

(19) (KR)
(12) (A)

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A61K 38/13

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(43)

10-2004-0019034
2004 03 04

(21) 10-2003-7017245

(22) 2003 12 30

2003 12 30

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WO 2003/004098

(86) 2002 07 02

(87)

2003 01 16

(30) 60/303,148 2001 07 06 (US)

(71) -6300 5

(72) 20854 11025

(74)

:

(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) .

FK506

2 가 (WO 00/66122)
(U. S. 가 60/283,169, PCT/JP02/03664).

가 2

2 2

가

; 가

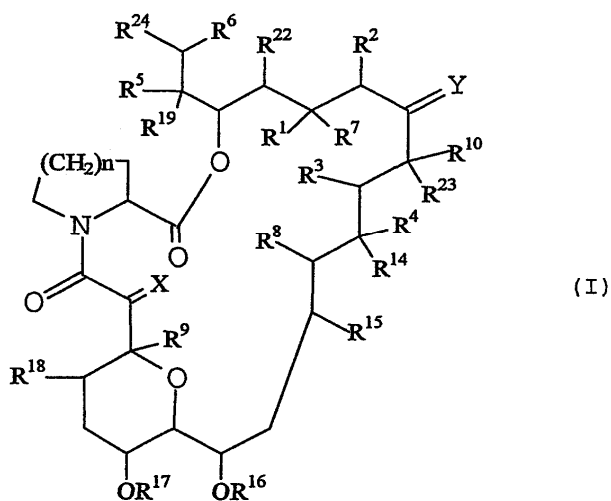
2 (, IL-2) /

가

(1) 2

(2) 2 가 (1)

(3) (I) (2)



, R¹ R², R³ R⁴, R⁵ R⁶

a) 2 (, R²) ,

b) ;

R⁷ , , R¹ ;

R 8 R 9 ;

R 10 , , , ;

X , (,), (,), -CH 2 O- ;

Y , (,), (,), N-NR 11 R 12 N-OR 13 ;

R 11 R 12 , , ;

R 13 , R 14 , R 15 , R 16 , R 17 , R 18 , R 19 , R 22 R 23 ;

R 24 ;

n 1 2 ;

, Y, R 10 R 23
5 6-
-CH 2 Se(C 6 H 5) , , , , , ,

(4) FK506 (3) .

(5) 가 (1) (4) .

(6) 가 , , , , , , , , , ,
(5) .

(7) (6) .

(8) / 가 2 .

(9) / 2 .

(10) 2 가 (9) .

(11) (I) (10)
)

(12) FK506 (11) .

(13) 가 (9) (12) .

(14) 가 , , , , , , , , , , , , ,
(13) .

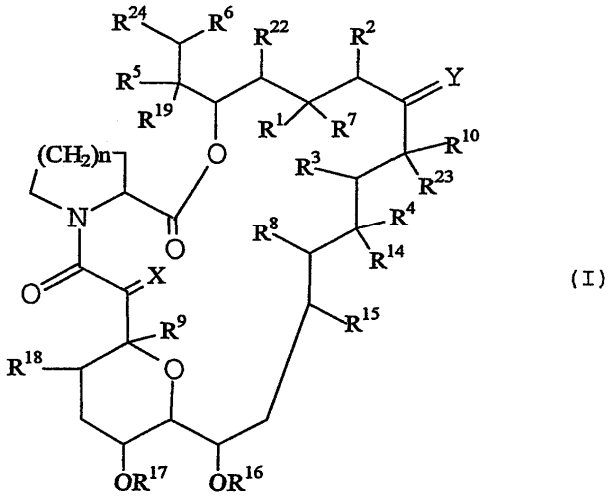
(15) (14) .

2 .

/ 가 2 .

IL-2 (FK506, IL-2) 가

(I)



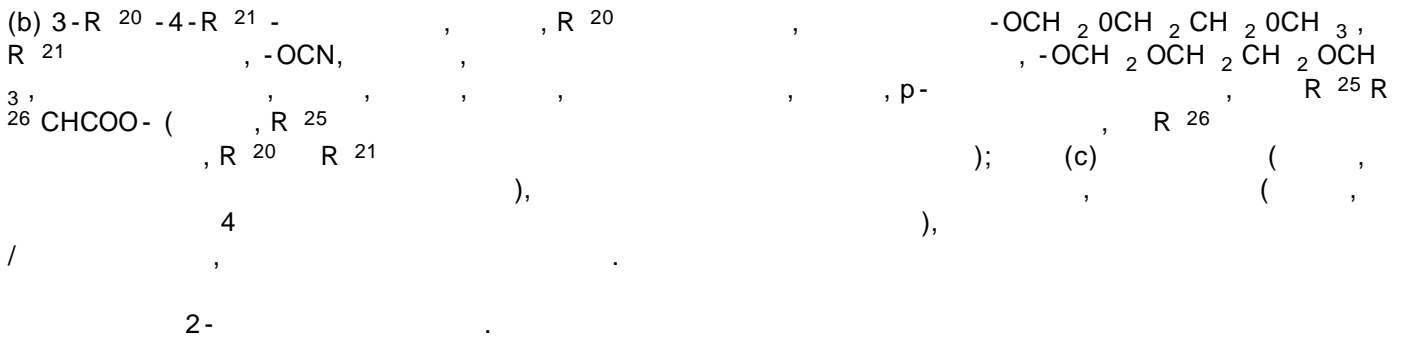
, R¹, R², R³, R⁴, R⁵, R⁶

- 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) , ,

(I) R²⁴ (C₅-C₇)

(a) 3,4-



(I)

, 1 6
 ,)
 (,)

1-()
 (), C₁-C₄, 가 , tert- , tert-
), tert- (C₁-C₄) C₁-C₄, 가 tert- tert-
 tert-

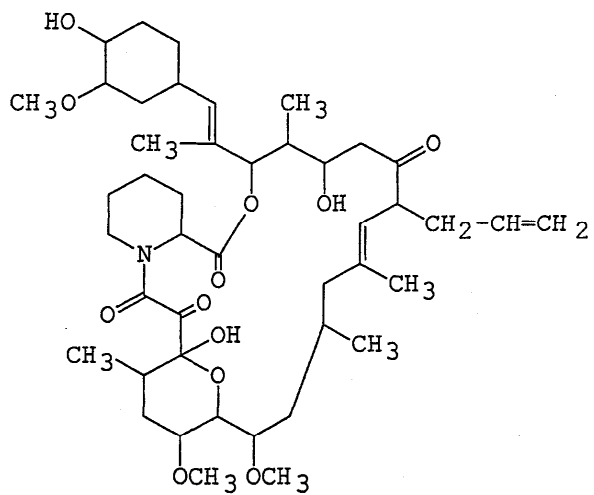
(,)
 () ; (,) ()
 , (,) () () () (,)
 , tert-

(,)
) ; (,)
 (,)
 -2- -2- , 2- -2- -2- , 2- , 2- -2- -2-

(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 hygroscopicus 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 가 . EP-A-0406791
) (,)
 가 가 가 가 가 (,)
 ; , 가)
 ()

50,

가 가 가
 , 0.001-10.0 W/V%,
 0.005-5.0 W/V% IL-2 , 1 0.0001-50.0 W/V%, 1 6 , 0.005-10.0 W/V%
 1 4
 , 0.0001-10.0 W/V%,
 0.005-5.0 W/V% IL-2 1 6 , 1 4 0.005-10.0 W/V%
 1 4
 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
([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
12 4 4 1 /). 50

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

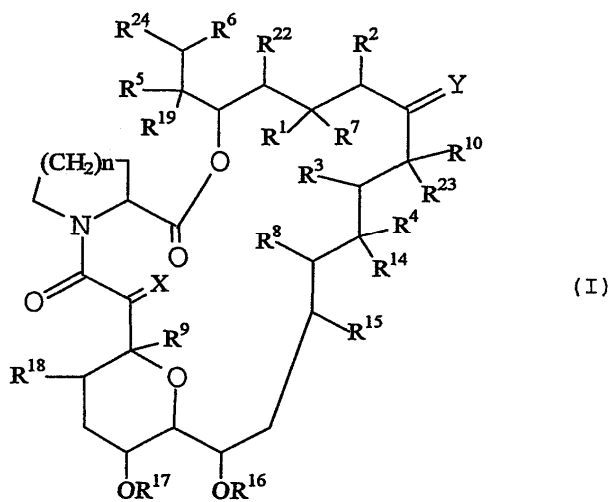
2.

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.

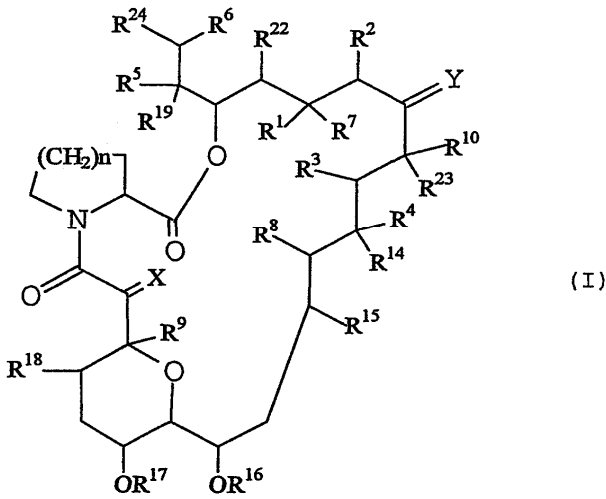
1

4

가

6.

5 , , 가 , , , , , ,
 , , , , , , , , , , , , ,
 6 7.
 8.
 / 가 2
 /
 9.
 / 2
 10.
 9 , 2 가
 11.
 10 , (I)
 :



, R¹ R², R³ R⁴, R⁵ R⁶

- a) 2 (, R²),
 b) ;
 R⁷ , , , R¹ ;
 R⁸ R⁹ ;
 R¹⁰ , , , ;
 X , (,) , (,) , -CH₂O- ;
 Y , (,) , (,) , N-NR¹¹ R¹² N-OR¹³ ;
 R¹¹ R¹² , , ;
 R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² R²³ ;

R²⁴

;

n 1 2 ;

, Y, R¹⁰ R²³
5 6-

/

-CH₂Se(C₆H₅)

12.

11

FK506

13.

9

12

가

14.

13

가

15.

14