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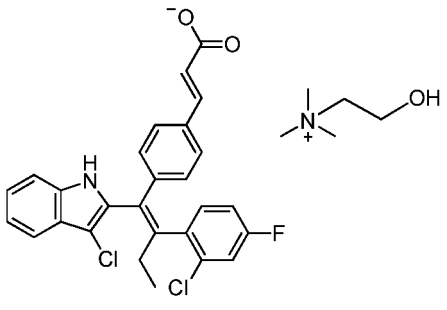
(54) **SALT FORM OF ESTROGEN RECEPTOR DOWNREGULATOR, CRYSTALLINE FORM THEREOF, AND PREPARATION METHOD THEREFOR**

(57) Provided are a salt form of an estrogen receptor down-regulator, a crystalline form thereof, and a preparation method therefor.



(I)

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Description

[0001] This application claims priority to Chinese patent application CN201811434915.8 filed on November 28, 2018. The contents of which are incorporated herein by its entirety.

Technical Field

[0002] The present disclosure relates to salt forms of estrogen receptor down-regulator, crystalline forms thereof, and processes of preparation therefor, and the use of the salt and crystal forms in the preparation of a drug for treating breast cancer.

Background arts

[0003] According to the statistics of WHO, breast cancer has become the second most prevalent cancer in the world and has the highest incidence among women. After years of research, the role of the estrogen-estrogen receptor signaling pathway in breast cancer development has already been identified; and the estrogen receptor (ER) has also been developed into the most important biomarker for breast cancer. Taking estrogen receptor expression as a discriminative index, breast cancer can be divided into estrogen receptor-positive breast cancer and estrogen receptor-negative breast cancer; wherein estrogen receptor-positive breast cancer accounts for more than 70% of the total number of breast cancer patients.

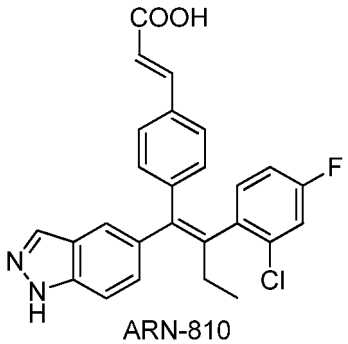
[0004] Endocrine Therapy (ET) targeting the estrogen-estrogen receptor signaling pathway in breast cancer cells has become the first choice for treating estrogen receptor-positive breast cancer because of its minimal harm and significant effect. Endocrine therapy mainly includes the following three treatment methods: ovarian suppression therapy, aromatase inhibitor (AI), and selective estrogen receptor modulator (SERM). Due to its unsatisfactory efficacy and low patient satisfaction, the ovarian suppression therapy is less commonly used than the other two treatment methods. Early aromatase inhibitors (first and second generation) had low target selectivity and large toxic and side effects. After many years of research, the third-generation aromatase inhibitors have been widely used since their selectivity has been greatly improved, which solved the problem of the early aromatase inhibitors. Among them, letrozole and the like have been used as first-line drugs for the treatment of estrogen receptor-positive breast cancer. Selective estrogen receptor modulators (SERMs) directly act on estrogen receptors to block this signaling pathway, which has a significant effect and a long history of application. Among them, tamoxifen is the most representative selective estrogen receptor modulator. As a first-line drug recommended for priority use, tamoxifen has shown significant clinical efficacy in the prevention and treatment of estrogen receptor-positive breast cancer.

[0005] Although the aromatase inhibitor letrozole and the selective estrogen receptor modulator tamoxifen have shown good efficacy in the treatment of estrogen receptor-positive breast cancer, with the application of the two types of drugs, the drug resistance problem of estrogen receptor-positive breast cancer to aromatase inhibitors and selective estrogen receptor modulators has also become increasingly prominent. A large amount of studies has shown that the resistance mechanisms of breast cancer to these two hormone therapies are not exactly the same. For aromatase inhibitors, the estrogen receptor can be mutated accordingly. The mutated estrogen receptor can maintain an excited conformation in the absence of estrogen, allowing it to continue to perform the receptor function to promote breast cancer cell proliferation. The resistance mechanism of breast cancer cells to the selective estrogen receptor modulator tamoxifen is complex and diverse. First, breast cancer cells can compensate for the loss of function of estrogen receptor activation functional domain-2 (AF-2) caused by tamoxifen through activating the function of estrogen receptor activation functional domain-1 (AF-1). At the same time, breast cancer cells can adjust the structure or concentration of the estrogen receptor co-activator to adapt to the conformation of the estrogen receptor bound to tamoxifen, resulting in the recovery of the function of the estrogen receptor, thereby producing drug resistance.

[0006] Selective estrogen receptor down-regulator (SERD) has shown its unique superiority in the treatment of breast cancer resistant to the above two hormone therapies. Mechanistically, selective estrogen receptor down-regulators antagonize the function of estrogen receptor, which can greatly accelerate the ubiquitination degradation of estrogen receptors in breast cancer cells (normal or mutated) and completely block estrogen/estrogen receptor signaling pathway, thereby achieving the purpose of inhibiting the growth and proliferation of normal or drug-resistant breast cancer cells. Studies have shown that selective estrogen receptor down-regulators can effectively inhibit the proliferation of hormone-resistant breast cancer cells. Fulvestrant, which is the only commercially available selective estrogen receptor down-regulator, has shown good effects in the treatment of hormone-resistant breast cancer, confirming the unique advantages of selective estrogen receptor down-regulators. However, fulvestrant itself has many problems. First, because of its poor PK properties, fulvestrant shows zero oral bioavailability; meanwhile, fulvestrant has a higher blood clearance. For these two reasons, this drug can only be administered by intramuscular injection. However, due to its strong lipophilic structure, fulvestrant administered by intramuscular injection also has serious problems in terms of tissue distribution. Therefore,

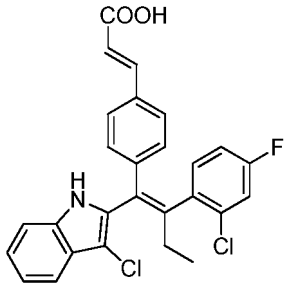
the development of selective estrogen receptor down-regulators with oral bioavailability is an urgent medical requirement.

[0007] WO2012037411A2 reported an oral selective estrogen receptor down-regulator ARN-810, and a phase II clinical trial of this molecule in the treatment of ER-positive breast cancer is ongoing. According to reports [J.Med.Chem.2015,58 (12), 4888-4904], the important pharmacophore of the molecule is the indazole structure on the left side of the molecule, and the nitrogen atoms in the indazole structure bind to the estrogen receptor as a hydrogen bond acceptor.



ARN-810

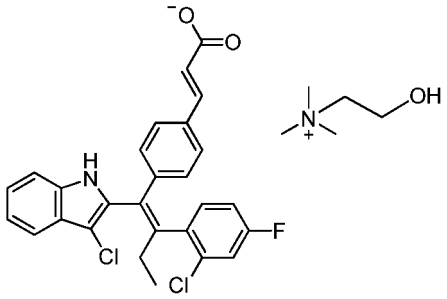
[0008] WO2017162206A1 reports a series of orally selective estrogen receptor down-regulation, including the preparation and biological activity of compound 1-8 (Example 8 in WO2017162206A1):



I-8

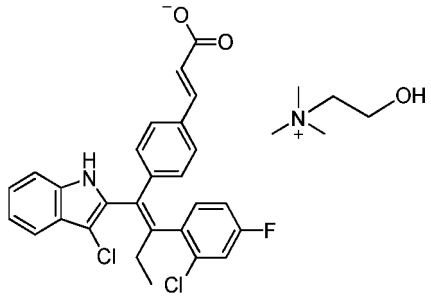
Content of the present invention

[0009] The present invention provides a compound of formula (I),



(I)

[0010] The present invention also provides a crystal form A of the compound of formula (I), wherein the X-ray powder diffraction pattern under Cu-Kα radiation has characteristic diffraction peaks at the following 2θ angles: 5.52± 0.2°, 13.68± 0.2°, 19.98± 0.2°, 20.80± 0.2°, 22.02± 0.2°, 22.44± 0.2°, 24.94± 0.2° and 26.96± 0.2°,



(I)

[0011] In some embodiments of the present invention, the crystal form A, has nine or more than nine, ten or more than ten, or eleven or more than eleven characteristic diffraction peaks in the X-ray powder diffraction pattern under Cu-Kα radiation at the 2θ angles selected from the group consisting of 5.52±0.2°, 13.68±0.2°, 18.86±0.2°, 19.98±0.2°, 20.80±0.2°, 21.62±0.2°, 22.02±0.2°, 22.44±0.2°, 23.34±0.2°, 24.94±0.2°, 26.96±0.2° and 28.42±0.2°.

[0012] In some embodiments of the present invention, the X-ray powder diffraction pattern of the crystal form A under Cu-Kα radiation is shown in FIG. 1.

[0013] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form A is shown in Table 1.

Table 1. Analysis data of the XRPD pattern of the crystal form A of the compound of formula (I)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.519	16.0002	891	84.0	21	23.341	3.808	377	35.5
2	10.023	8.8181	138	13.0	22	24.939	3.5676	413	38.9
3	10.483	8.4319	169	15.9	23	25.957	3.4298	156	14.7
4	10.962	8.0646	306	28.8	24	26.96	3.3045	755	71.1
5	11.739	7.5328	259	24.4	25	27.561	3.2338	322	30.3
6	12.419	7.1213	283	26.6	26	28.038	3.1798	202	19.0
7	13.68	6.468	581	54.7	27	28.419	3.138	409	38.5
8	15.401	5.7486	208	19.6	28	29.454	3.0301	63	5.9
9	16.239	5.4539	114	10.8	29	29.863	2.9895	98	9.2
10	16.973	5.2196	165	15.5	30	30.459	2.9324	129	12.2
11	17.579	5.041	113	10.6	31	31.062	2.8769	123	11.5
12	18.241	4.8596	194	18.3	32	31.638	2.8258	47	4.4
13	18.859	4.7018	374	35.2	33	32.499	2.7528	186	17.5
14	19.181	4.6234	201	18.9	34	33.841	2.6467	88	8.3
15	19.979	4.4405	573	54.0	35	34.643	2.5872	36	3.4
16	20.482	4.3327	598	56.4	36	35.035	2.5591	47	4.4
17	20.802	4.2667	605	57.0	37	36.013	2.4918	42	3.4
18	21.618	4.1075	373	35.1	38	37.44	2.4001	69	4.0
19	22.019	4.0335	655	61.7	39	38.058	2.3625	93	6.5
20	22.437	3.9593	1061	100.0					

[0014] In some embodiments of the present invention, the differential scanning calorimetric curve of the crystal form A has an endothermic peak at 239.46°C±3°C.

[0015] In some embodiments of the present invention, the differential scanning calorimetric curve pattern of the crystal form A is shown in FIG. 2.

[0016] The present invention also provides a crystal form B of the compound of formula (I), wherein the X-ray powder diffraction pattern under Cu-Kα radiation has characteristic diffraction peaks at the following 2θ angles: 5.68 ± 0.2°, 12.36 ± 0.2°, 19.24 ± 0.2°, 19.86 ± 0.2°, 20.62 ± 0.2°, 21.64 ± 0.2°, 22.68 ± 0.2° and 24.96 ± 0.2°.

[0017] In some embodiments of the present invention, the crystal form B has nine or more than nine, ten or more than ten, or eleven or more than eleven characteristic diffraction peaks in the X-ray powder diffraction pattern under Cu-Kα radiation at the 2θ angle selected from the group consisting of 5.68 ± 0.2°, 12.36 ± 0.2°, 13.42 ± 0.2°, 19.24 ± 0.2°, 19.86 ± 0.2°, 20.62 ± 0.2°, 21.64 ± 0.2°, 22.68 ± 0.2°, 24.96 ± 0.2°, 26.38 ± 0.2°, 27.44 ± 0.2° and 30.62± 0.2°.

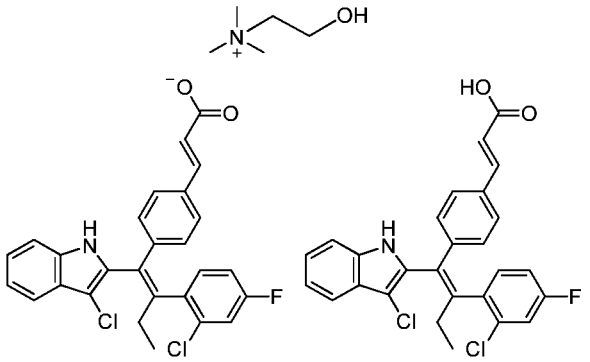
[0018] In some embodiments of the present invention, the X-ray powder diffraction pattern of the crystal form B under Cu-Kα radiation is shown in FIG. 3.

[0019] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form B is shown in Table 2.

Table 2. Analysis data of the XRPD pattern of the crystal form B of the compound of formula (I)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.677	15.5537	459	73.3	18	24.959	3.5648	397	63.4
2	9.756	9.0589	103	16.5	19	25.240	3.5257	222	35.4
3	11.315	7.8134	53	8.5	20	26.378	3.3760	278	44.4
4	12.363	7.1538	352	56.2	21	27.059	3.2926	66	10.6
5	13.420	6.5923	315	50.4	22	27.438	3.2480	249	39.8
6	14.798	5.9815	68	10.9	23	28.098	3.1732	79	12.6
7	15.406	5.7470	41	6.6	24	28.482	3.1313	93	14.9
8	16.481	5.3744	62	9.9	25	29.483	3.0272	66	10.6
9	17.281	5.1273	128	20.5	26	30.002	2.9760	127	20.3
10	17.721	5.0009	146	23.3	27	30.622	2.9171	267	42.6
11	18.898	4.6920	253	40.5	28	31.080	2.8752	219	34.9
12	19.239	4.6096	432	68.9	29	33.402	2.6804	41	6.6
13	19.860	4.4668	481	76.7	30	34.198	2.6199	51	8.1
14	20.619	4.3041	422	67.3	31	34.985	2.5627	79	12.7
15	21.641	4.1032	626	100.0	32	38.698	2.3249	49	7.8
16	22.681	3.9173	390	62.2	33	39.020	2.3065	67	10.6
17	23.258	3.8213	98	15.6	/	/	/	/	/

[0020] The present invention also provides a compound of formula (II),



(II)

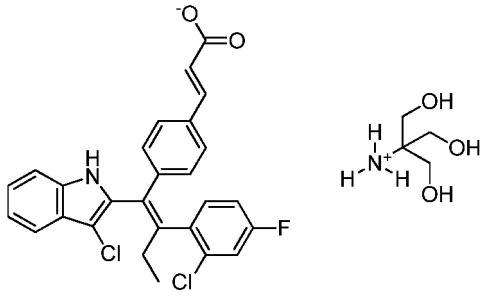
[0021] The present invention also provides a crystal form C of the compound of formula (II), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 4.

[0022] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form C is shown in Table 3.

Table 3. Analysis data of the XRPD pattern of the crystal form C of the compound of formula (II)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	6.476	13.6374	325	34.6	20	24.980	3.5618	217	23.1
2	11.021	8.0219	518	55.1	21	25.460	3.4957	154	16.4
3	11.777	7.5081	100	10.6	22	26.022	3.4215	290	30.8
4	12.106	7.3051	42	4.5	23	26.361	3.3782	465	49.4
5	12.920	6.8463	138	14.7	24	27.156	3.2811	558	59.4
6	13.997	6.3222	508	54.1	25	27.962	3.1883	174	18.5
7	15.427	5.7389	92	9.8	26	28.222	3.1596	369	39.2
8	15.797	5.6054	222	23.7	27	28.619	3.1166	244	26.0
9	16.557	5.3497	149	15.9	28	30.803	2.9004	304	32.4
10	17.282	5.1271	237	25.2	29	31.120	2.8716	247	26.3
11	17.561	5.0460	285	30.3	30	31.759	2.8153	139	14.8
12	18.238	4.8605	123	13.1	31	32.080	2.7878	132	14.0
13	18.721	4.7362	596	63.4	32	33.422	2.6789	144	15.3
14	19.579	4.5305	786	83.6	33	33.880	2.6437	71	7.6
15	20.361	4.3581	586	62.3	34	34.858	2.5718	59	6.3
16	21.221	4.1833	298	31.7	35	35.800	2.5062	53	5.6
17	22.138	4.0121	940	100.0	36	36.804	2.4401	46	4.9
18	24.018	3.7021	763	81.2	37	38.760	2.3213	54	5.7
19	24.334	3.6547	190	20.2	/	/	/	/	/

[0023] The present invention also provides a compound of formula (III),



(III)

[0024] The present invention also provides a crystal form D of the compound of formula (III), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 5.

[0025] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form D is shown in Table 4.

Table 4. Analysis data of the XRPD pattern of the crystal form D of the compound of formula (III)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.798	15.2301	346	29.5	17	24.021	3.7017	210	17.9
2	9.7	9.1108	95	8.1	18	24.532	3.6257	239	20.4
3	10.033	8.8092	235	20.1	19	25.406	3.503	123	10.5
4	11.475	7.705	142	12.1	20	26.288	3.3873	300	25.6
5	12.265	7.2103	238	20.3	21	26.623	3.3455	539	46
6	13.271	6.6661	651	55.5	22	27.964	3.188	344	29.4
7	14.433	6.1318	120	10.2	23	28.657	3.1125	177	15.1
8	16.525	5.36	215	18.3	24	29.661	3.0094	169	14.4
9	17.866	4.9607	167	14.2	25	30.69	2.9108	93	7.9
10	18.378	4.8234	121	10.3	26	31.059	2.8771	63	5.4
11	19.149	4.6311	860	73.4	27	31.491	2.8385	71	6.1
12	19.901	4.4578	88	7.5	28	32.009	2.7938	223	19
13	20.396	4.3505	1082	92.3	29	33.249	2.6923	160	13.7
14	20.845	4.258	355	30.3	30	33.604	2.6647	99	8.4
15	21.416	4.1456	501	42.7	31	38.144	2.3574	91	7.8
16	22.797	3.8975	1172	100	32	38.632	2.3287	58	4.9

[0026] The present invention also provides a crystal form E of the compound of formula (III), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 6.

[0027] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form E is shown in Table 5.

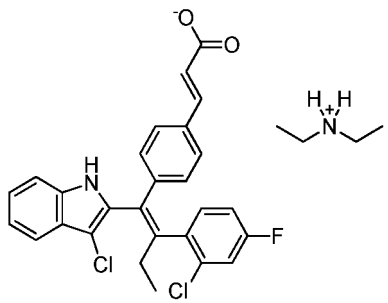
Table 5. Analysis data of the XRPD pattern of the crystal form E of the compound of formula (III)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	4.896	18.0349	88	7.9	13	21.375	4.1535	232	28.9

(continued)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
2	9.679	9.1306	69	6.2	14	22.602	3.9307	199	17.8
3	10.373	8.5209	337	30.2	15	23.631	3.7619	112	10
4	11.788	7.5012	72	6.5	16	24.04	3.6987	205	18.4
5	12.54	7.0531	122	10.9	17	25.064	3.5499	195	17.5
6	13.324	6.6395	84	7.5	18	26.011	3.4228	135	12.1
7	14.377	6.1558	431	38.6	19	28.122	3.1705	153	13.7
8	15.717	5.6338	521	46.7	20	28.458	3.1338	304	27.2
9	17.22	5.1453	154	13.8	21	30.074	2.969	125	11.2
10	17.967	4.9329	76	6.8	22	30.763	2.9041	70	6.3
11	19.326	4.5891	206	18.5	23	31.631	2.8263	145	13
12	20.944	4.2381	1116	100	24	33.189	2.6971	90	8.1

[0028] The present invention also provides a compound of formula (IV),



(IV)

[0029] The present invention also provides a crystal form F of the compound of formula (IV),wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 7.

[0030] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form F is shown in Table 6.

Table 6. Analysis data of the XRPD pattern of the crystal form F of the compound of formula (IV)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.102	17.3079	350	39.2	16	19.801	4.48	434	48.7
2	6.9	12.8008	368	41.3	17	20.41	4.3477	269	30.2
3	7.785	11.3466	892	100	18	21.017	4.2234	146	16.4
4	10.827	8.165	376	42.2	19	22.305	3.9825	172	19.3
5	11.359	7.7833	68	7.6	20	22.852	3.8883	343	38.5
6	11.869	7.45	345	38.7	21	24.095	3.6904	178	20
7	12.461	7.0973	73	8.2	22	24.888	3.5746	138	15.5

(continued)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
8	13.23	6.6868	241	27	23	25.243	3.5251	229	25.7
9	13.606	6.5026	587	65.8	24	26.227	3.395	221	24.8
10	14.078	6.2855	710	79.6	25	26.821	3.3213	108	12.1
11	14.866	5.9543	84	9.4	26	27.334	3.26	198	22.2
12	16.664	5.3156	227	25.4	27	28.931	3.0836	97	10.9
13	17.393	5.0944	114	12.8	28	29.297	3.046	72	8.1
14	18.04	4.9132	158	17.7	29	30.841	2.8968	67	7.5
15	19.287	4.5983	236	26.5	30	34.874	2.5705	71	8

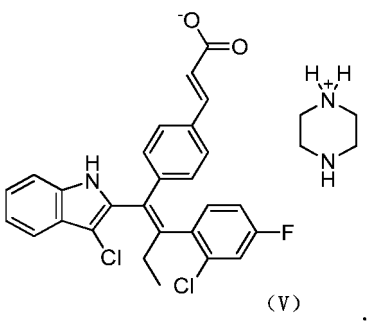
[0031] The present invention also provides a crystal form G of the compound of formula (IV),wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 8.

[0032] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form G is shown in Table 7.

Table 7. Analysis data of the XRPD pattern of the crystal form G of the compound of formula (IV)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	4.57	19.3182	195	44.5	12	19.901	4.4576	105	24
2	6.021	14.6669	161	36.8	13	21.079	4.2112	152	34.7
3	6.962	12.6869	438	100	14	22.301	3.983	142	32.4
4	7.33	12.0502	172	39.3	15	24.792	3.5883	157	35.8
5	11.055	7.9966	141	32.2	16	25.913	3.4355	95	21.7
6	12.207	7.2446	272	62.1	17	26.386	3.375	96	21.9
7	12.719	6.9543	369	84.2	18	26.861	3.3164	69	15.8
8	16.863	5.2533	101	23.1	19	28.811	3.0962	72	16.4
9	17.955	4.9363	74	16.9	20	29.684	3.0071	73	16.7
10	18.93	4.6841	156	35.6	21	31.477	2.8398	76	17.4
11	19.324	4.5894	75	17.1	22	33.411	2.6797	59	13.5

[0033] The present invention also provides a compound of formula (V),



(V)

[0034] The present invention also provides a crystal form H of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 9.

[0035] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form H is shown in Table 8.

Table 8. Analysis data of the XRPD pattern of the crystal form H of the compound of formula (V)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	6.566	13.4503	197	31.3	12	20.686	4.2904	283	44.9
2	7.69	11.4875	167	26.5	13	21.494	4.1307	206	32.7
3	10.478	8.4359	66	10.5	14	22.836	3.8911	435	69
4	11.961	7.3932	80	12.7	15	23.744	3.7441	278	44.1
5	12.599	7.02	248	39.4	16	25.105	3.5442	229	36.3
6	15.224	5.8149	491	77.9	17	26.643	3.343	230	36.5
7	16.369	5.4108	152	24.1	18	28.536	3.1254	293	46.5
8	16.879	5.2484	119	18.9	19	29.643	3.0112	69	11
9	17.551	5.0489	630	100	20	30.824	2.8984	151	24
10	18.557	4.7775	126	20	21	32.6	2.7444	56	8.9
11	19.837	4.472	106	16.8	22	34.099	2.6272	69	11

[0036] The present invention also provides a crystal form I of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 10.

[0037] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form H is shown in Table 9.

Table 9. Analysis data of the XRPD pattern of the crystal form I of the compound of formula (V)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.157	17.1214	110	26.3	11	19.939	4.4493	213	51
2	8.102	10.903	221	52.9	12	20.529	4.3228	298	71.3
3	11.155	7.9256	108	25.8	13	20.823	4.2623	151	36.1
4	11.807	7.4894	176	42.1	14	21.83	4.068	77	18.4
5	12.205	7.2456	84	20.1	15	23.073	3.8516	417	99.8
6	12.789	6.916	62	14.8	16	23.744	3.7442	78	18.7
7	14.492	6.1071	243	58.1	17	24.533	3.6255	147	35.2
8	14.945	5.923	171	40.9	18	25.816	3.4481	158	37.8
9	17.651	5.0205	418	100	19	26.265	3.3902	119	28.5
10	18.813	4.7129	237	56.7	20	27.687	3.2192	224	53.6

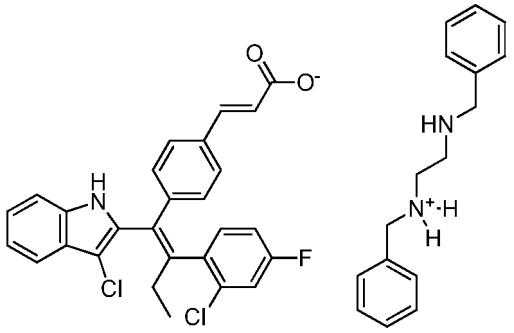
[0038] The present invention also provides a crystal form J of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 11.

[0039] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form J is shown in Table10.

Table 10. Analysis data of the XRPD pattern of the crystal form J of the compound of formula (V)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
1	5.03	17.5537	118	41.3	12	19.602	4.525	216	75.5
2	7.569	11.671	199	69.6	13	20.431	4.3432	209	73.1
3	8.005	11.0357	125	43.7	14	21.688	4.0942	73	25.5
4	11.638	7.5975	183	64	15	21.986	4.0395	96	33.6
5	13.073	6.7665	286	100	16	22.444	3.958	111	38.8
6	13.547	6.531	137	47.9	17	22.894	3.8813	146	51
7	14.375	6.1566	106	37.1	18	24.832	3.5826	76	26.6
8	14.869	5.9532	129	45.1	19	25.522	3.4873	115	40.2
9	16.464	5.3796	102	35.7	20	25.939	3.4322	120	42
10	17.825	4.9719	204	71.3	21	27.509	3.2397	88	30.8
11	19.127	4.6362	181	63.3	/	/	/	/	/

[0040] The present invention also provides a compound of formula (VI),



(VI)

[0041] The present invention also provides a crystal form K of the compound of formula (VI), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 12.

[0042] In some embodiments of the present invention, the analysis data of the XRPD pattern of the crystal form K is shown in Table 11.

Table 11. Analysis data of the XRPD pattern of the crystal form K of the compound of formula (VI)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Inte nsity	Relative intensity (%)
1	5.935	14.8801	194	19.9	17	22.975	3.8677	616	63.1
2	6.763	13.0593	126	12.9	18	23.288	3.8164	570	58.3
3	11.219	7.8806	609	62.3	19	23.922	3.7168	536	54.9
4	12.009	7.3638	196	20.1	20	24.965	3.5637	703	72
5	13.035	6.7864	218	22.3	21	26.128	3.4077	226	23.1
6	13.564	6.5229	92	9.4	22	27.705	3.2172	366	37.5

(continued)

No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)	No.	2θ Angle (°)	d-spacing (Å)	Intensity	Relative intensity (%)
7	14.627	6.0511	162	16.6	23	28.355	3.1449	128	13.1
8	15.164	5.8378	371	38	24	29.145	3.0614	374	38.3
9	16.031	5.524	977	100	25	29.8	2.9956	109	11.2
10	16.621	5.3292	244	25	26	30.482	2.9301	87	8.9
11	17.451	5.0777	433	44.3	27	30.941	2.8877	72	7.4
12	17.807	4.977	551	56.4	28	32.223	2.7757	90	9.2
13	18.671	4.7484	846	86.6	29	33.584	2.6663	103	10.5
14	20.132	4.4071	666	68.2	30	36.224	2.4778	57	5.8
15	21.039	4.2191	267	27.3	31	38.159	2.3565	57	5.8
16	22.403	3.9652	382	39.1	32	38.91	2.3127	69	7.1

[0043] The present invention also provides uses of the compounds or the crystal forms mentioned above in manufacturing a medicament for treating the breast cancer.

Technical effects

[0044] Compared with the free acid form of the compound 1-8 reported in WO2017162206A1, the solubility of the compound of formula (I) of the present invention and the crystal form thereof in water is nearly hundredfold improved; in the solubility test of biological media, the solubility of the compound of formula (I) and the crystal form thereof has also been significantly improved; in *in vivo* pharmacokinetic studies, the compound of formula (I) and the crystal form thereof exhibited superior properties, and the amount of exposure in the organism was significantly increased. These good properties of the compound of formula (I) and the crystal form thereof make it more conducive to the preparation of medicines, benefit patients, and meet clinical needs.

Definitions and explanations

[0045] Unless otherwise indicated, the following terms and phrases used herein are intended to have the following meanings. A particular term or phrase should not be considered uncertain or unclear without a special definition, but should be understood according to its ordinary meaning. When a trade name appears herein, it is intended to refer to its corresponding product or its active ingredient.

[0046] The intermediate compounds of the present invention can be prepared by a variety of synthetic methods well known to those skilled in the art, including the following specific embodiments, the embodiments formed by combining them with other chemical synthesis methods, and equivalent alternatives well known to those skilled in the art, preferred embodiments include, but are not limited to, the embodiments of the present invention.

[0047] The chemical reactions of the specific embodiments of the present invention are performed in suitable solvents, and the solvents must be suitable for the chemical changes of the present invention and the reagents and materials required for the same. In order to obtain the compounds of the present invention, it is sometimes necessary for those skilled in the art to modify or select the synthetic steps or reaction schemes based on the existing embodiments.

[0048] The present invention will be described in detail below through embodiments, which do not imply any limitation to the present invention.

[0049] All solvents used in the present invention are commercially available and can be used without further purification.

[0050] The present invention uses the following abbreviations: MW stands for microwave; r.t. stands for room temperature; aq stands for aqueous solution; DCM stands for dichloromethane; THF stands for tetrahydrofuran; DMSO stands for dimethyl sulfoxide; NMP stands for *N*-methylpyrrolidone; EtOAc stands for ethyl acetate; EtOH stands for ethanol; MeOH stands for methanol; dioxane stands for dioxane; HOAc stands for acetic acid; Boc stands for *tert*-butoxycarbonyl, Cbz stands for benzyloxycarbonyl, both of Boc and Cbz are amine protecting groups; Boc_2O stands for di-*tert*-butyl dicarbonate; DIPEA stands for ethyldiisopropylamine; TEA or Et_3N stands for triethylamine; BnNH2 stands for benzylamine; $PMBNH_2$ stands for p-methoxybenzylamine; KOAc stands for potassium acetate; NaOAc stands for

sodium acetate; Cs_2CO_3 stands for cesium carbonate; K_2CO_3 stands for potassium carbonate; $NaHCO_3$ stands for sodium bicarbonate; Na_2SO_4 stands for sodium sulfate; pyridine stands for pyridine; NaOH stands for sodium hydroxide; TEA or Et_3N stands for triethylamine; NaH stands for sodium hydrogen; LiHMDS stands for lithium bis(trimethylsilyl)amide; *i*-PrMgBr stands for isopropylmagnesium bromide; *t*-BuOK stands for potassium *t*-butoxide; *t*-BuONa stands for sodium *t*-butoxide; $Pd_2(dba)_3$ stands for tris(dibenzylideneacetone)dipalladium; $Pd(PPh_3)_4$ stands for tetrakis(triphenylphosphine)palladium; $Pd(dppf)Cl_2CH_2Cl_2$ stands for 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex; $Pd(OAc)_2$ stands for palladium acetate; $Pd(PPh_3)_2Cl_2$ stands for palladium bis(triphenylphosphine)dichloride; $Pd(PPh_3)_3Cl$ stands for stands for rhodium tris(triphenylphosphine)chloride; $Pd(OH)_2$ stands for palladium hydroxide; Xantphos stands for 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Xphos stands for 2-(dicyclohexylphosphino)-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl; BINAP stands for (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Xantphos stands for 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Xphos-Pd-G1 stands for chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-aminoethyl) phenyl]palladium(II); Xphos-PD-G_2 stands for chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-b iphenyl)]palladium(II); Xphos-Pd-G3 stands for methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl)(2'-a mino-1,1'-biphenyl-2-yl)palladium(II); I_2 stands for iodine; LiCl stands for lithium chloride; HCl stands for hydrochloric acid; maleic acid stands for maleic acid.

[0051] Compounds are named by hand or Chemdraw® software, and commercially available compounds use the supplier catalog names thereof.

X-Ray Powder Diffractometer (XRPD) method

[0052] Instrument model: Bruker D8 advance X-ray diffractometer.
[0053] Test method: about 10-20mg sample was used for XRPD detection.
[0054] X-ray Tube: Cu, Kα, (λ=1.54056 Å).
[0055] X-ray tube voltage: 40 kV, X-ray tube current: 40 mA.
[0056] Divergence slit: 0.60 mm.
[0057] Detector slit: 10.50 mm.
[0058] Anti-scattering slit: 7.10 mm.
[0059] Scanning range: 3-40 deg or 4-40 deg.
[0060] Step diameter: 0.02 deg.
[0061] Step length: 0.12 seconds.
[0062] Rotation speed of sample tray: 15 rpm.

Differential Scanning Calorimeter (DSC) method

[0063] Instrument model: TA Q2000 differential scanning calorimeter.
[0064] Test method: samples (about 1 mg) were sealed in DSC aluminum pans for testing, and heated at a heating rate of 10°C/min from room temperature to 250°C (or 280°C), at a flow rate of 50 mL/min N_2.

Thermal Gravimetric Analyzer (TGA) method

[0065] Instrument model: TA Q5000 thermal gravimetric analyzer.
[0066] Test method: samples (2 to 5 mg) were disposed in TGA platinum pans for testing. The samples were heated from room temperature to 300°C or 20% weight loss at 25 mL/min N2 with a heating rate of 10°C/min.

Brief Description of the Drawings

[0067]

Fig.1 is an XRPD pattern of the crystal form A of the compound of formula (I).

Fig. 2 is a DSC pattern of the crystal form A of the compound of formula (I).

Fig. 3 is an XRPD pattern of the crystal form B of the compound of formula (I).

Fig. 4 is an XRPD pattern of the crystal form C of the compound of formula (II).

Fig. 5 is an XRPD pattern of the crystal form D of the compound of formula (III).

Fig. 6 is an XRPD pattern of the crystal form E of the compound of formula (III).

Fig. 7 is an XRPD pattern of the crystal form F of the compound of formula (IV).

Fig. 8 is an XRPD pattern of the crystal form G of the compound of formula (IV).

Fig. 9 is an XRPD pattern of the crystal form H of the compound of formula (V).

Fig. 10 is an XRPD pattern of the crystal form I of the compound of formula (V).

Fig. 11 is an XRPD pattern of the crystal form J of the compound of formula (V).

Fig. 12 is an XRPD pattern of the crystal form K of the compound of formula (VI).

Detailed description of the embodiment

[0068] In order to better understand the content of the present invention, the following Embodiments further illustrate the present invention, but the present invention is not limited.

Embodiment 1: Preparation for the Crystal Form A of the Compound of Formula (I)

[0069] Anhydrous methanol (4.9 L), choline aqueous solution (49.5% by weight, 467.60 g), and anhydrous methanol (0.12 L) were added to the reaction kettle successively and the temperature was adjusted to 25°C. Then a solution of compound 1-8 (1004.15 g) in anhydrous methanol (4.90 L) was added dropwise to the reaction kettle, and the temperature was controlled between 20-25°C. After the addition, the mixture was stirred at around 35°C for 5h before the termination of the heating and stirring. Ethyl acetate (10.04 L) was added to the reaction solution, followed by concentrating to constant weight at 40°C, and the process was repeated twice. Ethyl acetate (16.58 L) was added again, the mixture was heated to 79°C and refluxed for 42 hours, then the stirring stopped after the mixture was cooled down to room temperature. The mixture was filtered, and the filter cake was washed with ethyl acetate (3.00 L), collected and dried at ambient temperature (15-25 °C) for 19h. The filter cake was dried at 45-50°C and -0.8MPa for about 28h to obtain the crystal form A of the compound of formula (I).
1H NMR (400MHz, DMSO-d6) δ = 12.14 (br s, 1H), 7.53 - 7.45 (m, 1H), 7.45 - 7.41 (m, 1H), 7.41 - 7.33 (m, 1H), 7.31 - 7.22 (m, 1H), 7.22 - 7.08 (m, 5H), 7.02 - 6.89 (m, 3H), 6.25 (d, J=16.0 Hz, 1H), 3.94 - 3.77 (m, 2H), 3.47 - 3.41 (m, 2H), 3.13 (s, 9H), 2.49 - 2.31 (m, 2H), 0.88 (t, J=7.6 Hz, 3H)

Embodiment 2: Preparation for the Crystal Form B of the Compound of Formula (I)

[0070] At 20°C, hydroxycholine methanol solution (45% by weight, 1g) was added to compound 1-8 (1g) and ethyl acetate (10mL) and the mixture was stirred at 20°C for 16 hours to obtain a yellow solution, which became a yellow suspension due to gradual precipitation. The mixture was filtered and the filter cake was washed with ethyl acetate (5 mL$\times$3) to obtain the crystal form B of the compound of formula (I) by drying in vacuum.
1H NMR (400MHz, DMSO-d6) δ = 11.88 (br s, 1H), 7.47 (d, J=8.4 Hz,1H), 7.41 (d, J=8.4 Hz,2H), 7.28 (d, J=8.4 Hz,1H), 7.20 - 7.08 (m, 5H), 6.98 - 6.90 (m, 3H), 6.26 (d, J=16.0 Hz, 1H), 3.88 - 3.80 (m, 2H), 3.45 - 3.38 (m, 2H), 3.11 (s, 9H), 2.47 - 2.35 (m, 2H), 0.87 (t, J=7.2 Hz, 3H)

Embodiment 3: Preparation for the Crystal Form C of the Compound of Formula (II)

[0071] 1g Compound 1-8 was dissolved in 10mL ethyl acetate and the mixture was stirred at 50°C for 30 min, hydroxycholine aqueous solution (50% by weight, 248.86 mg) was added at 50°C and the mixture was stirred at 50°C for 5h, then cooled to 20°C and stirred for 12h. Solids were precipitated, then filtered off, and the filter cake was washed with ethyl acetate (3 mL x 3) and concentrated to give 1.08g white solid of the crystal form C of the compound of formula **(II).**
1H NMR (400MHz, DMSO-d6) δ = 11.62 (br s, 1H), 7.49 (d, J=8.4 Hz,1H), 7.41 (d, J=8.4 Hz,2H), 7.32 - 7.25 (m, 3H), 7.20 - 7.08 (m, 4H), 6.97 (d, J=8.4 Hz,2H), 6.38 (d, J=16.0 Hz, 1H), 3.88 - 3.82 (m, 1H), 3.43 - 3.38 (m, 1H), 3.11 (s, 4.5H), 2.50 - 2.32 (m, 2H), 0.89 (t, J=7.6 Hz, 3H)

Embodiment 4: Preparation for the Crystal of the Compound of Formula (III)

1)Preparation for the Crystal Form D of the Compound of Formula (III)

[0072] 0.2g Free acid was dissolved in acetonitrile (2 mL) and the mixture was stirred at 50°C for 30 minutes, 55.48mg trometamol was added and the mixture was stirred at 50°C for 5 hours, then cooled to 25°C and stirred for 16 hours. Solids were precipitated, and then filtered off, the filter cake was washed with *n*-heptane (5 mL), and the solid was concentrated to obtain 145mg bright yellow solid.
1H NMR (400MHz, DMSO-d6) δ = 11.52 (br s, 1H), 7.49 (d, J=8.0 Hz,1H), 7.40 (d, J=8.0 Hz,2H), 7.32 - 7.23 (m, 3H), 7.22 - 7.10 (m, 4H), 6.97 (d, J=8.0 Hz,2H), 6.32 (d, J=15.6 Hz, 1H), 3.41 (s, 6H), 2.48 - 2.39 (m, 2H), 0.87 (t, J=7.6 Hz, 3H)

2)Preparation for the Crystal Form E of the Compound of Formula (III)

[0073] 0.2g Free acid was dissolved in isopropanol (2 mL) and the mixture was stirred at 50°C for 30 minutes. 55.48mg Tristearin was added and the mixture was stirred at 50°C for 5 hours, then cooled to 25°C and stirred for 16 hours. The solution was kept clear and poured into a glass vial containing 20 mL *n*-heptane, then the mixture was filtered to obtain a viscous oil, and concentrated to obtain 103mg bright yellow solid diethylamine salt.
1H NMR (400MHz, DMSO-d6) δ = 11.50 (br s, 1H), 7.48 (d, J=8.0 Hz,1H), 7.40 (d, J=8.0 Hz,2H), 7.33 - 7.22 (m, 3H), 7.21 - 7.08 (m, 4H), 6.96 (d, J=8.0 Hz,2H), 6.31 (d, J=16.0 Hz, 1H), 3.38 (s, 6H), 2.50 - 2.39 (m, 2H), 0.88 (t, J=7.6 Hz, 3H)

Embodiment 5: Preparation for the Compound of Formula (IV)

[0074] 1)Preparation for the Crystal Form F of the Compound of Formula (IV) 0.2g Free acid was dissolved in acetone (2mL) and the mixture was stirred at 50°C for 30 mins, 33.50mg diethylamine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetone (2mL×3), and the filter cake was concentrated to obtain 161mg white solid.
1H NMR (400MHz, DMSO-d6) δ = 11.56 (br s, 1H), 7.51 (d, J=7.2 Hz,1H), 7.40 (d, J=7.6 Hz,2H), 7.31 - 7.28 (m, 3H), 7.20 - 7.10 (m, 4H), 6.96 (d, J=8.4 Hz,2H), 6.32 (d, J=16.0 Hz, 1H), 2.76 (d, J=7.2 Hz, 4H), 2.51 - 2.43 (m, 2H), 1.11 (d, J=7.2 Hz, 6H), 0.89 (t, J=7.6 Hz, 3H)

2)Preparation for the Crystal Form G of the Compound of Formula (IV)

[0075] 0.2g Free acid was dissolved in isopropanol (2mL) and the mixture was stirred at 50°C for 30 mins, 33.50mg diethylamine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetone (2mL×3), and the filter cake was concentrated to obtain 163mg white solid piperazine salt.
1H NMR (400MHz, DMSO-d6) δ = 11.56 (br s, 1H), 7.51 (d, J=7.2 Hz,1H), 7.40 (d, J=7.6 Hz,2H), 7.31 - 7.28 (m, 3H), 7.20 - 7.10 (m, 4H), 6.97 (d, J=8.0 Hz,2H), 6.33 (d, J=16.0 Hz, 1H), 2.76 (d, J=7.2 Hz, 4H), 2.51 - 2.43 (m, 2H), 1.11 (d, J=7.2 Hz, 6H), 0.89 (t, J=7.6 Hz, 3H)

Embodiment 6: Preparation for the Crystal of the Compound of Formula (V)

1)Preparation for the Crystal Form H of the Compound of Formula (V)

[0076] 0.2g Free acid was dissolved in acetone (2mL) and the mixture was stirred at 50°C for 30 mins, 39.45mg piperazine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetone (2mL×3), and the filter cake was concentrated to obtain white solids.
1H NMR (400MHz, DMSO-d6) δ = 11.55 (br s, 1H), 7.49 (d, J=8.0 Hz,1H), 7.43 - 7.37 (m, 2H), 7.31 - 7.29 (m, 3H), 7.19 - 7.11 (m, 4H), 6.96 (d, J=8.4 Hz,2H), 6.32 (d, J=15.6 Hz, 1H), 2.78 (s, 8H), 2.50 - 2.41 (m, 2H), 0.89 (t, J=7.6 Hz, 3H)

2)Preparation for the Crystal Form I of the Compound of Formula (V)

[0077] 0.2g Free acid was dissolved in acetonitrile (2mL) and the mixture was stirred at 50°C for 30 mins, 39.45mg piperazine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetone (2mL×3), and the filter cake was concentrated to obtain white solids.
1H NMR (400MHz, DMSO-d6) δ = 11.55 (br s, 1H), 7.49 (d, J=8.0 Hz,1H), 7.43 - 7.37 (m, 2H), 7.31 - 7.29 (m, 3H), 7.19

- 7.12 (m, 4H), 6.96 (d, J=8.0 Hz,2H), 6.32 (d, J=16.0 Hz, 1H), 2.78 (s, 8H), 2.50 - 2.41 (m, 2H), 0.89 (t, J=7.6 Hz, 3H)

3)Preparation for the Crystal Form J of the Compound of Formula (V)

[0078] 0.2g Free acid was dissolved in isopropanol (2mL) and the mixture was stirred at 50°C for 30 mins, 39.45mg piperazine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetone (2mL×3), and the filter cake was concentrated to obtain white solids.
1H NMR (400MHz, DMSO-d6) δ = 11.54 (br s, 1H), 7.50 (d, J=8.0 Hz,1H), 7.43 - 7.37 (m, 2H), 7.33 - 7.25 (m, 3H), 7.21 - 7.14 (m, 4H), 6.96 (d, J=8.4 Hz,2H), 6.33 (d, J=16.0 Hz, 1H), 2.76 (s, 8H), 2.50 - 2.35 (m, 2H), 0.89 (t, J=7.6 Hz, 3H)

Embodiment 7: Preparation for the Crystal Form K of the Compound of Formula (VI)

[0079] 0.2g Free acid was dissolved in acetonitrile (2mL) and the mixture was stirred at 50°C for 30 mins, 110.08mg benzathine was added and the mixture was stirred at 50°C for 5h, then cooled to 25°C and stirred for 16h. A large amount of white solid was precipitated, filtered off, and the filter cake was washed with acetonitrile (2mL×3), and the filter cake was concentrated to obtain white solids.
1H NMR (400MHz, DMSO-d6) δ = 11.53 (br s, 1H), 7.51 (d, J=7.2 Hz,1H), 7.45 - 7.05 (m, 19H), 7.01 - 6.98 (m, 2H), 6.39 (d, J=16.0 Hz, 1H), 3.73 (s, 4H), 2.66 (s, 4H), 2.50 - 2.42 (m, 2H), 0.91-0.89 (m, 3H)

Embodiment 8: Solubility Test

[0080] Assay materials: compound 1-8, crystal form A of the compound of the formula (I), water, FaSSIF (simulated pre-meal intestinal fluid), FeSSIF (simulated post-meal intestinal fluid).

[0081] Assay method: compound 1-8 and the crystal form A of the compound of formula (I) were weighed in four portions and added to a 4mL glass vial respectively, then 2mL biological vehicle (FaSSIF, FeSSIF) and purified water were added respectively, the mixtures were mixed uniformly and the magnets were added to the suspensions, the mixtures were placed on a magnetic stirring heater for stirring (at 37°C, protected from light). Samples were taken after 24h, and the sample solution was quickly centrifuged, and the supernatant was diluted suitable folds and its concentration was determined by HPLC.

[0082] Assay results: see Table 12.

Table 12 Solubility Comparison-solubility of different biological vehicle

Compounds to be tested	Biological vehicle		
	H_2O(mg/mL)*	FaSSIF(mg/mL)*	FeSSIF(mg/mL)*
compound I-8	0.008	0.117	0.440
Crystal Form A of the compound of formula (I)	0.870	1.650	3.590
"*": the solubility of the crystal form A of the compound of formula (I) was calculated based on the free acid.			

[0083] Experiment conclusion: compared with compound 1-8, the solubility of the crystal form A of the compound of formula (I) has been significantly improved.

Embodiment 9: *In vivo* PK experiments

[0084] Assay materials: beagle dogs, three dogs per group, two groups in total (administered by compound 1-8 and crystal form A of the compound of formula (I) respectively)

[0085] Assay methods: the animals in each group were administered with corresponding compounds by orally gavage once, and blood samples were collected before and 2h (±2min), 4h (±5min), 6h (±5min), 8h (±5min), 12h (±5min), and 24h (±10min) after the administration. The samples were detected by LC-MS/MS, and AUC, C_{max}, and T_{max} parameters were calculated by employing WinNonlin version 6.4.

[0086] Assay results: see Table 13.

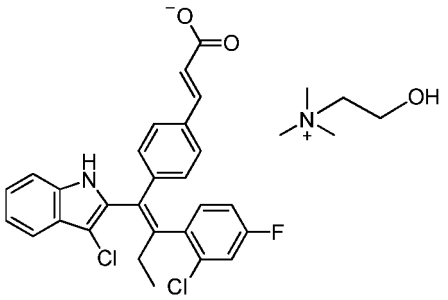
Tables 13.

Parameters	Compound 1-8	Crystal Form A of the compound of formula (I)
P.O. dose (mg/kg)	300	300
C_{max} (nM)	43467	75167
T_{max} (h)	6	9.3
$AUC_{0\text{-}last}$ (nM.h)	613021	1309787
$MRT_{0\text{-}last}$ (h)	10.6	13.3

[0087] Assay conclusion: The crystal form A of the compound of formula (I) has good pharmacokinetic properties.

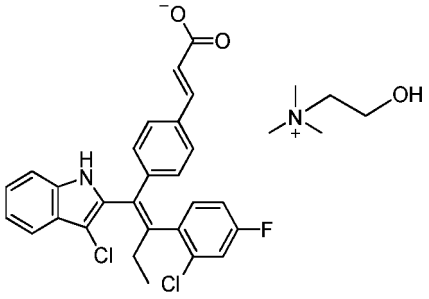
Claims

1. A compound of formula (I),



(I)

2. A crystal form A of the compound of formula (I), wherein the X-ray powder diffraction pattern under Cu-Kα radiation has characteristic diffraction peaks at the following 2θ angles: 5.52± 0.2°, 13.68± 0.2°, 19.98± 0.2°, 20.80± 0.2°, 22.02± 0.2°, 22.44± 0.2°, 24.94± 0.2° and 26.96± 0.2°,



(I)

3. The crystal form A of claim 2, wherein the X-ray powder diffraction pattern under Cu-Kα radiation has nine or more than nine, ten or more than ten, or eleven or more than eleven characteristic diffraction peaks at the 2θ angles selected from the group consisting of 5.52±0.2°, 13.68±0.2°, 18.86±0.2°, 19.98±0.2°, 20.80±0.2°, 21.62±0.2°, 22.02±0.2°, 22.44±0.2°, 23.34±0.2°, 24.94±0.2°, 26.96±0.2° and 28.42±0.2°.

4. The crystal form A of claim 3, wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 1.

5. The crystal form A of any one of claims 2 to 4, wherein the differential scanning calorimetric curve has an endothermic peak at 239.46°C±3°C.

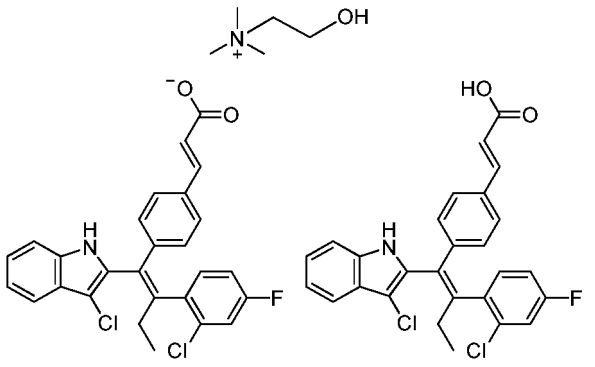
6. The crystal form A of claim 5, wherein the differential scanning calorimetric curve pattern is shown in FIG. 2.

7. A crystal form B of the compound of formula (I), wherein the X-ray powder diffraction pattern under Cu-Kα radiation has characteristic diffraction peaks at the following 2θ angles: 5.68 ± 0.2°, 12.36 ± 0.2°, 19.24 ± 0.2°, 19.86 ± 0.2°, 20.62 ± 0.2°, 21.64 ± 0.2°, 22.68 ± 0.2° and 24.96 ± 0.2°.

8. The crystal form B of claim 7, wherein the X-ray powder diffraction pattern under Cu-Kα radiation has nine or more than nine, ten or more than ten, or eleven or more than eleven characteristic diffraction peaks at the 2θ angles selected from the group consisting of 5.68 ± 0.2°, 12.36 ± 0.2°, 13.42 ± 0.2°, 19.24 ± 0.2°, 19.86 ± 0.2°, 20.62 ± 0.2°, 21.64 ± 0.2°, 22.68 ± 0.2°, 24.96 ± 0.2°, 26.38 ± 0.2°, 27.44 ± 0.2° and 30.62± 0.2°.

9. The crystal form B of claim 8, wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 3.

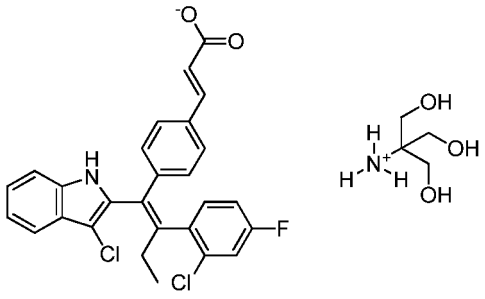
10. A compound of formula (II),



(II)

11. A crystal form C of the compound of formula (II), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 4.

12. A compound of formula (III),

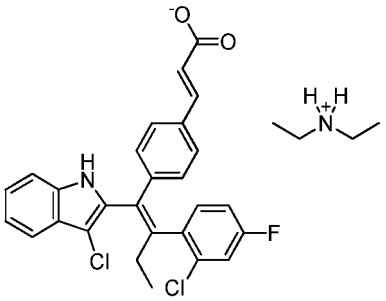


(III)

13. A crystal form D of the compound of formula (III), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 5.

14. A crystal form E of the compound of formula (III), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 6.

15. A compound of formula (IV),

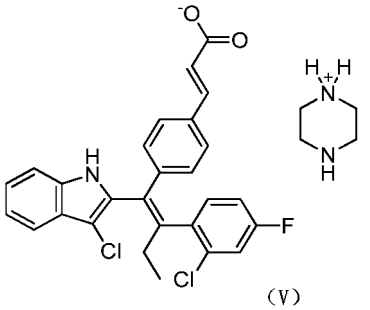


(IV)

16. A crystal form F of the compound of formula (IV), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 7.

17. A crystal form G of the compound of formula (IV), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 8.

18. A compound of formula (V),



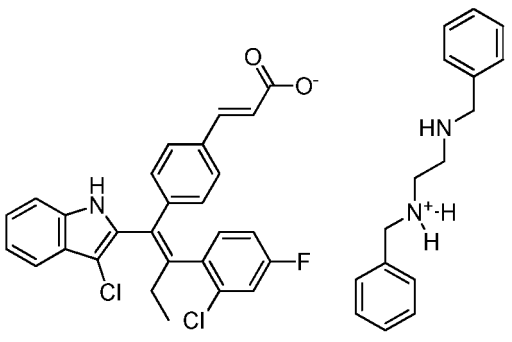
(V)

19. A crystal form H of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 9.

20. A crystal form I of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 10.

21. A crystal form J of the compound of formula (V), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 11.

22. A compound of formula (VI),



(VI)

23. A crystal form K of the compound of formula (VI), wherein the X-ray powder diffraction pattern under Cu-Kα radiation is shown in FIG. 12.

24. Use of the compound or the crystal form of any one of claims 1 to 23 in the preparation of a medicament for treating breast cancer.

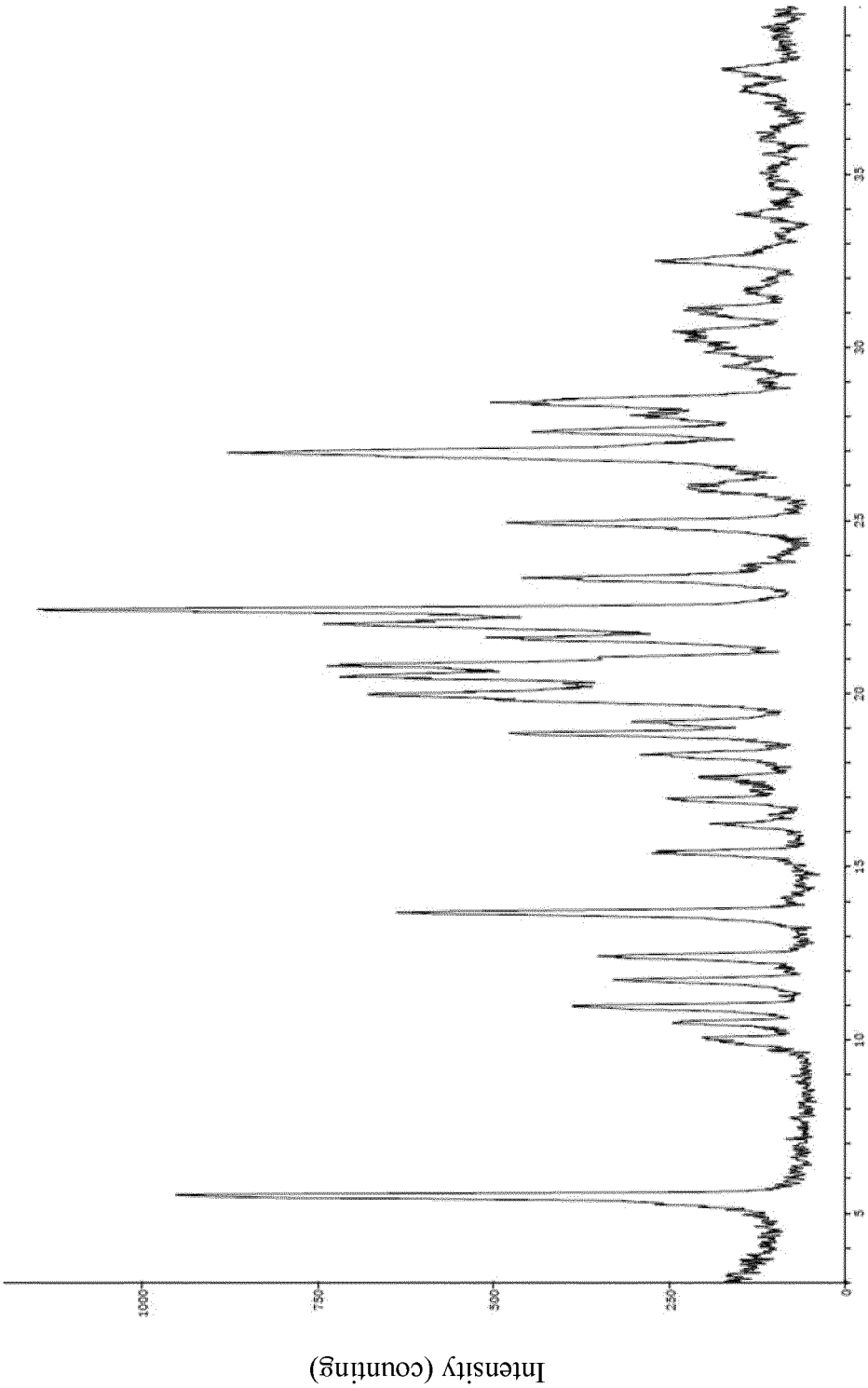
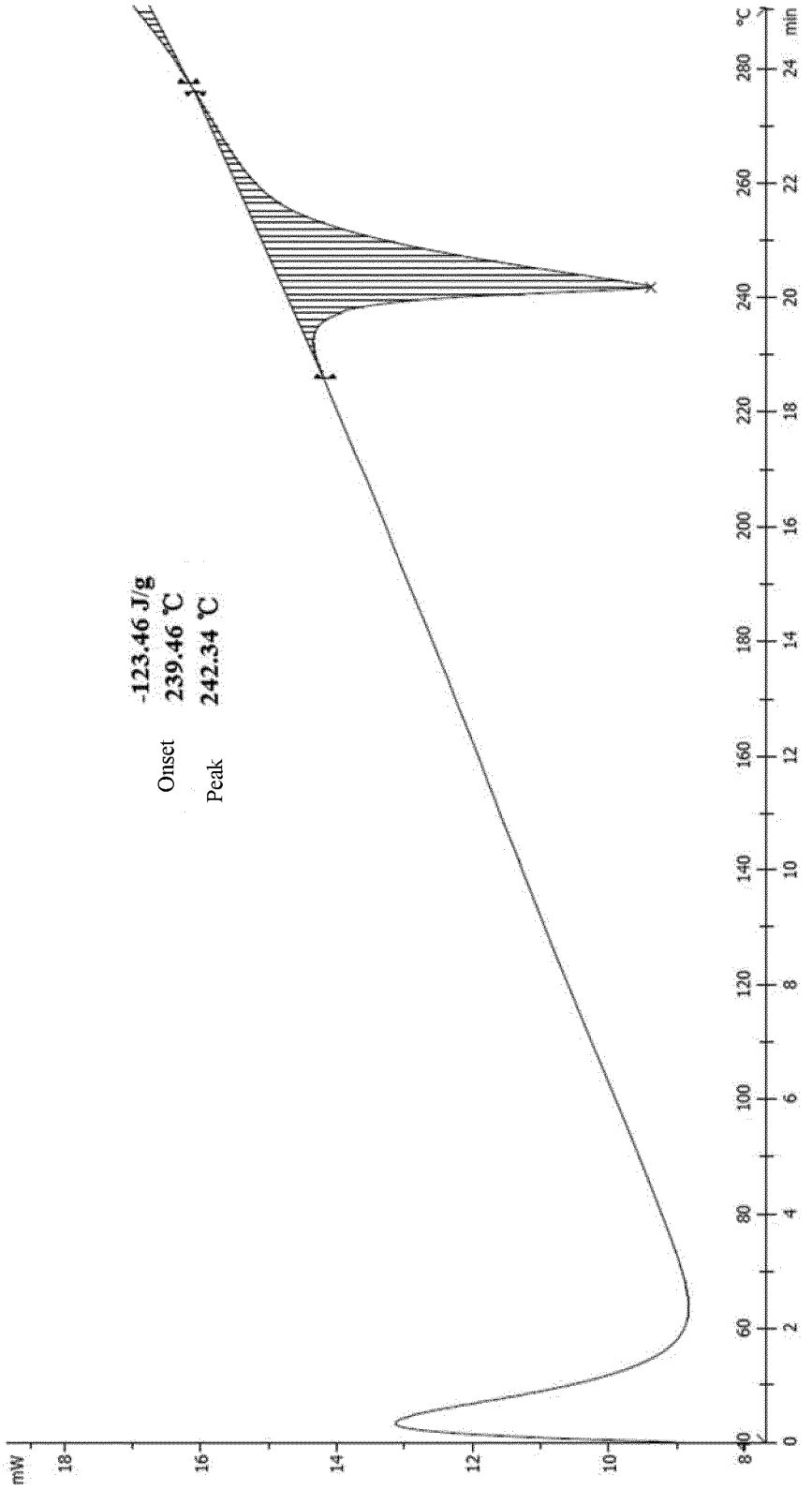


Figure 1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Onset 239.46 ℃
Peak 242.34 ℃
mW
18
16
14
12
10
8
0
2
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6
8
10
12
14
16
18
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140
160
180
200
220
240
260
280
℃

Figure 2

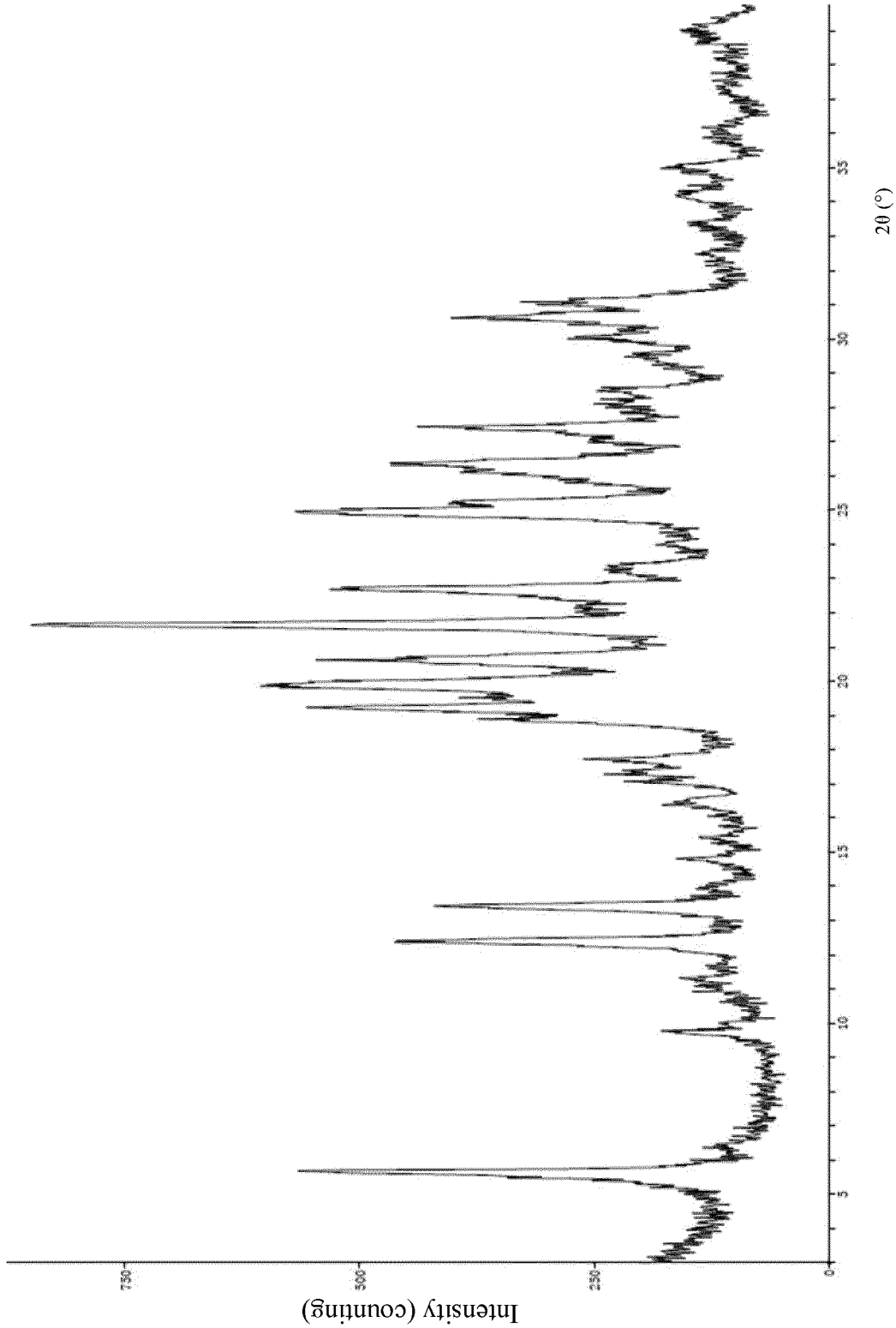


Figure 3

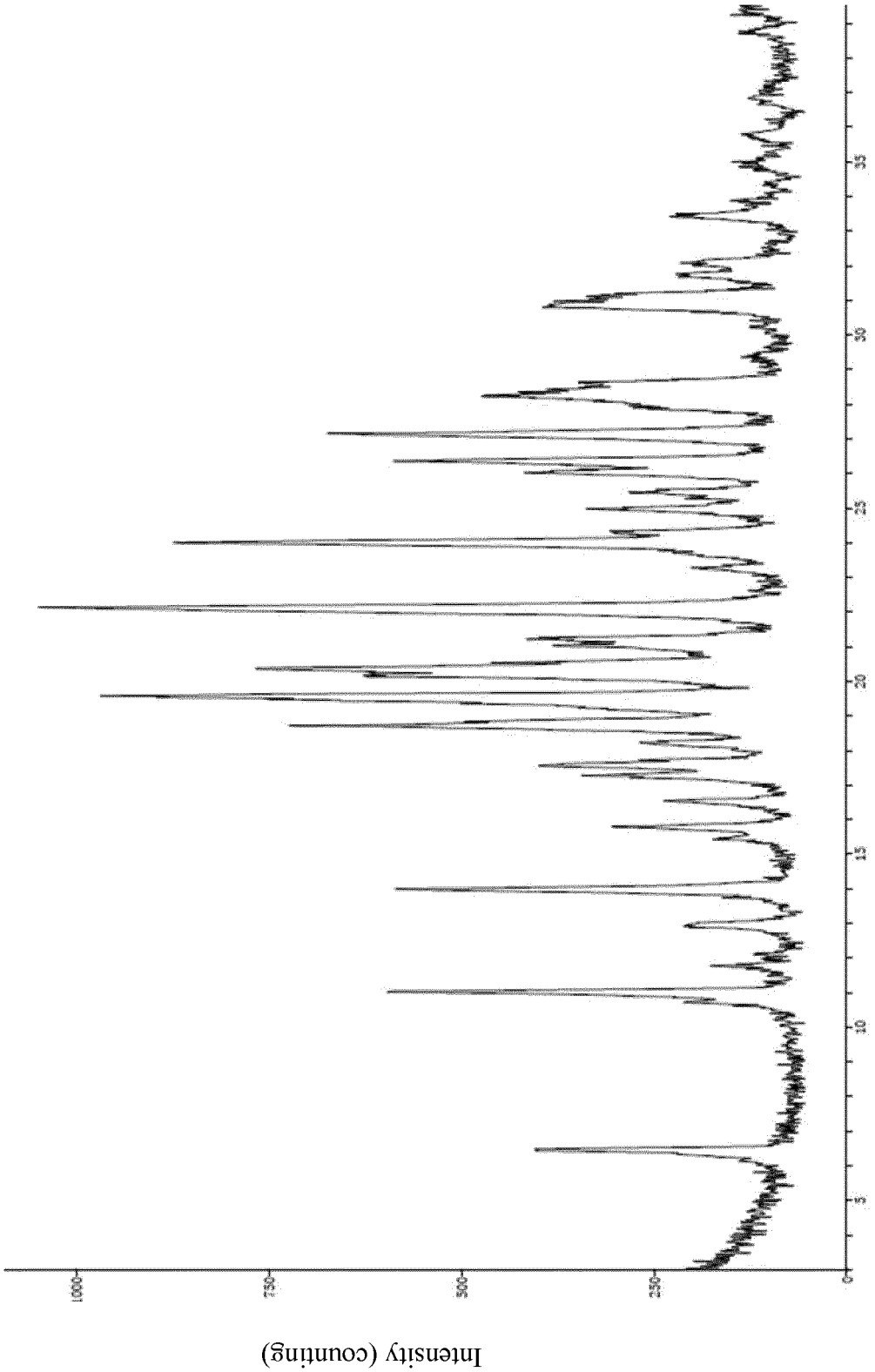


Figure 4

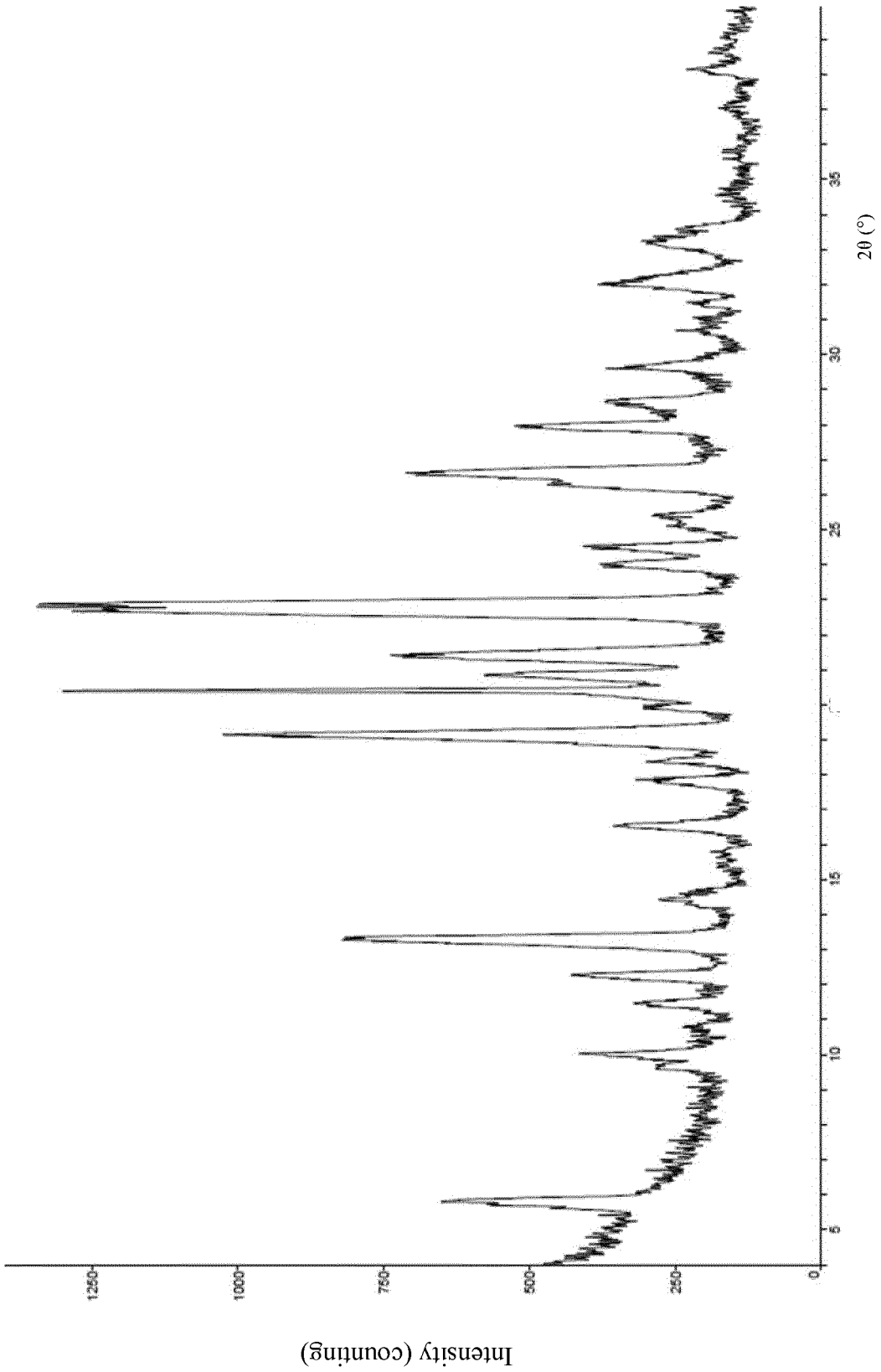
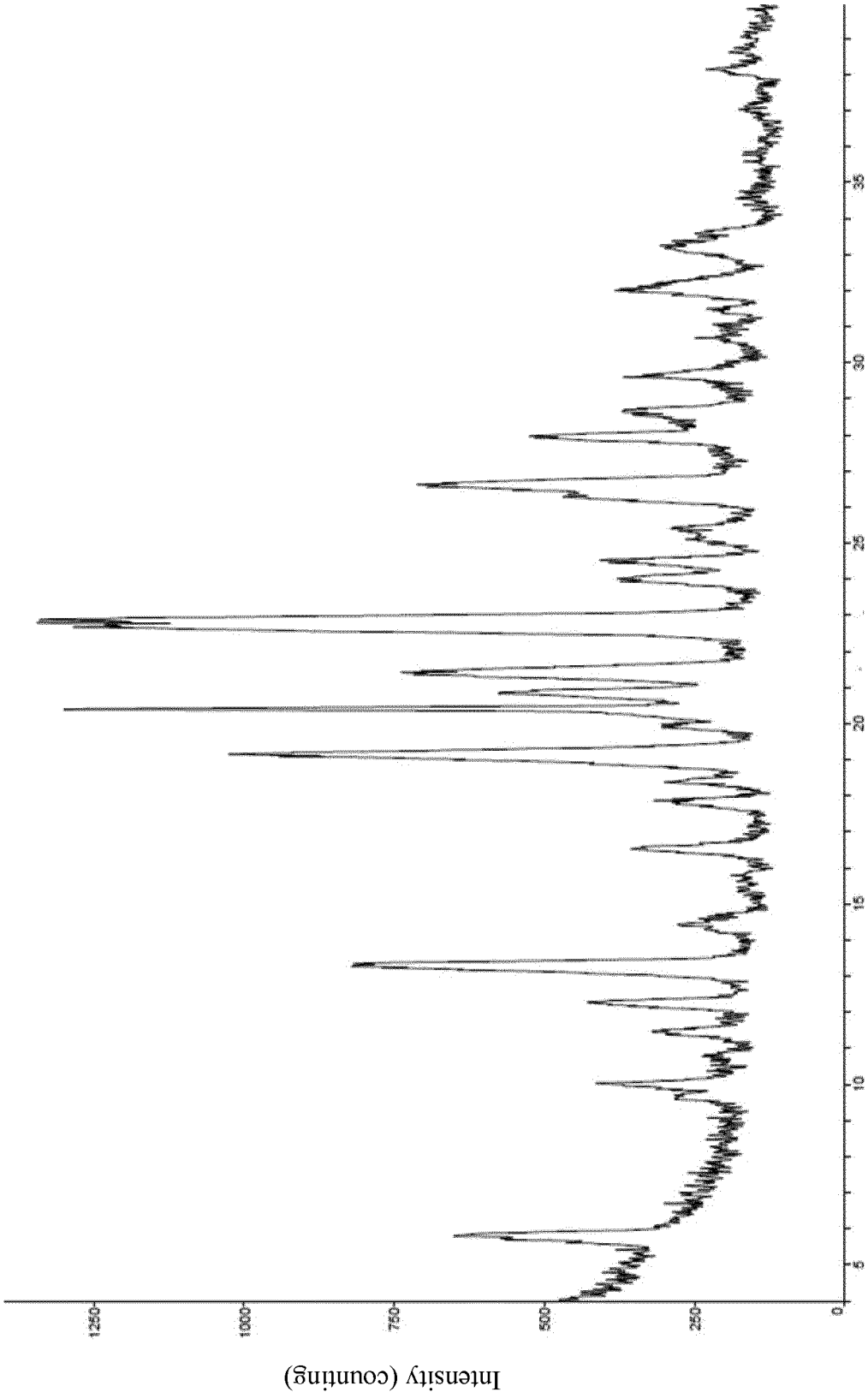


Figure 5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2θ (°)

Figure 6

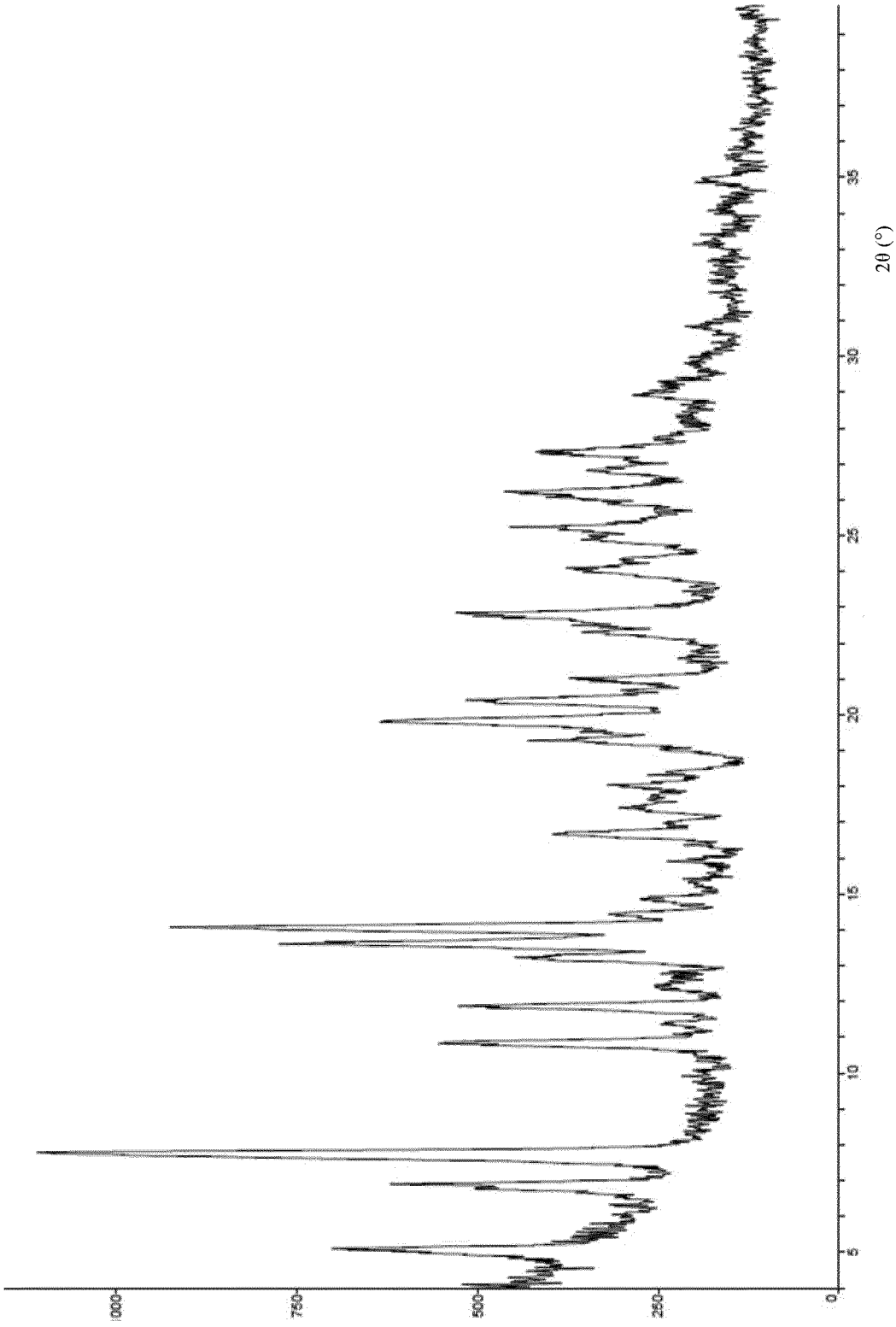


Figure 7

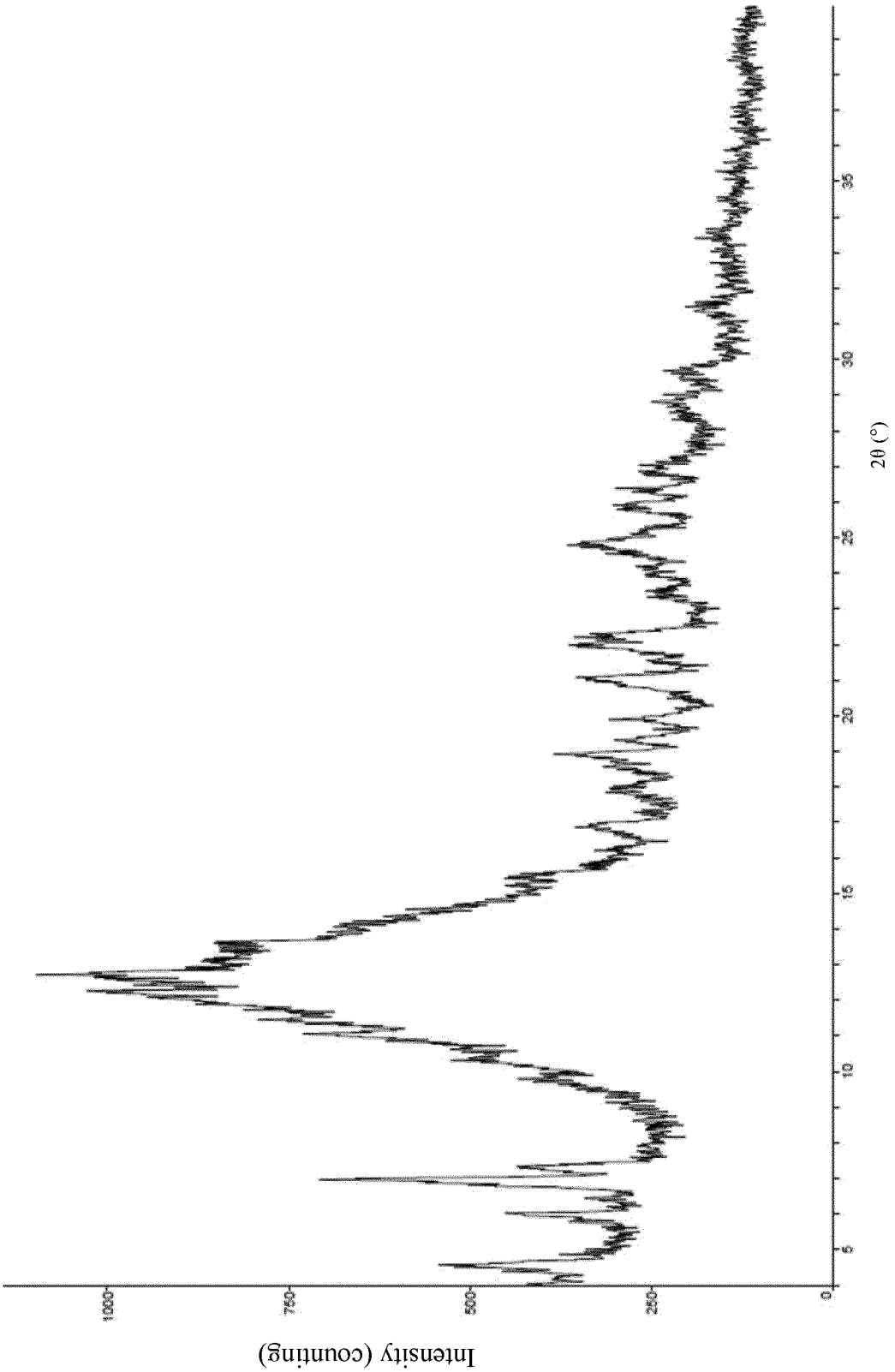


Figure 8

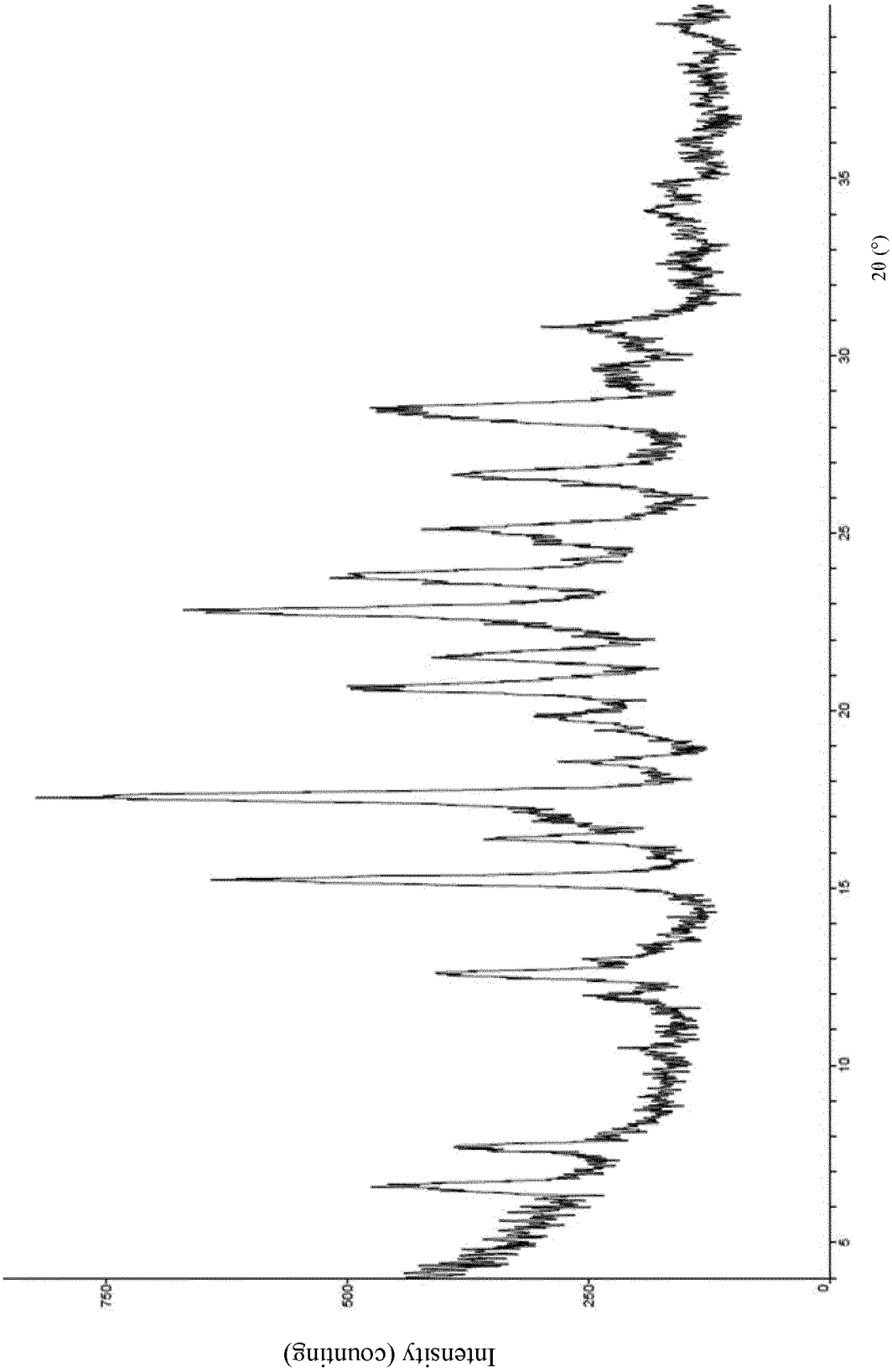
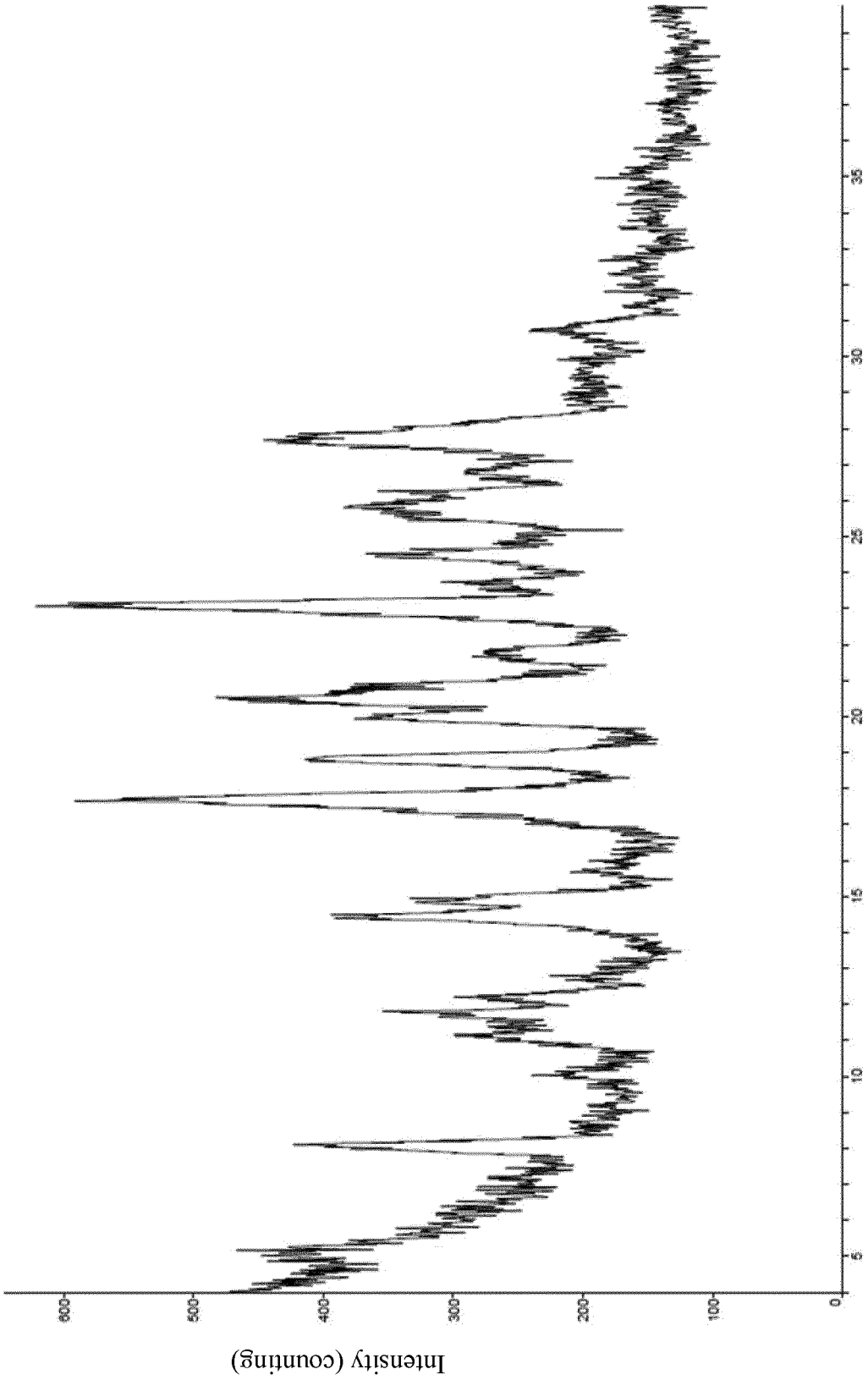


Figure 9


Intensity (counting)
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300
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5
10
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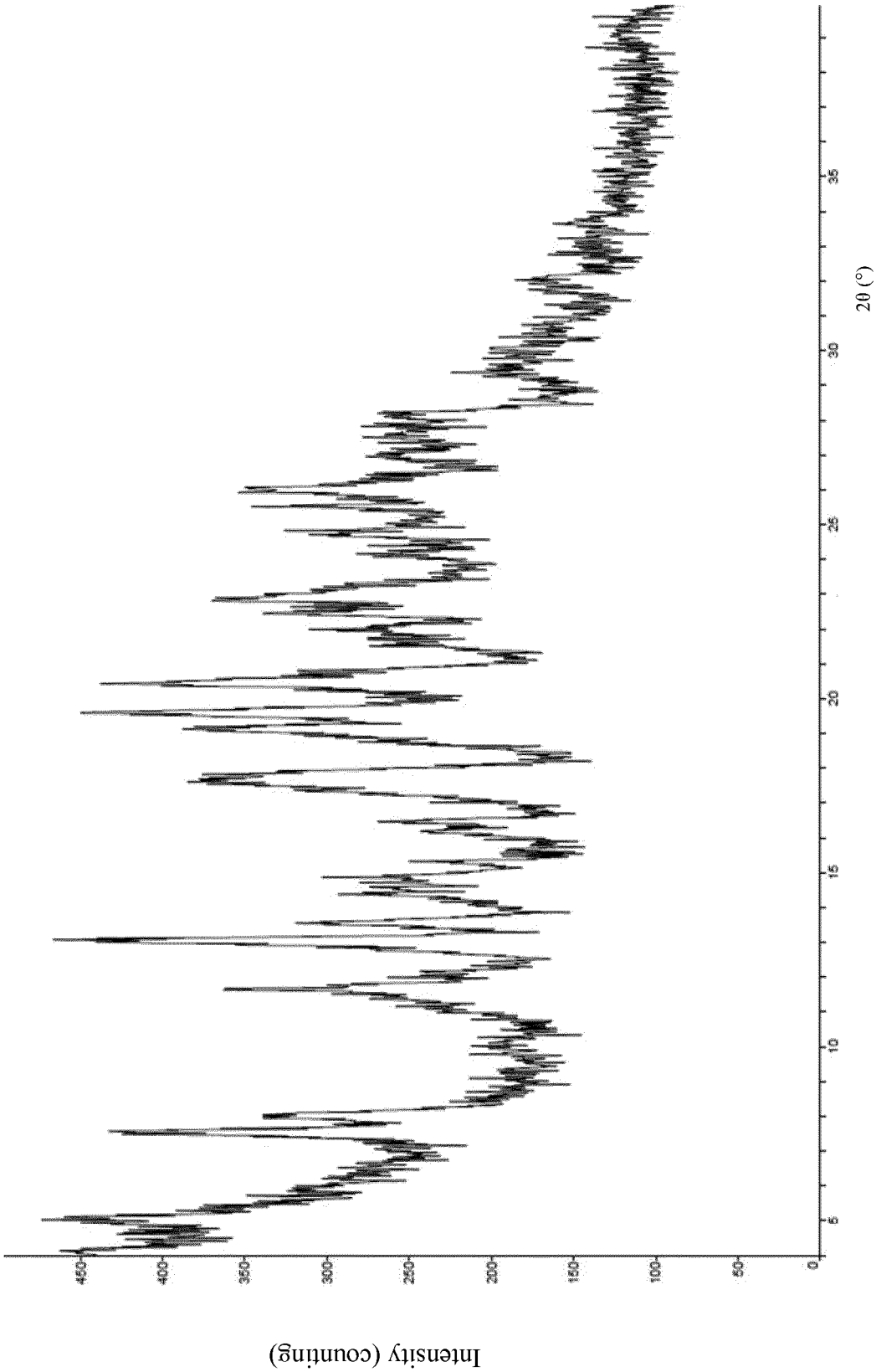
20
25
30
35
2θ (°)

Figure 10


Intensity (counting)
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50
100
150
200
250
300
350
400
450
5
10
15
20
25
30
35
2θ (°)

Figure 11

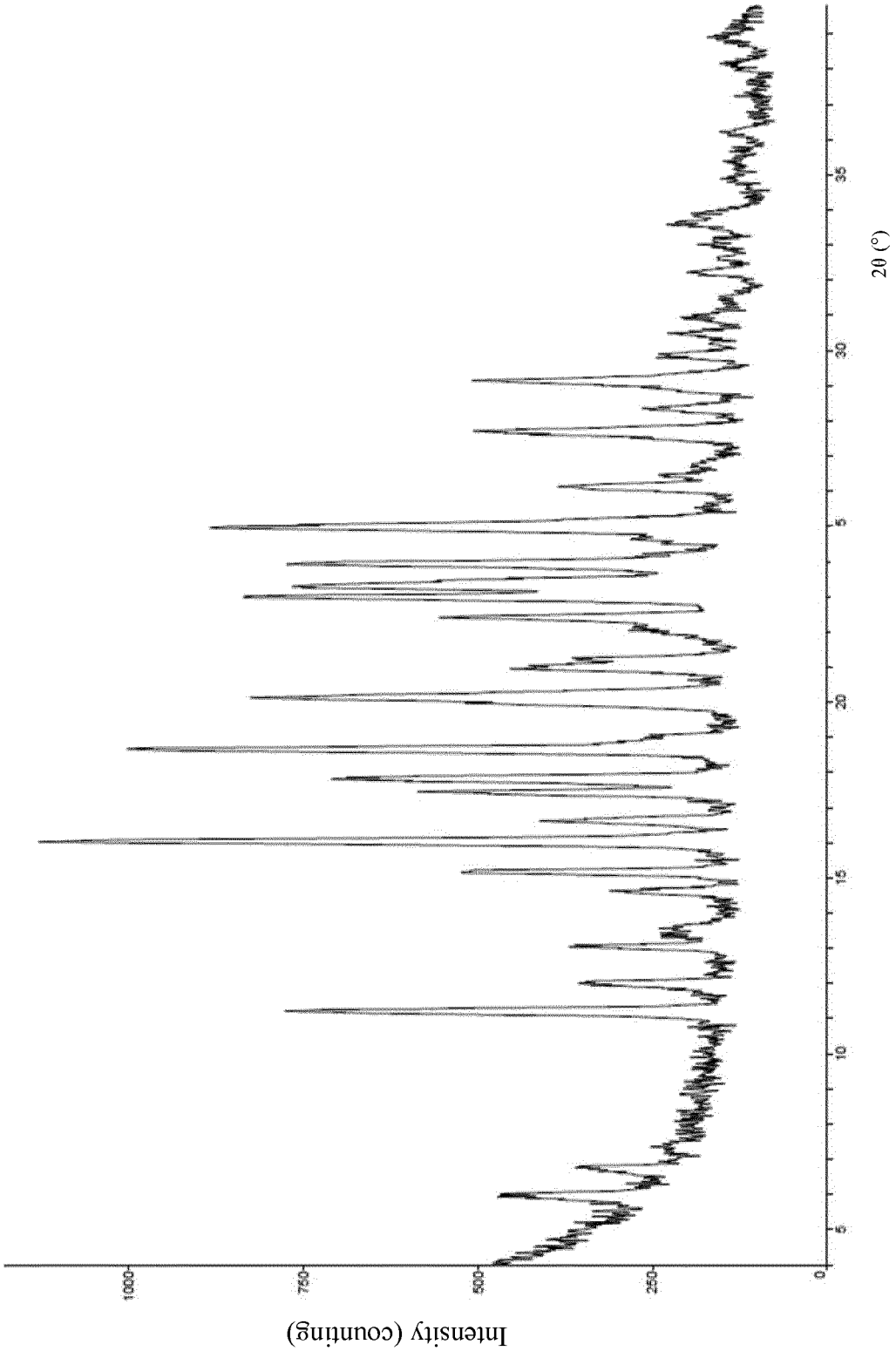

Figure 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/111624

A. CLASSIFICATION OF SUBJECT MATTER

C07D 209/18(2006.01)i; A61K 31/404(2006.01)i; A61P 35/00(2006.01)i

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)

C07D209/-; A61K31/-; A61P35/-

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, CNPAT, WPI, EPODOC, STN: 罗欣药业, 吲哚, 晶体, 晶型, 雌激素, 乳腺癌, indole, crystal, estrogen, breast cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2019/057201 A1 (LUOXIN PHARMACEUTICAL (SHANGHAI) CO., LTD. et al.) 28 March 2019 (2019-03-28) description, page 1, lines 6 and 7, and page 2, lines 12-20	1-24
X	WO 2017/162206 A1 (MEDSHINE DISCOVERY INC. et al.) 28 September 2017 (2017-09-28) description, page 1, lines 4 and 5, page 2, line 11 to page 3, line 14, page 8, line 6 and page 17, lines 18-21	1, 7-24
A	WO 2017/162206 A1 (MEDSHINE DISCOVERY INC. et al.) 28 September 2017 (2017-09-28) description, page 1, lines 4 and 5, page 2, line 11 to page 3, line 14, page 8, line 6 and page 17, lines 18-21	2-6, 24
A	CN 106488767 A (F. HOFFMANN-LA ROCHE AG) 08 March 2017 (2017-03-08) entire document	1-24
A	CN 103189361 A (ARAGON PHARMACEUTICALS, INC.) 03 July 2013 (2013-07-03) entire document	1-24

☐ 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	Date of mailing of the international search report
27 December 2019	**15 January 2020**
Name and mailing address of the ISA/CN **China National Intellectual Property Administration (ISA/CN)** **No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088** **China**	Authorized officer
Facsimile No. **(86-10)62019451**	Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/111624

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		EP 2735562 B1	11 March 2015
		JP 2013544761 A	19 December 2013

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/111624

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		CL	2013000722	A1	26 July 2013
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		BR	112013006395	A2	24 September 2019
		WO	2012037410	A9	10 May 2012

Form PCT/ISA/210 (patent family annex) (January 2015)

REFERENCES CITED IN THE DESCRIPTION

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- CN 201811434915 **[0001]**
- WO 2012037411 A2 **[0007]**
- WO 2017162206 A1 **[0008] [0044]**

Non-patent literature cited in the description

- *J.Med.Chem.,* 2015, vol. 58 (12), 4888-4904 **[0007]**