

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

(51) . Int. Cl.<sup>7</sup>  
 C07F 3/04  
 C07D 405/06

(11) 10-2004-0086397  
 (43) 2004 10 08

(21)	10-2004-7012804		
(22)	2004 08 18		
	2004 08 18		
(86)	PCT/US2003/005216	(87)	WO 2003/070665
(86)	2003 02 19	(87)	2003 08 28

(30)	60/358,497	2002 02 19	(US)
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(71)	-	49131 . .	3190	5
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(72)	76217		5
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	2556	50
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(74)

:

(54) -

, 가 , , 가 , , 1%

2002 2 19 가 60/358,497

(atorvastatin)

(solvate)

가

, 가

)가 ( highly branched )

( solvate )'

가

가

( )

-5-(1-) -3- -4-[ ( ) ]-1H- ([R-(R\*,R\*)]-2-(4-1-

3

가  
가

, 가

가

5,273,995

(HPLC)

가  
가 , 12 (CaCl<sub>2</sub> · 2H<sub>2</sub>O)

1

5,298,627

N,N-

(workup)  
(Ca(OAc)<sub>2</sub>)

가

5,969,156

I, II III

'156

1 51-57  
4 60-7015-40  
'I

'( )

(seeding)

2 , I

II                    3                    I  
 IV                  IV                  III                  II                  95%      11

VI, VIII-

XII                  가                  2002/0183378                  VI  
 ,                  VII                  (polymorph)

VIII                  가                  ,                  6.9, 9.3, 9.6, 16.  
 3, 17.1, 19.2, 20.0, 21.6, 22.4, 23.9, 24.7, 25.6,       $26.5 \pm 0.2$       2                  X-                  VII  
 |                  VIII                  ; a = 18.55-18.7      , b = 5.52-5.53      , c = 31.0-31.2      a      c  
 97.5-99.5°                  (monoclinic)                  -                  (cross-polarized)/  
 (magic angle spinning) ('CP/MAS')  $^{13}\text{C}$                   17.8, 20.0, 24.8, 25.2, 26.1,  
 40.3, 40.8, 41.5, 43.4, 44.1, 46.1, 70.8, 73.3, 114.1, 116.0, 119.5, 120.1, 121.8, 122.8, 126.6, 128.8, 129.2, 1  
 34.2, 135.1, 137.0, 138.3, 139.8, 159.8, 166.4, 178.8, 186.5 ppm                  VIII  
 NMR                  VIII                  ppm  
 가; 2.2, 7.0, 7.4, 8.3, 22.5, 23.0, 23.7, 25.6, 26.3, 28.3, 53.0, 55.5, 96.3, 98.2, 101.7, 102.3, 104.0,  
 105.0, 108.8, 111.0, 111.4, 116.4, 117.3, 119.2, 120.5, 122.0, 142.0, 148.6, 161.0      168.7 ppm

'378                  IX                  X  
 ,                  ,                  ,  
 ,                  XI                  XII

'995, '627      '156      '378  
 ,                  ,                  ,  
 - 1 -                  1      %      5      %

가                  /                  ,      가                  /  
 ,                  ,                  ,      가                  (                  ,      가,  
 ),                  ,                  ,      ,      ,  
 /                  ,                  ,  
 가                  ,                  ,  
 )-                  (                  )                  6,080,759      (-)-      -4-(4'-      )-3-(3',4'-  
 . '759                  ,                  ,      1      , 13%      -2-  
 20                  ,                  ,                  ,                  A  
 ,                  ,                  ,  
 ,                  ,                  ,      6,002,011  
 1%                  ,                  ,      가                  ,  
 ,                  ,

1% 가  
966, 18, 190S-197S

Carless, J.E. et.al *J. Pharm. amp; Pharmacol.* 1

가

50 ppm

1%

0.5%

50 ppm

가

1  
0 - 60 ppm

VIII

CP/MAS  $^{13}$  C NMR

2

1  
18

CP/MAS  $^{13}$  C NMR

가

VIII

VIII

100%

(lot)  
0 - 60 ppm  
15.9 ppm    57.4 ppm

1

3  
III      X-      V

가

5,298,627

5,298,627    5,969,156,

5,273,995

2002/0183378

25

1

- 1 - ;      t-      ,      ,      - 1 - ,      - 2 - ,      - 1 -      2 -  
; N,N-



, VIII IX

4,444,129      4,624,058

가

가

(flux).

, 30, 70, , 40, 60, .  
, 3- 5% - 6-8  
0.2% -1- - 24

4.5 ± 1 wt.% , 2 wt.%  
1 wt.% 50 ppm .

HMG-CoA

( ) 가 ,  
      가 .

가 가

(Avicel?),

, ( ), , ( Klucel?), , , ( Methocel?), , , ( Kollidon?, Plasdone?), , .

(glidants)

3

(die)

가 , (pitting)

, , , , , (sachets), 가

10

가

/ , / 가 가 /

가

2 2

가

10 80 mg

g ml<sup>-1</sup> 가 100 m  
 (megabore) 가  
 7694 / 가  
 FT NMR BL-4CP/MAS / 1 H 가 Bruker DMX-500  
 5.0 kHz 13C CP/MAS NMR 125.76 MHz 4 mm  
 SELTICS

40 ° 2 가 SCINTAG X- X'TRA = 1.4518 2 -  
 3 PXRD -

50 ppm

1

2.5 wt.% VIII (500 mg)  
 100% , 4 cm  
 18 가

2.5 wt.% VIII (500 mg)  
 100% , 4 cm  
 4

23

4

50 wt.%

5

3% 0.2% 3.1%

6

4.5 wt.% 1.5 wt.%

7

5.5 wt.% 3.8 wt.%

VIII (30 g), 가  
VIII, 0.7%  
VIII (18 g) 60 7  
VIII  
VIII (50 g) 40 6  
VIII  
IX (12 g) 55 24 IX  
IX (12 g) 50 6 IX

(57)

1.

a)

b)

c)

2

1 , 1 5 %

3.

1 , 5 %

4.

1 , 가 , , N,N- , , ,

5

4 , 가 , , -1- , -2- , -1- , 2- , -1- ,  
, t- ; N,N- , N,N- , , ,

**6.**4 , 가 C<sub>1</sub>-C<sub>6</sub>**7.**6 , C<sub>1</sub>-C<sub>6</sub> , , -1- , -2- , -1- 2- -1**8.**

1 , 가 60% 100%

**9.**

1 , - 1 %

**10.**

9 , 50 ppm

**11.**

1 , - 3

**12.**

1 , -

**13.**

12 , - - II

**14.**

13 , - I, III, IV, V, VI, VII, VIII, IX, X, XI, XII

**15.**

14 , - VIII

**16.**

15 , - IX

**17.**

1 , 1 %

**18.**

1 , 0.5 %

**19.**

a) ,

b) 가 ,

c)

**20.**

- 19 , -
- 20 , - II
- 21 , - I, III, IV, V, VI, VII, VIII, IX, X, XI, XII
- 22 , - VIII
- 22 , - IX
- 19 ,
- 25 , 1 4 %
- 19 , 5 %
- 19 , 가 , , N,N- , , ,
- 28 , t- , 가 , , -1- , -2- , -1- , 2- -1- , ; N,N- , , ,
- 28 , 가 C<sub>1</sub>-C<sub>6</sub>
- 30 , 가 , , -1- , -2- , -1- 2- -1-
- 19 , 가 40% 100%
- 32 , 가 20 100
- 33 , 6 20 가
- 19 , - 1 %
- 35 , - 5

0 ppm

**37.**19  
- 3**38.**

19 1 %

**39.**

38 , 50 ppm

**40.**

- a) -  
b) ,  
c) 1 %

**41.**

- a) -  
b) ,  
c) 1 %

**42.**41 , VIII  
VIII**43.**41 , IX  
IX**44.**

41 , 가 , , , N,N-

**45.**

44 , t- , 가 , , -1- , -2- , -1- , 2- , -1- , ; N,N- , N,N- , , , ,

**46.**44 , 가 C<sub>1</sub>-C<sub>6</sub>**47.**

46 , 가 , , -1- , -2- , -1- , 2- , -1-

**48.**

41 , 가 40 60

49.  
41  
50.  
1 %  
51.

, 50 ppm

52.  
50

53.

가

52

54.  
52

55.

가

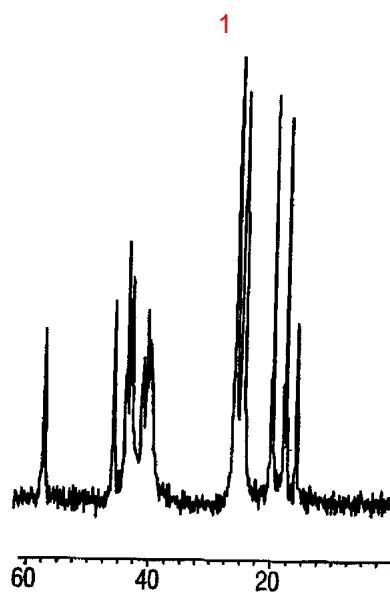
54

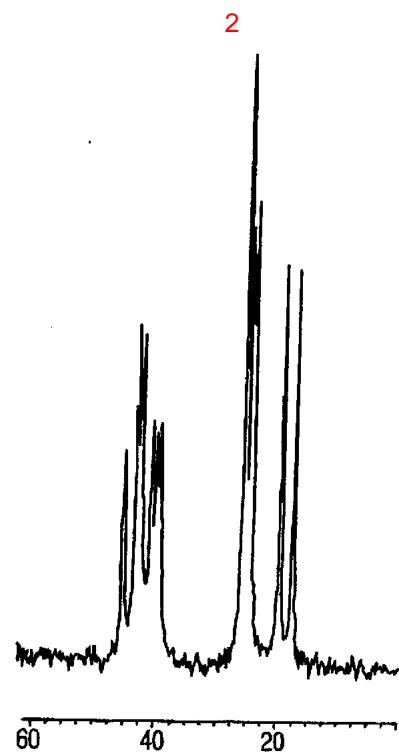
56.  
HMG-CoA

, 가

50

57.  
, 50





3

