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(12) (A)

(51) 。 Int. Cl.<sup>7</sup>  
C07D 409/12

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10-2004-0063144  
2004 07 12

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2004 05 07

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WO 2003/041708

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(87)

2003 05 22

(30) 60/344,636 2001 11 09 (US)

(71) 06877 , 368 900

(72) 06877-0368 368 900

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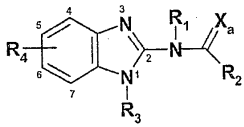
(74)

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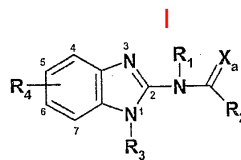
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> X<sub>a</sub>가

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2001 9 11 가 60/344,636

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R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> X<sub>a</sub>

Itk

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2 : (EGF) [ : S. Iwashita  
and M. Kobayashi, 1992, Cellular Signalling, 4, 123-132] [ : C. Chan et al., 1994,  
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T (Tsk) T -2 T (Itk) T  
xk, Tec, Btk Bmx Tec . Tec  
(PH), Tec (TH) Src SH3, SH2 SH1  
N C [ : S. Gibson et al., 1993, Blood, 82, 161-  
1572; J.D. Siliciano et al., 1992, Proc. Nat. Acad. Sci., 89, 11194-11198; N. Yamada et al., 1993 Biochem an  
d Biophys Res. Comm., 192, 231-240].

Itk T , T (TCR) T  
IgE . T , src  
Lck Itk Y511 [ : S.D. Heyeck et al., 1997, J. Biol. C

hem, 272, 25401-25408]. Zap-70 Itk PLC- [ : S. C. Bunnell et al., 2000, J. Biol. Chem., 275, 2219-2230]. PLC- PKC 1,4,5- ( ) (T ) [ : Y. Kawa kami et al., 1999, J. Leukocyte Biol., 65, 286-290].

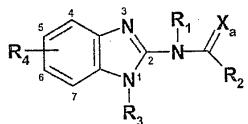
T Itk Itk . Itk CD4 + T Con A -CD3 [ : X.C. Liao and D.R. Litt man, 1995, Immunity, 3, 757-769]. Itk T TCR IL-2 , Itk CD4 + T (IL-4, IL-5 IL-13) [ : D.J. Fowell, 1999, I mmunity, 11, 399-409]. TCR

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Itk Itk 가 T 가 [ : A.T. Miller et al., 2002 The Journal of Immunology, 168, 2163-2172]. 가 T 가 [ : S.M. Kaech et al., Nature Reviews Immunology, 2, 251-262].



R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> X<sub>a</sub>

Itk

Tec

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$R_3$ ,  $L$ ,  $R_b$ ,  $-O-C(O)-$ ,  $-C(O)-$ ,  $-S(O)_m-$ ,  $C_{1-10}$ ,  $R_3$ ,  $-(CH_2)_n-L-R_6$   
 $R_b$ ,  $R_6$ ,  $C_{0-5}$ ,  $C_{3-7}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{0-5}$ ,  $C_{0-5}$   
 $C_{0-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{0-5}$ ,  $C_{0-5}$

$R_5$ 가,  $C_{1-5}$ ,  $C_{0-5}$ ,  $C_{3-7}$ ,  $C_{0-5}$ ,  $C_{0-5}$ ,  $R_5$ ,  $R_c$

$R_a, R_b, R_c$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{2-5}$ ,  $C_{2-5}$ ,  $C_{3-8}$ ,  $C_{1-5}$ ,  $C_{1-5}$   
 $C_{1-5}$ ,  $C_{1-5}$ ,  $($ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $R_a, R_b, R_c$ 가,  $C_{1-5}$ ,  $1$

$R_7$ ,  $C_{3-10}$ ,  $C_{1-5}$ ,  $X_a, X_b$ 가,  $I$

$R_2$ 가,  $($ ,  $R_a$ ,  $)$ ,  $R_2$

$R_6$ ,  $C_{0-5}$ ,  $C_{3-7}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{0-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$ ,  $C_{1-5}$

$n$  0 6

$R_5$ 가,  $C_{1-5}$ ,  $C_{3-7}$ ,  $C_{0-5}$ ,  $C_{0-5}$ ,  $C_{0-5}$ ,  $R_5$ ,  $R_c$

$R_7$ ,  $C_{1-3}$ ,  $I$

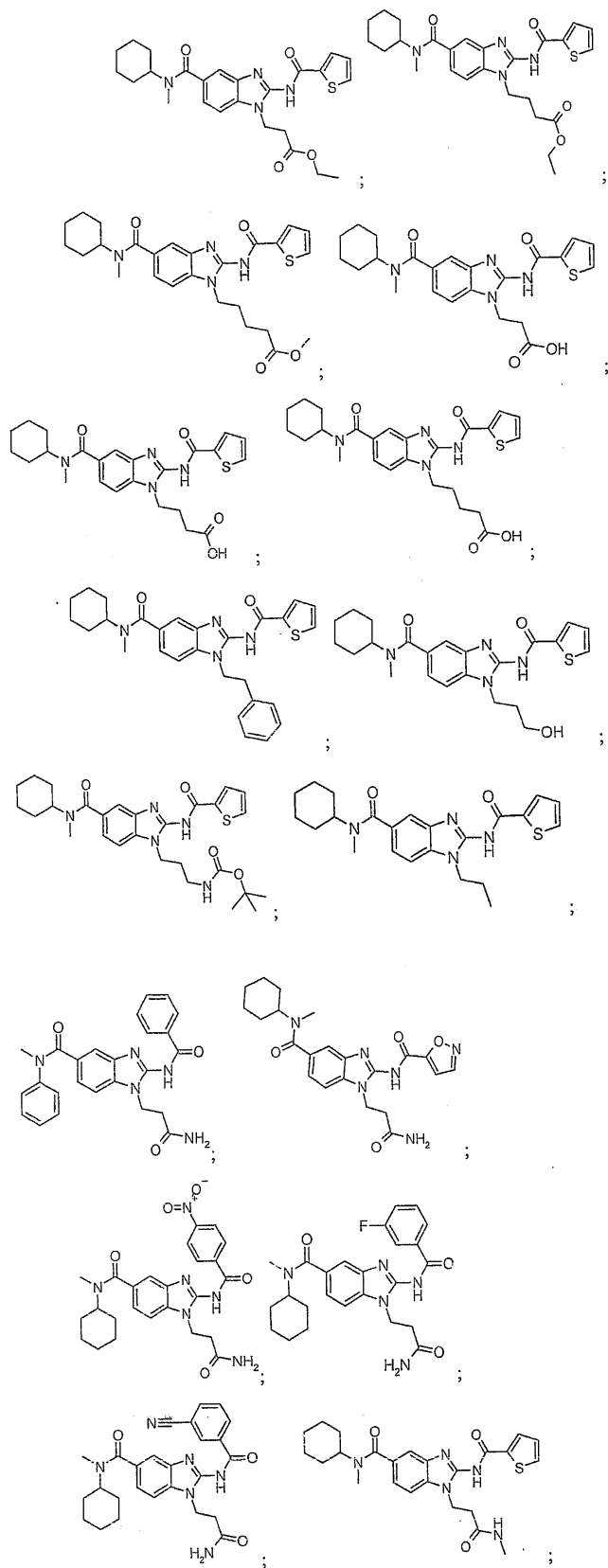
$R_2$ 가,  $($ ,  $R_2$ ,  $R_a$ ,  $)$

$R_3$ ,  $-(CH_2)_n-C(O)-R_6$ ,  $-(CH_2)_n-R_6$ ,  $R_6$ ,  $C_{1-5}$ ,  $C_{1-5}$   
 $C_{0-5}$ ,  $C_{3-7}$ ,  $C_{1-5}$ ,  $C_{1-5}$

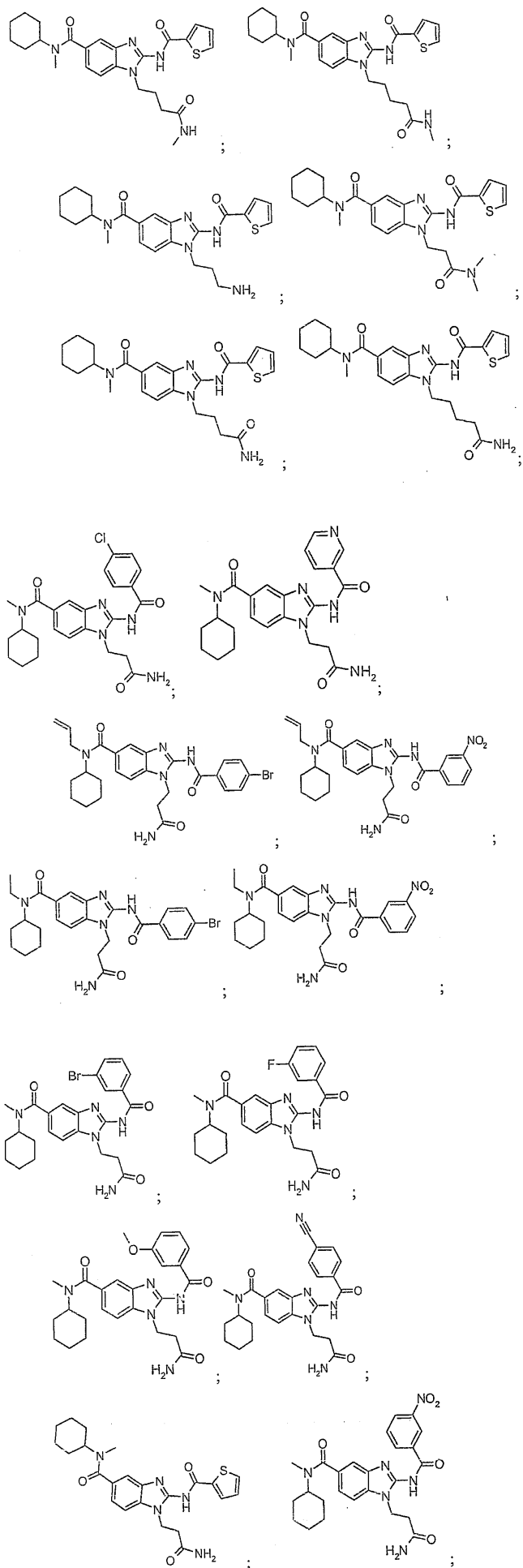
$R_5$ 가,  $C_{3-7}$ ,  $C_{0-5}$ ,  $R_c$

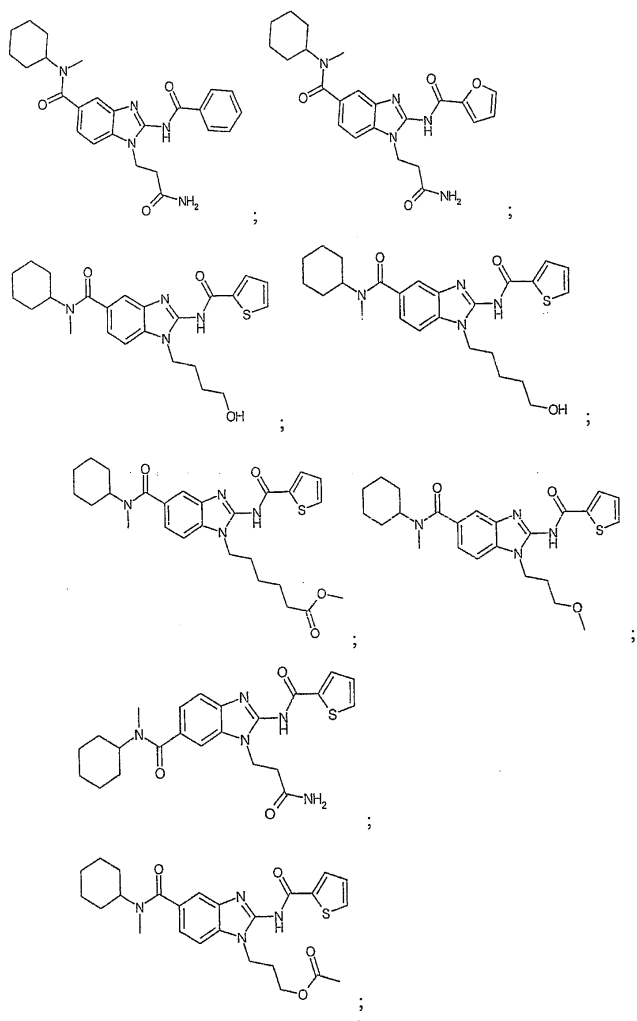


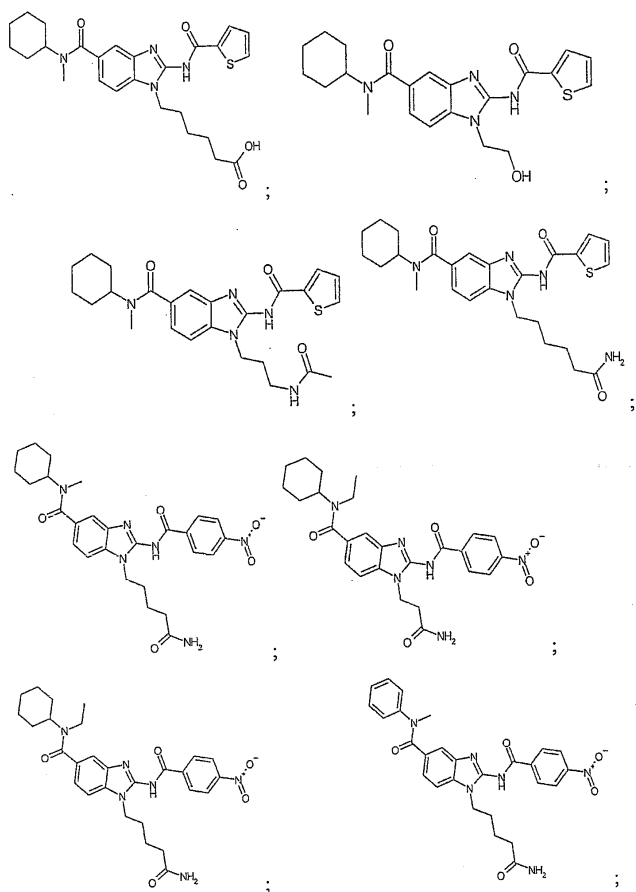














BOC t-BOC 3 -

t-Bu 3 -

DMF

EtOAc

EtOH MeOH

TFA

THF

DMSO

TBTU O-(1H- -1- )-N,N,N',N'-

Fmoc 9-

3 12  
3 10

8 11 4 8 ( , 5 6 )

1 4

11 N, O S 1 4 5 8 8

O, N, S P

, N NH 가 가 O, S N

-CH<sub>2</sub>- >C=O

4

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

-S(O)<sub>2</sub>-C<sub>1-6</sub> -S-C<sub>1-6</sub>

-CH<sub>2</sub>CHF<sub>2</sub> -CF<sub>3</sub>

가

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(

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-p-

-2-

가

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( , ), ( , ), N-(C<sub>1</sub>-C<sub>4</sub>)<sub>4+</sub>

가

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Txk, Tec, Btk  
Tec

Bmx

ltk

Tec

(COPD), (ARDS), Itek  
 Itek Tec  
 Itek 가 T 가 T  
 가 가 가 T  
 가 가 가  
 가 가  
 5% (w/w) 20% ( )

[ : H.C. Ansel and N.G. Popovich, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger(1990)]

가 70kg  
 1 1000mg/ 1 가 5  
 , 2000mg 가 가

Itek  
 Itek GST-  
 Glu<sub>4</sub>:Tyr<sub>1</sub> (PGTYR) DELFIA(Dissolution Enhanced Lanthanide Fluoroimmunoassay)  
 (Zymark Allegro) UHTS  
 (50mM HEPES, pH 7.0, 25mM MgCl<sub>2</sub>, 5mM MnCl<sub>2</sub>, 50mM KCl, 100 μM Na<sub>3</sub>VO<sub>4</sub>, 0.2% BSA, 0.01% CHAPS, 200 μM TCEP)  
 ( 3μg/ml 1 3 9 ) 384  
 가  
 TYR- (CIS Biointernational) 10 μL( / ) 15 μM ATP 9ng/ μL PG 384  
 (PIERCE) 가 20 μL/ 20 μL/ (7nM ) 가  
 20 μL 가 30  
 100 μL (50mM -HCl, pH 7.4, 150mM NaCl, 0.05% 20, 0.2% BSA) 3 . 50mM -HCl, pH 7.8, 150mM NaCl, 10 μM DTPA, 0.05% 40, 0.2% BSA, 0.05% BGG(1nM ) 50 μL (Eu<sup>3+</sup> -PT66, Wallac C R04-100) 가 30 , 100 μL

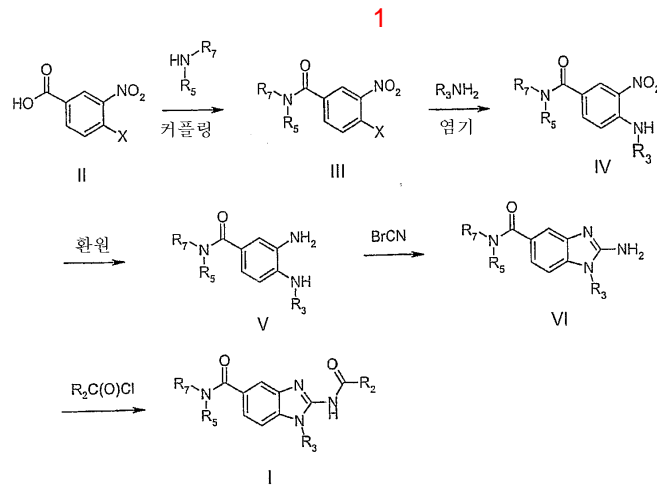
4 DELFIA (Wallac) 50  $\mu$  L 가 . 15 , 250 $\mu$ s  
 LJL (360nm , 620nm , EU400 Dichroic Mirror)  
 1  $\mu$  M

가

가

R I I R

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, X,

(II) R<sub>5</sub> R<sub>7</sub>

1(3-

)-3-

(EDC)  
DMSO

V

, R<sub>5</sub> R<sub>7</sub> NH

II

IV

EtOH

2-

VI

EtOH

R<sub>2</sub>

VI

I 가  
p-

. 6-

R<sub>4</sub>

R

가

2-  
-2638]

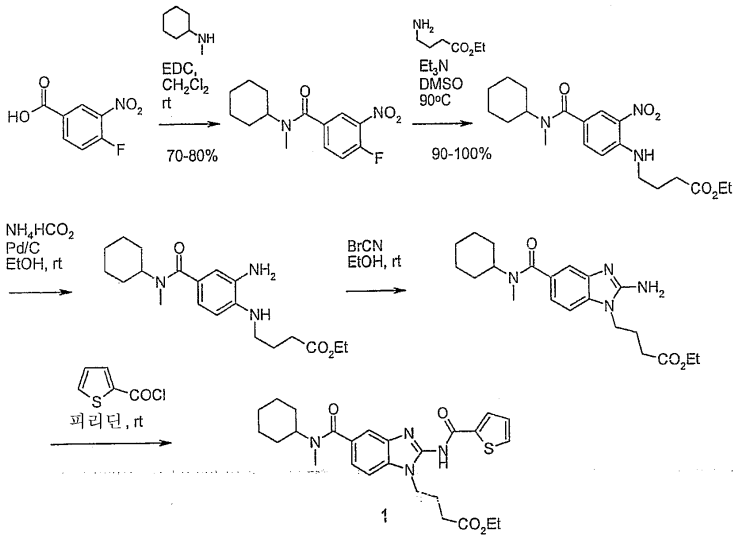
[ : J. Lee et al., Tetrahedron Letters, 2001, 42, 2635  
2

DMF

MeOH  
LC-MS







CH<sub>2</sub>Cl<sub>2</sub> (30ml) 4- -3- (6g, 0.32mmol) 1-[3-( )]-3-  
 ) 가 6 (8g, 0.42mmol) 가 N- (4.2ml, 0.32mmol)  
 (10ml) 1N HCl(10ml)  
 : 65 67 ) 100% EtOAc  
 (6.0g, 67%)

DMSO(25ml) (2g, 7.1mmol), 4- (2.4g, 14.2mmol)  
 (2.5ml, 18.0mmol) 8 80 가 (150ml)  
 (150ml) 4-[4-(N- -N- - )-2- - ]- (2.8g  
 , 100%)

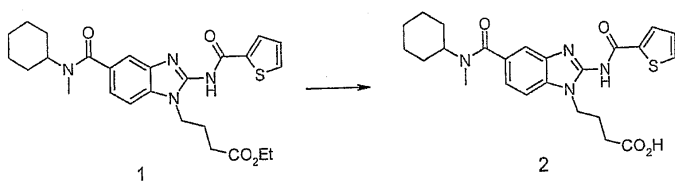
H(25ml) (2.2g, 5.6mmol) 가 (0.22g) 10% EtOH(5ml) 가 EtO  
 32 4-[2- -4-(N- -N- - )- ]- (3.9g, 61.8mmol) 가  
 EtOH 25ml

(0.9g, 8.4mmol) 가 24  
 EtOAc(20ml) (10ml) 5 50% MeOH/  
 ]- (0.7g, 32%) 4-[2- -5-( - )- ]- -1-

(10ml) 가 6 (0.7g, 1.8mmol) 2- (0.41ml, 3  
 .8mmol) 가 1% MeOH/  
 (0.61g, 67%)( : 82 84 )

2

4-{5-( - - )-2-[( -2- )- ]- -1- }-

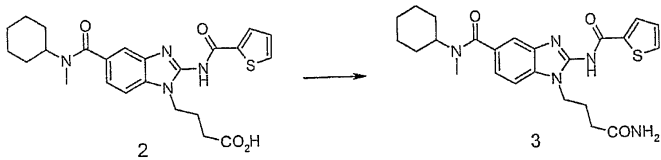


MeOH(10ml) (10ml) 4-{5-(N- -N- - )-2-[( -2- )- ]-

가 . -1- }- ( 1)(0.5g, 1.0mmol) NaOH(0.12g, 3mmol)  
 . 4 . 1N HCl CH<sub>2</sub>Cl<sub>2</sub> (20ml)  
 . 10% MeOH/  
 (0.43g, 92%)( : 256-258 ) .

3

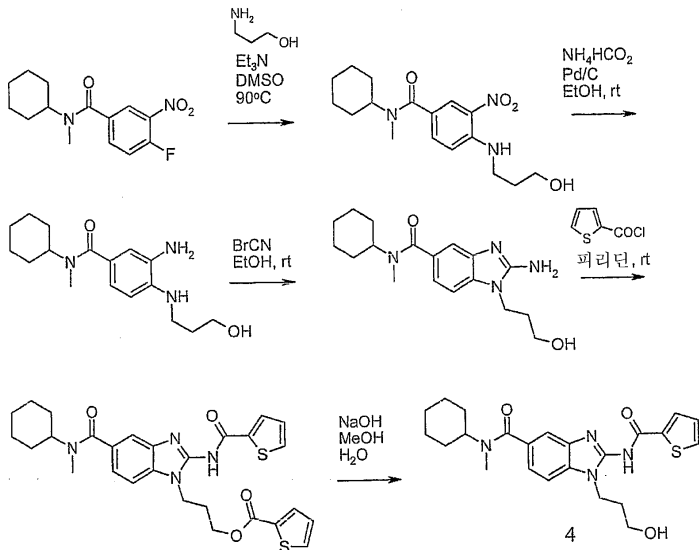
1-(3- )-2-[( -2- )- ]-1H- -5- -N- -N-



DMF(5ml) 4-{5-(N- -N- - )-2-[( -2- )- ]- -1- }  
 - ( 2)(0.05g, 11mmol) 1- (0.02g, 16mmol) 가  
 1-[3-( ) ]-3- (0.03g, 16mmol) 가  
 1 (5ml) 가 . 48 1M HCl  
 EtOAc(10ml) (10ml) (10ml) (3 x 10ml)  
 5% MeOH/ (0.02  
 g, 40%)( : 112 115 ) .

4

1-(3- - )-2-( -2- ) -1H- -5- - -



DMSO(25ml) N- -N- -4- -3- - ( 1)(1.5g, 5.3mmol) 3-  
 -1- (0.82ml, 10.7mmol) 8 80 가 . (100  
 ml) (100ml) (5 x 50ml)  
 N- -4-(3- - )-N- -3- (1.9g, 79%)

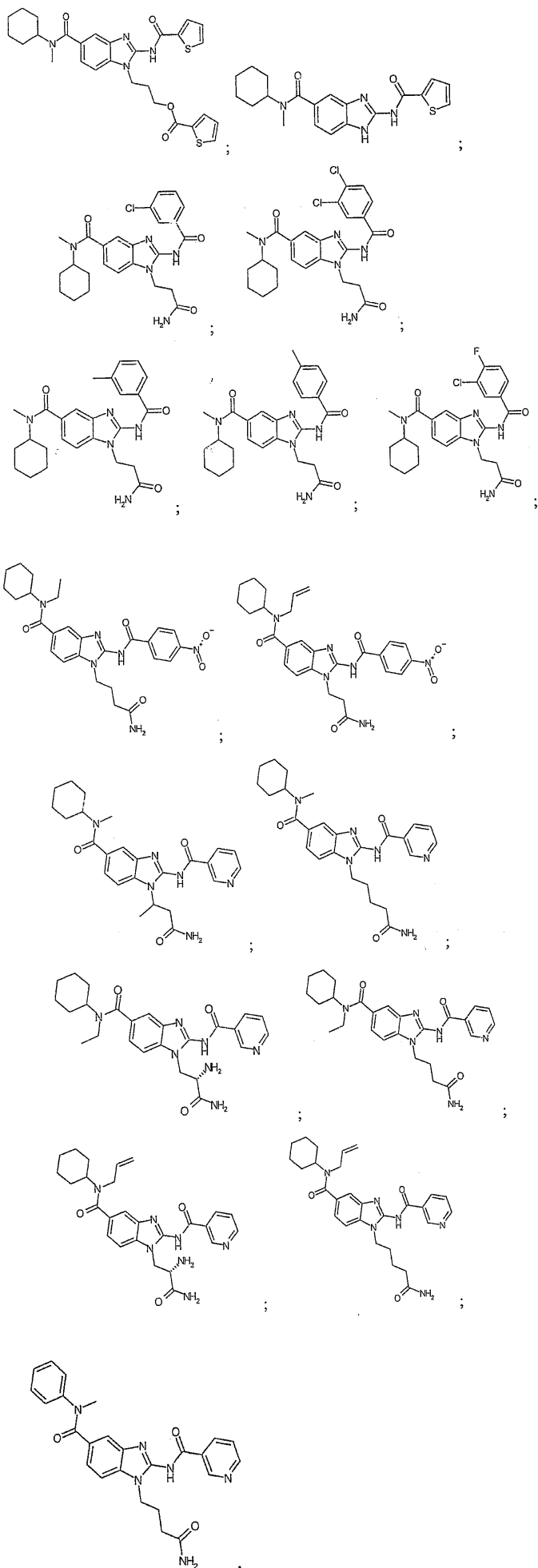
H(15ml) (1.9g, 5.7mmol) 가 10% (0.19g) EtOH(5ml) 가 . EtO  
 7 (3.9g, 62mmol) 가  
 . 3- -N- -4-(3- )-N- - 15ml

(0.9g, 8.6mmol) 가 48  
 EtOAc(20ml) (10ml) (10ml)  
 , 5 50% MeOH/  
 )-1H- -5- N-  
 -N- (0.7g, 37%) 2- -1-(3-  
 (10ml) (0.7g, 2.1mmol) 2- (0.68ml, 6  
 .4mmol) 가 6 , 1% MeOH/  
 -2- )- ]- -1- }- -2- 3-{5-( )-2- [(  
 (0.50g, 43%)( 92 94 )  
 MeOH(5ml) (5ml) (0.4g, 0.72mmol) NaOH(0.12g, 2.9mmol)  
 가 6 1M HCl EtOAc(10ml)  
 (0.09g, 28%)( : 105 107 ) 5% MeOH/  
 5  
 3-{5-( - - )-2- [( -2- )- ]- -1- }-  
 THF(10ml) 1-(3- - )-2- [( -2- )- ]-1H- -5-  
 (0.02ml, 0.17mmol) 가 (0.07g, 0.16mmol) 가 (0.02ml, 0.19mmol) 가  
 0ml) 48 1M HCl(1  
 (0.05g, 65%)( : 74 76 ) 5% MeOH/  
 I  
 6  
 2- -1-( - )-1H- -5-  
 (100mg, 0.52mmol/g, 0.052mmol) 가 , DMF(20ml) 가  
 가 10 . TBTU(83mg, 0.26mmol) N,N- (90μl, 0  
 .52mmol) 1 가 Fmoc- (81mg, 0.26mmol) 가  
 24 DMF, MeOH (20ml , 10 )  
 3  
 Fmoc 3 20ml 1:1 DMF: DMF, MeOH (20ml , 10 ) 3  
 Fmoc  
 , DMSO(20ml) 10 4- -3- (48mg, 0.  
 26mmol) N,N- (90μl, 0.52mmol) 가 , 24  
 3 DMF 3 , DMF:H<sub>2</sub>O(1:1) 1 (20ml )  
 , DMF(20ml) 10 - -  
 (PyBroP)(121mg, 0.26mmol), (90μl, 0.52mmol) N-  
 (34μl, 0.26mmol) 가 , 24  
 DMF, MeOH (20ml , 10 ) 3  
 LC-MS  
 DMF(20ml) SnCl<sub>2</sub> 2.0M 가 24  
 DMF, MeOH (20ml , 10 ) 3 |  
 LC-MS



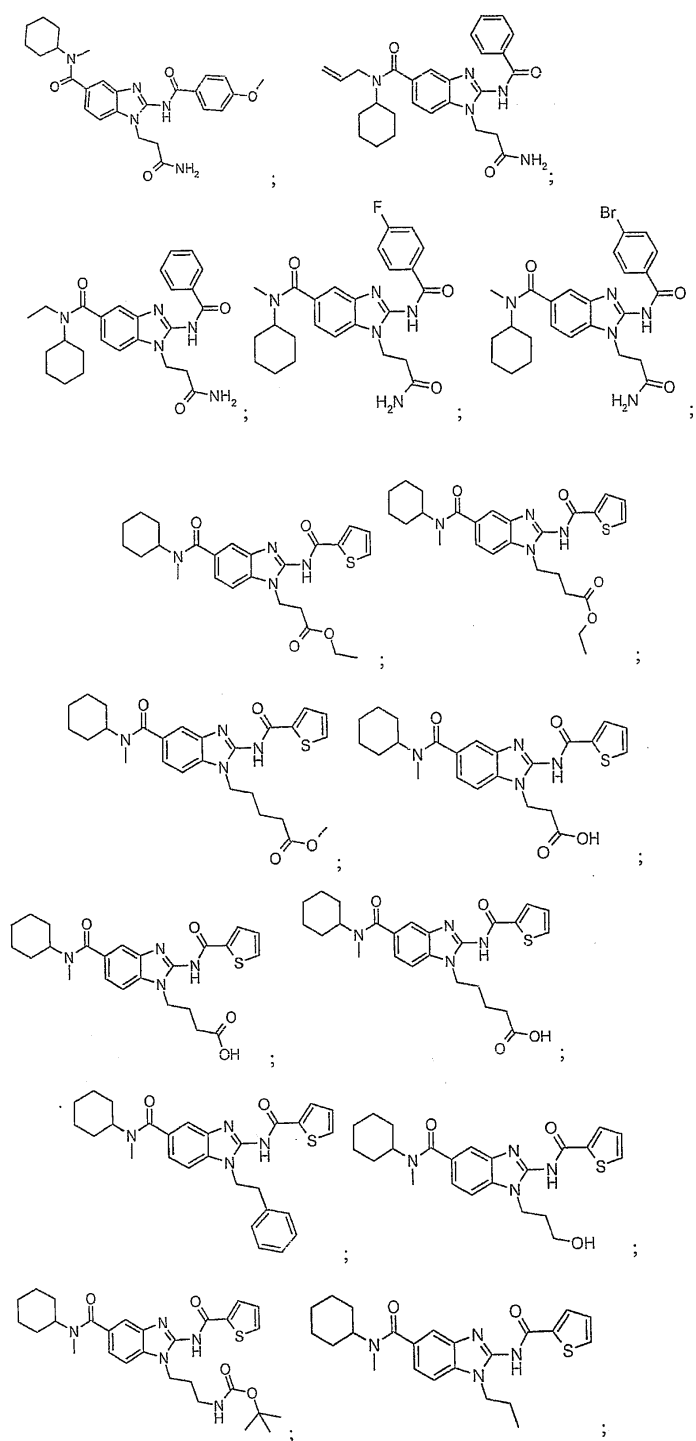


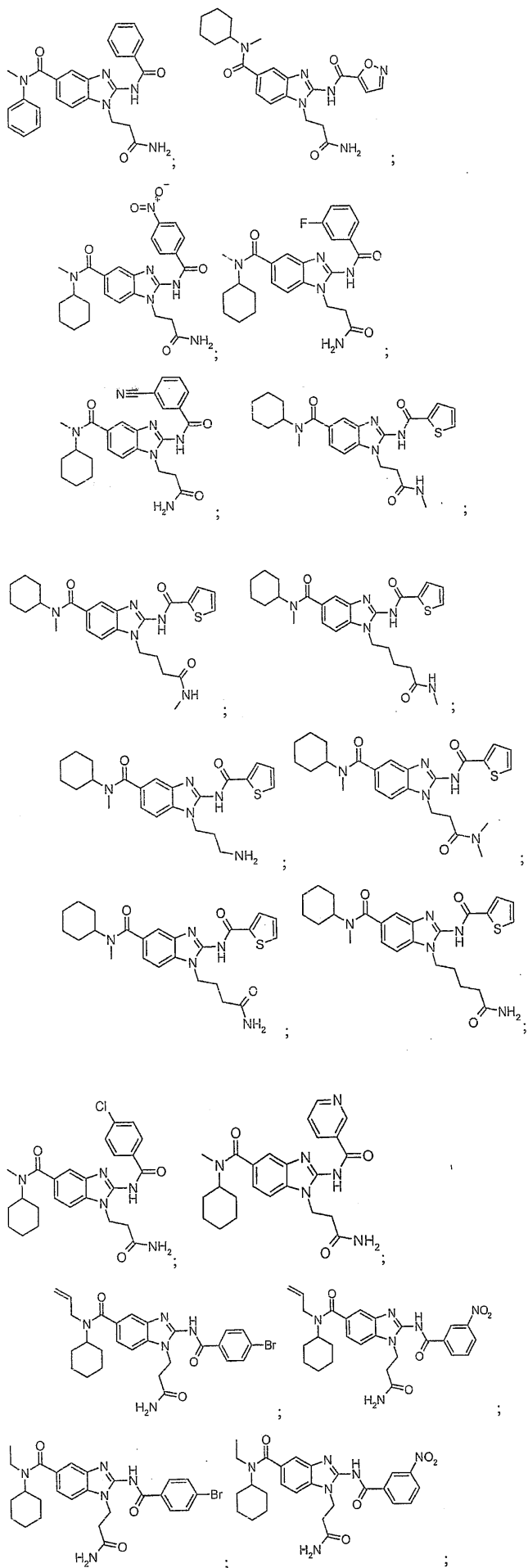


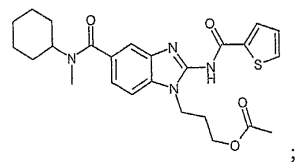
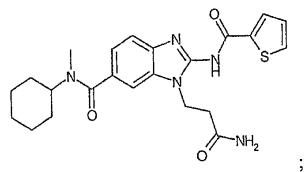
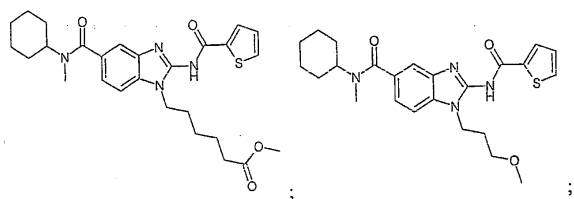
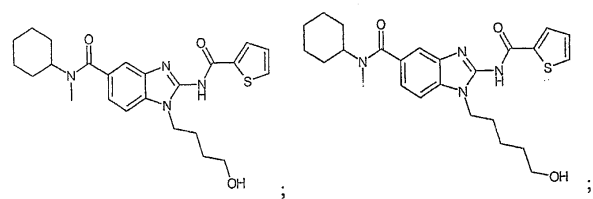
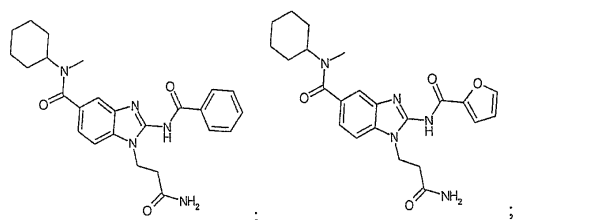
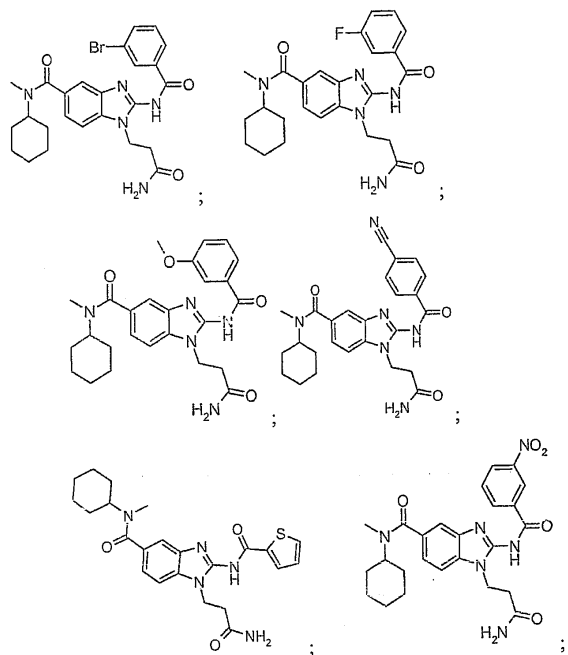


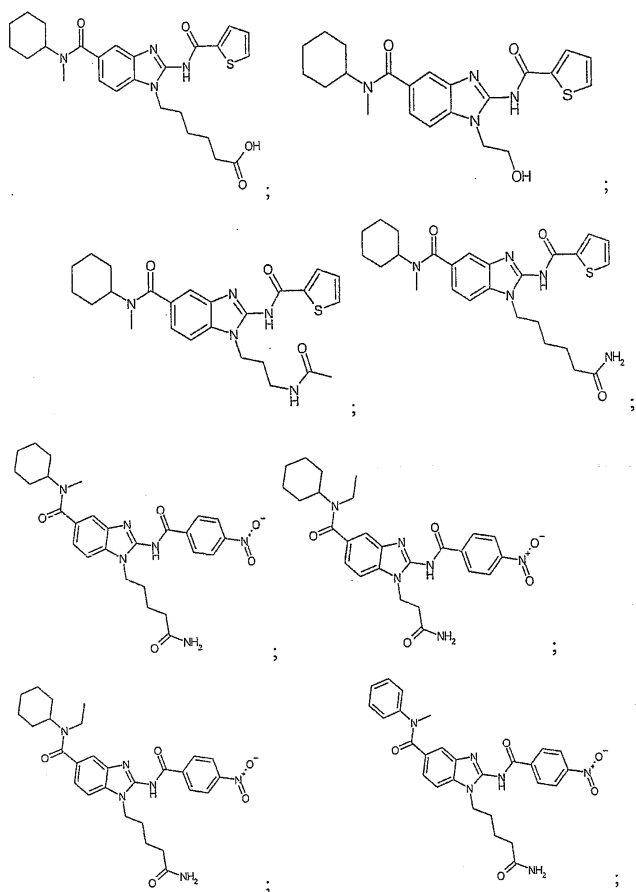


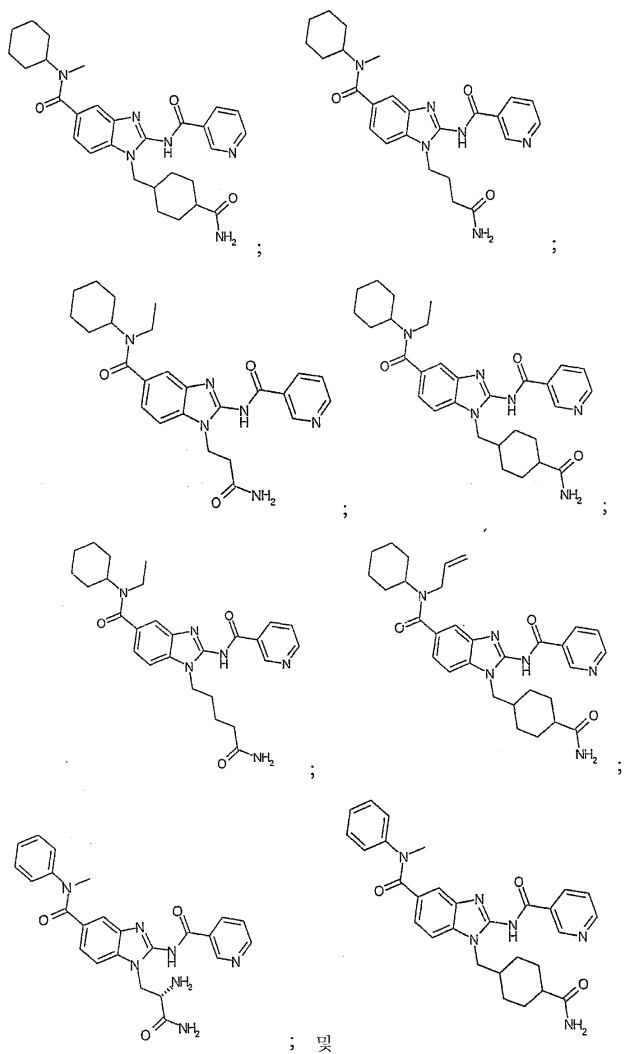
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(COPD),

(ARDS),

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X가

(II) R<sub>5</sub> R<sub>7</sub>

III

III

R<sub>3</sub>

IV

IV

R<sub>2</sub>

VI

V

VI 2-

, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> R<sub>7</sub> 1

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