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SUPERINDUSTRIA Y COMERCIO

Radicación : 03065425 00000005

Folios: 2

Fecha (MM): 2005-05-04 17:10:42

Trámite : 011 PCT-POTENT 379 FASE INICI 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite :011

Evento :379

Actuación :538

Referencia : Expediente No. 03.065.425

Asunto : Solicitud de patente para
"MODIFICACIÓN CRISTALINA DE UN
DEPSIPÉPTIDO CÍCLICO CON ACTIVIDAD
MEJORADA"

Solicitante : BAYER AKTIENGESELLSCHAFT

Publicada en : la Gaceta No. 546 del 30 de noviembre de 2004

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud PCT Capítulo II en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo correspondiente por valor de \$186.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 31980 del 24 de diciembre de 2004.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, - 4 MAYO 2005
Señora Jefe,

EMILI FERRER
T.P.A. No. 31.929

COLO 00898-841-019-4
DLM/DLM/ID-001859/WPCL0898

N I T. 860.041.367-3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03065425 00000005 Folios: 2
Fecha (MM): 2005-05-04 17:10:42
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176089-2

RECIBO OFICIAL DE CAJA : 05 - 25,695
FECHA : ABRIL 11 DE 2005

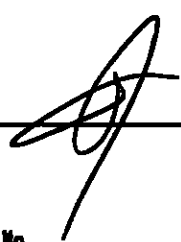
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	40117911	11/04/2005	48,485,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	186,000.00
	TOTAL :	\$ 186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : 
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

010 00698-841-019-4

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 65425

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION –
PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 546,
DE FECHA 30 DE NOVIEMBRE DE 2004, EL TERMINO HABIL SEÑALADO
POR LA LEY EXPIRA EL 24 DE FEBRERO DE 2005.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐ ☐

NO ☒ ☐

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N° **4344**

REFERENCIA	Radicación	03 65425
	Trámite	002
	Evento	001
	Actuación	430
	Folios	008

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 03 65425, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 31-42
- . Ejemplos: folios 43-46
- . Capítulo reivindicatorio estudiado: folios 47-49
- . Se reivindica prioridad, presentada en Alemania el 01.02.01, bajo el número 10104362.7

Objeto de la invención

Según las reivindicaciones 1 a 9 de la presente solicitud, se refiere a un medicamento que contiene el desipeptido de la fórmula (I) como producto sólido en la modificación cristalina I.

Clasificación internacional de patentes A 61 K 31/505

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

Teniendo en cuenta lo anterior, si bien se está reivindicando un medicamento que contiene la modificación (I) de desipeptido, en ninguna parte de la descripción se revelan formulaciones farmacéuticas específicas que permitan reivindicar el medicamento que se pretende proteger.

Favor hacer las aclaraciones y correcciones del caso

Excepciones a la patentabilidad

El art. 20 d de la decisión 486 contempla que *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

El contenido de la reivindicación 9 que trata de "Procedimiento para la lucha contra endoparásitos...", no es patentable.

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

El contenido de las reivindicaciones 6-8, que trata de "Empleo del depsipéptido...", no es patentable, debido a que la legislación vigente únicamente contempla los productos o procedimientos como objeto de patente.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 01.02.01-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	EP 1031565	"Cristal novedoso de depsipéptido y proceso para producirlo"	30.08.00

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 establece que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación EP 1031565 revela la modificación I del compuesto depsipéptido (ver ejemplo 6), se menciona además que el compuesto tiene acción anti parasitaria y que la forma cristalina tiene buenas propiedades de filtración para la producción industrial de medicamentos.

La presente solicitud reivindica un medicamento que contiene la forma I de depsipéptido.

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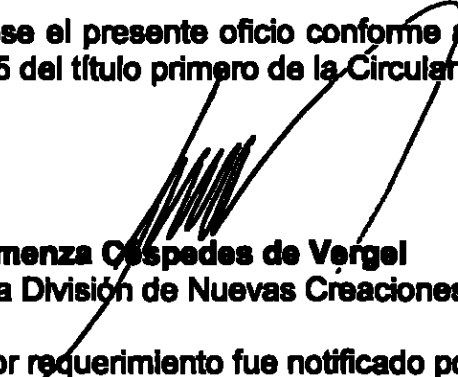
Comparando elemento por elemento, la anterioridad citada ya enseña medicamentos que contienen la modificación I de depsipéptido y, por lo tanto, puede afectar la novedad de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	EP 1031585	1-5	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001


Álex Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 ABR 2007

CONCEPTO TÉCNICO Número 0552	EXAMINADOR TÉCNICO Código 202024
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EUROPEAN PATENT APPLICATION
published in accordance with Art. 158(3) EPC

(43) Date of publication:
30.08.2000 Bulletin 2000/35

(51) Int. Cl.⁷: C07D 273/00

(21) Application number: 98947985.4

(86) International application number:
PCT/JP98/04782

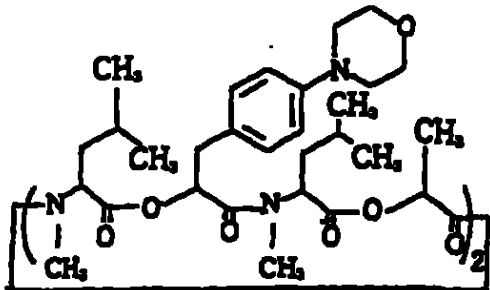
(22) Date of filing: 20.10.1998

(87) International publication number:
WO 99/24412 (20.05.1999 Gazette 1999/20)

(84) Designated Contracting States: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE (30) Priority: 10.11.1997 JP 30753597 (71) Applicant: FUJISAWA PHARMACEUTICAL CO., LTD. Osaka-shi, Osaka-fu 541-8514 (JP) (72) Inventors: • YAMAMURA, Atsushi Osaka-shi, Osaka-fu 532-0002 (JP)	• YAMANISHI, Ryo Tsukuba-shi, Ibaraki-ken 305-0046 (JP) • IKUSHIMA, Muneharu Osaka-shi, Osaka-fu 533-0004 (JP) (74) Representative: Gille Hirbel Struck Naldeln Prop Roon Patentanwalte, Brucknerstrasse 20 40383 Düsseldorf (DE)
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(54) NOVEL CRYSTAL OF DEPSIPEPTIDE DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

(57) Crystal (I) of depsipeptide derivative (IV) represented by the following formula:



of the present invention is characterized in that the crystal (I) substantially has the powdery X-ray diffraction characteristic properties described in Table 1 and has an endothermic peak substantially at 155°C by differential thermal analysis.

Table 1

2 θ value (°)	Relative intensity (%)	2 θ value (°)	Relative intensity (%)	2 θ value (°)	Relative intensity (%)	2 θ value (°)	Relative intensity (%)
5.87	100.0	13.15	19.52	19.88	15.18	28.48	2.33
6.48	0.41	14.58	8.83	20.19	10.19	28.93	1.22
7.36	1.01	15.01	42.59	20.47	8.81	27.86	5.24
7.92	3.12	15.44	81.33	20.84	7.03	28.03	4.70

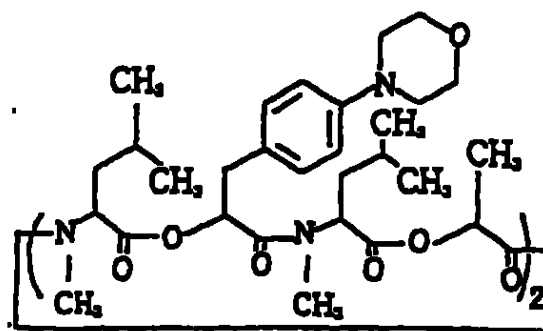
Description

TECHNICAL FIELD

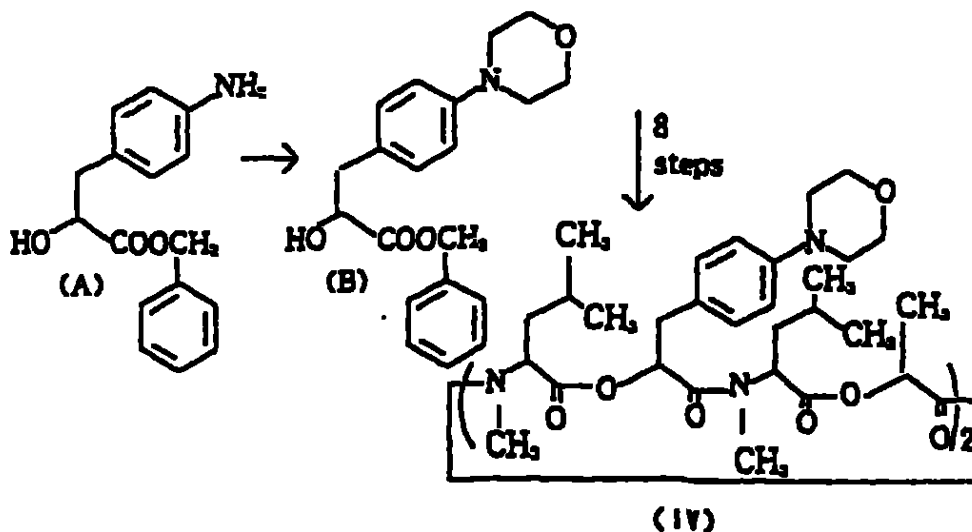
[0001] The present invention relates to novel crystals of depsipeptide derivative (IV) with an antiparasitic activity, and a method for producing the same.

BACKGROUND ART

[0002] The depsipeptide derivative (IV) represented by the following formula has been known as a compound with an excellent antiparasitic activity to animals and human beings, and WO 93/19053 and WO 97/02256 disclose a method for producing the same.



[0003] The former WO 93/19053 specifically discloses a method for producing amorphous depsipeptide derivative (IV) by way of the following processes (nine processes in total).



[0004] According to the method, however, all the intermediate products produced during the course by way of the compound (B) to the objective compound (IV) have basic morpholino groups within the molecules and therefore, they should be handled with precise caution and they are purified by re-crystallization with much difficulty. Because the resulting objective compound (IV) itself is poor in terms of crystallinity, the compound has a variety of disadvantages in terms of production efficiency and handle-ability such that the compound requires purification by column chromatography and the like. Hence, it cannot be said that the method is suitable for industrial scale.



to dissolve the crystal at ambient temperature (25°C). By dropwise adding water (20 ml) to the solution over about 30 minutes, a crystal was deposited. After stirring further for 2 hours at ambient temperature, the deposited crystal was filtered off and washed with a mixture solution (5 ml) of acetone and water (1:2). The resulting crystal was dried at 40°C for 5 hours under reduced pressure to recover the crystal (I) (1.90 g) of the depsipeptide derivative (IV).

Example 2: Production of crystal (I) (No.2)

[0046] The crystal (II) of the depsipeptide derivative (IV) was produced in the same manner as in Example 5 described below. Then, the crystal (II) (1.5 g) was charged to a 50 ml three-necked flask, followed by addition of 3 ml of tetrahydrofuran to dissolve the crystal at ambient temperature (25°C) and subsequent reflux under heating. By cooling the resulting solution under stirring down to around 60°C, isopropyl ether (30 ml) was dropwise added to the resulting solution, followed by further reflux under heating. By cooling the resulting solution under stirring down to around 60°C, seed crystal [crystal (V)] (15 mg) was added to the resulting solution. Then, the solution was cooled down to ambient temperature, followed by stirring at the same temperature for 2 hours. The deposited crystal was filtered off and washed with a mixture solution (1.5 ml) of isopropyl ether and tetrahydrofuran (10:1). The resulting crystal was dried in air at ambient temperature for about one week, to thereby recover the crystal (I) (1.44 g) of the depsipeptide derivative (IV).

Example 3: Production of crystal (I) (No.3)

[0047] The crystal (II) of the depsipeptide derivative (IV) was produced in the same manner as in Example 5 described below. Then, the crystal (1.5g) was charged to a 60 ml three-necked flask, followed by addition of 3 ml of acetonitrile to dissolve the crystal at ambient temperature (25°C) and subsequent reflux under heating. By cooling the resulting solution under stirring down to around 60°C, isopropyl ether (30 ml) was dropwise added to the resulting solution, followed by further reflux under heating. By cooling the resulting solution under stirring down to around 60°C, seed crystal [crystal (V)] (15 mg) was added to the resulting solution. Then, the solution was cooled down to ambient temperature, followed by stirring at the same temperature for 2 hours. The deposited crystal was filtered off and washed with a mixture solution (3 ml) of isopropyl ether and acetone (10:1). The resulting crystal was dried in air at ambient temperature for about one week, to thereby recover the crystal (I) (1.31 g) of the depsipeptide derivative (IV).

Example 4: Production of crystal (I) (No.4)

[0048] The crystal (II) of the depsipeptide derivative (IV) was produced in the same manner as in Example 5 described below. Then, the crystal (1.5 g) was charged to a 50 ml three-necked flask, followed by addition of 3 ml of acetonitrile to dissolve the crystal at ambient temperature (25°C) and subsequent reflux under heating. By cooling the resulting solution under stirring down to around 50°C, isopropyl ether (30 ml) was dropwise added to the resulting solution, followed by further reflux under heating. By cooling the resulting solution under stirring down to around 50°C, seed crystal [crystal (V)] (15 mg) was added to the resulting solution. Then, the solution was cooled down to ambient temperature, followed by stirring at the same temperature for 2 hours. The deposited crystal was filtered off and washed with a mixture solution (3 ml) of isopropyl ether and acetone (10:1). The resulting crystal was dried in air at ambient temperature for about one week, to thereby recover the crystal (I) (1.41 g) of the depsipeptide derivative (IV).

Example 5: Production of crystal (II)

[0049] The crystal (I) (15.0 g) of the depsipeptide derivative (IV) as recovered in Example 1 was charged to a 300 ml three-necked flask, followed by addition of 30 ml of ethanol to dissolve the crystal while refluxing under heating. After removing ethanol (15 ml) while refluxing under heating, the resulting solution was once cooled down to 50°C. Subsequently by adding isopropyl ether (300 ml) to the solution while gradually cooling the solution down to ambient temperature (25°C), a crystal was deposited. By stirring further the solution at ambient temperature for one hour, the deposited crystal was filtered off and washed with isopropyl ether (5 ml). The resulting crystal was dried at 60°C for 4 hours under reduced pressure and further dried in air at ambient temperature for one day, to recover the crystal (II) (12.0 g) of the depsipeptide derivative (IV).

Example 6: Production of crystal (III)

[0050] The crystal (II) (40 g) of the depsipeptide derivative (IV) recovered in the Example 5 above was charged to a one liter three-necked flask, followed by addition of 80 ml of ethyl acetate to subsequently heat the resulting mixture at 40°C and dissolve the mixture therein under stirring. After subsequently refluxing the resulting solution under heating, the resulting solution was cooled down to 80°C, followed by addition of 200 ml of isopropyl ether to deposit a crystal.

Subsequently, isopropyl ether (600 ml) was dropwise added to the resulting mixture over at 70 °C about 35 minutes, and thereafter, the mixture was stirred at the same temperature for 20 minutes. After cooling the mixture under stirring down to ambient temperature (27 °C), the mixture was further stirred at the temperature (27 °C) for 4 hours, to filter off the deposited crystal. The resulting crystal was dried in air for about one week, whereby the crystal (II) (37.8 g) of the decapeptide derivative (IV) was recovered.

Experimental Example 1

[0051] The crystals (I), (II) and (III) of the decapeptide derivative (IV), thus recovered in the aforementioned manners, were examined about the filtration properties during crystallization, the specific volume and water content, by using the prior art crystal (V) for comparison.

[0052] The filtration properties during crystallization were evaluated on the following standards under observation with the naked eye.

- ⊕ : very great filtration properties
- : good filtration properties
- Δ : poor filtration properties
- X : very poor filtration properties

[0053] As to the specific volume, each crystal (5 g) was put in a 20 ml measuring cylinder, followed by tapping, and the value (ml/g) of a volume not any more decreased even after tapping was measured.

[0054] As to the water content, additionally, each crystal was left to stand at ambient temperature until its weight reached constant value, wherein an amount of water containing in the crystal was measured in %.

[0055] These results are collectively shown in Table 6.

Table 6

	Filtration property during crystallization	Specific volume (ml/g)	Water content (%)
Crystal (I)	X	12.5/5.0	3.16
Crystal (II)	⊕	8.2/5.0	0.98
Crystal (III)	○	16.2/5.0	0.20
Prior art Crystal (V)	X	16.0/5.0	2.45

[0056] The following were discussed on the basis of the Table. Herein the "good filtration properties during crystallization" and "small specific volume" herein function as indicators of production efficiency.

[0057] Firstly, the prior art crystal (V) has poor filtration properties during crystallization and a large specific volume, so the production efficiency thereof is markedly reduced in such manners that the number of the batches thereof during drying process is increased and that the drying time thereof is also prolonged and the like. Not shown in the Table, furthermore, the prior art crystal (V) has poor fluidity (large adhesion properties). Therefore, the crystal readily adheres to a conical drying machine during the course of discharge it from the machine, resulting in a prominent reduction of the yield because of such adhesion.

[0058] On the other hand, the crystal (II) of the present invention has great filtration properties during crystallization and a small specific volume, thereby resulting in the improvement of the production efficiency. In addition, as the crystal (II) has great fluidity, the crystal loss due to the adhesion to machines during the production process is reduced, resulting in increases the yield of the crystal.

[0059] Additionally, the crystal (I) of the present invention has such a small specific volume that the production efficiency can be improved.

[0060] Furthermore, the crystal (III) of the present invention has good filtration properties during crystallization, so the production efficiency thereof can be increased, compared with the prior art crystal (V).

INDUSTRIAL APPLICABILITY

[0061] Because the novel crystals (I), (II) and (III) of the decapeptide derivative (IV) in accordance with the present invention are composed in above fashion, the yield of the crystals and production efficiency can be increased highly compared with the prior art crystal (V).

05/1

Table 2

	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)
5	4.79	35.88	13.59	47.83	19.10	47.83	25.00	8.48
	4.89	35.50	14.20	32.70	19.51	32.02	25.36	6.63
10	5.58	14.69	14.84	30.02	19.91	17.57	26.06	4.65
	7.00	1.16	15.75	41.82	21.39	23.82	27.31	8.61
	9.09	8.79	15.56	52.50	22.02	13.34	27.95	8.61
	9.69	5.45	16.26	66.32	22.54	14.01	29.06	6.48
15	10.52	100.0	16.63	40.67	22.84	16.59	29.80	3.12
	10.85	31.10	17.07	40.29	23.16	17.32	30.36	3.79
	11.49	7.10	18.34	32.70	23.82	26.21	31.75	2.07
20	12.40	11.86	18.73	24.40	24.44	9.51		

4. A method for producing the crystal (II) of the depsipeptide derivative (IV), comprising adding the crystal (I) of the depsipeptide derivative (IV) to ethanol to dissolve the depsipeptide derivative (IV) therein and subsequently further adding isopropyl ether to the resulting mixture for crystallization.
5. Crystal (III) of depsipeptide derivative (IV), characterized in that the crystal (III) substantially has the powdery X-ray diffraction characteristic properties described in Table 3 and has an endothermic peak substantially at 194 °C by differential thermal analysis.

Table 3

	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)	2 θ value (°)	Relative Intensity (%)
35	6.02	100.0	12.17	30.33	19.04	14.75	26.07	3.63
	6.20	87.04	13.20	5.81	19.44	7.76	26.73	2.76
	6.30	50.17	14.45	16.17	19.96	10.99	28.19	2.66
	6.82	2.60	15.19	19.22	21.21	11.72	29.13	1.61
40	8.08	1.22	16.10	19.22	21.99	17.36	30.05	1.22
	9.45	2.32	16.70	26.47	22.16	11.97	30.61	1.26
	9.64	1.60	16.87	24.10	22.66	8.40	31.27	0.76
45	10.48	2.10	17.14	6.62	22.99	9.94		
	12.03	20.51	18.45	7.36	24.26	10.52		

6. A method for producing the crystal (II) of the depsipeptide derivative (IV), comprising adding the crystal (II) of the depsipeptide derivative (IV) to ethyl acetate to dissolve the crystal (II) of the depsipeptide derivative (IV) therein and subsequently further adding isopropyl ether to the resulting mixture for crystallization.

