

(74)

:

(54) -

[2-(4-)] . G-
 IgE

H₁ (Ash, A. S. F. and Schild, H. O., Br. J. Pharmacol., 1966, 27, 427)
 (:)

H₂ (Black, J. W., Duncan, W. A. M., Durant, C. J., Ganel
 lin, C. R. and Parsons, E. M., Nature, 1972, 236, 385) H₂ (:)
 -H₃ 가 (Arrang, J.-M., Garba
 rg, M., and Schwartz, J.-C., Nature 1983, 302, 832)
 , GABA (-)

H₃ 가 H₃
 (See: 'The histamine H₃ receptor - A Targ
 et for New Drugs', Leurs, R., and Timmerman, H., (Editors), Elsevier, 1998; Morisset et al., Nature, 2000, 40
 8, 860-864.) -H₄ - 가 Oda (J. Biol. Chem., 2000, 275, 36781-36786)

/ / H₃ (Lin et al, Br.
 Res., 1990, 523, 325; Monti et al Eur. J. Pharmacol., 1991, 205, 283).
 (McLeod et al Abstr. Society Neuroscience, 1996, 22, 2010).
 (Imamura et al J. Pharmacol.
 Expt. Ther., 1994, 271, 1259). (NANC)

H₃ (Ichinose et al
 Eur. J. Pharmacol., 1989,174, 49).

H₃ (:) H₃
 (Panula et al Abstr. Society Neuroscience
 , 1995, 21,1977), (Yokoyama et al Eur. J. Pharmacol., 1993, 234, 129) , (Machidori et al
 Brain Research 1992, 590, 180), , (ADHD), (Barnes
 et al Abstr. Society Neuroscience, 1993,19,1813), (Schlicker et al Naunyn-Schmiedeberg's Arch.
 Pharmacol., 1996, 353, 290-294); (also see; Stark et al Drugs Future, 1996,21, 507 and Leurs et al Progress
 in Drug Research, 1995, 45, 107). H₁
 H₃ (U.S. Pat. Nos. 5,21
 7,986; 5,352,707 and 5,869,479). CNS H₃ (GT-2331)가 Gli
 atech Inc. (Gliatech Inc. Press Release Nov. 5, 1998; Bioworld Today, Mar. 2, 1999).

H₃ 가 ('The Histamine H₃ receptor - A Target for New Drugs', Leurs, R., and Timmerman, H., (Editors), Elsevier, 1998).
가 (Krause et al and Phillips et al). 4 가

H₃ 가 (See, Ali et al J. Med. Chem., 1999, 42, 903 and Stark et al, Drugs Future, 1996, 21, 507).

(See, Rouleau et al J. Pharmacol. Exp. Ther. 1997, 281, 1085).

P450

(Kapetanovic et al Drug Metab. Dispos. 1984,12, 560; Sheets et al Drug Metab. Dispos. 1984, 12, 603; Back, et al Br. J. Pharmacol. 1985, 85, 121; Lavrijsen et al Biochem. Pharmacol. 1986, 35,1867; Drug Saf., 1998, 18, 83).

H₃ (Ganellin et al Arch. Pharm. (Weinheim, Ger.) 1998, 331, 395).

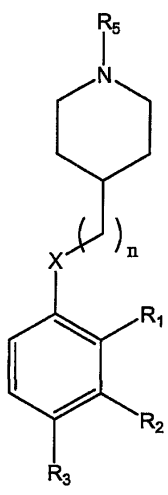
H₃ 가 ; Ganellin et al Arch. Pharm. (Weinheim, Ger.) 1998, 331, 395; Walczynski et al Arch. Pharm. (Weinheim, Ger.) 1999, 332, 389; Walczynski et al Farmaco 1999, 684; Linney et al J. Med. Chem. 2000, 2362; Tozer and Kalindjian Exp. Opin. Ther. Patents 2000, 10, 1045-1055; U.S. Pat. No. 5,352,707; PCT Application WO99/4245 8, Aug. 26, 1999; and European Patent Application 0978512, Feb. 9, 2000.

(liability) H₃ (See Lovenberg et al Mol. Pharmacol. 1999, 1107).

(Garbarg et al J. Pharmacol. Exp. Ther. 1992, 263, 304), (West et al Mol. Pharmacol., 1990, 610), (Korte et al Biochem. Biophys. Res. Commun. 1990, 978)

H₃

(I) 가 , , :



X O ;

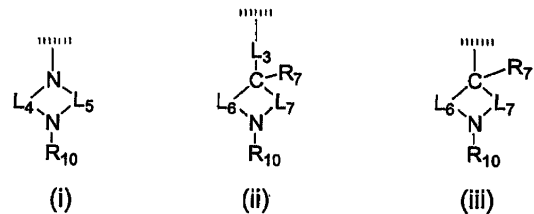
n 0 3 ;

R_5 , C_{1-10} , C_{3-8} , C_{3-8} , $(C_{3-8})C_{1-6}$, $()C_{1-6}$, $()$
 C_{3-8} , $(C_{1-8})C_{1-8}$; ;

R_1, R_2, R_3 , G , W , H
 ;

G - ;

$-OL_1Q, -L_2Q, -N(L_1Q)R_5, -L_3C(L_1Q)R_6R_7, -C(L_1Q)R_6R_7,$



L_1 , C_{2-6} , C_{3-8} , C_{4-6} , C_{4-6} , C_{2-5} , $()C_{1-6}$, $()C_{1-6}$
 $()C_{1-6}$, $(C_{2-5})C_{1-6}$, $(C_{2-5})C_{1-6}$;

L_2 , C_{1-6} , C_{3-8} , C_{3-8} , C_{3-8} , C_{2-5} , $()C_{1-6}$, $()C_{1-6}$
 $()C_{1-6}$, $(C_{1-5})C_{1-6}$, $(C_{1-5})C_{1-6}$;

L_3 , C_{1-6} , C_{2-6} , C_{2-6} , C_{2-5} , $()C_{1-6}$, $()C_{1-6}$, $()C_{1-6}$
 C_{1-6} , C_{1-5} , $()C_{1-6}$, $()C_{1-6}$, $(C_{1-5})C_{1-6}$, $()C_{1-6}$;

L_4 , C_{1-5} ;

L_5 , C_{1-5} ;

L_6 , C_{1-5} ;

L_7 , C_{1-5} ;

Q - NR_8R_9 , C_{2-15} , O, S, N , $1, 3$ 가 ;

R_6 , C_{1-8} , C_{1-6} , C_{2-8} , C_{3-7} , $(C_{3-7})C_{1-6}$, $()C_{1-6}$, C_{2-15} , $(C_{2-7})C_{1-6}$;

R_7 , H , C_{2-6} , $L_6, L_7 (R_6)$ 가 ;

R_8, R_9 , C_{1-6} , C_{1-8} , C_{3-8} , C_{3-7} , $(C_{3-7})C_{1-6}$, $()C_{1-6}$, C_{2-15} , $(C_{2-15})C_{1-6}$;

R_{10} , H, C_{1-8} , C_{3-8} , C_{3-7} , $(C_{3-7})C_{1-6}$, $()C_{1-6}$, $(C_{2-15})C_{1-6}$;

W - $CN, -CHO, C_{1-8}, (C_{1-8})-O-, ()C_{1-6}$ -
 $O-, -C(=O)R_x, -C(OH)R_xR_y, C_{1-8}, C_{1-8}, -NR_xR_y$;

, R_x R_y H, C₁₋₆, C₁₋₆, C₁₋₈,

, C₁₋₃, 1, 3,

Q 가, C₂₋₆, C₁₋₈, N(C₁₋₆)(C₁₋₈), NH
(C₁₋₈), (C₁₋₃)(C₁₋₈), O(C₁₋₈), O(C₁₋₆), O(C₃₋
6 (C₁₋₃), N(C₁₋₆)(C₁₋₃), O(C₁₋₃), C₁₋₃)

가

;

() 가

()

(ADHD), / / (:), H₃

³NEXTM), (ALLEGRATM) H₁ (ZYRTECTM) (CLARITINTM), H (CLARI

, (PAXILTM) (PROZACTM), (SSRI) H₃ (ZOLOFTTM)

가

A.

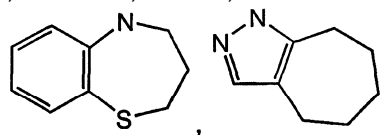
가

1가

CH₂), (-CH₂-CH₂-) 1 4 (-CH₂CH₂CH₂-) 2 가 (

, n-, s-, t-, n-

3- 8-
 3- 8-
 -1,3-
 .2가
 (-C₆H₄-) -1,4- -1,3-
 , (C=O) S 1 4 가 5-, 6- 7- N, O, SO, SO₂
 13- 14- , 9- 10-
 1 2 가 1 3
 4- , 2- , 2- , 2- , 2-
 , N- -
 , 1,3- -1,2-
 , Q가 - Q
 N-(C₁₋₆)
 N-
 , ()C₁₋₆ , 2,3- , 2-
 , ()C₁₋₆ , ()C₁₋₆ , ()C₁₋₆
 1 3 가
 Q 4-(4- -2-) - -1- ; 4-(4- -2-) -
 -1- ; 2-([1,2,4] -) - -1- ; 3-(-2-) -1- ; 4-(-1-)
 -1- ; 4-(-2-) -1- ; 4-(-2-) -1- ; 4-(-2-)
 -1- ; 4-(4- -2-)-[1,4] -1- ; 5-(-5-)-2,5- - [2.2.
 1] -2-
 -N-
 [2,3-c] , [3,1-b] , [2,3-b] , (, 1,2,3,4-
 (, 3,4- -4- -) , (, 1,2,3,4-) ,
 (4,5,6,7-) ,



RT	=	
TEA	=	
TFA	=	
THF	=	

B.

(I)

- (a) R₅ C₁₋₅, C₃₋₄, C₃₋₆, (C₃₋₆) C₁, () C₁₋₃,
() C₃₋₄ ;
- (b) R₅ C₃₋₅, C₃₋₆, (C₃₋₆) C₁ ;
- (c) R₂ R₃ G ;
- (d) R₂ G ;
- (e) R₃ G ;
- (f) L₁ C₂₋₃ ;
- (g) L₂ C₁₋₆, (C₁₋₅) C₁₋₆, -C₁₋₆ ;
- (h) L₂ ;
- (i) L₃ , , , ;
- (j) Q - - C₂₋₅ ;
- (k) Q , N-(C₁₋₆) , , , , ;
- (l) Q , , C₁₋₆, C₁₋₈, N(C₁₋₆)(C₁₋₈), NH(C₁₋₈), (C₁₋₃)(C₁₋₈), O(C₁₋₈), O(C₁₋₆), O(C₃₋₆),
1 3), (C₁₋₃) , N(C₁₋₆)(C₁₋₃) , O(C₁₋₃)
N- N- (, 1 3
, , C₁₋₃) ;
- (m) Q , , , , (C₁₋₆) , , , 2,3-
, , 2- , (C₁₋₆) , , (C₁₋₆)
, , (C₁₋₆) , C₁₋₆ ;
- (n) Q N- ;
- (o) Q NR₈R₉(, R₈ R₉, C₁₋₈, C₃₋₈, C₃₋₇, (C₃₋₇)
) C₁₋₆, C₂₋₅ , (C₂₋₅) C₁₋₆, () C₁₋₆ ;
- (p) R₈ R₉ ;

4-[4-(1-)-]- , [4-(1-)-]- , 4-[4-(1-)-]-
)-]- , 4-[4-(1-)-]-)-]- , 4-[4-(1-)-]-

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

가

H₃-

(PET)

(SPECT)

['Protective Groups in Organic Chemistry', ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene amp; P. G. M. Wuts, 'Protective Groups in Organic Synthesis', 3ed., John Wiley amp; Sons, 1999]

가

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

1- , 1-(2-) , 1- -1- , 1- -1-
 , 1- -1- -2- , 2,2,2- , 2- , 2-() , t-
 , p- , p- , 2,4-

p- , 3,4- , o- , p- , p- , 2,6-
 , p- , 2- 4- , 3- -2- N- , , p,p'-
 , 5- , , p- , (p-)
) , 4,4',4''- () , 4,4',4''- (4,5-)
) (4',4''-) , 1,1- (4-) -1'- , 3-(-1-
 -10-) , 1,3- -2- S,S- 가 , 9-(9-) , 9-(9-

t-

, 2,7- -t- -[9-(10,10- , 9- -10,10,10,10- , 9-(2-) , 9-(2,7-)] 4-

, 1,1- -2- 2,2,2- , 2- , 2- , 1-(1-)-1-
) , 1-(3,5- -t- , 1,1- -2,2- , 1,1- -2,2,2- , 1- -1-(4
) , t- , 1- , , , 1- , 2-(2'- 4'-) , 2-(N,N-
, , , , p- , p- , p- , p- , 4- , 8- , N-
, 9- , , 2,4- , 4-

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

-(10)- , N'-p- N'-

-(10)- , N'-p- N'-

, t- , S- , p- , ,
) , 1,1- , p- , 2,2- , o-(N,N-
, 2- , -3-(N,N-) , 1,1- || (2-) , 2-
, 1- , -1- , , 1- , p-(p'-) , 1- , 1-
, 1- -1- , 1- -1-(4-) , -1-(3,5-) , 1- || -1-(p-)
) 2,4,6- , p-() , 2,4,6- -t- , 4-(

가 :

N- , N- , N- , N- , N- , N- , N- , N- , N-3- , N-3-
, N- , N-3- , N- , N- , N-p- .

N-o- , N-o- , N- , (N'-) , N-
3-(p-) , N-3-(o-) , N-2- -2-(o-) , N-
-2- -2-(o-) , N-4- , N-3- -3- , N-o- , N-
, N- , N-o- , N-o-() 4,5- -3- -2- .

N- , N- , N-2,3- , N-2,5- , N-1,1,4,4-
 가 , 5- 1,3- -1,3,5- -2- , 5- 1,3- -1,3,5-
 -2- 1- 3,5- -4- .

-NH

NH N- , N- 가 :

N- N-

N- , N- , N-[2-()] , N-3- , N-(1- -4- -2- -
 3- -3-), 4 , N- , N-4- , N- (4-) , N-5- , N-
 , N-(4-) , N-9- , N-2,7- -9- , N-
 N-2- N'- .

N-1,1- , N- , N-p- , N- , N-[(2-)]
 N-(N',N'-).

, (2,2,2-), , (2-)

3- , 1,3- , 4- 1,3- , 5- -1,3- , 5,5- -1,3- , 5-(2-)-1,
)-1,3- , 4,5- -1,3- , 4-(3-)-1,3- , 4- -1,3- , 4-(2-
 -1,3- , O,O'- 1,5- -3H-2,4-

S'- , S,S'- S,S'- S,S'- , S,S'- , S,S'- , S,S'- , S,
 S,S'-

1,3- , 1,3- 1,5- -3H-2,4-

-S-2-() O- -S- , O- -S- -S- , O-

1,3-

O-

O- , O- , O-1- O-

N,N- 2,4-

O- , O- O-

, 2,3-) (MAD) 가 -1,3- , , 1- -2-(1'-) , N,N'- (2,6- -t- -4-

- -
- - , 4- -1,3- , , S- , 가 , i- ,
가 .

, 9- , 2-() , , p- , -
, p- , N-

2-
2- , 1,3- 2,2,2- , 2- , 가- , 2-() ,
2- , 2-() , 2-(p-) , 2-(p-) , 2-(2'-) ,
, 2-() , 1- -1- , t- , , 3- -1- , 4-(
) -2- -1- , , - , p-() .

) , 5- , 1- , 2-((o-) , 9- , 2-(9,10-
, 4- , o- , p- , p- , 2,6-) -6- , 2,4,6- , p-
, p-P- , 4-() , 4- ,

-t- , t- , i- ,

, 2- -1,3- , 4- -5- -1,3- , 5- -4- -1,3-
(III) 가 .

-n-

, N,N- , 5,6- , o- , N-7-
, N-8- -1,2,3,4- p-P- 가 .

N- N,N'-

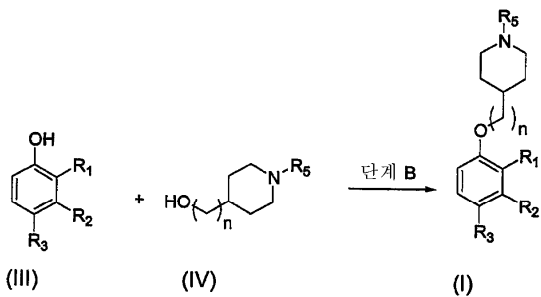
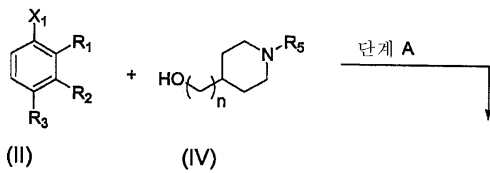
C.

1-10 1-86 ,

R₁ R₂ R₃ , R₃

(I) 1

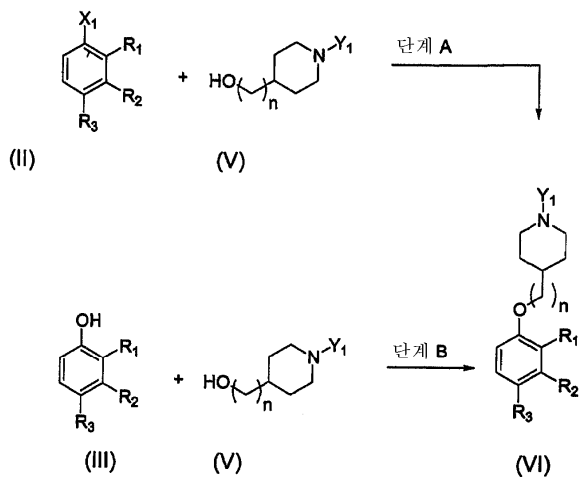
1



(I) (II) (III) (IV) 1
 Cs₂CO₃, K₂CO₃, Na₂CO₃, NaOH, KOH, LDA, LHMDS
 200 , DMF, DMA, THF, DME, DCM, DMSO
 (IV) Cs₂CO₃, Na₂CO₃, DMF, DMF, DMA
 Cs₂CO₃ 80, K₂CO₃ 150, Na₂CO₃, DMF, X₁, Cs₂CO₃
 NO₂, -CHO, -CN, CO₂R₁₅, COR₁₆, -CONR₁₇R₁₈, R₁, R₃, X₁, R₁, R₃, (IV)
 Br, -F, -Cl, R₁, R₃, -NO₂, -CHO, -CN, X₁, COR₁₆, -F, -Cl, -
 X₁, DBAD, DEAD, Mitsunobu () (III)
 (IV) (I) (I) (III)

(VI) 2 (V)

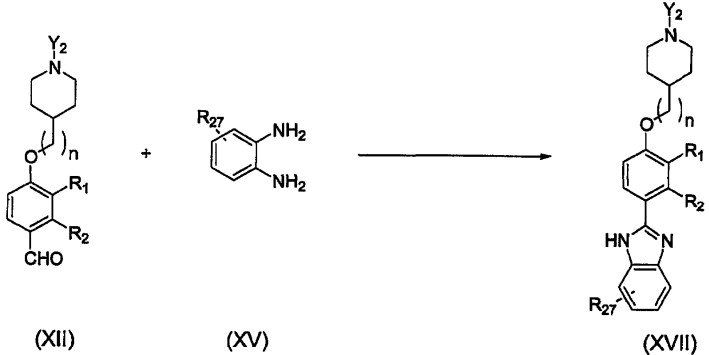
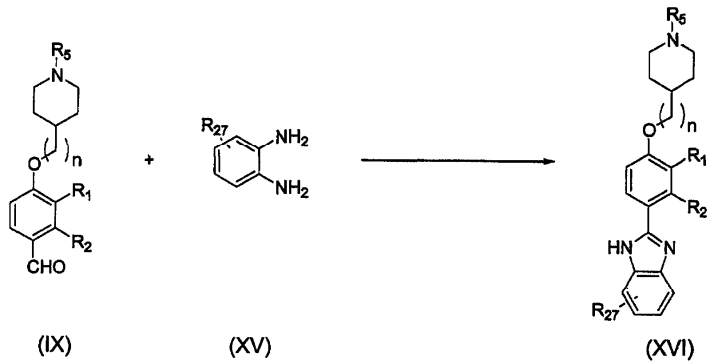
2



(VI) (V) (II) (III) 1 A
 B Y₁
 ; - ,2,2,2- ; - ; ,4-

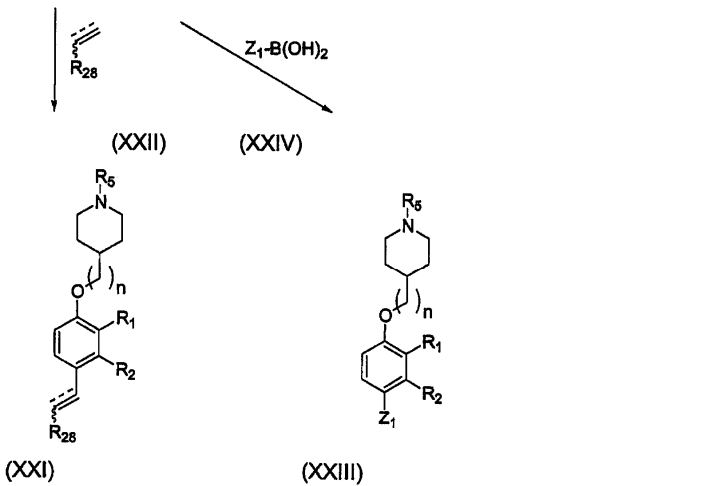
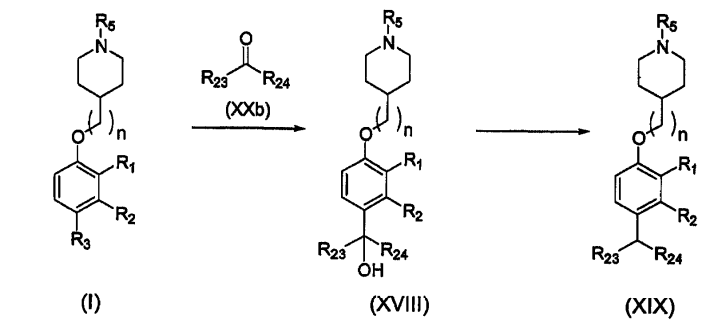
(XI) 3 (VI)

3



(XVI) 가 (XVI) (IX) 80 120 (XV) DMA (IX) (XVII) , Y₂ 가 (XII) (XV) (XXI), (XXIII) (XIX) 5 (XVII) 5

5



(XXI)

(XXII)

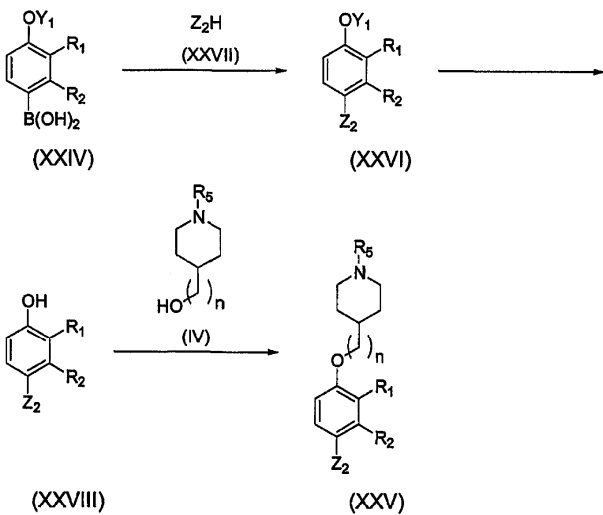
Sonogashira

Heck

(XXII)

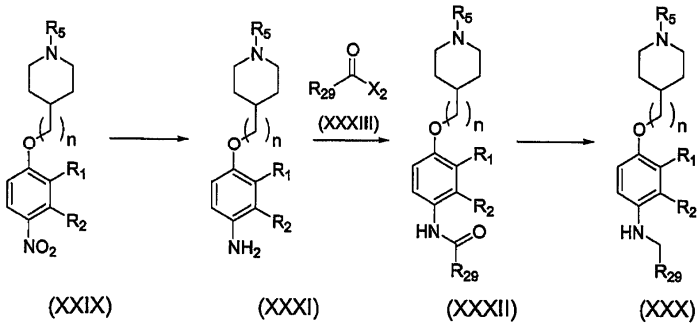
Br I I가 R₃가 (I) (I)
 (XXII) Pd₂(dba)₃, PdCl₂ Pd(OAc)₂ 가
 (XXII) Cu(I) CuI가 (, XXII가) 가
 3, DMF, DME, DMA, , DCM K₂CO₃ , Na₂CO₃, K₂CO₃ THF,
 THF DME (XXIII) R₃가 , Br I (I)
 (XIX) (I) (XXIV) (I)
 (XXb) R₃가 , Br I (I)
 (XIX) (XVIII) -100 0 , -78 THF n-BuLi .
 , HCl, AcOH, TFA , THF (XVIII)
 (XVIII) TFA TFA
 DCM (XXV) 6 (XXIV)

6



Y₁ (XXVII) (XXIV) Z₂H가 (XXVI) , -
 A (XXVII) Z₂가 Cu(OAc)₂ , (XXVI) , DCM 4
 1 (XXVIII) , (XXV) Y
 1 B (IV) (XXVIII) (XXV)
 (XXX) 7 (XXIX)

7



(XXXI) (XXIX) (XXXII) (XXX)

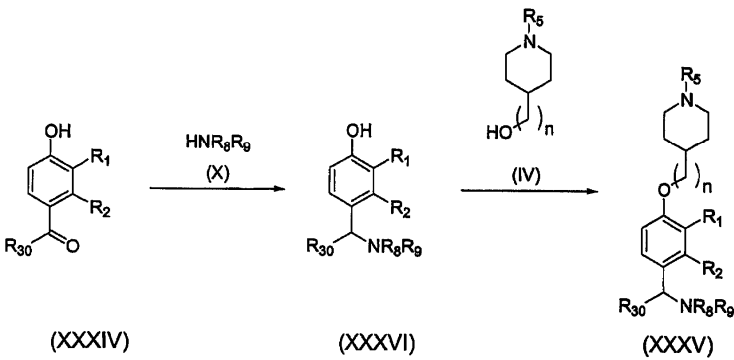
(XXXI) X₂ 가 X₂ Cl OH (XXXIII) SnCl₂ (XXXII)

DCC X₂ 가 OH (XXXI) DCM THF (XXXIII) (XXXI)

l) ; BH₃:THF, BH₃:Me₂S. (XXX) (XXXI)

(XXXV) 8 BH₃:Me₂S DCM THF (XXXIII) THF (XXXI)

8



(XXXIV) (XXXVI) (XXXV)

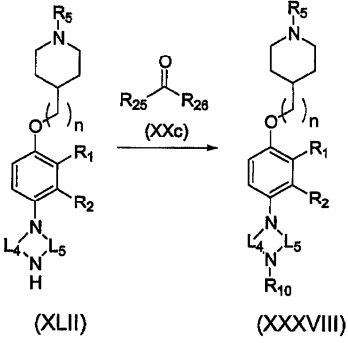
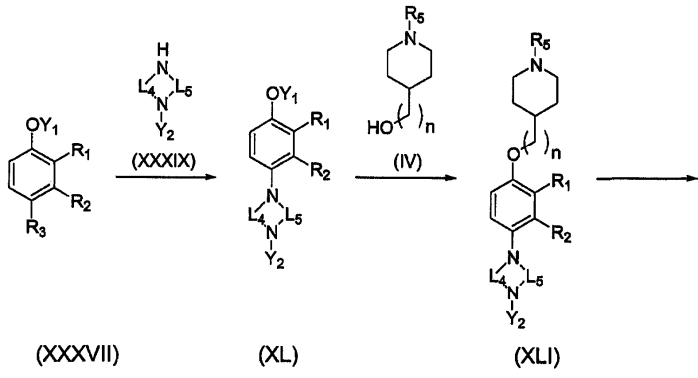
(X) 가 (XXXVI) , 1,2- pH 7 pH

(X) 가가 (XXXVI) , (IV) 가 pH

(X) 2 (XXXVI) (IV) 1 B

(XXXVIII) 9

9



R₃ 가 Br, I, t-, BINAP(2,2'-bis(1,1'-naphthyl)-1,1'-diyl) (XXXVII) (O), THF, 18-

-6() (XXXIX) (XL) (XL) Y₁ (XLII) (IV) 1, B (XLI) (ortho)

nal protection) (XXXVIII) Y₁ Y₂ 가 (XLII) (XLI) (ortho)

, 1,2- (XLII) (XXc) 가 (XXXVIII)

pH 7 pH 가 가가 ,

(XLIV) 10 (XLIII)

르

, ed. H. Bundgaard, Elsevier, 1985

가

가

가

가

(,)

가

가

, H₁

SSRI

(
)

)

(

1 , 1

0 mg, 150 mg

5 1000 mg

, 5 mg, 7 mg, 10 mg, 15 mg, 20 mg, 35 mg, 50 mg, 75 mg, 100 mg, 12

가

가

)- -p- -1-

(-)- -p- -d- / (+

HPLC

1

1

1

2, 3

4

가

가

가

가,

ADHD 가

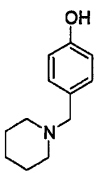
1 1 1 1,000 mg
 00, 250 500 1.0, 5.0, 10.0, 15.0, 25.0, 50.0, 1
 mg/kg 0.01mg/kg 20mg/kg 0.05mg/kg 10mg/kg 1 1 1 0.02
 10mg/kg 1 4

2.

H₁, H₂ SSRI (NSSRI)

b) (a) 2 가 ;(
 , (c) ;
 가 ; .3

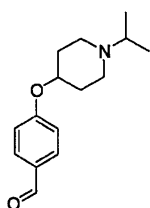
1



4- -1- -

DCE(200ml) 4- (24g) (10g), (8.9ml) (4.7ml)
 0ml) DCM(5 x 100ml) . 16 (5.5g) . (10

2



K_i = 36 nM

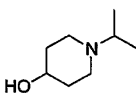
4-(1- - -4-)-

DMF(40ml) 3 (5.7g), 4- (1.7ml) (13mg)
 100 ° C 22 가 (100ml) 가 (3 x 100ml)
) (2.0g) (0-15% 2M

¹H NMR

(400 MHz, CDCl₃): 9.86 (s, 1H), 7.81 (d, J=8.6 Hz, 2H), 6.99 (d, J=8.6 Hz, 2H), 4.43 (m, 1H), 2.82-2.72 (m, 3H), 2.42 (m, 4H), 2.08-2.00 (m, 2H), 1.89-1.80 (m, 2H), 1.06 (d, J=6.6 Hz, 6H).

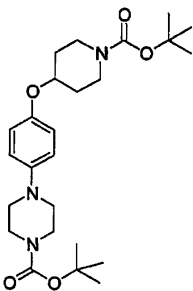
3



1- - -4-

(350ml) 1- - -4- (51.2g) 가 50 ° C
 (300ml) 5% NaOH (300ml) (7.30g) . 48 DCM
 (35.3g) . 6 (68 , 1.5mm Hg) DCM

4



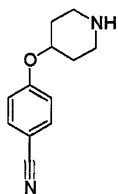
4-[4-(1-tert- - -4-)-]- -1- tert-
 4-(4- -)- -1- tert- (3.11g), 4- - -1-
 -tert- (3.51g), (3.78g) . 24 (6.25g; : 3 mmol/g) DCM 100ml

(15-30%

/)

(3.20g)

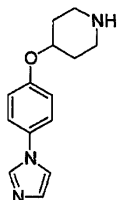
5



4-(4-(piperidin-4-yloxy)phenyl)benzonitrile

DMF (100ml) 4- (500ml) - (300ml) -1- (60%, 3.8g) (1L) tert- (14.99g) (3x400 ml) (20ml) DCM(3x300 ml) 4- (10.65) 16 , 5% (12.23g)

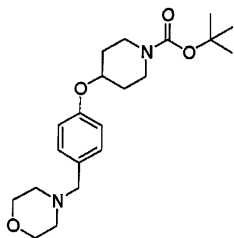
6



4-(4-(piperidin-4-yloxy)phenyl)imidazole

THF(10ml) 4- (2.4g) -1- THF(5ml) tert- (1.6g), 4- (2.1g) -1- (1.2g) .24 (1.9g) (10ml) (0-10% 2M 2M) /DCM (14ml) .24 (1.1g) 10% DCM (2x15ml) (781ml) 1:1 (20ml) DCM(20ml) 가 .10 (1.2g)

7

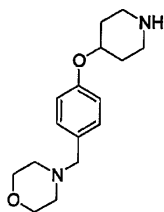


4-(4-(tert-butoxycarbonylpiperidin-4-yloxy)phenyl)morpholine

DMF(320ml) tert- (52.5g) 4- (3x500 ml) -1- 48 110 가 (32.4g), 4- (100ml) 가 (20.0g)) (7.0g) (2x200ml) 가 (2.4ml) (1.3ml) (100ml) (100ml) (47.2g) . DCM(300ml) (5.9)

g) . 16 (100ml) 10% (50 ml) DCM (2 x 500 ml)
 (0.5 - 5.5% 2M) (100ml) /DCM (6.6g)

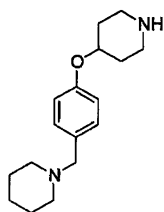
8

K_i = 1600 nM

4 - [4 - () -] -
 (40ml) 11 (6.6g) (30ml) 4N
 16 10% (50mL)
 DCM(2x500ml) (200ml) (200ml)
 (5.4g)

¹H NMR (400 MHz, CDCl₃): 7.21 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.38-4.34 (m, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.43 (s, 2H), 3.19-3.13 (m, 2H), 2.42 (t, J = 4.3 Hz, 2H), 2.10-2.00 (m, 2H), 1.73-1.65 (m, 2H).

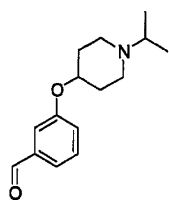
9

K_i = 48 nM

1 - [4 - () -] -
 DMF(320mL) tert - (32.4g), 4- (20.0g),
 (52.5g) 110 48 가 (400mL) 가
 (3x500mL) (2x200mL) (3x200ml) (200ml)
 2g) DCM(300mL) (7.0g), (2.8mL), (1.2mL) (47.
 , DCM(2x500mL) (5.9g) 16 10% (50mL)
 (8.6g) (100ml) (200ml) /DCM
 (30ml) (40ml) 4N
 16 10% (50mL) DCM(2x500ml)
 ((0.5 - 5.5% 2M) /DCM) (3.4g)

¹H NMR (400 MHz, CDCl₃): 7.20 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.37-4.30 (m, 1H), 3.40 (s, 2H), 3.17-3.11 (m, 2H), 2.75-2.68 (m, 2H), 2.35 (br s, 4H), 2.03-1.99 (m, 2H), 1.69-1.61 (m, 2H), 1.59-1.53 (m, 2H), 1.43-1.39 (m, 2H).

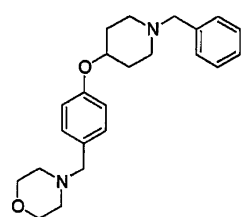
10



3-(1- - -4-)-

THF (5mL) 3 (716mL), 3- (672mL) (1.6g)
 THF (5mL) -tert- (1.4g) . 16 (20mL)
 (20mL) 20% (20mL) (20mL)
 (0.1-10% 2M /DCM) (50
 mg)

11

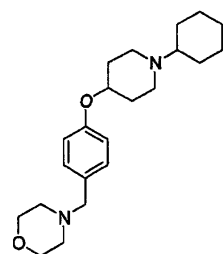
K_i = 92 nM

4-[4-(1- - -4-)-]

(0.068mL) THF (1mL) 10 (137mL), (0.051mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5-5.5% 2M /DCM) (94mg)

¹H NMR (400 MHz, CDCl₃): 7.33-7.23 (m, 5H),
 7.20 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.32-4.23 (m, 1H), 3.69 (t, J = 4.6
 Hz, 4H), 3.53 (s, 2H), 3.42 (s, 2H), 2.77-2.73 (m, 2H), 2.42 (t, J = 4.3 Hz, 4H), 2.32-
 2.26 (m, 2H), 2.02-1.96 (m, 2H), 1.85-1.77 (m, 2H).

12

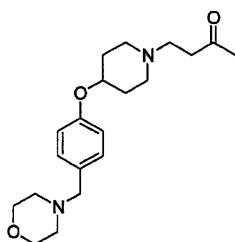
K_i = 3.0 nM

4-[4-(1- - -4-)-]

(0.068mL) THF (1mL) 10 (137mL), (0.052mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5-5.5% 2M /DCM) (73mg)

¹H NMR (400 MHz, CDCl₃): 7.21 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.33-4.29 (m, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.42 (s, 2H), 2.92-2.86 (m, 2H), 2.57-2.51 (m, 2H), 2.43-2.28 (m, 7H), 2.09-2.02 (m, 2H), 1.92-1.81 (m, 6H), 1.31-1.20 (m, 4H).

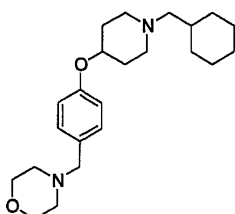
13

K_i = 62 nM

4-[4-(4-(0.068mL) THF (1mL) 10 (137mL), 4-(0.036mL) 가 .16 가 (44mL) 가 .4 (0.5-5.5% 2M /DCM) DCM(3x3mL) (33mg) .

¹H NMR (400 MHz, CDCl₃): 7.04 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.32-4.27 (m, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.42 (s, 2H), 2.74-2.62 (m, 4H), 2.43 (t, J = 4.2 Hz, 4H), 2.33-2.27 (m, 2H), 2.18 (s, 3H), 2.02-1.76 (m, 6H).

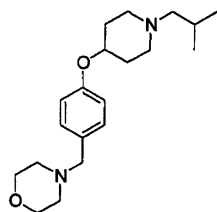
14

K_i = 154 nM

4-[4-(1-(0.068mL) THF (1mL) 10 (137mL), (0.061mL) 가 .16 가 (0.036mL) 가 .4 (0.5-5.5% 2M /DCM) DCM(3x3mL) (100mg) .

¹H NMR (400 MHz, CDCl₃): 7.20 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.29-4.23 (m, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.42 (s, 2H), 2.70 (t, J = 4.6 Hz, 2H), 2.43 (t, J = 4.2 Hz, 4H), 2.20 (t, J = 9.1 Hz, 1H), 2.13 (d, J = 7.1 Hz, 1H), 2.00-1.64 (m, 9H), 1.52-1.43 (m, 1H), 1.28-1.13 (m, 3H), 0.91-0.82 (m, 2H).

15



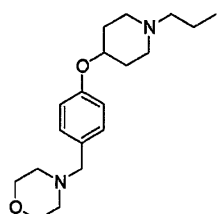
$K_i = 3.5 \text{ nM}$

4 - [4 - - -4 -) -]

(0.068mL) THF (1mL) 10 (137mL), (0.091mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5 - 5.5% 2M /DCM) (198mg) .

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.20 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 4.29-4.23 (m, 1H), 3.70 (t, $J = 4.7$ Hz, 4H), 3.42 (s, 2H), 2.72-2.69 (m, 2H), 2.42 (t, $J = 4.4$ Hz, 4H), 2.19 (t, $J = 9.0$ Hz, 1H), 2.09 (d, $J = 7.3$ Hz, 1H), 2.00-1.95 (m, 2H), 1.83-1.72 (m, 3H), 0.90 (d, $J = 6.6$ Hz, 6H).

16



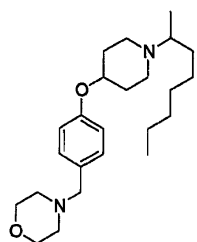
$K_i = 6.0 \text{ nM}$

4 - [4 - - -4 -) -]

(0.068mL) THF (1mL) 10 (137mL), (0.072mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5 - 5.5% 2M /DCM) (85mg) .

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.21 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 4.34-4.28 (m, 1H), 3.70 (t, $J = 4.7$ Hz, 4H), 3.42 (s, 2H), 2.79-2.75 (m, 2H), 2.42 (t, $J = 4.3$ Hz, 4H), 2.37-2.33 (m, 4H), 2.06-1.99 (m, 2H), 1.88-1.80 (m, 2H), 1.59-1.50 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 6H).

17



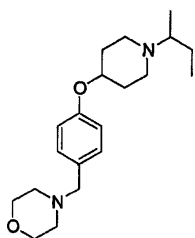
$K_i = 380 \text{ nM}$

4 - { 4 - [1 -) - -4 -] - }

(0.068mL) THF (1mL) 10 (137mL), 2- (0.156mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 .5-5.5% 2M /DCM) (108mg) . (0

¹H NMR (400 MHz, CDCl₃): 7.20 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.29-4.24 (m, 1H), 3.70 (t, J = 4.7 Hz, 4H), 3.42 (s, 2H), 2.80-2.73 (m, 2H), 2.60-2.57 (m, 1H), 2.48-2.33 (m, 6H), 1.99 (m, 2H), 1.84-1.74 (m, 1H), 1.57-1.54 (m, 9H), 0.94 (d, J = 6.5 Hz, 3H), 0.90-0.87 (m, 3H).

18

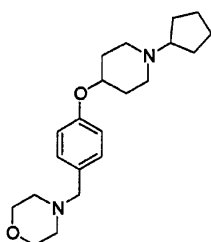
K_i = 1.9 nM

4- [4-(1-2 - - 4-)-]

(0.068mL) THF (1mL) 10 (137mL), 2- (0.089mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5-5.5% 2M /DCM), (75mg) .

¹H NMR (400 MHz, CDCl₃): 7.20 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.29-4.24 (m, 1H), 3.70 (t, J = 4.7 Hz, 4H), 3.42 (s, 2H), 2.81-2.73 (m, 2H), 2.51-2.32 (m, 6H), 2.05-1.95 (m, 2H), 1.83-1.75 (m, 2H), 1.62-1.56 (m, 1H), 1.34-1.26 (m, 2H), 0.99 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H).

19

K_i = 1.8 nM

4- [4-(1- - 4-)-]

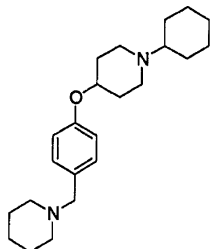
(0.068mL) THF (1mL) 10 (137mL), (0.088mL)
 (13mg) 가 . 16 가 (0.036mL) 가 . 4
 DCM(3x3mL)
 (0.5-5.5% 2M /DCM), (168mg) .

¹H NMR (400 MHz, CDCl₃): 7.22 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.44-4.35 (m, 1H), 3.70 (t, J = 4.7 Hz, 4H), 3.43 (s, 2H), 2.95-2.88 (m, 1H), 2.76-2.54 (m, 2H), 2.42 (t, J = 4.4 Hz, 4H), 2.16-2.08 (m, 2H), 1.94-1.91 (m, 4H), 1.78-1.72 (m, 2H), 1.62-1.57 (m, 4H).

¹H NMR (400

MHz, CDCl₃): 7.34-7.23 (m, 5H), 7.21 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.32-4.26 (m, 1H), 3.53 (s, 2H), 3.48 (s, 2H), 2.90 (bs, 1H), 2.76-2.72 (m, 2H), 2.43 (bs, 3H), 2.39 (t, J = 8.7 Hz, 2H), 2.01-1.96 (m, 2H), 1.85-1.77 (m, 2H), 1.63-1.57 (m, 4H), 1.47-1.38 (m, 2H).

25

K_i = 6.9 nM

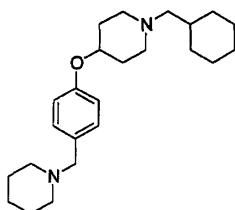
1 - [4 - (1 - - - 4 -) -] -

L) (0.068mL) THF (1mL) 9 (137mL), (137mL), (0.052m
 (13mg) 가 . 16
 DCM(3x3mL) . (0.5-5.5% 2M
 /DCM), (141mg) .

¹H NMR (400

MHz, CDCl₃): 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.30-4.25 (m, 1H), 3.40 (s, 2H), 2.88-2.83 (m, 2H), 2.50-2.45 (m, 2H), 2.40-2.29 (m, 5H), 2.07-1.74 (m, 8H), 1.65-1.62 (m, 1H), 1.59-1.54 (m, 4H), 1.45-1.42 (m, 4H), 1.30-1.19 (m, 4H), 1.14-1.07 (m, 1H).

26

K_i = 10 nM

1 - [4 - (1 - - - 4 -) -] -

(0.068mL) THF (1mL) 9 (137mL), (0.061mL),
 (13mg) 가 . 16
 DCM(3x3mL) . (0.5-5.5% 2M
 /DCM), (163mg) .

¹H NMR (400

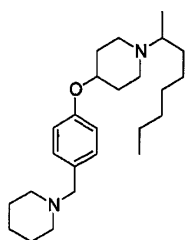
MHz, CDCl₃): 7.19 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.27-4.23 (m, 1H), 3.40 (s, 2H), 2.76-2.64 (m, 2H), 2.43-2.28 (bs, 4H), 2.24-2.08 (m, 4H), 2.03-1.92 (m, 2H), 1.65-1.62 (m, 1H), 1.85-1.36 (m, 13H), 1.30-1.09 (m, 4H), 0.93-0.79 (m, 2H).

27

(0.068mL) THF (1mL) 9 (137mL), (0.091mL),
 (13mg) 가 . 16
 DCM(3x3mL) . (91mg) . (0.5-5.5% 2M
 /DCM),

¹H NMR (400
 MHz, CDCl₃): 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.28-4.23 (m, 1H),
 3.39 (s, 2H), 2.72-2.69 (m, 2H), 2.35 (bs, 4H), 2.21-2.16 (m, 2H), 2.09 (d, 2H), 2.01-
 1.95 (m, 3H), 1.59-1.53 (m, 3H), 1.44-1.38 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H).

30

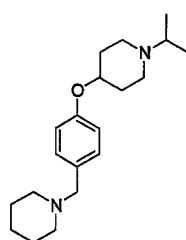
K_i = 16 nM

1 - { 4 - [1 - (1 -) - 4 -] - } -

(0.068mL) THF (1mL) 9 (137mL), 2- (0.156mL),
 (13mg) 가 . 16
 DCM(3x3mL) . (228mg) . (0.5-5.5% 2M /DCM),

¹H NMR (400
 MHz, CDCl₃): 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.28-4.22 (m, 1H),
 3.40 (s, 2H), 2.79-2.72 (m, 2H), 2.59-2.55 (m, 1H), 2.46-2.31 (m, 6H), 1.83-1.73 (m,
 2H), 1.57-1.53 (m, 4H), 1.43-1.38 (m, 8H), 1.32-1.21 (m, 10H), 0.98 (d, J = 6.5 Hz,
 3H), 0.89 (t, J = 6.8 Hz, 3H).

31

K_i = 0.5 nM

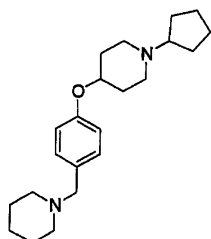
4 - [4 - [1 - 2 - - 4 -) -] -

(0.068mL) THF (1mL) 9 (137mL), 2- (0.089mL),
 (13mg) 가 . 16
 DCM(3x3mL) . (164mg) . (0.5-5.5% 2M /DCM),

¹H NMR (400

MHz, CDCl₃): 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.28-4.22 (m, 1H),
3.39 (s, 2H), 2.89-2.72 (m, 2H), 2.50-2.31 (m, 6H), 1.98-1.95 (m, 2H), 1.83-1.72 (m,
2H), 1.59-1.53 (m, 6H), 1.43-1.37 (m, 2H), 1.34-1.23 (m, 1H), 0.98 (d, J = 6.5 Hz,
3H), 0.90 (t, J = 7.4 Hz, 3H).

32

K_i = 0.7 nM

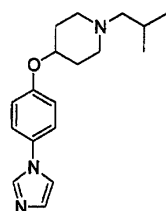
1 - [4 - [1 - - 4 -) -] -

(0.068mL) THF (1mL) 9 (137mL), (0.088mL),
(13mg) 가 . 16
DCM(3x3mL) . (0.5-5.5% 2M /DC
M), (250mg) .

¹H NMR (400

MHz, CDCl₃): 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.34-4.23 (m, 1H),
3.39 (s, 2H), 2.87-2.73 (m, 2H), 2.55-2.47 (m, 1H), 2.40-2.26 (m, 6H), 2.05-1.95 (m,
2H), 1.91-1.79 (m, 4H), 1.73-1.49 (m, 8H), 1.46-1.37 (m, 4H).

33

K_i = 9 nM

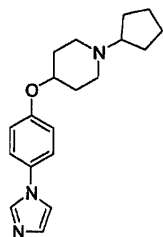
4 - (4 - - 1 - -) - -

THF (1mL) 6 (130mL), (0.06mL), (3mg)
(0,07mL) . 16 (0-8% 2M
/DCM), (18mg) .

¹H

NMR (400 MHz, CDCl₃): 7.75 (t, J = 1.2 Hz, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.20 (t, J =
1.4 Hz, 1H), 7.18 (t, J = 1.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 4.35-4.27 (m, 1H),
2.76-2.67 (m, 2H), 2.26-2.18 (m, 2H), 2.10 (d, J = 7.24 Hz, 2H), 2.05-1.96 (m, 2H),
1.87-1.73 (m, 3 H), 0.90 (d, J = 6.5 Hz, 6H).

34



$K_i = 1.4 \text{ nM}$

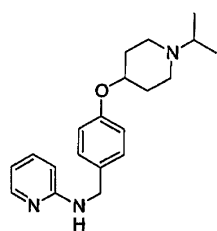
1- (4-(4-cyclopentylpiperidin-1-yl)phenoxy)pyrrole

THF (0.1mL) 6 (130mL), (0.06mL), (3mg)
 (0.07mL) .16 (0-8% 2M
 /DCM), (57mg)

^1H

NMR (400 MHz, CDCl_3): 7.75 (t, $J = 1.2 \text{ Hz}$, 1H), 7.28 (d, $J = 9.0 \text{ Hz}$, 2H), 7.20 (t, $J = 1.2 \text{ Hz}$, 1H), 7.17 (t, $J = 1.2 \text{ Hz}$, 1H), 6.99 (d, $J = 9.0 \text{ Hz}$, 2H), 4.39-4.29 (m, 1H), 2.87-2.77 (br m, 1H), 2.57-2.48 (m, 1H), 2.40-2.30 (m, 2H), 2.08-1.99 (m, 2H), 1.94-1.82 (m, 5H), 1.75-1.64 (m, 2H), 1.61-1.61 (m, 2H), 1.47-1.37 (m, 2H).

35



$K_i = 3.4 \text{ nM}$

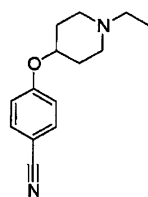
[4-(1-(4-isopropylpiperidin-1-yl)phenoxy)pyrrole]

DCM (7mL) 2 (522mL), 2- (230mg), (0.013mL)
 (720mL) .16 10% (8mL)
 DCM(3x10mL) (1-7% 2M /DCM), (417mg)

^1H NMR (400 MHz, CDCl_3): 8.10 (m, 1H), 7.40

(m, 1H), 7.28-7.24 (m, 2H), 6.9-6.85 (m, 2H), 6.58 (m, 1H), 6.37 (m, 1H), 4.77 (m, 1H), 4.41 (d, $J=5.8 \text{ Hz}$, 2H), 4.28 (m, 1H), 2.82-2.71 (m, 4H), 2.39 (m, 3H), 2.05-1.97 (m, 3H), 1.85-1.76 (m, 3H), 1.06 (d, $J=6.6 \text{ Hz}$, 6H).

36



$K_i = 600 \text{ nM}$

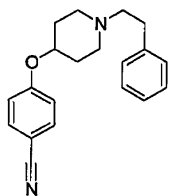
4-(1-(4-ethylpiperidin-1-yl)phenoxy)pyrrole

DCM (3mL) 5 (226mg), (0.5mL), (0.019mL)

(360mL) . 16 (10% (5mL)
 DCM(3x10mL) .
 (1 - 7% 2M /DCM), (67mg) .

¹H NMR (400 MHz, CDCl₃): 7.53 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H),
 4.37 (m, 1H), 2.71 (m, 2H), 2.41 (q, J=7.1, 2H), 2.28 (m, 2H), 1.99 (m, 2H), 1.82 (m,
 2H), 1.07 (t, J=7.1, 3H).

37

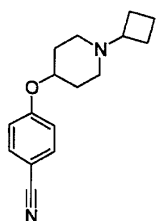
K_i = 6000 nM

4-(1- - -4-)-

DCM (3mL) 5 (203mg), (0.14mL), (0.08mL)
 (320mL) . 16 10% (5mL)
 DCM(3x10mL) () .
 (1 - 7% 2M /DCM), (145mg) .

¹H NMR (400 MHz, CDCl₃): 7.58 (d, J=8.8 Hz,
 2H), 7.32-7.28 (m, 2H), 7.21 (m, 3H), 6.94 (d, J=8.8 Hz, 2H), 4.45 (br, 1H), 2.84 (br,
 4H), 2.66 (br, 2H), 2.42 (br, 1.5H), 2.04 (br, 1.5H), 1.91 (br, 2H), 1.55 (br, 1H).

38

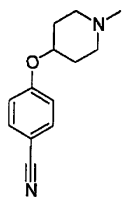
K_i = 24 nM

4-(1- - -4-)-

DCM (3mL) 5 (206mg), (0.1mL), (0.08mL)
 (320mL) . 16 10% (5mL)
 DCM(3x10mL) () .
 (1 - 7% 2M /DCM), (66mg) .

¹H NMR (400 MHz, CDCl₃): 7.58 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H),
 4.41 (br, 1H), 2.81-2.54 (br, m, 3H), 2.23-1.46 (br, m, 12H).

39



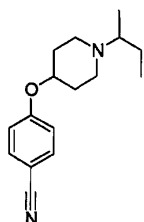
$K_i = 5000 \text{ nM}$

4-(1-(4-cyanophenoxy)pyrrolidin-4-yl)butane-1-thiol

DCM (3mL) 5 (213mg), (0.52g), (0.08mL)
 (340mL) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (91mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.57 (d, $J=9.1\text{Hz}$, 2H), 6.93 (d, $J=9.1 \text{ Hz}$, 2H), 4.40 (m, 1H), 2.69 (br, 2H), 2.37-2.29 (br, 2H), 2.32 (s, 3H), 2.03 (m, 2H), 1.87 (m, 2H).

40



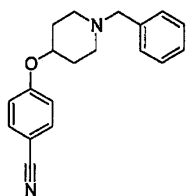
$K_i = 26 \text{ nM}$

4-(1-(4-cyanophenoxy)pyrrolidin-4-yl)butane-1-thiol

DCM (3mL) 5 (211mg), 2- (0.13mL), (0.07mL)
 (330mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (91mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.56 (d, $J=9.1 \text{ Hz}$, 2H), 6.93 (d, $J=9.1 \text{ Hz}$, 2H), 4.36 (br, 1H), 2.77 (br, 2H), 2.50 (br, 2H), 2.37 (br, 1H), 2.02 (br, 2H), 1.81 (br, 2H), 1.58 (br, 1H), 1.30 (m, 1H), 1.0 (br, d, $J=6.1 \text{ Hz}$, 3H), 0.91 (t, $J=7.3 \text{ Hz}$, 3H).

41



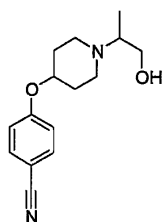
$K_i = 5000 \text{ nM}$

4-(1-(4-cyanophenoxy)pyrrolidin-4-yl)butane-1-thiol

DCM (3mL) 5 (203mg), (0.13mL), (0.07mL)
 (330mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (112mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.56 (d, $J=8.8$ Hz, 2H), 7.33 (m, 3H), 7.27 (m, 2H), 6.93 (d, $J=8.8$ Hz, 2H), 4.40 (br, 1H), 3.54 (br, 2H), 2.73 (br, 2H), 2.32 (br, 2H), 1.99 (br, 2H), 1.84 (br, 2H), 1.56 (br, 1H).

42



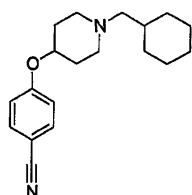
$K_i = 2000$ nM

4 - [1 - (2 - - 1 - -) - - 4 -) -

DCM (3mL) 5 (205mg), 1 - - 2 - (0.14mL), (0.08mL)
 (330mg) . 16 10% (5mL)
 , DCM(3x10mL) . () .
 (1 - 7% 2M /DCM), (161mg) .

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.57 (d, $J=8.8$ Hz, 2H), 6.93 (d, $J=8.8$ Hz, 2H), 4.42 (m, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 2.88 (m, 2H), 2.64 (m, 2H), 2.33 (m, 1H), 2.03 (m, 2H), 1.84 (m, 2H), 0.92 (d, $J=6.6$ Hz, 3H).

43



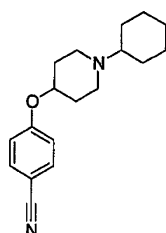
$K_i = 6000$ nM

4 - (1 - - - 4 -) -

DCM (3mL) 5 (221mg), (0.2mL) (0.08mL)
 (340mg) . 16 10% (5mL)
 , DCM(3x10mL) . () .
 (1 - 7% 2M /DCM), (205mg) .

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.57 (d, $J=9.1$ Hz, 2H), 6.93 (d, $J=9.1$ Hz, 2H), 4.37 (br, 1H), 2.69 (br, 2H), 2.22 (br, 2H), 2.14 (br, 2H), 1.98 (br, 2H), 1.86-1.63 (m, 7H), 1.47 (br, 1H), 1.29-1.10 (m, 3H), 0.88 (m, 2H).

44



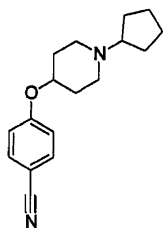
$K_i = 52$ nM

4-(1-(4-cyanophenoxy)piperidin-4-yl)pyrrolidine

DCM (3mL) 5 (202mg), (0.17mL) (0.08mL)
 (340mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (241mg)

¹H NMR (400 MHz, CDCl₃): 7.56 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 4.37 (m, 1H), 2.84 (m, 2H), 2.47 (m, 2H), 2.32 (br, 1H), 2.01 (br, 2H), 1.89-1.77 (m, 6H), 1.63 (m, 1H), 1.30-1.17 (m, 4H), 1.10 (m, 1H).

45

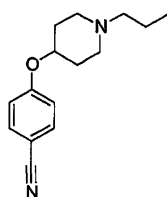
K_i = 19 nM

4-(1-(4-cyanophenoxy)piperidin-4-yl)pyrrolidine

DCM (3mL) 5 (210mg), (0.14mL) (0.08mL)
 (330mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (237mg)

¹H NMR (400 MHz, CDCl₃): 7.57 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.9 Hz, 2H), 4.40 (br, 1H), 2.91-2.23 (brr, m, 5H), 2.13-1.35 (m, 12H).

46

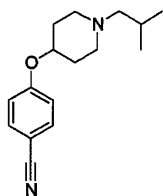
K_i = 250 nM

4-(1-(4-cyanophenoxy)piperidin-4-yl)pyrrolidine

DCM (3mL) 5 (211mg), (0.15mL) (0.07mL)
 (330mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (64mg)

¹H NMR (400 MHz, CDCl₃): 7.57 (d, J=9.1 Hz, 2H), 6.93 (d, J=9.1 Hz, 2H), 4.42 (br, 1H), 2.76 (br, 2H), 2.35 (br, 3H), 2.05 (br, 2H), 1.87 (br, 2H), 1.56 (br, 2H), 0.92 (t, J=7.3 Hz, 3H).

47

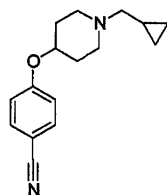
K_i = 76 nM

4-(1-(4-(4-isopropylpiperidin-1-yloxy)phenyl)benzodiazonitrile)-

DCM (3mL) 5 (202mg), (0.21mL) (0.07mL)
 (360mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (211mg) .

¹H NMR (400 MHz, CDCl₃): 7.56 (d, J=9.1 Hz, 2H), 6.93 (d, J=9.1 Hz, 2H), 4.37 (br, 1H), 2.69 (br, 2H), 2.22 (br, 2H), 2.09 (br, 2H), 1.98 (br, 2H), 1.87-1.73 (m, 3H), 0.90 (d, br, J=7.3 Hz, 6H).

48

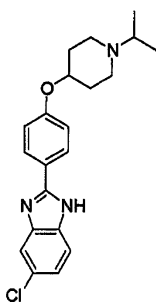
K_i = 72 nM

4-(1-(4-(4-(propylideneamino)pyrrolidin-1-yloxy)phenyl)benzodiazonitrile)-

DCM (3mL) 5 (215mg), (0.16mL) (0.07mL)
 (340mg) . 16 10% ()
 5mL , DCM(3x10mL) ()
 (1-7% 2M /DCM), (173mg) .

¹H NMR (400 MHz, CDCl₃): 7.56 (d, J=9.1 Hz, 2H), 6.93 (d, J=9.1 Hz, 2H), 4.40 (m, 1H), 2.83 (m, 2H), 2.40 (m, 2H), 2.29 (d, J=6.6 Hz, 2H), 2.03 (m, 2H), 1.87 (m, 2H), 0.88 (m, 1H), 0.52 (m, 2H), 0.11 (m, 2H).

49

K_i = 14 nM

5-(4-(4-(4-isopropylpiperidin-1-yloxy)phenyl)-1H-indazole)-

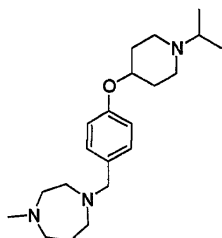
DMA (2mL) 2 (260mg), 4- (156mg) (280mg)
 100 12 가 . (1-7% 2M /

DCM), (191mg) .

¹H NMR (400

MHz, CDCl₃): 7.99 (d, J=9.1 Hz, 2H), 7.54 (m, 1H), 7.51 (m, 1H), 7.21 (m, 1H), 7.09 (d, J=9.1 Hz, 2H), 4.51 (m, 1H), 2.84 (m, 2H), 2.77 (m, 1H), 2.51 (m, 2H), 2.07 (m, 2H), 1.82 (m, 2H), 1.10 (d, J=6.6 Hz, 6H).

50

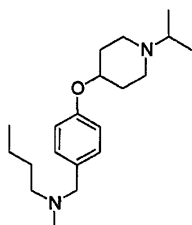
K_i = 1.0 nM

1-[4-(1- - -4-)-]-4- -[1,4]

DCM (3mL) 2 (171mg), N- (0.09mL) (0.07mL)
 (220mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (121mg) .

¹H NMR (400 MHz, CDCl₃): 7.22 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 4.26 (m, 1H), 3.55 (s, 2H), 2.82-2.72 (m, 3H), 2.71-2.63 (m, 6H), 2.61-2.57 (m, 2H), 2.41-2.36 (m, 2H), 2.35 (s, 3H), 2.00 (m, 2H), 1.85-1.76 (m, 4H), 1.06 (d, J=6.6 Hz, 6H).

51

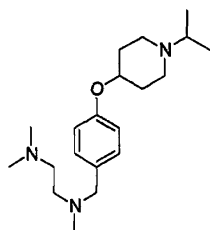
K_i = 1.7 nM

- [4-(1- - -4-)-]- -

DCM (3mL) 2 (167mg), - - (0.08mL) (0.07mL)
 (220mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (157mg) .

¹H NMR (400 MHz, CDCl₃): 7.19 (d, J=8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 4.27 (m, 1H), 3.40 (s, 2H), 2.82-2.71 (m, 3H), 2.39 (m, 2H), 2.34 (m, 2H), 2.16 (s, 3H), 2.00 (m, 2H), 1.85-1.76 (m, 2H), 1.52-1.45 (m, 2H), 1.38-1.27 (m, 2H), 1.06 (d, J=6.6 Hz, 6H), 0.90 (t, J=7.3 Hz, 3H).

52



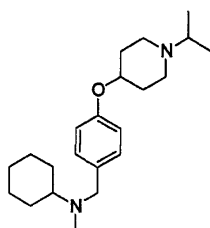
$K_i = 1.5 \text{ nM}$

N-[4-(1-(4-(2-(dimethylamino)ethyl)piperidin-1-yl)phenoxy)piperidin-1-yl]ethan-1-amine

DCM (3mL) 2 (171mg), N,N',N'- (220mg) -1,2- (0.09mL) (0.07mL)
 (5mL) , DCM(3x10mL) .16 10%
 (1-7% 2M /DCM), (126mg)

$^1\text{H NMR}$ (400 MHz; CDCl_3): 7.19 (d, $J=8.6 \text{ Hz}$, 2H), 6.84 (d, $J=8.6 \text{ Hz}$, 2H), 4.26 (m, 1H), 3.44 (s, 2H), 2.82-2.71 (m, 3H), 2.48-2.34 (m, 6H), 2.22 (s, 3H), 2.20 (s, 6H), 2.04-1.96 (m, 2H), 1.85-1.75 (m, 2H), 1.06 (d, $J=6.6 \text{ Hz}$, 6H).

53



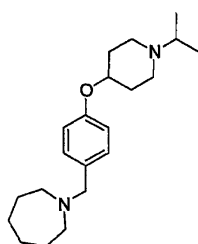
$K_i = 1.7 \text{ nM}$

N-[4-(1-(4-(2-(dimethylamino)ethyl)piperidin-1-yl)phenoxy)cyclohexyl]ethan-1-amine

DCM (3mL) 2 (169mg), (220mg) -1,2- (0.09mL) (0.07mL)
 , DCM(3x10mL) .16 10% (5mL)
 (1-7% 2M /DCM), (165mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.19 (d, $J=8.6 \text{ Hz}$, 2H), 6.84 (d, $J=8.6 \text{ Hz}$, 2H), 4.26 (m, 1H), 3.48 (s, 2H), 2.82-2.70 (m, 3H), 2.46-2.33 (m, 3H), 2.17 (s, 3H), 2.04-1.96 (m, 2H), 1.89-1.76 (m, 6H), 1.62 (m, 1H), 1.34-1.15 (m, 4H) 1.05 (d, $J=6.6 \text{ Hz}$, 6H).

54



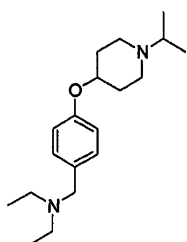
$K_i = 1.2 \text{ nM}$

1-[4-(1-(4-(2-(dimethylamino)ethyl)piperidin-1-yl)phenoxy)azepan-1-yl]ethan-1-amine

DCM (3mL) 2 (167mg), (0.08mL) (0.07mL)
 (220mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1 - 7% 2M /DCM), (163mg)

¹H NMR (400 MHz, CDCl₃): 7.22 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 4.26 (m, 1H), 3.56 (s, 2H), 2.85-2.71 (m, 3H), 2.60 (m, 4H), 2.38 (m, 2H), 2.04-1.96 (m, 2H), 1.85-1.76 (m, 2H), 1.60 (m, 9H), 1.06 (d, J=6.6 Hz, 6H).

55

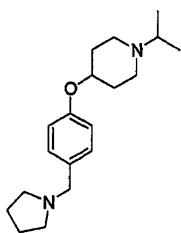
K_i = 1.9 nM

- [4 - (1 - - - 4 -) -] -

DCM (3mL) 2 (170mg), (0.08mL) (0.07mL)
 (220mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1 - 7% 2M /DCM), (78mg)

¹H NMR (400 MHz, CDCl₃): 7.21 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 4.26 (m, 1H), 3.49 (s, 2H), 2.82-2.70 (m, 4H), 2.50 (q, J=7.1 Hz, 4H), 2.37 (m, 2H), 2.04-1.96 (m, 2H), 1.85-1.76 (m, 2H), 1.60 (m, 9H), 1.07-1.00 (m, 12H).

56

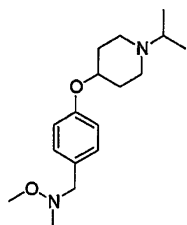
K_i = 1.9 nM

1 - - 4 - (- - 1 - -) -

DCM (3mL) 2 (169mg), (0.06mL) (0.07mL)
 (220mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1 - 7% 2M /DCM), (144mg)

¹H NMR (400 MHz, CDCl₃): 7.21 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.26 (m, 1H), 3.53 (s, 2H), 2.82-2.71 (m, 3H), 2.48 (m, 4H), 2.37 (m, 2H), 2.03-1.96 (m, 2H), 1.85-1.74 (m, 6H), 1.05 (d, J=6.6 Hz, 6H).

57



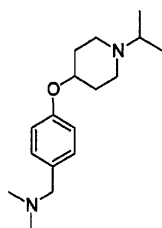
$K_i = 25 \text{ nM}$

N-[4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)ethyl)pyrrolidin-2-yl]pyrrolidine

DCM (3mL) 2 (170mg) O,N- (0.15g)
 (220mg) . 16 10% (5mL)
) , DCM(3x10mL) ()
 (1-7% 2M /DCM), (179mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.24 (d, $J=8.8 \text{ Hz}$, 2H), 6.85 (d, $J=8.8 \text{ Hz}$, 2H), 4.27 (m, 1H), 3.70 (s, 2H), 3.37 (s, 3H), 2.81-2.70 (m, 3H), 2.58 (s, 3H), 2.48 (m, 4H), 2.37 (m, 2H), 2.03-1.96 (m, 2H), 1.85-1.76 (m, 2H), 1.05 (d, $J=6.6 \text{ Hz}$, 6H).

58



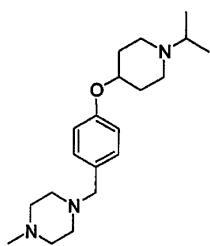
$K_i = 3.0 \text{ nM}$

[4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)ethyl)pyrrolidin-2-yl]pyrrolidine

DCM (3mL) 2 (170mg) (0.12g)
 (220mg) . 16 10% (5mL)
 DCM(3x10mL) ()
 (1-7% 2M /DCM), (163mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.18 (d, $J=8.6 \text{ Hz}$, 2H), 6.85 (d, $J=8.6 \text{ Hz}$, 2H), 4.27 (m, 1H), 3.34 (s, 2H), 3.37 (s, 3H), 2.81-2.70 (m, 3H), 2.38 (m, 2H), 2.21 (s, 6H), 2.05-1.96 (m, 2H), 1.85-1.75 (m, 2H), 1.05 (d, $J=6.6 \text{ Hz}$, 6H).

59



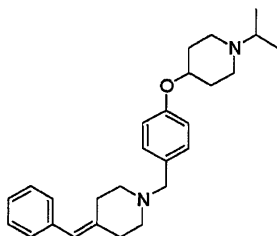
$K_i = 1.7 \text{ nM}$

1-[4-(1-(4-(2-(dimethylamino)ethoxy)phenyl)ethyl)pyrrolidin-2-yl]pyrrolidine

DCM (3mL) 2 (173mg), N- (0.08mL) (0.08g)
 (220mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (217mg) .

¹H NMR (400 MHz, CDCl₃): 7.19 (d, J=8.6 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 4.26 (m, 1H), 3.42 (s, 2H), 2.81-2.70 (m, 3H), 2.55-2.33 (m, 8H), 2.26 (s, 3H), 2.03-1.97 (m, 2H), 1.84-1.74 (m, 2H), 1.04 (d, J=6.6 Hz, 6H).

60

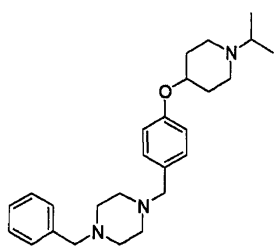
K_i = 2.2 nM

4 - [4 - (4 - - 4 -) -] - 1 - -

DCM (3mL) 2 (136mg), 4- - (94mL), (0.05g)
 (190mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (54mg) .

¹H NMR (400 MHz, CDCl₃): 7.32-7.27 (m, 2H), 7.23-7.16 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 6.27 (s, 1H), 4.28 (m, 1H), 3.46 (s, 2H), 2.83-2.71 (m, 3H), 2.54-2.49 (m, 4H), 2.43-2.35 (m, 6H), 2.05-1.97 (m, 2H), 1.86-1.76 (m, 2H), 1.06 (d, J=6.6 Hz, 6H).

61

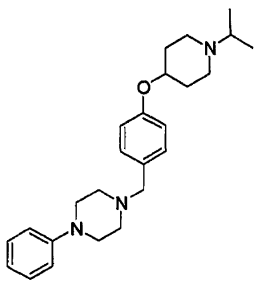
K_i = 2.0 nM

1 - - 4 - [4 - (- 4 -) -] -

DCM (3mL) 2 (188mg), N- (0.13mL), (0.06g)
 (260mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM), (239mg) .

¹H NMR (400 MHz, CDCl₃): 7.31-7.29 (m, 4H), 7.25-7.23 (m, 1H), 7.18 (d, J=8.6 Hz, 2H) 6.84 (d, J=8.6 Hz, 2H), 4.26 (m, 1H), 3.50 (s, 2H), 3.43 (s, 2H), 2.82-2.70 (m, 3H), 2.54-2.34 (m, 9H), 2.03-1.96 (m, 2H), 1.84-1.75 (m, 2H), 1.06 (d, J=6.6 Hz, 6H).

62



$K_i = 2.0 \text{ nM}$

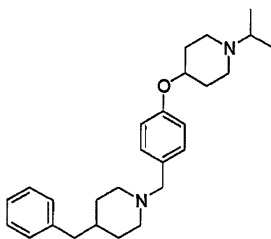
1 - [4 - (1 - 4 -) -] - 4 -

DCM (3mL) 2 (140mg), N- (0.09mL), (0.05g)
 (190mg) .16 10% (5mL)
 DCM(3x10mL) ()
 (1 - 7% 2M /DCM), (78mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.30-7.22 (m, 4H),

6.65-6.82 (m, 5H), 4.29 (m, 1H), 3.50 (s, 2H), 3.19 (m, 2H), 3.16-3.12 (m, 2H), 2.83-2.71 (m, 3H), 2.59 (m, 2H), 2.39 (m, 2H), 2.06-1.99 (m, 2H), 1.87-1.78 (m, 2H), 1.07 (d, $J=6.6 \text{ Hz}$, 6H).

63



$K_i = 1.5 \text{ nM}$

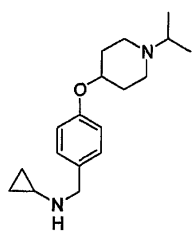
1 - [4 - (1 - 4 -) -] - 4 -

DCM (3mL) 2 (188mg), N- (0.13mL), (0.05g)
 (250mg) .16 10% (5mL)
 DCM(3x10mL) ()
 (1 - 7% 2M /DCM), (160mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.29-7.23 (m, 3H),

7.19-7.10 (m, 4H), 6.83 (m, 2H), 4.26 (m, 1H), 3.39 (s, 2H), 2.87-2.70 (m, 5H), 2.52 (d, $J=7.1 \text{ Hz}$, 2H), 2.38 (m, 2H), 2.03-1.96 (m, 2H), 1.59 (m, 2H), 1.50 (m, 1H), 1.29 (m, 2H), 1.06 (d, $J=6.6 \text{ Hz}$, 6H).

64



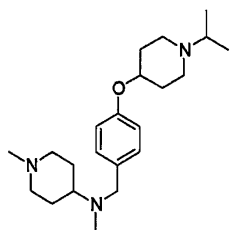
$K_i = 2.0 \text{ nM}$

- [4 - (1 - 4 -) -] -

DCM (3mL) 2 (250mg), (0.10mL), (0.07g)
 (340mg) . 16 10% (5mL)
 , DCM(3x10mL) ()
 (1-7% 2M /DCM) (88mg) .

¹H NMR (400 MHz, CDCl₃): 7.19 (d, J=8.6 Hz, 2H),
 6.84 (d, J=8.6 Hz, 2H), 4.25 (m, 1H), 3.74 (s, 2H), 2.81-2.69 (m, 3H), 2.37 (m, 2H),
 2.12 (m, 1H), 2.03-1.95 (m, 2H), 1.83-1.74 (m, 2H), 1.04 (d, J=6.6 Hz, 6H), 0.44-
 0.33 (m, 4H).

65

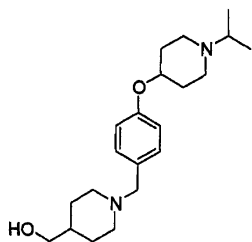
K_i = 1.5 nM

[4-(1- - -4-)-]- -(1- - -4-)-

DCM(3Mℓ) 2 (146mg), 1- -4- () (0.09Mℓ) (0.09Mℓ)
 (200mg) . 16 , 10% ()
 5Mℓ) , DCM(3x10Mℓ) .
 (1-7% 2 M /DCM) (137mg) .

¹H NMR (400 MHz, CDCl₃): 7.16 (d,
 J=8.6 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.24 (m, 1H), 3.47 (s, 2H), 2.88 (m, 2H),
 2.79-2.68 (m, 3H), 2.43-2.32 (m, 3H), 2.23 (s, 3H), 2.15 (s, 3H), 2.01-1.94 (m, 2H),
 1.89 (m, 2H), 1.82-1.73 (m, 4H), 1.69-1.59 (m, 2H) 1.03 (d, J=6.6 Hz, 6H).

66

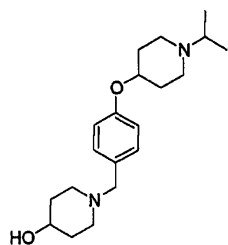
K_i = 1.0 nM

{1-[4-(1- - -4-)-]- -4- }-

DCM(3Mℓ) 2 (158mg), 4- (78mg) (0.08Mℓ)
 (220mg) . 16 , 10% (5Mℓ)
 , DCM(3x10Mℓ) .
 (1-7% 2M /DCM) (166mg) .

¹H NMR (400 MHz, CDCl₃): 7.17 (d, J=8.6 Hz,
 2H), 6.82 (d, J=8.6 Hz, 2H), 4.25 (m, 1H), 3.24 (d, J=6.6 Hz, 2H), 3.39 (s, 2H), 2.87
 (m, 2H), 2.80-2.69 (m, 3H), 2.37 (m, 2H), 2.02-1.94 (m, 2H), 1.90 (m, 2H), 1.83-1.74
 (m, 2H), 1.69 (m, 2H) 1.45 (m, 1H), 1.23 (m, 2H), 1.04 (d, J=6.6 Hz, 6H).

67

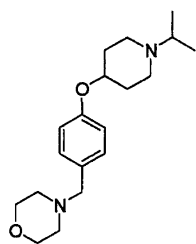
K_i = 1.5 nM

1 - [4 - (1 - - -4 -) -] - -4 -

DCM(3Mℓ) 2 (167mg), 4- (73mg) (0.08Mℓ)
 (220mg) . 16 , 10% (5Mℓ)
 , DCM(3x10Mℓ) (1-7% 2M) /DCM) (168mg)

¹H NMR (400 MHz, CDCl₃): 7.17 (d, J=8.6 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.25 (m, 1H), 3.64 (m, 1H), 3.42 (s, 1H), 3.40 (s, 2H), 2.80-2.69 (m, 5H), 2.36 (m, 2H), 2.08 (m, 2H), 2.02-1.94 (m, 2H), 1.87-1.74 (m, 2H), 1.55 (m, 2H), 1.04 (d, J=6.6 Hz, 6H).

68

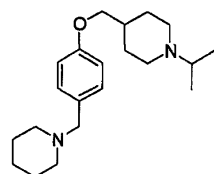
K_i = 2.4 nM

4 - [4 - (1 - - -4 -) -] -

DCM(5Mℓ) 2 (360mg), (0.12Mℓ) (0.09Mℓ)
 (450mg) . 16 , 10% (10Mℓ)
 , DCM(3x20Mℓ) (1-7% 2M) /DCM) (366mg)

¹H NMR (400 MHz, CDCl₃): 7.20 (d, J=8.6 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.27 (m, 1H), 3.69 (m, 4H), 3.42 (s, 2H), 2.82-2.70 (m, 3H), 2.41 (m, 4H), 2.36 (m, 2H), 2.04-1.96 (m, 2H), 1.84-1.75 (m, 2H), 1.05 (d, J=6.6 Hz, 6H).

69

K_i = 2.2 nM

1 - [4 - (1 - - -4 -) -] -

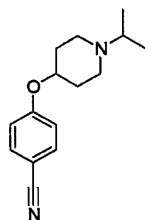
DCM(3Mℓ) 4- (23.1g), (40Mℓ), (12Mℓ)
 (62g) . 10%

pH 12-13 (3x150Mℓ)
 (4Mℓ) (151mg) (31.47g) (595mg)
 (521mg) 가 . 30 (2Mℓ) 4-
 (200Mℓ) 가 . 18 65-68 가 ,
 /DCM) (23mg) , 0 (5% 2M
 1M 2.2Mℓ) 가 가 16 (1Mℓ)
 (1M 2.2Mℓ) 가 , 5 , DCM(2x30Mℓ)
 E(3Mℓ) (100mg), (38μℓ), (22μℓ) (5% 2M /DCM) DC
) 1N (1Mℓ) , DCM(3x20Mℓ)
 CM) (13mg) (5% 2M /D

¹H NMR (400 MHz, CDCl₃): 7.20

(d, J = 8.59 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 3.78 (d, J = 6.3 Hz, 2 H), 2.95 (d, J = 12 Hz, 2 H), 2.75 (m, 1 H), 2.37 (br s, 4 H), 2.19 (m, 3 H), 1.83 (m, 4 H), 1.57 (m, 4 H), 1.42 (m, 4 H), 1.08 (d, J = 6.6 Hz, 6 H).

70



K_i = 63 nM

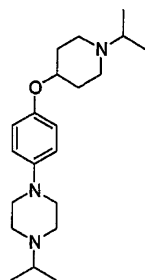
4-(1- - -4-)-

DMF(100Mℓ) 3 (10.74g) 4- - (11.45g) NaH(60%, 3.7g)
 , (3x400Mℓ) 16 65 가 , (1.5)
 (16.6g)

¹H NMR (400 MHz, CDCl₃): 7.56 (d, J=8.6

Hz, 2H), 6.93 (d, J=8.6 Hz, 2H), 4.37 (m, 1H), 2.81-2.72 (m, 3H), 2.41 (m, 4H), 2.06-1.98 (m, 2H), 1.87-1.77 (m, 2H), 1.06 (d, J=6.6 Hz, 6H).

71



K_i = 0.2 nM

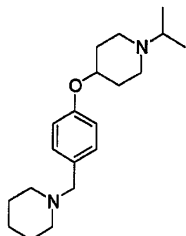
1- -4-[4-(1- - -4-)-]-

DCM(10Mℓ) 74 (0.061mg), (2Mℓ) (0.012Mℓ)

(59mg) .16 , 10% (5Ml) (40g)
 DCM(2x50Ml) (10Ml), (10Ml)
 (4-10% 2M)

¹H NMR (400 MHz, CDCl₃): 6.90-6.83 (m, 4H), 4.19-4.15 (m, 1H), 3.11 (t, J = 5.0 Hz, 4H), 2.81-2.67 (m, 8H), 2.38-2.33 (m, 2H), 2.02-1.95 (m, 2H), 1.82-1.74 (m, 2H), 1.09 (d, J = 6.5 Hz, 6H), 1.05 (d, J = 6.6 Hz, 6H).

72

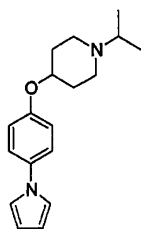
K_i = 0.4 nM

1-[4-(1-(4-(tert-butyl)piperidin-1-yl)phenoxy)piperidin-4-yl]piperidine

DCM(5Ml) 3 (129mg), 1 (172mg) (600 mg) -tert- DCM(3x1Ml) (311mg) 16 (1-6% 2M /DCM) (75mg)

¹H NMR (400 MHz, CDCl₃): 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.29-4.25 (m, 1H), 3.40 (s, 2H), 2.82-2.71 (m, 3H), 2.41-2.35 (m, 6H), 2.40-2.26 (m, 6H), 2.03-1.99 (m, 2H), 1.85-1.77 (m, 2H), 1.59-1.53 (m, 4H), 1.43-1.38 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H),

73

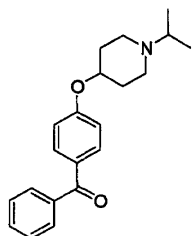
K_i = 10 nM

1-(4-(1-(4-(tert-butyl)piperidin-1-yl)phenoxy)pyrrolidin-2-yl)piperidine

DCM(5Ml) 3 (129mg), 4-(1H-) -1-) (143mg) 0mg -tert- DCM(3x1Ml) (311mg) 16 (1-6% 2 /DCM) (92mg)

¹H NMR (400 MHz, CDCl₃): 7.27 (d, J = 8.9 Hz, 2H), 6.99-6.98 (m, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.31-6.30 (m, 2H), 4.30-4.26 (m, 1H), 2.82-2.71 (m, 3H), 2.42-2.36 (m, 2H), 2.04-2.00 (m, 2H), 1.86-1.78 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H).

74



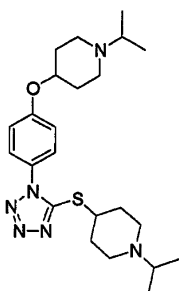
$K_i = 2.9 \text{ nM}$

[4-(1- - -4-)-]- -

DCM(6Mℓ) 66 (258mg), (357g) (1.2g)
 -tert- (622mg) 16
 DCM(3x1Mℓ) , (106% 2
 M /DCM) , (151mg) .

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.81 (d, $J = 8.9 \text{ Hz}$, 2H), 7.76-7.74 (m, 2H),
 7.59-7.54 (m, 1H), 6.96 (d, $J = 8.8 \text{ Hz}$, 2H), 4.46-4.40 (m, 1H), 2.83-2.73 (m, 3H),
 2.46-2.40 (m, 2H), 2.08-2.03 (m, 2H), 1.90-1.82 (m, 2H), 1.07 (d, $J = 6.5 \text{ Hz}$, 6H).

77



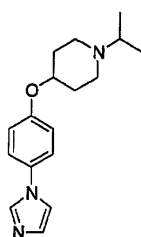
$K_i = 1.0 \text{ nM}$

N- -4-{4-[5-(1- - -4-)- -1-]- }-

DCM(6Mℓ) 66 (258mg), 1-(4-)-1H- -6- (175mg)
 (1.2g) -tert- (622mg)
 16 (1-6% 2M /DCM) , DCM(3x1Mℓ) , (54mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.44-7.41 (m, 2H), 7.05-7.02 (m, 2H), 4.39-4.36
 (m, 1H), 3.97-3.92(m, 1H), 2.86-2.70 (m, 6H), 2.46-2.40 (m, 4H), 2.38-2.24 (m, 2H),
 2.07-2.03 (m, 2H), 1.89-1.74 (m, 4H), 1.07 (d, $J = 6.5 \text{ Hz}$, 6H), 1.04 (d, $J = 6.6 \text{ Hz}$,
 6H).

78



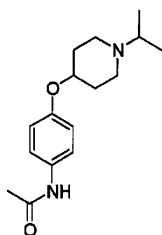
$K_i = 6.3 \text{ nM}$

4-(4- -1- -)-1- -

DCM(6Mℓ) 66 (258mg), 4-(tert-butyl)pyridine (114mg) (1.2g)
 2g) -tert-butylpyridine (622mg) 16 (1-6%
 % 2M /DCM) , DCM(3x1Mℓ) (67mg)

¹H NMR (400 MHz, CDCl₃): 7.76 (s, 1H), 7.30-7.26 (m, 2H), 7.21-7.18 (m, 2H), 7.01-6.97 (m, 2H), 4.36-4.30 (m, 1H), 2.85-2.75 (m, 3H), 2.44-2.39 (m, 2H), 2.07-2.01 (m, 2H), 1.88-1.80 (m, 2H), 1.07 (d, J = 6.6 Hz, 6H).

79

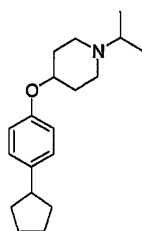
K_i = 17 nM

N-[4-(1-(tert-butyl)piperidin-4-yl)phenyl]acetamide

DCM(6Mℓ) 66 (258mg), 4-(tert-butyl)pyridine (136mg) (1.2g)
 -tert-butylpyridine (622mg) 16 (1-6%
 M /DCM) , DCM(3x1Mℓ) (82mg)

¹H NMR (400 MHz, CDCl₃): 8.14 (s, 1H), 7.39-7.35 (m, 2H), 6.84-6.80 (m, 2H), 4.24-4.18 (m, 1H), 2.80-2.72 (m, 3H), 2.39-2.33 (m, 2H), 2.10 (s, 3H), 2.00-1.95 (m, 2H), 1.81-1.73 (m, 2H), 1.05 (d, J = 6.6 Hz, 6H).

80

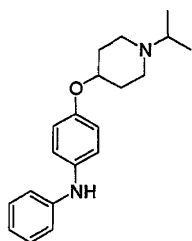
K_i = 19 nM

4-(4-(1-(tert-butyl)piperidin-4-yl)phenyl)cyclopentanecarboxamide

DCM(6Mℓ) 66 (258mg), 4-(tert-butyl)pyridine (146mg) (1.2g)
 -tert-butylpyridine (622mg) 16 (1-6%
 2M /DCM) , DCM(3x1Mℓ) (19mg)

¹H NMR (400 MHz, CDCl₃): 7.15-7.12 (m, 2H), 6.85-6.81 (m, 2H), 4.28-4.22 (m, 1H), 2.97-2.88 (m, 1H), 2.42-2.36 (m, 2H), 2.07-1.99 (m, 4H), 1.85-1.49 (m, 8H), 1.06 (d, J = 6.6 Hz, 6H).

81



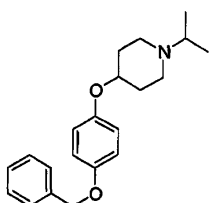
$K_i = 3.7 \text{ nM}$

[4-(1- - -4-)-]- -

DCM(6Mℓ) 66 (258mg), 4-((136mg)
 (1.2g) -tert- (622mg) 16
 (1-6% 2M /DCM) , DCM(3x1Mℓ)
 (25mg)

$^1\text{H NMR}$ (400 MHz, CDCl_3): 7.23-7.19 (m, 2H), 7.06-7.03 (m, 2H), 6.93-6.91 (m, 2H), 6.88-6.81 (m, 3H), 4.26-4.20 (m, 1H), 2.84-2.74 (m, 3H), 2.44-2.38 (m, 2H), 2.06-2.00 (m, 2H), 1.07 (d, $J = 6.6 \text{ Hz}$, 6H).

82



$K_i = 6 \text{ nM}$

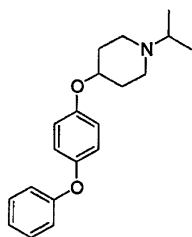
4-(4- -)-1- -

DCM(6Mℓ) 66 (258mg), 4-() (180mg) (1.2g)
 -tert- (622mg) 16
 , DCM(3x1Mℓ) (1-6%
 2M /DCM) , (102mg)

$^1\text{H NMR}$

(400 MHz, CDCl_3): 7.43-7.28 (m, 5H), 6.91-6.82 (m, 4H), 5.00 (s, 2H), 4.18-4.13 (m, 1H), 2.81-2.69 (m, 3H), 2.38-2.32 (m, 2H), 2.01-1.95 (m, 2H), 1.82-1.74 (m, 2H), 1.05 (d, $J = 6.6 \text{ Hz}$, 6H).

83



$K_i = 7.5 \text{ nM}$

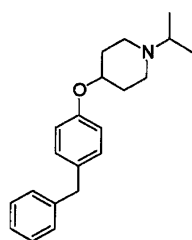
1- -4-(4- -)-

DCM(6Mℓ) 66 (258mg), 4- (168mg) (1.2g)
 - tert - (622mg) 16
 M /DCM) , DCM(3x1Mℓ) , (1-6% 2
 (77mg)

¹H NMR (400

MHz, CDCl₃): 7.31-7.26 (m, 2H), 7.05-7.01 (m, 1H), 6.97-6.92 (m, 4H), 6.90-6.86 (m, 2H), 4.25-4.20 (m, 1H), 2.83-2.72 (m, 3H), 2.41-2.35 (m, 2H), 2.05-1.99 (m, 2H), 1.86-1.77 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H).

84



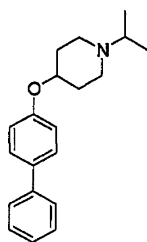
K_i = 7.5 nM

4-(4-(4-(tert-butyl)piperidin-1-yl)phenoxy)benzylbenzene

DCM(6Mℓ) 66 (258mg), 4- (166mg) ()
 1.2g) - tert - (622mg) 16 ()
 1-6% 2M /DCM) , DCM(3x1Mℓ) , ()
 (108mg)

¹H NMR (400 MHz, CDCl₃): 7.30-7.26 (m, 2H), 7.20-7.16 (m, 3H), 7.09-7.06 (m, 2H), 6.84-6.81 (m, 2H), 4.27-4.21 (m, 1H), 3.91 (s, 2H), 2.81-2.67 (m, 3H), 2.40-2.34 (m, 2H), 2.02-1.92 (m, 2H), 1.83-1.75 (m, 2H), 1.05 (d, J = 6.6 Hz, 6H).

85



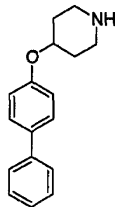
K_i = 6.0 nM

4-(4-(4-(tert-butyl)piperidin-1-yl)phenoxy)benzophenone

DCM(6Mℓ) 66 (258mg), (0.039Mℓ) (1.2g)
 - tert - (622mg) 16
 /DCM) , DCM(3x1Mℓ) , (1-6% 2M
 (91mg)

¹H NMR (400 MHz, CDCl₃): 7.55-7.49 (m, 4H), 7.42-7.38 (m, 2H), 7.30-7.26 (m, 1H), 6.98-6.95 (m, 2H), 4.36-4.31 (m, 1H), 2.83-2.73 (m, 3H), 2.46-2.41 (m, 2H), 2.09-2.05 (m, 2H), 1.90-1.82 (m, 2H), 1.08 (d, J = 6.6 Hz, 6H).

86



K_i = 4000 nM

4-(4-)-

DCM(10Mℓ) tert-4-1-tert- (497mg), 4- (300mg)
 (1.2g) (608mg)
 16 (5Mℓ) DCM(3x5Mℓ) 4N 5Mℓ
 16 10% (20Mℓ) DCM(2*
 500Mℓ) (1-6%
 2M /DCM) (107mg)

¹H

NMR (400 MHz, CDCl₃): 7.56-7.49 (m, 4H), 7.42-7.39 (m, 2H), 7.31-7.27 (m, 1H),
 6.99-6.96 (m, 2H), 4.43-4.37 (m, 1H), 3.18-3.13 (m, 3H), 2.77-2.70 (m, 2H), 2.07-
 2.01 (m, 2H), 1.73-1.64 (m, 2H).

87

(in vitro)

SK-N-MC

10cm

2

가

1/5

10cm

10%

5% CO₂ 37

400μℓ

0.4cm

(Bio-Rad 3#165-2088)

0.25kV

H₃ cDNA 1
960μF

가

10Mℓ

10cm

1:20, 1:10, 1:15

4

가

(600 μg/Mℓ G418

)

가

24

10

SK-N-MC

가

가

[³H]-N-

H₃

SK-N-MC

20 mM TrisHCl/0.5mM EDTA

800g TrisHCl/0.5mM EDTA(pH 7.4)

30

30,000g

50 mM

/

(0.3%

4

0.8nM [³H]-N-
) GF/C

가

800pM K_d 800 pM

([L])

pK_i

4Mℓ

10 μ M

$$K_i = (IC_{50}) / (1 + ([L] / (K_d)))$$

(in vivo)

H₃ -

H₃ -

(~300)

1mg/Mø

0.5%

10 mL/kg (10mg/kg)

0.8

2

0.1mL

가

50 mL

8

1

6

24

48

CO

0.3mL 6%

14,000 rpm

5)

6%

(

3 mL/g

(LC-MS/MS)

LC

RP (2X50 mm)

(

1%)

H₃

1

(AUC)

H₃

(log)

(AUMC)

(MRT)

LC-MS/MS

(AUMC:AUC)

(index)

AUC /AUC

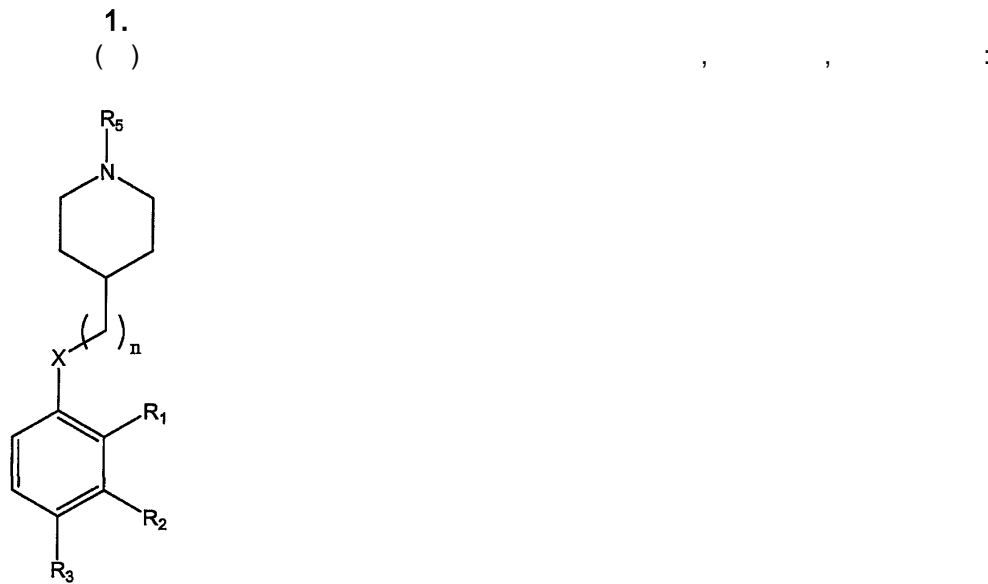
F.

가

가

가

(57)



X O ;

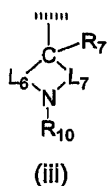
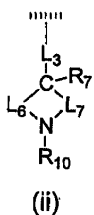
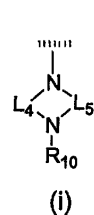
n 0 3 ;

R₅ C₁₋₁₀, C₃₋₈, C₃₋₈, (C₃₋₈)C₁₋₆, ()C₁₋₆, ()
 C₃₋₈, (C₁₋₈)C₁₋₈ ;

R₁, R₂, R₃ G W , H ;

G - ;

-OL₁Q, -L₂Q, -N(L₁Q)R₅, -L₃C(L₁Q)R₆R₇, -C(L₁Q)R₆R₇,



L₁ C₂₋₆, C₃₋₈, C₄₋₆, C₄₋₆, C₂₋₅, ()C₁₋₆
 , ()C₁₋₆, (C₂₋₅)C₁₋₆, ()C₁₋₆, (C₂₋₅)C₁₋₆ ;

L₂ C₁₋₆, C₃₋₈, C₃₋₈, C₃₋₈, C₂₋₅, ()C₁₋₆
 , ()C₁₋₆, (C₁₋₅)C₁₋₆, ()C₁₋₆, (C₁₋₅)C₁₋₆ ;

L₃ C₁₋₆, C₂₋₆, C₂₋₆, C₂₋₅, ()C₁₋₆, ()
 C₁₋₆, C₁₋₅ ()C₁₋₆, ()C₁₋₆, (C₁₋₅)C₁₋₆, ()C₁₋₆, ()
 C₂₋₅ ;

L₄ C₁₋₅ ;

L₅ C₁₋₅ ;

L₆ C₁₋₅ ;

L₇ C₁₋₅ ;

Q -NR₈R₉ C₂₋₁₅ O, S, N 1 3 가 ;

R₆ C₁₋₈, C₁₋₆, C₂₋₈, C₃₋₇, (C₃₋₇)C₁₋₆, C
 2-15, (C₂₋₇)C₁₋₆ ;

R₇ H, C₂₋₆ L₆ L₇ (R₆) 가 ;

R₈ R₉ C₁₋₆, C₁₋₈, C₃₋₈, C₃₋₇, (C₃₋₇)C₁₋₆, ()C₁₋₆
 6, C₂₋₁₅, (C₂₋₁₅)C₁₋₆ ;

R₁₀ H, C₁₋₈, C₃₋₈, C₃₋₇, (C₃₋₇)C₁₋₆, (C₂₋₁₅

)C₁₋₆, ()C₁₋₆; ;
W -CN, -CHO, C₁₋₈, (C₁₋₈)-O-, ()C₁₋₆ -
O-, -C(=O)R_x, -C(OH)R_xR_y, C₁₋₈, C₁₋₈, -NR_xR_y; ;
, R_x R_y H, C₁₋₆, C₁₋₆, C₁₋₈, ;

, C₁₋₃, 1, 3, ;

Q 가 , C₂₋₆, C₁₋₈, N(C₁₋₆)(C₁₋₈), NH
(C₁₋₈), (C₁₋₃)(C₁₋₈), O(C₁₋₈), O(C₁₋₆), O(C₃₋
6 (, 1, 3, N(C₁₋₆)(C₁₋₃), O(C₁₋₃), C₁₋₃).

2. 1, R₅ C₁₋₅, C₃₋₄, C₃₋₆, (C₃₋₆)C₁, ()C₁₋₃, ()C₃₋₄.

3. 2, R₅ C₃₋₅, C₃₋₆, (C₃₋₆)C₁.

4. 1, R₂ R₃ 가 G .

5. 4, R₂ 가 G .

6. 4, R₃ 가 G .

7. 1, L₁ C₂₋₃ .

8. 1, L₂ 가 C₁₋₆, (C₁₋₅)C₁₋₆, -C₁₋₆ .

9. 8, L₂ 가 .

10. 1, L₂ 가 , , .

11. 1, Q가 - C₂₋₅ .

12. 11, Q가 , N-(C₁₋₆) , , .

13. 11, Q가 , C₁₋₆, C₁₋₈, N(C₁₋₆)(C₁₋₈), NH(C₁₋₈), (C₁₋₃)(C₁₋₆), O(C₁₋₈), O(C₁₋₆), O(C₃₋₆), (C₁₋₃), N(C₁₋₆)(C₁₋₃), O(C₁₋₃) .

C 1-3 1 3) , N-

14.

13 , Q가 , , 2- , (C 1-6) , , (C 1-6) , (C 1-6) , (C 1-6)

15.

14 , Q가 N-

16.

1 , Q가 NR 8 R 9 , R 8 R 9 , C 1-8 , C 3-8 , C 3-7 , (C 3-7)C 1-6 , C 2-5 , (C 2-5)C 1-6

17.

16 , R 8 R 9 가 .

18.

17 , R 8 H R 9 가 , C 1-3 1-3 C 1-8 .

19.

18 , R 9 가 , , , (C 1-6) , (C 1-6) , 2- , (C 1-6) , (C 1-6)

20.

18 , R 5 C 1-5 , C 3-4 , C 3-6 , (C 3-6)C 1 , ()C 1-3 , ()C 3-4 .

21.

1 , n 0 1 .

22.

21 , n 0 .

23.

1 , G가

(4) L 4 L 5 가 C 2-3 () ,

(5) L 6 가 C 2-3 L 7 C 2-3 () ,

(6) L 2 가 C 1-6 , C 1-4 (C 1-5)C 1-4 L 2 Q

(7) L 1 C 2-3 OL 1 Q .

24.

23 , G가

(8) L 4 L 5 가 C 2 () ,

(9) L 6 L 7 C 2 () ,

40.

39 , 4-(4- -1- -)-1- - , 4-(4- -1- -)-1-
 - , 5- -2-[4-(1- - -4-)-]-1H-

41.

1 , [4-(1- - -4-)-]- - , 4-(-4-)-1-
 - , 4-(4- -)-1- - , 1- -4-(4- -)- , 4
 -(4- -)-1- - , [4-(1- - -4-)-]- - , N-[4-(
 1- - -4-)-]- , 4-(4- -)-1- - , 4
 -(1- - -4-)- , 4-(1- - -4-)- , 4-(1-
 sec- - -4-)- , 4-(1- - -4-)- , 4-(1-
 - -4-)- , 4-(1- - -4-)- , 4-(1-
 - -4-)- , 4-(1- - -4-)- , 4-(1-
 -4-)-

42.

1 , 4-(-4-)-1- - , 4-(4- -)-1- - ,
 4-(4- -)-1- - , 1- -4-(4- -)- , N-[4-(1-
 - -4-)-]-

43.

1 , 1- -4-[4-(1- - -4-)-]- , 1-[4-(1-
 - -4-)-]- , 1-[4-(1- - -4-)-]-

44.

1 , 1-[4-(1- - -4-)-]- , 4-[4-(1-sec- - -4-
)-]- , 1-[4-(1- - -4-)-]- , 1-[4-(1- -
 -4-)-]- , 1-N- -4-{4-[5-(1- - -4-)-]- -1-
]- }- , {1-[4-(1- - -4-)-]- -4- }- , 1-[4-(1-
 - -4-)-]-4- -[1,4] , 1-[4-(1- - -4-)-]-
 , 1-[4-(1- - -4-)-]- , 1-[4-(1- - -4-)-]-
]- -4- , [4-(1- - -4-)-]- -(1- - -4-)- , 1-[4-(
 1- - -4-)-]-4- - , N-[4-(1- - -4-)-]-
 N,N',N'- - -1,2- , 1-[4-(1- - -4-)-]-4- - ,
 -[4-(1- - -4-)-]- - , -[4-(1- - -4-)-]-
]- - , 4-[4-(1- - -4-)-]- , 1- -4-(4- -1-
 -)- , -[4-(1- - -4-)-]- , 4-[4-(1-sec- -
 -4-)-]- , 1-[4-(1- - -4-)-]-4- - , 1- -
 4-[4-(1- - -4-)-]- , 4-[4-(4- - -1-)-]- 1
 - , 4-[4-(1- - -4-)-]- , [4-(1- -
 4-)-]- - , 4-[4-(1- - -4-)-]- , 4-[4-(1-
 - -4-)-]- , 4-[4-(1- - -4-)-]- , 1-[4-(1-
 - -4-)-]- , 1-[4-(1- - -4-)-]- , 1-[4-(1-
 - -4-)-]- , 4-[4-(4- -1- -)-]- -1-]
 - -2-

45.

1 , 1-[4-(1- - -4-)-]- , 4-[4-(1-sec- - -4-
)-]- , 1-[4-(1- - -4-)-]- , 1-[4-(1- -
 -4-)-]- , 1-N- -4-{4-[5-(1- - -4-)-]- -1-
]- }- , {1-[4-(1- - -4-)-]- -4- }- , 1-[4-(1-
 - -4-)-]-4- -[1,4] , 1-[4-(1- - -4-)-]-
 , 1-[4-(1- - -4-)-]- , 1-[4-(1- - -4-)-]-
]- -4- , [4-(1- - -4-)-]- -(1- - -4-)- , 1-[4-(
 1- - -4-)-]-4- - , N-[4-(1- - -4-)-]-
 N,N',N'- - -1,2- , 1-[4-(1- - -4-)-]-4- - ,

-[4-(1-)-]- , -[4-(1-)-]- , 1- -4-(4- -1)- , 4-[4-(1-sec-)-]- , 1-[4-(1-)-]-4- , 1- -4-[4-(1-)-]- , 4-[4-(4- -1-)-]-1- , 4-[4-(1-)-]- , [4-(1-)-]-4- , 4-[4-(1-)-]- , 4-[4-(1-)-]- , 4-[4-(1-)-]- , 4-[4-(1-)-]- , 4-[4-(1-)-]- .

46.

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

47.

1 23 , PET SPECT 가 .

48.

1 , .

49.

1 , 23 , 45 46 H₃ H₃ .

50.

1 , 23 , 45 46 , H₃ .

51.

50 , / , / , , , , () , , , , , , , .

52.

(a) 23 , 45 46 H₁ , (b) 1 , H₁ H₃ .

53.

52 , H₁ 1 , 23 , 45 , 46 .

54.

(a) 26 , 27 41 H₂ , (b) 1 , H₂ H₃ .

55.

54 , H₂ 1 , 26 , 27 41 .

56.

1 , 23 , 45 46 , / , / .

57.

1 , 23 , 45 46
(ADHD) .

58.

1 , 23 , 45 46 , ,
(), , , , , .

59.

1 , 23 , 45 46 , , .

60.

(PET) ¹⁸F- 1 23 ,
H₃ .

- - ,