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(54) Title: PROCESS FOR THE PREPARATION OF A NOVEL INTERMEDIATE FOR CASPOFUNGIN
(57) Abstract: The present invention provides a process for preparing a novel intermediate of Formula (FV) which can be effectively used for the preparation of antifungal agent such as caspofungin, derivatives, and pharmaceutically acceptable salts thereof.

Formula IV

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WO 2010/064219 A1
PROCESS FOR THE PREPARATION OF A NOVEL INTERMEDIATE FOR CASPOFUNGIN

Field of the Invention

The present invention provides a process for preparing a novel intermediate of Formula IV,

which can be effectively used for the preparation of antifungal agent such as caspofungin, derivatives, and pharmaceutically acceptable salts thereof.

Background of the Invention

Echinocandins and echinocandin-like cyclohexapeptide compounds are described in literature as highly effective antifungal agents, particularly against yeast causing myotic infections such as Candida albicans, Candida parapsilosis, and the like. Some of these compounds are natural products produced by the cultivation of microorganisms, such as Aspergillus rugulosus, Aspergillus nidulans and Acrophialophoria lemonispora described in U.S. Patent Nos. 4,024,245; 4,024,246; and 4,173,629 respectively. Some of these compounds are semisynthetic and can be produced by modifying the natural products as described in U.S. Patent Nos. 4,293,489; 4,320,053; 4,370,054; 4,322,338; 5,378,804; 5,965,525; and 5,376,634.

Cancidas® (caspofungin acetate), 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N²-(10,12-dimethyl-loxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3R)-3-hydroxy-L-ornithine] pneumocandin B diacetate (salt), is the first of a new class of antifungal drugs (echinocandins) that inhibit the synthesis of β(1,3)-D-glucan, an integral component of the fungal cell wall. It is indicated in adults and pediatric patients for empirical therapy for presumed fungal infections in febrile, neutropenic patients and used for treatment of
candidemia, and the following Candida infections like: intra-abdominal abscesses, peritonitis and pleural space infections. It is also indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid Formulations of amphotericin B, and/or itraconazole). It is further indicated for the treatment of esophageal candidiasis.

Several processes have been reported for the preparation of caspofungin, its derivatives, and pharmaceutically acceptable salts.

U.S. Patent No. 5,378,804 discloses the reaction of pneumocandin B₀ with 2-aminoethanethiol in the presence of an acid, followed by oxidation to give sulfone which is made to react with ethylene diamine to give caspofungin in low yields; resulting from the lack of stereoselectivity and chemoselectivity of the process.

U.S. Patent No. 5,552,521 describes the process for the preparation of caspofungin involving the reduction of the pneumocandin B₀ followed by the reaction with thiophenol and displacement of phenyl-thio group with ethylene diamine.

U.S. Patent No. 5,936,062 describes the process involving the reaction of pneumocandin B₀ with boronic acid, followed by reduction and then reaction with thiophenol, which upon displacement with ethylene diamine, provides caspofungin.

An improved method directed to the minimization of the epimerization of benzylic position and enhancing the α/β stereo selectivity of the product is described in U.S. Patent No. 7,214,768, this involves the reaction of pneumocandin with boronic acid, dehydrating the resulting borate with cyanuric chloride followed by reduction of the nitrile and reaction with phenylsulfide and finally displacement of the phenyl-thio group with the ethylene diamine to yield caspofungin. All the processes described above are not significantly stereoselective and/or high yielding.

Taking into account the drawbacks of the aforementioned methods, the present invention provides a process for preparing a novel intermediate which can be effectively used for the preparation of antifungal agents such as caspofungin, derivatives, and pharmaceutically acceptable salt thereof.
Summary of the Invention

The present invention provides a process for preparing a novel intermediate of Formula IV,

\[
\begin{align*}
\text{R}_1 & \quad \text{hydrogen, } \text{C}_1-\text{C}_4 \text{ alkyl, halogen, nitro, hydroxy, } \text{C}_1-\text{C}_4 \text{ alkoxy;} \\
\text{R}_2 & \quad \text{C}_1-\text{C}_2 \text{ alkyl, } \text{C}_1-\text{C}_2 \text{ alkoxy, } \text{C}_2-\text{C}_2 \text{ alkenyl, aryl optionally substituted with } \text{R}_x, \text{ wherein } \text{R}_x \text{ is hydrogen, halogen, amino, hydroxyl, } \text{C}_1-\text{C}_0 \text{ alkyl, } \text{C}_1-\text{C}_0 \text{ alkoxy, aryl or Cs-Ceheteroaryl,}
\end{align*}
\]

which can be effectively used for the preparation of antifungal agents. The invention further provides a process for preparing caspofungin, derivatives, and pharmaceutically acceptable salts thereof.

One aspect of the present invention provides a process for preparing a novel intermediate of Formula IV,

\[
\begin{align*}
\text{R}_1 & \quad \text{hydrogen, } \text{C}_1-\text{C}_4 \text{ alkyl, halogen, nitro, hydroxy, } \text{C}_1-\text{C}_4 \text{ alkoxy;} \\
\text{R}_2 & \quad \text{C}_1-\text{C}_2 \text{ alkyl, } \text{C}_1-\text{C}_2 \text{ alkoxy, } \text{C}_2-\text{C}_2 \text{ alkenyl, aryl optionally substituted with } \text{R}_x, \text{ wherein } \text{R}_x \text{ is hydrogen, halogen, amino, hydroxyl, } \text{C}_1-\text{C}_0 \text{ alkyl, } \text{C}_1-\text{C}_0 \text{ alkoxy, aryl or Cs-Ceheteroaryl,}
\end{align*}
\]
The process comprises the steps of:

a) converting a compound of Formula I

\[ \text{Formula I} \]

... to a compound of Formula III

\[ \text{Formula III} \]

wherein \( R_2 \) is as defined above;

b) reacting a compound of Formula III with a compound of Formula VI

\[ \text{Formula VI} \]

... to give a compound of Formula IV, wherein \( R_1 \) and \( R_2 \) are as defined above.

Another aspect of the present invention provides a process for preparing a compound of Formula V.
pharmaceutically acceptable salts thereof, wherein R₂ is C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₂-
C₂₀ alkenyl, aryl optionally substituted with Rx, wherein Rx is hydrogen, halogen, amino,
hydroxyl, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, aryl or C₅-C₆ heteroaryl.

The process comprises the steps of:

a) reacting a compound of Formula I with cyanuric chloride to give a compound of Formula II;

b) reducing a compound of Formula II to a compound of Formula III;

c) reacting a compound of Formula III with a compound of Formula VI to give a compound of Formula IV;
converting a compound of Formula IV to a compound of Formula V or pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a novel intermediate of Formula IV,

pharmaceutically acceptable salts thereof, wherein \( R_1 \) is hydrogen, \( C_1-C_4 \) alkyl, halogen, nitro, hydroxy, \( C_1-C_4 \) alkoxy; \( R_2 \) is \( C_1-C_2 \) alkyl, \( C_1-C_2 \) alkoxy, \( C_2-C_2 \) alkenyl, aryl optionally substituted with \( R_x \), wherein \( R_x \) is hydrogen, halogen, ammo, hydroxyl, \( Q-C_1 \) alkyl, \( C_1-C_1 \) alkoxy, aryl or Cs-Cgheteroaryl.

According to yet another aspect of the present invention, there is provided a pharmaceutical composition comprising:

a) a compound of Formula V
and/or a pharmaceutically acceptable salt thereof wherein

$R_2$ is \((\text{CH}_2\text{SCH} (\text{CH}_3)\text{CH}_2\text{CH} (\text{CH}_3)\text{CH}_2\text{C H}_3)\); and

b) one or more compound selected from

According to a preferred embodiment, the compounds in component b) are present in an amount up to 2% (suitably up to 0.2%), based upon 100% total weight of components a) and b). The compound in component a), i.e., the active ingredient is preferably present in an amount greater than 95% and more preferably greater than 98% or 99% based upon 100% total weight of component a) and b).

**Detailed Description of the Invention**

The following definitions apply to terms, as used herein:

The term "alkyl" refers to a straight or branched chain alkyl group optionally substituted with 1-3 halogen, $C_1 - C_5$ alkoxy, hydroxy or amino. Representative examples
include C₁-C₂₀ alkyl such as methyl, ethyl, propyl, butyl or -
(CH₂)SCH(CH₃)CH₂CH(CH₃)CH₂CH₃).

The term "alkoxy" includes straight or branched alkyl as defined above attached
via an oxygen linkage to the rest of the molecule. Representative examples include
methoxy or ethoxy.

The term "alkenyl" includes straight or branched alkyl group as defined above
having unsaturation.

The term "aryl" includes aromatic radicals having in the range of 6 to 14 carbon
atoms such as phenyl, napthyl, biphenyl, and the like.

The term "heteroaryl" includes saturated or unsaturated 5 or 6 membered cyclic
radical where-in one or two carbon atoms in the ring may be replaced by N or O; which
may be optionally substituted with C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, halogen or amino.

The term "halogen" includes fluorine, chlorine, bromine or iodine.

The term "room temperature" means a temperature range of about 25°C to about
30°C.

The term "pharmaceutically acceptable salts" includes the acid addition salts of
inorganic acids, (e.g., hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid
or the like), or organic acids, (e.g., acetic acid, trifluoroacetic acid fumaric acid, citric acid,
succinic acid, tartaric acid, maleic acid, oxalic acid, malic acid, glutamic acid, or the like).

The present invention provides a process for preparing a novel intermediate of
Formula IV,
The process comprises the steps of:

a) converting a compound of Formula I to a compound of Formula III

wherein $R_2$ is as defined above;

b) reacting a compound of Formula III with a compound of Formula VI to give a compound of Formula IV, wherein $R_1$ and $R_2$ are same as defined above.

In the above process, the step a) involves converting a compound of Formula I to a compound of Formula III, wherein the conversion can be effected by dehydrating the compound of Formula I to give a compound of Formula II, which upon reduction gives a compound of Formula III. The dehydrating agent used in step a) can be selected from pharmaceutically acceptable salts thereof, wherein $R_i$ is hydrogen, $C_iC_j$ alkyl, halogen, nitro, hydroxy, $C_iC_j$ alkoxy; $R_2$ is $C_iC_j$ alkyl, $C_iC_j$ alkoxy, $C_2C_2$ alkenyl, aryl optionally substituted with $R_x$, wherein $R_x$ is hydrogen, halogen, amino, hydroxyl, $C_iC_j$ alkyl, $C_iC_j$ alkoxy, aryl or $C_iC_j$ heteroaryl.
anhydrides (e.g., acetic anhydride or trifluoroacetic anhydride); acid chlorides (e.g., cyanuric chloride, oxalyl chloride, phosphorus oxychloride, thionyl chloride, p-toluenesulfonyl chloride or chlorosulfonyl isocyanate); phosphonium reagents (e.g., phosphorus pentaoxide, phosphorus pentachloride, triphenylphospbine/carbon tetrachloride, triphenylphosphonium ditriflate or triphenylphosphonium dichloride); carbodiimides (e.g., dicyclohexylcarbodiimide or the like) or other dehydrating agents (e.g., aluminum chloride, titanium tetrachloride or ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt). Suitable solvents used in the dehydration step may include from polar aprotic solvents (e.g., dimethylformamide, dimethylsulfoxide, N-methylpyrrolidinone or dimethylacetamide), weakly basic solvents (e.g., pyridine, collidine or the like). The reducing agent used in this step may include metal hydrides (e.g., sodium borohydride, sodium borohydride with cobaltous chloride, sodium borohydride with nickel chloride hexahydrate, lithium aluminum hydride, diborane, disobutyl aluminum hydride or the like), catalytic reducing agents (e.g., palladium on carbon, platinum oxide, or rhodium on alumina or the like). Step a) may also be carried out by reducing a compound of Formula I directly to a compound of Formula III, wherein the reducing agents may include borane complex (e.g., borane in tetrahydrofuran, dimethylsulfoxide, diphenylsulfoxide, dibenzylsulfoxide, 1,4-oxathiane or chloroborohydride in dimethylsulfoxide), metal boride (sodium borohydride with zirconium chloride or titanium chloride, titanium or zirconium borides), or as exemplified in U.S. Patent Nos. 5,344,940; 5,378,804, or 6,030,944.

Step b) can be carried out in presence of an acid in a polar aprotic solvent to give a compound of Formula IV. The acid may be organic acids (e.g., acetic acid, formic acid, camphor sulfonic acid, methane sulfonic acid, trifluoromethanesulfonic acid, monochloroacetic acid, dichloroacetic acid, trichloroacetic acid or trifluoroacetic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid or phosphoric acid), or a mixture thereof. The polar aprotic solvent may include dimethylformamide, dimethylsulfoxide, acetate (e.g., ethyl acetate or the like), nitriles (e.g., acetonitrile, propionitrile, or the like), ketones (e.g., acetone, diethylketone, methyl ethyl ketone or the like) or a mixture thereof.

In one embodiment of the present invention, a compound of Formula I may be treated with acid chloride such as cyanuric chloride, oxalyl chloride, phosphorus
oxychloride or thionyl chloride, suitably cyanuric chloride in dimethylformamide at low temperature to give a compound of Formula II. In another embodiment, the compound of Formula II may be reduced using any reducing agent known to a person of ordinary skill in the art including for example, sodium borohydride in the presence of nickel chloride hexahydrate. In yet another embodiment, the compound of Formula III is reacted with a compound of Formula VI, (e.g., 1-hydroxybenzotriazole) in the presence of trifluoroacetic acid in acetonitrile to give an intermediate of Formula IV.

According to one embodiment, the intermediate of Formula IV may be prepared by reacting a compound of Formula I with a compound of Formula VI to give a compound of Formula IIa,

which upon either reduction or dehydration, followed by a reduction, gives the intermediate of Formula IV.

According to another embodiment, the intermediate of Formula IV may be prepared by dehydrating a compound of Formula I to give a compound of Formula II, which upon reaction with a compound of Formula VI, gives a compound of Formula IIia.
The compound of Formula Ilia can be reduced to give intermediate of Formula IV.

According to yet another embodiment the above process further comprises converting an intermediate of Formula IV to a compound of Formula V (e.g., caspofungm), or pharmaceutically acceptable salts thereof.

According to a preferred embodiment of the present invention Ri is hydrogen and R₂ is C₁₀ alkyl group, preferably -(CH₂)₈CH(CH₃)CH₂CH(CH₃)CH₂CH₂CH₃).

The present invention also provides a process for preparing a compound of Formula V,

![Formula V](image)

and/or pharmaceutically acceptable salts thereof, wherein R₂ is C₁₀ alkyl, C₁₀ alkoxy, C₂-C₁₀ alkenyl, aryl optionally substituted with Rx, wherein Rx is hydrogen, halogen, ammo, hydroxyl, C₁₀ alkyl, C₁₀ alkoxy, aryl or C₅-C₇ heteroaryl.

The process comprises the steps of:

a) reacting a compound of Formula I with cyanuric chloride

![Formula I](image)

to give a compound of Formula II;
In the above process, step a) may be carried out in a solvent including a polar aprotic solvent (e.g., dimethylformamide, dimethylsulfoxide, N-methylpyrrolidine or
dimethylacetamide), weakly basic solvent (e.g., pyridine, collidine or the like), or a mixture thereof.

Step b) may be carried out in presence of one or more reducing agents including metal hydrides (e.g., sodium borohydride, sodium borohydride with cobaltous chloride, sodium borohydride with nickel chloride hexahydrate, aluminum hydride, diborane, diisobutyl aluminum hydride or the like), catalytic reducing agents (e.g., palladium on carbon, platinum oxide, or rhodium on alumina or the like), or a mixture thereof.

Step c) may be carried out in the presence of an acid in a polar aprotic solvent. The acid may include organic acids (e.g., acetic acid, formic acid, camphor sulfonic acid, methane sulfonic acid, trifluoromethanesulfonic acid, monochloroacetic acid, dichloroacetic acid, trichloroacetic acid or trifluoroacetic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid or phosphoric acid), or mixtures thereof. The polar aprotic solvent may include dimethylformamide, dimethylsulfoxide, acetate (e.g., ethyl acetate or the like), nitriles (e.g., acetonitrile, propionitrile or the like), ketones (e.g., acetone, diethylketone, methylethylketone or the like), or mixtures thereof.

Step d) involves reacting a compound of Formula IV with ethylene diamine and optionally converting the compound of Formula V (wherein R1 is hydrogen, R2 - (CH₂)₄CH(CH₃)CH₂(CH₃)₂CH₂CH₃) to a pharmaceutically acceptable salt such as caspofungin diacetate using acetic acid in ethanol.

The present invention further provides a compound having the structure of Formula IV

![Formula IV](image)

and/or pharmaceutically acceptable salts thereof, wherein R1 is hydrogen, C₁-C₄ alkyl, halogen, nitro, hydroxy, C₁-C₄ alkoxy; R₂ is C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₂-C₂₀ alkenyl,
aryl optionally substituted with Rx, wherein Rx is hydrogen, halogen, amino, hydroxyl, Ci-Ci0 alkyl, Ci-Ci0 alkoxy, aryl or C5-C6 heteroaryl.

According one embodiment of the present invention R1 is hydrogen and R2 is Ci-C20 alkyl group, preferably -(CH$_2$)$_8$CH(CH$_3$)CH$_2$CH(CH$_3$)CH$_2$CH$_3$).

Having thus described the invention with the reference to the particular preferred embodiment and illustrative examples, those in art can appreciate the modifications to the invention as described and illustrated that do not depart from the spirit and the scope of the invention as disclosed in the specifications. The examples are set forth to aid the understanding of the invention but are not intended to and should not be construed to limit its scope in any way. Absent statement to the contrary, any combination of the specific embodiment described above are consistent with and are encompassed by the present invention.

Examples

Example 1: Preparation of a Compound of Formula II (wherein R3 is -)

(CH$_2$)$_3$CH(CH$_3$)$_2$CH(CH$_3$)$_2$CH(CH$_3$)$_2$CH$_3$)

Cyanuric chloride (3.11 g; 16.90 mmole) was added to a solution of Pneumocandin B$_9$ (20 g, 18.78 mmole) in dry dimethylformamide (200 mL; water content below 0.10% (w/w)) at about -30°C for about 20 hours. After the completion of reaction, water (200 mL) was added over 15 minutes and the mixture was warmed to room temperature.

The above mixture was slowly poured into vigorously stirred water (2400 mL) at ambient temperature. The suspension was stirred for about 2 hours and filtered. The product was thoroughly washed with water and dried to obtain crude solid (18.4 g), which was further crystallized from solvent mixture of methanol: water: ethyl acetate in the ratio 55: 2.75: 220 mL.

Dry Weight = 10 g
% Yield = 50%
HPLC purity = 95%
Example 2: Preparation of a Compound of Formula III (wherein R₇ is -
(propyl)thio) 

To a solution of compound of Formula II (Example 1; 9.95 g, 9.50 mmole) and nickel chloride hexahydrate (NiCl₂·6H₂O; 9.04 g, 38.03 mmole) in methanol (99.5 mL) sodium borohydride (7.17 g, 190.18 mmole) was added in lots at a temperature range of about -10°C to about 0°C. The reaction mixture was stirred at 0°C until the starting material was around 2%.

After recovery of methanol at room temperature, reaction mixture was poured into ortho phosphoric acid solution in water (7%; 373 mL) at about 0°C. After the addition of tetrahydrofuran (200 mL), the above suspension was stirred at about 0°C to 5°C for 3 to 4 hours. The above solution was saturated with sodium chloride (55 g). The organic layer was separated and mixed with water (300 mL) at a temperature range of about 5°C to 10°C. The pH of the mixture was adjusted to about 6.5 using sodium bicarbonate solution in water (5%; 140 mL). The above suspension was stirred at a temperature range of about 5°C to 10°C for about 1 hour. The solid was isolated by filtration further washed with acetonitrile (50 mL) and dried at room temperature.

Dry Weight = 9.90 g
% Yield = 99
HPLC purity = 88%

Example 3: Preparation of a Compound of Formula IV (wherein R₂ is -
(propyl)thio) 

Commercially available dry 1-hydroxy benzotriazole (3.21 g, 23.76 mmole; Aldrich sigma) was added to a suspension of a compound of Formula III (Example 2; 5.0 g, 4.76 mmole) in dry acetonitrile (140 mL) at around about -10°C. Trifluoroacetic acid (14.0 mL) was added to the reaction mixture at a temperature below about -5°C and reaction mixture was stirred at a temperature range of about -1°C to 0°C until the content of the compound of the Formula III was below 2% in the reaction mixture (ca. 24 hours). Pre-cooled water (0°C; 280 mL) was added to the reaction mixture maintaining the temperature below 0°C. The pH of the above suspension was adjusted to about 6.5 using saturated dipotassium hydrogen phosphate (K₂HPΟ₆·14H₂O; 100 mL) at 0°C. After decanting the
upper clear solution, sticky solid thus obtained was stirred with water (50 ml) at room
temperature for 1 hour and the solid was filtered. The solid was collected and dried at
room temperature.

Dry Weight = 4.36 g

% Yield = 78.5

Example 4: Preparation of Caspofungin

The compound of Formula IV [Example 3; 5.0 g, 4.28 mmole) was added to
ethylene diamine (16 mL) at a temperature range of about 10° C to about 15° C. The
resulting solution was stirred for about 1 hour at 10° C to 15° C. The above solution was
poured into acetonitrile (160 mL) at room temperature and stirred for 30 minutes at room
temperature. After decanting the upper clear solution, fresh acetonitrile (100 mL) was
added and stirred for 30 minutes at room temperature. After decanting the upper clear
solution, water (100 mL) was added and stirred for about 1 hour at room temperature. The
solid was isolated by filtration and washed with water (25 mL).

Dry Weight = 3.7 g

The above solid was purified by reverse phase chromatography using the
acetonitrile and orthophosphoric acid (0.1% in water) as eluent in the ratio 20:80. The rich
cuts were combined and concentrated to provide 0.5 g of compound of Formula V with
97% HPLC purity.

Alternatively, the above solid can be purified by reverse phase chromatography
using acetonitrile and acetic acid (0.1% in water) as eluent in the ratio 20:80.

Example 5: Preparation of Caspofungin Diacetate

The compound of Formula V (Example 4; 0.20 g) was dissolved in ethanol (2.30
mL) and water (0.20 mL) at room temperature. To this solution was added acetic acid
(0.012 mL) at about 10° C followed by slow addition (1 hour) of ethyl acetate (5.0 mL).
After stirring at room temperature for 30 minutes, the solid was filtered under inert
atmosphere to get caspofungin diacetate.

Dry Weight = 0.12 g

% Yield = 60
HPLC purity = 95%

$^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.12 (d, 2H), 6.75 (d, 2H), 4.98 (bs, IH), 4.91 (d, IH), 4.67 (bs, IH), 4.60-4.43 (m, 4H), 4.31 (bs, 3H), 4.26-4.16 (m, 2H), 4.10-3.95 (m, 3H), 3.85-3.73 (m, 2H), 3.10-2.72 (m, 6H), 2.48-2.36 (dd, IH), 2.30-2.15 (m, 3H), 2.11-1.78 (m, 5H), 1.90 (s, 6H), 1.58 (m, 2H), 1.53-1.19 (m, 15H), 1.16 (d, 3H), 1.13-1.00 (m, 2H), 0.98-0.84 (m, 10H).

$^{13}$C NMR (100 MHz, CD$_3$OD): 5180.1, 176.4, 174.2, 173.7, 173.5, 172.7, 172.7, 168.9, 158.5, 133.0, 129.6 (2C), 116.2 (2C), 77.3, 75.6, 75.1, 72.1, 71.3, 70.2, 69.3, 68.2, 64.4, 62.7, 58.4, 57.1, 56.2, 56.1, 51.2, 47.1, 45.9, 43.9, 40.3, 39.0, 38.5, 38.1, 36.9, 35.8, 34.6, 32.9, 31.2, 31.1, 30.8, 30.8, 30.6, 30.3, 30.3, 28.0, 27.1, 24.1, 20.7, 20.2, 19.9, 11.5.

IR (KBr, cm$^{-1}$): 1631, 1547, 1456, 1411, 1236, 1088.

Mass (m/z): 1093.8 (M + H$^+$), 1094.8 (M + 2H$^+$)
WE CLAIM

1. A process for preparing a novel intermediate of Formula IV, or pharmaceutically acceptable salts thereof, wherein \( R_1 \) is hydrogen, \( C_1-C_4 \) alkyl, halogen, nitro, hydroxy, \( C_1-C_4 \) alkoxy; \( R_2 \) is \( C_1-C_2 \) alky, \( C_1-C_3 \) alkoxy, \( C_2-C_3 \) alkenyl, aryl optionally substituted with \( R_x \), wherein \( R_x \) is hydrogen, halogen, amino, hydroxyl, \( C_1-C_{10} \) alkyl, \( C_1-C_{10} \) alkoxy, aryl or \( C_S-C_{10} \) heteroaryl, the process comprising the steps of:

a) converting a compound of Formula I to a compound of Formula III

wherein \( R_2 \) is as defined above;

b) reacting a compound of Formula III with a compound of Formula VI
to give a compound of Formula IV, wherein R₁ and R₂ are as defined above.

2. The process according to claim 1, further comprising the step of treating a compound of Formula I with one or more dehydrating agents in a solvent to give a compound of Formula II.

3. The process according to claim 2, wherein the one or more dehydrating agents comprises from cyanuric chloride, oxalyl chloride, phosphorus oxychloride, thionyl chloride, p-toluenesulfonyl chloride or chlorosulfonyl isocyanate.

4. The process according to claim 3, wherein the dehydrating agent comprises cyanuric chloride.

5. The process according to 2, wherein the solvent comprises a polar aprotic solvent or a weakly basic solvent.

6. The process according to 5, wherein the polar aprotic solvent comprises dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone or dimethylacetamide.

7. The process according to claim 2, further comprises reducing the compound of Formula II in the presence of one or more reducing agents to give a compound of Formula III.

8. The process according to claim 7, wherein the reducing agent comprises sodium borohydride, sodium borohydride with cobaltous chloride, sodium borohydride with nickel chloride hexahydrate, lithium aluminum hydride or diisobutyl aluminum hydride.

9. The process according to claim 8, wherein the reducing agent comprises sodium borohydride with nickel chloride hexahydrate.
10. The process according to claim 1, wherein step b) is carried out in the presence of an acid in a solvent.

11. The process according to claim 10, wherein the acid comprises acetic acid, formic acid, camphor sulfonic acid, methane sulfonic acid, trifluoromethanesulfonic acid, monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, trifluoroacetic acid, hydrochloric acid, sulfuric acid, phosphoric acid, or a mixture thereof.

12. The process according to claim 11, wherein the acid comprises trifluoroacetic acid.

13. The process according to claim 10, wherein the solvent comprises dimethylformamide, dimethylsulfoxide, alkyl acetates, nitriles, ketones, or a mixture thereof.

14. The process according to claim 13, wherein the polar aprotic solvent comprises a acetonitrile or propionitrile.

15. The process according to claim 1, further comprising converting a compound of Formula IV to a compound of Formula V, or pharmaceutically acceptable salts thereof.

16. A process for the preparation of a compound of Formula V,

or a pharmaceutically acceptable salt thereof, wherein R₂ is C₁-C₅ alkyl, C₁-C₅ alkoxy, C₂-C₂₀ alkenyl, aryl optionally substituted with Rx, wherein Rx is hydrogen, halogen, amino, hydroxyl, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryl or C₅-C₆ heteroaryl.

The process comprising the steps of:

a) reacting a compound of Formula I with cyanuric chloride
to give a compound of Formula II,

b) reducing a compound of Formula II to a compound of Formula III,

c) reacting a compound of Formula III with a compound of Formula VI

to give a compound of Formula IV, and
d) converting a compound of Formula IV to a compound of Formula V, or pharmaceutically acceptable salt thereof.

17. The process according to claim 16, wherein step a) is carried out in a solvent comprising a polar aprotic solvent, a weakly basic solvent, or a mixture thereof.

18. The process according to claim 17, wherein the polar aprotic solvent comprises dimethylformamide, dimethylsulfoxide, N-methylpyrrolidine, or dimethylacetamide.

19. The process according to claim 16, wherein step b) is carried out in presence of one or more reducing agents comprising sodium borohydride, sodium borohydride with cobaltous chloride, sodium borohydride with nickel chloride hexahydrate, lithium aluminum hydride, or diisobutyl aluminum hydride.

20. The process according to claim 19, wherein the reducing agent comprises sodium borohydride with nickel chloride hexahydrate.

21. The process according to claim 16, wherein step c) is carried out in presence of an acid comprising from acetic acid, formic acid, camphor sulfonic acid, methane sulfonic acid, trifluoromethanesulfonic acid, monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, trifluoroacetic acid, hydrochloric acid, sulfuric acid, phosphoric acid, or a mixture thereof.

22. The process according to claim 21, wherein the acid comprises trifluoroacetic acid.

23. The process according to claim 16, wherein step c) is carried out in a polar aprotic solvent comprising dimethylformamide, dimethylsulfoxide, alkyl acetates, nitriles, ketones, or a mixture thereof.

24. The process according to claim 23, wherein the polar aprotic solvent comprises acetonitrile, or propionitrile.

25. The process according to claim 16, wherein step d) comprises reacting a compound of Formula IV with ethylene diamine.

26. The process according to claim 16, wherein the compound of Formula V is caspofungin.

27. A compound having the structure of Formula IV
or pharmaceutically acceptable salts thereof, wherein \( R_1 \) is hydrogen, \( C_1-C_4 \) alkyl, halogen, nitro, hydroxy, \( C_i-C_4 \) alkoxy; \( R_2 \) is \( C_i-C_4 \) alkyl, \( C_i-C_2 \) alkoxy, \( C_2-C_2 \) alkynyl, aryl optionally substituted with \( R_x \), wherein \( R_x \) is hydrogen, halogen, amino, hydroxyl, \( C_1-C_1 \) alkyl, \( C_i-Q_o \) alkoxy, aryl, or Cs-C heteroaryl.

28. The compound according to claim 27, wherein \( R_1 \) is hydrogen and \( R_2 \) is - (\( CH_2 \))SCH(CH_3)CH_2CH(CH_3) CH_2CH_3).
A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K7/56 C07K7/54

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)
C07K

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, COMPENDEX, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>W O 96/24613 A1 (MERCK &amp; CO INC [US]; BELYK KEVIN M [US]; BENDER DEAN R [US]; BLACK REG) 15 August 1996 (1996-08-15) abstract; claim 1; compound II claim 15; compounds 1-1</td>
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Further documents are listed in the continuation of Box C

See patent family annex

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Date of the actual completion of the international search

3 March 2010

Date of mailing of the international search report

12/03/2010

Name and mailing address of the ISA/
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Jenn, Thierry

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