

(19)
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A61K 31/192

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(43)

10-2004-0068589
2004 07 31

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2004 06 16

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(87)

WO 2003/051826

(86) 2002 12 18

(87)

2003 06 26

(30) 0104333-0 2001 12 19

(SE)

(71) 151 85

(72) -431 83 , -

-431 83

-431 83

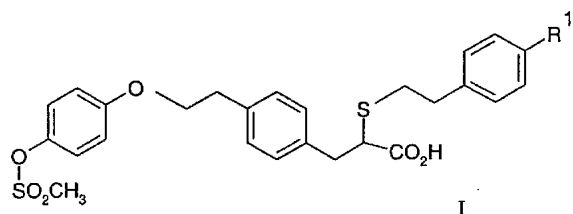
(74)

:

(54) P P A R -

3- -2-

I (, R¹ , ,), ; ; ;
가 () ; ; ;
;



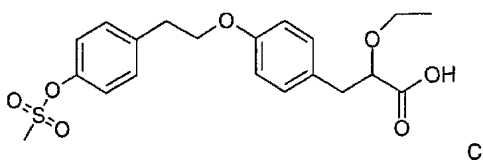
3-
(-2-)

(2 VLDL(), ,가 LDL 2 HDL(가)) ,

가 2 , 80%

, 가 , 가

PCT C 2- -3-[4-(2-{4- })] S-
W0 99/62872



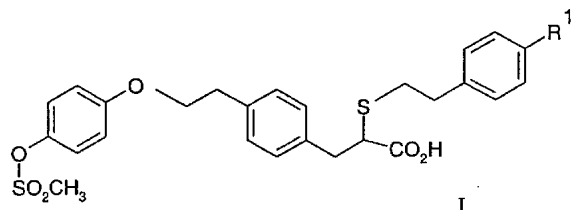
(peroxisome proliferator-activated receptor(PPAR), PPAR

T. M. Willson et al, J Med Chem 2000, Vol 43, 527)

AR 가 (Structure, 2001, Vol 9, 699, P. Cronet et al). PPAR /PP

PPAR

I ; ; 가 , ,



, R 1

(S R 가 , (+) (-))

가

()
 , Chira
 HPLC
 (, R)
 가 I

- a) Design of Prodrugs, H. Bundgaard (Elsevier, 1985) Methods in Enzymology. 42: 309-396, K. Widd er, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, Krogsgaard-Larsen H. Bundgaard , Chapter 5 'Desi gn and Application of Prodrugs', H. Bundgaard p.113-191(1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8: 1-38(1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77: 285(1988);
- e) N. Kakeya, et al., Chem Pharm Bull, 32: 692(1984).

a) e) 가 가 (가 가) (parent)
 가 I 가 가 가 가
 ; C₁₋₆ ; C₁₋₆ ; C₃₋₈
 , 5- -1,3- -2- ; C₁₋₆ ; 1,3- -2- , 1- 가 가 ((/
 가), I 가 가 ()
 - 가 가 가 가 가 가
 N-()-N- (), 가 (),
 가 3- 4-
 I EC₅₀ PPAR 가 , I PPAR 10 , EC₅₀ , PPAR

2-{{2-(4-) }-3-[4-(2-{4-[()]- })] ; (R)-
 (S)- ;
 2-{{2-(4-) }-3-[4-(2-{4-[()]- })] ; (R)
 (S)- ;
 2-{{2-(4-) }-3-[4-(2-{4-[()]- })] ; (R)

FDA Orange Book
 가 () 1, 2
 2
 FDA

HMG-CoA (3- -3- A) 가
 . HMG-CoA
 가
 가
 (E)-7-[4-(4-)-6- -2-[()-]- -5-](3R,5S)-3,5-
 -6- , [(E)-7-[4-(4-)-6- -2-[N- -N-()-]
 -5-](3R,5S)-3,5- -6-] 가
)-]- -5-](3R,5S)-3,5- (E)-7-[4-(4-)-6- -2-[-(
 EP-A-0521471, Bioorganic and Medicinal Chemistry(1997), 5(2), 437-444

HMG-CoA
 ()
 (IBAT)

IBAT 가 WO 93/16055, WO 94/18183, WO 94/18184,
 WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO
 99/32478, WO 99/35135, WO 98/40375, WO99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/4
 7568, WO 00/61568, WO 00/62810, WO01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727
 , WO 00/38728, WO 00/38729, WO01/68906, WO01/66533, WO 02/32428, WO 02/50051, EP 864582, EP 48
 9423, EP 549967, EP 573848, EP 624593, EP 624594, EP 624595 EP 624596

IBAT WO 00/01687, WO 96/08484 WO 97/3388
 2 IBAT
 1
 1,2- , 1,4- 1,5- IBAT 가
 1,2,5-

IBAT 가 (3R,5R)-3- -3- -1,1- -5- -2,3,4,5-
 -1,4- -8- -D- (EP 864 582) IBAT
 1,1- -3,3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-()] }
)-2,3,4,5- -1,5- ;
 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-()]-4- }
)-2,3,4,5- -1,5- ;
 1,1- -3,3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-(2-)] }
)-2,3,4,5- -1,5- ;
 1,1- -3- -3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-(2-)] }
)-2,3,4,5- -1,5- ;
 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }

)-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }
)-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(2-)] }
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }
)-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(5-)] }
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)] }
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{ -[N'-(2-)]-2- }
)-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(R)-(2- -1-)
] })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(R)-(2- -1-)]
 })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-{{N-[(R)- -(N'-(R)-1-[N'-(R)-(2- -1-)
]-2- })-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{ -[N'-()] })
 -2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-(N-{{ -[N'-()] })
)-2,3,4,5- -1,5- ;

1,1- -3- -3- -5- -7- -8-{{N-[(R)- -(N'-{2-[()] })
)] })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2- -1-)] }
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-{{N-[(R)- -(N'-{2-[()] })] })-4-
] })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-{{N-[(R)- -(N'-{2-[()] })] })
 -4-] })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[(R)-N'-(2- -1-)]
 })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-[N-{{(R)- -[N'-(2-)]-4- }
]-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N-((R)-1- -2- -)]-
 4- })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N-((S)-1- -2-(R)-)
]-4- })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1- -2-)]-4-
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-)]-4-
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-)] }
)-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-)] }
)-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1- -2-(R)-)
] })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-(2-)]-4- }
)-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-)]-4-
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((R)-1- -2-)]
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-[N-((S)-2- -1-)
] }] })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1- -2-)]
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-((S)-1-)]-4-
 })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-[N-((R/S)- -{N-[1-(R)-2-(S)-1- -1-(3,4-
) -2-] }-4-)]-2,3,4,5- -1,2,5-
 ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-
)]-4- })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- -[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-
)] })-2,3,4,5- -1,2,5- ;

가 , , 가 .

가 , , 가 , , 가 , ,

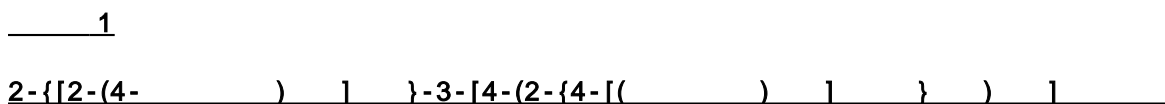
CETP() , WO 00/38725, 7 ,
22 ~ 10 , 17 ;

SCH 58235 US 5,767,115

MTP() , Science, 282, 751-54, 1998 ;

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s
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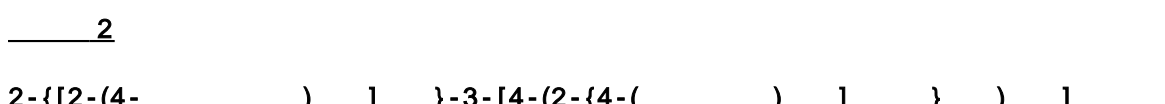
(i) 2-(4-)
 1-(2-)-4- (0.700 g, 4.00 mmol), (0.320 g, 4.20 mmol) (0.425
 g, 4.20 mmol) MeOH(8 ml) 150 900 가 .

(ii) 2-{{2-(4-) } }-3-[4-(2-{4-[()] })]
 MeOH(0.2 ml) (56.5 mg, 0.800 mmol)
 0.8 ml(0.400 mmol) 가 (0.800 ml) 2-
 - 3-[4-(2-{4-[()] })] (0.200 g, 0.484 mmol, 2
)) 가 16 , 35
 . 0.5 M LiOH (THF/ 7:1) 2 ml 가 , 20 . 12 M
 HCl(100 μℓ) , 1 가 (crude) Teflon™ ,
 HPLC(0.2 % TFA/MeCN,) 가 ,
 18 mg (7%).

¹ H NMR(400 MHz, CDCl₃): 2.75-2.95(m, 5H), 3.06(t, 2H), 3.10(s, 3H), 3.16(dd, 1H), 3.45(dd, 1H), 4.14(d, 2H), 6.87(d, 2H), 7.05(d, 2H), 7.11-7.27(m, 8H).

(iii) (-)-2-{{2-(4-) } }-3-[4-(2-{4-[()] })]
 2-{{2-(4-) } }-3-[4-(2-{4-[()] })] (-)-
 Chiralpak AD JF003(250 x 20 mm i.d.) ,
 / 100/0.1% (2 g) (20 mg/ml) ,
 , UV- = 99.2% (0.9 g) . 0.5 g/10
 0 ml []²⁰ D = -29° . 589 nm
 20 .

¹ H NMR(500 MHz, CD₃OD): 7.18-7.25(6H, m), 7.15(2H, d), 7.13(2H, d), 4.16(2H, t), 3.45(1H, t), 3.14(3H, s), 3.11(1H, m), 3.04(2H, t), 2.77-2.90(5H, m).



(i) 2- -3-[4-(2-)]
 2-(4-) (11 g, 81 mmol) 32 ml HCl , 0 . 20 ml
 (5.6 g, 81 mmol) 가 0 , (70 g
 , 808 mmol) CuI(1.6 g, 8 mmol) 가 (< 0).
 , 가 . EtOAc 3 , (MgSO₄) ,
 EtOAc 65:35

가 . HPLC(CH₃CN/5% CH₃CN - 0.1M NH₄OAc)
 9.7 g (49%).

¹H NMR(400 MHz, CDC1₃): 2.84(t, 3H), 3.15(dd, 1H), 3.35(dd, 1H), 3.75(s, 3H), 3.84(t, 3H), 4.43(t, 1H), 7.17(d, 4H).

(ii) 3-(4-{2-[4-()] })-2-

(2.4 g, 9 mmol) 20 ml 2- -3-[4-(2-)]
 (2.1 g, 8.5 mmol) 4-() (1.7 g, 8 mmol) 가 . 55 가
 , (1.8 g, 9 mmol) 가 . 55

2.28 g EtOAc 80:20
 (61%).

¹H NMR(400 MHz, CDC1₃): 3.05(t, 2H), 3.16(dd, 1H), 3.36(dd, 1H), 3.75(s, 3H), 4.12(t, 2H), 4.45(t, 1H), 5.01(s, 2H), 6.82(m, 2H), 6.90(m, 2H), 7.13-7.27(m, 4H), 7.29-7.47(m, 5H).

(iii) 2- -3-{4-[2-(4-)] })

3-(4-{2-[4-()] })-2- (1.0 g, 2.4 mmol) (0.9
 g, 14 mmol) 60 ml CH₂C1₂ (2.0 g, 14 mmol)
 가 가 . 2 가 가
 (0.4g, 2.87mmol) 가 , (,), (MgSO₄) , CH₂C1₂ 2
 % CH₃CN - 0.1M NH₄OAc HPLC 가 , CH₃CN/5
 0.55 g (52%).

¹H NMR(400 MHz, CDC1₃): 3.04(t, 2H), 3.16(dd, 1H), 3.35(dd, 1H), 3.75(s, 3H), 4.10(t, 2H), 4.40(t, 1H), 6.75(m, 4H), 7.12-7.29(m, 4H).

(iv) 2- -3-[4-(2-{4-[()] })]

2- -3-{4-[2-(4-)] } (334 mg, 1.0 mmol) (303
 mg, 3.0 mmol) 20 ml , -20 (114
 mg, 1.0 mmol) 가 . 가 2 ,
 (,), (Na₂SO₄) , 394 mg (96%).

¹H NMR(400 MHz, CDC1₃): 3.02-3.11(m, 5H), 3.15(dd, 1H), 3.35(dd, 1H), 3.74(s, 3H), 4.14(t, 2H), 4.44(t, 1H), 5.29(s, 2H), 6.88(d, 2H), 7.14-7.25(m, 6H).

(v) 2-({2-[4-()] })-3-[4-(2-{4-[()] })]

2-[4-()] (334 mg, 1.4 mmol), 2- -3-[4-(2-{4-[()] })]
)] (394 mg, 0.95 mmol) (189 mg, 1.4 mmol) 14 ml DMF ,

CH₃CN/5% CH₃CN - 0.1M NH₄OAc (,), (MgSO₄) ,
 477 mg (75%). HPLC 가 ,

¹H NMR(400 MHz, CDC1₃): 2.76-2.89(m, 4H), 2.95(dd, 1H), 3.09(m, 5H), 3.20(dd, 1H), 3.53(m, 1H), 3.70(s, 3H), 4.15(t, 2H), 5.06(s, 2H), 6.91(m, 4H), 7.07-7.24(m, 8H), 7.31-7.48(m, 5H).

(vi) 2-[2-(4-)] }-3-[4-(2-{4-[()] })]

2-([2-(4-())])-3-[4-(2-{4-[()] })] (47
 7 mg, 0.8 mmol) 15 ml (239 mg, 3.8 mol)
 (545 mg, 3.8 mmol) 가 18 가
 2 (MgSO₄) 2
 74 mg (67%).

¹H NMR(400 MHz, CDCl₃): 2.70-2.85(m, 4H), 2.91(dd, 1H), 3.05(t, 2H), 3.10(s, 3H), 3.17(dd, 1H), 3.49(m, 1H), 3.68(s, 3H), 4.13(t, 2H), 6.72(d, 2H), 6.87(d, 2H), 6.99(d, 2H), 7.10-7.22(m, 6H)

(vii) 2-{[2-(4-())] }-3-[4-(2-{4-[()] })]

2-{[2-(4-())] }-3-[4-(2-{4-[()] })] (10
 5 mg, 0.2 mmol) THF 7:1 6.5 ml (9.4 ml)
 g, 0.4 mmol) 가 24 가 THF
 , 1M EtOAc(x3) (,), (MgSO₄)
 4), HPLC(: CH₃CN/5% CH₃CN - 0.1M NH₄OAc)
 74 mg (97%).

¹H NMR(400 MHz, CDCl₃): 2.68-2.95(m, 5H), 3.05(t, 2H), 3.10(s, 3H), 3.17(dd, 1H), 3.47(m, 1H), 4.12(t, 2H), 6.70(d, 2H), 6.86(d, 2H), 6.97(d, 2H), 7.12-7.21(m, 6H).

¹³C NMR(100 MHz, CDCl₃): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) (-)-2-{[4-()] }-3-[4-(2-{4-[()] })]

2-{[2-(4-())] }-3-[4-(2-{4-[()] })]
 Chiralpak AD JDB01 + AS003(
 336 x 100 mm i.d.) / 100/0.01% (9 g)
 , UV- > 99% (4.1 g) 0.6
 4 g/100 ml []_D²⁰ = -33° 589 nm
 m 20

¹H NMR(500 MHz, CD₃OD): 7.17-7.22(6H, m), 6.99(2H, d), 6.94(2H, d), 6.69(2H, d), 4.17(2H, t), 3.46(1H, t), 3.16(3H, s), 3.13(1H, dd), 3.05(2H, t), 2.69-2.88(SH, m).

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2-{[2-(4-())] }-3-[4-(2-{4-[()] })]

(i) [2-(4-())]

- DMF(60 ml) (2.1 g, 28 mmol) (9.1 g, 28 mmol) 가
 . 1-(2-())-4- (4 g, 25 mmol) 가
 , (NaSO₄) , 5 g (99%).
 EtOAc

¹H NMR(400 MHz, CDCl₃): 2.33(s, 3H), 2.83(t, 2H), 3.09(t, 2H), 6.98(t, 2H), 7.17(m, 2H).

³C NMR(100 MHz, CDCl₃): 30.8, 30.9, 35.3, 115.4, 115.6, 130.2, 130.3, 135.9, 160.7, 195.8.

(ii) 2-[2-(4-())] }-3-[4-(2-{4-[()] })]

[2-(4-())] (96 mg, 0.48 mmol) 1 ml
 (33.9 mg, 0.48 mmol) 가 30 , 2 ml CH₃CN 2-
 -3-[4-(2-{4-[()] })] (200 mg, 0.48 mmol) 가

HPLC(CH₃CN/5% CH₃CN - 0.1M NH₄OAc) (), (MgSO₄) ,
 82 mg (32%).

¹ H NMR(500 MHz, CDCl₃): 2.82-3.00(m, 5H), 3.10(t, 2H), 3.14(s, 3H), 3.22(dd, 1H), 3.53(m, 1H), 3.72(s, 3H), 4.18(t, 2H), 6.92(d, 2H), 7.0(t, 2H), 7.15(m, 4H), 7.23(m, 4H).

(iii) 2-[2-(4-)] }-3-[4-(2-{4-[()]- })]

2-{{2-(4-) }-3-[4-(2-{4-[()]- })] } (77
 mg, 0.14 mmol) THF 4:1 2.5 ml , (6.9 m
 g, 0.29 mmol) 가 2 , 가 . THF 1
 M HCl , EtOAc 3 , (,), (MgSO₄) .
 HPLC(: CH₃CN/5% CH₃CN - 0.1M NH₄OAc)
 24 mg (30%).

¹ H NMR(500 MHz, CDCl₃): 2.82-3.00(m, 5H), 3.10(t, 2H), 3.14(s, 3H), 3.21(dd, 1H), 3.52(m, 1H), 4.18(t, 2H), 6.90(d, 2H), 6.99(t, 2H), 7.13(m, 2H), 7.16-7.26(m, 6H).

DMSO 16 mM (stock)

DMSO 가

Packard() Boehringer , Vent New Eng
 land Biolabs

U2-OS() ATCC() 가 , 가 6
 25 mM , 2 mM 4 mM L- -L- , 10%
 (DMEM) 5% CO₂ 가
 BS) Gibco() , 96- Wallach (P)

A DNA Ausubel(7) pGL5UAS GAL4 DN
 5'-CGACGGAGTACTGTCTCCGAGCT-3' 5 가 pGL3- (Promega) SacI/XhoI
 . UAS . SacI/XhoI

T P04386 pSG5(Stratagene) GAL4 DNA (EcoRI/NheI , NheI/KpnI
 1-145) (5-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-
 3') PPAR , PPAR KpnI/Bam
 HI PCR , GAL4 DNA

	PPAR	1
pSGGALhPPa	PPAR	S74349, nt 625-1530

pSGGALmPPa	PPAR	X57638, nt 668-1573
pSGGALhPPg	PPAR	U63415, nt 613-1518
pSGGALmPPg	PPAR	U09138, nt 652-1577

1

6, 8 가 . DNA 가 , 가 PBS
 , 270xg 2 , 50 µg DNA ,
 18 x 10⁶ /ml . DNA 가 , 5
 0.5 ml Biorad's Gene Pulser™ 230 V, 960 µF . 2.5 µg , 25 µg 22.5 µg DNA
 0.5 ml 가 , 2.5 µg , 25 µg 22.5 µg DNA(pBI
 uescript, Stratagene)가 .
 가 DMEM 320,000 /ml , 25,00
 0 / 96- , 가 3
 7 3~4 . PPAR , - (FCS)
 , FCS , FCS
 . 500 ml - FCS 10 g 25 g Bio-Rad , FCS
 200-400 가 , , FCS
 4~6 , FCS ,

DMSO

75 µl , 50 µl 가 . , 100 µl
 가 , 24 가 . 20 ,
 1420 Multiwell (Victor, Wallach) 가 .

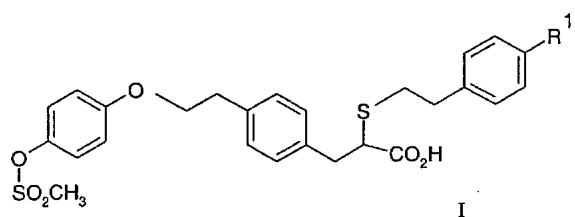
TZD (ETYA) PPAR PPAR . 5,8,11,14-

EC₅₀ , - 2 3 % (.
) , . EC₅₀
 , 50% .
 I PPAR 5 µmol/l EC₅₀ 가 , 1.0 µmol/l EC₅₀
 가 , , EC₅₀ (PPAR) : EC₅₀ (PPAR) 가 25:1 .
 , DMPK() 가 , ,
 가 .

(57)

1.

가 , ,



, R¹ , .

2.

2-{{2-(4-) }-3-[4-(2-{4-[()] })] } ;

2-{{2-(4-) }-3-[4-(2-{4-[()] })] } ;

2-{{2-(4-) }-3-[4-(2-{4-[()] })] } ;

가 , , .

3.

(-)-2-{{2-(4-) }-3-[4-(2-{4-[()]- })] } .

4.

(-)-2-{{2-(4-) }-3-[4-(2-{4-[()]- })] } .

5.

2-{{2-(4-) }-3-[4-(2-{4-[()]- })] } (R)-
(S)- .

6.

가 , / 1 5

7.

가 , / 1 5

8.

1 5 () ,

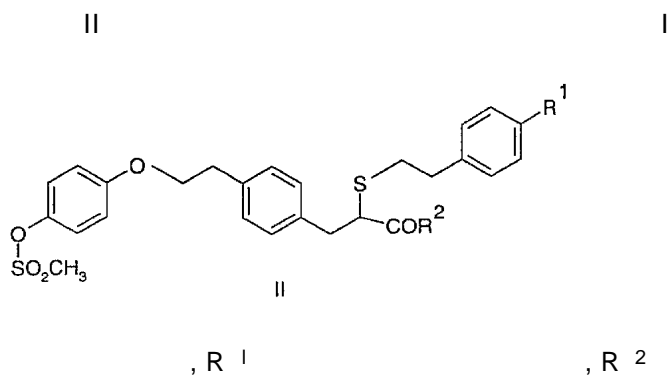
9.

() 1 5

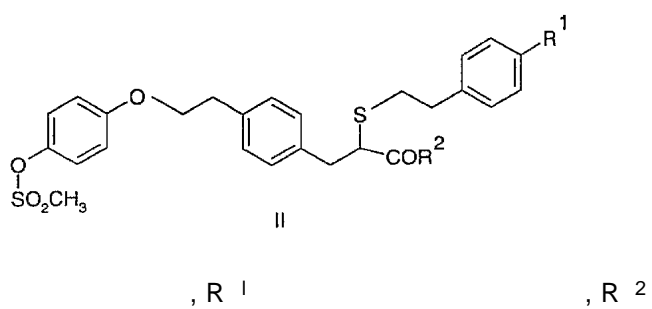
10.

1 5 2 | .

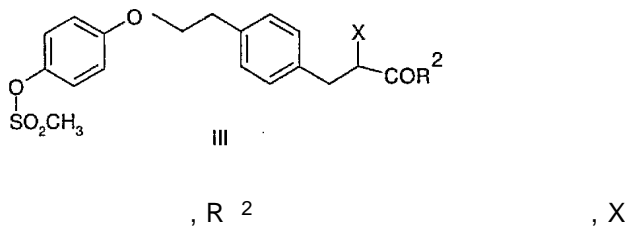
11.



12.



13.



14.

, 1 , 5

15.

PPAR 1 5

16.

- 1 5

17.

HMG-CoA 1 5

18.

가 , , 1 5

19.

가 1 5

20.

IBAT

1

5

21.

20

, IBAT

가

- 1,1- -3,3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-()] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-()]-4- }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-(2-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{(R)-1'- -1'-[N'-(2-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(2-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)]-4- }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(5-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(2-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{ -[N'-(2-)]-2- }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{(R)- -[N'-(R)-(2- -1-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-(N-{{(R)- -[N'-(R)-(2- -1-)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3,3- -5- -7- -8-{{N-[(R)- -(N'-(R)-1-[N'-(R)-(2- -1-)] }
]-2- } -2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{ -[N'-()] }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-(N-{{ -[N'-(() () -)] }
)-2,3,4,5- -1,5- ;
- 1,1- -3- -3- -5- -7- -8-{{N-[(R)- -(N'-{2-[() ()] }
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)-(-[N'-(2- -1-)] })
)-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-{N-[(R)- (N'-(2-[() ()] })-4-
] }-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-{N-[(R)- (N'-(2-[() ()] }))
 -4-] }-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- [(R)-N'-(2- -1-)])
 })-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-[N-((R)- (-[N'-(2-)]-4-)
]-2,3,4,5- -1,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((R)-1- -2- -)]-
 4-) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1- -2-(R)-))
]-4-) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1- -2-)]-4-
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1-)]-4-
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1-)] })
)-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1- -2-(R)-))
] })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-(2-)]-4-)
)-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1-)]-4-
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((R)-1- -2-)])
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1-[N-((S)-2- -1-))
] })-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1- -2-)])
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-(N-((R)- (-[N-((S)-1-)]-4-
) }-2,3,4,5- -1,2,5- ;

1,1- -3,3- -5- -7- -8-[N-((R/S)- (-{N-[1-(R)-2-(S)-1- -1-(3,4-
) -2-] }-4-)]-2,3,4,5- -1,2,5- ;

