

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

(51) 。 Int. Cl.⁷ (11) 10-2004-0023660
A61K 31/585 (43) 2004 03 18

(21) 10-2004-7000846
(22) 2004 01 19
2004 01 19
(86) PCT/US2002/022896 (87) WO 2003/007993
(86) 2002 07 18 (87) 2003 01 30

(30) 60/306,336 2001 07 19 (US)
(71) 63167 800
(72) , , .
63017 1861
63126 9154
, , .
60031 . 5314
(74)

:
(54) H M G C O A

H M G Co - A () , ,
H M G Co - A .

H M G Co - A , , ,

effect) () , (dyslipidemia) (pathogenic effect) , HMG CoA 가

(ALDO) 가 ,
(K⁺) , Na⁺ , ALDO-
(Mg²⁺) , Na⁺ . ALDO
ALDO 가 , ALDO 가
가 가 ALDO ALDO
K⁺ , ACTH) . ALDO
- - (RAAS) /
II , II
가, ,
II 가 II
가 가 . II

)]). , ([F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]). , (ascites) (intolerant) 1 mg 400 mg/ 가 (, 1 mg/ , 5 mg/ , 20 mg/] ([P. A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug,1986)]). II , .([D. Klug et al, Am. J. Cardiol. , 71 (3), 46A-54A (1993)]). ([C. G. Brilla et al, J. Mol. Cell. Cardiol., 25 (5), 563-575 (1993)]).

mg 100 mg (regimen) , 1 25
cians'Desk Reference, 55th Edn., p. 2971, Medical Economics Company Inc., Montvale, N. J. (2001)) (Physi
(ACE) , II

(HMG Co-A) HMG Co-A
HMG Co-A LDL
([Sacks et al., 'The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels', New England Journal of Medicine, 335 (14):1001-9 (1996)]).

LDL .([Fujioka et al., 'The Mechanism of Comparable Serum Cholesterol Lowering Effect of Pravastatin Sodium, a 3-hydroxy-3-methylglutaryl Coenzyme A Inhibitor, between Once- and Twice-Daily Treatment Regimens in Beagle Dogs and Rabbits', Jpn. J. Pharmacol., Vol. 70, pp. 329-335 (1996)]).

HMG Co-A (apical) - (ASBT)
PCT W098/40375 .

HMG Co-A
HMG Co-A [Vega et al., 'Treatment of Primary Moderate Hypercholesterolemia With Lovastatin (Mevinolin) and Cholestipol', JAMA, Vol. 257(1), pp. 33-38 (1987)]
HMG Co-A [Pan et al., 'Pharmacokinetics and pharmacodynamics of pravastatin alone and with cholestyramine in hypercholesterolemia', Clin. Pharmacol. Ther., Vol. 48, No. 2, pp. 201-207 (August 1990)]
(CETP) HMG Co-A
-A 5,932, 587 .

[Ginsberg, 'Update on the Treatment of Hypercholesterolemia, with a Focus on HMG Co-A Reductase Inhibitors and Combination Regimens', Clin. Cardiol., Vol. 18 (6), pp. 307-315 (June 1995)] , HMG Co-A
-A ,

[Pasternak et al., 'Effect of Combination Therapy with Lipid-Reducing Drugs in Patients with Coronary Heart Disease and 'Normal' Cholesterol Levels', Annals of Internal Medicine, Vol. 125, No. 7, pp. 529-540 (October 1, 1996)] HMG Co-A
LDL

. ASBT HMG CoA
No. 09/037,308 .

[J. Sasaki et al.]
'750 mg/ 가

[L. Cashin-Hemphill et al. (J. Am. Med. Assoc., 264 (23), 3013-17 (1990))]

HDL
[(N. Hoogerbrugge et al., J. Internal Med., 241, 151-55 (1997))].

가 (margarine) [H. Gylling et al. (J. Lipid Res., 37, 1776-85 (1996))]
- - LDL

[Brown et al. (New Eng. J. Med., 323 (19), 1289-1339 (1990))]
가

B CETP [Chang et al. PCT No. WO 9823593]

[Buch et al. (PCT No. WO 9911263)] , ,

PCT

No. WO 9911259

[Scott et al. (PCT

No. WO 9911260)]

[(Dettmar)

(Gibson) (

No. GB 2329334 A)]

HMG CoA

HMG CoA

otency), ()

1. HMG CoA
(dyslipidemia) ()

2. HMG CoA

3. 가

4. 가

5. HMG Co-A

6. HMG Co-A

7. HMG Co-A

8. , HMG Co-A

9. , HMG Co-A

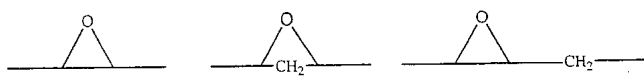
) HMG Co-A (HMG Co-A (dyslipidemia)

() , HMG CoA

X (cachexia)

가

'D' 가



1,3-

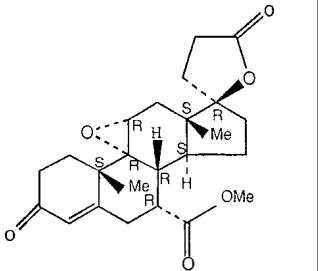
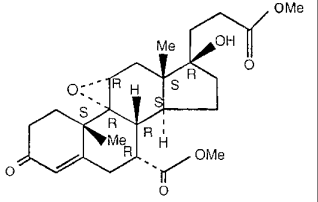
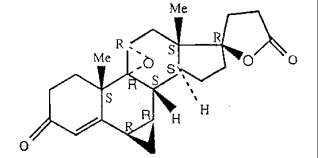
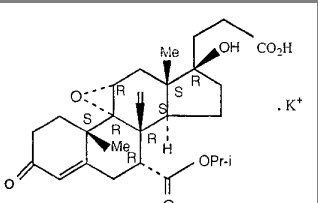
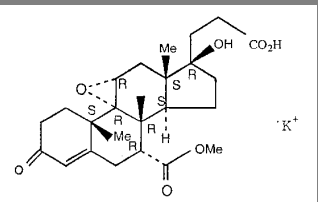
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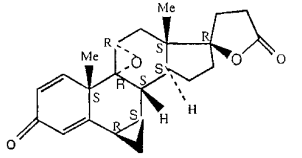
'A', 'B', 'C' 'D' 가

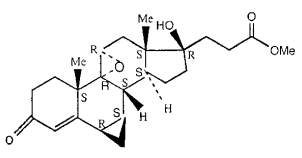
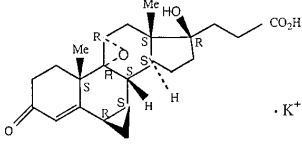
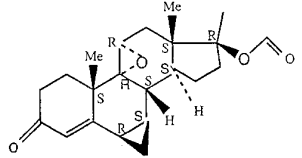
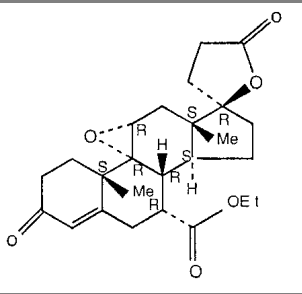
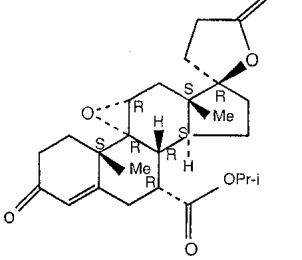
9' ,11' - 'C'
20- 1 11 9'
,11' -

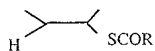
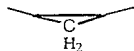
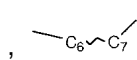
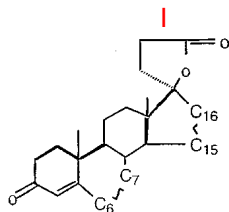
No. 4,559,332
Ng W097/21720 Ng W098/25948 . 9,11-

[1]

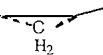
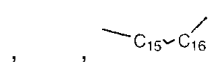
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2		-4- -7,21- , 9,11- -17- -3- -, , (7 ,11 ,17)-
3		3'H- [6,7] -4,6- -21- , 9,11- - 6,7- -17- -3- -, (6 ,7 ,11 ,17)-
4		-4- -7,21- , 9,11- -17- -3- -, - , 7-(1-) , 1 (7 ,11 ,17)-
5		-4- -7,21- , 9,11- -17- -3- -, 7-) , 1 (7 ,11 ,17)

6		3'H- -6,7-	[6,7] -17-	-1,4,6- -3-	-21- -	, 9,11- (6 ,7 ,11)-
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7		3'H- ,7-	[6,7] -17-	-4,6- -3-	-21- -	, 9,11- , (6 ,7 ,11 ,17)- -6
8		3'H- 6,7-	[6,7] -17-	-4,6- -3-	-21- -, 1	, 9,11- , (6 ,7 ,11 ,17)- - . K ⁺
9		3'H- -6,7-	[6,7] -17-	-1,4,6- -3-	-21- -	, 9,11- (6 ,7 ,11 ,17)-
10		-4- -,	-7, 21- (7 ,11 ,17)-	, 9,11- -	-17- -	-3- -,
11		-4- , 1-	-7,21- (7 ,11 ,17)	, 9,11- -	-17- -	-3- -,



R 5



, , n-

I

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7 - -3- -4,15- -[17(-1')- -5'] -2'- ;

3- -7 - -4,15- -[17(-1')- -5'] -2'- ;

6 ,7 - -3- -4,15- -[17(-1')- -5'] -2'- ;

15 ,16 - -3- -4,7 - -4- [17(-1')- -5'] -2'- ;

6 ,7 ,15 ,16 - -3- -4- [17(-1')- -5'] -2'- ;

7 - -15 ,16 - -3- -4- -[17(-1')- -5'] -2'- ;

15 ,16 - -3- -7 - -4- -[17(-1')- -5'] -2'- ;

6 ,7 ,15 ,16 - -3- -4- -[17(-1')- -5'] -2'- .

I

1978 12 12

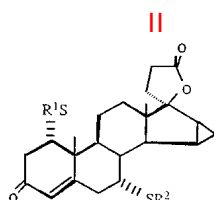
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- -

II

.

, R¹ C₁₋₃ -C₁₋₃, R² HC₁₋₃ -

.

II

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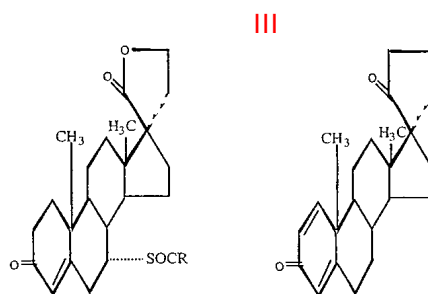
1 - -15 ,16 - -7 - -3- -17 - -4- -21,17- ; 15 ,16
 - -1 ,7 - -3- -17 - -4- -21,17- .

II 1988 12 6

No. 4,789,668

- -

III



, R

:

3 ,21- -17 - -5,15- -17- - ;
 3 ,21- -17 - -5,15- -17- - 3- ;
 3 ,21- -17- -5- -17- - ;
 3 ,21- -17- -5- -17- - 3- ;
 21- -3- -17 - -4- -17- - ;
 21- -3- -17 - -4,6- -17- - ;
 21- -3- -17 - -1,4- -17- - ;
 7 - -21- -3- -17 - -4- -17- - ;
 7- -21- -3- -17 - -4- -17- - .

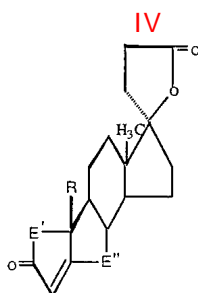
III 1966 6 21

No. 3,257,390

- -

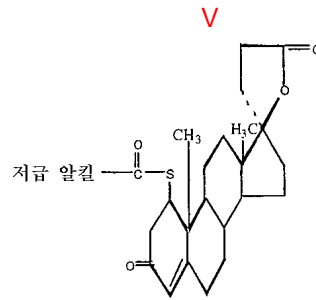
IV

:



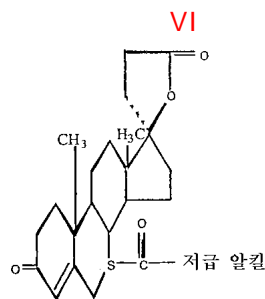
E'가 , (, E') , () () (, R) , E' E' () .

IV - - V :



V 1- -17 -(2-)-17 (3- - -4- -3 - .

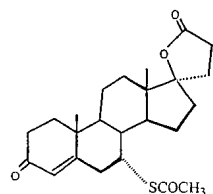
IV - - VI :



VI :

7 - -17 -(2-)-17 (3- - -4- -3- ;
 7 - -17 -(2-)-17 - - -4- -3- ;
 1 ,7 - -17 -(2-)-17 - - -4,6- -3- ;
 7 - -17 -(2-)-17 - - -1,4- -3- ;
 7 - -17 -(2-)-17 - -19- -4- -3- ;
 7 - -17 -(2-)-17 - -6 - -4- -3- .

IV VI , ' ' 1 8
 . '() ' -C(=O)-S- .



17- -7 - -3- -17 - -4- -21-
 IV VI 1961 12 12 No. 3,013,
 012 G. D. (Seoul amp; Co.)
 (ALDACTONE) 25 mg, 50 mg 100 mg
 , [6R-(6,7,8,9,10,13,14,15,16,17)-1,3',4',6,7,8,9,10,11,12,13,14,15,16,20,21-10,13-[17H-[6,7:15,16][a]-17,2'(5'H)-]-3,5'(2H)-, CAS 67392-87-4
 GB 1550568 1979, DE 2652761 1976

HMG Co-A

HMG Co-A

HMG Co-A

HMG Co-A

가

HMG Co-A

HMG Co-A

2

HMG Co-A

2 HMG Co-A

2

[2a]

화합물 및 화합물 부류	특정 및 대표적 화합물에 대한 CAS 번호	참고문헌
벤플루오렉스	23602-78-0	ES 474498, 제르비어
플루바스타틴	93957-54-1	EP 244364, 산도스
로바스타틴	75330-75-5	EP 22478, 머크 앤 코
프라바스타틴	81093-37-0	DE 3122499, 산교
심바스타틴	79902-63-9	EP 33538, 머크 앤 코
아도바스타틴	134523-00-5	EP 409281, 워너 랩버트
세리바스타틴	145599-86-6	JP 08073-432, 바이엘
베르바스타틴 및 관련 벤조피란	132017-01-7	EP 380392, 머크 KGaA
ZD-9720		WO97/06802
ZD-4522 (로수바스타틴 으로도 지칭)	147098-20-2 (칼슘 염); 147098-18-8 (나트륨 염)	EP 521471; Bioorg. Med. Chem., Vol. 5(2), pp. 437-444 (1997); Drugs Future, Vol. 24 (5), pp. 511-513 (1999)
BMS 180431	129829-03-4; 157243-11-3	Sit, Parker, Motoc, Han, Balasubramanian, Catt, Brown, Harte, Thompson, and Wright, J. Med. Chem., (1990), 33(11), 2982-99; 브리스톨 마이어스 스킵
NK-104 (피타바스타틴 및 니스바스타틴으로도 지칭)	141750-63-2	Takano, Kamikubo, Sugihara, Suzuk, Ogasawara, Tetrahedron: Assymetry, (1993), 4(2), 201-4; 닛산 케미컬
SR-12313	126411-39-0	스미스클라인 비첨
카르바스타틴	125035-66-7	도비시 야구닌 코교 Co. Ltd.
PD-135022	122548-95-2	파르케-데이비스 앤 코
크릴바스타틴	120551-59-9	펜 매디카

[2b]

화합물 및 화합물 부류	특정 및 대표적 화합물에 대한 CAS 번호	참고문헌
S-4522를 비롯한 (카르복시디히드록시-헵테날) -설폰닐피롤	148966-78-3, 139993-44-5, 139993-45-6, 139993-46-7, 139993-47-8, 139993-48-9, 139993-49-0, 139993-50-3, 139993-51-4, 139993-52-5, 139993-53-6, 139993-54-7, 139993-55-8, 139993-56-9, 139993-57-0, 139993-58-1, 139993-59-2, 139993-60-5, 139993-61-6, 139993-62-7, 139993-63-8, 139993-64-9, 139993-65-0, 139993-66-1, 139993-67-2, 139993-68-3, 139993-69-4, 139993-70-7, 139993-71-8, 139993-72-9, 139993-73-0, 139993-74-1, 139993-75-2, 139993-76-3, 139993-77-4, 139993-78-5, 139993-79-6, 139993-80-9, 140110-63-0, 140128-98-9, 140128-99-0, 140157-62-6	EP 464845; 시오노기
다-및 트리펩티드의 보론 유사체	125894-01-1, 125894-02-2, 125894-03-3, 125894-04-4, 125894-05-5, 125894-08-8, 125894-09-9, 125914-96-7	Sood, Sood Spielvogel, Hall, Eur. J. Med. Chem., (1990), 25(4), 301-8; Boron Biologicals
자라고즈산	157058-13-4, 157058-14-5, 157058-15-6, 157058-16-7, 157058-17-8, 157058-18-9, 157058-19-0	GB 2270312
u-88156을 비롯한 세코-옥시스테롤 유사체	157555-28-7, 157555-29-8	Larsen, Spilman, Yagi, Dith, Hart and Hess, J. Med. Chem., (1994), 37(15), 2343-51; 파미시아 엔 업존
U-9888; U-20685; U-51862; 및 U-71690	39945-32-9	파미시아 엔 업존

[2c]

화합물 및 화합물 부류	특정 및 대표적 화합물에 대한 CAS 번호	참고문헌
아시테메이트를 비롯한 피리도피리미딘	64405-40-9, 101197-99-3	Hermecz, Meszaros, Vasvari- Debreczy, Hovarth, Virag, and Sipos, Hung. Arzneim-Forsch., (1979), 29(12), 1833-5; Mitsubishi University
BMV 22566	129829-03-4	Sit, Parker, Motoc, Han, Balasubramanian, Catt, Brown, Harte, Thompson, and Wright, J. Med. Chem., (1990), 33(11), 2982-99
콜레스테롤	50673-97-7	Raulston, Mishaw, Parish and Schroepfer, Biochem. Biophys. Res. Commun., (1976), 71(4), 984-9; American Home Products
CP-83101	130746-82-6, 130778-27-7	Wint and McCarthy, J. Labelled Compd. Radiopharm., (1988), 25(11), 1289-97; Pfizer
달바스타틴	132100-55-1	Kuttar, Windisch, Trivedi and Golebiowski, J. Chromatogr., A (1994), 678(2), 259-63; Rhône-Poulenc Rorer
다히드로메비놀린	77517-29-4	Falck and Yang, Tetrahedron Lett., (1984), 25(33), 3563-66; Merck & Co.
DMP-565	199480-80-3	Ko, Trzaskos, Chen, Hauster, Brosz, and Srivastava, Abstr. Papers Am. Chem. Soc. (207 th National Meeting, Part 1, MED1 10, 1994); Dupont Merck

[2d]

화합물 및 화합물 부류	특정 및 대표적 화합물에 대한 CAS 번호	참고문헌
글렌바스틴을 비롯한 피리딘 및 피리미디닐-에테닐데스메틸 메발로네이트	122254-45-9	Beck, Kessler, Baader, Bartmann, Bergmann, Granzer, Jendralla, Von Kerekjarto, Krause, et al., J. Med. Chem., (1990), 33(1), 52-60; 픽스트 마리온 루셀
GR 95030	157243-22-6	US 5316765; 글락소 웰컴 EP 369323
이속사졸릴피리딘-메발로네이트 카르복실산 및 에스테르	130581-42-9, 130581-43-0, 130581-44-1, 130581-45-2, 130581-46-3, 130581-47-4, 130581-48-5, 130581-49-6, 130581-50-9, 130581-51-0, 130581-52-1, 130619-07-7, 130619-08-8, 130619-09-9	
6-페녹시-3,5-디히드록시-핵산산	127502-48-1, 13606-66-1, 136034-04-3	Jenderella, Granzer, Von Kerekjarto, Krause, Schnacht, Baader, Bartmann, Beck, Bergmann, et al., J. Med. Chem., (1991), 34(10), 2962-83; 픽스트 마리온 루셀
L 659699	29066-42-0	Chiang, Yang, Heck, Chabala, and Chang, J. Org. Chem., (1989), 54(24), 5708-12; 머크 앤 코
L 669262	130468-11-0	Stokker, J. Org. Chem., (1994), 59(20), 5983-6; 머크 앤 코
메바스타틴	73573-88-3	JP 56051992; 산쿄
판노린	137023-81-5	Ogawa, Hasumi, Sakai, Murzkwa and Endo, J. Antibiot., (1991), 44(7), 762-7; 도요코 노코 대학

[2e]

화합물 및 화합물 부류	특정 및 대표적 화합물에 대한 CAS 번호	참고문헌
로소놀	125111-69-5	Cane, Troupe, Chan, Westley and Faulkner, Phytochemistry, (1989), 28(11), 2917-19; 스미스-클라인 비썬
RP 61969	126059-69-6	EP 326386; 폰-플랑 로리
Na S-2467 및 S-2468를 비롯한 담즙산 유래 HMG Co-A 환원 효소 저해제		Kramer, Wess, Enhsen, Bock, Falk, Hoffmann, Neckermann, Grantz, Schulz, et al., Biochim. Biophys. Acta D, (1994), 1227(3), 137-54; 픽스트 마리온 루셀
SC 32561	76752-41-5	US 4230626;
SC 45355	125793-76-2	EP 329124; 비공업적 문헌
SQ 33600를 비롯한 인 함유 HMG Co-A 환원 효소 저해제	133983-25-2	US 5274155; 브리스틀-마이어스 스쿼
6-Aryloxymethyl-4-hydroxytetra-hydropyran-2-ones, carboxylic acids and salts	135054-71-6, 136215-82-2, 136215-83-3, 136215-84-4, 136215-85-5, 136315-18-9, 136315-19-0, 136315-20-3, 136315-21-4, 136316-20-6	EP 418648
Atorvastatin calcium (CI 981)	134523-03-8	Baumann, Butler, Deering, Mennen, Millar, Nanninga, Palmer and Roth, Tetrahedron Lett., (1992), 33(17), 2283-4
Mevinolin Analogs		EP 245003
Pyranone Derivatives		US 4937259
1,2,4-Triazolidine-3,5-diones	16044-43-2	WO 9000897
Isoazolidine-3,5-diones	124756-24-7	EP 321090

[2f]

	CAS	
CS-514	81181-70-6	DE 3122499
1,10- (-)	32827-49-9	DE 2038835
N- , , -		Huang Hall, Eur. J. Med. C hem., (1996), 31 (4), 281-90
3- - -1-(3-)- - 1- 3- -1-(2,3,4- -, -)- -1-		Huang Hall, Arch. Pharm., (1996), 329 (7), 339-346
	64769-68-2	US 4049813
		JP 07089898
4-[1-()-2- - -4-]		Watanabe, Ogawa, Ohno, Yan o, Yamada Shirasaka, Eur. J. Med. Chem. , (1994), 29 (9) , 675-86
(- - , -)		US 5134155
HMG Co-A		British Biotech amp; Japan T obacco
HMG Co-A		
A-1233		
BAY-w-9533		
BB-476		
BMS-180436		-

[2g]

	CA S	
BMV-22566		DE 3122499
HMG Co-A		-
HMG Co-A		Ono
HMG Co-A ,		Chiroscience
HMG Co-A , -		
HMG Co-A , -		am p;
HMG Co-A ,		

HMG Co - A , 6- -3,5-		
		-
N - ((1 -) -) - 8 - (2 - (- 4 - - 6 - - 2H - - 2 -)		
N - (1 -) - 4 , 10 - - 8 - - - - 3 -		
P - 882222		
S - 853758A		
(S) - 4 - ((2 - (4 - (4 -) - 5 - - 2 - (1 -) - 6 - - 3 -) -) - 3 - ,		-
SDZ - 265859		

[2h]

	CAS	
(4R - (4 , 6 (E))) - 6 - (2 - (5 - (4 -) - 3 - (1 -) - 1 - (2 - H - - 4 -) - - 4 - - 2H - - 2 -		-
5 - -		
6 - - 2 - - 5 - - 4 -		
6 - - 6 - - (4 - - 2 -)		

, ZD - 4522 (, , , BMS180431, NK - 104 (, , , , PD - 135022, , DMP - 565, , L - 659699, L - 669262, S - 2467, S - 2468

, 3 . 3 ,

[3]

화합물 번호	관용명	CAS Registry Number	Patent/Literature Reference for Preparation of Compound <i>Per Se</i>
B-1	에바스타틴	73573-88-3	U.S. 3,983,140
B-2	로바스타틴	75330-75-5	U.S. 4,231,938
B-3	심바스타틴	79902-63-9	U.S. 4,444,784
B-4	프라바스타틴	81093-37-0	U.S. 4,346,227
B-5	플루바스타틴	93957-54-1	U.S. 4,739,073; U.S. 5,354,772
B-6	아토르바스타틴	134523-00-5	EP 409281; U.S. 5,273,995
B-7	세리바스타틴	145599-86-6	U.S. 5,177,080
B-8	ZD-4522 (로수바스타틴 으로도 지칭)	147098-20-2	EP 521471, 실시예 7; Bioorg. Med. Chem., Vol. 5(2), pp. 437-444 (1997); Drugs Future, Vol. 24 (5), pp. 511-513 (1999)
B-9	NK-104 (피타바스타틴, 니스바스타틴, 이타바스타틴 으로도 지칭)	141750-63-2	EP 0304063; CA 1336714

), NK-104 (), ZD-4522 ()

), ZD-4522 (

_____, _____, _____, _____, ZD-4522 (_____)

, ZD-4522 () NK-104 (,)

, ZD-4522 () NK-104 (, ,) .

1 2 3 4

HMG Co - A

(prodrug)' HMG Co-A

1. *Journal of the American Medical Association*, 1997; 277: 1039-1043.

가 , , -
가

H, L, , ,
: WO 98/25948, WO00/33847, WO01/41535, WO01/41770 WO01/42272.

(subject) , , ,
(treatment) , (process), , ,

(prophylaxis prevention)

(combination therapy) 2

(therapeutically effective)

가 (phatmaceutically acceptable) 가

가

가

4

4

(N-

)

, N,N'-

가

가

[IUPAC Handbook of Pharmaceutical Salts, P. H. Stahl, et al., eds. (Wiley - VCH, 2002)]

HMG Co-A

가

가

/

;

HMG Co-A

가

HMG Co-A

가
가

HMG Co-A

LDL

가

HMG Co-A

가

HMG Co-A

LDL

() , HMG Co-A (rhabdo) , , (flatulence), , (:) HMG Co-A 가 . HMG Co-A , HMG Co-A

6 HMG Co-A
.
HMG Co-A
가 . HMG Co-A
HMG Co-A

1 0.5 500 mg, 0.75 250 mg, 1 100 mg 0.1 2000 mg, 1 4 1 0.001 30 mg/kg 0.005 20mg/kg 0.01 5 mg/kg 0.01 15 mg/kg 0.05 10 mg/kg

endothelins

, C- ('NPR-A') , ('CNP') ('ANP') , ('BNP')
 A- , 3',5'- ANP BNP
 , (lusitropic) (cGMP)
 BNP
 (Uusimaa : *Int. J. Cardiol* 1999; 6
 9:5-14).

cGMP , cGMP 가
 . cGMP 가

BNP

(GFR) , 0.3g
 24 가

HMG Co-A

g	1,000 mg	,	1	HMG Co-A	0.01 mg	500 mg	,	1	0.05	1	0.001 m
				HMG Co-A		1					HMG Co-A
(, ZOCOR())	(5	, LIPITOR())	(10	80 mg;		
)	10	40 mg;	(, MEVACOR())	(, PRAVACHOL())	20	80 mg;	
(, BAYCOL())	(0.2	0.4 mg;	(, LESCOL				

()) 20 80 mg .

HMG Co-A

가

), (: 가

LDL

HMG Co-A
가

HMG Co-A

가
HMG Co-A

1
HMG Co-A

2
HMG Co-A

HMG Co-A

가

가
HMG Co-A

가

가 , , ; 2 HMG Co-A
1
HMG Co-A ,
가 .

1 2
HMG Co-A H

MG Co-A ()

가 가

가 가

0.05 % 95 %

가 HMG Co-A (, HMG Co-A

가

가 0.1 2000 mg, 0.5
mg 500 mg, 0.75 250 mg, 1 100 mg 0.1 50 mg HMG Co-A (

0.01 500 mg, 500 mg, 0.75 mg 0.75 mg 100 mg, 0.1 50 mg HMG Co-A

HMG Co-A

pH pH (b

oadhesion), 가

(cachets), (lozenges),) ; ;

가). 가

(:) () /

가 , , ,

() 가

G Co-A HM

가

[Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Dekker, New York, N. Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999]

[4]

	HMG CO - A (- 3)
	B - 1
	B - 2
	B - 3
	B - 4
	B - 5
	B - 6
	B - 7
	B - 8
	B - 9
	B - 1
	B - 2
	B - 3
	B - 4
	B - 5
	B - 6
	B - 7
	B - 8
	B - 9

Diagram illustrating the regulation of HMG Co-A synthase by phosphorylation and dephosphorylation:

- Top Left:** HMG Co-A synthase (represented by a circle) is phosphorylated (P) at site 1, leading to an inactive state (represented by a circle with a dot).
- Top Right:** HMG Co-A synthase (represented by a circle) is phosphorylated (P) at site 2, leading to an inactive state (represented by a circle with a dot).
- Bottom Left:** HMG Co-A synthase (represented by a circle) is dephosphorylated (P) at site 1, leading to an active state (represented by a circle with a dot).
- Bottom Right:** HMG Co-A synthase (represented by a circle) is dephosphorylated (P) at site 2, leading to an active state (represented by a circle with a dot).

1² HMG Co-A² 3
HMG Co-A²

1:

HMG Co-A

Pitt, et al. NEJM 341,709-717 (1999)

Pitt, et al. Cardiovasc Ther 15: 79-87 (2001)

De Gasparo, et al. J Pharm Exp Ther 240,650-656 (1986)

Blazer-Yost, et al. Am. J. Physiol 272, C1928-C1935 (1997)

Vijan, et al. J Gen Intern Med 12, 567-580 (1997)

Gentile, et al. 2,355-362 (2000)

Sheng-Fang, et al. Am J Cardiol 86,514-518 (2000)

Jick, et al. Lancet 356,1627-1631 (2000)

Albert, et al. JAMA 286,64-70 (2001)

Ridker, et al. NEJM 344,1959-1965 (2001)

Wang, et al. JAMA 283,3211-3216 (2000)

Meier, et al. JAMA 283,3205-3210 (2000)

Sugiyama, et al. Biochem Biophys Res Commun 271,688-692 (2000)

Mundy, et al. Science 286,1946-1949 (1999)

Xiao, et al. J Endocrinol 165,533-536 (2000)

US 5,730, 992, US 5,932, 587, US 6,180, 597

WO 00/69446, WO 00/69445, WO 00/45818, WO 00/45817, WO 99/66930,

WO 99/11260, WO 01/34132, WO 00/51642

2:

가 HMG Co-A (, HMG Co-A
가)
/

WO01/41770, WO 00/33847

3:

5a

120 mg

•

•

[5a]

	(mg)
	25
	20
	54
	15
	3
	2
	1
	120

4:

5b

120 mg

•

•

[5b]

	(mg)
	25
	5
	69.5
	15
	0.5
	2.5
	2
	0.5
	120

5:

5c

120 mg

•

•

[5c]

	(mg)
	25
	20
	54
	15
	3
	2
	1
	120

6:

5d

120 mg

:

[5d]

	(mg)
	25
	5
	69.5
	15
	0.5
	2.5
	2
	0.5
	120

7:

5e

120 mg

:

[5e]

	(mg)
	25
	10
	64
	15
	3
	2
	1

120

8:

5f

105 mg

:

[5f]

	(mg)
	10
	2.5
	72
	15
	0.5
	2.5
	2
	0.5
	105

9:

HMG CO - A

HMG Co - A

,

:

US 4,559, 332, US 4,129, 564, US 4,789, 668, US 3,257, 390, US 3,013, 012, GB 15
50568

WO 97/21720, WO 98/25948

HMG Co - A :

ES 474498 EP 244364 EP 22478, DE 3122499, EP 33538,

EP 409281, JP 08073-432, EP380392, WO 97/06802, EP 521471,

Bioorg. Med. Chem. 5 (2), pp. 437-444 (1997)

Drugs Future 24 (5), pp. 511-513 (1999)

J. Med. Chem 33 (11), 2982-99 (1990)

Tetrahedron: Assymetry 4 (2), 201-4 (1993)

10:

HMG CO - A

, 가 , , 가 ,
 . H, L, . ,
 : WO 98/25948, WO00/33847, WO01/41535, WO01/41770 WO01/42272.

11:

HMG CoA -

mg/dl (LDL - /HDL 가 > 6 (endpoint event trial) < 130) HDL - LDL - < 45mg/dl 130-190

HMG CoA -

HMG CoA HMG CoA

1 (: , -

2) (1) - (2) , (3) -

, (4) , (5) - 가 ,

, HMG CoA

4- HMG CoA 가 , 가 ,

(Apo AI Apo B), ,

1 , 가 4 , 가 (),

가 .

4 :

:

1- -

2-

3-

2 :

1-

2-

3- MI

4-

5-

12: / 가

HMG CoA
 18~80
 (QCA) 가 (focal lesion),
 30% 50% 1 2 가 (branch), (circumflex),
 , B- 가
 HMG CoA HMG CoA 3
 B-
 3
 B- 가
 가
 (QCA)
 HMG CoA
 12 (, Mean Max)
 가 HMG CoA HMG CoA
 ()
 가
 가
 () , ' (a, an)', ' (the)', ' (said)' 1
 가 (comprising, including)', '가 (having)'

(57)

1. 1 2 HMG Co-A
2. 1 가
3. 1 가
4. 1 , 2 HMG Co-A , HMG Co-A 가
1 2

5. 가 9 -,11 -
6. 가
7. 가 -
8. 가
9. HMG Co - A 가 , , , 가 , , (conjugate acids),
10. HMG Co - A 가 , , , , ,
11. HMG Co - A 가
12. HMG Co - A 가
13. HMG Co - A 가
14. HMG Co - A 가
15. HMG Co - A 가
16. HMG Co - A 가
17. HMG Co - A 가
18. HMG Co - A 가
19. HMG Co - A 가
20. HMG Co - A HMG Co - A 가 10:1 1:2 가

20	21.	,	가	5:1	1:1	.			
20	22.	,	가	2:1	1:1	.			
4	23.	,	HMG Co-A		2	0.05 mg	100 mg	.	
4	24.	,			1	0.75 mg	200 mg	.	
4	25.	,		가		,	HMG Co-A	가	
,	,	,	가	,	,	,	,	,	.
,									
4	26.	,		가		,	HMG Co-A	가	
,	,	,		,		,	가	,	,
									.
4	27.	,		가		,	HMG Co-A	가	
		.							
4	28.	,		가		,	HMG Co-A	가	
		.							
4	29.	,		가		,	HMG Co-A	가	
		.							
4	30.	,		가		,	HMG Co-A	가	
		.							
4	31.	,		가		,	HMG Co-A	가	
		.							
4	32.	,		가		,	HMG Co-A	가	
		.							
4	33.	,		가		,	HMG Co-A	가	
		.							
4	34.	,		가		,	HMG Co-A	가	
		.							
4	35.	,		가		,	HMG Co-A	가	
		.							

36	52.	,	HMG Co - A	가	.
36	53.	,	HMG Co - A	가	.
36	54.	,	가 9 -,11 -		-
36	55.	,	가		.
36	56.	,	가	-	.
36	57.	,	가		.
36	58.	,	HMG Co - A	가	,
,	,	,	,	,	가
36	59.	,	HMG Co - A	가	,
		가	,	,	.
36	60.	,	HMG Co - A	가	.
36	61.	,	HMG Co - A	가	.
36	62.	,	HMG Co - A	가	.
36	63.	,	HMG Co - A	가	.
36	64.	,	HMG Co - A	가	.
36	65.	,	HMG Co - A	가	.
36	66.	,	HMG Co - A	가	.
36	67.	,	HMG Co - A	가	.
36	68.	,	HMG Co - A	가	.

69. 36 , HMG Co-A 가 HMG Co-A 10:1 1:2 가, .
70. 69 , 가 5:1 1:1 .
71. 69 , 가 2:1 1:1 .
72. 36 , HMG Co-A 2 0.05 mg 100 mg .
73. 36 , 1 0.75 mg 200 mg .
74. 36 , 가 , HMG Co-A 가 , , , 가 , , , .
75. 36 , , 가 , HMG Co-A 가 , , , .
76. 36 , 가 , HMG Co-A 가 .
77. 36 , 가 , HMG Co-A 가 .
78. 36 , 가 , HMG Co-A 가 .
79. 36 , 가 , HMG Co-A 가 .
80. 36 , 가 , HMG Co-A 가 .
81. 36 , 가 , HMG Co-A 가 .
82. 36 , 가 , HMG Co-A 가 .
83. 36 , 가 , HMG Co-A 가 .

36	84.	,	가	,	HMG Co - A	가
		.				
1	85.		2	HMG Co - A		.
85	86.	,	가 9	- , 11	-	
-		-				.
85	87.	,	가		.	
85	88.	,	가	-		.
85	89.	,	가		.	
85	90.	,	HMG Co - A	가	,	,
,		,	,	,	,	가
,		,	,	,	,	.
85	91.	,	HMG Co - A	가	,	,
		가	,	,	,	.
85	92.	,	HMG Co - A	가		.
85	93.	,	HMG Co - A	가		.
85	94.	,	HMG Co - A	가		.
85	95.	,	HMG Co - A	가		.
85	96.	,	HMG Co - A	가		.
85	97.	,	HMG Co - A	가		.
85	98.	,	HMG Co - A	가		.
85	99.	,	HMG Co - A	가		.
85	100.	,	HMG Co - A	가		.

101.	85	HMG Co-A	HMG Co-A	가	10:1	1:2	가
102.	101	가	5:1	1:1			
103.	101	가	2:1	1:1			
104.	85	HMG Co-A	2	0.05 mg	100 mg		
105.	85		1	0.75 mg	200 mg		
106.	85	가		HMG Co-A	가		
107.	85	가		HMG Co-A	가		
108.	85	가		HMG Co-A	가		
109.	85	가		HMG Co-A	가		
110.	85	가		HMG Co-A	가		
111.	85	가		HMG Co-A	가		
112.	85	가		HMG Co-A	가		
113.	85	가		HMG Co-A	가		
114.	85	가		HMG Co-A	가		
115.	85	가		HMG Co-A	가		

85 **116.** , 가 HMG Co-A 가 .