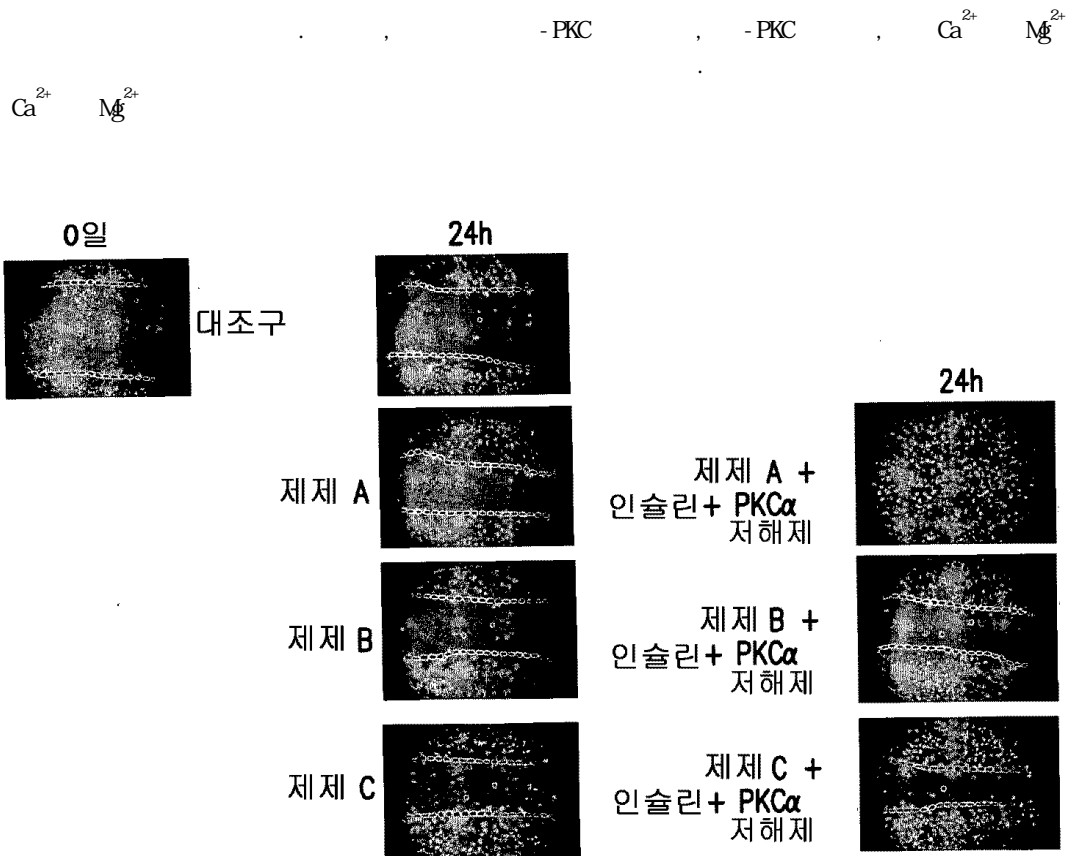
	(19) (12)	(KR) (A)	(11) (43)	10-2010-0040912 2010 04 21
(51)	Int. Cl.		(71)	
	<i>A61K 38/28</i> (2006.01) <i>A61K 38/17</i> (2006.01)			
	<i>A61K 31/553</i> (2006.01) <i>A61P 17/02</i> (2006.01)		5, 3	76702
(21)	10-2010-7002645			
(22)	( ) 2008 07 30		(72)	
	2010 02 05			
(85)	2010 02 05		12	96105
(86)	PCT/IL2008/001049			
(87)	WO 2009/016629		27	75400
	2009 02 05			
(30)	( )			
	60/962,706 2007 07 30 (US)		(74)	
	: 116			

(54)

(57)



(72)

3

8

55900

4

1

-PKC, -PKC, Ca<sup>2+</sup> Mg<sup>2+</sup>

2

1, -PKC

3

2, -3, 4, 5, L-

4

2,

5

4,

6

2, -PKC (S)-2, 6 -N[(1-(1- )-2- ) ] ; 4 - N IX ; 12-(2- )-6, 7, 12, 13 -13- -5- -5H [2, 3-a] [3, 4-c] ; 2-[1-(3- )-1H -3- ]-3 (1H -3- ) ; (apri nocarsen)

7

2,

-PKC : 2 : 3 : 4 : 5  
 : 6 : 7, : 8 : 9 : 10 : 11,  
 : 12 : 13, : 14 : 15 : 16  
 : 17, : 18 : 19 : 20 : 21,  
 : 22 : 23 : 24 : 26 : 27,  
 : 28 : 29 : 30 : 31, : 32,  
 : 33 : 34 : 35 : 36 : 37,  
 : 38 : 39 : 40 : 41, : 42,  
 : 43 : 44 : 45 : 46 : 47,  
 : 48 : 49 : 50 : 51, : 52,  
 : 53 : 54 : 55

**8**

2 ,  
-PKC : 25

**9**

2 ,  
-PKC : 1

**10**

1 9 ,  
Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,  
1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

**11**

Ca<sup>2+</sup> Mg<sup>2+</sup> : 1  
0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L  
Na<sub>2</sub>HPO<sub>4</sub>

**12**

11 ,  
0.0001 /L 0.1 /L 1 μ M 100 μ M

**13**

12 ,  
0.0001 /L 1 μ M

**14**

-PKC , -PKC , Ca<sup>2+</sup> Mg<sup>2+</sup> ,

**15**

14 ,

**16**

15 ,  
-PKC

**17**

16 , , , , L - -

3, 4, 5-

**18**

16

**19**

18

**20**

16

-PKC (S)-2,6-N[(1-(1- )-2- ) ] ; 4-  
 N ; IX ; 12-(2- )-6, 7, 12, 13-  
 -13- -5- -5H [2, 3-a] [3, 4-c] ; 2-[1-(3- )-1H -3- ]-3-  
 (1H -3- ) ;

**21**

16

-PKC : 2 : 3 : 4 : 5  
 : 6 : 7 : 8 : 9 : 10 : 11,  
 : 12 : 13 : 14 : 15 : 16  
 : 17, : 18 : 19 : 20 : 21,  
 : 22 : 23 : 24 : 26 : 27,  
 : 28 : 29 : 30 : 31, : 32,  
 : 33 : 34 : 35 : 36 : 37,  
 : 38 : 39 : 40 : 41, : 42,  
 : 43 : 44 : 45 : 46 : 47,  
 : 48 : 49 : 50 : 51, : 52,  
 : 53 : 54 : 55

**22**

16

-PKC : 25

**23**

16

-PKC , : 1

**24**

23

0.0001 /L 0.1 /L 1 μ M 100 μ M

**25**

23 ,  
 0.0001 /L 1 μ M .

**26**

14 25 ,

**27**

26 ,

Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

**28**

a) -PKC , -PKC , Ca<sup>2+</sup> Mg<sup>2+</sup> ;

b) -PKC , -PKC , Ca<sup>2+</sup> Mg<sup>2+</sup> ;

**29**

28 ,

-PKC .

**30**

29 ,

3, 4, 5 , , , , L - -

**31**

29 ,

**32**

31 ,

**33**

29 ,

-PKC (S)-2,6 -N[(1-(1- )-2- ) ] ; 4-  
 N IX ; 12-(2- )-6, 7, 12, 13  
 -13 -5 -5H [2, 3-a] [3, 4-c] ; 2-[1-(3- )-1H -3- ]-3  
 (1H -3- ) ;

**34**

29

-PKC : 2 : 3 : 4 : 5  
 : 6 : 7 : 8 : 9 : 10 : 11  
 : 12 : 13 : 14 : 15 : 16  
 : 17 : 18 : 19 : 20 : 21  
 : 22 : 23 : 24 : 26 : 27  
 : 28 : 29 : 30 : 31 : 32  
 : 33 : 34 : 35 : 36 : 37  
 : 38 : 39 : 40 : 41 : 42  
 : 43 : 44 : 45 : 46 : 47  
 : 48 : 49 : 50 : 51 : 52  
 : 53 : 54 : 55

**35**

29

-PKC : 25

**36**

29

-PKC : 1

**37**

36

0.0001 /L 0.1 /L 1 μ M 100 μ M

**38**

36

0.0001 /L 1 μ M

**39**

28 38

Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,  
 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

**40**

a) -PKC, -PKC, Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ;  
 b) ;

41

40

-PKC

42

41

3, 4, 5

43

41

44

43

45

41

-PKC (S)-2,6 -N[(1-(1- )-2- ) ] ; 4-  
N ; IX ; 12-(2- )-6, 7, 12, 13-  
-13- -5- -5H [2, 3-a] [3, 4-c] ; 2-[1-(3- )-1H -3- ]-3-  
(1H -3- ) ;

46

41

-PKC : 2 : 3 : 4 : 5  
: 6 : 7 : 8 : 9 : 10 : 11,  
: 12 : 13 : 14 : 15 : 16  
: 17, : 18 : 19 : 20 : 21,  
: 22 : 23 : 24 : 26 : 27,  
: 28 : 29 : 30 : 31, : 32,  
: 33 : 34 : 35 : 36 : 37,  
: 38 : 39 : 40 : 41, : 42,  
: 43 : 44 : 45 : 46 : 47,  
: 48 : 49 : 50 : 51, : 52,  
: 53 : 54 : 55

47

41

-PKC : 25

48

41

-PKC

: 1

49

48

0.0001 /L

0.1 /L

1 μ M

100 μ M

50

48

0.0001 /L

1 μ M

51

40

50

g/L KCl, 0.2 g/L

KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,

, Ca<sup>2+</sup> Mg<sup>2+</sup>

1.15 g/L

Na<sub>2</sub>HPO<sub>4</sub>

0.2

52

a) -PKC

-PKC

, Ca<sup>2+</sup> Mg<sup>2+</sup>

b)

53

52

-PKC

54

53

3, 4, 5-

55

53

56

55

57

53

-PKC (S)-2,6-N[(1-(1-)-2-)] ; 4-  
 N ; IX ; 12-(2)-6,7,12,13  
 -13 -5- -5H [2,3-a] [3,4-c] ; 2-[1-(3)-1H -3]-3  
 (1H -3- ) ;

**58**

53 ,

-PKC : 2 : 3 : 4 : 5  
 : 6 : 7 : 8 : 9 : 10 : 11  
 : 12 : 13 : 14 : 15 : 16  
 : 17, : 18 : 19 : 20 : 21,  
 : 22, : 23 : 24 : 26 : 27,  
 : 28, : 29 : 30 : 31, : 32,  
 : 33, : 34 : 35 : 36 : 37,  
 : 38, : 39 : 40 : 41, : 42,  
 : 43, : 44 : 45 : 46 : 47,  
 : 48, : 49 : 50 : 51, : 52,  
 : 53, : 54 : 55

**59**

52 ,

-PKC : 25

**60**

52 ,

-PKC , : 1

**61**

60 ,

0.0001 /L 0.1 /L 1 μ M 100 μ M

**62**

60 ,

0.0001 /L 1 μ M

**63**

52 62 ,

Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,  
 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

**64**

Ca<sup>+</sup> Mg<sup>2+</sup>

**65**

64 , , , , , L - -  
 3, 4, 5 , - , .

**66**

64 , , , .

**67**

66 , .

**68**

64 ,  
 0.0001 /L 0.1 /L .

**69**

64 ,  
 0.0001 /L .

**70**

64 69 ,  
 $Ca^{2+}$   $Mg^{2+}$  0.2 g/L KCl, 0.2 g/L  $KH_2PO_4$ , 8 g/L NaCl,  
 1.15 g/L  $Na_2HPO_4$  .

**71**

0.0001 /L 0.1 /L  $Ca^{2+}$   $Mg^{2+}$  .

**72**

71 , , , .

**73**

72 , .

**74**

71 73 ,  
 $Ca^{2+}$   $Mg^{2+}$  0.2 g/L KCl, 0.2 g/L  $KH_2PO_4$ , 8 g/L NaCl,  
 1.15 g/L  $Na_2HPO_4$  .



**82**

76 ,  
-PKC : 25

**83**

76 ,  
-PKC , : 1

**84**

83 ,  
0.0001 /L 0.1 /L 1 μ M 100 μ M

**85**

83 ,  
0.0001 /L 1 μ M

**86**

75 85 ,  
Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,  
1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

**87**

-PKC , -PKC , K<sup>+</sup> Ca<sup>2+</sup> Mg<sup>2+</sup>

**88**

87 ,  
-PKC

**89**

88 ,  
3, 4, 5 , , , , L - -

**90**

88 ,

**91**

90 ,

**92**

88 ,  
 -PKC (S)-2,6 -N[(1-(1- )-2 ) ] ; 4-  
 N ; IX ; 12-(2 )-6,7,12,13  
 -13 -5 -5H [2,3-a] [3,4-c] ; 2-[1-(3 )-1H -3 ]-3  
 (1H -3 ) ;

**93**

88 ,  
 -PKC : 2 : 3 : 4 : 5  
 : 6 : 7 : 8 : 9 : 10 : 11  
 : 12 : 13 : 14 : 15 : 16  
 : 17, : 18 : 19 : 20 : 21,  
 : 22 : 23 : 24 : 26 : 27,  
 : 28 : 29 : 30 : 31, : 32  
 : 33 : 34 : 35 : 36 : 37,  
 : 38 : 39 : 40 : 41, : 42  
 : 43 : 44 : 45 : 46 : 47,  
 : 48 : 49 : 50 : 51, : 52  
 : 53 : 54 : 55

**94**

88 ,  
 -PKC : 25 ,

**95**

88 ,  
 -PKC , : 1

**96**

-PKC K<sup>+</sup> Ca<sup>2+</sup> Mg<sup>2+</sup>

**97**

96 ,  
 -PKC

**98**

97 ,  
 , , , , L - -  
 3,4,5 , - ,

**99**

97

**100**

99

**101**

-PKC, Ca<sup>2+</sup>, Mg<sup>2+</sup>

**102**

101

-PKC (S)-2,6-N[(1-(1- )-2- ) ] ; 4-  
 N ; IX ; 12-(2- )-6,7,12,13-  
 -1,3-5-5H [2,3-a] [3,4-c] ; 2-[1-(3- )-1H -3- ]-3-  
 (1H -3- ) ;

**103**

101

-PKC : 2 : 3 : 4 : 5  
 : 6 : 7 : 8 : 9 : 10 : 11,  
 : 12 : 13 : 14 : 15 : 16  
 : 17, : 18 : 19 : 20 : 21,  
 : 22 : 23 : 24 : 26 : 27,  
 : 28 : 29 : 30 : 31, : 32,  
 : 33 : 34 : 35 : 36 : 37,  
 : 38 : 39 : 40 : 41, : 42,  
 : 43 : 44 : 45 : 46 : 47,  
 : 48 : 49 : 50 : 51, : 52,  
 : 53 : 54 : 55

**104**

101

-PKC : 25

**105**

101

-PKC, : 1

**106**

105

1 μ M                      100 μ M

**107**

106

1 μ M

**108**

101                      107                      , Ca<sup>2+</sup>                      Mg<sup>2+</sup>                      0.2  
 g/L KCl, 0.2 g/L                      KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,                      1.15 g/L                      Na<sub>2</sub>HPO<sub>4</sub>

**109**

a) -PKC                      Ca<sup>2+</sup>                      Mg<sup>2+</sup>

b)

**110**

109  
 -PKC                      (S)-2,6                      -N[(1-(1-                      )-2-                      )]                      ; 4-  
 N                      ;                      IX                      ; 12-(2-                      )-6,7,12,13  
 -1,3-                      -5-                      -5H                      [2,3-a]                      [3,4-c]                      ; 2-[1-(3-                      )-1H                      -3-                      ]-3  
 (1H                      -3-                      )                      ;

**111**

109  
 -PKC                      : 2                      : 3                      : 4                      : 5  
 : 6                      : 7,                      : 8                      : 9                      : 10                      : 11,  
                     : 12,                      : 13,                      : 14,                      : 15,                      : 16,  
                     : 17,                      : 18,                      : 19,                      : 20,                      : 21,  
                     : 22,                      : 23,                      : 24,                      : 26,                      : 27,  
                     : 28,                      : 29,                      : 30,                      : 31,                      : 32,  
                     : 33,                      : 34,                      : 35,                      : 36,                      : 37,  
                     : 38,                      : 39,                      : 40,                      : 41,                      : 42,  
                     : 43,                      : 44,                      : 45,                      : 46,                      : 47,  
                     : 48,                      : 49,                      : 50,                      : 51,                      : 52,  
                     : 53,                      : 54,                      : 55

**112**

109  
 -PKC  
                     : 25

**113**

109

- PKC , : 1

**114**

109 ,

1  $\mu$  M 100  $\mu$  M

**115**

114 ,

1  $\mu$  M

**116**

107

115 ,

Ca<sup>2+</sup> Mg<sup>2+</sup>

0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl,

1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

[0001]

[0002]

2007 7 30 " " 60/962, 706

[0003]

[0004]

(Fuchs and Byrne 1994; Goldsmith 1991).

[0005]

(Fuchs and Byrne 1994).

, DNA

(Tennenbaum et al. 1991; Wysocki 1999).

[0006]

Wysocki 1999).

(Green 1977;

(Nash et al. 2004; Querleux et al. 2002).

[0007]

(spinous layer)

(Adams and Witt 1990, Eckert 1989, Yuspa et al. 1980).

[0008] (i) ;(ii) ;(iii) ;(iv) ;(v) ; vi)  
: 6  
(Keast and  
Orsted 1998; Kirsner and Eaglstein 1993; Williams and Armstrong 1998).

[0009] (Goodson and Hint 1979; Grunfeld 1992).  
(Shaw and Boulton 1997).  
(Musley 2003; Silhi 1998).  
1/3  
(Diegelmann and Evans 2004).

[0010]  
[0011] 2  
( , dehiscence)  
(Grunfeld 1992;  
Knol and Wsselink 1996; Yerahmet al. 1992; Yimet al. 2007).

[0012] (acral lick ulcer),  
(horse)  
( " Proud flesh")  
(5 8 )  
(De I and Theoret 2004; Stone 1986).

[0013] (Acral Lick Dermatitis) (rodent  
ulcers)  
(Witte 1990;  
Yerahmet al. 1992).

[0014] C(PKC) ATP  
11 (isoform)  
(Nshizuka 1995).  
PKC  
PKC

[0015] / C(PKC) Nshizuka  
(Kikkawa et al. 1989), Nshizuka (DAG)

PKC (Castagna et al. 1982). PKC (phorbol)

[0016] PKC, N, C, (C1-C4), (VI-V5) (Nshizuka 1988), PKC (Blumberg 1991; Huse and Kemp 1987). PKC (notif), aPKC( I, II, ), nPKC( / ), (Azzi et al. 1992; Kikkawa et al. 1989; Svetek et al. 1995).

[0017] PKC, cPKC (Ca<sup>2+</sup>), DAG, DAG, nPKC Ca<sup>2+</sup> (Kazani et al. 1993). aPKCs Ca<sup>2+</sup>, DAG, PKC (Chauhan et al. 1990). (Eichholtz et al. 1993; Hofmann 1997).

[0018] PKC, PKC, PKC, PKC

[0019] PKC

[0020] /

[0021] -PKC, -PKC, Ca<sup>2+</sup>, Mg<sup>2+</sup>

[0022] : 1, 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>, Ca<sup>2+</sup>, Mg<sup>2+</sup>

[0023] 0.2 L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

[0024] -PKC, -PKC, Ca<sup>2+</sup>, Mg<sup>2+</sup>

[0025] - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; ,

[0026] - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; ,

[0027] - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; ,

[0028] Ca<sup>2+</sup> Mg<sup>2+</sup>

[0029] 0.0001 /L 0.1 /L Ca<sup>2+</sup> Mg<sup>2+</sup>

[0030] - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; ,

[0031] - PKC , - PKC , K<sup>+</sup> Ca<sup>2+</sup> Mg<sup>2+</sup>

[0032] - PKC K<sup>+</sup> Ca<sup>2+</sup> Mg<sup>2+</sup>  
 - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>

[0033] - PKC Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ; ,

[0034]

[0035] Ca<sup>2+</sup> Mg<sup>2+</sup>

[0036] 1A ,  
 (Axiovert 25 Zeiss x50 ) .

1B 24 %

2A A

2B  
 3  
 4  
 5 PKC Myr- PKC  
 6A (Axi overt 25 Zeiss x200 ).  
 6B 24 %  
 6C  
 7 7 2  
 + PKC  
 8A  
 8B 0 60  
 9 0 , 3 6  
 10 0 , 30 60  
 11 0 , 2 3 5  
 12 HMLOG® (rDNA ) 1  
 13 NOVLOG® (rDNA ) 1  
 14 LANIUS® (rDNA ) 1  
 15 NOVLIN® R HMLIN® R 1  
 16 A  
 (Hml), (Novo), (LANIUS®), HMLIN® R(Hml)  
 17 HMLIN® R(Hml), USP (Ins USP), PKC (pep)  
 18 HMLIN® R(Hml), (Hml), PKC (pep)  
 19 A B 1 L - -  
 3, 4, 5 , -, 7 2  
 1

PKC , /

[0038]

[0039]

A) 0.2 g/L(KCl)

[0040]

B) ( ) 0.2 g/L(K<sub>2</sub>HPO<sub>4</sub>)

[0041]

C) 8.0(g/L) (NaCl)

[0042]

D) ( ) 1.15(g/L) (Na<sub>2</sub>HPO<sub>4</sub>)

[0043]

[0044]

PKC , PKC PKC (Myr\*- Phe- Ala- Arg- Lys- Gly- Ala- Leu- Arg- Gln- CH<sub>3</sub> : 1 CAS [147217-25-2])  
 PKC  
 PKC 1

[0045]

1. PKC

Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val	서열식별번호 : 2
Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His Glu Val Lys Asn	서열식별번호 : 3
Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His Glu Val Lys Asn Leu Lys Gly Ala	서열식별번호 : 4
Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Leu Ala Val	서열식별번호 : 5
Arg Phe Ala Arg Lys Gly Ala Leu Ala Gln Lys Asn Val	서열식별번호 : 6
Arg Phe Ala Arg Lys Gly Ala Leu Arg	서열식별번호 : 7
Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe (Xaa는 어떠한 자연 발생적 아미노산일 수 있음)	서열식별번호 : 8
Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala	서열식별번호 : 9
Ala Arg Arg Lys Arg Lys Gly Ala Phe Phe Tyr Gly Gly	서열식별번호 : 10
Arg Arg Arg Arg Arg Lys Gly Ala Phe Arg Arg Lys Ala	서열식별번호 : 11
Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val Tyr	서열식별번호 : 12
Asp Ala Arg Lys Gly Ala Leu Arg Gln Asn Lys Val	서열식별번호 : 13
Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val	서열식별번호 : 14
Gly Pro Arg Pro Leu Phe Cys Arg Lys Gly Ala Leu Arg Gln Lys Val Val	서열식별번호 : 15
Gln Lys Arg Pro Ala Gln Arg Ser Lys Tyr Leu	서열식별번호 : 16
Gln Lys Arg Pro Ser Gln Arg Ala Lys Tyr Leu	서열식별번호 : 17
Gly Gly Pro Leu Arg Arg Thr Leu Ala Val Arg Arg	서열식별번호 : 18
Gly Gly Pro Leu Ser Arg Arg Leu Ala Val Arg Arg	서열식별번호 : 19
Gly Gly Pro Leu Ser Arg Thr Leu Ala Val Arg Arg	서열식별번호 : 20
Gly Gly Pro Leu Ser Arg Arg Leu Ala Val Ala Arg	서열식별번호 : 21
Gly Gly Pro Leu Arg Arg Thr Leu Ala Val Ala Arg	서열식별번호 : 22
Val Arg Lys Ala Leu Arg Arg Leu	서열식별번호 : 23
Gly Gly Arg Leu Ser Arg Thr Leu Ala Val Ala Arg	서열식별번호 : 24
Thr Arg Lys Arg Gln Pro Ala Met Arg Arg Arg Val His Gln Ile Asn Gly	서열식별번호 : 25

[0046]

이 펩티드는 N 말단에서 미리스토일화되고 C 말단에서 아미드화되어 있음	
Arg Lys Arg Gln Arg Ala Met Arg Arg Arg Val His	서열 식별 번호: 26
Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val	서열 식별 번호: 27
Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala	서열 식별 번호: 28
Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe Xaa는 어떠한 자연 발생적 아미노산일 수 있음	서열 식별 번호: 29
Ala Arg Arg Lys Arg Lys Gly Ala Phe Phe Tyr Gly Gly	서열 식별 번호: 30
Arg Arg Arg Arg Arg Lys Gly Ala Phe Arg Arg Lys Ala	서열 식별 번호: 31
Ala Ala Ala Lys Ile Gln Ala Ala Trp Arg Gly His Met Ala Arg Lys Lys Ile Lys Ser	서열 식별 번호: 32
Ala Ala Ala Lys Ile Gln Ala Ala Phe Arg Gly His Met Ala Arg Lys Lys Ile Lys	서열 식별 번호: 33
Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val	서열 식별 번호: 34
Val Arg Lys Ala Leu Arg Arg Leu	서열 식별 번호: 35
Lys Lys Lys Lys Lys Arg Phe Ser Phe Lys Lys Ala Phe Lys Leu Ser Gly Phe Ser Phe Lys Lys	서열 식별 번호: 36
Gly Pro Arg Pro Leu Phe Cys Arg Lys Gly Ala Leu Arg Gln Lys Val Val	서열 식별 번호: 37
Glu Ser Thr Val Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val	서열 식별 번호: 38
Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val	서열 식별 번호: 39
Arg Phe Ala Arg Leu Gly Ala Leu Arg Gln Lys Asn Val	서열 식별 번호: 40
Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe Xaa는 어떠한 자연 발생적 아미노산일 수 있음	서열 식별 번호: 41
Arg Arg Phe Lys Arg Gln Gly Ala Phe Phe Tyr Phe Phe	서열 식별 번호: 42
Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala	서열 식별 번호: 43
Ala Arg Arg Lys Arg Lys Gly Ser Phe Phe Tyr Gly Gly	서열 식별 번호: 44
Phe Lys Leu Lys Arg Lys Gly Ser Phe Lys Lys Phe Ala	서열 식별 번호: 45
Arg Arg Phe Lys Arg Gln Gly Ser Phe Phe Tyr Phe Phe	서열 식별 번호: 46

Tyr Tyr Xaa Lys Arg Lys Met Ser Phe Phe Glu Phe Phe Xaa는 어떠한 자연 발생적 아미노산일 수 있음	서열 식별 번호: 47
Arg Arg Arg Arg Arg Lys Gly Ser Phe Arg Arg Lys Ala	서열 식별 번호: 48
Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ser Val Arg Arg Arg Val	서열 식별 번호: 49
Met Asn Arg Arg Gly Ser Ile Lys Gln Ala Lys Ile	서열 식별 번호: 50
Met Phe Ala Val Arg Asp Arg Arg Gln Thr Val Lys Lys Gly Val Ile Lys Ala Val Asp Ala Val	서열 식별 번호: 51
Phe Gly Glu Ser Arg Ala Ser Thr Phe Cys Gly Thr Pro Asp	서열 식별 번호: 52
Lys Ala Arg Leu Ser Tyr Ser Asp Lys Asn	서열 식별 번호: 53
Ser Ala Phe Ala Gly Phe Ser Phe Val Asn Pro Lys Phe	서열 식별 번호: 54
Lys Lys Lys Lys Lys Arg Phe Ser Phe Lys Lys Ser Phe Lys Leu Ser Gly Phe Ser Phe Lys Lys	서열 식별 번호: 55

[0047]

[0048]

[0049]

[0050]

[0051]

PKC :

A) NPC 15437 - (5)-2,6 -N[(1-(I - )-2 ) ]  
(Signa)  
- C<sub>25</sub>H<sub>50</sub>N<sub>4</sub>O<sub>2</sub> · 2HCl · xH<sub>2</sub>O

[0052] - 511.61( )

[0053] CAS - 141774-20-1( )

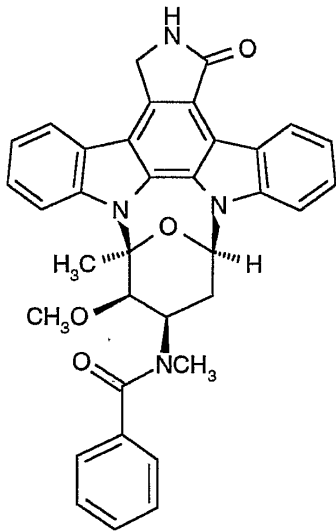
[0054] ML - MFCD00210207

[0055] PubChem ID - 24897504

[0056] B) CGP41251 - [4'-N ] [Midostaurin]. PKC 412(CGP 41251)  
C(PKC)

[0057] - C<sub>35</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>

[0058] - 570.65



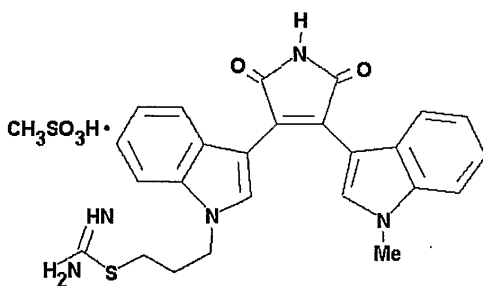
[0059]

[0060] C) Ro 31-8220 - IX . (Upstate Biotechnology)

[0061] - C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub> · CH<sub>3</sub>OS

[0062] - 553.66

[0063] # 19-163 :



[0064]

[0065] D) Co6976, 12-(2- )-6, 7, 12, 13- -13- -5- -5H [2,3-a] [3,4-c]  
PKC 1 .

[0066] E) GF-109203X, 2-[1-(3- )]-1H -3- ]-3-(1H -3- ) ,  
C .

[0067] F) ISIS 3521/LY900003 (aprinocarsen) , ( : 56)  
, Isis Pharmaceuticals, Inc., Carlsbad, CA 20-

[0068] 5' - GTTCTCGCTGGTGAGTTCA 3'

[0069] , , 9 , PKC PKC

[0070] :

[0071] a) 0.2 g/L(KCl)

[0072] b) ( ) 0.2 g/L(K<sub>2</sub>HPO<sub>4</sub>)

[0073] c) 8.0(g/L)(NaCl)

[0074] d) ( ) 1.15(g/L)(Na<sub>2</sub>HPO<sub>4</sub>)

[0075] e) Myr\*-Phe-Ala-Arg-Lys-Gly-Ala-Leu-Arg-Gln-CH<sub>3</sub> : 1) (1-100 μM

[0076] f) ( : 0.1-10 /ml)

[0077]

[0078]

PKC

[0079] PKC

0.1-10 /mL PKC  
 1 100 μM 1 mL 0.1 (10<sup>-6</sup> M  
 (10<sup>-6</sup> M) 1 μg

[0080]

-3, 4, 5- ( L- ) L-

[0081]

B-28 B-29  
 B-28  
 A-21 C  
 (*Saccharomyces cerevisiae*) rDNA

[0082]

(adiocytkine)  
 L- Ca<sup>2+</sup> PKC  
 L- (plekstrin homolog) (PH)  
 1(GRP1) NH3T3 (actin)  
 (ruffling)

[0083]

( )

[0084]

[0085]

[0086]

" - PKC " PKC  
 PKC NM\_002737( (*Homo sapiens*) PKC ), XM\_548026  
 ( (*Canis lupus familiaris*) PKC ), XM\_001494589( (*Equus caballus*) PKC ), NM\_011101( (*Mus musculus*) PKC )  
 PKC CLUSTALW  
 PKC 95% - PKC  
 PKC  
 PKC - PKC PKC  
 2 ( PKC PKC  
 PKC RNAs  
 (silencing) ) PKC

[0087]

" - PKC " PKC  
 PKC PKC  
 NM\_006254( (*Homo sapiens*) PKC ), NM\_001008716( (*Canis lupus familiaris*)  
 PKC ), XM\_001915127( (*Equus caballus*) PKC ), NM\_011103( (*Mus musculus*) PKC )  
 PKC CLUSTALW PKC  
 85% - PKC  
 PKC PKC  
 , PKC - PKC PKC  
 2 ( PKC PKC  
 PKC )  
 PKC - PKC PKC  
 PKC

[0088]

[0089]

A B

[0090]

( - -1)

2

PKC

[0091]

" " 25 +/- 2 1  
 ( mol/L, M /nh, μg/nh )



[0102]

[0103]

DNA

(archaeal),

[0104]

, -PKC (S)-2,6 -N[(1-(1- )-  
 2- ) ] ; 4'-N ; IX  
 ; 12-(2- )-6,7,12,13- -13- -5- -5H [2,3-a] [3,4-c] ;  
 2-[1-(3- )-1H -3- ]-3-(1H -3- ) ;  
 PKC  
 PKC

[0105]

, -PKC : 2 : 3  
 : 4 : 5 : 6 : 7 : 8  
 : 9 : 10 : 11 : 12 : 13 :  
 14 : 15 : 16 : 17 : 18 : 19  
 : 20 : 21 : 22 : 23 : 24 SEQ  
 ED NO 26 : 27 : 28 : 29 : 30  
 : 31 : 32 : 33 : 34 : 35 :  
 36 : 37 : 38 : 39 : 40 : 41  
 : 42 : 43 : 44 : 45 : 46  
 : 47 : 48 : 49 : 50 : 51  
 : 52 : 53 : 54 : 55

[0106]

t-BOC FMOC

(Coligan et al., Current Protocols in Immunology, Wiley Interscience, 1991, Unit 9).  
 0.1-1.0 mM /g ( - ) Merrifield(85 J.  
 Am Chem Soc. 2149(1962)), Stewart Young Solid Phase Peptide Synthesis, (Freeman, San  
 Francisco, 1969, pp. 27-62)  
 , 0 1/4 1 HF-10%  
 , 1%  
 5% Sephadex G-15

[0107]

(Frederich M Ausubel, et al.,  
 Current Protocols in Molecular Biology, Wiley Interscience, 1989)  
 , GST (Erangionic Neel, Analytical  
 Biochemistry, 210:179, 1993) (Sigma)

(Cadena Gil, Protein Expression and Purification 4:177, 1993). Merrifield  
 the Applied Biosystems 431A-C Peptide Synthesizer (Mountain View, Calif.)  
 Houghten, Proc. Natl. Acad. Sci., USA 82:5131(1985)

[0108] (t-Boc) (Fmoc) t-  
 (Sigma Chemical Co.; Advanced Chemtec)

[0109] (Orn) Arg (homoArg)

[0110]

[0111] -PKC : 25

[0112] -PKC : 1

[0113] Ca<sup>2+</sup> Mg<sup>2+</sup>  
 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

[0114] ; : 1  
 ; Ca<sup>2+</sup> Mg<sup>2+</sup> 0.2 g/L KCl, 0.2 g/L KH<sub>2</sub>PO<sub>4</sub>, 8 g/L NaCl, 1.15 g/L Na<sub>2</sub>HPO<sub>4</sub>

[0115] 1 μM 100 μM 0.0001 /L 0.1 /L

[0116] 0.0001 /L 1 μM

[0117] -PKC, -PKC, Ca<sup>2+</sup> Mg<sup>2+</sup>

[0118]

[0119]

- [0120] a) - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
; b) - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
;
- [0121]
- [0122] a) - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
; b)
- [0123]
- [0124] , H & E , 14 ,  
RBC/WBC
- [0125]
- [0126] a) - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>  
; b)
- [0127] ( x200 >100 ) ; >20% WBC (x200)  
WBC/RBC( / ) ;
- [0128] Ca<sup>2+</sup> Mg<sup>2+</sup>
- [0129] , 0.0001 /L 0.1 /L
- [0130] , 0.0001 /L
- [0131] , 0.0001 /L 0.1 /L  
Ca<sup>2+</sup> Mg<sup>2+</sup>
- [0132] - PKC , - PKC , Ca<sup>2+</sup> Mg<sup>2+</sup>

- [0133] -PKC , -PKC ,  $K^+$   $Ca^{2+}$   $Mg^{2+}$   
 $(KCl)$ ,  
 $(KHCQ)$ ,  $(KH_2PO_4)$  .  $K^+$
- [0134] -PKC  $K^+$   $Ca^{2+}$   $Mg^{2+}$
- [0135] -PKC ,  $Ca^{2+}$   $Mg^{2+}$
- [0136] ,  $1 \mu M$   $100 \mu M$  -PKC
- [0137] ,  $1 \mu M$  -PKC
- [0138] -PKC  $Ca^{2+}$   $Mg^{2+}$   
 ;  
 ;
- [0139] \_\_\_\_\_
- [0140] \_\_\_\_\_
- [0141] : Biological Industries
- [0142] (Beit Haneke, Israel) . BioRad (Israel) (ECL)  
 p-tyr Upstate Biotechnology Inc. (Lake Placid, NY, USA)  
 PKC Santa Cruz (California, USA)  
 Transduction Laboratories (Lexington, KY) . . . .  
 IgG Bio-Rad (Israel) . , PMSF, DTT, Na- ,  
 Sigma Chemicals (St. Louis, MO) (humulinR) Eli Lilly  
 France SA (Fergersheim, France) . IGF1 Cytolab (Rehovot, Israel) .  
 14 Babco-Convance (Richmond, CA) BDNF-BB R&D systems (Minneapolis)  
 PKC Calbiochem (San Diego, CA)  
 Calbiochem (San Diego, CA)
- [0143] (HML00®, Eli Lilly), (NOV00®, Novo  
 Nordisk), (LANIUS®, Sanofi Aventis), (HMLIN® R, Eli Lilly  
 y) . (ALEXIS Corporation, Lausen, Switzerland,  
 ALX-201-318-C050) L- - -3, 4, 5- , - ,  
 (Calbiochem 524615) (L- ) .
- [0144] 1 2 .
- [0145] : 1  
 8% Chel ex (Chel ex-100, BioRad)  
 (EMEM) .  $Ca^{2+}$  0.05 mM  
 5 7 .

- [0146] A B 8% CHELEX™ Biological Industries (Israel)  
 MEM CHELEX™ Ca<sup>2+</sup> Mg<sup>2+</sup>  
 ng/ml A KCl B KCl 0.4
- [0147] : Ca<sup>2+</sup>/Mg<sup>2+</sup> - PBS  
 (20 μg ; 10 μg/ml ; 0.1 nM  
 PMSF; 1 nM DTT; 200 μM ; 2 μg/ml ) RIPA (50 nM -HCl pH  
 7.4; 150 mM NaCl; 1 nM EDTA; 10 mM NaF; 0.1% SDS, 1%  
 4 20
- [0148] : 25 μL A/G (Santa Cruz, CA, USA) 300 μg  
 (preclear) , 4 30 4  
 10 , 30 μL A/G  
 ( 1:100) . 4 4  
 10 RIPA . 15,000  
 x g (4 10 ) TBST . (0.5 M -HCl pH 6.8; 10%  
 SDS; 10% ; 4% 2- - ; 0.05% ) , 5 ,  
 SDS-PAGE
- [0149] : Saito et al. 54 J. Virol. 711(1985)
- [0150] PKC : PKC  
 PKC PKC  
 MEM 10 - - Ca<sup>2+</sup> MEM 24
- [0151] PKC : PKC  
 NaF RIPA . SignaTECT PKC  
 (Proteoga, Madison, WI, USA) . PKC
- [0152] : 6 [ <sup>3</sup>H ] . [ <sup>3</sup>H ] (3 μ  
 G/ml) . PBS 5 5% TCA  
 , 1 M NaCl . TRI-  
 CARB™ <sup>3</sup>H
- [0153] PKC : PKC Dr. P. Blumberg (NIH, NH )  
 Dr. Marcello G. Kazanietz (University of Pennsylvania, School of Medicine) . 1  
 500 μl 1% Triton Lysis ( 1 x PBS 1% Triton-X 100, 10 μg/ml  
 , 2 μg/ml , 1 nM PMSF, 1 nM EDTA, 200 μM Na<sub>2</sub>VO<sub>4</sub>, 10 mM NaF)  
 4 30 , 16,000 x g 4 30  
 . 6/GoHb (PharMingen) 5 μg/ A/G Plus (Santa Cruz) 30 μl/  
 4 RIPA , 50 nM  
 /HCl pH 7.5 . 35 μL (1 nM CaCl<sub>2</sub>, 20 mM MgCl<sub>2</sub>, 50 nM -HCl pH  
 7.5) , DMSO 10 nM TPA 5.5 μl  
 / PKC . 10 μl 125 nM AIP (1.25  
 μG/ [ -<sup>32</sup>P] ATP, Amersham) / , 30 10  
 RIPA . 30 μl (loading) (3 x Laemmli,  
 5% SDS) / 5 . 8.5% SDS-PAGE

, Prottran (Schleicher & Schuell) PKC

[0154] C57BL/6J ( ) (back)  
(20nm )

[0155] : Sanbrook et al., Molecular Cloning: A Laboratory Manual (3d ed. 2001)

[0156] , PKC : 1  
"Ins USP"

[0157] 1

[0158] ( $10^{-6}$  M 0.1 /ml) PKC (Myr- PKC , 1  $\mu$  M)

[0159] , Alt et al. 2004; Li et al. 1996  
1 8% Chel ex(Chel ex-100, BioRad)  
(EMEM)  
Ca<sup>2+</sup> 0.05 mM

[0160] 5 , (confluent)  
+ PKC A Dulbecco's (DPBS-); B  
(PBS) ; C (CAS [77-86-1])  
[77-86-1] D (CAS [77-86-1]) KCl 0.4 ng/ml ;  
7.2 pH

[0161] 24 , A + PKC 1A  
1B 24 % (p<0.05)

[0162] 2

[0163] PKC

[0164] C57BL/6J ( ) (20nm )  
( A-C ( $10^{-6}$  M 0.1 /ml);  
PKC , 1  $\mu$  M PKC ); + PKC (Myr- PKC , 1  $\mu$  M 0.1 )

[0165] 7 , B C  
A + PKC  
2A 7 2B

[0166] 3

[0167] PKC (PKC )

[0168] C57BL/6J ( ) (20nm )  
( A-C Myr- PKC , 1  $\mu$  M  
7 ,

(x200) , (2) ( x200 >100 ) , (3) >20% VEC  
 VEC/RBC( / ) . 3 A  
 PKC , B C

[0169] \_\_\_\_\_ 4

[0170]

[0171] C57BL/6J ( ) (20nm )  
 ( A O Myr- PKC , 1 μ M O 1  
 /nh

[0172] 7 , HRE  
 HRE + PKC , A + PKC  
 B C  
 4

[0173] \_\_\_\_\_ 5

[0174] PKC PKC

[0175] PKC 5 , (confluent)  
 Alt et al. 2001; Alt  
 et al. 2004; Gartsbein et al. 2006 PKC  
 MEM  
 10 - Ca<sup>2+</sup> - MEM 24

[0176] 24 , ( A B ) PKC (Myr-  
 PKC , 1 μ M 15

[0177] PKC , 1 500μ L 1% Triton Lysis  
 (1 x PBS 1% Triton-X 100, 10 μ g/nh , 2 μ g/nh , 1 nM PMSF, 1 nM  
 EDTA 200 μ MN<sub>2</sub>VO<sub>4</sub>, 10 nM NaF) . 4 30 , 16,000  
 x g 30 4 - 6/GoH(PharMingen)  
 5 μ g/ A/G Plus (Santa Cruz) 30 μ l/ 4  
 35 μ L (1 nM CaCl<sub>2</sub>, 20 nM MgCl<sub>2</sub>, 50 nM -HCl pH 7.5)  
 , DMSO 10 nM TPA 5.5 μ l / PKC  
 , 10 μ l 125 nM AIP (1.25 μ G / [ -32P] ATP, Amersham) /  
 , 30 10 RIPA  
 . 30 μ l (loading) (3 x Laemmli, 5% SDS) /  
 5 8 5% SDS-PAGE , Protran (Schleicher &  
 Schuell) PKC

[0178] PKC , Si gnaTECT C (Pronoga, Madison, W, USA)  
 PKC

[0179] A PKC PKC  
 PKC PKC % 5 , PKC

[0180] \_\_\_\_\_ **6**

[0181]

[0182] . . . . . 5 , (confluent)

. . . . . (  $10^{-6}$  )  
M 0.1 /ml) ( C D ) , 48  
3  
6B , 48 %  
6A

[0183] , 6 ( 60 )

24 [<sup>3</sup>H] (3 μG/ml)  
PBS 5 5% TCA , 1 M  
NaOH <sup>3</sup>H

[0184] 6A-C , KCl , -

[0185] \_\_\_\_\_ **7**

[0186] + PKC B  
(confluent) 5 (7-10 2 ) MEM A 5  
, B( ) 24 ,  
+ PKC  
( QIA127 ; Calbiochem) 6 ( )  
) 7 B 24 -  
+ PKC

[0187] \_\_\_\_\_ **8A**

[0188] A( 8A ) C( 8A )  
+ PKC 12  
A + PKC 12 , C +  
PKC  
MISITRAK® (Smith & Nephew) 12  
( ) .

[0189] \_\_\_\_\_ **8B**

[0190] A( 8B ) C( 8B )  
) + PKC 60  
A + PKC 60 , C + PKC  
8B 0 60

[0191] \_\_\_\_\_ **9**

[0192] 1 + PKC , 3 A  
6

[0193] 9

[0194] \_\_\_\_\_ **10**

[0195] 2

A + PKC , 30  
10 , 1  
, 2

[0196] 11

[0197] ( )  
A + PKC , 11  
2 . 3 5 ,

[0198] 12

[0199] A  
C57BL/6J ( )  
(20mm ) , A( ) 0.1 /mL (HumR),  
(Novo), (LANTUS®), HUMLIN® R(HumR) . 7 ,  
HRE

[0200] 14  
HRE  
>70%

[0201] A  
16 . 16 ,  
"HumR", "Novo", "LANTUS®", HUMLIN® R "HumR".

[0202] 13

[0203] , 17 , USP , PKC  
C57BL/6J ( ) (20mm )  
, 17 , PKC (1 µg/ml) , 0.1 /mL  
, USP , A PKC (1 µg/ml)  
7 , HRE  
HRE  
>70%

[0204] , PKC USP  
+ PKC  
PKC

[0205] 17 . 17 , USP "HumR"  
"Ins USP" . PKC "pep"

[0206] 14

[0207] , PKC ,  
[0208] C57BL/6J ( )  
18 , PKC (1 µ  
g/ml), 0.1 /mL , A 0.1 /mL

[0209] H&E

[0210] (1)

[0211] (2) (>100 x200)

[0212] (3) >20% WBC (x200) , WBC/REC

[0213]

[0214] A PKC 18

[0215] "Hml" 18 PKC "Hml" "pep"

[0216] 15

[0217] 1 A B (L-) (Cal bi ochem 524615 )

[0218] (7-10 2 ) 1 A( MEM ) ( A ) 5 , B( )

[0219] 19 ( 19B) L- A ( 19A) B /nh 0.0001 μ g

[0220] 0.05 nM 0.12 nM 24 1

[0221] 1 (spi nous) 1

[0222] A L- 1 ( 19A) B 1 ( 19B) L- A

[0223]

[0224] 1

[0225] + PKC

[0226] (confl uent) 5

[0227] PKC (  $10^{-6}$  M 0.1 /nh), Myr- PKC , 1  $\mu$  M  
 ( C D ) 24 ,  
 A PKC  
 3 1A  
 1B 24 (p<0.05).

[0228] 2

[0229] + PKC A  
 [0230] C57BL/6J ( ) (20nm )  
 ( A-O ) ( $10^{-6}$  M 0.1 /nh), PKC ( )  
 PKC , 1  $\mu$  M + PKC ( PKC , 1  $\mu$  M 0.1 )  
 7 ,  
 2A , A  
 + PKC , B  
 C  
 2B

[0231] 3

[0232] PKC A  
 [0233] C57BL/6J ( ) (20nm )  
 ( A-O ) PKC ( PKC , 1  $\mu$  M )  
 7 ,  
 : (1)  
 (2) (>100 x200), (3) >20% WBC  
 (x200) WBC/RBC( / )  
 A PKC B  
 C

[0234] 4

[0235] + PKC A  
 [0236] C57BL/6J ( ) (20nm )  
 ( A-O ) PKC ( PKC )  
 , 1  $\mu$  M 0.1 /nh) 7 ,  
 H&E H&E A  
 PKC B C

[0237] 5

[0238] PKC PKC  
 [0239] 5 (confluent) PKC  
 24 5 ( A B ) PKC (Myr- PKC )  
 , 1  $\mu$  M 15 PKC PKC  
 A PKC  
 PKC PKC  
 PKC

[0240] 6

[0241]

[0242] 5 (confluent) (10<sup>-6</sup> M 0.1 /ml) ( C

D)

[0243] 48 (A) (B) 48 (C) (D) KCl 6A-6C

[0244] 7

[0245] B - + PKC

[0246] (7-10 2 ) 5 (confluent) QIA127 ; Calbiochem MEM 5 B

[0247] 24 + PKC 6 ( ) B 24 + PKC 7

[0248] 8

[0249] C A + PKC

[0250] C ( 8 A ) + PKC 12 A ( 8 A ) + PKC 12 C + MSITRAK® (Smith & Nephew) 12 ( 8A )

[0251] PKC A ( 8B ) C ( 8B ) + PKC 60 C + PKC 60 0 60 8B

[0252] 9

[0253] A + PKC

[0254] 1 + PKC 3 A 6

[0255] 10

[0256] A + PKC

[0257] 2 A + PKC 30 10 1 2

[0258] 11

[0259] A + PKC ( ) .

[0260] ( )  
 . A + PKC .  
 2 . 3.5 , .

[0261] 12

[0262] HMLOG® (rDNA ) ( : 57) ( : 58) .

[0263] 13

[0264] NOVLOG® (rDNA ) 1 ( : 57) ( : 59) .

[0265] 14

[0266] LANIUS® (rDNA ) 1 LANIUS® ( : 60) ( : 61) .

[0267] 15

[0268] HMLIN® R NOVLIN® R 1 HMLIN® R ( : 57) ( : 62) .

[0269] 16

[0270] A .

[0271] C57BL/6J ( ) (20nm )  
 , A ( ) 6 0.1 /mL  
 ("HumL"),  
 ("Novo"), ("LANIUS®"), ("HumR") 7 , ,  
 H&E

[0272] 14  
 H&E  
 . >70%

[0273] : "HumL",  
 "Novo", "LANIUS®", HMLIN® R "HumR".

[0274] 17

[0275] PKC USP HMLIN® R + PKC .

[0276] C57BL/6J ( ) (20nm )  
 , A ( ) PKC (1 µg/nh) 0.1 /mL  
 HMLIN® R USP . 7 ,  
 H&E H&E  
 . >70%

[0277] USP "HumR" "Ins USP," . PKC

"pep"

[0278]

18

[0279]

PKC

[0280]

C57BL/6J ( )

19 , PKC (1  
 $\mu$ g/ml) 0.1 /ml HMLIN® R A ( )

7 , H&E

[0281]

:

[0282]

(1)

[0283]

(2) (>100 x200)

[0284]

(3) >20% WBC (x200) , WBC/RBC

[0285]

[0286]

[0287]

HMLIN® R "HmlR" "Hml" PKC  
 "pep"

[0288]

19

[0289]

A B L- 1

[0290]

(7-10 2 ) 1 A(MEM

A 5 , B( )

L- A B

[0291]

0.05 nM 0.12 nM 24

1

1

[0292]

( , , )

[0293]

\_\_\_\_\_

[0294]

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[0295]

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[0298]

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 Lys Asn  
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&lt;210&gt; 14

&lt;211&gt; 16

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Val

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Lys Ile Lys

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Gly Phe Ser Phe Lys Lys

20

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Val

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 1 5 10

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1 5 10

&lt;210&gt; 45

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 45

Phe Lys Leu Lys Arg Lys Gly Ser Phe Lys Lys Phe Ala

1 5 10

&lt;210&gt; 46

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 46

Arg Arg Phe Lys Arg Gln Gly Ser Phe Phe Tyr Phe Phe

1 5 10

&lt;210&gt; 47

&lt;211&gt; 13

&lt;212&gt; PRT

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&lt;222&gt; (3)

&lt;223&gt; Any amino acid

&lt;400&gt; 47

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1 5 10

&lt;210&gt; 48

&lt;211&gt; 13

<212> PRT  
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 <400> 48

Arg Arg Arg Arg Arg Lys Gly Ser Phe Arg Arg Lys Ala  
 1 5 10

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Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ser Val Arg Arg Arg Val  
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Met Asn Arg Arg Gly Ser Ile Lys Gln Ala Lys Ile  
 1 5 10

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Met Phe Ala Val Arg Asp Arg Arg Gln Thr Val Lys Lys Gly Val Ile  
 1 5 10 15

Lys Ala Val Asp Ala Val

20

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Phe Gly Glu Ser Arg Ala Ser Thr Phe Cys Gly Thr Pro Asp

1 5 10

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Lys Ala Arg Leu Ser Tyr Ser Asp Lys Asn

1 5 10

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Ser Ala Phe Ala Gly Phe Ser Phe Val Asn Pro Lys Phe

1 5 10

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Lys Lys Lys Lys Lys Arg Phe Ser Phe Lys Lys Ser Phe Lys Leu Ser

1 5 10 15

Gly Phe Ser Phe Lys Lys

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<210> 56

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<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

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Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu

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10

15

Glu Asn Tyr Cys Asn

20

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<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

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Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1

5

10

15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Lys Pro Thr

20

25

30

<210> 59

<211> 30

<212> PRT

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 59

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Asp Lys Thr

20 25 30

&lt;210&gt; 60

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 60

Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu

1 5 10 15

Glu Asn Tyr Cys Gly

20

&lt;210&gt; 61

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 61

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg

20 25 30

&lt;210&gt; 62

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 62

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
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 Lys Thr Glu Asn Ser Lys Leu Arg Lys Val Lys Tyr Glu Glu Thr Val  
 20 25 30  
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 35 40 45  
 Val Thr Lys Glu Lys Ile Gln Glu Ala Lys Asp Val Tyr Lys Glu His  
 50 55 60  
 Phe Gln Asp Asp Val Phe Asn Glu Lys Gly Trp Asn Tyr Ile Leu Glu  
 65 70 75 80  
 Lys Tyr Asp Gly His Leu Pro Ile Glu Ile Lys Ala Val Pro Glu Gly  
 85 90 95  
 Phe Val Ile Pro Arg Gly Asn Val Leu Phe Thr Val Glu Asn Thr Asp  
 100 105 110  
 Pro Glu Cys Tyr Trp Leu Thr Asn Trp Ile Glu Thr Ile Leu Val Gln  
 115 120 125  
 Ser Trp Tyr Pro Ile Thr Val Ala Thr Asn Ser Arg Glu Gln Lys Lys  
 130 135 140  
 Ile Leu Ala Lys Tyr Leu Leu Glu Thr Ser Gly Asn Leu Asp Gly Leu  
 145 150 155 160  
 Glu Tyr Lys Leu His Asp Phe Gly Tyr Arg Gly Val Ser Ser Gln Glu  
 165 170 175  
 Thr Ala Gly Ile Gly Ala Ser Ala His Leu Val Asn Phe Lys Gly Thr  
 180 185 190  
 Asp Thr Val Ala Gly Leu Ala Leu Ile Lys Lys Tyr Tyr Gly Thr Lys  
 195 200 205  
 Asp Pro Val Pro Gly Tyr Ser Val Pro Ala Ala Glu His Ser Thr Ile

210                      215                      220  
 Thr Ala Trp Gly Lys Asp His Glu Lys Asp Ala Phe Glu His Ile Val  
 225                      230                      235                      240  
 Thr Gln Phe Ser Ser Val Pro Val Ser Val Val Ser Asp Ser Tyr Asp  
                          245                      250                      255  
 Ile Tyr Asn Ala Cys Glu Lys Ile Trp Gly Glu Asp Leu Arg His Leu  
                          260                      265                      270  
 Ile Val Ser Arg Ser Thr Gln Ala Pro Leu Ile Ile Arg Pro Asp Ser  
                          275                      280                      285  
 Gly Asn Pro Leu Asp Thr Val Leu Lys Val Leu Glu Ile Leu Gly Lys  
                          290                      295                      300  
 Lys Phe Pro Val Thr Glu Asn Ser Lys Gly Tyr Lys Leu Leu Pro Pro  
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 Tyr Leu Arg Val Ile Gln Gly Asp Gly Val Asp Ile Asn Thr Leu Gln  
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Glu

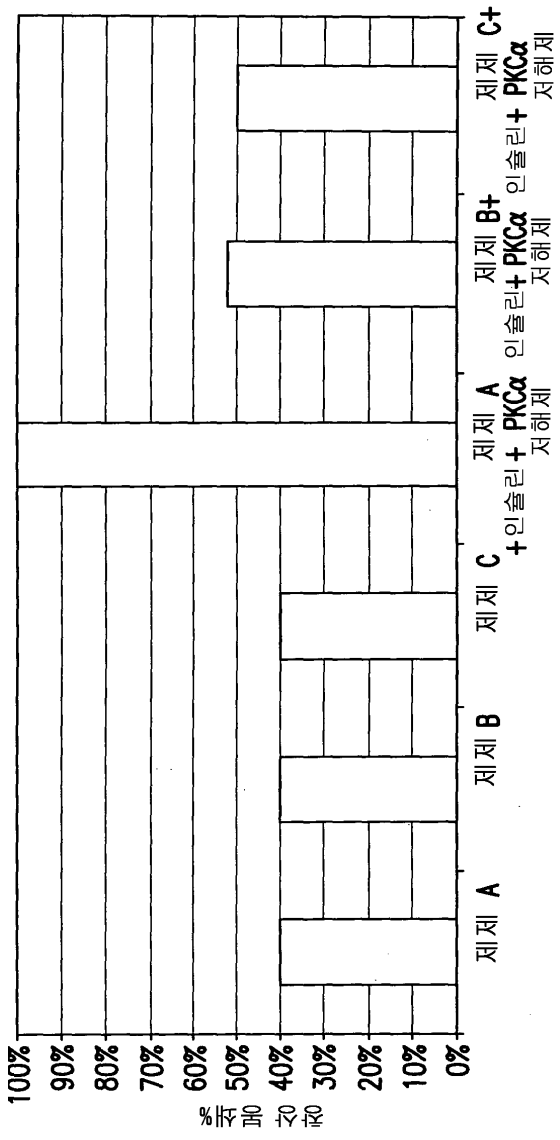
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Met Asn Ala Ala Ala Glu Ala Glu Phe Asn Ile Leu Leu Ala Thr Asp  
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 Ser Tyr Lys Val Thr His Tyr Lys Gln Tyr Pro Pro Asn Thr Ser Lys  
                          20                      25                      30  
 Val Tyr Ser Tyr Phe Glu Cys Arg Glu Lys Lys Thr Glu Asn Ser Lys  
                          35                      40                      45  
 Val Arg Lys Val Lys Tyr Glu Glu Thr Val Phe Tyr Gly Leu Gln Tyr  
                          50                      55                      60  
 Ile Leu Asn Lys Tyr Leu Lys Gly Lys Val Val Thr Lys Glu Lys Ile  
   65                      70                      75                      80  
 Gln Glu Ala Lys Glu Val Tyr Arg Glu His Phe Gln Asp Asp Val Phe  
                          85                      90                      95  
 Asn Glu Arg Gly Trp Asn Tyr Ile Leu Glu Lys Tyr Asp Gly His Leu  
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 Pro Ile Glu Val Lys Ala Val Pro Glu Gly Ser Val Ile Pro Arg Gly

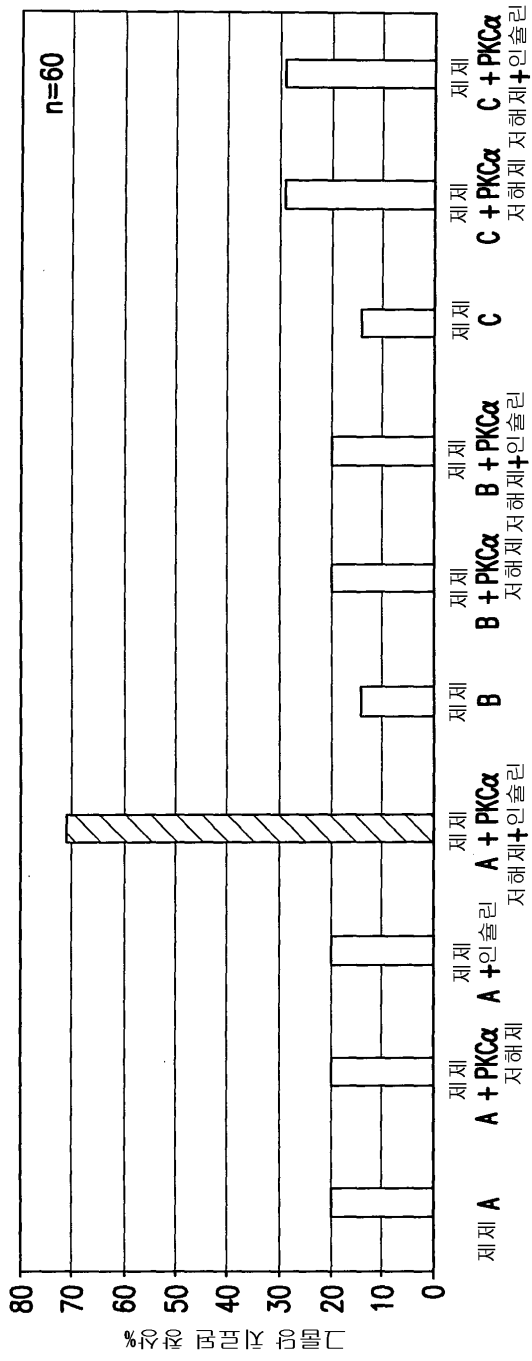




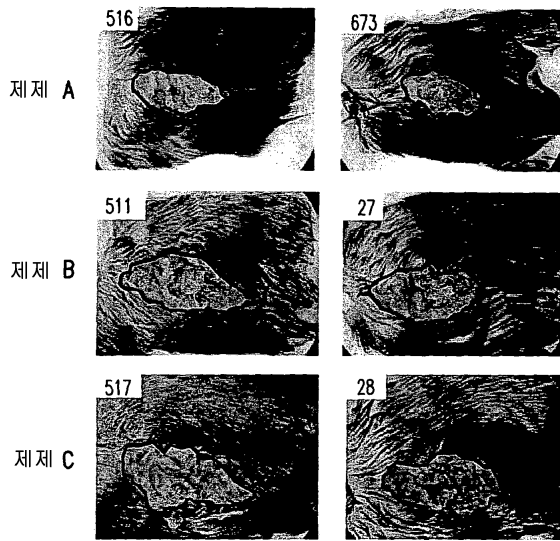
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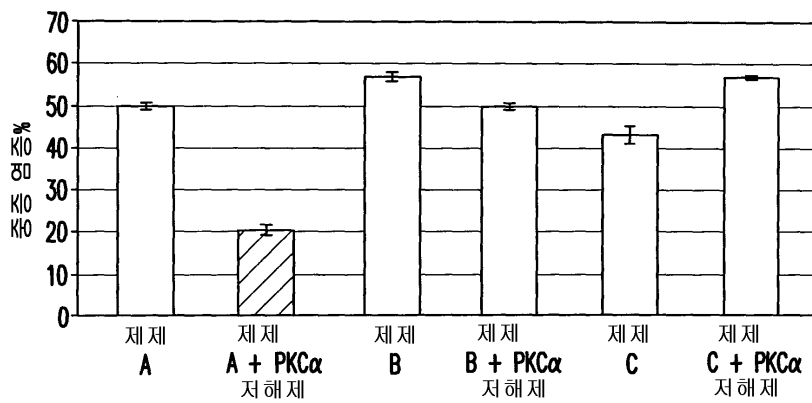
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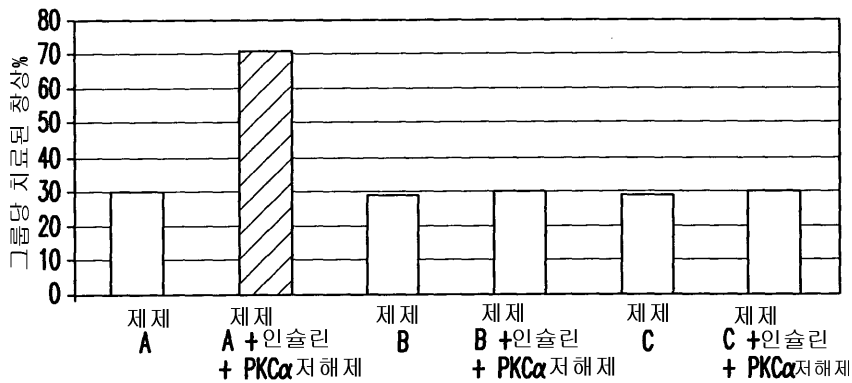
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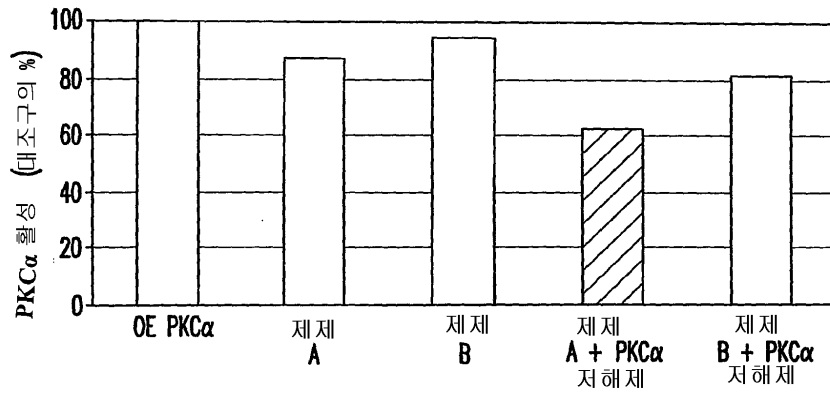
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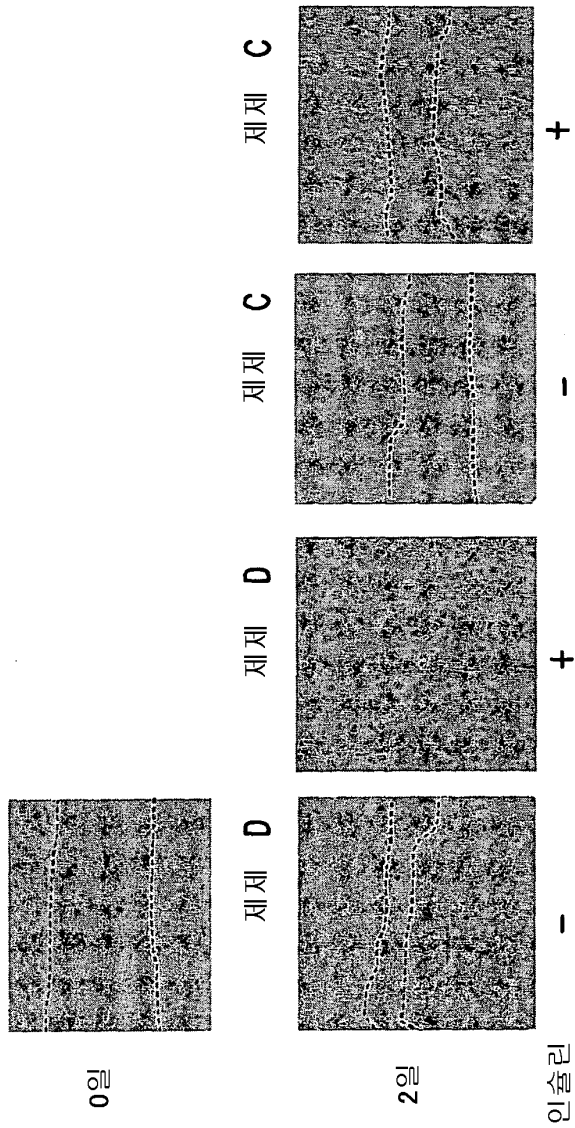
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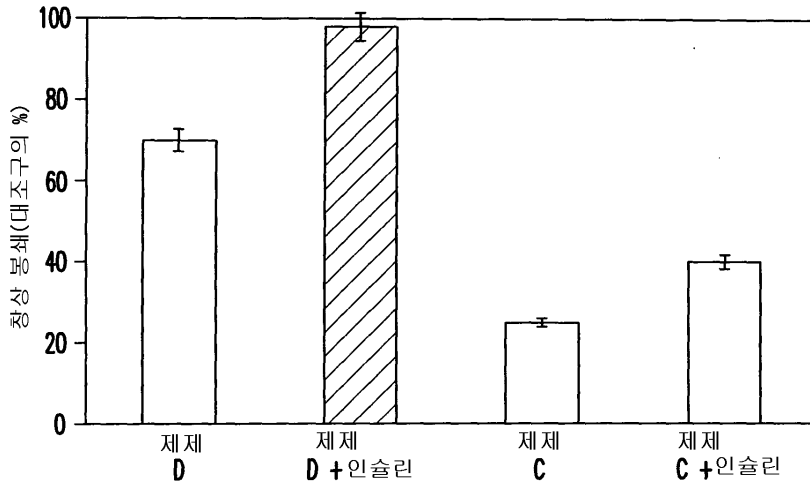
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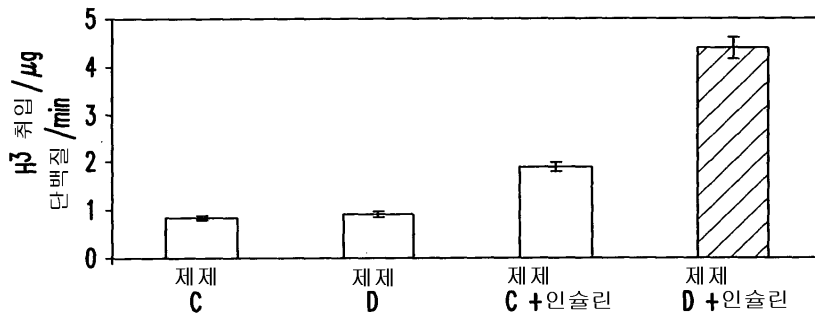
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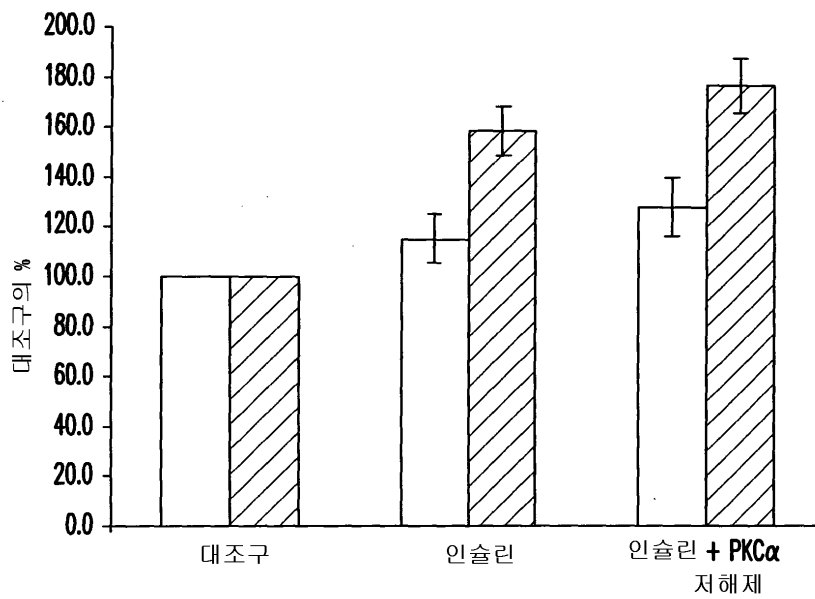
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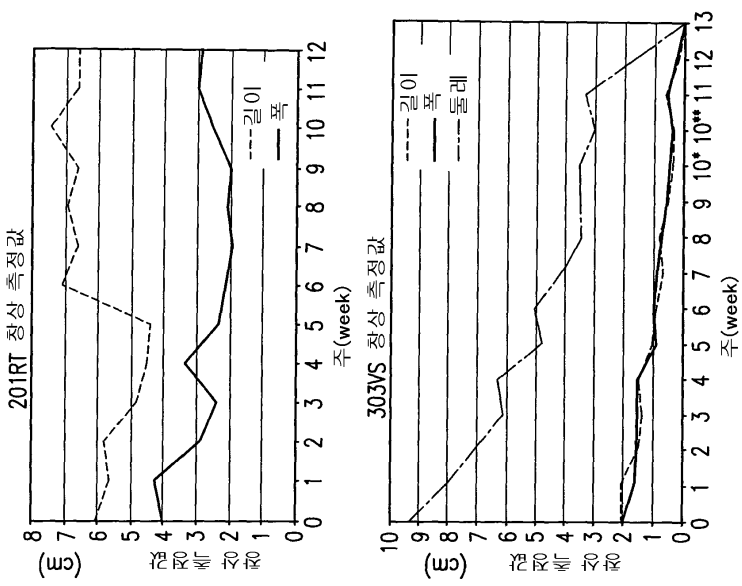


7



— 매체 B 내에서의 처리  
 — 매체 B 내에서의 예비-인큐베이션(24시간동안)

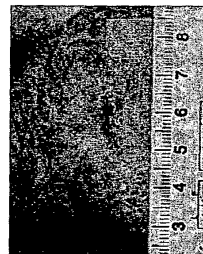
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제제 C + 인슐린 + PKC $\alpha$  저해제  
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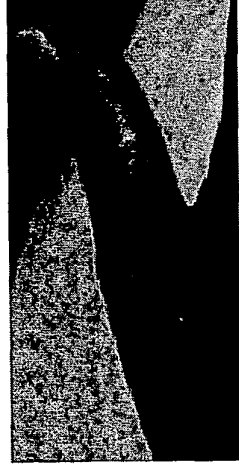


제제 A + 인슐린 + PKC $\alpha$  저해제  
봉쇄까지 12주



88

제제 A 왼쪽



제제 C 오른쪽



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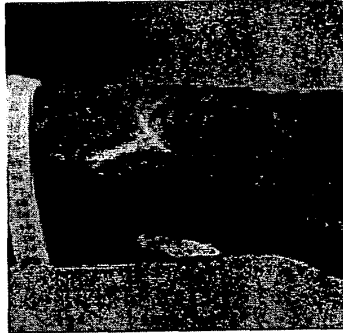
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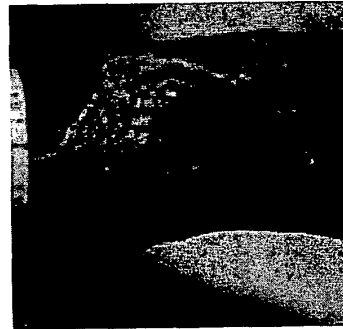
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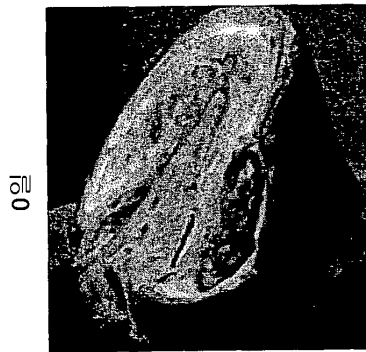
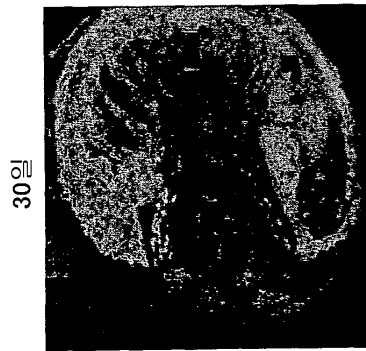
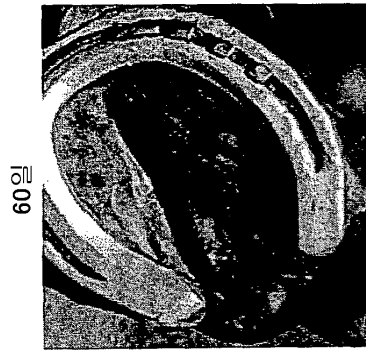
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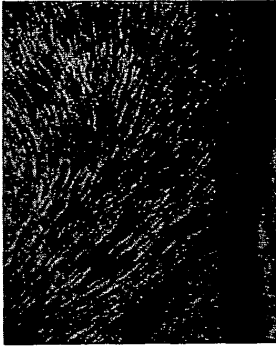


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11

3.5개월



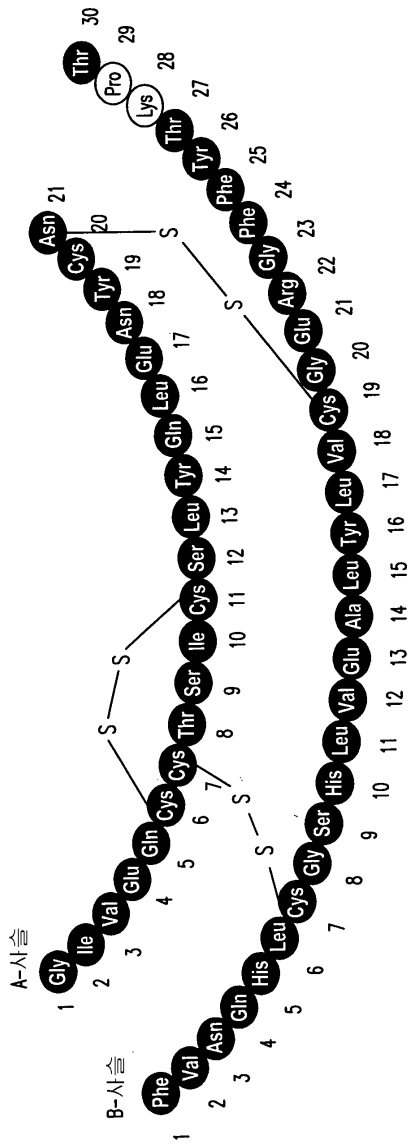
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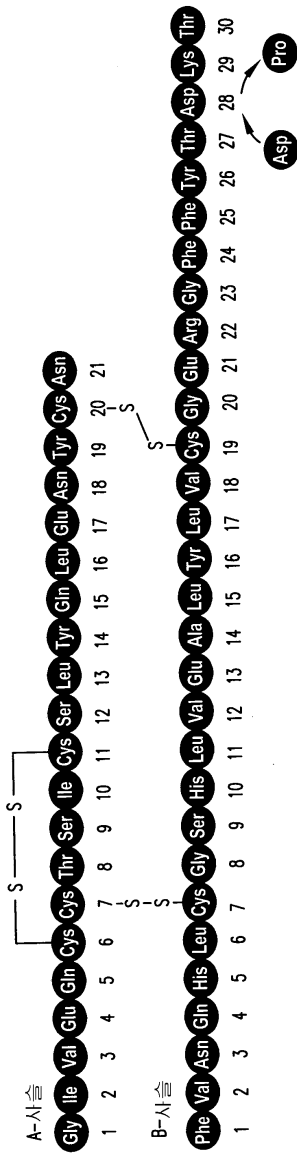
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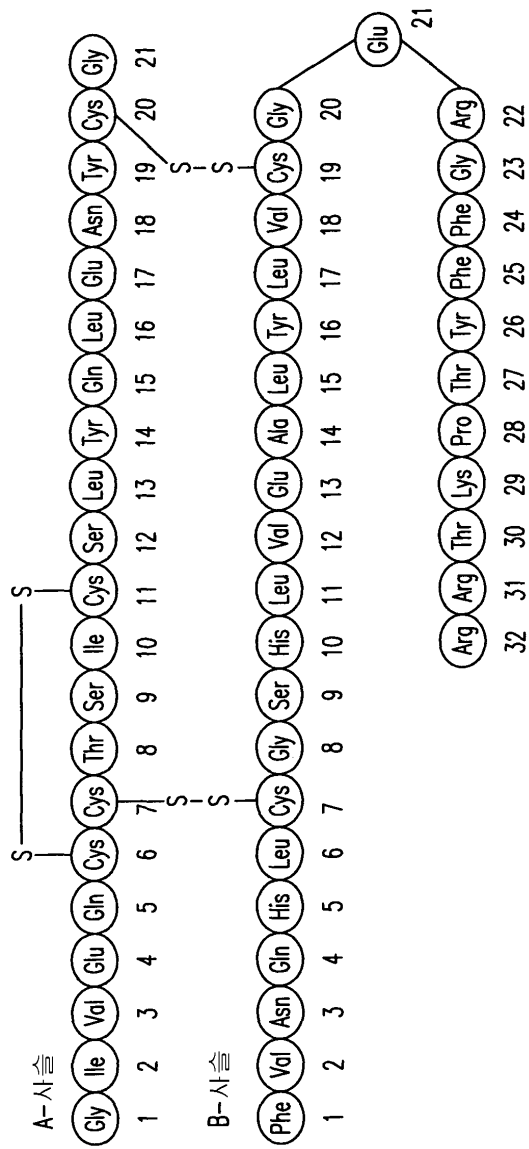
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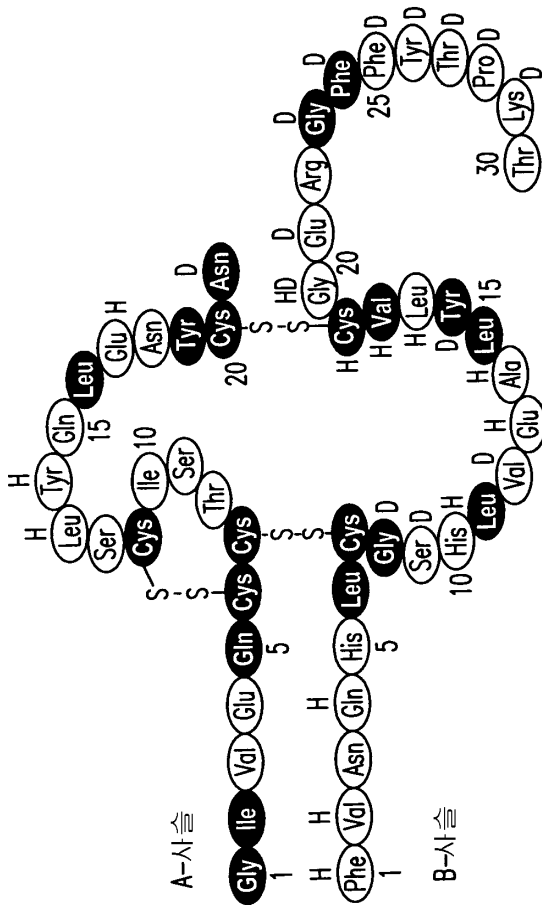
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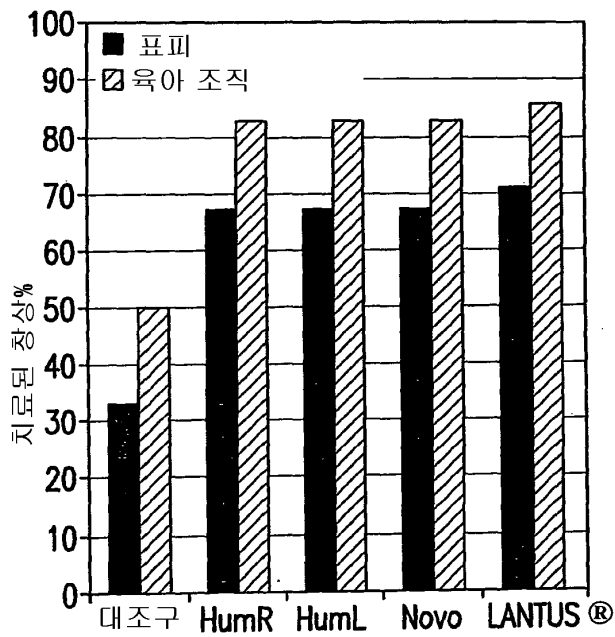
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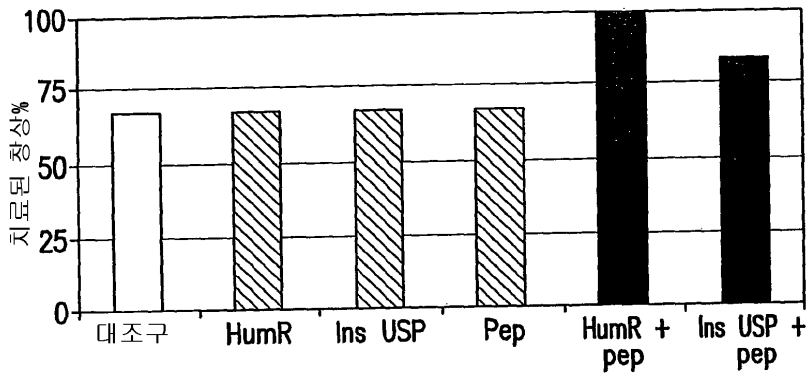
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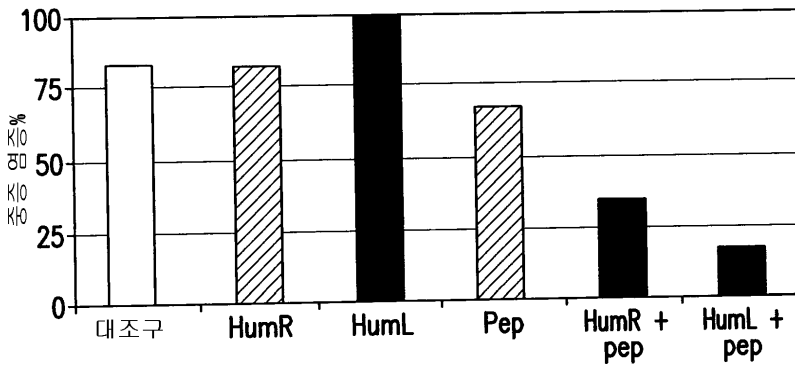
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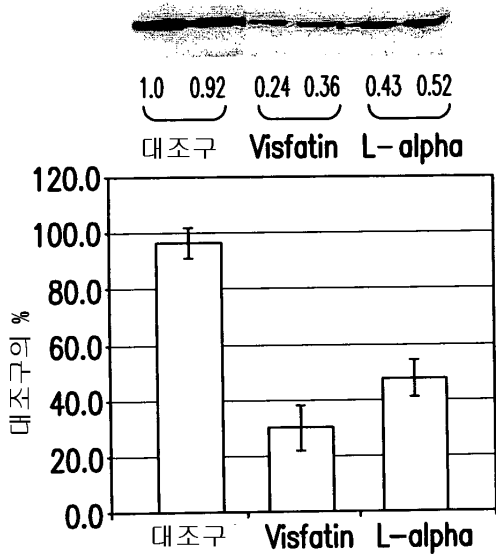
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18



19a





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1 5 10

<210> 3

<211> 18

<212> PRT

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Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His Glu Val

1 5 10 15

Lys Asn

<210> 4

<211> 22

<212> PRT

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Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His Glu Val

1 5 10 15

Lys Asn Leu Lys Gly Ala

20

<210> 5

<211> 13

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Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Leu Ala Val

1                    5                    10  
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Arg Phe Ala Arg Lys Gly Ala Leu Ala Gln Lys Asn Val

1                    5                    10  
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Arg Phe Ala Arg Lys Gly Ala Leu Arg

1                    5  
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Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe

1                    5                    10  
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Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala

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 <210> 10  
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Ala Arg Arg Lys Arg Lys Gly Ala Phe Phe Tyr Gly Gly

1 5 10  
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Arg Arg Arg Arg Arg Lys Gly Ala Phe Arg Arg Lys Ala

1 5 10  
 <210> 12  
 <211> 14  
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Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val Tyr

1 5 10  
 <210> 13  
 <211> 12  
 <212> PRT  
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Asp Ala Arg Lys Gly Ala Leu Arg Gln Asn Lys Val

1 5 10  
 <210> 14  
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Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val

1 5 10 15  
 <210> 15  
 <211> 17  
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Gly Pro Arg Pro Leu Phe Cys Arg Lys Gly Ala Leu Arg Gln Lys Val

1 5 10 15  
 Val  
 <210> 16  
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Gln Lys Arg Pro Ala Gln Arg Ser Lys Tyr Leu

1 5 10  
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Gln Lys Arg Pro Ser Gln Arg Ala Lys Tyr Leu

1 5 10

<210> 18

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Gly Gly Pro Leu Arg Arg Thr Leu Ala Val Arg Arg

1 5 10

<210> 19

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Gly Gly Pro Leu Ser Arg Arg Leu Ala Val Arg Arg

1 5 10

<210> 20

<211> 12

<212> PRT

<213> Artificial Sequence

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<400> 20

Gly Gly Pro Leu Ser Arg Thr Leu Ala Val Arg Arg

1 5 10

<210> 21

<211> 12

<212> PRT

<213> Artificial Sequence

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Gly Gly Pro Leu Ser Arg Arg Leu Ala Val Ala Arg

1 5 10

<210> 22

<211> 12

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 22

Gly Gly Pro Leu Arg Arg Thr Leu Ala Val Ala Arg

1 5 10

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 23

Val Arg Lys Ala Leu Arg Arg Leu

1 5

<210> 24

<211> 12

<212>

> PRT

<213> Artificial Sequence

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Gly Gly Arg Leu Ser Arg Thr Leu Ala Val Ala Arg

1 5 10

<210> 25

<211> 17

<212> PRT

<213> Artificial Sequence

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<223> N-term myristoylated

<220><221> BINDING

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<223> C-term amidated

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1 5 10 15

Gly

<210> 26

<211> 12

<212> PRT

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Arg Lys Arg Gln Arg Ala Met Arg Arg Arg Val His

1 5 10

<210> 27

<211> 16

<212> PRT

<213> Artificial Sequence

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<400> 27

Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val

1 5 10 15

<210> 28

<211> 13

<212> PRT

<213> Artificial Sequence

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Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala

1 5 10

<210> 29  
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<220><221> MD\_RES

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Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe  
 1 5 10

<210> 30  
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Ala Arg Arg Lys Arg Lys Gly Ala Phe Phe Tyr Gly Gly  
 1 5 10

<210> 31  
 <211> 13  
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Arg Arg Arg Arg Arg Lys Gly Ala Phe Arg Arg Lys Ala  
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<210> 32  
 <211> 20  
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1 5 10 15

Lys Ile Lys Ser

20

<210> 33

<211> 19

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<400> 33

Ala Ala Ala Lys Ile Gln Ala Ala Phe Arg Gly His Met Ala Arg Lys

1 5 10 15

Lys Ile Lys

<210> 34

<211> 16

<212> PRT

<213> Artificial Sequence

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Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val

1 5 10 15

<210> 35

<211> 8

<212> PRT

<213> Artificial Sequence

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<400> 35

Val Arg Lys Ala Leu Arg Arg Leu

1 5

<210> 36

<211> 22

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 36

Lys Lys Lys Lys Lys Arg Phe Ser Phe Lys Lys Ala Phe Lys Leu Ser

1 5 10 15

Gly Phe Ser Phe Lys Lys

20

<210> 37

<211> 17

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 37

Gly Pro Arg Pro Leu Phe Cys Arg Lys Gly Ala Leu Arg Gln Lys Val

1 5 10 15

Val

<210> 38

<211> 17

<212> PRT

<213> Artificial Sequence

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<400> 38

Glu Ser Thr Val Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn

1 5 10 15

Val

<210> 39

<211> 16

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 39

Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ala Val Arg Arg Arg Val

1 5 10 15

<210> 40

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 40

Arg Phe Ala Arg Leu Gly Ala Leu Arg Gln Lys Asn Val

1 5 10

<210> 41

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<220><221> MD\_RES

<222> (3)

<223> Any amino acid

<400> 41

Tyr Tyr Xaa Lys Arg Lys Met Ala Phe Phe Glu Phe Phe

1 5 10

<210> 42

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 42

Arg Arg Phe Lys Arg Gln Gly Ala Phe Phe Tyr Phe Phe

1 5 10

<210> 43

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 43

Phe Lys Leu Lys Arg Lys Gly Ala Phe Lys Lys Phe Ala

1 5 10

<210> 44

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 44

Ala Arg Arg Lys Arg Lys Gly Ser Phe Phe Tyr Gly Gly

1 5 10

<210> 45

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 45

Phe Lys Leu Lys Arg Lys Gly Ser Phe Lys Lys Phe Ala

1 5 10

<210> 46

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 46

Arg Arg Phe Lys Arg Gln Gly Ser Phe Phe Tyr Phe Phe

1 5 10

<210> 47

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<220><221> MD\_RES

<222> (3)

<223> Any amino acid

<400> 47

Tyr Tyr Xaa Lys Arg Lys Met Ser Phe Phe Glu Phe Phe

1 5 10

<210> 48

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 48

Arg Arg Arg Arg Arg Lys Gly Ser Phe Arg Arg Lys Ala

1 5 10

<210> 49

<211> 16

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 49

Glu Arg Met Arg Pro Arg Lys Arg Gln Gly Ser Val Arg Arg Arg Val

1 5 10 15

<210> 50

<211> 12

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 50

Met Asn Arg Arg Gly Ser Ile Lys Gln Ala Lys Ile

1 5 10

<210> 51

<211> 22

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 51

Met Phe Ala Val Arg Asp Arg Arg Gln Thr Val Lys Lys Gly Val Ile

1 5 10 15

Lys Ala Val Asp Ala Val

20

<210> 52

<211> 14

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 52

Phe Gly Glu Ser Arg Ala Ser Thr Phe Cys Gly Thr Pro Asp

1 5 10

<210> 53

<211> 10

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 53

Lys Ala Arg Leu Ser Tyr Ser Asp Lys Asn

1 5 10

<210> 54

<211> 13

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 54

Ser Ala Phe Ala Gly Phe Ser Phe Val Asn Pro Lys Phe

1 5 10

<210> 55

<211> 22

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 55

Lys Lys Lys Lys Lys Arg Phe Ser Phe Lys Lys Ser Phe Lys Leu Ser

1 5 10 15

Gly Phe Ser Phe Lys Lys

20

<210> 56

<211> 20

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 56

gttctcgctg gtgagttca 20

<210> 57

<211> 21

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 57

Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu

1 5 10 15

Glu Asn Tyr Cys Asn

20

<210> 58

<211> 30

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 58

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Lys Pro Thr

20 25 30

<210> 59

<211> 30

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 59

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Asp Lys Thr

20 25 30

<210> 60

<211> 21

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 60

Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu

1 5 10 15

Glu Asn Tyr Cys Gly

20

<210> 61

<211> 32

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic peptide

<400> 61

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg

20 25 30

&lt;210&gt; 62

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;&lt;223&gt; Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; 62

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr

20 25 30

&lt;210&gt; 63

&lt;211&gt; 337

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 63

Pro Pro Asn Thr Ser Lys Val Tyr Ser Tyr Phe Glu Cys Arg Glu Lys

1 5 10 15

Lys Thr Glu Asn Ser Lys Leu Arg Lys Val Lys Tyr Glu Glu Thr Val

20 25 30

Phe Tyr Gly Leu Gln Tyr Ile Leu Asn Lys Tyr Leu Lys Gly Lys Val

35 40 45

Val Thr Lys Glu Lys Ile Gln Glu Ala Lys Asp Val Tyr Lys Glu His

50 55 60

Phe Gln Asp Asp Val Phe Asn Glu Lys Gly Trp Asn Tyr Ile Leu Glu

65 70 75 80

Lys Tyr Asp Gly His Leu Pro Ile Glu Ile Lys Ala Val Pro Glu Gly

85 90 95

Phe Val Ile Pro Arg Gly Asn Val Leu Phe Thr Val Glu Asn Thr Asp

100 105 110

Pro Glu Cys Tyr Trp Leu Thr Asn Trp Ile Glu Thr Ile Leu Val Gln

115 120 125

Ser Trp Tyr Pro Ile Thr Val Ala Thr Asn Ser Arg Glu Gln Lys Lys

130                      135                      140  
 Ile Leu Ala Lys Tyr Leu Leu Glu Thr Ser Gly Asn Leu Asp Gly Leu  
 145                      150                      155                      160  
 Glu Tyr Lys Leu His Asp Phe Gly Tyr Arg Gly Val Ser Ser Gln Glu  
                          165                      170                      175  
 Thr Ala Gly Ile Gly Ala Ser Ala His Leu Val Asn Phe Lys Gly Thr  
                          180                      185                      190  
 Asp Thr Val Ala Gly Leu Ala Leu Ile Lys Lys Tyr Tyr Gly Thr Lys  
  
 195                      200                      205  
 Asp Pro Val Pro Gly Tyr Ser Val Pro Ala Ala Glu His Ser Thr Ile  
 210                      215                      220  
 Thr Ala Trp Gly Lys Asp His Glu Lys Asp Ala Phe Glu His Ile Val  
 225                      230                      235                      240  
 Thr Gln Phe Ser Ser Val Pro Val Ser Val Val Ser Asp Ser Tyr Asp  
                          245                      250                      255  
 Ile Tyr Asn Ala Cys Glu Lys Ile Trp Gly Glu Asp Leu Arg His Leu  
                          260                      265                      270  
  
 Ile Val Ser Arg Ser Thr Gln Ala Pro Leu Ile Ile Arg Pro Asp Ser  
                          275                      280                      285  
 Gly Asn Pro Leu Asp Thr Val Leu Lys Val Leu Glu Ile Leu Gly Lys  
                          290                      295                      300  
 Lys Phe Pro Val Thr Glu Asn Ser Lys Gly Tyr Lys Leu Leu Pro Pro  
 305                      310                      315                      320  
 Tyr Leu Arg Val Ile Gln Gly Asp Gly Val Asp Ile Asn Thr Leu Gln  
                          325                      330                      335  
 Gu

&lt;210&gt;

64

&lt;211&gt; 491

&lt;212&gt; PRT

&lt;213&gt; Mis sp.

&lt;400&gt; 64

Met Asn Ala Ala Ala Glu Ala Glu Phe Asn Ile Leu Leu Ala Thr Asp  
1 5 10 15  
Ser Tyr Lys Val Thr His Tyr Lys Glu Tyr Pro Pro Asn Thr Ser Lys  
20 25 30  
Val Tyr Ser Tyr Phe Glu Cys Arg Glu Lys Lys Thr Glu Asn Ser Lys  
35 40 45  
Val Arg Lys Val Lys Tyr Glu Glu Thr Val Phe Tyr Gly Leu Glu Tyr  
50 55 60  
Ile Leu Asn Lys Tyr Leu Lys Gly Lys Val Val Thr Lys Glu Lys Ile  
65 70 75 80  
Glu Glu Ala Lys Glu Val Tyr Arg Glu His Phe Glu Asp Asp Val Phe  
85 90 95  
Asn Glu Arg Gly Trp Asn Tyr Ile Leu Glu Lys Tyr Asp Gly His Leu  
100 105 110  
Pro Ile Glu Val Lys Ala Val Pro Glu Gly Ser Val Ile Pro Arg Gly  
115 120 125  
Asn Val Leu Phe Thr Val Glu Asn Thr Asp Pro Glu Cys Tyr Trp Leu  
130 135 140  
Thr Asn Trp Ile Glu Thr Ile Leu Val Glu Ser Trp Tyr Pro Ile Thr  
145 150 155 160  
Val Ala Thr Asn Ser Arg Glu Glu Lys Lys Ile Leu Ala Lys Tyr Leu  
165 170 175  
Leu Glu Thr Ser Gly Asn Leu Asp Gly Leu Glu Tyr Lys Leu His Asp  
180 185 190  
Phe Gly Tyr Arg Gly Val Ser Ser Glu Glu Thr Ala Gly Ile Gly Ala  
195 200 205  
Ser Ala His Leu Val Asn Phe Lys Gly Thr Asp Thr Val Ala Gly Ile  
210 215 220  
Ala Leu Ile Lys Lys Tyr Tyr Gly Thr Lys Asp Pro Val Pro Gly Tyr  
225 230 235 240  
Ser Val Pro Ala Ala Glu His Ser Thr Ile Thr Ala Trp Gly Lys Asp  
245 250 255

H s G u L y s A s p A l a P h e G u H s I l e V a l T h r G n P h e S e r S e r V a l  
 260 265 270  
 P r o V a l S e r V a l V a l S e r A s p S e r T y r A s p I l e T y r A s n A l a C y s G u  
 275 280 285  
 L y s I l e T r p G y G u A s p L e u A r g H s L e u I l e V a l S e r A r g S e r T h r  
 290 295 300  
 G u A l a P r o L e u I l e I l e A r g P r o A s p S e r G y A s n P r o L e u A s p T h r  
 305 310 315 320  
 V a l L e u L y s V a l L e u A s p I l e L e u G y L y s L y s P h e P r o V a l T h r G u  
 325 330 335  
 A s n S e r L y s G y T y r L y s L e u L e u P r o P r o T y r L e u A r g V a l I l e G n  
 340 345 350  
  
 G y A s p G y V a l A s p I l e A s n T h r L e u G n G u I l e V a l G u G y M t  
 355 360 365  
 L y s G n L y s L y s T r p S e r I l e G u A s n V a l S e r P h e G y S e r G y G y  
 370 375 380  
 A l a L e u L e u G n L y s L e u T h r A r g A s p L e u L e u A s n C y s S e r P h e L y s  
 385 390 395 400  
 C y s S e r T y r V a l V a l T h r A s n G y L e u G y V a l A s n V a l P h e L y s A s p  
 405 410 415  
 P r o V a l A l a A s p P r o A s n L y s A r g S e r L y s L y s G y A r g L e u S e r L e u  
 420 425 430  
 H s A r g T h r P r o A l a G y A s n P h e V a l T h r L e u G u G u G y L y s G y  
 435 440 445  
 A s p L e u G u G u T y r G y H s A s p L e u L e u H s T h r V a l P h e L y s A s n  
 450 455 460  
 G y L y s V a l T h r L y s S e r T y r S e r P h e A s p G u V a l A r g L y s A s n A l a  
 465 470 475 480  
 G n L e u A s n I l e G u G n A s p V a l A l a P r o H s  
 485 490