

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl.⁷
C07D 265/30
A61K 31/7056

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(43)

10-2004-0095347
2004 11 12

(21) 10-2004-7015447

(22) 2004 09 25

2004 09 25

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(87)

WO 2003/082291

(86) 2003 03 27

(87)

2003 10 09

(30) 0207449.0

2002 03 28

(GB)

(71) 6 0

(72) ' 1 2 '

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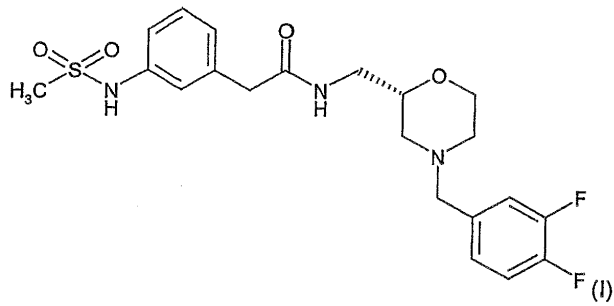
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(74)

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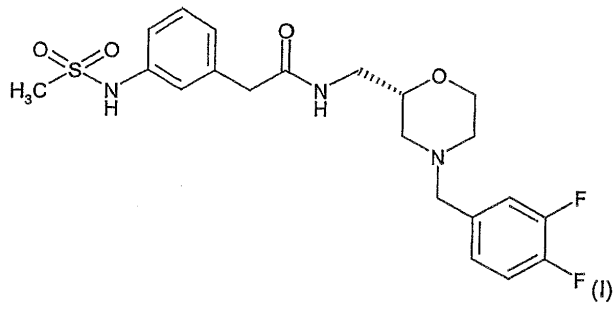
(54)	CCR3	N - { [(2S)-4-(3,4-)	-2
-]	3-[()] }		

3-(f [{{{[(2S)-4-(3,4-
 (I) : Hsc H H '(0) IIZZ V;
 CCR3



1 (,) (가
 1 , 가
 2 (Th2) IL-4 IL-5 가 T-
 (pro-inflammatory)
 가

, Th2
 , , ,
 [: Luster, New Eng. J. Med., 38, 436-445 (1998)].
 CC- () , G- 7 - 가 , T B CXC- ()
 (: Luster, 1998). 가,
 Th2 , CC 가 , RANTES, MCP-3 MCP-4 CCR-3
 CC- -3 CCR-3
 -2 . CCR-3 , CCR-3
 . CCR-3
 [: Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)]. , -CCR-3
 [Heath, H. et al., (1997) J. Clin. Invest. 99 (2), 178-184], CCR-3 가
 [Gonzalo et al., J. Exp. Med., 188, 157-167 (1998)]. , CCR-3
 가 가
 RANTES MCP-3
 3 CC [: Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997]. , CXCR-4, CCR-5 CCR-3 (HIV)
 , CCR-3
 HIV CCR-3
 WO 01/24786 (Shionogi amp; Co. Ltd.)
 가 . WO 00/69830 (Torrey Pines Institute for Molecular Studies)
 , 가 . WO 00/18767 (Neurogen Corporation) D4 가 6,0
 31,097 WO 99/21848 (Neurogen Corporation)
 가 . WO 99/06384 (Recordati Industria Chimica)
 가 . WO 98/56771 (Schering Aktiengesellschaft)
 가 . WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.) D
 . WO 96/39386 (Schering Corporation)
) 가 . WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) . WO
 95/32196 (Merck Sharp amp; Dohme Limited) 5-HT1D-
 5,389,635 (E.I. Du Pont de Nemours and Company)
 -II 0 306 440 (Schering Aktiengesellschaft) 가
 CCR-3 /
 Th2-
 ,
 , 가 N- {[(2S)-4-(3,4-) -2-] }-
 2-{3-[()] } (I) :



(I)

(I)

가

, 1- -2-

(I)

(I)

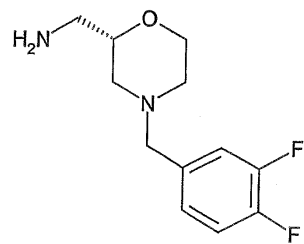
(II)

(I)

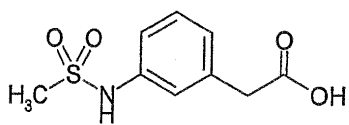
II)

(i)

(ii)



(II)



(III)

(II) (III)

12 24

1-(3-

) -3-
N,N-

3

N,N-

1-

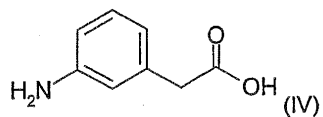
18

25

(III)

(IV)

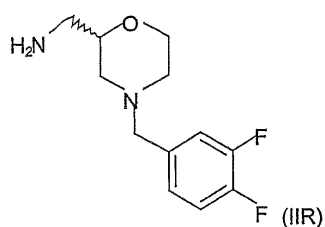
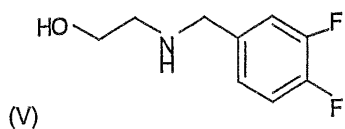
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(II) (a), (b), (c)

(a). (V) A가 (IIR) (VI)

:

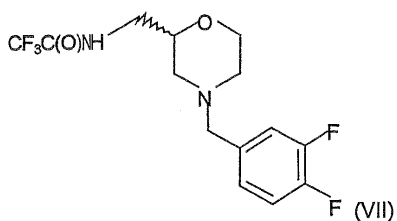


;

(b). (V) A가 (VI) (VI)



(c). (VII) 가 (IIR) :



(a) (IIBR) (b) (IIB) (V) (VI) (VIA) (Mitsunobu condition) :

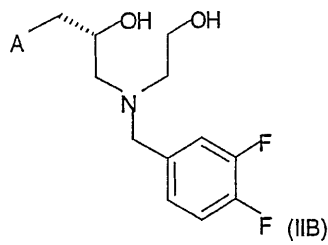
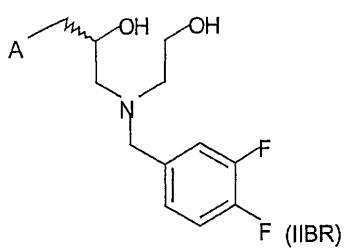
(V) (VI) (VIA)

20 24 가 가 0 5 7

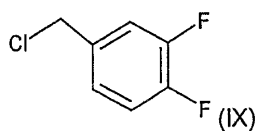
20 10 15 가 가 2 3 가 가

25 가 가 4 6 가 가

가 , 가 20 24 , ; 가 가 , . , 가 , 20 , 45 , 가 , 가 65 75 ; 가 가 1.5 3 , 20 , 35 45 (IIR) (II) . (II) , , 70 , 75 가 (IIR) , , 20 24 가 , , 20 , 25 , 80 , 가 . 가 가 , 가 20 25 가 , 0.8 (II) (IIR) (II) (IIBR) (IIB) A가 (VI) (VIA) ;



, (V) (VI) (VIA) 20 24 , 가 (V) 가 , 3 6 , 가 , 가 20 25 (IIBR) (IIB) , 가 (II) (V) (VI) (VIA) , (II) BR) (IIB) (c) , 가 (VII) , 20 2 , 5 가 , 16 20 , , (IIR) (II) (HPLC) , (V) (IX) :

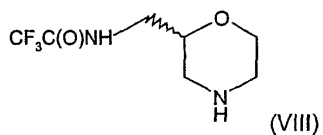


(VII)

(VIII)

40 60

3,4-



(VIII)

3,4-

N,N-

20 25

16 20

(VIII)

-2-

20 25

20 40

(IV) (VI)

[Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience]

(II), (IIBR), (IIB) (V)

(II)

(IIBR)

(IIB)

(V)

J Kocienski, Protecting Groups, (1994), Thieme]

[P

, 가

, 가 /

(I)

(I)

(a) CCR -3

CCR-3

SPA (

: scintillation proximity assay) CCR-3

25mg/M, 0.5% BSA) 가 SPA (1pM) 1.5 (30mM) CCR-3(2.5mg/) 가 , 96 (HEPES 50 mM, CaCl₂ 1 mM, MgCl₂ 5 mM, 20 pM [¹²⁵ I]) K562 (:Amersham) 2 22 가 100 μl 가 50% pIC₅₀ ([

(b) _____

가 (Miltenyi) (Motegi amp; Kita, 1998; J. Immunology. 161:4340-6) (magnetic Supermac magnet) CD16 RPMI 1640/10% FCS -AM() 37 30 가 4 00g 5 , 2.2 million/ml RPMI/FCS 가 (1 pM 30 mM) 37 30 RPMI/FCS 가 (EC₈₀) 96- (5μm :) 가 , 37 45 가

Br.J.Pharmacol 109: 1110-9) pK_i (fpK_i) (Lazareno amp; Birdsall, 1995.

$$fpKi = \frac{IC_{50}}{1 + \frac{[약용제]}{EC_{50}}}$$

CCR-3 / 8.0 pIC₅₀ 가 (a) (b) . CCR-3 8.4 fpKi 가 .

(,), (,) (COPD), () 2

(, ,) 가 , HIV AIDS, ,

가 , 가 , COPD ,

가 (I) (I)

(l)

(l)

가

(l)

(l)

(l)

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(tragacanth),

()

가

p-

()

가

, PDE-4
2a

, iNOS

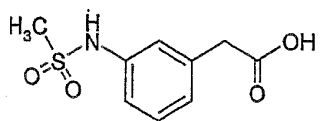
(NSAIDs),

-2

_____ (1.84g)

HPLC 28.5

4: 3[()] 1



(36Mℓ) 3- (3.2g) (5.44g)
 (1.7Mℓ) 가 85 4
 pH 2 4

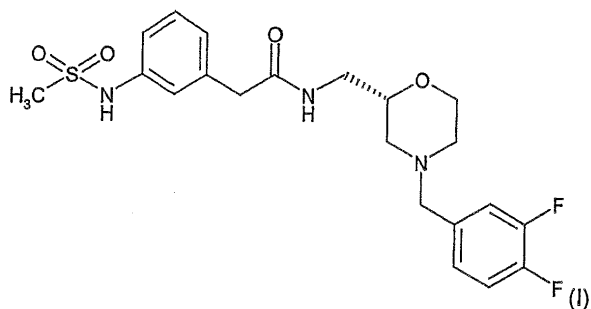
_____ (0.417g)

LC/MS : R_t = 2.00 , m/z 228 [MH⁻], m/z 247 [MNH₄⁺]

(57)

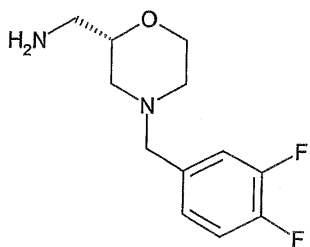
1.

(I) :

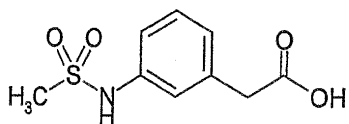


2.

(II) : (III) , (I)



(II)



(III)

3.

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4.

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가

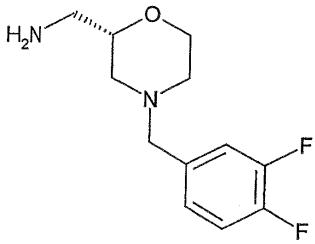
5.

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6.

(II)

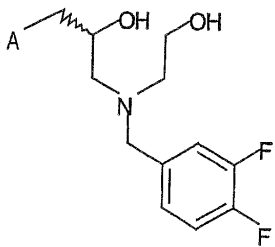
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7.

(IIBR)

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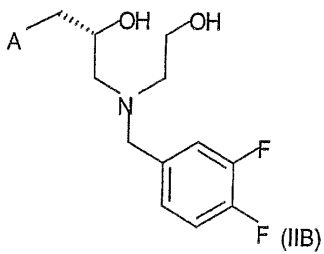


, A

8.

(IIB)

:



, A

9.

(V)

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