

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. 7
C07D 487/16

(11)
(43)

2001 - 0080402
2001 08 22

(21) 10 - 2001 - 7005818
(22) 2001 05 08
2001 05 08
(86) PCT/US1999/26984
(86) 1999 11 12

(87) WO 2000/27850
(87) 2000 05 18

(30)	09/190,958	1998	11	12	(US)
	09/400,744	1999	09	21	(US)

(71)

92121 10555

(72)

92104 3545

92126 11036

16077 1037

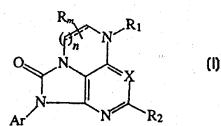
(74)

:

(54) C R F

CRF

() : , n, m, R, R₁, R₂, X Ar
가



CRF

, , , ,

CRF

CRF(cortisone - releasing factor)

41

(Vale et al., Science 213:1394 - 1397, 1981).

CRF

, CRF 41

7 가

(River et al., Proc.

Natl. Acad. Sci. USA 80:4851, 1983; Shibahara et al., EMBO J. 2:775, 1983).

CRF 가

, drenocorticotropic hormone),

CRF

ACTH(a

POMC(pro - opiomelanocortin) -

(Vale et al., Science 213:1394 - 1397, 1981).

RF (DeSouza et al., Science 224:1449 - 1451, 1984), (DeSouza et al., Methods Enzymol. 124:56

0, 1986; Wyne et al., Biochem. Biophys. Res. Comm. 110:602 - 608, 1983), (Udelsman et al., Nature 319

:147 - 150, 1986) (Webster, E. L., and E.B. DeSouza, Endocrinology 122:609 - 617, 1988)

CRF

cAMP(Bilezikjian, L. M., and W.W. Vale, Endocrinology 113:657 - 662, 1983)

CRF -

가

GTP -

(Perrin et al., Endocrinology 118:1171 - 1179, 1986)

CRF

.

(Perrin et al., Endo 133(6):3058 - 3061, 1993),

(Chen et al., PNA

S 90(19):8967 - 8971, 1993; Vita et al., FEBS 335(1):1 - 5, 1993)

7

415

(97%)

CRF ACTH POMC , ,
 , , 가, CRF , ,
 (Crofford et al., J. Clin. Invest. 90:2555 - 2564, 1992; Spolsky et al., Science 238:522 - 524, 1987; Tilders et al., Regul. peptides 5:77 - 84, 1982). , CFR

CRF , ,
 . , CRF (Sutton et al., Nature 297:331, 1982), (electrocephalogram) (Ehlers et al., Brain Res. 278:332, 1983), (Brown et al., Endocrinology 110:928, 1982), 가(Fisher et al., Endocrinology 110:22 22, 1982), 가(Brown et al., Life Sciences 20:207, 1982), (Williams et al., Am. J. Physiol. 253:G582, 1987), (Levine et al., Neuropharmacology 22:232, 1983), (Sirina thsinghji et al., Nature 305:232, 1983), (Irwin et al., Am. J. Physiol. 255:R744, 1988)
 CRF 가 , ,
 (DeSouza, Ann. Reports in Med. Chem. 25:215 - 223, 1990). ,
 가 CRF 가 /

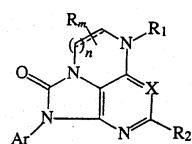
CRF (Rivier et al., U.S. Patent No. 4,605,642; Rivier et al., Science 224:889, 1984) . CRF 가 CRF
 , CFR 가
 , CRF 가 , , 4 - - 5 - - 3 -
 (Abreu et al., U.S. Patent No. 5,063,245) 2 - (Courtemanche et al., A ustralian Patent No. AU - A - 41399/93) 가 CRF
 RF가 1 - 10 μ M 0.1 - 10 μ M , C

CRF
 : WO94/13643, WO94/13644, WO94/13661, WO94/13676, WO94/13677, WO95/10506, WO95/33750, WO 96/35689, WO97/00868, WO97/35539, WO97/35580, WO97/35846, WO97/44038, WO98/03510, WO98/056 61, WO98/08846, WO98/08847, WO98/11075, WO98/15543, WO98/21200 WO98/29413.

CRF , CRF 가 CRF
 가 . , CRF ,

CRF CRF 가 ,
 CRF 가 . , CRF ,

, CFR ,
 가 () CFR



, m, n, X, R, R₁, R₂ Ar

CRF

가 ,
CRF

가

1

CRF

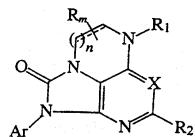
가

가

(CRF)

CRF

가



, n 1 2; m 0, 1, 2 3; X N CR'; R C 1-6 , C 3-6 C 1-6
 C_{1-6} Ar ; R' , C 1-6 ; R 1 - C(H) 0.1 (R 3)(R 4); R 2
 C_{1-6} ; R 3 , C 1-6 , (C 3-6) , C 3-6 , C 3-6
 C_{1-6} , C 1-6 C 1-6 , C 1-6 , C 1-6 ,

R₄ , AR₁, C₁₋₆ Ar¹, OAr¹, C₁₋₈ , C₁₋₆ , C₃₋₆ , - (C₃₋₆
) , C₃₋₆ , C₃₋₆ , C₁₋₆ C₁₋₆ , C₁₋₆ Ar¹, C₁₋₆ , C₁₋₆ C₁₋
 6 , C₁₋₆ , C₁₋₆ C₁₋₆ , , - (C₁₋₆) , (C₁₋₆) (A
 r¹) , (C₁₋₆) , (C₁₋₆ Ar¹) , (C₁₋₆) (Ar¹) , C₁₋₆ C₁₋₆ ,
 C₁₋₆ C₁₋₆ , (C₁₋₈) , C(=O)C₁₋₆ , C₁₋₈ , Ar¹, O
 Ar¹, NHAr¹, C(=O)Ar¹, C(=O)NHAr¹ - C(=O)NH₂, - (C₁₋₆) - Y - (CO)_{0.1} - Ar¹
 (, Y O, NH,),

Ar , , C₃₋₁₂ , , , C₁₋₆ , C₁₋₆ , , , O(C₁
 -6) , (C₁₋₆) (C₁₋₆) , , , 1, 2 3 가 ,
 / , C₁₋₆ , C₁₋₆ ;

Ar^1 , , C_{3-12} , , (C_{1-6}) , C_{1-6} , , (C_{1-6}) , (C_{1-6}) , (C_{1-6}) , C_{1-6}

" " = "O "

" C₁₋₆ " " C₁₋₈ " , , n - , , n - , , n -
 1 6 1 8 가

" C₁₋₆ " , - O(C₁₋₆)

" C₁₋₆ " - SCH₃, - SCH₂CH₃ - S(C₁₋₆)

" C₃₋₆ " , , , , 3 6

" C₅₋₈ " , , 5 8

" C₅₋₈ " 5 8

" C₃₋₆ " 3 6 가 , , 1- , 2- , 2-

" C₃₋₆ " 3 6 가 , , 1- , 2- , 2-

" C₁₋₆ " - CH₂OH, - CH(OH)CH₃ C₁₋₆

" - (C₃₋₆) "

" C₁₋₆ C₁₋₆ " - COC₁₋₆ C₁₋₆

" C₁₋₆ C₁₋₆ " - COOC₁₋₆ C₁₋₆

" C₁₋₆ C₁₋₆ " - OC₁₋₆ C₁₋₆

" C₁₋₆ C₁₋₆ " - SC₁₋₆ C₁₋₆

" (C₁₋₆)" - SO₂ - SO₂(C₁₋₆)

" - (C₁₋₆) "

" (C₁₋₆)(C₁₋₆) "

" (C₁₋₆) C₁₋₆ " - (C₁₋₆) C₁₋₆

" C₁₋₆ ' (- CH₂ -), (- CH₂CH₂ -) 2가 C₁₋₆

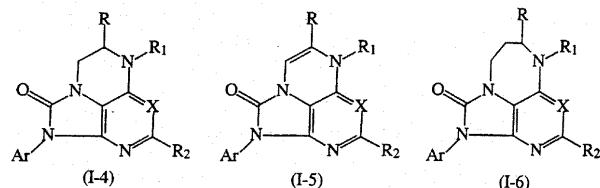
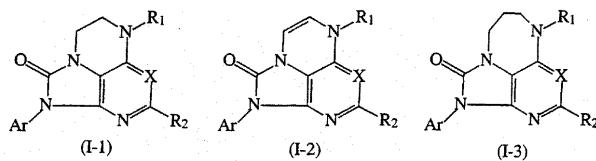
" , , /
" - OCH₂O - , - OCH₂CH₂O - , , , (" CH₂ ") C₁₋₆

" C₃₋₁₂

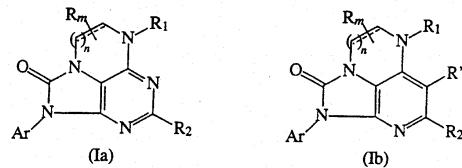
, , , , , , (1, 3, 5), , , , , , (isoxazoly), 3 12

" " , , .

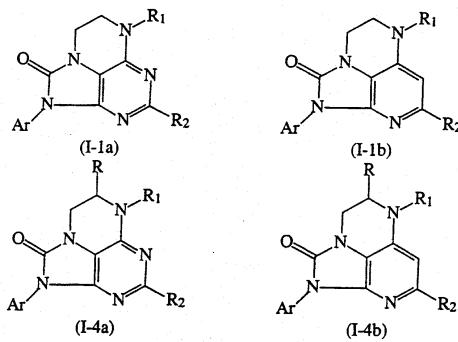
- CH₂CH₂ - - CH="CH - " 1 2 R (, n="1" m="0," 1 2)
- CH₂CH₂CH₂ - . , R (, n="2" m="0," 1, 2, 3)
(- 1), (- 2), (- 3), (- 4), (- 5) (- 6);



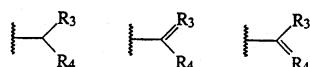
, X , CRF (a) (b)



CRF , CRF (b) (, R' (a) . (- 1a), (- 1
b), (- 4a) (- 4b) :



$$\begin{array}{lll} , R_1 & - CH(R_3)(R_4) & - C(R_3)(R_4) \\ R_1 & : & \end{array} \quad - C(H)_{0.1}(R_3)(R_4)$$

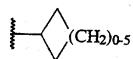


, R_3 가 , R_1

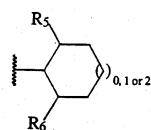


$$(-\text{C}(=\text{O})\text{R}_4, -\text{C}(=\text{O})\text{OR}_4, -\text{C}(=\text{O})\text{NH}_2, -\text{C}(=\text{O})\text{NH}(\text{C}_{1-6}), -\text{C}(=\text{O})\text{N}(\text{C}_{1-6})(\text{C}_{1-6}))$$

$R_1 R_3 R_4$ 가 C_{3-8} , R_1 가 :

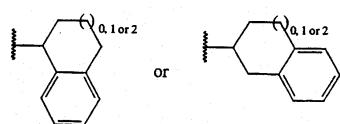


C_{3-8} , C_{1-6} , C_{5-7} , R_1 가 :



, R₅ R₆ C₁₋₆

$$, R_1 \quad R_3 \quad R_4 \quad Ar \quad C_{5-8} \quad , \quad R_1$$



Ar 2,4,6 - , 2 - - 4 - , 2 -
 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 -
 , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2,4 - , 2,6
 - - 4 - , 4 - , 2,4 - , 2,4 - , 2 - , 3 - , 2 -
 - 4 - , 3,4 - , 3,5 - , 4 - , 4 - , 2,4,6 -
 , 2 - - 4 - N()₂ , 2 - - 4 - (OCF₃) , 4 - - 2 - - 3 - , 4 -
 - 6 - - 2 - , 4 - - 3 - , 4 - N(CH₃)(COCH₃) - , 3,4 -
 3,4 - .

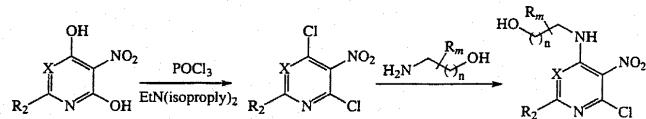
$$R - C_6H_4 - n - C_6H_4 - C - C_6H_4 - C - C_6H_4 - = \text{CH}_2 = \text{CHCH}_3$$

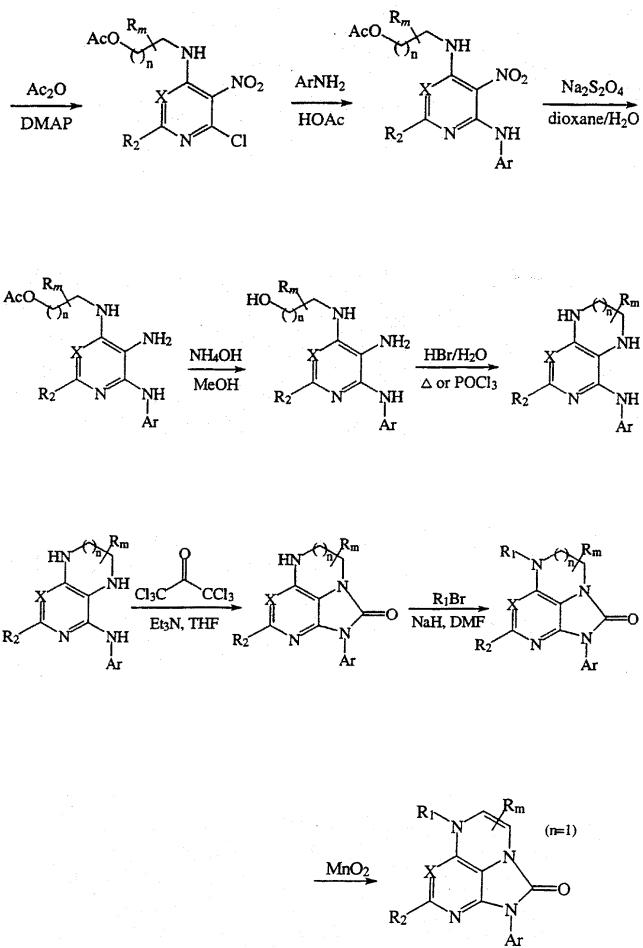
R' , , , , ,

$$R_2 = \frac{1}{2} \left(R_1 + R_3 \right)$$

· , 가

, () , 1 2





CRF
CRF
,
al., Synapse 1:572, 1987)
가
. CRF
. (D

CRF

CRF
. . ()
(battaglia et
CRF
(,
CRF

$$K_i = \frac{IC_{50}}{1 + L/K_D}$$

, $L = " "$ $K_D = " "$ (Cheng and Prusoff, Biochem. Pharmacol. 22:2099, 1973) .

CRF CRF CRF

(Battaglia et al., supra, 1987) CRF - (supra, 1987) cAMP

CRF, CRF, 1 μM, 10 μM, Ki 가 .
 , CRF, 1 μM, 0.25 μM(, 250nM) Ki
 , 4 .
 Ki (- 1) (- 25) (- 29) (- 33) .

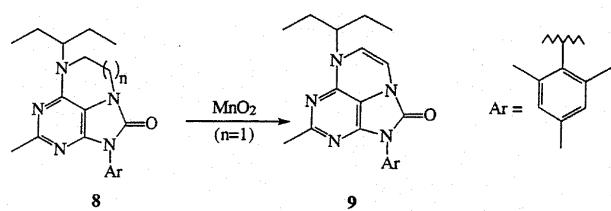
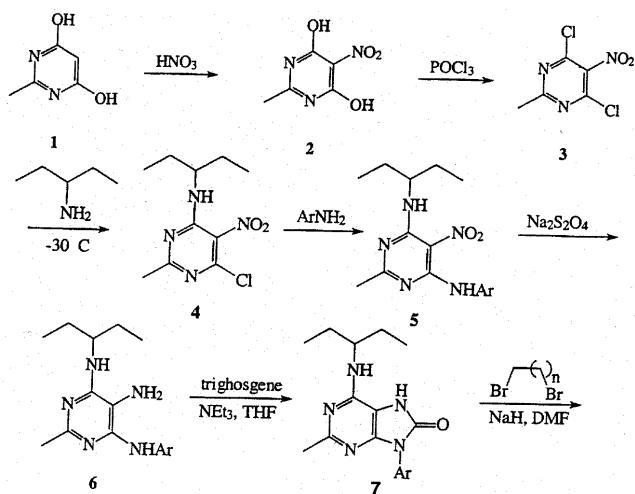
, CRF
() 가 / . CRF
- , CRF
0 mg, 1 mg 60 mg . CRF 0.1 mg 25

가 / . , , , , ,
가 / . , , , , ,
가 . , , , , , ,
CRF . , , , , ,
가 . , , , , ,
Remington's P
harmaceutical Sciences, Gennaro, Ed., Mack publishing Co., Easton, PA 1990)
CRF . , ,

CRF . 4 (Ki) , 5 CRF -

1

A



(4)

- 30 EtOH(30mL) 4,6 -
mmol) EtOH 1 - . - 2 - - 5 -
(870mg, 10mmol) (3; J. Chem. Soc. 1954, 3836)(2.23g, 11
- 30 1 EtOAC
() () (4)

(5)

(15mL) (4)(2.07g, 8 mmol)
, (1.52g, 15mmol) 2,4,6 -
EtOAc 2
() (5)

(6)

(5)(2.14g, 6mmol) 1:1 / (20mL)
(3.12g, 18mmol) 가 8
EtOAc
() (6)

(7)

THF(10mL) (6)(654mg, 2 mmol) (500mg) (217mg, 0.73m
mol) 1
EtOAc
() (7)

(8)

DMF(3 mL) (7)(353mg, 1 mmol) NaH(120mg, 3 mmol, 60% in oil)
1,2 - (654mg, 3 mmol) 가 10 EtO
Ac
(8) LC - MS 380(MH+).
()

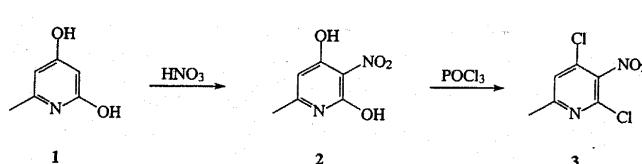
(9)

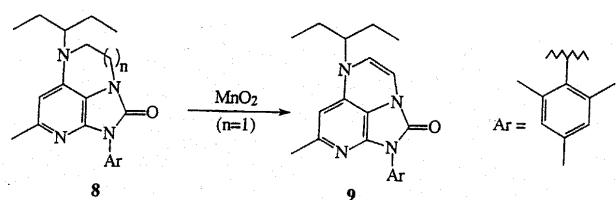
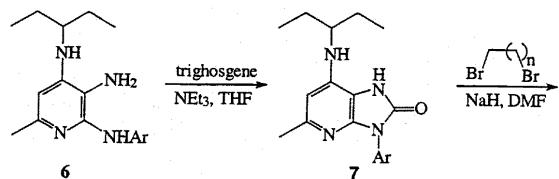
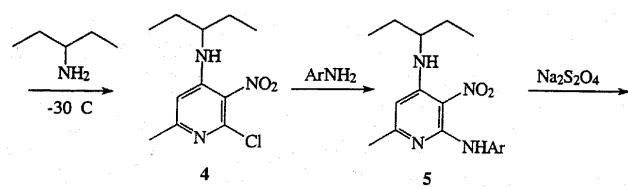
(2ml) (8)(38mg, 0.1 mmol) (100mg) 16
1:1) TLC() (9)
2

B

B

1 , (1)

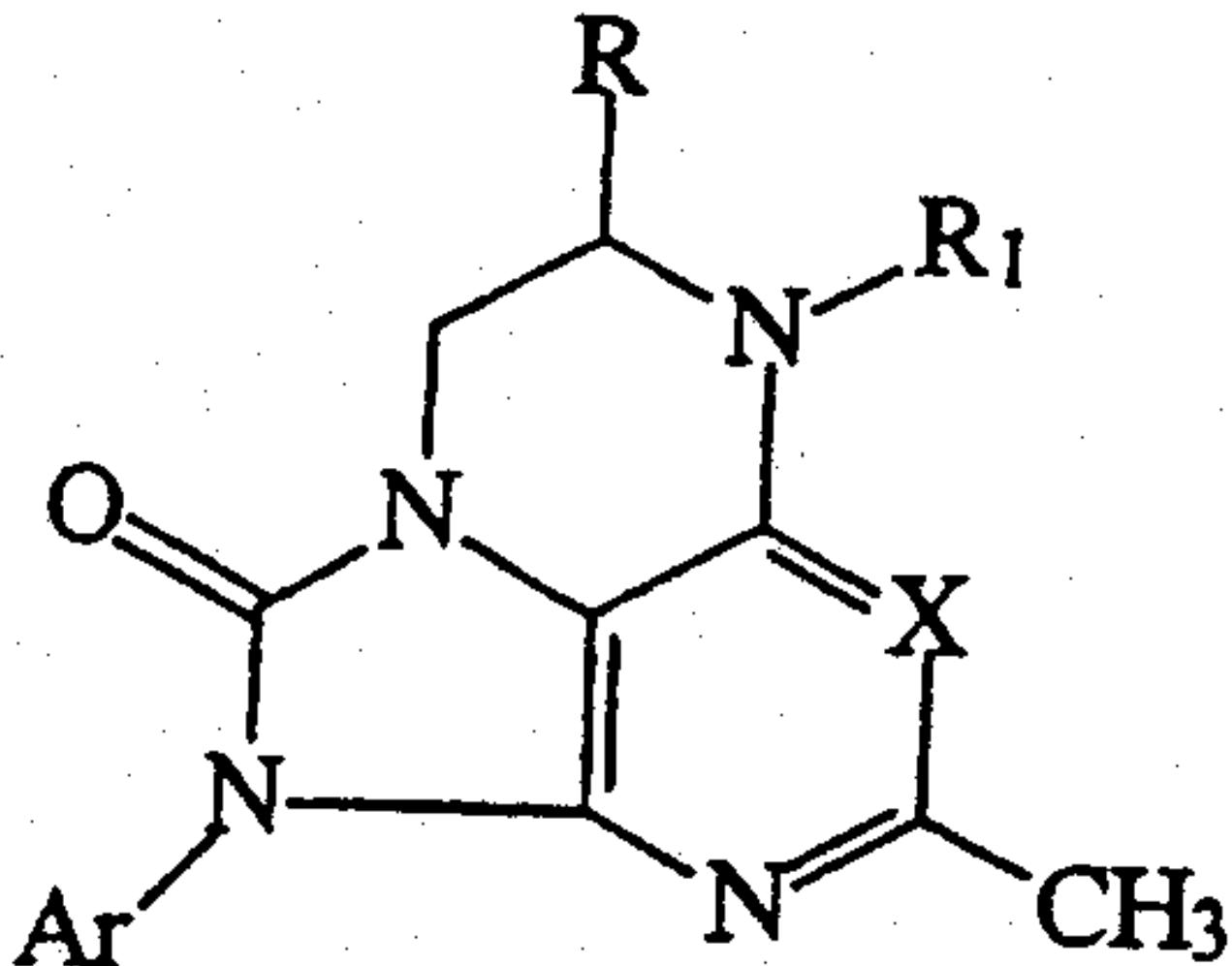




3

/ 1 2

[1]



	R	X	R ₁	Ar
(- 1)	H	N	- CH(CH ₂ CH ₂ CH ₃) ₂	2,4,6 -
(- 2)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 -
(- 3)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 -
(- 4)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2,4 -
(- 5)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2,6 - - 4 -
(- 6)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 -
(- 7)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 -
(- 8)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 -

	R	X	R ₁	Ar
(- 9)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2,4 -
(- 10)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 -
(- 11)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	3,4 -
(- 12)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 -
(- 13)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 -
(- 14)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2,4,6 -
(- 15)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 - ()
(- 16)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	
(- 17)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2 - - 4 - (OCF ₃)
(- 18)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	3 -
(- 19)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	2,4 -
(- 20)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	
(- 21)	H	CH	- CH(CH ₂ CH ₃)((CH ₂) ₃ CH ₃)	2 - - 4 -
(- 22)	H	CH	- CH(CH ₂ CH ₃) ₂	2 - - 4 -
(- 23)	H	CH	- CH(CH ₂ CH ₃)((CH ₂) ₂ CH ₃)	2 - - 4 -
(- 24)	H	CH	- CH(CH ₂ CH ₃)((CH ₂) ₄ CH ₃)	2 - - 4 -
(- 25)	H	CH	- CH((CH ₂) ₂ CH ₃)((CH ₂) ₃ CH ₃)	2 - - 4 -
(- 26)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	3,5 -
(- 27)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	3 - (5 -)
(- 28)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 -
(- 29)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - - 3 -
(- 30)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - - 3 -
(- 31)	(S)	CH	- CH ₂ CH ₂ OCH ₃	4 -
(- 32)	(S)	CH	- CH ₂ CH ₂ OH	4 -
(- 33)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - (N - - N -)
(- 34)	(S)	CH	- CH ₂ CH ₂ N(CH ₂ CH ₃) ₂	4 -
(- 35)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - (COOMe)
(- 36)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - - 3 -
(- 37)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - (COMe)
(- 38)	H	CH	- CH(CH ₂ CH ₂ CH ₃) ₂	4 - (CH(OH)(CH ₃) ₂)
(- 39)	(S)	CH	C(O)CH ₃	4 -
(- 40)	(S)	CH	C(O)CH ₂ Ph	4 -
(- 41)	(S)	CH	C(O)Ph	4 -
(- 42)	(S)	CH	C(O)CH ₂ CH ₃	4 -
(- 43)	(S)	CH	C(O)CH ₂ CO ₂ CH ₂ CH ₃	4 -

	R	X	R ₁	Ar
(- 44)	(S)	CH	C(O)	4 -
(- 45)	(S)	CH	C(O)CH(Ph)CH ₂ CH ₃	4 -
(- 46)	(S)	CH	C(O)4 -	4 -
(- 47)	(S)	CH	C(O)4 - (N,N -)	4 -
(- 48)	(S)	CH	C(O)CH ₂ OCH ₃	4 -
(- 49)	(S)	CH	C(O)3 -	4 -
(- 50)	(S)	CH	C(O)CH(CH ₂ CH ₃)CH ₂ CH ₃	4 -
(- 51)	(S)	CH	C(O)CH ₂ CH ₂ CH ₂ CH ₃	4 -
(- 52)	(S)	CH	C(O)CH ₂ CH(CH ₃) ₂	4 -
(- 53)	(S)	CH	C(O)CH ₂ CH ₂ CH ₃	4 -
(- 54)	(S)	CH	C(O)CH ₂ CH ₂ Ph	4 -
(- 55)	(S)	CH	CH ₂ - 3 -	4 -
(- 56)	(S)	CH	CH ₂ CH ₂ NHPh	4 -
(- 57)	(S)	CH	CH ₂ CH ₂ CO ₂ CH ₂ CH ₃	4 -
(- 58)	(S)	CH	CH ₂ CH ₂ CH ₂ Ph	4 -
(- 59)	(S)	CH	CH ₂ CH ₂ - N -	4 -
(- 60)	(S)	CH	CH ₂ CH ₂ CH ₂ CO ₂ CH ₂ CH ₃	4 -
(- 61)	(S)	CH	CH ₂ CH ₂ OCH ₂ CH ₃	4 -
(- 62)	(S)	CH	CH ₂ CH(CH ₃) ₂	4 -
(- 63)	(S)	CH	CH ₂ CO ₂ CH ₂ CH ₃	4 -
(- 64)	(S)	CH	CH ₂ C(O)(4 -)	4 -
(- 65)	(S)	CH	CH ₂ CH ₂ OPh	4 -
(- 66)	(S)	CH	CH ₂ CH ₂ CH ₂ CH ₂ - N -	4 -
(- 67)	(S)	CH	CH ₂ CO ₂ tBu	4 -
(- 68)	(S)	CH	CH ₂ CH ₂ CH((CH ₃) ₂	4 -
(- 69)	(S)	CH	CH ₂ C(O)NH ₂	4 -
(- 70)	(S)	CH	CH ₂ - 4 - (SO ₂ CH ₃)Ph	4 -
(- 71)	(S)	CH	CH ₂ CH ₂ -	4 -
(- 72)	(S)	CH	CH ₂ Ph	4 -

	(MS/ 1 H NMR)
(- 1)	
(- 2)	
(- 3)	
(- 4)	
(- 5)	LC?MS 471 (M + H)
(- 6)	
(- 7)	
(- 8)	
(- 9)	LC/MS 425 (M + H)
(- 10)	LC/MS 395 (M + H)
(- 11)	LC/MS 425 (M + H)
(- 12)	LC/MS 433 (M + H)
(- 13)	LC/MS 395 (M + H)
(- 14)	
(- 15)	
(- 16)	
(- 17)	
(- 18)	
(- 19)	
(- 20)	

	(MS/ 1 H NMR)
(- 21)	
(- 22)	
(- 23)	
(- 24)	
(- 25)	
(- 26)	
(- 27)	
(- 28)	
(- 29)	
(- 30)	
(- 31)	
(- 32)	
(- 33)	
(- 34)	
(- 35)	
(- 36)	

	(MS/ 1 H NMR)
(- 37)	
(- 38)	

(DeSouza et al., J. Neurosci. 7:88 - 100, 1987)

CRF

가

CRF

CRF

가

CRF

, 10^6

CRF

1.5m

(sauvagine),

10 mM (urotensin) CRF(, 1 μ M) 0.1 ml, [125 I] CRF(200pM
 K_D) 0.1ml CRF 22 2

80%

(Munson and Rodbard, Anal. Biochem. 107:220, 1990)

LIGAND

5

CRF -

가

가

CRF -

CRF -

(battaglia et al., Synapse 1:572, 1987)

MEM , 0.5ml : 2mM L - , 20mM HEPES, D
 1 mM IMBX. CRF 가 24 - CRF -
 37 1 cAMP 95% 20mM 300 μ l 가
 - 20 16 18 1.5ml 가
 / 200 μ l 500 μ l
 cAMP (Biomedical technologies Inc., Sto
 ughton, MA) CRF cAM
 P 80% (10 $^{-12}$ 10 $^{-6}$ M)

가

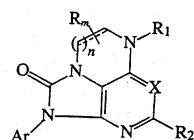
가

가

(57)

1.

가



n 1 2;

m 0, 1, 2 3;

X N CR';

R , C₁₋₆ , C₃₋₆ C₁₋₆ C₁₋₆ Ar ;

R' , C₁₋₆ ;

$$R_1 = C(H)_{0.1} (R_3)(R_4);$$

$$R_2 \quad C_{1-6} \quad ; \\ R_3 \quad , \quad , C_{1-6} \quad , \quad (C_{3-6} \quad) \quad , C_{3-6} \quad , C_{3-6} \quad , \quad C_{1-6}$$

R₄) , AR₁, C₁₋₆ Ar¹, OAr¹, C₁₋₈ , C₁₋₆ , C₃₋₆ , - (C₃₋₆
) , C₃₋₆ , C₃₋₆ , C₁₋₆ C₁₋₆ , C₁₋₆ Ar¹, C₁₋₆ , C₁₋₆ (A
 6 , C₁₋₆ , C₁₋₆ C₁₋₆ , (C₁₋₆ Ar¹) , (C₁₋₆)(Ar¹) , C₁₋₆ C₁₋₆ ,
 r¹) , (C₁₋₆) , (C₁₋₆ Ar¹) , (C₁₋₆)(Ar¹) , C₁₋₆ C₁₋₆ ,
 C₁₋₆ C₁₋₆ , (C₁₋₈), C(=O)C₁₋₆ , C₁₋₈ , Ar¹, O
 Ar¹, NHAr¹, C(=O)Ar¹, C(=O)NHAr¹ - C(=O)NH₂, -(C₁₋₆) - Y - (CO)_{0.1} - Ar¹
 (, Y - O, NH,),

R_3 , R_4 , Ar^1 , C_{5-8} ; C_{5-8} , C_{1-6} ; C_{3-12} , , ,

Ar , , C₃₋₁₂ , , , , 1-6 , , O(), , C₁₋₆ , , , , - (C₁₋₆)) , (C₁₋₆) (C₁₋₆) , , 1, 2 3 가 , / , C₁₋₆ , C₁₋₆ ;

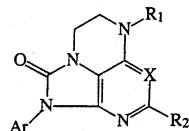
Ar^1 , , C_{3-12} , , (C_{1-6}) , C_{1-6} , , (C_{1-6}) , , (C_{1-6})

2.

1 , n - 1 .

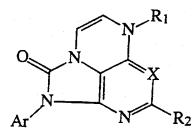
3.

2 , .



4.

2

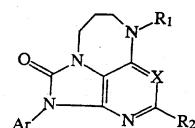


5.

1 , n 2

6.

5

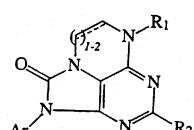


7.

1 , m 0

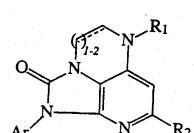
8.

7



9.

7

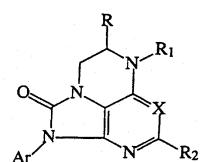


10.

1 , m 1

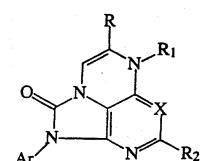
11.

10 ,



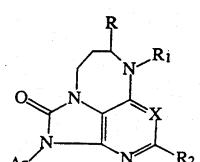
12.

10 ,



13.

10 ,



14.

1 , X \neq CR' R'

15.

1 , X N

16.

1 , R C₁₋₆

17.

1 , R

18.

1 , R .

19.

1 , Ar 2,4,6 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 - , 2 - - 4 -
 , 2 - - 4 - , 2 - - 4 - , 2,4 - , 2 - - 4 - , 2,6 - - 4 - , 4 - , 2,4 -
 , 2,4 - , 2 - , 3 - , 2 - - 4 - , 3,4 - , 3,5 -
 , 4 - , 4 - , 2,4,6 - , 2 - - 4 - N()₂ , 2 -
 - 4 - (OCF₃) , 4 - - 2 - - 3 - , 4 - - 6 - - 2 - , 4 -
 - 3 - , 4 - N(CH₃)(COCH₃) - , 3,4 - 3,4 - .

20.

1 , Ar 2,4,6 - , 2 - - 4 - , 2 - - 4 - , 2,4 - , 2,
 6 - - 4 - , 2 - - 4 - , 4 - 4 - .

21.

1 , R₁ , n - , - , n - , - , n - , - , n - , - ,
 - , - CH()₂, - CH(n -)₂, - CH(n -)₂, - CH₂CH₂OCH₃, - CH()(CH₂OCH₃), - CH()
 (CH₂OCH₃), - CH(n -)(CH₂OCH₃), - CH(n -)(CH₂OCH₃), - CH(-)(CH₂OCH₃), - CH(C
 H₂OCH₃)₂, - CH()(CH₂OCH₃), - CH(4 -)(CH₂OCH₃), - CH(CH₂OCH₃)(CH₂CH₂SCH₃), - CH
 ()(CH₂O), - C CH, - CH()(), - CH()(n -),
 - CH()(CH₂CH₂CH₂CH(CH₃)₂), - CH()(n -),
 - CH(n -)(n -), - CH(n -)(n -), , , , , 2 - ,
 3 - , 1,2,3,4 - (1 - 2), , 2 - , - CH()(), - CH()(), - CH(n -)(), - CH₂()
 (H₂CH₃), - CH₂CH()CH₂CH₃, - CH₂C()₃, - CH₂CC CH, - CH₂C(=O) , " - C(=O)
 - C(=O)NH , " - C(=O) , " - C(=O) , " - C(=O) , " - C(=O) , " - C(=O)CH₂C(=O)O , "
 - C(=O)CH() , " C(=O) , " - C(=O)(4 - N,N' -) , " - C(=O)CH₂O , - C(=O)
 OCH()₂, - C(=O)n - , " - C(=O)CH₂CH₂()₂, - C(=O)n - , " - C(=O)CH₂CH₂ , - CH
 2 , - CH₂CH₂NH , - CH₂CH₂C(=O)O , " - CH₂CH₂CH₂ , - CH₂CH₂- N - , - CH₂CH
 2 CH₂C(=O)O , " - CH₂CH₂O , - CH₂CH()₂, - CH₂C(=O)O , " - CH₂C(=O) , " - C
 H₂CH₂O , - CH₂CH₂CH₂CH₂- N - , - CH₂C(=O)Ot - , " - CH₂CH₂CH()₂, - CH₂C(=O)
 NH₂, - CH₂- 4 - (SO₂CH₃) , - CH₂CH₂ .

22.

1 , R₁ - CH()₂, - CH(n -)₂, - CH()(n -) - CH()(n -) .

23.

1 가

24.

23

CRF

25.

24

가

26.

24

가