyzed and identified by using TA Q2000 differential scanning calorimetry (DSC) with a scan rate of 10 °C/minute, comprising endothermic peaks at 106.98 °C, 193.82 °C and 203.62 °C. The error margin in the melting peaks is $\pm 3^\circ\text{C}$.

[00265] (4) The TGA curve of amorphism was analyzed and identified by using TA Q500 thermal gravity analysis (TGA) with a scan rate of 10 °C/minute, the weight loss ratio is 16.59%. The error margin in the weight loss ratio is $\pm 0.1\%$.

Example 7

Solubility tests.

[00266] To a 15 mL of cone-shaped tube was added water (10 mL), and to the water was added sample and the cone-shaped tube was oscillated till the sample dissolving was halted. The cone-shaped tube was placed in thermostatic water bath at 37 °C and oscillated for 24 hours, and the oscillation velocity was 40 rpm. After that, the mixture was filtered through hydrophilic microporous membrane filter (0.45 μm , Φ 13 mm). The initial filtrate was abandoned, and the subsequent filtrate (500 μL) was precisely transferred and diluted with acetonitrile/water (500 μL , v/v = 60/40). The mixture was oscillated until homogeneous to give the test solution.

[00267] The test solution (40 μL) was detected by HPLC and the concentration was calculated by the external standard one point method. For detailed data, see the table 5 below.

[00268] The control group is the compound named 5-chloro-*N*-(((3*S*,3*aS*)-1-oxo-7-(3-oxomorpholino-4-yl)-1,3,3*a*,4-tetrahydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-3-yl)methyl)thiophene-2-carboxamide (Formula (I)) synthesized according to patent WO2014110971.

Table 5: Solubilities of the crystalline form I, form II and amorphism

Sample	The control group	Crystalline form I	Crystalline form II	Amorphism
Solubility (mg/mL)	0.010	0.059	0.017	0.053

Results:

[00269] The data of table 1 indicated that the solubilities of crystalline form I, form II and amorphism are all better than the solubility of control group.

Example 8

The pharmacokinetic experiments

[00270] Male Beagle dogs weighting 8-12 kg were divided into three groups, 3 in each group, and administered orally capsules filled with the test samples, the dose was 2.5 mg/kg. Blood collection was carried out at 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12 and 24 h after administration. The test sample concentration was measured in MRM mode by using AB SCIEX API4000 LC-MS/MS, and the quantitative analysis was carried out to establish the standard curve. The

pharmacokinetic parameters were calculated according to non-compartment model based on drug concentration-time curve using WinNonLin 6.3 software. For detailed data, see the table 2 below.

Table 6 The PK values of the crystalline form I, form II and amorphism disclosed herein

PK test						
The test sample	AUC _{INF} (h*ng/mL)	AUC _{last} (h*ng/mL)	C _{max} (ng/mL)	MRT _{INF} (h)	T _{1/2} (h)	T _{max} (h)
Form I	3440±476	3100±346	516±149	7.38±1.95	5.71±1.58	2.00±0.00
Form II	2180±1110	1670±662	220±139	14.00±8.11	4.14±2.10	4.00±0.00
Amorphism	3130±1570	3090±1530	583±287	5.29±0.443	3.19±1.01	1.67±0.577

Results:

[00271] The data of table 6 indicated that the crystalline form I, form II and amorphism have higher exposure levels.

Example 9

The stability tests of the crystalline forms and amorphism disclosed herein

[00272] (1) High temperature test: an appropriate amount of test sample was placed in flat weighing bottle and spread into a thin layer (thickness ≤ 5 mm). The whole was placed at 60 °C for 10 days, sampling and observing change in the sample color at the fifth day and tenth day, the purity of the sample was detected by HPLC. The experiment results are as shown in table 7.

Table 7: The high temperature tests of the crystalline form I, form II or amorphism disclosed herein

Test sample		Form I	Form II	Amorphism
Appearance	the zeroth day	white	white	light yellow
	the fifth day	white	white	light yellow
	the tenth day	white	white	light yellow
Purity/%	the zeroth day	99.94	99.94	99.52
	the fifth day	99.92	99.92	99.50
	the tenth day	99.94	99.94	99.29

[00273] (2) High humidity test: an appropriate amount of test sample was placed in flat weighing bottle and spread into a thin layer (thickness ≤ 5 mm). The whole was placed at 25 °C under RH 90%±5% for 10 days, sampling and observing change in the sample color at the fifth

day and tenth day, the purity of the sample was detected by HPLC. The experiment results are as shown in table 8.

Table 8: The high humidity test of the crystalline form I, form II or amorphism disclosed herein

Test sample		Form I	Form II	Amorphism
Appearance	the zeroth day	white	white	light yellow
	the fifth day	white	white	light yellow
	the tenth day	white	white	light yellow
Purity/%	the zeroth day	99.94	99.94	99.52
	the fifth day	99.96	99.96	99.58
	the tenth day	99.96	99.96	99.44

[00274] Conclusion: As can be seen in table 7 and table 8, the appearances and purities of the crystalline form I, form II and amorphism of the invention have no obvious change at high temperature (60 °C) under high humidity (25 °C, RH 90% ±5%), so which have good stabilities and are suitable for pharmaceutical use.

Example 10

The hygroscopicity tests of the crystalline forms and amorphism disclosed herein

[00275] An appropriate amount of test sample was sampled, and the hygroscopicity of which was detected on a dynamic vapor sorption instrument. The experiment results are as shown in table 9; the dynamic vapor sorption profiles of the crystalline form I, form II and amorphism are substantial the same as shown in Figures 25-27.

Table 9: The hygroscopicity tests of the crystalline form I, form II and amorphism

Test sample	Weigh increase rate% under RH 80%	Weigh increase rate% under RH 95%
Form I	0.22	0.30
Form II	0.15	0.37
Amorphism	2.24	3.33

[00276] Conclusion: As can be seen in table 9 and Figures 25 to 27, form I has 0.22% of weigh increase under relative humidity (RH) 80%, which belongs to Slight hygroscopicity according to the definition standard of hygroscopic weight gain; form II has 0.15% of weigh increase under relative humidity (RH) 80%, which belongs to No or almost no hygroscopicity; amorphism has 2.24% of weigh increase under relative humidity (RH) 80%, which belongs to Hygroscopicity

but there is no obvious in the weight increase of the hygroscopicity; *i.e.* the crystalline form I, form II or amorphism is not easy to deliquesce under high humidity conditions.

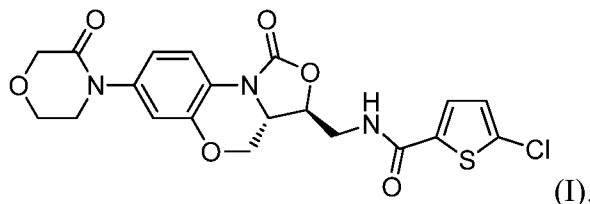
[00277] The foregoing has described the invention including basic instructions. Any equivalent alterations according the technology of the present invention that would be apparent to the skilled person are within the scope of the invention.

[00278] Reference throughout this specification to “one embodiment”, “an embodiment”, “some embodiments”, “explanatory embodiment”, “an example”, “a specific example” or “some examples”, means that a particular feature, structure, material or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as “in some embodiments”, “in one embodiment”, “in an embodiment”, “in another example”, “in an example”, “in a specific examples”, or “in some examples” in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials or characteristics may be combined in any suitable manner in one or more embodiments or examples. In addition, those skilled in the art can integrate and combine different embodiments, examples or the features of them as long as they are not contradictory to one another.

[00279] Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments can be not construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure.

What is claimed is:

1. A crystalline form of a compound having formula (I), wherein the crystalline form is form I, form II, form III, form IV or form V,



2. The crystalline form of claim 1, which is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$ and $34.27^\circ \pm 0.2^\circ$.
3. The crystalline form of claim 1, which is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $16.26^\circ \pm 0.2^\circ$, $16.95^\circ \pm 0.2^\circ$, $18.01^\circ \pm 0.2^\circ$, $18.69^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $20.75^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $22.96^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $27.08^\circ \pm 0.2^\circ$, $27.25^\circ \pm 0.2^\circ$, $28.96^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$, $31.61^\circ \pm 0.2^\circ$, $32.10^\circ \pm 0.2^\circ$, $32.86^\circ \pm 0.2^\circ$, $34.27^\circ \pm 0.2^\circ$ and $39.34^\circ \pm 0.2^\circ$.
4. The crystalline form of claim 1, which is form I having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $5.41^\circ \pm 0.2^\circ$, $11.06^\circ \pm 0.2^\circ$, $12.64^\circ \pm 0.2^\circ$, $16.26^\circ \pm 0.2^\circ$, $16.66^\circ \pm 0.2^\circ$, $16.95^\circ \pm 0.2^\circ$, $18.01^\circ \pm 0.2^\circ$, $18.69^\circ \pm 0.2^\circ$, $18.93^\circ \pm 0.2^\circ$, $19.39^\circ \pm 0.2^\circ$, $19.57^\circ \pm 0.2^\circ$, $20.13^\circ \pm 0.2^\circ$, $20.75^\circ \pm 0.2^\circ$, $21.05^\circ \pm 0.2^\circ$, $21.72^\circ \pm 0.2^\circ$, $22.23^\circ \pm 0.2^\circ$, $22.96^\circ \pm 0.2^\circ$, $23.39^\circ \pm 0.2^\circ$, $23.85^\circ \pm 0.2^\circ$, $24.68^\circ \pm 0.2^\circ$, $24.96^\circ \pm 0.2^\circ$, $25.74^\circ \pm 0.2^\circ$, $26.36^\circ \pm 0.2^\circ$, $27.08^\circ \pm 0.2^\circ$, $27.25^\circ \pm 0.2^\circ$, $27.73^\circ \pm 0.2^\circ$, $28.53^\circ \pm 0.2^\circ$, $28.96^\circ \pm 0.2^\circ$, $29.36^\circ \pm 0.2^\circ$, $29.70^\circ \pm 0.2^\circ$, $30.21^\circ \pm 0.2^\circ$, $30.83^\circ \pm 0.2^\circ$, $31.61^\circ \pm 0.2^\circ$, $32.10^\circ \pm 0.2^\circ$, $32.86^\circ \pm 0.2^\circ$, $33.08^\circ \pm 0.2^\circ$, $33.76^\circ \pm 0.2^\circ$, $34.27^\circ \pm 0.2^\circ$, $35.34^\circ \pm 0.2^\circ$, $36.09^\circ \pm 0.2^\circ$, $37.20^\circ \pm 0.2^\circ$, $38.47^\circ \pm 0.2^\circ$ and $39.34^\circ \pm 0.2^\circ$.
5. The crystalline form of claim 1, which is form I having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 1.
6. The crystalline form of claim 1, which is form I having a differential scanning calorimetry thermogram comprising an endothermic peak at $204.81^\circ\text{C} \pm 3^\circ\text{C}$.
7. The crystalline form of claim 1, which is form I having a differential scanning calorimetry thermogram substantially the same as shown in Figure 2.
8. The crystalline form of claim 1, which is form I having a Raman spectrogram comprising

absorption peaks at about 163 cm^{-1} , about 246 cm^{-1} , about 280 cm^{-1} , about 389 cm^{-1} , about 516 cm^{-1} , about 582 cm^{-1} , about 672 cm^{-1} , about 690 cm^{-1} , about 715 cm^{-1} , about 730 cm^{-1} , about 796 cm^{-1} , about 971 cm^{-1} , about 1035 cm^{-1} , about 1084 cm^{-1} , about 1117 cm^{-1} , about 1296 cm^{-1} , about 1325 cm^{-1} , about 1428 cm^{-1} , about 1556 cm^{-1} , about 1609 cm^{-1} , about 1666 cm^{-1} , about 2958 cm^{-1} and about 2991 cm^{-1} .

9. The crystalline form of claim 1, which is form I having a Raman spectrogram substantially the same as shown in Figure 3.

10. The crystalline form of claim 1, which is form I having a Fourier transform infrared spectrogram comprising absorption peaks at about 418 cm^{-1} , about 455 cm^{-1} , about 480 cm^{-1} , about 498 cm^{-1} , about 516 cm^{-1} , about 555 cm^{-1} , about 568 cm^{-1} , about 582 cm^{-1} , about 605 cm^{-1} , about 637 cm^{-1} , about 687 cm^{-1} , about 715 cm^{-1} , about 739 cm^{-1} , about 809 cm^{-1} , about 883 cm^{-1} , about 909 cm^{-1} , about 937 cm^{-1} , about 965 cm^{-1} , about 996 cm^{-1} , about 1025 cm^{-1} , about 1048 cm^{-1} , about 1087 cm^{-1} , about 1115 cm^{-1} , about 1153 cm^{-1} , about 1188 cm^{-1} , about 1217 cm^{-1} , about 1237 cm^{-1} , about 1290 cm^{-1} , about 1324 cm^{-1} , about 1344 cm^{-1} , about 1385 cm^{-1} , about 1427 cm^{-1} , about 1474 cm^{-1} , about 1510 cm^{-1} , about 1560 cm^{-1} , about 1625 cm^{-1} , about 1642 cm^{-1} , about 1673 cm^{-1} , about 1766 cm^{-1} , about 2870 cm^{-1} , about 2927 cm^{-1} , about 2970 cm^{-1} , about 3065 cm^{-1} , about 3101 cm^{-1} and about 3292 cm^{-1} .

11. The crystalline form of claim 1, which is form I having a Fourier transform infrared spectrogram substantially the same as shown in Figure 4.

12. The crystalline form of claim 1, which is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$, $27.56^\circ \pm 0.2^\circ$, $28.18^\circ \pm 0.2^\circ$ and $37.84^\circ \pm 0.2^\circ$.

13. The crystalline form of claim 1, which is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $14.65^\circ \pm 0.2^\circ$, $15.85^\circ \pm 0.2^\circ$, $16.90^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $20.99^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $23.07^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$, $27.56^\circ \pm 0.2^\circ$, $28.18^\circ \pm 0.2^\circ$, $30.36^\circ \pm 0.2^\circ$, $30.86^\circ \pm 0.2^\circ$, $33.43^\circ \pm 0.2^\circ$, $34.68^\circ \pm 0.2^\circ$, $35.22^\circ \pm 0.2^\circ$, $36.24^\circ \pm 0.2^\circ$ and $37.84^\circ \pm 0.2^\circ$.

14. The crystalline form of claim 1, which is form II having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $9.39^\circ \pm 0.2^\circ$, $12.70^\circ \pm 0.2^\circ$, $14.65^\circ \pm 0.2^\circ$, $15.41^\circ \pm 0.2^\circ$, $15.85^\circ \pm 0.2^\circ$, $16.90^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.96^\circ \pm 0.2^\circ$, $20.99^\circ \pm 0.2^\circ$, $21.98^\circ \pm 0.2^\circ$, $22.45^\circ \pm 0.2^\circ$, $23.07^\circ \pm 0.2^\circ$, $23.32^\circ \pm 0.2^\circ$, $24.73^\circ \pm 0.2^\circ$, $25.42^\circ \pm 0.2^\circ$, $27.23^\circ \pm 0.2^\circ$,

$27.56^{\circ} \pm 0.2^{\circ}$, $28.18^{\circ} \pm 0.2^{\circ}$, $29.94^{\circ} \pm 0.2^{\circ}$, $30.36^{\circ} \pm 0.2^{\circ}$, $30.86^{\circ} \pm 0.2^{\circ}$, $31.36^{\circ} \pm 0.2^{\circ}$, $33.43^{\circ} \pm 0.2^{\circ}$, $34.14^{\circ} \pm 0.2^{\circ}$, $34.37^{\circ} \pm 0.2^{\circ}$, $34.68^{\circ} \pm 0.2^{\circ}$, $35.22^{\circ} \pm 0.2^{\circ}$, $36.24^{\circ} \pm 0.2^{\circ}$, $36.85^{\circ} \pm 0.2^{\circ}$, $37.07^{\circ} \pm 0.2^{\circ}$, $37.84^{\circ} \pm 0.2^{\circ}$, $38.31^{\circ} \pm 0.2^{\circ}$ and $39.10^{\circ} \pm 0.2^{\circ}$.

15. The crystalline form of claim 1, which is form II having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 5.

16. The crystalline form of claim 1, which is form II having a differential scanning calorimetry thermogram comprising an endothermic peak at $194.90^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

17. The crystalline form of claim 1, which is form II having a differential scanning calorimetry thermogram substantially the same as shown in Figure 6.

18. The crystalline form of claim 1, which is form II having a Raman spectrogram comprising absorption peaks at about 174 cm^{-1} , about 198 cm^{-1} , about 270 cm^{-1} , about 336 cm^{-1} , about 401 cm^{-1} , about 448 cm^{-1} , about 524 cm^{-1} , about 559 cm^{-1} , about 669 cm^{-1} , about 696 cm^{-1} , about 729 cm^{-1} , about 797 cm^{-1} , about 880 cm^{-1} , about 1078 cm^{-1} , about 1092 cm^{-1} , about 1234 cm^{-1} , about 1294 cm^{-1} , about 1328 cm^{-1} , about 1390 cm^{-1} , about 1428 cm^{-1} , about 1478 cm^{-1} , about 1562 cm^{-1} , about 1605 cm^{-1} , about 1642 cm^{-1} , about 1770 cm^{-1} , about 2877 cm^{-1} , about 2926 cm^{-1} , about 2955 cm^{-1} , about 2987 cm^{-1} and about 3089 cm^{-1} .

19. The crystalline form of claim 1, which is form II having a Raman spectrogram substantially the same as shown in Figure 7.

20. The crystalline form of claim 1, which is form II having a Fourier transform infrared spectrogram comprising absorption peaks at about 421 cm^{-1} , about 481 cm^{-1} , about 497 cm^{-1} , about 512 cm^{-1} , about 558 cm^{-1} , about 584 cm^{-1} , about 607 cm^{-1} , about 637 cm^{-1} , about 682 cm^{-1} , about 727 cm^{-1} , about 749 cm^{-1} , about 798 cm^{-1} , about 829 cm^{-1} , about 881 cm^{-1} , about 938 cm^{-1} , about 962 cm^{-1} , about 985 cm^{-1} , about 999 cm^{-1} , about 1014 cm^{-1} , about 1027 cm^{-1} , about 1058 cm^{-1} , about 1098 cm^{-1} , about 1129 cm^{-1} , about 1157 cm^{-1} , about 1184 cm^{-1} , about 1204 cm^{-1} , about 1237 cm^{-1} , about 1291 cm^{-1} , about 1328 cm^{-1} , about 1348 cm^{-1} , about 1372 cm^{-1} , about 1391 cm^{-1} , about 1426 cm^{-1} , about 1448 cm^{-1} , about 1478 cm^{-1} , about 1504 cm^{-1} , about 1560 cm^{-1} , about 1642 cm^{-1} , about 1770 cm^{-1} , about 1933 cm^{-1} , about 2745 cm^{-1} , about 2820 cm^{-1} , about 2870 cm^{-1} , about 2924 cm^{-1} , about 2955 cm^{-1} , about 2983 cm^{-1} , about 3035 cm^{-1} , about 3090 cm^{-1} and about 3286 cm^{-1} .

21. The crystalline form of claim 1, which is form II having a Fourier transform infrared spectrogram substantially the same as shown in Figure 8.

22. The crystalline form of claim 1, which is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $12.14^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$ and $34.49^\circ \pm 0.2^\circ$.

23. The crystalline form of claim 1, which is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.94^\circ \pm 0.2^\circ$, $12.14^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $16.13^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.49^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $22.40^\circ \pm 0.2^\circ$, $23.43^\circ \pm 0.2^\circ$, $23.83^\circ \pm 0.2^\circ$, $24.45^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $25.05^\circ \pm 0.2^\circ$, $25.77^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.52^\circ \pm 0.2^\circ$, $29.73^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$, $33.88^\circ \pm 0.2^\circ$, $34.05^\circ \pm 0.2^\circ$, $34.49^\circ \pm 0.2^\circ$ and $39.33^\circ \pm 0.2^\circ$.

24. The crystalline form of claim 1, which is form III having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $4.73^\circ \pm 0.2^\circ$, $8.94^\circ \pm 0.2^\circ$, $9.46^\circ \pm 0.2^\circ$, $12.14^\circ \pm 0.2^\circ$, $14.23^\circ \pm 0.2^\circ$, $15.22^\circ \pm 0.2^\circ$, $16.13^\circ \pm 0.2^\circ$, $17.39^\circ \pm 0.2^\circ$, $17.97^\circ \pm 0.2^\circ$, $19.00^\circ \pm 0.2^\circ$, $19.75^\circ \pm 0.2^\circ$, $20.49^\circ \pm 0.2^\circ$, $20.89^\circ \pm 0.2^\circ$, $22.40^\circ \pm 0.2^\circ$, $23.43^\circ \pm 0.2^\circ$, $23.83^\circ \pm 0.2^\circ$, $24.45^\circ \pm 0.2^\circ$, $24.87^\circ \pm 0.2^\circ$, $25.05^\circ \pm 0.2^\circ$, $25.77^\circ \pm 0.2^\circ$, $26.12^\circ \pm 0.2^\circ$, $27.10^\circ \pm 0.2^\circ$, $28.67^\circ \pm 0.2^\circ$, $29.06^\circ \pm 0.2^\circ$, $29.52^\circ \pm 0.2^\circ$, $29.73^\circ \pm 0.2^\circ$, $29.97^\circ \pm 0.2^\circ$, $30.76^\circ \pm 0.2^\circ$, $31.47^\circ \pm 0.2^\circ$, $32.66^\circ \pm 0.2^\circ$, $33.32^\circ \pm 0.2^\circ$, $33.88^\circ \pm 0.2^\circ$, $34.05^\circ \pm 0.2^\circ$, $34.49^\circ \pm 0.2^\circ$, $35.21^\circ \pm 0.2^\circ$, $36.29^\circ \pm 0.2^\circ$, $37.08^\circ \pm 0.2^\circ$, $37.62^\circ \pm 0.2^\circ$, $38.19^\circ \pm 0.2^\circ$, $39.33^\circ \pm 0.2^\circ$ and $39.43^\circ \pm 0.2^\circ$.

25. The crystalline form of claim 1, which is form III having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 9.

26. The crystalline form of claim 1, which is form III having a differential scanning calorimetry thermogram comprising an endothermic peak at $125.24^\circ\text{C} \pm 3^\circ\text{C}$.

27. The crystalline form of claim 1, which is form III having a differential scanning calorimetry thermogram substantially the same as shown in Figure 10.

28. The crystalline form of claim 1, which is form III having a Raman spectrogram comprising absorption peaks at about 201 cm^{-1} , about 245 cm^{-1} , about 283 cm^{-1} , about 367 cm^{-1} , about 407 cm^{-1} , about 450 cm^{-1} , about 510 cm^{-1} , about 525 cm^{-1} , about 571 cm^{-1} , about 639 cm^{-1} , about 665 cm^{-1} , about 693 cm^{-1} , about 714 cm^{-1} , about 742 cm^{-1} , about 769 cm^{-1} , about 802 cm^{-1} , about 864 cm^{-1} , about 903 cm^{-1} , about 949 cm^{-1} , about 974 cm^{-1} , about 1005 cm^{-1} , about 1034 cm^{-1} , about 1080 cm^{-1} , about 1099 cm^{-1} , about 1231 cm^{-1} , about 1272 cm^{-1} , about 1291 cm^{-1} , about 1309 cm^{-1} , about 1328 cm^{-1} , about 1388 cm^{-1} , about 1426 cm^{-1} , about 1507 cm^{-1} , about 1554 cm^{-1} ,

about 1608 cm^{-1} , about 1640 cm^{-1} , about 1662 cm^{-1} , about 1762 cm^{-1} , about 2834 cm^{-1} , about 2874 cm^{-1} , about 2939 cm^{-1} , about 2981 cm^{-1} and about 3089 cm^{-1} .

29. The crystalline form of claim 1, which is form III having a Raman spectrogram substantially the same as shown in Figure 11.

30. The crystalline form of claim 1, which is form III having a Fourier transform infrared spectrogram comprising absorption peaks at about 416 cm^{-1} , about 430 cm^{-1} , about 451 cm^{-1} , about 469 cm^{-1} , about 484 cm^{-1} , about 498 cm^{-1} , about 510 cm^{-1} , about 525 cm^{-1} , about 554 cm^{-1} , about 570 cm^{-1} , about 584 cm^{-1} , about 616 cm^{-1} , about 639 cm^{-1} , about 665 cm^{-1} , about 688 cm^{-1} , about 713 cm^{-1} , about 727 cm^{-1} , about 755 cm^{-1} , about 769 cm^{-1} , about 801 cm^{-1} , about 816 cm^{-1} , about 833 cm^{-1} , about 880 cm^{-1} , about 904 cm^{-1} , about 939 cm^{-1} , about 953 cm^{-1} , about 974 cm^{-1} , about 996 cm^{-1} , about 1022 cm^{-1} , about 1034 cm^{-1} , about 1064 cm^{-1} , about 1079 cm^{-1} , about 1098 cm^{-1} , about 1119 cm^{-1} , about 1142 cm^{-1} , about 1159 cm^{-1} , about 1185 cm^{-1} , about 1203 cm^{-1} , about 1237 cm^{-1} , about 1285 cm^{-1} , about 1310 cm^{-1} , about 1324 cm^{-1} , about 1347 cm^{-1} , about 1374 cm^{-1} , about 1428 cm^{-1} , about 1504 cm^{-1} , about 1556 cm^{-1} , about 1580 cm^{-1} , about 1606 cm^{-1} , about 1640 cm^{-1} , about 1661 cm^{-1} , about 1764 cm^{-1} , about 2809 cm^{-1} , about 2865 cm^{-1} , about 2928 cm^{-1} , about 2965 cm^{-1} , about 2979 cm^{-1} , about 3032 cm^{-1} , about 3081 cm^{-1} , about 3306 cm^{-1} and about 3340 cm^{-1} .

31. The crystalline form of claim 1, which is form III having a Fourier transform infrared spectrogram substantially the same as shown in Figure 12.

32. The crystalline form of claim 1, which is form IV having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $14.98^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm 0.2^\circ$, $26.56^\circ \pm 0.2^\circ$ and $29.67^\circ \pm 0.2^\circ$.

33. The crystalline form of claim 1, which is form IV having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.84^\circ \pm 0.2^\circ$, $14.98^\circ \pm 0.2^\circ$, $17.76^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $18.97^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $22.64^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm 0.2^\circ$, $24.56^\circ \pm 0.2^\circ$, $26.56^\circ \pm 0.2^\circ$, $29.39^\circ \pm 0.2^\circ$, $29.67^\circ \pm 0.2^\circ$, $33.64^\circ \pm 0.2^\circ$, $34.30^\circ \pm 0.2^\circ$, $34.59^\circ \pm 0.2^\circ$ and $37.00^\circ \pm 0.2^\circ$.

34. The crystalline form of claim 1, which is form IV having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at $8.84^\circ \pm 0.2^\circ$, $9.48^\circ \pm 0.2^\circ$, $14.26^\circ \pm 0.2^\circ$, $14.98^\circ \pm 0.2^\circ$, $16.12^\circ \pm 0.2^\circ$, $16.63^\circ \pm 0.2^\circ$, $17.76^\circ \pm 0.2^\circ$, $18.26^\circ \pm 0.2^\circ$, $18.97^\circ \pm 0.2^\circ$, $19.93^\circ \pm 0.2^\circ$, $20.41^\circ \pm 0.2^\circ$, $20.76^\circ \pm 0.2^\circ$, $22.07^\circ \pm 0.2^\circ$, $22.64^\circ \pm 0.2^\circ$, $23.13^\circ \pm 0.2^\circ$, $24.28^\circ \pm$

0.2°, 24.56° ± 0.2°, 25.08° ± 0.2°, 25.43° ± 0.2°, 26.56° ± 0.2°, 28.68° ± 0.2°, 29.39° ± 0.2°, 29.67° ± 0.2°, 30.35° ± 0.2°, 31.21° ± 0.2°, 32.39° ± 0.2°, 32.72° ± 0.2°, 33.64° ± 0.2°, 34.30° ± 0.2°, 34.59° ± 0.2°, 36.07° ± 0.2°, 37.00° ± 0.2°, 37.92° ± 0.2° and 39.44° ± 0.2°.

35. The crystalline form of claim 1, which is form IV having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 13.

36. The crystalline form of claim 1, which is form IV having a differential scanning calorimetry thermogram comprising an endothermic peak at 116.97 °C ± 3 °C.

37. The crystalline form of claim 1, wherein the crystalline form is form IV which transforms to form I at a temperature from about 150 °C to about 215 °C, and form IV has a differential scanning calorimetry thermogram comprising an endothermic peak at 203.20 °C ± 3 °C.

38. The crystalline form of claim 1, which is form IV having a differential scanning calorimetry thermogram substantially the same as shown in Figure 14.

39. The crystalline form of claim 1, which is form IV having a Raman spectrogram comprising absorption peaks at about 202 cm⁻¹, about 241 cm⁻¹, about 283 cm⁻¹, about 381 cm⁻¹, about 510 cm⁻¹, about 668 cm⁻¹, about 692 cm⁻¹, about 714 cm⁻¹, about 742 cm⁻¹, about 800 cm⁻¹, about 1035 cm⁻¹, about 1081 cm⁻¹, about 1228 cm⁻¹, about 1273 cm⁻¹, about 1305 cm⁻¹, about 1327 cm⁻¹, about 1428 cm⁻¹, about 1554 cm⁻¹, about 1608 cm⁻¹, about 1643 cm⁻¹, about 1703 cm⁻¹, about 1765 cm⁻¹, about 2924 cm⁻¹, about 2987 cm⁻¹ and about 3085 cm⁻¹.

40. The crystalline form of claim 1, which is form IV having a Raman spectrogram substantially the same as shown in Figure 15.

41. The crystalline form of claim 1, which is form IV having a Fourier transform infrared spectrogram comprising absorption peaks at about 421 cm⁻¹, about 481 cm⁻¹, about 496 cm⁻¹, about 511 cm⁻¹, about 558 cm⁻¹, about 584 cm⁻¹, about 606 cm⁻¹, about 637 cm⁻¹, about 681 cm⁻¹, about 727 cm⁻¹, about 749 cm⁻¹, about 798 cm⁻¹, about 829 cm⁻¹, about 840 cm⁻¹, about 880 cm⁻¹, about 894 cm⁻¹, about 938 cm⁻¹, about 961 cm⁻¹, about 985 cm⁻¹, about 999 cm⁻¹, about 1014 cm⁻¹, about 1027 cm⁻¹, about 1058 cm⁻¹, about 1098 cm⁻¹, about 1114 cm⁻¹, about 1128 cm⁻¹, about 1157 cm⁻¹, about 1184 cm⁻¹, about 1204 cm⁻¹, about 1237 cm⁻¹, about 1291 cm⁻¹, about 1328 cm⁻¹, about 1348 cm⁻¹, about 1372 cm⁻¹, about 1390 cm⁻¹, about 1426 cm⁻¹, about 1449 cm⁻¹, about 1478 cm⁻¹, about 1504 cm⁻¹, about 1561 cm⁻¹, about 1606 cm⁻¹, about 1642 cm⁻¹, about 1771 cm⁻¹, about 1933 cm⁻¹, about 2745 cm⁻¹, about 2820 cm⁻¹, about 2869 cm⁻¹, about 2923 cm⁻¹, about 2955 cm⁻¹, about 2983 cm⁻¹, about 3035 cm⁻¹, about 3090 cm⁻¹, about 3285

cm⁻¹ and about 3383 cm⁻¹.

42. The crystalline form of claim 1, which is form IV having a Fourier transform infrared spectrogram substantially the same as shown in Figure 16.

43. The crystalline form of claim 1, which is form V having the following structural parameters analyzed from monocrystal:

Crystal System:	triclinic system
Space Group:	P 1
Unit Cell Dimensions:	a = 6.8155(2) Å, α = 90.550(2)°, b = 9.1213(2) Å, β = 96.294(2)°, c = 19.5897(5) Å, γ = 91.719(2)°
Cell Volume:	1209.83(5) Å ³
Molecules per unit cell (Z):	2.

44. The crystalline form of claim 1, which is form V having a single-crystal structure substantially the same as shown in Figure 21.

45. The crystalline form of claim 1, which is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at 8.97° ± 0.2°, 14.16° ± 0.2°, 19.18° ± 0.2°, 19.92° ± 0.2°, 20.20° ± 0.2°, 22.53° ± 0.2°, 24.73° ± 0.2°, 27.13° ± 0.2° and 31.75° ± 0.2°.

46. The crystalline form of claim 1, which is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at 8.97° ± 0.2°, 14.16° ± 0.2°, 17.58° ± 0.2°, 17.98° ± 0.2°, 19.18° ± 0.2°, 19.92° ± 0.2°, 20.20° ± 0.2°, 20.40° ± 0.2°, 22.53° ± 0.2°, 24.73° ± 0.2°, 26.39° ± 0.2°, 27.13° ± 0.2°, 28.77° ± 0.2°, 31.75° ± 0.2° and 33.21° ± 0.2°.

47. The crystalline form of claim 1, which is form V having an X-ray powder diffraction (XRPD) pattern comprising peaks expressed in degrees 2θ at 4.50° ± 0.2°, 8.97° ± 0.2°, 10.55° ± 0.2°, 13.14° ± 0.2°, 14.16° ± 0.2°, 16.10° ± 0.2°, 16.50° ± 0.2°, 17.58° ± 0.2°, 17.98° ± 0.2°, 19.18° ± 0.2°, 19.92° ± 0.2°, 20.20° ± 0.2°, 20.40° ± 0.2°, 20.96° ± 0.2°, 21.23° ± 0.2°, 22.53° ± 0.2°, 23.07° ± 0.2°, 23.47° ± 0.2°, 24.11° ± 0.2°, 24.73° ± 0.2°, 25.94° ± 0.2°, 26.39° ± 0.2°, 26.70° ± 0.2°, 27.13° ± 0.2°, 28.42° ± 0.2°, 28.77° ± 0.2°, 29.41° ± 0.2°, 29.77° ± 0.2°, 30.01° ± 0.2°, 30.38° ± 0.2°, 31.41° ± 0.2°, 31.75° ± 0.2°, 32.13° ± 0.2°, 33.21° ± 0.2°, 34.59° ± 0.2°, 37.24° ± 0.2° and 39.04° ± 0.2°.

48. The crystalline form of claim 1, which is form V having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 22.

49. The crystalline form of claim 1, which is form V having a differential scanning calorimetry thermogram comprising an endothermic peak at $106.98\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

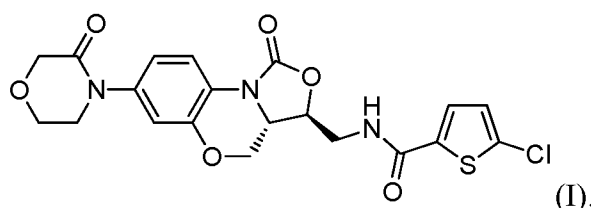
50. The crystalline form of claim 1, wherein the crystalline form is form V which transforms to form I and form II at a temperature from about $175\text{ }^{\circ}\text{C}$ to about $210\text{ }^{\circ}\text{C}$, and form V has a differential scanning calorimetry thermogram comprising endothermic peaks at $193.82\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ and $203.62\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

51. The crystalline form of claim 1, which is form V having a differential scanning calorimetry thermogram substantially the same as shown in Figure 23.

52. The crystalline form of claim 1, which is form V having a weight loss ratio of $16.59\% \pm 0.1\%$ measured by thermogravimetric analysis in a temperature range from about $50\text{ }^{\circ}\text{C}$ to about $150\text{ }^{\circ}\text{C}$.

53. The crystalline form of claim 1, which is form V having a thermogravimetric analysis diagram substantially the same as shown in Figure 24.

54. An amorphism of a compound having formula (I), wherein the amorphism has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 17,



55. The amorphism of claim 54, which has a glass transition temperature of $107.44\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

56. The amorphism of claim 54, wherein the amorphism transforms to form I at a temperature from about $140\text{ }^{\circ}\text{C}$ to about $215\text{ }^{\circ}\text{C}$, and the amorphism has a differential scanning calorimetry thermogram comprising an endothermic peak at $203.43\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$.

57. The amorphism of claim 54, which has a differential scanning calorimetry thermogram substantially the same as shown in Figure 18.

58. The amorphism of claim 54, which has a Raman spectrogram comprising absorption peaks at about 181 cm^{-1} , about 276 cm^{-1} , about 392 cm^{-1} , about 425 cm^{-1} , about 512 cm^{-1} , about 672 cm^{-1} , about 694 cm^{-1} , about 739 cm^{-1} , about 795 cm^{-1} , about 1080 cm^{-1} , about 1120 cm^{-1} , about 1298 cm^{-1} , about 1328 cm^{-1} , about 1427 cm^{-1} , about 1549 cm^{-1} , about 1612 cm^{-1} , about 2981 cm^{-1} and about 3088 cm^{-1} .

59. The amorphism of claim 54, which has a Raman spectrogram substantially the same as shown in Figure 19.

60. The amorphism of claim 54, which has a Fourier transform infrared spectrogram comprising absorption peaks at about 419 cm^{-1} , about 487 cm^{-1} , about 516 cm^{-1} , about 548 cm^{-1} , about 581 cm^{-1} , about 605 cm^{-1} , about 636 cm^{-1} , about 689 cm^{-1} , about 720 cm^{-1} , about 747 cm^{-1} , about 816 cm^{-1} , about 883 cm^{-1} , about 939 cm^{-1} , about 968 cm^{-1} , about 998 cm^{-1} , about 1023 cm^{-1} , about 1060 cm^{-1} , about 1099 cm^{-1} , about 1121 cm^{-1} , about 1156 cm^{-1} , about 1191 cm^{-1} , about 1216 cm^{-1} , about 1245 cm^{-1} , about 1291 cm^{-1} , about 1327 cm^{-1} , about 1347 cm^{-1} , about 1390 cm^{-1} , about 1427 cm^{-1} , about 1478 cm^{-1} , about 1514 cm^{-1} , about 1551 cm^{-1} , about 1585 cm^{-1} , about 1648 cm^{-1} , about 1759 cm^{-1} , about 2873 cm^{-1} , about 2932 cm^{-1} , about 2970 cm^{-1} , about 3091 cm^{-1} , about 3308 cm^{-1} and about 3469 cm^{-1} .
61. The amorphism of claim 54, wherein the amorphism has a Fourier transform infrared spectrogram substantially the same as shown in Figure 20.
62. The amorphism of claim 54, wherein the amorphism has a weight loss ratio of about 1.75% to about 4.10% measured by thermogravimetric analysis at a temperature from about $50\text{ }^{\circ}\text{C}$ to about $150\text{ }^{\circ}\text{C}$.
63. A method for preparing the crystalline form of a compound having formula (I) of any one of claims 1 to 11, wherein the crystalline form is form I, and the method comprises: transforming an amorphism of the compound to form I by heating.
64. The method of claim 63, wherein the transforming an amorphism of the compound to the form I by heating is carried out at a temperature from about $170\text{ }^{\circ}\text{C}$ to about $200\text{ }^{\circ}\text{C}$.
65. The method of claim 64, wherein the transforming an amorphism of the compound to the form I by heating is carried out at a temperature from about $180\text{ }^{\circ}\text{C}$ to about $190\text{ }^{\circ}\text{C}$.
66. The method of claim 65, wherein the transforming an amorphism of the compound to the form I by heating is carried out at a temperature of about $185\text{ }^{\circ}\text{C}$.
67. The method of claim 63, wherein the transforming an amorphism of the compound to the form I by heating is carried out for about 2 hours to about 24 hours.
68. The method of claim 67, wherein the transforming an amorphism of the compound to the form I by heating is carried out for about 5 hours to about 7.5 hours.
69. The method of claim 63, wherein the transforming an amorphism of the compound to the form I by heating is carried out under an aerobic or anaerobic condition.
70. The method of claim 69, wherein the anaerobic condition is vacuum or under an inert gasprotection.

71. The method of claim 63, wherein the heating is carried out by vacuum drying or blast drying.
72. A pharmaceutical composition comprising the crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or a combination thereof.
73. The pharmaceutical composition of claim 72 further comprising a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.
74. Use of the crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73 in the manufacture of a medicament for preventing, managing, treating or lessening a thromboembolism disease.
75. The use of claim 74, wherein the thromboembolism disease is myocardial infarction, stenocardia, reocclusion and restenosis after angioplasty or aortocoronary artery bypass surgery, stroke, a transitory ischaemic attack, a peripheral arterial occlusive disease, a pulmonary embolism or a deep venous thrombosis.
76. Use of the crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73 in the manufacture of a medicament for inhibiting the activity of blood coagulation factor Xa.
77. The crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73 for use in preventing, managing, treating or lessening a thromboembolism disease in a patient.
78. The crystalline form of claim 77, wherein the thromboembolism diseases comprise myocardial infarction, stenocardia, reocclusion and restenosis after angioplasty or aortocoronary artery bypass surgery, stroke, a transitory ischaemic attack, a peripheral arterial occlusive disease, a pulmonary embolism or a deep venous thrombosis.
79. The crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73 for use in inhibiting the activity of blood coagulation factor Xa.
80. A method of preventing, managing, treating or lessening a thromboembolism disease comprising administering to the patient a therapeutically effective amount of the crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73 to a subject.
81. The method of claim 80, wherein the thromboembolism disease is myocardial infarction, stenocardia, reocclusion and restenosis after angioplasty or aortocoronary artery bypass surgery,

stroke, a transitory ischaemic attack, a peripheral arterial occlusive disease, a pulmonary embolism or a deep venous thrombosis.

82. A method of inhibiting the activity of blood coagulation factor Xa comprising administering to the patient with a therapeutically effective amount of the crystalline form of any one of claims 1 to 53 or the amorphism of any one of claims 54 to 62 or the pharmaceutical composition of claims 72 or 73.

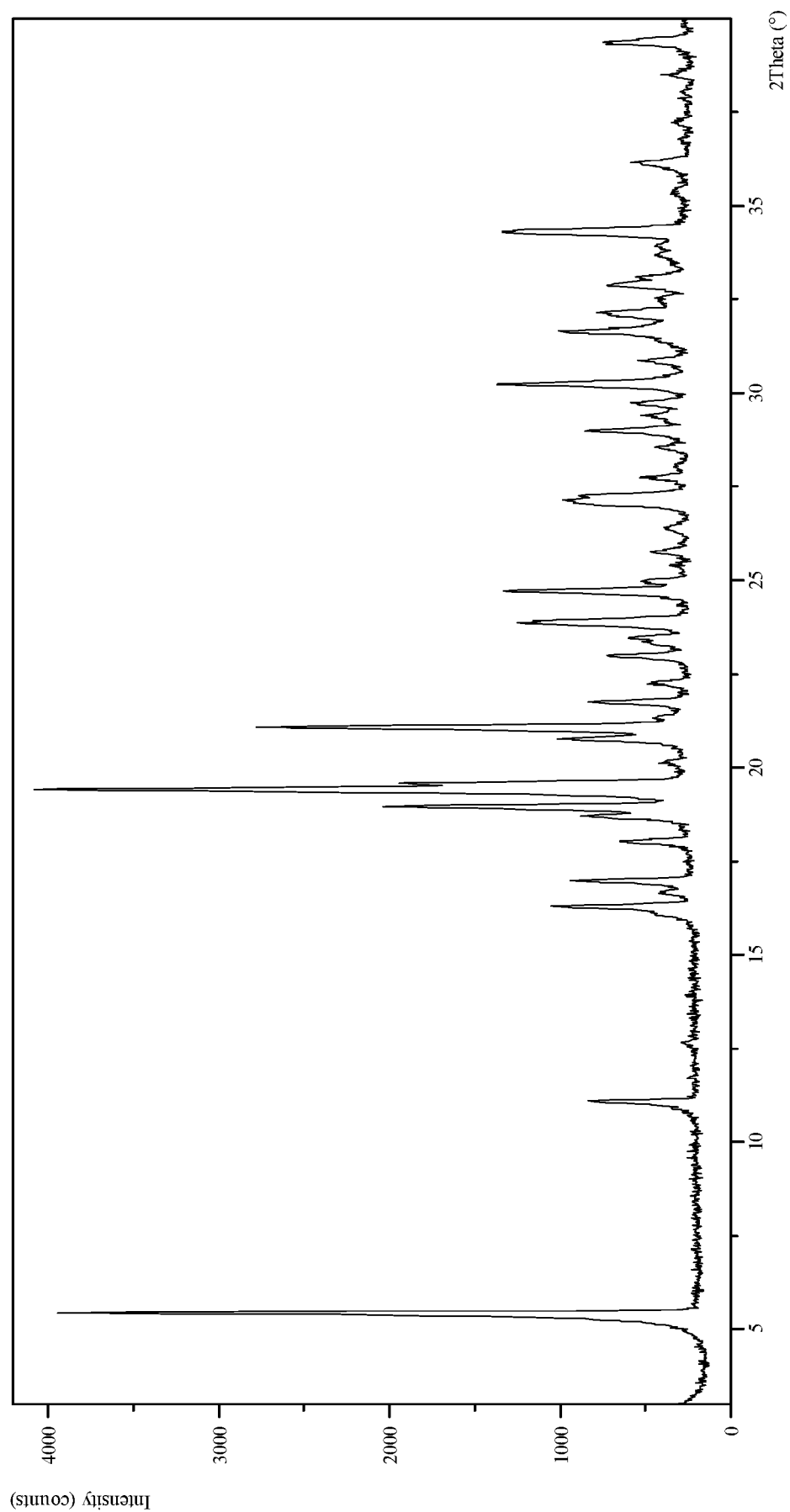


Figure 1

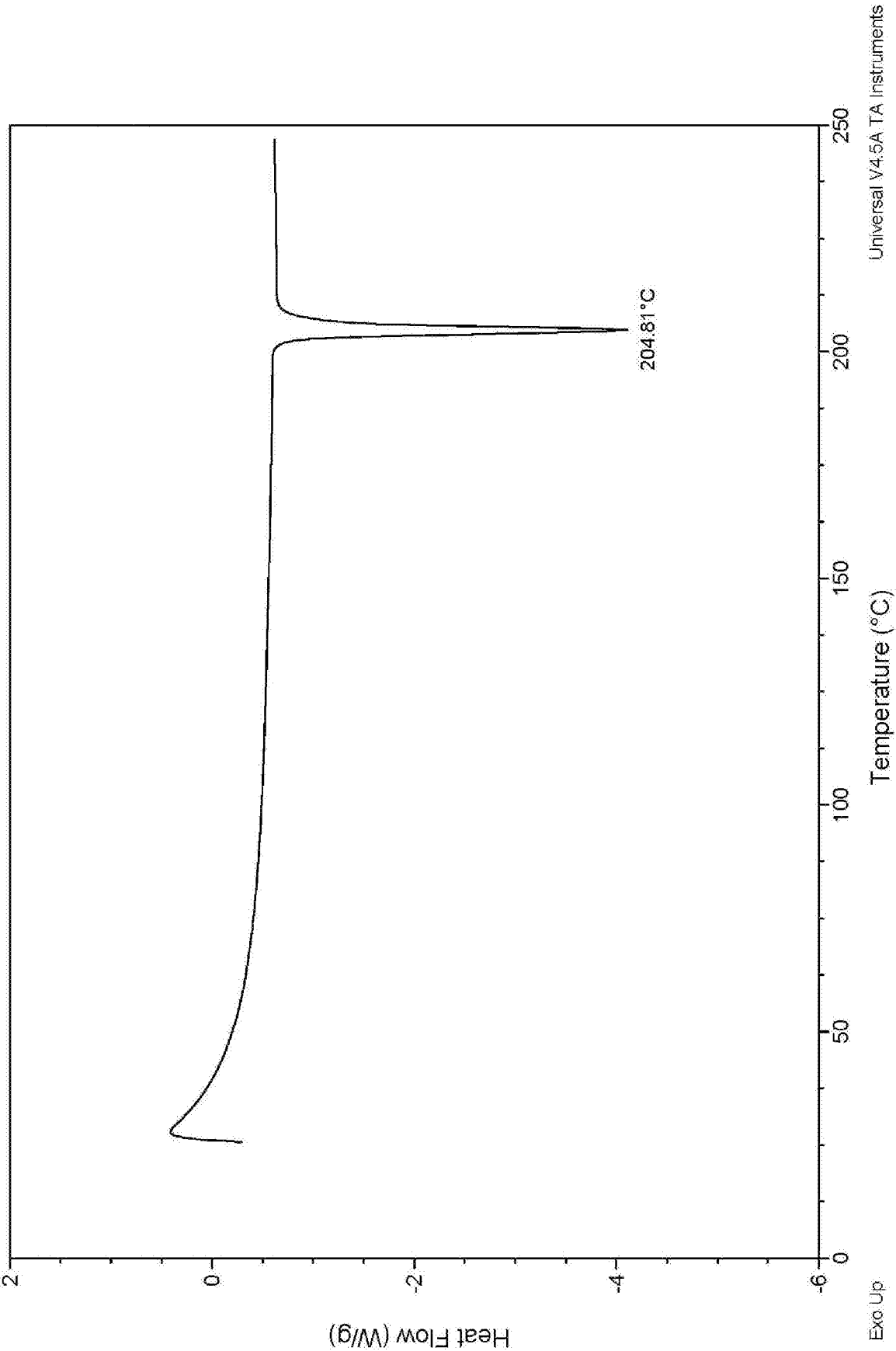


Figure 2

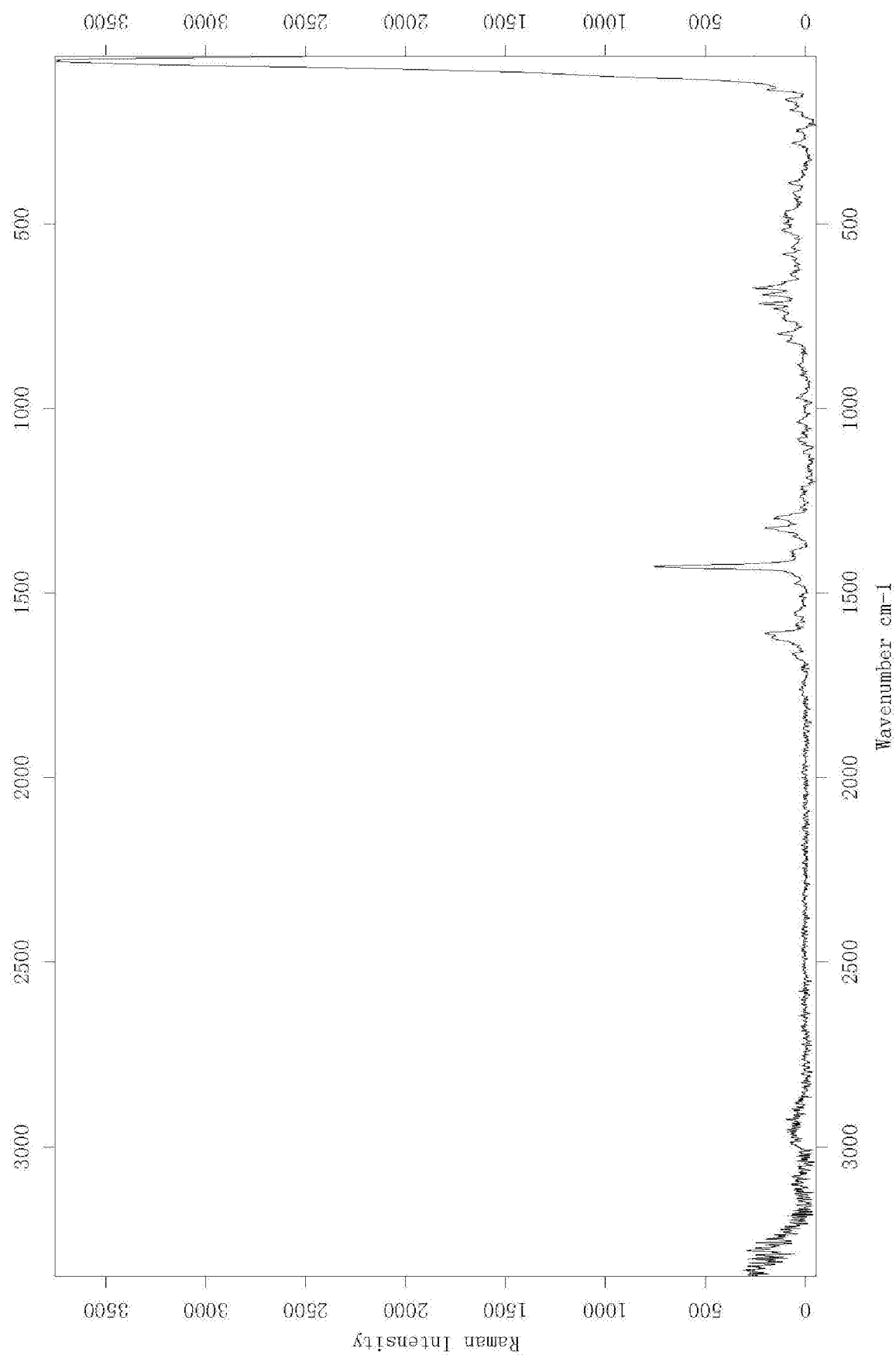


Figure 3

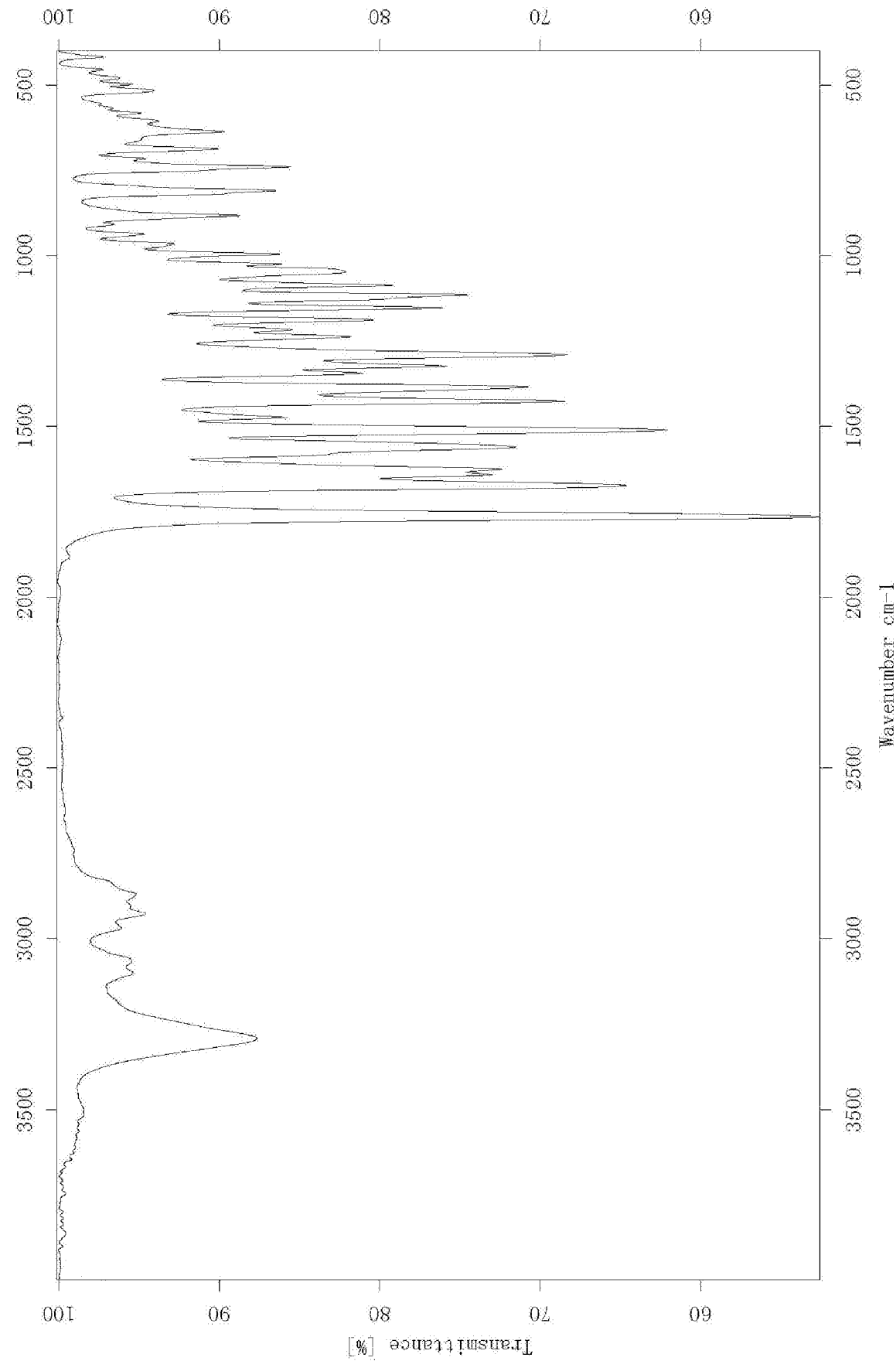


Figure 4

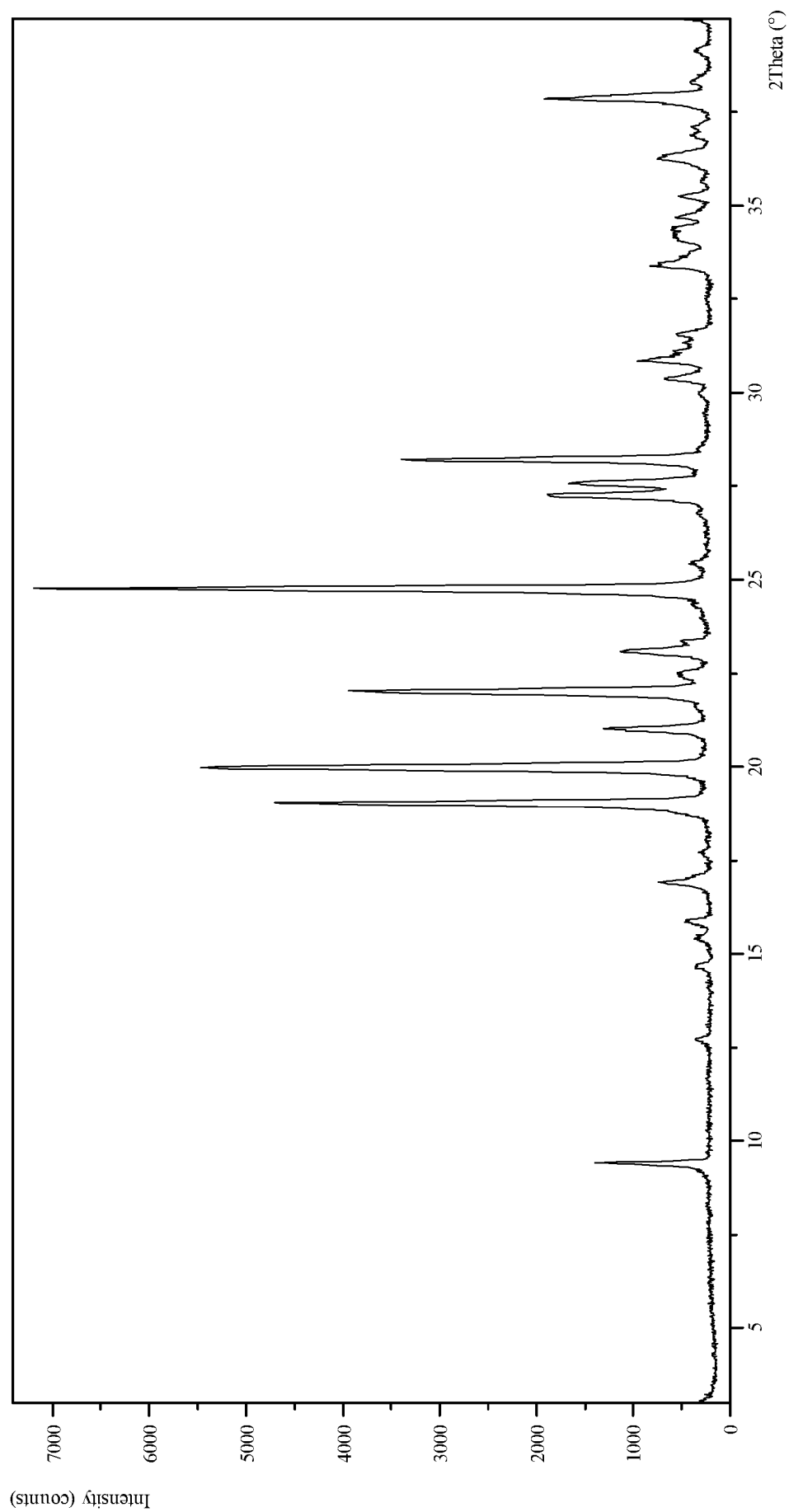


Figure 5

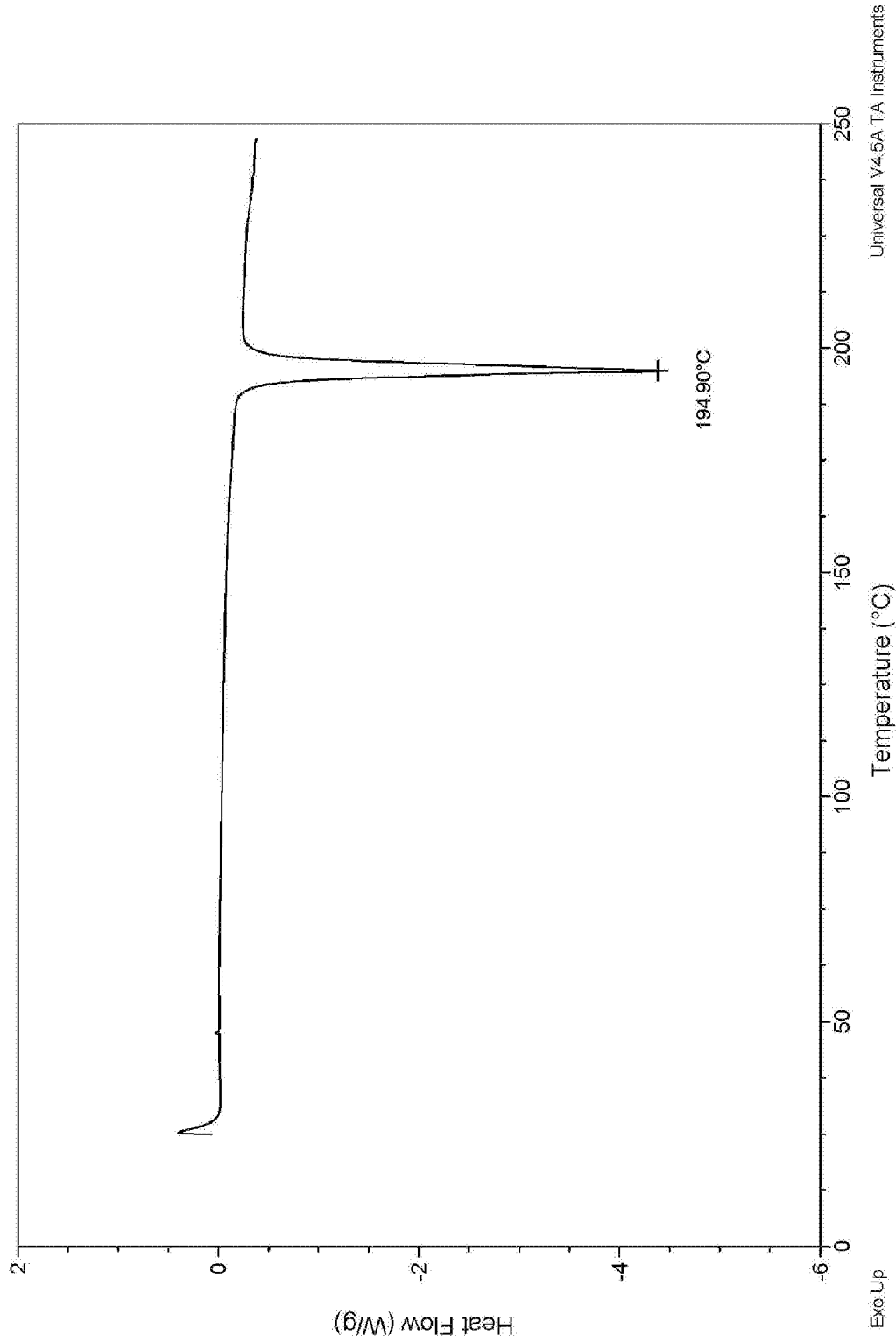


Figure 6

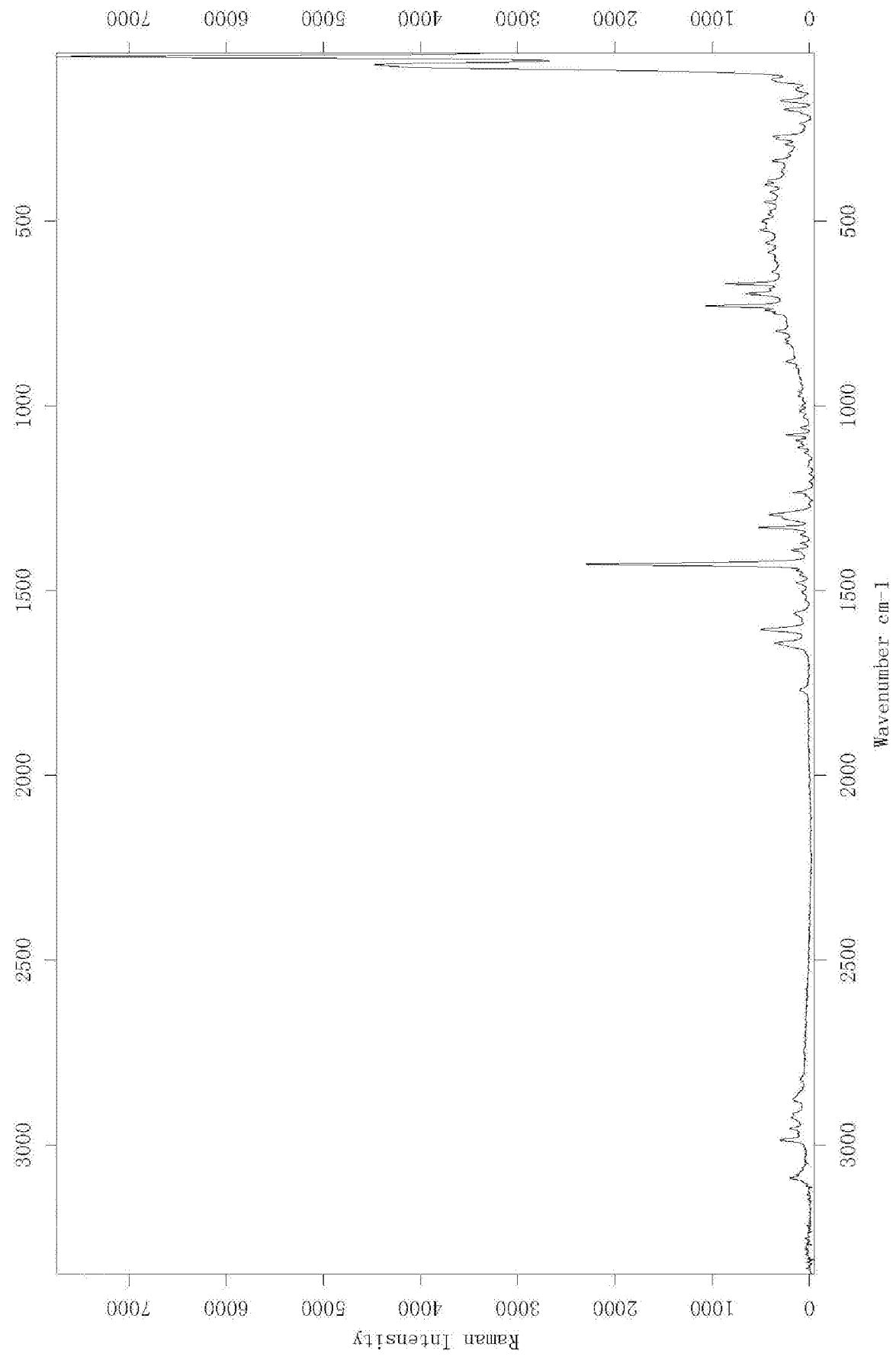


Figure 7

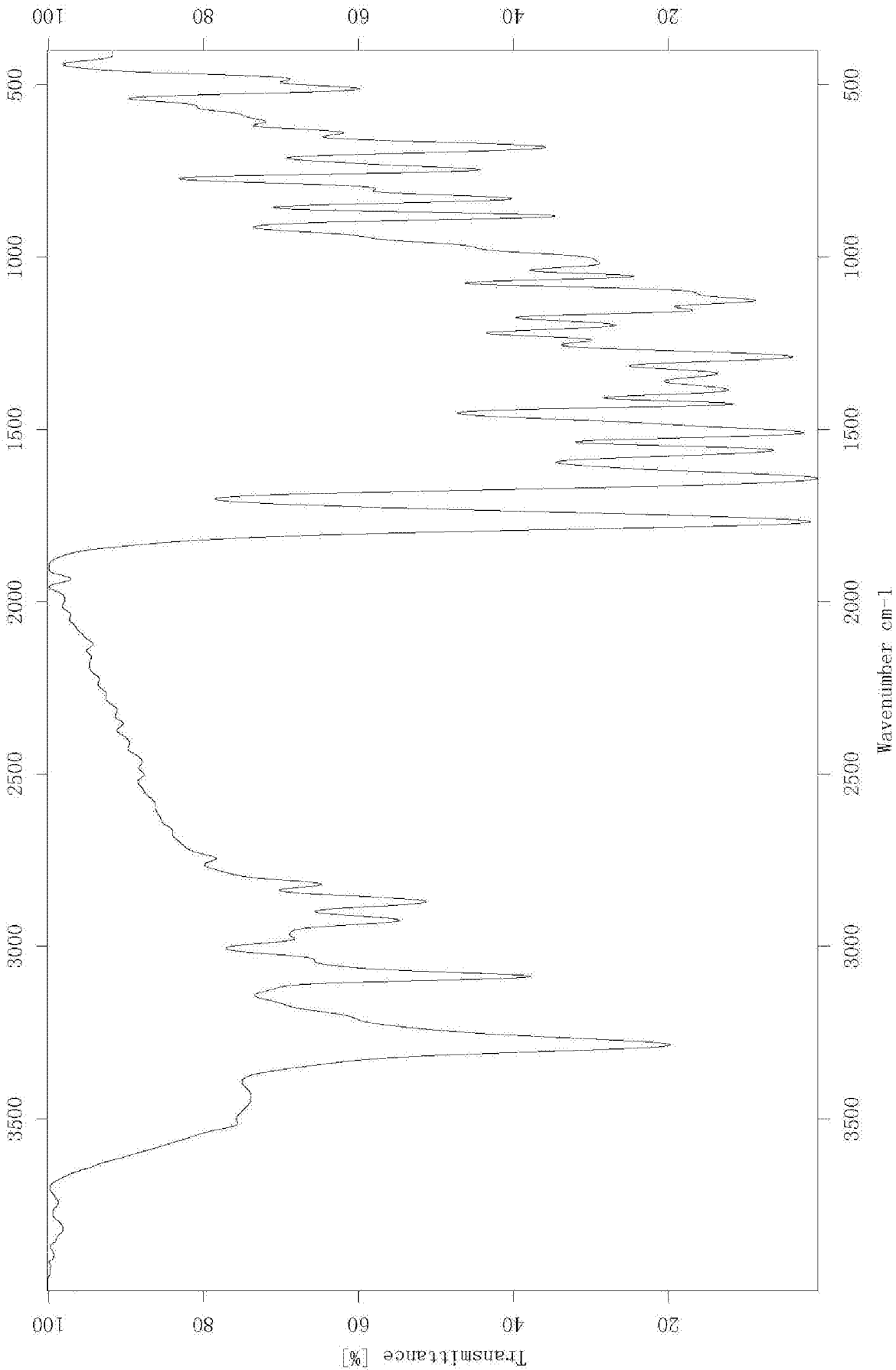


Figure 8

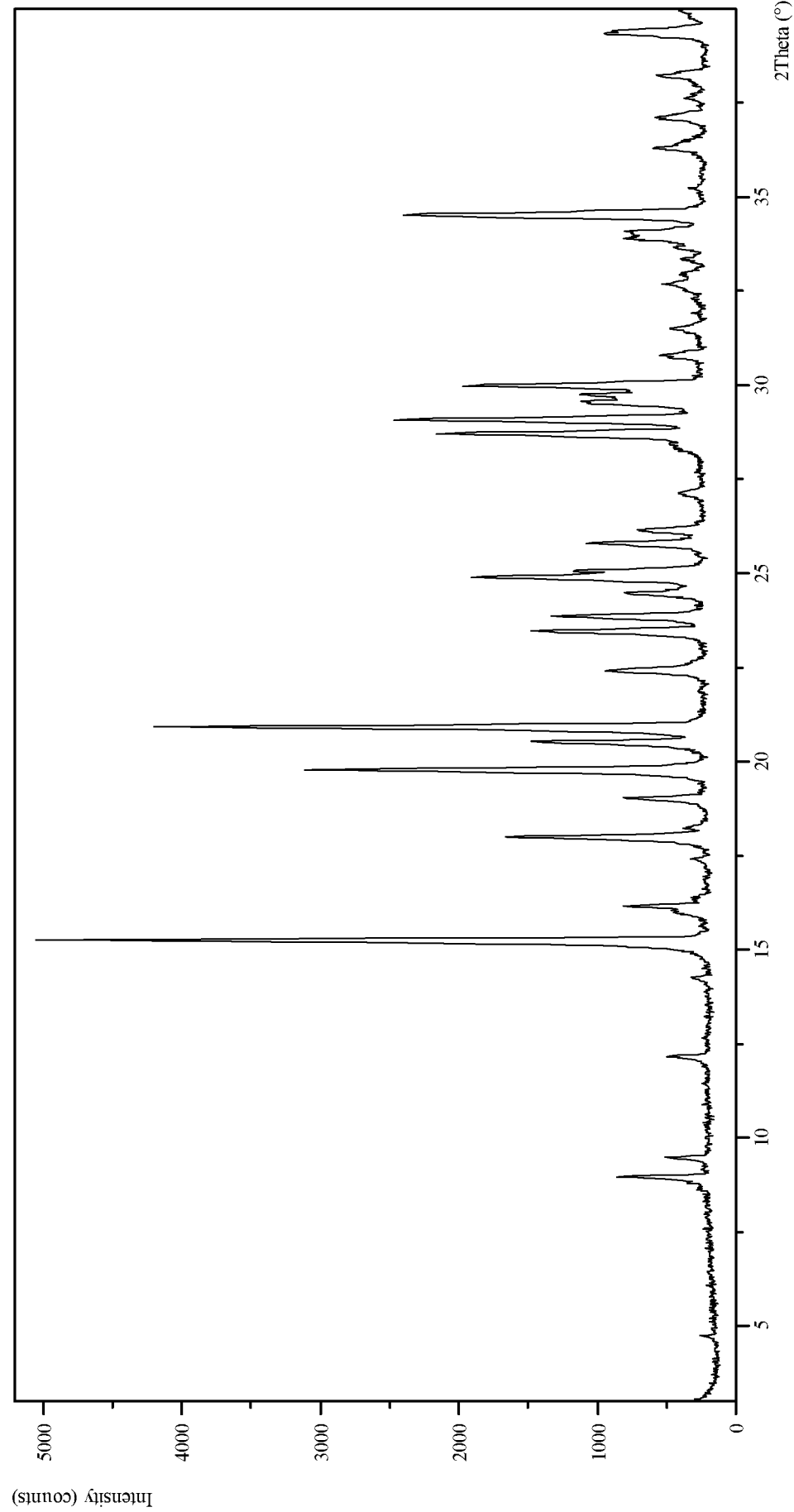


Figure 9

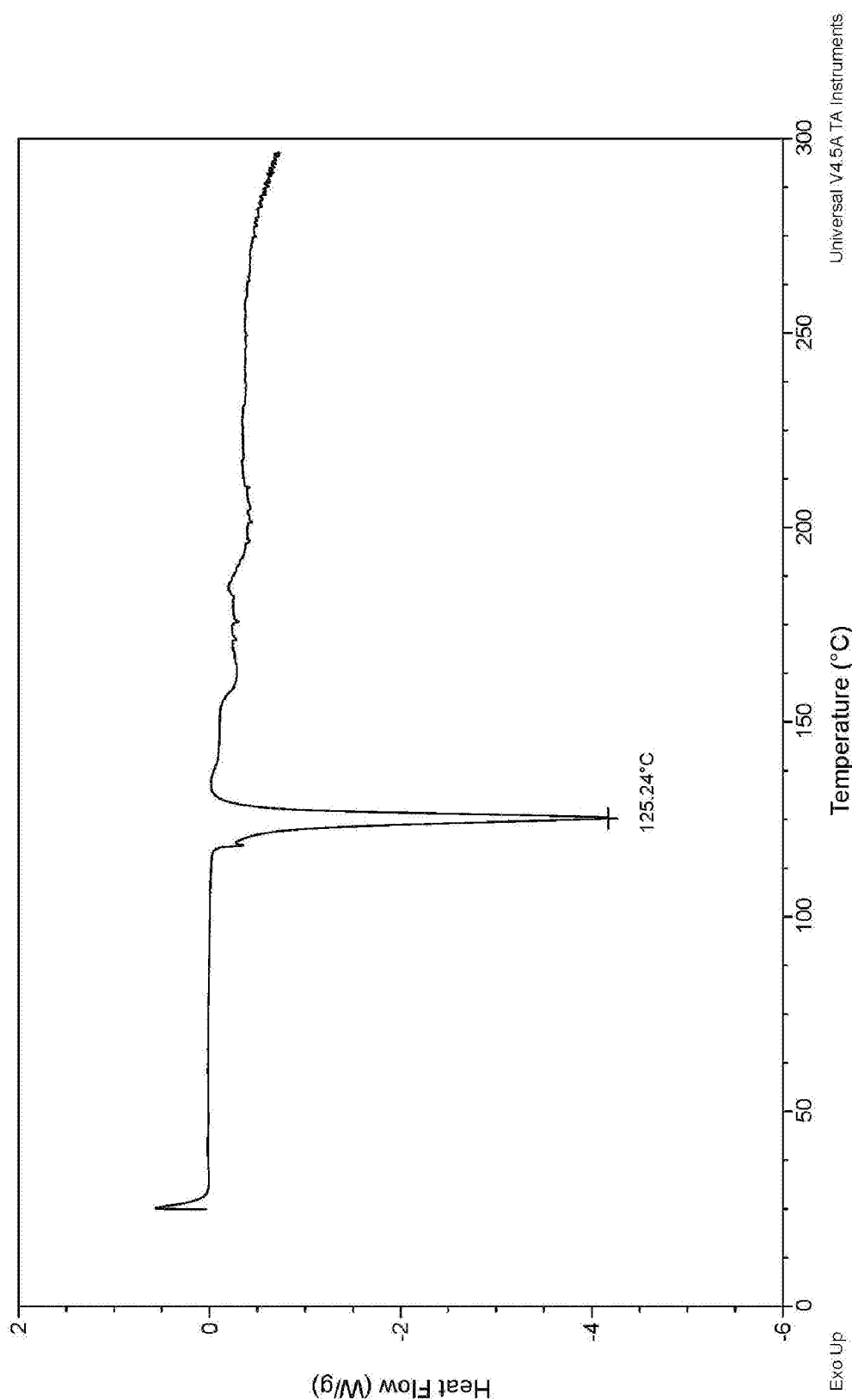


Figure 10

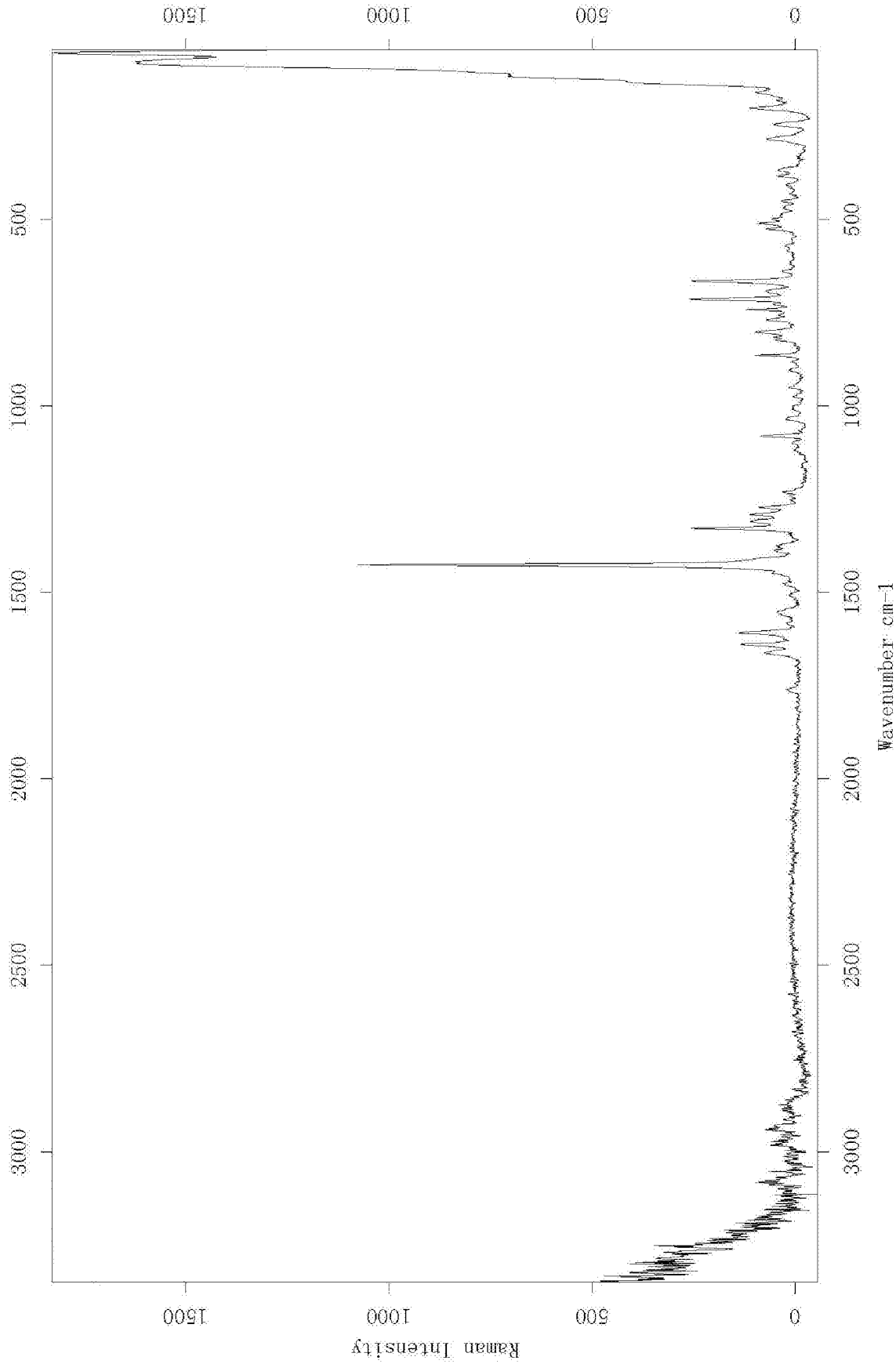


Figure 11

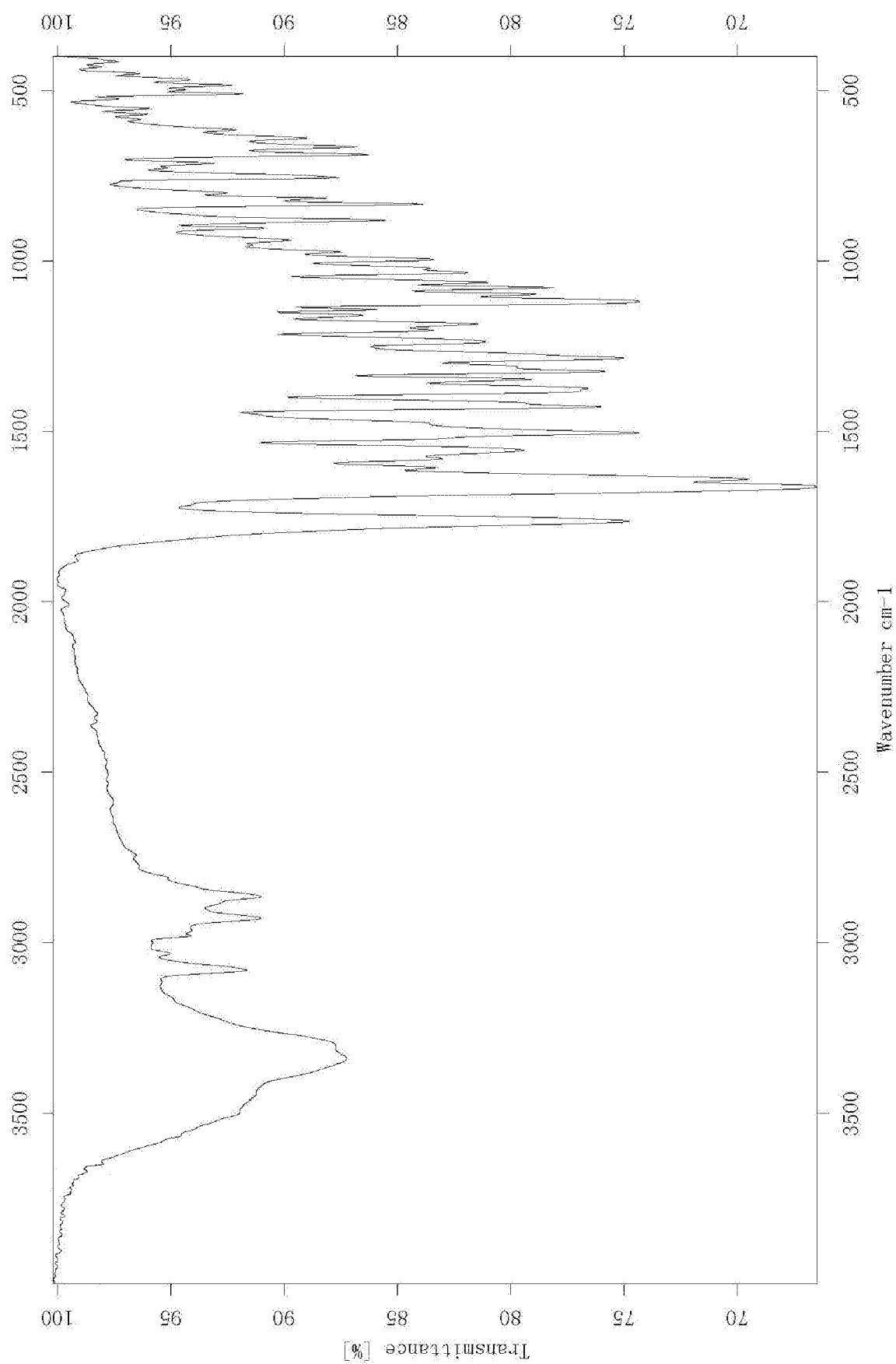


Figure 12

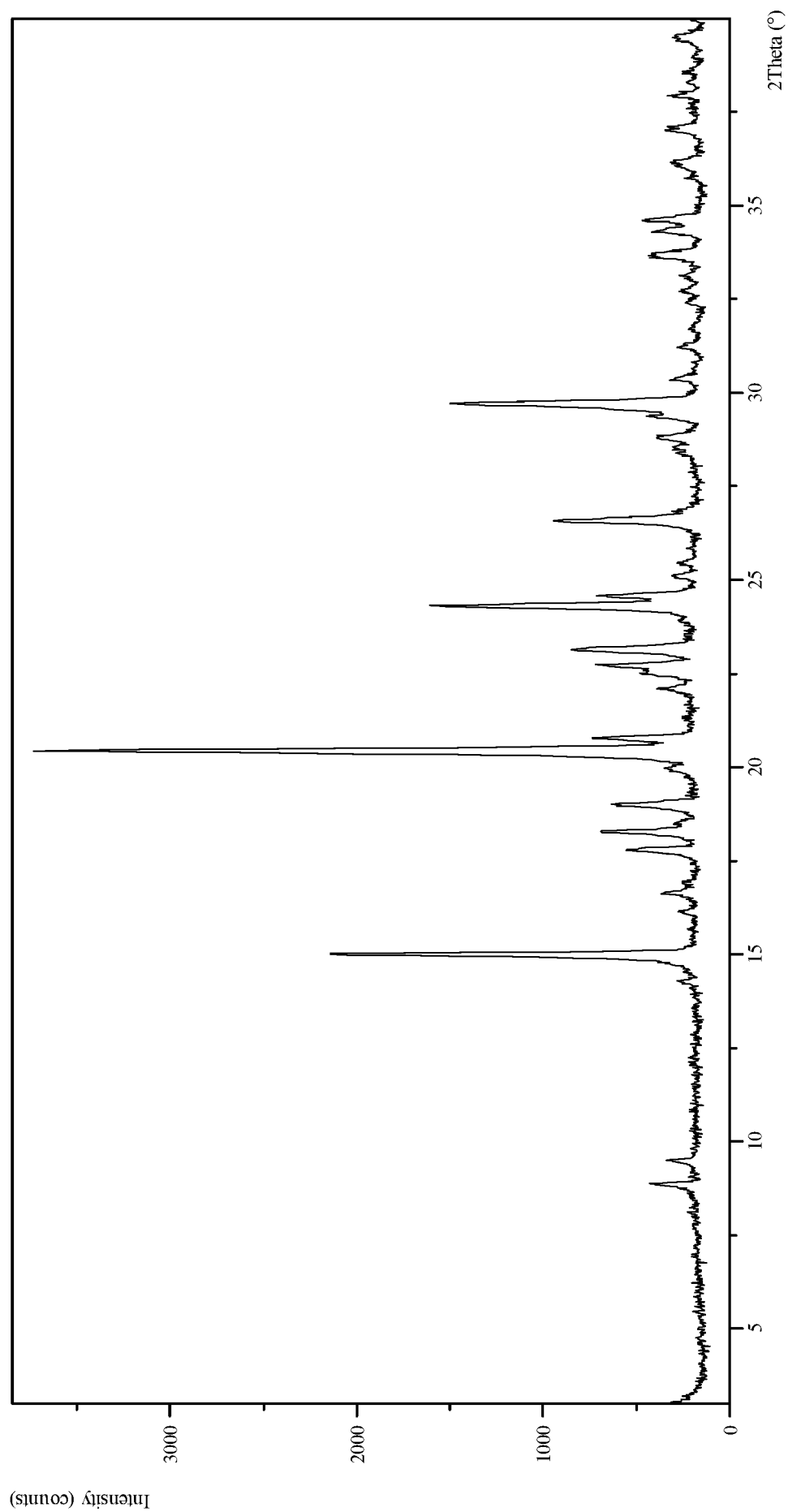


Figure 13

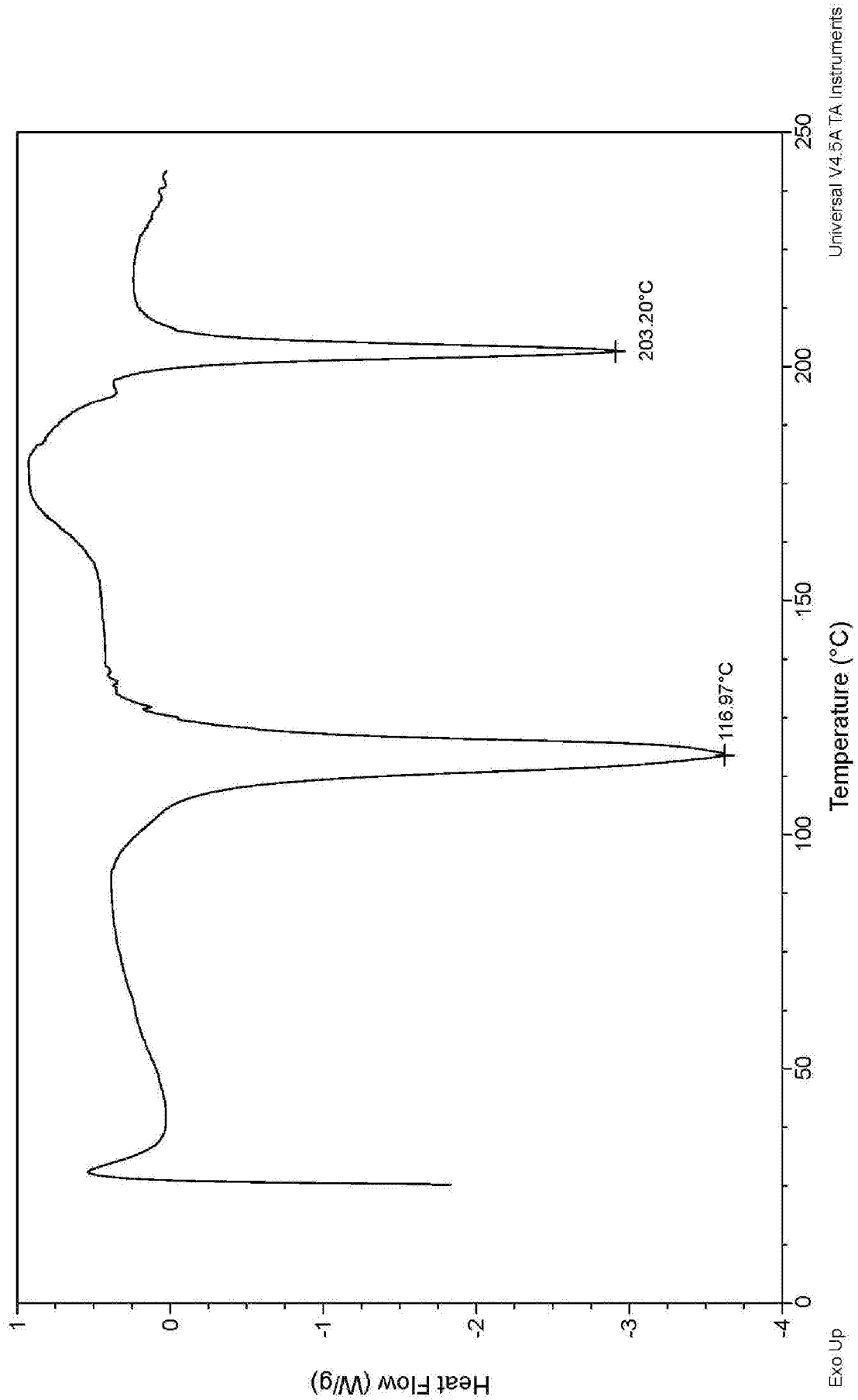


Figure 14

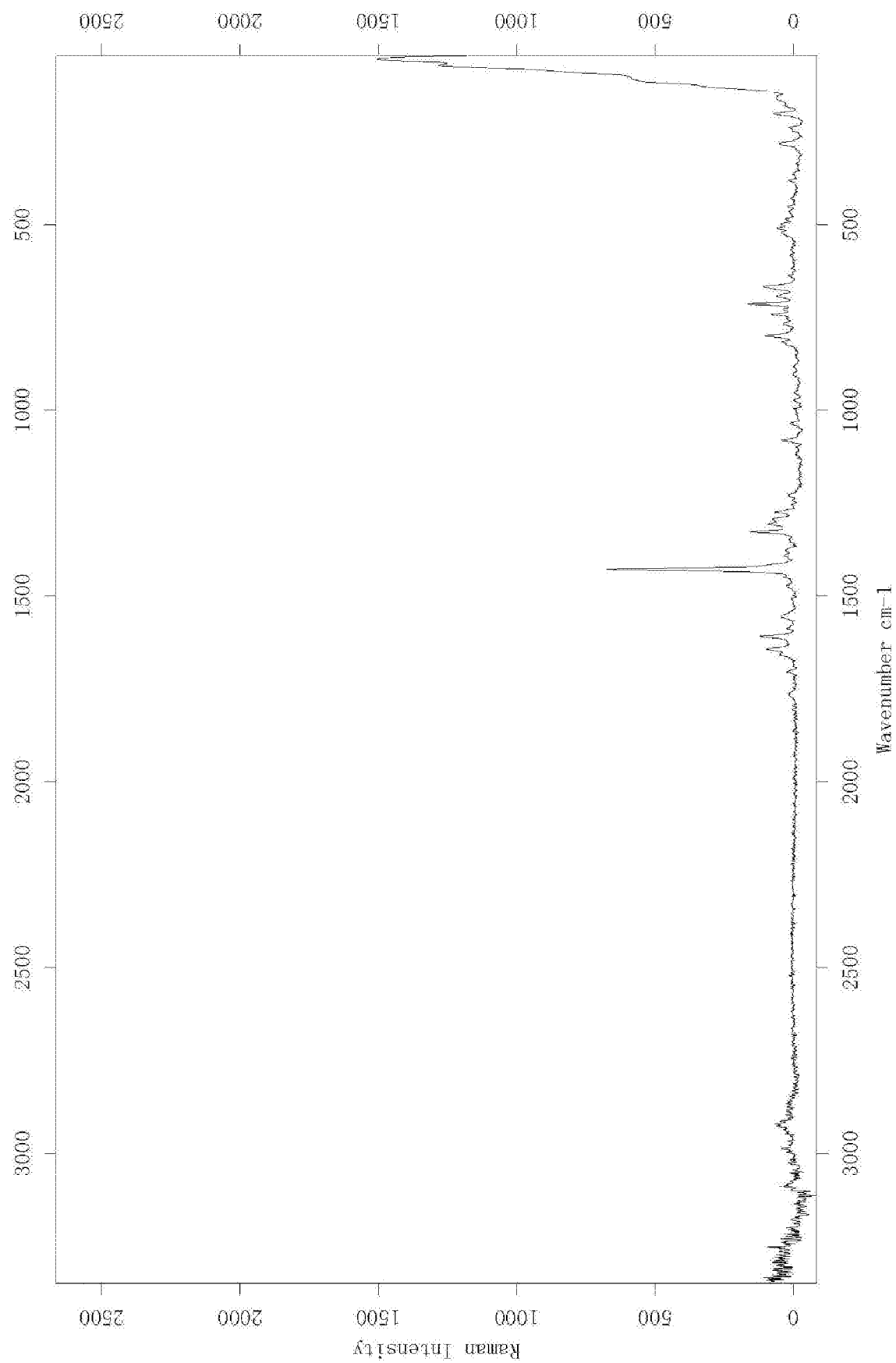


Figure 15

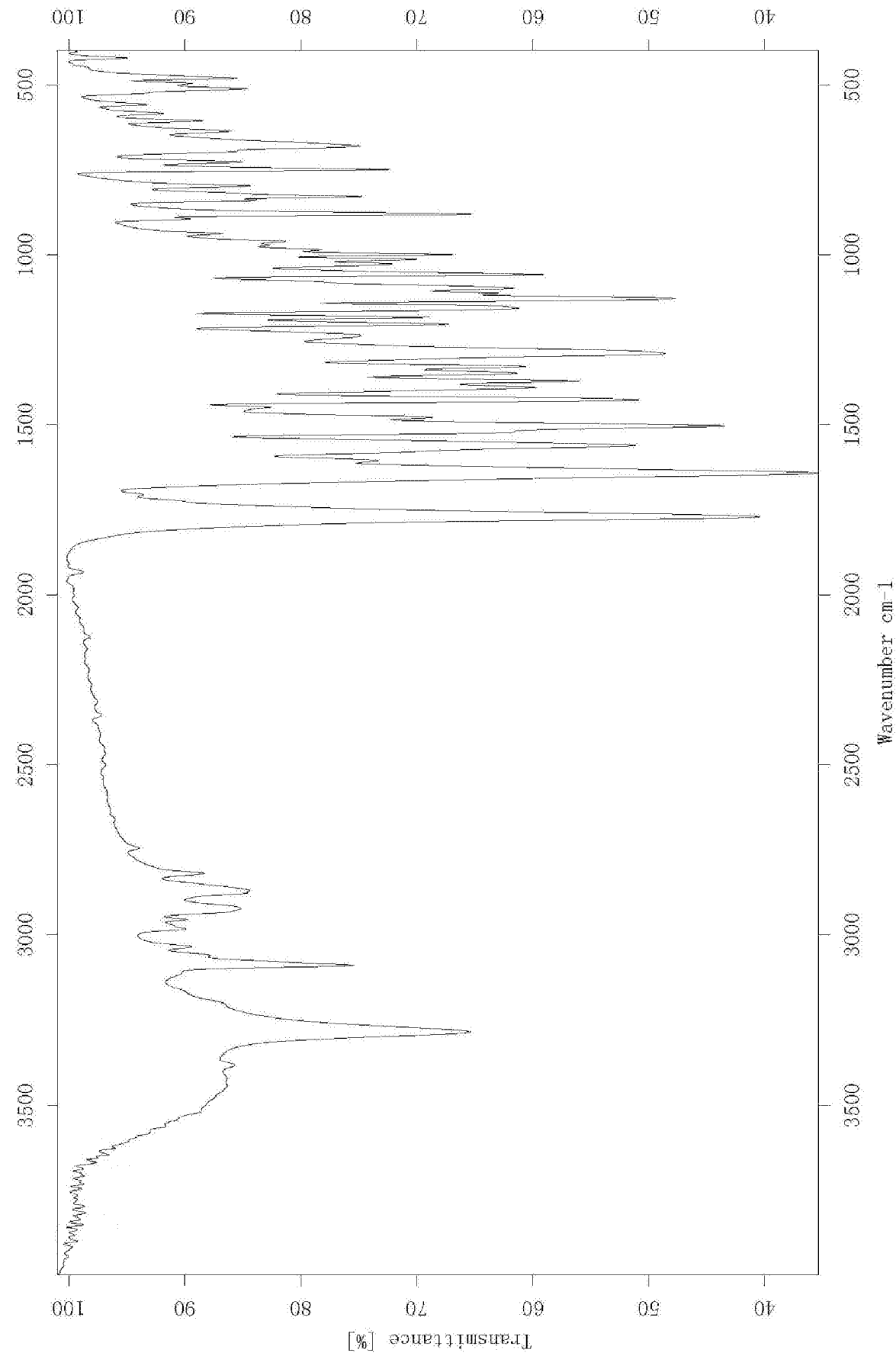


Figure 16

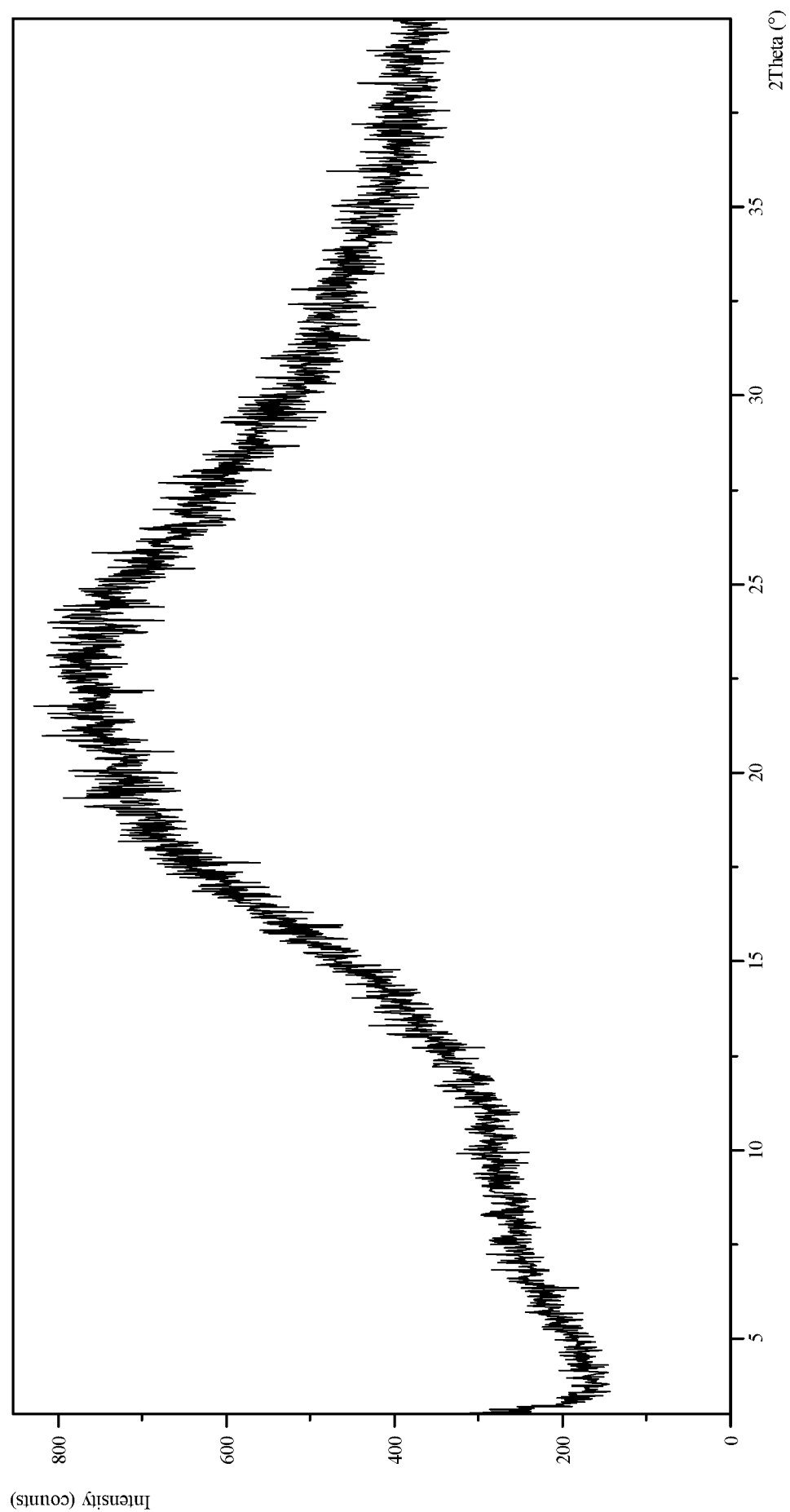


Figure 17

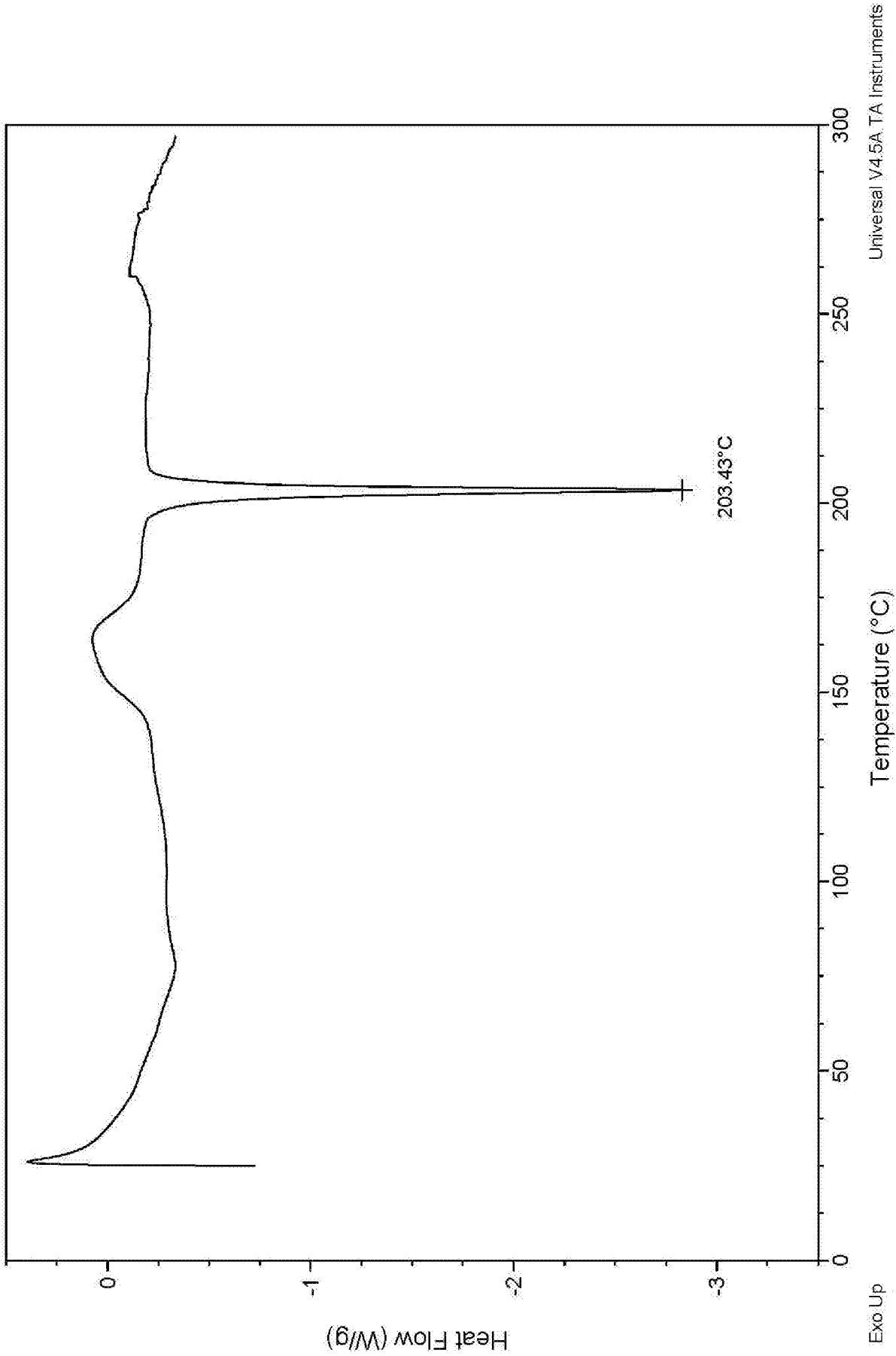


Figure 18

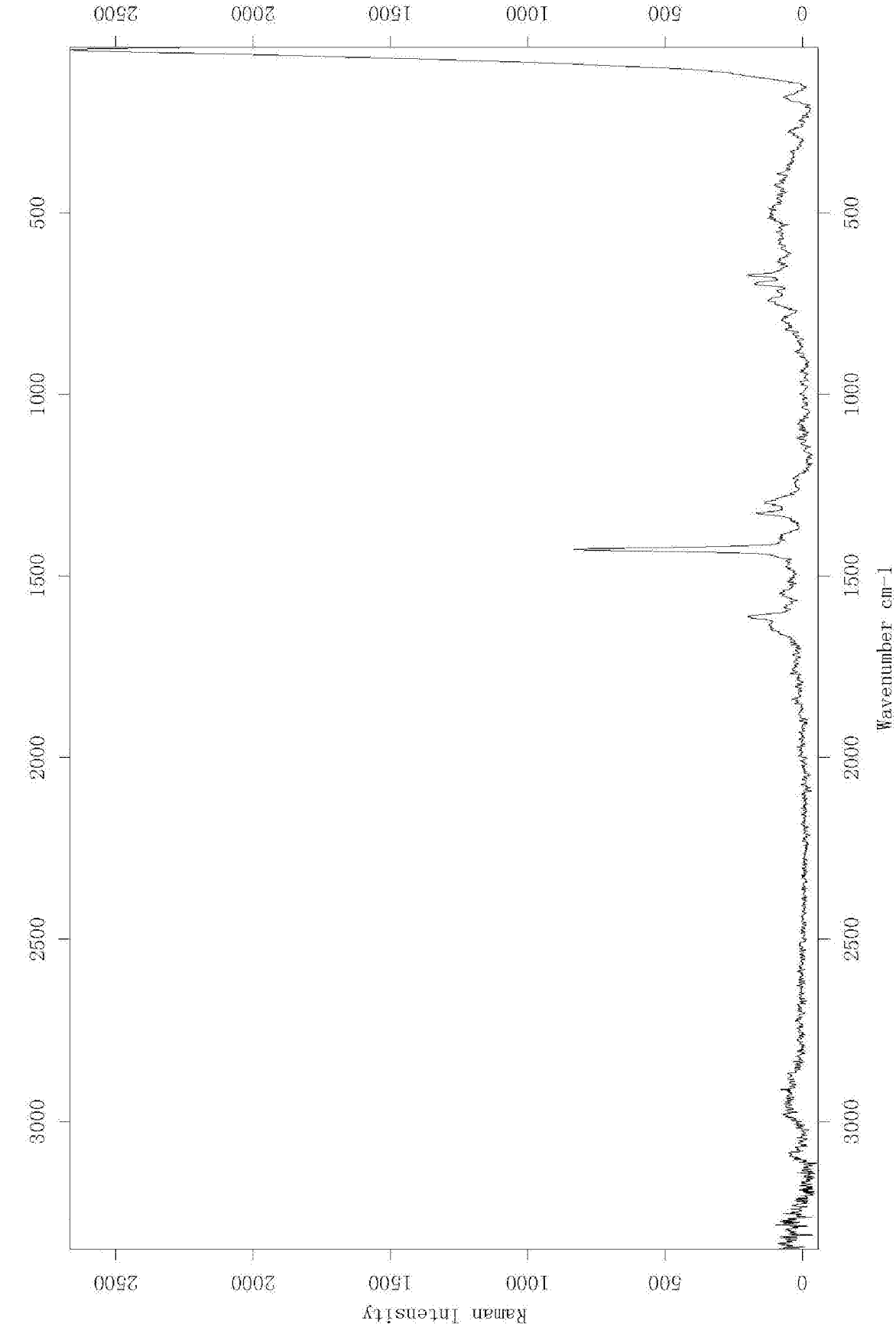


Figure 19

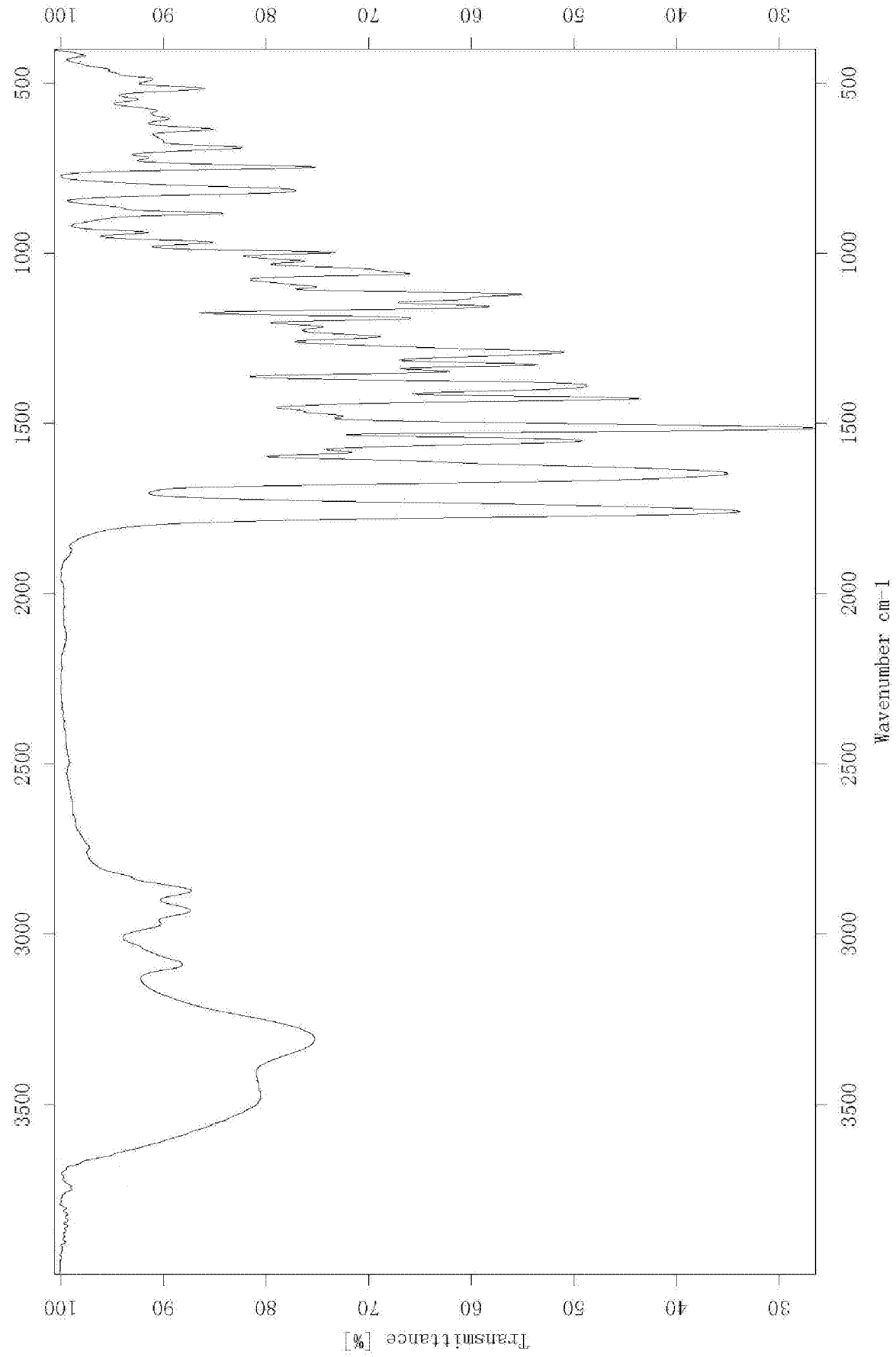


Figure 20

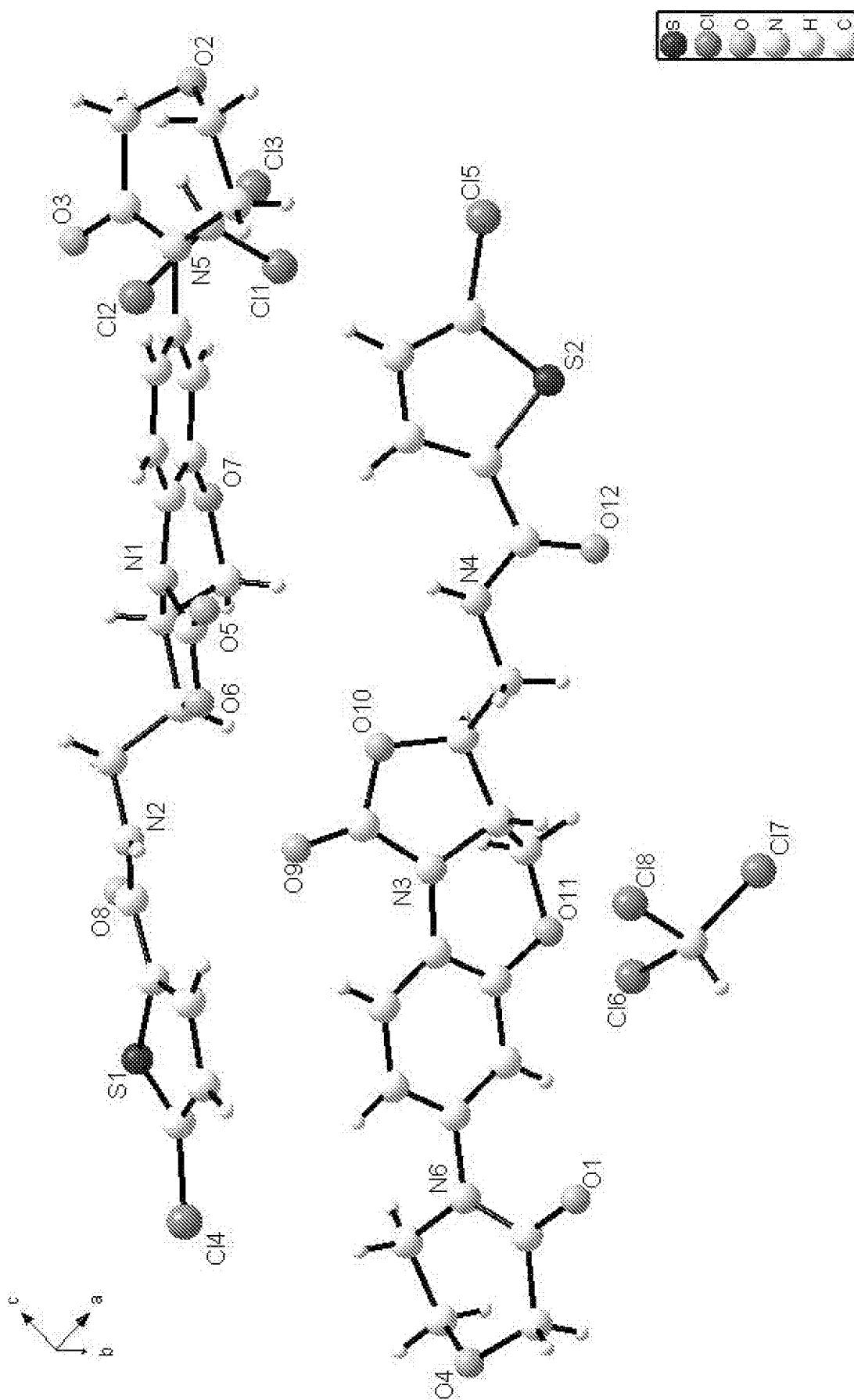


Figure 21

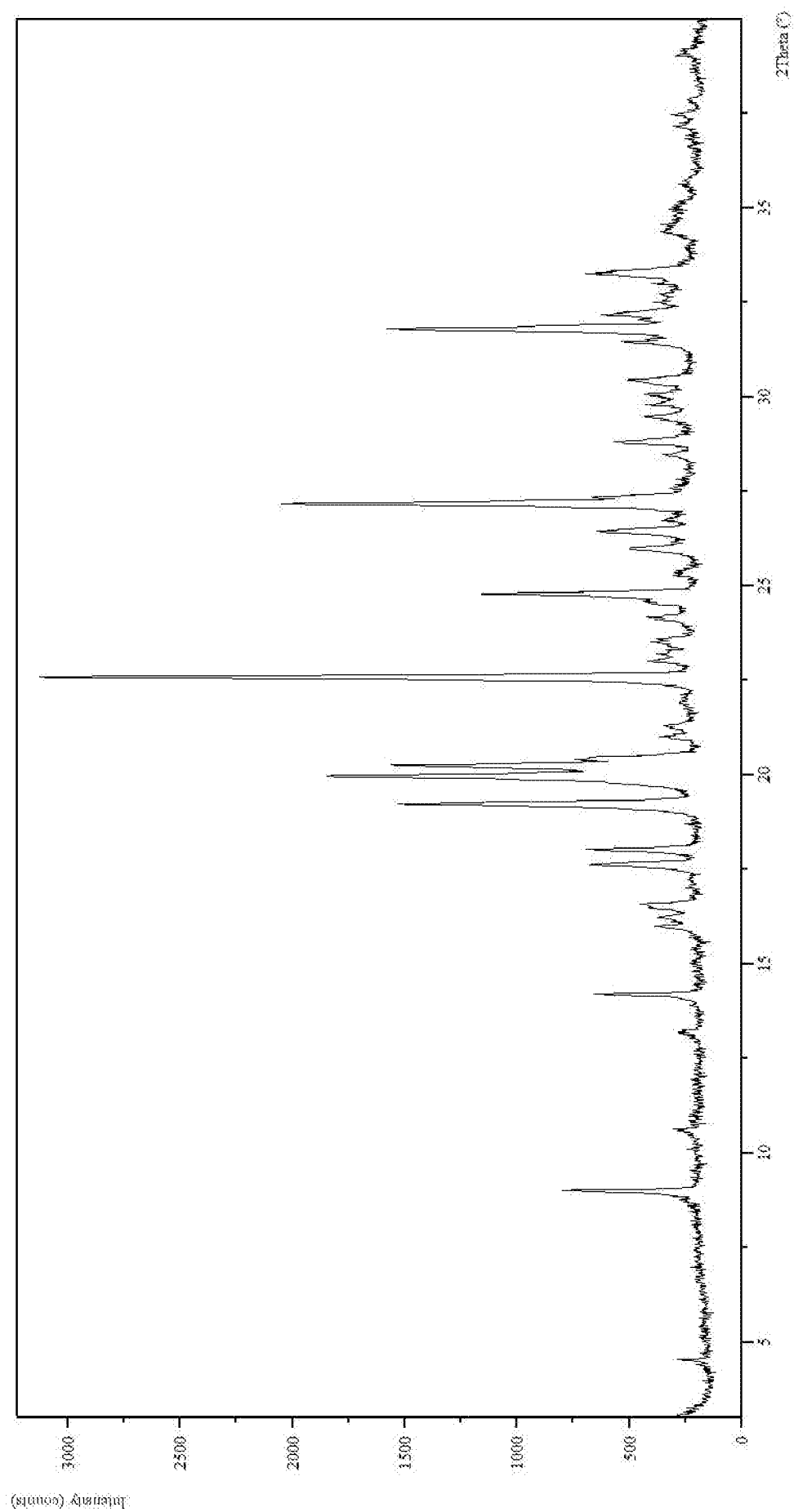


Figure 22

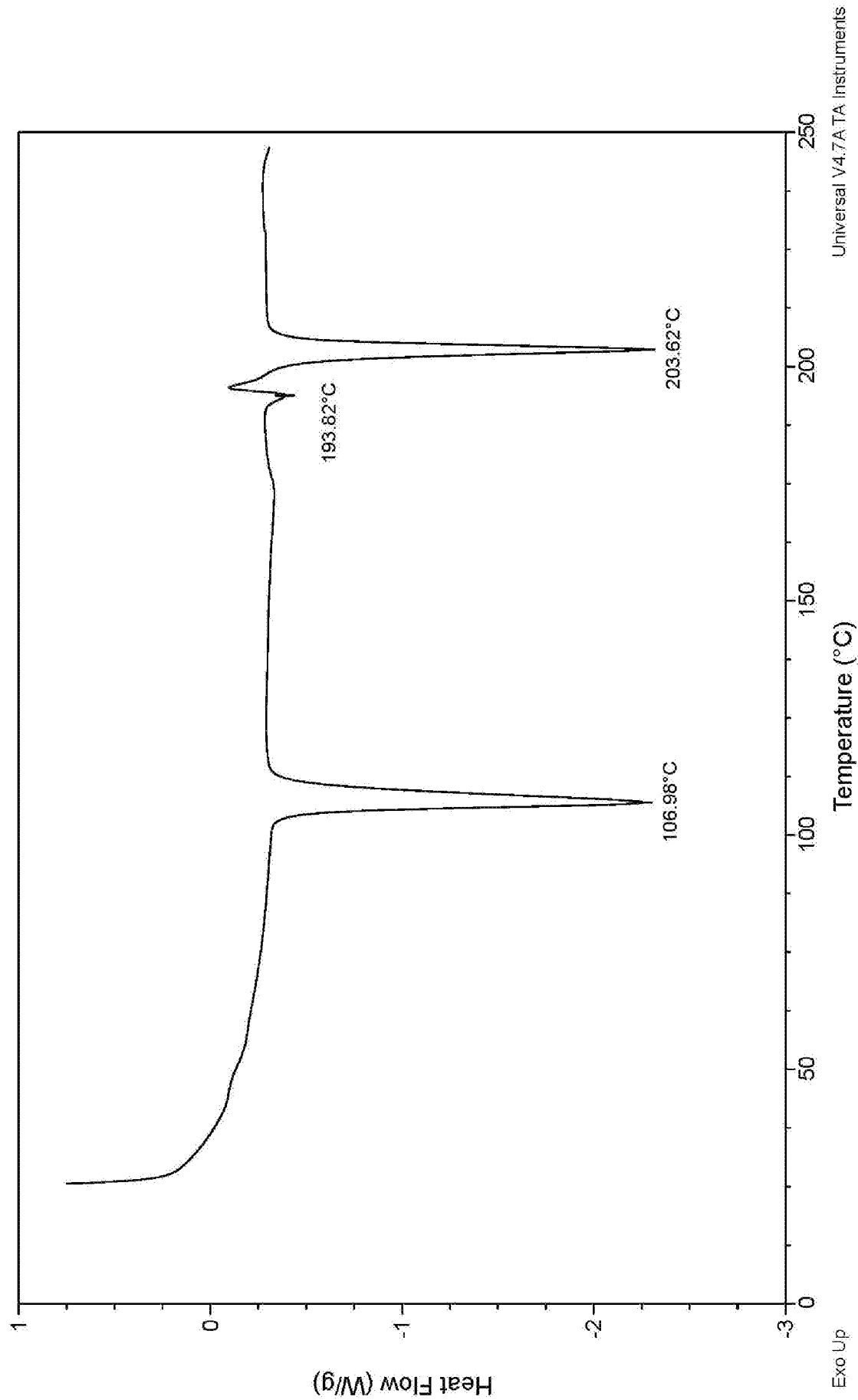


Figure 23

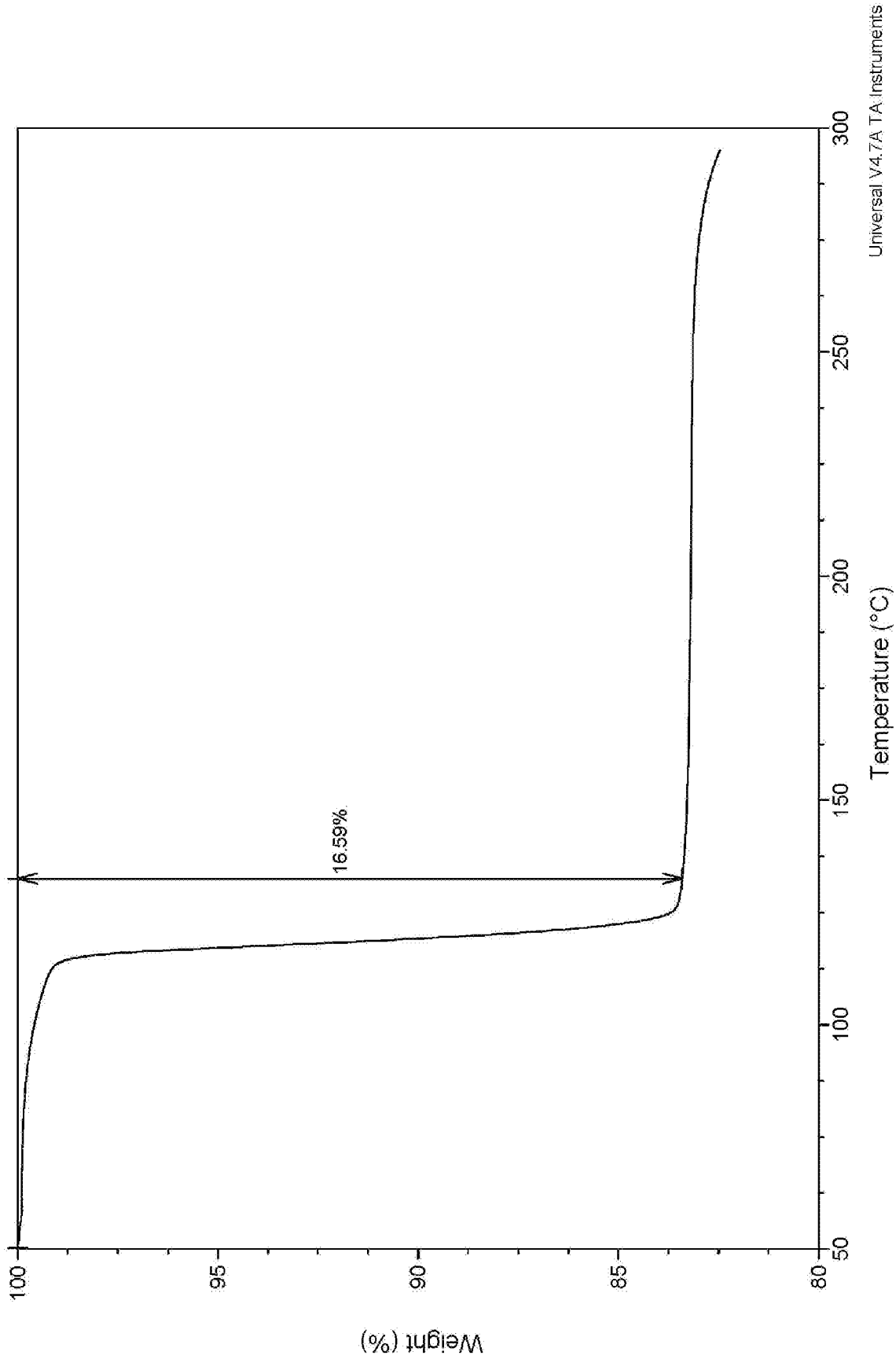


Figure 24

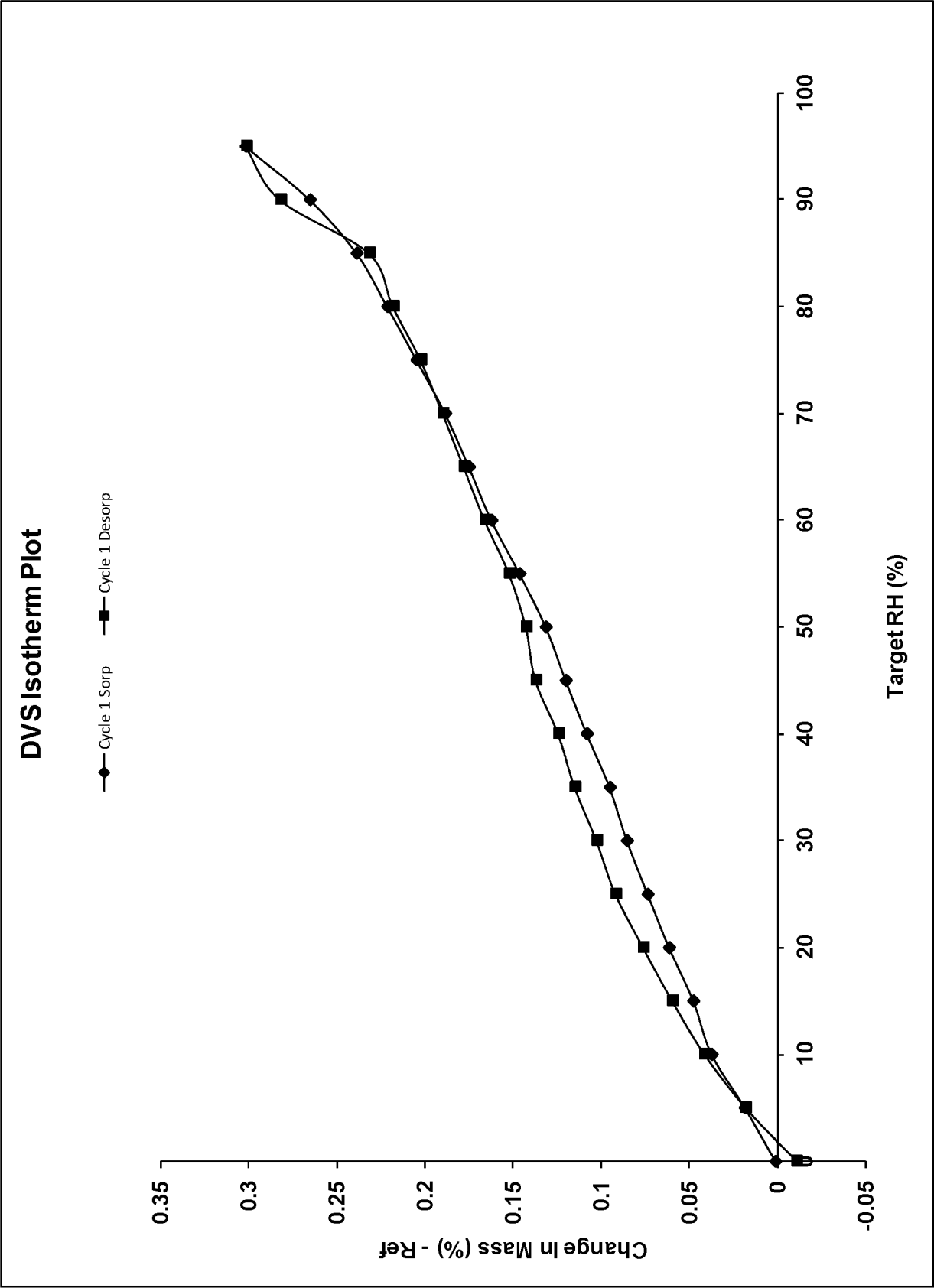


Figure 25

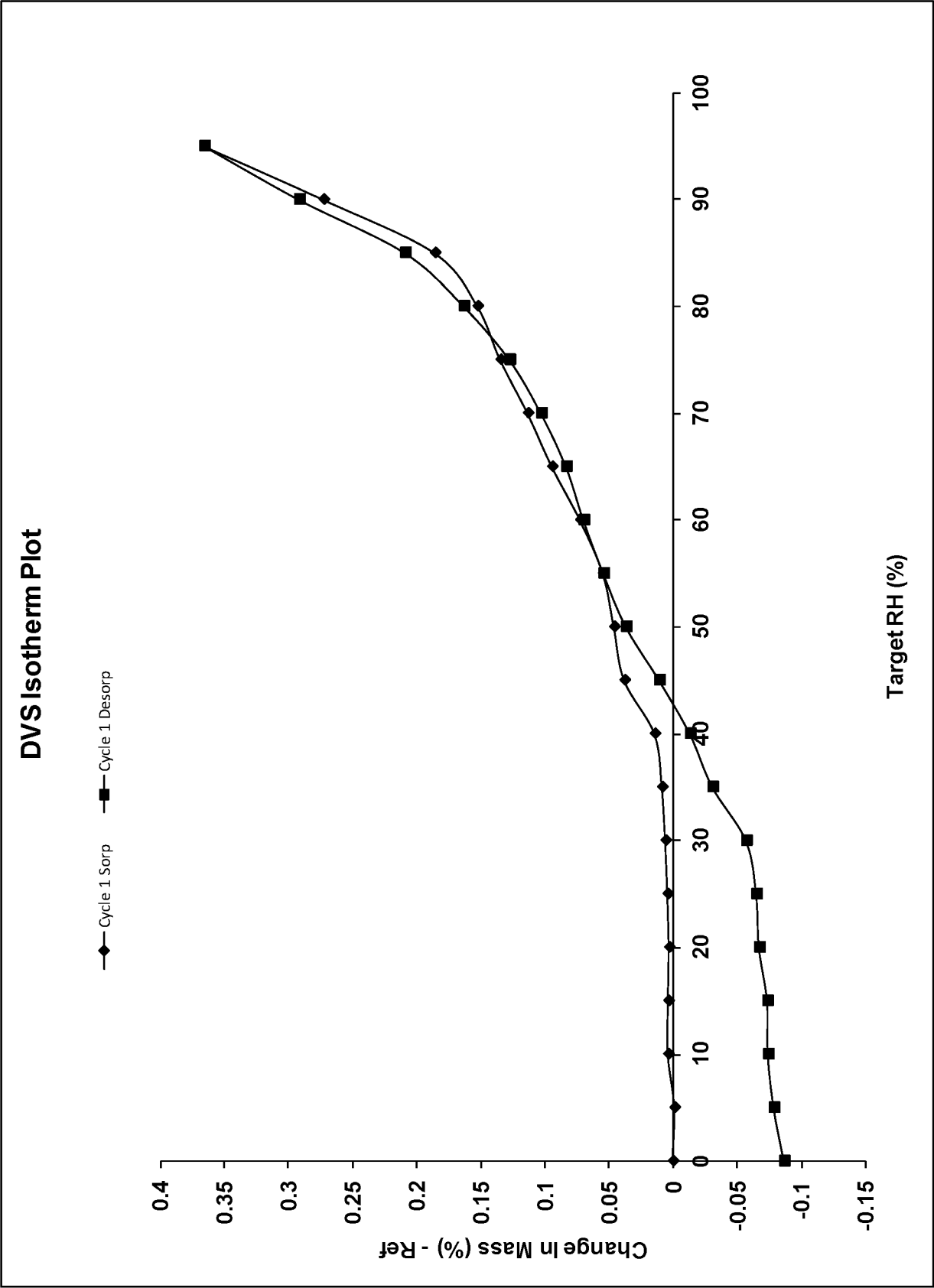


Figure 26

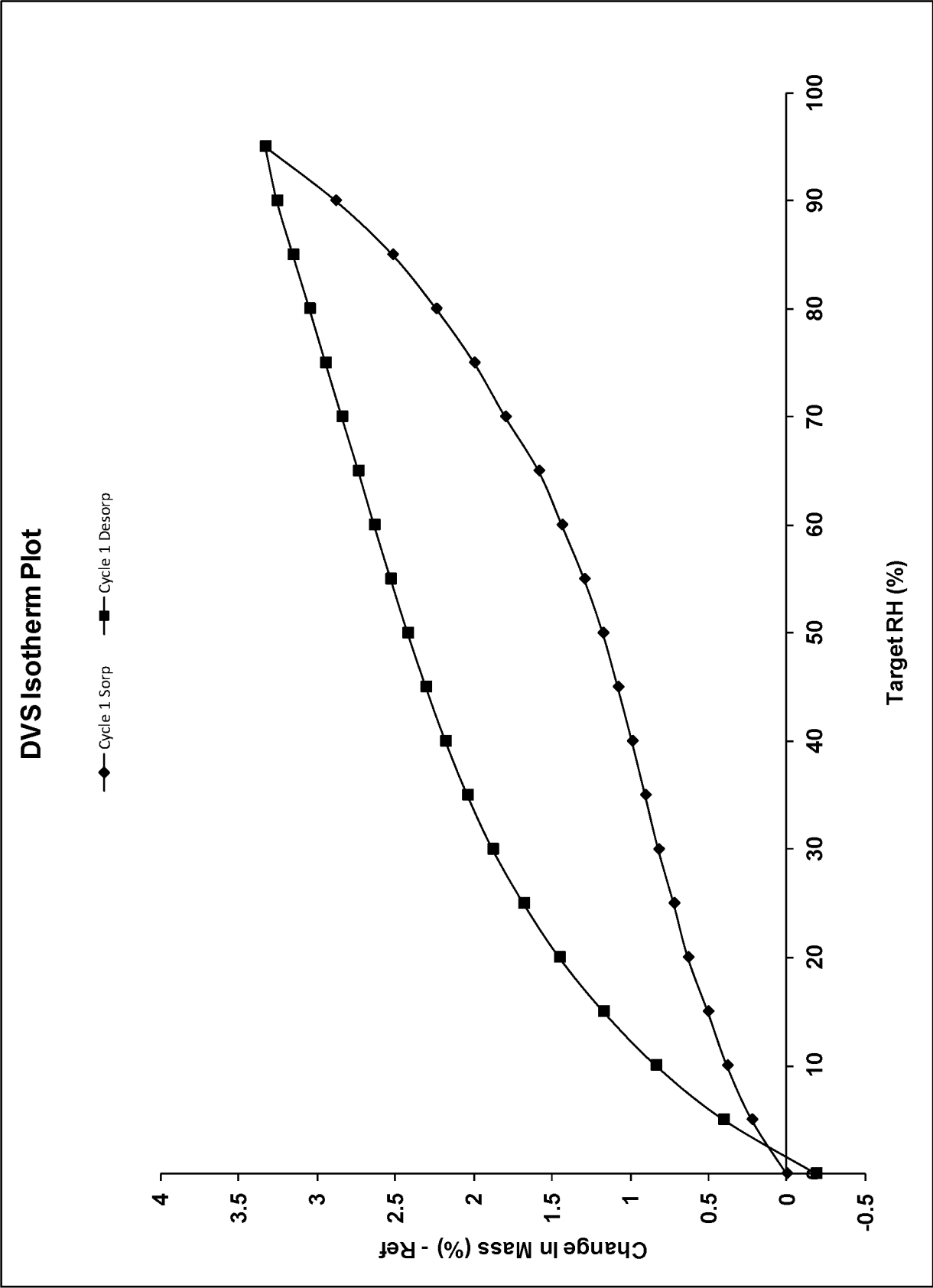


Figure 27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/079522

A. CLASSIFICATION OF SUBJECT MATTER

C07D 498/04(2006.01)i; A61K 31/5383(2006.01)n; A61P 7/02(2006.01)n

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNKI,CNABS, VEN,REGISTRY,CAPLUS (STN):oxazolidinone, oxomorpholino, tetrahydrobenzo,oxazolo,oxazin, thiophene, carboxamide, C20H18CIN3O6S, crystalline, amorphism, thromboembolism, blood coagulation factor Xa, 1620474-28-3, 1620473-89-3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 103936763 A (SHANGHAI INST MATERIA MEDICA ET AL.) 23 July 2014 (2014-07-23) claims 4 and 6-10, preparation example 1 and biological activity test paragraphs [0553]-[0595]	1-79
PX	WO 2015043364 A1 (NORTH CHINA PHARMACEUTICAL NEW DRUG R & D CO LTD) 02 April 2015 (2015-04-02) Claim 8 and example 1	1-79
PX	TAO XUE ET AL. "Design, Synthesis, and Structure-Activity and Structure-Pharmacokinetic Relationship Studies of Novel [6, 6, 5] Tricyclic Fused Oxazolidinones Leading to the Discovery of a Potent, Selective, and Orally Bioavailable FXa Inhibitor" <i>Journal of Medicinal Chemistry</i> , Vol. vol.57, No. no.08, 02 September 2014 (2014-09-02), page 7770-7791	1-79
A	WO 2007039132 A1 (BAYER HEALTHCARE AG) 12 April 2007 (2007-04-12) the whole document	1-79

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 August 2015

Date of mailing of the international search report

26 August 2015

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088, China

Facsimile No. (86-10)62019451

Authorized officer

ZHOU, Yu

Telephone No. (86-10)62086359

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/079522

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **80-82**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] Claims 80-82 are directed to methods for the treatment of the human by therapy. Thus, claims 80-82 are not required to be searched by this Authority. (Rule 39.1(iv) PCT)
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2015/079522

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	103936763	A	23 July 2014	WO	2014110971	A1	24 July 2014
WO	2015043364	A1	02 April 2015	None			
WO	2007039132	A1	12 April 2007	PT	1934208	E	01 June 2011
				US	8188270	B2	29 May 2012
				CA	2823159	A1	12 April 2007
				RU	2011115874	A	27 October 2012
				CA	2624310	C	07 January 2014
				KR	101364400	B1	17 February 2014
				SV	2009002858	A	28 July 2009
				DK	1934208	T3	18 July 2011
				AU	2006299126	B2	28 June 2012
				JP	2009510140	A	12 March 2009
				EP	1934208	B1	23 March 2011
				MY	145616	A	15 March 2012
				SG	166126	A1	29 November 2010
				IL	190204	A	31 August 2014
				RU	2429236	C2	20 September 2011
				NO	20082059	A	30 April 2008
				CA	2624310	A1	12 April 2007
				HK	1125103	A1	07 February 2014
				US	2010152189	A1	17 June 2010
				AU	2006299126	A1	12 April 2007
				DE	502006009169	D1	05 May 2011
				CA	2823159	C	21 October 2014
				BR	PI0616801	A2	28 June 2011
				EP	1934208	A1	25 June 2008
				EC	SP088341	A	30 June 2008
				NZ	567092	A	27 May 2011
				CR	9863	A	19 February 2009
				JP	5416408	B2	12 February 2014
				KR	20080050465	A	05 June 2008
				IL	190204	D0	03 November 2008
				AT	502937	T	15 April 2011
				RU	2008116834	A	10 November 2009
				CN	101282968	A	08 October 2008