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C07D 215/38

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2004 08 12

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(87)

2003 08 21

(30) 02003115.9 2002 02 13 EP(EP)

(71) -
-4070 124

(72) -4313 4

79206 21

-
79639 - 14

79110 5

-4058 52

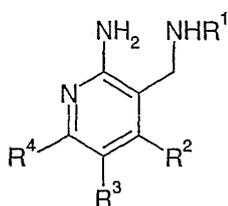
(74)

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(54) - -

I 가 :

I

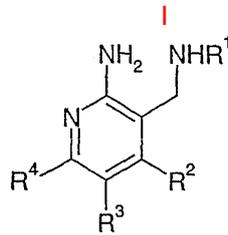


R¹, R², R³, R⁴

DPP-IV

/

I 가 :



R¹ ;
 R² ;
 R³ R⁴ ;
 S 5-, 6- 7- O, N S
 5- 6- O, N

DPP-IV IV (EC.3.4.14.5, DPP-IV)
 가 GLP-1 1(GLP-1)
 . DPP-IV 2
 , DPP-IV 2
 ((Vilhauer) WO 98/19998)
 WO 99/38501 , 19616486 , 1983459
 1 , WO 01/40180 , 01/55105 , 6110949 ,
 00/34241 6011155

DPP-IV

DPP-IV

(Morbus Crohn),

DPP-IV

(:)

가

1 6 ,

1 4

가 .가

1 10

1가

1 20,

1 16,

가 ,n- ,3-

가 ,n- ,2-

1 6,

1 4

1 ,t-

가

R' R'-O-

R' - R'-O-

가

가

[1,3]

1가

가

1가

가

p-

I

, R¹

, R¹

, R²

R²

[1,3]

, R²

가

R² 2,4-

, R³ R⁴

, R³ R⁴

O, N S

, 5-, 6-

7-

(A)

O, N S

5-

6-

(B)

(:)

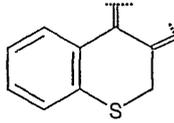
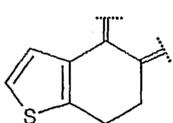
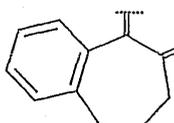
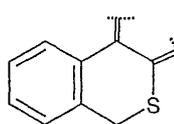
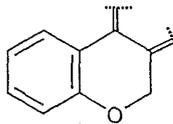
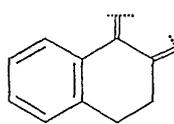
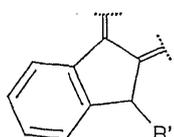
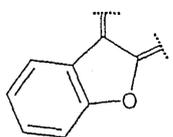
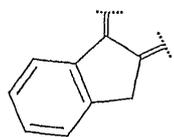
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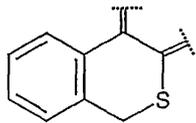
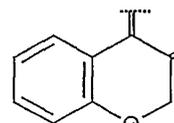
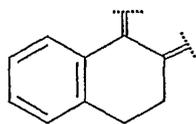
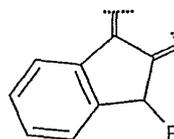
(:)

A

B



, R'



및

, R'

)

(:

R¹

; R²

(:

)

(:

3 R⁴

O, N S

2,4-

; R

-, 6- 7- O, N S
 5- 6- (:), (:), (:)
 -, - - | . (:) (:)
 I 가 :

3- -4-(2,4- -)-5,6- - [h] -2- ;
 3- -4-(2,4- -)-5H- [1,2-b] -2- ;
 3- -4-(2,4- -)-6,7- -5H- [6,7] [1,2-b] -2- ;
 3- -4-(2,4- -)-7- -5H- [1,2-b] -2- ;
 3- -4-(2,4- -)-7,8- -5H- [1,2-b] -2- ;
 3- -4-(2,4- -)- [4,5] [3,2-b] -2- ;
 2- -1-(2,4- -)-10H-9- -4- - -3- ;
 3- -4-(2,4- -)-5,6- - [2,3-h] -2- ;
 2- -1-(2,4- -)-6- -10H-9- -4- - -3- ;
 2- -1-(2,4- -)-10H-9- -4- - -3- ;
 3- -4-(2,4- -)-5- -5H- [1,2-b] -2- ;
 2- -1-(2,4- -)-9H-10- -4- - -3- ;
 3- -2- -4-(2,4- -)-10- -6,7- -5H- [6,7] [1,2-b] ;
 2- -1-(2,4- -)-10H-9- -4- - -3- ;
 3- -4-(2,4- -)-5- -5H- [1,2-b] -2- ;
 3- -4-(2,4- -)-7- -5H- [1,2-b] -2- ;
 3- -4-(2,4- -)-8- -5H- [1,2-b] -2- ;
 3- -4-(2,4- -)-9- -5,6- - [h] -2- ;
 2- -6- -1-(2,4- -)-10H-9- -4- - -3- ;
 3- -4-(2,4- -)-7,9- -5,6- - [h] -2- ;
 2- -1-(2,4- -)-6- -10H-9- -4- - -3- ;
 3- -7- -4-(2,4- -)-5H- [1,2-b] -2- ;
 3- -4-p- - -2- ;
 3- -6- -4-(2- -)- -2- ;
 3- -6- -4-(2- -)- -2- ;

3- -4- -6- - -2- ;

3- -4-(2- -)- -2- ;

3- -4-(2,4- -)- -2- ;

3- -4-(2- -)- -2- ;

3- -4-(4- -)- -2- ;

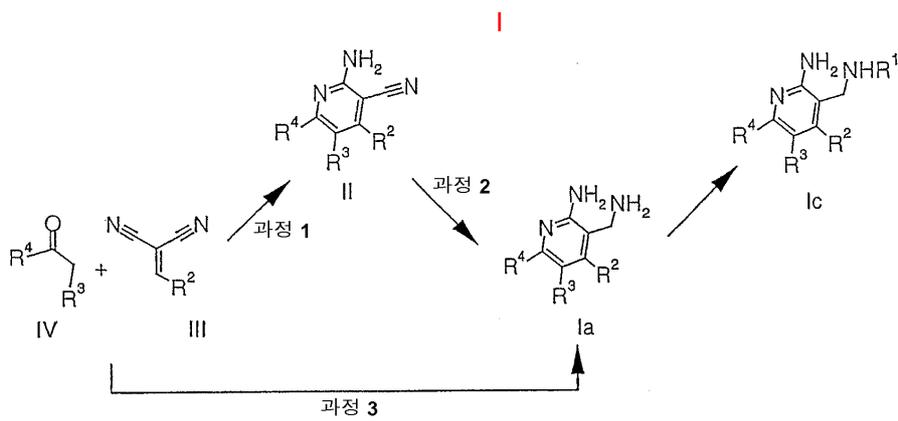
3- -4- - -2- .

R² 가 - I

I I 가

I 가 가

I II :



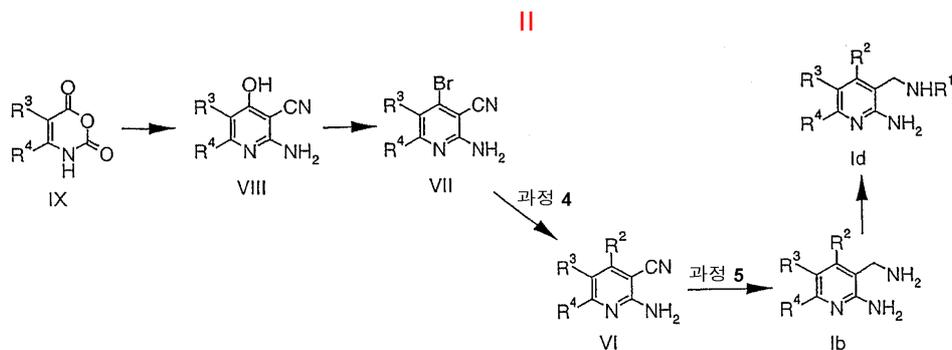
I, R³, R⁴, O, N, S

5-, 6-, 7-, O, N, S

5- 6-

; R¹, R

2



II, R³, R⁴, ; R¹, R²

I, V, II, VI
Ia, Ib

II, III, IV, 2-(2,4-)

VI, Suzuki coupling), Pd(OAc)₂, 2-(N,N-), K₃PO₄, 가, 가, 2-, -4-

Ic, Id, on Lett. 1998, 39, 2663], (: [Bar-Haim, G.; Kol, M. Tetrahedr, Ia, Ib

가

DPP-IV

DPP-IV

DPP-IV

가

2-(2,4-...)-
 (350ml), 2,4- (30.00g, 171mmol) (13.59g, 206mmol) 1
 가 .15 , 8 가 . 가 3 (MS:
 m/e = 222.8(M +)) (35.34g, 92%)

¹H-NMR(300MHz, d⁶-DMSO, 25): (ppm) = 7.45(1H, m), 7.59(1H, m), 8.18(2H, m).

2

2-... (l 1)
 2-...-4-(2,4-...)-5,6-... [h] -3-
 2-(2,4-...)-... (1.125g, 5mmol), ... (735mg, 5mmol), (5
 78mg, 7.5mmol) (5ml) 3
 satd. NaHCO₃, satd. NaCl, Na₂SO₄
 (868mg, 47%), (MS: m/e = 365.9(M+H +))
)

2-... :
 2-...-4-(2,4-...)-5H-... [1,2-b] -3- (MS: m/e = 352.0(M+H +)) 1
 (322mg, 18%)

2-...-4-(2,4-...)-6,7-...-5H-... [6,7] [1,2-b] -3-
 (MS: m/e = 379.9(M +)) 1- (730mg, 38%)

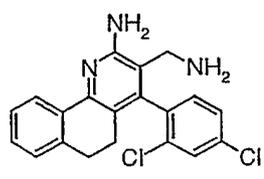
2-...-4-(2,4-...)-7-...-5H-... [1,2-b] -3- (MS: m/e = 381.8(M
 +) 5-...-1- (715mg, 37%)

2-...-4-(2,4-...)-7,8-...-5H-... [1,2-b] -3- (MS: m/e = 412.
 0(M+H +)) 5,6-...-1- (180mg, 9%)

2-...-4-(2,4-...)-... [4,5] [3,2-b] -3- (MS: m/e = 354.0(M+H +))
 -3-(2H) (128mg, 13%)

3

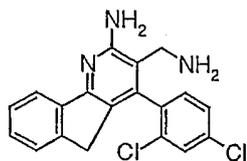
3-...-2-... (l 2)
 3-...-4-(2,4-...)-5,6-... [h] -2-



... THF(1ml) 2-...-4-(2,4-...)-5,6-... [h] -3-
 (200mg, 0.58mmol) THF(1ml) LiAlH₄ (162mg, 4.26mmol) 가
 2 -20 (0.2ml) 가 .15 ,
 가 (MS: m/e = 369.
 9(M+H +)) (53mg, 26%)

4

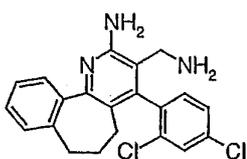
3- -4-(2,4- -)-5H- [1,2-b] -2-



(MS: m/e = 355.8(M+H⁺)) 2- -4-(2,4- -)-5H- [1,2-b] -3-
3 (64mg, 67%) .

5

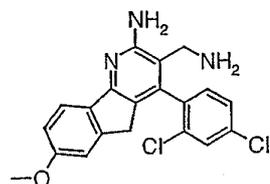
3- -4-(2,4- -)-6,7- -5H- [6,7] [1,2-b] -2-



(MS: m/e = 383.9(M⁺)) 2- -4-(2,4- -)-6,7- -5H- [6,7]
[1,2-b] -3- 3 (40mg,
25%) .

6

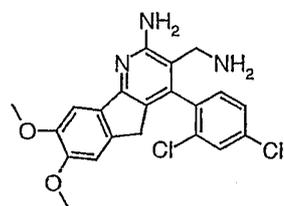
3- -4-(2,4- -)-7- -5H- [1,2-b] -2-



(MS: m/e = 385.9(M⁺)) 2- -4-(2,4- -)-7- -5H- [1,2-b]
-3- 3 (14mg, 9%) .

7

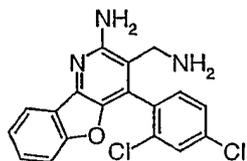
3- -4-(2,4- -)-7,8- -5H- [1,2-b] -2-



(MS: m/e = 415.9(M⁺)) 2- -4-(2,4- -)-7,8- -5H- [1,2-b]
-3- 3 (9mg, 6%) .

8

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

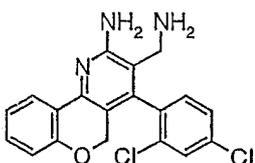


(MS: m/e = 357.8(M +)) 2- -4-(2,4- -)- [4,5] [3,2-b] -3-
3 (0.8mg, 62%)

9

3- - -2- (1 3)

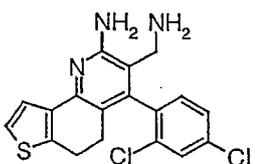
2- -1-(2,4- -)-10H-9- -4- - -3-



2-(2,4- -)- (95mg, 0.4mmol), -4- (59mg, 0.4mmol),
(78mg, 1.2mmol) (4ml) 118
(45) HPLC(YMC (CombiPrep) C18 50x
20mm, 6.0 0.1% TFA(aq) 5 95% CH₃ CN, =230nm, 40ml/)
(28mg) THF(1ml) THF 1ml
100mg (0) 가 2 40
4 가
(45) (DMF, 1ml) HPLC(YMC C18 50x20mm
, 6.0 0.1% TFA(aq) 5 95% CH₃ CN, =230nm, 40ml/)
((MS: m/e = 371.9(M+H +)) 11mg(7%)

10

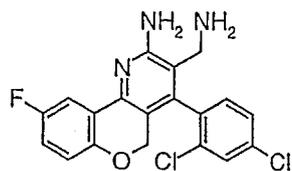
3- -4-(2,4- -)-5,6- - [2,3-h] -2-



(MS: m/e = 376.0(M+H +)) 6,7- -5H- [b] -4- 9

11

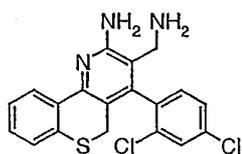
2- -1-(2,4- -)-6- -10H-9- -4- - -3-



(MS: m/e = 390.2(M+H +)) 6- - -4- 9

12

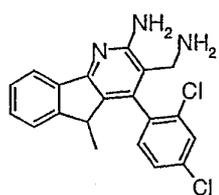
2- -1-(2,4- -)-10H-9- -4- - -3-



(MS: m/e = 388.2(M+H +)) -4- 9

13

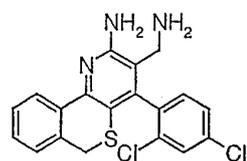
3- -4-(2,4- -)-5- -5H- [1,2-b] -2-



(MS: m/e = 370.1(M+H +)) 3- - -1- 9

14

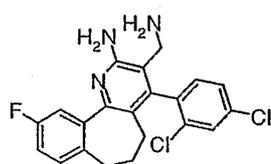
2- -1-(2,4- -)-9H-10- -4- - -3-



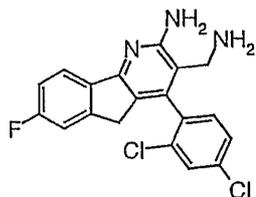
(MS: m/e = 388.2(M+H +)) -4- 9

15

3- -2- -4-(2,4- -)-10- -6,7- -5H- [6,7] [1,2-b]

(MS: m/e = 402.0(M+H +)) 3- -6,7,8,9- - -5-
916

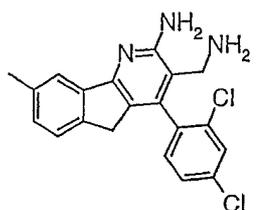
3- -4-(2,4- -)-7- -5H- [1,2-b] -2-



(MS: m/e = 374.3(M+H⁺)) 5- -1- 9

17

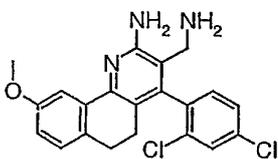
3- -4-(2,4- -)-8- -5H- [1,2-b] -2-



(MS: m/e = 370.0(M+H⁺)) 6- - -1- 9

18

3- -4-(2,4- -)-9- -5,6- - [h] -2-



(MS: m/e = 400.3(M+H⁺)) 7- -3,4- -2H- -1- 9

19

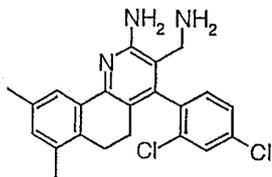
2- -6- -1-(2,4- -)-10H-9- -4- - -3-



(MS: m/e = 422.0(M+H⁺)) 6- - -4- 9

20

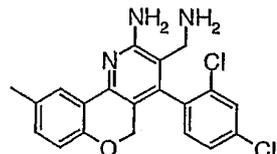
3- -4-(2,4- -)-7,9- -5,6- - [h] -2-



9 (MS: m/e = 398.0(M+H⁺)) 5,7- -3,4- -2H- -1-

21

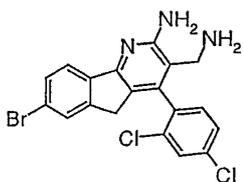
2- -1-(2,4- -)-6- -10H-9- -4- - -3-



(MS: m/e = 386.2(M+H⁺)) 6- - -4- 9

22

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



(MS: m/e = 435.0(M+H⁺)) 5- - -1- 9

23

-3-

a) 2- -4- - -3-

(60%, 6.05g, 151.3mmol) DMF(210ml) (10g, 151.4mmol) 가
 30 / 1.4 , (22.2g, 136.1mmol) 가 60 30
 40 HCl 37% , 1 ,
 DMF(100ml) 120 10 가
 (MS: m/e = 185.1(M⁺)) 24.33g(9
 6%) 50

b) 2- -4- - -3-

2- -4- - -3- (6g, 32.4mmol) (2) 3
 (33g, 11.5ml, 122mmol) (19.15g, 6.15ml, 120mmol) 가 가
 1N NaOH (MS: m/e = 248.2(M⁺)) 5.05g(6
 2%) , ,

24

2- -4- - -3- (II 4)

2- -4-p- - -3-

2- -4- - -3- (248mg, 1mmol), 4- (204mg, 1.5mmol), (II)
 (11mg, 0.05mmol), 2- -2'-(N,N-) (39mg, 0.10mmol)
 K₃PO₄ (425mg, 2mmol) 4ml () 21 100 가 .
 , aq. NaOH , Na₂SO₄ .
 (MS: m/e = 259.9(M+H⁺)) 46mg(18%) (, / = 100:
 0 - 85:15)

2- -4- - -3- :

2- -6- -4-(2- -)- -3- (MS: m/e = 298.2(M+H⁺)) 2-
 2- -4- -6- - -3- (54mg, 10%) .

2- -6- -4- - -3- (MS: m/e = 279.8(M+H⁺)) 2- -4-
 -6- - -3- (60mg, 11%) .

2- -6- -4-(2- -)- -3- (MS: m/e = 313.7(M+H⁺)) 2-
 2- -4- -6- - -3- (33mg, 5%) .

2- -4-(2- -)-6- - -3- (MS: m/e = 339.8(M+H⁺)) 2-
 2- -4- -6- - -3- (72mg, 12%) .

2- -4- -6- - -3- (MS: m/e = 313.8(M+H⁺)) 2-
 -4- -6- - -3- (47mg, 6%) .

2- -4-(2- -)- -3- (MS: m/e = 275.7(M+H⁺)) 2-
 (35mg, 5%) .

2- -4-(2,4- -)- -3- (MS: m/e = 314.0(M+H⁺)) 2,4-
 (8mg, 2.4%) .

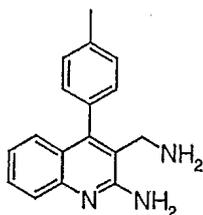
2- -4-(2- -)- -3- (MS: m/e = 279.9(M+H⁺)) 2-
 (61mg, 11%) .

2- -4-(4- -)- -3- (MS: m/e = 279.9(M+H⁺)) 4-
 (52mg, 9%) .

25

3- -4- - -2- (II 5)

3- -4-p- - -2-

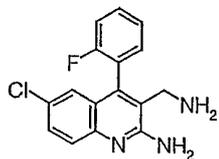


F(1ml) LiAlH₄ (67.3mg, 1.77mmol) THF(0.5ml) 2- -4-p- - -3- (46mg, 0.177mmol) TH
 -20 , 0.3ml 가 15 가 40 2 .
 (Na₂SO₄), .

(DMF, 1ml) HPLC(YMC C18 50×20mm, 6.0 0.1% TFA(a
 q) 5 95% CH₃ CN, =230nm, 40ml/) 5mg(11%)

26

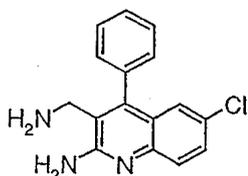
3- -6- -4-(2- -)- -2-



(MS: m/e = 302.2(M+H⁺)) 2- -6- -4-(2- -)- -3-
 25 (4mg, 8%)

27

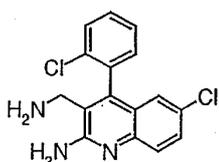
3- -6- -4- - -2-



(MS: m/e = 283.1(M+H⁺)) 2- -6- -4- - -3-
 25 (4mg, 7%)

28

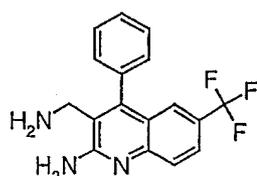
3- -6- -4-(2- -)- -2-



(MS: m/e = 316.9(M+H⁺)) 2- -6- -4-(2- -)- -3-
 25 (3mg, 10%)

29

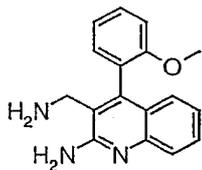
3- -4- -6- - -2-



(MS: m/e = 317.3(M+H⁺)) 2- -4- -6- - -3-
 25 (4mg, 9%)

30

3- -4-(2- -)- -2-



(MS: m/e = 279.1(M+H⁺)) 2- -4-(2- -)- -3-
25 (1mg, 2%) .

31

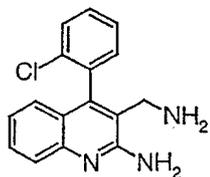
3- -4-(2,4- -)- -2-



(MS: m/e = 317.1(M+H⁺)) 2- -4-(2,4- -)- -3-
25 (6mg, 14%) .

32

3- -4-(2- -)- -2-



(MS: m/e = 284.0(M+H⁺)) 2- -4-(2- -)- -3-
25 (3mg, 2%) .

33

3- -4-(4- -)- -2-



(MS: m/e = 284.0(M+H⁺)) 2- -4-(4- -)- -3-
25 (2mg, 6%) .

34

3- -4- - -2-



(fp.: 225-226) 2- -4- - -3-
(0.56mg, 12%)

3

A

:

성분	mg/정제	
내용물:		
화학식 I의 화합물	10.0	200.0
미세결정 셀룰로즈	23.5	43.5
락토오스 수화물	60.0	70.0
포비돈(Povidone) K30	12.5	15.0
나트륨 전분 글리콜레이트	12.5	17.0
스테아르산 마그네슘	1.5	4.5
(내용물 중량)	120.0	350.0
코팅막:		
하이드록시프로필 메틸 셀룰로즈	3.5	7.0
폴리에틸렌 글리콜 6000	0.8	1.6
활석	1.3	2.6
산화철(황색)	0.8	1.6
이산화티탄	0.8	1.6

120 350mg

/

B

:

성분	mg/캡슐
화학식 I의 화합물	25.0
락토오스	150.0
옥수수 전분	20.0
활석	5.0

2

C

:

화학식 I의 화합물	3.0mg
폴리에틸렌 글리콜 400	150.0mg
아세트산	pH 5.0까지 적당량
주사 용액을 위한 물	1.0ml까지

400 가 1.0ml () , pH 5.0 ,

D

성분	mg/캡슐
캡슐 내용물:	
화학식 I의 화합물	5.0
황색의 왁스	8.0
수소화된 대두유	8.0
부분적으로 수소화된 식물유	34.0
대두유	110.0
캡슐 내용물의 중량	165.0
젤라틴 캡슐:	
젤라틴	75.0
글리세롤 85%	32.0
카리온(Karion) 83	8.0(건조 물질)
이산화티탄	0.4
산화철(황색)	1.1

가

E

(sachet)

성분	mg/사켓
화학식 I의 화합물	50.0
락토오스, 미세 분말	1015.0
미세결정 셀룰로즈(아비셀(AVICEL) PH 102)	1400.0
나트륨 카복시메틸 셀룰로즈	14.0
폴리비닐피롤리돈 K30	10.0
스테아르산 마그네슘	10.0
향미제	1.0

R 2 가 2,4-

7.

1 6

R 3 R 4 가

8.

7

R 3 R 4 가

9.

1 6

R 3 R 4 가

O, N S

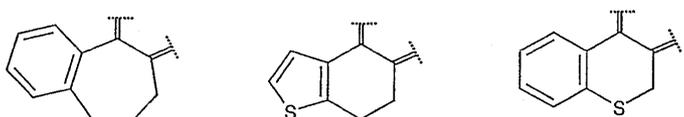
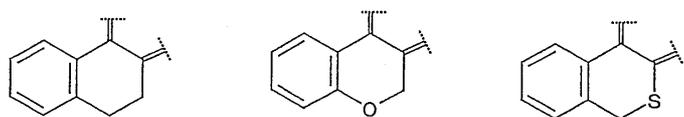
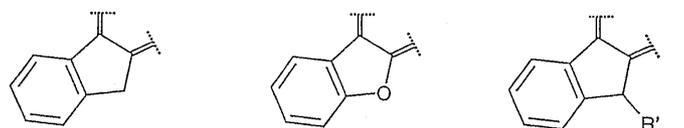
, 5-, 6- 7-
5- 6-

O, N S

10.

9

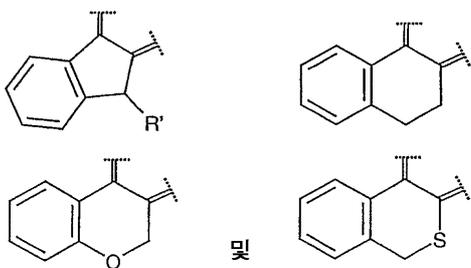
R 3 R 4 가



11.

9

R³ R⁴ 가



12.

1 11

R¹ ;

R² ; , , - , -

R³ R⁴ , O, N S

, 5-, 6- 7- , O, N S - -
5- 6- - , - -

13.

1 11

R¹ ;

R² , - / - ;

R³ R⁴ - - -
6- 5-, 6- 7- O S , - 5-

14.

- 1 13 ,
- 3- -4-(2,4- -)-5,6- - [h] -2- ;
- 3- -4-(2,4- -)-5H- [1,2-b] -2- ;
- 3- -4-(2,4- -)-6,7- -5H- [6,7] [1,2-b] -2- ;
- 3- -4-(2,4- -)-7- -5H- [1,2-b] -2- ;
- 3- -4-(2,4- -)-7,8- -5H- [1,2-b] -2- ;
- 3- -4-(2,4- -)- [4,5] [3,2-b] -2- ;
- 2- -1-(2,4- -)-10H-9- -4- - -3- ;
- 3- -4-(2,4- -)-5,6- - [2,3-h] -2- ;
- 2- -1-(2,4- -)-6- -10H-9- -4- - -3- ;
- 2- -1-(2,4- -)-10H-9- -4- - -3- ;
- 3- -4-(2,4- -)-5- -5H- [1,2-b] -2- ;
- 2- -1-(2,4- -)-9H-10- -4- - -3- ;
- 3- -2- -4-(2,4- -)-10- -6,7- -5H- [6,7] [1,2-b] ;
- 3- -4-(2,4- -)-7- -5H- [1,2-b] -2- ;
- 3- -4-(2,4- -)-8- -5H- [1,2-b] -2- ;
- 3- -4-(2,4- -)-9- -5,6- - [h] -2- ;
- 2- -6- -1-(2,4- -)-10H-9- -4- - -3- ;
- 3- -4-(2,4- -)-7,9- -5,6- - [h] -2- ;
- 2- -1-(2,4- -)-6- -10H-9- -4- - -3- ;
- 3- -7- -4-(2,4- -)-5H- [1,2-b] -2- ;
- 3- -4-p- - -2- ;
- 3- -6- -4-(2- -)- -2- ;
- 3- -6- -4- - -2- ;
- 3- -6- -4-(2- -)- -2- ;
- 3- -4- -6- - -2- ;
- 3- -4-(2- -)- -2- ;

3- -4-(2,4- -)- -2- ;

3- -4-(2- -)- -2- ;

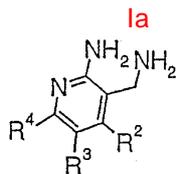
3- -4-(4- -)- -2- ;

3- -4- - -2-

가 .

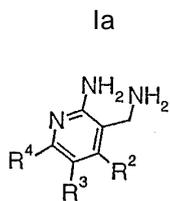
15.

(a) II la :



[,
 R^2, R^3, R^4 1 14];

(b) Ia Ic :



[,
 R^1, R^2, R^3, R^4 1 14]

, 1 14 | .

16.

1 14 ,

15 .

17.

1 14 가 /

18.

1 14 ,

19.

1 14 ,

DPP-IV / .

20.

1 14 , , (Morbus Crohn), , 가 ,

, / , , DPP-IV / .

21.

DPP-IV / DPP-IV 1 14 .

22.

, , / , , / , , 1 , , 14 , 가

23.

DPP-IV / DPP-IV 1 14 .

24.

, , / , , / , , , 1 , 가 14

25.

, , / .