

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

(51) 。 Int. Cl.⁷ (11) 10-2004-0016844
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(86) PCT/EP2002/003131 (87) WO 2002/76979
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(30) 0103422 2001 03 27 EP(EP)
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(71) 4123, 16

(72) , , -68270, 01

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(54) 1,2,3,4-

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2 cDNA
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GPR-14

SENR

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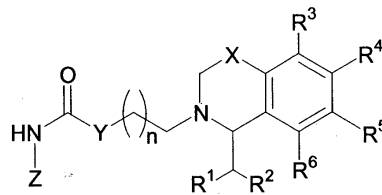
. WO-2001/45700

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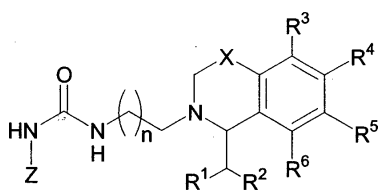
28434 (neurokinin) P 1,2,3,4- . EP 4
H⁺ - ATPase . WO-99/21835
. WO-01/009088 CCR-3


$$X \quad -CH_2-, -CH_2CH_2-, -C(CH_3)_2- \quad ;$$
$$Y \quad , \quad NH \quad ;$$
$$n \quad 1 \quad 2 \quad ;$$
$$Z$$

2, 6 8 - 2, 6 2, 8 -
-4- ; 7 [1, 8] -4- ; 2 R⁷ R⁸ N-
6 가 -4- ;

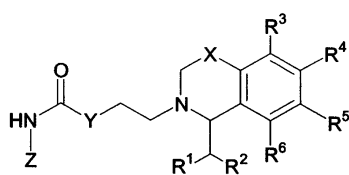
[illegible]
$$R^2 = \frac{(\sum_{i=1}^n R_i^1 E_i Z)^2}{\left(\sum_{i=1}^n R_i^1 \right) \left(\sum_{i=1}^n E_i Z \right)}$$

[illegible]



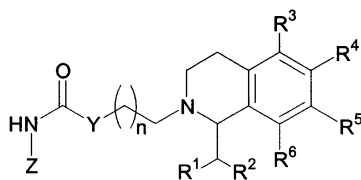
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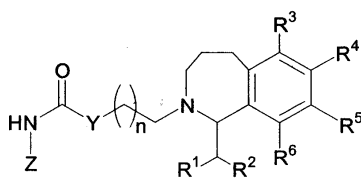
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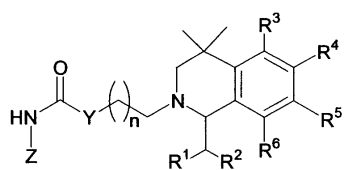
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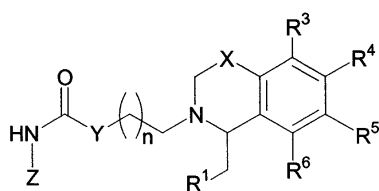
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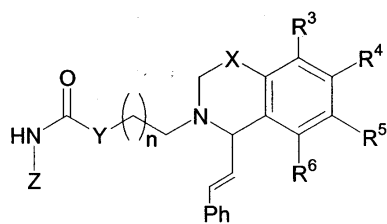
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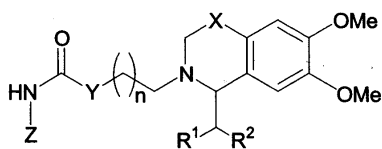
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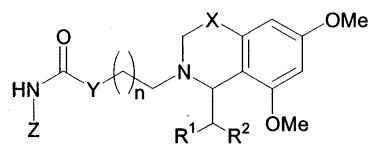
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-, - - , $R^3, R^4, R^5, R^6, X, Y, Z, n$ I .

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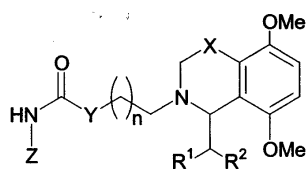
, R¹, R², X, Y, Z, n I .

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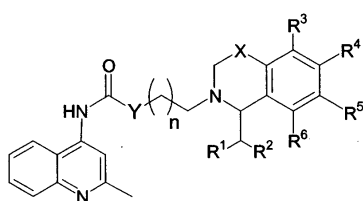
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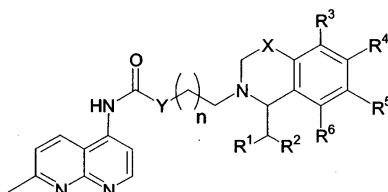
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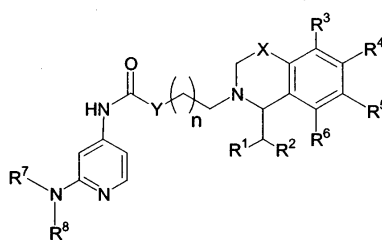
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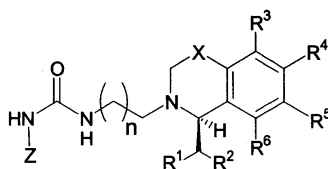
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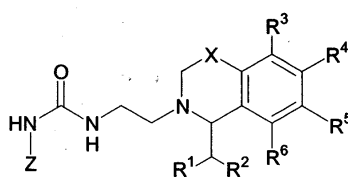
, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X, Y, n$ I .

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4, R^5, R^6, X, Z, n I 1 R ; R^1, R^2, R^3, R

I :



, R³, R⁴, R⁵, R⁶; R¹, R², Z I

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 $-$ $;$

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

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

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 $-4-$ $-$ $;$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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(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, Ahmend 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-1,4,5,6,7-tetrahydrothiazolo[5,4-c] pyridines: novel selective beta3-adrenoceptor antagonists.' J Med Chem

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

-2-

(1989) 111, 4859-4863).

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1-

(Polniasz R.P. et al., J. Am. Chem. Soc.

Bischler-Napieralski

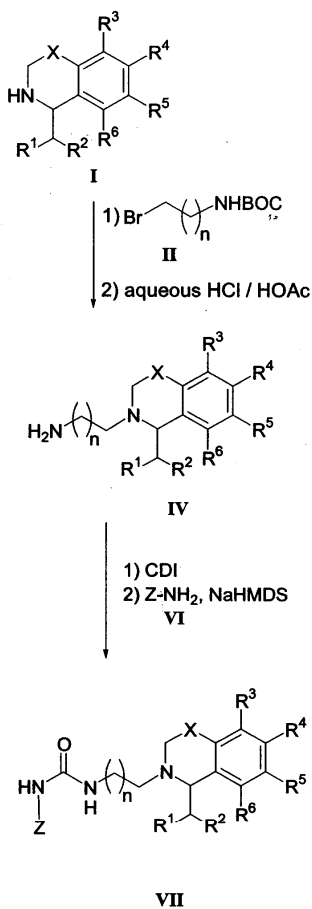
(R)-1- -2-
가 (R)-(+)- -

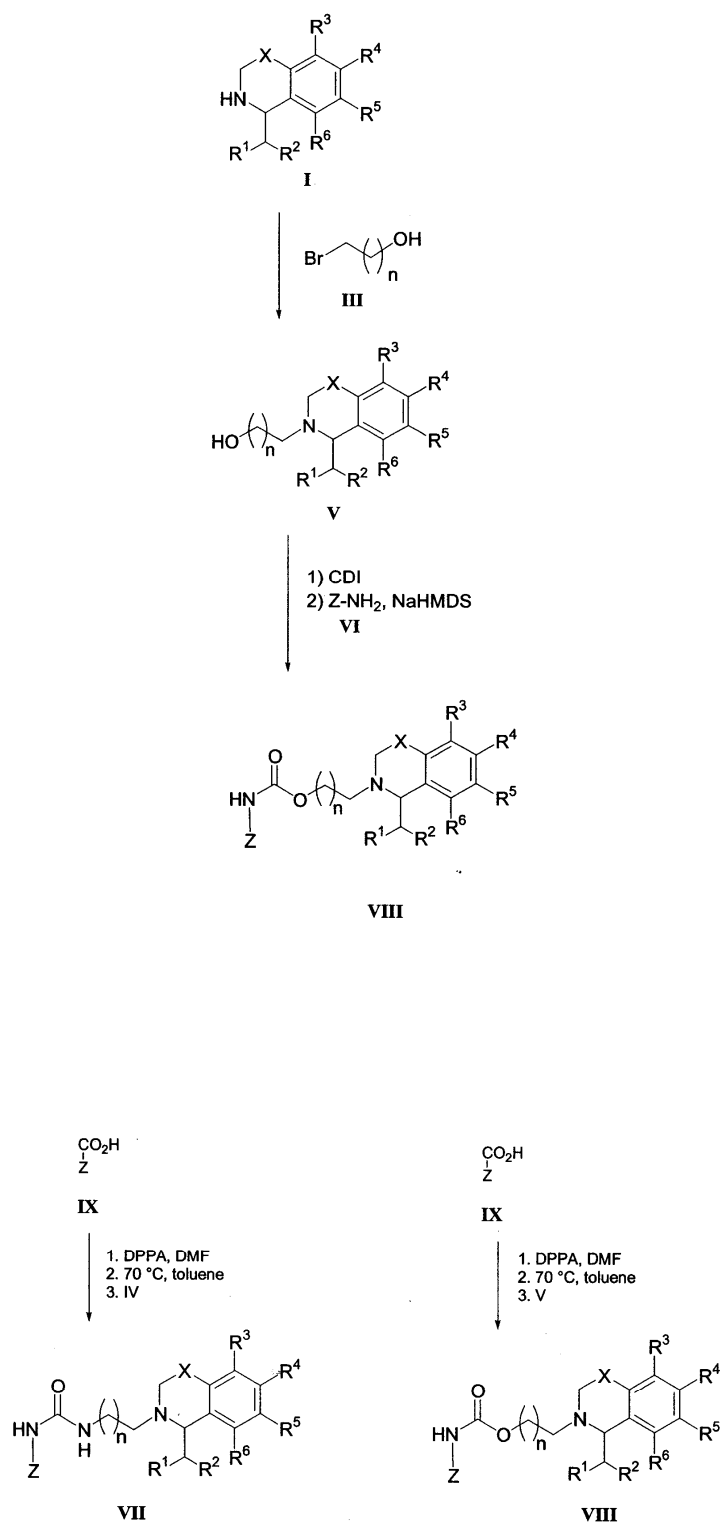
I , I 1,2,3,4-
() ()

1,2,3,4- [c]
() N-

X, Z, R¹ R⁶

() Y NH O , n,





I

DPPA

(thermal rearrangement)

, n, X, Y, Z, R¹ R⁶ I

I

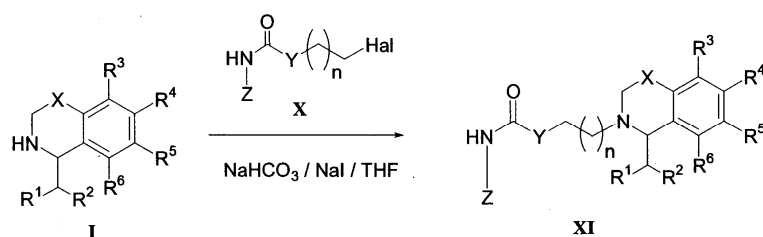
NaHO₃

(Russel RK et al. 'Thiophene Systems. 9 Thienopyrimidinedione Derivatives as Potential Anti

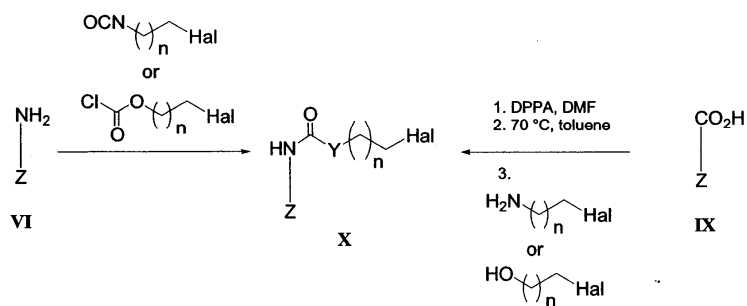
I 1,2,3,4-
THF

hypertensive Agents' J Med Chem 1988, 31, 1786- 1793) N-
n, X, Y, Z, R¹ R⁶ I

?,



Hal, Y, Z, n I
가
()



AcOH:

BSA:

CDI:

DIPEA

DMAP 4-

DMF:

DMSO

DPPA:

EDC: N-(3-)-N'- -

EDTA: -

EtOAc:

Et₂O:

Hex:

HOBT: 1 -

HPLC:

HV:

LC-MS: -

LAH:

MeOH:

min:

MHz: 가

NaHMDS: ()

NMR:

ppm: 100 1

PBS: -

PyBOP: (-1-)-

rt:

sat.:

TEA:

TFA:

THF:

TLC:

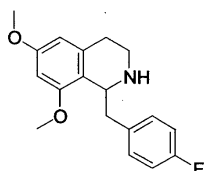
t_R:

, Finnigan HP1100 50 N₂ 가 , LC-MS ESI
 Navigator AQA

0.45 Ml/min 4.6 x 30 mm C18 0.5%
 6 2-95% CH₃ CN (t_R) . TLC -
 60 F254 - (MERCK) HPLC 21 x 60 mm C18 0.
 5% 1 2-95% CH₃ CN 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- -

CH₃ CN(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) NaBH₄ (340 mg, 8.61 mmol) 0
 가 14 . (15 Ml) CH
 2 Cl₂ 4 MgSO₄ .
 (CH₂ Cl₂ /MeOH, 9:1) .

A2-A4

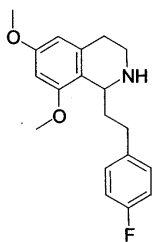
A1 :

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- -



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

2-(3,5-)- (1.20 g, 6.62 mmol) DMF(50 Mℓ) , 3-(4-)
 (1.113 g, 6.62 mmol), PyBOP(3.77 g), DIPEA(2.61 Mℓ, 15 mmol) 가 . 14
 (60 Mℓ) 가 , EtOAc(4 x 60 Mℓ) .
 MgSO₄ (EtOAc/Hex, 7:3
)

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

CH₃CN(12 Mℓ) N-[2-(3,5-)-]-3-(4-)- (1.25 g, 3.77
 mmol) POCl₃ (1.04 Mℓ, 11 mmol) 가 . 30
 , MeOH(35 Mℓ) . NaBH₄ (1.00 g, 26.4 mmol) 0
 가 , 14 . (40 Mℓ) CH₂
 Cl₂ (4 x 40 Mℓ) . MgSO₄ .
 (CH₂Cl₂/MeOH, 9:1)

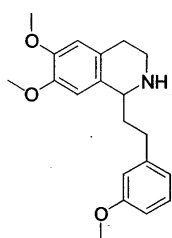
A6-A7

A5 :

A6 . 1-[2-(2,4-)-]-6,8- -1,2,3,4- -

A7 . 1-[2-(3,4-)-]-6,8- -1,2,3,4- -

A8 . 6,7- -1-[2-(3-)-]-1,2,3,4- -



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

THF(20 Mℓ) 3-(3-)- (1.19 g, 6.62 mmol) 3-)- -
 (1.33 g, 6.95 mmol) 2-(3,4-)- (1.20 g, 6.62 mmol) 가
 14 H₂O(100 Mℓ) EtOAc(100 Mℓ) .
 , 10% ,

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

THF(50 Mℓ) N-[2-(3,4-)-]-3-(3-)- (2.21 g, 6.44 mm
 ol) POCl₃ (4.91 g, 32.2 mmol) 가 , 1 .
 (20 Mℓ) 0 ,
 (40 Mℓ) NaBH₄ (1.21 g, 32.0 mmol) 가 . 16

MgSO₄ (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- -

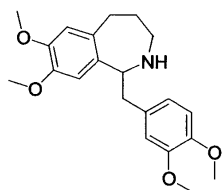
A41 . 6,7- -1- -2- -1,2,3,4- -

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

A43 . 7- -1-(3,4- -)-6- -1,2,3,4- -

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

A45. 1-(3,4- -)-7,8- -2,3,4,5- -1H- [c]



3-(3,4- -)-

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

3-(3,4- -)-

THF(400 Mℓ) 3-(3,4- -)- (11.1 g, 53.0 mmol) THF(1
 70 Mℓ) LiAlH₄ (4.02 g, 106 mmol) 가 가 가 ,
 2 . 0 , H₂O(5 Mℓ) NaOH 1N(5 Mℓ) 가 ,
 . H₂O(40 Mℓ) CH₂Cl₂ (100 Mℓ)
 NaHCO₃ MgSO₄

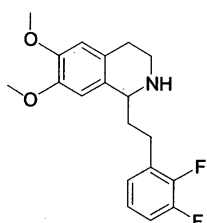
2-(3,4- -)-N-[3-(3,4- -)-]-

THF(70 Mℓ) 3-(3,4- -)- (12.5 g, 64.1 mmol) TEA(10 Mℓ, 71.8 mmol)
 0 THF(28 Mℓ) (3,4- -)- (13.8 g, 64.1 mmol)
 가 . 13 , NaHCO₃ 가 , EtO
 Ac₃ MgSO₄

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

(185 Mℓ) 2-(3,4- -)-N-[3-(3,4- -)-]-
 (6.16 g, 16.5 mmol) POCl₃ (4.95 Mℓ, 54.1 mmol) 4
 MeOH(125 Mℓ) 0
 mmol) 가 , 0 2 , H₂O NaBH₄ (4.31 g, 114
 3 (CH₂Cl₂/MeOH: 9:1) MgSO₄ CH₂Cl₂

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



3-(2,3- -)-

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

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

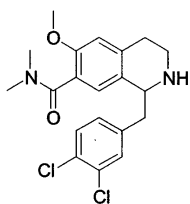
A8 3-(2,3- -)- 2-(3,4- -)-

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

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

(100 Mℓ) 3,4- (10.6 g, 51.7 mmol) 2-(4- -3- -)-
 (12.1 g, 47 mmol) Dean-Strak 17 가 . 16 가
 . Dean-Strak 2 2
 , 가

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

CH₃CN(100 Mℓ) N-[2-(4- -3- -)-]-2-(3,4- -)- (13
 .3 g, 30 mmol) (8.1 Mℓ, 13.5 g, 88 mmol) 가 .
 가 , MeOH(100 Mℓ) MeOH(100 Mℓ)
) , 0 . NaBH₄ (3.61 g, 95 mmol) 가 가
 16 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- (30 Mℓ) 7- -1-(3,4- -)-6- -1,2,3,4-
 - (14.1 g, 30 mmol) 50% Pd(500 mg) 가 .
 , 16 , Hyflo 가

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

28 mmol) (30 Mℓ) 1-(3,4- -)-6- -1,2,3,4- - -7- (9.6 g,
 1M NaOH(30 Mℓ) di-tert- - (6.7 g, 30.8 mmol) 가 .
 30 , EtOAc(50 Mℓ) (50 Mℓ) 가 .

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

tert-

CH₂Cl₂ (100 Mℓ) 1-(3,4- -)-7- -6- -3,4- -1H- -2
 - tert- (12 g, 27 mmol) Et₃N(3.8 Mℓ, 27 mmol) 가 . 0
 (4.45 Mℓ, 27 mmol) 가 . 30
 NaHCO₃ (100 Mℓ) CH₂Cl₂ (2 x 100 Mℓ) ,
 (MgSO₄) MeOH
 (mother liquor) (:Et₂O, 9:1) 가 .

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

-3,4- 4A DMF(15 Mℓ) 1-(3,4- -)-6- -7-
 -1H- -2- (10 g, 17 mmol) 20
 . DMF(15 Mℓ) (4.6 g, 34 mmol) ()
 가 가 120
)- (1.0 g) 가 , 120 2
 EtOAc NaHCO₃ Hyflo . EtOAc(3 x 40 Mℓ)
 . MgSO₄
 Et₂O
 (EtOAc: , 1:4) 가 .

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

(10 Mℓ) 7- -1-(3,4- -)-6- -3,4- -1H- -2-
 tert- (3.60 g, 8.06 mmol) KOH(3.00 g) 가 , 160 0.5

2M HCl EtOAc(3 x 20 Ml)
MgSO₄
CH₂Cl₂:MeOH 19:1, MeOH

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

CH₂Cl₂ (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), HOBt(65 mg, 0.43 mmol),
DMAP(52 mg, 0.43 mmol), EDC (493 mg, 2.6 mmol) 가
MgSO₄ CH₂Cl₂ (10 Ml) 1M HCl NaHCO₃

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

4M HCl 1-(3,4- -)-7- -6- -3,4- -1H-
-2- tert- (1.0 g, 2.0 mmol) 0 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

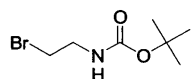
:

A51 . (R)-1-(3,4- -)-6,7- -1,2,3,4- -

A52 . (R)-1-(4- -)-6,7- -1,2,3,4- -

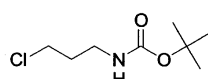
B.

B1. (2- -)- tert-



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

B2. (3- -)- tert-



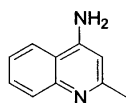
3-

B1

C

C1. 4-

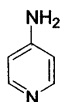
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가

C2. 4-

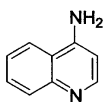
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가

C3. 4-

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

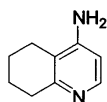
4-

N-

C4. 4-

-6,7,8,9-

-

6,7,8,9-

-

-N-

THF(125 Mℓ)

5,6,7,8-

m-

(3.8 g, 22 mmol)

NaOH(1M, 20 Mℓ)

가

(2.66 Mℓ, 20 mmol)

. 0.5 ,
(10%, 20 Mℓ)

0

THF(25 Mℓ)

CH₂Cl₂ (75 Mℓ)4--6,7,8,9-

-

-N-

5,6,7,8-

-N-

2

(298 mg, 2 mmol)
80 가HNO₃ (100%, 0.5 Mℓ)
(100 g)H₂SO₄ (98%, 0.7 Mℓ)
CH₂Cl₂ (30 Mℓ)4--6,7,8,9-

-

C3

4-

-6,7,8,9-

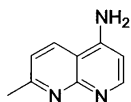
-

-N-

C5. 4-

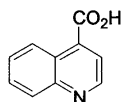
-7-

-[1.8]-



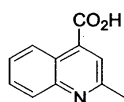
Barlin GB, Tan WL, 'Potential Antimalarials. I 1,8-naphthyridines', Aust J Chem(1984) 37, 1065-1073. radiv
ov R, Haimova M, Simova E 'Synthesis of 4-Amino-3-Pyridiyl and 4-Amino-5-Pyrimidyl Aryl Ketones and
Related Compounds via an ortho-Liyhiation reaction', Synthesis(1986), 886-891

C6. -4-



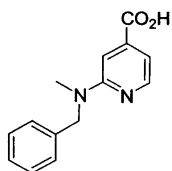
가 .

C7. 2- - -4-



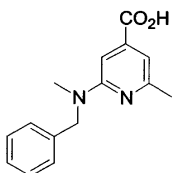
Brasyunas VB et al., 'Synthesis of Quinoline-4-carboxylic acid and its derivatives', Chem. Heter
ocycl. Compd.(engl. Transl.)(1988) 670-673 (isatin)

C8. 2-(- -)-



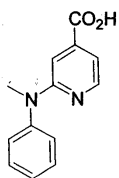
2- mmol) - -4- 12 (300 mg, 1.9 mmol), CH₂Cl₂ (30 Ml) (230 mg, 1.9 mmol), (192 mg, 1.9
pH 2 EtOAc(6 x 5 Ml) 1M NaOH(3 x 5 Ml)
(MgSO₄)

C9. 2-(- -)-6- -



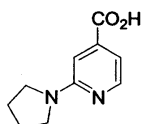
C8 2- -6- - -4-

C10. 2-(- -)-



C8 2- - -4- N-

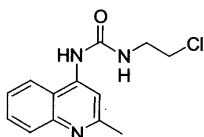
C11. 2- -1- -



C8 2- - -4-

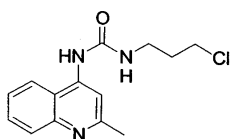
D

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



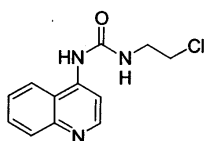
THF(480 Mℓ) 4- -2- (C1, 12.6 g, 80 mmol) 2- (10
 .2 Mℓ, 120 mmol) 가 . 40 MeOH(100 Mℓ) 가 ,
 가 1 , CH₂Cl₂ 1N HCl(250 Mℓ)
 , CH₂Cl₂ (100 Mℓ), NaHCO₃ (2 x 100 Mℓ), (
 4 x 100 Mℓ) . HV 14 .

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



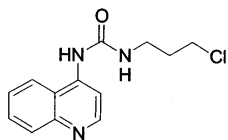
D1 4- -2- (C1) 3-

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



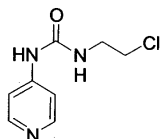
D1 4- -2- (C3) 2-

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



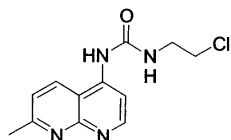
D1 4- -2- (C3) 3-

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



D1 4- - (C2) 2-

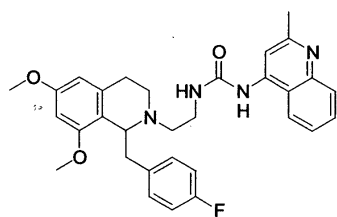
D6. 1-(2- -)-3-(7- -[1,8]- -4-)-



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

1

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



THF(2.5 Mℓ) 1-(4- -)-6,8- -1,2,3,4- - (A1,
50 mg, 0.16 mmol) 1-(2- -)-3-(2- - -4-)- (D1, 43.8 mg, 0.16 mmol),
TEA(34.6 μℓ, 0.25 mmol), NaI(2.5 mg, 0.017 mmol) 가 75 , 5
HPLC

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

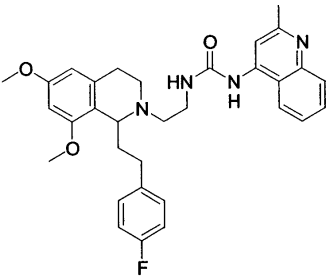
2-6

가 1 A1 A4 D1 D3

실시예 번호	실시예	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- -)-]-6,8- -3,4- -1H- -2- }-)-3-(2-



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

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

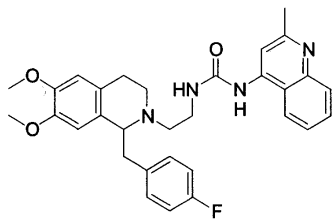
8-9

가 7 A5 A7 D1 D3

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



THF(2 Mℓ) 1-(4- -)-6,7- -1,2,3,4- - (A31, 0.16 g, 0.50 mmol) 1-(2- -)-3-(2- - -4-)- (D1, 0.18 g, 0.60 mmol), NaHCO₃ (50 mg, 0.6 mmol), NaI(15 mg, 0.1 mmol) 가 70 , 5 HPLC .

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

실시예 번호	실시예	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-phenoxy-methyl-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

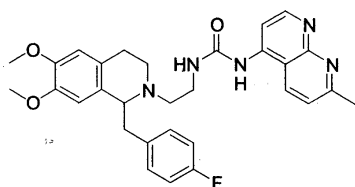
76	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.99	477.12
77	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.07	527.11
78	1-{3-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1 <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- <i>g</i>]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- <i>g</i>]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- <i>g</i>]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-6H-[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-1H-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.14	573.11
89	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.10	523.07
90	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.12	573.08
91	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.09	447.15
92	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1H-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-1H-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-1H-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-1H-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-1H-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-1H-isoquinolin-2-yl]-ethyl]-3-quinolin-4-yl-urea	1.29	585.29
98	1-[2-[(R)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.05	571.35

99	1-{2-[(R)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.01	557.14
100	1-{2-[(R)-1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.77	529.08
101	1-{2-[7-Benzyloxy-1-(3,4-dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1H-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-1H-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- -)-6,7- -3,4- -1H- -2-]- }-3-(7- -[1,8]-
-4-)-



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

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

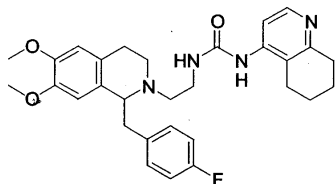
106.2. 1-{2-[1-(4- -)-6,7- -3,4- -1H- -2-]- }-3-(7-
-[1,8]- -4-)-

가 AcOH(1 Mℓ) {2-[1-(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 . 30 , 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-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-3-(5,6,7,8-tetrahydroquinolin-2-yl)-1H-imidazo[4,5-f]quinoline-4-carboxamide

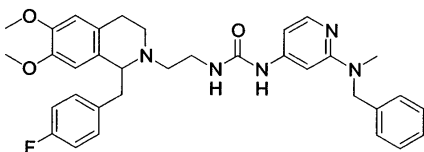


107.1. 1-{2-[1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-3-(5,6,7,8-tetrahydroquinolin-2-yl)-1H-imidazo[4,5-f]quinoline-4-carboxamide
 5 tert-butyl (106.1, 0.22 g, 0.5 mmol)
 CHCl₃ (20 Ml) 1N NaOH(15 Ml)
 CDI(0.2 g, 0.6 mmol, 1.2 eq.)
 -5,6,7,8- (C4, 0.19 g, 0.6 mmol) 가
 1.25 Ml, 2.5 mmol) 가
 HPLC

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

108

1-[2-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-3-{2-[1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-1H-imidazo[4,5-f]quinoline-4-carboxamide



108.1. 1-[2-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-3-{2-[1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-1H-imidazo[4,5-f]quinoline-4-carboxamide

DMF(10 Ml) 2-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl (C8, 780 mg, 3.2 mmol) (360 mg, 3.5 mmol) 0 가 . 5 , DPPA(975 mg, 3.5 mmol) 가 0 2 , 20 12
 (10 g) Et₂O(6 x 30 Ml) N
 aHCO₃ (2 x 15 Ml) (2 x 10 Ml) 가
 16 Ml) 2 가

108.2. 1-[2-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-3-{2-[1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl]-1H-imidazo[4,5-f]quinoline-4-carboxamide

CH₂Cl₂ (1 Ml) 2-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroquinolin-2-yl (106.1, 0.22 g, 0.5 mmol) -1H- -2-]- }
 tert- (TFA(1 Ml) 가 . 2 ,
 CH₂Cl₂ (20 Ml) 1N NaOH(15 Ml) (MgSO₄)
 CH₂Cl₂ (2 Ml) (2 Ml) - (4- - -2-)- -
 (108.1, 95.7 mg, 0.40 mmol) 가 . 20 15
 HPLC

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

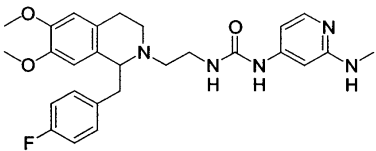
109-111

가 108 106.1 C9 C11

실시예 번호	실시예	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-1H-isoquinolin-2-yl]-ethyl}-urea	0.76	598.43
110	1-[2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-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-1H-isoquinolin-2-yl]-ethyl]-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea	0.77	534.09

112

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

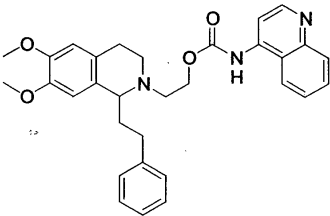


eOH(10 Mℓ) 1-[2-(- -)- -4-]-3-{2-[1-(4- -)-6,7- -3,4-
-1H- -2-]- }- (108, 0.12 g, 0.2 mmol) Pd(10%, 20 mg)
HCl(1N, 0.2 Mℓ) 가 . 0.5 , 15

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 , 5 , HPLC

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

THF(1 Mℓ) 2-(6,7- -1- -3,4- -1H- -2-)- (113.1, 29.
 7 mg, 0.087 mmol) CDI(28.2 mg, 0.174 mmol, 2.0 eq.) 가 . 3
 , 4- - (C3, 14 mg, 0.1 mmol) 가 . 1 NaHMDS(2M/THF, 218
 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

실시예 번호	실시예	t _R	[M+H] ⁺
114	Quinolin-4-yl-carbamic acid 2-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-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-1H-isoquinolin-2-yl]-ethyl ester	1.12	516.16
116	Quinolin-4-yl-carbamic acid 3-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propyl ester	1.05	512.15
117	Quinolin-4-yl-carbamic acid 3-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1H-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-1H-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-1H-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-1H-isoquinolin-2-yl]-propyl ester	1.08	530.12

121

I

1) [¹²⁵I] -

[¹²⁵I] - (Breu V et al., In Vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214) - TE-671 (Deutsche Sammlung Von Mikroorganismen und Zellkulturen, cell line #ACC-263)

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 μℓ
 . 300'000 20 pM [¹²⁵I] (Anawa Trading SA, Wagnen,

Switzerland, 2130Ci/mmol) 가 가 20 4
 100 nM U -
 GF/C (Packard, CatNo 6005174)
 50 μ l (Packard, MicroScint 20, CatNo 6013621)
 가 (Packard Bioscience, TopCount NXT)
 100% DMSO 10 가
 DMSO 1.0% IC50
 [¹²⁵ I] U - 50%
 0.206 nM IC50 U -
 1 10000 nM IC50 IC50

	IC50[nM]
20	67
22	63
29	125
58	550

2) -

Wilstar (CO₂) 3 mm, #1 #3 37 95% O₂ 5% CO₂ Krebs- Henseleit (mM; NaCl 115, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.5, NaHCO₃ 25, CaCl₂ 2.5, 10; pH 7.4) 10 Mℓ (isometric tension) (EMKA Technologies SA, Paris, France). 3g (resting tension) 10⁻¹ 1 M 10⁻⁸ M) 가 1.09 ± 0.1 nM EC50 U- pD₂' 가 : pD₂' = Log(CR - 1) - Log[B], CR [B] pD₂'

	pD ₂ '
29	5.23
93	5.45

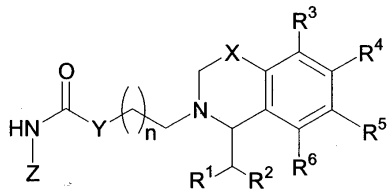
(57)

1.

가

•

•



X = -CH₂-, -CH₂CH₂-, -C(CH₃)₂- ;

$$Y \quad , \quad NH \quad ;$$
$$n \quad 1 \quad 2 \quad ;$$
$$Z$$

2, 6 8 - 2,6 2,8 -
-4- ; 7 [1,8] -4- ; 2 R⁷ R⁸ N-
6 가 -4- ;

[illegible]

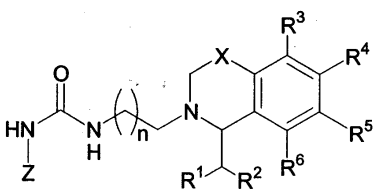
R² , , R¹ E Z , - , -
 , , ,
 - ;

$$\begin{array}{cccccccc} R^3, R^4, R^5, R^6 & & & & & & & \\ R^5 & \text{가} & R^7 R^8 NCO & ; & & & & \end{array}$$
$$R^4 \quad R^5 \quad , 1 \quad 2 \quad 5 \quad 6$$
$$R^7, R^8, \dots, N,$$

2.

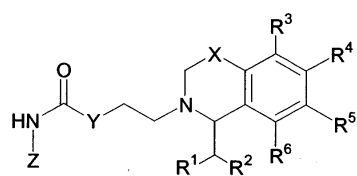
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$$, R^1, R^2, R^3, R^4, R^5, R^6, X, Z, n \quad |$$

3.

$$\vdots$$

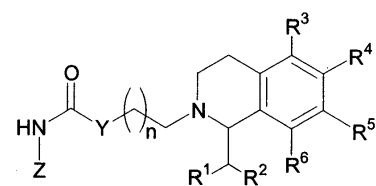


, R¹, R², R³, R⁴, R⁵, R⁶, X, Y, Z

I

4.

:

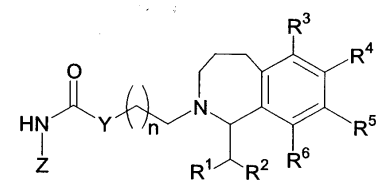


, R¹, R², R³, R⁴, R⁵, R⁶, Y, Z, n

I

5.

:

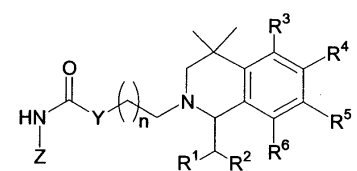


, R¹, R², R³, R⁴, R⁵, R⁶, Y, Z, n

I

6.

:

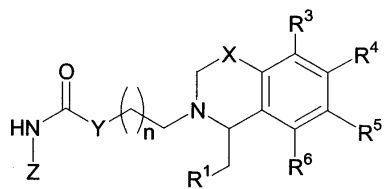


, R¹, R², R³, R⁴, R⁵, R⁶, Y, Z, n

I

7.

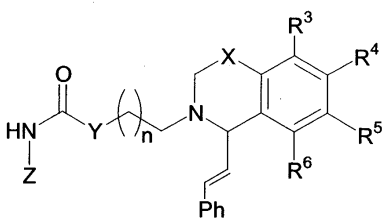
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, R¹, R³, R⁴, R⁵, R⁶, X, Y, Z, n | .

8.

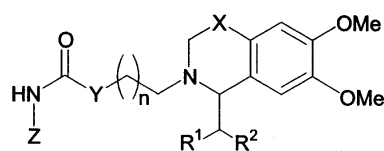
:



, Ph ; , R³, R⁴, R⁵, R⁶, X, Y, Z, n | .

9.

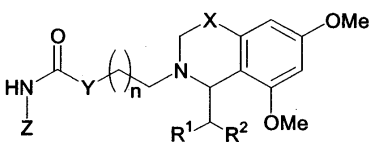
:



, R¹, R², X, Y, Z, n | .

10.

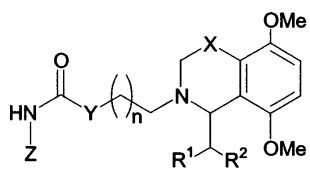
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, R¹, R², X, Y, Z, n | .

11.

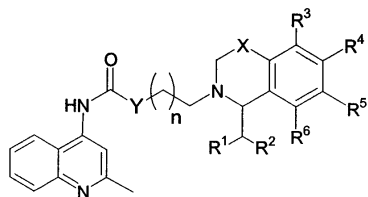
11 :



, R¹, R², X, Y, Z, n I .

12.

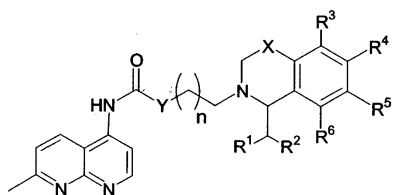
12 :



, R¹, R², R³, R⁴, R⁵, R⁶, X, Y, n I .

13.

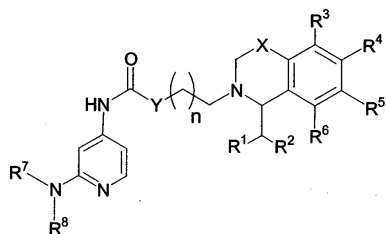
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, R¹, R², R³, R⁴, R⁵, R⁶, X, Y, n I .

14.

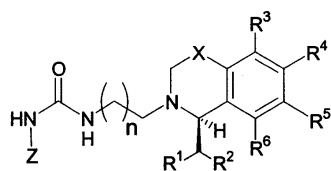
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, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, X, Y, n I .

15.

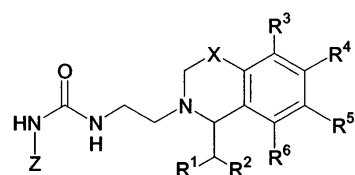
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, 1,2,3,4-
4, R⁵, R⁶, X, Z, n I . ; R¹, R², R³, R⁴

16.

:



, R³, R⁴, R⁵, R⁶ ; R¹, R², Z I .

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$1-[2-(1-$ $-5,8-$ $-3,4-$ $-1H-$ $-2-)-$ $\}-3-$ $-4-$ $-$;

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

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

$1-[2-(1-$ $-5,8-$ $-3,4-$ $-1H-$ $-2-)-$ $\}-3-$ $-4-$ $-$;

$1-[2-(1-$ $-5,8-$ $-3,4-$ $-1H-$ $-2-)-$ $\}-3-$ $-4-$ $-$;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

-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.

1 17

19.

1 17

[illegible]

20.

1 17

21.

18 20

18, 20, ACE, TNF, (peroxisome), 1, 17

22.