

FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

608609

APPLICATION FOR A STANDARD PATENT

I\We,

FARMITALIA CARLO ERBA s.r.l.

of

VIA CARLO IMBONATI, 24
20159 MILAN
ITALY

hereby apply for the grant of a standard patent for an invention entitled:

N-IMIDAZOLYL DERIVATIVES OF BICYCLIC COMPOUNDS
USEFUL IN MEDICINE

which is described in the accompanying complete specification

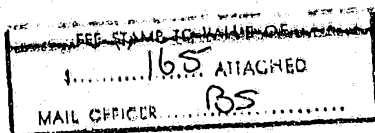
Details of basic application(s):

Number of basic application	Name of Convention country in which basic application was filed	Date of basic application
8712995	GB	03 JUN 87
8712994	GB	03 JUN 87

My/our address for service is care of CLEMENT HACK & CO., Patent Attorneys, 601 St. Kilda Road, Melbourne 3004, Victoria, Australia.

DATED this 31st day of May 1988

FARMITALIA CARLO ERBA s.r.l.



CLEMENT HACK & CO.

[Signature]

TO: The Commissioner of Patents.

COMMUNICATION ACCEPTED AND AMENDMENTS
3-1-91

LODGED AT
31 MAY 1988
Melbourne



Australia Patent Declaration Form

Forms 7 and 2

AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION OR NON-CONVENTION
APPLICATION FOR A PATENT OR PATENT OF ADDITION

Name(s) of
Applicant(s)

In support of the application made by FARMITALIA CARLO ERBA S.r.l.

Title

for a patent for an invention entitled "N-IMIDAZOLYL DERIVATIVES
OF BICYCLIC COMPOUNDS USEFUL IN MEDICINE"

Name(s) and
address(es)
of person(s)
making
declaration

I/we, VITTORINO FERRARIO
of VIA CARLO IMBONATI 24, 20159 MILAN, ITALY

do solemnly and sincerely declare as follows:-

1. I am ~~XXXXXX the applicant(s) for the patent, or~~
am/are authorised by the abovementioned applicant
to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141
of the Act was/were made in the following country
or countries on the following date(s) by the
following applicant(s) namely:-

in Great Britain on June 3, 1987
by Farmitalia Carlo Erba S.p.A.
in Great Britain on June 3, 1987
by Farmitalia Carlo Erba S.p.A.

3. The said basic application(s) was/were the first
application(s) made in a Convention country in respect
of the invention the subject of the application.

4. The actual inventor(s) of the said invention is/are
Paolo Cozzi, via Zanella 48/5, Milan, Italy; Corrado Ferti, via Quasimodo 3,
Barlassina (Milan), Italy; Patricia Salvati, via Valera 16, Arese (Milan),
Italy; Germano Carganico, via Domodossola 7, Milan, Italy; Antonio Pillan,
via Milani 1, Milan, Italy.

5. The facts upon which the applicant(s) is/are entitled
to make this application are as follows:-
The Applicant would be entitled to have assigned to it a patent granted
to any one or more of the actual inventors in respect of the invention.

DECLARED at Milan, this 9th day of May, 1988

Vittorino Ferrario

(12) PATENT ABRIDGMENT (11) Document No. AU-B-16905/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 608609

(54) Title
N-IMIDAZOLYL DERIVATIVES OF BICYCLIC COMPOUNDS USEFUL IN MEDICINE

International Patent Classification(s)
 (51)⁴ **A61K 031/415**

(21) Application No. : **16905/88**

(22) Application Date : **31.05.88**

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8712994	03.06.87	GB UNITED KINGDOM
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(71) Applicant(s)
FARMITALIA CARLO ERBA S.R.L.

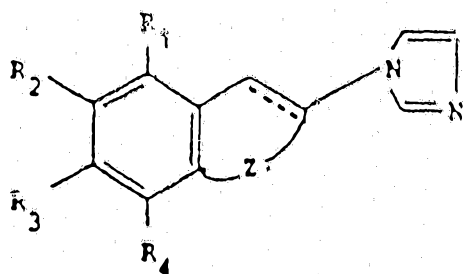
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GRIFFITH HACK & CO, GPO Box 1285K, MELBOURNE VIC 3001

(56) Prior Art Documents
US 4492707
US 4510149
US 4602022

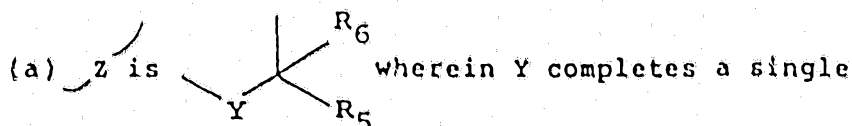
(57) Claim

1. A method of treatment of nephropathies in mammals comprising the step of administering to a mammal an effective amount of a compound of formula (I)



(I)

wherein



bond or is oxygen or a $-CH_2-$ group and the symbol

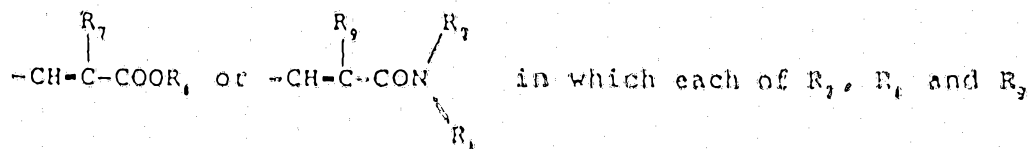
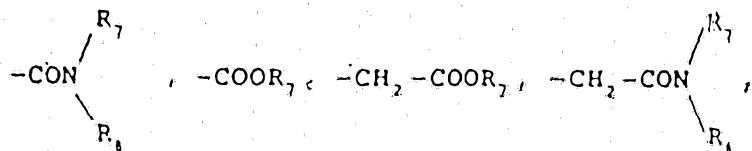
represents a single or a double bond or (b)

(11) AU-B-16905/88
(10) 608609

-2-

and the symbol $\equiv$ represents a double bond;

one of R_1 , R_2 , R_3 and R_4 is $-\text{CH}_2\text{OH}$, C_1-C_6 acyl,



is independently hydrogen or C_1-C_6 alkyl and the others are independently chosen from hydrogen, hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy and $-\text{COOR}_7$, wherein R_7 is as defined above, and one of R_5 and R_6 is hydrogen and the other is hydrogen, C_1-C_6 alkyl or phenyl; or a pharmaceutically acceptable salt thereof.

AUSTRALIA

608609

PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:

Lodged:

Complete Specification-Lodged:

Accepted:

Lapsed:

Published:

This document contains the
amendments made under
Section 49 and is correct for
printing

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:

FARMITALIA CARLO ERBA s.r.l.

Address of Applicant: VIA CARLO IMBONATI, 24

20159 MILAN

ITALY

Actual Inventor:

Address for Service:

CLEMENT HACK & CO.,

691 St. Kilda Road,

Melbourne, Victoria 3004,

Australia.

Complete Specification for the invention entitled:

N-IMIDAZOLYL DERIVATIVES OF BICYCLIC COMPOUNDS

USEFUL IN MEDICINE

The following statement is a full description of this invention
including the best method of performing it known to me:-

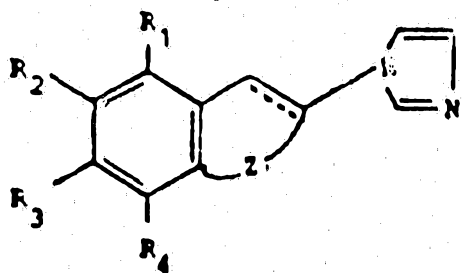
DESCRIPTION

"N-IMIDAZOLYL DERIVATIVES OF BICYCLIC
COMPOUNDS USEFUL IN MEDICINE"

This invention relates to N-imidazolyl derivatives of bicyclic compounds.

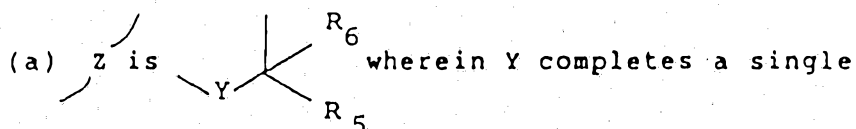
N-imidazolyl derivatives containing a naphthalene, indene or chroman nucleus, and the pharmaceutically acceptable salts thereof, are described in US-A-4,510,149 and in GB-B-2,141,705. They are known to be endowed with pharmaceutical activity, in particular as vasodilators or blood platelet aggregation inhibitors. Additionally, these compounds, and their pharmaceutically acceptable salts, are known to be useful in the treatment of migraine, diabetic microangiopathy, rheumatoid arthritis, hypertension, peptic ulcers, osteoporosis, angina pectoris, atherosclerosis and dislipidaemias.

We have now found that certain compounds having the following general formula (I), which are described in the above-identified US and British patents



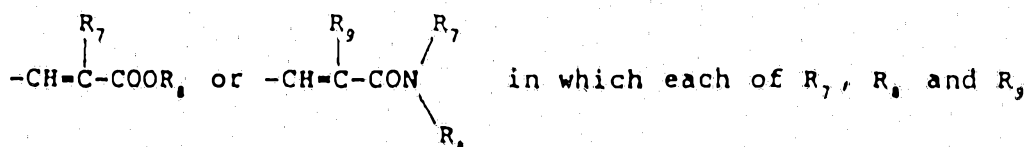
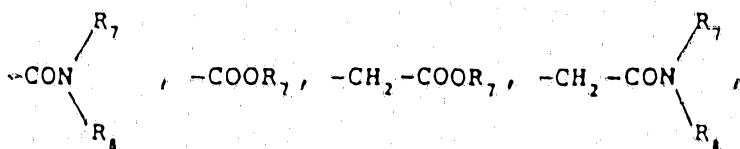
(I)

wherein



and the symbol --- represents a double bond;

one of R_1 , R_2 , R_3 and R_4 is $-\text{CH}_2\text{OH}$, C_2-C_4 acyl,



is independently hydrogen or C_1-C_4 alkyl and the others are

independently chosen from hydrogen, hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy and $-\text{COOR}_7$ wherein R_7 is as defined

above, and one of R_5 and R_6 is hydrogen and the other is

hydrogen, C_1-C_4 alkyl or phenyl; or a pharmaceutically

acceptable salt thereof, are also useful for the treatment, in

mammals, of nephropathies, as e.g. some forms of glomerulo-

nephritis, microalbuminuria in diabetic patients or

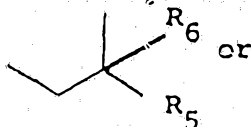
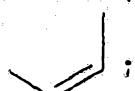
nephropathies secondary to systemic lupus erythematosus

(SLE), and of hyperlipidaemias, namely hypercholesterolaemias

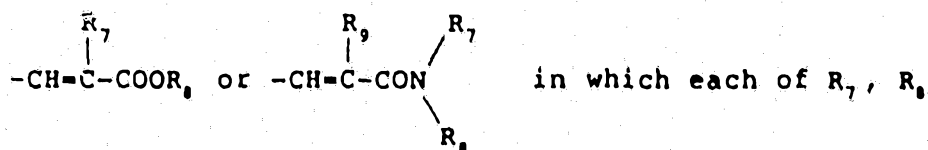
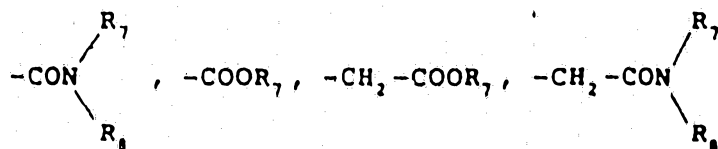
and hypertriglyceridaemias, secondary to nephrotic syndrome.

It has to be noticed that among the compounds disclosed by US Patent 4,510,149 and British Patent 2,141,705 only those having a $-O-\overset{\overset{R'}{\parallel}}{C}-\overset{\underset{R''}{\parallel}}{C}OOR$ group, wherein each of R, R' and R'' independently is hydrogen or C₁-C₆ alkyl, are endowed with high activity in lowering cholesterol and triglycerides, in increasing the total serum HDL cholesterol, as well as in increasing the ratio between α -lipoprotein and β -lipoprotein total cholesterol.

As is known, drugs having such activities are useful in prevention and therapy of atherosclerosis: Glueck C.J., Artery, 2, 196 (1976); Day C.E. in Frank-H-Clarke (Ed.) Annual reports in Medicinal Chemistry, 13, 184, chapter 2-Academic Press, N.Y. 1978. Therefore it is surprising the fact that the compounds of formula (I), according to the present invention, and the pharmaceutically acceptable salts thereof, are active in lowering elevated plasma levels of both total cholesterol and triglycerides in patients with nephropathy.

Preferred compounds of formula (I) are those wherein Z is  or ;

one of R₁, R₂, R₃ and R₄ is -CH₂OH, C₂-C₄ acyl,



and R₉ is independently hydrogen or C₁-C₄ alkyl and the others are hydrogen and R₃ and R₂ are hydrogen; and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of formula (I) are the following:

- 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-6-ethoxycarbonylnaphthalene;
- 5 1,2-dihydro-3-(1-imidazolyl)-6-hydroxymethylnaphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-7-carboxynaphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-6-(2-carboxyvinyl)-naphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-6-(2-ethoxycarbonylvinyl)-naphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-6-carboxymethylnaphthalene;
- 1,2,3,4-tetrahydro-2-(1-imidazolyl)-7-carboxynaphthalene;
- 2-(1-imidazolyl)-7-carboxynaphthalene;
- 2-(1-imidazolyl)-6-carboxynaphthalene;

and the pharmaceutically acceptable salts thereof and, when appropriate, the C_1 - C_4 alkyl esters thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts, with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric, acids, or organic, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids, and salts with inorganic, e.g. alkali metal, especially sodium or potassium, bases or alkaline-earth metal, especially calcium or magnesium, bases, or with organic bases, 20 e.g. alkylamines, preferably triethylamine. The alkyl and alkoxy groups may be branched or straight chain groups.

A halogen atom is, for example, fluorine, chlorine or bromine, preferably chlorine or bromine.

A C_1-C_4 or $-C_6$ alkyl group is preferably methyl or ethyl.

A C_1-C_4 alkoxy group is preferably methoxy or ethoxy.

5 As stated above, the compounds of formula (I), as well as the preferred ones hereabove specifically mentioned, are already described in US Patent 4,510,149 and GB Patent 2,141,705. The details inherent to the methods of their preparation are described in the above-identified US and British patents.

10 The compounds of formula (I), as stated above, are useful for the treatment of nephropathies in mammals, especially humans, as shown e.g. by the fact that they have proved to be active in reducing proteinuria and creatinine serum levels in the doxorubicin induced nephrosis in rats and in reducing proteinuria and increasing the glomerular filtration rate (GFR) in spontaneous focal glomerulonephritis in the Milan Normotensive Strain (MNS) rats.

15 Compound 1,2-dihydro-3-(1-imidazolyl)-6-carboxy-
20 -naphthalene (internal code FCE 22178), for ins-

tance, in the doxorubicin induced nephrosis, at the oral dosage of 50 mg/kg b.i.d. for 7 days starting from the 21st after doxorubicin injection, reduced both proteinuria (from 1018 ± 102 to 751 ± 49 mg/24 h $p < 0.05$) and creatinine serum levels (from 1.85 ± 0.26 to 0.97 ± 0.09 mg/dl $p < 0.001$). This effect was paralleled by significant inhibition of both serum and urine TxB_2 levels: serum levels were reduced from 536 ± 55 ng/ml to 92 ± 8.3 ng/ml and urine levels from 20.3 ± 2.5 ng/24 h to values under the detec-

tion limit of the method. Moreover, in the spontaneous focal glomerulonephritis of the MNS rats, FCE 22178 was administered at the dosage of 50 mg/kg p.o. die + 100 mg/kg/die in drinking water starting from the first month of age and all along the life of the animal and in comparison with a not treated group. During the development of the disease MNS rats showed an increased production of TxA₂ (measured as TxB₂ levels) in isolated glomeruli (4.44 ± 1.2 ng/mg prot. $p < 0.01$ at 8 months of age) which was greatly reduced by FCE 22178 (2.77 ± 0.53 ng/mg prot. $p < 0.01$). The same pattern was observed in urine. In adult control MNS rats a progressive increase in proteinuria paralleled by a decrease in GFR was also observed: FCE 22178 treatment reduced proteinuria (237 ± 30.3 vs 428.8 ± 42.3 mg/24 h $p < 0.01$) and increased GFR towards normal values (1210 ± 38 in controls vs 816 ± 45 μ l/min/g k.w. in treated rats $p < 0.01$).

Histological evaluation: light microscopy of the kidneys of aged (14 months) control MNS rats revealed that 27% of the glomeruli display an increase in mesangial matrix and segmental glomerulosclerosis. Sclerotic glomeruli show massive deposition of PAS-stained material.

Ultrastructural investigation of non sclerotic glomeruli showed that an age-related process takes place in MNS rats; in particular, the thickening of the glomerular basement membrane (GMB) and the increase in mesangial matrix appear to be strictly related to the structural modifications of

the epithelial cells. Flattening and fusion of the foot processes, as well as formation of blebs and of electron dense lysosomes, together with the frequent detachment of the cell from the GMB is regarded to be related to the massive leakage of proteins through the glomerulus. Treatment for example with compound FCE 22178 significantly ($p < 0.05$) reduced the number of sclerotic glomeruli (22%). More impressive and relevant were the ultrastructural differences between treated and untreated animals in non sclerotic glomeruli: the entity of flattening and fusion of foot processes was found to be definitely lower in treated animals, pointing to a significant effect of the treatment in preventing the full picture typical of untreated MNS rats.

The activity of compound FCE 22178, for example, was evaluated also in the model of subtotal renal ablation in the rat. This model as known results in proteinuria, hypertension and progressive kidney disease. Rats with a remnant kidney (RRM) have increased excretion in the urine and glomerular production of Thromboxane B_2 (TxB_2).

Methods: Charles River C.D. male rats of 6 weeks of age were used for this experiment. The left kidney was surgically reduced for the 60% and one week later the right kidney was removed. Four weeks after the second operation the blood pressure was measured and the rats were placed in metabolic cages for evaluation of proteinuria, measured by the method of Lowry. Only the animals with a blood pressure ≥ 170 mm Hg and an urinary protein excretion ≥ 100 mg/day were used. Comparative experiments were performed using sham operated rats. Also the in vitro TxA_2 synthase inhibiting activities in serum and in isolated glomeruli were studied and compared. Glomerular preparation was per-

formed according to the method previously described and TxB_2 was measured by RIA.

Compound FCE 22178 was tested at concentrations ranging from 4×10^{-12} M to 2×10^{-8} M. For comparison purposes the well known thromboxane synthase inhibitor (E)-3-[4-(1H-imidazol-1-ylmethyl)-phenyl]-2-propenoic acid monohydrochloride monohydrate, coded as OKY046 and disclosed by U.S. patent 4,226,878, was tested at the same concentrations.

Results: Compound FCE 22178 showed a greater activity in inhibiting glomerular than serum TxB_2 production in RRM rats: the IC_{50} were 3.2×10^{-11} M in glomeruli and 1.7×10^{-9} M in serum. Compound OKY046 showed a slightly greater potency in inhibiting serum TxA_2 synthesis: IC_{50} 6×10^{-10} M, but a lower activity on glomeruli as compared to compound FCE 22178: IC_{50} 9×10^{-11} M.

These results indicate compound FCE 22178 possesses a greater selectivity for glomerular TxA_2 synthase as compared to compound OKY046. This fact is even more evident in control sham operated rats, where compound FCE 22178 maintained a greater activity in glomeruli: IC_{50} 7×10^{-11} M vs. 1×10^{-9} M in serum, whereas compound OKY046 lost his selectivity: IC_{50} 1×10^{-9} in glomeruli vs. 5×10^{-5} M in serum.

The compounds of formula (I), as stated above, are also useful for the treatment of hyperlipidaemias secondary to nephrotic syndrome as shown e.g. by the fact that they have proved to be active in reducing cholesterol, triglycerides and phospholipids in aged Milan Normotensive Strain (MNS) rats and in

reducing triglycerides in doxorubicin treated rats. On the other hand hyperlipidemia is characteristic of the nephrotic syndrome: elevated plasma levels of both total cholesterol and triglycerides have been reported in patients with nephropathy (Appel G.B. et al. - New England J. Med. 312, 24, 1544, 1985 and Chopra J.S. et al. - Lancet February 1, 317, 1971). This metabolic disorder can be reproduced in doxorubicin induced nephrosis (Calandra S. et al. - Exp. Mol. Pathology 39, 282, 1983).

10 Compound 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene, internal code FCE 22178, for instance, in this model at the oral dosage of 50 mg/kg b.i.d. for 7 days starting from the 21st after doxorubicin injection lowered triglycerides serum levels from 783 ± 152 to 481.8 ± 84 mg/dl.

15 Also in spontaneous glomerulonephritis of MNS rats this metabolic disorder is present and FCE 22178 was very active in ameliorating the disease: in fact in this model the product lowered, in 14 months old rats treated for 2 months, total cholesterol from 223 ± 36 to 130.5 ± 2.2 mg/dl, triglycerides from 399.6 ± 105 to 169.3 ± 26.1 mg/dl and phospholipids from 338.6 ± 56 to 197.8 ± 21 mg/dl.

20 The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy. Mice and rats which had been deprived of food for nine hours were treated orally with single administrations of increasing doses of compounds of the invention, then housed and normally fed. The orientative acute toxicity (LD_{50}) was assessed on the seventh day after the treatment and was higher than 800 mg/kg.

In view of their high therapeutic index the compounds of formula (I) can be safely used in medicine.

The dosage level suitable for oral administration to adult humans of the compounds of formula (I), e.g. 1,2-dihydro-3-(1-imidazolyl)-6-carboxy-naphthalene, may range from about 100mg to about 800 mg per dose 1 to 3 times a day, preferably from about 200mg to about 400 mg per dose 1 to 3 times a day.

The exact dosage depends on the disease, age, weight, condition of the patient and administration route.

The compounds can be administered in a variety of dosage forms, e.g., orally, in the form of tablets, capsules, sugar, or film coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly; or by intravenous injection or infusion.

The invention includes pharmaceutical compositions comprising a compound of formula (I) in association with a pharmaceutically acceptable excipient (which can be a carrier or diluent).

The pharmaceutical compositions can be usually prepared following conventional methods and administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants,

e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions, and suspensions. The syrup may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may

contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

Example 1

Tablets, each weighing 300 mg and containing 100 mg of the active substance can be manufactured as follows:

Compositions (for 10,000 tablets)

1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene	1000 g
lactose	1420 g
corn starch	475 g
talc powder	75 g
magnesium stearate	30 g

1,2-dihydro-3-(1-imidazolyl)-6-carboxy-naphthalene, lactose and a half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (36 mg) is suspended in warm water (350 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium are added, carefully mixed, and processed into tablets using punches of 10 mm diameter.

Example 2: Intramuscular injection

An injectable pharmaceutical composition can be manufactured by dissolving 100 mg of 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene sodium salt in sterile water or sterile normal saline solution (1-2 ml).

Example 3: Capsules (100 mg)

1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene	100 mg
lactose	248 mg
corn starch	50 mg
magnesium stearate	2 mg
Total	400 mg

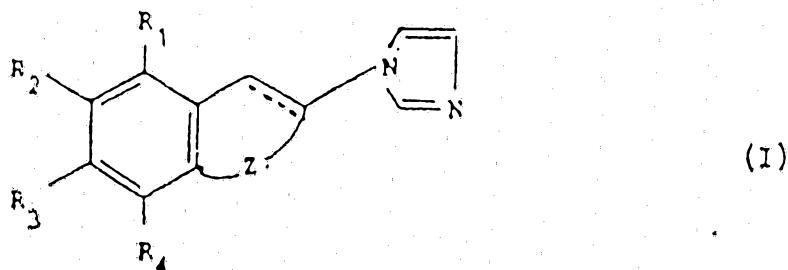
Encapsulate in two-piece hard gelatine capsules.

Example 4: Suppository (100 mg)

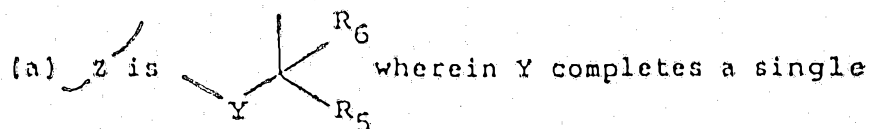
1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene	0.10 g
lecithin	0.14 g
cocoa butter	1.76 g
Total	2.00 g

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treatment of nephropathies in mammals comprising the step of administering to a mammal an effective amount of a compound of formula (I)



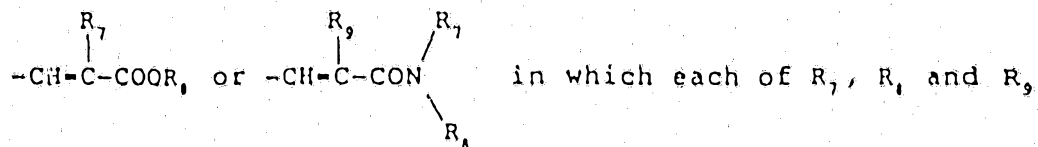
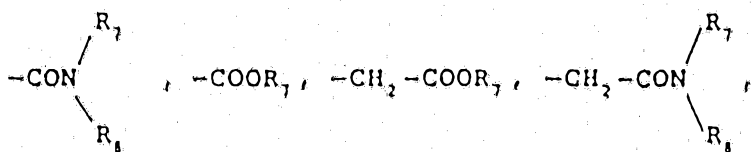
wherein



or is oxygen or a $-\text{CH}_2-$ group and the symbol --- represents a single or a double bond or (b) Z is

and the symbol = represents a double bond;

one of R_1 , R_2 , R_3 and R_4 is $-\text{CH}_2\text{OH}$, C_1-C_4 acyl,



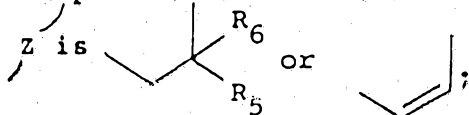
is independently hydrogen or C_1-C_4 alkyl and the others are independently chosen from hydrogen, hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy and $-\text{COOR}_7$ wherein R_7 is as defined above, and one of R_5 and R_6 is hydrogen and the other is hydrogen, C_1-C_6 alkyl or phenyl; or a pharmaceutically acceptable salt thereof.



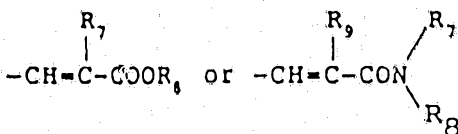
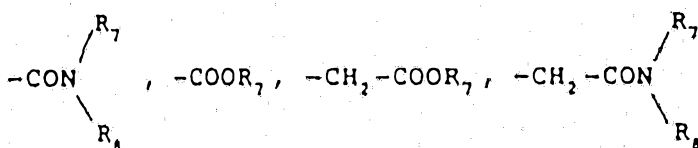
~~for use in the treatment of nephropathies in mammals~~

2. ^{A method} Use according to claim 1, where in the

compound of formula (I)



one of R_1 , R_2 , R_3 and R_4 is $-\text{CH}_2\text{OH}$, C_2-C_4 acyl,



in which each of R_7 , R_8 and

R_9 is independently hydrogen or C_1-C_4 alkyl and the others are hydrogen, and R_5 and R_6 are hydrogen.

3. ^{A method} Use according to claim 1, where the compound of formula (I) is 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene.

4. ^{A method} Use according to claim 1, wherein the compound of formula (I) is chosen from:

1,2-dihydro-3-(1-imidazolyl)-6-ethoxycarbonylnaphthalene;

1,2-dihydro-3-(1-imidazolyl)-6-hydroxymethylnaphthalene;

1,2-dihydro-3-(1-imidazolyl)-7-carboxynaphthalene;

1,2-dihydro-3-(1-imidazolyl)-6-(2-carboxyvinyl)-naphthalene;

1,2-dihydro-3-(1-imidazolyl)-6-(2-ethoxycarbonylvinyl)-naphthalene;

1,2-dihydro-3-(1-imidazolyl)-6-carboxymethylnaphthalene;



1,2,3,4-tetrahydro-2-(1-imidazolyl)-7-carboxynaphthalene;
2-(1-imidazolyl)-7-carboxynaphthalene; and
2-(1-imidazolyl)-6-carboxynaphthalene.

5. A method of treatment of glomerulonephritis in humans comprising the step of administering to a human an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

6. A method of treatment of microalbuminuria in diabetic patients comprising the step of administering to a human an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

7. A method of treatment of nephropathies in humans secondary to lupus erithematosus comprising the step of administering to a human an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

8. A method of treatment of hyperlipidaemias secondary to nephrotic syndrome comprising the step of administering to a mammal an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

9. A method of treatment of hypercholesterolaemias secondary to nephrotic syndrome comprising the step of administering to a mammal an effective amount of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

10. A method of treatment of hypertriglyceridaemias secondary to nephrotic syndrome comprising the step of administering to a mammal an effective amount of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

11. A compound as defined in any one of claims 1 to 4
when used in the treatment of nephropathies in mammals.

DATED THIS 19TH DAY OF OCTOBER
FARMITALIA CARLO ERBA Srl

By its Patent Attorneys:
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