

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

(51) 。 Int. Cl.7
C07D 403/12
A61K 31/497

(11)
(43)

10-2004-0077767
2004 09 06

(21)	10-2004-7011337		
(22)	2004 07 22		
	2004 07 22		
(86)	PCT/US2003/001752	(87)	WO 2003/062228
(86)	2003 01 21	(87)	2003 07 31

(30)	60/350,931	2002 01 23	(US)
(71)	07033		2000
(72)	08807		18
	07016		38
	08873	13	
	08820	9	
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	07901	2	

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35

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(74)

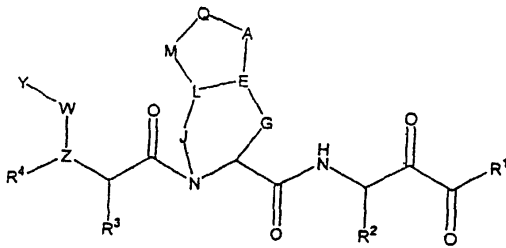
(54) C

NS3-

HCV

I

HCV



HCV

, HCV

, C

2002 1 23

60/350,931

C

('HCV')

C

HCV NS3/NS4a

2002 1 18

10/052,386

C

(HCV)
(+)-
EP381 216

A, B
RNA
) . NANBH
(CMV)

1

(NANBH),
(

NANBH(BB - NANBH)
WO 89/04669
(EBV),
(HAV), B
(Epstein-Barr virus: EBV)

(HDV),

HCV

가

(

5,712,145) .

3000

(C), (E1 E2) (NS1, 2, 3, 4a, 5a 5b) . NS3 HC
V 1893 68kda , 2 ; (b) C RNA-
: (a) 200 N- ATPase . NS3 , 3
, tPA PSA . HCV NS3 , Xa , ,
NS5a/NS5b () NS3/NS4a, NS4a/NS4b, NS4b/NS5a
4
HCV NS3
6kda , NS4a NS3 (co-factor)
. NS3/NS4a NS3/NS4a 가 (,) ,
(,)
HCV P1 P1' ,
NS4a/NS4b, NS4b/NS5a NS5a/NS5b . NS3/NS4a P1
P1' . NS3/NS4a Cys Thr
[: Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91 : 888-892,
Failla et al. (1996) Folding amp; Design 1 : 35-42]. NS3/NS4a
[: Kollykhalov et al. (1994) J. Virol. 68: 7525-7533].
[: Komoda et al. (1994) J. Virol. 68 : 7351-73
57].

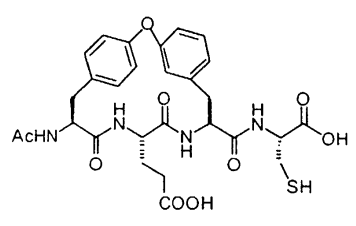
HCV (: WO 98/14181),
[: WO 98/17679 , Landro et al. (1997) Biochem. 36 : 9340-9348, Ing
allinella et al. .

(1998) Biochem. 37 : 8906-8914, Llinas-Brunet et al. (1998) Bioorg. Med. Chem.
Lett. 8 : 1713-1718], 70
: 11459-11468], (hpSTI-C3) [: Martin et al. (1998) Biochem. 37
: 11459-11468], (minibody repertoires: MBip)
[: Dimasi et al. (1997) J. Virol. 71 : 7461-7469] , cV_H E2 (' (cameli
zed)') [: Martin et al. (1997) Protein Eng. 10 : 607-614], 1-
(ACT)[: Elzouki et al. (1997) J. Hepat. 27 : 42-28] . C RNA
[: BioWorld Today 9 (217) : 4 (1998 11 10)
].

PCT WO 98/17679 [1998 4 30 , : (Vertex P
harmaceuticals Incorporated)]; WO 98/22496 [1998 5 28 , : - (F.
Hoffmann-La Roche AG) WO 99/07734 [1999 2 18 , :
(Boehringer Ingelheim Canada Ltd.) .

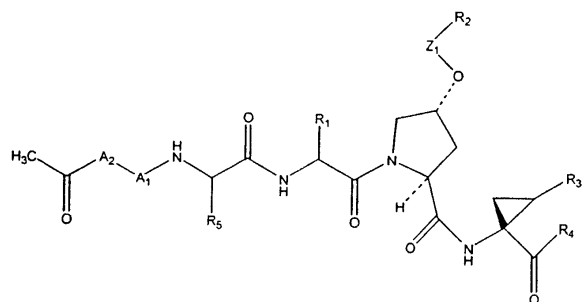
HCV . HCV . HCV
HCV 가 가 가
4 50% 가 가 5
10 30% , 가 가 1%

HCV NS3 [: A. Marchetti et al, Synlett
, S1, 1000-1002(1999)] .

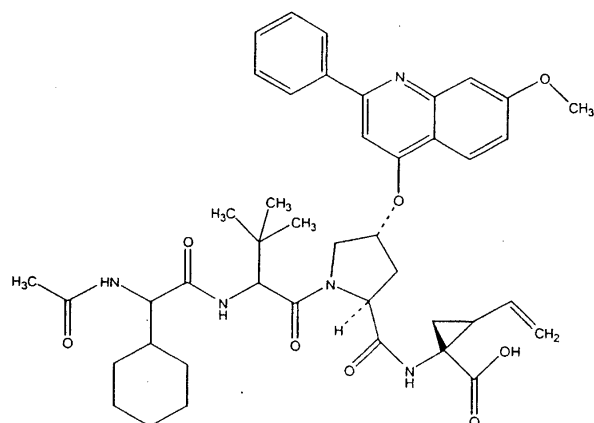


: W. Han et al., Bioorganic amp; Medicinal Chem. Lett. (2000) 10 , 711-713]

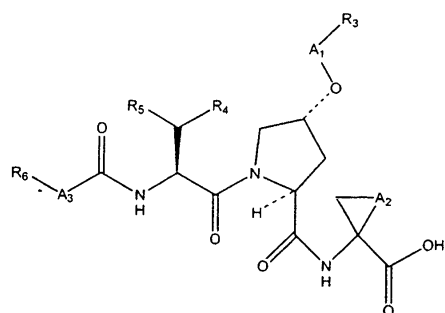
24) : WO 00/09558 (: , 2000



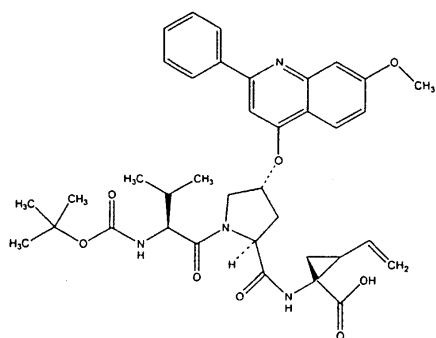
(,).



24) : WO 00/09543 (: ; 2000 2

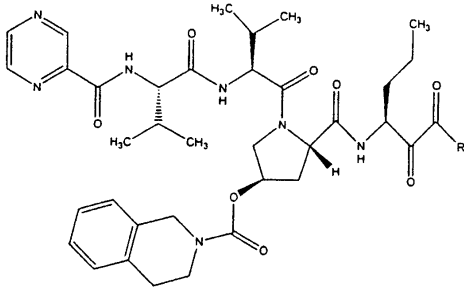


(,).

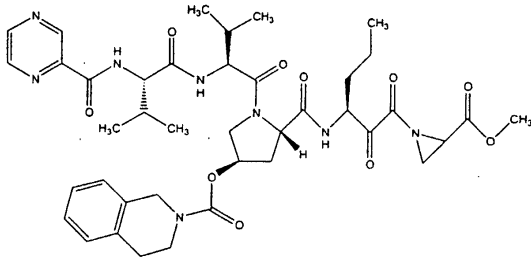


C - (INF) [: Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2) : 98-112]. [: Hoofnagle et al. (1997) N. Engl. J. Med. 336 :347]. , HCV

가 , C NS3- , 2001
 10 11 WO 01/74768 (: (Vertex Pharmaceutica
 Is Inc) .(, R).



WO 01/74768



2001 4 3 09/825,399 (2001 10 18 PCT WO
 01/77133); 2001 4 17 09/836,636 (2001 11 1 PCT
 WO 01/81325); 2001 7 19 09/909,077 (2002 1 31
 PCT WO 02/08198); 2001 7 19 09/909,062 ()
 2002 1 31 PCT WO 02/08256); 2001 7 19
 09/909,012 (2002 1 31 PCT WO 02/08187); 2001 7 19
 09/908,955 (2002 1 31 PCT WO 02/08244); 2001 12 10
 10/013,071 (2002 6 20 PCT WO 02/48172); 2001 7
 19 09/909,164 (2002 1 31 PCT WO 02/08251)
 ; 10/052,386 (2002 1 18) C NS-3

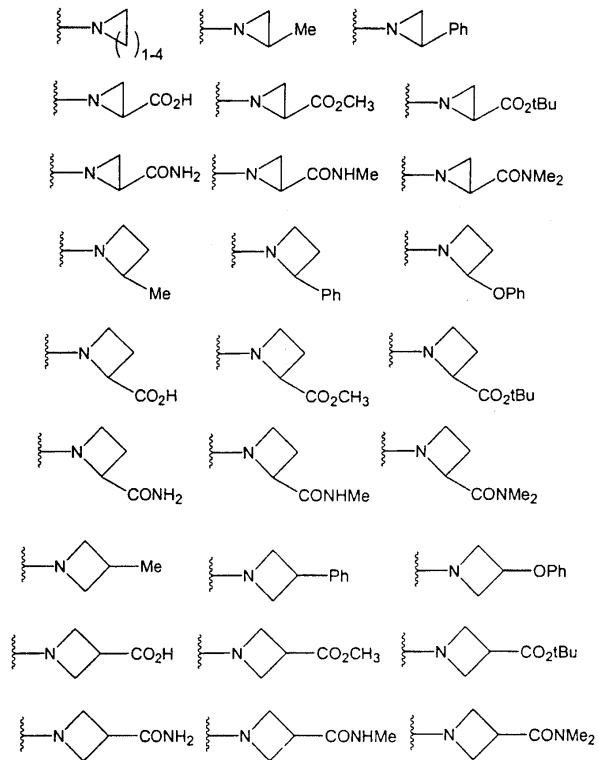
, HCV

C

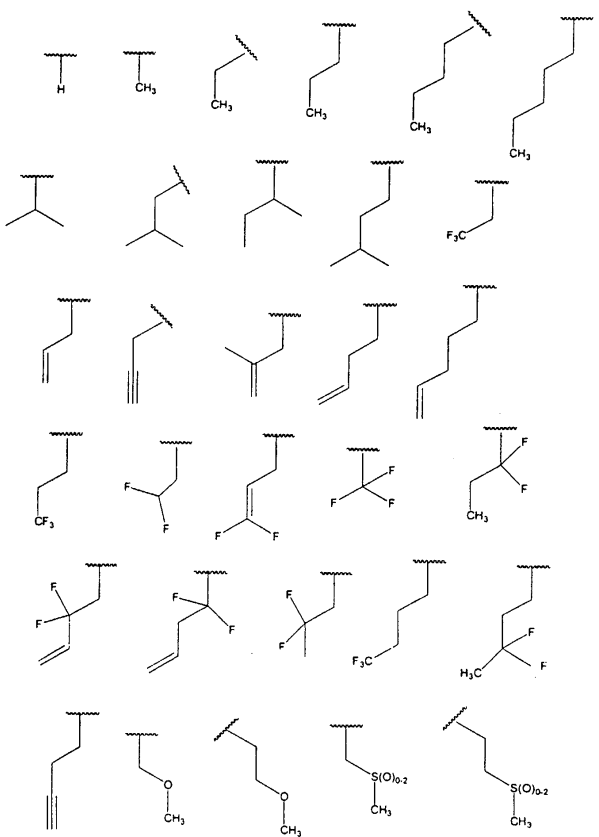
가 C

가 , HCV NS3/NS4a

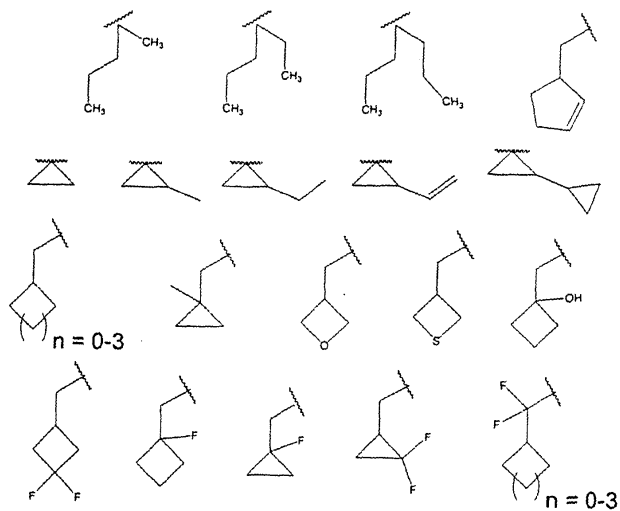
HCV



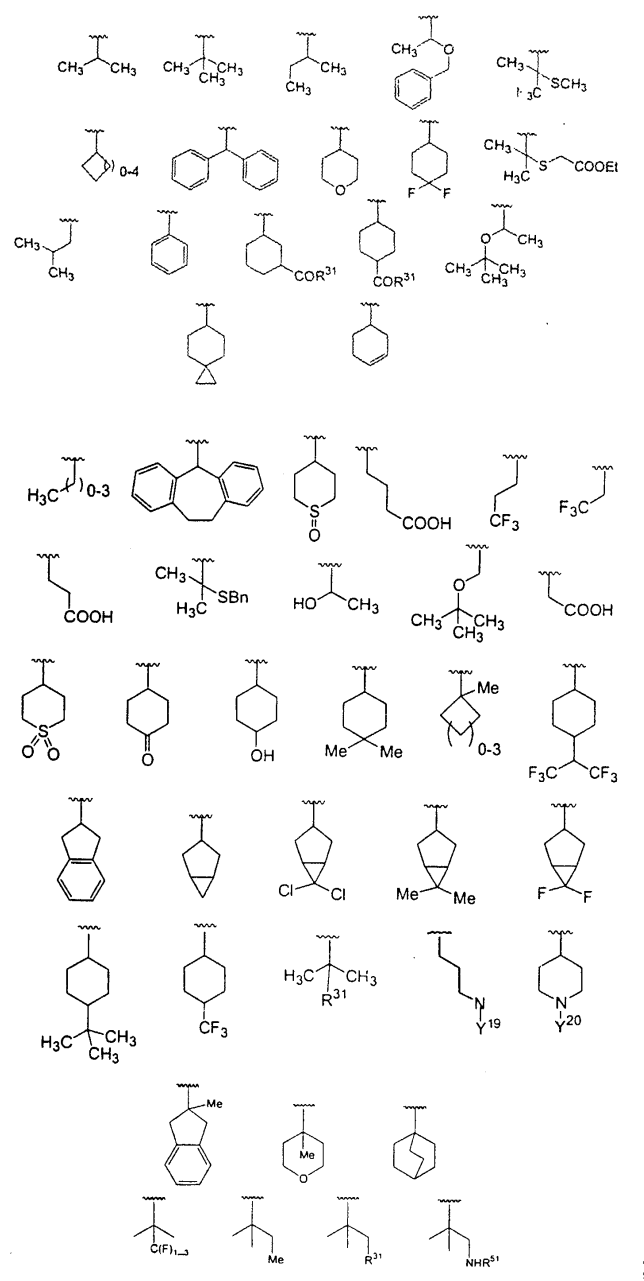
R 2

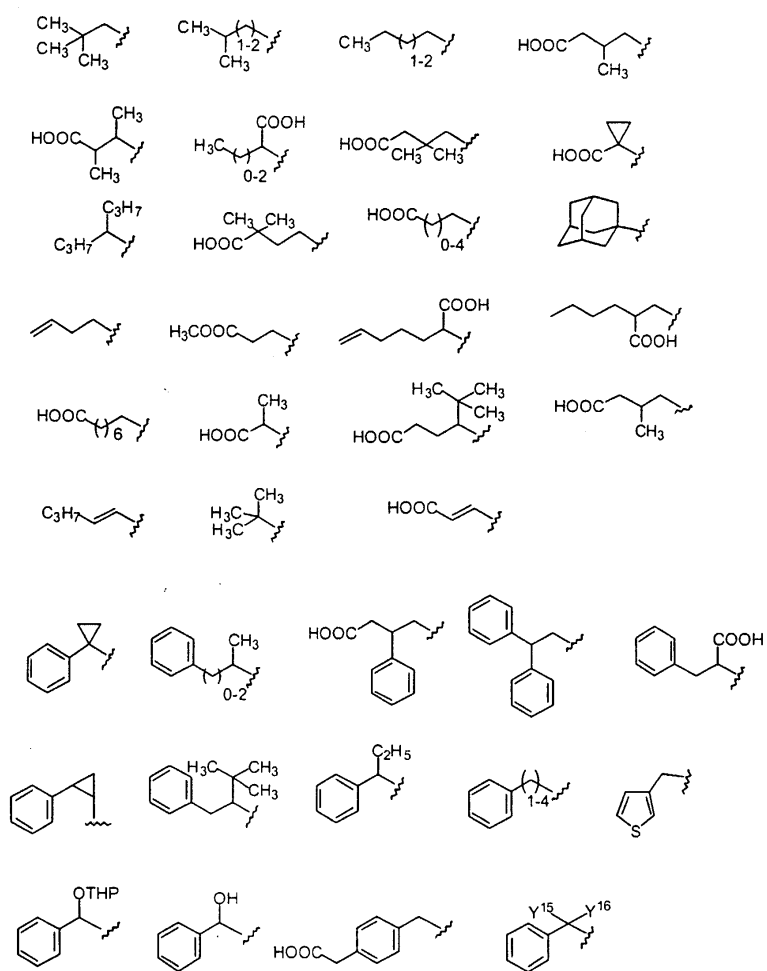


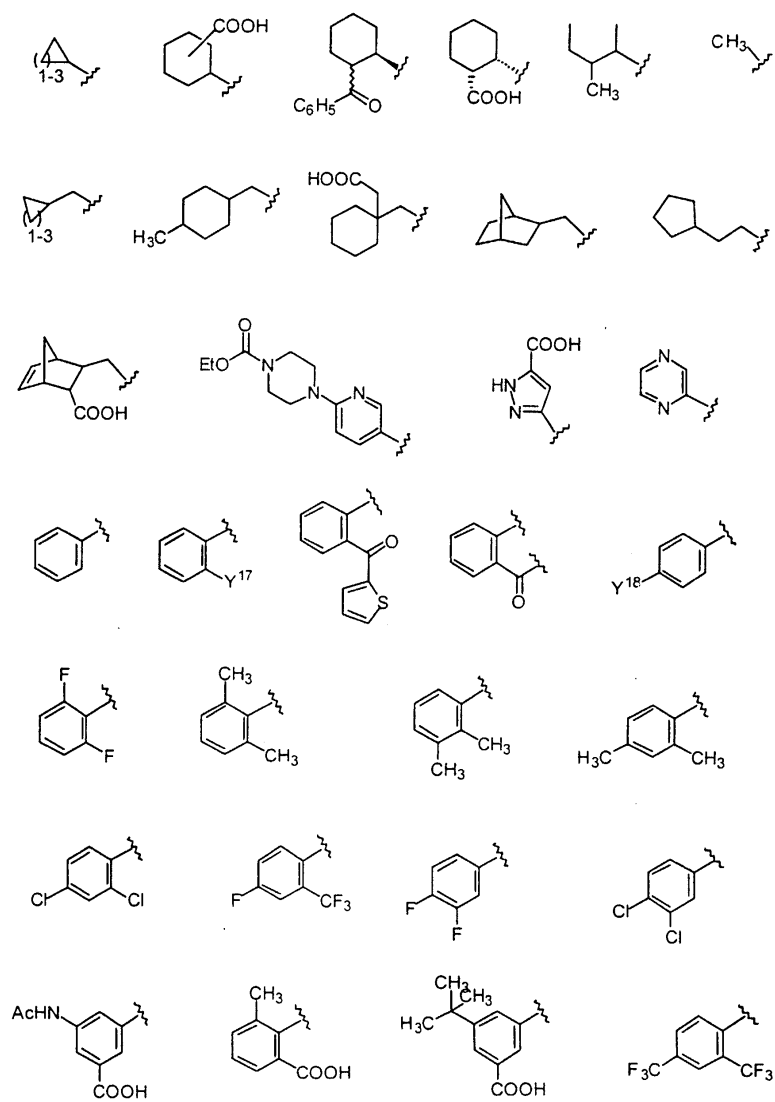
R 2 가

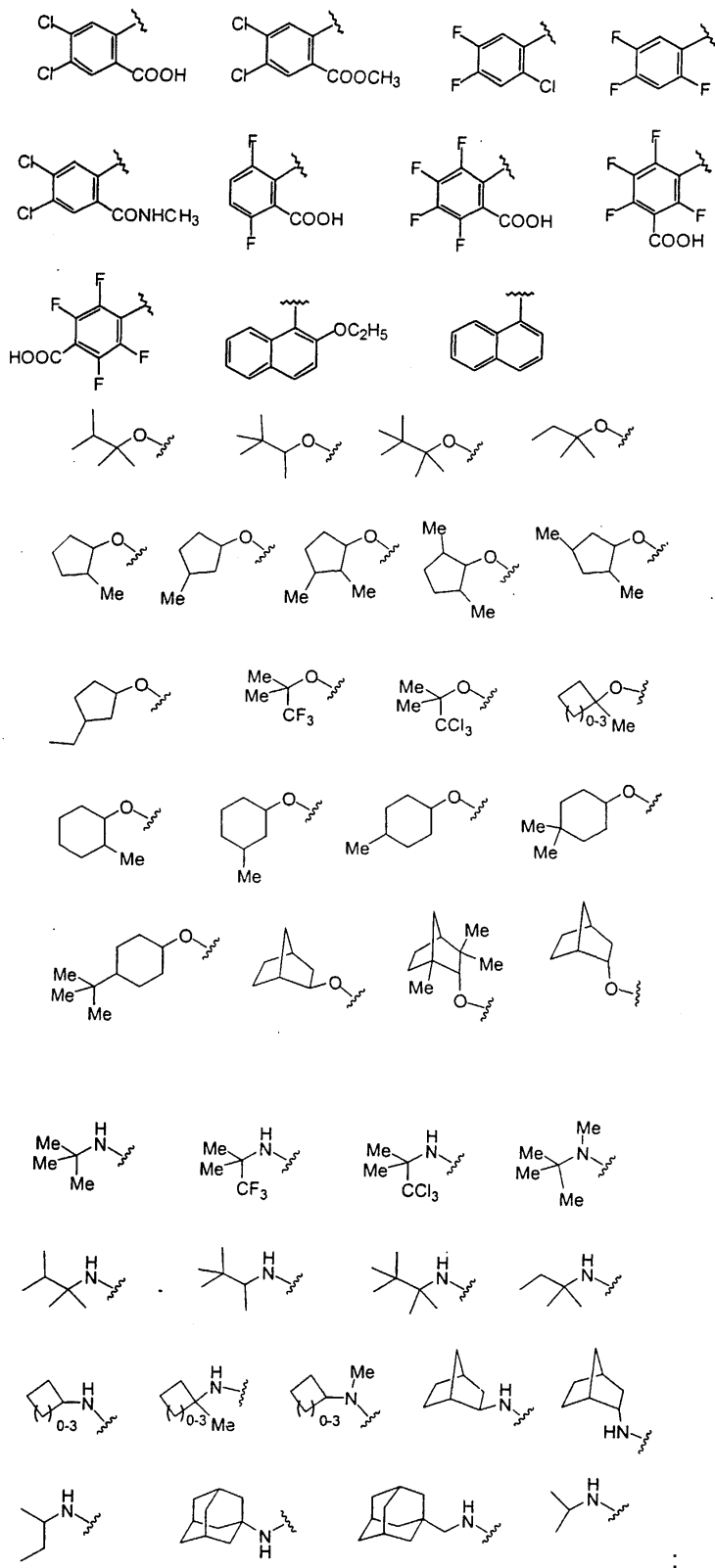


R 3 ;





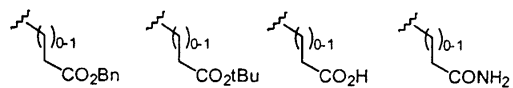
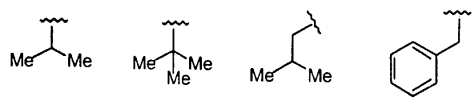
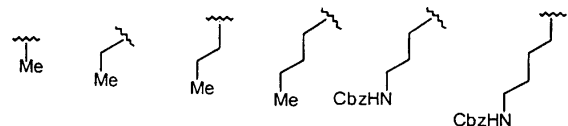




Y 11 H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NPh, CH(Me)₂, 1-HCH₂COOH ; N

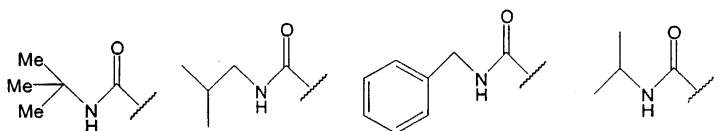
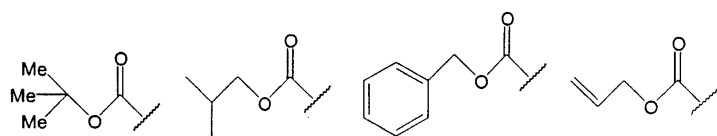
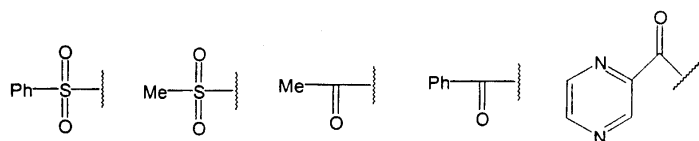
Y 12 H, COOH, COOMe, OMe, F, Cl Br ;

Y 13 ;



Y 14

;



Y 15 Y 16

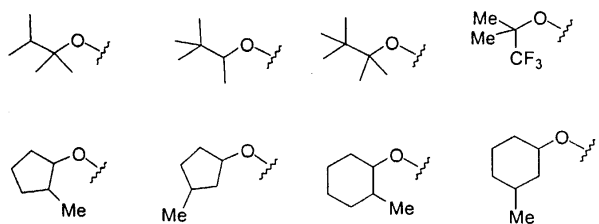
,

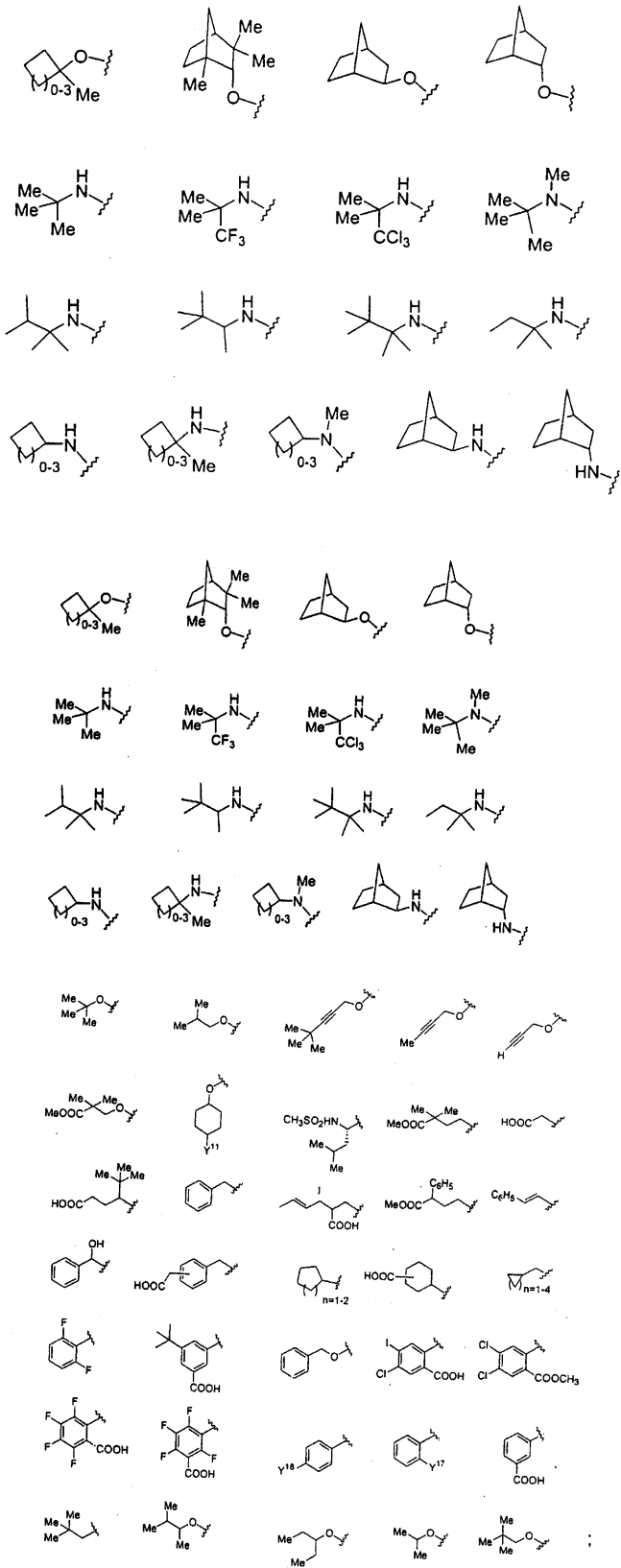
;

Y 17 CF₃, NO₂, CONH₂, OH, COOCH₃, OCH₃, OC₆H₅, C₆H₅, COC₆H₅, NH₂ COO H ;

Y 18 COOCH₃, NO₂, N(CH₃)₂, F, OCH₃, CH₂COOH, COOH, SO₂NH₂ NHCOCH₃ ;

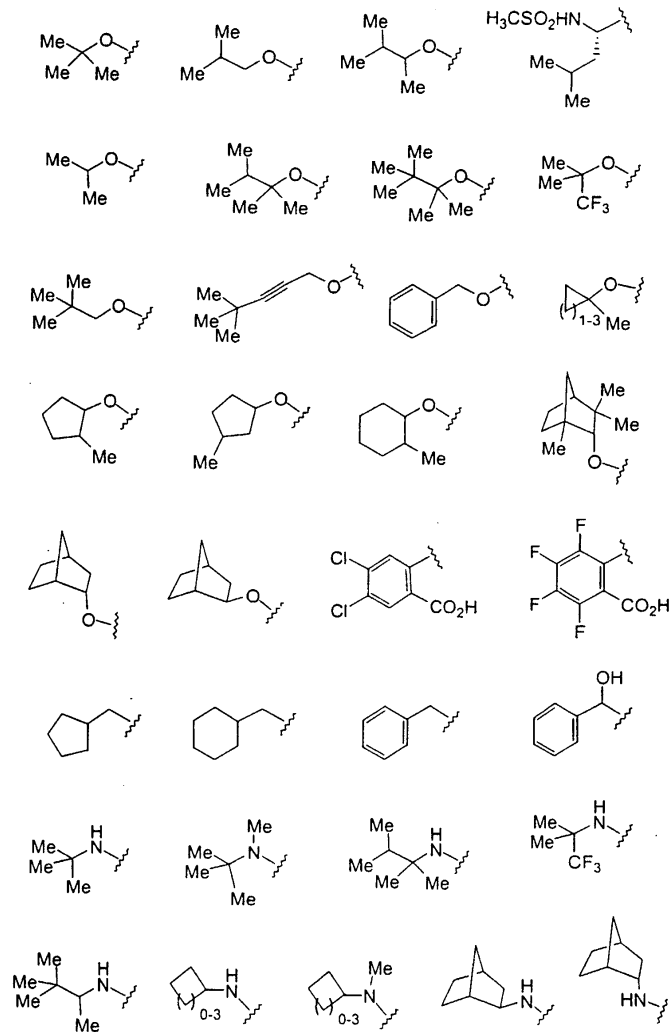
Y





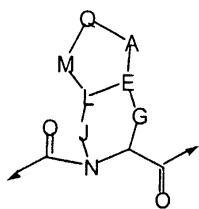
여기서,
 Y^{17} ≡ $CF_3, CONH_2, OH, NH_2$, 또는 $COOH$ 이고,
 Y^{18} 은 $F, COOH$ 이다.

Y



1

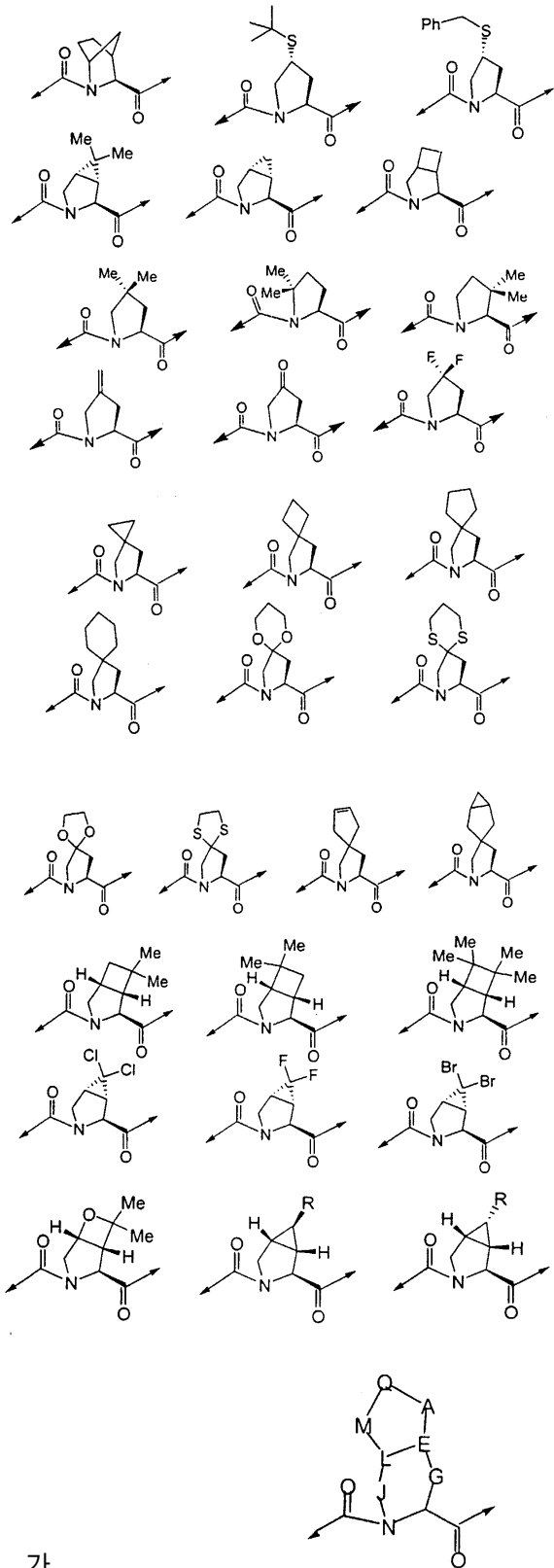
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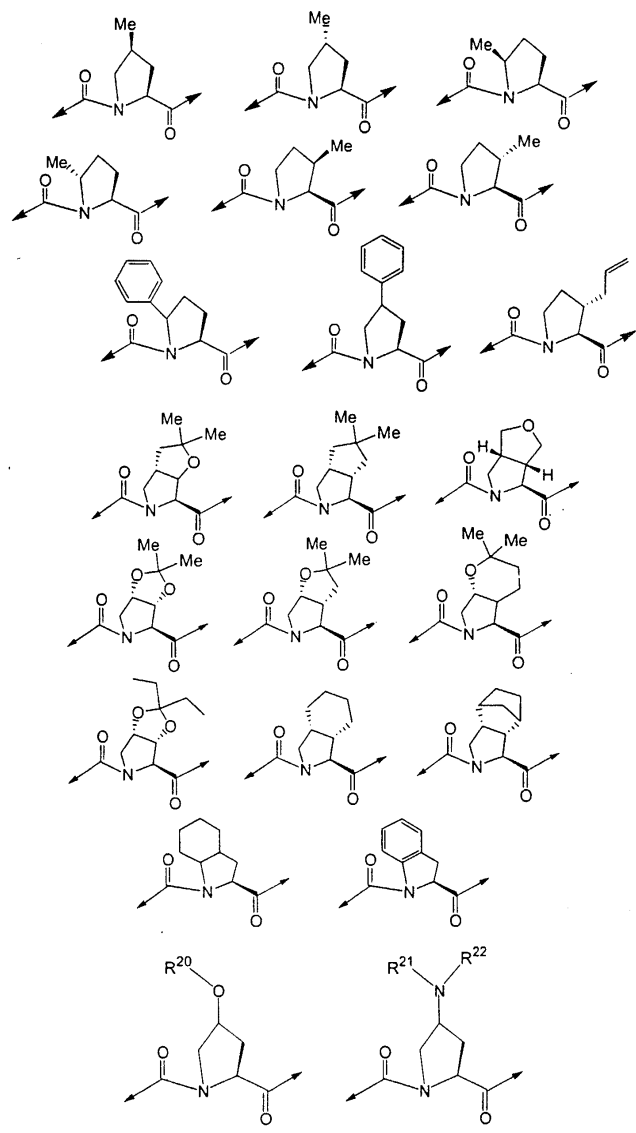


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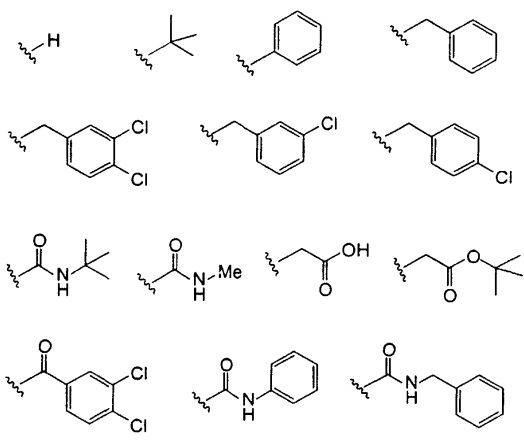
6

, 5





R²⁰



R²¹ R²²

가 가

()

가

[: T. W. Greene et al, Protective Groups in organic Synthesis (1991), Wiley, New York]

(: , , R²)

I 1

III

[: T. Higuchi V

. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed. , American Pharmaceutical Association and Pergamon Press]

가 가

가 H₂O

NS3/NS4

I)' / , I / (, , (') , ' ()' (, , I) ,

가

[: S. Berge et al., Journal of Pharmaceutical Sciences (1977) 66 (1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al., The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food amp; Drug Administration, Washington, D. C. on their website]

, t- (:) , (: , (: , (: ,

4,), (:)

I, (,)
(,), (atropisomer)
(,)가 (, 4- 3-) (,)
IUPAC 1974

S R

I, , HCV, AIDS()

HCV, AIDS

I 가

, C

, HCV

, C

(HCV)

. HCV
C

NS3 NS4a
(HCV)

가

I (,)

) 가

HCV

(C

(- , -), , , , ,

()

가

5 95%

(: , , ,)

가

가 ,

, , HCV

가

가 , ,

000mg,
mg

1.0mg

950mg,

1.0mg

500mg,

1.0mg
1

1,
250

가

1 1 2

1

1

1.0mg

1,000mg

:

,가

(compaction)

30 60 %,

10

90

%,
12

60 %

25

75 %,

가 ()

; 가 (:);

[: (locust bean),

가]; (:); (:); (:);

가가

PPTS :

TsOH : p-

DHP :

THP :

EDCI : 1- (3-)

HOObt : 3- (1,2,3- (4(3H)-

NMM : 4-

HATU : 0-(7- (1-)-N,N,N',N-

DMSO :

Cbz-Cl :

Boc : 3 -

HOObt : 3- (1,2,3- (4-(3H)-

EDCI : 1-(3-)-3-

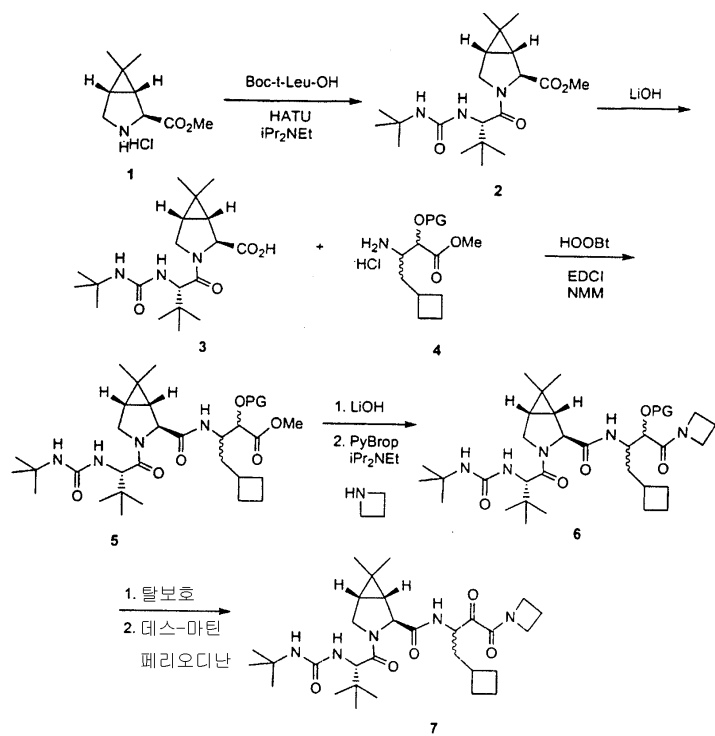
NMM : 4-

PyBrop : ()

HATU : [0-(7- (1-)-1,1,3,3-]

iPr₂ Net :

Boc-t-Leu-OH : N-Boc-3 -

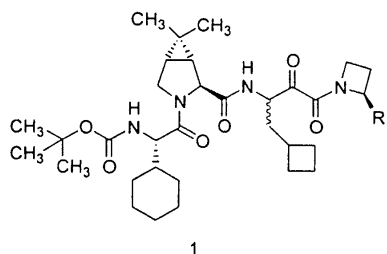


, PG
. R

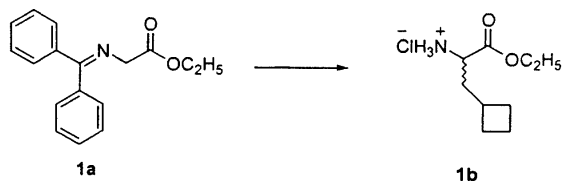
. PG

, 3 -

1: 1 :

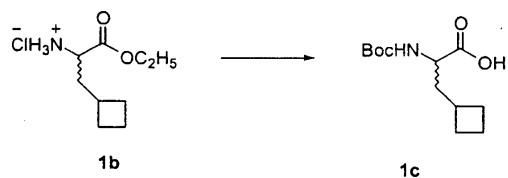


1



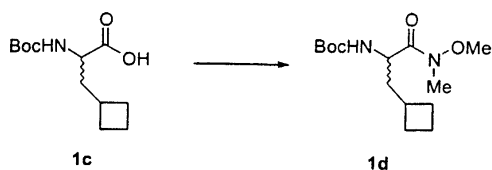
N_2 THF(400 mL) (1a)(50 g, 187.1 mmol) -78 THF
 $K^+ tBuO^-$ (220 mL, 1.15 M) 1M 0 가 1
 (28 mL, 249 mmol) 48
 Et₂O (300 mL) HCl (2M, 300 mL)
 5 Et₂O(1 L) NaOH (50 %) pH 12 14
 CH₂Cl₂ (3X300 mL) (MgSO₄)
 (1 b, 18 g)

2



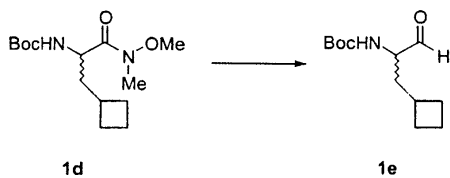
0 CH₂Cl₂ (250 ml) (1b)(18g, 105.2mmol) -3 - (23 g, 105.4 mmo
 l) 12 (TLC),
 THF/H₂O (200 ml, 1:1) LiOH · H₂O (6.5 g, 158.5 mmol)
 Et₂O (MgSO₄) , HCl pH 1 2
 CH₂Cl₂ (1c) 가

3



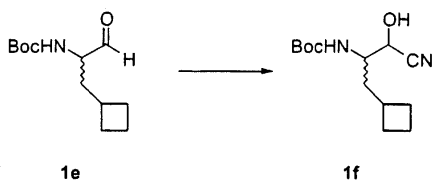
CH₂Cl₂ (250 ml) (1c)(15.0 g, 62 mmol) BOP (41.1 g, 93 mmol), N- (27 mL)
 N,O- (9.07 g, 93 mmol)
 1N HCl (250 mL) , CH₂Cl₂ (3X300 ml)
 (MgSO₄) , (SiO₂ , EtOAc/Hex 2:3)
 (1d) (15.0 g)

4



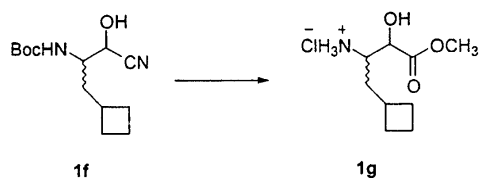
THF(200ml) (1d) (15 g, 52.1 mmol) 0 LiAlH₄ (1M, 93 mL, 93 mmol)
 가 1 0 KHSO₄ (10%)
 0.5 HCl(1 M), NaHCO₃ CH₂Cl₂ (3X200
 mL) (MgSO₄)
 (1e)(14g)

5



CH₂Cl₂ (50ml) (1e) (14 g, 61.6 mmol) Et₃N (10.73 mL, 74.4 mmol)
 (10.86 g, 127.57 mmol) 24
 HCl (1 M, 200 ml) CH₂Cl₂ (3X200 mL) H₂O
 , (MgSO₄) , (SiO₂ , EtOAc/Hex 1:4)
 (1f) (10.3 g)

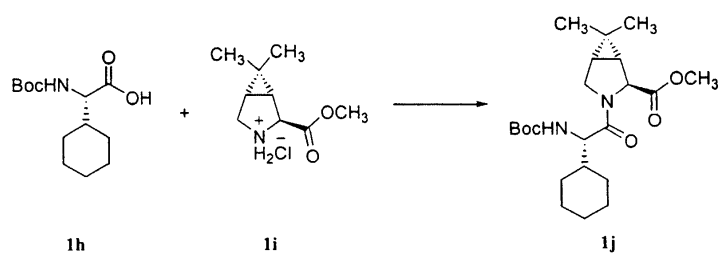
6



0 HCl 가 24 CH₃ OH(700ml) 가 HCl * (1g) (1f)

* , AcCl 가 6M HCl

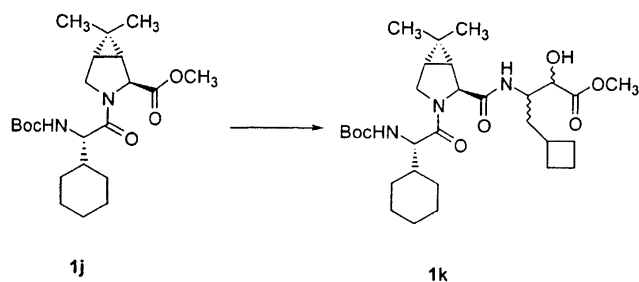
7



Boc- HCl Boc , [: R. Z (1i) J. S. Madalenoitia (J. Org. Chem. 1999, 64, 330)]

0 CH₂ Cl₂ (100 ml) Boc-Chg-OH, (1h)[: (Senn chemica (1i)(4.5 g, 22 mmol) BOP
15 L) , 1M HCl EtOAc(3X200 m
NaHCO₃ (200ml) , (MgSO₄)
(SiO₂ , EtOAc/Hex 3:7) (1j)n (6.0 g)

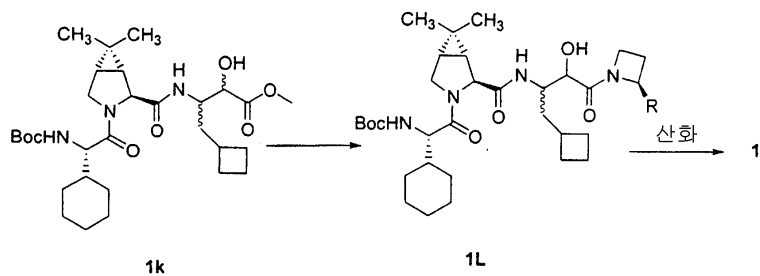
8



THF/H₂O(1:1) (1j)(4.0g, 9.79 mmol) LiOH · H₂O (401 mg, 9.79 mmol)
3 HCl

DMF/CH₂ Cl₂ (1:1 50ml) -10 (1g)(1.0) , EDCI(1.5) , HOObt(1.25) N
MM(4.0) 0 48
1M HCl CH₂ Cl₂ NaHCO₃ , HCl ,
(MgSO₄) (1k)

9



(1k) THF/H₂O LiOH(1.5) 가

CH₂Cl₂/DMF(3 ml) (100 mg, 0.19 mmol) (S)-
 COOCH₃ . 52 mg, 0.38 mmol), HATU(73 mg, 0.19 mmol) -2- (, R
 12 CH₂Cl₂ (100 ml) NMM(63 mg, 0.6 mmol) 0
 HCO₃ (100ml) (100ml) , (MgSO₄) HCl(1 M, 100 ml), Na
 (1L) (1L)

(1L) CH₂Cl₂ (5 ml) (Dess Martin reagent)(200 mg)
 3 NaHSO₃ NaHCO₃ (20 ml) CH
 2 Cl₂ (100 ml) NaHCO₃ MgSO₄
 , 59 mg) (1) (, R' COOCH₃

1

[1]

엔트리	구조식	활성
1		A

2.		A
3		A
4.		A

A: < 5 μM

HCV _____ :

: HCV

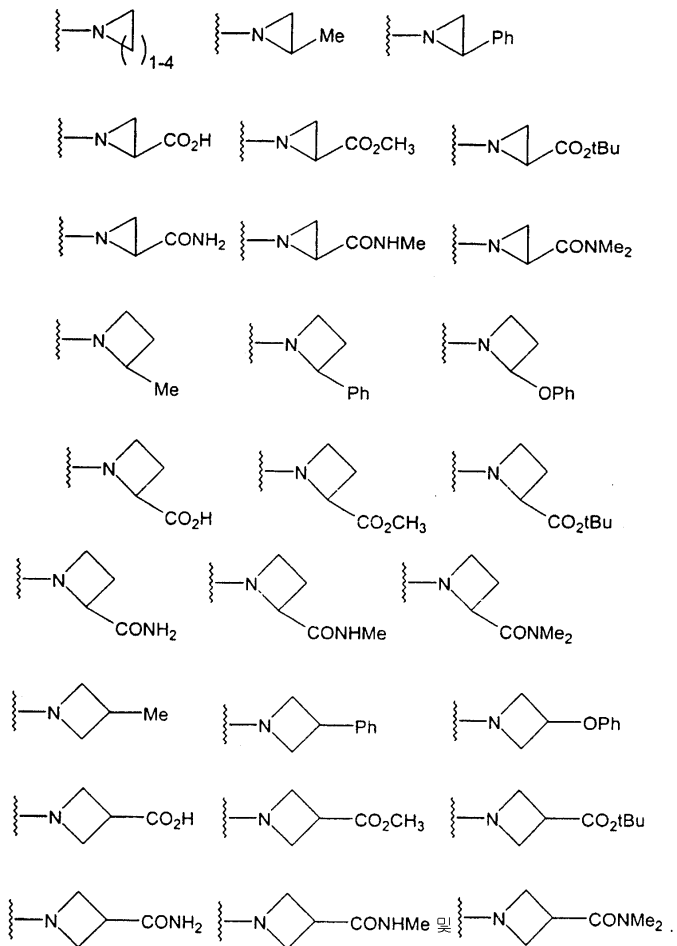
2/08244

2002 1 31

PCT

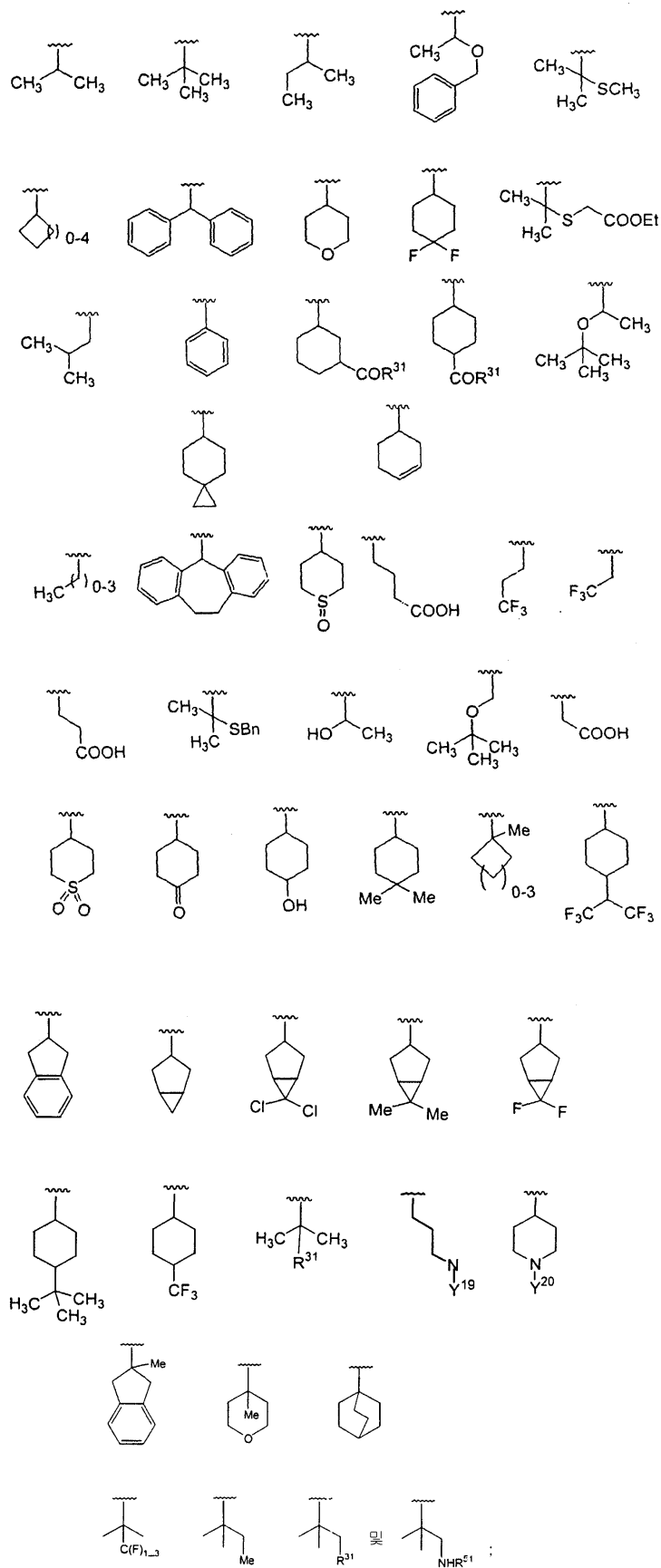
WO 0

1



3.

2, R³

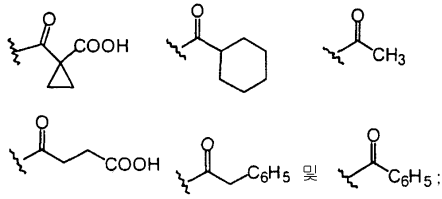


R³¹ OH O- ;

R⁵¹ H, COCH₃, COOtBu CONHtBu ;

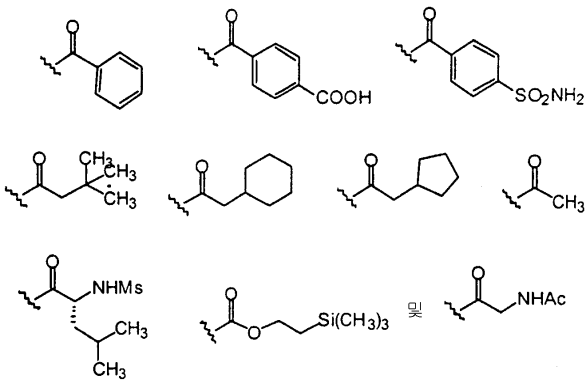
Y 19

:



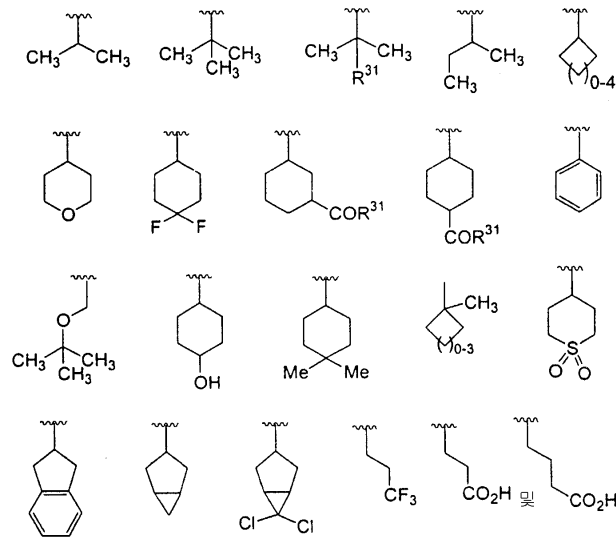
Y 20

;



4.

3, R³



5.

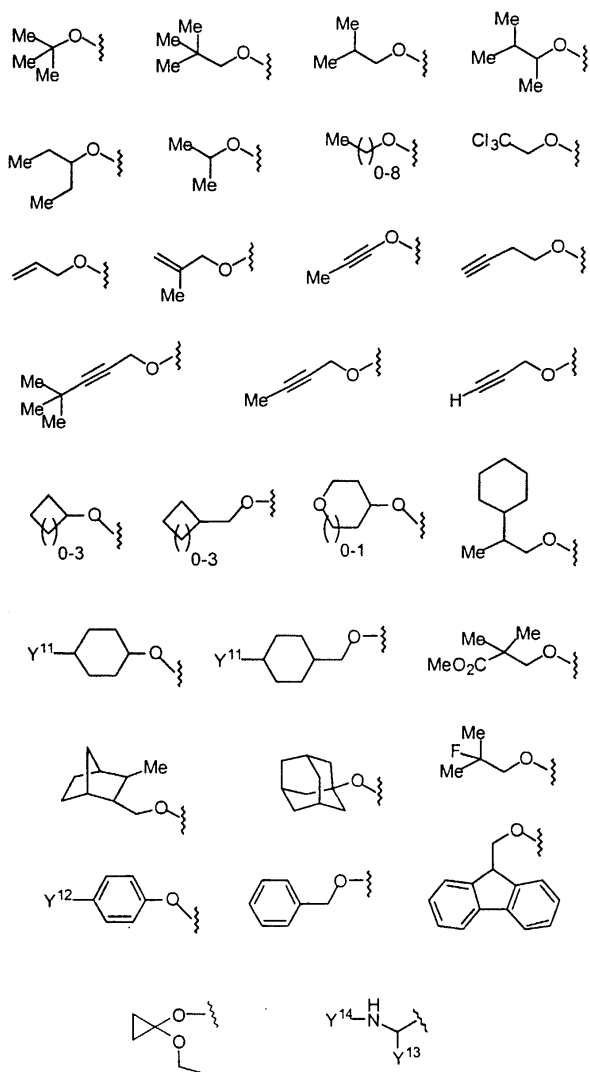
4, Z가 N, R⁴가 H

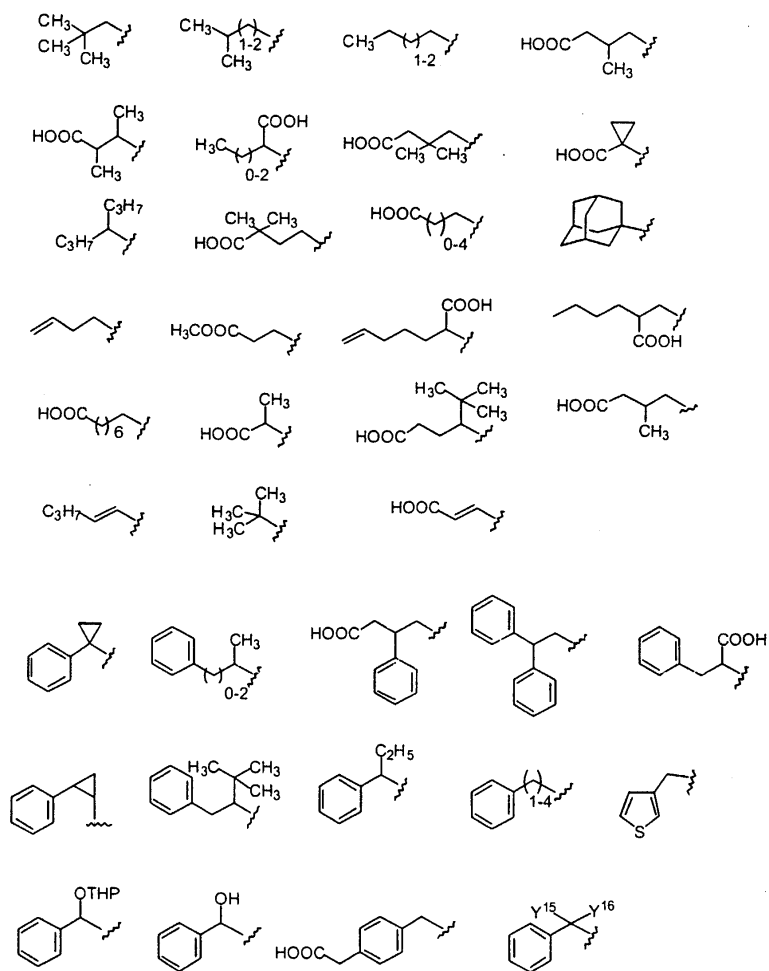
6.

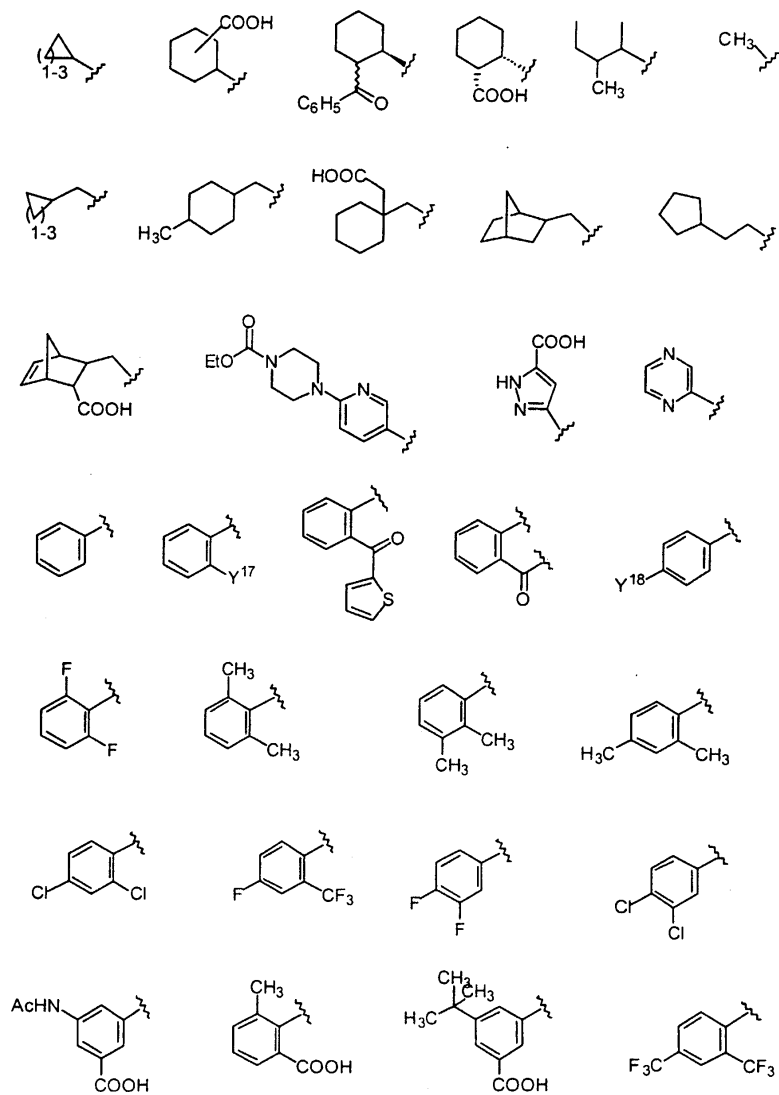
5, W가 C=O

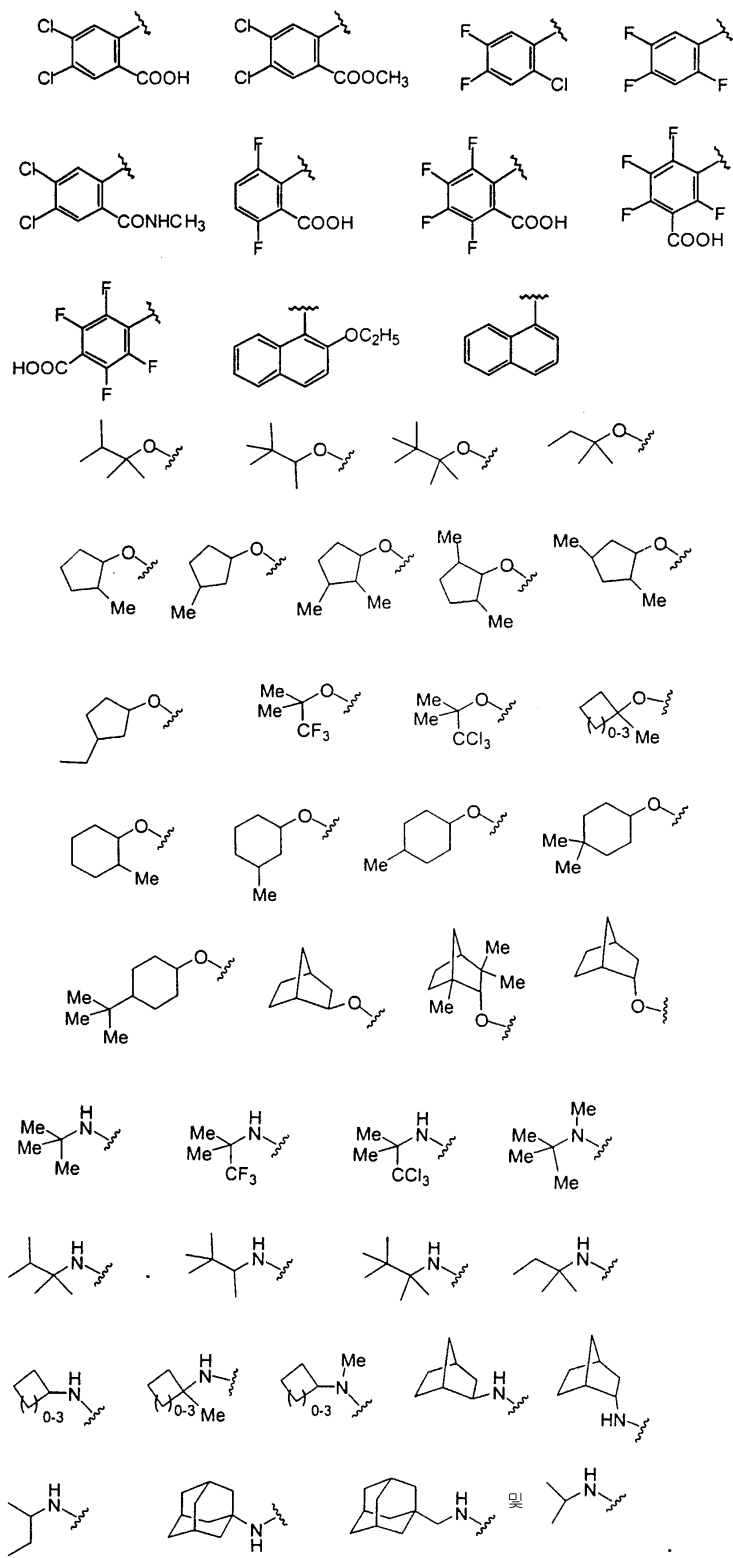
7.

6, Y가





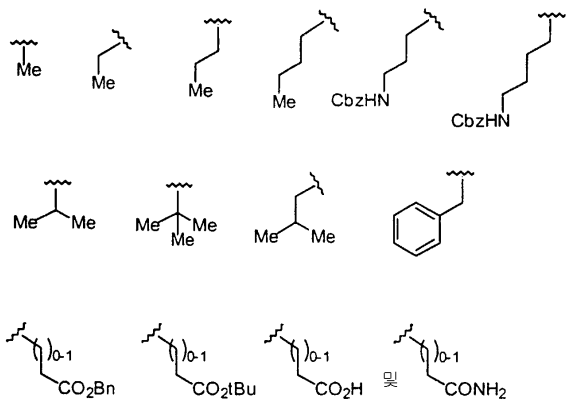




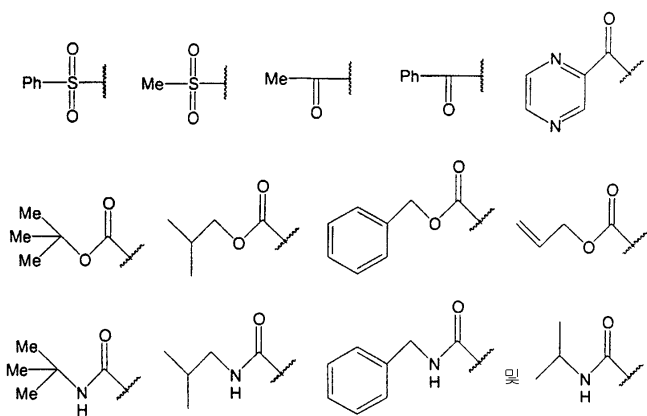
Y¹¹ H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NPh, CH(Me)₂, 1-HCH₂COOH ; N

Y¹² H, COOH, COOMe, OMe, F, Cl Br ;

Y¹³ ;



Y 14 ;



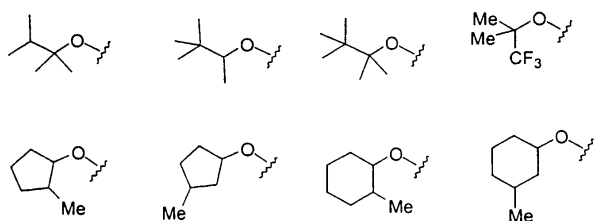
Y 15 Y 16 , , ;

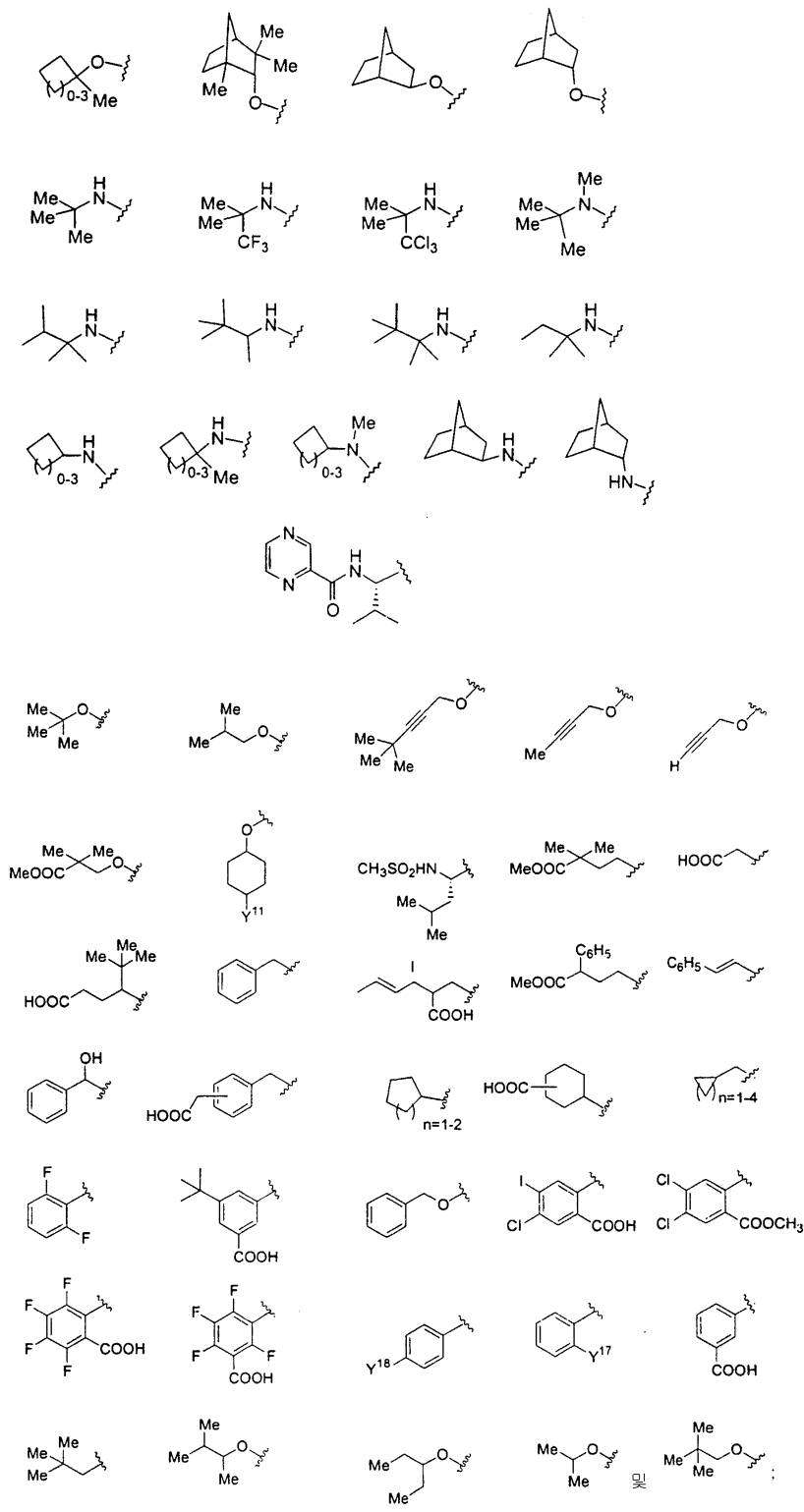
Y 17 CF_3 , NO_2 , $CONH_2$, OH , $COOCH_3$, OCH_3 , OC_6H_5 , C_6H_5 , COC_6H_5 , NH_2 COO
H ;

Y 18 $COOCH_3$, NO_2 , $N(CH_3)_2$, F , OCH_3 , CH_2COOH , $COOH$, SO_2NH_2 $NHCOCH_3$.

8.

7 , Y가 .



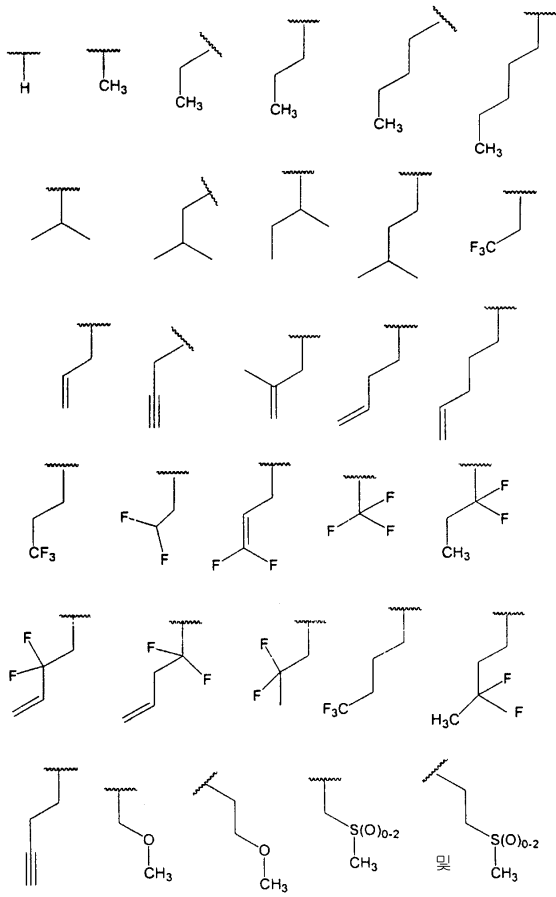


Y 17 CF₃, CONH₂, OH, NH₂ COOH ;

Y 18 F COOH .

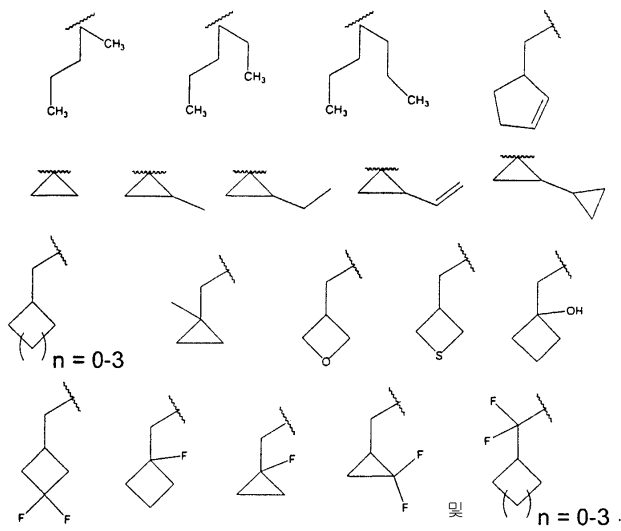
9.

8 , Y가



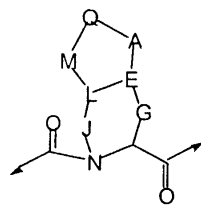
11.

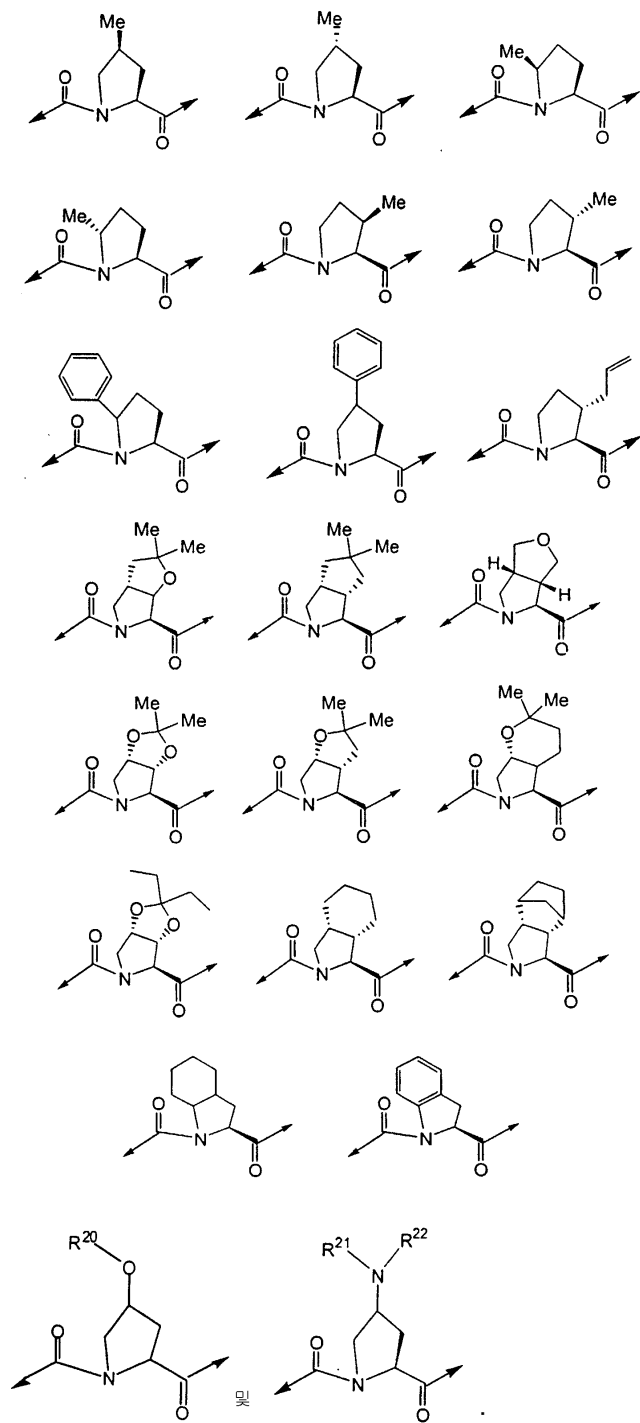
9, R 2 가



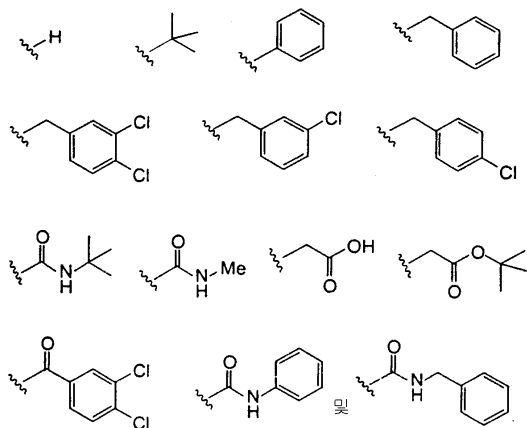
12.

10

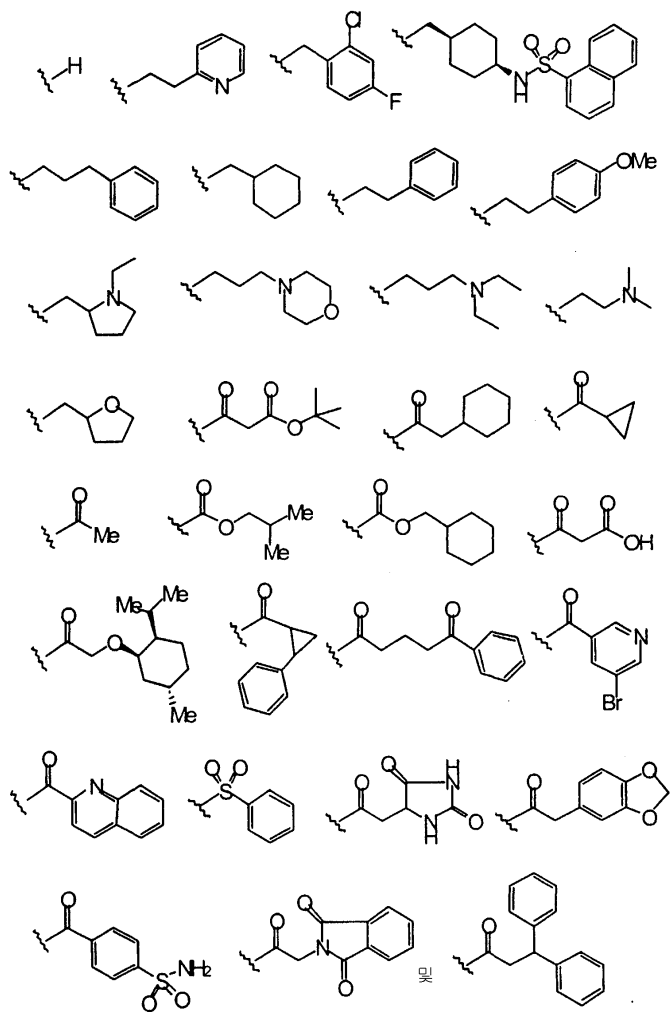




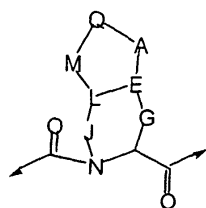
R 20



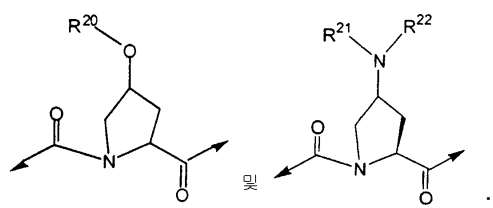
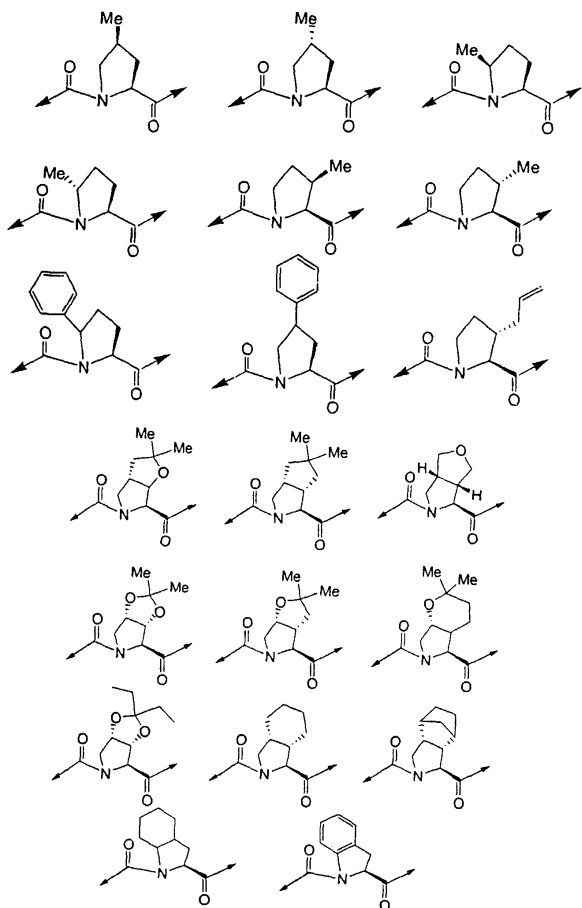
R 21 R 22



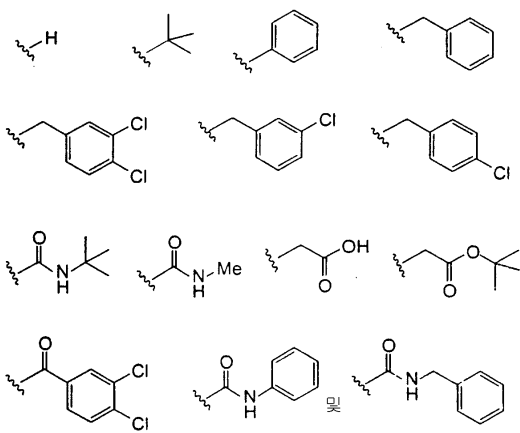
13.



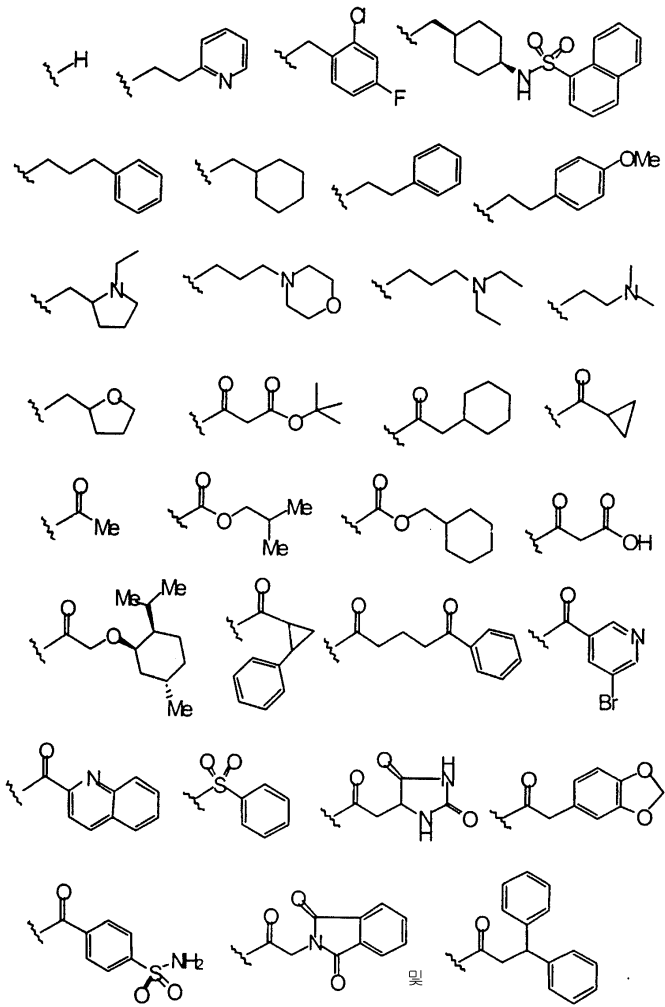
11



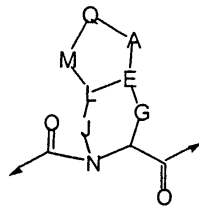
R 20 ;



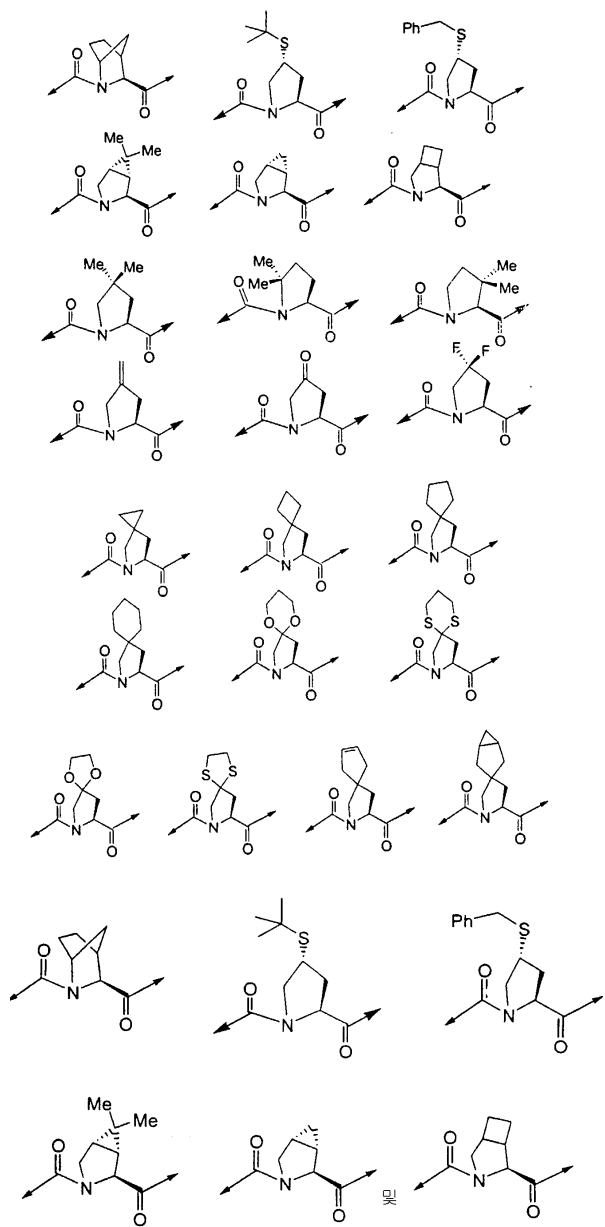
R 21 R 22 ;



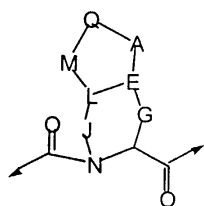
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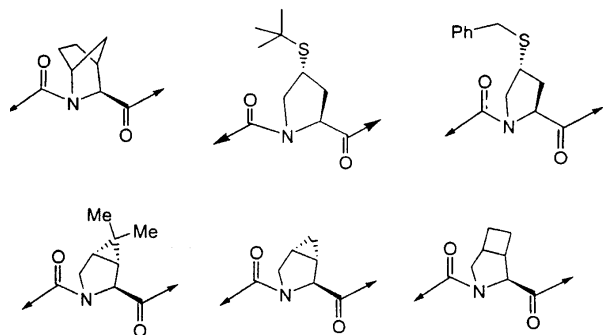
10

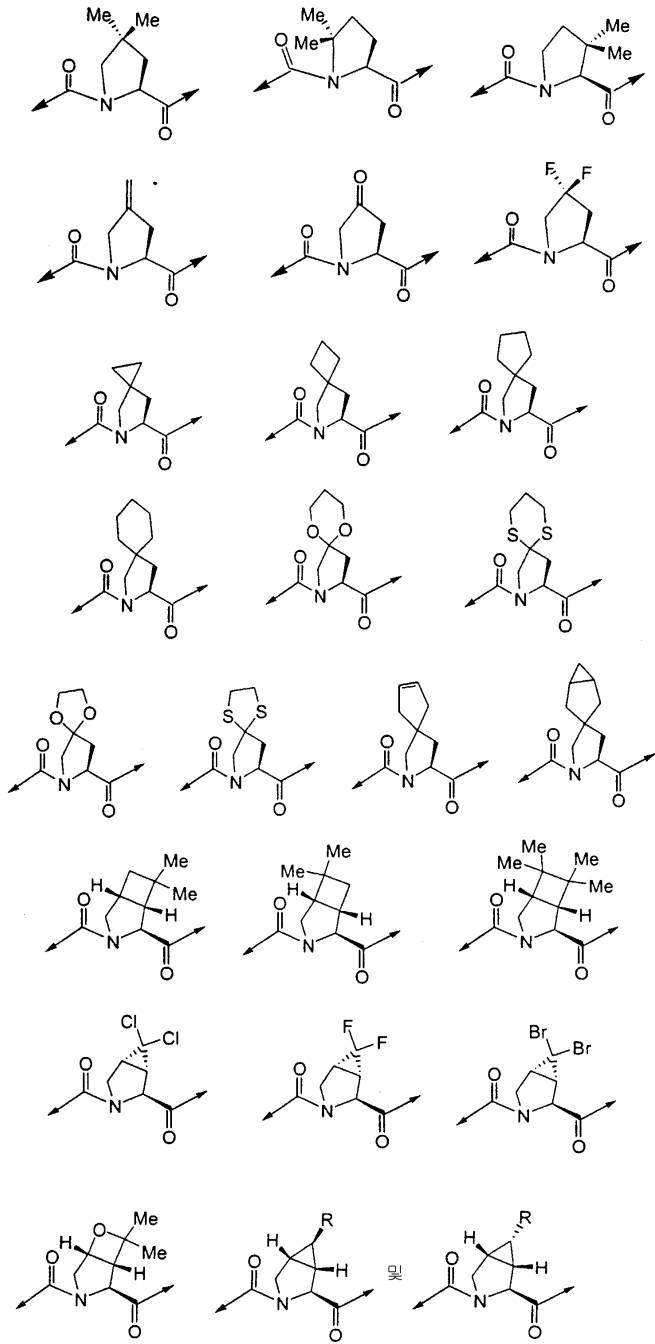


15.



11





16.

1

17.

16 , HCV

18.

16 , 가

19.

18 , 가

20.

19 , 가

21.

20 , 가 - .

22.

가 1 , HCV HCV

23.

22 , 가 .

24.

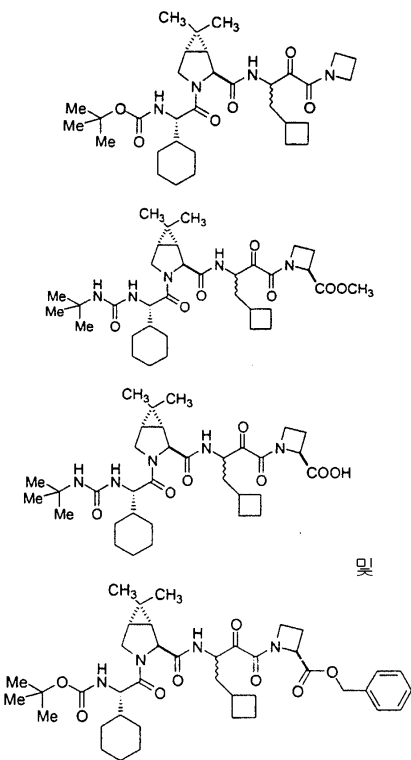
HCV , 1 .

25.

1 , HCV

26.

1 , , .



27.

26 , HCV

28.

27 , 가 .

29.

27 , 가 .

30.

28 , 가 - .