

(19) (12) (KR) (A)

(51) 。 Int. Cl.<sup>7</sup> (11) 10-2004-0098013  
C07D 235/08 (43) 2004 11 18  
C07D 413/06

|      |                   |      |                |
|------|-------------------|------|----------------|
| (21) | 10-2004-7014206   |      |                |
| (22) | 2004 09 10        |      |                |
|      | 2004 09 10        |      |                |
| (86) | PCT/US2003/007565 | (87) | WO 2003/077855 |
| (86) | 2003 03 13        | (87) | 2003 09 25     |

(30) 60/364,164 2002 03 13 (US)

(71) 80301 3200

(72) 80540 1727

80027 1720

80304 #22 3725

80304 #57 2722

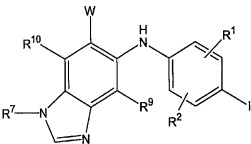
(74)

:

(54) ME K N3

(I) ( W, t, R <sup>1</sup> , R <sup>2</sup> , R <sup>7</sup> , R <sup>9</sup> , R <sup>10</sup> , R <sup>11</sup> R <sup>12</sup> 가 )  
가 MEK ,

< I>



MEK ,

(1H- -5- )-(4- - )- . , , .

(Cell signalling)  
( , PDGF EGF ) MAP  
가 가 MAP  
Ras/Raf GTP- Ras Raf (MEK1 S218 S222 MEK2 S2  
22 S226) [Ahn et al., Methods in Enzymology 2001, 332, 417-431]. , MEK  
, MAP , ERK1 ERK2 . MEK ERK ERK1 Y204 T2  
02 , ERK2 Y185 T183 [Ahn et al., Methods in Enzymology 2001, 332, 417-431].  
ERK [Khokhlatchev et al., Cell 1998, 93, 605-61  
5]. , ERK , DNA , mRNA  
, [Ahn et al., Molecular Cell 2000, 6, 1343-1354  
]. ERK1 ERK2 가  
[Lewis et al., Adv. Cancer Res. 1998, 74, 49-139].

, ERK  
( )

GTP- Ras MAP  
. Ras 50% 90%  
[Kohl et al., Science 1993, 260, 1834-1837]. , bRaf  
60% [Davies, H. et al., Nature 2002, 417, 949-954]. bRaf  
MAP (cascade) . 1  
MAP [Hoshino, R. et al., Oncogene 1999,  
18, 813-822]. MAP

MAP  
. MEK Ras Raf  
가 , MEK MAP , ERK1 2 , MEK  
MEK MEK  
([Sebolt-Leopold et al., Nature - Medicine 199  
9, 5 (7), 810-816]; [Trachet et al., AACR April 6-10, 2002, Poster #5426]; [Teclé, H. IBC 2<sup>nd</sup> Internationa  
I Conference of Protein Kinases, September 9-10, 2002]), (2001 1 25  
WO 01/05390), [Milella et al., J Clin Invest 2001, 108  
(6), 851-859]

MEK 가 13 가 : 1995 1 24  
US 5,525,625; 1998 10 8 WO 98/43960; 1999 1 14 WO 99/01421;  
1999 1 14 WO 99/01426; 2000 7 20 WO 00/41505; 2000 7 20  
WO 00/42002; 2000 7 20 WO 00/42003; 2000 7 20 WO 00/41994;  
2000 7 20 WO 00/42022; 2000 7 20 WO 00/42029; 2000 11 16

- 3 -

$R^3$   $R^4$  4 10- ,  
 $-NR'SO_2R''''$ ,  $-SO_2NR'R''$ ,  $-C(O)R'$ ,  $-C(O)OR'$ ,  $-OC(O)R'$ ,  $-NR'C(O)OR''''$ ,  $-NR'C(O)R''$ ,  $-C(O)NR'R''$ ,  $-SO_2R''''$ ,  $-NR'R''$ ,  $-NR'C(O)NR''R'''$ ,  $-NR'C(NCN)NR''R'''$ ,  $-OR'$ ,  
 1 3 ;

$R^4$   $R^5$   $C_1-C_6$  ;

$R^4$   $R^5$  4 10- ,  
 $SO_2R''''$ ,  $-SO_2NR'R''$ ,  $-C(O)R''''$ ,  $-C(O)OR'$ ,  $-OC(O)R'$ ,  $-NR'C(O)OR''$ ,  $-NR'C(O)R''$ ,  $-C(O)NR'R''$ ,  $-SO_2R''''$ ,  $-NR'R''$ ,  $-NR'C(O)NR''R'''$ ,  $-NR'C(NCN)NR''R'''$ ,  $-OR'$ ,  
 1 3 ;

$R^6$  ,  
 $C_1-C_{10}$  ,  $C_3-C_{10}$  ,  
 ( , , , , ,  
 $-NR'SO_2R''''$ ,  $-SO_2NR'R''$ ,  $-C(O)R'$ ,  $-C(O)OR'$ ,  
 $-OC(O)R'$ ,  $-NR'C(O)OR''''$ ,  $-NR'C(O)R''$ ,  $-C(O)NR'R''$ ,  $-SO_2R''''$ ,  $-NR'R'$ ,  $-NR'C(O)NR''R'''$ ,  $-NR'C(NCN)NR''R'''$ ,  
 $-OR'$ ,  
 1 5 ) ;

$R^7$  ,  
 $C_1-C_{10}$  ,  $C_2-C_{10}$  ,  $C_2-C_{10}$  ,  $C_3-C_{10}$  ( ,  $C_3-C_{10}$  , , ,  
 $-NR^4SO_2R^6$ ,  $-SO_2NR^3R^4$ ,  $-C(O)R^3$ ,  $-C(O)OR^3$ ,  $-OC(O)R^3$ ,  $-NR^4C(O)OR^6$ ,  $-NR^4C(O)R^3$ ,  $-C(O)NR^3R^4$ ,  $-SO_2R^6$ ,  $-NR^3R^4$ ,  $-NR^5C(O)NR^3R^4$ ,  $-NR^5C(NCN)NR^3R^4$ ,  $-OR^3$ ,  
 1 5 ) ;

$W$  ,  $-C(O)OR^3$ ,  $-C(O)NR^3R^4$ ,  $-C(O)NR^4OR^3$ ,  $-C(O)R^4OR^3$ ,  $-C(O)(C_3-C_{10})$ ,  $-C(O)(C_1-C_{10})$ ,  $-C(O)( )$ ,  $-C(O)( )$   $-C(O)( )$

$-NR^3R^4$ ,  $-OR^3$ ,  $-R^2$ ,

$C_1-C_{10}$  1 2 ,  $C_2-C_{10}$   $C_2-C_{10}$  (  $-NR^3R^4$   $-OR^3$  1 5 ) ;

$m$  0, 1, 2, 3, 4 5 ;

$j$  1 2 .

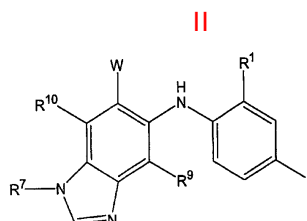
I

가

,  $R^7$   $C_1-C_{10}$  ,  $C_3-C_7$  ,  $C_3-C_7$  ,  $-NR^4SO_2R^6$ ,  $-SO_2NR^3R^4$ ,  $-C(O)R^3$ ,  $-C(O)OR^3$ ,  $-OC(O)R^3$ ,  $-SO_2R^3$ ,  $-NR^4C(O)OR^6$ ,  $-NR^4C(O)R^3$ ,  $-C(O)NR^3R^4$ ,  $-NR^3R^4$ ,  $-NR^5C(O)NR^3R^4$ ,  $-NR^5C(NCN)NR^3R^4$ ,  $-OR^3$ ,  
 1 3

I

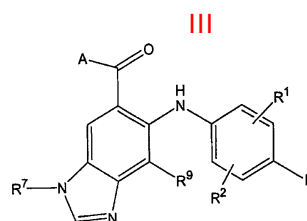
,  $R^9$  가 ,  $R^{10}$  이 .

$$W가 -C(O)OR^3 \quad -C(O)NR^4 \text{ OR }^3 \quad |$$
$$, \quad \quad \quad \parallel \quad \quad \quad :$$


$\{W, R^1, R^7, R^9, R^{10}\}$  I.

[illegible]
$$, R^9 \text{ 가 } \quad , R^{10} \quad \text{ II} \quad .$$
$$W가 -C(O)OR^3 \quad -C(O)NR^4 OR^3 \quad II$$

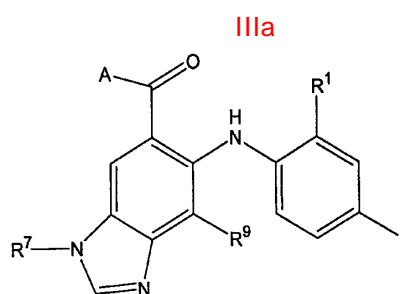
III :


$$\begin{array}{c} \text{R}^1, \text{R}^2, \text{R}^7 \\ \text{R}^3 \quad \text{R}^4 \end{array} \quad \text{R}^9 \quad \text{I} \quad \text{I} \quad \text{A} \quad -\text{OR}^3 \quad -\text{NR}^4 \text{C(O)R}^3$$
$$\begin{aligned} & \text{, } \quad \text{R}^7 \quad \text{C}_1 - \text{C}_{10} \quad \text{, } \text{C}_3 - \text{C}_7 \quad \text{C}_3 - \text{C}_7 \quad \text{,} \\ & \text{-SO}_2 \text{NR}^3 \text{R}^4 \text{, } \text{-C(O)R}^3 \text{, } \text{-C(O)OR}^3 \text{, } \text{-OC(O)R}^3 \text{, } \text{-SO}_2 \text{R}^3 \text{, } \text{-NR}^4 \text{C(O)OR}^6 \text{, } \text{-NR}^4 \text{C(O)R}^3 \text{, } \text{-C} \\ & \text{(O)NR}^3 \text{R}^4 \text{, } \text{-NR}^3 \text{R}^4 \text{, } \text{-NR}^5 \text{C(O)NR}^3 \text{R}^4 \text{, } \text{-NR}^5 \text{C(NCN)NR}^3 \text{R}^4 \text{, } \text{-OR}^3 \text{,} \\ & \text{, } \quad \text{III} \quad \text{, } \quad \text{1} \quad \text{3} \end{aligned}$$

R 9 가 III .

$$\text{A가 } -\text{OR}^3 \quad \text{R}^3 \quad ; \text{A가 } -\text{NR}^4 \text{C(O)R}^3 \quad \text{R}^4$$

IIIa


$$\begin{array}{c} \text{R}^1, \text{R}^2, \text{R}^7, \text{R}^9 \\ \text{R}^3, \text{R}^4 \end{array} \quad \text{I} \quad \text{A} \quad -\text{OR}^3 \quad -\text{NR}^4 \text{C(O)R}^3$$

$$\text{R}^7, \text{C}_1-\text{C}_{10}, \text{C}_3-\text{C}_7, \text{C}_3-\text{C}_7$$

$$\begin{array}{c} -\text{SO}_2 \text{NR}^3 \text{R}^4, -\text{C(O)R}^3, -\text{C(O)OR}^3, -\text{OC(O)R}^3, -\text{SO}_2 \text{R}^3, -\text{NR}^4 \text{C(O)OR}^6, -\text{NR}^4 \text{C(O)R}^3, -\text{C(O)NR}^3 \text{R}^4, \\ -\text{NR}^3 \text{R}^4, -\text{NR}^5 \text{C(O)NR}^3 \text{R}^4, -\text{NR}^5 \text{C(NCN)NR}^3 \text{R}^4, -\text{OR}^3, \end{array}$$

$$\text{IIIa} \quad 1 \quad 3$$

$\text{R}^9$  가  $\text{IIIa}$  .  
 $\text{A}$ 가  $-\text{OR}^3$   $\text{R}^3$  ;  $\text{A}$ 가  $-\text{NR}^4 \text{C(O)R}^3$   $\text{R}^4$   
 $\text{IIIa}$  .

[illegible]

'C<sub>2</sub>-C<sub>10</sub>      '      '      '      2      10      1  
, , , , , -2- . 3 5

' , ' ( , ), 가  
( , 1,2,3,4- ) ,  
, , , , , - , - ,

[illegible]



( ), / ,

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, 2- (2-

) , N-

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, D-, D-

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m t (CR<sup>4</sup>R<sup>5</sup>)<sub>m</sub> (CR<sup>4</sup>R<sup>5</sup>)<sub>t</sub> 가 , R<sup>4</sup> R<sup>5</sup> 1  
-CH<sub>2</sub>CH<sub>2</sub>- -CH(CH<sub>3</sub>)C(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)- (CR<sup>4</sup>R<sup>5</sup>)<sub>m</sub> (CR<sup>4</sup>R<sup>5</sup>)<sub>t</sub>가 2 , R<sup>4</sup> R<sup>5</sup>

가 , 가 .

가  
<sup>2</sup>H, <sup>3</sup>H, <sup>13</sup>C, <sup>14</sup>C, <sup>15</sup>N, <sup>18</sup>O, <sup>17</sup>O, <sup>31</sup>P, <sup>32</sup>P, <sup>35</sup>S, <sup>18</sup>F, <sup>36</sup>Cl  
( ) 가  
H <sup>14</sup>C - 14, <sup>14</sup>C 가 ( )  
가 , <sup>3</sup>H  
가  
가  
( )  
가  
2 ( 2, 3  
4 ) 가  
3  
20 , 4-  
, 3- 가  
[Advanced Drug Delivery Reviews 19  
96, 19, 115]  
가  
가  
( )

( )  
1996, 39, 10]

[J. Med. Chem.

2

가

가

(BPH))

가

가

가

가

가

가

(vasculogenesis)

(angiogenesis)

(epidermoid)

가

가

(BPH))

가

가

가

가

가

가

(  
),  
,  
(,  
) , CNS  
가 .  
  
가  
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가  
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가  
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가  
.  
가

MMP-2 ( - 2) , MMP-9 ( - 9)  
COX-II ( COX-II ) (CELEBREX, ), 가  
WO 96/33172 (1996 10 24 ), WO 96/27583 (1996 3 7 ), 97304971.1 (1997 7 8 ), 9930861 7.2 (1999 10 29 ), WO 98/07697 (1998 2 26 ), WO 98/03516 (1998 1 29 ), WO 98/34918 (1998 8 13 ), WO 98/34915 (1998 8 13 ), WO 98/3376 8 (1998 8 6 ), WO 98/30566 (1998 7 16 ), 606,046 (1994 7 13 ), 931,788 (1999 7 28 ), WO 90/05719 (1990 5 31 ), WO 99/52910 (1999 10 21 ), WO 99/52889 (1999 10 21 ), WO 99/2966 7 (1999 6 17 ), PCT PCT/IB98/01113 (1998 7 21 ), 99302232.1 (1999 3 25 ), 9912961.1 (1999 6 3 ), 가 60/148,464 (1999 8 12 ), 5,863,949 (1999 1 26 ), 5,861,510 (1999 1 19 ) 780,386 (1997 6 25 )  
MMP-2 MMP-9 MMP-1  
( , MAP-1, MMP-3, MMP-4, MMP-5, MMP-6 , MMP-7, MMP-8, MMP-10, MMP-11, MMP-12 MMP-13) MMP-2 ( ) MMP-9

MMP

AG-3340, RO 32-3555 RS 13-0830

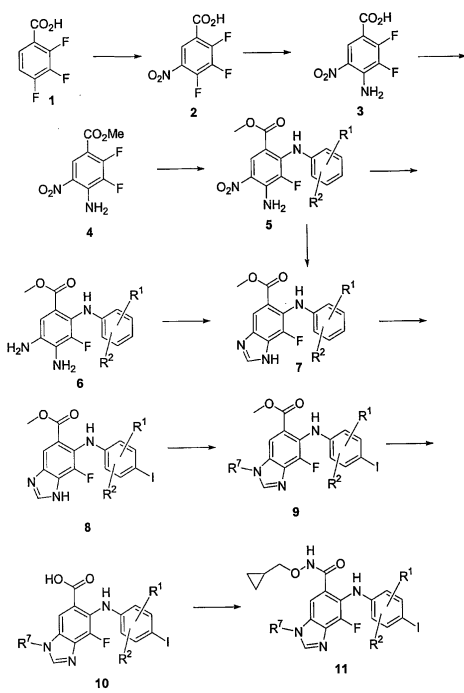
( ) ; (2) 가  
 ; (3) ; (4) /  
 ; (5) 가

가  
 가  
 가

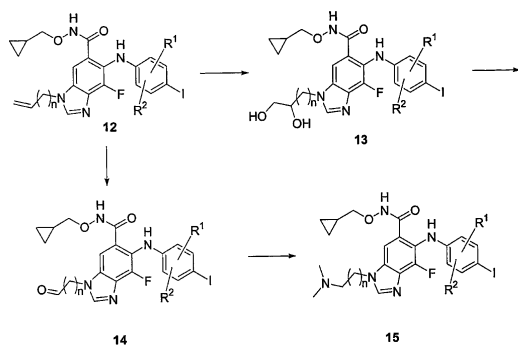
가

1 3

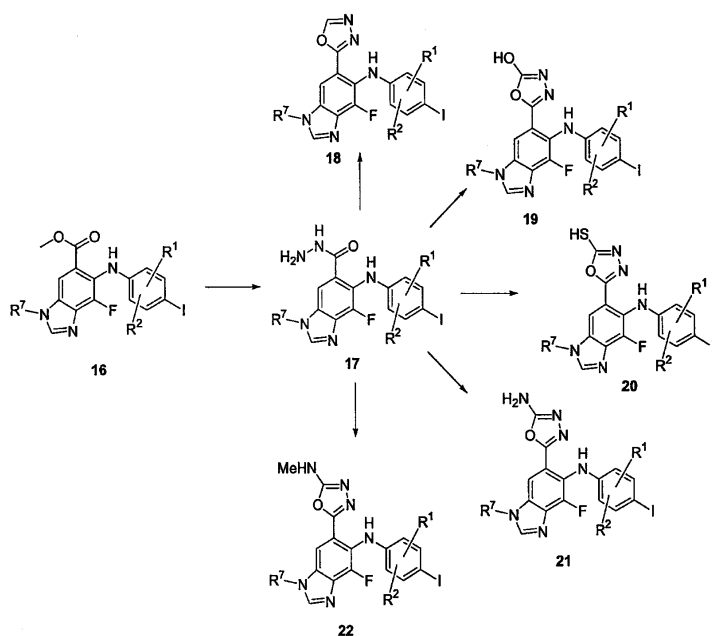
N 1



N 2



3



PCT

WO 00/420

22 (2000 7 20 )

1 3

1

2

1

 $H_2SO_4$ 

pH 0 가  
PhMe/MeOH THF/MeOH

 $NH_4OH$ TMSCHN<sub>2</sub>(MeOH,  $H_2SO_4$ ),

가 (60 200 )

d/C Pd(OH)<sub>2</sub>/C

(Raney Nickel), AcOH

$H_2$ , EtOH  
Fe, AcOH Zn

10 THF

MeOH Zn,  $NH_4Cl$  (aq

P

)

EtOH

가

6

$\text{OH})_2 / \text{C}$  ,  $\text{R}^1$   $\text{R}^2$  가 , 7  $\text{Pd}(\text{N}^3$   
 $\text{8} \quad \text{THF} \quad \text{Pd/C} \quad \text{MeOH}$  가 ,  
 $\text{ZnCl}_2$  ,  $\text{NIS}$   $\text{pTsOH}$   $\text{AcOH}$  , 9  
 $\text{NaH}$  80  $\text{K}_2\text{CO}_3$   $\text{DMF}$   $\text{THF}$  ,  $\text{R}^7$   $\text{N}^1$   $\text{N}^3$   
 $\text{HOBt}$  가 , 11  $\text{DMF, THF}$   $\text{EDCI}$ ,  
 $\text{PyBOP}$  .  
 $\text{KMnO}_4$   $\text{N}^3$   $\text{I}_2$  ,  $\text{AgOAc}$ ,  $\text{AcOH}$ ,  
 $\text{b(OAc)}_4$  가 , 2 ( 3),  $\text{OsO}_4$   $\text{P}$   
 $\text{KMnO}_4$  ,  $\text{NaIO}_4$   $\text{NaIO}_4 / \text{OsO}_4$   
 $\text{Ac}_3\text{BH}$ ,  $\text{NMe}_4\text{BH(OAc)}_3$   $\text{THF}$   $\text{AcOH}$   $\text{Na(CN)BH}_3$ ,  $\text{Na(O}^4$   
 $\text{MeCN}$  ,  $\text{Me}_4\text{NBH(OAc)}_3$  .  
 $\text{W}$ 가 , 1 , 50 10  
 $\text{EtOH}$  ,  
 $(50 \quad 100)$   $\text{EtOH}$  (18)  
 $\text{pTsOH}$  (19) 50  
 $120$  가 (20) (50 100)  $\text{EtOH}$  (21)  
 $\text{KOH}$  ,  
 $\text{BrCN}$ ,  $\text{NaHCO}_3$   $\text{DMF}$   $\text{THF}$   
 $(22)$  25 100  $\text{EDCI}$   
 $80$   $\text{THF}$   $\text{DMF}$  ,  
 $\text{가}$  ,  
 $( \quad , \quad )$   
 $( \quad , \text{가} \quad )$  .  
 $\text{N-}^6 \text{His-}$   $\text{MEK1 (2-3}$   
 $[ \text{Ahn et al. Science 1994, 265, 966-970} ]$ .  $\text{ME}$   
 $\text{K1}$   $\text{MEK1}$   $\text{N-}^33 \text{P-ATP}$   $\text{N-}^33 \text{P-}$  가 , 96-  
 $\text{N-}^33 \text{P-ATP}$   $\text{His-}$   $\text{ERK2}$  가 .  
 $(100 \mu\ell)$  25 mM  $\text{Hepes}$ , pH 7.4, 10 mM  $\text{MgCl}_2$ , 5 mM  $\text{Na-}$   
 $\text{Na-}$  , 100  $\mu\text{M}$   $\text{Na-}$  , 5 mM  $\text{DTT}$ , 5 nM  $\text{MEK1}$  1  $\mu\text{M}$   $\text{ERK2}$   $\text{DMSO}$   
 $\text{N-}^33 \text{P-ATP/}$  ) 가 , 45 10  $\mu\text{M}$   $\text{ATP (0.5 } \mu\text{Ci}$   
 $\text{ATP}$  (Tomtec)  $\text{MACH III}$   $\text{B}$  , 30  $\mu\ell$ /  
 $(\text{Packard Microscint})$  20 가 ,  $(\text{Packard TopCount})$   
 $50$   $\text{IC}_{50}$  .

|     |
|-----|
| 11a |
| 11b |
| 11c |
| 11d |
| 11e |
| 11f |
| 11g |
| 11h |
| 11i |
| 11j |

( , ' ( ) )

( , , , )

가 .

1 35 mg/kg/ 1 1 kg 0.001 100 mg, 0.05 7 g/ 0.05 2.5 g/ . 70 kg ,

239362

, N - (5 - [ N - (3,4 - -2 - -4 - -6 - ) - N - ] -2 - ) - L -

(Casodex, ) (4' - (Nolvadex, ( ) ) -3 - (4 - ) -2 - -2 - -3' - (

가

가

( [Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 15<sup>th</sup> Edition (1975)] ).

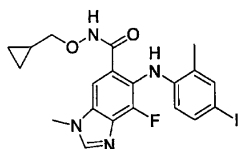
가

1 , , . 2

, , . /

가

1



7- -6-(4- -2- - )-3- -3H- -5- -  
 ( 11a )

A: 2,3,4- -5- -

3 3 H<sub>2</sub>SO<sub>4</sub> 125 Mℓ 가 (8.4 Mℓ, 199 mmol),  
 . 2,3,4- (25 g, 142 mmol) 5 g 90 가  
 60 , (MgSO<sub>4</sub>), 1  
 (3×600 Mℓ) . (clean) 2  
 9 g (92%) (off-yellow) 30

B: 4- -2,3- -5- -

( 30%) (35 Mℓ, 271 mmol) 0 30 Mℓ 2,3,4- -5- -  
 (15 g, 67.8 mmol) 가 가  
 가 2.5 , 0 HCl pH가 0 가  
 가 (30 Mℓ) , (3×50 Mℓ)  
 (MgSO<sub>4</sub>), 14 g (95%)

C: 4- -2,3- -5- -

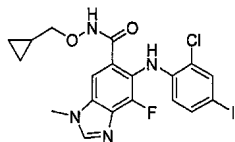
TMS 2 M (6.88 Mℓ, 13.75 mmol) 0 4:1 THF:MeOH 25 Mℓ 4-  
 -2,3- -5- - (2.00 g, 9.17 mmol) 가 가  
 가 0.5 , 가 TMS  
 , , 1.95 g (92%)

D: 4- -3- -5- -2-o- -

4- -2,3- -5- - (12.0 g, 51.7 mmol) (60 Mℓ) 가 .  
 36 , 가 (55.2 Mℓ, 517 mmol). , 10% HCl .  
 1 (2 ) . 2 (1 ) , 3 (1 ) . 3  
 11.2 g (68%)  
 E: 7- -6-o- -1H- -5-  
 EtOH 25 Mℓ 4- -3- -5- -2-o- - (1.57 g, 4.92 mmol),  
 (25 Mℓ, 26.5 mmol) 20% Pd(OH)<sub>2</sub>/C (1.57 g, 2.95 mmol) 95 가 . 16 ,  
 , 20% Pd(OH)<sub>2</sub>/C 0.5 g 10 Mℓ 가 .  
 95 가 . 16 , (Celite) EtO  
 H 가 . EtOH  
 1.09 g (74%)  
 F: 7- -6-(4- -2- - )-1H- -5-  
 7- -6-o- -1H- -5- (1.47 g, 4.92 mmol) 1:1 THF:Me  
 OH (44 Mℓ) , -78 THF (2 Mℓ) NIS (1.66 g, 7.39 mmol)  
 가 , TsOH · H<sub>2</sub>O (1.87 g, 9.84 mmol) MeOH (2 Mℓ) 가 . 30 ,  
 0 가 , 1 Mℓ 가 . 16  
 가 . 10% Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> 가 .  
 O<sub>4</sub> ), MeOH . 1.45 g (69%) (Na<sub>2</sub>S  
 G: 7- -6-(4- -2- - )-3- -3H- -5-  
 7- -6-(4- -2- - )-1H- -5- (100 mg, 0.235  
 mmol) DMF (2.5 Mℓ) , 0 . NaH (95%) (6 mg, 0.238 mmol)  
 가 . 10 , Mel (15 μℓ, 0.238 mmol) 가 . 45 , 가 . 1.5  
 ,  
 (Na<sub>2</sub>SO<sub>4</sub>) . FCC (10:  
 1 : ) N3 36 mg (36%) N1 43 mg (43  
 %) .  
 H: 7- -6-(4- -2- - )-3- -3H- -5-  
 7- -6-(4- -2- - )-3- -3H- -5- (34 mg,  
 0.077 mmol) 1:1 THF:MeOH (2 Mℓ) , 20% NaOH (500 μℓ) 가 . 16 ,  
 0 1 M HCl pH가 1 2가 가 .  
 3 mg (100%) (MgSO<sub>4</sub>) 3  
 I: 7- -6-(4- -2- - )-3- -3H- -5-  
 7- -6-(4- -2- - )-3- -3H- -5- (30 mg, 0.071 mmol)  
 DMF (1 Mℓ) , HOBt (11 mg, 0.085 mmol) 가 (22 μℓ, 0.162 mmol) 가  
 . (10 mg, 0.085 mmol) (WO 0042022) 가 E  
 DCI (18 mg, 0.092 mmol) 가 . 16 ,  
 . NH<sub>4</sub>Cl, , NaHCO<sub>3</sub> , (MgSO<sub>4</sub>)  
 20:1 :MeOH FCC ,  
 ( 11a ) 21 mg (61%) : MS APCI (+) m/z 495 (M+1) ; MS APCI (-  
 ) m/z 493 (M-1) ;

$^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  11.62 (s, 1H), 8.38 (s, 1H), 7.69 (s, 1H), 7.57 (s, 1H), 7.43 (d, 1H), 7.25 (dd, 1H), 6.12 (dd, 1H), 3.89 (s, 3H), 3.58 (d, 2H), 2.23 (s, 3H), 1.01 (m, 1H), 0.47 (m, 2H), 0.19 (m, 2H);  $^{19}\text{F}$  NMR (376MHz, DMSO- $d_6$ )  $\delta$  -133.71 (s).

## 2



6-(2-(4-(3-(3H-5- (11b)

A: 4-(3-(5-(2-

4-(2,3-(5-(23.48 g, 101.1 mmol) (125 Ml) (125 Ml) 125 16 N<sub>2</sub>

22.22 g (72.78 mmol)

5.47 g (17.91 mmol) 27.69 g (90%) : MS APCI (-)  $m/z$  304 (M-1)

B: 7-(6-(3H-5-

(250 Ml) 4-(3-(5-(2-(16.70 g, 54.71 mmol), (250 Ml, 6.63 mol) 20% Pd(OH)<sub>2</sub>/C (9.00 g, 16.91 mmol) 40 2 N<sub>2</sub> 95 16

13.47 g (86%) : MS APCI (+)  $m/z$  286 (M+1) ; MS APCI (-)  $m/z$  284 (M-1)

C: 7-(6-(4-(3H-5-

7-(6-(3H-5-(1.47 g, 4.91 mmol) 1:1 THF:MeO H (40 Ml) , -78 pTsOH (1.5 g, 7.4 mmol) 가 5 NIS (1.2 g, 5.2 mmol) 가 15 , 0 가 16 가 10% NaHSO<sub>3</sub> 가 30 , (Na<sub>2</sub>SO<sub>4</sub>) 1.47 g (69%)

: LC/MS ESI (+)  $m/z$  412 (M+1)

D: 6-(2-(4-(3H-5-

7-(6-(4-(3H-5-(1.4 g, 3.5 mmol) DMF (60 Ml) NCS (470 mg, 3.51 mmol) 가 144 10% NaHSO<sub>3</sub> (Na<sub>2</sub>SO<sub>4</sub>) 1.24 g (80%) :

$^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  8.50 (s, 1H), 7.97 (s, 1H),

7.78 (d, 1H), 7.42 (dd, 1H), 6.1 (bs, 1H), 3.82 (s, 3H).

E: 6-(2-(4-(3-(3H)-5-

6-(2-(4-(3-(3H)-5-(205 mg, 0.46 mmol) DMF (3 Ml), K<sub>2</sub>CO<sub>3</sub> (76 mg, 0.55 mmol) 가 MeI (36  $\mu$ l, 0.58 mmol) 가 , NaHCO<sub>3</sub> (Na<sub>2</sub>SO<sub>4</sub>) . 9:1 :MeCN FCC , 35 mg (17%) :

<sup>1</sup>H NMR (400MHz, MeOH-d<sub>4</sub>)  $\delta$  8.38 (s, 1H), 8.17

(s, 1H), 7.67 (d, 1H), 7.39 (dd, 1H), 6.40 (dd, 1H), 3.98 (s, 3H), 3.93 (s, 3H); <sup>19</sup>F NMR

(376MHz, MeOH-d<sub>4</sub>)  $\delta$  -133.8 (s).

F: 6-(2-(4-(3-(3H)-5-

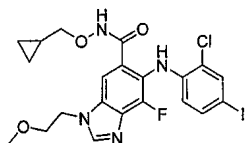
6-(2-(4-(3-(3H)-5-(11b) : 6-(2-(4-(3-(3H)-5-

<sup>1</sup>H NMR (400 MHz, 아세톤-d<sub>6</sub>)  $\delta$  8.24 (s, 1H), 7.79

(s, 1H), 7.68 (d, 1H), 7.45 (dd, 1H), 6.41 (dd, 1H), 4.01 (s, 3H), 3.75 (m, 2H), 1.09 (m,

1H), 0.51 (m, 2H), 0.23 (m, 2H).

### 3



6-(2-(4-(3-(3H)-5-(11c) : 6-(2-(4-(3-(3H)-5-

6-(2-(4-(3-(3H)-5-(11c) 6-(2-(4-(3-(3H)-5- : 1-2-

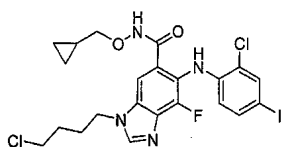
<sup>1</sup>H

NMR (400 MHz, MeOH-d<sub>4</sub>)  $\delta$  8.32 (s, 1H), 7.72 (s, 1H), 7.63 (m, 1H), 7.33 (dd, 1H),

6.27 (m, 1H), 4.50 (t, 2H), 3.77 (t, 2H), 3.61 (dd, 2H), 3.37 (s, 3H), 1.06 (m, 1H), 0.51

(m, 2H), 0.22 (m, 2H); <sup>19</sup>F NMR (376 MHz, MeOH-d<sub>4</sub>)  $\delta$  -134.91 (s).

### 4

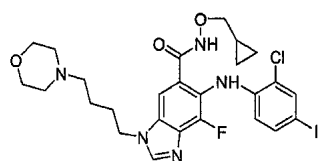


3-(4-(3-(3H)-5-(11d) : 3-(4-(3-(3H)-5-

3-(4-(3-(3H)-5-(11d) : 3-(4-(3-(3H)-5-

(-) *m/z* 589, 591, 593 (M<sup>+</sup>, Cl<sup>-</sup>) . MS APCI

5



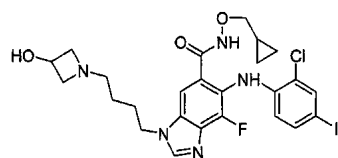
6-(2- -4- - )-7- -3-(4- -4- - )-3H- -5-  
- ( 11e )

3-(4-(6-(2-(4-(7-(3H-5-(  
(**11d**) (45 mg, 0.076 mmol) DMF (0.5 Mℓ), NaI (19 m  
g, 0.12 mmol) 가 (22 μℓ, 0.25 mmol) 가 (purge)  
, 16 65 가 ,  
(Na<sub>2</sub>SO<sub>4</sub>) . 95:5 CH<sub>3</sub>CN:MeO  
H FCC , (**11e**) 36 mg (66%) : MS APCI (-) *m/z* 6  
40, 642 (M<sup>+</sup>, Cl<sup>-</sup>) ;

<sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ

8.37 (s, 1H), 7.71 (s, 1H), 7.63 (m, 1H), 7.33 (dd, 1H), 6.27 (m, 1H), 4.38 (t, 2H), 3.65 (m, 6H), 2.41 (m, 6H), 1.96 (m, 2H), 1.56 (m, 2H), 1.05 (m, 1H), 0.50 (m, 2H), 0.22 (m, 2H).

## 6

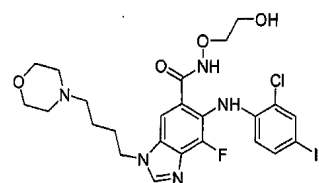

$$\begin{array}{ccccccc} 6-(2- & -4- & - & )-7- & -3-[4-(3- & - & -1- & )- & ]-3H- \\ 5- & & & & & & & & \end{array}$$

6-(2- 4- - )-7- -3-[4-(3- - -1- )- ]-3H-  
5- - ( 11f ) -3-  
: MS APCI (-)  $m/z$  626, 628 (M<sup>-</sup>, Cl<sup>-</sup>) ;

<sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ 8.34 (s, 1H), 7.72

(s, 1H), 7.63 (m, 1H), 7.34 (dd, 1H), 6.27 (m, 1H), 4.34 (m, 3H), 3.61 (m, 3H), 3.38 (m, 2H), 2.86 (m, 2H), 2.54 (m, 2H), 1.95 (m, 2H), 1.41 (m, 1H), 1.06 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H);  $^{19}\text{F}$  NMR (376 MHz, MeOH- $d_4$ )  $\delta$  -133.38 (s).

## 7





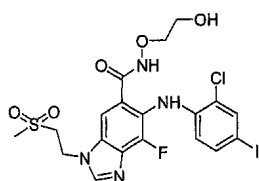
B: 6-(2-(4-(3-(2-(3H-5-

가 ( 11h ) : MS APCI (-)  $m/z$  605, 607 (M-, Cl ) ;

$^1\text{H}$  NMR (400 MHz, 아세톤- $d_6$ )  $\delta$  10.95 (bs, 1H), 8.37 (s, 1H), 8.21 (bs, 1H), 7.92 (s, 1H), 7.70 (d, 1H), 7.46 (dd, 1H), 6.44 (m, 1H), 4.93 (t, 2H), 3.85 (t, 2H), 3.75 (dd, 2H), 2.98 (s, 3H) 1.09 (m, 1H), 0.44 (m, 2H), 0.24 (m, 2H);  $^{19}\text{F}$  NMR (376 MHz, 아세톤- $d_6$ )  $\delta$  -132.31 (s).

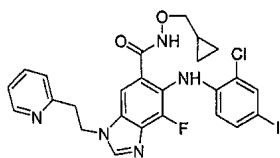
9

(Michael)



6-(2-(4-(3-(2-(3H-5-(2- ( 11i ) : MS APCI (-)  $m/z$  595, 597 (M-, Cl ) ;

$^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  8.39 (s, 1H), 7.78 (s, 1H), 7.64 (d, 1H), 7.34 (dd, 1H), 6.28 (m, 1H), 4.87 (t, 2H), 3.93 (m, 2H), 3.79 (t, 2H), 3.67 (m, 2H) 2.98 (s, 3H);  $^{19}\text{F}$  NMR (376 MHz, MeOH- $d_4$ )  $\delta$  -134.00 (s).



6-(2-(4-(3-(2-(2-(3H-5-(2- ( 11j ) : MS APCI (+)  $m/z$  606, 608 (M+, Cl ) ; MS APCI (-)  $m/z$  604, 606 (M-, Cl ) ;

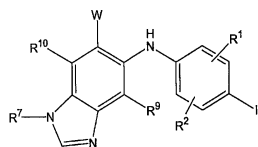
$^1\text{H}$  NMR (400 MHz, MeOH- $d_4$ )  $\delta$  8.47 (d, 1H), 8.13 (s, 1H), 7.65 (dt, 1H), 7.62 (m, 2H), 7.35 (dd, 1H), 7.26 (dd, 2H), 7.20 (d, 1H), 6.25 (dd, 1H), 4.75 (t, 2H), 3.62 (d, 2H), 3.39 (t, 2H), 1.09 (m, 1H), 0.51 (m, 2H), 0.25 (m, 2H);  $^{19}\text{F}$  NMR (376 MHz, MeOH- $d_4$ )  $\delta$  -134.62 (s).

(57)

1.

I

&lt; I&gt;



$R^1, R^2, R^9, R^{10}$   
 $-, -OR^3, -C(O)R^3, -C(O)OR^3, NR^4C(O)OR^6, -OC(O)R^3, -NR^4SO_2R^6, -SO_2NR^3R^4$   
 $-, -NR^4C(O)R^3, -C(O)NR^3R^4, -NR^5C(O)NR^3R^4, -NR^5C(NCN)NR^3R^4, -NR^3R^4,$

$C_1-C_{10}, C_2-C_{10}, C_2-C_{10}, C_3-C_{10}, C_3-C_{10}, -S(O)$   
 $j(C_1-C_6), -S(O)_j(CR^4R^5)_m-, -O(CR^4R^5)_m-, -NR^4(CR^4R^5)_m-, -O(CR^4R^5)_m-, -NR^4(CR^4R^5)_m-$   
 $4R^5)_m-, -O(CR^4R^5)_m-, -NR^4(CR^4R^5)_m-$

$-, -NR^4SO_2R^6, -SO_2NR^3R^4, -C(O)R^3, -C(O)OR^3, -OC(O)R^3, -NR^4C(O)OR^6, -NR^4C(O)R^3, -C(O)NR^3R^4, -NR^3R^4, -NR^5C(O)NR^3R^4$   
 $-, -NR^5C(NCN)NR^3R^4, -OR^3,$   
 $1 \quad 5$

$R^3,$   
 $C_1-C_{10}, C_2-C_{10}, C_2-C_{10}, C_3-C_{10}, C_3-C_{10},$   
 $-, -NR'SO_2R''', -SO_2NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''',$   
 $-NR'C(O)R'', -C(O)NR'R'', -SR''', -S(O)R''', -SO_2R', -NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR',$   
 $1 \quad 5$

$R', R'', R''',$   
 $R''',$   
 $R', R'', R''', R''', 2 \quad 4 \quad 10-$   
 $1 \quad 3$

$R^3, R^4, 4 \quad 10-$   
 $-, -NR'SO_2R''', -SO_2NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO_2R''',$   
 $R''', -NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR',$   
 $1 \quad 3$

$R^4, R^5, C_1-C_6,$   
 $R^4, R^5, 4 \quad 10-$   
 $SO_2R''', -SO_2NR'R'', -C(O)R''', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'C(O)R'', -C(O)NR'R'', -SO_2R''',$   
 $-NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR',$   
 $1 \quad 3$









6.

5, R<sup>9</sup>가 .

7.

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

8.

5, A가 -C(O)NR<sup>4</sup> OR<sup>3</sup> .

9.

1, ,

R<sup>7</sup> C<sub>1</sub>-C<sub>10</sub> , C<sub>3</sub>-C<sub>7</sub> , C<sub>3</sub>-C<sub>7</sub> , C<sub>3</sub>-C<sub>7</sub> C<sub>3</sub>-  
 C<sub>7</sub> , -NR<sup>4</sup>SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -C(O)R<sup>3</sup>, -C(O)OR<sup>3</sup>, -OC(O)R<sup>3</sup>, -SO<sub>2</sub>R<sup>3</sup>, -NR<sup>4</sup>C(O)OR<sup>6</sup>, -NR<sup>4</sup>C(O)R<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>3</sup>R<sup>4</sup>, -NR<sup>5</sup>C(O)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>5</sup>C(NCN)N  
 R<sup>3</sup>R<sup>4</sup>, -OR<sup>3</sup>, 1 3 ;

R<sup>9</sup>가 ;R<sup>10</sup> ;W가 -C(O)OR<sup>3</sup> -C(O)NR<sup>4</sup> OR<sup>3</sup> .

10.

9, W가 -C(O)NR<sup>4</sup> OR<sup>3</sup> .

11.

2, ,

R<sup>7</sup> C<sub>1</sub>-C<sub>10</sub> , C<sub>3</sub>-C<sub>7</sub> , C<sub>3</sub>-C<sub>7</sub> , C<sub>3</sub>-C<sub>7</sub> C<sub>3</sub>-  
 C<sub>7</sub> , -NR<sup>4</sup>SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -C(O)R<sup>3</sup>, -C(O)OR<sup>3</sup>, -OC(O)R<sup>3</sup>, -SO<sub>2</sub>R<sup>3</sup>, -NR<sup>4</sup>C(O)OR<sup>6</sup>, -NR<sup>4</sup>C(O)R<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>3</sup>R<sup>4</sup>, -NR<sup>5</sup>C(O)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>5</sup>C(NCN)N  
 R<sup>3</sup>R<sup>4</sup>, -OR<sup>3</sup>, 1 3 ;

R<sup>9</sup>가 ;R<sup>10</sup> ;W가 -C(O)OR<sup>3</sup> -C(O)NR<sup>4</sup> OR<sup>3</sup> .

12.

11, W가 -C(O)NR<sup>4</sup> OR<sup>3</sup> .

13.

1, ,

7- -6-(4- -2- - )-3- -3H- -5-  
 ;

6-(2- -4- - )-7- -3- -3H- -5-  
 ;

6-(2- -4- - )-7- -3-(2- - )-3H- -5-  
 - ;

3-(4- - )-6-(2- -4- - )-7- -3H- -5-  
 - ;

6-(2- -4- - )-7- -3-(4- -4- - )-3H- -5-  
 - ;

6-(2- -4- - )-7- -3-[4-(3- - -1- )- ]-3H- -  
 5- - ;

6-(2- -4- - )-7- -3-(4- -4- - )-3H- -5- (  
 2- - )- ;

6-(2- -4- - )-7- -3-(2- - )-3H- -5-  
 - ;

6-(2- -4- - )-7- -3-(2- - )-3H- -5- (2-  
 - )- ;

6-(2- -4- - )-7- -3-(2- -2- - )-3H- -5-  
 - .

**14.**

1 가 .

**15.**

13 가 .

**16.**

1 , MEK .

**17.**

1 , .