

(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
(22)	2004 12 04
	2004 12 04
(86)	PCT/EP2003/004930
(86)	2003 05 12

(87)

WO 2003/104204  
2003 12 18

(30) 10224888.5 2002 06 05 (DE)

(71) 64293 250

(72) 64287 - 49

64297 59

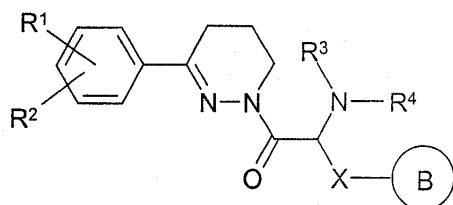
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(54)

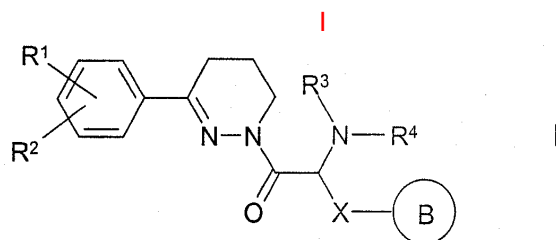
I , , , IV , , , AIDS  
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가

[ 1 ]



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I 가 ,  
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( ,

$R^1$   $R^2$  , , H, OH,  $OR^8$  ,  $-SR^8$  ,  $-SOR^8$  ,  $-SO_2R^8$  Hal ,

$R^1$   $R^2$   $-OCH_2O-$   $-OCH_2CH_2O-$  ,

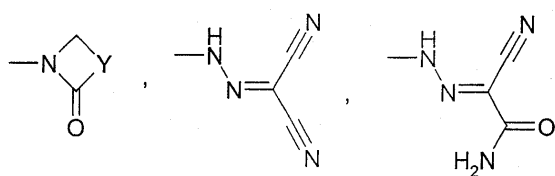
$R^3$  H,  $A'R^9$  ,  $COA'R^9$  ,  $COOA'R^9$  ,  $CONH_2$  ,  $CONHA'R^9$  ,  $CON(A'R^9)(A''R^9)$  ,  $NH_2$  ,  $NHA'R^9$  ,  $N(A'R^9)(A''R^9)$  ,  $NCOA'R^9$  ,  $NCOOA'R^9$  ,

$R^4$  H,  $A'R^9$  ,  $COA'R^9$  ,  $COOA'R^9$  ,  $CONH_2$  ,  $CONHA'R^9$  ,  $CON(A'R^9)(A''R^9)$  ,

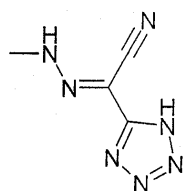
B  $R^5$  ,  $R^6$  /  $R^7$  ,

X 가 F / Cl  $CH_2$  가 O, S, SO,  $SO_2$  , NH  $NA'R^9$  , 1 7 H  
10 2 8 H 가  $R^{11}$  /  $R^{12}$  , 1

$R^5$  ,  $R^6$   $R^7$  , , H,  $A'R^9$  , OH,  $OA'R^9$  ,  $NH_2$  ,  $NHA'R^9$  ,  $N(A'R^9)(A''R^9)$  ,  $NHC$   
 $OA'R^9$  ,  $NHCOOA'R^9$  ,  $NHCONH_2$  ,  $NHCONHA'R^9$  ,  $NHCON(A'R^9)(A''R^9)$  , Hal, COOH,  $COOA'R^9$  ,  $CON$   
H  $_2$  ,  $CONHA'R^9$  ,  $CON(A'R^9)(A''R^9)$  ,



또는



$R^8$  A, 3 7 4 8 ,

$R^9$  H, COOH, COOA,  $CONH_2$  ,  $CONHA$  ,  $CONAA'$  ,  $NH_2$  ,  $NHA$  ,  $NAA'$  ,  $NCOA$  ,  $NCOOA$  , OH, OA,  $(CH_2)_n$   
-  $(CH_2)_n$  Het ,

$R^{10}$  ,  $CH_2$  가 O, S, SO,  $SO_2$  , NH, NMe, NEt /  $-CH=CH-$   
1 7 H 가 F / Cl / 1 H 가  $R^9$

2, 8, 1, 10, 3, 7, 4, 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, 가 F / Cl, CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH, NR<sup>10</sup>  
2, 8, Het,

A, A', 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>, 2, 7,

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

A', A'', 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>, 2, 7,

Hal, R<sup>14</sup>, OR<sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, COOR<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, COOR<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).

1- {J. Med. Chem. 38, 4878 (1995)}  
4099, EP 0 922 036, EP 1 124 809 WO 01/0

가 .

I

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가

I CAMP 가 IV (N. Sommer et al., Nature Medicine, 1, 244-248 (1995)). PDE IV (C.W. Davis in Biochim. Biophys. Acta 797, 354-362 (1984)). IC<sub>50</sub> ( 50% )

Torphy et al. in Thorax, 46, 512-523 (1991))  
26, 438-447 (1971))

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),

이러한 결과로부터 TNF- $\alpha$ 가 혈관 내피세포에 작용하여 NO의 생성을 억제하고, 혈관 수축을 유도하는 것으로 보인다.

가  
L. Sekut et al., Clin. Exp  
{N. Sommer et al., Nature Medicine 1, 244-248 (1995),  
. Immunol. 100, 126-1 32 (1995)}

Costelli et al., J. Clin. Invest. 95, 2367ff. (1995); J.M. Argiles et al., Med. Res. Rev. 17, 477 ff. (1997)).

PDE IV (D. Marko et al., Cell Biochem. Biophys. **28**, 75 ff. (1998)).  
7 399 WO 96 00 215

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

V , , , AIDS . PDE I , , , EP 77 92 91 .

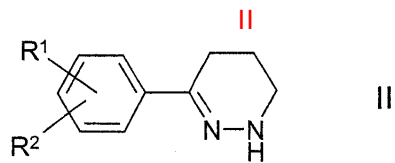
WO 01/57025

me) , , PDE IV (isozy

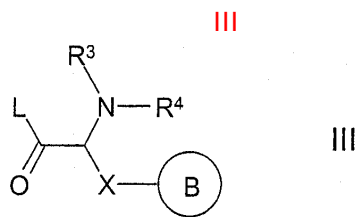
WO 01/57025 , I

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

a) II III , , :



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



( , L Cl, Br, I , , OH / OH , R<sup>3</sup>, R<sup>4</sup>, X B ),

b) b) i) ,  
 ii) OH ,  
 iii) / B I R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> / B ,  
 , ( ), , , ,  
 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<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X, B L I, II III .

1, 2, 3, 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, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 84





, , , , , .  
 , Het , OH OA , 1 2  
 N / O , 2- -1- , 2- -1- , 2- -1H- -1- , 3- , Het -4-  
 , 4- -1H- -1- , 2,6- -1- , 2- -1- , 2,6- -1- , 2,5-  
 -1- , 2- -1,3- -3- , 3- -2H- -2- , 2- -1- (=2-  
 -1- ), 2- -6- -1- , 2- -6- -1- , 2- [2.2.2]-  
 -3- -2- , 2- -1- .

n 0 1 .

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 (sub-formulae) 1a 1k ,  
 I I ,

la ,

R<sup>1</sup> R<sup>2</sup> , , H, , , , , F,  
 Cl, , ;

lb ,

R<sup>1</sup> R<sup>2</sup> , , , , , F ;

lc ,

R<sup>1</sup> 4- ,

R<sup>2</sup> 3- ;

ld ,

R<sup>4</sup> H ;

le ,

R<sup>3</sup> H, COO(CH<sub>2</sub>)<sub>n</sub> - , COA'H, COOA'H, A'NAA', A'- A'Het ;

lf ,

X , , ;

lg ,

B OH, OA, NH<sub>2</sub>, NAA', O- -NAA' O- -OH ,  
 , , N- , , , , , , ,  
 , , ;

lh , B OR<sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, O- -N(R<sup>13</sup>)<sub>2</sub> O- -OH  
 ;

li ,

R<sup>1</sup> R<sup>2</sup> , , H, , , , , F,  
 Cl, , ,

$$\text{R}^1 \quad \text{R}^2 \quad \text{-OCH}_2\text{O-} \quad \text{-OCH}_2\text{CH}_2\text{-O-},$$
$$\text{R}^3, \text{H}, \text{A}'\text{R}^9, \text{COA}'\text{R}^9, \text{COOA}'\text{R}^9, \text{CONH}_2, \text{CONHA}'\text{R}^9, \text{CON}(\text{A}'\text{R}^9)(\text{A}''\text{R}^9), \text{NH}_2, \text{NHA}'\text{R}^9, \text{N}(\text{A}'\text{R}^9)(\text{A}''\text{R}^9), \text{NCOA}'\text{R}^9, \text{NCOOA}'\text{R}^9,$$
 $R^4 H$  ,

X

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

$$R^9 \quad H, (CH_2)_n - \quad (CH_2)_n \text{Het} \quad ;$$

lj ,

R<sup>1</sup> R<sup>2</sup> , H, , , , , F, Cl, , ,

$$R^1 \quad R^2 \quad -OCH_2O- \quad -OCH_2CH_2O-,$$
$$\text{R}^3, \text{H}, \text{A}'\text{R}^9, \text{COA}'\text{R}^9, \text{COOA}'\text{R}^9, \text{CONH}_2, \text{CONHA}'\text{R}^9, \text{CON}(\text{A}'\text{R}^9)(\text{A}''\text{R}^9), \text{NH}_2, \text{NHA}'\text{R}^9, \text{N}(\text{A}'\text{R}^9)(\text{A}''\text{R}^9), \text{NCOA}'\text{R}^9, \text{NCOOA}'\text{R}^9,$$
 $R^4 \quad H,$ 

X

$$A', A'', \dots, 1, 2, 3, 4, \dots$$
$$R^9 \quad H, (CH_2)_n - \quad (CH_2)_n \text{Het} \quad ,$$

OR 13

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

Het

B OR <sup>13</sup>, N(R<sup>13</sup>)<sub>2</sub>, O- -N(R<sup>13</sup>)<sub>2</sub> O- -OH ,  
;

Ik ,

$$R^1, R^2, \dots, R^m$$

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

 $R^4 H$  ,

X

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

Het \_\_\_\_\_,

B  $\text{OR}^{13}$ ,  $\text{N(R}^{13})_2$ ,  $\text{O-}$   $\text{-N(R}^{13})_2$   $\text{O-}$   $\text{-OH}$  ,

I  
hen Chemie[ , Georg-Tieme-Verlag, Stuttgart ( , Houben-Weyl, Methoden der organisc )

II III ,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{X}$  B , 가 .

II . ,

III , L Cl, Br, I  
OH , ) 6 10 6 ( ( p- , Houben-W  
eyl, Methoden der organischen Chemie[ ], Georg-Tieme-Verlag, Stuttgart )

, HOBt N- 가 .

, I

I II III .

I , :



COOR" 가 , , I -COOH R"가 - -

가 .

가 / 가 .

( )

( 8 ) ; , 1 20, 1

2,2,2- ; CBZ ( ' ), 4- ; POA ;

Mtr BOC Mtr, CBZ, Fmoc,

1 10 가 . , 4- , p- 1 20, p-

tert- tert- TFA , p-

가 가 ,

, DMF , TFA 가

0 70% 50 ° , 9:1 15 30 ° (

) .

, 15 30 ° TFA , 15 30 ° DMF 3 5N HCl BO

C, OBut Mtr Fmoc ,

가 ( CBZ, )

, DMF 가 0 100 ° , 1 200 bar ,

0% Pd/C , 20 30 ° 1 10 bar /DMF CBZ Pd/C 가 , 5 1

( )

2- , , , 1,

; , , n- , n- tert- ; ,

(THF) ;

( ) ;

, N- (NMP) (DMF) ;

(DMSO) ;

0 100 ° , , /THF / NaOH KOH ,  
 .  
 / , , -60 +30 ° THF /  
 CH<sub>3</sub>-C(=N  
 H)-OEt .

Pd/ , COOH 가 ), , / , 가 /  
 R<sup>2</sup>, R<sup>3</sup> / R<sup>4</sup> , I R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> / R<sup>4</sup> R<sup>1</sup>,  
 .

(非) . , 가  
 . I 가  
 . I - 가 , , ;  
 , ; N-  
 , I , ;  
 가 , , , -  
 , , , , ,  
 - 가 , , I 가 - 가 ,  
 : , , ,  
 , ( ), , , , ,  
 , , , , , ( ,  
 ), , , , , , 2-  
 , , , , , , 2-  
 , 3- , , , , ,  
 , , , , , , (III), (II),  
 , (III), (II), , ;  
 , I , , 1 , 2 3 가 , ,  
 , N,N'- ( ), , 2- , 2  
 - , , , N- , N- , N-D- , , ,  
 , , , , , , -(  
 )- ( ) .

tert- (C<sub>1</sub>-C<sub>4</sub>) , , , ,  
 ; (C<sub>1</sub>-C<sub>4</sub>) , , , ,  
 ; (C<sub>10</sub>-C<sub>18</sub>) , , , ,  
 ; (C<sub>1</sub>-C<sub>4</sub>) , , , ,  
 4 (quaternise) . (oil-soluble)  
 가 .







가  
(t/2), (C<sub>max</sub>), (AUC) F 가 ;  
(clearance),  
:  
가  
가 - 100 % (parent)  
I -  
- (C-H) 가 가 ,  
가  
- 가 , [Hanzlik , J. Org. Chem. 55, 3992-3997, 1990], [Reider , J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14,1-40,1985], [Gillette , Biochemistry 33(10) 2927-2937, 1994] [Jarman , Carcinogenesis 16(4), 683-688, 1993]

가  
가 , 가  
가  
PTCA (restenosis) (stent) ,  
(in)- - 가 / ,  
가 TH<sub>1</sub> TH<sub>2</sub> (helper)  
가 TNF- , IL-1 , IL-2 IL-6 , IL-10 IL-13  
(Pulkki KJ: Cytokines and cardiomyocyte death. Ann.Med. 1997;29: 339-343. Birks EJ, Yacoub MH: The role of nitric oxide and cytokines in heart failure. Coron.Artery.Dis. 1997 8: 389-402).

(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 and function: a tale of two cytokines. J. Card. Fail. 1996 2: S165-S172. 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- 가 (Herskowitz A, Choi S, Ansari AA, Wesselingh S: Cytokine mRNA expression in postischemic/ reperused 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



ler) 가 (Loeff  
- (Churg-Strauss) (PAN)

(phacoantigenic)

(Stevens-Johnson)  
(Basedow)

(Wegner)

(CD)

(IBD),

(UC),

(HIV)

, HIV-1, HIV-2 HIV-3, , CMV, ,  
 , 가 TNF- 가 , 가 TNF-  
 ;  
 , TNF- TNF  
 B, , B B  
 ;  
 , 가 , 가 , HIV ,  
 , I (1) , ; (2) , ,  
 , ; (3) , ,  
 ; (4) 가 , GvH ,  
 ; (5) (HIV) , AIDS (AR  
 C), , AIDS , 1 ,  
 가 , (member) I  
 :  
 (a) : , ABT-761, , Abbott-79175, Abbott-85761, N-(5-  
 )- -2- , 2,6- -tert- , Zeneca ZD-2138  
 , SB-210661 , L 739,010 - 2- -  
 , L-746,530 2- - , MK-591, Mk-886 BAY x 1005  
 (FLAP) ; (b) L-651,392 5- (5-LO) 5-  
 -3- , CGS-25019c  
 , BIIL 284/260 (MK-679), RG-1  
 2525, Ro-245913, (CGP 45715A) BAY x7195 가  
 LTB<sub>4</sub> , LTC<sub>4</sub> , LTD<sub>4</sub> , LTE<sub>4</sub> ; (c) PDE IV ; (d) 5-  
 (5-LO) ; 5- (FLAP) ; (e) 5- (5-LO)  
 (PAF) ; (f) LTB<sub>4</sub> , LTC<sub>4</sub> , LTD<sub>4</sub> , LTE<sub>4</sub>  
 (LTRA); (g) H<sub>1</sub> ; (h) H<sub>2</sub> ; (i) ,  
 , , ,  
 (j) 5- (5-LO) 1<sup>-</sup> 2<sup>-</sup> 1<sup>-</sup> 2<sup>-</sup> ; (k)  
 ; (l)  
 ; (m)  
 -1 (NSAID); COX-2 (M1, M2 M3) ; (p) COX  
 1 (IGF-1) ; (r) ; (s) NSAID; (q)  
 ; (t) ; (u) (PAF)  
 ; (v) ; (w) IPL 576; (x) D2E7  
 (TNF ) ; (y) DMARD; (z) TCR ; (aa)  
 (ICE) ; (bb) IMPDH ; (cc) VLA-4 ; (dd) ; (ee) MAP

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

가

(a)  $\left( \begin{array}{c} \text{ } \\ \text{ } \end{array} \right)$   $\left( \begin{array}{c} \text{ } \\ \text{ } \end{array} \right)$ ; ,

(b)  $\vdots$  ,  $(\quad)$  ,  $(\quad)$

(c)

$$\left( \begin{array}{c} \vdots \\ \vdots \\ \vdots \end{array} \right) \quad \left( \begin{array}{c} \vdots \\ \vdots \\ \vdots \end{array} \right) \quad ; \quad \left( \begin{array}{c} \vdots \\ \vdots \\ \vdots \end{array} \right) \quad \left( \begin{array}{c} \vdots \\ \vdots \\ \vdots \end{array} \right)$$

(d)  $\frac{1}{(1-\alpha)} \frac{1}{(1-\alpha)} \frac{1}{(1-\alpha)}$  , , ,

: 5- (5-LO) 5- (FLAP)

5-  
(5-LO  
COX-1  
COX-2

[illegible]

5- (blocking) 5-

(a) N-  
([Ford-Hutchinson, '5-  
, Ann. Rev. Biochem. **63**, 383- 15 417,1994]; [Weitzel and Wendel, 'Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide tone', 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 ([Larsson, 'Effects of 1-(2,4,6-trinitrophenyl)-5-mercapto-2,4,6-trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis', *Biochem. Pharmacol.* 55, 863-71, 1998]);

(c) 5- ([Ford-Hutchinson, *ibid.*]; [Hamel, 'substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase inhibitors - synthesis, biological profile and pharmacokinetics of L-739,010', *J. Med. Chem.* 40, 2866-75, 1997]).

가 5-

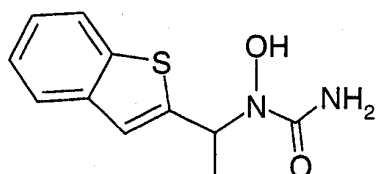
5-

, N-

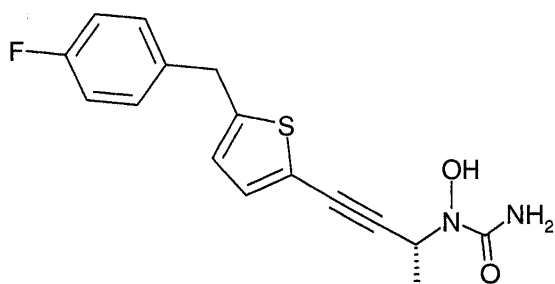
ABT-761

,

:



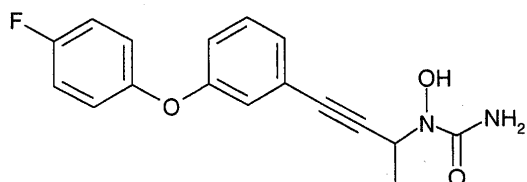
질레우톤 ;



ABT-761

N-

(Abbott-76745):

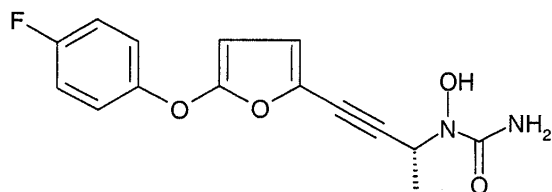


팬레우톤

N-

Abbott-79175

:



Abbott-79175.

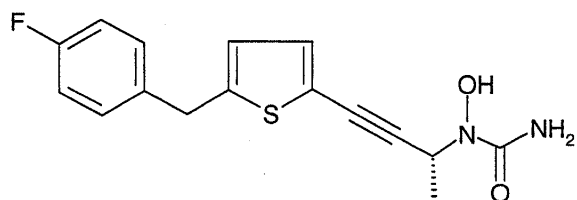
Abbott-79175  
,1995].

; [Brooks, *J. Pharm. Exp. Therapeut* 272 724

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-LO

가 LT

, LT

, 5-LO

5-

, 5-

, LT

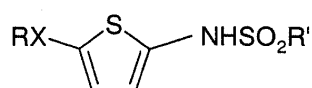
N -

5-

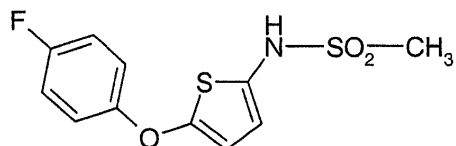
N - (5 -

)-

-2

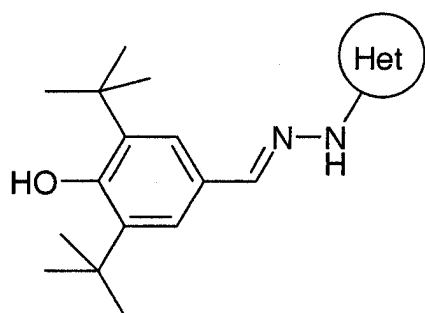


( $\text{X}$ ,  $\text{O}$ ,  $\text{S}$ ;  $\text{R}'$ ,  $n\text{-C}_6\text{H}_{13}$ ,  $n\text{-C}_8\text{H}_{17}$ ,  $\text{R}$ ,  $n\text{-C}_6\text{H}_{13}$ ,  $n\text{-C}_8\text{H}_{17}$ ,  $\text{Cl}$ ,  $\text{F}$ ,  $\text{Br}$ ,  $\text{CH}_3$ ,  $\text{OCH}_3$ ,  $\text{SCH}_3$ ,  $\text{SO}_2\text{CH}_3$ ,  $\text{CF}_3$ ,  $\text{CN}$ ).  
:



[Beers, 'N-(5-substituted) thiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase', *Bioorganic and Medicinal Chemistry* 5(4), 779-786, 1997].

5-  
rt-butylphenol hydrazones as 5-lipoxygenase inhibitors', Bioorganic amp; Medicinal Chemistry 6,173-180, 1  
998]



( ,

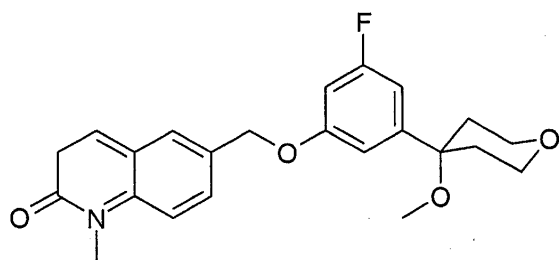


'Het' -2- , -2- , -2- , -2- , 4- -2- ,  
 4,6- -2- , 4- -2- , 4,6- -2- , 4- -2- , 4,6-  
 -2- 4- -6- -2- ).

N-(5- )- -2- 2,6- -tert-  
 |

가 5-  
 :

Zeneca ZD-2138

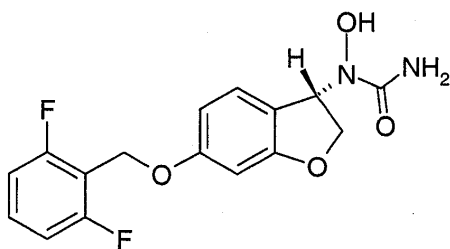


ZD-2138.

ZD-2138

가 . ZD-2138 [Crawley , J. Med. Chem., 35, 26  
 00,1992], [Crawley , J. Med. Chem. 36, 295,1993]

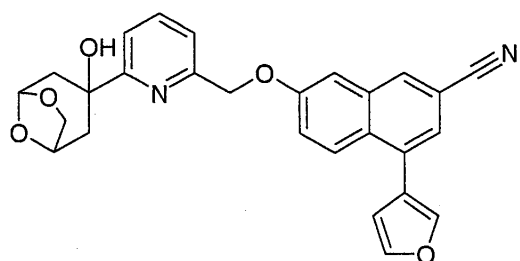
5- SmithKline Beecham SB-210661 :



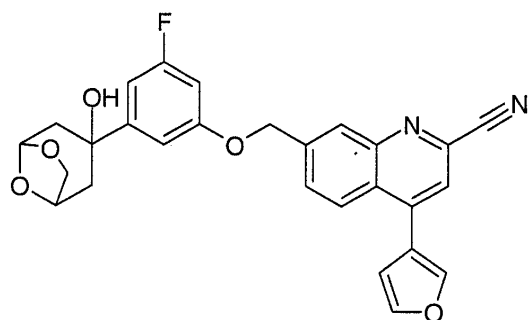
2 가 , 5-  
 2- L-739,010 L-746,530 2-  
 :

Merck Frosst

2 5-



L-739,010



L-746,530

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

L 739,010

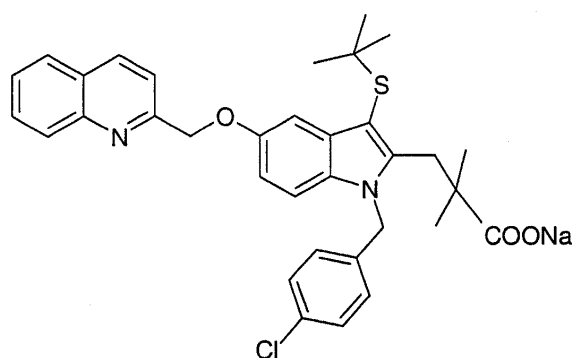
SB-210661

L-746,530

5- (FLAP) 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 an anti-IgE challenge in human airways', J. Pharmacol. Exp. Ther. 268, 868-72, 1994] ).

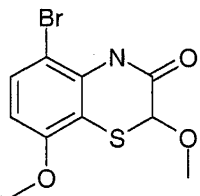
MK-591



MK-591

MK-591, IVIK-886 BAY x1005

LTB<sub>4</sub> , LTC<sub>4</sub> , LTD<sub>4</sub> , LTE<sub>4</sub> ( ) LTB<sub>4</sub> , LTC<sub>4</sub> , LTD<sub>4</sub> , LTE<sub>4</sub> LTB<sub>4</sub> LTD<sub>4</sub> L-651,392 5,083 (Lau ) 4- -2,7- -3H- -3- US 4,939,145 (Guindon ) US 4,84



L-651,392.

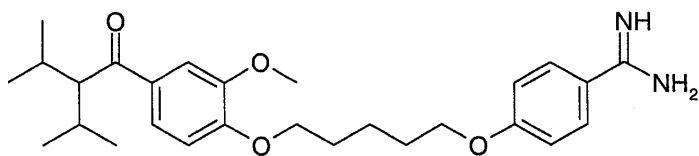
CGS-25019c

US 5,451,700 (Morrissey Suh); US 5,488,160 (Morrissey)

, US 5,639,768 (Morrissey Suh)

LTB<sub>4</sub>

CGS-25019c :

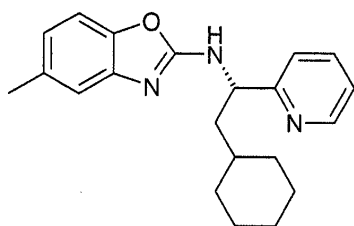


CGS-25019c

LTB<sub>4</sub>

EP 535 521 (Anderskewitz )

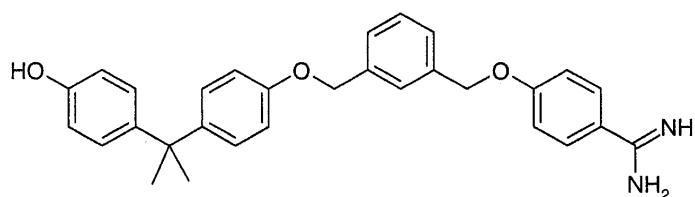
:

LTB<sub>4</sub>

Anderskewitz ) WO 98/11119 (Anderskewitz )

, BIIL 284/260

WO 97/21670 (



BIIL 284/260

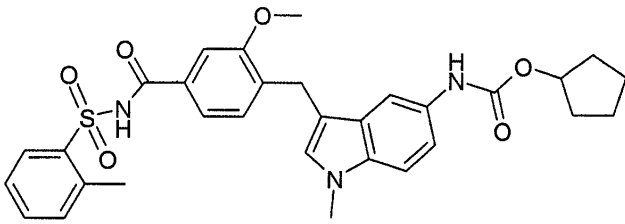
Accolate ®

LTC<sub>4</sub>, LTD<sub>4</sub> LTE<sub>4</sub>

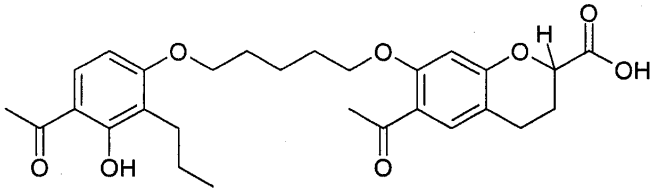
US 4,859,6

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 )

:



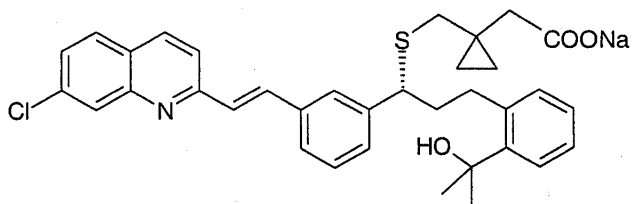
Ro 23-3544/001

LTD<sub>4</sub>Singular <sup>®</sup>LTD<sub>4</sub>

, US 5,565,473

•

•



LTD 4  
GP 45715A) BAY x7195 가

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

(C

, L - 651,392

- 3 -

, CGS-25019c

, BIL 284/260,  
가

(a) PDE IV ;

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

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

(d) LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, (LTRA);

(e)  $H_1$  ;



(ee)	B <sub>1</sub>	B <sub>2</sub>	:
(ff)			:
(gg)	,	,	:
(hh)	,	:	
(ii)		,	:
(jj)	,	,	
(kk)	,	,	:
(ll)		:	
(mm)	-1 (MMP-3),	(MMP) -1 (MMP-1), -2 (MMP-10)	, , -2 (MMP-8), -3 (MMP-11); -3 (MMP-13),
(nn)		(TGF ):	
(oo)		(PDGF);	
(pp)		,	(bFGF);
(qq)		(GM-CSF);	
(rr)	:		
(ss)	NKP-608C; SB-233412 ( );	D-4418	NK <sub>1</sub> NK <sub>3</sub>
(tt)	UT-77 ZD-0892		:
(uu)	A2a .		



가 . , , p- , , , , 4 - , , , (EDTA) 가 .

0.01 %                      2 %

가 .

pH

EDTA 가

(tinea versicolor)

(tinea corporis),

(tinea pedis),

(candidiasis)

가

가

(emollient)

20 - , C 10 -C 20 -  
(oil-in-water) (200-600),

$$C_{10} - C_{20} - C_{10} - 0$$

1 -  
p-  
-2-

(DMSO);

, 4

가 .

(water - in - oil)

2      20

$$, (C_{10} - C_{20})^2$$



20 , , MW 200-6000 , MW 200-3000 , C<sub>10</sub>-C<sub>20</sub>

가 . 가

(C<sub>10</sub>-C<sub>50</sub>) , (C<sub>10</sub>-C<sub>30</sub>) , (C<sub>10</sub>-C<sub>30</sub>)-

가 910, 934, 934P, 940, 941 1342

/ 2- 가

. 4 가

가

가

-2- (DMSO) , 1-

가

가

p-

4

가 ; 6, 7 8

15

가

가

4, 9,

-4, -9 -10, (p- ) 15, -(p- )-

( , 30, -(p- )-

[illegible]

..

PDE VII

I

: (1)

(c) (depot) (cavities) ( ), (2)

(c) (a) (b) (3)

(c) (a) (b)

(a) (4) (b).

가 : (1)

(lozenge), (troche) (2) (a) (caplet),

가 (b) 24 (c) (d) (e) (f)

(g) (h)

PDE VII

: (1)

(a)

(b)

(c) (2)

(b)

(a) (3)

(c)

가

pH 가 pH

/ 가

I

가

가



가 .

PDE IV

[illegible]

g 0.001  $\mu\text{g}$  /kg 10.0 mg /kg , 1 0.5  $\mu\text{g}$  /kg 0.1 mg /kg  
/kg , 가 1 2.0  $\mu\text{g}$  /kg 1.0  $\mu\text{g}$  /kg 0.05 mg /kg

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

1, 가 .  
1, 50.0  $\mu$ g, 10.0 mg, 1, 4

(a)  $\frac{1}{2}$  가 ,

(b)                   가                   .

가

(MS): EI ( ) M<sup>+</sup>

FAB ( ) (M+H) <sup>+</sup>



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> 30 ml 2.6 g (1) 5.0 g Fmoc-Tyr(tBu)-  
 OH (3) 가 . 16 .  
 , ( / 1:1) , 2.  
 3 g I-A-8 .

3.2 ( -PS) I-A-8 Fmoc  
 . 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 .  
 , 303 mg I-A-10 .

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

3.5 3.4 , I-A-10 -4- I-A-12 .

4

4.1 3.3 g DAPECI [N-(3- )-N- 1.7 g NMM (N- )  
 10 ml DMF 5.0 g BOC-D-Tyr(Me)-OH (4) 2.6 g HOBT 가 .  
 4 , 3.9 g (1) , 16 . 가 DAP  
 ECI 가 , 16 . 8.1 g I-A-13 .

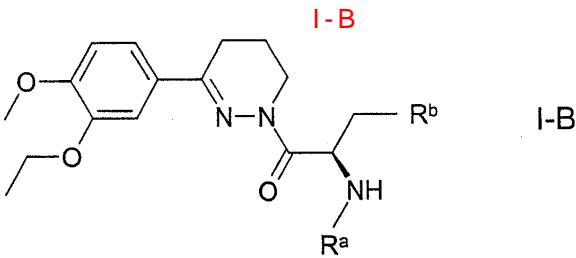
4.2 3.3 g DAPECI 1.7 g NMM 10 ml DMF 5.0 g BOC-Tyr(Me)-OH (5) 2.6 g HOBT  
 가 . , 3.9 g (1) , 16  
 . 가 DAPECI 가 , 16 .  
 7.0 g I-A-14 .

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 .  
 16 .  
 , ( / 1:1) , 0.3 g I-A-15 .

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



[ 2]

	R <sup>a</sup>	R <sup>b</sup>	
I-B-1	BOC	3-	
I-B-2	H	3-	
I-B-3	BOC	4-	
I-B-4	H	4-	

5.2 4 ml 0.4 g I-B-1 1 ml TFA 16 . TFA  
DCM , , 164 mg I-B-2 .

5.3 0.8 g DAPECI 0.43 ml NMM 5 ml DMF 1.0 g BOC-D-4- (8) 0.6 g  
HOBT 가 . 4 0.9 g (1) , 16  
0.4 g I-B-3 .

5.4 10 ml 0.35 g I-B-3 1 ml TFA 1 . TF  
A DCM , , 0.19 g I-B-4 .

I: T- I

Lymphoprep (PBMC) , 96  
- - 가 (96-well flat-base microtitre plate) 200,000 PBMCs RPMI164  
O 5% - (heat-deactivated) (AB ) 37 5 10% CO<sub>2</sub>  
2 . PBMC T- CD3 .  
3 .

I DMSO 10<sup>-2</sup> M . 3 H- 가 ,  
DMSO . 18 . 3 가  
% ( ±SFN) . IC<sub>50</sub> .



II:

I

Lymphoprep (PBMCs)  
 6- (96-well flat-base microtitre plate) 200,000 PBMCs , 9  
 40 5% 가 (AB ) 10% CO<sub>2</sub> 37 5 RPMI16  
 3 DMSO I 10<sup>-2</sup> M  
 DMSO .3  
 ELISA  
 % / IC<sub>50</sub> EC<sub>50</sub>

A:

3 2 100 g I 5 g 2N  
 pH 6.5 , 5 mg ,

B:

20 g I 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 I 99.5 g .

E:

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

F:

E , , , ,

G:

2 kg I 20 mg

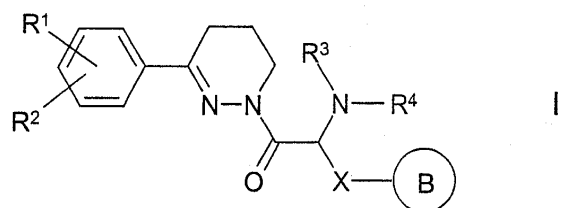
H:

60 1 kg I , 10 mg .

1.

I 가 ,  
:

[ I]



( ,

 $R^1, R^2$  , , H, OH, OR<sup>8</sup>, -SR<sup>8</sup>, -SOR<sup>8</sup>, -SO<sub>2</sub>R<sup>8</sup> Hal ,

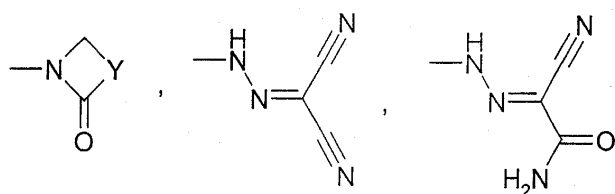
 $R^1, R^2$  -OCH<sub>2</sub>O- -OCH<sub>2</sub>CH<sub>2</sub>O- ,

 $R^3$  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> ,

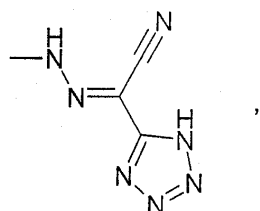
 $R^4$  H, A'R<sup>9</sup>, COA'R<sup>9</sup>, COOA'R<sup>9</sup>, CONH<sub>2</sub>, CONHA'R<sup>9</sup> CON(A'R<sup>9</sup>)(A''R<sup>9</sup>) ,

 $B$  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  
 10 2 8 H 가 R<sup>11</sup> / R<sup>12</sup> , 1

 $R^5, R^6, R^7$  , 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, COOH, COOA'R<sup>9</sup>, CON  
 H<sub>2</sub>, CONHA'R<sup>9</sup>, CON(A'R<sup>9</sup>)(A''R<sup>9</sup>),


또는


 $R^8$  A, 3 7 4 8 ,

 $R^9$  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 ,

 $R^{10}$  , CH<sub>2</sub> 가 O, S, SO, SO<sub>2</sub>, NH, NMe, NEt / -CH=CH-

$$\begin{array}{ccccccc} , & 1 & 7 & H & 가 F & / & Cl \\ , & & 1 & 10 & , & 3 & 7 \end{array}, \quad \begin{array}{ccccc} , & 1 & H & 가 R^9 \\ , & 4 & 8 & & \end{array}$$
$$\begin{aligned} &R^{11} \quad H, A, COOA'R^9, CONH_2, CONHA'R^9, CON(A'R^9)(A''R^9), NH_2, NHA'R^9, N(A'R^9)(A''R^9), \\ &NCOA'R^9, NCOOA'R^9, OH \quad OA'R^9, \end{aligned}$$
$$R^{12} \quad H, A, COOAR^9, CONH_2, CONHA'R^9 \quad CON(A'R^9)(A''R^9) \quad ,$$

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

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

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

$$\text{Hal, R}^{14}, \text{OR}^{13}, \text{N(R}^{13})_2, \text{NO}_2, \text{CN, COOR}^{13}, \text{CON(R}^{13})_2, \text{NR}^{13}\text{COR}^{13}, \text{NR}^{13}\text{CON(R}^{13})_2, \text{NR}^{13}\text{SO}_2\text{A, COR}^{13}, \text{SO}_2\text{N(R}^{13})_2, \text{S(O)}_m\text{R}^{14},$$

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

R 14 1 6 .

$$\text{Het} \quad \text{R}^{13} \text{COR}^{13}, \text{NR}^{13} \text{CON(R}^{13})_2, \text{NR}^{13} \text{SO}_2 \text{R}^{14}, \text{COR}^{13}, \text{SO}_2 \text{NR}^{13} / \text{S(0)}_m \text{R}^{14}, \text{N, O} / \text{S}, \text{Hal, R}^{14}, \text{OR}^{13}, \text{N(R}^{13})_2, \text{NO}_2, \text{CN, COOR}^{13}, \text{CON(R}^{13})_2, \text{N}$$

Hal F, Cl, Br I ,

$$m = 0, 1, 2, \dots$$
$$n = 0, 1, 2, 3, 4, \dots).$$

2.

1. R<sup>1</sup>, R<sup>2</sup>, H, F, Cl, 가

**3.**

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

4.





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

14.

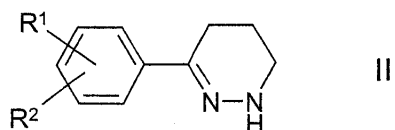
1 13 , IV I .

15.

I ,

a) II III , , , :

[ II]

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



[illegible]



(HIV)

; ;

- ;

, ,

, HIV-1, HIV-2 HIV-3, CMV,

가 TNF- 가 TNF-

TNF- TNF-

B, B B

- 가 가 , HIV

**20.**

17 19 : 1 13  
I :

(1) ; (2) ; (3)  
; (4) 가 GvH ;  
(5) AIDS  
(HIV), AIDS (ARC),

1 .

**21.**

17 1 13 I

.

**22.**

21 1 13  
I .

**23.**

17 , 가 / -  
(in-stent) - (stent-in-stent)  
, 1 13 I .

**24.**

(member) 1 13 :

- (a) : , ABT-761, , Abbott-79175, Abbott-85761, N-(5-  
) -2- , 2,6- -tert- , Zeneca ZD-2138, SB-210661, -  
2- L 739,010, 2- L-746,530, MK-591, MK-8  
86 BAY x 1005 5- (5-LO) 5-  
(FLAP) ;
- (b) -3- L-651,392, CGS-25019c, ,  
BIIL 284/260, ,  
(MK-679), RG-12525, Ro-245913, (CGP 45715A) BAY x7195  
LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub> LTE<sub>4</sub> ;
- (c) PDE IV ;
- (d) 5- (5-LO) ; 5- (FLAP) ;
- (e) 5- (5-LO) (PAF) ;
- (f) LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub> LTE<sub>4</sub> (LTRA);
- (g) , , , , , ,  
H<sub>1</sub> ;
- (h) H<sub>2</sub> ;
- (i) , , , , , ,  
 , , , 1<sup>-</sup> 2<sup>-</sup>  
 ;
- (j) (a) 5- (5-LO) (i)  
1<sup>-</sup> 2<sup>-</sup> ;
- (k) , , , , ,  
 ;
- (l) , , , , , , , , , ,  
 , 1<sup>-</sup> 4<sup>-</sup> ;
- (m) ;
- (n) ;
- (o) (M1, M2 M3) ;
- (p) COX-1 (NSAID) NSAID;
- (q) COX-2 ;
- (r) 1 (IGF-1) ;
- (s) ;
- (t) , , , , , , , , , ,  
 , ;
- (u) ;

- (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) , - 1 (MMP-1), - 2 (MM  
P-8), - 3 (MMP-13), - 1 (MMP-3), - 2 (MMP-10) - 3 (M  
MP-11) (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.**

13 / 가  
,  
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26.

( ):

(a) 1 13 | / 가

b)                    가                    .