

(19) (KR)
(12) (A)

(51) Int. Cl.⁷
C07D 471/16

(11)
(43)

10-2004-0015205
2004 02 18

(21) 10-2003-7014159

(22) 2003 10 29

2003 10 29

(86) PCT/GB2002/001981

(87)

WO 2002/087573

(86) 2002 04 30

(87)

2002 11 07

(30) 0110579.0 2001 04 30 (GB)

0110566.7 2001 04 30 (GB)

0117423.4 2001 07 17 (GB)

0203203.5 2002 02 11 (GB)

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(72) , -37100 2

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(74)

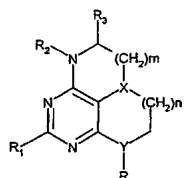
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(54) C R F

I ; ; ; (prodrug) -

(CRF)

< |>



, R , C1-C6 , C1-C6 , C1-C6
 , C2-C6 , C2-C6 , C1-C6 , C1-C6 ; R₁ , C1-C6
 , C2-C6 , C2-C6 , C1-C6 , C1-C6 , NH₂ , C2-C6 , C2-C6 ; R₂
 C(H)_n(R₅)_q(CH₂)_pZR₆ ; R₃ , C2-C6 , C2-C6 [CH(R₅)(CH
 2) p] m ZR₆ ; R₄ C3-C7 ; ; 5-6
 ; R₄ , C1-C6 , C1-C6 , C1-C6 , C2-C6 , C2-C6
 , C1-C6 , C1-C6
 ; R₅ , C2-C6 , C2-C6 , (CH₂)_pZR₆ ; R₆ ,
 C1-C6 , C2-C6 , C2-C6 , C1-C6 , C1-C6 , C1-C6
 , R₄ ; Y X
 ; m n 0 1 ; p 0 1 4 ; q 1 2 ; Z
 , O, NH S .

, CRF, CRF

(CRF) , 41- (V
 ale , Science 213: 1394-1397, 1981).

CRF . CRF ('ACTH')
 , (Bendorphin), (propiomelanocortin, 'POMC')-
 - (Vale , Science 213: 1394-1397, 19
 81).

ACTH POMC , CRF

CRF 가 , ,

CRF 가 CRF

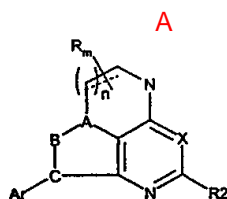
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CRF (, River , 4,605,642 ; Rivier , Science 224:
 889, 1984). CRF 가 CRF
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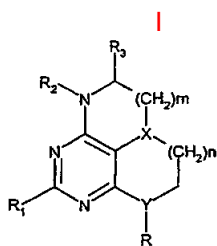
CRF 가

WO 00/27846

A CRF 가



, A, B C
 , A, B C 가 , A-B B-C
 .
 CRF , CRF CRF CRF
 .
 CRF CRF 가 CRF CRF
 F 가 , CRF 가 CRF
 , .
 , - (CRF)
 | , (prodrug)



R , C2-C6 , C1-C6 R , C1-C6 , C1-C6 , C1-C6 , C2-C6
 , C2-C6 , C1-C6 1 4 ;
 R₁ , C1-C6 , C2-C6 , C2-C6 , C1-C6 , C1-C6 , NH₂ ,
 ;
 R₂ C(H)_n(R₅)_q(CH₂)_pZR₆ ;
 R₃ , C2-C6 , C2-C6 [CH(R₅)(CH₂)_p]_mZR₆ ;
 R₄ C3-C7 ; ; 5-6 ;
 C1-C6 R₄ , C1-C6 , C1-C6 , C1-C6 , C2-C6 , C2-C6 ,
 , C1-C6 ;
 R₅ , C2-C6 , C2-C6 (CH₂)_pZR₆ ;

R₆ , C1-C6 , C2-C6 , C2-C6 , C1-C6 , C1-C6 , C1-C6
 ; R₄ C1-C6
 Y X ;
 m n 0 1 ;
 p 0 1 4 ;
 q 1 2 ;
 Z , O, NH S .

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C1-C6

1

6

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C3-C7

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C1-C6
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, 1 2

C2-C6

, 2 6

-2-

3-

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C1-C6
-2-

C1-C6

C1-C6

OCHF₂

OCF₃

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C1-C6

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C1-C6

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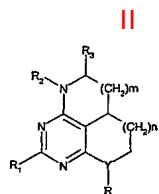
14

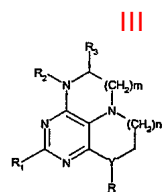
(

5-6

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II III

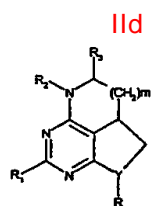
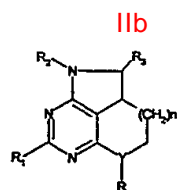
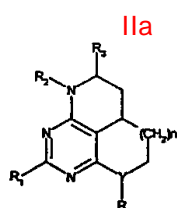




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X가

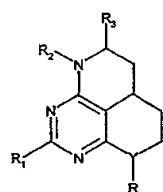
IIa, IIb, IIc, IId



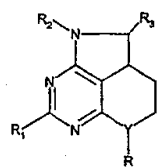
X

Ia-1, Ib-1, Ic-1

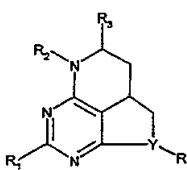
Ia-1



Ib-1



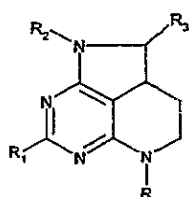
Ic-1



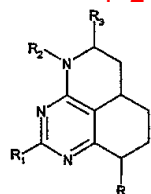
X Y ,

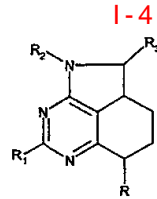
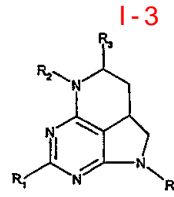
I-1, I-2, I-3 I-4 ,

I-1



I-2





Ib-1, Ic-1; I-1, I-2, I-3, I-4 R₂ R₃ 가 I, II, III, IIa, IIb, IIc, IID; Ia-1,

가 R₁ C1-C3 C1-C3 ,
I, II, III, IIa, IIb, IIc, IID; Ia-1, Ib-1, Ic-1; I-1, I-2, I-3, I-4

R₂ R₃ 가 ;

R₁ C1-C3 C1-C3 , I, II,
III, IIa, IIb, IIc, IID; Ia-1, Ib-1, Ic-1; I-1, I-2, I-3, I-4

R₂ R₃ 가 ;

R₁ C1-C3 C1-C3 , ;

R 2,4- , 2- -4- , 2- -4- , 2- -4- , 2,4,5-
 , 2,4- - , 2- -4- , 2- -4- , 2- -4- , 2,4-
 , 2- -4- , 2- -4- , 3- -4- , 2,5- , 2,4-
 -4- , 2- -4- , 2- -4- , 2- -4- , 2- -4- , 2
 - -4- , 2- -4- , 2,4- , 2- -4- -4- -4-
 - , 2- -4- , 2- -4- , 4- -6- -3- -4
 -6- - -3- , 6- - -3- 4- - -3- -3- , 4
 I, II, III, IIa, IIb, IIc, IID; Ia-1, Ib-1, Ic-1; I-1, I-2, I-3, I-4

5-(2,4-)-1-(1-)-7- -1,2,2a,3,4,5- -1,5,6,8- (I-

5-(2,4-)-1-(2-)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8-

(I-1-2);

5-(2,4-)-1-(2- -1-)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8-
 (1-1-3);

7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a,3,4,5-
 -1,5,6,8- (1-1-4);

7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a(S),3,4,5-
 -1,5,6,8- ;

7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a(R),3,4,5-
 -1,5,6,8- ;

5-(2,4-)-7- -1-(1-)-1,2,2a,3,4,5- -1,5,6,8- (1-
 1-5);

5-(2,4-)-7- -1-(1-)-1,2,2a-(S),3,4,5,5a,8b- -1,5,6,8-
 ;

5-(2,4-)-7- -1-(1-)-1,2,2a-(R),3,4,5,5a,8b- -1,5,6,8-
 ;

9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4 H -1,3,4- (
 1) 9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4 H -1,3,4- (
 (2) (2-1-1);

5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- (
 3-1-1);

1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-
 1-2);

1-(2,4-)-5-(1-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-
 1-3);

1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-1
 -4);

1-(2,4-)-7- -5-(1-)-1,2,2a,3,4,5- -1,5,6,8- (3-
 1-5);

7- -5-(1-)-1-[4-(1,1,2- -)-2-]-1,2,2a,3,4,5-
 -1,5,6,8- (3-1-6);

5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8-
 (3-1-7);

4- -5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8-
 (3-1-8);

5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8-
 (3-1-9);

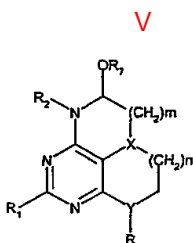
4,5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-1-10);

5-(2,4-)-1-(1-)-7- -1,2,2a,3,4,5- -1,6,8- (4-1-1
).

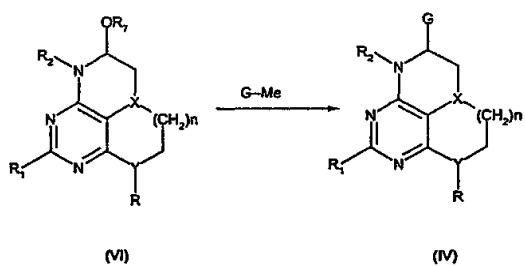
R, R₁, R₂, R₃, R₄, R₅, R₆, X, Y, Z, m, n, p, q

i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z

I, IV, V, VI, G가 R₃, R₇, C1-C4, m, 1

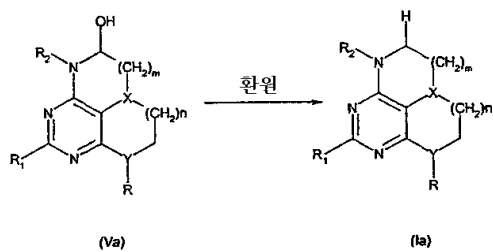


VI, GM, IV

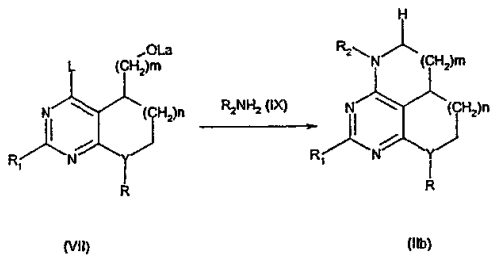


(, M, .)

R₃, V, I, (, la, Va, R₇,)



R₃, II, IIb, VII

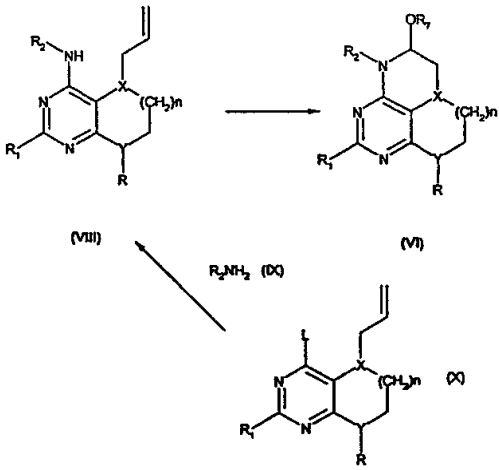


(, L , , La OLa가 (, ,)가)

$R_2NH_2 (IX)$, 가 .

VI

VIII



N- (NMO)

C1-C4

C1-C4

VIII

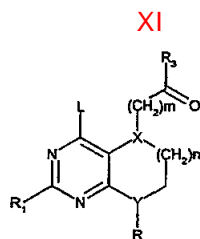
X

$R_2NH_2 (IX)$

IIa

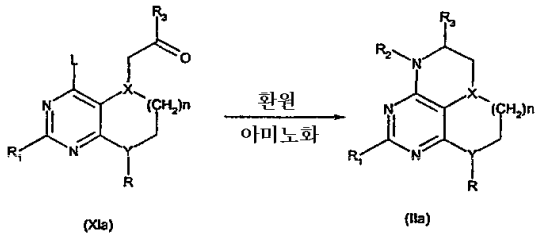
XI

(IX)

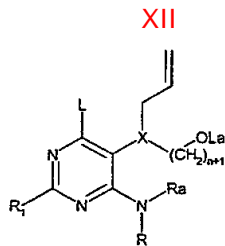
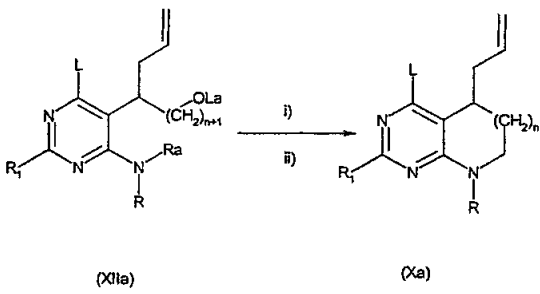


XIa

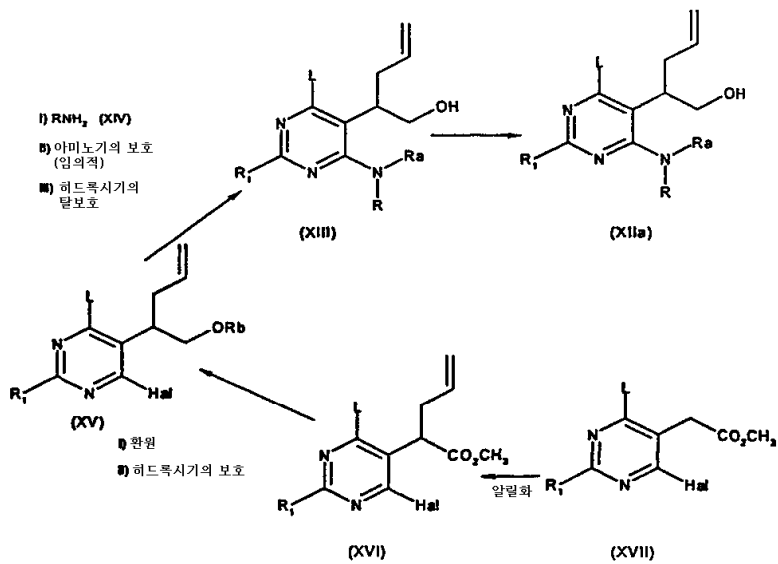
, m 1



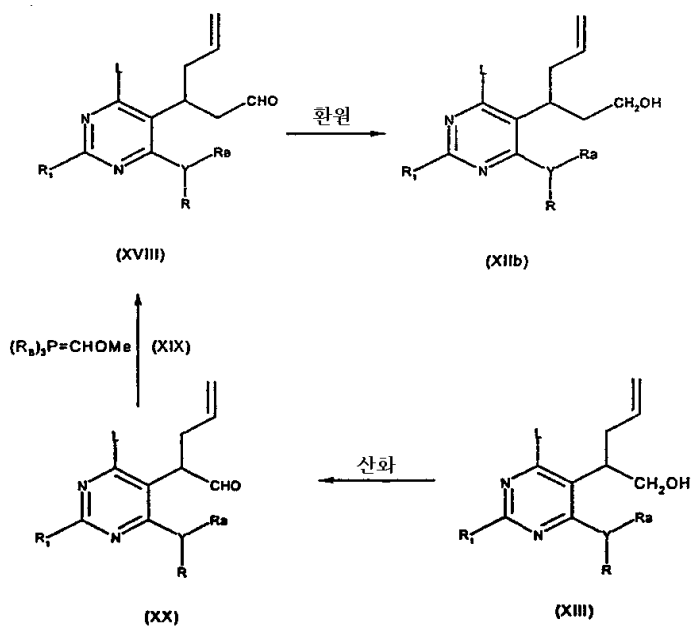
Y가 X가 X (Xa), Ra가 X가 La가 OLa가
 가 XII (XIIa), Ra가 X가 La가 OLa가
 Y가 X가 X (Xa), Ra가 X가 La가 OLa가
 가 XII (XIIa), Ra가 X가 La가 OLa가



XIIa
 i) Ra ;
 ii) ,
 N,N- (),
 X가 , n 0 XII La XIIa , Hal, Ra, n
 XIII



XIII) Rb가 XV (XIV) , ()
 DMF () , (,)
 XV XVI
 XVI XVII (,)
 (,)
 n 1 X가 XII XIIb , XVIII



XVIII (XX) 가 R_8 (XIX) (Wittig)

XX

XIII

(Swern)

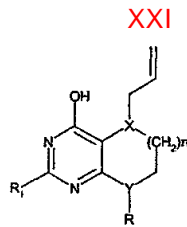
Y가

X가

X

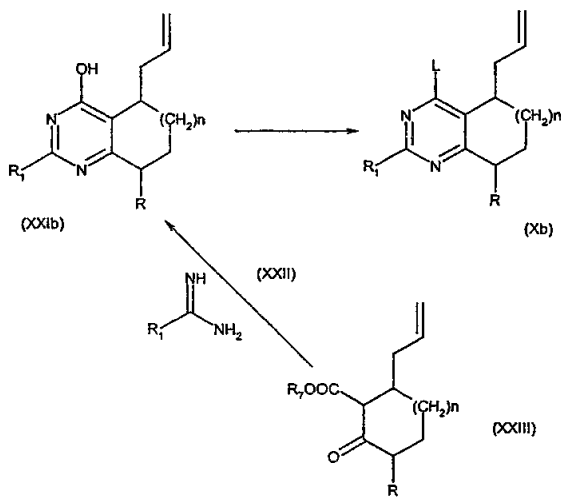
Xb

XXI



, X Y가

XXIb



Hal) 3 (, 가)

PO(

XXIb (, R 7)
XXII) (,)

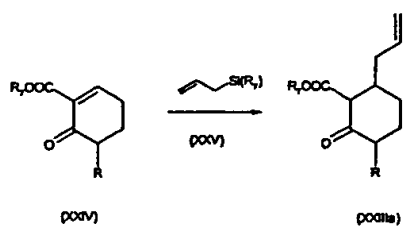
(

C1 - C4 (,) ,

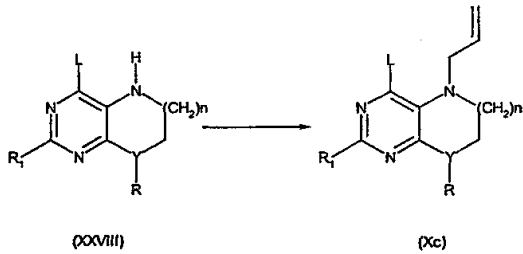
n 1 XXIb (, R 7)
XXV) (, R 7)

XXIV

(



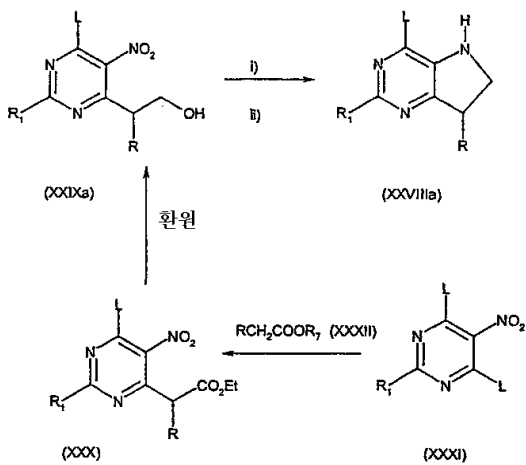
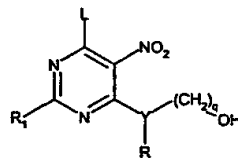
n 0, R₇, R₇' R₇ XXIII XXIIIb, XXVI (, R₇)
 M) (R₉)₂ M (XXVII) (, R₉)
 X가 X Xc, XXVIII (,
 , N,N-)



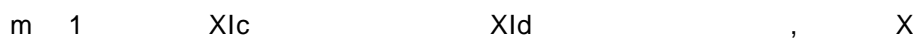
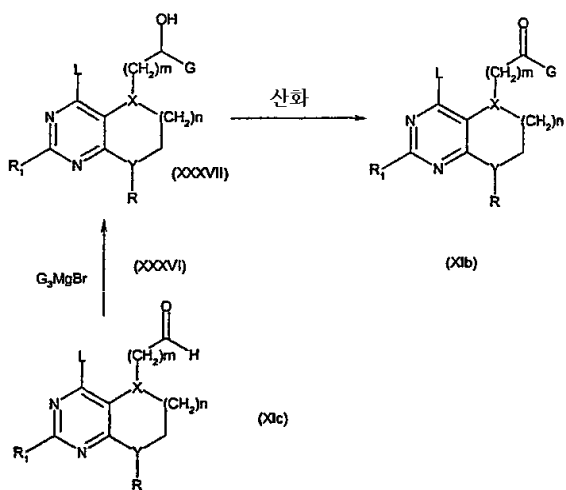
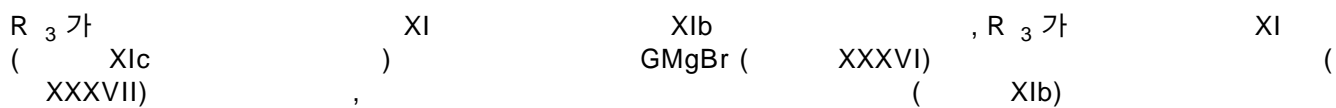
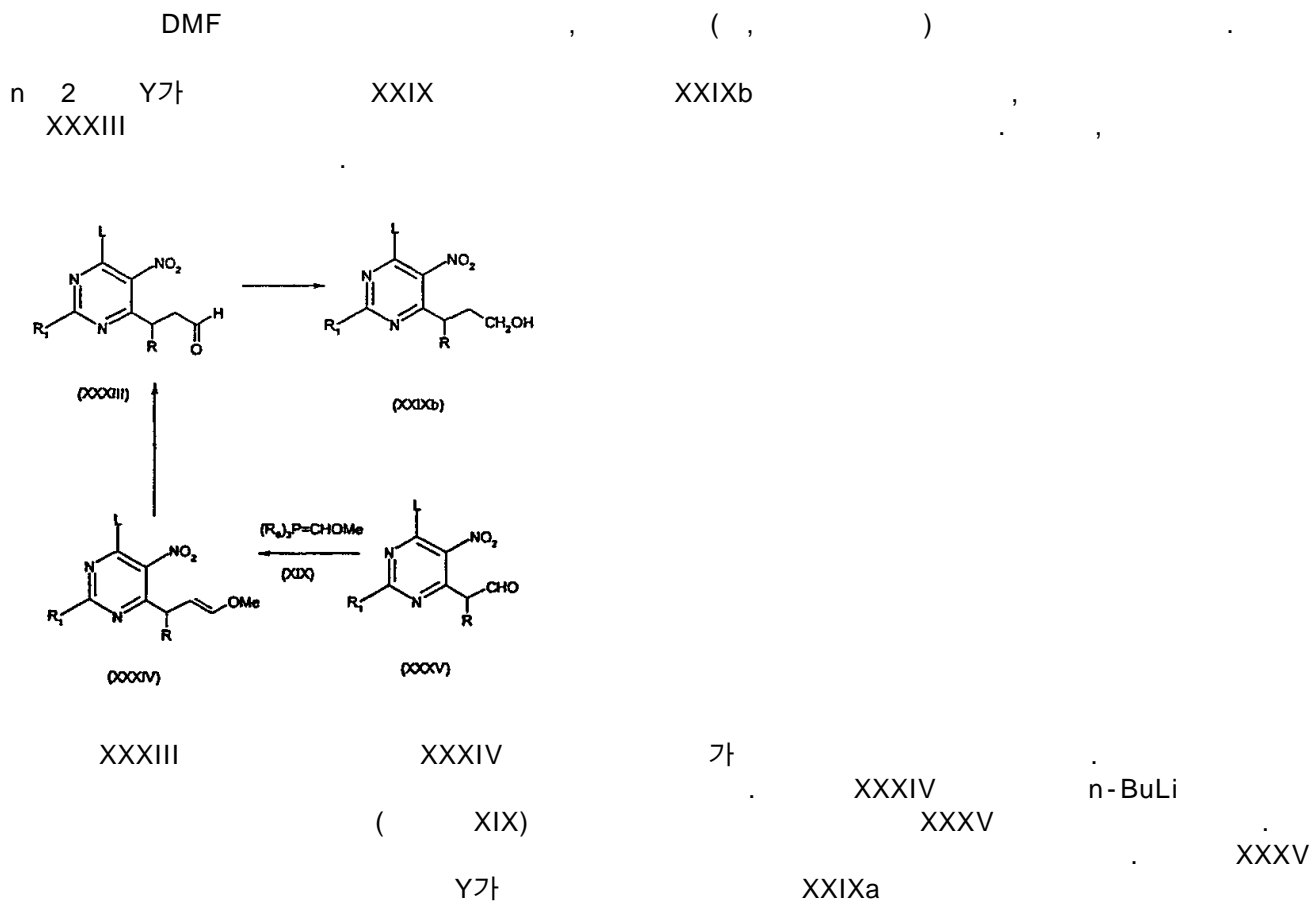
n 0 Y가 XXVIII XXVIIIa, q가 1 Y가, XXIX (, q
) XXIXa

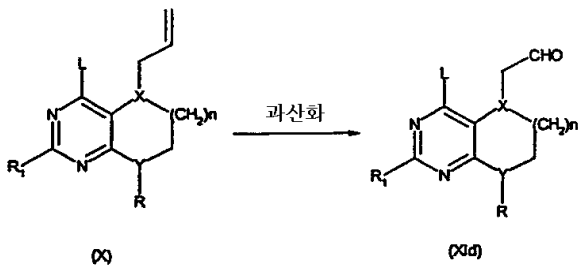
- i)
- ii) Na₂S₂O₄,

XXIX



0 가, XXX XXX, XXXI, XXXII 40-10

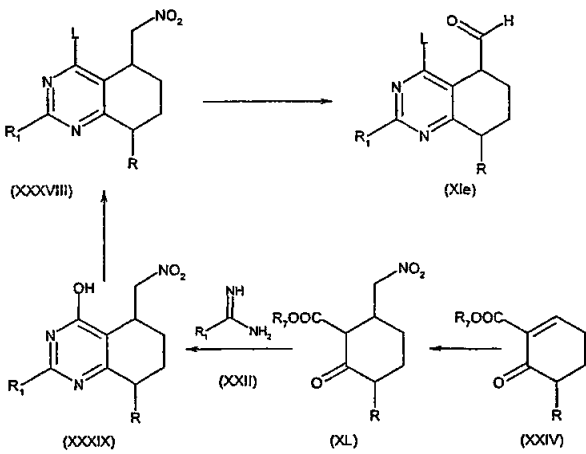




-78

N- (NMO)

X Y가 , m 0 , n 1 Xlc Xle , XXXVIII



XXXVIII

XXXIX

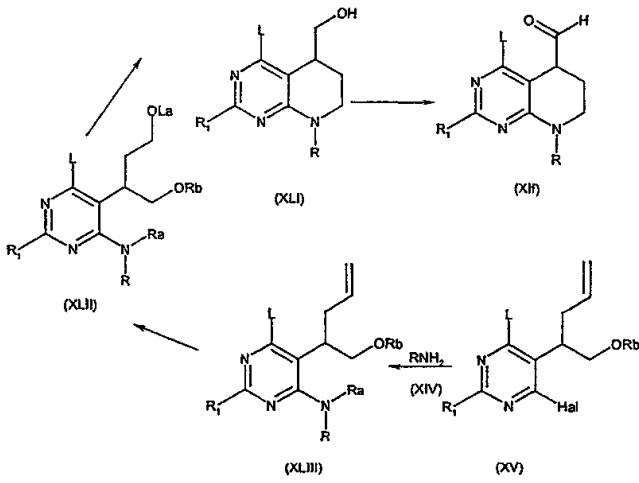
XXIX

XL

XL

XXIV (, R 7)

X가 , m 0 , n 1 , Y가 Xlc Xlf , X



XLI
)

XLII (, La

, Ra Rb

- i) , ,
- ii)
- iii) Rb

XLII

XLIII

-78

XLIII

XV

(XIV)

XLI

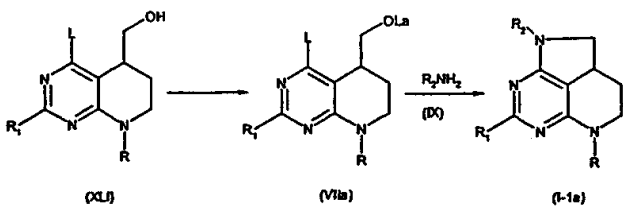
VIIa

, X가

, Y가

, m n 1

VII



VIIa

R₃

I-1

I-1a

X Y가

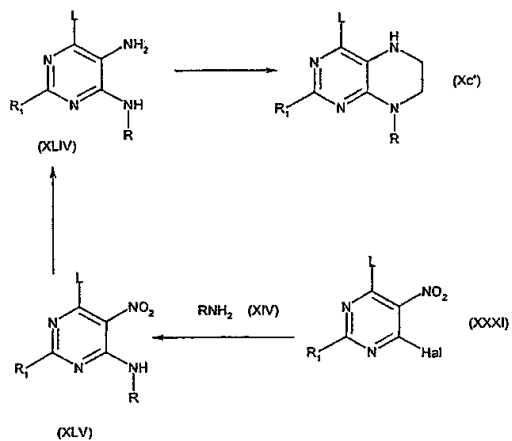
, n 1

Xc

Xc'

XLIV

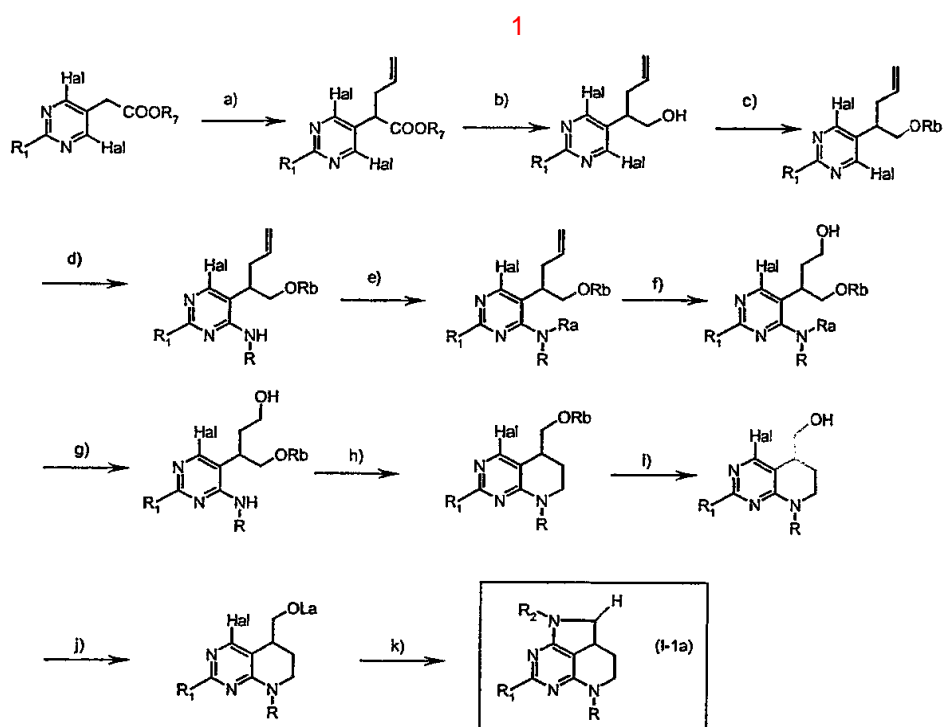
N,N-



XLIV XLV XLV XXXI (XIV)
 XVII, XXIV, XXVI XXXI

I-1a

1



Hal, R, R₁, R₇, R₂, La, Ra Rb
 Ra t- , Rb t-BuPh₂ Si , OLa , R₇ , Ha

a 0 , (, LiHMDS)
 [Wayne G. C. , J. Prakt. Chem., (2000), 342(5), 504-7]

b (CH₂Cl₂, 0) , DIBA1-H

c DMF, DMAP (0), t-BuPh₂SiCl

d RNH₂ (XIV);

e DMAP (BOC)₂O,

f i) / OsO₄, ii) THF/ NaIO₄, iii)
(, EtOH) NaBH₄;

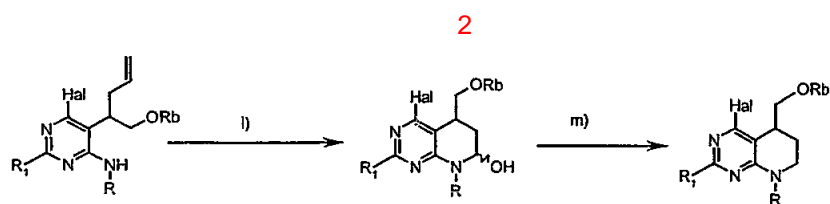
g (, CH₂Cl₂ CF₃CO₂H);

h (, Et₃N);

i (, 40 DMF Et₃N-3HF);

j ();

k (IX).
, 2 ()

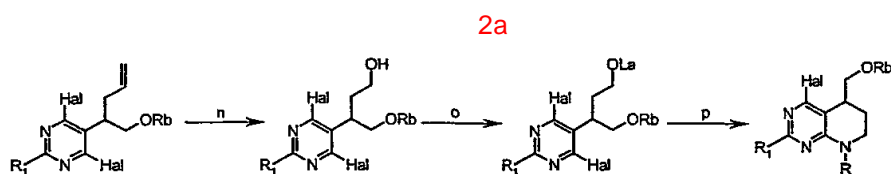


l f,

m BF₃-Et₂O Et₃SiH.

, 1.

, 2a ()



n f;

o j ;

p RNH₂ (XIV)

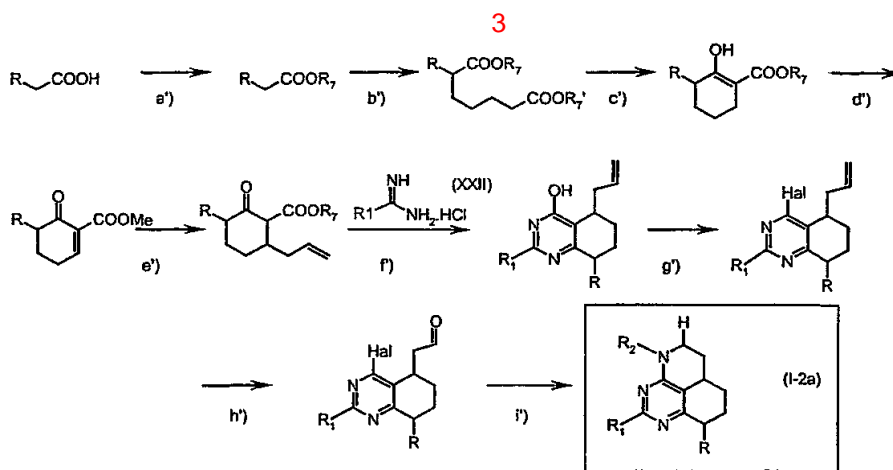
1

, R₃ 가

I-2

I-2a

3



, Hal, R, R₁, R₂, R₇, Rb, t-BuPh₂Si, OLa, R₇, Hal

a' (R₇ OH, ;)

b' (, LiHMDS 5-) ;

c' (, MeONa,) ;

d' H₂O₂ ;

e' TiCl₄ 1,4- 가 ;

f' (XXII) ;

g' (, POCl₃) ;

h' , ;

i' NaBH₃CN , (IX)

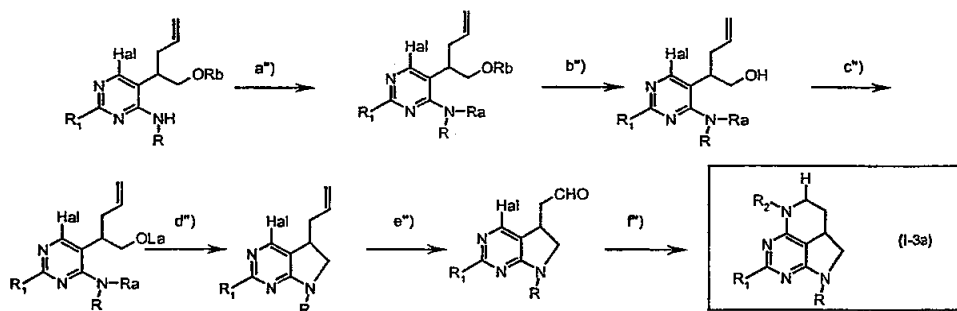
, R₃ 가

I-3

I-3a

4

4



a' DMAP (BOC)₂O

b' i ;

c' (, Et₃N) ;

d' TFA , Et₃N ;

e' h' , l ;

f' i' .

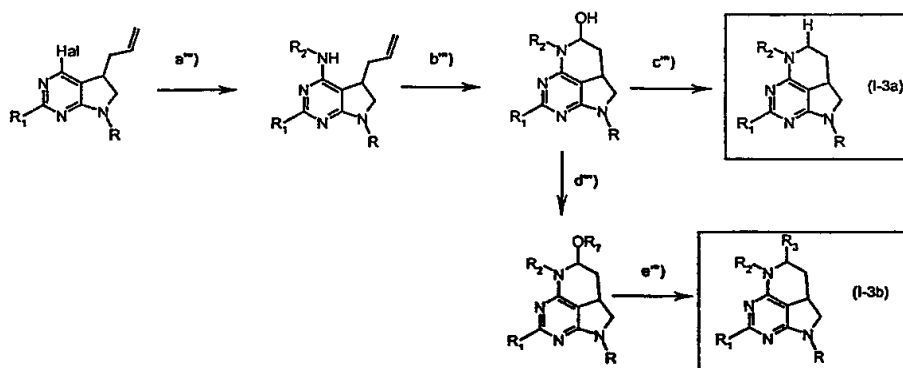
I-3

I-3b

5

, R₃가

5



a'' k ;

b'' l ;

c'' Et₃SiH, TFA ;

d'' PTSA ;

e'' BF₃·Et₂O

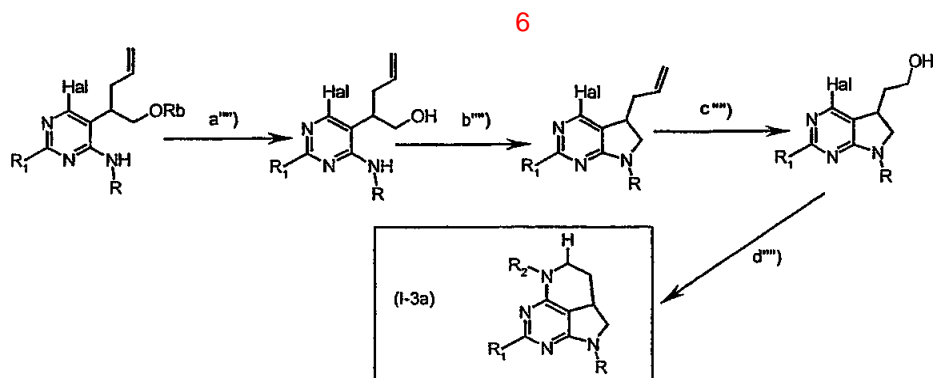
R₃Cu

-

I-3a

가

6



a'' i ;

b'' j , ;

c'' f ;

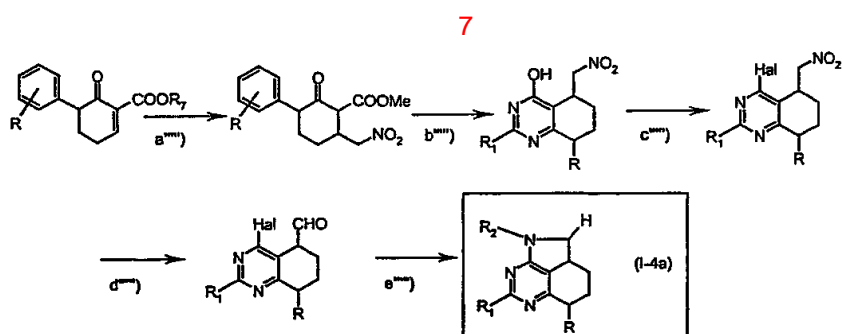
d'' j k .

I-4a

, R₃가

I-4

7



a''' ;

b''' (XXII) ;

c''' g' ;

d''' KOH , KMnO₄

;

e'''

i'

t-

([Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)])

, Ra가

가

t-

([Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)]) , Rb가 t-

HPLC

³H, ¹¹C, ¹⁴C, ¹⁸F, ¹²³I, ¹²⁵I

()

, ³H, ¹⁴C

가

-14

, ¹⁴C

SPECT (

, ¹¹C ⁸F

, ³H

PET (

, ¹²⁵I

, ²H

, 가

,

가

()

CRF

CRF 1

CRF 2

CRF

, CRF

CRF

CRF

[DeSouza (J. Neuroscience 7:88, 1987)

CRF

Battaglia (Synapse 1: 572, 1987)]

CRF

CRF

가

CRF

(SPA)

, SPA

CRF

2-(4,6- -2- -5-)-4-

THF (8 ml) 1 (1.33 g, 5.68 mmol) N₂ () ()
 1M , 11.5 ml, 2) 0 15 (0.99 ml, 2) 가 .
 4 (20 ml) (quenching) EtOAc (2 x 15 ml)
 , H₂O (2 x 15 ml) (1 x 15 ml) , Na₂SO₄
 (, EtOAc/cHex 1:9) (673.8
 mg)

NMR (¹H, CDCl₃): δ 5.77 (m, 1H), 5.03 (m, 2H), 4.43 (dd, 1H), 3.76 (s, 3H), 3.12 (m, 1H),
 2.78 (m, 1H), 2.73 (s, 3H).
 MS (m/z): 374[M] + 2Cl.

3

2-(4,6- -2- -5-)-4- -1-

CH₂Cl₂ (9.3 ml) 2 (257 mg) DIBA1-H (1M , 5.6 ml, 6) -78
 , N₂ 가 . 가가 , -78 1 0 2
 . HCl 0.5 N (20 ml) , CH₂Cl₂ (3 x 10 ml)
 Na₂SO₄ , (200 mg)

NMR (¹H, CDCl₃): δ 5.76 (m, 1H), 5.12 (m, 1H), 5.01 (m, 1H), 4.16 (m, 1H), 4.06 (m, 1H),
 3.91 (m, 1H), 2.8-2.6 (m, 2H), 2.70 (s, 3H), 1.50 (t, 1H).
 MS (m/z): 247 [M]⁺, 2Cl

4

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

DMF (12 ml) 3 (200 mg) tert- - (245 mg, 2)
 (553 mg, 10) 0 , N₂ 가 . 2 tert-
 - (61 mg, 0.5) 가 . 1 , NH₄Cl (15 ml) EtOAc (15 ml)
 가 , 가 EtOAc (2 x 15 ml) . H₂O (10 ml) , Na₂
 SO₄ (, cHex/EtOA
 c 19:1) (237 mg)

NMR (¹H, CDCl₃): δ 5.72 (m, 1H), 5.10 (d, 1H), 4.98 (d, 1H), 4.11 (m, 1H), 3.94 (m, 2H),
 2.69 (s, 3H), 2.6-2.7 (m, 2H), 0.82 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).
 MS (m/z): 361 [M]⁺, 2Cl

5

{5-[1-(tert- - -)]-3-]-6- -2- -4- }-(2,4-)

THF (12 ml) 2,4- - (192 mg) N₂ , 0 15 ()
 80%, 393 mg) , THF (4 ml) 4 (434 mg, 1.19 mmol) 가 .
 3 가 , (20 ml) . EtOAc (2 x 20 ml) , Na
 2 SO₄ , (, EtOAc/cHex 9:1)
 (419 mg)

NMR (^1H , CDCl_3 , $T=55^\circ\text{C}$): δ 8.35 (bs, 1H), 8.13 (bd, 2H), 7.42 (d, 1H), 7.25 (dd, 1H), 5.73 (m, 1H), 5.03 (m, 2H), 4.10 (dd, 1H), 3.99 (dd, 1H), 3.65 (bm, 1H), 2.75 (m, 2H), 2.47 (s, 3H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

MS (m/z): 486 $[\text{MH}]^+$, 3Cl.

6

{5-[1-(tert-)- -3-]-6- -2- -4- }-(2,4-)- tert-

CH_2Cl_2 (17 ml) 5 (419 mg) , (Boc) $_2$ O (376 mg, 2) DMAP () N_2 가 . 18 (10 ml) , EtOAc (3 x 15 ml) . Na_2SO_4 , (, cHex/EtOAc 9:1) (420 mg) .

NMR (^1H , CDCl_3 , 40°C): δ 7.47 (d, 1H), 7.30 (d, 1H), 7.14 (dd, 1H), 5.66 (m, 1H), 5.03-4.89 (m, 2H), 3.98-3.8 (m, 2H), 3.43 (b, 1H), 2.8-2.6 (m, 2H), 2.56 (bs, 3H), 1.41 (s, 9H), 0.77 (s, 9H), -0.02 (s, 3H), -0.10 (s, 3H).

IR (nujol, cm^{-1}): 1716.

MS (m/z): 588 $[\text{MH}]^+$, 3Cl

7

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

DMF (1 ml) 6 (50 mg) TEA · 3HF (21 μl , 1.5) N_2 가 . 18 (10 ml) , EtOAc (3 x 15 ml) . Na_2SO_4 , (, cHex/EtOAc 8:2) (30 mg) .

NMR (^1H , DMSO, $T=70^\circ\text{C}$): δ 7.69 (d, 1H), 7.43-7.33 (m, 2H), 5.64 (m, 1H), 5.00-4.88 (m, 2H), 4.54 (1H, m), 3.71 (m, 2H), 3.29 (m, 1H), 2.66 (m, 2H), 2.5 (s, 3H), 1.31 (s, 9H).

MS (m/z): 472 $[\text{MH}]^+$, 3Cl

8

2-{4-[tert- -(2,4-)-]-6- -2- -5- }- -4-

CH_2Cl_2 (5.52 ml) 7 (130 mg) Et_3N (192 μl , 5) $\text{CH}_3\text{SO}_2\text{Cl}$ (43 μl , 2) 가 . 18 (20 ml) . , EtOAc (3 x 25 ml) . Na_2SO_4 , (, cHex/EtOAc 8:2) (148 mg) .

NMR (^1H , DMSO, $T=70^\circ\text{C}$): δ 7.72 (d, 1H), 7.36 (dd, 1H), 7.28 (d, 1H), 5.56 (m, 1H), 5.00 (d, 1H), 4.92 (d, 1H), 4.46 (m, 2H), 3.51 (m, 1H), 3.02 (s, 3H), 2.65 (m, 1H), 2.54 (s, 3H), 2.50 (m, 1H), 1.38 (s, 9H).

IR (cm^{-1}): 1725, 1641, 1362

MS (m/z): 550 $[\text{MH}]^+$, 3Cl

9

5- -4- -7-(2,4-)-2- -6,7- -5H- [2,3-d]

TFA 20%/CH₂Cl₂ (7 ml) 8 (120 mg) 2 TFA
 , CH₂Cl₂ 가 , , H₂O
 THF (5 ml) , Et₃N (284 μl, 5) 가 1 ,
 가 , EtOAc (3 x 10 ml) Na₂SO₄ ,
 (124 mg) .

NMR (¹H, CDCl₃): δ 7.49 (dd, 1H), 7.30 (d+s, 2H), 5.77 (m, 1H), 5.16-5.12 (m, 2H), 4.00 (t, 1H), 3.77 (m, 1H), 3.57 (m, 1H), 2.7 (m, 1H), 2.47 (m, 1H), 2.45 (s, 3H).

MS (m/z): 354 [MH]⁺, 3Cl

10

[4- -7-(2,4-)-2- -6.7- -5H- [2,3d] -5-]-

CH₂Cl₂ (4 ml) 9 (30 mg) -78 5 (5 g.h⁻¹).
 (cHex/EtOAc 75/25 TLC), 20
 (CH₃)₂S (25 μl, 4) 가 ,
 18 (, cH
 ex/EtOAc 3:1) (8 mg) .

NMR (¹H, CDCl₃): δ 9.87 (s, 1H), 7.48 (t, 1H), 7.30 (m, 2H), 4.23 (t, 1H), 3.90 (m, 1H), 3.60 (dd, 1H), 3.29 (dd, 1H), 2.90 (dd, 1H), 2.42 (s, 3H).

MS (m/z): 356 [MH]⁺, 3Cl.

11

5-[1-(tert- - -)- -3-]-4.6- -2- -

DMF (4 ml) 3 (152 mg) DMAP (3.8 mg), (420 mg) Ph₂tBuSiCl (0.32 ml)
 0 N₂ 가 2 5 ml
 NH₄Cl 가 , Et₂O (2 x 15 ml) ,
 , Na₂SO₄ ,
 (, cHex/EtOAc 95:5) (270 mg).

NMR (¹H, CDCl₃): δ 7.65 (dd, 2H), 7.56 (dd, 2H), 7.49-7.36 (m, 6H), 5.67 (m, 1H), 5.03 (dd, 1H), 4.94 (dd, 1H), 4.17 (m, 1H), 4.00 (m, 2H), 2.70 (s, 3H), 2.69 (m, 1H), 2.55 (m, 1H), 0.98 (s, 9H).

MS (m/z): 485 [MH]⁺, 2Cl.

12

{5-[1-(tert- - -)- -3-]-6- -2- - -4- }-(2,4-)-

THF (1 ml) 2,4- (80 mg) NaH (80%, 31 mg) 0 N₂ 11
 가 , 30 가 . 0 THF (2 ml) 11
 (227 mg, 0.467 mmol) 가 5 ,
 (20 ml) , Et₂O (4 x 20 ml) ,
 Na₂SO₄ ,
 (, cHex/EtOAc 95:5) (131.6 mg).

NMR (¹H, CDCl₃): δ 8.2-7.7 (broad d, 1H), 7.55 (d, 2H), 7.50 (d, 2H), 7.40-7.20 (m, 9H), 5.70 (m, 1H), 5.07 (dd, 1H), 4.94 (dd, 1H), 4.06 (m, 2H), 3.70 (m, 1H), 2.71 (m, 2H), 2.50 (m, 3H), 0.95 (s, 9H).

MS (m/z): 610 [MH]⁺, 3 Cl.

13

{5-[1-(tert- - -)- -3-]-6- -2- - -4- }-(2,4-
)- - tert-

CH₂Cl₂ (2 ml) 12 (128 mg) Boc₂O (61 mg) DMAP (3 mg) N₂
가 . 16 . . Boc₂O (58 m
g + 46 mg) DMAP 가 2 . , CH₂Cl₂ (2
x 5 ml) . Na₂SO₄ .
(, cHex/EtOAc 9:1)
(138 mg).

NMR (¹H, DMSO, 70 °C): δ 7.67 (d, 1H), 7.54-7.30 (m, 5H+5H), 7.19 (m, 2H), 5.51 (m, 1H),
4.87 (d, 1H), 4.82 (d, 1H), 3.94 (m, 1H), 3.84 (bm, 1H), 3.53 (m, 1H), 2.57 (s, 3H), 2.62 (m,
1H), 2.35 (m, 1H), 1.35 (s, 9H), 0.90 (s, 9H).

IR (nujol, cm⁻¹): 1732.

MS (m/z): 710 [MH]⁺, 3 Cl, 722 [M+Na]⁺, 610 [MH-Boc+H]⁺.

14

{5-[1-(tert- - -)-3- -]-6- -2- - -4- }-(2,4-
)- - tert-

3 ml CH₂Cl₂ /CH₃OH (9:1) 13 (108 mg) -78 . O₃
가 . 30 (bubbling) . , NaBH₄ (23.1 mg) N₂
x 5 ml) . NH₄Cl . , Na₂SO₄ , CH₂Cl₂ (2
1) . (, cHex/EtOAc 9:
(59 mg).

NMR (¹H, DMSO, 70 °C): δ 7.65 (d, 1H), 7.48-7.34 (m, 5H+5H), 7.28 (d, 1H), 7.12 (bd, 1H),
5.51 (m, 1H), 4.18 (t, 1H), 4.02 (bt, 1H), 3.82 (bm, 1H), 3.51 (m, 1H), 3.29 (bm, 2H), 2.55 (s,
3H), 2.05 (m, 1H), 1.84 (bm, 1H), 1.35 (s, 9H), 0.89 (s, 9H).

IR (film, cm⁻¹): 1733.

MS (m/z): 714 [MH]⁺, 3 Cl, 736 [M+Na]⁺, 3 Cl, 678 [MH-HCl]⁺, 2 Cl, 614 [MH-Boc+H]⁺.

15

3-{4-tert- - - (2,4- -)- -]-6- -2- - -5- }-4-(tert
- - -)-

CH₂Cl₂ (1 ml) 14 (57 mg) Et₃N (55 μl) MsCl (13 μl) N₂
가 . 5 . , CH₂Cl₂ (2 x 5 ml) .
, Na₂SO₄ .
(60 mg).

NMR (¹H, DMSO, 70 °C): δ 7.65 (d, 1H), 7.50-7.34 (m, 5H+5H), 7.24 (bd, 1H), 7.15 (bd,
1H), 4.20-4.00 (m, 3H), 3.80-3.60 (m, 2H), 3.02 (s, 3H), 2.56 (s, 3H), 2.30-2.10 (m, 2H), 1.35
(s, 9H), 0.89 (s, 9H).

IR (nujol, cm⁻¹): 1725.

MS (m/z): 794 [MH]⁺, 3 Cl, 694 [MH-Boc+H]⁺.

16

4-(tert- - -)-3-[4- -6-(2,4- -)-2- - -5-
]-

CH₂Cl₂ (1 ml) _____ 15 (58 mg) TFA (200 μl, 35) N₂ 가
 16 , , CH₂Cl₂ ,
 _____ (64 mg)

MS (m/z): 694 [MH]⁺, 3 Cl.

17

5-(tert- - -)-4- -8-(2,4-)-2- -5,6,7,8- - [2,3-d]

THF (1 ml) _____ 16 (64 mg) Et₃N (100 μl) 0 N₂ 가
 16 , , Et₂O (2 x 20 ml) ,
 , Na₂SO₄ (, cHex/EtOAc 95:5) ,
 (26.4 mg).

NMR (¹H, CDCl₃): δ 7.74-6.98 (m, 5H+5H+1H+2H), 4.10-3.90, 3.76-3.55, 3.48-3.28 (m, 5H), 2.58-2.38 (m, 1H), 2.24, 2.22 (s, 3H), 2.1-1.9 (m, 1H), 1.07 (s, 9H).

MS (m/z): 598 [MH]⁺, 3 Cl.

18

[4- -8-(2,4-)-2- -5,6,7,8- - [2,3-d]- -5-]-

DMF (2 ml) _____ 17 (22 mg) Et₃N3HF (20 μl) N₂ 가
 60 4 , , Et₂O (3 x 20 ml) ,
 , Na₂SO₄ (, cHex/EtOAc 2:1) ,
 (13 mg).

NMR (¹H, DMSO, 90 °C): δ 7.66 (bs, 1H), 7.50-7.42 (m, 2H), 4.66 (m, 1H), 3.82 (bt, 1H), 3.68 (m, 1H), 3.66-3.36 (m, 2H), 3.20 (m, 1H), 2.33 (m, 1H), 2.14 (s, 3H), 1.94 (m, 1H).

MS (m/z): 358 [MH]⁺, 3 Cl, 360.

19

4- -8-(2,4-)-2- -5,6,7,8- - [2,3-d] -5-

CH₂Cl₂ (1 ml) _____ 18 (13 mg) Et₃N (20.0 μl) MsCl (6.0 μl) 0 N₂
 가 , 16 , , CH₂Cl₂ (3 x 10 ml)
 , Na₂SO₄ ,
 _____ (14.7 mg).

NMR (¹H, CDCl₃): δ 7.50 (dd, 1H), 7.40-7.15 (m, 2H), 4.50-4.15 (m, 2H), 3.90-3.70 (m, 1H), 3.65-3.30 (m, 2H), 3.05 (s, 3H), 2.45-2.2 (m, 1H), 2.25 (s, 3H), 2.2-2.0 (m, 1H).

MS (m/z): 438 [MH]⁺, 3 Cl.

20

5- -

(63 ml) 4- (14 g) NaI (11.5 g) 가 , 2
 가 , 5% NaHSO₃ (3 x 100 ml) _____ (1 x 100 ml)
 , Na₂SO₄ ,

(15.85 g).

NMR (^1H , CDCl_3): δ 3.68 (s, 3H), 3.19 (t, 2H), 2.34 (t, 2H), 1.86 (m, 2H), 1.74 (m, 2H).MS (m/z): 242 $[\text{M}]^+$, 211 $[\text{M}-\text{OMe}]^+$, 115 $[\text{M}-\text{I}]^+$.21

2-(2,4-)-

THF (27 ml) 2,4- (2 g) THF (10.04 ml) LHMDS 1M
 -78 N₂ 가 , -78 30 , 20 (2.
 87 g, 1.3) -78 가 ,
 , (3 x 20 ml) (1 x 30 ml) , THF (2 ml) ,
 , Na₂SO₄ ,
 (, cHex/EtOAc 9:1)
 (2.7 mg).

NMR (^1H , CDCl_3): δ 7.39 (d, 1H), 7.30 (d, 1H), 7.22 (dd, 1H), 4.10 (t, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 2.29 (t, 2H), 2.05 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.40-1.20 (m, 2H).IR (film, cm^{-1}): 1738.MS (m/z): 332 $[\text{M}]^+$, 300 $[\text{M}-\text{CH}_2\text{OH}]^+$, 159.22

3-(2,4-)-2- -1-

(0.7 g) 0 , N₂ , MeOH (26 ml) 가
 , (100 ml) 가 , MeOH/ (36 ml) - 가
 . (Dean-Stark)
 3.5 , 21 (2.52 g) (15 ml) 가
 EtOAc (2 x 20 ml) , AcOH (2 x 20 ml), (2 x 20 ml) , N
 a₂SO₄ , (: 1.8 g.)
 , cHex/EtOAc 95:5)

NMR (^1H , CDCl_3): δ 12.19 (s, 1H), 7.40 (d, 1H), 7.19 (dd, 1H), 7.08 (d, 1H), 4.07 (t, 1H), 3.81 (s, 3H), 2.35 (m, 2H), 2.01 (m, 1H), 1.73 (m, 1H), 1.60 (m, 2H).MS (m/z): 300 $[\text{M}]^+$, 265, 233.23

5-(2,4-)-6- -1-

(2.44 g) , CH₂Cl₂ (21 ml) .
 0 (0.9 ml) 가 , 0 30 .
 CH₂Cl₂ (12 ml) 22 (1.5 g) 0 가 , 4.5
 , CH₂Cl₂ 0 , 1M HCl (2 x 10 ml) (3 x 10 ml) .
 0 10 , H₂O₂ (3 ml) H₂O₂ (30% w/w, 3 ml) 가 ,
 , 가 NaHCO₃ (2 x 10 ml) (1 x
 10 ml) , Na₂SO₄ , (1.
 45 g) , 가 .

NMR (^1H , CDCl_3): δ 7.77 (m, 1H), 7.43 (d, 1H), 7.24 (dd, 1H), 7.11 (d, 1H), 4.12 (dd, 1H), 3.83 (s, 3H), 2.70 (m, 2H), 2.40-2.20 (m, 2H).IR (film, cm^{-1}): 1737, 1673.MS (m/z): 298 $[\text{M}]^+$, 263 $[\text{M}-\text{Cl}]^+$, 126.

24

5- -8-(2,4-)-2- -5,6,7,8- -4-

CH₂Cl₂ (6.5 ml) 23 (690 mg) TiCl₄ (0.255 ml) -78 가 . 가
 -78 5 , CH₂Cl₂ (6.5 ml) (0.440 ml) 가
 가 . -78 1.5 , , CH₂Cl₂ , , Na₂SO₄
 CH₂Cl₂ , (1 x 10 ml) , (676 mg)
 (140 mg, 3) N₂ 가 MeOH (6 ml) 가 .
 (600 mg) 가 . 10 , NaCl MeOH (2 ml)
 (676 g) 가 , 18
 (, CH₂Cl₂/MeOH 98:2
 97:3) 가 3:1 (538 mg).

NMR (¹H, CDCl₃)(안티 이성질체): δ 11.82 (bs, 1H), 7.42 (d, 1H), 7.10 (dd, 1H), 6.58 (d, 1H), 5.87 (m, 1H), 5.06 (m, 2H), 4.34 (d, 1H), 3.01 (m, 1H), 2.68 (m, 1H), 2.37 (s, 3H), 2.20 (m, 1H), 2.07 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.49 (m, 1H).
 NMR (¹H, CDCl₃)(신 이성질체): δ 11.70 (bs, 1H), 7.36 (d, 1H), 7.12 (dd, 1H), 6.81 (d, 1H), 5.83 (m, 1H), 5.02 (m, 2H), 4.23 (bt, 1H), 2.98 (m, 1H), 2.66 (m, 1H), 2.28 (s, 3H), 2.20 (m, 1H), 2.02-1.80 (m, 2H), 1.62-1.47 (m, 2H).
 MS (m/z): 348 [M]⁺, 307 [M-알킬]⁺.

25

-5- -4- -8-(2,4-)-2- -5,6,7,8- (1) -5-
 -4- -8-(2,4-)-2- -5,6,7,8- (2)

24 (538 mg) POCl₃ (5 ml) , 2 . POCl₃ ,
 CH₂Cl₂ , NH₄OH 가 , CH₂Cl₂ (3 x 1
 0 ml) (2 x 10 ml) , Na₂SO₄ ,
 (, cHex/EtOAc 95:5)
 1 (262 mg) 2 (94 mg)

이성질체 1 :NMR (¹H, CDCl₃): δ 7.44 (d, 1H), 7.06 (dd, 1H), 6.20 (d, 1H), 5.86 (m, 1H), 5.14 (m, 2H), 4.63 (d, 1H), 3.16 (m, 1H), 2.60 (m, 1H), 2.59 (s, 3H), 2.30 (m, 1H), 2.16 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.64 (m, 1H).
 MS (m/z): 367 [M+H]⁺.
 이성질체 2 :NMR (¹H, CDCl₃): δ 7.36 (d, 1H), 7.15 (dd, 1H), 6.83 (bd, 1H), 5.82 (m, 1H), 5.10-5.06 (m, 2H), 4.35 (m, 1H), 3.12 (m, 1H), 2.62 (m, 1H), 2.48 (s, 3H), 2.25 (m, 1H), 2.22-2.00 (m, 2H), 1.90-1.78 (m, 2H).
 MS (m/z): 367 [M+H]⁺.

26

[5- -7-(2,4-)-2- -6,7- -5H- [2,3-d] -4-]-

(0.5 ml) 9 (160 mg, 0.451 mmol) 130 ((screw
 cap vial) 4 가 , (, CH
 2 Cl₂/EtOAc 9:1 7:3) (162 mg, 0.416 mmol, 92%)

NMR (^1H , CDCl_3): δ 7.43 (d, 1H), 7.36 (d, 1H), 7.24 (dd, 1H), 5.86 (m, 1H), 5.20-5.13 (m, 2H), 4.39 (bt, 1H), 3.88 (dd, 1H), 3.71 (dd, 1H), 3.40-3.30 (m, 3H), 2.46 (m, 1H), 2.35 (m, 1H), 2.36 (s, 3H), 1.08 (m, 1H), 0.60-0.27 (m, 4H).

MS (m/z): 389 $[\text{M}+\text{H}]^+$ (2 Cl).

27

5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- -

mg, 2) 가 , OsO₄ 4% 26 (160 mg, 0.411 mmol) N- -N- (100
5 (0.260 ml, 0.1) 가 , 3.
EtOAc (3 x 10 ml) , Na₂SO₄ Na₂SO₃ (50 ml) 가 .
THF 1:1 (8 ml) , NaIO₄ (132 mg, 1.5) 가 .
45 , EtOAc (3 x 10 ml) .
Na₂SO₄ (, cHex/EtOAc 1:1) .
(111 mg, 0.284 mmol, 69%).

NMR (^1H , $\text{DMSO}-d_6$): δ 7.68 (d, 1H), 7.44 (m, 2H), 5.92 (d, 1H), 5.17 (m, 1H), 4.13 (t, 1H), 3.79 (m, 1H), 3.76 (dd, 1H), 3.50 (m, 1H), 3.15 (dd, 1H), 2.24 (m, 1H), 2.21 (s, 3H), 1.43 (dt, 1H), 1.06 (m, 1H), 0.50-0.20 (m, 4H).

MS (m/z): 391 $[\text{M}+\text{H}]^+$ (2 Cl).

28

5- -1-(2,4-)-4- -7- -1,2,2a,3,4,5- -1,5,6,8- -

MeOH (1.5 ml) PTSA (1.5 mg, 0.042) 27 (73 mg, 0.187 mmol) 가 ,
18 , CH₂Cl₂ (10 ml)
NaHCO₃ (1 x 10 ml), (1:1, 10 ml) 가 , CH₂C
I₂ (2 x 10 ml) , NaCl (1 x 10 ml) , N
a₂SO₄ 가 .
(68 mg, 0.168 mmol, 90%).

NMR (^1H , 아세톤- d_6): δ 7.53 (d, 1H), 7.47 (d, 1H), 7.35 (dd, 1H), 4.93 (t, 1H), 4.23 (t, 1H), 4.05 (dd, 1H), 3.78 (dd, 1H), 3.51 (m, 1H), 3.39 (s, 3H), 3.13 (dd, 1H), 2.53 (dddd, 1H), 2.25 (s, 3H), 1.40 (dt, 1H), 1.09 (m, 1H), 0.50-0.20 (m, 4H).

MS (m/z): 405 $[\text{MH}]^+$ (2 Cl).

29

2 : 2-[4- -7-(2,4-)-2- -6,7- -5H- [2,3-d]

CH₂Cl₂/MeOH 2:1 10 (93 mg, 0.261 mmol) NaBH₄ (20 mg, 2) 0
, N₂ 가 . 1 (10 ml)
EtOAc (3 x 10 ml) , Na₂S
O₄ 가 . (80
mg, 0.223 mmol, 85%), 가 .

NMR (^1H , CDCl_3): δ 7.54 (d, 1H), 7.40-7.30 (m, 2H), 4.20 (t, 1H), 3.93 (dd, 1H), 3.87 (m, 2H), 3.75 (m, 1H), 2.57 (s, 3H), 2.27 (m, 1H), 1.99 (m, 1H).

MS (m/z): 358 $[\text{MH}]^+$ (3Cl).

30

2-[4-(7-(2,4-)-2-(6,7-)-5H-[2,3-d]-5-)]-

CH₂Cl₂ (2 ml) (35 μl, 2 (10 ml))
 29 (80 mg, 0.223 mmol) , N₂ 가 . (155 μl, 5) ,
 1
 , CH₂Cl₂ (3 x 10 ml) .
 , Na₂SO₄ (, cHex/EtOAc 1:1) . (71
 mg, 0.163 mmol, 73%).

NMR (¹H, CDCl₃): δ 7.48 (m, 1H), 7.32 (m, 2H), 4.38 (m, 2H), 4.09 (t, 1H), 3.82 (dd, 1H),
 3.66 (m, 1H), 3.00 (s, 3H), 2.46 (m, 1H), 2.42 (s, 3H), 2.14 (m, 1H).
 MS (m/z): 436 [MH]⁺ (3Cl).

31

{5-[1-(tert- - -)-3-]-6--2--4-}-(2,4--
 -)-

DMF (45 ml) 2,4- () (2.11 g, 9.21 mmol) NaH 80%/ (608 mg,
 2.2) 0 N₂ 가 . 30 , 가 . 30 , DMF (30
 ml) 11 (4.46 g, 9.21 mmol) 가 . 15 , 0
 , EtOAc (3 x 50 ml) , (50 ml), (50 ml)
 , Na₂SO₄ (, cHex/EtOAc 97:3) (4.546 g, 6.71 mmol, 73%)

NMR (¹H, DMSO): δ 8.34 (s, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.48 (d, 1H), 7.54-7.31 (m,
 10H), 5.7 (m, 1H), 4.97 (d, 1H), 4.90 (d, 1H), 4.11 (m, 1H), 3.99 (m, 1H), 3.72 (m, 1H), 2.56
 (m, 2H), 2.18 (s, 3H), 0.91 (s, 9H).
 MS (m/z): 678 [MH]⁺.

32

5-(tert- - -)-4--2--8-(2,4-- -)-5,6,7,8-
 - [2,3-d]-7-

/H₂O 8:1 (36 ml) 31 (2 g, 2.95 mmol) N- - -N- (716
 mg, 2) OsO₄ 4%/H₂O (1.8 ml, 0.1) 가 . 3.5 , , Na₂
 SO₃ 가 . EtOAc (2 x 20 ml) , Na₂SO₄
 , NaIO₄ (947 mg, 1.5) 가 . 18 , (45 ml)
 , EtOAc (3 x 20 ml) , Na₂SO₄
 4 , (1.932 g, 2.85 mmol, 96%) 가

NMR (¹H, 아세톤):

이성질체 1: δ 8.15 (m, 2H), 7.72 (m, 5H), 7.44 (m, 6H), 6.19 (d, 1H), 5.27 (m, 1H), 4.41 (t,
 1H), 4.08 (dd, 1H), 3.52 (m, 1H), 2.81 (m, 1H), 2.35 (m, 1H), 2.15 (s, 3H), 1.07 (s, 9 H).

이성질체 2: δ 8.15 (m, 2H), 7.72 (m, 5H), 7.44 (m, 6H), 5.8-5.4 (m, 2H), 4-3.8 (m, 2H), 3.6-3.4
 (m, 1H), 3-2.8 (m, 1H), 2.35 (m, 1H), 2.15 (s, 3H), 1.07 (s, 9H).

MS (m/z): 680 [MH]⁺.

33

5-(tert-butyl)-4-(2-(8-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro[2,3-d]

CH₂Cl₂ (50 ml) 32 (1.93 g, 2.84 mmol) Et₃SiH (1.82 ml, 4 mmol) BF₃·Et₂O (1.58 ml, 4.4 mmol) 가 , -78 가 , NaHCO₃ 가 , CH₂Cl₂ (3 x 50 ml) , 18 , Na₂SO₄ (, cHex/EtOAc 95:5) (0.607 g, 9.16 mmol, 32%)

NMR (¹H, CDCl₃): δ 7.98-7.94 (d, 1H), 7.88-7.80 (dd, 1H), 7.7-7.58 7.44-7.32 (m, 10H), 7.35-7.14 (d, 1H), 3.98-3.94 (dd, 1H), 3.73-3.55 (m, 1H), 3.63-3.59 (m, 1H), 3.44-3.36 3.38-3.3 (2m, 2H), 2.55-2.4 (m, 1H), 2.17-2.15 (s, 3H), 2.04-1.9 (m, 1H), 0.98 (s, 9H).
MS (m/z): 664[MH]⁺.

34

{4-(2-(8-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro[2,3-d]-5-

DMF (15 ml) 33 (600 mg, 0.91 mmol) Et₃N·3HF (1.25 ml, 8.4 mmol) N₂ 가 , 40 6.5 가 , Na₂SO₄ (, cHex/EtOAc 6:4) (337 mg, 0.8 mmol, 88%)

NMR (¹H, DMSO): δ 8.26-8.12 (m, 2H), 7.9-7.8 (d, 1H), 5.08-4.98 (t, 1H), 3.9-3.6 (2H), 3.7-3.3 (2H), 3.24-3.10 (1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.0-1.8 (m, 1H).
MS (m/z): 426[MH]⁺.

35

4-(2-(8-(2,4-dimethylphenyl)-5,6,7,8-tetrahydro[2,3-d]-5-

CH₂Cl₂ (10 ml) 34 (200 mg, 0.47 mmol) Et₃N (0.26 ml, 4 mmol) MsCl (73 μl, 2 mmol) 가 , 18 가 , Na₂SO₄ (, cHex/EtOAc 6:4) (203 mg, 0.4 mmol, 86%)

NMR (¹H, DMSO): δ 8.3 8.14 (m, 2H), 7.95-7.8 (d+d, 1H), 4.56-4.20 (2H), 3.9-3.4 (m, 3H), 3.25 (s, 3H), 2.11 (s, 3H), 2.2-1.9 (m, 2H).
MS (m/z): 504[MH]⁺.

36

DMF (15 ml) 31 (0.6 mg, 0.886 mmol) Et₃N·3HF (1.22 ml, 8.4 mmol) N₂ 가 , 18 가 , Na₂SO₄ (, cHex/EtOAc 8:2) (346 mg, 89%) , CH₂Cl₂ (15 ml) , Et₃N (0.44 ml, 4 mmol) MsCl (0.122 ml, 2 mmol) 가 , 18 가 , Na₂SO₄ (, cHex/EtOAc 8:2) (276 mg, 83%) , /H₂O 8:1 (18 ml) , N- -N- (230 mg, 2 mmol) OsO₄ (403 μl, 0.1 mmol) 가 .

6, Na₂SO₃ 가
 EtOAc (3 x 20 ml) , Na₂SO₄ (15 ml) , NaIO₄ (210 mg, 1.5) 가
 THF/H₂O 9:1 (18) , EtOAc (3 x 20 ml)
 Na₂SO₄ ,
 (250 mg, 0.59 mmol, 90%)

NMR (¹H, CDCl₃): δ 9.86 (s, 1H), 8.05 (s, 1H), 7.93 (d, 1H), 7.5 (d, 1H), 4.24 (m, 1H), 3.93 (m, 1H), 3.65 (dd, 1H), 3.25 (dd, 1H), 2.93 (dd, 1H), 2.4 (s, 3H).
 MS (m/z): 424[MH]⁺.

37

2-{4- -2- -7-(2,4- -)-6,7- -5H- [2,3-d]
 -5- }-

CH₂Cl₂/MeOH 9:1 (15 ml) 36 (250 mg, 0.59 mmol) NaBH₄ (44 mg, 2)
 N₂ 가 0 30 HCl pH가 7
 가 CH₂Cl₂ (3 x 20 ml)
 Na₂SO₄ (231 mg, 0.54 mmol, 93%) CH₂Cl₂ (15 ml) 0
 Et₃N (302 μl, 4) MsCl (85 μl, 2) 가 18
 CH₂Cl₂ (3 x 20 ml) Na₂S
 O₄ (252 mg, 0.50 mmol, 93%) (, cH
 ex/EtOAc 6:4)

NMR (¹H, CDCl₃): δ 8.05 (bs, 1H), 7.94 (bd, 1H), 7.53 (bd, 1H), 4.42 (m, 2H), 4.07 (t, 1H), 3.83 (dd, 1H), 3.71 (m, 1H), 3.04 (s, 3H), 2.46 (m, 1H), 2.43 (s, 3H), 2.13 (m, 1H).
 MS (m/z): 504[MH]⁺.

38 39

(S)-2- - 4- -2- -8-(2,4- -)-5,6,7,8- -
 [2,3-d] -5(S)- (S)-2- - 4- -2- -8-(2,4- -
 -)-5,6,7,8- - [2,3-d] -5(R)-

CH₂Cl₂ (7 ml) 34 (320 mg, 0.753 mmol) DMAP (230 mg, 2.5) , Et₃N (0.73 ml, 7
) (S)-2- (0.61 ml, 6.4) 0 N₂ 가
 0 30 가 , NaHCO₃ CH₂Cl₂
 2 (3 x 30 ml) , Na₂SO₄ (, cHex/EtOAc 8:2) 가
 hplc : 38 (97 mg, 0.18 mmol, d.e. = 97%) 39 (89.7 m
 g, 0.17 mmol, d.e >99%)가

NMR (¹H, 아세톤):
 중간체 38: δ 8.22-8.13 (m, 2H), 7.96-7.8 (d+d, 1H), 5.06 (m, 1H), 4.56-4.34 (m, 2H), 4.07-3.54 (m, 3H), 2.34-2.05 (m, 2H), 2.7 (s, 3H), 2.06 (s, 3H), 1.48 (d+d, 3H).
 중간체 39: δ 8.22-8.14 (m, 2H), 7.96-7.81 (d+d, 1H), 5.06 (m, 1H), 4.5-4.3 (m, 2H), 4.1-3.54 (m, 3H), 2.7 (s, 3H), 2.3-2.0 (m, 2H), 2.13 (s, 3H), 1.47 (d,3H).
 MS (m/z): 540[MH]⁺.

HPLC:

:
 - / : (Filter Rhodyne)

: (Daicel) CHIRALPAK AD

[cm]: 25

[mm]: 2

[$\mu\ell$]: 500

: n- -IPA 90/10 v/v

[ml/]: 6.5

: DAD

[nm]: 225,292

_____ 38: 21.8, ()

_____ 39: 26.5, ()

_____:

- / :

: CHIRALPAK AD

[cm]: 25

[mm]: 4.6

[μm]: 5

[]:

(Autosampler) []:

[$\mu\ell$]: 20

: n- / 90/10 v/v

[ml/]: 1.0

: DAD

[nm]: 225

_____ 38: 6.88, ()

- / :

: CHIRALPAK AD

[cm]: 25

[mm]: 4.6

[]:

[]:

: n- /2- 90/10 v/v

[ml/]: 1.0

: DAD

[nm]: 220-350

39: 8.29, ()

40

{4- -2- -8-(2,4- -)-5,6,7,8- - [2,3-d] -5(S)- }-

THF/H₂O 4:1 (5 ml) 38 (90 mg, 0.167 mmol) LiOH (14 mg, 2) 0
 가 , 50 , Et₂O (2 x 10 ml)
 EtOAc (1 x 10 ml) Na₂SO₄ ,
 (, cHex/AcOEt 6:4)
 (65 mg, 0.15 mmol, 92%, e.e = 97%)

NMR (¹H, DMSO): δ 8.3-8.1 (m, 2H), 7.88-7.81 (d+d, 1H), 5.00 (broad, 1H), 3.9-3.6 (m, 2H), 3.7-3.3 (m, 2H), 3.2-3.1 (m, 1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.00-1.8 (m, 1H).
 MS (m/z): 426[MH]⁺.

HPLC:

_____:

- / :

: CHIRALPAK AD

[cm]: 25

[mm]: 0.46

[]:

[]:

[μl]: 20

: n- /IPA/EtOH

1: - (Reserv).A- .B: 95/3.5/1.5

[ml/]: 1.0

: DAD

[nm]: 225

40: 10.28, ()

41

4- -2- -8-(2,4- -)-5,6,7,8- [2,3-d]
-5(S)-

CH₂Cl₂ (5 ml) 40 (62 mg, 0.145 mmol) Et₃N (80 μl, 4) MsCl (23 μl, 2)
N₂ 가 . 가 가 , 1 .
CH₂Cl₂ (3 x 20 ml) , Na₂SO₄ , cHex/EtOAc 6:4)
(67 mg, 0.13 mmol, 92%, e.e = 95%)

NMR (¹H, DMSO): δ 8.3-8.14 (m, 2H), 7.94-7.83 (d, 1H), 4.55-4.20 (2H), 3.94-3.4 (m, 3H),
3.25 (s, 3H), 2.11 (s, 3H), 2.25-1.94 (m, 2H).

MS (m/z): 504[MH]⁺.

HPLC:

: :

- / :

: CHIRALPAK AD

[cm]: 25

[mm]: 4.6

[μm]: 5

[]:

(Autosampler) []:

[μl]: 20

: n- /EtOH/IPA 73.5/1.5/25 v/v

[ml/]: 1.0

: DAD

[nm]: 225

41: 6.52, ()

42

{4- -2- -8-(2,4- -)-5,6,7,8- [2,3-d] -5(R)-
}-

THF/H₂O 4:1 (5 ml) 39 (83 mg, 0.154 mmol) LiOH (14 mg, 2) 0
가 , 20 , Et₂O (2 x 10 ml)
EtOAc (1 x 10 ml) , Na₂SO₄ ,
(61 mg, 0.14 mmol, 93%, e.e >99%) (, cHex/EtOAc 7:3)

NMR (¹H, DMSO): δ 8.26-8.12 (m, 2H), 7.9-7.8 (d, 1H), 5.08-4.98 (t, 1H), 3.9-3.6 (m, 2H), 3.7-3.3 (m, 2H), 3.24-3.1 (m, 1H), 2.3 (m, 1H), 2.09 (s, 3H), 2.00-1.8 (m, 1H).
 MS (m/z): 426[MH]⁺.

HPLC:

_____:

- / :

: CHIRALPAK AD

[cm]: 15

[mm]: 4.6

[μℓ]: 10

: n- / /IPA

1: - (Reserv).A- .B: 95/1.5/3.5 v/v

[ml/]: 1.0

: DAD

[nm]: 225

_____ 42: 9.417, ()

43

_____ 4- -2- -8-(2,4- - -)-5,6,7,8- - [2,3-d]
 -5(R)-

CH₂Cl₂ (5 ml) _____ 42 (58 mg, 0.136 mmol) Et₃N (76 μℓ, 4) MsCl (21 μℓ, 2)
) 0 N₂ 가 . 가 가 , 1
 CH₂Cl₂ (3 x 20 ml) , Na₂SO₄
 (, cHex/EtOAc 7:3)
 _____ (57.6 mg, 0.11 mmol, 85%, e.e> 99%)

NMR (¹H, DMSO): δ 8.3-8.14 (m, 2H), 7.95-7.8 (d, 1H), 4.56-4.20 (2H), 3.9-3.4 (m, 3H), 3.25 (s, 3H), 2.11 (s, 3H), 2.2-1.9 (m, 2H).

HPLC:

_____:

- / :

: CHIRALPAK AD

[cm]: 25

[mm]: 4.6

[μm]: 3

[μ l]: 10

: n- / /IPA

1: - (Reserv).A- .B: 75/1.5/23.5 v/v

[ml/]: 1.0

: DAD

[nm]: 225

43: 4.703, ()

44

3-(2,4- -)-2- -6- - -1-

Et₂O/THF (0.5 ml/0.1 ml) 23 (26 mg, 0.087 mmol) (0.005 ml, 1
 .1) (Amberlyst) A21 (: 260 mg) 가 .
 . 2.5 , Et₂O Et₂O (7x) 가
 , (, cHex/EtOAc 9:1)
 (25 mg, 80%)

NMR (¹H, CDCl₃): δ 12.72 (s, 1H), 7.41 (d, 1H), 7.24 (dd, 1H), 7.03 (d, 1H), 4.64 (dd, 1H),
 4.50 (t, 1H), 4.07 (bm, 1H), 3.87 (s, 3H), 3.58 (m, 1H), 2.08 (bm, 1H), 1.85 (bm, 3H).

MS (m/z): 359 [MH]⁺ (2 Cl).

45

8-(2,4- -)-2- -5- -5,6,7,8- - -4-

(21 mg, 3.1) MeOH (1.5 ml) N₂ 가 .
 , (96 mg, 3.3) 가 . 10 , NaCl ,
 MeOH (2 ml) 44 (106 mg, 0.294 mmol) 가 ,
 18 , (, EtOAc/cHex
 8:2) (81 mg, 75%).

MS (m/z): 368 [MH]⁺ (2 Cl).

46

4- -8-(2,4- -)-2- -5- -5,6,7,8- -

POCl₃ (2 ml) 45 (73 mg, 0.198 mg) 2.5 가 . POCl₃
 , CH₂Cl₂ . NH₄OH , CH₂
 Cl₂ (3 x 10 ml) NaCl , Na₂SO₄
 . (68 mg, 89%)

MS (m/z): 386 [MH]⁺ (3 Cl).

47

4- -8-(2,4- -)-2- -5,6,7,8- - -5-

MeOH (1 ml) 46 (64 mg, 0.166 mml) KOH (0.1 M, 2.3 ml) -10

N_2 가 10 15 , H_2O (2.5 ml) $KMnO_4$ (18 mg, 0.7) $MgSO_4$ (20 mg, 1) 가 (0).
 CH_2Cl_2 (3 x 10 ml) , CH_2Cl_2 , Na_2SO_4 ,
 8:2) , _____ 65:35 (, cHex/EtOAc 9:1 (27 mg, 46%,)

MS (m/z): 355 [MH]⁺ (3 Cl).

1

I-1

5-(2,4-)-1-(1- -)-7- -1,2,2a,3,4,5- -1,5,6,8- - (I-1-1)

3- (60 μ l) _____ 19 (14 mg) 120 8 ,
 , Et_2O (3 x 10 ml) , , ,
 Na_2SO_4 (, cHex/EtOAc 8:2) _____ (5.9 mg)

5-(2,4-)-1-(2- -)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8- - (I-1-2)

2- -n- (100 μ l) _____ 19 (10.0 mg) 120 7
 , _____ (1.9 mg) , /EtOAc 95:5)

5-(2,4-)-1-(2- -1- -)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8- - (I-1-3)

2- -1-() (52.6 mg) _____ 19 (16.5 mg) 150 ((/EtOAc 6:4) _____ (4.2 mg)

7- -1-(1-)-5-(2,4- -)-1,2,2a,3,4,5- -1,5,6,8- - (I-1-4)

_____ 35 (135 mg, 0.27 mmol) 4- (0.5 ml, 12) 130 () 3
 가 , _____ , CH_2Cl_2 ,
 (, cHex/EtOAc 9:1) _____ (29.4 mg, 0.06 mmol, 23 %)

1

7- -1-(1-)-5-(2,4- -)-1,2,2a(S),3,4,5- -1,5,6,8- -

_____ 41 (60 mg, 0.119 mmol) 4- (178 μ l, 10) 130 () 3
 가 _____ CH_2Cl_2 , _____ (19.4 mg, 0.04 mmol, e.e. = 95%) (

HPLC:

—:

: CHIRALPAK OD

[cm]: 25

[mm]: 4.6

[]: 35

[μl]: 10

: CO₂/EtOH (0.15% lpa) 85/15

[ml/]: 2.5

: UV

[nm]: 225

[]: 150

: 2.55, ()

¹H-NMR MS I-1-4 1 .

2

7- -1-(1-)-5-(2,4- -)-1,2,2a(R),3,4,5- -1,5,6,8-

43 (55 mg, 0.019 mmol) 4- (163 μl, 10) 130 () 3
 가 CH₂Cl₂ , cHex/EtOAc 95:5) (25.7 mg, 0.053 mmol, 49%, e.e.> 99%) (

HPLC:

—:

: CHIRALPAK OD

[cm]: 25

[mm]: 4.6

[]: 35

[μl]: 10

: CO₂/EtOH (0.15% lpa) 85/15

[ml/]: 2.5

: UV

[nm]: 225

[]: 150

: 2.12, ()

¹H-NMR MS I-1-4 1 .

5-(2,4-)-7- -1-(1-)-1,2,2a,3,4,5- -1,5,6,8- - (I-1-5)

4- (100 μℓ) 19 (20 mg, 0.046 mmol) 130 () 18
 가 . ,
 (7 mg, 0.017 mmol, 36%) (, /EtOAc 9:1 8:2)

1

5-(2,4-)-7- -1-(1-)-1,2,2a-(S),3,4,5,5a,8b- -1,5,6,8- -

47 (120 mg, 0.276 mmol) 4- (0.412 ml, 10) 130 () 18
 , CH₂Cl₂ (5 ml) ,
 (, cHex/EtOAc 9.5:0.5) (62 mg, 53 %, ee > 99%)

HPLC:

—:

- / : (Rheodyne filter)

: CHIRALPAK AD

(cm): 25

(mm): 4.6

(μℓ): 5

():

():

(μℓ): 20

: n- /tert- 90/10 a/a

(ml/): 1

: DAD

(nm): 220-350

: 10.2, ()

¹H-NMR MS I-1-5 1 .

2

5-(2,4-)-7- -1-(1-)-1,2,2a-(R),3,4,5,5a,8b- -1,5,6,8- -

49 (130 mg, 0.298 mmol) 4- (0.342 ml, 10) 130 () 18
 CH₂Cl₂ (5 ml)
 (, cHex/EtOAc 9.5:0.5) (74 mg, 59 %, ee% = 90%)

HPLC:

:

- / : (Rheodyne filter)

: CHIRALPAK AD

(cm): 25

(mm): 4.6

(μl): 5

():

():

(μl): 20

: n- /tert- 90/10 a/a

(ml/): 1

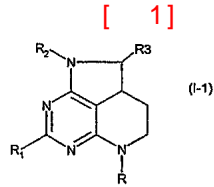
: DAD

(nm): 220-350

: 7.5, (), 90%

¹H-NMR MS I-1-5 1 .

1 .



화합물 번호	R	R ₁	R ₂	R ₃	분석 데이터
1-1-1	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃ , 55 °C): δ 7.46 (d, 1H), 7.35-7.25 (m, 2H), 3.86 (m, 1H), 3.69 (m, 1H), 3.63 (bm, 2H), 3.42 (m, 1H), 3.23 (m, 1H), 2.27 (s, 3H), 2.24 (m, 1H), 1.77 (m, 1H), 1.70-1.40 (m, 4H), 1.00 (t, 3H), 0.82 (t, 3H). MS (m/z): 391 [MH] ⁺ , 2 Cl.
1-1-2	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.46 (s, 1H), 7.26 (m, 2H), 3.86 (m, 1H), 3.60 (m, 2H+1H), 3.40 (m, 1H), 3.06 (m, 1H), 2.70 (dd, 1H), 2.35-2.20 (m, 2H), 2.29 (s, 3H), 1.60 (m, 1H), 1.40-1.20 (m, 4H), 0.94 (t, 6H). MS (m/z): 405 [MH] ⁺ .
1-1-3	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃ , 55 °C): δ 7.43 (bs, 1H), 7.23 (bs, 2H), 4.30 (bm, 1H), 3.80 (bm, 1H), 3.59 (m, 5H), 3.40 (bm, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 2.26 (bs, 3H), 2.24 (bm, 1H), 1.75 (bm, 1H). MS (m/z): 423 [MH] ⁺ .
1-1-4	2,4-트리플루오로-메틸페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.99 (s, 1H), 7.83 (d, 1H), 7.48 (d, 1H), 4.06-3.24 (bm, 5H), 2.23-2.2 (bm, 4H), 1.74-1.1 (bm, 10H), 0.97 (t, 3H), 0.91 (t, 3H). MS (m/z): 487[MH] ⁺ .
1-1-5	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.46 (d, 1H), 7.29 (d, 1H), 7.26 (dd, 1H), 4.04 (m, 1H), 3.67 (t, 1H), 3.64 (bm, 2H), 3.41 (m, 1H), 3.20 (t, 1H), 2.27 (m, 4H), 1.55-1.10 (m, 8H), 0.95 (t, 3H), 0.88 (t, 3H). MS (m/z): 419 [MH] ⁺ 2Cl.

2

1-2

9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4H-1,3,4- ()
 1) 9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4H-1,3,4- ()
 2) (2-1-1)

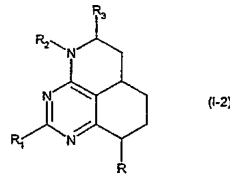
25 (1) CH₂Cl₂ (6 ml) , O₃ (5 g/) -78 20
 (1 ml) 가 , 가 , Na
 2 SO₄ , , (106 mg)
 1:1 , 가 .

MeOH (1 ml) (30 mg) 1- (0.010 ml) 가 ,
 3 , THF (0.162 ml) NaBH₃CN 1M 가 ,
 65 . THF (0.080 ml) 1M NaBH₃CN 가 ,
 3 EtOAc . EtOAc
 (4 x 10 ml) , (2 x 10 ml) , Na₂SO₄ .
 (, CH₂Cl₂/EtOAc 7:3)
 (16 mg) 가 .

가 TLC (/EtOAc 95:5 1% NH₄OH) _____ 1 ()
 5.4 mg) _____ 2 (5.6 mg)

2

[2]



화합물 번호	R	R ₁	R ₂	R ₃	분석 데이터
2-1-1	2,4-디클로로-페닐	CH ₃		H	이성질체 1 :NMR (¹ H, CDCl ₃): δ 7.31 (d, 1H), 7.14 (dd, 1H), 7.01 (bs, 1H), 5.01 (bs, 1H), 4.41 (bs, 1H), 3.34 (bd, 1H), 3.17 (dt, 1H), 2.68 (m, 1H), 2.40-2.30 (m, 1H), 2.37 (bs, 3H), 2.04 (m, 2H), 1.67 (bd, 1H), 1.55 (m, 4H), 1.50-1.35 (m, 2H), 0.87 (t, 3H), 0.79 (t, 3H). MS (m/z): 404 [M+H].
	2,4-디클로로-페닐	CH ₃		H	이성질체 2:NMR (¹ H, CDCl ₃): δ 7.40 (bs, 1H), 7.05 (dd, 1H), 6.36 (d, 1H), 5.03 (bs, 1H), 5.00-4.50 (broad, 1H), 3.40 (bd, 1H), 3.22 (dt, 1H), 2.60 (m, 1H), 2.45 (bs, 3H), 2.16-2.06 (m, 2H), 2.03 (m, 1H), 1.75 (bd, 1H), 1.70-1.50 (m, 4H), 1.45 (dq, 1H), 1.24 (m, 1H), 0.86 (t, 6H). MS (m/z): 404 [M+H].

3

I-3

5- (3-1-1) -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- -

CH₃ OH (1 ml) 10 (20 mg) () (5 μl, 1) 가 .
90 , NaBH₃ CN 1.0M/THF (113 μl) 가 .
가 18 , H₂O (10 ml) . EtOAc (2 x 15 ml) ,
(Na₂SO₄ , cHex/EtOAc 9:1) (5 mg)

1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- - (3-1-2)

THF (1 ml) 10 (16 mg) 2- - (4 μl) 가 .
90 , NaBH₃ CN 1.0M/THF (90 μl) 가 . 가 18
, H₂O (10 ml) . EtOAc (2 x 15 ml) . Na
2 SO₄ 가 , , (2 ml) TEA (30
μl) 가 10 , H₂O . EtOAc (2 x 10
ml) Na₂SO₄ , - TL
C (cHex/EtOAc 75:25) 2 mg (12%) (1.6 mg, 7%)
(3 : 1: cHex 100%, 2: cHex/EtOAc 75:25, 3: cHex/EtOAc 50:50).

1-(2,4-)-5-(1-)-7- -1,2,2a,3,4,5- -1,5,6,8- - (3-1-3)

THF (1 ml) 10 (20 mg) 1- - (6.5 μl) 가 .
90 , NaBH₃ CN 1.0M/THF (112 μl) 가 . 가 18
, H₂O (10 ml) . EtOAc (2 x 10 ml) .
Na₂SO₄ 18 가 , H₂O (10 ml) , EtOAc (3 x 10 ml) (2 ml)
Na₂SO₄ , - TLC (cHex/EtOAc 7

5:25) _____ (1.6 mg, 7%)

1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-1-4)

MeOH (2 ml) _____ 10 (35.5 mg) 2- (0.014 ml) N₂ 가
 , 90 , NaBH₃CN (THF 1M , 0.2 ml)
 가 , 70 3 가 , EtOAc (3 x 5 ml) , H₂O (5 ml)
 가 NaCl (5 ml) , Na₂SO₄ ,
 (0.018 g) (, cHex 100% cHex/EtOAc 95:5)

1-(2,4-)-7- -5-(1-)-1,2,2a,3,4,5- -1,5,6,8- (3-1-5)

4- (100 μl) _____ 30 (20 mg, 0.046 mmol) 130 () 6.5 ,
 18 가 , (, cH
 ex/EtOAc 9:1) _____ (9 mg, 0.021 mmol, 47%).

7- -5-(1-)-1-(2,4- -)-1,2,2a,3,4,5- -1,5,6,8- (3-1-6)

_____ 37 (230 mg, 0.457 mmol) 4- (0.68 ml, 10) 130 () 14
 가 , CH₂Cl₂ ,
 , cHex/EtOAc 95:5) _____ (54 mg, 0.11 mmol, 24%)

5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8- (3-1-7)

Et₂O (0.8 ml) CuBr · Me₂S (48 mg, 5) PrMgBr 1M/THF (0.188 ml, 4) -50
 N₂ 가 , -50 45 -78
 , BF₃ · Et₂O (0.024 ml, 4) 가 , -78 20
 THF (0.5 ml) _____ 28 (19 mg, 0.047 mmol) 가 , 3
 4 , NH₄OH NH₄Cl 1:1 (2 ml) 가 ,
 15 , EtOAc 가 , EtOAc (3 x 10 ml)
 , Na₂SO₄
 (, cHex/EtOAc 9:1)
 (3 mg, 0.007 mmol, 15%).

4- -5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-1-8)

Et₂O (1 ml) CuBr · Me₂S (72 mg, 4.3) n-BuLi 1.6M/ (0.21 ml, 4.15) -5
 N₂ 가 , -50 40 -78
 , BF₃ · Et₂O (0.043 ml, 4.15) 가 , -78 15 , THF (0.
 5 ml) _____ 28 (33 mg, 0.081 mmol) 가 , 3
 3.5 , NH₄OH NH₄Cl 1:1 (1 ml) 가 , 15
 , EtOAc 가 , EtOAc (3 x 10 ml)
 , Na₂SO₄
 (, cHex/EtOAc 9:1) _____ (,
 1:) (16 mg, 0.037 mmol, 46%). 27

5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8- (3-1-9)

Et₂O (0.2 ml) CuBr · SMe₂ (27 mg, 2) (0.2 ml, 2) :

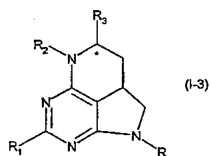
Et₂O (1.5 ml) Mg (27 mg, 1.1 mmol) N₂ 가
) -60 N₂ 가
 , -60 30 , -78 THF (0.4 ml) 28 (27 mg, 0.067 mmol) N₂ 1 가
 가 . 10 , -78 (4). , BF₃ · Et₂O (17 μl, 2)
 , 10 가 , NH₄OH/ NH₄Cl 1:1
 H₂O (2 x 20 ml) , Na₂SO₄ CH₂Cl₂ (4 x 20 ml)
 (4 mg, 0.009 mmol, 14%) (, 9:1 7:3 cHex/EtOAc)

4,5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- (3-1-10)

Et₂O (1 ml) CuBr · Me₂S (65 mg, 4.3) BuLi 1.6M (0.184 ml, 0.295 mmol, 4
) -50 N₂ 가 . -50 -40 40
 , -78 , BF₃ · Et₂O (0.037 ml, 4) 가 . -78 15
 , 28 (30 mg, 0.074 mmol) THF (0.5 ml) , 3
 . 3.5 , NH₄OH NH₄Cl 1:1 (1 ml) 가 ,
 15 . EtOAc 가 , EtOAc (3 x 10 ml)
 . (28 mg) , Na₂SO₄ .
 28 mmol, 37%) (cHex/EtOAc 9:1) . (12 mg, 0.0

3a 3b

[3a]



화합물 번호	R	R ₁	R ₂	R ₃	분석 데이터
3-1-1	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.41 (d, 1H), 7.36 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.7 (dd, 1H), 3.55 (t, 1H), 3.54-3.44 (m, 3H), 3.25 (dd, 1H), 2.37 (s, 3H), 2.24 (m, 1H), 1.66 (m, 1H), 1.00 (m, 1H), 0.52 (m, 2H), 0.29 (m, 1H). MS (m/z): 375 [MH] ⁺ , 2Cl.
3-1-2	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.41 (d, 1H), 7.35 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.94 (m, 1H), 3.62-3.47 (m, 5H), 3.37 (s, 3H), 2.38 (s, 3H), 2.21 (m, 1H), 1.64 (m, 1H). MS (m/z): 379 [MH] ⁺ , 2Cl.
3-1-3	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.41 (d, 1H), 7.35 (d, 1H), 7.22 (dd, 1H), 4.23 (t, 1H), 3.94 (m, 1H), 3.62-3.47 (m, 5H), 3.37 (s, 3H), 2.38 (s, 3H), 2.21 (m, 1H), 1.64 (m, 1H). MS (m/z): 379 [MH] ⁺ , 2Cl.
3-1-4	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.56-7.30 (m, 3H), 4.25 (t, 1H), 3.68-3.40 (m, 3H), 2.56 (s, 3H), 2.45-2.27 (m, 2H), 1.67 (m, 6H), 0.95 (m, 8H). MS (m/z): 405 [MH] ⁺ .
3-1-5	2,4-디클로로-페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.35 (m, 2H), 7.20 (d, 1H), 4.80 (m, 1H), 4.20 (t, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 2.30 (s, 3H), 2.20 (m, 1H), 1.60-1.15 (m, 9H), 0.90 (m, 6H). MS (m/z): 419 [MH] ⁺ .
3-1-6	2,4-트리플루오로-메틸페닐	CH ₃		H	NMR (¹ H, CDCl ₃): δ 7.93 (s, 1H), 7.73 (d, 1H), 7.59 (d, 1H), 4.84 (m, 1H), 4.14 (t, 1H), 3.52 (m, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H),

[3b]

					1.6-1.2 (m, 9H), 0.92 (m, 6H). MS (<i>m/z</i>): 487[MH] ⁺ .
3-1-7	2,4-디클로로-페닐	CH ₃			NMR (¹ H, CDCl ₃): δ 7.40 (d, 1H), 7.35 (d, 1H), 7.20 (dd, 1H), 4.27-4.10 (m, 2H), 3.68 (m, 1H), 3.55-3.42 (m, 2H), 3.03 (dd, 1H), 2.35 (s, 3H), 2.40-2.25 (m, 1H), 1.85-1.75 (m, 1H), 1.75-1.50 (m, 2H), 1.45-1.25 (m, 2H), 0.95 (t, 3H), 0.85 (m, 1H), 0.55-0.25 (m, 4H). MS (<i>m/z</i>): 417 [MH] ⁺ 2Cl.
3-1-8	2,4-디클로로-페닐	CH ₃			이성질체 1 (신): NMR (¹ H, CDCl ₃): δ 7.42 (d, 1H), 7.37 (d, 1H), 7.24 (dd, 1H), 4.24 (m, 1H), 4.18 (dd, 1H), 3.72 (m, 1H), 3.53 (m, 1H), 3.49 (m, 1H), 3.06 (dd, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.62 (q, 1H), 1.45-1.25 (m, 4H), 1.02 (m, 1H), 0.94 (t, 3H), 0.52 (m, 1H), 0.44 (m, 1H), 0.38 (m, 1H), 0.30 (m, 1H). MS (<i>m/z</i>): 431 [M+H] ⁺ (2 Cl).
	2,4-디클로로-페닐	CH ₃			이성질체 2 (안티): NMR (¹ H, CDCl ₃): δ 7.43 (d, 1H), 7.39 (d, 1H), 7.23 (dd, 1H), 4.27 (m, 1H), 4.08 (dd, 1H), 3.69 (m, 1H), 3.57 (m, 1H), 3.49 (m, 1H), 2.99 (dd, 1H), 2.39 (s, 3H), 2.24 (m, 1H), 1.80-1.20 (m, 7H), 1.02 (m, 1H), 0.94 (t, 3H), 0.55 (m, 1H), 0.46 (m, 1H), 0.29 (m, 2H). MS (<i>m/z</i>): 431 [M+H] ⁺ 2Cl.
3-1-9	2,4-디클로로-페닐	CH ₃			NMR (¹ H, 아세톤-d ₆): δ 7.55 (d, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 5.03 (t, 1H), 4.25 (t, 1H), 4.03 (dd, 1H), 3.78 (dd, 1H), 3.56 (m, 3H), 3.15 (dd, 1H), 2.54 (m, 1H), 2.25 (s, 3H), 1.59 (m, 2H), 1.43 (td, 1H), 1.11 (m, 1H), 0.92 (t, 3H), 0.50-0.24 (m, 4H). MS (<i>m/z</i>): 433 [MH] ⁺ .
3-1-10	2,4-디클로로-페닐	CH ₃			NMR (¹ H, CDCl ₃): δ 7.54 (d, 1H), 7.47 (d, 1H), 7.36 (dd, 1H), 4.39 (m, 1H), 4.19 (m, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.50 (m, 1H), 3.07 (m, 1H), 2.40 (m, 1H), 2.20 (s, 3H), 1.90-1.70 (m, 3H), 1.60-1.50 (m, 3H), 1.40-1.20 (m, 5H), 0.95 (2t, 6H). MS (<i>m/z</i>): 433 [M+H] ⁺ (2 Cl).

4

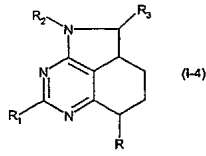
1-4

5-(2.4-)-1-(1-)-7- -1.2,2a,3,4,5- -1.6,8- (4-1-1)

MeOH (1 ml) _____ 47 (22 mg, 0.062 mmol) 1- (9 μl, 1.25)
 N₂ 가 , 1.2 , NaBH₃CN 1.0M/THF (0.15
 ml, 2.4) 가 , 2 , -18 4
 , EtOAc/H₂O , EtOAc (3 x 5 ml)
 NaCl (1 x 5 ml) , Na₂SO₄ ,
 (, cHex/EtOAc 9:1 8:2)
 _____ (3 mg, 0.008 mmol, 12%).

4

[4]



화합물 번호	R	R ₁	R ₂	R ₃	분석 데이터
4-1-1	2,4-디클로로-페닐	CH ₃		H	MS (m/z): 390 [MH] ⁺ (2 Cl).

5

CRF
 CRF (Chinese Hamster Ovary, CHO) CRF
 CRF1 CRF2 SPA ¹²⁵I-oCRF ¹²⁵I- (Sauvagine) CRF
 SPA (HEPES/KOH 50 mM, EDTA 2 mM; MgCl₂ 10 mM, pH 7.4) T- CHO 50 ml
 ytron) (4 5 50'000 g: JA20 (Beckman) (Pol)).
 SPA 100 μl 1 μl (100% DMSO) 가
 (Optiplate) SPA, WGA SPA (2.5 mg/ml), BSA (1 mg/ml) (CRF1 CR
 F2 50 5 μg /ml) 50 pM
 (>18) , WGA - SPA ¹²⁵I (Packard
 Topcount)

6

CRF
 , cAMP 가 . CRF-CHO CRF
 T- CHO G418 , 96- , 25'000c/ , 100 μl
 / (5 mM KCl, 5 mM NaHCO₃, 154 mM NaCl, 5 mM HEPES, 2.3 mM CaCl₂, 1 mM MgCl₂; 1 g/L
 , pH 7.4, 1 mg/ml BSA 1 mM IBMX가 가), DMSO 1 μl
 CO₂ 가 37 가 10 , DMSO 1 μl
 538 가 cAMP , (Amersham) RPA

가

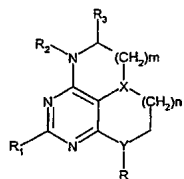
(57)

1.

I

(prodrug)

< I >



R, C2-C6, C1-C6, R, C1-C6, C1-C6, C1-C6, C2-C6, R₄

R₁, C1-C6, C2-C6, C2-C6, C1-C6, C1-C6, NH₂,

R₂ C(H)_n(R₅)_q(CH₂)_pZR₆;

R₃, C2-C6, C2-C6 [CH(R₅)(CH₂)_p]_mZR₆;

R₄ C3-C7; 5-6;

C1-C6, R₄, C1-C6, C1-C6, C1-C6, C2-C6, C2-C6,

R₅, C2-C6, C2-C6 (CH₂)_pZR₆;

R₆, C1-C6, C2-C6, C2-C6, C1-C6, C1-C6, C1-C6, C1-C6, C1-C6, R₄

Y X;

m n 0 1;

p 0 1 4;

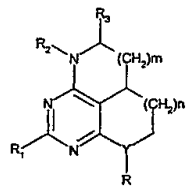
q 1 2;

Z, O, NH S.

2.

1, II.

< II >

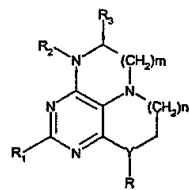


R, R₁, R₂, R₃, m, n Y 1 .

3.

1 , III .

< III >

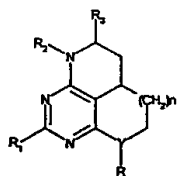


R, R₁, R₂, R₃, m, n Y 1 .

4.

2 , IIa .

< IIa >

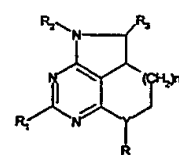


R, R₁, R₂, R₃, n Y 1 .

5.

2 , IIb .

< IIb >

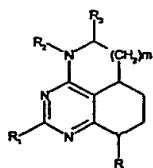


R, R₁, R₂, R₃, n Y 1 .

6.

2 , IIC .

< IIC >

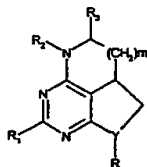


R, R₁, R₂, R₃, m Y 1 .

7.

2 , IId .

< IId >

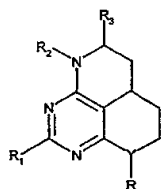


R, R₁, R₂, R₃, m Y 1 .

8.

6 , Ia-1 .

< Ia-1 >

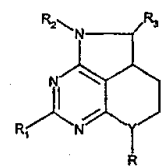


R, R₁, R₂, R₃ Y 1 .

9.

6 , Ib-1 .

< Ib-1 >

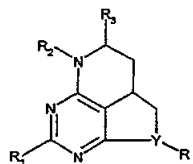


R, R_1, R_2, R_3 Y 1 .

10.

6 , Ic-1 .

< Ic-1 >

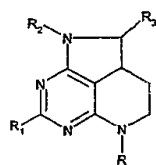


R, R_1, R_2, R_3 Y 1 .

11.

9 , I-1 .

< I-1 >

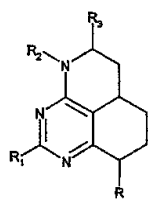


R, R_1, R_2, R_3 1 .

12.

8 , I-2 .

< I-2 >

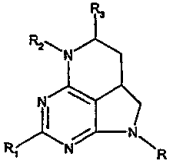


R, R_1, R_2, R_3 1 .

13.

7 , I-3 .

< I-3 >

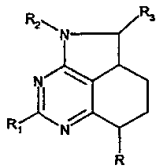


R, R₁, R₂, R₃ 1

14.

9, I-4

< I-4 >



R, R₁, R₂, R₃ 1

15.

1 14, R₂ R₃ 가 가

16.

1 15, R₁ C1-C3 C1-C3

17.

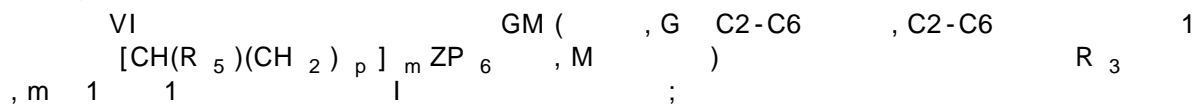
1 16, R 2,4-, 2-, 4-, 2-, 4-
 , 2-, 4-, 2,4,5-, 2,4-, 2-, 4-, 2-, 4-
 , 2-, 4-, 2,4-, 2-, 4-, 2-, 4-
 , 3-, 4-, 2,5-, 4-, 2-, 4-, 2-, 4-
 , 2-, 4-, 2-, 4-, 2-, 4-, 2,4-
 , 2-, 4-, 2-, 4-, 2-, 4-
 , 4-, 6-, 3-, 4-, 6-, 3-, 6-
 3- 4- - 3-

18.

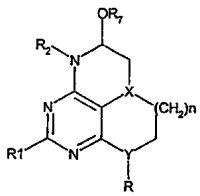
1 17,
 5-(2,4-)-1-(1-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
 5-(2,4-)-1-(2-)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8- ;
 5-(2,4-)-1-(2- -1-)-7- -1,2,2a,3,4,5,5a,8b- -1,5,6,8- ;
 7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a,3,4,5-
 -1,5,6,8- ;
 7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a(S),3,4,5-
 -1,5,6,8- ;

- 7- -1-(1-)-5-[4-(1,1,2-)-2-]-1,2,2a(R),3,4,5-
-1,5,6,8- ;
- 5-(2,4-)-7- -1-(1-)-1,2,2a,3,4,5- -1,5,6,8- ;
- 5-(2,4-)-7- -1-(1-)-1,2,2a-(S),3,4,5,5a,8b- -1,5,6,8-
;
- 5-(2,4-)-7- -1-(1-)-1,2,2a-(R),3,4,5,5a,8b- -1,5,6,8-
;
- 9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4 H -1,3,4- (
1) 9-(2,4-)-4-(1-)-2- -5,6,6a,7,8,9- -4 H -1,3,4-
(2);
- 5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
- 1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
- 1-(2,4-)-5-(1-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
- 1-(2,4-)-5-(2-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
- 1-(2,4-)-7- -5-(1-)-1,2,2a,3,4,5- -1,5,6,8- ;
- 7- -5-(1-)-1-[4-(1,1,2- -)-2-]-1,2,2a,3,4,5-
-1,5,6,8- ;
- 5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8-
;
- 4- -5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8-
;
- 5- -1-(2,4-)-7- -4- -1,2,2a,3,4,5- -1,5,6,8-
;
- 4,5- -1-(2,4-)-7- -1,2,2a,3,4,5- -1,5,6,8- ;
- 5-(2,4-)-1-(1-)-7- -1,2,2a,3,4,5- -1,6,8-

19.



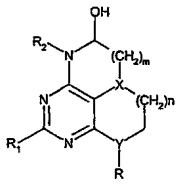
< VI >



$R, R_1, R_2, X, n = 1$

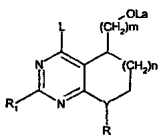
$R_7 = C1-C4$

< Va >



$R, R_1, R_2, X, m, n = 1$

< VII >



$R, R_1, m, n = 1$

L

$La = R_2NH_2$ (IX) OLa 가

20. CRF () 1 18

21. 20

22. 20, IBS () IBD ()

23. 1 18, CRF ()

24.

1 18

25.

1 18

, IBS () IBD ()

26.

1 18

1

27.

1 18

, CRF

28.

27

, 1 18

29.

27

, 1 18

) IBD ()

, IBS (

30.

1 18