NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

Field of the invention

The present invention is directed to a new use of nitric oxide-releasing Non Steriodal Antiinflammatory Drugs (NO-releasing NSAIDs). More particularly the invention is directed to the use of NO-releasing NSAIDs for the manufacture of a medicament for the treatment of bacterial infections, paticularly caused or mediated by *Helicobacter pylori* as well as a combination with acid susceptible proton pump inhibitors for the treatment of bacterial infections.

Background of the invention and prior art

NSAIDs, are among the most commonly prescribed and used drugs world wide. Despite the therapeutic benefits of NSAIDs, their use is limited. The use of NSAIDs may lead to gastric mucosal damage due to inhibited production of prostaglandins which increases the risk of gastrointestinal side-effects.

A recent proposal for reducing the side-effects associated with NSAIDs treatment is to use nitric oxide-releasing NSAID derivatives (NO-releasing NSAIDs) (*del Soldato P et al., NO-releasing NSAID:s , A novel class of safer and effective antiinflammatory agents; Inflammopharmacology, 1996; 4; 181-188*). NO-releasing NSAIDs reduce the gastrointestinal side-effects but still have the pharmacological activity characteristic of the frequently used NSAIDs.

NO-releasing NSAIDs and pharmaceutically acceptable salts thereof are for instance described in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

Helicobacter pylori is a gram-negative spirilliform bacteria which colonises in the gastric mucosa. The relationship between gastrointestinal disorders and infections with

Helicobacter pylori proposed in 1983 by Warren (*Warren JR Lancet 1983;1.1273*) is well established today.

A number of different therapies have been proposed for the treatment of *Helicobacter pylori* infections. Combination therapies are commonly used. The most commonly used comprise a proton pump inhibitor in combination with one or more antibacterial compounds such as claritromycin and amoxicillin. For instance WO93/00327 discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH, and an acid degradable antibacterial compound. Some of these therapies also comprise a bismuth compound, se for instance WO 98/03219 and WO98/22117, which latter application discloses a composition containing bismuth, an antimicrobial agent and a non-steriodal antiinflammatory agent for the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

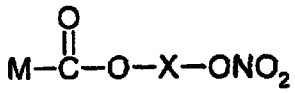
In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

Outline of the invention

It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

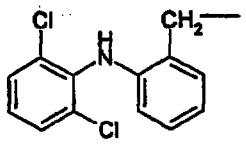
The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

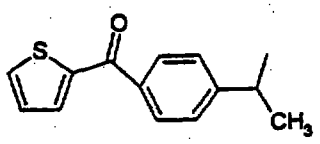
Preferably the NO-releasing NSAID is defined by the formula I

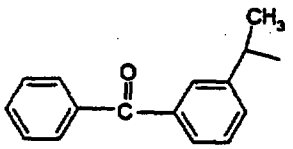


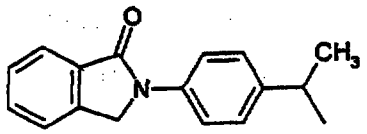
I

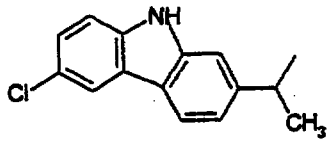
wherein M is selected from anyone of

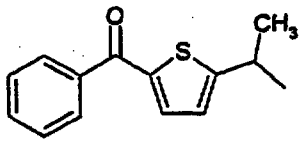


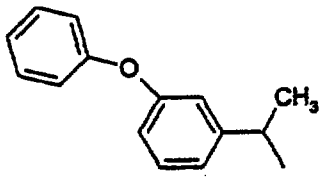


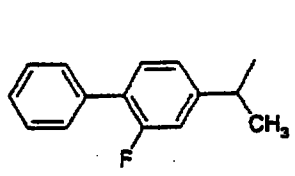


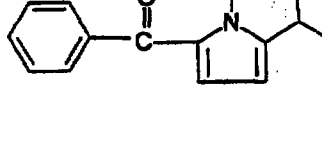


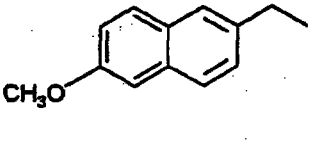


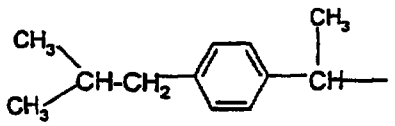


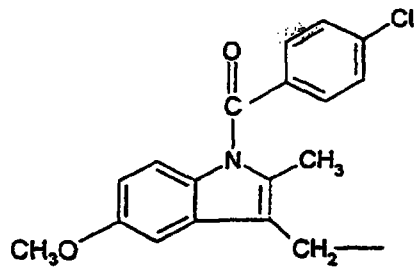


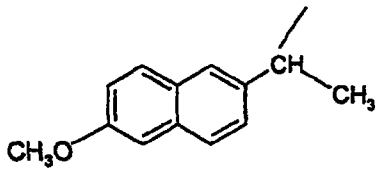


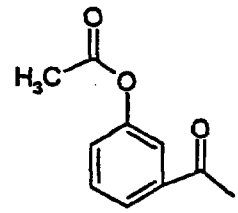










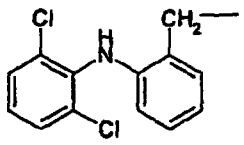
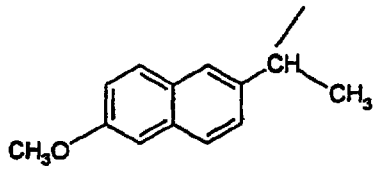
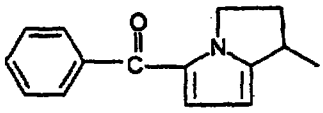
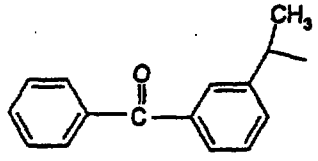


and X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID moiety, or a pharmaceutically acceptable salt or enantiomer thereof;

X is preferably selected from linear, branched or cyclic $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

M is not limited by the above definition but may be any other compound giving the corresponding NSAID by hydrolysis of the compound according to formula I.

In a preferred embodiment of the invention M is selected from

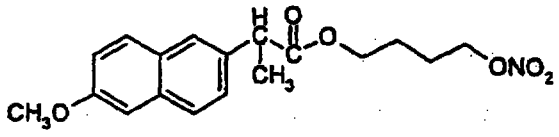





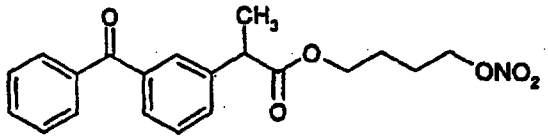
and X is selected from

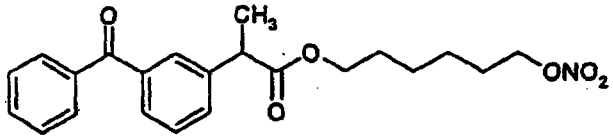
linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6;

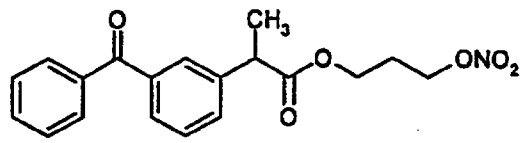
$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

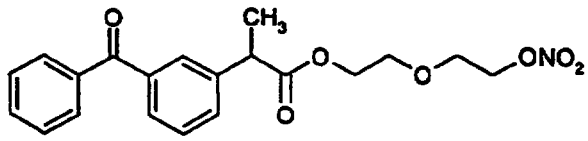
In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas

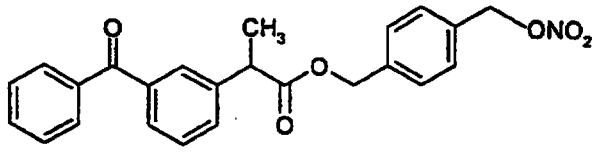

(Ia)
;

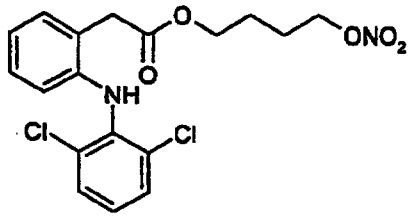

(Ib)
;

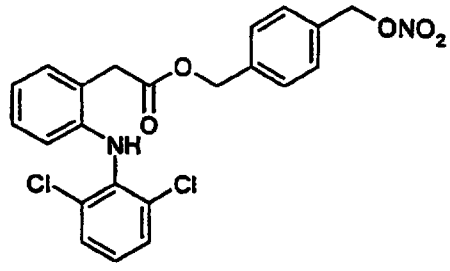

(Id)
;

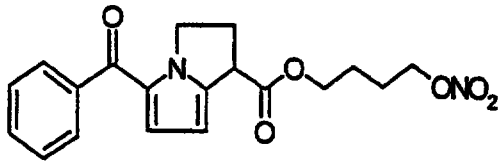

(Ic) ;

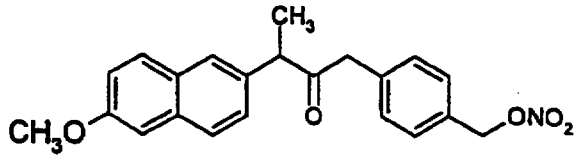

(Ie) ;

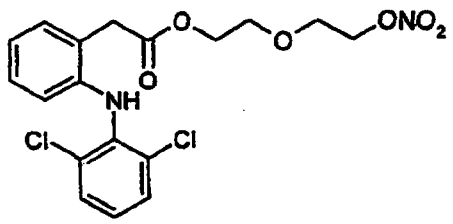

(If) ;


(Ig) ;

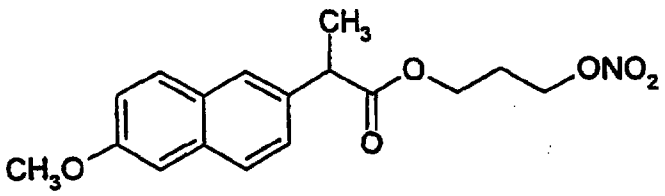

(Ii) ;


(Ij) ;

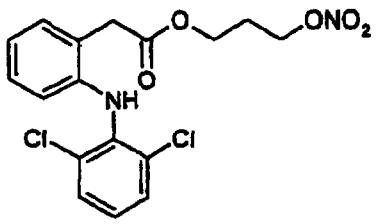

(Ik) ;



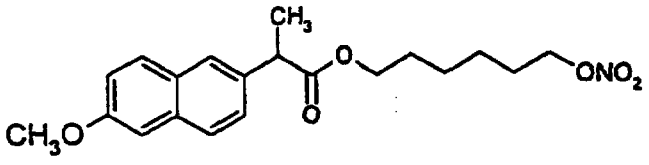
(IL) ;



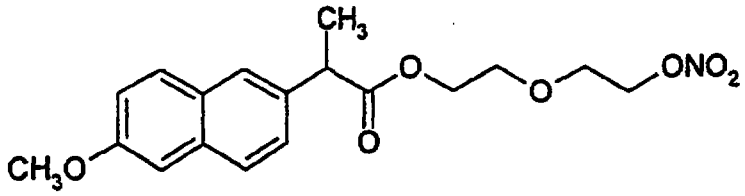
(Im) ;



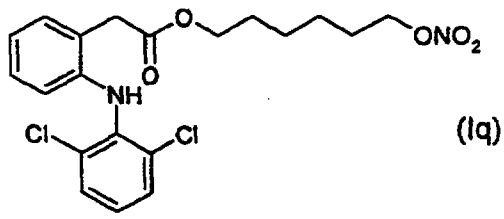
(In) ;



(Io) ;



(Ip) ; and



(Iq)

In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

A further aspect of the invention is the use of a NO-releasing NSAID, preferably a compound of the formula I above, in the manufacture of a medicament for use in the treatment of *Helicobacter pylori* infections, especially in the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori.*

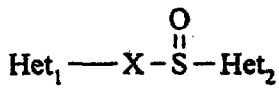
Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

Also a pharmaceutical formulation suitable for use in the treatment of bacterial infections, which formulation comprising a NO-releasing NSAID, preferably a compound of the formula I, is within the scope of the invention.

Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultanous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

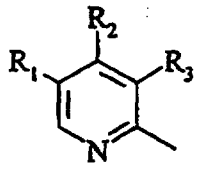
An acid susceptible proton pump inhibitor is, for instance, a compound of the general formula II



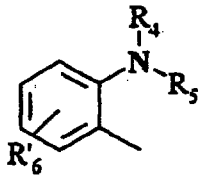
II

wherein

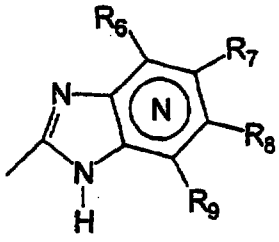
Het_1 is



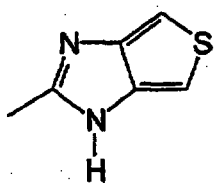
or



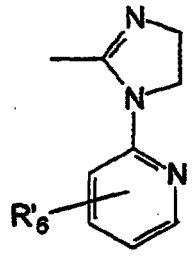
Het_2 is



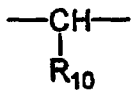
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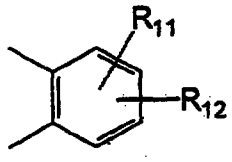
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

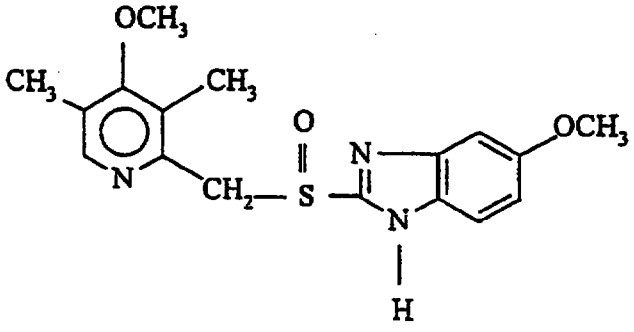
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

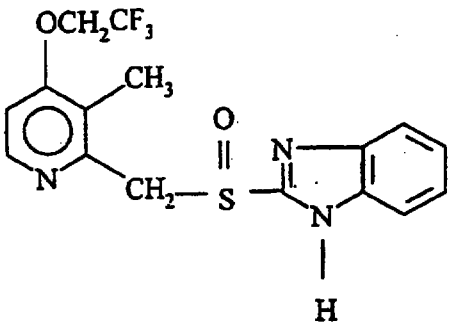
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof. The substituents may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

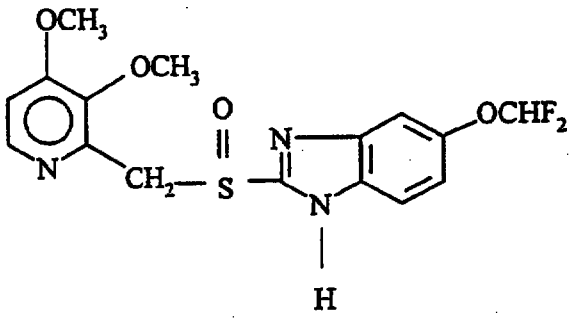
Examples of proton pump inhibitors according to formula II are



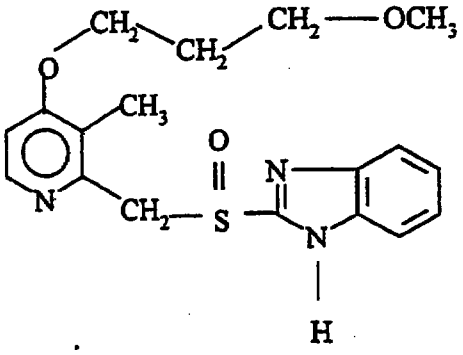
Omeprazole



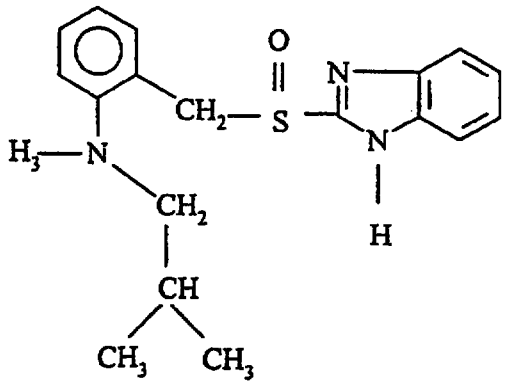
Lansoprazole



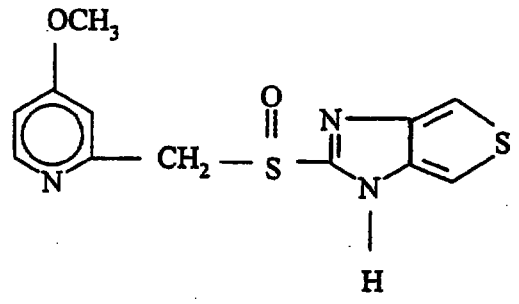
Pantoprazole

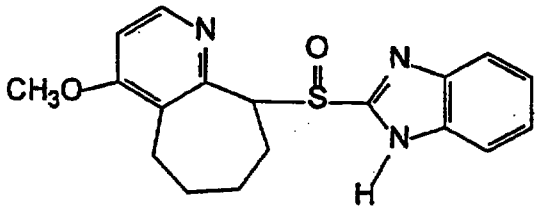


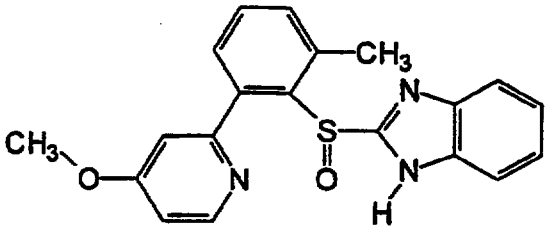
Pariprazole

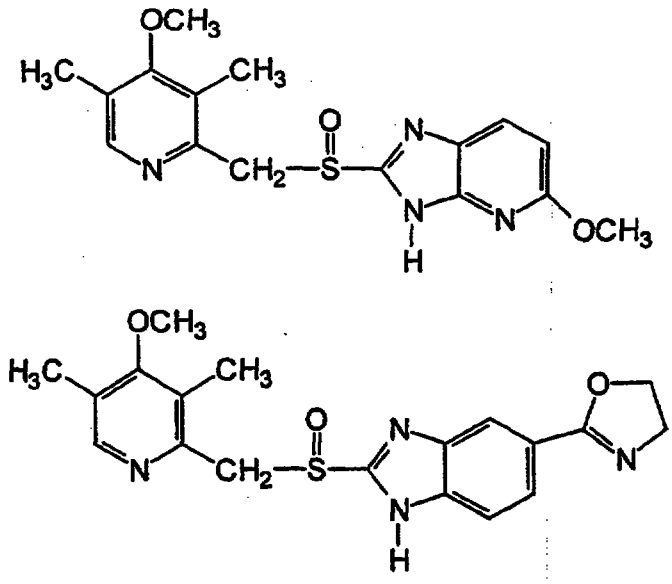


Leminoprazole









The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

Preferably the proton pump inhibitor omeprazole, or an alkaline salt of omeprazole, such as the magnesium salt, or (*S*)-omeprazole or an alkaline salt of (*S*)-omeprazole, such as the magnesium salt is used in the claimed combination.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, and further the especially suitable compounds are described in WO95/01977 and WO94/27988.

According to the invention there is further provided a method for treating bacterial infections, particularly *Helicobacter Pylori* infections, which method comprises simultaneous, separate or sequential administration to a subject suffering from a bacterial infection one or more pharmaceutical formulations comprising a NO-releasing NSAID, preferably a compound according to the formula I, and an acid susceptible proton pump

inhibitor. Also pharmaceutical formulations for simultaneous, separate or sequential administration to be used in the treatment of bacterial infections, which formulations comprise an NO-releasing NSAID, preferably a compound of the formula I and an acid susceptible proton pump inhibitor are within the scope of the invention.

The NO-releasing NSAID alone or in combination with an acid susceptible compound may be in a dosage form administered orally, rectally, epidurally, intravenously, intramuscularly, subcutanously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

The active compound(-s) are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active compound(-s) varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.5 – 5000 mg, preferably 5 – 1000 mg, of the NO-releasing NSAID. If a combination with a proton pump inhibitor is used 0.5 – 5000 mg of the NO-releasing NSAID, and 0.1 – 200 mg of the proton pump inhibitor will be comprised in each dosage form, or in two separate dosage forms. Preferably, the amount of the NO-releasing NSAID in each dosage form is 5 – 1000 mg, and the amount of the proton pump inhibitor 10 - 80 mg.

Detailed description of the invention

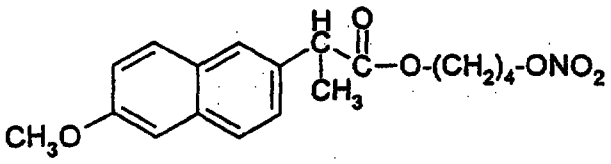
The invention is described in more detail by the following non-limiting examples.

The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

Example 1.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (National Type Culture Collection, from Smittskyddsinstitutet in Solna, Sweden), an antibiotic sensitive reference strain

Substance:



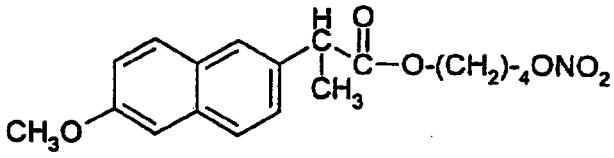
Ia

Helicobacter pylori was grown on blood agar plates, having a diameter of 90 mm, for three days under microaerophilic conditions at 37°C. The bacteria were suspended in PBS (phosphate buffer saline) to approximately 10^8 cfu/ml. Approximately 2 ml of the suspension was added to one agar plate and spread even on the surface of the agar. Overflow was removed with a syringe. Wells, like small holes, 3 mm in diameter, were made in the agarplate by removing agar. Three wells per plate were made.
A stock solution of a compound of the formula Ia having the concentration 100 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.
Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 2.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (see Example 1), an antibiotic sensitive reference strain

Substance:



Ia

The plates with the wells were prepared according to Example 1.

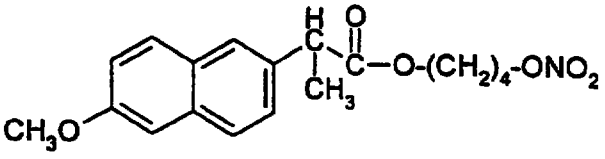
A stock solution of a compound of the formula Ia having the concentration 10 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 3.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

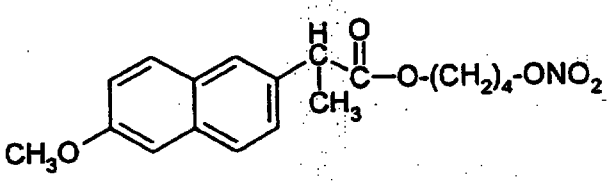
The plates with the wells were prepared according to Example 1.
A stock solution of a compound of the formula Ia having the concentration 1 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 13 mm.

Example 4.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

The plates with the wells were prepared according to Example 1.

A stock solution of a compound of the formula Ia having the concentration 100 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 10.4 mm.

Comparative tests

Example A

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around the each well was 16.6 mm.

Example B

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 1000 µg/ml was prepared.
30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example C

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 100 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example D

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

The plates with the wells were prepared according to Example 1.

A stock solution of SNAP with the concentration 10 000 µg/ml was prepared.
30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example E

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Di-methyl-sulphate-oxide (DMSO)

The plates with the wells were prepared according to Example 1.

A solution of DMSO alone with the concentration 20 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

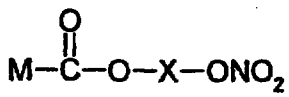
Result: No inhibition zones around the wells were formed.

Claims

1. Use of a NO-releasing NSAID as well as a pharmaceutically acceptable salt or an enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections.

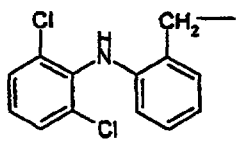
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential administration in the treatment of bacterial infections.

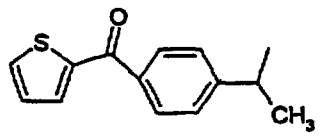
3 Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I

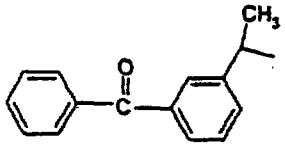


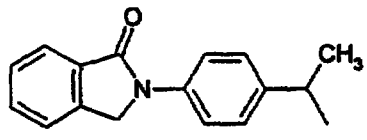
I

wherein M is selected from anyone of

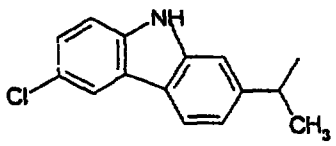
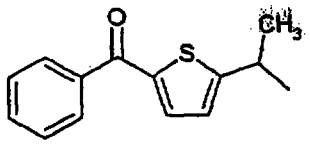
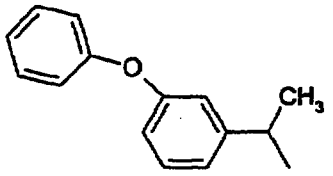
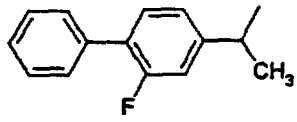
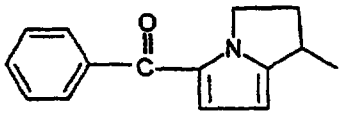
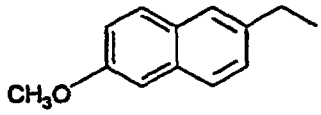
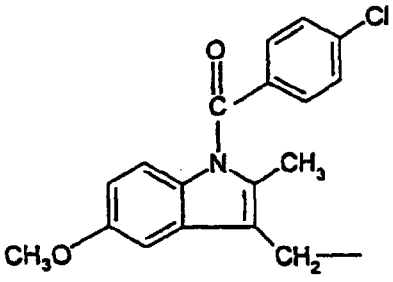
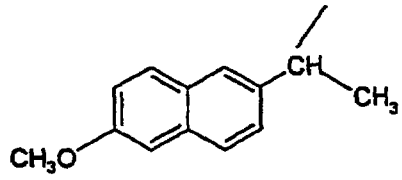
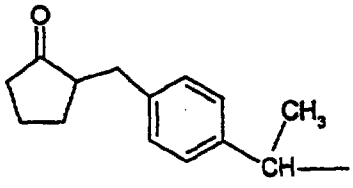
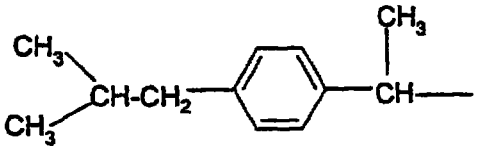








* C L M S *

and X is selected from

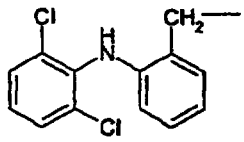
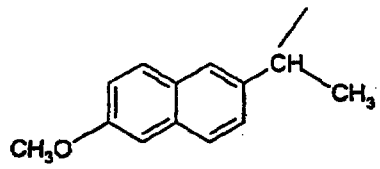
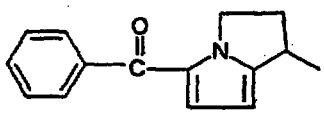
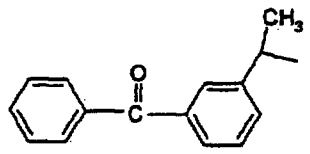
linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to10; and $-CH_2-pC_6H_4-CH_2-$,

or a pharmaceutically acceptable salt or enantiomer thereof.

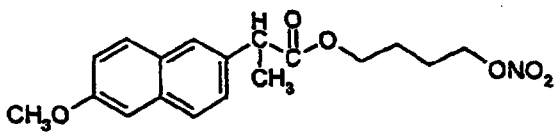
4. Use according to claim 3 wherein M in formula I is selected from

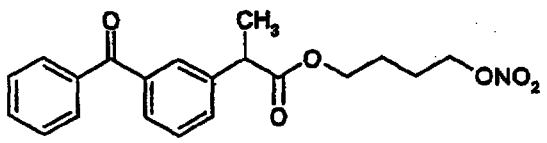
* C L M S *

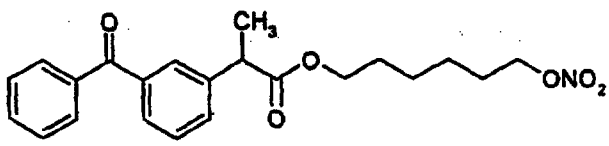





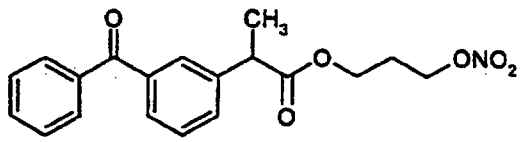
5. Use according to claim 3 or 4 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

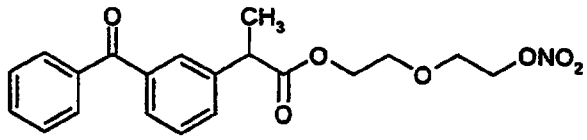
6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq

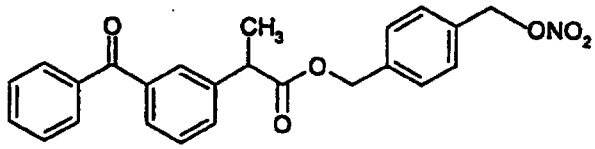

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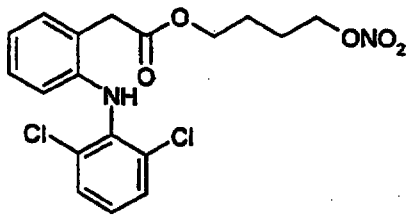

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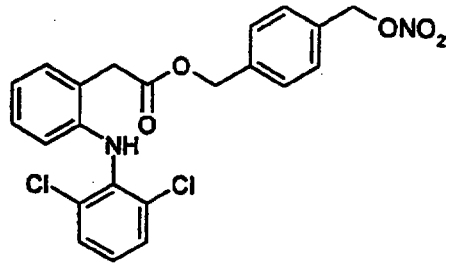

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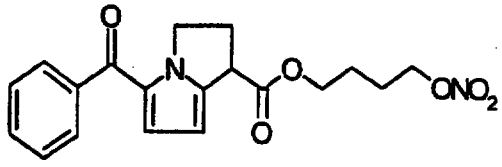

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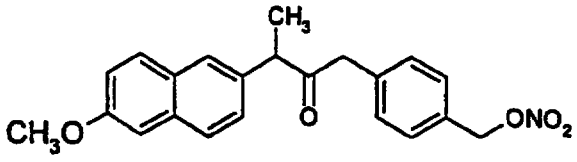

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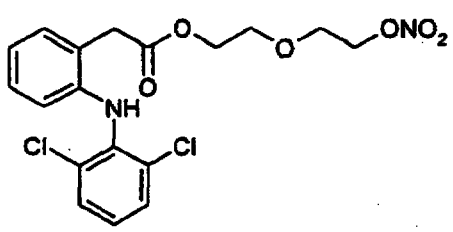

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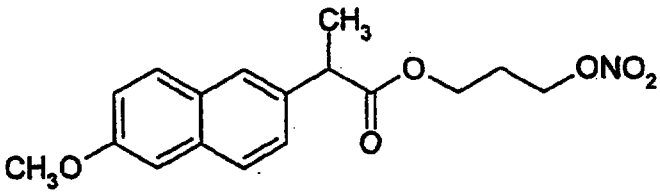

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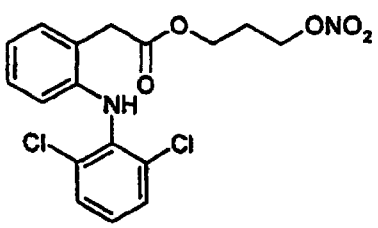

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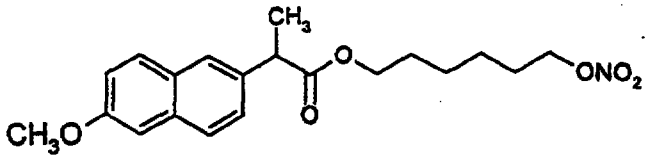
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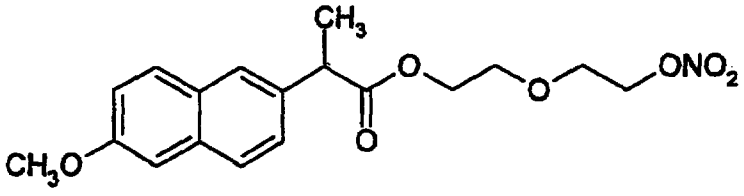
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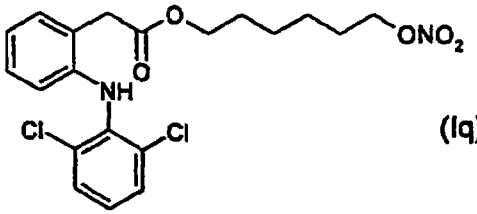
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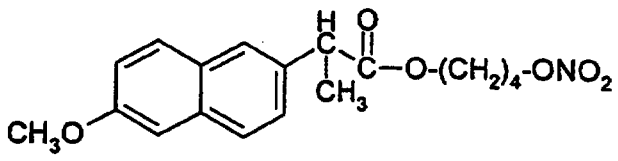
(Ip) ; and



(Iq)

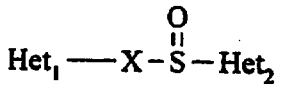
CLMS

7. Use according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

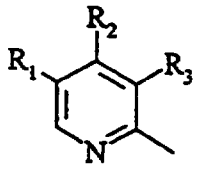
8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



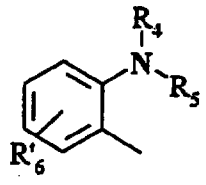
II

wherein

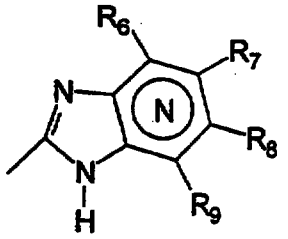
Het_1 is



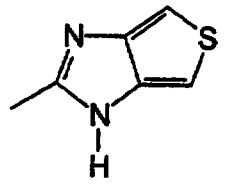
or



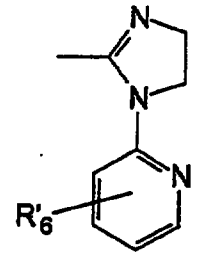
Het_2 is



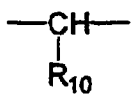
or



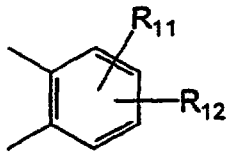
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

9. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof.

* C L M S *

10. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

11. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

12. Use according to any one of the preceeding claims 1 to 11, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

13. Use according to claim 1, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

14. Use according to claim 13, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

15. Use according to claim 2, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

16. Use according to claim 15, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

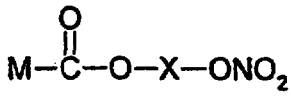
17. A method for the treatment of a bacterial infection, comprising administering to a patient suffering from said bacterial infection, an effective amount of a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof.

18. A method for the treatment of a bacterial infection, comprising simultaneously, separately or sequentially administration to a patient suffering from said bacterial infection,

* C L M S *

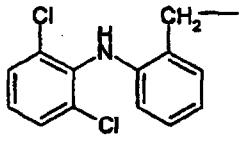
an effective amount of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer.

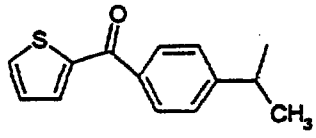
19. A method according to claim 17 or 18 wherein the NO-releasing NSAID is a compound of the formula I

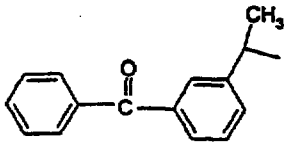


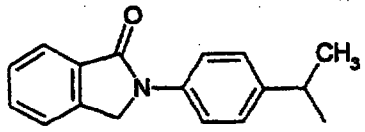
I

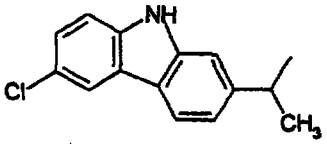
wherein M is selected from

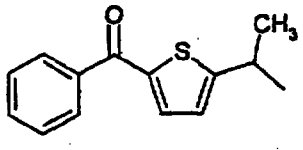


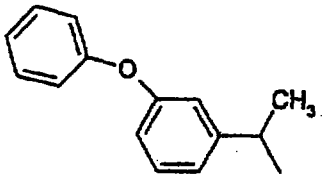


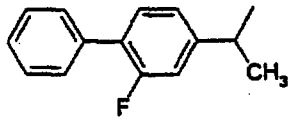


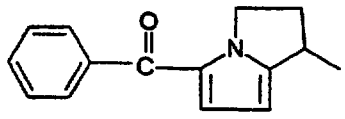
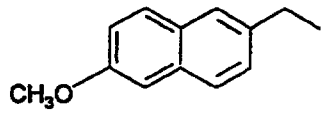
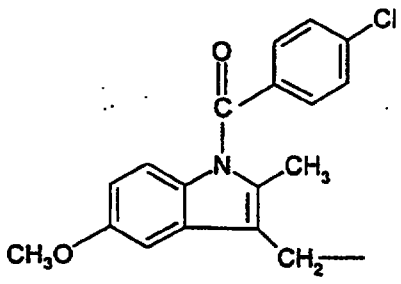
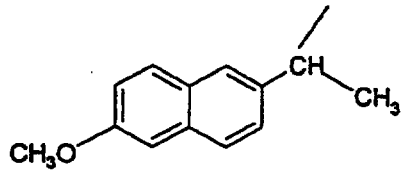


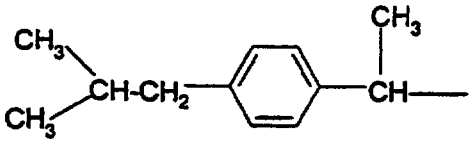










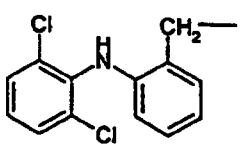
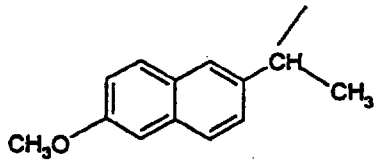
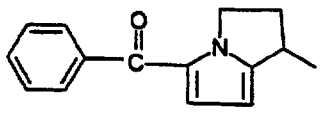
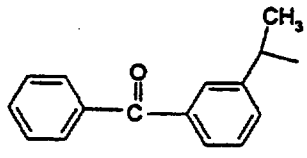
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

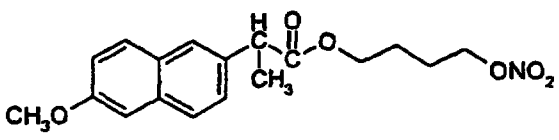
or a pharmaceutically acceptable salt or enantiomer thereof.

20. A method according to claim 19 wherein M in formula I is selected from

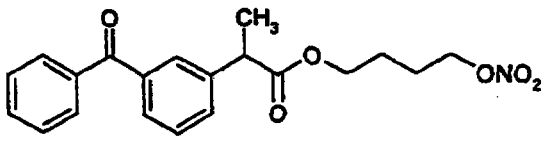





21. A method according to claim 19 or 20 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

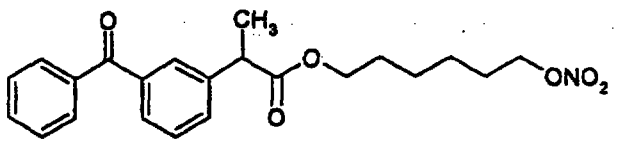
22. A method according to any one of claim 17 – 19, wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq



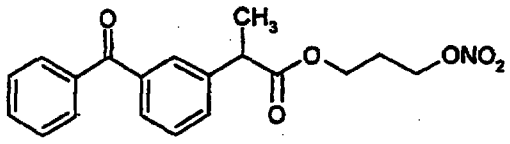
(Ia) ;



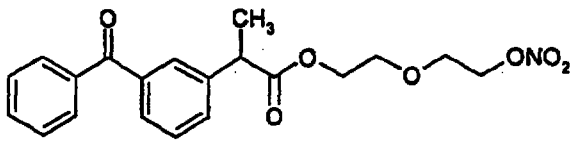
(Ib) ;



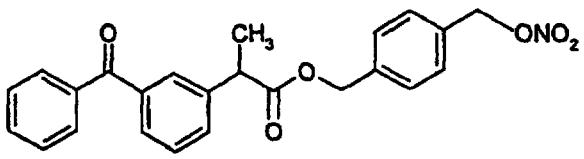
(Id) ;



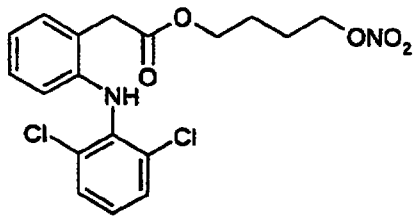
(Ic) ;



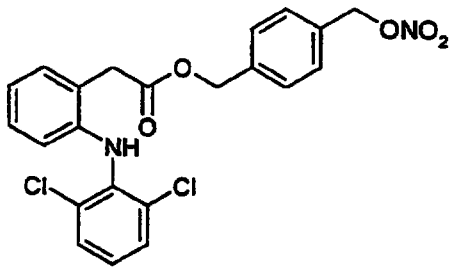
(Ie) ;



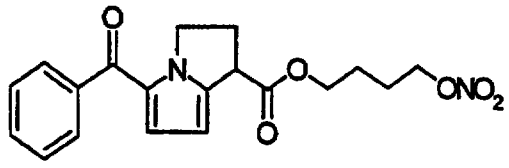
(If) ;



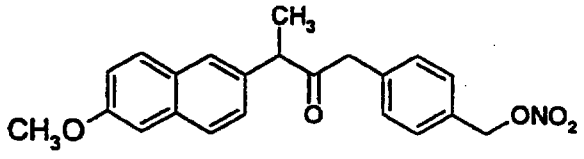
(Ig) ;



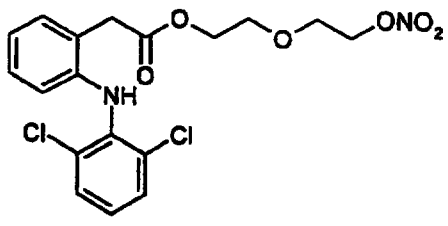
(Ii) ;



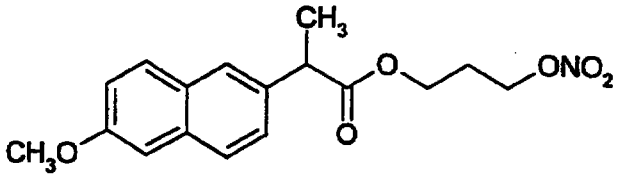
(Ij) ;



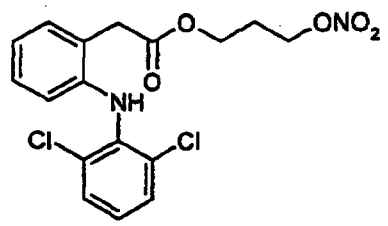
(Ik) ;



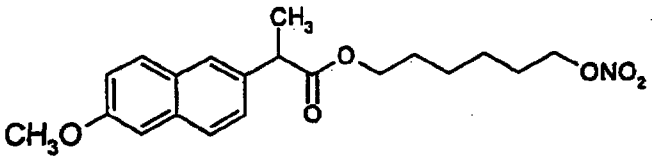
(IL) ;



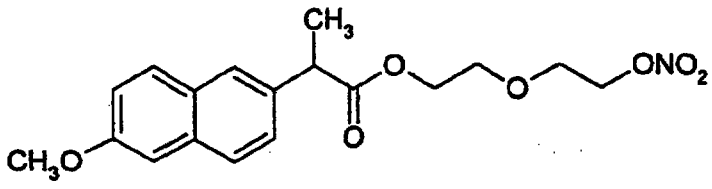
(Im) ;



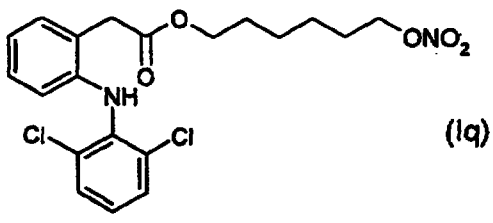
(In) ;



(Io) ;

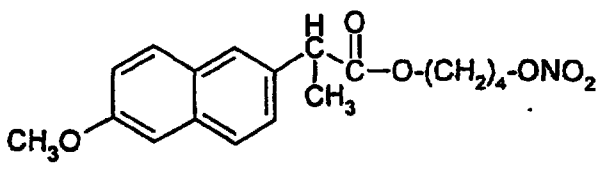


(Ip) ; and



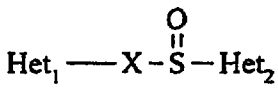
(Iq)

23. A method according to claim 22, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

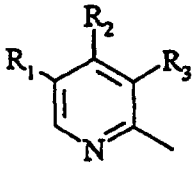
24. A method according to claim 18 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



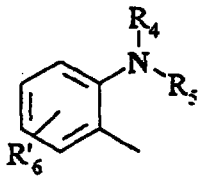
II

wherein

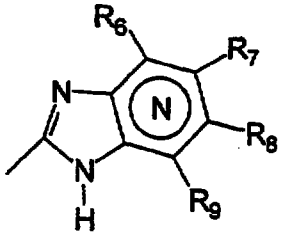
Het_1 is



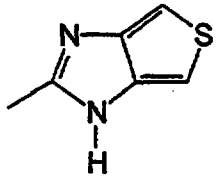
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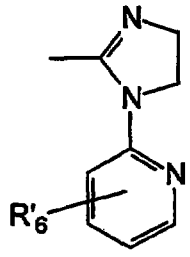
Het_2 is



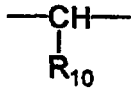
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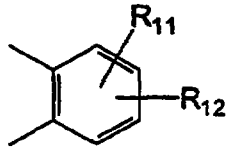
or



X=



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

* C L M S *

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

25. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof.

26. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

27. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

28. A method according to any one of the preceeding claims 17 to 27, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

29. A method according to claim 17, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

30. A method according to claim 29, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

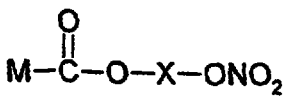
31. A method according to claim 18, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

32. A method according to claim 31, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

33. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof as active agent.

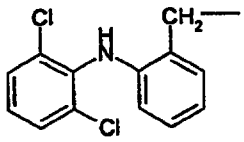
34. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer as active agents.

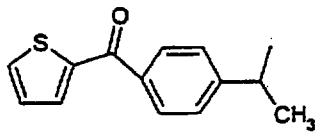
35. A pharmaceutical formulation according to claim 25 or 26 wherein the NO-releasing NSAID is a compound of the formula I

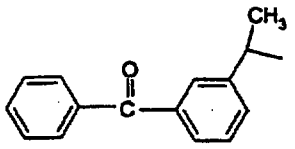


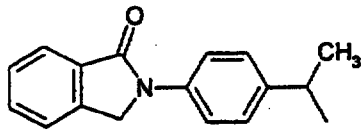
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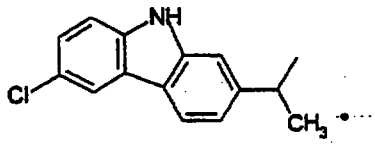
wherein M is selected from

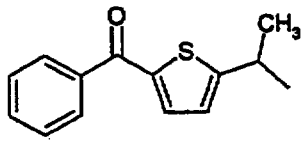


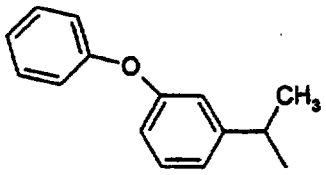


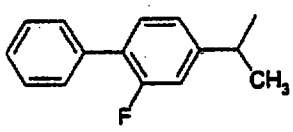


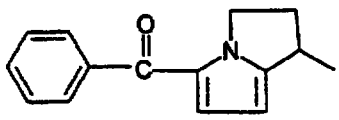


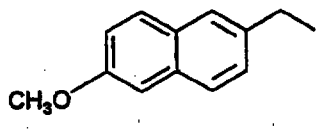


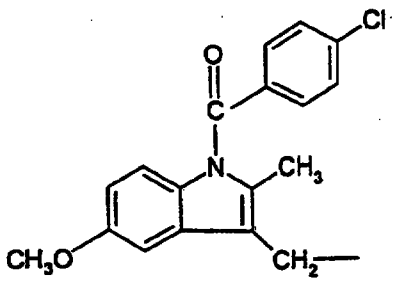


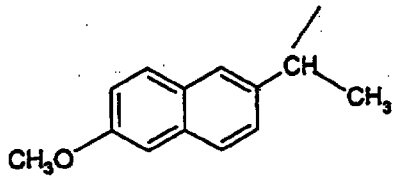


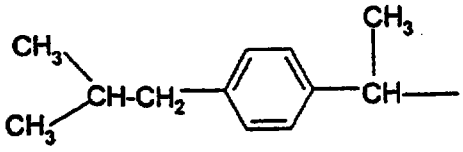


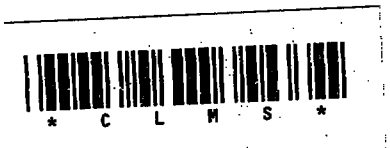












and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$;

or a pharmaceutically acceptable salt or enantiomer thereof.

