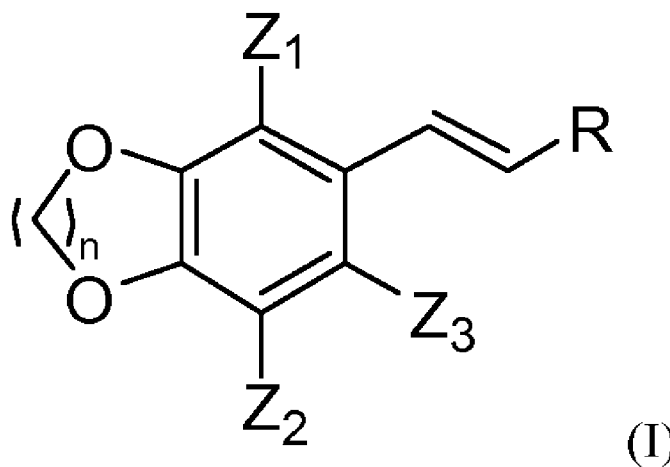




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(54) **Title:** USE OF STIRIPENTOL AND THEIR DERIVATIVES FOR DECREASING URINARY OXALATE CONCENTRATION IN AN INDIVIDUAL



(57) **Abstract:** The present invention relates to a compound of formula (I) : wherein: - n is 1 or 2; Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and - R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents chosen from a hydroxyl, an oxo and a thiol group; or one of its pharmaceutically acceptable salts; for use to decrease urinary oxalate concentration in an individual. The present invention further relates to a compound of formula (I) for use in the prevention and/or treatment of diseases and/or conditions related to a high urinary oxalate concentration in an individual.

## USE OF STIRIPENTOL AND THEIR DERIVATIVES FOR DECREASING URINARY OXALATE CONCENTRATION IN AN INDIVIDUAL

The present invention relates to compounds for their use to decrease urinary oxalate concentration in an individual and in particular for their use in the prevention  
5 and/or treatment of diseases and/or conditions related to a high urinary oxalate concentration in an individual.

As used herein, the term "urinary oxalate concentration" means oxalic acid and/or oxalate concentration in an individual's urine. This term may also refer to the quantity of oxalic acid and/or oxalate urinary excretion in a 24-hour period.

10 An increased content of urinary oxalate is one of the major causes of calcium oxalate supersaturation that lead to the formation of calcium oxalate crystals and thus to kidney stones. Indeed, most of the kidney stones are made of calcium oxalate crystals.

Urinary oxalate may come from oxalate intakes in food such as spinach, rhubarb, chocolate or tea which are well known to contain high amounts of oxalate.  
15 However, it mostly originates from an endogenous production of oxalate by the liver notably due to the oxidation reaction of glyoxylate to oxalate by lactate dehydrogenase isoform 5 (LDH-5).

It has to be noticed that oxalate may also be produced by the metabolization of ethylene glycol that could be ingested accidentally.

20 Thus, many diseases and/or conditions, like urolithiasis, also called urinary stone disease, hyperoxaluria and nephrocalcinosis are related to a high urinary oxalate concentration. Some renal failures may also be related to a high urinary oxalate concentration.

Hyperoxaluria is characterized by an urinary oxalate concentration above 0.25  
25 mmol/L or urinary oxalate excretion above 0.25 mmol/24 hours (Daudon M., *Ann Urol (Paris)*, 2005 Dec;39(6):209-31).

Regarding urolithiasis, it means a condition characterized by the presence of kidney stones in the kidney or in the urinary tract. This disease affects about 10 % of the population in western countries. Since a majority of urinary stones (75-80%) are made of  
30 calcium oxalate, the control of concentration of oxalate in urine is an important part of a medical treatment program to prevent stone formation or recurrence. Unfortunately, control of urinary oxalate concentration through the diet can produce only a partial effect,

because dietary oxalate contribution to urinary oxalate is only 8 to 40%, with the rest of it synthesized endogenously, mainly in liver.

At last, primary hyperoxaluria is a genetic disorder resulting from the mutation of liver enzymes and inducing increased production of glyoxylate that is converted into oxalate by LDH-5 (Cochat P *et al.*, *Nephrol Dial Transplant*. 2012 May;27(5):1729-36).

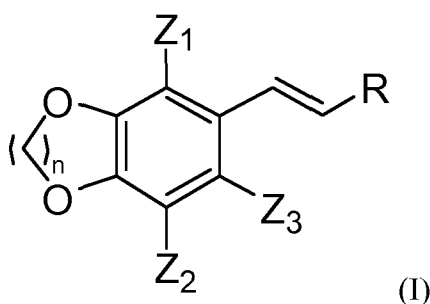
Three forms of the disease coexist: Type I, Type II and Type III primary hyperoxaluria which are respectively caused by mutations in the AGXT gene, in the GRHPR gene and in the HOGA1 gene.

In this disease, high amounts of oxalate are therefore excreted in the urine, leading to recurrent stone disease and kidney failure in young patients. These patients often need combined kidney and liver allografts.

For obvious reasons, lowering urinary oxalate in these patients can alleviate the severity of stone disease and avoid costly transplantation procedures.

It is accordingly essential to have efficient compounds that are able to decrease urinary oxalate concentration and thus to be used in the prevention and/or treatment of diseases and/or conditions related to a high urinary oxalate concentration.

Therefore, according to one of its aspects, the present invention relates to a compound of formula (I):



20

wherein:

- n is 1 or 2;
  - Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and
  - R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents chosen from a hydroxyl, an oxo and a thiol group;
- or one of its pharmaceutically acceptable salts;

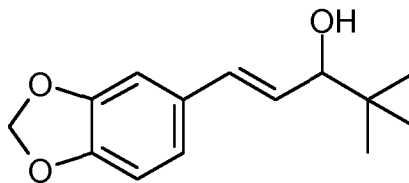
25

said compound of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms;

for use in the prevention and/or treatment of diseases and/or conditions related to a high urinary oxalate concentration in an individual.

5

Stiripentol, or 4,4-dimethyl-1-[(3,4-methylenedioxy)-phenyl]-1-penten-3-ol, is already proposed as an antiepileptic indicated in severe myoclonic epilepsy in infancy, in addition to the combination of sodium valproate and clobazam when the latter proves to be insufficient in controlling crises (Chiron *et al.* (2000) *Lancet* 356:1638-1642).



10

Stiripentol

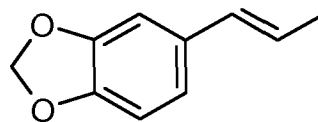
Among its main effects, Stiripentol inhibits the uptake of gamma-aminobutyric acid (GABA) and is also an inhibitor of several cytochrome P450 isoenzymes, especially CYP1A2 and CYP3A4 (Tran *et al.* (1997) *Clin. Pharmacol. Ther.* 62:490-504).

15

Stiripentol is also known for its use in the prevention or the treatment of peripheral neuropathy (EP 2 229 943 A1).

In particular, it has been shown that both Stiripentol and Isosafrole (3,4-methylenedioxyphenyl-1-propene) inhibit the pyruvate to lactate conversion by lactate dehydrogenase 1 and 5 (LDH-1 and LDH-5) in neurons (Sada N *et al.*, *Science* 2015 Mar 20;347(6228):1362-7).

20



Isosafrole

However, to the knowledge of the inventors, these compounds are proposed for the first time as active agent for lowering the content of urinary oxalate in an individual.

25

As shown in the following example, the inventors have unexpectedly identified that compounds of formula (I) enable to lower the content of urinary oxalate in an individual.

As a consequence, they are very efficient to limit calcium oxalate supersaturation and consequently the formation of kidney stones.

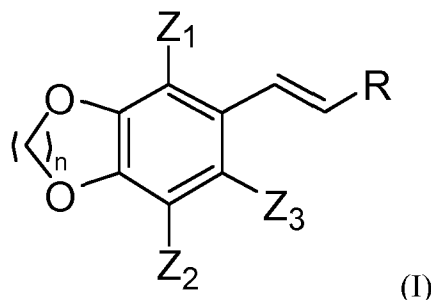
They are thus very useful for preventing or treating diseases characterized by a elevated urinary oxalate concentration such as urolithiasis and hyperoxaluria, more particularly primary hyperoxaluria.

For the purposes of the present invention:

- An “*individual*” is intended to mean an animal, preferably a mammal, including a non-human mammal, and is in particular a human.
- The term “*prevent*” means at least partly reducing the risk of manifestation of a given phenomenon, *i.e.*, in the present invention, a disease or a condition related to a high urinary oxalate concentration. A partial reduction implies that the risk remains, but to a lesser extent than before implementing the invention.
- A “*high urinary oxalate concentration*” or an “*elevated urinary oxalate content*” means an urinary oxalate concentration above 0.25 mmol/L, preferably above 0.3 mmol/L and more preferably above 0.5 mmol/L; or an urinary oxalate excretion above 0.25 mmol/24 hours, in particular above 0.3 mmol/24 hours and more particularly above 0.5 mmol/24 hours; or an oxalate/creatinine molar ratio above 0.03, preferably above 0.04 and more preferably above 0.05.

It has to be noticed that these values correspond to those of adults or children of more than 5 years old. In younger children, urinary oxalate excretion is physiologically more elevated and decreases progressively during infancy.

The present text also describes a compound of formula (I):



wherein:

- n is 1 or 2;
- Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and

- R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents chosen from a hydroxyl, an oxo and a thiol group;  
or one of its pharmaceutically acceptable salts;  
said compound of formula (I) being in all the possible racemic, enantiomeric and  
5 diastereoisomeric isomer forms;  
for use to decrease urinary oxalate concentration in an individual.

Other features and advantages of the invention will emerge more clearly from the description, the example which follow given by way of non-limiting illustration, and  
10 from the figure 1.

Figure 1 represents a graph that gives the average urinary oxalate/creatinine molar ratio measured in urine from 6 rats in cases a) (before the administration of Stiripentol), b) (after the two-days intake of Stiripentol at a daily dose of 100 mg/kg of rat) and c) (ten days after the two-day intake of Stiripentol).

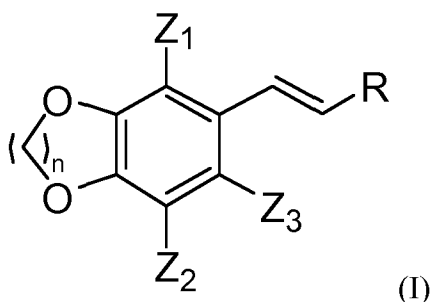
15 Figure 2 represents a graph that gives the percentages of kidney section coverage by calcium oxalate crystals measured in rats exposed to ethylene glycol and that have been or not treated with Stiripentol.

Figure 3 represents a graph that shows the benefit effect of Stiripentol on the renal function assessed by serum creatinine levels observed on rats intoxicated with  
20 ethylene glycol.

Figure 4 represents a graph that shows the benefit effect of Stiripentol on the preserved renal function assessed by serum creatinine levels observed on calcium-oxalate kidney stone murine.

## 25 COMPOUNDS OF FORMULA (I)

As above-mentioned, the compounds used according to the invention correspond to general formula (I):



wherein:

- n is 1 or 2;
- Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and
- R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents chosen from a hydroxyl, an oxo and a thiol group;

or one of its pharmaceutically acceptable salts;

said compound of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms.

Accordingly, the compounds of the invention may comprise one or several asymmetric carbon atoms. They thus may exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention. Further, the alkene function that is present in the compound of formula (I) can either be in the Z or in the E configuration, preferably, this alkene is in the E configuration.

The compounds of the invention may also exist in the form of bases or of acid-addition salts. These salts are pharmaceutically acceptable acids and also form part of the invention.

The term “*pharmaceutically acceptable*” means what is useful in preparing a pharmaceutical composition generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes what is acceptable for veterinary as well as human pharmaceutical use.

In addition to pharmaceutically-acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of the compounds, in the

preparation of other salts, or in the identification and characterization of the compounds or intermediates.

The compounds of the invention may also exist in the form of hydrates or solvates, *i.e.* in the form of associations or combinations with one or more molecules of  
5 water or with a solvent such as methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent. Such solvates are within the scope of the present invention.

10 In the context of the present invention, the following definitions apply:

- a halogen atom: a fluorine, a chlorine, a bromine or an iodine atom.
- C<sub>t</sub>-C<sub>z</sub>: a carbon-based chain possibly containing from t to z carbon atoms in which t and z may take values from 1 to 10; for example, C<sub>1</sub>-C<sub>3</sub> is a carbon-based chain possibly containing from 1 to 3 carbon atoms.

15 - an alkyl: a linear or branched saturated aliphatic group, in particular comprising from 1 to 6 carbon atoms. Examples that may be mentioned include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl. The alkyl groups may be more particularly selected from methyl and neopentyl groups.

- a hydroxyl group: a radical -OH.

20 - an oxo group: a radical =O.

- a thiol group: a radical -SH.

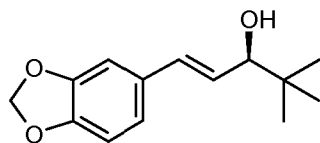
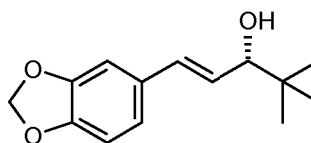
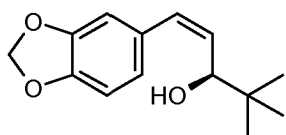
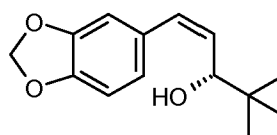
According to a preferred embodiment, n is 1 in the compound used in the invention.

25 According to another preferred embodiment, at least one from Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> is a hydrogen atom, in the compound used in the invention.

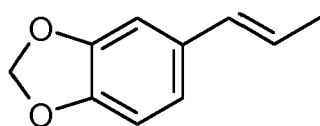
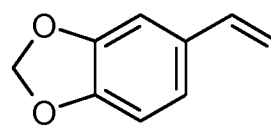
More preferably Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> are hydrogen atoms.

According to yet another preferred embodiment, the compound used in the invention is selected from 4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol  
30 (Stiripentol), 3,4-methylenedioxyphenyl-1-propene (Isosafrole) and their mixtures.

The four following stereoisomers of Stiripentol exist depending of the absolute configuration of the asymmetric carbon and of the alkene function:

*(R)-(E)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol*(S)-(E)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol*(S)-(Z)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol*(R)-(Z)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol

The two following stereoisomers of Isosafrole exist depending of the absolute configuration of the alkene function:

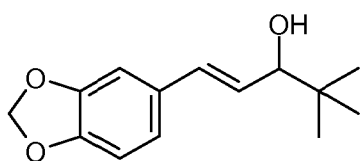
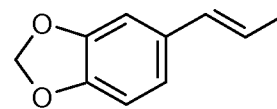
*(E)*-3,4-methylenedioxyphenyl-1-propene*(Z)*-3,4-methylenedioxyphenyl-1-propene

5

For both Stiripentol and Isosafrole, the alkene is preferably in the *(E)* configuration.

Concerning Stiripentol, it is preferably in the form of a racemic mixture of *(R)* and *(S)* enantiomer.

Thus, the compound used in the invention is more particularly selected from *(RS)-(E)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol, *(E)*-3,4-methylenedioxyphenyl-1-propene and their mixtures.

*(RS)-(E)*-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol*(E)*-3,4-methylenedioxyphenyl-1-propene

FR 2 173 691 describes the synthesis of Stiripentol starting from pinacolone and piperonal.

The skilled artisan is able to easily prepare the other compounds used in the invention starting from the teaching of FR 2 173 691 and by using methods well-known by the man skilled in the art.

15

Some compounds used in the invention are commercially available. Stiripentol (in the form of a racemic mixture with the alkene is in the (E) configuration) for instance, may be provided under the name Diacomit® sold by Laboratoires Biocodex.

5                    **THERAPEUTIC USE**

As specified previously and clearly illustrated by the following example, according to one of its aspects, the present invention relates to a compound of the present invention for use to decrease urinary oxalate concentration in an individual.

10                   In other terms, the invention concerns the use of a compound of the present invention to decrease urinary oxalate concentration in an individual.

In particular, as shown in the following example, some compounds of the invention like Stiripentol enable to reduce the urinary oxalate/creatinine molar ratio of an individual by at least 10%, preferably by at least 20%, more preferably by at least 30 % and even more preferably by at least 40 %.

15                   More particularly, the invention relates to a compound of the present invention for use in the prevention and/or the treatment of diseases and/or conditions related to a high urinary oxalate concentration in an individual.

20                   In other words, the invention concerns the use of a compound of the present invention to prevent and/or treat diseases related to a high urinary oxalate concentration in an individual.

In yet other words, the invention concerns the use of a compound of the present invention for the preparation of a medicament intended to prevent and/or to treat diseases and/or conditions related to a high urinary oxalate concentration in an individual.

In particular, said diseases and/or conditions may be selected from:

- 25                   - hyperoxaluria, in particular primary hyperoxaluria, preferably Type I, Type II or Type III primary hyperoxaluria,
- urolithiasis also called urinary stone disease in particular due to primary hyperoxaluria,
- nephrocalcinosis in particular due to primary hyperoxaluria, and
- 30                   - some renal failures, i.e. renal failures related to a high urinary oxalate concentration in an individual.

The compound according to the invention may also be useful to prevent and/or treat troubles caused by oxalate precipitation due to ethylene glycol poisoning.

According to another of its aspects, the invention is directed to a method for preventing and/or treating diseases and/or conditions related to a high urinary oxalate concentration in an individual, comprising at least a step of administering to said individual at least an effective amount of at least one compound in accordance with the invention as above defined.

The compound according to the invention may be used in a composition comprising a pharmaceutically acceptable excipient.

Such a composition is considered as a pharmaceutical composition or as a medicament and may more particularly contain an effective dose of at least one compound according to the invention as above defined.

An “*effective dose*” means an amount sufficient to induce a positive modification in the condition to be regulated or treated, but low enough to avoid serious side effects. An effective dose may vary with the pharmaceutical effect to obtain or with the particular condition being treated, the age and physical condition of the end user, the severity of the condition being treated/prevented, the duration of the treatment, the nature of other treatments, the specific compound or composition employed, the route of administration, and like factors.

A compound used according to the invention may be administered in an effective dose by any of the accepted modes of administration in the art.

In one embodiment, this compound may be used in a composition intended to be administrated by oral, rectal or parenteral injection route, preferably by oral route, in particular diluted in a drink such as water.

The term “*parenteral injection*” refers to an administration via injection under or through one or more layers of skin or mucus membranes of an individual. This injection may be for instance intradermal, subcutaneous, intravenous or intramuscular.

The route of administration and the galenic formulation will be adapted by one skilled in the art pursuant to the desired pharmaceutical effect.

One of ordinary skill in the art of therapeutic formulations will be able, without undue experimentation and in reliance upon personal knowledge, to ascertain a therapeutically effective dose of a compound of the invention for a given indication.

The compound of the invention may be administered to a subject once a week, twice a week, four times a week, once a day, twice a day, three times a day or more if necessary, and such administration can be for one day, two days, three days, four days, five days, or a week, two weeks, three weeks, a month, two months, four months, six months, more than six months, one year, two years, or continuously through the life of the patient. Such treatment may be continued to maintain the desired oxalate levels in a subject.

The daily dose may ranges from 20 to 150, preferably from 50 to 100 mg of compound of formula (I) or of its pharmaceutically acceptable salt/kg of the treated individual.

According to a preferred embodiment, the composition used in the invention is suitable for administering a daily dose comprising from 20 to 150, preferably from 50 to 100 mg of compound of formula (I) or of its pharmaceutically acceptable salt/kg of said individual, for a period of at least 1 day.

It has to be noted that such a daily dose may as well be administered for a period of 2 days, 1 week, 1 month, several months, one year and even for a longer duration.

A pharmaceutical composition of the invention may be formulated with any known suitable pharmaceutically acceptable excipients according to the dose, the galenic form, the route of administration and the likes.

As used herein, "*pharmaceutically acceptable excipients*" include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. Except insofar as any conventional excipient is incompatible with the active compounds, its use in a medicament or pharmaceutical composition of the invention is contemplated.

A medicament or pharmaceutical composition of the invention may be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, sprays, gels, soft and hard gelatine capsules, suppositories, sterile injectable solutions or sterile packages powders.

According to one embodiment, a pharmaceutical composition of the invention may be intended to be administered separately, sequentially or simultaneously with an agent useful for the prevention and/or the treatment of a disease and/or condition related to a high urinary oxalate concentration, in particular hyperoxaluria, nephrocalcinosis,

urolithiasis or some renal failures said agent being different from the compound of formula (I) of the invention and its pharmaceutically acceptable salts.

Among such agents the following ones may be cited: pyridoxamine, inhibitors of aldehyde dehydrogenase, inhibitors of glycolate oxidase; or in combination with therapies such as extracorporeal shock wave lithotripsy and reduced oxalate level diets. As used herein, the term "reduced oxalate level diet" means diet from which oxalate-rich foods (rhubarb, spinach and other leafy vegetables, cashews, almonds, and strong tea) have been eliminated.

10                   **EXAMPLE 1: Stiripentol assay (*in vivo*)**

The efficiency of Stiripentol to decrease the urinary oxalate concentration in rats has been evaluated in this example.

**Protocol**

15                   The experiment has been performed on 6 adult Sprague-Dawley rats that have not previously been treated.

100 mg/kg of rat of Stiripentol (Diacomit® sold by Laboratoires Biocodex) has been administered to the rats by oral route in drinking water over a period of 24 hours. This protocol has been repeated the next day.

Rats had a free access to water during the experiment.

20                   In order to obtain more reliable data, the urinary oxalate/creatinine molar ratio has been measured instead of the urinary oxalate concentration. Indeed, the content of creatinine, which is a metabolic waste of creatine excreted in the urine, is constant over 24 hours for an individual, whereas the urinary oxalate concentration may varies depending on the quantity of drink consumption. The urinary oxalate/creatinine molar ratio measurement thus enables to overcome the problem of dilution of the urines.

25                   This ratio has been measured in the urine of the 6 rats by using metabolic cages (commercialized by Techniplast) that collect urine during 24 hours. More particularly, the oxalate urine level has been measured by chromatography with a column commercialized by Dionex and the urine creatinine level has been measured by an enzymatic method with a Konelab apparatus.

30                   For the 6 rats, the urinary oxalate/creatinine molar ratio has been measured three times in the urine collected in the metabolic cages:

- a) before the administration of Stiripentol,
- b) after the two-days intake of Stiripentol, and
- c) ten days after the two-day intake of Stiripentol.

5 The urinary calcium/creatinine molar ratio has been measured for the 6 rats in cases a), b) and c) in the same way as the urinary oxalate/creatinine molar ratio to ensure that Stiripentol affects oxalate concentration and not creatinine concentration in the oxalate/creatinine molar ratio (control measurements).

### **Statistical analysis**

10 Statistical analysis was done using unpaired Student t test and Mann Whitney test.

A p value of less than 0.05 was considered as significant.

Statistical analysis was completed using Statview software

### **Results**

15 The average urinary oxalate/creatinine molar ratios obtained for the 6 rats in cases a), b) and c) are presented in Figure 1.

It can be seen that measures a) and c) gave the same result, *i.e.* an urinary oxalate/creatinine molar ratio of about 0,163, whereas measure b) gave a ratio of about 0,093 ( $p=0.03$ ).

20 Regarding the control measurements (not represented in Figure 1), the intake of Stiripentol has shown no effect on the urinary calcium/creatinine molar ratio.

It thus appears that Stiripentol is able to significantly reduce the urinary oxalate concentration and therefore to decrease calcium oxalate supersaturation and the risk of calcium oxalate stone formation.

25 Stiripentol is thus suitable for the prevention and/or treatment of a disease and/or condition related to a high urinary oxalate concentration such as primary hyperoxaluria, urolithiasis, nephrocalcinosis and some renal failures.

### **EXAMPLE 2**

30 Efficiency of Stiripentol to protect against ethylene glycol intoxication has been evaluated in this example.

A murine model of ethylene glycol poisoning has been prepared by giving 6g/kg ethylene glycol orally once to twelve adult Sprague-Dawley rats (single oral administration).

5 Among these rats, 6 received in addition 300 mg/kg Stiripentol (Diacomit®) at the time of the intoxication and in drinking water at day one and day 2 after intoxication (4g/L). Rats had a free access to water during the experiments.

Rats have been sacrificed 48 hours after ethylene glycol intake, blood and urine parameters have been collected and kidneys have been removed for histopathological analyses.

10 The histopathological analyses of kidneys from rats exposed to ethylene glycol show that these kidneys were full of calcium oxalate crystals whereas those receiving Stiripentol in addition contained much less crystals (Figure 2,  $p=0.004$ ).

Renal function assessed by serum creatinine levels was remarkably less impaired in animals receiving stiripentol (Figure 3,  $p=0.009$ ).

15 Accordingly, these results show that Stiripentol at therapeutic range (and by extent isosafrole) decreases urinary oxalate excretion induced by ethylene glycol poisoning and therefore decreases calcium oxalate supersaturation and the risks of calcium oxalate crystals formation and renal failure.

20

### **EXAMPLE 3**

Efficiency of Stiripentol to protect against calcium oxalate kidney stones has been evaluated in this example.

25 A calcium-oxalate kidney stone murine model has been generated. Twelve adult Sprague-Dawley rats received calcium chloride (2 g/l) and hydroxyproline (20g/L), an aminoacid transformed into oxalate by liver enzymes including LDH-5, in drinking water.

The rats have been exposed for 4 month to this diet.

30 Among these rats, 6 received in addition Stiripentol (Diacomit®) in drinking water at 4g/L, corresponding to about 150 mg/Kg in adult rats.

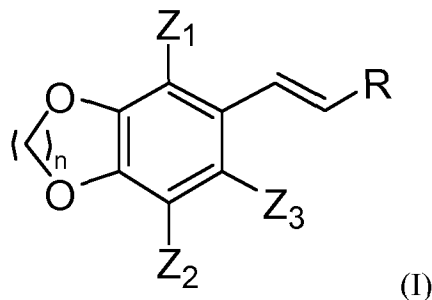
Rats have been sacrificed at the end of the protocol and kidneys have been removed for analyses.

Rats receiving Stiripentol had less calcium oxalate crystals in urine and a preserved renal function assessed by serum creatinine levels when compared to controls at the end of the 4-months protocol (Figure 4;  $p=0.002$ ).

Thus, stiripentol is clearly efficient to prevent calcium oxalate stone formation,  
5 particularly in cases at risk of renal failure such as patients affected by primary hyperoxaluria and more generally in kidney stone formers affected by hyperoxaluria.

### CLAIMS

1. Compound of formula (I) :



5 wherein:

- n is 1 or 2;
- Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and
- R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents

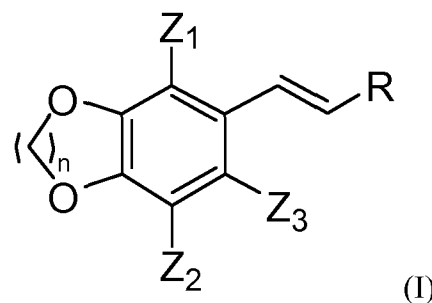
10 chosen from a hydroxyl, an oxo and a thiol group;

or one of its pharmaceutically acceptable salts;

said compound of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms;

15 for use in the prevention and/or treatment of diseases and/or conditions related to an urinary oxalate concentration above 0.25 mmol/L, or an urinary oxalate excretion above 0.25 mmol/24 hours or an oxalate/creatinine molar ratio above 0.03 in an individual.

2. Compound of formula (I) :



wherein:

- 20
- n is 1 or 2;
  - Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, identical or different, are selected from a hydrogen atom, a halogen atom and a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; and

- R is an optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl group by one or more substituents chosen from a hydroxyl, an oxo and a thiol group;

or one of its pharmaceutically acceptable salts;

said compound of formula (I) being in all the possible racemic, enantiomeric and  
5 diastereoisomeric isomer forms;

for use in the prevention and/or treatment of diseases and/or conditions related to a high urinary oxalate concentration in an individual,

said diseases and/or conditions being selected from hyperoxaluria, in particular primary hyperoxaluria, urolithiasis, nephrocalcinosis and some renal failures.

10           3. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to claim 1 or 2, wherein n is 1.

4. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of the preceding claims, wherein at least one from Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> is a hydrogen atom, preferably Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> are hydrogen atoms.

15           5. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of the preceding claims, selected from 4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol (Stiripentol), 3,4-methylenedioxyphenyl-1-propene (Isosafrole) and their mixtures, preferably selected from (RS)-(E)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol, (E)-3,4-methylenedioxyphenyl-1-propene  
20 and their mixtures.

6. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of the preceding claims, wherein the individual is a mammal, in particular a human.

25           7. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of the claims 1 and 3 to 6, wherein the diseases and/or conditions are selected from hyperoxaluria, in particular primary hyperoxaluria, urolithiasis, nephrocalcinosis and some renal failures.

30           8. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of the preceding claims, wherein it is in a composition comprising a pharmaceutically acceptable excipient.

9. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to claim 8, wherein the composition is administered by oral, rectal or parenteral injection route, preferably by oral route.

5 10. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to claim 8 or 9, wherein the composition is in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, sprays, gels, soft and hard gelatine capsules, suppositories, sterile injectable solutions or sterile packages powders.

10 11. Compound for use of formula (I) or one of its pharmaceutically acceptable salts according to any one of claims 8 or 10, wherein the composition is suitable for administering a daily dose comprising from 20 to 150, preferably from 50 to 100 mg of compound of formula (I) or of its pharmaceutically acceptable salt/kg of said individual, for a period of at least 1 day.

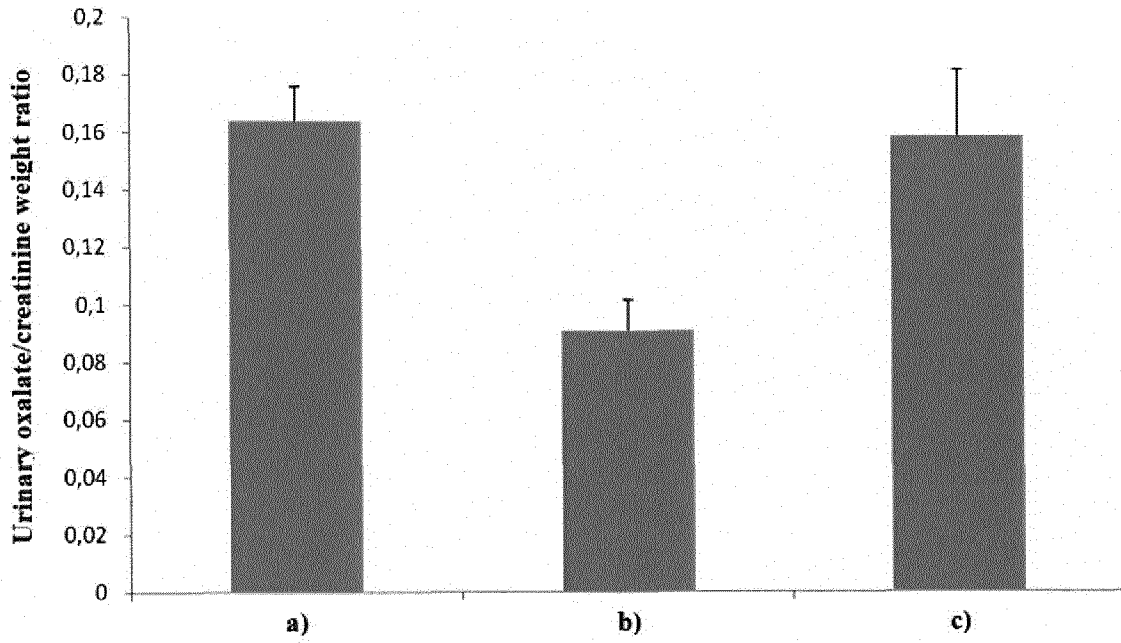


FIGURE 1

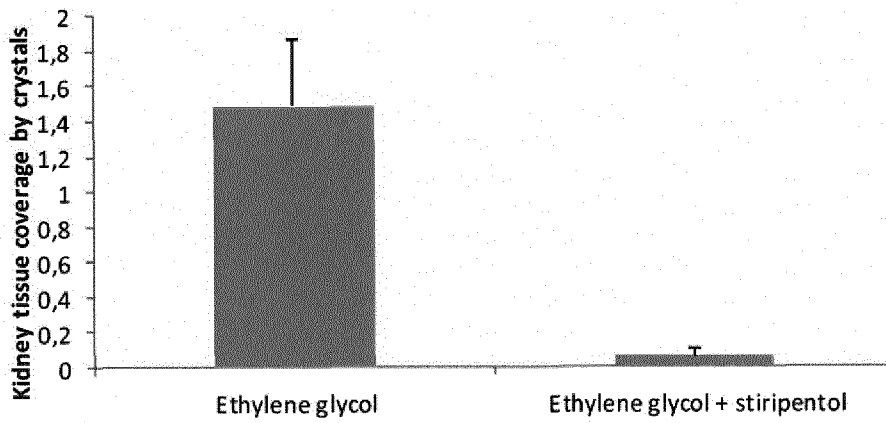
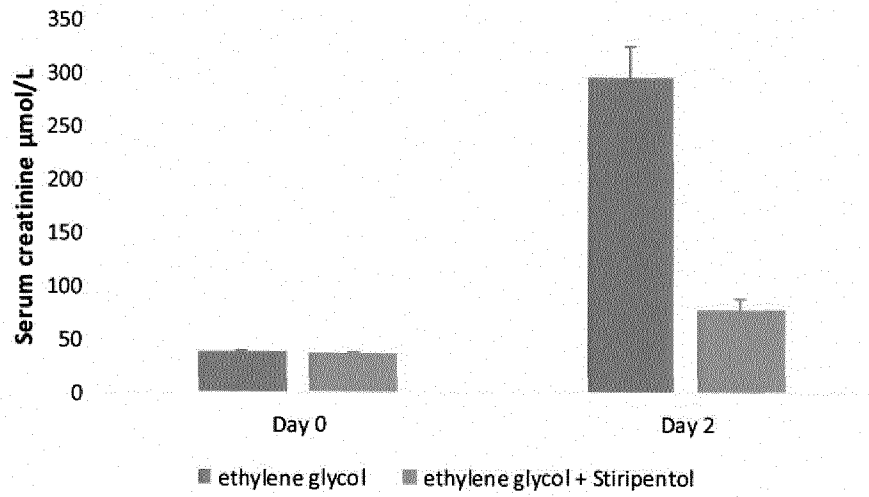
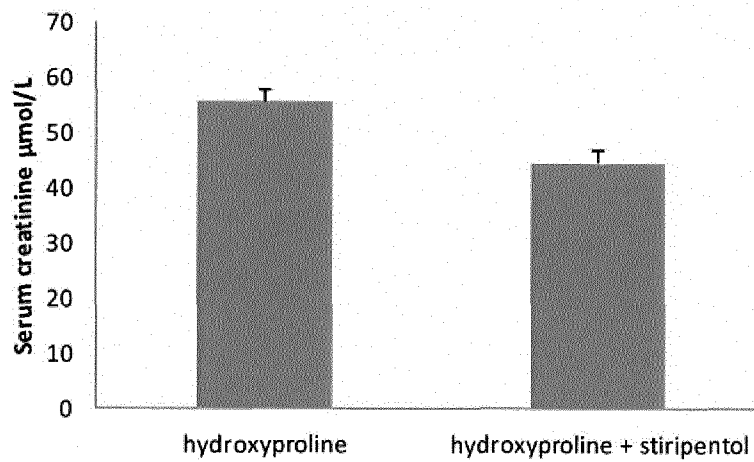


FIGURE 2



**FIGURE 3**



**FIGURE 4**

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/053245

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D317/54 A61K31/343 A61P13/04 A61P13/12 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Antônio Da Silva Novaes ET AL: "Diuretic and antilithiasic activities of ethanolic extract from Piper amalago (Piperaceae)", Phytomedicine, vol. 21, no. 4, 1 March 2014 (2014-03-01), pages 523-528, XP055262277, AMSTERDAM, NL ISSN: 0944-7113, DOI: 10.1016/j.phymed.2013.10.014 page 526, paragraph Discussion - page 527; compounds 3, 4	1-11
A	----- WO 2008/058269 A2 (FOLDRX PHARMACEUTICALS INC [US]; BULAWA CHRISTINE [US]; FLEMING JAMES) 15 May 2008 (2008-05-15) page 90; claims 1,12; compound Piperine ----- -/--	1-11
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance	"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	
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 22 March 2017	Date of mailing of the international search report 06/04/2017	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sotoca Usina, E	

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/053245

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/159839 A2 (ARDEA BIOSCIENCES INC [US]; OUK SAMEDY [US]; VERNIER JEAN-MICHEL [US];) 22 December 2011 (2011-12-22) Page 125 compounds on second row second column and fifth row first column; paragraph [00232]; claims 17, 31-32 -----	1-11
A	WO 2009/062118 A2 (FOLDRX PHARMACEUTICALS INC [US]; BULAWA CHRISTINE ELLEN [US]; DEVIT MI) 14 May 2009 (2009-05-14) Compounds on: - Figure 1b, 5th page of the figures: first column fifth row -Figure 1d, 17th page of the figures: first column second row; claims 1,72 -----	1-11

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International application No

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