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(21) International Application Number: PCT/EP90/01010 (22) International Filing Date: 25 June 1990 (25.06.90) (30) Priority data: 8914525.4 23 June 1989 (23.06.89) GB (71) Applicant (for all designated States except US): FARMITAL- IA CARLO ERBA S.R.L. [IT/IT]; Via Carlo Imbonati, 24, I-20159 Milan (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : SALVATI, Patricia [IT/ IT]; Via Valera, 16, I-20020 Arese (IT). FERTI, Corrado [IT/IT]; Via Quasimodo, 3, I-20030 Barlassina (IT). COZZI, Paolo [IT/IT]; Via Zanella, 48/5, I-20133 Milan (IT). ALESSANDRINI, Paola [IT/IT]; San Marco, 552, I-30124 Venezia (IT).		(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU (GB). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent)*, DK (European patent), ES (European pa- tent), FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European pa- tent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: COMBINED USE OF N-IMIDAZOLYL DERIVATIVES OF BICYCLIC COMPOUNDS AND CYCLOSPORINE IN THERAPY (I) (a) (II) (α) (III) (IV) (V) (VI) (VII) (57) Abstract The invention relates to the use of N-imidazolyl derivatives of bicyclic compounds of general formula (I), wherein (a) compound α is (II) wherein Y completes a single bond or is oxygen or a -CH₂- group and the symbol --- represents a single or double bond or (b) compound α' is (III) and the symbol --- represents a double bond; one of R₁, R₂, R₃ and R₄ is -CH₂OH, C₂-C₄ acyl, (IV), -COOR₇, -CH₂COOR₇, (V), (VI) or (VII) in which each of R₇, R₈ and R₉ is independently hydrogen or C₁-C₄ alkyl, and the others are independently chosen from hydrogen, hydroxy, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and -COOR₇ wherein R₇ is as defined above; and one of R₅ and R₆ is hydrogen and the other is hydrogen, C₁-C₆ alkyl or phenyl; or a pharmaceutically acceptable salt thereof, in particular in combination with cyclosporin A. The compounds obtained are useful in preventing and/or treating cyclosporin A-induced nephrosis in mammals.		

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COMBINED USE OF N-IMIDAZOLYL DERIVATIVES OF BICYCLIC
COMPOUNDS AND CYCLOSPORINE IN THERAPY

The present invention relates to the use of N-imidazolyl derivatives of bicyclic compounds, in particular in combination with cyclosporin A, in therapy.

Cyclosporin A (CyA) is an effective immunosuppressive agent that dramatically improves allograft survival in human transplantation. At the same time, the use of cyclosporin A has been applied to various diseases thought to have auto-immune basis (including for example: multiple sclerosis, Guillan Barre syndrome, uveitis, myasthenia gravis, Heymann nephritis, juvenile diabetes type I, systemic lupus erythematosus, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopaenia, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, auto-immune male infertility, psoriasis and psoriatic arthiritis, Steven-Johnson syndrome, idiopathic sprue, Chron's disease, sarcoidosis, glomerulonephritis, interstitial lung fibrosis and primary biliary cirrhosis) and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an auto-immune component such as arthritis and rheumatic diseases.

Reports and results in vitro, in animal models and in clinical trials in the above-mentioned diseases are widespread in literature. However, the therapeutic potential of

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this drug is often limited by renal dysfunction characterized by a dose-dependent decrease in glomerular filtration rate (GFR) and creatinine clearance and increased blood urea nitrogen levels, as reported in Ann. Inter. Med. 99, 851 (1983); Lancet 1, 470 (1981) and N. Engl. J. Med. 311, 699 (1984).

The mechanism responsible for CyA-induced renal failure has not been fully elucidated. However, on the other hand, preservation of tubular function with the absence of frank tubular necrosis does not support a direct toxic effect of CyA on tubular cells. Therefore, the nephrotoxic effect of CyA may be more likely caused by altered hemodynamics, as it is associated with reduced renal blood flow and a progressive narrowing of the afferent arteriolar luminal diameter, as shown by scanning electron microscopy. The basis for renal vasoconstriction is unclear, but it has been suggested that thromboxane (TxA_2) is a potential mediator of altered hemodynamics.

TxA_2 , a cyclooxygenase metabolite of arachidonic acid, is a potent vasoconstrictor and platelet proaggregatory agent that has been implicated in many pathological processes. For instance increased renal TxA_2 synthesis has recently been associated with the immunologically mediated renal injury characteristic of murine lupus.

Cyclosporin A has been reported to alter arachidonic

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acid (A.A.) metabolism in some in vitro models of cultured monocytes and of smooth muscle cells [Lipids, 18, 566 (1983) and Transplantation 38, 377 (1984)]. Moreover in vivo studies have shown that chronic administration of CyA in the rat induces a progressive increase in the renal synthesis of TxA_2 (Am. J. Physiol. 251, F 581-587 (1986)). Therefore, means of reducing this side effect would clearly be of major benefit.

We have now found that cyclosporin A-induced nephrotoxicity can be limited by concomitant administration of a therapeutically effective amount of a N-imidazolyl derivative of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof. Accordingly in one aspect the present invention relates to a method of preventing or treating cyclosporin A-induced nephrotoxicity in mammals by administration of a therapeutically effective amount of a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof.

In another aspect the invention provides the use of a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for use in preventing or treating cyclosporin A-induced nephrosis.

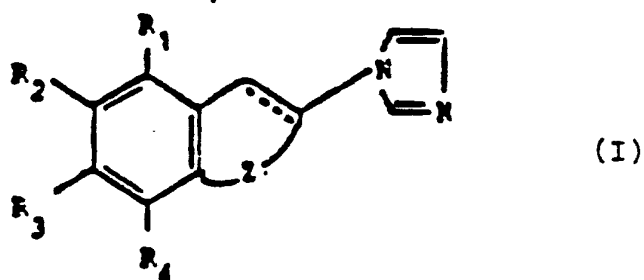
The present invention further provides a method of treating a disease having an auto-immune basis, which method comprises concomitantly administering (1) a pharmaceutical composition containing a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutical composition comprising cyclosporin A as active agent.

The invention also provides products containing a compound of formula (I) or pharmaceutically acceptable salt thereof and cyclosporin A as a combined preparation for simultaneous or sequential use in treating a disease having an autoimmune basis.

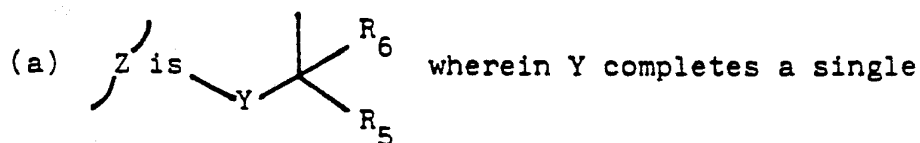
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The N-imidazolyl derivatives, according to the method of prevention or treatment provided by the present invention, are described in US-A-4,510,149 and in GB-B-2,141,705 and have the following formula (I)

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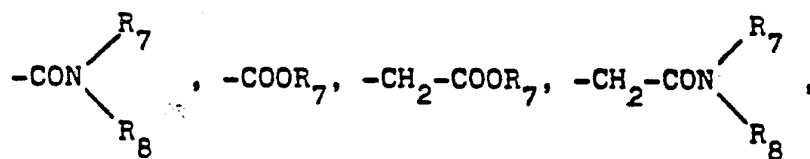


wherein



10

one of R₁, R₂, R₃ and R₄ is -CH₂OH, C₂-C₄ acyl, -CON , -COOR₇, -CH₂-COOR₇, -CH₂-CON ,



R₉ is independently hydrogen or C₁-C₄ alkyl, and the others

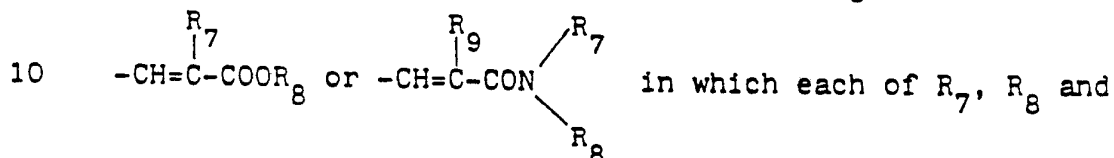
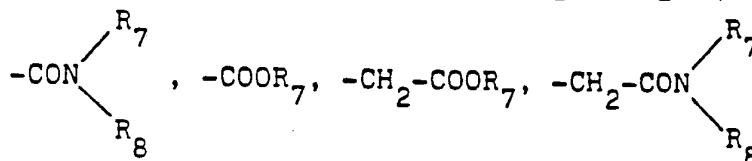
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are independently chosen from hydrogen, hydroxy, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and -COOR₇ wherein R₇ is as defined above; and one of R₅ and R₆ is hydrogen and the other is hydrogen, C₁-C₆ alkyl or phenyl.

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



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



R₉ is independently hydrogen or C₁-C₄ alkyl, and the others are hydrogen and R₅ and R₆ are hydrogen; and the pharmaceutically acceptable salts thereof.

15 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;
- 1,2-dihydro-3-(1-imidazolyl)-6-hydroxymethylnaphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-7-carboxynaphthalene;
- 20 1,2-dihydro-3-(1-imidazolyl)-6-(2-carboxyvinyl)-naphthalene;
- 1,2-dihydro-3-(1-imidazolyl)-6-(2-ethoxycarbonylvinyl)-naphthalene;

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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 C₁-C₄ 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 salicyclic 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, e.g. alkylamines, preferably triethylamine.

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

The alkyl and alkoxy groups may be branched or straight chain groups.

A C₁-C₆ alkyl group may be a C₁-C₄ alkyl group. Preferably the alkyl group is methyl or ethyl. A C₁-C₄ alkoxy group is preferably methoxy or ethoxy.

As stated above, the compounds of formula (I), as

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well as the preferred ones hereabove specifically mentioned, are already described in US-A-4,510,149 and GB-B-2,141,705. The details of their preparation are described in the above-identified US and British patents.

The compound of formula (I) or salt thereof and the cyclosporin A are typically formulated separately and presented for use in separate pharmaceutical compositions. The separate formulations may be administered simultaneously or sequentially. By "concomitant" and "combined" administration according to the present invention is therefore meant both separate and substantially contemporaneous administrations of cyclosporin A and of a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof.

The separate treatment with a compound of formula (I), or a pharmaceutically acceptable salt thereof, can commence prior to cyclosporin A treatment or subsequent to the commencement of cyclosporin A treatment. A compound of formula (I) or one of its salts can therefore be administered 1 or 2 days in advance of commencing cyclosporin A treatment, so as to limit the nephrotoxic effects of cyclosporin A. Alternatively the treatment with the compound of formula (I) or salt thereof may begin at the same time as or at any time after commencement of cyclosporin A treatment, i.e. when the nephrotoxic effect of cyclosporin A is detected or when it is desired to prevent it.

Doses of cyclosporin A to be administered in practising the invention will of course vary depending upon, e.g., the mode of administration, the condition to be treated (e.g. whether treatment is for the purposes of immunosuppression or otherwise, and if for immunosuppression whether for use in relation to e.g. organ transplant, bone

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marrow transplant, or the treatment of auto-immune disease), as well as the effect desired. In addition, dosaging will generally require adjustment for individual patients in order to establish an appropriate long term drug serum concentration e.g. by administration of an initial daily starting or "loading" dose with subsequent dose adjustment (generally dose reduction) in accordance with serum levels, e.g. as determined by regular radioimmunoassay (RIA) monitoring.

- 10 In general, amounts administered will be of the same order to those conventionally employed in cyclosporin A therapy, i.e. required to achieve (i) immunosuppressive or (ii) anti-inflammatory effectiveness. Thus, in general, satisfactory results are obtained on administration in a dose range of from about 5 or about 10 to about 20 mg/kg/day during the initial phase of therapy, reducing to a maintenance dose of from about 1 to about 5 to about 10 mg/kg/day administered to the patient orally, once or in divided doses 1 or 3 times a day. Where i.v. administration is required, e.g. administration by infusion (for example in the initial phase of treatment) lower dosages, e.g. of the order of from about 1 or about 3 to about 5 mg/kg/day for an initiating dose, or to about 2.5 mg/kg/day for a maintenance dose, are generally indicated.
- 25 The toxicity of the compounds of formula (I) 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 100 mg to about 800 mg per dose 1 to 3 times a day, preferably from about 200 mg to about 400 mg per dose 1 to 3 times a day. The exact dosage depends on the age, weight, condition of the patient and administration route.

Cyclosporin A and a compound of formula (I), or a pharmaceutically acceptable salt thereof, 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 present invention also provides a kit comprising in separate containers (1) a pharmaceutical composition containing an effective amount of a compound of formula (I), as

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herein defined, or a pharmaceutically acceptable salt thereof, as active ingredient, and (2) a pharmaceutical composition containing an effective amount of cyclosporin A, as active ingredient.

- 5 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, sac-
10 charose, 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
15 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.

- 20 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
25 as carrier, for example, saccharose or saccharose with gly-

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cerine 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.

5 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.

10 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.

15 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.

20

Example 1

The activity of a representative compound according to the present invention, i.e. 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene, internal code FCE 22178, was evaluated by the following method:

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Three groups of male Sprague-Dawley rats with initial weights of 250-275 g were used in this study. All animals were housed in a constant-temperature room with a 12-h light-dark cycle, fed standard rat chow (Altromin-Rieper, Vandoies, Italy), and had free access to tap water.

Group I received CyA (Sandoz, Basle, Switzerland) orally by gastric tube for 12 months at the dose of 40 mg/kg every other day. Thereafter the drug was discontinued and the animals were monitored for another 2 months without any treatment. Group 2 received for 12 months an oral dose of the vehicle, polyoxyethylenated castor oil (Sabo, Bergamo, Italy), in which CyA (40 mg/kg) was dissolved and was considered as control group. Group 3 received an oral dose of CyA of 40 mg/kg every other day, the compound FCE 22178 at the daily dose of 50 mg/kg per os and a further amount of compound FCE 22178 at the dose of 100 mg/kg dissolved in drinking water both for 12 months. Compound FCE 22178 was administered concomitantly to CyA treatment, i.e. either just before or just after CyA treatment.

Twenty-four-hour urine samples were collected at monthly intervals using metabolic cages and were immediately frozen and stored at -20°C until the extraction and the radio-immunoassay (RIA) for thromboxane (TX) B₂, 6-keto-prostaglandin F_{1α} (PGF_{1α}), and prostaglandin (PG) E₂, which reflects the renal synthesis of TXA₂, prostacyclin (PGI₂), and PGE₂, respectively, was performed. Blood samples for determination

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of serum TXB_2 concentration were collected from the tail vein at monthly intervals. In addition, every month five rats from each group underwent renal clearance studies. After the clearances, the kidneys were removed and analyzed by light microscopy.

Concomitant administration of compound FCE 22178 markedly inhibited TXA_2 synthesis (measured as TXB_2 levels) in whole blood and reduced the significant increase of TXB_2 urinary excretion, creatinine and blood urea nitrogen: i.e. parameters that are indicative of abnormal renal function. Therefore the concomitant administration of compound FCE 22178 ameliorated the renal function.

Example 2

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
20	Talc powder	75 g
	Magnesium stearate	30 g
	1,2-dihydro-3-(1-imidazolyl)-carboxy-naphthalene, lactose	

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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

5 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 3: Intramuscular injection

10 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 4: Capsules (100 mg)

15	1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene	100 mg
	Lactose	248 mg
	Corn starch	50 mg
	Magnesium stearate	2 mg
20		Total 400 mg

Encapsulate in two-piece hard gelatine capsules.

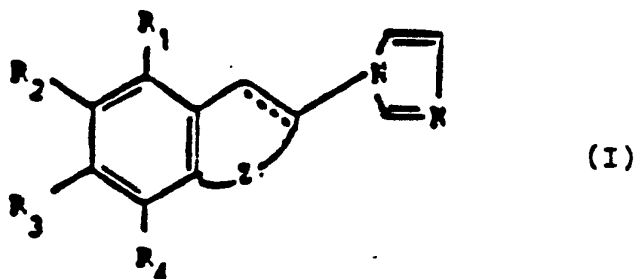
EXAMPLE 5: Suppository (100 mg)

	1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene	0.10 g
	Lecithin	0.14 g
25	Cocoa butter	1.76 g
		Total 2.00 g

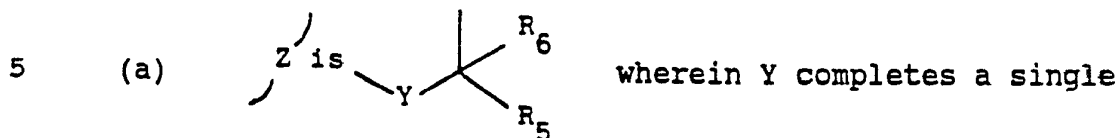
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CLAIMS

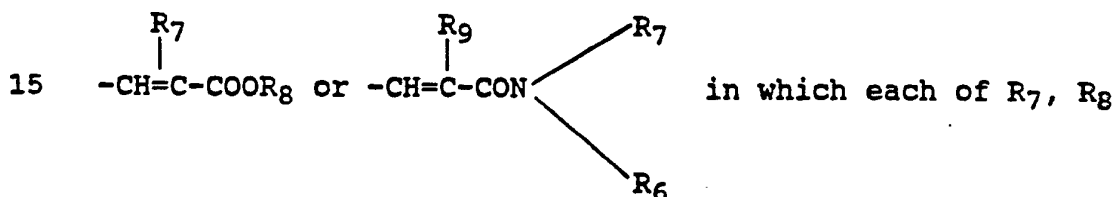
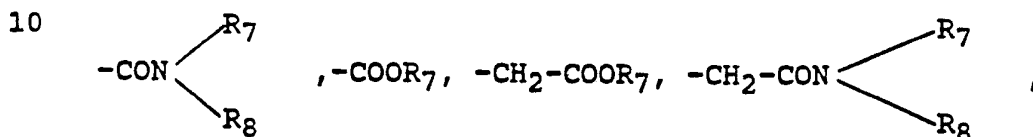
1) The use of a compound of formula (I)



wherein

bond 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_2 - C_4 acyl,and R_9 is independently hydrogen or C_1 - C_4 alkyl, and the others

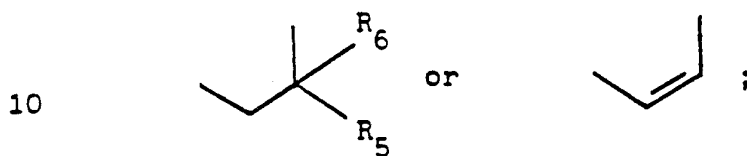
- 16 -

are independently chosen from hydrogen, hydroxy, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and -COOR₇ wherein R₇ is as defined above; and one of R₅ and R₆ is hydrogen and the other is hydrogen, C₁-C₆ alkyl or phenyl;

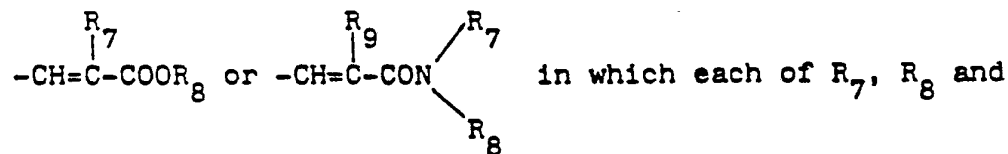
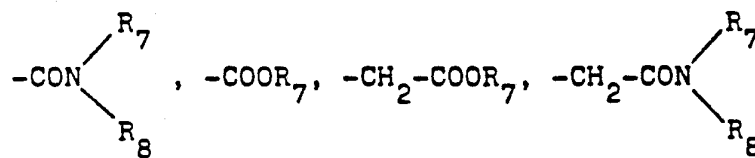
- 5 or a pharmaceutically acceptable salt thereof; in the preparation of a pharmaceutical composition for use in preventing or treating cyclosporin A-induced nephrosis.

- 2) The use according to claim 1, wherein in formula (I)

Z is



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



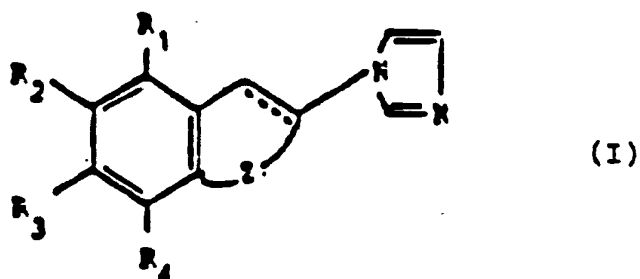
- 15 R₉ is independently hydrogen or C₁-C₄ alkyl, and the others are hydrogen; and R₅ and R₆ are hydrogen.

- 3) The use according to claim 1, wherein the said compound of formula (I) or salt thereof is selected from the group consisting of:

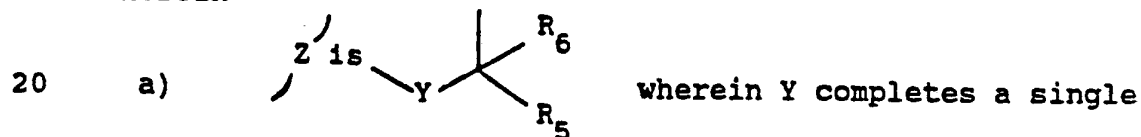
- 17 -

- 1,2-dihydro-3-(1-imidazolyl)-6-carboxynaphthalene;
 1,2-dihydro-3-(1-imidazolyl)-6-ethoxycarbonylnaphthalene;
 1,2-dihydro-3-(1-imidazolyl)-6-hydroxymethylnaphthalene;
 1,2-dihydro-3-(1-imidazolyl)-7-carboxynaphthalene;
 5 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;
 10 1,2,3,4-tetrahydro-2-(1-imidazolyl)-7-carboxynaphthalene;
 2-(1-imidazolyl)-7-carboxynaphthalene;
 2-(1-imidazolyl)-6-carboxynaphthalene;
 or the pharmaceutically acceptable salts thereof.

- 4) A method of treating a disease having an auto-immune
 15 basis, which comprises concomitantly administering (1) a
 pharmaceutical composition containing a compound of
 formula (I)



wherein



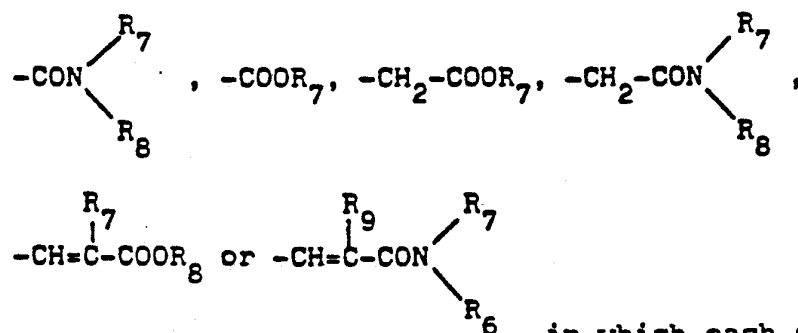
bond or is oxygen or a -CH₂- group and the symbol

represents a single or a double bond or (b) Z is

and the symbol --- represents a double bond;

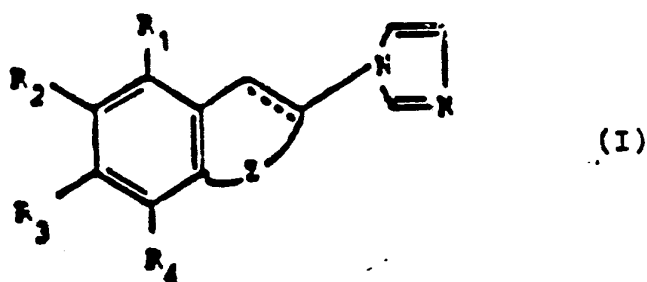
one of R₁, R₂, R₃ and R₄ is -CH₂OH, C₂-C₄ acyl,

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in which each of R_7 , R_8 and

R_9 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 $-COOR_7$ 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; and (2) a pharmaceutical composition comprising cyclosporin A as active agent.

- 10 5) A kit for use in treating a disease having an auto-immune basis, which kit comprises in separate containers (1) a pharmaceutical composition containing a compound of formula (I)



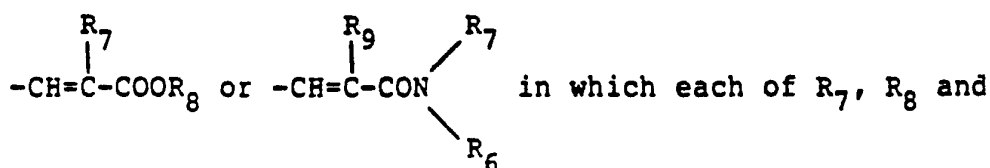
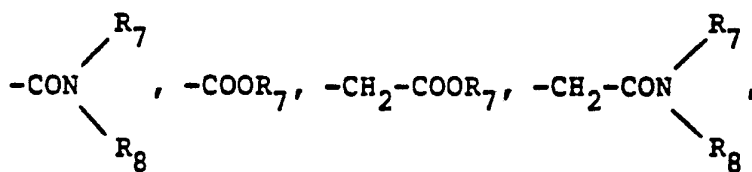
wherein

- 15 a) Z is $\begin{array}{c} R_6 \\ | \\ Y-C \\ | \\ R_5 \end{array}$ wherein Y completes a single bond or is oxygen or a $-CH_2-$ group and the symbol $\begin{array}{c} \text{---} \\ | \\ \text{---} \end{array}$ represents a single or double bond or (b) Z is $\begin{array}{c} \text{---} \\ | \\ \text{---} \end{array}$

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and the symbol --- represents a double bond;

one of R_1 , R_2 , R_3 and R_4 is $-\text{CH}_2\text{OH}$, $\text{C}_2\text{-C}_4$ acyl,



R_9 is independently hydrogen or $\text{C}_1\text{-C}_4$ alkyl, and the others are independently chosen from hydrogen, hydroxy, halogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ 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, $\text{C}_1\text{-C}_6$ alkyl or phenyl; or a pharmaceutically acceptable salt thereof; and (2) a pharmaceutical composition comprising cyclosporin A as active agent.

6. A method according to claim 4, wherein the said compound of formula (I) or salt thereof is as defined in claim 2 or 3.

7. A kit according to claim 5, wherein the said compound of formula (I) or salt thereof is as defined in claim 2 or 3.

8. Products containing a compound of formula (I) or pharmaceutically acceptable salt thereof as defined in claim 1 and cyclosporin A as a combined preparation for simultaneous or sequential use in treating a disease having

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an autoimmune basis.

9. Products according to claim 8, wherein the said compound of formula (I) or salt thereof is as defined in claim 2 or 3.

10. A method of preventing or treating cyclosporin A-induced nephrotoxicity in mammals, which method comprises administering to a mammal in need of it a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 3.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 90/01010

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : A 61 K 37/02, //(A 61 K 37/02, 31:415)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X,Y	EP, A, 0300675 (MERCK FROSST CANADA INC.) 25 January 1989 see page 9, lines 40-41,58, claims 1,3 --	1-3,5,7-9
Y	GB, A, 2141705 (FARMITALIA CARLO ERBA SPA) 3 January 1985 see abstract, especially last lines; page 9, line 44 cited in the application -----	1-3,5,7-9
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
26th September 1990	19. 10. 90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Mme N. KUIPER	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers *) because they relate to subject matter not required to be searched by this Authority, namely:

*) Claims: 4,6,10 PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. ☐ Claim numbers 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. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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 of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ 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 claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

EP 9001010
SA 38295

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82