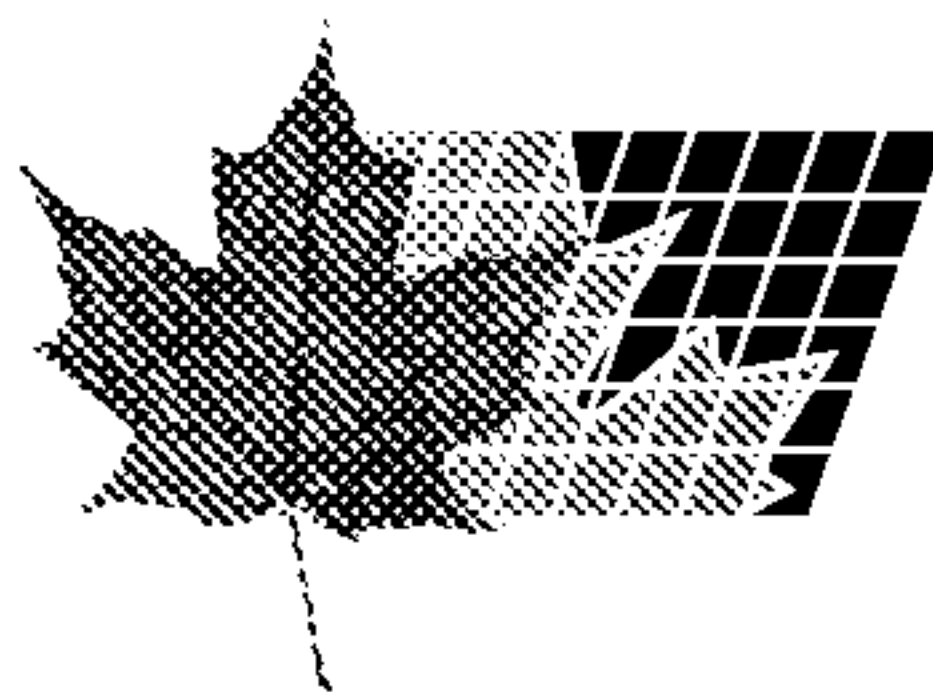




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(54) **EXCRETION D'AZOTE NON PROTEIQUE DANS L'INTESTIN
PAR DES DERIVES DE L'ACIDE PROSTANOIQUE**

(54) **IMPROVEMENT OF EXCRETION OF NONPROTEIN
NITROGEN INTO THE INTESTINE BY PROSTANOIC ACID
DERIVATIVES**

(57) The present invention is directed to a pharmaceutical composition which improves excretion of nonprotein nitrogen into the intestine. The composition comprises a prostanoic acid derivative in association with a pharmaceutically acceptable carrier, diluent or excipient.



Abstract

5 The present invention is directed to a pharmaceutical composition which improves excretion of nonprotein nitrogen into the intestine. The composition comprises a prostanoid acid derivative in association with a pharmaceutically acceptable carrier, diluent or excipient.

Improvement of Excretion of Nonprotein Nitrogen
Into the Intestine by Prostanic Acid Derivatives

The present invention relates to a pharmaceutical composition which improves the excretion of nonprotein nitrogen into the intestines, said composition comprising a prostanic acid derivative.

The object of the present invention is to improve excretion, via the intestinal wall, of nonprotein nitrogen, e.g. urea nitrogen, creatinine etc., as a substitute for usual treatments, e.g. extracorporeal dialysis, peritoneal dialysis, etc., for removal of the above nitrogens, in a subject whose nonprotein nitrogen concentration in the blood is elevated, e.g. by renal insufficiency.

Renal insufficiency refers to a condition in which renal function is impaired by renal diseases, e.g. glomerulonephritis, nephrotic syndrome, nephrosclerosis, renal carcinoma, lupus nephritis, etc. One important parameter for renal insufficiency is the excreting function of kidney and especially the concentration of nonprotein nitrogen, e.g. urea, creatinine, etc., in the blood. These are pooled in the body by impaired excretion. Symptoms of uremia appear as the pooling progresses.

Traditional means effective in the treatment of renal insufficiency is dialysis in which the blood is contacted with a dialysate with a semipermeable membrane between them whereby substances in the blood may be removed through diffusion by osmotic gradient. Dialysis includes hemodialysis in which the arterial blood is introduced into an artificial kidney and returned to a vein and peritoneal dialysis in which blood substances are dispersed into a dialysate, which is introduced into the peritoneal cavity and discharged periodically, through capillary vessels serving as a semipermeable membrane. However, the former has the disadvantage that it requires a surgical operation, e.g. shunt operation, while the latter has disadvantages in that it has inferior dialysis efficacy and requires infection-preventing measures.

The present inventor and co-workers formerly discovered that 15-keto-16-halo-prostaglandins (hereinafter, prostaglandin is referred to as PG) have an enteropooling activity (activity of pooling water in intestines) (EP-A-310305). Enteropooling activity of 16,16-dimethyl-PGE₂ has also been described in Prostaglandins, 11, 809 - 828 (1976). However, nothing has been reported regarding a compound exhibiting the activity of excreting nonprotein nitrogen into the intestines.

As a result of extensive studies concerning PG compound properties, the present inventors unexpectedly discovered that these compounds exhibit the activity of excreting nonprotein nitrogen in the blood into the intestines.

In a first aspect, the present invention provides a method for improving excretion of nonprotein nitrogen into the intestines which comprises administering, to a subject in need of such improvement, a prostanoid acid derivative in an amount effective to improve excretion of nonprotein nitrogen into the intestines.

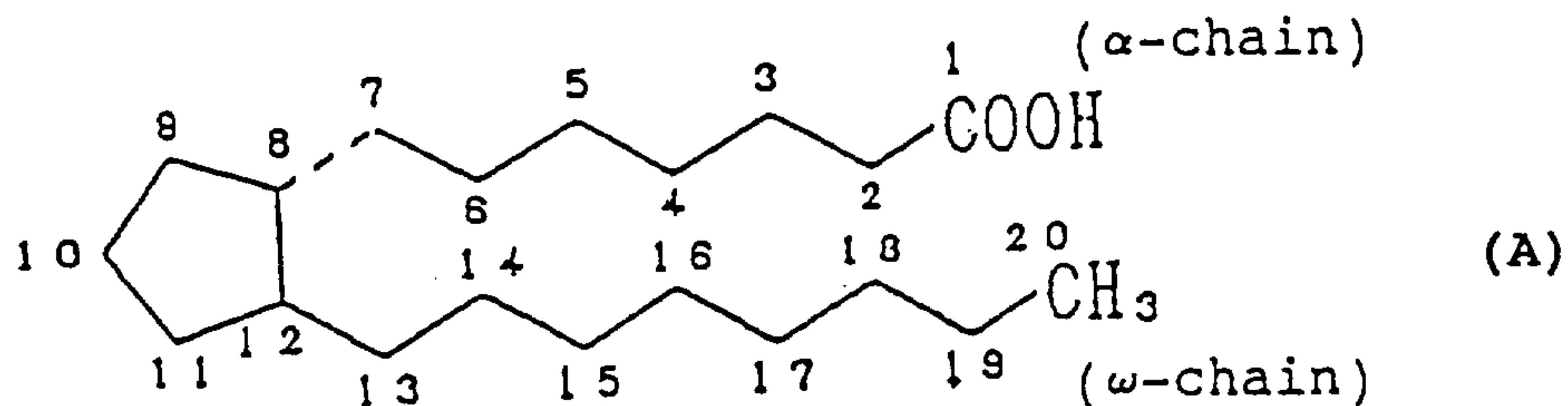
In a second aspect, the present invention provides a use of a prostanoid acid derivative for the manufacture of a medicament for improving excretion of nonprotein nitrogen into the intestine.

In a third aspect, the present invention provides a pharmaceutical composition for improving excretion of nonprotein nitrogen into the intestine comprising a prostanoid acid derivative in association with a pharmaceutically acceptable carrier, diluent or excipient.

As used herein, the term "nonprotein nitrogen" includes urea, uric acid, creatine, creatinine, amino acids, ammonia etc., with urea and creatinine being most important.

The words "excretion into the intestine" mean active or passive transport of substances (water, nonprotein nitrogen, etc.) in body fluids, principally in the blood, into the intestine ranging from the duodenum to the large intestine, principally into the small intestine.

The term "prostanoid acid" refers to the basic skeleton, shown by the formula below, as the common structural feature the naturally occurring PGs.



The primary PGs are classified based on the structural feature of the five-membered cycle moiety into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs, and also on the presence or absence of unsaturation and oxidation in the chain moiety as:

Subscript 1 - - - 15-OH

Subscript 2 - - - 5,6-unsaturated-15-OH

Subscript 3 - - - 5,6- and 17, 18-diunsaturated-15-OH

Further, PGFs are sub-classified according to the configuration of the hydroxy group at position 9 into α (hydroxy group being in the alpha configuration) and β (hydroxy group being in the beta configuration). Some synthetic analogues have somewhat modified skeletons.

The term "derivative" refers to a compound in which one or more atoms or groups in the prostanoic acid shown by the formula (A) is replaced by another atom or group or is eliminated. Such derivatization includes the modifications known in the synthetic PG analogues and other modifications.

Nomenclature of prostanoic acid derivatives herein uses the numbering system of prostanoic acid represented in formula (A) shown above.

While formula (A) shows a basic skeleton having twenty carbon atoms, the 15-keto-PG compounds used in the present invention are not limited to those having the same number of carbon atoms. The carbon atoms in formula (A) are numbered 2 to 7 on the α -chain starting from the α -carbon atom adjacent to the carboxylic carbon atom which is numbered 1 and towards the five-membered ring, 8 to 12 on the said ring starting from

the carbon atom on which the α -chain is attached, and 13 to 20 on the ω -chain starting from the carbon atom adjacent to the ring. When the number of carbon atoms is decreased in the α -chain, the number is deleted in order starting from position 2 and when the number of carbon atoms is increased in the α -chain, compounds are named as substituted derivatives having respective substituents at position 1 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω -chain, the number is deleted in order starting from position 20 and when the number of carbon atoms is increased in the ω -chain, compounds are named as substituted derivatives having respective substituents at position 20. Stereochemistry of the compounds is the same as that of above formula (A) unless otherwise specified.

In general, PGDs, PGEs and PGFs have (A) hydroxy group(s) on the carbon atom(s) at position 9 and/or 11 but in the present specification PGs include those having a group other than a hydroxyl group at position 9 and/or 11. Such PGs are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds.

As stated above, nomenclature of the prostanoic acid derivative is based upon the prostanoic acid and sometimes utilizes the abbreviation "PG" for convenience, when the derivative in question has a partial structure common with PGs. These compounds, however, can also be named according to the IUPAC naming system. For example, 13,14-dihydro-15-keto-16R,S-fluoro-PGE₂ is (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(4R,S)-4-fluoro-3-oxo-1-octyl]-5-oxocyclopentyl]-hept-5-enic acid. 13,14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methyl-PGE₂ methyl ester is methyl 7-[(1R,2S,3S)-3-methyl-2-[3-oxo-1-decyl]-5-oxo-cyclopentyl]-hept-5-enoate. 13,14-dihydro-6,15-diketo-19-methyl-PGE₂ ethyl ester is ethyl 7-[(1R,2S,3S)-3-hydroxy-2-(7-methyl-3-oxo-1-octyl)-5-oxo-cyclopentyl]-6-oxo-heptanoate. 13,14-dihydro-15-keto-20-ethyl-PGF_{2 α} isopropyl ester is isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxo-1-decyl)-cyclopentyl]-hept-5-enoate. 13,14-dihydro-15-keto-20-methyl-PGF_{2 α} methyl ester is methyl (Z)-7-

[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxo-1-nonyl)-cyclopentyl]-hept-5-enonate.

Preferred prostanoid acid derivatives used in the present invention are those having an oxo group at position 15 of the prostanoid acid in place of the hydroxy group, or having at least one halogen atom on the prostanoid acid skeleton, or having both of these features. These derivatives may have a single bond (15-keto-PG₁ compounds), a double bond (15-keto-PG₂ compounds) between positions 5 and 6, or two double bonds (15-keto-PG₃ compounds) between positions 5 and 6 as well as positions 17 and 18.

The term "halogen" refers to fluorine, chlorine, bromine and iodine with fluorine being preferred.

Examples of substitution products or derivatives include esters at the carboxy group at the alpha chain, pharmaceutically or physiologically acceptable salts, unsaturated derivatives having a double bond or a triple bond between positions 2 and 3 or positions 5 and 6, respectively, substituted derivatives having substituent(s) on carbon atom(s) at position 3, 6, 16, 17, 19 and/or 20 and compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group, of the above PGs.

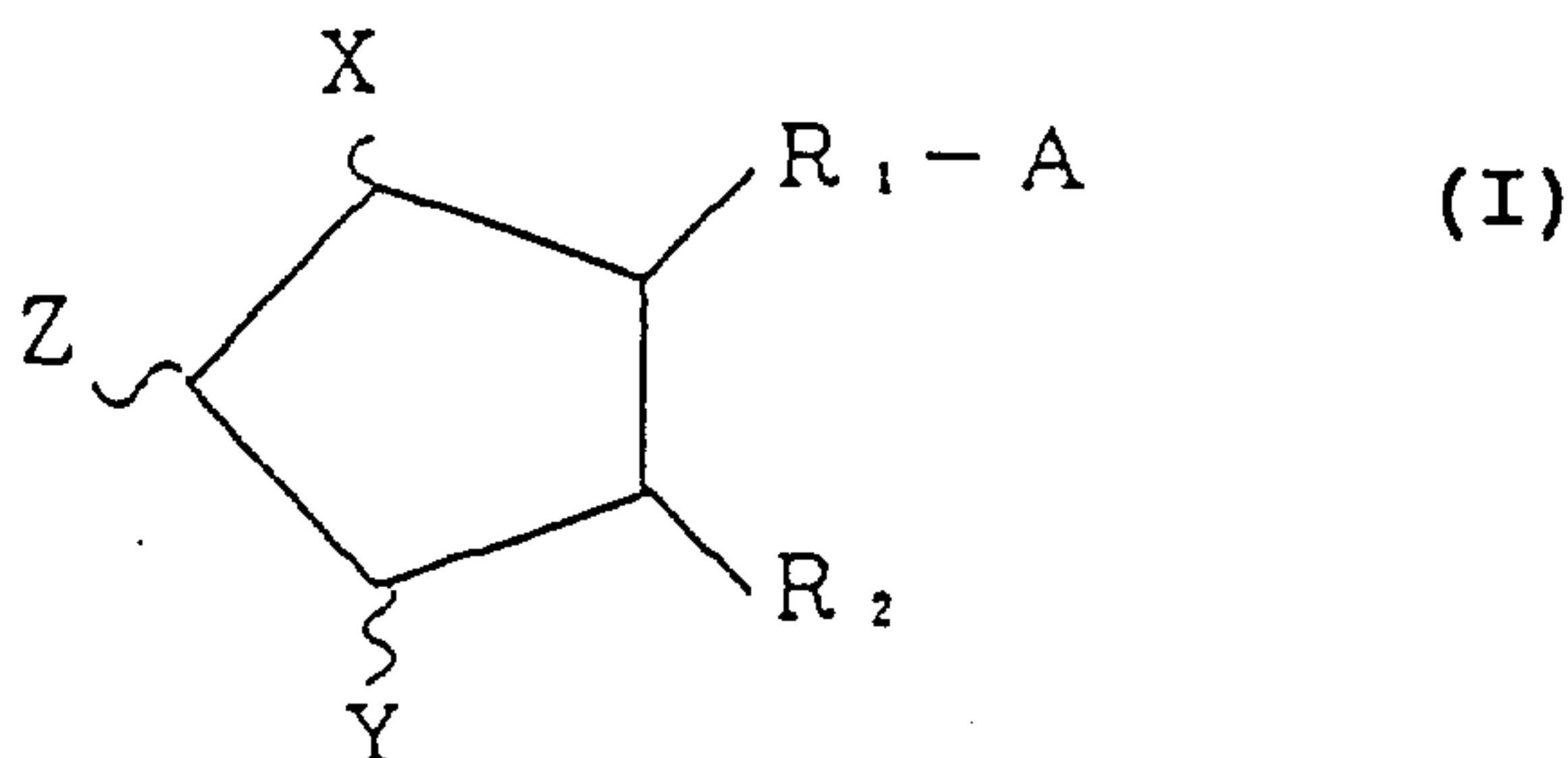
Examples of substituents present in preferred compounds are as follows: Substituents on the carbon atom at position 3, 17 and/or 19 include lower alkyl, for example, C₁₋₄ alkyl, especially methyl and ethyl. Substituents on the carbon atom at position 16 include lower alkyl e.g. methyl, ethyl, etc., hydroxy and halogen atom e.g. chlorine, fluorine, phenyl and phenoxy, the last two being unsubstituted or substituted. Substituents on the carbon atom at position 20 include saturated and unsaturated lower alkyl e.g. C₁₋₄ alkyl, lower alkoxy, e.g. C₁₋₄ alkoxy and lower alkoxy (lower) alkyl, e.g. C₁₋₄ alkoxy-C₁₋₄ alkyl. Substituents on the carbon atom at position 6 include an oxo group forming carboxyl. Stereochemistry of PGs having hydroxy, lower alkyl or lower

(hydroxy) alkyl substituent on the carbon atom at position 9 and/or 11 may be alpha, beta or mixtures thereof.

Said derivatives may have an alkoxy, phenoxy or phenyl group at the end of the omega chain where the chain is shorter than the primary PGs.

In the present invention, preferred compounds are those having at least one halogen atom on the prostanoic acid derivative, and the position of the halogen atom is not limited but is preferably on the omega chain and more preferably one or two halogen atoms are present at position 16.

A group of preferred compounds used in the present invention has the formula (I)



wherein X and Y are hydrogen, hydroxy, halo, lower alkyl, hydroxy (lower)alkyl, or oxo, with the proviso that at least one of X and Y is a group other than hydrogen, and 5-membered rings may have at least one double bond, Z is hydrogen or halogen, A is -CH₂OH, -COCH₂OH, -COOH or its functional derivative, R₁ is bivalent saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with halo, oxo or aryl, R₂ is saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with oxo, hydroxy, halo, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, aryl or aryloxy, with the proviso that the third carbon atom counted from the 5-membered ring is substituted with an oxo group.

In the above formula, the term "unsaturated" in the definitions for R₁ and R₂ is intended to include at least one and optionally more than one double bond and/or triple bond

isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to usual nomenclature, an unsaturation between two serial positions is represented by denoting the lower number of said two positions, and an unsaturation between two distal positions is represented by denoting both of the positions. Preferred unsaturation is a double bond at position 2 and a double or triple bond at position 5.

10 The term "lower or medium aliphatic hydrocarbon residue" refers to a straight or branched chain hydrocarbyl group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms being preferred) and preferably 2 to 8 carbon atoms for R_1 and 6 to 12 carbon atoms for R_2 .

15 The term "halo" denotes fluoro, chloro, bromo and iodo. The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

20 The term "lower alkyl" as a group or a moiety in hydroxy(lower)alkyl includes saturated and straight or branched chain hydrocarbon radicals containing 1 to 6 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to the group lower-alkyl-O- wherein lower alkyl is as defined above.

25 The term "hydroxy(lower)alkyl" refers to alkyl as defined above and substituted with at least one hydroxy group, e.g. hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

30 The term "lower alkanoyloxy" refers to a group of the formula: $RCO-O-$ wherein $RCO-$ is an acyl group formed by oxidation of a lower alkyl group as defined above, e.g. acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above.

35 The term "aryl" includes unsubstituted or substituted aromatic carbocyclic or heterocyclic (preferably monocyclic) groups, e.g. phenyl, tolyl, xylyl and thienyl. Examples of

substituents are halo and halo(lower)alkyl wherein halo and lower alkyl are as defined above.

The term "aryloxy" refers to a group of the formula: ArO- wherein Ar is aryl as defined above.

5 The term "functional derivative" of carboxy as A includes salts (preferably pharmaceutically acceptable salts), esters and amides.

10 Suitable "pharmaceutically acceptable salts" include conventional non-toxic salts, and may be a salt with an inorganic base, for example a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, a salt with an organic base, for example, an amine salt (e.g. methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, monomethyl-monoethanolamine salt, procaine salt, caffeine salt, etc.), a basic amino acid salt (e.g. arginine salt, lysine salt, etc.), tetraalkylammonium salt and the like. 15
20 These salts can be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

25 Examples of the esters are aliphatic esters, for example, lower alkyl ester e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, 1-cyclopropylethyl ester, etc., lower alkenyl ester e.g. vinyl ester, allyl ester, etc., lower alkynyl ester e.g. ethynyl ester, propynyl ester, etc., 30
30 hydroxy(lower) alkyl ester e.g. hydroxyethyl ester, lower alkoxy(lower)-alkyl ester e.g. methoxymethyl ester, 1-methoxyethyl ester, etc., and aromatic esters, for example, optionally substituted aryl ester e.g. phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxy-phenyl ester, benzamidophenyl ester, etc., aryl(lower)alkyl ester e.g. benzyl ester, trityl ester, benzhydryl ester, etc. 35
 Examples of the amides are mono- or di- lower alkyl amides

e.g. methanamide, ethanamide, dimethanamide, etc., arylamide
e.g. anilide, toluidide, and lower alkyl- or aryl-
sulfonylamide e.g. methylsulfonylamide, ethylsulfonylamide,
tolylsulfonylamide etc.

5 Preferred examples of A include $-\text{COOH}$, $-\text{COOCH}_3$,
 $-\text{COOCH}_2\text{CH}_3$, $-\text{COOCH}(\text{CH}_3)_2$ and $-\text{CONHSO}_2\text{CH}_3$.

The configuration of the ring and the α - and/or omega
chain in the above formula (I) may be the same as or different
from that in the primary PGs. However, the present invention
10 also includes a mixture of a compound having a primary
configuration and that of an unprimary configuration.

Examples of the typical compounds of the present
invention are 15-keto-PGs, 13,14-dihydro-15-keto-PGs and their
e.g. 6-keto-derivatives, Δ^2 -derivatives, 3R,S-methyl-
15 derivatives, 16R,S-methyl derivatives, 16,16-dimethyl-
derivatives, 16R,S-fluoro derivatives, 16,16-difluoro-
derivatives, 17S-methyl derivatives, 19-methyl derivatives, 20-
methyl derivatives and 16-desbutyl-16-phenoxy derivatives.

When 15-keto-PG compounds of the present invention have a
20 saturated bond between positions 13 and 14, these compounds
may be in the keto-hemiacetal equilibrium by forming a
hemiacetal between the hydroxy group at position 11 and the
ketone at position 15.

The proportion of both tautomeric isomers, when present,
25 varies depending on the structure of the rest of the molecule
or type of substituent present and, sometimes, one isomer may
be predominant in comparison with the other. However, in this
invention, it is to be appreciated that the compounds used in
the invention include both isomers. Further, while the
30 compounds used in the invention may be represented by a
structure or name based on a keto-form regardless of the
presence or absence of the isomers, it is to be noted that
such structure or name is not intended to eliminate hemiacetal
type compounds.

35 In the present invention, any of the individual
tautomeric isomers, mixtures thereof, or optical isomers,

mixtures thereof, a racemic mixture, and other isomers, e.g. steric isomers can be used for the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in Japanese Patent Publication (unexamined) No. A-52753/1989.

Alternatively, these compounds may be prepared by a process analogous to that described herein or to known processes.

A practical preparation of the prostanoic acid derivative, e.g. 13,14-dihydro-15-keto compounds, involves the following steps; referring to the synthetic charts (I) to (III), reaction of the aldehyde (2) prepared by the Collins oxidation of commercially available (-)-Corey lactone (1) with dimethyl (2-oxoheptyl)phosphate anion to give α,β -unsaturated ketone (3), reduction of the α,β -unsaturated ketone (3) to the corresponding saturated ketone (4), protection of the carbonyl group of the ketone (4) with a diol to the corresponding ketal (5), and deprotection of the p-phenylbenzoyl group to give the corresponding alcohol (6) followed by protection of the newly derived hydroxy group with dihydropyrane to give the corresponding tetrahydropyranyl ether (7). According to the above process, a precursor of PGEs wherein the ω -chain is a 13,14-dihydro-15-keto-alkyl group is prepared.

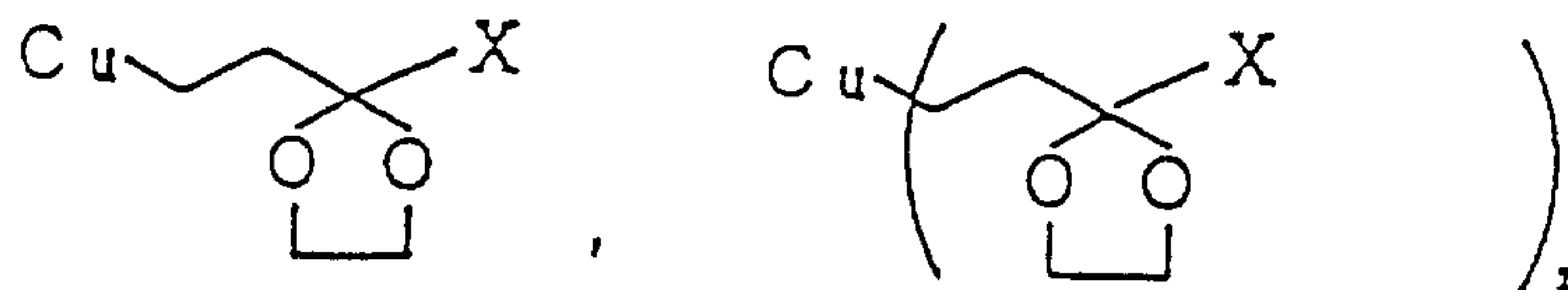
Using the above tetrahydropyranyl ether (7), 6-keto-PGE₁s (15) of which a group made up of carbon atoms of positions 5, 6 and 7 is $-\text{CH}_2-\text{C}(=\text{O})-\text{CH}_2-$, may be prepared

by the following steps; reduction of the tetrahydropyranyl ether (7) with, for example, diisobutyl aluminum hydride to give the corresponding lactol (8), reaction of the lactol (8), with the ylide generated from (4-carboxybutyl)triphenyl phosphonium bromide followed by esterification (10), cyclization between the 5,6-double bond and the hydroxyl group at position 9 with NBS or iodine to give the halogenated compound (11), dehydrohalogenation of the compound (11) with, for example, DBU to give the 6-keto compound (13) followed by Jones oxidation and removal of the protecting groups.

Furthermore, PGE₂s (19) of which a group made up of carbon atoms of positions 5, 6 and 7 is $-\text{CH}_2-\text{CH}=\text{CH}-$ may be prepared by the following steps; as shown in the synthetic chart II, reduction of the above tetrahydropyranyl ether (7) to give the lactol (8), reaction of the resultant lactol (8) with the ylide derived from (4-carboxybutyl)triphenyl phosphonium bromide to give the carboxylic acid (16) followed by esterification to give ester (17), Jones oxidation of the esters (17) to give the compound (18), and removal of the protecting groups.

Using the above tetrahydropyranyl ether (7) as the starting material, the compound having $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ may be prepared by using the same process as that for preparing PGE₂ having $-\text{CH}_2\text{CH}=\text{CH}-$ and subjecting the resultant compound (18) to catalytic reduction to reduce the double bond between position 5 and 6 followed by removal of the protective groups.

Synthesis of 5,6-dehydro-PGE₂s having $-\text{CH}_2-\text{C}\equiv\text{C}-$ may be carried out by capturing a copper enolate formed by 1,4-addition of a monoalkylcopper complex or a dialkylcopper complex of the following formulae:



to 4R-t-butyldimethylsilyloxy-2-cyclopenten-1-one with 6-alkoxycarbonyl-1-iodo-2-hexyne or the derivatives.

The 11-β type PGEs can be prepared according to the synthetic chart III.

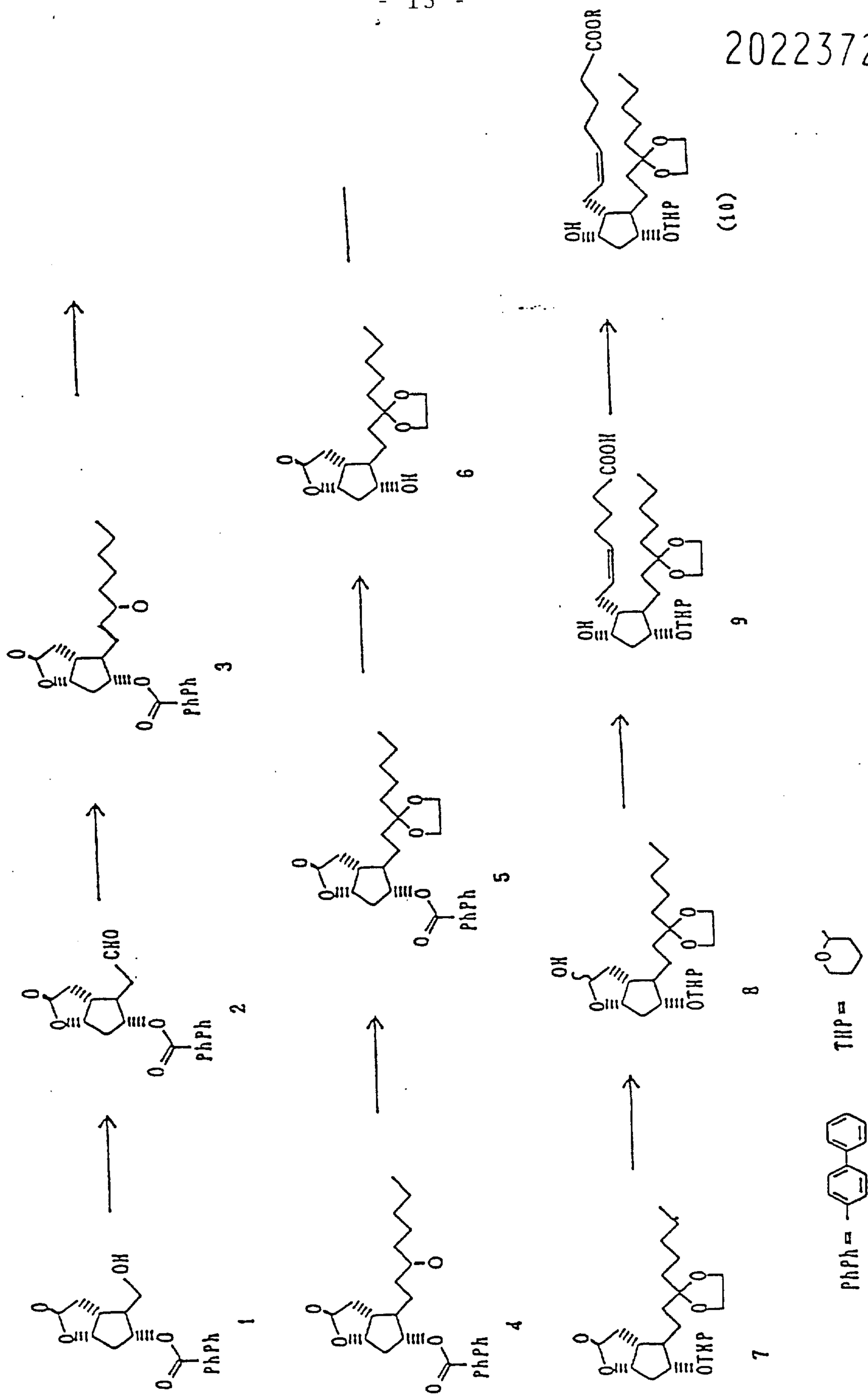
PGE derivatives having a methyl group at position 11 in place of a hydroxy can be prepared by reacting a dimethyl copper complex with PGA-type compound obtained by subjecting 9-hydroxy-11-tosylate to the Jones oxidation. Alternatively, they can be prepared by protecting the carbonyl of saturated ketone (4) produced by reducing unsaturated ketone (3),

eliminating p-phenylbenzoyl and tosylating the produced alcohol, treating with DBU to form a lactol, introducing the alpha-chain by Wittig reaction, oxidizing the alcohol at position 9 to give PGA-type compound, and reacting the product with dimethyl copper complex in order to introduce a methyl group into position 11 to give an 11-methyl-PGE-type compound, which on reduction with, e.g. sodium borohydride, gives an 11-methyl-PGF-type compound. An 11-hydroxymethyl-PGE-type compound, is obtained by a benzophenone-sensitized photoaddition of methanol of PGA-type compound, which is reduced with, e.g. sodium borohydride, to give an 11-hydroxymethyl-PGF-type compound. The synthetic route for the compounds used in the present invention is not limited to that described above and may vary using different protecting, reducing and/or oxidizing methods.

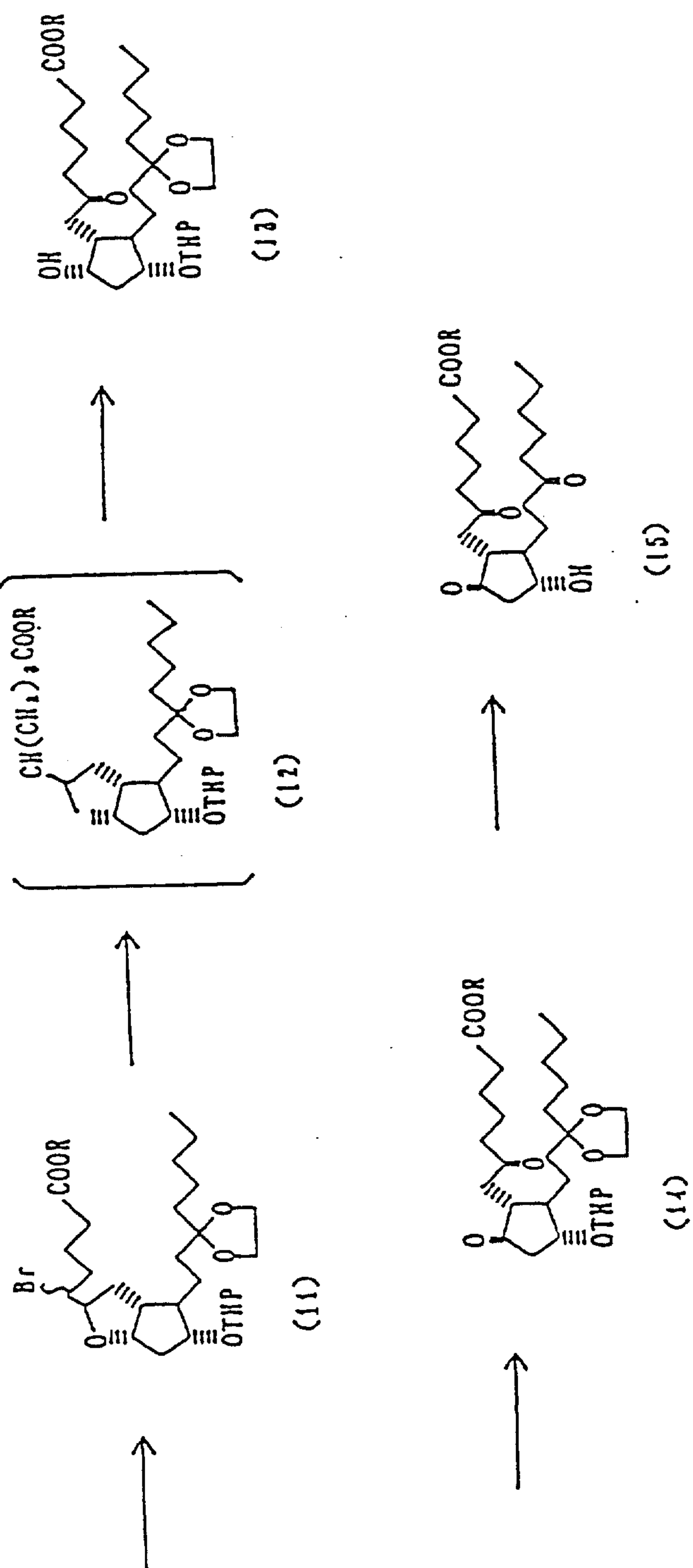
Corresponding other PG compounds can be produced analogously.

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Synthetic Chart I

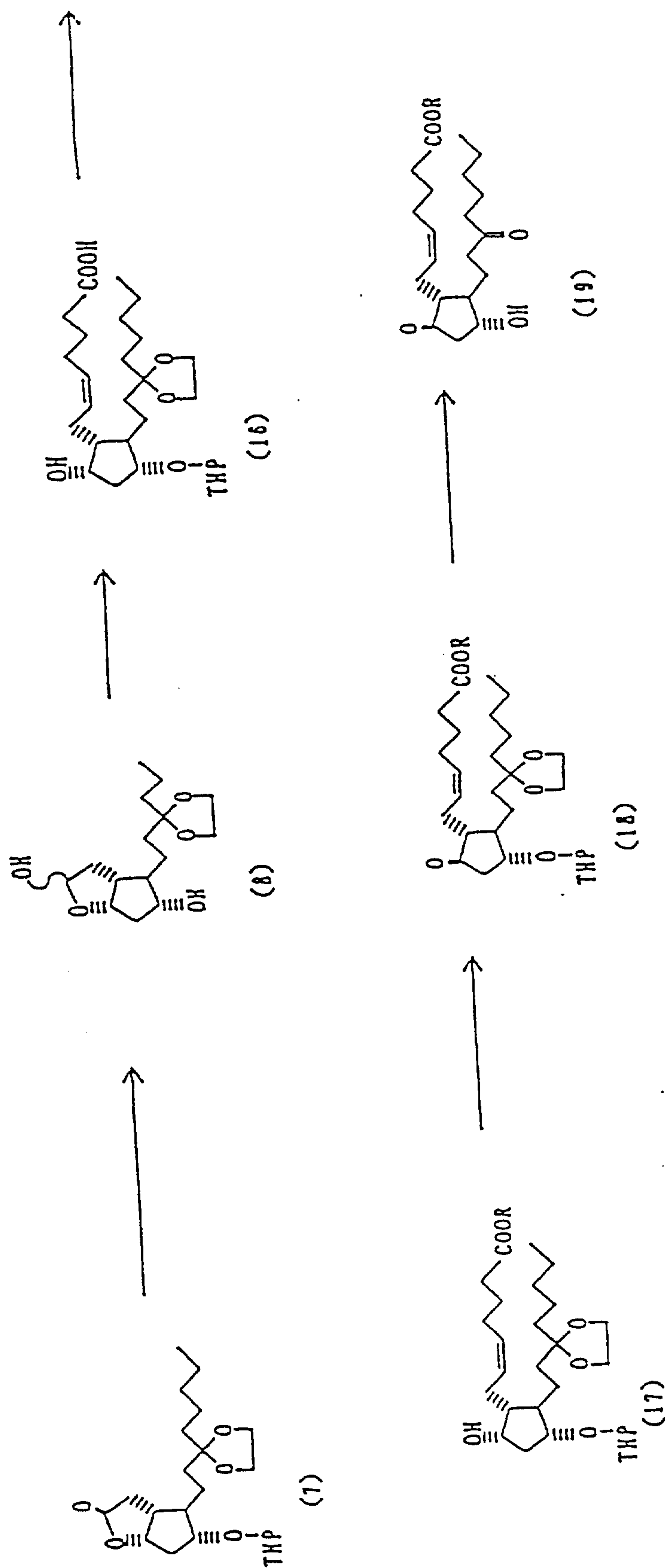


Synthetic Chart I (continued)



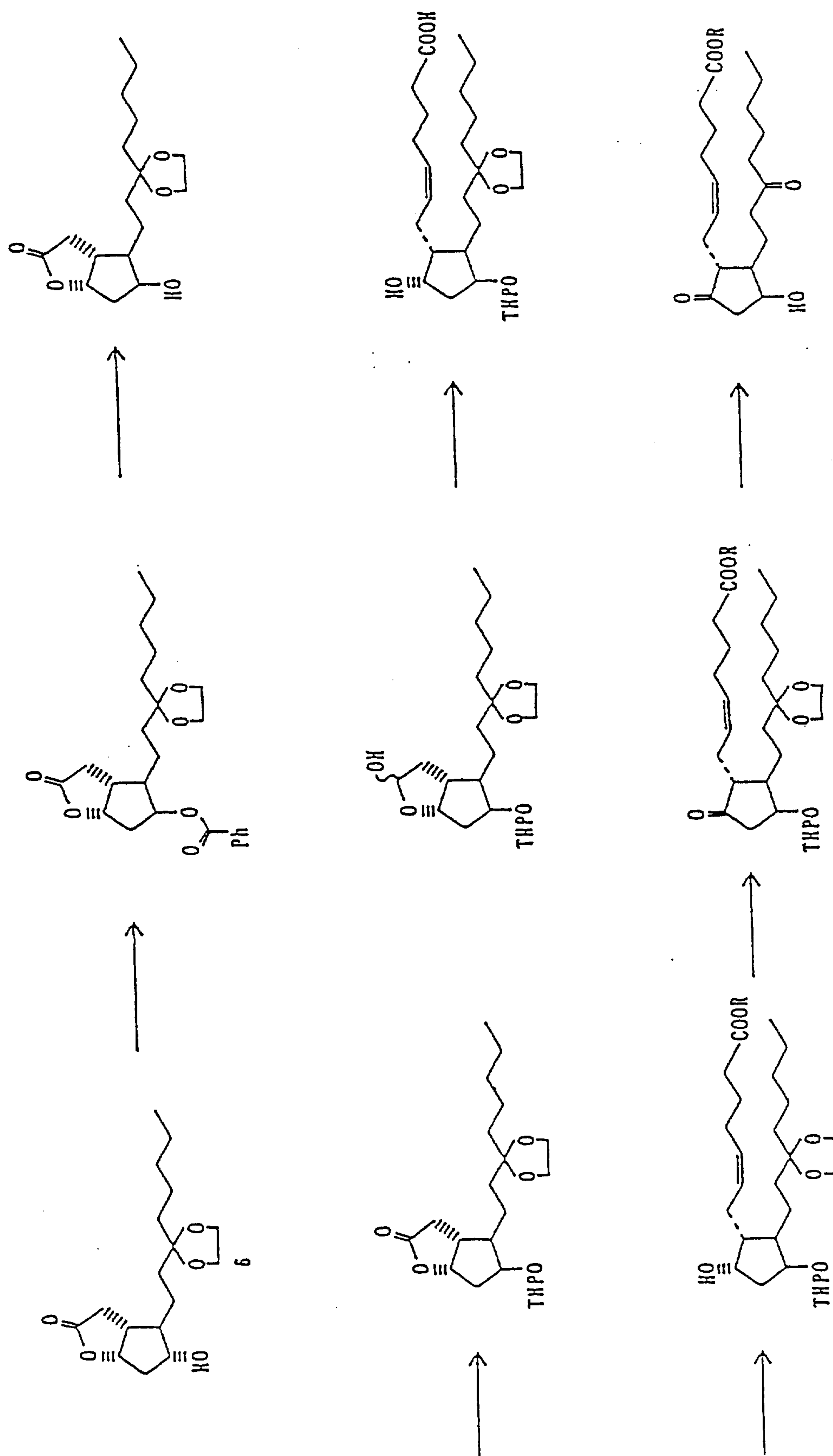
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Synthetic Chart II



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Sythetic Chart III



The compounds used in the present invention may be used as a medicine for animals and human beings and is usually administered systemically or locally by such methods as oral administration, intravenous injection (including
5 instillation), subcutaneous injection, suppository and the like. While the dosage will vary depending on the particular animal or human patient, age, body weight, symptoms to be treated, desired therapeutic effect, administration route, length of treatment and the like, satisfactory effects will be
10 obtained with a dosage of 0.001 - 500 mg/kg administered in 2 to 4 divided doses a day or as a sustained form.

As a solid composition of this invention for oral administration, tablets, troches, buccals, capsules, pills, powders, granules and the like are included. The solid
15 composition containing one or more active substances is mixed with at least an inactive diluent, e.g. lactose, mannitol, glucose, hydroxypropyl cellulose, fine crystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate. The composition may contain additives other
20 than the inactive diluent, for example, lubricants e.g., magnesium stearate, a disintegrator e.g. cellulose calcium gluconates, stabilizers e.g. α -, β - or γ -cyclodextrins, etherated cyclodextrins (e.g. dimethyl- α -, dimethyl- β -, trimethyl- β -, or hydroxypropyl- β -cyclodextrins), branched
25 cyclodextrins (e.g. glucosyl- or maltosyl-cyclodextrins), formyl cyclodextrins, sulfur-containing cyclodextrins, misoprotols or phospholipids. Such cyclodextrins may increase the stability of the compounds by forming inclusion compounds. The stability may often be increased by forming lyposomes with
30 phospholipids. Tablets and pills may be coated with an enteric or gastroenteric film e.g. white sugar, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalates and the like, if necessary, and furthermore they may be covered with two or more layers. Additionally, the
35 composition may be in the form of capsules made of an easily absorbed substance e.g. gelatin. The composition may be in the form of buccals, when an immediate effect is desired. For

this purpose, a base e.g. glycerine, lactose, may be used.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and may contain a generally used inactive diluent e.g. purified water or ethyl alcohol. The composition may contain additives e.g. wetting agents, suspending agents, sweeteners, flavours, perfumes and preservatives.

The composition of the present invention may be a spray which may contain one or more active ingredients and which can be prepared according to well known methods.

An injection of this invention for non-oral administration includes sterile aqueous or nonaqueous solutions, suspensions, and emulsions. Diluents for the aqueous solution or suspension include, for example, distilled water for injection, physiological saline and Ringer's solution. Diluents for the nonaqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, vegetable oils e.g. olive oil, alcohols, e.g. ethanol and polysorbates. The composition may contain other additives, e.g. preservatives, wetting agents, emulsifying agents, dispersing agents and the like. These are sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, gas sterilization or radiation sterilization. These can be prepared by producing a sterilized water or a sterilized solvent for injection before use.

Another formulation according to the present invention is a rectal or vaginal suppository. This can be prepared by mixing at least one active compound according to the invention with a suppository base e.g. cacao butter and optionally containing a nonionic surfactant to improve absorption.

The compounds used in the medicament for improving excretion of nonprotein nitrogen into the intestines according to the present invention have the effect of improving excretion of nonprotein nitrogen in the blood into the intestine or feces.

Accordingly, the compounds used in the present invention are useful for the treatment (e.g. prevention, cure, relief and arrest or relief of development) of conditions wherein nonprotein nitrogen levels in the blood are elevated and of uremia, irrespective of cause, e.g. disease, drug or food.

Further, the compounds of the present invention are also useful in the case where renal excretion of nonprotein nitrogen is damaged due to a reduction in or loss of renal function e.g. by renal failure.

A more complete understanding of the present invention can be obtained by reference to the following Formulation Examples and Test Examples which are provided herein for the purpose of illustration only and are not intended to limit the scope of the invention.

Formulation Example 1

(Hard gelatin capsules)

13,14-dihydro-15-keto-16R,S-fluoro-PGE ₂	50 mg
lactose	200 mg

The above ingredients were mixed and hard gelatin capsules were filled therewith.

Formulation Example 2

(Powders for injection)

(Parts by weight)

13,14-dihydro-15-keto-16,16-difluoro-PGE ₂	1
mannitol	5
distilled water	0.4

The above ingredients were mixed, stirred, sterilized, filtered and lyophilized to give powders for injection.

Formulation Example 3

(Injectable solution)

(Parts by weight)

13,14-dihydro-15-keto-16,16-dimethyl-PGE ₂	0.2
nonion surfactant	2
distilled water	98

The above ingredients were mixed and sterilized to give an injectable solution.

Formulation Example 4

13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₂ (50 mg) dissolved in methanol (10 ml) was mixed with mannitol (18.5g). The mixture was screened (with a sieve, the pore size of which was 30 mm in diameter), dried and screened again. The powders thus obtained were mixed with fine-grain silica gel (Aerosil*, 200g) and filled in No. 3 hard gelatin capsules (100) to give enteric capsules which contain 0.5 mg of 13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₂ per capsule.

Formulation Example 5

(Powders for oral administration)

(Parts by weight)

13,14-dihydro-15-keto-16,16-difluoro-PGF _{2a}	
methyl ester	5
light anhydrous silicic acid	5
Abicel*	20
lactose	70

The above ingredients were mixed to give powders for oral administration.

Formulation Example 6

(Soft gelatin capsules)

(Parts by weight)

13,14-dihydro-15-keto-20-methyl-PGE ₂	
methyl ester	1
light anhydrous silicic acid	899
Pansate*	20

The above ingredients were mixed and filled in soft gelatin capsules.

Formulation Example 7

(Enteric capsules)

16-desbutyl-13,14-dihydro-15-keto-16-(m-trifluoromethyl)phenoxy-PGF_{2a} methyl ester (50 mg) dissolved in methanol (10 ml) was mixed with mannitol (18.5g). The mixture was screened (with a sieve, the pore size of which was 30 mm in diameter), dried for 90 minutes at 30°C and screened again.

* Trademark

The powders thus obtained were mixed with fine-grain silica gel (Aerosil, 200 g) and filled in No. 3 hard gelatin capsules (100) to give enteric capsules which contain 0.5 mg of 13,14-dihydro-15-keto-16-desbutyl-16-m-trifluoromethylphenoxy-PGF_{2α} methyl ester per capsule.

In the above formulation examples, the active ingredient can be replaced by any other compound within the compounds used in the invention.

Test Example 1

Thirty male Crj: Wistar rats (5 weeks old, obtained from Charles River) were quarantined and acclimatized for about 1 week. Then the animals were divided into groups with even mean weight and standard deviation.

All the animals were bred in individual stainless steel cages (190x380x180mm) at a temperature of 24±1°C and with a humidity of 55±5% with 12 hour light and dark cycle (illumination 8:00 - 20:00) supplied with fresh aseptic air. They were bred (with NMF, Oriental Yeast Industries, Ltd.) and watered ad libitum except the last day of medication, on which day they were fasted.

Test compound 13,14-dihydro-15-keto-16-R,S-fluoro-prostaglandin E₂ was dissolved in an aliquot of ethanol and the solution was evaporated in a test tube under nitrogen. The residue was combined with a predetermined amount of distilled water and sonicated to form a homogeneous test suspension.

Starting from day 1 to day 14, the rats received (between 9:00 and 12:00) a daily dosage of 1 ml/1 kg of the test suspension through a disposable plastic syringe (1 ml) equipped with a P.O. administration needle for rat based on the body weight measured just before the administration.

Design of the experiment was as follows:

Group	Dose(mg/kg)	Number of rats
1	0	5
2	0.1	5
3	2.0	5

All the animals were observed twice a day for mortality and general conditions, e.g. diarrhea except the last day, on which observation was made only once directly before the post mortem. The body weight and intake were measured every day at the predetermined time (between 9:00 - 10:00) before the medication. Urine collection (24hr) was made between post-medication on day 13 and pre-medication on day 14 under fasting.

Directly after the last medication, rats were sacrificed by cervical dislocation and subjected to celiotomy. Intestine was ligated at the pyloric part of the stomach and the upper cecal part. The whole of the small intestine was removed and the intraintestinal content was collected, volume was measured and centrifuged at 1000 rpm and a supernatant was separated.

The urine, serum and supernatant were assayed for urea nitrogen (UN) and non-protein nitrogen (NPN) concentrations.

The results are summarized in the following tables.

Table 1 : Body weight

Dosage	Day	Weight(g)													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
O (Control)	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	mean	277.7	280.0	291.9	296.2	307.3	312.3	320.4	329.7	334.9	340.8	346.4	350.1	356.0	318.0
	S.D.	4.1	7.9	6.7	7.6	10.8	10.9	12.5	10.8	11.7	14.1	15.6	15.2	16.5	13.5
0.1mg/kg	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	mean	277.6	281.1	293.4	297.1	300.3	310.8	320.8	330.4	335.8	339.4	344.5	351.3	355.9	317.0
	S.D.	4.1	4.9	7.4	6.0	13.0	7.1	6.7	8.4	8.3	6.6	12.4	8.8	11.1	10.9
2.0mg/kg	n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	mean	277.6	274.7	283.0	286.7	296.9	300.7	309.6	319.9	322.7	327.8	330.8	334.1	345.9	304.9
	S.D.	3.0	5.0	3.7	4.5	4.8	4.8	4.6	8.2	6.5	8.7	6.8	7.7	7.9	6.6

2022372

Table 2 :Intake

Dosage	Intake (g)												
	Day	1	2	3	4	5	6	7	8	9	10	11	12
O (Control)	n	5	5	5	5	5	5	5	5	5	5	5	5
	mean	27.8	28.5	29.8	28.2	28.2	30.0	29.1	29.1	30.1	29.3	29.9	29.7
	S.D.	3.1	2.6	2.6	1.9	3.0	2.1	2.4	2.4	2.7	3.1	2.1	2.9
0.1mg/kg	n	5	5	5	5	5	5	5	5	5	5	5	5
	mean	25.9	28.6	29.1	24.4	29.3	30.7	29.5	29.3	28.8	29.4	29.1	28.6
	S.D.	2.9	1.3	1.4	6.6	2.5	1.5	2.5	0.1	0.9	3.4	1.0	1.7
2.0mg/kg	n	5	5	5	5	5	5	5	5	5	5	5	5
	mean	*19.3	24.8	26.1	25.2	26.3	28.1	29.0	27.8	28.7	29.1	28.0	30.9
	S.D.	1.4	1.6	2.6	2.3	2.3	2.3	2.7	1.0	1.0	2.7	2.7	2.5
"DINNETH" ANALYSIS)													

*:0.05>P>0.01 (DUNNET ANALYSIS)

Table 3 : Nitrogen
(I.C.:Intraintestinal content)

Dosage	I.C.		Urine		UN		NPN	
	ml		(3hr)		I.C.		Urine	
			ml		mg	mg	mg	mg
0 (Control)	mean	2.2	3.9		0.200	5.282	2.19	4.23
	S.D.	1.2	2.1		0.215	3.484	1.36	2.36
0.1mg/kg	mean	2.0	1.6		0.317	*1.354	2.12	*1.67
	S.D.	0.4	0.8		0.150	0.885	0.46	0.84
2.0mg/kg	mean	**4.8	1.8		**0.637	1.882	*4.40	1.97
	S.D.	1.8	1.0		0.165	1.219	1.13	1.03
			** : 0.1 > P		* : 0.05 > P > 0.01	(DUNNET analysis)		

From the above results, it can be easily understood that excretion of urea nitrogen and nonprotein nitrogen into the intestine was dose-dependently increased in the medicated group. Almost no influence was observed in the medicated group in respect to body weight and water intake.

Test Example 2

Male Wistar rats (8 weeks old) were anaesthetized with pentobarbital (40 mg/kg) and cortices of their left kidneys were partly removed. After 3 to 7 days, their whole right kidneys were removed. The overall kidney excision amounted to 1 plus three-fourths to 1 plus four-fifths. As the test compound, 13,14-dihydro-15-keto-16-R,S-fluoro-prostaglandin E₂ methyl ester was suspended in distilled water and administered orally to the surgically injured animals (3 per group) at a dose of 2mg/kg/ml on 14 continuous days starting from 15 days after the operation. The dose was increased to 3mg/kg on and after day 10 of administration because the animals did not have diarrhea about that day. The control group received the same volume of distilled water. One week after the start of medication, blood samples were taken from the tail vein of each animal and serum was assayed for blood urea nitrogen (UN) and creatinine (CRE) concentrations.

In addition two weeks after the start of medication, the total blood was taken from ventral aorta of each animal and serum was assayed for urea nitrogen (UN) and creatinine (CRE) concentrations. Two hours after the last medication, feces were collected and extracted with a predetermined amount of water. The extract was centrifuged and the supernatant was assayed for electrolytes. Weight and water intake of the rats were measured almost daily.

The results are summarized in the following Tables.

2022372

Table 4: Weight (g)

Days of medication	Control group		Test group	
	mean	SD	mean	SD
0	332.2	31.3	341.7	23.9
1	345.9	35.3	321.8	24.3
2	324.0	23.0	311.8	15.7
3	345.4	25.7	313.8	10.8
4	339.4	22.5	319.3	10.3
5	344.9	25.1	336.7	12.8
7	352.7	31.0	351.6	15.5
8	348.9	25.7	341.9	17.4
9	335.6	26.0	341.0	15.6
10	360.6	32.8	348.6	23.5
11	360.6	21.1	359.6	20.3
12	355.2	28.2	356.7	17.1
13	357.9	27.2	359.5	20.2
14	337.7	8.6	364.8	15.0

2022372

Table 5: Water intake (ml/day)

Days of medication	Control group		Test group	
	mean	SD	mean	SD
1	77.6	12.4	44.2	7.1
2	72.1	10.2	51.4	4.5
3			48.3	13.7
4	69.0	10.2	66.3	16.3
5	74.6	9.5	99.8	18.3
8	70.6	5.1	99.8	18.3
9	73.4	7.0	95.9	16.1
10	75.4	5.0		
11	71.3	7.1	88.8	5.2
12	73.8	3.2	81.5	9.8
13	72.1	4.3	89.5	5.9

2022372

Table 6: Serum

Group	BUN (mg/dl)	CRE (mg/dl)
untreated	mean 25.1	0.4
	±SD ±2.6	±0
2 weeks after operation	mean 92.7	1.35
	±SD ±23.8	±0.44
medicated control	mean 91.8	1.57
	±SD ±19.1	±0.4
1 week medicated	mean 62.9**	1.03**
	±SD ±5.2	±0.15
medicated control	mean 102.1	1.57
	±SD ±32.7	±0.40
2 weeks medicated	mean 75.7**	1.00**
	±SD ±14.4	±0.15
* P<0.05		** P<0.1

2022372

Table 7: Serum

	control	2mg/kg
	mean $\pm$ S.D.	mean $\pm$ S.D.
UN (mg/dl)	102.1 $\pm$ 32.7	75.7 $\pm$ 14.4
CRE (mg/dl)	1.6 $\pm$ 0.4	1.0 $\pm$ 0.2

Table 8: Feces (2 weeks medication)

group		UN	CRE
		mg	mg
control	mean	3.05	0.058
test	mean	12.01	0.25
	$\pm$ SD	$\pm$ 5.48	$\pm$ 0.06

From the above results, it can be clearly seen that, after two weeks of renal injury, urea nitrogen and creatine concentrations in the blood increased in the injured group by about 3.7 and 3.4 times, respectively as compared with the intact group and that, two weeks after the onset of medication, urea nitrogen and creatinine concentrations were decreased in the medicated group as compared with the control group wherein concentrations were at high levels and further, 2 hours after medication, urea nitrogen and creatinine in the feces of the medicated group were four times larger than in the feces of the control group.

Test Example 3

Male Wistar rats (8 weeks old) were anaesthetized by pentobarbital (40mg/kg, i.p.) and cortex of the left kidney was partly excised. After 3 to 7 days, the right kidney was totally excised. The overall kidney excision amounted to 1 plus three-fourths to 1 plus four-fifths. As the test compound, 13,14-dihydro-15-keto-16R,S-fluoro-PGE₂ was suspended in distilled water, homogenized and then orally administered, at a rate of 3mg/kg/ml, continuously for a period of two weeks starting 15 days after the excision of the kidneys (three animals per group). The control group orally received the same volume of distilled water.

Feces were collected one week after the administration and the intestinal contents were collected two weeks after the administration. These were assayed for excretion of urea nitrogen (UN) and creatinine (CRE).

In addition, blood samples were collected from the jugular vein without anaesthesia one week after the administration and assayed for urea nitrogen and creatinine. Also, body weight and water intake were measured from a day before the experiment to the last day of the experiment. The results are shown in the following Tables, in which * denotes $P < 0.1$, ** $P < 0.05$ and *** $P < 0.01$.

2022372

Table 9
Body Weight and Water Intake

Day	Body weight				Water Intake			
	Control		Medicated		Control		Medicated	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
-2	316	±20	322	±12				
-1	317	±26	330	±15	84.7	±20.4	101.9	±14.0
0	307	±42	324	±10				
1	316	±35	325	±14	98.6	±19.1	53.3	±12.2
2	315	±31	321	±21	98.6	±19.1	53.3	±12.2
3	317	±27	320	±31	87.8	±12.1	62.7	±21.7
4	320	±24	328	±31	100.0		76.2	±26.8
5	322	±27	327	±35	96.0	±14.8	68.6	±19.7
6	327	±28	333	±33	96.0	±14.8	68.6	±17.7
7	331	±25	347	±36	94.7	±18.8	78.3	±13.9
8	321	±21	334	±30	94.7	±18.8	78.3	±13.9
9	315	±30	342	±25				
10	316	±35	341	±26	82.3	±10.0	105.8	± 2.8
11	317	±38	335	±30	82.3	±10.7	105.8	± 2.8
12	324	±27	347	±31	96.8	±13.4	94.4	±17.7
13	320	±25	356	±31				
14	333	±31	349	±34	96.8	±13.4	94.4	±17.7

Table 10
Assay of Serum

		UN mg/dl	CRE mg/dl
Control	Mean	141.2	1.7
	S.D.	±33.0	±0.4
Medicated (3.0mg/kg)	Mean	97.3*	1.3
	S.D.	±24.8	±0.3

From the above results, it can be easily understood that urea nitrogen and creatinine in the blood were significantly decreased in the medicated group.

Almost no influence was observed in the medicated group in respect to body weight and water intake.

Table 11
Assay of Feces

Day		UN mg	CRE mg
2	Control	Mean	1.07
		S.D.	±0.01
	Medicated	Mean	0.12**
		S.D.	±0.06
7	Control	Mean	0.14
		S.D.	±0.05
	Medicated	Mean	0.29
		S.D.	±0.09

2022372

From the above results, it can be clearly seen that urea nitrogen and creatinine were significantly excreted in the feces or the intestinal contents.

Test Examples 4

The procedure of Test Example 3 was repeated except that 13,14-dihydro-15-keto-16,16-difluoro-PGE₂ (1.0mg/kg) was used as the test compound. Assays were performed with the feces at day 5 and the intestinal contents at day 14. The results are shown in the following Tables.

Table 12

Assay of Feces

Day		UN mg	CRE mg
5	Control	Mean	3.42
		S.D.	±1.86
	Medicated	Mean	3.57
		S.D.	±0.99
			0.051
			±0.025
			0.235**
			±0.124

Table 13

Assay of Intestinal Contents

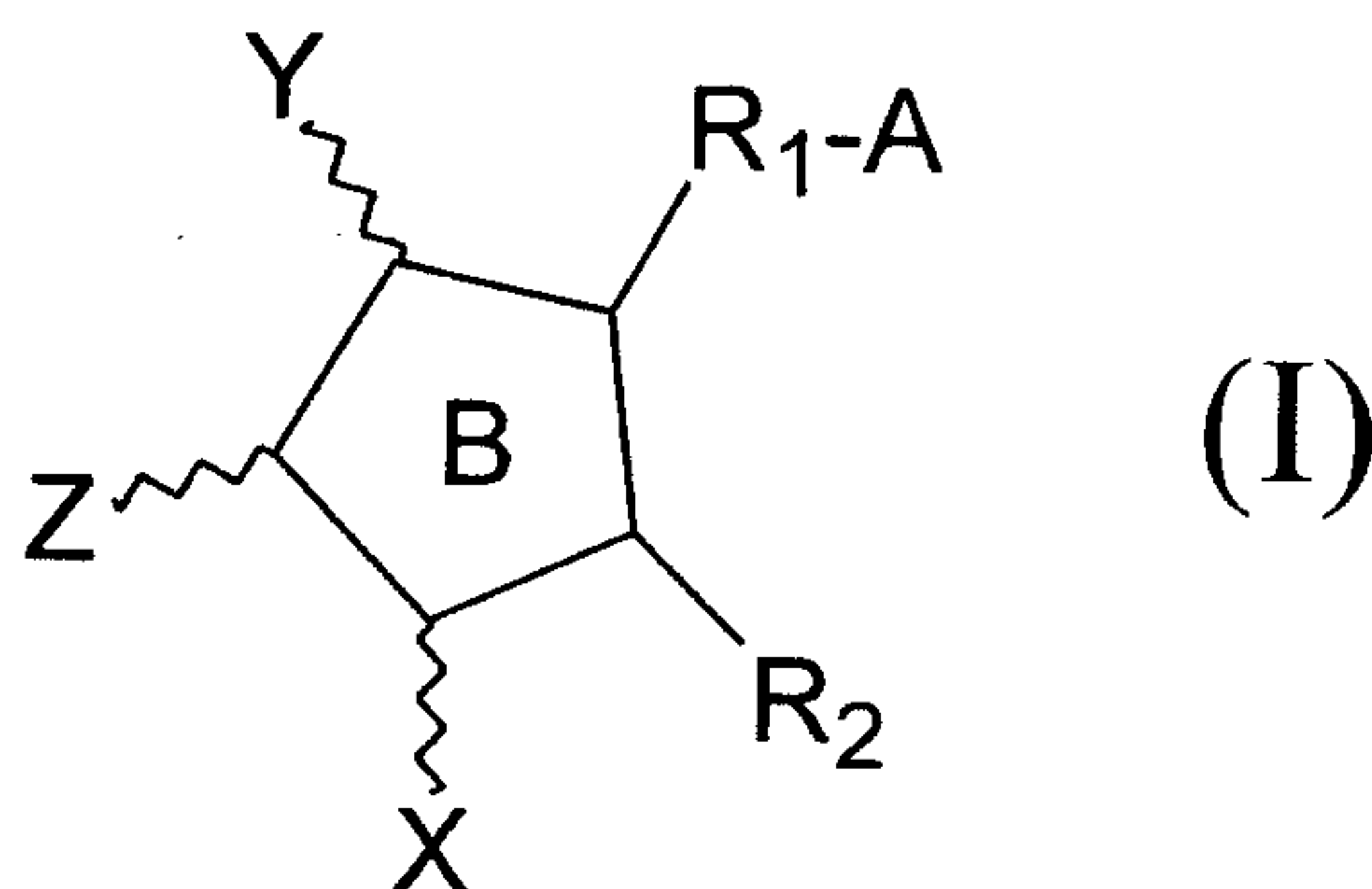
Day		UN mg	CRE mg
14	Control	Mean	0.07
		S.D.	±0.07
	Medicated	Mean	0.64**
		S.D.	±0.41
			0.17
			±0.06
			0.21
			±0.06

- 35 -

Claims:

1. A pharmaceutical composition for improving excretion of nonprotein nitrogen into the intestine comprising a prostanoid acid derivative in association with a pharmaceutically acceptable carrier, diluent or excipient.

2. The composition according to Claim 1, wherein the prostanoid acid derivative is represented by the formula (I):



in which ring B is saturated or contains at least one double bond, each of X and Y is independently selected from the group consisting of a hydrogen atom, hydroxy, a halogen atom, lower alkyl, hydroxy(lower)alkyl and oxo, at least one of X and Y not being hydrogen, Z is hydrogen or halogen atom, A is -CH₂OH, -COCH₂OH, or -COOH or a pharmaceutically acceptable salt, ester or amide of -COOH, R₁ is a bivalent saturated or unsaturated, lower or medium length aliphatic hydrocarbon residue which is unsubstituted or substituted by halo, oxo or aryl, and R₂ is a saturated or unsaturated, lower or medium length aliphatic hydrocarbon residue, which is unsubstituted or substituted with oxo, hydroxy, halo, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, aryl or aryloxy, with the proviso that in R₂ the third carbon atom counted from ring C is substituted by oxo.

3. The composition according to Claim 1 or 2, for reducing nonprotein nitrogen concentration in the blood.

4. The composition according to Claim 1 or 2, wherein the nonprotein nitrogen is urea nitrogen or creatinine.

- 36 -

5. The composition according to Claim 1 or 2, for compensating reduced renal function.

6. The composition according to Claim 1 or 2, for treating renal insufficiency.

5 7. The composition according to Claim 1 or 2, wherein the prostanoic acid derivative has one or two halogen atoms at position 16.

10 8. The composition according to Claim 1 or 2, wherein the prostanoic acid derivative has an oxo group at position 15.

9. The composition according to Claim 1 or 2, wherein the prostanoic acid derivative has a saturated bond between positions 13 and 14.

15 10. The composition according to Claim 1 or 2, wherein the prostanoic acid is a prostaglandin derivative.

11. The composition according to Claim 1 or 2, wherein the prostanoic acid derivative is a 15-keto-16-mono- or -di-fluoroprostaglandin compound.

20 12. The composition according to Claim 2, wherein in R_2 the fourth carbon atom counted from ring B is substituted by halo.

13. The composition according to Claim 12, wherein said fourth carbon atom is substituted by one halogen atom.

25 14. The composition according to Claim 12, wherein said fourth carbon atom is substituted by two halogen atoms.

15. The composition according to Claim 2, wherein in R_2 the bond between the first and second carbon atoms, counted from ring C is saturated bond.

30 16. The composition according to Claim 2, wherein R_1 and R_2 each is straight or branched-chain hydrocarbyl group having 1 to 14 carbon atoms.

- 37 -

17. The composition according to Claim 2, wherein R_1 is a straight or branched-chain hydrocarbyl group having 2 to 8 carbon atoms and R_2 is a straight or branched-chain hydrocarbyl group having 6 to 12 carbon atoms.