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(71) Applicant *(for all designated States except US)*: **ORCHID CHEMICALS AND PHARMACEUTICALS LIMITED** [IN/IN]; Orchid Towers, 313, Valluvar Kottam High Road, Nungambakkam, Chennai 600 034 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **UDAYAMPALAYAM PALANISAMY, Senthilkumar** [IN/IN]; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, R&D Centre, Old Mahaballipuram Road, Sholinganallur, Chennai 600 119 (IN). **GNANAPRAKASAM, Andrew** [IN/IN]; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, R&D Centre, Old Mahaballipuram Road, Sholinganallur, Chennai 600 119 (IN). **GANAPATHY, Veeramani** [IN/IN]; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, R&D Centre, Old Mahaballipuram Road, Sholinganallur, Chennai 600 119 (IN). **KANAGARAJ, Sureshkumar** [IN/IN]; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, R&D Centre, Old Mahaballipuram Road, Sholinganallur, Chennai 600 119 (IN). **SINGARAVEL, Mohan** [IN/IN]; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, R&D Centre, Old Mahaballipuram Road, Sholinganallur, Chennai 600 119 (IN).

(74) Agent: **UDAYAMPALAYAM PALANISAMY, Senthilkumar**; Orchid Chemicals and Pharmaceuticals Ltd, 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai 600 119 (IN).

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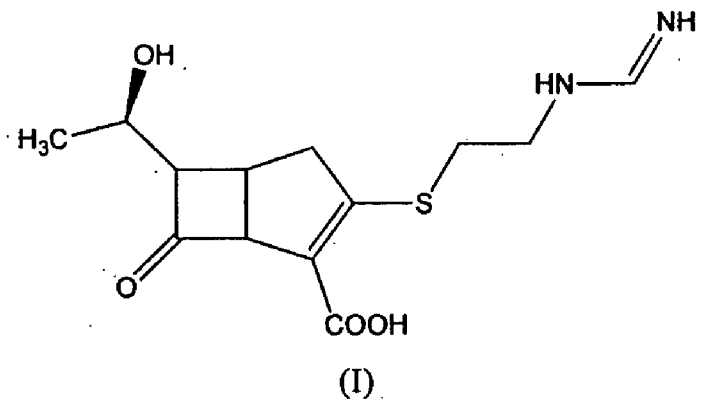
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— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF IMIPENAM



(I)

(57) Abstract: A process for the preparation of Imipenem (formula (I)) or its hydrates comprising (i) deprotection of a carboxylic ester via catalytic hydrogenation in the presence of a catalyst deactivating agent and/or (ii) rapid dissolution of Imipenem in water at high temperature, followed by rapid cooling and isolation of the Imipenem in order to improve yield and purity and facilitate preparation of sterile Imipenem.

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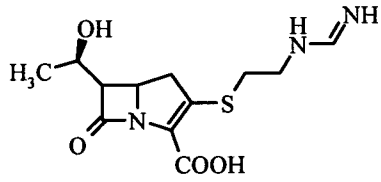
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AN IMPROVED PROCESS FOR THE PREPARATION OF IMIPENEM

Field of the Invention

The present invention provides an improved process for the preparation of the carbapenem antibiotic of formula (I) or its hydrates.

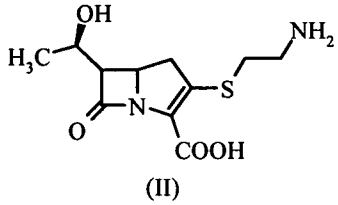


(I)

The compound of the formula (I) is known as Imipenem and exhibits broad-spectrum antibiotic activity. The chemical name of Imipenem is (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. Imipenem in combination with Cilastatin sodium and sodium bicarbonate is marketed in US as PRIMAXIN®.

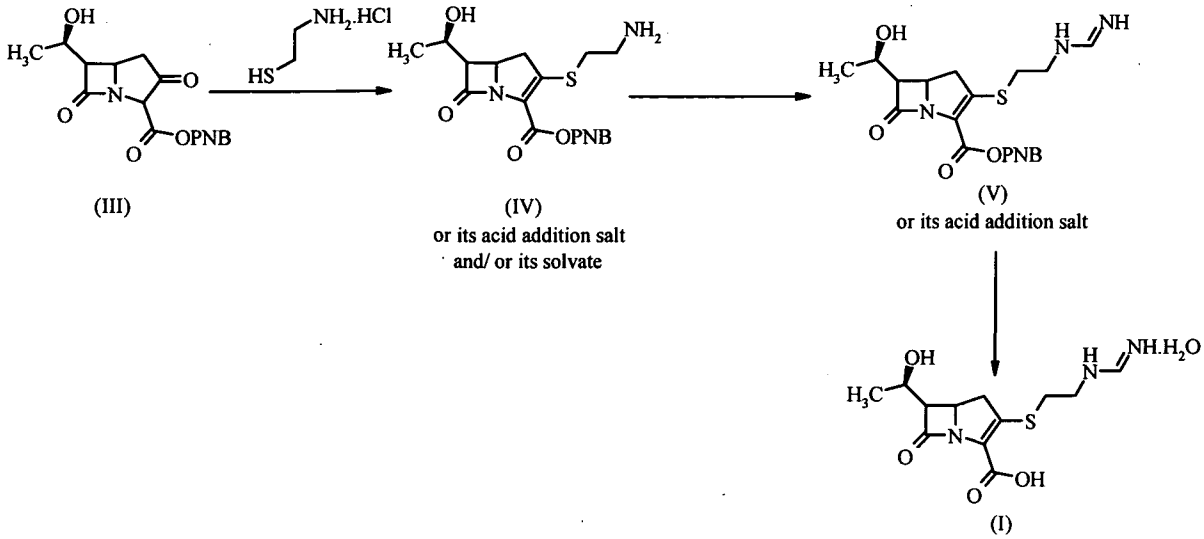
Background of the Invention

Imipenem is a broad spectrum β-lactam antibiotic, belonging to the group carbapenems. It is derived from a compound called thienamycin (THN) of formula (II).



(II)

Various literatures reported the preparation of Imipenem, in which one of the widely used process is shown in scheme-I.



Scheme-I

The said process involves the conversion of THN Cyclic of formula (III) into thienamycin 4-nitrobenzylester (Thienamycin PNB) of formula (IV) or its acid addition salt and/or its solvate, which on reaction with alkyl or aryl formimidate yields Imipenem PNB of formula (V) or its acid addition salt. The compound of formula (V) is converted into Imipenem of formula (I) or its hydrate by catalytic hydrogenation.

US 4,292,436 patent utilizes platinum oxide as a hydrogenation catalyst for the deprotection of 4-nitrobenzyl (PNB) group from PNB protected Imipenem. According to the specification the yield of the product is only 59 % which is very less.

US 5,245,069 patent utilizes palladium hydroxide as a hydrogenation catalyst for the deprotection of PNB group from PNB protected Imipenem. Use of palladium hydroxide-on-carbon in hydrogenation is expensive and the yield of the product obtained is not mentioned in the specification.

US 2002/0095034 describes a process for the preparation of Imipenem by activating (3R,5R,6S)-2-oxo-6-[(1R)-1-hydroxyethyl]carbapenem-3-carboxylic

acid 4-nitrobenzylester (THN Cyclic) with diphenylphosphorohydrochloride followed by reacting the activated compound with cysteamine hydrochloride in the presence of a base to produce thienamycin 4-nitrobenzylester hydrochloride (Thienamycin PNB) (IV) in the form of N-methylpyrrolidinone solvate; which is reacted with alkyl formimidate to produce Imipenem 4-nitrobenzylester (IMI PNB) (V), followed by deprotection using palladium catalyst to yield Imipenem. This patent publication provides thienamycin 4-nitrobenzylester in the form of hydrochloride, or hydrochloride solvated with a solvating agent chosen from the group consisting of N-methylpyrrolidinone, N-ethylpyrrolidinone and N,N-dimethylacetamide.

KR 848752 patent provides thienamycin PNB in the form of solvate with 1,3-dimethyl-2-imidazolidine (DMI), 1,3-diethyl-2-imidazolidine (DEI) and the like, and its use in the preparation of Imipenem.

All the reported prior art process utilizes either palladium or platinum for the deprotection of 4-nitrobenzylester in Imipenem 4-nitrobenzylester of formula (V). One of the problems associated in the deprotection step is the degradation of Imipenem formed during reaction, because of which the overall yield is reduced thereby increasing the cost of manufacturing.

US 7,332,600 (Publication number US 2005/004359 A1 and its Indian patent application number: 1152/DEL/2001) describes a process for the preparation of crystalline Imipenem monohydrate which comprises: (a) dissolving crude Imipenem monohydrate in warm water to which some base has been added to obtain a solution; (b) subjecting the resultant solution to activated carbon treatment; and (c) adding an organic solvent to precipitate Imipenem monohydrate as a crystalline product. All carbapenem compounds are susceptible for degradation at high temperature (45-60 °C) and pH hence we need to cool the solution containing carbapenem compounds to lower

temperature. This patent requires cooling the resultant solution to lower temperature with in 5-10 minutes. The specification does not provide any method for cooling the reaction solution with a short span of time.

In our co-pending application 2259/CHE/2009 we have provided an improved process for the preparation of Imipenem monohydrate compound of formula (I), comprising the steps of: i) dissolving Imipenem or its hydrate in water in the presence of inorganic salt; ii) optionally adjusting the pH of the step (i) solution to 6.5 – 7.8; iii) treating the solution with carbon and/or decolorizing agent selected from the reagent consisting of silica, alumina, or clay; iv) optionally seeding with Imipenem monohydrate; v) adding an organic solvent; and vi) isolating Imipenem monohydrate.

With our continued research for developing a process for the preparation of compound of formula (I), we have come up with a process in which the activity of the catalyst used for the hydrogenation is deactivated using deactivating agent and hence overall yield of Imipenem monohydrate was high when compared to the product obtained by prior art processes.

Further, we have developed a process for the preparation of compound of formula (I) by rapid dissolution of the product in water at high temperature followed by rapid cooling and isolation of product from water with better yield and purity

Objectives of the Invention

The main objective is to provide a simple and commercially viable, industrially scalable processes for the preparation Imipenem of formula (I) or its hydrates with higher yield.

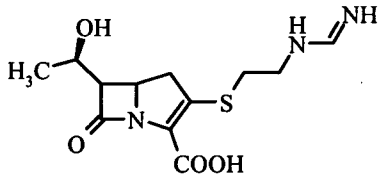
Another objective is to provide a simple and commercially viable, industrially scalable process for the preparation of Imipenem monohydrate in high yield.

Still another objective is to provide a simple and commercially viable industrially scalable process for the rapid dissolution of Imipenem.

Yet another objective is to provide a process for the preparation of sterile Imipenem or its hydrates from water.

Summary of the Invention

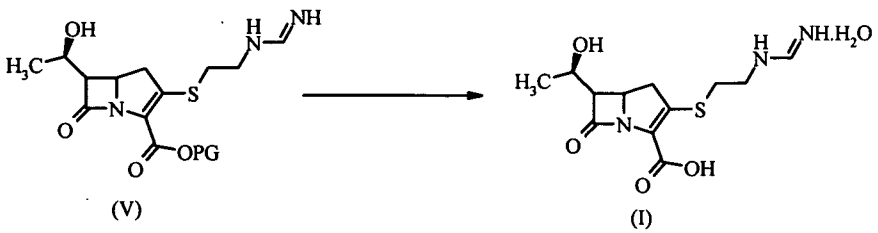
Accordingly, the present invention provides an improved process for preparation of compound of the formula (I) or its hydrate.



(I)

The said process comprises deprotecting the compound of formula (V) by catalytic hydrogenation using metal catalyst in the presence of "catalyst deactivating agent".

The said process is shown in the following scheme.



(V) (I)

wherein PG represents carboxylic acid protecting group selected from allyl, substituted or unsubstituted benzyl group.

Another aspect of the present invention provides an improved process for the preparation of Imipenem of formula (I) or its hydrate comprising the steps of:

i) dissolving Imipenem in water by heating in an apparatus composed of an outer tube containing an inner tube, wherein aqueous suspension of Imipenem is passed through an inner tube and hot material is circulated in outer tube;

ii) cooling the solution obtained in step i) using an apparatus composed of an outer tube containing an inner tube, wherein aqueous solution of Imipenem obtained in step i) is passed through an inner tube and cold material is circulated in outer tube;

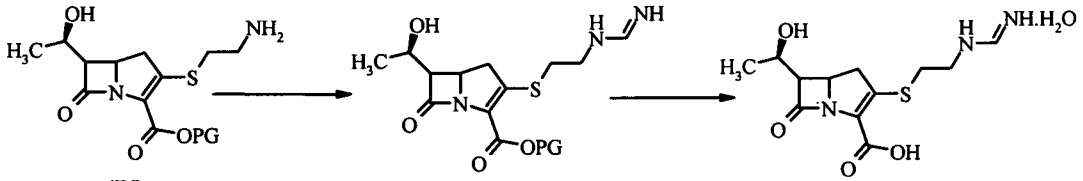
iii) isolating Imipenem of formula (I) or its hydrate.

Another aspect of the present invention provides an improved process for the preparation of aqueous solution of Imipenem comprising continuously passing the slurry of Imipenem in water to an inner tube of an apparatus composed of an outer tube containing inner tube, wherein the dissolution is done by circulating hot material in the outer tube.

Another aspect of the present invention provides an improved process for rapid cooling of an aqueous solution of Imipenem comprising continuously passing the solution through an inner tube of an apparatus composed of an outer tube containing inner tube, wherein the cooling is done by circulating cold material through an outer tube.

Detailed Description of the Invention

In an embodiment, the compound of formula (V) is prepared by conventional methods, for example by reacting compound of formula (IV) or its acid addition salt and/or its solvate with alkyl formimidate hydrochlorides or aralkyl formimidate hydrochlorides in the presence of solvent and a base. The compound of formula (V) thus formed is isolated or taken for next stage without isolation. The compound of formula (IV) used in the form of hydrochloride or hydrochloride solvated with a solvating agent chosen from the group consisting of N-methylpyrrolidinone, N-ethylpyrrolidinone, 1,3-dimethyl-2-imidazolidinone (DMI), 1,3-diethyl-2-imidazolidinone (DEI), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), Tetramethylurea (TMU) and the like. The said process is depicted below:



wherein PG represents carboxylic acid protecting group.

In another embodiment of the present invention the carboxylic acid protecting group represented by PG denotes allyl, substituted or unsubstituted benzyl such as 4-nitrobenzyl, 4-chlorobenzyl etc.

In yet another embodiment of the present invention, deprotection of the compound of formula (V) is carried out in the presence of solvent such as THF, dioxane, ethyl acetate, butyl acetate, dichloromethane, DMF, isopropanol, butanol, ethanol, methanol, acetonitrile, water and the like or mixtures thereof.

The solvent system may also contain buffer solution such as morpholinoalkylsulfonic acid or it salt such as morpholinopropanesulfonic acid, morpholinoethanesulfonic acid and their sodium salt.

In still another embodiment of the present invention the metal catalyst used for deprotection is selected from Palladium on carbon(Pd/C), Platinum on carbon (Pt/C) , Platinum (Pt), Platinum oxide, Rhodium, Lindlar catalyst and the like.

The use of Pd/C, Pt/C as suggested by prior art for the deprotection of 4-nitrobenzylester in Imipenem 4-nitrobenzylester of formula (V) resulted in poor yield of Imipenem. Applicant observed that, the factor which affects the yield could be due to the degradation of Imipenem formed during reaction. One of the probable reasons for the degradation of Imipenem could be the prolonged contact of Imipenem with Palladium, which not only removes the protecting group of the Imipenem, but may possibly attacks the imine functional group of Imipenem.

In one more embodiment of the present invention, the "catalyst deactivating agent" used is selected from barium sulfate, calcium carbonate, lead acetate, lead oxide, iron oxide, sulfur, quinoline and the like. The "catalyst deactivating agent" reduces the activity of catalyst used; in other words, this act is known as "catalyst poisoning". Catalyst poisoning refers to the effect that a catalyst can be 'poisoned' if it reacts with another compound that bonds chemically but does not release or chemically alters the catalyst. This effectively reduces the usefulness of the catalyst. Applicant surprisingly found that the use of "catalyst deactivating agent" along with metal catalyst for deprotection yields Imipenem in higher quantity when compared to metal catalyst alone.

In one more embodiment of the present invention, use of catalyst deactivating agent as described in the process of the present invention can be extended to other carbapenems such Meropenem, Ertapenem, Doripenem, Panipenem, Sulopenem, Biapenem, Faropenem, Tomipenem, Tebipenem and the like.

Since Imipenem is a parental drug it needs to be prepared under sterile condition which requires series of micron filter including 0.2 μ filter and subsequent precipitation and isolation of Imipenem as sterile product. In order to perform micron filtration, the product must be in the form of solution which on subsequent micron filtration, crystallization and isolation as sterile product.

In another embodiment of the present invention, the apparatus used for rapid dissolution of Imipenem and rapid cooling of Imipenem solution as described in step (i) and step (ii) is composed of an outer tube containing an inner tube. The apparatus is made up of glass, stainless steel, metal, alloy, wherein the inner tube is running to the length of the outer tube similar to a Graham condenser. The outer tube has two connections as like glass condenser for circulating hot or cold material. The inner tube can be of any shape such straight or spiral or zig-zag; preferably spiral or zig-zag.

The hot material used for circulation during rapid dissolution of Imipenem is selected from hot water, hot oil or steam and cold material used for circulation during cooling Imipenem is selected from chilled water, cold methanol, anti-freeze mixture and the like.

In still another embodiment of the present invention, outlet of the inner tube of the step (i) apparatus is connected to step (ii) apparatus, which facilitates the rapid heating of aqueous slurry of Imipenem by passing through the inner tube of the step (i) apparatus, in which hot water is circulated through the outer

tube and passing the resultant Imipenem solution through the inner tube of the step (ii) apparatus wherein cold water is circulated at the outer tube of the step (ii) apparatus to cool the solution of Imipenem. The temperature of hot water is maintained about 40 to about 100° C, preferably about 50 – 90° C and the temperature of cold material is maintained in the range of 5-15° C. The time taken for Imipenem to reach step (ii) apparatus from step (i) is about 3 minute, which helps rapid dissolution of aqueous Imipenem slurry by heating.

In yet another embodiment of the present invention the Imipenem or its hydrate is taken in 20 to 80 times of water, based on the weight of input Imipenem, to provide aqueous slurry or suspension of Imipenem. The length of the inner tube and outer tube is designed based on the amount of Imipenem needs to be dissolved. The slurry of Imipenem is slowly passed through the inner tube and the flow can be either by gravity or by applying pressure or by pumping the slurry.

Though the Imipenem is soluble in water at higher temperature it tends to degrade as it is sensitive towards heat, apart from this, the dissolution of Imipenem in large scale would take more time, which severely affects the yield and quality of Imipenem obtained. The applicant observed that the rapid dissolution of aqueous suspension of Imipenem by heating for a short time, i.e for about less than 3 minute preferably less than 1 minute, more preferably less than 30 sec helps to avoid the degradation of Imipenem solution and provide a continuous process for preparing the Imipenem solution. This process can also used for the preparation of Meropenem solution.

After the dissolution, cooling the hot solution of Imipenem needs to be performed rapidly to avoid degradation, the conventional process of receiving the solution of Imipenem in a reservoir followed by cooling the hot solution of Imipenem to lower temperature will take more time which is sufficient enough

to degrade the thermally sensitive material resulting inferior quality and poor yield of the product. Hence, the process provided in the prior art is not satisfactory in large scale manufacturing. According to the present invention, solution of Imipenem is cooled immediately after dissolution by passing through second apparatus in which cold water is circulated in outer tube, which facilitates rapid cooling of Imipenem solution. Thus the present invention provides a process for the preparation of Imipenem solution by rapid heating of the aqueous slurry or suspension of Imipenem by passing continuously in an apparatus followed by rapid cooling the solution by passing the solution continuously in an apparatus.

In an another embodiment of the present invention, the solution obtained in step ii) was collected and treated with carbon and chelating agent selected from but not limited to ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA) O,O'-bis(2-aminoethyl)ethyleneglycol-N,N, N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA)or a pharmaceutically acceptable salt thereof (normally as its sodium salt).

In one more embodiment of the present invention, isolation of Imipenem of formula (I) or its hydrate is performed by conventional technique like freeze-drying or by mixing the aqueous solution with an organic solvent selected from acetone, ethyl methyl ketone, diethyl ketone, ethanol, 1-propanol, 2-propanol, n-butanol, isobutanol, acetonitrile or mixtures thereof.

In still one more embodiment of the present invention, mixing can be performed either by adding the clear aqueous solution to the organic solvent or adding organic solvent to the clear aqueous solution.

In yet one more embodiment of the present invention, the crystallized Imipenem monohydrate of formula (I) was isolated from the reaction mixture by conventional technique such as filtration and washing the product with mixture of water and an organic solvent and/or organic solvent which is used for crystallization.

The following examples are provided by way of illustration only and should not be construed to limit the scope of the invention.

Preparation of starting materials:

Preparation of THN-PNB (Thienamycin 4-nitrobenzylester) DMI HCl solvate (IV):

To a mixture of dichloromethane and 1,3-dimethyl-2-imidazolidinone (DMI), THN Cyclic ((3R,5R,6S)-2-oxo-6-[(1R)-1-hydroxyethyl]carbapenem-3-carboxylic acid 4-nitrobenzylester; 50 g) was added followed by N-ethyldiisopropylamine, N,N-dimethylaminopyridine (0.2 g), and diphenyl chlorophosphate were added at –30°C and stirred. The reaction mass was cooled to –60 °C. N-ethyldiisopropylamine (30 mL) and Cysteamine HCl (24 g in 150 mL of DMI) were added. After completion of reaction, acetone (alternatively any water miscible solvent can be employed) was added to precipitate the compound and the solid was filtered, washed and dried. (Yield 65 g).

Preparation of THN-PNB NMP HCl solvate (IV):

To a mixture of dichloromethane and N-methylpyrrolidone (NMP), THN Cyclic (50 g) was added followed by N-ethyldiisopropylamine (40 mL), N,N-dimethylaminopyridine (0.2 g), and diphenyl chlorophosphate (45 mL)

were added at –30 °C and stirred. The temperature of reaction mass was cooled to –60 °C. N-ethyldiisopropylamine (30 mL) and Cysteamine HCl (24 g in 150 mL of NMP) were added. After completion of reaction, acetone (alternatively any water miscible solvent can be employed) was added to precipitate the compound and the solid was filtered, washed and dried. Similar to above examples other solvates of THN-PNB can be prepared.

Preparation of Imipenem monohydrate with catalyst deactivating agent:

Example-1:

To a solution of THN-PNB (Thienamycin 4-nitrobenzylester) DMI HCl solvate (40 g) in acetonitrile N-ethyldiisopropylamine (40 mL) and benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched into (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C in the presence of calcium carbonate at 10 to 15 °C with 5 to10 kg hydrogen pressures. After completion of reaction, Pd/C was removed by filtration and aqueous layer was washed with dichloromethane. The aqueous layer was treated with carbon and degassed with nitrogen. Acetone was charged to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone and dried to yield Imipenem monohydrate. (Yield 16 g; Assay >99.8 %.; Purity 99.3 %)

Example-2:

To a solution of THN-PNB NMP HCl solvate (40 g) in acetonitrile N-ethyldiisopropylamine (40 mL) and benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched in to (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C in presence of calcium carbonate at 10 to 15 °C

with 10 kg hydrogen pressure. After completion of reaction, Pd/C was removed by filtration and the aqueous layer washed with dichloromethane. The aqueous layer was treated with carbon and degassed with nitrogen. Acetone was added to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone and dried to yield Imipenem monohydrate. (Yield 15.8 g)

Example-3:

To a solution of THN-PNB DMAc HCl solvate (40g) in acetonitrile, N-ethyldiisopropylamine (40 mL) and Benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched into (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C in presence of calcium carbonate at 10 to 15 °C with 10 kg hydrogen pressure. After the completion of reaction, Pd/C was removed by filtration and the aqueous layer was washed with dichloromethane. The aqueous layer was treated with carbon and degassed with nitrogen. Acetone was added to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone and dried to yield Imipenem monohydrate. (Yield 15.7 g)

Example-4:

To a solution of THN-PNB NEP HCl solvate (40 g) in acetonitrile N-ethyldiisopropylamine (40 mL) and benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched into (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C in presence of barium sulfate at 10 to 15 °C with 10 kg hydrogen pressure. After the completion of reaction, Pd/C was removed by filtration and aqueous layer was washed with dichloromethane. The aqueous layer was treated with carbon and degassed with nitrogen. Acetone was charged

to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone and dried to yield Imipenem monohydrate.

Example-5:

To a solution of THN-PNB NMP HCl solvate (40 g) in acetonitrile N-ethyldiisopropylamine (40 mL) and benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched into (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C in presence of calcium carbonate at 10 to 15 °C with 10 kg hydrogen pressure. After the completion of reaction, Pd/C was removed by filtration and the aqueous layer washed with dichloromethane. The aqueous layer degassed with nitrogen in presence of activated carbon and EDTA. Acetone was charged to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone and dried to yield Imipenem monohydrate. (Yield 16.1 g; Purity 99.4 %)

Reference example:

Preparation of Imipenem monohydrate without catalyst deactivating agent:

To a solution of THN-PNB NMP HCl solvate (40gm) in acetonitrile N-ethyldiisopropylamine (40 mL) and benzyl formimidate (20 g) were added at –20 °C. The reaction mass was quenched into (3-(4-morpholino)propanesulphonic acid) buffer solution and washed with ethyl acetate. Layers were separated. To the aqueous layer ethanol was added and the mass hydrogenated with Pd/C at 10 to 15 °C with 10 kg hydrogen pressure. After the completion of reaction, Pd/C was removed by filtration and the aqueous layer was washed with dichloromethane. The aqueous layer was treated with carbon and degassed with nitrogen. Acetone was charged to precipitate Imipenem monohydrate. The solid obtained was filtered, washed with acetone

and dried to yield Imipenem monohydrate. (Yield 7.1 g; Assay 99.5% Purity 99.01%).

Quality and Yield comparison:

THN-PNB NMP HCl solvate input (g)	Catalyst deactivating agent used	Yield of Imipenem monohydrate (g)	Assay (% w/w)	Purity (%)
40	$CaCO_3$	**16.1**	>99.8	99.40
40	-	7.1	99.5	99.01

Advantage: The use of calcium carbonate (catalyst deactivating agent) along with metal catalyst increase the yield of Imipenem monohydrate to an extent of greater than **80%** as evidenced by the yield pattern of Imipenem monohydrate in examples with the yield of Reference example.

Example-6:

Preparation of Imipenem monohydrate Sterile:

A Slurry of Imipenem monohydrate non-sterile (5 g) in water (200 mL) was slowly passed (gravity motion) through inner spiral coil (or tube) of a condenser (for e.g., Graham condenser) by circulating the hot water having the temperature of 75 °C through the outer coil of the condenser. The clear solution obtained was cooled by passing it through another water condenser by circulating the cold water having the temperature of 15 °C through the outer coil of the condenser. The clear solution was treated with activated carbon, EDTA and sodium sulphite. The clear solution was filtered through 0.2 micron filter. To the clear filtrate, acetone was charged slowly (optionally seeded with Imipenem monohydrate). The product formed was filtered, washed with

aqueous acetone followed by acetone and dried to yield Imipenem monohydrate sterile. (Yield 4.5 g).

Example-7:

Preparation of Imipenem monohydrate Sterile:

A Slurry of Imipenem monohydrate non-sterile (10 g) and sodium chloride (1 g) in water (400 mL) was passed through an inner tube of a condenser by maintaining the temp at 45-75 °C and the clear solution obtained was cooled by passing it through another condenser by maintaining the temp at 5-15 °C. The clear solution was treated with activated carbon, EDTA and sodium sulphite. The clear solution was filtered through 0.2 micron filter. To the clear filtrate, 2-propanol was charged slowly. The product formed was filtered, washed with aqueous 2-propanol followed by 2-propanol and dried to yield Imipenem monohydrate sterile. (Yield 8.6 g).

Table-1:

Process Details	Input (g)	Output (g)	Yield (% w/w)
According to Example-6 of the present invention	5	4.5	**90**
Examples according to US 7,332,600 (1152/DEL/2001)	100	65-76	65-76

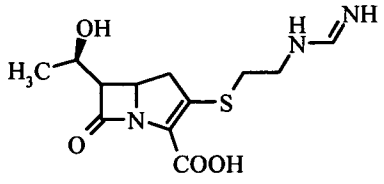
Table-2:

Process	Input Purity (%)	Output Purity (%)	Thienamycin (%)	β-Lactam ring opened impurities
According to Example-6 of the present invention	99.27	99.51	0.39	**0.02**
Prior art process	99.27	99.26	0.52	**0.16**

Conclusion: The samples were analyzed as per the related substance method provided in the official EP monograph. The above table(s) clearly indicates that the process of the present invention is superior in terms of yield and quality than the prior art process, which makes this process feasible in large scale preparation with lower cost of manufacturing.

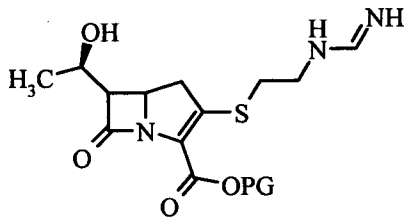
We Claim:

1. An improved process for preparation of Imipenem of formula (I) or its hydrate



(I)

which comprises, deprotecting the compound of formula (V)



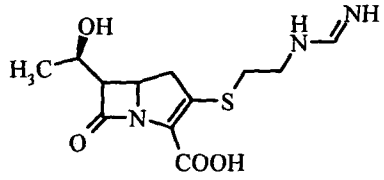
(V)

wherein PG represents carboxylic acid protecting group selected from allyl, substituted or unsubstituted benzyl group, by catalytic hydrogenation using metal catalyst in the presence of catalyst deactivating agent.

2. A process as claimed in claim 1, wherein the metal catalyst employed for deprotection is selected from Palladium on carbon (Pd/C), Platinum on carbon (Pt/C) , Platinum (Pt), Platinum oxide, Rhodium and Lindlar catalyst under hydrogen pressure; preferably Palladium on carbon (Pd/C) under hydrogen pressure.

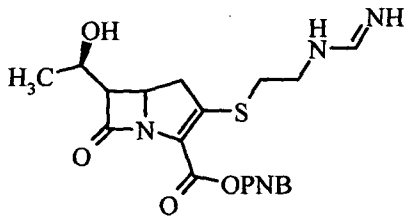
3. A process as claimed in claim 1, wherein the "catalyst deactivating agent" used is selected from barium sulfate, calcium carbonate, lead acetate, lead oxide, iron oxide, sulfur and quinoline; preferably calcium carbonate.

4. An improved process for preparation of compound of the formula (I) or its hydrate



(I)

which comprises, deprotecting the compound of formula (V)



(V)

wherein PNB represents 4-nitrobenzyl by catalytic hydrogenation using metal catalyst in the presence of calcium carbonate.

5. An improved process for the preparation of Imipenem of formula (I) or its hydrate comprising the steps of:
   i) dissolving Imipenem in water by heating in an apparatus composed of an outer tube containing an inner tube, wherein aqueous suspension of Imipenem is passed through an inner tube and hot material is circulated through an outer tube;
   ii) cooling the solution obtained in step (i) using an apparatus composed of an outer tube containing an inner tube, wherein aqueous solution of Imipenem obtained in step (i) is passed through an inner tube and cold material is circulated through an outer tube;
   iii) isolating Imipenem of formula (I) or its hydrate.

6. A process as claimed in claim 5, where in the temperature of hot material is maintained is in the range of 40-100 °C and hot material is selected from hot water, hot oil, hot vapour and steam, more preferably between 50-90 °C.

7. A process as claimed in claim 5, where in the temperature of cold material is maintained is in the range of 5-15 °C.

8. A process for the preparation of aqueous solution of Imipenem comprising continuously passing aqueous slurry of Imipenem to an inner tube of an apparatus composed of an outer tube containing an inner tube, wherein the dissolution is done by circulating hot material in the outer tube.

9. A process for rapid cooling the hot aqueous solution of Imipenem comprising continuously passing the solution to an inner tube of an apparatus composed of an outer tube containing an inner tube, wherein the cooling is done by circulating cold material in the outer tube.

10. A process as claimed in claim 8, wherein the apparatus is a condenser preferably graham condenser.

11. A process as claimed in claim 5, wherein the shape of the inner tube is spiral or zig-zag.

12. A process as claimed in claim 5, wherein the aqueous slurry of Imipenem is passed through an inner tube of step (i) apparatus continuously.

13. A process as claimed in claim 5, wherein time taken for dissolution of Imipenem is less than 3 minutes, preferably less than 1 minute.

14. A process as claimed in claim 5, wherein time taken for Imipenem to reach step (ii) apparatus is less than 3 minutes, preferably less than 1 minute.

15. A process as claimed in claim 5, wherein the isolation of Imipenem or its hydrate was carried out by lyophilization or by adding organic solvent selected from acetone, ethyl methyl ketone, diethyl ketone, ethanol, 1-propanol, 2-propanol, n-butanol, isobutanol, acetonitrile or mixtures thereof and vice-versa.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/001466

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 477/08 (2006.01) ***C07D 477/20*** (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus: registry number and keywords: hydrogenation, catalyst, platinum, palladium, deprotection and like terms
WPI and EPODOC: keywords: penem, hydrogenation, poison, deprotection, deactivate and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1426376 A1 (EISAI CO., LTD.) 9 June 2004 See paragraph [0038]; paragraphs [0078]-[0081]	1-4
Y	US 4292436 A (LIU et al.) 29 September 1981 See column 3, lines 5-13	1-4
Y	WO 2002/094828 A1 (RANBAXY LABORATORIES LIMITED) 28 November 2002 See page 8, lines 4-10	1-4
Y	SAJIKI, H. et al. 'The formation of a novel Pd/C-ethylenediamine complex catalyst: Chemoselective hydrogenation without deprotection of the *O*-Benzyl and *N*-Cbz groups', Journal of Organic Chemistry. 1998, vol. 63, pages 7990-7992 See Table 1, page 7991; Result and Discussion section	1-4

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2010	12 OCT 2010
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **SARAH SMITH** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 2713

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SAJIKI, H. et al. 'Pd/C-catalyzed chemoselective hydrogenation in the presence of a phenolic MPM protective group using pyridine as a catalyst poison', Chemical and Pharmaceutical Bulletin. 2003, vol. 51, pages 320-324 See Abstract; Table 2, page 322	1-4
L	SAJIKI, H. et al. 'Markedly chemoselective hydrogenation with retention of benzyl ester and *N*-Cbz functions using a heterogenous Pd-fibroin catalyst', Tetrahedron Letters. 2003, vol. 44, pages 8437-8439 See Table 1, page 8438	
L	MORI, A. et al. 'Pd/C catalyzed chemoselective hydrogenation in the presence of diphenylsulfide', Organic Letters. 2006, vol. 8, pages 3279-3281 See Abstract; Table 4, page 3281	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/001466

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

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

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

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Supplemental Box
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No: III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have considered those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

(i) Claims 1-4 are directed towards a process for the preparation of imipenem comprising deprotection of a protected carboxylic acid moiety via catalytic hydrogenation with a deactivated catalyst. It is considered that *deprotection via catalytic hydrogenation with a deactivated catalyst* comprises a first distinguishing feature.

(ii) Claims 5-7 (in part), 8, 10 and 11-15 (in part) are directed towards a process for the preparation of imipenem comprising dissolution of imipenem in water with heating by passing a suspension of imipenem through an inner tube surrounded by an outer tube of circulating hot material. It is considered that *dissolution of imipenem via heating* comprises a second distinguishing feature.

(iii) Claims 5-7 (in part), 9 and 11-15 (in part) are directed towards a process for the preparation of imipenem comprising cooling a hot solution of imipenem by passing the solution through an inner tube surrounded by an outer tube of circulating cold material. It is considered that *cooling a hot solution of imipenem* comprises a third distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one of more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

Each of the above mentioned groups of claims has a different distinguishing feature and they do not share any feature which could satisfy the requirement for being a special technical feature. Because there is no common special technical feature it follows that there is no technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention *a priori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB2010/001466

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	1426376	JP	2003128674	US	2004198973	WO	03016312
US	4292436	US	4329481				
WO	0236594	AU	12591/02	BG	107852	CA	2427762
		CN	1481384	EE	200300206	EP	1334105
		IN	191798	MX	PA03003916	US	2004054167
		US	7078534	ZA	200303338		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX