

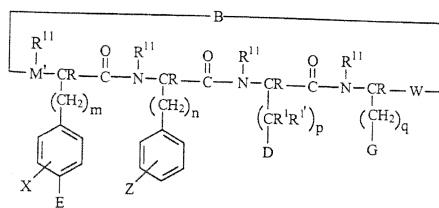
(74)

:

(54)

I MC - 4 / MC - 3 :

[I]



(, B, X, Z, D, G, R, R¹, R^{1'}, R¹¹, m, n, p, q) . MC
 - 4 / MC - 3
 (cachexia) CNS

(MC - 1) MC - 4 / MC - 3

() MC -
 - MSH ((melanocyte)), - MSH, - MSH, ACTH (. MSH
)
 (Eberle 1988), ACTH (Simpson Waterman, 1988).
 (motivation),
 (aldosteron) (tone),
 (thyroxin) FSH

ACTH (core) His - Phe - Arg - Trp
 - (POMC) 가 , 5
 (subtype) . MC 7 (trans
 membrane) G - . MC - 1, MC - 2, MC - 3, MC - 4, MC - 5
 5 MC cAMP , MC - 2 ACTH ,
 MSH . MC - 1 (melanoma) .
 MC - 2 . MC - 3 mRNA ,
 (Gantz , 1993a, Desarnaud , 1994, Roselli Rehfuss , 1993). MC - 4
 (Gantz , 1993b; Mountjoy , 1994). MC - 5 (Chh
 ajlani , 1993; Gantz 1994; Griffon 1994; Labbu , 1994; Barrett , 1994; Fathi , 1995).
 MC - 가
 (Chhajlani, 1996).

MC - 3 (feeding) . MC - 4 (hypothalamus)
 . MC - 4/MC - 3 (intracere
 broventricular) 가 (agonist)
 (antagonist) . Fan, W. , "
 Role of Melanocortinergic Neurons in Feeding and the Agouti Obesity Syndrome" ,Nature, 385(6612), pp.
 165~8(1997. 1. 9)

MC - 4 . Hus
 zer, D. , " Targeted Disruption of the Melanocortin - 4 Receptor Results in Obesity in Mice" ,Cell, pp. 13
 1~141 (1997); Klebig, M.L. , " Ectopic Expression of the Agouti Gene in Transgenic Mice Causes Obes
 ity, Features of Type II Diabetes, and Yellow Fur" ,Proc. Natl Acad Sci., Vol. 92, pp. 4728~32 (1995); K
 arbon, W. , " Expression and Function of Argt, a Novel Gene Related to Agouti" ,Abstract from the Nine
 teenth Annual Winter Neuropeptide Conference(1998); Fan, W. , " Role of Melanocortinergic Neurons in
 Feeding and the Agouti Obesity Syndrome" ,Nature, Vol. 385, pp. 165~168 (1997); Seely, R.J., " Melano
 cortin Receptors in Leptin Effects" ,Nature, Vol. 390, p. 349 (1997); Comuzzie, A.G., " A Major Quantita
 tive Trait Locus Determining Serum Leptin Levels and Fat Mass is Located on Human Chromosome 2" ,Na
 t. Gen., Vol. 15, pp. 273~276 (1997); Chagnon, Y.C. , " Linkage and Association Studies Between the M
 elanocortin Receptors 4 and 5 Genes and Obesity - Related Phenotypes in the Quebec Family Study" ,Mol.
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 n the Regulation of Body Weight" , WO 97/47316 (1997); Shutter, J.R. , " Hypothalam
 ic Expression of ART, a Novel Gene Related to Agouti, is Up - Regulated in Obese and Diabetic Mutant Mi
 ce" ,Gen. & Dev.Vol. 11, pp. 593~602 (1997) . MSH MC - 4
 (leptin) . MC - 4

MC - 4 / MC - 3 가 ,
 MC - 1 MC
 MC - 4 / MC - 3

- (G) G (bicyclic) ;
- (H) R¹¹ ; R ; R
- (I) W , -CH₂ - -C(=O) - ;
- (J) M' , -N- -CH- ;
- (K) B M' W (bridge) ,
 25 , Z D - (" D - Phe" " f") ,
 B가 I Cys ()
 MC - 3 MC - 4

I. :

" (Ala; A), (Arg; R), (Asn; N), (Asp; D), (Cys; C), (Glu; Q), (Gln; E), (Gly; G), (His; H), (Ile; I), (Leu; L), (Lys; K), (Met; M), (Phe; F), (Pro; P), (Ser; S), (Thr; T), (Trp; W), (Tyr; Y), (Val; V) . 3 1 (3)

: p - (Bpa); - (2 -) - (Nal); - (Cha); 3,4 - (3,4 - Dcp); 4 - (4 - Fpa); 4 - (4 - Npa); 2 - (Tha); 1,2, 3,4 - - 3 - (Tic); 3 - (3 - Bal); 4 - (4 - Yp a); 4 - (4 - lpa); 4 - (4 - Rpa); 4,4' - (Bip); (Pfp); , - (Dip). I A , 1 .

" D - Nal" " D - Phe" , 3 " D" D -
 3 " L" L -
 , " D" " L" 가 D - L -
 1 가 , L -
 D - .

" Ac" (, CH₃C(=O) -) .
 " " 가 , (, -O -) . (MeO), , .

가 , MC - 4 MC - 3 " MC - 3 " MC - 4 MC - 3 가
 MC - 4 MC - 3
 MC - 4/MC - 3
 Amersham Pharmacia Biotech BioTrak TM cAMP (EIA)
 MC cAMP 가 , MC - 1, MC - 3 MC - 4
 cAMP 가
 HEK 96 (well) 가
 MC 1
 ELISA cAMP
 MC cAMP MC cAMP MC
 cAMP %

" MC - 4 " MC - 3 " MC - 4 MC - 3 MC - 3
 MC MC - 4/MC - 3

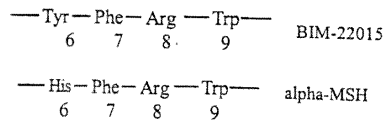
" MC - 3 " MC - 4 " MC - 3 MC - 4 (splice)
 MC - 3 Gantz (MC - 3); Desarnaud ,
 (MC - 3) L. Reyfuss , " Identification of a Receptor for Gamma Melanotropin and Other Pr
 oopiomelanocortin Peptides in the Hypothalamus and Limbic System.,Proc. Natl. Acad. Sci. USA, vol. 90,
 pp. 8856~8860 (1993) (MC - 3) MC - 4 Gantz , (MC - 4), J.D.
 Alvaro , " Morphine Down - Regulates Melanocortin - 4 Receptor Expression in Brain Regions that Mediat
 e Opiate Addiction" ,Mol - Pharmacol. Sep, vol. 50 (3), pp. 583~91 (1996) (MC - 4) Takeuchi, S.
 Takahashi, S., " Melanocortin Receptor Genes in the Chicken - - Tissue Distributions" ,Gen - Comp - Endocr
 inol., vol. 112(2), pp. 220~31 (Nov. 1998) (MC - 4)

" 가 " 가 가

" 가 " () , (,)
)
 87/05297 (Johnston , 1987 9 11)
 () , ()
 () , 가 ,

27
 25 27 가 , B
 , MC - 3/MC - 4
 , I .

BIM - 22015가 MC - 3 MC - 4
 가 , 6~9 - MSH 6 (- MSH) His 가
 Tyr , I MC - 4 / MC - 3
 , Schioth, H.B. , " Selectivity of [Phe - 17], [Ala6] and [D - Ala4,Gln5, Tyr6] Substitute
 d ACTH(4~10) Analogues for the Melanocortin Receptors" , Peptides, vol. 18(5), pp. 761~3 (1997) .



- Tyr - Phe - Arg - Trp - BIM - 22015
 6 His Phe Tyr 6 His
 , MC - 3 MC - 4
 , MC - 4/MC - 3
 Tyr MC
 MC - 1

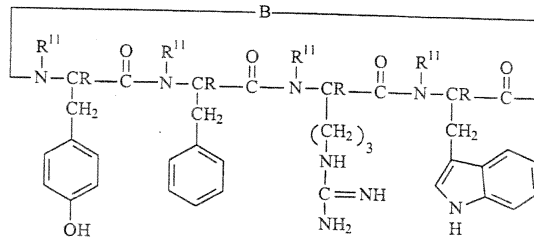
B , , (,) , - (,)
) ,
 , B 2 , 6
 Cys 3 , B가
 () I M' W I

4 6 가 가 , .

s Orn , Asp Glu Ly
 , . (" - "

, B, X, Z, M', W, R, R¹, R^{1'}, R², R³, R⁴, R⁵, R¹¹; R⁶,
 SO_xR¹² (x = 0, 1, 2, R¹²); Y
 -NR⁷-, -CR^{7'}R^{7'}, -CR^{7'}=CR^{7'}, -CR^{7'}=N- -N=CR^{7'}- (R⁷, R^{7'},
 R⁷, R^{7'}, Y, A, R⁶, -CH₂-
) ; Q, -OR¹⁰, -SR¹⁰, -NR¹⁰R^{10'},
 R¹⁰, R^{10'},
) ; Q, I, G
 A, m, n, q, 1, p, 3, D, G
 11, 12

B



, R, R¹¹ B

A

Q, -OR¹⁰, -NR¹⁰R^{10'},
 ; 가 Q, R¹⁰, R^{10'},
 ; R¹⁰, R^{10'}

R⁶

R⁷

(cyclization) ([]) 가 Ac-
 -NH₂ () , "Nal" , "Orn"

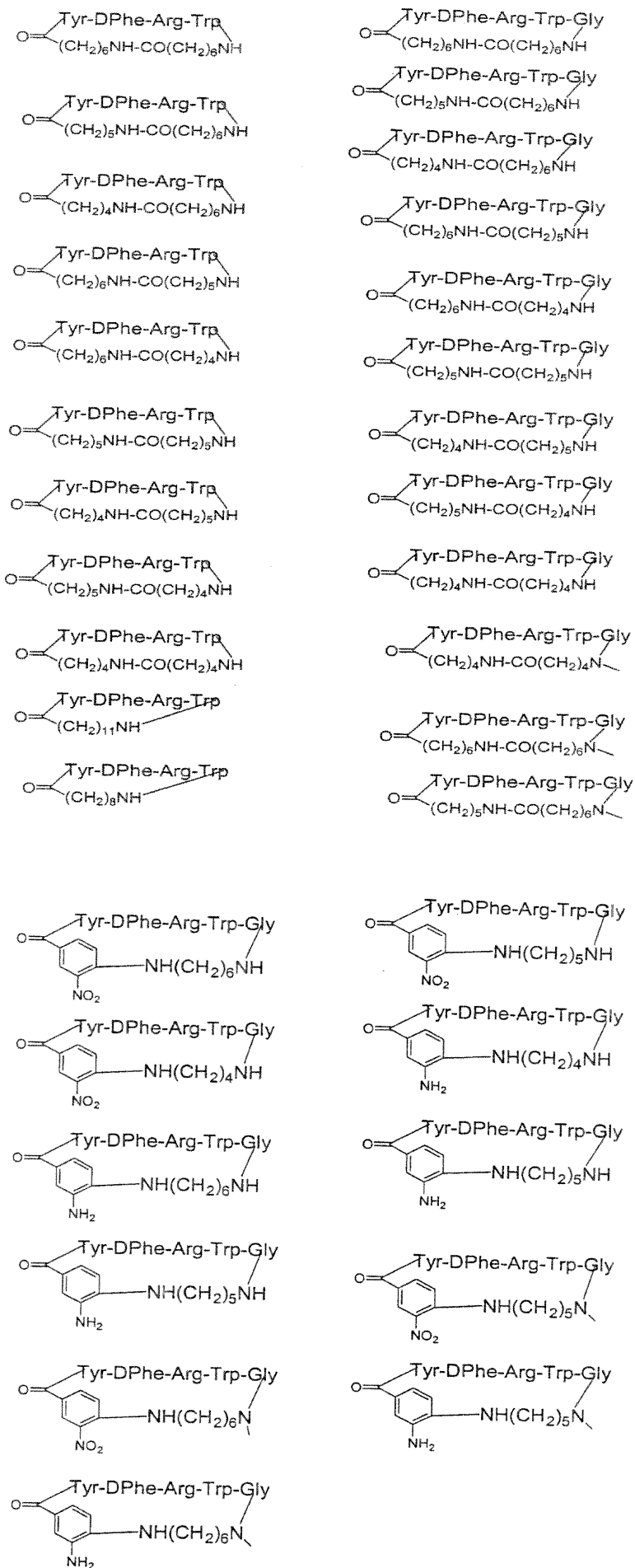
aDYfRWK - NH₂a[DYfRWK] - NH₂

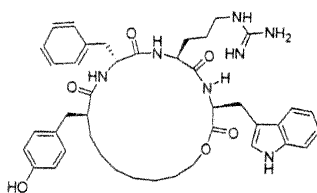
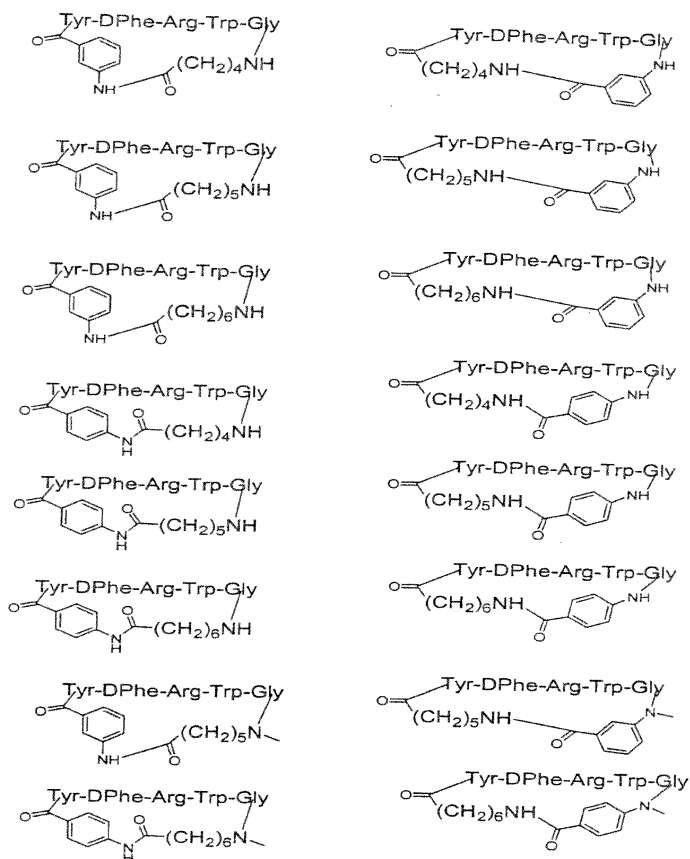
a[DY(D-2-Nal)RWK]-NH₂
 Ac-a[DYfRWK]-NH₂
 Ac-a[DY(D-1-Nal)RWK]-NH₂
 Ac-a[EYfRWG(Orn)]-NH₂
 Ac-GGga[DYfRWGK]-NH₂
 Ac-aEYfRWGK-NH₂
 Ac-a[DYfRWGK]-NH₂
 Ac-aDYfRWG(Orn)-NH₂
 Ac-aEYfRWG(Orn)-NH₂
 Ac-a[EFfRWGK]-NH₂
 Ac-a[DyfRWGK]-NH₂
 Ac-a[DYyRWGK]-NH₂
 Ac-[DY(D-Phe(4-I))RWGK]-NH₂
 Ac-a[DY(D-Phe(4-I))RWG(Orn)]-NH₂
 Ac-[DY(D-Phe(4-I))RWG(Orn)]-NH₂
 Ac-[EYfRWG(Orn)]-NH₂
 [GYfRWGGG]
 [GGYfRWGGGG]
 [GGYfRWGK]-OH
 [GGYfRWGLAG]
 [AGYfRWGGG]
 Ac-[D(Tyr(3-OH))fRWGK]-NH₂
 Ac-DYfRWK-NH₂
 Ac-EYfRWGOrn-NH₂
 Ac-[DY(D-Phe(4-Cl))RWK]-NH₂
 Ac-[DY(D-Phe(4-Cl))RWGK]-NH₂
 Ac-a[DYfR(Trp(5-Br)GK)]-NH₂
 Ac-a[DYfR(Trp(5-OMe)GK)]-NH₂
 Ac-a[DYfR(Trp(6-F)GK)]-NH₂
 Ac-a[DYfR(Trp(4-F)GK)]-NH₂
 Ac-a[DYfR(Trp(7-Me)GK)]-NH₂
 Ac-a[EYfR(Trp(6-OH))G(Orn)]-NH₂
 Ac-a[E(Tyr(Me))fRWG(Orn)]-NH₂
 Ac-[E(Tyr(2-Br))fRWG(Orn)]-NH₂
 Ac-aDYfRWK-NH₂
 Ac-a[DY(D-Phe(4-Cl))RWK]-NH₂
 Ac-[EYfRWGK]-NH₂
 Ac-SYsa[DYfRWGK]-NH₂
 Ac-[DY(D-1-Nal)RWGK]-NH₂
 Ac-aDYfRWGK-NH₂
 Ac-a[EYfRWGK]-NH₂
 Ac-a[DYfRWG(Orn)]-NH₂
 Ac-a[EYfRWG(Orn)]-NH₂
 Ac-a[DFfRWGK]-NH₂
 Ac-[DYfRWGK]-NH₂
 Ac-a[DY(D-Phe(4-I))RWGK]-NH₂
 Ac-a[EY(D-Phe(4-I))RWGK]-NH₂
 Ac-[EY(D-Phe(4-I))RWGK]-NH₂
 Ac-[EYfRWGK]-NH₂
 Ac-[DYfRWG(Orn)]-NH₂
 [GGYfRWGGG]
 [GGYfRWGK]-NH₂
 [GGYfRWGGAG]
 [GGYfRWGFAG]
 [GGYfRWAAA]
 Ac-[DF(D-Phe(4-I))RWGK]-NH₂
 Ac-DYfRWGK-NH₂
 Ac-a[DY(D-Phe(4-I))RWGK]-NH₂
 Ac-[D(Tyr(3-OH))fRWGK]-NH₂
 Ac-a[D(Tyr(Me))fRWGK]-NH₂
 Ac-a[DYfR(Trp(5-F)GK)]-NH₂
 Ac-a[DYfR(Trp(5-Me)GK)]-NH₂
 Ac-a[DYfR(Trp(1-Me)GK)]-NH₂
 Ac-a[DYfR(Trp(6-Br)GK)]-NH₂
 Ac-a[EYfR(Trp(5-OH))G(Orn)]-NH₂
 Ac-a[EYfR(Trp(6-Cl))G(Orn)]-NH₂
 Ac-a[E(Tyr(CH₂Ph))fRWG(Orn)]-NH₂
 Ac-[E(Tyr(3-F))fRWG(Orn)]-NH₂

Ac-[E(Tyr(3-I))fRWG(Orn)]-NH₂
 Ac-[D(Tyr(3-NO₂))fRWGK]-NH₂
 Ac-[D(Tyr(3-MeO))fRWGK]-NH₂
 Ac-a[DY(D-Phe(5-Br))RWGK]-NH₂
 Ac-a[DY(D-Phe(4-NO₂))RWGK]-NH₂
 Ac-[DY(D-Phe(2,5-OH))RWGK]-NH₂
 Ac-[DY(D-Phe(5-F))RWGK]-NH₂
 Ac-[EY(D-Phe(3-NH₂))RWGOm]-NH₂
 Ac-[EY(D-Phe(3-I))RWGOm]-NH₂
 Ac-[DYfRW(Gly-(N-CH₃))K]-NH₂
 Ac-[E(Phe(4-Br))fRWGK]-NH₂
 Ac-a[DYFRW(Gly-(N-CH₃))K]-NH₂
 Ac-a[D(Phe(4-Cl))FRWGK]-NH₂
 Ac-[D(Phe(4-Br))FRWGK]-NH₂
 Ac-[D(Phe(4-F))fRWGK]-NH₂
 Ac-[D(Phe(4-F))fRWGK]-NH₂
 Ac-[D(Phe(4-NO₂))fRWGK]-NH₂
 Ac-[D(Phe(4-NH₂))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-[D(Phe(4-Cl))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-[D(Phe(4-NO₂))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-[D(Phe(4-NHCOCH₃))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-a[E(Phe(4-Cl))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-a[E(Phe(4-Cl))fRW(Gly-(N-CH₃))(Orn)]-NH₂
 Ac-[E(Phe(4-Cl))fRW(Gly-(N-CH₃))(Orn)]-NH₂
 Ac-a[D(Phe(4-F))fRW(Gly-(N-CH₃))K]-NH₂
 Ac-a[D(Phe(4-F))FRW(Gly-(N-CH₃))K]-NH₂
 Bc-DYfRW(Gly-(N-CH₃))K-NH₂
 Bc-EYfRW(Gly-(N-CH₃))K-NH₂
 Bc-EYfRWGK-NH₂
 Bc-D(Phe(4-Cl))fRW(Gly-(N-CH₃))K-NH₂
 Bc-D(Phe(4-Cl))fRWGK-NH₂
 Bc-E(Phe(4-Cl))fRW(Gly-(N-CH₃))K-NH₂
 Bc-[D(Phe(4-Cl))fRW(Gly-(N-CH₃))K]-NH₂
 Bc-[DY(D-2-Nal)RWGK]-NH₂
 Ac-[E(Tyr(2,5-OH))fRWG(Orn)]-NH₂
 Ac-[D(Tyr(3-NH₂))fRWGK]-NH₂
 Ac-[D(Tyr(3-Cl))fRWGK]-NH₂
 Ac-a[DY(D-Phe(4-NH₂))RWGK]-NH₂
 Ac-[DY(D-Phe(4-F))RWGK]-NH₂
 Ac-[DY(D-Phe(3-F))RWGK]-NH₂
 Ac-[EY(D-Phe(3-MeO))RWGOm]-NH₂
 Ac-[EY(D-Phe(3-NO₂))RWGOm]-NH₂
 Ac-[D(Phe(4-Cl))fRWGK]-NH₂
 Ac-[D(Phe(4-NH₂))fRWGK]-NH₂
 Ac-a[D(Phe(4-Cl))fRWGK]-NH₂
 Ac-[DYFRW(Gly-(N-CH₃))K]-NH₂
 Ac-[D(Phe(4-Cl))FRWGK]-NH₂
 Ac-[D(Phe(4-CN))fRWGK]-NH₂
 Ac-[E(Phe(4-F))fRWG(Orn)]-NH₂
 Ac-[DYf(Arg-(N-CH₃))WGK]-NH₂
 Bc-[DYfRWGK]-NH₂
 Bc-DYfRWGK-NH₂
 Bc-[DYfRW(Gly-(N-CH₃))K]-NH₂
 Ac-[D(Phe(4-NO₂))fRW(Gly-(N-CH₃))K]-NH₂
 Bc-aEYfRWGK-NH₂
 Bc-aEYfRWGK-NH₂
 Bc-a[E(Phe(4-Cl))fRW(Gly-(N-CH₃))K]-NH₂
 Bc-a[E(Phe(4-Cl))fRW(Gly-(N-CH₃))(Orn)]-NH₂
 Bc-a[E(Phe(4-Cl))fRW(Gly-(N-CH₃))(Orn)]-NH₂
 Bc-a[D(Phe(4-F))fRW(Gly-(N-CH₃))K]-NH₂
 Bc-a[D(Phe(4-F))FRW(Gly-(N-CH₃))K]-NH₂
 Bc-DYfRW(Gly-(N-CH₃))K-NH₂
 Bc-EYfRW(Gly-(N-CH₃))K-NH₂
 Bc-EYfRWGK-NH₂
 Bc-D(Phe(4-Cl))fRW(Gly-(N-CH₃))K-NH₂
 Bc-D(Phe(4-Cl))fRWGK-NH₂
 Bc-E(Phe(4-Cl))fRW(Gly-(N-CH₃))K-NH₂
 Bc-[D(Phe(4-Cl))fRW(Gly-(N-CH₃))K]-NH₂
 Bc-[DY(D-2-Nal)RWGK]-NH₂

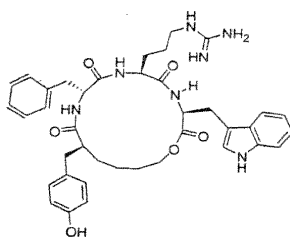
Bc-[DY(L-2-Nal)RWGK]-NH₂
 Bc-[DY(D-1-Nal)RWGK]-NH₂
 Bc-[DY(Phe(4-Br))RWGK]-NH₂
 Ac-[DY(D-2-Nal)RWGK]-NH₂
 Bc-EY(D-2-Nal)RWGK-NH₂
 Bc-EY(D-2-Nal)RW(Gly-(N-CH₃))K-NH₂
 Ac-[DYf(homo-Arg)WGK]-NH₂
 Ac-[DYyRWGK]-NH₂
 Ac-[DYYRWGK]-NH₂
 DYfRWGK-NH₂
 Ac-a[DY(D-2-Nal)RWGK]-NH₂
 Ac-DYfRWGK-NH₂
 Ac-EYfRWGK-NH₂
 Ac-EY(D-2-Nal)RWGK-NH₂
 Ac-[EY(D-2-Nal)RWGK]-NH₂
 Ac-a[DY(D-2-Nal)RWK]-NH₂
 a[DY(D-1-Nal)RWK]-NH₂

, " D " " L " 가 L - .

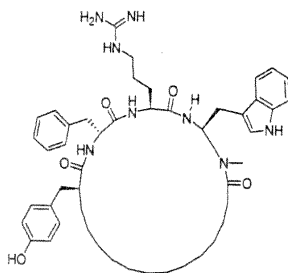




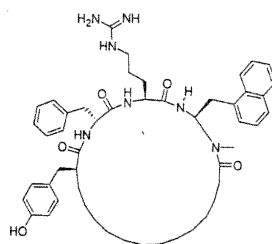
N - { 3 - [9 - 12 - (4 - -) - 3 - (1H - 3 -) - 2,5,8,11 - 1 - - 4,7,10 -
 - - 6 -] - } -



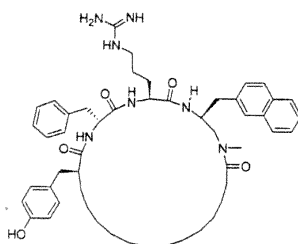
N - { 3 - [9 - 12 - (4 - -) - 3 - (1H - 3 -) - 2,5,8,11 - 1 - - 4,7,10 -
 - - 6 -] - } -



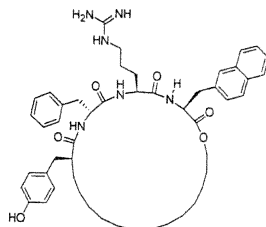
N - { 3 - [2 - 24 - (4 - -) - 8 - (1H - - 3 -) - 10 - - 3,6,11,25 - - 1,4,7, 10 - - 5 -] - } -



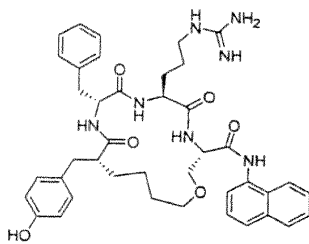
N - { 3 - [2 - 24 - (4 - -) - 10 - - 8 - - 1 - - 3,6,11,25 - - 1,4,7,10 - - 5 -] - } -



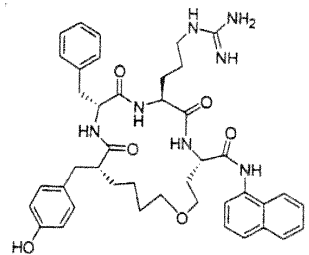
N - { 3 - [2 - 24 - (4 - -) - 10 - - 8 - - 2 - - 3,6,11,25 - - 1,4,7,10 - - 5 -] - } -



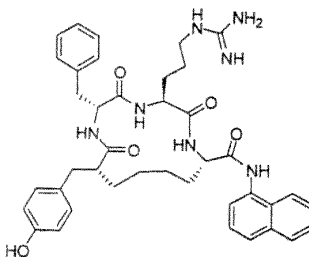
N - { 3 - [9 - 12 - (4 - -) - 3 - - 2 - - 2,5,8,11 - - 1 - - 4,7,10 - - 6 -] - } -



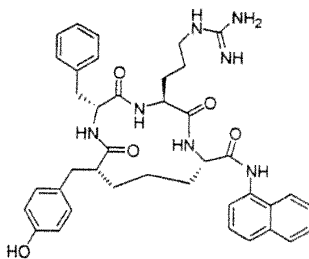
9 - -6 - (3 - -) - 12 - (4 - -) - 5,8,11 - - 1 - - 4,7,10 - -
- 3 - - 1 -



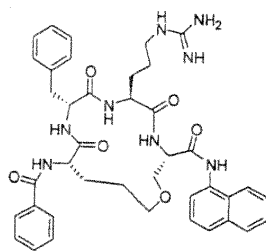
10 - -7 - (3 - -) - 13 - (4 - -) - 6,9,12 - - 1 - - 5,8,11 - -
- 4 - - 1 -



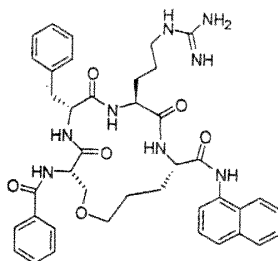
2 - -5 - (3 - -) - 13 - (4 - -) - 3,6,14 - - 1,4,7 - -
- 8 - - 1 -



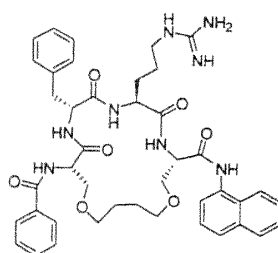
2 - -5 - (3 - -) - 12 - (4 - -) - 3,6,13 - - 1,4,7 - -
- 8 - - 1 -



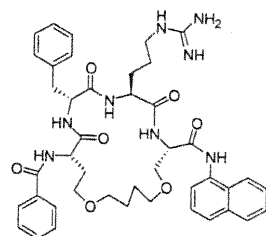
12 - -9 - -6 - (3 - -) - 5,8,11 - -1 - -4,7,10 - -
 -3 - -1 -



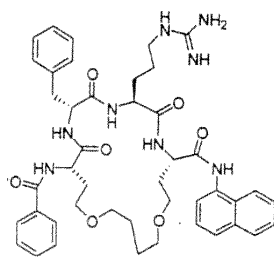
3 - -6 - -9 - (3 - -) - 4,7,10 - -1 - -5,8,11 - -
 -12 - -1 -



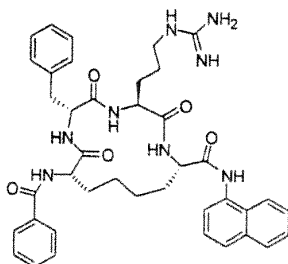
12 - -9 - -6 - (3 - -) - 5,8,11 - -1,14 - -4,7,10 - -
 -3 - -1 -



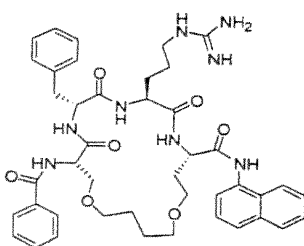
12 - -9 - -6 - (3 - -) - 5,8,11 - -1,15 - -4,7,10 - -
 -3 - -1 -



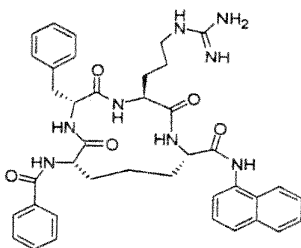
13 - -10 - -7 - (3 - -) - 6,9,12 - - 1,16 - - 5,8,11 - -
-4 - -1 -



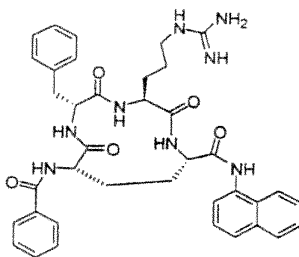
13 - -2 - -5 - (3 - -) - 3,6,14 - - 1,4,7 - - - 8
- -1 -



13 - -10 - -7 - (3 - -) - 6,9,12 - - 1,15 - - 5,8,11 - -
-4 - -1 -



12 - -2 - -5 - (3 - -) - 3,6,13 - - 1,4,7 - - - 8 -
-1 -

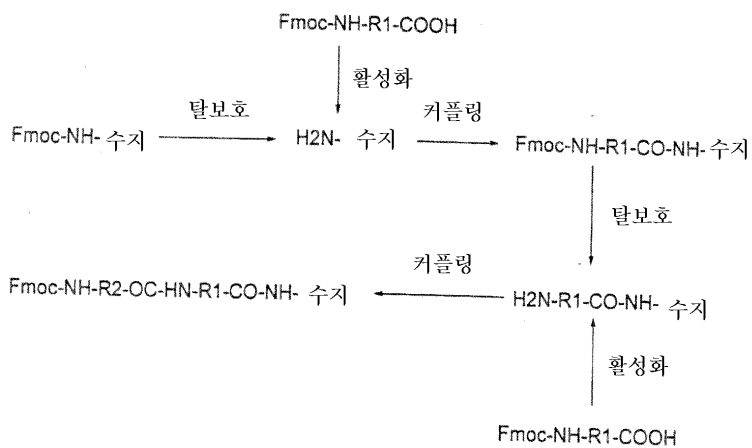


11 - -2 - -5 - (3 - -) -3,6,12 - - 1,4,7 - - -8 -
 -1 -

1 18

Fmoc (NH₂

9 -



R

I

R

: Perkin - Elmer Applied Biosystem Division (PE - ABD) Model 433

Spec tMoc (chemistry) : 1) PE - ABD SPPS (Fmoc) ; 2) (Fmoc - L - Arg - Pbf Ana 0.1 mmole Fas Fmoc ; 3)

2 - (1H - oc N,N - (NMP)) - 1 -) - 1,1,3,3 - (DIEA), 1 - Fmoc (HBTU) FastM HBTU, N - (DMF) 가 N - Rink Amide N - (4.75% V:V NMP , 0.2% H (DCM)

OBt W:V, NMP 2.25% DIEA) . (cocktail) (93 (TFA), 2.3%) 1.5~2.0 ml 1.5~3.0 (OtBu), (Boc)] Arg - 5 - (Pbf), Trp, Orn, Lys Ser t - O - t - 15 ml 20

6 (MS) : (RP - HPLC) 가 DMF DPPA 가 DPPA 4 2 4 2.1 mm, RP - HPLC MS HP1090 HPLC 15 cm, (pore) 300 , 10 μm Vydac C - 8 . U V , DPPA, 50% 300 Vydac C - 8 , DMF UV 가 1.0 cm, 25 cm, Beckman Syste m Gold HPLC Pharmacia MS 가

가

mistry(Wiley), Carey and Sundberg,Advanced Organic Chemistry(Vol.2)

March,Advanced Organic Che
가

/ 가

, T.Greene,Protecting Groups in Organic Synthesis
가

IV.

가

cAMP , Chen , 1995 (Anal Biochem, 1995, 226, 349~54)

cAMP

(Cytosensor Microphysiometer) (Boyfield , 1996)
가

MSH -

(,) MC - 4 / MC - 3

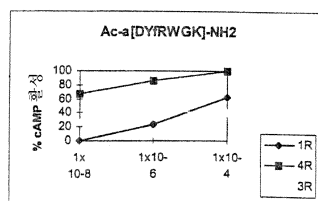
- 4) EC₅₀ , MC - 1 MC - 3 (EC₅₀ - MC - 3) / MC - 4 (EC₅₀ - MC
EC₅₀ (" EC₅₀ - MC - 1")

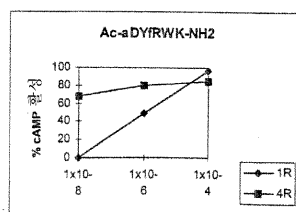
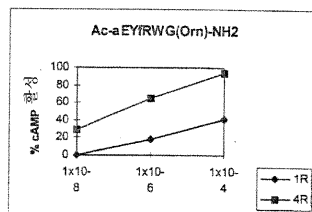
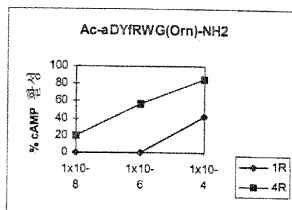
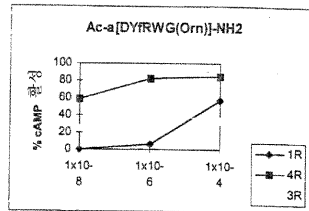
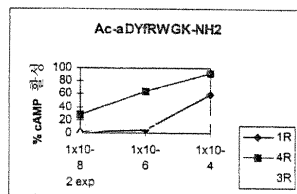
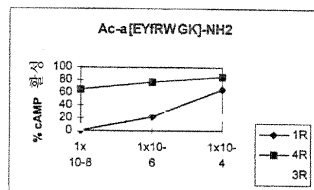
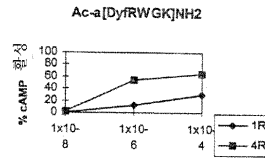
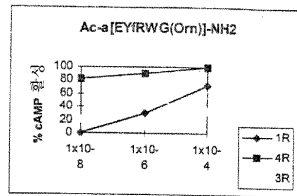
$$MC - 3 = [EC_{50} - MC - 1] / [EC_{50} - MC - 3]$$

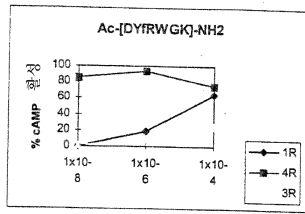
$$MC - 4 = [EC_{50} - MC - 1] / [EC_{50} - MC - 4]$$

" MC - 3 " MC - 3 - " 10 ,
100 , 500

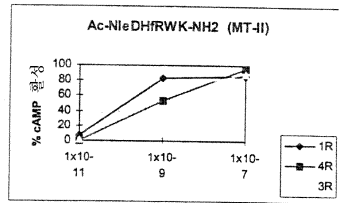
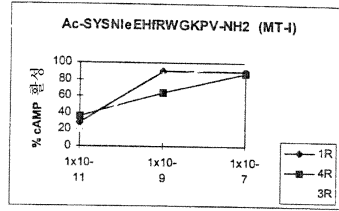
" MC - 4 " MC - 4 - " 10 , 100
500







Tyr 가 His , MC - 1



V. :

MC - 4 / MC - 3

가 MC - 3 MC - 4
가

on 's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa.,
elivery, Marcel Dekker, NY, 1991

.Remingt
Peptide and Protein Drug D

a. I ; ,

b. 가 .

I , " " , / ' MC -
(, ,) , /

(hydrotrope),

가

:Modern Pharmaceutics, 9 10 (B
anker & Rhodes, editors, 1979); Lieberman ,Pharmaceutical Dosage Forms: Tablets(1981); Ansel,Int
roduction to Pharmaceutical Dosage Forms 2 (1976).

5%

25%

50%

(enteric) -

가

(croscarmellose)

가

(glidant)

. FD& C

가

가

,가 ,

(elixir),

가

, Avicel?RC - 591,

가

80

pH

, Eudragit?

(shell

ac)

) 가 3 300 mg

가 ; (acacia),

VI.

가

가

()

00 mg (70 kg) , 0.003 mg 300 mg, 0.03 mg 1

(70 kg 가), 0.001 mg 100 mg

0.1 mg 100 mg , 0.01 mg 100 mg,

가

(, Zlokovic, B.V.,Pharmaceutical Research, Vol. 12, pp. 1395~1406 (1995)).
(Fukuta, M. ,Pharmaceutical Res., Vol. 11, pp. 1681~1688 (1994)).
Zlokovic, B.V.,Pharmaceutical Res., Vo I. 12, pp. 1395~1406 (1995) Pardridge, WM,Pharmacol. Toxicol., Vol. 71, pp. 3~10 (1992))

VII.

:

OtBu: tert - [- O - C(CH₃)₃] tBu: tert - [- C(CH₃)₃]

Pbf: Boc: tert -

TFA: DMF: N,N -

Fmoc: 9 - DPPA:

HOAt: 1 - - 7 - HOBt: N -

EDCI: 1 - (3 -) - 3 -

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

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

Pmc: 2,2,5,7,8 - - 6 -

Trt:

A.

1

Ac - a[DYfRWGK] - NH₂ , [M+H]⁺ : 1065.2

Rink Amide 0.55 mmole/g , 0.182 g 0.1 mmole
 가 , PE - ABD 433
 . Fmoc : Asp - OtBu, Tyr - OtBu, Arg - Pbf, Trp - Boc, Lys - Boc, Gly 1 mmole
 . Fmoc - ala (311 mg, 1 mmole) Fmoc - phe (387 mg, 1 mmole)
 가 4
 . NAc - 0.1 mmole MonPrePk
 , Fmoc 5%
 HPLC 90% ()

(2 x 2 ml) 2 (2 ml) 가 TFA
 () (3 x 20 ml) MS HPLC
 HPLC 가 90%

DMF (15ml) , K₂HPO₄ (60mg) 가 .
 , DPPA (70μl) , 20 , 4 가 . 가 , DPPA
 2 가 . 24 . DMF .
 50% , 0~70% B A 70 , 3 ml/
 C8 HPLC A B : A: 0.1% TFA, 2% ;
 B: 95% 0.1% TFA. 0.5 . MS RP -
 HPLC ([M+H]⁺ : 1066.2) UV 220 nm
 RP - HPLC (95
 %)

, 1

2

Ac - [DYfRWGK] - NH₂ , [M+H]⁺ : 995.1

Fmoc - D - Ala가 , 1 .

3

Ac - a[DYfRWGK] - NH₂ , [M+H]⁺ : 1066.2

Fmoc - D - Tyr - OtBu Fmoc - L - Tyr - OtBu , 1 .

4

Ac - a[EYfRWG(Orn)] - NH₂ , [M+H]⁺ : 1052.1

Fmoc - L - Glu - OtBu Fmoc - L - Orn - Boc Fmoc - Asp - OtBu Fmoc - Lys - Boc
 , 1 .

5

Ac - a[EYfRWGK] - NH₂ , [M+H]⁺ : 1080.2

Fmoc - L - Glu - OtBu Fmoc - L - Asp - OtBu , 1 .

6

Ac - a[DYyRWGK] - NH₂ , [M+H]⁺ : 1082.2

Fmoc - D - Tyr - OtBu Fmoc - D - Phe , 1 .

7

Ac - a[DY(D - Phe(pCl))RWK] - NH₂ , [M+H]⁺ : 1061.7

Fmoc - D - Phe(pCl) Fmoc - D - Phe , 1 .

8

Ac - SYSa[**DYfRWGK**] - NH₂ , [M+H]⁺ : 1403.5

가 (Fmoc - L - Ser - OtBu, Fmoc - L - Tyr - OtBu Fmoc - L - Ser - OtBu) 1
 N - , 1 .

9

Ac - [EYfRWGK] - NH₂ , [M+H]⁺ : 1009.2

Fmoc - L - Glu - OtBu Fmoc - L - Asp - OtBu , Fmoc - D - Ala ,
 1 .

10

Ac - a[**DY(D - Nal)RWK**] - NH₂ , [M+H]⁺ : 1060.2

Fmoc - D - Nal Fmoc - D - Phe , Fmoc - L - Gly , 1
 .

11

Ac - a[**DYfRWK**] - NH₂ , [M+H]⁺ : 1009.1

Fmoc - L - Gly , 1 .

12

Ac - GGGa[**DYfRWGK**] - NH₂ , [M+H]⁺ : 1237.3

가 (Fmoc - L - Gly, Fmoc - L - Gly Fmoc - Gly) 1 N -
 , 1 .

13

Ac - [DY(D - Nal)RWGK] - NH₂ , [M+H]⁺ : 1045.1

Fmoc - D - Nal Fmoc - D - Phe , Fmoc - D - Ala , 1
 .
 , 14 ~17 1

14

Ac - a**DYfRWK** - NH₂ , [M+H]⁺ : 1010.0

Fmoc - L - Gly , 1 .

15

Ac - aEYfRWGK - NH₂ , [M+H]⁺ : 1098.2

Fmoc - L - Glu - OtBu Fmoc - L - Asp - OtBu , 1 .

16

Ac - aDYfRWGK - NH₂ , [M+H]⁺ : 1084.2

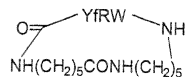
1 , .

17

Ac - aDYfRWG(Orn) - NH₂ , [M+H]⁺ : 1070.1

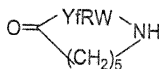
Fmoc - L - Orn - Boc Fmoc - Lys - Boc , 1 .

18

[(5 - Ava)YfRW(5 - Ava)] , [M+H]⁺ :1 . Fmoc -
D, a, G, K .

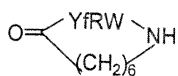
: Y, f, R, W, 5 - Ave; Fmoc -

19

[(5 - Ava)YfRW] , [M+H]⁺ :1 . Fmoc -
D, a, G, K .

: Y, f, R, W, 5 - Ave; Fmoc -

20

[(6 - Ahx)YfRW] , [M+H]⁺ :

1 Fmoc - : Y, f, R, W, 6 - Ahx; Fmoc -
D, a, G, K .

21

Ac - [DYfRWG(Orn)] - NH₂ , [M+H]⁺ : 980.2

Fmoc - L - Orn - Boc Fmoc - Lys - Boc , Fmoc - D - Ala
1 . ,

22

Ac - [DYf(homoArg)WGK] - NH₂ , [M+H]⁺ : 1008.6

Fmoc - homoArg - (Pmc) Fmoc - L - Arg - Pbf , Fmoc - D - Ala
1 . ,

23

[GGYfRWGGG] , [M+H]⁺ : 938.5

Fmoc - D - Ala, Fmoc - Asp - OtBu, Fmoc - Lys - Boc , 가 (Fmoc - Gly, Fmoc
- Gly) N - C - , 1 .

24

Ac - [DYfHWGK] - NH₂ , [M+H]⁺ : 975.5

Fmoc - L - His - Trt Fmoc - L - Arg - Pbf , Fmoc - D - Ala
1 . ,

25

Ac - [DYfR(D - Nal)GK] - NH₂ , [M+H]⁺ : 1043.4

Fmoc - D - Nal Fmoc - L - Trp , Fmoc - D - Ala , 1
.

26

Ac - Nle[DYfRWGK] - NH₂ , [M+H]⁺ : 1191.7

Fmoc - L - Nle Fmoc - D - Ala , 1 .

27

Ac - a[DHfRWGK] - NH₂ , [M+H]⁺ : 1039.4

Fmoc - L - His - Trt Fmoc - L - Tyr - OtBu , 1 .

28

Ac - a[D(homoTyr)fRWGK] - NH₂ , [M+H]⁺ : 1079.2

Fmoc - L - homoTyr - OtBu Fmoc - L - Tyr - OtBu , 1 .

29

Ac - a[DFfRWGK] - NH₂ , [M+H]⁺ : 1049.5

Fmoc - L - Phe Fmoc - L - Tyr - OtBu , 1 .

30

Ac - Nle[DHyrWK] - NH₂ , [M+H]⁺ : 1040.6

Fmoc - Nle Fmoc - D - Ala , Fmoc - His - Trt Fmoc - L - Tyr - OtBu , Fmoc - L - Gly , 1 .

31

Ac - a[DYfRWG(Orn)] - NH₂ , [M+H]⁺ : 1051.5

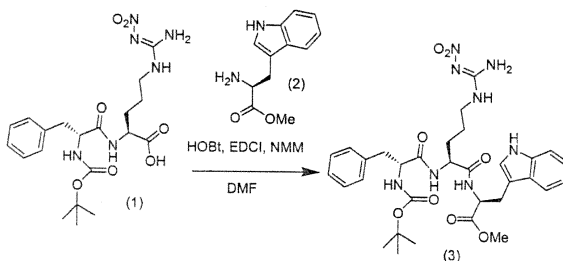
Fmoc - L - Orn - Boc Fmoc - L - Lys - Boc , 1 .

PE - ABD 433

32

N - { 3 - [9 - 12 - (4 -) - 3 - (1H - 3 -) - 2,5,8,11,14 - 1,4,7,10,13 - 6 -] - } -

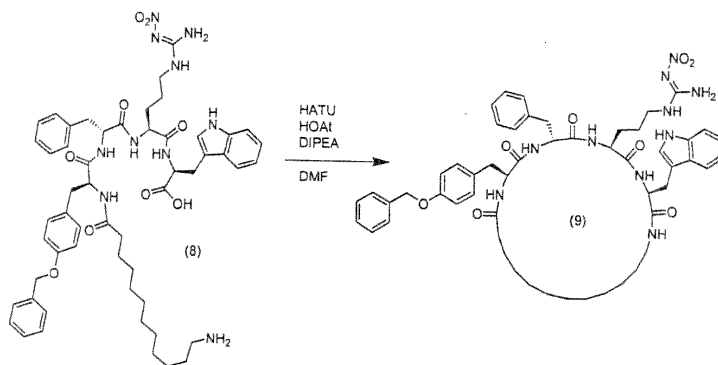
(a) 1:

(1 ml)
5 mmol), HOBT (0.135 g, 1.0 mmol),(1) (0.233 g, 0.5 mmol), L -
N - (0.17 ml, 1.5 mmol)(2) (0.127 g, 0.
EDCI (0.115 g, 0.

3 (5 ml) (6) (0.233 g, 0.21 mmol) 1N NaOH (0.5 ml)
 1 N HCl pH 2
 0.226 g (7)

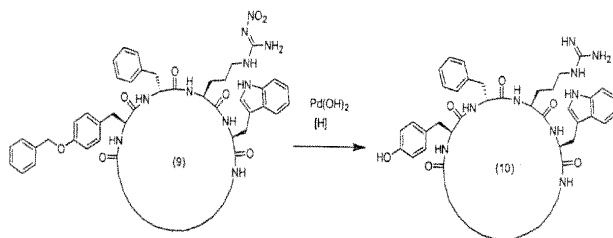
(7) (2 ml) 25% (v/v) 2
 1,2- (10 ml) , 0.1%
 HPLC C4 0.155 g (8)

(e) 5:



(8) (100 mg, 0.1 mmol), HATU (46 mg, 0.12 mmol) HOAt (14 mg, 0.1 mmol)
 (100 ml) 가 , 0
 DIPEA (0.053 ml, 0.3 mmol) 가 , 3
 , (macrocyclic) (9) 90 mg 15:1

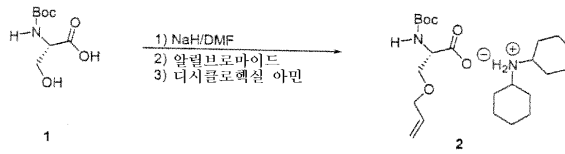
(f) 6:



(9) (0.09 g) (20 ml) 20% Pd(OH)₂ , 45 psi 48
 (Celite) , C4
 HPLC , 0.1% ,
 {3-[9-12-(4- -)-3-(1H-3-)-2,5,8,11,14- -1,4,7,10,13
 -6-]- } - (10) N-

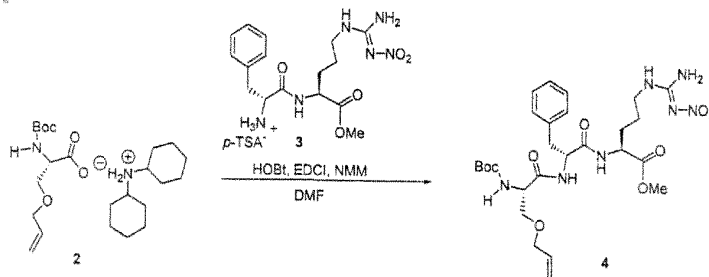
12 - - 9 - - 6 - (3 - -) - 5,8,11 - - 1,14 - - 4,7,10 - -
 - 3 - - 1 -

(a) 1:



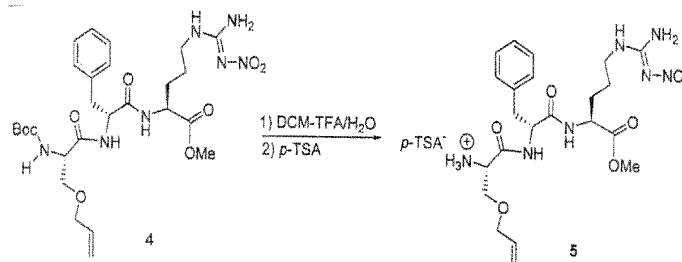
DMF (30 ml) Boc - Ser - OH (1, 2.05 g, 10 mmol) 0 DMF (30 ml) (
 60 %, 880 mg, 22 mmol) 가 가 (0.9
 5 ml, 11 mmol) 가 (50 ml) 가 ,
 , 1.0NHCl pH 3.0 , (2 x 20 ml)
 (20 ml), (20 ml) (5 x 20 ml)
 Boc - Ser() - OH (1.96 g) (30 ml)
 (1.594 ml, 8.0 mmol) , 1:9 /
 2 (2.26 g) 가 2 (0.58 g)

(b) 2:



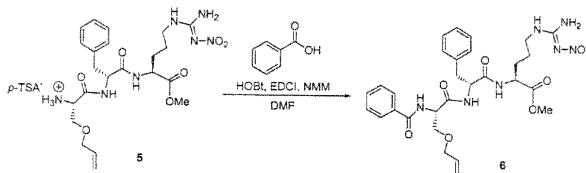
DMF (40 ml) (3, 1.382 g, 2.5 mmol), Boc - Ser() - OH · DCA (2, 1.067 g, 2.5 mmol),
 HOBt (0.338 g, 2.5 mmol), N - (0.6 ml, 5.5 mmol) EDCI (0.527 g, 2.75 mmol)
 16 (300 ml) (5
 0 ml), 5% (2 x 25 ml), 5% (2 x 25 ml), (25 ml)
 4 (1.519 g)

(c) 3:



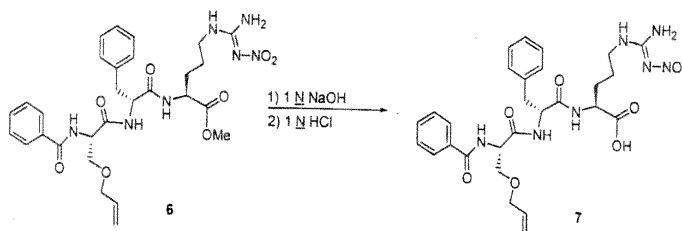
(6.0 ml) Boc - Ser() - D - Phe - Arg(NO₂) - OMe (4, 1.519 g, 2.5 mmol),
 (30 ml) (0.6 ml) 가 , 3 , p -
 (0.380 g, 2.00 mmol) 가 , (50 ml)
 , 5 (1.46 g)

(d) 4:



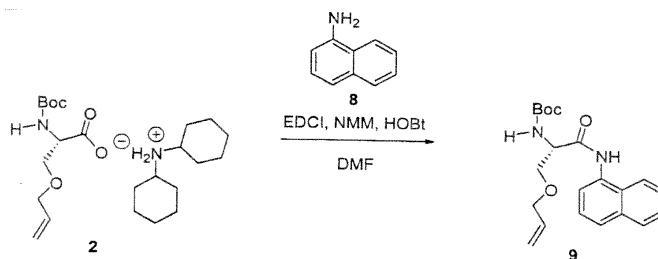
DMF (22 ml) (5, 1.46 g, 2.15 mmol), (0.263 g, 2.15 mmol), HOBt (0.291 g, 2.15
 mmol), N - (0.52 ml, 4.7 mmol) EDCI (0.454 g, 2.37 mmol)
 16 (220 ml) , (50 ml), 1NHCl (
 2 x 25 ml), 1N (2 x 25 ml), (25 ml)
 , 6 (1.10 g)

(e) 5:



(1.0N, 3.0 ml, 3.0 mmol) (18 ml) - (6,
 1.10 g, 1.80 mmol) 가 , 2.5 ,
 (20 ml) , 1NHCl (3.2~3.5 ml)
 pH 3 , (1 x 70 ml, 2 x 25 ml)
 , 7 (0.884 g)

(f) 6:



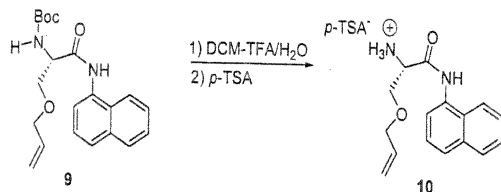
N - (0.33 ml, 3.0 mmol) 0 , DMF (28 ml) Boc - Ser() - OH · DCA (2, 1.06
 7 g, 2.5 mmol), 1 - (8, 0.358 g, 2.5 mmol), HOBt (0.338 g, 2.5 mmol) EDCl (0.527 g, 2.75 m
 mol) 가 . 0 0.5 , 16
 1N (200 ml) , (50 ml), 1NHCl (2 × 25 ml),
 1N (2 × 25 ml), (20 ml) .

HPLC/MS

8 9

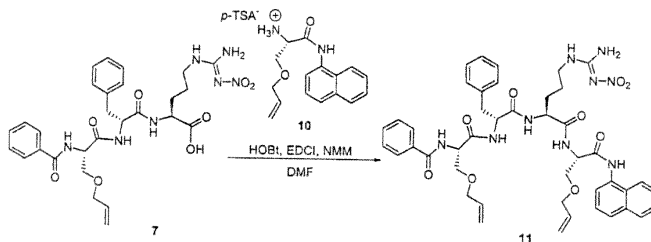
, 0.1% HPLC
 C4 , 0.26 g 9 .

(g) 7:



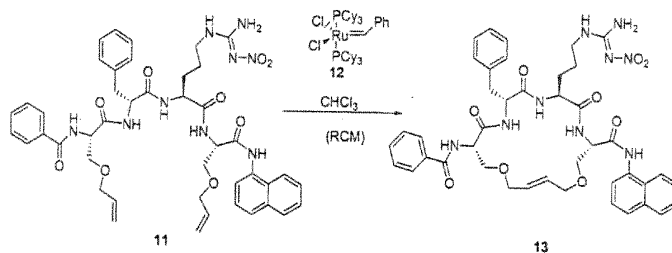
(1.0 ml) Boc - Ser() - 1 - (9, 0.26 g, 0.702 mmol),
 (5.0 ml), (0.1 ml) 가 . 88 , p -
 (0.133 g, 0.7 mmol) 가 , / (1:1, 25 ml)
 , 10 (0.311 g)

(h) 8:



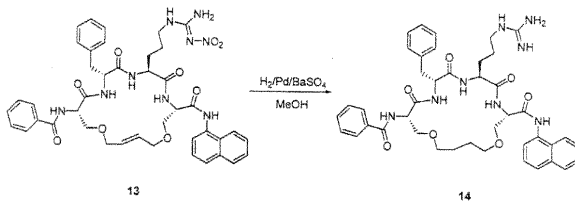
N - (0.18 ml, 1.61 mmol) 0 DMF (6 ml) - (7, 0.436 g, 0.73 m
 mol), H - Ser() - 1 - p - TSA (10, 0.322 g, 0.73 mmol), HOBt (0.099 g, 0.73 mmol) ED
 Cl (0.154 g, 0.803 mmol) 가 . 0 0.5 ,
 16 (100 ml) , (15 m
 l), 1NHCl (2 × 10 ml), (15 ml), 1N (2 × 10 ml), (2 × 10 ml) .
 11 (0.531 g)

(i) 9:



(5.0 ml) (Grubb 's) (12, 0.0504 g, 0.061 mmol)
 (20 ml) (11, 0.260 g, 0.306 mmol) 가 .
 22 (5.0 ml) (0.0504 g) 가 ,
 5 (5.0 ml) (0.0504 g) 가 . 60
 , (3.0 ml) 가 ,
 1:9 / (0.125
 g) , 0.1% HPLC C4
 13 (8 mg) E Z 1:1 .

(j) 10:



(10 ml) (13, 8 mg, 0.097 mmol) (, 1 mg) 10%
 , (40psi) 48 . ,
 14 , 5% / , 14 (8 mg) TFA

B.

A

130 kg 15 ml : , 6

[1]

	(mg/ml)
1	5175101 ml pH 5

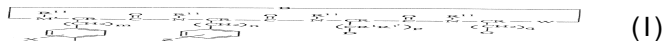
, 가 .

(57)

1.

I ,

[I]



25, Z, D- (" D - Phe" " f")
 B가 Cys
 () l

2.

1, D가 -N(R²)C(=NR³)NR⁴R⁵

3.

1, 2, R², R³, R⁴, R⁵

4.

1, 3, G 가

5.

1, 4, X 가, -OR⁸, -NR⁸R^{8'}, -OR⁸,
 -NR⁸R^{8'},); Z, X, -OR⁸,
 OR⁹, -NR⁹R^{9'}, -OR⁹, -NR⁹R^{9'},

6.

1, 5, R¹, R^{1'}

7.

1, 6, R¹¹; R

8.

1, 7, B, B 25 27

9.

1, 8, B

10.

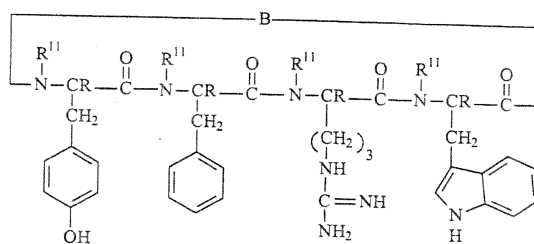
- (F) R^4 R^5 ; R^4 R^5
- (G) R^6 $SO_x R^{12}$ (x 0, 1 2 , R^{12}) ;
- (H) R^{11} ; R^{11} ; R R
- (I) W , -CH₂ - -C(=O) - ;
- (J) M' , -N- -CH- ;
- (K) B , I Tyr Trp , 3

25 , X D- (" D - Phe" " f")
 B가 Cys
 () A

12.

B

[B]



(A) R^{11} ; R^{11} ; R R

(B) B , I Tyr Trp , 3

