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IMPROVED PROCESS FOR THE PREPARATION OF LURBINECTEDIN

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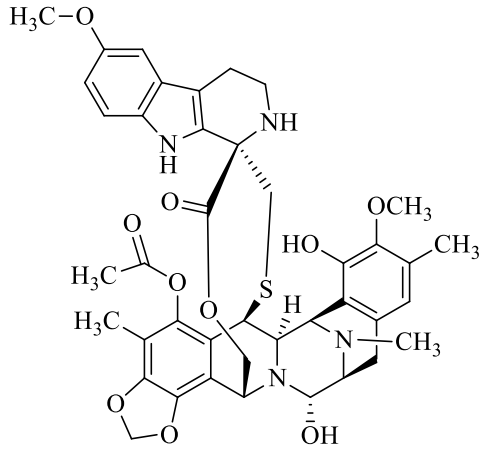
IMPROVED PROCESS FOR THE PREPARATION OF LURBINECTEDIN

Introduction:

The present disclosure relates to an improved process for the preparation of Lurbinectedin of formula-1which is structurally shown as below:

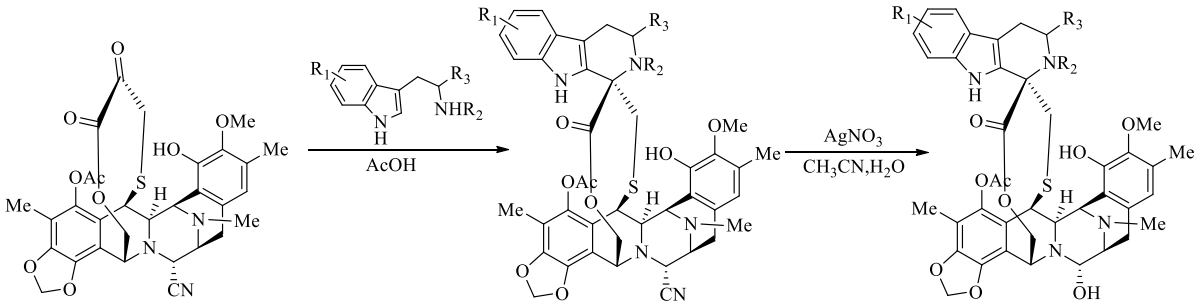


Formula-1

Background of the invention:

Lurbinectedin is chemically known as (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro [7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3] benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate which is a synthetic tetrahydropyrrolo [4,3,2-de]quinolin-8(1H)-one alkaloid analogue with potential antineoplastic activity. It is approved by USFDA under brand name of Zepzelca for the treatment of adults with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy..

WO 00/069862 A2 discloses a process for the preparation of Lurbinectedin as shown in below



Brief description of the invention:

The present invention provides improved process for the preparation of Lurbinectedin.

Detailed description of the invention

The term "solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" selected from dimethyl ether, diisopropyl ether, diethyl ether, methyl tert-butyl ether (MTBE), 1,2-dimethoxy ethane, tetrahydrofuran, Trifluoroacetic anhydride, 1,4-dioxane and the like; "ester solvents" selected from methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; "polar-aprotic solvents selected from dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and the like; "chloro solvents" selected from dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "nitrile solvents" selected from acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” selected from methanol, ethanol, n- propanol, isopropanol, n-butanol, isobutanol, t-butanol, n-pentanol, isopentanol, 2-nitroethanol, ethylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, benzyl alcohol, phenol, or glycerol and the like; “polar-aprotic solvents" selected from dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "polar solvents" selected from water or mixtures thereof.

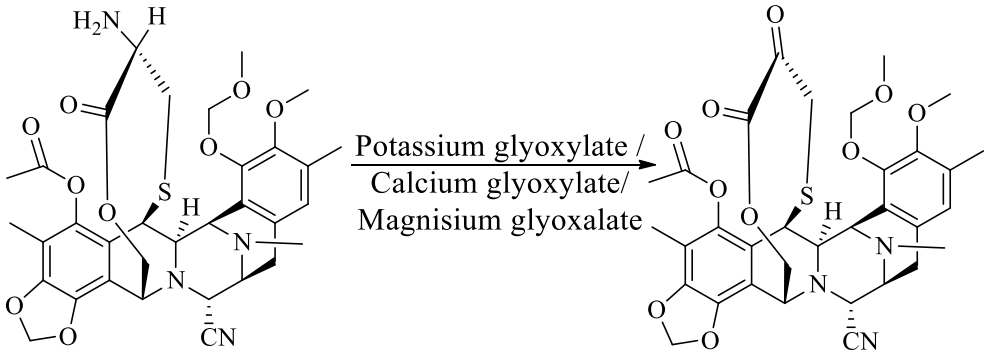
As used herein the present invention, the term “base” is selected from inorganic bases like “alkali metal hydroxides” such as lithium hydroxide, sodium hydroxide, potassium

hydroxide and the like; “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; “alkali metal hydrides” such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia; and organic bases such as “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; triethyl amine, methyl amine, ethylamine, 1,8-diaza bicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithiumdiiso propylamide (LDA), n-butyl lithium, tribenzylamine, isopropyl amine, diisopropylamine, diisopropylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylamino pyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methyl imidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

As used herein the term “solid-state forms” referred in the present invention relates to crystalline or amorphous forms.

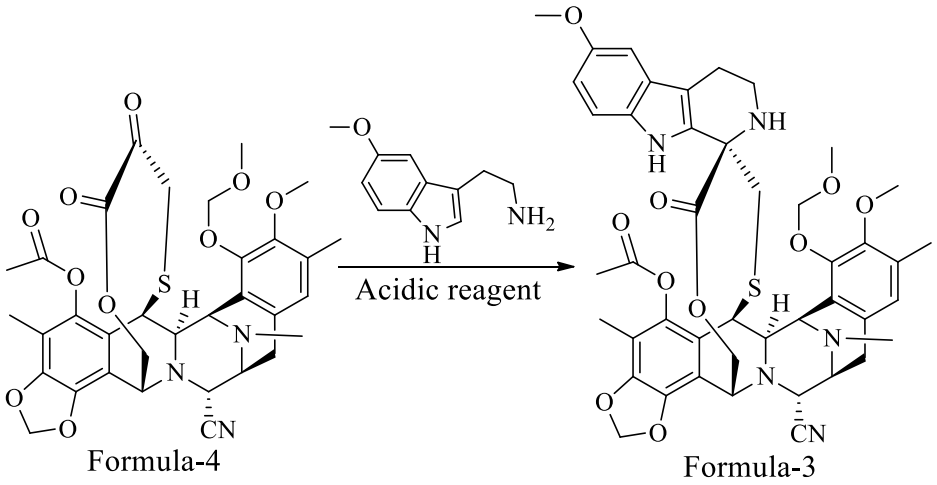
In the first embodiment, the present invention provides a process for the preparation of Lurbinectedin, which comprises:

a) reacting compound of formula-5 with potassium glyoxylate / calcium glyoxylate to get compound of formula-4,



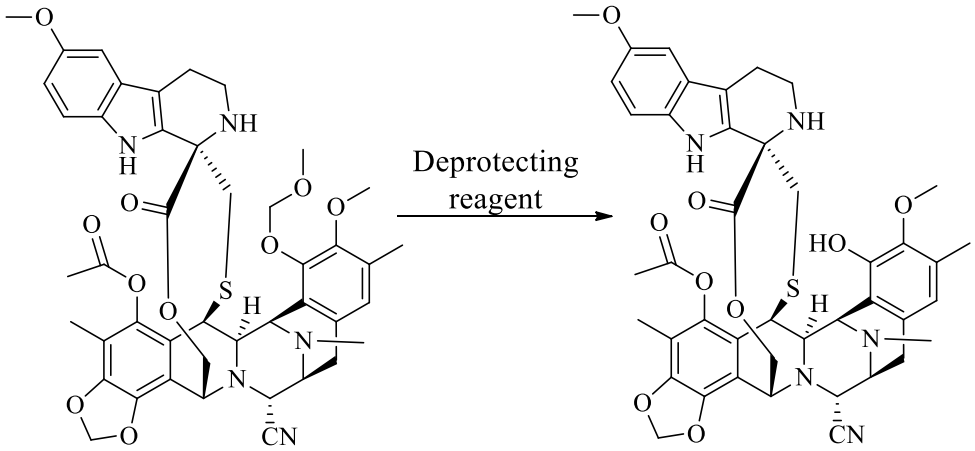
Formula-5 Formula-4

b) treating compound of formula-4 with 2-(5-methoxy-1H-indol-3-yl)ethanamine in presence of acidic reagent to get compound formula-3,



Formula-4 Formula-3

c) deprotecting compound of formula-3 with deprotecting reagent to get compound of formula-2,



Formula-3 Formula-2

d) converting the compound of formula-2 to Lurbinectedin.

The “acidic reagent” is used in step b) is selected from organic and inorganic acids such as acetic acid, trifluoroacetic acid, propanephosphonic acid anhydride, phosphoric acid, acetic anhydride, toluenesulfonic acid, methanesulfonic acid, perfluoro acid anhydrides includes trifluoroacetic anhydride, pentafluoropropionic anhydride, heptafluorobutyric anhydride, and combinations thereof.

The “deprotecting reagent” is used in step c) is selected from trifluoro acetic acid, aqueous HCl, trimethylsilyl halides such as trimethylsilyl chloride, trimethylsilyl iodide, trimethylsilyl fluoride and trimethylsilyl bromide, preferably trimethylsilyl bromide.

The “solvent” used in step a) to step c) are selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof.

According to first embodiment of the invention, the reaction is carried out in step b) in presence/ absence of solvent.

In first aspect of the first embodiment, the reaction in step c) is carried out at the temperature ranging at about -25°C to -40°C.

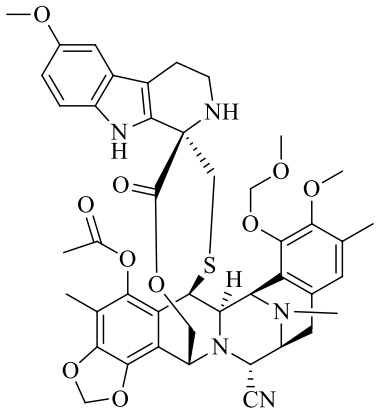
In second aspect of the first embodiment, pure Lurbinectedin is having purity greater than 99.5%, preferably greater than 99.8%.

In third aspect of the first embodiment, pure Lurbinectedin is having mom impurity is less than about 0.15%, preferably less than about 0.10%, more preferably less than about 0.05%.

In fourth aspect of the first embodiment, the Lurbinectedin obtained in step d) is characterized in figure-1.

In fifth aspect of the first embodiment, the Lurbinectedin obtained in step e) is characterized in figure-2.

In second embodiment, the present invention provides compound of formula-3



Formula-3

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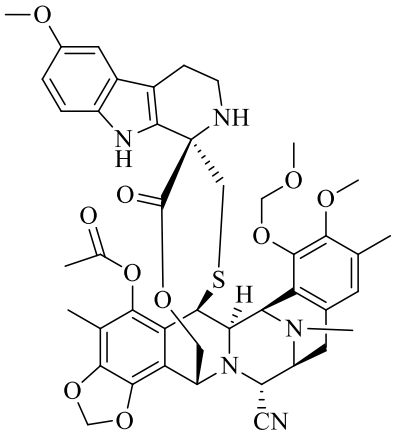
In third embodiment, the present invention provides solid-state forms of compound of formula-3



Formula-3

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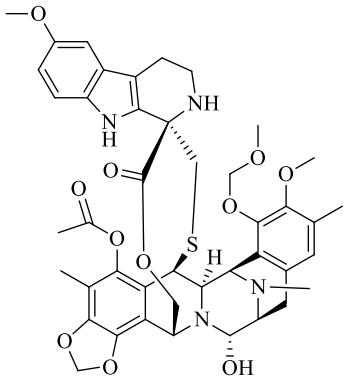
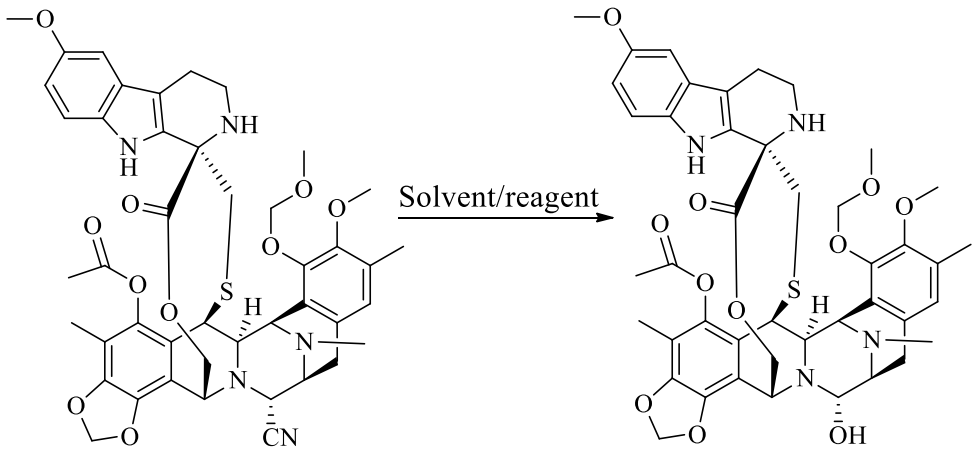
In fourth embodiment, the present invention provides Mom-impurity compound of formula-7



Formula-7

In fifth embodiment of the present invention provides process for the preparation of Mom-impurity compound of formula-7, which comprises treating compound of formula-3 with a reagent in a solvent to get Mom-impurity compound of compound of formula-7.



Formula-3 Formula-7

The "solvent" used in fifth embodiment is selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof. Preferably acetonitrile and water.

The reagent used in fifth embodiment is silver nitrite.

In sixth embodiment of the present invention provides crystalline form of Lurbinectedin of formula-1.

In first aspect of the sixth embodiment, the present invention provides crystalline form of Lurbinectedin of formula-1, which is hereinafter referred to as Form-M.

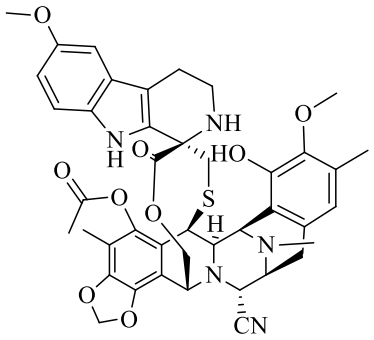
In second aspect of the sixth embodiment, the present invention provides crystalline form-M of Lurbinectedin of formula-1, which is characterized by its powder X-Ray diffractogram as illustrated in Figure-1.

In third aspect of the sixth embodiment, the present invention provide a process for the preparation of crystalline form-M of Lurbinectedin, comprising of treating Lurbinectedin with a suitable solvent selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof, preferably acetonitrile.

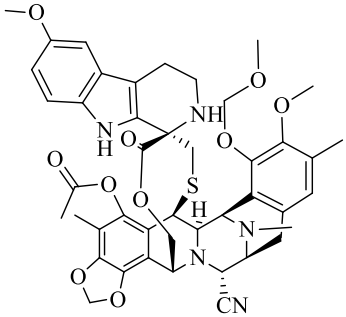
The compound of formula-2 obtained according to the present invention further converted to Lurbinectedin can be carried out by the methods known in the art.

The starting material compound of formula-5 used in the present invention can be prepared by the methods known in the art.

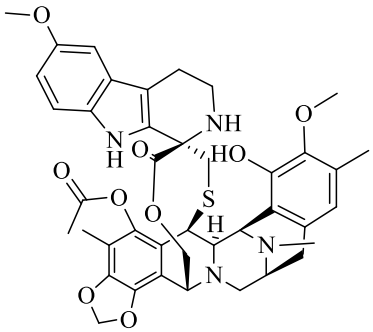
Lurbinectedin obtained according to the present invention is having Cyano des mom impurity, Des hydroxy impurity, MOM impurity, Des acetyl impurity, Cyano mom impurity less than about 0.05% as measured by HPLC.



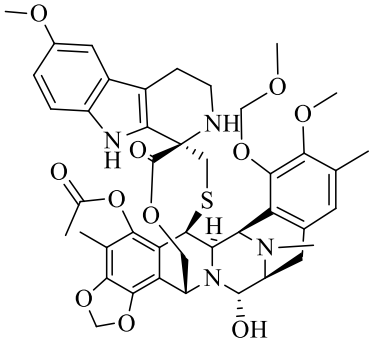
Cyano des mom impurity



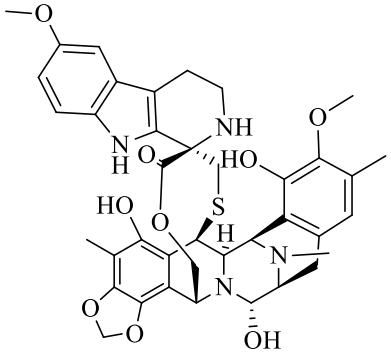
Cyano mom impurity



Des hydroxyl impurity



MOM impurity



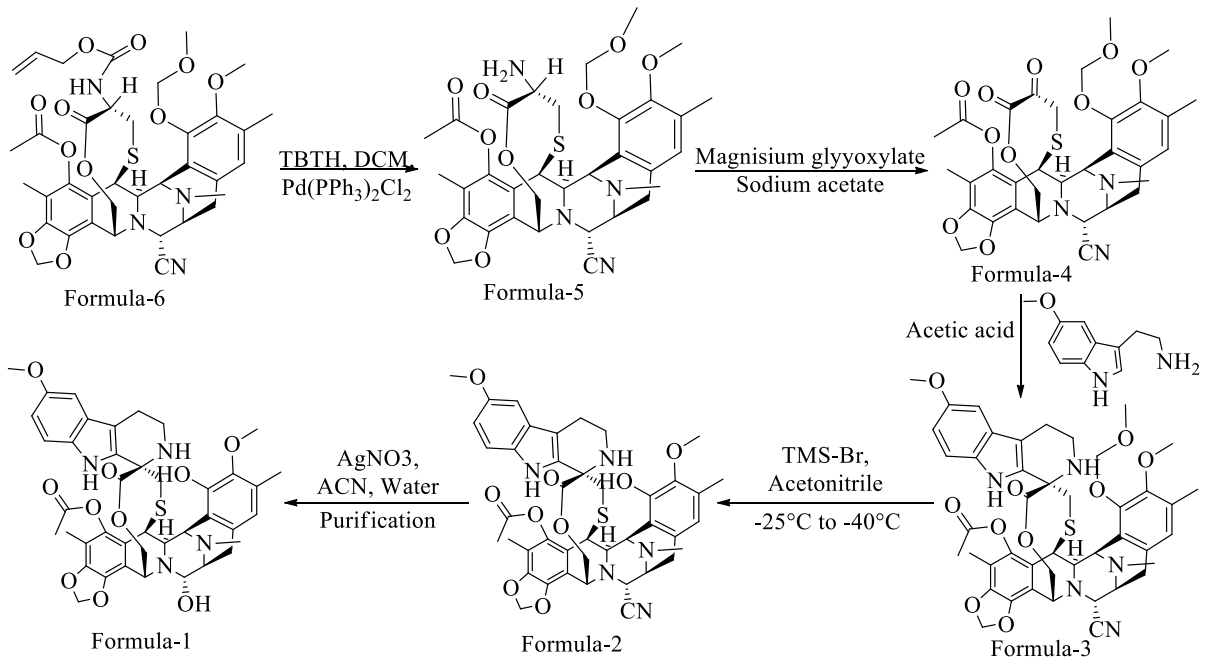
Des acetyl impurity

In another embodiment, Lurbinectedin of formula-1 obtained by the present invention can be used in the preparation of various pharmaceutical compositions, formulated in a manner suitable for the route of administration to be used.

In yet another embodiment, the present invention encompasses pharmaceutical compositions comprising Lurbinectedin of formula-1 obtained by the process of the present invention and one or more pharmaceutical acceptable excipient.

As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The process of the present invention can be represented schematically as follows:



P-XRD Method of Analysis:

The powder X-ray diffraction (PXRD) analysis of compound of formula-1 of the present invention were carried out by using BRUKER/D8 ADVANCE or BRUKER/D2 PHASER diffractometer using CuKα radiation of wavelength 1.5406A°.

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be construed as limitation of the scope of the invention.

Examples

Example-1: Preparation of compound of formula-4.

Acetonitrile (1.66 ml) was added to compound formula-5 (100 mg) at 25-30°C and stirred for 10 minutes. Sodium acetate (10.45 mg) and molecular sieves (20 mg) were added to the mixture at 25-30°C and stirred for 10 minutes. Zinc sulfate (12.08 mg) and calcium glyoxylate (279.16 mg) were added to the mixture at 25-30°C and stirred for 23 hours. Water (10 ml) was added to the mixture at 25-30°C and stirred for 10 minutes. Dichloromethane (5 ml) was added to mixture and stirred for 10 minutes. Filtered the mixture and washed with dichloromethane (5.0 ml). Layers were separated and aqueous layer washed with dichloromethane. Combined the total organic layers and washed with aqueous sodium bicarbonate solution. Distilled off the solvent completely under reduced pressure to get the title compound. Yield: 75 mg.

Example-2: Preparation of compound of formula-4.

Acetonitrile (1.66 ml) was added to compound formula-5 (100 mg) at 25-30°C and stirred for 10 minutes. Sodium acetate (10.45 mg) and molecular sieves (20 mg) were added to the mixture at 25-30°C and stirred for 5 minutes. Zinc sulfate (12.08 mg) and potassium glyoxylate (336.35 mg) were added to the mixture at 25-30°C and stirred for 6 hours. Water (10 ml) was added to the mixture at 25-30°C and stirred for 10 minutes. Dichloromethane (5 ml) was added to mixture and stirred for 10 minutes. Filtered the mixture and washed with dichloromethane (5.0 ml). Layers were separated and aqueous layer washed with dichloromethane. Combined the total organic layers and washed with aqueous sodium bicarbonate solution. Distilled off the solvent completely under reduced pressure to get the title compound. Yield: 70 mg.

Example-3: Preparation of compound of formula-4.

Acetonitrile (16.6 ml) was added to compound formula-5 (1.0 g) at 25-30°C and stirred for 10 minutes. Sodium acetate (104.5 mg) and molecular sieves (200 mg) were added to the mixture at 25-30°C and stirred for 15 minutes. Zinc sulfate (120.2 mg) and magnesium

glyoxylate (310.4 mg) were added to the mixture at 25-30°C and stirred for 6 hours. Water (10 ml) was added to the mixture at 25-30°C and stirred for 15 minutes. Dichloromethane (5 ml) was added to mixture and stirred for 10 minutes. Filtered the mixture and washed with dichloromethane (5.0 ml). Layers were separated and aqueous layer washed with dichloromethane. Combined the total organic layers and washed with aqueous sodium bicarbonate solution. Distilled off the solvent completely under reduced pressure to get the title compound. Yield: 0.93 gm.

Example-4: Preparation of compound of formula-3.

Acetic acid (2 ml) was added to compound of formula-4 (100 mg) at 25-30°C and stirred for 10 minutes. 5-Methoxytryptamine (37.15 mg) was added to the mixture at 25-30°C and stirred for 4 hours. Cooled the reaction mixture to 5-10°C and stirred for 20 minutes. Water (5.0 ml) was added to mixture at 5-10°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 5-10°C and stirred for 15 minutes. Dichloromethane (5 ml) was added to the mixture at 5-10 °C and stirred for 10 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 15 minutes. Layers were separated and aqueous layer washed with dichloromethane. Combined the total organic layers, washed with water, and dried the organic layer with sodium sulfate. Distilled off the solvent completely under reduced pressure to get the title compound. Yield: 85 mg.

Example-5: Preparation of compound of formula-3.

Ethanol (5.0 ml) was added to compound of formula-4 (0.5 mg) at 25-30°C and stirred for 10 minutes. 5-Methoxytryptamine (185.75 mg) and Propanephosphonic acid anhydride (T3P) (360 mg) were added to the mixture at 25-30°C and stirred for 20 minutes. Raised the temperature of the mixture to 40-45°C and stirred for 4-5 hours. Cooled the reaction mixture to 25-30°C and stirred for 15 minutes. Water (5 ml) was added to mixture at 25-30°C and stirred for 10 minutes. Cooled the reaction mixture to 10-15°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 10-15°C and stirred for 15 minutes. Dichloromethane was added to the mixture at 5-10 °C and stirred for 10 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 10 minutes. Layers were separated and aqueous layer charged with dichloromethane. Combined the total organic layers and washed with water, and dried the organic layer with sodium sulfate. Distilled off the

solvent completely under reduced pressure to get crude compound. Acetonitrile (2.5 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Water (2.5 ml) was added to the mixture and stirred for 10 minutes. Cooled the mixture to 5-10°C, added water (7.5 ml) to the mixture and stirred for 1 hour. Raised the temperature of the mixture to 25-30°C, dichloromethane (20 ml) was added to the mixture and stirred for 10 minutes. Layers were separated and distilled off the organic layer completely under reduced pressure to get the title compound. Yield: 230 mg.

Example-6: Preparation of compound of formula-2.

Acetonitrile (200 ml) was added to compound formula-3 (100 mg) at 25-30°C and stirred for 10 minutes. Water (200 ml) was added to the mixture at 25-30°C and stirred for 10 minutes. Cooled the reaction mixture to 0-5°C and stirred for 10 minutes. Trifluoroacetic acid (600 ml) was added to mixture at 5-10°C and stirred for 3 hours. Raised the temperature of the mixture to 20-25°C and stirred for 15 hours. Cooled the reaction mixture to 5-10°C and stirred for 10 minutes. Water (5 ml) and ethyl acetate (5 ml) was added to the mixture at 5-10°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 5-10°C and stirred for 15 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 10 minutes. Layers were separated and aqueous layer washed with ethyl acetate. Combined the total organic layers, washed with water, and dried with sodium sulfate. Distilled off the solvent completely under reduced pressure to get the crude compound. Ethanol (2 ml) was added to obtained compound at 25-30°C and stirred for 10 minutes. Filtered the mixture and washed with ethanol to get solid compound. Combine the filtrates, added activated carbon to the mixture at 25-30 ° C and stirred for 30 minutes. Filtered the mixture through hyflow bed, and washed the bed with ethanol. Distilled off the solvent completely under reduced pressure to get the title compound. Yield: 58 mg.

Example-7: Preparation of compound of formula-2.

Ethanol (5 ml) was added to compound formula-3 (50 mg) at 25-30°C and stirred for 10 minutes. Cooled the mixture to 5-10°C and stirred for 30 minutes. Aqueous hydrochloric acid solution (65 mg) was added to the mixture at 5-10°C and stirred for 6 hours. Raised the temperature of the mixture to 20-25°C and stirred for 44 hours. Aqueous hydrochloric acid solution was added to the mixture at 25-30°C and stirred for 50 hours. Water (10 ml) was added

to the mixture at 25-30°C and stirred for 5 minutes. Cooled the mixture to 5-10°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 5-10°C and stirred for 15 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 10 minutes. Layers were separated and aqueous layer washed with dichloromethane. Combined the total organic layers, water was added to the mixture and stirred for 10 minutes. Separated the layers and distilled off the solvent from the organic layer completely under reduced pressure to get the title compound. Yield: 25 mg.

Example-8: Preparation of compound of formula-2.

Dichloromethane (6 ml) and molecular sieves were added to compound of formula-3 at 25-30°C. Cooled the mixture to -25 to -30°C and stirred for 25 minutes. Trimethylsilyl bromide was added to the mixture at -25 to -30°C and stirred for 6 hours. Water (5 ml) was added to the mixture at -25 to -30°C and stirred for 10 minutes. Raised the temperature of the mixture to 10-15°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 25-30°C and stirred for 5 minutes. Raised the temperature of the mixture to 20-25°C and stirred for 10 minutes. Layers were separated and aqueous layer was extracted with dichloromethane. Combined the total organic layers, water was added to the organic layer and stirred for 5 minutes. Layers were separated. Distilled off the solvent from the organic layer completely under reduced pressure to get the crude compound. Ethanol was added to the obtained compound at 25-30°C and stirred for 10 minutes. N-heptane was added to mixture at 25-30°C and stirred for 10 minutes. Cooled the mixture to 5-10°C and stirred for 30 minutes. Filtered the solid, washed with a mixture of ethanol & n-heptane solution, and dried get title compound. Yield: 140.0 mg.

Example-9: Preparation of compound of formula-5.

Bistriphenylphosphine palladium (II) chloride (0.075 gms) and acetic acid (1.5 ml) were added the solution of the compound of formula-6 (2.0 gms) in dichloromethane (400 ml) at 25-30°C and stirred for 10 minutes at the same temperature under argon atmosphere. Tributyltin hydride (1.6 ml) was added to the mixture at 25-30°C and stirred for 1 hour. Thiophenol resin (2.0 gms) was added to the mixture at 25-30°C and stirred for 30 minutes. Filtered the mixture through hyflow bed and washed the bed with dichloromethane. The obtained filtrate was washed with aqueous potassium fluoride solution and followed by with

water. The organic layer was dried with sodium sulfate. Distilled off the solvent completely from the organic layer under reduced pressure. Ethyl acetate was added to the obtained compound at 25-30°C and stirred for 15 minutes. Filtered the unwanted material and washed with ethyl acetate. Distilled off the solvent completely from the filtrate under reduced pressure. Methanol was added to obtained compound at 25-30°C and stirred. Methanol layer was separated from the mixture. Distilled off the solvent completely under reduced pressure and co-distilled with isopropanol. To the obtained compound, isopropanol (4.0 ml) was added at 25-30°C and stirred for 10 minutes. Cooled the mixture to 0-5°C and stirred. Filtered the solid, washed with isopropanol and n-heptane and then dried get title compound. Yield: 1.5 gms.

Example-10: Preparation of compound of formula-4

The compound formula-5 (1.5 gms) was added to the mixture of acetonitrile (24.9 ml) and molecular sieves (0.3 gms) at 25-30°C and stirred for 10 minutes. Cooled the temperature of the mixture to 0-5°C. A solution of sodium acetate (0.15 gms) in acetic acid (24.9 ml) was slowly added to the mixture at 0-5°C. Zinc sulfate (0.19 gms) and magnesium glyoxylate (0.76 gms) were added to the mixture at 0-5°C and stirred for 3 hours. Water followed by the mixture of methanol and dichloromethane were added to the mixture at 10-15°C and stirred at 25-30°C. Filtered the mixture and washed with a mixture of methanol and dichloromethane. Layers were separated. Aqueous layer was extracted with mixture of methanol and dichloromethane. Combined the total organic layers and washed with water. Organic layer washed with aqueous sodium bicarbonate solution and followed by with washed with water. Neutral carbon was added to the organic layer and stirred for 10 minutes. Filtered the mixture through hyflow bed and washed with a mixture of methanol and dichloromethane. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with cyclohexane to get the title compound.

Yield: 1.4 gms.

Example-11: Preparation of compound of formula-3.

Acetic acid (4.5 ml) was added to compound of formula-4 (0.9 gms) at 25-30°C and stirred for 10 minutes. Cooled the reaction mixture to 15-20°C and stirred for 10 minutes. 5-Methoxytryptamine (0.33 gms) was added to the mixture at 15-20°C and stirred for 10 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 4 hours. The mixture was

slowly added to the pre-cooled water at 0-5°C and stirred for 10 minutes. Adjusted the pH of the mixture to 7.5 using aqueous dipotassium hydrogen phosphate solution at 0-5°C and stirred for 2 hours. Filtered the solid, washed with water. The obtained solid was added to acetone at 25-30°C and stirred for 10 minutes. Distilled off the solvent from the mixture under reduced pressure and co-distilled with acetone. Acetone (5.0 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes at the same temperature. Cooled the mixture to 0-5°C and stirred. Filtered the solid, washed with pre-cooled acetone and dried to get the title compound.

Yield : 0.91 gms.

Example-12: Preparation of compound of formula-2.

The compound of formula-3 (15.0 gms) was added to acetonitrile (450 ml) at 25-30°C and stirred for 10 minutes. Cooled the mixture to -35 to -40°C. Trimethylsilyl bromide (23.62 ml) was added to the above mixture at -35 to -40°C and stirred for 10 minutes. Raised the temperature of mixture to -30 to -35°C and stirred for 12 hours. Water was added to the mixture at -30 to -35°C and stirred for 30 minutes. Raised the temperature of the mixture to 0-5°C and stirred for 10 minutes. Aqueous sodium bicarbonate solution was added to mixture at 0-5°C and stirred for 1 hour. Filtered the solid, washed with water and followed by pre-cooled methanol. To the obtained compound, methanol (75 ml) was added at 25-30°C and stirred for 5 minutes. Cooled the mixture to 0-5°C and stirred for 2 hours. Filtered the solid, washed with pre-cooled methanol and dried to get the title compound. Yield: 10.0 gms.

Example-13: Preparation of crystalline form-M of Lurbinectedin of formula-1.

Compound of formula-2 (3.0 gms) was added to the mixture acetonitrile (252 ml) and water (168 ml) at 25-30°C under argon atmosphere at 25-30°C and stirred for 15 minutes. Silver nitrate (19.25 gm) was added to the mixture at 25-30°C and stirred for 15 minutes. Cooled the temperature of the mixture to 15-20°C and stirred for 20 hours. Further, cooled the mixture to 0-5°C and stirred for 15 minutes. A pre-cooled aqueous sodium bicarbonate solution and then aqueous sodium chloride solution were added to the mixture at 0-5°C and stirred for 10 minutes. A mixture of 20% methanol in methyl tert-butyl ether was added to the mixture at 0-5°C and stirred for 20 minutes. Filtered the mixture through hyflow bed and washed the bed with a mixture of methanol in methyl tert-butyl ether. Layers were separated from the filtrate

and aqueous layer was extracted with a mixture of methanol and methyl tert-butyl ether. Combined the organic layers and washed with a pre-cooled mixture of aqueous sodium bicarbonate solution and aqueous sodium chloride solution. Obtained organic layer was washed with aqueous sodium chloride solution and followed by with water. Distilled off the solvent under reduced pressure and then co-distilled with acetonitrile. The obtained compound was added to pre-cooled acetonitrile at 0-5°C under argon atmosphere and stirred for 2 hours. Filtered the solid, washed with pre-cooled acetonitrile. Ethyl acetate was added to the obtained compound at 25-30°C and stirred for 30 minutes. Cooled the mixture to 0-5°C and stirred for 2 hours. Filtered the solid, washed with pre-cooled acetonitrile and dried to get the title compound. Yield: 2.30 gms. Purity by HPLC: 97.46%.

The PXRD of the obtained compound was depicted in Figure 1.

Example-14: Preparation pure Lurbinectedin of formula-1.

Lurbinectedin (2.0 gms) obtained in Example-13 was purified by flash column chromatography using aqueous citric acid and methanol as eluents. Combined the all pure fractions (3500 ml), cooled to 0-5°C and stirred for 25 minutes. Adjusted the pH of the mixture to 7.6 using buffer solution (the mixture of ammonia and ammonium chloride solution) at 0-5°C and stirred for 10 minutes. Pre-cooled dichloromethane was added to the mixture at 0-5°C and stirred for 5 minutes. Layers were separated and aqueous layer was extracted with dichloromethane. Combined the total organic layers and washed with water. Organic layer dried with sodium sulfate. Filtered the mixture and washed with a mixture of methanol and dichloromethane. Distilled off the solvent from the filtrate under reduced pressure and co-distilled with acetonitrile. To the obtained compound, acetonitrile was added at 25-30°C and stirred for 5 minutes. Cooled the mixture to 0-5°C and stirred for 2 hours. Filter the solid, washed with pre-cooled acetonitrile and dried to get the title compound.

Yield: 1.32 gms. Purity by HPLC: 99.81%, Des hydroxy impurity: 0.03%.

The PXRD of the obtained compound was depicted in Figure 2.

Example-15: Preparation of MOM impurity compound of formula-7.

Compound of Formula-3 (0.5 gms) was added to the mixture of acetonitrile (42 ml) and water (28 ml) at 25-30°C and stirred for 10 minutes under argon atmosphere. Silver nitrate (3.04 gms) was added to the above mixture at 25-30°C and stirred for 15 minutes. Cooled the

mixture to 15-25°C and stirred for 20 hours. Cooled the temperature of the mixture to 0-5°C and stirred for 5 minutes. A mixture of pre-cooled aqueous sodium bicarbonate and aqueous sodium chloride solution was added to the mixture at 0-5°C and stirred for 5 minutes. A mixture of pre-cooled methanol and methyl tert-butyl ether was added to the mixture. Filtered the mixture through hyflow bed and washed the bed with a mixture of methanol and methyl tert-butyl ether. Layers were separated. Aqueous layers were extracted with a mixture of methanol and methyl tert-butyl ether. Combined the organic layers and washed with a mixture of pre-cooled aqueous sodium bicarbonate and aqueous sodium chloride solution, then washed with aqueous sodium chloride solution and followed by with pre-cooled water. Carbon was added to the organic layer and stirred for 2 hours at 0-5°C. Filtered the mixture through hyflow bed and washed the bed with a mixture of methanol and methyl tert-butyl ether. Distilled off the solvent completely from the filtrate under reduced pressure to get the title compound. Yield: 0.4 gms.

Figures

Figure 1: Illustrates the PXRD pattern of crystalline form-M of Lurbinectedin formula-1.

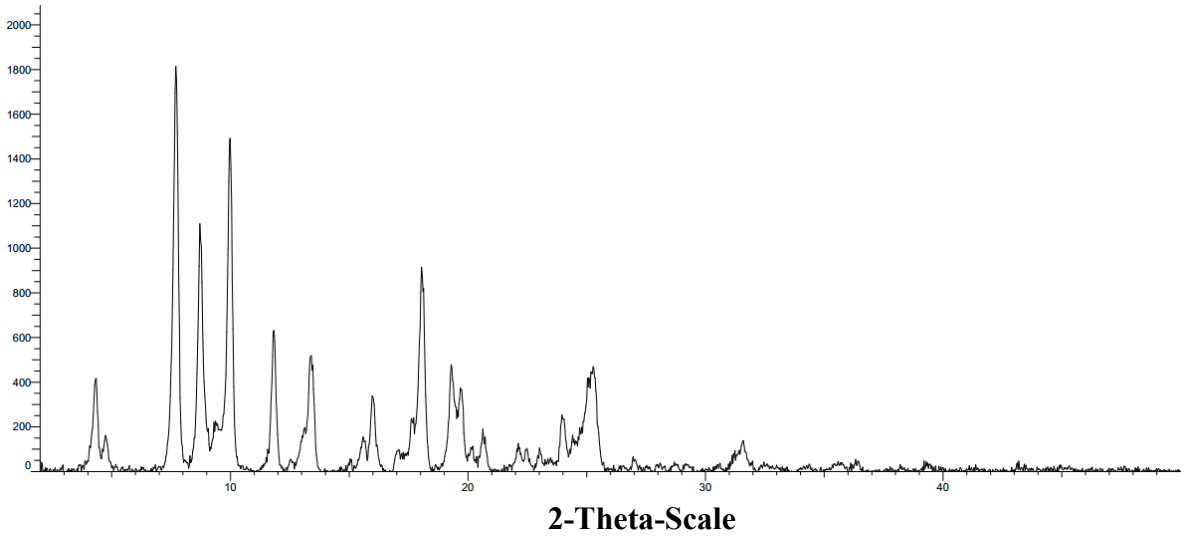
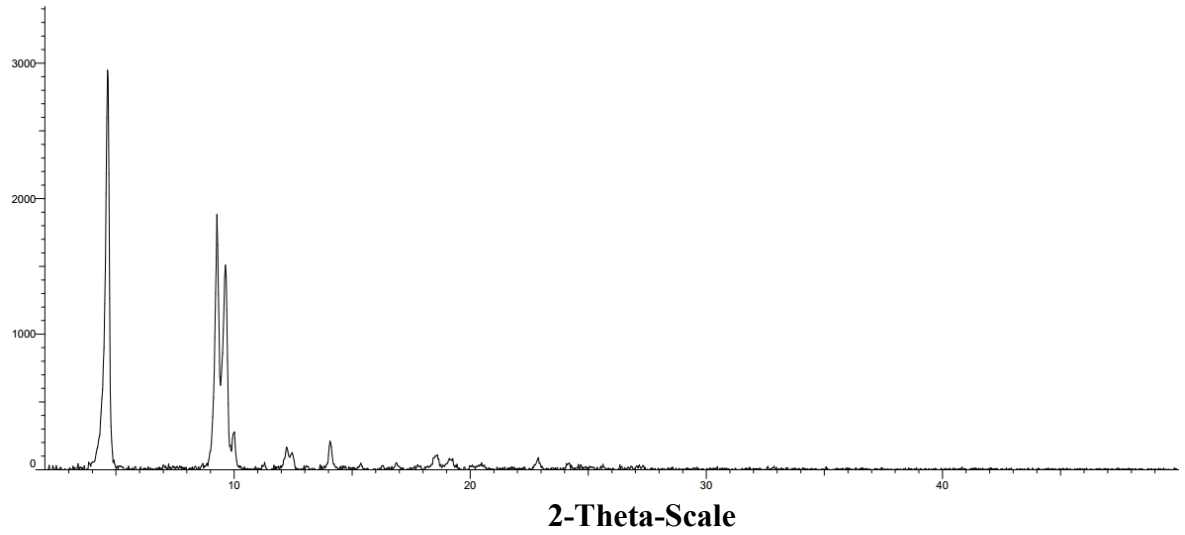


Figure 2: Illustrates the PXRD pattern of crystalline form of Lurbinectedin formula-1.



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