

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. ⁷
C07D 235/30

(11)
(43)

2001 - 0079520
2001 08 22

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| (21) | 10 - 2001 - 7000359 |
| (22) | 2001 01 09 |
| | 2001 01 09 |
| (86) | PCT/EP1999/04673 |
| (86) | 1999 07 06 |

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| (87) | WO 2000/03973 |
| (87) | 2000 01 27 |

(81)

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AP ARIPO : 가

EA :

EP :

OA OAPI :

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(30) 19831710.7 1998 07 15 (DE)

(71)

64293 250

(72)

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| - 64342 | - | 6 |
| - 64286 | 8 | |
| - 65824 | - | - 53 |
| - 80799 | 77 | |
| - 81543 | 3 | |

(74)

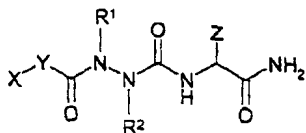
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(54)

$$X, Y, Z, R^1 \quad R^2 \text{가} \quad 1$$

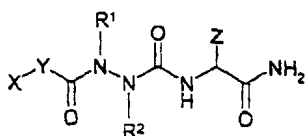
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(,

$$X \quad H_2N-C(=NH)-, H_2N-C(=NH)-NH-, A-C(=NH)-NH-, Het^1- \quad Het^1-NH-$$
$$Y \quad -(CH_2)_n- \cdot -(CH_2)_m- \text{---} \text{---} (CH_2)_o-$$
$$-(\text{CH}_2)_s-\text{CH}(\text{R}^4)-(\text{CH}_2)_t-(\text{CH}_2)_p-\text{Het}^2-(\text{CH}_2)_q-$$
$$Z = (\text{CH}_2)_r - \text{R}^5,$$
$$R^1, R^2 \quad H \quad A \quad ,$$

R^3 H, F, Cl, Br, A, OA OCF_3 ,

R^4 F, Cl, Br, A, OA OCF_3 ,

R^5 COOH, COOA, $CONH_2$, SO_3H , PO_3H_2 ,

Het¹ NH_2 - 1 4 -

Het² F, Cl, Br, A, OA OCF_3 - 1 4 /
5 - 6 - ,

A 1 6 ,

n 0, 1, 2, 3, 4, 5, 6, 7 8 ,

m, o, p, q, r, s, t 0, 1, 2, 3, 4 5 .)

, US 5,741,796 .

I , , 3 - , v - , 3 -
5 - v 1, v 3, v 5, IIb 3 v 6
v 8 ; , v 3
.

, {J.W.Smith et al. in J. Biol. Chem.265, 12267 - 12271(1990)}

{P.C. Brooks, R.

A. Clark D.A. Cheresh in Science264, 569 - 71(1994)} .

(apoptosis,
) 가 {P.C. Brooks, A.M. Montgomery, M. Rosenfeld, R.A. Reisfeld, T. - Hu, G. Klier
D.A. Cheresh in Cell79, 1157 - 64(1994)} .

(IIb/IIIa)
I GPIIb/IIIa 가 .
:

, 가
, {P.C. Brooks et al., Cell 85, 683 - 693(1996)} , - RGD
v 3 MMP - 2(- 2) .

() 가

가 ,
 , 가 , GPIIa/IIIb

ty, 2851 - 2855 (1988) } . {P. Valentin - Weigund et al. in Infection and Immunity .

UV - 가 ,

Ac

Asp

$$\text{Aza - Gly } \text{H}_2\text{N} - \text{NH} - \text{COOH}$$

BOC 3 -

CBZ Z

DCCI

DCM

DIPEA

DMF

EDCI N - - N,N' - () -

Et

Fmoc 9 -

Gly

HATU O - (7 - - 1 -) - N,N,N',N' - -

HOBt 1 -

Me

MBHA 4 -

Mtr 4 - - 2,3,6 -

NMP N -

HONSu N -

OBzl

OtBu 3 -

Oct

OMe

OEt

Pbf 2,2,4,6,7 - - 5 -

POA

Sal

TBTU O - (1H - - 1 -) - N,N,N',N' -

TFA

Trt ().

, D L) (, DL) , (

(prodrug) ,

I ,

{ , Int. J. Pharm, 115, 61 - 67 (1995) }

, ,

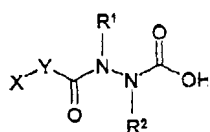
가 I 가 , , -

, , 가 가 . , ,

1 I , ,

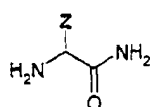
a) II

II

(, X, Y, R¹ R² 1 , .)

III ,

III

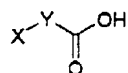


(, Z 1 , .)

,

b) IV

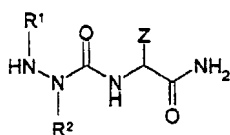
IV



(, X Y 1 , .)

V ,

V



(, R¹, R² Z 1 , .)
;

c) 가 가 , I
,
/ I .

, 1 -, 2 - 3 - , 1,1 -, 1,2 - 2,2 - , 1 - , 2 - 3 - 4
- , 1,1 -, 1,2 -, 1,3 -, 2,2 -, 2,3 - 3,3 - , 1 - 2 - , 1 - - 1 - ,
1 - - 2 - , 1,1,2 - 1,2,2 - .

, 2,2,2 - , BOC, 2 - , POA,
, FMOC, Mtr , CBZ(" ") , 4 -

R¹ H A, , H Me .

R² H, .

OA , , , .

R⁴ F, Cl, Br, , , , OCF₃ ,
- , o -, m - p - , o -, m - p -
, o -, m - p - , o -, m - p - , o -, m - p - 3 - , o -, m -
p - , o -, m - p - , o -, m - p - , o -, m - p - , o -,
m - p - , o -, m - p - .

R⁵ COOH, COOCH₃, COOC₂H₅, COO(t -), CONH₂, PO₃H₂, SO₃H .

Het¹ - - NH₂ - 1 -, 2 - 3 - , 1 -, 2 -, 4 - 5 -
, 1 -, 3 -, 4 - 5 - , 2 -, 3 - 4 - , 2 -, 4 -, 5 - 6 - ,
1,2,3 - - 1 -, - 4 - - 5 - , 1,2,4 - - 1 -, - 3 - - 5 - , 1 - 5 - ,
3 - 4 - , , 1 -, 2 -, 3 -, 4 -, 5 -, 6 - 7 - , 1 -, 2 -, 4 - 5 -
, 1 -, 3 -, 4 -, 5 -, 6 - 7 - , 2 -, 3 -, 4 -, 5 -, 6 -, 7 - 8 - , 1 -, 3 -, 4 -, 5 -, 6 -,
7 - 8 - , 3 -, 4 -, 5 -, 6 -, 7 - 8 - , 2 -, 4 -, 5 -, 6 -, 7 - 8 - , 1H -
[4,5 - b] - 2 - 1,8 - - 7 - .

, Het¹ , 2,3- -1-, -2-, -3-, -4- -5- , 2,5- -1-, -2-,
 -3-, -4- -5- , 1-, 2- 3- , -1-, -2- -4- , 2,3-
 -1-, -2-, -3-, -4- -5- , -1-, -3- -4- , 1,4- -1
 -, -2-, -3- -4- , 1,2,3,4- -1-, -2-, -3-, -4-, -5- -6- , 1-, 2-,
 3- 4- , -1-, -3- -4- , -1-, -2-, -4- -5-
 , 1-, 2- 3- , 1,2,3,4- -1-, -2-, -3-, -4-, -5-, -6-, -7- -8-
 , 1,2,3,4- -1-, -2-, -3-, -4-, -5-, -6-, -7- -8- 1,2,3,4-
 -1,8- -7- .

Het² -F-, -Cl-, -Br-, -A-, -OA- -OCF₃- 2,3-, 2,4-, 2,5-
 3,4- , 2,3-, 2,4-, 2,5- 3,4- , 2,4-, 2,5- 4,5- , 2,3-, 2,4-, 2,6-
 3,5- , 2,4-, 2,5-, 2,6-, 4,5- 5,6- .

n 2, 3, 4, 5 6 , 0, 1, 7 8 ; n 3, 4 5 .


m o 0, 1 2 , 0 .

s t 1 2 .

p q 0 1 , 0 .

, I la li ,
 I 가 ,

Ia) , X H₂N-C(=NH)-NH- ,

Ib) , Y  ,


Ic) , Z -CH₂-COOH ,

Id) , X H₂N-C(-NH)-NH- , A-C(=NH)-NH- " Het¹-NH- ,


Ie) , X H₂N-C(=NH)-NH- " Het¹-NH- ,

R¹ R² H ,

If) , X H₂N-C(=NH)-NH- " Het¹-NH- ,

Y  - (CH₂)_s-CH(R⁴)-(CH₂)_t- ,

Ig) , X H₂N-C-(=NH)-NH- " Het¹-NH- ,


Y  ,

- (CH₂)_s - CH(R⁴) - (CH₂)_t - ,

Z - CH₂ - COOH ,

R⁴ Cl - ,

lh) , X H₂N - C(= "NH) - NH - " A - C(= "NH) - NH - " Het¹ - NH - ,

Y  ,

- (CH₂)_s - CH(R⁴) - (CH₂)_t - (CH₂)_p - Het² - (CH₂)_q - ,

Z - CH₂ - COOH ,

R⁴ Cl - ,

Het¹ - NH₂ - , ,

, , , ,

2,3- , ,

s t 1 ,

m, o, p, q 0 1 ,

li) , X H₂N - C(= "NH) - NH - " Het¹ - NH - ,

Y  ,

- 2,5 - - (CH₂)_s - CH(R⁴) - (CH₂)_t - ,

Z - CH₂ - COOH ,

R⁴ Cl - ,

Het¹ - NH₂ - , ,

, , , ,

2,3- , ,

s t 1 ,

m o 0 .

I (, Houben - Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg - Thieme - Verlag, Stuttgart)

II, 1 806 (1974))

, I II III ,

IV, V, I.

{ Angew. Chem,92, 129(1980) }, DCCI EDCI 2 - , - N - , - 1,2 - , , DMF , - 10 40, 0 30 ° .

14.

II / IV

nischen Chemie, Georg - Thieme - Verlag, Stuttgart (, Houben - Weyl, Methoden der organischen Chemie, Georg - Thieme - Verlag, Stuttgart) .

가, HOBt N -

I, _____, (Angew. Chem.97, 801 - 812 1985),
가 _____.

, | 가 , 가 , 가 .

가 가 I , /

, NH₂ NHR' (, R' BOC CBZ N H)

, R" O- (H , R") , , I ,
 , - / 가 .
 가 , .
 " " , ()
 , . 가 . (,
) , , 1 - 20, , 1 - 8 가
 . " " 가 . ,
 , , ,
 ; ; POA ;
 ; CBZ(" , 2,2,2 - , BOC, 2 -
 "), 4 - , FMOC ; Mtr
 . BOC Mtr , CBZ, Fmoc, .
 " " ,
 , 가 , 가 .
 1 - 20, , 1 - 10 가 , p- , p
 - , 3 - COOH
 3 - { , Asp(OBut)} .
 I - - , TFA
 , - p-
 , 가
 , DMF , 가 , ,
 가 , TFA
 70% 9:1
 0 50 ° 가 , 15 30 ° ()
 .
 BOC, OBut Mtr , 15 - 30 TFA 3 5N HCl
 , FMOC 15 - 30 ° DMF ,
 5 50% .
 가 (, CBZ) , (,
) DMF 가 0 100 ° ,

1. 200 bar, 20 - 30 ° 1 - 10 bar . CBZ 가
5 10% Pd/C, 20 - 30 ° /DMF Pd/C (

[illegible]

이 / 가

[illegible]

이러한 결과를 바탕으로, 본 연구에서는 다음과 같은 결론을 도출하였다.

1 I 가

US - A - 4 472 305
0.05 500mg, 0.5 100mg
1kg 0.01 2mg
가

I
Asp

(sepharose) (Sephadex)
(Tentakelpolymere)

I 가
D L
(
82:15:3
/ /

10
Rf ; n - / / 3:1:1(A), / 9:1(B)
RT = " " , HPLC ():

: - 5 - C₁₈ (Nucleosil - 5 - C₁₈) (250 x 4; 5 μm).

TFA가 0.1% (B) TFA가 0.1% (A) (%
) R_t 1 ml/

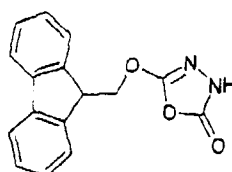
220 254 nm .

(MS) : ESI() (M+H) ⁺

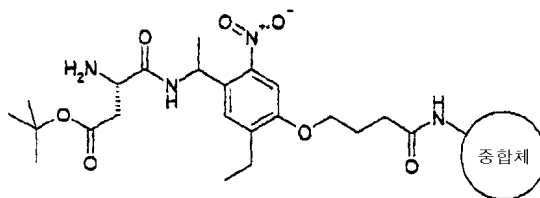
1

1. 5 - (9H - - 9 -) - 3H - [1,3,4] - 2 - :

(1.89M; 4.2ml) 995mg 9H - - 9 - - 40
 ml 40ml NaHCO₃ 가 . 15
 , 5 - (9H - - 9 -) - 3H - [1,3,4] - 2 - (" A") .

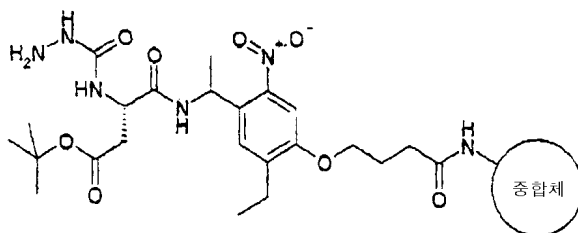
58mg; IR (KBr): 3300s, 1780s, 1650s, 1451m, 1426m, 1347m, 1224m, 918m, 758w, 740m cm⁻¹ .2. - Asp(OtBu) - NH₂ 2 (" B"):

1.86g 4 - (4 - (1 - (9 -)) - 2 - - 5 -) R - (R - TentaGel) (0.18 mmol/ g) 20 ml DMF , DMF 20% 15 ml
 (deprotect) . DMF , 0.27g Fmoc - Asp(OtBu) - OH, 0.1g HOB
 t 0.211g TBTU 6 ml DMF . DIPEA 0.22 ml 가 (pH 7),
 1 DMF (6 x 20 ml) , DMF 20% 15 ml
 DMF (5 x 20 ml), (3 x 20 ml) (2 x 20 ml)

3. - Aza - Gly - Asp(OtBu) - NH₂ 2 (" C")

1.12g " B" DCM (3 x 7 ml) , 0.176g " A" 5 ml DCM , 1

DCM (5 x 7 ml), NMP (5 x 7 ml), DMF (3 x 7 ml), DMF 20% 7 ml
DMF (5 x 7 ml), (3 x 7 ml) (2 x 7 ml),

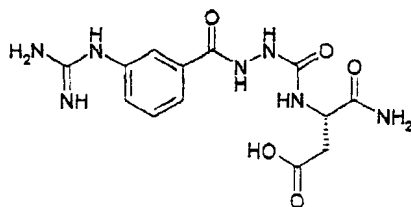


4. (3S) - 3 - [4 - (3 -)] :

0.349g "C" NMP (5 x 5 ml) DMF (1 x 5 ml), 53 mg 3 - (9H - - 9 -
) , 56 mg HATU 0.24 ml 1.5 ml DMF , 1

, 0.24g N,N' - - BOC - 1 - ("D") 2 ml , 5
0 ° 16 DCM,

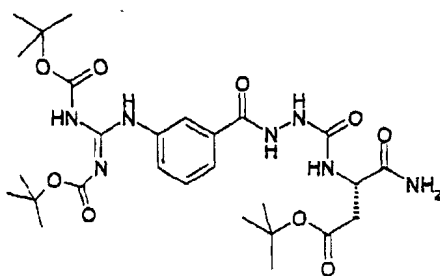
BOC , 95% TFA 5% H₂O (5ml) 1 DC
M, DCM , DCM, , A
CN/H₂O (6 ml) 1:1 , TQ 150
8 HPLC (3S) - 3 - [4 - (3 -)]



4.8 mg; R_t = "10.8" (0 20, A B, 30); MS(ESI) 352 [M+H]⁺

2

1 N,N' - - BOC - 1 - 1 t - (3S) - 3 - [4 - (3 -)
] [3 - (9H - - 9 -) Aza - Gly - Asp(OtBu) - NH₂
Fmoc] 40 ° 10 , t
- (3S) - 3 - [4 - (3 - (N,N' - - BOC -))]

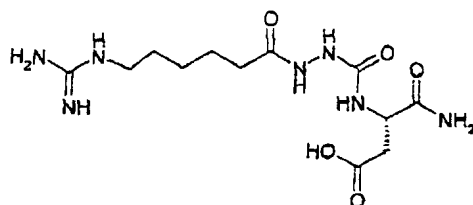


BOC, t-DCM, 95% TFA 5% H₂O 10
(3S) - 3 - [4 - (3 -)]
3

1 N,N' - - BOC - 1 - , 1 Aza - Gly - Asp(OtBu) - NH₂ 1 HATU 3
0° 10 , t- (3S) - 3 - [4 - (3 - (N,N' -
- BOC -))] .

BOC, t-DCM, 95% TFA 5% H₂O 10
(3S) - 3 - [4 - (3 -)]
4

1 , 336mg " C" 49mg 5 - (Fmoc -) , Fmoc
, 35mg " D" , TFA Boc , (3S) - 3 - [
4 - (5 -)] .



6.0mg; R_t = "10.6" (0 30, A B, 30); MS (ESI) 332

, " C" 4 - (Fmoc -) - 3 - " D" (3
S) - 3 - [4 - (4 - - 3 -)] {MS (ESI) 382} ;

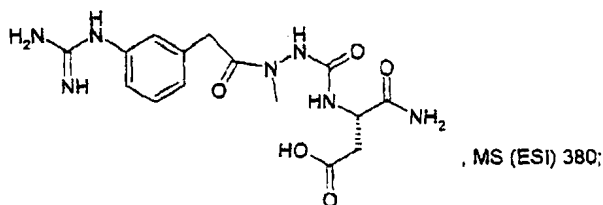
" C" 2 - (Fmoc -) - 5 - " D" (3S) - 3
- [4 - (2 - - 5 -)] {MS (ESI) 353} .

, - Aza - N' - Me - Gly - Asp(OtBu) - NH₂

5 - (Fmoc -) " D" (3S) - 3 - [4 - (5 -
) - 4 -] {MS (ESI) 346} ;

3 - (Fmoc -) " D" (3S) - 3 - [4 - (3 -
) - 4 -] {MS (ESI) 366} ;

3 - (Fmoc -) " D" (3S) - 3 - [4 - (3 -
) - 4 -]



, MS (ESI) 380;

3 - (Fmoc -) " D" (3S) - 3 - [4 - (3 -) - 4 -] {MS (ESI) 380} ;

4 - (Fmoc -) " D" (3S) - 3 - [4 - (4 -) - 4 -] {MS (ESI) 366} .

, - Aza - N - Me - Gly - Asp(OtBu) - NH₂

5 - (Fmoc -) " D" (3S) - 3 - [4 - (5 -) - 3 -] ,

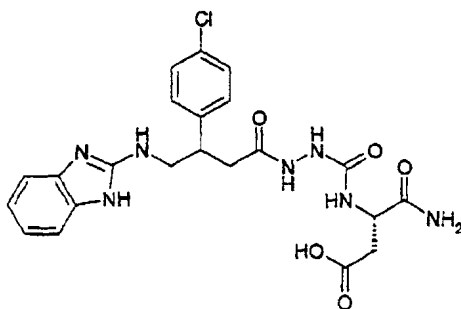
3 - (Fmoc -) " D" (3S) - 3 - [4 - (3 -) - 3 -] ,

3 - (Fmoc -) " D" (3S) - 3 - [4 - (3 -) - 3 -] .

5

1 , " C"

4 - (1H - - 2 -) - 3 - (4 -) , (3S) - 3 - {4 - [4 - (1H - - 2 -) - 3 - (4 -)]} ,

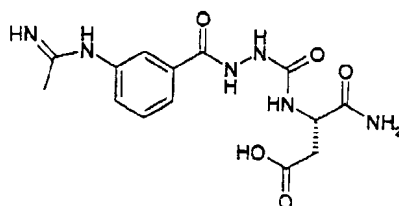


4 - (2 -) - 3 - (4 -) , (3S) - 3 - {4 - [4 - (2 -) - 3 - (4 -)]} ,

3 - - 5 - (2 -) , (3S) - 3 - {4 - [3 - - 5 - (2 -)]} ,

3 - (1H - - 2 -) , (3S) - 3 - {4 - [3 - (1H - - 2 -)]} ,

3 - , (3S) - 3 - {4 - [3 -]} ,



:

A:

6.5 I 100g 2 5g 3 2N pH
 , 5mg ,

B:

I 20g 100g 1400g
 20mg

C:

I 1g, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ 9.38g, $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ 28.48g 0.1g
 940MØ pH 6.8 , 1

D:

I 500mg 99.5g

E:

I 1kg, 4kg, 1.2kg, 0.2kg 0.1kg
 가 10mg

F:

E , , , 가

G:

I 2kg 20mg

H:

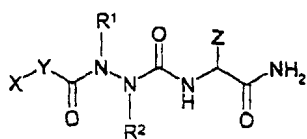
I 1kg 60 10mg ,

I:

I 14g NaCl 10 , 1 (0.1ml) 0.14mg

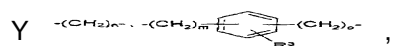
(57)

1.



(,

X = H₂N - C(=NH) - , H₂N - C(=NH) - NH - , A - C(=NH) - NH - , Het¹ - Het¹ - NH - ,



- (CH₂)_s - CH(R⁴) - (CH₂)_t - (CH₂)_p - Het² - (CH₂)_q - ,

Z = (CH₂)_r - R⁵ ,

R¹, R² = H , A ,

R³ = H, F, Cl, Br, A, OA , OCF₃ ,

R⁴ = F, Cl, Br, A, OA , OCF₃ ,

R⁵ = COOH, COOA, CONH₂, SO₃H, PO₃H₂ ,

Het¹ = NH₂ - 1 4 -

Het² = F, Cl, Br, A, OA , OCF₃ - 1 4 / 5 - 6 - ,

A = 1 6 ,

n = 0, 1, 2, 3, 4, 5, 6, 7 8 ,

m, o, p, q, r, s, t = 0, 1, 2, 3, 4 5 .).

2.

1 I

a) (3S) - 3 - [4 - (3 -)] ;

b) (3S) - 3 - [4 - (5 -)] ;

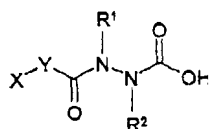
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3.

1 I ,

a) II

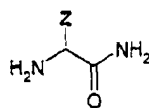
II



(, X, Y, R¹ R² 1 , .)

III ,

III

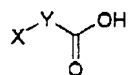


(, Z 1 , .)

,

b) IV

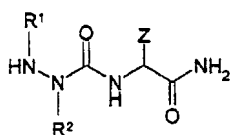
IV



(, X Y 1 , .)

V ,

V



($R^1, R^2 \in Z$ 1, .)
;

c) 가 가 , l ,
/ l .

4.

1 l / 가 가 , .

5.

1 l / 가 .

6.

1 , , l , , , 가 , .

7.

1 l / 가 .

8.

1 , l , / , , , 가 , .

9.

1 l / 가 .