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(51) . Int. Cl.⁷
C07D 401/12

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(43)

10-2004-0016844
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(74)

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(54) 1,2,3,4-

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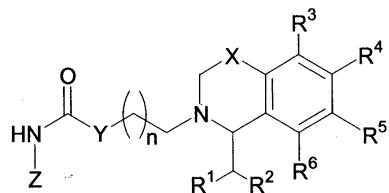
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 H+-ATPase WO-01/009088 CCR-3



$$X - \text{CH}_2 - , -\text{CH}_2\text{CH}_2 - , -\text{C}(\text{CH}_3)_2 - ;$$

Y , NH ;

n 1 2 ;

z

R², , , , R¹ E Z , , , - , -

$$\mathbb{R}^4 \quad \mathbb{R}^5 \quad \vdots \quad , \quad 1 \quad 2 \quad 5 \quad 6$$

$$R^7 \quad R^8 \quad , \quad , \quad , \quad , \quad N$$

I , ' ' 1 7 , , 1 4
; 3 6 , sec- , tert- , n- , n- , n- ,
, , n- , , - ,

-O-, , , , - , , , - , sec- , tert- ,

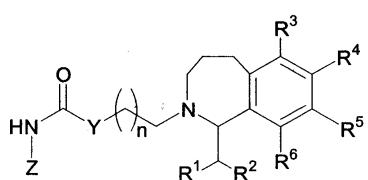
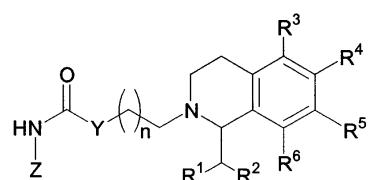
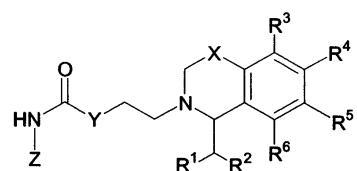
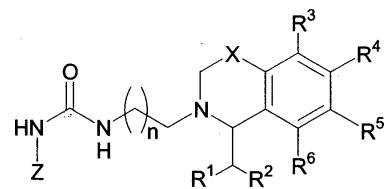
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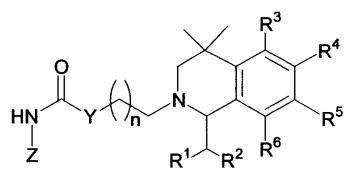
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(heteromorph)

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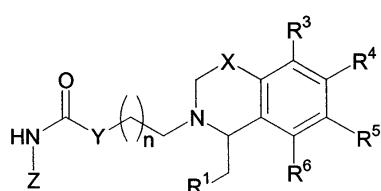




, R¹, R², R³, R⁴, R⁵, R⁶, Y, Z, n

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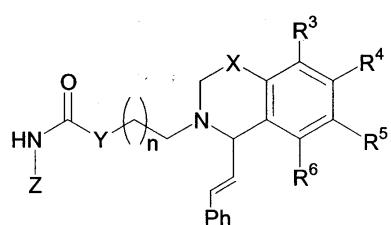
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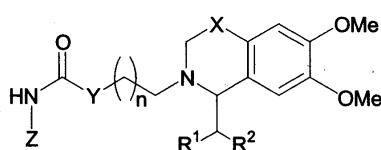
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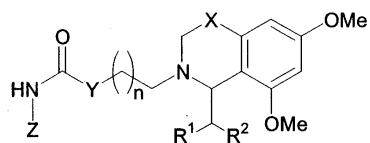
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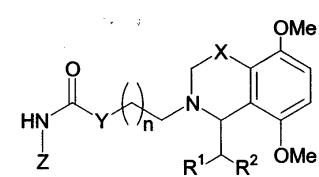
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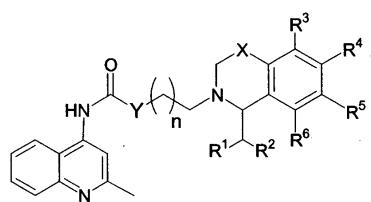
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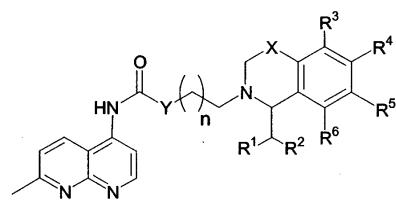
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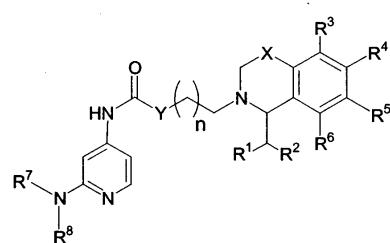
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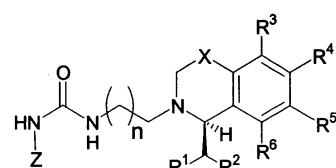
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, R⁴, R⁵, R⁶, X, Z, n

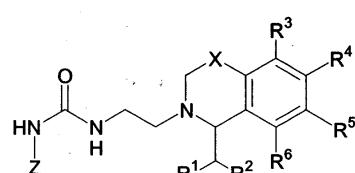
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R

; R¹, R², R³, R

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, R³, R⁴, R⁵, R⁶ ; R¹, R², Z |

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-4-)- ;

1-{2-[1-(3- -4-)-6,8- -3,4- -1H- -2-]- }-3-(2- -
- ;

1-{2-[1-(3,4- -)-6,8- -3,4- -1H- -2-]- }-3- -4-
- ;

1-{2-[1-(3- -4-)-6,8- -3,4- -1H- -2-]- }-3-
-4- - ;

1-{2-[1-(4- -)-6,8- -3,4- -1H- -2-]- }-3- -4- -
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1-(2-{1-[2-(4- -)-]-6,8- -3,4- -1H- -2- }-)-3-(2-
-4-)- ;

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-4- - ;

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-4- - ;

1-(2-{1-[2-(3,4- -4-)-]-6,8- -3,4- -1H- -2- }-)-3-
-4- - ;

1-(2-{1-[2-(4- -)-]-6,8- -3,4- -1H- -2- }-)-3- -
4- - ;

1-{2-[1-(4- -)-6,7- -3,4- -1H- -2-]- }-3-(2- -
4-)- ;

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-4-)- ;

1-(2-{1-[(E)-2-(2,4- -)-]-6,7- -3,4- -1H- -2- }-)-3
-(2- - -4-)- ;

1-(2-{1-[(E)-2-(2,5- -)-]-6,7- -3,4- -1H- -2- }-)-3
-(2- - -4-)- ;

1-(2-{1-[2-(2,3- -4-)-]-6,7- -3,4- -1H- -2- }-)-3-(2- -
-4-)- ;

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 -4-)- ;]-6,7- -3,4- -1H- -2- }-)-3-(2-

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 -4-)- ;]-6,7- -3,4- -1H- -2- }-)-3-(2-

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 -4-)- ;]-6,7- -3,4- -1H- -2- }-)-3-(2-

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 -4-)- ;]-6,7- -3,4- -1H- -2- }-)-3-(2-

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 -4-)- ; -1-[2-(2- -)-]-3,4- -1H- -2- }-)-3-(2-

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 1-[2-(1- -6,7- -3,4- -1H- -2-)-]-3-(2- - -4-)- ;

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1-[2-(1- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -2- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -2- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[3-(1- -6,7- -3,4- -1H- -2-)-]-3-(2- - -4-)- ;
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 1-{2-[1-(2,6- -4-)-]- }-3-(2- - ;
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 1-{2-[1-(3,4- -)-6,7- -3,4- -1H- -2-]- }-3- -4- - ;
 1-{2-[1-(3,4- -4-)-]- }-3-(5,6,7,8- - ;
 1-{2-[1-(3,4- -4-)-]- }-3-(2- - ;
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1 - {2 - [1 - (3,4 -
 ;) - 6 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3 -
 - 4 -) - - 4 - -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 -

 1 - {2 - [1 - (3 -
 - 3 - (2 - - 4 -) - - 5 - -) - 6,7 - - 3,4 - - 1H - - 2 -] - }

 1 - {2 - [1 - (4 -
 ;) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (4 -
 ;) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

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 ;) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

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 - ; - 1 - (2,3,4 - -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

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 - 4 -) - ; - 1 - (3,4,5 - -) - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

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

(enteral)

가

가

가

가

(),

가

1가

70 kg

3 mg 3g,
1 3

10 mg 1 g,

5 mg

300 mg

가

$$(R^1 \quad R^9, X, Y, Z, n) \text{가}$$

(: Protective Groups in Organic Synthesis, T.W. Greene, Wiley-Interscience, 1981).

V
 () . , () . , () . , () .

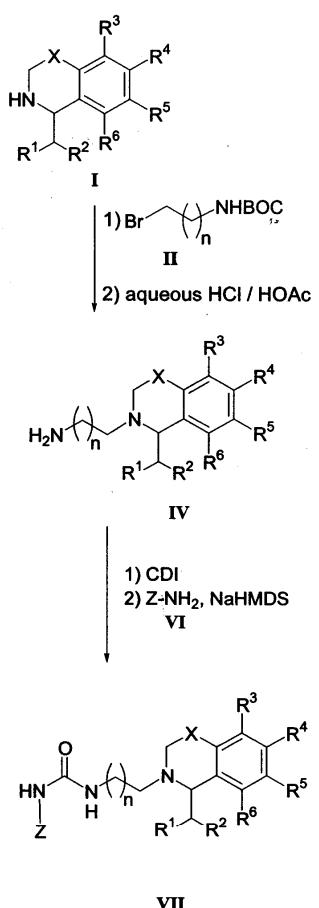
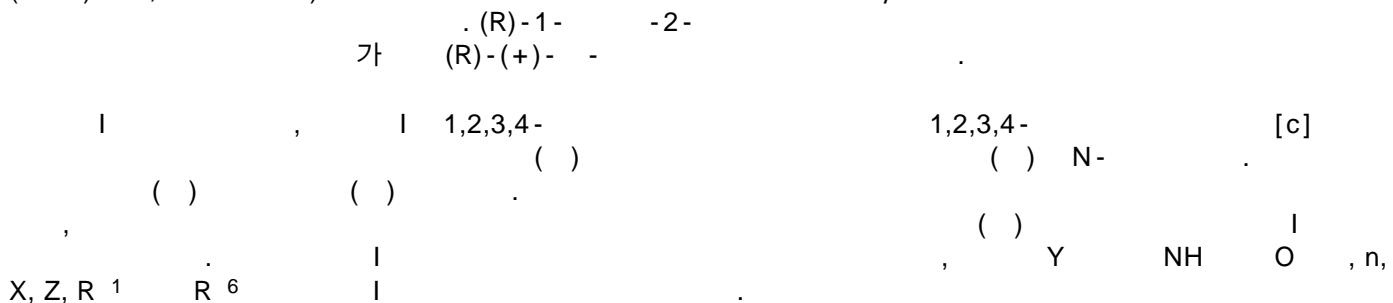
1,2,3,4- 1,2,3,4- [c]
 가 . 가 POCl
 3 NaBH₄

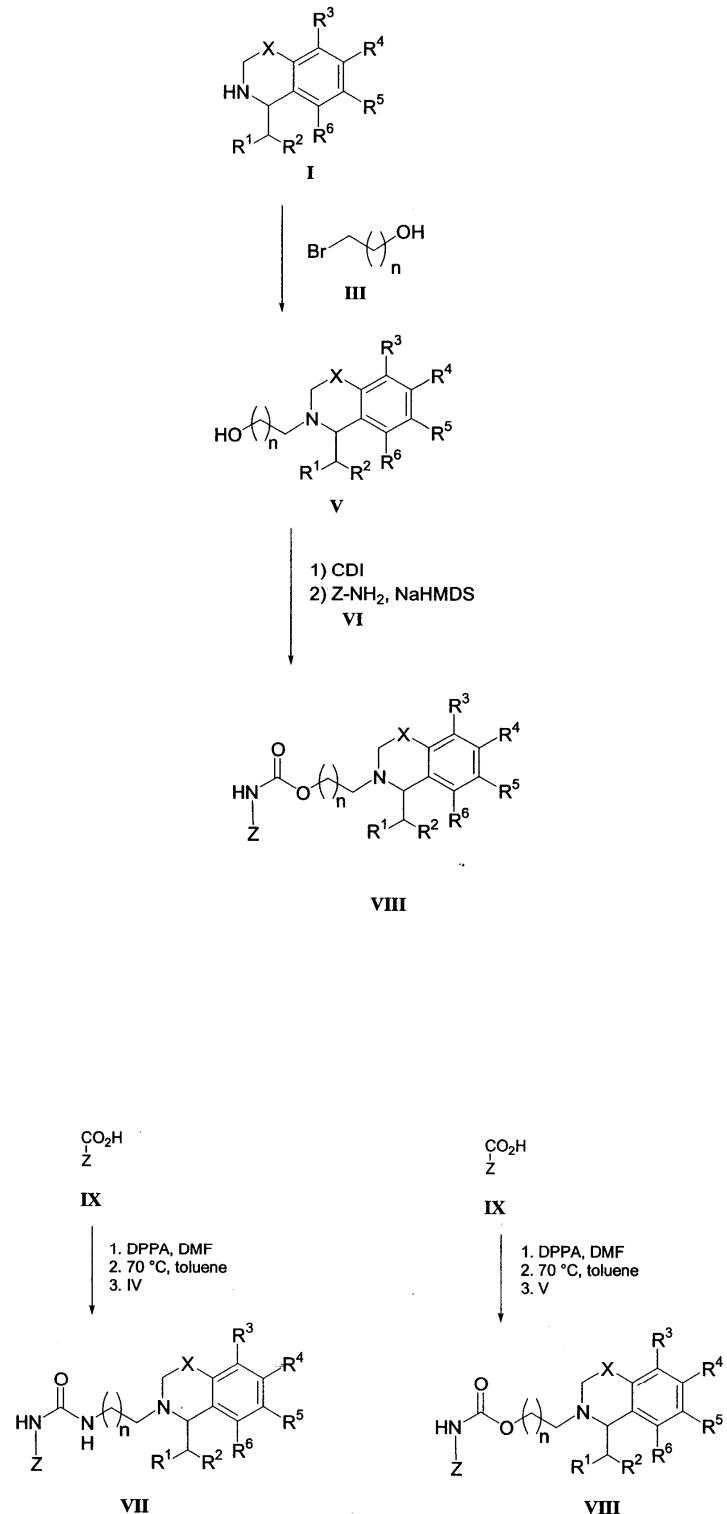
(Whaley WM, Govindachari TR 'The Preparation of 3,4-dihydroisoquinolines and related compounds by the Bischler-Napieralski reaction.' Org. React. (1951) 6, 74-106. Finkelstein J, Chiang E, Brossi A 'Synthesis of 1,2,3,4-tetrahydro-1,1,2,3,3,4,4-heptamethyl-6,7-dimethoxyisoquinoline and related compounds as potential hypotensive agents.' J. Med. Chem. (1971) 14, 584-588. Ukaji Z, Shimizu Y, Kenmoku Y, Ahmed A, Inomata K 'Catalytic asymmetric addition of dialkylzinc to 3,4-dihydroisoquinoline N-oxides utilizing tartaric acid ester as a chiral auxiliary.' Bull. Chem. Soc. Jpn. (2000), 73, 447-452. Zheng W, Nikulin VI, Konkar AA, Vansol SS, Shams G, Feller DR, Miller DD '2-Amino-4-benzyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridines: novel selective beta3-adrenoceptor antagonists.' J. Med. Che.

m(1999), 42, 2287-2294).

-2-

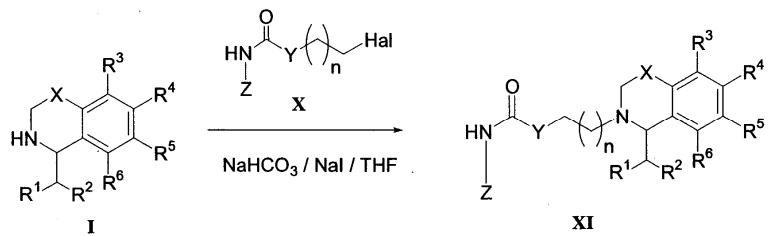
(1989) 111, 4859-4863).





hypertensive Agents' J Med Chem 1988, 31, 1786- 1793) N-
n, X, Y, Z, R ¹ R ⁶ I

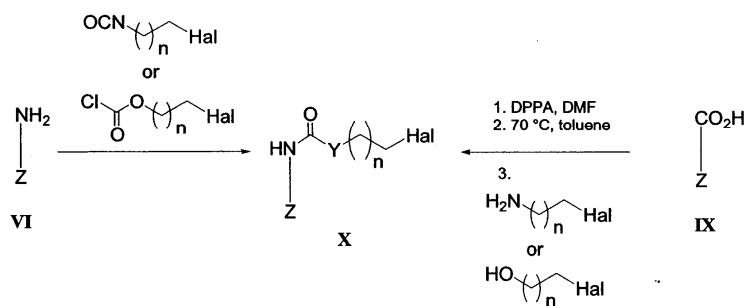
?



Hal

가

()

Y, Z, n
가

AcOH:

BSA:

CDI:

DIPEA

DMAP 4-

DMF:

DMSO

DPPA:

EDTA:

EtOAc:

Et_2O :

Hex:

HOBT: 1 -

HPLC:

HV:

LC-MS:

LAH:

MeOH:

min:

MHz: 가

NaHMDS:

NMR:

ppm: 100

PBS:

PyBOP: (- 1 -) -

rt:

sat.:

TEA:

TFA:

THF:

TLC:

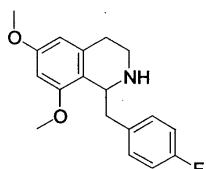
t_R :



6 2-95% CH₃CN 0.45 Mℓ/min 4.6 x 30 mm C18 0.5% TLC
 60 F254 - (MERCK) (t_R) HPLC 21 x 60 mm C18 0.
 5% 1 2-95% CH₃CN Varian/Gilson

A

A1. (4- -)-6,8- -1,2,3,4-



2-(3,5- -)-

THF(30 Mℓ) LiAlH₄ (1.76 g, 46.4 mmol) THF(70 Mℓ) 1,3- -5-(2-
 - (2.43 g, 11.6 mmol; Gairaud CB, Lappin GR, J Org Chem 1953, 18, 1) 0 가
 30 , 4 2N NaOH(20 Mℓ)
 가 15 EtOAC 3
 MgSO₄

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

DMF(50 Mℓ) 2-(3,5- -)- (1.01 g, 5.57 mmol) 4-
 (860 mg, 5.57 mmol), PyBOP(3.17 g), N- (2.2 Mℓ, 12.8 mmol) 가
 14 (60 Mℓ) 가 , EtOAc(4 x 60 Mℓ)
 MgSO₄ (EtOAc
 /Hex, 7:3)

1-(4- -)-6,8- -1,2,3,4-

CH₃CN(3 Mℓ) N-[2-(3,5- -)-]-2-(4- -)- (404 mg, 1.27 m
 mol) POCl₃ (350 μl, 3.82 mmol) 가 30
 , MeOH(10 Mℓ) 14 NaBH₄ (340 mg, 8.61 mmol) 0 CH
 2 Cl₂ 4 MgSO₄
 (CH₂Cl₂/MeOH, 9:1)

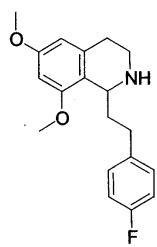
A2-A4A1

A2. 1-(3,4- -)-6,8- -1,2,3,4-

A3. 1-(3,4- -)-6,8- -1,2,3,4-

A4. 1-(3- - 4- -)-6,8- -1,2,3,4-

A5. 1-[2-(4- -)-]-6,8- -1,2,3,4-

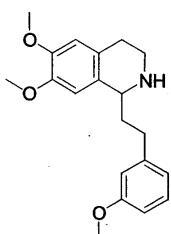


<u>N-[2-(3,5-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine</u>	-	-	-	-	-	-	-	-
2-(3,5-dimethoxyphenyl)quinoxaline-2-amine (1.20 g, 6.62 mmol)	-	-	-	-	-	-	-	-
(1.113 g, 6.62 mmol), PyBOP (3.77 g), DIPEA (2.61 Ml, 15 mmol)	-	-	-	-	-	-	-	-
(60 Ml) 가, DMF (50 Ml) 가, EtOAc (4 x 60 Ml) 가	-	-	-	-	-	-	-	-
MgSO ₄ (60 Ml) 가	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-
<u>1-[2-(4-fluorophenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine</u>	-	-	-	-	-	-	-	-
CH ₃ CN (12 Ml) mmol)	-	-	-	-	-	-	-	-
POCl ₃ (1.04 Ml, 11 mmol)	-	-	-	-	-	-	-	-
, MeOH (35 Ml)	-	-	-	-	-	-	-	-
Cl ₂ (4 x 40 Ml) 가	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-
NaBH ₄ (1.00 g, 26.4 mmol) (40 Ml) 0	-	-	-	-	-	-	-	-
MgSO ₄ (CH ₂ Cl ₂ /MeOH, 9:1)	-	-	-	-	-	-	-	-

A6-A7

A5

<u>A6 . 1-[2-(2,4-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine</u>	-	-	-	-	-	-	-	-
<u>A7 . 1-[2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine</u>	-	-	-	-	-	-	-	-
<u>A8. 6,7-[1-[2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine]</u>	-	-	-	-	-	-	-	-



<u>-[2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine</u>	-	-	-	-	-	-	-	-
THF (20 Ml) 14, 10% (1.33 g, 6.95 mmol)	-	-	-	-	-	-	-	-
3-(3,4-dimethoxyphenyl)quinoxaline-2-amine (1.19 g, 6.62 mmol)	-	-	-	-	-	-	-	-
2-(3,4-dimethoxyphenyl)quinoxaline-2-amine (1.20 g, 6.62 mmol) H ₂ O (100 Ml) EtOAc (100 Ml) 가	-	-	-	-	-	-	-	-
6,7-[1-[2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)propyl]quinoxaline-2-amine]	-	-	-	-	-	-	-	-
THF (50 Ml) oil) (40 Ml) (2.21 g, 6.44 mmol)	-	-	-	-	-	-	-	-
POCl ₃ (4.91 g, 32.2 mmol) (20 Ml) NaBH ₄ (1.21 g, 32.0 mmol) 가	-	-	-	-	-	-	-	-
0 16	-	-	-	-	-	-	-	-

MgSO_4 (150 Mℓ) 가 CH₂Cl₂ (3 x 50 Mℓ)

A9-A45

A8

A9 . 1 - [(E)-2-(2,3-	-) -] - 6,7 -	- 1,2,3,4 -	-
A10 . 1 - [(E)-2-(2,4-	-) -] - 6,7 -	- 1,2,3,4 -	-
A11 . 1 - [(E)-2-(2,5-	-) -] - 6,7 -	- 1,2,3,4 -	-
A12 . 1 - [2-(2,5-	-	-) -] - 6,7 -	- 1,2,3,4 -
A13 . 1 - [2-(2,5-	-) -] - 6,7 -	- 1,2,3,4 -	-
A14 . 1 - [2-(3,4-	-) -] - 6,7 -	- 1,2,3,4 -	-
A15 . 1 - [2-(3,4-	-) -] - 6,7 -	- 1,2,3,4 -	-
A16 . 1 - [2-(3,5-	-	-) -] - 6,7 -	- 1,2,3,4 -
A17 . 1 - [2-(4-	-) -] - 6,7 -	- 1,2,3,4 -	-
A18 . 6,7 -	- 1 - [2-(2 -	-) -] - 1,2,3,4 -	-
A19 . 6,7 -	- 1 - [2-(4 -	-) -] - 1,2,3,4 -	-
A20 . 6,7 -	- 1 - [2-(4 -	-) -] - 1,2,3,4 -	-
A21 . 6,7 -	- 1 -	-	- 1,2,3,4 -	-	-
A22 . 1 -(2,5 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A23 . 1 -(2,6 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A24 . 1 -(3,4 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A25 . 1 -(3,4 -	-) - 6,7,8 -	-	- 1,2,3,4 -	-
A26 . 1 -(3,4 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A27 . 1 -(3,4 -	-) - 6,7 -	- 4,4 -	- 1,2,3,4 -	-
A28 . 1 -(3 -	- 4 -	-) - 6,7 -	- 1,2,3,4 -	-
A29 . 1 -(3 -	- 5 -	-) - 6,7 -	- 1,2,3,4 -	-
A30 . 1 -(4 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A31 . 1 -(4 -	-) - 6,7 -	-	- 1,2,3,4 -	-
A32 . 1 -	- 6,7 -	-	- 1,2,3,4 -	-	-
A33 . 1 -	[1,3]	- 5 -	- 6,7 -	- 1,2,3,4 -	-

A34 . 1 - - 6,7 - - 1,2,3,4 -

A35 . 6 - (3,4 - -) - 2,3,6,7,8,9 - - [1,4] [2,3 - g] -

A36 . 6,7- - 1 - (1 - -) - 1,2,3,4-

A37 . 6,7- - 1 - (2,3,4 - -) - 1,2,3,4 -

A38. 6,7- - 1 - (3,4,5- -) - 1,2,3,4-

A39 . 6,7- - 1 - (3 - -) - 1,2,3,4 -

A40 . 6,7- - 1 - (4 - -) - 1,2,3,4 -

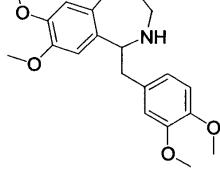
A41 . 6,7- - 1 - - 2 - - 1,2,3,

A42 . 6,7 - - 1 - - 1,2,3,4 -

A43 . 7 - - 1 - (3.4 - -) - 6

A44 1-(3,4,- -)-6- -1 2 3 4-

A45 1-(3,4-dihydro-2H-1,4-benzodioxin-6-yl)-7,8-dihydro-1,3-dihydro-2H-1,4-benzodioxin-6-yl



$$\underline{3 - (3,4 - \quad - \quad) -}$$

THF(175 mL) mmol) 3-(3,4-
mmol) 가 . 가 . (20) 15 30 , 1.5 NaHCO₃ 3 (10.0 g, 47.6 mmol),
- 10 , THF(105 mL) 가 . (25%, 105 mL) 가 .
-)- , (5.0 mL, 52 mmol)
TEA(7.3 mL, 52.4
CH₂Cl₂
MgSO₄

$$\underline{3 - (3,4 - \quad - \quad) - }$$

70 Mℓ THF(400 Mℓ) LiAlH₄ (4.02 g, 106 mmol) 2 3-(3,4-
0 가 , H₂O(5 Mℓ) NaOH 1N(5 Mℓ) 가
. H₂O(40 Mℓ) CH₂Cl₂ (100 Mℓ)
NaHCO₃ MgSO₄

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

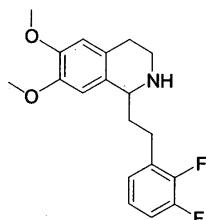
THF(70 Mℓ) 3-(3,4-THF(28 Mℓ) (3,4-) (12.5 g, 64.1 mmol) TEA(10 Mℓ, 71.8 mmol)
 0 13, -)- (13.8 g, 64.1 mmol)
 가 . NaHCO₃ 가 , EtO
 Ac 3 MgSO₄

1-(3,4- -)-7,8- - 2,3,4,5- - 1H- [c]

(185 Mℓ) (6.16 g, 16.5 mmol) POCl₃ (4.95 Mℓ, 54.1 mmol)
mmol) 가 , 0 2 , 0 , 0
MeOH(125 Mℓ) MgSO₄
(CH₂Cl₂/MeOH: 9:1)

- 4)-]- NaBH₄ (4.31 g, 114 CH₂Cl₂)
H₂O

A46. 1-[2-(2,3- -)-]-6,7- - 1,2,3,4- -



3-(2,3- -)-

(100 Mℓ) (7.5 bar) 2,3- 15 - (2.94 g, 16 mmol) Pd(10%, 50 mg) 가 ,

1-[2-(2,3- -)-]-6,7- - 1,2,3,4- -

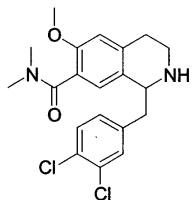
A8 3-(2,3- -)- 2-(3,4- -)-

A47

A46

A47. 1-[2-(2,4- -)-]-6,7- - 1,2,3,4- -

A48. 1-(3,4- -)-6- - 1,2,3,4- - 7-



2-(4- - 3- -)-

THF(300 Mℓ) - 3- LAH(8.0 g, 0.21 mmol)
- 4 (15.0 g, 52.6 mmol)
50 20 , THF(300 Mℓ) 4
EtOAc , 가 , (8 Mℓ), 15% 0.5
NaOH(8 Mℓ), (24 Mℓ)
가 ,

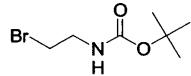
N-[2-(4- - 3- -)-]-2-(3,4- -)-

(100 Mℓ) (12.1 g, 47 mmol)	3,4-	Dean - Strak	(10.6 g, 51.7 mmol) 17	2-(4- 가 2)	-3-	-	-
,	,	,	Dean - Strak	,	16	,	가
가	,	,	2	2	,	,	,
7-	- 1 - (3,4-	-)- 6 -	- 1,2,3,4 -	-	-	-	-
CH ₃ CN(100 Mℓ) .3 g, 30 mmol)	N - [2 - (4- 가 ,	- 3 - ,	-) - (8.1 Mℓ, 13.5 g, 88 mmol) 3] - 2 - (3,4- 가 ,	-) - ,	-) - ,	(13 가 ,
)	,	0	NaBH ₄ (3.61 g, 95 mmol) 16	가	가	가	MeOH(100 Mℓ) EtOAc(200 Mℓ) (200 Mℓ)
)	,	EtOAc(3 x 200 Mℓ) ,	가	,	,	,	,
1 - (3,4 -	-)- 6 -	- 1,2,3,4 -	-	- 7 -	-	-	-
MeOH(150 Mℓ)	1,2 - (14.1 g, 30 mmol) 16 ,	(30 Mℓ) 16 ,	7 - 50% Pd(500 mg) Hyflo	- 1 - (3,4 - 가 ,	-)- 6 - -	-)- 6 - -	- 1,2,3,4 -
,	,	,	,	,	,	,	,
1 - (3,4 -	-)- 7 -	- 6 -	- 3,4 -	- 1H -	- 2 -	-	tert -
—	—	—	—	—	—	—	—
28 mmol)	(30 Mℓ) 1M 30	1 - (3,4 - NaOH(30 Mℓ) di-tert - ,	-)- 6 - ,	- 1,2,3,4 - (6.7 g, 30.8 mmol) EtOAc(50 Mℓ) (50 Mℓ) ,	-)- 7 - -	-)- 7 - -	(9.6 g, 가 ,
,	,	,	,	,	,	,	,
1 - (3,4 -	-)- 6 -	- 7 -	-	- 3,4 -	- 1H -	- 2 -	-
tert -	—	—	—	—	—	—	—
CH ₂ Cl ₂ (100 Mℓ) tert -	1 - (3,4 - (12 g, 27 mmol) (4.45 Mℓ, 27 mmol) NaHCO ₃ (100 Mℓ) (MgSO ₄) (mother liquor)	-)- 7 - -	- 6 - Et ₃ N(3.8 Mℓ, 27 mmol) 가 .	- 3,4 - 가 .	- 1H - .	- 1H - .	- 2 -
,	,	,	,	,	,	,	0
CH ₂ Cl ₂ (2 x 100 Mℓ) (: Et ₂ O, 9:1)	MeOH 가	,	,	,	,	,	30
7 -	- 1 - (3,4 -	-)- 6 -	- 3,4 -	- 1H -	- 2 -	-	tert -
—	—	—	—	—	—	—	—
- 3,4 -	4A -	DMF(15 Mℓ) -	1 - (3,4 - tert - -	-)- 6 - (10 g, 17 mmol) -	- 7 - (4.6 g, 34 mmol) -	20	-
)-	1H - 가 .	- 2 - .	DMF(15 Mℓ) 120 .	120 2 Hyflo	120 2 Hyflo	,	(
EtOAc (1.0 g)	NaHCO ₃ .	MgSO ₄).
Et ₂ O (EtOAc : , 1:4)	Et ₂ O ,	가	EtOAc(3 x 40 Mℓ)
1 - (3,4 -	-)- 6 -	- 3,4 -	- 1H -	- 2,7 -	-	2 - tert -	-
—	—	—	—	—	—	—	—
tert -	(10 Mℓ) (3.60 g, 8.06 mmol)	7 - -	- 1 - (3,4 - -	-)- 6 - KOH(3.00 g)	- 3,4 - 가 .	- 1H - .	- 2 - 160 0.5

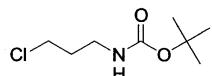
			2M MgSO ₄	HCl			EtOAc(3 x 20 Mℓ)
CH ₂ Cl ₂ :MeOH 19:1,			MeOH				
1-(3,4-	-) - 7 -	- 6 -	- 3,4 -	- 1H -	- 2 -	tert -
CH ₂ Cl ₂ (10 Mℓ)	1-(3,4 -	-) - 6 -	- 3,4 -	- 1H -	- 2,7 -		
2-tert -	(1.0 g, 2.1 mmol)			(0.35 g, 4.3 mmol), HOBr(65 mg, 0.43 mmol),			
DMAP(52 mg, 0.43 mmol), EDC	(493 mg, 2.6 mmol)	가			16		
CH ₂ Cl ₂ (10 Mℓ)		1M	HCl			NaHCO ₃	
MgSO ₄							
1-(3,4 -	-) - 6 -	- 1,2,3,4 -		- 7 -			
- 2 -	4M HCl	1-(3,4 -	-) - 7 -	0	- 6 -	- 3,4 -	- 1H -
tert -		(1.0 g, 2.0 mmol)			1		

A49-A50**A48**A49 . 1-(3,4 - -) - 6 - - 1,2,3,4 - - - 7 -A50 . 1-(3,4 - -) - 6 - - 1,2,3,4 - - - 7 -**A51-A52**

Polniaszek R.P. et al., J. Am. Chem. Soc. (1989) 111, 4859-4863

A51 . (R)-1-(3,4 - -) - 6,7 - - 1,2,3,4 - - -A52 . (R)-1-(4 - -) - 6,7 - - 1,2,3,4 - - -**B.****B1. (2 - -) - tert -**

1N NaOH(200 Mℓ) MeOH(400 Mℓ) 가 , 20 2-
 (25.0 g, 122 mmol) 1 가 , di-tert- (26.6 g, 122 mmol) 가 .
 2.5 MeOH , MgSO₄ CH₂Cl₂ (2 x 175 Mℓ)
 5% (300 Mℓ)

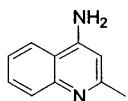
B2. (3 - -) - tert -

3-

B1

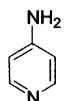
C

C1. 4- - 2-



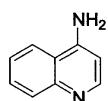
가

C2. 4- -



가

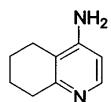
C3. 4- -



Shinkai et al., '4-Aminoquinolines: Novel Nociceptin Antagonists with Analgesic Activity', J. Med. Chem. (2000) 43, 4667-4677

4- N-

C4. 4- - 6,7,8,9-

6,7,8,9- - - N -

THF(125 mL)	5,6,7,8-	(2.66 mL, 20 mmol)	0	THF(25 mL)
m-	(3.8 g, 22 mmol)	가	.	CH ₂ Cl ₂ (75 mL)
.	NaOH(1M, 20 mL)	0.5	,	
.		(10%, 20 mL)		

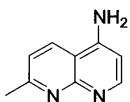
4- - 6,7,8,9- - N -

5,6,7,8-	- N -	(298 mg, 2 mmol)	HNO ₃ (100%, 0.5 mL)	H ₂ SO ₄ (98%, 0.7 mL)
.	2	80	가	CH ₂ Cl ₂ (30 mL)

4- - 6,7,8,9- -

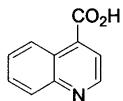
C3 4- - 6,7,8,9- - N -

C5. 4- - 7- - [1.8] -



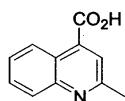
Barlin GB, Tan WL, 'Potential Antimalarials. I 1,8-naphthyridines', Aust J Chem(1984) 37, 1065-1073. radiv
ov R, Haimova M, Simova E 'Synthesis of 4-Amino-3-Pyridyl and 4-Amino-5-Pyrimidyl Aryl Ketones and
Related Compounds via an ortho-Liyhiation reaction', Synthesis(1986), 886-891

C6. -4-



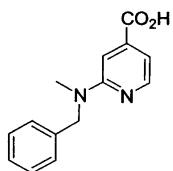
가

C7. 2- - -4-



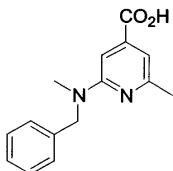
Brasyunas VB et al., 'Synthesis of Quinoline-4-carboxylic acid and its derivatives', Chem. Heterocycl. Compd.(engl. Transl.)(1988) 670-673
(isatin)

C8. 2-(- -)-



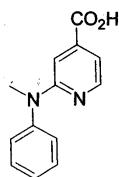
2- mmol)	-	-4-	(300 mg, 1.9 mmol), 120 가 pH 2	(230 mg, 1.9 mmol), CH ₂ Cl ₂ (30 mL) EtOAc(6 x 5 mL)	(192 mg, 1.9 1M NaOH(3 x 5 mL) (MgSO ₄)
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C9. 2-(- -)-6- -



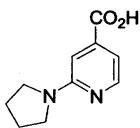
C8 2- -6- - -4-

C10. 2-(- -)-



C8 2- - -4- N-

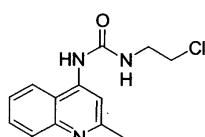
C11. 2- -1- -



C8 2- - -4-

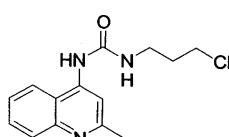
D

D1. 1-(2-) -)-3-(2- - -4-)-



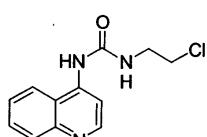
THF(480 Mℓ) 4- -2- (C1, 12.6 g, 80 mmol) 2- (10
 .2 Mℓ, 120 mmol) 가 . 40
 가 1 . , CH₂Cl₂ (100 Mℓ), MeOH(100 Mℓ) 가
 4 x 100 Mℓ) . HV 14 1N HCl(250 Mℓ)
 . NaHCO₃ (2 x 100 Mℓ), (

D2. 1-(3-) -)-3-(2- - -4-)-



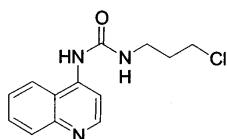
D1 4- -2- (C1) 3-

D3. 1-(2-) -)-3-(-4-)-



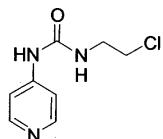
D1 4- -2- (C3) 2-

D4. 1-(3-) -)-3-(-4-)-



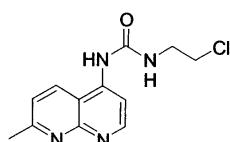
D1 4- -2- (C3) 3-

D5. 1-(2- -)-3-(- 4-)-



D1 4- - (C2) 2-

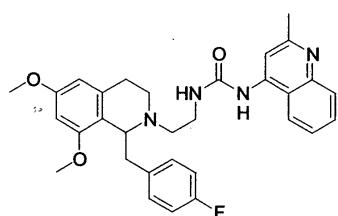
D6. 1-(2- -)-3-(7- - [1,8]- - 4-)-



D1 4- -7- - [1,8]- (C5) 2-

1

1-{2-[1-(4-4-fluorophenyl)methyl]-7-methylimidazo[1,2-a]pyridin-3-yl}-3-(2- -)-6,8- - 3,4- - 1H- - 2-]- }-3-(2- -)-



THF(2.5 M)
50 mg, 0.16 mmol)
1-(4-4-fluorophenyl)methylimidazo[1,2-a]pyridine (A1,
1-(2- -)-3-(2- -)-6,8- - 3,4- - 1H- - 2-]- }-3-(2- -)-
TEA(34.6 μl, 0.25 mmol), NaI(2.5 mg, 0.017 mmol),
D1, 43.8 mg, 0.16 mmol),
5
, HPLC

LC-MS(MeCN/H₂O, 1:1)t_R = 0.93 min, m/z = 529.3(M+1)

2-6

가

1

A1

A4

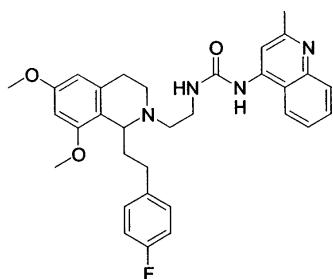
D1

D3

실시 예 번호	실시 예 :	t _R	[M+H] ⁺
2	1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.97	547.30
3	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.05	559.70
4	1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	0.80	533.30
5	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.13	545.24
6	1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	0.78	515.30

7

1-(2-[1-[2-(4-
- 4-)-
-)-]-6,8-
- 3,4-
- 1*H*-
- 2- }-)-3-(2-



1-[2-(4-
-)-]-6,8-
- 1,2,3,4-
(mol) THF(3.0 Mℓ), 1-(2-
-)-3-(2-
-)-4-
- (mol), TEA(66.2 μℓ, 0.475 mmol), NaI(4.8 mg, 0.032 mmol) 가 .
75 , HPLC (A5, 100 mg, 0.317 m
D1, 83.6 mg, 0.317 m
5

LC-MS(MeCN/H₂O, 1:1)t_R = 1.11 min, m/z = 543.5(M+1)

8-9

가

7

A5

A7

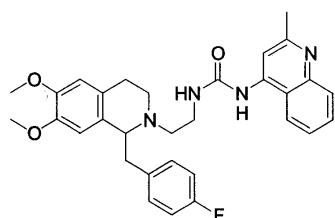
D1

D3

실시 예 번호	실시 예	t _R	[M+H] ⁺
8	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.16	561.34
9	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.15	547.32
10	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.16	561.33
11	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.16	547.31
12	1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.15	529.30

13

1 - {2 - [1 - (4 -) - 6,7 -] - 3,4 - 1*H* - } - 2 -] - } - 3 - (2 -) -



THF(2 Mℓ)
.50 mmol) 1 - (4 -) - 6,7 - 1,2,3,4 - (A31, 0.16 g, 0
HCO₃ (50 mg, 0.6 mmol), NaI(15 mg, 0.1 mmol) 1 - (2 -) - 3 - (2 -) - 4 - (D1, 0.18 g, 0.60 mmol), Na
, HPLC 70 , 5

LC-MS(MeCN/H₂O, 1:1)t_R = 1.10 min, m/z = 529.19(M+1)

14-105

가

13

A1

A52

D1

D5

실시 예 번호	실시 예	t _R	[M+H] ⁺
14	1-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.01	585.19
15	1-(2-{1-[(E)-2-(2,4-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	559.31
16	1-(2-{1-[(E)-2-(2,5-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	559.30
17	1-(2-{1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.33
18	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.34
19	1-(2-{1-[2-(2,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.18	661.30

20	1-(2-{1-[2-(2,5-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.32
21	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.32
22	1-(2-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.09	585.37
23	1-(2-{1-[2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.19	661.30
24	1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	543.32
25	1-(2-{6,7-Dimethoxy-1-[2-(2-methoxy-phenyl)-ethyl]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.36
26	1-(2-{6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.36
27	1-(2-{6,7-Dimethoxy-1-[2-(4-methoxy-phenyl)-ethyl]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.37
28	1-(2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.17	593.35
29	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.11	525.22
30	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.07	461.12

31	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.11	511.07
32	1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea	1.11	539.26
33	1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea	1.10	525.18
34	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.14	555.21
35	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.99	491.07
36	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.06	541.07
37	1-[2-(1-Benzyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.03	387.12
38	1-[2-(1-Benzyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.10	437.08
39	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.09	511.17
40	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.98	447.10
41	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.07	497.08
42	1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.06	417.09
43	1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.11	467.12

44	1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.10	497.10
45	1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.12	547.14
46	1-[2-(6,7-Dimethoxy-1-phenoxyethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.98	463.09
47	1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea	1.08	525.25
48	1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea	1.04	511.17
49	1-[2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-pyridin-4-yl-urea	1.04	507.10
50	1-[2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.10	557.11
51	1-{2-[1-(2,6-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.12	579.26
52	1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.04	483.10
53	1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.10	533.04
54	1-[2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.10	587.11

55	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.94	507.16
56	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.01	557.12
57	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea	0.83	561.30
58	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	571.21
59	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.08	507.16
60	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	557.18
61	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.02	477.10
62	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.08	527.10
63	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	559.33
64	1-{2-[1-(3-Fluoro-5-trifluoromethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.15	597.33

65	1-[2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-pyridin-4-yl-urea	1.09	481.04
66	1-[2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.11	531.08
67	1-(2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl)-3-pyridin-4-yl-urea	1.01	465.11
68	1-[2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.09	515.06
69	1-(2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl)-3-pyridin-4-yl-urea	1.00	537.17
70	1-[2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.08	587.09
71	1-[2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.12	601.29
72	1-[2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-pyridin-4-yl-urea	0.96	537.09
73	1-[2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.03	587.11
74	1-[2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-pyridin-4-yl-urea	1.00	477.11
75	1-[2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.08	527.10

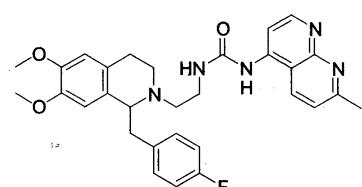
76	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.99	477.12
77	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.07	527.11
78	1-{3-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.09	547.18
79	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea	1.03	585.20
80	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.01	571.19
81	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	585.21
82	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.11	571.21
83	1-{3-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.07	529.22
84	1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5 <i>H</i> -[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-pyridin-4-yl-urea	0.99	491.09
85	1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5 <i>H</i> -[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-quinolin-4-yl-urea	1.07	541.08
86	1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6 <i>H</i> -[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-pyridin-4-yl-urea	1.00	505.07

87	1-[2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6 <i>H</i> -[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl]-3-quinolin-4-yl-urea	1.06	555.08
88	1-[2-(1-Benzhydryl-5,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.14	573.11
89	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.10	523.07
90	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.12	573.08
91	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.09	447.15
92	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.13	497.09
93	1-{2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	557.08
94	1-{2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.14	557.12
95	1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.08	475.12
96	1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	525.09
97	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-4,4-dimethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.29	585.29
98	1-{2-[(<i>R</i>)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.05	571.35

99	1-{2-[<i>(R</i> -1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.01	557.14
100	1-{2-[<i>(R</i> -1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.77	529.08
101	1-{2-[7-Benzyl-oxo-1-(3,4-dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.82	647.1
102	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.77	541.13
103	1-(3,4-Dichloro-benzyl)-6-methoxy-2-[2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl]-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid methylamide	0.78	606.13
104	1-(3,4-Dichloro-benzyl)-6-methoxy-2-[2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl]-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid propylamide	0.82	634.04
105	1-(3,4-Dichloro-benzyl)-6-methoxy-2-[2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl]-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid dimethylamide	0.78	620.00

106

1 - {2 - [1 - (4 -
- 4 -) -] - } - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (7 - - [1,8]



106.1. {2 - [1 - (4 -
- 4 -) -] - } - 6,7 - - 3,4 - - 1H - - 2 -] - } -

THF(40 Mℓ)
3.5 mmol) 1 - (4 -
(2 - -) -) - 6,7 - - 1,2,3,4 - - (A31, 1.05 g,
70 , tert - 5 (B1, 0.94 g, 4.2 mmol) DIPEA 가
HPLC . . . ,

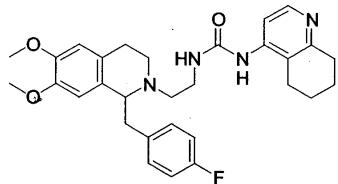
106.2. 1 - {2 - [1 - (4 -
- [1,8] - - 4 -) -] - } - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (7 -

가 AcOH(1 Mℓ) {2 - [1 - (4 -
- 7 - - 4 -) -] - } - 6,7 - - 3,4 - - 1H - - 2 -] -
} - tert - (106.1, 0.22 g, 0.5 mmol) conc. HCl(0.1 Mℓ) 가
5 , CHCl₃ (20 Mℓ) 1N NaOH(15 Mℓ) . . . DMSO(2
Mℓ) CDI(0.2 g, 0.6 mmol, 1.2 eq.) . . . 3 , 4 -
- 7 - - [1,8] - (C5, 0.19 g, 0.6 mmol) 가 . . . 1 NaHMDS(2M/THF, 1.2
5 Mℓ, 2.5 mmol) 가 . . . H₂O(0.4 Mℓ) 가 .

HPLC

LC-MS(MeCN/H₂O, 1:1) t_R = 0.92 min, m/z = 530.3(M+1)

107. 1-[2-[1-(4-
-4-)-]
-)-6,7- -3,4- -1H- -2-]- }-3-(5,6,7
,8-



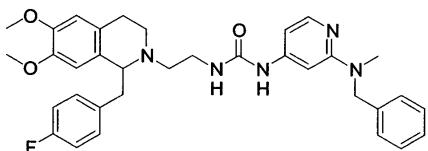
가 AcOH(1 Mℓ) {2-[1-(4-
} - tert- (-)-6,7- -3,4- -1H- -2-]-
5 , CHCl₃ (20 Mℓ) 1N NaOH(15 Mℓ) conc. HCl(0.1 Mℓ) 가
Mℓ) CDI(0.2 g, 0.6 mmol, 1.2 eq.) DMSO(2
-5,6,7,8- (C4, 0.19 g, 0.6 mmol) 3
1.25 Mℓ, 2.5 mmol) 가 30 , 1 NaHMDS(2M/THF,
, H₂O(0.4 Mℓ) 가 .

HPLC

LC-MS(MeCN/H₂O, 1:1) t_R = 0.92 min, m/z = 519.3(M+1)

108

1-[2-(
-2-]- }-
-4-]-3-{2-[1-(4-
-)-6,7- -3,4- -1H-



108.1. - (4- - -2-)- -

DMF(10 Mℓ) 2-(
mg, 3.5 mmol) 0 - -)- (C8, 780 mg, 3.2 mmol) (360
aHCO₃ (2 x 15 Mℓ) (2 x 10 Mℓ) 2 , DPPA(975 mg, 3.5 mmol) 0 2 , 20 12
16 Mℓ) 2 가 . Et₂O(6 x 30 Mℓ) 가 . N
N

108.2. 1-[2-(
-1H- -2-]- }- -4-]-3-{2-[1-(4-
-)-6,7- -3,4-

CH₂Cl₂ (1 Mℓ)
tert- {2-[1-(4-
CH₂Cl₂ (20 Mℓ) 1N NaOH(15 Mℓ)
CH₂Cl₂ (2 Mℓ) (2 Mℓ) - (4- -2-)-
(108.1, 95.7 mg, 0.40 mmol) 가 . 20 15
HPLC TFA(1 Mℓ) 가 . (MgSO₄) -

LC-MS(MeCN/H₂O, 1:1) t_R = 0.73 min, m/z = 584.3(M+1)

109-111

가

108

106.1

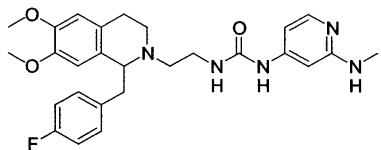
C9

C11

실시 예 번호	실시 예	t _R	[M+H] ⁺
109	1-[2-(Benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-urea	0.76	598.43
110	1-[2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-[2-(methyl-phenyl-amino)-pyridin-4-yl]-urea	0.80	570.10
111	1-[2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl]-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea	0.77	534.09

112

1-{2-[1-(4-
- 4-)- -)-6,7- - 3,4- - 1H- - 2-]- }-3-(2- - 1

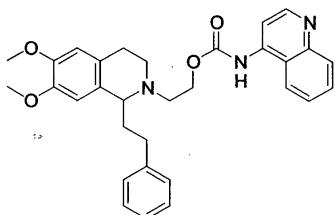


eOH(10 Mℓ) 1-[2-(- - -)- - 4-]-3-{2-[1-(4- -)-6,7- - 3,4-
- 1H- - 2-]- }- (108, 0.12 g, 0.2 mmol) Pd(10%, 20 mg)
HCl(1N, 0.2 Mℓ) 가 0.5 , 15

LC-MS(MeCN/H₂O, 1:1)t_R = 0.77 min, m/z = 534.09(M+1)

113

(- 4-)- 2-(6,7- - 1- - 3,4- - 1H- - 2-)-



113.1. 2-(6,7- - 1- - 3,4- - 1H- - 2-)-

(3 Mℓ) 6,7- - 1- - 1,2,3,4- - (A21, 59.5
mg, 0.2 mmol) 2- (28.3 μℓ, 0.4 mmol) DIPEA(68 μℓ, 0.4 mmol) ,
90 , HPLC

113.2. (- 4-)- 2-(6,7- - 1- - 3,4- - 1H- - 2-)-

THF(1 Mℓ) 2-(6,7-
7 mg, 0.087 mmol) CDI(28.2 mg, 0.174 mmol, 2.0 eq.) 가 .
, 4- (C3, 14 mg, 0.1 mmol) 가 .
μℓ, 0.44 mmol) 가 . 30 , H₂O/AcOH(9:1, 0.4 Mℓ) 가 .
HPLC

LC-MS(MeCN/H₂O, 1:1)t_R = 1.17 min, m/z = 512.19(M+1)

114-120

가

113

A1

A52

C1

C3

실시 예 번호	설시 예	t _R	[M+H] ⁺
114	Quinolin-4-yl-carbamic acid 2-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-ethyl ester	1.09	498.19
115	Quinolin-4-yl-carbamic acid 2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl ester	1.12	516.16
116	Quinolin-4-yl-carbamic acid 3-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl ester	1.05	512.15
117	Quinolin-4-yl-carbamic acid 3-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-propyl ester	1.10	526.19
118	Quinolin-4-yl-carbamic acid 3-[1-(3,4-difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl ester	1.10	548.18
119	Quinolin-4-yl-carbamic acid 3-[1-(3,4-dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl ester	1.10	572.25
120	Quinolin-4-yl-carbamic acid 3-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-propyl ester	1.08	530.12

121

1

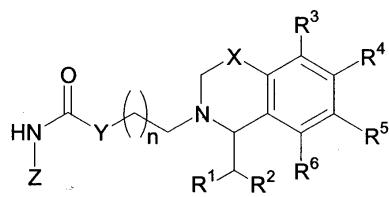
1)

[125] -

[125 I] -
zation of Ro-46-2005, a novel synthetic non-peptide
93, 334, 210-214) -
ikroorganismen und Zellkulturen, cell line #ACC-263)

(Breu V et al., In Vitro characteri
and ET_B receptors. FEBS Lett. 19
(Deutsche Sammlung Von M

가 (Nunc, CatNo 442587) 25 mM HEPES(Fluka, CatNo 05473), 1.0% DMSO(Fluka, CatNo 41644), 0.5%(w/v) BSA Fraction V(Fluka, CatNo 05473) 250 μ l . 300'000 20 pM [125 I] (Anawa Trading SA, Wagnen,



$$X - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C}(\text{CH}_3)_2 -$$

Y NH ·

n 1 2 :

7

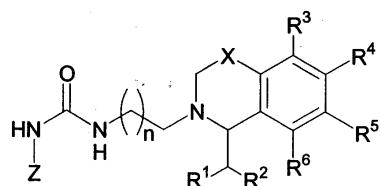
R 2 , , , , R 1 E Z
 , , , , , ,

R^3, R^4, R^5, R^6 , , , , , , ,
 R^5 가 $R^7 R^8 NCO$;

$$R^4 \quad R^5 \quad . \quad , \quad 1 \quad 2 \quad 5 \quad 6$$

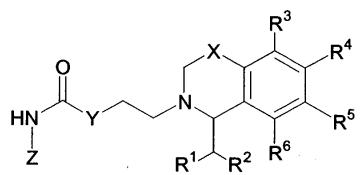
R_7 R_8 Z

2



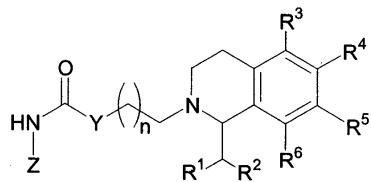
, R¹, R², R³, R⁴, R⁵, R⁶, X, Z, n

3.



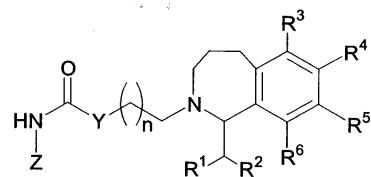
, $R^1, R^2, R^3, R^4, R^5, R^6, X, Y, Z$

4.



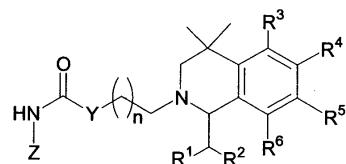
, $R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, n$

5.



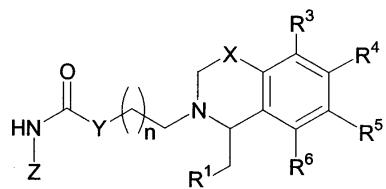
, $R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, n$

6.



, $R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, n$

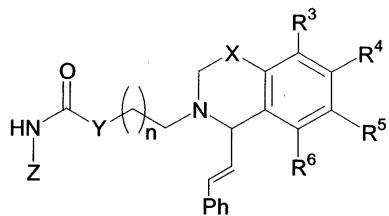
7.



, R¹, R³, R⁴, R⁵, R⁶, X, Y, Z, n

8.

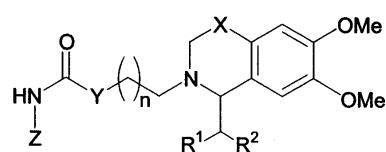
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, Ph ; , R³, R⁴, R⁵, R⁶, X, Y, Z, n

9.

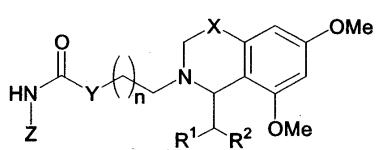
:



, R¹, R², X, Y, Z, n

10.

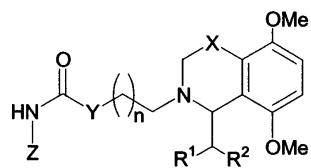
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, R¹, R², X, Y, Z, n

11.

11 :

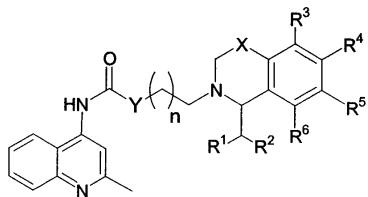


, R¹, R², X, Y, Z, n

|

12.

12 :

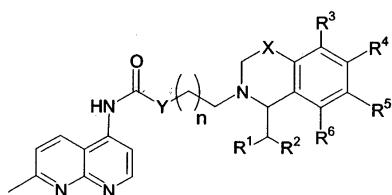


, R¹, R², R³, R⁴, R⁵, R⁶, X, Y, n

|

13.

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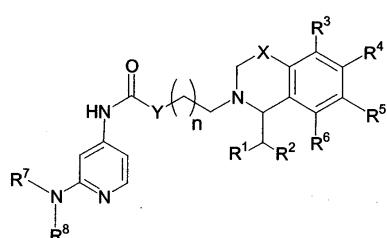


, R¹, R², R³, R⁴, R⁵, R⁶, X, Y, n

|

14.

:

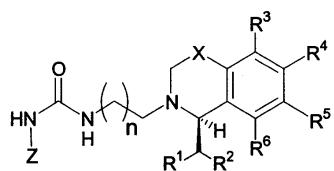


, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, X, Y, n

|

15.

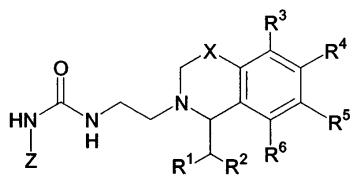
:



, 1,2,3,4-
 R_4 , R_5 , R_6 , X , Z , n | 1 R ; R^1 , R^2 , R^3 , R^4

16.

:



, R^3 , R^4 , R^5 , R^6 ; R^1 , R^2 , Z

17.

1 16

,

:

1-{2-[1-(4- -)-6,8- -3,4- -1H- -2-]- }-3-(2- -
 $-4-$)- ;

 1-{2-[1-(3,4- -)-6,8- -3,4- -1H- -2-]- }-3-(2- -
 $-4-$)- ;

 1-{2-[1-(3- -4-)- -4- -)-6,8- -3,4- -1H- -2-]- }-3-(2- -
 $-4-$ - - ;

 1-{2-[1-(3,4- -)-6,8- -3,4- -1H- -2-]- }-3- -4- -
 $-$;

 1-{2-[1-(3- -4-)- -4- -)-6,8- -3,4- -1H- -2-]- }-3- -4- -
 $-$;

 1-{2-[1-(4- -)-6,8- -3,4- -1H- -2-]- }-3- -4- -
 $-$;

 1-(2-{1-[2-(4- -4-)- -)-]-6,8- -3,4- -1H- -2- }-)-3-(2- -
 $-$;

 1-(2-{1-[2-(2,4- -4-)- -)-]-6,8- -3,4- -1H- -2- }-)-3-(2- -
 $-$;

 1-(2-{1-[2-(3,4- -4-)- -)-]-6,8- -3,4- -1H- -2- }-)-3-(2- -
 $-$;

1-(2-[1-[2-(3,4-
 -4- - ;
)-] -6,8- -3,4- -1H- -2- }-)-3-

 1-(2-[1-[2-(4-
 -4- - ;
)-] -6,8- -3,4- -1H- -2- }-)-3- -

 1-{2-[1-(4-
 -4- - ;
)-] -6,7- -3,4- -1H- -2-]- }-3-(2- -

 1-{2-[1-(3,4-
 -4-)- ;
)-] -7,8- -1,3,4,5- - [c] -2-]- }-3-(2-

 1-(2-[1-[(E)-2-(2,4-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3

 1-(2-[1-[(E)-2-(2,5-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3

 1-(2-[1-[2-(2,3-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[1-[2-(2,4-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[1-[2-(2,5-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[1-[2-(3,4-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[1-[2-(3,4-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[1-[2-(3,5-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3

 1-(2-[1-[2-(4-
 -4-)- ;
)-] -6,7- -3,4- -1H- -2- }-)-3-(2-

 1-(2-[6,7-
 -4-)- ;
)-1-[2-(2- -)-] -3,4- -1H- -2- }-)-3-(2- -

 1-(2-[6,7-
 -4-)- ;
)-1-[2-(3- -)-] -3,4- -1H- -2- }-)-3-(2- -

 1-(2-[6,7-
 -4-)- ;
)-1-[2-(4- -)-] -3,4- -1H- -2- }-)-3-(2- -

 1-(2-[6,7-
 -4-)- ;
)-1-[2-(4- -)-] -3,4- -1H- -2- }-)-3

 1-[2-(6,7- -1- -3,4- -1H- -2-)-] -3-(2- - -4-)- ;

 1-[2-(6,7- -1- -3,4- -1H- -2-)-] -3- -4- - ;

1-[2-(6,7- -1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[3-(6,7- -1- -3,4- -1H- -2-)-]-3-(2- - -4-)- ;
 1-[3-(6,7- -1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- [1,3] -5- -6,7- -3,4- -1H- -2-)-]-3-(2- -4-)- ;
 1-[2-(1- [1,3] -5- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- [1,3] -5- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6,7- -3,4- -1H- -2-)-]-3-(2- - -4-)- ;
 1-[2-(1- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(1- -6- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -2- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -2- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[2-(6,7- -1- -3,4- -1H- -2-)-]-3- -4- - ;
 1-[3-(1- -6,7- -3,4- -1H- -2-)-]-3-(2- - -4-)- ;
 1-[3-(1- -6,7- -3,4- -1H- -2-)-]-3- -4- - ;
 1-{2-[1-(2,5- -)-6,7- -3,4- -1H- -2-]- }-3- -4- - ;
 1-{2-[1-(2,5- -)-6,7- -3,4- -1H- -2-]- }-3- -4- - ;
 1-{2-[1-(2,6- -4-)-]-6,7- -3,4- -1H- -2-]- }-3-(2- - ;
 1-{2-[1-(3,4- -)-6,7- -3,4- -1H- -2-]- }-3- -4- - ;
 1-{2-[1-(3,4- -)-6,7- -3,4- -1H- -2-]- }-3- -4- -

1 - {2 - [1 - (3,4 -
 - ;
) - 6,7,8 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 -

 1 - {2 - [1 - (3,4 -
 - ;
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3,4 -
 - ;
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - (5,6,7,8 -

 1 - {2 - [1 - (3,4 -
 - 4 -) - ;
) - 6,8 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - (2 - -

 1 - {2 - [1 - (3,4 -
 - ;
) - 6,8 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3,4 -
 - ;
) - 6 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3,4 -
 - ;
) - 6 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3 -
 - 4 -) - ;
 - 4 -) -
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - (2 -

 1 - {2 - [1 - (3 -
 - 3 - (2 - -
 - 4 -) - ;
 - 5 -
 - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - - }

 1 - {2 - [1 - (4 -
 - ;
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (4 -
 - ;
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (4 -
 - ;
) - 6,7 -
 - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7 -
 - ;
 - 1 - (2,3,4 -
 -) - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 -

 1 - {2 - [6,7 -
 - ;
 - 1 - (2,3,4 -
 -) - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 -

 1 - {2 - [6,7 -
 - 4 -) - ;
 - 1 - (3,4,5 -
 -) - 3,4 -
 - 1H -
 - 2 -] - } - 3 - (2 - -

 1 - {2 - [6,7 -
 - ;
 - 1 - (3,4,5 -
 -) - 3,4 -
 - 1H -
 - 2 -] - } - 3 - - 4 - -

1 - {2 - [6,7-
 - ; } - 1 - (3,4,5-
 -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

 1 - {2 - [6,7-
 - ; } - 1 - (3- -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7-
 - ; } - 1 - (3- -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7-
 - ; } - 1 - (4- -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7-
 - ; } - 1 - (4- -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {3 - [1 - (3,4-
 - ; } -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

 1 - {3 - [1 - (3,4-
 - 4 -) - ; } -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

 1 - {3 - [1 - (3,4-
 - ; } -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

 1 - {3 - [1 - (3,4-
 - 4 -) - ; } -) - 6,8 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

 1 - {3 - [1 - (3,4-
 - ; } -) - 6,8 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

 1 - {3 - [1 - (4-
 - ; } -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [5 - (3,4-
 4 - - ; } -) - 7,8 - - 5H - [1,3] [4,5-g] - 6 -] - } - 3 - -

 1 - {2 - [5 - (3,4-
 4 - - ; } -) - 7,8 - - 5H - [1,3] [4,5-g] - 6 -] - } - 3 - -

 1 - {2 - [6 - (3,4-
 - 4 - - ; } -) - 2,3,8,9 - - 6H - [1,4] [2,3-g] - 7 -] - } - 3 -

 1 - {2 - [6 - (3,4-
 - 4 - - ; } -) - 2,3,8,9 - - 6H - [1,4] [2,3-g] - 7 -] - } - 3 -

 1 - [2 - (1 - 5,8 - - 3,4 - - 1H - - 2 -) -] - 3 - - 4 - - ;

 1 - [2 - (1 - 5,8 - - 3,4 - - 1H - - 2 -) -] - 3 - - 4 - - ;

 1 - [2 - (1 - 5,8 - - 3,4 - - 1H - - 2 -) -] - 3 - - 4 - - ;

 1 - [2 - (1 - 5,8 - - 3,4 - - 1H - - 2 -) -] - 3 - - 4 - - ;

1 - {2 - [1 - (2,5 -
 ;) - 5,8 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7 - - 1 - (1 - -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [6,7 - - 1 - (1 - -) - 3,4 - - 1H - - 2 -] - } - 3 - - 4 - -

 1 - {2 - [1 - (3,4 -
 - 4 - -) - 6,7 - - 4,4 - - 3,4 - - 1H - - 2 -] - } - 3 - -

 1 - {2 - [(R) - 1 - (3,4 -
 - 4 -) -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

 1 - {2 - [(R) - 1 - (3,4 -
 -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - - 4 -

 1 - {2 - [(R) - 1 - (4 -
 - 4 -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

 1 - {2 - [7 - - 1 - (3,4 -
 - - 4 -) -) - 6 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - -

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

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

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

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

 1 - {2 - [1 - (4 -
 - 4 -) -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (7 - - [1,8]

 1 - {2 - [1 - (4 -
 - 4 -) -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (5,6,7,8 -

 1 - [2 - (- - -) - - 4 -] - 3 - {2 - [1 - (4 - -) - 6,7 - - 3,4 - - 1H -

 1 - [2 - (- - -) - 6 - - - 4 -] - 3 - {2 - [1 - (4 - -) - 6,7 - - 3,4 - -

 1 - {2 - [1 - (4 - - -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - [2 - (- - -

 1 - {2 - [1 - (4 - - -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - - 1 -

 1 - {2 - [1 - (4 - - -) - 6,7 - - 3,4 - - 1H - - 2 -] - } - 3 - (2 - - 1 -

 - 4 - - 2 - (6,7 - - 1 - - 3,4 - - 1H - - 2 -) - ;

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

가

18.

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19.

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21.

18 20

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1 17 .

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