

**(19)**  
**(12)**

**(KR)**  
**(A)**

**(51) . Int. Cl.<sup>7</sup>**  
C07D 235/08  
C07D 413/06

(11)  
(43)

10-2004-0098013  
2004 11 18

(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)

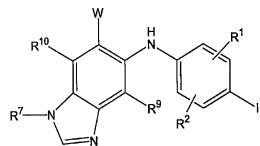
:

**(54) M E K**

**N3**

(I) 가 ( 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> ) ,  
MEK ,

< |>



MEK ,

(1H- -5-

)-(4- - )- . , , ,

(Cell signalling)  
( , PDGF  
가 ) EGF MAP  
Ras Raf GTP- Ras Raf ) MAP

Ras/Raf , Raf 2 MEK1 MEK2 (MEK1 S218 S222 MEK2 S2  
22 S226) [Ahn et al., Methods in Enzymology 2001, 332, 417-431]. ,  
, 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 [Hoshino, R. et al., Oncogene 1999,  
18, 813-822]. , MAP

MAP

. MEK Ras Raf  
가 , MEK MAP , ERK1 2 , MEK  
MEK , , ,  
([Sebolt-Leopold et al., Nature-Medicine 199  
9, 5 (7), 810-816]; [Trachet et al., AACR April 6-10, 2002, Poster #5426]; [Tecle, H. IBC 2<sup>nd</sup> Internationa  
l 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			

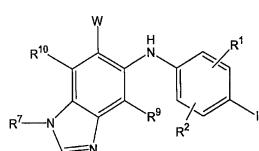
WO 00/68201; 2001 9 20

WO 01/68619; 2002 1 24

WO 02/0621

3.

)- 가 | (1H-, -5- )-(4-  
, 가 MEK



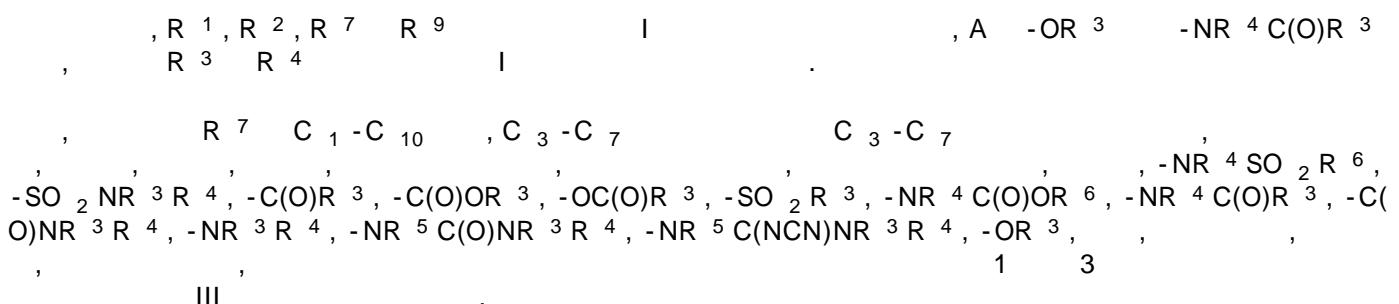
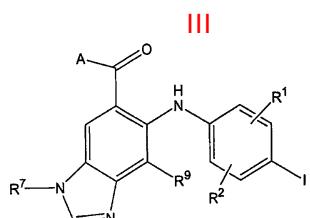
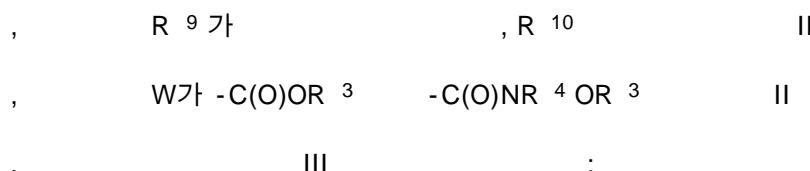
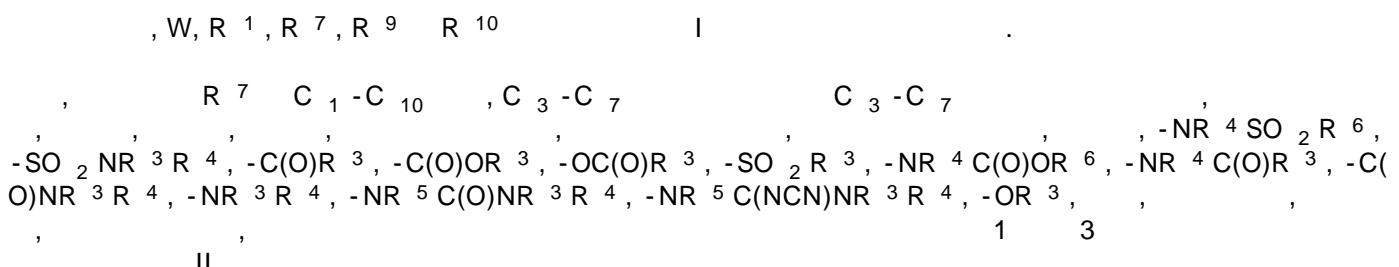
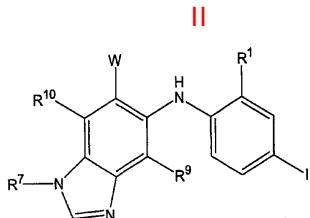
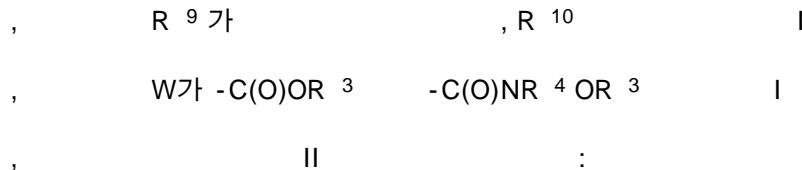
$R^3$ , , ,  
 $C_1-C_{10}$ ,  $C_2-C_{10}$ ,  $C_2-C_{10}$ ,  $C_3-C_{10}$ ,  $C_3-C_{10}$ , , ,  
 , , , , , ,  
 , , , , , ,  
 , , , , , ,  
 $-NR'SO_2R''', -SO_2NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''',$   
 $-NR'C(O)R'', -C(O)NR'R'', -SR''', -S(O)R''', -SO_2R', -NR'R', -NR'C(O)NR''R''',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

$$R', R'' = R''' \quad \text{and} \quad \alpha' = \alpha'' = \alpha'''$$

$$R^{***} = \frac{1}{\sqrt{2}}(R^{**} + iR^{**})$$

R', R'', R'''      R''''      2      4      10 -











(1996, 39, 10])

[J. Med. Chem.]

2

가

가

가

(BPH))

가

(가)

가

(vasculogenesis)

(angiogenesis)

(epidermoid)

(BPH))

가

가

가

가

가

가

가

, , , , , BPH, , , CMMI, , , ,  
, , , , , , , , , , , , , , ),  
, , , , ( , , , , ), , , ,  
, , , , , , , , CNS , , ,  
, , ), , , .

가

가

가

가

가

가

, MMP-2 (- 2), MMP-9 (- 9),  
COX-II (II) (CELEBREX, ( ), 가  
COX-II (WO 96/33172 (1996 10 24), WO 96/27583 (1  
996 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

( $\alpha_1, \alpha_2, \dots, \alpha_n$ ), (1)

(3); (2)

(1); (2); (5)

(4); (2)

가

/

가

가

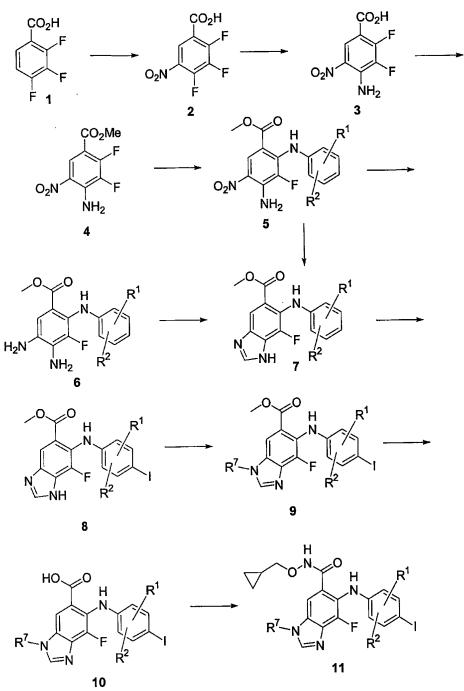
가

가

1 3

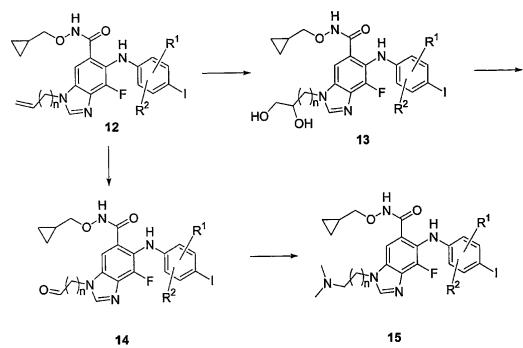
1

N

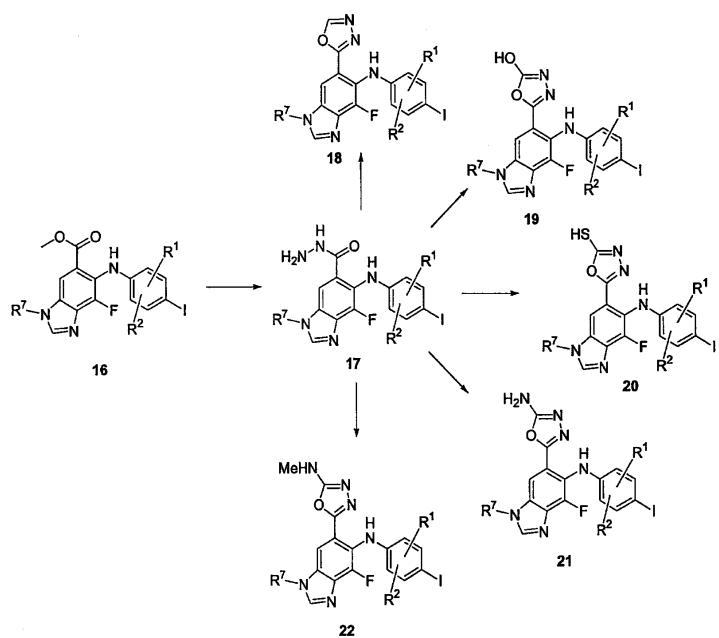


2

N



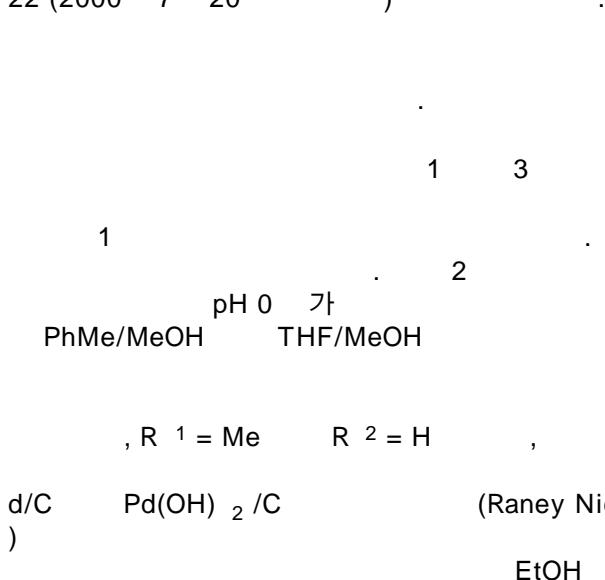
3



22 (2000 7 20 )

PCT

WO 00/420



OH)<sub>2</sub>/C<sub>8</sub> THF ZnCl<sub>2</sub>, R<sup>1</sup> Pd/C MeOH, NIS, pTsOH, AcOH, 가가, 7  
 , 9, N1 N3  
 0 NaH, 80 K<sub>2</sub>CO<sub>3</sub>, DMF, THF, 가가, R<sup>7</sup>, 10  
 HOEt PyBOP, 11, DMF, THF, EDCI,

0	3	W가 EtOH	.	1	,	50	10
				(18)			,
120	(50 100 )	pTsOH EtOH	.	(19)		50	
	가	KOH	.	(20)	,	(50 100 )	EtOH
							(21)
.	,		BrCN, NaHCO <sub>3</sub>			DMF	THF
.			(22)	25 100			
80		THF DMF				EDCI	

93) K1 MEK1, N- His-, ERK2, -<sup>33</sup>P-ATP, -<sup>33</sup>P-, . N- His- [Ahn et al. Science 1994, 265, 966-970]. MEK1 (2-3 가, 96- . (100 μl) 25 mM Hepes, pH 7.4, 10 mM MgCl<sub>2</sub>, 5 mM DMSO, 100 μM Na-, 5 mM DTT, 5 nM MEK1, 1 μM ERK2, . DMSO, 1% DMSO, . 10 μM ATP (0.5 μCi -<sup>33</sup>P-ATP/ ) 가, 45, . 25% TCA 가 B, . ATP (Tomtec) MACH III, 30 μl/ (Packard Microscint) 20, . (Packard TopCount) 50, IC<sub>50</sub>

- 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/

1

가

가

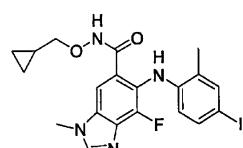
(  
n (1975) ). [Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 15<sup>th</sup> Editio

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 , : 1  
, (3×600 Mℓ) 30 (MgSO<sub>4</sub>), (clean) 2  
9 g (92%) (off-yellow)

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

(15 g, 67.8 mmol) 30% (35 Mℓ, 271 mmol) 0 30 Mℓ 2,3,4- -5-  
가 . 2.5 가 , 0 , 가 , pH 가 0 가  
가 , (30 Mℓ) , HCl , (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 , , TMS  
,

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

E: 7- -6-0- -1H- -5-

F: 7- -6-(4- -2- - )-1H- -5-

7-OH 가 0.10% Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, 1M $\ell$  가 16 . . . . . (Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>), 1.45 g (69%) . . . . .

G: 7- -6-(4- -2- - )-3- -3H- -5-

7-  
mmol) DMF (2.5 M), MeI (15  $\mu$ l, 0.238 mmol) 가 10, -6-(4-  
가 . 10, , -2-, - , )-1H-, 0, . 45, . NaH (95%) (6 mg, 0.238 mmol)  
가 . 1.5  
,

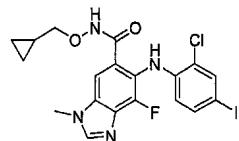
H: 7 - - 6 - (4 - - 2 - - - ) - 3 - - 3 H - - 5 -

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 pH 가 1 2가 가 .  
 . (MgSO<sub>4</sub>) 3  
 3 mg (100%) .

1: 7 - - 6 - (4 - - 2 - - - ) - 3 - - 3H - - 5 -

7-<sup>-6</sup>-(4-<sup>-2</sup>-<sup>-3</sup>-<sup>-3H-</sup><sup>-5</sup>- (30 mg, 0.071 mmol)  
DMF (1 M) , HOBr (11 mg, 0.085 mmol) 가 (22  $\mu$ l, 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) ;

<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 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); <sup>19</sup>F NMR (376MHz, DMSO-d<sub>6</sub>) δ -133.71 (s).

**2**

6-(2-	-4-	-	) - 7 -	- 3 -	- 3H -	- 5 -	-	-
( 11b )								
A: 4 -	- 3 -	- 5 -	- 2 -	-	-	-	-	-
4 -	- 2,3 -	- 5 -	-	(23.48 g, 101.1 mmol)	125	16	(125 Mℓ)	N <sub>2</sub>
,	(92 Mℓ, 1011 mmol)	가	.					
				22.22 g (72.78 mmol)				
5.47 g (17.91 mmol)				27.69 g (90%)			: MS APCI (-) <i>m/z</i> 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)	95	16	20% Pd(OH) <sub>2</sub> /C	(9.00 g, 16.91 mmol)	40	2	N <sub>2</sub>	
13.47 g (86%)				: MS APCI (+) <i>m/z</i> 286 (M+1)			; MS APCI (-) <i>m/z</i>	
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)	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 (+) <i>m/z</i> 412 (M+1)				
D: 6 -(2 -	- 4 -	-	) - 7 -	- 3H -	- 5 -			
7 -	- 6 -(4 -	-	) - 3H -	- 5 -			(1.4 g, 3.5 mmol)	DMF
(60 Mℓ)	60	가	NCS (470 mg, 3.51 mmol)	가	.		144	
		.	60	40	,			
					,			
							10% NaHSO <sub>3</sub>	
							(Na <sub>2</sub> SO <sub>4</sub> )	
				1.24 g (80%)				

<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 8.50 (s, 1H), 7.97 (s, 1H), 7.78 (d, 1H), 7.42 (dd, 1H), 6.1 (bs, 1H), 3.82 (s, 3H).

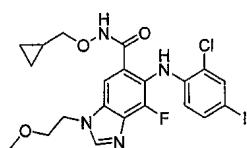
E: 6 - (2 - - 4 - - ) - 7 - - 3 - - 3H - - 5 -  
 6 - (2 - - 4 - - ) - 7 - - 3H - - 5 - (205 mg, 0.46  
 mmol) DMF (3 Mℓ), K<sub>2</sub>CO<sub>3</sub> (76 mg, 0.55 mmol), MeI (36 μℓ, 0.58 mmol)  
 2 , NaHCO<sub>3</sub> (Na<sub>2</sub>SO<sub>4</sub>) : 9:1 :MeCN  
 FCC , 35 mg (17%)

<sup>1</sup>H NMR (400MHz, MeOH-d<sub>4</sub>) δ 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>) δ -133.8 (s).

F: 6 - (2 - - 4 - - ) - 7 - - 3 - - 3H - - 5 -  
 6 - (2 - - 4 - - ) - 7 - - 3 - - 3H - - 5 -  
 1 - - 6 - (2 - - 4 - - ) - 7 - - 3 - - 3H -  
 - 5 - (11b)

<sup>1</sup>H NMR (400 MHz, 아세톤-d<sub>6</sub>) δ 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).

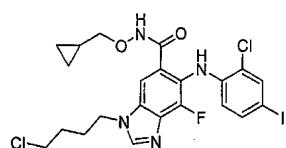
### 3



6 - (2 - - 4 - - ) - 7 - - 3 - (2 - - ) - 3H - - 5 -  
 (11c)  
 6 - (2 - - 4 - - ) - 7 - - 3 - (2 - - ) - 3H - - 5 -  
 1 - - 6 - (2 - - 4 - - ) - 7 - - 3H - - 5 -  
 - 2 - - , - 7 - - , - 3H - - 5 -

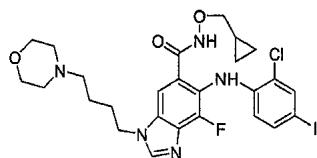
<sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ 8.32 (s, 1H), 7.72 (s, 1H), 7.63 (m, 1H), 7.33 (dd, 1H),  
 6.27 (m, 1H), 4.50 (t, 2H), 3.77 (t, 2H), 3.61 (dd, 2H), 3.37 (s, 3H), 1.06 (m, 1H), 0.51  
 (m, 2H), 0.22 (m, 2H); <sup>19</sup>F NMR (376 MHz, MeOH-d<sub>4</sub>) δ -134.91 (s).

### 4



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

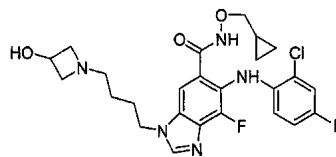
- ( 11d ) 6-(2-  
1- -4- - - - )-7- -3H- -5-  
(-) *m/z* 589, 591, 593 (M-, Cl ) ; : MS APCI

**5**

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

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

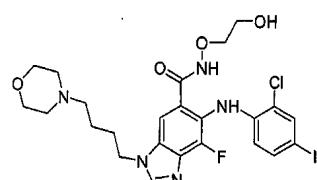
8.37 (s, 1H), 7.71 (s, 1H), 7.63 (m, 1H), 7.33 (dd, 1H), 6.27 (m, 1H), 4.38 (t, 2H), 3.65  
(m, 6H), 2.41 (m, 6H), 1.96 (m, 2H), 1.56 (m, 2H), 1.05 (m, 1H), 0.50 (m, 2H), 0.22 (m,  
2H).

**6**

6-(2- -4- - - )-7- -3-[4-(3- -1- )- ]-3H- -  
5- (-) ( 11f ) ; , NaI (19 m)  
6-(2- -4- - - )-7- -3-[4-(3- -1- )- ]-3H- -  
5- (-) ( 11f ) ; : MS APCI (-) *m/z* 626, 628 (M-, Cl ) ;

<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); <sup>19</sup>F NMR (376 MHz, MeOH-d<sub>4</sub>) δ -133.38 (s).

**7**

6-(2-  
2-  
- 4-  
- )-  
- ( 11g )

A: 6-(2-  
2-  
- 4-  
- )-  
- ( 11g )

3-(4-  
0.134 mmol)  
mg, 0.16 mmol)  
I) 가  
EDCI (31 mg, 0.16 mmol)  
NaHCO<sub>3</sub>, NH<sub>4</sub>Cl  
, O-(2-  
. 5  
. 16  
), 1:1  
(Na<sub>2</sub>SO<sub>4</sub>)  
80 mg (98%)  
5, 607, 609 (M-, Cl<sup>-</sup>)  
: MS APCI (-) m/z 60

B: 6-(2-  
(2-  
- 4-  
- )-  
- ( 11g )

6-(2-  
2-  
- 4-  
- )-  
3-(4-  
- 5-  
(2-  
- )-  
- ( 11g )  
- 3H-  
- 4-  
- )-  
- 3H-  
- 5-  
- 3H-  
: MS APCI (-) m/z 656,  
658 (M-, Cl<sup>-</sup>).  
.

C: 6-(2-  
(2-  
- 4-  
- )-  
- ( 11g )

6-(2-  
2-  
- 4-  
- )-  
(24 mg, 0.036 mmol)  
mmol) 가  
. 16  
, THF (1 Mℓ)  
, MgSO<sub>4</sub>  
FCC  
, NaHCO<sub>3</sub>  
, 1.0 N HCl  
, 10% MeOH:DCM  
12 mg (52%)  
Cl (-) m/z 630, 632 (M-, Cl<sup>-</sup>)  
: MS AP

<sup>1</sup>H NMR (400 MHz, MeOH-

d<sub>4</sub>) δ 8.39 (s, 1H), 7.74 (s, 1H), 7.63 (m, 1H), 7.33 (dd, 1H), 6.26 (m, 1H), 4.38 (t, 2H),  
3.92 (t, 2H), 3.66 (m, 6H), 2.41 (m, 6H), 1.97 (m, 2H), 1.56 (m, 2H); <sup>19</sup>F NMR (376  
MHz, MeOH- d<sub>4</sub>) δ -135.94 (s).

## 8



6-(2-  
- 4-  
- )-  
- ( 11h )

A: 6-(2-  
- 4-  
- )-  
- ( 11h )

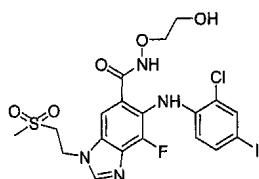
6-(2-  
mmol) 1:1 THF:DMF (2 Mℓ)  
(51 μℓ, 0.592 mmol)  
1:1 :MeCN  
- 4-  
- )-  
- 3H-  
- 5-  
, K<sub>2</sub>CO<sub>3</sub> (69 mg, 0.499 mmol)  
NaHCO<sub>3</sub>  
FCC  
,  
(Na<sub>2</sub>SO<sub>4</sub>)  
122 mg (45%)  
: (220 mg, 0.494  
가  
가  
.

M<sup>-</sup>, Cl<sup>-</sup>) : 가 ( 11h ) : MS APCI (-) *m/z* 60

<sup>1</sup>H NMR (400 MHz, 아세톤-d<sub>6</sub>) δ 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); <sup>19</sup>F NMR (376 MHz, 아세톤- d<sub>6</sub>) δ -132.31 (s).

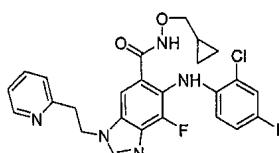
9

(Michael)



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

<sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ 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); <sup>19</sup>F NMR (376 MHz, MeOH-d<sub>4</sub>) δ -134.00 (s).



6 - (2 - - 4 - - - ) - 7 - - 3 - (2 - - 2 - - ) - 3H - - 5 -  
 M -, Cl ) ; ( 11j ): MS APCI (+) *m/z* 606, 608 (M+, Cl ) ; MS APCI (-) *m/z* 604, 606 (

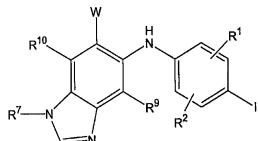
<sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ 8.47 (d, 1H), 8.13 (s, 1H), 7.65 (dt, 1H), 7.62 (m, 2H), 7.35 (dd, 1H), 7.26 (dd, 2H), 7.20 (d, 1H), 6.25 (dd, 1H), 4.75 (t, 2H), 3.62 (d, 2H), 3.39 (t, 2H), 1.09 (m, 1H), 0.51 (m, 2H), 0.25 (m, 2H); <sup>19</sup>F NMR (376 MHz, MeOH-d<sub>4</sub>) δ -134.62 (s).

가

(57)

1.

< | >



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

R', R'', R'''

R<sup>\*\*\*</sup>

R<sup>3</sup> R<sup>4</sup> 4 10-, ,  
- NR'SO<sub>2</sub>R'''', - SO<sub>2</sub>NR'R'', - C(O)R', - C(O)OR', - OC(O)R', - NR'C(O)OR''', - NR'C(O)R'', - C(O)NR'R'', - SO<sub>2</sub>R''', - NR'R'', - NR'C(O)NR''R''', - NR'C(NCN)NR''R''', - OR', , , , , , ,  
1 3 : :

R<sup>4</sup> R<sup>5</sup> C<sub>1</sub>-C<sub>6</sub>

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

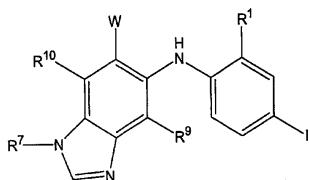
W , -C(O)OR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>4</sup>, -C(O)NR<sup>4</sup>OR<sup>3</sup>, -C(O)R<sup>4</sup>OR<sup>3</sup>, -C(O)(C<sub>3</sub>-C<sub>10</sub>), -C(O)(C<sub>1</sub>-C<sub>10</sub>), -C(O)( ), -C(O)( ), -C(O)( ) -C(O)( ), -NR<sup>3</sup>R<sup>4</sup>, -OR<sup>3</sup>, -R<sup>2</sup>.

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

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

j 1 2 .

2.



R<sup>1</sup>, R<sup>9</sup> R<sup>10</sup>, , , , , , , -OR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(O)OR<sup>3</sup>, NR<sup>4</sup>C(O)OR<sup>6</sup>, -OC(O)R<sup>3</sup>, -NR<sup>4</sup>SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>3</sup>, -C(O)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)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>3</sup>R<sup>4</sup>,

$$R', R'' - R''' \quad , \quad , \quad , \quad , \quad ;$$

$$R^{***} \quad \text{and} \quad R^{****}$$

$R^3$      $R^4$                           4      10- .

-NR'SO<sub>2</sub>R''', -SO<sub>2</sub>NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO<sub>2</sub>R''', -NR'R'', -NR'C(O)NR'R''', -NR'C(NCN)NR'R''', -OR', ;

R<sup>4</sup> R<sup>5</sup> C<sub>1</sub>-C<sub>6</sub>

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

R 6

$\text{C}_1\text{-C}_{10}, \text{C}_3\text{-C}_{10}$ , , , , , , , , , , ,  
 ( , , , , , , , , , , , , , ,  
 -NR'SO<sub>2</sub>R'', -SO<sub>2</sub>NR'R'', -C(O)R', -C(O)OR',  
 -OC(O)R', -NR'C(O)OR'', -NR'C(O)R'', -C(O)NR'R'', -SO<sub>2</sub>R'', -NR'R', -NR'C(O)NR'R'', -NR'C(NCN)NR'R'  
 '', -OR', , , , , ;  
 1 5 ) ;

R 7 ,

$\text{C}_1 - \text{C}_{10}, \text{C}_2 - \text{C}_{10}, \text{C}_2 - \text{C}_{10}, \text{C}_3 - \text{C}_{10}, \text{C}_3 - \text{C}_{10}$   
 $, , , , ( , , , ,$   
 $, , , , -\text{NR}^4 \text{SO}_2 \text{R}^6, -\text{SO}_2 \text{NR}^3 \text{R}^4, -\text{C(O)R}^3, -\text{C(O)OR}^3, -\text{OC(O)R}^3, -\text{N}$   
 $\text{R}^4 \text{C(O)OR}^6, -\text{NR}^4 \text{C(O)R}^3, -\text{C(O)NR}^3 \text{R}^4, -\text{SO}_2 \text{R}^6, -\text{NR}^3 \text{R}^4, -\text{NR}^5 \text{C(O)NR}^3 \text{R}^4, -\text{NR}^5 \text{C($   
 $\text{NCN})\text{NR}^3 \text{R}^4, -\text{OR}^3,$   
 $1 \quad 5 \quad , \quad , \quad ) \quad ;$

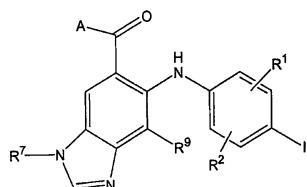
W , -C(O)OR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>4</sup>, -C(O)NR<sup>4</sup>OR<sup>3</sup>, -C(O)R<sup>4</sup>OR<sup>3</sup>, -C(O)(C<sub>3</sub>-C<sub>10</sub>), -C(O)(C<sub>1</sub>-C<sub>10</sub>), -C(O)( ), -C(O)( ) -C(O)( ), -NR<sup>3</sup>R<sup>4</sup>, -OR<sup>3</sup>, -R<sup>2</sup>.

**C** 1 -C 10 , C 2 -C 10 ) C 2 -C 10 ( 1 -NR 3 R 4 -OR 3 ;

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

j 1 2 .

3.



1

R<sup>1</sup>, R<sup>2</sup>, R<sup>9</sup>, -OR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(O)OR<sup>3</sup>, NR<sup>4</sup>C(O)OR<sup>6</sup>, -OC(O)R<sup>3</sup>, -NR<sup>4</sup>SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -NR<sup>4</sup>C(O)R<sup>3</sup>, -C(O)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)NR<sup>3</sup>R<sup>4</sup>, -NR<sup>3</sup>R<sup>4</sup>,

$$\mathbb{R}^3$$

$\text{C}_1\text{-C}_{10}, \text{C}_2\text{-C}_{10}, \text{C}_2\text{-C}_{10}, \text{C}_3\text{-C}_{10}, \text{C}_3\text{-C}_{10},$   
 $, , , , ( , , , ,$   
 $, , , , -\text{NR}'\text{SO}_2\text{R}''', -\text{SO}_2\text{NR}'\text{R}'', -\text{C(O)R}', -\text{C(O)OR}', -\text{OC(O)R}', -\text{NR}'\text{C(O)OR}''',$   
 $-\text{NR}'\text{C(O)R}''', -\text{C(O)NR}'\text{R}''', -\text{SR}', -\text{S(O)R}''', -\text{SO}_2\text{R}''', -\text{NR}'\text{R}''', -\text{NR}'\text{C(O)NR}'\text{R}''', -\text{NR}'\text{C(NCN)NR}'\text{R}''', -\text{OR}',$   
 $, , , , ) ;$ 
1 5

R', R'', R'''

R<sup>\*\*\*</sup>

$\mathbb{R}^3$      $\mathbb{R}^4$                   4        10-

-NR'SO<sub>2</sub>R'', -SO<sub>2</sub>NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO<sub>2</sub>R''', -NR'R'', -NR'C(O)NR''R'', -NR'C(NCN)NR''R'', -OR', , , , , ;

R<sup>4</sup> R<sup>5</sup>C<sub>1</sub>-C<sub>6</sub>; ;R<sup>4</sup> R<sup>5</sup>

4 10-

, , , , , , , , , , , , , , -NR'  
 SO<sub>2</sub>R''', -SO<sub>2</sub>NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO<sub>2</sub>R''',  
 -NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR', , , , , , ;

1 3

R<sup>6</sup>C<sub>1</sub>-C<sub>10</sub>, C<sub>3</sub>-C<sub>10</sub>

( , , , , , , , , , , , , , , -NR'SO<sub>2</sub>R''', -SO<sub>2</sub>NR'R'', -C(O)R', -C(O)OR',  
 -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO<sub>2</sub>R''', -NR'R', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''',  
 -OR', , , , ) ;

1 5

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

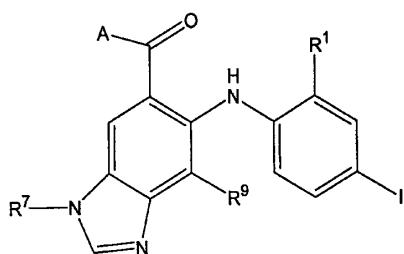
A -C(O)OR<sup>3</sup> -C(O)NR<sup>4</sup> OR<sup>3</sup> ;

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

j 1 2 .

**4.**

3

**5.**

4

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

, 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)NR<sup>3</sup>R<sup>4</sup>, -OR<sup>3</sup>,  
 1 3 ) ;

R<sup>9</sup> ↗ ;R<sup>1</sup>

**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  
 3 , -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  
 6 , -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