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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF (2R,3S)-2-(2,4- DIFLUQROPHENYL)-3-(5-FLUOROPYRIMIDIN-4-YL)-1-(1H-1,2,4-TRIAZOL-1-YL) BUTAN-2-OL

(57) Abstract: The present invention is directed to an improved industrially viable, cost effective process to manufacture substantially pure form of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (Voriconazole) with a chiral purity level of greater than 99.9% and impurity level of less than 0.1%.

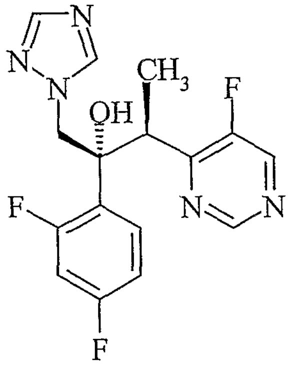
IMPROVED PROCESS FOR THE PREPARATION OF (2R,3S)-2-(2,4-DIFLUOROPHENYL)-3-(5-FLUOROPYRIMIDIN-4-YL)-1-(1H-1,2,4-TRIAZOL-1-YL)BUTAN-2-OL

TECHNICAL FIELD OF THE INVENTION

The present invention is directed to an improved industrially viable, cost effective process to manufacture substantially pure form of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (Voricaonazole) with a chiral purity level of greater than 99.9% and impurity level of less than 0.1%.

BACKGROUND OF THE INVENTION

2R,3S-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol commomly known as Voriconazole of Formula-I,



Formula-I

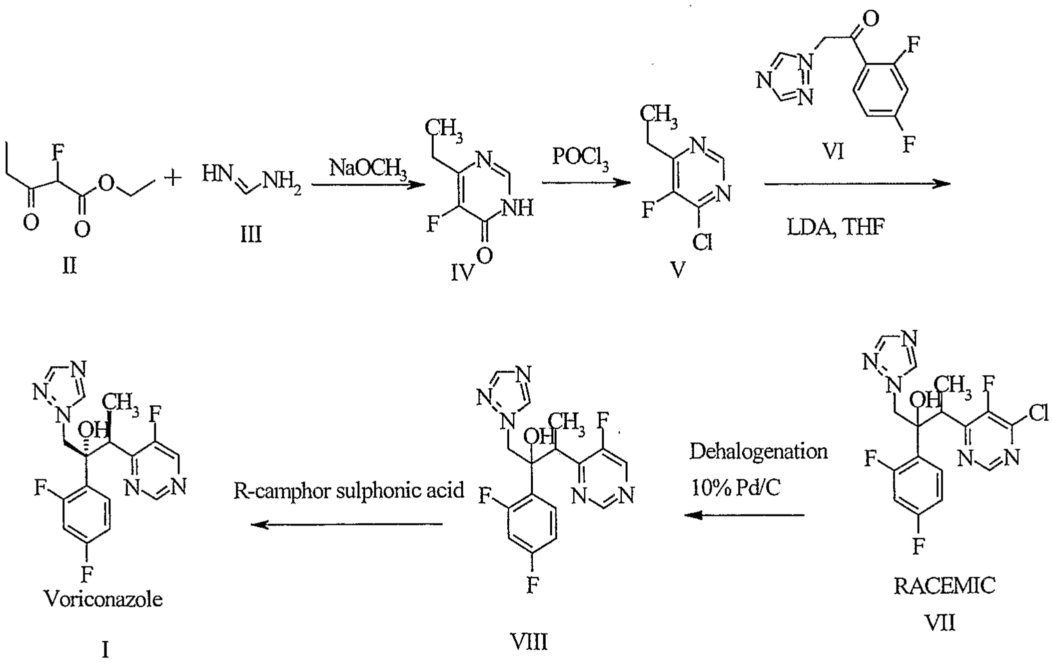
is a triazole antifungal medication used to treat various fungal infections. These include invasive candidiasis, invasive aspergillosis, and emerging fungal infections.

Voriconazole is commercially available as VFEND® in the form of lyophilized powder for solution in intravenous injection, film-coated tablets for oral administration, and as a powder for oral suspension.

US 5,567,817 and US 5,278,175 discloses a process for the preparation of voriconazole comprising reacting 4-chloro-6-ethyl-5-fluoropyrimidine of Formula IV with 1-

(2,4-difluoorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone of Formula VI in the presence of lithium diisopropylamine to yield 2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl) butan-2-ol which is further purified by column chromatography to give (2R,3S/2S,3R) enantiomeric pair of 2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoropyrimidin-6-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol of Formula VII which was dehalogenated with a 10% Pd/C in the presence of sodium acetate, followed by purification using flash chromatography to yield (2R,3S/2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol of Formula VIII and then resolved with R-(-)-10-camphor sulfonic acid in the presence of methanol and subsequent hydrolysis of the camphor sulfonate salt to free base with alkaline medium to yield Voriconazole of Formula I. The process can be represented as in scheme-I given below,

Scheme I

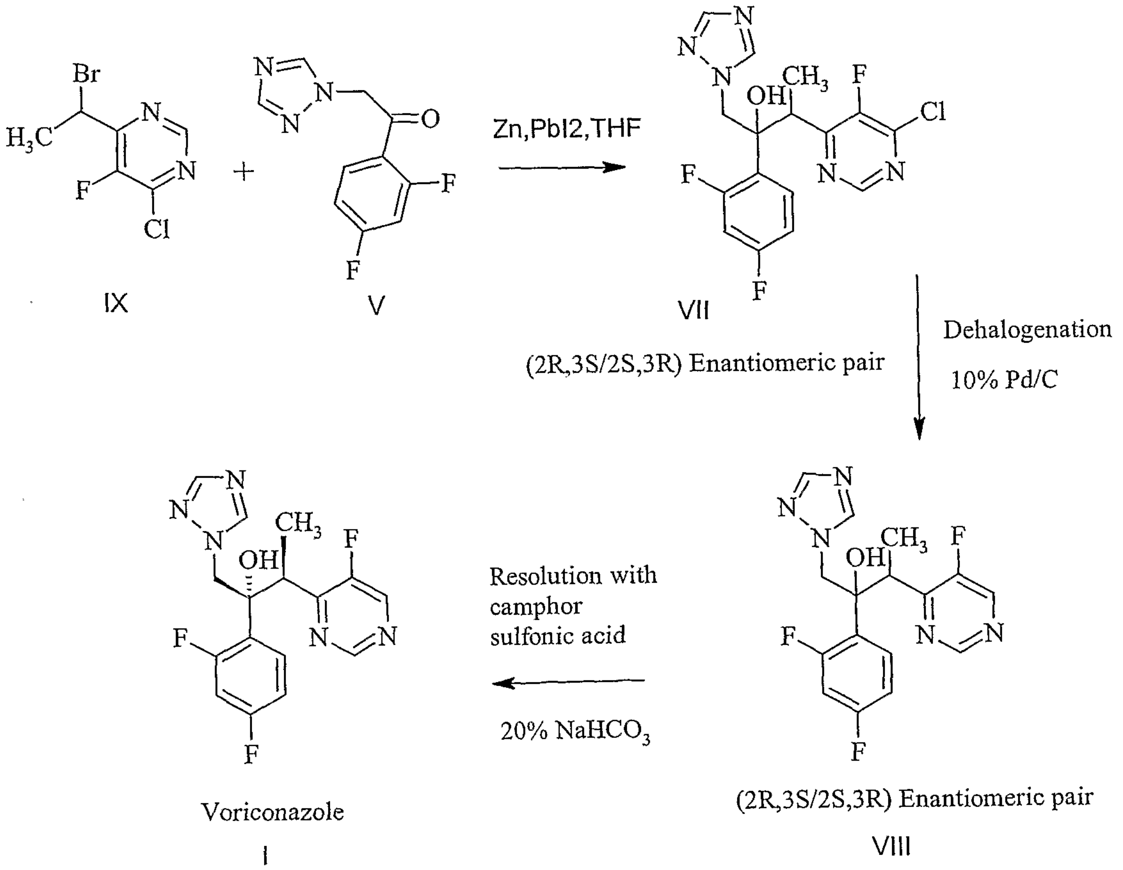


The drawbacks of this process are use of hazardous reagents as lithium diisopropylamine for the condensation, the reaction condition are very low temperature of -78°C which is difficult to maintain all the time at manufacturing scale production. The process describes chromatographic separation of the enantiomeric pair which is not advisable at plant scale production and use of palladium carbon for dehalogenation under pressure which is associated with safety problems at plant scale. Moreover the yields are very low.

US 6,586,594 and *Organic Process Research & Development (2001), 5(1), 28-36,* discloses a process for the preparation of voriconazole comprising reacting 6-(1-bromoethyl)-

2,4-dichloro-5-fluoropyrimidine of Formula IX with 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone of Formula V in the presence of Zinc, lead, iodine and tetrahydrofuran to yield the compound of Formula VII. It also has been disclosed that the compound after the condensation yields two different diastereomeric pairs such as (2R, 3S: 2S, 3R and 2S, 3S; 2R,3R). The desired pair is separated by forming hydrochloride salt. This hydrochloride salt is further dehalogenated with 10%Pd/C to yield compound of Formula VIII, which on resolution with R-(-)-camphor-10-sulphonic acid and further basification to give Voriconazole of Formula I. The process is represented in scheme-II given below

Scheme II

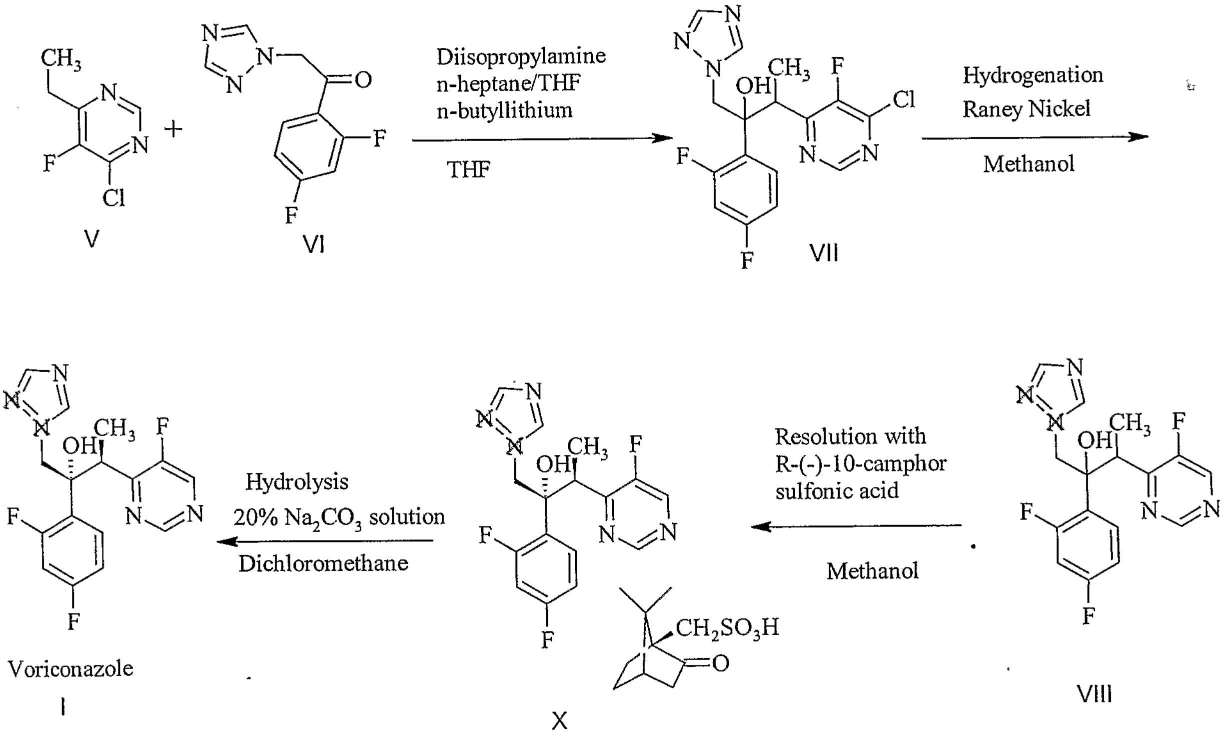


The drawbacks of this process are: the formation of HCl salt which requires further basification and thus increases the number of steps and makes the reaction as time consuming process. Moreover use of palladium carbon for dehalogination is not advisable because of the safety problem.

WO2006065726 discloses a process for the preparation of voriconazole comprising reacting 4-chloro-6-ethyl-5-fluoropyrimidine of Formula V with 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone of Formula VI in the presence of diisopropylamine, n-heptane/THF, n-butyl lithium to yield (2R,3S/2S,3R) 2-(2,4-difluorophenyl)-3-(4-chloro-5-

fluoropyrimidin-6-yl)-1-(1H-1,2,4-triazole-1-yl) butan-2-ol of Formula VII which is further reduced with Raney Nickel in the presence of sodium acetate to yield (2R,3S/ 2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol of Formula VIII and then resolution with R-(-)-10-camphor sulphonic acid in the presence of methanol to yield camphor sulfonate salt of Formula X followed by hydrolysis of the camphor sulfonate salt to free base with 20% sodium bicarbonate solution in the presence of dichloromethane to give Voriconazole of Formula I. The process is represented in scheme-III given below,

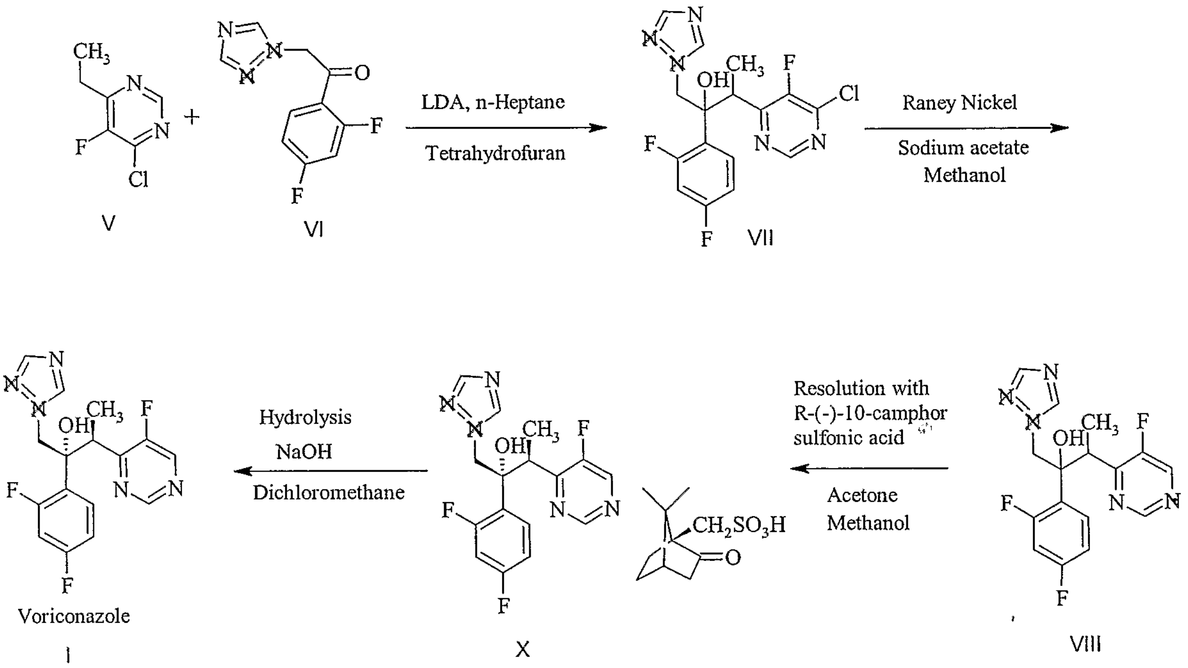
Scheme III



The drawbacks of this process are: use of hazardous reagents as lithium diisopropylamine for the condensation is not advisable, the reaction condition require low temperature maintainenance i.e. -78°C which is difficult to maintain all the time at manufacturing scale, the reaction requires chromatographic separation of the enantiomeric pair which is not advisable at plant scale production, use of Raney nickel for dehalogination under pressure is not advisable because of the safety problem. Moreover the yields are also very low.

WO2007013096 discloses the process for the preparation of voriconazole comprising reacting 4-chloro-6-ethyl-5-fluoropyrimidine of Formula V with 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone of Formula VI in the presence of lithium diisopropylamine, n-heptane, tetrahydrofuran to yield (2R,3S/2S,3R) 2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoropyrimidin-6-yl)-1-(1H-1,2,4-triazole-1-yl) butan-2-ol of Formula VII which is further reduced with Raney Nickel in the presence of sodium acetate to yield (2R,3S/2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol of Formula VIII (racemic Voriconazole) and then resolution with R-(-)-10-camphor sulphonic acid in the presence of methanol to yield camphor sulfonate salt of Formula X followed by hydrolysis of the camphor sulfonate salt to free base with sodium hydroxide solution in the presence of dichloromethane and 2-propanol gives voriconazole of Formula I. The process is represented in scheme-IV given below,

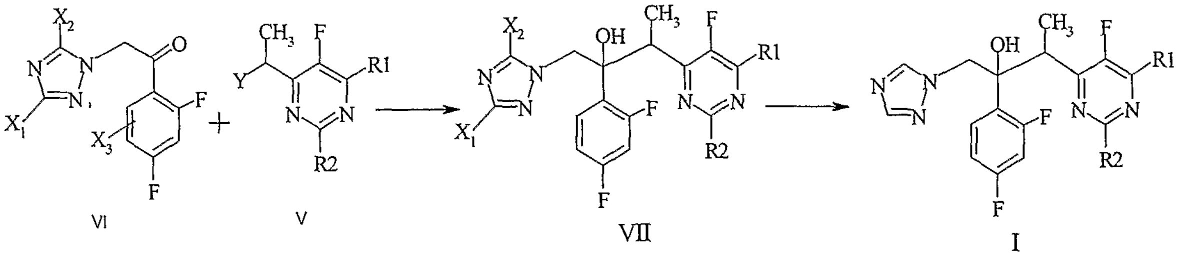
Scheme IV



The drawbacks of this process are use of hazardous reagents as lithium diisopropylamine for the condensation, the reaction has to be maintain at very low temperature of -78°C which is difficult to maintain all the time at manufacturing scale, the reaction requires chromatographic separation of the enantiomeric pair which cannot be done at plant scale, use of Raney nickel for dehalogination under pressure is not advisable because of the safety problem. Moreover the yields are very low.

CN1814597, CN1488629 and CN1488630 discloses the process for the preparation of voriconazole which is as follows:

Scheme V

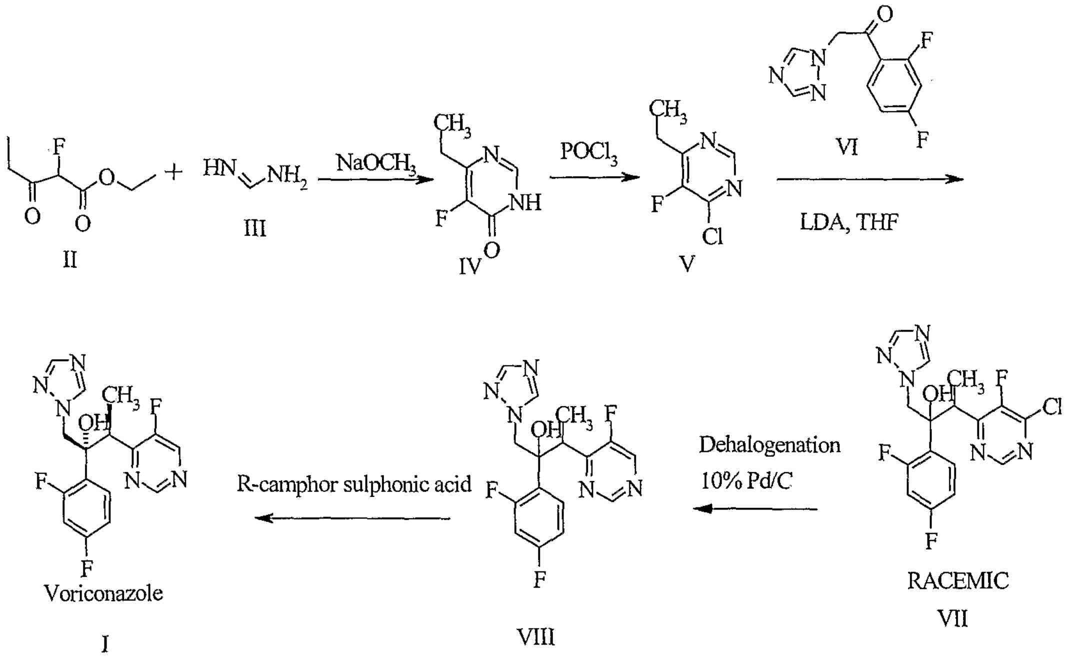


reacting the compound formula II with compound of formula III in an inert organic solvent in the presence of Zn, I_2 and a lewis acid, reducing the coupled compounds into I followed by basifying with suitable base to give compound of Formula I.

The drawbacks of this process are use of palladium carbon or Raney nickel for dehalogination is not advisable because of the safety problem. Moreover the yields are very low.

Voriconazole Antifungal. UK-109496.Drugs of the Future (1996), 21(3), 266-271 describes a process a given in scheme below :

Scheme VI



The drawbacks of this process are use of hazardous reagents as lithium diisopropylamine for the condensation, the reaction condition requires low temperature of -78°C which is difficult to maintain at all times at larger scale production and use of Raney nickel for dehalogination under pressure which is not viable at plant scale production, moreover the yields are very low.

It's apparent from most of the prior art that; the preparation of voriconazole has certain disadvantages such as

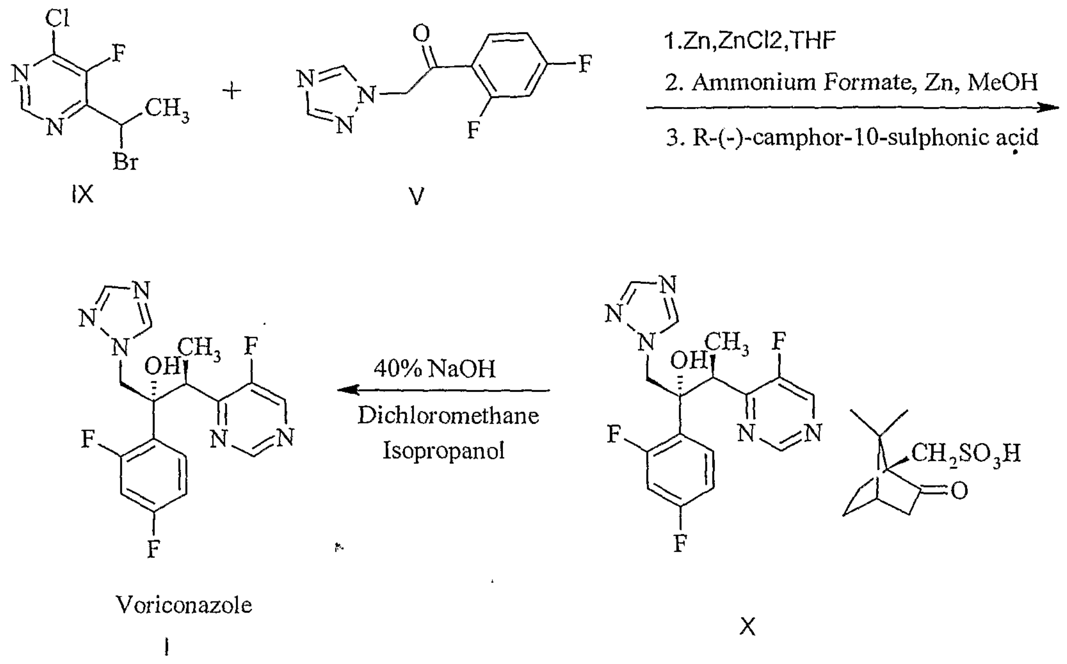
- The use of hazardous and costly raw materials like lithium diisopropyl amide, iodine, Pd/C, Raney Ni and n-butyl lithium
- Reaction requires to be maintained at lower temperature which is difficult to maintain all the time at commercial scale
- The processes involves chromatographic purification techniques which is not viable at commercial scale
- More reaction steps and lengthy work-up
- Overall higher cost of production
- Low yields and purity

Therefore, there is a continuing need for developing a new process for the manufacturing of voriconazole which is cost effective, industrially viable and eco-friendly.

SUMMARY OF THE INVENTION

The present invention describes an industrially viable and an improved process for the manufacturing of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (commonly known as Voriconazole). The process given in Scheme VII which comprises of :

Scheme VII



- reaction of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone in the presence of zinc powder, zinc chloride and THF, followed by dehalogenation in presence of zinc powder and ammonium formate, resolution with suitable resolving agent to give (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol salt all this in the one pot
- Formation of (2R, 3S)-2-(2, 4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol or Voriconazole by basification.

Another aspect of the present invention provides a process for preparation of racemic Voriconazole which process comprises condensation of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone in the presence of zinc powder, zinc chloride and THF followed by dehalogenation in suitable metal catalyst and base to give (2R,3S / 2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

Further aspect of the present invention provides a process for preparation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol salt which process comprises reacting racemic (2R,3S / 2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol with suitable resolving agent in suitable solvent .

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved process for the preparation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol compound of Formula I, which comprises of following steps:

a) activation of metal
b) condensation of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone
c) dehalogenation
d) resolution
e) formation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol by basification

Another embodiment of the present invention relates to the single pot synthesis of (2R, 3S)-2-(2, 4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol salt, which process comprises the following steps of

a) heating lewis acid and toluene solvent at reflux for 1-1.5 hrs, distilling off toluene, cooling to 60°C addition of the THF (co-solvent) followed by the metal, the mixture was again heated to reflux for 3 hrs to complete the activation of the metal, cooling the mixture to -5-0°C
b) addition of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone dissolved in a suitable solvent below 5°C to the activated metal mixture, maintaining the reaction temperature at 0-5°C for 30 minutes and distillation of excess solvent to get a thick slurry
c) dehalogenation of the compound obtained above by addition of suitable base salt and zinc metal and an organic solvent, stirring the reaction mixture at room temperature for 12-16 hrs, filtering the reacton mixture and quenching with a mixture of water and acetic acid
d) basification with saturated sodium carbonate solution followed by neutralization with conc. hydrochloride to form a slurry
e) filtration and extraction of the filtrate with ethyl acetate two to three times, combining the ethyl acetate layers, washing with 5% aq. EDTA disodium solution and water, drying over sodium sulphate and distilling off the ethyl acetate layer under reduced pressure at 43-45°C to obtain racemic 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
f) resolving the racemic mixture obtained with suitable resolving agent in presence of organic solvent to get the corresponding salt of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

Another embodiment provides a process for preparation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol salt which process comprises reacting racemic 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol with suitable resolving agent in suitable solvent .

Further embodiment of the present invention give a process for to manufacture (2R,3S/2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol by conversion of the salt to (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol using appropriate base.

The metal used in the step (a) can be selected form a group of organometals such as zinc, magnesium, manganese lead metal or mixture thereof

The lewis acid used in step (a) can be selected from zinc chloride or zinc iodide most preferably zinc chloride.

The solvent used for activation and condensation of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone is selected from a group of solvents consisting of toluene, tetrahydrofuran, diethylether, dimethylether diisopropyl ether, methyl tertiary-butyl ether or 1,4-dioxane; most preferably tetrahydrofuran.

The dehalogenation is carried out in the presence of suitable salt and in presence of suitable metal like zinc or magnesium most preferably zinc and suitable base such as ammonium formate, sodium formate, ammonium acetate or sodium acetate most preferably ammonium formate in presence of a suitable organic solvent such as methanol, ethanol or isopropanol most preferably methanol.

The resolving agent used in the step (f) is selected form a group consisting of R-(-)-camphor sulphonic acid, L-(-)-mandelic acid or L-(-)-tartaric acid most preferably R-(-)-camphor sulphonic acid in a suitable solvents selected from a group consisting of ketonic solvents such as acetone, butanone, propanone, ethylmethylketone; alcoholic solvents such as methanol, ethanol, isopropanol or their mixtures and more preferably mixture of ketone: alcohol as acetone: methanol.

The salt is converted in a free base in the presence of suitable base selected from sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate or sodium bicarbonate most preferably sodium hydroxide in a suitable organic solvents selected from a group consisting dichloromethane, chloroform, ethylacetate and more preferably dichloromethane.

The other isomer (2S, 3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol can be isolated from the mother liquor by the known prior art method.

(2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol commonly known as Voriconazole formed by the process disclosed above is crystalline form B.

The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

ADVANTAGES OF THE PRESENT INVENTION

The advantages of the present invention over the existing processes for the preparation of Voriconazole at a manufacturing scale are :

- Single pot reaction to form desired enantiomer
- Activation of the metal by heating reduces the overall time for the completion of the reaction.
- Use of Zn and ammonium formate in methanol for dehalogenation is cost effective and not hazardous.
- No column purification, which reduces the cost at a manufacturing scale.
- Higher yield and greater chiral purity of the desired compound.

EXAMPLES

Example 1: Preparation of (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, R (-)-10-camphor sulphonate.

Toluene (175 ml) and zinc chloride (39.7 g) were taken together heated to reflux for 1 hr in a Dean-Stark apparatus. Toluene was distilled off completely at atmospheric pressure, mixture cooled to 60°c. Tetrahydrofuran (315 ml) was added to the mixture followed by zinc metal (35 g).The mixture was refluxed for 3 hours, and further cooled to -5°C to0°C. A solution of 6-(1-Bromoethyl)-4-chloro-5-fluoropyrimidine (35gm) and 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (26gm) in tetrahydrofuran (175ml) was added to this reaction mixture at -5 to 5°C and stirred for 60 minutes. The solvent was distilled off under reduced pressure to get thick slurry. Methanol (175ml), zinc metal (35gm) and ammonium formate (35gm) was added to slurry solution under stirring and maintained for 16 hrs at ambient temperature. The mixture was filtered and then washed with methanol followed by pouring into an aqueous solution of water and acetic acid (350ml:17ml). The pH was adjusted above 10 using a saturated solution of sodium carbonate solution (~350ml) and further to pH 7.5-8 with conc. hydrochloric acid (60ml).The mixture was then filtered and washed with ethyl acetate (175ml). The filtrate obtained was again extracted with ethyl acetate (2X175ml). The ethyl acetate layer was washed with water (350mL), 5% aq. EDTA disodium (525ml) and water (350mL) again, dried over sodium sulphate, filtered and distilled under reduced pressure at 40-45°C. The residue is dissolved in acetone (560ml) and to it was added 1-(R)-camphor-10-sulphonic acid (16.6gm) under stirring, the reaction mixture is heated to 50°C and refluxed for an hr., cooled to 25-30°C and stirred at the same temperature for 15 hours, the solid is filtered off washed with acetone and dried at 45-50°C to get the desired compound. *(Dry weight: 13 g).*

Example 2: Preparation of (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

To a solution of (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, R (-)-10-camphor sulphonate (10g) in dichloromethane(50ml) and water (50ml) was added 40% sodium hydroxide solution(10ml) under stirring. The layers were separated and the aqueous layer was washed with dichloromethane (50ml). The dichloromethane layers were combined, washed with water (2X50ml), dried over sodium sulphate(25gm) and filtered. The solvent was distilled off till one volume of the solvent remained and to it was added isopropyl alcohol(50mL). The distillation is continued under reduced pressure at 40-45°C till 3 volumes of isopropanol remained. At this temperature the compound starts isolating. The reaction mixture is cooled to 0°C, stirred for one hour, filtered, washed with cold isopropyl alcohol and dried at 45-50°C to get the desired compound.. *(Dry weight: 5g, Chiral purity: 99.9%, HPLC purity: 99.9 %)*

Example 3: Preparation of 2-(2, 4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1, 2, 4-triazol-1-yl)-butan-2-ol.

2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol hydrochloride (2g) *(compound obtained referring to the process as in US 6,586,594)* was taken in methanol (20ml) and to it was added ammonium formate (4gm) and stirred for 10 minutes followed by the addition of zinc metal (2gm) and the stirring was continued till reaction completion. The mixture is filtered, washed with methanol and added to an aqueous solution of water and acetic acid (20ml: 1mL). The pH is adjusted above 10 with saturated solution of sodium carbonate solution (~20ml) and further to pH about 8 with conc. hydrochloric acid. The mixture is filtered and washed with ethylacetate (5ml). The filtrate is extracted with ethylacetate (3X10ml). The ethyl acetate layer is washed with water (20mL), 5% aq. EDTA disodium (30ml) and water (20mL) again, dried over sodium sulphate, filtered and distilled under reduced pressure at 40-45°C, to the residue is added isopropanol (10mL) and the distillation is continued till the volume is approximately 6mL. The resultant mixture is cooled to 0°C, stirred fro 15-20minutes at 0°C, filtered, washed with chilled isopropanol and dried to get the desired compound (Dry Weight : 1.2g)

Example 4: Preparation of 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol hydrochloride (2g) *(compound obtained refering to the process as in US 6,586,594))* was taken in methano l(20ml) and to it was added ammonium formate (2gm) and stirred for 10 minutes followed by the addition of magnesium metal (2gm) and the stirring was continued till reaction completion. The mixture is filtered, washed with methanol and added to an aqueous solution of water and acetic acid (20ml: 1mL). The pH is adjusted above 10 with saturated solution of sodium carbonate solution (~20ml) and further to pH about 8 with conc. hydrochloric acid. The mixture is filtered and washed with ethylacetate (5ml). The filtrate is extracted with ethylacetate (3X10ml). The ethyl acetate layer is washed with water (20mL), 5% aq. EDTA disodium (20ml) and water (2mL) again, dried over sodium sulphate, filtered and distilled under reduced pressure at 40-45°C, to the residue is added isopropanol (10mL) and the distillation is continued till the volume is approximately 6mL. The resultant mixture is cooled to, stirred for 15-20 minutes at 0°C, filtered, washed with chilled isopropanol and dried to get the desired compound (Dry Weight : 1.2g)

WE CLAIM

1.An improved process for manufacturing (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol comprising:

- activation of metal
- condensation of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone
- dehalogenation
- resolution
- formation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol by basification

2.One pot synthesis of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, R (-)-10-camphor sulphonate, comprising:

a) heating lewis acid and toluene solvent at reflux for 1-1.5 hrs, distilling off toluene, cooling to 60°C addition of the THF (co-solvent) followed by the metal, the mixture was again heated to reflux for 3 hrs to complete the activation of the metal, cooling the mixture to -5-0°C

b) addition of 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone dissolved in a suitable solvent below 5°C to the activated metal mixture, maintaining the reaction temperature at 0-5°C for 30 minutes and distillation of excess solvent to get a thick slurry

c) dehalogenation of the compound obtained above by addition of suitable base salt and zinc metal and an organic solvent, stirring the reaction mixture at room temperature for 12-16 hrs, filtering the reacton mixture and quenching with a mixture of water and acetic acid

d) basification with saturated sodium carbonate solution followed by neutralization with conc. hydrochloride to form a slurry

e) filtration and extraction of the filtrate with ethyl acetate two to three times, combining the ethyl acetate layers, washing with 5% aq. EDTA disodium solution and water, drying over sodium sulphate and distilling off the ethyl acetate layer under reduced pressure at 43-45°C to obtain racemic 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

f) resolving the racemic mixture obtained with suitable resolving agent in presence of organic solvent to get the corresponding salt of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

3. One pot synthesis of racemic (2R,3S/2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, process which comprises activation of metal followed by condensation with 6-(1-Bromoethyl)-4-chloro-5-fluoro pyrimidine and 1-(2,4-diflouorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone and further dehalogenation to give racemic (2R,3S/2S,3R)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.
4. A process according to claim 1, 2 and 3 wherein the lewis acid is selected from a group like Zinc chloride and Zinc bromide most preferably Zinc chloride and metal catalyst is selected from a group comprising organometal such as zinc, magnesium or manganese most preferably zinc powder.
5. A process according to claim 1, 2 and 3 wherein the solvent used in the activation and condensation as claim 1 and 2 are selected from a group comprising of tetrahydrofuran, diethylether, dimethylether, diisopropyl ether, methyl tertiary-butyl ether and 1,4-dioxane more preferably tetrahydrofuran.
6. A process according to claim 1, 2 and 3 wherein the dehalogenation is carried out in the presence of metal like zinc or magnesium most preferably zinc and suitable base such as ammonium formate, sodium formate, ammonium acetate or sodium acetate most preferably ammonium formate in presence of a suitable organic solvent such as methanol, ethanol or isopropanol most preferably methanol.
7. A process for the preparation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol according to of claim 1 and 2, wherein resolution of the racemic mixture is carried out in the presence of suitable resolving agent selected from R-(-)-camphor sulphonic acid, L-(-)-mandelic acid or L-(-)-tartaric acid most preferably R-(-)-camphor sulphonic acid, in suitable solvents selected from a group comprising of ketonic solvents such as acetone, butanone, propanone, ethylmethylketone; alcoholic solvents such as methanol, ethanol, isopropanol or their mixtures and more preferably mixture of ketone: alcohol as acetone and methanol.
8. A process for the preparation of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol according to claim 1 and 2 wherein the salt is converted in a free base or (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-

(1H-1,2,4-triazol-1-yl)butan-2-ol in the presence of suitable organic solvents selected from a group consisting dichloromethane, chloroform, ethylacetate and more preferably dichloromethane.

9. An improved process for the preparation of substantially pure crystalline form of (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (commonly known as Voriconazole) by basification of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol salt
10. Substantially pure crystalline form of (2R, 3S)-2-(2, 4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1, 2, 4-triazol-1-yl)butan-2-ol with a chiral purity of greater than 99.9% and impurity level of less than 0.1%.