

(74)

:

(54)

1999 7 7 가 60/142,550 1998 12 23 가 60 /113,955

(IBAT)

(LDL)

가 LDL

가

LDL

(CAD)

LDL (180 mg/dl) HDL (35 mg/dl) HDL/LDL

가

가

(Stedronsky) [" Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties, "Biochimica et Biophysica Acta,1210, 255 - 287 (1994)]

(Heubi, J.E)

IBAT

가

() [" Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport" ,Gastroenterology,83, 804 - 11 (1982)]

[Kramer, et al., " Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, 268(24), 18035 - 46 (1993)].

가

LDL

R1. 2,025,294

R2. 2,078,588

R3. 2,085,782

R4. 2,085,830

R5. EP 0 379 161

R6. EP 0 549 967

R7. EP 0 559 064

R8. EP 0 563 731

가 WO 93/3

21146

EP 508425

가

FR 2661676

가

WO 92/18462

5,994,391 ()

가 PCT/US95/10863

가

PCT/US97/04076

08/816,065

WO 93/16055

가

(, 2,3,4,5 -

- 1 - - 4 -

WO 96/05188

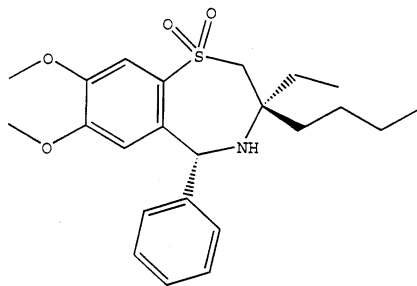
WO 96/05188

B - 2

가

WO 96/16051

B - 2



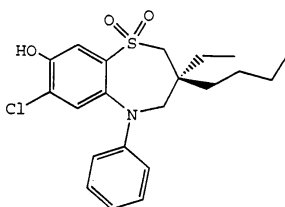
(3R,5R) - 3 - - 3 - - 2,3,4,5 - - 7,8 - - 5 - - 1 - 4 - - 1,1 -

PCT

WO 99/35135

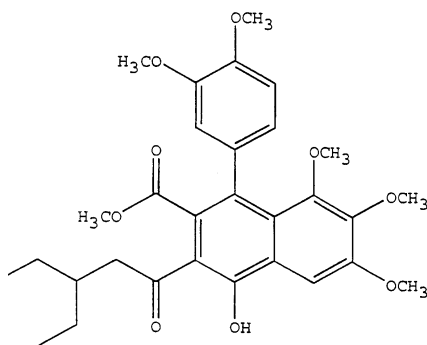
B - 7

B - 7



IBAT (T. Ichihashi) [J. Pharmacol. Exp. Ther., 284(1), 43 - 50 (1998)]
 - (3 -) - 4 - - 6,7,8 - - 2 - 가 , S - 8921(1 - (3,4 -) - 3
 B - 20)가 . S - 8921 가
 가 PCT WO 94/24087

B - 20



() 1955 (. , Arch.Biochem. Biophys.,
 54, 558 - 9(1955)) B - HDL VLDL LDL

Ther., 33(7), 420 - 26(1995)) (, Curr.Ther.Res., 55, 546 - 51). (Int.J.Clin.Pharm.
(5 - - 2 - 4 - , 4,002,750) 가

IBAT 가 HMG CoA
09/037,308

0 mg/ (J. Sasaki) () " 75
가

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

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

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

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

(Buch) PCT WO 99/11263 , ,

PCT WO 99/11259

(Scott) PCT WO 99/11260

(Dettmar) (Gibson) GB 2329334

HMG Co A

가 가 , 1 IBAT 2 , , 1
2 - , - IBAT - IBAT

1 , 가 2 , 1
2 - . , 1

2 , 1
2 , 1 2 -

2 1
2 , 1 2 -

가 , ,
가 , ,
가 , ,
가 , ,
가 , ,
가 , ,

a.

" " " IBAT" ASBT .

" IBAT " 2,3,4,5 - -1- 1,1- 가

" " -3- -2-

), , , , , . (

2

b.

가
(monotherapy)

가,

가

T/US95/10863
/04076
/816,065
98/40375

08/816,065
5,994,391

1
(enantiomer),

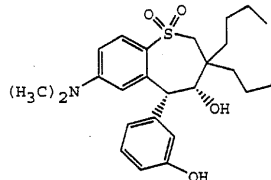
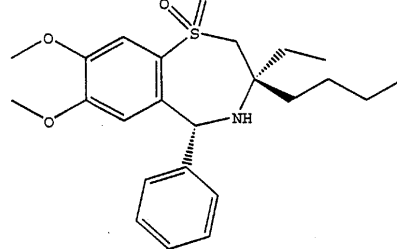
IBAT
IBAT
IBAT
가 IBAT
가 IBAT
PC
PCT/US97
08
WO

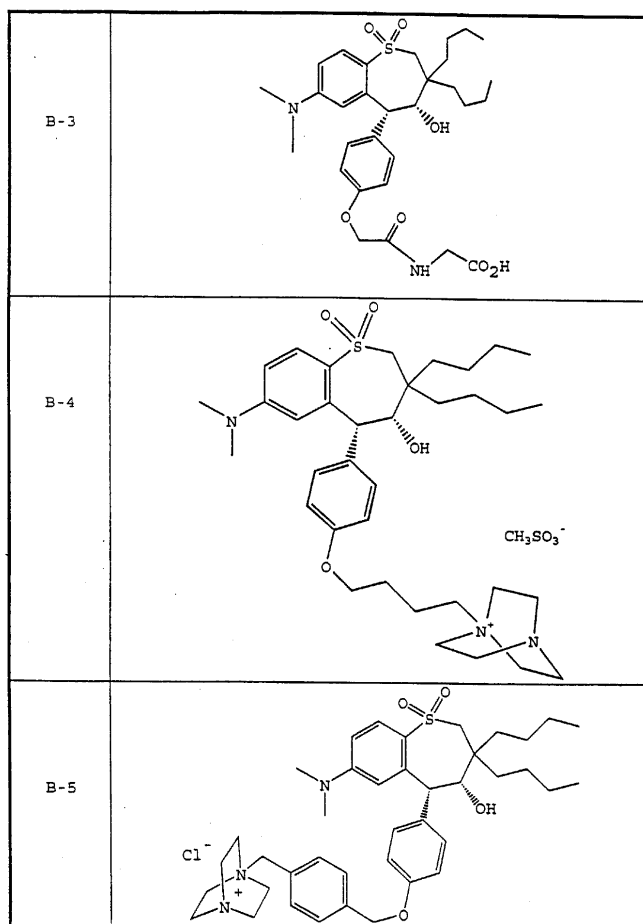
가 IBAT

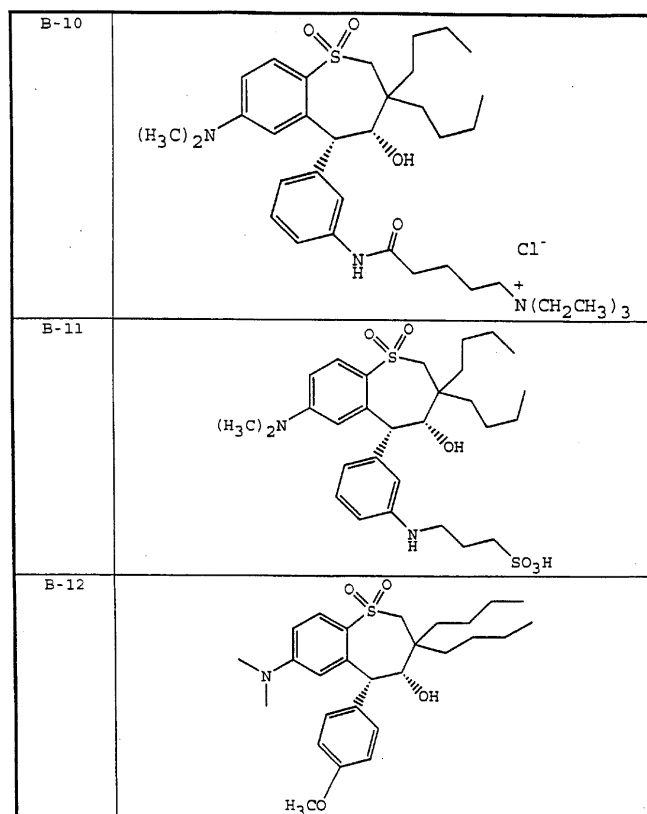
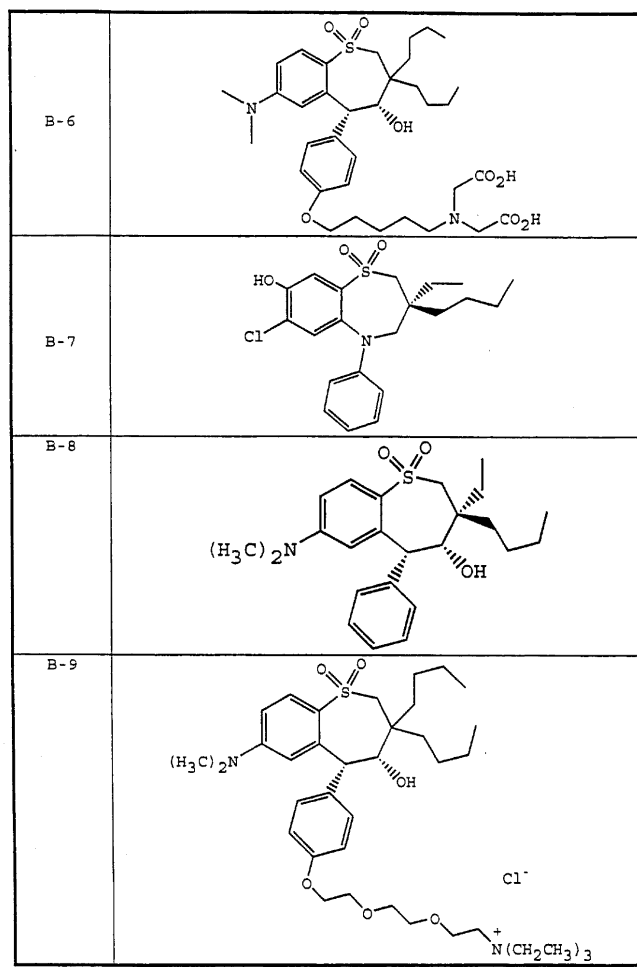
1 IBAT
(tautomers)

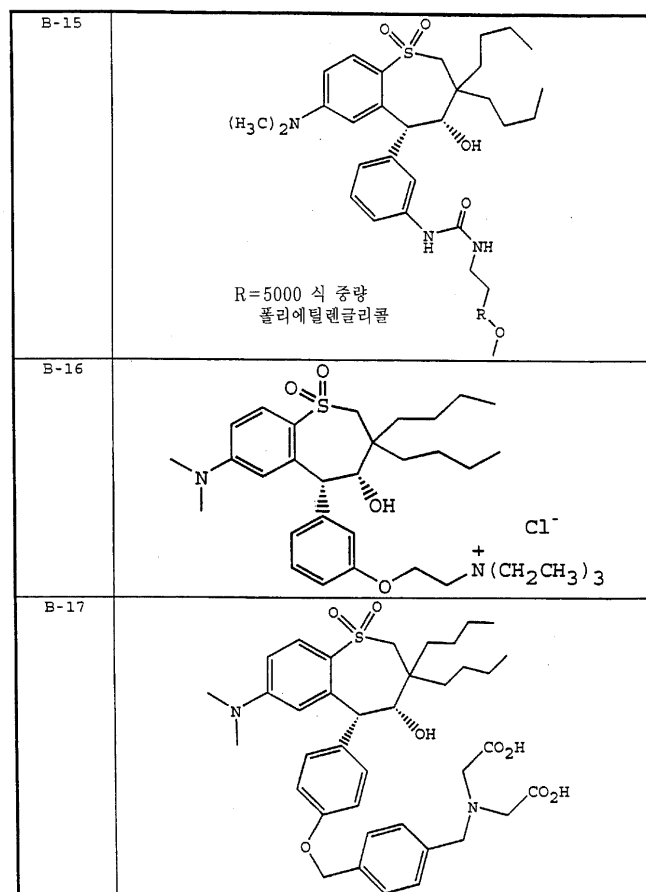
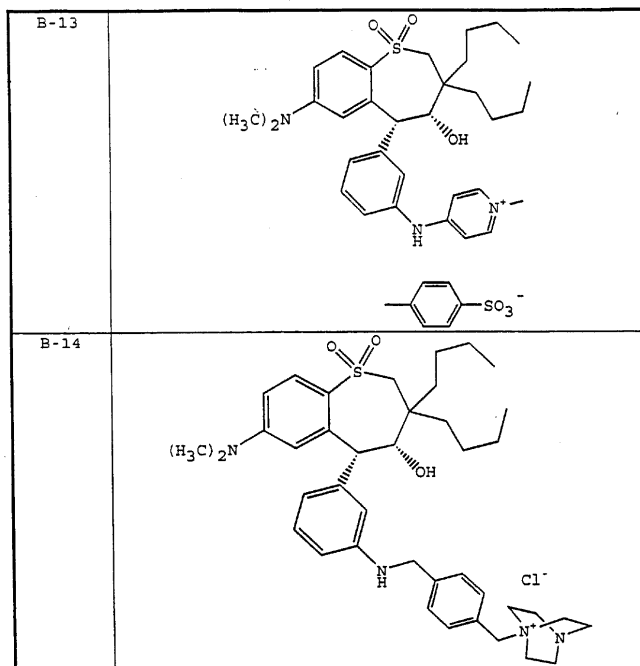
(diastereomer),

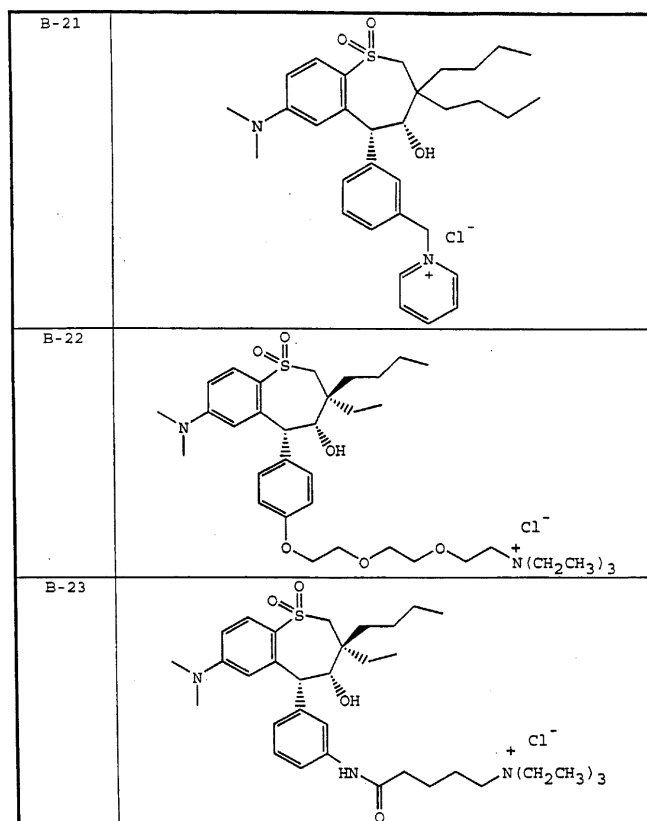
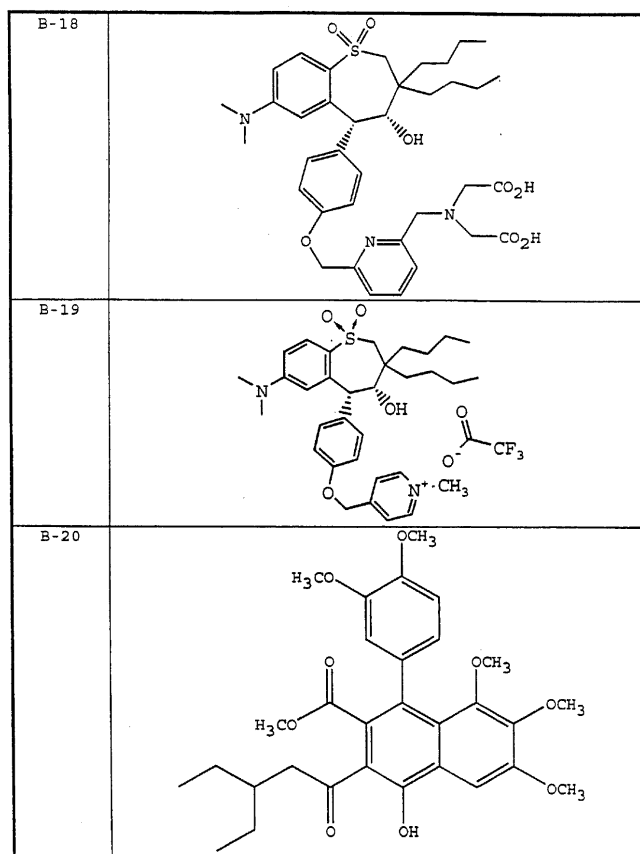
IBAT

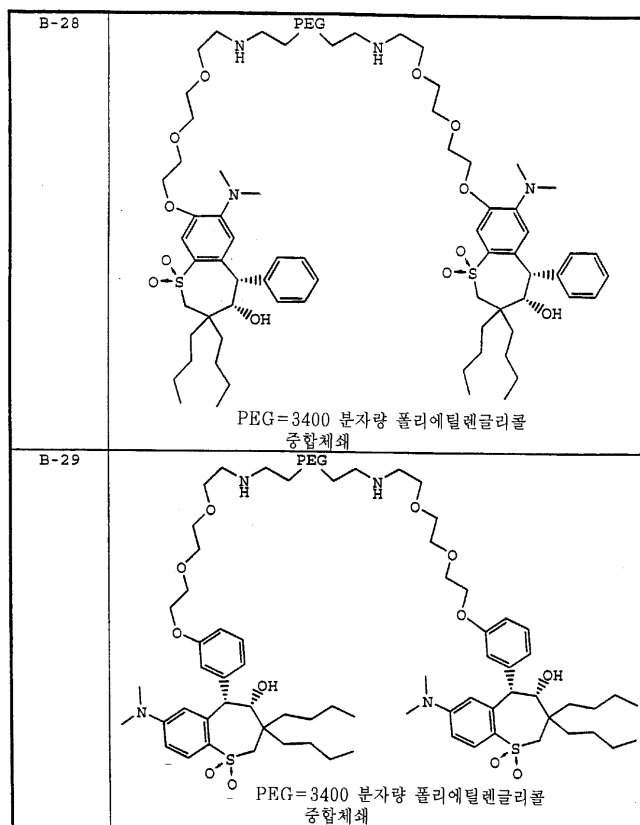
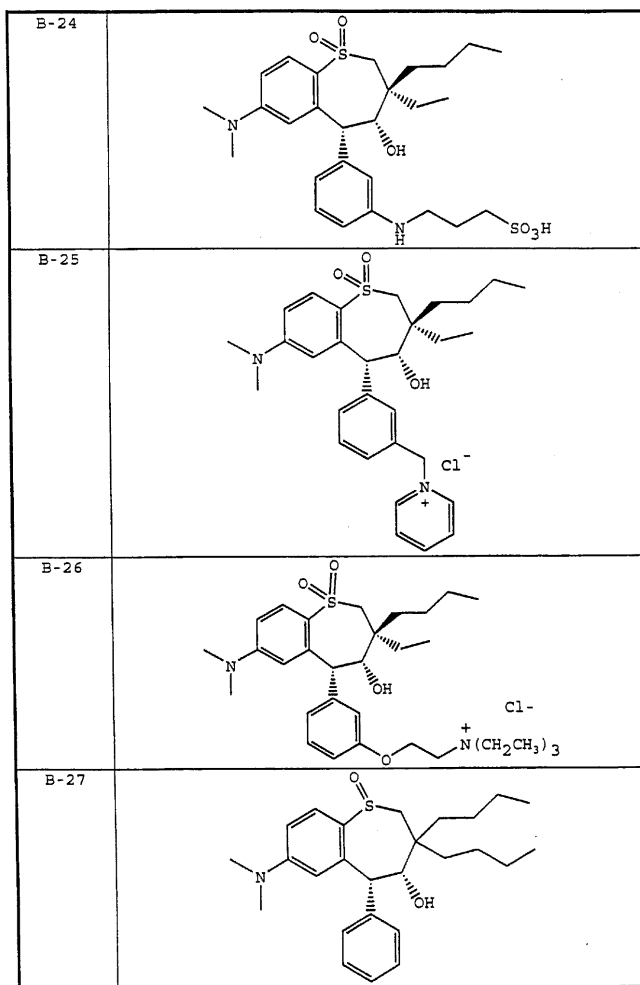
화합물 번호	구조
B-1	
B-2	 <p data-bbox="606 2027 973 2094">(3R,5R)-3-부틸-3-에틸-2,3,4,5-테트라히드로-7,8-디메톡시-5-페닐-1,4-벤조티아제핀 1,1-디옥사이드</p>

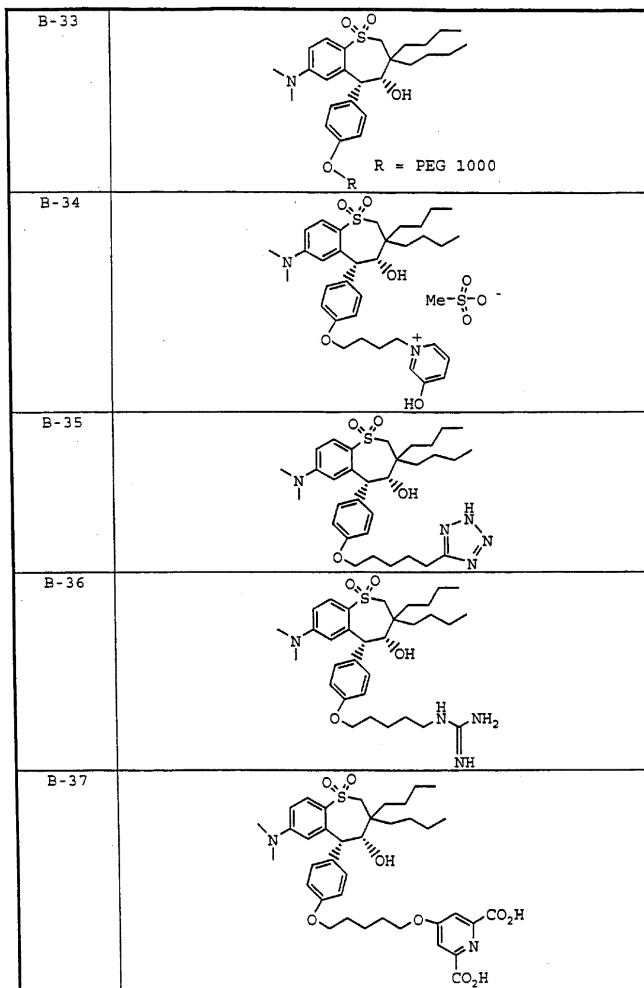
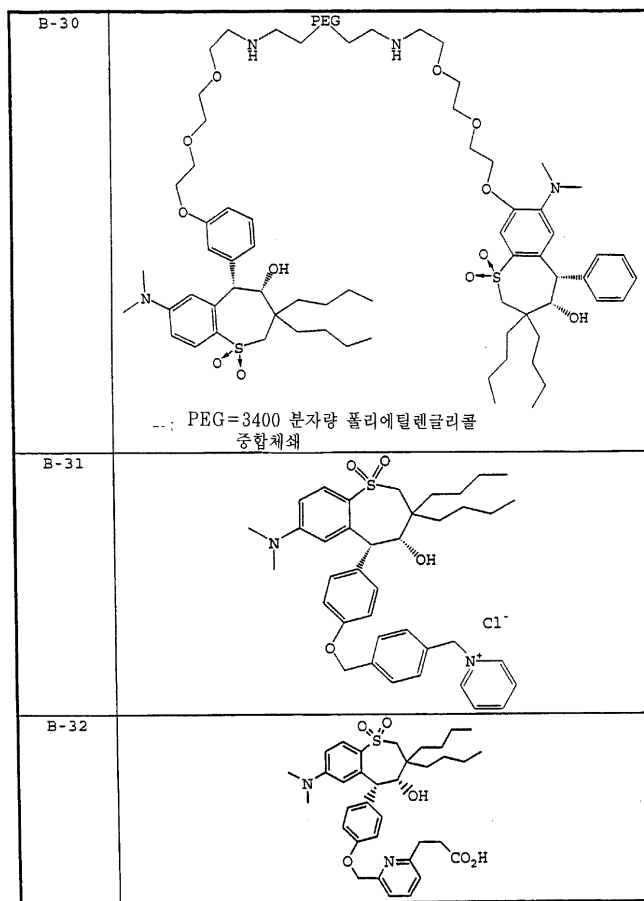


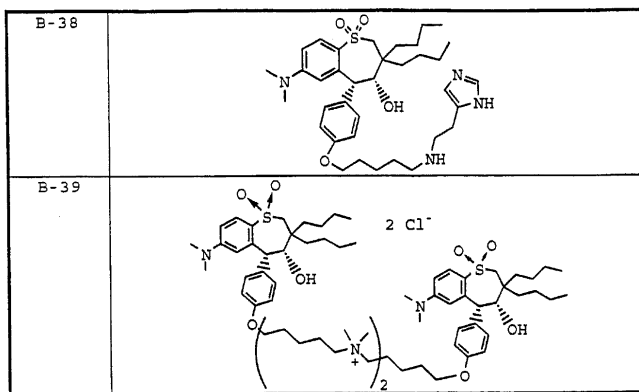












2 . 2 , , , , ,

[2]

		CAS	
G-118		59-67-6	
G-117		5868-05-3	GB 1022880
G-3		51037-30-0	GB 1351967

(,)
가 , 가 .

(,) , ,

(parent)
가 , 가 . 가

(土類)

가

가 (recipient)
0.05 95 %

(,)

가 , IBAT 1 10 mg/ 0.01 1000 mg/ , 0.1 50 mg/ ,

1000 8000mg/ , 3000 500 6000mg/ 10,000mg/ ,

2 6

pH

(retension),

pH

(,)

(, IBAT 가

),

IBAT 가 IBAT 가

300mg/kg 2000mg/kg 150mg/kg 3000mg/kg
500mg/kg 1000mg/kg

10 100 ng/kg
0.1 ng/Mℓ 10 mg/Mℓ, 1 mg 10 g 1 ng/Mℓ 10 mg/Mℓ

1mg 100 mg

() ()

) ;

() ()

(, 가) / / ()

() 가 ()

가 0.1 5 % w/w

(,)

(paste),
(,),
0.1 50 % w/w, 0.5 2 %

가 . , ,
 / ,
 1% 35%, 3% 15% . 가 , [Pha
 (electrotransport) (iontophoresis) ,
 rmaceutical Research,3(6), 318(1986)] .

가 (,) , 가 (,)
 가 (,) , 가 (,)

가 1,3- 가

0.01mg 500mg , IBAT 0.01mg/ 500mg/

/ , / , /

가

2

가

가

/

가

LDL

가

가

가

가 2 IBAT 1 , 1 2
 - - . ,
 IBAT .
 IBAT .

3 , 1 2 , - IBAT 1 - 2
 .

[3]

	1	2
1	B - 1	()
2	B - 2	()
3	B - 3	()
4	B - 4	()
5	B - 5	()
6	B - 6	()
7	B - 7	()
8	B - 8	()
9	B - 9	()
10	B - 10	()
11	B - 11	()
12	B - 12	()
13	B - 13	()
14	B - 14	()
15	B - 15	()
16	B - 16	()
17	B - 17	()
18	B - 18	()
19	B - 19	()
20	B - 20	()
21	B - 21	()
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23	B - 23	()
24	B - 24	()
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26	B - 26	()
27	B - 27	()
28	B - 28	()
29	B - 29	()
30	B - 30	()
31	B - 31	()
32	B - 32	()
33	B - 33	()
34	B - 34	()
35	B - 35	()
36	B - 36	()

37	B - 37	()
38	B - 38	()
39	B - 39	()
40	B - 1	
41	B - 2	
42	B - 3	
43	B - 4	
44	B - 5	
45	B - 6	
46	B - 7	
47	B - 8	
48	B - 9	
49	B - 10	
50	B - 11	
51	B - 12	
52	B - 13	
53	B - 14	
54	B - 15	
55	B - 16	
56	B - 17	
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58	B - 19	
59	B - 20	
60	B - 21	
61	B - 22	
62	B - 23	
63	B - 24	
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65	B - 26	
66	B - 27	
67	B - 28	
68	B - 29	
69	B - 30	
70	B - 31	

71	B - 32	
72	B - 33	
73	B - 34	
74	B - 35	
75	B - 36	
76	B - 37	
77	B - 38	
78	B - 39	
79	B - 1	
80	B - 2	
81	B - 3	
82	B - 4	
83	B - 5	
84	B - 6	
85	B - 7	
86	B - 8	
87	B - 9	
88	B - 10	
89	B - 11	
90	B - 12	
91	B - 13	
92	B - 14	
93	B - 15	
94	B - 16	
95	B - 17	
96	B - 18	
97	B - 19	
98	B - 20	
99	B - 21	
100	B - 22	
101	B - 23	
102	B - 24	
103	B - 25	
104	B - 26	
105	B - 27	

106	B - 28	
107	B - 29	
108	B - 30	
109	B - 31	
110	B - 32	
111	B - 33	
112	B - 34	
113	B - 35	
114	B - 36	
115	B - 37	
116	B - 38	
117	B - 39	

[14¹⁴ C] -

(FBA)

24 48

0.1

(/)

, NAD

3

(Clin.Chem., 27, 1352(1981)

).

(275 - 300g) IBAT

(0.2

% TWEEN 80) 4

(9:00 - 10:00 a.m.)

2ml/ kg

(TWEEN 80 ICI Specialty Chemicals(, ,)

20

)

48

(FBA)

가

FBA

(BBMV) [3³ H]

(Biochimica Biophysica Acta, 554,259(1979),

)

가 1

00 μ l 200 μ l

(1992),

M NaCl, 100mM

pH7.4

가

190 μ l

BBMV 가

(0.2 μ m)

(Biochimica Biophysica Acta, 1111, 93

(0.75 μ Ci), 20mM Tris, 100m

(60 - 120 μ g) 10 μ l 5

(20mM Hepes - tris, 150mM KC

5ml

l) 5ml 가

- CoA;

(ACAT)

(J.Biol.Chem., 255,9098(1980),

)

ACAT

0.25% BSA 200 μ g

50mM

, 2mM DTT pH7.4

24 μ M

- CoA(0.05 μ Ci)

2.0ml

- CoA

가

37

5

(2:1) 8.0ml 가

125 μ g

가

60TLC

/

(9:1)

TLC

(Packard Instaim

ager)

(HEPATIC CHOL)

: (2:1)

0(1974)(

Clin.Chem., 20,47

HMG CoA - (HMG - COA)

/

¹⁴C - HMG - CoA (Dupont - NEN)

37 60

HMG CoA

6N HCl 가

(: , , .(1990)J.Lipid R

es.31,2159).

7 - -

(7a - OHase)

/

NADPH

37 5

7 - -

C₁₈ HPLC

240nm

UV

.(: , . . .(1994)J.Clin.Invest.93,

2084).

(SER.CHOL, HDL - CHOL, TGI VLDL+LDL)

(,) ;

C11,

No.276 - 64909

(SER.CHOL)

HDL

No.

352 - 3(

) VLDL LDL

HDL

(HDL -

CHOL)

() (TGI)

GPO - Trinder,

N

o.337 - B

. VLDL LDL(VLDL+LDL)

HDL

(FBA)

24 48

0.1

, (/) , ,

, NAD

3 -

.(, . .Clin. Chem., 27, 1352 (1981),

).

가

(Dog Model)

6 - 12 kg

2

6 12

: (vehicle), i.g.; 1mg/kg, i.g.; 2mg/kg, i.g.; 4mg/kg, i.g.; 2mg/kg, p.o. (powder in capsule;

가 , 0.2% Tween 80 [(gavage tube)
])
 (HDL) 가
 2 2
 T - (student's T - test) (p .05)

(Vacutainer SST, Becton Dickinson and Co., Franklin Lakes)
 2000 rpm 20

(CII) (Wako Chemicals, Richmond, VA) , 96
 2 0.5 10 μg (가
 20 - 40 μl) 100 μl 가 37 15 가 100 μl 가 가
 500nm 가

HDL 352 - 3(St.Louis)
 150 μl 가 , HDL LDL VLDL
 0rpm 5 50 μl (Sigma 352 - 3) 15 μl 가 500
 200 μl

96 337
 1 24 μg (Sigma 339 - 11) (가 20
 - 40 μl) 가 가 100 μl 가 , 100 μl
 가 15 , 540nm
 (blank)

(FBA) 48 9 10 24
 (Cuisinart)
 1.4g 50% 3 / (2:0.6) , 37 45
 2000 x g 13 (mmole/day) 96 - (1,2)
 20 μl 96 - 가

$$[S] = [S]_0 e^{-kt}$$

$[S]_0$ $[S]$ 0 t ^{14}C , k

[J. Clin. Invest., 91, 1453 - 1458 (1993),]
 (Zeigler Bothers, Inc., Gardners) 0.3% 2%
 (100g/day)

EDTA - (Vacutainer; Becton Dickenson & Co.,
 Rutherford)
 (C.A. Allain et al., Clin. Chem., 20, 470 - 475 (1974),
 HDL LDL VLDL
 (Clin. Chem., 28, 1379 - 1388 (1982),)
 (Clin. Chem., Clin. Chem., 19, 476 - 482 (1973),)

, 10%
 O (0.3%)
 plaque) 가
 (Toshiba 3CCD)
 merican Innovision, Inc., San Diego)
 (true color image analyzer) (Videometric 150;A
 (threshold)
 (J. Biol. Chem. 226, 497 - 509 (1957),
 (2:1)

, 3 - mm , - 37
 가 (Grass Instrument Co., Quincy)
 가 II 가

(57)

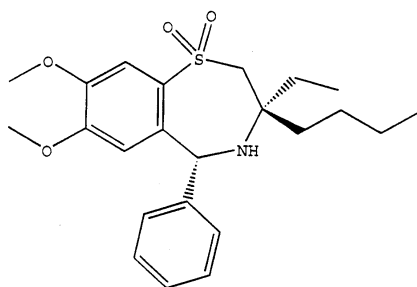
1.

1 (anti) 2 , 1 2

2.

1 , B - 2

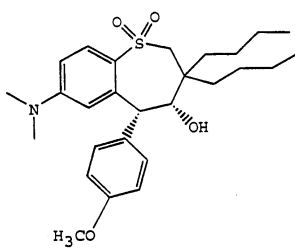
B - 2



3.

1 , B - 12

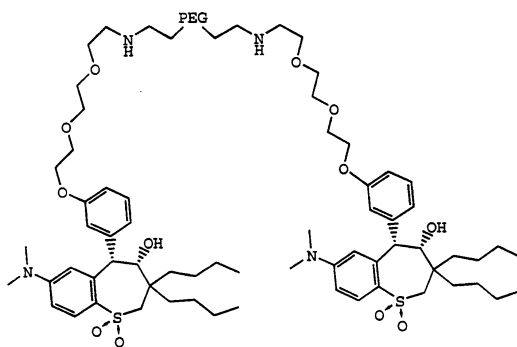
B - 12



4.

1 , B - 29

B - 29



, PEG

3000

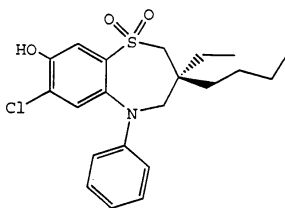
4000

5.

1 , .

B - 7

B - 7



6.

1 , .

가

7.

1 , .

가

8.

1 , .

가

9.

1 , .

10.

1

2

, 1

2

11.

1 2 , 1 2
,

12.

1 2 , 1 2
,