Abstract:
A process for the preparation of Caspofungin and its intermediates from Pneumocand-

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Declarations under Rule 4.17:
— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(iii))
— of inventorship (Rule 4.17(iv))

Published:
— with international search report (Art. 21(3))
"PROCESS FOR PREPARATION OF CASPOFUNGIN ACETATE AND INTERMEDIATES"

TECHNICAL FIELD

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

BACKGROUND

Caspofungin acetate is l-[(4R,5S)-5-[(2-aminoethyl)amino]-N2-(10,12-dimethyl-loxotetradecyl)-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.

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

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

(iv). Optionally reacting compound IV with BOC deprotecting reagent in a suitable solvent to isolate Caspofungin salt wherein Z is NHBOC
Optionally hydrogenating compound of formula IV in a suitable solvent to isolating the caspofungin salt wherein $Z$ is $N_3$:

\begin{center}
\includegraphics{formula_ii}
\end{center}

\textbf{Formula II}

Wherein, $R$ = any side chain consisting of heteroatom;

\begin{center}
\includegraphics{formula_iii}
\end{center}

\textbf{a compound of formula III.}
Formula III

Wherein, \( R \) is any side chain consisting of heteroatom.

a compound of formula IV,

Formula IV

Wherein, \( Z = \text{NHBOC or N}_3 \).

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1: Provides a process where pneumocandin \( B_0 \) 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 \( B_0 \) 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 acts of:

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

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

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

(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.

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.

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.

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, KMN04, and similar oxidizing agents.

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.

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.

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;

(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, Lil, Nal and mixtures thereof.

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, boron 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.

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

![Formula II](image)

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, \( Z = \text{NHBOC or N}_3 \).

In an embodiment of the present disclosure, the present disclosure provides a process for preparing Caspofungin acetate by reacting pneumocandin B\(_6\) and derivatives of pneumocandin B\(_6\). 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.

In another embodiment of the disclosure, the pneumocandin B₉ 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 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.

In still another embodiment of the present disclosure, the pneumocandin B₉ is reduced using borane dimethylsulphide 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 Pd/C to yield Caspofungin. Metal halide is selecting from KBr, KI, NaBr, LiBr, Lil, 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 chloroperbenzoic acid, KMN04, and other similar oxidizing agents.

**EXAMPLES:**

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

To a solution of Pneumocandin B₉ (250g) in acetonitrile (7.5 L), methoxy diethylborane (110 ml) and ethanethiol (52 ml) were added at room temperature under nitrogen. The reaction mass was 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:**

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.

**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.

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

Potassium bromide (67 g) was added to a solution of Pneumocandin B_0 (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 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 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.

**Example 6: Preparation of Capsofungin 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 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-LCl 10 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 B₉ to compound of formula II in a suitable solvent,

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

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

(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 B9 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.

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;

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 B0 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 NH₂C₆H₄CF₃-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, Lil, Nal 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 claim16, 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,

\[
\text{Formula II}
\]

Wherein, R = any side chain consisting of heteroatom.
A compound of formula III,

Formula III

Wherein, $R$ is any side chain consisting of heteroatom.

25. A compound of formula IV,

Formula IV

Wherein, $Z = \text{NHBOC or N}_3$. 

Figure 1
Figure 2
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No.**
PCT /IB201 1/05068 1

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl.

C07K 1/113 (2006.0)  A61P 31/04 (2006.01)  C07K 7/56 (2006.0)
A61K 38/12 (2006.0)  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 have been consulted during the international search (name of database 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.

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 l}perhydrodipyrrolo[2, 1-c:2', 1-
-][1,4,7,10, 13, 16]hexazacyclohexene-carboxylic acid, a diacetate, via new intermediate", IP.com Journal, 20 10, Vol. 10(6A), Page 28-29 (No. IPCOM000 196342D), and Pages 255-259, 31 May 2010

X  See the Scheme page 255, Example 1 page 256, Example 2 page 257, Example 3 page 258 and Examples 5 and 6 page 259  1-15, 23-25

A  I6-22

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

*A*  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)

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Date of the actual completion of the international search  03 May 2011

Date of mailing of the international search report  31 MAY 2011

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<td>See Example 1 Part B page 26</td>
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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.

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

END OF ANNEX