

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

(51) Int. Cl.⁷
C07F 9/40
C07D 491/06
A61K 31/395

(11)
(43)

10-2004-0083104
2004 09 30

(21)	10-2004-7011867		
(22)	2004 07 30		
	2004 07 30		
(86)	PCT/US2003/003030	(87)	WO 2003/064383
(86)	2003 02 03	(87)	2003 08 07

(30)	60/353,252	2002 02 01	(US)
	60/426,928	2002 11 15	(US)
	60/428,383	2002 11 22	(US)
	60/433,930	2002 12 17	(US)

(71) 02139 , 26

(72) 02468 , , 115

02492 , , ,3 70

01730 , , 4

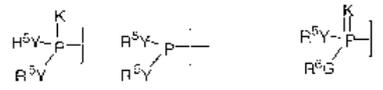
02460 , 45

(74)

:

(54)

JQA - , A -O-, -S
-NR²- , ; Q , (A가 -O-, -S- -NR²-) Q -V-, -
OV-, -SV- -NR²V- , V , VA, OVA, SVA NR²VA ; J
P ; K O S ; Y -O-, -S-, -NR²- R⁵



(*Streptomyces hygroscopicus*)

(macrolide) FK-506- FKBP12 :FKBP FRAP 3 Kd 200 pM :FKBP
FKBP FRAP [FKBP:]:[FRAP]
(adaptor)

CCI 779(Wyeth) SDZ Rad('RAD001', Novartis)

) , IgE () (T-

2001/0010920

FKBP FRAP , FKCP FRAP

Proc Natl Acad Sci USA 96, 8657-8662] , WO96/41865 , WO99/36553 , WO01/14387 , [,
[Ye, X. (1999) Science 283, 88-91]

가 , 가 (epimerization),

가 가

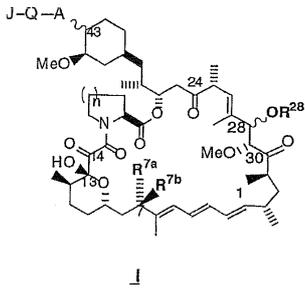
(' (rapalog)') 가 ; C7, C42 / C29 ; C13, C43 / C28
; C14, C24 / C30 ; 5
6
5,362,718 , 5,525,610 , 5,310,903
5,527,907 C-28
(WO01/14387).

가 ()

C-43 (CCI 779 SDZ RAD, [, K. , Endoc
rine- related Cancer (2001) 8, 249-258], [, B. , Cancer Res. (2001) 61 1527-1532] [Dancey,
Hematol Oncol Clin N Am 16 (2002), 1101-1114]).

(I)

:

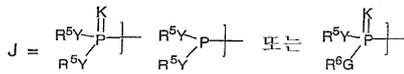


↓

(I)

A -O-, -S-, -NR²- (, JQ- C43);

Q (, J A C43), A가 -O-, -S- -NR²- , Q -V
 -, -OV-, -SV- -NR² V- , V , VA, OVA, SVA NR² VA ; J



K O S ;

Y -O-, -S-, -NR²- R⁵ P ;

R² R⁵ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) -C(O)(YR⁵) ; P H ; R⁶
 H가 (, -PR², -PR⁵ -PR⁶ -PH); R², R⁵ R⁶

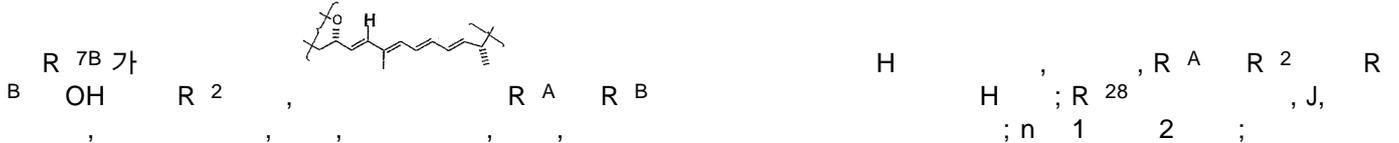
R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR²- , (M)_x R⁶ P ;

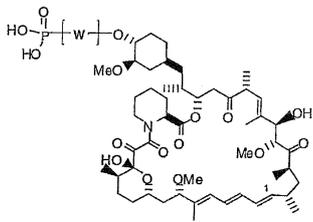
M , M- M'

x 0 6 ;

R^{7a} R^{7b} H , H, , -R^A, -OR^A, -SR^A, -OC(O)R^A, -OC(O)NR^AR^B, -
 NR^AR^B, -NR^BC(O)R^A, -NR^BC(O)OR^A, -NR^BSO₂R^A -NR^BSO₂NR^AR^B , R^{7a}

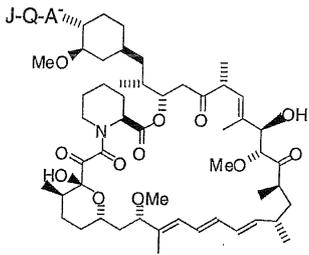


(a) JQA-가 (R² Y)(Me)(P=O)O- , (R² Y) (i)
 가 (ii) R² 15 , 10 ; (b)



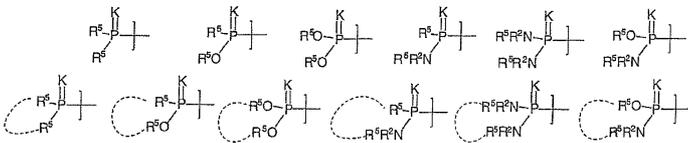
, W , U 6, O, S, SO SO₂);

(c)

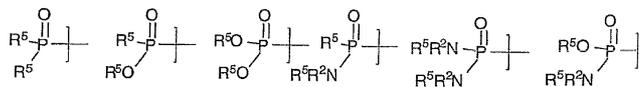


J-Q-A- (HO)₂(PO)-O- 가 , -

: , J 1



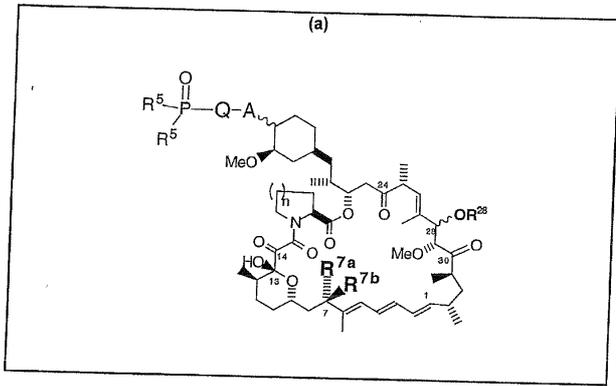
, K, R², R⁵ R⁶ . J K가



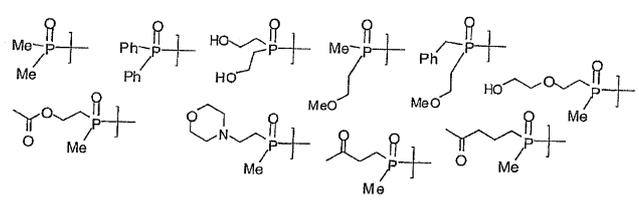
-OR⁵ , R⁵ H . ,

(-Q-A-가 -O 가 , J가
 (-PO₃H₂). , JQA-가 (R²Y)(Me)(P=O)O- , R²Y-가 15
 , 10 , 6

(a) :



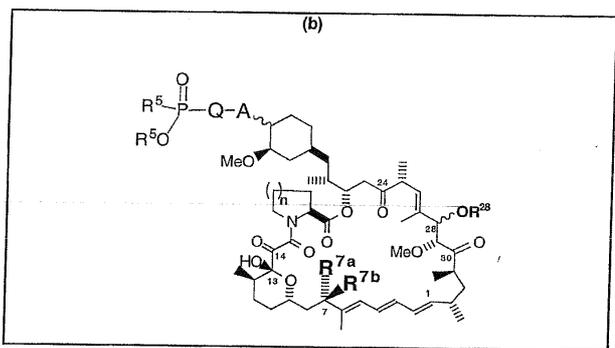
, R⁵) , (, C1-C6) , (, , , -O- (,)) ,
 : 가 , (a) J



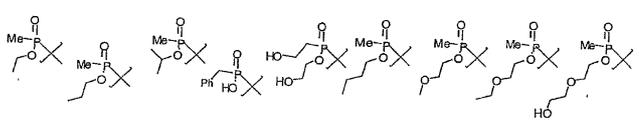
J-Q-A가 (R⁵)₂PO-O-

R², R⁵, R⁶ J
 R², R⁵, R⁶ J

(b) :

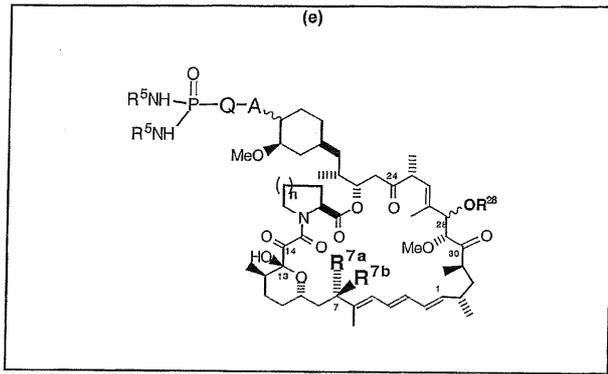


, R⁵) , (, , , (b) , - ,
 J :

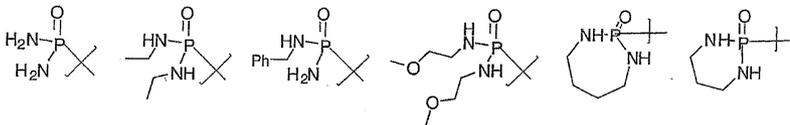


J-Q-A-가 (R⁵)(R⁵O)PO-O-

(e) :

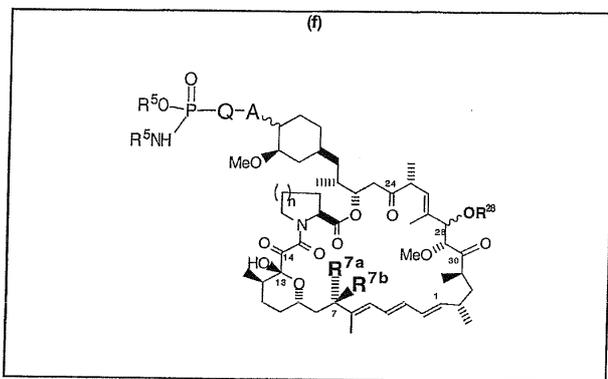


(, R⁵), (, H , , , , (, C1-C6)_J ,
 (e) :

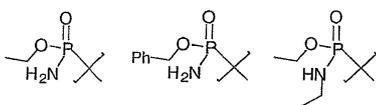


J-Q-A-가 (R⁵N)(R⁵N)PO-O-

(f) :

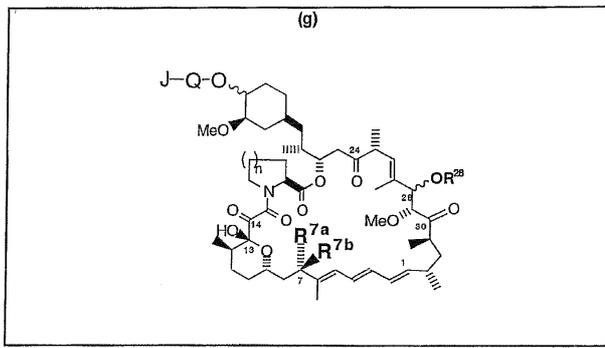


(, R⁵), (, H , , , , (, C1-C6)_J ,
 (f) :

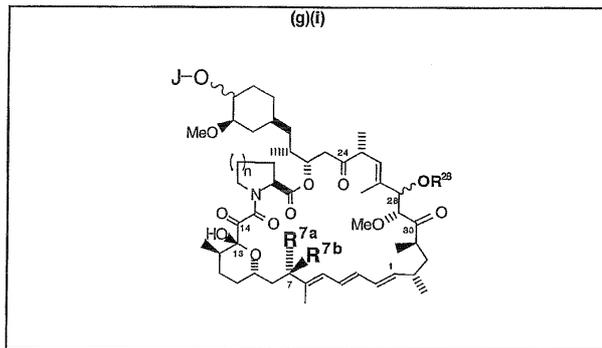


(d), (e) (f) , QA가 -O- -OVO- .

(g) :



(g)(i) , J, Q, n 가 R



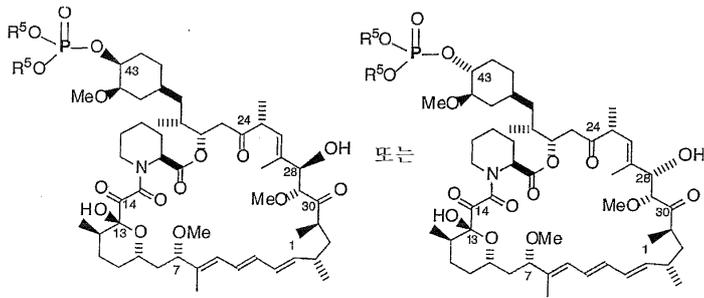
(O- , Q , , J
(g)(i)(a)

(g)(f) (a)

상기 식에서, J는 하기 화학식으로부터 선택된다:

- P(O)Me₂, -P(O)Ph₂, -P(O)(OMe)(Me), -P(O)(OnPr)(Me),
- P(O)(OPr)(Me), -P(O)(OnBu)(Me), -P(O)(Me)(OCH₂CH₂OMe),
- P(O)(Me)(OCH₂CH₂OEt), -P(O)(Me)(OCH₂CH₂OCH₂CH₂OH),
- P(O)(OMe)(Et), -P(O)(CH₂CH₂OH)₂, -P(O)(OEt)₂, -P(O)(NH₂)₂,

J (g)(i)(a) 가 , J -PO₃H₂ 가 , -PO₃Me₂ 가
C7 , C43 C28



, R⁵ H

(g)(ii)

(g)(

i)(a) :
 (a) 28 가 (C28-OH); (b) 24 30 가 H , C7 C43-O
 H). ; (d) 43 J -O-가 (C7 C43-O

Q가 -OV- (g)(iii)
 V가

, Q가 O- J

(g)(iii)

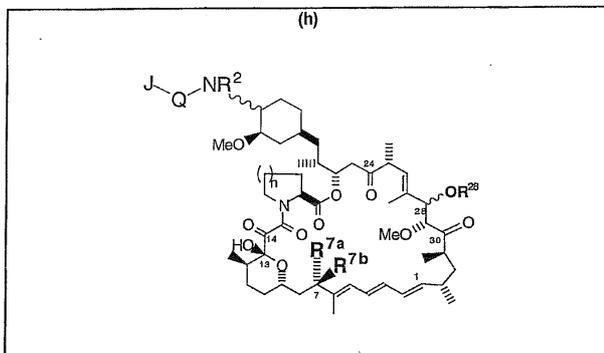
상기 식에서, J는 하기 화학식으로부터 선택된다:

- P(O)Me₂, -P(O)Ph₂, -P(O)(OMe)(Me), -P(O)(OnPr)(Me),
- P(O)(OPr)(Me), -P(O)(OnBu)(Me), -P(O)(Me)(OCH₂CH₂OMe),
- P(O)(Me)(OCH₂CH₂OEt), -P(O)(Me)(OCH₂CH₂OCH₂CH₂OH),
- P(O)(OMe)(Et), -P(O)(CH₂CH₂OH)₂, -P(O)(OEt)₂, -P(O)(NH₂)₂.

(h)

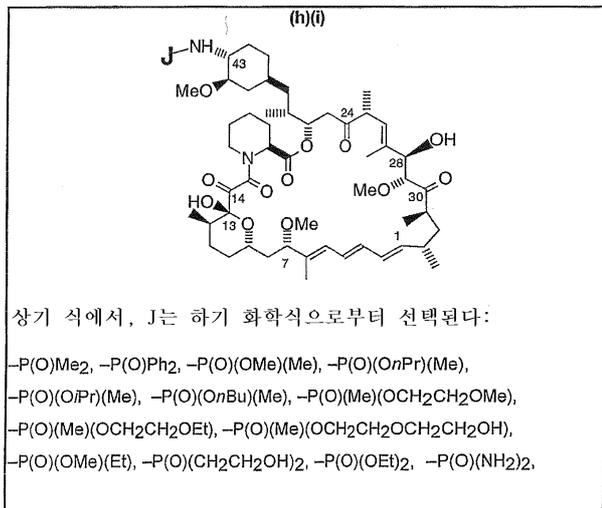
A가 -NR² -

:

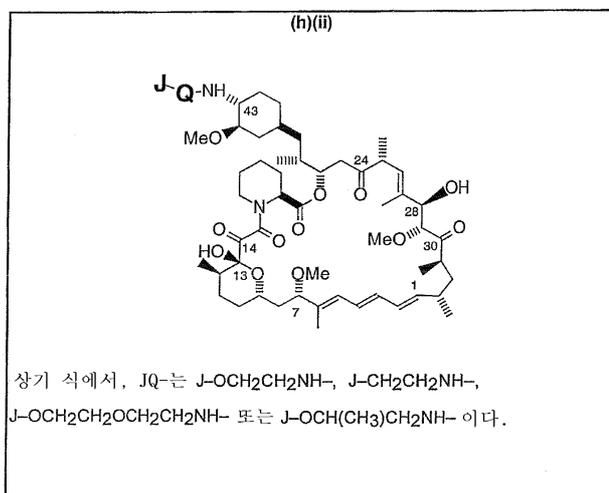


Q가 , J가 (h)(i)

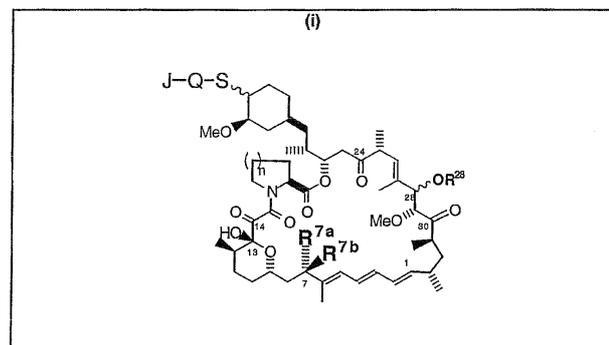
(,)



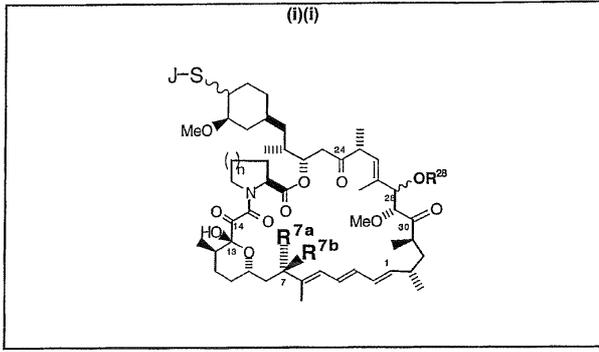
) (h) , Q가 (h)(ii) , , V , :



(i) :

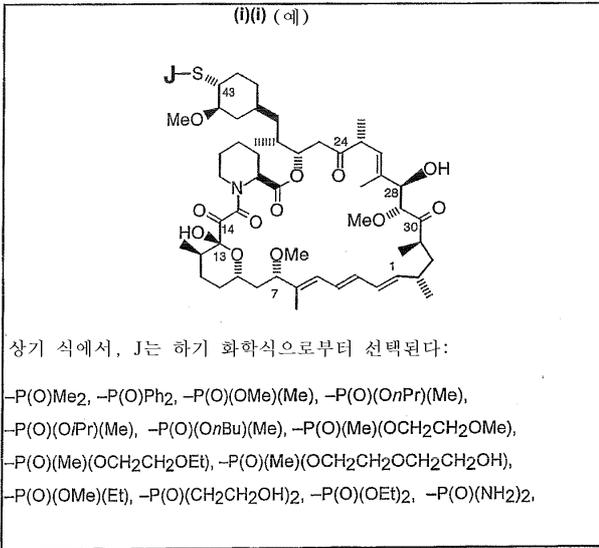


, J, Q, n 가 R (i)(i) ;



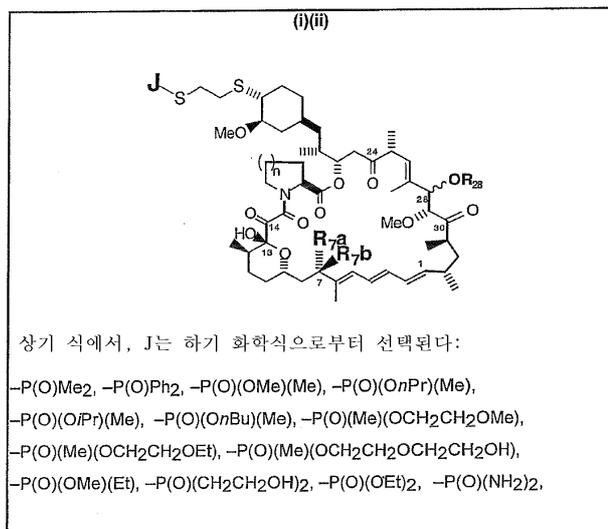
, Q , J
 : , J

(,) .



(i)(ii)

, Q가 O- J
 Q가 -SV- V



:

(j) (l) , JQA -

C-43

가 ,

C43

JQA

(k) (j) 가 C7 -OMe 가 ; C28 C43 ; ; ; C1 C6 24 30 ; /

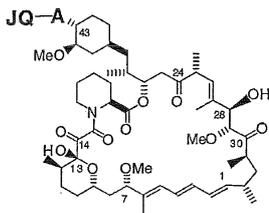
(l) J가 -PO₃H₂ (-PO₃Me₂)

(m) 1700 (1400 , 1200)

(n) 가 (-OH (WO 02/24706))

(o) T 5 0.01 , 0.1 , 0.

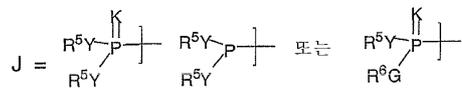
(p) :



, A -O-, -S- -NR² - , (, JQ C43) ;

Q (,) , (A가 -O-, -S- -NR² -) Q -V-, -OV-, -SV- -NR² V- , A , V , VA, OVA, SVA NR² VA ;

K O S ;

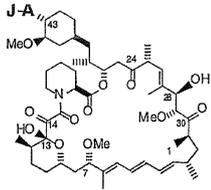


Y -O-, -S-, -NR² - R⁵ P ;

R² R⁵ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) , -C(O)(YR⁵) ; P H ; R⁶ R², R⁵ R⁶ ; G H가 ; R², R⁵ / R⁶ 2 ; M ; M -O-, -S-, -NR² -, (M)_x R⁶ P ; M ; x M-M' ; x

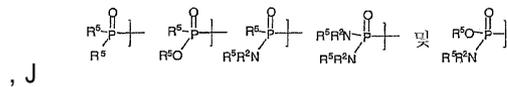
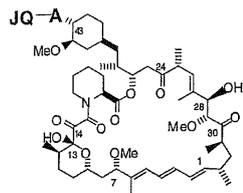
, J-Q-A- (HO)₂(P=O)O-, (MeO)₂(P=O)O-, (HO)₂(P=O)-W-O (HO)₂(P=O)-W-O
 , W 
 , U
 , O, S, SO SO₂; JQA-가 (R²Y)(Me)(P=O)O- (R²Y)
 , R²가 15
 , 10 , 6 ,)

(q) :



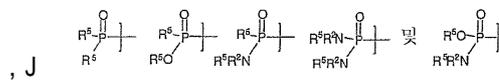
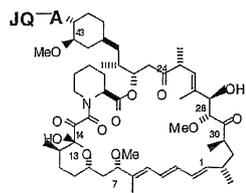
, A, J, K 가 (p)
 , J-A- (HO)₂(P=O)O- (MeO)₂(P=O)O-가 ; , JA-가 (R²Y)(Me)(P=O)O- (R²Y)
 , R²가 15 , 10 , 6 ,)

(r) :



가 (p) (q)
 (-OR⁵ , -NR²R⁵ -OH -NHR⁵)
 ;
 , JQA-가 (R²Y)(Me)(P=O)O- , (R²Y)가 ,

(s) :



A , -O-, -S- -NR²- ; Q , (A가 -O-, -S- -NR²-
) Q -V-, -OV-, -SV- -NR²V- , V ,
 , J , A , VA, OVA, SVA NR²VA

;

K O S ; Y -O-, -S-, -NR² - R⁵ P ; R²
R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) -C(O)(YR⁵) ; P H ; R⁶
H가 ; R², R⁵ R⁶

R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR² -, (M)_x R⁶ P ;

M ; x 0 6 ; M-M'

;

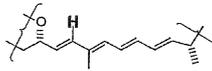
R² R⁵ -NR² R⁵ -OH -NHR⁵ , , JQA-가 (R² Y)(Me)(P=O)O- , (R² Y)가 15 -OR⁵

(t) (p) (s) , R² R⁵ 가 C1-C6 (, -OH, , , -OR⁵ -NR² R⁵ -OH -NHR⁵ ,) , , -OR⁵ -NR² R⁵ -OH -NHR⁵ ,

(u) (t) , R² R⁵ 가 , , n- , -OH, , n- , 2- , t- , , 가 , -OR⁵ -NR² R⁵ -OH -NHR⁵ , , -OH, ,

(v) (p) (u) , J R² R⁵ : 8 J 가 :

- (1) (5) :
- (1) 28 , -OR² -OC(=O)AR² 28 () ;
- (2) 24 , -OR² -OC(=O)AR² ;
- (3) 24 , -OR² -OC(=O)AR² ;
- (4) 7 -OMe / H, , -R^A, -OR^A, -SR^A, -OC(O)R^A, -OC(O)NR^AR^B, -NR^AR^B, -NR^BC(O)R^A, -NR^BC(O)OR^A, -NR^BSO₂R^A -NR^BSO₂NR^AR^B (, R^A R² , R^B OH R²) -OMe ;



- (5) 7 -OMe .
- (z) (y) , R² R⁵가 C1-C6 (, -OH, -, , -OR⁵ -NR²R⁵ -OH -NHR⁵ , R² R⁵가 , n- , n- , 2- , t- ,) ;
- (aa) (y) (z) , QA가 -OVO-, -OVNH- -SVS- , V
- (ab) (y) (z) , (v) J
- 가 , -P(O)(Me)(Z) 43 (, Z , -NH-, -S-, -O- P ,) .

US 2001/0010920 A1

5,000 10,000,000, 15,000 , 40,000

, ELISA ,

가 .

가

aflex) (Avantec)

(가 가)

43 , US 6,258,823 , WO 96/41865 , W
O 98/02441 , WO 99/36553 WO 01/14387

C7, C28, C13, C24 C30,

FKBP12

2 ,

1

FKBP

JQA-

()

가

가

가

가

50% , 98%

60% ,

(, 85% , % /

95% ,

(,)

가

(,

WO96/41865 , WO99/36553 WO01/14387 [VM, Y
e X, NL, J, F, JM M. (1999) Long-term regulated expression of growth hor
mone in mice following intramuscular gene transfer. Proc natl Acad Sci USA 96, 8657-8662] [Ye X,
VM, P, F Jr, MA, 가 G-p, JV, M JM (1999) regulated delivery of thera
peutic rproteins after in vito somatic cell gene transfer. Science 283, 88-91]

WO01/14387 18-24

. WO01/1438

7

28-

C7

가 ()
(: C.) ,

(:) ,

(:)

(,)

가 , ,

spp.

가,

6,258,823 (2001.7.10)

C7

6,25

8,823 가

H

C7

EC50

, T

C7

C7

H

T

DZ RAD(RAD 001) C7 가 T CCI 779 S C7 (-OMe)

/ 가 B , 가 / 가 E, , 가 / 가

D001 (CCI-779 RA) , (가)

CCI779 RAD001 가 (: ,) , 가,

5,530,006 , 5,516,770 5,616,588

PTEN(PTEN) PTEN /Akt-m-TOR 가 PTEN /Akt-mTOR (EGFR, PDGFR, IGF-R IL-2)

; PI3 ; PTEN ; Akt
; , , , ; , eIF-4E , ; 가 P16
; D ; 가 P16
, 1
(,
) 1
; (: , , , , , , , , TAT-59, , LY-353381,
CP-336156, MDL-103323, EM 800 ICI-182,780, WO 02/13802); Src, B
RC/Abl, kdr, -2, 3(GSK-3), (EGF-R)
(PDGF-R), Gleevec, Iressa, CP-358774(Tarceva), ZD-1839, SU-5416 NSC-64
9890 ; (: VEGF), 가
; (:); Velcade; IKK NF-kB
; 1
, (stent)
55] [, Marx and Marks, 2001, Circulation 104: 852-8
(,
) (: , , , ,) 가 ,
가 , 가 ,
가 , (-), - 가
, S , S (, 가
, 가 , ()
가 가 ()
가 (가)
()
1 가 ,
가
가 가
63 , 5,447,724 가 6,471,980 ; 6,096,070 . 5.824,049 , 5,624,411 , 5,609,629 , 5,569,4
WO02066092
PCT WO 01/01957 6,099,561 ; 6.071,305 ; 6,063,101 ; 5,997,46
8 ; 5,980,551 ; 5,980,566 ; 5,972,027 ; 5,968,092 ; 5,951,586 ; 5,893,840 ; 5,891,108 , 5,851,231
; 5,843,172 ; 5,837,008 ; 5,769,883 ; 5,735,811 ; 5,700,286 ; 5,679,400 ; 5,649,977 ; 5,637,113
; 5,591,227 ; 5,551,954 ; 5,545,208 ; 5,500,013 ; 5,464,450 ; 5,419,760 ; 5,411,550 ; 5,342,348
; 5,286,254 ; 5,163,952 6,051,276 ; 5,879,808 ; 5,87
6,452 ; 5,656,297 ; 5,543,158 ; 5,484,584 ; 5,176,907 ; 4,894,231 ; 4,897,268 ; 4,883,666 ; 4,832,
686 3,976,071
5,463,010 5,356,433 가
가 5,463,010 ; 5,112,457 5,067,491
가 6,031,375 ; 5,928,145 ; 5,735,811 ; 5,728,062 ; 5,725,494 ;

5,409,000 ; 5,368,557 ; 5,000,185 4,936,281
5,427,767 ; 5,225,282 ; 5,206,159 ; 5,069,216 ; 4,904,479 ; 4,871,716 ;
4,501,726 ; 4,357,259 , 4,345,588 4,335,094

가 , 1 가
2002/0082680 , 6,4741,979 ,

-L-

가

()

(LO)PC

가

PC

. PC

가 0.1

μm

. LO

WO 01/00109 , 01/01957 , 01/529

15 , 02/55121 , 02/55122

5,516,781 ; 6,153,2

52 ; 5,665,728 ; 5,646,160 5,516,781 , WO 01/01957 , 01/49338 , 01/8
7263 , 01/87342 , 01/87372 , 01/87373 , 01/87374 , 01/87375 01/87376

가

가

가

(: , ,)

2 가

(R R').

가

WO 01/14387

15-18

(), (,), ,

6

1-8 , 1-

tert- , n- , sec- , tert- , n- , -CH₂- , n- , sec- , tert- ,
tert- , -Ch₂- , n- , sec- , -CH₂- , tert- ,
가 가 가 가 가 가

가 1-8 , 1-6 , n- , sec- , tert- , tert- , 2- , 3- , 2- , 3-

가 2-8 , 2-6 , -2- , -2- , -3- , 2- , -2- , -2- , -5- , 2,3- , 2- , 가 2-8 , 2-6 , -2- , -2- , -3- , -2- , 3- , -4- , -2- , -5-

가 3-7 , 3-10 , 가

5-10 , 1-4 , 가 5-14 , N, O , S , 3-1H- , -2- , (1-)-2- , -3- , 2- , 3- , 4- , 3- , 2- , 3- , 1- , 2- , 4- , 3- , 4- , 1- , 2- , 2- , 2- , 3- , 4- , 2- , 4- , 3- , 1- , N- , 2- , 1- , 가

가 5-14 , 1- , 2- , 1- , 가 , 1- , 2- , 가

가 3-14 , 5-14 , 5 , ; 6 , [b] , [2,3-b]

(Handbook of heterocyclic Chemistry) , 2- , 3- , N- , 2- , 4- , 5- , 3- , 4- , 5- , 2- , 2- , 4- , 5- , 1- , 2- , 3- , 2- , 3- , 4- , 4- , 2- , 4- , 5- , 3- , 2- , 4- , 5- , 5- , 2- , 5- , 2- , 3- ,

가
 가 [3,4-d]
 ()
 가
 C(=O)R², -Y-C(=O)OR², -Y-C(=O)NR²R⁵, -Y-C(=NR^{2'})NR²R⁵, -COCOR², -COMCOR², J, -C
 N, -S(=O)R², -SO₂R², -SO₂NR²R⁵, -NO₂, -NR⁵SO₂R², -NR⁵SO₂NR²R⁵
 Y가 NR² -NR²C(=O)R⁵, -NR²C(=O)NR⁵, -NR²C(=O)
)OR⁵ -NR²C(=NH)NR⁵가 R² R⁵ R⁵
 ; ;
 , 1,2- , 1,2- OH(:
), -O- , -O-() , -O- (, -OCH₂CH₂C₆H₅
), -O-() , -C(O)CH₂C(O)R², -CO₂R², -C(=O)R²(, R²가 R²
 가 R²가), -C(=O)NR²R⁵, -OC(=O)NR²R⁵, -C(=NH)NR²R⁵, -OC(=NH)NR²R⁵

=O, =S, =NR², =NNR²R⁵, =NNHC(O)R², =NNHCO₂R², =NNHSO₂R²

, -R², -NR²R⁵, -C(=O)R²
 , -C(=O)OR², -C(=O)NR²R⁵, -C(=NR^{2'})NR²R⁵, -COCOR², -COMCOR², -CN, -NR⁵SO₂R²
 -NR⁵SO₂NR²R⁵

가 가 40 가 가
 1 가
 (tautomer)

R S
 가 (>90%, >95%, 가)
 I 43 28 R S
 가 가 14C가 가 13C

, JQA- (, 43-JQA) 43 0,1,2,3,4,5,6 7
() 43-JQA - 가 , , 43 JQA
C30 1, 2, 3, 4, 5 6 가 () JQA- C7, C13, C14, C24, C28
(WO 99/36553 III
, 1997, Proc Natl Acad Sci USA 94: 7825-7830),
WO01/14387 , 24-30 JQA-
가
JQA- R C7a 가 OMe
() (C7 JQA-) R 7a R 7b
가 H 가 -R A , -Z-R A , -Z-(CO)-R A , -Z(CO)Z-R A , -NR A SO 2 R A , -NSO 2 R A
, Z O, S NR A , -NH(CO)OR A , -NH(CO)R A , -NH(SO
2)R A -NH(SO 2)NHR A (, R A
, p-) , C7
JQA- , R 7a R 7b
H; C2-C8 ;
; (1 , 2 , 3 4); ; , R 7a 가 H; (R 7b) =O; ;
, R 7a R 7b 가 H , -OEt, -O- , -O- , -OCH 2 CH 2 -OH,
-O- , -O- (, 3- , 4- , 3- -4- , 3,4- 2-), -S-
Me, -S- , -O(C)Me, , -CH 2 C(Me)=CH 2 , -OCH 2 -CCH, -OCH 2 -CC-Me, -OCH 2 -CC-Et, -OC
H 2 -CC-CH 2 OH 2,4- , 2,4,6,- C7- JQA- C7-
) , C43 (가 C7-
. C7 JQA- 1,2,3,4,5 C7-
가
43 JQA- C7 JQA- 가
JQA- C24 C30
가 (=O) , C30 C24 가 WO 99/36553
, R C30 R C24 가 OH , R C7a R C7b
WO 01/14387 C7
, R C7a R C7b , 1,2,3,4 5 가
, C28 C30 가 ,
JQA- 가
JQA- , WO99/36553 , C13 C28
F JQA- JQA- 가 가
-JQA-
JQA- , =O R C24 가 , 가
가
JQA- , R C14 가 OH
, 1,2,3,4, 5,6 ,

, C7, C13, C24, C28 / C30 가 JQA-
 ; C6 -CH2OH -CH₂OMe ; C42 , C3, C4

C29- , C7- , C29-
 가

WO/014387 가

가

C7	, J Org Chem 59, 6512(1995); Chem amp; Biol 2(7), 471-481 (1995)
C14	, Angew Chemie Int Ed Engl 23, 167(1984)
C20	, 5,387,680
C24	5,373,014 5,378,836 ; , Synthesis 1975, p.136
C30	, Tet Lett 35, 6469 (1994)

678 , 5,130,307 , 5,177,203 5,194,447 , 5,100,883 , 5,118,677 , 5,118,

28- WO/014387 가

3- , 28- 2001/0010920 43 2

, 24 30 C-43 , 43

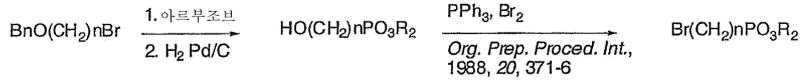
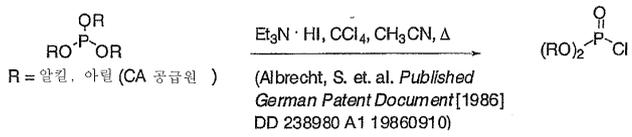
24- , 30- 24,30-

, 43-JQA-
 WO 93/13663 WO97/02358
 [, 1988, J. Bacteriology 180 (4):809-814]

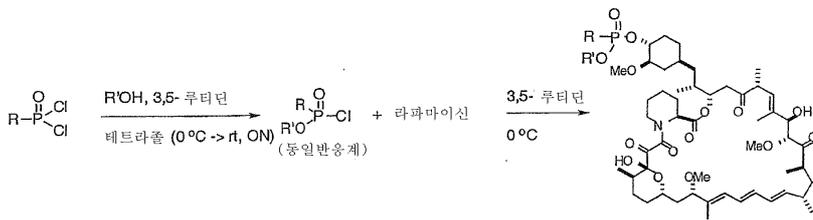
가

가 :

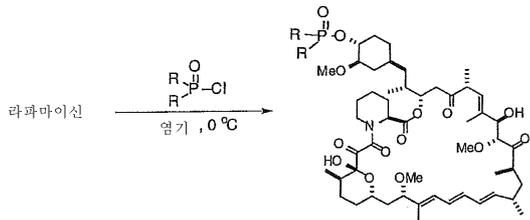
C-43



I II
I(2 ,)



II(1)



((R)(RO)P-Cl RR'P(=O)-Cl) , 'J',
() 가 . 가

가
. BIOTAGE

가

120 , 50 / HPLC, X NMR
50% , 5% HPLC (, 3
280 nm UV), 3
1D ¹H ³¹P NMR
가 HPLC

FKBP-12, T, FRAP-가, Drugs of the Future 2002, 27(1): 7-13]

FKBP12

P12 FRAP FKBP12, FRAP(FRB, TOR1 TOR2, hFKB / FKBP12, WO 96/41865 () FRAP FRB, 가 3

WO 95/33052

가 (, / 가

1 2 3 FKBP, FKBP가, Phe36, FKBP12, FKBP12

KKBP12,

FKBP

(FKBP, [FK506, 1989, Nature 341, 755-757]).

), FKBP () Kd, 가 (:), (: FK506, 200 nM, 1 nM

FK506, FP IC50, WO99/36553, WO96/41865, FKBP

FKBP, FP (FKBP12, 10, FK506, 1-5, IC50, 1000 nM, 300 nM, 100 nM, 가, 10 nM

가, DNA, 1, FKBP FRB, (effector), DNA, 2, DNA (,)

WO99/10510, WO99/36553, WO96/41865
 (가 가)
) , () , ELISA
 , SEAP, hGH, 가
 FP , IC50 / FK506 FKBP FKBP

01/14387, WO94/18317, WO95/02684, WO96/20951, WO95/41865, WO99/36553, WO
 가
 / / / / /
 가 ; 가 ;
 (; () (, Circulation, 2001, 103: 1
 92-195). (, Human Molecular Genetics, 2002, vol 11, No. 5, pp 525-534
) (, PNAS 98(18): 10314-10319; , PNAS 98(18) 01320
 -10325; PNAS 98(18): 10031-10033; , Oncogene (2000) 19, 6680-6686)
 , I , II , (Cushing)
 , (Ehlers-Dnalos) , (Marfan) , (Me
 nke) , (Sudeck) ,
 가

1.
 , 가
 'FRB') (FRAP FKBP , FKBP: (,
 DNA- DNA- , 2
 , 2가
 NA 가 , DNA- DNA- D
)
 가 PCT/US93/01617 WO96/41865 () ,
 , ()

가
: (1) RNA ; (2) RNA ; (3) RNA ; (4) 가
PCT/US95/10591

DNA

2

4.

, 'CCI-779' Drugs of the Future 2002, 27(1):7-13], WO 02/4000 WO 02/13802
CCI779

, Avastin (-VEGF),

(, MLN-591, MLN 591RL MLN2704),

, VP-16,

B

, 5-FU,

가

MLN576(XR11576)

, L-PAM,

C, , MLN518 MLN 608(flt-3 , PDGF-R c-kit),

가
, VM-26,

(RITUXAN),

(Herceptin -Her2), 2C4(

HER-2

, ATRA,

(),

;

/

),

T-

가

, CCI779 RAD 001

1

A, FK-506, OKT-3,

ATG

A

[Transplantation Proc. 23:507 (1991)]

5,496,832

5,387,589

5,286,731

5,286,730

가
 5,288,711 WO 01/97809

가
 5,665,728

가
 5,288,711 WO 01/97809

가
 5,665,728

(Bell's palsy),
 (Gullain-Barre)

5. ;

5,665,728

가

가

가

()

5,516,781 , 6,153,252 , 5,665,728 , 5,646,160 , 5,563,146 5,516,781 ,
 WO 01/01957, 01/49338, 01/87263, 01/87342, 01/87372, 01/87373, 01/87375 01/87376

가

5 µg/ 200 µg/ 10 µg/ 60 µg/
 100 µg 10 mg 300 µg 2 mg 500 µg 1.5

mg

가

(Duraflex Coronary Stent) ()가

S

Nitinol™

	8 mm	50 mm			()	5 mm	100 mm
0.5 mm	10 mm		0.8 mm	8 mm			1.0
mm	100 mm		2.0 mm	30 mm		0.025 mm	2.0 m
m		0.05 mm	0.5 mm				

가

300

Nitinol™

5,195,417 , 5,102,417 4,776,337

6,471,980

가

가

가

가

-1-

-e-

) (,)

(,)

(,)

1

2

6,471,980

가 / 가 (PTFE), PARALYST™ 가
 가 (PEG)
 가 0.01 가 100 가 0.1 가 10 가
 가 PTFE, PARYLAST™, 가
 가 1 가
 가 가 / 가
 가 가
 가 PARYLAST™ 가 50 nm 10
 가 1 가
 가 가
 가 6,471,980 가 (: IIb/IIIa)
 가 가
 가 1 가
 가 1 가
 가 10 µg/ 7 60 µg/ 21 가 1 45 5 µg/ 200 µg/
 가 가
 가 가 1 가 가 1 45 가 ()
 가 가 () 2 3 가 ()

가

가

(prosthesis)

가

1

12

3

50

4

24

2

8

가

가

(: pH

pH

N,N-

, DMSO,

0.01

100

0.1

10

가 3.0 mm_14mm

Duraflex™
25 mg/ml

100%

.75:25 PLLA/PCL

(
200 rpm

) 1.4-

10-30

25

-35

24

[, Circulation, 2001; 103:192], [

, Circulation, 2001; 104:2007] [

, N Engl J Med 2002; 346(23): 1773-1780]

Bx VELOCITY

5; 6:75-83; Revell , Biomaterials. 1998; 19:1579-1586]

316L

가

([- , J Appl Biomater. 199

가 5 μm

Bc VELOCITY(Cordis)

[FR]

FR

15

[SR]

28

80%가 30 SR

(140

$\mu\text{g} / \text{cm}^2$).

3 ng/mL, FR; 1 ng/mL, SR), 72
8 17 ng/mL

1 가 (2-
가

Bx VELOCITY

(>12)

가 18 mm 3 3.5 mm

12 (325 mg/d, 300) 75mg/d 60 300 mg

가

가

, , , , , , X , , ,

0.05 W/cm² 2-10 W/cm², 20 kHz 100 MHz, 0.1 MHz 20 MHz
1 mm 30 cm, 1 cm 0.5 W/cm² 2-5 W/cm²
5 30 1 15 가
37 48

가

가

2T 1 nm 100 nm 0.01 T

가

가

가

가

/

가

4

()

1

pH

가

1

99%

가

가

가

(
)
가

(1가

가

)

(

가

30

가

, Nattermann % Cie. GMBH)

0.01% Tween 80

, PHOSPAL PG-50(1,2-

가

25 mg

1 g

81%, 2%, 2% Tween 1%

(5%) (5%) (95%), (Azo ne)

가 가 가 가 가

가 5,182,293 4,837,311 (0 649 659 (1995.4.26) 0 648 494 (1995. 4.19) 5,145,684 () 5,989,59 1 () WO 98/56358 [, K. , Endocrine-related Cancer(2001), 8, 249-258] [, Cancer Res. (2001) 61 1527-1532]

mg/kg 0.01 100 mg/kg 0.1 10 1 1 2000 mg (:) 1 1 , 4-10 2-10 4-10 5 , 9 4-10 4 , 9

0.01-25 mg/kg, 0.01-5 mg/kg, 0.01 mg/kg, 100 mg/kg

10% 20%

가

1 ()

가

가

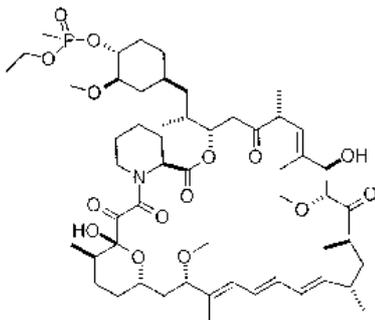
가

DNA,

[Molecular Cloning UA Laboratory Manual, 2, (1989)]; [DNA Cloning I II (D.N. (1985))]; [Oligonucleotide Synthesis (M.J. 가 (1984))]; [4,683,185]; [Nucleic Acid Hybridization (B.D. S.J. (1984))]; [Transcription and Translation (B.D. S.J. (1984))]; [Culture Of Animal Cells (R.I. R. (1987))]; [Immobilized Cells And Enzymes (IRL (1986))]; [B. (1984)]; [The Treatise, Methods In Enzymology (1987)]; [Gene Transfer Vectors For Mammalian Cells (J.H. M.P. (1987))]; [Methods In Enzymology, 154 155 (), Immunochemical Methods In Cell And Molecular Biology ((1987))]; [Handbook Of Experimental Immunology, I-IV (D.M. C.C. (1986))]; [Manipulating the Mouse Embryo ((1986))]

1:

C-43



(30 mL) 가 (15.2 g, 0.1 mmol) (0 mmol), PCl_5 (20.8 g, 0.1 mmol) POCl_3 12.7 g . b.p. 52-54 /1 mmHg; ^{31}P -NMR(121 MHz, CDCl_3) d 40 .7.

C-43

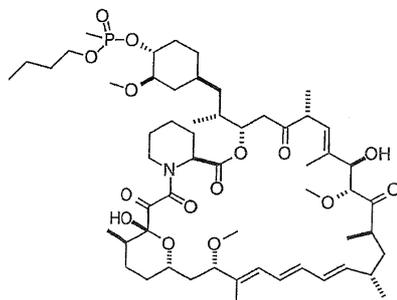
1.5 mL (0.088 g, 0.82 mmol) (0.1 g, 0.109 mmol) (0 mmol), 0.25 mL 3,5- (0.078 g, 0.547 mmol) 가 , 0.25 mL (MS (0 mmol) , 50:50 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, DMSO 1) , 20 mL EtOAc , EtOAc(150 mL) NaHCO_3 (100 mL) 1N HCl(100 mL 1), NaHCO_3 (100 mL 1) (100 mL 1) , MgSO_4 (0.5:10:3:3 MeOH/DCM/EtOAc/) , 0.024 g (2:1) : ^1H NMR(300 MHz, CDCl_3) d 4.19(m,1Ha,1Hb), 4.15-4.01(m,3Ha,3Hb), 1.56-1.27(m,6Ha,6Hb); ^{31}P NMR(121MHz, CDCl_3) d 32.1, 29.9; 1043 m/z(M+Na).

1.

8-13 가 .2 가 -5 ± 5 가) , 0 (3,5- 15-20 3 TLC(1:10:3:3 MeOH/DCM/EtOAc/) HPLC

2:

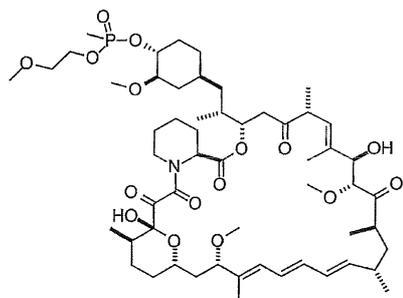
n- C-43



1H- (0.002 g, 0.028 mmol) , DCM 0.33 mL n- (0.041 g, 0.55 mmol) 가 , DCM 0.33 mL 3,5- (0.090 g, 0.84 mmol) 가 (0.073 g, 0.55 mmol) 가 , DCM 0.33 mL (0.1 g, 0.11 mmol) (0 mmol) , DCM 0.5 mL 3,5- (0.090 g, 0.84 mmol) 가 , DCM 0.5 mL (MS) . (0 mmol) 20 mL EtOAc , EtOAc(120 mL) 1N HCl(10 mL 1) , NaHCO_3 (100 mL 3) (100 mL 1) , MgSO_4 (MeOH/DCM/EtOAc/ 0.25:10:3:3 0.5:10:3:3) HPLC(85% MeOH/ H_2O) 0.063 g (2:1) : ^1H NMR(300 MHz, CDCl_3) d 4.15(m,1Ha,1Hb), 4.11-3.89(m,3Ha,3Hb), 3.04(m,1Ha,1Hb); ^{31}P NMR(121MHz, CDCl_3) d 32.1, 29.9; 1071 m/z(M+Na).

3:

2- - C-43



2

): ^{31}P NMR(121 MHz, CDCl_3) d 33.0, 30.8; 1073 m/z (M+Na).

(2:1

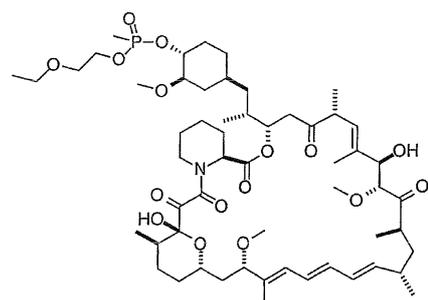
4:

-

2-

-

C-43



2

): ^{31}P NMR(121 MHz, CDCl_3) d 32.8, 30.8; 1087 m/z (M+Na).

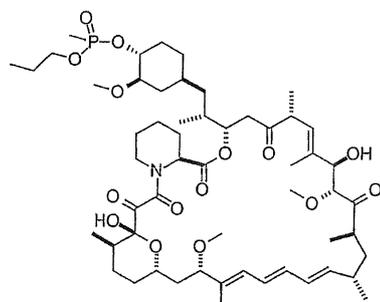
(2:1

5:

-

n-

C-43



2

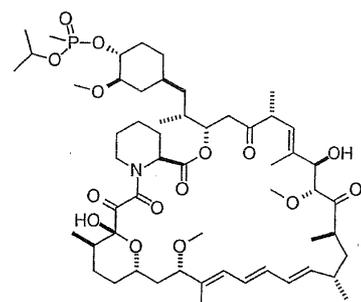
): ^{31}P NMR(121 MHz, CDCl_3) d 32.1, 29.9; 1057 m/z (M+Na).

(2:1

6:

-

C-43

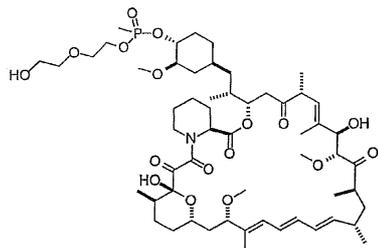


2

(2:1

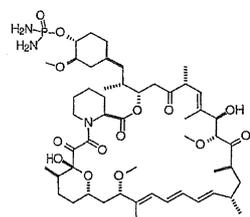
): ³¹P NMR(121 MHz, CDCl₃) δ 31.3, 28.8; 1057 m/z (M+Na).

7: 2-(2- -)- C-43



2 (2:1): ³¹P NMR(121 MHz, CDCl₃) δ 32.7, 30.9; 1103 m/z (M+Na).

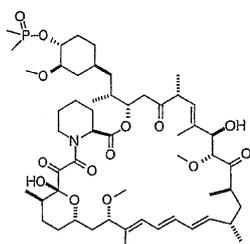
8: - C-43



C-43

DCM 5.0 mL (0.109 g, 0.12 mmol) 4- (0.072 g, 0.59 mmol)
 (0) , (0.050 mL, 0.54 mmol) 가 . 15 , DCM 5.0 mL
 , -78 . 2
 25 mL 25 mL EtOAc 75 mL 5% HCl 25 mL 2
 (9:1 / MgSO₄), 0.029 g . ³¹P NMR(121 MHz, CDCl₃) δ 16.4; 1014 m/z(M+Na).

9: - C-43



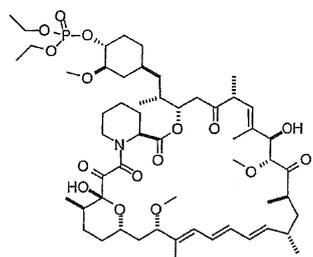
C-43

1.8 mL (0.1 g, 0.109 mmol) (0) , 2,6- -t- -4- 0.
 168 g(0.82 mmol) N₂ 가 , 0.2 mL (0.
 062 g, 0.547 mmol) 가 . 0 N₂ 3.5 ()
 TLC) . (0) 20 mL EtOAc , EtOAc(150 mL)
 NaHCO₃ (100 mL) , 1N HCl(100 mL 1)
) , NaHCO₃ (100 mL 1) (100 mL 1) , MgSO₄ .
 (1:10:3:3 MeOH/DCM/EtOAc/) ,
 0.092 g : ¹H NMR(300 MHz, CDCl₃) δ 4.18(m,1H), 4.10(m,1H), 3.05(m,1H), 1.51(m,6H); ³¹P NMR(121MHz, CDCl₃) δ 53.6; 1013 m/z(M+Na).

9.

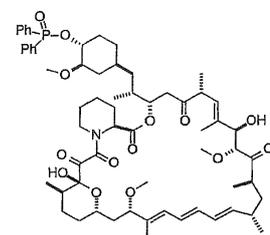
15-20 가 . 2 가 , , 3,5- (2.2) (2.0)
 1 , , NaHCO₃ -t- (MTBE),
 30 60 TLC(1:10:3:3 MeOH/
 DCM/EtOAc/) HPLC 1N HCl, NaHCO₃
 (2), NaCl , HPLC

10: C-43



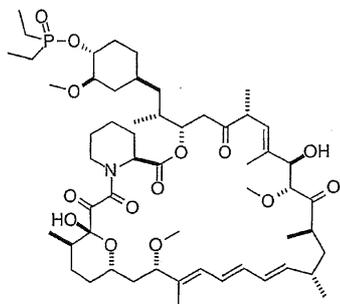
⁹ NMR(121 MHz, CDCl₃) δ -1.2; 1073 m/z(M+Na). ³¹P

11: - C-43



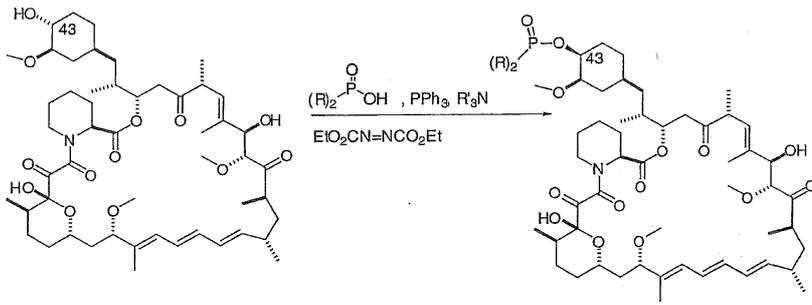
⁹ NMR(121 MHz, CDCl₃) δ 31.3; 1137 m/z(M+Na). ³¹P

12: - C-43



⁹ NMR(121 MHz, CDCl₃) δ 61.3; 1041 m/z(M+Na). ³¹P

13: C-43



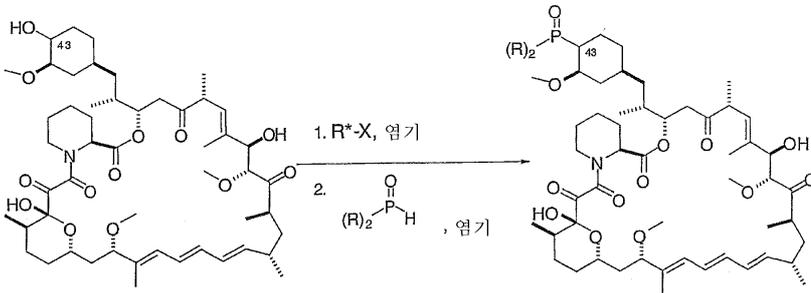
43-

[, P.B. , J Chem Soc, Perkin Trans. 1, 1987 [8], 1813-1815]

, R가 R'

-O-

14: - C-43



[, M. , Bull Chem Soc Japan, 1983, 56, 1871-1872]

, X

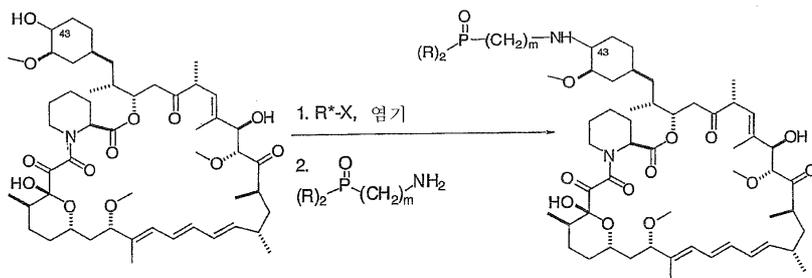
R * X

C-43 R * -O

, R

-O-

15: - C-43



[, E. , Tet. Lett., 1983, 24, 295-298]

, A. WO

98/09972

Or, Y.S.

5,583,139

, X

R * X

C-43 R *

-O

, m

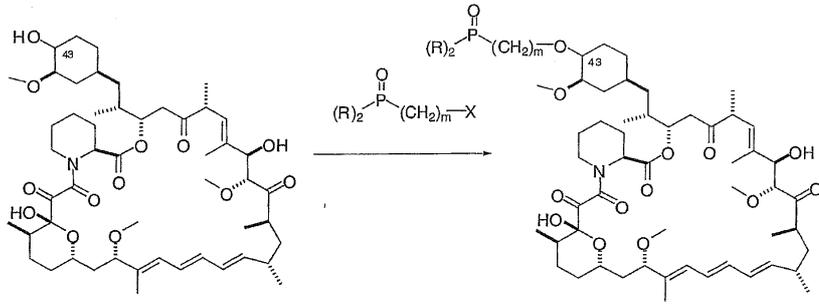
1

10

, R

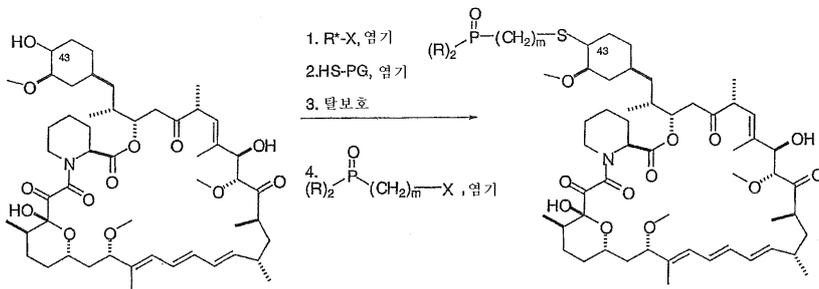
-O-

16: - C-43



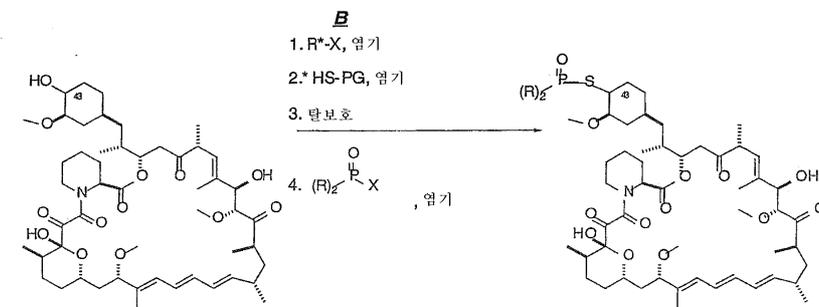
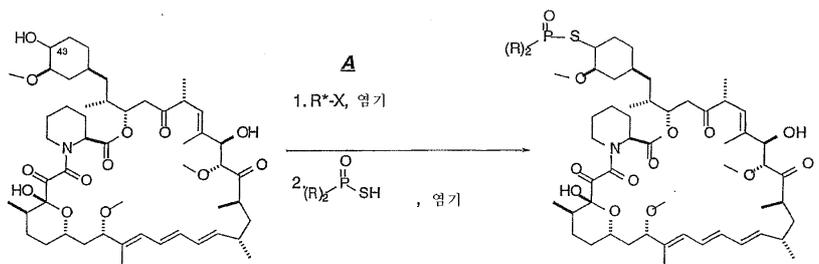
16, S PCT () WO94/09010, D. WO98/09970, X, m

17: C-43



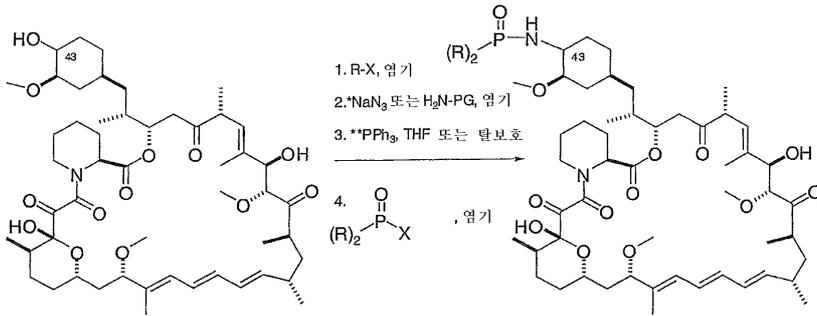
C-43 R* -O, m 1 10, PG, R * X, WO 98/09972

18: 가 C-43



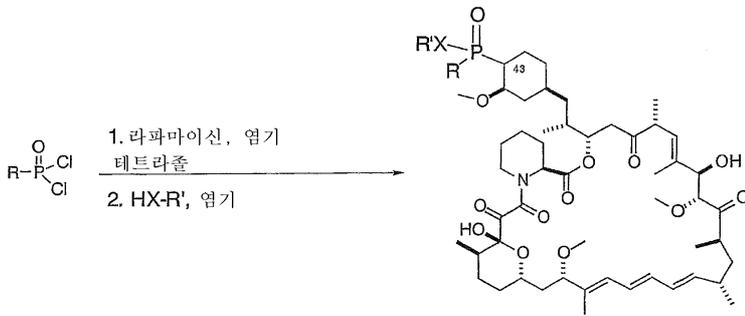
WO 98/09972 [, Synthesis, 1989, 1,48-50] (A) PCT
 [, Bull Soc Chim Fr, 1996, 133, 951-964] (B)
 * X, C-43 R* -O, m 1 10, R

19: C43



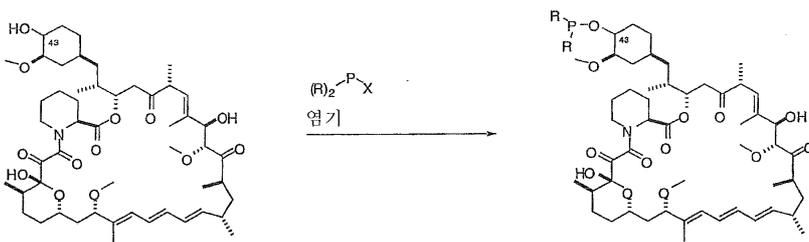
PCT WO9/09972 [, F. , Tetra
hedron: Assymetry, 2001, 12, 1635-1643] [M. , J. Org. Chem., 1995, 60, 7364-7365]
R * X , C-43 R * -O , m 1 , X , PG , R
-O-

20: C-43



[, K. , Tetrahedron, 1993, 49, 363-368]
, X NH, O S , R R'
(X가 NH , R' H)

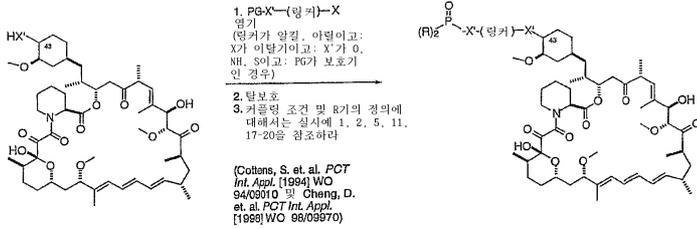
21: 가 O-P-



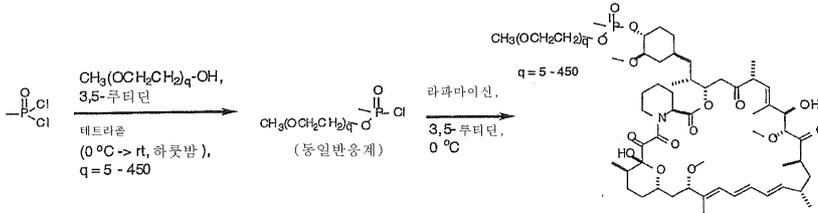
[, J.S. , Synthesis, 1993, 8, 819-823] [, E.E. , J. Organo
met. Chem., 1997, 529, 171-176]
, X

22: 가

C-43 (R 1,2,5,
11 17-20)



23 : - C-43 PEG



24:

70 μM 22906-8006, 가 60 (: , DCM) FLASH Biotage
8006) BIOTAGE, Inc. (가 30-

DCM (: , DCM) 0.5:10:3:3 MeOH/DCM/EtOAc/
TLC, HPLC 0.5:10:3:3 MeOH/DCM/EtOAc/
HPLC HPLC . 2 가

FLASH Biotage

(4-6)

가 (2)

25:

가 3.0 mm×14 mm Duraflex™ 100% ,
1-12 25 mg/ml . 75:25 PLLA/PCL (,
) 1,4- () 200 rpm 10
-30 , () ,
25-35 24

26: 가

Duraflex (3.0×13 mm) SS 가 가 10 mm
5 nm 가 가 . 1-12

1 45

27

1-12

ARYLAST™,
2 mg

1 45

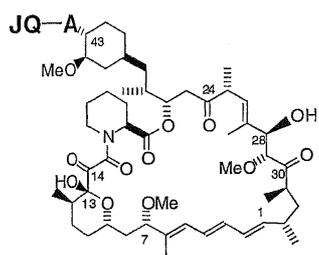
100 μg

28

25

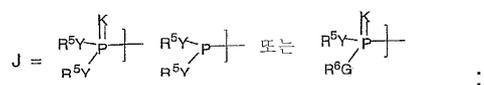
(57)

1.



A -O-, -S-, -NR²- ;

Q (A가 -O-, -S-, -NR²-) Q -V-, -OV-, -SV- -NR² V-
V , J , A
, VA, OVA, SVA NR² VA ;



K O S ;

Y -O-, -S-, -NR²- R⁵ P ;

R² R⁵ , H ;

R⁶ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) -C(O)(YR⁵) ; P R²,
R⁵ R⁶ H가 ;

R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR²-, (M)_x R⁶ P ;

M ; , M-M'

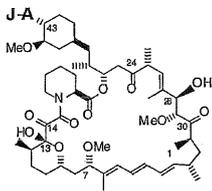
x 0 6 ;

, , , ;

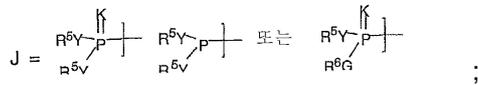
, JQA- (HO)₂(P=O)O-; (MeO)₂(P=O)O-; (R²Y)(Me)(P=O)O-, (HO)₂(P=O)-W-O (HO)₂(P=O)-W-O

(R²Y)₆, W , U, O, S, SO SO₂.

2.



A -O-, -S- -NR²- ;



K O S ;

Y -O-, -S-, -NR²- R⁵ P ;

R² R⁵ , H ;

R⁶ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) -C(O)(YR⁵) ; P R², R⁵ R⁶ H가 ;

R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR²-, (M)_x R⁶ P ;

M ; , M-M'

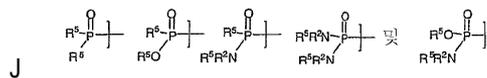
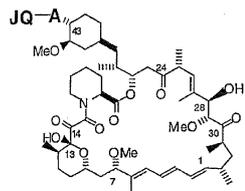
x 0 6 ;

, , , ;

, (a) J-A- (HO)₂(P=O)O- (MeO)₂(P=O)O-가 (b) JA-가 (R²Y)(Me)(P=O)O- , (R²Y)) ,

3.

:



A, -O-, -S-, -NR²- ;

Q, (A가 -O-, -S-, -NR²-) Q -V-, -OV-, -SV- -NR²V- , A , V , VA, OVA, SVA , NR²VA ;

K O S ;

Y -O-, -S-, -NR²- R⁵ P ;

R² R⁵ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) , -C(O)(YR⁵) ; P H ; R⁶ R², R⁵ R⁶ H가 ;

R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR²-, (M)_x R⁶ P ;

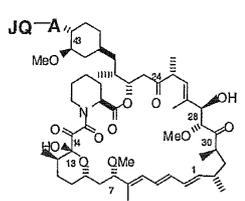
M , M-M' ;

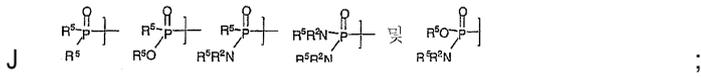
x 0 6 ;

-OR⁵ -NR²R⁵가 -OH -NHR⁵ , R² R⁵ ; , J-Q-A-가 (R²Y)(Me)(P=O)O- , (R²Y) ,

4.

:





A , -O-, -S- -NR² - ;

Q , (A가 -O-, -S- -NR² -) Q -V-, -OV-, -SV- -NR² V- , A ,
 V , VA, OVA, SVA , NR² VA ; , J

K O S ;

Y -O-, -S-, -NR² -, R⁵ P ;

R² R⁵ R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) , -C(O)(YR⁵) ; P H ; R⁶
 H가 ; R², R⁵ R⁶

R², R⁵ / R⁶ 2 ;

G -O-, -S-, -NR² -, (M)_x R⁶ P ;

M , M-M'
 ;

x 0 6 ;

, , , , , ;
 -OR⁵ -NR² R⁵ 가 -OH -NHR⁵ , R² R⁵
 ;

, J-Q-A-가 (R² Y)(Me)(P=O)O- , (R² Y) 15 .

5.

1 , -OR⁵ -NR² R⁵ 가 -OH -NHR⁵ , R² R⁵ 가
 , -OH, -, -, C1-C6 .

6.

2 , -OR⁵ -NR² R⁵ 가 -OH -NHR⁵ , R² R⁵ 가
 , -OH, -, -, C1-C6 .

7.

3 , -OR⁵ -NR² R⁵ 가 -OH -NHR⁵ , R² R⁵ 가
 , -OH, -, -, C1-C6 .

8.

4 , -OR⁵ -NR² R⁵ 가 -OH -NHR⁵ , R² R⁵ 가
 , -OH, -, -, C1-C6 .

9.

5 , R² R⁵ 가 , , n- , -- , n- , 2- , t- ,
 , -OH, -, -, - ,

OH, -NHR⁵, , 가 -OR⁵ -NR²R⁵가 -

10.

6, R² R⁵가, , n-, --, n-, 2-, t-, , -OH, -, 가 -OR⁵ -NR²R⁵가 -

OH, -NHR⁵, .

11.

7, R² R⁵가, , n-, --, n-, 2-, t-, , -OH, -, 가 -OR⁵ -NR²R⁵가 -

OH, -NHR⁵, .

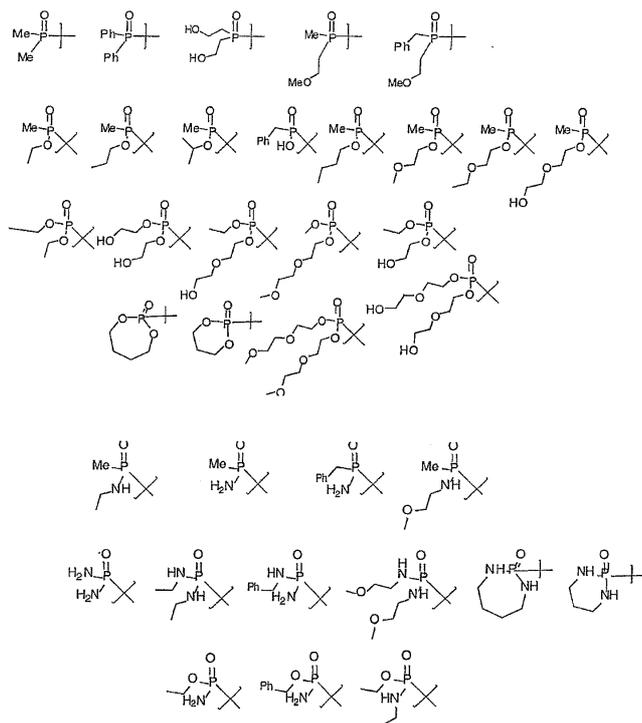
12.

8, R² R⁵가, , n-, --, n-, 2-, t-, , -OH, -, 가 -OR⁵ -NR²R⁵가 -

OH, -NHR⁵, .

13.

1, J가 :



14.

1, QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS-, , V가

15.

4, QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS-, , V

16.

5 , QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS- , V

17.

8 , QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS- , V가

18.

9 , QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS- , V

19.

13 , QA가 -O-, -OVO-, -NH-, -OVNH-, -S-, -SVS- V가 , JQA-

20.

1 19 , JQA- JA-가 (R²Y)(Me)(P=O)O- , R²Y-
가 15

21.

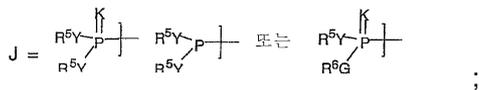
20 , JQA-가 (R²Y)(Me)(P=O)O- , R²Y-가 10

22.

43- - , 43 가 JQA-

A -O-, -S- -NR²- , ;

Q , (A가 -O-, -S- -NR²-) Q -V-, -OV-, -SV- -NR²V- , A ,
V , VA, OVA, SVA , NR²VA ; , J



K O S ;

Y -O-, -S-, -NR²- R⁵ P ;

R² R⁵ H ; R⁶
R⁵, -PK(YR⁵)(YR⁵), -SO₂(YR⁵) , R², R⁵ / R⁶ -C(O)(YR⁵) ; P R², R⁵ R⁶
H가 ; R², R⁵ / R⁶ 2 2 ;

G -O-, -S-, -NR²-, (M)_x R⁶ P ;

M , M-M'

x 0 6 ;

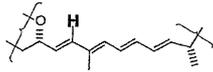
(a) (e) 가 :

(a) 28) ; , -OR² -OC(=O)AR² 28 (

(b) 24 , ; -OR² -OC(=O)AR²

(c) 24 , ; -OR² -OC(=O)AR²

(d) 7 -OMe / H, , -R^A, -OR^A, -SR^A, -OC(O)R^A, -OC(O)NR^AR^B,
 -NR^AR^B, -NR^BC(O)R^A, -NR^BC(O)OR^A, -NR^BSO₂R^A -NR^BSO₂NR^AR^B (, R^A
 R² , R^B OH R²) -OMe ;



(e) 7 -OMe .

23.

22 , -OR⁵ -NR²R⁵가 -OH -NHR⁵ , R² R⁵가
 , -OH, -, -, C1-C6 .

24.

23 , R² R⁵가 , , n- , -- , n- , 2- , t- ,
 , -OH, -, , 가 -OR⁵ -NR²R⁵가
 -OH -NHR⁵ .

25.

22 , QA가 -OVO-, -OVNH- -SVS- , V가 .

26.

22 25 , J가 :

