



(72)

60202	3	1133
60025		1800
60056		1832
63304		7345
63105	7572	
63017		66
63021	603	
60641		5318
60061	322	
63341		25
60025	813	

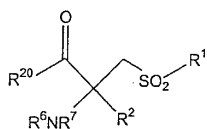
(74)

:

(54) - - -

A , (MMP) , MMP - 1  
 , TNF MMP - 2, MMP - 9 MMP - 13

[ A]



[ , R<sup>1</sup> 5 - 6 -  
 ; R<sup>20</sup> - O - R<sup>21</sup> , - NR<sup>13</sup> - O - R<sup>22</sup> , NR<sup>13</sup> - O - R<sup>14</sup> ;  
 ].

( )

(rigidity),

MMP)

I (MMP - 1, ; EC 3.4.24.3); (MMP - 8, ; EC 3.4.24.34), (MMP - 13), 1 (MMP - 3; EC 3.4.24.17), 2 (MMP - 10; EC 3.4.24.22), (MMP - 7), A (MMP - 2, 72 kDa , ; EC 3.4.24.24), B (MMP - 9, 92 kDa ; EC 3.4.24.35), 3 (MMP - 11), (MMP - 12, HME, ) MMP (MMP - 14) 가 . MMP MM

P

(TNF)

가

, TNF -

, TNF  
28 kD

17 kD

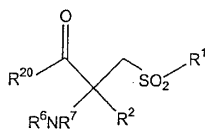


( , , , ) /  
 가  
 가  
 (stiffness) . 1 3  
 . Rasmussen , Pharmacol. Ther., 75(1): 69 - 75 (1997). MMP

MMP  
 가 ,  
 MMP - 2, MMP - 9 MMP - 13  
 MMP - 1 MMP - 1 MMP  
 TNF  
 MMP

P - 13 (MMP) , MMP - 2, MMP - 9 MM  
 MMP - 1

A



[ ,  
 R<sup>2</sup> , C<sub>1</sub> - C<sub>4</sub> , - C<sub>1</sub> - C<sub>4</sub> , C<sub>1</sub> - C<sub>4</sub> , - C<sub>1</sub> - C<sub>4</sub>  
 , C<sub>1</sub> - C<sub>4</sub> , C<sub>1</sub> - C<sub>4</sub> , (N - C<sub>1</sub> - C<sub>3</sub> )  
 , (N,N - - C<sub>1</sub> - C<sub>3</sub> ) , (N - ) , (N - ) , (N - )  
 ) , R<sup>2</sup> , , , ,  
 - N -











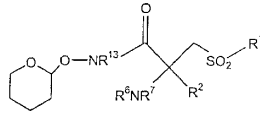
[ , R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>20</sup>  
2 ] .

, D 가 , -F -NO

MMP  
R<sup>13</sup>

, D , R<sup>1</sup>, R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup>,

[ D]



, MMP - 13 / MMP - 2

P - 13

MMP - 2

MMP - 1

( )

MM

MP - 1

MMP - 13 MMP - 2

M

가

, TNF가  
, TNF

가,

TNF

가

(" MMP" )



[ (iii) (i) (ii) (iv) N,N-  
가 5- 8- ];

R<sup>6</sup> R<sup>7</sup> ; 가 5 8

R<sup>6</sup> , R<sup>7</sup> ;

R<sup>20</sup> , (a) -O-R<sup>21</sup> [ , R<sup>21</sup> , C<sub>1</sub>-C<sub>6</sub>- , -C<sub>1</sub>-C<sub>6</sub>-  
2- , p- (MOZ), -C<sub>1</sub>-C<sub>6</sub>- o-  
( C<sub>1</sub>-C<sub>6</sub>- , -C<sub>1</sub>-C<sub>6</sub>- )  
] , R<sup>13</sup> , C<sub>1</sub>-C<sub>6</sub>- , (c) -NR<sup>13</sup>-O-R<sup>14</sup> [ , R<sup>13</sup>  
, R<sup>14</sup> , C(W)R<sup>15</sup> ( , W O S , R<sup>15</sup> C<sub>1</sub>-C<sub>6</sub>-  
, C<sub>1</sub>-C<sub>6</sub>- , -C<sub>1</sub>-C<sub>6</sub>- , C<sub>3</sub>-C<sub>8</sub>- -C<sub>1</sub>-C<sub>6</sub>- , -C<sub>1</sub>-C<sub>6</sub>-  
(i) , (ii) C<sub>1</sub>-C<sub>6</sub>- , -C<sub>1</sub>-C<sub>6</sub>- , C<sub>3</sub>-C<sub>8</sub>- -C<sub>1</sub>-C<sub>6</sub>-  
6- , -C<sub>1</sub>-C<sub>6</sub>- , C<sub>1</sub>-C<sub>6</sub>- , C<sub>1</sub>-C<sub>6</sub>-  
가 5- 8- (iii) C<sub>1</sub>-C<sub>6</sub>- ) ] .

R<sup>1</sup> SO<sub>2</sub>- 5- 6-  
-A-R-E-Y . -A-R-E-Y , A  
;

- (1) -O-;
- (2) -S-;
- (3) -NR<sup>k</sup>-;
- (4) -CO-N(R<sup>k</sup>) -N(R<sup>k</sup>)-CO-;
- (5) -CO-O- -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C-C-;

(10) -N=N-;

(11) -NH-NH-;

(12) -CS-N(R<sup>k</sup>)-N(R<sup>k</sup>)-CS-;

(13) -CH<sub>2</sub>-;

(14) -O-CH<sub>2</sub>-CH<sub>2</sub>-O-;

(15) -S-CH<sub>2</sub>-CH<sub>2</sub>-S-;

(16) -SO-;

(17) -SO<sub>2</sub>-;

(18) A, R, SO<sub>2</sub>-, 5-, 6-;

R, (i), (ii), C<sub>1</sub>-C<sub>2</sub>-;

E:

(1) -CO(R<sup>g</sup>)-(R<sup>g</sup>)CO-;

(2) -CON(R<sup>k</sup>)-(R<sup>k</sup>)NCO-;

(3) -CO-;

(4) -SO<sub>2</sub>-R<sup>g</sup>-R<sup>g</sup>SO<sub>2</sub>-;

(5) -SO<sub>2</sub>-;

(6) -N(R<sup>k</sup>)-SO<sub>2</sub>-SO<sub>2</sub>-N(R<sup>k</sup>)-;

(7) E, R, Y;

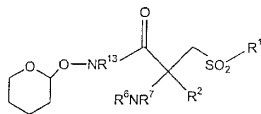






MMP, R<sup>7</sup>, R<sup>13</sup>, D, R<sup>1</sup>, R<sup>2</sup>, R<sup>6</sup>,

D



D, R<sup>2</sup>, R<sup>6</sup>, R<sup>13</sup>, R<sup>7</sup>, R<sup>7A</sup>, R<sup>1</sup>, (staggered conformation), R<sup>1</sup>, R<sup>1</sup>, R<sup>1</sup>, R<sup>1</sup>, R<sup>1</sup>, SO<sub>2</sub> - 1 - 4 - 5 - 6 - 7 - 8 - 9 - 10 - 11 - 12 - 13 - 14 - 15 - 16 - 17 - 18 - 19 - 20 - 21 - 22 - 23 - 24 - 25 - 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 - 56 - 57 - 58 - 59 - 60 - 61 - 62 - 63 - 64 - 65 - 66 - 67 - 68 - 69 - 70 - 71 - 72 - 73 - 74 - 75 - 76 - 77 - 78 - 79 - 80 - 81 - 82 - 83 - 84 - 85 - 86 - 87 - 88 - 89 - 90 - 91 - 92 - 93 - 94 - 95 - 96 - 97 - 98 - 99 - 100

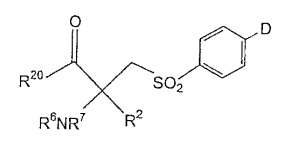
SO<sub>2</sub> - , R<sup>4</sup> 5 -  
 6 - . 6 - , SO<sub>2</sub> - ,  
 4 - R<sup>4</sup> - , 5 - , 3 - 4 - R<sup>4</sup> .

, R<sup>4</sup> 가  
 R<sup>1</sup> PhR<sup>4</sup> [ , R<sup>4</sup> SO<sub>2</sub> - (Ph) 4 - , R<sup>4</sup>  
 ] .  
 R<sup>4</sup> 가 SO<sub>2</sub> 4 - .  
 R<sup>4</sup> , 3 14 가 -  
 [ , C<sub>3</sub> - C<sub>14</sub>  
 O - C<sub>2</sub> - C<sub>14</sub> ], , [ - OC<sub>6</sub>H<sub>5</sub> ], [ -  
 NHC<sub>6</sub>H<sub>5</sub> ], [ - N<sub>2</sub>C<sub>6</sub>H<sub>5</sub> ], [ ; - SC<sub>6</sub>H<sub>5</sub> ], [ -  
 [ - NHC(O)C<sub>6</sub>H<sub>5</sub> ], [3 - NHC(O)C<sub>5</sub>H<sub>4</sub>N], ; - NHC(O)NH - C<sub>6</sub>H<sub>5</sub> ],  
 [2 - NHC(O)C<sub>5</sub>H<sub>4</sub>N] . 가 R<sup>4</sup> [4 - NHC(O)C<sub>5</sub>H<sub>4</sub>N],

, R<sup>4</sup> 10 6 -

[ , ( ) N - N,N -  
 가 5 - 8 - ] .

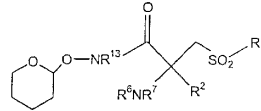
MMP - C  
 [ C]



[ , R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup> R<sup>20</sup> , D 가 , - F NO<sub>2</sub>  
 ], R<sup>2</sup> R<sup>6</sup> , R<sup>7</sup> R<sup>7A</sup> , R<sup>20</sup> , - O - R<sup>21</sup> (  
 , R<sup>21</sup> ) .

D , , R<sup>1</sup>, R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup> R<sup>13</sup>

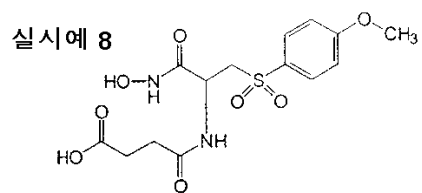
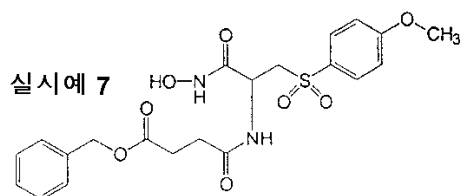
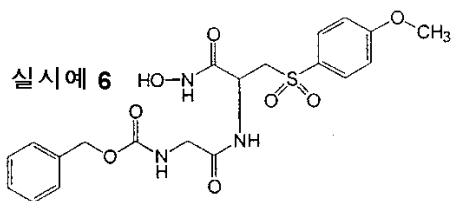
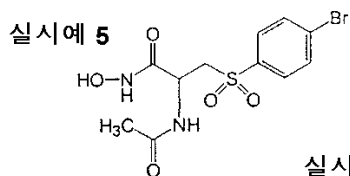
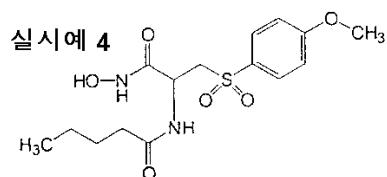
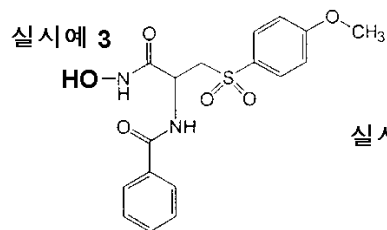
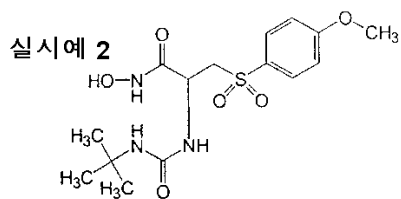
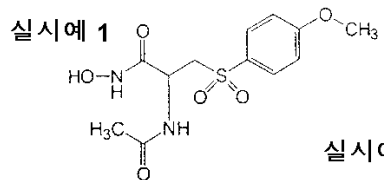
[ D]



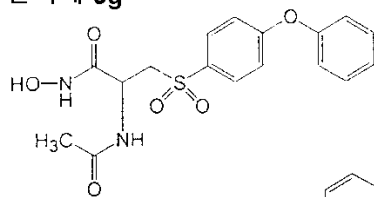
D , R<sup>2</sup>, R<sup>6</sup> R<sup>13</sup> , R<sup>7</sup> R<sup>7A</sup> .

1 9  
 P - 1 MMP - 13

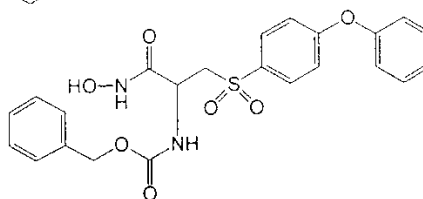
MM



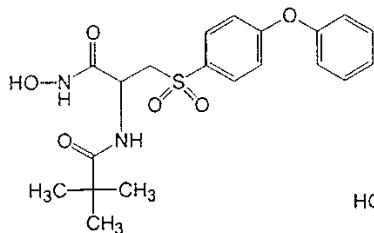
실시예 9g



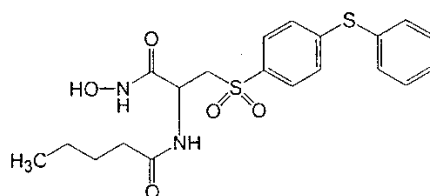
실시예 13c



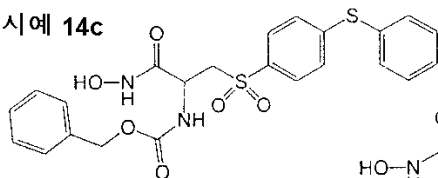
실시예 10d



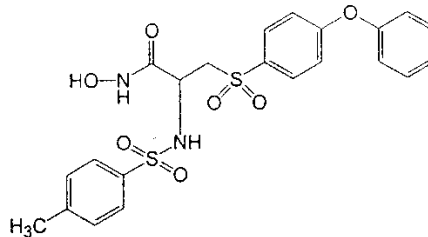
실시예 11g



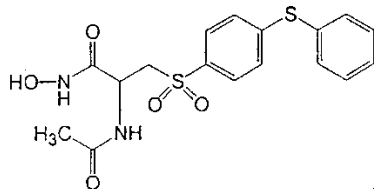
실시예 14c



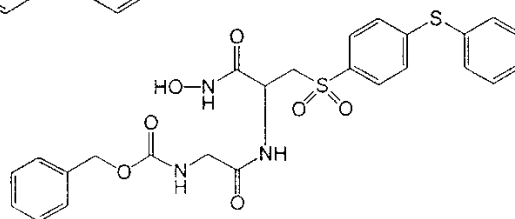
실시예 12c



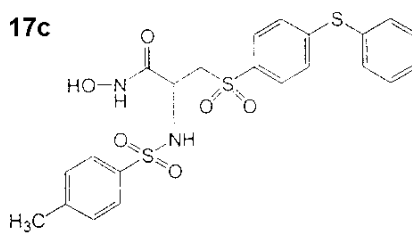
실시예 15b



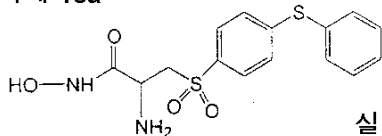
실시예 16c



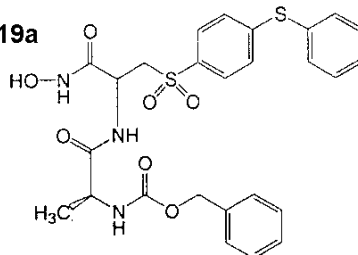
실시예 17c



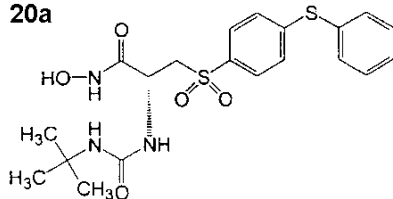
실시예 18a



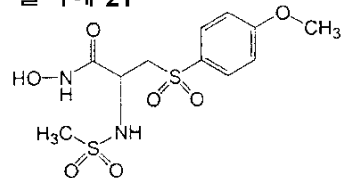
실시예 19a



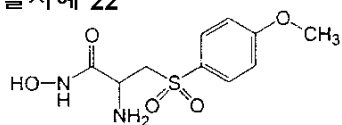
실시예 20a



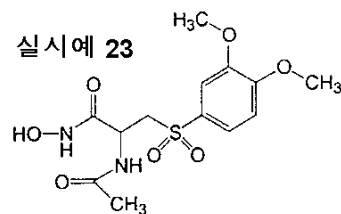
실시예 21



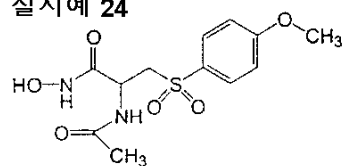
실시예 22

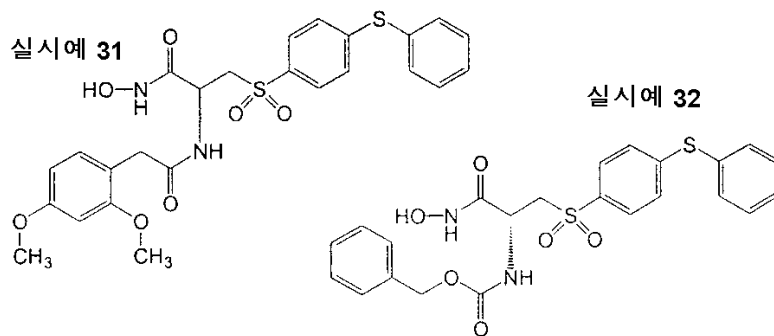
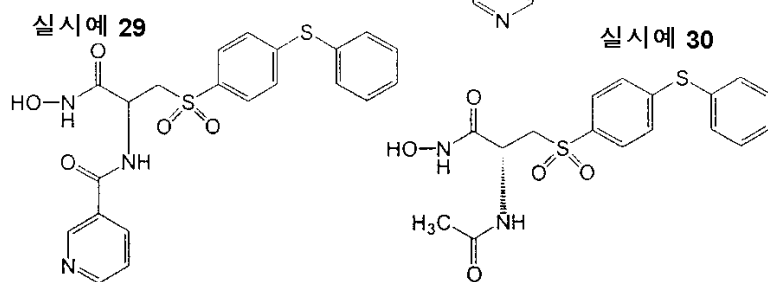
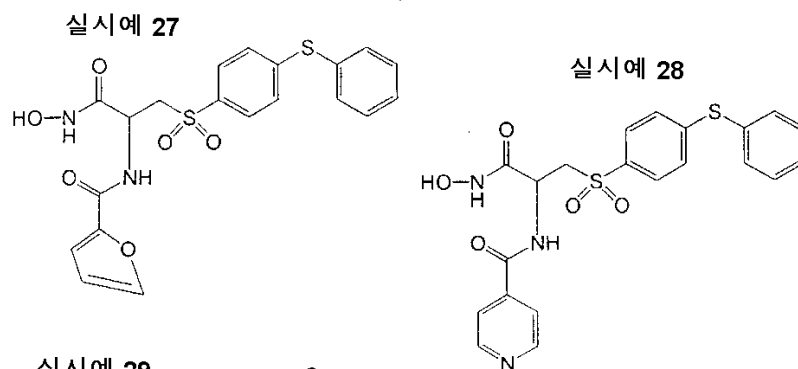
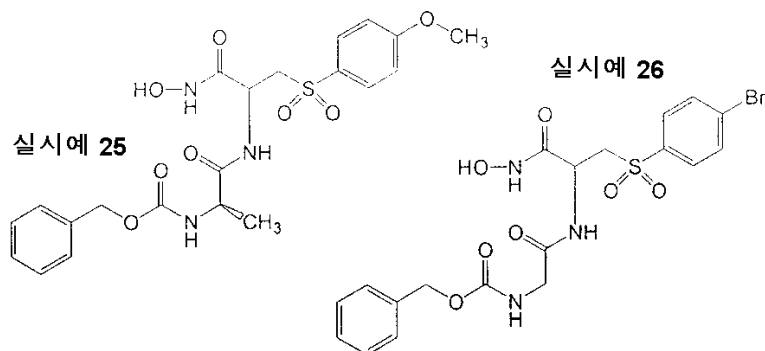


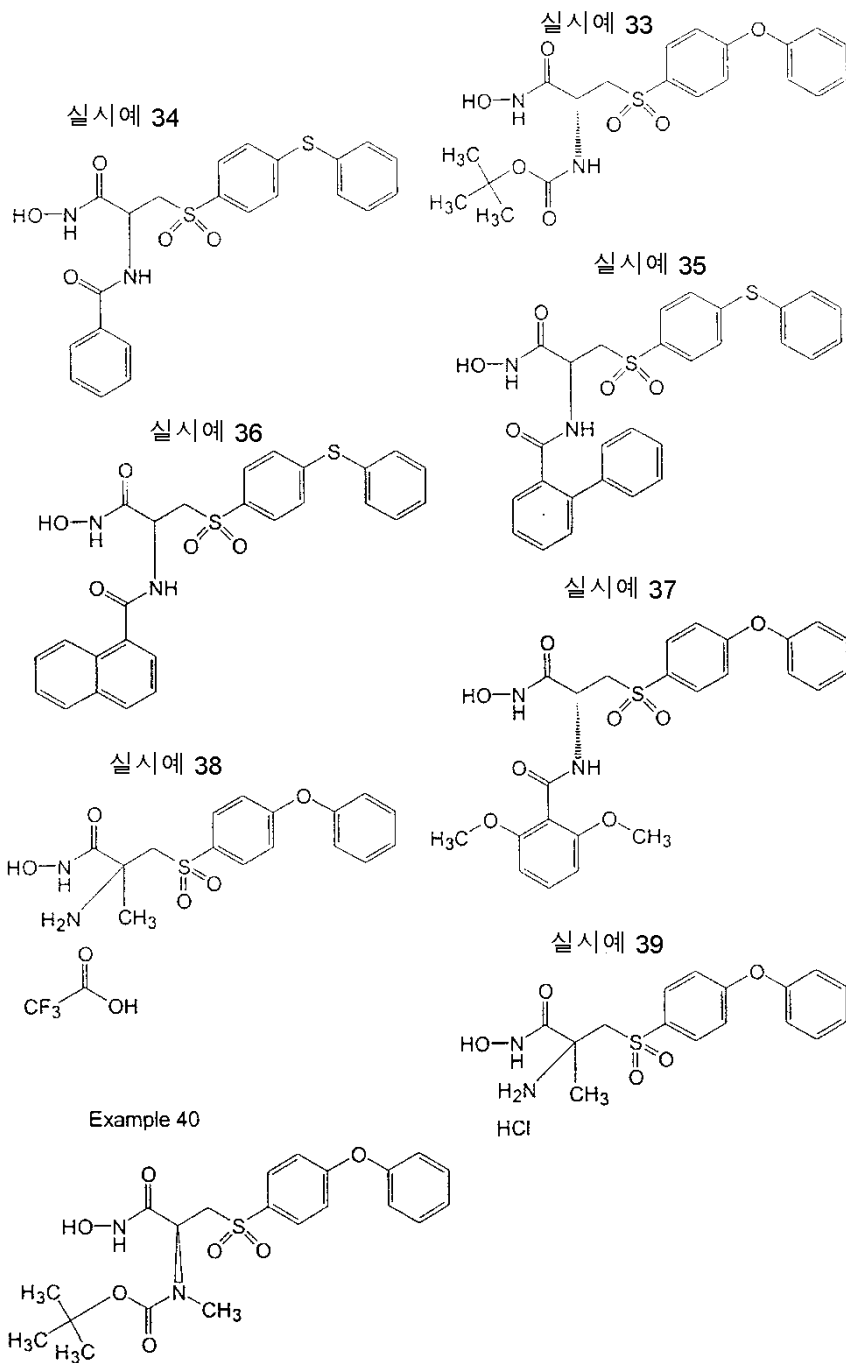
실시예 23



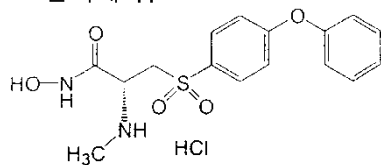
실시예 24



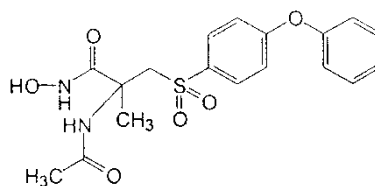




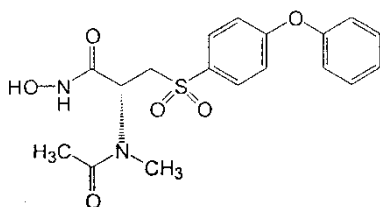
실시예 41



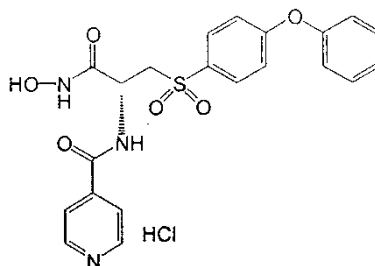
실시예 42



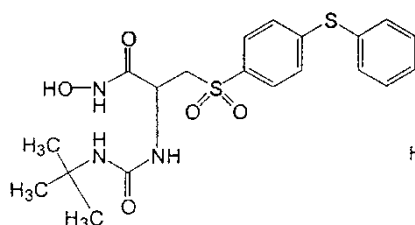
실시예 43



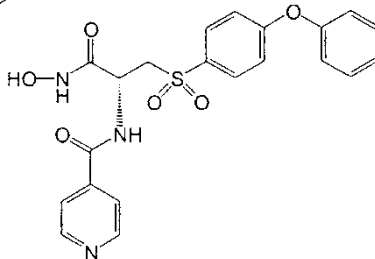
실시예 44



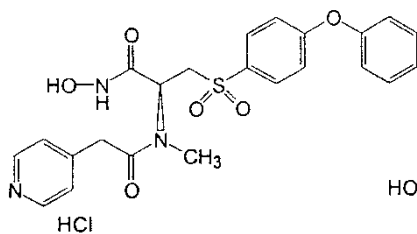
실시예 45



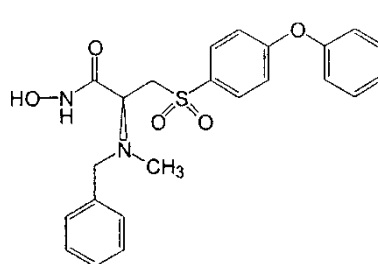
실시예 46

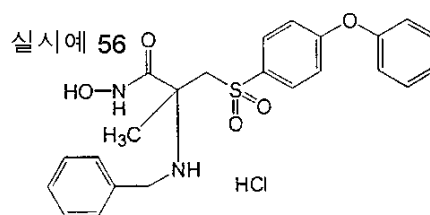
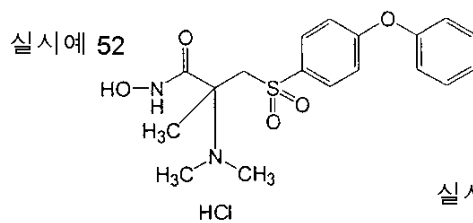
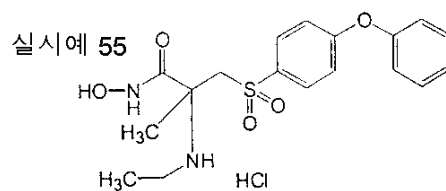
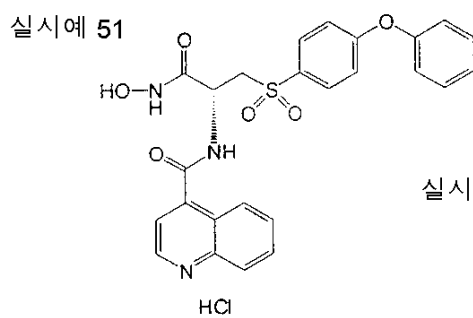
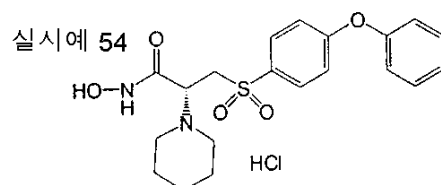
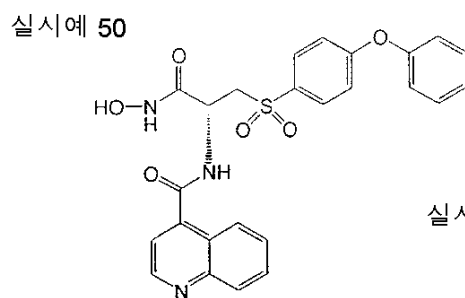
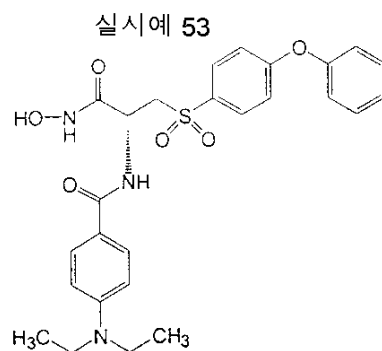
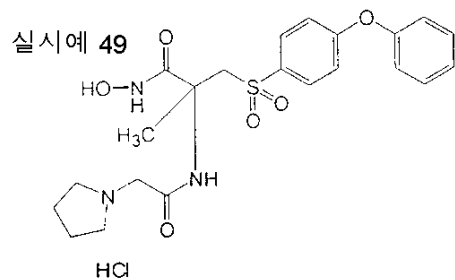


실시예 47

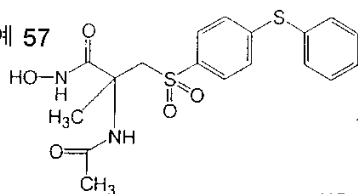


실시예 48

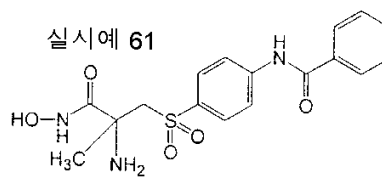




실시예 57

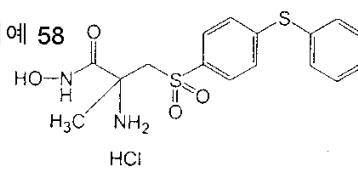


실시예 61



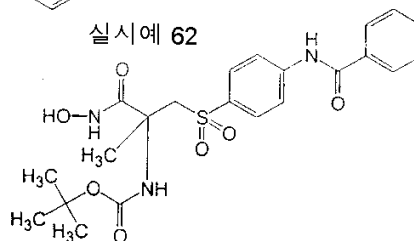
HCl

실시예 58

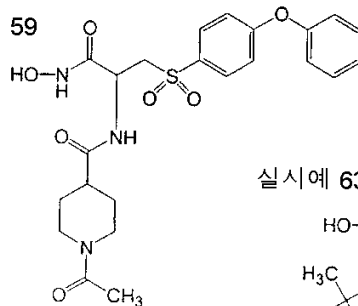


HCl

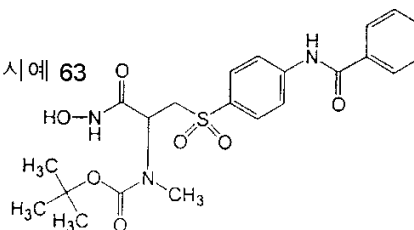
실시예 62



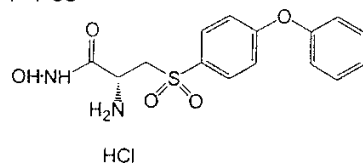
실시예 59



실시예 63

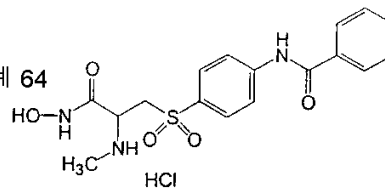


실시예 60



HCl

실시예 64



HCl



" " " " , -C(=O)- [ , ( 가)  
 -C(OH)<sub>2</sub> - .  
 " " " " , -SH " " "  
 " ; , 가 .  
 " " , -NH<sub>2</sub> , -N(  
 )<sub>2</sub>[ , ] , -N(  
 , , 1 (I°), 2 (II°) 3 (III°) , ,  
 , - N,N- . 4 ( ) (IV°) , ,  
 , 4 가 [-N<sup>+</sup>( )<sub>4</sub>] , N- 가  
 , [-N<sup>+</sup>( )<sub>3</sub>-O-] ; , 가 .  
 " " -C- -N(-C N) " " "  
 , -N- -N(-N N) " " " -OH .  
 " " , -NO<sub>2</sub> " " -N=N- [ ,  
 ] .  
 " " , -NH-NH- [ , ( 가)  
 가 ] 4 .  
 " " , -SO<sub>2</sub>- [ , ( 가)  
 ] " " , -SO- [ , ( 가)  
 ] .  
 " " , -SO<sub>2</sub>- [ , ( 가)  
 ] " " -SON= [ ,  
 ] " " , -S- [ ( 가)  
 ] .  
 " " [ , ] .  
 , , , n- , , n- , - , sec- ,  
 tert - .  
 " " , 3 8 " "  
 " , 3 8, 3 6 , , , , ,  
 .  
 , ( ) , , , ,  
 , , -1,4- . ,  
 ( , -NH- ) , , , / 2  
 ( , =N- ) , , , 가 3 3 N-

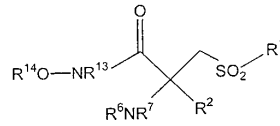






MMP - 1 , MMP  
TNF 가 B

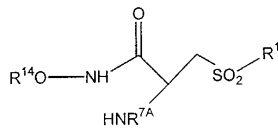
[ B]



[ , R<sup>1</sup>, R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>13</sup> R<sup>14</sup> ].

B1

[ B1]



[ , R<sup>1</sup> R<sup>14</sup> ],

TNF -  
가  
(惡液質)

MMP

, 2 - , 3 -

(C<sub>1</sub> - C<sub>6</sub>)

(C<sub>8</sub> - C<sub>20</sub>)

4

(酸)

4

MMP -	1		1	0.001	30 mg/kg	1	1	0.001
100 mg/kg							1	0.01
0 mg								1

가

/

가

가

가

(iontophoresis)

[Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975] [Lieberman, H.A. Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980]

1,3 -

가

가

/ 가

가

/

가

가

가

1A 1B

1A

1

N-

가( 1)

0

p- Oxone

2

.0

2

가

3

. N-

10

D

MF

3

4

11

4

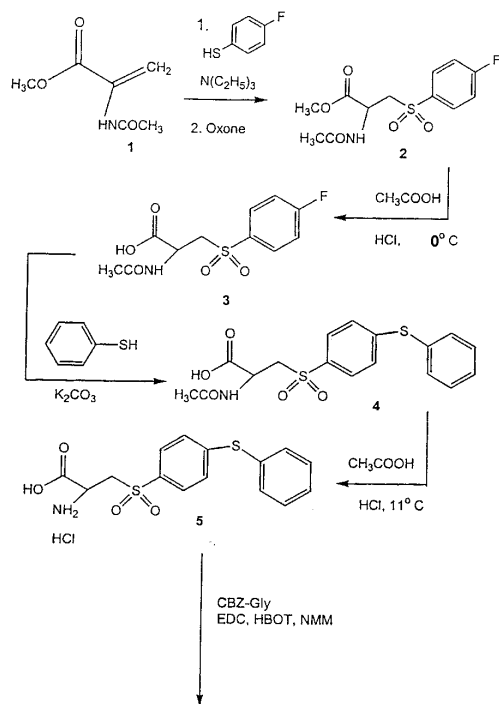
5

[1- (HOBT) 5 - 3- N- 1B - [3- (NMM) 6 - ] CBZ - (CBZ - Gly) N- ; EDC], 1 -

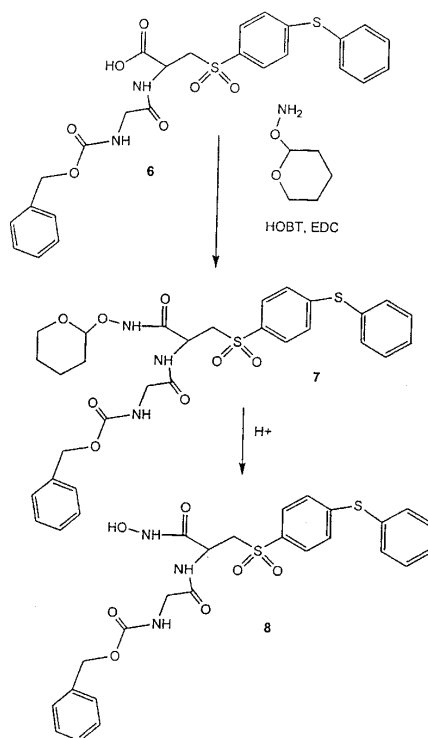
. HOBT 7 THP - EDC 8 THF O - -2H - -2 - - 7

6 THP -

1A



1B



가

가 가  
 (II.) (III.) 4 (I.),

1,5,5- N- , N,N'- , N- , 1,  
 N- , N- , N,N'- , 4 -  
 , N,N,N',N' - , N- -N' - , N,N-

tert- 가

4

(TBME), (DMF), (DMAc), (MeOH), (THF), (non - protic) 95% (aprotic) , tert - , N

, N-

( - 10 60 ) , -76

( )

4 -

2

1

(OXONE®),

, tert -

, tert -

, tert -

- 78

50

- 10

40

, 1

0

30

/ -10

( )

1

가

가

가

O-

- 2H -

- 2 -

(

; THPONH<sub>2</sub>),

(BnONH<sub>2</sub>)

(THP)

(Bn)

가

THP

가

가

/

, 1 -

(HOBT),

H,

THP

가

tert - (BOC), (Z) CBZ) N,N -  
 ( ) N -  
 3 가 가 가  
 가 / 가  
 가  
 가 P(R<sub>22</sub>)가  
 , THP, , Z, tert - (TBDMS)  
 ( )  
 tert - tert - (LDA)  
 tert -  
 , 1,2 - ( )가 가  
 , 1,2 - - , 1 - -2, , 1 - -2 -  
 1,2 - - . 1 - -2 -  
 가  
 가 . 1  
 가-  
 가-  
 R<sup>1</sup> (SN<sub>2</sub>) 4 - ( )  
 . HS - R<sup>1</sup>  
 . R<sup>1</sup>  
 2,3 -

LDA

2-

( )  
가

/

(n- )

tert -

(Ac)

N- -

가

/

2-

가

THF

(LDA)

( ) 가 가

1,2-

2- -

1- -

2-

( ) N- ( , , )  
 MF . , D

BaCO<sub>3</sub> Pd / Pd , Pd, Pd, Pt, PtO<sub>2</sub>

: , , :THF, 가  
 2

tert - (BOC, t - BOC) 가 (Z, CBZ, ),

tert - (BOC) (Z)

N- 3

, DMF THF , tert - , tert -  
 , - tert - THF , - tert - , tert -  
 가

R<sup>1</sup> , R<sup>1</sup> R<sup>1</sup> 8 6-61 ).

가 Rh, Pd, Pt, Ni 가  
 40 (psi)  
 R<sup>1</sup>

가 / 45 - 10

가 , 가

, -OH -SH

, -OH -SH (tautomer)

(rearrangement)

, HCl



HOBT = 1 -

MeOH =

MeCl<sub>2</sub> =

MsCl =

NMMOL NMM = N -

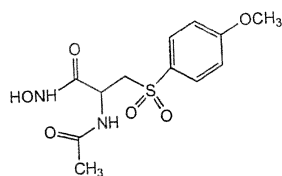
THF =

TsCl =

THP - O - = O - - O - - 2H - - 2 - -

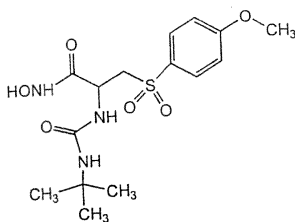
Z =

1 : N - - 3 - [(4 - ) ] - 2 - [( ) ]



A : 가 250 mL MeOH 100 mL N -  
 10.0 g, p - 9.9 g, NEt<sub>3</sub> 10 mL  
 1 NEt<sub>3</sub> 200 mL MeOH - 150 mL<sub>2</sub>O Oxone (E)  
 89 g (2.0 ) EtOAc -  
 14 g Et<sub>2</sub>O

B : 가 100 mL 8 mL MeOH/8 mL THF  
 500 mg, 50% 1.2 mL (2.0 ) ( 18 )  
 EtOAc 380 mg  
 2 : 2 - [ [(1,1 - ) ] ] - N - - 3 - [(4 - ) ]



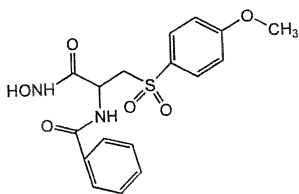
A : 가 250 mL 50 mL HCl 50 m  
 L 1 A 7.4 g 4  
 , 2 , HCl 6.55 g

B : 가 250 mL MeOH 70 mL  
 HCl 6.5 g SOCl<sub>2</sub> 2.5 mL (1.5 ) 3 가 ,  
 . EtO<sub>2</sub> HCl 6.9 g 가 EtOAc -

C : 가 100 mL MeCl<sub>2</sub> 20 mL  
 900 mg t- 288 mg ( 18 ) , 8  
 EtOAc -

D : 가 100 mL 2 mL MeOH/2 mL THF  
 90 mg 50% 0.2 mL (12.0 ) ( 18 )  
 , . Et<sub>2</sub>O 50 mg

3 : N- -3 - [(4- ) ] - 2 - [( ) ]



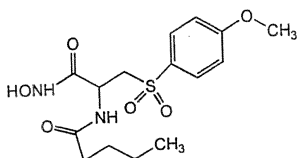
A : 가 500 mL 50 mL HCl 50 m  
 L 1 A 5.0 g (15.9 mmol) 4 가  
 , 2 2 HCl 4.6 g 가  
 , HCl (m/z=260) , m/z=260(M+H)

B : 가 500 mL MeOH 100 mL A  
 HCl 4.6 g (15.7 mmol) 1.7  
 mL (2.8 g, 23.5 mmol) 3 가 Et  
 OAc 1  
 , EtOAc 2.9 g  
 , (MgSO<sub>4</sub>),

C : 가 100 mL CH<sub>2</sub>Cl<sub>2</sub> 10 mL B  
 0.7 g (2.7 mmol) 0.6 mL (0.4 g, 4.0 mmol) ,  
 0.4 mL (0.5 g, 3.2 mmol) . 1 ,  
 EtOAc , EtOAc 1 5% ,  
 , (Na<sub>2</sub>SO<sub>4</sub>), 0.8  
 g 50% / m  
 /z=378(M+H) 0.6 g

D : 가 250 mL THF 20 mL C  
 0.6 g (1.6 mmol) . 50% 0.5 mL (0.5 g, 8.21 mmol)  
 . 65 , , 0.1 g (4.3 mmol) MeOH 5 mL  
 가 . (quench) . EtO  
 Ac/2N HCl , EtOAc , m/z=  
 379(M+H) 0.3 g .

4 : N - - 3 - [(4 - ) ] - 2 - [( ) ]



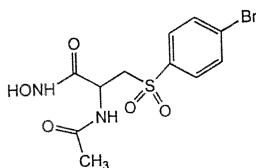
A : 가 500 mL 50 mL HCl 50 m  
 L , 1 A 5.0 g (15.9 mmol) . 4 가 .  
 , 2 2  
 HCl (m/z=260) , m/z=260(M+H) 4.6 g .

B : 가 250 mL MeOH 70 mL  
 6.5 g SOCl<sub>2</sub> 2.5 mL (1.5 ) . 3 가  
 . EtO<sub>2</sub> HCl 6.9 g .

C : 가 100 mL CH<sub>2</sub>Cl<sub>2</sub> 10 mL , B  
 HCl 1.0 g (3.2 mmol) 1.4 mL (1.0 g, 9.7 mmol) .  
 , 0.5 mL (0.5 g, 3.9 mmol) . 1  
 , 가 0.5 mL 0.4 mL 가 .  
 가 2 , EtOAc , EtOAc  
 1 , 5% , ( Na<sub>2</sub>SO<sub>4</sub> ),  
 m/z=358(M+H) 1.3 g ,  
 0.8 g .

D : 가 100 mL THF 20 mL MeOH 10 mL ,  
 C 0.8 g (2.3 mmol) . 50% 2.5 mL (1.4 g, 46.4 mmol)  
 ol) . 16 , EtOAc/  
 , , (Na<sub>2</sub>SO<sub>4</sub>), .  
 , m/z=359(M+H)  
 0.6 g .

5 : N - - 3 - [(4 - ) ] - 2 - [( ) ]

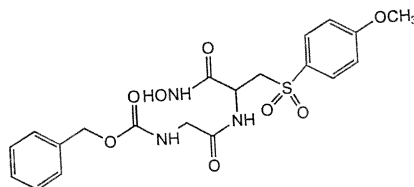


A : 가 1000 mL MeOH 400 mL 4 -  
 25.0 g (132.2 mmol) 19.9 g (138.8 mmol)  
 19.4 mL (14.0 g, 138.8 mmol) 1  
 가 , MeOH  
 27.6 g

B : 가 1000 mL MeOH 400 mL A  
 11.0 g (33.1 mmol) 가 40 mL Oxone (F 61.1 g (99.3  
 mmol) 4 , MeOH ,  
 EtOAc , EtOAc 2  
 (MgSO<sub>4</sub>),  
 m/z=370(M+Li) 6.7 g

C : 가 100 mL THF 5 mL MeOH 5 mL  
 B 0.7 g (1.9 mmol) 50% 2.1 mL (1.2 g, 38.4 mmol)  
 .17 , EtOAc/  
 3- ,  
 m/z=387(M+Na) 0.2 g

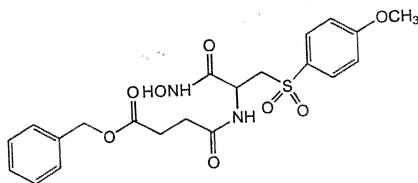
6 : - [2 - [[2 - ( ) - 2 - - 1 - [[[4 - ] ] ] ] ] - 2 - ]



A : 가 100 mL DMF 8 mL Z - Gly - OH  
 1.0 g, EDC 920 mg (1.0 ), HOBT 960 mg (1.5 ) 10  
 2 B 1.0 g .17 , EtOAc/  
 (HPLC > 95%) 1.25 g 10% KHSO<sub>4</sub> , ,

B : 가 100 mL THF 5 mL 70  
 0 mg, 50% 2.0 mL 2 . M  
 eCl<sub>2</sub> (HPLC > 97%)

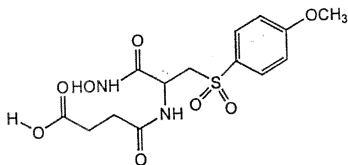
7 : 4 - [[1 - [( ) ] - 2 - [(4 - ) ] ] - 4 -



A : DMF 8 mL, 2.36 g (1.15 mmol), EDC 2.18 g (1.15 mmol), HOBT 2.0 g (1.5 mmol), 2.7 g (10% KHSO<sub>4</sub>), EtOAc, (HPLC 82%) 3.8 g, 3.1 g

B : 가 100 mL, MeOH 20 mL, THF 5 mL, 436 mg, 50% (HPLC 35%), 1.3 mL, (18%), 200 mg (HPLC 75%), 100% THF, EtOAc/, 100 mg

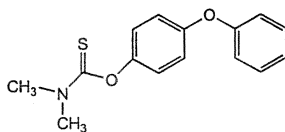
8 : 4 - [[1 - [( ) ] - 2 - [(4 - ) ] ] - 4 -



A : 가 300 mL Paar, MeOH 35 mL, AcOH 30 mL, THF 60 mL, 7 A, 436 mg, 10% Pd - C 100 mg, 50psi, (18%), Et<sub>2</sub>O, Celite (F), 630 mg (78%)

B : 가 100 mL, MeOH 4 mL, THF 5 mL, A 373 mg, 50%, 1.0 mL, (18%), Et<sub>2</sub>O, 250 mg

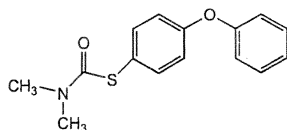
9a : O - (4 - ) - N,N -



Newman [Org. Syn., 51, 139 - 142] , 4 - (150 mmol, 27.9 g)  
 (100 mL) (150 mmol, 8.4 g) 0 가 ,  
 (THF; 40 mL) (150 mmol, 24.8 g) 가  
 12 ( 20 ) 가 , 가  
 10 KOH (10%, 50 mL) 가 , (3X 100 mL)  
 0 (10 mL) 2  
 5.9 g (63%)

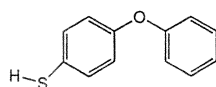
DSC 1 / : 52.5 - 56.2 .

9b : S - (4 - ) - N,N -



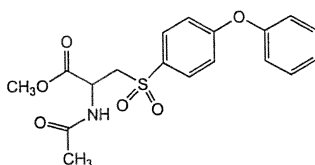
9a (25.91 g) 32 ( ) 가 15 .

9c : 4 - ( )



(75 mL), (10 mL) (9 g) 가 , 1  
 가 ( 200 mL) , (2X 150 mL)  
 HCl , (3X 75 mL)  
 (MgSO<sub>4</sub>), (9.5 g, 9b 49%)

9d : N - - 3 - [(4 - ) ] ,



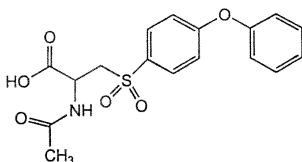
9c (15 mmol, 3.03 g) . 2 - ( ) - 2 - (15 mmol, 2.14 g) (15 mmol, 2.1 mL) 가 . 1 , 45 - 50 2 50 mL 가 0 . 100 mL Oxone (F (30 mmol, 18.45 g) 가 . 5 , (200 mL, 2 X 50 mL) 1 , 가 200 mL , , ( : 1:1) , (2.185 g, 39%) .

DSC 1 / : 127.0 - 129.8.

$C_{18}H_{19}NO_6S$  : C, 57.28; H, 5.07; N, 3.71.

: C, 57.10; H, 4.94; N, 3.51.

9e : N - - 3 - [(4 - ) ]

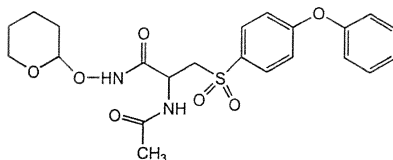


9d (2.1 mmol, 800 mg) 2 mL HCl 2 mL 1 70 가 . (3 X 5 mL) , ( ) .

$C_{17}H_{17}NO_6S$  MS  $MH^+$  : 364, : 364.

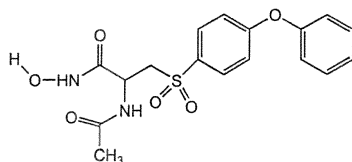
DSC 1 / : 193.0 - 195.1.

9f: N2 - - 3 - [(4 - ) ] - N1 - (3,4,5,6 - - 2H - - 2 - )



9e (2.1 mmol) (2.7 mmol, 365 mg), O - (3 m  
 mol, 0.35 g), N,N - (4 mL) N - (13 mmol, 1.43 mL) . EDC (2.7 m  
 mol, 518 mg) 가 (18 ) (20 mL) NaHCO<sub>3</sub> (20 mL)  
 (100 mL) (20 mL) , (glass)  
 (472 mg, 50%) . (6% ) ,

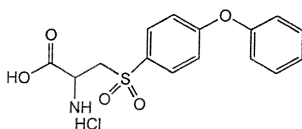
9 g : N22 - - N1 - - 3 - [(4 - ) ]



9f (1.0 mmol, 450 mg) (5 mL) . 6N HCl (0.5 mL) 가 ,  
 1 (120 mg, 32%) .

C<sub>17</sub> H<sub>18</sub> N<sub>2</sub> O<sub>6</sub> S MS MH<sup>+</sup> : 378, : 379.

10a : 3 - [(4 - ) ] ,

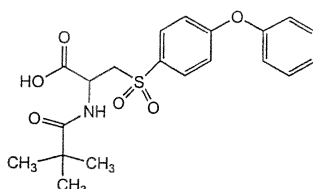


(18.5 mL) 9d (3.27 g, 8.66 mmol) 가 가  
 HCl (18.5 mL) 가 4 가 .  
 (3.04 g, 98%)

C<sub>15</sub> H<sub>16</sub> NO<sub>5</sub> SCl : C, 50.35; H, 4.51; N, 3.91; S, 8.96.

: C, 50.21; H, 4.43; N, 3.92; S, 9.04.

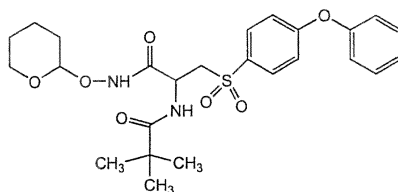
10b : N - [(1,1 - ) ] - 3 - [(4 - ) ]



(1.4 mmol, 500 mg) (2 mL), (5.6 mmol, 0.79 mL), (3 mL)

1, 0 가 (1.8 mmol, 0.22 mL) 5 가 (10 mL) (20% / ) (150 mL) 2N HCl (20 mL) (485 mg)

10c : N2 - (1,1 - ) - 3 - [(4 - ) ] - N1 - 3,4,5,6 - - 2H - - 2 - ( )

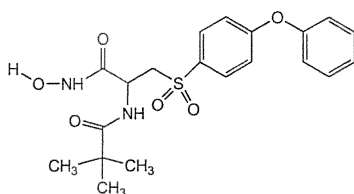


10b (0.89 mmol, 455 mg) EDC (1.00 mmol, 192 mg) 가  
 15 , THP - O - 가 20 (5 mL) , (260 mg, 58%) (6% / )

C<sub>24</sub> H<sub>31</sub> N<sub>2</sub> O<sub>7</sub> S (1/4 H<sub>2</sub>O) : C, 59.10; H, 6.25; N, 5.51

: C, 59.10; H, 6.50; N, 5.31.

10d : N2 - [(1,1 - ) ] - N1 - - 3[(4 - ) ]

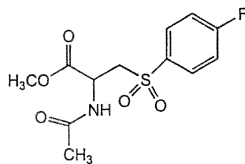


10c (250 mg) (10 mL) , (10 mg) 가 . 2 , 가 (10 mg) 가 , 가 (166 mg) (6% / )

C<sub>20</sub> H<sub>24</sub> N<sub>2</sub> O<sub>6</sub> S : C, 57.13; H, 5.75; N, 6.66

: C, 52.67; H, 5.32; N, 5.91.

11a : N - 3 - [(4 - ) ] ,

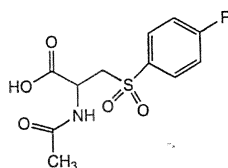


0 , 100 mL 2 - (10.0 g, 69.9 mmol) 4 -  
 (7.44 mL, 69.9 mmol) (9.74 mL, 69.9 mmol) 가 . 4  
 . H<sub>2</sub>O (250 mL) MeOH (125 mL) Oxone (86 g, 140 mmol)  
 . 18 , EtOAc (200 mL) H<sub>2</sub>O Na  
 HCO<sub>3</sub> (3 X 100 mL) (1 X 100 mL) ,  
 (16.3 g, 77%) .

C<sub>12</sub> H<sub>14</sub> NO<sub>5</sub> SF MS MH<sup>+</sup> : 304, : 304.

C<sub>12</sub> H<sub>14</sub> NO<sub>5</sub> SF HRMS : 303.0577, : 303.0581.

11b : N - 3 - [(4 - ) ]

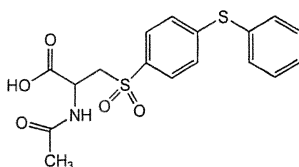


(135 mL) HCl (135 mL) 11a (17.9 g, 59.0 mmol) 2  
 7 가 . N<sub>2</sub> (17.0 g, ) .

C<sub>11</sub> H<sub>12</sub> NO<sub>5</sub> SF MS MH<sup>+</sup> : 290, : 290.

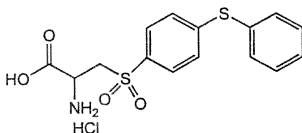
C<sub>11</sub> H<sub>13</sub> NO<sub>5</sub> SF HRMS : 290.0499, : 290.0520.

11c: N - 3 - [[4 - ( ) ] ]



DMF (200 mL) 11b (17.0 g, 59.0 mmol) K<sub>2</sub>CO<sub>3</sub> (24.4 g, 177 mmol)  
 (7.27 g, 71.0 mmol) 가 . 9 2 가 , N<sub>2</sub> .  
 1M KHSO<sub>4</sub> pH=1 , EtOAc (2X) , MgSO<sub>4</sub>  
 . , 가 .

11d: 3 - [[4 - ( ) ] ] ,

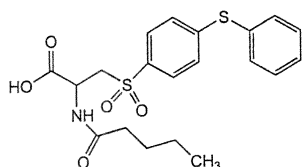


(100 mL) HCl (100 mL) 11c (30.0 g) 19 11 가  
 : (17.1 g, 3 78%)  
 :

$C_{15}H_{15}NO_4S_2 \cdot 1.1 HCl \cdot 0.25 H_2O$  : C, 47.16; H, 4.38; N, 3.67; Cl, 10.21.

: C, 47.16; H, 4.27; N, 3.91; Cl, 9.95.

11e: N - (1 - ) - 3 - [[4 - ( ) ] ]

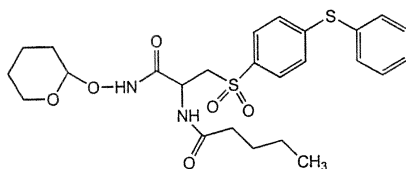


0 H<sub>2</sub>O (3 mL) (2 mL) 11d (1.0 g, 2.68 mmol)  
 (1.17 mL, 8.43 mmol) 가 , (2 mL) (0.30 mL, 2.52 mmol) 가  
 18 , 1M KHSO<sub>4</sub> (1x25 mL) (1x25 mL) , MgSO<sub>4</sub>  
 CH<sub>2</sub>Cl<sub>2</sub> (3X) , (690 mg, 61%) :  
 ,

$C_{20}H_{23}NO_5S_2$  MS M<sup>+</sup> : 421, 421.

$C_{20}H_{23}NO_5S_2$  HRMS : 421.1018, : 421.1025.

11f: N - [2 - - 1 - [[4 - ( ) ] ] ] - 2 - [[(3,4,5,6 - - 2H - - 2 - ) ] ]

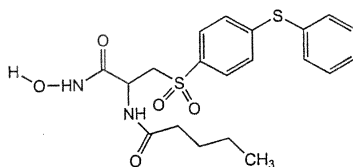


0 THF (40 mL) 11e (690 mg, 1.64 mmol) O - - 2H -  
 - 2 - - (192 mg, 1.64 mmol) EDC (330 mg, 1.72 mmol) HOBT (264 mg, 1.72  
 mmol) 가 .0 5 18 ,  
 EtOAc (50 mL) , 1M KHSO<sub>4</sub> (2x50 mL), NaHCO<sub>3</sub> (2x50 mL) (1x50 mL) ,  
 Na<sub>2</sub>SO<sub>4</sub> (1:1 EtOAc/ ) , (500 mg, 59%)  
 :

$C_{25}H_{32}N_2O_6S_2$  : C, 57.67; H, 6.19; N, 5.38.

: C, 57.48; H, 6.37; N, 5.11.

11g: N - [1 - [( ) ] - 2 - [[4 - ( ) ] ] ]

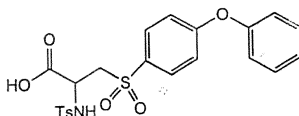


(20 mL) 11f (500 mg, 0.96 mmol) p- ( (6:94 Me  
40 mg, 0.21 mmol) 가 2 , (170 mg, 40%) :  
OH/CHCl<sub>3</sub> )

$C_{20}H_{24}N_2O_5S_2 \cdot 0.5H_2O$  : C, 53.91; H, 5.66; N, 6.29; S, 14.39.

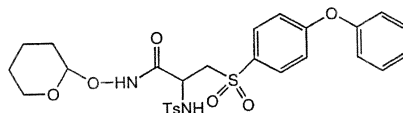
: C, 53.98; H, 5.44; N, 6.20; S, 14.47.

12a:



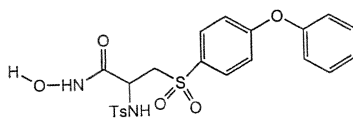
2.4 mL p- (TsCl; 0.779 g, 4.19 mmol) , 2.4 mL H<sub>2</sub>O 6.4  
mL 12a (1.50 g, 4.19 mmol) (2.36 mL, 16.9 mmol) 0  
가 3 , ,  
5 g, 38%) (5:95 MeOH/CHCl<sub>3</sub>) , (0.7  
. <sup>1</sup>H NMR

12b:



0 THF (22 mL) 12a (0.75 g, 1.6 mmol), HOBT (0.253 g, 1.7 mmol) O  
- 2H - 2 - - (0.18 g, 1.6 mmol) EDC (0.316 g, 1.7 mmol) 가  
 , H<sub>2</sub>O (18 ) ,  
(40:60 / ) . MgSO<sub>4</sub> ,  
NMR (0.22 g, 24%)

12c:

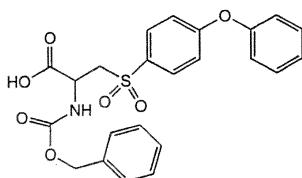


MeOH (5 mL) 12b (0.220 g, 0.383 mmol) p- (20 m  
g, 0.105 mmol) 2 , ET<sub>2</sub>O ,  
(50 mg, 43%) :

C<sub>22</sub> H<sub>22</sub> N<sub>2</sub> O<sub>7</sub> S<sub>2</sub> MS M<sup>+</sup> 490, 490.

C<sub>22</sub> H<sub>22</sub> N<sub>2</sub> O<sub>7</sub> S<sub>2</sub> HRMS : 490.0868, :490.0863.

13a: 3 - [(4 - ) ] - N - [( ) ]



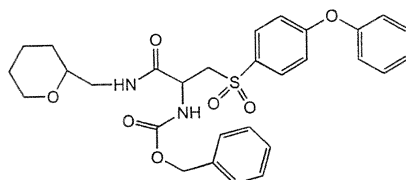
, 34a (0.892 g, 2.5 mmol) ,  
(0.43 mL, 3 mmol) , 10b . (689 mg, 66%)

C<sub>23</sub> H<sub>21</sub> NO<sub>7</sub> S MS MH<sup>+</sup> 456, 456.

C<sub>23</sub> H<sub>21</sub> NO<sub>7</sub> S : C, 59.47; H, 4.77; N, 3.02.

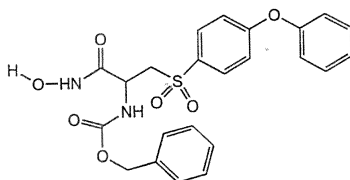
: C, 59.49; H, 4.35; N, 3.09.

13b: [2 - - 1 - [(4 - ) ] ] - 2 - [[3,4,5,6 - - 2H - - 2 - ) ] ]



O - THP , 208 mg 10c 15a (669 mg, 1.6 mmol) ,

13c: [1 - [( ) ] - 2 - [(4 - ) ] ]



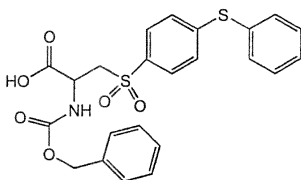
13b O - THP (203 mg, 0.36 mmol) (10 mL) , (20 mg) 가 . 1 , , , ( 74 mg, 20%) , .

$C_{23}H_{22}N_2O_7S$  MS  $MH^+$  470, 470.

$C_{23}H_{22}N_2O_7S \cdot (H_2O)$  : C, 56.53, ; H, 4.90; N, 5.65.

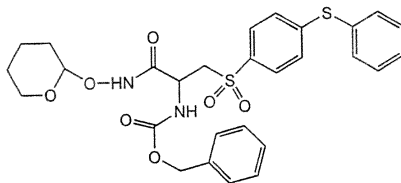
: C, 56.55; H, 4.95; N, 5.73.

14a: N - [( ) ] - 3 - [[4 - ( ) ] ]



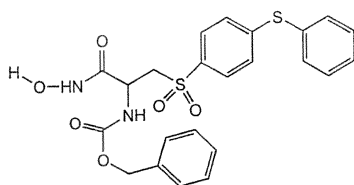
0  $H_2O$  (5 mL) (3 mL) 11d (1.5 g, 4.0 mmol) (1.8 mL, 12.6 mmol) 가 , (3 mL) (0.57 mL, 4.0 mmol) 가  $H_2Cl_2$  (3X) . 6 , 1M  $KHSO_4$  (1x25 mL) (1x25 mL) 1M  $KHSO_4$  , C (1.4 g, 72%)  $MgSO_4$

14b: - [2 - - 1 - [[4 - ( ) ] ] ] - 2 - [[3,4,5,6 - - 2H - - 2 - ] ] ] ] ]



0 DMF (20 mL) 14a (1.35 g, 2.87 mmol) O - - 2H - (336 mg, 2.87 mmol) EDC (578 mg, 3.01 mmol) HOBT (461 mg, 3.01 m mol) 가 . 0 1 , 2 , EtOAc  $H_2O$  . 1M  $KHSO_4$  (2x50 mL),  $NaHCO_3$  (2x50 mL) (1x50 mL) , N  $a_2SO_4$  . (1:1 EtOAc/ ) , (500 mg, 31%)

14c: - [2 - ( ) - 2 - - 1 - [[ [4 - ( ) - ] ] ] ]

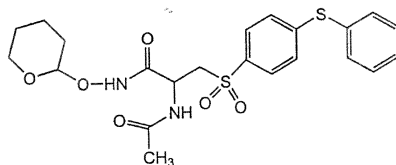


(20 mL) 14b (500 mg, 0.96 mmol) p - ,  
 (40 mg, 0.21 mmol) 가 1.5 ,  
 (120 mg, 28%) :

$C_{23}H_{22}N_2O_6S_2 \cdot 0.2H_2O$  : C, 56.36; H, 4.61; N, 5.72; S, 13.08.

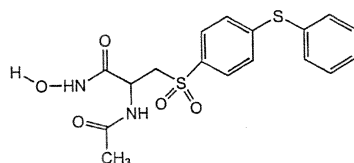
: C, 56.18; H, 4.21; N, 5.50; S, 13.31.

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



0 DMF (40 mL) 11c (930mg, 2.45 mmol) O - - 2H -  
 - 2 - - (287 mg, 2.45 mmol) EDC (493 mg, 2.57 mmol) HOBT (393 mg, 2.57 m  
 mol) 가 1 , 3 , EtOAc H<sub>2</sub>O  
 . 1M KHSO<sub>4</sub> (2x50 mL), NaHCO<sub>3</sub> (2x50 mL) (1x50 mL) , N  
 a<sub>2</sub>SO<sub>4</sub> (1:1 EtOAc/ ) , (400 mg, 34%)

15b: 2 - ( ) - N - - 3 - [[ [4 - ( ) ] ] ]

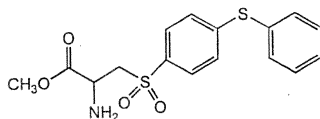


(40 mg) 15a (400 mg, 0.84 mmol) p - , ( )  
 40 mg, 0.21 mmol) 가 2 , (4:  
 96 MeOH/CHCl<sub>3</sub>) , (140 mg, 42%) :

$C_{17}H_{18}N_2O_5S_2 \cdot 0.8H_2O$  : C, 49.94; H, 4.83; N, 6.85; S, 15.68.

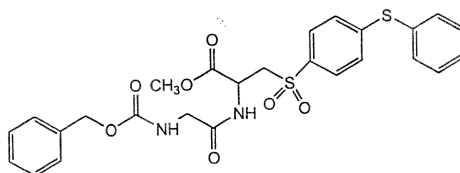
: C, 50.23; H, 4.62; N, 6.80; S, 15.29.

16a: 3 - [[4 - ( ) ] ] ,



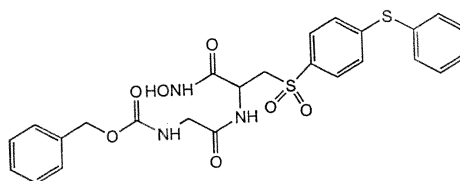
ol) (20 mL) 11d (1.5 g, 4.0 mmol) (0.44 mL, 6.0 mmol)  
 가 . 5 가 , . EtOAc 가 ,  
 . NaHCO<sub>3</sub> (2x50 mL) (1x50 mL) , MgSO<sub>4</sub> .  
 , (570 mg, 41%) .

16b: N - [2 - [( ) ] ] - 3 - [[4 - ( ) ] ] ,



0 (20 mL) 16a (570 mg, 1.6 mmol)  
 (500 mg, 1.6 mmol) 가 . 20 ,  
 EtOAc . 1M KHSO<sub>4</sub> (2x50 mL), NaHCO<sub>3</sub> (2x50 mL)  
 (1x50 mL) , MgSO<sub>4</sub> , (800 mg, 93%) .

16c: - [2 - [( ) ] ] - 2 - - 1 - [[4 - ( ) ] ] ] -  
 2 - ]



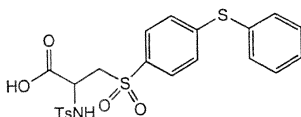
H (50% (9 mL) (3 mL) 16b (440 mg, 0.81 mmol) NH<sub>2</sub>O  
 , 0.74 mL, 12 mmol) 가 . 20 , .  
 (5:95 MeOH/CHCl<sub>3</sub>) , (80 mg, 18%) :

C<sub>25</sub> H<sub>25</sub> N<sub>3</sub> O<sub>7</sub> S<sub>2</sub> · 0.25H<sub>2</sub>O

: C, 54.78; H, 4.69; N, 7.67; S, 11.70.

: C, 54.78; H, 4.72; N, 7.46; S, 11.53.

17a:



0 H<sub>2</sub>O (6 mL) (3 mL) 11d (1.6 g, 4.28 mmol) ( (

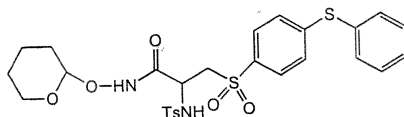
2.8 mL, 38.2 mmol) 가 , (3 mL) (TsCl; 1.24 g, 65.0 mmol) 가 .

18 , 10% KHSO<sub>4</sub> CH<sub>2</sub>Cl<sub>2</sub>

(1.3 g, 61.9%) .

C<sub>22</sub> H<sub>21</sub> NO<sub>6</sub> S<sub>3</sub> HRMS : 492.0609, : 492.0607

17b:



0 THF (12 mL) DMF (3 mL) 17a (0.6 g, 1.22 mmol) ED

C (0.280 g, 1.46 mmol) HOBT (0.198 g, 1.46 mmol) 가 . 0 30 , O-

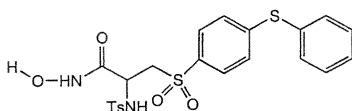
- 2H - - 2 - - (0.172 g, 1.46 mmol) 가 , 16

EtOAc (50 mL) , 10% (2x50 mL), NaH

CO<sub>3</sub> (2x50 mL) (1x50 mL) , MgSO<sub>4</sub> . (1.5/60/4

0 MeOH/EtOAc/ ) , (0.47 g, 65.3%) .

17c:



(13 mL) 17b (430 mg, 0.72 mmol) p-

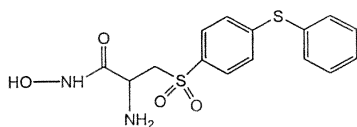
(47 mg, 0.25 mmol) 가 . 1.5 , ,

(280 mg, 75.7%) :

C<sub>22</sub> H<sub>22</sub> N<sub>2</sub> O<sub>6</sub> S<sub>3</sub> : C, 51.12; H, 4.58; N, 7.95; S, 18.20.

: C, 51.06; H, 4.59; N, 7.83; S, 18.45.

18a :

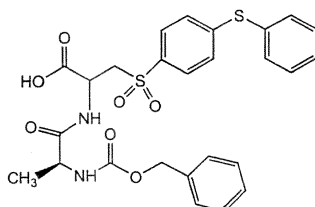


MeOH (2 mL) THF (2 mL) 16a (0.5 g, 1.4 mmol) NH<sub>2</sub>OH 50% (1 mL,  
13.5 mmol) 가 2 (10 mL X 3)

C<sub>15</sub> H<sub>16</sub> N<sub>2</sub> O<sub>4</sub> S<sub>2</sub> : C, 51.12; H, 4.58; N, 7.95; S, 18.20.

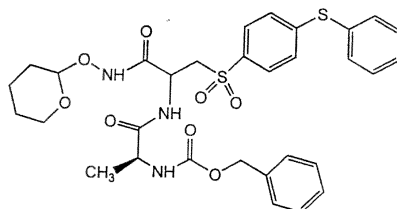
: C, 51.06; H, 4.59; N, 7.83; S, 18.45.

19a:



0 DMF Cbz- (1.43 g, 6.4 mmol) EDC (1.23 g, 6.4 mmol) HOBT (0.87 g, 6.4 mmo  
l) 가 .0 30 , 11d (2 g, 5.36 mmol) N- (1.82  
mL, 16.5 mmol) 가 . ( 18 )  
, 10% KHSO<sub>4</sub> , 10% K  
HSO<sub>4</sub> , MgSO<sub>4</sub> ,

19b:

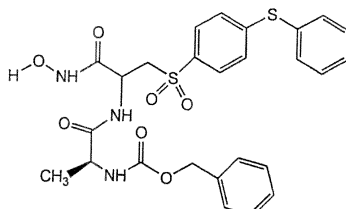


0 DMF (10 mL) 19a (1.0 g, 1.84 mmol) EDC (0.422 g, 2.2 mmo  
l) HOBT (0.299 g, 2.2 mmol) 가 .0 30 , O- -2H- -2- -  
(0.323 g, 2.6 mmol) 가 . , 16  
EtOAc (50 mL) , 10% (2x50 mL), NaHCO<sub>3</sub> (2x50 mL)  
(1x50 mL) , MgSO<sub>4</sub> .  
2/50/50/ MeOH/EtOAc/ ) , (0.6 g, 50.8%) .

C<sub>31</sub> H<sub>35</sub> N<sub>3</sub> O<sub>8</sub> S<sub>2</sub> : C, 58.02; H, 5.5; N, 6.55; S, 9.99.

: C, 57.69; H, 5.59; N, 6.35; S, 10.33.

19c :

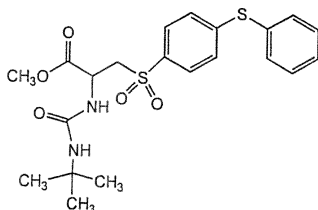


(1 mL) (4 mL) 19b (170 mg, 0.26 mmol) p -  
 (25 mg, 0.13 mmol) 가 ( 18 ) ,  
 (5/100 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) , (8  
 2 mg, 55.5%) .

C<sub>26</sub> H<sub>27</sub> N<sub>3</sub> O<sub>7</sub> S<sub>2</sub> : C, 56.00; H, 4.88; N, 7.54; S, 11.50.

: C, 56.11; H, 5.22; N, 7.28; S, 11.22.

20a:

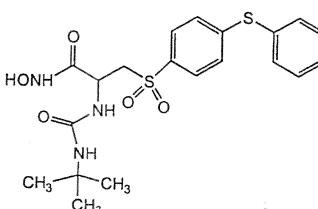


CH<sub>2</sub>Cl<sub>2</sub> 16a (0.43 g, 1.2 mmol) t - (0.48 mL, 4.2 mmol) 가  
 3 , (50 mL) , 10% (2x50 mL),  
 NaHCO<sub>3</sub> (2x50 mL) (1x50 mL) , MgSO<sub>4</sub> .

C<sub>21</sub> H<sub>26</sub> N<sub>2</sub> O<sub>5</sub> S<sub>2</sub> : C, 55.98; H, 5.82; N, 6.22; S, 14.25.

: C, 55.78; H, 6.00; N, 6.09; S, 14.25.

20b:



MeOH (2 mL) THF (2 mL) 20a (0.47 g, 1.04 mmol) NH<sub>2</sub>OH (0.9  
 mL, 15.8 mmol) 가 ( 18 ) ,  
 (5/100 MeOH//CH<sub>2</sub>Cl<sub>2</sub>) , (287 mg, 61.0%)

C<sub>20</sub> H<sub>25</sub> N<sub>3</sub> O<sub>5</sub> S<sub>2</sub> · H<sub>2</sub>O : C, 51.16; H, 5.80; N, 8.95; S, 13.66.

: C, 51.34; H, 5.60; N, 9.41; S, 13.57.

21 - 70 .

21:

FEBS Lett.296(3):263 (1992)] , 4 - [Knight et al. , (APMA) 5

MMP - 13 MMP - 1 CDNA MMP - 13 [V.A. Luckow, Insect Cell Expression Technology, P.183 - 218,Protein Engineering: Principles and Practice, J.L.Cleland et al. eds., Wiley - Liss, Inc., (1996) ]

[Luckow et al., J. Virol., 67:4566 - 4579 (1993); O'Reilly et al.,Baculovirus Expression Vectors : A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al.,The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992)]. 가 ,

APMA

(transfected) HT - 1080 MMP - 1 (St. Louis, MO) (Dr. Harold Welgus) APMA

가 가

:Enzyme Nomenclature, Academic Press, San Diego, Ca (1992)

Frije et al.,J. Biol. Chem., 26(24): 16766 - 16773 (1994).

MCA , Dpa 3 - (2,4 - ) - L - 2,3 - : MCA - ProLeuGlyLeuDpaAlaArgNH<sub>2</sub>, Ba ychem M - 1895

3) 100mmol Tris - HCl, 100 mmol NaCl, 10 mmol CaCl<sub>2</sub> 0.05 % (2 pH 7.5 , (DMSO) 1%

DMSO/ DMSO/ Microfluor<sup>TM</sup> White Plates (Dynatech) 10 , 가 4 μM

gly - leu , 2,4 - , Perkin Elmer L550 가 (328 nm /415 nm ). IC<sub>50</sub> (nM) IC<sub>50</sub>

## 억제 표

## MMP 효소 억제 프로파일

(nM, IC<sub>50</sub>)

실시예	MMP-1	MMP-2	MMP-13
1	300		15.0
2	1500		15.0
3	2000		25.0
4	400		3.5
5	100		200
6	40		<1.0
7	200		2.5
8	600		60.0
9g	770		1.1
10d	1600		2.7
11g	10000		6.0
12c	400	<0.1	0.6
13c	1400		1.1
14c	>10000		3.7
15b	>10000	2.2	5.9
16c	>10000		0.8
17c	600		0.4

18a	>10000		24.0
19a	>10000		0.8
20b	>10000		4.0
21	300		15.0
22	250		15.0
23	>10000		1500
24	5200		650
25	1.0		1.0
26			
27	>10000		14.0
28	>10000	5.5	13.0
29	>10000		7.0
30	10000	0.5	2.9
31	3000	0.8	0.4
32	8000		0.4
33	500	0.2	0.3
34	>10000		5.0
35	3000		0.2
36	>10000		2.5
37	350	0.25	0.4
38	170	0.5	0.5
39	114, 225	0.3, 0.8	0.3, 1.1
40	1600	0.3	0.3
41	440, 670	0.3, 0.5	0.4, 1.0
42	>10000	40.0	41.5
43	90.0	0.2	0.2
44	900	0.3	0.8
45	>10000		5.0
46	1310	0.3	1.1
47	258	0.6	45.3
48	475	<0.1	0.2
49	>10000	80.0	160
50	316	0.3	0.3

51	295	0.3	0.4
52	>10000	5.0	24.0
53	8100	0.3	2.1
54	345	0.2	0.3
55	1600	1.3	1.6
56	1200	0.2	0.3
57	>10000	540	580
58	4400	3.2	2.4
59	580	0.4	0.8
60	440	0.3	0.4
61	>10000	1.1	60.0
62	72.3	23.9	1200
63	3050	1.0	21.5
64	7000	0.4	8.1
65	>10000	184	161
66	2350	0.5	1.1
67	2400	1.3	2.4
68	>10000	0.4	1.4
69	700	0.2	0.6
70	130	0.2	0.4

22:

SG (R - 10) , U - 937 (ATCC CRL - 1593) . RPMI w/10 % FCS P

1. , 1.540 × 10<sup>6</sup> /mL R - 10 .

2. 96 - 65 μl R - 10 가. DMSO  
 (100 mM ) , 5 3 400 μM . 65 μl ( 3 )  
 100 μM, 33.3 μM, 11.1 μM, 3.7 μM, 1.2 μM 0.4 μM .

3. 130 μl , , (200,000 / ) 가 .

4. 1 5% CO<sub>2</sub> 37 , 45 .

5. 160 ng/mL PMA(Sigma) R - 10(65 μl) 가 .

6. , 100% 5% CO<sub>2</sub> 37 (18 - 20 ) .

7. ELISA 150 μl .

8. , 5 mL R - 10 50 μl , 5 mL MTS [CellTiter 96 AQueous  
 One Cell Proliferation Assay Cat. G#358/0,1 (Promega Biotech)] 250 μl PMS ,  
 가 , 5 % CO<sub>2</sub> 37 . 570 nm  
 , 630 nm .

TNF ELISA

4 Saran ( ( 18 - 20 ) , 0.1 M NaHCO<sub>3</sub> pH 8.0 1 μg  
 /mL Genzyme mAb 0.1 mL/ Immulon ( 2 .

, 4 Saran (F), 0.3 mL/

가 . 4 , rhTNF 0.1 mL/  
3 ( , ) .

1 37 .

. Genzyme - hTNF 1:200 0.1 mL/ 가.

. 1 µg/mL Jackson - IgG(H+L) - 0.1 mL/ 가 .

30 37 .

. 0.1 mL/ - ABTS 가 .

5 - 20 .

405nm OD .

12 :

Genzyme - TNF ( : 80 - 3399 - 01)

Genzyme - TNF ( : IP - 300)

Genzyme TNF ( : TNF - H)

Jacson Immunoresearch - - IgG (H+L) ( : 111 - 035 - 144)

Kirkegaard/Perry ABTS ( : 50 - 66 - 01)

Immulon 2 96 -

1X PBS 1mg/mL .

1 PBS 0.5 mL Tween (F) 20 .

:

TNF-α 방출의 억제

실시에 번호	마이크로몰 (µM) 로 나타낸 TNF-α 의 저해 백분율 또는 IC50 (µM)
--------	--

[ 평균 ]	
3	3.72% @ 10 μM (n=5)
7	IC <sub>50</sub> = >50 μM
4	-3.8% @10 (n=3) IC <sub>50</sub> = >50 μM
8	IC <sub>50</sub> = >50 μM
22	IC <sub>50</sub> = >29 μM
5	-10.8% @ 10 (n=3) IC <sub>50</sub> = >50 μM
23	IC <sub>50</sub> = >50 μM
24	IC <sub>50</sub> = >50 μM
25	IC <sub>50</sub> = 14.0 μM

가

가

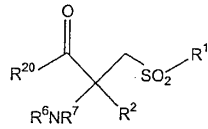
(57)

1.

A

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[ A ]



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R<sup>2</sup> , C<sub>1</sub> - C<sub>4</sub> , - C<sub>1</sub> - C<sub>4</sub> , C<sub>1</sub> - C<sub>4</sub> , - C<sub>1</sub> - C<sub>4</sub> ,  
 , C<sub>1</sub> - C<sub>4</sub> , C<sub>1</sub> - C<sub>4</sub> , (N - C<sub>1</sub> - C<sub>3</sub> )  
 , (N,N - - C<sub>1</sub> - C<sub>3</sub> ) ) , (N - ) , (N - ) (N - )

R<sup>1</sup> , SO<sub>2</sub> - , 5 -  
 6 - , R<sup>1</sup> , 6 -  
 SO<sub>2</sub> - 1 - 4 - 5 - SO<sub>2</sub> - 1 -  
 3,4 - 가 3 , 가 ) ;



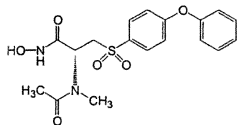






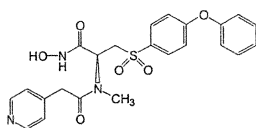
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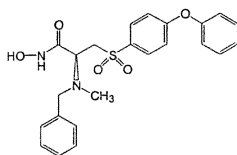
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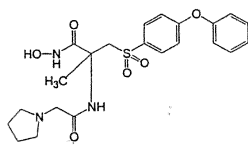
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6 , .



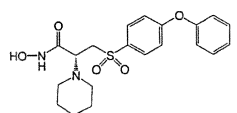
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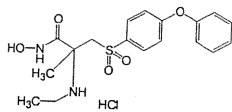
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6 , .



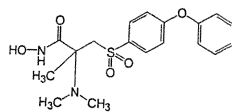
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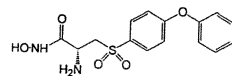
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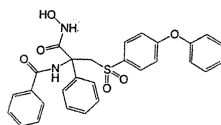
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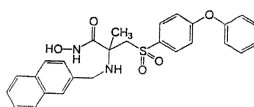
18.

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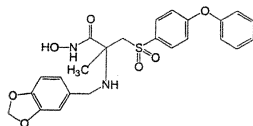
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6 , .



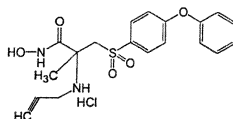
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6 , .



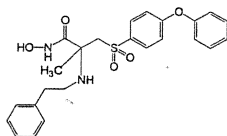
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6 , .



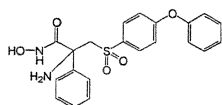
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6 , .



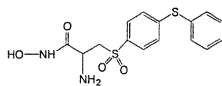
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6 , .



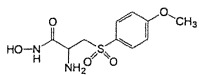
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6 , .



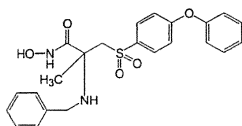
25.

6 , .



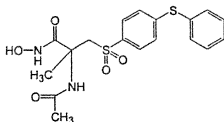
26.

6



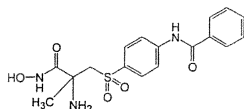
27.

6



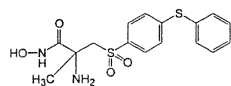
28.

6



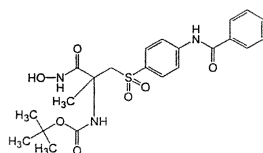
29.

6



30.

6













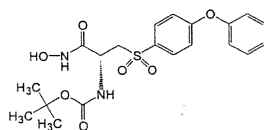


49.

45

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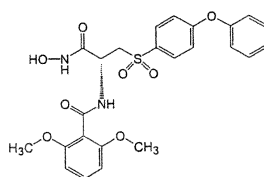


50.

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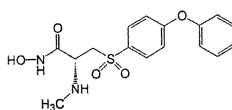


51.

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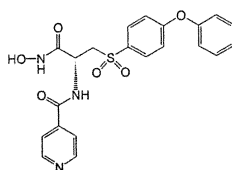


52.

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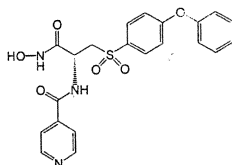


53.

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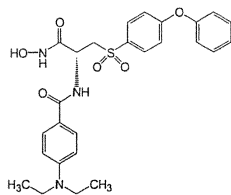


54.

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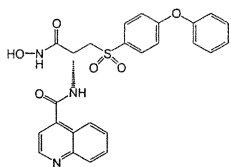


55.

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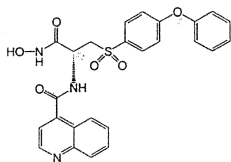


56.

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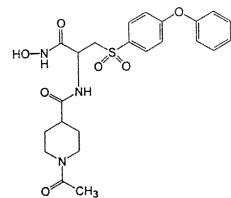


57.

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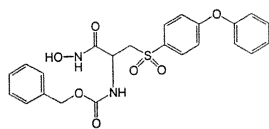


58.

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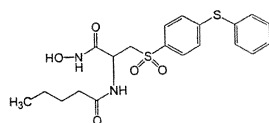


59.

37 , R<sup>1</sup> 가 4 - ( ) .

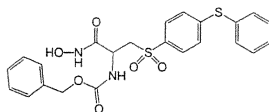
60.

59



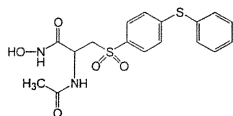
61.

59



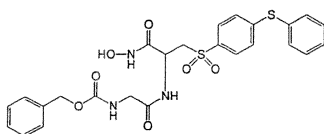
62.

59



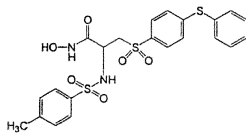
63.

59



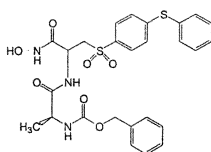
64.

59



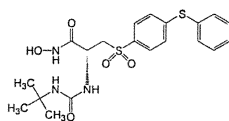
65.

59



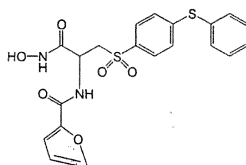
66.

59



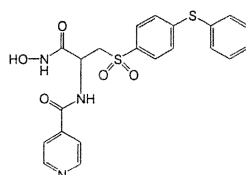
67.

59



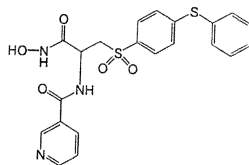
68.

59



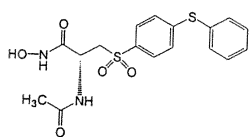
69.

59



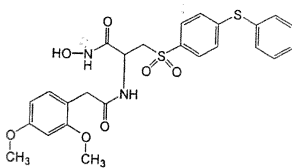
70.

59



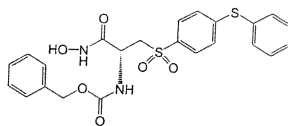
71.

59



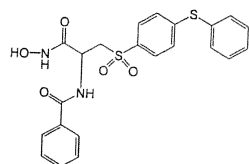
72.

59



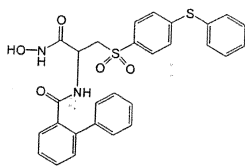
73.

59



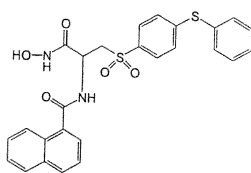
74.

59



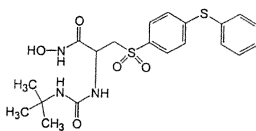
75.

59



76.

59



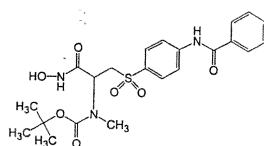
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37

R<sup>1</sup> 가 4 - ( )

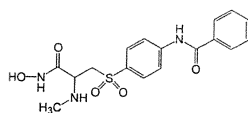
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77



79.

77

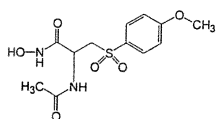


80.

35 , R<sup>1</sup> 가, -A-R-E-Y [ , A, E Y가 ]

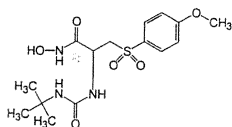
81.

80



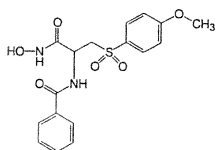
82.

80



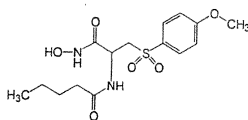
83.

80



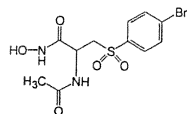
84.

80



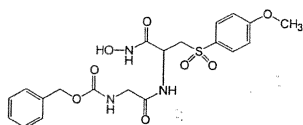
85.

80



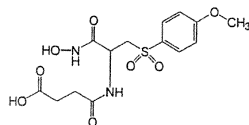
86.

80



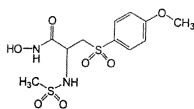
87.

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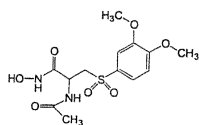
88.

80



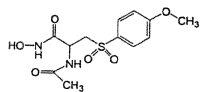
89.

80



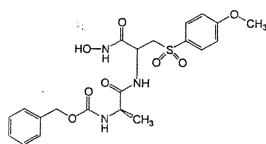
90.

80



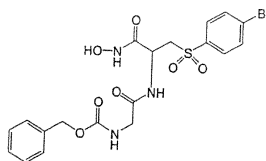
91.

80



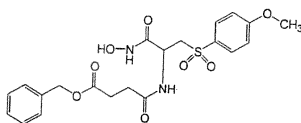
92.

80



93.

80



94.

B

(MMP)

MMP - 1  
MMP  
(MMP)

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[ B ]













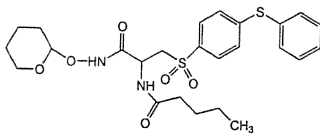


110.

98

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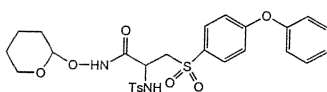


111.

98

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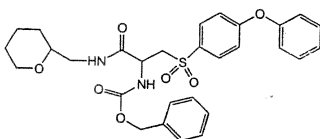


112.

98

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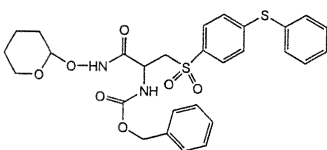


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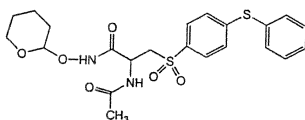


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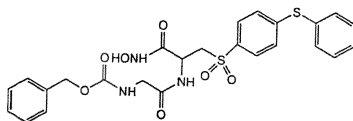


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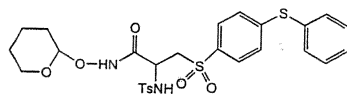


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