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(12)

(KR)
(A)

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A61K 31/33

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(43)

2001 - 0068676
2001 07 23

(21) 10 - 2000 - 0000706
(22) 2000 01 07

(71) 373 - 1 8105

(72) 108 - 901
211 - 1603
102 - 1302
105 - 204
464 - 1 103 - 1609
214 - 6301

(74)

:

(54) 5 3/ 4

HCV NS3/NS4

5 -

(5 - membered fused aromatic heterocyclic compound),

HCV NS3/NS4

HCV, HCV NS3/NS4

HCV(Hepatitis C Virus; C) 5 -
(5 - membered fused aromatic heterocyclic compound),
HCV NS3/NS4

C 1987 C 가 가 ,

HCV 가 30% AIDS C . C
가 , C
(epieope)

A가 10 가 (naked) DN

HCV 가 HCV
HCV E1,E2 (subunit) , HCV
DNA (native conformation) HCV E1, E2 HCV (core, NS3, NS4)
(HCV E2 가
(adjuvant)

DNA DNA HCV DNA

C helicase), NS3 , RNA , RNA (

(virus absorption blocker) 가
가 가 , NS3 NS4 (" NS3/NS4 "

가 , 가

가

가

osin) HCV NS3/NS4
1, NS3

HCV (thym
가

c compound), 1 5 - HCV NS3/NS4 (5 - membered aromatic heterocycli

HCV NS3/NS4 가 5 -

가 HCV NS3/NS4

(1)

(2) n -

(3) V NS3/NS4 가 (HPLC) HC

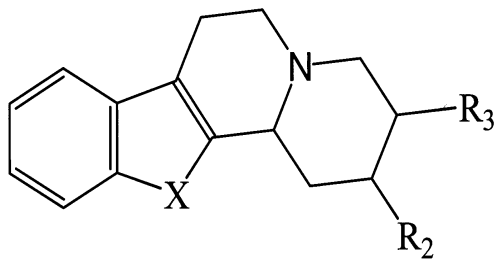
(4) 1H - NMR spectra(300.1MHz), (Mass spectrometer)

HCV NS3/NS4 1 HCV NS3/NS4
가

HCV NS3/NS4 5

1 5 (5 - membered fused aro
matic heterocyclic compound) HCV NS3/NS4

1



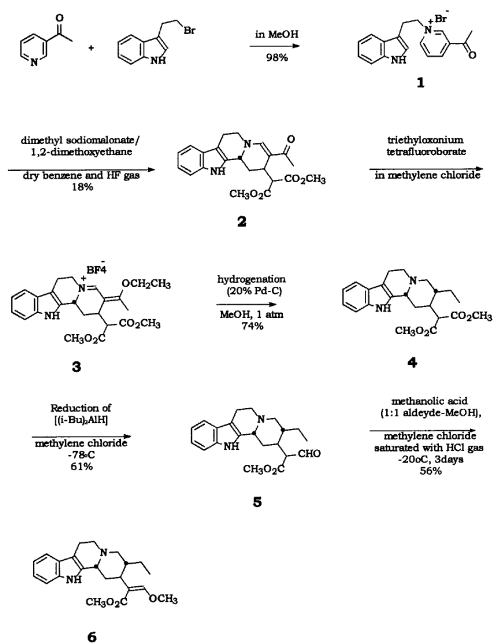
$$X = \text{NHR}_1, \text{O}, \text{S}(\text{O})_2$$

1 R1 (C1~C6), R2 R3 (C
 1~C6), (C1~C6), (C1~C6), (C
 가 , 1 2 가 1 2 가 1
 2 가 1 2 . 2 가 1
 6 가 1 2 . , , , t-

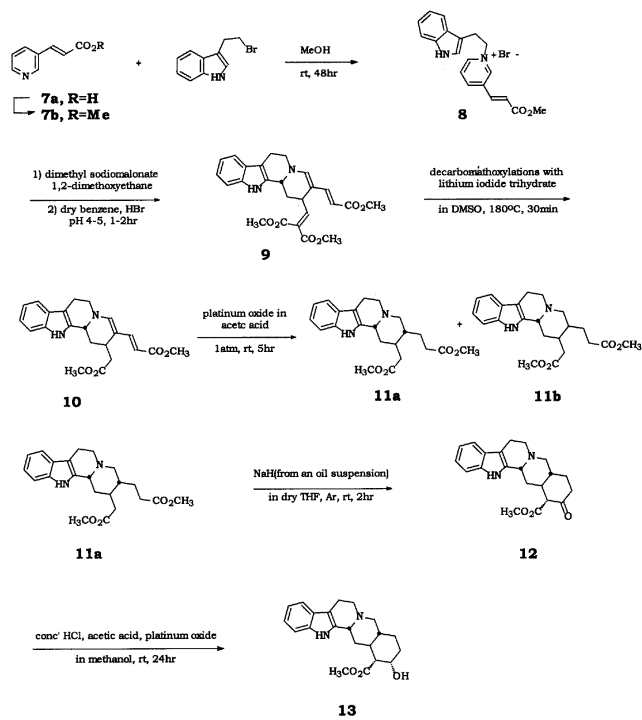
- 1) ;
- 2) 1 4 ;
- 3) 2 ;
- 4) 2 ;
- 5) 3 ;
- 6) 4 .

1

1 2 .



2



가

(1), (2), (4), (5), (6), (7a), (7b), (8), (9), (10), (11a), (12), (13)

1

1, 2

1

3 - Acetyl - 1 - [- (- indolyl)ethyl]pyridinium Bromide(1)

0.120mol (Tryptophyl bromide) 26.30g (0.120mol) 3 - (3 - acetylpyridine) 26.88g(30mL 10mL 24
3 - acetyl - 1 - [- (- indolyl)ethyl]pyridinium bromide salt (1) 40.70g (97%)

2

Indoloquinolizidine(2)

3 - acetyl - 1 - [- (- indolyl)ethyl]pyridinium bromide salt (1) 21.0g dimethyl sodio - malonate 12.0g
(80.0mmol) 1,2 - dimethoxyethane 250mL 5
300mL 1 200mL 가 가 HBr 가
HBr 가 30 가 pH 4 - 5 1
50mL 16.5g MPLC 2L
(indoloquinolizidine) (2), 3.90g (12%)

3

(Indoloquinolizidine diester) (4)

(2) 3.90g 1M triethyloxonium tetrafluoroborate 10mL 200mL
120mL 30 100mL 20% palladium charcoal 가 , 1
2 (celite) palladium charcoal
3.78g
(4) 3.1g 1H NMR (CDCl₃) 0.82(t, 3 J="6Hz," Me), 3.7
3(s, 6, (OMe)₂), 3.97(m, 1, H - 3), 6.6 - 7.2(m, 4, aromatic Hs), Anal. (C₂₂H₂₇O₄N₂) C, H, N.

4

(Indoloquinolizidine Aldehydoester)(5)

(4), 3.0g(7.82mmol) 70mL 가 - 78 ° C
DIBAL - H(diisobutylaluminium hydride), 1.0M 8mL 가 1 - 2
6N 20mL 가 100mL (NaHCO₃)
(brine) (Na₂SO₄)
2.8g
(5) 2.1g (76%) 1H NMR (CDCl₃) 0.80(m, 3, Me), 3.
80(s, 3, OMe), 4.53(m, 1, H - 3), 6.9 - 7.6(m, 4, aromatic Hs), 8.00(s, 1, H - 17), Anal. (C₂₁H₂₅O₃N₂) C,
H, N.

5

(Hirsutine)(6)

(5) 2.0g(5.66mmol) 25ml 75mL 가 -20 ° C
 가 3 -20 ° C
 (NaHCO₃) (Na₂SO₄)
 100mL
 2.1g (6) 1.2g(57.77%)
 1H NMR (CDCl₃) 0.83(t, 3, Me), 3.58(s, 3, OMe), 3.79(s, 3, OMe), 4.21(m, 1, H), 6.91 - 7.62(m, 4, aromatic Hs), 7.90(s, 1, H - 17), Anal. (C₂₂H₂₈O₃N₂) C, H, N.

6

- (-) { - (- Pyridyl)acrylic acid} (7a)

Nicotinaldehyde, 1.07 g (0.01mol) malonic acid 2.40 g (0.023mol) 10mL
 90 ° C 130 ° C 3 (diethyl ether) 200mL
 r) 200mL (diethyl ether) 200mL
 - (-) (7a) 1.44 g(96%) 1H NMR (Me₂SO - d₆) 6.68(d, 1, J="16Hz," - H), 7.43(dd, 1, J="8.5Hz," H - 5), 7.63(d, 1, J="16Hz," - H), 8.83(d, 1, J="2Hz," H - 2). Anal.(C₈H₇O₂N) C, H, N.

7

Methyl - (- pyridyl)acrylate(7b)

- (- Pyridyl)acrylic acid(7a) 305mg(2.0mmol) 2.4mL 20mL
 20mL 10 25mL
 가 methyl - (- pyridyl)acrylate(7b), 317 mg(95%) 1H NMR (Me₂SO - d₆) 3.82(s, 3, OMe), 6.48(d, 1, J="16Hz," - H), 7.29(dd, 1, J="8Hz," H - 5), 7.65(d, 1, J="16Hz," - H), 7.79(dt, 1, J="8.2," 2Hz, H - 4), 8.56(dd, 1, J="5.2Hz," H - 6), 8.70(d, 1, J="2Hz," H - 2), Anal.(C₉H₉O₂N) C, H, N.

8

3 - (- Carbomethoxyvinyl) - 1 - [- (- indolyl)ethyl]pyridinium Bromide(8)

Tryptophyl bromide 263mg (12mmol) methyl - (- pyridyl)acrylate(7b) 191mg (12mmol) 3
 0mL 2
 10mL 24
 3 - (- carbomethoxyvinyl) - 1 - [- (- indolyl) ethyl]pyridinium bromide salt(8) 449mg(98%)
 1H NMR (Me₂SO - d₆) 3.45(t, 2, J="7Hz," benzylic CH₂), 3.78(s, 3, OMe), 4.92(t, 2, J="7Hz," N CH₂), 6.70(d, 1, J="16Hz," - H), 6.68 - 7.6(m, 4, aromatic Hs), 6.98(d, 1, J="16Hz," - H), 8.05(dd, 1, J="8," 5Hz, H - 5), 8.86(br d, 1, J="8Hz," H - 4), 8.97(br d, 1, J="5Hz," H - 6), 9.56(brs, 1, H - 2). Anal.(C₁₉H₁₉O₂N₂Br) C, H, N, Br.

9

1,2,6,7 - Tetrahydroindolo[2,3 - a]quinolizines(9, 10)

3 - (- Carbomethoxyvinyl) - 1 - [- (- indolyl)ethyl]pyridinium bromide(8) 200mg dimethyl sodioma
lonate 120mg(0.80mmol) 1,2 - dimethoxyethane 25mL 5

30mL 1 20mL 가 가 HBr 가
. HBr 가 30 가 pH 4 - 5

1

20mL 5mL

165mg MPLC

1,2,6,7 - Tetrahydroindolo[2,3 - a]quinolizines (9) 42mg (18%) . 1H NMR (Me₂SO - d₆) 3.58, 3.6
0, 3.81 (s, 3 each, OMe), 3.69(d, 1, J="10Hz," H - 16), 4.78(dm, 1, J="12Hz," H - 3), 5.21(d, 1, J="15Hz,"
H - 18), 6.8 - 7.5(m, 4aromatic Hs), 7.16(d, 1, J="15Hz," H - 19), 7.17(s, 1, H - 21), Anal. (C₂₄H₂₆O₆N₂)
C, H, N.

1,2,6,7 - Tetrahydroindolo[2,3 - a]quinolizines (9) 100mg(0.23mmol) lithium iodide trihydrate 48mg(0.2
6mmol) DMSO(Me₂SO) 5mL 180 ° C 30
15mL

MPLC

1,2,6,7 - Tetrahydroindolo[2,3 - a]quinolizines(10) 71mg (82%)

. 1H NMR (Me₂SO - d₆) 3.67, 3.73(s, 3 each, OMe), 4.56(dm, 1, J="12Hz," H - 3), 5.41(d, 1, J="15Hz,"
H - 18), 6.58(s, 1, H - 21), 6.9 - 7.6(m, 4, aromatic Hs), 7.22(d, 1, J="15Hz," H - 19), Anal. (C₂₄H₂₆O₄N₂) C, H, N.

10

(11a)

1,2,6,7 - Tetrahydroindolo[2,3 - a]quinolizines(10) 50mg(0.13mmol) platinum oxide 10mg 3mL
5 50mL Na2
SO4

(11a) 41mg, (11b) 6mg .(11a); 1H NMR (Me₂SO - d₆) 3.58, 3.67(s, 3
each, OMe), 3.91(m, 1, H - 3), 7.0 - 7.6 (m, 4, aromatic Hs), Anal. (C₂₂H₂₉O₄N₂) C, H, N, (11b); 1H NM
R (Me₂SO - d₆) 3.65, 3.72(s, 3 each, OMe), 3.91(m, 1, H - 3), 7.0 - 7.6 (m, 4, aromatic Hs), Anal. (C₂₂
H₂₉O₄N₂) C, H, N.

11

(Pseudoyohimbinone) (12)

11a 40mg(0.1mmol) (NaH) 5mg(0.2mmol) (tetrahydrofu
rane) 5mL , 50oC 2

(12) 47mg (0.13mmol) . 1H NMR (Me₂SO - d₆) 3.87(s, 3, OMe), 4.53(br
s, 1, H - 3), 6.9 - 7.5(m, 4, aromatic Hs), Anal. (C₂₁H₂₄O₃N₂) C, H, N.

12

(Pseudohydroxyohimbine) (13)

12, 16mg(0.04mmol) 0.1mL 0.5mL 10mL 가
 platinum oxide(PtO₂) 5mg 24 platinum o
 xide
 (13) 12mg (72%)

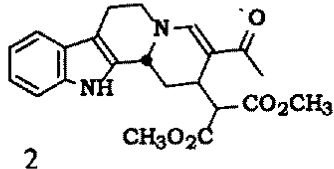
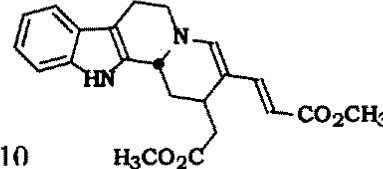
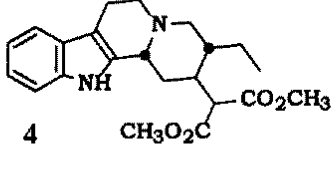
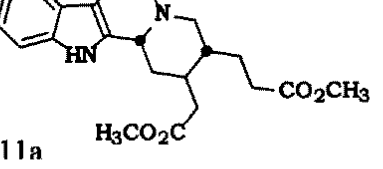
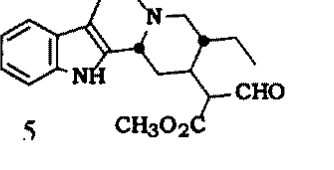
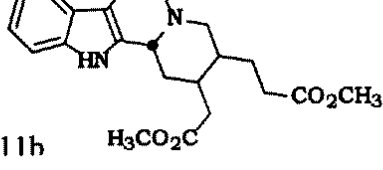
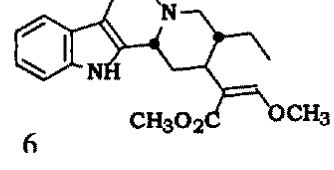
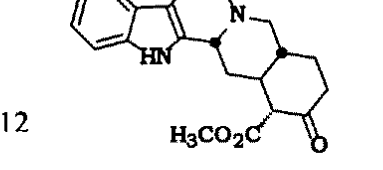
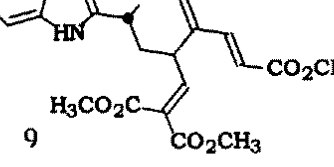
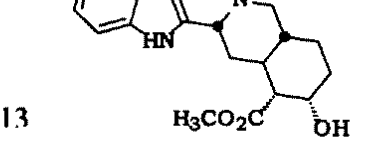
HCV NS3/NS4

1~12 HCV pH 8.3 2
 0mM 1mg/ml (dimethyl sulfoxide) 1mg/ml
 (fluorescein isothiocyanate) 50ul 1ml
 4oC 8 (50mM Tris, pH 7.6, 2% CHAPS, 10mM DTT, 30% Glycerol)

96 - 10mg 200ul
 10ug/ml HCV NS3/NS4 100ul 가 1
 200ul (50mM Tris,
 pH 7.6, 0.15M NaCl, 2% CHAPS, 10mM DTT, 30% Glycerol) 200ul . 96 -
 STORM 1

[1]

Concentration dependent HCV protease inhibition assay(IC₅₀)

화합물	Activity	화합물	Activity
 2	ND	 10	ND
 4	ND	 11a	ND
 5	ND	 11b	ND
 6	100nM	 12	ND
 9	ND	 13	ND

- IC₅₀ 이란 억제 테스트에서 최대 반응값의 1/2 값을 일으키는데 필요한 억제제의 농도를 말하는 것이다.
- ND: 측정하지 않음.

HCV NS3/NS4

가

HCV

(57)

1.

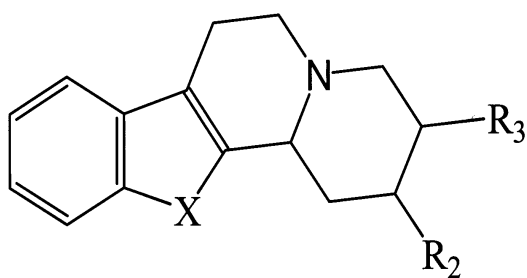
lic compound),

[1]

5

HCV NS3/NS4

(5 - membered fused aromatic heterocyc



X = NHR₁, O, S(O)₂

(, 1 R1 (C1~C6), (C1~C6), R2 R3 (C1~C6), , , , 1 2 , 1 2 가 1 2 가 1 2 .)

2.

1 , 5

HCV NS3/NS4

5

3.

1 2 ,

HCV NS3/NS4

가

5