

DESCRIPTION

FLUORINE-CONTAINING 1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES

5

Technical Field

This invention relates to novel fluorine-containing 1,4-disubstituted piperidine derivatives, processes for preparing them, pharmaceuticals containing them
10 and their use as medicines, especially in the treatment or prophylaxis of various diseases of the respiratory, urinary and digestive systems.

Background Art

15 Antagonism to muscarinic receptors are known to cause bronchodilation, gastrointestinal hypokinesia, gastric hyposecretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia and the like ["Basic and Clinical Pharmacology",
20 4th ed., APPLETON & LANGE, pp. 83-92 (1989); Drug News & Perspective, 5(6), pp. 345-352 (1992)].

It has been made clear that there are at least three subtypes of muscarinic receptors; the M_1 receptors being present mainly in the brain, the M_2 receptors
25 mainly in the heart, and the M_3 receptors, on smooth muscles and glandular tissues. Whereas, all of the large number of compounds heretofore known to exhibit antagonism to muscarinic receptors non-selectively antagonize the three subtypes of muscarinic receptors.
30 Consequently, attempts to use these compounds as therapeutic or prophylactic agents for diseases of the respiratory system have caused undesirable side effects such as dry mouth, nausea and mydriasis. Still in addition, particularly serious side effects associated with the
35 central nervous system, such as dementia, attributable to the M_1 receptors and those associated with the heart,

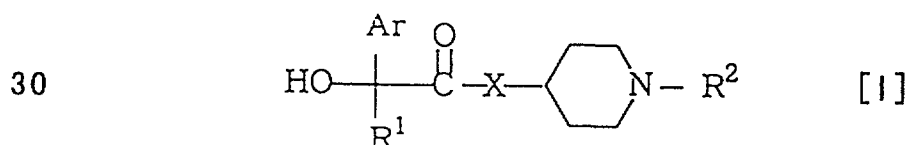
such as tachycardia mediated by the M_2 receptors pose problems and their solution is strongly demanded.

We have disclosed, as a drug meeting the demand, 1,4-disubstituted piperidine derivatives (see: PCT W096/33973). However, creation of even more excellent drug has been in demand.

An object of the present invention is to create even a better drug than said known compounds, whereby to provide pharmaceuticals exhibiting highly selective antagonism to M_3 receptors and minimizing adverse side effect and which, therefore, provide safe and effective pharmaceuticals for treatment or prophylaxis of diseases associated with muscarine M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness.

Disclosure of the Invention

According to the present invention, there are provided novel fluorine-containing 1,4-disubstituted piperidine derivatives of the general formula [I]



and pharmaceutically acceptable salts thereof, wherein:

Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3

hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino);

5 R^1 represents C_3-C_8 cycloalkyl whose any 1-4 hydrogen atoms may be substituted with fluorine atoms(s);

R^2 represents C_5-C_{15} saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen
10 atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, aryl-
15 alkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino); and

 X stands for O or NH,

20 provided that at least either one of R^1 and R^2 contains one or more fluorine atoms.

 The compounds of the above formula [I] which are provided by the present invention have potent and selective antagonistic activity for muscarinic M_3 recep-
25 tors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe. Hence, they are very useful in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary dis-
30 eases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and fre-
35 quency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and

chronic cystitis: and motion sickness.

Hereinafter the meaning of the technical terms used in the present specification are elucidated and the invention is explained in further details.

5 "An aryl group (any 1 to 3 hydrogen atoms on the ring in said aryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)" signifies a substituted or unsubstituted C_6-C_{11} aryl group, examples of which including
10 unsubstituted phenyl group, naphthyl group or those containing the above-named substituent(s).

As examples of "a heteroaryl group having 1-2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the
15 ring of said heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)", unsubstituted 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 2-quinolinyl,
20 2-benzothienyl and 2-indolyl group; and those which are substituted with the above-named substituents can be named.

Also examples of " C_3-C_6 cycloalkyl whose 1-4 hydrogen atoms may be substituted with fluorine atom(s)"
30 include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-fluorocyclopropyl, 1-fluorocyclobutyl, 1-fluorocyclopentyl, 1-fluorocyclohexyl, 2-fluorocyclopropyl, 2-fluorocyclobutyl, 2-fluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclobutyl, 3-fluorocyclopentyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclopropyl, 2,2-difluorocyclobutyl, 2,2-

difluorocyclopentyl, 2,2-difluorocyclohexyl, 3,3-
 difluorocyclobutyl, 3,3-difluorocyclopentyl, 3,3-di-
 fluorocyclohexyl, 4,4-difluorocyclohexyl, 3,3,4,4-tetra-
 fluorocyclopentyl, 3,3,4,4-tetrafluorocyclohexyl, 2,3-
 5 difluorocyclobutyl, 2,3-difluorocyclopentyl, 3,4-di-
 fluorocyclopentyl, 2,3-difluorocyclohexyl, 3,4-difluoro-
 cyclohexyl, 2,2,3,3-tetrafluorocyclobutyl and 2,2,3,3-
 tetrafluorocyclopentyl groups.

Examples of "C₅-C₁₅ saturated or unsaturated
 10 aliphatic hydrocarbon groups whose any 1 to 6 hydrogen
 atoms may be substituted with fluorine atoms" include
 C₅-C₁₅ straight chain or branched alkyl, alkenyl,
 alkynyl, cycloalkylidenealkyl; cycloalkylalkyl, cyclo-
 alkylalkenyl or cycloalkylalkynyl in which optionally
 15 hydrogen atom(s) on the cycloalkyl ring may be substi-
 tuted with lower alkyl; and cycloalkenylalkyl or cyclo-
 alkenylalkenyl in which optionally hydrogen atom(s) on
 the cycloalkenyl ring may be substituted with lower
 alkyl; and those whose any 1 to 6 hydrogen atom(s) are
 20 substituted with fluorine atom(s).

Specific examples of such aliphatic hydrocar-
 bon groups include:

unsubstituted or fluorine-substituted alkyl
 groups such as 2-methylbutyl, 3-methylbutyl, pentyl,
 25 neopentyl, 2-methylpentyl, 3-methylpentyl, 4-methyl-
 pentyl, hexyl, 2-methylhexyl, 3-methylhexyl, 4-methyl-
 hexyl, 5-methylhexyl, 2,4-dimethylpentyl, 2-ethylhexyl,
 4,5-dimethylhexyl, 4,4-dimethylpentyl, heptyl, 4-methyl-
 heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl,
 30 tetradecyl, pentadecyl, 3-fluoromethylbutyl, 1-fluoro-
 pentyl, 4-fluoropentyl, 5-fluoropentyl, 1,1-difluoro-
 pentyl, 4,4-difluoropentyl, 5,5,5-trifluoropentyl,
 1,1,4,4-tetrafluoropentyl, 1,1,5,5,5-pentafluoropentyl,
 1-fluorohexyl, 5-fluorohexyl, 6-fluorohexyl, 1,1-
 35 difluorohexyl, 5,5-difluorohexyl, 6,6,6-trifluorohexyl,
 1,1,5,5-tetrafluorohexyl, 1,1,6,6,6-pentafluorohexyl, 1-

fluoro-4-methylpentyl, 2-fluoro-4-methylpentyl, 3-fluoro-4-methylpentyl, 4-fluoro-4-methylpentyl, 4-fluoromethylpentyl, 1,1-difluoro-4-methylpentyl, 4-trifluoromethylpentyl, 5,5,5-trifluoro-4-trifluoro-

5 methylpentyl, 1,1-difluoro-4-trifluoromethylpentyl, 1,1,5-trifluoro-4-methylpentyl, 1-fluoro-4-methylhexyl, 4-fluoro-4-methylhexyl, 5-fluoro-4-methylhexyl, 6-fluoro-4-methylhexyl, 1,1-difluoro-4-methylhexyl, 5,5-difluoro-4-methylhexyl, 4-trifluoromethylhexyl, 6,6,6-

10 trifluoro-4-methylhexyl, 6,6,6-trifluoro-4-trifluoromethylhexyl, 1,1-difluoro-4-trifluoromethylhexyl and 1,1-difluoro-6,6,6-trifluoro-4-methylhexyl;

unsubstituted or fluorine-substituted alkenyl groups such as 3-methyl-2-butenyl, 2-pentenyl, 3-

15 pentenyl, 4-pentenyl, 3-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-2-pentenyl, 4-methyl-3-pentenyl, 4-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 4-methyl-2-hexenyl, 4-methyl-3-hexenyl, 4-methyl-4-hexenyl, 5-methyl-2-hexenyl, 5-methyl-3-hexenyl, 5-methyl-4-

20 hexenyl, 5-methyl-2-heptenyl, 5-methyl-3-heptenyl, 5-methyl-4-heptenyl, 5-methyl-5-heptenyl, 3,4-dimethyl-2-pentenyl, 3,4-dimethyl-3-pentenyl, 4,5-dimethyl-2-hexenyl, 4,5-dimethyl-3-hexenyl, 4,5-dimethyl-4-hexenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tri-

25 decenyl, tetradecenyl, pentadecenyl, 1-fluoro-4-methyl-3-pentenyl, 2-fluoro-4-methyl-3-pentenyl, (E)-4-fluoromethyl-3-pentenyl, (Z)-4-fluoromethyl-3-pentenyl, 1,1-difluoro-4-methyl-3-pentenyl, 2,2-difluoro-4-methyl-3-pentenyl, (E)-4-trifluoromethyl-3-pentenyl, (Z)-4-tri-

30 fluoromethyl-3-pentenyl, (E)-1,1-difluoro-4-trifluoromethyl-3-pentenyl, (Z)-1,1-difluoro-4-trifluoromethyl-3-pentenyl, 5,5,5-trifluoro-4-trifluoromethyl-3-pentenyl, 1-fluoro-4-methyl-2-pentenyl, 4-fluoro-4-methyl-2-pentenyl, 4-fluoromethyl-2-pentenyl, 1,1-difluoro-4-methyl-

35 2-pentenyl, 4-trifluoromethyl-2-pentenyl, 4-fluoro-1,1-difluoro-4-methyl-2-pentenyl, 1,1-difluoro-4-trifluoro-

methyl-2-pentenyl, 1-fluoro-4-methyl-4-pentenyl, 2-
 fluoro-4-methyl-4-pentenyl, 3-fluoro-4-methyl-4-pen-
 tenyl, 4-fluoromethyl-4-pentenyl, 1,1-difluoro-4-methyl-
 4-pentenyl, 2,2-difluoro-4-methyl-4-pentenyl, 3,3-
 5 difluoro-4-methyl-4-pentenyl, 4-trifluoromethyl-4-pen-
 tenyl, 1,1-difluoro-4-trifluoromethyl-4-pentenyl,
 1,1,3,3-tetrafluoro-4-methyl-4-pentenyl, 1-fluoro-4-
 methyl-3-hexenyl, 2-fluoro-4-methyl-3-hexenyl, 4-fluoro-
 methyl-3-hexenyl, 6-fluoro-4-methyl-3-hexenyl, 4-tri-
 10 fluoromethyl-3-hexenyl, 1,1-difluoro-4-methyl-3-hexenyl,
 2,2-difluoro-4-methyl-3-hexenyl, 4-trifluoromethyl-3-
 hexenyl, 5,5-difluoromethyl-3-hexenyl, 6,6,6-trifluoro-
 4-methyl-3-hexenyl, 1,1-difluoro-4-trifluoromethyl-3-
 hexenyl, 1,1,-difluoro-6,6,6-trifluoromethyl-3-hexenyl
 15 and 6,6,6-trifluoro-4-trifluoromethyl-3-hexenyl;

2-pentynyl, 3-pentynyl, 4-pentynyl, 4-methyl-
 2-pentynyl, octynyl, nonynyl, decynyl, undecynyl,
 dodecynyl, tridecynyl, tetradecynyl and pentadecynyl,
 and those alkynyl groups in which optionally any 1 to 6
 20 hydrogen atoms are substituted with fluorine atom(s);

unsubstituted and fluorine-substituted cyclo-
 alkylalkyl groups in which any of hydrogen atom(s) on
 the cycloalkyl ring may be substituted with lower alkyl,
 such as cyclopropylethyl, cyclopropylpropyl, cyclo-
 25 propylbutyl, cyclopropylpentyl, cyclopropylhexyl, cyclo-
 propylheptyl, cyclobutylmethyl, cyclobutylethyl, cyclo-
 butylpropyl, cyclobutylbutyl, cyclobutylpentyl, cyclo-
 pentylmethyl, cyclopentylethyl, cyclopentylpropyl,
 cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl,
 30 cyclohexylpropyl, cyclohexylbutyl, cycloheptylmethyl,
 cycloheptylethyl, cycloheptylpropyl, cycloheptylbutyl,
 cyclooctylmethyl, cyclooctylethyl, cyclooctylpropyl,
 cyclooctylbutyl, 1-methylcyclopentylmethyl, 2-methyl-
 cyclopentylmethyl, 3-methylcyclopentylmethyl, 1-ethyl-
 35 cyclopentylmethyl, 2-ethylcyclopentylmethyl, 3-ethyl-
 cyclopentylmethyl, 2-cyclopentylethyl, 2-(1-methylcyclo-

pentyl)ethyl, 2-(2-methylcyclopentyl)ethyl, 2-(3-methyl-
 cyclopentyl)ethyl, 2-(1-ethylcyclopentyl)ethyl, 2-(2-
 ethylcyclopentyl)ethyl, 2-(3-ethylcyclopentyl)ethyl, 1-
 methylcyclohexylmethyl, 2-methylcyclohexylmethyl, 3-
 5 methylcyclohexylmethyl, 4-methylcyclohexylmethyl, 1-
 ethylcyclohexylmethyl, 2-ethylcyclohexylmethyl, 3-
 ethylcyclohexylmethyl, 4-ethylcyclohexylmethyl, cyclo-
 hexylethyl, 2-(1-methylcyclohexyl)ethyl, 2-(2-methyl-
 cyclohexyl)ethyl, 2-(3-methylcyclohexyl)ethyl, 2-(4-
 10 methylcyclohexyl)ethyl, 2-(1-ethylcyclohexyl)ethyl,
 2-(2-ethylcyclohexyl)ethyl, 2-(3-ethylcyclohexyl)ethyl,
 2-(4-ethylcyclohexyl)ethyl, 1-methylcycloheptylmethyl,
 2-methylcycloheptylmethyl, 3-methylcycloheptylmethyl,
 4-methylcycloheptylmethyl, 1-ethylcycloheptylmethyl,
 15 2-ethylcycloheptylmethyl, 3-ethylcycloheptylmethyl,
 4-ethylcycloheptylmethyl, 2-cycloheptylethyl, 2-(1-
 methylcycloheptyl)ethyl, 2-(2-methylcycloheptyl)ethyl,
 2-(3-methylcycloheptyl)ethyl, 2-(4-methylcycloheptyl)-
 ethyl, 2-(1-ethylcycloheptyl)ethyl, 2-(2-ethylcyclo-
 20 heptyl)ethyl, 2-(3-ethylcycloheptyl)ethyl, 2-(4-ethyl-
 cycloheptyl)ethyl, 1-methylcyclooctylmethyl, 2-methyl-
 cyclooctylmethyl, 3-methylcyclooctylmethyl, 4-methyl-
 cyclooctylmethyl, 5-methylcyclooctylmethyl, 1-ethyl-
 cyclooctylmethyl, 2-ethylcyclooctylmethyl, 3-ethyl-
 25 cyclooctylmethyl, 4-ethylcyclooctylmethyl, 5-ethyl-
 cyclooctylmethyl, 2-(1-methylcyclooctyl)ethyl, 2-(2-
 methylcyclooctyl)ethyl, 2-(3-methylcyclooctyl)ethyl, 2-
 (4-methylcyclooctyl)ethyl, 2-(5-methylcyclooctyl)ethyl,
 2-(1-ethylcyclooctyl)ethyl, 2-(2-ethylcyclooctyl)ethyl,
 30 2-(3-ethylcyclooctyl)ethyl, 2-(4-ethylcyclooctyl)ethyl,
 2-(5-ethylcyclooctyl)ethyl, 1-fluoro-1-cyclohexylmethyl,
 2-fluorocyclohexylmethyl, 3-fluorocyclohexylmethyl, 4-
 fluorocyclohexylmethyl, 1,1-difluoro-1-cyclohexylmethyl,
 2,2-difluorocyclohexylmethyl, 3,3-difluorocyclohexyl-
 35 methyl, 4,4-difluorocyclohexylmethyl, 1-fluoro-1-cyclo-
 heptylmethyl, 2-fluorocycloheptylmethyl, 3-fluorocyclo-

heptylmethyl, 4-fluorocycloheptylmethyl, 1,1-difluoro-1-cycloheptylmethyl, 2,2-difluorocycloheptylmethyl, 3,3-difluorocycloheptylmethyl, 4,4-difluorocycloheptylmethyl, 1-fluoro-1-(3-methylcyclohexyl)methyl, 2-fluoro-
 5 3-methylcyclohexylmethyl, 3-fluoro-3-methylcyclohexylmethyl, 4-fluoro-3-methylcyclohexylmethyl, 1,1-difluoro-1-(3-methylcyclohexyl)methyl, 2,2-difluoro-3-methylcyclohexylmethyl, 3-trifluoromethylcyclohexylmethyl, 4,4-difluoro-3-methylcyclohexylmethyl, 1-fluoro-2-
 10 cyclopentylethyl, 2-(2-fluorocyclopentyl)ethyl, 2-(3-fluorocyclopentyl)ethyl, 1,1-difluoro-2-cyclopentylethyl, 2-(2,2-difluorocyclopentyl)ethyl, 2-(3,3-difluorocyclopentyl)ethyl, 1,1-difluoro-2-(2,2-difluorocyclopentyl)ethyl and 1,1-difluoro-2-(3,3-difluorocyclo-
 15 pentyl)ethyl;

cycloalkylidenealkyl groups such as cyclopropylideneethyl, cyclopropylidenepropyl, cyclopropylidenebutyl, cyclopropylidenepentyl, cyclobutylideneethyl, cyclobutylidenepropyl, cyclobutylidenebutyl, cyclo-
 20 butylidenepentyl, cyclopentylideneethyl, cyclopentylidenepropyl, cyclopentylidenebutyl, cyclopentylidenepentyl, cyclohexylideneethyl, cyclohexylidenepropyl, cyclohexylidenebutyl, cyclohexylidenepentyl, cycloheptylideneethyl, cycloheptylidenepropyl, cycloheptyli-
 25 denebutyl, cycloheptylidenepentyl, cyclooctylideneethyl, cyclooctylidenepropyl, cyclooctylidenebutyl and cyclooctylidenepentyl, and those cycloalkylidene alkyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

30 cycloalkylalkenyl groups in which any of hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl, such as cyclopropylpropenyl, cyclopropylbutenyl, cyclopropylpentenyl, cyclopropylhexenyl, cyclopropylheptenyl, cyclobutylpropenyl, cyclo-
 35 butylbutenyl, cyclobutylpentenyl, cyclopentylpropenyl, cyclopentylbutenyl, cyclopentylpentenyl, cyclohexylpro-

penyl, cyclohexylbutenyl, cyclohexylpentenyl, cycloheptylpropenyl and cyclooctylpropenyl, and those cycloalkylalkenyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

- 5 cycloalkylalkynyl groups in which any of hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl, such as cyclopropylpropynyl, cyclopropylbutynyl, cyclopropylpentynyl, cyclopropylhexynyl, cyclopropylheptynyl, cyclobutylpropynyl, 10 cyclobutylbutynyl, cyclobutylpentynyl, cyclopentylpropynyl, cyclopentylbutynyl, cyclopentylpentynyl, cyclohexylpropynyl, cyclohexylbutynyl and cyclohexylpentynyl, and those cycloalkylalkynyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine 15 atom(s);

- cycloalkenylalkyl groups in which any optional hydrogen atom(s) on the cycloalkenyl ring may be replaced by a lower alkyl group(s), such as cyclopropenylethyl, cyclopropenylpropyl, cyclopropenylbutyl, 20 cyclopropenylpentyl, cyclopropenylhexyl, cyclopropenylheptyl, cyclobutenylmethyl, cyclobutenylethyl, cyclobutenylpropyl, cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cycloheptenylmethyl, cycloheptenylethyl, cyclooctenylmethyl, cyclooctenylethyl, 25 (1-methyl-2-cyclopentenyl)methyl, (1-methyl-3-cyclopentenyl)methyl, (2-methyl-1-cyclopentenyl)methyl, (2-methyl-2-cyclopentenyl)methyl, (2-methyl-3-cyclopentenyl)methyl, (5-methyl-2-cyclopentenyl)methyl, (5-methyl-1-cyclopentenyl)methyl, (3-methyl-1-cyclopentenyl)methyl, (3-methyl-2-cyclopentenyl)methyl, (3-methyl-3-cyclopentenyl)methyl, (4-methyl-2-cyclopentenyl)methyl, (4-methyl-1-cyclopentenyl)methyl, (1-methyl-2-cyclohexenyl)methyl, (1-methyl-3-cyclohexenyl)-methyl, (2-methyl-1-cyclohexenyl)methyl, (2-methyl-2-cyclohexenyl)methyl, (2-methyl-3-cyclohexenyl)methyl, 35 (6-methyl-3-cyclohexenyl)methyl, (6-methyl-2-cyclo-

hexenyl)methyl, (6-methyl-1-cyclohexenyl)methyl, (3-
 methyl-1-cyclohexenyl)methyl, (3-methyl-2-cyclohexen-
 yl)methyl, (3-methyl-3-cyclohexenyl)methyl, (5-methyl-3-
 cyclohexenyl)methyl, (5-methyl-2-cyclohexenyl)methyl,
 5 (5-methyl-1-cyclohexenyl)methyl, (4-methyl-1-cyclohexen-
 yl)methyl, (4-methyl-2-cyclohexenyl)methyl, (4-methyl-3-
 cyclohexenyl)methyl, (1-methyl-2-cycloheptenyl)methyl,
 (1-methyl-3-cycloheptenyl)methyl, (1-methyl-4-cyclohep-
 tenyl)methyl, (2-methyl-1-cycloheptenyl)methyl, (2-
 10 methyl-2-cycloheptenyl)methyl, (2-methyl-3-cyclohepten-
 yl)methyl, (2-methyl-4-cycloheptenyl)methyl, (7-methyl-
 3-cycloheptenyl)methyl, (7-methyl-2-cycloheptenyl)-
 methyl, (7-methyl-1-cycloheptenyl)methyl, (3-methyl-1-
 cycloheptenyl)methyl, (3-methyl-2-cycloheptenyl)methyl,
 15 (3-methyl-3-cycloheptenyl)methyl, (3-methyl-4-cyclo-
 heptenyl)methyl, (6-methyl-3-cycloheptenyl)methyl, (6-
 methyl-2-cycloheptenyl)methyl, (6-methyl-1-cyclohepten-
 yl)methyl, (4-methyl-1-cycloheptenyl)methyl, (4-methyl-
 2-cycloheptenyl)methyl, (4-methyl-3-cycloheptenyl)-
 20 methyl, (4-methyl-4-cycloheptenyl)methyl, (5-methyl-3-
 cycloheptenyl)methyl, (5-methyl-2-cycloheptenyl)methyl,
 (5-methyl-1-cycloheptenyl)methyl, (1-methyl-2-cyclo-
 octenyl)methyl, (1-methyl-3-cyclooctenyl)methyl, (1-
 methyl-4-cyclooctenyl)methyl, (2-methyl-1-cyclooctenyl)-
 25 methyl, (2-methyl-2-cyclooctenyl)methyl, (2-methyl-3-
 cyclooctenyl)methyl, (2-methyl-4-cyclooctenyl)methyl,
 (8-methyl-4-cyclooctenyl)methyl, (8-methyl-3-cyclo-
 octenyl)methyl, (8-methyl-2-cyclooctenyl)methyl, (8-
 methyl-1-cyclooctenyl)methyl, (3-methyl-1-cyclooctenyl)-
 30 methyl, (3-methyl-2-cyclooctenyl)methyl, (3-methyl-3-
 cyclooctenyl)methyl, (3-methyl-4-cyclooctenyl)methyl,
 (7-methyl-4-cyclooctenyl)methyl, (7-methyl-3-cycloocten-
 yl)methyl, (7-methyl-2-cyclooctenyl)methyl, (7-methyl-1-
 cyclooctenyl)methyl, (4-methyl-1-cyclooctenyl)methyl,
 35 (4-methyl-2-cyclooctenyl)methyl, (4-methyl-3-cyclo-
 octenyl)methyl, (4-methyl-4-cyclooctenyl)methyl,

(6-methyl-4-cyclooctenyl)methyl, (6-methyl-2-cyclo-octenyl)methyl, (6-methyl-1-cyclooctenyl)methyl, (5-methyl-1-cyclooctenyl)methyl, (5-methyl-2-cyclo-octenyl)methyl, (5-methyl-3-cyclooctenyl)methyl and
 5 (5-methyl-4-cyclooctenyl)methyl, and those cycloalkenyl-alkyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s); and
 cycloalkenylalkenyl groups in which any of hydrogen atoms on the cycloalkenyl ring may be substi-
 10 tuted with lower alkyl such as cyclopropenylpropenyl, cyclopropenylbutenyl, cyclobutenylbutenyl, cyclopentenylpropenyl, cyclopentenylbutenyl, cyclopropenyl-pentenyl, cyclopropenylhexenyl, cyclopropenylheptenyl, cyclobutenylpropenyl, cyclohexenylpropenyl and cyclo-
 15 hexenylbutenyl, and those cycloalkenylalkenyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s).

"Aralkyl (optionally any 1 to 3 hydrogen atoms on the ring in the aralkyl group may be substituted with
 20 lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)" signifies unsubstituted or substituted C_7 - C_{12} aralkyl groups. As their examples, unsubstituted benzyl, phenethyl, phenylpropyl and naphthyl-
 25 methyl, and those substituted with above-listed substituents may be named.

"Arylalkenyl (optionally any 1-3 hydrogen atoms on the ring in the arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano,
 30 hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)" signifies unsubstituted or substituted C_8 - C_{12} arylalkenyl groups, examples of which include unsubstituted phenylpropenyl and naphthylpropenyl, and those substituted with above-
 35 listed substituents.

Examples of "heteroarylalkyl having 1 to 2

hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1-3 hydrogen atoms on the ring in the heteroarylalkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino)" include unsubstituted 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thiazolylmethyl, 4-thiazolylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-imidazolylmethyl, 2-imidazolylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 3-pyrazolylmethyl, 4-pyrazolylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyrrolylmethyl, 3-pyrrolylmethyl, 2-pyrimidinylmethyl, 4-pyrimidinylmethyl, 5-pyrimidinylmethyl, pyrazinylmethyl, 3-pyridazinylmethyl, 4-pyridazinylmethyl, 3-quinolylmethyl, 4-quinolylmethyl, 5-quinolylmethyl, 6-quinolylmethyl, 7-quinolylmethyl, 8-quinolylmethyl, 1-isoquinolylmethyl, 3-isoquinolylmethyl, 4-isoquinolylmethyl, 5-isoquinolylmethyl, 6-isoquinolylmethyl, 7-isoquinolylmethyl, 8-isoquinolylmethyl, 2-benzothienylmethyl, 3-benzothienylmethyl, 4-benzothienylmethyl, 5-benzothienylmethyl, 6-benzothienylmethyl, 7-benzothienylmethyl, 2-indolylmethyl, 3-indolylmethyl, 4-indolylmethyl, 5-indolylmethyl, 6-indolylmethyl, 7-indolylmethyl, 2-benzimidazolylmethyl, 4-benzimidazolylmethyl, 5-benzimidazolylmethyl, 2-benzothiazolylmethyl, 4-benzothiazolylmethyl, 5-benzothiazolylmethyl, 6-benzothiazolylmethyl, 7-benzothiazolylmethyl, 2-benzoxazolylmethyl, 4-benzoxazolylmethyl, 5-benzoxazolylmethyl, 6-benzoxazolylmethyl, 7-benzoxazolylmethyl, 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl, 2-pyridylethyl, 2-pyridylpropyl, 3-pyridylethyl, 4-pyridylethyl, 2-thiazolylethyl, 2-thienylethyl, 3-thienylethyl, 1-imidazolylethyl, 2-imidazolylethyl, 3-pyrazolylethyl, 4-pyrazolylethyl, 2-furylethyl, 3-furylethyl, 2-pyrrolylethyl, 3-pyrrolylethyl, 2-

pyrimidinylethyl, 4-pyrimidinylethyl, 5-pyrimidinylethyl, pyrazinylethyl, 3-pyridazinylethyl, 4-pyridazinylethyl, 2-quinizylethyl, 2-benzothienylethyl, 3-benzothienylethyl, 4-benzothienylethyl, 5-benzothienylethyl, 6-benzothienylethyl, 7-benzothienylethyl, 2-indolylethyl, 3-indolylethyl, 4-indolylethyl, 5-indolylethyl, 6-indolylethyl, 7-indolylethyl, 2-benzimidazolylethyl, 4-benzimidazolylethyl, 5-benzimidazolylethyl, 2-benzothiazolylethyl, 4-benzothiazolylethyl, 5-benzothiazolylethyl, 6-benzothiazolylethyl, 7-benzothiazolylethyl, 2-benzoxazolylethyl, 4-benzoxazolylethyl, 5-benzoxazolylethyl, 6-benzoxazolylethyl, 7-benzoxazolylethyl, 2-benzofuranylethyl, 3-benzofuranylethyl, 4-benzofuranylethyl, 5-benzofuranylethyl, 6-benzofuranylethyl and 7-benzofuranylethyl, and those which are substituted with above-listed substituents.

As examples of "heteroarylalkenyl having 1-2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino)", unsubstituted 2-pyridylpropenyl, 3-pyridylpropenyl, 4-pyridylpropenyl, 2-thiazolylpropenyl, 2-thienylpropenyl, 3-thienylpropenyl, 1-imidazolylbutenyl, 2-imidazolylpropenyl, 3-pyrazolylpropenyl, 4-pyrazolylpropenyl, 2-furylpropenyl, 3-furylpropenyl, 2-pyrrolylpropenyl, 3-pyrrolylpropenyl, 2-pyrimidinylpropenyl, 4-pyrimidinylpropenyl, 5-pyrimidinylpropenyl, pyrazinylpropenyl, 3-pyridazinylpropenyl, 4-pyridazinylpropenyl, 2-quinidylpropenyl, 2-benzothienylpropenyl and 2-indolylpropenyl, and those substituted with above-named substituents may be named.

"Halogen" include fluorine, chlorine, bromine and iodine.

"Lower alkyl" signifies C_1 - C_6 straight chain

or branched alkyl groups, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, hexyl and isohexyl groups.

5 "Lower alkoxy" signifies C_1-C_6 straight chain or branched alkoxy groups, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, isobutoxy, t-butoxy, pentyloxy, isopentyloxy, hexyloxy and isohexyloxy groups.

10 "Lower alkoxycarbonyl" signifies C_1-C_7 straight chain or branched alkoxycarbonyl groups, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, hexyloxycarbonyl and
15 isohexyloxycarbonyl groups.

"Aralkyloxycarbonyl" signifies C_7-C_{10} aralkyloxycarbonyl groups, for example, benzyloxycarbonyl and phenethyloxycarbonyl groups.

20 "Lower alkylamino" signifies C_1-C_6 straight chain or branched alkylamino groups, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino, t-butylamino, pentylamino, isopentylamino, hexylamino, isohexylamino, dimethylamino, diethylamino and dipropylamino groups.

25 "Protected hydroxyl groups" signify hydroxyl groups which are protected with acyl such as acetyl, alkylsilyl such as trimethylsilyl and t-butyldimethylsilyl, aralkyl such as benzyl and trityl, ether group such as methoxymethyl, and in the form of alkylidene-
30 ketal such as isopropylideneketal.

"Protected oxo groups" signify oxo groups which are protected in the form of acetal or ketal such as ethylene ketal, trimethylene ketal and dimethyl ketal.

35 "Protected amino or lower alkylamino groups" signify amino or lower alkylamino groups which are

protected with, for example, aralkyl groups such as benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl and trityl; lower alkanoyl groups such as formyl, acetyl and propionyl; arylalkanoyl groups such as phenylacetyl and
 5 phenoxyacetyl; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl and t-butoxycarbonyl; alkenyloxycarbonyl groups such as 2-propenyloxycarbonyl; aralkyloxycarbonyl groups such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl, and
 10 lower alkylsilyl groups such as trimethylsilyl and t-butyldimethylsilyl. In particular, amino or lower alkylamino groups which are protected with t-butoxycarbonyl and benzyloxycarbonyl groups are preferred.

Also "deprotection" signifies removal of protective groups by the means conventionally used in the
 15 field of organic chemistry, such as hydrolysis, hydrogenolysis and the like.

Referring to the general formula [I],

(1) Ar represents an aryl group or a hetero-
 20 aryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or hetero-aryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl,
 25 halogen, lower alkoxy, amino or lower alkylamino). In particular, unsubstituted phenyl or substituted phenyl having above-named substituents are preferred.

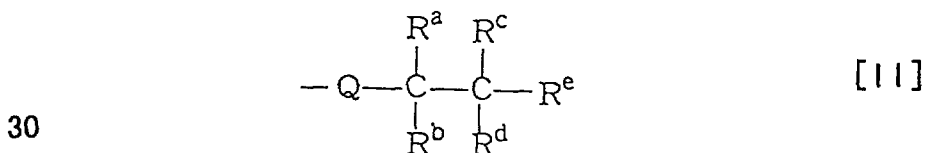
(2) R¹ is a C₃-C₆ cycloalkyl which may have 1 to 4 fluorine atoms on the ring; cyclobutyl, cyclopentyl, cyclohexyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-
 30 fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl

and 4,4-difluorocyclohexyl being preferred.

Of these, particularly 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl,
 5 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl and 4,4-difluorocyclohexyl are preferred.
 10 3,3-Difluorocyclopentyl is the best preferred.

(3) X represents O or NH, NH being the preferred.

(4) R^2 represents C_5-C_{15} saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6
 15 hydrogen atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said
 20 aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino). Of these, the groups expressed by the following
 25 formula [II], in which any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s),



[in which

Q represents methylene, ethylene, trimethylene or tetramethylene;

35 R^a and R^c each represents a hydrogen atom or are combined to form a single bond; and

THIS SHEET HAS BEEN
REPLACED

R^b , R^d and R^e may be the same or different and each represents a hydrogen atom, a lower alkyl group, C_3-C_8 cycloalkyl or cycloalkenyl, or R^b and R^d , or R^d and R^e together form each a C_3-C_8 cycloalkyl or cycloalkenyl], benzyl, phenethyl, phenylpropyl, phenylpropenyl or 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thiazolylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-imidazolylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyrrolylmethyl, 3-pyrrolylmethyl (any 1 to 3 hydrogen atoms on the ring of said benzyl, phenethyl, phenylpropyl, phenylpropenyl or heteroarylalkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino) are preferred.

In particular, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, amino, lower alkylamino or lower alkoxy) are preferred, inter alia, 6-aminopyridin-2-ylmethyl group is preferred.

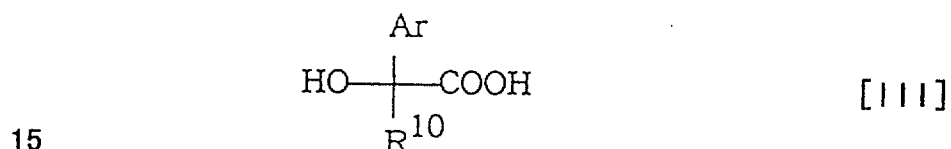
According to the manner of substitution, the compounds of the present invention may exist in the form of stereoisomers such as optical isomers, diastereoisomers and geometrical isomers. It is to be understood that the compounds of the present invention also include all such stereoisomers and mixtures thereof.

Moreover, the compounds of the present invention may exist in the form of pharmaceutically acceptable salts. Such salts include inorganic acid salts such as hydrochlorides, sulfates, nitrates, phosphates

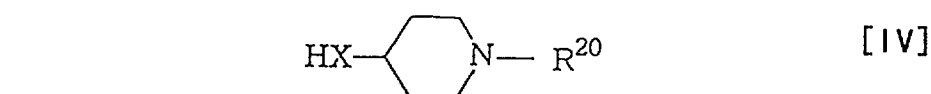
and perchlorates; organic carboxylic acid salts such as maleates, fumarates, succinates, tartrates, citrates and ascorbates; organic sulfonic acid salts such as methane-sulfonates, isethionates, benzenesulfonates and
 5 p-toluenesulfonates; and the like.

The compounds of the above general formula [I] in accordance with the present invention can be prepared, for example, by:

- 10 (a) reacting a carboxylic acid of the general formula [III]



[wherein Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, tri-fluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino); and R¹⁰ represents a C₃-C₈ cycloalkyl in which any 1 to 4 hydrogen atoms may be substituted with fluorine atom(s) or a C₃-C₈ cycloalkyl having 1 to 2 protected or unprotected hydroxyl or oxo group(s)]
 20
 25
 30 or a reactive derivative thereof with a compound of the general formula [IV]



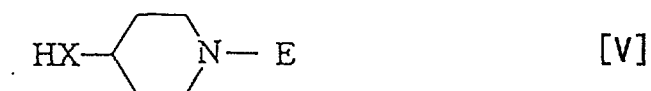
[wherein R²⁰ represents a C₅-C₁₅ saturated or

unsaturated aliphatic hydrocarbon group in which any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), C_5-C_{15} saturated or unsaturated aliphatic hydrocarbon group having 1-2 protected or unprotected hydroxyl or oxo group(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, unprotected or protected amino, unprotected or protected lower alkylamino or aralkyloxy, carbonyl group) and X stands for NH or O] or a salt thereof;

and when either R^{10} or R^{20} has unprotected or protected 1 to 2 hydroxyl or oxo group(s) converting said hydroxyl or oxo groups to fluorine atom(s) either as they are or after removing the protective group(s); when R^{10} or R^{20} has protected amino or protected lower alkylamino group(s), removing the protective group(s); and when R^{10} or R^{20} has lower alkoxy, carbonyl or aralkyloxy, carbonyl, converting the same to amino; or

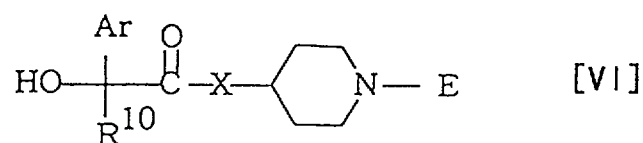
(b) reacting a carboxylic acid of the above general formula [III] or a reactive derivative thereof with a compound of the general formula [V]

30



[wherein E is a protective group for the imino group, and X is as defined above]

or a salt thereof; deprotecting the resulting compound of the general formula [VI]



5 [wherein Ar, R^{10} , X and E are as defined
above] hereafter reacting the same with a com-
pound of the general formula [VII]



10

[wherein L represents a leaving group, and R^{20}
is as defined above]

in the presence of a base, if necessary, and again if
necessary conducting a conversion reaction of R^{10} and
15 R^{20} similar to the above; or

(c) deprotecting a compound of the above
general formula [VI] and subjecting it to a reductive
alkylation reaction with a compound of the general
formula [VIII]

20



25

[wherein R^{21} represents a C_4-C_{14} saturated or
unsaturated aliphatic hydrocarbon group in
which any 1 to 6 hydrogen atom(s) may be sub-
stituted with fluorine atom(s), C_4-C_{14} satu-
rated or unsaturated aliphatic hydrocarbon
group having unprotected or protected 1 to 2
hydroxyl or oxo group(s), aryl, aralkyl, aryl-
30 alkenyl or heteroaryl, heteroarylalkyl or
heteroarylalkenyl having 1 to 2 hetero atoms
selected from a group consisting of nitrogen,
oxygen and sulfur (optionally any 1-3 hydrogen
atoms on the ring in said aryl, aralkyl, aryl-
35 alkenyl, heteroaryl, heteroarylalkyl or
heteroarylalkenyl group may be substituted

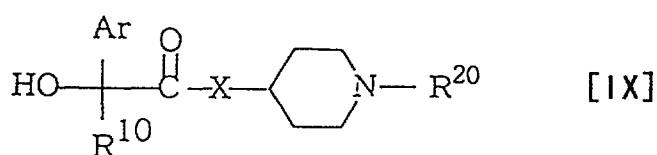
with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, unprotected or protected amino, unprotected or protected lower alkyl-amino or aralkyloxy carbonyl)],

and if necessary conducting the conversion reaction of R^{10} and R^{21} similar to the foregoing.

In the above formula [VII], "leaving groups" represented by L include, for example, halogen atoms such as chlorine, bromine and iodine; alkylsulfonyloxy groups such as methanesulfonyloxy; and arylsulfonyloxy groups such as p-toluenesulfonyloxy.

In the above formulae [V] and [VI], "protective groups for the imino group" represented by E signify similar protective groups to those for amino as above.

In the above-described process variant (a), a carboxylic acid of formula [III] is reacted with a compound of formula [IV] or a salt thereof in the presence of a suitable condensing agent. Thus, there is obtained a coupled compound of the general formula [IX]



[wherein Ar, R^{10} , X and R^{20} are as defined above].

The carboxylic acid of formula [III] used as a starting material in the above condensation reaction can be prepared, for example, by the method as described in Referential Examples.

The condensing agent to be used in the above-described reaction may be any of those which are commonly used in the field of organic synthetic chemistry for condensation reactions of carboxyl groups with

hydroxyl or amino groups, and examples thereof include N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide and dipyridyl disulfide-triphenylphosphine. Of these,
5 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is preferred.

Use rate of these condensing agents are subject to no critical limitation, while normally it may be within a range of 1 to 5 equivalents, preferably 1 to 2
10 equivalents, per mole of the compound of formula [III].

If necessary, the above-described condensation reaction may be carried out in the presence of a base. Bases which can be used for this purpose include, for example, aliphatic tertiary amines such as triethylamine
15 and diisopropylethylamine; and aromatic amines such as pyridine, 4-dimethylaminopyridine, quinoline. 4-Dimethylaminopyridine is particularly preferred.

The condensation reaction is preferably carried out in an inert solvent. Suitable inert organic
20 solvents include, for example, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of these,
25 diethyl ether, tetrahydrofuran, N,N-dimethylformamide and dioxane are preferred.

The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C . Under
30 these conditions, the reaction can usually be completed in a period of time ranging from 5 minutes to 7 days and preferably from 10 minutes to 24 hours.

The proportion of the compound of formula [IV] or a salt thereof to the compound of formula [III] is
35 not critical and may vary according to the kinds of individual compounds, the reaction conditions employed

and other factors. Whereas, the compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to 5 moles, preferably 1 to 2 moles, per mole of the compound of formula [III].

5 The coupled compound of the above formula [IX] can also be obtained by converting the carboxylic acid of formula [III] into a reactive derivative thereof and condensing it with the compound of formula [IV] or a salt thereof.

10 Suitable reactive derivatives of the carboxylic acid of formula [III] include, for example, compounds which are commonly used in the field of organic synthetic chemistry for activation of carboxyl group(s) in an esterification or amidation reaction, such as mixed acid
15 anhydrides, active esters and active amides.

 Mixed acid anhydrides of the carboxylic acid of formula [III] can be obtained by reacting the carboxylic acid of formula [III] with an alkyl chlorocarbonate, e.g., ethyl chlorocarbonate, an aliphatic carboxylic acid chloride, e.g., acetyl chloride, pivaloyl
20 chloride or the like according to conventional method. Reactive esters thereof can be obtained by reacting the carboxylic acid of formula [III] with an N-hydroxy compound, e.g., N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole; or a phenol compound,
25 e.g., 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, pentachlorophenol or the like; in the presence of a condensing agent, e.g., N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
30 diphenylphosphoryl azide or dipyridyl disulfide-triphenylphosphine, according to conventional method. Reactive amides thereof can be obtained by reacting the carboxylic acid of formula [III] with 1,1'-carbonyldiimidazole, 1,1'-carbonylbis(2-methylimidazole) or the
35 like according to conventional method.

 The condensation reaction of a reactive deriv-

ative of a carboxylic acid of formula [III] with a compound of formula [IV] or a salt thereof is preferably carried out in an inert solvent. Suitable inert organic solvents include, for example, diethyl ether, tetra-
5 hydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of these, diethyl ether, chloroform, tetrahydrofuran, N,N-
10 dimethylformamide and dioxane are preferred.

The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C .

The proportion of the compound of formula [IV] or a salt thereof to the reactive derivative of a
15 carboxylic acid of formula [III] is not critical and may vary according to the kind of the reactive derivative and other factors, while the compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to
20 5 moles, preferably 1 to 2 moles, per mole of the reactive derivative of the carboxylic acid of formula [III].

In the coupled compounds expressed by the general formula [IX], when R^{10} is a $\text{C}_3\text{-C}_6$ cycloalkyl group having 1-2 unprotected or protected hydroxyl or
25 oxo group(s), or R^{20} is an aliphatic hydrocarbon group having 1-2 unprotected or protected hydroxyl or oxo group(s), the hydroxyl or oxo group(s) are converted to fluorine atom(s) either as they are or after removing the protective group(s).

30 Removal of protective groups from hydroxyl and oxo groups which are protected in the form of ketals in the compounds of formula [IX] can normally be effected in aqueous solvent, using an inorganic acid, an organic acid, a weakly acidic salt or the like. Suitable inor-
35 ganic acids include, for example, hydrochloric acid and sulfuric acid; suitable organic acids include, for

example, p-toluenesulfonic acid, benzenesulfonic acid, camphor-sulfonic acid and acetic acid; and suitable weakly acidic salts include, for example, ammonium chloride and pyridinium p-toluenesulfonate. Preferred
 5 aqueous solvents include aqueous methanol, aqueous ethanol, aqueous tetrahydrofuran, aqueous dioxane and the like. The reaction may usually be carried out in the presence of a catalytic amount to 5 equivalents, preferably a catalytic amount to 1 equivalent, of such
 10 an acid or salt at a temperature ranging from 0°C to 100°C and preferably from room temperature to 80°C.

Conversion of the hydroxyl or oxo group(s) to fluorine atom(s) can normally be effected by causing the compound to react in an inert solvent which is not
 15 detrimental to the reaction, e.g., methylene chloride, chloroform, tetrahydrofuran, methanol, acetonitrile, dimethylsulfoxide or pyridine, or in the absence of a solvent, using one equivalent to an excessive amount, preferably 1-2 equivalents, of a fluorinating agent such
 20 as sulfur tetrafluoride, diethylaminosulfur trifluoride, cesium fluorosulfate, tetrabutylammonium fluoride, tris(dimethylamino)sulfonium-difluorotrimethylsilicate, hydrogen fluoride or tosyl fluoride, preferably at temperatures ranging -80°C - 180°C for 10 minutes to 72
 25 hours.

When R^{20} in the compounds expressed by general formula [IV] or [IX] has protected amino group(s) or protected lower alkylamino group(s), the protective group(s) are removed if necessary; when lower alkoxy-carbonyl or aryloxycarbonyl group(s) are present, the
 30 functional group(s) are suitably converted to amino group(s). Removal of amino-protective groups can be effected by processes known per se, for example, any of those described in Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons Co. (1981) or methods analogous thereto, for example, solvolysis using an
 35



acid or base, chemical reduction using a metal hydride complex or the like and catalytic reduction using palladium-on-carbon, Raney-nickel or the like.

Solvolysis with an acid can normally be carried out by treating the compound with an acid such as formic acid, trifluoroacetic acid, hydrochloric acid or sulfuric acid, in an inert solvent such as methylene chloride, anisole, tetrahydrofuran, dioxane, methanol or ethanol or a mixture of such a solvent and water, or in the absence of solvent, preferably at a temperature in the range from about 0° to about 100°C, for a period of time ranging from 10 minutes to 24 hours.

Solvolysis with a base can normally be carried out by treating the compound with an alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide; an alkali metal carbonate, e.g., sodium carbonate or potassium carbonate, in an inert solvent which exerts no adverse effect on the reaction, e.g., methanol, ethanol, isopropanol, tetrahydrofuran or dioxane or a mixture of such a solvent and water, preferably at a temperature in the range of from about -20 to about 80°C, for a period of time ranging from 10 minutes to 24 hours.

Catalytic reduction can normally be carried out in the presence of a catalyst such as palladium-on-carbon, palladium hydroxide, Raney nickel or platinum oxide, in an inert solvent, e.g., methanol, ethanol, water or acetic acid or a mixture of such solvents, preferably under a pressure of hydrogen of about 1 to about 20 kg/cm², preferably at a temperature in the range of from about 0 to about 40°C, for a period of time ranging from 10 minutes to 24 hours.

Conversion of the lower alkoxycarbonyl or aryloxycarbonyl to amino can be conducted by either reacting the compound with hydrazine to form an acid hydrazide and thereafter converting it to the corres-

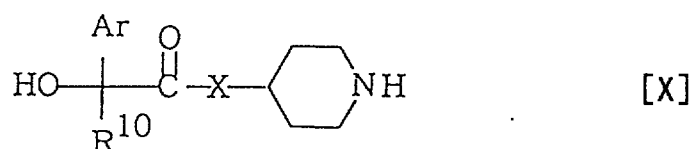
ponding acid azide; or converting the compound to a carboxylic acid by hydrolysis, then to an acid azide, followed by rearrangement and hydrolysis.

In the process variant (b), the condensation
 5 reaction of a carboxylic acid of formula [III] or a reactive derivative thereof with a piperidine derivative of formula [V] in the first stage can be practiced in the manner similar to the condensation reaction of a carboxylic acid of formula [III] or a reactive deriva-
 10 tive thereof with a compound of formula [IV] in the process variant (a).

The compound of the foregoing formula [VI] obtained through this condensation reaction is then removed of the protective group(s) of imino group(s).

15 Removal of said imino-protective groups from a compound of formula [VI] can be effected in the manner similar to above-described removal of amino-protective groups.

Thus obtained compounds of the general formula
 20 [X]



25

[wherein Ar, R¹⁰ and X are as defined above] is reacted with a compound of formula [VII] in the second stage, if necessary in the presence of a base.

The reaction of the compound of formula [X]
 30 with the compound of formula [VII] is usually carried out in a suitable solvent by using the compounds in substantially equimolar amounts or using either of the compounds in slight excess (e.g., using the compound of formula [VII] in an amount of 1 to 1.3 moles per mole of
 35 the compound of formula [X]). If desired, however, either of the compounds may be used in large excess.

Moreover, a suitable base and/or an additive may be used.

Suitable solvents include, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; and mixtures thereof.

Bases which can be used for above-described reaction include, for example, alkali metal bicarbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; alkali metal carbonates such as sodium carbonate and potassium carbonate; tertiary aliphatic amines such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); and aromatic amines such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline and isoquinoline. Of these, N,N-diisopropylethylamine and potassium carbonate are preferred.

Additives which can be used for above-described reaction include, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide. Of these, potassium iodide is preferred.

The reaction temperature may usually range from about 0°C to the boiling point of the solvent, and the reaction time may usually range from 10 minutes to 48 hours. If desired, however, reaction conditions beyond these limits may be used.

If necessary, furthermore, conversion reactions of R^{10} and R^{20} as described as to the process variant (a) are conducted.

The reductive alkylation reaction of a compound of the above formula [X] with an aldehyde of formula [VIII] according to the process variant (c) is

normally carried out in an inert solvent which exerts no adverse effect on the reaction. Suitable inert solvents include, for example, alcohols such as methanol and ethanol; ethers such as diethyl ether, tetrahydrofuran
5 and dioxane; aromatic hydrocarbons such as benzene and toluene; and mixtures thereof. Of these, methanol, ethanol, tetrahydrofuran and toluene are preferred.

The reaction temperature may usually range from about -30°C to about 200°C and preferably from
10 about 0°C to about 100°C . The reaction time may usually range from 10 minutes to 7 days and preferably from 10 minutes to 24 hours.

The above-described reductive alkylation reaction is preferably carried out under weakly acidic
15 conditions which facilitate formation of Schiff bases. Acids which can be used for the necessary pH control include, for example, p-toluenesulfonic acid, hydrochloric acid, acetic acid and trifluoroacetic acid.

The reductive alkylation can be effected, for
20 example, using a metal hydride complex such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride or sodium triacetoxyborohydride, or by catalytic reduction using a palladium-on-carbon catalyst, a Raney nickel catalyst or the like. Preferably, it is effected
25 using a metal hydride complex such as sodium borohydride or sodium cyanoborohydride. Especially when the reductive alkylation is carried out under weakly acidic conditions which facilitate formation of Schiff bases, it is preferable to use sodium cyanoborohydride or the
30 like which are relatively stable in the acidic pH range.

When a metal hydride complex is used as the reducing agent, the amount of reducing agent used may usually range from 1 mole to excessive moles, preferably from 1 to 10 moles, per mole of the compound of formula
35 [X].

If necessary, then the conversion reactions of

R^{10} and R^{21} as described as to the process variant (a) are carried out.

The compounds of formula [I] which are obtained according to the above-described process variants
5 (a), (b) and (c) can be isolated and purified by those methods known per se, i. e. such customarily used separation means as column chromatography using silica gel, adsorbent resin or the like, liquid chromatography, thin-layer chromatography, solvent extraction or recrystallization and reprecipitation.
10

The compounds of the present invention and intermediates thereof exist in stereoisomeric forms such as enantiomeric isomers, diastereoisomers and geometrical isomers. It is to be understood that the compounds
15 of the present invention also include all such stereoisomerically pure substances and mixtures thereof. When the compounds of the present invention and intermediates thereof are racemates, their optical resolution can be achieved by conventional means such as high-performance
20 liquid chromatography using a chiral carrier or fractional crystallization of a diastereomeric salt.

The compounds of formula [I] obtained in the above-described manner may be converted into pharmaceutically acceptable salts thereof according to usual
25 manner. Conversely, such salts may also be converted into the corresponding free amines according to usual manner.

The compounds of formula [I] in accordance with the present invention exhibit potent and selective
30 inhibitory activity for binding to muscarinic receptors, a potent and selective antagonism to muscarinic receptors in vitro and, furthermore, potent and durable bronchodilatory action in vivo. These activities exhibited by the compounds of the present invention are
35 demonstrated by the following tests on the inhibition of binding to muscarinic receptors and tests on antagonism

against various muscarinic receptors.

Tests on inhibition of binding to muscarinic receptors

These tests were performed according to a modification of the method of Hargreaves et al. (Br. J. Pharmacol. 107: 494-501, 1992). Muscarinic receptors m1-m5 expressed in CHO cells (Receptor Biology, Inc.) were incubated with 0.2 nM [3 H]-N-methylscopolamine (84Ci/mmol, New England Nuclear, Inc.) and a test compound to be tested in 0.5 ml of 50 mM Tris-HCl - 10 mM MgCl₂ - 1 mM EDTA (pH 7.4) for 120 minutes at room temperature (about 20-25°C), followed by suction filtration over glass filters (UniFilter-GF/C; Packard). Then the filter was washed four times with 1 ml of ice-cold Tris-HCl buffer and dried at 50°C for an hour. After adding a scintillator (Microscinti 0; Packard), the radioactivity of [3 H]-N-methylscopolamine binding to the filter was counted by a microplate scintillation counter (TopCountTM; Packard). Non-specific binding of [3 H]-N-methylscopolamine was measured by adding 1 μ M N-methylscopolamine. According to the method of Cheng and Prussoff (Biochem. Pharmacol. 22: 3099-3108, 1973), the binding affinity (K_i value) of a compound of the present invention for muscarinic receptors was calculated from the concentration of the test compound which achieved 50% inhibition of binding of [3 H]-N-methylscopolamine, labeled ligand (IC₅₀ value).

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Table 1

Inhibitory Effects on Binding to
Muscarinic m_2 and m_3 Receptors

5

10

15

20

	K _i (nM)		m_2/m_3
	m_2	m_3	
Compound of Example 1	3200	5.5	590
Compound of Example 10	17000	8.9	1900
Compound of Example 11	460	3.2	140
Compound of Example 12	8600	30	290
Compound of Example 14	1400	10	140
Compound of Example 15	1000	3.5	290
Compound of Example 20	550	3.0	180
Compound of Example 21	50000	22	2300
Compound of Example 22	13000	19	680
Compound of Example 26	24000	22	1100
Compound of Example 27	4200	20	210
Compound of Example 31	10000	19	520

As is clear from the results indicated in
above Table 1, those compounds of the present invention
exhibited far higher binding-inhibitory activity to m_3
receptor, than to m_2 receptor.

Tests for Antagonism to Muscarinic Receptors (in vitro)

1) Tests for antagonism to M_2 receptor in an isolated
rat right atrium

These tests were performed according to a
conventional method. A male SD strain rat (weighing
300-500 g) was killed by exsanguination, and the right
atrium was isolated. This preparation was isometrically
suspended in organ bath filled with 20 ml of Krebs-

Henseleit solution (gassed with 95% O₂ - 5% CO₂ and kept at 32°C) with an initial tension of 0.5 g. The heart rate was recorded with a heart rate counter. After the preparation was equilibrated for 30 minutes, carbachol (10⁻⁹ to 10⁻⁸ M) was cumulatively administered in three-fold increasing doses. Thus, a decrease in heart rate was measured to obtain a dose-response curve for the control experiment. After the preparation was washed with fresh solution to restore the heart rate, a test compound was administered thereto. Ten minutes later, carbachol was cumulatively administered again. Responses to carbachol were expressed as percentages based on the heart rate before administration of carbachol as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with individual test compound of the present invention.

2) Tests for antagonism to the airway M₃ receptor in an isolated rat trachea

These tests were performed according to a conventional method. A male SD strain rat (weighing 300-500 g) was killed by exsanguination, and the trachea was isolated. Annular segments (2 mm wide) were cut out from the trachea and cut transversely at the anterior cartilage part to make open ring preparation. A preparation was suspended in a Magnus tube filled with 5 ml of Krebs-Henseleit solution (gassed with 95% O₂ - 5% CO₂ and kept at 32°C) with an initial tension of 1.0 g and a resting tension of 0.6 g. The tension of the preparation was recorded isometrically. After being equilibrated for an hour, the preparation was made to contract twice by treatment with 10⁻⁴ M carbachol, and the second contraction induced by carbachol was used as the reference contraction. After the preparation was washed with fresh solution to be restored to the base line, a test compound was administered thereto (or no treatment was

given). Ten minutes later, carbachol (10^{-8} to 10^{-3} M) was cumulatively administered in three-fold increasing doses to obtain a dose-response curve. The dose-response curve was plotted by expressing responses as percentages based on the reference contraction of the preparation as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with the test compound.

TABLE 2

Antagonism to Muscarinic Receptors (in vitro)

	K_B (nM)		M_2/M_3
	right atrium M_2	Trachea M_3	
Compound of Example 1	1000	6.3	160
Compound of Example 11	610	0.95	640
Compound of Example 20	2100	1.6	630

As is clear from the results indicated in above Table 2, the compounds of the present invention exhibited far more powerful antagonism to the trachea M_3 receptor than to the right atrium M_2 receptor. Therefore, the compounds of the present invention are more selective for trachea M_3 receptor.

Tests for antagonism against muscarinic M_3 receptor (in vivo)

1-A) Tests for bronchodilation in rats (i.v.)

Eight- to eleven-weeks-old male rats of the Sprague-Dawley strain, weighing 380-420 g, were anesthetized with urethane (750 mg/kg, i.p.) and α -chloralose (37.5 mg/kg, i.p.). The bronchus of each rat was intubated, and the right jugular vein was cannulated for

drug administration. After spontaneous respiration was fully suppressed by succinylcholine (5 mg/body, s.c.), the airway resistance was measured under artificial ventilation by means of a Pulmonary Mechanics Model 6 (Buxco). The acetylcholine (50 μ g/kg, i.v.)-induced airway resistance increase was measured 5 minutes before and 5 minutes after administration of test compound, and the ratio of the airway resistance of the latter to the former was calculated. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the calculated ratio of the airway resistance being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50} , and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

1-B) Tests for bronchodilation in rats (p.o.)

Eight- to eleven-weeks-old male rats of Sprague-Dawley strain weighing 380-420 g were orally administered with a test compound. The rats were treated in the identical manner as in the i.v. test, starting 30 minutes after the administration, and their airway resistance values were measured. The acetylcholine-(50 μ g/kg, i.v.) induced airway resistance increase were measured 60 minutes after the administration of test compounds. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the airway resistance values being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50} , and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

TABLE 3

Antagonism to Muscarinic Receptor (in vivo)

	Inhibition of Airway Contraction ED ₅₀ (mg/kg)	
	iv	po
Compound of Example 1	0.033	—
Compound of Example 11	0.032	0.22
Compound of Example 20	0.040	0.37
Compound of Example 26	0.37	0.95
atropine	0.0043	—
ipratropium	0.0015	—

2) Tests for bronchodilation in dogs (p.o.)

Twelve- to twenty-four-months-old male beagle dogs (weighing 10-15 kg) were anesthetized with pento-
 20 barbital (30 mg/kg, i.v.) and intubated in their bron-
 chus. Their airway sensitivity (methacholine inhalation
 threshold value) were measured by means of the metha-
 choline provocation test at least twice at two-weeks
 interval, and the dogs showing a reproducible metha-
 25 choline reaction threshold values¹⁾ were selected. To
 those dogs whose methacholine reaction threshold value
 had been confirmed, the test compounds were orally
 administered (1 mg/kg). Four hours after the adminis-
 30 tration, the methacholine provocation test was con-
 ducted, and then the methacholine reaction threshold
 value²⁾ after administration of the test compound was
 obtained.

The bronchodilator activity of the test com-
 pound was determined following equation:

shift value =

methacholine reaction threshold value¹⁾
after drug administration

methacholine reaction threshold value²⁾
without drug administration

5

The methacholine provocation test was conducted using Astograph TCK-6100H Model (Chest). Methacholine chloride was used as bronchoconstrictor, which was diluted with isotonic sodium chloride solution in 10-grade concentration levels starting from 40,000 $\mu\text{g/ml}$, as 20,000, 10,000, 5,000, 2,500, 1,250, 625, 312.5, 156 and 78 $\mu\text{g/ml}$. These methacholine aerosols were inhaled to the test animal each for 1 min, starting from the lowest concentration level, and respiration resistance was continuously recorded. The concentration level at which the respiration resistance reached twice the initial value was recorded as the methacholine threshold value.

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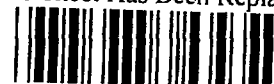


TABLE 4

Bronchodilation Activity in Dogs
(Oral Administration)

25

	Methacholine Provocation Test (1 mg/kg, p.o.)
	shift value (after 4 hrs.)
Compound of Example 11	21
Compound of Example 20	>69
Compound of Example 26	>64

30

35

As clearly demonstrated in above Table 4, the compounds of the present invention exhibited powerful

bronchodilation action and long duration of the action.

As above, the compounds of formula [I] of the present invention, which are characterized by introduction of fluorine atom(s) thereinto, exhibit potent and
5 selective antagonistic activity against muscarinic M_3 receptors and exhibit excellent oral activity, duration of action and pharmacokinetics. Hence, they can be administered to patients orally or parenterally as safe pharmaceuticals exhibiting little side effects, in the
10 treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contrac-
15 tion of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis: and motion sickness.

20 In practically using the compounds of the present invention for the treatment or prophylaxis of such diseases, they may be combined with pharmaceutically acceptable adjuvants in the usual manner to prepare pharmaceutical compositions suitable for administration.
25 For this purpose, there can be used a variety of adjuvants which are commonly used in the field of pharmaceuticals. Such adjuvants include, for example, gelatin, lactose, sucrose, titanium oxide, starch, crystalline cellulose, hydroxypropylmethylcellulose, carboxymethyl-
30 cellulose, corn starch, microcrystalline wax, white petrolatum, magnesium aluminate metasilicate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropyl cellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxy-
35 ethylene, hardened castor oil, polyvinyl pyrrolidone, magnesium stearate, light anhydrous silicic acid, talc,

vegetable oil, benzyl alcohol, acacia, propylene glycol, polyalkylene glycol, cyclodextrin and hydroxypropyl-cyclodextrin.

5 The dosage forms of pharmaceutical compositions prepared by using these adjuvants include solid preparations such as tablets, capsules, granules, powders and suppositories; liquid preparations such as syrups, elixirs and injections; and the like. These preparations may be formulated according to conventional
10 techniques well-known in the field of pharmaceuticals. Liquid preparations may be in a form which is dissolved or suspended in water or other suitable medium prior to use. In particular, injections may be in the form of a solution or suspension in physiological saline solution
15 or a glucose solution, or in powder form for reconstitution by dissolution or suspension in physiological saline or a glucose solution prior to use. If desired, such injections may contain buffer agents and/or preservatives.

20 As preparations for oral administration, such formulation forms, besides ordinary tablets, capsules, granules, powders and the like, aerosols or dry powders for inhalation, elixirs containing spices or coloring agents or suspensions may be employed.

25 In these pharmaceutical compositions, a compound in accordance with the present invention may be present at a ratio of from 1.0 to 100% by weight, preferably 1.0 to 60% by weight, based on the total weight of the composition. These pharmaceutical compositions
30 may additionally contain other therapeutically effective compounds.

 When the compounds of the present invention are used as drugs, their dosage level and dosage schedule may vary according to the sex, age and body weight
35 of the patient, the severity of symptoms, the type and range of the desired therapeutic effect, and the like.

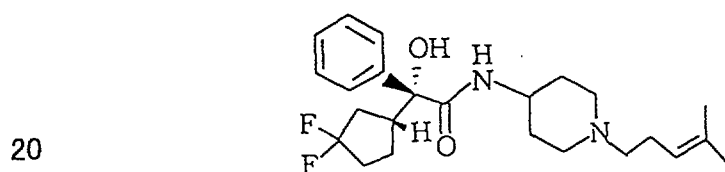
Generally for oral administration, they are preferably administered in a daily dose of 0.1 to 100 mg/kg for adults and this daily dose may be given at a time or in several divided doses. For parenteral administration, they are preferably administered in a daily dose of 0.001 to 10 mg/kg for adults and this daily dose may be given at a time or in several divided doses.

Hereinafter the present invention is more specifically explained with reference to working examples, it being understood that the examples are in no way limitative of the scope of the invention.

Example 1

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



Step 1. Synthesis of 1-(4-methyl-3-pentenyl)-4-piperidone

To a solution of 2.5 g of 4-piperidone monohydrochloride monohydrate in 150 ml of acetonitrile, 11 g of potassium carbonate, 2.62 g of 5-bromo-2-methyl-2-pentene and 800 mg of potassium iodide were added sequentially, and the mixture was heated under reflux for 3 hours. The reaction mixture was diluted with ethyl acetate, washed with water and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 2.24 g of the title compound was obtained as a white solid.

Step 2. Synthesis of 4-amino-1-(4-methyl-3-pentenyl)-piperidine

To a solution of 2.2 g of 1-(4-methyl-3-

pentenyl)-4-piperidone in 60 ml of methanol, 1.1 g of ammonium acetate and 860 mg of sodium cyanoborohydride were added sequentially, at room temperature, followed by stirring overnight at same temperature. Distilling the methanol off under reduced pressure, the pH of the reaction media was adjusted to 3 with 1N hydrochloric acid, followed by washing with diethyl ether. The aqueous layer was basified with 1N aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 1.9 g of the title compound was obtained as a colorless oil.

Step 3. Synthesis of (2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

To a solution of 75 mg of (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid in 3 ml of N,N-dimethylformamide, 55 mg of 1,1'-carbonyldiimidazole was added at room temperature, followed by stirring for 2 hours at the same temperature. Then 60 mg of 4-amino-1-(4-methyl-3-pentenyl)piperidine and 5 mg of 4-dimethylaminopyridine were added sequentially, followed by stirring overnight at room temperature. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by preparative thin layer chromatography [KieselgelTM 60F₂₅₄, Art 5744 (Merck); chloroform / methanol = 10/1], to provide 23 mg of the title compound as an oil.



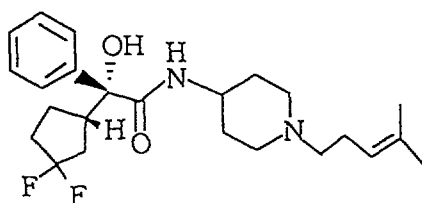
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.32–1.50 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 1.58–2.34 (12H, m), 2.43–2.49 (1H, m), 2.73–2.82 (3H, m), 3.23–3.36 (1H, m), 3.48 (1H, brs), 3.62–3.73 (1H, m), 5.03–5.08 (1H, m), 6.29–6.33 (1H, m), 7.25–7.39 (3H, m), 7.54–7.57 (2H, m)

low resolution FAB-MS (m/e , ($\text{C}_{24}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_2 + \text{H}^+$): 421.

Example 2

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



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The title compound was prepared in the same manner as described in step 3 of Example 1 using (2R)-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

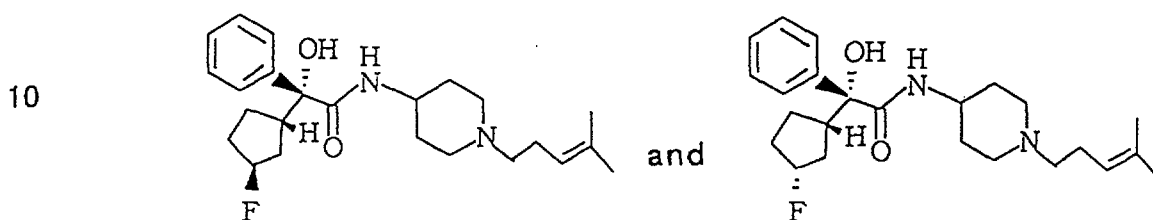
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.60 (3H, s), 1.68 (3H, s), 1.35–2.48 (15H, m), 2.75–2.86 (3H, m), 3.22–3.36 (1H, m), 3.48 (1H, brs), 3.61–3.76 (1H, m), 5.03–5.08 (1H, m), 6.27 (1H, d, $J = 8.0 \text{ Hz}$), 7.26–7.40 (3H, m), 7.55–7.58 (2H, m)

low resolution FAB-MS (m/e , ($\text{C}_{24}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_2 + \text{H}^+$): 421.

Example 3

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-
[(1S, 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl-
acetamide and (2R)-N-[1-(4-methyl-3-pentenyl)-
5 piperidin-4-yl]-2-[(1S, 3R)-3-fluorocyclopentyl]-2-
hydroxy-2-phenylacetamide

Structural formulae



The title compounds were prepared using (2R)-
15 [(1S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic
acid, in the same manner as described in step 3 in
Example 1, and separated in the final step.

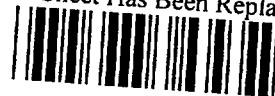
(2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-
[(1S, 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl-
20 acetamide

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1. 60 (3H, s), 1. 68
(3H, s), 1. 31-2. 33 (15H, m), 2. 44-2. 49
(1H, m), 2. 69-2. 81 (2H, m), 3. 19-3. 30
25 (1H, m), 3. 62-3. 74 (1H, m), 3. 90 (1H,
b r s), 5. 03-5. 28 (2H, m), 5. 87-5. 91 (1H,
m), 7. 25-7. 40 (3H, m), 7. 53-7. 57 (2H, m)

low resolution FAB-MS (m/e , ($\text{C}_{24}\text{H}_{35}\text{FN}_2\text{O}_2$ +
30 H^+): 403

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(2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1S,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

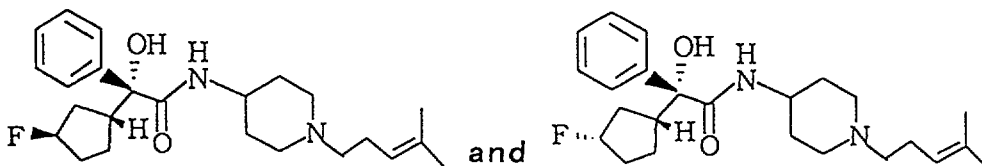
5 $^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1. 61 (3H, s), 1. 68 (3H, s), 1. 37-2. 26 (14H, m), 2. 32-2. 37 (2H, m), 2. 75-2. 90 (2H, m), 3. 43-3. 56 (1H, m), 3. 62-3. 76 (1H, m), 5. 04-5. 13 (2H, m), 6. 91-6. 95 (1H, m), 7. 23-7. 35 (3H, m), 7. 67-7. 71 (2H, m)

low resolution FAB-MS (m/e , ($\text{C}_{24}\text{H}_{35}\text{FN}_2\text{O}_2 + \text{H}^+$): 403.

Example 4

15 (2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide and (2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1R,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

20 Structural formulae



25

The title compounds were prepared using (2R)-[(1R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, in the same manner as described in step 3 in Example 1, and separated in the final step.

30 (2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1. 60 (3H, s), 1. 70 (3H, s), 1. 38-2. 17 (14H, m), 2. 27-2. 32 (2H, m), 2. 70-2. 81 (2H, m), 3. 19-3. 32

(1 H, m), 3.63–3.74 (1 H, m), 3.93 (1 H, brs), 5.00–5.21 (2 H, m), 5.96–6.02 (1 H, m), 7.26–7.38 (3 H, m), 7.55–7.58 (2 H, m)

5 low resolution FAB-MS (m/e, (C₂₄H₃₅FN₂O₂ + H)⁺): 403

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

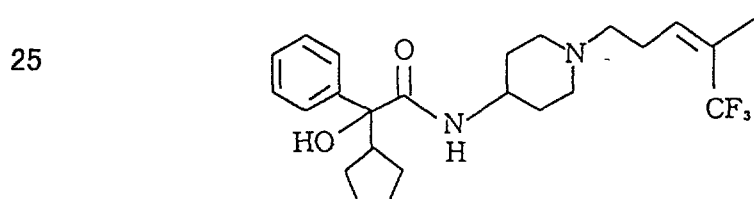
10 ¹H-NMR (CDCl₃, δ ppm): 1.60 (3 H, s), 1.68 (3 H, s), 1.38–2.32 (6 H, m), 2.74–2.88 (2 H, m), 3.41–3.52 (1 H, m), 3.63–3.74 (1 H, m), 5.02–5.21 (2 H, m), 6.90 (1 H, d, J = 8.2 Hz), 7.23–7.35 (3 H, m), 7.66–7.69 (2 H, m)

low resolution FAB-MS (m/e, (C₂₄H₃₅FN₂O₂ + H)⁺): 403.

20 Example 5

N-[1-[(3Z)-4-trifluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

Structural formula



30 Step 1. Synthesis of N-(piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide

To a solution of 3.51 g of 2-cyclopentyl-2-hydroxy-2-phenylacetic acid in 40 ml of N,N-dimethylformamide, 2.63 g of 1,1'-carbonyldiimidazole was added and stirred at room temperature for 2 hours. To the reaction mixture 3.96 g of 4-amino-1-(t-butoxycarbonyl)-piperidine monohydrochloride, 200 mg of 4-dimethylamino-

pyridine and 6.9 ml of diisopropylethylamine were added, followed by stirring overnight at room temperature. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture followed by an extraction with
5 diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 3/1) to
10 provide 2.84 g of a white solid. The solid was dissolved in 30 ml of 10% hydrochloric acid-methanol, and stirred overnight at room temperature. Distilling the methanol off under reduced pressure, the residue was diluted with water and washed with diethyl ether. The
15 aqueous layer was made basic with sodium hydroxide and extracted with chloroform. The organic layer was washed with water and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 2.15 g of the title compound was
20 obtained as a white solid.

Step 2. Synthesis of (3Z)-4-trifluoromethyl-3-pentenyl t-butyldiphenylsilyl ether

To a solution of 2.94 g of (3-t-butyldiphenylsilyl oxypropyl)triphenylphosphonium bromide in 40 ml of
25 tetrahydrofuran, 2.5 ml of 1.7 M hexane solution of n-butyllithium was added dropwise at -78°C . The temperature was raised to -20°C . After stirring for an hour at said temperature, reaction mixture was cooled to -78°C into which 0.5 ml of trifluoroacetone was added drop-
30 wise, followed by stirring overnight while raising the temperature to room temperature. The reaction liquid was diluted with hexane, washed with 10% hydrochloric acid, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under
35 reduced pressure, resulting residue was purified by silica gel column chromatography (developing solvent:

hexane / ethyl acetate = 9/1) to provide 1.44 g of the title compound.

Step 3. Synthesis of (3Z)-4-trifluoromethyl-3-pentenol

To a solution of 1.44 g of (3Z)-4-trifluoro-
5 methyl-3-pentenyl t-butyl-diphenylsilyl ether in 8 ml of tetrahydrofuran, 4.4 ml of 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added, followed by stirring for 2 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with
10 water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: ethyl acetate) to provide 414 mg of the title compound.

15 Step 4. Synthesis of (3Z)-4-trifluoromethyl-3-pentenyl p-toluenesulfonate

To a solution of 414 mg of (3Z)-4-trifluoromethyl-3-pentenol in 6 ml of pyridine, 565 mg of p-toluenesulfonyl chloride was added under cooling with
20 ice, followed by stirring for 16 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by
25 silica gel column chromatography (developing solvent: hexane / ethyl acetate = 9/1) to provide 412 mg of the title compound.

Step 5. Synthesis of N-[1-[(3Z)-4-trifluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide
30

To a solution of 77 mg of N-(piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide in 3 ml of N,N-dimethylformamide, 74 mg of (3Z)-4-trifluoromethyl-3-pentenyl p-toluenesulfonate, 102 mg of potassium carbonate and 43 mg of potassium iodide were added by the
35 order stated at room temperature, followed by 3 hours'

heating under reflux. The reaction liquid was diluted with diethyl ether, washed with water and saturated saline solution by the order stated, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art 5744 (Merck) chloroform / methanol = 9/1) to provide 27 mg of the title compound as an oily substance.

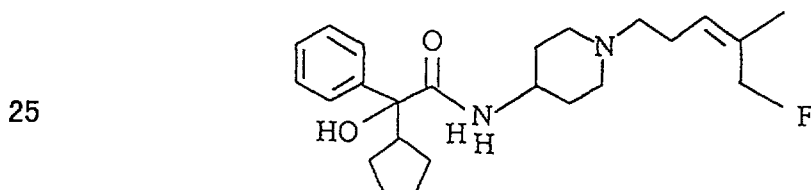
¹H-NMR (CDCl₃, δ ppm) : 1. 12-1. 88 (16 H, m), 1. 83 (3 H, s), 2. 01-2. 13 (2 H, m), 2. 68-2. 80 (2 H, m), 2. 97-3. 10 (1 H, m), 3. 13 (1 H, br s), 3. 62-3. 76 (1 H, m), 5. 65-5. 72 (1 H, m), 6. 32 (1 H, d, J=8. 5 Hz), 7. 23-7. 36 (3 H, m), 7. 59 (2 H, d, J=7. 3 Hz)

low resolution FAB-MS (m/e, (C₂₄H₃₃F₃N₂O₂ + H)⁺): 439.

Example 6

N-[1-[(3Z)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared by the procedures similar to steps 2-5 of Example 5, using fluoroacetone.

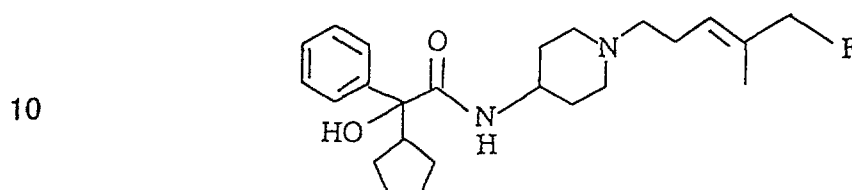
¹H-NMR (CDCl₃, δ ppm) : 1. 04-2. 16 (14 H, m), 1. 79 (3 H, s), 2. 16-2. 28 (2 H, m), 2. 28-2. 40 (2 H, m), 2. 66-2. 86 (2 H, m), 2. 94-3. 24 (2 H, m), 3. 62-3. 78 (1 H, m), 4. 86 (2 H, d, J=47. 5 Hz), 5. 34-5. 44 (1 H, m), 6.

3.6 (1H, d, $J = 8.3$ Hz), 7.22–7.40 (3H, m),
7.56–7.64 (2H, m)

Example 7

5 N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



Step 1. Synthesis of (2E)-5-bromo-2-methyl-2-pentenol

To a solution of 681 mg of selenium dioxide in
15 10 ml of dichloromethane, 2.5 ml of t-butyl peroxide was
added at room temperature, stirred for 30 minutes at
said temperature, and further 2.0 g of 5-bromo-2-methyl-
2-pentene was added, followed by stirring for 2 hours.
The reaction mixture was diluted with diethyl ether,
20 washed with aqueous sodium thiosulfate solution, 10%
aqueous potassium hydroxide solution, and then with
brine, and dried over anhydrous magnesium sulfate.
Distilling the solvent off under reduced pressure, the
residue was purified by silica gel column chromatography
25 (developing solvent: hexane / ethyl acetate = 20/1 -
4/1) to provide 1.24 g of the title compound.

Step 2. Synthesis of (2E)-5-bromo-2-methyl-2-pentenyl t-butyldimethylsilyl ether

To a solution of 300 mg of (2E)-5-bromo-2-
30 methyl-2-pentenol in 10 ml of N,N-dimethylformamide, 302
mg of t-butyldimethylsilyl chloride and 137 mg of imida-
zole were added, followed by stirring for an hour at
room temperature. The reaction liquid was diluted with
diethyl ether, washed with water and then with brine,
35 and dried over anhydrous magnesium sulfate. Distilling
the solvent off under reduced pressure, 604 mg of the

title compound was obtained.

Step 3. Synthesis of N-[1-[(3E)-4-t-butyldimethylsilyloxymethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

5 The title compound was prepared by the method similar to step 5 of Example 5, using (2E)-5-bromo-2-methyl-2-pentenyl t-butyldimethylsilyl ether.

Step 4. Synthesis of N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

10 To a solution of 59 mg of tetrabutylammonium fluoride trihydrate in 3 ml of tetrahydrofuran, 200 mg of molecular sieves 4A, 31 mg of N-[1-[(3E)-4-t-butyldimethylsilyloxymethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide and 22 mg of p-toluenesulfonyl fluoride were added sequentially, followed by overnight heating under reflux at 80°C. After removal of the insoluble material by filtration, the solvent was distilled off under reduced pressure.

20 The remaining residue was purified by preparative thin layer chromatography [KieselgelTM 60F₂₅₄, Art 5744 (Merck); chloroform / methanol = 20/1], to provide 11 mg of the title compound as an oily substance.

25 ¹H-NMR (CDCl₃, δ ppm) : 1.10-1.76 (10H, m), 1.70 (3H, s), 1.76-1.95 (2H, m), 1.95-2.42 (6H, m), 2.72-2.88 (2H, m), 2.94-3.24 (2H, m), 3.62-3.78 (1H, m), 4.69 (2H, d, J=47.8 Hz), 5.44-5.54 (1H, m), 6.37 (1H, d, J=8.0 Hz), 7.22-7.40 (3H, m), 7.56-7.64 (2H, m)

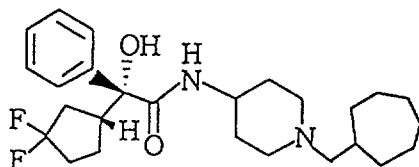
30

low resolution FAB-MS (m/e, (C₂₄H₃₅FN₂O₂ + H)⁺): 403

Example 8

(2R)-N-(1-cycloheptylmethylpiperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

5 Structural formula



10

The title compound was prepared by a method similar to the steps 1 and 5 of Example 5, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid and cycloheptylmethyl methanesulfonate.

15

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1. 03–2. 27 (27 H, m) , 2. 63–2. 71 (2 H, m) , 3. 21–3. 33 (1 H, m) , 3. 49 (1 H, br s) , 3. 61–3. 72 (1 H, m) , 6. 23 (1 H, d, $J = 8.3 \text{ Hz}$) , 7. 27–7. 39 (3 H, m) ,
20 7. 53–7. 57 (2 H, m)

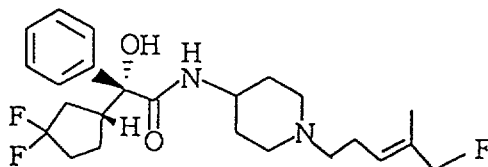
low resolution FAB-MS (m/e , $(\text{C}_{28}\text{H}_{38}\text{F}_2\text{N}_2\text{O}_2 + \text{H})^+$): 449.

Example 9

25 (2R)-N-[1-[(3E)-4-fluoromethyl-3-pentenyl]-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula

30



The title compound was prepared by a method similar to Example 7, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

35

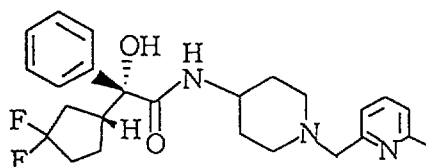
¹H-NMR (CDCl₃, δ ppm) : 1.34-1.52 (2H, m), 1.69 (3H, s), 1.75-2.31 (12H, m), 2.31-2.46 (2H, m), 2.72-2.86 (2H, m), 3.24-3.38 (1H, m), 3.43 (1H, brs), 3.62-3.78 (1H, m), 4.69 (2H, d, J=47.8 Hz), 5.42-5.52 (1H, m), 6.34 (1H, d, J=7.9 Hz), 7.24-7.42 (3H, m), 7.52-7.60 (2H, m)

low resolution FAB-MS (m/e, (C₂₄H₃₃F₃N₂O₂ + H)⁺): 439.

Example 10

(2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



Step 1. Synthesis of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

The title compound was prepared by a method similar to the step 1 of Example 5, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

Step 2. Synthesis of (2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

To a solution of 17 mg of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide in 2 ml of tetrahydrofuran, 3 μl of acetic acid, 12 mg of 6-methylpyridine-2-carbaldehyde and 21 mg of sodium triacetoxyborohydride were added sequentially at room temperature, and stirred overnight at the same temperature. The reaction mixture was

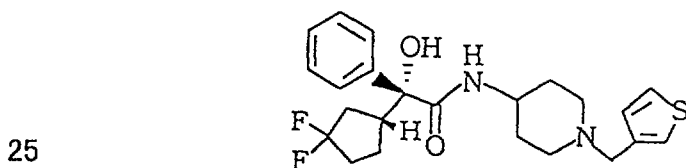
diluted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (Kiesel-
 5 gel™ 60F₂₅₄, Art 5744 (Merck) chloroform / methanol = 10/1) to provide 9 mg of the title compound as a solid substance.

¹H-NMR (CDCl₃, δ ppm) : 1.35–1.50 (2 H, m), 1.72–2.23 (10 H, m), 2.53 (3 H, s), 2.
 10 70–2.80 (2 H, m), 3.21–3.35 (1 H, m), 3.59 (2 H, s), 3.60–3.78 (1 H, m), 6.31 (1 H, d, J = 8.5 Hz), 7.02 (1 H, t, J = 7.6 Hz), 7.18 (1 H, d, J = 7.6 Hz), 7.28–7.39 (3 H, m), 7.
 15 50 (1 H, d, J = 7.6 Hz), 7.53–7.59 (2 H, m)

Example 11

(2R)-N-[1-(3-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
 20 amide

Structural formula



The title compound was prepared by a method similar to the step 2 of Example 10 using thiophene-3-aldehyde.

30 ¹H-NMR (CDCl₃, δ ppm) : 1.30–1.50 (2 H, m), 1.56–2.30 (10 H, m), 2.66–2.82 (2 H, m), 3.22–3.37 (1 H, m), 3.40 (1 H, s), 3.49 (2 H, s), 3.61–3.78 (1 H, m), 6.25 (1 H, d, J = 8.2 Hz), 7.02 (1 H, dd, J = 1.1 Hz, 7.6 Hz),
 35

7. 06-7. 12 (1H, m), 7. 22-7. 42 (4H, m), 7. 50-7. 60 (2H, m)

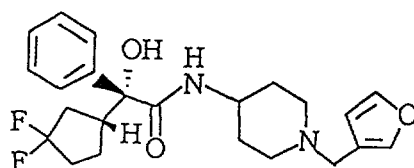
low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_2S + H)^+$): 435.

5 Example 12

(2R)-N-[1-(3-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

Structural formula

10



15

The title compound was prepared by a method similar to the step 2 of Example 10, using furan-3-aldehyde.

1H -NMR ($CDCl_3$, δ ppm) : 1. 32-1. 47 (2H, m), 1. 73-2. 27 (10H, m), 2. 70-2. 78 (2H, m), 3. 24-3. 35 (1H, m), 3. 33 (2H, s), 3. 42 (1H, s), 3. 62-3. 75 (1H, m), 6. 26 (1H, d, $J = 7.2$ Hz), 6. 34 (1H, s), 7. 27-7. 40 (5H, m), 7. 52-7. 57 (2H, m)

25

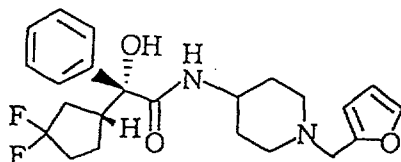
low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_3 + H)^+$): 419.

Example 13

(2R)-N-[1-(2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

Structural formula

35



The title compound was prepared by a method similar to the step 2 of Example 10, using furan-2-aldehyde.

¹H-NMR (CDCl₃, δ ppm) : 1.35–1.49 (2H, m), 1.73–2.25 (10H, m), 2.70–2.80 (2H, m), 3.23–3.35 (1H, m), 3.48 (1H, s), 3.49 (2H, s), 3.61–3.73 (1H, m), 6.17 (1H, d, J = 3.0 Hz), 6.27–6.31 (2H, m), 7.27–7.38 (4H, m), 7.52–7.56 (2H, m)

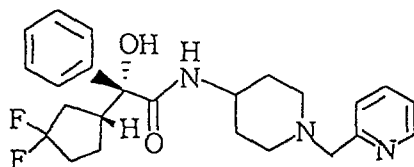
low resolution FAB-MS (m/e, (C₂₃H₂₈F₂N₂O₃ + H)⁺): 419.

Example 14

(2R)-N-[1-(2-pyridylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula

20



The title compound was prepared by a method similar to the step 2 of Example 10, using pyridine-2-aldehyde.

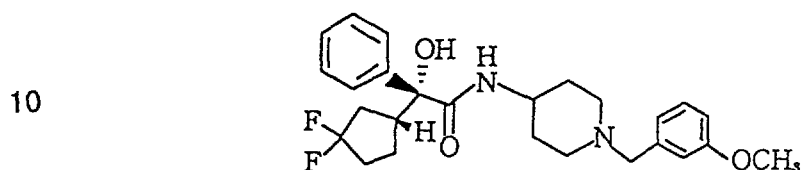
¹H-NMR (CDCl₃, δ ppm) : 1.39–1.52 (2H, m), 1.75–2.25 (10H, m), 2.70–2.80 (2H, m), 3.24–3.36 (1H, m), 3.58 (1H, s), 3.61 (2H, s), 3.67–3.77 (1H, m), 6.32 (1H, d, J = 7.8 Hz), 7.15 (1H, ddd, J = 1.2 Hz, 4.8 Hz, 7.6 Hz), 7.27–7.39 (4H, m), 7.53–7.57 (2H, m), 7.63 (1H, td, J = 1.8 Hz, 7.6 Hz), 8.52 (1H, ddd, J = 1.2 Hz, 1.8 Hz, 3.0 Hz)

low resolution FAB-MS (m/e , $(C_{24}H_{29}F_2N_3O_2 + H)^+$): 430.

Example 15

(2R)-N-[1-(3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-
3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

Structural formula



To a solution of 71 mg of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl-
 15 acetamide in 2 ml of N,N-dimethylformamide, 74 mg of 3-methoxybenzyl chloride and 80 mg of potassium carbonate were added at room temperature, followed by stirring for about 12 hours. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and
 20 dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (KieselgelTM 60F₂₅₄, Art 5744 (Merck) chloroform / methanol = 9/1) to provide 75 mg of the title compound
 25 as a white solid.

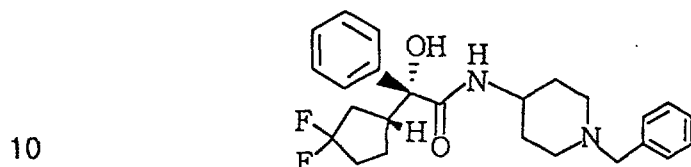
¹H-NMR (CDCl₃, δ ppm) : 1.32-1.54 (2 H, m), 1.65-2.30 (10 H, m), 2.68-2.85 (2 H, m), 3.21-3.39 (1 H, m), 3.42 (1 H, s) 3.45
 30 (2 H, s), 3.62-3.78 (1 H, m), 3.80 (3 H, s), 6.27 (1 H, d, J=8.2 Hz), 6.76-6.83 (1 H, m), 6.84-6.90 (2 H, m), 7.21 (1 H, t, J=8.0 Hz), 7.24-7.40 (3 H, m), 7.51-7.59 (2 H, m)
 35

low resolution FAB-MS (m/e , $(C_{28}H_{32}F_2N_2O_3 + H)^+$): 459.

Example 16

5 (2R)-N-(1-benzylpiperidin-4-yl)-2-[(1R)-3,3-
difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared in the same manner as described in Example 15 using benzyl bromide.

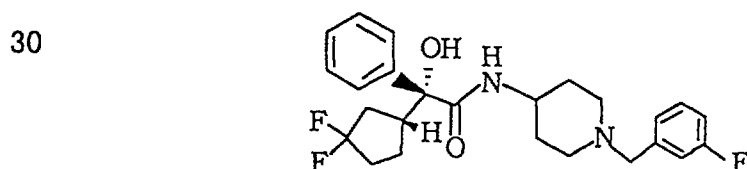
15 1H -NMR ($CDCl_3$, δ ppm) : 1.35–1.52 (2H, m), 1.70–2.23 (10H, m), 2.70–2.81 (2H, m), 3.22–3.34 (1H, m), 3.41 (1H, s) 3.48 (2H, s), 3.60–3.80 (1H, m), 6.27 (1H, d, $J = 8.0$ Hz), 7.24–7.39 (8H, m), 7.54–7.56
20 (2H, m)

low resolution FAB-MS (m/e , $(C_{25}H_{30}F_2N_2O_2 + H)^+$): 429.

Example 17

25 (2R)-N-[1-(3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-
3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

Structural formula



35 The title compound was prepared in the same manner as described in Example 15 using 3-fluorobenzyl chloride.

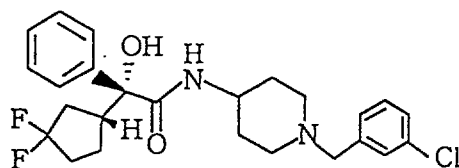
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.34–1.52 (2H, m), 1.52–2.30 (10H, m), 2.65–2.80 (2H, m), 3.22–3.38 (1H, m), 3.40 (1H, s) 3.72 (2H, s), 3.60–3.80 (1H, m), 6.28 (1H, d, $J = 7.7 \text{ Hz}$), 6.88–6.97 (1H, m), 7.00–7.10 (2H, m), 7.20–7.42 (4H, m), 7.51–7.60 (2H, m)

low resolution FAB-MS (m/e , $(\text{C}_{25}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_2 + \text{H})^+$): 447.

Example 18

(2R)-N-[1-(3-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared in the same manner as described in Example 15 using 3-chlorobenzyl chloride.

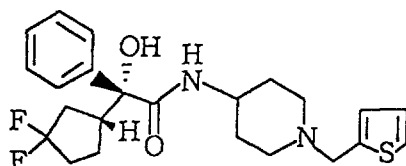
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.33–1.50 (2H, m), 1.60–2.25 (10H, m), 2.67–2.77 (2H, m), 3.24–3.38 (1H, m), 3.44 (2H, s) 3.63–3.76 (1H, m), 6.29 (1H, d, $J = 8.0 \text{ Hz}$), 7.13–7.40 (7H, m), 7.53–7.57 (2H, m).

low resolution FAB-MS (m/e , $(\text{C}_{25}\text{H}_{29}\text{ClF}_2\text{N}_2\text{O}_2 + \text{H})^+$): 463.

Example 19

(2R)-N-[1-(2-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

5 Structural formula



10

The title compound was prepared in the same manner as described in Example 15 using 2-thienylmethyl chloride.

15 $^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.32–1.50 (2H, m), 1.52–2.30 (10H, m), 2.70–2.82 (2H, m), 3.22–3.36 (1H, m), 3.41 (1H, s) 3.62–3.76 (1H, m), 3.68 (2H, s), 6.26 (1H, d, $J=7.9\text{ Hz}$), 6.87 (1H, dd, $J=3.2\text{ Hz}$, 4.8 Hz),
 20 6.92 (1H, dd, $J=3.2\text{ Hz}$, 4.8 Hz) 7.21 (1H, dd, $J=1.5\text{ Hz}$, 4.8 Hz), 7.24–7.40 (3H, m), 7.50–7.58 (2H, m)

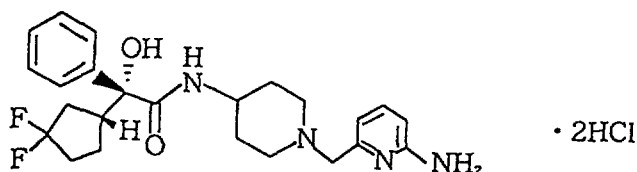
25 low resolution FAB-MS (m/e , ($\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_2\text{O}_2\text{S} + \text{H}$) $^+$): 435.

Example 20

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide dihydrochloride

30

Structural formula



35

The compound of Example 20 was prepared by the following methods 1, 2 and 3.

Method 1:

Step 1. Synthesis of 6-tert-butyl diphenylsilyloxy-
5 methylpyridine-2-carboxylic acid

To a solution of 1.8 g of ethyl 6-hydroxy-methylpyridine-2-carboxylate in 55 ml of N,N-dimethylformamide, 1.4 g of imidazole and 3.9 g of tert-butyl-diphenylsilane chloride were added under cooling with
10 ice, sequentially, followed by stirring for 12 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under
15 reduced pressure, the residue was dissolved in 60 ml of methanol. To the solution 7.5 ml of 4N aqueous sodium hydroxide solution was added, stirred for 20 hours at room temperature and for further 2 hours at 60°C. Distilling the methanol off under reduced pressure, the
20 residue was made acidic with 1N hydrochloric acid. The system was extracted with chloroform, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by silica
25 gel column chromatography (developing solvent: hexane / ethyl acetate = 4/1) to provide 895 mg of the title compound as a white solid.

Step 2. Synthesis of 6-tert-butyloxycarbonylamino-
pyridin-2-ylmethyl tert-butyl diphenylsilyl ether

30 To a solution of 890 mg of the 6-tert-butyl diphenylsilyloxymethylpyridine-2-carboxylic acid as obtained in above step 1 in 30 ml of toluene, 0.63 ml of triethylamine, 3.2 ml of tert-butanol and 887 mg of diphenylphosphoryl azide were added sequentially at room
35 temperature, followed by heating for 16 hours at 100°C under stirring. The reaction mixture was diluted with

ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, 10% aqueous citric acid solution, water and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under
 5 reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 4/1) to provide 863 mg of the title compound as an oily substance.

Step 3. Synthesis of 6-tert-butyloxycarbonylamino-
 10 pyridine-2-methanol

The title compound was prepared in the same manner as described in the step 3 of Example 5 using the 6-tert-butyloxycarbonylamino-pyridin-2-ylmethyl tert-butyl-diphenylsilyl ether as obtained in above step 2.

15 Step 4. Synthesis of 6-tert-butyloxycarbonylamino-
pyridin-2-ylmethyl methanesulfonate

To a solution of 61 mg of the 6-tert-butyloxycarbonylamino-pyridine-2-methanol as obtained in above step 3 in 2 ml of chloroform, 0.19 ml of triethylamine
 20 and 0.032 ml of methanesulfonyl chloride were added under cooling with ice, followed by stirring for an hour at the same temperature. The reaction liquid was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, water and brine by the
 25 order stated and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 124 mg of the title compound as an oil.

Step 5. Synthesis of (2R)-N-[1-(6-tert-butyloxycar-
bonylamino-pyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-
 30 3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

The title compound was prepared in the same manner as described in Example 15 using the 6-tert-butyloxycarbonylamino-pyridin-2-ylmethyl methanesulfonate as obtained in the step 4 above.

Step 6. Synthesis of (2R)-N-[1-(6-aminopyridin-2-yl-methyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

The title compound was obtained as a white solid, upon treating the (2R)-N-[1-(6-tert-butyloxycarbonylamino-5 pyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 5 with hydrochloric acid according to usual manner.

¹H-NMR (CD₃OD, δ ppm) : 1.76-2.14 (10 H, m), 3.20-3.63 (5 H, m), 3.85-4.00 (1 H, m), 4.44 (2 H, s), 7.07-7.34 (2 H, m), 7.25-7.34 (3 H, m), 7.58-7.60 (2 H, m), 7.89-7.94 (1 H, m)

low resolution FAB-MS (m/e, (C₂₄H₃₀F₂N₄O₂ + H)⁺): 445.

Method 2:

Step 1. Synthesis of ethyl 6-tert-butyloxycarbonyl-aminopyridine-2-carboxylate

The title compound was prepared in the same manner described in the step 2 of above method 1, using 6-ethoxycarbonylpyridine-2-carboxylic acid.

Step 2. Synthesis of 6-tert-butyloxycarbonylamino-pyridine-2-methanol

To a solution of 500 mg of calcium chloride in 10 ml of ethanol, 150 mg of sodium borohydride was added under cooling with ice, followed by stirring for 15 minutes at the same temperature. To the reaction mixture 1.1 g of the ethyl 6-tert-butyloxycarbonylamino-30 pyridine-2-carboxylate as obtained in above step 1 was added and stirred for 13 hours at room temperature. The ethanol was distilled off under reduced pressure, and the residue was suspended in chloroform-water mixture to be removed of insoluble material. The organic layer was 35 washed with water and then brine and dried over anhy-

drous magnesium sulfate. Thus 996 mg of the title compound was obtained as a light yellow oil.

Step 3. Synthesis of 4-tert-butyloxycarbonylamino-1-(6-tert-butyloxycarbonylamino-2-ylmethyl)piperidine

5 The title compound was prepared by a method similar to the steps 4 to 5 of above production method 1 using the 6-tert-butyloxycarbonylamino-2-methanol as obtained in the above step 2 and 4-tert-butyloxycarbonylamino-piperidine.

10 Step 4. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

163 mg of the 4-tert-butyloxycarbonyl-amino-1-(6-tert-butyloxycarbonylamino-2-ylmethyl)piperidine as obtained in above step 3 was dissolved in 5 ml
15 of 10% HCl-methanol solution, followed by stirring for 13 hours at 40°C. Distilling the methanol off under reduced pressure, the remaining residue was suspended in 15 ml of chloroform, to which 0.16 ml of triethylamine,
20 86 mg of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, 114 mg of hydroxybenzotriazole and 75 mg of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide were added under cooling with ice sequentially, followed by stirring for 1.5 hours at room
25 temperature. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the resulting
30 residue was purified by silica gel column chromatography (developing solvent: chloroform / methanol = 50/1 to 20/1) to obtain 101 mg of the title compound as a white solid.

35 ¹H-NMR (CDCl₃, δ ppm) : 1.35-1.51 (2H, m), 1.70-2.25 (10H, m), 2.68-2.80 (2H, m), 3.21-3.35 (1H, m), 3.41 (2H, s), 3.52

(1H, brs), 3.62–3.77 (1H, m), 4.40 (2H, brs), 6.28 (1H, d, $J=8.2$ Hz), 6.36 (1H, d, $J=8.2$ Hz), 6.67 (1H, d, $J=7.3$ Hz), 7.27–7.40 (4H, m), 7.53–7.57 (2H, m)

5

Step 5. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

The title compound was prepared by treating
10 the (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in the above step 4 with hydrochloric acid according to the accepted practice.

Method 3:

15 Step 1. Synthesis of 2-tert-butyloxycarbonylamino-6-methylpyridine

To a solution of 2 g of 6-methyl-2-aminopyridine in 30 ml of chloroform, 5 g of di-tert-butyl-oxycarbonate was added at room temperature. Then the
20 mixture was heated to 70°C, to which 2.5 g of 4-dimethylaminopyridine was added, followed by stirring for 2 hours at the same temperature. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography
25 (developing solvent: hexane / ethyl acetate = 20/1) to provide 4.1 g of the title compound as a white solid.

Step 2. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

30 To a solution of 100 mg of the 2-tert-butyloxycarbonylamino-6-methylpyridine as obtained in above step 1 in 3 ml of carbon tetrachloride, 90 mg of N-bromosuccinimide and 10 mg of benzoyl peroxide were added sequentially at room temperature, followed by
35 heating for 6 hours under reflux with stirring. Filtering the insoluble materials off, the solvent was dis-

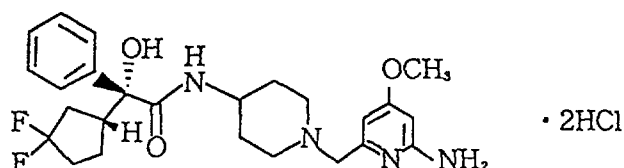
tilled off under reduced pressure. The title compound was prepared by a method similar to the step 5 of method 1 and the steps 4-5 of the method 2, using the resulting residue and 4-tert-butyloxycarbonylaminopyridine.

5 Example 21

(2R)-N-[1-(6-amino-4-methoxypyridin-2-ylmethyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

Structural formula

10



15 The title compound was prepared by a method similar to Example 20, using ethyl 6-hydroxymethyl-4-methoxypyridine-2-carboxylate.

¹H-NMR (CD₃OD, δ ppm) : 1. 69-2. 21 (10 H, m), 3. 10-3. 70 (5 H, m), 3. 83-3. 97 (1 H, m), 3. 98 (3 H, s), 4. 30-4. 46 (2 H, m), 6. 39-6. 47 (1 H, m), 6. 74-6. 89 (1 H, m), 7. 20-7. 38 (3 H, m), 7. 58 (2 H, d, J=6. 9 Hz)

25 low resolution FAB-MS (m/e, (C₂₅H₃₂F₂N₄O₃ + H)⁺): 475.

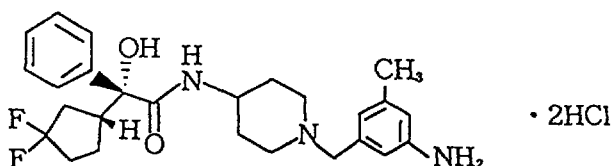
Example 22

(2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

30

Structural formula

This Sheet Has Been Replaced



35

Step 1. Synthesis of N-(tert-butyloxycarbonyl)-3,5-dimethylaniline

To a solution of 1.2 g of 3,5-dimethylaniline in a liquid mixture of 20 ml of dioxane and 10 ml of 10% aqueous sodium hydroxide solution, 2.7 g of di-tert-butyl-dicarbonate were added, followed by heating for 1.5 hours at 100°C with stirring. The reaction mixture as diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 9/1) to provide 1.8 g of the title compound as an oil.

Step 2. Synthesis of 3-(tert-butyloxycarbonylamino)-5-methylbenzyl bromide

To a solution of 1.8 g of the N-(tert-butyloxycarbonyl)-3,5-dimethylaniline as obtained in above step 1 in 20 ml of carbon tetrachloride, 1.5 g of N-bromosuccinimide and 53 mg of 2,2'-azobis(isobutyronitrile) were added, followed by heating for 3 hours at 100°C under stirring. The reaction mixture was diluted with hexane, filtered and the solvent was distilled off under reduced pressure to provide 2.8 g of the title compound as an oil.

Step 3. Synthesis of (2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

The title compound was prepared by a method similar to the steps 5-6 of the production method 1 of Example 20, using the 3-(tert-butyloxycarbonylamino)-5-methylbenzyl bromide as obtained in above step 2.

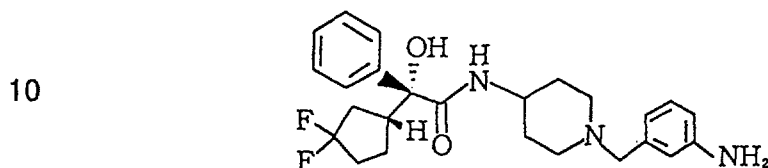
¹H-NMR (CD₃OD, δ ppm) : 1.66-2.11 (12H, m), 2.99-3.48 (3H, m), 3.26 (3H, s), 3.78-3.98 (1H, m), 4.28 (2H, s), 7.18-7.60 (8H, m)

low resolution FAB-MS (m/e , $(C_{28}H_{33}F_2N_3O_2 + H)^+$): 458.

Example 23

5 (2R)-N-[1-(3-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

Structural formula



Step 1. Synthesis of (2R)-N-[1-(3-nitrobenzyl)-
piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-
15 hydroxy-2-phenylacetamide

The title compound was prepared by a method similar to Example 15, using 3-nitrobenzyl chloride.

Step 2. Synthesis of (2R)-N-[1-(3-aminobenzyl)-
piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-
20 hydroxy-2-phenylacetamide

6.5 mg of the (2R)-N-[1-(3-nitrobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 1 was heated to 60°C together with 2 mg of iron powder in aqueous
25 ethanol. After adding thereto 1 drop of conc. hydrochloric acid, the heating was continued at 100°C for about 1 hour under stirring. The reaction mixture was made basic with 4N aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was dried
30 over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to provide 4.8 mg of the title compound as a white solid.

¹H-NMR (CDCl₃, δ ppm) : 1.30-1.48 (2H, m), 1.50-2.25 (10H, m), 2.68-2.78 (2H, m), 3.24-3.40 (1H, m), 3.38 (2H, s), 3.43

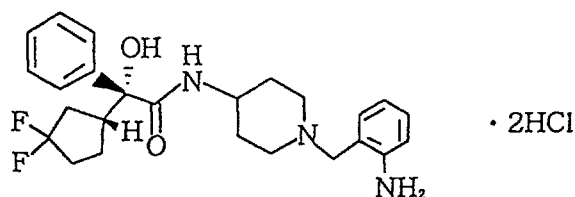
(1H, s), 3.52–3.80 (1H, m), 6.26 (1H, d, $J = 7.9$ Hz), 6.57 (1H, dd, $J = 1.5$ Hz, 7.8 Hz), 6.65 (1H, d, $J = 1.5$ Hz), 6.66 (1H, d, $J = 7.8$ Hz), 7.08 (1H, t, $J = 7.8$ Hz), 7.28–7.39 (3H, m), 7.53–7.57 (2H, m)

low resolution FAB-MS (m/e , $(C_{25}H_{31}F_2N_3O_2 + H)^+$): 444.

10 Example 24

(2R)-N-[1-(2-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

Structural formula



The title compound (free base) was obtained by a method similar to Example 23, using 2-nitrobenzyl chloride, which was treated with hydrochloric acid and to provide the title compound.

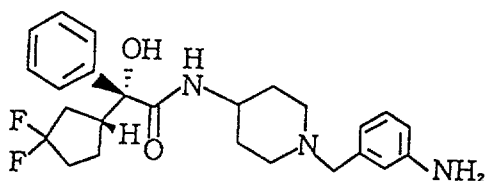
1H -NMR (CD_3OD , δ ppm) : 1.50–1.95 (10H, m), 2.92–3.07 (2H, m), 3.07–3.20 (1H, m), 3.24–3.38 (2H, m), 3.67–3.80 (1H, m), 4.15–4.27 (2H, m), 7.05–7.45 (9H, m)

low resolution FAB-MS (m/e , $(C_{25}H_{31}F_2N_3O_2 + H)^+$): 444.

Example 25

(2R)-N-[1-(4-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

5 Structural formula



10 The title compound was prepared by a method similar to Example 23, using 4-nitrobenzyl chloride.

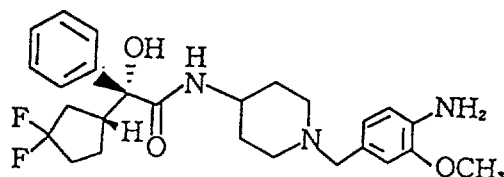
¹H-NMR (CDCl₃, δ ppm) : 1.35-1.52 (2H, m), 1.70-2.23 (10H, m), 2.70-2.82 (2H, m), 3.23-3.35 (1H, m), 3.41 (2H, s), 3.30-3.70 (3H, m), 3.65-3.75 (1H, m), 6.29 (1H, d, J=7.4 Hz), 6.63 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz), 7.28-7.39 (3H, m), 7.52-7.56 (2H, m)

low resolution FAB-MS (m/e, (C₂₅H₃₁F₂N₃O₂ + H)⁺): 444.

Example 26

(2R)-N-[1-(4-amino-3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide

 Structural formula



30 The title compound was prepared by a method similar to Example 23, using 3-methoxy-4-nitrobenzyl chloride.

This Sheet Has Been Replaced



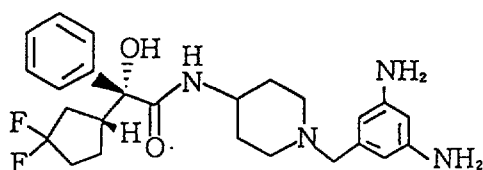
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.35–1.60 (2H, m), 1.70–2.30 (10H, m), 2.70–2.90 (2H, m), 3.22–3.38 (1H, m), 3.44 (2H, s), 3.40–3.60 (1H, m), 3.62–3.85 (3H, m), 3.85 (3H, s), 6.36 (1H, d, $J=7.9\text{ Hz}$), 6.60–6.70 (2H, m), 6.81 (1H, s), 7.24–7.40 (3H, m), 7.51–7.58 (2H, m)

low resolution FAB-MS (m/e , $(\text{C}_{26}\text{H}_{33}\text{F}_2\text{N}_3\text{O}_3 + \text{H})^+$): 474.

Example 27

(2R)-N-[1-(3,5-diaminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared by a method similar to Example 23, using 3,5-dinitrobenzyl chloride.

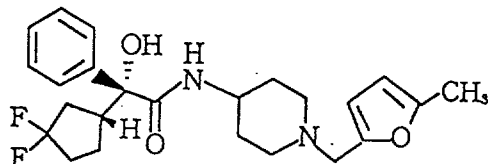
$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.30–2.20 (12H, m), 2.70–2.80 (2H, m), 3.23–3.36 (1H, m), 3.28 (2H, s), 3.44 (1H, s), 3.60–3.73 (1H, m), 5.93 (1H, t, $J=2.0\text{ Hz}$), 6.07 (2H, d, $J=2.0\text{ Hz}$), 6.23 (1H, d, $J=7.5\text{ Hz}$), 7.29–7.40 (3H, m), 7.53–7.57 (2H, m)

low resolution FAB-MS (m/e , $(\text{C}_{25}\text{H}_{32}\text{F}_2\text{N}_4\text{O}_2 + \text{H})^+$): 459.

Example 28

(2R)-N-[1-(5-methylfuran-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

5 Structural formula



10

Step 1. Synthesis of 4-(tert-butyloxycarbonylamino)-1-(5-methyl-2-furylmethyl)piperidine

To a solution of 200 mg of 4-(tert-butyloxycarbonylamino)piperidine in 5 ml of tetrahydrofuran, 0.1 ml of 5-methylfuran-3-aldehyde, 0.06 ml of acetic acid and 318 mg of sodium triacetoxymethylborohydride were added at room temperature, followed by stirring for 12 hours. To the reaction mixture, saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After distilling the solvent off under reduced pressure, the residue was recrystallized from ethyl acetate / n-hexane to provide 198 mg of the title compound.

25 Step 2. Synthesis of (2R)-N-[1-(5-methyl-2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

To 88 mg of the 4-(tert-butyloxycarbonylamino)-1-(5-methyl-2-furylmethyl)piperidine as obtained in above step 1, 2 ml of 10% hydrogenchloride solution in methanol was added at room temperature, followed by stirring for about 12 hours. The solvent was distilled off under reduced pressure, and to a solution of the resultant residue in 4 ml of chloroform, 59 mg of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, 93 mg of hydroxybenzotriazole, 0.2 ml of

triethylamine and 66 mg of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide were added sequentially at room temperature, followed by stirring for 2 hours. After addition of water, the reaction mixture was extracted
 5 with chloroform. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: chloroform / methanol = 50/1) to
 10 provide 63 mg of the title compound as a white solid.

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.35–1.54 (2H, m), 1.60–2.25 (10H, m), 2.27 (3H, s), 2.71–2.86 (2H, m), 3.22–3.36 (1H, m), 3.40
 15 (1H, s), 3.45 (2H, s), 3.60–3.76 (1H, m), 5.85–5.90 (1H, m), 6.05 (1H, d, $J = 3.0$ Hz), 6.25 (1H, d, $J = 7.9$ Hz), 7.26–7.40 (3H, m), 7.50–7.56 (2H, m)

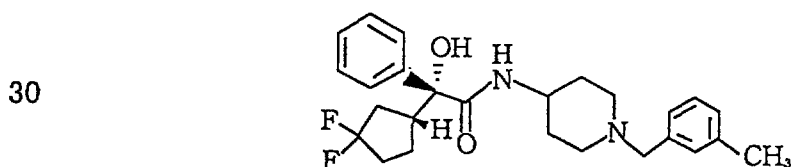
20

low resolution FAB-MS (m/e , $(\text{C}_{24}\text{H}_{30}\text{F}_2\text{N}_2\text{O}_3 + \text{H})^+$): 433.

Example 29

(2R)-N-[1-(3-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
 25 amide

Structural formula



Step 1. Synthesis of 4-(tert-butyloxycarbonylamino)-1-(3-methylbenzyl)piperidine

35 The title compound was prepared by a method similar to Example 15, using 4-(tert-butyloxycarbonyl-

amino)piperidine and 3-methylbenzyl bromide.

Step 2. Synthesis of (2R)-N-[1-(3-methylbenzyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

5 The title compound was prepared by a method similar to Example 28, using the 4-(tert-butyloxycarbonylamino)-1-(3-methylbenzyl)piperidine as obtained in above step 1.

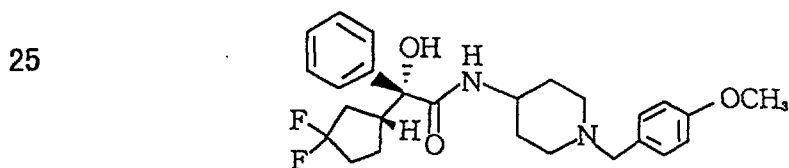
10 $^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.24–1.50 (2H, m), 1.50–2.25 (10H, m), 2.33 (3H, s), 2.60–2.82 (2H, m), 3.20–3.55 (3H, m), 3.42 (2H, s), 6.25 (1H, d, $J=8.1\text{ Hz}$), 7.00–7.14 (3H, m), 7.19 (1H, t, $J=7.6\text{ Hz}$), 7.23–
15 7.42 (3H, m), 7.50–7.60 (2H, m)

low resolution FAB-MS (m/e , $(\text{C}_{26}\text{H}_{32}\text{F}_2\text{N}_2\text{O}_2 + \text{H})^+$): 443.

Example 30

20 (2R)-N-[1-(4-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



30 The title compound was prepared by a method similar to the step 2 of Example 10, using p-anisaldehyde.

35 $^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.32–1.47 (2H, m), 1.75–2.23 (10H, m), 2.65–2.76 (2H, m), 3.22–3.36 (1H, m), 3.42 (2H, s), 3.46 (1H, s), 3.63–3.76 (1H, m), 3.79 (3H, s),

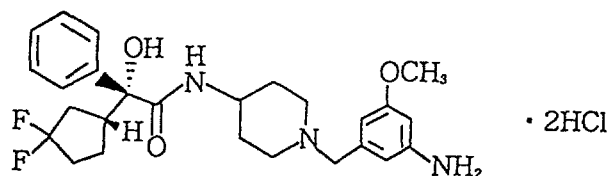
6. 27 (1H, d, $J=8.2$ Hz), 6. 84 (2H, d, $J=8.6$ Hz), 7. 19 (2H, d, $J=8.6$ Hz), 7. 28–7. 39 (3H, m), 7. 52–7. 56 (2H, m)

low resolution FAB-MS (m/e , $(C_{26}H_{32}F_2N_2O_3 + H)^+$): 459.

Example 31

(2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

10 Structural formula



15

Step 1. Synthesis of methyl 3-tert-butoxycarbonylamino-5-methoxybenzoate

To a solution of 864 mg of methyl 3-methoxy-5-nitrobenzoate in 15 ml of methanol, 1.0 g of di-tert-butyl-dicarbonate and 912 mg of 10% palladium-on-carbon were added, followed by stirring for 7 hours at room temperature in a hydrogen atmosphere. The reaction liquid was filtered through Celite. Distilling the solvent off under reduced pressure, 1.28 g of the title compound was obtained as a white solid.

Step 2. Synthesis of 3-tert-butoxycarbonylamino-5-methoxybenzyl alcohol

To a solution of 1.28 g of the methyl 3-tert-butoxycarbonylamino-5-methoxybenzoate as obtained in above step 1 in 8 ml of toluene, 12.1 ml of 1.0 M solution of diisobutylaluminum hydride in tetrahydrofuran was added at -78°C , followed by stirring for an hour at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with water and then brine and dried over anhydrous magnesium sulfate. After distilling the solvent off under reduced pressure, the result-

ing residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 7/3) to provide 262 mg of the title compound as an oil.

Step 3. Synthesis of 3-tert-butoxycarbonylamino-5-methoxybenzaldehyde

To a solution of 194 mg of the 3-tert-butoxycarbonylamino-5-methoxybenzyl alcohol as obtained in above step 2 in 10 ml of chloroform, 1.89 g of manganese dioxide was added at room temperature, followed by stirring for 2 hours. The reaction mixture was filtered through Celite. Distilling the solvent off under reduced pressure, 132 mg of the title compound was obtained as an oily substance.

Step 4. Synthesis of (2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

The title compound was prepared by a method similar to the step 2 of Example 10 and the step 6 of method 1 of Example 20, using the 3-tert-butoxycarbonylamino-5-methoxybenzaldehyde as obtained in above step 3.

$^1\text{H-NMR}$ (CD_3OD , δ ppm) : 1.74–2.14 (10H, m), 3.00–3.15 (2H, m), 3.27–3.52 (3H, m), 3.82–3.92 (1H, m), 3.89 (3H, s) 4.32 (2H, s), 7.01 (1H, s), 7.18–7.35 (5H, m), 7.56–7.60 (2H, m)

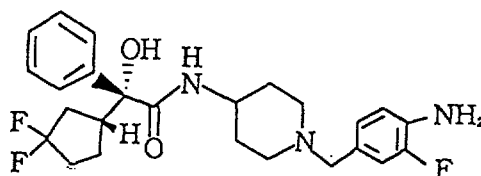
low resolution FAB-MS (m/e , $(\text{C}_{26}\text{H}_{33}\text{F}_2\text{N}_3\text{O}_3 + \text{H})^+$): 474.

Example 32

(2R)-N-[1-(4-amino-3-fluorobenzyl)piperidin-4-yl]-
2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide

5

Structural formula



10

The title compound was prepared by a method similar to Example 22, using 3-fluoro-4-aminotoluene.

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.28–1.50 (2H, m), 1.50–2.32 (10H, m), 2.60–2.80 (2H, m), 3.20–3.38 (1H, m), 3.33 (2H, s), 3.45 (1H, s), 3.55–3.76 (3H, m), 6.25 (1H, d, $J=8.2\text{ Hz}$), 6.69 (1H, dd, $J=8.1, 8.9\text{ Hz}$), 6.82 (1H, dd, $J=1.6, 8.1\text{ Hz}$), 6.93 (1H, dd, $J=1.6, 12.0\text{ Hz}$), 7.24–7.40 (3H, m), 7.50–7.58 (2H, m)

20

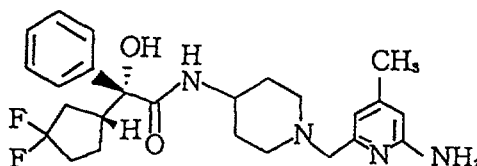
low resolution FAB-MS (m/e , $(\text{C}_{25}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_2 + \text{H})^+$): 462.

25 **Example 33**

(2R)-N-[1-(6-amino-4-methylpyridin-2-yl)piperidin-
4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide

Structural formula

30



35

Step 1. Synthesis of 6-chloromethyl-4-methyl-2-acetylaminopyridine

To a solution of 23 mg of 6-acetylamino-4-methylpyridine-2-methanol in 2 ml of chloroform, 0.05 ml
 5 of thionyl chloride was added at room temperature, followed by heating for 15 minutes with stirring under reflux. Distilling the solvent off under reduced pressure, the title compound was obtained.

Step 2. Synthesis of (2R)-N-[1-(6-acetylamino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
 10

The title compound was prepared by a method similar to Example 15, using the 6-chloromethyl-4-methyl-2-acetylaminopyridine as obtained in above step
 15 1.

Step 3. Synthesis of (2R)-N-[1-(6-amino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

To a solution of 16.5 mg of the (2R)-N-[1-(6-acetylamino-4-methylpyridin-2-yl)piperidin-4-yl]-2-
 20 [(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 2 in 1 ml of methanol, 0.5 ml of 3M aqueous sodium hydroxide solution was added, and stirred for 1.5 hours at 60°C. The reaction
 25 liquid was diluted with diethyl ether, washed with water and brine by the order stated and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by preparative thin-layer chromatography [KieselgelTM
 30 60F₂₅₄, Art 5744 (Merck); chloroform / methanol = 10/1) to provide 14 mg of the title compound as an oily substance.

¹H-NMR (CDCl₃, δ ppm) : 1.30-1.50 (2H, m), 1.71-2.30 (10H, m), 2.33 (3H, s), 2.62-2.76 (2H, m), 3.21-3.38 (1H, m), 3.29

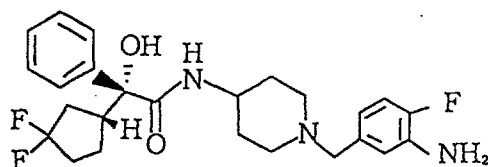
(2 H, s), 3. 60–3. 78 (1 H, m), 4. 35–4. 51 (2 H, m), 6. 26 (1 H, s), 6. 35 (1 H, d, J = 8. 1 Hz), 6. 45 (1 H, s), 7. 25–7. 40 (3 H, m), 7. 52–7. 60 (2 H, m)

low resolution FAB-MS (m/e, (C₂₅H₃₂F₂N₄O₂ + H)⁺): 459.

Example 34

(2R)-N-[1-(3-amino-4-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

Structural formula



The title compound was prepared by a method similar to Example 22, using 2-fluoro-5-methylaniline.

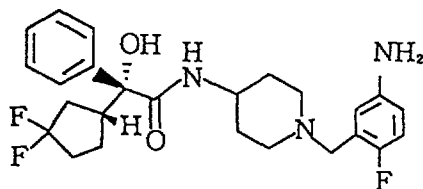
¹H-NMR (CD₃OD, δ ppm) : 1. 68–2. 11 (10 H, m), 3. 00–3. 50 (5 H, m), 3. 79–3. 90 (1 H, m), 4. 32 (2 H, s), 7. 18–7. 30 (3 H, m), 7. 43 (1 H, d, J = 8. 4 Hz), 7. 52–7. 56 (2 H, m), 7. 57–7. 65 (1 H, m), 7. 73–7. 78 (1 H, m)

low resolution FAB-MS (m/e, (C₂₅H₃₀F₃N₃O₂ + H)⁺): 462.

Example 35

(2R)-N-[1-(5-amino-2-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared by a method similar to the step 2 of Example 22 and Example 23, using 2-fluoro-5-nitrotoluene.

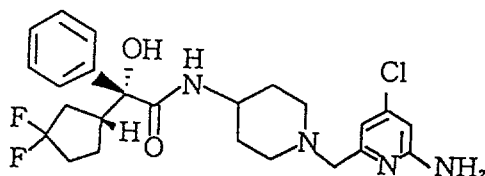
¹H-NMR (CDCl₃, δ ppm) : 1.36–1.49 (2H, m), 1.57–2.26 (10H, m), 2.71–2.78 (2H, m), 3.24–3.36 (1H, m), 3.42–3.57 (5H, m), 3.66–3.75 (1H, m), 6.24 (1H, d, J=8.1 Hz), 6.51–6.56 (1H, m), 6.65–6.68 (1H, m), 6.82 (1H, t, J=9.0 Hz), 7.29–7.40 (3H, m), 7.53–7.57 (2H, m)

low resolution FAB-MS (m/e, (C₂₅H₃₀F₃N₃O₂ + H)⁺): 462.

Example 36

(2R)-N-[1-(2-amino-4-chloropyridin-6-yl)methyl]-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared by a method similar to method 2 of Example 20, using methyl 4-chloro-6-hydroxymethylpyridine-2-carboxylate.

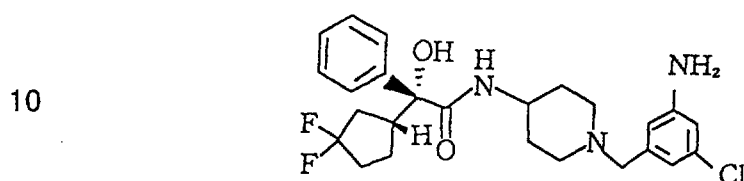
¹H-NMR (CDCl₃, δ ppm) : 1.42–1.54 (2H, m), 1.78–2.26 (10H, m), 2.76–2.79 (2H, m), 3.28–3.38 (1H, m), 3.42–3.47 (3H, m), 3.67–3.75 (1H, m), 4.53–4.56 (2H, m), 6.36 (1H, d, J=7.2 Hz), 6.38 (1H, d, J=1.6 Hz), 6.72 (1H, d, J=1.6 Hz), 7.25–7.39 (3H, m), 7.53–7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{29}ClF_2N_4O_2 + H)^+$): 479.

Example 37

5 (2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-
 2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
 phenylacetamide

Structural formula



15 Step 1. Synthesis of 3-chloro-5-nitrobenzyl methanesul-
 fonate

To a solution of 92 mg of 3-chloro-5-nitrobenzyl alcohol in 3 ml of chloroform, 0.3 ml of triethylamine and 0.1 ml of methanesulfonyl chloride were added at room temperature, followed by stirring for 40 minutes, addition of saturated aqueous sodium bicarbonate solution and further stirring for 30 minutes. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution and then brine and dried over anhydrous magnesium sulfate.

25 Distilling the solvent off under reduced pressure, 119 mg of the title compound was obtained as an oil.

Step 2. Synthesis of (2R)-N-[1-(3-amino-5-chloro-
benzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-
2-hydroxy-2-phenylacetamide

30 The title compound was obtained by a method similar to Example 23, using the 3-chloro-5-nitrobenzyl methanesulfonate as obtained in above step 1.

¹H-NMR (CDCl₃, δ ppm) : 1.30-1.44 (2H, m), 1.73-2.22 (10H, m), 2.68-2.73 (2H, m), 3.24-3.36 (1H, m), 3.32 (2H, s), 3.44

35

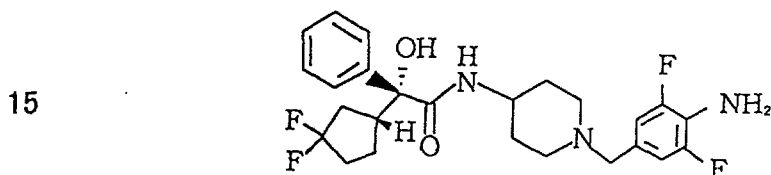
(1H, brs), 3.61–3.77 (3H, m), 6.28 (1H, d, $J=8.4$ Hz), 6.49 (1H, d, $J=1.9$ Hz), 6.55 (1H, dd, $J=1.7, 1.9$ Hz), 6.66 (1H, d, $J=1.7$ Hz), 7.29–7.39 (3H, m), 7.53–7.56 (2H, m)

low resolution FAB-MS (m/e , $(C_{25}H_{30}ClF_2N_3O_2 + H)^+$): 459.

Example 38

(2R)-N-[1-(4-amino-3,5-difluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

Structural formula



The title compound was prepared by a method similar to the step 2 of Example 10, using 4-amino-3,5-difluorobenzaldehyde.

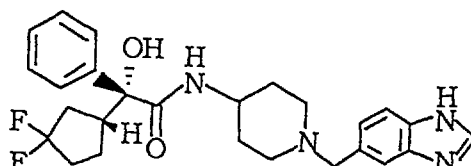
1H -NMR ($CDCl_3$, δ ppm) : 1.24–2.22 (12H, m), 2.66–2.72 (2H, m), 3.27–3.41 (4H, m), 3.66–3.71 (3H, m), 6.28 (1H, d, $J=7.8$ Hz), 6.77 (2H, d, $J=8.3$ Hz), 7.28–7.39 (3H, m), 7.54–7.56 (2H, m)

low resolution FAB-MS (m/e , $(C_{25}H_{29}F_4N_3O_2 + H)^+$): 480.

Example 39

(2R)-N-[1-(benzimidazol-5-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

5 Structural formula



The title compound was prepared by a method similar to the step 2 of Example 10, using benzimidazole-5-carbaldehyde.

15 $^1\text{H-NMR}$ (CD_3OD , δ ppm) : 1.45–2.25 (10H, m), 2.25–2.48 (2H, m), 2.90–3.10 (2H, m), 3.20–3.42 (1H, m), 3.56–3.75 (1H, m), 3.82 (2H, s), 7.18–7.40 (4H, m), 7.51–7.75 (4H, m), 8.17 (1H, s)

20

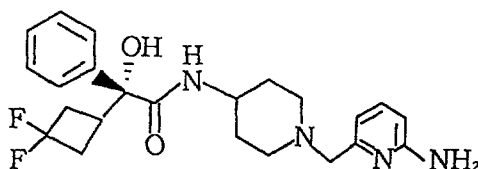
low resolution FAB-MS (m/e , ($\text{C}_{28}\text{H}_{30}\text{F}_2\text{N}_4\text{O}_2 + \text{H}$) $^+$): 469.

Example 40

25 (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetamide

Structural formula

This Sheet Has Been Replaced



The title compound was prepared by a method similar to the step 4 of method 2 of Example 20, using
35 (2R)-2-(3,3-difluorocyclobutyl)-2-hydroxyphenylacetic acid
and 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine

trihydrochloride.

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.20–1.52 (2H, m), 1.60–1.86 (2H, m), 2.08–2.22 (2H, m), 2.40–2.82 (6H, m), 3.07–3.21 (1H, m), 3.41 (2H, s), 3.60–3.80 (1H, m), 3.84 (1H, brs), 4.40 (2H, brs), 6.01 (1H, d, $J=8.1\text{ Hz}$), 6.36 (1H, d, $J=8.2\text{ Hz}$), 6.66 (1H, d, $J=8.2\text{ Hz}$), 7.28–7.42 (4H, m), 7.43–7.50 (2H, m)

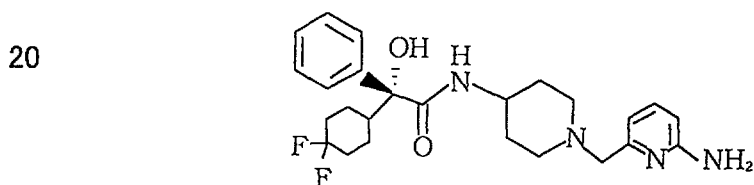
low resolution FAB-MS (m/e , $(\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_4\text{O}_2 + \text{H})^+$): 431.

Example 41

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-(4,4-difluorocyclohexyl)-2-hydroxy-2-phenylacetamide

Structural formula

This Sheet Has Been Replaced



The title compound was prepared by a method similar to the step 4 of method 2 of Example 20, using (2R)-(4,4-difluorocyclohexyl)-2-hydroxyphenylacetic acid and 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine trihydrochloride.

$^1\text{H-NMR}$ (CDCl_3 , δ ppm) : 1.20–1.97 (10H, m), 1.97–2.22 (4H, m), 2.44–2.68 (1H, m), 2.70–2.92 (3H, m), 3.42 (2H, s), 3.62–3.80 (1H, m), 4.42 (2H, brs), 6.36 (1H, d, $J=8.2\text{ Hz}$), 6.62 (1H, d, $J=7.9\text{ Hz}$), 6.67 (1H, d, $J=8.2\text{ Hz}$), 7.24–7.42 (4H, m), 7.55–7.62 (2H, m)

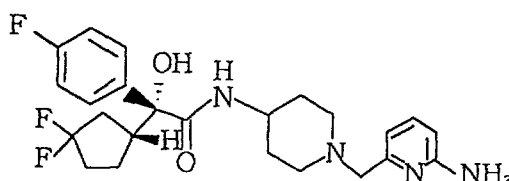
low resolution FAB-MS (m/e , $(C_{25}H_{32}F_2N_4O_2 + H)^+$): 459.

Example 42

5 (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetamide

Structural formula

10



This Sheet Has Been Replaced



15 The title compound was prepared by a method similar to the method 1 of Example 20, using (2R)-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetic acid.

20 1H -NMR ($CDCl_3$, δ ppm) : 1.39-1.55 (2H, m), 1.70-2.22 (10H, m), 2.73-2.81 (2H, m), 3.23-3.36 (1H, m), 3.43 (2H, s), 3.65-3.77 (1H, m), 4.43 (2H, brs), 6.31 (1H, d, $J=7.6$ Hz), 6.37 (1H, d, $J=8.2$ Hz), 6.67 (1H, d, $J=7.4$ Hz), 7.01-7.08 (2H, m), 7.37 (1H, dd, $J=7.4, 8.2$ Hz), 7.51-7.58 (2H, m)

low resolution FAB-MS (m/e , $(C_{24}H_{29}F_3N_4O_2 + H)^+$): 463.



THIS SHEET HAS BEEN REPLACED

Referential Example 1

(2R)-[(1R)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one and (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

To a mixture of 510 mg of (2R,5R)-2-(t-butyl)-5-phenyl-1,3-dioxolan-4-one which had been synthesized by the method of D. Seebach, et al. [Tetrahedron. Vol. 40, pp. 1313-1324 (1984)] in 20 ml of tetrahydrofuran and 1 ml of hexamethylphosphoric triamide, 1.7 ml of 1.5M lithium diisopropylamide solution in hexane was added dropwise at -78°C, followed by stirring for 30 minutes. Then a solution of 285 mg of cyclopentenone in 1.5 ml of tetrahydrofuran was added, and the reaction mixture was stirred for 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, resulting residue was purified by medium pressure silica gel column chromatography (developing solvent: hexane / ethyl acetate = 15/1 - 10/1). Thus 150 mg and 254 mg, respectively, of the title compounds were obtained as oil. Configuration of each of the compounds was determined from NOE of NMR.

Step 2. Synthesis of (2R)-[(1R)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

To a solution of 61 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 3 ml of methanol, 1 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring for 3 hours at room temperature. Distilling the methanol off under reduced pressure, the residue was diluted with water and washed with diethyl ether. The aqueous layer was made

acidic with 1N hydrochloric acid and extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate to provide 48 mg of the title compound.

5 Referential Example 2

(2R)-[(1S)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to the step 2 of Referential Example 1, using
10 (2R, 5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 3

(2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

15 Step 1. Synthesis of (2R, 5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

To a solution of 256 mg of (2R, 5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 3 ml of chloroform, 0.34 ml of diethylamino-
20 sulfur trifluoride was added under cooling with ice, followed by stirring for 20 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off
25 under reduced pressure, resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 20/1) to provide 115 mg of the title compound.

30 Step 2. Synthesis of (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R, 5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.



Referential Example 4

(2R)-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to Referential Example 3, using (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 5

(2R)-[(1S)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxolan-4-one

To a solution of 169 mg of (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 2 ml of methanol, 71 mg of sodium borohydride was added under cooling with ice, followed by stirring for 30 minutes at the same temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 157 mg of the title compound was obtained as a colorless oil.

Step 2. Synthesis of (2R)-[(1S)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R,5R)-2-(t-butyl)-5-[(1S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 6

(2R)-[(1R)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to Referential Example 5, using (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.



THIS SHEET HAS BEEN
REPLACED

Referential Example 7

(2R)-[(1S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to Referential Example 3, using (2R)-[(1S)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid.

Referential Example 8

(2R)-[(1R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to Referential Example 3, using (2R)-[(1R)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid.

Referential Example 9

2-cyclopentyl-2-hydroxy-2-phenylacetic acid

To a solution of 23.5 g of ethyl phenylglyoxylate in 200 ml of tetrahydrofuran, 70 ml of 2.0 M cyclopentylmagnesium chloride solution in diethyl ether was added dropwise under cooling with ice, followed by stirring for 30 minutes at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 30/1 - 20/1) to provide 11 g of ethyl 2-cyclopentyl-2-hydroxy-2-phenylacetate, which was dissolved in 40 ml of methanol. To the solution 20 ml of 4N aqueous sodium hydroxide solution was added at room temperature, followed by stirring for 2 hours at the same temperature and further for 1 hour at 50°C. Distilling the methanol off under reduced pressure, the aqueous layer was made weakly acidic with 4N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and then brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pres-

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sure, the residue was washed with 1 : 1 mixture of diethyl ether and hexane. Thus, 8.7 g of the title compound was obtained.

Referential Example 10

5 (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1S,2R,5R,6S,7R)-3-oxotricyclo[5.2.1.0^{2,6}]dec-8-en-5-yl]-5-phenyl-1,3-dioxolan-4-one

10 To a solution of 32 g of (2R,5R)-2-(t-butyl)-5-phenyl-1,3-dioxolan-4-one in 1.1 l of tetrahydrofuran, 105 ml of 1.5 M lithium diisopropylamide solution in hexane was added dropwise at -78°C, followed by stirring for 30 minutes, addition of 23.4 g of (1S,2R,6S,7R)-
15 tricyclo[5.2.1.0^{2,6}]dec-4,8-dien-3-one as dissolved in 300 ml of tetrahydrofuran, and further stirring for 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water and then brine, and dried over anhydrous
20 magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was recrystallized from hexane-ethyl acetate. Thus 36.9 g of the title compound was obtained as a white solid.

25 Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1S)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one

 A solution of 25.6 g of the (2R,5R)-2-(t-butyl)-5-[(1S,2R,5R,6S,7R)-3-oxo-8-tricyclo[5.2.1.0^{2,6}]-dec-8-en-5-yl]-5-phenyl-1,3-dioxolan-4-one as obtained in above step 1 in 350 ml of 1,2-dichlorobenzene was
30 heated at 175°C for 7 hours with stirring, under nitrogen atmosphere. Thus precipitated solid was recovered by filtration and washed with hexane to provide 14 g of the title compound as a white solid.

35 Step 3. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

 To a solution of 19.1 g of the (2R,5R)-2-(t-

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butyl)-5-[(1S)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2 in 700 ml of ethyl acetate, 2.0 g of 10% palladium-on-carbon was added, followed by stirring for 2 hours at ordinary
5 temperature under hydrogen atmosphere. Filtering the catalyst off then distilling the solvent off under reduced pressure, the residue was recrystallized from hexane-ethyl acetate to provide 14 g of the title compound as a white solid.

10 Step 4. Synthesis of (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one as obtained in above step 3.

Referential Example 11

(2R)-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetic acid

The title compound was prepared by a method
20 similar to the step 1 of Referential Example 1 and Referential Example 3, using (R)-4-fluoromandelic acid.
Referential Example 12

(2R)-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetic acid

25 Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-(3-benzyloxy-1-hydroxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one

The title compound was prepared by a method similar to the step 1 of Referential Example 1, using 3-benzyloxycyclobutanone.

30 Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-(3-benzyloxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one

To a solution of 2.82 g of the (2R,5R)-2-(t-butyl)-5-(3-benzyloxy-1-hydroxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 1 in 80 ml of
35 chloroform, 2.6 g of 4-dimethylaminopyridine was added under cooling with ice, followed by stirring for an hour

at the same temperature. To the reaction mixture, 1 ml of methyl chloroglyoxylate was added, followed by stirring for an hour. The reaction mixture was diluted with chloroform, washed with water and then brine, and dried
5 over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was mixed with hexane / ethyl acetate = 1/1 liquid mixture and filtered through a silica gel column. Distilling the solvent of the filtrate off under reduced pressure, the
10 residue was dissolved in 80 ml of toluene, and to the solution 56 mg of 2,2'-azobis(isobutyronitrile) and 2.3 ml of tri-n-butyltin hydride were added at room temperature, followed by heating for 4 hours at 110°C with stirring. Distilling the solvent off under reduced
15 pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 8/1) to provide 1.82 g of the title compound as an oily substance.

Step 3. Synthesis of (2R,5R)-2-(t-butyl)-5-(3-oxocyclobutyl)-5-phenyl-1,3-dioxolan-4-one
20

To a solution of 1.82 g of the (2R,5R)-2-(t-butyl)-5-(3-benzyloxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2 in 40 ml of ethanol, 430 mg of palladium hydroxide-carbon was added, followed
25 by stirring for 6 hours at ordinary temperature under hydrogen atmosphere. The reaction mixture was filtered through Celite. Distilling the solvent off under reduced pressure, the residue was dissolved in 5 ml of dichloromethane, and the resulting solution was added
30 dropwise at -78°C to a reaction mixture formed by adding 0.63 ml of oxalyl chloride to 1.1 ml of dimethylsulfoxide in 50 ml of dichloromethane at -78°C and stirring for 5 minutes. After stirring for 15 minutes at the same temperature, 0.5 ml of triethylamine was added to
35 the reaction mixture and stirred for 30 minutes while raising the temperature to room temperature. The reac-

tion liquid was diluted with chloroform, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 8/1) to provide 1.36 g of the title compound as an oily substance.

Step 4. Synthesis of (2R)-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetic acid

10 The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-(3-oxocyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 3.

Referential Example 13

15 (2R)-(4,4-difluorocyclohexyl)-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-(1,4-dioxaspiro[4.5]-dec-8-yl)-5-phenyl-1,3-dioxolan-4-one

20 The title compound was prepared by a method similar to the steps 1 and 2 of Referential Example 12, using 1,4-dioxo-8-oxospiro[4.5]decane.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-(4-oxocyclohexyl)-5-phenyl-1,3-dioxolan-4-one

25 To a solution of 83 mg of the (2R,5R)-2-(t-butyl)-5-(1,4-dioxaspiro[4.5]dec-8-yl)-5-phenyl-1,3-dioxolan-4-one in a mixture of 4 ml of acetone and 0.4 ml of water, 52 mg of p-toluenesulfonic acid was added at room temperature, followed by stirring for 13 hours at 50°C. Distilling the acetone off under reduced pressure, the residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 70 mg of the title compound was obtained as an oil.

35



Step 3. Synthesis of (2R)-(4,4-difluorocyclohexyl)-2-hydroxyphenylacetic acid

The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-(4-oxocyclohexyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2.

Referential Example 14

(2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

10 Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3-hydroxyiminocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

To a solution of 46 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 1.5 ml of pyridine, 85 mg of hydroxylamine hydrochloride was added and the mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 55 mg of the title compound.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

To a mixture of 20 mg of nitrosonium tetrafluoro borate and 0.5 ml of 70% hydrogen fluoride-pyridine, a solution of 34 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-hydroxyiminocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 0.5 ml of dichloromethane was added under ice-cooling. The mixture was stirred for 10 minutes at 0°C and 5 hours at room temperature. Water was added to the reaction mixture under ice-cooling and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 35 mg of the title compound.



Step 3. (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The title compound was prepared by a method similar to the step 2 of Referential Example 1, using
5 (2R,5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Industrially utilizability

The fluorine-containing 1,4-disubstituted
10 piperidine derivatives of the present invention have selective antagonistic activity for muscarinic M_3 receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe and effective. Hence, they
15 are very useful in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain
20 accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis: and motion sickness.

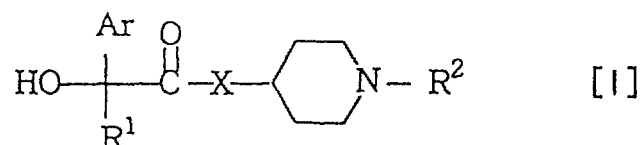
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CLAIMS

1. Novel fluorine-containing 1,4-disubstituted piperidine derivatives represented by the general formula [I]



and pharmaceutically acceptable salts thereof,

[wherein:

Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkyl-amino);

R¹ represents C₃-C₆ cycloalkyl whose any 1-4 hydrogen atoms may be substituted with fluorine atom(s);

R² represents C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl,



halogen, lower alkoxy, amino or lower alkyl-amino); and

X stands for O or NH,

provided that at least either one of R^1 and R^2 contains one or more fluorine atoms].

2. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which Ar is phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy-carbonyl, halogen, lower alkoxy, amino and lower alkyl-amino.

3. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R^1 is C_3-C_6 cycloalkyl in which any 1 to 4 hydrogen atoms are substituted with fluorine atom(s).

4. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R^1 is cyclobutyl, cyclopentyl, cyclohexyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl or 4,4-difluorocyclohexyl.

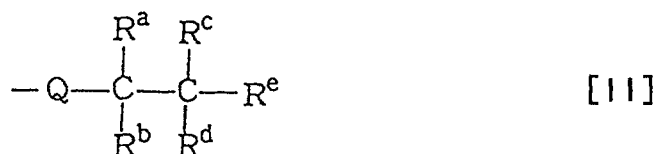
5. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R^1 is 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl or 4,4-difluorocyclohexyl.

6. The compounds or their pharmaceutically accep-



table salts according to Claim 1, in which X is NH.

7. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R² is a group whose any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s) and is represented by the formula below:



[in which

Q represents methylene, ethylene, trimethylene or tetramethylene;

R^a and R^c each represents a hydrogen atom or are combined to form a single bond; and

R^b, R^d and R^e may be the same or different and each represents a hydrogen atom, a lower alkyl group, C₃-C₈ cycloalkyl or cycloalkenyl, or R^b and R^d, or R^d and R^e together form each a C₃-C₈ cycloalkyl or cycloalkenyl],

8. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R² is C₅-C₁₅ straight chain or branched alkyl, alkenyl, alkynyl, cycloalkylalkyl or cycloalkylalkenyl in which any hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl; cycloalkenylalkyl or cycloalkenylalkenyl in which any hydrogen atom(s) on the cycloalkenyl ring may be substituted with lower alkyl; cycloalkylalkynyl or cycloalkenylalkynyl; or those in which any 1 to 6 hydrogen atoms are substituted with fluorine atom(s).

9. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R² is benzyl, phenethyl, phenylpropyl, phenylpropenyl, 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 3-pyridyl-



methyl, 4-pyridylmethyl, 2-thiazolylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-imidazolylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 3-pyrazolylmethyl, 4-pyrazolylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyrrolylmethyl, 3-pyrrolylmethyl, 2-pyrimidinylmethyl, 4-pyrimidinylmethyl, 5-pyrimidinylmethyl, pyrazinylmethyl, 3-pyridazinylmethyl, 4-pyridazinylmethyl, 2-quinidylmethyl, 2-benzothienylmethyl or 2-indolylmethyl (any 1 to 3 hydrogen atoms on the ring of said benzyl, phenethyl, phenylpropyl, phenylpropenyl or heteroarylalkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino).

10. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which R¹ is 3,3-difluorocyclopentyl and R² is 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino).

11. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which the compound represented by the general formula [I] is:

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacet-



amide

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-
[(1R, 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-
[(1R, 3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

N-[1-[(3Z)-4-trifluoromethyl-3-pentenyl]piperidin-
4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

N-[1-[(3Z)-4-fluoromethyl-3-pentenyl]piperidin-4-
yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-4-
yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide,

(2R)-N-(1-cycloheptylmethylpiperidin-4-yl)-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-
4-yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide

(2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-
yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenyl-
acetamide

(2R)-N-[1-(3-thienylmethyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-furylmethyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-furylmethyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-pyridylmethyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-(1-benzylpiperidin-4-yl)-2-[(1R)-3, 3-
difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-
3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-chlorobenzyl)piperidin-4-yl]-2-[(1R)-



3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-thienylmethyl)piperidin-4-yl]-2-[(1R)-

3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-

yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenyl-
acetamide

(2R)-N-[1-(6-amino-4-methoxypyridin-2-ylmethyl)-

piperidin-4-yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-
hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-

[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(3-aminobenzyl)piperidin-4-yl]-2-[(1R)-

3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-aminobenzyl)piperidin-4-yl]-2-[(1R)-

3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

N-[1-(4-aminobenzyl)piperidin-4-yl]-2-[(1R)-3, 3-

difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-amino-3-methoxybenzyl)piperidin-4-yl]-

2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(3, 5-diaminobenzyl)piperidin-4-yl]-2-

[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(5-methylfuran-2-ylmethyl)piperidin-4-yl]-

2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(3-methylbenzyl)piperidin-4-yl]-2-[(1R)-

3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-methoxybenzyl)piperidin-4-yl]-2-[(1R)-

3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-

2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(4-amino-3-fluorobenzyl)piperidin-4-yl]-2-

[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-



amide,

(2R)-N-[1-(6-amino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide,

(2R)-N-[1-(3-amino-4-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(5-amino-2-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-amino-4-chloropyridin-6-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-amino-3,5-difluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(benzimidazol-5-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[3,3-difluorocyclobutyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[4,4-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide, or

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-(4-fluorophenyl)-2-hydroxyacetamide.

12. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which the compounds represented by the general formula [I] is:

(2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl-



acetamide

(2R)-N-[1-(3-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-pyridylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-(1-benzylpiperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-amino-4-methoxypyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(2-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

N-[1-(4-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-amino-3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-



amide

(2R)-N-[1-(3,5-diaminobenzyl)piperidin-4-yl]-2-
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(5-methylfuran-2-ylmethyl)piperidin-4-yl]-
2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(3-methylbenzyl)piperidin-4-yl]-2-[(1R)-
3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(4-methoxybenzyl)piperidin-4-yl]-2-[(1R)-
3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-
2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(4-amino-3-fluorobenzyl)piperidin-4-yl]-2-
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(6-amino-4-methylpyridin-2-yl)piperidin-4-
yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl-
acetamide

(2R)-N-[1-(3-amino-4-fluorobenzyl)piperidin-4-yl]-2-
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

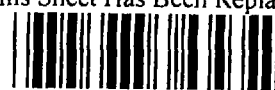
(2R)-N-[1-(5-amino-2-fluorobenzyl)piperidin-4-yl]-2-
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(2-amino-4-chloropyridin-6-ylmethyl)-
piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-
hydroxy-2-phenylacetamide

(2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-2-
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacet-
amide

(2R)-N-[1-(4-amino-3,5-difluorobenzyl)piperidin-4-
yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-
phenylacetamide

(2R)-N-[1-(benzimidazol-5-ylmethyl)piperidin-4-yl]-

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2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[3,3-difluorocyclobutyl]-2-hydroxy-2-phenylacetamide

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[4,4-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide, or

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-(4-fluorophenyl)-2-hydroxyacetamide.

13. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide or a pharmaceutical acceptable salt thereof.

14. A pharmaceutical composition composed of a compound of the general formula [I] as presented in Claim 1 or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable adjuvant.

15. A pharmaceutical composition as defined in Claim 13 which is used for treatment or prophylaxis of diseases associated with muscarinic M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma, chronic respiratory obstruction, fibroid lung and rhinitis; digestive diseases such as irritable bowel syndrome, spasm or hyperanalkinesia of digestive tract, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like dysuria such as pollakiuria, urinary urgency and urinary incontinence; and motion sickness.

16. A method for treatment or prophylaxis of diseases associated with muscarinic M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma, chronic respiratory obstruction, fibroid lung and rhinitis; digestive



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diseases such as irritable bowel syndrome, spasm or hyperanalkinesia of digestive tract, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like dysuria such as pollakiuria, urinary urgency and urinary incontinence: and motion sickness characterized in that a compound of the general formula [I] as presented in Claim 1 or a pharmaceutically acceptable salts thereof is used.

17. A process for preparation of a fluorine-containing 1,4-disubstituted piperidine derivative of the general formula [I] as presented in Claim 1 which comprises

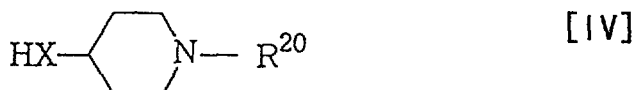
(a) reacting a carboxylic acid of the general formula [III]



[wherein Ar has the same signification as defined in Claim 1, and R^{10} represents a $\text{C}_3\text{-C}_6$ cycloalkyl in which any 1 to 4 hydrogen atoms may be substituted with fluorine atom(s) or a $\text{C}_3\text{-C}_6$ cycloalkyl having 1 to 2 protected or unprotected hydroxyl or oxo group(s)]

or a reactive derivative thereof with a compound of the general formula [IV]

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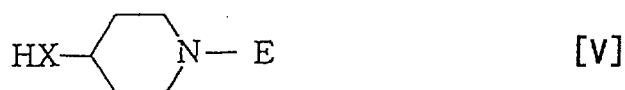


[wherein R^{20} represents a $\text{C}_5\text{-C}_{15}$ saturated or unsaturated aliphatic hydrocarbon group in which any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), $\text{C}_5\text{-C}_{15}$ saturated

or unsaturated aliphatic hydrocarbon having 1-2 protected or unprotected hydroxyl or oxo group(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, unprotected or protected amino, unprotected or protected lower alkylamino or aralkyloxycarbonyl group) and X stands for NH or O] or a salt thereof;

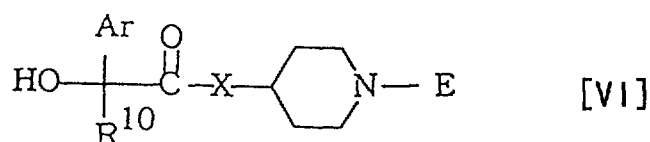
and when either R^{10} or R^{20} has unprotected or protected 1 to 2 hydroxyl or oxo group(s), converting said hydroxyl or oxo group(s) to fluorine atom(s) either as they are or after removing the protective group(s); when R^{10} or R^{20} has protected amino or protected lower alkylamino group(s), removing the protective group(s); and when R^{10} or R^{20} has lower alkoxy, carbonyl or aralkyloxycarbonyl, converting the same to amino; or

(b) reacting a carboxylic acid of the above general formula [III] or a reactive derivative thereof with a compound of the general formula [V]



[wherein E is a protective group for an imino group, and X is as defined above]

or a salt thereof; deprotecting the resulting compound of the general formula [VI]





[wherein Ar has the signification as defined in Claim 1 and R^{10} , X and E are as defined above]

thereafter reacting the same with a compound of the general formula [VII]



[wherein L represents a leaving group, and R^{20} is as defined above]

if necessary in the presence of a base, and again if necessary conducting a conversion reaction of R^{10} and R^{20} similar to the above; or

(c) deprotecting a compound of the above general formula [VI] and subjecting it to a reductive alkylation reaction with a compound of the general formula [VIII]



[wherein R^{21} represents a C_4-C_{14} saturated or unsaturated aliphatic hydrocarbon in which any 1 to 6 hydrogen atom(s) may be substituted with fluorine atom(s), C_4-C_{14} saturated or unsaturated aliphatic hydrocarbon having unprotected or protected 1 to 2 hydroxyl or oxo group(s), aryl, aralkyl, arylalkenyl or heteroaryl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1-3 hydrogen atoms on the ring in said aryl, aralkyl, arylalkenyl, heteroaryl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy carbonyl, halo-



gen, lower alkoxy, unprotected or protected amino, unprotected or protected lower alkyl-amino or aralkyloxycarbonyl),

and if necessary conducting the conversion reaction of R^{10} and R^{21} similar to the above.

18. (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

19. 6-tert-butyloxycarbonylaminopyridine-2-methanol, 6-tert-butyloxycarbonylaminopyridin-2-yl-methyl methanesulfonate, 6-tert-butyloxycarbonylaminopyridin-2-ylmethyl chloride or 6-tert-butyloxycarbonylamino-pyridin-2-ylmethyl bromide.