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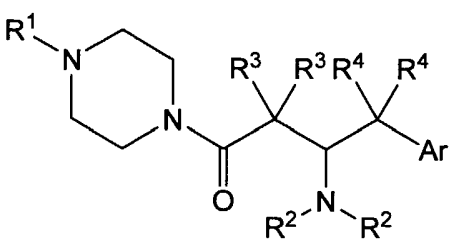
(54) Title: PIPERAZINYL COMPOUNDS



(I)

(57) Abstract: A compound of formula (I) or a pharmaceutically acceptable salt thereof: [wherein Ar is aryl or heteroaryl, optionally substituted; R1 is acyl; R2 is H or lower alkyl; R3 is H, and the like; R4 is H, and the like.] having the activity inhibiting DPP-IV activity. They are therefore useful in the treatment or prevention of conditions mediated by DPP-IV, such as Type 2 Diabete Mellitus.

DESCRIPTION

PIPERAZINYL COMPOUNDS

TECHNICAL FIELD

This invention relates to the compound and pharmaceutically acceptable salt thereof which inhibit dipeptidyl peptidase-IV (DPP-IV).

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above-mentioned compound or pharmaceutically acceptable salt thereof as an active ingredient, a method for treatment and/or prevention of the disease mediated by DPP-IV, use of the above compound, and the like.

BACKGROUND ART

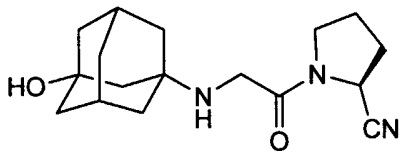
It is known that DPP-IV has various physiological functions in living body, especially has the action which inactivates Glucagon-like peptide-1 (GLP-1) by cleaving the N-terminal dipeptide (His-Ala) and decomposes some cytokines. That is, the resultant peptide is the receptor antagonist of GLP-1 and totally reduces the activity of GLP-1.

This GLP-1 has very important role in glucose metabolism. For example, GLP-1 (1) intensifies the secretion of insulin, (2) stimulates expression of genes which are indispensable for the secretion of insulin, (3) stimulates proliferation of β-cell, (4) suppresses secretion of glucagon, (5) suppresses the

function involving secretion and motility of digestive organs (especially, peristalsis), and (6) suppresses appetite. That is, GLP-1 restricts food ingestion, postpones the process of digestion and absorption, and raises the use of the glucose in blood.

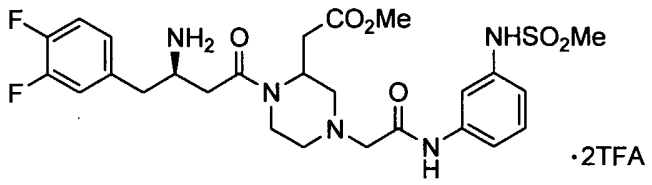
Therefore, the inhibitor of DPP-IV can maintain the activity of GLP-1, so it is expected as a medicine to treat and prevent various diseases, especially type 2 diabetes mellitus (T2DM).

Hitherto, such inhibitors of DPP-IV are known so far. For example in WO 00/34241, 2-cyanopyrrolidine compounds having substituted adamantyl structure like following are disclosed.



"LAF-237"
Pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano, (S)

In WO 03/000181, β-amino acid derivatives as following are described.



DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that the compound of this invention has the outstanding activity to inhibit DPP-IV, and the inventors completed this invention.

Accordingly, this invention relates to DPP-IV inhibitor. More particularly, this invention relates to DPP-IV inhibitor useful for treating or preventing conditions mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (type 1 and type 2), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

That is, one object of this invention is to provide new compound and pharmaceutically acceptable salt thereof, of which activity to inhibit DPP-IV is remarkably improved against known compounds, preferably having a good oral activity and a high safety profile.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound or pharmaceutically acceptable salt thereof as an active ingredient.

A further object of this invention is to provide an inhibitor of DPP-IV and a method for inhibiting DPP-IV comprising administering an effective amount of the compound or pharmaceutically acceptable salt thereof.

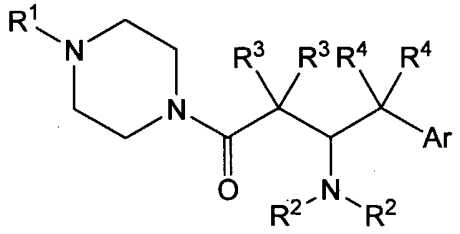
A further object of this invention is to provide a use of the compound and pharmaceutically acceptable salt thereof as medicaments.

A further object of this invention is to provide the compound and pharmaceutically acceptable salt thereof which are useful for the manufacture of medicaments for treating or preventing conditions

mediated by DPP-IV inhibition, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (type 1 and type 2), diabetic neuropathy, diabetic nephropathy, and secondary diseases in mammals caused by diabetes mellitus, especially T2DM.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

The present invention is directed to the following compound of the formula (I) or pharmaceutically acceptable salt thereof.



(I)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

R^1 is acyl;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl.]

In the above and subsequent description of the

present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphthyl, indenyl, biphenyl, and the like, and it is preferably (C6-C10)aryl, more preferably phenyl.

The "cycloalkyl" includes a cycloalkyl group having 3 to 10 carbon atoms, that may be crosslinked, preferably a cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl group.

The "heterocycle" includes a saturated or unsaturated 4- to 8-membered heterocyclic group which has 1 to 4 hetero atoms selected from N, S and O, and which may be a monocyclic ring, or may form a bicyclic or tricyclic fused ring by being fused with heterocycle(s), aryl(s) or cycloalkyl(s).

The "saturated heterocyclic group" means preferably 5- to 7-membered heterocyclic group and may fuse with cycloalkyl(s). The "saturated heterocyclic group" may include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, piperadinyl, morpholinyl, thiomorpholinyl, azepanyl and diazepanyl.

The "unsaturated heterocyclic group" includes heteroaryl and partially saturated heteroaryl. The "partially saturated heteroaryl" includes pyrrolinyl, imidazolinyl, pyrazolinyl, dihydrothiazolyl, dihydroisothiazolyl, dihydrooxazolyl,

dihydroisoxazolyl, dihydrothiadiazolyl, dihydrooxadiazolyl, dihydrofuranyl, pyranyl, dihydropyranyl, dihydrothiopyranyl, tetrahydroazepinyl, dihydroazepinyl, azepinyl, diazepinyl, 3,4-dihydro-2H-1,4-benzoxadinyl, 3,4-dihydro-2H-1,4-benzothiadinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, chromanyl, isochromanyl, 3,4-dihydro-2H-1-benzothiopyranyl, 3,4-dihydro-1H-2-benzothiopyranyl, indolinyl, isoindolinyl, 1,2,3,4-tetrahydroquinolyl and 1,2,3,4-tetrahydroisoquinolyl.

The "heteroaryl" means preferably 5- or 6-membered or condensed aromatic heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen and sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazol, or the like; 6-membered heteroaryl group such as pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like; and condensed heteroaryl group such as indolyl, isoindolyl, indazolyl, purinyl, quinolyl, isoquinolyl, benzopyrrolyl, benzoimidazolyl, benzotriazolyl, benzofuranyl, isobenzofuranyl, phthalanyl, chromenyl, chromonyl, benzothienyl, isobenzothienyl, benzothiazolyl, phthalimidyl, or the like.

The term "acyl" can be exemplified by R-C(=O)-, R-S(=O)-, $R-S(=O)_2-$, R-C(=NR)-, in which R is not specified. It is preferably, R-C(=O)-, R-S(=O)- or

R-S(=O)$_2$-, more preferably, R-C(=O)- or R-S(=O)$_2$-, most preferably R-C(=O)-.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Therefore, the "lower alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like. It is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "lower alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, hexoxy, and the like. It is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, more preferably a fluorine atom or a chlorine atom, most preferably a fluorine atom.

The "halogenated lower alkyl" means the above lower alkyl substituted by halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, and the like. It is preferably halogenated (C1-C4)alkyl, more preferably halogenated (C1-C2)alkyl, more preferably fluorinated

(C1-C4)alkyl, more preferably fluorinated (C1-C2)alkyl, most preferably trifluoromethyl.

The "aryl-(lower alkyl)" means the "lower alkyl" group mentioned above substituted by the aryl group, and includes benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, and the like. It is preferably phenyl-(lower alkyl), more preferably phenyl-(C1-C4)alkyl, more preferably phenyl-(C1-C3)alkyl.

The "heterocycle-(lower alkyl) " means the "lower alkyl" group mentioned above substituted by the heterocyclic group. It is preferably heterocycle-(C1-C4)alkyl, more preferably heterocycle-(C1-C2)alkyl, more preferably heterocycle-methyl.

The "aryl-(lower alkoxy)" means the "lower alkoxy" group mentioned above substituted by the aryl group, and includes benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 1-naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, and the like. It is preferably phenyl-(lower alkoxy), more preferably phenyl-(C1-C4)alkoxy, more preferably phenyl-(C1-C2)alkoxy, most preferably benzyloxy.

The "heteroaryl-(lower alkoxy)" means the "lower alkoxy" group mentioned above substituted by the heteroaryl group. It is preferably heteroaryl-(C1-C4)alkoxy, more preferably

heteroaryl-(C1-C2)alkoxy, more preferably heteroaryl-methoxy.

The "(lower alkoxy)-carbonyl" means carbonyl group substituted by the above mentioned lower alkoxy group, and includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like. It is preferably (C1-C4)alkoxy-carbonyl, more preferably, methoxycarbonyl or t-butoxycarbonyl, most preferably t-butoxycarbonyl.

Though the "substituent" in the definition of Compound (I) is not limited, it means general substituent. The "substituent" can be preferably selected from the group consisting of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, nitro, amino, carbamoyl, aminosulfonyl, carboxy, (lower alkoxy)-carbonyl, R^6-S-, R^6-S(O)-, R^6-SO_2-, R^6-SO_2NH-, R^6-CONH-, R^6-$CONHSO_2$-, R^6-SO_2NHCO-, lower alkyl substituted by 1 to 3 of R^7, heteroaryl, and oxo; wherein R^6 is lower alkyl, halogenated lower alkyl, or phenyl optionally substituted with halogen, lower alkyl or halogenated lower alkyl; R^7 is hydroxy, lower alkoxy, carboxy, (lower alkoxy)-carbonyl, carbamoyl; and any nitrogen atoms in carbamoyl or aminosulfonyl may be substituted by lower alkyl.

The number of substituent may be two or more if possible, preferably up to 5, more preferably up to 3. In case that the number of substituent is plural, they may be identical or different to each other. For

example, in case where both "Ar" and "R^5" in the definition of the present invention have two or more substituents, the substituents may be the same or different to each other.

The Compound (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and this invention includes both mixtures and separate individual tautomers.

The Compound (I) and their salts may be in a form of a solvate such as hydrate, which is included within the scope of the present invention.

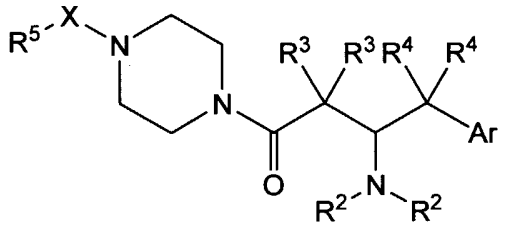
Also included in the scope of this invention are radiolabelled derivatives of Compound (I) which are suitable for biological studies.

In the scope of the present invention, the prodrug of the Compound (I) is included, which prodrug is capable of undergoing metabolic conversion to Compound (I) following administration in body. Further, in the scope of the present invention, metabolites of Compound (I) are included, which metabolites may be therapeutically active in the treatment of the targeted medical condition.

The compound of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include an organic acid salt (e.g., acetate, maleate, tartrate,

methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, or the like), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, or the like), a salt with an amino acid (e.g., aspartate, glutamate, or the like), or the like.

The compound (I) may preferably include Compound (Ia) as following:



(Ia)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl;

R^5 is lower alkyl,

halogenated lower alkyl,

aryl optionally substituted,

heterocycle optionally substituted,

cycloalkyl optionally substituted,

aryl-O optionally substituted,

heterocycle-O optionally substituted,

aryl-(lower alkyl) optionally substituted

on the aryl,

heterocycle-(lower alkyl) optionally substituted on the heterocycle,

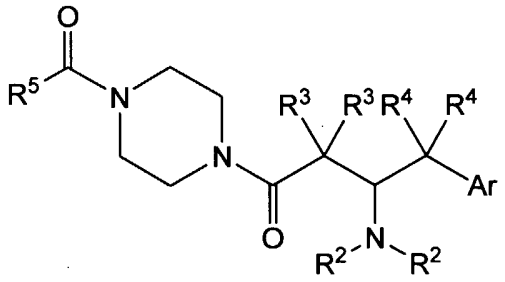
aryl-(lower alkoxy) optionally substituted on the aryl, or

heterocycle-(lower alkoxy) optionally substituted on the heterocycle;

X is $-C(=O)-$ or $-S(=O)_2-$;

the same applies hereinafter.]

The compound (I) may more preferably include Compound (Ib) as following:



(Ib)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl;

R^5 is lower alkyl,

halogenated lower alkyl,

aryl optionally substituted,

heterocycle optionally substituted,

cycloalkyl optionally substituted,

aryl-O optionally substituted,
heterocycle-O optionally substituted,
aryl-(lower alkyl) optionally substituted on the aryl,
heterocycle-(lower alkyl) optionally substituted on the heterocycle,
aryl-(lower alkoxy) optionally substituted on the aryl, or
heterocycle-(lower alkoxy) optionally substituted on the heterocycle;

the same applies hereinafter.]

In the each definition of the Compound (I), preferably,

(1) Ar is aryl optionally substituted;

(2) Ar is phenyl optionally substituted;

(3) the substituent(s) of Ar is selected from the group consisting of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, nitro, amino, carbamoyl, aminosulfonyl and carboxy;

(4) the substituent(s) of Ar is selected from the group consisting of lower alkyl, halogen, cyano, nitro, carbamoyl, aminosulfonyl and carboxy;

(5) the substituent(s) of Ar is halogen;

(6) the substituent(s) of Ar is selected from the group consisting of a fluorine atom and a chlorine atom;

(7) the substituent(s) of Ar is a fluorine atom;

(8) R^1 is $-C(=O)-R^5$ or $-S(=O)_2-R^5$, wherein R^5 is lower alkyl, halogenated lower alkyl, aryl optionally substituted, heterocycle optionally substituted,

cycloalkyl optionally substituted, aryl-O optionally substituted, heterocycle-O optionally substituted, aryl-(lower alkyl) optionally substituted on the aryl, heterocycle-(lower alkyl) optionally substituted on the heterocycle, aryl-(lower alkoxy) optionally substituted on the aryl, or heterocycle-(lower alkoxy) optionally substituted on the heterocycle;

(9) R^1 is $-C(=O)-R^5$;

(10) R^1 is $-C(=O)-R^5$, wherein R^5 is lower alkyl, halogenated lower alkyl, aryl optionally substituted, heteroaryl optionally substituted, cycloalkyl optionally substituted, aryl-O optionally substituted, heteroaryl-O optionally substituted, aryl-(lower alkyl) optionally substituted on the aryl, heteroaryl-(lower alkyl) optionally substituted on the heteroaryl, aryl-(lower alkoxy) optionally substituted on the aryl, or heteroaryl-(lower alkoxy) optionally substituted on the heteroaryl;

(11) R^1 is $-C(=O)-R^5$, wherein R^5 is lower alkyl, halogenated lower alkyl, aryl optionally substituted, heteroaryl optionally substituted, aryl-(lower alkoxy) optionally substituted on the aryl, or heteroaryl-(lower alkoxy) optionally substituted on the heteroaryl;

(12) R^1 is $-C(=O)-R^5$, wherein R^5 is lower alkyl, aryl optionally substituted, heteroaryl optionally substituted, aryl-O optionally substituted, heteroaryl-O optionally substituted or aryl-(lower alkoxy) optionally substituted on the aryl;

(13) R^1 is $-C(=O)-R^5$, wherein R^5 is lower alkyl;

(14) R^1 is $-C(=O)-R^5$, wherein R^5 is aryl optionally substituted or heteroaryl optionally substituted;

(15) R^1 is $-C(=O)-R^5$, wherein R^5 is aryl optionally substituted;

(16) R^1 is $-C(=O)-R^5$, wherein R^5 is heteroaryl optionally substituted;

(17) the substituent(s) of R^5 is selected from the group consisting of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, nitro, amino, carbamoyl, aminosulfonyl, carboxy, (lower alkoxy)-carbonyl, R^6-S-, R^6-S(O)-, R^6-SO_2-, R^6-SO_2NH-, R^6-CONH-, R^6-$CONHSO_2$-, R^6-SO_2NHCO-, lower alkyl substituted by 1 to 3 of R^7, heteroaryl, and oxo; wherein R^6 is lower alkyl, halogenated lower alkyl, or phenyl optionally substituted with halogen, lower alkyl or halogenated lower alkyl; R^7 is hydroxy, lower alkoxy, carboxy, (lower alkoxy)-carbonyl, carbamoyl; and any nitrogen atoms in carbamoyl or aminosulfonyl may be substituted by lower alkyl;

(18) the substituent(s) of R^5 is selected from the group consisting of lower alkyl, lower alkoxy, halogen, carbamoyl, aminosulfonyl, carboxy and (lower alkoxy)-carbonyl;

(19) the substituent(s) of R^5 is selected from the group consisting of lower alkoxy, halogen, aminosulfonyl, carboxy and (lower alkoxy)-carbonyl;

(20) R^2 is H;

(21) R^2 is (C1-C4)alkyl;

(22) R^2 is (C1-C2)alkyl;

(23) R^3 is H;

(24) R^3 is (C1-C4)alkyl;

(25) R^3 is (C1-C2)alkyl;

(26) R^4 is H;

(27) R^4 is (C1-C4)alkyl;

(28) R^4 is (C1-C2)alkyl.

The combination of any two or more of (1) to (28) is more preferable.

The Compound (I) is preferably selected from:

(2R)-1-(3,4-Difluorophenyl)-4-[4-(2-methoxybenzoyl)-1-piperazinyl]-4-oxo-2-butanamine hydrochloride;

(2R)-4-[4-(2-Methoxybenzoyl)-1-piperazinyl]-4-oxo-1-(2,4,5-trifluorophenyl)-2-butanamine hydrochloride;

(2R)-1-(3,4-Difluorophenyl)-4-[4-(2,6-dimethoxybenzoyl)-1-piperazinyl]-4-oxo-2-butanamine hydrochloride;

(2R)-1-(3,4-Difluorophenyl)-4-[4-(5-fluoro-2-methoxybenzoyl)-1-piperazinyl]-4-oxo-2-butanamine hydrochloride;

3-({4-[(3R)-3-Amino-4-(3,4-difluorophenyl)-butyryl]-1-piperazinyl}-carbonyl)-4-methoxybenzenesulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butyryl]-1-piperazinyl}carbonyl)-4-methoxybenzenesulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(3,4-difluorophenyl)-butyryl]-1-piperazinyl}carbonyl)benzenesulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-

butanoyl]-1-piperazinyl}carbonyl)benzoic acid hydrochloride;

4-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)benzoic acid hydrochloride;

5-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)isophthalic acid hydrochloride; and

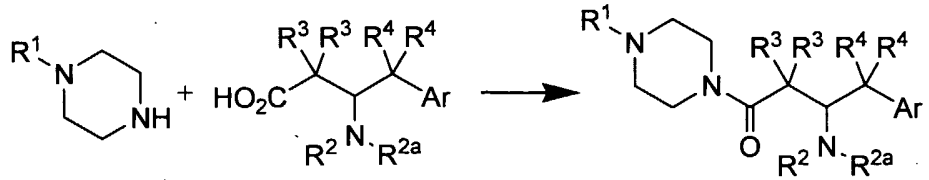
5-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)nicotinic acid dihydrochloride.

The Compound (I) of the present invention can be prepared according to the following Process A to C.

In the following production methods, it is sometimes effective from the viewpoint of the production technique to replace a certain functional group depending on the type with an appropriate protective group, namely a group readily convertible to the functional group, at the stage of a raw material or intermediate. Afterwards, the protective group can be eliminated, if necessary, to obtain the desired compound. Examples of such a functional group include an amino group, hydroxyl group, carboxyl group and the like. Protective groups thereof are, for example, those described in Protective Groups in Organic Synthesis, the third edition (T. W. Green and P. G. M. Wuts, eds., JOHN WILLY & SONS, INC. (the contents of which are hereby incorporated by reference)). These may be appropriately used depending on the reaction

conditions. For introducing and eliminating such protective groups, the methods described in the reference can be suitably applied.

Process A



(II) (III) (I-1)

In the above formula, in case where R^2 is H, R^{2a} is a protective group, such as (lower alkoxy)-carbonyl, and when R^2 is lower alkyl, R^{2a} is lower alkyl or a protective group; the same applies hereinafter. These combinations of R^2 and R^{2a} hardly have adversely effects on the above reaction.

This process is carried out by reacting piperazinyl compound (II) with carboxylic acid Compound (III).

Compounds (II) and (III) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

In this process, general amide-forming reaction such as reaction using condensating agent can be employable. The condensating agent employable in this process is not particularly limited so long as it accelerates forming amide bond and may include carbodiimide compounds such as dicyclohexyl-carbodiimide (DCC), diisopropylcarbodiimide (DIPCI), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (water solvable carbodiimide: WSCD).

In this case, additive is generally used. The

additive employable in this process is not particularly limited so long as it can mainly make the carboxyl groups of Compound (III) active or suppress the racemization, and may include 1-hydroxybenzotriazole (HOBt), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HOOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HONSu).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as dimethylformamide (DMF) and dimethylacetamide (DMA); aromatic hydrocarbons such as benzene, toluene; ethers such as tetrahydrofuran (THF), 1,4-dioxane; halogenated hydrocarbons such as dichloromethane, chloroform.

This process is generally carried out by adding Compound (II), to the solution of Compound (III), condensing agent and additive.

Generally, when Compound (II) is added, the mixture is cooled. The temperature after addition depends on the starting material, the solvent, or the like, and it is usually room temperature.

The reaction time after the adding depends on the starting material, the solvent, or the like, and it is usually from 1hr to 24hrs.

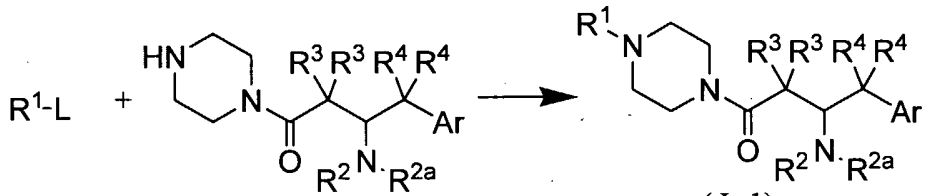
After the reaction, the mixture is quenched with water, and extracted with organic solvent insoluble with water such as ethyl acetate, chloroform, or the like. The organic layer is washed by water such as hydrochloric acid, saturated aqueous $NaHCO_3$, brine, or

the like. The washed organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel chromatography to obtain Compound (I).

The deprotection reactions, if necessary, can be carried out according to the method described in the aforementioned "Protective Groups in Organic Synthesis", the third edition.

Compound (I) can also be synthesized by following Process B.

Process B



(IV) (V) (I-1)

In the above formula, L is OH or a leaving group; the same applies hereinafter.

This process is carried out by reacting Compound (IV) such as carboxylic acid compound with piperazinyl compound (V) in the presence of catalyst in solvent.

Compounds (IV) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds, since the structure of Compound (IV) is relatively simple. Compounds (V) can be obtained in Process C mentioned after.

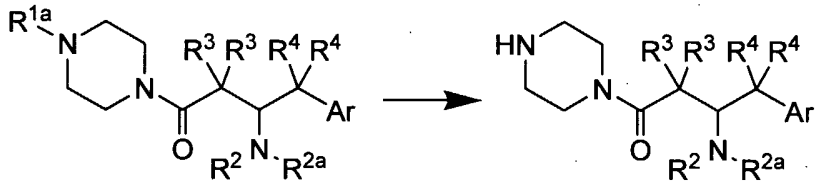
The condition described in the above mentioned Process A can be applied to this Process B, when

carboxylic acid is used as compound (IV).

In case that L is a leaving group, an acid halide (acid chloride, or the like) or an acid anhydride can be used as compound (IV), and then a base [an inorganic base such as potassium carbonate, sodium hydroxide, or the like, or an organic base such as triethylamine (TEA), diisopropylethylamine, pyridine, or the like] is preferably added.

The Compound (V) which is starting material of the above Process B can be prepared according to the following Process C.

Process C



(I-2) (V)

R^{1a} represents aryl-(lower alkoxy)-C(=O)- or heteroaryl-(lower alkoxy)-C(=O)- in the definition of R^1, or lower alkoxy-C(=O)-, that is, each acyl group can be easily cleaved as protective group of amino group.

Process C is the process for removing of acyl group from amino group of piperazinyl moiety.

Compound (I-2) can be synthesized by Process A mentioned above.

The condition of Process C can be carried out according to the method described in the aforementioned "Protective Groups in Organic Synthesis", the third edition.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

The patents, patent applications and publications cited herein are incorporated by reference.

The pharmaceutical composition of the invention, which contains as effective components one type or two or more types of the compound of the invention, can be prepared according to a method usually used by using pharmaceutical carriers, excipients and the like for general use in this field. Administration thereof may be either oral via tablets, pills, capsules, granules, powders, liquids, and the like or parenteral dosing via injections such as intravenous injections, intramuscular injections, and the like, external agents such as ointments, plasters, creams, jellies, cataplasm, sprays, lotions, eye drops, eye ointments, and the like, suppositories, inhalation agents, and the like.

As the solid composition for oral administration, tablets, powders, granules and the like are used. In such a solid composition, one or more active substances are mixed with at least one inert excipient, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, or the like. According to general methods, the composition may contain inert additives such as

lubricants, e.g., magnesium stearate, or the like; disintegrators, e.g., sodium carboxymethyl starch, or the like; and dissolution auxiliary agents. The tablets or pills may be coated with sugar coating or stomach-soluble or enteric coating.

Examples of the liquid composition for oral administration include pharmaceutically acceptable emulsions, liquids, suspensions, syrups, elixirs, or the like, in which inert solvents for general use such as purified water, ethanol, or the like can be incorporated. In addition to the inert solvents, the composition may further contain auxiliary agents such as solubilizing agents, moistening agents and suspending agents; sweetening agents; flavoring agents; aromatic agents and preservatives.

Examples of the injections for parenteral administration include sterile aqueous or non-aqueous liquids, suspensions and emulsions. The aqueous solvents include, for example, distilled water for injections and physiological saline. The non-aqueous solvents include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, Polysorbate 80 (under trade name) and the like. Such compositions may further contain isotonic agents, preservatives, moistening agents, emulsifying agents, dispersing agents, stabilizers and dissolution auxiliary agents. These are sterilized by filtering through bacteria-retaining filters, by incorporating sterilizing agents, or by irradiation. Alternatively, these may be produced

into a sterile solid composition and then dissolved or suspended in sterile water or sterile solvents for injections prior to use.

While the dosage of therapeutically effective amount of the Compound (I) depend upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the Compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day. The dose is administered once or in separate portions.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

The following abbreviations are used in the Tables. Ex: Example number, REx: Reference example number, Str: Structure, Dat: physicochemical data (FAB: FAB-MS(M+H)$^+$, FAB-N: FAB-MS(M-H)$^-$, ESI: ESI-MS(M+H)$^+$, ESI-N: ESI-MS(M-H)$^-$, NMR1: δ(ppm) of characteristic peaks of ^{1}H-NMR in DMSO-d_6, NMR2: δ(ppm) of characteristic peaks of ^{1}H-NMR in $CDCl_3$), Sal: salt (HCl: hydrochloride, TsOH: p-toluenesulfonate, Ox: oxalate, Frm: formate, "-" or blank column: free compound, the numeral before a component means molar ratio, for example 2HCl means dihydrochloride), Syn: production method (each numeral indicates a similarly produced

Example or Reference example number), Me: methyl, Et: ethyl, Pr: 1-propyl, tBu: tert-butyl, Ac: acetyl, Ph: phenyl, Bn: benzyl, Boc: tBu-O-C(=O)-, and Ms: Me-S(=O)$_2$-. In addition, the numeral before each substituent shows the position of substitution, for example, 2,6-(OMe)$_2$-Ph means 2,6-dimethoxyphenyl and 2-F-6-OMe-Ph means 2-fluoro-6-methoxyphenyl.

Reference example 1

To a stirred mixture of 3-(R)-t-butoxycarbonylamino-4-(3,4-difluorophenyl)butyric acid (75 mg) and HOBt (35 mg) in DMF (3 mL), was added WSCD hydrochloride (50 mg) at ice-bath temperature. The mixture was stirred for 30 minutes at room temperature, then 1-acetylpiperazine (32 mg) was added to the mixture at ice-bath temperature. After addition, the resulting mixture was stirred for overnight at room temperature. The reaction mixture was poured into water (15 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with chloroform/methanol (50:1 to 10:1) to give t-Butyl [(2R)-4-(4-acetyl-1-piperazinyl)-1-(3,4-difluorophenyl)-4-oxobutyl]carbamate (100 mg).

Reference example 2

To a solution of t-butyl [(2R)-4-(4-benzyloxycarbonyl-1-piperazinyl)-1-(3,4-difluoro-phenyl)-4-oxobutyl]carbamate (333 mg) in ethanol (10 mL), was added 10% palladium on carbon (70 mg). The resulting mixture was stirred under atmospheric hydrogen at room temperature for 4.5 hours. The mixture was filtered through Celite and washed with ethanol. The filtrate was concentrated in vacuo to give t-Butyl [(2R)-4-(1-piperazinyl)-1-(3,4-difluoro-phenyl)-4-oxobutyl]carbamate (246 mg) as a colorless solid.

Reference example 3

To a stirred mixture of 2-methoxybenzoic acid (15.0 mg) and HOBt (14.7 mg) in DMF (300 µL), was added WSCD hydrochloride (20.8 mg) at ice-bath temperature. The mixture was stirred for 1 hour at room temperature, then a solution of t-butyl [(2R)-4-(1-piperazinyl)-1-(3,4-difluorophenyl)-4-oxobutyl]carbamate (37.8 mg) in DMF (150 µL) was added dropwise to the mixture at ice-bath temperature. After addition, the resulting mixture was stirred for overnight at room temperature. The reaction mixture was poured into saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with chloroform/methanol (50/1 to 20/1) to give t-Butyl [(2R)-4-(2-methoxybenzoyl-1-piperazinyl)-1-(3,4-

difluorophenyl)-4-oxobutyl]carbamate (50.8 mg).

Reference example 4

To a solution of diethyl 5-({4-[(benzyloxy)-carbonyl]-1-piperazinyl}carbonyl)isophthalate (1.10 g) in ethanol (5 mL) was added a solution of potassium hydroxide (136 mg) in ethanol (4 mL) at room temperature, and the mixture was stirred at same temperature for 5.5 hours. The reaction mixture was evaporated in vacuo and the residue was dissolved in water. The aqueous layer was washed with ethyl ether, adjusted to pH3 with 1 mol/L hydrochloric acid, and extracted with chloroform. The organic layer was dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from a mixture of hexane and isopropyl ether (1/1) to give 3-({4-[(benzyloxy)carbonyl]-1-piperazinyl}carbonyl)-5-(ethoxycarbonyl)benzoic acid (810 mg) as crystals.

Reference example 5

To a mixture of 3-({4-[(benzyloxy)carbonyl]-1-piperazinyl}carbonyl)-5-(ethoxycarbonyl)benzoic acid (1.00 g), THF (12.5 mL), and t-butanol (12.5 mL) were added di-t-butyl dicarbonate (495 mg) and 4-dimethylaminopyridine (27 mg) at room temperature under nitrogen, and the mixture was stirred at room temperature for 18 hours. To the mixture were added di-t-butyl dicarbonate (495 mg) and

4-dimethylaminopyridine (10 mg), and the reaction mixture was stirred for another 8 hours. The solvent was removed in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. Obtained colorless solid was triturated with a mixture of petroleum ether and hexane (1/1) to give t-butyl ethyl 5-({4-[(benzyloxy)carbonyl]-1-piperazinyl}-carbonyl)isophthalate (1.00 g) as a colorless powder.

Reference example 6

To a suspension of chelidamic acid monohydrate (1.0 g) in ethanol (10 mL) was added sulfuric acid (1 mL) on an ice-water bath, and the mixture was heated to reflux with stirring for 1 hour. After cooling, the reaction mixture was concentrated in vacuo. The residue was adjusted to pH5 with saturated sodium bicarbonate aqueous solution, and the precipitates formed were filtered off. The filtrate was washed with ether, and concentrated in vacuo. The residue was dissolved in water, and the solution was filtered through HP-20. The solution was concentrated in vacuo, and the residue was triturated with isopropyl ether to give 6-(ethoxycarbonyl)-4-hydroxy-2-pyridinecarboxylic acid (260 mg) as a powder.

Reference example 7

To a solution of 3-(ethoxycarbonyl)-5-nitrobenzoic acid (2.00 g) in methanol (30 mL) was added Pd/C (200 mg). The mixture was agitated under 2.5 atm hydrogen atmosphere for 4 hours at room temperature. The reaction mixture was filtrated and the filtrate was concentrated in vacuo. The residue (1.74 g) was dissolved in pyridine (20 mL). To the solution was added methylsulfonyl chloride (644μL) and stirred for 3 hours at room temperature. The reaction mixture was concentrated in vacuo. To the residue was added ethyl acetate and 1 mol/L hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated in vacuo to obtain 3-(ethoxycarbonyl)-5-[(methylsulfonyl)amino]-benzoic acid as pale red solid (1.29 g).

Reference example 8

To a mixture of t-Butyl [(2R)-4-[4-(4-methoxycarbonylbenzoyl)-1-piperazinyl]-1-(2,4,5-trifluorophenyl)-4-oxobutyl]carbamate (190 mg), THF (5.0 mL) and methanol (1.5 mL) was added 1 mol/L NaOH aqueous solution (1.0 mL) at 0°C. After the reaction mixture was stirred at room temperature for 1.5 hours, 1 mol/L hydrochloric acid (1.0 mL) was added to the reaction mixture at 0°C. The solution was concentrated under reduced pressure and was added water. The precipitates were collected by filtration, then washed with water to give t-Butyl [(2R)-4-[4-(4-carboxybenzoyl)-1-piperazinyl]-1-(2,

4,5-trifluorophenyl)-4-oxobutyl]carbamate (180 mg) as white solid.

Reference example 9

A mixture of t-Butyl [(2R)-4-[4-(4-cyanobenzoyl)-1-piperazinyl]-1-(2,4,5-trifluorophenyl)-4-oxobutyl]carbamate (250 mg), NaN_3 (75 mg), NH_4Cl (65 mg) and DMF (10.0 mL) was stirred at 100°C for 20 hours. The reaction mixture was diluted with water and extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0 to 85:15) to give t-Butyl [(2R)-4-[4-(4-tetrazol-5-ylbenzoyl)-1-piperazinyl]-1-(2,4,5-trifluorophenyl)-4-oxobutyl]carbamate (240 mg) as colorless solid.

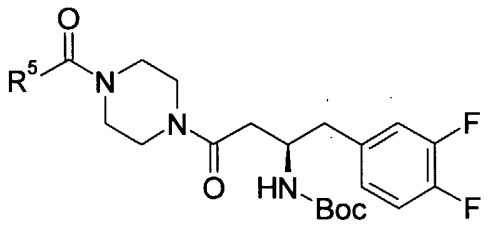
Reference example 10

Triethylamine (0.44 mL) was added to a suspension of hydroxylamine hydrochloride (250 mg) in dimethylsulfoxide (DMSO, 5.0 mL). An insoluble material was filtered off and washed with THF. The Filtrate was concentrated in vacuo to remove THF, and t-Butyl [(2R)-4-[4-(4-cyanobenzoyl)-1-piperazinyl]-1-(2,4,5-trifluorophenyl)-4-oxobutyl]carbamate (250 mg) was added to the DMSO solution. After stirring at 75°C for 18 hours, the reaction mixture was diluted with

water and extracted with ethyl acetate. To the aqueous solution was added 1 mol/L NaOH aqueous solution and extracted with ethyl acetate (3 x 30 mL). The combined organic solution was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (chloroform:methanol=100:0 to 75:25). The obtained compound (180 mg) was dissolved in pyridine (0.050 mL) and DMF (2.0 mL) and 2-ethylhexyl chloroformate (0.060 mL) was added dropwise to the solution under ice-cooling. After stirring at 0°C for 30 min, the reaction mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was dissolved in xylene (3.0 mL). The solution was heated under reflux for 2 hours. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (chloroform:methanol=100:0 to 90:10) to give t-Butyl [(2R)-4-[4-[4-(5-oxo-1,2,4-oxadiazol-3-yl)benzoyl]-1-piperazinyl]-1-(2,4,5-trifluorophenyl)-4-oxobutyl]carbamate (100 mg).

In a similar manner to the above Reference examples, the compounds of Reference examples 11 to 154 shown in the following Tables 1 to 5 were obtained, respectively. Structures and physicochemical data of the compounds of Reference examples 1 to 154 are shown in Tables 1 to 5.

Table 1-1



REx	R^5	Dat	Syn
1	Me	NMR2: 1.39 (9H, s), 2.13 (3H, s), 2.53 (2H, d, J=5Hz), 2.75-3.10 (2H, m), 3.30-3.75 (8H, m), 4.07 (1H, brs), 5.38 (1H, brs), 6.80-7.20 (3H, m); ESI: 426.	REx 1
3	2-OMe-Ph	NMR1: 1.28 (9H, s), 2.53-2.38 (2H, m), 2.69-2.56 (1H, m), 2.89-2.71 (1H, m), 3.20-3.01 (2H, m), 3.44-3.31 (2H, m), 3.64-3.44 (4H, m), 3.79 (3H, s), 4.03-3.84 (1H, m), 6.83-6.70 (1H, m), 7.43-6.97 (7H, m); ESI: 518.	REx 3
11	2,6-$(OMe)_2$-Ph	NMR1: 1.28 (9H, s), 2.68-2.40 (3H, m), 2.84-2.70 (1H, m), 3.20-2.97 (2H, m), 3.62-3.21 (6H, m), 3.73 (3H, s), 3.73 (3H, s), 4.08-3.82 (1H, m), 6.84-6.66 (3H, m), 7.09-6.97 (1H, m), 7.41-7.12 (3H, m); ESI: 548.	REx 3
12	2-OMe-5-F-Ph	NMR1: 1.28 (9H, s), 2.67-2.38 (3H, m), 2.84-2.68 (1H, m), 3.21-3.02 (2H, m), 3.72-3.30 (6H, m), 3.77 (3H, s), 4.04-3.88 (1H, m), 6.83-6.71 (1H, m), 7.40-6.99 (6H, m); ESI: 536.	REx 3
13	2-OMe-5-Cl-Ph	NMR1: 1.28 (9H, s), 2.55-2.41 (2H, m), 2.71-2.56 (1H, m), 2.85-2.71 (1H, m), 3.20-3.02 (2H, m), 3.72-3.30 (6H, m), 3.79 (3H, s), 4.07-3.86 (1H, m), 6.83-6.70 (1H, m), 7.08-6.91 (1H, m), 7.12 (1H, d, J = 8.5 Hz), 7.41-7.17 (3H, m), 7.46 (1H, d, J = 8.5 Hz); ESI: 553.	REx 3

Table 1-2

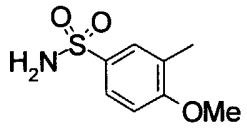
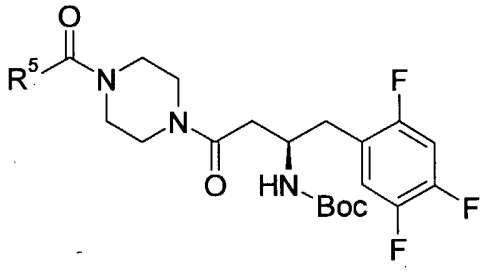
14	2,4,6-(OMe)$_3$-Ph	NMR1: 1.28 (9H, s), 2.70-2.41 (3H, m), 2.86-2.70 (1H, m), 3.20-3.01 (2H, m), 3.70-3.21 (6H, m), 3.72 (3H, s), 3.72 (3H, s), 3.80 (3H, s), 4.09-3.82 (1H, m), 6.26 (1H, s), 6.26 (1H, s), 6.85-6.72 (1H, m), 7.10-6.94 (1H, m), 7.41-7.12 (2H, m); ESI: 578.	REx 3
15		NMR1: 1.28 (9H, s), 2.70-2.41 (3H, m), 2.86-2.71 (1H, m), 3.23-3.04 (2H, m), 3.80-3.36 (6H, m), 3.87 (3H, s), 4.11-3.81 (1H, m), 6.84-6.70 (1H, m), 7.08-6.92 (1H, m), 7.41-7.12 (3H, m), 7.31 (2H, bs), 7.65 (1H, s), 7.85 (1H, d, J = 8.5 Hz); ESI: 597.	REx 3
16	2-F-6-OMe-Ph	NMR1: 1.28 (9H, s), 2.68-2.41 (3H, m), 2.83-2.69 (1H, m), 3.25-3.08 (2H, m), 3.68-3.33 (6H, m), 3.80 (3H, s), 4.08-3.82 (1H, m), 6.84-6.70 (1H, m), 6.89 (1H, dd, J = 9.0,10.5 Hz), 6.96 (1H, d, J = 10.5 Hz), 7.08-6.96 (1H, m), 7.58-7.12 (3H, m); ESI: 536.	REx 3

Table 2-1



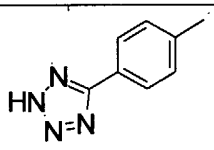
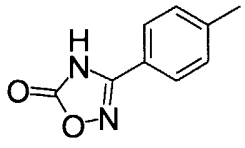
REx	R^5	Dat	Syn
8	4-(CO_2H)-Ph	ESI: 550.	REx 8
9		ESI: 574.	REx 9
10		ESI-N: 588.	REx 10

Table 2-2

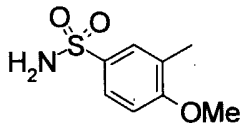
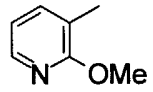
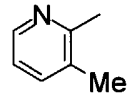
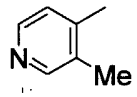
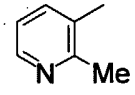
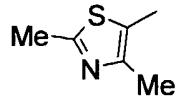
20	2-OMe-Ph	NMR1: 1.26 (9H, s), 2.21 (3H, s), 2.75-2.38 (3H, m), 2.97-2.77 (1H, m), 3.20-3.01 (2H, m), 3.88-3.20 (6H, m), 4.11-3.96 (1H, m), 6.82-6.69 (1H, m), 7.60-7.14 (6H, m); ESI: 536.	REx 3
21	2-Me-Ph	NMR1: 1.26 (9H, s), 2.21 (3H, s), 2.75-2.38 (3H, m), 2.97-2.77 (1H, m), 3.20-3.01 (2H, m), 3.88-3.20 (6H, m), 4.11-3.96 (1H, m), 6.82-6.69 (1H, m), 7.60-7.14 (6H, m); ESI: 520.	REx 3
22		NMR1: 1.27 (9H, s), 2.71-2.40 (3H, m), 2.93-2.79 (1H, m), 3.22-3.01 (2H, m), 3.78-3.33 (6H, m), 3.87 (3H, s), 4.14-3.91 (1H, m), 6.83-6.70 (1H, m), 7.58-7.22 (3H, m), 7.31 (2H, bs), 7.65 (1H, s), 7.86 (1H, d, J = 9.0 Hz); ESI: 615.	REx 3
23		ESI: 637, 639.	REx 3
24	2-F-6-OMe-Ph	ESI: 554.	REx 3
25	2,6-$(OMe)_2$-Ph	ESI: 566.	REx 3
26	3-Ms-Ph	ESI: 584.	REx 3
27		ESI: 537.	REx 3
28		ESI: 521.	REx 3
29		ESI: 521.	REx 3
30		ESI: 521.	REx 3
31	3-CN-Ph	ESI: 531.	REx 3
32	2-OMe-3-F-Ph	ESI: 554.	REx 3
33		ESI: 541.	REx 3
34	3-(NHAc)-Ph	ESI: 563.	REx 3

Table 2-3

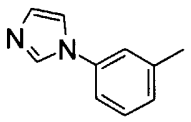
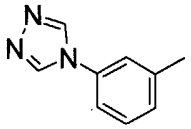
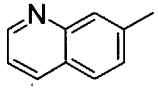
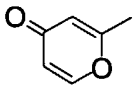
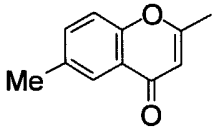
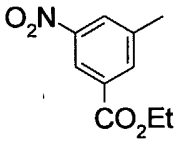
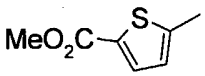
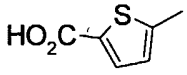
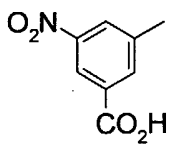
35		ESI: 572.	REx 3
36		ESI: 573.	REx 3
37	Ph	ESI: 528.	REx 3
38	4-CN-Ph	ESI: 531.	REx 3
39	2-OMe-4-SMe-Ph	ESI: 582.	REx 3
40		ESI: 557.	REx 3
41		ESI: 524.	REx 3
42		ESI: 588.	REx 3
43	Me	ESI: 466.	REx 1
44	2-OMe-4-F-Ph	ESI: 576.	REx 3
45	3-CO_2Me-Ph	ESI: 586.	REx 3
46	3-CO_2H-Ph	ESI: 572.	REx 8
47	2-OMe-5-Cl-Ph	ESI: 592, 594.	REx 3
48		ESI: 623.	REx 3
49	4-(CO_2Me)-Ph	ESI: 564.	REx 3
50		ESI: 584.	REx 3
51		ESI: 556.	REx 8
52		ESI: 595.	REx 8

Table 2-4

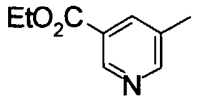
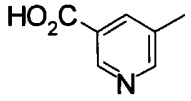
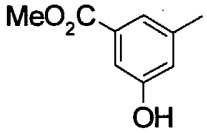
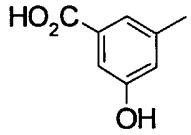
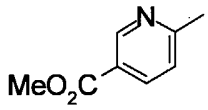
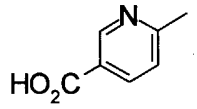
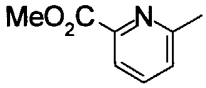
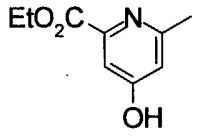
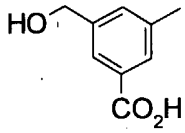
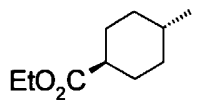
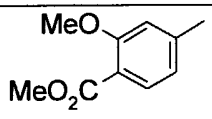
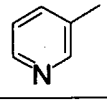
53	3,5-$(CO_2Et)_2$-Ph	ESI: 650.	REx 3
54	3,5-$(CO_2H)_2$-Ph	ESI: 594.	REx 8
55		ESI: 578.	REx 3
56		ESI: 551.	REx 8
57		ESI: 580.	REx 3
58	2-(CO_2Et)-Ph	ESI: 578.	REx 3
59		ESI: 566.	REx 8
60		ESI: 565.	REx 3
61		ESI: 551.	REx 8
62		ESI: 565.	REx 3
63		ESI: 595.	REx 3
64		ESI: 580.	REx 8
65		ESI: 584.	REx 3
66		ESI: 594.	REx 3
67		ESI: 507.	REx 3

Table 2-5

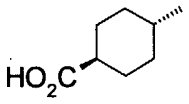
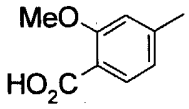
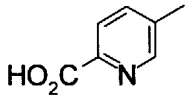
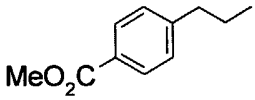
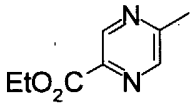
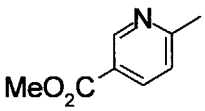
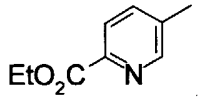
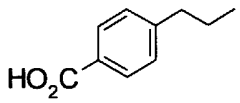
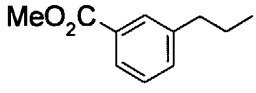
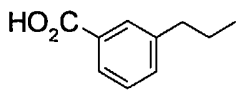
68		ESI: 556.	REx 8
69	4-($CONH_2$)-Ph	ESI: 549.	REx 3
70		ESI: 580.	REx 8
71		ESI: 551.	REx 8
72		ESI: 592.	REx 3
73		ESI: 580.	REx 3
60		ESI: 565.	REx 3
74	4-(CH_2CO_2H)-Ph	ESI: 564.	REx 8
75	4-(NHMs)-Ph	ESI: 599.	REx 3
76	4-(SO_2NH_2)-Ph	ESI: 585.	REx 3
77	4-(NHAc)-Ph	ESI: 563.	REx 3
78		ESI: 579.	REx 3
79	4-(CH_2CO_2Me)-Ph	ESI: 578.	REx 3
80	4-(CH_2OH)-Ph	ESI: 536.	REx 3
81	3-(CH_2CO_2Me)-Ph	ESI: 578.	REx 3
82		ESI: 578.	REx 8
83		ESI: 592.	REx 3
84		ESI: 578.	REx 8

Table 2-6

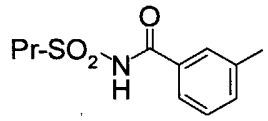
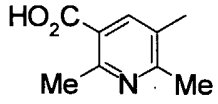
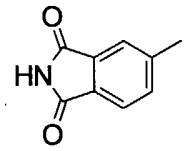
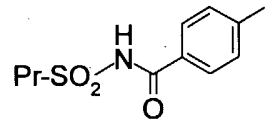
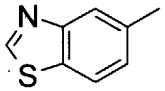
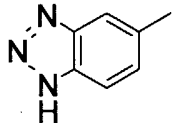
85	3-(CH_2CO_2H)-Ph	ESI: 564.	REx 8
86	4-[$(CH_2)_3CO_2H$]-Ph	ESI: 592.	REx 8
87	4-(CO_2Me)-Bn	ESI: 578.	REx 3
88	4-[$(CH_2)_2CO_2Et$]-Ph	ESI: 606.	REx 3
89	4-[$(CH_2)_2CO_2H$]-Ph	ESI: 578.	REx 8
90	4-(NHBoc)-Ph	ESI: 621.	REx 3
91	4-(CO_2H)-Bn	ESI: 564.	REx 8
92	3-(CO-NH-Ms)-Ph	ESI: 627.	REx 3
93		ESI: 655.	REx 3
94	4-(CO-NH-Ms)-Ph	ESI: 627.	REx 3
95		ESI: 579.	REx 8
96		ESI: 575.	REx 3
97	3-Br-5-CO_2H-Ph	ESI: 628, 630.	REx 8
98	3-tBu-5-CO_2H-Ph	ESI: 606.	REx 8
99		ESI: 655.	REx 3
100		ESI: 563.	REx 3
101		ESI: 547.	REx 3

Table 2-7

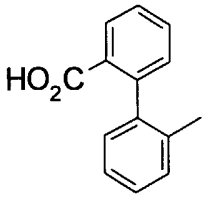
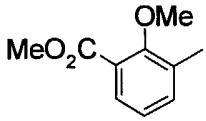
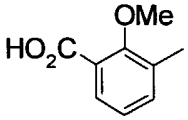
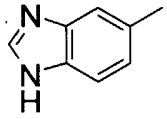
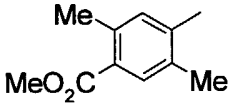
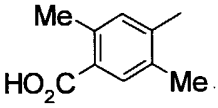
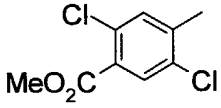
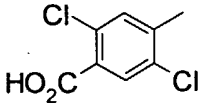
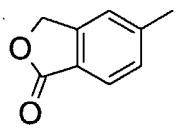
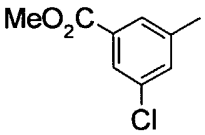
102		ESI: 626.	REx 3
103		ESI: 594.	REx 3
104		ESI: 580.	REx 8
105		ESI: 546.	REx 3
106		ESI: 592.	REx 3
107		ESI: 578.	REx 8
108		ESI: 632, 634.	REx 3
109		ESI: 618, 620.	REx 8
110	3-[$(CH_2)_2CO_2Et$]-Ph	ESI: 606.	REx 3
111		ESI: 562.	REx 3
112		ESI: 598, 600.	REx 3

Table 2-8

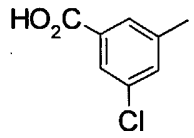
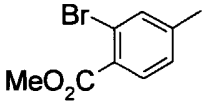
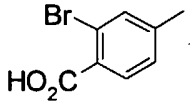
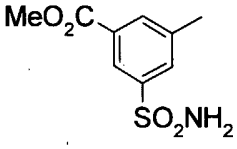
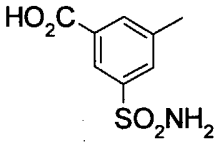
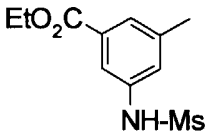
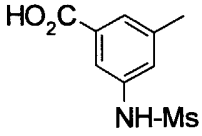
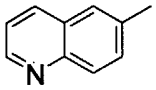
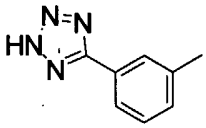
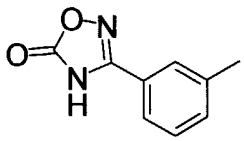
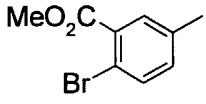
113		ESI: 584, 586.	REx 8
114		ESI: 642, 644.	REx 3
115		ESI: 628, 630.	REx 8
116		ESI: 643.	REx 3
117		ESI: 629.	REx 8
118		ESI: 671.	REx 3
119		ESI: 643.	REx 8
120		ESI: 579 (+Na).	REx 3
121		ESI: 574.	REx 9
122		ESI: 590.	REx 10
123	3,4-$(CO_2H)_2$-Ph	ESI-N: 592.	REx 8
124		ESI: 642, 644.	REx 3

Table 2-9

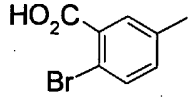
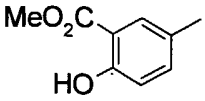
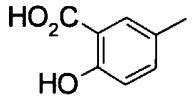
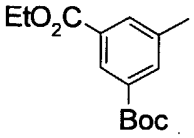
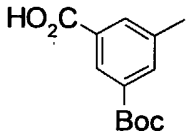
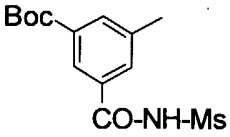
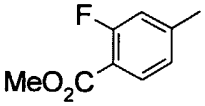
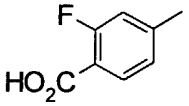
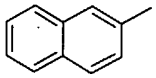
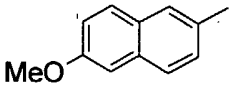
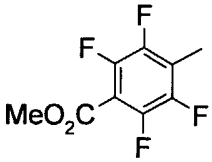
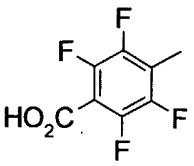
125		ESI: 628, 630.	REx 8
126		ESI: 580.	REx 3
127		ESI: 564.	REx 8
128		ESI: 678.	REx 1
129		ESI: 650.	REx 8
130		ESI: 727.	REx 3
131		ESI: 582.	REx 3
132		ESI: 566.	REx 8
133		ESI: 556.	REx 3
134		ESI: 586.	REx 3
135		ESI: 636.	REx 3
136		ESI: 622.	REx 8

Table 2-10

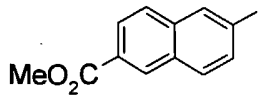
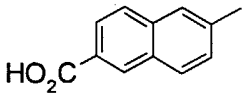
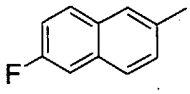
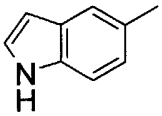
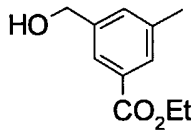
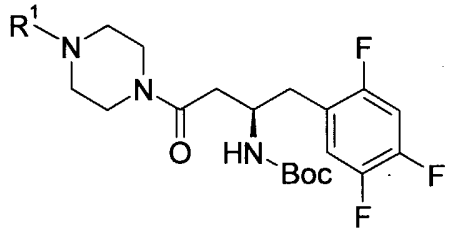
137		ESI: 614.	REx 3
138		ESI: 600.	REx 8
139		ESI: 574.	REx 3
140		ESI: 545.	REx 3
141	3-[$(CH_2)_2CO_2H$]-Ph	ESI: 578.	REx 8
142		ESI: 608.	REx 3

Table 3



REx	R^1	Dat	Syn
143	H	NMR1: 1.27(9H, s), 2.71-2.36(8H, m), 2.85(1H, dd, J = 4.5, 13.5 Hz), 3.56-3.20(4H, m), 4.10-3.88(1H, m), 7.80-7.68(1H, m), 7.58-7.20(2H, m); ESI: 402.	REx 2
144	Ph-O-CO-	ESI: 522.	REx 3
145	Bn-O-CO-	NMR1: 1.25(9H, s), 2.63-2.40(3H, m), 2.86(1H, dd), 3.59-3.24(8H, m), 4.12-3.91(1H, m), 5.10(2H, s), 6.82-6.70(1H, m), 7.53-7.22(7H, m); ESI: 536.	REx 1
146	Ph-SO_2-	ESI: 542.	REx 3

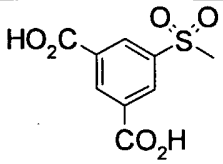
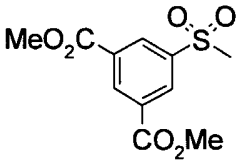
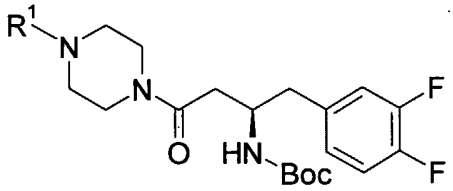
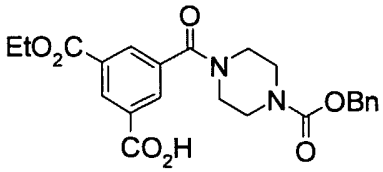
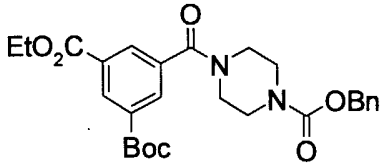
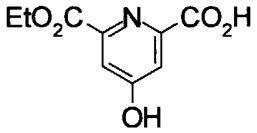
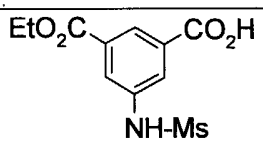
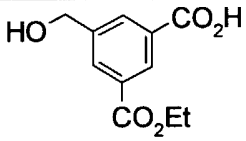
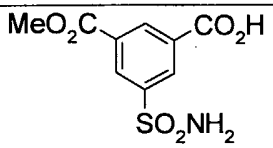
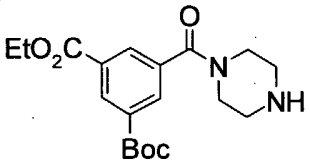
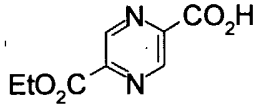
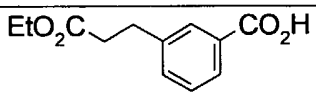
147		ESI: 630.	REx 8
148		ESI: 658.	REx 3

Table 4



REx	R^1	Dat	Syn
2	H	NMR2: 1.39 (9H, s), 2.45-3.20 (7H, m), 3.40-3.85 (6H, m), 3.90-4.15 (1H, brs), 5.20-5.45 (1H, br), 6.80-7.20 (3H, m); ESI: 384.	REx 2
149	Bn-O-CO-	NMR2: 1.39 (9H, s), 2.40-2.60 (2H, m), 2.80-3.05 (2H, m), 3.25-3.70 (8H, m), 4.05 (1H, brs), 5.15 (2H, s), 5.42 (1H, brs), 6.85-7.15 (3H, m), 7.30-7.45(5H, m); ESI: 518.	REx 1

Table 5

REx	Str	Dat	Syn
4		ESI: 441.	REx 4
5		ESI: 497.	REx 5
6		ESI: 212.	REx 6
7		ESI-N: 286.	REx 7
150		ESI: 225.	REx 4
151		ESI-N: 258.	REx 4
152		ESI: 363.	REx 2
153		ESI: 197.	REx 4
154		ESI-N: 221.	REx 2

Example 1

[(2R)-4-(4-Acetyl-1-piperazinyl)-1-(3,4-difluoro-phenyl)-4-oxobutyl]amine hydrochloride

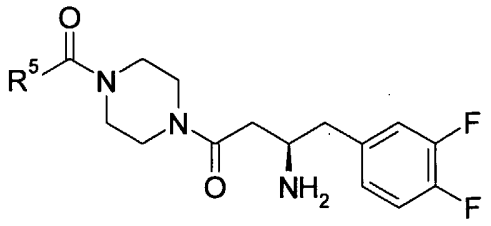
To an ice cooled solution of t-butyl [(2R)-4-(4-acetyl-1-piperazinyl)-1-(3,4-difluorophenyl)-4-oxobutyl]carbamate (95 mg) in CH_2Cl_2 (2 mL), was added 4 mol/L hydrogenchloride in dioxane (407 µL). The mixture was stirred at room temperature for 1 hour. The solvent was concentrated in vacuo, and the residue was triturated with isopropylether/ethyl acetate to give the target compound (73 mg) as a white solid.

Example 2

(2R)-4-[4-(4-fluorobenzoyl)-1-piperazinyl]-4-oxo-1-(2,4,5-trifluorophenyl)-2-butanamine hydrochloride was prepared by a similar manner to the method in Reference example 3, followed by the method in Example 1.

In a similar manner to the above Examples 1 or 2, the compounds of Examples 3 to 132 shown in the following Tables 6 to 8 were obtained, respectively. Structures and physicochemical data of the compounds of Examples 1 to 132 are shown in Tables 6 to 8.

Table 6-1



Ex	R^5	Sal	Dat	Syn
1	Me	HCl	NMR1: 2.02 (3H, s), 2.66 (2H, d, J=6Hz), 2.75-3.15 (2H, m), 3.25-3.85 (9H, m), 7.05-7.50 (3H, m), 8.05 (2H, brs); ESI: 326.	Ex 1
3	2-OMe-Ph	HCl	NMR1: 2.62 (1H, d, J = 6.0 Hz), 2.69 (1H, d, J = 6.0 Hz), 3.01-2.76 (2H, m), 3.22-3.03 (2H, m), 3.77-3.38 (7H, m), 3.79 (3H, s), 7.26-6.95 (4H, m), 7.51-7.28 (3H, m), 8.02 (2H, bs); ESI: 418.	Ex 1
4	2,6-$(OMe)_2$-Ph	HCl	NMR1: 2.61 (1H, d, J = 6.0 Hz), 2.68 (1H, d, J = 6.0 Hz), 3.02-2.78 (2H, m), 3.17-3.02 (2H, m), 3.78-3.30 (7H, m), 3.57 (3H, s), 3.74 (3H, s), 6.71 (2H, d, J = 8.5 Hz), 7.21-7.04 (1H, m), 7.50-7.22 (3H, m), 8.00 (2H, bs); ESI: 448.	Ex 1
5	2-OMe-5-F-Ph	HCl	NMR1: 2.60 (1H, d, J = 3.0 Hz), 2.68 (1H, d, J = 3.0 Hz), 2.91-2.81 (1H, m), 3.02-2.94 (1H, m), 3.19-3.08 (2H, m), 3.77-3.41 (7H, m), 3.78 (3H, s), 7.20-7.09 (3H, m), 7.30-7.21 (1H, m), 7.45-7.33 (2H, m), 7.98 (2H, bs); ESI: 436.	Ex 1
6	2-OMe-5-Cl-Ph	HCl	NMR1: 2.61 (1H, d, J = 3.1 Hz), 2.68 (1H, d, J = 3.1 Hz), 2.91-2.81 (1H, m), 3.03-2.92 (1H, m), 3.19-3.08 (2H, m), 3.75-3.41 (7H, m), 3.80 (3H, s), 7.17-7.10 (2H, m), 7.30-7.26 (1H, m), 7.49-7.38 (3H, m), 7.98 (2H, bs); ESI: 452, 454.	Ex 1
7	2,4,6-$(OMe)_3$-Ph	HCl	NMR1: 2.62 (1H, d, J = 6.0 Hz), 2.68 (1H, d, J = 6.0 Hz), 3.02-2.78 (2H, m), 3.19-3.02 (2H, m), 3.62-3.24 (7H, m), 3.73 (6H, s), 3.80 (3H, s), 6.27 (2H, s), 7.21-7.08 (1H, m), 7.50-7.32 (2H, m), 8.03 (2H, bs); ESI: 478.	Ex 1

Table 6-2

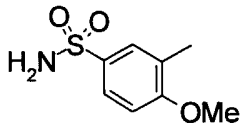
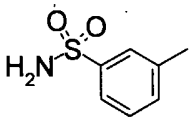
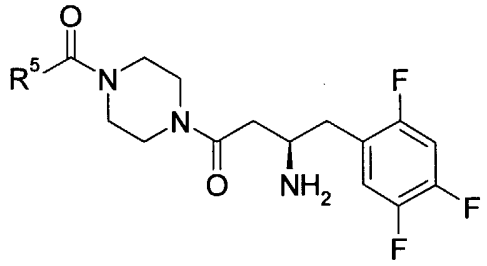
8		HCl	NMR1: 2.61 (1H, d, J = 6.0 Hz), 2.68 (1H, d, J = 6.0 Hz), 3.05-2.78 (2H, m), 3.21-3.06 (2H, m), 3.81-3.38 (7H, m), 3.87 (3H, s), 7.20-7.04 (1H, m), 7.28 (1H, d, J = 9.5 Hz), 7.32 (2H, s), 7.51-7.32 (2H, m), 7.66 (1H, s), 7.86 (1H, d, J = 9.5 Hz), 7.94 (2H, bs); ESI: 497.	Ex 1
9	2-F-6-OMe-Ph	HCl	NMR1: 2.61 (1H, d, J = 6.0 Hz), 2.68 (1H, d, J = 6.0 Hz), 3.09-2.77 (2H, m) 3.28-3.09 (2H, m), 3.79-3.37 (7H, m), 3.81 (3H, s), 6.89 (1H, dd, J = 8.5, 10.0 Hz), 6.97 (1H, d, J = 8.5 Hz), 7.20-7.02 (1H, m), 7.99 (2H, bs), 7.52-7.32 (3H, m); ESI: 436.	Ex 1
10		HCl	NMR1: 2.76-2.59 (2H, m), 3.05-2.79 (2H, m), 3.80-3.31 (9H, m), 7.21-7.06 (1H, m), 7.47-7.32 (2H, m), 7.49 (2H, bs), 7.67 (1H, d, J = 4.5 Hz), 7.67 (1H, d, J = 4.5 Hz), 7.86 (1H, s), 7.97-7.87 (1H, m), 7.98 (2H, bs); ESI: 467.	Ex 1
11	3-CO_2H-Ph	HCl	ESI: 432.	Ex 1

Table 7-1



Ex	R^5	Sal	Dat	Syn
2	4-F-Ph	HCl	ESI: 423.	Ex 2
12	2-OMe-Ph	HCl	NMR1: 2.64 (1H, d, J = 5.7 Hz), 2.72 (1H, d, J = 6.0 Hz), 3.02-2.86 (2H, m), 3.21-3.02 (2H, m), 3.71-3.38 (7H, m), 3.79 (3H, s), 7.01 (1H, dd, J = 7.0, 8.5 Hz), 7.09 (1H, d, J = 8.5 Hz), 7.21 (1H, d, J = 7.0 Hz), 7.41 (1H, dd, J = 7.0, 8.5 Hz), 7.64-7.48 (2H, m), 8.19 (2H, bs); ESI: 436.	Ex 1

Table 7-2

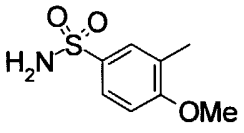
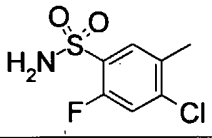
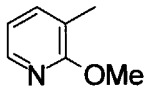
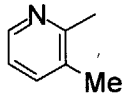
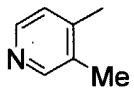
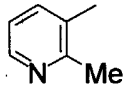
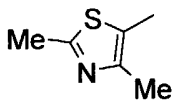
13	2-Me-Ph	HCl	NMR1: 2.22 (3H, s), 2.64 (1H, d, J = 5.0 Hz), 2.74 (1H, d, J = 6.0 Hz), 3.02-2.82 (2H, m), 3.21-3.02 (2H, m), 3.80-3.42 (7H, m), 7.38-7.14 (4H, m), 7.65-7.48 (2H, m), 8.13 (2H, bs); ESI: 420.	Ex 1
14		HCl	NMR1: 2.66 (1H, d, J = 6.0 Hz), 2.73 (1H, d, J = 5.5 Hz), 3.03-2.88 (2H, m), 3.21-3.04 (2H, m), 3.80-3.35 (7H, m), 3.88 (3H, s), 7.29 (1H, d, J = 9.0 Hz), 7.33 (2H, bs), 7.62-7.48 (2H, m), 7.65 (1H, s), 7.86 (1H, d, J = 9.0 Hz), 8.11 (2H, bs); ESI: 515.	Ex 1
15		HCl	ESI: 537, 539.	Ex 1
16	2-F-6-OMe-Ph	HCl	ESI: 454.	Ex 1
17	2,6-$(OMe)_2$-Ph	HCl	ESI: 466.	Ex 1
18	3-Ms-Ph	HCl	ESI: 484.	Ex 1
19		2HCl	ESI: 437.	Ex 1
20		2HCl	ESI: 421.	Ex 1
21		2HCl	ESI: 421.	Ex 1
22		2HCl	ESI: 421.	Ex 1
23	3-CN-Ph	HCl	ESI: 431.	Ex 1
24	2-OMe-3-F-Ph	HCl	ESI; 454.	Ex 1
25		HCl	ESI: 441.	Ex 1
26	3-(NHAc)-Ph	HCl	ESI: 463.	Ex 1

Table 7-3

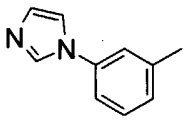
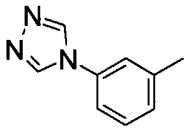
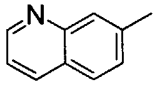
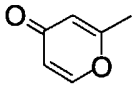
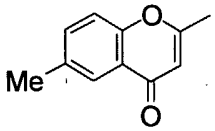
27		2HCl	ESI: 472.	Ex 1
28	3-NO_2-Bn	HCl	ESI: 465.	Ex 2
29		2HCl	ESI: 473.	Ex 1
30	Ph	HCl	ESI: 406.	Ex 1
31	4-OMe-Ph	HCl	ESI: 435.	Ex 2
32	4-NO_2-Ph	HCl	ESI: 450.	Ex 2
33	4-Ms-Ph	HCl	ESI: 483.	Ex 2
34	4-CN-Ph	HCl	ESI: 431.	Ex 1
35	2-OMe-4-SMe-Ph	HCl	ESI: 482.	Ex 1
36		2HCl	ESI: 457.	Ex 1
37		HCl	ESI: 424.	Ex 1
38		HCl	ESI: 488.	Ex 1
39	Me	HCl	ESI: 344.	Ex 1
40	2-OMe-4-F-Ph	HCl	ESI: 454.	Ex 1
41	3-CO_2H-Ph	HCl	NMR1: 2.6-2.8 (2H, m), 2.85-3.15 (4H, m), 3.3-3.8 (7H, m), 7.5-7.75 (4H, m), 7.95 (1H, s), 8.03 (1H, dt, J = 7.4, 1.4 Hz); ESI: 450.	Ex 1
42	2-OMe-5-Cl-Ph	HCl	ESI: 470, 472.	Ex 1

Table 7-4

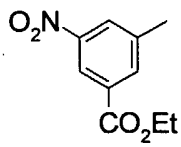
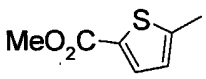
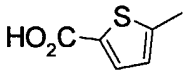
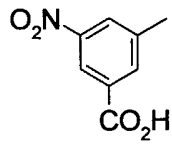
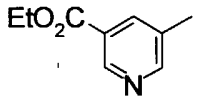
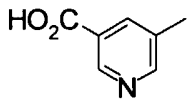
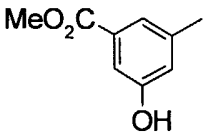
43		HCl	FAB: 523.	Ex 1
44	4-(CO_2Me)-Ph	HCl	FAB: 464.	Ex 1
45	4-(CO_2H)-Ph	HCl	NMR1: 2.61-2.81 (2H, m), 2.86-2.98 (1H, m), 2.98-3.09 (1H, m), 3.21-3.36 (2H, m), 3.36-3.55 (4H, m), 3.58-3.68 (2H, m), 3.68-3.78 (1H, m), 7.49-7.65 (2H, m), 7.54 (2H, d, J = 8.8 Hz), 8.00 (2H, d, J = 8.8 Hz), 8.16 (2H, br s), 13.12 (1H, br s); FAB: 450.	Ex 1
46		HCl	ESI: 484.	Ex 1
47		HCl	ESI: 456.	Ex 1
48		HCl	ESI: 495.	Ex 1
49	3,5-(CO_2Et)$_2$-Ph	HCl	FAB: 550.	Ex 1
50	3,5-(CO2H)$_2$-Ph	HCl	NMR1: 2.61-2.81 (2H, m), 2.87-2.97 (1H, m), 2.98-3.15 (2H, m), 3.39-3.63 (6H, m), 3.62-3.70 (1H, m), 3.69-3.78 (1H, m), 7.48-7.64 (2H, m), 8.15 (2H, d, J = 1.6 Hz), 8.15 (2H, br s), 8.52 (1H, dd, J = 1.6, 1.6 Hz); FAB: 494.	Ex 1
51		2HCl	ESI: 479.	Ex 1
52		2HCl	NMR1: 2.60-2.81 (2H, m), 2.86-3.10 (2H, m), 3.25-3.81 (9H, m), 7.49-7.66 (2H, m), 8.12 (3H, br), 8.30 (1H, t, J=2.2 Hz), 8.86 (1H, d, J=2.2 Hz), 9.14 (1H, d, J=2.2 Hz); ESI: 451.	Ex 1
53		HCl	FAB: 480.	Ex 1
54	2-(CO_2Et)-Ph	HCl	FAB: 478.	Ex 1

Table 7-5

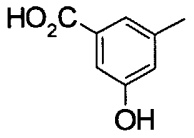
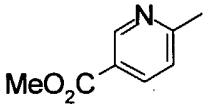
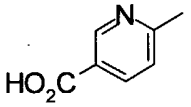
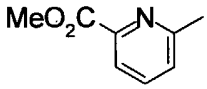
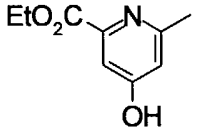
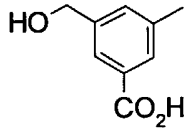
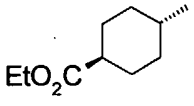
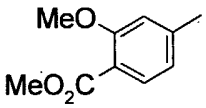
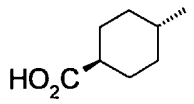
55		HCl	NMR1: 2.57-2.82 (2H, m), 2.86-2.98 (1H, m), 2.98-3.09 (1H, m), 3.34-3.52 (4H, m), 3.52-3.67 (4H, m), 3.67-3.81 (1H, m), 7.03 (1H, dd, J = 1.5, 0.9 Hz), 7.36 (1H, dd, J = 0.9, 0.9 Hz), 7.42 (1H, dd, J = 1.5, 0.9 Hz), 7.49-7.64 (2H, m), 8.13 (2H, br s), 10.21 (1H, s), 13.07 (1H, br s); FAB: 466.	Ex 1
56		2HCl	ESI: 465.	Ex 1
57		2HCl	ESI: 451.	Ex 1
58		HCl	ESI: 465.	Ex 1
59		2HCl	ESI: 495.	Ex 1
60		HCl	NMR1: 2.38-2.55 (1H, m), 2.53-2.69 (2H, m), 2.78-2.92 (1H, m), 3.11-3.41 (2H, m), 3.30-3.80 (6H, m), 3.94-4.13 (1H, m), 4.60 (2H, d), 5.36-5.51 (1H, m), 7.21-7.38 (1H, m), 7.38-7.55 (1H, m), 7.59 (1H, s), 7.80 (1H, s), 7.99 (1H, s), 8.13 (2H, br s), 13.11 (1H, br s); ESI: 480.	Ex 1
61		HCl	FAB: 484.	Ex 1
62		HCl	ESI: 494.	Ex 1
63		2HCl	FAB: 407.	Ex 1
64		HCl	FAB: 456.	Ex 1
65	4-($CONH_2$)-Ph	HCl	FAB: 449.	Ex 1

Table 7-6

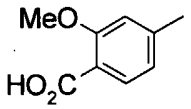
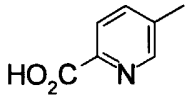
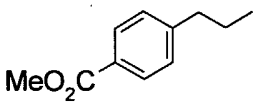
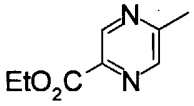
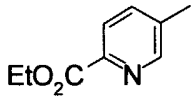
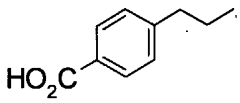
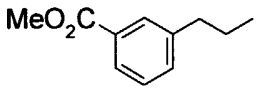
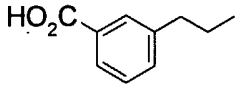
66		-	ESI: 480.	Ex 1
67		2HCl	NMR1: 2.61-2.79 (2H, m), 2.84-3.08 (2H, m), 6.21-3.90 (9H, m), 7.49-7.65 (2H, m), 8.03 (1H, d, J=8.1 Hz), 8.06-8.17 (3H, m), 8.75 (1H, s); ESI: 451.	Ex 1
68		HCl	ESI: 492.	Ex 1
69		2HCl	ESI: 480.	Ex 1
70	4-(CH_2CO_2H)-Ph	HCl	ESI: 464.	Ex 1
71	4-(NHMs)-Ph	HCl	FAB: 499.	Ex 1
72	4-(SO_2NH_2)-Ph	HCl	FAB: 485.	Ex 1
73	4-(NHAc)-Ph	HCl	FAB: 463.	Ex 1
74		2HCl	ESI: 479.	Ex 1
75	4-(CH_2CO_2Me)-Ph	HCl	ESI: 478.	Ex 1
76	4-(CH_2OH)-Ph	HCl	ESI: 436.	Ex 1
77	3-(CH_2CO_2Me)-Ph	TsOH	ESI: 478.	Ex 1
78		-	ESI: 478.	Ex 1
79		HCl	ESI: 492.	Ex 1
80		-	ESI: 478.	Ex 1
81	3-(CH_2CO_2H)-Ph	HCl	ESI: 464.	Ex 1

Table 7-7

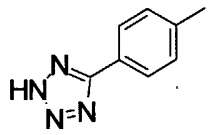
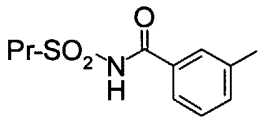
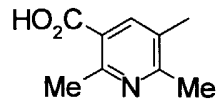
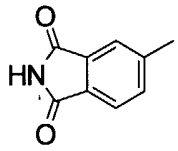
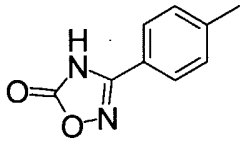
82	4-[$(CH_2)_3CO_2H$]-Ph	HCl	ESI: 492.	Ex 1
83	4-(CO_2Me)-Bn	HCl	ESI: 478.	Ex 1
84	4-[$(CH_2)_2CO_2Et$]-Ph	Ox	ESI: 506.	Ex 1
85	4-[$(CH_2)_2CO_2H$]-Ph	HCl	FAB: 478.	Ex 1
86	4-NH_2-Ph	2HCl	ESI: 421.	Ex 1
87		HCl	FAB-N: 472.	Ex 1
88	4-(CO_2H)-Bn	-	ESI: 464.	Ex 1
89	3-(CO-NH-Ms)-Ph	HCl	ESI: 527.	Ex 1
90		HCl	ESI: 555.	Ex 1
91	4-(CO-NH-Ms)-Ph	HCl	ESI: 527.	Ex 1
92		2HCl	ESI: 479.	Ex 1
93		HCl	ESI: 475.	Ex 1
94	3-Br-5-CO_2H-Ph	HCl	ESI: 528, 530.	Ex 1
95		HCl	FAB: 490.	Ex 1
96	3-tBu-5-CO_2H-Ph	-	ESI: 506.	Ex 1

Table 7-8

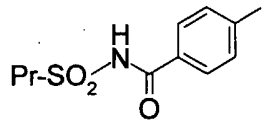
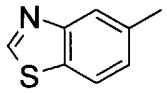
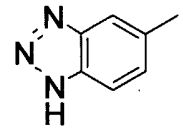
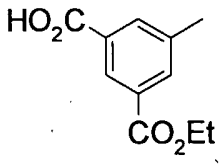
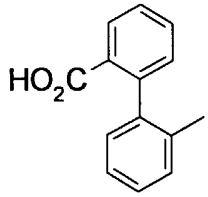
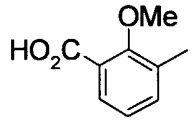
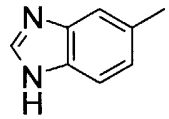
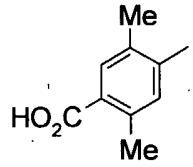
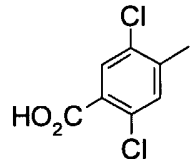
97		HCl	ESI: 555.	Ex 1
98		HCl	FAB: 463.	Ex 1
99		HCl	FAB: 447.	Ex 1
100			ESI: 522.	Ex 1
101		HCl	ESI: 526.	Ex 1
102		HCl	ESI: 480.	Ex 1
103		HCl	ESI: 446.	Ex 1
104		HCl	ESI: 478.	Ex 1
105		HCl	ESI: 518, 520.	Ex 1
106	3-[$(CH_2)_2CO_2Et$]-Ph	Ox	FAB: 506.	Ex 1

Table 7-9

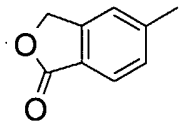
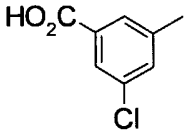
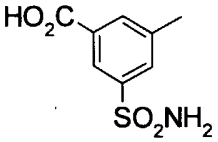
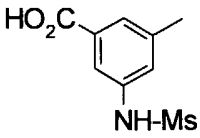
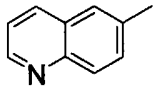
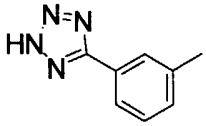
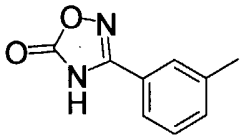
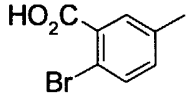
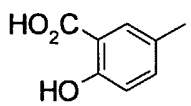
107		HCl	ESI: 462.	Ex 1
108		HCl	ESI: 484, 486.	Ex 1
109		HCl	ESI: 528, 530.	Ex 1
110		HCl	NMR1: 2.60-2.84 (2H, m), 2.88-3.12 (2H, m), 3.20-4.25 (9H, m), 7.50-7.60 (2H, m), 7.65 (2H, br.s), 8.08 (1H, s), 8.14 (1H, s), 8.24 (2H, br.s), 8.44 (1H, s); ESI: 529.	Ex 1
111		HCl	NMR1: 2.88-2.98 (2H, m), 2.98-3.10 (2H, m), 3.07 (3H, s), 3.25-3.85 (9H, m), 7.48 (1H, s), 7.50-7.60 (2H, m), 7.66 (1H, s), 7.88 (1H, s), 8.15 (2H, br.s), 10.25 (1H, s); ESI: 543.	Ex 1
112		2HCl	ESI: 457.	Ex 1
113		HCl	FAB: 474.	Ex 1
114		HCl	FAB: 490.	Ex 1
115	3,4-$(CO_2H)_2$-Ph	HCl	FAB: 494.	Ex 1
116		HCl	ESI: 528, 530.	Ex 1
117		HCl	NMR1: 2.60-2.76 (2H, m), 2.84-3.06 (2H, m), 3.12-3.26 (2H, m), 3.26-3.77 (7H, m), 7.00 (1H, d, J = 8.4 Hz), 7.49-7.64 (2H, m), 7.73 (1H, d, J = 2.2 Hz), 7.84 (1H, dd, J = 8.4, 2.2 Hz), 8.06 (2H, br s), 10.86 (1H, br s), 12.68 (1H, br s); ESI: 466.	Ex 1

Table 7-10

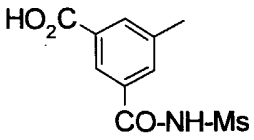
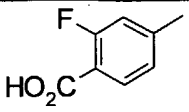
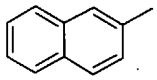
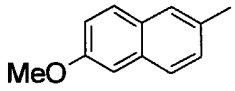
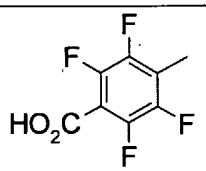
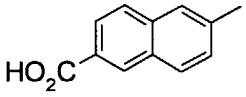
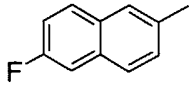
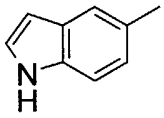
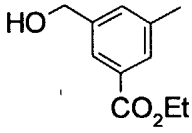
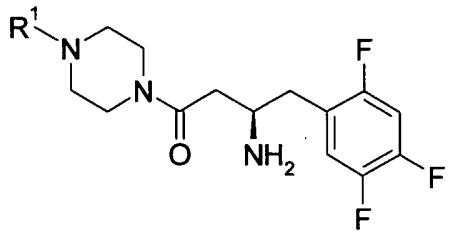
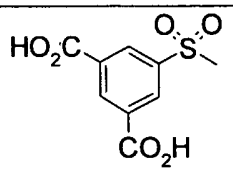
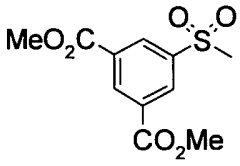
118		Frm	NMR1: 2.48-2.80 (2H, m), 2.80-3.04 (5H, m), 3.04-3.85 (9H, m), 7.44-7.66 (2H, m), 7.74-8.04 (3H, m), 8.14 (1H, s), 8.16 (1H, dd, J=1.8, 1.5 Hz), 8.60 (1H, dd, J=1.8, 1.5 Hz); ESI: 571.	Ex 1
119		HCl	ESI: 468.	Ex 1
120		HCl	FAB: 456.	Ex 1
121		HCl	FAB: 486.	Ex 1
122		HCl	ESI: 522.	Ex 1
123		HCl	ESI: 500.	Ex 1
124		HCl	FAB: 474.	Ex 1
125		2HCl	FAB: 445.	Ex 1
126	3-[$(CH_2)_2CO_2H$]-Ph	HCl	FAB: 478.	Ex 1
127		HCl	FAB: 508.	Ex 1

Table 8



Ex	R^1	Sal	Dat	Syn
128	Ph-O-CO-	TsOH	ESI: 422.	Ex 1
129	Bn-O-CO-	-	FAB: 436.	Ex 1
130	Ph-SO_2-	HCl	ESI: 442.	Ex 1
131		HCl	ESI: 530.	Ex 1
132		HCl	ESI: 558.	Ex 1

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

Inhibition test of human plasma DPP-IV :

(i) Material and Method :

The effect of test compounds on DPP-IV activity in human plasma was evaluated with a modified version of the assay described by Hughes et al (Biochemistry, 38, pp11597-11603 (1999)).

Briefly, 20 μL of human plasma were mixed with 20 μL of 80 mM $MgCl_2$ in assay buffer (25 mM HEPES, 140 mM NaCl, 1% RIA-grade BSA, pH7.8), and were incubated in

room temperature for 60 minutes. Then the reaction was initiated by the addition of both 20 µL of test compounds and 20 µL of 0.2mM substrate (H-glycine-proline-AMC; AMC is 7-amino-4-methylcoumarine), which were dissolved in the assay buffer.

After 20 minutes incubation in room temperature (kept in the dark), fluorescence was measured (Excitation 380nm, Emission 460nm). A fluorescence-concentration curve of free AMC was obtained using AMC solution in the assay buffer with appropriate concentration. Plasma DPP-IV activities, with or without the test compounds, were expressed as the amount of product per minute per mL. The potency of the test compounds as DPP-IV inhibitor was expressed as IC_{50}.

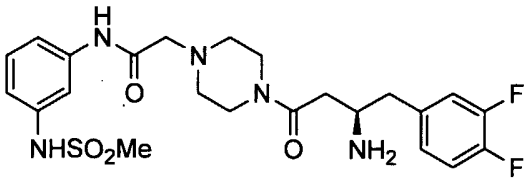
(ii) Results :

The following IC_{50} values were obtained.

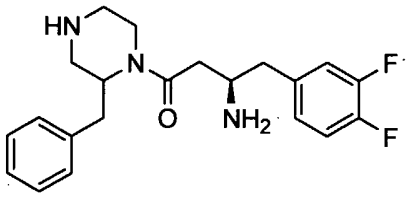
Table 9

Compound	IC_{50} value for human plasma DPP-IV (nM)
Example 14	12
Example 52	2.0
Example 71	9.4
Ref. A	260
Ref. B	162

Ref. A



Ref. B



Reference compounds Ref. A and Ref. B are disclosed in WO 03/000181, Example 12 and 45, respectively.

It appeared, from the above-mentioned inhibition test, that the compound (I) or pharmaceutically acceptable salt thereof of the present invention has an inhibiting activity against DPP-IV.

Therefore, the compound (I) or pharmaceutically acceptable salt thereof is useful for treating or preventing disease mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (type 1 and type 2), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

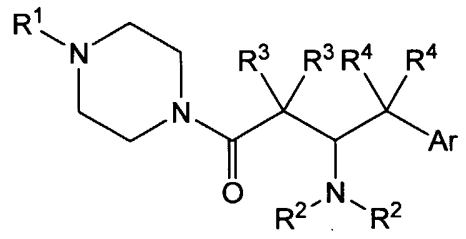
Further, the compound (I) or pharmaceutically acceptable salt thereof is useful for treating or preventing autoimmune disease, arthritis, rejection of transplanted organs, systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS), hypertension, atherosclerosis, gallbladder disease, cancer, intestinal disease and dwarfism.

This application is based on Australian Provisional Patent Application No.2005901293 filed on March 16, 2005, the content of which is hereby

incorporated by references.

C L A I M S

1. A compound of formula (I) or pharmaceutically acceptable salt thereof.



(I)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

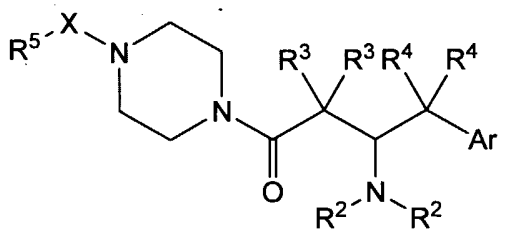
R^1 is acyl;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl.]

2. A compound of formula (Ia) or pharmaceutically acceptable salt thereof.



(Ia)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl;

R^5 is lower alkyl,

halogenated lower alkyl,

aryl optionally substituted,

heterocycle optionally substituted,

cycloalkyl optionally substituted,

aryl-O optionally substituted,

heterocycle-O optionally substituted,

aryl-(lower alkyl) optionally substituted on the aryl,

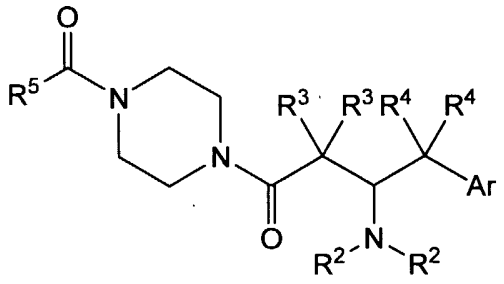
heterocycle-(lower alkyl) optionally substituted on the heterocycle,

aryl-(lower alkoxy) optionally substituted on the aryl, or

heterocycle-(lower alkoxy) optionally substituted on the heterocycle;

X is $-C(=O)-$ or $-S(=O)_2-$.]

3. A compound of formula (Ib) or pharmaceutically acceptable salt thereof.



(Ib)

[wherein

Ar is aryl or heteroaryl, optionally substituted;

each R^2 is independently selected from the group consisting of H and lower alkyl;

each R^3 is independently selected from the group consisting of H and lower alkyl;

each R^4 is independently selected from the group consisting of H and lower alkyl;

R^5 is lower alkyl,

halogenated lower alkyl,

aryl optionally substituted,

heterocycle optionally substituted,

cycloalkyl optionally substituted,

aryl-O optionally substituted,

heterocycle-O optionally substituted,

aryl-(lower alkyl) optionally substituted on the aryl,

heterocycle-(lower alkyl) optionally substituted on the heterocycle,

aryl-(lower alkoxy) optionally substituted on the aryl, or

heterocycle-(lower alkoxy) optionally substituted on the heterocycle.]

4. The compound of Claim 1, wherein Ar is phenyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, nitro, amino, carbamoyl, aminosulfonyl and carboxy.

5. The compound of Claim 1, wherein Ar is phenyl optionally substituted with halogen atom(s).

6. The compound of Claim 3, wherein R^5 is aryl optionally substituted or heteroaryl optionally substituted; each substituent(s) is(are) selected from the group consisting of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, nitro, amino, carbamoyl, aminosulfonyl, carboxy, (lower alkoxy)-carbonyl, R^6-S-, R^6-S(O)-, R^6-SO_2-, R^6-SO_2NH-, R^6-CONH-, R^6-$CONHSO_2$-, R^6-SO_2NHCO-, lower alkyl substituted by 1 to 3 of R^7, heteroaryl and oxo; wherein R^6 is lower alkyl, halogenated lower alkyl, or phenyl optionally substituted with halogen, lower alkyl or halogenated lower alkyl; R^7 is hydroxy, lower alkoxy, carboxy, (lower alkoxy)-carbonyl or carbamoyl; and any nitrogen atoms in carbamoyl or aminosulfonyl may be substituted by lower alkyl.

7. The compound of Claim 3, wherein R^5 is aryl optionally substituted with substituent(s) selected from the group consisting of lower alkoxy, halogen, aminosulfonyl, carboxy and (lower alkoxy)-carbonyl.

8. The compound any one of Claims 1 to 6, wherein R^2 is H.

9. The compound any one of Claims 1 to 8, wherein R^3 is H.

10. The compound any one of Claims 1 to 9, wherein R^4 is H.

11. A compound selected from:

(2R)-1-(3,4-Difluorophenyl)-4-[4-(2-methoxy-benzoyl)-1-piperazinyl]-4-oxo-2-butanamine hydrochloride;

(2R)-4-[4-(2-Methoxybenzoyl)-1-piperazinyl]-4-oxo-1-(2,4,5-trifluorophenyl)-2-butanamine hydrochloride;

(2R)-1-(3,4-Difluorophenyl)-4-[4-(2,6-dimethoxy-benzoyl)-1-piperazinyl]-4-oxo-2-butanamine hydrochloride;

(2R)-1-(3,4-Difluorophenyl)-4-[4-(5-fluoro-2-methoxybenzoyl)-1-piperazinyl]-4-oxo-2-butan-amine hydrochloride;

3-({4-[(3R)-3-Amino-4-(3,4-difluorophenyl)-butyryl]-1-piperazinyl}-carbonyl)-4-methoxy-benzenesulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butyryl]-1-piperazinyl}carbonyl)-4-methoxybenzene-sulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(3,4-difluorophenyl)-butyryl]-1-piperazinyl}carbonyl)benzenesulfonamide hydrochloride;

3-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)benzoic acid hydrochloride;

4-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)benzoic acid hydrochloride;

5-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-

butanoyl]-1-piperazinyl}carbonyl)isophthalic acid hydrochloride; and
5-({4-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)-butanoyl]-1-piperazinyl}carbonyl)nicotinic acid dihydrochloride.

12. A compound of any one of Claims 1 to 11 for use as a medicament.

13. The compound of Claim 12 for use in the treatment and/or prevention of Type 2 Diabete Mellitus in human beings or animals.

14. A medicament comprising a compound of any one of Claims 1 to 11 as an active ingredient.

15. A pharmaceutical composition comprising a compound of any one of Claims 1 to 11 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

16. An inhibitor of DPP-IV consisting of a compound of any one of Claims 1 to 11.

17. A method for treatment and/or prevention of Type 2 Diabete Mellitus which comprises administering an effective amount of the compound of any one of Claims 1 to 11 to human beings or animals.

18. Use of the compound of any one of Claims 1 to 11

for treatment and/or prevention of Type 2 Diabete Mellitus in human beings or animals.

19. A commercial package comprising the pharmaceutical composition containing the compound identified in any one of Claims 1 to 11 and a written matter associated therewith, wherein the written matter states that the compound can or should be used for preventing or treating Type 2 Diabete Mellitus.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/305064

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D295/18 A61K31/495 A61K31/496 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/000181 A (MERCK & CO., INC; BROCKUNIER, LINDA; PARMEE, EMMA; WEBER, ANN, E) 3 January 2003 (2003-01-03) cited in the application claim 24; examples 12,45	1-19
A	WO 2004/043940 A (MERCK & CO., INC; COLANDREA, VINCENT, J; EDMONDSON, SCOTT, D; MATHVINK) 27 May 2004 (2004-05-27) page 3, line 13 - line 16; table 3	1-19
P,A	EP 1 541 143 A (GRAFFINITY PHARMACEUTICALS AKTIENGESELLSCHAFT) 15 June 2005 (2005-06-15) claim 22; examples 10,11,13	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2006	07/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/305064

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	EP 1 598 341 A (SANTHERA PHARMACEUTICALS AKTIENGESELLSCHAFT) 23 November 2005 (2005-11-23) claims 23,29	1-19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 17, 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.Although claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/305064

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17, 18
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2006/305064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000181 A	03-01-2003	AT 318139 T	15-03-2006
		CA 2450475 A1	03-01-2003
		EP 1406622 A2	14-04-2004
		JP 2005500308 T	06-01-2005
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		BR 0315796 A	13-09-2005
		CA 2504735 A1	27-05-2004
		EP 1562925 A1	17-08-2005
		JP 2006509839 T	23-03-2006
		MA 27556 A1	03-10-2005
		MX PA05004890 A	22-07-2005
EP 1541143 A	15-06-2005	AU 2004296553 A1	23-06-2005
		WO 2005056003 A1	23-06-2005
EP 1598341 A	23-11-2005	WO 2005113510 A1	01-12-2005