

(72)	-		
	33326		121
	33183	142	8320
	19713	101	
	33332	2966	
	33327		2563

(74)

:

(54)

(thrombosis)

(fibrinolysis)

(L. Stryer, Biochemistry, 3rd Ed, W. H. Freeman Co., New York; and A. G. Gilman et al., The Pharmacological Basis of Therapeutics, 8th Edition, McGraw Hill Inc., New York, pp.1311 - 1331).

(TF), 263 (integral) (protease)
 plasma) (F) (subendothelial) ()
 TF Xa, (F a) (zymogen) F
 F a 가 TF F a
 가 가 (F) (F) (cofactor) TF/ a F a
 (atherosclerosis) (microvascular graft), (angioplasty),

(deployment of an implanted device)(, ,),
(endarterectomy) (invasive surgical procedure) ,
TF - (angina),

((embolization) ,)
(coagulopathies) .

(,)

(coumarin) (, (warfin) (dicumarol)) (,)
, Gilmanet al.,supra, R. J. Beigeringet al., Ann. Hemathol., 72:177(1996);J. D. Willerson,Ci
rculation, 94:866(1996)

, ReoPro™
(angina)
, ReoPro™
(J. T. Willerson,Circulation, 94:886(1996); M. L. Simmonset al., Circ
ulation, 89:596(1994)).

, " - (white - clot)" , ,
가 (Gilmanet al.).

가, 가 /
(,)

가

(TF) / / a

TF / TF/ a가 TF

TF - TF TF/ a TF -

in vitro TF

in vitro TF TF/ a TF -

in vitro TF/ a TF -

" " " " TF - TF -

" " TF - TF -

" " TF - TF -

50% TF/ a F 100 μM 70% 10 μM IC₅₀ (TF

1) a TF/ a

2) 가 a

3)

TF - TF/ a

1) 가 가

TF TF/ a TF TF

TF TF/ a in vitro
200 μM 10 μM IC₅₀ ()
50% : ,

- 1) F a TF/ a ,
- 2) 가 F a ,
- 3) TF/ a a

F a TF- TF/ a-
가 가 1) 가 , 가

가 (PT)

가 .PT TF- PT 5% 10%()

- 1) 가 ,
- 2) ,
- 3) (PT) .

PT T 가 .P

/ PT). (,

F/ a / F a TF- TF/ a- T
TF- TF- in vitro ,

" " 가 .

, TF- 가 .

가 가 가 , 가
 TF - TF , 가
 F a, F a, F a (Activated Partial Thromboplastin Time; APTT)

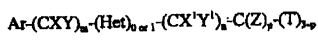
" TF ", " TF "

PCT TF 1999 9 24 09/406269 , 1999 9 24
 PCT/US99/22238

가 TF

(-COOH), (-C(=O)-N
 (-S(O)-), (-S(O)₂-), (-C(=S)-N-, (SO₃) (NO₂)
 3 , 5 8 1-3 (N,O S) 가

가



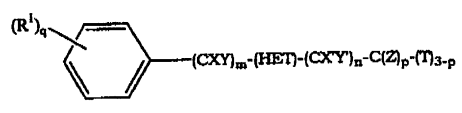
I

Ar ;
 Het N, O S ;
 T (-C(=O)-N-,), (, -
 C(=S)-N-,), (SO₃)

X, Y, X', Y', Z ; ; ; ; ;
 1 12 , 1 6 ; ; 2
 12 , 2 6 ; ; 2 1
 2 , 2 6 ; ; 1 12
 , 1 6 ; ; 1 12
 , 1 6 ; ; 1 12
 2 , 1 6 ; ; 1 1
 1 12 , 1 6 ; ;

m 0 (가) 4 , 0, 1, 2 ;
 n 0 4 , n 1 2 ;
 p 1(T 가) 2(T 가) .

가 Ar ,
 가 :

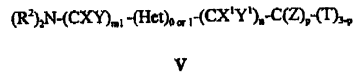


X, Y, Het, T, X', Y', Z, m, p ;

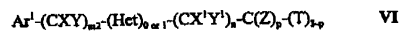
R¹ (F, Cl, Br, I); ; ; ; ;
 1 20 , 1 10 , 1 6
 ; 2 20 , 2 10
 , 2 6 ; 2 20
 , 2 10 , 2 6 ,
 ; 1 20 , 1 10 ,
 1 6 ; 1 20 ,
 1 10 , 1 6 ; 1 20 ,
 ; 1 20 , 1 10 ,
 1 6 ; 1 20 ,
 ; 1 10 ; 1 6 ;

q 0(가) 5 , m 0, 1, 2 3 .

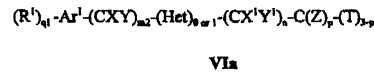
가 , Het가 ;



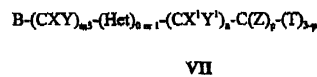
X, Y, Het, X¹, Y¹, Z, T, n, g, p ; R²
 C₁₋₈ ; m1 0() 4 ; 0, 1, 2 ;
 X, Y, X¹, Y¹ ; Het가 0 ; Z가 ; m1, n, p 1
 가 ;
 가 :



X, Y, X¹, Y¹, Z, n, p ; Ar¹
 2 3 ; m2 0() 4 ;
 0, 1, 2 ;
 가 a 가
 , Ar¹ :

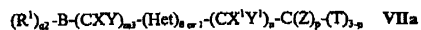


R¹ ; m2 ; X, Y, X¹, Y¹, Z, g, n, p ; q1 0() 7 ;
 q1 0, 1, 2, 3, 4 ;
 a , Ar¹ , R¹ , m2 n 0, Het
 , Z , p 1, q1 1, 2 3 ;
 가 가 ,
 :



B 5 8 ; (endocyclic) 가 ; T, X,
 Y, X¹, Y¹, Z, n, p ; m3 0() 가
) 4 , 0, 1 2 ;

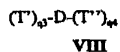
가 a B , , , 가 :



R¹, m₃ , X, Y, X¹, Y¹, Z, g, n p ; q₂ 0(B 가) 10 , q₂ 0, 1, 2, 3 .

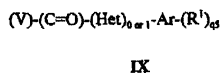
0 ; g 1 ; Het ; Z , R¹ ; B ; m₃ n ; q₂ 1 ; p 2 ; 가 .

가 T , , 가 : .



T¹ T² T D D T¹ T² C₁₋₆ , , T¹가 D ; T²가 , ; q₃ q₄가 1 .

가 가 :



V 1 3 , 5 8 , 1-3 (N, O, S) ; R¹ ; q₅ 0(Ar ; Ar, Het) 5 , q₅ 0, 1, 2, 3 .

V가 , (isoxazolyl), , , ; / , Het .

a, b, c, d 가 ;

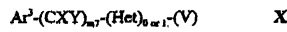
a V가

5- ; b Ar^{2a}, Ar^{2b} Ar^{2c} 가 ; V가 4-
 q10, q11, q12 q13 1 ; Het¹ Het²가 ; R^{3a}, R^{3b} R^{3c} 가
 ; R^{3d}, R^{3e} 가 -NO₂⁺ 가

c Ar^{2a} Ar^{2b} 가 ; R^{1f} 가
 ; m, m1 m2 q1, q2, q3, q4, q5, q6가 1 ; Het¹ Het²가 , X Y가
 1 , R^{1a}, R^{1b} R^{1c} 가 가

d Ar^{3a} 가 ; R^{3a} 가 ; X Y
 가 ; m6가 1 ; V^{1a} V^{1b} 가 , , ,
 가

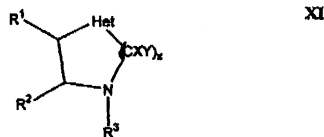
가 TF 가 ,



Ar³
 ; X, Y Het X Y가 ,
 ; m7 0(Ar³ Het) 4 , 0, 1, 2
 ; V a

1999 9 24 09/406269
 3, 4, 5, 6 25 / 가 , 1, 2 3 0, 1, 2 3 -
 (Fosamax) TF 가 09/406269 (, PO₃),

가 (member) 가 ,
 5 10 가 (N, O S),
 5 6 가 5, 6, 7, 8
 가 :



R¹, R², R³, X Y R¹ ;
 R¹, R² 1-3 (,),
 (member) 1 3 (N, O, S) 가 , 1 3 ,
 3 8 ;

Het , N, S, S(O) S(O)₂ ;
 X 1(5- (member)), 2(6- (member)), 3(7- (member)), 4(8- (member))

가 ,
 :



R¹ R¹ ; x 1 10 .
 FX가 가 TF/ a (TF) , FX (FXa) TF " "

(TF) TF 가 " "
 (restenosis) (,)
 (,)
 (fulminanas),

가 , , 가 , ,

in vivo in vivo
in vitro 가

가

1
2(1)

in vitro

TF
TF-

(TF- TF/ a- , PT)
plastin Time; APTT)
a, a

TF
(Activated Partial Thromo
a,

in vitro T
F- , - , -
가 가, - TF , in vit
ro

10 μM IC₅₀ 100 μM TF/ a-

1) 0.1nM TF/ a (), 180nM FX, 0.5 μl)
10 μl (37 (DMSO)

2) (EDTA) (ch
elating agent)

3) 가 F a(, Spectrozyme F a S - 2765)
37

4) (chromophore)

" TF/ a - "
1)~4) TF/ a -
405nm F a 1
TF TF TF TF TF
TF TF TF TF TF
100mM NaCl pH 8.0 TRITON[®]X - 100 ((10) pH
0.05% 0.5%(w/v) TF
1

가 TF TF/ a - 1

가 TF/ a - 200 μ M
10 μ M IC₅₀

1) 0.7nM TF/ a 300 nM 1000nM , 0.5 μ l
10 μ l ((DMSO))
37 F a F a

2) F EDTA (chelating agent)

3) F a(, Spectrozyme F a) 37

4) (chromophore)

" TF/ a - "
1)~4) . 405nm
1

가 20% 100% , PT 20% 500%
가 3 nM (lipidated) PT 가 (, 가
PT TF -

:

1) 0.1ml 가 (DMSO) , 0.5 μl 10 μl 3 10

2) 0.2ml(, 1 - 3nM) 5 - 10mM

3) (PT) .
 " PT " 1) - 3) . PT
 [Williams Hematology, 5th Ed.(Beutler, E. et al. Eds.) M
 cGraw - Hill, Inc. Health Professions Div., New York]

TF
 in vitro
 " " - TF

(RVV) 가 TF a(F a), a(F a), a(F a), , , TF -

DMSO 2% 10% " " " " - TF

(TF) / a

" " a, a, a, a, a. b, c, d) F, Cl, Br I .

1 3 4

1 5 6

(SO) (SO₂) 1 5 6 1 5 6

4 1 3

4 5 1 3 6

18 (member) -

1 3 3 8 1 3 (N, O S) 가

" "

C₁₋₆ ; 1 12

1 6 ; 2

12 1 12 2 6 1 6 12 1

6 ; 1 12 1

1 12 1 6 ;

N 1 12 1 6 ;

; 6 ;

3 6 18 ; O-

3 6 18 ; 1 3

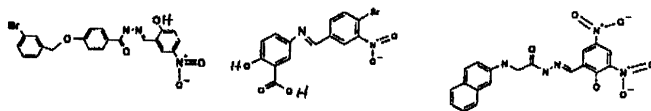
3 8 (member) N, O S

" " R¹, W, X, Y Z

가 1, 2 3

1 19()

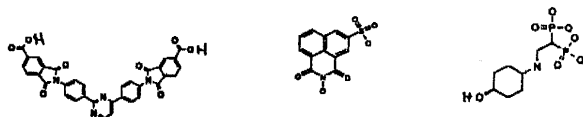
가



화합물 1

화합물 2

화합물 3



화합물 4

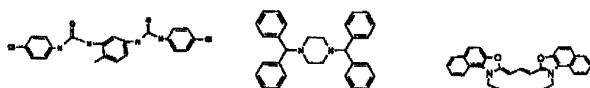
화합물 5

화합물 6



화합물 7

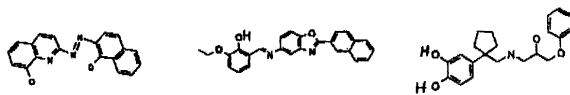
화합물 8



화합물 9

화합물 10

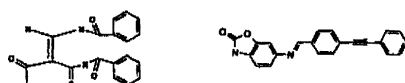
화합물 11



화합물 12

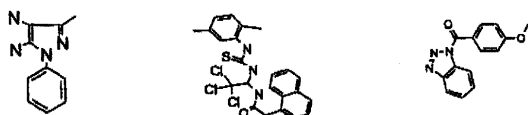
화합물 13

화합물 14



화합물 15

화합물 16



화합물 17

화합물 18

화합물 19

istry,(4th Ed. 1992)]

[March, Advanced Organic Chem

(A A)

" TF

", " TF

"

FX

PT

TF

TF

, F

F 가 TF

,

F

F

"

"

(end - points)

, 가

가

가

TF

, tPA,

(, ReoPro

가

가
(protonated)

가

(Russell's) Enzyme Research Labora
 tories Inc. (chromogenic) S-
 2222, S - 2288, S - 2238 S - 2765 Boehringer Mannheim
 n Diagnostica Inc. DiaPharma Group Inc. , Spectrozyme F a America
) E. coli (truncated) (243
) (immunoaffinity)
 (native) TF 0.1M NaCl, 1mM EDTA, 0.3% Tri
 ton X - 100 50 mM Tris - HCl, pH 8.0 J82
 TF Sigma

1 / a(TF/ a) TF/ a- FX ()
 (FX), FX TF/ a , F a
 (F a), EDTA F
 가 F -> F a TF/ a F a
 S - 2222, S - 2765, Spectrozyme F a F a-
 a- F TF (hits) TF/
 가 TF/ a- F (~0.833 mM) (1)
 a(F a), a(F a), (RVV), a(F a),
 (PT) 가 TF/ a-
 TF - 가

A. : TF/ a- F
 TF/ a- F 96 -
 (DMSO) , 25 mM HEPES - NaOH, 5 mM CaCl₂, 1
 50 mM NaCl, 0.1 % BSA, pH 7.5 TF가
 TF(100 nM) 37 30 50 mM Tris - HCl, pH 7.5, 0.1% (BSA)
 (0.07 mg/ml) (0.03 mg/ml) TF/ a
 100 nM TF 100 nM F a 37 30
 (aliquoted) - 70
 , 5 μl (DMSO 10 mM) DMSO 96 - , 45
 μl TF/ a (0.1 nM) 가 . 37 15 30
 180 nM) 가 . 3 15 37 10 μl F ()
 400 mM) 가 . 10 F a (5 mM Spectrozyme F a, 3.2 mM S - 2765) F
 a 가 . 37 15
 , F a 20 μl 50% . 405 nm ELISA . OD₄₀
 5nm TF/ a- F (%)

(%) = 100 - (100 × A/B)

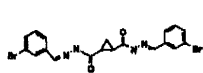
A B OD TF/ a- F 70%

B.

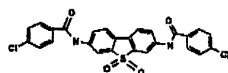
10-, 50-, 100- TF/ a- F
 (1) 가 ,
 , RVV, , F a, F a, F a 가
 F (F)가 TF/ a TF a
 F (F) 가 , 1 19
 (< 0.1 mM) TF/ a- F
 TF 가
 2 1 .
 가,

(57)

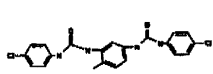
1. (TF) TF
- 2.
- 1 , , , , ,
3. TF TF/ a / -
- 4.
- 3 , TF
- 5.
- 1 4 TF/ a-
100 μM IC₅₀ .
- 6.



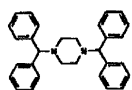
화합물 7



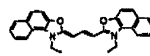
화합물 8



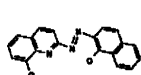
화합물 9



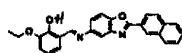
화합물 10



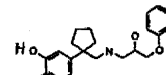
화합물 11



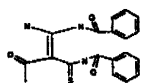
화합물 12



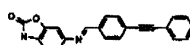
화합물 13



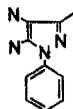
화합물 14



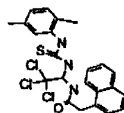
화합물 15



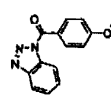
화합물 16



화합물 17



화합물 18



화합물 19

12.

, , , a, , a, , , a, , , , a, b, c, d, , ,

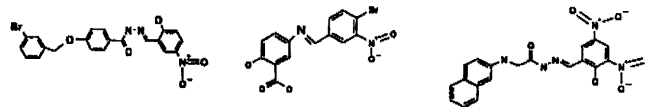
13.

12 , TF/ a- 100 μM IC₅₀

14.

12 , TF/ a- 200 μM IC₅₀

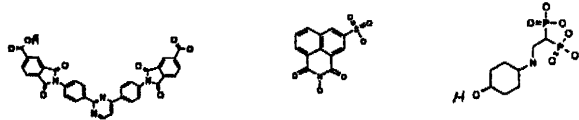
15.



화합물 1

화합물 2

화합물 3



화합물 4

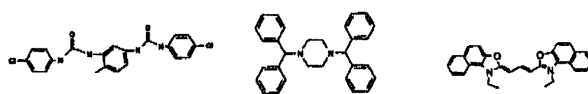
화합물 5

화합물 6



화합물 7

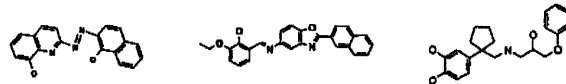
화합물 8



화합물 9

화합물 10

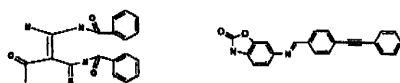
화합물 11



화합물 12

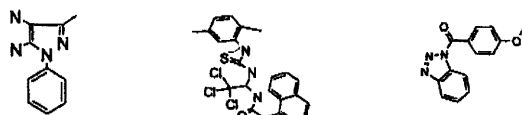
화합물 13

화합물 14



화합물 15

화합물 16



화합물 17

화합물 18

화합물 19

16.

12 15

17.

12 16

18.

12 16

19.

12 16

20.

19 가

21.

19 가 (restenosis)

22.

19

23.

19 가

24.

19 TF/ a- 23 100 μ M IC₅₀

25.

12 16 TF

26.

25 , 가 , , , .

27.

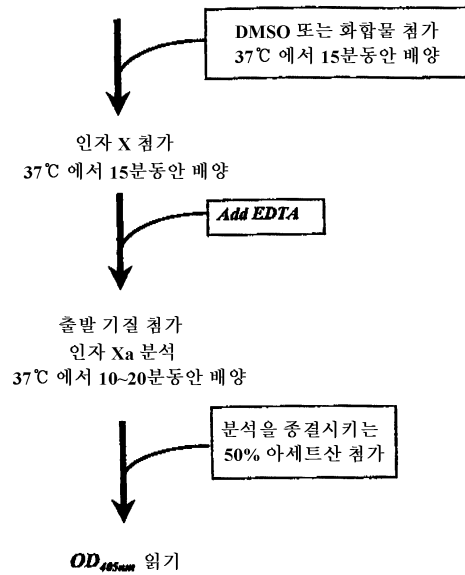
25 , 100 μ M IC₅₀ TF/ a - .

28.

17 27 , .

TF/FVIIa-의존성 인자 X 활성 ¹

TF/FVIIa + 인자 X /Ca⁺⁺



2

표 1

FX & FLX 활성 및 *FXa & FVIIa*
활성 분석의 IC_{50} 수치

화합물 번호	μM 단위의 IC_{50}			
	인자 <i>X</i> 활성	인자 <i>Xa</i> 활성	인자 <i>VIIa</i> 활성	트립신 활성
1	6	>833	>833	>833
2	1.9	>833	>833	>833
3	28.6	>833	>833	>833
4	3.7	>833	>833	>833
5	34	>833	>833	>833
6	15	>833	>833	>833
7	9.5	>833	>833	>833
8	1	>833	>833	>833
9	17.4	>833	>833	>833
10	2.4	>833	>833	>833
11	0.9	>833	>833	>833
12	9.5	>833	>833	>833
13	13.9	>833	>833	>833
14	10	>833	>833	>833
15	8.2	>833	>833	>833
16	>100	>833	>833	>833
17	26.4	>833	>833	>833
18	10.9	>833	>833	>833
19	10	>833	>833	>833

n.d. - 결정되지 않음.