

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. 7
C07D 235/30

(11)
(43)

2001 - 0079520
2001 08 22

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

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

(30) 19831710.7 1998 07 15 (DE)

(71)

64293 250

(72)

- 64342 - 6

- 64286 8

53

- 80799 77

- 81543 3

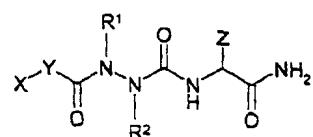
(74)

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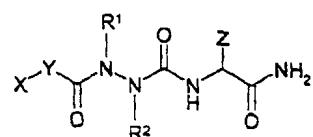
(54)

X, Y, Z, R¹ R² 가 1

|



|



(

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X H₂N - C(=NH) - , H₂N - C(=NH) - NH - , A - C(=NH) - NH - , Het¹ - Het¹ - NH - ,Y -(CH₂)_n- -(CH₂)_m- -(CH₂)_o- ,- (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 .)

, US 5,741,796

,
 |
 , , , 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)}

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)
 | 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

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

UV - 가

, ³H
가

Ac

Asp

Aza - Gly H₂N - NH - 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)

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

가

가

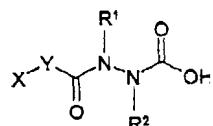
가

1

I

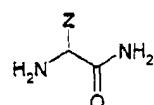
a)

II

(, X, Y, R¹ R² 1 , .)

III

III

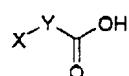


(, Z 1 , .)

b)

IV

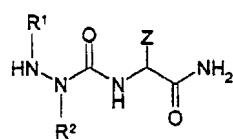
IV



(, X Y 1 , .)

V

V



c) 가 가 , |

/

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

, , , ,

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

R¹ H A_n H Me

R² H.

OA

R⁴ F, Cl, Br, , , , OCF₃,
- - - , O-, m-, p-, O-, m-, p-, O-, m-, p- 3 - , O-, m-, p-, O-, m-,
, O-, m-, p-, O-, m-,
p-, O-, m-, p-, O-, m-, p-, O-, m-, p-, O-, m-, p-, O-, m-, p-, O-, m-,
m-, p-, O-, m-,

R^5 COOH, COOCH_3 , COOC_2H_5 , $\text{COO}(\text{t}-)$, CONH_2 , PO_3H_2 , SO_3H

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 - , 2,3 -
 - 3 - , - 4 - - 5 - , 1 - , 2 - 3 - , - 1 - , - 2 - , - 4 - , 1,4 - - 1
 - 1 - , - 2 - , - 3 - , - 4 - - 5 - , - 1 - , - 2 - , - 3 - , - 4 - , - 5 - - 6 - , 1 - , 2 - ,
 - 2 - , - 3 - - 4 - , 1,2,3,4 - - 1 - , - 2 - , - 3 - , - 4 - , - 5 - - 6 - , 1 - , 2 - ,
 3 - 4 - , 1 - , 2 - 3 - , 1,2,3,4 - - 1 - , - 2 - , - 3 - , - 4 - , - 5 - - 6 - , - 7 - - 8 -
 , 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 Ia II , ,

II , ,

Ia) , X H₂N - C(=NH) - NH - ,

Ib) , Y -(CH₂)_m--(CH₂)_n- ,

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)_m--(CH₂)_n- - (CH₂)_s - CH(R⁴) - (CH₂)_t - ,

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

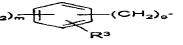
Y -(CH₂)_m--(CH₂)_n-

- (CH₂)_s - CH(R⁴) - (CH₂)_t - ,

Z - CH₂ - COOH ,

R⁴ Cl - ,

Ih) , 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 - , , ,

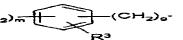
, , , , ,

2,3 - , , , , ,

s t 1 ,

m, o, p, q 0 1 ,

II) , 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 .

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

{ , Houben - Weyl, 1.c., 15
/II , 1 806 (1974)}

II III

IV V

, DCCI EDCI
{ Angew. Chem, 92, 129(1980) }, 2 - , - N - , - 1,2 -

, DMF

, - 10 40, 0

30 °

14

II / IV II / IV

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

, HOBt N - 가

가 (Angew. Chem. 97, 801 - 812 1985)

가

가 , 가 , 가

가 가 | , / , NHR' (, R' BOC , CBZ , N H)

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

기 (), 기 (), (), CO₂)

, 1 1 가

, , , | , , Asp

, , | 가
", " , 가 , pH 2
", , /
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/ .

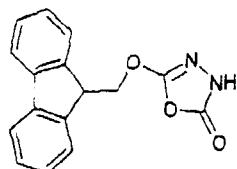
220 254 nm

(MS) : ESI() (M+H)⁺

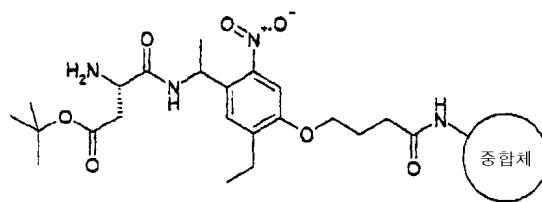
1

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

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

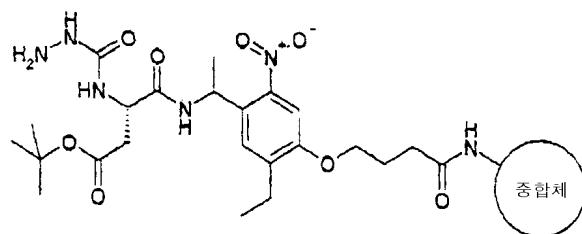
58mg; IR (KBr): 3300s, 1780s, 1650s, 1451m, 1426m, 1347m, 1224m, 918m, 758w, 740m cm⁻¹.2. - Asp(OtBu) - NH₂ ("B"):

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

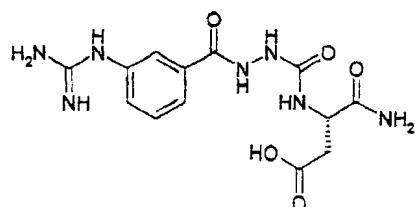


4. (3S) - 3 - [4 - (3 -)] :

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,

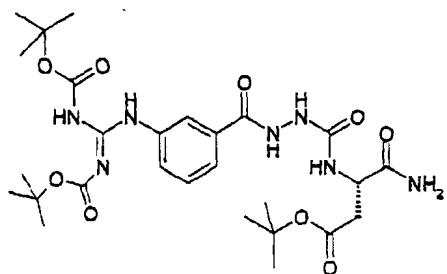
BOC , 95% TFA 5% H₂O (5ml) 1 , DC
M, DCM , DCM,
CN/H₂O (6 ml) 1:1 , , , , TQ 150
8 HPLC (3S) - 3 - [4 - (3 -)]



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 , t
Fmoc] 40 ° 10 - (3S) - 3 - [4 - (3 - (N,N' - - BOC -)))]



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

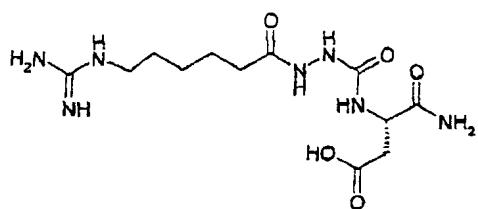
3

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 - , 95% TFA 5% H₂O 10
 . DCM , , , (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} ;

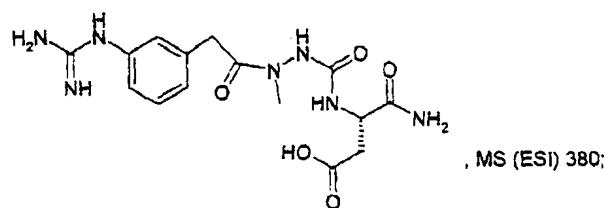
" C" 2 - (Fmoc -) - 5 - " D" , (3S) - 3
 - [4 - (2 - - 5 -)] {MS (ESI) 353} ;

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

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

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

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

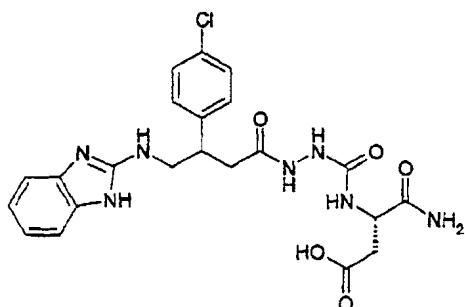
3 - (Fmoc -) - 3 -) " D"] , (3S) - 3 - [4 - (3 -

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

5

1 , " C"

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

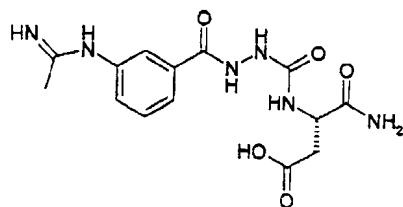


4 - (2 -) - 3 - (4 -) , (3S) - 3 - {4 - [4 - (2 -) - 3 - (4 -

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

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

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



A:

| 100g 2 5g 3 2N pH
 6.5 , , , ,
 . 5mg

B:

| 20g 100g 1400g
 . 20mg

C:

| 1g, NaH₂PO₄ · 2H₂O 9.38g, Na₂HPO₄ · 12H₂O 28.48g 0.1g
 940Mℓ pH 6.8 , 1 ,

D:

| 500mg 99.5g

E:

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

F:

E , , , , , 가

G:

| 2kg 20mg

H:

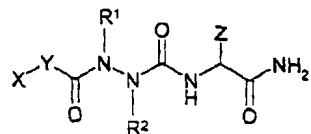
| 1kg 60 , , 10mg , ,

I:

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

1.

| ,
|



(,

X H₂N - C(=NH) - , H₂N - C(=NH) - NH - , A - C(=NH) - NH - , Het¹ - Het¹ - NH - ,Y -(CH₂)_n - -(CH₂)_m--(CH₂)_p - ,- (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 |

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

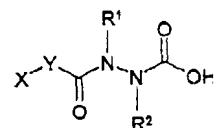
b) (3S)-3-[4-(5-
)] ;

3.

1 I ,

a) II

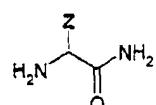
II



(, X, Y, R¹ R² 1 , .)

III ,

III

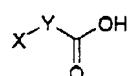


(, Z 1 , .)

,

b) IV

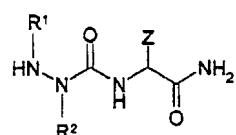
IV



(, X Y 1 , .)

V ,

V



c) 가 가 , |
/ | .

4.

1 | / 가 가 ,

5.

1 | / 가

6.

, , , , , , ,
1 | 가

7.

가 .

8.

9.

1 | / 가 .