

reaction solution was stirred at 25°C for 30 minutes before concentration to give the titled compound (336 mg) having the following physical properties.

¹H-NMR (CD₃OD): δ 1.01 (d, 6H), 1.34 (d, 3H), 1.50-1.58 (m, 3H), 1.67-1.88 (m, 2H), 1.92-2.02 (m, 2H), 3.03 (dt, 1H), 3.27-3.38 (m, 2H).

[0254] Example 25: 2-{4-[3-(4-fluorophenoxy)-5-{{(4-hydroxy-4-isobutyl-2-methyl-1-piperidiny)carbonyl}amino}phenoxy]phenyl}-2-methylpropanoic acid

The titled compound (60 mg) having the following physical properties was obtained by carrying out the processes with the same purposes as Example 8 → Example 9 using the compound prepared in Example 24 (48 mg) and the compound prepared in Example 7 (100 mg).

TLC: R_f 0.33 (chloroform:methanol = 19:1);

¹H-NMR (CDCl₃): δ 0.97 (dd, 6H), 1.36 (t, 2H), 1.38 (d, 3H), 1.47-1.75 (m, 10H), 1.77-1.89 (m, 1H), 3.36 (dt, 1H), 3.71-3.79 (m, 1H), 4.26-4.35 (m, 1H), 6.29 (t, 1H), 6.38 (s, 1H), 6.69 (t, 1H), 6.81 (t, 1H), 6.96-7.02 (m, 6H), 7.35 (d, 2H).

[0255] Example 26: Ethyl 2-(benzhydryli+deneamino)-2-[4-{3-(4-fluorophenoxy)-5-nitro-phenoxy}phenyl]acetate

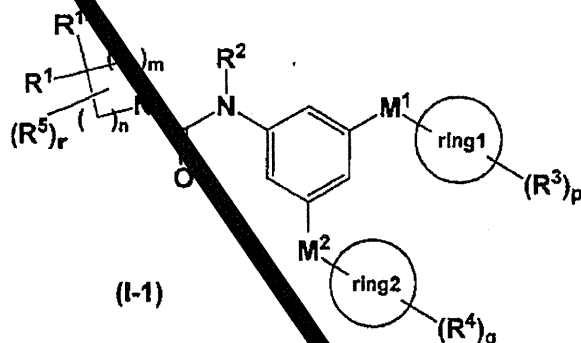
To the compound prepared in Example 11 (1.0 g) were added ethyl[(diphenylmethylene)amino]acetate (652 mg) and potassium phosphate (1.41 g) and suspended in toluene (7.4 mL). The reaction system was degassed, purged with argon, added with Pd(t-Bu₃P)₂ (23 mg), degassed again and purged with argon. The reaction solution was stirred at 100°C for 17 hours, cooled to 0°C, adjusted to pH 7 by addition of water and 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was sequentially washed with water and a saturated sodium chloride solution and dried over anhydrous magnesium sulphate. The resulting residue obtained after concentration was purified by silica gel chromatography (hexane:ethyl acetate = 100:0 → 9:1) to give the titled compound (456 mg) having the following physical properties.

TLC: R_f 0.36 (hexane:ethyl acetate = 3:1).

[0256] Example 27: Ethyl amino{4-[3-(4-fluorophenoxy)-5-

CLAIMS

A compound represented by the formula (I-1):
 [011]



wherein R^1 represents (1) a C1-8 alkyl group which may be substituted with 1 to 5 R^{21} group(s), (2) a C2-8 alkenyl group which may be substituted with 1 to 5 R^{21} group(s), (3) a C2-8 alkynyl group which may be substituted with 1 to 5 R^{21} group(s), (4) a C3-7 carbocycle which may be substituted with 1 to 5 substituent(s) selected from the group consisting of a C1-4 alkyl group, a C1-4 haloalkyl group, a C1-4 alkoxy group and a halogen atom, or (5) $-\text{CONR}^{31}\text{R}^{32}$;

R^{21} represents (1) a halogen atom, (2) $-\text{OR}^{22}$ (in the group, R^{22} represents (1) a hydrogen atom, (2) a C1-4 alkyl group or (3) a C1-4 haloalkyl group), (3) $-\text{NR}^{23}\text{R}^{24}$ (in the group, R^{23} and R^{24} each independently represent (1) a hydrogen atom or (2) a C1-4 alkyl group) or (4) an oxo group;

R^{31} and R^{32} each independently represent (1) a hydrogen atom or (2) a C1-4 alkyl group;

R^2 represents (1) a hydrogen atom, (2) a C1-4 alkyl group or (3) a C1-4 haloalkyl group;

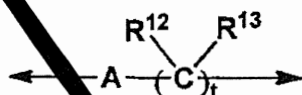
R^3 and R^4 each independently represent (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a hydroxy group, (6) $-\text{L}-\text{CONR}^6\text{R}^7$, (7) $-\text{L}-\text{SO}_2\text{R}^8$ or (8) $-\text{L}-\text{COOR}^9$;

R^5 represents (1) a halogen atom, (2) a C1-4 alkyl group or (3) a C1-4 haloalkyl group;

L represents (1) a bond, (2) a group represented by the

formula:

[C 2]



wherein A represents (1) a bond or (2) an oxygen atom; R^{12} and R^{13} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) a hydroxy group or (4) NH_2 or (5) R^{12} and R^{13} together with the carbon atom to which they are attached may form a C3-7 carbocycle; and the arrow on the right hand side binds to $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^8$ or $-\text{COOR}^9$, (3) a C2-4 alkenylene group, (4) a $-\text{O}-\text{C}2-4$ alkenylene group, (5) an oxygen atom or (6) a nitrogen atom which may be substituted with a C1-4 alkyl group;

R^6 and R^7 each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a hydroxy group, (5) $-\text{CONR}^{15}\text{R}^{16}$, (6) $-\text{SO}_2\text{NR}^{15}\text{R}^{16}$, (7) $-\text{COR}^{17}$ or (8) $-\text{SO}_2\text{R}^{17}$, or R^6 and R^7 together with the nitrogen atom to which they are attached may form a 4- to 7-membered nitrogen-containing saturated heterocycle that may be substituted with a hydroxy group;

R^8 represents (1) a C1-4 alkyl group, (2) a C1-4 haloalkyl group or (3) $\text{NR}^{10}\text{R}^{11}$;

R^9 represents (1) a hydrogen atom or (2) a C1-8 alkyl group;

R^{10} and R^{11} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) $-\text{CONR}^{15}\text{R}^{16}$, (4) $-\text{SO}_2\text{NR}^{15}\text{R}^{16}$, (5) $-\text{COR}^{17}$ or (6) $-\text{SO}_2\text{R}^{17}$;

the ring 1 and the ring 2 each independently represent a 5- to 7-membered cyclic group;

R^{14} represents (1) a hydrogen atom or (2) a hydroxy group;

R^{15} and R^{16} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group or (3) a 5- to 7-membered cyclic group;

R^{17} represents (1) a C1-4 alkyl group or (2) a 5- to 7-membered cyclic group;

M¹ and M² each independently represent (1) a bond, (2) -C(O)-, (3) -O-, (4) -S-, (5) -C(O)O-, (6) -CH₂O- or (7) -C(O)NH-;

n represents an integer of 1 to 2;

m represents an integer of 1 to 2;

p represents an integer of 0 to 5;

q represents an integer of 0 to 5;

r represents an integer of 0 to 4;

t represents an integer of 1 to 4;

when p is 2 or more, a plurality of R³ groups may be the same or different;

when q is 2 or more, a plurality of R⁴ groups may be the same or different;

when r is 2 or more, a plurality of R⁵ groups may be the same or different; and

when t is 2 or more, a plurality of R¹² and R¹³ groups may be respectively the same or different;

a salt thereof, a solvate thereof, an N-oxide thereof or a prodrug thereof.

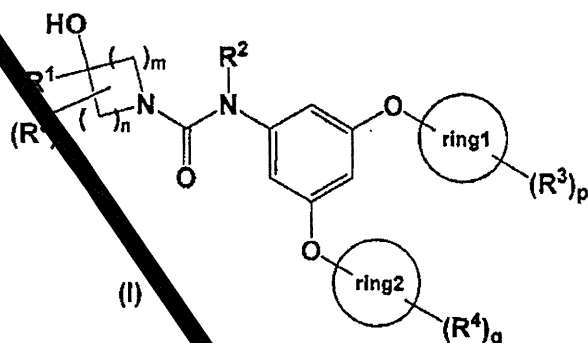
2. The compound according to claim 1, wherein R¹⁴ is a hydroxy group.

3. The compound according to claim 1 or 2, wherein M¹ and M² each independently are (1) -C(O)-, (2) -O-, (3) -S-, (4) -C(O)O- or (5) -CH₂O-.

4. The compound according to claim 3, wherein M¹ and M² are -O-.

5. The compound according to claim 1, which is represented by the formula (I):

[C 3]



wherein all the symbols have the same meanings as above.

6. The compound according to claim 5, wherein R^1 is (1) a C1-8 alkyl group which may be substituted with 1 to 5 R^{21} group(s) or (2) a C3-7 carbocycle which may be substituted with 1 to 5 substituent(s) selected from the group consisting of a C1-4 alkyl group, a C1-4 alkoxy group, a halogen atom and a trifluoromethyl group.

7. The compound according to claim 5 or 6, wherein R^2 is a hydrogen atom.

8. The compound according to any of claims 5 to 7, wherein the ring 1 and the ring 2 each independently are (1) a benzene, (2) cyclohexane or (3) pyridine ring.

9. The compound according to any of claims 1 to 8, which is (1) 4-(2-ethylbutyl)-N-{3-[4-(ethylcarbamoyl)phenoxy]-5-(4-fluorophenoxy)phenyl}-4-hydroxy-1-piperidine carboxamide, (2) 4-[3-(4-fluorophenoxy)-5-({[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]carbonyl}amino)phenoxy]benzoic acid, (3) 4-(2-ethylbutyl)-N-[3-(4-fluorophenoxy)-5-{4-[(4-hydroxy-1-piperidinyl)carbonyl]phenoxy}phenyl]-4-hydroxy-1-piperidine carboxamide, (4) 2-{4-[3-(4-fluorophenoxy)-5-({[4-hydroxy-4-isobutyl-1-piperidinyl]carbonyl}amino)phenoxy]phenyl}-2-methylpropanoic acid, (5) 1-{4-[3-(4-fluorophenoxy)-5-({[4-hydroxy-4-(3-pentanyl)-1-piperidinyl]carbonyl}amino)phenoxy]phenyl}cyclopropanecarboxy

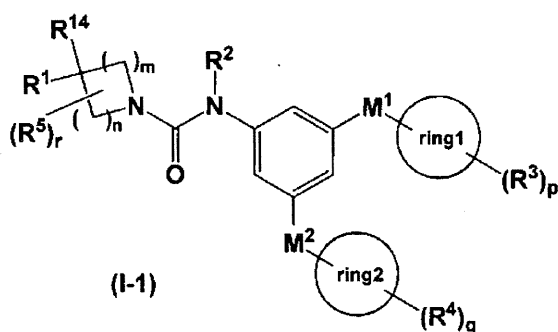
ic acid, (6) 2-{4-[3-(4-fluorophenoxy)-5-{{(3-hydroxy-3-isobutyl-1-azetidiny)carbonyl}amino}phenoxy]phenyl}-2-methylpropanoic acid, (7) 4-[3-{{[4-(2-ethylbutyl)-4-hydroxy-1-piperidiny]carbonyl}amino}-5-(4-fluorophenoxy)phenoxy]benzoic acid, (8) 2-{4-[3-{{[4-(2-ethylbutyl)-4-hydroxy-1-piperidiny]carbonyl}amino}-5-(4-fluorophenoxy)phenoxy]phenyl}-2-methylpropanoic acid or (9) 2-{4-{{[3-(4-fluorophenoxy)-5-{{[4-hydroxy-4-isobutyl-1-piperidiny]carbonyl}amino}benzoyl]oxy}phenyl}-2-methylpropanoic acid.

10. A compound represented by the formula (I-1) according to claim 1, the salt thereof, the solvate thereof, the N-oxide thereof or the prodrug thereof in use for prophylaxis and/or therapy of a S1P₂-mediated disease.

11. Use of the compound represented by the formula (I-1) according to claim 1, the salt thereof, the solvate thereof, the N-oxide thereof or the prodrug thereof for producing a prophylactic and/or therapeutic agent for a S1P₂-mediated disease.

CLAIMS

1. A compound represented by the formula (I-1):



wherein R^1 represents (1) a C1-8 alkyl group which may be substituted with 1 to 5 R^{21} groups, (2) a C2-8 alkenyl group which may be substituted with 1 to 5 R^{21} groups, (3) a C2-8 alkynyl group which may be substituted with 1 to 5 R^{21} groups, (4) a C3-7 carbocycle which may be substituted with 1 to 5 substituents selected from the group consisting of a C1-4 alkyl group, a C1-4 haloalkyl group, a C1-4 alkoxy group and a halogen atom, or (5) $-\text{CONR}^{31}\text{R}^{32}$;

R^{21} represents (1) a halogen atom, (2) $-\text{OR}^{22}$ (in the group, R^{22} represents (1) a hydrogen atom, (2) a C1-4 alkyl group or (3) a C1-4 haloalkyl group), (3) $-\text{NR}^{23}\text{R}^{24}$ (in the group, R^{23} and R^{24} each independently represent (1) a hydrogen atom or (2) a C1-4 alkyl group) or (4) an oxo group;

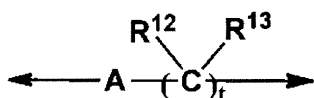
R^{31} and R^{32} each independently represent (1) a hydrogen atom or (2) a C1-4 alkyl group;

R^2 represents a hydrogen atom;

R^3 and R^4 each independently represent (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a hydroxy group, (6) $-L-CONR^6R^7$, (7) $-L-SO_2R^8$ or (8) $-L-COOR^9$;

R^5 represents (1) a halogen atom, (2) a C1-4 alkyl group or (3) a C1-4 haloalkyl group;

L represents (1) a bond, (2) a group represented by the formula:



wherein A represents (1) a bond or (2) an oxygen atom; R^{12} and R^{13} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) a hydroxy group or (4) NH_2 or (5) R^{12} and R^{13} together with the carbon atom to which they are attached may form a C3-7 carbocycle; and the arrow on the right hand side binds to $-CONR^6R^7$, $-SO_2R^8$ or $-COOR^9$, (3) a C2-4 alkenylene group, (4) a $-O-C2-4$ alkenylene group, (5) an oxygen atom or (6) a nitrogen atom which may be substituted with a C1-4 alkyl group;

R^6 and R^7 each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a hydroxy group, (5) $-CONR^{15}R^{16}$, (6) $-SO_2NR^{15}R^{16}$, (7) $-COR^{17}$ or (8) $-SO_2R^{17}$, or R^6 and R^7 together with the nitrogen atom to which they are attached may form a 4- to 7-membered nitrogen-containing saturated heterocycle

that may be substituted with a hydroxy group;

R^8 represents (1) a C1-4 alkyl group, (2) a C1-4 haloalkyl group or (3) $NR^{10}R^{11}$;

R^9 represents (1) a hydrogen atom or (2) a C1-8 alkyl group;

R^{10} and R^{11} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group, (3) $-CONR^{15}R^{16}$, (4) $-SO_2NR^{15}R^{16}$, (5) $-COR^{17}$ or (6) $-SO_2R^{17}$;

the ring 1 and the ring 2 each independently represent benzene or pyridine ring;

R^{14} represents a hydroxy group;

R^{15} and R^{16} each independently represent (1) a hydrogen atom, (2) a C1-4 alkyl group or (3) a 5- to 7-membered cyclic group;

R^{17} represents (1) a C1-4 alkyl group or (2) a 5- to 7-membered cyclic group;

M^1 and M^2 each independently represent (2) $-C(O)-$, (3) $-O-$, or (5) $-C(O)O-$;

n represents an integer of 1 to 2;

m represents an integer of 1 to 2;

p represents an integer of 0 to 5;

q represents an integer of 0 to 5;

r represents an integer of 0;

t represents an integer of 1 to 4;

when p is 2 or more, a plurality of R^3 groups may be the same or different;

when q is 2 or more, a plurality of R^4 groups may be the same or different;

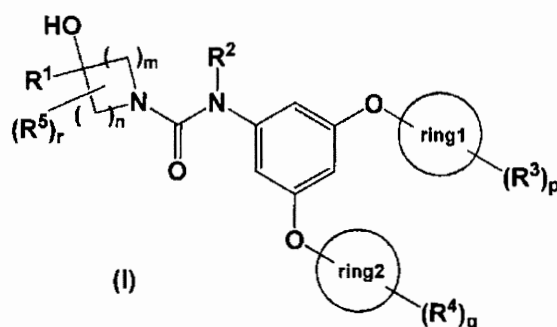
and

when t is 2 or more, a plurality of R^{12} and R^{13} groups may be respectively the same or different;

a salt thereof.

2. The compound according to claim 1, wherein M^1 and M^2 are -O-.

3. The compound according to claim 1, which is represented by the general formula (I):



wherein all the symbols have the same meanings defined in claim 1.

4. The compound according to claim 3, wherein R^1 is (1) a C1-8 alkyl group which may be substituted with 1 to 5 R^{21} groups or (2) a C3-7 carbocycle which may be substituted with 1 to 5 substituents selected from the group consisting of a C1-4 alkyl group, a C1-4 alkoxy group, a halogen atom and a trifluoromethyl group.

5. The compound according to any of claims 1 to 4, which is
(1)

4-(2-ethylbutyl)-N-{3-[4-(ethylcarbamoyl)phenoxy]-5-(4-fluorophenoxy)phenyl}-4-hydroxy-1-piperidine carboxamide, (2)

4-[3-(4-fluorophenoxy)-5-({[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]carbonyl}amino)phenoxy]benzoic acid, (3)

4-(2-ethylbutyl)-N-[3-(4-fluorophenoxy)-5-{4-[(4-hydroxy-1-piperidinyl)carbonyl]phenoxy}phenyl]-4-hydroxy-1-piperidine carboxamide, (4)

2-{4-[3-(4-fluorophenoxy)-5-{[(4-hydroxy-4-isobutyl-1-piperidinyl)carbonyl]amino}phenoxy]phenyl}-2-methylpropanoic acid, (5)

1-{4-[3-(4-fluorophenoxy)-5-({[4-hydroxy-4-(3-pentanyl)-1-piperidinyl]carbonyl}amino)phenoxy]phenyl}cyclopropanecarboxylic acid, (6)

2-{4-[3-(4-fluorophenoxy)-5-{[(3-hydroxy-3-isobutyl-1-azetidinyl)carbonyl]amino}phenoxy]phenyl}-2-methylpropanoic acid, (7)

4-[3-({[4-(2-ethylbutyl)-4-hydroxy-1-piperidinyl]carbonyl}amino)-5-(4-fluorophenoxy)phenoxy]benzoic acid, (8)

2-{4-[3-({[4-(2-ethylbutyl)-4-hydroxy-1-piperidinyl]carbonyl}amino)-5-(4-fluorophenoxy)phenoxy]phenyl}-2-methylpropanoic acid or (9)

2-(4-{[3-(4-fluorophenoxy)-5-{[(4-hydroxy-4-isobutyl-1-piperidinyl)carbonyl]amino}benzoyl]oxy}phenyl)-2-methylpropanoic acid.

6. A compound represented by the general formula (I-1) according to claim 1, the salt thereof for use for prophylaxis and/or therapy a S1P₂-mediated disease.

7. 2-{4-[3-(4-fluorophenoxy)-5-{[(4-hydroxy-4-isobutyl-1-piperidinyl)carbonyl]amino}phenoxy]phenyl}-2-methylpropanoic acid.