

(19)  
(12)(KR)  
(A)(51) . Int. Cl.<sup>7</sup>  
C07D 401/06  
C07D 237/02(11)  
(43)10-2005-0009735  
2005 01 25

(21)	10-2004-7019787		
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(86)	PCT/EP2003/004930	(87)	WO 2003/104204
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(30) 10224888.5 2002 06 05 (DE)

(71) 64293 250

(72) - 64287 49

64297 59

(74)

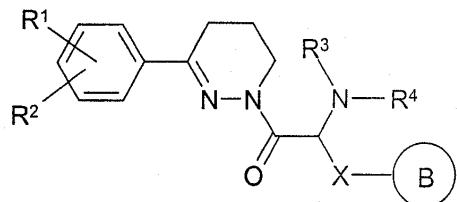
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(54)

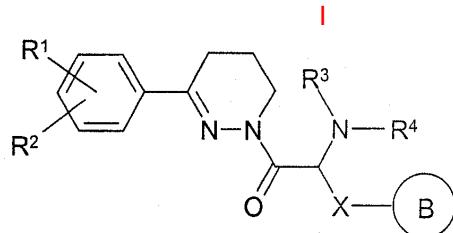
I , IV , , , , , , , , AIDS

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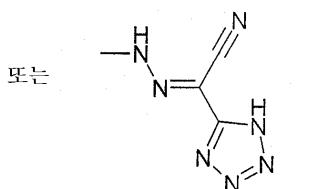
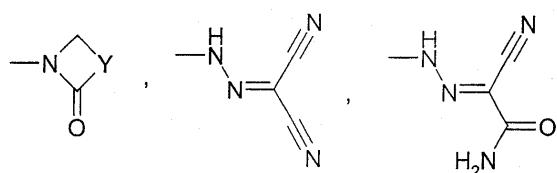
[ I ]



가



( ),

R<sup>1</sup> R<sup>2</sup> , , H, OH, OR<sup>8</sup>, -SR<sup>8</sup>, -SOR<sup>8</sup>, -SO<sub>2</sub>R<sup>8</sup> Hal ,R<sup>1</sup> R<sup>2</sup> -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>O- ,R<sup>3</sup> H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NCOA'R<sup>9</sup> NCOOA'R<sup>9</sup> ,R<sup>4</sup> H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup> CON(A'R<sup>9</sup>)(A''R<sup>9</sup>) ,B R<sup>5</sup>, R<sup>6</sup> / R<sup>7</sup> , ,X CH<sub>2</sub> / 가 O, S, SO, SO<sub>2</sub>, NH / 1 2 H / 11 / 12 , 1 7 , H 1  
가 F / Cl 10 2 8 , ,R<sup>5</sup>, R<sup>6</sup> R<sup>7</sup> , , H, A'R<sup>9</sup>, OH, OA'R<sup>9</sup>, NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NHC OA'R<sup>9</sup>, NHCOOA'R<sup>9</sup>, NHCONH<sub>2</sub>, NHCONHA'R<sup>9</sup>, NHCON(A'R<sup>9</sup>)(A''R<sup>9</sup>), Hal, C00H, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>),R<sup>8</sup> A, 3 7 4 8 , ,R<sup>9</sup> H, COOH, COOA, CONH<sub>2</sub>, CONHA, CONAA', NH<sub>2</sub>, NHA, NAA', NCOA, NCOOA, OH, OA, (CH<sub>2</sub>)<sub>n</sub> -(CH<sub>2</sub>)<sub>n</sub>Het ,R<sup>10</sup> , , CH<sub>2</sub> / 가 O, S, SO, SO<sub>2</sub>, NH, NMe, NET / -CH=CH- , 1 H / 1 / 1 H 가 R<sup>9</sup>  
H / 1 / 1 H 가 R<sup>9</sup>

2 , 1 10 , 3 7 , 4 8  
 2 8 ,

R<sup>11</sup> H, A, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>),  
 NCOA'R<sup>9</sup>, NCOOA'R<sup>9</sup>, OH OA'R<sup>9</sup>,

R<sup>12</sup> H, A, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup> CON(A'R<sup>9</sup>)(A''R<sup>9</sup>) ,

Y , CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH NR<sup>10</sup> / , 1 7  
 H 가 F / Cl , 1 10 2 8 ,

A A' / , 1 7 , H , CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH NR<sup>10</sup>  
 2 8 , Het , Cl , 1 10

A A' , 2 7 CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH, NR<sup>10</sup>, NCOR<sup>10</sup> NCOO  
 R<sup>10</sup> ,

A' A'' , 1 7 , H , CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH , 1 10  
 0 , 2 8 / 3 7 Het , Cl , ,

A' A'' , 2 7 CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH, NR<sup>10</sup>, NCOR<sup>10</sup> NCO  
 OR<sup>10</sup> ,

Hal, R<sup>14</sup>, OR<sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, C00R<sup>13</sup>, CON(R<sup>13</sup>)<sub>2</sub>, NR<sup>13</sup> COR<sup>13</sup>, NR<sup>13</sup> CON(R<sup>13</sup>)<sub>2</sub>, NR<sup>13</sup> SO<sub>2</sub> A, COR<sup>13</sup>, SO<sub>2</sub> N(R<sup>13</sup>)<sub>2</sub> S(O)<sub>m</sub> R<sup>14</sup>,  
 , , , ,

R<sup>13</sup> H 1 6 ,

R<sup>14</sup> 1 6 ,

Het , Hal, R<sup>14</sup>, OR<sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, C00R<sup>13</sup>, CON(R<sup>13</sup>)<sub>2</sub>, N  
 R<sup>13</sup> COR<sup>13</sup>, NR<sup>13</sup> CON(R<sup>13</sup>)<sub>2</sub>, NR<sup>13</sup> SO<sub>2</sub> R<sup>14</sup>, COR<sup>13</sup>, SO<sub>2</sub> NR<sup>13</sup> / S(O)<sub>m</sub> R<sup>14</sup>,  
 , 1 2 N, O / S , ,

Hal F, Cl, Br I ,

m 0, 1 2 ,

n 0, 1, 2, 3 4 ).

1995)}  
 4099

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{J. Med. Chem. 38, 4878 (1995), EP 0 922 036, EP 1 124 809 WO 01/0

가 .

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가

I cAMP 가  
al., Nature Medicine, 1, 244-248 (1995)). PDE IV  
a 797, 354-362 (1984)) .  
IV (N. Sommer et  
(C.W. Davis in Biochim. Biophys. Act  
IV  
 $IC_{50}$  ( 50% )

Torphy et al. in Thorax, 46, 512-523 (1991)} . PDE IV , , {T. Olsson, Acta allergologica 26, 438-447 (1971)} . , , {T.J.

cAMP (S. Kasugai et al., M 681, and K. Miyamoto, M 682, in Abstracts of the American Society for Bone and Mineral Research, 18<sup>th</sup> Annual Meeting, 1996),

TNF ( ) , 가

,  
{N. Sommer et al., Nature Medicine 1, 244-248 (1995),  
. Immunol. 100, 126-132 (1995)}  
가  
L. Sekut et al., Clin. Exp.

TNF-<sup>(P.)</sup>  
Costelli et al., J. Clin. Invest. 95, 2367ff. (1995); J.M. Argiles et al., Med. Res. Rev. 17, 477 ff. (1997)).

PDE IV  
ophys. 28, 75 ff. (1998)).  
7 399 WO 96 00 215

PDE IV

(D. Marko et al., Cell Biochem. Bi  
, WO 95 35 281, WO 95 1

PDE IV (W. Fischer et al., Biochem. Pharmacol. 45, 2399ff. (1993)).

AIDS

PDE I

가

(PDE IV )

WO 01/57025

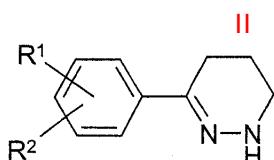
PDF IV

, , PDE IV (isozy  
me) , |  
가 .

WO 01/57025 , I

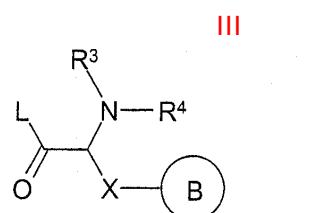
I PDE IV 가 . PDE IV , PDE IV  
 pro-inflammatory) 3',5'- (cAMP) 가 . cAMP  
 , . cAMP , , PDE IV (superoxide) , , ,  
 (TNF) PDE

a)



$$(\quad, R^1 \quad R^2)$$

1 )



( $\text{Cl}, \text{Br}, \text{I}$ )  
1

$\text{OH} / \text{OH}$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{X}$  B).

b) b) i)

ii) OH

iii)  
/ B  
|

R 1 , R 2 R 3 | R 4 / B

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>

( ),

가

가

(prodrug)

{Int. J. Pharm. 115, 61-67 (1995)}

Abu 4-

Aha 6- , 6-

Ala

Asn

Asp

Arg

Cys

Dab 2,4-

Dap 2,3-

Gln

Glp

Glu

Gly

His

homo-Phe -

Ile

Leu

Lys

Met

Nle

Orn

Phe

Phg

4-Hal-Phe 4-

Pro

Ser

Thr

Trp

Tyr

Val .  
:  
Ac  
BOC tert-  
CBZ Z  
DCCI  
DMF  
EDCI N - - N,N' - ( )  
Et  
FCA  
FITC  
Fmoc 9-  
FTH  
HOBt 1 -  
Me  
MBHA 4-  
Mtr 4 - - 2,3,6-  
HONSu N -  
OBut tert-  
Oct  
OMe  
OEt  
POA  
Sal  
TFA  
Trt ( ).  
1

, , R 1 , R 2 , R 3 , R 4 , X, B L I, II III







$R^1 R^2$  -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>-O-,  
 $R^3$  H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NCOA'R<sup>9</sup> NCOOA'R<sup>9</sup>,  
 $R^4$  H ,  
X , , , ,  
A' A'' , , , 1, 2, 3 4 ,  
R<sup>9</sup> H, (CH<sub>2</sub>)<sub>n</sub> - (CH<sub>2</sub>)<sub>n</sub> Het ;  
Ij ,  
R<sup>1</sup> R<sup>2</sup> , , H, , , , , , , , , F,  
Cl,  
R<sup>1</sup> R<sup>2</sup> -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>-O-,  
R<sup>3</sup> H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NCOA'R<sup>9</sup> NCOOA'R<sup>9</sup>,  
R<sup>4</sup> H ,  
X , , , ,  
A' A'' , , , 1, 2, 3 4 ,  
R<sup>9</sup> H, (CH<sub>2</sub>)<sub>n</sub> - (CH<sub>2</sub>)<sub>n</sub> Het ,  
OR<sup>13</sup> , , , , , , , , , , , , ,  
R<sup>13</sup> H 1 6 ,  
Het , N- , , , , , , , , , , , , ,  
B OR<sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, O- -N(R<sup>13</sup>)<sub>2</sub> 0- -OH ,  
;  
Ik ,  
R<sup>1</sup> R<sup>2</sup> , , , , , , ,  
R<sup>3</sup> H, , , , tert- , , , N,N-  
, , ,  
R<sup>4</sup> H ,  
X , , , ,  
R<sup>13</sup> H 1 6 ,  
Het ,

B OR  $^{13}\text{C}$ , N( $^{13}\text{C}$ )<sub>2</sub>, O- - N( $^{13}\text{C}$ )<sub>2</sub> O- - OH ,

I , , ( , Houben-Weyl, Methoden der organischen Chemie[ ], Georg-Tieme-Verlag, Stuttgart )

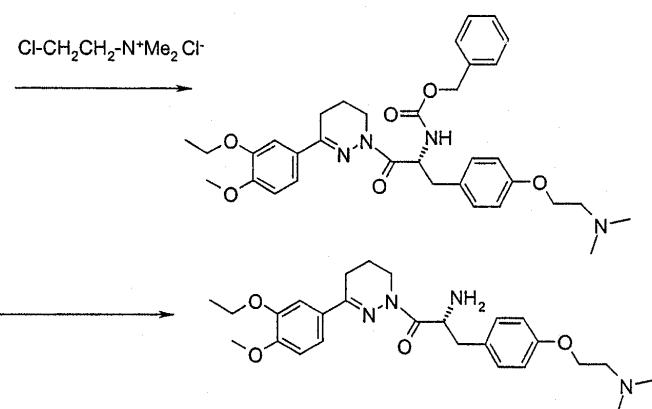
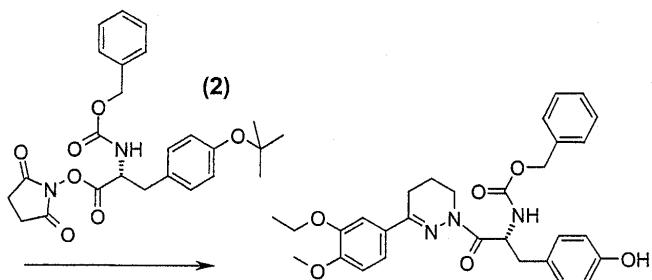
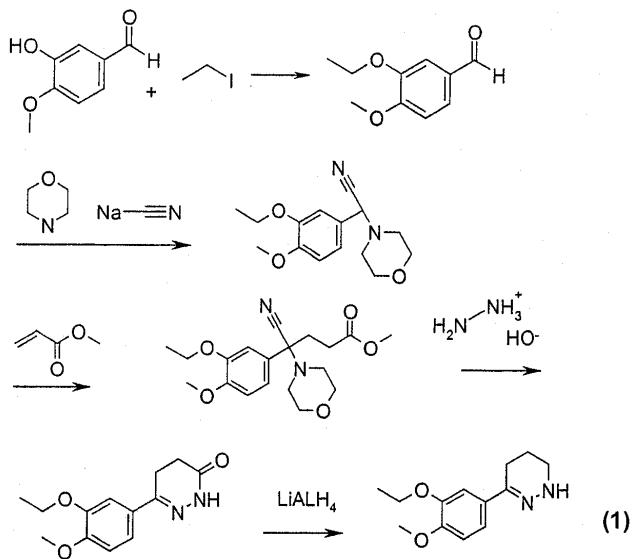
II III , R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X B , 가 .

|| . ,

III OH , L Cl, Br, I 1 6 ) . ( - p- ( , Houben-Weyl, Methoden der organischen Chemie[ ], Georg-Tieme-Verlag, Stuttgart )

, HOBt N- 가

| , : |



, -20 °, 150 °, 20 °, 100 °, ,

, , , , ; ; ; , , , , 1,2  
 , n- , n- tert- ; ; ; ; ; ; ;  
 (THF) (DMF) (DMSO) ; ; ; ; ; ; ;

| 가 가

가 가 , | / H  
- 가 , HN R'가 - R'-N 가 , / H



0      100 °      , , /THF      /      NaOH      KOH      ,  
       /      ,      THF  
       , -60      +30 °      ,  
       CH<sub>3</sub>-C(=N  
H)-OEt  
Pd/      /      (      ,  
, COOH      가      /      ,  
R<sup>2</sup>, R<sup>3</sup> / R<sup>4</sup>      ,      |      R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> / |      R<sup>4</sup>  
R<sup>1</sup>,

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N,N'- , . , , , , , N- - D -

가

가

가

가

가

가

가

가

가 , , ,  
(propulsion), , , (intestinal flora),  
가

가

가 2

가

가

가

(handedness)



가 , , , , | 가 | ;  
 (t/2), (C<sub>max</sub>), (AUC) F 가 ;  
 (clearance),

가 , , , (parent)  
가 - , 100 %

- (C-H) 가 가 , 가 가 ,  
 가 가, [Hanzlik , J. Org. Chem. 55, 3992-3997,  
 Seider , J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14,1-40,1985], [Gillette ,  
 Try 33(10) 2927-2937, 1994] [Jarman , Carcinogenesis 16(4), 683-688, 1993]

가

가 . , 가 . , 가 .  
가 .

, PTCA (restenosis) (stent),  
 가 / ,  
 (in)- 가 TH<sub>1</sub> TH<sub>2</sub> (helper)  
 가 TNF- IL-1 IL-2 IL-6 IL-10 IL-13

(species) 가 , TNF- , 가 ,  
 (Ceconi C, Curello S, Bachetti T, Corti A, Ferrari R: Tumor necrosis factor in congestive heart failure: a mechanism of disease for the new millennium? Prog. Cardiovasc. Dis. 1998; 41 : 25-30.

Mann DL: The effect of tumor necrosis factor-alpha on cardiac structure 15 and function: a tale of two cytokines. J. Card. Fail. 1996 2: S165-S1 72. Squadrito F, Altavilla D, Zingarelli B, et al: Tumor necrosis factor involvement in myocardial ischaemia-reperfusion damage. Eur. J. Pharmacol. 1993 237: 223-230).

TNF- $\alpha$  (Herskowitz A, Choi S, Ansari AA, Westling S: Cytokine mRNA expression in postischemic/reperfused myocardium. Am. J. Pathol. 1995; 146:419-428), , , (Arras M, Strasser R, Mohri M, et al: Tumor necrosis factor-alpha is expressed by monocytes/macrophages following cardiac microembolisation and is antagonised by cyclosporine. Basic

c. Res. Cardiol. 1998 93: 97-107), A (Arras M, Strasser R, Mohri M, et al: Tumor necrosis factor- $\alpha$  is expressed by monocytes/macrophages following cardiac microembolisation and is antagonised by cyclosporine. Basic. Res. Cardiol. 1998 93: 97-107. Squadrito F, Altavilla D, Squadrito G, et al: cyclosporin-A reduces leukocyte accumulation and protects against myocardial ischaemia reperfusion damage in rats. Eur. J. Pharmacol. 1999 364:159-168) (Squadrito F, Altavilla D, Zingarelli B, et al: The effect of cloricromene, a coumarine derivative, on leukocyte accumulation, myocardial necrosis and TNF-alpha production in myocardial ischaemia-reperfusion damage. Life Sci. 1993 53: 341-355) 가 TNF-

| PDE IV T - . T  
· , PDE IV 가

PDE III                  PDE IV                  ,                  PDE IV

가 .

| 가 가 ,

가 , 가 가 /

| / ,  
가

, , , , , , , , , IgE -  
, , , , , , , , ,  
(wheezy)

, (COPD), COPD, COPD, (ARDS), , , , , 가

, , , ( ), , (chalcosis),

(phacoantigenic)

가 / , 가 , , , (Wegner)  
 , , , ,  
 , - (Stevens - Johnson) , , ,  
 (Basedow) , , ,

가 / .

(IBD), (UC), ;

(HIV)



; (ff) 6- ; (ii) , ; (gg) B<sub>1</sub>, B<sub>2</sub> ; (hh) ;  
(jj) , ; (kk) , ; (mm) , ; (oo) (matrix) ; (ll) ;  
MP) , , -2 (MMP-8), -3 (MMP-13), -1 (MMP-3), -1 (M  
MMP-1), MP-10) -3 (MMP-11); (pp) (TGF ); (qq) (PDGF); (r  
r) (GM-CSF); (tt) ; (uu) NKP-608C, SB233412 ( ) D-4418  
Nk<sub>1</sub> NK<sub>3</sub> ; (vv) UT-77 ZD-0892 (colony)

2  
PDE IV

(a) ( ) ( ) ;  
(b) ; ( ) ( ) ;  
(c) ( ) ( ) ;  
(d) / / ;  
\_\_\_\_\_  
: 5- (5-LO) 5- (FLAP)

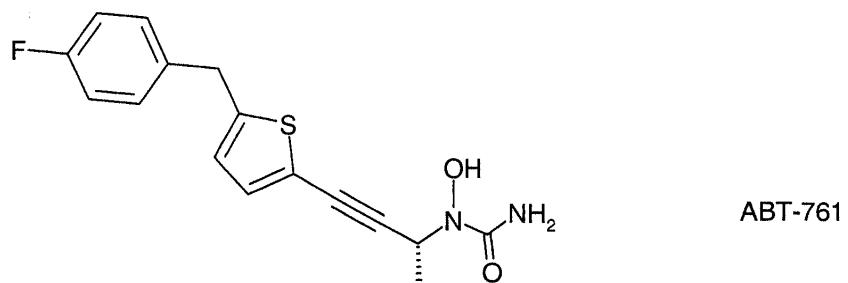
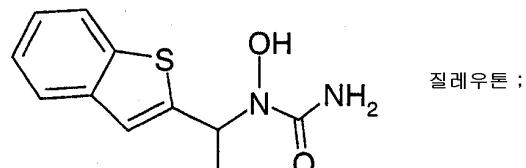
5- , | ( ) , , 5- , , 5-  
) 2 , , COX-1 COX-2  
5- 5- 5- ; , 5-  
5- (blocking) |  
5- :  
\_\_\_\_\_  
: 5- (5-HPETE) 18 kDa

(a) N- , N- , , , , Ann. Rev. Biochem. 63, 383- 15 417,1994]; [  
([Ford-Hutchinson , '5- , , , , Weitzel and Wendel, 'Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide ton e', J. Biol. Chem. 268, 6288-92, 1993]; [Bjornstedt , 'Selenite incubated with NADPH and mammalian thioredoxin reductase yields selenide, which inhibits lipoxygenase and changes the electron spin resonance spectrum of the active site iron', Biochemistry 35, 8511-6,1996]; [Stewart , 'Structure-activity relationships of N-hydroxyurea 5-lipoxygenase inhibitors', J. Med. Chem. 40, 1955-68,1997] );

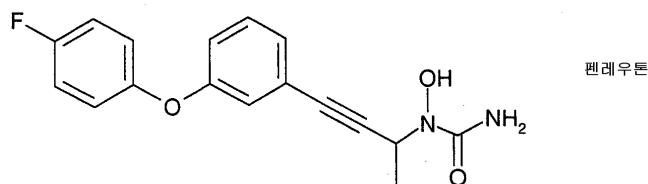
(b) SH ([Larss  
on , 'Effects of 1- -2,4,6-trinitrobenzen on 5-lipoxygenase activity and cellular leukotriene synthesis', Biochem. Pharmacol. 55, 863-71, 1998] );

(c) 5-  
5- ([Ford-Hutchinson , Ibid.]; [Hamel , 'substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase inhibitors - synthesis, biological profile and pharmacokinetics of L-739,01 0', J. Med. Chem. 40, 2866-75, 1997] ).

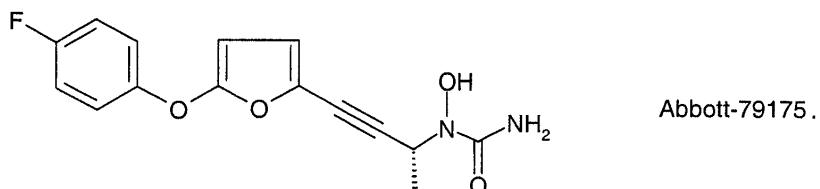
가 5- ABT-761 5- :



N- (Abbott-76745):

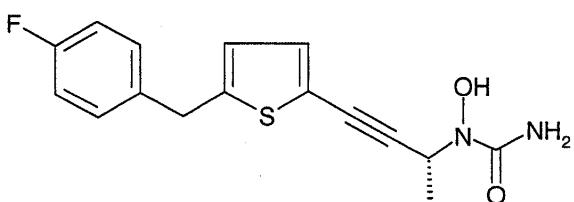


N- Abbott-79175 :



Abbott-79175 ; [Brooks , J. Pharm. Exp. Therapeut 272 724 ,1995].

N- Abbott-85761 :



Abbott-85761

Abbott - 85761

Gupta , 'Pulmonary delivery of the 5-lipoxygenase inhibitor, Abbott- 85761, in beagle dogs', International Journal of Pharmaceutics 147, 207-218,1997].

, Abbott-79175, Abbott-85761

5-LO

.5-

5 -

5-LO  
가 LT

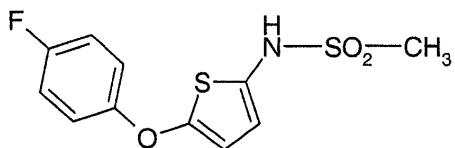
17

. 5-LO

1

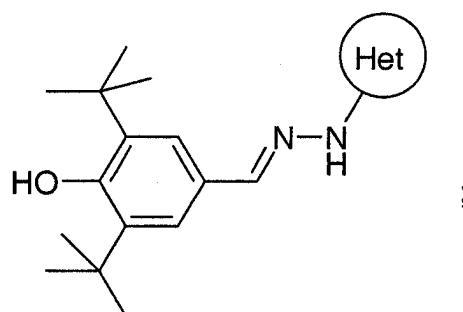
가

$$\text{RX}-\text{C}(\text{S})=\text{C}(\text{R})-\text{CH}_2-\text{NHSO}_2\text{R}'$$



[Beers , 'N - (5 - substituted) th iophene - 2 - alkylsulfonamides as potent inhibitors of 5 - lipoxygeneflas', Bioorganic amp; Medicinal Chemistry 5(4), 779 - 786, 1997] .

5- [Cuadro , 'Synthesis and biological evaluation of 2,6-di-tert-butylphenol hydrazones as 5-lipoxygenase inhibitors', Bioorganic and Medicinal Chemistry 6,173-180, 1998] 2,6-di-tert-butylphenol hydrazones as 5-lipoxygenase inhibitors

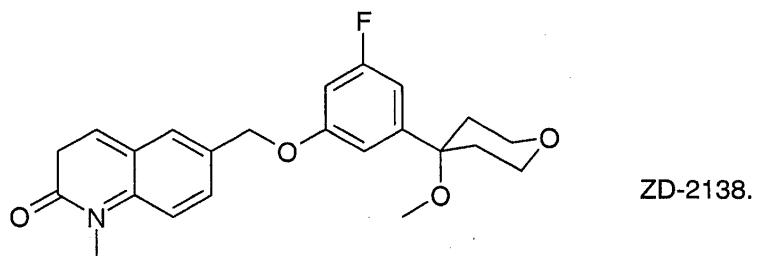


'Het'  
4,6-  
-2- , -2- , 4-  
-2- 4- -6-  
-2- ).  
N-(5- )- -2-  
|  
2,6- -tert-

가

5-

Zeneca ZD-2138



ZD-2138

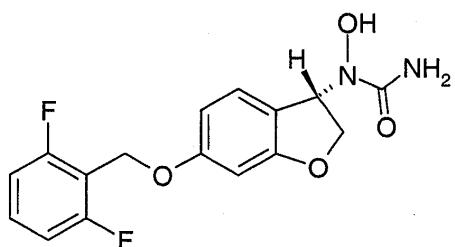
가 . ZD-2138  
00,1992], [Crawley , J. Med. Chem. 36, 295,1993]

[Crawley , J. Med. Chem., 35, 26

5-

SmithKline Beecham

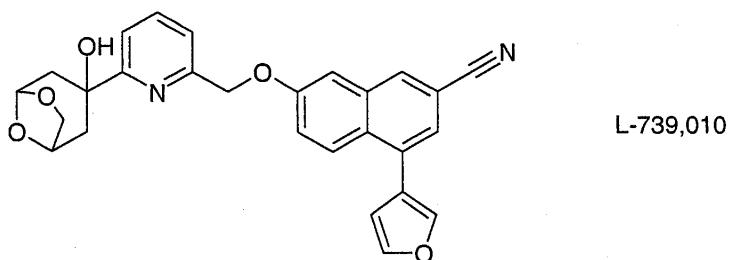
SB-210661

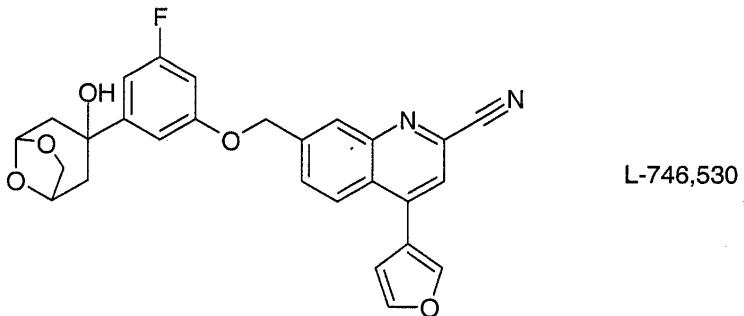


2 가 , 5-  
2- L-739,010 L-746,530

Merck Frosst

2 5-





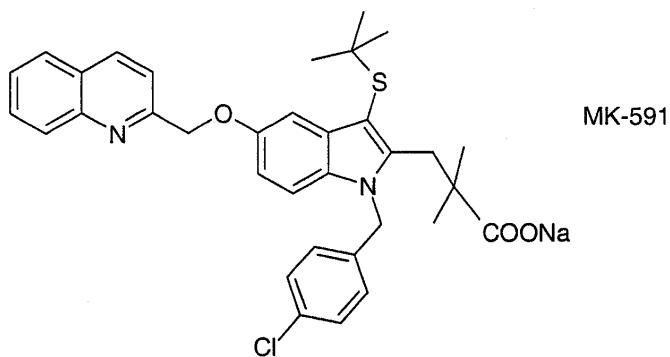
L-739,010 L-746,530 가 [Dube , 'Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530', Bioorganic and Medicinal Chemistry 8, 1255-1260, 1998], WO 95/03309 (Friesen ).

Zeneca ZD-2138 , SB - 210661  
L 739,010 - 2- , L - 746,530  
2- , |

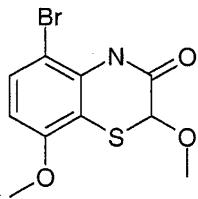
5- , 5- (FLAP) . 5- , 5- 가

5- , (pool)  
([Ford-Hutchinson , Ibid., Rouzer , 'WK-886, a potent and specific leukotriene biosynthesis inhibitor blocks and reverses the membrane association of 5-lipoxygenase in ionophore-challenged leukocytes', J. Biol. Chem. 265,1436-42,1990], [Gorenne , '[(R)-2-quinolin-2-yl-methoxy)phenyl]-2-cyclopentyl } (BAY x1005), a potent leukotriene synthesis inhibitor: effects on anti-IgE challenge in human airways', J. Pharmacol. Exp. Ther. 268, 868-72, 1994] ).

MK-591



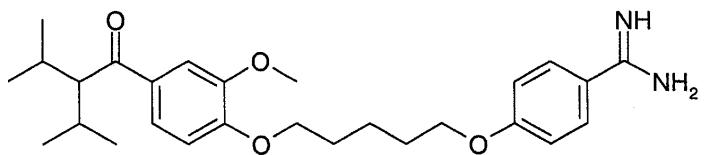
MK-591, IVIK-886 BAY ×1005



L-651,392.

CGS-25019c  
, US 5,639,768 (Morrissey Suh)  
CGS-25019c :

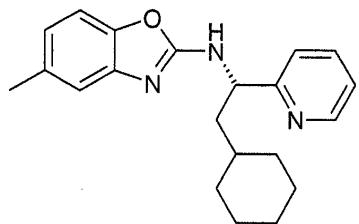
US 5,451,700 (Morrissey Suh); US 5,488,160 (Morrissey)  
LTB<sub>4</sub>



CGS-25019c

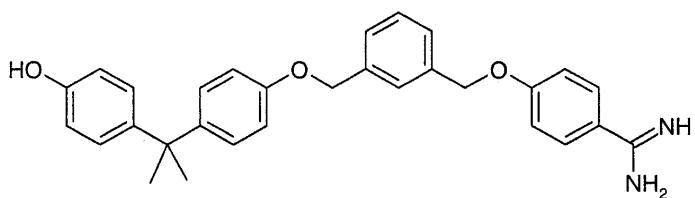
LTB<sub>4</sub>

EP 535 521 (Anderskewitz ) :



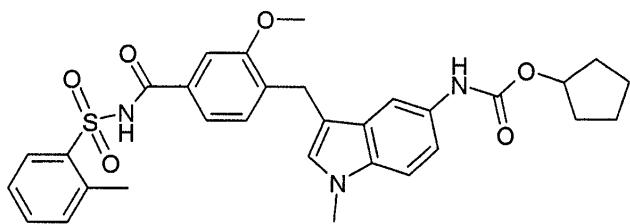
Anderskewitz ) WO 98/11119 (Anderskewitz ) , BIIL 284/260

WO 97/21670 (



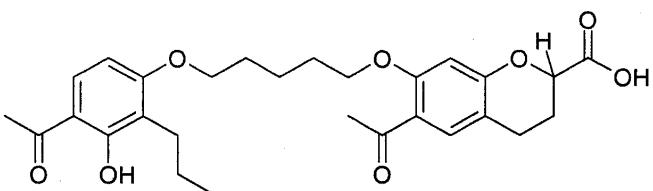
BIIL 284/260

Accolate® LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub> . US 4,859,6  
92 (Bernstein ), US 5,319,097 (Holohan Edwards), US 5,294,636 (Edwards Sherwood), US 5,482,963,  
US 5,583,152 (Bernstein ), US 5,612,367 (Timko )



Ro 23-3544/001

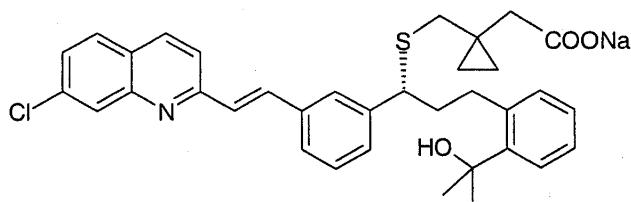
LTD 4



Singulair ®

LTD 4

, US 5,565,473

LTD 4  
GP 45715A) BAY x7195 가

(MK-679), RG-12525, Ro-245913,

(C

, L-651,392

, -3-, CGS-25019c

, BIIL 284/260,

가

(a) PDE IV ;

(b) 5- (5-LO) 5- (FLAP) ;

(c) 5- (5-LO) (PAF) ;

(d) LTD<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub> LTE<sub>4</sub> , (LTRA);(e) H<sub>1</sub> , , ;

(f) H<sub>2</sub>; ;

(g), , , , , , ; 1 - 2 - ;

(h) 5- (5-LO) 1 - 2 - ;

(i); , , , , , , , ;

(j), , , , , , , , , , , ;

(k); 1 - 4 - ;

(l); ;

(m) (MI, M2 M3);

(n) COX-1 (NSAID); NSAID COX-2 ;

(o) 1 (IGF-1);

(p);

(q), , , , , , , ;

(r); ;

(s) (PAF); ;

(t); ;

(u) IPL 576;

(v), D2E7 (TNF );

(w) DMARD;

(x) TCR ;

(y) (ICE); ;

(z) IMPDH ;

(aa) VLA-4 ;

(bb); ;

(cc) MAP ;

(dd) 6- ;

(ee) B<sub>1</sub> B<sub>2</sub> ;

(ff)

(gg) , , , ;

(hh) , ;

(ii) , ;

(jj) , , ,

(kk), , ;

(II)

(mm) (MMP) , , ,  
-1 (MMP-3), -1 (MMP-1), -2 (MMP-8), -3 (MMP-13),  
-2 (MMP-10) -2 (MMP-11);

(nn) (TGF );

(oo) (PDGF);

(pp) , (bFGF);

(qq) (GM - CSF);

(rr) ;

(ss) NKP-608C; SB-233412 ( ); D-4418 NK 1 NK 3  
;

(tt) UT-77 ZD-0892

(uu) A2a

가 , , , , | 가 , , , ,

가 , 가 , 가 , 가

가

가

가

1

가

pH

가

가

가

가

가

가 , , , , 가 ,  
가

가 가

가 가 , pH

가

가

가

가 가

가

0.01 % 2 %

가

pH

## EDTA 가

(*tinea versicolor*)

(*tinea corporis*).

,  
(tinea pedis).

(candidiasis)

(emollient)

(water-in-oil)

$$2 \quad 20 \quad . \quad , \quad , \quad C_{10} - C_{20} \quad , \quad (C_6 - C_{12}) \quad 2$$



1

95, 가 70 95, 가 . . . . , 60  
+ , 가 , 5, 60, , 20 10 30  
+ , 가 , 가 55, 가 . . . .

13- 가 가

HCIX

가 , 가

가

가

PDE VII

(c) (depot), (cavities) (a), (b), (3), (4), (a), (b).  
 (c) (lozenge), (trochee), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), (x), (y), (z).

PDE VII

- 35 -

DE VII

PDF IV

가

PDE IV

, 50.0 mg /kg , 10.0 µg /kg 1 5.0 µg /kg 1.0 mg /kg 0.1 µg /kg 5.0 mg /kg , 가 1 20.0 µg /kg 0.5 mg /kg .

g 0.001 µg /kg 0.5 mg /kg , 가 1 , 10.0 mg /kg , 2.0 µg /kg , 1.0 µg /kg , 0.05 mg /kg , 0.5 µg /kg , 0.1 mg /kg 1

1	10 kg	100 kg	,	1	1.0 - 10.0 µg	500.0 - 5000.0 mg
,	I		,	1	50.0 - 500.0 µg	50.0 - 500.0 mg
,			,	1	100.0 - 1000.0 µg	10.0 - 100.0 mg
, 가			,	1	200.0 - 2000.0 µg	5.0 - 50.0 mg

1 , ,  
 . , ,  
 , ,  
 1 , 50.0  $\mu$ g 10.0 mg

| / 가 ,

(b) 가 .

‘ , ’ / , ’ 가 , ’

pH 2 10 , , , 가 ,

(MS): EI ( ) M +

FAB ( ) (M + H) +

1

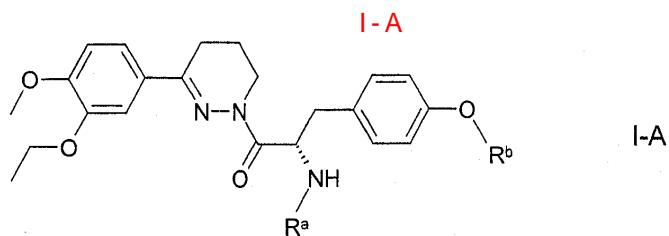
1.1            25 Mℓ      2.5 g      (1)      Z-Tyr(tBu)-OSu (2) 5.0 g      가 ,      16  
       .      500 ml      ,      I-A-1 6.27 g      ,      ( 1 )      /  
       2:1)      ,      I-A-2

1.2                 I-A-2

1.3 4            가      DMF      I-A-2  
       I-A-3

1.4            30 ml      Pd/C      93 mg      93 mg      I-A-3  
       ,      59 mg      I-A-4

I-A



[ 1 ]

	R <sup>a</sup>	R <sup>b</sup>	
I-A-1		tert-	
I-A-2		H	
I-A-3		CH <sub>2</sub> CH <sub>2</sub> OH	
I-A-4	H	CH <sub>2</sub> CH <sub>2</sub> OH	
I-A-5		CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	
I-A-6	CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	
I-A-7	H	CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	
I-A-8	Fmoc	tert-	
I-A-9	H	tert-	
I-A-10	H	H	
I-A-11		H	
I-A-12	-4-	H	
I-A-13	BOC	CH <sub>3</sub>	R
I-A-14	BOC	CH <sub>3</sub>	
I-A-15	CH <sub>3</sub> -CO-	tert-	
I-A-16	CH <sub>3</sub> -CO-	H	

2

2.1 DMF 5 ml      I-A-2 1.06 g, 1-      -2-(N,N-      - )      290 mg      2  
g                    50                    100            16  
,      HTP (      (high throughput purifier);      )      , 287 mg      I-A  
-5    21 mg      I-A-6      ( 1).

2.2 287 mg I-A-5 5 g THF 400 mg Pd/C  
                  , 159 mg I-A-7 .

3

3.1 1.1 ml POCl<sub>3</sub>  
OH (3) 7  
3 g I-A-8 , 30 ml 16 ( / 1:1) , 2.

3.2 ( -PS) I-A-8 Fmooc  
. 2.3 g 1.4 g I-A-9 .

3.3 1 ml                          3 ml                          454 mg I-A-9                          가 ,  
            16                          .                          , DCM                          , 1 g  
            가 ,                          16                          .

3.4 100 mg - 3 ml 80 mg I-A-10, 0.021 ml  
 0.3 ml 가 , 16 .  
 Genevac ® HTP 0.053 g I-A-11

3.5.3.4 I-A-10 - 4 - I-A-12

4

4.2 3.3 g DAPECI 1.7 g NMM 10 ml DMF 5.0 g BOC-Tyr(Me)-OH (5) 2.6 g HOEt  
 가 . 가 4 , 3.9 g (1) , 16 .  
 . . DAPECI 가 , 16 .  
 7.0 g I-A-14 .

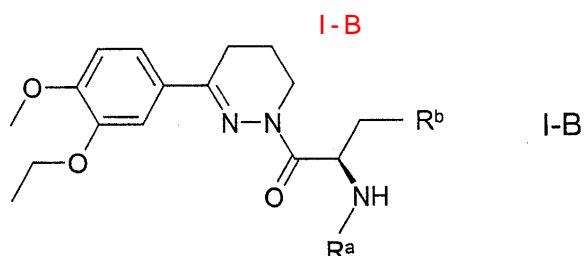
4.3 0.36 ml POCl<sub>3</sub> 10 ml 0.8 g (1) 1.0 g Ac-Tyr(tBu)-O  
H (6) 가 . , . 0.3 g |-A-15  
16 ( / 1:1 ) , .

4.4 20 ml                    1.0 g    I-A-15    5 ml    TFA                    1                    . TF  
 A    DCM                    .                    .    0.8 g    I-A-16                    .

5

5.1 0.38 ml POCl<sub>3</sub>  
)-D-Ala-OH (7) 가 . 10 ml 0.9 g (1) 1.0 g BOC- -(3-  
,  
0-20%) , 0.4 g I-B- 1 , 16 ( 2 ). ( /

| - B



[ 2 ]

	R a	R b	
I-B-1	BOC	3-	
I-B-2	H	3-	
I-B-3	BOC	4-	
I-B-4	H	4-	

5.3 0.8 g DAPECI 0.43 ml NMM 5 ml DMF 1.0 g BOC-D-4-  
HOBt 가 . 4 , 0.9 g (1) , (8) 0.6 g  
0.4 g L-B-3 .

$\mathbf{I} \cdot \mathbf{T}_\perp$

1

Lymphoprep  
- - 가 (96-well flat-base microtitre plate) (PBMC)  
O 5% - (heat-inactivated) (AB) 200,000 PBMCs RPMI1640  
2 . PBMC T- 37 5 10% CO<sub>2</sub>

	DMSO	$10^{-2}$ M						
%	DMSO		18		$^3\text{H-}$		가	가
( $\pm$ SFN)				3				
					$\text{IC}_{50}$			

11

Lymphoprep  
6-  
40 5% 3  
- -  
가 (96-well flat-base microtitre plate)  
(AB ) 10% CO<sub>2</sub>  
DMSO |  
DMSO 10<sup>-2</sup> M  
ELISA  
%, % / ,  
(PBMCs) 200,000 5  
PBMCs RPMI16  
3  
3  
IC<sub>50</sub> EC<sub>50</sub>

A

3      2                  100 g                  |                  5 g  
       pH 6.5                  ,                  ,                  ,  
       .                  5 mg                  .

B.

20 g | 100 g 1400 g  
20 mg

C:

940 ml 2 1 g I , 9.38 g NaH<sub>2</sub>PO<sub>4</sub> · 2H<sub>2</sub>O, 28.48 g Na<sub>2</sub>HPO<sub>4</sub> · 12H<sub>2</sub>O 0.1 g . pH 6.8 , 1

D-  
■

500 mg | 99.5 g

F.

1 kg | , 4 kg , 1.2 kg , 0.2 kg 0.1 kg  
가 10 mg

F·

G

2 kg | 20 mg

H-

(57)

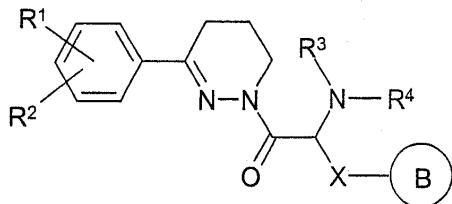
1.

I

가 ,

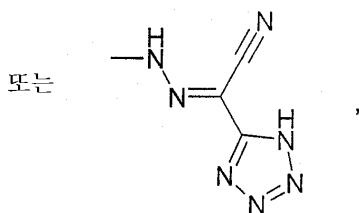
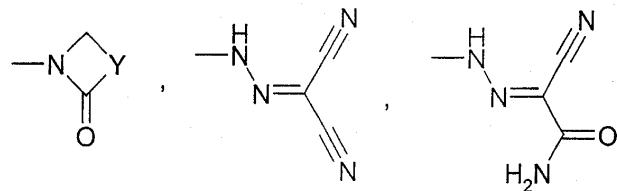
:

[ I ]



I

( ,

R<sup>1</sup> R<sup>2</sup> , , H, OH, OR<sup>8</sup>, -SR<sup>8</sup>, -SOR<sup>8</sup>, -SO<sub>2</sub>R<sup>8</sup> Hal ,R<sup>1</sup> R<sup>2</sup> -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>O- ,R<sup>3</sup> H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NCOA'R<sup>9</sup> NCOOA'R<sup>9</sup> ,R<sup>4</sup> H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup> CON(A'R<sup>9</sup>)(A''R<sup>9</sup>) ,B R<sup>5</sup>, R<sup>6</sup> / R<sup>7</sup> , ,X 가 F / Cl CH<sub>2</sub> / 가 O, S, SO, SO<sub>2</sub>, NH NA'R<sup>9</sup> , 1 7 H 1  
10 2 8 가 R<sup>11</sup> / R<sup>12</sup> , ,R<sup>5</sup>, R<sup>6</sup> R<sup>7</sup> , , H, A'R<sup>9</sup>, OH, OA'R<sup>9</sup>, NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A'R<sup>9</sup>)(A''R<sup>9</sup>), NHC OA'R<sup>9</sup>, NHCOOA'R<sup>9</sup>, NHCONH<sub>2</sub>, NHCONHA'R<sup>9</sup>, NHCON(A'R<sup>9</sup>)(A''R<sup>9</sup>), Hal, C00H, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>),R<sup>8</sup> A, 3 7 4 8 ,R<sup>9</sup> H, COOH, COOA, CONH<sub>2</sub>, CONHA, CONAA', NH<sub>2</sub>, NHA, NAA', NCOA, NCOOA, OH, OA, (CH<sub>2</sub>)<sub>n</sub> -(CH<sub>2</sub>)<sub>n</sub>Het ,R<sup>10</sup> , CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH, NMe, NET / -CH=CH-

2.

3.

4.

1 , R 1 4 - , R 2 3 - 가 ,

$$5. \quad 1 \quad 4 \quad , \quad R^4 \quad H \quad , \quad g \quad ,$$

6. 1 A'Het 5 , R<sup>3</sup> H, COO(CH<sub>2</sub>)<sub>n</sub>- , COA'H, COOA'H, A'NAA', A'-가 .

9.  $\text{O}^-$  1 8 -OH , B OR  $^{13}\text{N}(\text{R}^{13})_2$ , O-  $-\text{N}(\text{R}^{13})_2$  가 .

10.  
 1        9 ,  
 1    R 2 , H, , , , , , , , F,  
 , , ,  
 1    R 2 -OCH 2 O- -OCH 2 CH 2 -O- ,  
 3    H, A'R 9 , COA'R 9 , COOA'R 9 , CONH 2 , CONHA'R 9 , CON(A'R 9 )(A''R 9 ), NH 2 , NHA'R 9 , N(A  
 9 )(A''R 9 ), NCOA'R 9      NCOOA'R 9 ,  
 4    H ,

11. 10 ,  
 1 R<sup>2</sup> , H, , , , , , , , , F,  
 , , ,  
 1 R<sup>2</sup> -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>-O- ,  
 3 H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>), NH<sub>2</sub>, NHA'R<sup>9</sup>, N(A

'R<sup>9</sup>')(A'R<sup>9</sup>), NCOA'R<sup>9</sup> NCOOA'R<sup>9</sup> ,

$$R^4 \quad H \quad ,$$

X , , , ,

A' A'' , , 1, 2, 3 4

$$R^9 - H, (CH_2)_n - \quad (CH_2)_n Het \quad ,$$

OR 13 , , , ,

R 13 H 1 6 ,

12.

1 11 ,

$$R^1, R^2, \dots, R^{n-1}, R^n,$$

R<sup>3</sup>H, , , tert-, , , N,N-

$$R^4 \quad H,$$

X , , , , ,

R 13 H 1 6 ,

Het

B OR  $^{13}\text{N}$ ( $^{13}\text{R}$ )  $\gamma$ , O-

13.

- a) {1-(1S)-(4-tert-  
}) -2-[3-(3-  
-4-  
- )-5,6-  
-4H-  
-1- ]-2-

b) {2-[3-(3-  
-4-  
- )-5,6-  
-4H-  
-1- ]-1-(1S)-(4-  
}) -2-

c) 2-(2S)-  
-1-[3-(3-  
-4-  
- )-5,6-  
-4H-  
-1- ]-3-[4-(2-  
)  
]  
-1- ,

d) 3-[4-(2-  
6-  
-4H-  
-1- ]-2-(2S)-(2-  
-1- ,  
)-1-[3-(3-  
-4-  
- )-5,

- e) 2-(2S)-  
-1- ] -3-[4-(2-  
-1- , )] -1-[3-(3- -4- )-5,6- -4H-  
-4-
- f) 9H-  
-1- ]-2- {1-(1S)-(4-tert- )-2-[3-(3- -4- )-5,6- -4H-  
-4-
- g) 2-(2S)-  
-1- , -3-(4-tert- )-1-[3-(3- -4- )-5,6- -4H- -1- }  
-4-
- h) 2-(2S)-  
-1- , -1-[3-(3- -4- )-5,6- -4H- -1- ]-3-(4- )  
-4-
- i) 2-(2S)-  
-1- , -1-[3-(3- -4- )-5,6- -4H- -1- ]-3-(4- )  
-4-
- j) 1-[3-(3- -4- )-5,6- -4H- -1- ]-3-(4- )-2-(2S)-[(-4-  
-1- ]-1- , -4-
- k) tert- {1-(1R)-(4- )-2-[3-(3- -4- )-5,6- -4H- -1- ]-2-  
-4-
- l) tert- {1-(1S)-(4- )-2-[3-(3- -4- )-5,6- -4H- -1- ]-2-  
-4-
- m) N-{1-(1S)-(4-tert- )-2-[3-(3- -4- )-5,6- -4H- -1- ]-2-  
-4-
- n) N-[2-[3-(3- -4- )-5,6- -4H- -1- ]-1-(1S)-(4- )-2-  
-4-
- o) tert- {2-[3-(3- -4- )-5,6- -4H- -1- ]-2- -1-(1R)-( -3-  
-4-
- p) 2-(2R)- -1-[3-(3- -4- )-5,6- -4H- -1- ]-3- -3- -1-  
-4-
- q) tert- {2-[3-(3- -4- )-5,6- -4H- -1- ]-2- -1-(1R)-( -4-  
-4-
- r) 2-(2R)- -1-[3-(3- -4- )-5,6- -4H- -1- ]-3- -4- -1-  
-4-

**14.**

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13

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IV

I

**15.**

I

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a)

II

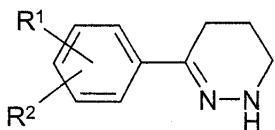
III

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,

;

[ II]



II

( , R<sup>1</sup> R<sup>2</sup> 1 )









- (v) (PAF);
- (w);
- (x) IPL 576;
- (y), D2E7 (TNF );
- (z) DMARD;
- (aa) TCR ;
- (bb) (ICE);
- (cc) IMPDH ;
- (dd) VLA-4 ;
- (ee);
- (ff) MAP ;
- (gg) 6- ;
- (hh) B<sub>1</sub> B<sub>2</sub> ;
- (ii);
- (jj), ;
- (kk) (colchicine);
- (ll);
- (mm), ;
- (nn);
- (oo);
- (pp), -3 (MMP-13), , -1 (MMP-3), , -1 (MMP-1), -2 (MMP-10), -2 (MM-3 (MMP));
- (qq) (TGF );
- (rr) (PDGF);
- (ss) (bFGF);
- (tt) (colony) (GM-CSF);
- (uu);
- (vv) NKP-608C; SB233412 ( ) D-4418 NK<sub>1</sub> NK<sub>3</sub> ;

(ww) UT-77 ZD-0892 ;

(xx) A2a .

**25.**

1 13 | / 가

, ,

**26.**

( ):

(a) 1 13 | / 가

, ,

b) 가 .