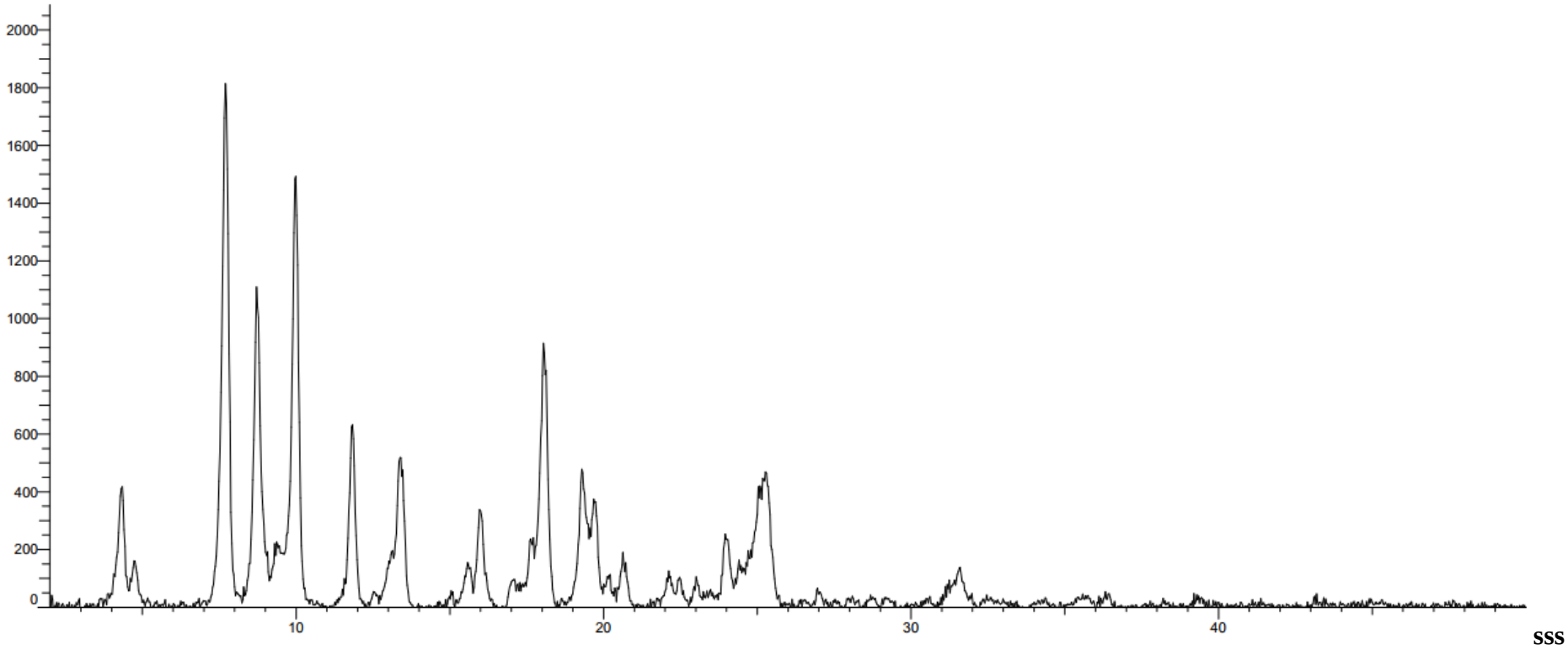
MSN Laboratories Private Limited, R&D Center

No of sheets: 2

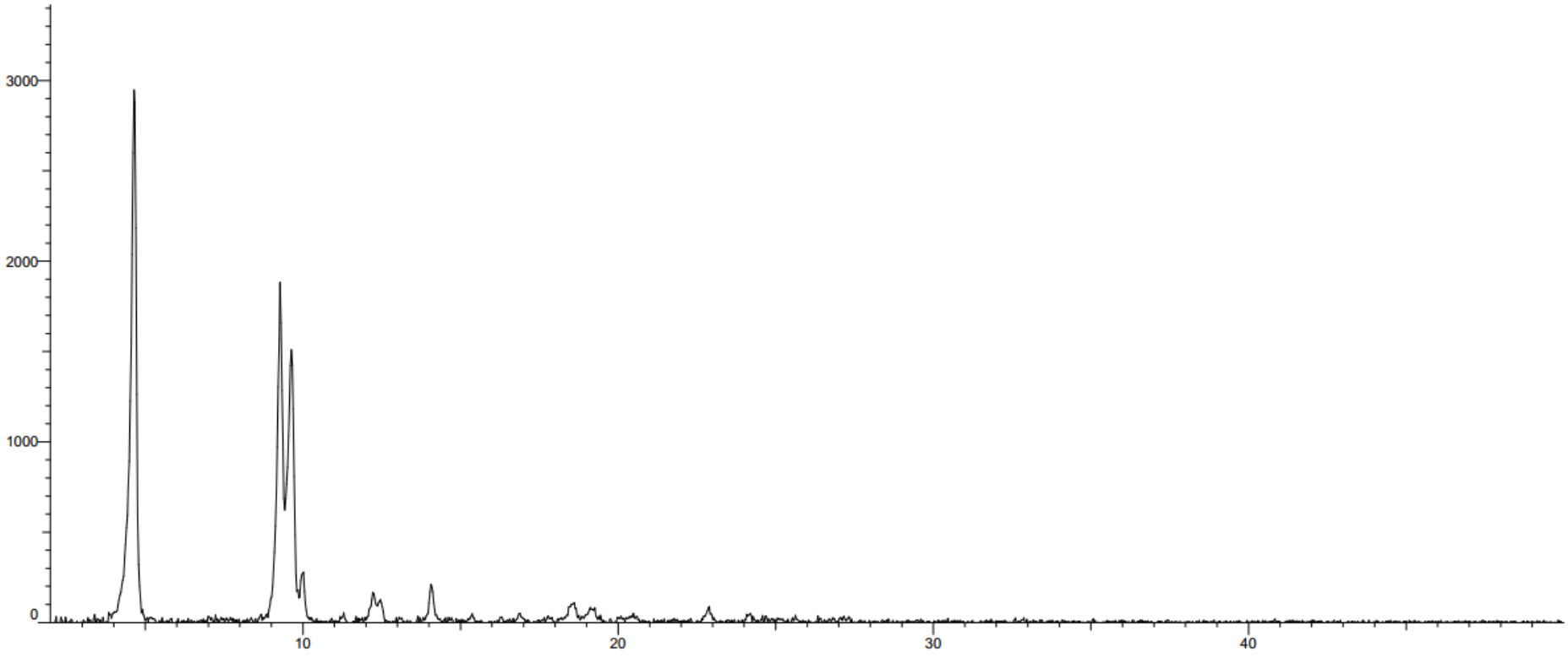
Sheet No: 1



2-Theta-Scale

Figure-1

Signature & Date



2-Theta-Scale

Figure-2

Signature & Date

FORM-2

THE PATENT ACT 1970

(39 of 1970)

&

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

1. **TITLE OF THE INVENTION**

Improved process for the preparation of Lurbinectedin

2. **APPLICANT (S)**

a) NAME: **MSN LABORATORIES PRIVATE LIMITED, R&D CENTER**

b) NATIONALITY: Indian

c) ADDRESS:

Plot No. 12, Phase-IV,
Sy No. 119 to 140, 258, 275 to 280, IDA,
Pashamylaram (Vill),
Patancheru (Mdl),
Sangareddy (Dist),
Telangana State.
India -502 307

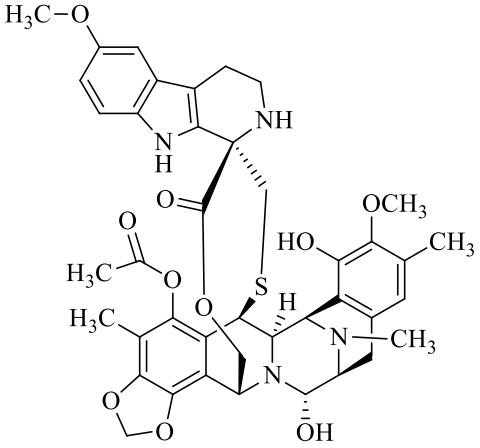
3. **PREAMBLE TO THE DESCRIPTION**

COMPLETE

The following specification particularly describes the invention and the manner in which it is to be performed.

Field of the invention:

The present invention relates to an improved process for the preparation of Lurbinectedin which 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 represented as formula-1.

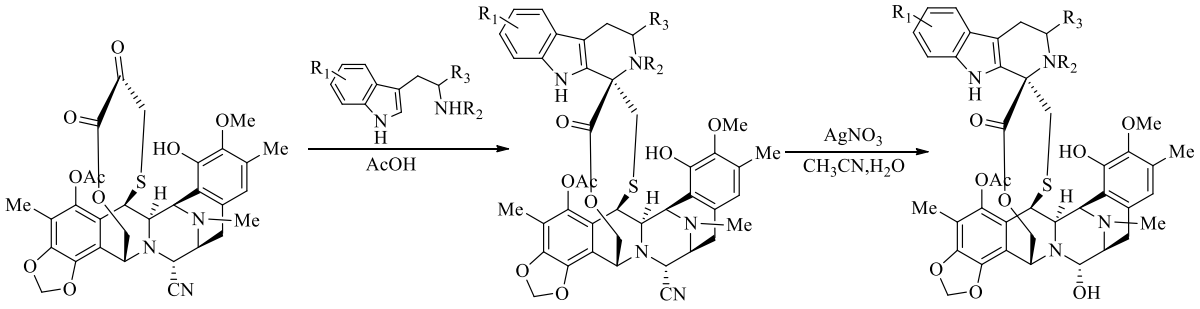


Formula-1

Background of the invention

Lurbinectedin is a synthetic tetrahydropyrrolo[4,3,2-de]quinolin-8(1H)-one alkaloid analogue with potential antineoplastic activity. It is indicated for the treatment of adults with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. It is approved by USFDA under brand name of Zepzelca.

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.

Brief description of the Drawings:

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.

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.

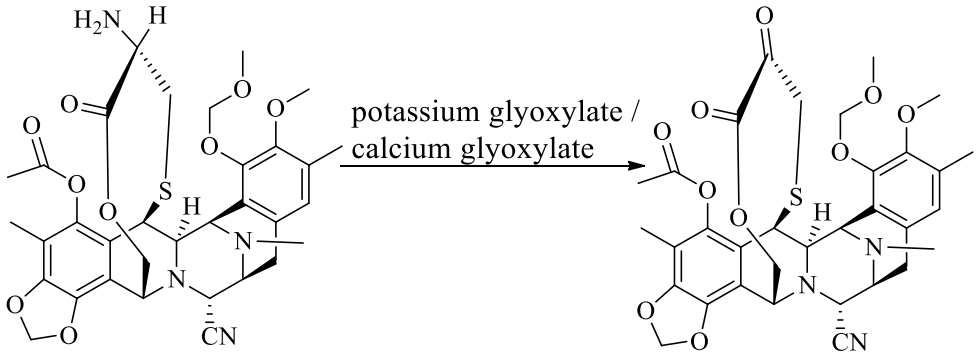
As used herein the present invention, the term “base” is selected from inorganic bases like “alkali metal hydroxides” such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate and the like;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

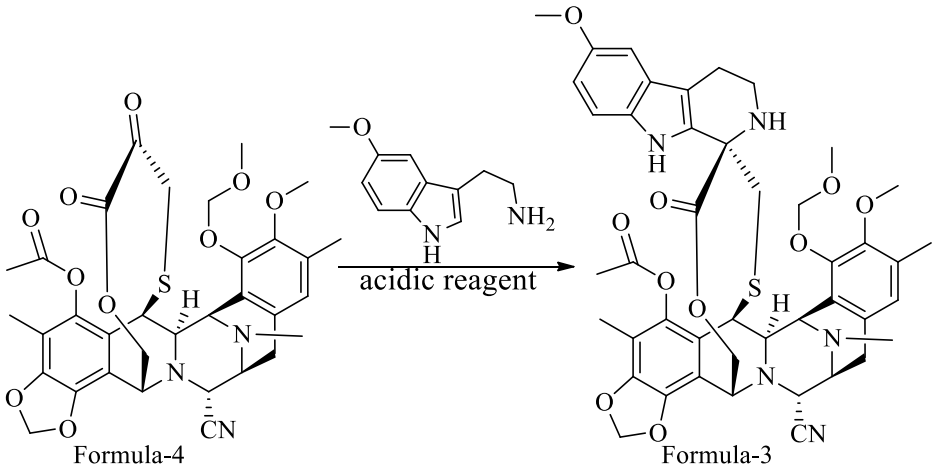
In the first embodiment, the present invention provides a process for the preparation of Lurbinectedin, which comprises:

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

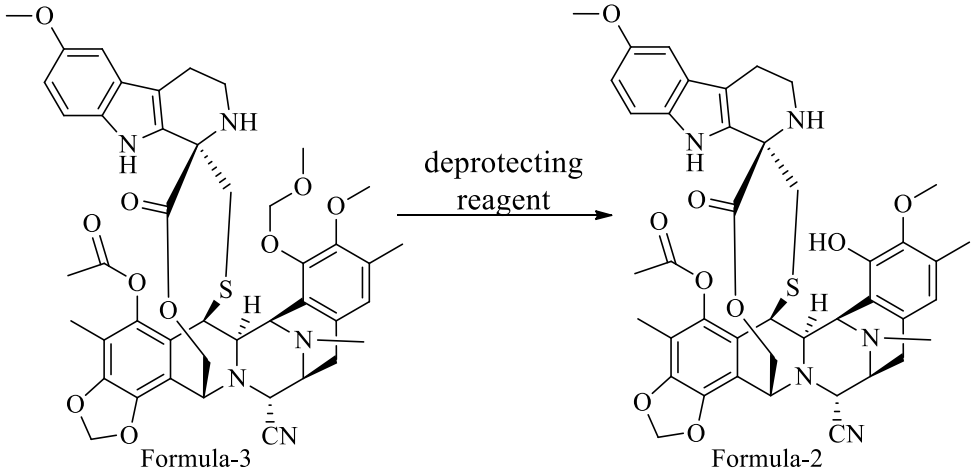


Formula-5 Formula-4

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,



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

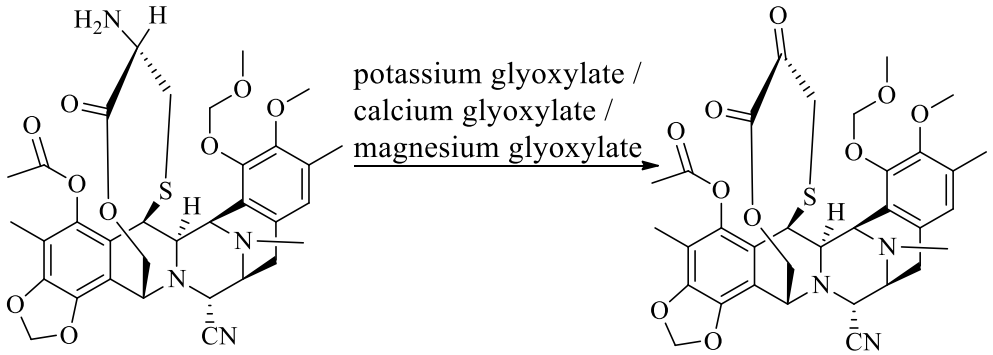
The “solvent” used in step a) to step c) are selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof.

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

The “temperature” is used in step c) is selected from temperature of -25°C to -40°C.

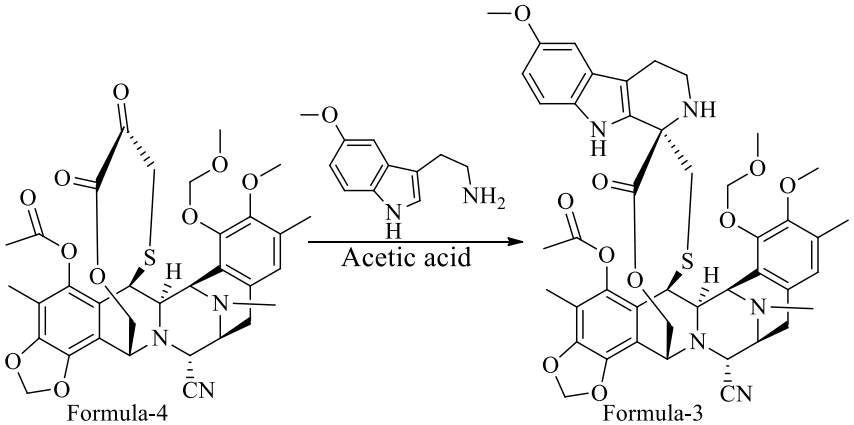
In first aspect of the first embodiment, the present invention provides a process for the preparation of Lurbinectedin, which comprises:

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



Formula-5 Formula-4

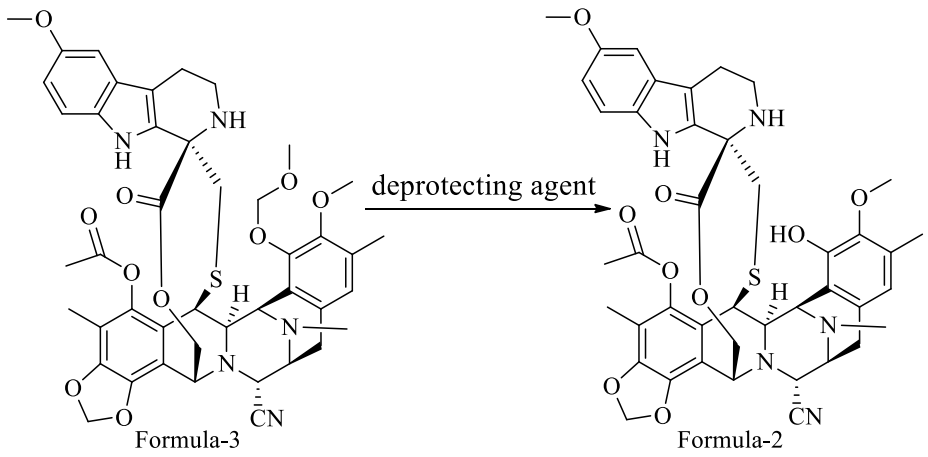
b) treating compound of formula-4 with 2-(5-methoxy-1H-indol-3-yl)ethanamine in presence of acidic reagent to get compound formula-3,



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,

e) optionally purified to get pure Lurbinectedin of formula-1.

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

According to first aspect of the first embodiment of the invention, the "deprotecting reagent" is selected from trimethylsilyl bromide.

According to first aspect of the first embodiment the deprotecting carried out at a temperature 0 to -50°C, preferably -25°C to -40°C.

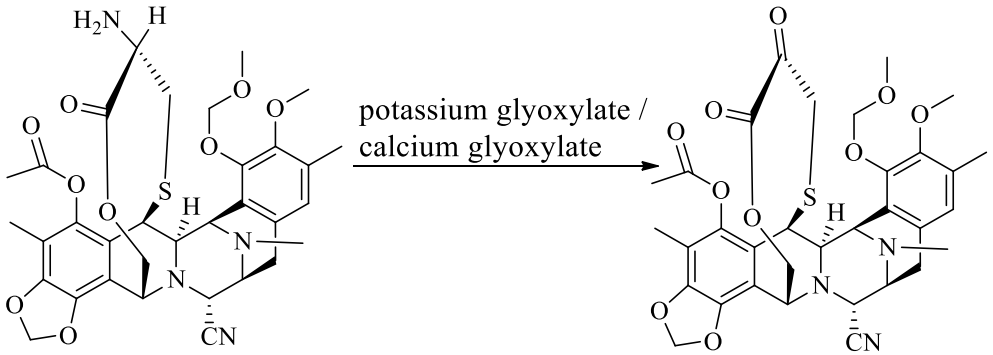
In second aspect of the first embodiment, pure Lurbinectedin is having purity greater than 99.5%, preferably greater than 99.8%.

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.

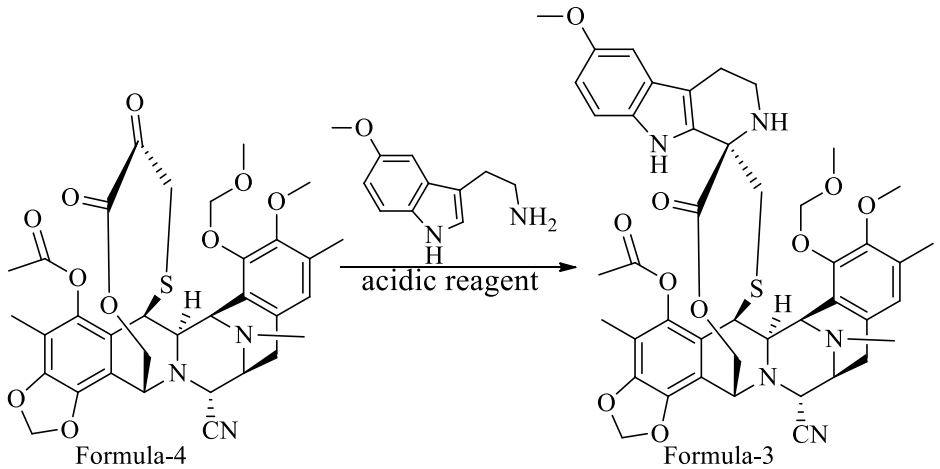
In the second embodiment, the present invention provides a process for the preparation of formula-4, which comprises reacting compound of formula-5 with potassium glyoxylate / calcium glyoxylate to get compound of formula-4.



Formula-5 Formula-4

The "solvent" used in second 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.

In the third embodiment, the present invention provides a process for the preparation of formula-3, which comprises treating compound of formula-4 with 2-(5-methoxy-1H-indol-3-yl)ethanamine in presence of acidic reagent to get compound formula-3;

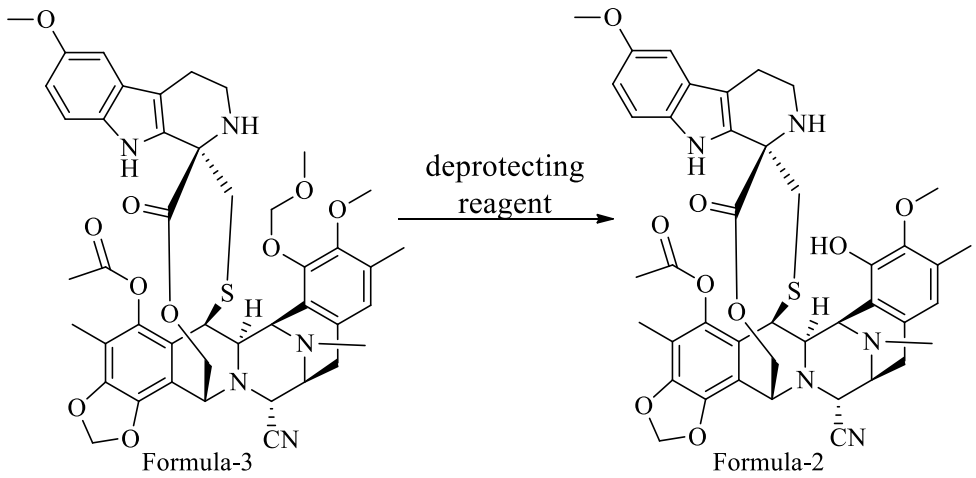


Formula-4 Formula-3

The “solvent” used in third 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.

The acidic reagent is used in third embodiment 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 include trifluoroacetic anhydride, pentafluoropropionic anhydride, heptafluorobutyric anhydride, and combinations thereof

In the fourth embodiment, the present invention provides a process for the preparation of formula-2, which comprises deprotecting compound of formula-3 with deprotecting reagent to get compound of formula-2.

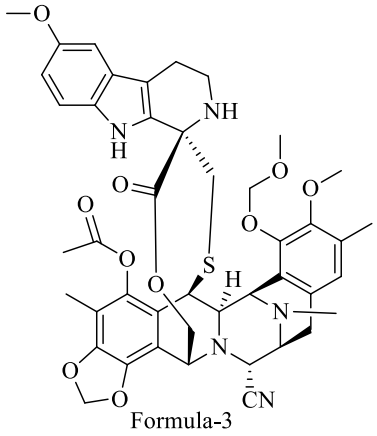


The “solvent” used in fourth embodiment is selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof.

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

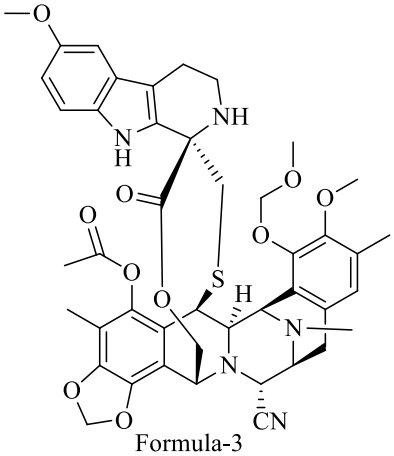
The “temperature” is used in fifth embodiment is selected from temperature of -25°C to -40°C.

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



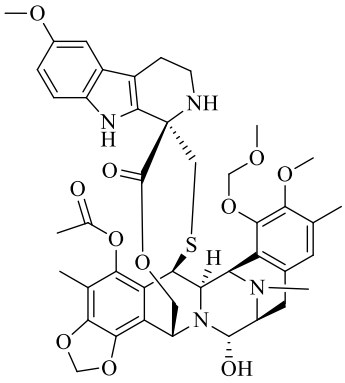
Formula-3

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



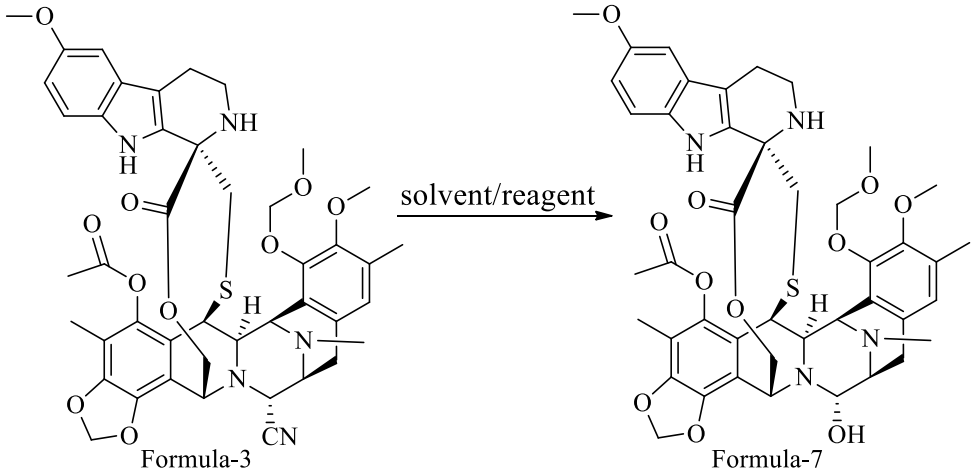
Formula-3

In seventh embodiment, the present invention provides compound of formula-7



Formula-7

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



Formula-3 Formula-7

The "solvent" used in eighth 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 is used in eighth embodiment is selected from silver nitrite.

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

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

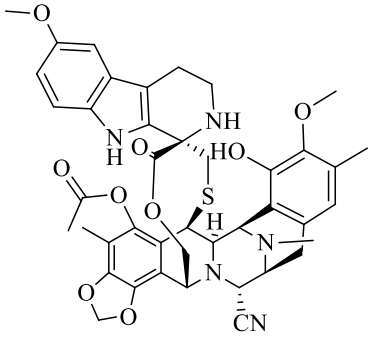
In second aspect of the ninth embodiment, the present invention provides crystalline form-M of Lurbinectedin of formula-1, which is characterized by its powder X-Ray diffractogram as illustrated in Figure-1.

In third aspect of the ninth 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.

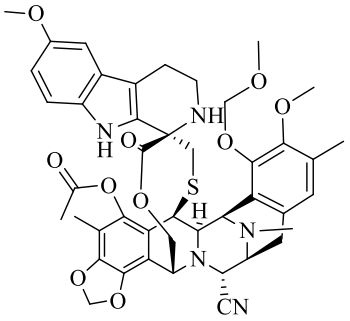
Conversion of compound formula-2 to Lurbinectedin can be carried out by the methods known in the art.

The starting material compound of formula-5 used in the present invention is carried out by the methods known in the art.

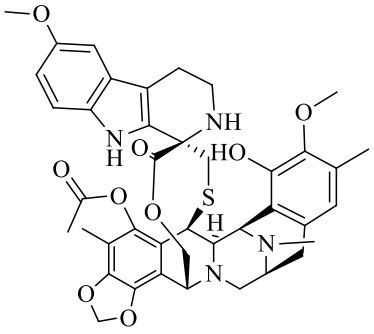
Lurbinectedin obtained according to the present invention is having Cyano des mom impurity, Des hydroxy impurity, MOM impurity, Des acetyl impurity, Cyano mom impurity less than about 0.05% as measured by HPLC.



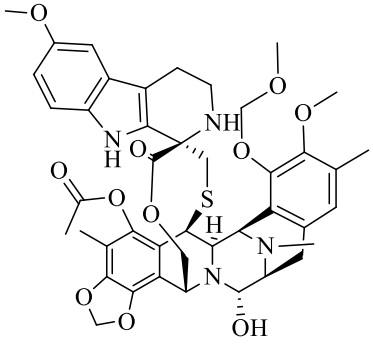
Cyano des mom impurity



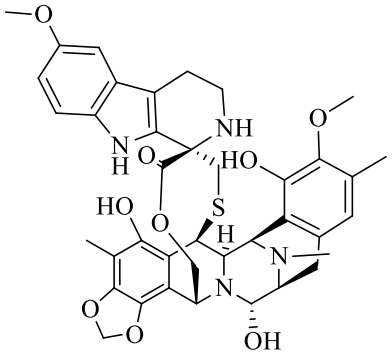
Cyano mom impurity



Des hydroxyl impurity



MOM impurity



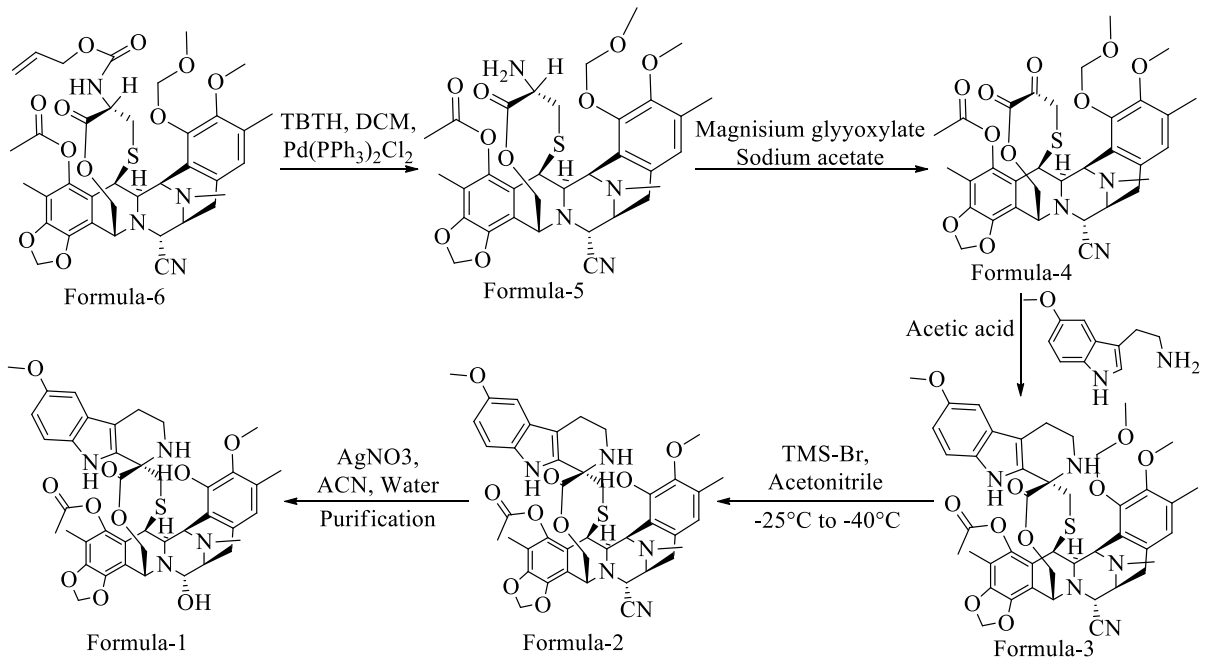
Des acetyl impurity

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.

Dichloromethane (400 ml) was added to compound of formula-6 (2.0 gms) at 25-30°C and stirred for 45 minutes. Bistriphenylphosphine palladium (II) chloride (0.075 gms) and acetic acid (1.5 ml) were added to the mixture at 25-30°C and stirred for 10 minutes. 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. Filter the mixture through hyflow bed and washed the bed with dichloromethane. The obtained filtrated was washed with aqueous potassium fluoride. Layers were separated and organic layer washed with

water. Combined the total organic layers and washed with sodium sulfate solution. Distilled off the solvent completely under reduced pressure. Ethyl acetate (200 ml) was added to the obtained compound at 25-30°C and stirred for 15 minutes. Distilled off the solvent completely from the filtrate under reduced pressure. Methanol (300 ml) was added to obtained compound at 25-30°C and stirred for 15 minutes. Layers were separated. Methanol (100 ml) was added to mixture at 25-30°C and stirred for 20 minutes. Layers were separated and combined total the organic layers. Distilled off the solvent completely under reduced pressure and co-distilled with isopropanol. To the obtained compound, isopropanol (4.0 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Cooled the mixture to 0-5°C and stirred for 30 minutes. Filtered the precipitated solid, washed with isopropanol and dried get title compound. Yield: 1.5 gms.

Example-10: Preparation of compound of formula-4

Acetonitrile (24.9 ml) and molecular sieves (0.3 gms) were added to compound formula-5 (1.5 gms) at 25-30°C and stirred for 10 minutes. Cooled the temperature of the mixture to 0-5°C and stirred for 10 minutes. A mixture of sodium acetate (0.15 gms) and acetic acid (24.9 ml) was slowly added to the mixture at 25-30°C and stirred for 10 minutes. Zinc sulfate (0.19 gms) and magnesium glyoxylate (0.76 gms) were added to the mixture at 25-30°C and stirred for 1 hours. Water, methanol and dichloromethane were added to the mixture at 25-30°C and stirred for 20 minutes. 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. Layers were separated. Combined the total organic layers and washed with water. Organic layer washed with aqueous sodium bicarbonate solution. Layers were separated and organic layer and washed with water. Layers were separated. 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 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. Slowly the mixture was added to the pre-cooled water at 0-5°C and stirred for 10 minutes. Adjust the pH of the mixture to 2.3 using aqueous dipotassium hydrogen phosphate solution at 0-5°C and stirred for 15 minutes. Filtered the mixture, washed with water. Acetone (1.8 ml) was added to the mixture at 25-30°C and stirred for 10 minutes. Distilled off the mixture under reduced pressure. 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 reaction mixture to 0-5°C and stirred for 3 hours. Filtered the precipitated 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.

Acetonitrile (450 ml) was added to compound of formula-3 (15.0 gms) 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 mixture at -35 to -40°C and stirred for 15 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 temperature of 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.

Acetonitrile (252 ml) was added to the water (168 ml) at 25-30°C and stirred for 5 minutes. Compound of formula-2 (3.0 gms) was added to the mixture under argon 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 was 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 and aqueous layer was extracted with a mixture of methanol and methyl tert-butyl ether. Combined the organic layer and added a pre-cooled mixture of aqueous sodium bicarbonate solution and aqueous sodium chloride solution. Layers were separated. Aqueous sodium chloride solution was added to the organic layer. Layers were separated. Water was added to the organic layer. Layers were separated. A mixture of methanol and methyl tert-butyl ether was added to the organic layer. Layers were separated. Carbon was added to the organic layer. Filter the mixture through hyflow bed and washed the bed with a mixture of methanol and methyl tert-butyl ether. Combine the filtrates. Distilled off the solvent from the filtrates under reduced pressure and then co-distilled with acetonitrile. The obtained compound was added to pre-cooled acetonitrile at 0-5°C and stirred for 2 hours. Filtered the precipitated solid, washed with pre-cooled acetonitrile. Ethyl acetate was added to the obtained compound at 25-30°Cand stirred for 30 minutes. Cooled the mixture to 0-5°C and stirred for 2 hours. Filtered the precipitated 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.

Crude Lurbinectedin (2.0 gms) obtained in Example-13 was purified by flash column chromatography. The obtained fractions (3500 ml) were cooled to 0-5°C and stirred for 25 minutes. Adjusted the pH of the mixture using buffer solution (ammonia and ammonium chloride solution) (64 ml) at 0-5°C and stirred for 10 minutes. Dichloromethane (1000 ml) was added to the mixture at 0-5°C and stirred for 5 minutes. Layers were separated and aqueous layer was extracted with dichloromethane. Layers were separated. Combined the total organic layers and washed with water. Layers were separated. Organic layer dried with sodium sulfate. Filtered the mixture through hyflow bed 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 precipitated 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.

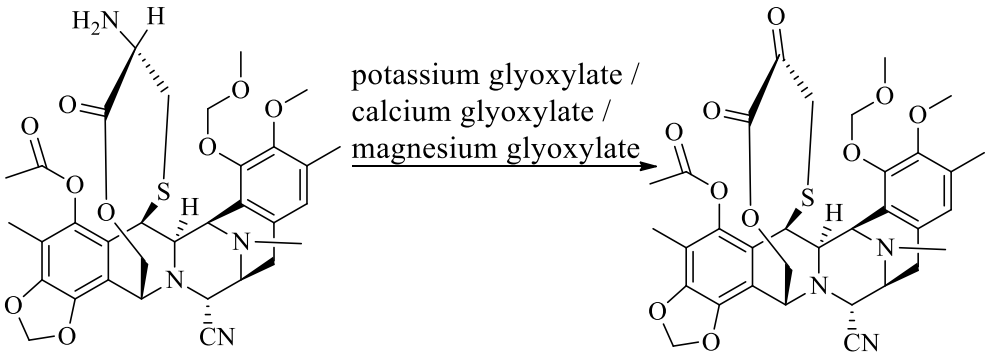
Example-15: Preparation of MOM impurity of formula-7.

Acetonitrile (42 ml) and water (28 ml) were added at 25-30°C and stirred for 10 minutes. Compound of Formula-3 (0.5 gms) was added to the mixture at 25-30°C and stirred for 15 minutes. Silver nitrate (3.04 gms) was added to the mixture at 25-30°C and stirred for 15 minutes. Cooled the temperature of 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. Layers were separated. Combined the organic layers and washed with a mixture of pre-cooled aqueous sodium bicarbonate and aqueous sodium chloride solution. Layers were separated. Organic layer is washed with aqueous sodium chloride solution. Layers were separated. Organic layer was washed with pre-cooled water. Layers were separated. 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.

We Claim:

1. A process for the preparation of pure Lurbinectedin having purity greater than 99.8%, wherein mom impurity having less than 0.05%, wherein the process comprises:

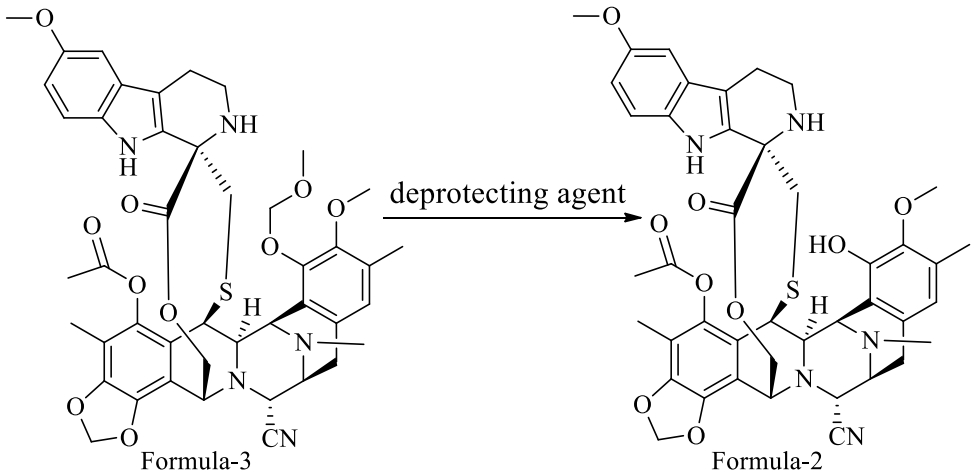
   a) reacting compound of formula-5 with potassium glyoxylate / calcium glyoxylate/ magnesium glyoxylate to get compound of formula-4,



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,

   c) treating the 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,

   e) optionally purifying to provide pure Lurbinectedin of formula-1.

2. The process as claimed in claim 1, wherein step b), the reaction is carried out in

presence absence of solvent.

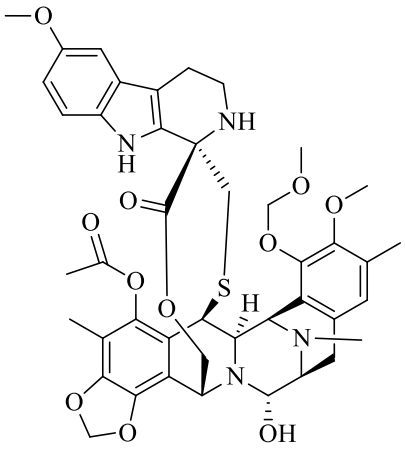
3. The process as claimed in claim 1, wherein solvent used in step a) to step c) is selected from ketone solvents, nitrile solvents, alcohol solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar aprotic solvents, ether solvents and polar solvents like water or mixture thereof.

4. The process as claimed in claim 1, wherein the deprotecting agent is TMS-Br.

5. The process as claimed in claim 1, wherein the deprotecting carried out at a temperature 0 to -50°C, preferably -25°C to -40°C.

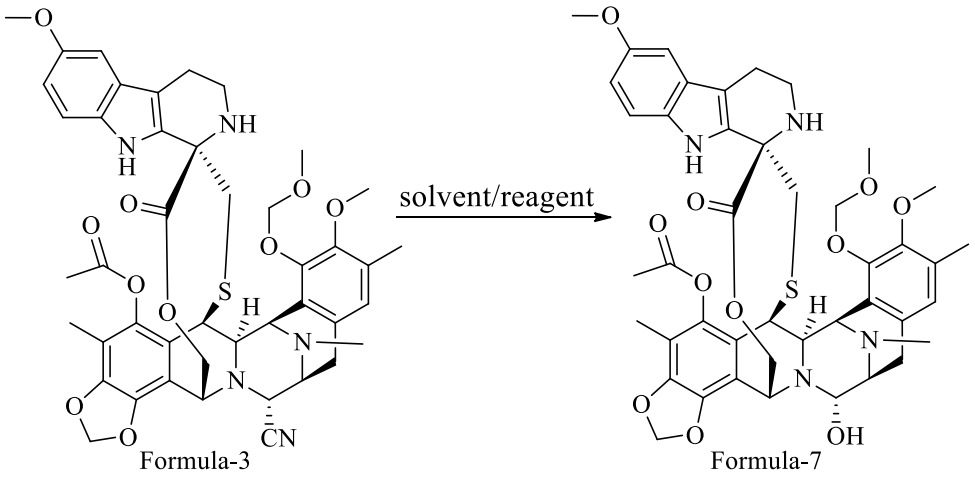
6. The process according to claim 1, the Lurbinectedin obtained in step d) is characterized in figure-1.

7. A compound of formula-7



Formula-7

8. A process for the preparation of formula-7, which comprises treating compound of formula-3 with a reagent in a solvent to get compound of formula-7.



Formula-3 Formula-7

9. The process as claimed in claim 8, wherein solvent 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.

10. The process as claimed in claim 8, wherein reagent is selected from silver nitrite.

Dated this 16th day of September 2023

Authorized Signatory

(Srinivasan Thirumalai Rajan)

Head- IPM & Technical

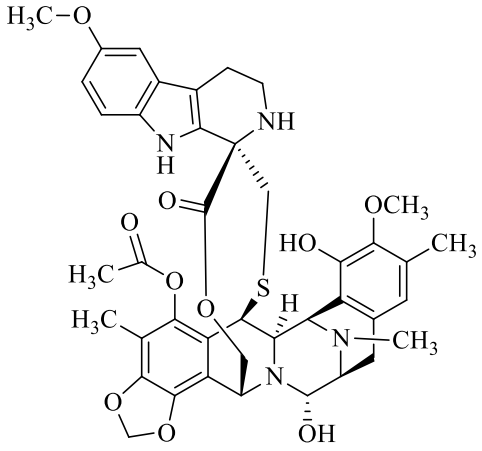
MSN Laboratories Private Limited, R & D Center

****

ABSTRACT

Title of the Invention: Improved process for the preparation of Lurbinectedin

The present invention relates to an improved process for the preparation of Lurbinectedin. Which 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 represented as formula-1.



Formula-1