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2003 01 16

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(71) -6300 5

(72) 20854 11025

(74)

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(54) 2

, 2 / (I) 가 2 ,

, / 2 2 ,

2 2 2 . T 가 2 2 T 2 가 . 2 2

2 가

, FK506

가
(U. S. 5,514,686 , 5,385,907).
2 가 (WO 00/66122)
(U. S. 가 60/283,169, PCT/JP02/03664).

FK506

, 가 2

, 2 2

; 가

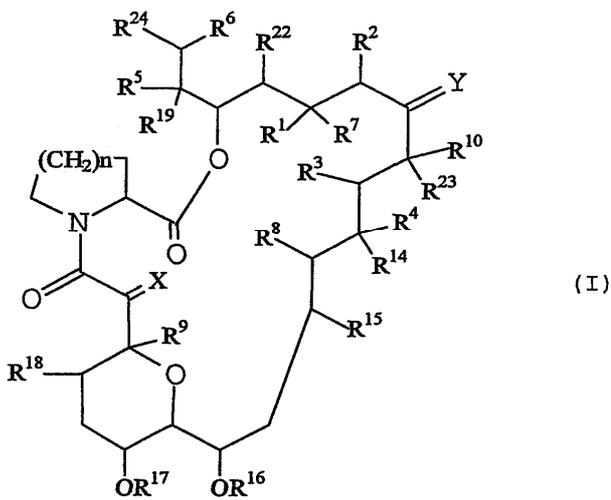
가

가 2 (, IL-2) /

(1) 2

(2) 2 가 (1)

(3) (I) (2)



, R 1 R 2 , R 3 R 4 , R 5 R 6

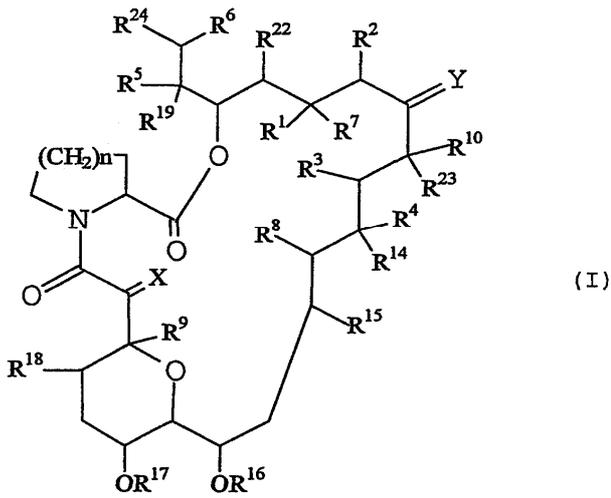
a) 2 (, R 2) ,

b) ;

R 7 , R 1 ;

IL-2 (FK506, IL-2) 가

(I)



, R¹, R², R³, R⁴, R⁵, R⁶

a) 2 (, R²),

b) ;

R⁷ , , , R¹ ;

R⁸, R⁹ ;

R¹⁰ , , , ;

X , (,), (,), -CH₂O- ;

Y , (,), (,), N-NR¹¹R¹² N-OR¹³ ;

R¹¹, R¹² , , ;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²², R²³ ;

R²⁴ ;

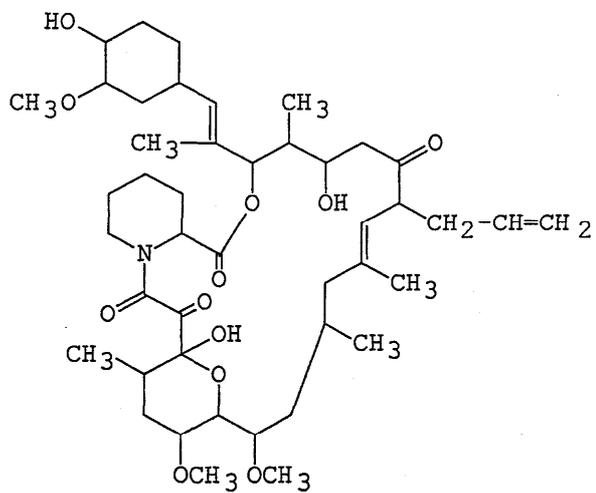
n 1 2 .

가 Y, R¹⁰, R²³ /
 5 6-
 -CH₂Se(C₆H₅) , ,

(C_1-C_4) , (C_1-C_4) , (C_5-C_6) , (C_1-C_4) , (C_1-C_4) , (C_1-C_4) , (C_1-C_4) , (C_1-C_4)
 (C_1-C_4) , 가, (C_1-C_4) , (C_1-C_4) , (C_1-C_4) , (C_1-C_4)
 , 2-, -2-, -2-, 5 6-
 EP-A-532,088
 I R 1 1- -5-

(I) EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, W089/05303, W093/05058, W096/31514, W091/13889, W091/19495, W093/5059

FR900506(=FK506), FR900520(), FR900523 FR900525
 (*Streptomyces tsukubaensis*), No. 9993 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depository, Central 6, 1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), : October 5, 1984, : FERM BP-927)
 (*Streptomyces hygrosopicus subsp. Yakushimaensis*), No. 7238 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depository, Central 6,1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: National Institute of Bioscience Human Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), : January 12,1985, : FERM BP-928 (EP-A0184162)) , FK506 (:



: 17- -1, 14- -12-[2-(4- -3-)-1-]-23,25-
 -13,19,21,27-tetra- -11,28- -4- [22.3.1.0 4,9] -18- -2,3,10,16-

(I) ,
 R 3 R 4 , R 5 R 6
 R 8 R 23 ;
 R 9 ;

IL-2 가 ((I) , IL-2)
 ; (,)
); (,); (,); (,); (,);
 (,); (,); (,); (,);
 (,) 2 .

가 (,) 가 (,)
 가 (,) EP-A-0406791 가 (,)
 가 (,) , (,) , (,) ; ,
 ; , , 가)
 ()
 , 50, 가 , ,
 가

0.005-5.0 W/V% IL-2 , 1 , 0.0001-50.0 W/V%, , 0.0001-10.0 W/V%,
 1 4 , 1 6 , 0.005-10.0 W/V%
 0.005-5.0 W/V% IL-2 , 1 6 , 1 4 , , 0.0001-10.0 W/V%,
 1 6 , 1 4 , 0.005-10.0 W/V%
 가
 IL-2 2 가

IL-2 가 , , , ,

IL-2 IL-2 ()

1

| |
|---------------------|
| 1 |
| FK-506 0.3 mg 0.03% |
| 3 mg 0.3% |
| 0.1 mg 0.01% |
| 8.56 mg 0.856% |
| 0.05 mg 0.005% |
| 0.76 mg 0.076% |
| / |
| pH 5.0 ± 0.5 |
| 1 mL 100% |

1 ()

NAC 가 (*Pseudomonas aeruginosa*) IID1210 (provided by Departm
ent of Ophthalmology, Yokohama City University School of Medicine, Japan) 2 mL
(heart infusion broth) , 37 . 100
10 mL , 37 12 .
12 (13 Std: JW/CSK, Japan SLC, Inc.) (25 mg/kg)
, 0.4% Hat
ano H (Japanese Review of Clinical Ophthalmology 79: 1153,1985) 6 mm
27- 40
/). 50 (1, 21:00). , 4 (3 -6
(2, 9:00) 12

0.06% FK-506 (2), 0.03% (3), 0.06% FK-506 0.03%
 (4) (1) .

4
 6-mm , (0.1 mL) NAC 가 , 37 1 mL 24
 , 3 , 3
 ([CFU])

1 . FK-506 . 0.3% . 0.06% FK-506 0.3%
 FK-506
 FK-506 IL-2

1

| | | | ± SE |
|---|----------------------|---|---------------|
| 1 | () | 6 | 43382 ± 16081 |
| 2 | 0.06% FK-506 | 6 | 31225 ± 7204 |
| 3 | 0.3% | 6 | O a),b) |
| 4 | 0.06% FK-506 0.3% | 6 | O a),b) |

a) 1 p < 0.05 (Tukey test)

b) 2 p < 0.01 (Tukey test)

2 ()

12 , 4 (3 -6 (13 : JW/CSK) 1
 4 4 /). 50
 12 1

60 Kuriyama H 48 가
 (0-8) (0-3) 가
 (0-4), (0-4), (0-3) (0-3)
 가

2 , 0.06% FK-506 0.3%
 . 0.06% FK506 0.3%

2

| | | | () ± SE |
|--|--|--|-------------|
| | | | |

| | | | |
|---|----------------------|---|--------------|
| 1 | () | 6 | 7.3 ± 0.6 |
| 2 | 0.06% FK-506 | 6 | 6.7 ± 0.4 |
| 3 | 0.3% | 6 | 6.0 ± 0.5 |
| 4 | 0.06% FK-506 0.3% | 6 | 5.5 ± 0.3 a) |

a) 1 p < 0.05 (Tukey test)

3, 0.06% FK-506, 0.3%
0.06% FK-506 0.3% 0
0.06% FK-506 0.3% 0.06% FK-506

3

| | | | |
|---|----------------------|---|-----------------|
| | | | ± SE |
| 1 | () | 6 | 7.3 ± 1.0 |
| 2 | 0.06% FK-506 | 6 | 6.0 ± 0.0 |
| 3 | 0.3% | 6 | 2.1 ± 0.4 a) |
| 4 | 0.06% FK-506 0.3% | 6 | 1.6 ± 0.3 a),b) |

a) 1 p < 0.01 (Tukey test)

b) 2 p < 0.05 (Tukey test)

FK-506

/ , 가 /

가

2

60/303,148

(57)

1.

2

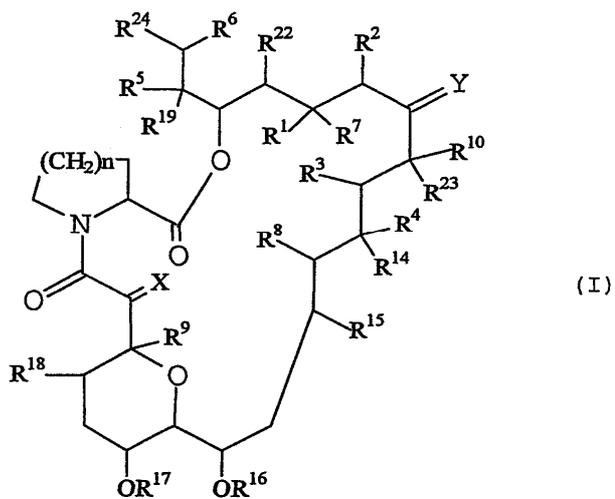
2.

1 , 2 가

3.

2

(I)



(I)

, R¹, R², R³, R⁴, R⁵, R⁶

- a) 2 (, R²),
- b) ;
- R⁷ , , , R¹ ;
- R⁸ R⁹ ;
- R¹⁰ , , , ;
- X , (,), (,), -CH₂O- ;
- Y , (,), (,), N-NR¹¹R¹² N-OR¹³ ;
- R¹¹ R¹² , , ;
- R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² R²³ ;
- R²⁴ ;
- n 1 2 ;

, Y, R¹⁰ R²³ /
 5 6-
 , -CH₂Se(C₆H₅) , , , ,

4.

3

FK506

5.

1

6.

R²⁴

;

n 1 2 ;

, Y, R¹⁰ R²³
5 6-

/

-CH₂Se(C₆H₅)

12.

11

FK506

13.

9

12

가

14.

13

가

15.

14