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**EP 1 196 155 B1**

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### (54) NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

NEUE VERWENDUNG VON VERBINDUNGEN ALS ANTIBAKTERIELLE MITTEL

NOUVELLE UTILISATION DE COMPOSES COMME AGENTS ANTIBACTERIENS

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**WO-A1-94/04484 WO-A1-94/12463  
WO-A1-95/09612 WO-A1-95/09831  
WO-A1-95/30641 WO-A1-97/31654  
WO-A1-98/22117 WO-A1-99/67210**

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**EP 1 196 155 B1**

**Description**Field of the invention

[0001] 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, particularly 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

[0002] 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.

[0003] 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.

[0004] 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.

[0005] *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.

[0006] 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*.

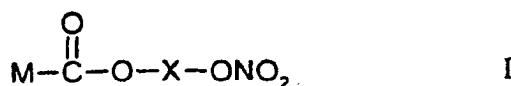
[0007] In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

Outline of the invention

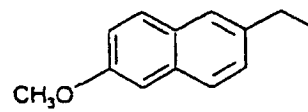
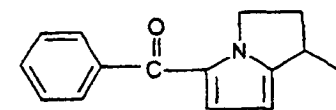
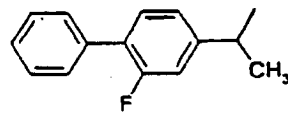
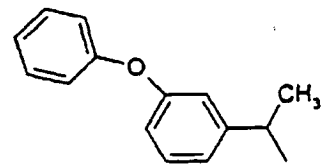
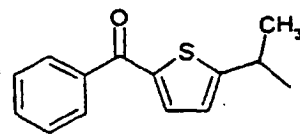
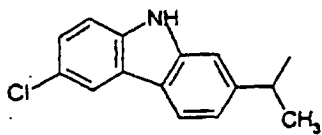
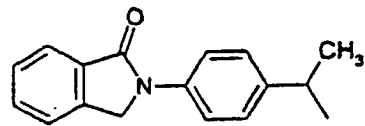
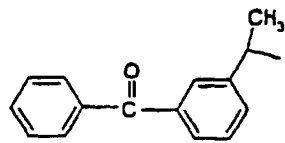
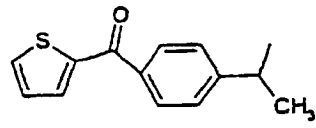
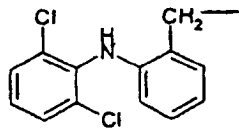
[0008] It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

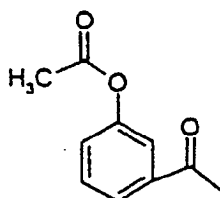
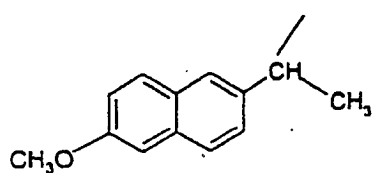
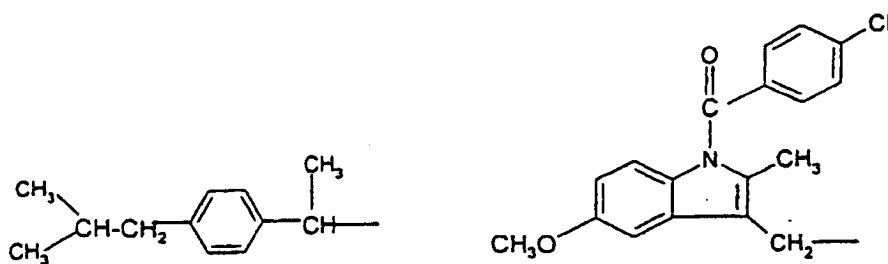
[0009] The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

[0010] Preferably the NO-releasing NSAID is defined by the formula 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.

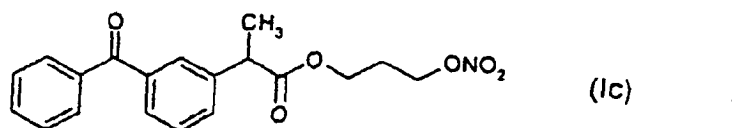
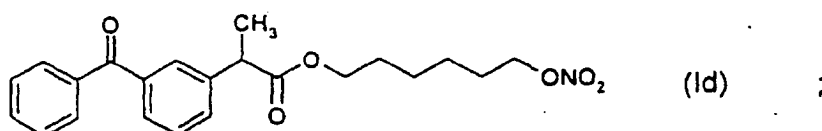
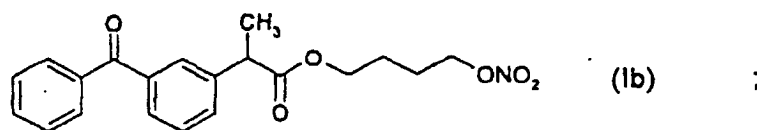
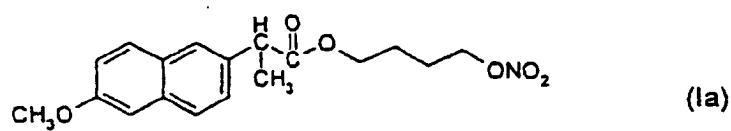
[0011] In a preferred embodiment of the invention M is selected from

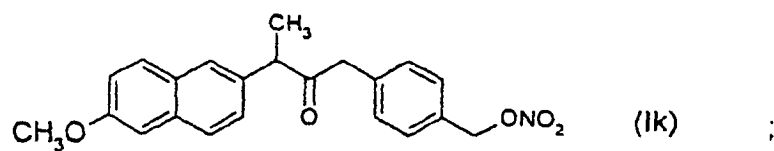
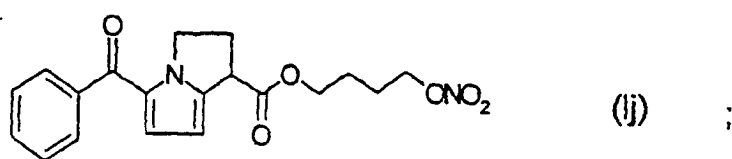
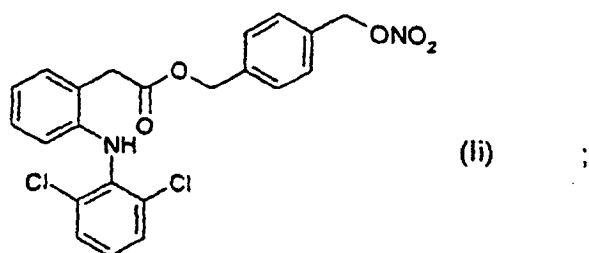
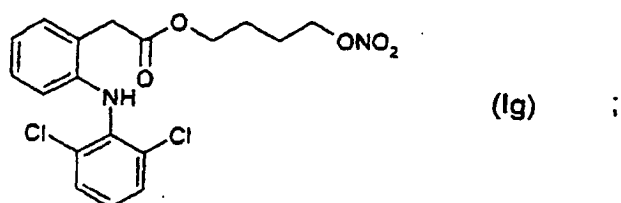
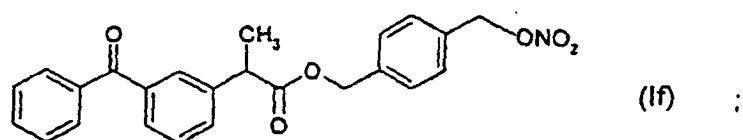
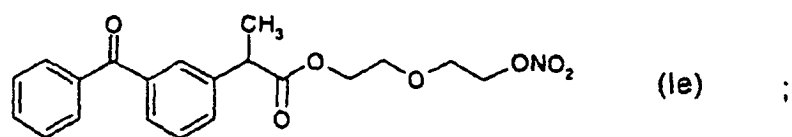


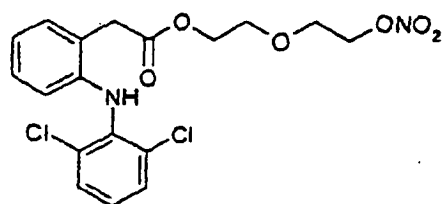


and X is selected from  
linear  $-(CH_2)_n-$  wherein n is an integer of from 2 to 6;  
-  $(CH_2)_2-O-(CH_2)_2-$  and  $-CH_2-pC_6H_4-CH_2-$ .

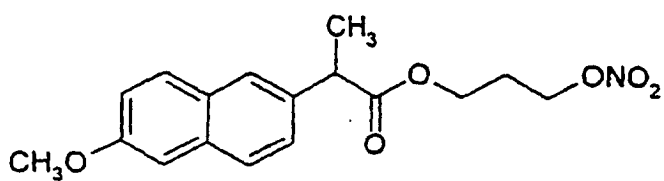
**[0012]** In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas



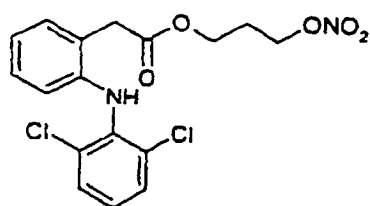




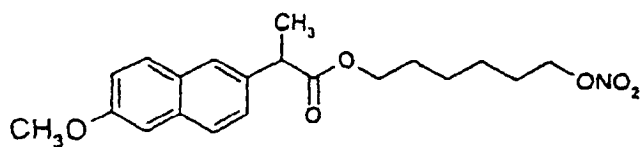
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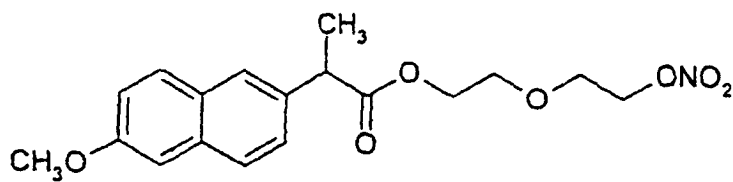
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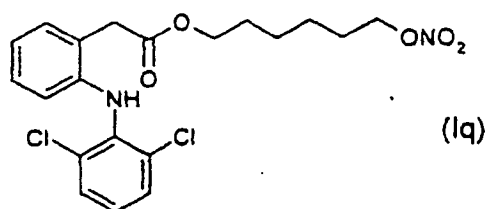


(Io) ;



(Ip) ;

and



[0013] In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

[0014] 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*.

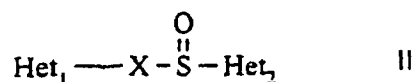
[0015] Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

[0016] 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.

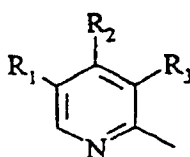
[0017] Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

[0018] The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

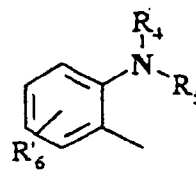
[0019] An acid susceptible proton pump inhibitor is, for instance, a compound of the general formula II



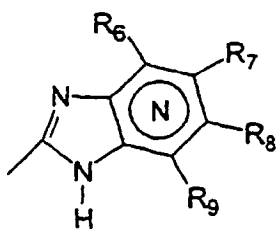
wherein  
Het<sub>1</sub> is



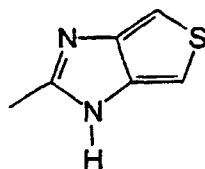
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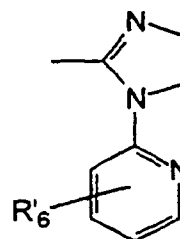
Het<sub>2</sub> is



or



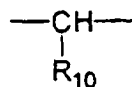
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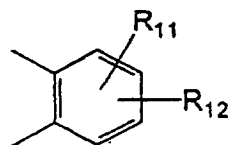


X=

5



or



10

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;

15

$R_1$ ,  $R_2$  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;

20

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

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

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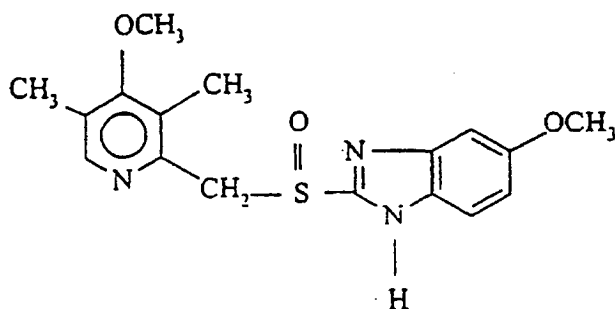
$R_{10}$  is hydrogen or forms an alkylene chain together with  $R_3$  and

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

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[0020] Examples of proton pump inhibitors according to formula II are

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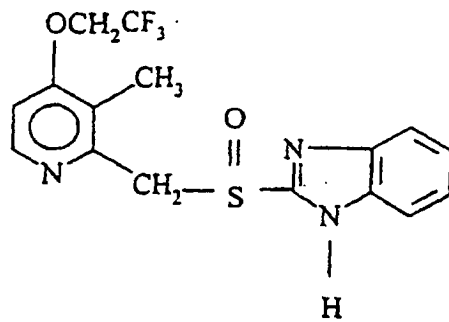
Omeprazole

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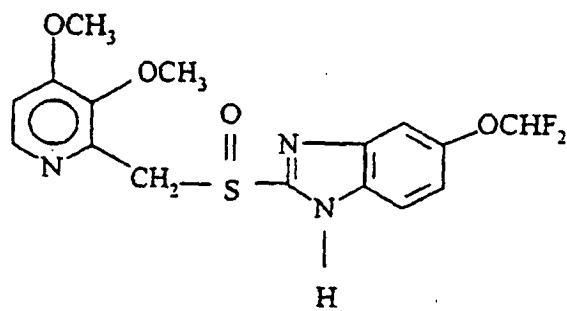
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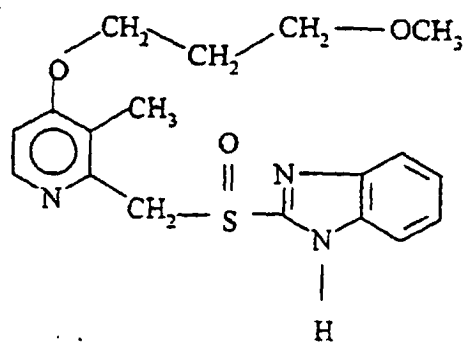
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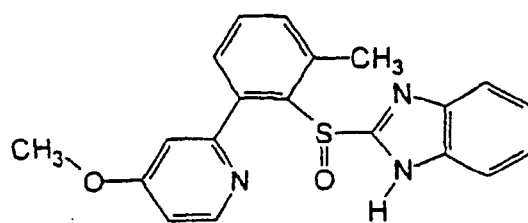
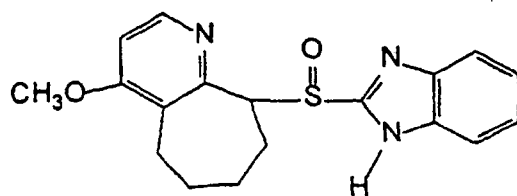
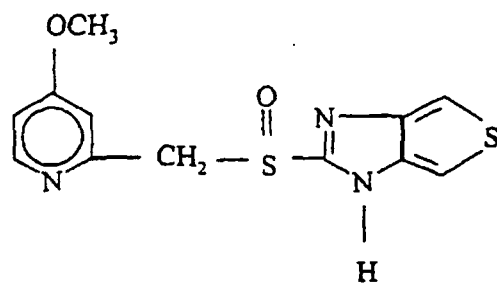
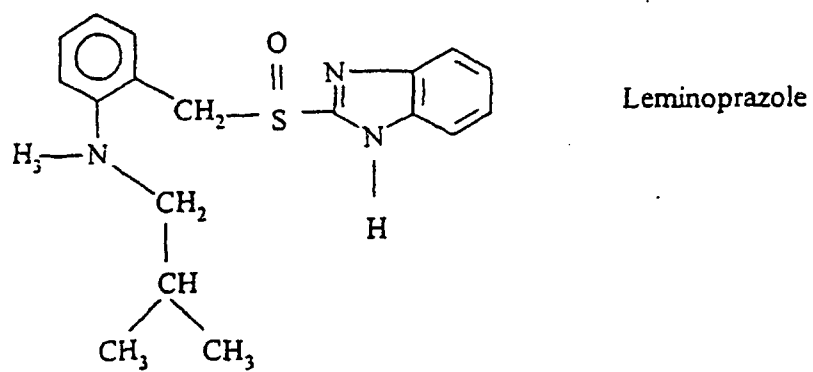
Lansoprazole

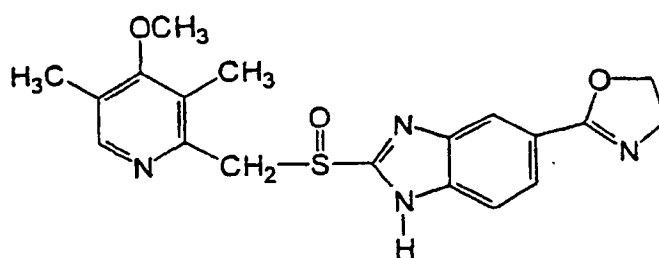
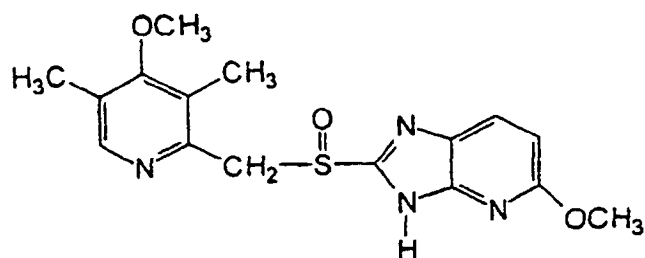


Pantoprazole



Pariprazole





[0021] The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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, subcutaneously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

[0026] 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

[0027] The invention is described in more detail by the following non-limiting examples.

[0028] The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

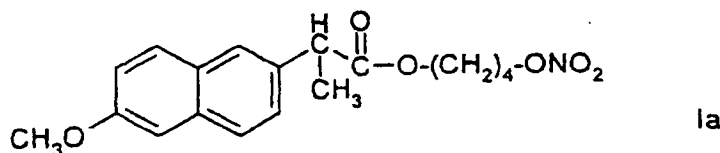
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### Example 1.

[0029]

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

Substance:



*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 agar plate by removing agar. Three wells per plate were made.

A stock solution of a compound of the formula 1a 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.

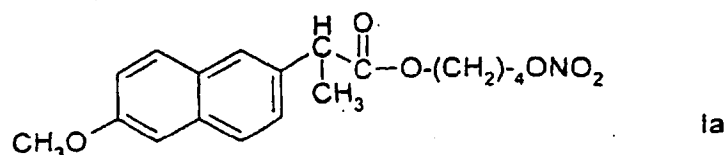
Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

### Example 2.

[0030]

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

Substance:



[0031] The plates with the wells were prepared according to Example 1.

[0032] A stock solution of a compound of the formula 1a 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.

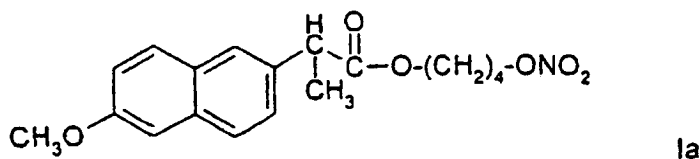
[0033] Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

### Example 3.

[0034]

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

Substance:



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

A stock solution of a compound of the formula 1a 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.

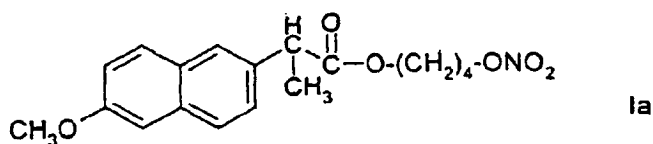
15 [0035] Result: The inhibition zone around each well was 13 mm.

#### Example 4.

[0036]

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

Substance:



[0037] The plates with the wells were prepared according to Example 1.

35 [0038] A stock solution of a compound of the formula 1a 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.

[0039] Result: The inhibition zone around each well was 10.4 mm.

#### Comparative tests

#### Example A

[0040]

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

Substance: Naproxen

[0041] The plates with the wells were prepared according to Example 1.

50 [0042] 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.

[0043] Result: The inhibition zone around the each well was 16.6 mm.

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### Example B

[0044]

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

[0045] The plates with the wells were prepared according to Example 1.

[0046] 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.

[0047] Result: No inhibition zones around the wells were formed.

### Example C

[0048]

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

[0049] The plates with the wells were prepared according to Example 1.

[0050] 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.

[0051] Result: No inhibition zones around the wells were formed.

### Example D

[0052]

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)  
Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

[0053] The plates with the wells were prepared according to Example 1.

[0054] 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.

[0055] Result: No inhibition zones around the wells were formed.

### Example E

[0056]

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)  
Substance: Di-methyl-sulphate-oxide (DMSO)

[0057] The plates with the wells were prepared according to Example 1.

[0058] 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.

[0059] Result: No inhibition zones around the wells were formed.

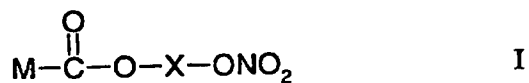
### Claims

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

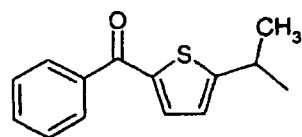
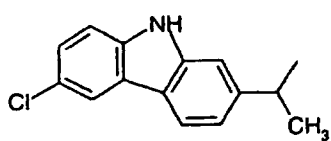
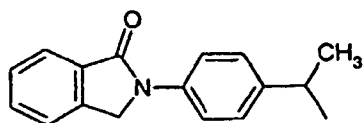
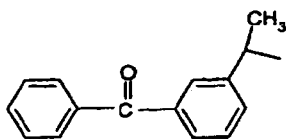
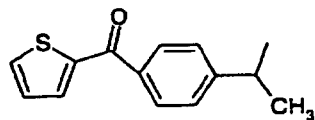
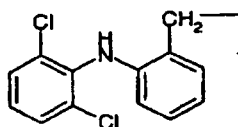
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manufacture of a medicament for the treatment of disorders caused or mediated by *Helicobacter pylori*.

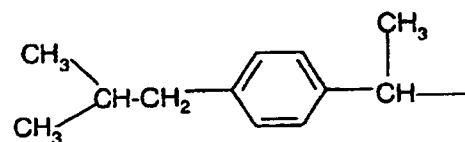
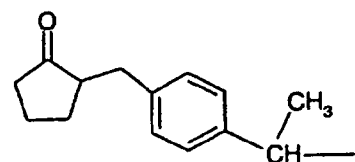
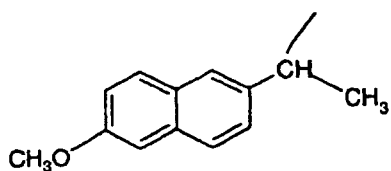
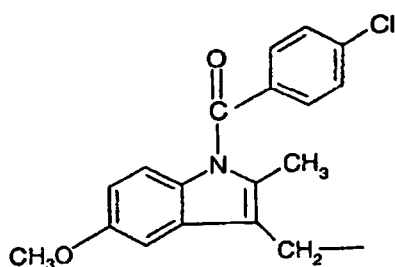
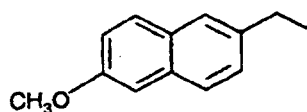
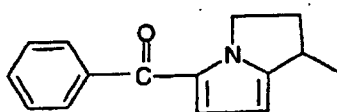
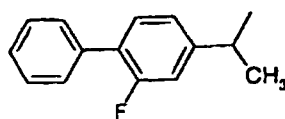
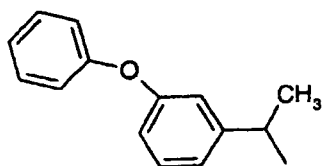
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor either of them in the form of a salt or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential administration in the treatment of disorders caused or mediated by *Helicobacter pylori*.
3. Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I



wherein M is selected from anyone of







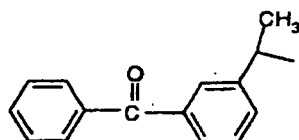
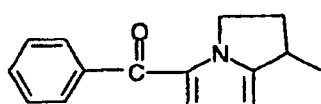
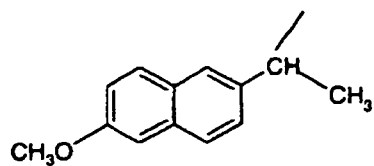
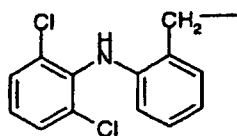
and X is selected from

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

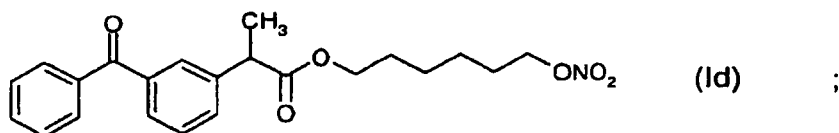
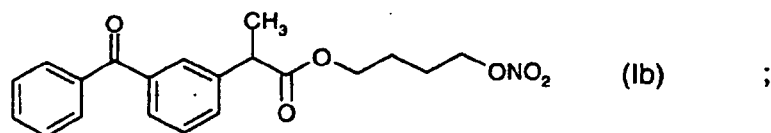
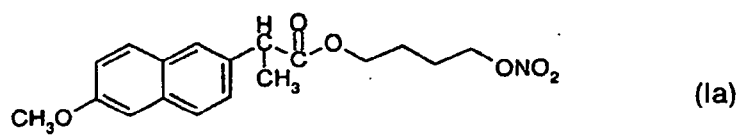
$-(CH_2)_m-O-(CH_2)_p-$  wherein m and p are integers of from 2 to 10; and  $-CH_2-pC_6H_4-CH_2-$ ,

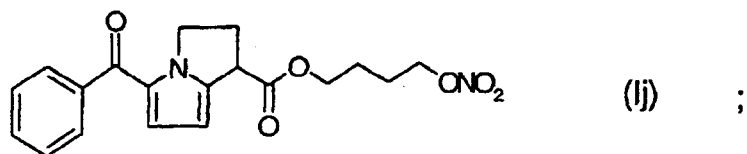
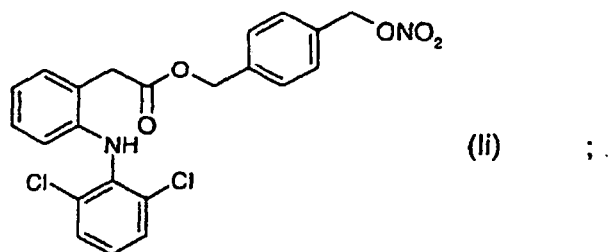
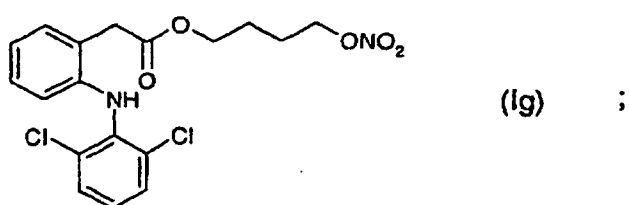
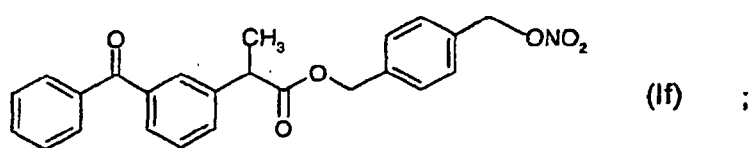
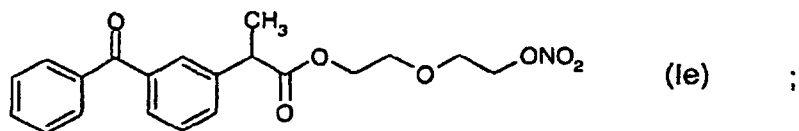
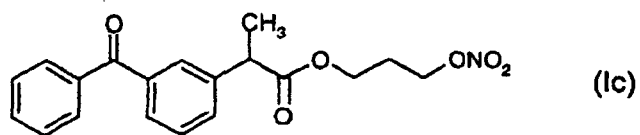
or a pharmaceutically acceptable salt or enantiomer thereof.

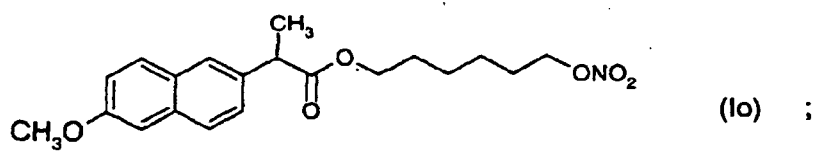
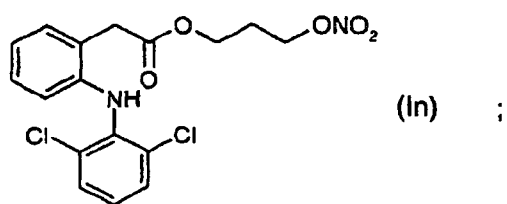
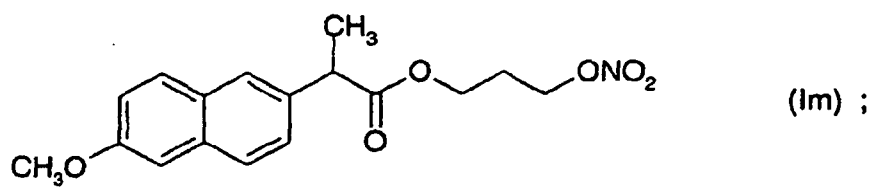
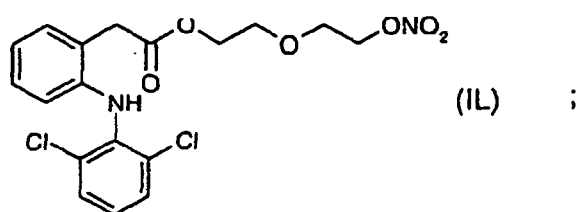
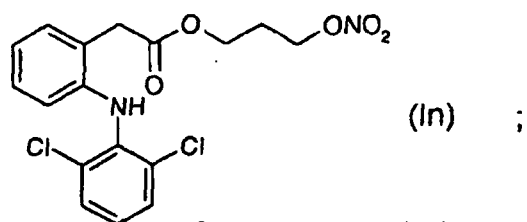
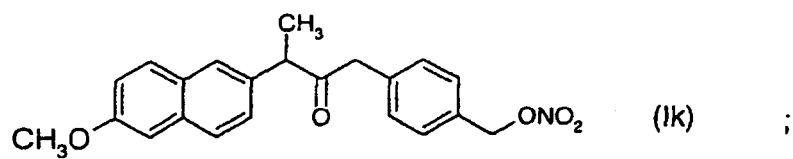
4. Use according to claim 3 wherein M in formula I is selected from

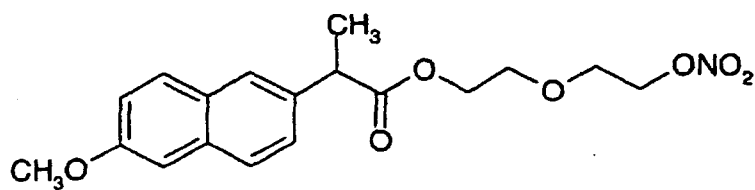


5. Use according to claim 3 or 4 wherein X in formula I is selected from linear  $-(CH_2)_n-$  wherein n is an integer of from 2 to 6,  $-(CH_2)_2-O-(CH_2)_2-$  and  $-CH_2-pC_6H_4-CH_2-$ .
6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq



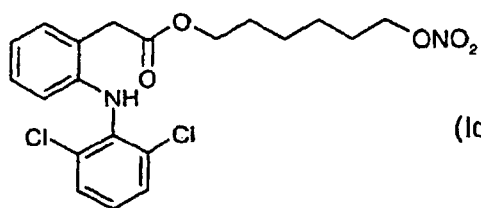






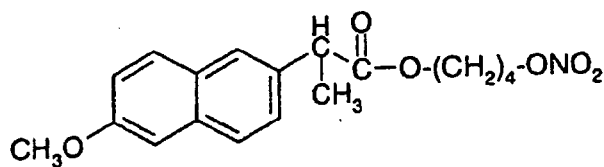
(Ip) ;

and



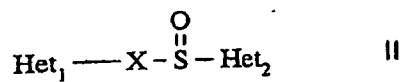
(Iq)

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

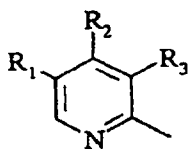


(Ia)

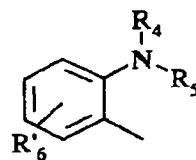
8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



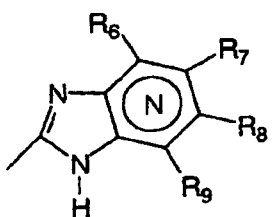
wherein  
Het<sub>1</sub> is



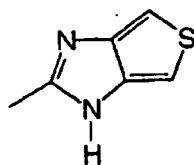
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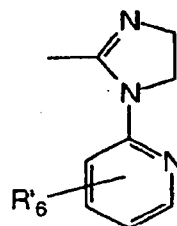
Het<sub>2</sub> is



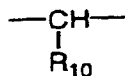
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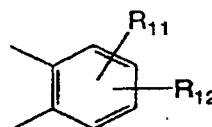
or



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, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, 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 moieties 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.

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 claim 2 wherein the NO-releasing NSAID is a compound of formula Ia and the acid susceptible proton pump inhibitor is omeprazole, an alkaline salt thereof, (S)-omeprazole or an alkaline salt thereof.

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 and claim 12, 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.

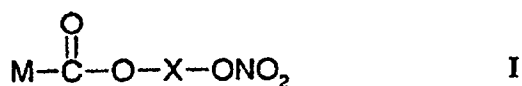
16. Use according to claim 2 and claim 12, wherein the amount of NO-releasing NSAID is 5 - 1000 mg and the amount of proton pump inhibitor is 10 - 80 mg.

# Patentansprüche

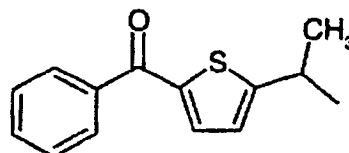
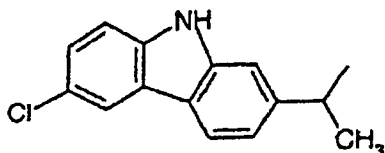
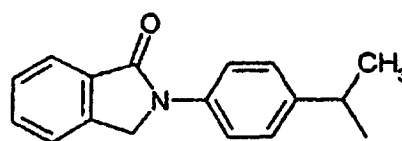
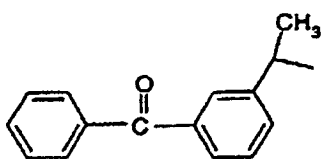
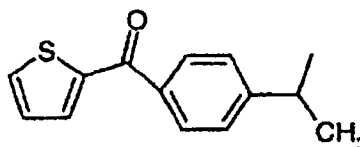
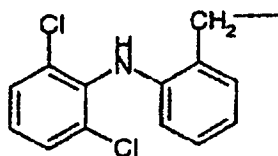
1. Verwendung eines NO-freisetzenden NSAID sowie eines pharmazeutisch annehmbar Salzes oder eines Enantiomers davon zur Herstellung eines Arzneimittels zur Behandlung von durch *Helicobacter pylori* verursachten oder vermittelten Erkrankungen.

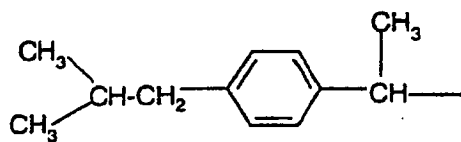
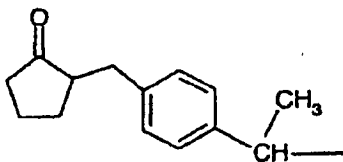
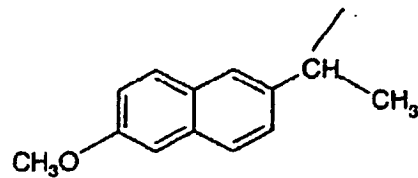
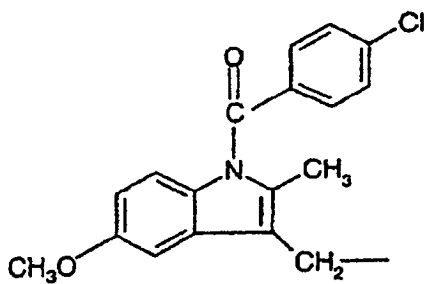
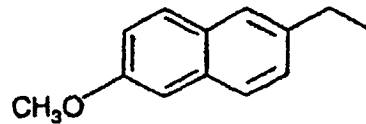
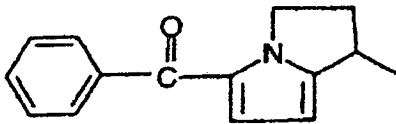
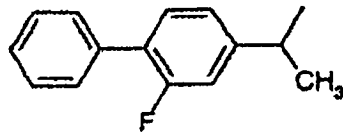
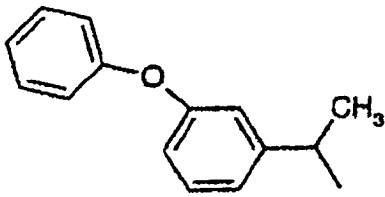
2. Verwendung eines NO-freisetzenden NSAID und eines säureempfindlichen Protonenpumpenhemmers, jeweils in Form eines Salzes oder eines Enantiomers oder eines Salzes des Enantiomers, bei der Herstellung von pharmazeutischen Formulierungen zur gleichzeitigen, separaten oder sequentiellen Verabreichung bei der Behandlung von durch *Helicobacter pylori* verursachten oder vermittelten Erkrankungen.

3. Verwendung nach Anspruch 1 oder 2, bei der es sich bei dem NO-freisetzenden NSAID um eine Verbindung der Formel I



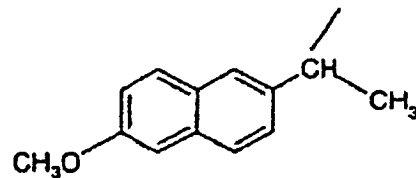
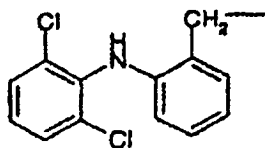
worin M unter





ausgewählt ist und X unter geradkettigem, verzweigtem oder cyclischem  $-(CH_2)_n-$ , wobei n für eine ganze Zahl von 2 bis 10 steht,  $-(CH_2)_m-O-(CH_2)_p-$ , wobei m und p für ganze Zahlen von 2 bis 10 stehen, und  $-CH_2pC_6H_4-CH_2-$  ausgewählt ist, oder ein pharmazeutisch annehmbar Salz oder Enantiomer davon handelt.

4. Verwendung nach Anspruch 3, bei der M in Formel I unter



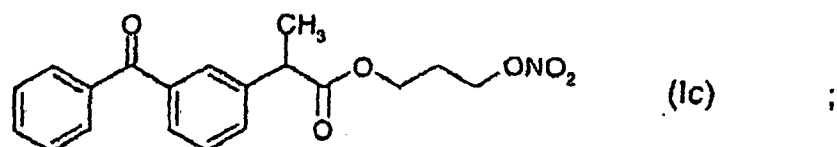
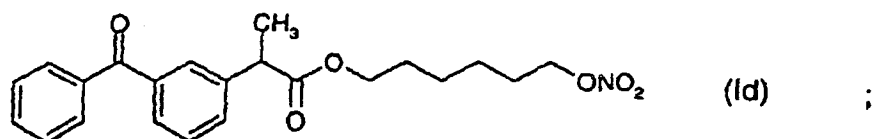
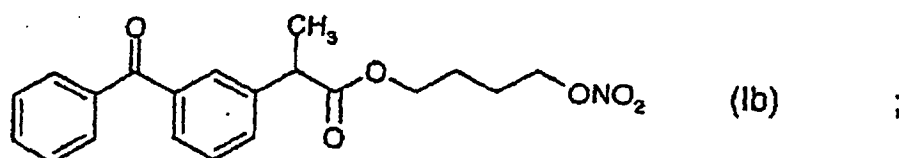
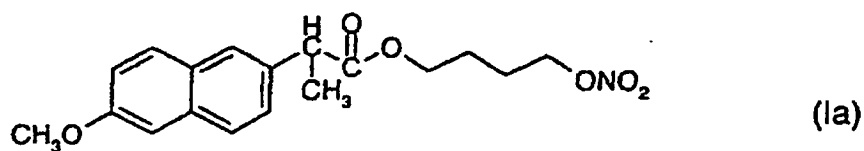


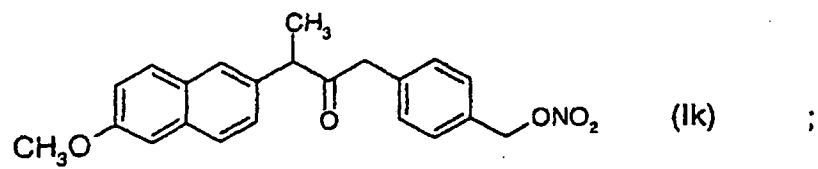
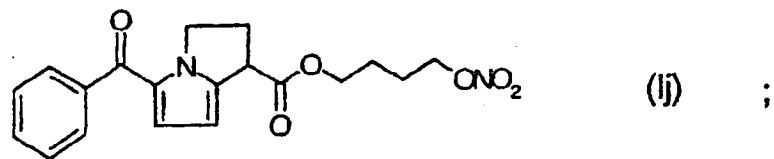
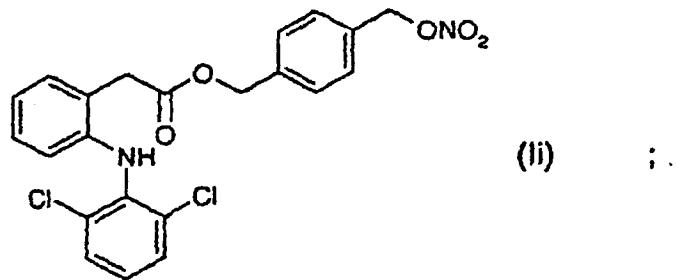
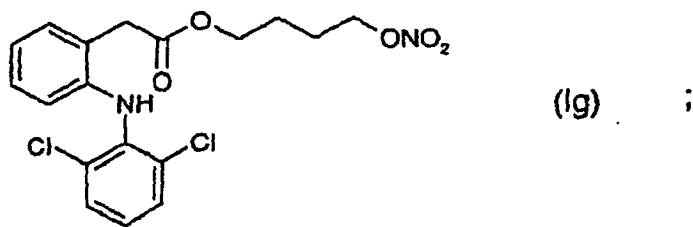
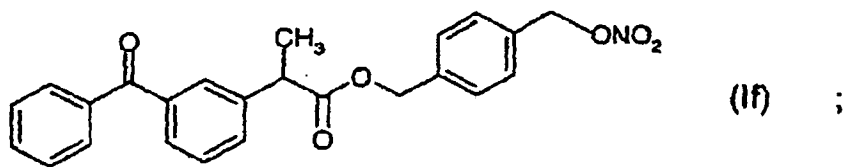
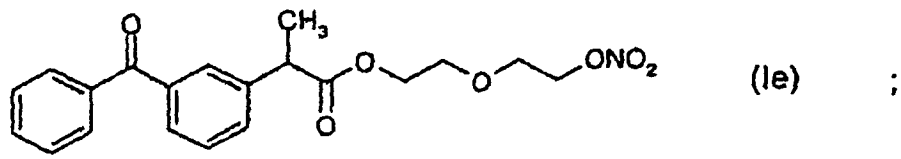


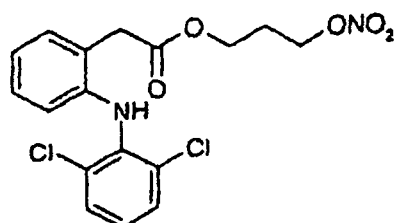
ausgewählt ist.

5. Verwendung nach Anspruch 3 oder 4, bei der X in Formel I unter linearem  $-(CH_2)_n-$ , wobei n für eine ganze Zahl von 2 bis 6 steht,  $-(CH_2)_2-O-(CH_2)_2-$  und  $-CH_2-pC_6H_4-CH_2-$  ausgewählt ist.

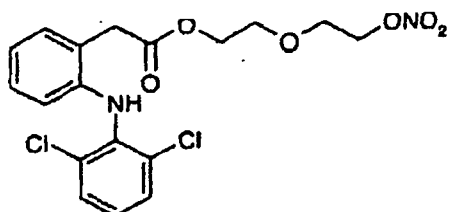
6. Verwendung nach einem der Ansprüche 1-3, bei der es sich bei dem NO-freisetzenden NSAID um eine Verbindung einer der Formeln Ia-Iq



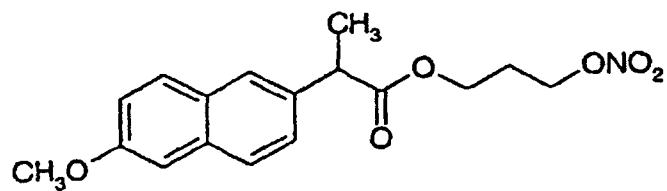




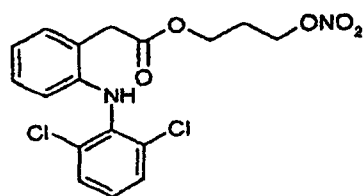
(In) ;



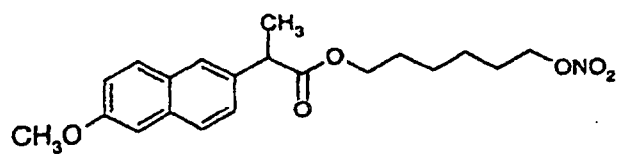
(IL) ;



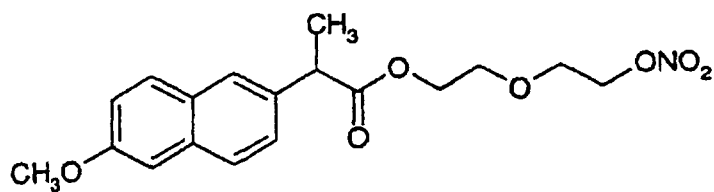
(Im) ;



(In) ;

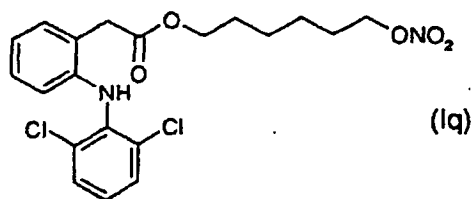


(Io) ;



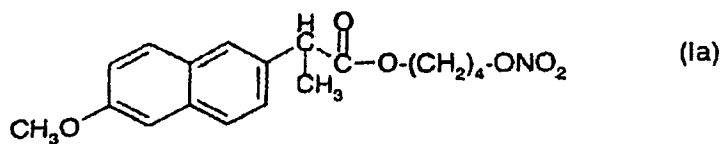
(Ip) ;

und



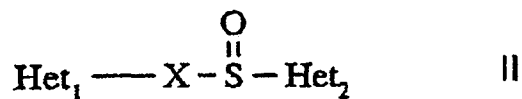
handelt.

7. Verwendung nach Anspruch 6, bei der es sich bei dem NO-freisetzenden NSAID um eine Verbindung der Formel Ia

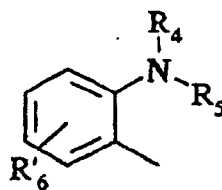
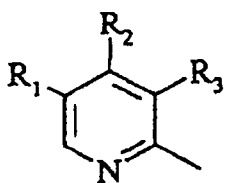


handelt.

8. Verwendung nach Anspruch 2, bei der es sich bei dem säureempfindlichen Protonenpumpenhemmer um eine Verbindung der Formel II

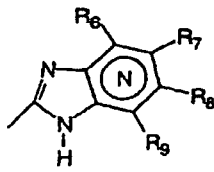


worin  
Het<sub>1</sub> für

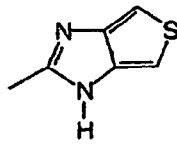


oder

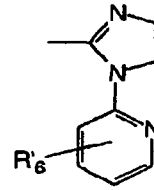
steht,  
Het<sub>2</sub> für



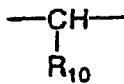
oder



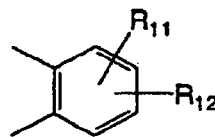
oder



steht und  
X für



oder



steht,  
wobei

N in der Benzimidazolgruppierung bedeutet, daß eines der durch  $R_6$ - $R_9$  substituierten Kohlenstoffatome gegebenenfalls durch ein Stickstoffatom ohne Substituenten ersetzt sein kann;

$R_1$ ,  $R_2$  und  $R_3$  gleich oder verschieden sind und unter Wasserstoff, Alkyl, gegebenenfalls durch Fluor substituiertem Alkoxy, Alkylthio, Alkoxyalkoxy, Dialkylamino, Piperidino, Morpholino, Halogen, Phenyl und Phenylalkoxy ausgewählt sind;

$R_4$  und  $R_5$  gleich oder verschieden sind und unter Wasserstoff, Alkyl und Aralkyl ausgewählt sind;

$R_6$  für Wasserstoff, Halogen, Trifluormethyl, Alkyl und Alkoxy steht;

$R_6$ - $R_9$  gleich oder verschieden sind und unter Wasserstoff, Alkyl, Alkoxy, Halogen, Halogenalkoxy, Alkylcarbonyl, Alkoxycarbonyl, Oxazolyl, Trifluoralkyl ausgewählt sind oder benachbarte Gruppen  $R_6$ - $R_9$  Ringstrukturen, die weiter substituiert sein können, bilden;

$R_{10}$  für Wasserstoff steht oder gemeinsam mit  $R_3$  eine Alkylkette bildet und

$R_{11}$  und  $R_{12}$  gleich oder verschieden sind und unter Wasserstoff, Halogen oder Alkyl ausgewählt sind, wobei Alkylgruppen, Alkoxygruppen und Teilstrukturen davon verzweigte oder geradkettige  $C_1$ - $C_9$ -Ketten sein können oder cyclische Alkylgruppen enthalten können, beispielsweise Cycloalkylalkyl; handelt.

9. Verwendung nach Anspruch 8, bei der der säureempfindliche Protonenpumpenhemmer unter Omeprazol, einem alkalischen Salz davon, (S)-Omeprazol und einem alkalischen Salz davon ausgewählt ist.

10. Verwendung nach Anspruch 8, bei der es sich bei dem säureempfindlichen Protonenpumpenhemmer um Lansoprazol oder ein pharmazeutisch annehmbares Salz davon oder ein Enantiomer oder ein Salz des Enantiomers handelt.

11. Verwendung nach Anspruch 8, bei der es sich bei dem säureempfindlichen Protonenpumpenhemmer um Pantoprazol oder ein pharmazeutisch annehmbares Salz davon oder ein Enantiomer oder ein Salz des Enantiomers handelt.

12. Verwendung nach Anspruch 2, bei der es sich bei dem NO-freisetzenden NSAID um eine Verbindung der Formel Ia und bei dem säureempfindlichen Protonenpumpenhemmer um Omeprazol, ein alkalisches Salz davon, (S)-Omeprazol oder ein alkalisches Salz davon handelt.

13. Verwendung nach Anspruch 1, bei der die Menge an NO-freisetzendem NSAID in jeder Dosisform 0,5-5000 mg beträgt.

14. Verwendung nach Anspruch 13, bei der die Menge an NO-freisetzendem NSAID in jeder Dosisform 5-1000 mg beträgt.

15. Verwendung nach Anspruch 2 und 12, bei der die Menge an NO-freisetzendem NSAID 0,5-5000 mg und die Menge an Protonenpumpeninhibitor 0,1-200 mg gemeinsam in einer Dosisform oder in zwei separaten Dosisformen beträgt.

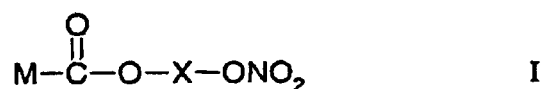
16. Verwendung nach Anspruch 2 und 12, bei der die Menge an NO-freisetzendem NSAID 5-1000 mg und die Menge an Protonenpumpeninhibitor 10-80 mg beträgt.

### Revendications

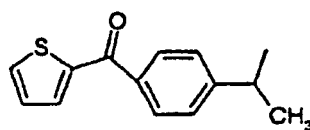
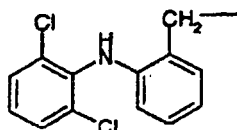
1. Utilisation d'un AINS à libération de NO, ainsi qu'un sel pharmaceutiquement acceptable ou un énantiomère de celui-ci, pour la fabrication d'un médicament pour le traitement de troubles provoqués ou médiés par *Helicobacter pylori*.

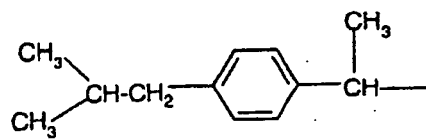
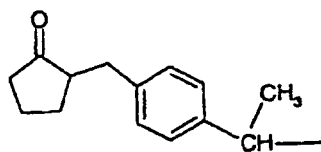
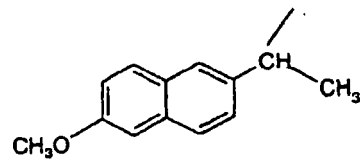
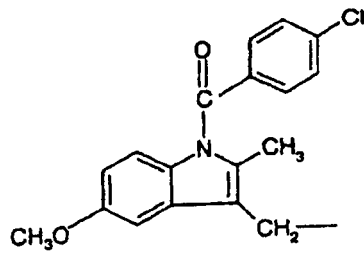
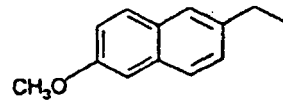
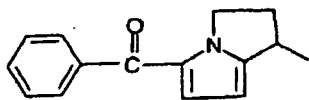
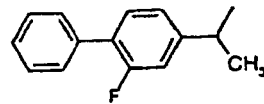
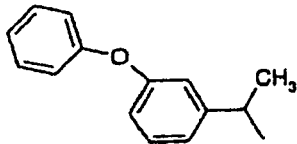
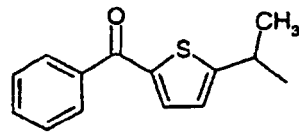
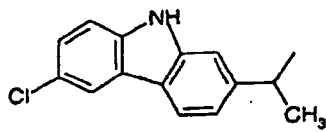
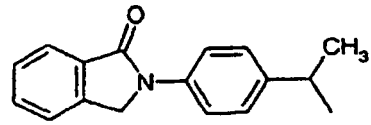
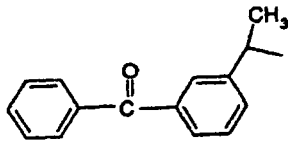
2. Utilisation d'un AINS à libération de NO, et d'un inhibiteur de pompe à protons sensible à l'acide, l'un ou l'autre sous la forme d'un sel ou d'un énantiomère ou d'un sel de l'énantiomère, dans la fabrication de formulations pharmaceutiques prévues pour une administration simultanée, séparée ou séquentielle, dans le traitement de troubles provoqués ou médiés par *Helicobacter pylori*.

3. Utilisation selon la revendication 1 ou 2, dans laquelle l'AINS à libération de NO est un composé de formule I



dans laquelle M est choisi parmi un quelconque parmi



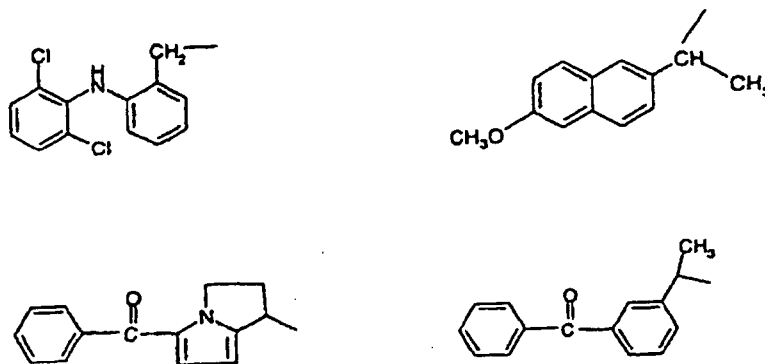


et X est choisi parmi

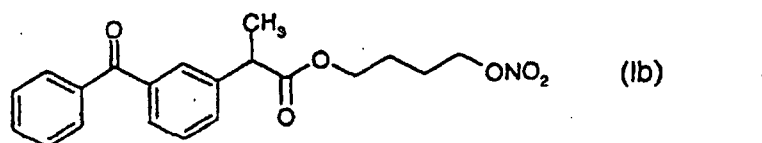
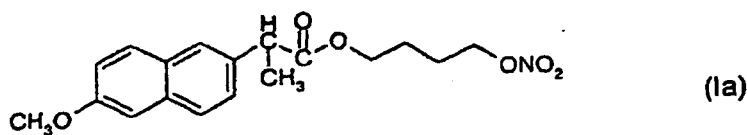
- $(\text{CH}_2)_n$  linéaire, ramifié ou cyclique, dans lequel n est un nombre entier allant de 2 à 10 ;
- $(\text{CH}_2)_m\text{-O-(CH}_2)_p$  dans lequel m et p sont des nombres entiers allant de 2 à 10 ; et  $-\text{CH}_2\text{-PC}_6\text{H}_4\text{-CH}_2-$ ,

ou un sel pharmaceutiquement acceptable ou un énantiomère de celui-ci.

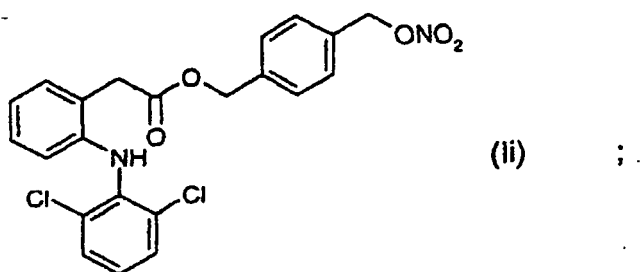
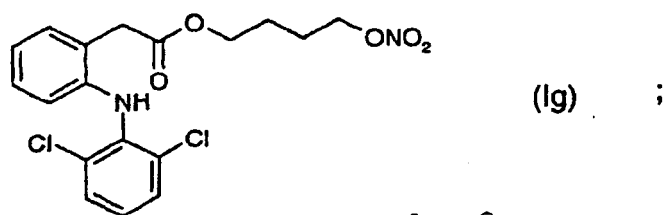
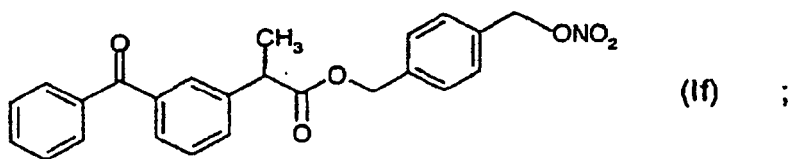
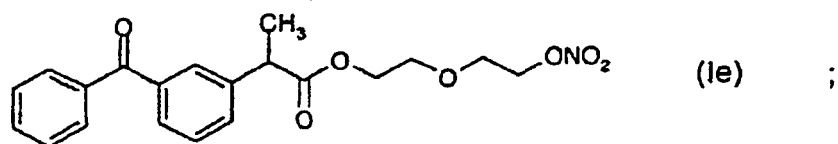
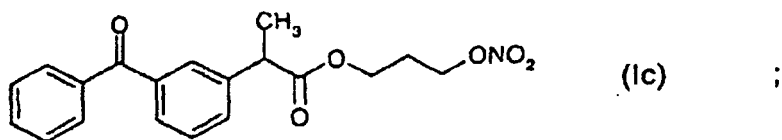
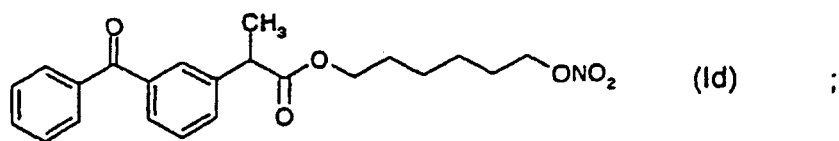
4. Utilisation selon la revendication 3, dans laquelle M dans la formule I est choisi parmi

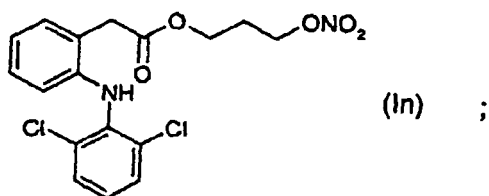
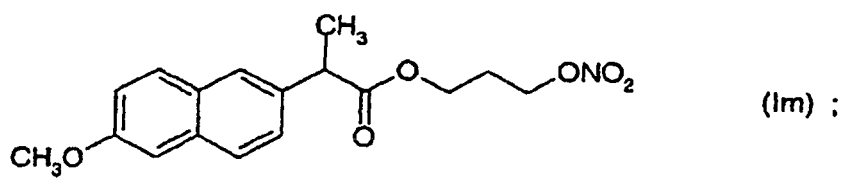
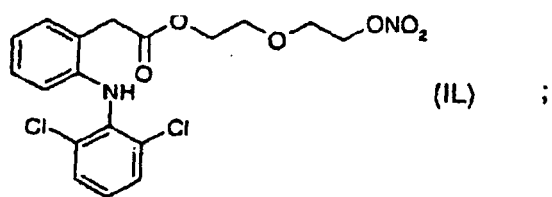
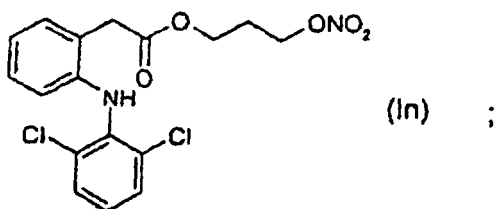
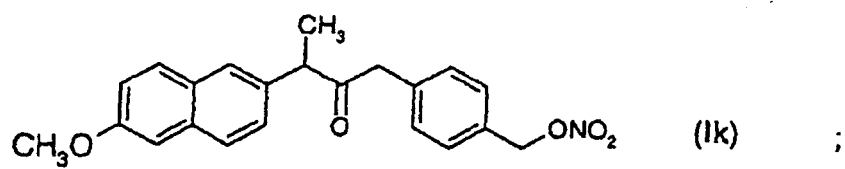
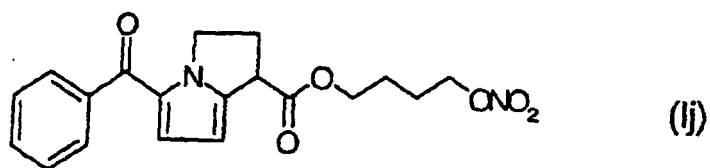


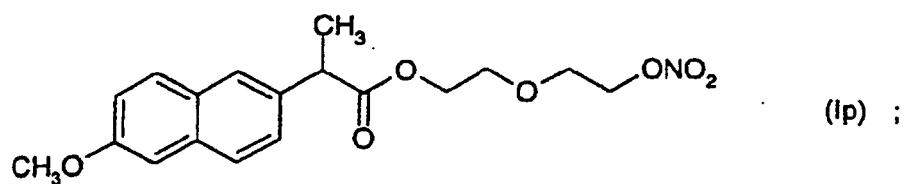
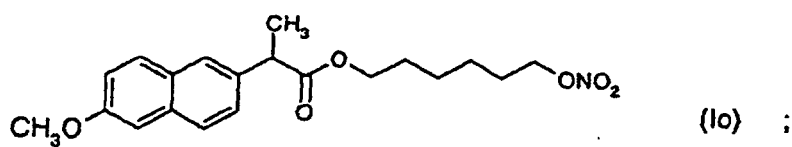
5. Utilisation selon la revendication 3 ou 4, dans laquelle X dans la formule I est choisi parmi  $-(\text{CH}_2)_n$  linéaire, dans lequel n est un nombre entier allant de 2 à 6,  $-(\text{CH}_2)_2\text{-O-(CH}_2)_2-$  et  $-\text{CH}_2\text{-pC}_6\text{H}_4\text{-CH}_2-$ .
6. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle l'AINS à libération de NO est un composé selon l'une quelconque des formules Ia - Iq



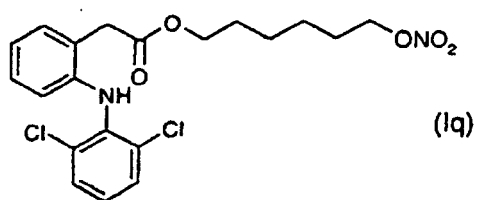




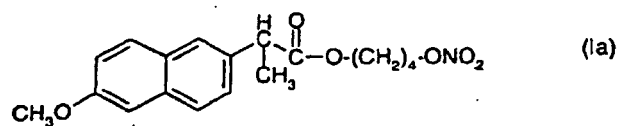




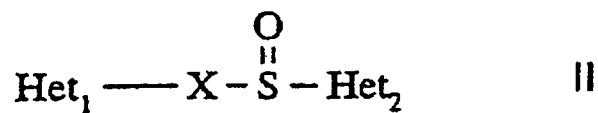
20 et



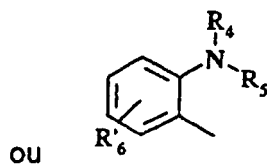
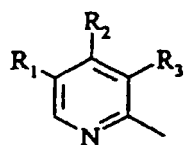
7. Utilisation selon la revendication 6, dans laquelle l'AINS à libération de NO est un composé de formule Ia



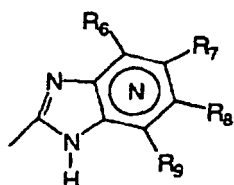
8. Utilisation selon la revendication 2, dans laquelle l'inhibiteur de pompe à protons sensible à l'acide est un composé de formule II



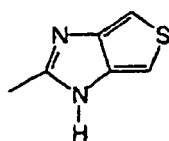
dans laquelle  
Het<sub>1</sub> est



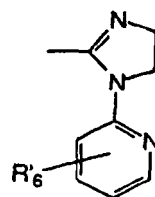
ou

Het<sub>2</sub> est

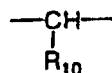
ou



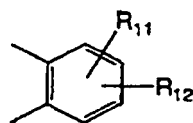
ou



X =



ou



dans lesquelles

N dans le motif benzimidazole signifie que l'un des atomes de carbone substitué par R<sub>6</sub>-R<sub>9</sub> peut éventuellement être échangé pour un atome d'azote sans aucun substituant ;

R<sub>1</sub>, R<sub>2</sub> et R<sub>3</sub> sont identiques ou différents et sont choisis parmi hydrogène, alkyle, alcoxy éventuellement substitué par fluor, alkylthio, alcoxyalcoxy, dialkylamino, pipéridino, morpholino, halogène, phényle et phénylalcoxy ;

R<sub>4</sub> et R<sub>5</sub> sont identiques ou différents et sont choisis parmi hydrogène, alkyle et aralkyle ;

R<sub>6</sub>' est hydrogène, halogène, trifluorométhyle, alkyle et alcoxy ;

R<sub>6</sub>-R<sub>9</sub> sont identiques ou différents et sont choisis parmi hydrogène, alkyle, alcoxy, halogène, halogénoalcoxy, alkylcarbonyl, alcoxycarbonyl, oxazolyle, trifluoroalkyle, ou les groupements adjacents R<sub>6</sub>-R<sub>9</sub> forment des structures cycliques pouvant être substituées davantage ;

R<sub>10</sub> est hydrogène ou forme une chaîne alkylène conjointement avec R<sub>3</sub>, et

R<sub>11</sub> et R<sub>12</sub> sont identiques ou différents et sont choisis parmi hydrogène, halogène ou alkyle, des groupements alkyle, des groupements alcoxy et des motifs de ceux-ci, ils peuvent être des chaînes en C<sub>1</sub>-C<sub>9</sub> linéaires ou ramifiées ou comprendre des groupements alkyle cycliques, tels que cycloalkylalkyle.

9. Utilisation selon la revendication 8, dans laquelle l'inhibiteur de pompe à protons sensible à l'acide est choisi parmi l'oméprazole, un sel alcalin de celui-ci, le (S)-oméprazole et un sel alcalin de celui-ci.

10. Utilisation selon la revendication 8, dans laquelle l'inhibiteur de pompe à protons sensible à l'acide est le lansoprazole ou un sel pharmaceutiquement acceptable de celui-ci ou un énantiomère ou un sel de l'énantiomère.

11. Utilisation selon la revendication 8, dans laquelle l'inhibiteur de pompe à protons sensible à l'acide est le pantoprazole ou un sel pharmaceutiquement acceptable de celui-ci ou un énantiomère ou un sel de l'énantiomère.

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12. Utilisation selon la revendication 2, dans laquelle l'AINS à libération de NO est un composé de formule Ia et l'inhibiteur de pompe à protons sensible à l'acide est l'oméprazole, un sel alcalin de celui-ci, le (S)-oméprazole ou un sel alcalin de celui-ci.

13. Utilisation selon la revendication 1, dans laquelle la quantité d'AINS à libération de NO dans chaque forme de dosage est de 0,5-5000 mg.

14. Utilisation selon la revendication 13, dans laquelle la quantité d'AINS à libération de NO est de 5-1000 mg.

15. Utilisation selon la revendication 2 et la revendication 12, dans laquelle la quantité d'AINS à libération de NO est de 0,5-5000 mg, et la quantité d'inhibiteur de pompe à protons est de 0,1-200 mg, conjointement dans une seule forme de dosage ou dans deux formes de dosage distinctes.

16. Utilisation selon la revendication 2 et la revendication 12, dans laquelle la quantité d'AINS à libération de NO est de 5-1000 mg, et la quantité d'inhibiteur de pompe à protons est de 10-80 mg.