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- (71) Applicant (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **DAGDELEN, Nuray** [DE/DE]; Passauerstrasse 169, 81369 Muenchen (DE). **KRELL, Hans-Willi** [AT/DE]; Zugspitzstrasse 14a, 82377 Penzberg (DE). **ROESKEN, Frank** [DE/DE]; Diefenbachstrasse 18, 81479 Muenchen (DE). **SAFAK, Okan** [DE/DE]; Balanstrasse 97b, 81539 Muenchen (DE). **SOMMERHOFF, Christian** [DE/DE]; Thomassstrasse 7, 81929 München (DE).
- (74) Agent: **SCHREINER, Siegfried**; Roche Diagnostics GmbH, Patent Department (TR-E), Postfach 11 52, 82372 Penzberg (DE).
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(54) Title: USE OF A TRIOXOPYRIMIDINE FOR THE TREATMENT OF CHRONIC WOUNDS

(57) Abstract: The invention provides the use of a trioxypyrimidine compound having an inhibitory activity against MMP-1, MMP-2, MMP-3, MMP-9 and MMP-14 defined as a) an IC₅₀ value of less than 5 µM for MMP-2, MMP-9 and MMP-14 each; b) a ratio of more than 100 for the IC₅₀ values of MMP-1:MMP-2, MMP-1: MMP-9, MMP-1:MMP-14; and c) a ratio of more than 10 for the IC₅₀ values of MMP- 3:MMP-2, MMP-3: MMP-9, MMP-3:MMP-14, for the manufacturing of a medicament for the promoting of wound healing.



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Use of a trioxopyrimidine for the treatment of chronic wounds

The present invention relates to the use of a trioxopyrimidine compound for the treatment and prevention of chronic wounds.

Introduction

5 Destruction of tissue results in a complex cascade of cellular and biochemical reactions Winkeltau, G., and Schumpelick, V., Ablauf der Wundheilung, Schumpelick, V., Bleese, N. M., and Mommsen, U. (eds.), Ferdinand Enke Verlag, Stuttgart, 1999, pp. 42-46, leading to the defined process of wound healing. Normal
10 healing of wounds requires careful orchestration of different factors which are important for a physiological milieu within the wound area. An imbalance of pro-inflammatory cytokines in the wound induce high concentration of proteases. This can lead to a higher degradation of extra cellular matrix, cytokines and growth factors and their receptors. As a consequence, these processes can convert an acute healing wound into to a chronic one leading to persistent inflammation reaction
15 within the wound area and to a dysregulation in cutaneous and subcutaneous repair mechanism of the tissue.

Proteases, especially Matrix Metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs) play a major role by their physiological function in tissue modeling. The MMP family of proteases are zink-dependent endopeptidases that
20 can degrade essentially all extracellular matrix (ECM) components. MMPs are produced by several different types of cells in skin including fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils. In general, MMPs are not constitutively expressed in skin but are induced temporarily in response to exogenous signals such as cytokines, growth factors, cell-matrix
25 interactions and altered cell-to-cell contacts. MMPs also play important roles in various normal physiologic situations, including morphogenesis of tissues during embryological development, angiogenesis, parturition, ovulation and remodelling of scar tissue by proteolytically restructuring the extra-cellular matrix. However, MMPs can also contribute to pathological conditions that are characterized by the
30 excessive breakdown of ECM components such as in rheumatoid arthritis, tumor cell invasion and metastasis.

In normal wound healing, MMPs seem to be involved in various processes. In the first phase of wound repair, MMPs participate in the removal of de-vitalized tissue. During the repair phase, MMP activities are necessary for angiogenesis, for contraction of wound matrix, for migration of fibroblasts, and for keratinocyte migration and epithelialisation. During the final phase of wound healing, MMPs participate in the remodeling of newly synthesized connective tissue. In summary, spatially and temporally controlled expression of several distinct MMPs is necessary for normal wound healing and tissue repair. An important mechanism for the regulation of the activity of MMPs is via binding to members of the family of proteins referred to as TIMPs (TIMP-1 to TIMP-4). TIMPs are relatively small proteins (21 000 to 29 000 M r) yet they have several biological functions, including inhibition of active MMPs, stimulation of cell division, binding to ECM, inhibition of angiogenesis and induction of apoptosis.

Matrix metalloproteases (MMPs) are a family of zinc- and calcium-dependent proteases that are capable of degrading the extracellular matrix (ECM) and basement membrane (Egeblad, M., and Werb, Z., *Nat. Rev. Cancer* 2 (2002) 161-174; Overall, C.M., and Lopez-Otin, C., *Nat. Rev. Cancer* 2 (2002) 657-672). They are believed to have pivotal roles in embryonic development and growth (Holmbeck, K., et al., *Cell* 99 (1999) 81-92; Vu, T.H., et al., *Cell* 93 (1998) 411-422) as well as in tissue remodeling and repair (Shapiro, S.D., *Curr. Opin. Cell Biol.* 10 (1998) 602-608; Lund, L.R., et al., *EMBO J.* 18 (1999) 4645-4656). Excessive or inappropriate expression of MMPs may therefore contribute to the pathogenesis of many tissue-destructive processes, including tumor progression (Egeblad, M., and Werb, Z., *Nat. Rev. Cancer* 2 (2002) 161-174; Overall, C.M., and Lopez-Otin, C., *Nat. Rev. Cancer* 2 (2002) 657-672) and aneurysm formation (Carmeliet, P., et al., *Nat. Genet.* 17 (1997) 439-444). MMP effects are far from being restricted to ECM degradation (Chang, C., and Werb, D., *Trends Cell Biol.* 11 (2001) S37-43). Peptide growth factors that are sequestered by ECM proteins become available once degraded by MMP-9 (Manes, S., et al., *J. Biol. Chem.* 274 (1999) 6935-6945). MMPs can increase the bioavailability of VEGF (Bergers, G., et al., *Nat. Cell Biol.* 2 (2000) 737-744) but also generate angiogenesis inhibitors such as angiostatin by cleavage of plasminogen (Dong, Z., et al., *Cell* 88 (1997) 801-810).

Inhibition of MMPs, either with the naturally occurring Tissue Inhibitors of Metalloproteases (TIMPs), or with low molecular weight inhibitors, resulted in

impressive anti-tumor and anti-metastatic effects in animal models (Brown, P.D., Med. Oncol. 14 (1997) 1-10). Most of the low-molecular weight inhibitors of MMPs are derived from the hydroxamic acid compound class and inhibit MMPs in a broad manner, being not selective for MMP-2 and MMP-9, the key MMPs in tumor invasion, metastatic spread, and angiogenesis. However, MMP inhibiting molecules from another structural class, the trioxypyrimidines, have been described, e.g. in WO 97/23465 and WO 01/25217. This class of compounds is extremely potent, and highly selective, with an almost exclusive specificity for MMP-2, MMP-9, while sparing most other members of the MMP family of proteases.

Several MMP inhibitors, predominantly of the hydroxamic acid substance class with broad substrate specificity were, and in part still are, in clinical testing for anti-tumor treatment. All of the published clinical results with these inhibitors were disappointing, showing little or no clinical efficacy (Fletcher, L., Nat. Biotechnol. 18 (2000) 1138-1139). The reason for this lack of efficacy in the clinic most likely is the fact that patients could not be given high enough doses for anti-tumor or anti-metastatic activity because of the side effects associated with these broadly acting inhibitors. These dose-limiting side effects were predominantly arthralgias and myalgias (Drummond, A.H., et al., Ann. N.Y. Acad. Sci. 878 (1999) 228-235). As a possible way to circumvent this problem, the combination of MMP inhibitors with classical cytostatic/cytotoxic compounds was evaluated in animal studies. Indeed, in these experiments, MMP inhibitors, in combination with cytostatic/cytotoxic drugs, showed enhanced tumor inhibiting efficacy (Giavazzi, R., et al., Clin. Cancer Res. 4 (1998) 985-992). In addition, International Patent Application No. PCT/EP02/04744 shows the combination of trioxypyrimidine based gelatinase inhibitors and cytotoxic/cytostatic compounds such as cisplatin, Paclitaxel, Gemcitabine or Etoposide.

The use of inhibitors of metalloproteinases for wound healing in general is known in the state of the art. Such inhibitors are for example hydroxamic acids (US 2003/0,050,310; US 6,465,508).

Description of the Invention

5 It was surprisingly found that trioxypyrimidine-based MMP inhibitors which are highly selective for MMP-2, MMP-9 and MMP-14 are useful for the promoting of wound healing, preferably of skin wounds, especially of chronic skin wounds.

The invention therefore provides the use of a trioxypyrimidine compound having an inhibitory activity against MMP-1, MMP-2, MMP-3, MMP-9 and MMP-14 defined as

- a) an IC_{50} value of less than 5 μ M for MMP-2, MMP-9 and MMP-14 each;
- 10 b) a ratio of more than 100 for the IC_{50} values of MMP-1:MMP-2, MMP-1:MMP-9, MMP-1:MMP-14; and
- c) a ratio of more than 10 for the IC_{50} values of MMP-3:MMP-2, MMP-3:MMP-9, MMP-3:MMP-14,

for the promoting of wound healing.

15 IC_{50} values are measured by an in vitro assay for MMP enzymatic activity. Such an assay is described by Stack, M.S., and Gray, R.D., J. Biol. Chem. 264 (1989) 4277-4281. This assay is based on the determination of MMP enzymatic activity on a dinitrophenol substrate and fluorescence measurement of the substrate after cleaving by MMPs.

20 The invention further provides the use of such trioxypyrimidine compounds for the manufacturing of a medicament for the promoting of wound healing.

The term "wound" as used herein denotes a bodily injury with disruption of the normal integrity of tissue structures in the skin. The term is also intended to encompass the terms "sore", "lesion", "necrosis" and "ulcer". Normally, the term
25 "sore" is a popular term for almost any lesion of the skin and the term "ulcer" is a local defect, or excavation, of the surface of an organ or tissue, which is produced by the sloughing of necrotic tissue. Lesion generally relates to any tissue defect.

Necrosis is related to dead tissue resulting from infection, injury, inflammation or infarctions.

5 The term "wound" as used herein denotes any wound and at any particular stage in the healing process including the stage before any healing has initiated, and especially a chronic wound.

10 Examples of wounds which can be prevented and/or treated in accordance with the present invention are, e.g., aseptic wounds, contused wounds, incised wounds, lacerated wounds, non-penetrating wounds (i.e. wounds in which there is no disruption of the skin but there is injury to underlying structures), open wounds, penetrating wound, perforating wounds, puncture wounds, septic wounds, subcutaneous wounds, etc. Examples of sores are bed sores, cancer sores, chrome sores, cold sores, pressure sores etc. Examples of ulcers are, e.g., peptic ulcer, duodenal ulcer, gastric ulcer, gouty ulcer, diabetic ulcer, hypertensive ischemic ulcer, stasis ulcer, ulcus cruris (venous ulcer), sublingual ulcer, submucous clear, symptomatic ulcer, trophic ulcer, tropical ulcer, venereal ulcer, e.g. caused by gonorrhoea (including urethritis, endocervicitis and proctitis). Conditions related to wounds or sores which may be successfully treated according to the invention are burns, anthrax, tetanus, gas gangrene, scalatina, erysipelas, sycosis barbae, folliculitis, impetigo contagiosa, or impetigo bullosa, etc. Therefore as mentioned above, in the present context the term "wound" encompasses the term "ulcer", "lesion", "sore" and "infarction".

25 The term "skin" is used in a very broad sense embracing the epidermal layer of the skin and--in those cases where the skin surface is more or less injured--also the dermal layer of the skin. Apart from the stratum corneum, the epidermal layer of the skin is the outer (epithelial) layer and the deeper connective tissue layer of the skin is called the dermis.

30 Under normally circumstances, the body provides mechanisms for healing injured skin or mucosa in order to restore the integrity of the skin barrier or the mucosa. The repair process for even minor ruptures or wounds may take a period of time extending from hours and days to weeks. However, in ulceration, the healing can be very slow and the wound may persist for an extended period of time, i.e. months or even years.

Matrix metalloproteinases are well-known in the state of the art and are defined, e.g., by their EC numbers (MMP-1 EC 3.4.24.7; MMP-2 EC 3.4.24.24; MMP-3 EC 3.4.24.17, MMP-9 EC 3.4.24.35, MMP-14 EC 3.4.24).

5 Trioxypyrimidines useful for the invention are compounds from a well-known structural class. Such compounds are described in, for example, US Patent Nos. 6,242,455 and 6,110,924; WO 97/23465, WO 98/58915, WO 01/25217, which are incorporated herein by reference, and Grams, F., et al., Biol. Chem. 382 (2001) 1277-1285, and are effective and highly selective for MMP-2, MMP-9, and MMP-14.

10 According to the invention, the following compounds are particularly preferred:

5-Biphenyl-4-yl-5-[4-(4-nitro-phenyl)-piperazin-1-yl]pyrimidine-2,4,6-trione
(Compound I)

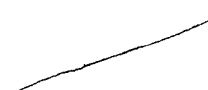
15 5-(4-Phenoxy-phenyl)-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
(Compound II)

5-[4-(4-Chloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
(Compound III)

20 5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
(Compound IV)

5-[4-(4-Bromo-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
(Compound V).

25 The exact dosage of the MMP inhibitors will vary, but can be easily determined. In general, the daily dosage of the inhibitors will range between 1 nmol/kg and day to 1 mmol/kg and day.



- The pharmaceutical compositions are aqueous compositions having physiological compatibility. The compositions include, in addition, auxiliary substances, buffers, preservatives, solvents and/or viscosity modulating agents. Appropriate buffer systems are based on sodium phosphate, sodium acetate or sodium borate.
- 5 Preservatives are required to prevent microbial contamination of the pharmaceutical composition during use. Suitable preservatives are, for example, benzalkonium chloride, chlorobutanol, methylparabene, propylparabene, phenylethyl alcohol, sorbic acid. Such preservatives are used typically in an amount of 0.01 to 1% weight/volume.
- 10 Suitable auxiliary substances and pharmaceutical formulations are described in Remington's Pharmaceutical Sciences, 16th ed., 1980, Mack Publishing Co., edited by Oslo et al. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of a pharmaceutically acceptable substances include saline, Ringer's solution and
- 15 dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5.

- The compositions of the invention for parenteral administration contain as excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes, and the like. In particular,
- 20 biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxethylene-polyoxypropylene copolymers are examples of excipients for delayed release of a compound of the invention in vivo. Other suitable parenteral delivery systems include ethylene-vinyl acetate copolymer particles and liposomes. Formulations for inhalation administration may contain excipients such as lactose,
- 25 if desired.

- The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used.
- 30 Examples of lipids useful in liposome production include phosphatidyl compounds, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, cerebrosides, and gangliosides. Particularly useful are diacylphosphatidylglycerols, where the lipid

moiety contains from 14-18 carbon atoms, particularly from 16-18 carbon atoms, and is saturated.

5 The therapeutic agents useful in the method of the invention can be administered parenterally by injection or by gradual perfusion over time. Administration may be intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

10 Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents and inert gases and the like.

20 The following examples and the figure are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Description of the Figure

25 **Figure 1** shows the growth of granulation tissue after local application of Compound I in mice in contrast to untreated animals and non-diabetic animals.

Example 1

Treatment of chronic wounds

Gelatinase-selective MMP-Inhibitors were investigated using a rat wound model. Male SD rats with a body weight of 300-500g (n=32) were narcotized with

Isofluran gas (1.5%/3l O₂). Under sterile conditions a 3 cm median section in the dorsum was performed and a subcutaneous pocket was formed on both sides of the section. Afterwards, a preliminary cut was made with a punch (diameter 1.1 cm) above each pocket and skin as well as subcutaneous tissue was excised by using
5 microsurgical forceps and scissors to create a circular wound area on the top of the latissimus dorsi muscle. To prevent wound contraction, which is usually observed for loose skin animals, a polyethylene ring was implanted on the fascia of latissimus dorsi muscle and fixed by four sutures (Prolene 4.0, Ethicon). The ring consist of eight perforations arranged circularly at the side of the ring (Diameter 0.4 cm) to
10 facilitate the growth of granulating tissue and epithelium string from the margin of the wound.

Three days before starting the experiments induction of diabetic situation was initiated by i.p. application of the cytostatic compound streptozotocine (65mg/kg body weigh) leading to an impaired wound healing. The animals have been staged
15 by blood sugar level of >350 mg/dl as determined with RefloCheck (Roche Diagnostics). The area of the open wound was documented by digital image analysis in a standardized format. The pictures of the wound have been analyzed off-line by computer-assisted planimetry. Parallel documentation of body weight, blood sugar and healthy status. Blood sugar was measured using venous blood from
20 the tail vain.

50 mg of a selective MMP-Inhibitor (Compound I) was dissolved in 300µl DMSO and administered on the wound surface. Immediately after application the wound was covered by a semi permeable membrane. The whole area was closed by a bandage. As a control, animal (n=8) have been treated with a buffer solution
25 instead of streptozotocine for the normal wound healing. In a second control, streptozotocine treated animals have been treated with DMSO instead of Gelatinase-inhibitor. The further treatment was analog to the treated group. For the statistical analysis the program SigmaStat was used.

Result:

30 Gelatinase inhibitor could not detected in the serum after local application within the wound area. In contrast, serum levels around 150µg/ml could be detected in

orally treated animals. As a consequence, systemic side effects can be eliminated by the local treatment.

The planimetric analysis of the wound surface area showed a significantly accelerated reduction of the wound in treated animals compared to control (day 12: [mean $\pm$ sd]: 85.8% $\pm$ 5.4 vs. 65.1% $\pm$ 4.2). Additionally, complete wound closure by coverage of granulation tissue was also dramatically improved in animals, which received the inhibitor solution in contrast to control animals ([mean $\pm$ sd]: 16 $\pm$ 3.1 days vs. 19 $\pm$ 2.7 days). In addition, the treated group showed an enhanced re-epithelialization (day 12: [mean $\pm$ sd]: 67.3% $\pm$ 8.9 vs. 51.1% $\pm$ 9.4 controls). The results are shown in Figure 1.

Example 2

Determination of MMP enzymatic activity

Inhibitors were tested in a modified fluorescence-assay as described by Stack, M.S., and Gray, R.D., J. Biol. Chem. 264 (1989) 4277-4281. Human MMP-1, MMP-2, MMP-3, MMP-9 and MMP-14 are commercially available (e.g. Calbiochem). The pro-enzymes were activated with 1 mM APMA (incubation for 30 min at 37°C) immediately before testing. Activated enzyme is diluted to 100 ng/ml in incubation buffer (50 mM Tris, 100 mM NaCl, 10mM CaCl₂, pH 7.6). The compounds were dissolved in 100% DMSO. For IC₅₀ determination a minimum of 8 dilution steps between 0.5 - 1000 nM have been prepared. DNP-substrate (Bachem M1855, 255 μ M) was dissolved in incubation buffer.

The test tube contains 970 μ l incubation buffer, 10 μ l inhibitor solution and 10 μ l enzyme solution. The reaction was started by adding the 10 μ l substrate solution.

Kinetics of activity were determined using excitation at 280 nm and emission at 346 nm measured on a FluoroMax™ (Spex Industries Inc., Edison, NJ, USA) over 120 sec. DMSO has been used as control instead of inhibitor solution.

IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

IC₅₀ values (nM) are shown in Table 1.

Table 1

	MMP-1	MMP-2	MMP-3	MMP-9	MMP-14
Compound I [nM]	53,000	65	3,500	260	1

List of References:

- Bergers, G., et al., Nat. Cell Biol. 2 (2000) 737-744
Brown, P.D., Med. Oncol. 14 (1997) 1-10
Carmeliet, P., et al., Nat. Genet. 17 (1997) 439-444
5 Chang, C., and Werb, D., Trends Cell Biol. 11 (2001) S37-43
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10 Giavazzi, R., et al., Clin. Cancer Res. 4 (1998) 985-992
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Lund, L.R., et al., EMBO J. 18 (1999) 4645-4656
Manes, S., et al., J. Biol. Chem. 274 (1999) 6935-6945
15 Overall, C.M., and Lopez-Otin, C., Nat. Rev. Cancer 2 (2002) 657-672
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by Oslo et al.
Shapiro, S.D., Curr. Opin. Cell Biol. 10 (1998) 602-608
Stack, M.S., and Gray, R.D., J. Biol. Chem. 264 (1989) 4277-4281
20 US 2003/0,050,310
US 6,110,924
US 6,242,455
US 6,465,508
Vu, T.H., et al., Cell 93 (1998) 411-422
25 Winkeltau, G., and Schumpelick, V., Ablauf der Wundheilung, Schumpelick, V.,
Bleese, N. M., and Mommsen, U. (eds.), Ferdinand Enke Verlag,
Stuttgart, 1999, pp. 42-46
WO 01/25217
WO 97/23465
30 WO 98/58915

Patent Claims

1. Use of a trioxypyrimidine compound having an inhibitory activity against MMP-1, MMP-2, MMP-3, MMP-9 and MMP-14 defined as
- 5 a) an IC_{50} value of less than 5 μ M for MMP-2, MMP-9 and MMP-14 each;
 b) a ratio of more than 100 for the IC_{50} values of MMP-1:MMP-2, MMP-1: MMP-9, MMP-1:MMP-14; and
 c) a ratio of more than 10 for the IC_{50} values of MMP-3:MMP-2, MMP-3: MMP-9, MMP-3:MMP-14,
- 10 for the manufacturing of a medicament for the promoting of wound healing.
2. Use according to claim 1, characterized in that said trioxypyrimidine compound is selected from the group consisting of
- 15 5-Biphenyl-4-yl-5-[4-(4-nitro-phenyl)-piperazin-1-yl]pyrimidine-2,4,6-trione
 5-(4-Phenoxy-phenyl)-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
 5-[4-(4-Chloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
 5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione
20 5-[4-(4-Bromo-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione.
3. Use of a trioxypyrimidine compound having an inhibitory activity against
- 25 MMP-1, MMP-2, MMP-3, MMP-9 and MMP-14 defined as
- a) an IC_{50} value of less than 5 μ M for MMP-2, MMP-9 and MMP-14 each;
 b) a ratio of more than 100 for the IC_{50} values of MMP-1:MMP-2, MMP-1: MMP-9, MMP-1:MMP-14; and
 c) a ratio of more than 10 for the IC_{50} values of MMP-3:MMP-2, MMP-3: MMP-9, MMP-3:MMP-14,
- 30

for the promoting of wound healing.

4. Use according to claim 3, characterized in that said trioxypyrimidine compound is selected from the group consisting of

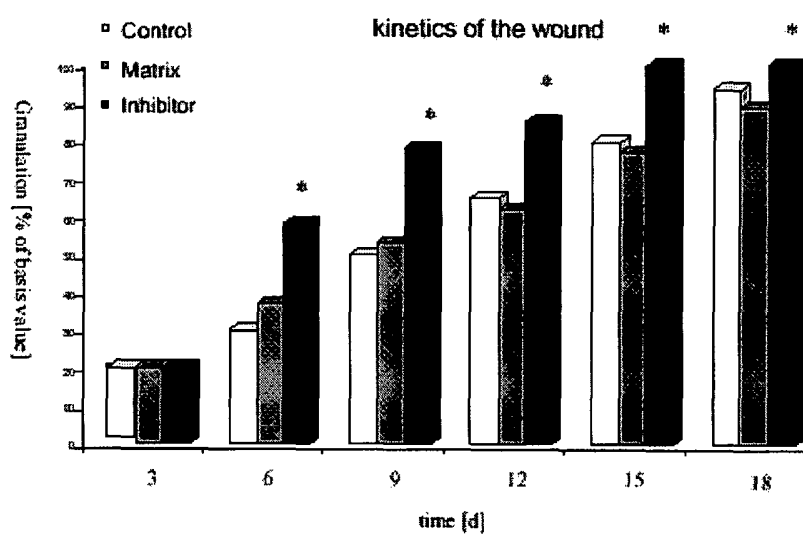
5-Biphenyl-4-yl-5-[4-(4-nitro-phenyl)-piperazin-1-yl]pyrimidine-
2,4,6-trione

5-(4-Phenoxy-phenyl)-5-(4-pyrimidin-2-yl-piperazin-1-yl)-
pyrimidine-2,4,6-trione

5-[4-(4-Chloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-
yl)-pyrimidine-2,4,6-trione

5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-
1-yl)-pyrimidine-2,4,6-trione

5-[4-(4-Bromo-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-
yl)-pyrimidine-2,4,6-trione.

Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/515 A61P17/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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 practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Economou, D

INTERNATIONAL SEARCH REPORT

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