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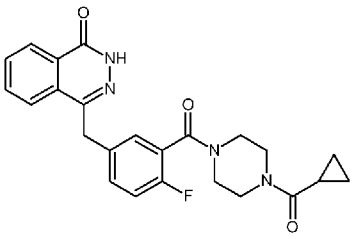
(54) Title: PROCESS FOR THE PREPARATION OF OLAPARIB AND POLYMORPHS THEREOF



Formula-I

(57) Abstract: The present invention is directed to process for preparation of Olaparib of formula (I). The present invention further relates to novel polymorphic forms of Olaparib, pharmaceutical compositions containing them, and method of treatment using the same.

WO2©17/191562 A1

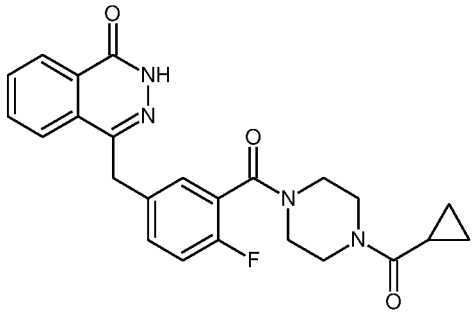
TITLE: PROCESS FOR THE PREPARATION OF OLAPARIB AND POLYMORPHS THEREOF

RELATED APPLICATIONS

This application claims the benefit of priority of our Indian patent application numbers 201621015481 filed on 4th May 2016, 201621019497 filed on 7th June 2016 and 201621028186 filled on 19th August 2016 which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is directed to process for preparation of Olaparib of formula-I. The present invention further relates to polymorphic forms of Olaparib, pharmaceutical compositions containing them, and method of treatment using the same.



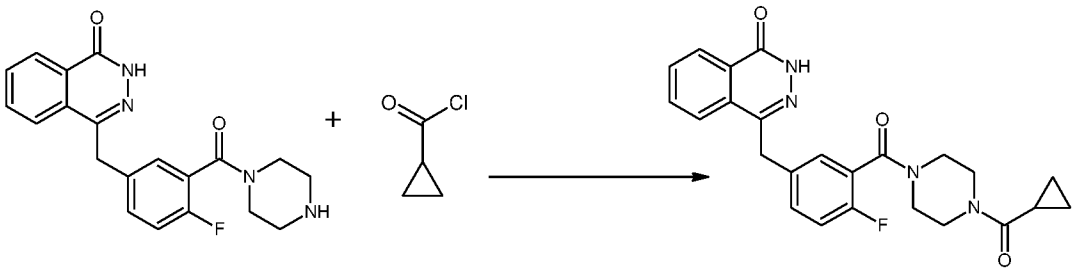
Formula-I

BACKGROUND OF THE INVENTION

Olaparib is a PARP-inhibitor, inhibiting poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair. It acts against cancers in people with hereditary BRCA1 and BRCA2 mutations, which include some ovarian, breast and prostate cancer. Olaparib is marketed as LYNPARZA™ by AstraZeneca for the treatment of patients with advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

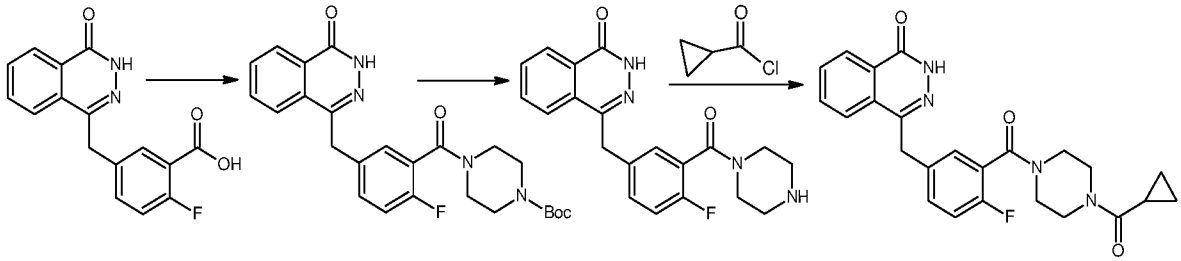
Olaparib is chemically known as 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1 -one.

WO2004080976 discloses different phthalazinone derivatives including Olaparib and as provided in Example 9, compound 168, it also discloses process for preparation of Olaparib as shown below:



However the above process step of preparation of Olaparib is not satisfactory from purity point of view and requires column chromatography purification step providing less yields. Accordingly methods involving column chromatography purifications cannot be used for large-scale operations, thereby making the process commercially not viable.

WO2008047082 discloses process for the preparation of Olaparib as shown below:



CN1 058201 26 and CN1 05985294 disclose process for the preparation of Olaparib. CN1 05061 328 disclose process for the purification of Olaparib.

WO2008047082 further discloses Olaparib in crystalline form A. WO2009050469 discloses Olaparib in crystalline form L. WO201 6 165650 discloses co-crystal of Olaparib and urea. CN1 05254572, CN1 05439961 and CN1 05777651 disclose crystalline form of Olaparib.

However the prior art processes described above for the preparation of Olaparib have major drawbacks such as difficulties with respect to removal of process related impurities; poor commercial viability due to use of hazardous reactants; use of column chromatography and/ or low yields and purity of intermediates and final product. Therefore, there remains a need to develop such a process, which overcomes one or more of the above drawbacks associates with prior art process for preparation of Olaparib.

The acid halides to amide reactions reported in general state of art are highly exothermic and additional base is required. Acid halide are mostly unstable hence convert back to acids, while EDC, DDC, and CDI methods of amide

couplings require additional base and reagents which provides low yield and purity due to backward reactions and side reactions. Surprisingly the present inventors have identified the use of benzotriazole for the activation of carboxylic acid which undergo transamidation with amines without using any additional base, reagents, catalyst, additives or harsh conditions to complete reactions, and produce good to excellent yields and with high quality.

The presently available coupling agents that are used for activation of carboxylic acid group in the Kinase inhibitor drug synthesis suffer several disadvantages, ranging, for example, from chemical inefficiency in terms of side products and low coupling aptitude and yield, and low compatibility with synthesizing techniques to production, maintenance and waste disposal costs. Surprisingly, the present inventors have identified the use of benzotriazole for the activation of carboxylic acid which is more effective than commonly used coupling agents, simple to produce and use in the activation of carboxylic acid functional group.

Considering the importance of Olaparib in the pharmaceutical treatment, there is a need to develop alternative process for the preparation of Olaparib. Applicant diligently did research on the same and identified the use of benzotriazole for the activation of carboxylic acid group in the synthesis of Olaparib not only found to cost effective and also safe in commercial manufacturing.

The present process also discloses novel polymorphic forms of Olaparib and the process for preparing the same.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a process for preparation of Olaparib.

In another aspect, the present invention relates to novel intermediates useful in preparation of Olaparib, process for preparing such intermediates and process for the preparation of Olaparib which utilize these intermediates.

In one aspect, present invention relates to crystalline form of Olaparib.

In another aspect, the present invention provides crystalline form of Olaparib having enhanced stability and dissolution properties and process for preparation thereof.

In one aspect, the present invention relates to crystalline form of Olaparib characterized by X-ray diffraction pattern having characteristic peaks at about 6.4°, 6.8°, 8.3°, 12.6°, 15.0°, 15.8°, 16.3°, 16.6°, 19.7°, 20.7 and 22.0°± 0.2° 2Θ.

In one aspect, the present invention relates to crystalline form of Olaparib having XPRD pattern as shown in as shown in figure 1.

In one aspect, the present invention relates to process for the preparation of crystalline form of Olaparib comprising steps of:

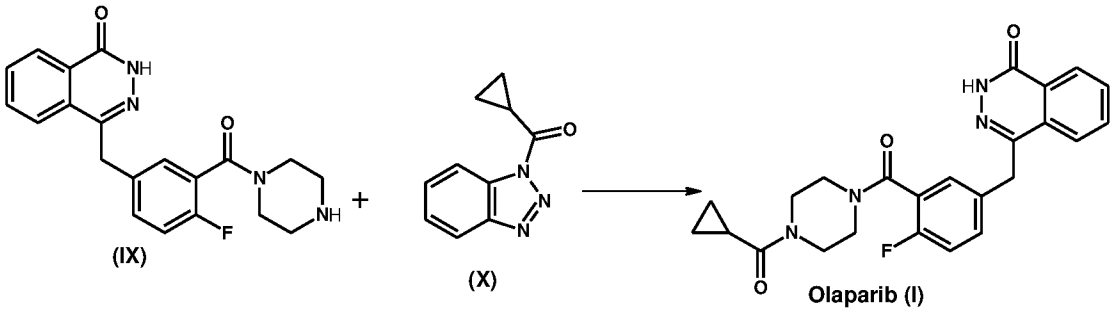
a) dissolving Olaparib in a water;

b) isolating crystalline form of Olaparib.

In one aspect, present invention relates to process for the preparation of form A of Olaparib.

In another aspect, the present invention relates to process for the preparation of crystalline form A of Olaparib comprising steps of:

a) reacting 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1(2H)-one (IX) with 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) in organic solvent;



b) isolating crystalline form A of Olaparib.

In another aspect, the present invention provides Olaparib which is substantially free of impurity A to G.

In one aspect, the present invention provides pharmaceutical compositions comprising crystalline form of Olaparib.

In one aspect, the present invention provides stable activated carboxylic acids having benztriazole as leaving group.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration of a PXRD pattern of crystalline form of Olaparib (I)

Figure 2 is an illustration of a Differential Scanning Calorimetry (DSC) curve of crystalline form of Olaparib (I)

Figure 3 is an illustration of a PXRD pattern of From A of Olaparib (I)

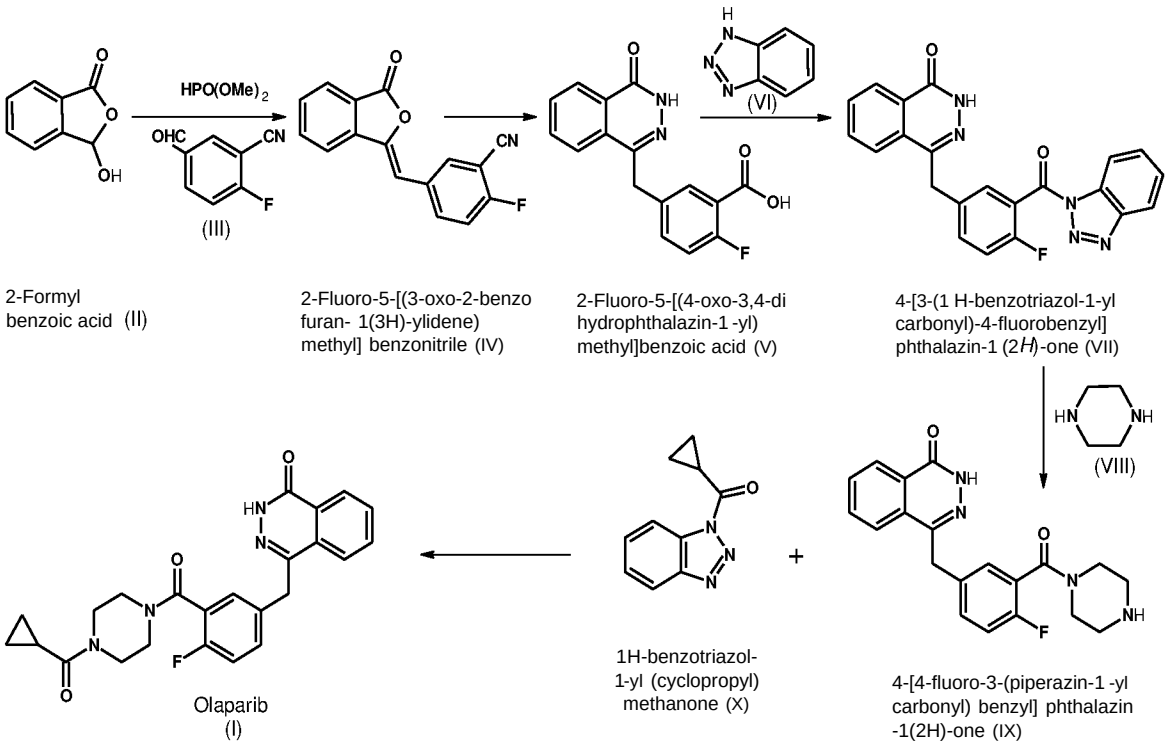
Figure 4 is an illustration of a PXRD pattern of 4-[3-(1 H-benzotriazol-1 -yl carbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII)

Figure 5 is an illustration of a PXRD pattern of 1/-/-benzotriazol-1 -yl (cyclopropyl)methanone (X)

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

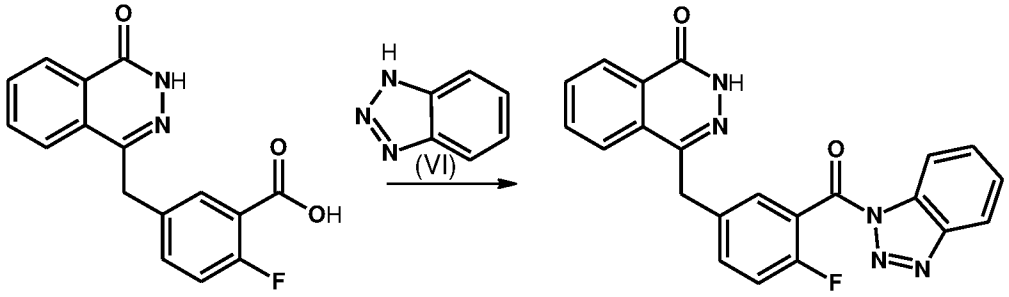
The present invention relates to a process for preparation of Olaparib with improved yields making it reliable for large scale production as described below:



2-formyl benzoic acid-(ll) [3-hydroxy-2-benzofuran-1 (3/-/)-one (II)] undergoes phosphorylation with diethyl phosphite in the presence of base in aqueous medium to provide a stabilized in situ phosphorus ylide intermediate which reacts with 2-flouro-5-formyl benzonitrile (III) to obtain 2-fluoro-5-[(3-oxo-2-benzofuran-1 (3H)-ylidene)methyl] benzonitrile (IV) which is further hydrolyzed using base and then reacted with hydrazine hydrate to produce 2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzoic acid (V). The acid (V) so obtained is converted to an acid derivative which is reacted with 1H-benzotriazole (VI) to produce 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII). The compound (VII) undergoes transamidation with piperazine (VIII) to produce 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX).

Finally Olaparib is produced [high purity (HPLC: >99%) and good yield (>90%)] by reacting 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX) with 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) using suitable solvent(s).

In one embodiment the present invention provides process for the preparation of 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII), as described below:



2-Fluoro-5-[(4-oxo-3,4-di hydrophthalazin-1-yl)methyl]benzoic acid (V)

4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII)

2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1 -yl)methyl]benzoic acid (V) is reacted with 1H-benzotriazole (VI) to produce 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII). The reaction can be optionally carried out in presence of a base and a reagent selected from the group comprising: sulphonyl halide, alkane sulfonyl halides, aryl sulfonyl halide, cyanuric halide, Alkyl halo format, Alkanoyl halide, oxalyl halide, acid anhydride. Sulphonyl halide can be thionyl chloride or the like. Alkane sulphonyl halide can be methane sulfonyl chloride, ethane sulphonyl chloride, trifluoro methanesulfonyl chloride or the like.

Aryl suphonyl halide can be tosyl suphonyl chloride or the like. Cyanuric halide can be Cyanuric chloride or the like. Alkyl halo format can be ethyl chloro format or methyl chloro format or the like. Alkanoyl halide can be pivaloyl chloride or the like. Oxalyl halide can be oxalyl chloride or the like. Acid anhydrides can be acetic anhydride or the like. Solvents that used for the reaction is methylene chloride or acetonitrile or the like. The reaction may be carried out at temperature ranging from about 25°C to about 60°C or higher. The reaction may be carried out for time periods ranging from about 30 minutes to about 3 hours, or longer.

The use of benzotriazole for the activation of carboxylic acid is beneficial for use in industrial manufacturing and found to be chemically efficient (i.e. to be reactive with a wide variety of substrates; reactive in stoichiometric quantities; can be simply monitored during the coupling reaction; prone to only no or few side reactions; simple to purify from its secondary products after coupling; exhibit a high conversion rate at mild conditions), cost efficient and safe for use (i.e safe for the environment; be non-toxic, non-corrosive and not self-reactive; and be stable with relatively low sensitivity to friction, spark, and electrostatic discharge, particularly during transportation and subsequent storage).

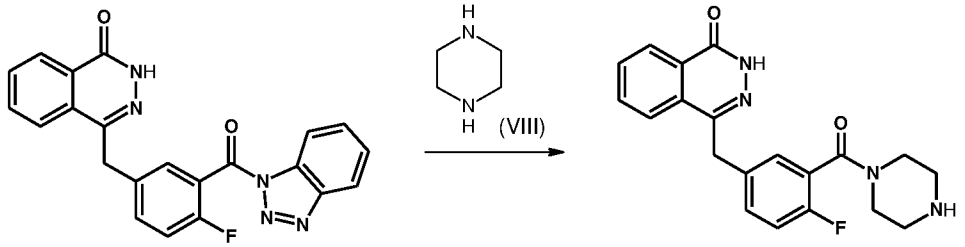
Olaparib prepared according to present invention process not only provides an economically and commercially viable process but also provides better purity and yields thereby overcoming drawbacks associated with prior art process.

In one embodiment, present invention provides crystalline form of 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII).

In another embodiment, the present invention provides to crystalline form of 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII) characterized by X-ray diffraction pattern having characteristic peaks at about 3.1 °, 6.6°, 8.3°, 11.6°, 13.9°, 15.0°, 18.5°, 18.9°, 19.9°, 21.2°, 21.7°, 23.0°, 25.2° and 26.5° ± 0.2° 2Θ.

In one embodiment, the present invention relates to crystalline form of 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII) having XPRD pattern as shown in figure 4.

In one embodiment the present invention provides process for the preparation of 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX), as described below:

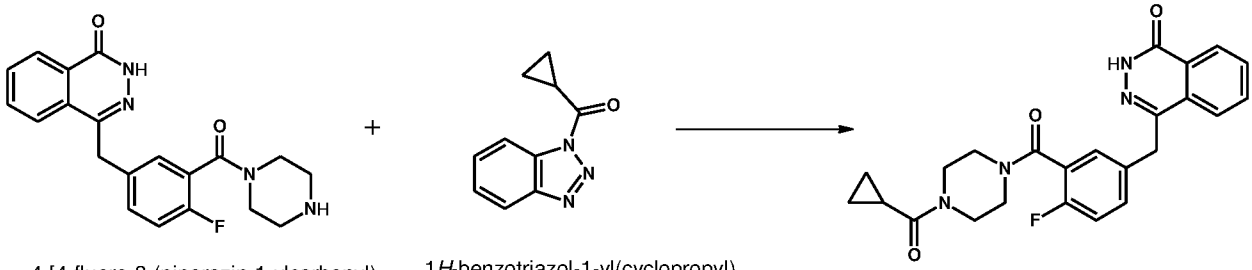


4-[3-(1 /-/-benzotriazol-1 -ylcarbonyl)-4-fluor obenzyl]phthalazin-1 (2H)-one (VII)

4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX)

4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII) is reacted with piperazine (VIII) to produce 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX). Solvents that used for the reaction is isopropyl alcohol or the like. The reaction may be carried out at temperature ranging from about 25°C to about 60°C or higher. The reaction may be carried out for time periods ranging from about 1 hours to about 4 hours, or longer.

In one embodiment the present invention provides process for the preparation of Olaparib (I), as described below:



4-[4-fluoro-3-(piperazin-1-ylcarbonyl) benzyl] phthalazin-1(2*H*)-one (IX)

1*H*-benzotriazol-1-yl(cyclopropyl) methanone (X)

Olaparib (I)

4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX) is reacted with 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) to produce Olaparib (I). Solvent(s) used for the reaction is acetonitrile or the like. The reaction may be carried out at temperature ranging from about 25°C to about 60°C or higher. The reaction may be carried out for time periods ranging from about 30 minutes to about 2 hours, or longer. Preferably the reaction is carried out in absence of a base.

In one embodiment, the present invention provides stable activated carboxylic acids wherein benztriazole is leaving group. The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the benztriazole molecule to form a good leaving group which can then be displaced by an amine during nucleophilic substitution. Use of

Carboxylic acid activated by benztriazole to form an amide linkage is an important reaction and can be used in the synthesis of therapeutically important molecules including but not limited to cobimetinib, Nilotinib, Dasatinib, Bosutinib, Bafetinib, saracatinib, Tozasertib, Danusertib, ubrogepant, Avatrombopag, Encenicline, Momelotinib, Prucalopride, Bentiromide, Conivaptan, Leflunomide, Nitazoxanide, piroxicam, Pranlukast, Sorafenib, Zafirlukast, sunitinib malate, Ensartinib, Dacomitinib, Foretinib, Capmatinibn, Nazatinib, Itacitinib, apatinib, imatinib mesylate, masitinib mesylate, tafetinib malate, flumatinib mesylate, radotinib dihydrochloride, merestinib, ulixertinib, entrectinib, fruquintinib, defactinib hydrochloride, acalabrutinib, ponatinib hydrochloride, telatinib mesylate, lucitanib, axitinib, capmatinib lumacaftor ivacaftor tezacaftor and the like.

In one embodiment, present invention provides crystalline form of Olaparib.

In another embodiment, the present invention provides crystalline form of Olaparib having enhanced stability and dissolution properties and process for preparation thereof.

In one embodiment, the present invention provides to crystalline form of Olaparib characterized by X-ray diffraction pattern having characteristic peaks at about 6.4°, 6.8°, 8.3°, 12.6°, 15.0°, 15.8°, 16.3°, 16.6°, 19.7°, 20.7 and 22.0° ± 0.2° 2Θ.

In one embodiment, the present invention relates to crystalline form of Olaparib having XPRD pattern as shown in figure 1.

In another embodiment, the present invention relates to Differential Scanning Calorimetry (DSC) curve of crystalline form of Olaparib as shown in figure 2.

In one embodiment, the present invention provides process for the preparation of crystalline form of Olaparib comprising steps of:

a) dissolving Olaparib in a water,

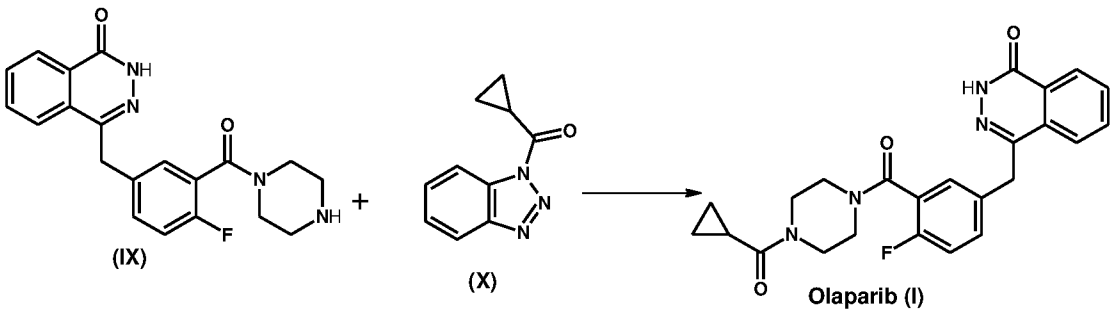
b) isolating crystalline form of Olaparib.

Preferably, the starting material, Olaparib used for the preparation of crystalline form (illustrated in Figure 1) is prepared according to process disclosed in WO2004080976.

In one embodiment, present invention provides process for the preparation of form A of Olaparib.

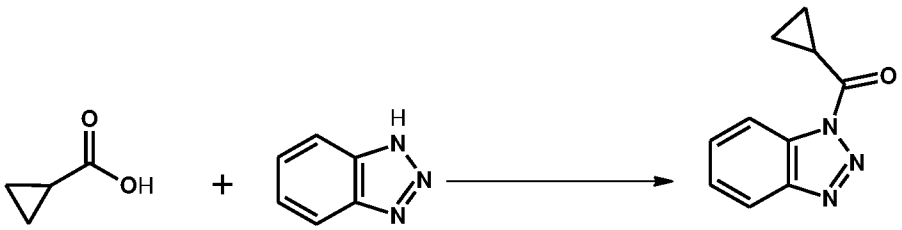
In another embodiment, the present invention provides process for the preparation of crystalline form A of Olaparib comprising steps of:

a) reacting 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1(2H)-one (IX) with 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) in organic solvent;



b) isolating crystalline form A of Olaparib.

In another embodiment the present invention provides process for the preparation of 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X), as described below:



cyclopropanecarboxylic acid (XI) 1H-benzotriazole (VIII) 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X)

1H-benzotriazole (VIII) is reacted with cyclopropanecarboxylic acid (XI) in presence of a chlorinating agent, preferably thionyl chloride to produce 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X). Solvent(s) used for the reaction is methylene chloride or the like. The reaction may be carried out at temperature ranging from about 25°C to about 60°C or higher. The reaction may be carried out for time periods ranging from about 2 hours to about 6 hours, or longer. Preferably the reaction is carried out in absence of a base.

In one embodiment, present invention provides crystalline form of 1*H*-benzotriazol-1 -yl(cyclopropyl)methanone (X).

In another embodiment, the present invention provides to crystalline form of 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) characterized by X-ray diffraction pattern having characteristic peaks at about 8.7°, 11.0°, 15.9°, 17.4°, 18.7° and 22.0° ± 0.2° 2Θ.

In one embodiment, the present invention relates to crystalline form of 1*H*-benzotriazol-1 -yl(cyclopropyl)methanone (X) having XPRD pattern as shown in figure 5.

In one embodiment, the present invention provides pharmaceutical compositions comprising Olaparib.

In another embodiment the present invention provides a process of preparing a pharmaceutical composition of Olaparib which process comprises the step of mixing of Olaparib substantially as hereinbefore described together with a pharmaceutically acceptable carrier. Conveniently the following combinations of carrier or excipient and co- precipitation medium can be employed in a process according to the present invention.

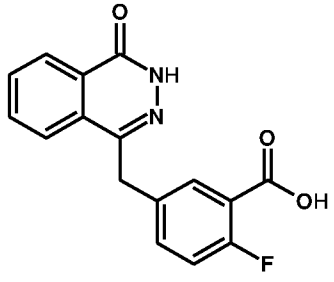
Suitable premixing agents are pharmaceutically acceptable carrier or excipients include polymers/agents used in the process for manufacturing of the premix may be selected from group of cellulose derivatives but not limited to Croscarmellose Sodium, micro crystalline cellulose, hydroxyethylcellulose(HEC), hydroxypropylcellulose(HPC), hydroxypropyl methylcellulose (HPMC), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC), methylcellulose (MC), cellulose esters, cellulose glycolate, hydroxypropyl methyl cellulose phthalate, polymethylacrylate (HPMCP), hypromellose, vinylpyrrolidone monomers but not limited to polyvinylpyrrolidone and polyol but not limited to mannitol. The said polymers/agents are used to facilitate the presence of Olaparib.

Crystalline form of Olaparib as obtained by present invention is stable and not contaminated with any crystalline form.

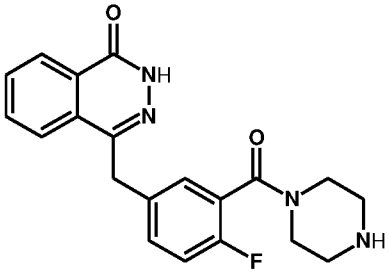
In one embodiment, the present invention provides Olaparib having particle size Dgo <200pm; preferably, D_{go} ≤50µm, more preferably D_{go} ≤20µm.

In another embodiment, the present invention provides Olaparib which is substantially free from impurity A to G.

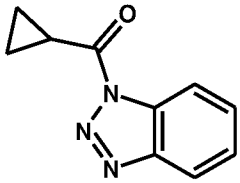
i) Impurity-A:



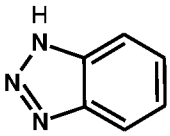
ii) Impurity-B :



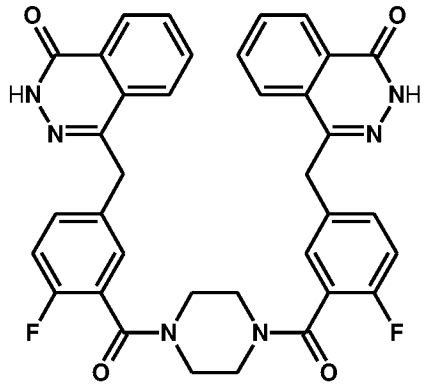
iii) Impurity-C :



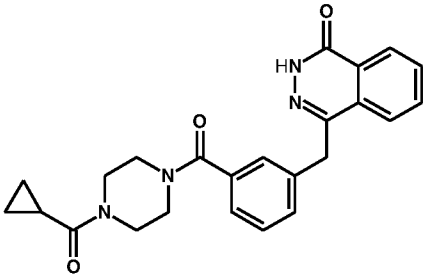
iv) Impurity-D :



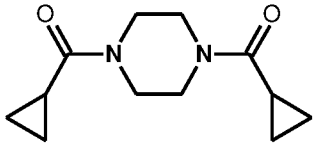
v) Impurity-E :



vi) Impurity-F:



vii) Impurity-G:



The term "organic solvent" or "solvent" as used herein includes but not limited to polar protic and aprotic solvents as well as non-polar solvents selected from water, hydrocarbons, ketones, alcohols, ethers, esters, halogenated solvents, dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), pyridine, phenol, DMA, carbon disulphide, acetic acid, acetonitrile and mixtures thereof.

Hydrocarbons include but not limited to such as benzene, toluene, xylene, pentane, hexane, heptane, cyclo hexane and tetraline.

Ketones include but not limited to such as acetone, methyl ethyl ketone, cyclohexanone and methyl isobutyl ketone.

Alcohols include but not limited to such as methanol, ethanol, propanol, butanol, octanol, ethanediol, 1, 2-propane diol and S (+)-1 , 2-propane diol.

Ethers include but not limited to such as diethyl ether, di isopropyl ether, di butyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and cyclo pentyl methyl ether.

Halogenated solvents include but not limited to such as chloroform, carbon tetrachloride, methylene chloride and 1, 2-dichloro ethane.

Esters include but not limited to such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and n-propyl acetate.

The tern "base" as used herein includes but not limited to inorganic base such as ammonia or hydroxide, carbonate, or bicarbonate of a metal cation or ammonia or organic bases such as organic primary, secondary, or tertiary amine. The base may be chosen as appropriate depending on various reaction conditions known to those skilled in the art.

The term "Olaparib substantially free of impurity A to G" as used herein relates to Olaparib having purity greater than 99.5 % by HPLC and the amount of impurity A to G present is not more than 0.1 5% by HPLC.

Examples

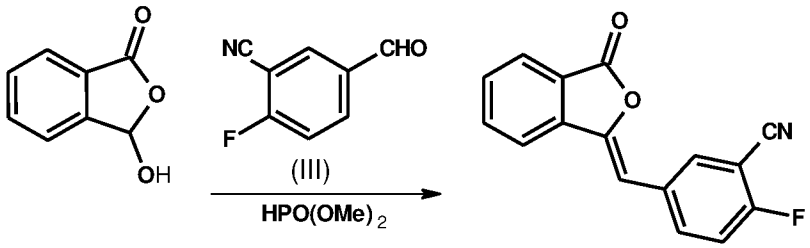
The following examples are provided here to enable one skilled in the art to practice the invention and merely illustrate the process of this invention. However, it do not intended in any way to limit the scope of the present invention.

1H NMR spectra are recorded at 300 MHz on a Bruker Avance III instrument. Dimethyl sulfoxide (99.8% D) is used as solvent, and tetramethylsilane (TMS) is used as internal reference standard.

X-Ray powder diffractograms were measured on a PANalytical X'Pert PRO X-Ray Diffractometer using CuKα1 radiation. The samples were measured in reflection mode in the 26-range 2.5-40° using an X'celerator detector.

The melting points are measured using Differential Scanning Calorimetry (DSC). The equipment is a TA-Instruments DSC-Q1 000 calibrated at 10°/min to give the melting point as onset value. About 2 mg of sample is heated 10°/min in a loosely closed pan under nitrogen flow.

Example-1 : Preparation 2-fluoro-5-[(3-oxo-2-benzofuran-1(3H)-ylidene) methyl] benzonitrile (IV)



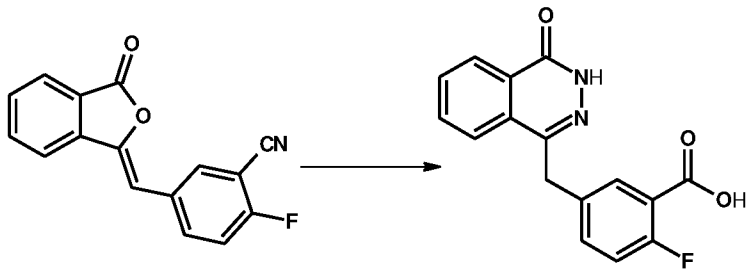
2-Formyl benzoic acid (II)

2-Fluoro-5-[(3-oxo-2-benzofuran-1 (3H)-ylide ne)methyl] benzonitrile (IV)

To a stirring solution of $NaHCO_3$ (42 g) in water (400 mL) were added 2-formyl benzoic acid (II) (50 g) and dimethyl hydrogen phosphite (73.3 g) at room temperature. The resulting reaction mixture was stirred at room temperature. The reaction mixture was acidified by adding cone. HCl solution after consuming of 2-formyl benzoic acid (II) and the stirring was continued. The reaction mixture was then diluted by addition of water. $NaHCO_3$ (168 g) was added followed by addition of 2-flouro-5-formyl benzonitrile (III) (50 g). The reaction mixture was stirred at room temperature. After completion of reaction, the obtained precipitate was filtered and washed with water, then suck dried by using vacuum to afford 2-fluoro-5-[(3-oxo-2-

benzofuran-1 (3/-/)-ylidene)methyl] benzonitrile (IV). The resulting wet compound was used to next reaction without further purification and drying. (Yield: 72%)

Example-2: Preparation of 2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl) methyljbenzoic acid (V)

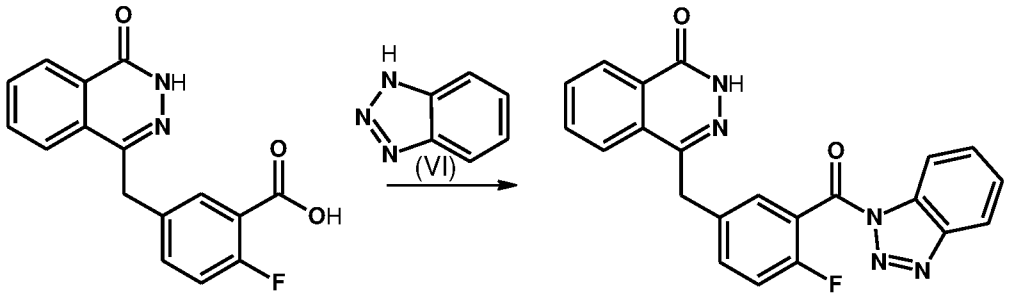


2-Fluoro-5-[(3-oxo-2-benzofuran-1 (3H)-ylide ne)methyl] benzonitrile (IV)

2-Fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzoic acid (V)

The above semi dried compound 2-fluoro-5-[(3-oxo-2-benzofuran-1 *{3H)*-ylidene)methyl] benzonitrile (IV) as obtained by example-1 was suspended in water (500 imL) at room temperature followed by addition of aqueous solution of NaOH (50 g). The resulting reaction mixture was stirred at 60°C to 70 °C. After completion of the hydrolysis, it was cooled to room temperature and acidified by addition of cone. HCI until the pH was changed to 5-6. Then hydrazine hydrate (167 g) was added. The resulting reaction mass was stirred at 60°C to 70 °C. The reaction mass was cooled to room temperature, acidified by addition of cone. HCI until the pH was changed 4.0-4.5. The stirring was continued further at room temperature. The obtained precipitate was filtered and washed with water. The crude compound was purified by using isopropanol (or any other polar solvent) to afford pure 2-fluoro-5-[(4-oxo-3,4-di hydrophthalazin-1 -yl)methyl]benzoic acid (V) as a solid (70 g). (Yield: 68%)

Example-3: Preparation of 4-[3-(1 H-benzotriazol-1-ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2H)-one (VIII)

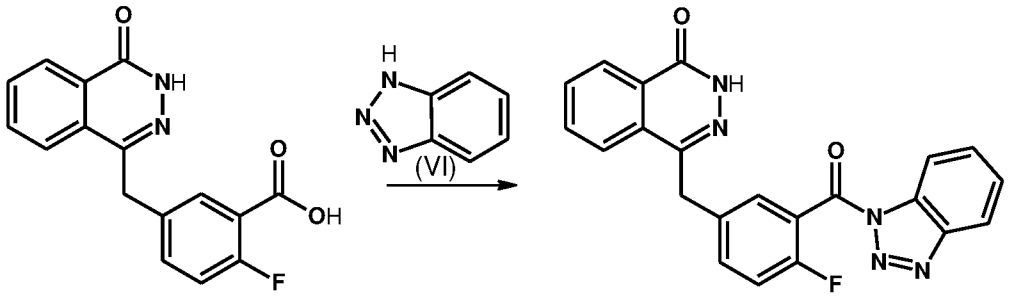


2-Fluoro-5-[(4-oxo-3,4-di hydrophthalazin - 1-yl)methyl]benzoic acid (V)

4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluor obenzyl]phthalazin-1 (2H)-one (VII)

Thionylchloride (22.0 mL) was added to a cold and stirring solution of 1*H*-benzotriazole (VI) (85 g) and triethylamine (148 mL) in methylene chloride (700 mL). The resulting reaction mass stirred at 0-10 °C. Then 2-fluoro-5-[(4-oxo-3, 4-dihydro-phthalazin-1 -yl) methyl] benzoic acid (V) (70 g) was added at 0-10 °C and the resulting suspension was stirred at room temperature till completion of reaction. The organic volatiles of reaction mass were removed under reduced pressure after completion of the reaction. The crude compound was re-crystallized in water/isopropanol and dried under vacuum at 50-60 °C to afford 4-[3-(1 *H*-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2/-/)-one (VII) as a white solid (84 g). The PXRD pattern of 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2H)-one (VII) as thus obtained is illustrated in figure-4. (Yield: 81%, HPLC purity: 99%) **^{1}H NMR (300 MHz, DMSO-*£/$_6$*):** δ 12.63 (s, 1H), 8.30-8.25 (m, 3H), 8.04-8.01 (d, 1H, *J* = 7.8 Hz), 7.95-7.81 (m, 4H), 7.77-7.72 (m, 1H), 7.69 -7.63 (m, 1H), 7.46-7.40 (m, 1H), 4.43 (s, 2H); **^{13}C NMR (75 MHz, DMSO-*d$_6$*):** δ 164.00, 160.41 , 159.85, 157.08, 145.93, 145.21 , 135.78, 135.66, 135.10, 135.06, 133.99, 132.12, 132.03, 131.56, 131.29, 129.55, 128.34, 127.44, 126.52, 125.91 , 121.38, 121.20, 120.68, 116.91 , 116.63, 114.47, 36.89; **MS (ESI):** *m/z* [M+H] calcd. for C22H15FN5O2: 400.3; found: 400.3.

Example-4: Preparation of 4-[3-(1 H-benzotriazol-1-ylcarbonyl)-4-fluorobenzyl] phthalazin-1(2H)-one (VIII)

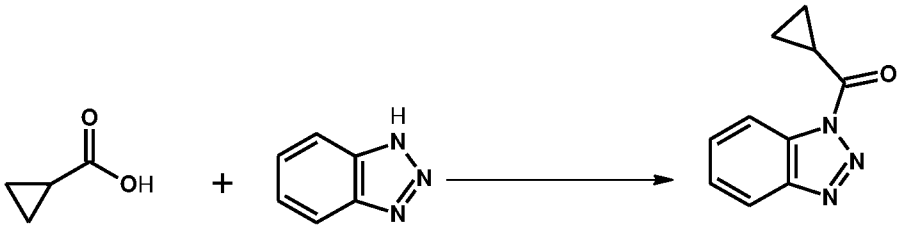


2-Fluoro-5-[(4-oxo-3,4-di hydrophthalazin-1-yl)methyl]benzoic acid (V)

4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl]phthalazin-1 (2H)-one (VII)

Methanesulfonyl chloride (20.0 ml_) was added to a cold and stirring solution of 1H-benzotriazole (VI) (85 g) and triethylamine (148 imL) in methylene chloride (700 imL). The resulting reaction mass stirred at 0-10 °C. Then 2-fluoro-5-[(4-oxo-3, 4-dihydro-phthalazin-1 -yl) methyl] benzoic acid (V) (70 g) was added at 0-10 °C and the resulting suspension was stirred at room temperature till completion of reaction. The organic volatiles of reaction mass were removed under reduced pressure after completion of the reaction. The crude compound was re-crystallized in water/isopropanol and dried under vacuum at 50-60 °C to afford 4-[3-(1 H-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2/-/)-one (VII) as a white solid (84 g). (Yield: 78%, HPLC purity: 98%)

Example-5: Preparation of 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X)



cyclopropanecarboxylic acid (XI)

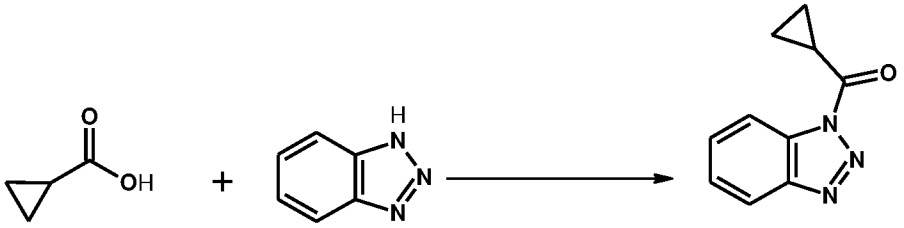
1H-benzotriazole (VI)

1H-benzotriazol-1 -yl(cyclopropyl)methanone (X)

Thionylchloride (55 imL) was added to a cold and stirring solution of 1H-benzotriazole (VI) (207 g) and the resulting reaction mass was stirred at 0-10 °C. Then cyclopropanecarboxylic acid (XI) (50 g) was added at 5-10 °C and the resulting suspension was stirred at room temperature. The organic volatiles of reaction mass were removed under reduced pressure after completion of the reaction. The crude compound was re-crystallized in methanol and dried under vacuum at 50-60 °C to afford 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) as a white solid (92 g). The PXRD pattern of 1H-benzotriazol-1 -

yl(cyclopropyl)methanone (X) as thus obtained is illustrated in figure-5. (Yield: 70%, HPLC purity: 98%) **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.30-8.27 (d, 1H, J = 8.1 Hz), 8.1 6-8.1 3 (d, 1H, *J* = 8.1 Hz), 7.68-7.63 (m, 1H), 7.55-7.48 (m, 1H), 3.45-3.38 (m, 1H), 1.50-1 .45 (m, 2H), 1.34-1 .28 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.35, 146.1 7, 13 1.08, 130.23, 126.01 , 120.02, 114.48, 13.63, 11.86; **MS (ESI):** *m/z* [M+H] calcd for $C_{10}H_{10}N_3O$: 188.3; found: 188.3.

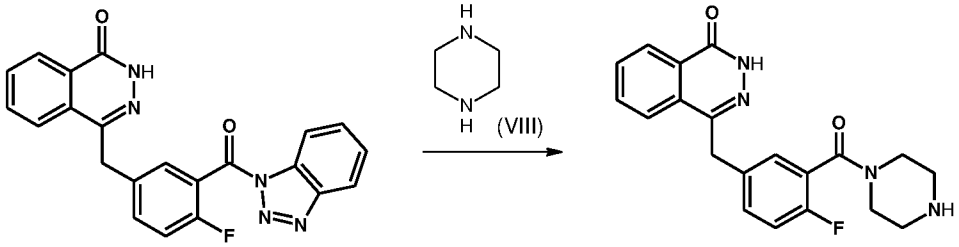
Example-6: Preparation of 1H-benzotriazol-1-yl(cyclopropyl)methanone (X)



cyclopropanecarboxylic acid (XI) 1/-/-benzotriazole (VI) 1/-/-benzotriazol-1 -yl(cyclopropyl)methanone (X)

Methanesulfonyl chloride (45 mL) was added to a cold and stirring solution of 1*H*-benzotriazole (VI) (1 96 g) and the resulting reaction mass was stirred at 0-1 0 °C. Then cyclopropanecarboxylic acid (XI) (40 g) was added at 5-1 0 °C and the resulting suspension was stirred at room temperature. The organic volatiles of reaction mass were removed under reduced pressure after completion of the reaction. The crude compound was re-crystallized in methanol and dried under vacuum at 50-60 °C to afford 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) as a white solid (81 g). (Yield: 67%, HPLC purity: 97%)

Example-7: Preparation of 4-[4-fluoro-3-(piperazin-1-ylcarbonyl) benzyl] phthalazin-1 (2*H*)-one (IX)



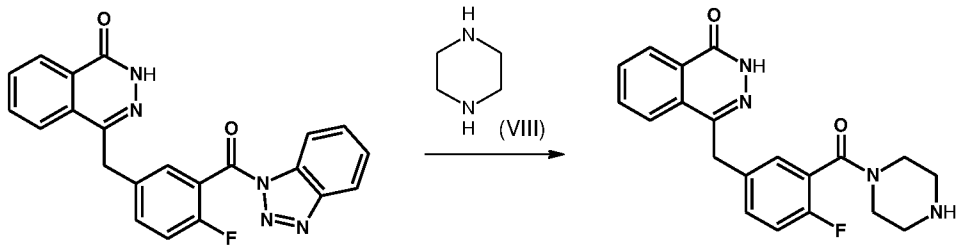
4-[3-(1 /-/-benzotriazol-1 -ylcarbonyl)-4-fluor obenzyl]phthalazin-1 (2H)-one (VII)

4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX)

To a solution of piperazine (VIII) (1 3 g) in acetonitrile (500 mL) was added 4-[3-(1 *H*-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2/-/)-one (VII) (50 g) at room temperature and the resulting reaction mixture was stirred. After completion of the

reaction, the obtained precipitate was filtered and washed with acetonitrile, then suck dried by using vacuum line to afford wet 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2/-/)-one (IX). The semi dried compound was used to next reaction without further purification and drying. (Yield: 72%, HPLC purity: 98%)

Example-8: Preparation of 4-[4-fluoro-3-(piperazin-1-ylcarbonyl) benzyl] phthalazin-1 (2*H*)-one (IX)

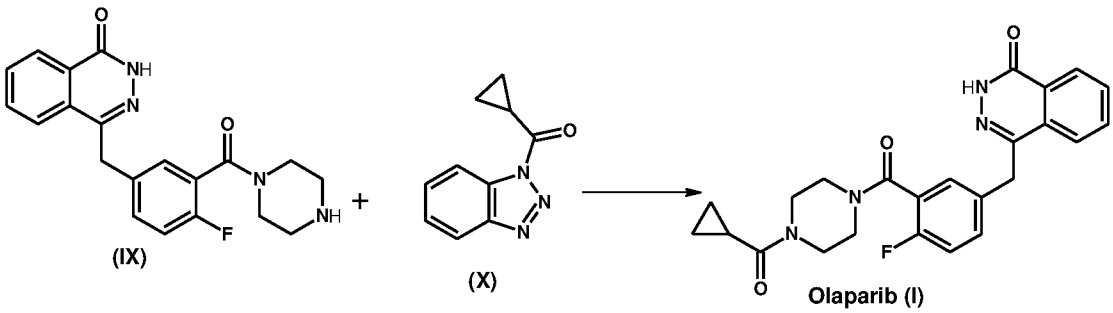


4-[3-(1 /-/-benzotriazol-1 -ylcarbonyl)-4-fluor obenzyl]phthalazin-1 (2H)-one (VII)

4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX)

To a solution of piperazine (VIII) (200 g) in isopropanol (500 mL) was added lot wise 4-[3-(1 /-/-benzotriazol-1 -ylcarbonyl)-4-fluorobenzyl] phthalazin-1 (2/-/)-one (VII) (150 g) at room temperature and the resulting reaction mixture was stirred. After completion of the reaction, the solvent was distilled out and the residue was treated acetic acid (or any other organic or inorganic acid) and water to form salt, which was washed with organic solvent and then treated with base to produce solid material. The obtained solid material was filtered and washed with water (100 mL), then suck dried by using vacuum line to afford wet 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX). (Yield: 80%, HPLC purity: 99%)

Example-9: Preparation of Olaparib (I)



(IX) (X) Olaparib (I)

4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1 (2H)-one (IX) (40.0 g, 0.11 mol) and 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X) (26 g, 0.14 mol) were stirred in acetonitrile (320 mL) and the progress of reaction was monitored by

HPLC. After completion of reaction, the resulted precipitate was filtered and washed with acetonitrile (40.0 mL) then dried to afford Olaparib (I) as a white to off-white solid. The PXRD pattern of Olaparib thus obtained matches with Form-A as illustrated in figure-3. (Yield: 90%, HPLC purity: 99.99%)

Example-10: Preparation of crystalline form of Olaparib

Olaparib (10.0 g) was taken in water (200 mL) and the resulting mixture was stirred at 25-30 °C for 10-12 hours to grow crystalline solid material. The obtained solid material was filtered and washed with water (50.0 mL) then dried at 50-60 °C for 10-12 hours to provide pale yellow to white crystalline form of Olaparib. The PXRD pattern of crystalline form of Olaparib thus obtained is illustrated in figure-1 . (Yield: 95%, HPLC purity: 99.98%)

Example-11: Preparation of crystalline form A of Olaparib

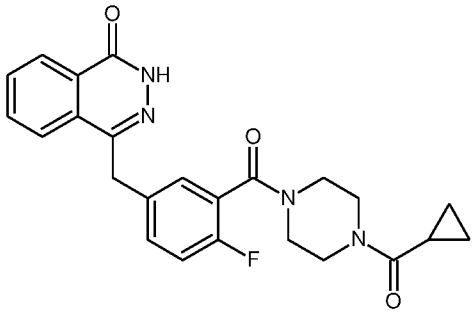
Olaparib (10.0 g) was dissolved in acetonitrile by heating; the resulting clear solution was cooled and stirred at 25-30 °C to grow crystalline solid material. The obtained solid material was filtered and dried at 50-60 °C to provide white to off-white Olaparib form-A. (Yield: 95%, HPLC purity: 99.98%)

Example-12: Preparation of crystalline form A of Olaparib

Olaparib (10.0 g) was dissolved in acetic acid by heating; water was added to the resulting clear solution then cooled and stirred at 25-30°C to grow crystalline solid material. The obtained solid material was filtered and washed with water then dried at 50-60 °C to provide white to off-white Olaparib form-A. (Yield: 91%, HPLC purity: 99.99%)

WE CLAIM:

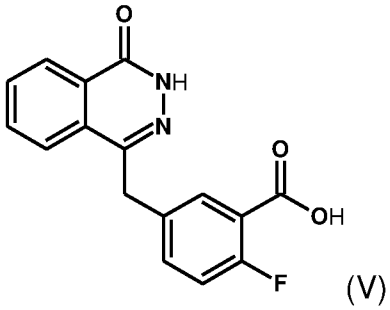
1. A process for the preparation of Olaparib (I)



(I)

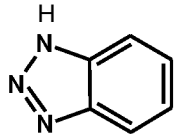
comprising:

a) reacting a compound of formula (V)



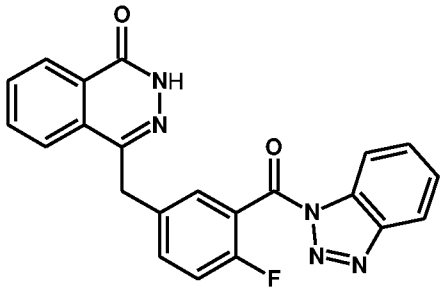
(V)

with 1H-benzotriazole (VI)



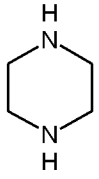
(VI)

to obtain compound of formula (VII) ;



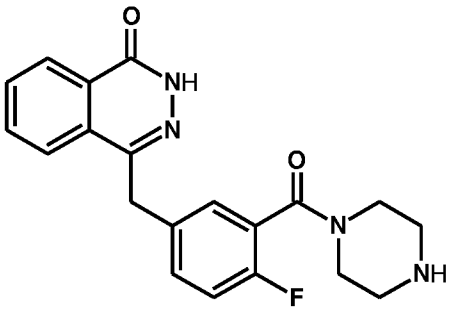
(VII);

b) reacting compound of formula (VII) with piperazine (VIII)

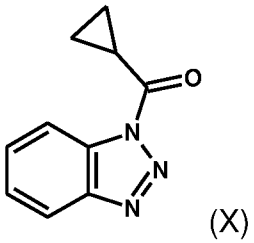


(VIII)

to obtain compound of formula (IX); and


(IX);

c) reacting compound of formula (IX) with compound of formula (X)

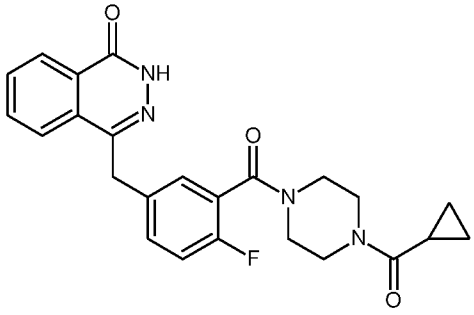

(X)

to obtain Olaparib (I).

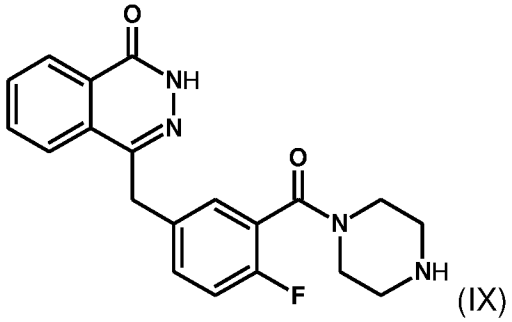
2. The process according to claim-1 , wherein step-a) is performed in presence of a base which is selected from group comprising of ammonia, sodium hydroxide, potassium hydroxide, sodium methoixde, sodium t-butoxide, potassium t-butoxide, sodium carbonate, sodium bicarbonate, triethylamnie or tert-butyl amine.

3. The process according to claim-1 , wherein step-a) is performed in presence of a reagent which is selected from group comprising of thionyl chloride, methane sulfonyl chloride, ethane sulphonyl chloride, trifluoro methanesulfonyl chloride, tosyl chloride, cyanuric chloride, ethyl chloro format, methyl chloro format, pivaloyl chloride, oxalyl chloride or acetic anhydride.

4. A process for the preparation of Olaparib (I)

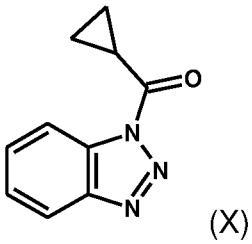

(I)

comprising reacting compound of formula (IX)



(IX)

with compound of formula (X)



(X)

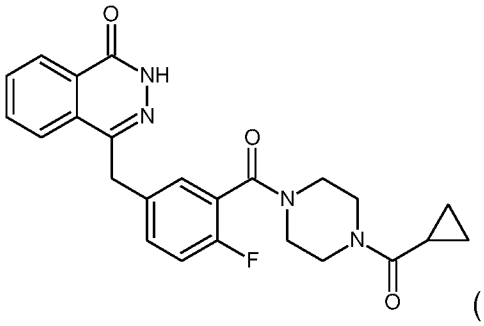
to obtain Olaparib (I).

5. Crystalline form of Olaparib having characteristic peaks in X-ray diffraction pattern at about 6.4°, 8.3°, 12.6°, 15.0°, 15.8° and 19.7° ± 0.2° 2Θ.

6. The crystalline form of Olaparib according to claim-5, having the following additional characteristic peaks in X-ray diffraction pattern at about 6.8°, 15.8°, 16.3°, 16.6°, 20.7 and 22.0° ± 0.2° 2Θ.

7. A process for the preparation of crystalline form of Olaparib comprising steps of:
   a) dissolving Olaparib in a water,
   b) isolating crystalline form of Olaparib.

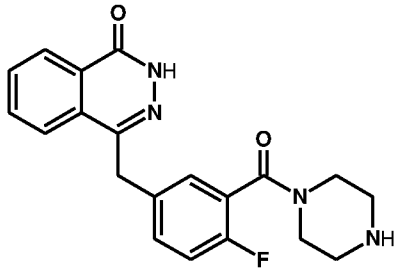
8. A process for the preparation of crystalline form A of Olaparib (I)



(I)

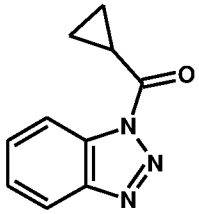
comprising steps of:

a) reacting 4-[4-fluoro-3-(piperazin-1 -ylcarbonyl) benzyl] phthalazin-1(2H)-one (IX)



(IX)

with 1H-benzotriazol-1 -yl(cyclopropyl)methanone (X)

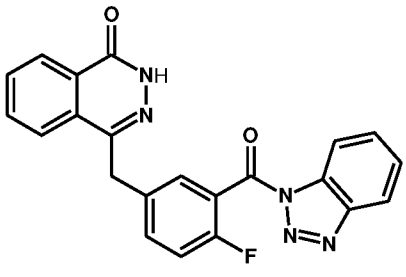


(X)

in organic solvent;

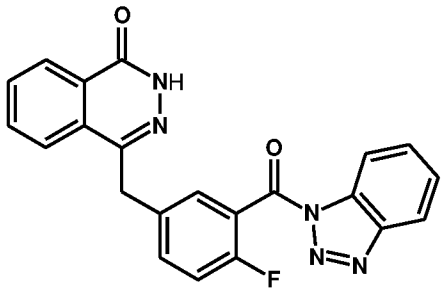
b) isolating crystalline form A of Olaparib.

9. A Compound of formula (VII):



(VII)

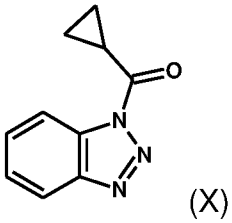
10. Crystalline form of compound of formula (VII):



(VII)

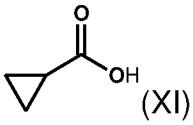
having characteristic peaks in X-ray diffraction pattern at about 3.1°, 6.6°, 11.6°, 13.9°, 15.0°, 21.2°, 21.7°, 25.2° and 26.5° ± 0.2° 2Θ.

11. A process for the preparation of compound of formula (X),



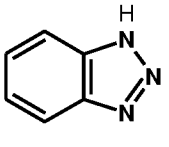
(X)

comprising reaction of compound of formula (j):



(XI)

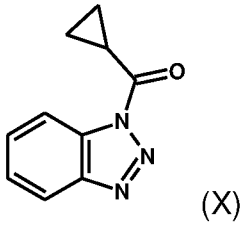
with compound of formula (e):



(VI)

wherein reaction is carried out in absence of a base.

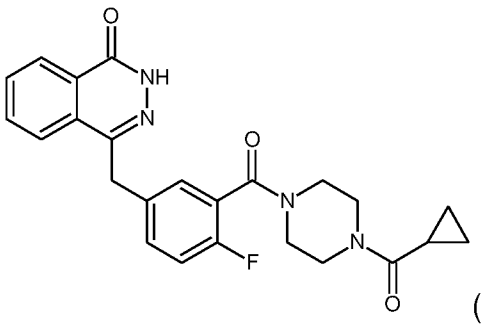
12. Crystalline form of compound of formula (X):



(X)

having characteristic peaks in X-ray diffraction pattern at about 8.7°, 11.0°, 15.9°, 17.4°, 18.7° and 22.0° ± 0.2° 2Θ.

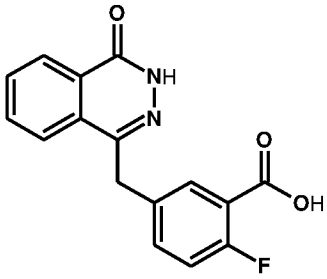
13. Olaparib of formula (I):



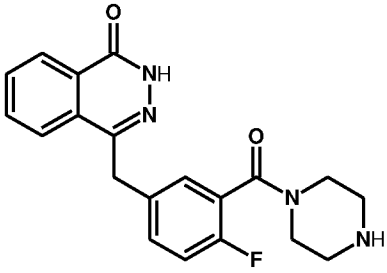
(I)

which is substantially free of:

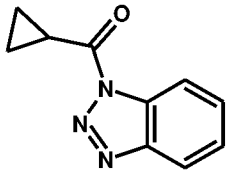
i) Impurity-A:



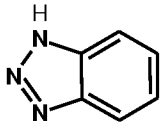
ii) Impurity-B:



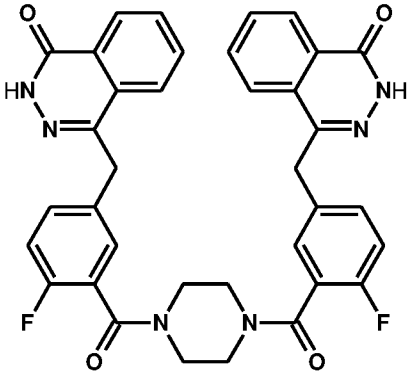
iii) Impurity-C:



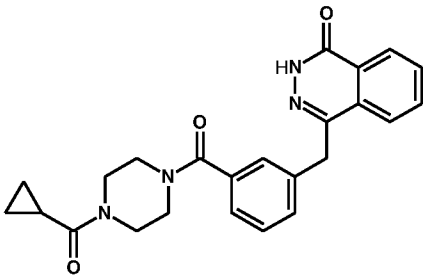
iv) Impurity-D:



v) Impurity-E:



vi) Impurity-F:



vii) Impurity-G:

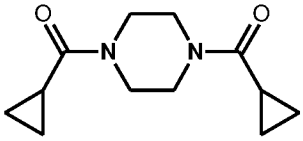


Figure 1

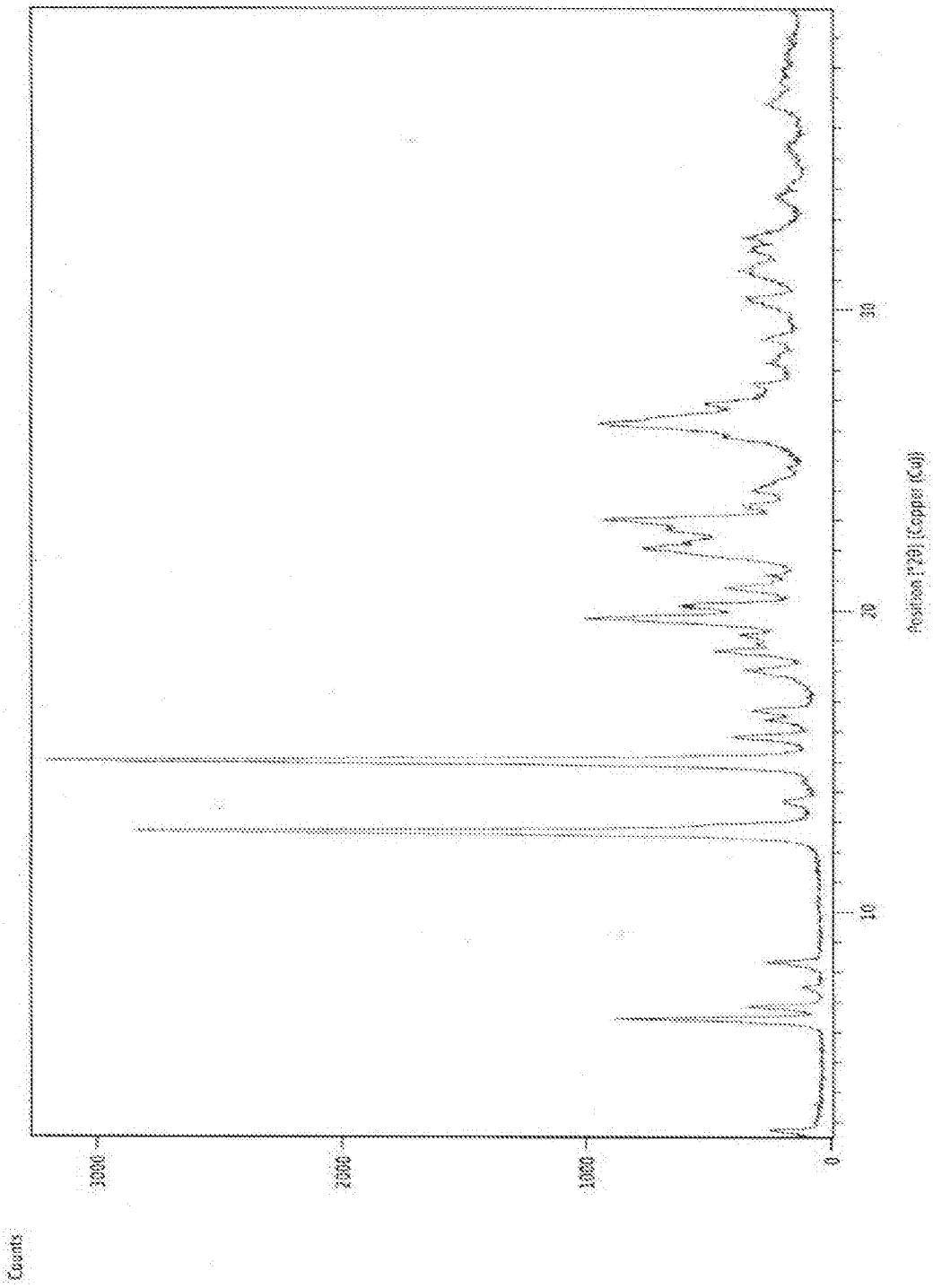


Figure 2

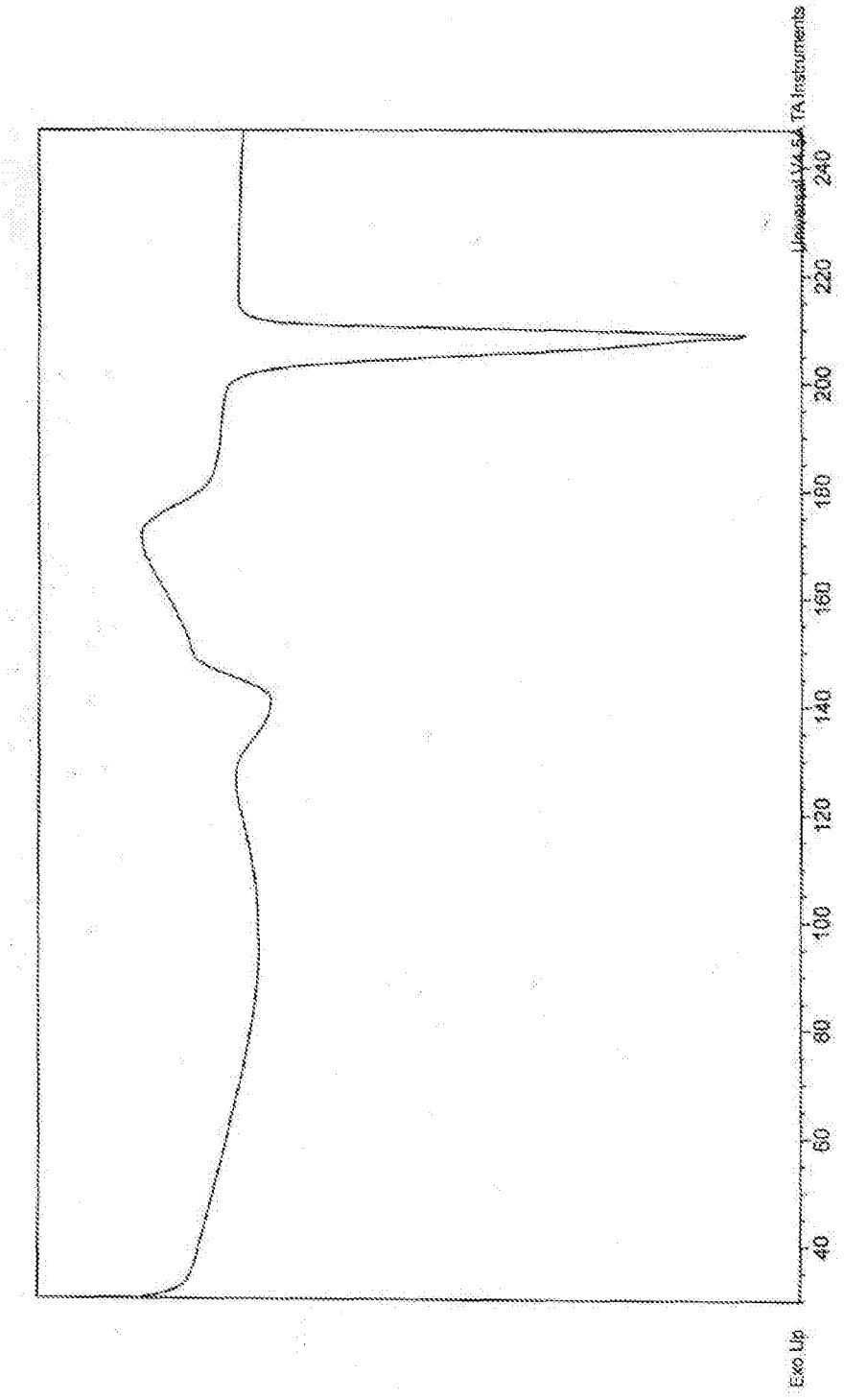

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Figure 3

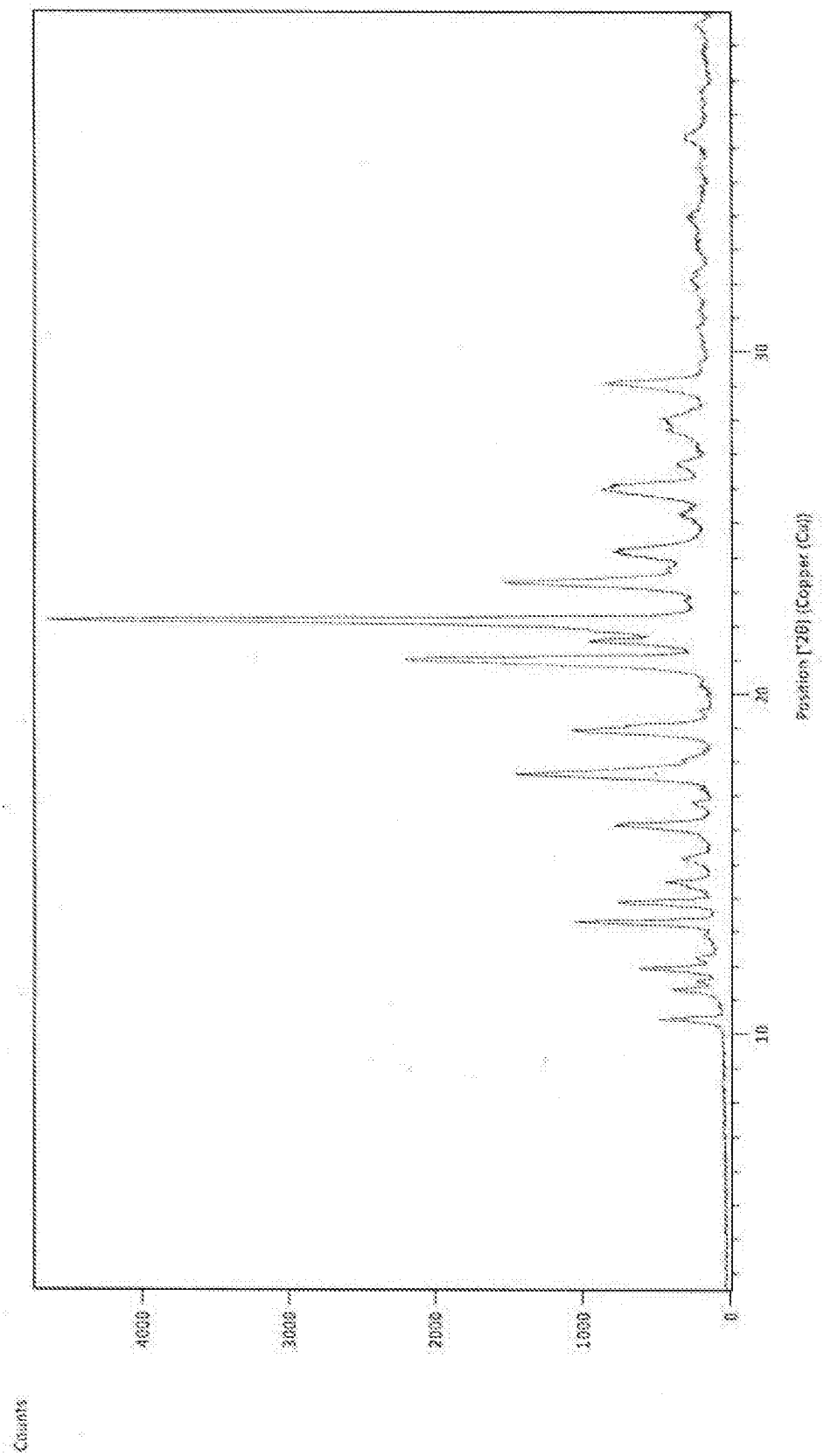


Figure 4

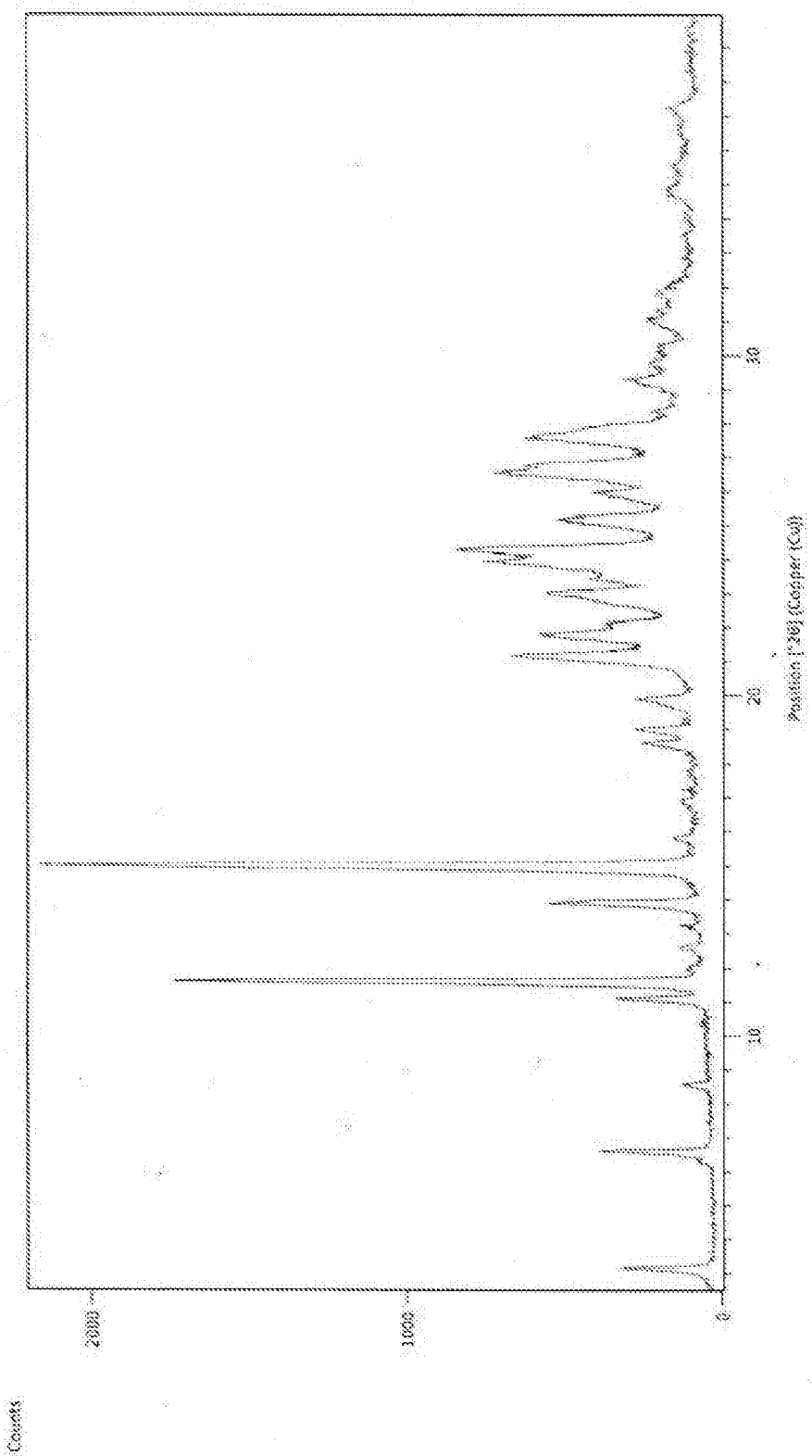
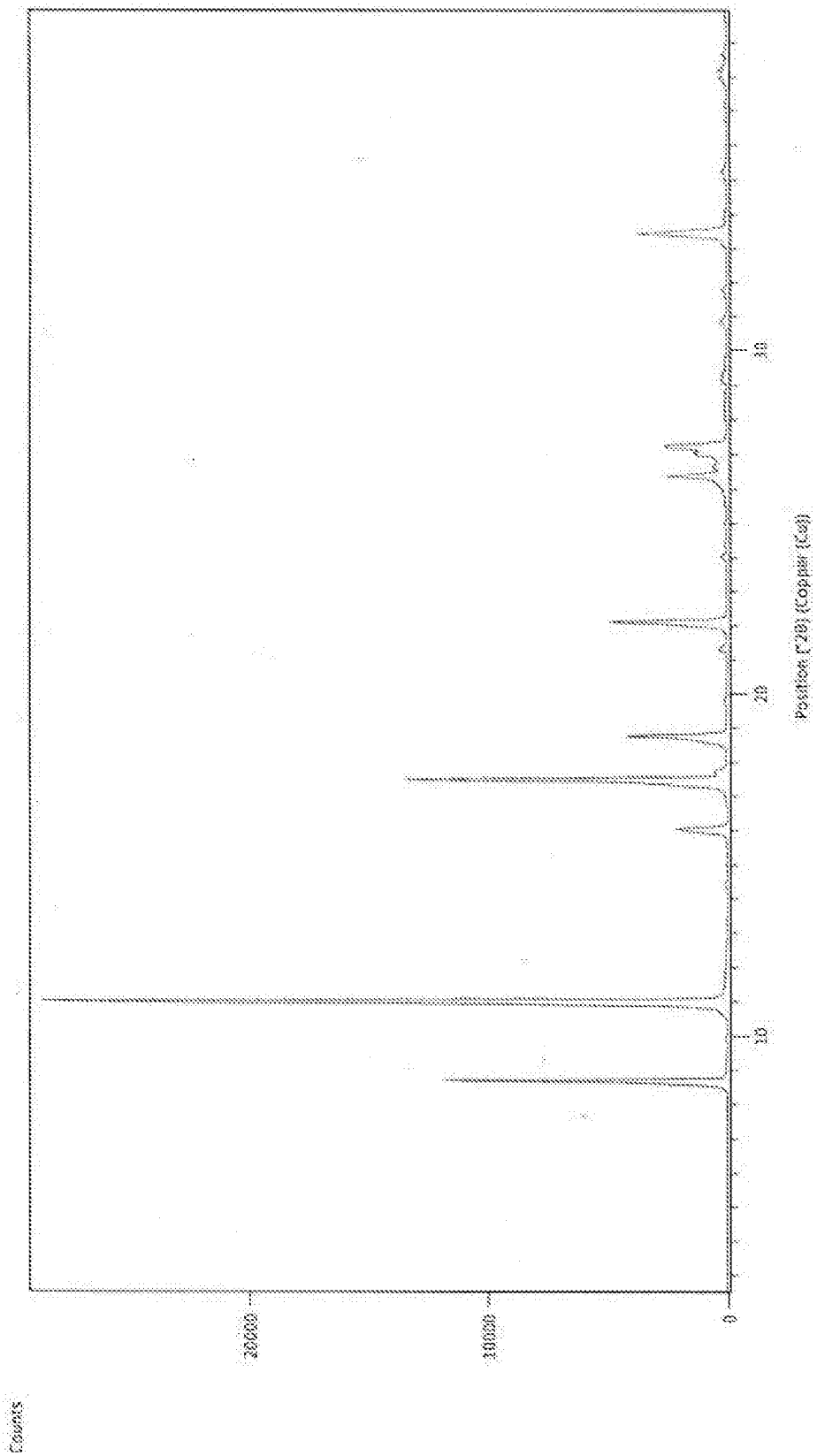


Figure 5



INTERNATIONAL SEARCH **REPORT**

International application No.
PCT/IB2017/052549

A. CLASSIFICATION OF SUBJECT MATTER
C07D409/12, A61P31/20 Vers ion=2 017.01

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

B. FIELDS SEARCHED

Minimum **documentation** searched (classification system followed **by** classification symbols)

C07D

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 Serins used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of **document,** with indication, **where** appropriate, of **the** relevant passages	Relevant to claim No.
A	WO2004080976 Al, 23 Sep 2004, KUDOS PHARMACEUTICALS LIMITED, MAYBRIDGE LIMITED *The Whole Document*	1-12
X	*The Whole Document*	13
A	WO200804 7082 A2, 24 Apr 2008, KUDOS PHARMACEUTICALS LIMITED *The Whole Document*	1-12
X	*The Whole Document*	13

☐ **Farther** 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 o be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"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; die 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
13-07-2017	13-07-2017

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No. 32, Sector 14,Dwarka, New Delhi-110075 Facsimile No.	Dr. Manmeet Kumar Telephone No. +91-1125300200

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/052549

Citation	Pub. Date	Family	Pub. Date
WO 2004080976 A1	23-09-2004	EP 1633724 B1	04-05-2011
		CA 2517629 A1	23-09-2004
WO 2008047082 A2	24-04-2008	EP 2064189 A2	03-06-2009
		CA 2664275 A1	24-04-2008