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(54) Title: NEW USE

(57) **Abrégé/Abstract:**

The present invention relates to a new use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. More particularly the invention is directed to the use of said compounds, and pharmaceutically acceptable salts thereof, for the treatment and/or prevention of NSAID (non-steroidal antiinflammatory drugs) induced gastric ulcer as well as a pharmaceutical composition in the unit dosage form for the prevention of NSAID induced gastric ulcer in a mammal comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compounds. Other pharmaceutically active compounds used in the present invention comprises COX-2 inhibitors, NO-NSAIDs and bisphosphonates.



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(54) Title: NEW USE

(57) Abstract: The present invention relates to a new use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. More particularly the invention is directed to the use of said compounds, and pharmaceutically acceptable salts thereof, for the treatment and/or prevention of NSAID (non-steroidal antiinflammatory drugs) induced gastric ulcer as well as a pharmaceutical composition in the unit dosage form for the prevention of NSAID induced gastric ulcer in a mammal comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compounds. Other pharmaceutically active compounds used in the present invention comprises COX-2 inhibitors, NO-NSAIDs and bisphosphonates.



WO 02/069968 A1

NEW USE

Field of the invention

- 5 The present invention relates to a new use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. More particularly the invention is directed to the use of said compounds, and pharmaceutically acceptable salts thereof, for the treatment and/or prevention of NSAID (non-steroidal antiinflammatory drugs) induced gastric ulcer as well as a pharmaceutical composition in
10 the unit dosage form for the prevention of NSAID induced gastric ulcer in a mammal comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compounds.

Background of the invention and prior art

- 15 Certain pharmacological agents are known to be useful in exerting a cytoprotective effect on the gastrointestinal tract. This cytoprotective effect is manifest in the ability of such compounds to treat or prevent inflammatory diseases of the gastrointestinal tract, such as gastric ulcer, duodenal ulcer, gastritis, and intestinal inflammatory diseases, such as Crohn's disease and inflammatory bowel disease.

20

- These inflammatory diseases are known to be caused by a wide variety of agents present in the gastrointestinal tract which are known to attack the surfaces thereof, producing the inflammatory disease response. Such agents include microorganisms, bacterial toxins, certain pharmaceuticals and chemical agents and indeed gastric acid itself is capable of
25 attacking the stomach lining and producing the inflammatory state.

- NSAID are a class of compounds that are used to relieve some symptoms caused by arthritis, such as inflammation, swelling, stiffness, and joint pain. NSAIDs are also used to relieve other kinds of pain or to treat other painful conditions, such as gout attacks,
30 bursitis, tendinitis, sprains, strains, or other injuries.

Any NSAID is known to cause side effects, especially when it is used for a long time or in large doses. One example of such side effects is induced gastric ulcer.

COX-2 inhibitors, the newest class of NSAIDS, work by blocking COX-2 enzyme which is involved in the inflammation pathway. By sparing COX-1 enzyme, gastrointestinal toxicity is reduced, but still present.

- 5 Nitric oxide (NO) is a molecule of versatility and importance in many guises. In the atmosphere it is a noxious chemical, but in the body in small and controlled doses it is extraordinary beneficial. It helps maintain blood pressure by dilating blood vessels, helps kill foreign invaders in the immune response, is a major biochemical mediator of penile erections, and is proposed to be a major biochemical component of long-term memory.
- 10 Nitric oxide releasing NSAIDs (NO-NSAIDs) are disclosed in e.g. WO 94/04484.

- Bisphosphonates are a class of compounds well known for their therapeutic benefits in a variety of disorders associated with abnormal bone resorption, e.g. osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, metastatic bone disease, hypercalcemia
- 15 of malignancy, multiple myeloma, periodontal disease and tooth loss. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal woman. Examples of such bisphosphonate compounds is alendronate, risedronate, tiludronate, ibandronate, zoledronate and etidronate. Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract.
- 20 If oral administration of the bisphosphonate is desired relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. However oral administration of high doses of bisphosphonates are associated with adverse gastrointestinal effects, especially those relating to the esophagus. Pamidronate has for example been associated with esophageal ulcers, see E.G. Lufkin et al.,
- 25 Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International, 4: 320-322 (1994).

- For the treatment of ulcer disease, various drugs such as antacid, anticholinergic agent, H₂-receptor antagonist and proton pump inhibitor have been used. The commercial
- 30 success of omeprazole has rekindled the interest in this field. The proton pump inhibition by omeprazole is irreversible and a reversible proton pump inhibitor has been suggested to have therapeutical benefits and thus attempts to develop a reversible proton pump inhibitor have been made. For example WO 96/05177 disclose certain 1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine compounds as a reversible proton pump inhibitor.

Further, tricyclic imidazo[1,2-a]pyridine compounds in WO 94/14795 have also been reported and pyrrolopyridazine compounds in EP 742 218.

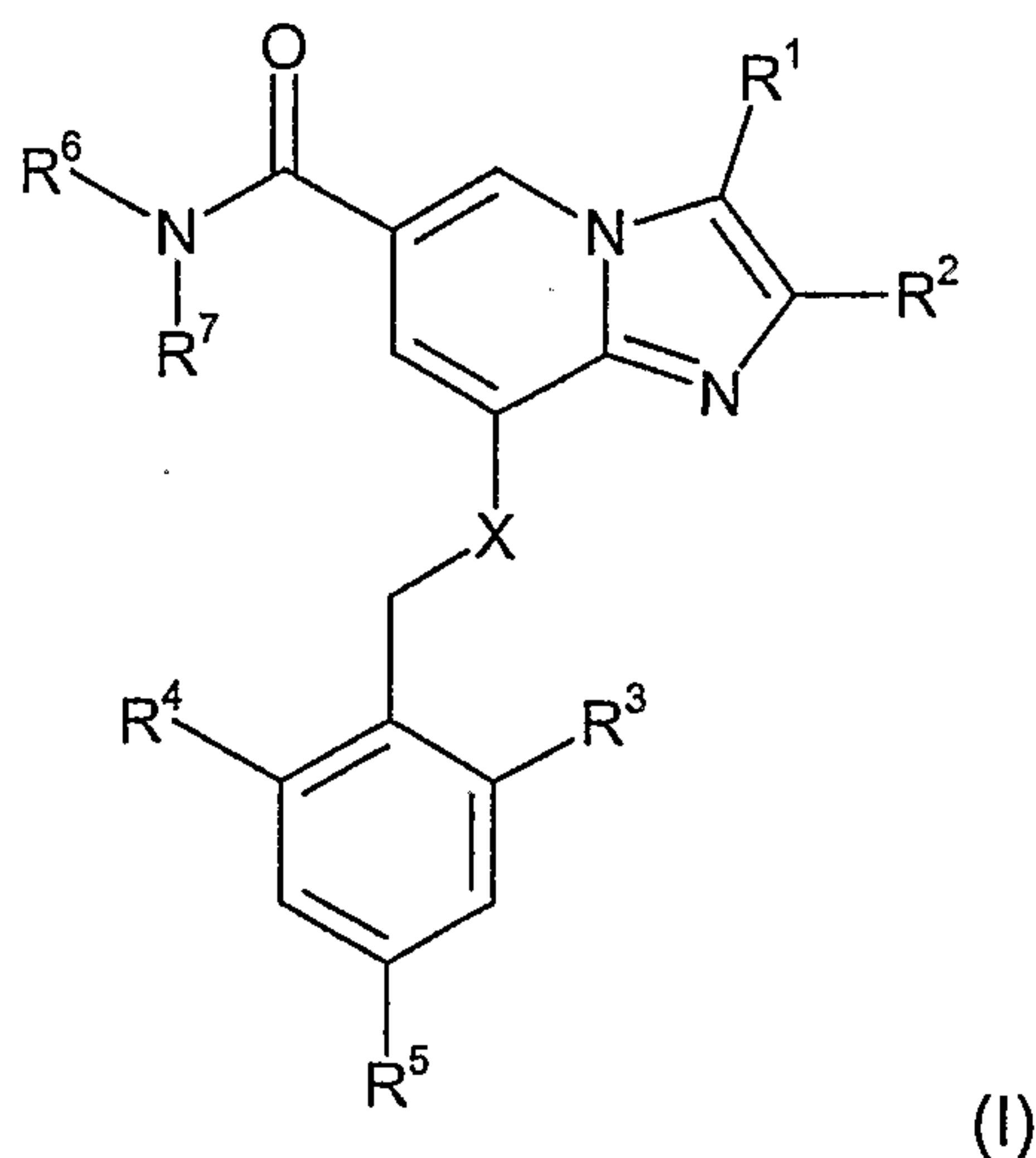
Certain 6-carboxamido-imidazo[1,2-a]pyridine compounds, as well as methods for producing said compounds, is described in WO 99/55706 and WO99/55705. Said compounds, and pharmaceutically acceptable salts thereof, is said to be effective in inhibiting secretion of gastric acid.

It has now surprisingly been found that certain pharmaceutically active compounds are useful in treatment and/or prevention of gastric ulcer induced by medicaments such as NSAID, COX-2 inhibitors, NO-NSAID and bisphosphonates.

Description of the invention

The present invention relates to the use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. The present invention can thus be used to prevent a common side-effect affecting users of these pharmaceutically effective compounds. This is easiest done by co-administration of the two medicaments.

One object of the present invention is thus the use of certain 6-carboxamido-imidazo[1,2-a]pyridine compounds, as well as pharmaceutically acceptable salts thereof, of the general Formula I



(I)

wherein R^1 is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

5 R^2 is

- (a) CH_3 , or
- (b) CH_2CH_3 ;

R^3 is

- (a) H,
- 10 (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl, or
- (d) halogen;

R^4 is

- (a) H,
- 15 (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl, or
- (d) halogen;

R^5 is

- (a) H, or
- 20 (b) halogen;

R^6 and R^7 are independently selected substituents, containing C, H, N, O, S, Se, P and halogen atoms, which give compounds of Formula I a molecular weight ≤ 600 ,

X is

- (a) NH, or
- 25 (b) O,

in the prevention of medicament induced gastric ulcer.

In a preferred embodiment of the present invention, R^1 is CH_3 or CH_2OH ; R^2 is CH_3 , R^3 is CH_3 or CH_2CH_3 ; R^4 is CH_3 or CH_2CH_3 ; R^5 is H, Br, Cl, or F; R^6 and R^7 are
30 independently

- (a) H,
- (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl,

- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl,
 (e) halogenated C₁-C₆ alkyl,
 (f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl,
 optionally substituted by one or more substituents selected from halogen, C₁-C₆
 5 alkyl, C₁-C₆ alkoxy, CF₃, OH, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, or CN;
 (g) aryl substituted C₁-C₆ alkyl, in which aryl represents phenyl, pyridyl, imidazolyl,
 indolyl, or naphthyl, optionally substituted with one or more substituents selected
 from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, or OH,
 (h) R⁸-(C₁-C₆) alkyl-, wherein R⁸ is NH₂C=O-, C₁-C₆ alkyl-NHC=O-, (C₁-C₆
 10 alkyl)₂NC=O-, C₁-C₆ alkyl-OOC-, cyano, C₁-C₆ alkyl-CO-NH-, C₁-C₆
 alkyl-OOCNH-, C₁-C₆ alkyl-O-, C₇-C₁₂ alkyl-O-, C₁-C₆ alkyl-SO-, C₁-C₆
 alkyl-S-, C₁-C₆ alkyl-C=O-, ArCONH-, Ar(C₁-C₆ alkyl)CONH-, ArC=O-,
 NH₂CONH-, C₁-C₆ alkyl-NHCONH-, (C₁-C₆ alkyl)₂-NCONH-, ArNHCONH-
 ,hydroxylated C₁-C₆ alkyl-O- or morpholinyl; wherein Ar represents phenyl,
 15 pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more
 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN,
 (i) C₇-C₁₂ alkyl,
 (j) OH,
 (k) R¹¹-(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R¹¹ is HOOC-, or C₁-C₆ alkyl -
 20 OOC-.

In a more preferred embodiment of the present invention, R¹ is

- (a) H,
 (b) CH₃, or
 (c) CH₂OH;

25 R² is

- (a) CH₃
 (b) CH₂CH₃

R³ is

- (a) H
 30 (b) C₁-C₆ alkyl,
 (c) hydroxylated C₁-C₆ alkyl

(d) halogen

R⁴ is

(a) H,

(b) C₁-C₆ alkyl,

5 (c) hydroxylated C₁-C₆ alkyl, or

(d) halogen;

R⁵ is

(a) H, or

(b) halogen;

10

R⁶, R⁷ are the same or different

(a) H,

(b) C₁-C₆ alkyl;

(c) hydroxylated C₁-C₆ alkyl

15 (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

X is

(a) NH, or

(b) O.

20 In a more preferred embodiment of the present invention, R¹ and R² are CH₃, R³ and R⁴ are the same or different C₁-C₆ alkyl, R⁵ is hydrogen, R⁶ and R⁷ are the same or different H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl, C₁-C₆ alkoxy-substituted or C₁-C₆ alkyl; and X is NH, or O.

25 As used herein, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

30 The term "halogen" includes fluoro, chloro, bromo and iodo.

The term "medicament induced gastric ulcer" consists of gastric ulcer induced or associated with the use of a medicament e.g. a medicant chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonates.

The term "prevent" or "prevention" is given its ordinary meaning and thus means the avoidance or alleviation of the serious consequences of a disease or a side-effect by early detection.

5

The pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention.

10

6-carboxamido-imidazo[1,2-a]pyridine of formula I above can thus be used in combination with NSAIDs and deliver the pharmaceutical effect of NSAID and surprisingly avoid the inherent noxious effect NSAIDS have on the stomach lining. It should be appreciated that there is no requirement that the components of the combination according to the present invention must be dosed simultaneously. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with an NSAID in therapy, e.g. for the treatment or prophylaxis of arthritis.

20

COX-2 inhibitors, the newest class of NSAIDS, work by blocking COX-2 enzyme which is involved in the inflammation pathway. By sparing COX-1 enzyme, gastrointestinal toxicity is reduced. A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with COX-2 inhibitors in therapy e.g. for the treatment or prophylaxis of arthritis. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with a COX-2 inhibitor for the treatment or prophylaxis of e.g. arthritis.

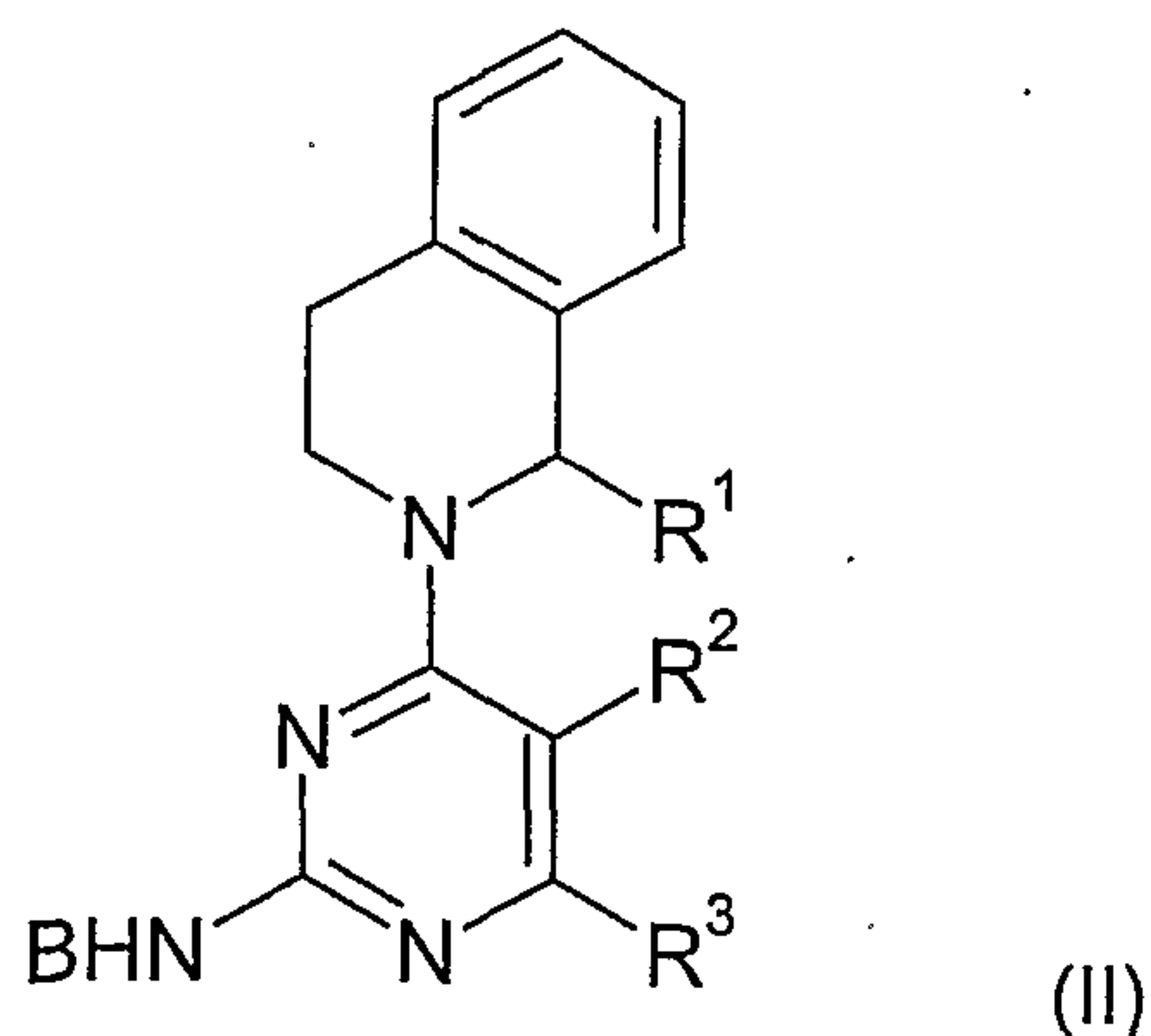
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Nitric oxide releasing NSAIDs (NO-NSAIDs) are disclosed in e.g. WO 94/04484. A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with an NO-NSAID e.g. for the treatment or prophylaxis of pain. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with an NO-NSAID for the treatment or prophylaxis of pain.

A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with bisphosphonates in therapy e.g. for the treatment or prophylaxis of osteoporosis. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with a bisphosphonate compound for the treatment or prophylaxis of e.g. osteoporosis.

Another object of the present invention is the use of certain 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II



wherein R^1 , R^2 and R^3 are independently selected from hydrogen or C_1 - C_3 alkyl; and

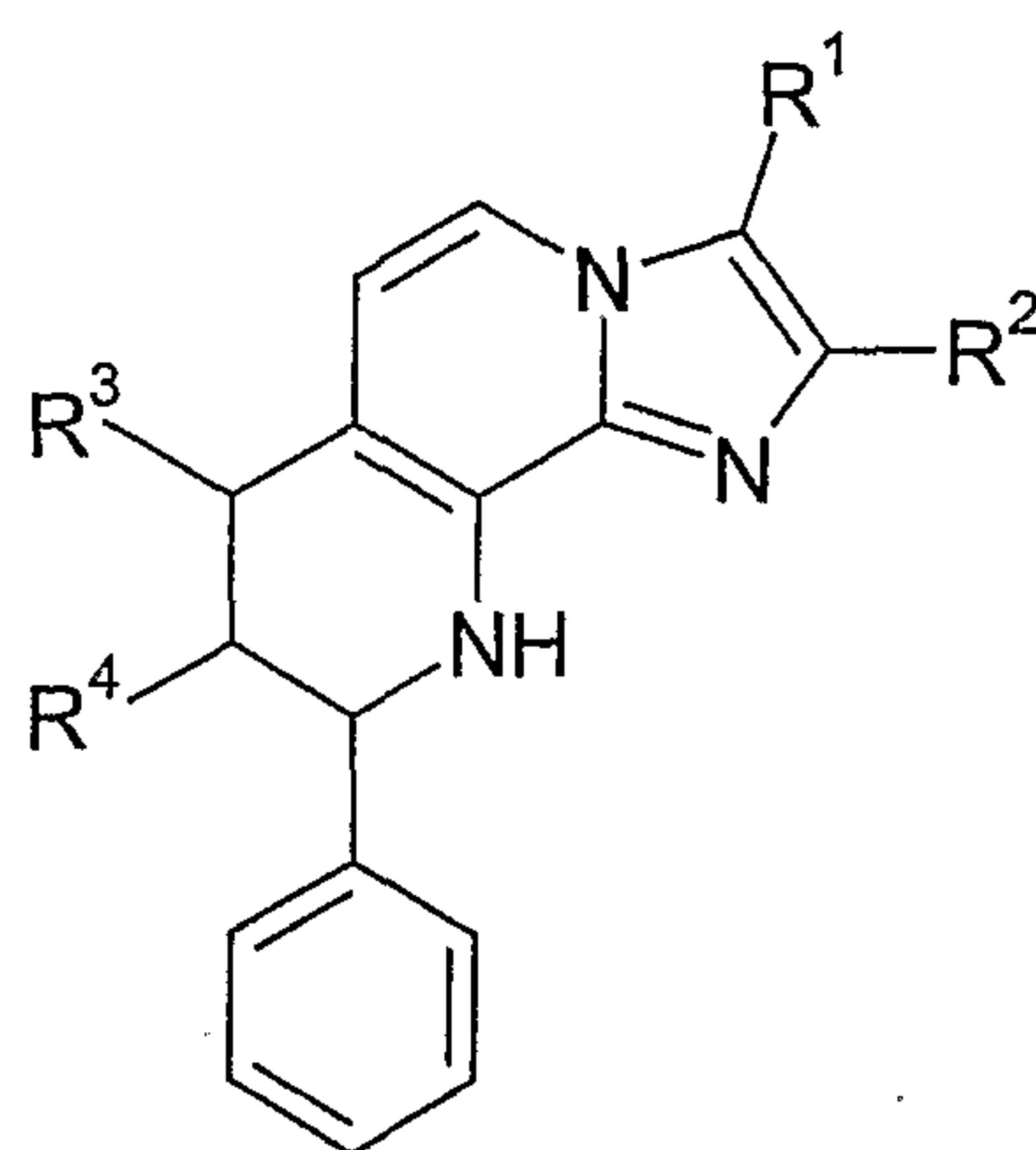
B is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₃-C₇ cycloalkyl, C₁-C₃ alkoxyethyl, substituted or unsubstituted phenylethyl, 3-trifluoromethylphenylmethyl, 4-fluorophenyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl;
in the prevention of medicament induced gastric ulcer.

5

In a more preferred embodiment of the present invention, R¹, R² and R³ of formula II are all methyl and B is 4-fluorophenyl.

Another object of the present invention is the use of certain tricyclic imidazo[1,2-a]pyridine compounds of formula III

10



(III)

wherein

15 R¹ is hydroxy C₁-C₄ alkyl;

R² is C₁-C₄ alkyl;

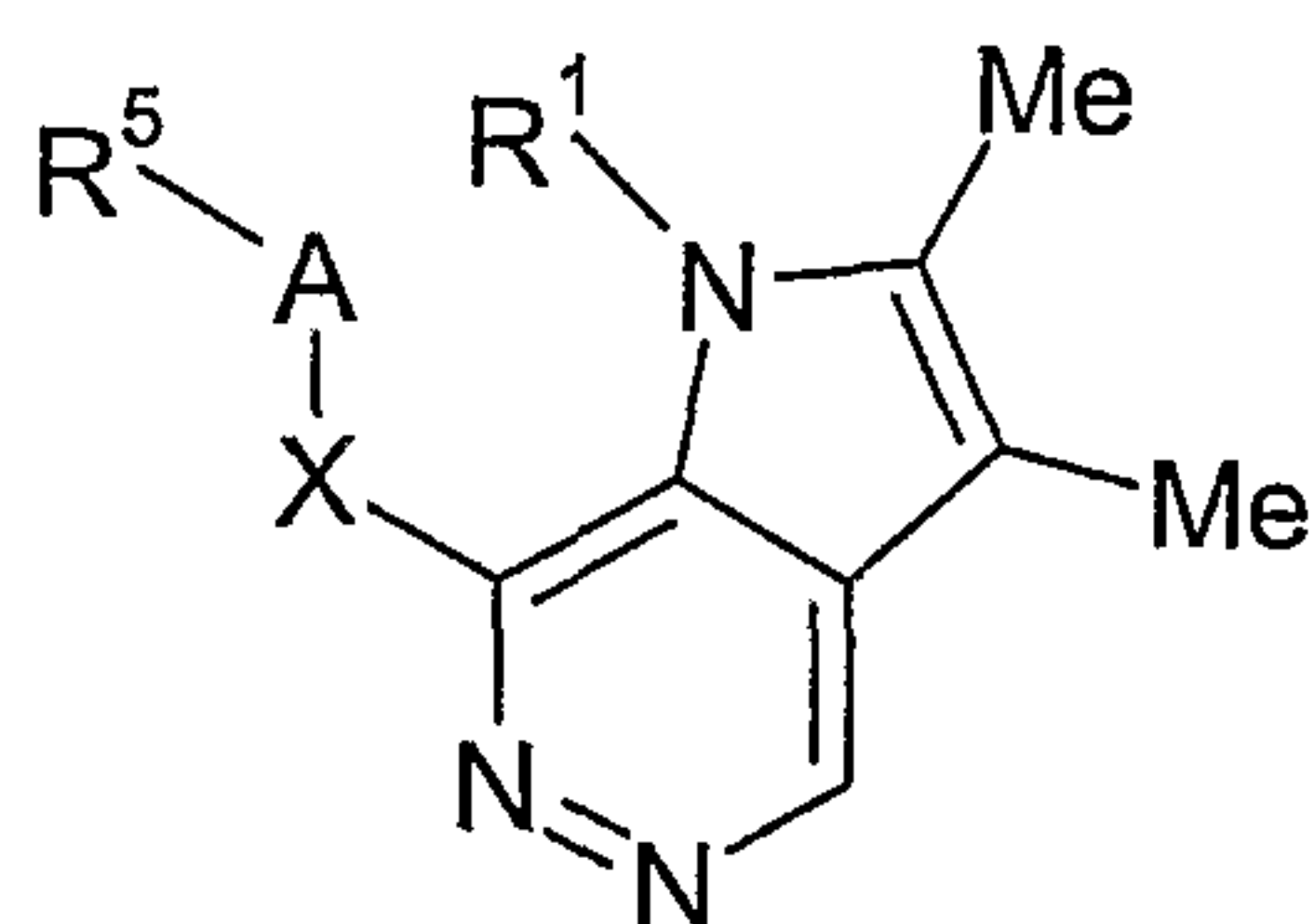
R³ and R⁴ are independently selected from hydrogen, hydroxy, C₁-C₄ alkoxy, halogenated C₁-C₄ alkoxy, C₁-C₄ alkoxy-C₁-C₄ alkoxy, halogenated C₁-C₄ alkoxy-C₁-C₄ alkoxy, C₁-C₄ alkylcarbonyloxy, halogenated C₁-C₄ alkylcarbonyloxy, or carbonyl;

20 in the prevention of medicament induced gastric ulcer.

In a more preferred embodiment of the present invention R¹ is hydroxymethyl; R² is methyl;

R³ and R⁴ are independently selected from hydrogen, hydroxy, C₁-C₄ alkoxy or C₁-C₄ alkoxy-C₁-C₄ alkoxy.

Another object of the present invention is the use of certain pyrrolopyridazine compounds of formula IV



(IV)

wherein

R^1 is 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-methyl-2-propenyl, 3-phenyl-2-propenyl, cyclo-propylmethyl, or 2-methylcyclopropylmethyl;

R^5 is a phenyl group optionally substituted with halogen;

A is methylene; and

X is oxygen;

in the prevention of medicament induced gastric ulcer.

A more preferred embodiment of the present invention is the use of certain

pyrrolopyridazine compounds of formula IV, wherein R^1 is 2-methylcyclopropylmethyl, and

R^5 is a p-fluorophenyl, A is methylene; and X is oxygen.

Another object of the present invention is the use of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, as well as pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the prevention of NSAID induced gastric ulcer.

Another object of the present invention is the use of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV for the manufacture of a medicament for the prevention of medicament induced gastric ulcer.

Another object of the present invention is the simultaneous, separate or sequential co-administration of NSAID with the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I for the prevention of NSAID induced gastric ulcer.

- 5 Another object of the present invention is the simultaneous, separate or sequential co-administration of a medicament chosen from the group consisting of NSAID, COX-2 inhibitor, NO-NSAID or bisphosphonate with a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV for
10 the prevention of medicament induced gastric ulcer.

Still a further object of the present invention is a method for the prevention of NSAID induced gastric ulcer, whereby an effective amount of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula 1, as well as pharmaceutically acceptable salts thereof,
15 as active agent is administered simultaneous, separate or sequential with an NSAID to a mammal.

Still a further object of the present invention is a method for the prevention of medicament induced gastric ulcer, whereby an effective amount of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV as
20 active agent is administered simultaneous, separate or sequential with a medicament chosen from a group consisting of COX-2 inhibitor, NO-NSAID, and bisphosphonate to a mammal.
25

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I to prevent NSAID induced gastric ulcer in a mammal.
30

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising a medicament chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonate together with a compound chosen from the

group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV to prevent medicament induced gastric ulcer in a mammal.

5

A pharmaceutical formulation comprising an medicament chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonate together with a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

15 The amount of the pharmaceutical active ingredients in the pharmaceutical formulation to prevent medicament induced gastric ulcer is an amount which varies according to the mammal being treated, the severity of the disease, the included pharmaceutical active ingredients, and the route of administration selected. Usually the amount of pharmaceutical active ingredients are between 0.1-95% by weight of the preparation, preferably between 0.1-20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising a COX-2 inhibitor together with a 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I in therapy, e.g. to prevent induced gastric ulcer in a mammal.

A pharmaceutical formulation comprising a COX-2 inhibitor together with the 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising an NO-NSAID together with a 6-carboxamido-imidazo[1,2-

a]pyridine compound of Formula I in therapy, e.g. to prevent induced gastric ulcer in a mammal.

A pharmaceutical formulation comprising a an NO-NSAID together with the 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

The present invention also relates to a kit comprising a dosage unit of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV and a dosage unit of a an NSAID, a COX-2 inhibitor, an NO-NSAID, or an bisphosphonate optionally with instructions for use.

Examples of NSAID to be used in the present invention include, but is not limited to,

Diclofenac,	Meloxicam,
Diflunisal,	Nabumetone,
Etodolac,	Naproxen,
Fenoprofen,	Oxaprozin,
Floctafenine,	Phenylbutazone,
Flurbiprofen,	Piroxicam,
Ibuprofen,	Sulindac,
Indomethacin,	Tenoxicam,
Ketoprofen,	Tiaprofenic Acid, and
Meclofenamate,	Tolmetin
Mefenamic Acid,	

Examples of COX-2 inhibitors to be used in the present invention include, but is not limited to, Celebrex (Celecoxib), Vioxx (Rofecoxib).

Examples of NO-NSAID to be used in the present invention include, but is not limited to, those disclosed in WO 96/32946, WO 96/35416, WO 96/38136, WO 96/39409, WO

00/50037, US 6,057,347, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/30641, WO 97/31654, WO 99/44595 and WO 99/45004.

5 Examples of bisphosphonates to be used in the present invention include, but are not limited to, alendronate, risedronate, tiludronate, ibandronate, zoledronate and etidronate.

The invention is illustrated, but in no way limited, by the following examples.

Examples

10

Groups of 10 male rats were given oral doses of vehicle, 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide(0.3, 1, 3 and 10 $\mu\text{mol/kg}$) or ranitidine (10 $\mu\text{mol/kg}$). Indomethacin 20 mg/kg, orally) was given 1 h after dosing. Stomach was removed 5 h after indomethacin and examined macroscopically

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Results:

Indomethacin induced ulcers in the corpus only, rumen and antrum were unaffected. Ulcers in the corpus were classified as pinhead (diameter 3 mm or less) or furrows (> 3 mm).

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2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide had a protective effect against gastric ulcers induced by indomethacin. This protective effect was dose-dependent and characterised by a decrease in the number of pinhead ulcers and ulcer furrows in the corpus. The decrease was statistically significant from the dose of 3 $\mu\text{mol/kg}$ and maximal at 10 $\mu\text{mol/kg}$. Ranitidine had no effect.

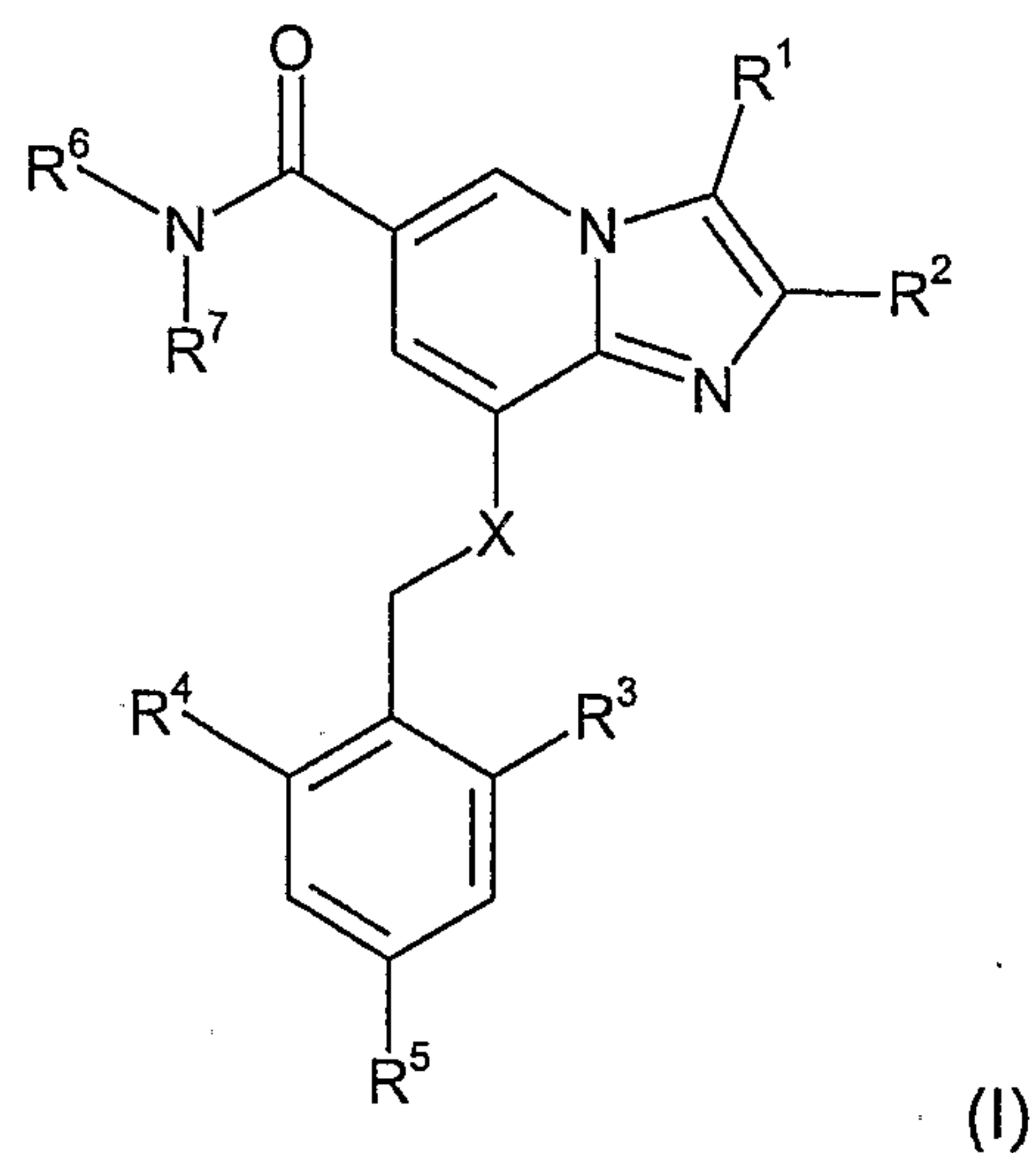
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Median number of gastric (corpus) ulcers induced by indomethacin

Group	Pinhead ulcers	Ulcer furrows
Vehicle	5	9
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)- imidazo[1,2-a]pyridine-6-carboxamide [0.3 µmol/kg]	5	8
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)- imidazo[1,2-a]pyridine-6-carboxamide [1 µmol/kg]	5	9
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)- imidazo[1,2-a]pyridine-6-carboxamide [3 µmol/kg]	2	1
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)- imidazo[1,2-a]pyridine-6-carboxamide [10 µmol/kg]	0	0
Ranitidine [10 µmol/kg]	7	11

CLAIMS

1. Use of a compound of formula I



5

or a pharmaceutically acceptable salt thereof, wherein R^1 is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

10 R^2 is

- (a) CH_3 , or
- (b) CH_2CH_3 ;

R^3 is

- (a) H,
- (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl, or
- (d) halogen;

15

R^4 is

- (a) H,
- (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl, or
- (d) halogen;

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R^5 is

- (a) H, or

(b) halogen;

R^6 and R^7 are independently selected substituents, containing C, H, N, O, S, Se, P and halogen atoms, which give compounds of Formula I a molecular weight ≤ 600 ,

X is

5 (a) NH, or

(b) O;

in the prevention of medicament induced gastric ulcer.

2. Use according to claim 1 wherein R^1 is CH_3 or CH_2OH ; R^2 is CH_3 , R^3 is CH_3 or

10 CH_2CH_3 ; R^4 is CH_3 or CH_2CH_3 ; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl,

(d) C_1-C_6 alkoxy-substituted C_1-C_6 alkyl,

15 (e) halogenated C_1-C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3 , OH, C_1-C_6 alkyl-NH-, $(C_1-C_6$ alkyl) $_2$ -N-, or CN-

(g) aryl substituted C_1-C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, 20 indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3 , or OH,

(h) $R^8-(C_1-C_6)$ alkyl-, wherein R^8 is $NH_2C=O-$, C_1-C_6 alkyl-NHC=O-, $(C_1-C_6$ alkyl) $_2$ NC=O-, C_1-C_6 alkyl-OOC-, cyano, C_1-C_6 alkyl-CO-NH-, C_1-C_6 alkyl-OOCNH-, C_1-C_6 alkyl-O-, C_7-C_{12} alkyl-O-, C_1-C_6 alkyl-SO-, C_1-C_6 25 alkyl-S-, C_1-C_6 alkyl-C=O-, ArCONH-, Ar(C_1-C_6 alkyl)CONH, ArC=O-, NH_2CONH- , C_1-C_6 alkyl-NHCONH-, $(C_1-C_6$ alkyl) $_2$ -NCONH-, ArNHCONH-, hydroxylated C_1-C_6 alkyl-O- or morpholinyl; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3 , OH, CN,

30 (i) C_7-C_{12} alkyl,

(j) OH,

(k) R^{11} -(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R^{11} is HOOC-, or C₁-C₆ alkyl - OOC₁₁.

3. Use according to claim 1 wherein R^1 is

- 5 (a) H,
(b) CH₃, or
(c) CH₂OH;

R^2 is

- (a) CH₃
10 (b) CH₂CH₃

R^3 is

- (a) H
(b) C₁-C₆ alkyl,
(c) hydroxylated C₁-C₆ alkyl
15 (d) halogen

R^4 is

- (a) H,
(b) C₁-C₆ alkyl,
(c) hydroxylated C₁-C₆ alkyl, or
20 (d) halogen;

R^5 is

- (a) H, or
(b) halogen;

25 R^6 , R^7 are the same or different

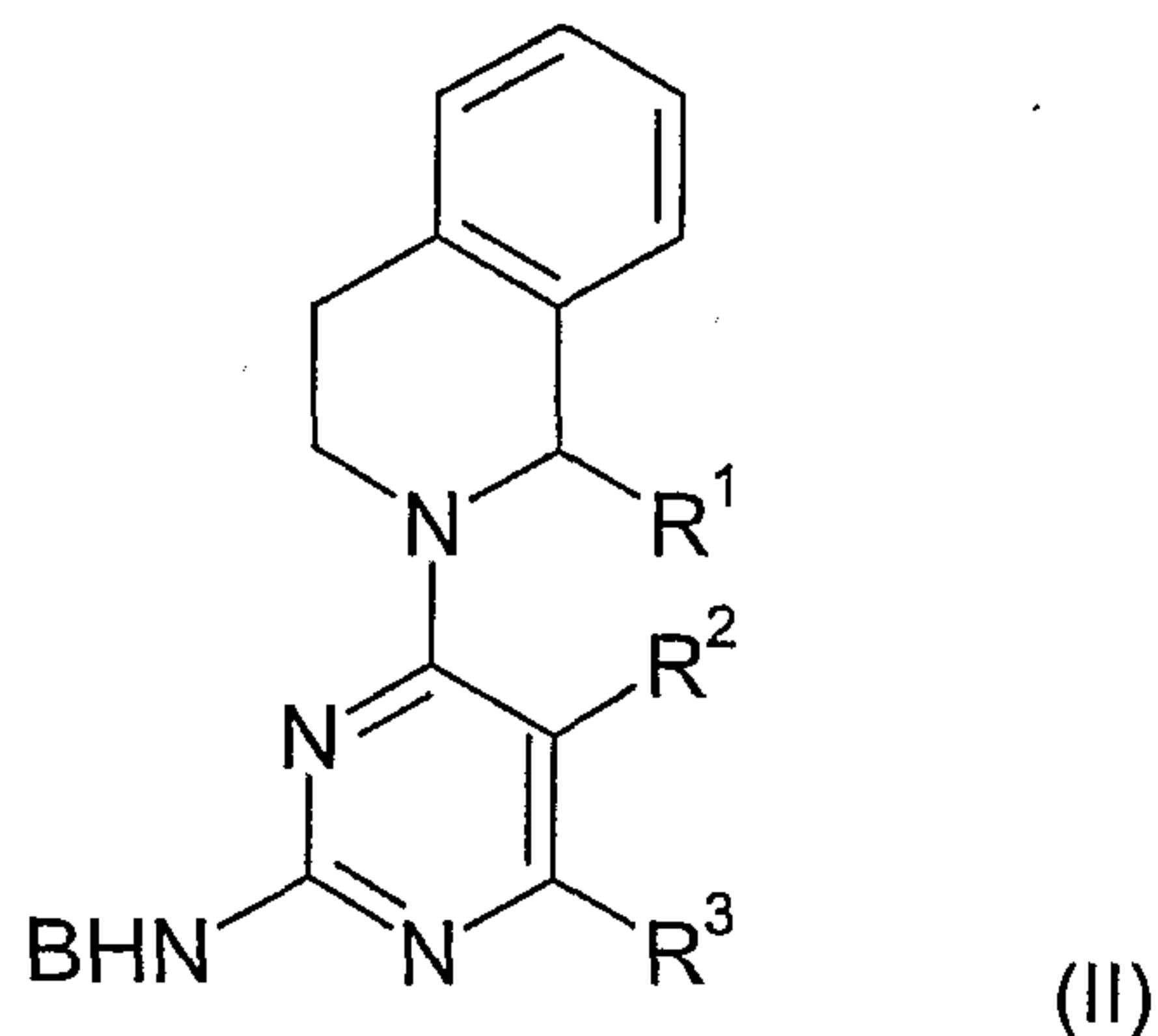
- (a) H,
(b) C₁-C₆ alkyl;
(c) hydroxylated C₁-C₆ alkyl
(d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

30 X is

- (a) NH, or
(b) O.

4. Use according to claim 1, wherein R^1 and R^2 are CH_3 , R^3 and R^4 are the same or different C_1 - C_6 alkyl, R^5 is hydrogen, R^6 and R^7 are the same or different H, C_1 - C_6 alkyl, hydroxylated C_1 - C_6 alkyl, C_1 - C_6 alkoxy-substituted or C_1 - C_6 alkyl; and X is NH, or O.

5. Use of a compound of formula II,



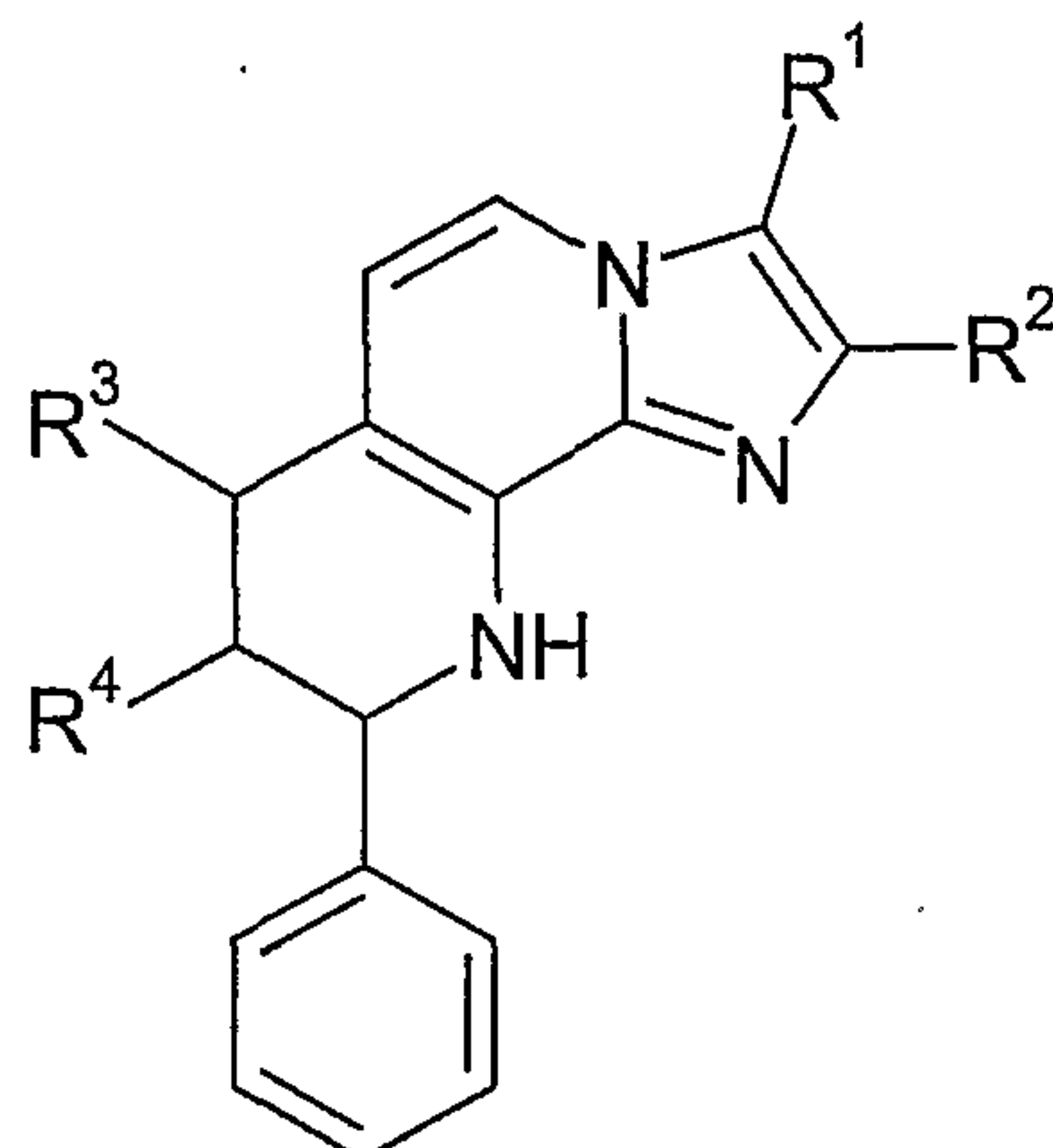
or a pharmaceutically acceptable salt thereof, wherein

10 R^1 , R^2 and R^3 are independently selected from hydrogen or C_1 - C_3 alkyl; and B is C_1 - C_3 alkyl, C_2 - C_4 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_3 alkoxyethyl, substituted or unsubstituted phenylethyl, 3-trifluoromethylphenylmethyl, 4-fluorophenyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl; in the prevention of medicament induced gastric ulcer.

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6. Use according to claim 5, wherein R^1 , R^2 and R^3 are all methyl and B is 4-fluorophenyl.

7. Use of a compound of formula III,



(III)

wherein

R¹ is hydroxy C₁-C₄ alkyl;

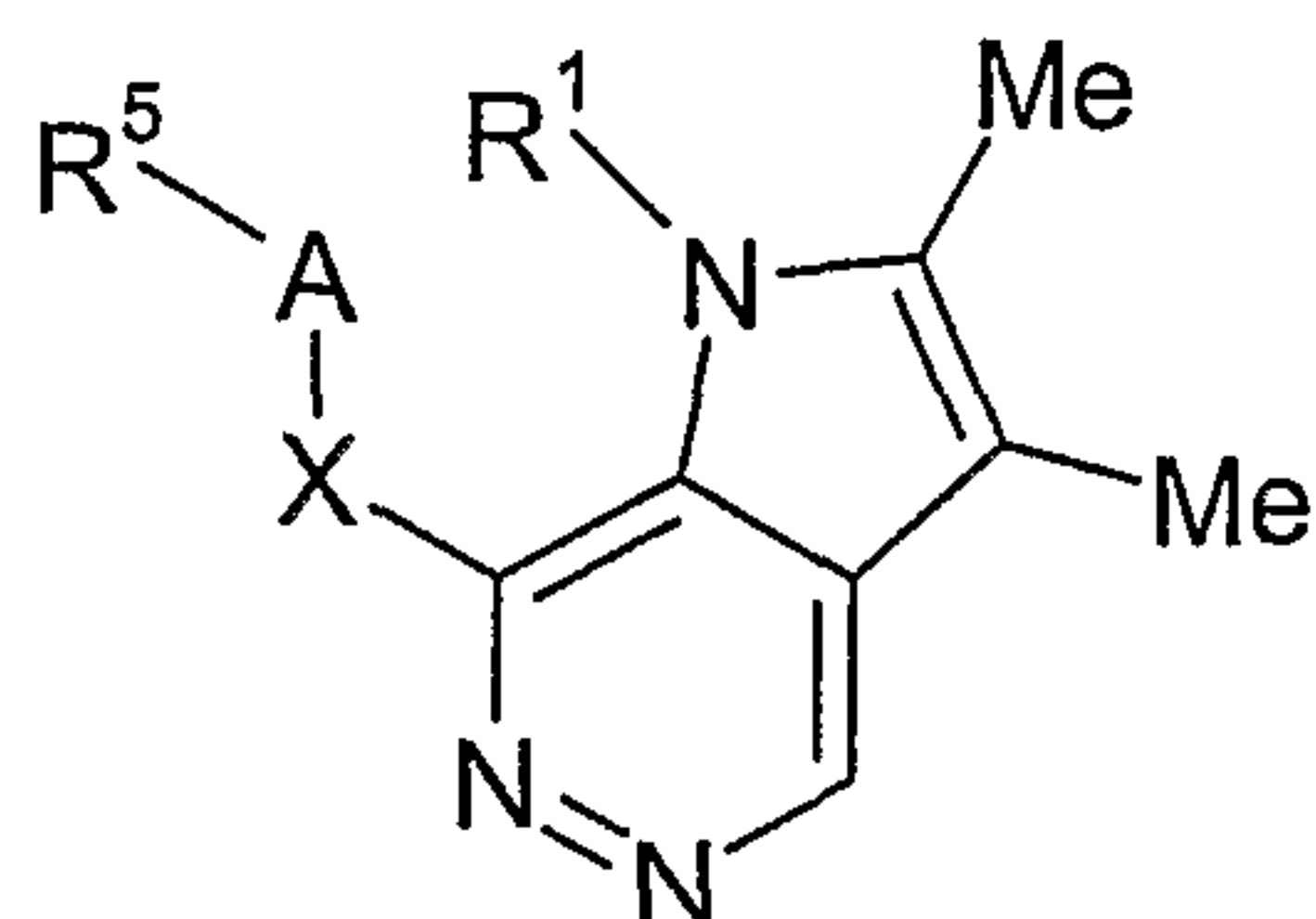
5 R² is C₁-C₄ alkyl;

R³ and R⁴ are independently selected from hydrogen, hydroxy, C₁-C₄ alkoxy, halogenated C₁-C₄ alkoxy, C₁-C₄ alkoxy-C₁-C₄ alkoxy, halogenated C₁-C₄ alkoxy-C₁-C₄ alkoxy, C₁-C₄ alkylcarbonyloxy, halogenated C₁-C₄ alkylcarbonyloxy, or carbonyl;
in the prevention of medicament induced gastric ulcer.

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8. Use according to claim 7, wherein R¹ is hydroxymethyl; R² is methyl; R³ and R⁴ are independently selected from hydrogen, hydroxy, C₁-C₄ alkoxy or C₁-C₄ alkoxy-C₁-C₄ alkoxy.

15 9. Use of a compound of formula IV,



(IV)

wherein

R¹ is 1 -propenyl, 2-propenyl, 1 -butenyl, 2-butenyl, 2-methyl-2-propenyl, 3-phenyl-2-propenyl, cyclo-propylmethyl, or 2-methylcyclopropylmethyl;

R⁵ is a phenyl group optionally substituted with halogen;

A is methylene; and

5 X is oxygen;

in the prevention of medicament induced gastric ulcer.

10. Use according to claim 9, wherein R¹ is 2-methylcyclopropylmethyl, and R⁵ is a p-fluorophenyl, A is methylene; and X is oxygen.

10

11. A combination comprising a compound as defined in claims 1 to 10 and an NSAID for simultaneous, sequential or separate use in therapy.

12. A combination comprising a compound as defined in claims 1 to 10 and a COX-2 inhibitor for simultaneous, sequential or separate use in therapy.

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13. A combination comprising a compound as defined in claims 1 to 10 and an NO-NSAID for simultaneous, sequential or separate use in therapy.

14. A combination comprising a compound as defined in claims 1 to 10 and a bisphosphonate for simultaneous, sequential or separate use in therapy.

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15. A pharmaceutical formulation comprising the combination according to any one of claims 11 to 14 and a pharmaceutically acceptable carrier or diluent.

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16. A first pharmaceutical formulation comprising a compound as defined in claims 1 to 10 and a pharmaceutically acceptable carrier or diluent; and a second pharmaceutical formulation comprising an NSAID, a COX-2 inhibitor, a bisphosphonate or an NO-NSAID and a pharmaceutically acceptable carrier or diluent.

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17. A kit comprising a dosage unit of a compound as defined in claims 1 to 10 and a dosage unit of a an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate,

optionally with instructions for use.

18. Use of a compound of claims 1 to 10 for the manufacture of a medicament for the prevention of medicament induced gastric ulcer.

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19. Method for prevention of medicament induced gastric ulcer, whereby an compound according to claim 1 to 10, as active agent is administered simultaneous, separate or sequential with an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate to a mammal.

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20. An oral pharmaceutical composition in unit dosage form for the prevention of medicament induced gastric ulcer in a mammal comprising either an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate together with a compound of claims 1 to 10.

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