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2004 11 16

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(22) 2004 07 29

2004 07 29

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(87)

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(86) 2003 01 31

(87)

2003 08 07

(30) 10204072.9
10300049.6

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2003 01 03

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(DE)

(71) 81379

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(72) , 81379 ,

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, 79108 ,

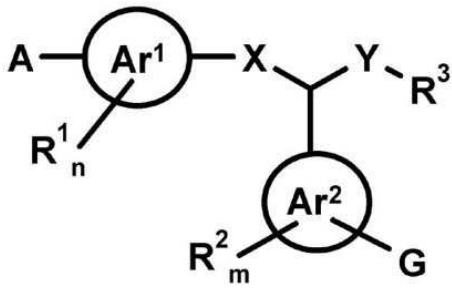
3

(74)

:

(54) X a

가 () , 가 , , /
Xa , , /



(), 가 , ,
 / , , , Xa
 , (diastereoisomer) - (pro-drugs), , (racemates)

(prolonged immobilisation), 가 , , ,
 가 가 가 , , ,
 (Venous thrombosis) 가
 (Arterial thrombosis) (pulmonary embolism)
 (ischaemic necrosis)
 (intermittent claudication)
 (blood clot)

가 , X가
 (Xa) (prothrombinase complex)
 Va Ca²⁺ Xa ,

K () 가 ,
 가 (ancrod) , 가

nfractionated heparin; UFH K (low-molecular-weight heparin; LMWH) 가 U
 FH LMWH , ,

UFH

(warfarin)

K

, Jule
s A. Shafer, Current Opinion in Chemical Biology, 1988, 2: 458-485, Joseph P. Vacca, Current Opinion in Ch
emical Biology, 2000, 4: 394-400 and also in Fahad Al-Obeidi and James A. Ostrem, DDT, Vol. 3, No. 5, Ma
y 1998: 223-231

가

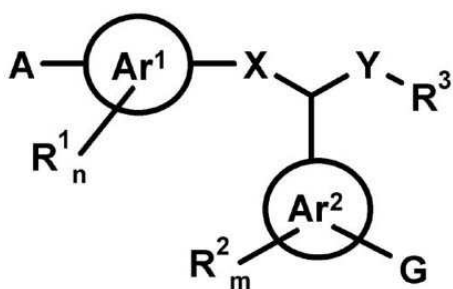
(in vivo)

Xa

Xa

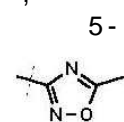
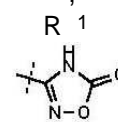
Xa

가
(pro-drugs),
가



A ; -NHC(=NR⁴)NH₂ , -C(=NR⁴)NH₂ ,

R⁴



Ar¹ , , ,
 Ar² , , ,
 R¹ , , , C₁ -, C₂ -, C₃ - C₄ - , , , C₁ -, C₂ -, C₃ - C₄ - ;

R² , , , C₁ -, C₂ -, C₃ - C₄ - , , , C₁ -, C₂ -, C₃ - C₄ - ;

R³ , , , , , ; , , , , ,

G ;

X NR⁵, O, CONR⁵, NR⁵CO, CH₂NR⁵, S, SO, SO₂, SO₂NH, NHSO₂, PO₂NH, NHPO₂, CH₂, CHMe CO, R⁵, C₁ -, C₂ -, C₃ - C₄ -, C₁ -, C₂ -, C₃ - C₄ -, C₇ -, C₈ -, C₉ -, C₁₀ -, C₁₁ - C₁₂ -, C₆ -, C₇ -, C₈ -, C₉ -, C₁₀ -, C₁₁ - C₁₂ - ;

Y CONR⁶, COCONR⁶, NR⁶, O, NR⁶CO, S, SO, SO₂, SO₂NH, NHSO₂, PO₂NH, NHPO₂, CH₂, CHMe CO, R⁶, C₁ -, C₂ -, C₃ - C₄ -, C₁ -, C₂ -, C₃ - C₄ -, C₇ -, C₈ -, C₉ -, C₁₀ -, C₁₁ - C₁₂ - ;

n 0, 1, 2, 3 4 ,

m 0, 1, 2, 3 4 .

가 1 20 , 1 12 , 1, 2, 3, 4, 5, 6 , tert- , n- , 2,2- n- 가 .

2, 3, 4, 5, 6 가 2 20 , 2 12 , () 가 . -2- 가 .

2, 3, 4, 5, 6 가 2 20 , 2 12 , (ethynyl) (pr opargyl) 가 . () 가 .

가 , , , 가 (F Cl) , 2,2,2-

(1, 2 3) 가 , , , , 가 . / () 가 . , , , , 가 .

R^a-O-Y^a-, R^a-S-Y^a-, R^a-N(R^b)-Y^a-, R^a-CO-Y^a-, R^a-O-CO-Y^a-, R^a-CO-O-Y^a-, R^a-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-Y^a-, R^a-O-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-O-Y^a-, R^a-N(R^b)-CO-N(R^c)-Y^a-, R^a-O-CO-O-Y^a-, R^a-N(R^b)-C(=NR^d)-N(R^c)-Y^a-, R^a-CS-Y^a-, R^a-O-CS-Y^a-, R^a-CS-O-Y^a-, R^a-CS-N(R^b)-Y^a-, R^a-N(R^b)-CS-Y^a-, R^a-O-CS-N(R^b)-Y^a-, R^a-N(R^b)-CS-O-Y^a-, R^a-N(R^b)-CS-N(R^c)-Y^a-, R^a-O-CS-O-Y^a-, R^a-S-CO-Y^a-, R^a-CO-S-Y^a-, R^a-S-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-S-Y^a-, R^a-S-C

가

Ar 6 14 가 6 10 (6) 가 (Ar)

가 , F, Cl, Br I, OH, SH, NH₂ NO₂ 4- 가

5 14 5, 6, 7, 8, 9 10(5 6) (

가 O, S N) (가 1, 2, 3 4) 가 (

2 NO₂ 가 4- , 2- , F, Cl, Br I, OH, SH, NH

, , , , , 2,3'- , 3- (, 6-), 가 , , ,

/ 가 .

, 0- , 1H- , 1,2,3,4-

10 (,) (, / 5 6), 1 2 6

(1, 2, 3 4) 가

(,) /

/ 가 /

5, 6, 7, 8, 9 10 (

), 1 2, 3, 4, 5 6 , 1, 2, 3 4 / , /

가 .

- - , - - , - - , - - , - - , - - , - - , - -

가 . , 4- , 2-, 3- 4- , 2- 3- - , 4- , 2-, 3-

NO₂ (=O, =S =NH 가 , F, Cl, Br I, OH, =O, SH, =S, NH₂, =NH 가 .

2, =NH NO₂ 가 F, Cl, Br I, OH, =O, SH, =S, SO₂ NH₂, NH
 -C₉ C₁-C₆ , C₂-C₆ , C₂-C₆ , C₁-C₆ , C₃-C₁₀ , C₂
 가 , C₆-C₁₀ , C₁-C₉ , C₇-C₁₂ C₂-C₁₁ , C₂

O-) 가 OH (fucose), -D- , N- , N-
 -O-, -S-, -N- -C- (

R⁹ () Y CONR⁶ , R³ -CHR⁷ -CO-NR⁸ R⁹ 가 , R⁷, R⁸
 , R⁸ R⁹

R⁸, R⁹ () Y CO , R³ -NR¹⁰ -CHR⁷ -CO-NR⁸ R⁹ 가 , R⁷,
 7 R¹⁰ R⁸ R⁹ / R
 -Y-R³ 가

-C(=O)-NR-CR'R'' -C(=O)-N(R''')R , R, R', R'', R''' R

, Ar¹ A가 -C(=NR⁴)NH₂ (-C(=NH)NH₂) A X가
 가

, A -C(=NR⁴)NH₂

, A 가

, R⁴ , C₁-, C₂-, C₃- C₄- 가 ; R⁴ 가

, Ar¹ 5, 6, 7, 8, 9 10 가 ; O, S N Ar¹ , A 1, 2, 3 4
 가

, Ar² 5 6 가 ; O, S N Ar² 가 1, 2 3

, X NH, NMe NAc가 ; X NH 가

, n 0, 1 2, 0 1

, R¹ Ar¹ , A 가

, m 0 1; R² G ; m 0

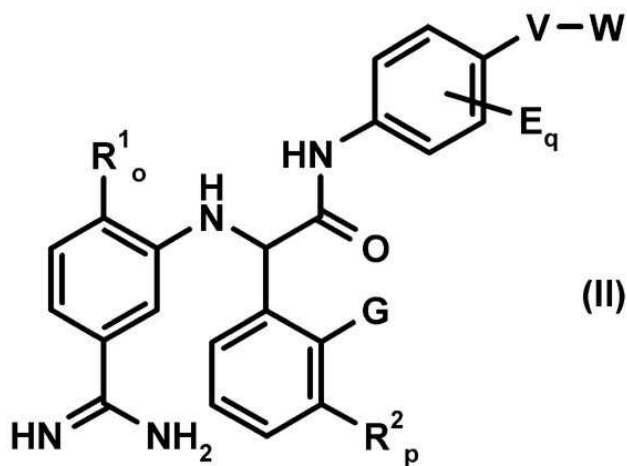
, Y CONH 가

, R³ -U-V-W 가 , U 6~10 12
 , 5, 6, 7, 8, 9 10 O, S N 1, 2, 3 4 (NR¹¹
 (R¹¹ 1 2) , C₁-, C₂-, C₃- C₄- , C₁-, C₂-, C₃- ; V C₄- , C₇-, C₈

-, C₉-, C₁₀-, C₁₁-, C₁₂-
), CO, SO, SO₂ SO₂NH, C₆-, C₇-, C₈-, C₉-, C₁₀-, C₁₁-, C₁₂-
 W, , , , , , ,
 , U 가 , - 가 .
 , V 가 .
 , W C₁-, C₂-, C₃- C₄- , O, N S C₁-, C₂-, C₃-
 C₄- , 3~7 (5 6) , C₃-, C₄-, C₅-, C₆- C₇-
 1, 2 3 (, 5 6
 O, S N) , 5 6 가
 O, S N 1, 2, 3 4

() Y CONR⁶ , R³ -CHR⁷-CO-NR⁸R⁹가 , R⁷, R⁸
 R⁹ 2002 2 22 AG PCT PCT/EP 02/01934(WO 02/068390) R⁵, R⁶ R
 7 R⁷, R⁸ R⁹ 2001 8 23 AG PCT PCT/EP 01/0975
 3(WO 02/16312) R⁵, R⁶ R⁷

()



p 0 , E , F, Cl Br , R¹, R², G, V W , o 0 1,
 V q 0, 1 R¹ , R² , G -D-
 (C=O)가 .

W -N(CH₂CH₂)₂Q 가 , Q NR¹² , R¹²
 , C₁-, C₂-, C₃- C₄- C₁-, C₂-, C₃- C₄- (,
 -C(=N)NH₂ -C(=N)CH₃) .

, () (U =) () , V W V SO
 2 NH₂ SO₂

, () , A Ar¹ X가 6

, () , n 0, A Ar¹ 6- , X CONH, m 0, Ar² ,
 Y CO R³ (-N(CH₂CH₂)₂CH-CH(CH₂
 CH₂)₂NMe) ; (R) 가 .

() ()
 (enantiomers) (diastereoisomers),

2-(3-Carbamimidoyl-phenylamino)-N-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₂N₄O₉ (580.5998)

ESI-TOF MS: 581 [M+H]

3 : 2-(3-
-6-

2-(3-Carbamimidoyl-phenylamino)-N-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₃₇N₅O₈ (571.6358)

ESI-TOF MS: 572 [M+H]

4 : 2-(3-
-2-

2-(3-Carbamimidoyl-phenylamino)-N-(4-phenoxy-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₃H₃₄N₄O₈ (614.6609)

ESI-TOF MS: 615 [M+H]

5 : 2-(3-
-2-

2-(3-Carbamimidoyl-phenylamino)-N-(3,3-diphenyl-propyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₆H₄₀N₄O₇ (640.7428)

ESI-TOF MS: 641 [M+H]

6 : 2-(3-
-2-

2-(3-Carbamimidoyl-phenylamino)-N-(3-phenoxy-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₃H₃₄N₄O₈ (614.6609)

ESI-TOF MS: 615 [M+H]

7 : 2-(3-
-2-

2-(3-Carbamimidoyl-phenylamino)-N-(4-methoxy-biphenyl-3-yl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₄H₃₆N₄O₈ (628.6880)

ESI-TOF MS: 629 [M+H]

8 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(4-morpholin-4-yl-phenyl))-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₇N₅O₈ (607.6692)

ESI-TOF MS: 608 [M+H]

9 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(4-benzoyl-phenyl))-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-benzoyl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₄H₃₄N₄O₈ (626.6721)

ESI-TOF MS: 627 [M+H]

10 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(3-benzoyl-phenyl))-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(3-benzoyl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₄H₃₄N₄O₈ (626.6721)

ESI-TOF MS: 627 [M+H]

11 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(4-tert-butyl-benzyl))-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-tert-butyl-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₂H₄₀N₄O₇ (592.6982)

ESI-TOF MS: 593 [M+H]

12 : 2-(2-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(4-morpholin-4-yl-phenyl))-acetamide

2-(2-Hydroxy-5-carbamimidoyl-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₇N₅O₉ (623.6686)

ESI-TOF MS: 624 [M+H]

13 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(3-methoxy-benzyl))-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(3-methoxy-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₄N₄O₈ (566.6163)

ESI-TOF MS: 567 [M+H]

14 : N-(4- -)-2-(3- -)-2-[2-(3,4,5- -6- -)-2- -]-

N-(4-Acetyl-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₂N₄O₈ (564.6004)

ESI-TOF MS: 565 [M+H]

15 : 2-(3- -)-N-(3- -)-2-[2-(3,4,5- -6- -)-2- -]-

2-(3-Carbamidoyl-phenylamino)-N-(3-trifluoromethyl-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₁F₃N₄O₇ (604.5882)

ESI-TOF MS: 605 [M+H]

16 : 2-(3- -)-N-(2- -1- -)-2-[2-(3,4,5- -6- -)-2- -]-

2-(3-Carbamidoyl-phenylamino)-N-(2-cyclohex-1-enyl-ethyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₈N₄O₇ (554.6488)

ESI-TOF MS: 555 [M+H]

17 : 2-(3- -)-N-[2-(3,4- -)-]-2-[2-(3,4,5- -6- -)-2- -]-

2-(3-Carbamidoyl-phenylamino)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₈N₄O₉ (610.6699)

ESI-TOF MS: 611 [M+H]

18 : 2-(3- -)-N-(3- -4- -)-2-[2-(3,4,5- -6- -)-2- -]-

2-(3-Carbamidoyl-phenylamino)-N-(3-morpholin-4-yl-propyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₃₉N₅O₈ (573.6517)

ESI-TOF MS: 574 [M+H]

19 : 2-(3- -)-N-(4- -)-2-[2-(3,4,5- -6- -)-2- -]-

2-(3-Carbamidoyl-phenylamino)-N-(4-trifluoromethyl-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₁F₃N₄O₇ (604.5882)

ESI-TOF MS: 605 [M+H]

20 : N-[1-(4- -)-]-2-(3- -)-2-[2-(3,4,5- -6-

N-[1-(4-Bromo-phenyl)-ethyl]-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₃BrN₄O₇ (629.5130)

ESI-TOF MS: 630 [M+H]

21 : N-[1,3] -5- -2-(3- -)-2-[2-(3,4,5- -6-

N-Benzo[1,3]dioxol-5-ylmethyl-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₂N₄O₉ (580.5998)

ESI-TOF MS: 581 [M+H]

22 : 2-(3- -)-N-(3- -)-2-[2-(3,4,5- -6-

2-(3-Carbamimidoyl-phenylamino)-N-(3-phenyl-propyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₀H₃₆N₄O₇ (564.6440)

ESI-TOF MS: 565 [M+H]

23 : 2-(3- -)-N-(3,5- -)-2-[2-(3,4,5- -6-

2-(3-Carbamimidoyl-phenylamino)-N-(3,5-dimethyl-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₀H₃₆N₄O₇ (564.6440)

ESI-TOF MS: 565 [M+H]

24 : 2-(3- -)-N-(3- -)-2-[2-(3,4,5- -6-

2-(3-Carbamimidoyl-phenylamino)-N-(3-cyano-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₂₉N₅O₇ (547.5726)

ESI-TOF MS: 548 [M+H]

25 : 2-(3- -)-N-(3,4- -)-2-[2-(3,4,5- -6-

2-(3-Carbamimidoyl-phenylamino)-N-(3,4-dichloro-benzyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₃₀Cl₂N₄O₇ (605.4799)

ESI-TOF MS: 606 [M+H]

26 : N-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(3,4-dichlorobenzyl)-2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-acetamide

N-(3-Acetyl-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₂N₄O₈ (564.6004)

ESI-TOF MS: 565 [M+H]

27 : 2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(1,2,2-trimethyl-propyl)-2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-acetamide

2-(3-Carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-N-(1,2,2-trimethyl-propyl)-acetamide

C₂₇H₃₈N₄O₇ (530.6265)

ESI-TOF MS: 531 [M+H]

28 : N-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-allyl-2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-acetamide

N-Allyl-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₄H₃₀N₄O₇ (486.5293)

ESI-TOF MS: 487 [M+H]

29 : N-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(3,7-dimethyl-octa-2,6-dienyl)-2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-acetamide

N-(3-Butoxy-propyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₄₀N₄O₈ (560.6530)

ESI-TOF MS: 561 [M+H]

30 : 2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(3,7-dimethyl-octa-2,6-dienyl)-2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(3,7-dimethyl-octa-2,6-dienyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₄₂N₄O₇ (582.7030)

ESI-TOF MS: 583 [M+H]

31 : 2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenylamino)-furan-2-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

C₂₆H₃₀N₄O₈ (526.5510)

ESI-TOF MS: 527 [M+H]

32 : 2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-propyl)-furan-2-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

2-(3-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-propyl)-phenylamino)-furan-2-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

C₂₇H₃₈N₄O₈ (546.6259)

ESI-TOF MS: 547 [M+H]

33 : 3-{2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-propionic acid ethyl ester

3-(2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-propionic acid ethyl ester

C₂₆H₃₄N₄O₉ (546.5823)

ESI-TOF MS: 547 [M+H]

34 : N-tert-butyl-2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-furan-2-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

N-tert-Butyl-2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-furan-2-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

C₂₅H₃₄N₄O₇ (502.5723)

ESI-TOF MS: 503 [M+H]

35 : 2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-pyridin-4-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-pyridin-4-yl)methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

C₂₇H₃₁N₅O₇ (537.5774)

ESI-TOF MS: 538 [M+H]

36 : 2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

2-(3-(2-(3-(4-(2-(3-(4,5-dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy)-phenyl)-acetamido)-phenyl)-acetamino)-methyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)oxy]-phenyl]-acetamide

C₂₂H₂₈N₄O₇ (460.4911)

ESI-TOF MS: 461 [M+H]

37 : 2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(1,3-dimethyl-butyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(1,3-dimethyl-butyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₇H₃₈N₄O₇ (530.6265)

ESI-TOF MS: 531 [M+H]

38 : N-(4-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

N-(4-Benzoyl-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₄H₃₄N₄O₈ (626.6721)

ESI-TOF MS: 627 [M+H]

39 : 2-(5-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-2-hydroxy-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(5-Carbamimidoyl-2-hydroxy-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₇N₅O₉ (623.6686)

ESI-TOF MS: 624 [M+H]

40 : 2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(2,6-dimethyl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(2,6-dimethyl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₄N₄O₇ (550.6169)

ESI-TOF MS: 551 [M+H]

41 : 2-(3-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenylamino)-N-(4-nitro-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-nitro-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₇H₂₉N₅O₉ (567.5603)

ESI-TOF MS: 568 [M+H]

42 : N-(4-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

N-(4-Amino-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₇H₃₁N₅O₇ (537.5774)

ESI-TOF MS: 538 [M+H]

43 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetylamino)-phenylamino)-benzoic acid methyl ester

2-(2-(3-Carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamino)-benzoic acid methyl ester

C₂₉H₃₂N₄O₉ (580.5998)

ESI-TOF MS: 581 [M+H]

44 : 2-(5-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-2-chloro-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(5-Carbamimidoyl-2-chloro-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₆N₅O₈ (642.1143)

ESI-TOF MS: 643 [M+H]

45 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-[4-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-[4-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₂H₃₇N₅O₉ (635.6798)

ESI-TOF MS: 636 [M+H]

46 : 2-(5-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-2-methylamino-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(5-Carbamimidoyl-2-methylamino-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₂H₄₀N₆O₈ (636.7110)

ESI-TOF MS: 637 [M+H]

47 : N-(2-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

N-(2-Bromo-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₇H₂₉BrN₄O₇ (601.4588)

ESI-TOF MS: 602 [M+H]

48 : 2-(2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-{2-(3-Carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetylamino}-benzoic acid

C₂₈H₃₀N₄O₉ (566.5727)

ESI-TOF MS: 567 [M+H]

49 : 2-(3- -)-N- -6- -2-[2-(3,4,5- -6- -
- -2-)-]-

2-(3-Carbamimidoyl-phenylamino)-N-quinolin-6-yl-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₀H₃₁N₅O₇ (573.6109)

ESI-TOF MS: 574 [M+H]

50 : 2-{2-{3-[N-(3- -)-]- }-2-[2-(3,4,5- -6- -
- -2-)-]- }-

2-{2-{3-[N-(3-Fluoro-benzyl)-carbamimidoyl]-phenylamino}-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetylamino}-benzoic acid methyl ester

C₃₆H₃₇FN₄O₉ (688.7161)

ESI-TOF MS: 689 [M+H]

51 : N-(2- -4- -)-2-(3- -)-2-[2-(3,4,5- -6- -
- -2-)-]-

N-(2-Benzoyl-4-chloro-phenyl)-2-(3-carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₄H₃₃ClN₄O₈ (661.1171)

ESI-TOF MS: 662 [M+H]

52 : 2-(3- -)-N-[3- -4-(-4-)-]-2-[2-(3,4,5-
-6- - -2-)-]-

2-(3-Carbamimidoyl-phenylamino)-N-[3-chloro-4-(morpholin-4-carbonyl)-phenyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₂H₃₆ClN₅O₉ (670.1248)

ESI-TOF MS: 671 [M+H]

53 : 2-(3- -)-N-[2- -4-(-4-)-]-2-[2-(3,4,5-
-6- - -2-)-]-

2-(3-Carbamimidoyl-phenylamino)-N-[2-methyl-4-(morpholin-4-carbonyl)-phenyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₃H₃₉N₅O₉ (649.7069)

ESI-TOF MS: 650 [M+H]

54 : 2-(5-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-[4-(morpholin-4-carbonyl)-phenyl]-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₂H₃₇N₅O₁₀ (651.6792)

ESI-TOF MS: 652 [M+H]

55 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(3,4-difluoro-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(3,4-difluoro-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₇H₂₈F₂N₄O₇ (558.5436)

ESI-TOF MS: 559 [M+H]

56 : 4-{2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamino}-benzoic acid methyl ester

4-{2-(3-Carbamimidoyl-phenylamino)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamino}-benzoic acid methyl ester

C₂₉H₃₂N₄O₉ (580.5998)

ESI-TOF MS: 581 [M+H]

57 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(3,4-dimethoxy-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(3,4-dimethoxy-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₉H₃₄N₄O₉ (582.6157)

ESI-TOF MS: 583 [M+H]

58 : 3,4,5-triacetoxy-6-{2-[(5-carbamimidoyl-2-hydroxy-phenylamino)-(4-morpholin-4-yl-phenyl)carbamoyl]-methyl}-phenoxy-tetrahydro-pyran-2-ylmethyl ester

Acetic acid 3,4,5-triacetoxy-6-{2-[(5-carbamimidoyl-2-hydroxy-phenylamino)-(4-morpholin-4-yl-phenyl)carbamoyl]-methyl}-phenoxy-tetrahydro-pyran-2-ylmethyl ester

C₃₉H₄₅N₅O₁₃ (791.8192)

ESI-TOF MS: 792 [M+H]

59 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₇N₅O₈ (607.6692)

ESI-TOF MS: 608 [M+H]

60 : 2-(5-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(4-morpholin-4-yl-phenyl)-acetamide

2-(5-Carbamimidoyl-2-hydroxy-phenylamino)-N-(4-morpholin-4-yl-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₃₁H₃₇N₅O₉ (623.6686)

ESI-TOF MS: 624 [M+H]

61 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(4-methoxy-phenyl)-acetamide

2-(3-Carbamimidoyl-phenylamino)-N-(4-methoxy-phenyl)-2-[2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-acetamide

C₂₈H₃₂N₄O₈ (552.5892)

ESI-TOF MS: 553 [M+H]

62 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-[4-(morpholine-4-carbonyl)-phenyl]-acetamide

2-(3-Carbamimidoyl-phenylamino)-2-[3-ethoxy-2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-N-[4-(morpholine-4-carbonyl)-phenyl]-acetamide

C₃₄H₄₁N₅O₁₀ (679.7334)

ESI-TOF MS: 680 [M+H]

63 : 2-(3-(2-(2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl)-acetamido)-phenylamino)-N-(4-morpholin-4-yl-phenyl)-acetamide

2-(3-Carbamimidoyl-phenylamino)-2-[3-ethoxy-2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-N-(4-morpholin-4-yl-phenyl)-acetamide

C₃₃H₄₁N₅O₉ (651.7228)

ESI-TOF MS: 652 [M+H]

Xa (chromogenic)
 Xa (amidolytic activity)
 (microtitre plates) (DMSO) (1mM,
 100uM, 10uM, 1uM) 5µl (pH : 8.0, 50mM NaCl, 100mM NaCl, 0.1 % PEG 6000 0.05 %
 80) Xa(Enzyme Research Laboratories, South Bend, IN, USA) 2.15nM 35µl
 가 25uM MeSO₂-D-CHA-Gly-Arg-AMC ('Spectrozym f
 Xa', American Diagnostica, Pfungstadt, Germany) 10µl 가 가 20 (: 36
 0nm, : 465nm) Spectra Fluor Plus spectrophotometer(Tecan, Crailsheim, Germany) . IC
 50 'GraFit 4' (Erithacus Software Ltd., Staines, Middlesex, UK)
 가 , Cheng-Prusoff K_i 가 (Cheng and Prusoff,
 Biochemical Pharmacology 1973, 22: 3099-3108): K_i = IC₅₀ / (1 + [S]/K_m).

(pH 7.8) - - - -4- (tosyl-glycyl-prolyl
 -lysine-4-nitrilide acetate) , (Prom
 ega, Madison, WI, USA) .

15.

1 , 2 , 3 , 4 , 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 14 /

16.

Xa 1 , 2 , 3 , 4 , 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 15

17.

, / (arterial restenosis), Xa
1 , 2 , 3 , 4 , 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 15

18.

1 , 2 , 3 , 4 , 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 15