(54) Title: USE OF ANGIOTENSIN II ANTAGONISTS FOR THE TREATMENT OF HYPERLIPIDAEMIA

(57) Abstract

A lipids-lowering agent which comprises an angiotensin II antagonist as an active ingredient.
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DESCRIPTION

USE OF ANGIOTENSIN II ANTAGONISTS FOR THE TREATMENT OF HYPERLIPIDAEMIA

Technical Field

The present invention relates to a new use of a compound having angiotensin II antagonism.

More particularly, the present invention relates to a new use of a compound having angiotensin II antagonism (hereinafter referred to as "angiotensin II antagonist") for lowering lipids in living bodies.

Disclosure of the Invention

Accordingly, one object of the present invention is to provide a lipids-lowering agent which comprises an angiotensin II antagonist as an active ingredient.

Another object of the present invention is to provide a new use of an angiotensin II antagonist as a lipids-lowering agent.

Further object of the present invention is to provide a new use of an angiotensin II antagonist for manufacturing a medicament for treating or preventing lipids-associated diseases and conditions such as hypercholesterolemia, hyperlipidemia, hyperlipemia, hyperlipoproteinemia, atherosclerosis, and the like.
Still further object of the present invention is to provide a method for treating or preventing lipids-associated diseases and conditions as mentioned above which comprises administering an effective amount of an angiotensin II antagonist to a host such as animals including human.

It is reported that angiotensin II, which is a kind of hormones existing in living bodies of animals and is mainly produced by angiotensin II converting enzyme from angiotensin I, possesses strong vasoconstrictive action and releasing action for aldosterone from the adrenal cortex. Therefore, it is known that an angiotensin II antagonist exhibits vasodilating activity, and is of use for treating hypertension and some heart failures.

The inventors of the present invention extensively investigated various effects of the angiotensin II antagonists, and during such investigations, it has been found that an angiotensin II antagonist further exhibits lipids-lowering activity in living bodies of animals, particularly in blood. This finding is really new and is not expectable at all for a person skilled in this field.

In the present invention, so-called "lipids" include various cholesterols, particularly high and low density lipoprotein cholesterols (HDL-C, LDL-C), phospholipids, neutral fats (e.g. triglycerides of fatty acids, etc.), and the like. Therefore, according to the present invention, any angiotensin II antagonist is capable of lowering the level of various lipids including the above lipids in living bodies of animals, particularly total cholesterols, LDL-C and phospholipids in blood serum of human.

The angiotensin II antagonist used in the present invention is not limitative and includes any compound which
exhibits angiotensin II antagonism, particularly non-peptide angiotensin II antagonist.

The preferred embodiment of the angiotensin II antagonist of the present invention can be represented by the following general formula:

\[
[A] \quad \text{[I]}
\]

in which \( R^1 \) is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, amino or acylamino,

\( R^2 \) is a group of the partial formula:

\[
[\text{or}]
\]

in which \( R^3 \) and \( R^4 \) are each hydrogen or an imino-protective group,

\( R^5, R^6 \) and \( R^7 \) are each hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkylthio, mono or di or trihalo-(lower)alkyl, oxo(lower)alkyl, hydroxy(lower)alkyl or optionally esterified carboxy; or

\( R^5 \) and \( R^6 \) are linked together to form 1,3-butadienylene,

\( X \) is N or CH, and

\( Y \) is NH, O or S.
A is lower alkylene, and

\[ \text{is condensed or uncondensed imidazolyl which may be substituted by suitable substituent(s), or a pharmaceutically acceptable salt thereof.} \]

Another embodiment of the angiotensin II antagonist used in the present invention is a compound of the formula:

\[ Z-\text{CH}_2-\text{Ra} ^2 \]  

[II]

in which \( Z \) is 2-lower alkyl-4-halo-5-hydroxy(lower)-alkylimidazol-1-yl;

2-lower alkylquinolin-4-yloxy;

2-lower alkoxy-7-carboxy (or esterified carboxy)-1H-benimidazol-1-yl; or

2- or 2,7-di or 2,5,7-tri-(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl; and

\( \text{Ra} ^2 \) is a group of the formula:

\[ \text{or} \]

\( Z \) is 2- or 2,7-di or 2,5,7-tri-(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl; 2-lower alkoxy-7-carboxy (or esterified carboxy)-1H-benzimidazol-1-yl; or 2-lower alkoxy-5,7-di(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl; and

\( \text{Ra} ^2 \) is a group of the formula:
wherein $R^5$, $R^6$ and $R^7$ are each as defined above; or

$Z$ is 2-(lower)alkyl-5-carboxy (or esterified carboxy)-4-haloimidazol-1-yl, and

$R_a^2$ is combined with the adjacent benzene ring to form a group of the formula:

```
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or a pharmaceutically acceptable salt thereof.

Among the compound of the formula [II], the compound of the following general formula is particularly preferable.

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[III]

in which $Z_a$ is 2-lower alkyl-4-halo-5-hydroxy(lower)-

alkylimidazol-1-yl;

2-lower alkylquinolin-4-yloxy;

2-lower alkoxy-7-carboxy (or esterified carboxy)-1H-benzimidazol-1-yl; or

2- or 2,7-di or 2,5,7-tri-(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl; and

$R_b^2$ is a group of the formula:

```
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\includegraphics{formula3.png}
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; or

$Z_a$ is 2- or 2,7-di or 2,5,7-tri-(lower)alkyl-
3H-imidazo[4,5-b]pyridin-3-yl; 2-lower alkoxy-7-carboxy (or esterified carboxy)-1H-benzimidazol-1-yl; or 2-lower alkoxy-5,7-di(lower)alkyl-3H-imidazo[4,5-b] pyridin-3-yl; and

$R^2_D$ is a group of the formula:

![Chemical Structure](image)

wherein $R^5$, $R^6$ and $R^7$ are each as defined above;

or a pharmaceutically acceptable salt thereof.

In the compounds of the formulae [I], [II] and [III], a suitable pharmaceutically acceptable salt of these compounds includes conventional one such as acid addition salt with an organic or inorganic acid (e.g. hydrochloride, sulfate, formate, acetate, etc.), or a salt with a base such as alkaline metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, etc.), organic basic salt (e.g. cyclohexylamine salt, etc.), and the like.

The most preferred embodiment of the angiotensin II antagonist used in the present invention is as follows.

-2-butyl-4-chloro-5-hydroxymethyl-1-[[2'-{(1H-tetrazol-5-yl)biphenyl-4-yl}methyl]imidazole or its alkali metal salt (e.g. sodium salt or potassium salt);

-2-ethyl-4-[[2'-{(1H-tetrazol-5-yl)biphenyl-4-yl}methoxy]guinoline or its acid addition salt (e.g. hydrochloride, etc.) or its alkali metal salt (e.g. sodium salt or potassium salt);

-2-ethoxy-1-[[2'-{(1H-tetrazol-5-yl)biphenyl-4-yl}methyl]-1H-benzimidazole-7-carboxylic acid or its alkali metal
salt (e.g. sodium salt, disodium salt, potassium salt, etc.) or its ester [e.g. 1-(cyclohexyloxycarbonyloxy)ethyl ester, etc.];
-2-butyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-3H-imidazo[4,5-b]pyridine or its acid addition salt (e.g. hydrochloride, etc.) or its alkali metal salt (e.g. sodium salt, potassium salt);
-2-butyl-5-carboxy-4-chloro-1-[3-bromo-2-[2-(1H-tetrazol-5-yl)phenyl]benzofuran-5-ylmethyl]imidazole or its alkali metal salt (e.g. sodium salt, potassium salt);
-2-propyl-7-methyl-3-[4-[2-methyl-5-(1H-tetrazol-5-yl)pyrrol-1-yl]benzyl]-3H-imidazo[4,5-b]pyridine or its acid addition salt (e.g. hydrochloride, etc.) or its alkali metal salt (e.g. sodium salt, potassium salt);
-2-ethyl-5,7-dimethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)pyrrol-2-yl]benzyl]-3H-imidazo[4,5-b]pyridine or its acid addition salt (e.g. hydrochloride, etc.) or its alkali metal salt (e.g. sodium salt, potassium salt);
-2-ethoxy-1-[4-[4-methyl-2-(1H-tetrazol-5-yl)-1-pyrrolyl]-benzyl]-7-benzimidazolecarboxylic acid or its alkali metal salt (e.g. sodium salt, potassium salt, etc.) or its ester [e.g. 1-[(propionyloxy)ethyl ester, etc.];
-2-ethoxy-5,7-dimethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)pyrrolyl-2-yl]benzyl]-3H-imidazo[4,5-b]pyridine or its acid addition salt (e.g. hydrochloride, etc.) or its alkali metal salt (e.g. sodium salt, potassium salt, etc.).

The compounds of the general formulae [I], [II] and [III], and the specific compounds mentioned above are new or known compounds, and the methods for preparation thereof are described, for example, in the following publications, or they can be prepared by a conventional method.

European Patent Publication 0399731A
European Patent Publication 0399732A
The suitable examples and illustrations of the various definitions used in the compounds of the formulae [I], [II] and [III] are explained in detail in the following.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl group in the term "lower alkylthio" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, preferably one having 1 to 5 carbon atoms, and the like.

Suitable "lower alkenyl" may include vinyl, 1-propenyl, allyl, 1-butenyl, 2-butenyl, 2-pentenyl, and the like, preferably one having 2 to 4 carbon atoms, in which the most preferred one is vinyl.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, dimethylethylene, hexamethylene, and the like, in which the preferred one is methylene.

Suitable "halogen" and "halo" means fluoro, chloro, bromo and iodo.

Suitable "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which the preferable one is C₁-C₄ alkoxy.
Suitable acyl group in the term "acylamino" may include carbamoyl, thiocarbamoyl, sulfamoyl, aliphatic acyl, aromatic acyl, heterocyclic acyl, in which the preferable one is aliphatic acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, hexanoyl, etc.).

Suitable "mono or di or trihalo(lower)alkyl" may include chloromethyl, fluoromethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trifluoromethylpropyl, and the like.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, hydroxyethyl, and the like.

Suitable "oxo(lower)alkyl" may include formyl, formylmethyl, formylethyl, and the like.

Suitable "ester moiety" in "esterified carboxy group" may include pharmaceutically acceptable, easily removable one such as lower alkyl ester (e.g. methyl ester, ethyl estr, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), lower alkoxy(lower)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.), lower alkylthio(lower)alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, ester, isopropylthiomethyl ester, etc.), carboxy-substituted-lower alkyl ester (e.g. carboxymethyl ester, 2-carboxyethyl ester, 3-carboxypropyl ester, etc.), protected carboxy-substituted lower alkyl ester such as lower alkoxy carbonyl-substituted-lower alkyl ester (e.g. methoxycarbonylmethyl ester, tert-butoxycarbonylmethyl ester, 2-tert-butoxycarbonyl-ethyl ester, 3-tert-butoxycarbonylpropyl ester, etc.), protected carboxy-substituted lower alkenyl ester such as lower
alkoxycarbonyl-substituted-lower alkenyl ester (e.g.
2-isobutoxycarbonyl-2-pentenyl ester, etc.), mono(or di or
tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester,
2,2,2-trichloroethyl ester, etc.), lower
alkanoyloxy(lower)alkyl ester [e.g. acetoxyethyl ester,
propionyloxymethyl ester, butyryloxymethyl ester,
valeryloxymethyl ester, pivaloyloxymethyl ester,
hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2
or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl
ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or
3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester,
1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl
ester, 1(or 2)-hexanoyloxymethyl ester, isobutyryloxymethyl
ester, 2-ethylbutyryloxymethyl ester,
3,3-dimethylbutyryloxymethyl ester, 1(or
2)-pentanoxyloxyethyl ester, etc.], higher
alkanoyloxy(lower)alkyl ester [e.g. heptanoyloxymethyl
ester, octanoyloxymethyl ester, nonanoyloxymethyl ester,
decanoyloxymethyl ester, undecanoyloxymethyl ester,
lauroyloxymethyl ester, tridecanoyloxymethyl ester,
myristoyloxymethyl ester, pentadecanoyloxymethyl ester,
palmitoyloxymethyl ester, heptadecanoyloxymethyl ester,
stearoyloxymethyl ester, nonadecanoyloxymethyl ester,
eicosanoyloxymethyl ester, 1(or 2)-heptanoyloxymethyl ester,
1(or 2)-octanoyloxymethyl ester, 1(or 2)-nonanoyloxymethyl
ester, 1(or 2)-decanoyloxymethyl ester, 1(or
2)-undecanoyloxymethyl ester, 1(or 2)-lauroxyloxyethyl ester,
1(or 2)-tridecanoyloxymethyl ester, 1(or 2)-myristoyloxymethyl
ester, 1(or 2)-pentadecanoyloxymethyl ester, 1(or
2)-palmitoyloxymethyl ester, 1(or 2)-heptadecanoyloxymethyl
ester, 1(or 2)-stearoyloxymethyl ester, 1(or
2)-nonadecanoyl-oxyethyl ester, 1(or 2)-eicosanoyloxymethyl
ester, etc.], cycloalkyloxy(lower)alkyl ester [e.g.
cyclohexylcarbonyloxymethyl ester, 1(or
2)-cyclopentylcarbonyloxyethyl ester, 1(or 2)-cyclohexylcarbonyloxyethyl ester, etc.), aroyloxy(lower)alkyl ester such as benzoyloxy(lower)alkyl ester [e.g. 1(or 2)-benzoyloxyethyl ester, etc.], heterocyclic carbonyloxy(lower)alkyl ester such as lower alkylpiperidylcarbonyloxy(lower)alkyl ester [e.g. 1(or 2)-(1-methylpiperidyl)carbonyloxyethyl, etc.], lower alkoxy carbonyloxy(lower)alkyl ester [e.g. methoxycarbonyloxy methyl ester, ethoxycarbonyloxy methyl ester, propoxycarbonyloxy methyl ester, isopropanoxycarbonyl-oxy methyl ester, tert-butoxycarbonyloxy methyl ester, 1(or 2)-methoxycarbonyloxyethyl ester, 1(or 2)-ethoxycarbonyloxyethyl ester, 1(or 2)-propoxycarbonyloxyethyl ester, 1(or 2)-isopropanoxycarbonyloxyethyl ester, 1(or 2)-butoxycarbonyloxyethyl ester, 1(or 2)-isobutoxycarbonyloxyethyl ester, 1(or 2)-tert-butoxycarbonyloxyethyl ester, 1(or 2)-hexyloxy carbonyloxy-ethyl ester, 1(or 2 or 3)-methoxycarbonyloxy propyl ester, 1(or 2 or 3)-ethoxycarbonyloxy propyl ester, 1(or 2 or 3)-isopropanoxycarbonyloxy propyl ester, 1(or 2 or 3 or 4)-ethoxycarbonyloxy butyl ester, 1(or 2 or 3 or 4)-butoxycarbonyloxy butyl ester, 1(or 2 or 3 or 4 or 5)-pentyloxy carbonyloxy penty l ester, 1(or 2 or 3 or 4 or 5)-neopentyloxy carbonyloxy penty l ester, 1(or 2 or 3 or 4 or 5 or 6)-ethoxycarbonyloxy hexyl ester, etc.], cycloalkylcarbonyloxy(lower)alkyl ester [e.g. cyclohexyloxy carbonyloxy methyl ester, 1(or 2)-cyclopentylcarbonyloxyethyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester,
(5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.), (5-lower alkyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, (5-tert-butyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], (5-aryl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester, etc.), ar(lower)alkyl ester which may have one or more substituent(s) such as mono- (or di or tri-) phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xyleyl ester, misityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, 1(or 2)-phthalid-3-ylideneethyl ester, etc.), and the like.

Suitable "imino-protective group" may include conventional one, and the preferable example thereof is ar(lower)alkyl such as mono- (or di- or tri-) phenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), acyl such as lower alkoxy carbonyl (e.g. tert-butoxycarbonyl, etc.), lower alkanesulfonyl (e.g. mesyl, etc.), arenesulfonyl (e.g. tosyl, etc.), and the like, in which the most preferred one is trityl.

The term "condensed or uncondensed imidazolyl" means 1H-imidazol-1-yl which may be condensed with aromatic or heterocyclic ring, and such group may include benzene, naphthalene, 5 or 6-membered aromatic heteromonocyclic group such as 5 or 6 membered aromatic heteromonocyclic group containing 1 to 2-nitrogen atom(s) (e.g. pyrrole, imidazole,
pyrazole, pyridine, pyrimidine, etc.), 5 or 6-membered aromatic heteromonocyclic group containing 1-oxygen atom (e.g. furan, etc.), 5 or 6-membered aromatic heteromonocyclic group containing 1 sulfur atom (e.g. thiophene, etc.), and the like.

Suitable substituent in the term "condensed or uncondensed imidazolyl which may have suitable substituent(s)" is conventional one used in a pharmaceutical field and may include lower alkyl, halogen, lower alkoxy, hydroxy(lower)alkyl as mentioned above, respectively; optionally esterified carboxy such as carboxy and esterified carboxy as mentioned above; and the like.

Particularly, the preferred embodiment of \( \frac{N}{N} \) is as follows.

2-lower alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl, 2-propyl-3H-imidazo[4,5-b]pyridin-3-yl, 2-butyl-3H-imidazo[4,5-b]pyridin-3-yl, etc.); 2,7-di(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl, 7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl, 2-butyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl etc.), 2,5,7-tri(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl, 5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl, etc.); 5-halo-2-lower alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-butyl-5-chloro-3H-imidazo[4,5-b]pyridin-3-yl, etc.), 5-lower alkoxy-2-lower alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-butyl-5-methoxy-3H-imidazo[4,5-b]pyridin-3-yl, etc.), 6-lower alkoxy carbonyl-2-lower alkyl-1H-benzimidazol-1-yl (e.g. 2-butyl-6-ethoxycarbonyl-1H-benzimidazol-1-yl, etc.).
2-lower alkyl-3H-imidazo[4,5-d]pyrimidin-3-yl (e.g. 2-butyl-3H-imidazo[4,5-d]pyrimidin-3-yl, etc.), 2-lower alkyl-1H-thieno[3,4-d]imidazol-1-yl (e.g. 2-butyl-1H-thieno[3,4-d]imidazol-1-yl, etc.), 2-lower alkyl-4-halo-5-hydroxy(lower)alkyl-1H-imidazol-1-yl (e.g. 2-butyl-4-chloro-5-hydroxymethyl-1H-imidazol-1-yl, etc.) 2-lower alkoxy-7-lower alkanoyloxy(lower)alkoxycarbonyl-1H-benzimidazol-1-yl (e.g. 2-ethoxy-7-[1-(propionyloxy)ethoxycarbonyl]-1H-benzimidazol-1-yl, etc.), 2-lower alkoxy-5,7-di(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl (e.g. 2-ethoxy-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl, etc.) and more preferably 2-lower alkyl-3H-imidazo[4,5-b]pyridin-3-yl, 2,7-di(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl, 2,5,7-tri(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl, 2-lower alkoxy-7-lower alkanoyloxy(lower)alkoxycarbonyl-1H-benzimidazol-1-yl and 2-lower alkoxy-5,7-di(lower)alkyl-3H-imidazo[4,5-b]pyridin-3-yl.

For therapeutic or preventive administration, the lipids-lowering agent of the present invention are used in the form of conventional pharmaceutical preparation which contains the angiotensin II antagonist, as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparation may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade, and the like.

If needed, there may be included in the above preparation auxiliary substances, stabilizing agents,
wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the angiotensin II antagonist may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the angiotensin II antagonist to be applied, and the like. In general, amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg, 200 mg, or 300 mg of the angiotensin II antagonist may be used in lowering the lipids in the body.

In addition to the new lipids-lowering activity of the angiotensin II antagonist of the present invention, the compound of the general formula [II], particularly the compound of the formula [III] further exhibits suppressive effect on abnormal increase of heart, liver and kidney weights, on renal functional diseases and inflammation of arteria renalis, and on a diuretic effect. For these additional effects, the same preparation and dosage form as mentioned above are applicable.

In order to show the usefulness of the present inventions, the following examples are given.

**Example 1**

**Lipids-Lowering Effects on serum LDL-C and Phospholipids**

[Test Method]

Male adult spontaneously hypertensive rats (SHR, 16 weeks old) were used in this test. 10 mg/kg/Day of each Test Compound was administered by incorporation into a diet for 20 weeks. Blood samples were collected from the thoracic aorta at the end of a period of drug administration, and an
aliquot of serum with EDTA was provided for analysis of serum lipids.

[Test Compound]
Sodium salt of 2-butyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-3H-imidazo[4,5-b]pyridine [hereinafter referred to as Compound A]

[Test Results]

<table>
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<tr>
<th></th>
<th>LDL-C (mg/dl)</th>
<th>Phospholipids (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33 ± 1.7</td>
<td>104 ± 2.5</td>
</tr>
<tr>
<td>Compound A</td>
<td>19 ± 1.1</td>
<td>90 ± 2.3</td>
</tr>
</tbody>
</table>

Example 2
Suppressive Effect on Abnormal Increase of Heart and Liver Weights

[Test Method]
After collecting blood sample from SHR in the above Example 1, heart and liver were removed and rinsed in Tyrode's solution. Weight of each tissue was measured.

[Test Compound]
Compound A

[Test Results]

<table>
<thead>
<tr>
<th></th>
<th>Heart Weight (mg)</th>
<th>Liver Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1465 ± 47</td>
<td>12.73 ± 0.21</td>
</tr>
<tr>
<td>Compound A</td>
<td>1301 ± 17</td>
<td>11.61 ± 0.26</td>
</tr>
</tbody>
</table>
Example 3
Suppressive Effect on Renal Functional Diseases and Inflammation of Arteria Renalis

[Test Method]
The blood sample collected from SHR in the above Example 1 was provided for analysis of blood urea nitrogen (BUN). BUN was measured by a conventional method.

Also, kidneys were removed from the tested SHR at the end of a period of drug administration and subjected to pathological analysis.

[Test Compound]
Compound A

[Test Results]
(1) BUN

<table>
<thead>
<tr>
<th></th>
<th>BUN (mg/dl)</th>
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<tbody>
<tr>
<td>Control</td>
<td>21.9 ± 1.0</td>
</tr>
<tr>
<td>Compound A</td>
<td>18.6 ± 0.5</td>
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</tbody>
</table>

(2) Pathological Analysis
Control: Inflammation of artery renalis was observed.
Compound A: No inflammation of artery renalis was observed.

Example 4
Diuretic Effect

[Test Method]
Male adult spontaneously hypertensive rats (SHR, 16 weeks old) were used in this test. 10 Mg/kg/Day of each Test Compound was administered by incorporation into a diet for 19 weeks. Urine sample was collected for six hours after
period of drug administration, and the volume of the urine was measured.

[Test Compound]

Compound A

[Test Results]

<table>
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<tr>
<th></th>
<th>Urine (ml/kg)</th>
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<tr>
<td>Control</td>
<td>10.2 ± 0.98</td>
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<td>Compound A</td>
<td>14.0 ± 1.16</td>
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As evident from the Test Results in Example 1, the angiotensin II antagonist shows strong lowering activity of lipids such as cholesterol, phospholipid, neutral fats, and the like, particularly total cholesterol, LDL-C and phospholipids, and therefore is of much use for treating and preventing lipids-associated diseases and conditions such as hypercholesterolemia, hyperlipidemia, hyperlipemia, hyperlipoproteinemia, atherosclerosis, and the like.

Further, from the Test Results in Examples 2 to 4, the angiotensin II antagonist of the compounds of the formula [II], particularly the compound of the formula [III] are considered to be of use for treating cardiac hypertrophy, renal functional diseases and nephropathy (e.g. renal insufficiency, inflammation of arteria renalis, etc.), hepatopathy (e.g. hepatic insufficiency, hepatic hypertrophy, etc.), and the like, and also of use as a diuretic.
Furthermore, it is expected that the compound of the formula \([\text{II}]\) wherein \(R_2^a\) is a group of the formula:

![Chemical Structure Diagram]

are useful for treating congestive heart failure, disorder of intracellular homeostasis, hyperuricemia, diabetic nephropathy, diabetic neuropathy, and the like.

Reference Example

To a mixture of 2-ethyl-5,7-dimethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)pyrrol-2-yl]benzyl]-3H-imidazo-[4,5-b]pyridine (3.54 g) and ethanol (18 ml) was added 12N hydrochloric acid (0.8 ml), and the reaction mixture was heated in a boiling bath for a few minutes. The resultant solution was evaporated in vacuo, and the residue was crystallized from a mixture of 1N hydrochloric acid and ethanol to afford 2-ethyl-5,7-dimethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)pyrrol-2-yl]benzyl]-3H-imidazo-[4,5-b]pyridine hydrochloride (2.38 g). m.p. 246-248°C
CLAIMS

1. A lipids-lowering agent which comprises an angiotensin II antagonist as an active ingredient.

2. A use of an angiotensin II antagonist as a lipids-lowering agent.

3. A use of an angiotensin II antagonist for manufacturing a medicament for treating or preventing lipids-associated diseases and conditions.

4. A method for treating or preventing lipids-associated diseases and conditions which comprises administering an effective amount of an angiotensin II antagonist to a host.
A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/52

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)
IPC 5 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>YAYAMA, K. ET AL 'DUP 753 PREVENTS THE DEVELOPMENT OF PUROMYCIN AMINONUCLEOSIDE-INDUCED NEPHROSIS' see the whole document</td>
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<td>WO,A,93 08169 (AMERICAN HOME PRODUCTS CORPORATION) 29 April 1993 see the whole document especially page 10, line 10-32 &amp; page 13, line 16-page 14, line 3</td>
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</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
'A' document defining the general state of the art which is not considered to be of particular relevance
'B' 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 novel or 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.

A document member of the same patent family

Date of the actual completion of the international search
29 October 1993

Date of mailing of the international search report
15.11.93

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tél. (+31-70) 340-2040, Tél. 31-651 epo nl, Fax (+31-70) 340-3516

Authorized officer
MAIR, J
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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 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. ☑️ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   REMARK: Although claim 4 is directed towards 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.

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 II  Observations where unity of invention is lacking (Continuation of item 2 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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
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