(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2016 (10.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/179123 A1

(51) International Patent Classification:
A61K 31/4706 (2006.01) *C07D 215/233* (2006.01)
A61K 31/4709 (2006.01) *C07D 215/42* (2006.01)

(21) International Application Number:
PCT/US2016/030483

(22) International Filing Date:
3 May 2016 (03.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/156,734	4 May 2015 (04.05.2015)	US
62/205,272	14 August 2015 (14.08.2015)	US
15/143,630	2 May 2016 (02.05.2016)	US

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(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.

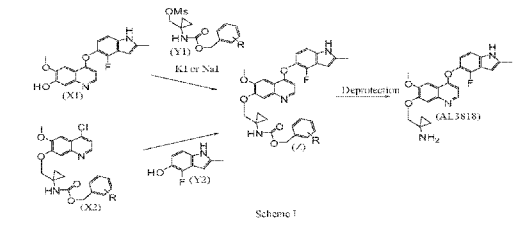
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

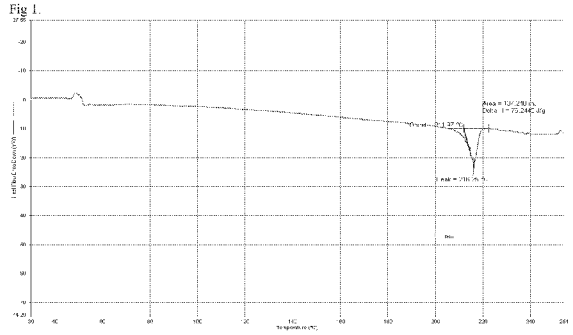
[Continued on next page]

(54) **Title**: PROCESS FOR PREPARING AN ANTI-CANCER AGENT, 1-((4-(4-FLUORO-2-METHYL-1H-INDOL-5-YLOXY)-6-METHOXYQUINOLIN-7-YLOXY)METHYL) CYCLOPROPANAMINE, ITS CRYSTALLINE FORM AND ITS SALTS



Scheme I

Fig 1.



(57) **Abstract**: The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818). A stable crystalline form of A13818 has been prepared. Salts and their crystalline forms of AL3818 have been also prepared. Anti-cancer and optometric activities of AL3818 and its salts have been further tested. New process has been outlined in Scheme I.

WO 2016/179123 A1

Published:

— *with international search report (Art. 21(3))*

Process for preparing an anti-cancer agent, 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine, its crystalline form and its salts

This application claims the benefit of U.S. Provisional Applications 62/156,734 filed on May 4, 2015 and 62/205,272 filed on August 14, 2015

FIELD OF THE INVENTION

The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818). A stable crystalline form of Al3818 has been prepared. Salts and their crystalline forms of AL3818 have been also prepared. Anti-cancer and optometric activities of AL3818 and its salts have been further tested.

BACKGROUND OF THE INVENTION

1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)-cyclopropanamine (AL3818) has been structurally disclosed in WO2008112407 as an agiogenesis inhibitor with few preparation methods.

SUMMARY OF THE INVENTION

Abbreviations and Definitions

The following abbreviations are used and have the meaning below for ease of reference.

EtOH: ethanol, MeOH: methanol, IPA: isopropanol, EtOAc: ethyl acetate, RT: room temperature, DIPEA: diisopropylethylamine, DCM: Dichloromethane, DMF: *N,N*-dimethylformamide, DMAP: 4-N,N-dimethylaminopyridine, MsCl: methanesulfonyl chloride, THF: tetrahydrofuran, TFA: trifluoroacetic acid, TEA: triethylamine, Pd/C: Palladium on active Carbon,

eq: equivalent, g: gram, mg: milligram, ml: milliliter, min: minutes, bis=di: two or double

DSC: differential scanning calorimetric, TGA: thermogravimetric analysis, XRPD: X-ray powder diffraction, Exo: exotherm, Endo: endotherm.

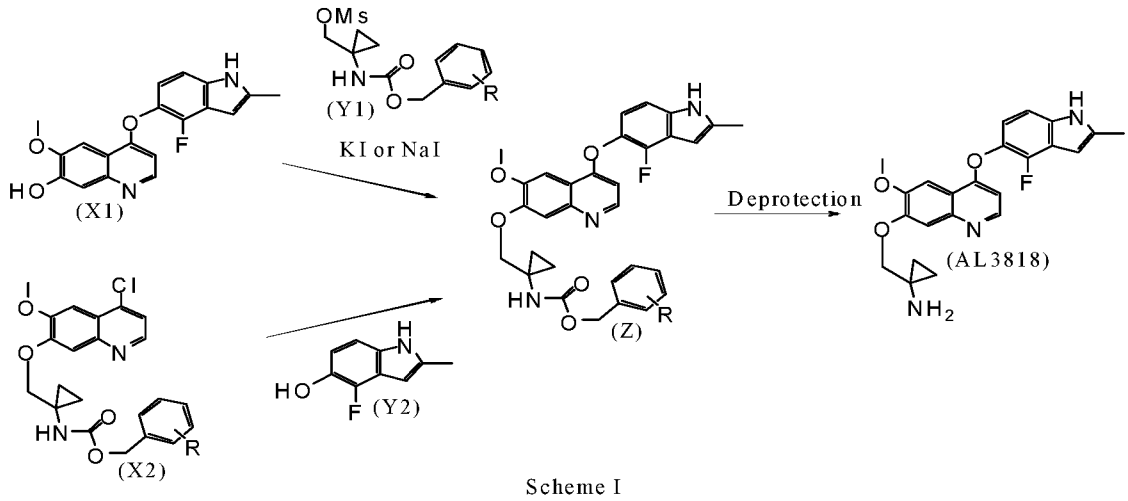
ALL: Acute Lymphocytic or Lymphoblastic Leukemias, CLL: Chronic Lymphocytic or Lymphoblastic Leukemias, AML: Acute Myelogenous or Myeloid Leukemias, CML: Chronic Myelogenous or Myeloid Leukemias

The term "C_1-C_6alkyl", as used herein, unless otherwise indicated, includes 1 to 6 saturated monovalent hydrocarbon radicals having straight or branched moieties, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, and the like.

The term "C_1-C_6alkoxy", as used herein, unless otherwise indicated, includes –OC_1-C_6alkyl groups wherein C_1-C_6alkyl is as defined above, such as methoxy and ethoxy.

Invention Scope

The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818) by condensing intermediate (X1) with (Y1) in a solvent at the presence of KI or NaI, or intermediate (X2) with (Y2) in a solvent to form intermediate (Z) which is deprotected to give the final compound (AL3818) in Scheme I. A stable crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine and its salts as well as crystalline forms of salts have also been prepared.



Scheme I

Wherein, R is selected from H and C_1-C_6alkoxy.

DESCRIPTION OF DRAWINGS

Fig 1. DSC graph of a crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 2. TGA graph of a crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 3. XRPD graph of a crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 4. DSC graph of a crystalline form of bishydrochloride acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 5. TGA graph of a crystalline form of bishydrochloride acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 6. XRPD graph of a crystalline form of bishydrochloride acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 7. DSC graph of a crystalline form of bishydrochloridehydrate acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 8. TGA graph of a crystalline form of bishydrochloridehydrate acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 9. XRPD graph of a crystalline form of bishydrochloridehydrate acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 10. DSC graph of a crystalline form of bismaleic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 11. TGA graph of a crystalline form of bismaleic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 12. XRPD graph of a crystalline form of bismaleic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 13. DSC graph of a crystalline form of succinic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 14. TGA graph of a crystalline form of succinic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 15. XRPD graph of a crystalline form of succinic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropanamine

Fig 16. Effect of AL3818 and its salts on human endometrial cancer Ishikawa xenografted athymic mice

Fig 17. Effect of AL3818 salts combined with Carboplatin (CBX)/Paclitaxel (Taxol) on human endometrial cancer Ishikawa xenografted athymic mice

Fig 18. Effects of oral administration of AL3818 on laser-induced CNV

Fig 19. Effects of AL3818 (0.15 mg/kg body weight) and intravitreal anti-VEGF antibody on laser-induced CNV

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818) by condensing intermediate (X1) with (Y1) in a solvent at the presence of KI or NaI, or intermediate (X2) with (Y2) in a solvent to form intermediate (Z) which is deprotected to give the final compound (AL3818) in Scheme I.

Wherein, R is selected from H and C_1-C_6alkoxy, preferably selected from H and –OMe;

The present invention relates to prepare a stable crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine;

The present invention relates to prepare the salts or stable crystalline salt forms of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine;

The present invention relates to bishydrochloride acid, bishydrochloridehydrate acid, bismaleic acid and succinic acid salt, and their stable crystalline salt forms or stable crystalline free base form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine.

The present invention relates to prepare a pharmaceutical composition that comprises a stable crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine and a pharmaceutically acceptable carrier;

The present invention relates to prepare a pharmaceutical composition that comprises the salts or stable crystalline salt forms of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)-methyl)cyclopropanamine and a pharmaceutically acceptable carrier;

The present invention relates to a stable crystalline form or the salts or stable crystalline salt forms of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine for a method in treating a neoplastic disease;

The present invention relates to a stable crystalline form or the salts or stable crystalline salt forms of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl) cyclopropanamine for use in the manufacture of a medicament for a method in the treating a neoplastic disease;

The present invention relates to a stable crystalline form or the salts or stable crystalline salt forms of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine for a method in mono therapy or combining with chemotherapy agents, selected from platinum based or taxane based agents in treating solid tumors, selected from lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian, cervical and endometrial cancers; and blood cancers, selected from ALL, CLL, AML, CML and Multiple Myeloma;

The present invention relates to bishydrochloride acid, bishydrochloridehydrate acid, bismaleic acid and succinic acid salt, and their stable crystalline salt forms or stable crystalline free base form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine for a method in mono therapy or combining with chemotherapy agents, selected from platinum based or taxane based agents in treating solid tumors, selected from lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma,

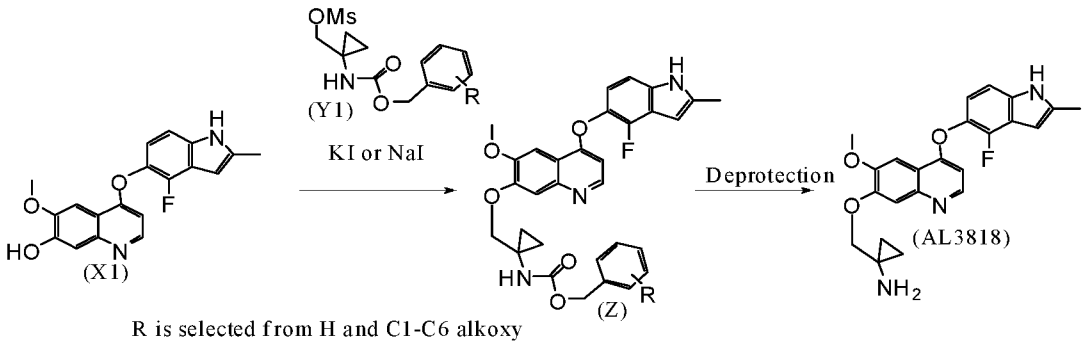
breast, ovarian, cervical and endometrial cancers; and blood cancers, selected from ALL, CLL, AML, CML and Multiple Myeloma;

The present invention relates to bishydrochloride acid, bishydrochloridehydrate acid, bismaleic acid and succinic acid salt, and their stable crystalline salt forms or stable crystalline free base form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine for a method in mono therapy or combining with chemotherapy agents, selected from platinum based or taxane based agents in treating lung, colorectal, gastric, thyroid, pancreatic, liver, prostate, sarcoma, breast, ovarian, cervical and endometrial cancers.

The present invention relates to bishydrochloride acid, bishydrochloridehydrate acid, bismaleic acid and succinic acid salt, and their stable crystalline salt forms or stable crystalline free base form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)-cyclopropanamine for a method in combining with immunotherapy agents, selected from PD-1 or PD-L1, SLAM7, oncolytic virus therapy, bispecific T cell engagers (BiTE) and chimeric antigen receptor (CAR) T cell therapy based agents, such as nivolumab, pembrolizumab, ipilimumab, blinatumomab, elotuzumab, daratumumab, talimogene laherparepvec, in treating solid tumors, selected from lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian, cervical and endometrial cancers; and blood cancers, selected from ALL, CLL, AML, CML and Multiple Myeloma;

The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818) by condensing intermediate (X1) with (Y1) in a solvent at the presence of KI or NaI to form intermediate (Z) which is deprotected to give the final compound (AL3818) according to Process A.

Process A

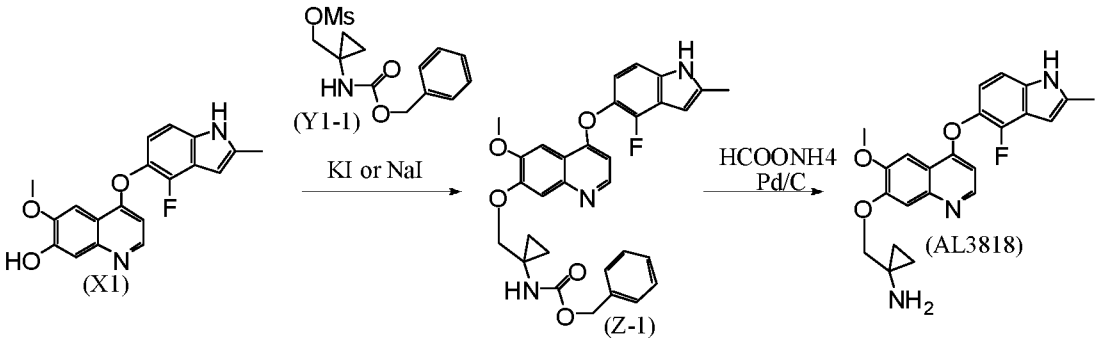


R is selected from H and C1-C6 alkoxy

The final compound (AL3818) was prepared according to Process A1 when R is H by deprotecting intermediate (Z-1) with $HCOONH_4$ (ammonium formate) and Pd/C in an alcoholic solvent, such as MeOH, at 25°C-80°C for 0.1-4 hours. (Z-1) was prepared by reacting

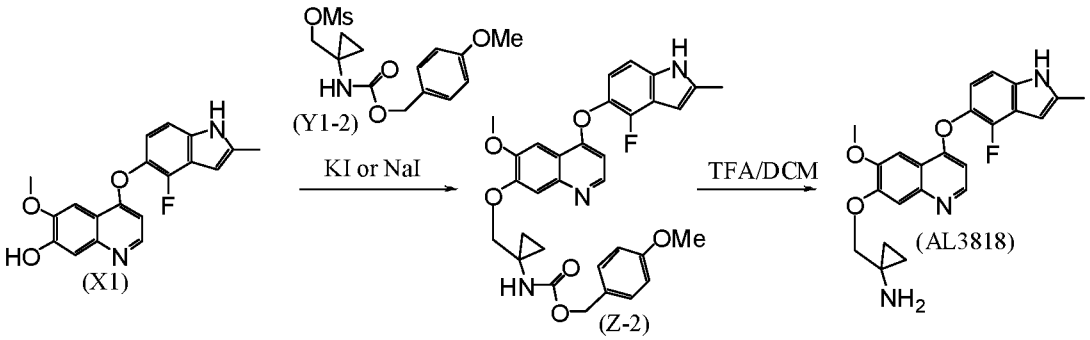
intermediate (X1) with (Y1-1) at the presence of KI or NaI with K_2CO_3 in a solvent, such as acetone or DMF, at a temperature of 60°C-160°C for 2-24 hours.

Process A1 (R=H)



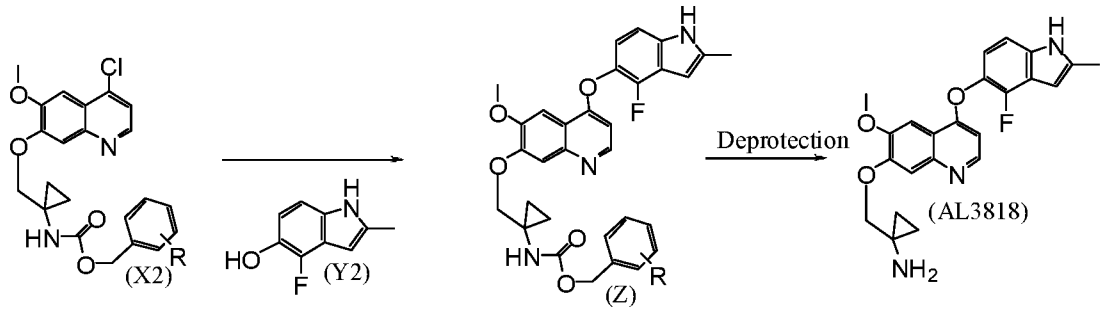
The final compound (AL3818) was prepared according to Process A2 when R is 4-OMe by deprotecting intermediate (Z-2) with TFA in DCM at 0°C-30°C for 1-24 hours. (Z-2) was prepared by reacting intermediate (X1) with (Y1-2) at the presence of KI or NaI with K_2CO_3 in a solvent, such as acetone or DMF, at a temperature of 60°C -160°C for 2-24 hours.

Process A2 (R=4-OMe)



The present invention relates a new process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine (AL3818) by reacting intermediate (X2) with (Y2) in a solvent to form intermediate (Z) which is deprotected to give the final compound (AL3818) according to Process B.

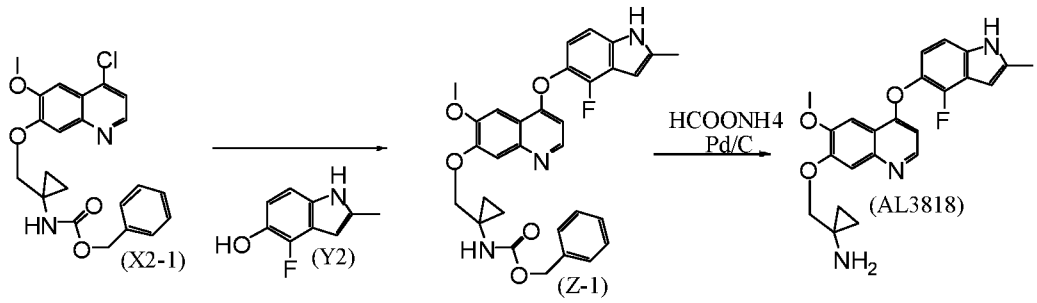
Process B



R is selected from H and C1-C6 alkoxy

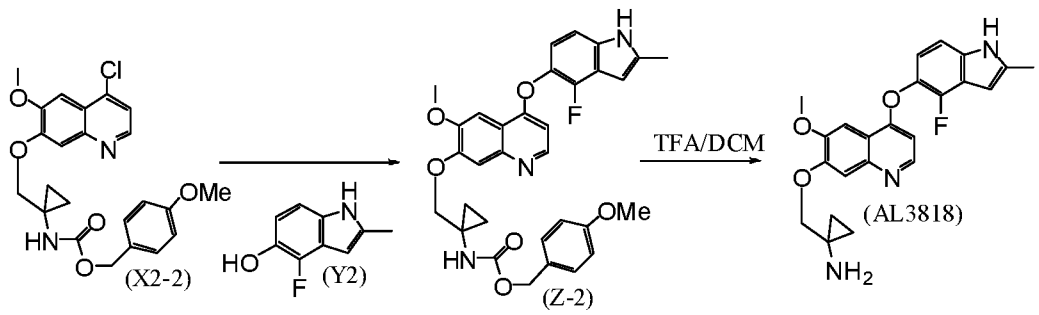
The final compound (AL3818) was prepared according to Process B1 when R is H by deprotecting intermediate (Z-1) with $HCOONH_4$ (ammonium formate) and Pd/C in an alcoholic solvent, such as MeOH, at 25°C-80°C for 0.1-4 hours. (Z-1) was prepared by reacting intermediate (X2-1) with (Y2) in a solvent, such as pyridine or lutidine, at a temperature of 60°C - 160°C for 1-12 hours.

Process B1 (R=H)



The final compound (AL3818) was prepared according to Process B2 when R is 4-OMe by deprotecting intermediate (Z-2) with TFA in DCM at 0°C-30°C for 1-24 hours. (Z-2) was prepared by reacting intermediate (X2-2) with (Y2) in a solvent, such as pyridine or lutidine, at a temperature of 60°C -160°C for 1-12 hours.

Process B2 (R=4-OMe)



The following examples further illustrate the present invention, but should not be construed as in any way to limit its scope.

Example 1

Representation of Process A, Process A1

Process for preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine (AL3818)

To a stirred mixture of benzyl 1-(hydroxymethyl)cyclopropylcarbamate (50 g) and DCM (200 ml) was added DIPEA (39g). The result solution was cooled to 0-5^{0}C with ice/water and further stirred under this temperature for 15 min. MsCl (30g) was added via an addition funnel dropwise keeping temperature below 5^{0}C for about 1.5 hours. After completion of addition, the reaction mixture was allowed stirring at 0-5^{0}C for 30 min and quenched with saturated $NaHCO_3$ (150 ml). The solution was extracted with 150 ml DCM twice. The combined DCM layer was washed with 0.1 N HCl (400 ml) followed by brine. It was dried over Na_2SO_4 and concentrated to obtain an off-white solid 60 gram as (1-(benzyloxycarbonylamino)cyclopropyl)methyl methanesulfonate (Y1-1), MS: (M+1) 300.

To a stirred mixture of (Y1-1) (16 g), X1 [(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-hydroxyquinoline, 12 g] , K_2CO_3 (21 g) and KI (21 g) was added DMF (100 ml), the reaction suspension was heated at 80^{0}C for 10 hours and (Y1-1) (10 g) was added to continuously heated 80^{0}C for 10 hours. The reaction then was quenched with water (150 ml) and extracted with 150 ml DCM twice. The combined DCM layer was washed with 2 N NaOH (100 ml) followed by water and brine. It was dried over Na_2SO_4 and concentrated, further recrystallized from EtOH to obtain a yellow solid as benzyl 1-((4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropylcarbamate (Z-1) 9.5 g. MS: (M+1) 542.

To a stirred mixture of (Z-1) (9.5 g), $HCOONH_4$ (4.7 g) and Pd/C (10%, wet 50%, 4.7g) was added MeOH, the reaction mixture was heated at 45^{0}C for 1.5 hours. It was then cooled and filtered through Celite, further evaporated. 2N HCl (200 ml) was added and extracted with DCM/MeOH (10/1, 100 ml) twice. The aqueous layer was basified with 3N NaOH to adjust pH 11-12 to generate a solid precipitation. The solid was filtered and washed with water to neutral, further suction dry. The solid was dissolved into a mixture of DCM/MeOH (250 ml, 10/1) and further washed with water and brine. It was dried with $MgSO_4$ and filtered, further evaporated to give a light yellow solid 5.5 g crude product. Further purification was conducted by dissolving the crude product into DCM/MeOH (40 ml, 10/1) to triturate with petroleum ether (40 ml) for 2 hours slow stirring. The precipitate was filtered and dried in an oven to give the final crystalline

product 4.4 g (MP: 203-208^{0}C) and it can be further purified by recrystallizing from EtOH to give purer final product as a same crystalline form. MS: (M+1) 408; ^{1}H NMR(DMSO-d_6) δ 0.60-0.63(d, 4H), 2.41(s, 1H), 2.42-2.51(t, 2H), 3.31(s, 2H), 3.96(s, 3H), 4.04(s, 2H), 6.27(s, 1H), 6.31-6.32(m, 1H), 6.97-7.02(t, 1H), 7.20-7.22(d, 1H), 7.36(s, 1H), 7.60(s, 1H), 8.40-8.42(d, 1H), 11.41(s, 1H). MP: 208-210^{0}C; DSC Melting Range (Endo): 207-220^{0}C with Peak Temp=216^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 210^{0}C (between 205-215^{0}C). XRPD having pattern comprising characteristic 10 peaks with intensity% greater than 10% expressed in d values and angles as follows:

Angle	d value	Angle	d value
13.344	6.62986	20.650	4.29771
15.858	5.58405	21.633	4.10463
16.799	5.27326	23.087	3.84934
17.640	5.02377	25.128	3.54112
18.770	4.72373	26.607	3.34755

XRPD having pattern compromising 26 characteristic peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	10.892	8.11623	2.1	14	25.128	3.54112	14.6
2	11.589	7.62991	6.1	15	25.669	3.46768	3.8
3	12.195	7.25174	5.9	16	26.607	3.34755	18.0
4	13.344	6.62986	36.2	17	26.607	3.34755	3.1
5	15.858	5.58405	31.5	18	29.050	3.07132	5.7
6	16.799	5.27326	77.9	19	29.797	2.99602	1.5
7	17.640	5.02377	18.8	20	30.681	2.91167	4.3
8	18.770	4.72373	11.9	21	31.853	2.80718	1.2
9	19.987	4.43884	7.2	22	33.524	2.67095	2.8
10	20.650	4.29771	42.0	23	34.789	2.57667	2.6
11	21.633	4.10463	15.3	24	35.873	2.50131	2.2
12	23.087	3.84934	100.0	25	37.391	2.40313	3.9
13	24.356	3.65157	3.5	26	38.637	2.32846	1.4

Graphs of DSC, TGA and XRPD are represented by Fig 1, Fig 2 and Fig 3 respectively.

Example 2

Representation of Process A, Process A2

Process for preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine (AL3818)

It was similar prepared according to the preparation procedures of (Z-1) described in Example 1 by using 4-methoxybenzyl 1-(hydroxymethyl)cyclopropylcarbamate to first generate (1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methyl methanesulfonate (Y1-2) then to give 4-methoxybenzyl 1-((4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)-methyl)cyclopropylcarbamate (Z-2), MS: (M+1) 572

To a stirred mixture of (Z-2) (1.5 g) in DCM (15 ml) at 0°C was added TFA (1.5 ml) for about 30 min and warmed up to RT. The reaction was stirred at RT for 2 hours and added into water (30 ml). The aqueous layer was extracted with DCM twice (100 ml X 2) and basified with 2N NaOH to adjust pH 11-12. The mixture was extracted with DCM (100 ml x 3) and further washed with brine (100 ml). It was dried with $MgSO_4$ and filtered. The solution was evaporated to give 1.05 g crude final product. Further purification was conducted to dissolve the crude product into DCM/MeOH and triturated with petroleum ether and dried in an oven to give the final pure product 0.8 g AL3818 with the same crystalline form.

Example 3

Representation of Process A, Process B1

Process for preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine (AL3818)

To a mixture of benzyl 1-((4-chloro-6-methoxyquinolin-7-yloxy)methyl)cyclopropyl-carbamate (X2-1) (5 g), 4-fluoro-2-methyl-1H-indol-5-ol (Y2) (5 g) and DMAP (4 g) was added 1,6-lutidine (15 ml). The reaction was stirred and heated at 135°C for 5 hours and was cooled followed by adding IPA with slow stirring for 2 hours at RT. The solid was filtered and further washed with IPA, dried to give (Z-1) 5.2 g as a solid. It was then similarly prepared according to deprotection procedures described of (Z-1) in Example 1 to give the final compound AL3818 with the same crystalline form.

Example 4

Representation of Process A, Process B2

Process for preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine (AL3818)

(Z-2) was similarly prepared according to the procedures described in Example 3 by using 4-methoxybenzyl 1-((4-chloro-6-methoxyquinolin-7-yloxy)methyl)cyclopropylcarbamate (X2-2) and (Y2). It was then similarly prepared according to deprotection procedures of (Z-2) described in Example 2 to give the final compound AL3818 with the same crystalline form.

Example 5

Preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)-methyl)cyclopropanamine bishydrochloride acid salt and its crystalline

To a 25 ml flask was added 250 mg free base (AL3818), 4N HCl in dioxane 0.625 mL (2.5mmol, 4 eq.) in 10ml EtOH, the reaction was heated at 75°C for 30 minutes, cooled to RT and stirred for O.N. The solid was filtered and rinsed with acetone twice. It was dried in oven at 50°C for 4 hours to give 126mg white solid as the bishydrochloride salt as a crystalline and further

recrystallized from EtOH to give a purer product as a same crystalline form. ^{1}H NMR(DMSO-d_6) δ 1.09-1.24(m, 4H), 2.43(s, 3H), 4.08(s, 3H), 4.40(s, 2H), 6.32(s, 1H), 6.76(s, 1H), 7.05-7.11(t, 1H), 7.27-7.30(d, 1H), 7.65(s, 1H), 7.82(s, 1H), 8.64(s, 2H), 8.70-8.73(m, 1H), 11.51(s, 1H). Chloride ion chromatography showed 2 molecular ratio ions (16.1%). DSC Melting Range (Exo): 249-280 with Peak Temp=268^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 230^{0}C (between 225-235^{0}C). XRPD having pattern comprising 21 characteristic peaks with intensity% greater than 10% or 27 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	7.640	11.56173	19.5	14	22.814	3.89483	11.2
2	8.642	10.22328	20	15	23.398	3.79886	11.6
3	9.361	9.43969	13.3	16	24.455	3.63702	76.6
4	10.091	8.75881	100.0	17	25.524	3.48708	34.6
5	13.740	6.43957	26.4	18	26.703	3.33576	21.7
6	14.479	6.11252	54.7	19	27.337	3.25978	18.4
7	15.186	5.82962	10.1	20	28.061	3.17732	18.5
8	15.766	5.61643	20.3	21	28.801	3.09732	6.3
9	17.206	5.14957	7.4	22	29.845	2.99133	13.8
10	18.569	4.77448	18.6	23	31.331	2.85271	7.1
11	19.271	4.60215	11.0	24	31.621	2.82721	9.5
12	20.041	4.42696	49.5	25	32.840	2.72504	10.5
13	22.211	3.99909	58.4	26	33.714	2.65632	3.8
				27	38.348	2.34534	9.6

Graphs of DSC, TGA and XRPD are represented by Fig 4, Fig 5 and Fig 6 respectively.

Example 6

Preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine bishydrochloridehydrate acid salt and its crystalline

To a 10mL flask, charged 140mg of 3818-2HCl salt from above Example 4 and 0.7mL(x5 with salt volume) of 80% MeOH in H_2O. The result suspension was heated to 70^{0}C to form a solution and cooled to RT and further stirred for O.N. The solid was filtered and rinsed with acetone twice. It was dried in oven at 50^{0}C for 4 hours to obtain off-white solid 110mg as the crystalline bishydrochloride hydrate salt. ^{1}H NMR(DMSO-d_6) δ 1.09(s, 2H), 1.22(s, 2H), 2.44(s, 1H), 2.52(s, 2H), 4.09(s, 3H), 4.44(s, 2H), 6.32(s, 1H), 6.81-6.82(d, 1H), 7.08-7.14(t, 1H), 7.29-7.32(d, 1H), 7.79(s, 1H), 7.85(s, 1H), 8.75-8.78(d, 1H), 8.85(s, 2H), 11.66(s. 1H). Chloride ion chromatography showed 2 molecular ratio ions (17.8%). DSC Melting Range (Exo): 207-260 ^{0}C with Peak Temp=226^{0}C. TGA demonstrating 2.68% (~3%, 1 water) weight loss till 120^{0}C (between 115-125^{0}C) and further weight loss at about 170^{0}C (between 165-175^{0}C). XRPD having pattern comprising 9 characteristic peaks with intensity% greater than 10% or 12 peaks with all

intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)
1	5.506	16.03679	28.0
2	6.817	12.95694	100
3	8.087	10.92445	29.9
4	9.766	9.04936	20.6
5	13.318	6.64283	22.3
6	14.332	6.17523	7.0
7	16.159	5.48067	15,7
8	19.474	4.55451	8.8
9	20.920	4.24296	6.5
10	20.920	3.87231	28.2
11	25.087	3.54678	20.2
12	25.874	3.44064	22.7

Graphs of DSC, TGA and XRPD are represented by Fig 7, Fig 8 and Fig 9 respectively.

Example 7

Preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)-methyl)cyclopropanamine bismaleic acid salt and its crystalline

To a 25mL flask was added 50mg free base (AL3818) in 1.5mL EtOH, the reaction was heated to 70^0C with stirring. To the result solution was added 36mg (2.5eq) maleic acid as solid and stirred at 70^0C for 0.5hr. It was cooled to RT and stirred for O.N. The solid was filtered and rinsed with acetone twice further dried in oven at 50^0C for 4hours to obtain 68mg of as a crystalline solid and further recrystallized from EtOH to give a purer product as a same crystalline form as two (bis) maleic acid salt. ^{1}H NMR(DMSO-d_6) δ 0.73(s, 2H), 0.88(s, 2H), 3.43(s, 2H), 3.53(s, 2H), 3.59(s, 2H), 3.86(s, 4H), 3.97(s, 3H), 4.41(s, 1H), 6.07(s, 2H), 7.26(s, 1H), 7.44-7.50(t, 1H), 7.76-7.79(d, 1H), 7.88(s, 1H), 8.10-8.12(d, 1H), 8.55(s, 1H), 9.54(s. 1H). Maleic ion chromatography showed 2 molecular ratio ions (37.1%). DSC Melting Range (Endo): 165-202^0C with Peak Temp=183^0C. TGA demonstrating as an unsolvated material with weight loss at about 160^0C (between 155-165^0C). XRPD having pattern comprising 22 characteristic peaks with intensity% greater than 10% or 35 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	6.716	13.14986	29.7	19	22.876	3.88434	5.8
2	8.816	10.02189	34.3	20	23.204	3.83021	19.0
3	9.743	9.07069	15.3	21	23.622	3.76332	78.4
4	10.033	8.80923	21.4	22	24.418	3.64247	6.3
5	11.777	7.50803	21.2	23	26.140	3.40621	87.0
6	13.418	6.59342	6.2	24	26.958	3.30469	26.5
7	14.816	5.97445	11.0	25	27.383	3.25443	61.3
8	16.089	5.50434	9.5	26	28.154	3.16697	41.5
9	16.801	5.27279	24.5	27	29.554	3.02013	6.8

10	17.360	5.10409	87.9	28	30.611	2.91815	23.7
11	17.179	5.15755	70.7	29	31.373	2.84906	14.3
12	18.190	4.87308	20.2	30	33.457	2.67620	6.7
13	18.704	4.74028	16.7	31	34.541	2.59465	2.8
14	19.296	4.59623	5.0	32	35.137	2.55199	3.8
15	19.920	4.45371	12.6	33	35.734	2.51067	2.5
16	20.824	4.26227	65.5	34	37.129	2.41949	8.6
17	21.457	4.13785	100.0	35	39.704	2.26833	3.9
18	22.411	3.96393	4.5				

Graphs of DSC, TGA and XRPD are represented by Fig 10, Fig 11 and Fig 12 respectively.

Example 8

Preparation of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine succinic acid salt and its crystalline

To a 50 mL flask was added 100mg free base (AL3818) in 4mL EtOH, the reaction was heated to 75^{0}C with stirring. To the result solution was added succinic acid as solid 36mg (0.308mmol, 1.25eq) and stirred at 75^{0}C for 0.5 hr. It was cooled to RT and stirred for overnight. The solid was filtered and rinsed with acetone twice further dried in oven at 50^{0}C for 4 hours to obtain a crystalline solid 84mg and further recrystallized from EtOH to give a purer product as a same crystalline form. ^{1}H NMR(DMSO-d_6) δ 0.72(s, 4H), 2.37-2.42(m, 7H), 3.99(s, 3H), 4.10(s, 2H), 6.27(s, 1H), 6.32-6.33(d, 1H), 6.97-7.02(t, 1H), 7.20-7.23(d, 1H), 7.39(s, 1H), 7.61(s, 1H), 8.42(s, 2H), 11.41(s, 1H). Succinic ion chromatography showed 1 molecular ratio ions (23.2%). DSC Melting Range: Melting Range (Endo): 176-202^{0}C with Peak Temp=198^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 180^{0}C (between 175-185^{0}C). XRPD having pattern comprising 11 characteristic peaks with intensity% greater than 10% or 19 peaks with all intensity%:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	5.765	15.31849	12.9	11	23.167	3.83630	1.8
2	8.038	10.98994	7.4	12	24.085	3.69200	16.9
3	11.639	7.59700	27.7	13	24.485	3.63268	14.6
4	12.950 6	6.83065	100	14	25.737	3.45874	13.7
5	16.141 5	5.48683	18.0	15	28.621	3.11637	6.4
6	17.483 5	5.06846	18.7	16	29.255	3.05025	22.1
7	18.385	4.82175	17.8	17	31.357	2.85048	0.9
8	19.394	4.57325	1.1	18	31.967	2.79743	2.1
9	20.756	4.27609	13.4	19	35.630	2.51780	2.4
10	22.034	4.03092	2.8				

Graphs of DSC, TGA and XRPD are represented by Fig 13, Fig 14 and Fig 15 respectively.

Example 9

In vitro MTT (proliferation) assay was performed with compound from above examples to give following inhibition results:

Sample Name	AL3818-H1 (2HCl)	AL3818-H2 (2HCl.HCl)	AL3818-S (Succinic)	AL3818-M (Bismaleic)	AL3818-F (Free Base)
Cancer Cell Lines	IC50 (μM)	IC50 (μM)	IC50 (μM)	IC50 (μM)	IC50 (μM)
PANC-1 (pancreatic)	1.58	1.55	1.24	1.15	1.34
NC1-H157 (lung)	7.18	2.29	2.28	2.02	1.83
MDA-MB-231 (breast)	10.25	5.71	6.1	5.37	5.56
Hela (cervical)	3.7	4.07	4.66	3.94	3.23
PC-3 (prostate)	5.53	3.88	4.41	3.62	5.11
BEL7404 (liver)	2.75	1.74	1.43	1.15	0.93
MKN45 (gastric)	1.77	3.9	4.16	2.65	3.11
Ishikawa (endometrial)	5.67	1.56	1.32	1.34	1.04
Saos-2 (sarcoma)	4.68	4.98	5.68	5.49	5.13
SKOV3 (ovarian)	5.34	5.7	7.6	6.56	5.97
SW579 (thyroid)	2.33	1.29	2.61	1.15	1
HCT116 (colon)	3.45	3.34	3.94	4.62	3.25

Example 10

Based on the inventor's research experience using AL3818 free base, its 2HCl salts, its bis-maleic acid salt and its succinic salt, the following tumor inhibition results are expected in a MTT assay according to Example 9.

2-10 μM ± 1.7 μM in vitro inhibition activities are expected on various solid tumor cell lines, such as renal, melanoma, head/neck, bladder, brain; and blood cancers, such as ALL, CLL, AML, CML and Multiple Myeloma.

Example 11

Animal antitumor activity in vivo testing with endometrial Ishikawa cell line (xenograft) is performed as follows:

The well grown tumor tissue of endometrial cancer Ishikawa was cut into 3mm pieces, and each nude mouse was subcutaneously inoculated with one piece into the right armpit. The animals were grouped and administrated as following:

1) AL3818-H1 (Bishydrochloride acid salt, 2HCl), MW: 480, 3.54mg/kg
2) AL3818-H2 (Bishydrochloridehydrate acid salt, $2HCl.H_2O$), MW: 598, 3.67mg/kg
3) AL3818-S (Succinic acid salt), MW: 525, 3.87mg/kg
4) AL3818-M (Bismaleic acid salt), MW: 639, 4.71mg/kg
5) AL3818-F (Free Base), MW: 407, 3mg/kg
6) Control

Treatments were initiated when the tumors size reached above $100mm^3$ after 13 days. According

to the size of tumor, the animals with oversize or undersize tumors were eliminated, and the animals were grouped with similar average tumor volume. Then the animals were oral administrated daily for continuous 14 days with volume of 0.5ml/20g as the above. The large diameter a (mm) and the small diameter b (mm) were measured with caliper twice a week after inoculation for 13 days. The tumor volume was calculated by formular: $TV = ab^2/2$. The relative tumor volume was calculated as: RTV = Vt/Vo， Vo represents the tumor volume on the first day of treatment; Vt represents the tumor volume on each measurement day. The animals were executed and tumors were got by dissection 30 days after inoculation (D18). Then, the individual body weight and tumor weight were determined, and calculate as following formula.

Tumor inhibition activities are between 50-95%. Results are shown in **Fig 16.**

Example 12

Based on the inventor's research experience using AL3818 free base, its HCl salts (mono or bis), its bis-maleic acid salt and its succinic salt, the following in vivo tumor inhibition results (xenografts) are expected according to Example 11.

50%-100% in vivo tumor inhibition activities are expected on various solid tumor cell lines, such as lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian, cervical and endometrial cancers; and blood cancers, such as ALL, CLL, AML, CML and Multiple Myeloma.

Example 13

AL3818 bis HCl salt and bis-maleic acid salt were also tested in combining with chemotherapy by using platinum based, taxane based or both; such as: cisplatin, carboplatin, paclitaxel or cisplatin/paclitaxel, carboplatin/paclitaxel combined. The experiment of combination with carboplatin/paclitaxel was carried out similar to the description of Example 11. Tumor inhibition activities are between 50 to >100%. Results are shown in **Fig 17.**

Example 14

Based on the inventor's research experience using AL3818 free base, its HCl salts (mono or bis), its bis-maleic acid salt and its succinic salt, the following in vivo combining chemotherapy (standard of care, such as platinum based, taxane based or both chemotherapy) tumor inhibition results (xenografts) are expected according to Example 13, especially combing with cisplatin, carboplatin, paclitaxel or cisplatin/paclitaxel, carboplatin/paclitaxel together.

50 to >100% regression in vivo tumor inhibition activities are expected on various solid tumor cell lines, such as lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian and cervical cancers; and blood cancers, such as ALL, CLL, AML, CML and Multiple Myeloma.

Example 15

Based on the inventor's research experience using AL3818 free base, its HCl salts (mono or bis), its bis-maleic acid salt and its succinic salt, the following in vivo combining effects are expected, which in combining with immunotherapy agents, selected from PD-1 or PD-L1, SLAM7, oncolytic virus therapy, bispecific T cell engagers (BiTE) and chimeric antigen receptor (CAR) T cell therapy based agents, such as nivolumab, pembrolizumab, ipilimumab, blinatumomab, elotuzumab, daratumumab, talimogene laherparepvec but not limited, in treating solid tumors, selected from lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian, cervical and endometrial cancers; and blood cancers, selected from ALL, CLL, AML, CML and Multiple Myeloma

50 to >100% regression in vivo tumor inhibition activities are expected on various solid tumor cell lines, such as lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian and cervical cancers; and blood cancers, such as ALL, CLL, AML, CML and Multiple Myeloma.

Example 16

A mouse model of laser-induced choroidal neovascularization (CNV)

(1) Experiments were performed in C57 BL/6 mice at 10 to 12 weeks of age. Laser CNV was induced with a 532 nm diode laser mounted on a slit lamp, using 50 μm spot size, 100 ms duration and 100 mW laser energy. Each eye received 4 laser burns. Stock solution of AL3818-H1 was made by dissolving the compound in water to 25 mg/ml concentration, and further diluted to working solution of either 250 or 25 μg/ml in water. Mice were orally gavaged at dosage of 2.5 or 0.25 mg/kg body weight, in volume of 200 μl per 20 gram of body weight, once every day starting at one day before laser treatment until 10 days afterwards. Control group mice will receive gavage with water which is used to dissolve the compound. By the end of the experiment, mice were subjected to fluorescence angiography to exclude the spots with hemorrhage and other mechanic injuries caused by the procedures. Mice were sacrificed and CNV size was measured by immunostaining of RPE/choroid flat mount co-stained with FITC-conjugated isolectin B4 and anti-ICAM2 antibody. For groups of control, 0.25 mg/kg and 2.5 mg/kg, we examined 43, 44 and 49 eyes on RPE/choroid flat mount. After immunostaining, images were taken on a Zeiss fluorescence microscope. CNV size was measured in Image J software. Our results (**Fig. 18**) show that mice treated with AL3818 at 0.25 or 2.5 mg/kg body weight had nearly 70% reduction in average size of laser-induced CNV.

(2) The potential synergistic or additive effects between AL3818-M and anti-VEGF antibody was also studied. Immediately after laser burn, mice were treated with a monoclonal VEGF neutralizing antibody from R&D Systems (mAb AF564) at 1 μg dosage by intravitreal injection.

We had 4 experimental groups: control (treated with water), AL3818-M, anti-VEGF, and AL3818-M+anti-VEGF. A total of 75 laser spots were analyzed. Mice in control or AL3818-M alone group received the intravitreal injection of saline in the same 2 μl volume. The results **((Fig. 19)** showed that eyes treated with 0.15 mg/kg AL3818 and 1 μg anti-VEGF antibody had a nearly 30% reduction in laser CNV as compared to the control group ($P<0.01$, one-way ANOVA, Dunnett post-hoc test).

Example 17

Based on the inventor's research experience using AL3818 free base, its HCl salts (mono or bis), its bis-maleic acid salt and its succinic salt, in vivo animal model CNV efficacies which related to effective treatment of an optometric disease, such as AMD (Age-Related Macular Degeneration) but not limited, are definitely expected according to Example 16; or combing these compounds with anti-VEGF antibody or VEGF trap, such as ranibizumab or aflibercep but not limited, to generate a synergistic treatment effect are definitely expected according to Example 16 as well.

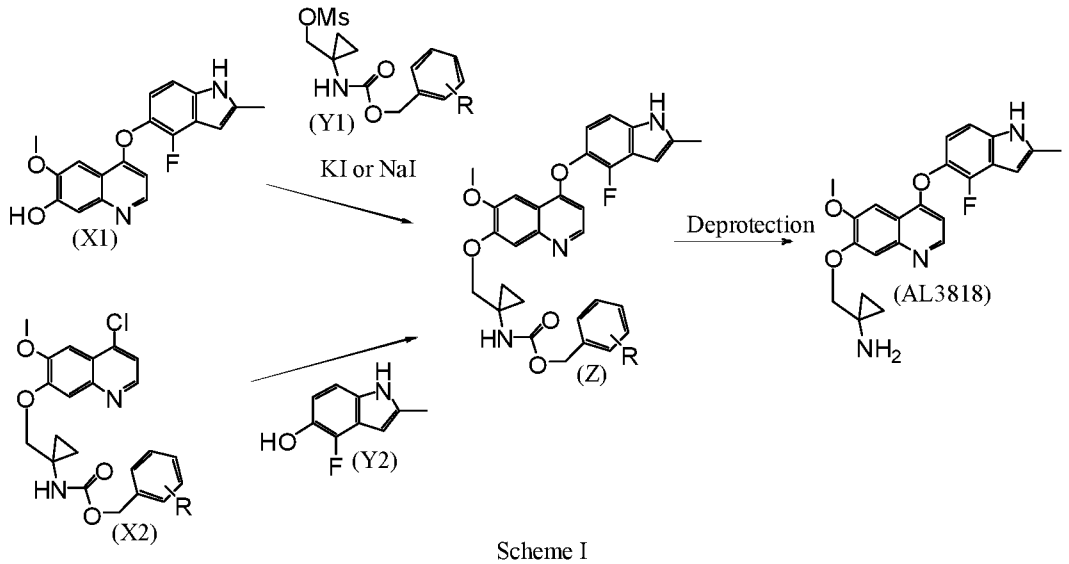
Example 18

Conventional water solubility test has been conducted to give the following results:

Sample Name	AL3818-H1 (2HCl)	AL3818-H2 (2HCl.H2O)	AL3818-S (Succinic)	AL3818-M (2Maleic)	AL3818-F (Free Base)
	(mg/ml)	(mg/ml)	(mg/ml)	(mg/ml)	(mg/ml)
water solubility	6	7	0.1	0.5	0.02

What is claimed is:

1. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quinolin-7-yloxy)methyl)cyclopropanamine (AL3818) by condensing intermediate (X1) with (Y1) in a solvent at the presence of KI or NaI, or intermediate (X2) with (Y2) to form intermediate (Z) which is deprotected to give the final compound (AL3818) in Scheme I.



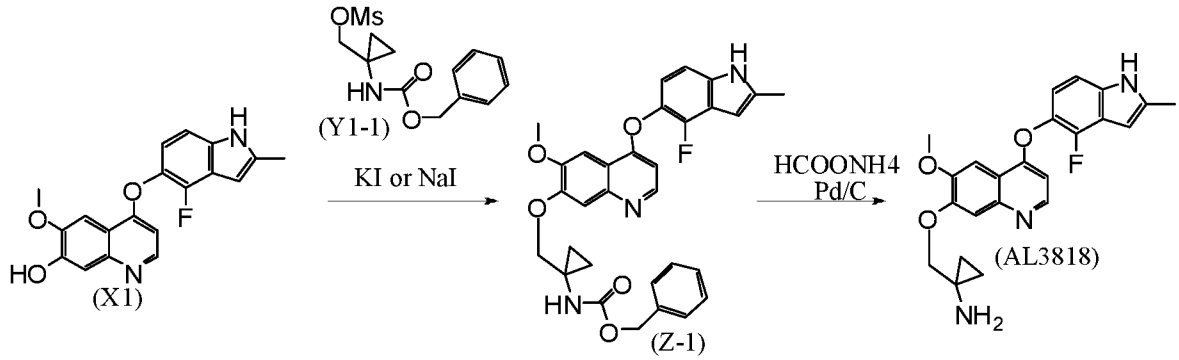
Scheme I

Wherein

R is selected from H and C_1-C_6alkoxy; R is further selected from H and –OMe.

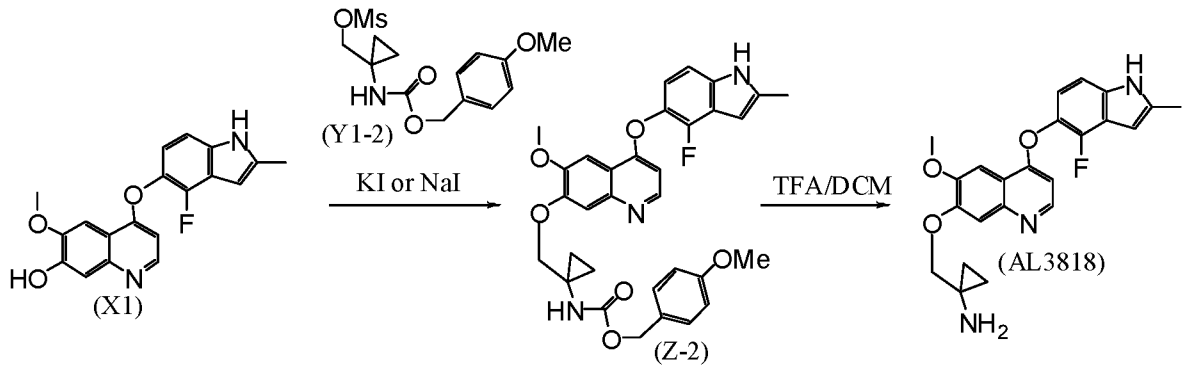
2. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine (AL3818) according to claim 1 where AL3818 can be prepared according to Process A1 when R is H by deprotecting intermediate (Z-1) with HCOONH4 (ammonium formate) and Pd/C in an alcoholic solvent at 25°C-80°C for 0.1-4 hours. (Z-1) can be prepared by reacting intermediate (X1) with (Y1-1) at the presence of KI or NaI with K_2CO_3 in acetone or DMF at a temperature of 60°C-160°C for 2-24 hours.

Process A1 (R=H)



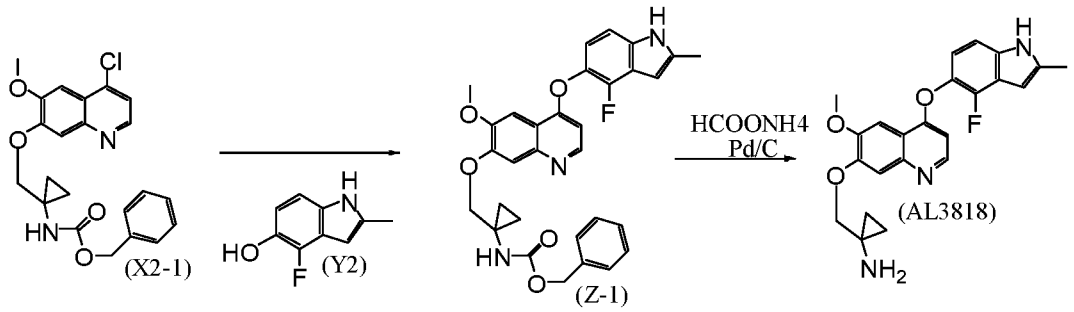
3. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine (AL3818) according to claim 1 where AL3818 can be prepared according to Process A2 when R is 4-OMe by deprotecting intermediate (Z-2) with TFA in DCM at 0°C-30°C for 1-24 hours. (Z-2) can be prepared by reacting intermediate (X1) with (Y1-2) at the presence of KI or NaI with K_2CO_3 in acetone or DMF at a temperature of 60°C -160°C for 2-24 hours.

Process A2 (R=4-OMe)



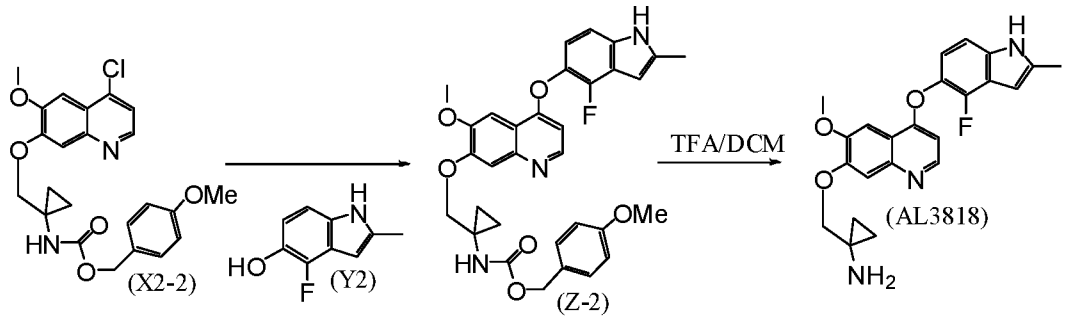
4. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine (AL3818) according to claim 2 where (Z-1) can be prepared according to Process B1 by reacting intermediate (X2-1) with (Y2) in pyridine or lutidine at a temperature of 60°C -160°C for 1-12 hours.

Process B1 (R=H)



5. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine (AL3818) according to claim 3 where (Z-2) can be prepared according to Process B2 by reacting intermediate (X2-2) with (Y2) in pyridine or lutidine at a temperature of 60°C -160°C for 1-12 hours.

Process B2 (R=4-OMe)



6. A process to prepare intermediate (Z) according to claim 1, wherein R is H or –OMe, KI is used according to first step of Process A1 and A2 with DMF at 80°C. Lutidine is used according to first step of Process B1 and B2 at 135°C.

7. A process to synthesize 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine (AL3818) according to claim 1, wherein R is H, HCOONH4/Pd/C is used for the deprotection step at 45°C; wherein R is –OMe, DCM/TFA (10/1) is used for the deprotection step at 25°C.

8. A crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine of AL3818 exhibiting at least one of following characters:

a melting point at 208°C-210°C;

a DSC Melting Range (Endo): 207-220°C with Peak Temp=216°C, pattern shown in Fig 1;

a TGA themogram that doesn't exhibit significant weight loss until at 205-215°C, pattern shown in Fig 2;

9. A crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine according claim 8 exhibiting a XRPD having pattern shown in Fig 3 comprising 10 characteristic peaks with intensity% greater than 10% expressed in d values and angles as follows:

Angle	d value	Angle	d value
13.344	6.62986	20.650	4.29771
15.858	5.58405	21.633	4.10463
16.799	5.27326	23.087	3.84934
17.640	5.02377	25.128	3.54112
18.770	4.72373	26.607	3.34755

10. A crystalline form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)cyclopropanamine according claim 8 exhibiting a XRPD having pattern shown in Fig 3 comprising 26 characteristic peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	10.892	8.11623	2.1	14	25.128	3.54112	14.6
2	11.589	7.62991	6.1	15	25.669	3.46768	3.8
3	12.195	7.25174	5.9	16	26.607	3.34755	18.0
4	13.344	6.62986	36.2	17	26.607	3.34755	3.1
5	15.858	5.58405	31.5	18	29.050	3.07132	5.7
6	16.799	5.27326	77.9	19	29.797	2.99602	1.5
7	17.640	5.02377	18.8	20	30.681	2.91167	4.3
8	18.770	4.72373	11.9	21	31.853	2.80718	1.2
9	19.987	4.43884	7.2	22	33.524	2.67095	2.8
10	20.650	4.29771	42.0	23	34.789	2.57667	2.6
11	21.633	4.10463	15.3	24	35.873	2.50131	2.2
12	23.087	3.84934	100.0	25	37.391	2.40313	3.9
13	24.356	3.65157	3.5	26	38.637	2.32846	1.4

11. A salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)-methyl)-cyclopropanamine is selected from: bishydrochloride acid salt, bishydrochloridehydrate acid salt, bismaleic acid salt and succinic acid salt

12. A bishydrochloride salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quino-lin-7-yloxy)methyl)cyclopropanamine according claim 11 is a crystalline form exhibiting a XRPD having pattern shown in Fig 6 comprising 21 characteristic peaks with intensity% greater than 10% or 27 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	7.640	11.56173	19.5	14	22.814	3.89483	11.2
2	8.642	10.22328	20	15	23.398	3.79886	11.6
3	9.361	9.43969	13.3	16	24.455	3.63702	76.6
4	10.091	8.75881	100.0	17	25.524	3.48708	34.6
5	13.740	6.43957	26.4	18	26.703	3.33576	21.7
6	14.479	6.11252	54.7	19	27.337	3.25978	18.4
7	15.186	5.82962	10.1	20	28.061	3.17732	18.5
8	15.766	5.61643	20.3	21	28.801	3.09732	6.3
9	17.206	5.14957	7.4	22	29.845	2.99133	13.8
10	18.569	4.77448	18.6	23	31.331	2.85271	7.1
11	19.271	4.60215	11.0	24	31.621	2.82721	9.5
12	20.041	4.42696	49.5	25	32.840	2.72504	10.5
13	22.211	3.99909	58.4	26	33.714	2.65632	3.8
				27	38.348	2.34534	9.6

13. A bishydrochloridehydrate acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quino-lin-7-yloxy)methyl)cyclopropanamine according claim 11 is a crystalline form exhibiting a XRPD having pattern shown in Fig 9 comprising 9 characteristic peaks with intensity% greater than 10% or 12 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)
1	5.506	16.03679	28.0
2	6.817	12.95694	100
3	8.087	10.92445	29.9
4	9.766	9.04936	20.6
5	13.318	6.64283	22.3
6	14.332	6.17523	7.0
7	16.159	5.48067	15,7
8	19.474	4.55451	8.8
9	20.920	4.24296	6.5
10	20.920	3.87231	28.2
11	25.087	3.54678	20.2
12	25.874	3.44064	22.7

14. A bismaleic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quino-lin-7-yloxy)methyl)cyclopropanamine according claim 11 is a crystalline form exhibiting a XRPD having pattern shown in Fig 12 comprising 22 characteristic peaks with intensity% greater than 10% or 35 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	6.716	13.14986	29.7	19	22.876	3.88434	5.8
2	8.816	10.02189	34.3	20	23.204	3.83021	19.0
3	9.743	9.07069	15.3	21	23.622	3.76332	78.4
4	10.033	8.80923	21.4	22	24.418	3.64247	6.3
5	11.777	7.50803	21.2	23	26.140	3.40621	87.0
6	13.418	6.59342	6.2	24	26.958	3.30469	26.5
7	14.816	5.97445	11.0	25	27.383	3.25443	61.3
8	16.089	5.50434	9.5	26	28.154	3.16697	41.5
9	16.801	5.27279	24.5	27	29.554	3.02013	6.8
10	17.360	5.10409	87.9	28	30.611	2.91815	23.7
11	17.179	5.15755	70.7	29	31.373	2.84906	14.3
12	18.190	4.87308	20.2	30	33.457	2.67620	6.7
13	18.704	4.74028	16.7	31	34.541	2.59465	2.8
14	19.296	4.59623	5.0	32	35.137	2.55199	3.8
15	19.920	4.45371	12.6	33	35.734	2.51067	2.5
16	20.824	4.26227	65.5	34	37.129	2.41949	8.6
17	21.457	4.13785	100.0	35	39.704	2.26833	3.9
18	22.411	3.96393	4.5				

15. A succinic acid salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-quino-lin-7-yloxy)methyl)cyclopropanamine according claim 11 is a crystalline form exhibiting a XRPD having pattern in Fig 15 comprising 11 characteristic peaks with intensity% greater than 10% or 19 peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	Intensity (%)	NO.	Angle	d value	Intensity (%)
1	5.765	15.31849	12.9	11	23.167	3.83630	1.8
2	8.038	10.98994	7.4	12	24.085	3.69200	16.9
3	11.639	7.59700	27.7	13	24.485	3.63268	14.6
4	12.950 6	6.83065	100	14	25.737	3.45874	13.7
5	16.141 5	5.48683	18.0	15	28.621	3.11637	6.4
6	17.483 5	5.06846	18.7	16	29.255	3.05025	22.1
7	18.385	4.82175	17.8	17	31.357	2.85048	0.9
8	19.394	4.57325	1.1	18	31.967	2.79743	2.1
9	20.756	4.27609	13.4	19	35.630	2.51780	2.4
10	22.034	4.03092	2.8				

16. A salt of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquino-lin-7-yloxy)methyl)-cyclopropanamine according to claim 11 with DSC and TGA having following characteristics:

bishydrochloride acid salt with DSC Melting Range (Exo): 249-280 with Peak Temp=268^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 230^{0}C (between 225-235^{0}C), shown in Fig 4, Fig 5;

bishydrochloridehydrate acid salt with DSC Melting Range (Exo): 207-260^{0}C with Peak Temp=226^{0}C. TGA demonstrating 2.68% (~3%, 1 water) weight loss till 120^{0}C (between 115-125^{0}C) and further weight loss at about 170^{0}C (between 165-175^{0}C), shown in Fig 7, Fig 8;

bismaleic acid salt with DSC Melting Range (Endo): 165-202^{0}C with Peak Temp=183^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 160^{0}C (between 155-165^{0}C), shown in Fig 10, Fig 11;

succinic acid salt with DSC Melting Range: Melting Range (Endo): 176-202^{0}C with Peak Temp=198^{0}C. TGA demonstrating as an unsolvated material with weight loss at about 180^{0}C (between 175-185^{0}C), shown in Fig 13, Fig 14.

17. A pharmaceutical composition that comprises as an active ingredient a compound as defined in any one of claims 8-16 of the compound and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition that comprises as an active ingredient selected from bishydrochloride acid, bishydrochloridehydrate acid, bismaleic acid and succinic acid salt, and their stable crystalline salt forms or stable crystalline free base form of 1-((4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yloxy)methyl)cyclopropanamine and a pharmaceutically acceptable carrier.

19. A method of treating a neoplastic disease, said method comprising administering a compound as defined in any one of claims 8-16 or pharmaceutical composition comprising a compound as defined in any one of claims 8-16 and pharmaceutically acceptable excipients to a subject in need thereof; or combining with chemotherapy agents or immunotherapy agents to a subject in need thereof.

20. A method of treating as claimed in claim 19, wherein the neoplastic disease is solid tumors, selected from lung, renal, colorectal, gastric, melanoma, head/neck, thyroid, pancreatic, liver, prostate, bladder, brain, sarcoma, breast, ovarian, cervical and endometrial cancers; and blood cancers, selected from ALL, CLL, AML, CML and Multiple Myeloma.

21. A method of treating as claimed in claim 19, wherein the combining chemotherapy agents are selected from platinum based or taxane based agents.

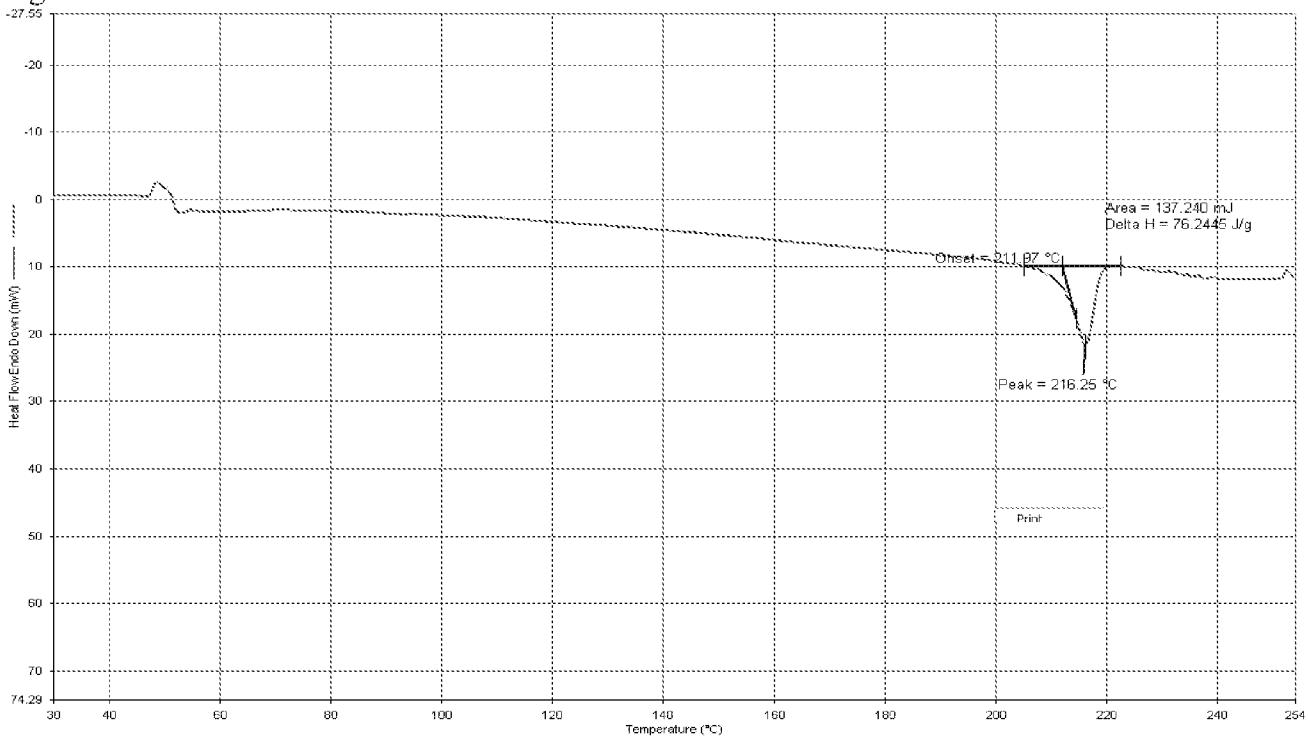
22. A method of treating as claimed in claim 19 and 21, wherein the combing chemotherapy agents are selected from cisplatin, carboplatin, paclitaxel or cisplatin/paclitaxel or carboplatin/paclitaxel.

23. A method of treating as claimed in claim 19, wherein the combining immunotherapy agents are selected from nivolumab, pembrolizumab, ipilimumab, blinatumomab, elotuzumab, daratumumab, talimogene laherparepvec.

24. A method of treating an optometric disease, said method comprising administering a compound as defined in any one of claims 8-16 or pharmaceutical composition comprising a compound as defined in any one of claims 8-16 and pharmaceutically acceptable excipients to a subject in need thereof; or combing with anti-VEGF antibody, or VEGF trap to a subject in need thereof.

25. A method of treating as claimed in claim 23, wherein an optometric disease is AMD and the combing anti-VEGF antibody is ranibizumab, or the VEGF trap is aflibercep.

Fig 1.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Heat Flow Endo Down (mW)
Temperature (°C)

Fig 2.

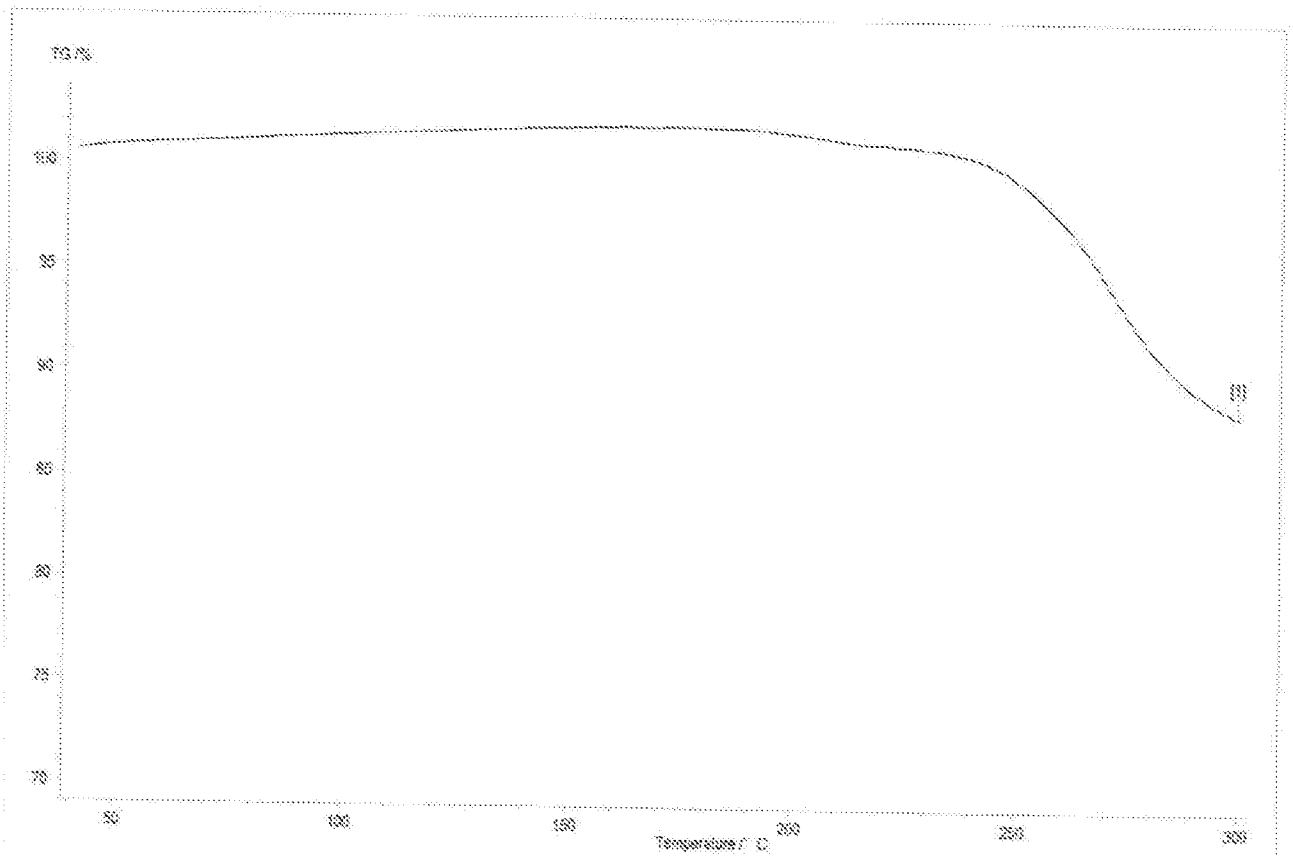
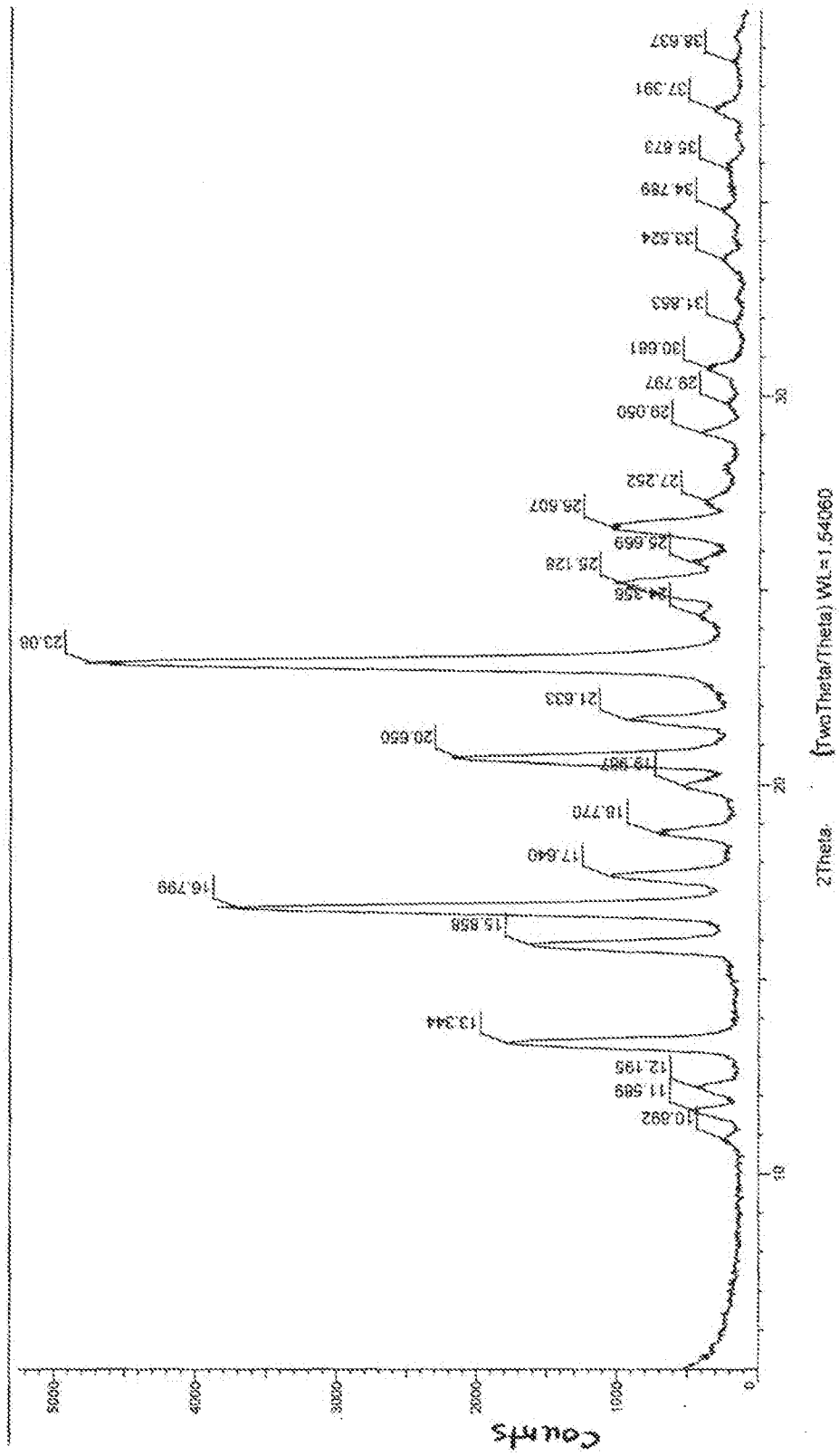


Fig 3.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13.344
15.858
16.799
17.640
18.770
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20.650
21.633
23.088
24.456
25.128
25.669
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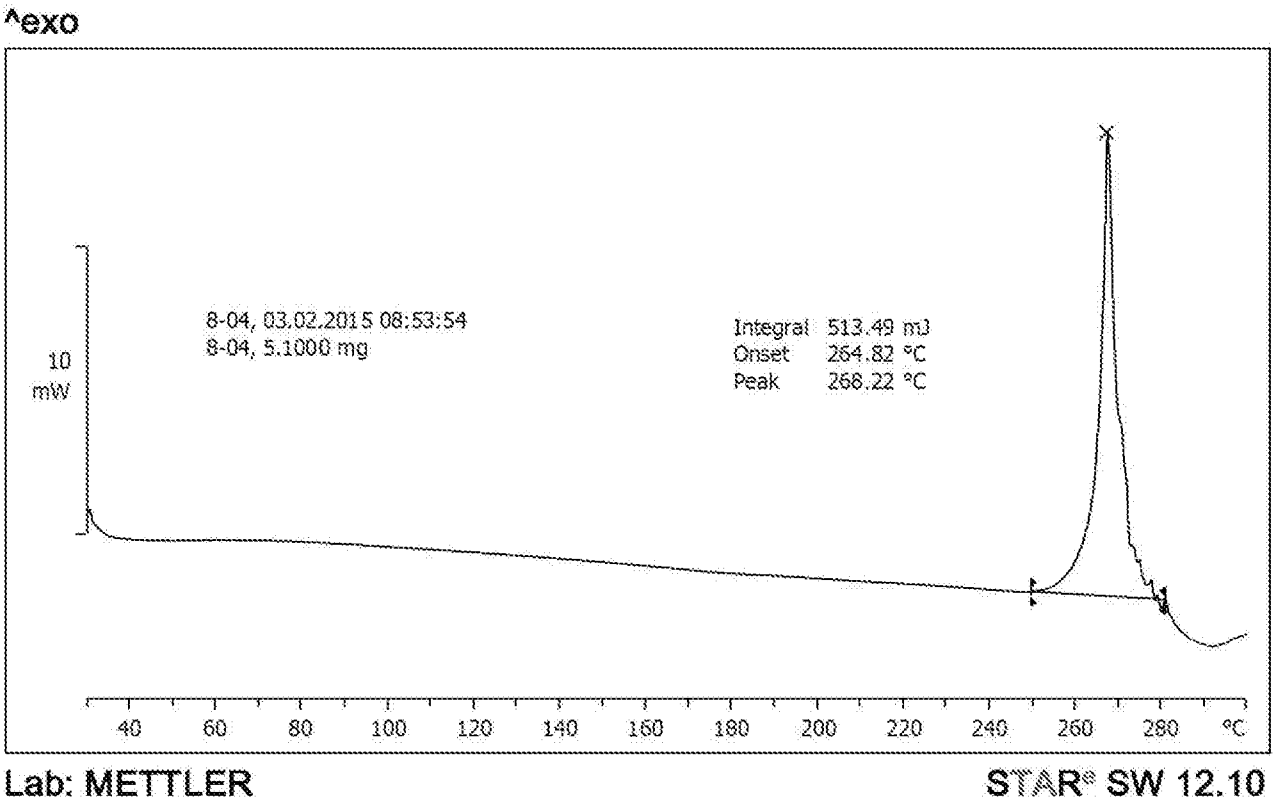
37.391
38.637

Fig 4.


^exo
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Onset 264.82 °C
Peak 268.22 °C
10
mW
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
Lab: METTLER
STAR® SW 12.10

Fig 5.

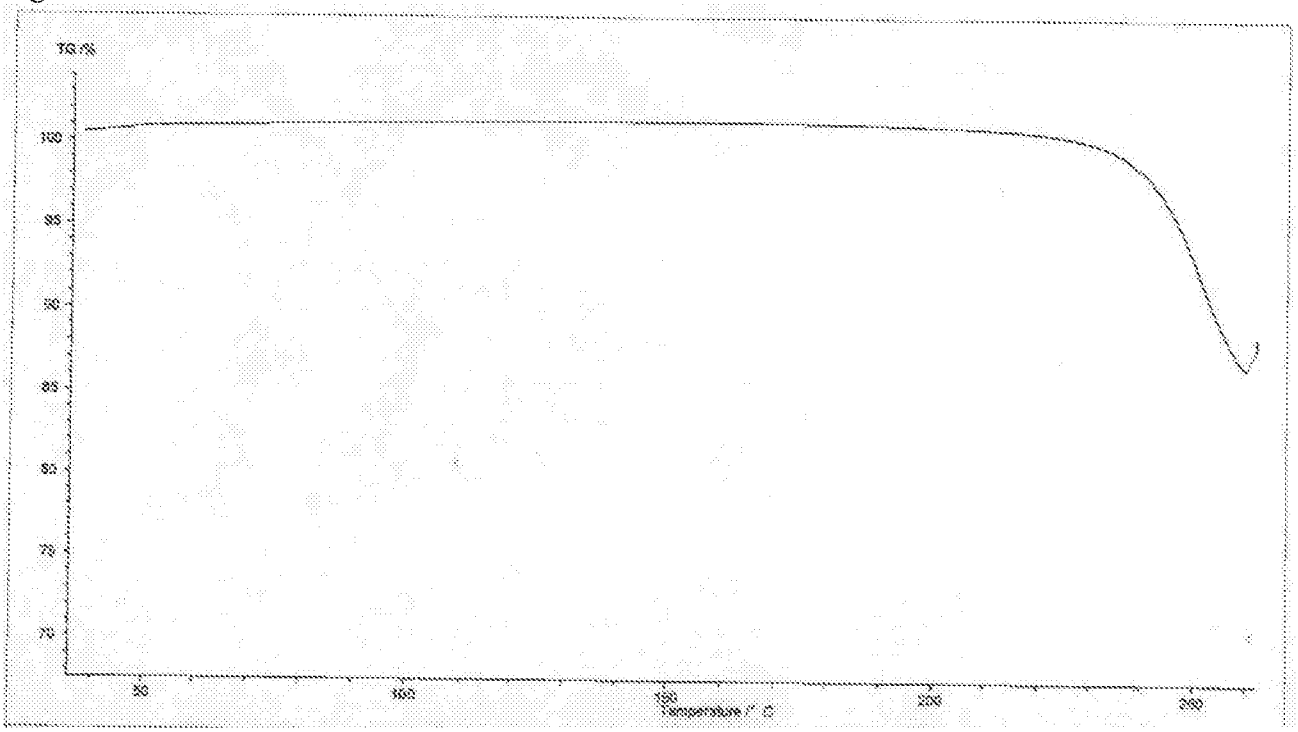
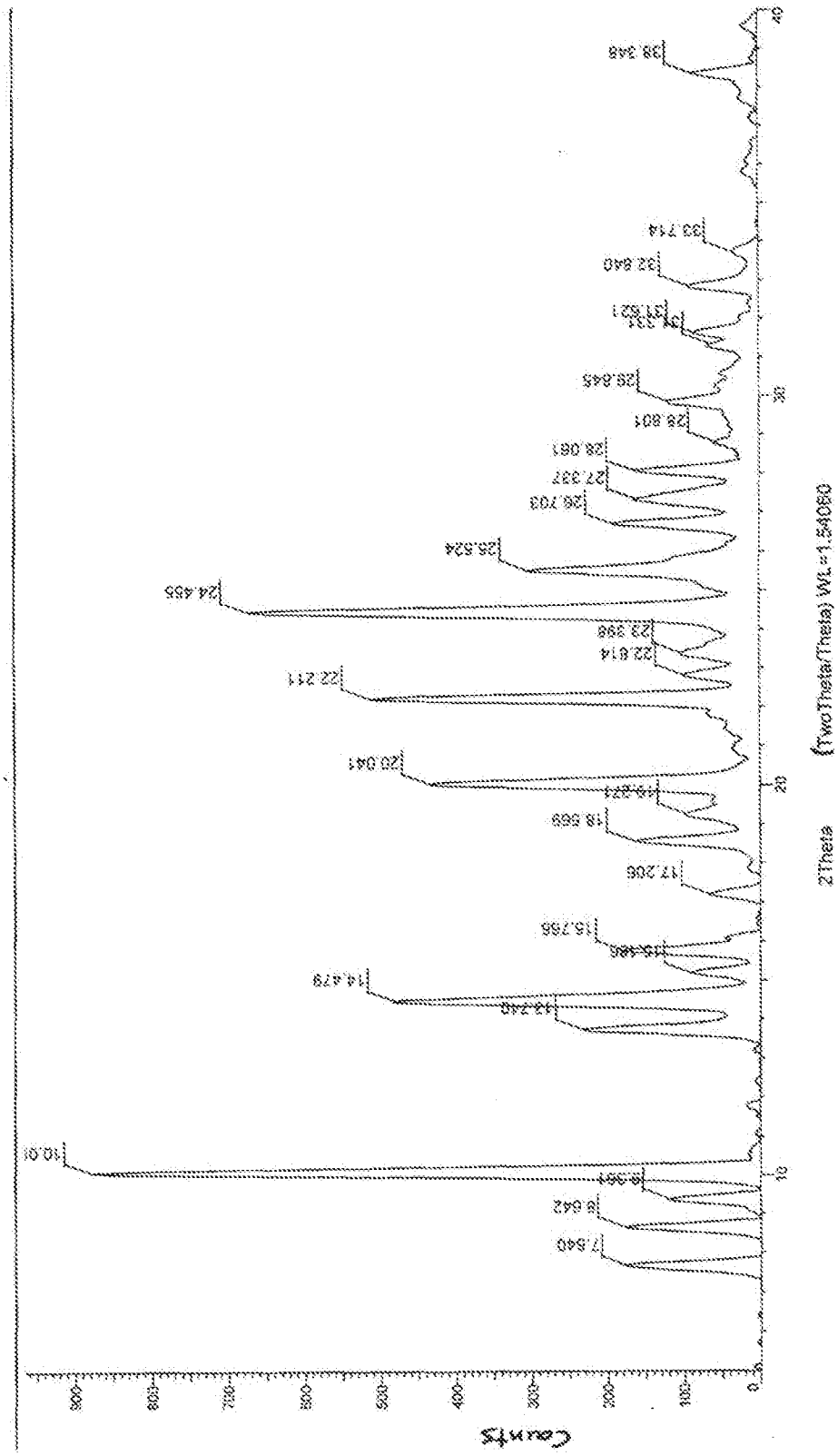


Fig 6.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17.206
18.569
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22.211
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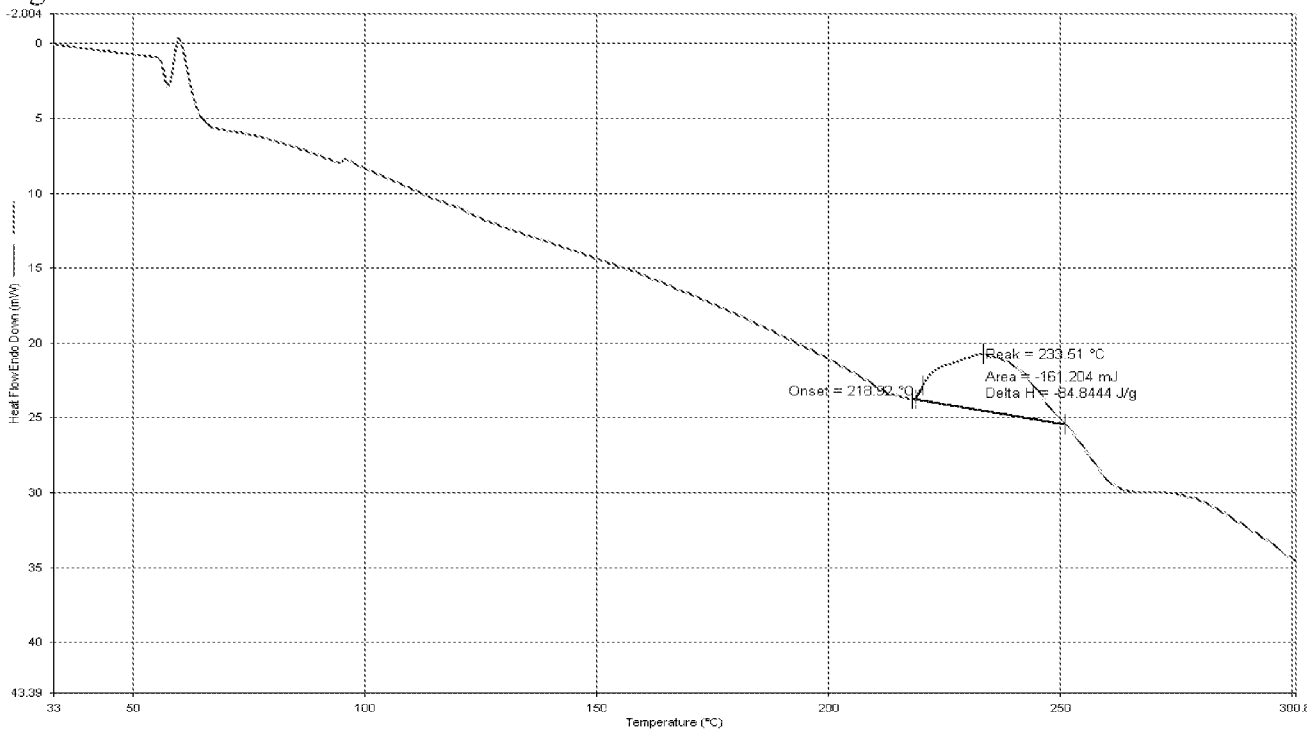
39.348

Fig 7.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10
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20
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200
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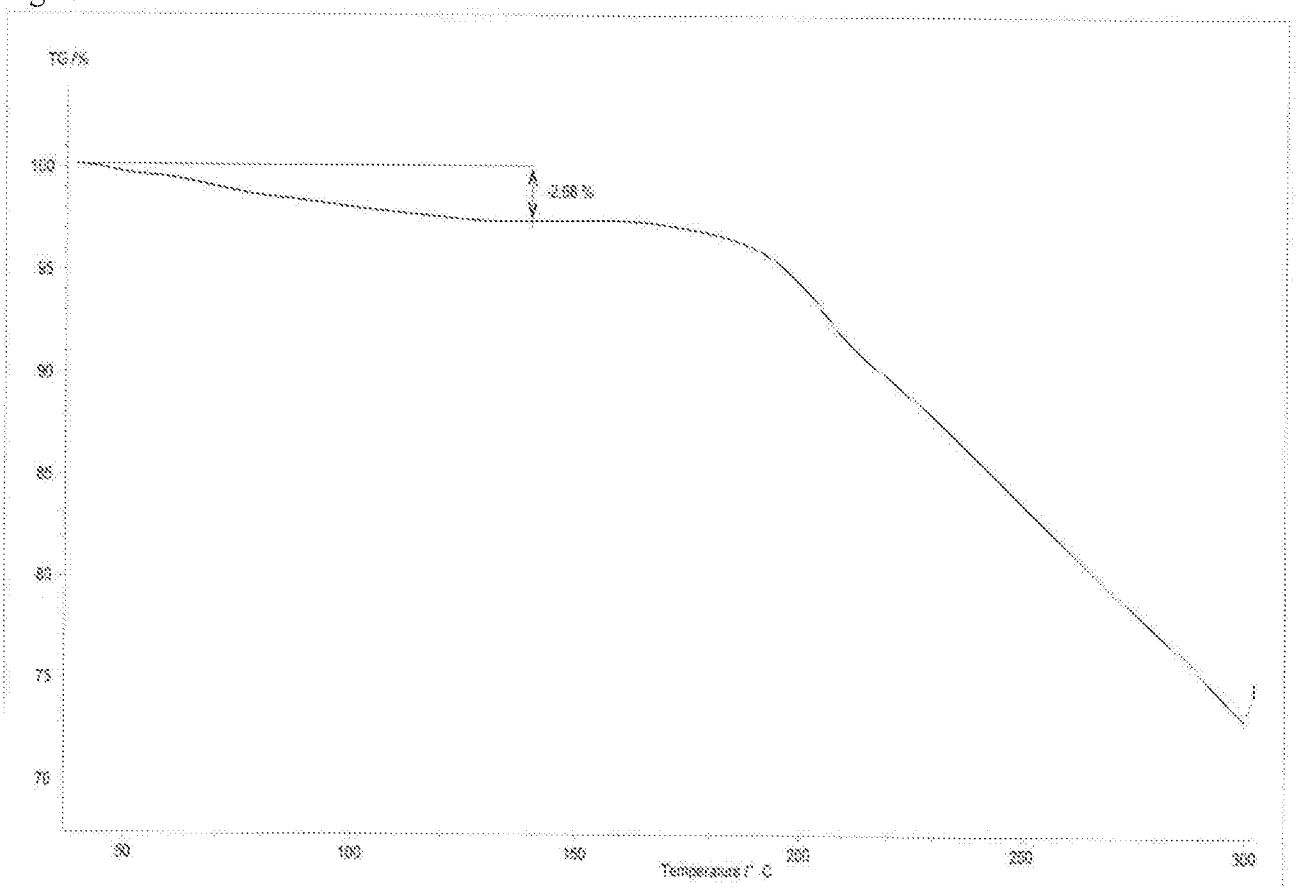
Onset = 218.92 °C

Fig 8.


TG/%
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85
80
75
70
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50
100
150
200
250
300
Temperature / °C

Fig 9.

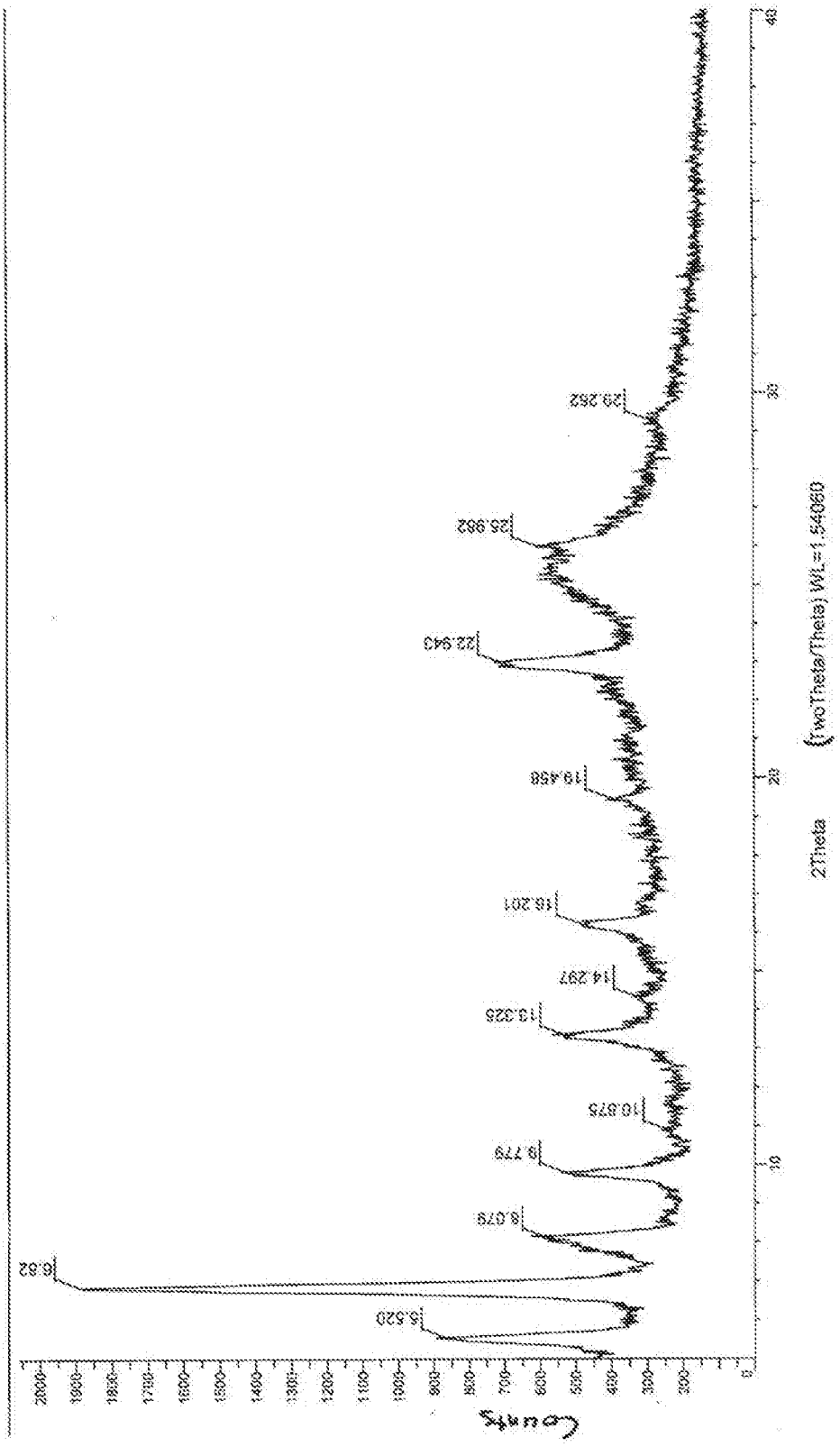
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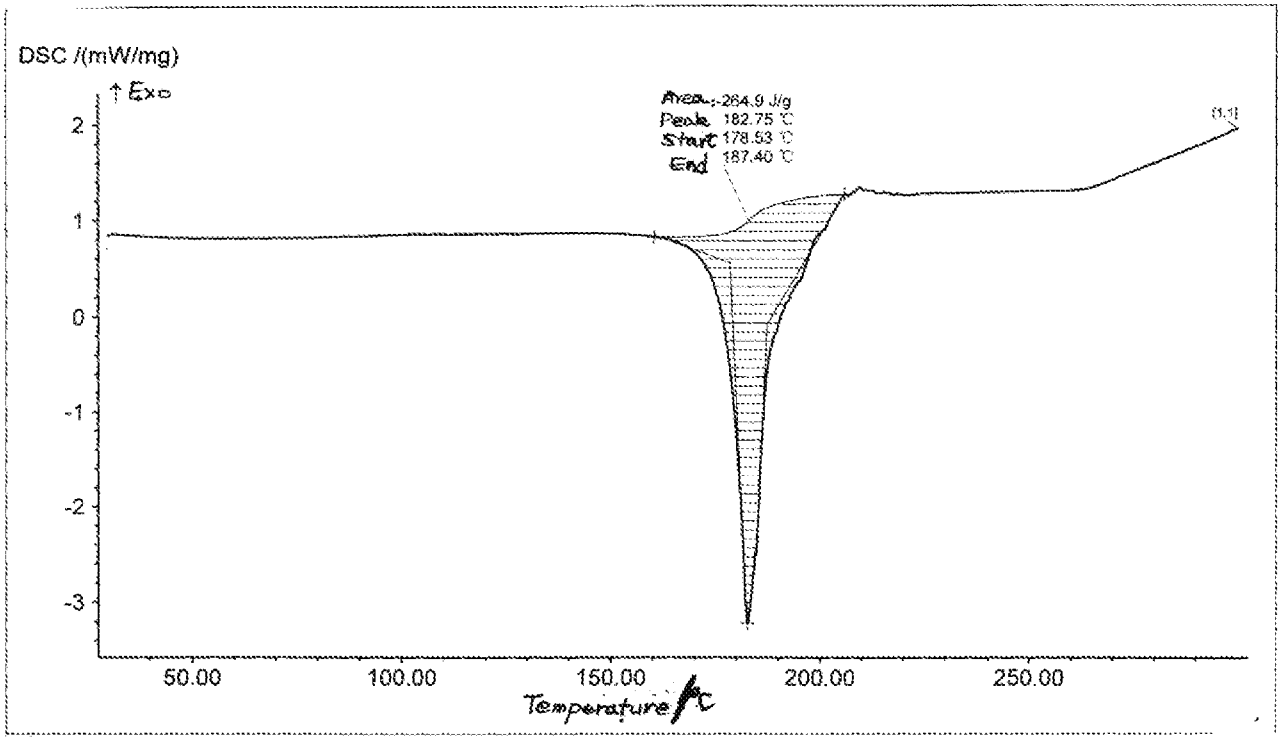
Fig 10.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Start 178.53 °C
End 187.40 °C
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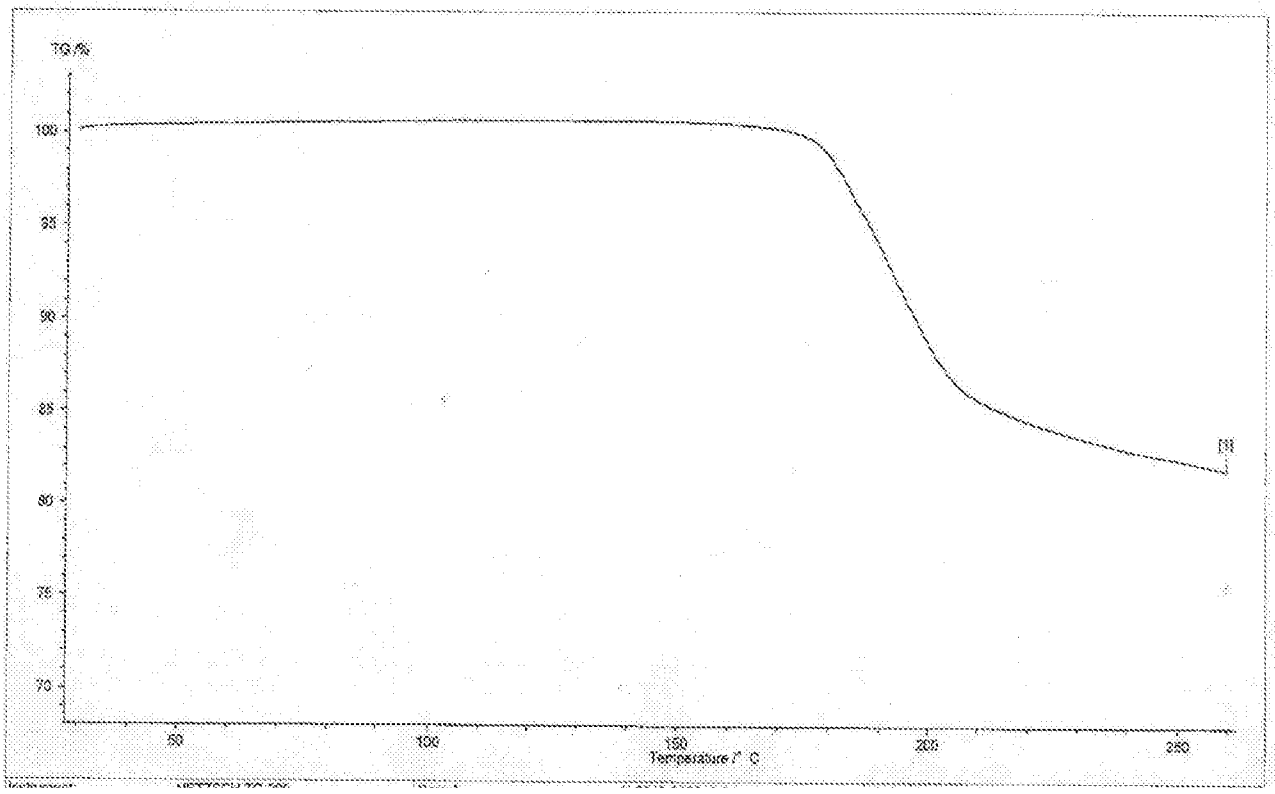
250.00
Temperature /°C

Fig 11.


TG/%
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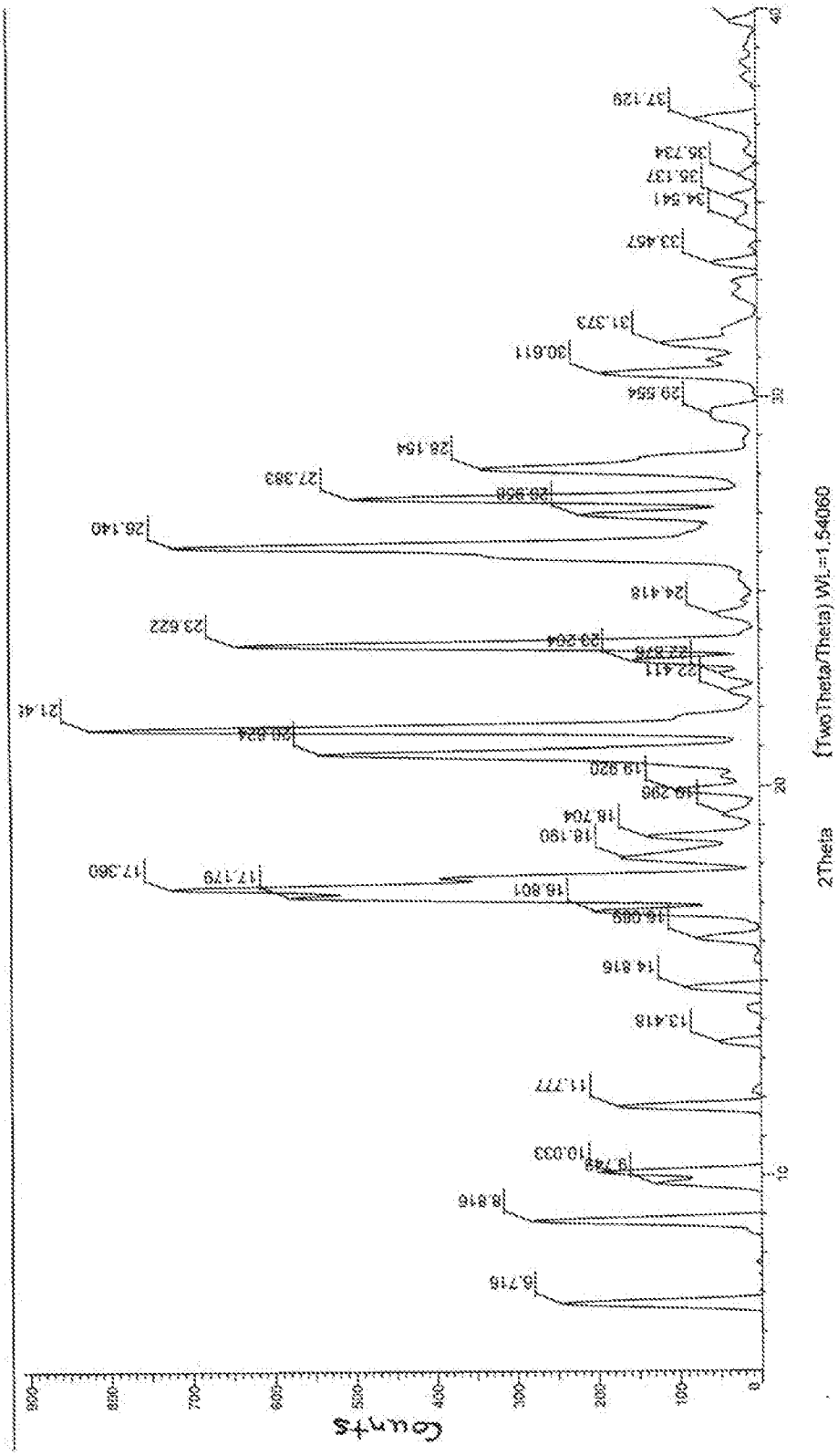
50
100
150
200
250
Temperature /° C

Fig 12.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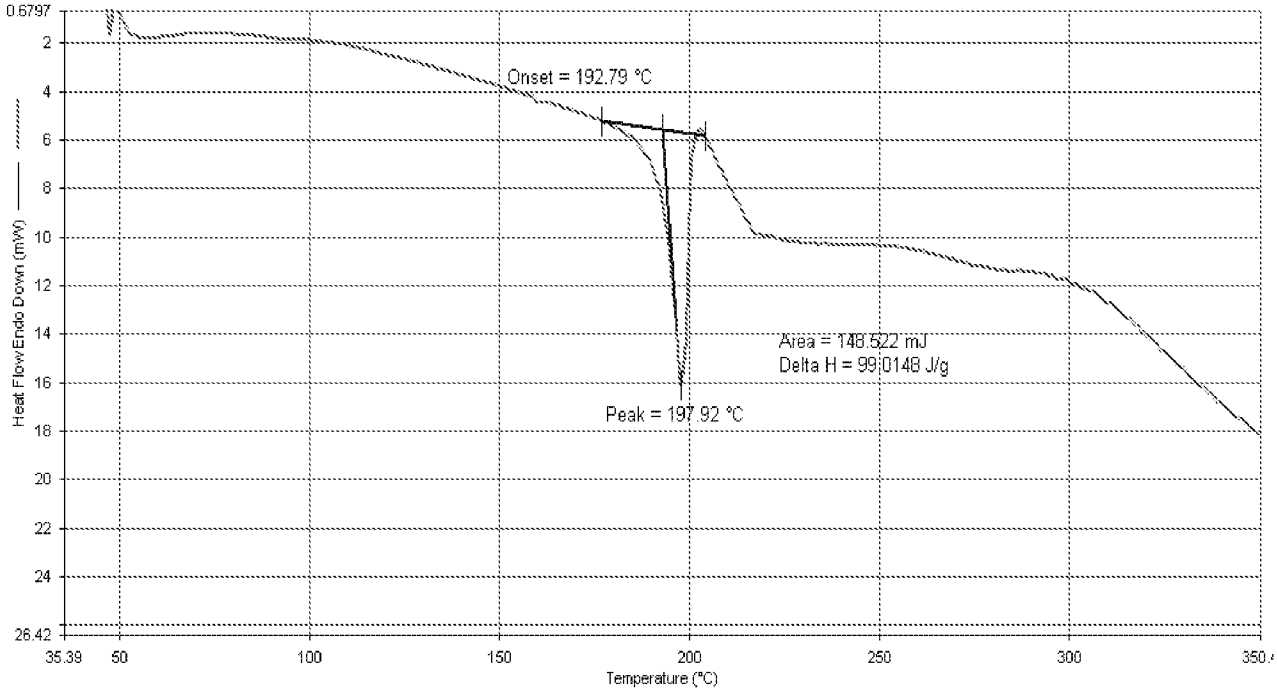
37.129

Fig 13.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Area = 148.522 mJ
Delta H = 99.0148 J/g
Peak = 197.92 °C
35.39
50
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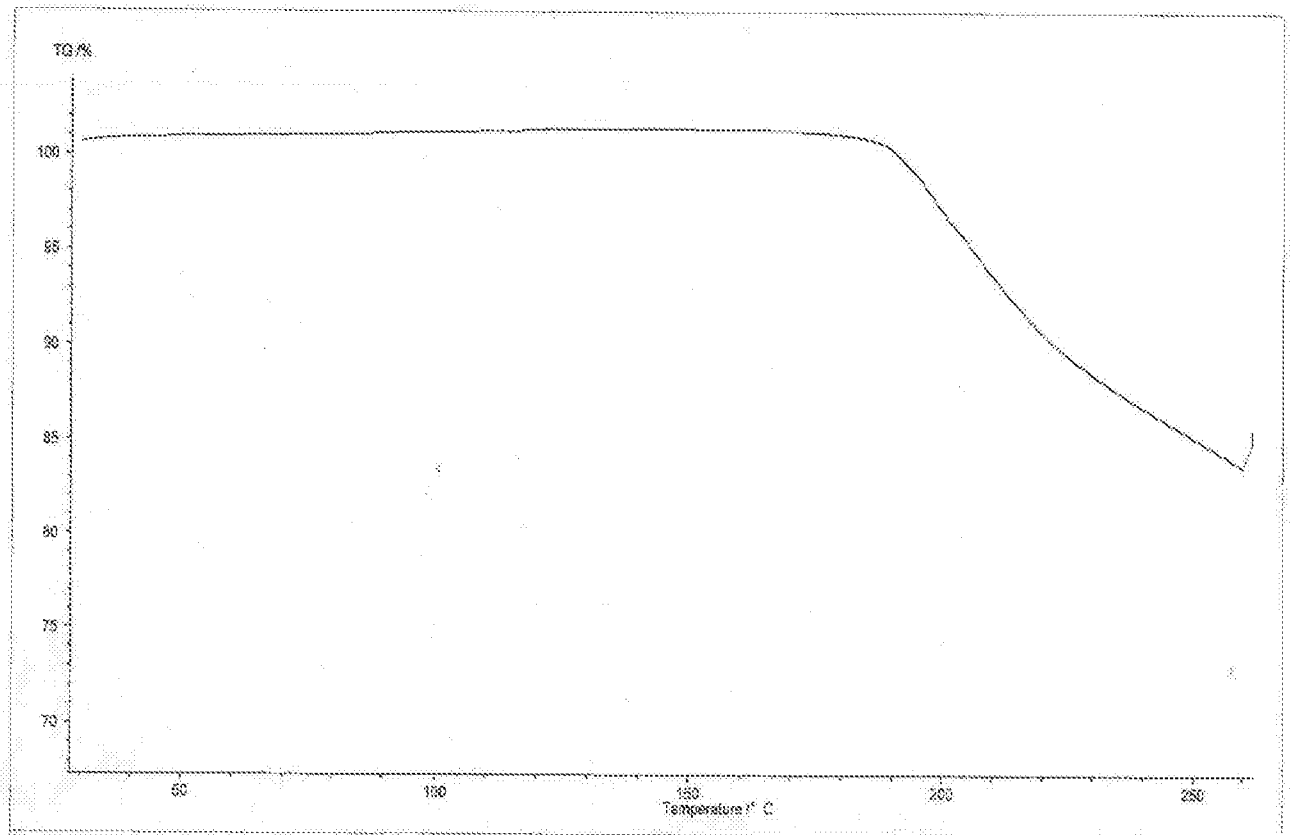
200
250
300
350
Temperature (°C)

Fig 14.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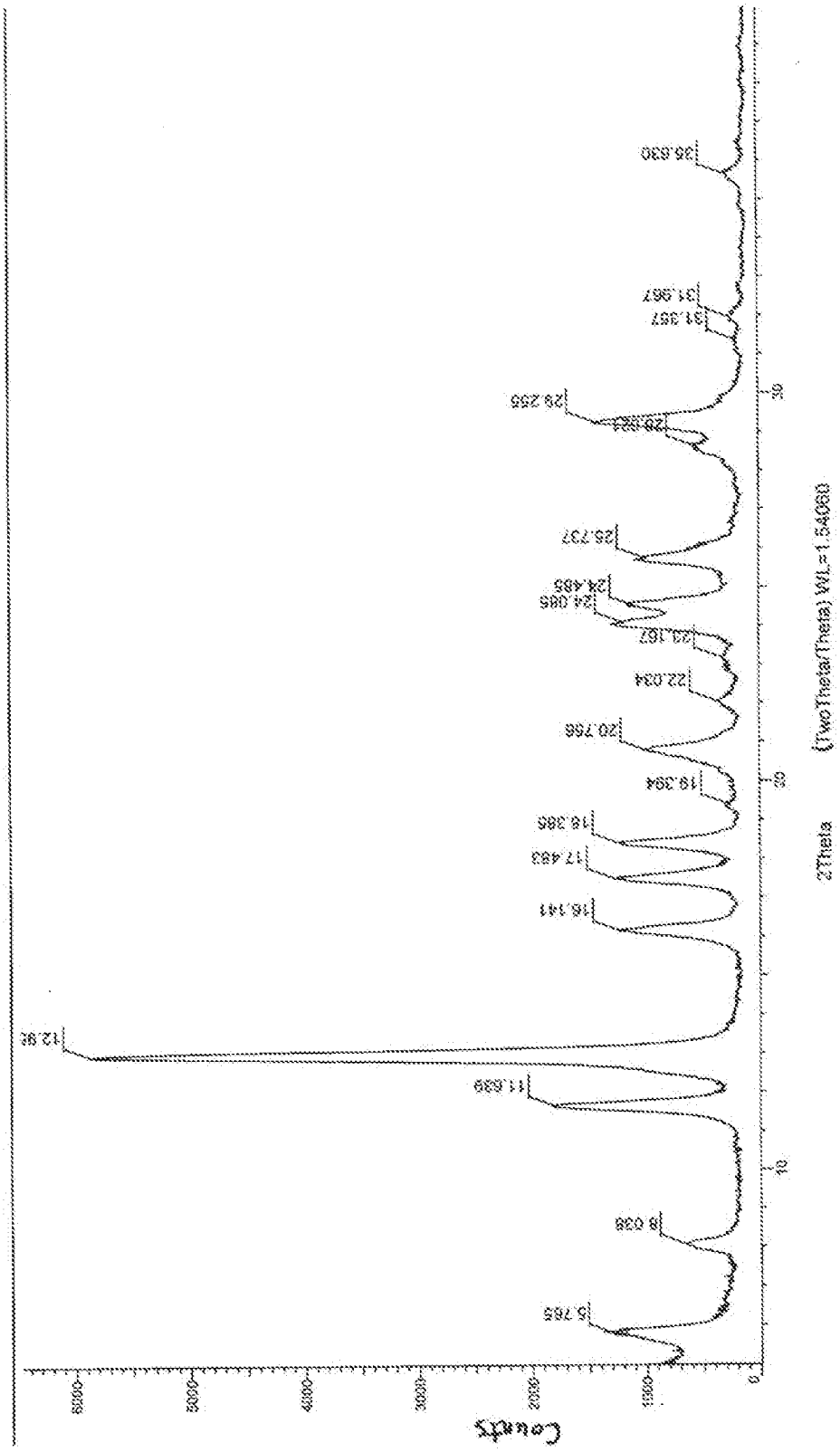
70
50
100
150
200
250
Temperature / °C

Fig 1S.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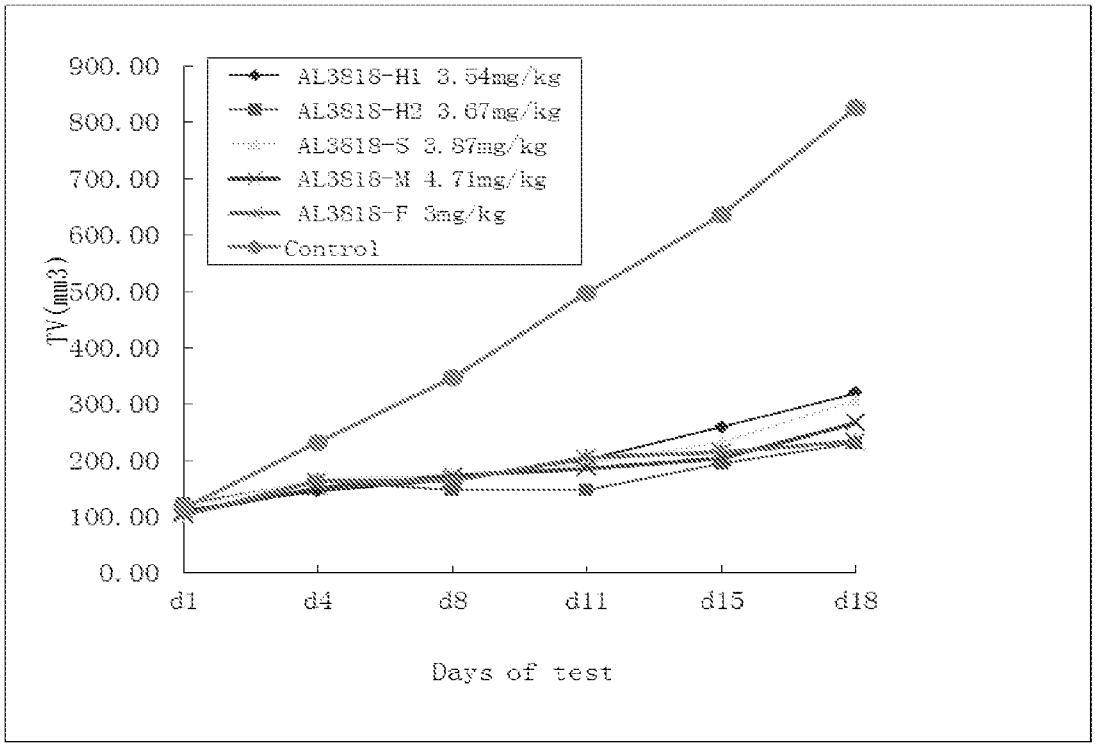
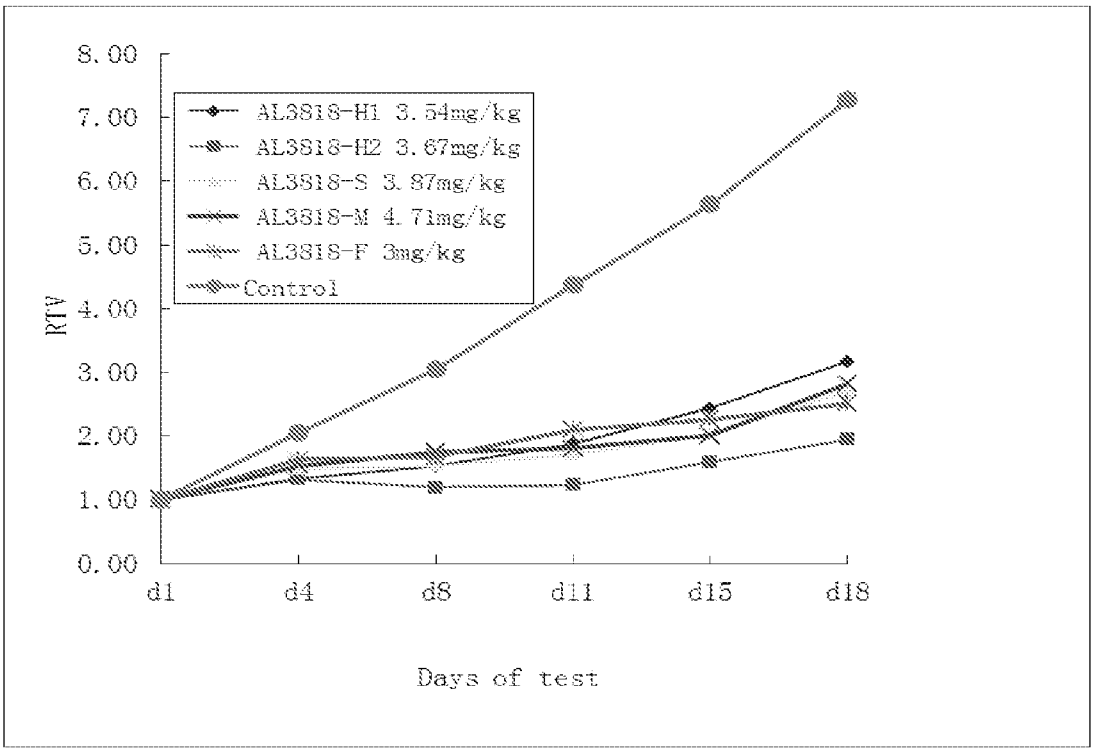
36.630

Fig 16

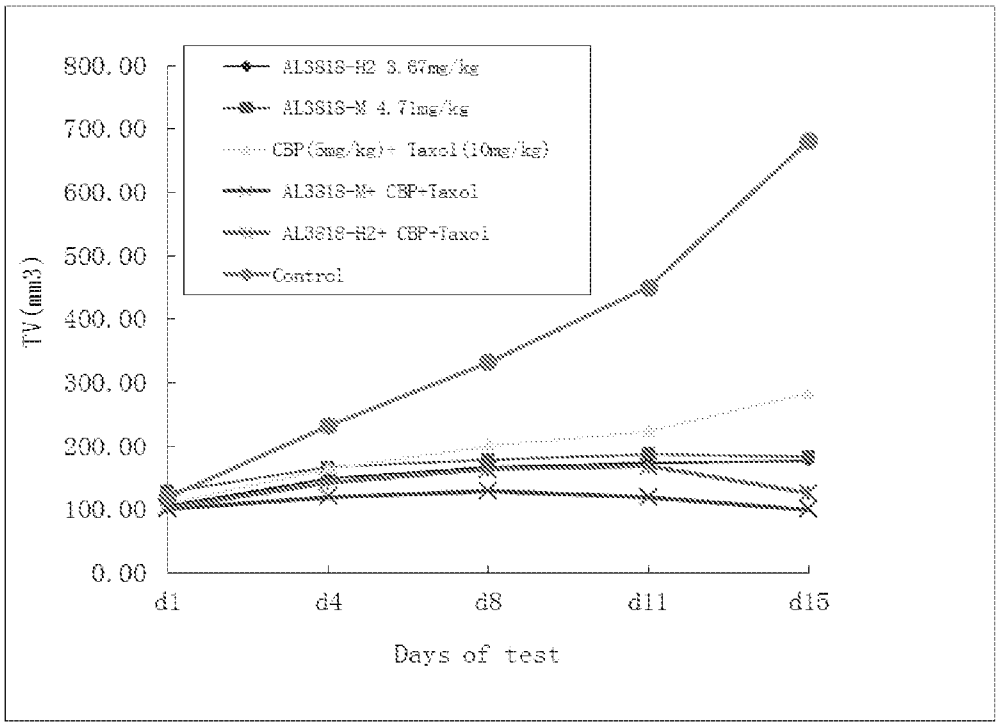


Effect of AL3818 on Tumor volume of human endometrial cancer Ishikawa xenografted athymic nude mice

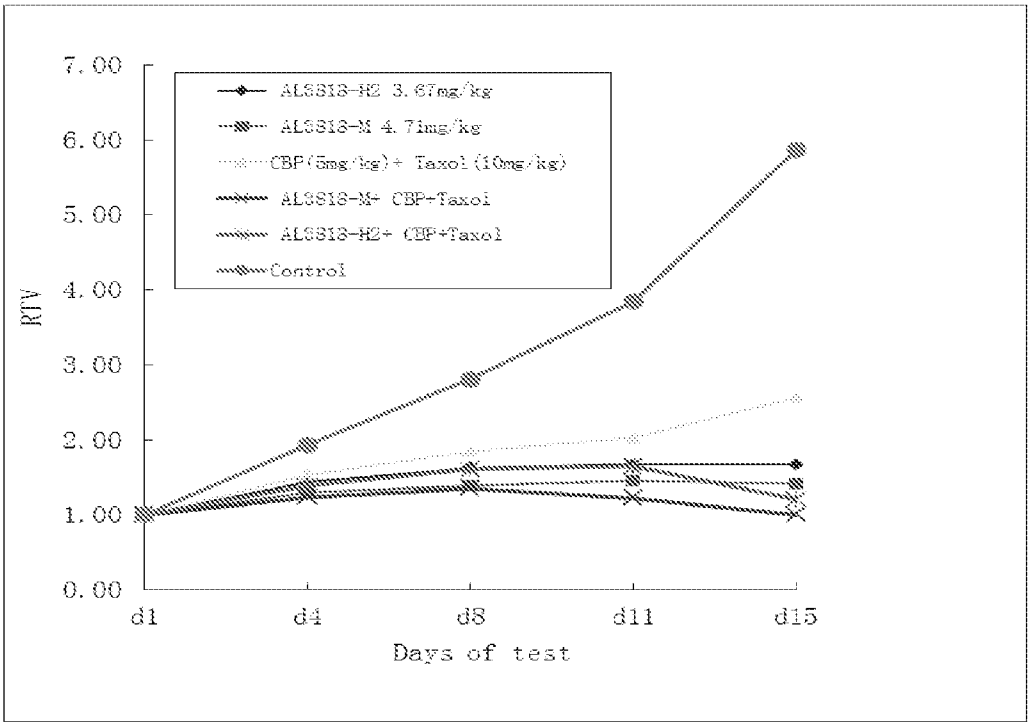


Effect of AL3818 on Relative Tumor volume of human endometrial cancer Ishikawa xenografted athymic nude mice

Fig 17

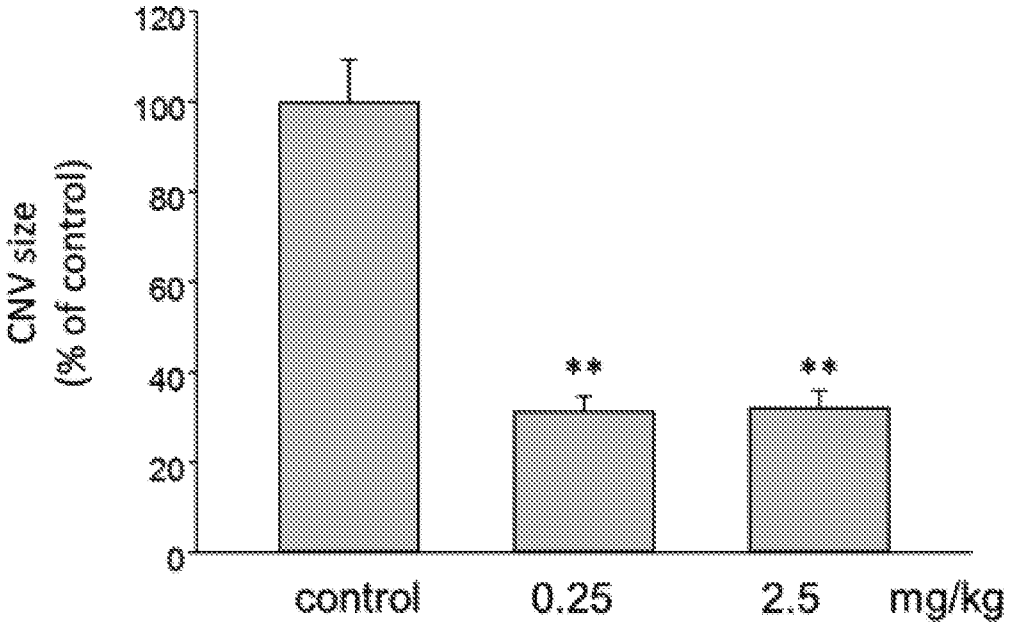


Effect of AL3818 salts combined with Carboplatin (CBX)/Paclitaxel (Taxol) on Tumor volume of human endometrial cancer Ishikawa xenografted athymic nude mice



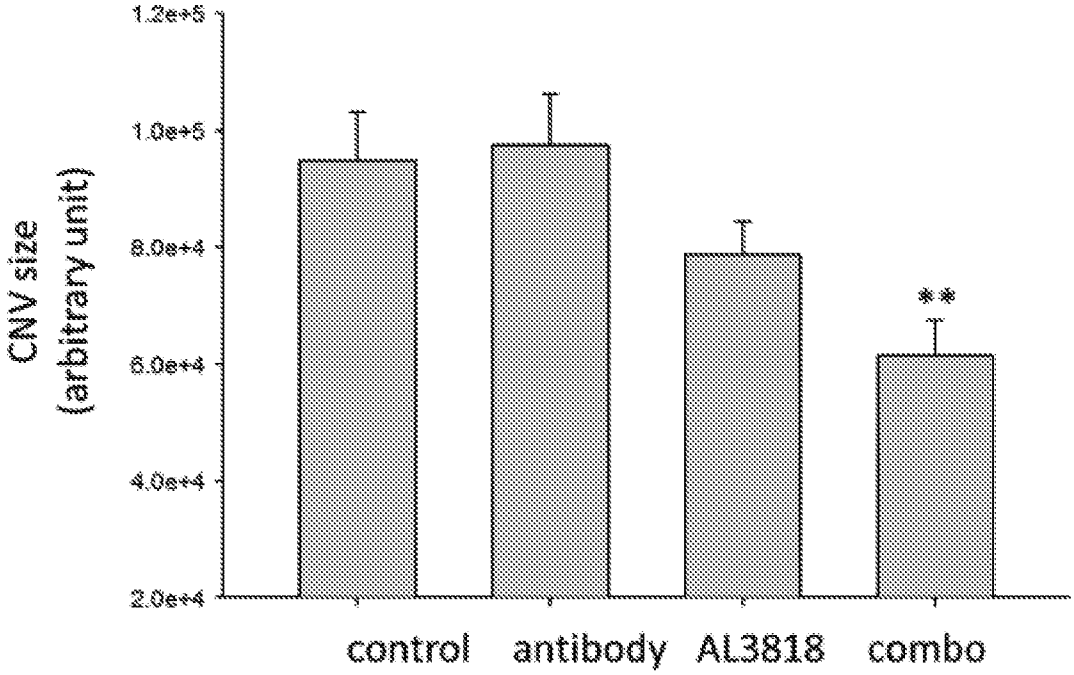
Effect of AL3818 salts combined with Carboplatin (CBX)/Paclitaxel (Taxol) on Relative Tumor volume of human endometrial cancer Ishikawa xenografted athymic nude mice

Fig 18.



Effects of oral administration of AL3818 on laser-induced CNV

Fig 19.



Effects of AL3818 (0.15 mg/kg body weight) and intravitreal anti-VEGF antibody on laser-induced CNV

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/30483

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4706, 31/4709; C07D 215/233, 215/42 (2016.01)
CPC - C07D 239/74, 401/12, 239/88
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)
IPC(8): A61K 31/4706, 31/4709; C07D 215/233, 215/42 (2016.01)
CPC: C07D 239/74, 401/12, 239/88

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google/Google Scholar, IP.com: cyclopropanamine, AL3818, crystalline, cancer, optometric, salt, synthesis, deprotect, condense, solvent, KI, NaI, iodide, pyridine, lutidine, DSC, TGA, XRPD, diffraction, x-ray, powder, tumor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	CN 102344438 A (JIANGSU CHIA TAI TIANQING PHAR) 08 February 2012; English translation; abstract; claim 1	11 --- 18
Y	US 2008/0227811 A1 (CHEN, GP) 18 September 2008; paragraphs [0010]-[0020], [0065], [0033], [0035], [0038], [0045], [0083], scheme 1	18
A	WO 2008/112408 A2 (ADVENCHEN LABORATORIES, LLC) 18 September 2008; pages 2-3, 5-6, 9, 14	1-10, 12-16, 17/8-16, 19/8-16, 20/19/8-16, 21/19/8-16, 23/19/8/-16, 24/8-16, 25/23/19/8/-16
A	WO 2014/130612 A1 (KALA PHARMACEUTICALS, INC.) 28 August 2014; paragraphs [0006], [00026], [00046], [000100]	1-7
A	US 2010/0093727 A1 (XI, N) 15 April 2010; entire document	1-10, 12-16, 17/8-16, 19/8-16, 20/19/8-16, 21/19/8-16, 23/19/8/-16, 24/8-16, 25/23/19/8/-16
A	WO 2014/032019 A1 (GEORGETOWN UNIVERSITY) 27 February 2014; entire document	1-10, 12-16, 17/8-16, 19/8-16, 20/19/8-16, 21/19/8-16, 23/19/8/-16, 24/8-16, 25/23/19/8/-16

☐ 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
23 June 2016 (23.06.2016)	29 JUL 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/30483

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: **22**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.