ISOSORBIDE MONONITRATE DERIVATIVES FOR THE TREATMENT OF INTESTINAL DISORDERS

FIELD OF THE INVENTION

The present invention relates to the use of disulfide, sulfide, sulfoxide and sulfone derivatives of dianhydrohexite mononitrate of formula (I), tautomers, pharmaceutically acceptable salts, prodrugs and solvates thereof in the prevention and/or treatment of intestinal disorders.

BACKGROUND

Inflammatory bowel disease (IBD) is the generic term for a disease of an unknown cause that produces chronic inflammation or ulceration of the mucosa of the large and small intestine. This inflammatory bowel disease includes such diseases as ulcerative colitis and Crohn's disease.

The presently available medical treatments for IBD generally involve drug therapy directed towards the suppression of gastrointestinal inflammation. The most commonly used medicaments to treat IBD are anti-inflammatory drugs such as salicylates. The salycilate preparations may be effective in treating mild to moderate disease. Examples of salicylates include sulfasalazine, olsalazine and mesalamine. All of these medicaments are given orally in high doses for maximal therapeutic benefit. These medicaments are not without side effects including heartburn, nausea, vomiting, diarrhea and headache. People with more severe IBD can be treated with corticosteroids, such as prednisone and hydrocortisone, which are more potent and faster-acting than salicylates in the treatment of IBD, but are endowed with potential side effects. In IBD patients that do not response to salicylates or corticosteroids, medicaments that suppress the immune system are used. However, immunosuppressants cause increase risk of infection, renal failure, and may increase the need for hospitalization. Drugs like antidiarrheals, laxatives and pain relievers can be also given to help relieve symptoms. Since all the available medical treatments for IBD are rather unsatisfactory and often ineffective, there is currently a great need for novel drugs capable of treating IBD and preventing relapse.

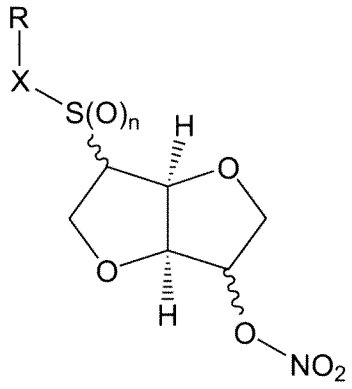
Disulfide, sulfide, sulfoxide and sulfone derivatives of dianhydrohexite mononitrate have been used or evaluated in various studies related to different pathological conditions mediated by defects in the NO pathway, such as cardiovascular disorders [WO00/20420 and WO2005/037842]. However, with all of these studies, there has been no recognition that these compounds are capable of being effective in the treatment of intestinal disorders, such as intestinal inflammatory.

BRIEF DESCRIPTION OF THE INVENTION

The inventors have found surprisingly that compounds of formula (I), and specially 2-acetylthioisosorbide-5-mononitrate, have potential therapeutic effect against intestinal disorders, more specifically intestinal inflammation.

The new application of these compounds is based on the results obtained by *in vivo* experiments in animals subjected to different stimulus such as intestinal inflammation, wherein it has been observed that administration of compounds of formula (I) reduces significantly the adverse effect. Therefore, these compounds have a great efficacy in the reduction of intestinal disorders caused by different stimulus.

Accordingly, the present invention relates to the use of a compound of formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

wherein:

n is an integer selected from 0, 1 and 2;

X is $-S(O)_m-$, -(C=O)- or a single bond, wherein m is an integer selected form 0, 1 and 2, with the proviso that when X is –(C=O)- then n is 0;

R is hydrogen or a residue R^a, wherein R^a is selected from the group consisting of:

C_{1-6} alkyl;

C_{2-6} alkenyl;

C_{3-8} cycloalkyl;

C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;

C_{4-8} cycloalkenyl;

phenyl;

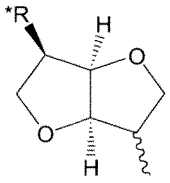
pyridyl;

thiophenyl;

nitrosyl;

S-cysteinyl;

S-glutathionyl; and



wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

and wherein R^a is optionally substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

as active ingredient(s) in the manufacture of a pharmaceutical composition for the prevention and/or treatment of intestinal disorders.

In a particular embodiment, the intestinal disorder is intestinal inflammation.

In another aspect, the present invention refers to a compound of formula (I) as defined above for the treatment or prophylaxis of an intestinal disorder.

Finally, another aspect of the present invention relates to a method of preventing and/or treating an intestinal disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) as defined above or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

In the above definition of compounds of formula (I) used in the present invention, the following terms have the meaning indicated:

"C_{1-6} alkyl" as used herein refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing no insaturation, having one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, e. g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, etc.

"C_{2-6} alkenyl" as used herein refers to a straight or branched chain alkenyl moiety consisting of carbon and hydrogen atoms, having one to six carbon atoms and at least one double bond of either E or Z stereochemistry where applicable, e.g., vinyl, allyl, 1- and 2-butenyl, and 2-methyl-2-propenyl.

"C_{3-8} cycloalkyl" as used herein refers to an alicyclic group consisting of carbon and hydrogen atoms, having three to eight carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Accordingly, the term "C_{3-8} cycloalkyl wherein one CH_2 group is replaced by O, S, NH or NCH_3" as used herein refers to an alicyclic group having from three to eight carbon atoms wherein one CH_2 group is replaced by O, S, NH o NCH_3, e.g., tetrahydropyrane, tetrahydrofurane, pyrrolidine, piperidine and tetrahydrothiophene.

"C_{4-8} cycloalkenyl" as used herein refers to an alicyclic group consisting of carbon and hydrogen atoms, having four to eight carbon atoms, e.g., cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

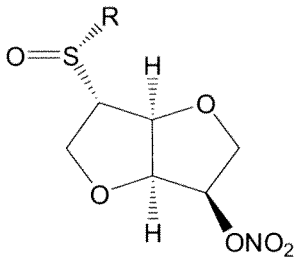
"Halogen" as used herein refers to fluorine, chlorine, bromine or iodine, whereof bromine is preferred.

It is preferred that R represents hydrogen C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, (C_{1-6} alkyl)C_{3-8} cycloalkyl, (C_{1-6} alkyl)C_{4-8} cycloalkenyl, phenyl or (C_{1-6} alkyl)phenyl, whereas C_{1-6} alkyl is especially preferred.

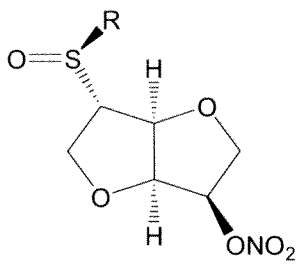
It is further preferred that in formula (I) either one or both of m and n is 0.

Also it is preferred that X represents a single bond or –S-.

It is especially preferred that in the compounds of formula (I), $RXS(O)_n$- and ONO_2 are trans to each other with respect to the ring plane. The compound of formula (I) also include (R) and (S) diastereoisomers according to the formula (Ia) and (Ib):



(Ia)



(Ib)

Especially preferred compounds of formula (I) are:

2-thioisosorbide 5-mononitrate;

5,5'-dinitrate-2,2'-dithiodiisosorbide;

2-methylthioisosorbide 5-mononitrate;

2-[(R)-methylsulfinyl]isosorbide 5-mononitrate;

2-[(S)-methylsulfinyl]isosorbide 5-mononitrate;

2-methylsulfinylisosorbide 5-mononitrate;

2-methylsulfonylisosorbide 5-mononitrate;

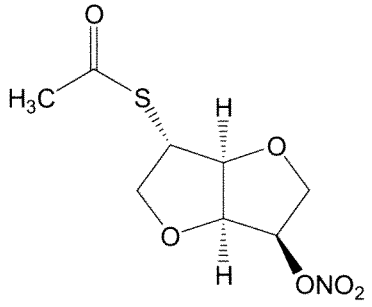
S-nitroso-2-thioisosorbide 5-mononitrate;

2-(tetrahydropyran-2-yl-thio) isosorbide 5-mononitrate;

2-(isosorbidyl-2'-dithio) isosorbide 5-mononitrate; and

2-(5'-acetyloxyisosorbidyl-2'-dithio) isosorbide 5-mononitrate.

Further it is especially preferred to use 2-acetylthio-isosorbide-5-mononitrate:



a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof as active ingredient for the manufacture of a pharmaceutical composition for the prevention and/or treatment of an intestinal disorder.

In a particular embodiment the intestinal disorder is intestinal inflammation.

Unless otherwise stated, the compounds used in the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

The term "pharmaceutically acceptable salts, solvates, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs and derivatives can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds used in the invention are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium, ammonium, magnesium, aluminium and lithium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylenethanolamine, triethanolamine, glucamine and basic aminoacids salts.

Particularly favoured derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a

biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, depending on the functional groups present in the molecule and without limitation, the following derivatives of the present compounds: esters, amino acid esters, phosphate esters, metal salts sulfonate esters, carbamates, and amides. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al. "Textbook of Drugdesign and Discovery" Taylor & Francis (april 2002).

The compounds used in the present invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates).

The compounds of formula (I) or their salts or solvates used in the invention are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, "inter alia", having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I), or of its salts, solvates or prodrugs.

The compounds used in the present invention represented by the formula (I) can include enantiomers, depending on the presence of chiral centers, and/or depending on the presence of multiple bonds (for example Z, E). The pure isomers, enantiomers or diastereoisomers and their mixtures are within the scope of the present invention.

The compounds of formula (I) used in the invention can be obtained by available synthetic procedures. Some examples of these procedures are described in WO2005/037842 and references therein. The content of these documents is incorporated herein by reference in its entirety.

In a particular embodiment of the present invention, the compounds of formula (I) used in the treatment of intestinal disorders, are formulated in a suitable pharmaceutical composition, in a therapeutically effective quantity, together with one or more pharmaceutically acceptable carriers, adjuvants or excipients.

The pharmaceutical composition may be administered in the form of different preparations. Non limiting examples are preparations for oral administration, e.g. tablets, capsules, syrups or suspensions; ophthalmological administration, e.g. solutions, suspensions, ointments or creams; and parenteral administration, e.g. aqueous and non-aqueous sterile injection solutions or aqueous and non-aqueous sterile suspensions. Also, the pharmaceutical composition may include topical compositions, e.g. creams, ointments or pastes, or transdermic preparations such as patches or plasters. The pharmaceutical composition may also be prepared for vaginal or for rectal administration, e.g. rectal gel or suppository.

Generally an effective administered amount of a compound used in the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.01 to 100 mg/kg/day.

The compounds used in the present invention may also be administered with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

In another particular embodiment the invention refers to the use of a compound of formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof, for the elaboration of a pharmaceutical composition for the treatment and/or prevention of an intestinal disorder. In a preferred embodiment, the intestinal disorder is an intestinal inflammation.

In vivo experiments in animals subjected to different stimulus such as high intestinal inflammation have shown that administration of compounds of formula (I), reduce significantly these adverse effects. Therefore, these compounds have a great efficacy in the reduction of intestinal disorders caused by different stimulus.

EXAMPLES

Example 1.- *Results derived from the administration of 2-acetylthioisosorbide-5-mononitrate in mice which have been subjected to indomethacin-induced intestinal inflammation.*

Intestinal inflammation were induced by administration of two subcutaneous injections of 7.5 mg/kg indomethacin, as previously described Porras M., Martin MT., Soler M. and Vergara P., "Intestinal motor disorders associated with cyclical bacterial overgrowth in a rat model of enteritis". *Am. J. Physiol. Gastrointest. Liver Physiol.* (2004), **287**:G58-G64, and Porras M., Martin MT., Torres R. and Vergara P., "Cyclical upregulated iNOS and long-term downregulated nNOS are the bases for relapse and quiescent phases in a rat model of IBD". *Am. J. Physiol. Gastrointest. Liver Physiol.* (2006), **290**:G423-G430.

Once the intestinal inflammation has been induced, one group of mice were treated with 30 mg of the compound 2-acetylthioisosorbide-5-mononitrate per kg of body weight, being dissolved this compound in water and administered orally. For comparative data, the compound isosorbide-5-mononitrate (IS-5-MN), structurally similar to 2-acetylthioisosorbide-5-mononitrate, was also administered to another group of mice.

Myeloperoxidase (MPO) activity was measured as an inflammation index in homogenized tissue samples after centrifugation using a specific ELISA kit (HyCult biotechnology, Uden, The Netherlands). In addition, since the barrier function of the intestinal mucus is deteriorated when the epithelium is inflamed and, as a consequence, the exposed bacteria cross the membrane and enter in the blood current, bacterial translocation was measured by detection of viable enteric bacteria in mesenteric lymph nodes as described by [M Mainous MR., Tso P., Berg R.D. and Deitch E.A., *Arch Surg* (1991) **126**:33-37] as additional measure of inflammation degree.

Studies of the route, magnitude, and time course of bacterial translocation in a model of systemic inflammation were achieved as describe in *Arch Surg* **126**:33-37, 1991. Bacterial translocation was expressed as the number of positive cultures with respect to the total number of samples in each group and motor activity was measured as the contracting activity expressed as the total number of spontaneous contractions recorded at duodenum per minute. Results are given in Table 1.

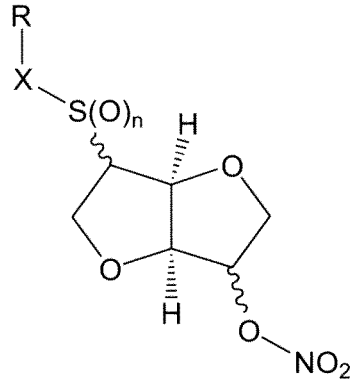
Table 1

Group	Bacterial translocation		MPO activity ng/ml	Contractions/min
	E. coli	Enterococcus sp		
Control	1/6	0/6	5±1	0.25±0.1
Intestinal inflammation	4/6	4/6	25±2	0.6±0.1
IS-5-MN	3/6	3/6	19±4	0.5±0.1
2-acetyl thioisosorbide-5-mononitrate	2/6	1/6	10±2*	0.2±0.1

These results point out that compound 2-acetylthioisosorbide-5-mononitrate leads to a significant reduction of MTO activity when compared to a structurally similar compound. In addition, the bacterial translocation is also reduced avoiding the entry of bacteria to the blood current, therefore confirming the utility of the compounds of the invention for treating intestinal inflammation.

CLAIMS

1. Use of a compound of formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

wherein:

n is an integer selected from 0, 1 and 2;

X is –S(O)m-, -(C=O)- or a single bond, wherein m is an integer selected form 0, 1 and 2, with the proviso that when X is –(C=O)- then n is 0;

R is hydrogen or a residue Ra, wherein Ra is selected from the group consisting of:

C_{1-6} alkyl;

C_{2-6} alkenyl;

C_{3-8} cycloalkyl;

C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;

C_{4-8} cycloalkenyl;

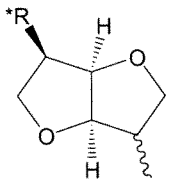
phenyl;

pyridyl;

thiophenyl;

S-cysteinyl;

S-glutathionyl; and



wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

and wherein R^a is optionally substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

as active ingredient(s) in the manufacture of a pharmaceutical composition for the prevention and/or treatment of intestinal disorders.

2. The use according to claim 1 wherein the intestinal disorder is intestinal inflammation.

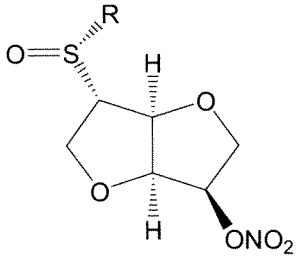
3. The use according to claims 1 or 2 wherein either one or both of m and n is 0.

4. The use according to any one of claims 1 to 3 wherein X represents a single bond or –S-.

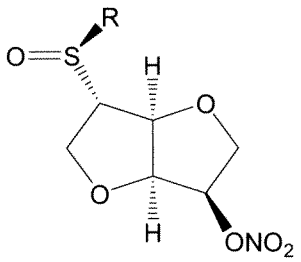
5. The use according to any one of claims 1 to 4 wherein R is hydrogen C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, (C_{1-6} alkyl)C_{3-8} cycloalkyl, (C_{1-6} alkyl)C_{4-8} cycloalkenyl, phenyl or (C_{1-6} alkyl)phenyl.

6. The use according to any one of claims 1 to 5 wherein R is C_{1-6} alkyl.

7. The use according to any one of claims 1 to 6 wherein the compound according to formula (I) is a compound of formula (Ia) or (Ib):



(Ia)



(Ib)

8. The use according to any one of claims 1 to 7 wherein the compound of formula (I) is selected from:

2-thioisosorbide 5-mononitrate;

5,5'-dinitrate-2,2'-dithiodiisosorbide;

2-methylthioisosorbide 5-mononitrate;

2-[(R)-methylsulfinyl]isosorbide 5-mononitrate;

2-[(S)-methylsulfinyl]isosorbide 5-mononitrate;

2-methylsulfinylisosorbide 5-mononitrate;

2-methylsulfonylisosorbide 5-mononitrate;

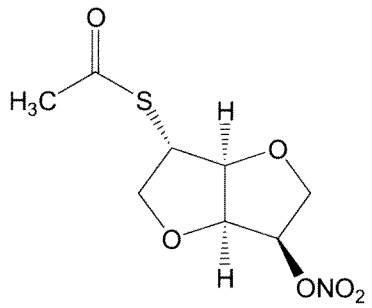
S-nitroso-2-thioisosorbide 5-mononitrate;

2-(tetrahydropyran-2-yl-thio) isosorbide 5-mononitrate;

2-(isosorbidyl-2'-dithio) isosorbide 5-mononitrate; and

2-(5'-acetyloxyisosorbidyl-2'-dithio) isosorbide 5-mononitrate.

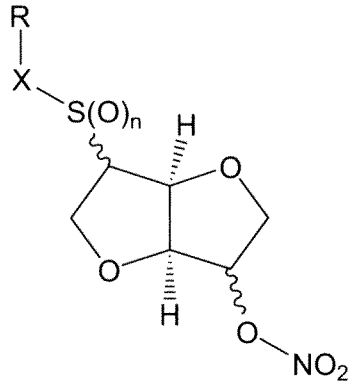
9. The use according to claim 1 wherein the compound is 2-acetylthioisosorbide 5-mononitrate which is represented by the following formula:



10. A compound of formula (I) as defined in any of claims 1 or 3 to 9, for the treatment or prophylaxis of intestinal disorders.

11. The compound according to claim 10 wherein the intestinal disorder is intestinal inflammation.

12. A method of preventing and/or treating intestinal disorders, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

wherein:

n is an integer selected from 0, 1 and 2;

X is –S(O)m-, -(C=O)- or a single bond, wherein m is an integer selected form 0, 1 and 2, with the proviso that when X is –(C=O)- then n is 0;

R is hydrogen or a residue Ra, wherein Ra is selected from the group consisting of:

C_{1-6} alkyl;

C_{2-6} alkenyl;

C_{3-8} cycloalkyl;

C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;

C_{4-8} cycloalkenyl;

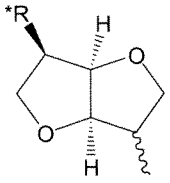
phenyl;

pyridyl;

thiophenyl;

S-cysteinyl;

S-glutathionyl; and



wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

and wherein R^a is optionally substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen.