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(51) 。 Int. Cl. ⁷
A61K 7/06

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(43)

2002 - 0039528
2002 05 27

(21) 10 - 2000 - 0069393
(22) 2000 11 22

(71)

20

(72)

| | | |
|---------|----------|------|
| 462 - 5 | 106 | 102 |
| 462 - 5 | 107 | 1106 |
| | 106 | 404 |
| 3 | 270 - 27 | |
| | 1 | 105 |
| 386 - 4 | 1 | 402 |
| | 1 | 103 |
| | 1 | 106 |
| | 110 | 1405 |
| | 102 | 1001 |

(74)

:

(54) 7 -

(Cyclosporin)

가

가

7 -

(Cyclosporin 7 - Thioamide)

, ,

(cyclosporin)

7 -

(Cyclosporin 7 - Thioamide)

atagen),
100

10
(telogen)

15

3 6

가

(anagen),

(c
50

가

가

가

FDA

가

가

가

가

(dermal papilla)

(VEGF; vascular endothelial growth factor)

가

(

Br. J. of Dermatol., 1998; 138; 407 411)

(Skin Pharmacol., 1996; 9; 3 8)

(J. Invest. Dermatol., 1989; 92; 315 320)

가

(Merck)

(Propecia)

(finasteride)

. 1997

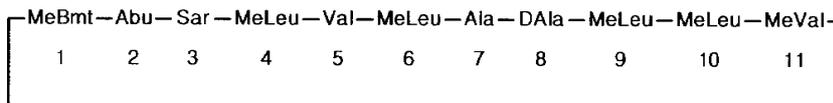
12

1mg

FDA

(J. Am. Acad. Dermatol., 1998
; 39; 578 589). 가

(Advances in Pharmacol., 199
6; 35; 114 246 Drug Safety, 1994; 10; 310 317).
(N - methyl amino acid) 8 D - (D - alanine) 11
1



MeBmt N - - (4R) - 4 - [(E) - 2 -] - 4 - - L - (N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine)

Abu L - (L - aminobutyric acid)

Sar (Sarcosine)

MeLeu N - - L - (N - methyl - L - leucine)

Val L - (L - valine)

Ala L - (L - alanine)

DAla D - (D - alanine)

MeVal N - - L - (N - methyl - L - Valine)

A L - (L - configuration)
1 MeBmt 1 MeVal (N - - L - (N - methyl
- L - Valine) 11 A Z
(Helv. Chim. Acta, 1987;70;13 - 36). A 2 Abu(L -
, L - aminobutyric acid) (L - alanine) B
C [Ala]² [Thr]²

4, 7, 4 7 (sulfur) 3
 7 - (Cyclosporin 7 - Thioamide, [⁷ ⁸CS - NH]),
 4 - (Cyclosporin 4 - Thioamide, [⁴ ⁵CS - NH]), 4,7 -
 () (Cyclosporin 4,7 - Bis(thioamide), [⁴ ⁵CS - NH; ⁷ ⁸CS - NH]) (Helv. Chim. A
 cta 1991, 74; 1953 - 1990, J. Org. Chem. 1993, 58;673 - 677, J Org. Chem. 1994, 59;7249 - 7258)

가 () 가
 (Arch, Dermatol. Res., 1996; 288; 408 410),
 (J. Am. Acad. Dermatol., 1990; 22; 242 250), (J. Am. Acad. Dermatol., 1990; 22;
 251 253 Skin Pharmacol., 1994; 7; 101 104) (Cli
 n. Lab. Invest., 1995; 190; 192 196 Am. J. Pathol., 1997; 150; 1433 1441)
 100

가

, 60 - 243008 , 62 - 19512 , 62 - 19513 8 가
 (0414632B1), (PCT 93/17039),
 (PCT WO 00/51558)
 , 5,807,820 2,218,334A 가

7 (sulfur) 가 4, 7, 4
 (sulfur)
 (Helv. Chim. Acta 1991, 74; 1953 - 1990, J. Org. Chem. 1993, 58;673 - 677, J Org.
 Chem. 1994, 59;7249 - 7258). 4, 7, 4 7
 (sulfur) 3 7 - (Cyclosporin 7 - Thioamide,
 [⁷ ⁸CS - NH]), 4 - (Cyclosporin 4 - Thioamide), 4,7
 - () (Cyclosporin 4,7 - Bis(thioamide)) 가 가
 7 - (Cyclosporin 7 - Thioamide) ([⁷ ⁸CS - NH]),
 C₆₂ H₁₁₁ N₁₁ O₁₁ S) 가

7 - (Cyclosporin 7 - Thioamide, [⁷ ⁸CS - NH]) 1 , C₆₂ H₁₁₁
 N₁₁ O₁₁ S)

1

A-B-C-D-E-F-Alathio-G-H-I-J



A N - (4R) - 4 - [(E) - 2 -] - 4 - - L - {MeBmt, N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine), (2S,3R,4R,6E) - 3 - - 4 - - 2 - () - 6 - { (2S,3R,4R,6E) - 3 - sulfhydryl - 4 - methyl - 2 - (methylamino) - 6 - octenoic acid} (2S,4R,6E) - 3 - - 4 - - 2 - () - 6 - {(2S,4R,6E) - 3 - oxo - 4 - methyl - 2 - (methylamino) - 6 - octenoic acid}

B L - (Abu, L - aminobutyric acid), L - (Ala, L - alanine), L - (Thr, L - threonine), L - (Val, L - valine), L - (Nva, L - norvaline),

C (Sarcosine), D - {(D) - methylalanine, (D) - N(CH₃) - CH(CH₃) - CO - }, D - 2 - () - 4 - {(D) - 2 - (Methylamino) pent - 4 - enoyl, (D) - N(CH₃) - CH(CH₂CHCH₂) - CO - }, D - 2 - () - 4 - {(D) - 2 - (Methylamino)pent - 4 - ynoyl, (D) - N(CH₃) - CH(CH₂CCH) - CO),

D - {(D) - Sar(2 - SMe), (D) - N(CH₃) - CH(SCH₃) - CO - },

D N - - L - (N - methyl L - leucine), N - L - (- hydroxy N - methyl L - leucine) L - (L - valine),

E L - (L - valine) L - (L - norvaline),

F N - - L - (N - methyl - L - leucine) N - L - (- hydroxy N - methyl L - leucine) L - (L - Leucine),

Alathio L - {L - alanine thioamide, [⁷ ⁸CS - NH], NH - CHCH₃ - CS - },

G D - (D - alanine) D - (D - serine),

H N - L - (N - methyl L - leucine), N - - L - (- hydroxy - N - methyl L - leucine) L - (L - leucine),

I N - L - (N - methyl L - leucine), N - L - (- hydroxy - N - methyl - L - leucine) L - (L - leucine),

J N - - L - (N - methyl - L - valine) L - (L - valine).

1 2 가 7 -
(Cyclosporin 7 - Thioamide)

2

MeBmt-A'-B'-C'-D'-E'-Alathio-F'-G'-H'-MeVal



MeBmt N - (4R) - 4 - [(E) - 2 -] - 4 - - L - { N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine) ,

A' L - (Abu, L - aminobutyric acid), L - (Ala, L - alanine), L - (Thr , L - threonine), L - (Val, L - valine),

L - (Nva, L - norvaline)

B' (Sarcosine), D - { (D) - methylalanine, (D) - N(CH₃) - CH(CH₃) - CO - }, D - 2 - () - 4 - { (D) - 2 - (Methylamino) pent - 4 - enoyl, (D) - N(CH₃) - CH(CH₂CHCH₂) - CO - }, D - 2 - () - 4 - { (D) - 2 - (Methylamino)pent - 4 - ynoyl, (D) - N(CH₃) - CH(CH₂CCH) - CO), D - { (D) - Sar(2 - SMe), (D) - N(CH₃) - CH(SCH₃) - CO -) ,

C' N - - L - (N - methyl - L - leucine), N - - L - (- hydroxy - N - methyl L - I eucine) L - (L - valine) ,

D' L - (L - valine) L - (L - norvaline) ,

E' N - - L - (N - methyl - L - leucine) N - L - (- hydroxy N - methyl L - leuci ne) L - (L - Leucine) ,

Alathio L - { L - alanine thioamide, [⁷ ⁸CS - NH] , NH - CHCH₃ - CS - } ,

F' D - (D - alanine) D - (D - serine),

G' N - L - (N - methyl L - leucine), N - - L - (- hydroxy - N - methyl L - I eucine) L - (L - leucine) ,

H' N - L - (N - methyl L - leucine), N - L - (- hydroxy - N - methyl - L - leu cine) L - (L - leucine) ,

1 3 가 7 -
(Cyclosporin 7 - Thioamide)

3

MeBmt-A''-Sar-MeLeu-Val-B''-Alathio-DAla-C''-D''-MeVal



MeBmt N - (4R) - 4 - [(E) - 2 -] - 4 - - L - {N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine} ,

A' ' L - (Abu, L - aminobutyric acid), L - (Ala, L - alanine), L - (Thr, L - threonine), L - (Val, L - valine), L - (Nva, L - norvaline) ,

Sar (Sarcosine) ,

MeLeu N - - L - (N - methyl - L - leucine) ,

Val L - (L - valine) ,

B' ' N - - L - (N - methyl - L - leucine), L - (L - leucine)

Alathio L - {L - alanine thioamide, [⁷ ⁸CS - NH], NH - CHCH₃ - CS - } ,

DAla D - (D - alanine) ,

C' ' N - - L - (N - methyl - L - leucine), L - (L - leucine)

D' ' N - - L - (N - methyl - L - leucine), L - (L - leucine)

MeVal N - - L - (N - methyl - L - valine) .

1 가 7 - (Cyclosporin 7 - Thioamide)

* A 7 - (Cyclosporin A 7 - Thioamide) [⁷ ⁸CS - NH] A

* B 7 - (Cyclosporin B 7 - Thioamide) [Ala] ² - [⁷ ⁸CS - NH]

* C 7 - (Cyclosporin C 7 - Thioamide) [Thr] ² - [⁷ ⁸CS - NH]

* D 7 - (Cyclosporin D 7 - Thioamide) [Val] ² - [⁷ ⁸CS - NH]

* G 7 - (Cyclosporin G 7 - Thioamide) [Nva] ² - [⁷ ⁸CS - NH]

* I 7 - (Cyclosporin I 7 - Thioamide) [Val] ² - [⁷ ⁸CS - NH] - [Leu] ¹⁰

* M 7 - (Cyclosporin M 7 - Thioamide) [Nva] ² - [Nva] ⁵ - [⁷ ⁸CS - NH] -

* N 7 - (Cyclosporin N 7 - Thioamide) [Nva] ² - [⁷ ⁸CS - NH] - [Leu] ¹⁰

* O 7 - (Cyclosporin O 7 - Thioamide) [Nva] ² - [⁷ ⁸CS - NH]

- * T 7 - (Cyclosporin T 7 - Thioamide) [⁷ ⁸CS - NH] - [Leu] ¹⁰
- * U 7 - (Cyclosporin U 7 - Thioamide) [Leu] ⁶ - [⁷ ⁸CS - NH]
- * X 7 - (Cyclosporin X 7 - Thioamide) [Nva] ² - [⁷ ⁸CS - NH] - [Leu]⁹
- * Y 7 - (Cyclosporin Y 7 - Thioamide) [Nva] ² - [Leu]⁶ - [⁷ ⁸CS - NH]

Ala L - (L - alanine), Thr L - (L - threonine), Val L - (L - valine), Nva L - (L - norvaline), Leu L - (L - leucine), [⁷ ⁸CS - NH] L - {L - alanine thioamide, NH - CHCH₃ - CS - } . A Z Abu (L - aminobutyric acid) (L - alanine) A₂ B [Ala]² [Thr]² (Helv. Chim. Acta, 1987;70;13 - 36). , (Cyclosporin 7 - Thioamide) 7 (C₆₂ H₁₁₁ N₁₁ O₁₁ S) (sulfur) { [⁷ ⁸CS - NH] , NH - CHCH₃ - CS - }

, 7 - (Cyclosporin 7 - Thioamide) , , ,

7 - (Cyclosporin 7 - Thioamide) .

1 1

1. A (Acetylcyclosporin A)

A(cyclosporin A)(2.4g, 2.0mmol) 4 - (4 - (dimethylamino)pyridine)(0.24g, 2.0mmol) 20mL (pyridine) 20mL (acetic anhydride) 18 (MgSO₄) 100ml (methylene chloride) 가 2.3g .

2 - 1. A 4,7 - () (Acetylcyclosporin A 4,7 - Bis(thioamide))

A(1.8g, 1.45mmol) (xylene)(50mL) 130 가 (Lawesson reagent)(0.35g, 0.87mmol) 가 . 130 30 (MgSO₄) 100ml (methylene chloride) 가 (0.57g) . (M)

2 - 2. A 4 - (Acetylcyclosporin A 4 - thioamide)

A(1.8g, 1.45mmol) (xylene)(50mL) 130 가 (Lawesson reagent)(0.35g, 0.87mmol) 가 . 130 30 (MgSO₄) 100ml (methylene chloride) 가 (0.08g) . (M)

3 - 1 A 4,7 - () (Cyclosporin A 4,7 - Bis (thioamide)

32g, 0.25mmol) (MeOH) (50mL) 0.5M (NaOMe in MeOH) (20mL, 10 mmol) 가 (Acetic acid) (MgSO₄)
100ml (methylene chloride) 가 HPLC 0.27g

3 - 2 A 4 - (Cyclosporin A 4 - Thioamide)

(MeOH) (50mL) 0.5 M (Acetic acid) (NaOMe in MeOH) (20mL, 10mmol) 가 4 (methylene chloride) 가 HPLC (MgSO₄) 100ml 0.16g

1. B 7 - (Cyclosporin B 7 - Thioamide) 1. B 7 - (Cyclosporin B 7 - Thioamide)

1. B (Acetylcyclosporin B)

B (cyclosporin B) (2.4g) 4 - (4 - (dimethylamino)pyridine) (0.24g, 2.0mmol) 20mL (pyridine) 20mL (acetic anhydride) 18 (MgSO₄) 100ml (methylene chloride) 가 2.3g

2. B 7 - (Acetylcyclosporin B 7 - thioamide)

B (1.8g) (xylene) (50mL) 130 가 (Lawesson reagent) (0.35g, 0.87mmol) 가 130 30 (MgSO₄) 100ml (methylene chloride) 가 (0.19g)

3. B 7 - (Cyclosporin B 7 - Thioamide)

(MeOH) (50mL) 0.5M (Acetic acid) (NaOMe in MeOH) (20mL, 10mmol) 가 4 (methylene chloride) 가 HPLC (MgSO₄) 100ml 0.17g

2. C 7 - (Cyclosporin C 7 - Thioamide) 2. C 7 - (Cyclosporin C 7 - Thioamide)

1. C (Acetylcyclosporin C)

C (cyclosporin C) (2.4g) 4 - (4 - (dimethylamino)pyridine) (0.24g, 2.0mmol) 20mL (pyridine) 20mL (acetic anhydride) 18 (MgSO₄) 100ml (methylene chloride) 가 2.1g

2. C 7 - (Acetylcyclosporin C 7 - thioamide)
- C (1.8g) (xylene) (50mL) 130 가 (Lawesson
 reagent) (0.35g, 0.87mmol) 가 . 130 30 .
 100ml (methylene chloride) 가 (MgSO₄)
 (0.16g) .
3. C 7 - (Cyclosporin C 7 - Thioamide)
- C 7 - (Acetylcyclosporin C 7 - thioamide) (0.2g, 0.16mmol)
 (MeOH) (50mL) 0.5M (NaOMe in MeOH) (20mL, 10mmol) 가
 4 (Acetic acid) . 100ml
 (methylene chloride) 가 (MgSO₄)
 HPLC 0.15g .
3. D 7 - (Cyclosporin D 7 - Thioamide) 3. D 7 -
 (Cyclosporin D 7 - Thioamide)
1. D (Acetylcyclosporin D)
- D (cyclosporin D) (2.4g) 4 - (4 - (dimethylamino)pyridine) (0.24g, 2.0mm
 ol) 20mL (pyridine) 20mL (acetic anhydride) 18
 . 100ml (methylene chloride) 가 (MgS
 O₄) 2.1g .
2. D 7 - (Acetylcyclosporin D 7 - thioamide)
- D (1.6g) (xylene) (50mL) 130 가 (Lawesson
 reagent) (0.35g, 0.87mmol) 가 . 130 30 .
 100ml (methylene chloride) 가 (MgSO₄)
 (0.18g) .
3. D 7 - (Cyclosporin D 7 - Thioamide)
- D 7 - (Acetylcyclosporin D 7 - thioamide) (0.2g)
 (MeOH) (50mL) 0.5M (NaOMe in MeOH) (20mL, 10mmol) 가 4
 (Acetic acid) . 100ml (methyle
 ne chloride) 가 (MgSO₄)
 HPLC 0.16g .
4. G 7 - (Cyclosporin G 7 - Thioamide) 4. G 7 -
 (Cyclosporin G 7 - Thioamide)
1. G (Acetylcyclosporin G)
- G (cyclosporin G) (2.4g) 4 - (4 - (dimethylamino)pyridine) (0.24g, 2.0mm
 ol) 20mL (pyridine) 20mL (acetic anhydride) 18
 . 100ml (methylene chloride) 가 (MgS
 O₄) 2.1g .

2. G 7 - (Acetylcyclosporin G 7 - thioamide)
 reagent) (0.35g, 0.87mmol) G (1.8g) (xylene) (50mL) 130 가 (Lawesson
 100ml (methylene chloride) 가 30 (MgSO₄)
 (0.15g)
3. G 7 - (Cyclosporin G 7 - Thioamide)
 (MeOH) (50mL) G 7 - (Acetylcyclosporin G 7 - thioamide) (0.2g)
 0.5M (NaOMe in MeOH) (20mL, 10mmol) 가 4
 (Acetic acid) (MgSO₄) 100ml (methylene chloride) 가
 HPLC 0.15g
5. I 7 - (Cyclosporin I 7 - Thioamide) 5. I 7 -
 (Cyclosporin I 7 - Thioamide)
 1 I 7 - (Cyclosporin I 7 - Thioamide)
6. M 7 - (Cyclosporin M 7 - Thioamide) 6. M
 7 - (Cyclosporin M 7 - Thioamide)
 1 M 7 - (Cyclosporin M 7 - Thioamide)
7. N 7 - (Cyclosporin N 7 - Thioamide) 7. N 7
 - (Cyclosporin N 7 - Thioamide)
 1 N 7 - (Cyclosporin N 7 - Thioamide)
8. O 7 - (Cyclosporin O 7 - Thioamide) 8. O 7
 - (Cyclosporin O 7 - Thioamide)
 1 O 7 - (Cyclosporin O 7 - Thioamide)
9. T 7 - (Cyclosporin T 7 - Thioamide) 9. T 7
 - (Cyclosporin T 7 - Thioamide)
 1 T 7 - (Cyclosporin T 7 - Thioamide)
10. U 7 - (Cyclosporin U 7 - Thioamide) 10.
 U 7 - (Cyclosporin U 7 - Thioamide)
 1 U 7 - (Cyclosporin U 7 - Thioamide)

11. X 7 - (Cyclosporin X 7 - Thioamide) 11. X
 7 - (Cyclosporin X 7 - Thioamide)

1 , X 7 - (Cyclosporin X 7 - Thioamide)

12. Y 7 - (Cyclosporin Y 7 - Thioamide) 12. Y
 7 - (Cyclosporin Y 7 - Thioamide)

1 , Y 7 - (Cyclosporin Y 7 - Thioamide)

1 C 7 - (Cyclosporin C 7 - Thioamide)) 1
 C 7 - (Cyclosporin C 7 - Thioamide))

1 3 가
 1 가

1 1 0.1% A

[1]

| | 1 | 2 | 3 |
|----------|--------|------|------|
| 1. | 40.0 | 40.0 | 40.0 |
| 2. C 7 - | 0.1 | 1.0 | 8.0 |
| 3. | 0.1 | 0.1 | 0.1 |
| 4. | 0.3 | 0.3 | 0.3 |
| 5. - | 0.3 | 0.3 | 0.3 |
| 6. 20 | 0.5 | 0.5 | 0.5 |
| 7. | | | |
| 8. | | | |
| 9. | 100 %가 | 가 | |

2 G 7 - (Cyclosporin G 7 - Thioamide)) 2
 G 7 - (Cyclosporin G 7 - Thioamide))

2 3 가
 1 가

2 1 0.1% A

[2]

| | 1 | 2 | 3 |
|----------|--------|------|------|
| 1. | 40.0 | 40.0 | 40.0 |
| 2. G 7 - | 0.1 | 1.0 | 8.0 |
| 3. | 0.1 | 0.1 | 0.1 |
| 4. | 0.3 | 0.3 | 0.3 |
| 5. - | 0.3 | 0.3 | 0.3 |
| 6. 20 | 0.5 | 0.5 | 0.5 |
| 7. | | | |
| 8. | | | |
| 9. | 100 %가 | 가 | |

3. C 7 -

3. C 7 -

3 3 가 80 가 .
 가 . 100 % 가 .
 1 가 3 C 7 - 0.1% 0.
 1% A .

[3]

| | | | |
|----------|--------|-------|------|
| 1. | 5.0 | 5.0 | 5.0 |
| 2. | 5.5 | 5.5 | 5.5 |
| 3. | 5.5 | 5.5 | 5.5 |
| 4. | 3.0 | 3.0 | 3.0 |
| 5. | 3.0 | 3.0 | 3.0 |
| 6. | 0.3 | 0.3 | 0.3 |
| 7. C 7 - | 0.1 | 1.0 | 8.0 |
| 8. | 7.0 | 7.0 | 7.0 |
| 9. | 20.0 | 20.0 | 20.0 |
| 10. | 5.0 | 5.0 | 5.0 |
| 11. | 1 - 11 | 100%가 | 가 |
| 12. | | | |
| 13. | | | |

4. G 7 -

4. G 7 -

4 3 가 80 가 .
 가 . 100 % 가 .
 1 가 4 G 7 - 0.1% 0.
 1% A .

[4]

| | | | | |
|-----|-------|--------|-------|------|
| 1. | | 5.0 | 5.0 | 5.0 |
| 2. | | 5.5 | 5.5 | 5.5 |
| 3. | | 5.5 | 5.5 | 5.5 |
| 4. | | 3.0 | 3.0 | 3.0 |
| 5. | | 3.0 | 3.0 | 3.0 |
| 6. | | 0.3 | 0.3 | 0.3 |
| 7. | G 7 - | 0.1 | 1.0 | 8.0 |
| 8. | | 7.0 | 7.0 | 7.0 |
| 9. | | 20.0 | 20.0 | 20.0 |
| 10. | | 5.0 | 5.0 | 5.0 |
| 11. | | 1 - 11 | 100%가 | 가 |
| 12. | | | | |
| 13. | | | | |

5. C 7 -

5. C 7 -

5 3 가 , , 가 가 100 %

[5]

| | | | | |
|--------|-------|--------|------|------|
| 1. POE | (30%) | 40.0 | 40.0 | 40.0 |
| 2. | | 3.0 | 3.0 | 3.0 |
| 3. | | 2.0 | 2.0 | 2.0 |
| 4. | | 0.2 | 0.2 | 0.2 |
| 5. | | 2.0 | 2.0 | 2.0 |
| 6. | C 7 - | 1.0 | 3.0 | 10.0 |
| 7. | | 0.3 | 0.3 | 0.3 |
| 8. - | | 0.3 | 0.3 | 0.3 |
| 9. | | | | |
| 10. | | | | |
| | | 100 %가 | 가 | |

6. G 7 -

6. G 7 -

6 3 가 , , 가 가 100 %

[6]

| | | | |
|--------------|-------|------|------|
| 1. POE (30%) | 40.0 | 40.0 | 40.0 |
| 2. | 3.0 | 3.0 | 3.0 |
| 3. | 2.0 | 2.0 | 2.0 |
| 4. | 0.2 | 0.2 | 0.2 |
| 5. | 2.0 | 2.0 | 2.0 |
| 6. G 7 - | 1.0 | 3.0 | 10.0 |
| 7. | 0.3 | 0.3 | 0.3 |
| 8. - | 0.3 | 0.3 | 0.3 |
| 9. | | | |
| 10. | | | |
| | 100 % | 가 | 가 |

7. C 7 -

7. C 7 -

7 3 가
80
가

80 가
100 % 가

[7]

| | | | |
|----------|------|------|------|
| 1. | 3.0 | 3.0 | 3.0 |
| 2. | 2.0 | 2.0 | 3.0 |
| 3. | 10.0 | 10.0 | 10.0 |
| 4 C 7 - | 1.0 | 5.0 | 10.0 |
| 5. | 2.0 | 2.0 | 2.0 |
| 6. (25%) | 8.0 | 8.0 | 8.0 |
| 7. | 0.2 | 0.2 | 0.2 |
| 8. | 0.3 | 0.3 | 0.3 |
| 9. - | 0.3 | 0.3 | 0.3 |
| 10. | 100% | 가 | 가 |
| 11. | | | |
| 12. | | | |

8. G 7 -

8. G 7 -

8 3 가
80
가

80 가
100 % 가

1.

가 1 7 - (Cyclosporin 7 - Thioamide)
:

1

A-B-C-D-E-F-Alathio-G-H-I-J



A N - (4R) - 4 - [(E) - 2 -] - 4 - - L - { MeBmt, N - methyl - (4R) - 4 - [(E) - 2 - buteny
I] - 4 - methyl - L - threonine), (2S,3R,4R,6E) - 3 - - 4 - - 2 - () - 6 - { (2S,3
R,4R,6E) - 3 - sulfhydryl - 4 - methyl - 2 - (methylamino) - 6 - octenoic acid} (2S,4R,6E) - 3 - - 4 -
- 2 - () - 6 - { (2S,4R,6E) - 3 - oxo - 4 - methyl - 2 - (methylamino) - 6 - octenoic acid} ,

B L - (Ala, L - alanine), L - (Thr , L - threonine), L - (Val, L - valine), L -
(Nva, L - norvaline) ,

C (Sarcosine), D - { (D) - methylalanine, (D) - N(CH₃) - CH(CH₃) - CO - }, D - 2 - (
) - 4 - { (D) - 2 - (Methyl amino)pent - 4 - enoyl, (D) - N(CH₃) - CH(CH₂CHCH₂) - CO - }, D - 2 - (
) - 4 - { (D) - 2 - (Methylamino)pent - 4 - ynoyl, (D) - N(CH₃) - CH(CH₂CCH) - CO),

D - { (D) - Sar(2 - SMe), (D) - N(CH₃) - CH(SCH₃) - CO -) ,

D N - - L - (N - methyl L - leucine), N - L - (- hydroxy N - methyl L - leuci
ne) L - (L - valine) ,

E L - (L - valine) L - (L - norvaline) ,

F N - - L - (N - methyl - L - leucine) N - L - (- hydroxy N - methyl L - leucin
e) L - (L - Leucine) ,

Alathio L - { L - alanine thioamide, [⁷ ⁸CS - NH], NH - CHCH₃ - CS - } ,

G D - (D - alanine) D - (D - serine),

H N - L - (N - methyl L - leucine), N - - L - (- hydroxy - N - methyl L - le
ucine) L - (L - leucine) ,

I N - L - (N - methyl L - leucine), N - L - (- hydroxy - N - methyl - L - leuc
ine) L - (L - leucine) ,

J N - - L - (N - methyl - L - valine) L - (L - valine) .

2.

1 , 2 가 7 - (Cyclosporin 7 - Thioamide)

2

MeBmt-A'-B'-C'-D'-E'-Alathio-F'-G'-H'-MeVal



MeBmt N - (4R) - 4 - [(E) - 2 -] - 4 - - L - { N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine) ,

A' L - (Ala, L - alanine), L - (Thr , L - threonine), L - (Val, L - valine), L - (Nva, L - norvaline),

B' (Sarcosine), D - { (D) - methylalanine, (D) - N(CH₃) - CH(CH₃) - CO - }, D - 2 - () - 4 - { (D) - 2 - (Methyl amino)pent - 4 - enoyl, (D) - N(CH₃) - CH(CH₂CHCH₂) - CO - }, D - 2 - () - 4 - { (D) - 2 - (Methylamino)pent - 4 - ynoyl, (D) - N(CH₃) - CH(CH₂CCH) - CO),

D - { (D) - Sar(2 - SMe), (D) - N(CH₃) - CH(SCH₃) - CO -) ,

C' N - - L - (N - methyl - L - leucine), N - - L - (- hydroxy - N - methyl L - leucine) L - (L - valine) ,

D' L - (L - valine) L - (L - norvaline) ,

E' N - - L - (N - methyl - L - leucine) N - L - (- hydroxy N - methyl L - leucine) L - (L - Leucine) ,

Alathio L - { L - alanine thioamide, [⁷ ⁸CS - NH] , NH - CHCH₃ - CS - } ,

F' D - (D - alanine) D - (D - serine),

G' N - L - (N - methyl L - leucine), N - - L - (- hydroxy - N - methyl L - leucine) L - (L - leucine) ,

H' N - L - (N - methyl L - leucine), N - L - (- hydroxy - N - methyl - L - leucine) L - (L - leucine) .

3.

1 , 3 가 7 - (Cyclosporin 7 - Thioamide)

3

MeBmt-A''-Sar-MeLeu-Val-B''-Alathio-DAla-C''-D''-MeVal



MeBmt N - (4R) - 4 - [(E) - 2 -] - 4 - - L - { N - methyl - (4R) - 4 - [(E) - 2 - butenyl] - 4 - methyl - L - threonine) ,

A' L - (Ala, L - alanine), L - (Thr , L - threonine), L - (Val, L - valine), L - (Nva, L - norvaline) ,

Sar (Sarcosine) ,

MeLeu N - - L - (N - methyl - L - leucine) ,

Val L - (L - valine) ,

B' N - - L - (N - methyl - L - leucine), L - (L - leucine) ,

Alathio L - { L - alanine thioamide, [⁷ ⁸CS - NH], NH - CHCH₃ - CS - } ,

DAla D - (D - alanine) ,

C' N - - L - (N - methyl - L - leucine), L - (L - leucine) ,

D' N - - L - (N - methyl - L - leucine), L - (L - leucine) ,

MeVal N - - L - (N - methyl - L - valine) .

4.

1 , B 7 - (Cyclosporin B 7 - Thioamide) [Ala] ² - [⁷ ⁸CS - NH]

5.

1 , C 7 - (Cyclosporin C 7 - Thioamide) [Thr] ² - [⁷ ⁸CS - NH]

6.

1 , D 7 - (Cyclosporin D 7 - Thioamide) [Val] ² - [⁷ ⁸CS - NH]

7.

1 , G 7 - (Cyclosporin G 7 - Thioamide) [Nva] ² - [⁷ ⁸CS - NH]

| | | | | |
|------------------------|----|-------|-------------------------------|--|
| 8. | | | | |
| 1 u] ¹⁰ | , | I 7 - | (Cyclosporin I 7 - Thioamide) | [Val] ² - [⁷ ⁸ CS - NH] - [Le |
| 9. | | | | |
| 1 - NH] - | , | M 7 - | (Cyclosporin M 7 - Thioamide) | [Nva] ² - [Nva] ⁵ - [⁷ ⁸ CS |
| 10. | | | | |
| 1 eu] ¹⁰ | , | N 7 - | (Cyclosporin N 7 - Thioamide) | [Nva] ² - [⁷ ⁸ CS - NH] - [L |
| 11. | | | | |
| 1 | , | O 7 - | (Cyclosporin O 7 - Thioamide) | [Nva] ² - [⁷ ⁸ CS - NH] |
| 12. | | | | |
| 1 | , | T 7 - | (Cyclosporin T 7 - Thioamide) | [⁷ ⁸ CS - NH] - [Leu] ¹⁰ |
| 13. | | | | |
| 1 | , | U 7 - | (Cyclosporin U 7 - Thioamide) | [Leu] ⁶ - [⁷ ⁸ CS - NH] |
| 14. | | | | |
| 1 Leu] ⁹ | , | X 7 - | (Cyclosporin X 7 - Thioamide) | [Nva] ² - [⁷ ⁸ CS - NH] - [|
| 15. | | | | |
| 1 - NH] | , | Y 7 - | (Cyclosporin Y 7 - Thioamide) | [Nva] ² - [Leu] ⁶ - [⁷ ⁸ CS |
| 16. | | | | |
| 1 | 15 | , | , | , |
| , | | , | , | , |