The present invention relates to proton pump inhibitors such as omeprazole, esomeprazole, rabeprazole, lanoprazole, pantoprazole, ilaprazole, tenaprazole, dexlansoprazole, their salts or their mixtures, for use in anti-inflammatory therapy.
The present invention relates to proton pump inhibitors for use in anti-inflammatory therapy. In greater detail, the invention relates to proton pump inhibitors (PPI) such as omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts or their mixtures, for use in anti-inflammatory therapy. It is largely accepted that excessive or deregulated inflammation is an important cause of tumours and many other human diseases, acute (such as sepsis) and chronic (autoimmune diseases and auto-inflammatory diseases, diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis etc.) (4-6). Anti-inflammatory therapies already existing, essentially based on non-steroidal anti-inflammatory drugs and cortisone, have numerous drawbacks. The first drawback is represented by the numerous undesired effects. All non-steroidal anti-inflammatory drugs (NSAIDs) are associated to gastro-intestinal toxicity, sometimes serious; the greatest risk is for the elderly (7). Other undesired effects are analgesic nephropathy and inhibition of the platelet function. In the case of steroid anti-inflammatory drugs the undesired effects are osteoporosis and reduction of collagen synthesis, oedema and water retention, stimulation of peptic ulcers (8, 9).

New-generation biological drugs inhibiting Tumor Necrosis Factor (TNF)-alpha and Interleukin-1 (IL-I)beta, two most significant inflammation mediators in the pathogenesis and physiopathology of inflammation-based diseases (5, 6, 10), have been developed (5), but are extremely expensive, and not available in many areas of the world.

A further problem in treatment of inflammatory diseases is that in many cases the anti-inflammatory drugs today available have a low therapeutic effectiveness. Sepsis, an inflammation-based pathology with
high mortality, is in fact resistant to any treatment (1).

In the light of the above it is therefore clear that there is a need to have available new anti-inflammatory drugs having low toxicity and high efficiency and therefore able to obviate the drawbacks of the anti-inflammatory drugs at present known.

It is known that compounds known under the generic term of proton pump inhibitors (PPI: Omeprazole, Esomeprazole, Rabeprazole, Lansoprazole) are effective on inhibition of gastric secretion and have a protective activity on the gastric mucosa. Also known as proton pump inhibitors are compounds such as pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole. The above-mentioned compounds are used in prevention and treatment of pathologies connected to gastric acidity such as for example gastritis, gastric and duodenal ulcer, gastro-oesophageal reflux. They are therefore drugs that are registered or under registration procedure for these uses. For clinical effectiveness and the absence of tachyphylaxis, proton pump inhibitors have largely replaced H-2 receptor antagonists in treatment of gastric hyperacidity disorders (1,2).

Further, experimental data indicate an effectiveness of these drugs in the prevention and treatment of tumours (3).

It has been found that proton pump inhibitors are able to inhibit secretion of the pro-inflammatory cytokines IL-1beta and TNF-alpha. Therefore, said inhibitors, such as Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, can be advantageously used in anti-inflammatory treatment of acute inflammatory states (comprising sepsis in its various forms) and chronic inflammatory states, both as a monotherapy and in association with other drugs.

In more detail, according to the present invention, an *in vitro* study was made concerning the effectiveness of proton pump inhibitors on the production of IL-1beta by primary human monocytes and murine
macrophages, and on the production of TNF alpha and on the survival in a
murine model of sepsis from bacterial endotoxin (LS) in vivo. In all the
tested experimental systems the proton pump inhibitors inhibited the
secretion of pro-inflammatory cytokines; they have also increased survival
or induced healing in mice with endotoxin shock. The proton pump
inhibitors (PPI) can therefore be advantageously used as blockers of the
production of IL-1beta and TNF-alpha pro-inflammatory cytokines and
therefore as an effective drug in treatment of inflammatory diseases,
including sepsis.

Further, as mentioned above, proton pump inhibitors are protectors
of the gastric mucosa used orally to prevent the most frequent collateral
effect of conventional anti-inflammatories, non-steroidal anti-inflammatory
drugs or steroids, i.e. gastric damage.

Therefore, the use of proton pump inhibitors in treatment of acute
and chronic inflammatory states offers important advantages in
comparison to conventional anti-inflammatory drugs: low or nil toxicity
even if injected intravenously at high dosage (16); low cost; high efficiency
in pathologies in which the conventional anti-inflammatories have a low or
nil effectiveness.

The invention therefore specifically relates to a proton pump
inhibitor compound for use in anti-inflammatory therapy.

In the present invention, the proton pump inhibitor compound can
be selected from the group consisting of omeprazole, esomeprazole,
rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole,
dexlansoprazole, their salts, or their mixtures (i.e. combinations of proton
pump inhibitor compounds or of their salts). From among the proton pump
inhibitor compounds, the preferred one is esomeprazole (which is the S-
enantiomer of the racemate omeprazole) as it is eliminated more slowly
than the enantiomer R-omeprazole and therefore has the kinetic
advantage of having a longer half-life. Further, esomeprazole has already
been used in Humans intravenously to inhibit gastric secretion (16).

In particular, the compound according to the present invention can be used in treatment of acute or chronic inflammatory diseases, selected from a group consisting of sepsis, autoimmune diseases, such as for example Systemic lupus erythematosus, rheumatoid arthritis, Hashimoto’s thyroiditis, scleroderma and dermatomyositis, autoimmune diseases (17), diabetes, atherosclerosis, obesity, cardiovascular diseases, osteoarthritis, diseases of the central nervous system such as depression and Parkinson’s.

As regards treatment of sepsis, this term comprises neonatal sepsis, necrotizing enterocolitis, Systemic inflammatory response syndrome (SIRS), trauma shock, grave or severe sepsis (septic shock).

The proton pump inhibitor compound according to the present invention, its salts or combinations of said compounds or their salts can be administered parenterally such as for example by intravenous, intramuscular, subcutaneous injection.

The compound according to the present invention can be administered in combination with at least one drug selected from the group consisting of NSAIDs, corticosteroid, sulfasalazine, biological drugs (receptor antagonists or monoclonal antibodies) which act as inhibitors of the main inflammatory cytokines, TNF-alpha, IL-1 and IL-6.

When said compound is for use in anti-inflammatory therapy of sepsis, it can be administered in combination with beta-lactam antibiotics, P2X7 receptor inhibitor drugs, which at present are drugs under development (18) and bisphosphonates (19), extracellular ATP hydrolysing drugs, (apyrase, 20), TLR4 receptor antagonists which at present are tested in clinical trials (21).

The present invention further concerns a combination of a proton pump inhibitor compound with a drug selected from the group consisting of NSAIDs, corticosteroid, sulfasalazine, TNF-alpha inhibitor, IL-1 inhibitor or
IL-6 antagonist, for separate, simultaneous or sequential use in anti-inflammatory therapy.

As mentioned above, the proton pump inhibitor compound can be selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, salts thereof, or mixtures thereof (i.e. combinations of proton pump inhibitors or their salts).

In particular, the combination according to the present invention can be used in treatment of acute or chronic inflammatory diseases selected from the group consisting of sepsis, autoimmune diseases, among which for example Systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, scleroderma and dermatomyositis, autoinflammatory diseases (17), diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis, diseases of the central nervous system such as depression and Parkinson's.

The present invention further concerns a combination of a proton pump inhibitor compound with a drug selected from the group consisting of NSAIDs, corticosteroid, sulfasalazine, TNF-alpha inhibitor, IL-1 inhibitor or IL-6 antagonist, for separate, simultaneous or sequential use in anti-inflammatory therapy of sepsis.

As mentioned above, the proton pump inhibitor compound can be selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts, or their mixtures (i.e. combinations of proton pump inhibitors or of their salts).

Further, the proton pump inhibitor compound is administered parenterally such as for example by intravenous, intramuscular, subcutaneous injection.

The present invention further concerns a pharmaceutical composition comprising or consisting of a proton pump inhibitor
compound, as active ingredient, in association with one or more excipients and/or adjuvants, for use in anti-inflammatory therapy. As mentioned above, the proton pump inhibitor compound can be selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts, or their mixtures. In particular, the pharmaceutical composition according to the present invention can be used in treatment of acute or chronic inflammatory diseases selected from the group consisting of sepsis, autoimmune diseases, autoinflammatory diseases, diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis, diseases of the central nervous system such as depression or Parkinson's.

The term sepsis comprises neonatal sepsis, necrotizing enterocolitis, Systemic inflammatory response syndrome, trauma shock, grave or severe sepsis.

The pharmaceutical composition according to the present invention can further comprise at least a drug selected from the group consisting of NSAIDs, corticosteroid, sulfasalazine, TNF-alpha inhibitor, IL-1 inhibitor or IL-6 antagonist.

When the pharmaceutical composition is for use in anti-inflammatory therapy of sepsis, said pharmaceutical composition can further comprise beta-lactam antibiotics, receptor P2X7 inhibitor drugs, extracellular ATP hydrolysing drugs, TLR4 receptor antagonists.

The pharmaceutical compound according to the present invention can be administered parenterally such as for example by intravenous, intramuscular, subcutaneous injection.

The present invention will now be described, by way of non-limiting illustration, with particular reference to some illustrative examples and to the figures of the accompanying drawings, in which:

Figure 1 shows that omeprazole inhibits secretion of IL-1β and TNF-α induced by various antagonists of Toll-like Receptors (TLR) in
human monocytes coming from healthy subjects or patients affected by an auto-inflammatory disease due to mutation of the cryopyrin gene (Cryopyrin Associated Periodic Syndrome, CAPS). (a) Healthy monocytes were cultivated in a neutral pH medium (pH 7.4) or acid (pH 6.5) and stimulated with LPS (100 ng/ml) in the absence or presence of omeprazole (OME, 300 pM). The secretion of IL-1β and TNF-α was quantified in supernatants using ELISA at 18 and 6 hours from stimulation, respectively. (b) secretion of IL-1β and TNF-α in the supernatants of stimulated monocytes with various agonists of TLRs, LPS (100 ng/ml), R848 (5 µg/ml) and zymosan (ZYM, 20 µg/ml), alone or in combination (LRZ). The data is expressed in ng/ml (mean of 5 experiments of different subjects ±S.E.M.). (c) monocytes of CAPS patients (n=4) and healthy donors (HD; n=4) were stimulated with 100 ng of LPS alone or in combination with omeprazole (OME, 300 µM). IL-1β was quantified by ELISA in 18 h supernatants.

Figure 2 shows the inhibition of the secretion of IL-1β and TNF-α by scalar doses of PPI. The monocytes from healthy donors were stimulated with LPS and dose-response experiments (from 10 µM to 300 µM) were carried out with omeprazole (A), esomeprazole (B), lansoprazole (C), pantoprazole (D) and rabeprazole (E). The supernatants were collected after 18h and 6h so as to detect the levels of IL-1β (left panels) and TNF-α (right panels). The data is expressed as a percentage of the secretion in the presence of PPI vs the secretion induced by the LPS alone; mean ± SEM of 4 experiments.

Figure 3 shows that treatment with omeprazole down-modulates the mRNA of TNF-α and prevents activation of the inflammasome, preventing outflow of K+. (A) RT-PCR of IL-1β and TNF-α mRNA extracted 3h following exposure to LPS ± omeprazole. The data is expressed as a percentage of the levels of mRNA (normalised expression mean) in cells stimulated with LPS + OME vs LPS (mean ±
SEM of 4 independent experiments). (B) Secretion of IL-1p and TNF-a by monocytes (same subjects analysed in a) stimulated with LPS or LPS + OME for 6h (TNF-a) and 18h (IL-1β). The data is expressed as a percentage of the secretion by the cells stimulated with LPS+OME vs cells stimulated with LPS alone (mean ± SEM of 4 independent experiments). (C) Western Blot Analysis of intracellular pro-IL-1β in various moments after the LPS stimulation, with or without omeprazole (OME). α-tubulin is used as a control (a representative experiment on 5 carried out). (d, e) Human monocytes (d) or murine peritoneal macrophages (e) were treated with LPS for 3h (d) or 18 hours (E) and then exposed to 1 mM ATP (30 min) or 20 µM Nigericin (Nig, 20 min) with or without omeprazole (OME). IL-1β secretion was analysed by ELISA. The data is expressed in ng/ml (mean ± SEM of 4 independent experiments). (F) Western blot of p10 caspase-1 in cell lysates of murine macrophages stimulated for 18h with LPS, and then for 20 min. with 5 mM ATP or 20 µM nigericin (Nig), with or without omeprazole (OME). (G) The monocytes stimulated for 3 hours with LPS were treated with PBFI (a potassium-sensitive fluorophore) and incubated in medium with LPS (LPS) or with 40 µM Nigericin (LPS+Nig) or 40 µM Nigericin plus 300 µM omeprazole (LPS+Nig+OME). The fluorescence of the PBFI was measured every 60s for 20 min. The data is expressed as a ratio 340/380 of the intensity of PBFI fluorescence (mean of 3 independent experiments ±SEM). (H) Intensity of PBFI fluorescence after 20 min. in the various culture conditions shown in panel G is expressed as a percentage with respect to time 0. *P <0.05, **P <0.01, *** P <0.001

Figure 4 shows that Esomeprazole (ESO) protects the mice from endotoxin shock, suppresses the systemic production of TNF-a and IL-1β and induces resistance to re-injection of LPS. (A) Forty mice were iv injected with LPS (12.5mg/Kg. Other mice also received ip ESO (12.5 mg / Kg) 30 minutes before (N = 40), 30 minutes after (N = 10) or 90
minutes after (N=7) the injection LPS. The mice were monitored for survival. (B) TNF-a (left panel) and IL-1β (right panel) in the serum of mice treated with LPS and LPS + ESO were quantified by ELISA (ng/ml) 90 min (TNF-a) or 4 h (IL-1β) after the injection of LPS (mean±SEM, n=11). (C) Fifteen mice treated with ESO and surviving the first shock with LPS (survived LPS+ESO) were re-injected with LPS, with no treatment, 3 weeks after the first injection. As a control, 10 naive mice were injected with LPS. The mice were monitored for survival. (D) the levels of TNF-a (on the left) and IL-1β (on the right) were quantified in the naive mice serum or re-injected using ELISA (ng/ml; mean ± SEM; N=8 for TNF-a, N = 2 for IL-1β). * P <0.05, ′′ P <0.01 , ′′′ P <0.001.

Figure 5 shows that the macrophages from mice that survived the re-injection of LPS secrete less TNF-a and IL-1β in response to various TLR agonists, (a, b) peritoneal macrophages from mice treated with ESO and which survived the first LPS shock (N = 4) and macrophages from naive mice (N = 6) were stimulated with LPS, zymosan (ZYM), R848, Pam3CSK4 (PAM3), Poly-I:C and flagellin (Flag) for 4 (a) or 18 h (b). TNF-a (a) and iL-1β (b) were quantified in supernatants after 4 or 18 h. (c) peritoneal macrophages from mice treated with ESO and which survived the first LPS shock (N = 4) and macrophages from naive mice (N = 6) were stimulated with LPS, PAM3 or poly-I:C for 18 h followed by 30 min with 5 mM ATP and IL-1β secreted was quantified in the supernatants (ng/ml; mean ± SEM; N = 4). * P <0.05; ′′ P <0.01 ; ′′′ P <0.001.

Figure 6 shows that mice treated with Esomeprazole that survived LPS are resistant to the generalised inflammation induced by zymosan. Mice treated with Esomeprazole healed after the first injection with LPS (survived LPS+ESO, N=5) and naive mice were injected with zymosan (Zym, 1g/Kg). The mice were monitored for survival (a) and loss of body weight (b; N = 4). (C) the levels of TNF-a (on the left; N=4) and IL-1β (on the right; N=2) were quantified (ng/ml; mean ± SEM. * P <
Figure 7 shows that Esomeprazole comes from peritonitis induced by Thioglycollate. The isolated non-treated mouse peritoneal cells (Controls, Con) or cells from mice intraperitoneally injected with Thioglycollate alone (Thio) or with Thioglycollate 30 minutes following ip injection with ESO (Thio + ESO) were counted. The data is expressed as total number of inflammatory cells present in the peritoneal wash (mean ± SEM; N = 3). * P < 0.05; *** P < 0.001.

**EXAMPLE 1:** In vitro study on the ability of Omeprazole to inhibit secretion of IL-1beta and TNF-alpha in human monocytes and by murine macrophages stimulated with LPS and ATP

**Materials and Methods**

For the in vitro study on the ability of omeprazole to inhibit secretion of IL-1 beta of TNF-alpha in human monocytes, peripheral blood monocytes of healthy donors or patients affected by cryopyrin-associated periodic syndrome (CAPS, ref. 13)(1 0^6/ml) were enriched by fractioning on the Ficoll gradient and adhesion on a dish and then stimulated with 100 ng/ml of LPS as described (12) in the presence or absence of 100 microM Omeprazole (OME) for 18 h. At the end of the incubation the secretion of IL-1beta and of TNF-alpha was measured in the supernatants by ELISA as described (12). To evaluate the effect of exogenous ATP, a known inductor of inflammasome activation which increases and accelerates the secretion of IL-1b induced by LPS (14,15), the monocytes obtained from healthy donors (10^6/ml) were stimulated with 100 ng/ml of LPS for 3h, in the presence or absence of 100 microM OME during the third hour, and then incubated for a further 20 min without or with 1mM ATP (14).

Experiments on dose response with omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole were carried out on monocytes stimulated with LPS.

For the in vitro study on the ability of Omeprazole to inhibit
secretion of IL-1beta by the murine macrophages stimulated with LPS and ATP, macrophages obtained by peritoneal washing of pre-injected (by 72 hours) mice in peritoneum with 0.7 ml of 4% thioglycollate were plated at 10^6 cell/ml. After 1 hour the non-adhering cells were removed and the macrophages treated with LPS 100 ng/ml. After 12 hours of incubation, omeprazole (100 microM) or an equal volume of carrier were added to the cultures. After 1 hour, the cells were stimulated with 5 mM ATP for 20 minutes. IL-1 beta secreted in the supernatants was quantified by ELISA.

For the study of the molecular mechanism underpinning the inhibition of IL-1b and TNFα the following were carried out: 1. Real Time PCR experiments on the mRNA of monocytes stimulated with LPS±OME; 2. Western blot experiments for evaluating the intracellular levels of pro-IL-beta in the presence or absence of OME, and for evaluating the effect of OME on the activation of caspase-1; 3. Fluorimeter experiments with potassium-specific fluorophore to verify whether OME influences outflow of K+ necessary for activation of the inflammasome.

**Results**

On human cells: our data indicates that proton pump inhibitors inhibit secretion of IL-1beta and TNF-a by LPS-stimulated human monocytes at various pH (Figure 1a) and with various agonists of the Toll-like Receptors, such as LPS, zymosan, R848, alone or in combination (Figure 1b,c)(12). Omeprazole is also greatly effective in the inhibition of the hypersecretion of IL-beta which is observed in the LPS-stimulated monocytes of CAPS patients (N=4). The greatest inhibition (circa 80%) is obtained with concentrations of 100-200 microM, according to the proton pumps inhibitor compound used according to the compound of proton pumps used (Figure 2). The secretion of IL-beta induced by exogenous ATP on LPS-stimulated cells, both human and murine, is also greatly inhibited (Figure 3d, e).

**EXAMPLE 2: In vivo study of the effect of esomeprazole on survival**
in endotoxin shock

Materials and Methods

40 C57BI/6J mice were intravenously injected with LPS (12.5 mg/Kg in 0.1 ml of physiological solution), and in the peritoneum with Esomeprazole (12.5 mg/Kg in DMSO diluted 1:20 in physiological solution; 0.2 ml final) or solvent 30 min before. A further two groups of mice received ESO after 30 or 90 minutes from the injection with LPS. Esomeprazole was chosen (which is the S-enantiomer of the racemate omeprazole) as it is eliminated more slowly than the enantiomer R-omeprazole and therefore has the kinetic advantage of having a longer half-life. Further, esomeprazole has already been used in Humans intravenously to inhibit gastric secretion (16).

A group of control mice (N=40) was intravenously injected with LPS and solvent (DMSO 1:20 in physiological solution, 0.2 ml final) in the peritoneum. An ocular blood sample was taken at 1.5 or 4 hours following injection of LPS. The mice were monitored for survival (a), fatigue and loss of body weight for 15 days. Serum levels of TNF-alpha and IL1 beta were calculated by ELISA.

15 mice treated with Esomeprazole and survivors of the LPS injection were re-injected intravenously after two weeks with LPS (12.5 mg/Kg). 10 naive mice were intravenously injected with the same quantity of LPS. Both groups received no other treatments.

The mice peritoneal macrophages treated with ESO and survivors of the first LPS shock were stimulated in vitro with various TLR agonists, without or with ATP, and the secretion of TNF-alpha and IL1 beta was compared with the secretion obtained from macrophages of naive mice stimulated in the same way.

Results

Survival is greatly increased by the treatment with Esomeprazole: while 95% of the non-treated mice dies within 60 hours from the LPS injection, the mice treated with LPS + Esomeprazole have an increased
survival time, and 60% heal (Figure 4a). Serum dosage of TNF-Alpha, the most important and fastest marker of sepsis, and of IL-1beta are greatly reduced in mice treated with Esomeprazole (figure 4b).

The mice treated with Esomeprazole which survived the first LPS injection, re-injected after 2 weeks with the same dose of LPS which induces early death in naive mice, were revealed to be resistant and did not develop sepsis (Figure 4c).

The mice treated with Esomeprazole which survived the first LPS injection, re-injected after 2 weeks with the same dose of LPS which induces early death in naive mice, were revealed to be resistant and did not develop sepsis (Figure 4c).

The comparison between the secretion of TNF-alpha and IL-1beta by the peritoneal macrophages of naive mice or mice that survived the septic shock revealed that the latter group shows a smaller secretion of the two cytokines, not only in response to LPS but also to other TLR agonists with which they have never before come into contact (Figure 5).

**EXAMPLE 3:** In vivo study on the effect of esomeprazole on systemic inflammation induced by agents different to LPS, infective or sterile.

**Materials and Methods**

Mice treated with esomeprazole healed after the first injection with LPS (survived LPS+ESO, N=5) and naive mice (n=7) were injected with zymosan (Zym, 1g/Kg). The mice were monitored for survival and loss of body weight (N=4). (C) the levels of TNF-a (on the left; N=4) and IL-1β (on the right; N=2) were quantified (ng/ml; mean ± SEM).

Three mice were injected intraperitoneally with Thioglycollate alone; three mice were injected with Thioglycollate+esomeprazole; three naive mice were used as controls. After three days, the peritoneal cells were isolated from the three groups of mice and counted. The data is expressed as total number of inflammatory cells present in the peritoneal wash (mean ± SEM ; N = 3).

**Results**

The majority of the mice survived the injection of zymosan, but survival was greater in the mouse group that survived LPS plus...
esomeprazole (80 % vs 57 %, Figure 6a). Further, from the survivors among the naive mice, a significantly greater weight loss was observed in the first three days (Figure 6a), and more intense signs of disease. In the mice that survived the challenge with zymosan, the serum levels of TNF-a (but not IL-1β) were significantly lower in the surviving mouse group from LPS plus esomeprazole (Figure 6c).

Lastly, the esomeprazole was revealed to be effective also in the thioglycollate peritonitis model (sterile peritonitis: in fact esomeprazole prevents recruiting of inflammatory cells in the peritoneum (Figure 7).

Bibliography


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7. Agenzia Italiana del farmaco, Note 66.


1) Proton pump inhibitor compound for use in anti-inflammatory therapy.

2) Compound according to claim 1, for use as in claim 1, wherein said proton pump inhibitor compound is selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts or their mixtures.

3) Compound according to any one of the claims 1-2, for use as in claim 1, in treatment of acute or chronic inflammatory diseases selected from the group consisting of sepsis, autoimmune diseases, autoinflammatory diseases, diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis, diseases of the central nervous system such as depression or Parkinson's.

4) Compound according to any one of claims 1-3, for use as in claim 3, wherein the sepsis is selected from the group consisting of neonatal sepsis, necrotizing enterocolitis, systemic inflammatory response syndrome, trauma shock, grave or severe sepsis.

5) Compound according to any one of claims 1-4, for use according to any one of claims 1-4, wherein said compound is administered parenterally such as by intravenous, intramuscular, subcutaneous injection.

6) Compound according to any one of claims 1-5, for use according to any one of claims 1-5, wherein said compound is administered in combination with at least a drug selected from the group consisting of non-steroidal anti-inflammatory drugs, corticosteroid, sulfasalazine, TNF-alpha, IL-1 or IL-6 inhibitor biological drugs.

7) Compound according to any one of claims 1-5, for use according to any one of claims 1-5, wherein, when said compound is for use in anti-inflammatory therapy of sepsis, said compound is administered in combination with beta-lactam antibiotics, P2X7 receptor inhibitor drugs, such as bisphosphonates, extracellular ATP hydrolysing drugs, such as apyrase, TLR4 receptor antagonists.
8) Combination of a proton pump inhibitor compound with a drug selected from the group consisting of non-steroidal anti-inflammatory drugs, corticosteroid, sulfasalazine, TNF-alpha, IL-1 or IL-6 inhibitor biological drugs, for separate, simultaneous or sequential use in anti-inflammatory therapy.

9) Combination according to claim 8, for use as in claim 8, wherein said proton pump inhibitor compound is selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts or their mixtures.

10) Combination according to any one of the claims 8-9, for use according to any one of claims 8-9, in treatment of acute or chronic inflammatory diseases selected from the group consisting of sepsis, autoimmune diseases, autoinflammatory diseases, diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis, diseases of the central nervous system such as depression or Parkinson's.

11) Combination of a proton pump inhibitor compound with a drug selected from the group consisting of beta-lactam antibiotics, P2X7 receptor inhibitor drugs, such as bisphosphonates, extracellular ATP hydrolysing drugs, such as apyrase, TLR4 receptor antagonists, for separate, simultaneous or sequential use in anti-inflammatory therapy of sepsis.

12) Combination according to claim 11, for use as in claim 11, wherein said proton pump inhibitor compound is selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dexlansoprazole, their salts or their mixtures.

13) Combination according to any one of claims 8-12, for use according to any one of claims 8-12, wherein said proton pump inhibitor compound is administered parenterally such as by intravenous, intramuscular, subcutaneous injection.

14) Pharmaceutical composition comprising or consisting of a proton pump inhibitor compound, as active ingredient, in association with one or
more excipients and/or adjuvants, for use in anti-inflammatory therapy.

15) Pharmaceutical composition according to claim 14, for use as in claim 14, wherein said proton pump inhibitor compound is selected from the group consisting of omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole, ilaprazole, tenatoprazole, dextansoprazole, their salts or their mixtures.

16) Pharmaceutical composition according to any one of the claims 14-15, for use as in claim 14, in treatment of acute or chronic inflammatory diseases, selected from the group consisting of sepsis, autoimmune diseases, autoinflammatory diseases, diabetes, atherosclerosis, obesity, cardiovascular diseases, osteo-arthritis, diseases of the central nervous system such as depression or Parkinson's.

17) Pharmaceutical composition according to claim 15, for use as in claim 15, wherein the sepsis is selected from the group consisting of neonatal sepsis, necrotizing enterocolitis, systemic inflammatory response syndrome, trauma shock, grave or severe sepsis.

18) Pharmaceutical composition according to any one of claims 14-17, for use according to any one of claims 14-17, wherein said pharmaceutical composition further comprises at least one drug selected from the group consisting of non-steroidal anti-inflammatory drugs, corticosteroid, sulfasalazine, TNF-alpha, IL-1 or IL-6 inhibitor biological drugs.

19) Pharmaceutical composition according to any one of claims 14-17, for use according to any one of claims 14-17, wherein, when said pharmaceutical composition is for use in anti-inflammatory therapy of sepsis, said pharmaceutical composition further comprises beta-lactam antibiotics, P2X7 receptor inhibitor drugs, such as bisphosphonates, extracellular ATP hydrolysing drugs, such as apyrase, TLR4 receptor antagonists.

20) Pharmaceutical composition according to any one of the claims 14-19, for use according to any one of claims 14-19, wherein said pharmaceutical
composition is administered parenterally such as by intravenous, intramuscular, subcutaneous injection.
Fig. 1
Fig. 1
Fig. 2

**Graph a:**
- IL-1β secretion (% of LPS) vs. Omeprazole (μM)
- TNF-α secretion (% of LPS) vs. Omeprazole (μM)
- Data points with significance indicators (*, **, ***)

**Graph b:**
- IL-1β secretion (% of LPS) vs. Esomeprazole (μM)
- TNF-α secretion (% of LPS) vs. Esomeprazole (μM)
- Data points with significance indicators (*, **, ***)

**Graph c:**
- IL-1β secretion (% of LPS) vs. Lansoprazole (μM)
- TNF-α secretion (% of LPS) vs. Lansoprazole (μM)
- Data points with significance indicators (*, **, ***)

*Note: The graphs illustrate the effect of Omeprazole, Esomeprazole, and Lansoprazole on the secretion of IL-1β and TNF-α, with significance levels indicated by asterisks.
Fig. 2
Fig. 4
Fig. 5
Fig. 6
Fig. 7

Peritoneal cells (total number x 10^6)

Unt  Thio  Thio +ESO

***  ***
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4439 A61P29/00 A61K45/06

ADD.

According to International Patent Classification (IPC) into both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>DICKINSON J B: &quot;IS OMEPRAZOLE HELPFUL IN INFLAMMATORY BOWEL DISEASE?&quot;, JOURNAL OF CLINICAL GASTROENTEROLOGY, RAVEN PRESS LTD., NEW YORK, NY, US, vol. 18, no. 4, 1 June 1994 (1994-06-01), pages 317-319, XP000913822, ISSN: 0192-0790 abstract</td>
<td>1-2, 4-14, 15, 18, 20</td>
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Name and mailing address of the ISA'

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Authorized officer Bonzano, Camilla
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