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(71) Applicant (for all designated States except US): **BIOCON LIMITED** [IN/IN]; 20th KM, Hosur Road, Electronic City P.O., Bangalore, Karnataka, 560 100 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KOTHAKONDA, Kiran, Kumar** [IN/IN]; Flat 103, Sai massonette apt, 3-9-95, Ramdas gardens, West maredpally, Secunderabad, Andhra Pradesh, 500032 (IN). **SRIPATHI, Sandeep, Rao, Sanjivirao** [IN/IN]; #146, Samidha, 10th Cross, Sree Anathanagar, Electronic City, Bangalore, Karnataka, 560100 (IN). **VENKATA, Srinivas, Pullela** [IN/IN]; Flat no: 103,B-64, Avanti Mansions, DD colony, Hyderabad, Andhra Pradesh, 500007 (IN). **GEORGE, Lijo** [IN/IN]; Chembottil house, Urakam road, Pullur P. O, Irinjalakuda, Thrissur dist, Kerala, 680683 (IN). **PRASAD, Anegondi, Sreenivasa** [IN/IN]; C/O P.Panduranga Rao, Flat no: 5404, SrilaTowers, Behind, Guntur Vikas College, Hyder Nagar, KPHB, Hyderabad, Andhrapradesh, 500072 (IN).

(74) Agents: **KRISHNAMURTHY, Rama** et al.; K & S Partners, # 4121/B, 6th Cross, 19A Main, HAL II, Stage (Extension), Bangalore, Karnataka, 560 038 (IN).

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(54) Title: PROCESS FOR PREPARATION OF CASPOFUNGIN ACETATE AND INTERMEDIATES

(57) Abstract: The present invention discloses a process for the preparation of Caspofungin and its intermediates from Pneumocand- in B₀.

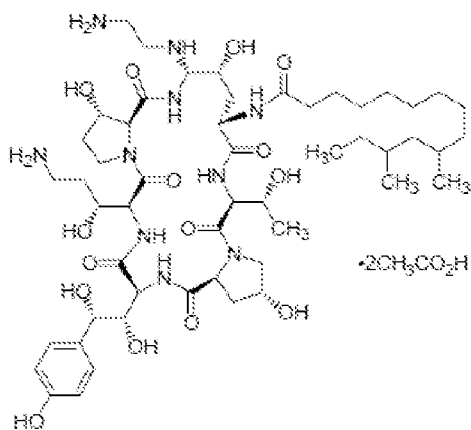


“PROCESS FOR PREPARATION OF CASPOFUNGIN ACETATE AND INTERMEDIATES”

TECHNICAL FIELD

5 The disclosure is directed to processes for preparing Caspofungin and intermediates and their use in preparation of Caspofungin salts thereof.

BACKGROUND



10 Caspofungin acetate is 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3R)-3-hydroxy-L-ornithine] pneumocandin B₀ diacetate salt. Caspofungin is sold under the brand name Candid. Caspofungin acetate is indicated in adults and pediatric patients (3 months and older) for empirical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and the following Candida infections (intra-abdominal abscesses, peritonitis and pleural space infections); treatment of esophageal candidiasis; and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

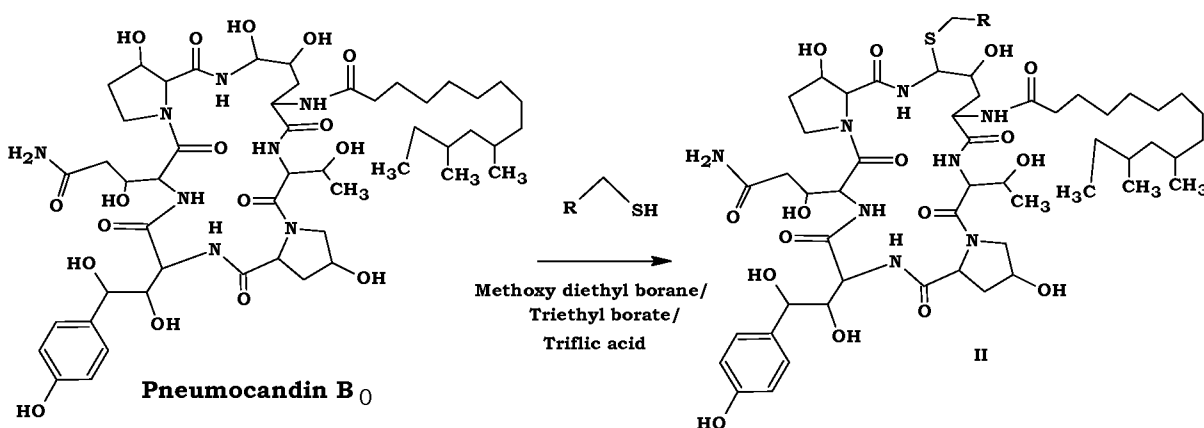
20 A number of relevant processes for preparation of Caspofungin and salts thereof are disclosed. Caspofungin, intermediates and their preparation are disclosed in EP 0 630 232. These methods for the preparation of Caspofungin are difficult to adopt during bulk production, more impurities are generated and very tedious to purify. EP 0 912 603 describes the process for the preparation of caspofungin using phenyl boronic acid and thiophenol. The intermediates generated during this reaction are not stable and also resulted in low yields. This patent further teaches the selective deprotection of phenyl boronic acid protection. This process results in tedious byproducts and low

yields. Nevertheless, there remains a need in the art for processes of preparing Caspofungin that are both cost effective, have fewer purification steps, and/or result in higher purity of the final product, thereby making them more suitable for industrial scale preparation. Meanwhile, during the process of investigation for the robust process for bulk synthesis the new process was identified. The new process for the preparation of Caspofungin is minimizing the formation of the impurities and relatively less tedious and results in better yields.

STATEMENT OF DISCLOSURE

Accordingly, the present disclosure is in relation to a process for preparation of Caspofungin, said process comprising acts of:

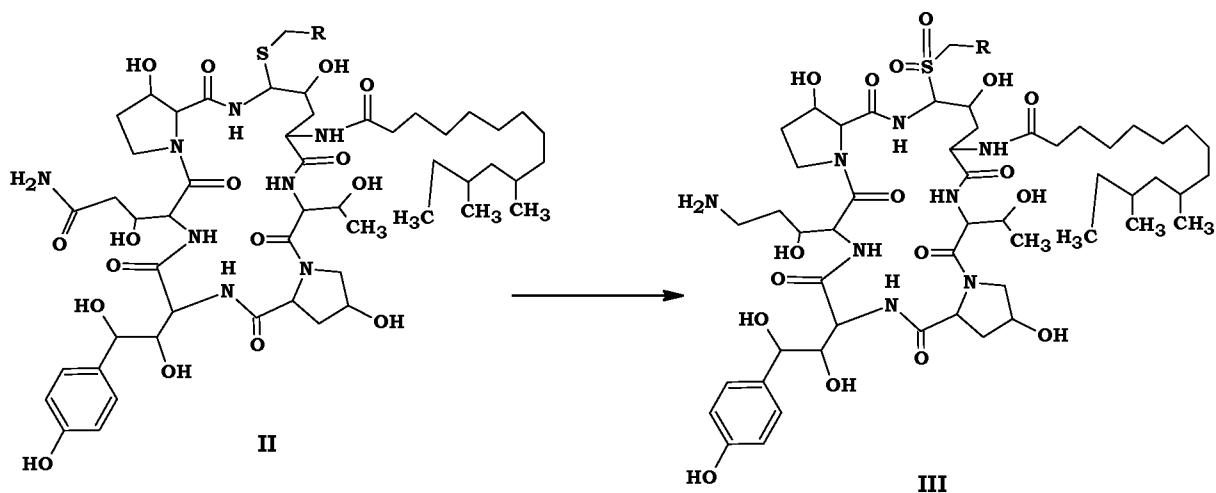
(i). conversion of pneumocandin B₀ to compound of formula II in a suitable solvent,



R=Alkyl/Aryl/Any chain with hetero atom

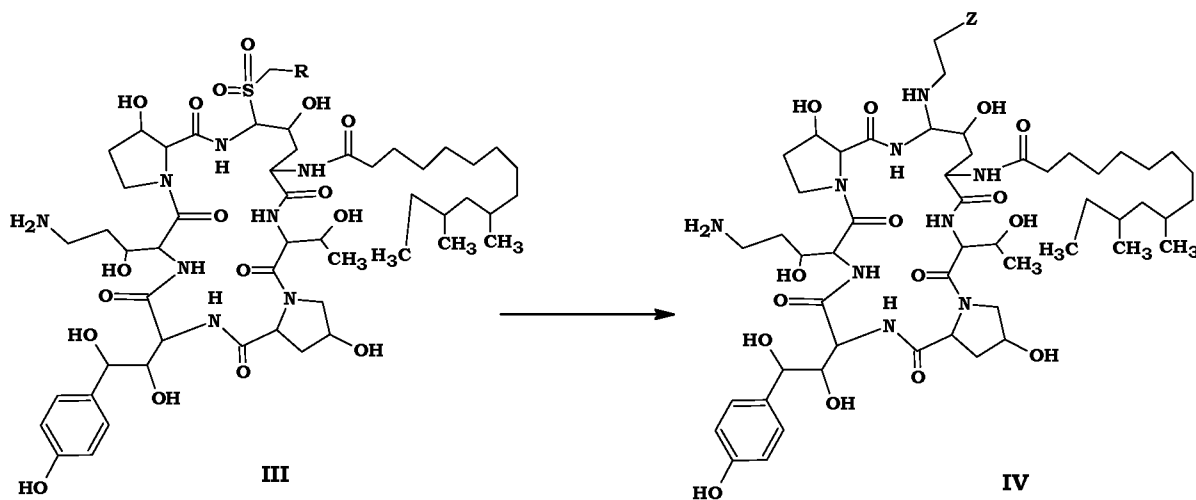
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(ii). conversion of formula II to III in a suitable solvent,



(iii). conversion of formula III to formula IV in a suitable solvent,

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Where Z is NHBOC or N3

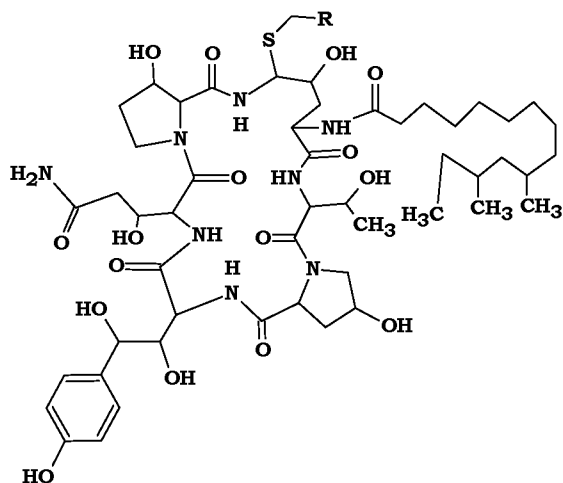
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(iv). Optionally reacting compound IV with BOC deprotecting reagent in a suitable solvent to isolate Caspofungin salt wherein Z is NHBOC

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(v). Optionally hydrogenating compound of formula IV in a suitable solvent to isolating the caspofungin salt wherein Z is N₃;

a compound of formula II,

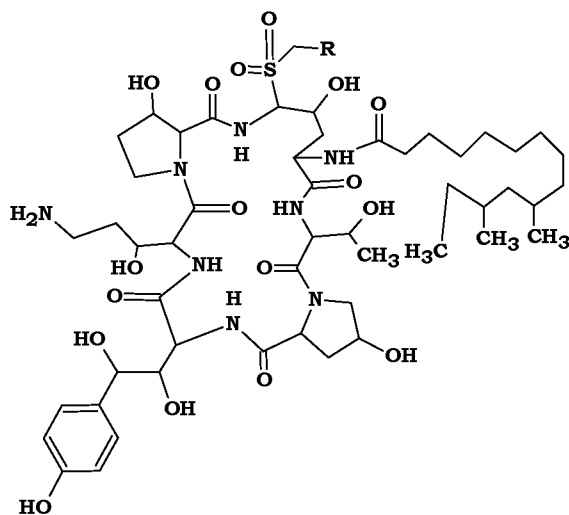


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Formula II

Wherein, R = any side chain consisting of heteroatom;

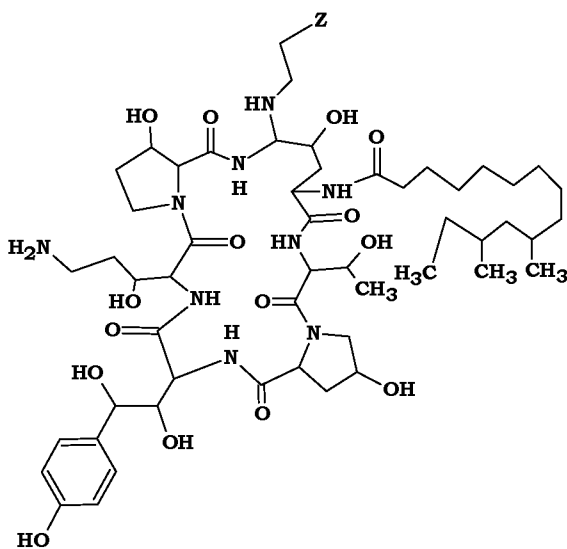
a compound of formula III,



Formula III

Wherein, R is any side chain consisting of heteroatom.

a compound of formula IV,



Formula IV

Wherein, Z = NHBOC or N₃.

10 **BRIEF DESCRIPTION OF THE FIGURES**

Figure 1: Provides a process where pneumocandin B₀ or derivatives are reacted with thiol compounds in anhydrous condition. This reaction is carried out by using the reagents methoxy diethyl borane or triethyl borate or mixtures thereof and triflic acid. The resulted compound is optionally reduced by employing boron dimethyl sulphide complex and further oxidized to get the sulphone of compound III. The reaction further proceeded by reacting the resulted intermediate with N-Boc ethylene diamine and followed by deprotected to form Caspofungin.

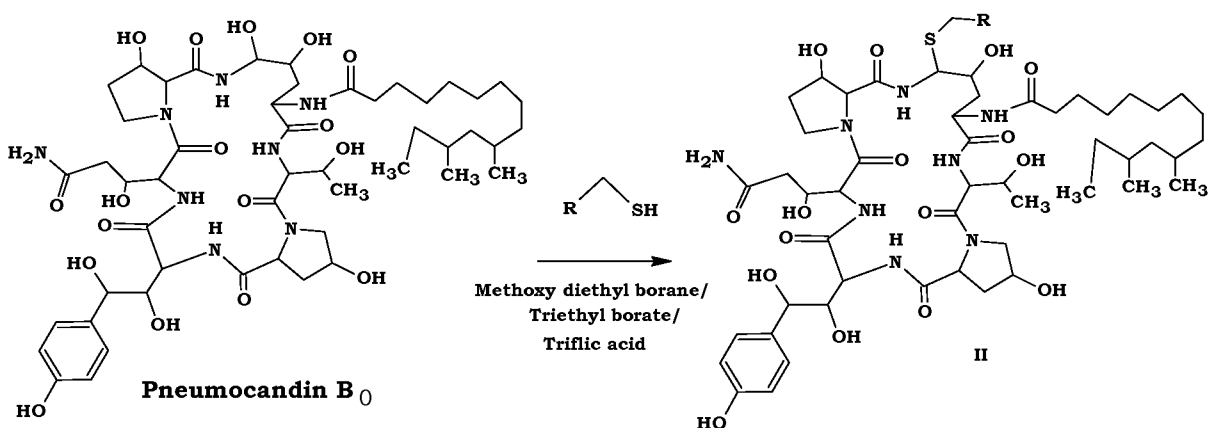
Figure 2: Provides a process where pneumocandin B₀ is reduced using borane dimethylsulfide complex and treated with metal halide in the presence of a Lewis acid to result compound of formula V which is further treated with N-Boc ethylene diamine followed by deprotection yields pure Caspofungin.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure relates to a process of preparation of Caspofungin, said process comprising

5 acts of:

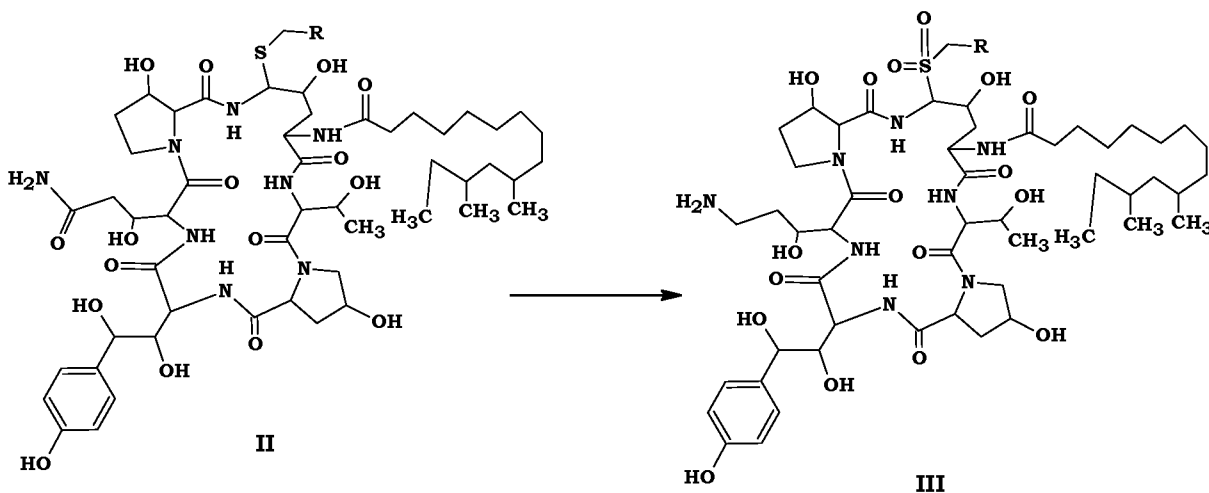
(i). conversion of pneumocandin B₀ to compound of formula II in a suitable solvent,



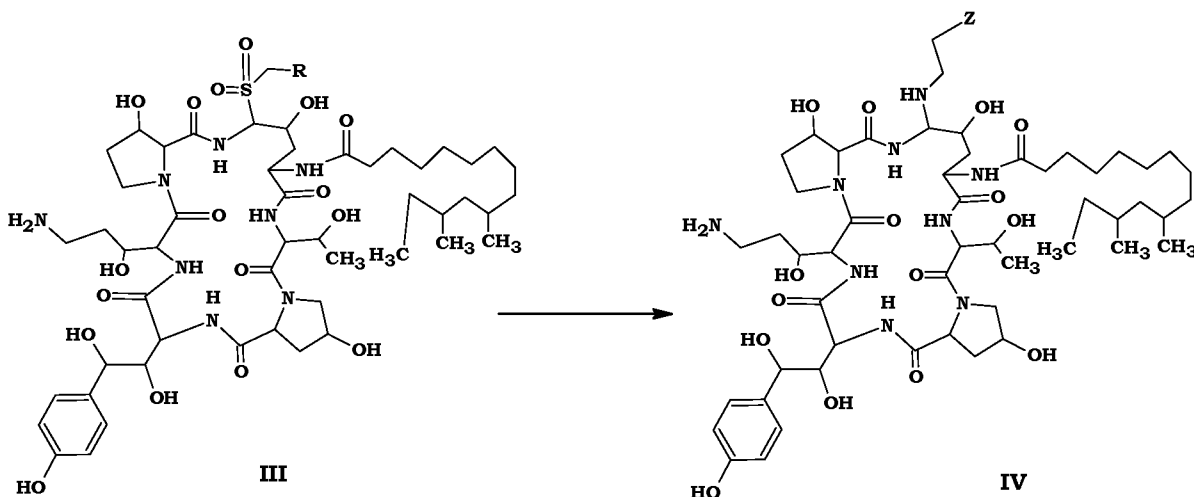
R=Alkyl/Aryl/Any chain with hetero atom

10

(ii) conversion of formula II to III in a suitable solvent,



(iii) conversion of formula III to formula IV in a suitable solvent,



5

Where Z is NHBOC or N₃

(iv) Optionally reacting compound IV with BOC deprotecting reagent in a suitable solvent to isolate Caspofungin salt wherein Z is NHBOC

10 (v). Optionally hydrogenating compound of formula IV in a suitable solvent to isolating the caspofungin salt wherein Z is N₃.

In an embodiment of the present disclosure, pneumocandin B₀ is reacted with RCH₂SH in presence of alkoxy dialkylborane or trialkyl borate or mixture thereof, and triflic acid in a suitable solvent to obtain compound of the formula II.

15

In another embodiment of the present disclosure, R is selected from a group comprising alkyl, aryl or any chain comprising a hetero atom, or mixture thereof.

In yet another embodiment of the present disclosure, alkoxy dialkylborane is methoxy diethylborane.

20 In still another embodiment of the present disclosure, trialkyl borate is triethyl borate.

In still another embodiment of the present disclosure, conversion of compound II to compound III further comprises.

- a) reducing compound of formula II with a reducing agent and,
- b) oxidizing with oxidizing agent to form sulphone of compound III.

- 5 In still another embodiment of the present disclosure, the reducing agent is borane complex of dimethyl sulphide.

In still another embodiment of the present disclosure, the oxidizing agent is selected from a group comprising of Sodium hypochlorite/acetic acid, Hydrogen peroxide / acetic acid, Oxone, sodium periodate, meta chloroperbenzoic acid, KMNO₄, and similar oxidizing agents.

- 10 In still another embodiment of the present disclosure, the compound of formula III is optionally reacted with Boc protected ethylene diamine in a suitable solvent to obtain compound IV.

In still another embodiment of the present disclosure, the compound of formula III is optionally reacted with 2-azido ethylamine in a suitable solvent to obtain compound IV.

- 15 In still another embodiment of the present disclosure, the Boc protected compound IV is treated with acetyl chloride in a suitable solvent to obtain Caspofungin.

In still another embodiment of the present disclosure, the azide protected compound IV is hydrogenated to obtain Caspofungin.

- 20 In still another embodiment of the present disclosure, hydrogenation is done by using Pd/C in a suitable solvent; the process further comprises a process for preparation of Caspofungin diacetate salt.

In still another embodiment of the present disclosure, Caspofungin is treated with acetic acid in a suitable solvent.

In still another embodiment of the present disclosure, preparation of compound IV further comprises;

- 25 (i) reacting pneumocandin Bo with metal halide in presence of an acid in a suitable solvent,
- (ii) reacting compound from step (i) with boran complex and
- (iii) reacting with NH₂CH₂CH₂-Z.

In still another embodiment of the present disclosure, the metal halide is selected from a group of alkaline or alkaline earth metal halide.

In still another embodiment of the present disclosure, the metal halide is selected from a group comprising of KBr, KI, NaBr, LiBr, LiI, NaI and mixtures thereof.

5 In still another embodiment of the present disclosure, the acid is lewis acid.

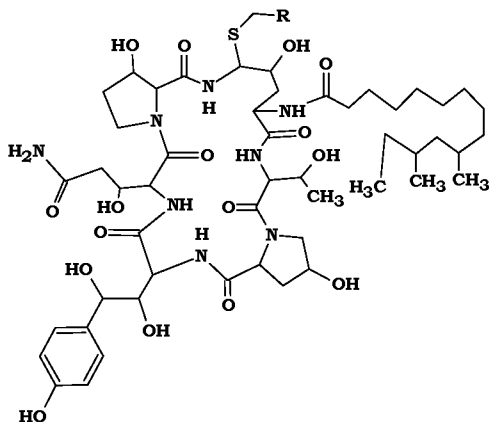
In still another embodiment of the present disclosure, lewis acid is selected from the group comprising of BF₃ etherate, Methoxy diethylboronate, triethyl borate, Tin (IV) chloride and mixtures thereof.

In still another embodiment of the present disclosure, boran complex is borane complex of dimethyl sulphide.

In still another embodiment of the present disclosure, Z is NHBOC or N₃.

In still another embodiment of the present disclosure, suitable solvent is selected from a group comprising of acetonitrile, ethylene diamine, methanol, acetic acid, THF, ethanol, isopropanol and mixtures thereof.

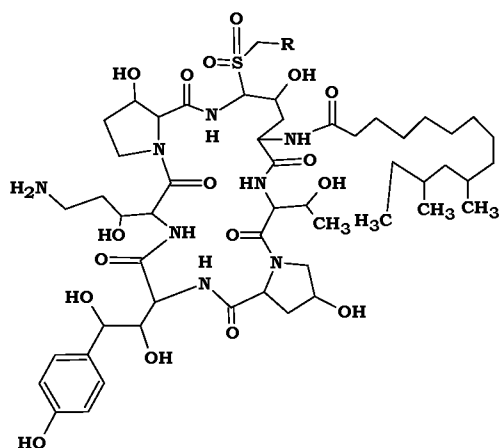
15 The present disclosure is also in relation to a compound of formula II



Formula II

Wherein, R = any side chain consisting of heteroatom.

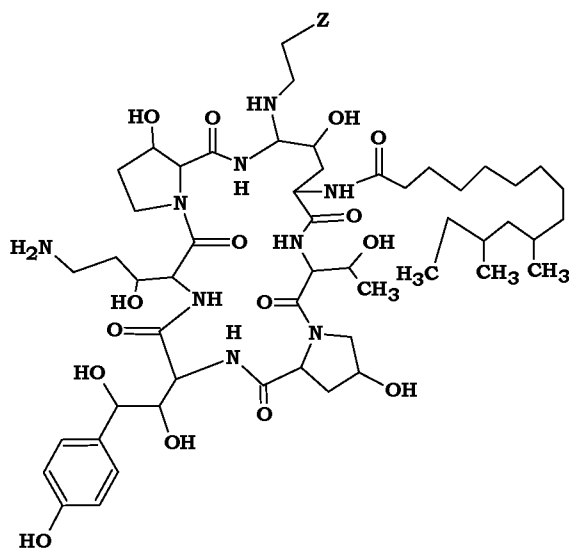
The present disclosure is also in relation to a compound of formula III



Formula III

Wherein, R is any side chain consisting of heteroatom.

The present disclosure is also in relation to a compound of formula IV



Formula IV

Wherein, Z = NHBOC or N₃.

In an embodiment of the present disclosure, the present disclosure provides a process for preparing Caspofungin acetate by reacting pneumocandin B₀ and derivatives of pneumocandin B₀. The present disclosure provides a novel and more efficient process for the preparation of Caspofungin and novel intermediates thereof. Majority of the intermediates from the present novel process for the preparation of Caspofungin are solids, they are easy to purify and handle. In another embodiment, the present novel process requires less amounts of low cost reagents, which

are easy to handle compared to any other existing process. Further, the present novel process for the preparation of Caspofungin and novel intermediates requires less reaction time. In another embodiment, the present disclosure produces less toxic water soluble by-products, which are easy to remove / destroy. The processes resulted from the present disclosure are easy to scale up.

- 5 In another embodiment of the disclosure, the pneumocandin B₀ or derivatives are reacted with thiol compounds in anhydrous condition. This reaction is carried out by using the reagents methoxy diethyl borane or triethyl borate or mixtures thereof and triflic acid. The resulted compound is optionally reduced by employing boron dimethyl sulphide complex and further oxidized to get the sulphone of compound III. The reaction further proceeded by reacting the
10 resulted intermediate with N-Boc ethylene diamine and followed by deprotection to form Caspofungin.

In yet another embodiment of the present disclosure, the intermediate which is the sulphone of compound III is treated with 2-azido ethylamine followed by hydrogenation using Pd/C results Caspofungin.

- 15 In still another embodiment of the present disclosure, the pneumocandin B₀ is reduced using borane dimethylsulfide complex and treated with metal halide in the presence of a lewis acid to result compound of formula V which is further treated with N-Boc ethylene diamine followed by deprotection yields pure Caspofungin. In another attempt of preparation of caspofungin, compound V is treated with 2-azido ethylamine. The resulted intermediate is hydrogenated with
20 Pd/C to yield Caspofungin. Metal halide is selecting from KBr, KI, NaBr, LiBr, LiI, NaI and mixtures thereof. In this process lewis acid is selected from the group of BF₃ etherate, Methoxy diethylboronate, triethyl borate, Tin (IV) chloride and mixtures thereof.

- In still another embodiment of the present disclosure, the oxidizing agents are selecting from Sodium hypochlorite/acetic acid, Hydrogen peroxide / acetic acid, Oxone, sodium periodate, meta
25 chloroperbenzoic acid, KMNO₄, and other similar oxidizing agents.

EXAMPLES:

Example 1: Preparation of ethane sulfide (compound II):

- To a solution of Pneumocandin B₀ (250g) in acetone (7.5 L), methoxy diethylborane (110 ml) and ethanethiol (52 ml) were added at room temperature under nitrogen. The reaction mass was
30 stirred for 30 mins. To the reaction mixture Triflic acid (62 ml) was added at – 20 °C and stirred for 1 h. After the completion of the reaction, sodium acetate solution was added and stirred for

complete precipitation. Filtered the solid, washed with acetonitrile (250 ml) and dried under vacuum to obtain ethane sulfide compound II (180g).

Example 2: Preparation of compound III from II:

5 a). To a solution of compound II (100g) in tetrahydrofuran (7 L) borane dimethylsulfide complex (48 ml) was added at -5 °C and stirred for 24h. After the completion of the reaction methanol (100 ml) was added and concentrated to dryness.

b). To a solution of oxone (64g) in water (1.8 L), compound obtained from step a (50 g) in methanol (1.8 L) was added at 0 °C and then stirred for completion of the reaction. The resulted solid was filtered, washed with water (1 L) and dried under vacuum to obtain compound III.

10 **Example 3:** Preparation of caspofungin acetate from compound III:

Ethylene diamine (89 ml) in methanol (120 ml) was added to a solution of compound III (30 g) in methanol (120 ml) at 10 °C and stirred for 4h. After the completion of the reaction, acetic acid (165 ml) was added followed by water (100 ml) and concentrated the reaction mass to obtain caspofungin acetate solution.

15 **Example 4:** Preparation of Caspofungin acetate via compound V:

Potassium bromide (67 g) was added to a solution of Pneumocandin B₀ (20 g) in acetonitrile (60 ml) and boron trifluoride diethylether complex (8 g) at -15 °C under nitrogen and stirred for 3h to obtain compound V. N-Boc ethylene diamine was added to the reaction mixture and then stirred at 30 °C for 12h. Water (95 ml) was added after the completion of reaction, further reaction mass
20 was concentrated to dryness under vacuum to obtain thick mass. This thick mass was dissolved in tetrahydrofuran (600 ml), borane dimethylsulfide complex (2.5 g) was added and stirred for 24h at -5 °C. Methanol (100 ml) was added after the completion of the reaction, and concentrated to dryness under vacuum. The crude mass was dissolved in methanol (600 ml) and acetyl chloride was added at 0 °C. After the completion of the reaction, concentrated the mass and purified to
25 obtain caspofungin acetate (1 g).

Example 5: Preparation of Caspofungin Acetate by N-BOC deprotection:

To a solution of Compound IV (N-BOC Caspofungin) (5 g) in methanol (600 ml), acetyl chloride (10 ml) was added at 0 °C and stirred vigorously till the completion of the reaction. The resulting mass was concentrated and purified to obtain caspofungin acetate.

30 **Example 6:** Preparation of Caspofungin Acetate by azide reduction:

To the crude Compound IV (Caspofungin azide) (5 g), methanol (500 g) was added and stirred vigorously to make uniform solution. 5% Pd/C (100 mg) was added to the reaction mixture under nitrogen, then evacuated with hydrogen, and then stirred the reaction mixture under hydrogen atmosphere for 12h till the completion of the reaction. Acetic acid (5 ml) was added and the
5 resulting mass was concentrated and purified to obtain caspofungin acetate (2 g).

Example 7: Purification of Caspofungin Acetate:

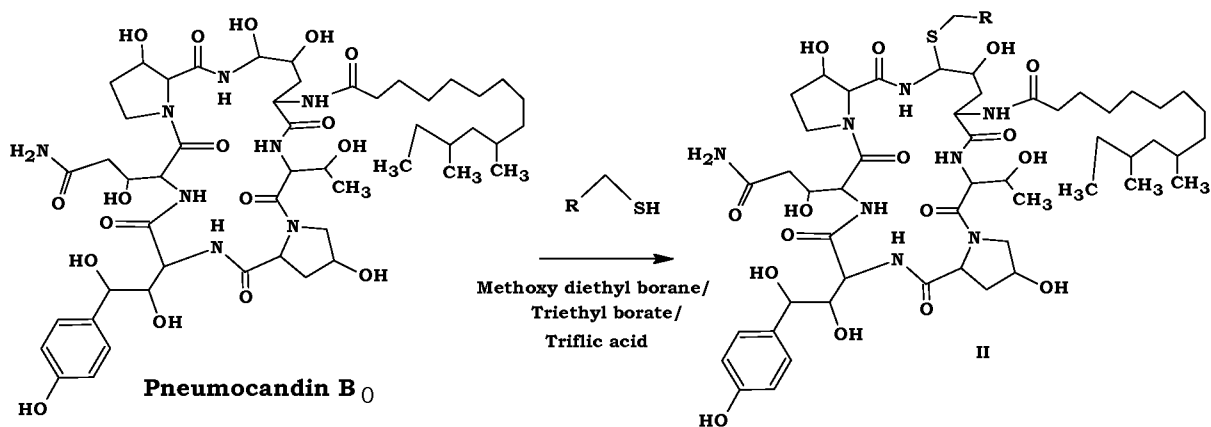
The crude Caspofungin acetate (Purity 20%) was passed through micron filter to remove solid particles and then purified by Novasep-LC110 using mobile phase: ACN/Water/0.01% Acetic acid. Pure fractions were pooled and concentrated to 40-50mg/ml.

WE CLAIM

1. A process preparation of Caspofungin; said process comprising acts of:

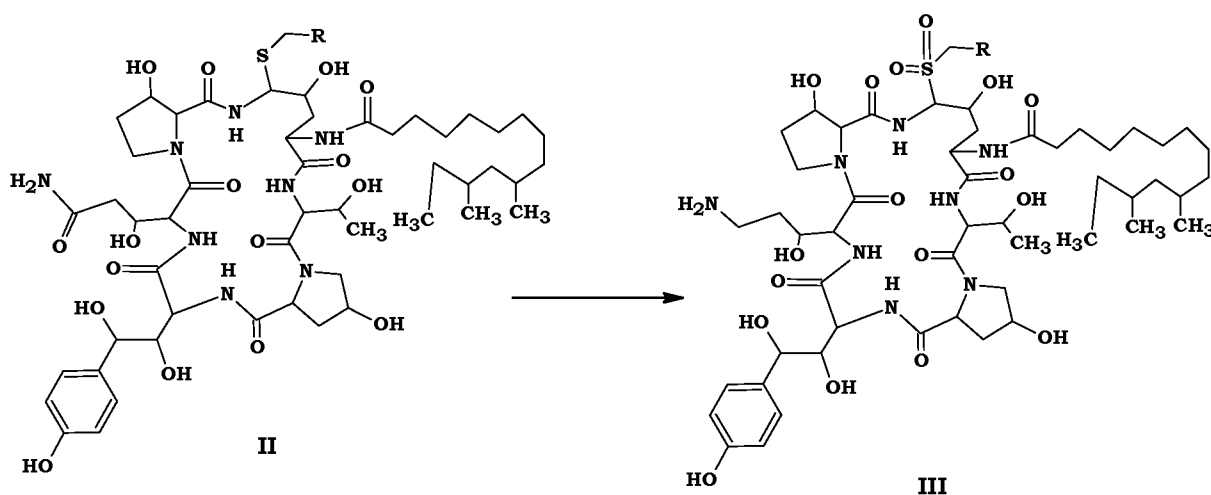
(i) conversion of pneumocandin B₀ to compound of formula II in a suitable solvent,

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R=Alkyl/Aryl/Any chain with hetero atom

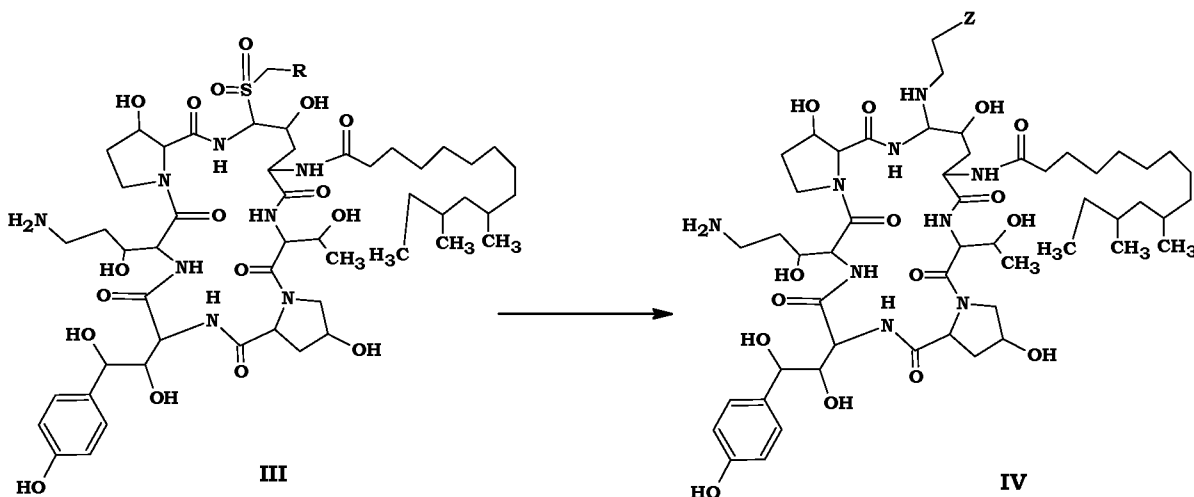
(ii) conversion of formula II to III in a suitable solvent,



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(iii) conversion of formula III to formula IV in a suitable solvent,



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Where Z is NHBOC or N₃

(iv) Optionally reacting compound IV with BOC deprotecting reagent in a suitable solvent to isolate Caspofungin salt wherein Z is NHBOC

10 (v) Optionally hydrogenating compound of formula IV in a suitable solvent to isolating the caspofungin salt wherein Z is N₃.

2. The process as claimed in claim 1, wherein in the step (i) pneumocandin B₀ is reacted with RCH₂SH in presence of alkoxy dialkylborane or trialkyl borate or mixture thereof, and triflic acid in a suitable solvent to obtain compound of the formula II.

15 3. The process as claimed in claim 2, wherein R is selected from a group comprising of alkyl, aryl or any chain comprising a hetero atom, or mixture thereof.

4. The process as claimed in claim 2, wherein alkoxy dialkylborane is methoxy diethylborane.

5. The process as claimed in claim 2, wherein trialkyl borate is triethyl borate.

6. The process as claimed in claim 1, wherein conversion of compound II to compound III further comprises;

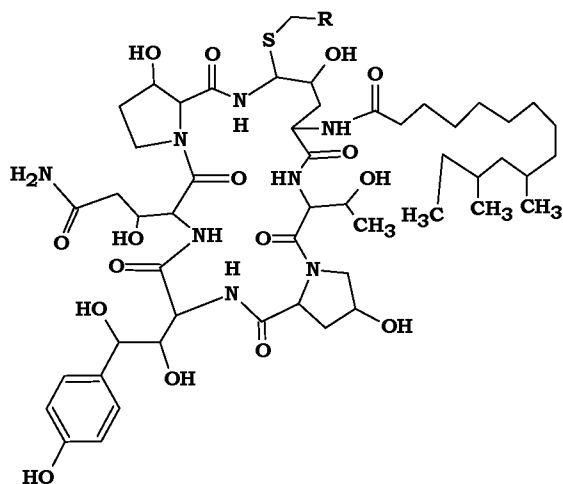
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a) reducing compound of formula II with a reducing agent and,

b) oxidizing with oxidizing agent to form sulphone of compound III.

7. The process as claimed in claim 6, wherein the reducing agent is borane complex of dimethyl sulphide.
8. The process as claimed in claim 6, wherein the oxidizing agent is selected from a group comprising of Sodium hypochlorite/acetic acid, Hydrogen peroxide / acetic acid, Oxone, sodium periodate, meta chloroperbenzoic acid, KMNO₄, and similar oxidizing agents.
9. The process as claimed in claim 1, wherein the compound of formula III is optionally reacted with Boc protected ethylene diamine in a suitable solvent to obtain compound IV.
10. The process as claimed in claim 1, wherein the compound of formula III is optionally reacted with 2-azido ethylamine in a suitable solvent to obtain compound IV.
11. The process as claimed in claim 9, wherein the Boc protected compound IV is treated with acetyl chloride in a suitable solvent to obtain Caspofungin.
12. The process as claimed in claim 10, wherein the azide protected compound IV is hydrogenated to obtain Caspofungin.
13. The process as claimed in claim 12, wherein hydrogenation is carried out by using Pd/C in a suitable solvent.
14. The process as claimed in claim 1 further comprises a for preparation of Caspofungin diacetate salt.
15. The process as claimed in claim 14, wherein Caspofungin is treated with acetic acid in a suitable solvent.
16. The process as claimed in claim 1, wherein preparation of compound IV further comprises of:
 - (i) reacting pneumocandin Bo with metal halide in presence of an acid in a suitable solvent,
 - (ii) reacting compound from step (i) with boran complex and
 - (iii) reacting with NH₂CH₂CH₂-Z to obtain compound IV.
17. The process as claimed in claim 16, wherein the metal halide is selected from a group comprising alkaline or alkaline earth metal halide.
18. The process as claimed in claim 17, wherein the metal halide is selected from a group comprising KBr, KI, NaBr, LiBr, LiI, NaI and mixtures thereof.

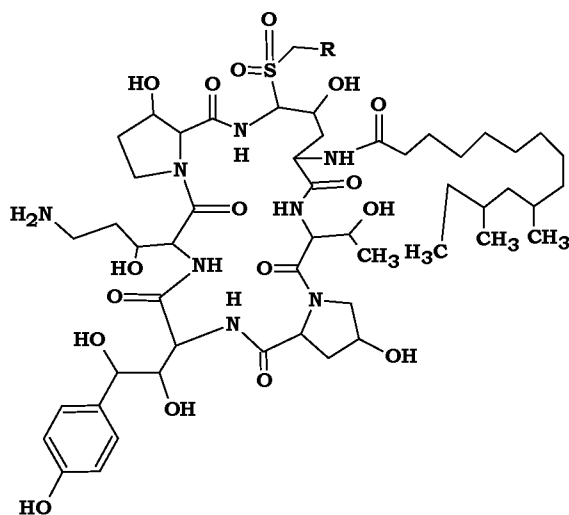
19. The process as claimed in claim 16, wherein the acid is lewis acid.
20. The process as claimed in claim 19, wherein lewis acid is selected from the group comprising BF₃ etherate, Methoxy diethylboronate, triethyl borate, Tin (IV) chloride and mixtures thereof.
21. The process as claimed in claim 16, wherein boran complex is borane complex of dimethyl sulphide.
22. The process as claimed in claim 16, wherein Z is NHBOC or N₃.
23. The process as claimed in claim 1, wherein the suitable solvent is selected from a group comprising acetonitrile, ethylene diamine, methanol, acetic acid, THF, ethanol, isopropanol and mixtures thereof.
24. A compound of formula II,



Formula II

Wherein, R = any side chain consisting of heteroatom.

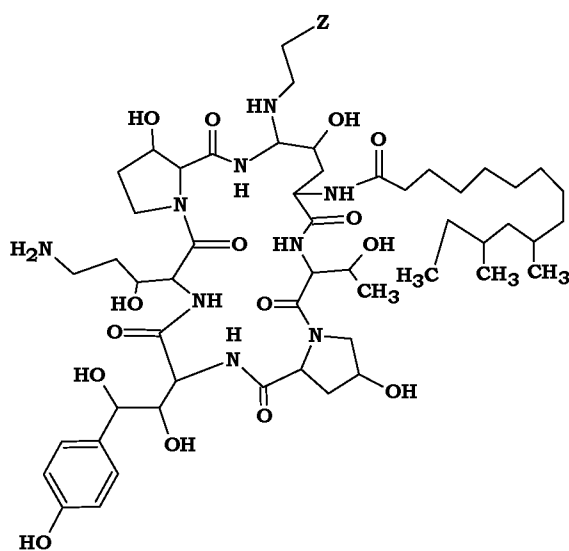
A compound of formula III,



Formula III

Wherein, R is any side chain consisting of heteroatom.

5 25. A compound of formula IV,



Formula IV

Wherein, Z = NHBOC or N₃.

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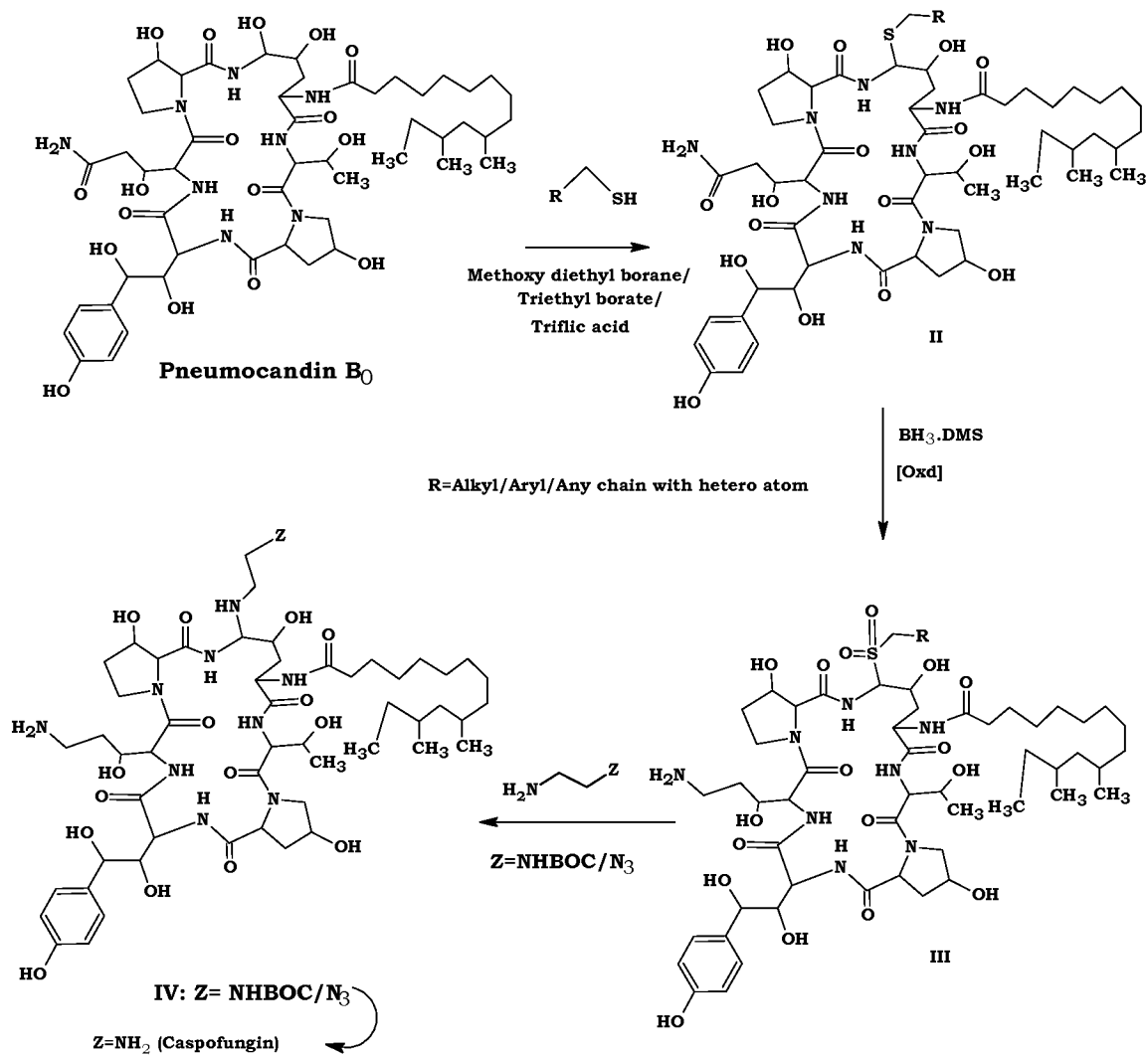


Figure 1

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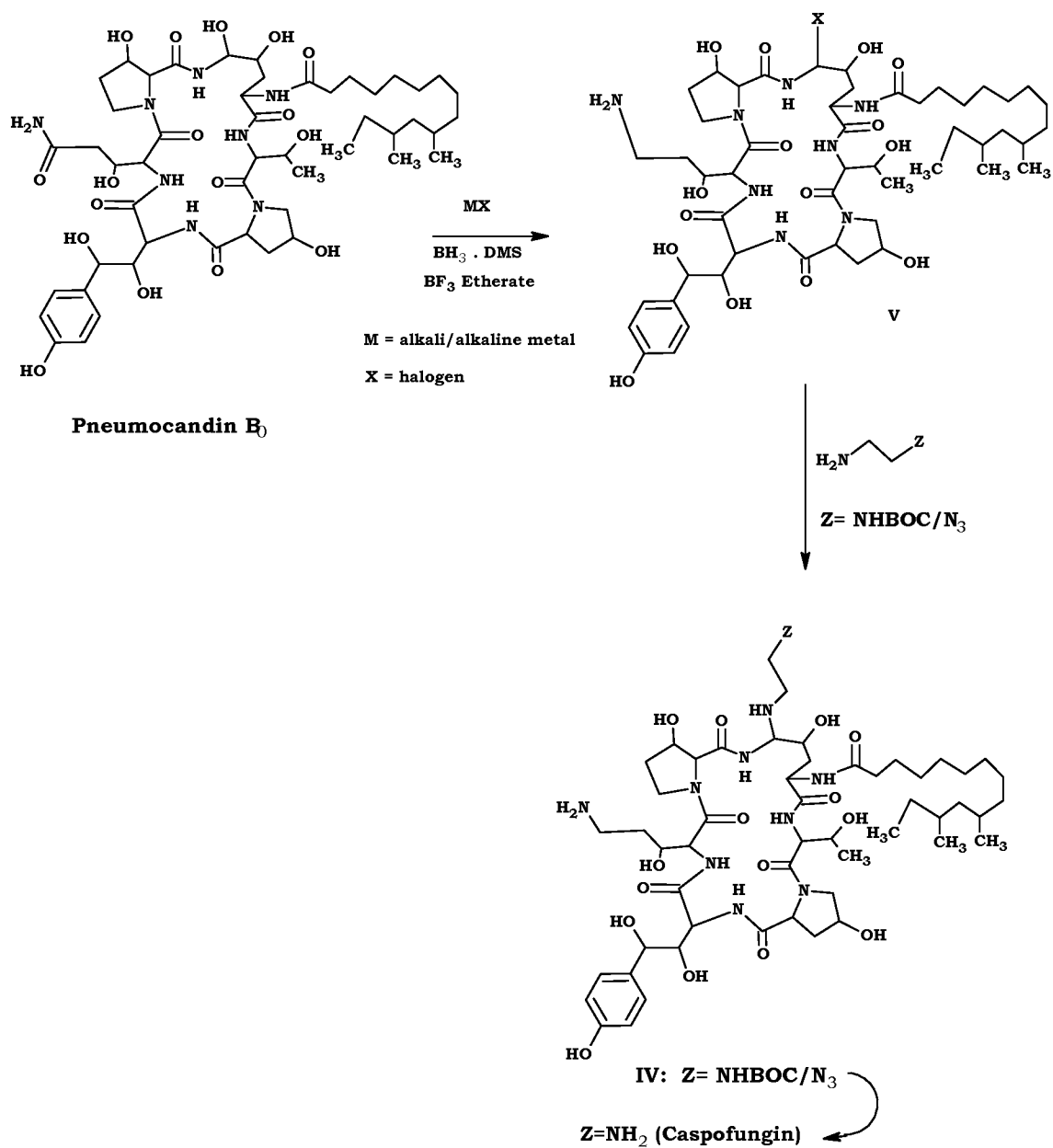


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2011/050681

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07K 1/113 (2006.01) *A61P 31/04* (2006.01) *C07K 7/56* (2006.01)
A61K 38/12 (2006.01) *A61P 31/10* (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)

STN: Sub-structure search in File Registry based on Formula II, III, IV and V and STN: Searched "Caspofungin" in File Registry and searched in a "preparatory role" in CAPLUS.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Author - ANONYMOUS, "Process for the preparation of (2R,6S,9S,11R,12S,14aS,15S,20S,23S,25aS)-12-(2-aminoethylamino)-20-[3-amino-1(R)-hydroxypropyl]-23-[1(S),2(S)-dihydroxy-2-(4-hydroxyphenyl)ethyl]-9-(10,12-dimethyltetradecanamido)-2,11,15-trihydroxy-6-[1(R)-hydroxyethyl]perhydrodipyrrolo[2,1-c:2',1'-l][1,4,7,10,13,16]hexaazacycloheneicosine-5,8,14,19,22,25-hexaone diacetate, via new intermediate", IP.com Journal, 2010, Vol. 10(6A), Page 28-29 (No. IPCOM000196342D), and Pages 255-259, 31 May 2010	1-15, 23-25
A	See the Scheme page 255, Example 1 page 256, Example 2 page 257, Example 3 page 258 and Examples 5 and 6 page 259	16-22

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:

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

"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

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

"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

"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)

"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

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

"&" document member of the same patent family

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

Date of the actual completion of the international search
03 May 2011Date of mailing of the international search report **31 MAY 2011**

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
 PO BOX 200, WODEN ACT 2606, AUSTRALIA
 E-mail address: pct@ipaustalia.gov.au
 Facsimile No. +61 2 6283 7999

Authorized officer

LORNA BARR

AUSTRALIAN PATENT OFFICE
 (ISO 9001 Quality Certified Service)

Telephone No : +61 2 6225 6146

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2011/050681

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 1996/013272 A1 (MERCK AND CO., INC) 9 May 1996 See Example 1 Part B page 26 See Pages 25-28	24 1-23,25
X	CAS RN 936021-58-8 STN entry date 29 May 2007	24
X	CAS RN 179463-19-5 STN entry date 13 August 1996	24
X	CAS RN 162634-54-0 STN entry date 3 May 1995	24
X	CAS RN 150240-03-2 STN entry date 23 September 1993	24
X	CAS RN 150337-31-8 STN entry date 30 September 1993	24
X	CAS RN 150240-01-0 STN entry date 23 September 1993	24
A	WO 1994/021677 A1 (MERCK & CO. INC.) 29 September 1994 See Schemes pages 7-8 and Example 2 page 27, especially Part A and Example 1 Part A page 24	1-25
A	US 5792746 A (BALKOVEC <i>et al</i>) 11 August 1998 See Examples 1 and 2 columns 15 and 16	1-25

Information on patent family members

PCT/IB2011/050681

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					
WO	1996/013272	AU	40164/95	CA	2202920	EP	0789579
		US	5516756				
WO	1994/021677	AU	57832/94	BG	99999	BR	1100273
		BR	9406009	CA	2118757	CN	1119441
		CZ	9502358	EP	0620232	FI	954327
		HK	1008674	HR	940161	HU	73496
		HU	9500565	IL	108892	JP	6321986
		LU	90875	LV	12574	NO	953648
		NZ	263360	PL	310634	SI	9420013
		SK	113695	US	5378804	US	5514650
		ZA	9401807				
US	5792746	NONE					
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. END OF ANNEX							