

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

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

(51) . Int. Cl.<sup>7</sup>  
C07D 233/44  
C07D 233/50

(11)  
(43) 10-2004-0074134  
2004 08 21

(21)	10-2004-7011589		
(22)	2004 07 27		
	2004 07 27		
(86)	PCT/EP2002/014299	(87)	WO 2003/064398
(86)	2002 12 16	(87)	2003 08 07

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(30) 02002352.9 2002 01 31 EP(EP)

(71) -55216 173

(72) 55218 30

88400 4

563-0104 4-12-9

가 563-0104 5-19-10

910-1134 3-18-3

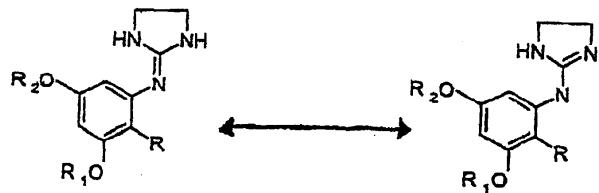
(74)

:

(54) 2'- -3',5'- -1' - - -2-

2'- -3',5'- -1' - - -2- , 2'- -3',5'-  
-2- /

|



, 2'- - , -3', 5' - - - 1' - - - 2 - , , 2' - - , -3', 5' - - -

- 2 - 2' - - , -3', 5' - - - 1' - - - 2 - , , 2' - - , -3', 5' - - -

2',6' - - - 1' - - - 2 - 가 . 가 ,

DE 2220906

JP 48-76870 , 2-( )-2-

, WO 96/32939

EP 0887346 (RR'NCONR''-), (RR'NSO<sub>2</sub>NR''-)  
- (RR'NSO<sub>2</sub>-) - 1L , 가

US 4244957

DE 2521709

EP 0202461

FR 2208671 , , 가 , /

EP 0902218 ,

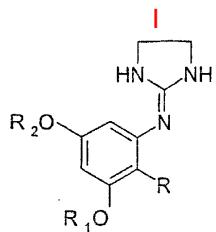
가

-1L-

가

, 1

( ) :

R F, Cl, Br, CF<sub>3</sub>, CH<sub>2</sub>F CHF<sub>2</sub>,

R <sub>1</sub>	R <sub>2</sub>	(Me),	(Et),	(Pr),	(iPr), 1-	(Bu), 2-	(2-Bu),
3	(tBu),	(Pen),	(Hex)	C <sub>1</sub>	C <sub>6</sub> -	.	.

R F, Cl, Br CF<sub>3</sub>, R<sub>1</sub> R<sub>2</sub> C<sub>1</sub> C<sub>6</sub>-R Cl, Br CF<sub>3</sub>, R<sub>1</sub> R<sub>2</sub> C<sub>1</sub> C<sub>4</sub>-R Cl Br, R<sub>1</sub> R<sub>2</sub>,

가

2'-	-3',5'-
4,5-	.

-1'- -

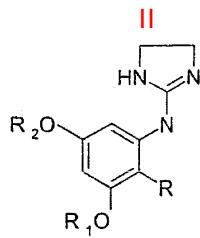
-2-

1

가 ,

II

:

, R, R<sub>1</sub> R<sub>2</sub>

(2'- - 3',5' - II - 2 - ) 2' - - 3',5' - - 1' - - 2 -

,

2' - - 3',5' - - 1' - - 2 - ( | R = Cl, R<sub>1</sub> = Me, R<sub>2</sub> = M  
e),

2' - - 3',5' - - 1' - - 2 - ( | R = Cl, R<sub>1</sub> = Et, R<sub>2</sub> = Et),

2' - - 3',5' - - 1' - - 2 - ( | R = Cl, R<sub>1</sub> = Pr, R<sub>2</sub> =  
Pr),

2' - - 3',5' - - 1' - - 2 - ( | R = Br, R<sub>1</sub> = Me, R<sub>2</sub> = M  
e),

2' - - 3',5' - - 1' - - 2 - ( | R = Br, R<sub>1</sub> = Et, R<sub>2</sub> = Et)

,

2' - - 3',5' - - 1' - - 2 - ( | R = Br, R<sub>1</sub> = Pr, R<sub>2</sub>  
= Pr), II

가

2' - - 3',5' - - 1' - - 2 - ( | R = Cl, R<sub>1</sub> = Me, R<sub>2</sub> = M  
e),

2' - - 3',5' - - 1' - - 2 - ( | R = Br, R<sub>1</sub> = Me, R<sub>2</sub> = M  
e), II 2

가

2' - - 3',5' - - 1' - - 2 - , 2' - - 3',5' -  
- 2 - , 가

2

|

II

가

가 ,

가

, , , , , , , p- , , , ,

가

.01mg 10mg . 0.001mg 1g , 0.001mg 100mg , 가 0

1

( , )

가 , 가 , 가 .  
가 - .

,  
(Tweens)}

(core)

가

가

가  
(vial)

(

1.

CYP2D6 2'- -3',5'- -1'- -2'- . 30 2.4%가

2.

2'- - - - - 3' 5' - - - - - 1' - - - - - 2'

65	66.2	0.64

	10 <sup>-5</sup> M	(%)	10 <sup>-5</sup> M	(%)
,				
3.a. 2'- - 3',5' - - 1' - - - 2 -				
1				
3,5 - 5 -	50g 63.5g	250Mℓ 163-165	가	32.4Mℓ ,
				가 N - , - 3,
2				
N - - 3, 5 - 150Mℓ - 2 - - 3,5 -	가 ,	56.5g 33.0g	200Mℓ 117-118	0 가 (paste) 2 32% 0.5 N -
3				
N - - 2 - 500Mℓ - 2 - - 3,5 -	가 ,	33.0g	2 2 - - 3,5 -	400Mℓ 2 × 250Mℓ 28g
4				
10 28g 3 × 600Mℓ 100Mℓ (2 - - 3,5 - ) -	14.4g 가	10 450Mℓ 35Mℓ 35g	10 3 35Mℓ 300Mℓ 159-162	14.2Mℓ 300Mℓ 700Mℓ 2 - 가 - 3,5 - 500Mℓ 가
5				
(2 - - 3,5 - 2 - 1,2 - 11Mℓ ,	) - 가	35g 8	150Mℓ ,	6.6Mℓ 110Mℓ 가
2' - - 3',5' - - - 1' - - - 2 -			53.3g	204-206
3.b. 2' - - 3',5' - - - 1' - - - 2 -				
2' - HCl / 1M	- 3',5' - 10Mℓ ,	- 1' - - - 2 -	2.2g	10Mℓ 가
2' - - 3',5' - - - 1' - - - 2 -			2.5g(95%)	203-205

<sup>1</sup> H NMR(400 MHz, DMSO-d6): δ=10.60(NH), 8.38(NH), 6.73(1H, d, J=2.7Hz, -H), 6.64(1H, d, J=2.7Hz, -H), 3.88(3, s, OCH<sub>3</sub>), 3.81(3H, s, OCH<sub>3</sub>)), 3.65(4H, s, -CH<sub>2</sub>). MS m/z 256/258(100/43

$(M+H)^+$

가	1	3,5-	3	,	6
---	---	------	---	---	---

4.

A:

2' - - 3',5' - - 1' - - - 1mg

105mg

30mg

30mg

5mg

5mg

3mg

1 mg

180mg

180mg

B:

2' - - 3',5' - - 1' - - - 1.0mg

18.0mg

2.0Mℓ

C:

2' - - 3',5' - - 1' - - - 1mg

178mg

1 mg

180mg

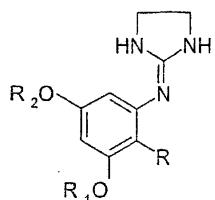
(57)

1.

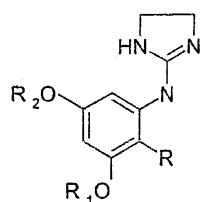
, II

2

I



II

R F, Cl, Br,  $CF_3$ ,  $CH_2F$        $CHF_2$  $R_1$      $R_2$                            $C_1$      $C_6$  -

2.

1 , R F, Cl, Br       $CF_3$        $R_1$      $R_2$                            $C_1$      $C_6$  -

3.

1 , R Cl, Br       $CF_3$        $R_1$      $R_2$                            $C_1$      $C_4$  -

4.

1 , R Cl      Br       $R_1$      $R_2$                           ,

5.

1 , R Cl       $R_1$      $R_2$ 

6.

1	,						
2'	-	-3',5'-	-	-1'-	-	-2-	,
2'	-	-3',5'-	-	-1'	-	-2-	,
2'	-	-3',5'-	-	-1'	-	-2-	,
2'	-	-3',5'-	-	-1'	-	-2-	,

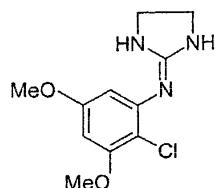
2'- - 3',5' - - 1' - - - 2 - ,

2'- - 3',5' - - 1' - - - 2 - ,

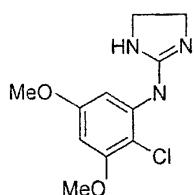
**7.**

I 2'- - 3',5' - - 1' - - - 2 - , II  
2'- - 3',5' - - 2 - 2

I



II

**8.**

I 1 7 , I

**9.**

I 1 7 , II

**10.**

I 1 9 ,

**11.**

I 1 10 , , ,

**12.**

I 1 11

**13.**

I 1 11 0.01mg 10mg 0.001mg 1g, 0.001mg 100mg

**14.**

I 12 13 ,

**15.**

12 13

**16.**

, 12 13

17.

, 1 11

12 16