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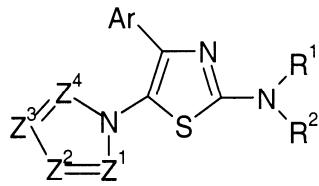
(71) -4056 35

(72) 125

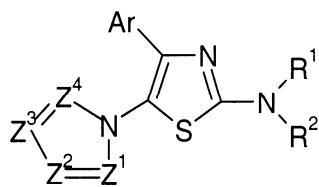
125

(74)

(54)



, (free)



, Ar C<sub>6</sub>-C<sub>15</sub> 1가 ,  
 R<sup>1</sup> -C<sub>1</sub>-C<sub>8</sub>- , , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- ,  
 1가 ,  
 R<sup>2</sup> , C<sub>1</sub>-C<sub>8</sub>- , -CON(R<sup>3</sup>)R<sup>4</sup> , R<sup>1</sup> , R<sup>2</sup> C<sub>1</sub>-C<sub>8</sub>- ,  
 -CON(R<sup>3</sup>)R<sup>4</sup> ,  
 R<sup>3</sup> R<sup>4</sup> C<sub>1</sub>-C<sub>8</sub>- , 5- 6-  
 ,  
 Z<sup>1</sup>, Z<sup>2</sup>, Z<sup>3</sup> Z<sup>4</sup> N CR<sup>5</sup> , CR<sup>5</sup> ,  
 R<sup>5</sup> , C<sub>1</sub>-C<sub>8</sub>- C<sub>1</sub>-C<sub>8</sub>- .

$\text{C}_1 - \text{C}_8 -$  , sec- , tert- , , , , , n-  
 $\text{C}_1 - \text{C}_8 -$  , , , , , , , , .  
 $\text{C}_1 - \text{C}_8 -$  , , , , , , , , .



$$4 \quad , \quad , \quad C_1 - C_4 - \quad - \quad , \quad N - (C_1 - C_4 - \quad )$$

R<sup>3</sup> R<sup>4</sup>, , , , C<sub>1</sub>-C<sub>4</sub>- , ,  
 , 6- . R<sup>3</sup> R<sup>4</sup>, , , , C<sub>1</sub>-C<sub>8</sub>- ,  
 , 5- 6- .  
 2 Z<sup>1</sup>, Z<sup>2</sup>, Z<sup>3</sup> Z<sup>4</sup> CR<sup>5</sup> Z<sup>1</sup>, Z<sup>3</sup> CR<sup>5</sup> R<sup>5</sup>  
 C<sub>1</sub>-C<sub>4</sub>- . N Z<sup>1</sup>, Z<sup>3</sup> Z<sup>4</sup> N , Z<sup>2</sup> Z<sup>4</sup> C  
 R<sup>5</sup> , Z<sup>2</sup> N , Z<sup>1</sup>, Z<sup>3</sup> Z<sup>4</sup> CR<sup>5</sup> , Z<sup>2</sup>, Z<sup>4</sup> R<sup>5</sup>  
 C<sub>1</sub>-C<sub>4</sub>- . N , Z<sup>1</sup> Z<sup>3</sup> N , Z<sup>2</sup> Z<sup>4</sup>  
 CH , Z<sup>1</sup> CR<sup>5</sup> , , R<sup>5</sup> C<sub>1</sub>-C<sub>4</sub>- , Z<sup>2</sup> N , Z<sup>4</sup>  
 3 Z<sup>4</sup> CH . .

$R^1$ ,  $C_1 - C_4$ , 1가 6- N-

R<sup>2</sup>, C<sub>1</sub>-C<sub>4</sub>-), C<sub>3</sub>-C<sub>6</sub>-), (, C<sub>1</sub>-C<sub>4</sub>-  
 CH<sub>1</sub> 2, Z<sup>1</sup> CR<sup>5</sup> (, R<sup>5</sup>, Z<sup>1</sup> Z<sup>3</sup> N-  
 . Z<sup>3</sup> Z<sup>4</sup> CH<sub>1</sub> ., Z<sup>2</sup> N-

Argonne National Laboratory, Argonne, IL 60439, USA

R 1 1가 6- N-

$\mathbb{R}^2$ ,

$Z^1 Z^3 N$        $, Z^2 Z^4$        $CH$        $, Z^1 CR^5$       (      , R<sup>5</sup>  
 $C_1 - C_4 -$       ),  $Z_2 N$        $, Z^3 Z^4$        $CH$       .

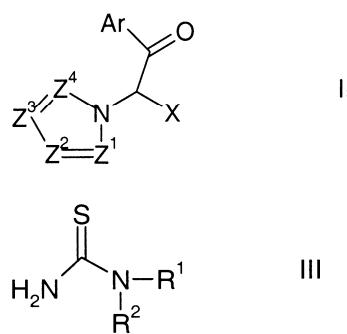
Ar 가

$\mathbb{R}^1$ ,

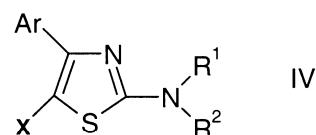
$$R^2, \quad , \quad C_1 - C_4 -$$

N , Z 2 Z 4 CH , Z 1 CR 5 , R 5 C 1 -C 4  
- , Z 2 N , Z 3 Z 4 CH .

가 , 가  
가 , , , ,  
; , , , ,  
, p- , , , 0-  
- , 1- -2- 3- -2-



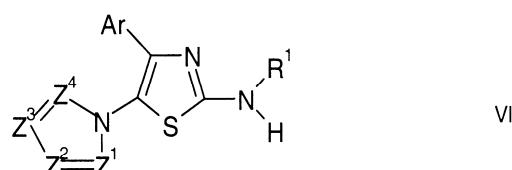
(B) | ( , R<sup>1</sup> 5- 6- ) ) , (IV) (Ar, R<sup>1</sup>, R<sup>2</sup> X ) (V) ,



$$\begin{array}{c} Z^4 \\ || \\ Z^3 \backslash \\ \diagdown \quad \diagup \\ Z^2 = Z^1 \\ | \quad | \\ NH \end{array} \quad V$$

$$(C) \quad | \quad ( \quad , R^2 \quad ) \quad -CON(R^3)R^4 \quad ) \quad , \quad , \quad (VI)$$

Cl-CON(R^3)R^4



, Ar, Z<sup>-1</sup>, Z<sup>-2</sup>, Z<sup>-3</sup>, Z<sup>-4</sup>, R<sup>-3</sup>, R<sup>-4</sup>

(ii) □

(A)

50

3

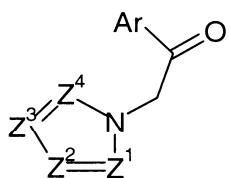
(B) , 80 160C ,

가

(C)

vii

X 3



vii

, Ar, Z<sup>-1</sup>, Z<sup>-2</sup>, Z<sup>-3</sup> Z<sup>-4</sup>

11

11

$$\begin{array}{c}
 \text{III} \\
 ( \quad , R^1 \quad R^2 \\
 \quad , \quad , \quad \text{NaOH}
 \end{array}$$

VIII  
가

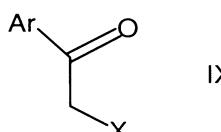
$$\begin{array}{c} & \diagup \\ & R^1 \\ H-N & \diagdown \\ & R^2 \end{array}$$

VIII

IV

IX

(brominating).



V

(A) (B)

VII

IX

VI  
V  
IX

A2b

A2b

A1 A2a

A2h

---

AZD

a) \_\_\_\_\_ (Chinese Hamster Ovary: CHO) A2b

- (pCRE-LUCI) A2b (pA2bRCV)  
 CHO 10% v/v (FCS), 2mM L-, , 0.4 mg/ml L-, 1  
 nM (selenite), 0.5 mg/ml (Hygromycin) B 1 mg/ml 가 Dulbecco'  
 s Modified Eagle (DMEM) 37 °C, 5% CO<sub>2</sub> 100% . /  
 EDTA , 5 1 .

b) \_\_\_\_\_

, CHO-A2b 50 µl DMEM 50,000 96-  
 (Packard) , 37 °C, 5% CO<sub>2</sub> 100 %

c) \_\_\_\_\_

DMSO, Cogener (XAC) (DMSO) 10 mM  
 DMSO 100 μM, 10 μM (DMSO) 10 mM  
 (deaminase: ADA) 가 (DMEM)  
 2.5 μM (40 μl) 가, (Ropivapine) 10 U/ml  
 μM, 37 °C, 5% CO<sub>2</sub>, 100% 250 nM  
 100nM 1

d) \_\_\_\_\_

5'-N- (NECA), A2b DMSO 10 nM , ,  
     100 μM . 100 0.01 μM  
     10 NECA . NECA 10 μl CHO-A2b  
     . (30 ) 가 , 10 0.0005 μM  
     . cAMP (CBP) cAMP 3 37 , 5%  
     CO<sub>2</sub> 100% 가 (lyse) ,  
     . 100 μl Steady-Glo, Promega . Topcount NXT microplate scintillation counter (ex Packar

d)  $(K_B - 5)^{-1} / (K_B + 1)$ , 5,  $K_B$ . Activitybase

$$(K_B = 1) / (-1)$$

300nM      K<sub>B</sub>      .      ,      12, 15, 16, 17,  
 27, 35, 36    38      31nM, 20nM, 24nM, 26.5nM, 10nM, 4nM, 17nM    12nM    K<sub>B</sub>      .  
 ,      I      A3  
 ,      WO 99/64418      A3      .      ,      7, 27,  
 30, 31, 34, 35    38      24nM, 16nM, 22nM, 11.5nM, 11nM, 10nM    4nM    K<sub>I</sub>

A2b | ( , (agent) ) , A2b  
A3 ,  
A3 (symptomatic)

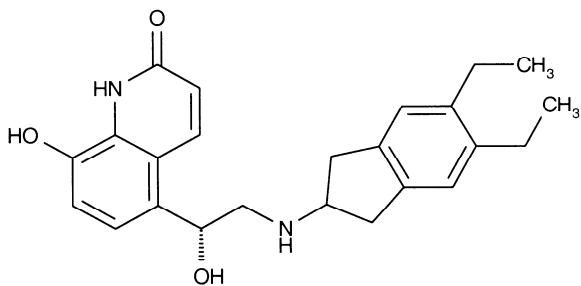
, , , , , ,  
 ) ( ) , , , , ,  
 , , , , (wheezy)  
 4 5  
 (wheezy - infant) ).

, , , , ,  
( , )  
(morning dipping)

ARDS), , (COPD, COAD COLD), (ALI), ( , , , , (arachidic), , (croupus), .

(phthinoid),  
(pemphisis), (acquisita),  
Churg-Strauss  
m

Szarka , J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin. Invest. (1995) 96:2924-2931; Cernadas (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8

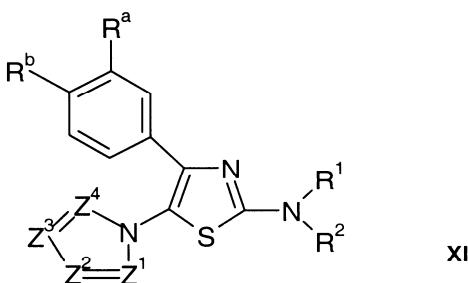


- (co-therapeutic)  
 (clemastine) , (cetirizine)  
 (fexofenadine) , (promethazine), (loratadine),  
 , PDE4 LTD4 , COPD , (desloratadine),  
 , COPD , -2  
 , COPD , LTB4

CR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 , CCR-1, CCR-2, CCR-3, C  
 Sering-Plough SC-351125, SCH-55700 CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, Sch  
 (4- )-5H- (aminium) (TAK-770) Takeda CCR-5 , N-[[4-[[[6,7-  
 00/66558 ( , 8), WO 00/66559 ( , 9) US 6166037 ( , 18 19), WO  
 00/66558 ( , 8), WO 00/66559 ( , 9) CCR-5

| , , A2b / A3  
 , , A2b / A3 가 , |

1-38



10 25,

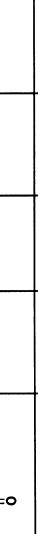
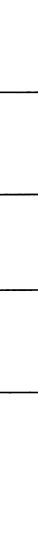
(MH<sup>+</sup>)

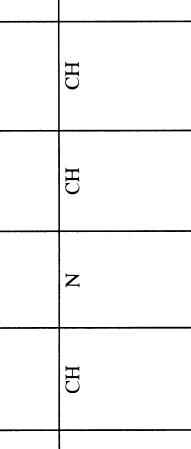
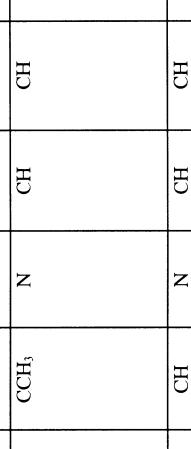
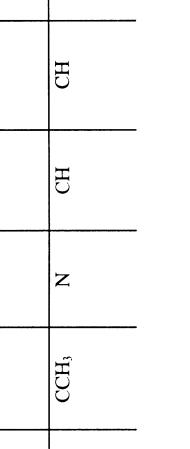
33

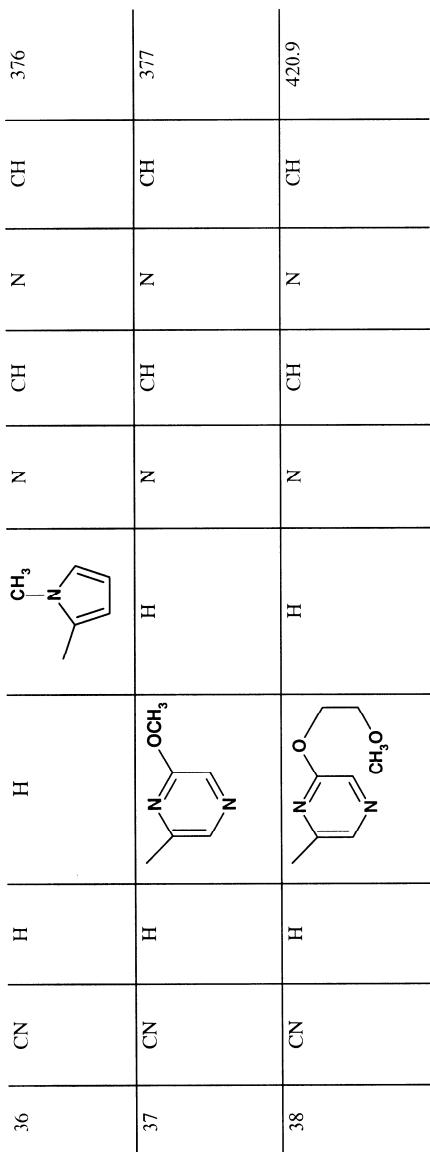
Ex	R <sup>a</sup>	R <sup>2</sup>	R <sup>b</sup>	R	R <sup>2</sup>	Z <sup>1</sup>	Z <sup>2</sup>	Z <sup>3</sup>	Z <sup>4</sup>	m/s
1	CN	H			H	CH	N	CH	CH	344
2	CN	H			H	N	CH	N	CH	243
3	CN	H			H	N	CH	N	CH	345
4	CN	H	H			N	CH	N	CH	362
5	CN	H	H			N	CH	N	CH	310
6	CN	H			H	N	CH	N	CH	345
7	CN	H			H	N	CH	N	CH	345



15	CN	H		H	N	CH	N	CH	359
16	CN	H		H	N	CH	N	CH	392
17	CN	H		H	CH	N	CH	CH	344
18	CN	H		H	N	CH	N	CH	345
19	CN	H		H	N	CH	N	CH	362
20	H	H		H	N	CH	N	CH	320
21	H	Me		H	N	CH	N	CH	334
22	CN	H		H	N	CH	N	CH	350

23	CN	H	H		N	CH	N	CH	373
24	CN	H		H	N	CH	N	CH	373
25	CN	H		H	N	CH	N	CH	369
26	CN	H		H	N	CH	N	CH	375
27	CN	H		H	N	CH	N	CH	346
28	F	H		H	N	CH	N	CH	338
29	F	H		H	N	CH	N	CH	338

30	F	H	H	H	N	CH	N	CH	338
31	CN	H		H	N	CH	N	CH	375
32	CN	H		H	CH	N	CH	CH	358
33	H	H		H	CCH3	N	CH	CH	372
34	CN	H		H	CH	N	CH	CH	345
35	CN	H		H	CCH3	N	CH	CH	360



12: N-[4-(3-  
- )-5-[1,2,4]-  
-1- - -  
-2- 1-4-

4 - (0.16ml, 1.36 mmol) (1.5ml) 3 - (2 - - 5 - [1,2,4] - 1 -  
- - 4 - ) - (0.15g, 0.56mmol) 2 30

m.s. ( $\text{MH}^+$ ) 402. m.p. 292-294 °C.

5, 9, 11 22

3 - (2 - -5 - [1,2,4] - 1 - - -4 - ) -

3-(2-  
(0.46g, 1.2mol) - 2-[1,2,4]  
95 °C - 1- 8 )- 가 .  
, 3M .  
9.54. pH 11. M.S. (MH+) 26

15: 3-[2-(6- - -2- )-5-[1,2,4] -1- - -4- ]-

3-(2-ml) -2-[1,2,4] -1- - )- (208mg, 1.34mmol) (500mg, 1.34mmol) 90 °C 2 (5  
 가 . , , , , , , ,  
 , , , , , , ,  
 60.0, m.p.236-237 °C. Mass Spec (APCI+) 3

## (6- - - -2- )-

6- mol) -2- (1.0g, 9.2mmol) (10ml) (1.24ml, 9.2m  
 가 . , 1M 40 °C 2  
 , , , , , , ,  
 . Mass Spec (APCI+) 168.

## 27 : (3-[2-( -2- )-5-[1,2,4] -1- - -4- ]- ):

3-([1,2,4] -1- - )- (150mg, 0.7mmol) (640l) (19l)  
 80 °C 6  
 , 3-(2- -2-[1,2,4] -1- - )- (200mg, 0.  
 5mmol) (2ml) -2- - (0.5mmol) 80 °C 10  
 가 , , , , , , ,  
 , , , , , , ,  
 , m.p. >250 °C, m.s. (AP+) 347.

3, 6-8, 10, 13-14, 17-18, 20-21, 24-26 28-31 II III

## 3-([1,2,4] -1- - )- :

3- (10.013g, 69mmol) (150ml) (3.53ml).  
 30 , , , , , , ,  
 가 , , , , , , ,  
 3M HCl (500ml) , , , , , , ,  
 , , , , , , ,  
 , m.p.172-173 °C, m.  
 s. (AP+) 213.

II

## -2- - :

10 (2g, 21.03mmol) (20ml) (2.82ml) 가  
 1M 80 °C 1  
 , , , , , , ,  
 , , , , , , ,  
 , m.p. 239-239.5 °C, m.  
 s. (AP+) 138 (M + -NH<sub>3</sub> ).

III

## 35: (3-[5-(2- - -1- )-2-( -2- )- -4- ]- ):

3-[5- mg, 6.98mmol] -2- ( -2- , 150 °C 16 -4- ]- (250mg, 0.698mmol) 2- (573  
 , , , , , , ,  
 , m.p.276-276.5 °C, m.s. 360 (TOF, ES+).

1, 2 32 - 34

IV V

$$3 - [2 - (-2 - \dots) - \dots - 4 - \dots] - \dots$$

$$3 - [5 - \dots - 2 - ( \dots - 2 - \dots ) - \dots - 4 - \dots ] - \dots$$

3-[2-(  
 $(0.275\text{ml})$   
 $\text{+ -Br})$ .  
 $\text{pH } 9$   
 $\text{m.p. } 215^\circ\text{C (dec.)}, \text{m.s. } 279 \text{ (ES+, M}$

IV                    IX            III

IX III

36: 1- -1H- -2- [4-(3- - )-5-[1,2,4] -1- - -2- ]-

1- -1H- -2- (110mg) (0.5ml) 3-(2- -5-[1,2,4] -1-  
 - -4- )- (50mg, 0.19mmol) 가 . 16 , (10ml) 가  
 . 3 . 20min .

Mass Spec. ( $MH^+$ ) 376, m.p. 245-247 °C.

4-5, 16, 19 23

37: 3 - [2 - (6 - - - - ) - 5 - [1,2,4] - 1 - - - - 4 - ]

3-(2-  
ml) -2-[1,2,4]  
. (6-  
가 . -  
- 2- )-  
- 1 - - )-  
- (0.67mmol)  
3M HCl  
(250mg, 0.67mmol)  
80 °C 10  
(2

. Mass Spec (APCI+) 377.1.

38

(6- - -2- )-

6- - - 2- (0.85g, 6.8mmol) 10 80 °C (7ml), (0.91ml)  
 가 . 1M (15ml) 1 가 .

39 : (3-[5-(2- - -1- )-2-( -2- )]- -4- ]- )

(3-[5-(2-  
(25ml) - | - )-2-( - 2- )- - 4- ]- (lg, 2.78mmol)  
, (25ml) (0.2ml, 3.06mmol) 가 ,  
, (25ml) , , ,

(20ml) . (2ml), (5ml) 가 , 4 °C .  
 , P<sub>2</sub>O<sub>5</sub> 80 °C, , m.p. 282 °C.

3-(2-  
-|- - )-

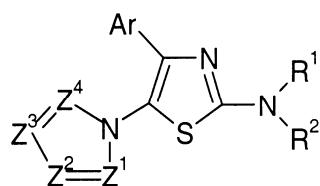
3-  
l)      가      ,      (50g, 0.345mol)      (600ml)      ,      (17.7ml, 0.345 mol)  
       30      ,      ,      ,      ,      ,      (300ml)  
       2-      (28.3g, 0.345 mol)      가      ,      1      ,  
       45      0 C      ,      ,      ,      ,      1      ,  
       ,      ,      ,      ,      ,      ,      ,      ,      ,  
       , m.s. 369 (MH<sup>+</sup>).

$$(3 - [5 - (2 - \dots - 1 - )] - 2 - ( \dots - 2 - \dots ) - \dots - 4 - ] - \dots ):$$

3-(2-  
  (15.6g, 0.06 mol)  
  )  
30  
, -I- - )- (60ml) (13.8g, 0.06 mol),  
, (50ml) 60 °C (9.4g, 0.06 mol),  
P<sub>2</sub>O<sub>5</sub> 40 °C, 17.5  
가 (50ml)

(57)

1.



, Ar C<sub>6</sub>-C<sub>15</sub> 1가

$$R^2 - C_1 - C_8 - , \quad -CON(R^3)R^4 , \quad R^1 , \quad R^2 - C_1 - C_8 - ,$$

$$R^3 - R^4 = C_1 - C_8 - \dots, \quad 5 - 6 -$$

8

2. Ar C C C C

3

3. Ar 가 C<sub>1</sub> ~ C<sub>8</sub> =

$$4. \quad \begin{matrix} 1 & , & 2 \\ \text{가} & 6- & \text{N-} \end{matrix} \quad 3 \quad , \quad R^1 \quad , \quad C_1 - C_4 - \quad , \quad 1$$

$$5. \quad 1^4, R^2, C_1 - C_4 - , C_3 - C_6 - , \\ (1, 5-, 6-, C_1 - C_4 - , ), \text{ 가 } ) .$$

6.  
1 , Ar ,  
1 , C<sub>1</sub>-C<sub>4</sub>- , 17| 6- N-  
,  
2 , C<sub>1</sub>-C<sub>4</sub>- , C<sub>3</sub>-C<sub>6</sub>- , ( , 5- 6- C<sub>1</sub>-C<sub>4</sub>-  
), 2 ( ) , ,  
1 , 2 ( ) , ,

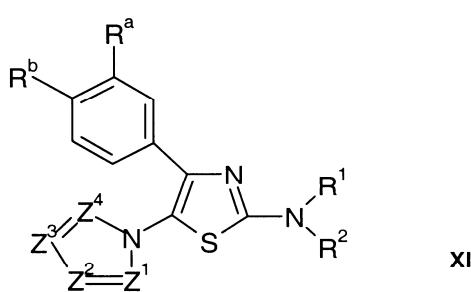
$$Z^1 \quad Z^3 \quad N \quad , \quad Z^2 \quad Z^4 \quad CH \quad , \quad Z^1 \quad CR^5 \quad ( \quad , \quad R^5 \\ C_1 - C_4 - \quad ), \quad Z_2 \quad N \quad , \quad Z^3 \quad Z^4 \quad CH \quad .$$

7.  
 1 , Ar ,  
 R 1 1가 6- N- ,  
 R 2 ,  
 Z 1 Z 3 N C 1 -C 4 - ), Z 2 N , Z 4 , CH Z 4 , Z 1 CR 5 CH ( , R 5 .

8.  
1 , Ar 가  
R<sup>1</sup> ,  
R<sup>2</sup> , , C<sub>1</sub>-C<sub>4</sub>- , ,  
, Z<sup>1</sup> Z<sup>3</sup> N C<sub>1</sub>-C<sub>4</sub>- , Z<sup>2</sup> N Z<sup>4</sup> CH , Z<sup>3</sup> Z<sup>4</sup> , Z<sup>1</sup> CR<sup>5</sup> CH , R<sup>5</sup> .

9.

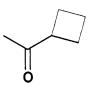
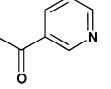
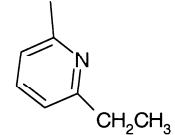
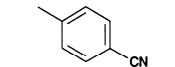
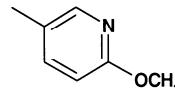
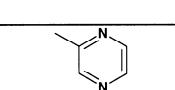
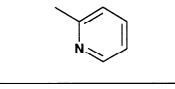
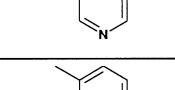
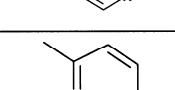
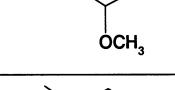
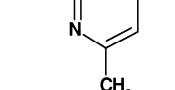
xli



, R<sup>a</sup>, R<sup>b</sup>, R<sup>1</sup>, R<sup>2</sup>, Z<sup>1</sup>, Z<sup>2</sup>, Z<sup>3</sup> Z<sup>4</sup>

R <sup>a</sup>	R <sup>b</sup>	R <sup>1</sup>	R <sup>2</sup>	Z <sup>1</sup>	Z <sup>2</sup>	Z <sup>3</sup>	Z <sup>4</sup>
CN	H		H	CH	N	CH	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H	H		N	CH	N	CH
CN	H	H	COCH <sub>3</sub>	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
H	Cl		H	N	CH	N	CH
CN	H	H		N	CH	N	CH

CN	H		H	N	CH	N	CH
CN	H	H		N	CH	N	CH
CN	H	H		N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H			N	CH	N	CH
H	H		H	N	CH	N	CH
H	Me		H	N	CH	N	CH

CN	H	H		N	CH	N	CH
CN	H	H		N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
F	H		H	N	CH	N	CH
F	H		H	N	CH	N	CH
F	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	CH	N	CH	CH

H	H		H	CCH <sub>3</sub>	N	CH	CH
CN	H		H	CH	N	CH	CH
CN	H		H	CCH <sub>3</sub>	N	CH	CH
CN	H	H		N	CH	N	CH
CN	H		H	N	CH	N	CH
CN	H		H	N	CH	N	CH

**10.**

1      9

,

**11.**

1      10

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,

**12.**

,

1

11

**13.**

A2b

1

11

**14.**

A3

1

11

**15.**

1

11

**16.**(i) (A) I (II, R<sup>1</sup>) 5- III 6-, , )

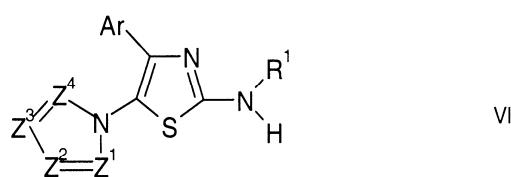
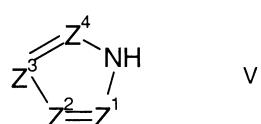
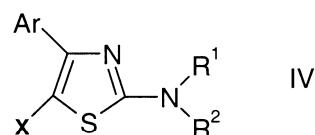
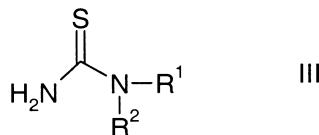
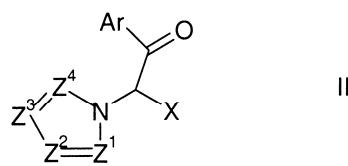
(B) I (IV) (V) 5- 6-, , )

(C) I (R<sup>2</sup>, -CON(R<sup>3</sup>)R<sup>4</sup>) , (VI)Cl-CON(R<sup>3</sup>)R<sup>4</sup>) , , , , : ,

(ii)

I

:



, Ar, Z<sup>-1</sup>, Z<sup>-2</sup>, Z<sup>-3</sup>, Z<sup>-4</sup>, R<sup>-3</sup>, R<sup>-4</sup> 1 ,

X

, C<sub>1</sub>-C<sub>8</sub>- III IV , R<sup>1</sup> , , , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , C<sub>1</sub>-C<sub>8</sub>- , R<sup>1</sup> 5- 6- 17| , R<sup>2</sup> H C<sub>1</sub>-C<sub>8</sub>- ,

VI R 1 1