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**SBGK Szabadalmi Ügyvivői Iroda, Budapest**(54) **A glomerulonefritisz kezelése**

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### (54) **Glomerulonephritis Treatment**

Behandlung von Glomerulonephritis

Traitement de la glomérulonéphrite

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## Description

[0001] This invention relates to the use of certain polyunsaturated long-chain ketones for the treatment of lupus nephritis or diabetic nephropathy and in particular to compositions as defined in the claims for use in such treatment.

[0002] Glomerulonephritis, also known as glomerular nephritis, abbreviated GN, is a renal disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria or as a nephrotic syndrome, acute renal failure, or chronic renal failure. Glomerulonephritis is categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Diagnosing the pattern of GN is important because the outcome and treatment differs in different types.

[0003] Primary causes of glomerulonephritis are those which are intrinsic to the kidney, whilst secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis) or cancers.

[0004] The glomerulus is a unique vascular network with three specialised types of cell: the endothelial cell, the mesangial cell and the visceral epithelial cell. Mesangial cells (MC) serve a number of functions in the renal glomerular capillary including structural support of the capillary tuft, modulation of the glomerular hemodynamics and a phagocytic function allowing removal of macromolecules and immune complexes. The proliferation of MC is a prominent feature of glomerular disease including IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis, and diabetic nephropathy.

[0005] Reduction of MC proliferation in glomerular disease models by treatment with, for example, a low protein diet has been shown to produce extracellular matrix expansion and glomerulosclerotic changes. MC proliferation inhibitors may therefore offer therapeutic opportunities for the treatment of proliferative glomerular disease.

[0006] Mesangial proliferative glomerulonephritis is a form of glomerulonephritis which involves inflammation at the kidney glomeruli. The mesangial cells which are a part of the glomerular capillaries increase in size giving the glomeruli a lumpy appearance. The disorder usually causes nephritic syndrome which represents protein loss in the urine. It may be present as acute, chronic or rapidly progressive glomerulonephritis and may progress to chronic renal failure.

[0007] It is known that MC proliferation is inhibited by a variety of pharmacological drugs, for example inhibitors against angiotensin converting enzyme (ACE), cyclin-dependent kinases (CDK), platelet derived growth factor and others.

[0008] The glomerulus also has potential to express several isoforms of nitric oxide synthase (NOS). Induction of inducible NOS occurs as part of a rapid initial response to immune injury in a glomerulonephritis. Whilst the role of NO generated by NOS in the glomerulus is still unclear, some studies have demonstrated that NO inhibition can alter the level of proteinuria and leukocyte infiltration and other manifestations of injury such as thrombosis, proliferation and matrix production.

[0009] It seems clear that reduction of NO will contribute to amelioration of mesangial proliferation and hence offer alleviation of the symptoms of glomerulonephritis.

[0010] The present inventors seek new treatments for GN and related conditions. As noted above, current proposed therapies may be based on angiotensin converting enzyme (ACE) inhibitors such as lisinopril and similar compounds. These inhibitors reduce blood pressure, a feature common to all anti-hypertensive drugs but they also possess inhibitory activity of intra renal MC proliferation and also seem to lower proteinurea. Other treatments include the use of CDK2 antagonists or calcium antagonists.

[0011] The present inventors have realised that the compounds claimed herein, some of which are new, others known, have potential in the treatment of proliferative conditions in general and glomerulonephritis in particular. The inventors have found that a certain class of compounds based upon long chain unsaturated fatty acid molecules are useful in the treatment of glomerulonephritis.

[0012] Some of the compounds proposed for use in this invention have been disclosed before, for example, in EP-A-1469859 but only there in the context of the treatment of psoriasis. The present inventors have realised that these compounds and others have utility also in the treatment of glomerulonephritis or other proliferative diseases.

[0013] Thus, viewed from one aspect the invention a compound of formula (I)



(wherein R is a C<sub>10-24</sub> unsaturated hydrocarbon group, said hydrocarbon group comprising at least 4 non-conjugated double bonds;

L is a linking group forming a bridge of 1 to 5 atoms between the R group and the carbonyl CO, wherein L comprises at least one heteroatom; and

X is CH<sub>3</sub> or a salt thereof for use in the treatment of lupus nephritis or diabetic nephropathy.

[0014] Viewed from another aspect the invention provides a method of treating lupus nephritis or diabetic nephropathy

comprising administering to an animal, preferably a mammal, e.g. human, an effective amount of a compound of formula (I) or a salt thereof as hereinbefore described.

**[0015]** Viewed from another aspect the invention provides use of a compound of formula (I) or a salt thereof as hereinbefore described for use in the manufacture of a medicament for treating lupus nephritis or diabetic nephropathy.

## Detailed Description

**[0016]** This disclosure involves the use of compounds of formula (I) or a salt thereof in the treatment of glomerulonephritis and related conditions. Glomerulonephritis is a renal disease characterized by inflammation of the glomeruli.

**[0017]** The group R preferably comprises 5 to 9 double bonds, preferably 5 or 8 double bonds, e.g. 5 to 7 double bonds such as 5 or 6 double bonds. These bonds should be non-conjugated. It is also preferred if the double bonds do not conjugate with the carbonyl functionality.

**[0018]** The double bonds present in the group R may be in the cis or trans configuration however, it is preferred if the majority of the double bonds present (i.e. at least 50%) are in the cis configuration. In further advantageous embodiments all the double bonds in the group R are in the cis configuration or all double bonds are in the cis configuration except the double bond nearest the carbonyl group which may be in the trans configuration.

**[0019]** The group R may have between 10 and 24 carbon atoms, preferably 12 to 20 carbon atoms, especially 17 to 19 carbon atoms.

**[0020]** The R group backbone contains only carbon atoms.

**[0021]** The R group may carry up to three substituents, e.g. selected from halo, C<sub>1-6</sub> alkyl e.g. methyl, C<sub>1-6</sub> alkoxy. If present, the substituents are preferably non-polar, and small, e.g. a methyl group. It is preferred however, if the R group remains unsubstituted.

**[0022]** The R group is preferably linear. It preferably derives from a natural source such as a long chain fatty acid or ester. In particular, the R group may derive from AA, EHA or DHA.

**[0023]** The linking group L provides a bridging group of 1 to 5 backbone atoms, preferably 2 to 4 backbone atoms between the R group and the carbonyl.

**[0024]** The backbone of the linker comprises heteroatoms such as N, O, S, SO.

**[0025]** Preferred components of the linking group are -CH<sub>2</sub>-, -CH(C<sub>1-6</sub>alkyl)-, -N(C<sub>1-6</sub>alkyl)-, -NH-, -S-, -O-, -CH=CH-, -CO-, -SO-, -SO<sub>2</sub>- which can be combined with each other in any (chemically meaningful) order to form the linking group.

Thus, by using two methylene groups and an -S- group the linker -SCH<sub>2</sub>CH<sub>2</sub>- is formed.

**[0026]** The linking group L contains at least one heteroatom in the backbone. It is preferred if the first backbone atom of the linking group attached to the R group is a heteroatom or group of heteroatoms.

**[0027]** It is highly preferred if the linking group L contains at least one -CH<sub>2</sub>- link in the backbone. Ideally the atoms of the linking group adjacent the carbonyl are -CH<sub>2</sub>-.

**[0028]** It is preferred that the group L (depending on the size of the L group) provides a heteroatom or group of heteroatoms positioned α, β, γ, or δ to the carbonyl, preferably β or γ to the carbonyl. Preferably the heteroatom is O, N or S or a sulphur derivative such as SO.

**[0029]** Highly preferred linking groups therefore are -NH<sub>2</sub>CH<sub>2</sub>-, -NH(Me)CH<sub>2</sub>-, -SCH<sub>2</sub>-, -SOCH<sub>2</sub>-, -COCH<sub>2</sub>-

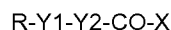
**[0030]** The substitution pattern is preferably such that the R and carbonyl substituents are alpha, gamma to each other (i.e. 1,3 or 2, 4 or 3, 5-split).

**[0031]** For the avoidance of doubt, it is stressed that the 1 to 5 atom bridge should be counted as the shortest route from the start of the linker to the carbonyl.

**[0032]** Highly preferred linking groups are SCH<sub>2</sub>, NHCH<sub>2</sub>, and N(Me)CH<sub>2</sub>.

**[0033]** The group X CHal<sub>3</sub>, especially CF<sub>3</sub>.

**[0034]** Thus, preferred compounds of formula (I) are those of formula (I')



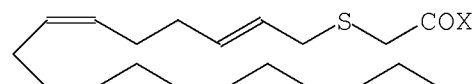
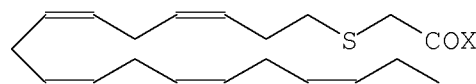
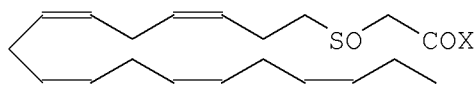
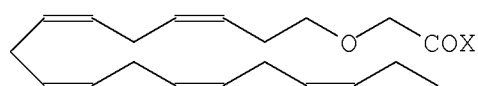
wherein R and X are as hereinbefore defined;

Y1 is selected from O, S, NH, N(C<sub>1-6</sub>-alkyl), SO or SO<sub>2</sub> and

Y2 is (CH<sub>2</sub>)<sub>n</sub> or CH(C<sub>1-6</sub> alkyl);

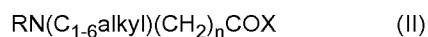
where n is 1 to 3, preferably 1.

**[0035]** Highly preferred (known) compounds for use in the invention are depicted below.

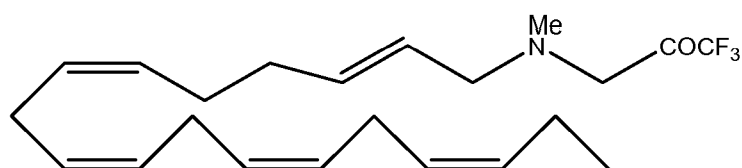


[0036] Certain compounds are new and form a further aspect of the invention.

[0037] Further compounds which are new include the compounds RN(C<sub>1-6</sub>alkyl)COX. Thus viewed from another aspect the invention provides a compound of formula (II)

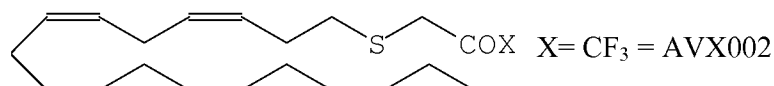
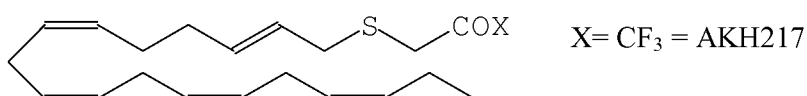


where R, n and X are as hereinbefore defined, especially the compound:



[0038] Viewed from another aspect the invention provides a pharmaceutical composition comprising any new compound as hereinbefore defined in combination with at least one pharmaceutically acceptable excipient.

[0039] The following compounds are highly preferred for use in the invention:



[0040] Where possible, the compounds of the invention can be administered in salt, solvate, prodrug or ester form, especially salt form. Preferably however, no such form is used.

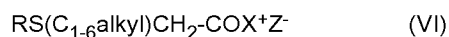
[0041] Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula (I) and the resulting mixture evaporated to dryness (lyophilised) to obtain the acid addition salt as a solid. Alternatively, a compound of formula (I) may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

[0042] Suitable addition salts are formed from inorganic or organic acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, trifluoroacetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate, gluconate, succinate, pyruvate, oxalate,

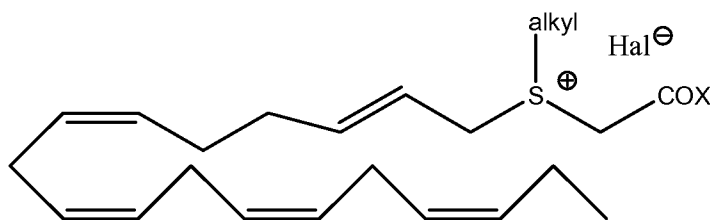
oxaloacetate, trifluoroacetate, saccharate, benzoate, alkyl or aryl sulphonates (eg methanesulphonate, ethanesulphonate, benzenesulphonate or p-toluenesulphonate) and isethionate. Representative examples include trifluoroacetate and formate salts, for example the bis or tris trifluoroacetate salts and the mono or diformate salts, in particular the tris or bis trifluoroacetate salt and the monoformate salt.

**[0043]** In a further highly preferred embodiment, the compound of the invention is a sulphonium salt. In such a compound, a sulphur atom in the backbone of the molecule, e.g. in the linker group, is functionalised to carry a C1-6-alkyl group. This can be achieved through reaction with an alkyl halide, e.g. methyl iodide. The halide ion forms the counterion of the salt.

**[0044]** In a further preferred embodiment therefore the invention provides a sulphonium salt of a compound of formula (I). Preferably the compound is of formula (VI)



where R and X are as hereinbefore defined and Z is a counterion, e.g. halide; e.g. the compound

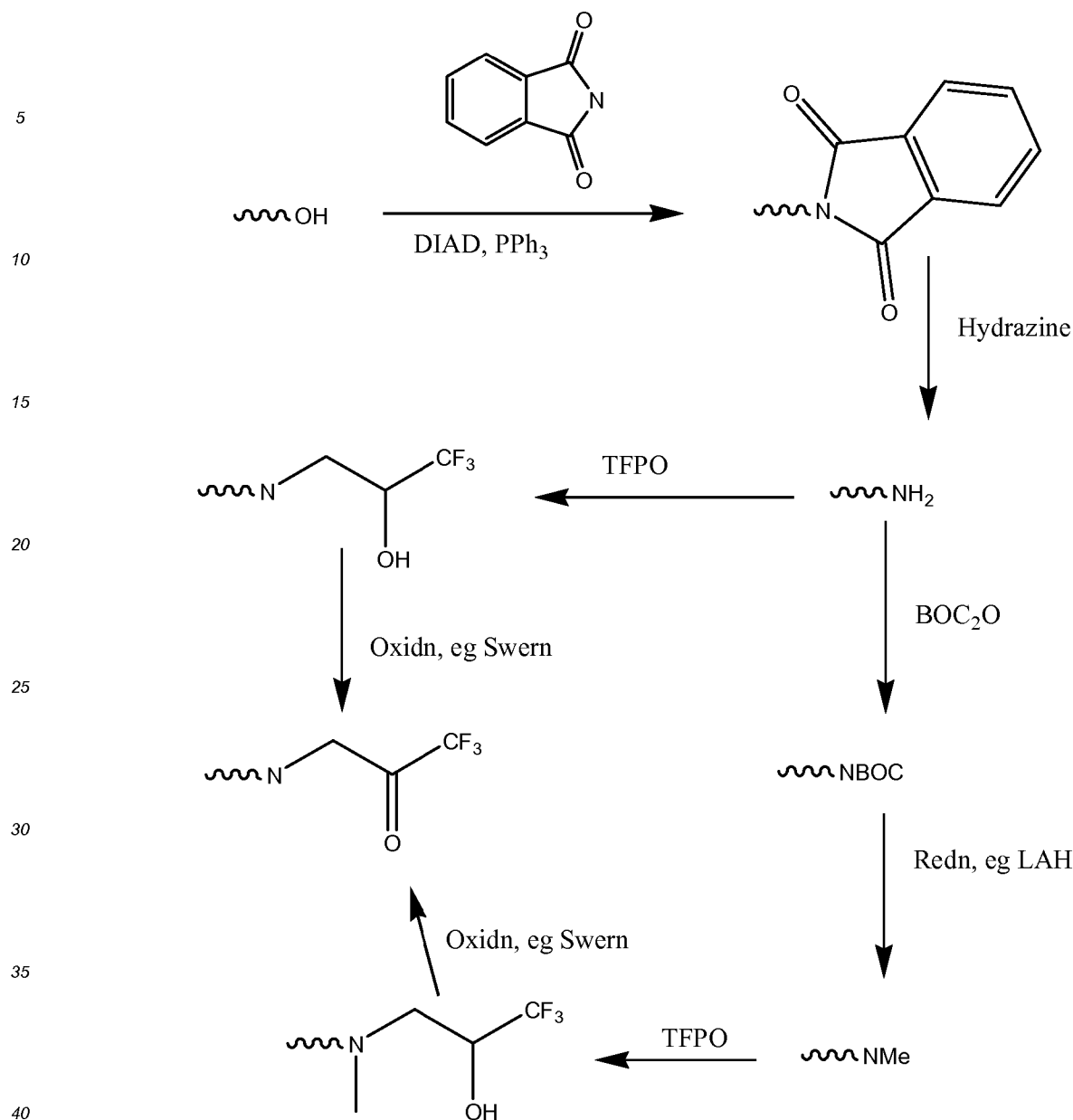


**[0045]** Compounds of formula (I) may be manufactured using known chemical synthetic routes. It is convenient to begin synthesis from the commercially available compounds arachidonic acid (AA), EPA (all-Z-eicosa-5,8,11,14,17-pentaenoic acid) or DHA (all-Z-docosa-4,7,10,13,16,19-hexaenoic acid). Conversion of the acid functionality of these compounds into, for example a  $-\text{COCF}_3$  group can be achieved readily, e.g. by converting the carboxylic acid into its corresponding acid chloride and reacting the same with trifluoroacetic anhydride in the presence of pyridine.

**[0046]** Introduction of a heteroatom into the carbon chain is also achieved readily. Conveniently, for example, the starting acid is reduced to an alcohol and, if required, converted to the corresponding thiol. The nucleophilic thiol may then be reacted with a group such as  $\text{BrCH}_2\text{COCF}_3$  thereby introducing the carbonyl and electron withdrawing species. Complete synthetic protocols may be found in J. Chem. Soc., Perkin Trans 1, 2000, 2271-2276 or J. Immunol., 1998, 161, 3421.

**[0047]** Where the backbone of the molecule contains a nitrogen atom, an alternative synthesis is required. Formation of a polyunsaturated alcohol can be achieved using protocols give in the above Perkin Trans paper. Thereafter, conversion of an alcohol  $-\text{OH}$  to  $-\text{NH}_2$  with, for example, phthalimide and subsequent hydrazine reduction allows formation of a  $-\text{NH}_2\text{CH}_2\text{COCF}_3$  group by reaction with trifluoropropyleneoxide (TFPO) and oxidation of the hydroxyl to a ketone. This reaction is shown below.

**[0048]** Methylation of the nitrogen can be effected before this reaction by the formation of an N-BOC group and reduction, e.g. with lithium aluminium hydride. Reaction with TFPO and oxidation yields the linker  $\text{NMe-CH}_2$ .



**[0049]** This forms a further aspect of the invention which therefore provides a process for the preparation of a compound of formula (I) comprising:

- (I) converting the compound R-OH to R-NH<sub>2</sub>;
- (II) optionally methylating the N atom;
- (III) reacting with TFPO; and
- (IV) oxidising the formed hydroxyl to a ketone.

**[0050]** The compounds of the disclosure are proposed primarily for use in the treatment of, *inter alia*, glomerulonephritis. Whilst the compounds of the disclosure are generally of use in the treatment of glomerulonephritis, the compounds are of particular utility in the treatment of the proliferative type of the disease.

**[0051]** By treating or treatment is meant at least one of:

- (i). preventing or delaying the appearance of clinical symptoms of the disease developing in a mammal;
- (ii). inhibiting the disease i.e. arresting, reducing or delaying the development of the disease or a relapse thereof or at least one clinical or subclinical symptom thereof, or



(iii). relieving or attenuating one or more of the clinical or subclinical symptoms of the disease.

[0052] The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician. In general a skilled man can appreciate when "treatment" occurs.

[0053] The word "treatment" is also used herein to cover prophylactic treatment, i.e. treating subjects who are at risk of developing a disease in question.

[0054] The compounds of the invention can be used on any animal subject, in particular a mammal and more particularly to a human or an animal serving as a model for a disease (e.g., mouse, monkey, etc.).

[0055] In order to treat a disease an effective amount of the active agent needs to be administered to a patient. A "therapeutically effective amount" means the amount of a compound that, when administered to an animal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated and will be ultimately at the discretion of the attendant doctor.

[0056] While it is possible that, for use in the methods of the invention, a compound of formula I may be administered as the bulk substance, it is preferable to present the active ingredient in a pharmaceutical formulation, for example, wherein the agent is in admixture with a pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

[0057] The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers are well known in the art.. The pharmaceutical compositions may also comprise any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s) and so on. The compositions can also contain other active components, e.g. other drugs for the treatment of glomerulonephritis.

[0058] It will be appreciated that pharmaceutical compositions for use in accordance with the present invention may be in the form of oral, parenteral, transdermal, inhalation, sublingual, topical, implant, nasal, or enterally administered (or other mucosally administered) suspensions, capsules or tablets, which may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. The compositions of the invention could also be formulated as nanoparticle formulations.

[0059] The compounds of the invention can be administered for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

[0060] The pharmaceutical compositions of the invention may contain from 0.01 to 99% weight - per volume of the active material.

[0061] A therapeutically effective amount of the compound of the present invention can be determined by methods known in the art. The therapeutically effective quantities will depend on the age and on the general physiological condition of the patient, the route of administration and the pharmaceutical formulation used. The therapeutic doses will generally be between about 10 and 2000 mg/day and preferably between about 30 and 1500 mg/day. Other ranges may be used, including, for example, 50-500 mg/day, 50-300 mg/day, 100-200 mg/day.

[0062] Administration may be once a day, twice a day, or more often, and may be decreased during a maintenance phase of the disease or disorder, e.g. once every second or third day instead of every day or twice a day. The dose and the administration frequency will depend on the clinical signs, which confirm maintenance of the remission phase, with the reduction or absence of at least one or more preferably more than one clinical signs of the acute phase known to the person skilled in the art.

[0063] It is advantageous if the medicament of the invention is taken orally.

[0064] The compounds of the disclosure may be used in the treatment of glomerulonephritis and related diseases. In particular, the compounds of the invention are for use to treat lupus nephritis and diabetic nephropathy.

[0065] The compounds of the disclosure may be used to treat glomerulonephritis in combination with other known pharmaceuticals for said purpose and this forms a further aspect of the invention. Other useful pharmaceuticals include corticosteroids, immunosuppressive drugs, antihypertensive agents and diuretic medications.

[0066] The invention is described further below with reference-to the following non-limiting examples and figures.

## Description of Figures:

### [0067]

Figure 1 shows the effect of the inhibitors of the examples on cytokine-stimulated PGE<sub>2</sub> formation in mesangial cells. Quiescent cells were stimulated with either DMEM (-), IL-1 $\beta$  (1nM), in the absence (-) or presence of the indicated concentrations of AKH-217 and AVX002. Supernatants were collected and taken for PGE<sub>2</sub> quantification using an ELISA. Data are expressed as % of maximal IL-1 $\beta$ -stimulated PGE<sub>2</sub> and are means  $\pm$  S.D. (n=3).

Figure 2 shows the effect of the inhibitors of the examples on cytokine-stimulated sPLA<sub>2</sub> protein (A) and mRNA (B) expression and promoter activity in mesangial cells. Quiescent cells were stimulated with either DMEM (-), or IL-1 $\beta$  (1nM) in the absence (-) or presence of AKH-217 (etOH), vehicle control.

(A) Supernatants were taken for protein precipitation and precipitated proteins were separated by SDS-PAGE and subjected to a Western blot analysis using a monoclonal antibody against rat sPLA<sub>2</sub>. Data show duplicates of a representative experiment.

(B). Cells were taken for RNA extraction and subjected to quantitative PCR analysis of rat IIA-sPLA<sub>2</sub> and 18 S RNA.  $\Delta\Delta C_t$  values were calculated and results are expressed as % of maximal IL-1 $\beta$ -stimulated response and are means  $\pm$  S.D. (n=3).

(C) Cells were transfected with the sPLA<sub>2</sub> promoter construct plus a plasmid coding for the Renilla luciferase. After transfection, cells were stimulated for 24h with vehicle (-), IL-1 $\beta$  (1nM), or IL-1 $\beta$  plus 10 $\mu$ M of AKH-217. sPLA<sub>2</sub> promoter activity was calculated and results are expressed as relative luciferase units (RLU) and are means  $\pm$  S.D. (n=3).

Figure 3 shows the effect of the inhibitors of the examples on cytokine-stimulated NO formation in mesangial cells. Quiescent cells were stimulated with either DMEM (-), IL-1 $\beta$  (1nM; +), in the absence or presence of the indicated concentrations of AKH-217, AVX002, or AACOCF3. Supernatants were collected and taken for nitric oxide (NO) quantification by using a Griess Reaction assay. Data are expressed as  $\mu$ M of NO in the supernatant and are means  $\pm$  S.D. (n=3).

Figure 4 shows the effect of the inhibitors of the examples on cytokine-stimulated iNOS protein (A) and mRNA (B) expression and promoter activity in mesangial cells. Quiescent cells were stimulated with either vehicle (DMEM), IL-1 $\beta$  (1nM), in the absence (-) or presence of the indicated concentrations (in  $\mu$ M) of AVX001 and AVX002. EtOH, vehicle control.

(A) Cells were taken for protein extraction and equal amount of protein were separated by SDS-PAGE and subjected to a Western blot analysis using a polyclonal antibody against iNOS at a dilution of 1:2000. Data are representative of at least 3 independent experiments giving similar results.

(B). Cells were taken for RNA extraction and subjected to quantitative PCR analysis of rat iNOS and 18 S RNA.  $\Delta\Delta C_t$  values were calculated and results are expressed as % of maximal IL-1 $\beta$  response and are means  $\pm$  S.D (n=3). (C) Cells were transfected with the rat iNOS promoter construct plus a plasmid coding for the Renilla luciferase. After transfection, cells were stimulated with vehicle (-), IL-1 $\beta$  (1nM), or IL-1 $\beta$  plus 10 $\mu$ M of AVX001. iNOS promoter activity was calculated and results are expressed as relative luciferase units (RLU) and are means  $\pm$  S.D.(n=3).

Figure 5 shows the effect of the inhibitors of the examples on [<sup>3</sup>H]thymidine incorporation in mesangial cells. Quiescent cells were stimulated for 24h with vehicle (DMEM), or 100 $\mu$ M of ATP in the absence (-) or presence of the indicated concentrations of AVX001 or AVX002, in the presence of [<sup>3</sup>H]thymidine. (B) Cells were stimulated for 24h with insulin (100ng/ml) or IGF (50ng/ml) in the absence (-) or presence of 10 $\mu$ M of AVX001 or AVX002, in the presence of [<sup>3</sup>H]thymidine. Thymidine incorporated into DNA was determined and results are expressed as % of control and are means  $\pm$  S.D. (n=3).

Figure 6 shows the effect of the inhibitors of the examples on IL-1  $\beta$ -stimulated NF $\kappa$ B activation in mesangial cells. Quiescent cells were stimulated for 30 min with either vehicle (DMEM), or IL-1 $\beta$  (2nM) in the absence (-) or presence (+) of AVX001 or AVX002 (10 $\mu$ M, pretreated 2h). Thereafter, cell lysates were separated by SDS-PAGE and subjected to a Western blot analysis using a polyclonal antibody against phospho-p65 (NF $\kappa$ B) (upper panel), HuR as a loading control (middle panel), and I $\kappa$ B (lower panel). Data in Fig 6A show duplicates of one representative experiments. Figures 6B and C show the densitometric evaluation of NF $\kappa$ B and I $\kappa$ B bands.

## Examples

[0068] The following compounds were used in the Experiments:

AKH-217/AVX001

AVX002

X = CF<sub>3</sub>Ref.  
AACOCF<sub>3</sub>

These compounds were synthesised based on. Chem. Soc., Perkin Trans 1, 2000, 2271-2276.

### Example 1

#### Effect of inhibitors on PGE<sub>2</sub> formation in rat renal mesangial cells

**[0069]** We investigated the effect of the inhibitors on PGE<sub>2</sub> formation in mesangial cells. PGE<sub>2</sub> formation is highly induced by stimulation of cells with the pro-inflammatory cytokine IL-1 $\beta$ . This induction of PGE<sub>2</sub> is dose-dependently reduced in the presence of the inhibitors. Maximal effects were seen with 3-10  $\mu$ M of AKH-217 (AVX001) and Compound B (AVX002) (Fig. 1).

**[0070]** It has been previously shown that the cytokine-induced PGE<sub>2</sub> formation in mesangial cells involves both sPLA<sub>2</sub> and cPLA<sub>2</sub> activation (Pfeilschifter et al., 1993), we then investigated the effect of the inhibitors above on sPLA<sub>2</sub> protein and mRNA expressions. As seen in Fig. 2, AKH-217 was able to reduce the IIA-sPLA<sub>2</sub> protein expression and secretion (Fig. 2A), but also IIA-sPLA<sub>2</sub> mRNA expression (Fig. 2B). This effect on sPLA<sub>2</sub> mRNA expression was due to a reducing effect on gene transcription. This was shown by a luciferase reporter gene assay that reflected sPLA<sub>2</sub> promoter activity.

**[0071]** To this end, a 2.26kb fragment of the rat IIA-sPLA<sub>2</sub> promoter was cloned according to Scholz-Pedretti et al. (2002). This fragment was ligated into a luciferase-containing vector (pGL3) and used to transfect mesangial cells. As seen in Fig. 2C, the IL-1 $\beta$ -stimulated promoter activity was completely reduced by AKH-217.

**[0072]** These data suggest that the inhibitors of the invention could affect some transcription factors, which are activated by IL-1 $\beta$  and are essential for sPLA<sub>2</sub> gene transcription. Potential candidates include NF $\kappa$ B and PPAR.

### Example 2

#### Effect of inhibitors on nitric oxide (NO) formation in rat renal mesangial cells

**[0073]** Nitric oxide (NO) is also considered a pro-inflammatory mediator which is generated by the inducible NO synthase (iNOS) upon cytokine treatment of mesangial cells. Various previous studies have indicated that iNOS expression is regulated by the same transcription factors as sPLA<sub>2</sub>. We investigated whether cytokine-triggered iNOS expression is also affected by the inhibitors.

**[0074]** NO formation in mesangial cells was highly induced by IL-1  $\beta$  treatment. This stimulated NO formation was reduced in a dose-dependent manner in the presence of AKH-217 and AVX002 (Fig. 3). Furthermore, the protein expression of iNOS, which is induced by IL-1  $\beta$  (Fig. 4A), is down-regulated in the presence of AKH-217 and AVX002 (Fig. 4A). A similar reducing effect was also seen on iNOS mRNA expression when quantitative RealTime PCR analyses were performed (Fig. 4B). To see whether this effect is due to altered gene transcription of iNOS, luciferase reporter gene assays were performed to measure iNOS promoter activity. A 4.5kb fragment of the rat iNOS promoter was kindly provided by Dr. K.F. Beck (pharmazentrum frankfurt). As seen in Fig. 4C, IL-1  $\beta$  stimulation of mesangial cells stimulated iNOS promoter by 10-fold. In the presence of AKH217, the promoter activity was completely lost.

[0075] These data suggest, that also in the case of iNOS, AVX inhibitors have a reducing effect on gene transcription, most probably affecting the same transcription factors as in the case of sPLA2 transcription.

### Example 3

#### Effect of inhibitors on mesangial cell proliferation

[0076] Glomerulonephritis is characterized in a first early phase by increased mesangial apoptosis which in a second phase is replaced by an opposite event, i.e. hyperproliferation of mesangial cells. Many previous studies have shown that quiescent mesangial cells in culture can re-enter the cell cycle when exposed to various growth factors, including PDGF, insulin, insulin-like growth factor (IGF), or extracellular nucleotides such as ATP and UTP. These data are confirmed here, as insulin, IGF and ATP trigger increased [<sup>3</sup>H]thymidine incorporation into DNA (Fig. 5A and 5B). In the presence of either AKH217 or AVX002, agonist-stimulated [<sup>3</sup>H]thymidine incorporation is reduced (Fig. 5A and 5B). Similar data were also obtained when cells were stimulated with PDGF. These data suggest an antiproliferative potential of the inhibitors.

### Example 4

#### Effect of inhibitors on NFκB activity in mesangial cells.

[0077] As we have seen in Examples 1 and 2, that iNOS and sPLA2 expression is regulated by the inhibitors in a similar manner, we further studied whether these inhibitors had an effect on NFκB activation. NFκB activation was measured by Western blot analyses by detecting the amount of phospho-p65 which represents the active transcription factor subunit. Short-term stimulation of cells with IL-1 β (3 revealed a small but clear increase of phospho-p65 (Fig. 6, upper panel) consistent with many previous reports that cytokines activate NFκB. This effect was reduced by AKH217 (Fig. 6). In addition, the inhibitor of κB (IκB), which is constitutively expressed in unstimulated cells, is downregulated by IL-1 β stimulation, and this downregulation is reverted by the inhibitors (Fig. 6, lower panel). For equal loading, the nuclear HuR stabilization factor was stained (Fig. 6, middle panel)

### Claims

1. A compound of formula (I)



wherein R is a C<sub>10-24</sub>, preferably C<sub>17-19</sub>, unsaturated hydrocarbon group which may carry up to three substituents, said hydrocarbon group comprising at least 4 non-conjugated double bonds;

L is a linking group forming a bridge of 1 to 5 atoms between the R group and the carbonyl CO wherein L comprises at least one heteroatom, e.g. O, S, N, or SO; and

X is CHal<sub>3</sub> where Hal is halide; or a salt thereof for use in the treatment of lupus nephritis or diabetic nephropathy.

2. A compound for use as claimed in any preceding claim wherein said hydrocarbon group has 5 to 7 double bonds.

3. A compound for use as claimed in claims 1 to 2 wherein no double bond is conjugated with the carbonyl group.

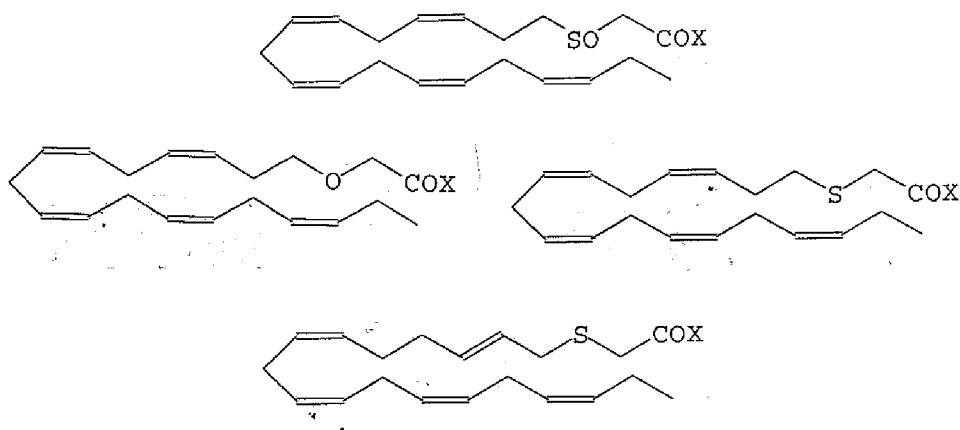
4. A compound for use as claimed in any one of claims 1 to 3 wherein all double bonds are in the cis configuration or wherein all double bonds are in the cis configuration except the double bond nearest the carbonyl.

5. A compound for use as claimed in any one of claims 1 to 4 wherein linking group L comprises -CH<sub>2</sub>-, -CH(C<sub>1-6</sub>alkyl)-, -N(C<sub>1-6</sub>alkyl)-, -NH-, -S-, -O-, -CH=CH-, -CO-, -SO-, or -SO<sub>2</sub>- which can be combined with each other in any (chemically meaningful) order to form the linking group, wherein L comprises at least one heteroatom.

6. A compound for use as claimed in any preceding claim wherein L is -NH<sub>2</sub>CH<sub>2</sub>-, -NH(Me)CH<sub>2</sub>-, -SCH<sub>2</sub>-, or -SOCH<sub>2</sub>-.

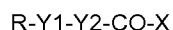
7. A compound for use as claimed in claim 1 to 6 wherein X is CF<sub>3</sub>.

8. A compound for use as claimed in claim 1 having the formula:



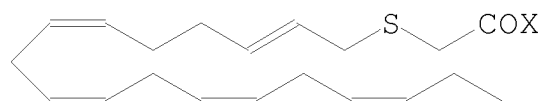
wherein X is  $\text{CHAl}_3$ .

9. A compound for use as claimed in any preceding claims having the formula (I')

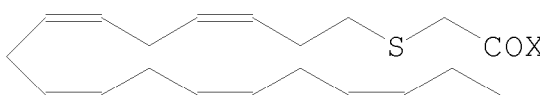


wherein R and X are as defined in claim 1;  
Y1 is selected from O, S, NH,  $\text{N}(\text{C}_{1-6}\text{-alkyl})$ , SO or  $\text{SO}_2$  and  
Y2 is  $(\text{CH}_2)_n$  or  $\text{CH}(\text{C}_{1-6}\text{ alkyl})$ ;  
where n is 1 to 3, preferably 1.

10. A compound for use as claimed in any preceding claims said compound having the formula



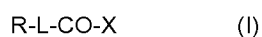
or



where X is  $\text{CF}_3$ .

## Patentansprüche

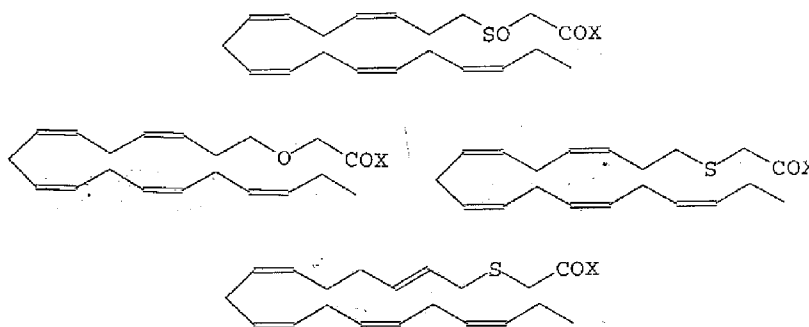
1. Verbindung der Formel (I)



wobei R für eine ungesättigte  $\text{C}_{10-24}$ , bevorzugt  $\text{C}_{17-19}$ -Kohlenwasserstoffgruppe, die bis zu drei Substituenten enthalten kann, steht, wobei  
die Kohlenwasserstoffgruppe wenigstens 4 unkonjugierte Doppelbindungen umfasst,  
L eine verbindende Gruppe ist, die eine Brücke von 1 bis 5 Atomen zwischen der R-Gruppe und dem Carbonyl-CO bildet, wobei L wenigstens ein Heteroatom, z.B. O, S, N oder SO, umfasst; und  
X für  $\text{CHAl}_3$  steht, wobei Hal für Halogen steht; oder ein Salz davon

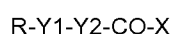
zur Verwendung in der Behandlung von Lupusnephritis oder diabetischer Nephropathie.

2. Verbindung zur Verwendung gemäß einem der vorherigen Ansprüche, wobei die Kohlenwasserstoffgruppe 5 bis 7 Doppelbindungen hat.
3. Verbindung zur Verwendung gemäß einem der Ansprüche 1 bis 2, wobei mit der Carbonylgruppe keine Doppelbindung konjugiert ist.
4. Verbindung zur Verwendung gemäß einem der Ansprüche 1 bis 3, wobei sich alle Doppelbindungen in cis-Konfiguration befinden oder wobei mit der Ausnahme der Doppelbindung, die dem Carbonyl am nächsten ist, sich alle Doppelbindungen in der cis-Konfiguration befinden.
5. Verbindung zur Verwendung gemäß einem der Ansprüche 1 bis 4, wobei die verbindende Gruppe -CH<sub>2</sub>-, -CH(C<sub>1-6</sub>-Alkyl)-, -N(C<sub>1-6</sub>-Alkyl)-, -NH-, -S-, -O-, -CH=CH-, -CO-, -SO-, oder -SO<sub>2</sub>- umfasst, welche auf jede (chemische sinnvolle) Weise miteinander kombiniert werden können, um die verbindende Gruppe zu bilden, wobei L wenigstens ein Heteroatom umfasst.
6. Verbindung zur Verwendung gemäß einem der vorherigen Ansprüche, wobei L für NH<sub>2</sub>CH<sub>2</sub>-, -NH(Me)CH<sub>2</sub>-, -SCH<sub>2</sub>- oder -SOCH<sub>2</sub>- steht.
7. Verbindung zur Verwendung gemäß den Ansprüchen 1 bis 6, wobei X für CF<sub>3</sub> steht.
8. Verbindung zur Verwendung gemäß Anspruch 1, welche folgende Formel aufweist:



wobei X für CHal<sub>3</sub> steht.

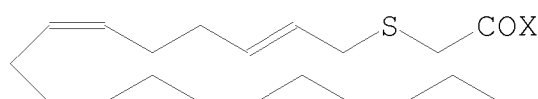
9. Verbindung zur Verwendung gemäß einem der vorherigen Ansprüche, welche die Formel (I')



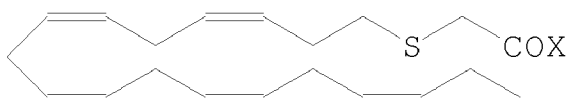
aufweist,

wobei R und X wie in Anspruch 1 definiert sind;  
Y1 ausgewählt ist aus O, S, NH, N(C<sub>1-6</sub>-Alkyl), SO oder SO<sub>2</sub>; und  
Y2 für (CH<sub>2</sub>)<sub>n</sub> oder CH(C<sub>1-6</sub>-Alkyl) steht;  
wobei n für 1 bis 3 steht, bevorzugt für 1.

10. Verbindung zur Verwendung gemäß einem der vorherigen Ansprüche, wobei die Verbindung die Formel



oder



aufweist,  
wobei X für  $\text{CF}_3$  steht.

## Revendications

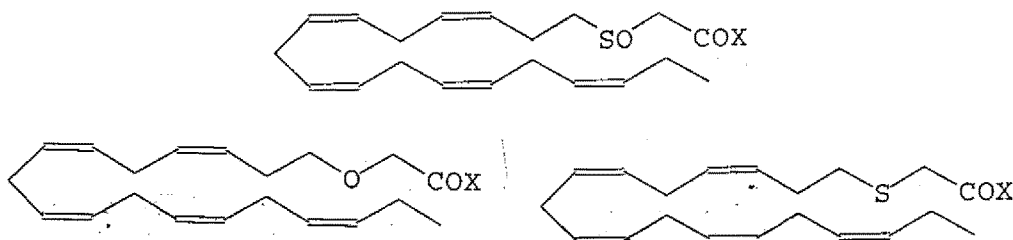
1. Composé de formule (I) :

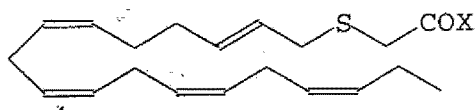


dans lequel R est un groupement hydrocarbure insaturé en  $\text{C}_{10}\text{-C}_{24}$ , de préférence en  $\text{C}_{17}\text{-C}_{19}$ , qui peut porter jusqu'à trois substituants, ledit groupe hydrocarbure comprenant au moins 4 doubles liaisons non conjuguées ; L est un groupe de liaison formant un pont de 1 à 5 atomes entre le groupement R et le carbonyle CO, dans lequel L comprend au moins un hétéroatome, par exemple O, S, N ou SO ; et X est  $\text{CHAl}_3$ , où Hal est un halogénure, ou un de ses sels,

pour usage dans le traitement du lupus néphrétique ou de la néphropathie diabétique.

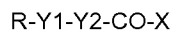
2. Composé pour usage selon l'une quelconque des revendications précédentes, dans lequel ledit groupement hydrocarbure présente 5 à 7 doubles liaisons.
3. Composé pour usage selon les revendications 1 et 2, dans lequel aucune double liaison n'est conjuguée avec le groupement carbonyle.
4. Composé pour usage selon l'une quelconque des revendications 1 à 3, dans lequel toutes les doubles liaisons sont en configuration cis ou dans lequel toutes les doubles liaisons sont en configuration cis, excepté la double liaison la plus proche du groupement carbonyle.
5. Composé pour usage selon l'une quelconque des revendications 1 à 4, dans lequel le groupement de liaison L comprend les suivants :  $-\text{CH}_2-$ ,  $-\text{CH}(\text{alkyle en } \text{C}_1\text{-C}_6)-$ ,  $-\text{N}(\text{alkyle en } \text{C}_1\text{-C}_6)-$ ,  $-\text{NH}-$ ,  $-\text{S}-$ ,  $-\text{O}-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CO}-$ ,  $-\text{SO}-$  ou  $-\text{SO}_2-$  qui peuvent être combinés l'un avec l'autre dans un ordre quelconque (au plan chimique) pour former le groupement de liaison, dans lequel L comprend au moins un hétéroatome.
6. Composé pour usage selon l'une quelconque des revendications précédentes, dans lequel L est  $-\text{NH}_2\text{CH}_2-$ ,  $-\text{NH}(\text{Me})\text{CH}_2-$ ,  $-\text{SCH}_2-$  ou  $-\text{SOCH}_2-$ .
7. Composé pour usage selon les revendications 1 à 6, dans lequel X est  $\text{CF}_3$ .
8. Composé pour usage selon la revendication 1, ayant pour formule :





dans lequel X est  $\text{CHAl}_3$ .

9. Composé pour usage selon l'une quelconque des revendications précédentes, ayant pour formule (I') :



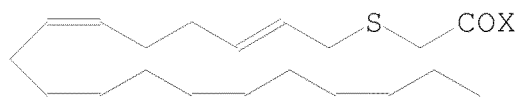
dans lequel R et X sont tels que définis dans la revendication 1 ;

Y1 est choisi parmi O, S, NH, N(alkyle en  $\text{C}_1\text{-C}_6$ ), SO ou  $\text{SO}_2$  et

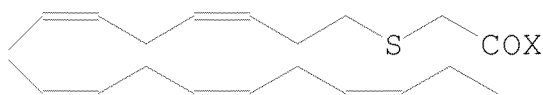
Y2 est  $(\text{CH}_2)_n$  où CH (alkyle en  $\text{C}_1\text{-C}_6$ ) ;

dans lequel n est égal à 1 à 3, de préférence à 1.

10. Composé pour usage selon l'une quelconque des revendications précédentes, ledit composé ayant pour formule :



ou



où X est  $\text{CF}_3$ .



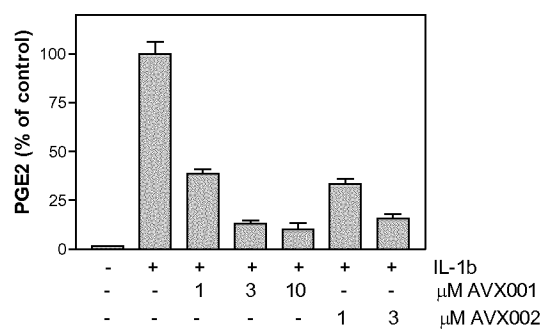


Fig. 1

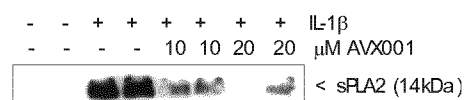


Fig. 2A

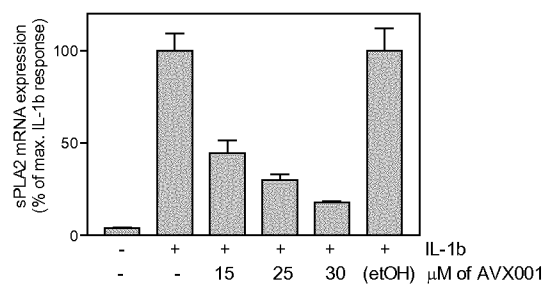


Fig. 2B

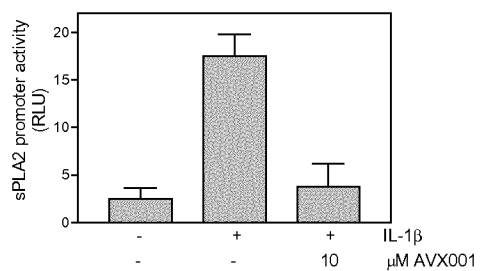


Fig. 2C

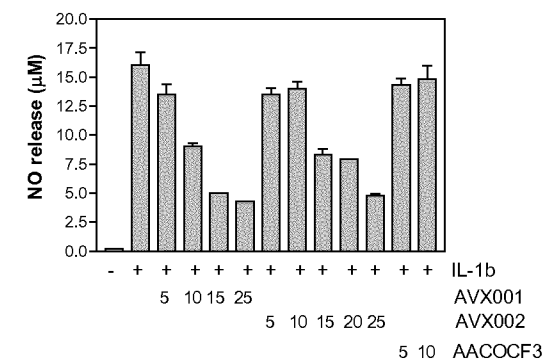


Fig. 3

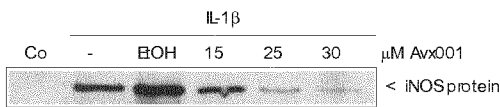


Fig. 4A

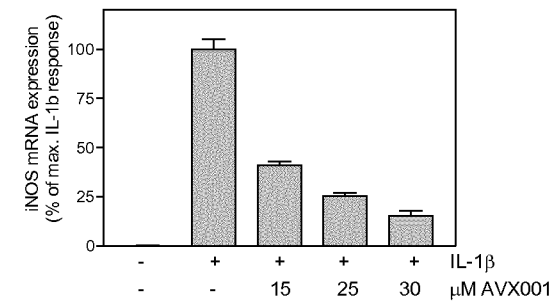


Fig. 4B

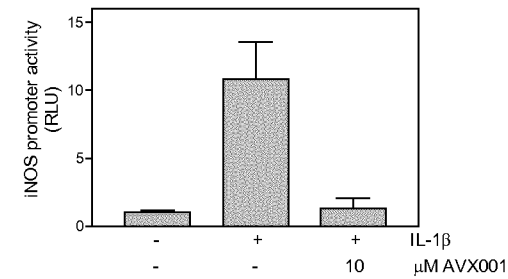


Fig. 4C

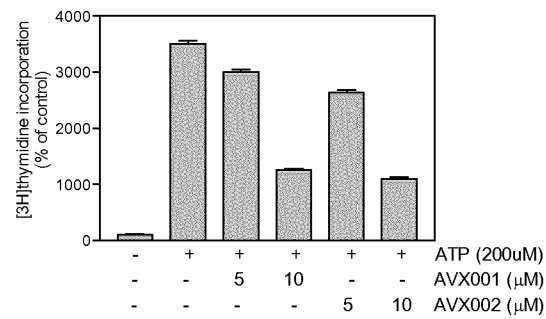


Fig. 5 A

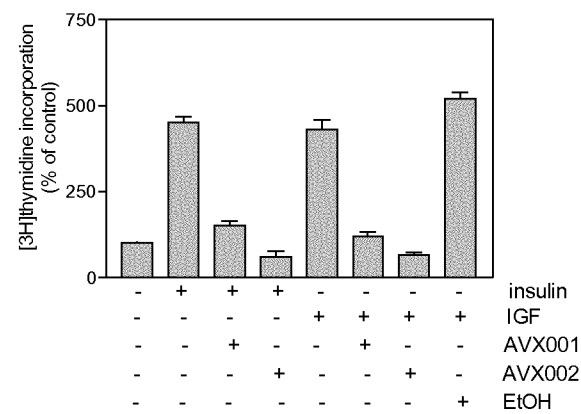


Fig. 5B

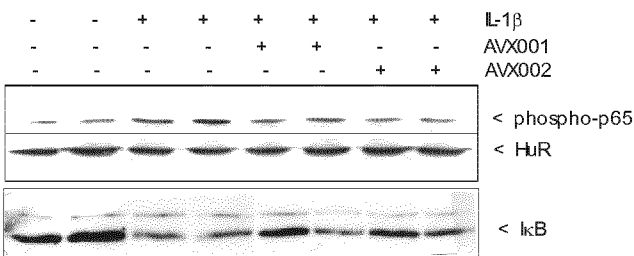
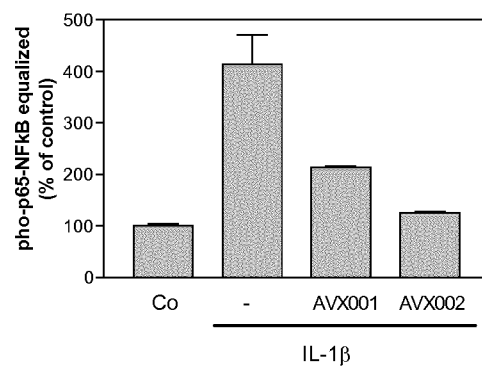
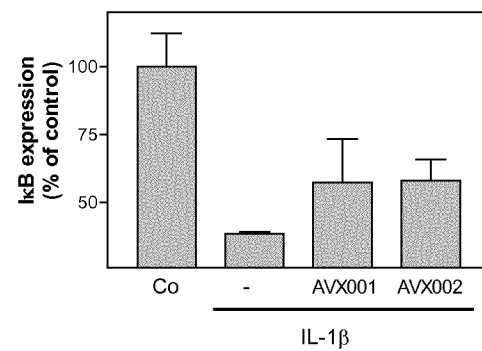


Fig. 6 A



**Fig. 6 B**



**Fig. 6 C**

**REFERENCES CITED IN THE DESCRIPTION**

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

**Patent documents cited in the description**

- EP 1469859 A [0012]

**Non-patent literature cited in the description**

- *J. Chem. Soc., Perkin Trans*, 2000, vol. 1, 2271-2276 [0046]
- *Chem. Soc., Perkin Trans*, 2000, vol. 1, 2271-2276 [0068]
- *J. Immunol.*, 1998, vol. 161, 3421 [0046]

## Szabadalmi igénypontok

1. Egy (I) képletű vegyület



ahol a képletben

R jelentése  $C_{10-24}$ , előnyösen  $C_{17-19}$ , telítetlen szénhidrogéncsoport, amely legfeljebb háromszorosan szubsztituált lehet, amely szénhidrogéncsoport legalább 4 nem-konjugált kettős kötést tartalmaz;

L jelentése összekötő csoport, amely 1-5 atomos hidat képez az R csoport és a karbonil CO között, ahol L legalább egy heteroatomot tartalmaz, pl.: O-, S-, N-, vagy SO-t; és

X jelentése  $CHal_3$ , ahol Hal jelentése halogén; vagy ennek egy sója lupus nephritis vagy diabéteszes nefropátia kezelésében történő alkalmazásra.

2. Egy vegyület az előző igénypontok bármelyike szerinti alkalmazásra, ahol a szénhidrogéncsoport 5 - 7 kettős kötést tartalmaz.

3. Egy vegyület az 1-2. igénypontok szerinti alkalmazásra, ahol nincs karbonilcsoporttal konjugált kettős kötés.

4. Egy vegyület az 1-3. igénypontok bármelyike szerinti alkalmazásra, ahol az összes kettős kötés cisz konfigurációjú, vagy ahol az összes kettős kötés cisz konfigurációjú kivéve a karbonilcsoporthoz legközelebbi kettős kötést.

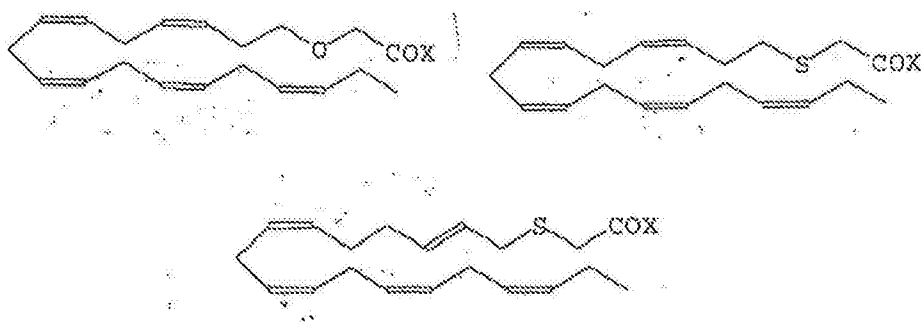
5. Egy vegyület az 1-4. igénypontok bármelyike szerinti alkalmazásra, ahol az L összekötő csoport  $-CH_2-$ ,  $-CH(C_{1-6}alkil)-$ ,  $-N(C_{1-6}alkil)-$ ,  $-NH-$ ,  $-S-$ ,  $-O-$ ,  $-CH=CH-$ ,  $-CO-$ ,  $-SO-$ , vagy  $-SO_2-$ csoportot tartalmaz, amelyek egymással bármely (kémiailag értelmes) elrendezésben kombinálhatók egy összekötő csoport képzésére, ahol L legalább egy heteroatomot tartalmaz.

6. Egy vegyület az előző igénypontok bármelyike szerinti alkalmazásra, ahol L jelentése  $-NH_2CH_2-$ ,  $-NH(Me)CH_2-$ ,  $-SCH_2-$ , vagy  $-SOCH_2-$ csoport.

7. Egy vegyület az 1-6. igénypontok szerinti alkalmazásra, ahol X jelentése  $CF_3$ .

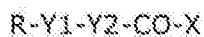
8. Egy vegyület az 1. igénypont szerinti alkalmazásra, amely alábbi képletű:





ahol a képletben X jelentése  $\text{CHAl}_3$ .

**9.** Egy (I') képletű vegyület az előző igénypontok bármelyike szerinti alkalmazásra



ahol a képletben

R és X jelentése az 1. igénypontban meghatározott;

Y1 jelentését az O, S, NH,  $\text{N}(\text{C}_{1-6}\text{-alkil})$ , SO vagy  $\text{SO}_2$  csoportok közül választjuk és

YZ jelentése  $(\text{CH}_2)_n$  vagy  $\text{CH}(\text{C}_{1-6}\text{ alkil})$  csoport; ahol

n értéke 1 és 3 közötti, előnyösen 1.

**10.** Egy alábbi képletű vegyület az előző igénypontok bármelyike szerinti alkalmazásra



vagy



ahol X jelentése  $\text{CF}_3$  csoport.

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