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(A)

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2004 01 24

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(22) 2003 05 02

2003 05 02

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(87)

WO 2002/42298

(86) 2001 11 19

(87)

2002 05 30

(81)

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EA : , , , , , ,
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EP

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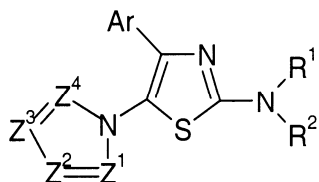
(72) 125

125

(74)

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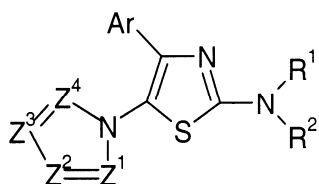
(54)



, Ar C₆-C₁₅ 1가
 C₈ -, C₁-C₈ -, C₁-C₈ -, R¹, C₁-C₈ -, C₁-
 5- 6- 1가
 -CON(R³)R⁴, R¹, R² C₁-C₈ -, R² C₁-C₈ -,
 R⁴ -CON(R³)R⁴, R³
 C₁-C₈ -, Z¹, Z², Z³ Z⁴ N CR⁵, CR⁵
 R⁵, C₁-C₈ -, C₁-C₈ -.

, .

, (free) I .



, Ar C₆-C₁₅ 1가
 R¹, C₁-C₈ -, C₁-C₈ -, C₁-C₈ -, C₁-C₈ -,
 -C₁-C₈ -, 5- 6-
 1가
 R², C₁-C₈ -, -CON(R³)R⁴, R¹, R² C₁-C₈ -,
 -CON(R³)R⁴,
 R³ R⁴ C₁-C₈ -, 5- 6-
 ,
 Z¹, Z², Z³ Z⁴ N CR⁵, CR⁵,
 R⁵, C₁-C₈ -, C₁-C₈ -.

:

, C₁-C₈ -, C₁-C₈ -, , , , n-
 , n-, , sec-, tert-, , C₁-C₈ -, C₁-C₄ -.
 ,
 C₁-C₈ -, C₁-C₈ -, , , , ,
 n-, , n-, , sec-, tert-, ,

[illegible]

$$4^{-}, \quad, C_1-C_4^{-} \quad, N-(C_1-C_4^{-})$$

R³, R⁴, , C₁-C₄-, ,
6- . R³, R⁴, , C₁-C₈-,
5- 6-

$$\begin{array}{ccccccc}
2 & Z^1, Z^2, Z^3 & Z^4 & CR^5 & & & R^5 \\
C_1 - C_4 - & . & & Z^1 & Z^3 & N & , Z^2 \quad Z^4 \\
R^5 & , Z^2 & N & , Z^1, Z^3 & Z^4 & & CR^5 \\
C_1 - C_4 - & . & & , Z^1 & Z^3 & N & , Z^2 \quad Z^4 \\
CH & , Z^1 & CR^5 & , & R^5 & C_1 - C_4 - & , Z^2 \quad N \\
Z^3 & Z^4 & CH & & & & , Z \\
& & & & & &
\end{array}$$

1 :

Ar

R^{-1} , $C_1 - C_4$, 1716- N-

$$\begin{array}{l} R^2 \quad , C_1 - C_4 - \quad , C_3 - C_6 - \\ \quad) , \quad (\quad , \quad (\quad , \quad C_1 - C_4 - \\ \quad 1 \quad 2 \quad 7 \mid) \quad , Z^1 \quad Z^3 \quad N^{5-} \quad 6- \\ \quad CH \quad , Z^1 \quad CR^5 \quad (\quad , R^5 \quad C_1 - C_4 - \quad), Z^2 \quad Z^4 \quad , \\ \quad , Z^3 \quad Z^4 \quad CH \quad . \end{array}$$

| :

Ar 가

R¹ 1가 6- N-

 R^2
$$\begin{array}{ccccccc} Z^1 & Z^3 & N & , Z^2 & Z^4 & CH & , Z^1 & CR^5 & (& , R^5 \\ & C_1 - C_4 - &) , Z_2 & N & , Z^3 & Z^4 & CH & . \end{array}$$

1 : 1

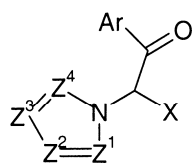
Ar 가 ,

 R^{-1}
$$\begin{array}{c} R^2 \\ | \\ N - C_1 - C_4 - CR^5 \\ | \quad | \quad | \quad | \\ Z^2 \quad Z^4 \quad CH \quad Z^1 \\ | \quad | \quad | \quad | \\ Z^2 \quad N \quad Z^3 \quad Z^4 \quad CH \end{array}$$

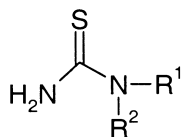
I _____가 , _____가 . I
_____가 , _____가

, p- , p- , 1- -2- 3- -2- , o-

(i) (A) I (, R¹ 5- 6-)
 , , , II (, X , C₁-C₈- , C₁-C₈-
 - , C₁-C₈- III (, R¹ , C₁-C₈- , C₁-C₈-
 , R¹ 5- 6- 17) , R² H C₁-C₈-
) ,

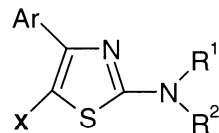


II

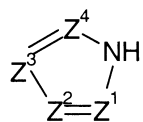


III

(B) I (, R¹ 5- 6-)
 , (IV) (Ar, R¹, R² X) (V) ,

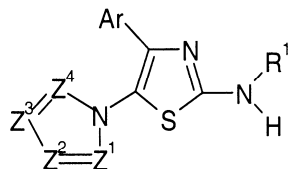


IV



V

(C) I (, R²) -CON(R³)R⁴) , (VI) (, R¹)
 I Cl-CON(R³)R⁴) ,



VI

, Ar, Z¹, Z², Z³, Z⁴, R³, R⁴ .

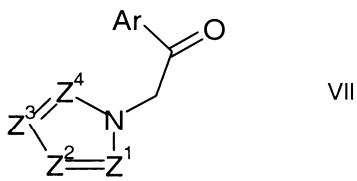
(ii) I .

(A) , 50 3 .

(B) , 80 160C 가 .

(C) .

II VII X₂ , :

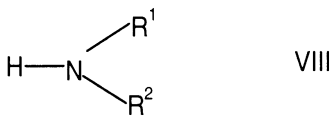


, Ar, Z¹, Z², Z³, Z⁴ .

II III I .

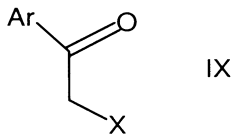
(III , R¹, R²) , , NaOH , , VIII 가

, 35-45 . 가 , 70 ,



VIII

III IV IX (, Ar X) II (brominating), , III ,



IX

V (A) (B) 가 VII IX VI V VIII IX

I A2b A1 A2a A2b

A2b

a) (Chinese Hamster Ovary: CHO) A2b

- (pCRE - LUCI) A2b (pA2bRCV) , 0.4 mg/ml L - , 1
nM (selenite), 0.5 mg/ml 10% v/v (FCS), 2mM L - (Hygromycin) B 1 mg/ml 가 Dulbecco'
s Modified Eagle (DMEM) 37 , 5% CO₂ 100% . /
EDTA , 5 1 .

b)

, CHO-A2b 50 μ l DMEM 50,000 96-
(Packard), 37, 5% CO₂ 100 %

c) _____

DMSO Cogener (XAC) (DMSO) 10 mM
100 μ M, 10 μ M (deaminase: ADA) 가 (DMEM) 10 μ M (Rolipram) 10 U/ml
2.5 μ M, (40 μ l) 가, 250 nM
 μ M, 37, 5% CO₂ 100% 100nM 1

d) _____

5' - N- (NECA), A2b DMSO 10 nM
100 μ M NECA 100 0.01 μ M
10 NECA (30) 가, CHO-A2b
cAMP (CBP) cAMP 10 0.0005 μ M
CO₂ 100% 3 37, 5%
100 μ l Steady-Glo, Promega 가 (lyse)
Topcount NXT microplate scintillation counter (ex Packar Activitybase

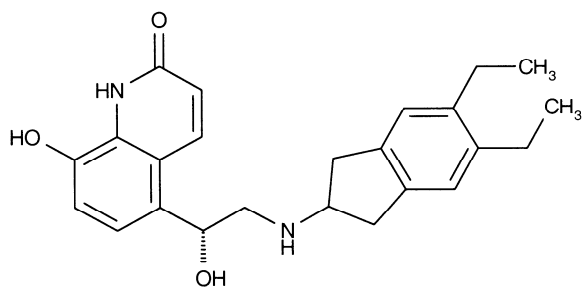
d) 5 K_B
(K_B = []/(-1)
27, 35, 36 38 300nM K_B 12, 15, 16, 17,
31nM, 20nM, 24nM, 26.5nM, 10nM, 4nM, 17nM 12nM K_B

WO 99/64418 A3 7, 27,
30, 31, 34, 35 38 24nM, 16nM, 22nM, 11.5nM, 11nM, 10nM 4nM K_I

A2b A3 (agent) A2b
A3 (symptomatic)
(wheezy)
4 5
(wheezy - infant).

(morning dipping)
4 6 am

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

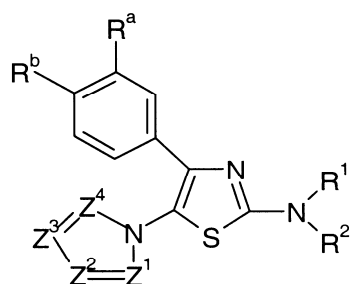


x

- (co-therapeutic) (cetirizine), (desloratidine),
 (clemastine), (promethazine), (loratidine),
 (fexofenadine) LTD4, COPD, PDE4, LTB4
 COPD, CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, Schering-Plough SC-351125, SCH-55700, SCH-D, CCR-5, N-[[4-[[[6,7-(4-)-5H-)-8-]]]-]-]-N,N-2H-4- (aminium) (TAK-770) Takeda, US 6166037 (, 18 19), WO 00/66558 (, 8), WO 00/66559 (, 9) CCR-5.

I , A2b / A3
 A2b / A3 가 , I

1-38











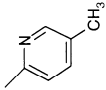


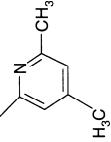
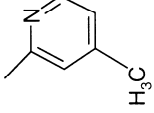
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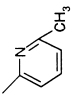
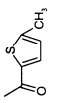
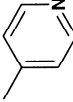
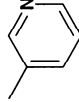
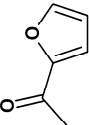


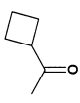
(MH+)

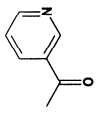
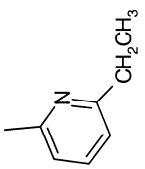
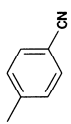
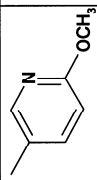



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
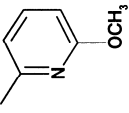
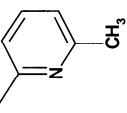
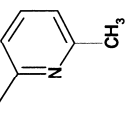


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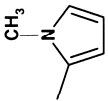
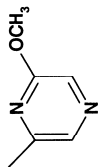
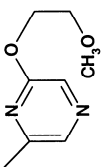
Ex	R ^a	R ^b	R ¹	R ²	Z ¹	Z ²	Z ³	Z ⁴	m/s
1	CN	H		H	CH	N	CH	CH	344
2	CN	H		H	N	CH	N	CH	243
3	CN	H		H	N	CH	N	CH	345
4	CN	H	H		N	CH	N	CH	362
5	CN	H	H	COCH ₃	N	CH	N	CH	310
6	CN	H		H	N	CH	N	CH	345
7	CN	H		H	N	CH	N	CH	345

8	H	Cl		H	N	CH	N	CH	355
9	CN	H	H		N	CH	N	CH	402
10	CN	H		H	N	CH	N	CH	359
11	CN	H	H		N	CH	N	CH	336
12	CN	H	H		N	CH	N	CH	402
13	CN	H		H	N	CH	N	CH	373
14	CN	H		H	N	CH	N	CH	359

15	CN	H		H		N	CH	N	CH	359
16	CN	H	H	H		N	CH	N	CH	392
17	CN	H		H	H	CH	N	CH	CH	344
18	CN	H		H	H	N	CH	N	CH	345
19	CN	H	H	H		N	CH	N	CH	362
20	H	H		H	H	N	CH	N	CH	320
21	H	Me			H	N	CH	N	CH	334
22	CN	H	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						CH	N	CH	338
31	CN	H		H						N	N	CH	375
32	CN	H		H						CH	N	CH	358
33	H	H		H						CCH ₃	N	CH	372
34	CN	H		H						CH	N	CH	345
35	CN	H		H						CCH ₃	N	CH	360

376	377	420.9
CH	CH	CH
N	N	N
CH	CH	CH
N	N	N
	H	H
H		
H	H	H
CN	CN	CN
36	37	38

:

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

4- (0.16ml, 1.36 mmol) (1.5ml) 3-(2- -5-[1,2,4] -1-
 - -4-)- (0.15g, 0.56mmol) 가 . 2 , 30
 , m.s. (MH+) 402, m.p.292-294 ° C.

5, 9, 11 22 .

:

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

3-(2- -2-[1,2,4] -1- -)- (1.848g, 5.00mmol),
 (0.46g, 1.2mol) 95 ° C 8 가 .
 , 3M . 가 . pH 11. M.S. (MH+) 26
 9.54.

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

3-(2- (6- (500mg, 1.34mmol) (208mg, 1.34mmol) 90 °C 2
 ml) 가 , 2 . Mass Spec (APCI+) 3
 60.0, m.p.236-237 °C.

(6- -2-)-

6- (1.0g, 9.2mmol) (10ml) (1.24ml, 9.2m
 mol) 가 10 40 °C 가 , 2 가 .
 , 1M (15ml) , 2 가 .
 . 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 가 ,
 , 3-(2- -2-[1,2,4] -1- -)- (200mg, 0.
 5mmol) (2ml) -2- - (0.5mmol) 가 , 80 °C 10
 가 , 3M HCl .
 , 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) 가 (3.53ml).
 30 , (100ml) (7g)
 가 , 3M HCl (500ml) 가 ,
 3-([1,2,4] -1- -)- , m.p.172-173 °C, m.
 s. (AP+) 213.

II

-2- - :

(2g, 21.03mmol) (20ml) , (2.82ml) 가 .
 10 80 °C 가 , 1 가 .
 1M (30ml) , m.p. 239-239.5 °C, m
 .s. (AP+) 138 (M + -NH₃).

III

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

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

1, 2 32-34

IV V

:

3-[2-(-2-)- -4-]- :

3- (1.0g, 6.88mmol) (15ml) , (353l, 6.88mmol) 가
 , -2- 30 (1.0g, 6.88mmol) 가 80 ° C 30 가 (15ml)
 , 3M HCl ,
 , m.p.203-204 ° C, m.s.280(ES+).

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

3-[2-(-2-)- -4-]- (1.5g, 5.36mmol) (10ml) ,
 (0.275ml) 가 pH 9 10 (ca. 100ml) 3-[
 5- -2-(-2-)- -4-]- , m.p. 215 ° C (dec.), m.s. 279 (ES+, M
 + -Br).

IV

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

3-(2- -2-[1,2,4] -1- -)- (250mg, 0.67mmol) (2
 ml) . (6- - -2-)- (0.67mmol) 가 80 ° C 10
 가 3M HCl ,
 . Mass Spec (APCI+) 377.1.

38

:

(6- - -2-)-

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

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

(3-[5-(2- - -1-)-2-(-2-)- -4-]- (lg, 2.78mmol)
 (25ml) , (0.2ml, 3.06mmol) 가 ,
 , (25ml) , ,

(20ml), (2ml), (5ml) 가 , 4 ° C ,
 , P₂O₅ 80 ° C, , m.p. 282 °
 C.

:

3-(2- -I- -)-

3- (50g, 0.345mol) (600ml) , (17.7ml, 0.345 mo
 l) 가 , 30 (28.3g, 0.345 mol) 가 , 1 , (300ml)
 . 2- (45 ° C , 1 , 40 ° C,
 , m.s. 369 (MH+).

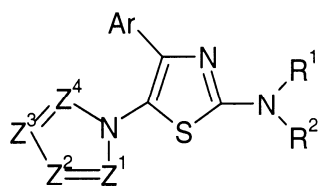
(3-[5-(2- - -1-)-2-(-2-)- -4-]-):

3-(2- -I- -)- (13.8g, 0.06 mol) -2- (9.4g, 0.06 mol),
 (15.6g, 0.06 mol) (60ml) 60 ° C (17.5
) , (50ml) 가 , (50ml)
 30 , P₂O₅ 40 ° C,

(57)

1.

I :



, Ar C₆-C₁₅ 1가 ,

R¹ , , , C₁-C₈- , C₁-C₈- , C₁-C₈- , C₁-C₈-
 -C₁-C₈- , 5- 6-
 1가 ,

R² , C₁-C₈- , -CON(R³)R⁴ , R¹ , R² C₁-C₈- ,
 -CON(R³)R⁴ ,

R³ R⁴ C₁-C₈- , 5- 6-
 ,

Z¹, Z², Z³ Z⁴ N CR⁵ , CR⁵ ,

R⁵ , C₁-C₈- C₁-C₈- .

2.

1 , Ar , C₁-C₈- C₁-C₈-
 .

3.

1 , Ar 가 , C₁-C₈-

4.
 1 , 2 3 , R^1 , C_1-C_4- , 1
 가 6- N-

5.
 1 4 , R^2 , C_1-C_4- , C_3-C_6-
 ($5-$ $6-$ C_1-C_4-), ($5-$ $6-$ C_1-C_4-)
 가)

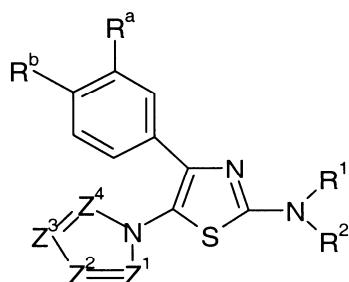
6.
 1 , Ar, R^1 , C_1-C_4- , 1가 6- N-
 R^2 , C_1-C_4- , C_3-C_6- ($5-$ $6-$ C_1-C_4-)
 1 2 가)
 Z^1 Z^3 N Z^2 Z^4 CH Z^1 CR⁵ (R^5
 C_1-C_4-), Z^2 N Z^3 Z^4 CH

7.
 1 , Ar 가
 R^1 1가 6- N-
 R^2
 Z^1 Z^3 N Z^2 Z^4 CH Z^1 CR⁵ (R^5
 C_1-C_4-), Z^2 N Z^3 Z^4 CH

8.
 1 , Ar 가
 R^1
 R^2 , C_1-C_4- , $5-$ $6-$
 Z^1 Z^3 N Z^2 Z^4 CH Z^1 CR⁵, R^5
 C_1-C_4- , Z^2 N Z^3 Z^4 CH









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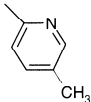


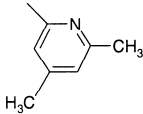
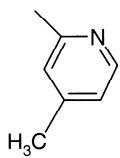


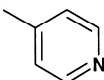
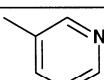
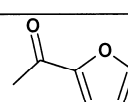


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
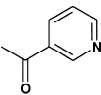
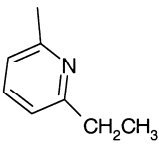
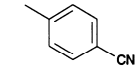
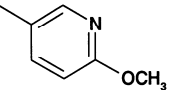




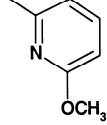
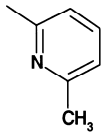


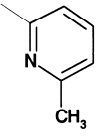


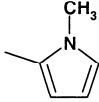
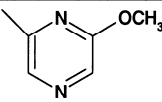
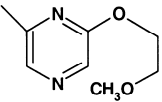
XI

, R^a, R^b, R¹, R², Z¹, Z², Z³, Z⁴

R ^a	R ^b	R ¹	R ²	Z ¹	Z ²	Z ³	Z ⁴
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 ₃	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	CH	N	CH	CH
CN	H		H	N	CH	N	CH
CN	H	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 ₃	N	CH	CH
CN	H		H	CH	N	CH	CH
CN	H		H	CCH ₃	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 , , , .

12.

, 1 11 .

13.

A2b

1 11 .

14.

A3

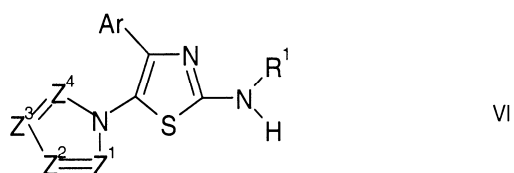
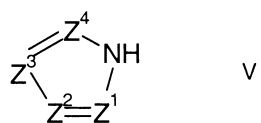
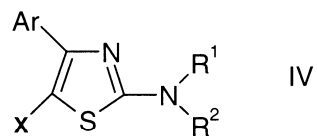
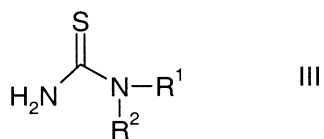
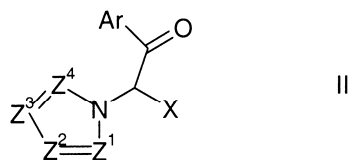
1 11 .

15.

1 11 .

16.

(i) (A) I (, R¹ 5- 6-)
II III ,(B) I (, R¹ 5- 6-)
(IV) (V) ,(C) I (, R² -CON(R³)R⁴)
Cl-CON(R³)R⁴) (VI) ,(ii) I
I :



, Ar, Z¹, Z², Z³, Z⁴, R³, R⁴ 1 ,

X ,

III IV , R¹ , , , C₁-C₈- , C₁-C₈- , C₁-C₈-
 , C₁-C₈- -C₁-C₈-
 , R¹ 5- 6- 17

, R² H C₁-C₈- ,

VI R¹ 1 .